SYNTHETIC AND MECHANISTIC APPROACHES TO BIOLOGICALLY POTENT AMINOGLYCOSIDES VIA DIVERSIFIED AZIRIDINATION PATTERNS

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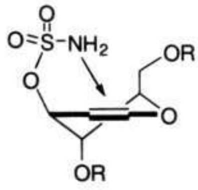
SUMMARY

The flexible installation of a sulfamate ester group on different positions of the glycal scaffold has been highlighted to be a new concept for synthesizing α– and β–aminoglycosides. The methodology incorporated three relevant steps: 1) the introduction of the sulfamate ester on the C3, C4, or C6 position of the glycal, 2) the intramolecular rhodium-catalyzed aziridination, and 3) regio- and stereoselective ring-opening of aziridines with readily available nucleophiles. With this rational design of substrates, the possibility, reactivity and limitation of forming aziridine-ring intermediates from **1**, **2**, and **3** have been performed based on the results from experimental observations and DFT calculations.



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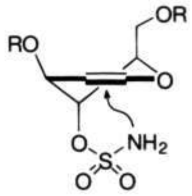

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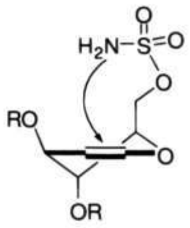

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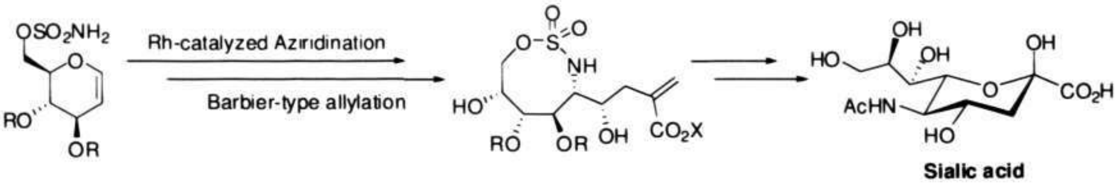
Based on this methodology, we have been trying to develop a protocol for direct *C*-aminoglycosylation. Herein, we describe our observation of a remarkable *C*-coupling reaction in sequential rhodium-catalyzed aziridination and Babier type allylation or propargylation at the anomeric position of D-glycal. The reaction proceeded selectively to form 8-membered oxathiazepanes in a single process. The reaction mechanism and structural characterization of products are presented.



Moreover, the strategy can be very useful for the synthesis of a library of biologically active sialic acids. Ozonolysis of the methylene functionality, followed by removal of the sulfamoyloxy moiety gave α-ketolactone. Under basic hydrolysis, a pyranose ring of sialic acid molecule will be reformed. Further investigation for the formation of a pyranose ring is still active in our laboratory.

INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux or heat
°C	degree centrigrade
Ac	acetyl
aq	aqueous
B3LYP	Becke, three-parameter, Lee-Yang-Parr
Bn	benzyl
Boc	tert-butoxycarbonyl
BPW91	Becke's exchange with the Perdew-Wang 1991
br	broad
brs	broad singlet
Bz	benzoyl
t-Bu	tert-butyl
calcd	calculated
CASSCF	complete-active-space self-consistent-field
cat	catalytic
Cbz	Benzyloxycarbonyl
d	doublet
dd	doublet of doublets
DBU	1,8-diazabicycloundec-7-ene
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DMA	*N,N*-dimethylacetamide
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplet
dq	doublet of quartet
e	dielectric constant
ECPs	effective core potentials
EI	electron impact ionization

equiv	equivalent
ESI	electronspray ionization
Et	ethyl
ether	diethyl ether
FAB	fast atomic bombardment
FTIR	Fourier transform infrared spectroscopy
G	Gibbs free energy
Hex	hexane
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
IRC	intrinsic reaction coordinate
i-Pr	isopropyl
ISC	intersystem crossing
J	coupling constants
K	Kelvin
kcal	kilocalorie
LTMP	lithium 2,2,6,6-tetramethylpiperidide
M^+	parent ion peak (mass spectrum)
m	multiplet
Me	methyl
min	minute
MS	molecular sieve
N	concentration (normality)
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser enhancement spectroscopy
Nu	nucleophile
OTf	trifluoromethanesulfonate
p	page
PES	potential energy surface
Ph	phenyl

Phth	phthalimide
ppm	parts per million
Py	pyridine
q	quartet
qd	quartet of doublets
quint	quintet
RT	room temperature
RBF	round bottom flask
s	singlet
sat	saturated
t	triplet
TBAF	*tetra*-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
td	triplet of doublets
Tf	triflate
TFA	trifluoroacetic acid
tfacam	trifluoroacetamide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tr	trityl
Troc	trichloroethoxycarbamate
TS	transition state

CHAPTER 1

One-pot rhodium-catalyzed aziridination and ring-opening of glycal: A direct access to 2-aminoglycosides

1. INTRODUCTION

A particular class of naturally occurring small molecules, namely the aminoglycosides, forms a large class of clinically important antibiotics with a broad antibacterial spectrum and proven efficacy, particularly against Gram-positive and Gram-negative pathagens.[1] In the last decade, aminoglycoside antibiotics have received much interest for the regulation of protein production at the RNA-level. The utilization of aminoglycoside antibiotics to specifically control important cellular functions as well as the transcription process has been intensively developed. Based on the commonly observed structural features of unusual sugars on aminoglycosides, Wong[2] and Chang[3] have proposed some binding motifs as exemplified in **Figure 1**. They are thought to function in a large part by binding to the decoding region of bacterial 16S ribosomal RNA, thereby causing premature termination and mistranslation of proteins and, consequently, bacterial death.[4] Given the therapeutic potential of targeting biologically relevant RNA sites, a number of groups have synthesized aminoglycoside derivatives in an attempt to tune the RNA affinity, site specificity, and inhibition activities of the resulting derivatives, thus opening new insights for drug discovery.[5]

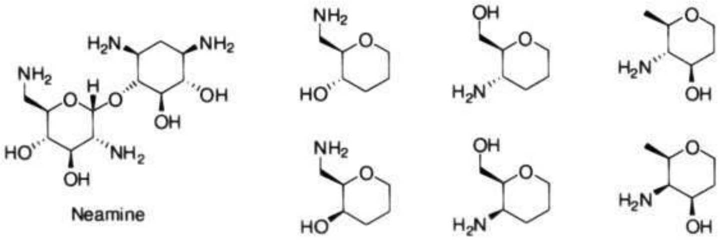


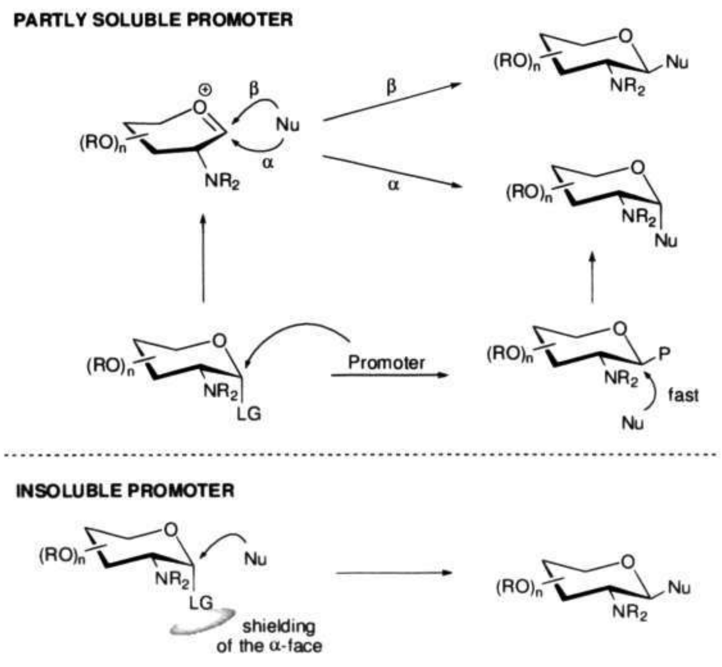
Figure 1 Neamine and common RNA-binding motifs of aminosugars

The biologically important carbohydrates are derived mainly from the natural occurrence of the numerous glycosides in the prokaryotic and eukaryotic glycoconjugates, which are comprised mainly of residues of the 2-amino-2-deoxyglycopyranosides (namely glucosamine). The vast majority of naturally occurring glycosamine residues is part of the structure of the polysaccharides chitosan and chitin, which compose the exoskeletons of crustaceans and arthropods, cell walls in fungi and many higher organisms. They are also found in human milk, in bacterial membranes containing the lipid-A, which is normally a phosphorylated glucosamine disaccharide decorated with multiple fatty acids, and in blood group substances. Other representative examples include peptidoglycans, mucopolysaccharides, heparan sulfates and chondroitin sulfates, which are implicated in cell division, neuronal development, angiogenesis, blood coagulation, inflammation, tumor progression, microbial and viral infection.[6, 7]

The essential role of 2-amino-2-deoxy carbohydrates in many biological processes and in the progression of diseases has been increasingly discovered over the past few years due to vast improvement in analytical techniques. Structures and chemical properties of many complex carbohydrates have been elucidated. Therefore, there is great interest in the development and modification of efficient synthetic methodology for these complex molecules in order to give structural and chemical evidence for or against the proposed stereostructures and also make them more accessible for biological studies in medical and biotechnological research.

Generally, the synthesis of 2-amino-2-deoxy carbohydrates have been achieved by one of two approaches: the modification of glucose or glucose amine, or a glycosylation of sugar containing a participating group as the amino protective function.

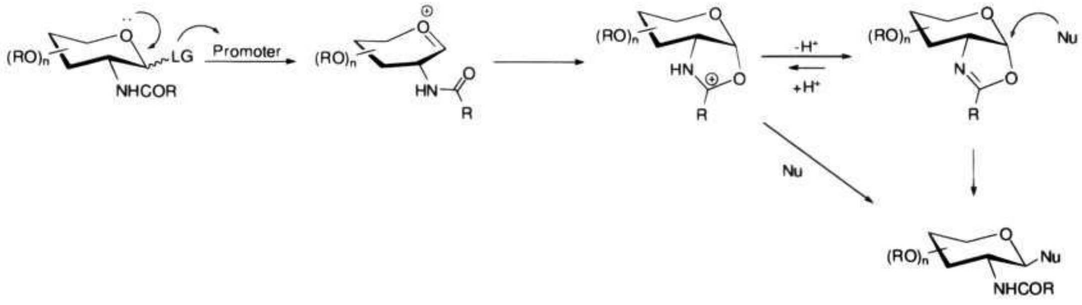
The modification of glucose or glucose amine usually involves a nucleophilic substitution of the carbohydrate containing a leaving group at the anomeric position. The sugar substrate is often called the glycosylation donor and the attacking nucleophile is called the glycosylation acceptor. This method usually requires extensive protecting group manipulation and catalytic amounts of a reaction activator such as a Lewis acid. The reaction activator or promoter could help the reaction in terms of stereoselectivity by assisting the departure of the anomeric leaving group in a way which prevents the formation of the oxocarbenium ion. The oxocarbenium intermediate, most often, leads to a mixture of α- and β-glycosides (Scheme 1). Alternatively, the employment of an insoluble promoter, which is able to shield the α-face of the glycosylation donor, can improve the stereoselectivity of the 1,2-trans glycosylated products.[8]



Scheme 1 Synthetic approach to 1,2-trans aminoglycoside via nucleophilic substitution of the carbohydrate containing a leaving group at the anomeric position.

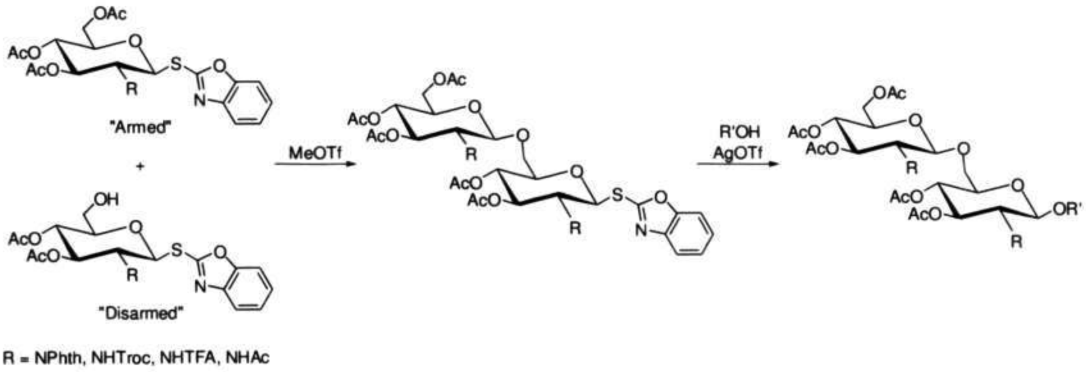
However, it has been shown that glycosylation using the above-mentioned method is usually impractical. The approach to 1,2-trans aminoglycosides involving the formation of a cyclic intermediate has gained considerable interest (Scheme 2). The neighboring group participation promotes the formation of the oxazoline or phthalimido intermediate, resulted in a blocking of the α-face of the glycosylation donor facilitating the addition of the acceptor from the β-face only. As a result, the reaction affords the 1,2-trans-glycoside with a high degree of stereoselectivity. In order to develop stable oxazoline donors for the synthesis of oligosaccharides containing 2-amino-2-deoxy sugars, a variety of 2-amino substituents have been reported, for example, *N*-trifluoroacetyl (trifluoroacetamido, NHTFA),[9] *N*-phthaloyl (phthalimido, Phth),[10, 11] *N*-trichloroethoxycarbonyl (trichloroethoxycarbamoyl, NHTroc),[12] and other substituents.[13-22]

The general mechanism of the oxazoline method is described in Scheme 2. The abstraction of the anomeric leaving group using a promoter generates the reactive oxazolinium ion, which can lose a proton to give the stable oxazoline intermediate. The latter usually acts as a glycopyranosyl donor in the glycosylation step. However, the oxazolinium ion can be reformed under acidic conditions and then react with the glycosylation acceptor to afford the expected 1,2-trans-glycoside.



Scheme 2 The oxazoline method for synthesis of selective 1,2-trans aminoglycosides.

Recently, Demchenko and co-workers[23] have developed the oxazoline method along with the application of novel thiomidoyl glycosidation methodology. The high-yielding synthesis of disaccharides of the 2-amino-2-deoxy series, chemoselective assembly of oligosaccharides containing multiple sequential residues of 2-amino-2-deoxysugars was achieved. The concept of their strategy is to use the stable *N*-substituted SBox as glycosyl donors, followed by coupling with disarmed SBox under the assistance of mildly electrophilic promoters such as AgOTf and MeOTf (Scheme 3).

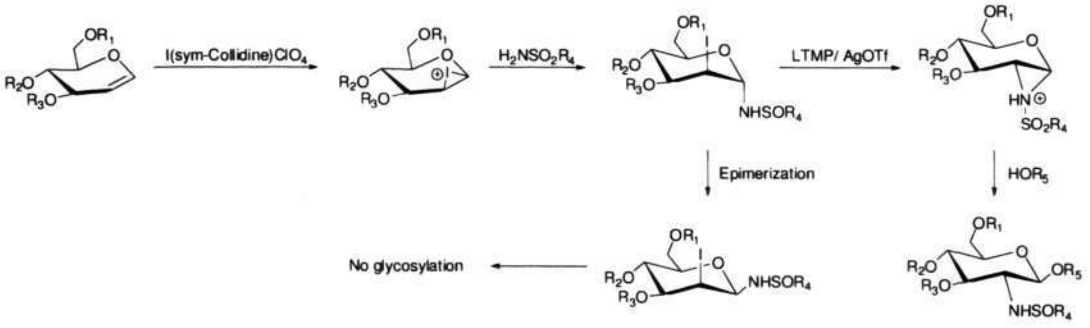


Scheme 3 The chemoselective glysosylation by using *N*-substituted SBox glycosyl donors.

The synthetic incorporation of 2-amino-2-deoxy residues in the preparation of oligosaccharides and glycoconjugates is particularly challenging for selective functionalization of the nitrogen moiety at the C-2 position as well as the glycosidic bond formation with appropriate glycosyl acceptors. Nowadays, glycals are often employed as versatile starting materials in the field of carbohydrate synthesis. Numerous methods have been developed for the direct introduction of a nitrogen substituent at the C-2 position of glycals. This methodology has become most extensively studied in last decade because of a shorter synthetic pathway. In spite of that, multistep syntheses involving the distinct transformation of nitrogen atom transfer and glycosylation are required. Efficient intermolecular installation of a nitrogen atom on a glycal scaffold generated an aziridine or oxazoline intermediate followed by ring-opening with a nucleophile has been developed to be a common mechanistic pathway to generate 2-aminosugars.

1.1 2-Aminoglycosylation via iodosulfonamidation

A pioneering work by Danishefsky showed a possibility for azaglycosylation of glycals, involving the generation of a 1,2-aziridinohexose.[24] In this procedure, a 1,2-glycal was transformed to its trans-diaxial-1,2-iodosulfonamide counterpart via treatment with iodonium di-sym-collidine perchlorate and sulfonamide (Scheme 4). Several attempts to trap the aziridine intermediate from the reaction of iodosulfonamide and base failed. Instead, rapid hydrolysis at the anomeric carbon took place predominantly. The reactive aziridine therefore was generated *in situ* and, subsequently, reacted with a glycosyl acceptor to afford β-coupled 2-amino-2-deoxy product. Typically, Danishefsky's glycosylation is treatment of the trans-1,2-iodosulfonamide with 2.2 equiv of lithium tetramethylpiperidide (LTMP) in dry THF at –78 °C containing 1.4 equiv of silver triflate (AgOTf) and a glycosyl acceptor, or with $AgBF_4$ in the presence of the stannyl alkoxide of the glycosyl acceptor.

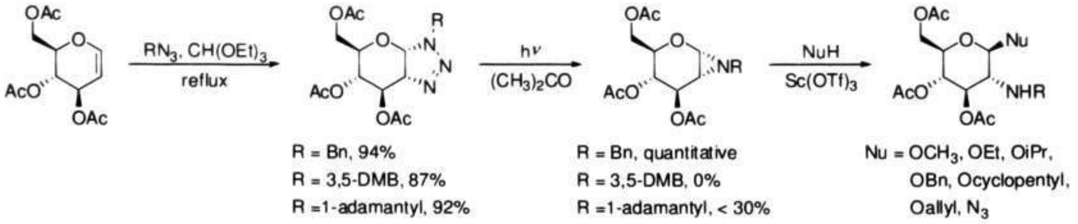


Scheme 4 Synthesis of 2-amino-2-deoxy glycosides by using the Danishefsky iodosulfonamidation methodology.

Notably, it is evident that some *trans*-1,2-iodosulfonamide derivatives readily epimerize at C-1 to the *cis* isomers under acid- and base-catalyzed conditions and also during the purification of the iodosulfonamide substrate.[25] The unexpected epimer, *cis*-1,2-iodosulfonamide, is thermodynamically stable and unable to couple with a glycosyl acceptor under the standard iodosulfonamidation methodology. Petillo and co-worker observed this transformation and extensively examined the factors that play a role in promoting the epimerization process. Trans-1,2-iodosulfonamides are prone to isomerization when 4,6-di-*O*-acetonide or ester possessed the electron-withdrawing group are used as protecting group. Solvents used in silica chromatographic separation, such as chloroform, diethyl ether, or petroleum ether result in rapid partial or complete epimerization.

1.2 2-Aminoglycosylation via dipolar cycloaddition of glycals

Introduction of the nitrogen functionality into a glycal scaffold via a dipolar cycloaddition is shown in Scheme 5.[26] In this course of study, reactions of glycals containing electron-withdrawing protecting groups and electron-rich azides at elevated temperature underwent cycloaddtion efficiently giving rise to triazoline adducts in good yield. The subsequent ring contraction of isolated triazolines to aziridines was critical. Only benzyl-substituted triazolines underwent clean, quantitative photochemical conversion to the corresponding aziridines, whereas 3,5-dimethoxybenzyl and adamantyl substituents led to cycloreversion and small amounts of aziridine intermediate. Although the reactive aziridine could not be isolated, its structural characterization was done by ^{1}H NMR spectroscopy of the crude photolytic solution in acetone-d_6. The ring opening of the reactive aziridine and nucleophiles was carefully examined. The presence of Lewis acid seems to be neccesary for aziridine-ring opening and glycosylation. After extensive observations, $Sc(OTf)_3$ is the reagent of their choice. A solution of the aziridine generated in acetone was transferred directly to a solution of nucleophile (2-3 equiv) in dry THF in the presence of $Sc(OTf)_3$ (0.2 equiv). The glycosylation proceeded smoothly with variuos nucleophiles to furnish the corresponding β-selective aminoglycosides.

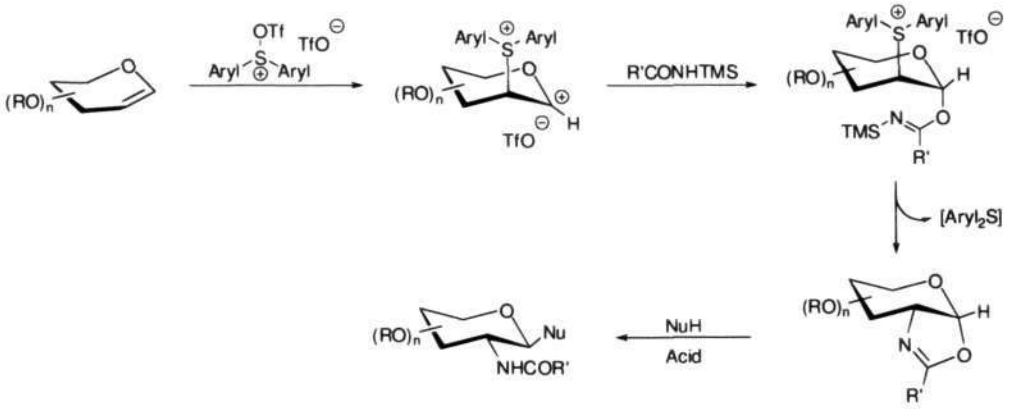


Scheme 5 Synthesis of β-aminoglycosides by dipolar cycloaddtion methodology.

1.3 2-Aminoglycosylation via one-pot acetamidoglycosylation

As 2-*N*-acetylamino-2-deoxy glycosides are a major class of naturally occurring C2-azasugars, the direct installation of acetamido group at C2 as well as the glycosidic bond formation with the desired glycosyl acceptor have been a central focus in carbohydrate synthesis. Liu and Gin[27] reported a novel method for nitrogen transfer to the C2 position of glycal donors, glycosidic coupling, and installation of the native *N*-acetyl functionality in which all are accomplished in one reaction vessel with good yield and excellent diastereoselectivity.

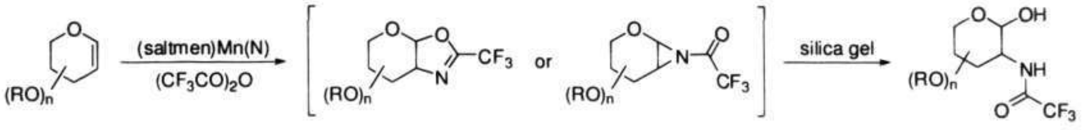
In this protocol, a sulfonium triflate species, generated *in situ* from the reagent combination of thianthrene-5-oxide (TSO) and triflic anhydride, activates the enol ether functionality of a glycal donor, leading to the formation of a pyranosyl intermediate that incorporates a sulfonium moiety at C-2 as well as an oxocarbenium functionality at C-1. Introduction of *N*-(TMS)acetamide as the nitrogen transfer reagent and *N,N*-diethylaniline as a TMSOTf scavenger generates the bicyclic oxazoline intermediate. This key intermediate was detected prior to addition of the glycosyl acceptor, which supports the regio- and stereoselective formation of C2-N and C1-O bonds as proposed in Scheme 6. Finally, sulfonic acids (Amberlyst-15, camphorsulfonic acid) or Lewis acids ($Cu(OTf)_2$, MgI_2, $LiClO_4$) can function as relatively mild acid promoters in the oxazoline ring-opening stage. It has been shown that the direct acetamidoglycosylation reaction is compatible with glycals bearing acid-labile protective groups. Also, a wide range of glycosyl acceptors, such as simple alkyl alcohols, primary and secondary hydroxyls within carbohydrates, and amino acids, can be glycosylated.



Scheme 6 Proposed reaction pathway for direct acetamidoglycosylation.

1.4 2-Aminoglycosylation using a stoichiometric (nitro)Mn(V) complex

In 1997, Carrier and co-workers have demonstrated the first example of a transition metal-mediated glycal amination for the construction of 2-amino-2-deoxy monosaccharides. The process employs easily prepared nitridomanganese(V) salen-derived complex that can be activated with trifluoroacetic anhydride for a CF_3CON unit transfer to an olefin moiety of glycals.[28] In practice, a high concentration of the glycal relative to the activated (saltmen)Mn(*N*) complex is required due to the fast consumption of the reactive manganese species in side-reactions. Therefore, the (saltmen)Mn(*N*) reagent was slowly added to a mixed solution of glycal and trifluoroacetic anhydride (TFAA), affording 2-trifluoroacetylamino alcohols with good yields and high levels of diastereoselectivity. The reaction mechanism was proposed to proceed through a labile intermediate aziridine or oxazoline, followed by ring-opening reaction upon the silica chromatographic separation (Scheme 7). This method can be applied not only to the pyranoid glycals, but also to furanoid sugars. The stereoselectivity of the nitrogen insertion at C-2 is controlled by the proximal stereocenter at C-3, which prefers to be trans to its neighboring group.

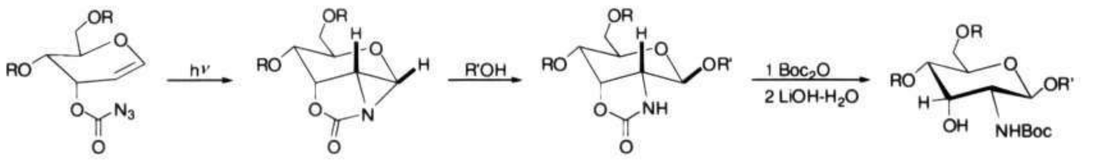


Scheme 7 The nitridomanganese(V) salen-mediated amination of glycals.

1.5 2-Aminoglycosylation using photoinduced acylnitrene aziridination on glycals

Although intermolecular reactions of glycal enol ether π-systems with nitrogen substituents can lead to stereoselective nitrogen installation at C-2 and subsequent glycosylation, they still have a limitation in the synthesis of other unusual aminosugars. Another route to achieve 2-aminoglycosides involves the intramolecular strategy that utilizes a nitrene as an electrophilic nitrogen source. Rojas first manipulated photoinduced acylnitrene aziridination on glycal derivatives (Scheme 8).[29]

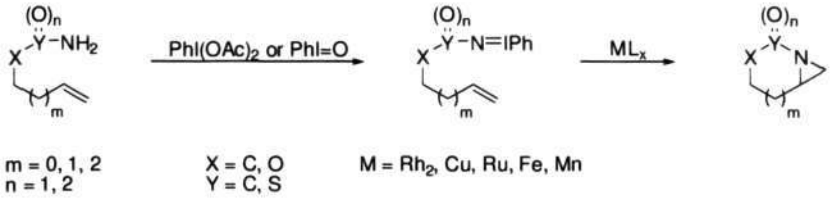
A solution of the potentially labile C-3 allal azidoformate in methylene chloride containing an alcohol nucleophile was photolyzed in a quartz tube using a Rayonet merry-go-round apparatus (254 nm lamp, Vycor filter). The reaction presumably generated a semi-stable aziridine intermediate as a highly reactive glycosyl donor for β-glycosylation. Finally, selective cleavage of the oxazolidinone functionality without disturbing the anomeric stereochemistry was completed under basic hydrolysis.



Scheme 8 Photolysis of C-3 allal azidoformate induced intramolecular nitrene insertion onto a π-system of glycal.

The process allowed a new sight of direct incorporation of C-N bond formation and glycosylation in an intramolecular fashion and posed an additional synthetic challenge in introducing a nitrogen atom on the more hindered glycal face, cis to an axial C-3 substituent. However, the efficiency of amidoglycosylation of azidoformate species was reasonable only with low molecular weight alcohols. Side reactions from Curtius rearrangement of the acyl nitrene and addition of alcohol to the resulting alkoxy isocyanate were observed. Moreover, azidoformate compounds are explosive hazards, we need to take into account the possibility of explosion at high temperature and bulk scale.

To date, transition metal-catalyzed nitrene delivery to the carbon-carbon double bond has been widely applied for the synthesis of unique heterocyclic structures having nitrogen-based functional group. Since an intriguing report by Breslow and Gellman in early 1980s, the value of *N*-arenesulfonyl iminoiodinanes as nitrene precursors has been recognized.[30] Many efforts have been made on searching useful nitrene precursors as well as suitable transition-metals for metal-catalyzed nitrene insertion to C-H and C=C bonds reactions. Sulfonamides, carbamates, and sulfamate esters are commonly employed nitrene precursors in the presence of dirhodium, copper, ruthenium, iron, and manganese catalysts. Breslow[30] and Müller[31] first introduced the conversion of sulfonamide substrates to respective $PhI{=}NSO_2R$ through reaction with iodosobenzene diacetate ($PhI(OAc)_2$). Dodd and co-workers have demonstrated the intramolecular aziridination of unsaturated sulfonamides and sulfamate esters with iodosylbenzene (PhI=O) in the presence of copper catalysts.[32] The groups of Che[33] and Du Bois[34, 35] independently reported the stereospecific intramolecular aziridination of unsaturated carbamate and sulfamate ester substrates with $PhI(OAc)_2$ and ruthenium, manganese, and dirhodium complexes.

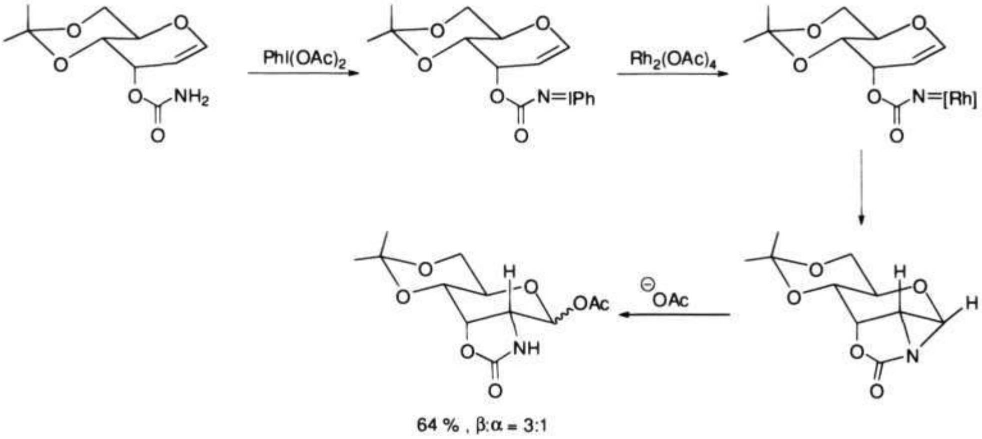


Scheme 9 Metal-catalyzed intramolecular aziridination with hypervalent iodine compounds.

1.6 Intramolecular oxidative aziridination of glycals

Considerable success in promoting intramolecular oxidative aziridination has attracted intensive interest from the chemistry community. Especially in the past few years, the application of this methodology has been successfully used for synthesis of natural and unnatural 2-aminoglycoside frameworks. For example, Rojas showed the use of copper and rhodium catalysts in amidoglycosylation reactions of allal 3-carbamates and glucal 3-carbamates to furnish 2-aminoglycosylated products.[36]

As discussed above that the highly reactive nature of the azidoformate obstructed the amidoglycosylation process, the Rojas research group envisaged the useful implementation of metalnitrenoid species in intramolecular nitrogen atom transfer to the enol ether π-system of glycal. Allal 3-carbamates which bear a carbamate group on the bottom face of the glycal molecule, were treated with iodosobenzene diacetate and catalytic dirhodium(II) acetate. The rhodium-nitrene ($RCO_2N=Rh$) complex was generated in a single process from primary carbamate, and simultaneously delivered to the 1,2-π-system of the glycal starting material, leading to a putative aziridine. The aziridine ring-opening occurred in a regioselective manner by attack of an acetate anion at the positively charged C-1. Apparently, the acetate derived from the decomposition of $PhI(OAc)_2$ and acted as nucleophile to give 2-aminoglycosyl acetate in moderate yield and α:β ratio (Scheme 10).



Scheme 10 Rhodium-catalyzed intramolecular aziridination of allal 3-carbamte.

Formation of other functionalized 2-amino sugars by this methodology was hampered by the *in situ* generation of the acetate anion. A large excess of nucleophiles (up to 20 equiv) was required to suppress the formation of glycosyl acetate. Therefore, iodosylbenzene was used in place of $PhI(OAc)_2$. As a result, much smaller amounts of glycosyl acceptors were used.

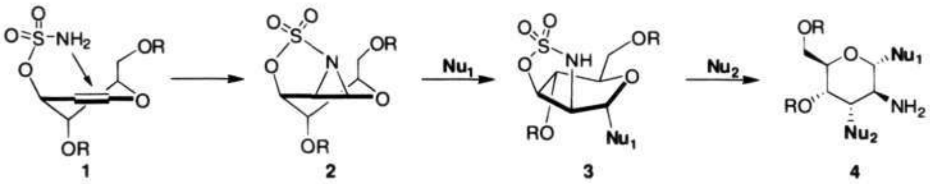
However, so far not many glycal acceptors have been used in this way. We therefore aim to develop the approach to 2-aminosugars with exceedingly complex glycoconjugates.[37, 38]

2. RESULTS AND DISCUSSION

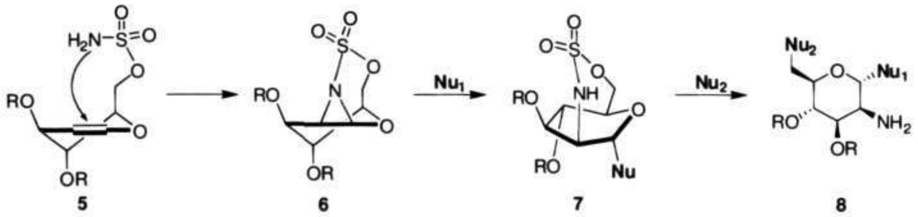
Carbohydrates feature prominently in many biological processes and in the progression of diseases. In recent years, much research has been done in the development of new methods for the synthesis of biologically relevant oligosaccharides, glycoconjugates, and their analogues.[39] In particular, 2-amino-2-deoxy glycosides, a major class of carbohydrates, are vital constituents of glycosaminoglycans, peptidoglycans, and blood group antigens.[40] These compounds serve as challenging synthetic targets to prepare and transform. In one study, the direct introduction of a nitrogen substituent at the C-2 atom of a glycal held considerable promise to access 2-amino sugars and other complex 2-aminoglycoside conjugates. Use of metal-catalyzed nitrene delivery to a double bond of glycal derivatives in inter- and intra-molecular fashions has received intense interest, but most of the common methods require subsequent manipulation to generate a useful glycal donor and complement with a variety of glycal acceptors.

We have pursued an intramolecular strategy that utilizes an iminoiodinane-derived sulfamate ester as an electrophilic nitrogen source[41] and generated a transient aziridine intermediate as a highly activated donor for selective 1,2-*trans* aminoglycosylation.[29,42-43] We envisioned the efficient synthesis of functionalized aminoglycosides by flexible installation of a sulfamate ester on the appropriate position of a glycal. The installation of a sulfamate ester group on the C-3 and C-6 atoms of the glycal substrate offers an approach to α-selective aminoglycosylation through nitrogen atom delivery to a π-bond system on the top face of a glycal scaffold as shown in Scheme 1a and b. A regio- and stereospecific ring-opening reaction of the aziridine with nucleophiles would simultaneously achieve the formation of [1,2,3]oxathiazepane-2,2-dioxides with α-linkage. The second nucleophilic replacement of sulfonyloxy moieties allows ready access to unusual aminoglycosides **4** and **8**. In turn, the facial preference on the bottom face of this glycal scaffold could be elaborated by introducing the sulfamate moiety on the C-4 atom, which gives an opportunity to produce functionalized β-linked 2-amino sugars (Scheme 1c).

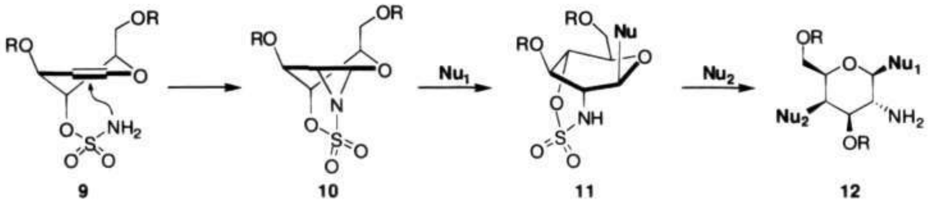
a) The sulfamate ester on the C-3 atom of glycal



b) The sulfamate ester on the C-6 atom of glycal



c) The sulfamate ester on the C-4 atom of glycal

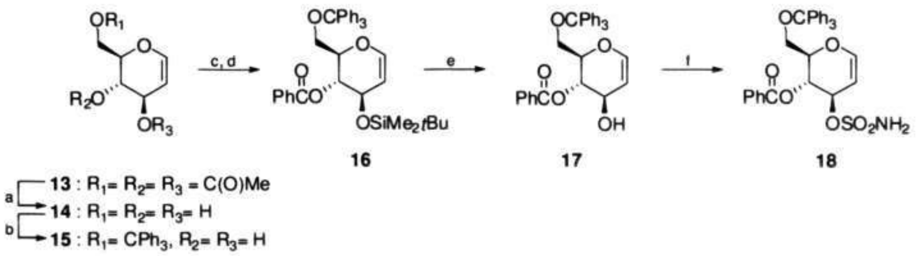


Scheme 1 Aziridination patterns of a sulfamate ester on C-3, C-4, and C-6 positions of glycal scaffold.

Therefore, the aim of this study is to synthesize a variety of usual and unusual 2-aminoglycosides based on the intramolecular nitrogen atom transfer to the carbon-carbon double bond of glycal scaffold. Furthermore, having the sulfamate ester moiety on the different positions of the glycal molecule allows us to investigate the reactivity, facial preference and steric hindrance of forming aziridine intermediates.

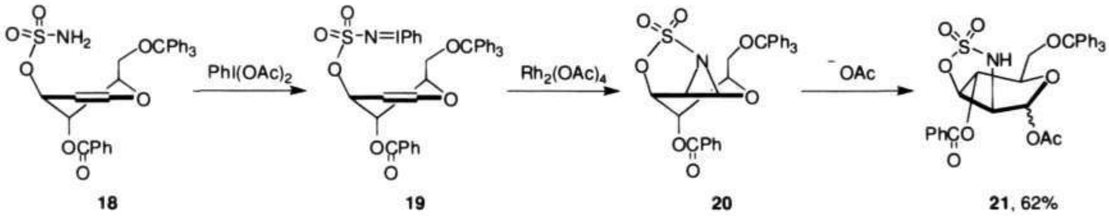
2.1 The aziridination and glycosylation of D-glycal-derived sulfamate ester at the C-3 position

The requisite glycal starting materials were constructed to incorporate a variety of commonly employed carbohydrate protecting groups. We first performed a model study on sulfamate glycal **1**, which was synthesized from readily available tri-*O*-acetyl-D-glycal (Scheme 2).[44] Treatment of tri-*O*-acetyl-D-glycal with sodium methoxide (NaOMe) in dry MeOH provided **14** in quantitative yield. In fact, the reactivity of three hydroxyl groups is different under various conditions, which is a key control element in the selective protection-deprotection. Orthogonal protecting groups for the synthesis of partially protected monosaccharides was used. Conceptually, they should be selectively protected and removed under the desired reaction conditions so that only a specific hydroxyl group remains reactive. The primary hydroxyl group was firstly protected with chlorotriphenylmethane in pyridine to obtain trityl product **15**. Trityl **15** was subsequently reacted with *tert*-butyldimethylsilyl chloride and benzoyl chloride to give a fully protected glycal **16**. The TBDMS protecting group in **16** was selectively cleaved by *tetra-n*-butylammonium fluoride. This step should be carefully monitored by TLC and the reaction should be kept at 0 °C because the adjacent benzoyl group can migrate from the C-4 to the C-3 position under basic conditions. We sometimes detected the migrated product in trace amounts and believe that this occurred via a five-membered transition state. The secondary alcohol **17** was treated with sulfamoyl chloride, which was generated *in situ* from chlorosulfonyl isocyanate and formic acid, and produced sulfamate **18** in moderate yield.



Scheme 2 Synthesis of sulfamate-protected glycal **18**. a) NaOMe/MeOH/RT/1 h/ quantitative yield. b) TrCl/DMAP/pyridine/RT/overnight/80 %. c) TBDMSCl/ imidazole/THF/RT/overnight/90 %. d) BzCl/DMAP/pyridine/RT/2 h/94 %. e) TBAF/THF/0 °C/95 %. f) $ClSO_2NCO/HCO_2H$/DMA/0 °C/2 h/68 %.

Typically, the combination of a rhodium (II) dicarboxylate and a hypervalent iodine oxidant has been widely used for the generation of the reactive rhodium-nitrene species.[34] We thus investigated the reaction scope by using commercially available $PhI(OAc)_2$ as an oxidant and a $Rh_2(OAc)_4$ catalyst. The substrate was treated with a mixture of 5 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO in dry dichloromethane. The mechanistic pathway for the formation of aminoglycosylated product is proposed in Scheme 3. Initially, the sulfamate moiety of **18** reacted with hypervalent iodine, $PhI(OAc)_2$, and generated the iminoiodinane intermediate **19**. The rhodium-catalyzed elimination of the PhI moiety generated the rhodium-nitrene species, followed by intramolecular nitrene insertion into the carbon-carbon double bond giving rise to a short lived aziridine intermediate **20**. The aziridine ring was formed on the top face of molecule due to the installation of the sulfamate group on the β-face. This would allow an acetate anion to attack from the opposite face regioselectively at the anomeric carbon. After 24 h, the suspension was filtered through celite and purified by silica gel column chromatography furnishing an inseparable mixture of α- and β-anomers (2:1) of **21** and only 75% conversion was observed. The loss of stereospecificity and long reaction time of **21** is supposedly caused by the strain of forming aziridine intermediate **20**.

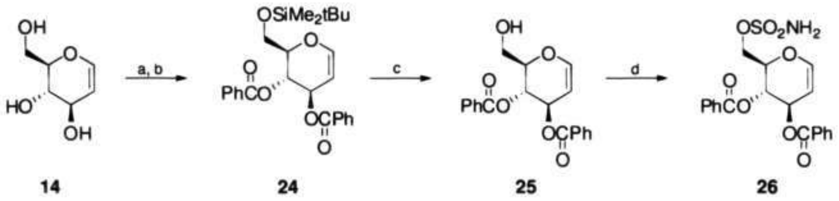


Scheme 3 Mechanism of rhodium-catalyzed aminoglycosylation.

In view of the poor stereoselectivity, the introduction of the sulfamate ester or carbamate at the C-3 atom is unlikely to be a good model to achieve pure aminoglycosides. We suggested that it could be solved by either increasing the ring size of the intermediate or elongating the arm of the sulfamate moiety. Consequently, to achieve α-aminoglycosides, the introduction of the sulfamate moiety on C-6 of the glycal molecule was carried out.

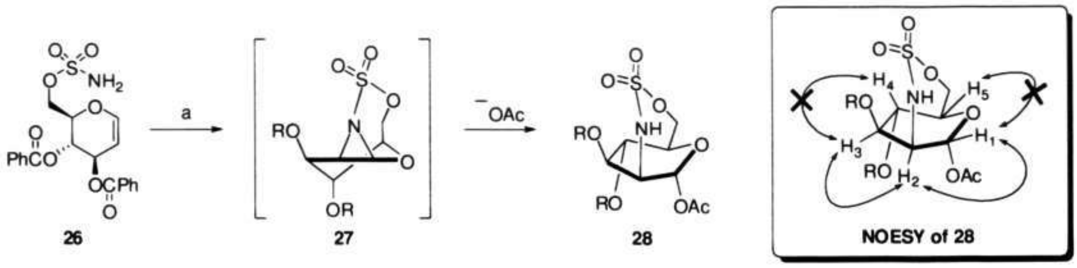
2.2 The aziridination and glycosylation of D-glycal-derived sulfamate ester at the C-6 position

To be more flexible in transferring the reactive nitrene to a double bond moiety, the sulfamate ester moiety was then introduced on the C-6 position of a glycal molecule. Preparation of sulfamate glycal **26** started from the unprotected glycal (**14**) and could be finished in 4 steps as shown in Scheme 4. Treatment of glycal **14** with *tert*-butyldimethylsilyl chloride in DMF selectively furnished monosilyl glycal in good yield. The full protection was completed by reacting compound **24** with benzoyl chloride in pyridine. Selective removal of the TBDMS protecting group in **25** was achieved under acidic conditions by using catalytic amounts of *p*-toluenesulfonic acid (0.5–0.8 equiv).[45] Alcohol **25** was transformed to sulfamate **26** by using sulfamoyl chloride generated *in situ* from chlorosulfonyl isocyanate and formic acid.



Scheme 4 Synthesis of sulfamate-protected glycal **26**. a) TBDMSCl/DMF/RT/overnight/80 %. b) BzCl (2.2 equiv)/DMAP/pyridine/RT/overnight/90 %. c) *p*-TsOH/THF/H_2O/0 °C/6 h/80 %. d) $ClSO_2NCO$/HCO_2H/DMA/0 °C/4 h/83 %.

Following the typical protocol, the sulfamate glycal **26** was treated with $PhI(OAc)_2$, MgO, and 5 mol % of $Rh_2(OAc)_4$ in dichloromethane. The amidoglycosylation reaction proceeded smoothly at room temperature to furnish glycosyl acetate **28** in 82% yield (Scheme 5). Presumably, the aziridine intermediate **27** could not be isolated due to the high reactivity of C-1 and the inherent ring strain. The semi-stable aziridine was simultaneously trapped by acetate anion, which was generated from the decomposition of $PhI(OAc)_2$. Evidence from ^1H and ^{13}C NMR data showed that only diastereomer **28** was obtained. This indicated that the formation of aziridine ring and its ring-opening step occurred in regio- and stereospecific manners. The structural characterization of the glycosyl acetate **28** was also confirmed by extensive NMR spectroscopic data (DEPT, COSY, and HMQC). The relative stereochemistry of aminoglycoside **28** was assigned by NOESY spectroscopy. There is a correlation of H2 and H3, indicating that these two protons locate in cis orientation. The trans–relationship of the acetate group and the amino moiety was further determined by the correlation between H1 and H2 as well as H1 and H5.



Scheme 5 Regio- and stereoselective aziridination and α-selective glycosylation. a) Sulfamate glycal **26** (69 mmol), 5% mol of $Rh_2(OAc)_4$, 1.5 equiv of $PhI(OAc)_2$, 5 equiv of MgO in DCM (3 mL) for 5h.

Aiming at a reliably regio- and stereoselective glycosylation of sulfamate glycal, we extensively investigated the utilization of iodobenzene diacetate, [$PhI(OAc)_2$], alone or in the presence of bases such as Al_2O_3, Cs_2CO_3,and MgO for the rhodium-catalyzed aziridination of glycal. Inspection of entries 1-4 in Table 1 revealed that the addition of base influenced the reaction outcome. The reaction could proceed smoothly, quickly, and with a high yield of glycosyl acetate **28** when MgO was used. On the other hand, Al_2O_3, Cs_2CO_3, and no additives resulted in sluggish reactions and only low yields of product. Subsequent examination of reactions between **26**, MgO, and $PhI(OAc)_2$ in the presence of $Rh_2(OAc)_4$ at elevated temperatures and in different solvents was carried out (entries 5-9). The reaction time was shorted by increasing the reaction temperature to 40-60 °C but the yield of product was slightly decreased. While other solvents such as toluene, acetonitrile, and diethyl ether, could not produce good result for this type of catalytic reaction. Therefore, it could be concluded that the $Rh_2(OAc)_4$-catalyzed aminoglycosylation is best carried out in dichloromethane at room temperature.

Table 1 Intramolecular aziridination of sulfamate glycal **26** with $PhI(OAc)_2$ catalyzed by $Rh_2(OAc)_4$ [a]

entry	additive	solvent	temperature (°C)	time (h)	% yield [b]
1	-	CH_2Cl_2	RT	36	67
2	Al_2O_3	CH_2Cl_2	RT	27	27
3	Cs_2CO_3	CH_2Cl_2	RT	24	34
4	MgO	CH_2Cl_2	RT	5	82
5	MgO	CH_2Cl_2	40	3.5	71
6	MgO	CH_2Cl_2	60	2	56
7	MgO	Toluene	RT	18	14 (21) [c]
8	MgO	CH_3CN	RT	18	22 (55) [c]
9	MgO	Et_2O	RT	18	No reaction

[a] Sulfamate glycal **26** (69 mmol) was treated with $Rh_2(OAc)_4$ (5 mol%), $PhI(OAc)_2$ (1.5 equiv), additive (5 equiv), and solvent (3 mL) in the presence of 4Å molecular sieve. [b] Isolated Yield. [c] Yield in parentheses denotes conversion.

Results from experimental observations suggested that the reaction did not proceed in the absence of Rh(II) catalyst; the starting material was recovered unchanged. These imply that the insertion reaction occurred via a rhodium-complexed nitrene rather than an iminoiodinane intermediate.

We next moved forward to utilize an alcohol as the external nucleophile. A variety of alcohols could be included in the reaction mixture, and this led directly to alkoxylated glycoside derivatives in a single step. Methanol was first employed as a model study. An excess amount of methanol (up to 20 equiv) was needed to suppress the formation of glycosyl acetate. The lower yield of coupled product was most probably due to the attack of a reactive acetoxy species. We then proceeded to investigate the origin of the acetoxy group by replacing the iodosobenzene diacetate with iodosylbenzene (PhI=O). It was fould that the glycosyl acetate was not observed on TLC, and moreover, the amount of methanol that was required could be reduced, which implies that the acetoxy group comes from the decomposition of $PhI(OAc)_2$. However, the combination of $Rh_2(OAc)_4$, PhI=O, MgO, and 2 equiv of MeOH gave only a moderate yield of product (78%). From these results, we selected the use $Rh_2(OAc)_4$, $PhI(OAc)_2$, and MgO as our standard protocol.

Notably, the internal nitrogen transfer to the π-system, and the nucleophilic addition of our sulfamate-protected glycal scaffold at C-1 is the facially selective version of a previously reported reaction that produces α-selective glycosylated products. A X-ray crystallographic study of a glycosyl methoxide **29a** confirmed the diaxial conformation of oxathiazepane ring and the trans-stereochemistry between the *N*-sulfamoyloxy moiety and the methoxy group (Figure 1). This observation allowed us to propose that a transient aziridine intermediate **27** exists in the reaction mixture by direct nitrogen delivery on the upper face of the molecule, and this subsequently fosters the nucleophilic attack on the opposite face. This proposed mechanism is further supported by DFT calculations, as detailed in the Computational Studies section (see in Part 2).

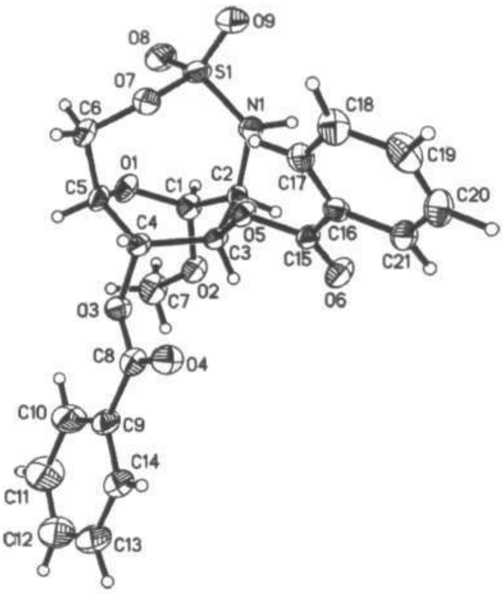
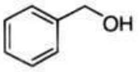
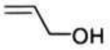
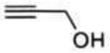
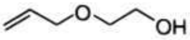


Figure 1 X-ray structure of a glycosyl methoxide **29a**.

To broaden the scope, other alcohols were examined and showed good results as tabulated in Table 2. Nevertheless, the large excess of alcohol required hampered the process, especially alcohols with high molecular weights. Another choice for specific aziridination and its ring opening was inspired by Du Bois.[35c] Rhodium trifluoroacetamide ($Rh_2(tfacam)_4$) showed good ability for catalytic amination of an unsaturated sulfamate ester,[46] while PhI=O helped in reducing the amount of nucleophile. Indeed, the aminoglycosylation was carried out smoothly and gave only α-stereospecifically glycosylated products (entries 4-7, Table 2).[47]

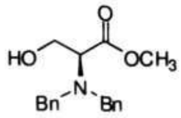
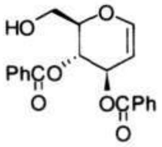
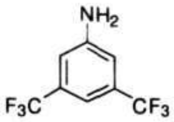
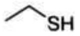
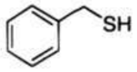
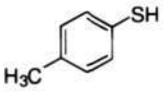
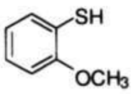
Table 2 Rhodium-catalyzed intramolecular C=C aziridination of sulfamate glycal **26** with various alcohols.

entry	nucleophile	condition[a]	product	% isolated yield
1	MeOH	A	**29a**	81
2	EtOH	A	**29b**	90
3	i-PrOH	A	**29c**	71
4		B	**29d**	92
5		B	**29e**	94
6		B	**29f**	89
7		B	**29g**	95

[a] Condition A : 5 mol% of [$Rh_2(OAc)_4$], $PhI(OAc)_2$ (1.5 equiv), MgO (5 equiv), alcohol (20 equiv) in CH_2Cl_2 at room temperature. Condition B: 5 mol% of [$Rh_2(tfacam)_4$], PhIO (1.5 equiv), MgO (5 equiv) in CH_2Cl_2 at room temperature. Nucleophile (2-5 equiv) was added after 30 mins.

Attempts to expand the scope of glycosylation to other nucleophiles, such as amino acid, monosaccharide, amine and thiol, were made. Unfortunately, these nucleophiles failed to attack the C-1 atom of the aziridine intermediate when catalytic amounts of $Rh_2(OAc)_4$ and $PhI(OAc)_2$ were used. Under these conditions, only glycosyl acetate, unreacted nucleophile and decomposed mixtures were detected. We thus turned to the combination of a rhodium trifluoroacetamide ($Rh_2(tfacam)_4$) and PhI=O. The $Rh_2(tfacam)_4$ shows higher stability in catalytic reaction than $Rh_2(OAc)_4$ due to the strong ligation of the rhodium metal and the amido ligands. We found that $Rh_2(tfacam)_4$ could prolong the lifetime of the aziridine intermediate, which was able to couple with various nucleophiles.[48] In the presence of PhI=O, MgO, and $Rh_2(tfacam)_4$, the iminoiodinane intermediate could be generated *in situ* by reaction of sulfamate substrate and iodosobenzene, followed by Rh-catalyzed intramolecular aziridination. A glycal acceptor was injected into the reaction mixture within 15 minutes to trap a semi-stable aziridine; this provided the desired oxathiazepane (Table 3). In the cases of thiol nucleophiles, the glycosylation step required activation by a Lewis acid, $BF_3 \cdot OEt_2$. Even though moderate yields of glycosylated products were obtained due to the instability of aziridine intermediate in reaction mixture, we were successful in the synthesis of di-amino sugar, disaccharide as well as other functionalized 2-amino sugars in a convenient one-step process.

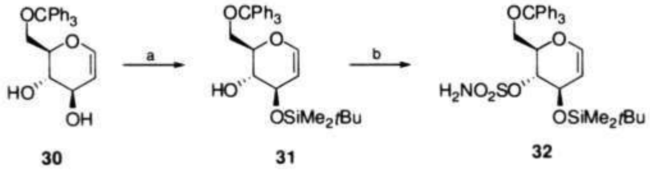
Table 3 Rhodium-catalyzed intramolecular C=C aziridination of sulfamate glycal **26** with amino acid, monosaccharide, amines and thiols.

entry	nucleophile	product	% isolated yield
1		**29h**	66
2		**29i**	37
3		**29j**	46
4	N_3^- [from $(CH_3)_3Si\text{-}N_3$] [b]	**29k**	80
5 [c]		**29l**	84
6 [c]		**29m**	83
7 [c]		**29n**	85
8 [c]		**29o**	78

[a] Unless otherwise noted, the reaction was carried out at room temperature by using substrate (69 mmol), 5 mol% of [Rh_2(tfacam)$_4$], PhIO (1.5 equiv), MgO (5 equiv), and CH_2Cl_2 (3 mL) in the presence of 4 Å MS. Nucleophile (2 equiv) was added after 30 mins. [b] N_3^- was generated by treatment of $(CH_3)_3Si\text{-}N_3$ (2 equiv) and TBAF (2 equiv) at 0 °C for 30 mins. [c] Using nucleophile (2 equiv) and $BF_3.OEt_2$ (0.1 equiv). [d] Isolated yield.

2.3 The aziridination and glycosylation of D-glycal-derived sulfamate ester at the C-4 position

To examine the nitrogen insertion on the bottom face of the glycal molecule, compound **32** was prepared as shown in Scheme 6. Trityl compound **30** was reacted with TBDMSCl in DMF furnishing alcohol **31**. The sulfamate ester **32** was finally obtained by treating alcohol **31** with chlorosulfonyl chloride. This sulfamate glycal was unstable at room temperature. It had to be used for the rhodium catalytic reaction immediately or else kept at -78 °C.

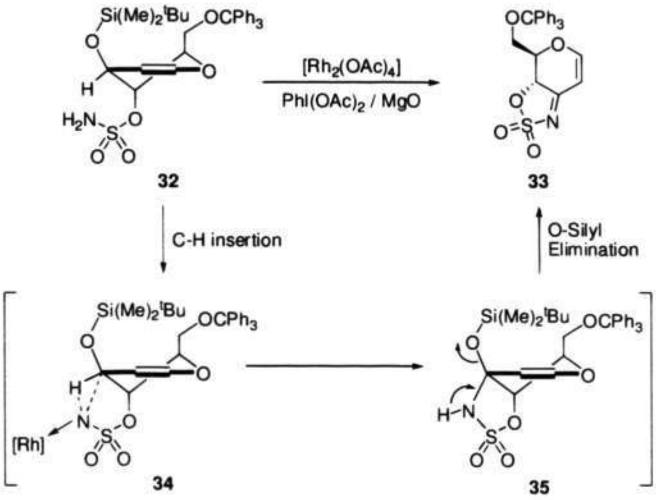


30 **31** **32**

Scheme 6 Synthesis of sulfamate-protected glycal **32**. a) TBDMSCl/TMF/RT/ overnight/90 %. b) $ClSO_2NCO/HCO_2H$/DMA/0 °C/1 h/95 %.

The initial investigation was made by subjecting sulfamate glycal **32** to the optimized catalytic conditions. Instead of a nitrogen atom insertion to the double bond, C-H insertion and the elimination of a siloxy group spontaneously took place, giving rise to compound **33** as a side product (Scheme 7). Investigation of forming unexpected product **33**, without addition of a rhodium catalyst, found that the reaction proceeded in the same manner but needed a longer reaction time and gave a lower conversion. Based on this result, the rhodium complex seems to play a crucial role in the catalytic system by increasing the rate of reaction, but it is still premature to conclude that having the *O*-silyl group adjacent to the allylic proton promotes the *N*-insertion to the C-H bond over the C=C bond.

The direct nitrogen atom insertion into the C-H bond was proposed to occur before the departure of the OTBDMS group. We therefore synthesized a scaffold similar to sulfamate ester **32** but using a galactal molecule as starting material. In this case, the sulfamate ester and the OTBDMS groups would be placed on the same face. As we expected, there was no insertion reaction observed. Only the starting material was recovered when it was introduced to the oxidative conditions with and without a rhodium catalyst.



Scheme 7 Proposed pathway for C-H insertion on sulfamate ester **32**.

The structure and absolute stereochemistry of compound **33** was confirmed by X-ray crystallography and identified as a hemi(ethanol) solvate (Figure 2). The asymmetric unit has one molecule of compound **33** in a general position and half of two molecules of ethanol [C26-C27-O6] lying about a twofold axis.

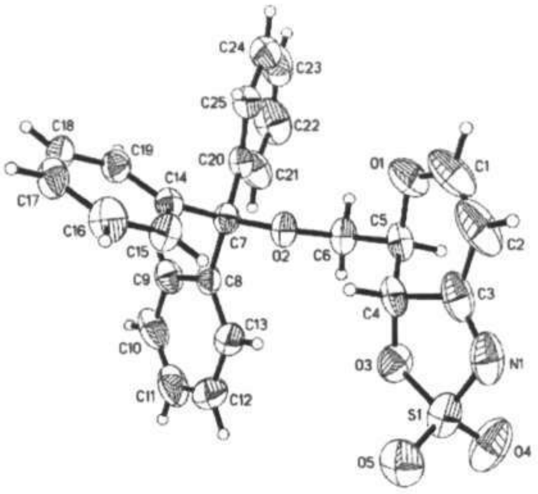
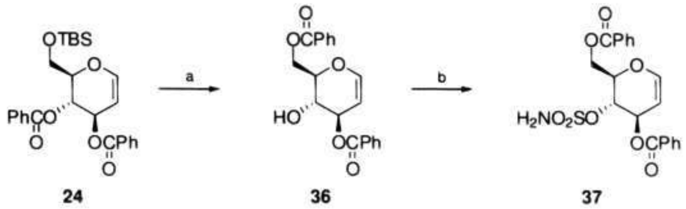


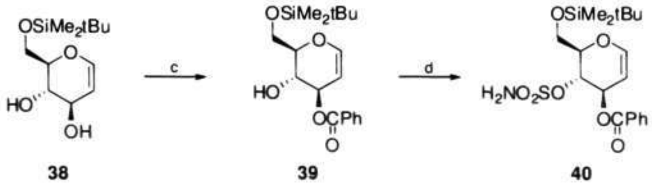
Figure 2 X-ray structure of compound **33**. The possibility chosen for the ellipsoids in the ORTEP plot is 50%.

It was realized that increasing the flexibility of sulfamte ester **26** for the formation of the aziridine intermediate could make the synthesis of 2-aminoglycosides successful. Our aim to succeed in β-aminoglycosylation was continued by removing a labile silane group from C-3 position. Replacement of a benzoyl protecting group in **37** and **40** gave stable substrates, which could be stored at -4 °C for more than a month (Scheme 8). Moreover, the nitrogen atom insertion to C=C bond could be accomplished within 1-2 hours and with virtually complete 1,2-*trans* stereochemistry. No C-H insertion products were seen for both **37** and **40**.

a) The preparation of sulfamate glycal 37

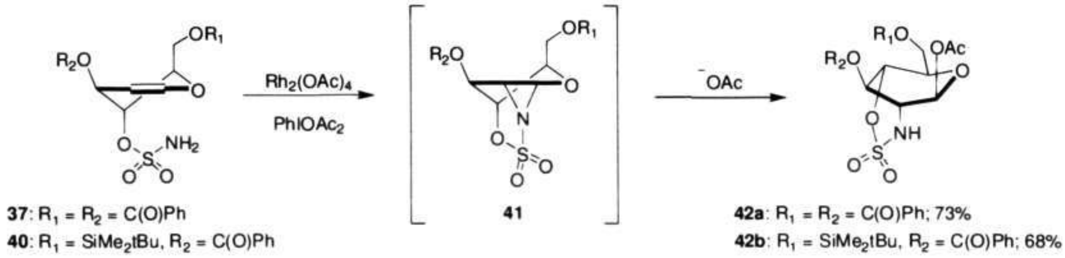


b) The preparation of sulfamate glycal 40



Scheme 8 Preparation of sulfamate-protected glycals **37** and **40**. a) TBAF/0 °C/15 h/ 91%. b) $ClSO_2NCO/HCO_2H$/DMA/0 °C/6 h/94%. c) BzCl (1.1 equiv)/DMAP/ pyridine/-40 to 0 °C/12 h/87%. d) $ClSO_2NCO/HCO_2H$/DMA/0 °C/2 h/79%.

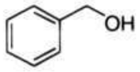
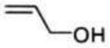
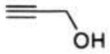
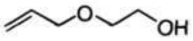
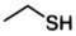
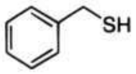
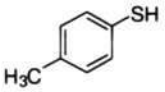
Under the standard catalytic condition, substrates **37** and **40** nicely underwent nitrogen atom delivery to the C=C bond from the bottom face, leading to β-aminoglycoside derivatives **42a** and **b** via specific ring-opening of an aziridine intermediate **41** (Scheme 9).



Scheme 9 Regio- and stereoselective aziridination and β-selective glycosylation.

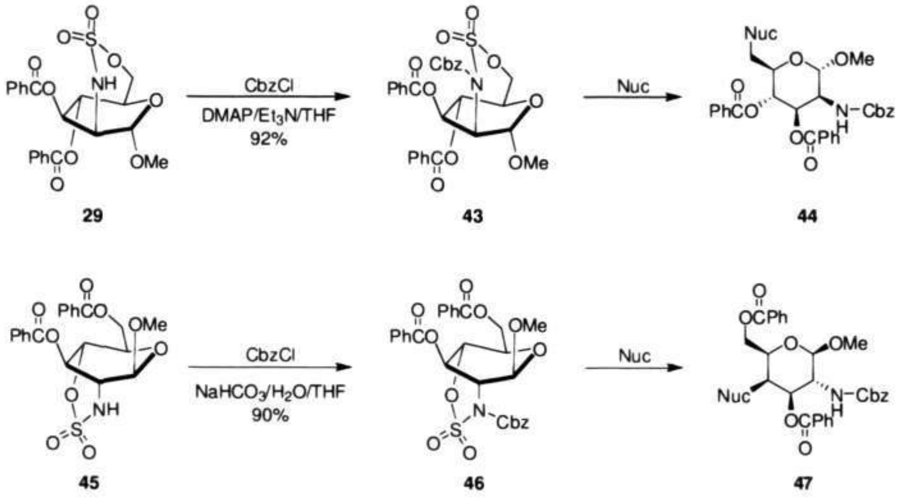
The intramolecular rhodium-catalyzed aminoglycosylation was generally accomplished in one pot because of the instability of the aziridine intermediates. Trapping such aziridine species became a challenging problem for synthesis of functionalized 1,2-aminolycosides. Though a $Rh_2(OAc)_4$ catalyst can be widely used with a variety of functionalized alcohols, none of desired products was detected for thiols, and amines. Those compounds presumably reduce the catalytic capability of $[Rh_2(OAc)_4]$. In contrast, the employment of $[Rh_2(tfacam)_4]$ and PhIO showed modest to good results in all cases. Alcohol nucleophiles could be introduced into the catalytic reactions without adding any promoters, but thiols required activation by a Lewis acid, $BF_3 \cdot OEt_2$. Another application of this methodology is to synthesize diamino sugars (entry 9, Table 4). An azide anion, N_3^-, was generated by treatment of trimethysilyl azide and TBAF at 0 °C and then slowly injected into the aziridine intermediate. The sulfamate ester-derived glycal **37** selectively furnished β- and α-aminoglycosides.

Table 4 β-Glycosylation of a sulfamate glycal **37** with various nucleophiles

entry	**nucleophile**	**product**	**% isolated yield**[a]
1 [b]	MeOH	**42c**	96 (82)
2 [b]	EtOH	**42d**	87 (84)
3 [b]	i-PrOH	**42e**	86 (70)
4 [b]		**42f**	77 (74)
5 [c]		**42g**	83 (61)
6 [c]		**42h**	80
7 [c]		**42i**	90
8 [c, d]		**42j**	79
9 [c, d]		**42k**	86
10 [c, d]		**42l**	78
11 [c]	N_3^- [from $(CH_3)_3Si\text{-}N_3$] [e]	**42m**	76

[a] Yields present in parenthesis for using sulfamate ester **40** as starting material. [b] 5 mol% of [$Rh_2(OAc)_4$], $PhI(OAc)_2$ (1.5 equiv), MgO (5 equiv), alcohol (20 equiv) in CH_2Cl_2 at room temperature. [c] 5 mol% of [$Rh_2(tfacam)_4$], PhIO (1.5 equiv), MgO (5 equiv) in CH_2Cl_2 at room temperature. Nucleophile (2 equiv) was added after 15 mins. [d] Using nucleophile (2 equiv) and $BF_3.OEt_2$ (0.1 equiv). [e] N_3^- was generated by treatment of $(CH_3)_3Si\text{-}N_3$ (2 equiv) and TBAF (2 equiv) at 0 °C for 30 mins.

Finally, we sought to access unusual amino sugars by the ring-opening reaction at the carbon atom that bears the sulfamate function.[49] The methoxy oxathiazepane **29** was selected to be a model compound for this reaction study. We had tried to introduce a second nucleophile on the sulfamate moiety without protection of the amino group of oxathiazepane. Unfortunately, none of desired products was observed when it was treated with nitrogen nucleophiles (such as NaN_3, K-phathalamide, and benzylamine) in refluxing DMF. Only starting material and trace amounts of unidentified compounds were detected. This presumably resulted from the reduced electrophilic reactivity of the eight-membered oxathiazepanes. Accordingly, the electron-withdrawing carboxybenzyloxy (Cbz) group was introduced at the nitrogen atom to give its *N*-Cbz analogue **43**. Treatment of **29** with benzyl chloroformate (CbzCl) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in Et_3N and THF afforded *N*-Cbz product **43** in excellent yield (**Scheme 10**). This preliminary result suggested that the oxathizepane **45** should be derivatized with CbzCl. Under the same conditions as **43**, the *N*-Cbz product **46** was obtained in a low yield (40%), but by changing the base from Et_3N to $NaHCO_3$, we managed to boost the yield to 90% (Scheme 10).

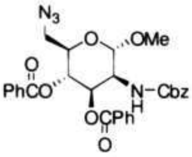
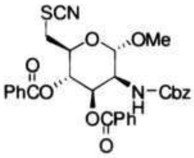
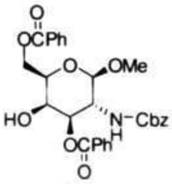
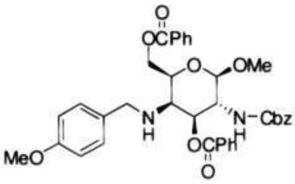


Scheme 10 Preparation of *N*-Cbz oxathiazepanes and their ring-opening

The nucleophilic displacement of a sulfamoyloxy moiety of **43** and **46** was subsequently achieved by treating with NaN_3, KSCN, *p*-methoxybenzylamine, and

H_2O to give rise to the corresponding coupled products in moderate to good yields as summarized in Table 5.

Table 5 Oxathiazepanes **43** and **46** ring-opening reaction

entry	reaction condition	product	% isolated yield
1	**43**/NaN_3/DMF/120 °C	 **48**	67
2	**43**/KSCN/DMF/150 °C	 **49**	78
3	**46**/H_2O/K_2CO_3/Acetone/RT	 **50**	80
4	**46**/*p*-$NH_2CH_2C_5H_6OMe$/DMF/70 °C	 **51**	75

The sulfamoyloxy ring-opening was proposed to proceed via S_N2-type reaction to give an inverted stereochemistry at the C-4 position. The stereochemistry of compound **50** was supported by X-ray crystallographic study as shown in Figure 3.

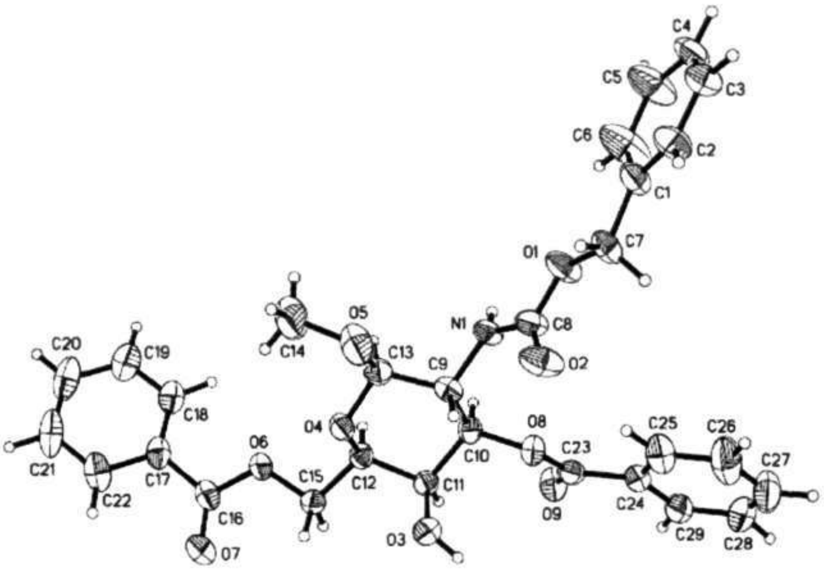


Figure 3 X-ray structure of 2-aminoglycoside **50**.

3. CONCLUSION

We have described a new route to aminoglycosides that is based on intramolecular oxidative aziridination on a glycal scaffold, followed by an efficient ring-opening of the aziridine with various nucleophiles (O, S, and N). Facial preference, which is controlled by substrate, was found to be the key factor that determines stereoselectivity. The experimental investigations show that a sulfamate ester at C-3 position did not result in stereoselective aminoglycosylation. On the contrary, installation of a sulfamate ester at the C6 position of a glycal substrate approaches α-aminoglycosides selectively. Also, introduction of the sulfamate moiety on C4 gives β-linked 2-amino sugars. This series of glycal glycosylations can be applied in the chemical synthesis of highly complex aminosaccharide conjugates.

In addition, we have performed the second nucleophilic replacement of the sulfonyloxy moieties of [1,2,3]oxathiazepane-2,2-dioxides, which allows ready access to unusual aminoglycosides with selective α- and β-linkages. With the concept described here, the intramolecular nitrogen atom transfer to a C=C bond on the glycal scaffold is highlighted as an attractive alternative to conventional methods of 2-aminoglycoside synthesis. A variety of glycal acceptors has selectively been coupled at the anomeric position, which results in high structural and functional group variability of carbohydrate substrates. This series of glycal glycosylations can be applied in the chemical synthesis of highly complex aminosaccharide conjugates.

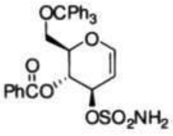
4. EXPERIMENTAL

Unless otherwise noted, all reactions were carried out in oven dried glassware under an atmosphere of nitrogen, and distilled solvents were transferred by syringe. Solvents and reagents were purified according to standard procedures prior to use. 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 nm). Technical grade solvents were used for chromatography and were distilled prior to use. NMR spectra were recorded at room temperature on a 300 MHz Bruker ACF 300, 400 MHz Bruker DPX 400, and 500 MHz Bruker AMX 500 NMR spectrometers. The residual solvent signals were taken as the reference (7.26 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra). Chemical shift (δ) is reported in ppm, coupling constants (*J*) are given in Hz. Infrared spectra were recorded on a Bio-RAD FTS 165 FTIR spectrometer and reported in cm^{-1}. Samples were prepared by using the thin film technique. HRMS (ESI) spectra were recorded on a Finnigan/MATLCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system. X-ray crystallographic data was collected by using a Bruker X8 Apex diffractometer with Mo$_{K\alpha}$ radiation (graphite monochromator).

Experimental Procedure and Spectroscopic Data

4.1 Typical Procedure for synthesis of sulfamate ester-derived glycal

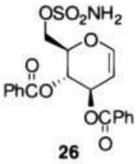
Formic acid (2 equiv) was added dropwise to chlorosulfonyl isocyanate (2 equiv) at 0 °C with rapid stirring. Vigorous gas evolution was observed during the addition process. The resulting viscous suspension was stirred for 5 mins at 0 °C, during which time the mixture solidified. Dry CH_3CN (10 equiv) was added, and the resulting clear solution was stirred for 1 h at 0 °C, then 6 h at room temperature. This solution mixture was cooled to 0 °C, and a solution of glycal (1 equiv) in *N,N*-dimethylacetamide (33 equiv) was added dropwise. The reaction was stirred at 0 °C over a 3 h period, and quenched by the addition of Et_3N. The mixture was poured into diethyl ether (20 mL) and water (10 mL), the organic phase was collected, and the aqueous layer was extracted with diethyl ether (3 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by flash chromatography (eluent: 30% ethyl acetate in hexane) afforded the desired sulfamate ester.



18

(2*R*,3*R*,4*R*)-4-(Sulfamoyloxy)-2-(trityloxymethyl)-3,4-dihydro-2H-pyran-3-yl benzoate (18)

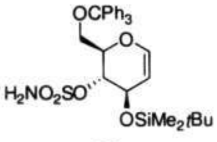
Yield: 68 %; colourless liquid. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm): 7.92 (m, 2H, Ph), 7.60 (m, 1H, Ph), 7.40 (m, 5H, Ph), 7.21 (m, 12H, Ph), 6.04 (d, J = 10.2 Hz, 1H, H1), 5.85 (d, J = 10.2 Hz, 1H, H2), 5.61 (br d, 1H, H3), 5.27 (d, J = 11.4 Hz, 1H, H4), 4.75 (br s, 2H, NH_2), 4.03 (m, 1H, H5), 3.50 (d, *J* = 9.2 Hz, 1H, CH_2), 3.44 (d, *J* = 9.2 Hz, 1H, CH_2); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 165.7 (CO), 143.3 (C1), 143.0 (Ph), 133.5 (Ph), 130.7 (Ph), 129.7 (Ph), 128.6 (Ph), 128.4 (Ph), 128.0 (Ph), 127.3 (Ph), 127.2 (Ph), 104.6 (C2), 77.5 (Cq), 69.2 (C5), 68.2 (C3), 65.6 (C4), 64.9 (CH_2); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3381, 3288, 3018, 1718, 1448 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{32}H_{29}NO_7SNa$: 594.1562 $[M+Na]^+$; found: 594.1574.



26

(2*R*,3*S*,4*R*)-2-(Sulfamoyloxymethyl)-3,4-dihydro-2H-pyran-3,4-diyl dibenzoate (26)

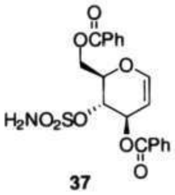
Yield: 83 %; colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 7.99 (m, 4H, Ph), 7.56 (m, 2H, Ph), 7.42 (m, 4H, Ph), 6.57 (d, *J* = 6.1 Hz, 1H, H1), 5.71 (br s, 2H, H3 and H4), 5.14 (br s, 2H, NH_2), 5.10 (d, *J* = 6.1 Hz, 1H, H2), 4.56 (m, 2H, H5 and CH_2), 4.46 (d, *J* = 8.2 Hz, 1H, CH_2); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 165.8 (CO), 165.5 (CO), 145.5 (C1), 133.8 (Ph), 133.4 (Ph), 129.9 (Ph), 129.7 (Ph), 129.3 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 99.2 (C2), 73.6 (C5), 67.6 (C4), 67.5 (CH_2), 67.3 (C3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3421, 3288, 3018, 1718, 1649, 1377 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{18}NO_8S$: 432.0748 $[M-H]^+$; found: 432.0733.



32

(2*R*,3*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-(trityloxymethyl)-3,4-dihydro-2H-pyran-3-yl sulfamate (32)

Yield: 77 %; colourless liquid. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 7.44 (m, 6H, Ph), 7.32-7.20 (m, 9H, Ph), 6.41 (d, J = 6.2 Hz, 1H, H1), 4.74 (dd, J = 5.7, 3.9 Hz, 1H, H2), 4.65 (t, J = 4.59 Hz, 1H, H3), 4.61 (br s, 2H, NH$_2$), 4.32 (br t, 1H, H5), 4.23 (t, J = 3.9 Hz, 1H, H4), 3.62 (dd, J = 11.0, 6.8 Hz, 1H, CH$_2$), 3.34 (dd, J = 11.0, 2.6 Hz, 1H, CH$_2$), 0.80 (s, 9H, CH$_3$), 0.04 (s, 3H, CH$_3$), 0.02 (s, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 143.4 (C1), 128.7 (Ph), 127.8 (Ph), 127.1 (Ph), 101.5 (C2), 86.9 (Cq), 78.6 (C3), 75.3 (C5), 64.6 (C4), 61.8 (CH$_2$), 25.7 (CH$_3$), 17.9 (CH$_3$), -4.7 (CH$_3$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3429, 3018, 1651, 1450 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{31}H_{39}NO_6SSiNa$: 604.2165 [M+Na]$^+$; found: 604.2154.

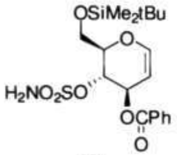


37

((2*R*,3*S*,4*R*)-4-(Benzoyloxy)-3-(sulfamoyloxy)-3,4-dihydro-2H-pyran-2-yl)methyl benzoate (37)

Yield: 94 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 7.99 (m, 4H, Ph), 7.57 (m, 2H, Ph), 7.40 (m, 4H, Ph), 6.56 (d, J = 6.1 Hz, 1H, H1), 5.70 (dd, J = 4.1, 3.6 Hz, 1H, H3), 5.49 (br s, 2H, NH$_2$), 5.16 (t, J = 5.5 Hz, 1H, H4), 4.98 (dd, J = 6.1, 3.6 Hz, 1H, H2), 4.77 (dd, J = 13.0, 6.9 Hz, 1H, CH$_2$), 4.59 (m, 2H, H5 and CH$_2$); **^{13}C**

NMR (100 MHz, $CDCl_3$): δ (ppm): 166.4 (CO), 166.3 (CO), 146.2 (C1), 133.6 (Ph), 133.4 (Ph), 129.8 (Ph), 129.7 (Ph), 129.2 (Ph), 129.1 (Ph), 128.5 (Ph), 128.4 (Ph), 98.0 (C2), 74.3 (C4), 73.7 (C5), 67.4 (C3), 61.5 (CH_2); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3385, 3275, 3020, 1718, 1647, 1382 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{18}NO_8S$: 432.0748 $[M-H]^+$; found: 432.0729.



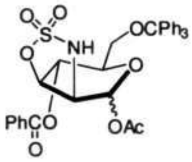
40

(2*R*,3*S*,4*R*)-2-((tert-Butyldimethylsilyloxy)methyl)-3-(sulfamoyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (40)

Yield: 79 %; white solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.06 (d, *J* = 8.1 Hz, 2H, Ph), 7.57 (t, *J* = 7.4 Hz, 1H, Ph), 7.44 (t, *J* = 7.7 Hz, 2H, Ph), 6.53 (d, *J* = 6.0 Hz, 1H, H1), 5.62 (t, *J* = 3.7 Hz, 1H, H3), 5.32 (br s, 2H, NH_2), 5.19 (t, *J* = 6.0 Hz, 1H, H4), 4.95 (dd, *J* = 6.0, 3.7 Hz, 1H, H2), 4.25 (dd, *J* = 11.0, 5.0 Hz, 1H, H5), 3.98 (dd, *J* = 11.0, 4.7 Hz, 2H, CH_2), 0.84 (s, 9H, CH_3), 0.08 (s, 3H, CH_3), 0.03 (s, 3H, CH_3); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm): 166.5 (CO), 146.3 (C1), 133.5 (Ph), 129.9 (Ph), 129.4 (Ph), 128.5 (Ph), 97.6 (C2), 76.1 (C5), 74.6 (C4), 67.9 (C3), 60.6 (CH_2), 25.7 (CH_3), 18.1 (Cq), -5.2 (CH_3), -5.4 (CH_3); **IR (nujol):** $\tilde{\nu}$ = 3373, 1699, 1647, 1463, 1456 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{19}H_{28}NO_7S$: 442.1350 $[M-H]^+$; found: 442.1340.

4.2 General procedure for rhodium-catalyzed aziridination with acetoxy anion as a nucleophile

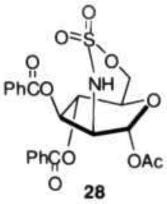
A mixture of sulfamate ester (1 equiv), [$Rh_2(OAc)_4$] (10 mol%), $PhI(OAc)_2$ (1.5 equiv), MgO (5 equiv), and 4 Å molecular sieves in dry CH_2Cl_2 (2 mL) was stirred at room temperature. The reaction was monitored by TLC. The suspension was filtered through a pad of Celite. The filter cake was rinsed with CH_2Cl_2 and the combined filtrates were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 30% ethyl acetate in hexane) as eluent to afford the desired oxathiazepane.



21

4-*O*-Acetyl 2-amino-2-*N*,3-*O*-sulfamoyl-2-deoxy-4-benzoyloxy-10-(trityloxy-methyl)-D-glucopyranoside (21)

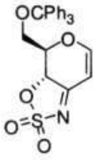
Yield: 62 %; white solid; an anomeric mixture (2:1) of acetate product. **^{1}H NMR (300 MHz, $CDCl_3$):** δ (ppm): 7.85 (m, 2H, Ph), 7.58 (m, 1H, Ph), 7.41 (m, 5H, Ph), 7.17 (m, 12H, Ph), 6.16 (s, 1H, H1), 5.89 (m, 1H, H4), 5.70 (m, 1H, H3), 4.23 (m, 1H, H5), 3.31 (m, 3H, H2 and CH_2), 2.13 (s, 3H, CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 2926, 1722, 1448 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{34}H_{30}NO_9S$: 628.1641 $[M-H]^+$; found: 628.1520.



28

9-*O*-Acetyl-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (28)

Yield: 82 %; white solid. **^{1}H NMR (500 MHz, d_6-acetone):** δ (ppm): 8.10 (m, 4H, Ph), 7.65 (m, 2H, Ph), 7.53 (m, 4H; Ph), 6.85 (d, J = 1.3 Hz, 1H, H1), 5.87 (dd, J = 5.7, 4.5 Hz, 1H, H3), 5.76 (d, J = 4.5 Hz, 1H, H4), 4.75 (m, 1H, H5), 4.72 (m, 2H, CH_2), 4.23 (dd, J = 5.7, 1.3 Hz, 1H, H2), 2.17 (s, 3H, CH_3); **^{13}C NMR (125 MHz, d_6-acetone):** δ (ppm): 168.4 (CO), 165.4 (CO), 164.8 (CO), 133.6 (Ph), 133.5 (Ph), 129.8 (Ph), 129.6 (Ph), 129.4 (Ph), 128.6 (Ph), 128.5 (Ph), 90.9 (C1), 77.6 (C5), 75.1 (CH_2), 71.9 (C4), 69.3 (C3), 51.8 (C2), 20.2 (CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3018, 1755, 1697 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{22}H_{21}NO_{10}SNa$: 514.0778 [M+Na]$^+$; found: 514.0759.

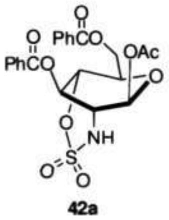


33

1,2-Dideoxy-6-trityloxymethyl-2-imino-2-*N*,4-*O*-sulfamoyl-D-erythro-hex-1-enopyran-3-glulose (33)

Yield: 84 %; white solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 7.47 (d, J = 5.5 Hz, 1H, H1), 7.43 (m, 6H, Ph), 7.35-7.27 (m, 9H, Ph), 5.93 (d, J = 5.5 Hz, 1H, H2), 5.53 (d, J = 12.6 Hz, 1H, H4), 4.32 (br dt, J = 12.6 Hz, 1H, H5), 3.70 (d, J = 11.5 Hz, 1H, CH_2), 3.41 (dd, J = 11.5, 3.4 Hz, 1H, CH_2); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 142.9 (C1), 128.5 (Ph), 128.1 (Ph), 127.4 (Ph), 95.7 (C2), 87.3 (Cq), 80.0 (C3), 77.0

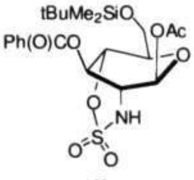
(C4), 75.9 (C5), 61.2 (CH_2); **IR ($CHCl_3$):** $\tilde{\nu}$ = 2926, 1707, 1653 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{25}H_{22}NO_5S$: 448.1219 $[M+H]^+$; found: 448.1261.



42a

8-*O*-Acetyl-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42a)

Yield: 73 %; colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 8.08 (d, J = 7.9 Hz, 2H, Ph), 8.01 (d, J = 7.9 Hz, 2H, Ph), 7.65 (t, J = 7.4 Hz, 1H, Ph), 7.58 (t, J = 7.4 Hz, 1H, Ph), 7.51 (t, J = 7.6 Hz, 2H, Ph), 7.44 (t, J = 7.6 Hz, 2H, Ph), 6.50 (s, 1H, H1), 6.09 (br s, 1H, NH), 5.94 (br t, 1H, H3), 5.06 (m, 1H, H4), 5.04 (t, J = 7.3 Hz , 1H, H5), 4.97 (dd, J = 11.0, 7.3 Hz, 1H, CH_2), 4.67 (dd, J = 11.0, 7.3 Hz, 1H, CH_2), 4.07 (m, 1H, H2), 1.81 (s, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 168.7 (CO), 165.9 (CO), 165.3 (CO), 134.4 (Ph), 133.5 (Ph), 129.9 (Ph), 129.7 (Ph), 129.0 (Ph), 128.9 (Ph), 128.5 (Ph), 127.9 (Ph), 91.1 (C1), 75.7 (C4), 72.7 (C5), 63.7 (CH_2), 62.2 (C3), 49.8 (C2), 20.8 (CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 1710, 1635, 1273 cm^{-1}; **HRMS (ESI)**: *m/z*: calcd for $C_{22}H_{20}NO_{10}S$: 490.0802 $[M-H]^+$; found: 490.0825.



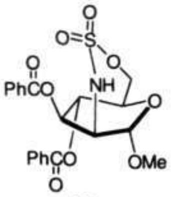
42b

8-*O*-Acetyl-9-benzoyloxy-10-((tert-Butyldimethylsilyloxy)methyl)-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42b)

Yield: 73 %; colourless oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.04 (d, J = 7.2 Hz, 2H, Ph), 7.65 (t, J = 7.5 Hz, 1H, Ph), 7.49 (t, J = 7.5 Hz, 2H, Ph), 6.48 (s, 1H, C1), 5.81 (m, 2H, H3 and NH), 5.21 (m, 1H, H4), 4.71 (dd, J = 10.2, 6.5 Hz, 1H, H5), 4.08 (t, J = 10.3 Hz, 1H, CH$_2$), 4.03 (m, 1H, H2), 3.94 (dd, J = 10.2, 6.5 Hz, 1H, CH$_2$), 1.82 (s, 3H, CH$_3$), 0.84 (s, 9H, CH$_3$), 0.04 (s, 3H, CH$_3$), -0.02 (s, 3H, CH$_3$); **^{13}C NMR (125 MHz, CDCl$_3$)**: δ (ppm): 168.7 (CO), 165.2 (CO), 134.3 (Ph), 129.8 (Ph), 128.7 (Ph), 128.3 (Ph), 91.4 (C1), 75.5 (C4), 74.5 (C5), 62.9 (C3), 62.2 (CH$_2$), 50.3 (C2), 25.6 (CH$_3$), 20.9 (CH$_3$), 18.0 (cq), -5.3 (CH$_3$), -5.6 (CH$_3$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3018, 2954, 2929, 1732, 1388 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{31}NO_9SSiNa$: 524.1381 [M+Na]$^+$; found: 524.1401.

4.3 General procedure for rhodium-catalyzed aziridination with alcohols as nucleophiles

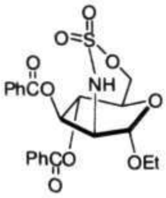
The nucleophile (20 equiv) was added dropwise to a mixture of sulfamate ester (1 equiv), [Rh$_2$(OAc)$_4$] (10 mol%), PhI(OAc)$_2$ (1.5 equiv), MgO (5 equiv), and 4 Å molecular sieves in dry CH$_2$Cl$_2$ (2 mL). The suspension was stirred vigorously at room temperature and monitored by TLC. The reaction mixture was filtered through a pad of Celite. The filter cake was rinsed with CH$_2$Cl$_2$ and the combined filtrates were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: 30% ethyl acetate in hexane) to afford the desired oxathiazepane.



29a

9-*O*-Methyl-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2azabicyclo[4.2.2]decane-3,3-dioxide (29a)

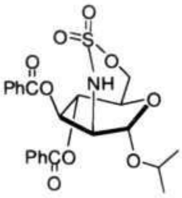
Yield: 81 %; white solid. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.06 (m, 4H, Ph), 7.60 (m, 2H, Ph), 7.44 (m, 4H, Ph), 5.84 (dd, J = 5.8, 4.0 Hz, 1H, H3), 5.53 (d, J = 4.0 Hz, 1H, H4), 5.51 (d, J = 1.1 Hz, 1H, H1), 5.18 (br d, J = 3.1 Hz, 1H, NH), 4.72 (dd, J = 12.4, 2.5 Hz, 1H, CH$_2$), 4.63 (dd, J = 12.4, 2.5 Hz, 1H, CH$_2$), 4.44 (m, 1H, H5), 4.03 (m, 1H, H2), 3.51 (s, 3H, OCH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.1 (CO), 165.1 (CO), 133.9 (Ph), 133.7 (Ph), 129.98 (Ph), 129.90 (Ph), 128.9 (Ph), 128.7 (Ph), 128.6 (Ph), 96.9 (C1), 76.6 (C5), 75.6 (CH$_2$), 72.1 (C4), 69.5 (C3), 55.4 (OCH$_3$), 53.3 (C2); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3018, 1714, 1697, 1269 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{20}NO_9S$: 462.0853 [M–H]$^+$; found: 462.0838.



29b

9-*O*-Ethyl-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29b)

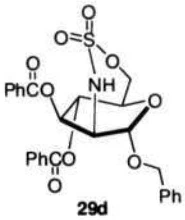
Yield: 90 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.07 (m, 4H, Ph), 7.61 (m, 2H, Ph), 7.47 (m, 4H, Ph), 5.88 (dd, J = 6.0, 3.6 Hz, 1H, H3), 5.60 (s, 1H, H1), 5.51 (d, J = 3.6 Hz, 1H, H4), 5.09 (br d, J = 2.9 Hz, 1H, NH), 4.72 (dd, J = 12.4, 2.3 Hz, 1H, CH$_2$), 4.62 (dd, J = 12.4, 2.3 Hz, 1H, CH$_2$), 4.43 (m, 1H, H5), 4.03 (m, 1H, H2), 3.91 (q, J = 7.2 Hz, 1H, CH_2CH$_3$), 3.63 (q, J = 7.2 Hz, 1H, CH_2CH$_3$), 1.27 (t, J = 7.2 Hz, 3H, CH$_2$CH_3); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.1 (CO), 165.1 (CO), 133.9 (Ph), 133.7 (Ph), 129.96 (Ph), 129.91 (Ph), 128.9 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 95.5 (C1), 76.5 (C5), 75.7 (CH$_2$), 72.2 (C4), 69.5 (C3), 63.8 (CH$_2$), 53.5 (C2), 15.1 (CH$_3$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3020, 1714, 1452, 1274 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{22}H_{23}NO_9SNa$: 500.0986 [M+Na]$^+$; found: 500.0967.



29c

9-*O*-Isopropyl-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29c)

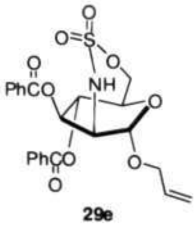
Yield: 70 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.08 (d, J = 7.6 Hz, 4H, Ph), 7.60 (m, 2H, Ph), 7.46 (m, 4H, Ph), 5.91 (dd, J = 5.8, 3.6 Hz, 1H, H3), 5.67 (s, 1H, H1), 5.50 (d, J = 3.6 Hz, 1H, H4), 5.11(br d, J = 3.2 Hz, 1H, NH), 4.71 (dd, J = 12.3, 2.0 Hz, 1H, CH$_2$), 4.62 (dd, J = 12.3, 2.0 Hz, 1H, CH$_2$), 4.43 (m, 1H, H5), 4.09 (quint, J = 6.1 Hz, 1H, CH(CH$_3$)$_2$), 3.98 (m, 1H, H2), 1.25 (d, J = 6.1 Hz, 3H, CH$_3$), 1.22 (d, J = 6.1 Hz, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.2 (CO), 165.1 (CO), 133.9 (Ph), 133.7 (Ph), 129.9 (Ph), 128.9 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 93.7 (C1), 76.4 (C5), 75.9 (CH$_2$), 72.3 (C4), 70.0 (CH(CH$_3$)$_2$), 69.6 (C3), 53.8 (C2), 23.5 (CH_3), 21.5 (CH_3); **IR ($CHCl_3$):** ṽ = 3018, 1718, 1452, 1377, 1276 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{25}NO_9SNa$: 514.1142 $[M+Na]^+$; found: 514.1118.



29d

9-*O*-Benzyl-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29d)

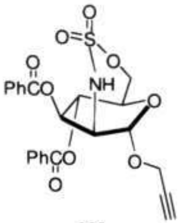
Yield: 71 %; colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.08 (d, J = 8.0 Hz, 2H, Ph), 7.96 (d, J = 8.0 Hz, 2H, Ph), 7.61 (t, J = 7.5 Hz, 1H, Ph), 7.56 (t, J = 7.5 Hz, 1H, Ph), 7.48 (t, J = 7.8 Hz, 2H, Ph), 7.34 (m, 7H, Ph), 5.90 (dd, J = 6.3, 3.2 Hz, 1H, H3), 5.67 (d, J = 1.6 Hz, 1H, H1), 5.53 (d, J = 3.2 Hz, 1H, H4), 5.09 (br d, J = 3.8 Hz, 1H, NH), 4.91 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.76 (dd, J = 12.6, 2.4 Hz, 1H, CH_2), 4.67 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.62 (dd, J = 12.6, 2.4 Hz, 1H, CH_2), 4.45 (m, 1H, H5), 4.12 (ddd, J = 6.3, 3.8, 1.6 Hz, 1H, H2); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 166.1 (CO), 165.0 (CO), 136.9 (Ph), 133.9 (Ph), 133.6 (Ph), 129.97 (Ph), 129.95 (Ph), 128.8 (Ph), 128.7 (Ph), 128.6 (Ph), 128.55 (Ph), 128.52 (Ph), 127.9 (Ph), 127.8 (Ph), 95.1 (C1), 76.5 (C5), 75.7 (CH_2), 72.1 (C4), 69.6 (CH_2Ph), 69.4 (C3), 53.2 (C2); **IR ($CHCl_3$):** ṽ = 3018, 1720, 1452 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{25}NO_9SNa$: 562.1142 $[M+Na]^+$; found: 562.1174.



29e

9-*O*-Allyl-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29e)

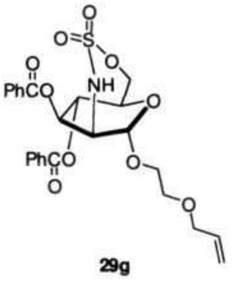
Yield: 94 %; white solid. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.07 (m, 4H, Ph), 7.60 (m, 2H, Ph), 7.46 (m, 4H, Ph), 5.95 (ABX system, J_{AX} = 16.1, J_{BX} = 10.6, J_{AB} = 5.5 Hz, 1H, C*H*=CH$_2$), 5.87 (dd, J = 6.1, 3.6 Hz, 1H, H3), 5.63 (br s, 1H, H1), 5.53 (d, J = 3.6 Hz, 1H, H4), 5.35 (d, J = 16.1 Hz, 1H, CH=C*H*$_2$), 5.24 (d, J = 10.6 Hz, 1H, CH=C*H*$_2$), 5.12 (br d, J = 2.1 Hz, 1H, NH), 4.73 (d, J = 12.5 Hz, 1H, CH$_2$), 4.61 (dd, J = 12.5, 2.3 Hz, 1H, CH$_2$), 4.43 (m, 1H, H5), 4.36 (dd, J = 12.8, 5.1 Hz, 1H, CH$_2$(allyl)), 4.14 (dd, J = 12.8, 5.1 Hz, 1H, CH$_2$(allyl)), 4.07 (m, 1H, H2); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.0 (CO), 165.0 (CO), 133.9 (Ph), 133.7 (=CH), 133.5 (Ph), 129.9 (Ph), 128.9 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 117.7 (=CH$_2$), 95.1 (C1), 76.5 (C5), 75.6 (CH$_2$), 72.0 (C4), 69.4 (C3), 68.6 (CH$_2$), 53.3 (CH$_3$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3053, 1720, 1602, 1452 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{23}NO_9SNa$: 512.0963 [M+Na]$^+$; found: 512.0978.



29f

9-*O*-Propargyl-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29f)

Yield: 89 %; white solid. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.08 (m, 4H, Ph), 7.61 (m, 2H, Ph), 7.47 (m, 4H, Ph), 5.84 (dd, J = 6.3, 3.2 Hz, 1H, H3), 5.78 (br s, 1H, H1), 5.53 (d, J = 3.2 Hz, 1H, H4), 5.08 (br d, J = 3.6 Hz, 1H, NH), 4.76 (d, J = 12.6 Hz, 1H, CH$_2$), 4.63 (dd, J = 12.6, 2.4 Hz, 1H, CH$_2$), 4.44 (m, 2H, CH$_2$), 4.40 (m, 1H, H5), 4.09 (m, 1H, H2), 2.46 (s, 1H, C≡CH); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.0 (CO), 165.0 (CO), 133.9 (Ph), 133.7 (Ph), 129.9, 128.8, 128.7, 128.5, 94.3 (C1), 78.4 (CH), 76.6 (CH$_2$), 75.5 (C5), 75.2 (CH$_2$), 72.0 (C4), 69.1 (C3), 54.6 (CH$_2$), 52.9 (C2); **IR (CHCl$_3$):** $\tilde{\nu}$ = 2304, 2150, 1637 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{21}NO_9SNa$: 510.0835 [M+Na]$^+$; found: 510.0844.

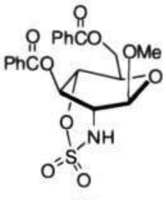


29g

9-*O*-Ethyloxyallyloxy-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2] decane-3,3-dioxide (29g)

Yield: 95 %; white solid. **^{1}H NMR (300 MHz, CDCl$_3$):** δ (ppm): 8.07 (m, 4H, Ph), 7.60 (m, 2H, Ph), 7.46 (m, 4H, Ph), 5.89 (m, 2H, H3 and C*H*=CH$_2$), 5.67 (br s, 1H, H1), 5.52 (d, J = 3.8 Hz, 1H, H4), 5.29 (d, J = 17.2 Hz, 1H, CH=C*H*$_2$), 5.19 (d, J = 10.4 Hz, 1H, CH=C*H*$_2$), 5.13 (br d, J = 3.6 Hz, 1H, NH), 4.72 (d, J = 12.5 Hz, 1H, CH$_2$), 4.63 (dd, J = 12.5, 2.5 Hz, 1H, CH$_2$), 4.44 (m, 1H, H5), 4.10 (m, 1H, H2), 4.02 (m, 2H, CH$_2$), 3.97 (m, 1H, CH$_2$), 3.79 (m, 1H, CH$_2$), 3.65 (m, 2H, CH$_2$); **^{13}C NMR (75 MHz, CDCl$_3$):** δ (ppm): 166.1 (CO), 165.0 (CO), 134.5 (Ph), 133.9 (=CH), 133.7 (Ph), 129.9 (Ph), 128.9 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 117.2 (=CH$_2$), 96.1

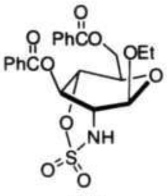
(C1), 76.7 (H5), 75.6 (CH_2), 72.2 (C4 and CH_2), 69.3 (C3), 68.9 (CH_2), 67.4 (CH_2), 53.3 (C2); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3055, 1718, 1653 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{25}H_{27}NO_{10}SNa$: 556.1253 $[M+Na]^+$; found: 556.1262.



42c

8-*O*-Methyl-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42c)

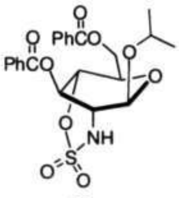
Yield: 96 %; colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ(ppm): 8.00 (m, 4H, Ph), 7.58 (m, 2H, Ph), 7.45 (m, 4H, Ph), 5.86 (m, 2H, H3 and NH), 5.20 (s, 1H, H1), 5.03 (m, 1H, H4), 4.98 (t, *J* = 7.4 Hz, 1H, H5), 4.88 (dd, *J* = 11.1, 7.4 Hz, 1H, CH_2), 4.73 (dd, *J* = 11.1, 7.4 Hz, 1H, CH_2), 3.99 (m, 1H, H2), 3.48 (s, 3H, OCH_3); **^{13}C NMR (125 MHz, $CDCl_3$):** δ(ppm): 165.9 (CO), 165.6 (CO), 134.0 (Ph), 133.4 (Ph), 129.9 (Ph), 129.7 (Ph), 129.2 (Ph), 128.8 (Ph), 128.5 (Ph), 128.3 (Ph), 99.5 (C1), 76.6 (C4), 71.8 (C5), 64.1 (CH_2), 63.0 (C3), 56.6 (OCH_3), 51.3 (C2); **IR ($CHCl_3$):** $\tilde{\nu}$ =1718, 1635, 1274 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{20}NO_9S$: 462.0853 $[M-H]^+$; found: 462.0869.



42d

8-*O*-Ethyl-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42d)

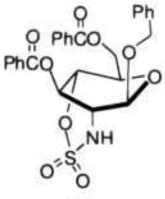
Yield: 87 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 7.99 (m, 4H, Ph), 7.59 (m, 2H, Ph), 7.45 (m, 4H, Ph), 5.87 (m, 1H, H3), 5.62 (br d, J = 4.2 Hz, 1H, NH), 5.26 (s, 1H, H1), 5.04 (m, 1H, H4), 4.96 (t, J = 7.4 Hz, 1H, H5), 4.88 (dd, J = 11.0, 7.4 Hz, 1H, CH$_2$), 4.77 (dd, J = 11.0, 7.4 Hz, 1H, CH$_2$), 4.01 (m, 1H, H2), 3.96 (q, J = 7.2 Hz, 1H, CH_2CH$_3$), 3.51 (q, J = 7.0 Hz, 1H, CH_2CH$_3$), 1.06 (t, J = 7.0 Hz, 3H, CH$_2$CH_3); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm) 165.9 (CO), 165.4 (CO), 134.0 (Ph), 133.4 (Ph), 129.9 (Ph), 129.6 (Ph), 129.2 (Ph), 128.7 (Ph), 128.5 (Ph), 128.3 (Ph), 98.1 (C1), 76.7 (C4), 71.8 (C5), 64.7 (CH$_2$), 64.1 (CH$_2$), 62.8 (C3), 51.3 (C2), 14.7 (CH$_3$); **IR (CHCl$_3$)**: $\tilde{\nu}$ = 3018, 1718, 1273, 1217 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{22}H_{22}NO_9S$: 476.1010 [M–H]$^+$; found: 476.0987.



42e

8-*O*-Isopropyl-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo-[3.3.1]decane-3,3-dioxide (42e)

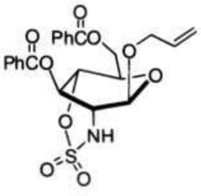
Yield: 86 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.02 (m, 4H, Ph), 7.59 (m, 2H, Ph), 7.45 (m, 4H, Ph), 5.84 (m, 1H, H3), 5.53 (br s, 1H, NH), 5.36 (s, 1H, H1), 5.05 (m, 1H, H4), 4.95 (t, *J* = 7.5 Hz, 1H, H5), 4.84 (m, 2H, CH_2), 4.09 (quint, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 3.97 (m, 1H, H2), 1.09 (d, *J* = 6.1 Hz, 3H, CH_3), 1.06 (d, *J* = 6.1 Hz, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 165.9 (CO), 165.4 (CO), 134.0 (Ph), 133.4 (Ph), 129.9 (Ph), 129.6 (Ph), 129.2 (Ph), 128.6 (Ph), 128.5 (Ph), 128.3 (Ph), 95.8 (C1), 76.7 (C4), 71.7 (C5), 70.4 ($CH(CH_3)_2$), 64.2 (CH_2), 62.9 (C3), 51.7 (C2), 22.9 (CH_3), 20.9 (CH_3); **IR ($CHCl_3$):** ṽ = 2926, 1722, 1645, 1273 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{24}NO_9S$: 490.1166 $[M-H]^+$; found: 490.1149.



42f

8-*O*-Benzyl-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42f)

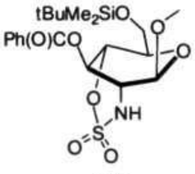
Yield: 77 %; colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 8.00 (d, *J* = 8.0 Hz, 2H, Ph), 7.84 (d, *J* = 8.0 Hz, 2H, Ph), 7.55 (m, 2H, Ph), 7.44 (m, 2H, Ph), 7.26 (m, 7H, Ph), 5.89 (m, 1H, H3), 5.45 (br d, *J* = 4.0 Hz, 1H, NH), 5.39 (s, 1H, H1), 5.05 (m, 1H, H4), 4.97 (m, 2H, H5 and CH_2Ph), 4.89 (dd, *J* = 11.1, 7.4 Hz, 1H, CH_2), 4.77 (dd, *J* = 11.1, 7.4 Hz, 1H, CH_2), 4.57 (d, *J* = 11.3 Hz, 1H, CH_2Ph), 4.03 (m, 1H, C2); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 166.1 (CO), 166.0 (CO), 136.2 (Ph), 133.8 (Ph), 133.4 (Ph), 130.0 (Ph), 129.9 (Ph), 129.7 (Ph), 129.6 (Ph), 129.5 (Ph), 129.2 (Ph), 128.8 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.1 (Ph), 128.0 (Ph), 97.7 (C1), 76.4 (C4), 72.1 (C5), 71.1 (CH_2Ph), 64.0 (CH_2), 62.5 (C3), 51.4 (C2); **IR ($CHCl_3$):** ṽ = 2954, 1708, 1635, 1269 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{24}NO_9S$: 538.1166 $[M-H]^+$; found: 538.1189.



42g

8-*O*-Allyl-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42g)

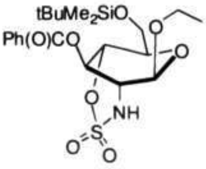
Yield: 81 %; colourless oil. **^{1}H NMR (300 MHz, CDCl$_3$):** δ (ppm): 8.01 (m, 4H, Ph), 7.58 (m, 2H, Ph), 7.36 (m, 4H, Ph), 5.88 (m, 1H, H3), 5.75 (ABX system, J_{AX} = 17.0, J_{BX} = 10.5, J_{AB} = 5.4 Hz, 1H, C*H*=CH$_2$), 5.55 (br d, J = 4.6 Hz, 1H, NH), 5.32 (s, 1H, H1), 5.05-5.17 (m, 3H; CH=CH_2 and H4), 4.97 (t, J = 7.4 Hz, 1H, H5), 4.88 (dd, J = 11.5, 7.4 Hz, 1H, CH$_2$), 4.80 (dd, J = 12.4, 5.4 Hz, 1H, CH$_2$(allyl)), 4.75 (dd, J = 11.5, 7.4 Hz, 1H, CH$_2$), 4.38 (dd, J = 12.4, 5.4 Hz, 1H, CH$_2$(allyl)), 4.03 (m, 1H, H2); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 165.8 (CO), 165.4 (CO), 134.0 (Ph), 133.5 (Ph), 132.8 (*C*H=CH$_2$), 130.0 (Ph), 129.6 (Ph), 129.2 (Ph), 128.7 (Ph), 128.5 (Ph), 128.2 (Ph), 118.2 (CH=*C*H$_2$), 97.5 (C1), 76.5 (C4), 71.9 (C5), 69.6 (CH$_2$(allyl)), 64.0 (CH$_2$), 62.7 (C3), 51.3 (C2); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3018, 1722, 1627, 1274 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{22}NO_9S$: 488.1010 [M–H]$^+$; found: 488.1003.



42c'

8-*O*-Methyl-9-benzoyloxy-10-((tert-Butyldimethylsilyloxy)methyl)-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42c')

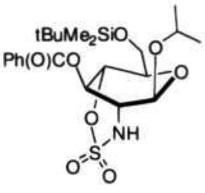
Yield: 82 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 7.99 (d, J = 8.4 Hz, 2H, Ph), 7.61 (t, J = 7.5 Hz, 1H, Ph), 7.46 (t, J = 7.5 Hz, 2H, Ph), 5.75 (t, J = 3.4 Hz, 1H, H3), 5.59 (br s, 1H, NH), 5.16 (s, 1H, H1), 5.12 (m, 1H, H4), 4.64 (dd, J = 10.1, 6.5 Hz, 1H, H5), 4.11 (t, J = 10.1 Hz, 1H, CH$_2$), 3.93 (dd, J = 10.1, 6.5 Hz, 1H, CH$_2$), 3.91 (m, 1H, H2), 3.42 (s, 3H, OCH$_3$), 0.89 (s, 9H, CH$_3$), -0.01 (s, 3H, CH$_3$), -0.06 (s, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 165.6 (CO), 133.9 (Ph), 129.9 (Ph), 128.7 (Ph), 128.6 (Ph), 99.1 (C1), 76.7 (C4), 73.9 (C5), 63.5 (C5), 62.2 (CH$_2$), 56.3 (OCH$_3$), 51.6 (C2), 25.6 (CH$_3$), 18.0 (Cq), -5.4 (CH$_3$), -5.6 (CH$_3$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3018, 2954, 2929, 1726, 1215 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{31}NO_8SSiNa$: 496.1432 [M+Na]$^+$; found: 496.1412.



42d'

8-*O*-Ethyl-9-benzoyloxy-10-((tert-Butyldimethylsilyloxy)methyl)-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42d')

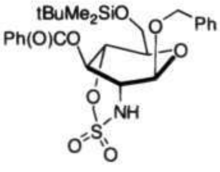
Yield: 84 %; colourless oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.02 (d, J = 8.3 Hz, 2H, Ph), 7.61 (t, J = 7.6 Hz, 1H, Ph), 7.45 (t, J = 7.6 Hz, 2H, Ph), 5.78 (t, J = 3.2 Hz, 1H, H3), 5.45 (d, J = 4.3 Hz, 1H, NH), 5.22 (s, 1H, H1), 5.13 (m, 1H, H4), 4.60 (dd, J = 10.2, 6.4 Hz, 1H, H5), 4.16 (t, J = 10.2 Hz, 1H, CH$_2$), 3.91 (m, 1H, H2), 3.88 (m, 2H, 2 × CH$_2$), 3.48 (dd, J = 9.3, 7.0 Hz, 1H, CH$_2$), 1.07 (t, J = 7.0 Hz, 3H, CH$_3$), 0.81 (s, 9H, CH$_3$), 0.00 (s, 3H, CH$_3$), -0.08 (s, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 165.4 (CO), 133.8 (Ph), 129.9 (Ph), 128.8 (Ph), 128.5 (Ph), 97.7 (C1), 76.5 (C4), 73.9 (C5), 64.3 (CH$_2$), 63.3 (C3), 62.2 (CH$_2$), 51.7 (C2), 25.6 (CH$_3$), 18.0 (Cq), 14.9 (CH_3), -5.4 (CH_3), -5.7 (CH_3); **IR ($CHCl_3$):** ṽ = 3018, 2929, 1726, 1269, 1215 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{22}H_{36}NO_9NSSi$: 518.1875 [M–H^++MeOH]; found: 518.1887.



42e'

8-*O*-Isopropyl-9-benzoyloxy-10-((tert-Butyldimethylsilyloxy)methyl)-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42e')

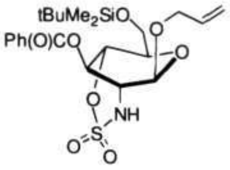
Yield: 70 %; colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* (ppm): 8.04 (d, *J* = 7.2 Hz, 2H, Ph), 7.60 (t, *J* = 7.6 Hz, 1H, Ph), 7.44 (t, *J* = 7.6 Hz, 2H, Ph), 5.76 (br t, 1H, H3), 5.71 (d, *J* = 4.1 Hz, 1H, NH), 5.32 (s, 1H, H1), 5.13 (br t, 1H, H4), 4.59 (dd, *J* = 10.7, 6.3 Hz, 1H, H5), 4.21 (t, *J* = 10.2 Hz, 1H, CH_2), 4.01 (m, 1H; CH), 3.87 (m, 2H, H2 and CH_2), 1.07 (d, *J* = 6.1 Hz, 3H, CH_3), 1.06 (d, *J* = 6.1 Hz, 3H, CH_3), 0.81 (s, 9H, CH_3), 0.00 (s, 3H, CH_3), -0.08 (s, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* (ppm): 165.4 (CO), 133.8 (Ph), 130.0 (Ph), 128.8 (Ph), 128.4 (Ph), 95.4 (C1), 76.5 (C4), 73.8 (C5), 69.8 (CH), 63.4 (C3), 62.5 (CH_2), 52.1 (C2), 25.6 (CH_3), 23.1 (CH_3), 21.0 (CH_3), 18.0 (Cq), -5.4 (CH_3), -5.7 (CH_3); **IR ($CHCl_3$):** ṽ = 3018, 1718, 1627, 1215 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{22}H_{34}NO_8SSi$: 500.1769 [M–H^+]; found: 500.1755.



42f'

8-*O*-Benzyl-9-benzoyloxy-10-((tert-Butyldimethylsilyloxy)methyl)-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42f')

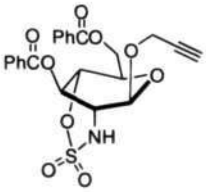
Yield: 74 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ (ppm): 7.84 (d, J = 7.2 Hz, 2H, Ph), 7.54 (t, J = 7.4 Hz, 1H, Ph), 7.24 (m, 7H, Ph), 5.80 (br t, J = 3.5 Hz 1H, H3), 5.51 (br s, 1H, NH), 5.36 (s, 1H, H1), 5.14 (br t, 1H, H4), 4.84 (d, J = 11.1 Hz, 1H, CH$_2$), 4.64 (dd, J = 10.6, 6.4 Hz, 1H, H5), 4.53 (d, J = 11.1 Hz, 1H, CH$_2$), 4.16 (t, J = 10.2 Hz, 1H, CH$_2$), 3.96 (m, 1H, H2), 3.91 (dd, J = 10.6, 6.4 Hz, 1H, CH$_2$), 0.78 (s, 9H, CH$_3$), -0.03 (s, 3H, CH$_3$), -0.14 (s, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$): δ** (ppm): 165.2 (CO), 136.6 (Ph), 133.7 (Ph), 129.9 (Ph), 128.5 (Ph), 128.4 (Ph), 128.1 (Ph), 128.0 (Ph), 97.5 (C1), 76.3 (C4), 74.1 (C5), 70.9 (CH$_2$), 63.1 (C3), 62.2 (CH$_2$), 51.7 (C2), 25.6 (CH$_3$), 18.0 (Cq), -5.5 (CH$_3$), -5.7 (CH$_3$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3018, 1708, 1627, 1215 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{26}H_{36}NO_8SSi$: 550.1925 [M+H$^+$]; found: 550.1938.



42g'

8-*O*-Allyl-9-benzoyloxy-10-((tert-Butyldimethylsilyloxy)methyl)-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42g')

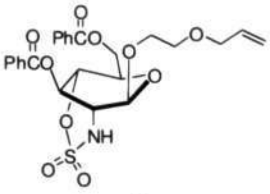
Yield: 61 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ (ppm): 8.01 (d, J = 8.1 Hz, 2H, Ph), 7.60 (t, J = 7.5 Hz, 1H, Ph), 7.44 (t, J = 7.5 Hz, 2H, Ph), 5.77 (m, 2H, H3 and C*H*=CH$_2$), 5.36 (br s, 1H, NH), 5.27 (s, 1H, H1), 5.13 (m, 3H, H4 and CH=C*H*$_2$), 4.62 (dd, J = 10.2, 6.5 Hz, 1H, H5), 4.29 (dd, J = 12.5, 5.2 Hz, 1H, CH$_2$), 4.15 (t, J = 6.5 Hz, 1H, CH$_2$), 4.01 (dd, J = 12.5, 5.2 Hz, 1H, CH$_2$), 3.91 (m, 2H, H2 and CH$_2$), 0.80 (s, 9H, CH_3), 0.00 (s, 3H, CH_3), -0.09 (s, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 165.2 (CO), 133.8 (Ph), 133.2 (*C*H=CH_2), 130.0 (Ph), 128.7 (Ph), 128.5 (Ph), 117.7 (CH=*C*H_2), 97.2 (C1), 76.4 (C4), 74.0 (C5), 69.3 (CH_2), 63.2 (C3), 62.2 (CH_2), 51.7 (C2), 25.6 (CH_3), 18.0 (Cq), -5.6 (CH_3), -5.4 (CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3018, 2927, 1718, 1647, 1627, 1215 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{22}H_{32}NO_8SSi$: 498.1612 [M−H$^+$]; found: 498.1619.



42h

8-*O*-Propargyl-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42h)

Yield: 80 %; colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 8.01 (m, 4H, Ph), 7.59 (m, 2H, Ph), 7.44 (m, 4H, Ph), 5.89 (m, 1H, H4), 5.85 (br d, *J* = 4.5 Hz, 1H, NH), 5.50 (s, 1H, H1), 5.05 (m, 1H, H3), 4.99 (t, *J* = 7.1 Hz, 1H, H5), 4.88 (dd, *J* = 11.1, 7.5 Hz, 1H, CH_2), 4.71 (dd, *J* = 11.1, 7.5 Hz, 1H, CH_2), 4.39 (m, 2H, C≡C*H*$_2$), 4.00 (m, 1H, H2), 2.41 (s, 1H, C≡C*H*); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 165.8 (CO), 165.5 (CO), 134.1 (Ph), 133.5 (Ph), 130.0 (Ph), 129.7 (Ph), 129.1 (Ph), 128.7 (Ph), 128.5 (Ph), 128.2 (Ph), 96.4 (C1), 78.1 (CH), 76.4 (C4), 75.4 (Cq), 72.0 (C5), 64.0 (CH_2), 62.6 (C3), 55.5 (CH_2), 51.3 (C2); **IR ($CHCl_3$):** $\tilde{\nu}$ = 2304, 2121, 1718, 1637 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{21}NO_9SNa$: 510.0835 [M+Na]$^+$; found: 510.0883.



42i

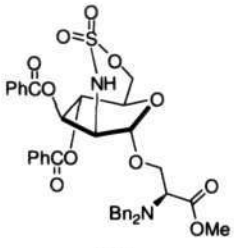
8-*O*-Ethyloxyallyloxy-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo[3.3.1] decane-3,3-dioxide (42i)

Yield: 90 %; colourless oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.02 (m, 4H, Ph), 7.59 (m, 2H, Ph), 7.46 (m, 4H, Ph), 5.85 (br t, $J = 3.2$ Hz, 1H, H4), 5.69 (ABX system, $J_{AX} = 17.2$, $J_{BX} = 10.4$, $J_{AB} = 5.4$ Hz, 1H, C*H*=CH$_2$), 5.37 (br d, $J = 4.6$ Hz, 1H, NH), 5.31 (s, 1H, H1), 5.12 (d, $J = 17.2$ Hz, 1H, CH=C*H*$_2$), 5.07 (d, $J = 10.4$ Hz, 1H, CH=C*H*$_2$), 5.04 (m, 1H, H3), 4.96 (t, $J = 7.3$ Hz, 1H, H5), 4.91 (dd, $J = 11.1$, 7.4 Hz, 1H, CH$_2$), 4.78 (dd, $J = 11.1$, 7.4 Hz, 1H, CH$_2$), 4.07 (m, 1H, H2), 4.04 (m, 1H, CH$_2$), 3.76 (m, 2H, CH$_2$), 3.66 (m, 1H, CH$_2$), 3.45 (m, 1H, CH$_2$), 3.40 (m, 1H, CH$_2$); **^{13}C NMR (125 MHz, CDCl$_3$):** δ (ppm): 165.8 (CO), 165.3 (CO), 134.3 (Ph), 133.9 (=CH), 133.4 (Ph), 129.9 (Ph), 129.6 (Ph), 129.2 (Ph), 128.7 (Ph), 128.4 (Ph), 128.3 (Ph), 117.1 (=CH$_2$), 98.5 (C1), 76.6 (C4), 72.0 (C5 and CH$_2$), 68.7 (CH$_2$), 68.4 (CH$_2$), 64.1 (CH$_2$), 62.8 (C3), 51.1 (C2); **IR (CHCl$_3$):** $\tilde{\nu} = 3053$, 1718, 1637 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{25}H_{27}NO_{10}SNa$: 556.1253 [M+Na]$^+$; found: 556.1225.

4.4 General procedure for rhodium-catalyzed aziridination with thiol, amine, amino acid, and glycal as nucleophiles

A mixture of sulfamate ester (1 equiv), [Rh$_2$(tfacam)$_4$] (10 mol%), PhIO (1.5 equiv), MgO (5 equiv), and 4 Å molecular sieves in dry CH$_2$Cl$_2$ (2 mL) was stirred at room temperature for 15 mins, then the nucleophile (1.5 equiv) was added dropwise.

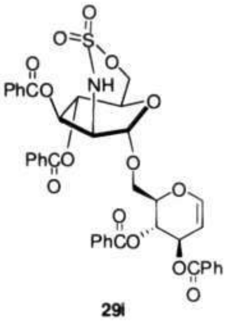
The suspension was stirred vigorously at room temperature and monitored by TLC. The resulting mixture was filtered through a pad of Celite. The filter cake was rinsed with CH_2Cl_2 and the combined filtrates were evaporated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: 30% ethyl acetate in hexane) to afford the oxathiazepane.



29h

9-*N*-[Methyl-*N*-(dibenzyl)-l-serinate-3-yl]-7,8-di-O-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29h)

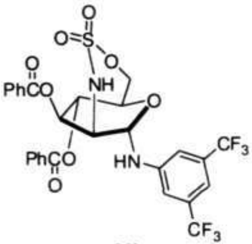
Yield: 66 %; colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.09 (m, 2H, Ph), 7.89 (m, 2H, Ph), 7.61 (m, 1H, Ph), 7.55 (m, 1H, Ph), 7.48 (m, 2H, Ph), 7.38 (m, 6H, Ph), 7.30 (m, 4H, Ph), 7.21 (m, 2H, Ph), 5.80 (dd, J = 5.6, 4.3 Hz, 1H, H3), 5.61 (d, J = 1.2 Hz, 1H, H1), 5.50 (d, J = 4.3 Hz, 1H, H4), 5.08 (br s, 1H, NH), 4.69 (dd, J = 12.1, 2.6 Hz, 1H, CH_2), 4.62 (dd, J = 12.1, 2.6 Hz, 1H, CH_2), 4.39 (m, 1H, H5), 4.18 (dd, J = 10.3, 6.3 Hz, 1H, CH_2O), 3.99 (dd, J = 5.6, 1.2 Hz, 1H, H2), 3.94 (d, J = 13.9 Hz, 1H, CH_2Ph), 3.85 (dd, J = 10.3, 6.3 Hz, 1H, CH_2O), 3.75 (m, 1H, CHN), 3.74 (s, 3H, OCH_3), 3.70 (d, J = 13.9 Hz, 1H, CH_2Ph); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 171.2 (CO), 166.1 (CO), 164.9 (CO), 139.2 (Ph), 133.9 (Ph), 133.6 (Ph), 129.9 (Ph), 129.8 (Ph), 128.77 (Ph), 128.73 (Ph), 128.6 (Ph), 128.5 (Ph), 128.3 (Ph), 127.1 (Ph), 95.9 (C1), 76.8 (C5), 75.7 (CH_2OSO_2), 72.0 (C4), 69.4 (C3), 66.3 (CH_2O), 61.0 (OCH_3), 55.2 (CH_2Ph), 53.3 (C2), 51.4 (CHN); **IR ($CHCl_3$):** $\tilde{\nu}$ = 2926, 1724, 1452, 1261 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{38}H_{39}N_2O_{11}S$: 731.2269 [M+H]$^+$; found: 731.2286.



29i

9-*O*-[3,4-Di-*O*-benzoyl-1,2-dideoxy-D-glcopyranosyl]-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29i)

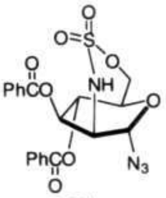
Yield: 68 %; colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ(ppm): 8.03 (m, 9H, Ph), 7.61 (m, 1H, Ph), 7.49 (m, 6H, Ph), 7.35 (m, 4H, Ph), 6.51 (d, J = 6.2 Hz, 1H, H1'), 5.86 (dd, J = 5.9, 3.9 Hz, 1H, H3), 5.76 (dd, J = 6.7, 5.7 Hz, 1H, H4'), 5.63 (m, 2H, H1 and H3'), 5.49 (d, J = 3.9 Hz, 1H, H4), 5.06 (dd, J = 6.2, 3.4 Hz, 1H, H2'), 4.98 (d, J = 3.6 Hz, 1H, NH), 4.66 (dd, J = 12.4, 2.5 Hz, 1H, CH_2OSO_2), 4.61 (dd, J = 12.4, 2.5 Hz, 1H, CH_2OSO_2), 4.56 (ABq, J = 11.2, 5.7 Hz, 1H, H5'), 4.49 (m, 1H, H5), 4.13 (dd, J = 11.2, 5.7 Hz, 1H, CH_2O), 4.06 (dd, J = 11.2, 5.7 Hz, 1H, CH_2O), 3.97 (m, 1H, H2); **^{13}C NMR (100 MHz, $CDCl_3$):** δ(ppm): 166.2 (CO), 165.8 (CO), 164.9 (CO), 164.8 (CO), 145.9 (C1'), 133.9 (Ph), 133.5 (Ph), 133.39 (Ph), 133.30 (Ph), 129.95 (Ph), 129.87 (Ph), 129.83 (Ph), 129.7 (Ph), 129.6 (Ph), 129.2 (Ph), 128.97 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.48 (Ph), 128.45 (Ph), 98.8 (C2'), 96.4 (C1), 76.7 (C5), 75.7 (CH_2OSO_2), 74.5 (C5'), 72.1 (C4), 69.3 (C3), 68.0 (C4'), 67.7 (C3'), 66.3 (CH_2O), 53.1 (C2); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3018, 1720, 1647, 1602, 1273 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{40}H_{35}NO_{14}SNa$: 808.1676 [M+Na]$^+$; found: 808.1468.



29j

9-*N*-(3,5-Bis(trifluoromethyl)phenyl-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29j)

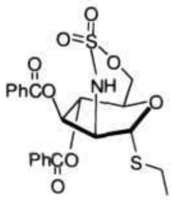
Yield: 76 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.07 (d, J = 7.4 Hz, 2H, Ph), 8.00 (d, J = 7.4 Hz, 2H, Ph), 4.10 (m, 1H, H2), 7.60 (m, 2H, Ph), 7.45 (m, 4H, Ph), 7.35 (s, 1H, Ph), 7.21 (s, 2H, Ph), 6.46 (d, J = 9.0 Hz, 1H, H1), 5.85 (dd, J = 6.6, 4.2 Hz, 1H, H3), 5.79 (d, J = 6.6 Hz, 1H, H4), 5.29 (br s, 1H, NH), 5.13 (br d, J = 9.0 Hz, 1H, NHPh), 4.89 (dd, J = 13.3, 1.5 Hz, 1H, CH$_2$), 4.80 (dd, J = 13.3, 1.5 Hz, 1H, CH$_2$), 4.52 (m, 1H, H5), 4.10 (m, 1H, H2); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.1 (CO), 165.7 (CO), 145.3 (Ph), 134.3 (Ph), 134.0 (Ph), 132.6 (Ph), 130.0 (Ph), 129.8 (Ph), 128.8 (Ph), 128.6 (Ph), 128.4 (Ph), 128.0 (Ph), 114.0 (CF$_3$), 113.4 (CF$_3$), 78.7 (C1), 77.6 (C5), 75.2 (CH$_2$), 71.8 (C4), 70.5 (C3), 55.1 (C2); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3018, 1720, 1624, 1473, 1388, 1278 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{28}H_{23}F_6N_2O_8S$: 661.1079 [M+H]$^+$; found: 661.1029.



29k

9-Azido-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-aza-bicyclo[4.2.2]decane-3,3-dioxide (29k)

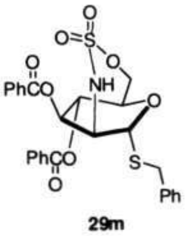
Yield: 80 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.06 (m, 4H, Ph), 7.60 (m, 2H, Ph), 7.46 (m, 4H, Ph), 6.23 (s, 1H, H1), 5.80 (dd, J = 5.2, 4.5 Hz, 1H, H3), 5.60 (d, J = 4.5 Hz, 1H, H4), 5.27 (br s, 1H, NH), 4.76 (d, J = 12.8 Hz, 1H, CH$_2$), 4.69 (dd, J = 12.8, 2.8 Hz, 1H, CH$_2$), 4.58 (m, 1H, H5), 3.88 (m, 1H, H2); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.0 (CO), 165.0 (CO), 134.1 (Ph), 133.9 (Ph), 130.0 (Ph), 129.9 (Ph), 128.7 (Ph), 128.6 (Ph), 128.3 (Ph), 84.6 (C1), 78.0 (C5), 75.2 (CH$_2$), 71.7 (C4), 68.8 (C3), 52.6 (C2); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3055, 2119, 1722, 1635 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{19}N_4O_8S$: 475.0918 [M+H]$^+$; found: 475.0899.



29l

9-Ethylthio-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29l)

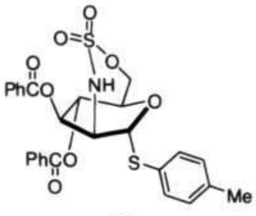
Yield: 84 %; white solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.06 (m, 4H, Ph), 7.59 (m, 2H, Ph), 7.45 (m, 4H, Ph), 6.23 (s, 1H, H1), 5.94 (dd, J = 6.1, 4.1 Hz, 1H, H3), 5.68 (d, J = 4.1 Hz, 1H, H4), 5.18 (br d, J = 2.3 Hz, 1H, NH), 4.80 (dd, J = 13.1, 3.8 Hz, 1H, CH$_2$), 4.71 (dd, J = 13.1, 1.3 Hz, 1H, CH$_2$), 4.47 (m, 1H, H5), 4.16 (m, 1H, H2), 2.88 (dt, J = 12.8, 7.4 Hz, 1H, CH$_2$), 2.80 (dt, J = 12.8, 7.4 Hz, 1H, CH$_2$), 1.37 (t, J = 7.4 Hz, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.3 (CO), 165.1 (CO), 134.0 (Ph), 133.8 (Ph), 130.0 (Ph), 128.7 (Ph), 128.5 (Ph), 78.0 (C5), 77.2 (C1), 75.4 (CH$_2$), 72.0 (C4), 71.0 (C3), 55.3 (C2), 25.7 (CH$_2$), 14.7 (CH0$_3$; **IR (CHCl$_3$):** $\tilde{\nu}$ = 3018, 1722, 1627 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{22}H_{23}NO_8S_2Na$: 516.0763 [M+Na]$^+$; found: 516.0765.



29m

9-Benzylthio-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29m)

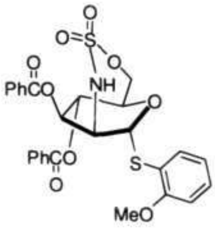
Yield: 83 %; white solid. **^{1}H NMR (300 MHz, CDCl$_3$):** δ (ppm): 8.03 (m, 4H, Ph), 7.59 (m, 2H, Ph), 7.45 (m, 4H, Ph), 7.33 (m, 5H, Ph), 6.07 (s, 1H, H1), 5.94 (dd, J = 5.9, 4.8 Hz, 1H, H3), 5.67 (d, J = 4.8 Hz, 1H, H4), 5.05 (br d, J = 2.7 Hz, 1H, NH), 4.79 (dd, J = 13.0, 3.6 Hz, 1H, CH$_2$), 4.69 (dd, J = 13.0, 1.4 Hz, 1H, CH$_2$), 4.47 (m, 1H, H5), 4.04 (m, 1H, H2), 4.03 (d, J = 13.2 Hz, 1H, CH$_2$), 3.94 (d, J = 13.2 Hz, 1H, CH$_2$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.3 (CO), 165.0 (CO), 136.9 (Ph), 134.0 (Ph), 133.8 (Ph), 130.0 (Ph), 129.9 (Ph), 129.0 (Ph), 128.7 (Ph), 128.6 (Ph), 128.4 (Ph), 127.5 (Ph), 78.0 (C5), 76.8 (C1), 75.4 (CH$_2$), 72.0 (C4), 70.8 (C3), 54.7 (C2), 35.5 (CH$_2$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3055, 1718, 1653, 1421 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{25}NO_8S_2Na$: 578.0919 [M+Na]$^+$; found: 578.0898.



29n

9-*p*-Tolylthio-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2]decane-3,3-dioxide (29n)

Yield: 85 %; colourless oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.06 (m, 4H, Ph), 7.59 (m, 2H, Ph), 7.51 (d, *J* = 8.0 Hz, 2H, Ph), 7.47 (m, 4H, Ph), 7.18 (d, *J* = 8.0 Hz, 2H, Ph), 6.27 (s, 1H, H1), 5.99 (t, *J* = 5.5 Hz, 1H, H3), 5.68 (d, *J* = 5.5 Hz, 1H, H4), 5.08 (br d, *J* = 2.9 Hz, 1H, NH), 4.77 (dd, *J* = 13.0, 3.5 Hz, 1H, CH$_2$), 4.71 (dd, *J* = 13.0, 1.5 Hz, 1H, CH$_2$), 4.51 (m, 1H, H5), 4.27 (br t, *J* = 3.8 Hz, 1H, H2), 2.36 (s, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.3 (CO), 165.0 (CO), 139.2 (Ph), 134.1 (Ph), 134.0 (Ph), 133.8 (Ph), 130.2 (Ph), 130.0 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 127.7 (Ph), 81.5 (C1), 78.4 (C5), 75.4 (CH$_2$), 71.9 (C4), 70.4 (C3), 54.5 (C2), 21.2 (CH$_3$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3018, 1722, 1273 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{25}NO_8S_2Na$: 578.0914 [M+Na]$^+$; found: 578.0939.

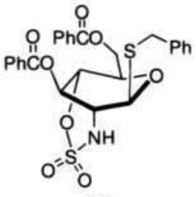


29o

9-(2-Methoxyphenylthio)-7,8-di-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo[4.2.2] decane-3,3-dioxide (29o)

Yield: 78 %; colourless oil. **^{1}H NMR (300 MHz, CDCl$_3$):** δ (ppm): 8.08 (m, 4H, Ph), 7.58 (m, 2H, Ph), 7.46 (m, 5H, Ph), 7.35 (m, 1H, Ph), 6.96 (m, 2H, Ph), 6.48 (s, 1H, H1), 6.12 (dd, *J* = 5.7, 3.2 Hz, 1H, H3), 5.67 (d, *J* = 5.7 Hz, 1H, H4), 5.09 (br d, *J* = 2.8 Hz, 1H, NH), 4.74 (m, 2H, CH$_2$), 4.50 (m, 1H, H5), 4.28 (m, 1H, H2), 3.92 (s, 3H, OCH$_3$); **^{13}C NMR (75 MHz, CDCl$_3$):** δ (ppm): 166.2 (CO), 164.9 (CO), 159.1 (Ph), 135.2 (Ph), 133.9 (Ph), 133.7 (Ph), 130.6 (Ph), 130.0 (Ph), 129.9 (Ph), 128.7 (Ph), 128.5 (Ph), 121.3 (Ph), 119.2 (Ph), 111.3 (Ph), 79.2 (C1), 78.3 (C5), 75.3 (CH$_2$), 72.0

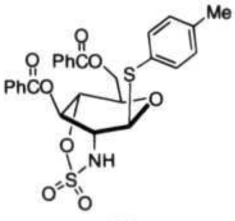
(C4), 70.1 (C3), 55.9 (OCH_3), 54.8 (C2); **IR ($CHCl_3$):** ṽ = 3053, 1718, 1637, 1452 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{25}NO_9S_2Na$: 594.0868 $[M+Na]^+$; found: 594.0874.



42k

8-Benzylthio-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42k)

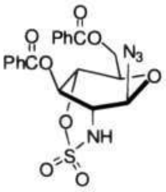
Yield: 86 %; colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** *δ* (ppm): 8.04 (m, 4H, Ph), 7.93 (s, 1H, H1), 7.64 (m, 1H, Ph), 7.58 (m, 1H, Ph), 7.48 (m, 5H, Ph), 7.40 (m, 2H, PH), 7.30 (m, 2H, Ph), 5.70 (m, 1H, H4), 5.61 (m, 1H, H5), 5.15 (br s, 1H, H3), 5.03 (d, *J* = 5.6 Hz, 1H, NH), 4.91 (dd, *J* = 12.6, 1.7 Hz, 1H, CH_2), 4.57 (dd, *J* = 5.6, 1.8 Hz, 1H, H2), 4.44 (dd, *J* = 12.6, 1.7 Hz, 1H, CH_2), 3.97 (m, 2H, CH_2); **^{13}C NMR (125 MHz, $CDCl_3$):** *δ* (ppm): 165.8 (CO), 165.0 (CO), 158.7 (Ph), 134.3 (Ph), 133.4 (Ph), 129.9 (Ph), 129.8 (Ph), 129.2 (Ph), 129.1 (Ph), 128.8 (Ph), 128.5 (Ph), 127.7 (Ph), 77.9 (C1), 66.7 (C4), 64.1 (C5), 61.3 (CH_2), 61.2 (C3), 36.0 (CH_2); **IR ($CHCl_3$):** ṽ = 3055, 1728, 1637, 1421 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{25}NO_8S_2Na$: 578.0919 $[M+Na]^+$; found: 578.0912.



42l

8-*p*-Tolylthio-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo-[3.3.1]decane-3,3-dioxide (42l)

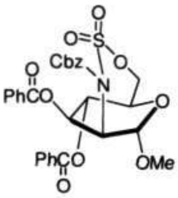
Yield: 78 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.08 (m, 2H, Ph), 8.00 (m, 2H, Ph), 7.67 (m, 1H, Ph), 7.54 (m, 3H, Ph), 7.42 (m, 4H, Ph), 7.14 (d, *J* = 7.9 Hz, 2H, Ph), 5.79 (m, 1H, H3), 5.58 (br s, 1H, NH), 5.37 (m, 1H, H5), 5.26 (m, 1H, H4), 5.12 (m, 1H, H2), 4.94 (m, 1H, H1), 4.86 (dd, *J* = 12.2, 3.7 Hz, 1H, CH$_2$), 4.25 (dd, *J* = 12.2, 3.7 Hz, 1H, CH$_2$), 2.33 (s, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 165.8 (CO), 164.8 (CO), 134.35 (Ph), 133.4 (Ph), 133.0 (Ph), 130.3 (Ph), 130.1 (Ph), 129.7 (Ph), 128.8 (Ph), 128.5 (Ph), 123.6 (Ph), 80.1 (C1), 66.7 (C4), 66.6 (C5 and C3), 62.7 (C2), 61.1 (CH$_2$), 21.1 (CH$_3$); **IR (CHCl$_3$):** ṽ = 3018, 2929, 1718, 1649, 1388, 1269 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{25}NO_8S_2Na$: 578.0914 [M+Na]$^+$; found: 578.0891.



42m

8-Azido-9,10-di-*O*-benzoyl-5,7-dioxa-3-thia-2-azabicyclo[3.3.1]decane-3,3-dioxide (42m)

Yield: 76 %; colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.04 (m, 4H, Ph), 7.60 (m, 2H, Ph), 7.46 (m, 4H, Ph), 5.93 (m, 1H, H1), 5.73 (m, 1H, H4), 5.37 (br d, *J* = 4.5 Hz, 1H, NH), 5.18 (t, *J* = 7.28 Hz, 1H, H5), 5.05 (m, 1H, H3), 4.87 (dd, *J* = 11.3, 7.3 Hz, 1H, CH$_2$), 4.69 (dd, *J* = 11.3, 7.3 Hz, 1H, CH$_2$), 3.89 (m, 1H, H2); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 165.9 (CO), 165.3 (CO), 134.3 (Ph), 133.5 (Ph), 130.0 (Ph), 129.7 (Ph), 128.9 (Ph), 128.5 (Ph), 86.1 (C1), 76.3 (C4), 72.0 (C5), 63.9 (CH$_2$), 63.3 (C3), 51.6 (C2); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3053, 2125, 1722, 1637 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{18}N_4O_8SNa$: 497.0743 $[M+Na]^+$; found: 497.0662.



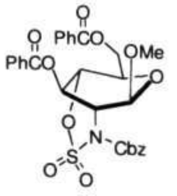
43

9-*O*-Methyl-7,8-di-*O*-benzoyl-2-benzyloxycarbonylamino-4,10-dioxa-3-thia-2-azido bicyclo-[4.2.2]decane-3,3-dioxide (43)

CbzCl (0.3 mL, 2.11 mmol) and DMAP (30 mg, 0.25 mmol) were sequentially added to a solution of oxathiazepane **29** (110 mg, 0.23 mmol) in THF (1 mL) and Et_3N (0.7 mL, 5.02 mmol) at 0 °C. The mixture was stirred at room temperature for 2.5 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (2 ×). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (eluent: 50 % ethyl acetate in hexane) to yield **43** (130 mg, 92 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.96 (d, *J* = 7.4 Hz, 2H, Ph), 7.88 (d, *J* = 7.4 Hz, 2H, Ph), 7.47 (m, 4H, Ph), 7.30 (m, 7H, Ph), 5.73 (dd, *J* = 10.1, 4.2 Hz, 1H, H3), 5.54 (t, *J* = 10.1 Hz, 1H, H4), 5.00 (s, 2H, CH_2), 4.85 (br s, 1H, H1), 4.72 (dd, *J* = 8.8, 4.3 Hz, 1H, H2), 4.21 (m, 1H, H5), 3.72 (dd, *J* = 12.1, 6.0 Hz, 1H, CH_2), 3.66 (dd, *J* = 12.1, 6.0 Hz, 1H, CH_2), 3.50 (s, 3H, OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 165.5 (CO), 165.4 (CO), 155.8 (CO), 136.0 (Ph), 133.6 (Ph), 133.0 (Ph), 129.8 (Ph), 129.7 (Ph), 129.3 (Ph), 128.7 (Ph), 128.59 (Ph), 128.51 (Ph), 128.29 (Ph), 128.22 (Ph), 100.4 (C1), 70.0 (C5), 69.7 (C4), 67.7 (C3), 67.1 (CH_2), 55.5 (OCH_3), 52.3 (C2), 43.8

(CH_2); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3018, 1726, 1512, 1274 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{29}H_{26}NO_{11}S$: 596.1221 [M–H]$^+$ found: 596.1226.



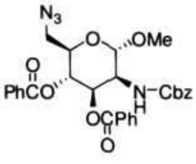
46

8-*O*-Methyl-9,10-di-*O*-benzoyl-2-benzyloxycarbonylamino-5,7-dioxa-3-thia-2-azido bicyclo-[3.3.1]decane-3,3-dioxide (46)

Aqueous $NaHCO_3$ (100 mg in 1 mL of water) and CbzCl (350 mL, 2.46 mmol) were sequentially added to a solution of oxathiazepane **45** (116 mg, 0.24 mmol) in THF (1 mL) with vigorous stirring at 0 °C. The reaction mixture was kept at this temperature for 1 h and then warmed up to room temperature overnight. The mixture was extracted with EtOAc (3 ×). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (eluent: 50 % ethyl acetate in hexane) to yield **46** (120 mg, 82 %) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 8.15 (d, *J* = 7.7 Hz, 2H, Ph), 8.05 (d, *J* = 7.7 Hz, 2H, Ph), 7.57 (m, 2H, Ph), 7.34 (m, 4H, Ph), 7.31 (m, 5H, Ph), 5.71 (d, *J* = 3.2 Hz, 1H, H3), 5.10 (ABq, *J* = 16.0, 12.2 Hz, 2H, CH_2), 4.59 (dd, *J* = 11.3, 6.5 Hz, 1H, CH_2), 4.49 (d, *J* = 7.9 Hz, 1H, H1), 4.38 (dd, *J* = 11.3, 6.5 Hz, 1H, CH_2), 4.12 (m, 1H, H4), 4.12 (m, 1H, H4), 4.08 (t, *J* = 6.4 Hz, 1H, H5), 3.71 (m, 1H, H2), 3.55 (s, 3H, OCH_3); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 166.2 (CO), 166.1 (CO), 157.4 (CO), 135.8 (Ph), 133.4 (Ph), 133.2 (Ph), 130.0 (Ph), 129.7 (Ph), 129.5 (Ph), 129.3 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 101.8 (C1), 71.5 (C5), 71.4

(C4), 69.5 (C3), 67.4 (CH_2), 62.4 (CH_2), 57.1 (OCH_3), 56.1 (C2); **IR (Nujol):** $\tilde{\nu}$ = 1720, 1714, 1273 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{29}H_{26}NO_{11}S$: 596.1221 $[M-H]^+$; found: 596.1221.



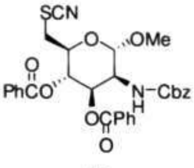
48

Methyl-6-azido-2-benzyloxycarbonylamino-3,4-di-*O*-benzoyl-2,6-dideoxy-D-glucopyranoside (48)

NaN_3 (6 mg, 9.2 × 10^{-2} mmol) was added to a solution of *N*-Cbz oxathiazepane **43** (28 mg, 4.7 × 10^{-2} mmol) in dry DMF (0.3 mL) in the presence of 4 Å molecular sieves. After heating at 120 °C for 5 h, the reaction mixture was cooled to room temperature. NaH_2PO_4 (2 mL, 1N) was added and the mixture was stirred for an hour. The mixture was filtered and the filtrate was washed with water (3 ×), dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by chromatography on silica gel (eluent: 50 % ethyl acetate in hexane) to yield **48** (18 mg, 67 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.94 (d, *J* = 7.4 Hz, 2H, Ph), 7.87 (d, *J* = 7.4 Hz, 2H, Ph), 7.49 (m, 3H, Ph), 7.35 (m, 8H, Ph), 5.71 (dd, *J* = 10.6, 4.1 Hz, 1H, H3), 5.47 (t, *J* = 10.6 Hz, 1H, H4), 5.20 (br d, *J* = 8.2 Hz, 1H, NH), 5.01 (m, 2H, CH_2), 4.84 (m, 1H, H1), 4.60 (m, 1H, H2), 4.13 (m, 1H, H5), 3.51 (s, 3H, CH_3), 3.48 (m, 2H, CH_2N_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 170.5 (CO), 165.3 (CO), 155.8 (CO), 133.6 (Ph), 133.0 (Ph), 129.8 (Ph), 129.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.28 (Ph), 128.20 (Ph), 100.3 (C1), 69.8 (C5), 69.5 (C3), 67.4 (CH_2), 67.1

(C4), 55.5 (OCH_3), 52.3 (CH_2N_3), 51.2 (C2); **IR ($CHCl_3$):** $\tilde{\nu}$ = 2102, 1724, 1672, 1273 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{29}H_{28}N_4O_8Na$: 583.1804 $[M+Na]^+$; found: 583.1822.

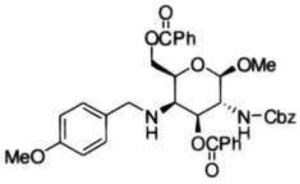


49

Methyl-6-thiocyanato-2-benzyloxycarbonylamino-3,4-di-*O*-benzoyl-2,6-dideoxy-D-glucopyranoside (49)

Potassium thiocyanate (23 mg, 0.23 mmol) was added to a solution of *N*-Cbz oxathiazepane **43** (28 mg, 4.7 × 10^{-2} mmol) in dry DMF (0.5 mL) in the presence of 4 Å molecular sieves. The mixture was stirred at 150 °C for 12 h under a nitrogen atmosphere. After cooling the reaction to room temperature, 1N NaH_2PO_4 (2 mL) was added and the mixture was stirred for another hour. The mixture was filtered and the filtrate was washed with water (3 ×), dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by chromatography on silica gel (eluent 50 % ethyl acetate in hexane) to yield **49** (21 mg, 78 %) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm): 7.98 (m, 2H, Ph), 7.89 (d, *J* = 7.4 Hz, 2H, Ph), 7.57 (t, *J* = 7.4 Hz, 2H, Ph), 7.50 (t, *J* = 7.4 Hz, 1H, Ph), 7.42 (t, *J* = 7.8 Hz, 2H, Ph), 7.34 (m, 7H, Ph), 5.78 (dd, *J* = 10.0, 4.1 Hz, 1H, H3), 5.43 (t, *J* = 10.0 Hz, 1H, H4), 5.22 (d, *J* = 9.1 Hz, 1H, NH), 5.05 (m, 2H, CH_2), 4.90 (m, 1H, H1), 4.63 (dd, *J* = 9.1, 4.1 Hz, 1H, CH_2), 4.29 (t, *J* = 7.9 Hz, 1H, H5), 3.57 (s, 3H, CH_3), 3.29 (dd, *J* = 13.9, 2.6 Hz, 1H, CH_2SCN), 3.15 (dd, *J* = 13.9, 8.4 Hz, 1H, CH_2SCN); **^{13}C NMR (125 MHz, $CDCl_3$):** δ(ppm): 165.9 (CO), 165.3 (CO), 155.7 (CO), 135.9 (Ph), 133.9 (Ph), 133.1 (Ph), 129.9 (Ph), 129.7 (Ph), 129.2 (Ph), 128.6 (Ph), 128.3 (Ph), 128.2 (Ph), 111.9 (CN), 100.5 (C1), 9.5 (C3), 69.2 (C4), 68.9 (C5), 67.2 (CH_2), 55.8 (OCH_3), 52.3 (C2), 35.9 (CH_2SCN); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3018, 1780, 1703, 1386, 1215 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{30}H_{28}N_2O_8SNa$: 599.1459 $[M+Na]^+$; found: 599.1445.

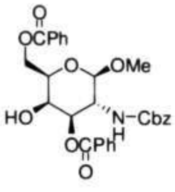


50

Methyl-*N*-4-methoxybenzylamino-2-benzyloxycarbonylamino-3,6-di-*O*-benzoyl-2,4-dideoxy-D-glucopyranoside (50)

A solution of compound **46** (11 mg, 2.4 × 10^{-2} mmol) in dry DMF (0.5 mL) was treated with *p*-methoxybenzylamine (15 μL, 11.4 × 10^{-2} mmol) under a nitrogen atmosphere. The reaction mixture was heated at 70 °C for 30 h and then cooled to room temperature. The solvent was removed under reduced pressure, then EtOAc (10 mL) was added to the residue, and the solution was washed with water (3 ×). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel (eluent: 30 % ethyl acetate in hexane) gave **50** (9 mg, 75 %) as a colorless viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.02 (d, *J* = 7.6 Hz, 2H, Ph), 7.77 (d, *J* = 8.0 Hz, 2H, Ph), 7.56 (m, 1H, Ph), 7.39 (m, 6H, Ph), 7.27 (m, 2H, Ph), 7.18 (m, 4H, Ph), 6.88 (d, *J* = 8.0 Hz, 2H, Ph), 5.30 (m, 1H, H1), 5.03 (m, 3H, CH_2 and NH), 4.59 (m, 5H, H3, CH_2 and CH_2N), 4.23 (m, 1H, H4), 4.15 (m, 1H, H2), 3.98 (m, 1H, H5), 3.80 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 2.50 (br s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 166.4 (CO), 166.1 (CO), 159.1 (CO), 136.2 (Ph), 134.4 (Ph), 133.5 (Ph), 133.3 (Ph), 131.5 (Ph), 130.2 (Ph), 129.9 (Ph), 129.7 (Ph), 129.5 (Ph), 129.3 (Ph), 129.1 (Ph), 128.59 (Ph), 128.52 (Ph), 128.4 (Ph), 128.3 (Ph), 127.9 (Ph), 127.7 (Ph), 126.9 (Ph), 114.2 (Ph), 73.2 (C5), 72.1 (C1), 66.8 (C4 and CH_2), 62.7 (C3 and CH_2), 56.9 (OCH_3), 55.3 (OCH_3), 52.4 (C2), 43.6 (CH_2); **IR (Nujol):** $\tilde{\nu}$ = 1720, 1689, 1635 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{37}H_{39}N_2O_9$: 655.2650 $[M+H]^+$; found: 655.2634.



51

Methyl-2-benzyloxycarbonylamino-3,6-di-*O*-benzoyl-2-deoxy-D-glucopyranoside (51)

A solution of compound **46** (7 mg, 1.2×10^{-2} mmol) in acetone (0.3 mL) and water (0.3 mL) was treated with K_2CO_3 (4 mg, 2.9×10^{-2} mmol). The reaction mixture was stirred at room temperature for 14 h and then quenched with 1N NaH_2PO_4 (0.5 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (2 ×). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel (eluent: 50 % ethyl acetate in hexane) gave **51** (5 mg, 80 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm): 8.04 (m, 4H, Ph), 7.58 (m, 2H, Ph), 7.44 (m, 4H, Ph), 7.20 (m, 5H, Ph), 5.32 (m, 1H, H1), 5.03 (q, *J* = 12.4 Hz, 2H, CH_2), 4.86 (br s, 1H, NH), 4.62 (m, 3H, H3 and CH_2), 4.23 (m, 1H, H4), 4.13 (q, *J* = 7.4 Hz, 1H, H2), 3.98 (t, *J* = 6.2 Hz, 1H, H5), 3.54 (s, 3H, OCH_3), 2.51 (br s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ(ppm): 166.4 (CO), 166.0 (CO), 156.1 (CO), 136.2 (Ph), 133.5 (Ph), 133.3 (Ph), 129.9 (Ph), 129.7 (Ph), 129.5 (Ph), 129.1 (Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 127.9 (Ph), 127.7 (Ph), 73.3 (C5), 72.1 (C1), 66.8 (C4 and CH_2), 62.7 (C3 and CH_2), 56.9 (OCH_3), 52.4 (C2); **IR (Nujol):** $\tilde{\nu}$ = 3294, 1722, 1685 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{29}H_{29}NO_9Na$: 558.1735 $[M+Na]^+$; found: 558.1760.

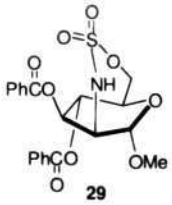
Preliminary efforts to couple the glycal substrates with an exogeneous nucleophile were encountered with the use of $PhI(OAc)_2$. Due to the *in situ* generation of a reactive acetate residue from $PhI(OAc)_2$, an excess amount of nucleophile was needed to suppress the attack of AcO^- (entries 1-2, Table 1). Consequently, the use of either PhIO or $[Rh_2(tfacam)_4]$ was examined (entries 3-6, Table 2). Not only could fewer equivalents of nucleophile be used, but also a higher yield as well as a shorter reaction time could be achieved.

Table 1 Optimized condition for aminoglycosylation of **26** and **37** [a]

Entry	Substrate	Catalyst	Oxidant	MeOH (equiv)	Time (h)	% Yield [b]
1	**26**	$Rh_2(OAc)_4$	$PhI(OAc)_2$	20	3.5	96
2	**37**	$Rh_2(OAc)_4$	$PhI(OAc)_2$	20	2	91
3	**26**	$Rh_2(OAc)_4$	PhIO	2	1	78
4	**37**	$Rh_2(OAc)_4$	PhIO	2	0.5	75
5	**26**	$Rh_2(tfacam)_4$	PhIO	2	2	93
6	**37**	$Rh_2(tfacam)_4$	PhIO	2	1	82

[a] Unless otherwise noted, the reaction was carried out at room temperature by using substrate (69 mmol), 5 mol% of rhodium catalyst, hypervalent iodine (1.5 equiv), MgO (5 equiv), and CH_2Cl_2 (3 mL) in the presence of 4 Å MS. [b] Isolated Yield.

Table 2 Crystal data and structure refinement for **29**



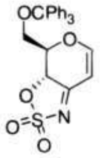
29

Empirical formula	$C_{21} H_{21} N O_9 S$	
Formula weight	463.45	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.2856(5) Å	α = 90°
	b = 10.3980(4) Å	β = 99.912(3)°
	c = 10.3520(5) Å	γ = 90°
Volume	1090.62(9) $Å^3$	
Z	2	
Density (calculated)	1.411 Mg/m^3	
Absorption coefficient	0.201 mm^{-1}	
F(000)	484	
Crystal size	0.25 x 0.15 x 0.10 mm^3	
The range for data collection	2.00 to 29.00°	
Index ranges	-13<=h<=14, -13<=k<=14, -14<=l<=14	
Reflections collected	10271	
Independent reflections	5138 [R(int) = 0.0369]	
Completeness to theta = 29.00°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9801 and 0.9514	

Table 2 Crystal data and structure refinement for **29** *(continued)*

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5138 / 44 / 367
Goodness-of-fit on F^2	1.157
Final R indices [I>2sigma(I)]	R1 = 0.0562, wR2 = 0.1498
R indices (all data)	R1 = 0.0640, wR2 = 0.1587
Absolute structure parameter	-0.04(11)
Largest diff. peak and hole	0.447 and -0.423 e.$Å^{-3}$

Table 3 Crystal data and structure refinement for compound **33**



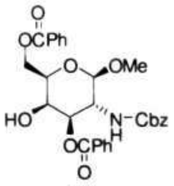
33

Empirical formula	$C_{26}H_{24}NO_{5.50}S$	
Formula weight	470.52	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 28.5943(12) Å	α = 90°
	b = 9.1264(4) Å	β = 90.748(2)°
	c = 9.5011(4) Å	γ = 90°
Volume	2479.22(18) $Å^3$	
Z	4	
Density (calculated)	1.261 Mg/m^3	
Absorption coefficient	0.168 mm^{-1}	
F(000)	988	
Crystal size	0.28 x 0.24 x 0.20 mm^3	
The range for data collection	2.14 to 27.15°	
Index ranges	-36<=h<=36, -11<=k<=11, -12<=l<=12	
Reflections collected	14828	
Independent reflections	5416 [R(int) = 0.0459]	
Completeness to theta = 27.15°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9671 and 0.9543	
Refinement method	Full-matrix least-squares on F^2	

Table 3 Crystal data and structure refinement for compound **33** *(continued)*

Data / restraints / parameters	5416 / 15 / 316
Goodness-of-fit on F^2	1.103
Final R indices [I>2sigma(I)]	R1 = 0.0700, wR2 = 0.2025
R indices (all data)	R1 = 0.0814, wR2 = 0.2216
Absolute structure parameter	0.02(12)
Largest diff. peak and hole	0.779 and -0.321 e. $Å^{-3}$

Table 4 Crystal data and structure refinement for compound **50**



50

Empirical formula	$C_{29}H_{28}NO_9 \cdot 0.5\ H_2O \cdot 0.25\ CH_3OH$	
Formula weight	548.55	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2	
Unit cell dimensions	a = 17.8848(7) Å	α= 90°
	b = 32.8391(13) Å	β= 90°
	c = 4.9429(2) Å	γ = 90°
Volume	2903.1(2) $Å^3$	
Z	4	
Density (calculated)	1.255 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	1157	
Crystal size	0.26 x 0.10 x 0.08 mm^3	
Theta range for data collection	1.68 to 29.00°	
Index ranges	-24<=h<=24, -44<=k<=44, -6<=l<=6	
Reflections collected	43151	
Independent reflections	7724 [R(int) = 0.0786]	
Completeness to theta = 29.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9925 and 0.9758	
Refinement method	Full-matrix least-squares on F^2	

Table 4 Crystal data and structure refinement for compound **50** (*continued*)

Data / restraints / parameters	7724 / 153 / 487
Goodness-of-fit on F^2	1.108
Final R indices [I>2sigma(I)]	R1 = 0.0693, wR2 = 0.1742
R indices (all data)	R1 = 0.1353, wR2 = 0.2449
Largest diff. peak and hole	0.616 and -0.386 e.Å^{-3}

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CHAPTER 2

Mechanistic insights into the substrate-controlled stereochemistry of glycals in one-pot rhodium-catalyzed aziridination and aziridine ring-opening

1. INTRODUCTION

Transition metal-catalyzed selective functionalization of alkenes is a fundamental process of paramount importance in organic synthesis.[1, 2] Significantly, the development of the metal-catalyzed aziridination by using nitrenes as a nitrogen source has become the most promising route for the synthesis of amines, and especially for the unique class of heterocyclic compounds.[3, 4] Since an intriguing report by Breslow and Gellman in the early 1980s,[5] considerable efforts in this area have been made to pursue the concept of metal-catalyzed *N*-atom transfer to double bonds in both inter- and intramolecular fashion.

Recent research has been undertaken largely by Che[6] and Du Bois.[7] Che's work has mainly been focused on intermolecular reactions, whereas Du Bois has contributed significantly to intramolecular reactions. Both have, however, reported success in the formation of aryliodinanes needed in the amination reactions as a one pot reaction. Du Bois and Espino also described the mechanism of C–H insertion of carbamates to form oxazolidinones.[8] The reaction mechanism shown in Figure 1 begins with the iodoimine **2** being formed from oxidation of the primary carbamate **1**. The iodoimine **2** then reacts with the dirhodium catalyst and decomposes generating the necessary metal-nitrenoid for amination to take place at the benzylic C–H site. This produces the favoured 5-membered heterocycle **4**. The dirhodium complex can now detach and react again. The carbamate reactions are found to form *syn* diastereoconfiguration and have preferences for the nitrogen atom insertion into benzylic sites over alkyl, with good regio- and stereocontrol. The preference for certain diastereoconfiguration and the retention of stereoconfiguration showed good proof of the reaction being controlled by an excited state nitrene intermediate.

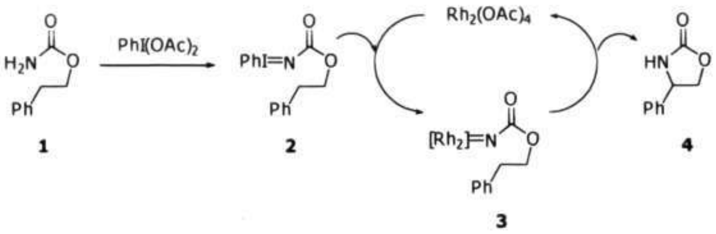
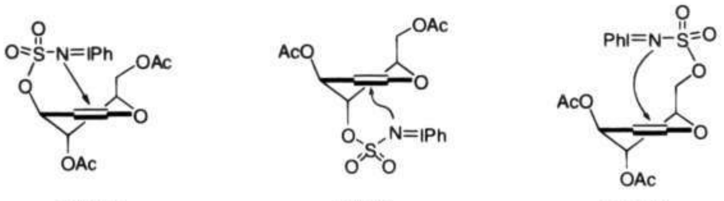


Figure 1 The reaction cycle of the formation of oxazolidinones from carbamate.

Du Bois investigated further the transformation of disubstituted carbamates into the corresponding oxazolidinones, which gave products with high stereoselectivity.[8] These results provide good support for the existence of the nitrene intermediate in the excited state as the reaction proceeded with stereocontrol, whereas a reaction involving a free tertiary radical would show no stereocontrol and, consequently, yield a mixture of enantiomers. Du Bois and co-workers were able to further prove that a nitrene intermediate existed in these reactions.

Due to the independent studies by Du Bois and Che *et al.*, the feasibility of dirhodium complexes in intramolecular aziridine formation with sulfamate esters as a nitrogen source greatly enhances the utility of iminoiodanes for organic synthesis. Especially, the value of this method has been applied for highly selective synthesis of aminoglycosides. Recently, we successfully synthesized 2-amino sugars with exclusive α– or β–selectivities.[9] Due to the presence of various stereogenic centers in the glycal scaffolds, the installation of a suitable nitrene precursor at different positions of the glycal allowed direct access to α– and β–aminosugars. In the course of our study, the sulfamate ester (–OSO_2NH_2) was a good tool for rhodium-catalyzed nitrene transfer into the C=C double bond of the glycal. Specifically, the diastereofacial preference of the nitrogen delivery on the sugar scaffold gave pure α– or β–aminoglycosylated products depending on the positions of the sulfamate ester moiety on the glycal.

Although there is increasing interest in understanding the mechanism of metal-assisted aziridination by experimental observation as well as computational study, the mechanistic detail remains inconclusive. Some aspects of the reaction mechanism based on copper or rhodium catalysts support a stepwise process via a radical intermediate.[10, 11] However, it has remained controversial for other systems.[12] For our unique substrate model shown in Figure 2, the mechanism of the rhodium-catalyzed aziridination was thoroughly studied using density functional theory (DFT). Results from DFT calculations would not only present a deeper understanding of the reaction mechanism, but also explain the stereospecificity of the nitrene transfer reactions. The different reactivities of all three substrates, **SM1(3)**, **SM1(4)**, and **SM1(6)**, in the catalytic system were investigated and compared with the experimental results. To be more reliable and realistic, the calculations are also explored with inclusion of solvent effects in the present work.



SM1(3) **SM1(4)** **SM1(6)**

Figure 2 Three model compounds for rhodium-catalyzed aziridination.

2. RESULTS AND DISCUSSION

In computational studies for nitrene chemistry, the overestimation of the energy difference between the singlet and triplet states of the nitrene species (E_{st}) when using the B3LYP functional has often been reported[13] Recently, Che and co-workers extensively investigated the effect of the functional and basis sets on the E_{st} values of rhodium–nitrene species.[14] After comparison with the more accurate CCSD(T) method, the BPW91 functional was found to be an economical and reliable method for the E_{st} prediction.[14] Therefore, the calculations reported herein were performed by using BPW91 together with two different combinations of mixed basis sets. The energy calculations were performed by using BSI for gas-phase calculations and BSII for solvent calculations by means of the polarizable continuum model (PCM)[15–17] in dichloromethane as the solvent. The LANL2DZ[18] basis for rhodium, and the LANL2DZ basis augmented with additional polarization functions for iodine,[19] are common to BSI and BSII. Harmonic frequency calculations were used to confirm all the stationary structures, whereas intrinsic reaction coordinate (IRC) calculations were used to confirm the transition-state structures.[20]

The rhodium-catalyzed aminoglycosylation discussed herein includes three relevant steps: the formation of a rhodium–nitrene intermediate, rhodium-catalyzed aziridination, and aziridine ring opening. For convenience, we have labeled each of the complexes along the reaction pathway, followed by the series number in parenthesis. The S and T in parentheses denote the closed-shell singlet and triplet states, respectively. The series number is given based on the position of the $-OSO_2NIPh$ group on the carbon skeleton of the sugar ring. $[Rh_2(OC(O)H)_4]$ was used to model the

$[Rh_2(OC(O)CH_3)_4]$ catalyst[14] and each protecting group on the sugar was represented with an acetyl group ($C(O)CH_3$).

It is known that the energies will change a bit when using modified ligand models to calculate instead of the real models. However, this is common when we have to deal with large complex systems. A recent report by Che clearly demonstrated that the calculated geometric parameters of the $[Rh_2(OC(O)H)_4]$ were similar to those of $[Rh_2(OC(O)CH_3)_4]$, which was obtained by X-rays. Since our complexes are quite large and we have three series of complex structures, this model rhodium complex would help to shorten the calculation time. Nevertheless, we had investigated the effect of using realistic and simplified ligands on the energy values and conformational changes. As expected, the Gibbs free-energy values are changed a little when using different ligand models. The $[Rh_2(OC(O)CH_3)_4]$ catalyst has lower energy values if comparing with using a $[Rh_2(OC(O)H)_4]$ as a model catalyst, but the energy differences between singlet and triplet nitrenes of those corresponding intermediates of all three series are almost equivalent. We then examined the bond distances of the intermediates. It was also found that the ligand of the catalyst did not affect the conformation or bond distance of these intermediates. Therefore, the mechanistic study of rhodium-catalyzed aziridination with ligand-modified rhodium catalyst has to rely on simplified model system because otherwise the calculations become exceedingly time-consuming (see more details in *Experimental Section*).

2.1 Formation of rhodium–nitrene complexes

We first describe the mechanistic pathway for the rhodium-catalyzed nitrene formation of **RhN(4)** in the singlet and triplet states. It is generally accepted that metal-bound nitrenes are involved in metal-catalyzed aziridination and even though those iodinane complexes are very nitrene-like, they are not reactive enough to attack the alkene before dissociation of PhI.[21] Espino and Du Bois[3a] and Müller *et al.*[10, 22] suggested that the direct binding of *N* and *Rh* atoms could occur in this process to give the reactive nitrene species without any transition states involved. As shown in Figure 2, the formation of an Rh_2–iodinane intermediate of series 4, denoted as **Ad1(4S)**, is energetically favored by a negative ΔG value (–9.6 kcal mol^{-1} at BPW91/BSI). The coordination of *Rh* and *N* atoms is associated with a weak interaction of the N–I bond, which is elongated from 2.134 to 2.809 Å. The decomposition of the IPh moiety from **Ad1(4S)** leads to singlet and triplet Rh_2–nitrenes with ΔG values of –13.4 and –23.1 kcal mol^{-1}, respectively. This indicates that the triplet nitrene is thermodynamically more stable due to the π back-bonding effect. The two singly occupied p orbitals of the N atom are degenerate and those of the triplet states are combined with Rh–Rh π* orbitals.[23] As a result, the N–Rh bond of **RhN(4T)** is slightly longer than that of **RhN(4S)**, which in turn effects a slight shortening of the Rh–Rh bond in **RhN(4T)**. The selected bond distances of complexes, **SM1(4S)**, **Ad1(4S)**, **RhN(4S)**, and **RhN(4T)**, were shown in Table 1.

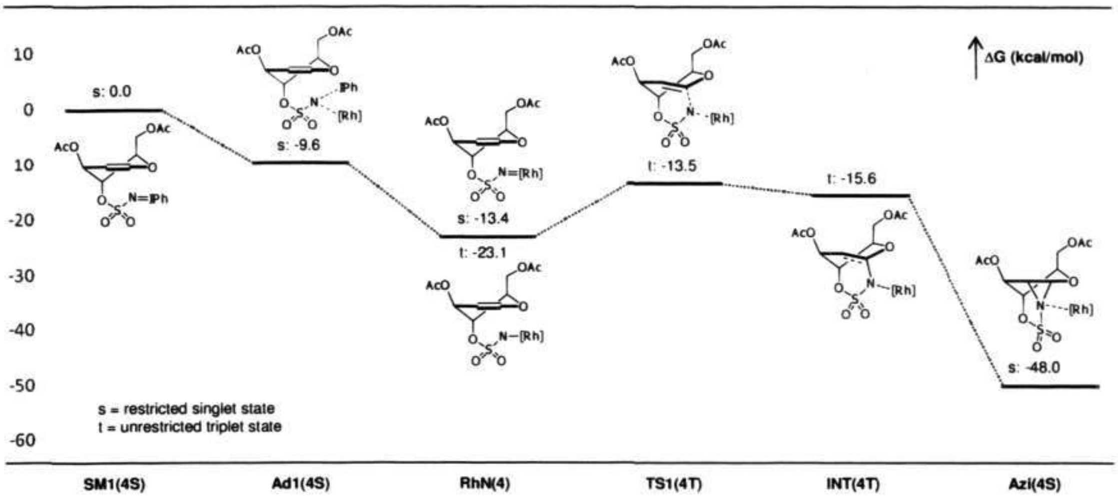


Figure 2 Computed Gibbs free energy profiles of the model system at BPW91/BSI level and 298 K. The substrate (**SM1**) in our model system was obtained by substituting the phenyl groups with methyl groups. The catalyst [$Rh_2(O_2CCH_3)_4$] was simplified by replacing the methyl groups with hydrogen atoms. **Ad1** = the adduct of SM1–[Rh_2]; RhN = rhodium-nitrene species; **TS1** = the transition state to form N-C1 bond; **INT** = the intermediate with a N–C1 bond in triplet state; **Azi** = catalyst-bound aziridine. The relative energy values (Δ*G*) are corresponding to substrate (**SM1**) and reported in kcal/mol.

Table 1 Selected bond distances (Å) for complexes of series 4 in the formation of rhodium-nitrene species.

Complex	O-C1	N-C1	N-C2	N-S	N-Rh	N-I	C1-C2
SM1(4S)	1.363	5.542	5.476	1.650	-	2.137	1.350
Ad1(4S)	1.359	5.713	5.569	1.668	1.979	2.793	1.351
RhN(4S)	1.360	4.509	4.988	1.663	1.929	-	1.352
RhN(4T)	1.362	4.691	4.003	1.657	1.952	-	1.351

2.1.1 The energy difference of singlet and triplet states of rhodium-nitrenes

It is well-documented that a common free nitrene or carbine is more stable in the triplet than in the singlet state. In light of their electronic and molecular structural differences, Cundari *et al.* recently revealed that the singlet and triplet states of copper nitrenes are the electronic ground state.[24a] Their DFT calculations indicated that a triplet ground state of copper nitrenes is a lower-energy excited state, whereas more expensive CASSCF methods indicated that a closed-shell singlet was the ground state, with only a small energy gap between singlet and triplet states. Similar to our results shown in Table 2, the free-energy differences between **RhN(4S)** and **RhN(4T)** are very small. Hence, we expect that the reaction pathway should proceed differently from closed-shell singlet and open-shell triplet states. This implies that a radical mechanism is involved.

Table 2 The free-energy difference ($\Delta\Delta G_{st}$) between singlet and triplet rhodium–nitrenes, **RhN(S)** and **RhN(T)**, in kcal mol^{-1}.

Method/basis set	$\Delta\Delta G_{st} = \Delta G_{RhN(4S)} - \Delta G_{RhN(4T)}$
BPW91/BSI	9.7
BPW91/BSII	7.8
BPW91/BSII//BPW91/BSI	8.8

Like glycal series 4, the *Rh*$_2$–nitrene active species of series 3 and 6 were generated by the rhodium-catalyzed elimination of the IPh moiety from iminoiodinanes (**SM1**). The rhodium catalyst binding to the nitrogen atom of the **Ad1(3S)** and **Ad1(6S)** complexes is energetically favorable and is further stabilized by departure of IPh moiety. The relative energy values for these transformations are shown in Table 3, entries 1-3. Comparison of their energy profiles showed a similar trend in forming **Ad1(S)**, **RhN(S)**, and **RhN(T)** (Table 3). Moreover, the triplet *Rh*$_2$–nitrenes are lower in energy than singlet ones and the ($\Delta\Delta G_{st}$ values become even smaller (0.3–3.1 kcal mol^{-1}, Table 3). The ΔG values of **Ad1(S)**, **RhN(S)**, and **RhN(T)** for all three series are relatively close to each other. This implies that the position of the nitrene moiety at the sugar ring does not effect these transformations due to a small difference in energy of each corresponding complex (0.8-3.8 kcal mol^{-1}).

Table 3 Gibbs free-energy values (ΔG)[a] for the formation of **Ad1(S)**, **RhN(S)**, and **RhN(T)** of the series 3, 4, and 6, in kcal mol^{-1}

Entry	Complex	BPW91/BSI		BPW91/BSII	
		series 3	series 6	series 3	series 6
1	Ad1(S)	-9.9	-11.2	-1.2	-0.3
2	RhN(S)	-26.2	-25.4	-9.2	-7.2
3	RhN(T)	-29.4	-25.6	-10.7	-9.1
4	$\Delta\Delta G_{st}$	3.1	0.3	0.6	1.1

[a] Relative to their corresponding substrates (**SM1(S)**)

2.2 Nitrogen insertion into the carbon-carbon double bond

To form the catalyst-bound aziridine, we proposed that the reaction mechanism could proceed in two different pathways. We attempted to search for transition states from both **RhN(S)** and **RhN(T)**.

On the triplet surface, the *N* atom of **RhN(4T)** carries a negative charge of –0.52 as calculated by Mulliken charge population analysis, whereas atoms *C1* and *C2* in the sugar ring carry a charge of +0.08 and –0.17, respectively. Thus, atom *C1* is electron deficient compared with atom *C2* due to its proximity to the electronegative *O* atom in the ring, making it more prone to intramolecular attack by the *N* atom. In **TS1(4T)**, the N–C1 bond (d = 2.023 Å) is much shorter than the distance between the *N* atom and the *C2* atom (d = 2.628 Å). A weak interaction between *N* and *C1* polarizes the double bond and leads to its elongation by 0.061 Å. This process has a moderately higher activation free energy of 9.6 kcal mol^{-1} with respect to that of **RhN(4T)** in the gas phase (Figure 2).

As **TS1(4T)** proceeds to **INT(4T)**, the N–C1 single bond is formed with a length of *d* = 1.491 Å and the *N* atom detaches from the *C2* atom with an N···C2 distance of 2.504 Å. The Δ*G* value of **INT(4T)** is higher than that of **RhN(4T)**. The barrier for the formation of **TS1(4T)** was calculated to be 8.2 kcal mol^{-1} by using BSI and insignificantly lower (7.8 kcal mol^{-1}) by using BSII, whereas the reverse barrier for **INT(4T)** to **TS1(4T)** was determined to be only 1.8 and 3.3 kcal mol^{-1} by using BSI and BSII, respectively. This indicates that the *N*-atom delivery step has a negative driving force on the triplet surface and led to the assumption that this species requires the intersystem crossing (ISC) process of the triplet excited state to the singlet ground state of the aziridine complex, denoted as **Azi(4S)**. The decay of nitrene species normally fall in the range of a few ns[25] and the triplet excited states of bicyclic alkenes, such as norbornene, have been experimentally observed to have a very short nonradiative lifetime of 250 ns.[26] In our case, the presence of the heavy atom *Rh* bonded to the *N* atom enhances the spin–orbit coupling and this accelerates the ISC process to the singlet ground state by several orders.[3] In practice, the intermediate in the transformation of **TS1(4T)** to **Azi(4S)** cannot be isolated, thus, we expect the reaction to proceed very fast.

2.2.1 The inter-system crossing process

Recently, Harvey and co-workers reported the DFT and ab initio CASSCF calculations of the potential energy crossing and of the spin–spin–orbit coupling for the treatment of surface crossing.[27] However, it should be noted that it is highly difficult to determine the intersection point by using the conical intersection method when dealing with the processes of large molecules.[28, 29] Herein, we used a simple approximation to estimate the crossing point involving the DFT calculations of the singlet and triplet potential energy surfaces. We believe that the reaction initially proceeds in the triplet ground state and that the ISC process occurs somewhere before or after the formation of the **INT** species. A detailed investigation of the optimized points through IRC calculations was carried out for all series. The single point calculations of the complexes at each point of the IRC calculations from **TS1** to **INT** were performed in the closed-shell singlet, open-shell singlet, and triplet states by using BSI basis.

For series 4: As depicted in Figure 3, the intersection point was located between the singlet diradical and triplet states. Investigation of the complex structure around the crossing point showed that the C1–C2, N–C1, and N–Rh distances are almost identical to the corresponding **TS1**. At this point, it is possible that the intermediate generated after the decay of the triplet **TS1** may convert to the **Azi** complex directly. Therefore, we attempted to locate the **INT** species on the unrestricted singlet wave function, but failed. The optimization of the singlet biradical **INT** always gave the **Azi(4S)**.

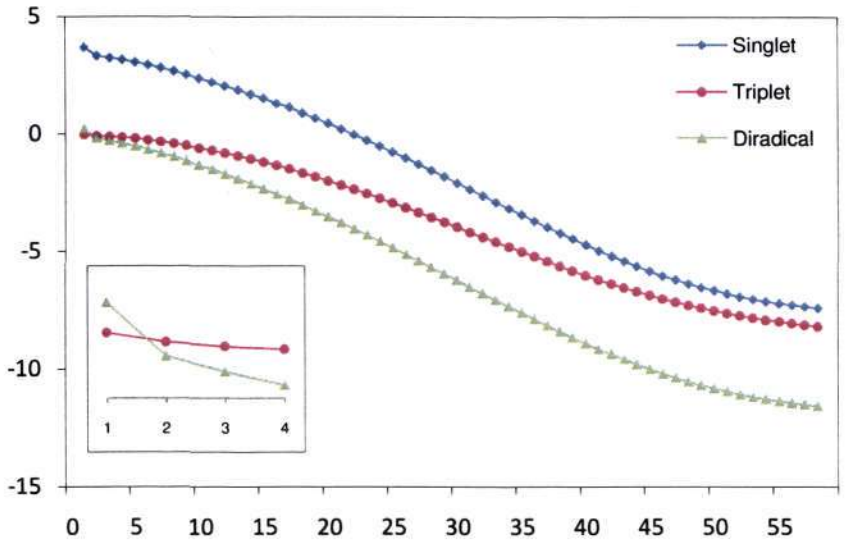


Figure 3 The single point calculations for singlet closed-shell, singlet diradical, and triplet electronic states along the triplet reaction path between **TS1(4T)** and **INT(4T)**.

For series 6: we also found a crossing point between the open-shell singlet and triplet states as plotted in Figure 4. The structural orientation of complexes around the crossing point was examined and found to be similar to **TS1(6T)** itself.

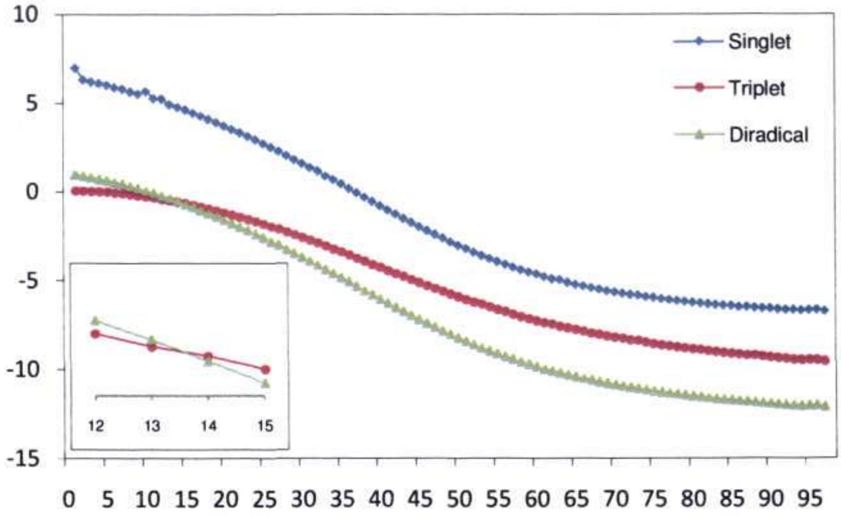


Figure 4 The single point calculations for singlet closed-shell, singlet diradical, and triplet electronic states along the triplet reaction path between **TS1(6T)** and **INT(6T)**.

For series 3: the reaction mechanism of the nitrene insertion to the carbon-carbon double bond for series 3 is likely to be different from the above cases. The intersection point could not be found on the potential energy surface for the conversion of **TS1(3T)** to **INT(3T)** (Figure 5). This indicates that the ISC process possibly occurs after the formation of the **INT** complex. Interestingly, we could locate a transition state on the unrestricted singlet surface at the step between **INT(3T)** and **Azi(3S)**. This diradical transition state is only 0.9 kcal mol^{-1} higher in energy than **INT(3T)** at BSI.

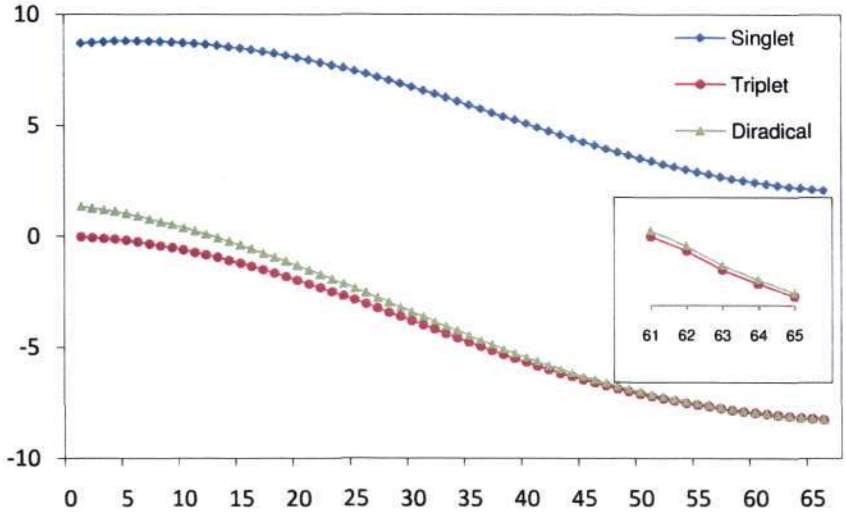


Figure 5 The single point calculations for singlet closed-shell, singlet diradical, and triplet electronic states along the triplet reaction path between **TS1(3T)** and **INT(3T)**.

In the PES calculations only the triplet excited state of **TS1** was located. It is not surprising because a large driving force was required for the reaction at the singlet closed-shell PES. Thus, we concluded that the reaction path for all glycal series preferably proceeds on the triplet surface from **RhN(T)** to **TS1(T)**. The **TS1(T)** of glycal series 4 and 6 undergoes aziridine ring closing in a single step along with or without the existence of a short-lived **INT** in the singlet diradical state, whereas the **TS1(T)** of series 3 occurs in a stepwise manner by forming the N–C1 single bond prior to the stable **Azi** complex.

Table 4 Gibbs free-energy values (ΔG)[a] for the formation of **TS1(S)**, **INT(T)**, and **Azi(S)** of the series 3, 4, and 6, in kcal mol^{-1}.

Entry	Complex	BPW91/BSI			BPW91/BSII		
		series 3	Series 4	Series 6	series 3	series 4	series 6
1	TS1(T)	-13.3	-13.5	-14.7	4.6	-1.6	2.7
2	INT(T)	-20.5	-15.6	-27.4	-4.8	-5.9	-12.1
3	Azi(S)	-62.9	-48.0	-50.9	-47.2	-39.4	-37.2
4	$\Delta\Delta G^b$	16.1	9.6	10.9	15.3	7.8	11.8

[a] Relative to their corresponding substrates (**SM1(S)**). [b] The energy difference between **RhN(T)** and **TS1(T)** reported in kcal mol^{-1}.

2.2.2 Relative reactivity of the nitrene insertion.

The PES computed by using BSI and BSII basis sets for the **TS1**, **INT**, and **Azi** complexes for all three series are presented in Table 4. As mentioned above, the position of the nitrene moiety on the substrate has no effect on the transformation from **SM1(S)** to **RhN(T)**, but a large change in energies was observed in the nitrene transfer step. The energy barriers for the formation of **TS1(T)** for all substrate series fall in the range of 7.8–16.1 kcal mol^{-1} as calculated by using BSI and BSII. The rate-determining step in this particular reaction is the transformation of **RhN(T)** to **TS1(T)**. As shown in Table 4, entry 4, the variation of ΔG within BSI and BSII for the formation of the **TS1** complex are in the order of series 4 < series 6 << series 3. These computational results are in well agreement with the experiments.[30] The reaction time for glycal series 3 was slower than that for series 4 and 6, respectively. The transition states and intermediates, as shown in Figure 6, were optimized at the BPW91/BSI level. We assume that the conformation changes from **TS1(T)** to **INT(T)** may affect the rate of the nitrogen insertion reaction. After the formation of the N–C1 bond in **INT(3T)**, the *C1*, *C2*, and *C3* atoms are part of a newly formed six-membered ring as well as the sugar ring. This makes the skeletal framework become rigid. To facilitate the attacking of the *N* atom to the *C1* atom, the *C3* atom is forced to move upward, causing a twist in the sugar ring that leads to a dramatically increased ring strain. In the case of **INT(6T)**, a new seven-membered ring is formed with a N–C1 bond length of $d = 1.494$ Å and the transition state, **TS1(6T)**, has less activation energy than **TS1(3T)**. This can be attributed to relaxation in the structure due to the presence of the elongated side chain, which causes less conformational changes in the sugar ring. However, there is repulsion between the sulfamate moiety and the substituent on the *C3* atom. In comparison to **TS1(3T)** and **TS1(6T)**, there is a large cavity on the bottom face of the sugar ring to facilitate the sulfamate moiety and the catalyst in **TS1(4T)** to attack the double bond without significant conformational changes in the skeletal framework. Therefore, **TS1(4T)** has the least structural strain among the three series, which is in turn reflected in the lowest barrier for *N* atom delivery.

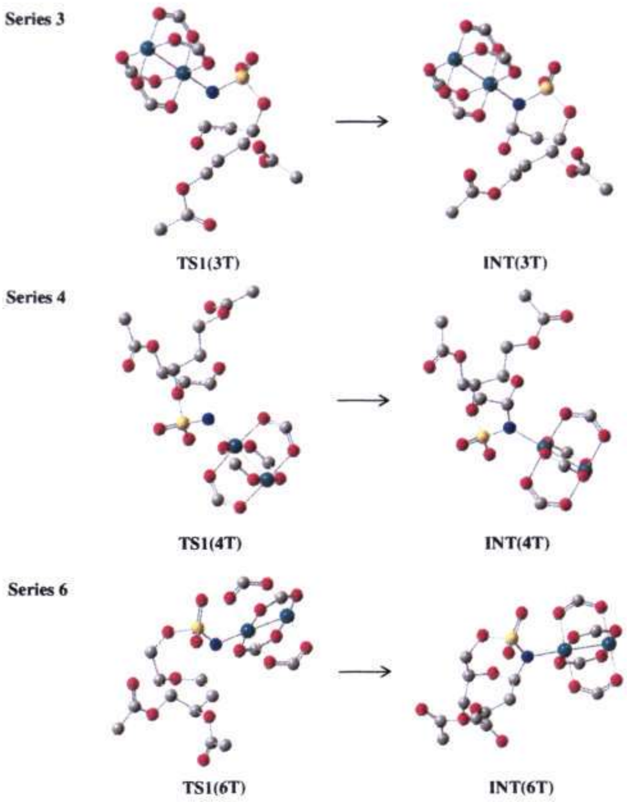
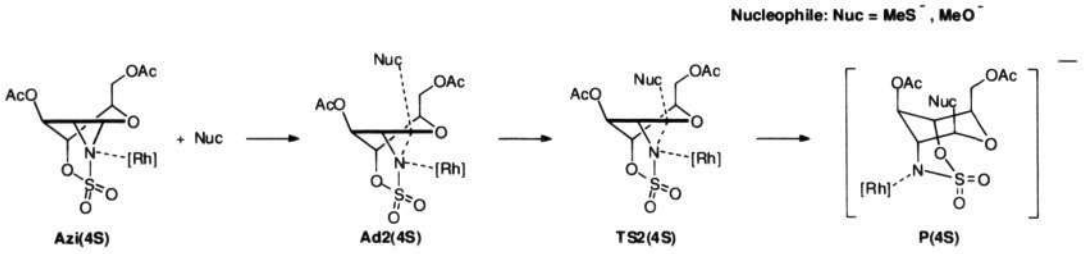


Figure 6 Optimized structures of transition states and intermediates at the BPW91/BSI level.

2.3 Aziridine ring opening by nucleophiles.

Series 4 was chosen as a model in this study to investigate the effect of anionic nucleophiles (MeS^-, MeO^-) in these experiments (Scheme 1. For this catalytic system, we assumed that the rhodium catalyst was still bound to the *N* atom of the aziridine ring while the ring opening reaction was taking place. Weak coordination of the *N* atom to the *Rh* atom in **Azi(4S)** would help to control the direction of the incoming nucleophile as well as to stabilize the product generated after the attack of the nucleophile. The reaction proceeds through a singlet surface. Prior to the attack of the nucleophile on the aziridine ring, a minimum energy structure of **Ad2(4S)** was located at a relative free energy (ΔG_{gas}) of –28.4 and –46.3 kcal mol^{-1} for MeS^- and MeO^-, respectively. We found that the attacking atom of the nucleophile is further away from the *C1* and *C2* atoms of the sugar ring in **Ad2(4S)** than in **TS2(4S)**. Investigating the **TS2(4S)** structure carefully, we noted that the sulfamate moiety and the rhodium catalyst completely block the bottom face of the sugar ring. Due to this arrangement, the nucleophile can only attack from the opposite face of the aziridine ring, which results in the facial preference. Moreover, the approaching nucleophile is closer to the *C1* atom than the *C2* atom in **TS2(4S)**. The nucleophile is more likely to form a single bond with the *C1* atom than with the *C2* atom because the *C1* atom carries a more positive charge due to the neighboring oxygen atom (for selected bond lengths, see in *Experimental Section*). The corresponding IRC calculations show concomitant formation of a new bond between the nucleophile and *C1* and the cleavage of the N–C1 bond. At this point, we can clearly conclude that nucleophilic addition to aziridine proceeds regio- and stereoselectively in one step, leading to the formation of 2-amino sugars.



Scheme 1 Reaction mechanism for aziridine ring opening in series 4 predicted by using different nucleophiles (Nuc = MeS^{-1}, MeO^{-1}).

The PES calculations of the different nucleophiles showed that ring opening is a fairly easy process with an excitation energy of only 2–3 kcal mol^{-1} in the gas phase

(Table 5). However, the low barrier vanished in the solvent calculations (BSII). Thus, we suggest that the rate-determining step should not lie in this process.

Table 5 Gibbs free energy values (ΔG)[a] in gas and solution phases for aziridine ring-opening reaction

Complex	BPW91/BSI		BPW91/BSII	
	MeS⁻	**MeO⁻**	**MeS⁻**	**MeO⁻**
Ad2(4S)	-28.4	-46.3	3.8	-9.0
TS2(4S)	-26.0	-43.1	3.3	-9.4
P(4S)	-59.0	-91.1	-37.4	-60.8

[a] Relative to the substrate, **SM2(4S)**.

3. CONCLUSION

We carried out the principles study on the reaction mechanism for rhodium-catalyzed intramolecular aziridination and aziridine ring-opening on a sugar template. A sulfamate ester group was introduced on the different positions of glycal to act as a nitrene source and, moreover, to study the relative reactivity of nitrene-transfers from different sites of the glycal molecule. The full optimization of each intermediate along the reaction pathway has been extensively made by using BPW91 functional. The crucial step is the *Rh*-catalyzed nitrene transfer to the double bond of glycal. Our investigation showed that such a reaction initially proceeds in the triplet ground state. An intersection point between the singlet and triplet states was determined along the reaction coordinate. The intersection point geometry of ISC process in the rhodium-catalyzed aziridination reaction was obtained by using DFT calculations thus indicating the existence of a reaction branch via the **TS1(T)**. The reaction can proceed from the pure triplet state PES to give a triplet **INT** and then yield the singlet state of aziridine complex by the decay of triplet to singlet opened-shell state. Alternatively, the appearance of early intersection between the triplet and singlet diradical state could lead to the aziridine in a single step manner along with or without the existence of a short-lived **INT** in the singlet diradical state. Our calculations also confirmed the experimental findings of radical character for the rhodium-catalyzed reaction in the triplet state.

Reaction of aziridine ring-opening is a spontaneous process because the energy barrier for formation of the transition state is very small and disappears in the solution calculations. The regio- and stereoselectivity of the reaction product is controlled by the electronic property of the anomeric carbon as well as the facial preference of nitrene insertion and nucleophilic addition. Our calculations indicate that the rate determining step is in line with the delivery step of the nitrene into the carbon-carbon bond. The relative reactivity of forming nitrene species toward aziridine resulting in the computed potential energy surface (PES) agrees well with the reaction time from experimental observation. Good agreement between the computed potential energy surface and the observed experimental reaction time for three series resolved the longstanding issue of the mechanism for the rhodium-catalyzed aziridination of the C=C bond.

4. EXPERIMENTAL

All DFT calculations were carried out by using the Gaussian 03 package and the BPW91 functional.[31] Effective core potential (ECP) with double-zeta valence basis (LANL2DZ)[18] was used for rhodium, whereas LANL2DZ basis augmented with an additional p and d polarization function, with exponents 0.00308 and 0.29400, respectively, was used for iodine.[19] The standard 6-31G(d) basis set was used for *H*, *C*, *N*, *O*, and *S* atoms. This combination of basis sets is denoted as BSI. The gas phase calculations for the complexes involved in the azridination reaction for series 3, 4, and 6, including their optimizations, were carried out by using BSI. For diradical complexes, unrestricted DFT calculations with the keyword "guess=mix" in the Gaussian 03 package were used with the initial orbital guess in the triplet state. In case of singlet diradical calculations, we found that the $<S^2>$ values after annihilation were less than 0.1, indicating negligible spin contamination.

The polarized continuum model (PCM) was used to study the solvent effects.[15–17] In BSII we replaced the 6-31G(d) basis for *H*, *C*, *N*, *O*, and *S* atoms by 6-311++G(d, p). The BSII was used for all calculations with solvent effects. Since re-optimizations using BSII are expensive, only single-point calculations were performed for structures optimized at a lower basis set for the above cases. Calculations including solvent effects were done for dichloromethane with a dielectric constant of e = 8.93 Fm^{-1} at 298 K.

We confirmed all stationary structures to be a true minimum or saddle point by harmonic frequency calculations. The transition states were further confirmed by intrinsic reaction coordinate (IRC) calculations,[20] where they were shown to connect the relevant reactants to their products.

4.1 Selected bond distances

The selected bond lengths of complexes involved in aziridination reaction for glycals series 3 and 6 are shown in Tables 1-2. The calculations were optimised at the BPW91 level using BSI basis set. These variations in bond length in addition to chemical intuition supplement in understanding the reaction mechanism based on the relative energies of the complexes involved in the reaction pathway.

Table 1 Select bond distances (Å) for complexes of **series 3** in the formation of aziridine

Complex[a]	**O-C1**	**N-C1**	**N-C2**	**N-S**	**N-Rh**	**N-I**	**C1-C2**
SM(3S)	1.368	5.954	4.753	1.650	-	2.134	1.346
Ad1(3S)	1.361	5.936	4.745	1.656	2.198	2.105	1.336
RhN(3S)	1.362	4.863	3.517	1.665	1.930	-	1.350
RhN(3T)	1.363	4.856	3.516	1.653	1.957	-	1.349
TS1(3T)	1.346	2.027	2.562	1.684	2.011	-	1.416
INT(3T)	1.430	1.508	2.438	1.710	2.064	-	1.487
Azi(3S)	1.381	1.506	1.480	1.787	2.262	-	1.494

Table 2 Select bond distances (Å) for complexes of series 6 in the formation of aziridine

Complex[a]	O-C1	N-C1	N-C2	N-S	N-Rh	N-I	C1-C2
SM(6S)	1.363	6.264	6.781	1.663	-	2.146	1.349
Ad1(6S)	1.364	7.069	7.265	1.679	1.986	2.694	1.349
RhN(6S)	1.361	3.341	4.217	1.666	1.933	-	1.352
RhN(6T)	1.363	4.690	5.295	1.660	1.951	-	1.350
TS1(6T)	1.353	2.089	2.709	1.666	2.005	-	1.403
INT(6T)	1.424	1.494	2.498	1.701	2.059	-	1.497
Azi(6S)	1.382	1.503	1.512	1.773	2.351	-	1.501

Table 3 Select bond distances (Å) for complexes in the aziridine ring-opening by nucleophiles

Bond Type[a]	**Complex with $^-$OMe**			**Complex with $^-$SMe**		
	Ad2(4S)	**TS2(4S)**	**P(4S)**	**Ad2(4S)**	**TS2(4S)**	**P(4S)**
O-C1	1.370	1.368	1.428	1.371	1.342	1.415
N-C1	1.554	1.554	2.431	1.556	1.746	2.426
N-C2	1.521	1.517	1.480	1.514	1.507	1.479
N-S	1.753	1.752	1.637	1.751	1.724	1.638
N-Rh	2.313	2.321	2.194	2.306	2.258	2.195
C1-C2	1.489	1.490	1.540	1.489	1.477	1.554
Nuc-C1	3.457	3.600	1.431	3.841	3.325	1.895
Nuc-C2	3.240	3.462	2.429	3.663	3.464	2.864

[a] *O*, *C1* and *C2* Atoms belong to the sugar ring. Nuc refers to the attacking atom of the nucleophile (Nuc = *O* for methoxide anion and *S* for methylthiolate anion)

4.2 Comparison of Gibbs free-energy values when using $Rh_2(O_2CCH_3)_4$ and $Rh_2(O_2CH)_4$ as model catalysts

We selected the singlet and triplet states of rhodium-nitrene species to investigate the effect of using relistic and simplified ligands on the energy values and conformational changes. As seen in Table 4 that the Gibbs free-energy values are a bit change when using different ligand models. The $Rh_2(O_2CCH_3)_4$ catalyst has lower energy values if comparing with using a $Rh_2(O_2CH)_4$ as a model catalyst, but the energy difference between singlet and triplet nitrenes of those corresponding intermedites are almost the same. We then examined the bond distance of each intermedites as shown in Table 5. It was also found that the ligand of catalyst do not effect the conformation or bond distance of these intermediates. Therefore, the mechanistic study of rhodium-catalyzed aziridination with ligand-modified rhodium catalyst has to rely on simplfied model system because otherwise the calculations become exceedingly time-consuming.

Table 4 Gibbs free-energy values when using $Rh_2(O_2CCH_3)_4$ and $Rh_2(O_2CH)_4$ as model catalysts

Complex	**ΔG_{gas} from $Rh_2(O_2CCH_3)_4$**			**ΔG_{gas} from $Rh_2(O_2CH)_4$**		
	Series 3	**Series 4**	**Series 6**	**Series 3**	**Series 4**	**Series 6**
RhN(S)	-30.48	-20.20	-30.21	-26.23	-13.45	-25.40
RhN(T)	-32.74	-29.94	-30.48	-29.37	-23.11	-25.66
G_{st} = $G_{RhN(S)}$-$G_{RhN(T)}$	2.26	9.73	0.27	3.14	9.66	0.26

Table 5 Bond distance when using $Rh_2(O_2CCH_3)_4$ and $Rh_2(O_2CH)_4$ as model catalysts

Complex	**Bond lenght from $Rh_2(O_2CCH_3)_4$**			**Bond lenght from $Rh_2(O_2CH)_4$**		
	N-S	**N-Rh**	**Rh-Rh**	**N-S**	**N-Rh**	**Rh-Rh**
RhN(3S)	1.664	1.930	2.431	1.665	1.930	2.446
RhN(3T)	1.650	1.956	2.420	1.653	1.957	2.437
RhN(4S)	1.660	1.930	2.426	1.663	1.929	2.441
RhN(4T)	1.647	1.953	2.416	1.657	1.952	2.433
RhN(6S)	1.665	1.929	2.429	1.666	1.933	2.445
RhN(6T)	1.654	1.954	2.417	1.660	1.951	2.432

4.3 Comparison of relative energy values obtained by BPW91 and B3LYP

In our initial work, we studied the reaction mechanism of rhodium-catalyzed aziridination by using B3LYP functional. As mentioned in the main text that the overestimation of energy difference between singlet and triplet nitrenes was often observed when using B3LYP. Here, we encountered the same problem and showed those results by comparing with more reliable functional, BPW91.

Results in Table 6 show that the relative energy values obtained by B3LYP for all three series have a similar trend in forming rhodium-nitrene species. Therefore, this confirms that the position of the nitrene moiety does not effect the transformation from **SM1(S)** to **RhN(T)**. On the other hand, the energy difference between two nitrenes species falls in the range of 9.1-14.1 kcal/mol at B3LYP/6-31G*, which is larger than that at BPW91/6-31G*

Table 6 Comparison of Gibbs free-energy values (ΔG) for rhodium-catalyzed aziridination using different functionals (BPW91 and B3LYP)

Complex	ΔG_{gas} from BPW91/6-31G*			ΔG_{gas} from B3LYP /6-31G*		
	Series 3	Series 4	Series 6	Series 3	Series 4	Series 6
SM1(S)	0.0	0.0	0.0	0.0	0.0	0.0
Ad1(S)	-9.9	-9.6	-11.2	-20.9	-22.4	-20.7
RhN(S)	-26.2	-13.4	-25.4	-7.7	-2.4	-9.2
RhN(T)	-29.3	-23.1	-25.6	-16.9	-16.5	-18.3
TS1(T)	-13.3	-13.4	-14.7	-5.2	-11.2	-11.0
INTT(T)	-20.4	-15.5	-27.3	-16.0	-12.2	-23.1
Azi(S)	-62.8	-47.9	-50.8	-64.7	-55.0	-58.8

Table 7 Cartesian coordinates of the stationary-points involved in the aziridination reaction of series 3

SM1(3S)

C	-2.10120100	-0.42087700	0.13940500	H	0.16456900	2.04088800	2.51160500
C	-1.46289300	-1.74192700	0.61334600	C	-4.30266800	0.72105000	-0.44330700
C	-2.19359300	-2.92017300	0.03311500	H	-4.07182200	0.88566500	-1.50836700
C	-3.63791600	-0.55183200	0.05964800	H	-3.95703500	1.59378900	0.12874000
O	-4.02410800	-1.61571500	-0.83837500	O	-5.73111900	0.56449500	-0.27339700
H	-3.84849600	-3.61471700	-1.16025400	C	-6.46460600	1.69499200	-0.51294900
H	-1.72860800	-3.90120100	0.13841900	O	-5.97199400	2.76416500	-0.83677900
O	-0.08239600	-1.81955400	0.12735500	C	-7.94211500	1.41286300	-0.32734300
S	1.14078500	-1.69994000	1.29851800	H	-8.13034200	0.95936800	0.65818300
O	0.97983500	-2.82602200	2.24859100	H	-8.50660700	2.34833300	-0.42552500
O	1.10044700	-0.30938900	1.81602000	H	-8.28612300	0.69389200	-1.08843000
H	-1.67712800	-0.13812300	-0.83654300	I	2.90917900	-0.81444200	-1.17404600
H	-4.02793800	-0.79990100	1.06592900	C	3.86071900	1.01421900	-0.46046700
H	-1.45224200	-1.76649900	1.71777700	C	3.04405900	2.12414300	-0.21762300
N	2.47848400	-2.14458600	0.43922000	C	5.24673600	1.02146200	-0.26500400
C	-3.33838800	-2.78644400	-0.66226200	C	3.66772300	3.30744000	0.21244300
O	-1.81670600	0.62027300	1.10465300	H	1.96057000	2.07907200	-0.35488400
C	-0.93006500	1.60481600	0.74653600	C	5.84394900	2.21574100	0.16776900
O	-0.44192000	1.71709900	-0.36874800	H	5.85049900	0.12973000	-0.44400100
C	-0.65071000	2.50088100	1.93037600	C	5.05679200	3.35358200	0.40363900
H	-0.33125200	3.49098900	1.57926400	H	3.05588800	4.19350200	0.40196300
H	-1.52834000	2.59040000	2.58584100	H	6.92568200	2.24942600	0.32300700

H	5.52903900	4.27954100	0.74241900

Ad1(3S)

Rh	4.55660700	-1.71247600	-0.18098500
Rh	2.46931800	-0.50303600	0.16945100
O	5.46567300	0.12156000	-0.53436100
O	4.03003200	-1.84732000	-2.19694300
O	3.53436700	-3.47083000	0.19787200
O	4.94526400	-1.50647800	1.83559600
O	3.51413500	1.26237900	-0.23912700
O	2.07578400	-0.72484900	-1.86482700
O	1.57680000	-2.34399700	0.51829500
C	2.93882400	-1.34011700	-2.56878200
C	4.75656800	1.16309900	-0.48274000
O	3.00878600	-0.34588400	2.16093200
C	4.09542800	-0.87752800	2.53229400
C	2.30012100	-3.38252500	0.45711600
H	5.27935800	2.11213300	-0.67519900
H	2.69482700	-1.43766100	-3.63704800
H	1.78168300	-4.33208700	0.65526900
H	4.32998000	-0.77682200	3.60171300
C	-3.90852800	-0.76718100	0.17297200
C	-2.63355200	-1.40497900	0.74389300
C	-2.48448800	-2.81464100	0.25452000
C	-5.05700500	-1.79214500	0.17027800
O	-4.71225400	-2.94067100	-0.61560600
H	-3.36930700	-4.44303700	-0.81264700
H	-1.52148200	-3.29017200	0.39914100
O	-1.46158500	-0.67535300	0.26928600
S	-0.66993900	0.30759200	1.34160900
O	-0.19966300	-0.48798800	2.46744000
O	-1.54017300	1.46204600	1.59262700
H	-3.71251900	-0.40171300	-0.83809300
H	-5.23788300	-2.12585200	1.20237500
H	-2.65480000	-1.35175900	1.83886400
N	0.66943500	0.72469500	0.46077500
C	-3.46730000	-3.44647100	-0.39401000
O	-4.31770600	0.32681100	1.01054600
C	-4.19140300	1.59870500	0.54157400
O	-3.83880300	1.87398900	-0.58544900
C	-4.54488100	2.58935700	1.61946600
H	-4.82045300	3.54317900	1.16595800
H	-5.35618600	2.21815500	2.25037100
H	-3.65757900	2.72606100	2.24669800
C	-6.34064800	-1.22211700	-0.40359600
H	-6.23936600	-1.04637200	-1.47931700
H	-6.59378400	-0.27739800	0.08203000
O	-7.38277300	-2.18175400	-0.16338600
C	-8.63176200	-1.78520300	-0.51194900

O	-8.87644300	-0.69828500	-0.98635700
C	-9.63809200	-2.87549800	-0.22969000
H	-9.57936100	-3.18570500	0.81848100
H	-10.64049000	-2.51127200	-0.45700000
H	-9.41630600	-3.75537100	-0.84313400
I	0.17368800	1.80453200	-1.27777600
C	-0.02648400	3.76663000	-0.45905400
C	-1.30765600	4.29111700	-0.30445000
C	1.13336200	4.44532500	-0.09068400
C	-1.41674200	5.58233400	0.21919400
H	-2.18933100	3.71353000	-0.56536900
C	0.99453100	5.72881800	0.44092300
H	2.10964600	3.98429900	-0.19869800
C	-0.27422900	6.29549800	0.58845700
H	-2.40136600	6.02260600	0.34755800
H	1.88026000	6.28115900	0.74086800
H	-0.37254200	7.29573400	1.00050600

RhN(3S)

Rh	4.76110900	-0.34178700	0.12273500
Rh	2.32422100	-0.13224400	0.10771800
O	4.55008700	-2.36905200	-0.20654900
O	4.69810600	-0.67267100	2.15373800
O	4.87762800	1.70288600	0.44306800
O	4.78122900	-0.00438800	-1.90780000
O	2.25164100	-2.20808400	-0.22229900
O	2.40808000	-0.49044100	2.16488100
O	2.58329800	1.89266100	0.46501700
C	3.55009700	-0.67899100	2.70654100
C	3.36533100	-2.83106600	-0.29720800
O	2.49298900	0.20037300	-1.93528200
C	3.65506700	0.19757600	-2.46840600
C	3.78000400	2.34145700	0.53781400
H	3.28226800	-3.92119100	-0.46417900
H	3.52832400	-0.87009700	3.79474900
H	3.85611000	3.43068200	0.70813900
H	3.67072600	0.39543600	-3.55510000
C	-4.05087600	0.22240000	-0.43588200
C	-2.62576200	-0.34532700	-0.31376600
C	-2.56180600	-1.73070500	-0.88103000
C	-5.07682200	-0.86820800	-0.05289300
O	-4.95546500	-2.01353800	-0.93235000
H	-3.67340300	-3.41422700	-1.64421400
H	-1.57836600	-2.14808400	-1.10022500
O	-1.74588300	0.52181600	-1.10991400
S	-0.45964700	1.25453200	-0.33122100
O	-0.92474700	1.81813100	0.96549800
O	0.09658300	2.12766100	-1.37401800
H	-4.22905700	0.57489200	-1.46430300

H	-4.87199400	-1.21622600	0.97748700	C	-6.51297000	-0.37611900	-0.14795900
H	-2.30180800	-0.29370600	0.73953000	H	-6.78988100	-0.17618900	-1.19558700
N	0.39378500	-0.10430900	0.11373100	H	-6.64379800	0.54975000	0.42988200
C	-3.68000500	-2.42780700	-1.17457200	O	-7.36303300	-1.41292900	0.39350000
O	-4.17999200	1.32823200	0.47586100	C	-8.65934800	-1.03076200	0.62537100
C	-4.46059300	2.56862000	-0.08001300	O	-9.07836200	0.09548000	0.41442300
O	-4.72666200	2.73729800	-1.25512700	C	-9.46230400	-2.19761400	1.16283900
C	-4.36828300	3.63317400	0.98720000	H	-8.97836200	-2.62202300	2.05631600
H	-4.73657700	4.58578900	0.58742600	H	-10.47571300	-1.85858500	1.41019700
H	-4.94447900	3.34471600	1.87956400	H	-9.51458700	-2.99898600	0.4084270
H	-3.31578300	3.73984800	1.29549800				

RhN(3T)

Rh	4.84719500	-0.28377100	0.16591600	C	3.75963500	2.33241400	0.56546500
Rh	2.41669000	-0.20596300	0.00326200	H	3.57076100	-3.91790900	-0.58075800
O	4.73784600	-2.30906500	-0.19852700	H	3.39764500	-0.90123200	3.75257500
O	4.65740100	-0.63951400	2.19196500	H	3.77453100	3.41908100	0.76439800
O	4.89162600	1.74706800	0.52239100	H	3.94691500	0.41113300	-3.57528200
O	4.97575300	0.07115400	-1.86656700	C	-4.15125600	0.25473000	-0.34149200
O	2.44806700	-2.25506200	-0.36758000	C	-2.71614100	-0.26078800	-0.14958300
O	2.35950400	-0.58521900	2.05597600	C	-2.58781300	-1.66930900	-0.64570000
O	2.59636000	1.82791900	0.40934900	C	-5.16141600	-0.84791900	0.04612700
C	3.47613700	-0.70823700	2.66688900	O	-4.96893700	-2.03142100	-0.76794100
C	3.58977100	-2.83094600	-0.38284400	H	-3.61866700	-3.42056600	-1.36696700
O	2.68006500	0.15618800	-2.03306300	H	-1.58534000	-2.06448100	-0.81549000
C	3.87242000	0.21309000	-2.49039400	O	-1.84379300	0.60653400	-0.96032700

S	-0.52236900	1.30369500	-0.22446500	H	-5.24129300	3.42602400	1.83444400
O	-0.89008500	1.69801900	1.15482700	H	-3.61614500	3.86229500	1.27214500
O	-0.07634300	2.30423000	-1.20600800	C	-6.60570800	-0.40776000	-0.14247600
H	-4.30425800	0.56510900	-1.38748300	H	-6.83619700	-0.26561400	-1.21034500
H	-4.99643800	-1.13929300	1.10123000	H	-6.79423000	0.54020000	0.38214100
H	-2.42695600	-0.13755000	0.90796000	O	-7.44644200	-1.44650900	0.40956400
N	0.47491200	-0.01306300	-0.15538700	C	-8.78372600	-1.14819500	0.43376000
C	-3.67256100	-2.41398700	-0.94506100	O	-9.24445100	-0.08826400	0.04239600
O	-4.33815300	1.39176000	0.52459200	C	-9.57180100	-2.31212100	0.99999700
C	-4.68650200	2.58904100	-0.08043300	H	-9.20547700	-2.57317900	2.00542600
O	-4.96487600	2.69599500	-1.26024500	H	-10.63417200	-2.04309900	1.04769400
C	-4.65543400	3.70016100	0.94350900	H	-9.44229700	-3.20256200	0.36415800
H	-5.05167400	4.62039300	0.49729200				

TS1(3S)

Rh	3.41472400	1.06048900	0.59056900	O	1.34085200	-0.97117600	1.73491800
Rh	1.42171400	-0.13105300	-0.15944300	C	2.24786700	-0.65597500	2.57763300
O	2.19951300	2.59859700	1.24438300	C	3.97177500	-1.48088400	-0.61600800
O	3.53315000	1.94921800	-1.27677100	H	0.31207800	3.29073700	1.45369600
O	4.58475100	-0.50191000	-0.07541500	H	2.72349300	2.13383800	-3.11896900
O	3.23468600	0.13931400	2.42968200	H	4.60085200	-2.31769100	-0.97034300
O	0.30770600	1.47926000	0.56834400	H	2.15586300	-1.14204900	3.56593600
O	1.64769700	0.84450400	-2.00195500	C	-3.13862700	-1.00426700	0.06797900
O	2.71757700	-1.62827400	-0.80884900	C	-2.86010800	-2.06271100	-1.02961500
C	2.63868000	1.64478000	-2.13049600	C	-2.27586100	-1.45215600	-2.26459500
C	0.94303300	2.45855400	1.09056000	C	-3.24573500	0.40263200	-0.55360400

O	-2.00870500	0.71402000	-1.26595500
H	-0.80025600	0.10980900	-2.77059200
H	-2.03196000	-2.10149400	-3.10529800
O	-1.93672000	-3.08031900	-0.50431800
S	-0.27292100	-2.84687700	-0.80980500
O	0.01559500	-3.38888500	-2.15610400
O	0.36876200	-3.43035900	0.37469100
H	-2.33510900	-1.01589100	0.81903700
H	-4.06884900	0.41865300	-1.29104600
H	-3.78443300	-2.62617400	-1.23279000
N	-0.15790500	-1.16651300	-0.85117500
C	-1.52632800	-0.26969200	-2.04886400
O	-4.38652900	-1.36553200	0.70437700
C	-4.41953700	-1.29293000	2.08394800
O	-3.50533300	-0.85579400	2.76060000

C	-5.73490500	-1.83331300	2.59767500
H	-5.82179000	-1.61996400	3.67013800
H	-6.57947600	-1.38854000	2.04978200
H	-5.77516500	-2.92325100	2.43837100
C	-3.44187700	1.51522600	0.47209300
H	-2.55818100	1.59476200	1.11701900
H	-4.34085100	1.31203900	1.06886700
O	-3.57281600	2.80544500	-0.17095700
C	-4.84183300	3.14209700	-0.57072500
O	-5.81430300	2.41725100	-0.42612400
C	-4.84404100	4.51877400	-1.20128700
H	-4.17952800	4.53578300	-2.07979400
H	-5.86568900	4.78022100	-1.50288700
H	-4.46069500	5.26652600	-0.489216

INT(3T)

Rh	3.33376700	0.70619200	0.52612700
Rh	1.21703200	-0.31770900	-0.09107100
O	3.63561600	1.20001800	-1.46044200
O	4.28268800	-1.10145400	0.22387100
O	2.96621600	0.18331400	2.48642600
O	0.33074000	1.50862300	0.32276100
O	1.61139900	0.28538200	-2.05434000
O	2.30543300	-2.06204700	-0.44666600
C	2.71511800	0.89044600	-2.28436500

C	1.07803300	2.48777500	0.67020500
O	0.96992400	-0.80135700	1.90708600
C	1.88232000	-0.44726700	2.72738500
C	3.55702200	-2.06339500	-0.19709600
H	0.54508500	3.43648600	0.85396500
H	2.88645100	1.17777800	-3.33817700
H	4.07261400	-3.02490100	-0.37298300
H	1.70226700	-0.72531100	3.78138500
C	-3.41215700	-0.70599500	-0.04719900

C	-3.18584900	-1.95770500	-0.94985800	C	-5.06220500	-0.62880300	1.71302900
C	-2.44576100	-1.58746300	-2.18634500	O	-4.20570700	-0.44292900	2.55821600
C	-3.13271100	0.60696100	-0.81834900	C	-6.54347600	-0.80601400	1.96675700
O	-1.83659400	0.61154400	-1.46491300	H	-6.76844700	-0.54457800	3.00806500
H	-0.64448800	-0.45349200	-2.71403100	H	-7.13756200	-0.18548100	1.27898700
H	-2.57008600	-2.09258800	-3.14215300	H	-6.82504100	-1.85690400	1.78837000
O	-2.40750800	-2.95822200	-0.17398600	C	-3.16446500	1.82903700	0.09602200
S	-0.74982100	-2.91052300	-0.48095400	H	-2.25372700	1.88452300	0.70656400
O	-0.49370300	-3.64524000	-1.73853200	H	-4.04906900	1.80269200	0.74986800
O	-0.13006900	-3.32580500	0.77641800	O	-3.27405000	3.01273300	-0.73574500
H	-2.78138600	-0.77468300	0.85146700	C	-2.49478600	4.08373000	-0.40501100
H	-3.91490900	0.71681400	-1.59500800	O	-1.74015700	4.12399700	0.55628400
H	-4.14840800	-2.44928800	-1.14709700	C	-2.70933600	5.20771600	-1.39908400
N	-0.51339300	-1.23634200	-0.74152200	H	-3.77882000	5.46045800	-1.46947400
C	-1.32433100	-0.65927900	-1.87507500	H	-2.13694900	6.08879300	-1.08380500
O	-4.80511800	-0.71613900	0.35743600	H	-2.38148600	4.89158700	-2.40236900

Singlet state of transition state at the step between INT(3T) and Azi(3S)

Rh	3.36377700	0.70391100	0.50324600	O	2.31137500	-2.09270700	-0.38170200
Rh	1.24434200	-0.32694600	-0.09150500	C	2.75260900	0.80937600	-2.31372300
O	2.38202600	2.49616200	0.76263900	C	1.11521800	2.49810100	0.59506100
O	3.66667000	1.14801200	-1.49458200	O	0.98819800	-0.74125800	1.92255300
O	4.29904500	-1.11796000	0.23700800	C	1.90533600	-0.37784200	2.73288000
O	2.99830400	0.23045100	2.47478500	C	3.56554400	-2.09071400	-0.14369400
O	0.36680800	1.51833600	0.25294400	H	0.58465800	3.45168500	0.76021600
O	1.65115800	0.20510900	-2.06947700	H	2.92706600	1.06541600	-3.37492300

H	4.07569000	-3.05981400	-0.29134800
H	1.72214200	-0.62424200	3.79418400
C	-3.45585800	-0.70694500	-0.07269700
C	-3.19349600	-1.95457100	-0.97205300
C	-2.41615300	-1.58066200	-2.18370900
C	-3.15358500	0.61599100	-0.81647000
O	-1.85477700	0.62304200	-1.45631000
H	-0.61570700	-0.42949000	-2.66339900
H	-2.54592700	-2.04249800	-3.16033100
O	-2.43073200	-2.94520600	-0.17044100
S	-0.76268300	-2.88384300	-0.41519700
O	-0.45463200	-3.63717600	-1.64923400
O	-0.18815500	-3.27212100	0.87226700
H	-2.85734100	-0.78577200	0.84733400
H	-3.92923300	0.74933000	-1.59549700
H	-4.14570000	-2.45350700	-1.19808500
N	-0.52433000	-1.21115900	-0.68924800
C	-1.31301800	-0.64496300	-1.84127000
O	-4.86256100	-0.72129100	0.28037200
C	-5.17062000	-0.64470300	1.62582600
O	-4.34705500	-0.45936100	2.50333800
C	-6.65785700	-0.83977200	1.82491400
H	-6.93721200	-0.50890100	2.83298200
H	-7.23596500	-0.29325400	1.06528900
H	-6.90182700	-1.91021300	1.72074400
C	-3.18356600	1.82128100	0.12165500
H	-2.26786600	1.87124300	0.72538800
H	-4.06254700	1.78067900	0.78208800
O	-3.30716000	3.02079300	-0.68648300
C	-2.51362900	4.08077100	-0.35628200
O	-1.72609700	4.09674300	0.57946300
C	-2.75495500	5.24528200	-1.29638900
H	-3.47371700	4.99791100	-2.08807300
H	-3.12756300	6.10288200	-0.71408400
H	-1.79614900	5.54841100	-1.74435500

Azi(3S)

Rh	4.07460800	0.31530400	-0.67339100
Rh	1.79048100	-0.05715000	0.06363500
O	3.44852700	2.09450500	-1.53856900
O	3.60740000	-0.70083100	-2.42690300
O	4.60268700	-1.46944900	0.22755200
O	4.43465400	1.30515800	1.10387600
O	1.27823700	1.74394600	-0.85511300
O	1.43922700	-1.06160400	-1.73622200
O	2.43186900	-1.84769400	0.90338200
C	2.42399400	-1.14968900	-2.55318800
C	2.21600700	2.39614300	-1.43379700
O	2.26711100	0.96094300	1.80418800

C	3.46172600	1.40013100	1.92429700
C	3.67386100	-2.13192700	0.79837600
H	1.90894300	3.34891400	-1.90512000
H	2.20989800	-1.69015200	-3.49513100
H	3.98189800	-3.08517700	1.26782800
H	3.67593900	1.93419900	2.86845300
C	-3.76805600	-1.35953800	0.22501600
C	-2.41430600	-1.74493500	0.85766600
C	-1.24389500	-1.30184000	-0.04088900
C	-3.73011800	0.07318500	-0.38579900
O	-2.52266000	0.79226400	-0.01166200
H	-0.84332000	0.57813700	-1.25796900
H	-0.73939500	-2.03875500	-0.66812000
O	-2.35192800	-1.04136500	2.11501800
S	-0.87194400	-0.26117600	2.3602110
O	0.02522100	-1.16897600	3.07338700
O	-1.14878800	1.10054500	2.80814600
H	-4.56073700	-1.44795000	0.98321700
H	-3.75198200	-0.02647900	-1.48645000
H	-2.37813200	-2.82930400	1.04406200
N	-0.38150700	-0.31107200	0.64248500
C	-1.36714600	0.14341600	-0.40157500
O	-4.00741700	-2.34055900	-0.81520400
C	-5.32204100	-2.72895900	-0.99526400
O	-6.25342200	-2.26008500	-0.36502900
C	-5.40891400	-3.79405000	-2.06436600
H	-6.46254300	-4.02912200	-2.25749200
H	-4.92211100	-3.45239100	-2.99091100
H	-4.88236500	-4.70405400	-1.73438400
C	-4.90389500	0.92527000	0.07196000
H	-4.79705300	1.19208000	1.13552100
H	-5.84572700	0.36883300	-0.05702200
O	-4.91109700	2.11755800	-0.74218300
C	-5.86887200	3.03908500	-0.40096600
O	-6.67536200	2.86692400	0.49748000
C	-5.75747000	4.26449400	-1.28436500
H	-5.75825100	3.97985700	-2.34796000
H	-6.59513100	4.94094800	-1.07497700
H	-4.80661600	4.78488700	-1.08511400

Table 8 Cartesian coordinates of the stationary-points involved in the aziridination reaction of series 4

SM1(4S)

C	-1.96772200	-0.44336000	-0.28022000	H	-1.73423000	6.13067200	0.09752700
C	-3.11527700	-1.33697000	0.21912600	H	-1.87273900	5.24187200	1.65584400
C	-3.32980600	-1.15817800	1.68753900	C	-6.42910000	-1.39740100	-1.52383100
C	-2.73228600	-0.15498400	2.36651800	H	-6.06450100	-1.12780400	-2.52757900
C	-1.96169400	0.94046900	0.39617600	H	-6.87187600	-0.49063000	-1.08143600
H	-2.04551400	-0.32331900	-1.37273300	H	-7.19354300	-2.18019800	-1.60337800
H	-1.01904700	1.44350500	0.14004300	I	2.63392800	-1.00441500	1.05968200
O	-1.94641600	0.82777900	1.84167700	C	4.22466000	0.07771300	0.02767900
H	-2.80429800	-0.04360000	3.45206800	C	5.54976500	-0.23057300	0.35283900
H	-3.93069100	-1.89072800	2.22695200	C	3.86638000	1.02903100	-0.93162900
O	-4.30223500	-0.94948000	-0.57785500	C	6.56743600	0.48327600	-0.30111100
H	-2.89176000	-2.38543600	-0.02671000	H	5.79436500	-1.00065100	1.08728100
O	-0.73947500	-1.14181400	0.07153700	C	4.90455400	1.71680500	-1.58154700
S	0.41905800	-1.20929200	-1.16995000	H	2.81985700	1.21304900	-1.18372900
O	-0.09159400	-2.12048600	-2.21895500	C	6.24543100	1.45123700	-1.26418300
O	0.71423500	0.20647000	-1.51771900	H	7.61190300	0.26632000	-0.06162600
N	1.61633700	-2.10175400	-0.46606300	H	4.65358700	2.46319600	-2.33988800
C	-5.28515600	-1.89834000	-0.66277700	H	7.04399000	1.99571000	-1.77487200
O	-5.23000500	-2.98869900	-0.11633500	C	-3.13616400	1.82834500	-0.04141700
O	-3.04683700	3.13705800	0.57471400	H	-3.13441100	1.93577700	-1.13666300
C	-2.31447300	4.07369000	-0.10556300	H	-4.09521400	1.41688300	0.29604200
O	-1.75541900	3.86601100	-1.17120900				
C	-2.31283300	5.38454100	0.65601700				
H	-3.34370400	5.74378400	0.80280100				

Ad1(4S)

Rh	3.76652300	-1.96292100	0.07932200	O	5.04082100	-0.32125600	0.08942000
Rh	1.89793500	-0.43162900	-0.30374800	O	3.43705600	-1.72945100	2.11171200

O	2.44389500	-3.54366000	0.04907500	N	0.52388600	0.90557600	-0.79447200
O	4.04706800	-2.16785800	-1.94397500	C	-2.88820400	-4.63792100	-0.19366600
O	3.29099000	1.13465400	-0.27351900	O	-1.70659300	-4.89721400	-0.01225100
O	1.69307200	-0.28297800	1.74706100	O	-6.52042400	-0.21009000	0.26268900
O	0.66983300	-2.11770600	-0.30197400	C	-6.95796300	0.59757000	-0.75659600
C	2.49920700	-0.95716000	2.48332100	O	-6.45203000	0.63285800	-1.86697900
C	4.51876000	0.82701000	-0.09213100	C	-8.14727100	1.41552200	-0.29578900
O	2.29999700	-0.72113800	-2.33822200	H	-8.95783600	0.75333400	0.04741600
C	3.24944300	-1.49999900	-2.68445300	H	-8.50190400	2.04191400	-1.12345800
C	1.21232800	-3.26676200	-0.13445600	H	-7.86225100	2.05092000	0.55782600
H	5.22040600	1.68276500	-0.09377100	C	-3.89548300	-5.57450900	-0.83094400
H	2.34821700	-0.84466200	3.57229900	H	-4.28143100	-5.13469300	-1.76457100
H	0.50569200	-4.11574900	-0.14323900	H	-4.75589600	-5.72731400	-0.16099600
H	3.39541100	-1.60444000	-3.77519700	H	-3.41388700	-6.53572200	-1.04873300
C	-2.82196800	-1.13522900	-0.07027800	I	0.34877200	2.73841500	1.30683300
C	-2.63449400	-2.41621900	0.76315500	C	0.36081500	4.54714400	0.15603700
C	-3.01589900	-2.19092000	2.18813600	C	1.40851400	5.45723100	0.35724400
C	-3.64753100	-1.06096700	2.57768400	C	-0.67697900	4.78442600	-0.75396200
C	-4.07353000	-0.34007500	0.34909000	C	1.39685900	6.65857800	-0.36791300
H	-2.88107300	-1.39825500	-1.13880200	H	2.21403600	5.24192900	1.06179500
H	-4.04098100	0.64766500	-0.13182800	C	-0.66020000	5.98833100	-1.47579000
O	-4.07899800	-0.05506200	1.77088600	H	-1.46191000	4.04436400	-0.91434500
H	-3.86021300	-0.82805700	3.62465900	C	0.36622000	6.92506400	-1.28200900
H	-2.71700300	-2.92083900	2.94257600	H	2.20293400	7.38198300	-0.21696400
O	-3.49093400	-3.46169700	0.15312100	H	-1.45982700	6.18724700	-2.19449500
H	-1.59495300	-2.75204000	0.66044800	H	0.36643700	7.86118400	-1.84670000
O	-1.62750300	-0.33596100	0.17074900	C	-5.37987100	-1.04878800	-0.03936900
S	-1.06147500	0.53530600	-1.16150300	H	-5.37387800	-1.28690000	-1.11372600
O	-1.01340200	-0.36621800	-2.33876100	H	-5.52603500	-1.96295700	0.54953700
O	-1.89656600	1.75517100	-1.24793000				

RhN(4S)

Rh	3.73850600	0.81022100	0.05093000	Rh	1.81487200	-0.69376700	0.06975100

O	3.50352700	1.10615800	2.08033800
O	4.96415400	-0.80321800	0.43113400
O	3.90890000	0.46157500	-1.98513700
O	2.49310400	2.40480200	-0.30964900
O	1.68465800	-0.30713100	2.13189600
O	3.16569900	-2.23018200	0.45875700
O	2.11459700	-0.98263600	-1.96338500
C	4.40837000	-1.94315400	0.55224800
C	2.54439300	0.48506300	2.64737900
O	0.68029600	1.00476300	-0.33789800
C	1.24792000	2.15213500	-0.40790600
C	3.07296600	-0.33844000	-2.51730900
H	2.43606300	0.64986300	3.73540100
H	5.07367000	-2.79977900	0.76265500
H	3.17974800	-0.51139800	-3.60369700
H	0.56470100	3.00586700	-0.56606600
C	-3.12045300	-0.93856300	-0.23644800
C	-4.43471900	-1.29571300	0.47788500
C	-4.36687400	-0.95890300	1.93149500
C	-3.36310400	-0.20637400	2.43579300
C	-2.51114800	0.37579100	0.29034900
H	-3.28568400	-0.85150100	-1.32119300
H	-1.48759400	0.47631500	-0.09380600
O	-2.36204700	0.38282100	1.72776100
H	-3.23510700	-0.01727200	3.50453600
H	-5.10378900	-1.39354100	2.60706500
O	-5.47641400	-0.52160200	-0.23259100
H	-4.66371400	-2.36194400	0.33062700
O	-2.23996900	-2.06030900	0.02924300
S	-0.82388600	-2.16858000	-0.88903600
O	-0.63925000	-3.61570400	-1.13855400
O	-0.95984000	-1.22158400	-2.01741900
N	0.27199400	-1.82690700	0.31470100
C	-6.74849700	-1.02441300	-0.12066500
O	-7.02786300	-2.02754100	0.51443600
O	-2.29665100	2.69620400	-0.11702600
C	-2.60862100	3.99177200	-0.44088900
O	-1.69215700	4.79249200	-0.51371100
C	-4.06889300	4.33723600	-0.67070800
H	-4.50052200	3.74303800	-1.49293100
H	-4.13897600	5.40260200	-0.92125100
H	-4.67022500	4.13678300	0.23155000
C	-7.72827300	-0.16054400	-0.89005000
H	-7.44105400	-0.10484300	-1.95191800
H	-7.72491200	0.86713700	-0.49330500
H	-8.73478500	-0.58701300	-0.80004200
C	-3.27176400	1.62841400	-0.16662600
H	-3.63442900	1.50127900	-1.20049400
H	-4.13098000	1.83251500	0.49106700

RhN(4T)

Rh	-4.43525600	-0.00450400	0.04777200
Rh	-2.00553400	-0.15883300	0.10258700
O	-4.39486100	0.40090400	2.07141500
O	-4.24646800	2.01037900	-0.36064400
O	-4.41388300	-0.41572900	-1.97256700
O	-4.56868600	-2.02423000	0.45341500
O	-2.10107100	0.28267100	2.13082900
O	-1.95091100	1.87843100	-0.32703600
O	-2.11909400	-0.57965600	-1.93838300
C	-3.06737300	2.48710900	-0.45724400

C	-3.25839000	0.45496700	2.64633500	S	0.95064600	-1.31634500	-0.86547500
O	-2.27333600	-2.17696800	0.55446500	O	1.22931300	-0.66172500	-2.16216200
C	-3.46275300	-2.63931500	0.61657400	O	0.56817400	-2.73572000	-0.79797900
C	-3.26836000	-0.61289700	-2.49656400	N	-0.06540900	-0.37261200	0.04164000
H	-3.26530500	0.68001700	3.72801000	C	2.97475300	3.43354600	-0.51849100
H	-2.99100000	3.56647900	-0.68125000	O	1.92657000	3.72482900	0.03464200
H	-3.25569300	-0.84217800	-3.57744500	O	7.04582000	-0.39135100	0.44514300
H	-3.53256900	-3.71847300	0.84443400	C	7.58527200	-1.41683300	-0.28941200
C	3.28778400	-0.16561300	-0.22253900	O	7.08650600	-1.85371300	-1.31506200
C	2.83218100	1.18891300	0.35366600	C	8.86469800	-1.90555400	0.35682500
C	3.12037500	1.27943400	1.81542300	H	9.58923500	-1.08060400	0.44491000
C	3.90033700	0.36726500	2.43588600	H	9.29221900	-2.71537900	-0.24694800
C	4.60656800	-0.65440900	0.40209700	H	8.65863800	-2.26853500	1.37628500
H	3.39464700	-0.09347300	-1.31543800	C	3.80626400	4.35835600	-1.38624400
H	4.75759000	-1.70503800	0.11601000	H	3.93713600	3.92579900	-2.39066200
O	4.56003400	-0.66926500	1.84701500	H	4.81028500	4.48943000	-0.95204200
H	4.06518200	0.35587800	3.51628000	H	3.30700600	5.33223900	-1.46251100
H	2.63446500	2.05966400	2.40176000	C	5.81660500	0.16902100	-0.07121400
O	3.56757800	2.20126800	-0.43562300	H	5.85045400	0.18510300	-1.17103200
H	1.75924300	1.34488500	0.15437200	H	5.77736300	1.19249800	0.32047200
O	2.31761700	-1.20915500	0.09430200				

TS1(4T)

Rh	-4.01725500	0.37736000	-0.45964400	C	-2.16898600	1.96439400	-2.02127800
Rh	-1.66651700	-0.04440200	0.02528400	O	-1.79861000	1.44510500	1.46653900
O	-3.41834800	1.78656100	-1.85480300	C	-2.92629400	2.02275800	1.63279400
O	-3.94908500	-1.09028600	-1.91739300	C	-3.58271000	-1.62938300	1.54349000
O	-4.54294900	-1.03915200	0.94625600	H	-1.87914500	2.71450300	-2.78050200
O	-4.02356900	1.82427800	1.01373400	H	-2.81270000	-2.45120400	-2.88755000
O	-1.19408000	1.38834800	-1.42277500	H	-3.86634800	-2.39048300	2.29290800
O	-1.71994600	-1.48471400	-1.49684900	H	-2.94344300	2.79858300	2.42004600
O	-2.32494500	-1.46218700	1.39302800	C	3.43570300	-0.47127900	1.07887600
C	-2.83163800	-1.67421500	-2.10051200	C	3.37579200	-1.64352400	0.08472700

C	2.32439600	-1.36841800	-0.93908600	O	4.25005000	-3.86649700	-1.14991500
C	1.69740400	-0.10343400	-0.96762900	C	5.19186800	3.49388500	0.10039100
C	3.42785600	0.89379800	0.36875900	O	5.59118500	3.16301800	1.20591800
H	4.35042400	-0.55412400	1.68677900	C	5.14582600	4.90436600	-0.44603600
H	3.28180700	1.66393300	1.13990700	H	5.67920000	4.96383500	-1.40748400
O	2.27288700	1.02949800	-0.51154000	H	5.59897900	5.59100500	0.27940400
H	0.93859100	0.12794000	-1.71682000	H	4.10113900	5.20067800	-0.63320900
H	1.86207700	-2.19509900	-1.47787700	C	6.47726400	-2.94712000	-1.54276600
O	4.73187900	-1.73044700	-0.48972600	H	7.16241600	-2.77852900	-0.69679400
H	3.16944600	-2.59415100	0.59770100	H	6.64368100	-2.13413800	-2.26692700
O	2.35852800	-0.45837700	2.05088800	H	6.69907300	-3.91352800	-2.01161700
S	0.82456800	-1.15636400	1.82572000	C	4.70543100	1.21974100	-0.41741100
O	1.00960500	-2.60974900	1.60915500	H	5.58765900	1.02050700	0.20935300
O	0.11348900	-0.66174800	3.00970300	H	4.76397700	0.63827700	-1.34488900
N	0.26227900	-0.45892000	0.41320900	O	4.70997000	2.60581100	-0.83132800
C	5.04065700	-2.94366000	-1.06221000				

INT(4T)

Rh	3.74917100	0.63769600	0.35037000	H	2.85277200	-1.29604300	3.63795300
Rh	1.51666100	-0.27999800	0.07198900	H	4.13785900	-2.91680200	-1.22736600
O	2.91231300	2.33494400	1.17780400	H	2.44732200	1.71958400	-3.17560600
O	3.82489600	-0.22804400	2.22239400	C	-3.19863800	-0.76236300	-1.20538300
O	4.53493100	-1.07615800	-0.48405500	C	-3.63209300	-1.64637900	-0.02332000
O	3.59865400	1.47444500	-1.52860700	C	-2.53685200	-1.71568200	0.98353100
O	0.79265000	1.48215900	0.91183200	C	-1.45111900	-0.69594100	0.87063800
O	1.69330200	-1.06094500	2.00308600	C	-2.64830200	0.61885000	-0.75531900
O	2.43392200	-1.98954100	-0.68669100	H	-4.04649300	-0.62651500	-1.89424600
C	2.79373600	-0.86066700	2.62363300	H	-1.88975600	0.92331700	-1.49997700
C	1.63994000	2.37144600	1.26542100	O	-2.04490600	0.57091400	0.54766300
O	1.48762600	0.60706000	-1.79711100	H	-0.92998800	-0.53125400	1.82427700
C	2.51462300	1.26899500	-2.16920500	H	-2.49567600	-2.51901200	1.71776600
C	3.70509800	-1.99414900	-0.80007100	O	-4.85555200	-0.99918700	0.50511600
H	1.20502600	3.28834900	1.70288600	H	-3.91411400	-2.65269900	-0.36879100

O	-2.22047600	-1.43575000	-2.04204900
S	-0.81840600	-2.11207000	-1.36707800
O	-1.18082400	-3.42397900	-0.78762300
O	0.14855600	-2.02305200	-2.45953500
N	-0.38946100	-1.04517900	-0.11664300
C	-5.67005900	-1.82076900	1.24614700
O	-5.42011400	-2.99166300	1.47599000
O	-3.02865300	2.96400400	-0.57668700
C	-3.71428600	4.14176100	-0.38386200
O	-3.07217400	5.16961700	-0.28292400
C	-5.23229500	4.07737100	-0.30761900
H	-5.66975500	3.60413700	-1.20211400
H	-5.61350700	5.10192300	-0.21852600
H	-5.56299700	3.49526400	0.56874200
C	-6.88809300	-1.05900000	1.72943000
H	-7.38171100	-0.53796900	0.89472400
H	-6.58447000	-0.29508800	2.46372500
H	-7.58818000	-1.75851300	2.20257000
C	-3.72175600	1.70872300	-0.70997000
H	-4.29916700	1.69170800	-1.65265000
H	-4.40147100	1.53076800	0.13711200

Azi(4S)

Rh	3.85788300	-0.39471300	-0.78624100
Rh	1.61640200	-0.14880400	0.11496800
O	3.02798700	-1.32340800	-2.45045500
O	3.62996500	1.45882000	-1.69400700
O	4.60143600	0.53039600	0.90088200
O	3.98465600	-2.22665900	0.16670700
O	0.89547800	-1.09004100	-1.61602300
O	1.49371800	1.68537500	-0.86306100
O	2.47877000	0.75774500	1.76610000
C	2.52144200	2.06345300	-1.52640400
C	1.76511900	-1.46114400	-2.48314000
O	1.85075100	-2.01014700	1.01181500
C	2.96749800	-2.60791700	0.83613800
C	3.74956300	0.88851700	1.78186200
H	1.35514700	-1.96724400	-3.37802500
H	2.42891900	3.04892300	-2.02088800
H	4.16219300	1.37923100	2.68258600
H	3.06010300	-3.59118500	1.33437800
C	-3.30219300	0.97102400	1.33709500
C	-2.54729700	1.53928600	0.12033100
C	-1.46576000	0.56055000	-0.29679900
C	-1.56410000	-0.85453700	0.19527200
C	-3.76088900	-0.48417600	1.14204700
H	-4.16038700	1.61684200	1.57974000
H	-4.17975600	-0.83423600	2.09772000
O	-2.62096100	-1.35160400	0.91982300
H	-1.03975000	-1.64635500	-0.34284500
H	-0.94343000	0.78328800	-1.23159900
O	-3.47451200	1.68954700	-0.97996900
H	-2.11793300	2.52592400	0.35634800
O	-2.46588000	0.98404900	2.52805200
S	-0.78741300	0.86329200	2.37698400
O	-0.26270300	2.22509800	2.25812600
O	-0.37287100	-0.08070300	3.40818800
N	-0.54738500	0.10907100	0.80026500
C	-3.60364400	2.97628000	-1.50026200
O	-3.01657700	3.94199800	-1.05626000
O	-5.39441100	-1.99290600	0.30880600

C	-6.27649300	-2.57165400	-0.58313800
O	-6.75493600	-3.64940400	-0.29390600
C	-6.58121800	-1.82106900	-1.87032100
H	-6.95422700	-0.80194500	-1.67661000
H	-7.34385100	-2.38544800	-2.42058500
H	-5.68123600	-1.73094600	-2.50164400
C	-4.56227800	2.96262800	-2.66842300
H	-5.55597600	2.61292200	-2.34656900
H	-4.20587000	2.27052400	-3.44749500
H	-4.64370400	3.97574900	-3.08010800
C	-4.82547400	-0.69626000	0.05827300
H	-5.60119900	0.08732600	0.14009200
H	-4.37648600	-0.63642700	-0.94449700

Table 9 Cartesian coordinates of the stationary-points involved in the aziridination reaction of series 6

SM1(6S)

C	2.53897400	-0.70951100	-1.24939700	C	4.72347400	-2.20428600	1.19421100
C	4.23460600	0.57768300	-2.34892600	O	4.35050400	-1.75902800	2.26724200
C	4.68285400	1.14881500	-1.21112900	C	2.76462300	3.67436600	1.94137500
C	3.38250900	-0.59947500	0.02503300	H	3.24581700	4.44018200	2.56241600
H	5.46249900	1.90964500	-1.26223100	H	2.21790500	4.16117000	1.11737100
H	4.63094500	0.82267500	-3.33812200	H	2.02943700	3.11119500	2.53667900
O	0.41058500	-0.18494800	-0.12997500	C	5.66398300	-3.37484200	0.99428000
S	-0.83203800	-1.27339300	-0.50623900	H	6.04505200	-3.70644700	1.96801600
O	-0.27941400	-2.31973100	-1.40154700	H	5.13117100	-4.20562600	0.50413400
O	-1.33655100	-1.59934900	0.84336400	H	6.50021600	-3.09031400	0.33709600
N	-1.88223200	-0.51617300	-1.55128500	I	-2.97397400	1.05729100	-0.58141800
C	1.27797500	0.17773200	-1.23270000	C	-4.69746100	0.10310600	0.36154900
H	1.53942300	1.23257400	-1.07051100	C	-5.96812600	0.40213000	-0.14162000
H	0.75547300	0.07620000	-2.19690800	C	-4.47542200	-0.77606800	1.42542200
O	3.27861100	-0.38818000	-2.45547000	C	-7.07639300	-0.19292500	0.48311500
C	4.17199400	0.71929500	0.12447300	H	-6.10350000	1.07312000	-0.99224900
H	2.73831500	-0.71296200	0.90923600	C	-5.60105900	-1.36808000	2.02192700
H	4.99056900	0.60851000	0.85055000	H	-3.46519800	-1.01431000	1.76323400
H	2.22533000	-1.75500800	-1.37938400	C	-6.89263600	-1.07410800	1.55917800
O	3.23600500	1.71090700	0.70395400	H	-8.08129200	0.02801800	0.11345300
C	3.82303300	2.74194300	1.38239400	H	-5.45717600	-2.06376200	2.85277800
O	5.03018100	2.88255600	1.50605200	H	-7.76016400	-1.53932100	2.03431500
O	4.32838900	-1.70461400	-0.02249900				

Ad1(6S)

Rh	3.83851800	-2.08909300	0.20408600	O	2.92864300	-2.42097700	2.03876300
Rh	2.03152000	-0.51219200	-0.29621300	O	2.70363500	-3.60915000	-0.61919600
O	4.69119100	-1.72106100	-1.63026700	O	3.00353600	-0.23600500	-2.13168700
O	4.91774000	-0.51443800	1.01061000	O	3.23996000	0.98779100	0.52525000

O	1.25287800	-0.91924500	1.57571900	H	-3.60611400	-0.00022400	-2.30677800
C	4.38549100	0.64184200	0.97662600	O	-3.93584000	-2.13640400	1.25833700
C	4.07761400	-0.88200400	-2.37141300	C	-4.32262100	-2.77584100	2.40330200
O	0.98256400	-2.14468900	-1.07695600	O	-5.48534800	-2.99690000	2.70533000
C	1.55314100	-3.28826500	-1.06331700	O	-5.60667300	0.33279600	-0.86245000
C	1.87025900	-1.77160000	2.30900900	C	-6.02213000	1.31292000	0.00549300
H	4.53372400	-0.68157600	-3.35840100	O	-5.52882200	1.50265700	1.10541600
H	4.99245000	1.46716100	1.39465200	C	-3.11071300	-3.14499600	3.23779300
H	1.41393800	-1.95746800	3.29858600	H	-3.41879400	-3.81305600	4.05183500
H	0.95685200	-4.11159900	-1.49967000	H	-2.34075900	-3.62916000	2.61811800
C	-3.71952000	-0.88917100	-1.66859700	H	-2.66482000	-2.23232800	3.66604400
C	-5.21229700	-2.75508500	-1.83824600	C	-7.15636100	2.10531700	-0.61066000
C	-5.51979600	-2.75807900	-0.52437600	H	-7.53692100	2.82757200	0.12203300
C	-4.48763900	-0.47875000	-0.40762500	H	-6.79885400	2.63971800	-1.50555300
H	-6.16198900	-3.54361300	-0.12475700	H	-7.96553100	1.43228400	-0.93389400
H	-5.59421000	-3.49664600	-2.54500100	I	-0.00773300	2.30124300	1.36692100
O	-1.47102400	-0.55667500	-0.67664500	C	0.53835700	4.18104600	0.49047600
S	-0.68126800	0.58061300	-1.63784500	C	-0.10416200	4.59566300	-0.68221300
O	-0.27713400	-0.04793100	-2.91776500	C	1.52584800	4.94818000	1.12348800
O	-1.56586400	1.76795800	-1.68313000	C	0.25922800	5.83708800	-1.22788000
N	0.74543000	0.91027300	-0.81477800	H	-0.84823700	3.96278300	-1.16835700
C	-2.32810300	-1.49195400	-1.37812100	C	1.86316300	6.19028900	0.56450200
H	-2.40557300	-2.35720900	-0.70756800	H	2.02251300	4.59261900	2.02804300
H	-1.85807700	-1.79972100	-2.32424800	C	1.23257800	6.63467600	-0.60735300
O	-4.43467400	-1.84484500	-2.49198100	H	-0.22737900	6.17577300	-2.14649400
C	-5.04175900	-1.67612500	0.38705100	H	2.62767700	6.80452200	1.04808300
H	-3.84180400	0.13182800	0.23901000	H	1.50397500	7.60140400	-1.03962800
H	-5.84327900	-1.33674200	1.05944200				

RhN(4S)

Rh	-4.11803900	0.08462200	-0.75923800	O	-3.85082300	2.10165600	-1.06507700
Rh	-1.83817200	-0.07089200	0.11008000	O	-3.37778400	-0.28888400	-2.65322000
O	-4.77363100	0.44886500	1.17216500	O	-4.35531000	-1.93497400	-0.43108400

O	-2.62516600	0.31857100	1.98773900
O	-1.69934000	1.98521700	-0.26372500
O	-1.21726600	-0.43567500	-1.86838700
C	-2.71303200	2.58702400	-0.75749700
C	-3.89105100	0.47727400	2.08929100
O	-2.21061500	-2.09455500	0.37945700
C	-3.36096300	-2.55751700	0.06623300
C	-2.12057800	-0.45570100	-2.77356000
H	-4.25230600	0.66573800	3.11653000
H	-2.57540500	3.66883000	-0.93727400
H	-1.75319400	-0.64525100	-3.79947000
H	-3.49586500	-3.63778300	0.25410600
C	3.56442700	-1.07286900	0.31355200
C	2.47908800	-0.07732800	-1.55723000
C	3.35623700	0.94918400	-1.63336400
C	4.86607200	-0.38940100	-0.15115300
H	3.16943200	1.76598700	-2.33076600
H	1.57766300	-0.14976500	-2.16735600
O	1.89049700	-1.22604300	2.05525500
S	0.38934900	-0.53343900	2.26030900
O	-0.37508700	-1.60761900	2.90866800
O	0.55836400	0.79295900	2.91367200
N	0.00564700	-0.13327800	0.68827500
C	2.95413600	-0.38100200	1.5407070
H	3.71093800	-0.30113200	2.33739600
H	2.58022800	0.62362200	1.30430300
O	2.58679000	-1.16350700	-0.74375200
C	4.60800500	0.96973700	-0.81705300
H	5.54567400	-0.28286000	0.70770900
H	5.47610400	1.25391200	-1.43134200
H	3.78484300	-2.11649600	0.58109400
O	4.52609500	1.94085600	0.29417300
C	4.79571000	3.24239500	-0.04447400
O	5.10586300	3.59878600	-1.17010800
O	5.51027400	-1.21106900	-1.15929700
C	6.34716900	-2.19151600	-0.67843500
O	6.54701700	-2.38669200	0.50959600
C	4.64698400	4.14341600	1.16438900
H	4.94002500	5.16540400	0.89421000
H	3.60091100	4.13830700	1.51080600
H	5.26873800	3.78129000	1.99787300
C	6.95942900	-2.96440600	-1.82606300
H	7.65340000	-3.71553900	-1.42959600
H	6.16900800	-3.46031500	-2.41167000
H	7.49143700	-2.28273600	-2.5079610

RhN(4T)

Rh	4.24507800	0.66268700	0.08871800
Rh	2.04108600	-0.35840800	0.20701800
O	5.03609300	-0.99436200	1.03661300
O	4.56778600	-0.23241400	-1.74013900
O	3.40722500	2.29738300	-0.86265600
O	3.87808300	1.53554200	1.91999800
O	2.95251300	-1.96391300	1.17817300
O	2.49765000	-1.22855000	-1.62985200
O	1.31230000	1.34749600	-0.75826600
C	3.62464900	-0.97261500	-2.17542200
C	4.21701900	-1.91642300	1.36137500
O	1.78720800	0.59044000	2.04161900
C	2.75334500	1.30790500	2.47584300
C	2.15004000	2.26368400	-1.06575000
H	4.64889400	-2.79670000	1.87137600
H	3.79260900	-1.46250400	-3.15126600

H	1.71636600	3.14287300	-1.57654700
H	2.58376300	1.78777700	3.45641500
C	-4.08780000	-1.01682400	0.32705000
C	-3.63342000	0.31301900	2.24342100
C	-4.03611400	1.45990900	1.65384700
C	-5.15860900	0.02494400	-0.05761100
H	-3.89787300	2.40918700	2.17174900
H	-3.18436100	0.27644300	3.23905300
O	-2.04207200	-2.09238000	-0.28990000
S	-0.52706200	-2.10951500	-0.96809700
O	-0.11076100	-3.51839100	-0.89381000
O	-0.57368400	-1.38547700	-2.25631400
N	0.28694700	-1.21260200	0.16808300
C	-2.82791300	-0.88751300	-0.53346800
H	-3.08666300	-0.83458500	-1.60172700
H	-2.24939800	0.00481000	-0.2554940
O	-3.74426000	-0.94454900	1.72829700
C	-4.74693300	1.44996500	0.3386080
H	-5.36212700	-0.04311800	-1.13675400
H	-5.63450900	2.10062600	0.36525000
H	-4.50528900	-2.02515400	0.19054700
O	-3.89342100	1.92779100	-0.76959000
C	-3.81049300	3.28806600	-0.90537500
O	-4.39277600	4.08063400	-0.18189500
O	-6.38135800	-0.25280100	0.67143200
C	-7.24652500	-1.13588900	0.06824600
O	-7.02475000	-1.67494900	-1.00370000
C	-2.90378100	3.64552700	-2.06653200
H	-2.85624300	4.73675500	-2.16912600
H	-1.89395200	3.23941300	-1.89676700
H	-3.28050500	3.19870300	-3.00014700
C	-8.47876400	-1.32551200	0.92578800
H	-9.18127700	-1.99223200	0.41104800
H	-8.19795500	-1.76039600	1.89832600
H	-8.95889300	-0.35548600	1.12869500

TS1(6T)

Rh	4.06028900	0.59160100	0.04933000
Rh	1.72766600	-0.13304700	0.00386200
O	4.63417800	-1.36647700	0.34449100
O	3.88789900	0.85130400	2.09813000
O	3.41292800	2.53862200	-0.25182200
O	4.15710400	0.29945600	-1.99058500
O	2.43831400	-2.06052400	0.31944600
O	1.68891500	0.17979100	2.07460700
O	1.20671100	1.87978300	-0.27799700
C	2.76440600	0.59554700	2.63521100
C	3.70099600	-2.23401400	0.40711500
O	1.94632200	-0.34682200	-2.04955200
C	3.08933300	-0.09736300	-2.56485900
C	2.15873300	2.73428000	-0.34043300
H	4.01866400	-3.28169100	0.56074300
H	2.69775500	0.74717900	3.72869700
H	1.83985100	3.78263700	-0.49343800
H	3.15004400	-0.24673500	-3.65851000
C	-4.04749200	-0.21659200	0.32530200
C	-3.48084600	1.19383700	0.55616800
C	-2.01300800	1.15456800	0.78724800
C	-1.45389000	0.07478200	1.48764800
C	-3.41342800	-1.30708700	1.24289100
O	-2.24482600	-0.89447400	2.00300500

H	-0.53468400	0.17935200	2.06837100	C	-6.30111300	-0.97883000	-0.07544300
H	-1.36589500	1.94995300	0.41921000	O	-5.90588700	-1.85024000	-0.83308000
O	-1.64342700	-2.81177600	0.26417900	O	-3.78528300	2.00299700	-0.60899100
S	-0.89496800	-1.88529100	-0.92935200	C	-4.61832000	3.07971300	-0.40272500
O	-1.95532900	-1.28909400	-1.77842000	O	-5.06700600	3.40062000	0.68543400
O	0.11006900	-2.78452600	-1.51198800	C	-4.87566400	3.78814300	-1.71461800
N	-0.19638900	-0.69968600	0.00995000	H	-5.50924100	4.66585700	-1.53789100
C	-3.05191300	-2.63397100	0.50013100	H	-5.37106000	3.10515800	-2.42288600
H	-3.62883900	-2.70938300	-0.43279900	H	-3.92400300	4.09649200	-2.17500200
H	-3.29637000	-3.49017800	1.14506100	C	-7.74633100	-0.68679100	0.26771400
H	-3.90473000	-0.48449100	-0.73035100	H	-8.39973400	-1.34413000	-0.31873700
H	-4.16046500	-1.53378300	2.01883800	H	-7.98582900	0.36800400	0.06224900
H	-4.00363700	1.66075600	1.41682700	H	-7.92056800	-0.85477600	1.34275600
O	-5.47240800	-0.12114200	0.60628000				

INT(6T)

Rh	3.90586900	0.36595700	-0.60222600	H	3.81674800	0.92328700	3.26273800
Rh	1.60686000	0.06800700	0.12986700	C	-3.45857500	0.84818400	1.24736200
O	4.23256900	-1.64712300	-0.30117100	C	-1.44039800	0.54966300	-0.06889600
O	3.29724300	-0.01169600	-2.54330300	C	-2.25992200	-0.34362300	-0.94774500
O	3.50609700	2.38016400	-0.87678200	C	-4.39099600	0.61463600	0.04484200
O	4.44902300	0.72941800	1.34925100	H	-1.72287900	-1.00310300	-1.62914100
O	2.05503000	-1.94590500	0.37970800	H	-0.86213800	1.26277800	-0.68367000
O	1.11571200	-0.29287000	-1.87048100	O	-2.01627500	-0.54066700	2.70895700
O	1.31949300	2.10327500	-0.21555400	S	-0.83858300	-1.33883900	1.82122400
C	2.06062600	-0.25093300	-2.73296600	O	0.24794400	-1.53752600	2.77724500
C	3.24272300	-2.33564100	0.11740500	O	-1.47469300	-2.47653400	1.12052800
O	2.26918000	0.49888000	2.04629400	N	-0.36516000	-0.17662000	0.67206000
C	3.51496200	0.71716700	2.21993800	C	-3.31977100	-0.45307300	2.09716400
C	2.32276000	2.78182400	-0.63200700	H	-4.03016400	-0.42748100	2.93684900
H	3.43017000	-3.41325800	0.27531100	H	-3.51028300	-1.36119400	1.50547800
H	1.75575600	-0.44869100	-3.77721800	O	-2.20016900	1.37169200	0.81155100
H	2.12738700	3.85740300	-0.79755000	C	-3.74958800	-0.32142300	-0.99647000

H	-5.35052800	0.19570800	0.38596700
H	-4.10453100	-0.05548500	-2.00798100
H	-3.86741100	1.65387800	1.87295200
O	-4.28800400	-1.66975100	-0.70709400
C	-4.27847200	-2.54837400	-1.76258400
O	-3.90467300	-2.25040400	-2.88568900
O	-4.64408500	1.87124900	-0.63594600
C	-5.68265000	2.61846300	-0.13406100
O	-6.35966600	2.27711100	0.82274500

C	-4.77291500	-3.90730600	-1.31537900
H	-4.92127000	-4.54853900	-2.19304400
H	-4.02374400	-4.36473700	-0.64868400
H	-5.71018400	-3.81767600	-0.74551700
C	-5.84410500	3.89322500	-0.93350600
H	-6.70212300	4.45803300	-0.54903500
H	-4.93113500	4.50496900	-0.85598200
H	-5.99290500	3.66226500	-1.99996700

Azi(6S)

Rh	3.74134800	-0.53374900	0.42787600
Rh	1.42814800	-0.10764000	-0.18171600
O	4.14748400	-0.89551100	-1.56423100
O	4.14733900	1.47002500	0.14850200
O	3.24114700	-0.14785500	2.40701900
O	3.24981800	-2.53700500	0.68563800
O	1.94711900	-0.53275400	-2.14800600
O	1.94957500	1.89037600	-0.39333500
O	1.04640700	0.24849700	1.83287400
C	3.16711400	2.21483500	-0.18867500
C	3.16959500	-0.81865500	-2.38243600
O	1.05648800	-2.14705000	0.10730300
C	2.04474100	-2.87934700	0.46726700
C	2.02645200	0.14858000	2.65172000
H	3.41250200	-1.02909700	-3.44098100
H	3.40043700	3.28767600	-0.32218400
H	1.77836600	0.34782700	3.71117700
H	1.81285200	-3.95253400	0.60668600
C	-3.86702100	-0.28657100	-1.38456400
C	-1.61222900	-1.04189700	-0.86968700
C	-1.66742200	-0.34646900	0.46045800
H	-0.98342300	-0.66316400	1.25057600

H	-0.96837500	-1.90692800	-1.03663900
O	-2.44101600	1.35473000	-2.57043100
S	-1.11137900	1.70247800	-1.63076200
O	-0.03653700	1.74608300	-2.61188600
O	-1.41552500	2.80040200	-0.70594000
N	-0.84685500	0.23657700	-0.66818500
C	-3.69450600	1.18750500	-1.88455900
H	-4.45506000	1.42392600	-2.64157700
H	-3.77715800	1.92054500	-1.06637000
O	-2.72081800	-1.10754300	-1.69328200
C	-3.02977500	0.09300400	1.00363100
H	-3.13558200	-0.43366500	1.96583400
H	-4.68003400	-0.76871700	-1.94329100
O	-3.12746200	1.50916100	1.25805800
C	-2.65982000	1.92451300	2.49417000
O	-2.25541900	1.15158600	3.34400800
O	-4.54860600	-1.67303300	0.50687700
C	-5.85852800	-2.04147400	0.29205100
O	-6.68879600	-1.30136200	-0.20991900
C	-6.08801100	-3.46070900	0.76043900
H	-5.85890600	-3.55035500	1.83411900
H	-7.13300000	-3.73949300	0.57812300

H	-5.41748500	-4.15119500	0.22480400	H	-2.00947600	3.86718000	1.88181600
C	-2.72704600	3.42857500	2.59320900	C	-4.20904300	-0.31954700	0.10690400
H	-3.72780400	3.79429500	2.31654000	H	-5.07342500	0.33714200	0.29286500
H	-2.47829600	3.73936100	3.61524500				

Table 10 Cartesian coordinates of the stationary-points involved in the nucleophilic addition of aziridine complex

Complex with $^{-}$SMe

Ad2(4S) with $^{-}$SMe

Rh	3.96437800	1.02003600	-0.18571300	H	-1.75870200	-1.67244200	2.28051100
Rh	1.84503000	-0.20389500	-0.17791300	O	-1.99263800	-3.24429900	0.13247400
O	2.90060200	2.76665600	-0.58154800	S	-0.34297600	-2.87210800	0.06406100
O	3.70615300	1.35187100	1.84970400	O	0.22089200	-3.18919900	1.38279700
O	4.94498700	-0.76185100	0.21593500	O	0.13943900	-3.50272000	-1.16470700
O	4.11717100	0.63413500	-2.22304500	N	-0.26617300	-1.13162200	-0.12045500
O	0.90767200	1.61363000	-0.58325200	C	-3.09039100	0.23885000	3.20690800
O	1.70764200	0.20082400	1.85698400	O	-2.08726300	0.00812700	3.85958700
O	2.95583800	-1.93159800	0.22268800	O	-5.28881000	-0.51669600	-1.89364000
C	2.65068900	0.87723800	2.38890900	C	-6.22857100	0.46192900	-2.13661100
C	1.63379500	2.66070300	-0.68306600	O	-6.76048700	0.47484300	-3.23561600
O	2.11552600	-0.51715800	-2.22273200	C	-6.53986300	1.43252800	-1.01801900
C	3.16864900	-0.03458000	-2.75720500	H	-6.92507100	0.89947200	-0.13112900
C	4.21981600	-1.80882400	0.32449600	H	-7.30488500	2.13476000	-1.37403300
H	1.08069000	3.59764200	-0.88369900	H	-5.63481900	1.98674000	-0.68111100
H	2.53193800	1.07770100	3.47140500	C	-4.19802800	1.19827600	3.54224700
H	4.76878000	-2.74732100	0.53790600	H	-5.18544700	0.73565500	3.39140500
H	3.27375500	-0.22475900	-3.84378300	H	-4.11667100	2.05139400	2.83268300
C	-2.94221600	-2.20467300	0.51466100	H	-4.08607100	1.54288500	4.57822000
C	-2.28588900	-1.17610700	1.45015000	C	-4.60110100	-0.56343100	-0.62050600
C	-1.30458800	-0.33625700	0.64388400	H	-5.29777100	-0.90046800	0.16903100
C	-3.47246900	-1.58515400	-0.79011000	H	-4.19569200	0.43031000	-0.34774200
H	-3.75004100	-2.73088300	1.04712100	C	-3.04772700	4.33294800	-0.38959400
H	-3.83810800	-2.40637800	-1.42578900	H	-2.07987300	4.35079200	-0.92237500
O	-2.36866100	-1.02727300	-1.54976900	H	-3.83824400	4.55561800	-1.12851900
H	-0.97734300	0.47564000	-1.40376700	H	-3.03350000	5.15981800	0.34374500
H	-0.90377400	0.55379800	1.13352800	C	-1.40565600	-0.35432100	-0.84166800
O	-3.34633000	-0.36290500	1.98071300	S	-3.31964000	2.71705900	0.44739400

TS2(4S) with $^{-}$SMe

Rh	-3.98865900	-0.98462300	-0.13293900
Rh	-1.83735800	0.18220100	-0.16688300
O	-2.98509400	-2.75742700	-0.55535700
O	-3.69821700	-1.32636800	1.89674400
O	-4.91272300	0.82215500	0.28930200
O	-4.17466700	-0.59201200	-2.16457900
O	-0.96242500	-1.65934600	-0.60811100
O	-1.66527700	-0.23752400	1.86311800
O	-2.88870900	1.93015400	0.27690200
C	-2.61717400	-0.88610200	2.41380000
C	-1.71941400	-2.68486800	-0.69266800
O	-2.14731500	0.51303100	-2.20239400
C	-3.22186300	0.05747500	-2.71576200
C	-4.15430500	1.84515200	0.39693500
H	-1.19881100	-3.63585400	-0.91412900
H	-2.48119200	-1.09251000	3.49321300
H	-4.66923900	2.79859800	0.62761300
H	-3.34532800	0.25510100	-3.79911400
C	2.94383700	2.20099100	0.27772600
C	2.28637900	1.31418400	1.34752600
C	1.28491400	0.38754500	0.66050400
C	3.53481000	1.39766900	-0.89369000
H	3.72829900	2.82477200	0.73656400
H	3.82855600	2.11939000	-1.67089000
O	2.48759200	0.60824000	-1.53652200
H	1.03353400	-0.78863200	-1.20654700
H	0.88251900	-0.40903000	1.29258000
O	3.34698700	0.55355000	1.95464600
H	1.77724400	1.91804000	2.11352900
O	1.98523100	3.12168800	-0.31452300
S	0.32351300	2.79729800	-0.17582900
O	-0.10123500	3.30753000	1.14045500
O	-0.24165900	3.32170800	-1.42021800
N	0.23707900	1.07528100	-0.17745000
C	3.07667200	0.03733300	3.21335000
O	2.07564900	0.32325000	3.84674700
O	5.46870000	0.35777100	-1.81212600
C	6.37100400	-0.67181600	-1.96755800
O	6.94983200	-0.76017600	-3.03887200
C	6.58508900	-1.60644400	-0.79508600
H	6.95510100	-1.05391600	0.08622300
H	7.32978100	-2.35841200	-1.08672700
H	5.63890200	-2.10058000	-0.48106600
C	4.16825600	-0.91747200	3.61681300
H	5.16428200	-0.48634000	3.43312200
H	4.06787200	-1.81679000	2.97347400
H	4.05194600	-1.18450100	4.67502400
C	4.73776600	0.50909600	-0.57096100
H	5.38367000	1.00185500	0.17851200
H	4.38729400	-0.46755400	-0.18555400
C	2.80783100	-4.08742100	-0.34884100
H	1.84162000	-4.52384500	-0.03752800
H	2.76610300	-3.92401100	-1.44058800
H	3.59026800	-4.84426600	-0.15839300
C	1.53784800	0.06431400	-0.75862100
S	3.16120700	-2.52336700	0.5559730

P(4S) with $^{-}$SMe

Rh	-4.08408000	-0.85386100	0.34087400
Rh	-1.86351700	0.06544500	-0.20322200

O	-3.19872400	-2.71955000	0.57252300
O	-3.69781300	-0.42962500	2.34362300
O	-4.87752400	1.04595500	0.08436600
O	-4.36335400	-1.22481000	-1.68095100
O	-1.10979000	-1.88154000	0.06337300
O	-1.61323700	0.42567300	1.83972200
O	-2.79272600	1.90802900	-0.41016300
C	-2.57077500	0.10147700	2.61925000
C	-1.94020400	-2.79662400	0.38224900
O	-2.27363800	-0.38168800	-2.19589100
C	-3.40310800	-0.90517800	-2.46353200
C	-4.05203400	1.97102300	-0.22690000
H	-1.50101900	-3.80675900	0.51313400
H	-2.39249900	0.31546600	3.69254700
H	-4.49092500	2.98012900	-0.35726800
H	-3.57791400	-1.11628000	-3.53793600
C	2.92411100	1.83272800	-0.76805500
C	2.20272300	1.55943800	0.56236100
C	1.20428400	0.41184600	0.32784400
C	3.62262000	0.56712200	-1.32662600
H	3.67536100	2.63431000	-0.63009700
H	3.82412000	0.77631300	-2.39042000
O	2.75347500	-0.57542800	-1.36454800
H	1.14285200	-1.50866700	-0.63070400
H	0.73050400	0.14038000	1.28605100
O	3.20836300	1.17023000	1.54253100
H	1.68547100	2.45593300	0.92704800
O	1.99295400	2.27005700	-1.77340100
S	0.30004900	2.25107200	-1.36380400
O	0.11676400	3.43201000	-0.47720400
O	-0.35699900	2.26003500	-2.67821100
N	0.16298700	0.77970600	-0.65623400
C	3.13189700	1.74097100	2.78827700
O	2.31702300	2.58273400	3.12281100
O	5.69284900	-0.64027200	-1.54719600
C	6.67051600	-1.46984000	-1.07682000
O	7.27828800	-2.16824100	-1.87271900
C	6.94472800	-1.48494800	0.42177000
H	7.19959800	-0.48180600	0.80172300
H	7.78437500	-2.16718400	0.60555400
H	6.05960600	-1.83279500	0.98074000
C	4.21380600	1.15899800	3.67971200
H	5.20766100	1.30776300	3.22871300
H	4.06283700	0.07331500	3.78831500
H	4.17450100	1.64322500	4.66364200
C	4.97181800	0.25534100	-0.66058400
H	5.56017100	1.18592600	-0.55236500
H	4.81734100	-0.19994500	0.32302800
C	2.85092400	-3.43739900	0.18594400
H	1.84143600	-3.83596400	-0.00140400
H	3.37441900	-3.29094900	-0.77042400
H	3.41329000	-4.15723400	0.79989500
C	1.92382000	-0.83941500	-0.24849300
S	2.77068300	-1.85583400	1.10954300

Table 11 Cartesian coordinates of the stationary-points involved in the nucleophilic addition of aziridine complex

Complex with $^{-}$OMe

Ad2(4S) with $^{-}$OMe

Rh	-3.91189200	-0.97821200	-0.12285900	H	1.99645100	1.92679300	2.08115100
Rh	-1.72602400	0.12652000	-0.11124900	O	2.13999700	3.12604400	-0.30501900
O	-3.02966900	-2.62729600	-1.03100300	S	0.49698300	2.77724100	-0.17511900
O	-3.45745300	-1.77248400	1.74460900	O	0.04211700	3.27568000	1.13044600
O	-4.71900400	0.70327500	0.78183500	O	-0.08670900	3.24672300	-1.43124800
O	-4.26611900	-0.13663900	-1.98928500	N	0.40492000	1.02786500	-0.10970400
O	-0.97110800	-1.59729100	-1.02506900	C	3.32327900	-0.12807000	3.06327900
O	-1.39868700	-0.73254700	1.75966400	O	2.26055400	-0.03027800	3.65528500
O	-2.66312200	1.75030600	0.79741100	O	5.22433000	-0.09455000	-1.96828000
C	-2.32076300	-1.47161100	2.24323200	C	5.93822200	-1.26993000	-2.07906500
C	-1.77902900	-2.55727800	-1.26551000	O	6.33329000	-1.58666800	-3.19184800
O	-2.19860200	0.88961200	-1.99047300	C	6.19738100	-2.05482800	-0.81268300
C	-3.33568200	0.58784900	-2.48184200	H	6.83326000	-1.46436200	-0.12773800
C	-3.91348400	1.66419400	1.02778100	H	6.73056500	-2.97623400	-1.08273000
H	-1.32517400	-3.44683000	-1.74298600	H	5.25603800	-2.27765700	-0.24417200
H	-2.09890100	-1.91102000	3.23499500	C	4.45325100	-1.06893700	3.34076100
H	-4.36375500	2.55273500	1.51238100	H	5.43204800	-0.57447100	3.24592600
H	-3.54507700	1.01820100	-3.48095200	H	4.35033600	-1.81995600	2.50901500
C	3.11123000	2.16329100	0.20842000	H	4.33660600	-1.52634200	4.33176800
C	2.50400600	1.30165500	1.32852200	C	4.64898700	0.27601700	-0.68984700
C	1.49162400	0.34124400	0.70347700	H	5.43203300	0.71293900	-0.04270600
C	3.58093900	1.32674500	-0.99672800	H	4.19157900	-0.60398900	-0.18377400
H	3.93920900	2.76689700	0.61129600	C	2.84060200	-3.29198600	0.47556200
H	3.95235200	2.01751500	-1.76964400	H	1.75080600	-3.10374500	0.26018400
O	2.42433300	0.70670300	-1.62232500	H	3.21889000	-3.85597500	-0.42439900
H	1.03445300	-0.73697700	-1.19769000	H	2.82796700	-4.05725400	1.30336200
H	1.11087500	-0.45170400	1.34832500	C	1.50348600	0.15153100	-0.77336200
O	3.61263200	0.62341500	1.92857200	O	3.55261500	-2.15809100	0.78311200

TS2(4S) with $^-$OMe

Rh	-3.93670900	-0.98208400	-0.15498600
Rh	-1.75248000	0.12165100	-0.10931900
O	-3.03536200	-2.63898200	-1.03180900
O	-3.52418900	-1.75551700	1.73143900
O	-4.76046500	0.70833500	0.71862200
O	-4.25274700	-0.15879100	-2.03854100
O	-0.97733800	-1.60894900	-0.99006800
O	-1.46355000	-0.72027300	1.77843200
O	-2.70490700	1.75434100	0.76203700
C	-2.39786500	-1.45122500	2.25083800
C	-1.78040400	-2.57053100	-1.24203300
O	-2.18279300	0.86206500	-2.00826700
C	-3.31024300	0.55735000	-2.51997300
C	-3.95968300	1.67167500	0.96998000
H	-1.31715200	-3.46250800	-1.70580000
H	-2.19916600	-1.87894500	3.25275200
H	-4.41809000	2.56558500	1.43643600
H	-3.49686500	0.97596800	-3.52859300
C	3.08721900	2.16184500	0.27222500
C	2.48101200	1.28154600	1.37810100
C	1.46077500	0.33882000	0.74172900
C	3.56311400	1.34990600	-0.94619900
H	3.91390900	2.75968100	0.68616100
H	3.91333900	2.06098100	-1.71071400
O	2.41813000	0.71168200	-1.57501100
H	1.02054800	-0.72738800	-1.17099100
H	1.06920700	-0.45299400	1.38215100
O	3.58690600	0.57288900	1.94813400
H	1.98646500	1.89338300	2.14988800
O	2.11582500	3.13274000	-0.22697100
S	0.47311600	2.77841200	-0.11195900
O	0.01114500	3.25192900	1.20025100
O	-0.10561300	3.26682700	-1.36294100
N	0.38470100	1.02835200	-0.07671500
C	3.30423100	-0.19524400	3.07788900
O	2.24708500	-0.09314000	3.68097600
O	5.24717000	0.01152500	-1.95777200
C	6.04388800	-1.10791200	-2.09112100
O	6.44766200	-1.38119100	-3.21214300
C	6.36548700	-1.88969500	-0.83814000
H	6.94239700	-1.26176500	-0.13490300
H	6.97537400	-2.75826100	-1.12041900
H	5.43791700	-2.20216400	-0.28692500
C	4.40822800	-1.17512500	3.29681500
H	5.39886600	-0.70243600	3.21393200
H	4.29025100	-1.88417200	2.41818300
H	4.28978200	-1.67813300	4.26519700
C	4.66518200	0.32661700	-0.66818500
H	5.43425400	0.77757300	-0.01308200
H	4.25074400	-0.58328600	-0.18287000
C	3.10964400	-3.45208300	0.34911100
H	2.00919500	-3.33764600	0.13610900
H	3.52498000	-3.94951200	-0.57229300
H	3.15622900	-4.24288900	1.15057200
C	1.48884300	0.15729500	-0.73773500
O	3.73204500	-2.27349600	0.6833140

P(4S) with $^-$OMe

Rh	-4.07017200	-0.83861000	0.20225100
Rh	-1.81750200	0.07202500	-0.21769300

O	-3.22697000	-2.73494700	0.31575500
O	-3.72459200	-0.56142000	2.23979500
O	-4.81826300	1.09548600	0.07165800
O	-4.30178700	-1.06161900	-1.84798300
O	-1.10744000	-1.90650000	-0.06843300
O	-1.61009800	0.28005900	1.84596900
O	-2.70624500	1.94316300	-0.32123100
C	-2.59401900	-0.07410400	2.57762700
C	-1.96489300	-2.82397200	0.15551800
O	-2.18462400	-0.22412300	-2.25124700
C	-3.31587400	-0.70615000	-2.58204700
C	-3.96713700	2.02105400	-0.15749800
H	-1.54947900	-3.85086700	0.22136400
H	-2.43798400	0.06333700	3.66681300
H	-4.38166400	3.04669200	-0.22451400
H	-3.46802500	-0.83818900	-3.67273700
C	3.02248500	1.76839700	-0.34914400
C	2.24270800	1.22292500	0.85737000
C	1.24982800	0.16870700	0.33092000
C	3.74551000	0.63845700	-1.12757900
H	3.76435300	2.51863900	-0.01266400
H	4.03990700	1.07822700	-2.09552700
O	2.85933700	-0.42833000	-1.48611700
H	1.21815600	-1.48593800	-1.06210700
H	0.74830300	-0.31334300	1.18543200
O	3.21768300	0.63775600	1.76882900
H	1.70587800	2.02137000	1.38574900

O	2.13859500	2.40330600	-1.28740600
S	0.43012000	2.34061800	-0.96044000
O	0.22212100	3.32597000	0.13532100
O	-0.16568800	2.62743000	-2.27328800
N	0.23616000	0.76186800	-0.56968000
C	2.97596100	0.76121000	3.10883900
O	2.04791500	1.37946500	3.60230500
O	5.83000100	-0.51658800	-1.47034400
C	6.99906800	-1.14205700	-1.14931300
O	7.66133200	-1.65143600	-2.03945800
C	7.41776700	-1.17200000	0.31655700
H	7.50360400	-0.15701500	0.73816500
H	8.38947000	-1.67720300	0.38388000
H	6.68183600	-1.71670500	0.93049800
C	4.03148300	-0.00464200	3.88912800
H	5.04339700	0.32882600	3.60947000
H	3.95879800	-1.07749300	3.64938000
H	3.87223700	0.14749200	4.96419300
C	5.03101100	0.14080600	-0.44695900
H	5.59819100	0.99878700	-0.04137300
H	4.78847000	-0.55540300	0.36409700
C	3.04332600	-3.03101600	-0.21913300
H	2.17831600	-3.56625500	-0.65970900
H	3.78107700	-2.83898000	-1.01897600
H	3.49882600	-3.66724500	0.55613700
C	1.97604900	-0.93426100	-0.48379000
O	2.63334300	-1.82585400	0.42326900

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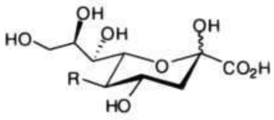
CHAPTER 3

Synthesis of monocyclic oxathiazepanes via sequential aziridination and Barbier-type allylation/propargylation of glycal: An approach to sialic acid

1. INTRODUCTION

Sialic acids are a diverse family of naturally occurring 2-keto-3-deoxynononic acids that are commonly found as the α-ketosidically linked terminal sugar on cell-surface glycoconjugates and are the most abundant terminal sugar in mammalian systems.[1] In 1936, a crystalline reducing acid was isolated by Blix from *bovine submandibular mucin* which was then named "sialic acid".[2] There are 43 different naturally occurring sialic acid derivatives that have been reported in nature thus far. The most ubiquitous derivatives are those derived from 5-acetamido-D-glycero-D-galacto-nonulosonic acid (*N*-acetylneuraminic acid, Neu5Ac, **1**). The 5-glycolylamido derivative N-glycolylneuraminic acid (Neu5Gc, **2**) and the non-aminated 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN, **3**) are also observed in biological systems, however, *N*-acetylneuraminic acid (Neu5Ac) remains the most abundant sialic acid (Figure 1).[3] Other naturally occurring derivatives involve acetylation, lactonylation, or phosphorylation of the hydroxyl groups, most commonly at C-9, and methylation or sulfation at C-8.[4]



1 R = NHAc (Neu5Ac)
2 R = NHGc (Neu5Gc)
3 R = OH (KDN)

Figure 1 Natural derivatives of sialic acids

The biological functions of sialic acids are categorized as follows: (i) to bring negative charge as glycoconjugates, (ii) to determine the tertiary structure of certain glycoproteins, (iii) to transfer information between cells, and (iv) to assist cell recognition.[5] In addition, homopolymerized Neu5Ac or Neu5Gc were also found in fish eggs and in the capsule of certain bacteria such as *Neisseria meningitides* group B in which the internal glycosidic linkages are α(2→8), α(2→9) or alternating α(2→8)/α(2→9).[1,6]

Various therapeutic agents and diagnostic reagents for infectious diseases have been developed based on the detailed understanding of the biological roles of Neu5Ac, which further promoted the discovery of anti-influenza drugs such as Zanamivir[7] (NeuAc2en, an influenza therapeutic agent) and Oseltamivir (a mimic of NeuAc) (Figure 2).[8]

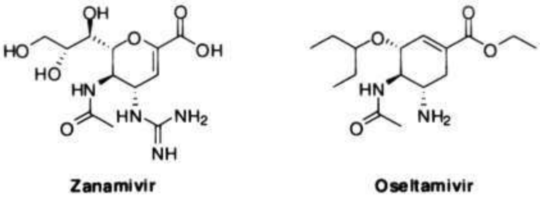


Figure 2 Examples of anti-influenza drugs, Zanamivir and Oseltamivir.

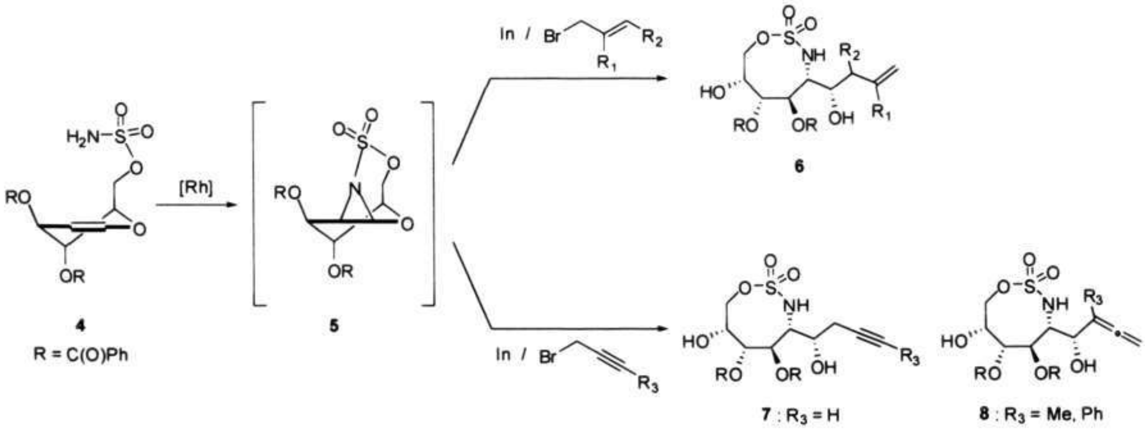
The growing realization of the significant roles of sialic acids in various disease states and physiological processes has resulted in extensive research into sialic acid chemistry and biochemistry. Several synthetic routes to sialic acids have started with stereochemically complex six-carbon fragments, most often carbohydrates to avoid the lengthy synthetic routes from non-carbohydrate and achiral precursors. The coupling reaction of six-carbon fragment with the three-carbon unit follows to form the nine-carbon backbone.[9] However, this step usually presents some drawbacks such as low diastereomeric ratios and yields of products.

In recent years, the nitrogen atom-transfer processes, particularly metal-catalyzed reactions of *in situ* generated nitrenes with olefins, have emerged as a very promising route for the preparation of aziridines and the unique class of heterocyclic compounds.[10] To increase the scope of this reaction, we have developed an intramolecular version of rhodium-catalyzed nitrene delivery to a glycal scaffold.[11] Specifically, the diastereofacial preference of the nitrogen atom-transfer process is controlled by the position of a sulfamate ester moiety on the glycal molecule. Installation of the sulfamate ester moiety on C4 and C6 positions gave pure β- and α-aminoglycosides, respectively. Based on this methodology, we have strong interest in the development of our protocol for synthesis of sialic acids by direct *C*-aminoglycosylation.

It is surprising that a method towards *C*-aminoglycosides has not been forth-coming because the presence of nitrogen-containing functionality in the neighborhood is not quite compatible with common *C*-glycosylation strategies. The present available methods to synthesize *C*-linked 2-amino sugar derivatives utilize Keck allylation, which is assisted by radical-mediated alkylation with alkynylstannanes and allyltrimethylsilanes.[12] Direct allylation of 2-deoxy-2-acetamido-α-D-galactopyranosyl chloride has been performed.[13] α-*C*-Glycosides of 2-amino-2-deoxymannosamine have been prepared from α-*C*-glycosides by S_N2 inversion of C-2 stereochemistry with azide nucleophiles.[14] Wittig-type reactions at the anomeric position, followed by recyclization to reform the pyranose or furanose have also been reported.[15]

2. RESULTS AND DISCUSSION

The study of *C*-glycosylation chemistry is of our interest. Here, we describe our observation of a remarkable *C*-coupling reaction in sequential rhodium-catalyzed aziridination and Barbier allylation or propargylation at the anomeric position of D-glycal (Scheme 1). The reaction proceeded selectively to form eight-membered oxathiazepanes (**6-8**) in a single process. The reaction mechanism and structural characterization of products will be further demonstrated.



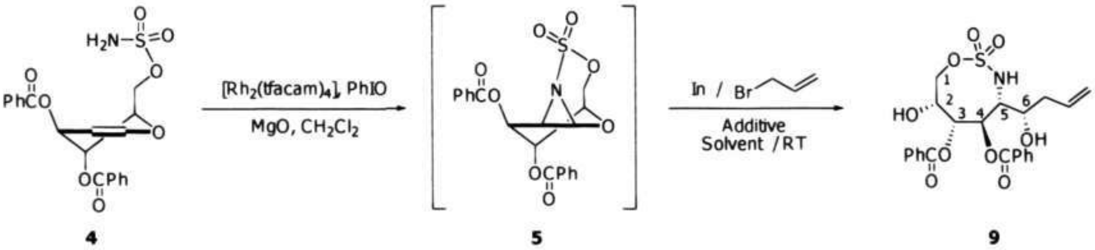
Scheme 1 One-pot reaction of rhodium-catalyzed aziridination and Barbier allylation/propargylation.

We first prepared sulfamate ester glycal (**4**) in its protected form and, then, treated it with PhIO, MgO, and 5 mol% of [$Rh_2(tfacam)_4$] in dichloromethane. The *in situ* generated nitrene was intramolecularly delivered to the double bond, forming a transient aziridine intermediate (**5**). In this course of study, trapping a short-lived aziridine intermediate by an appropriate carbon nucleophile was very critical.[16] The

Barbier allylation or propargylation has emerged as a powerful tool in carbon-carbon forming reaction,[17] so we applied this reaction into our synthetic system.

Initial investigation was focused on searching for a metal-mediated allylation of the transient aziridine intermediate. We found that nucleophiles generated from Mg were very reactive and could not deliver any coupled products. Other mild alkylating reagents such as In, Sn and Zn were next examined. Indeed, when the aziridine intermediate reacted with simple allyl bromide in the presence of indium metal and THF as solvent, a coupling reaction occurred and the oxathiazepane **9** was obtained in 72% yield (entry 2). Attempts were made to optimize the reaction conditions by exploiting InF_3, $InBr_3$, NaI or KI in conjunction with indium in THF (entries 3-6). Interestingly, the use of KI as additive showed a significant improvement in yield up to 85%; furthermore the stereochemical outcome in the product was retained. Changing the solvent to CH_2Cl_2 and DMF dramatically reduced the yields to 50% and 0%, respectively (entries 7 and 8). The employment of allyltin or -zinc species in different solvents showed no impact on *C*-glycosylation (entries 9-12). The reaction with the system of In/KI/THF conclusively was the best to give high yield and pure oxathiazepane **9**.

Table 1 Optimization of reaction conditions for metal-mediated allylation of D-glycal 4



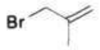
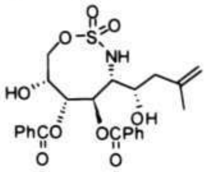
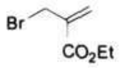
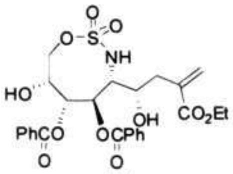
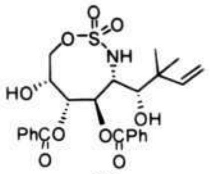
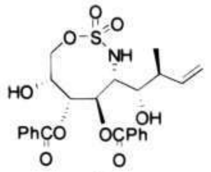
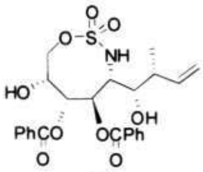
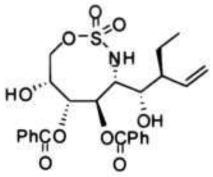
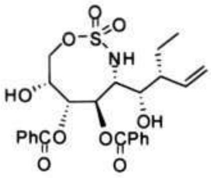
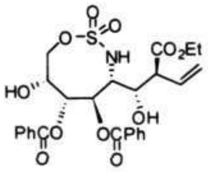
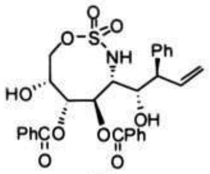
Entry	Metal	Additive	Solvent	Yield (%)
1	Mg	-	THF	-
2	In	-	THF	72
3	In	InF_3	THF	40
4	In	$InBr_3$	THF	30
5	In	NaI	THF	35
6	In	KI	THF	85
7	In	KI	CH_2Cl_2	50
8	In	KI	DMF	-
9	Sn	KI	THF	-
10	Zn	KI	THF	39
11	Zn	KI	CH_2Cl_2	-
12	Zn	KI	DMF	-

[a] Generation of aziridine intermediate: treatment of **4** (1 equiv) with 5 mol% of [Rh$_2$(tfacam)$_4$], PhIO (1.5 equiv), MgO (5 equiv) and 4Å molecular sieve in dry CH_2Cl_2 (3 ml) at RT for 30 mins. Preparation of allylindium nucleophile: a solution of indium powder (2 equiv), allyl bromide (3 equiv) and additive (1 equiv) in THF (1 ml) was stirred at RT for 1 h.

A variety of allyl bromides also coupled with glycal substrate under our optimized conditions. In all cases, *C*-coupled oxathiazepanes were obtained in good yields (Table 2, entries 1-7). The HRMS gave a clear *m/z* $[M+Na]^+$ base peak corresponding to the chemical formula of the oxathiazepane products, and, moreover, NOE experiments showed no correlation between H2–H6 (counting the carbon at $-CH_2SO_2NH$ moiety as C–1). The configuration at the stereogenic centers was assigned on the basis of the small coupling constants of cis-oriented protons ($J_{2,3}$ and $J_{5,6} < 1$ Hz) as well as the large coupling constants of trans-oriented protons ($J_{4,5} = 9.4$-9.8 Hz). The allylation reaction gave the regioselective products, where the substituent is α to the newly formed C–C bond (entries 3-7, Table 2). Based on the ^1H NMR spectra, products **13** and **14** were obtained as inseparable mixture of two diastereomers. We had tried to separate the diastereomeric mixture of compound **13** to identify its stereochemistry but unsuccessful.

However, the stereochemistry of the major diastereomer of **14** was unambiguously elucidated by single-crystal X-ray analysis and the α-substituent on the allylic moiety was assigned to be *S*-configuration as shown in Figure 1. With this evidence in hand, we assume that the allyl-linked oxathiazepanes **15** and **16** would preferably form *S*-configuration as major products due to the bulkiness of their α-substituent (entries 6 and 7). The plausible mechanism is described in *Section 2.1*.

Table 2 Barbier allylation of D-glycal **4**

Entry	Nucleophile	Product	% Yield[a]
1		 **10**	86
2		 **11**	93
3		 **12**	87
4		 **13a** +  **13b**	80 (1:1.6)[b]
5		 **14a** +  **14b**	72 (1.5:1)[b]
6[c]		 **15**	53
7		 **16**	74

[a] The isolated yield. [b] The number in parenthesis represent the diastereomeric ratio (the configuration assignment is based on *Computational Studies*). [c] 0.1 equiv of $InBr_3$ was used.

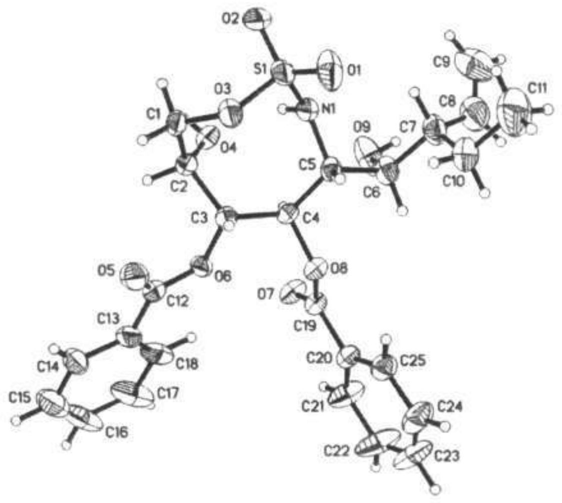
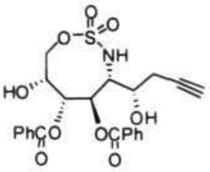
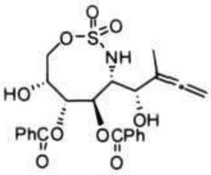
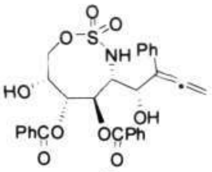


Figure 1 X-ray crystallography of the major diastereomer of oxathiazepane **14**.

After successful synthesis by using various allyl bromides, we switched nucleophile precursors to propargyl bromides. The coupling reaction of sulfamate ester **4** and propargyl bromide took place under the optimized conditions to give propargyl oxathiazepane (**17**) in 90% (Table 2, entry 1), while the substituted propargyl bromides such as methyl- and phenyl propargyl bromides gave the allene products solely (Table 3, entries 2 and 3). The presence of the allene moiety was clearly evidenced by ^{1}H and ^{13}C NMR data. The methylene protons of allenes **18** and **19** appear as multiplet at 5.30-5.42 ppm, while the characteristic ^{13}C signals of the central carbon of the allene moiety appear at 205.1-207.4 ppm. The further investigation of using bulky and electron-rich nucleophile in entry 4 failed; no desired product was detected.[18] As resulted, the formation of alkyne or allene products is dominated by the effect of the substituent on propargyl bromides.

Table 3 Barbier propargylation of D-glycal **4**

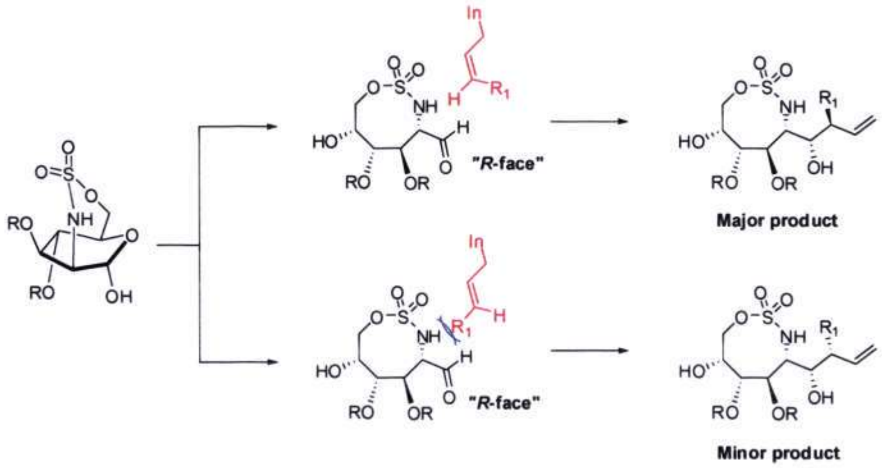
Entry	Nucleophile	Product	% Yield
1		 **17**	90
2		 **18**	89
3		 **19**	77
4		-	-

2.1 Proposed mechanism for the formation of oxathiazepanes

Formation of oxathiazepane products involves two sequential steps, which are allylation and sugar ring expansion. We propose that water plays a significant role in these particular steps. Although we had tried to generate the alkylindium reagent under nitrogen and anhydrous THF was used, we still could not get rid of the moisture contamination. Therefore, the water molecule possibly attacks the anomeric carbon atom before or after allylation/propargylation.

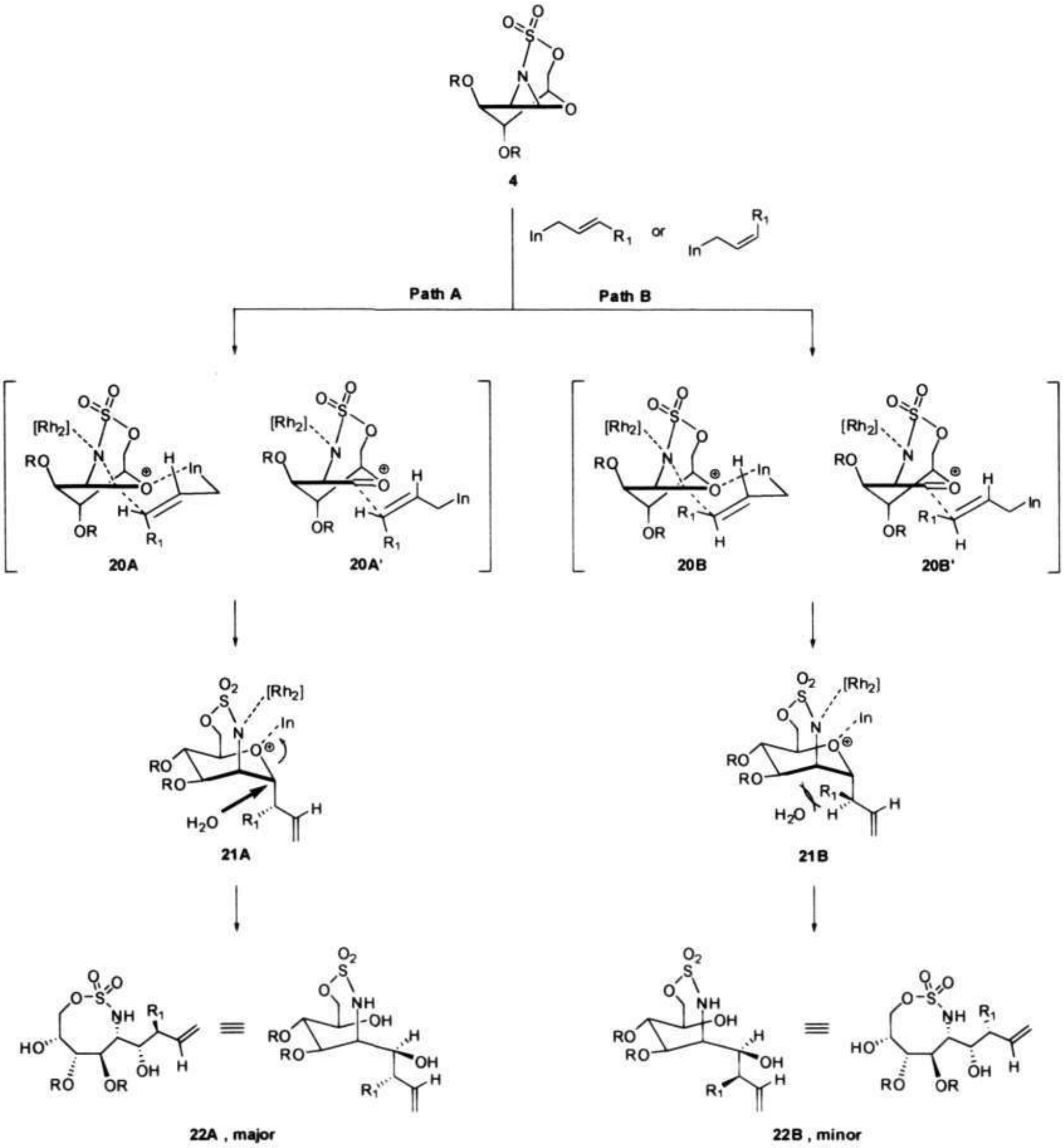
By experimental observations and computational results, there is strong evidence that glycosyl acceptor specifically attacks at the positively charged anomeric carbon from the opposite site of the aziridine ring. In the case of *O*– and *S*–nucleophiles, a newly formed glycosidic bond occurs coincidently with a N–C1 bond cleavage. Even though the nucleophile has been changed to be a *C*-species in the present work, we still believe that the glycosylation should proceed in a similar manner to *O*– and *S*–cases. We, however, need to be concerned about the stereochemical outcome of R_1 and hydroxyl group at C7 and C6, respectively.

The proposed mechanism of the sugar-ring expansion via hemiacetal was shown in Scheme 2. After forming the unstable aziridine intermediate, water acts as nucleophile to give hemiacetal. The readily hemiacetal was then transformed to aldehyde. The allylindium preferably approached the aldehyde intermediate on the *R*-face and pointed its R_1 substituent away from the bulky oxathiazepane moiety due to the steric factor.



Scheme 2 Plausible pathway for formation of oxathiazepanes via hemiacetal intermediate.

Scheme 3 depicts another alternative hypothesis to explain how regio- and stereoselectivity of indium-induced alkylation as well as sugar ring-opening is controlled, when allylation occurred prior to hydrolysis. The orientation of the R_1 substituent and the presence of indium metal seem to play a significant role in controlling the stereochemistry of products. The indium metal may or may not chelate with the *O* atom of the sugar ring when the allyl nucleophile is attacking the anomeric carbon. With the former hypothesis, the stereoinduction can be rationalized by forming a chair-like transition state as illustrated in **20A** and **B**, while the latter proceeds through oxonium ions (**20A'** and **B'**). In our complex system, the R_1 group of transition states **20A** and **A'** situates in pseudoaxial position, which is less energetically favoured than that of **20B** and **B'** but the energy barrier of forming complexes **20A** and **A'** may be overwhelmed by the approaching direction of water molecule in following hydrolysis step. As seen in complex **21A**, the water molecule can easily attack at the anomeric carbon because that R_1 group points away from the water's trajectory. On the other hand, the R_1 substituent of **21B** blocks the upper face; hence there is a large repulsion between the R_1 and the coming H_2O, especially, when R_1 is bulky. Therefore, indium-mediated alyllation of our study case prefers to proceed through pathway **A** rather than **B** to give the eight-membered oxathiazepane **22A** as a major diastereomer and **22B** as a minor product. Consequently, this may affect the lower yields of products **13-16** shown in Table 2, entries 4-7.



Scheme 3 Proposed mechanism of allylation prior to sugar ring-opening.

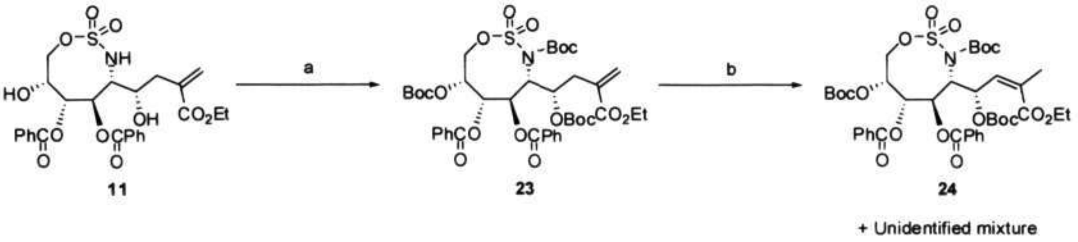
With knowledge of this structural requirement for efficient allylic addition, we conducted a series of computational studies designed to provide additional insights concerning the mechanism of this indium-mediated reaction. Herein, we utilized density functional theory (DFT) calculations to access the structures and energies of two key intermediates in the proposed allylation mechanism (**20** and **21** (**a-b**)).[19] To shorten the calculation time, the protecting groups of the sugar skeleton were modified by replacing benzoyl groups with acetyl groups and the rhodium catalyst was not included in this calculation.

In the case of R_1 = Me, two transition states **20A** and **21A** are higher in energy than their corresponding complexes **20B** and **21B** (2.03 and 0.79 kcal/mol, respectively). These results suggest that preference for forming transition states in the glycosylation and hydrolysis steps belongs to the pathway B. However, it is still premature to assign the diasteromeric ratio, when having a small substituent at the α-allylic position. While R_1 = Et, the energy gap between **20A** and **20B** is reduced to be 1.63 kcal/mol and the formation of complex **21A** becomes favoured by 2.52 kcal/mol (Table 4). Considering on the stereochemical outcome obtained from x-ray crystallography, we found that our calculation data agrees well with the experimental result. This makes us believe that the steric hindrance of the R_1 substituent is a key component to allow the reaction to proceed via pathway A predominantly. As resulted, the stereochemical assignment of other bulky R_1 substituents (Ph and CO_2Et) should follow pathway A as well.

Table 4 Gibbs free energy differences of complexes **20** and **21** (**A-B**).

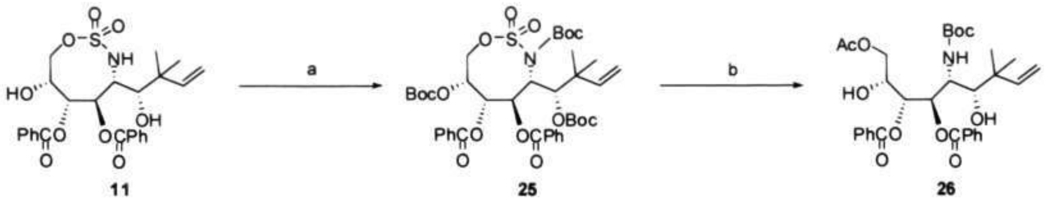
Complex	$\Delta G = G_{Path\ A} - G_{Path\ B}$	
	R_1 = Me	R_1 = Et
20	2.03	1.63
21	0.79	-2.52

We have developed a new strategy to construct the nine-carbon backbone that can be very useful for the library synthesis of biologically active sialic acids. To obtain the sialic acid molecule we thought we should cleave the sulfamoyloxy moiety of oxathiazepane **11** in order to access acyclic methylene compound. The following reactions, which are removal of two benzoyl protecting groups and ozonolysis, may allow a pyranose ring of sialic acid to automatically reform as in commonly reported methods.[20] From a synthetic standpoint, the nucleophilic displacement of sulphur trioxide, especially in the large-sized oxathiazepanes, can be activated by protecting a nitrogen atom with an electron-withdrawing group. In this study, we chose tert-butyl carbamate (Boc) as a protecting group for compound **11**. The formation of Boc-protected compound **23** was conducted under anhydrous conditions, by reaction with triethylamine and anhydrous Boc_2O in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP). We attempted to replace the sulfamoyloxy group by an acetate ion but, unfortunately, treament of Boc-protected oxathiazepane **23** with sodium acetate (NaOAc) in refluxing DMF gave a disappointing result. The methylene isomerisation and other unidentified compounds were detected instead (Scheme 4).



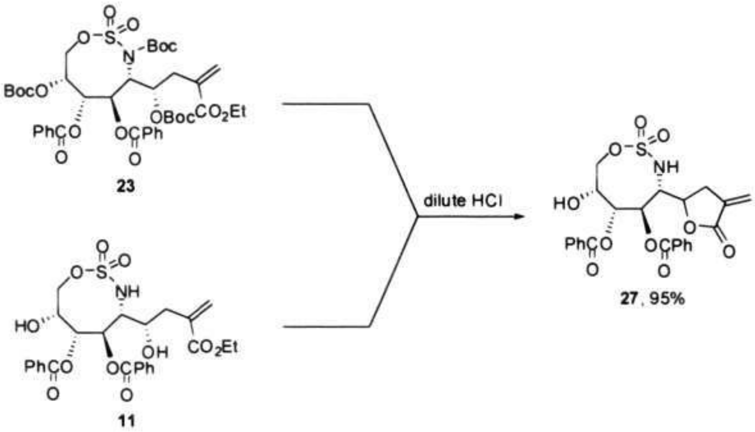
Scheme 4 Attempt to cleave the sulfamoyloxy moiety under basic condition. a) $Boc_2O/DMAP/Et_3N/THF/0\ °C/72\ \%$. b) NaOAc/DMF/80 °C.

On the contrary, the isomerisation was not observed in the case of using α,α'-dimethyl allyl **12** as starting material (Scheme 5). The sulfamoyloxy ring was nicely opened by the acetate anion while maintaining intact all stereogenic centers as well as alkene functionality.



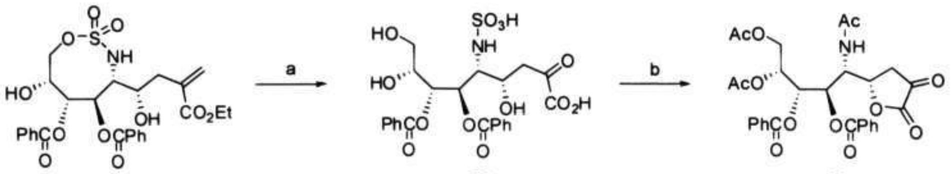
Scheme 5 Attempt to cleave the sulfamoyloxy moiety under basic condition. a) $Boc_2O/DMAP/Et_3N/THF/0$ °C/88 %. b) NaOAc/DMF/80 °C/95 %.

Next, we examined the possibility of removing the sulfamoyloxy functionality under acidic conditions. Treatment of the protected oxathiazepane **23** with dilute HCl in dioxane did not provide our desired product. The ester was readily cyclised to the corresponding α-methylene-γ-butyrolactone in good yield. This unexpected product is well-known in possessing many important biological activities such as allergic, cytotoxic, antitumor, and also growth-controlling and antimitotic.[21] Moreover, the synthetic route to α-methylene-γ-butylrolactone by using our strategy could be made without protection of amino and hydroxyl groups from compound **11** (Scheme 6).



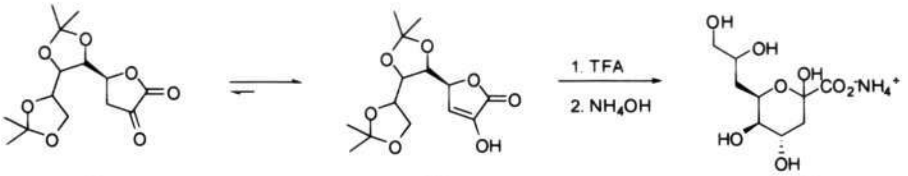
Scheme 6 Attempt to cleave the sulfamoyloxy moiety under acidic conditions.

Indeed, the cleavage of the sulfamate ester tethered olefin was encountered with the isomerisation of the terminal alkene to the more stable substituted-olefin (Scheme 3) as well as the lactonization of the ester (Scheme 5). To avoid these side reactions, we turned to the transformation of the exo-methylene moiety to the keto functionality. Surprisingly, the ozonolysis of compound **11** in methanol at -78 °C followed by addition of sodium sulfite (Na_2SO_3) gave the sulfamate ring-opened product in quantitative yield. Sodium sulfite in this case was used as an oxygen scavenger and at the same time acted as a weak base to hydrolyze the sulfamate and ethyl ester groups. We attempted to remove the benzoyl protective group of compound **28** by using dilute sodium hydroxide but the reaction proceeded very quickly and gave a complicated mixture. We then turned to remove the sulfonic group ($-SO_3H$) and protected the corresponding product with an acetyl group, giving rise to α-ketolactone **29** as shown in Scheme 7.



Scheme 7 The approach to naturally occurring sialic acid. a) i) O_3/MeOH/–78 °C ii) Na_2SO_3/RT/overnight iii) 1N NaH_2PO_4/RT/2 h b) AcCl/CH_2Cl_2/pyridine/0 °C/3h/ 62% overall yield.

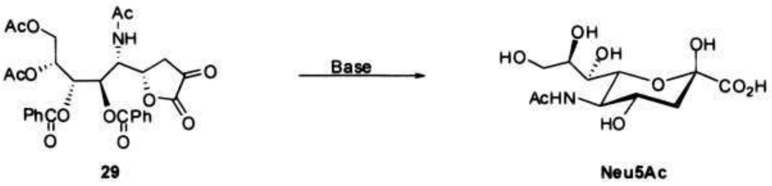
According to Shing's procedure,[22] α-ketolactone **30** is a key intermediate towards 3-deoxy-D-gluco-oct-2-ulosonic acid **32** (D-*gluco*-KDO). KDO has a significant role in prohibiting the biosynthesis of the Gram-negative bacterial lipopolysaccharide (LPS) and is a newly characterized to be a member of a biochemically important class of antibacterial agents. In $CDCl_3$ and d_6-acetone solutions, it was observed that α-ketolactone **30** is preponderantly as its enol tautomer **31**. After deacetylation of the lactone tautomers, **30** and **31**, with aqueous TFA, D-*gluco*-KDP was formed and isolated as its ammonium salt **32**.



30 **31** **32**

Scheme 8 The approach to 3-deoxy-D-gluco-oct-2-ulosonic acid **32** via hydrolysis of α-ketolactone **30**.

Applying to our synthetic molecule **29**, removal of the benzoyl protecting groups will produce a reactive hydroxyl group, which is ready for the pyranose ring cyclisation. We have been investigating the hydrolysis of the benzoyl protective groups by using NaOMe in MeOH. However, the structural identification of final product as well as reaction optimization of the final step are still underway in our laboratory.



Scheme 9 Hydrolysis of protecting groups to reform a pyranose ring: The final step for synthesis of sialic acid.

3. CONCLUSION

We have demonstrated a new route for *C*-aminoglycosylation that is based on the intramolecular aziridination on a glycal scaffold, followed by the selective *C*-glycosylation. With assistance of allylindium reagents, the sugar ring could be opened selectively to obtain a variety of *C*-linked oxathiazepanes. These oxathiazepanes can be applied to the synthesis of natural products with many interesting biological activities, especially, sialic acid and their analogues. Our methodology allows a quick synthesis of a library of sialic acid analogues for our H1N1 project.

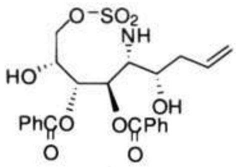
4. EXPERIMENTAL

All reactions were carried out under an atmosphere of nitrogen unless otherwise indicated. Flasks were oven dried and allowed to cooled under vacuum prior to use. Solvents and reagents were purified by standard methods and transferred by syringe.[23] Product purification by flash column chromatography was accomplished using silica gel 60 (0.010-0.063 nm). The ^{1}H and ^{13}C NMR data were obtained on a 300 MHz Bruker ACF 300, 400 MHz Bruker DPX 400, 400 MHz Jeol ECA 400 and 500 MHz Bruker AMX 500 NMR spectrometers, respectively. For ^{1}H NMR, chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are, in all cases, referenced to the residual proton resonance peaks: δ 7.26 for $CHCl_3$. The ^{13}C NMR chemical shifts were reported in ppm relative to the center peak of the multiplet for deuterated solvents: δ 77.0 (t) for $CDCl_3$. Coupling constants (*J*) for all spectra are reported in Hz. Infrared spectra were measured on a Bio-RAD FTS 165 FT-IR Spectrometer as thin films on sodium bromide plates and are recorded in units of cm^{-1}. HRMS (ESI) spectra were recorded on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system.

4.1 Experimental Procedure and Spectroscopic Data

4.1.1 Typical procedure for generation of aziridine intermediate and its ring-opening.

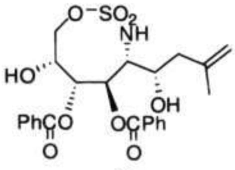
A mixture of sulfamate ester **4** (30 mg, 6.92×10^{-2} mmol), $Rh_2(tfacam)_4$ (2.5 mg, 3.83×10^{-3} mmol), PhIO (22 mg, 9.99×10^{-2} mmol), and MgO (14 mg, 0.347 mmol) in CH_2Cl_2 (3 ml) was stirred at room temperature for 30 mins under N_2. The allyl- or propargyl indium nucleophile was freshly prepared by the addition of alkyl bromide (0.205 mmol, 3 equiv) and KI (12 mg, 7.22×10^{-2} mmol) to a suspension solution of indium powder (16 mg, 0.138 mmol) in THF (1 ml). The mixure was stirred for an hour at room temperature and subsequently added to the rhodium catalytic mixure above. The suspension was stirred vigorously at room temperature and monitored by TLC. Upon the completion of the reaction, the mixture was filtered through a pad of Celite. The filter cake was rinsed with CH_2Cl_2 and the combined filtrates were evaporated under reduced pressure. The residue was purified by chromatography on silica gel (30 % ethyl acetate in hexane) as eluent to afford the oxathiazepane product.



9

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,6-Dihydroxy-8-ene-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (9)

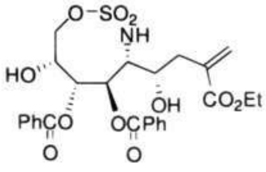
Yield: 78 %; colourless, viscous oil; **^{1}H NMR (500 MHz, $CDCl_3$):** δ(ppm): 7.89 (d, J = 7.3 Hz, 2H, Ph), 7.82 (d, J = 7.3 Hz, 2H, Ph), 7.46 (m, 2H, Ph), 7.32 (m, 2H, Ph), 7.27 (m, 2H, Ph), 6.09 (t, *J* = 10.0 Hz, 1H, H3), 5.79 (ABX system, J_{AX} = 17.1 Hz, J_{BX} = 10.1, J_{AB} = 7.0 Hz, 1H, $CH_2CH{=}CH_2$), 5.66 (d, *J* = 9.0 Hz, 1H, H4), 5.17 (dd, *J* = 10.1, 1.4 Hz, 1H, $CH_2CH{=}CH_2$), 5.12 (dd, *J* = 10.1, 1.4 Hz, 1H, $CH_2CH{=}CH_2$), 4.62 (dd, *J* = 12.6, 4.4 Hz, 1H, CH_2OSO_2), 4.56 (dd, *J* = 12.6, 4.4 Hz, 1H, CH_2OSO_2), 4.49 (m, 1H; H5), 4.23 (br s, 1H, NH), 3.74 (m, 2H, H1 and H2), 2.48 (dd, *J* = 14.4, 7.0 Hz, 1H, $CH_2CH{=}CH_2$), 2.41 (dd, *J* = 14.4, 7.0 Hz, 1H, $CH_2CH{=}CH_2$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.4 (CO), 165.9 (CO), 133.9 (Ph), 133.6 ($CH_2CH{=}CH_2$), 133.5 (Ph), 129.8 (Ph), 129.6 (Ph), 128.5 (Ph), 128.3 (Ph), 118.8 ($CH_2CH{=}CH_2$), 75.7 (C3), 73.1 (C5), 72.6 (CH_2), 68.8 (C4), 68.7 (C1), 56.8 (C2), 37.6 ($CH_2CH{=}CH_2$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 2956, 1714, 1600, 1367, 1278 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{25}NO_9SNa$: 514.1148 [M+Na]$^+$; found: 514.1161.



10

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,6-Dihydroxy-8-methyl-8-ene-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (10)

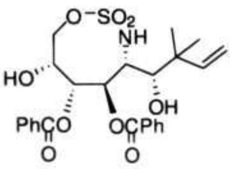
Yield: 86 %; colourless solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 7.91 (d, *J* = 7.4 Hz, 2H, Ph), 7.84 (d, *J* = 7.4 Hz, 2H, Ph), 7.49 (m, 2H, Ph), 7.34 (t, *J* = 7.4 Hz, 2H, Ph), 7.29 (t, *J* = 7.4 Hz, 2H, Ph), 6.27 (br s, 1H, NH), 6.11 (t, *J* = 9.6 Hz, 1H, H4), 5.63 (d, *J* = 8.8 Hz, 1H, H3), 4.87 (s, 1H, =CH$_2$), 4.82 (s, 1H, =CH$_2$), 4.62 (dd, *J* = 13.5, 2.2 Hz, 1H, CH_2OSO_2), 4.54 (dd, *J* = 13.5, 4.4 Hz, 1H, CH_2OSO_2), 4.50 (m, 2H, H2 and OH), 3.87 (m, 1H, H6), 3.79 (br s, 1H, OH), 3.71 (t, *J* = 8.6 Hz, 1H, H5), 2.47 (dd, *J* = 14.4, 8.7 Hz, 1H, CH$_2$), 2.32 (dd, *J* = 14.4, 4.4 Hz, 1H, CH$_2$), 1.67 (s, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 166.3 (CO), 166.1 (CO), 141.3 (=C$_q$), 133.9 (Ph), 133.8 (Ph), 133.7 (Ph), 130.2 (Ph), 129.8 (Ph), 129.7 (Ph), 129.2 (Ph), 128.6 (Ph), 128.57 (Ph), 128.51 (Ph), 114.0 (=CH_2), 76.0 (C3), 73.0 (C2), 72.4 (CH_2OSO_2), 69.5 (C4), 66.8 (C6), 57.3 (C5), 41.5 (CH_2), 22.7 (CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3507, 3291, 3019, 1721, 1602, 1451, 1277 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{24}H_{29}NO_{10}SNa$: 528.1299 $[M+Na]^+$; found: 528.1319.



11

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,6-Dihydroxy-8-ethoxycarbonyl-8-ene-3,4-di-*O*-benzoyl-[1,2] thiazepane -1,1-dioxide (11)

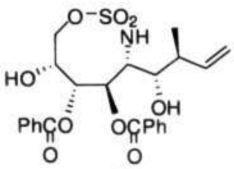
Yield: 93 %; colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 7.87 (d, J = 7.6 Hz, 2H, Ph), 7.83 (d, J = 7.6 Hz, 2H, Ph), 7.49-7.44 (m, 2H, Ph), 7.33-7.25 (m, 4H, Ph), 6.37 (br s, 1H, NH), 6.24 (s, 1H, =CH_2) 6.13 (t, J = 9.6 Hz, 1H, H4), 5.74 (s, 1H, =CH_2), 5.64 (d, J = 8.8 Hz, 1H, H3), 4.63 (dd, J = 13.5, 2.0 Hz, 1H, CH_2OSO_2), 4.56 (dd, J = 13.5, 4.3 Hz, 1H, CH_2OSO_2), 4.19 (br s, 1H, OH), 4.49 (m, 1H, H2), 4.02 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.90 (m, 1H, H6), 3.72 (t, J = 9.7 Hz, 1H, H5), 3.40 (br s, 1H, OH), 2.74 (dd, J = 14.1, 8.3 Hz, 1H, CH_2), 2.64 (dd, J = 14.1, 3.7 Hz, 1H, CH_2), 1.12 (t, J = 7.1 Hz, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 167.8 (CO), 166.2 (CO), 166.1 (CO), 136.6 (=C_q), 133.8 (Ph), 133.7 (Ph), 129.8 (Ph), 129.7 (Ph), 129.3 (=CH_2), 128.6 (Ph), 128.54 (Ph), 128.50 (Ph), 76.0 (C3), 72.9 (C2), 72.4 (CH_2OSO_2), 68.8 (C4), 68.6 (C6), 61.2 (CH_2CH_3), 57.7 (C5), 37.0 (CH_2), 14.0 (CH_2CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3462, 2956, 1712, 1629, 1450, 1278 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{25}NO_9SNa$: 586.1354 $[M+Na]^+$; found: 586.1373.



12

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,6-Dihydroxy-7,7-dimethyl-8-ene-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (12)

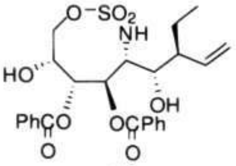
Yield: 87 %; colourless solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 7.89 (d, J = 7.1 Hz, 2H, Ph), 7.82 (d, J = 7.1 Hz, 2H, Ph), 7.52-7.42 (m, 2H, Ph), 7.36-7.30 (m, 4H, Ph), 6.25 (br d, J = 9.1 Hz, NH), 6.06 (t, J = 9.7 Hz, 1H, H4), 5.92 (ABX system, J_{AX} = 17.5, J_{BX} = 10.7, J_{AB} = 1.0 Hz, 1H, C*H*=CH$_2$), 5.64 (d, J = 9.4 Hz, 1H, H3), 5.16 (dd, J = 10.7, 1.0 Hz, 1H, CH=C*H*$_2$), 5.09 (dd, J = 17.5, 1.0 Hz, 1H, CH=C*H*$_2$), 4.60 (dd, J = 13.6, 4.8, 1H, CH$_2$OSO$_2$), 4.56 (dd, J = 13.6, 2.5, 1H, CH$_2$OSO$_2$), 4.46 (m, 1H, H2), 4.30 (br s, 1H, OH), 4.09 (t, J = 9.8 Hz, 1H, H5), 3.32 (s, 1H, H6), 3.10 (br s, 1H, OH), 1.13 (s, 3H, CH$_3$), 1.11 (s, 3H, CH$_3$); **^{13}C NMR (75 MHz, CDCl$_3$):** δ (ppm): 166.3 (CO), 165.8 (CO), 143.8 (=CH), 133.8 (Ph), 133.5 (Ph), 130.1 (Ph), 129.7 (Ph), 129.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 114.5 (=CH$_2$), 75.5 (C3), 75.2 (C6), 73.0 (C2), 72.0 (CH$_2$OSO$_2$), 70.4 (C4), 54.0 (C5), 41.2 (C$_q$), 23.6 (CH$_3$), 23.2 (CH$_3$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3019, 2922, 1721, 1602, 1451, 1277 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for C$_{25}$H$_{31}$NO$_{10}$SNa: 542.1455 [M+Na]$^+$; found: 542.1335.



13

(2*R*,3*R*,4*R*,5*R*,6*S*,7*S*)-2,6-Dihydroxy-7-methyl-8-ene-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (13)

Yield: 80 %; colourless oil. Diastereomeric ratio: 1:1.6 of two inseparable diastereomers; **^{1}H NMR (300 MHz, $CDCl_3$) of the major diastereomer:** δ (ppm): 7.87-7.80 (m, 4H, Ph), 7.52-7.44 (m, 2H, Ph), 7.37-7.25 (m, 4H, Ph), 6.18-6.04 (m, 2H, H4 and NH), 5.72-5.56 (m, 2H, H3 and CH=), 5.25 (dd, J = 17.3, 1.6 Hz, 1H, CH=CH_2), 5.14 (dd, J = 10.0, 1.6 Hz, 1H, CH=CH_2), 4.64-4.45 (m, 3H, CH_2 and H2), 3.92 (t, J = 10.6 Hz, 1H, H5), 3.48 (br s, 1H, OH), 3.31 (d, J = 10.6 Hz, 1H, H6), 2.62 (m, 1H, CH), 2.44 (br s, 1H, OH), 1.08 (d, J = 6.7 Hz, 1H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$) of the major diastereomer:** δ (ppm): 166.2 (CO), 165.8 (CO), 140.2 (=CH), 133.7 (Ph), 133.6 (Ph), 129.79 (Ph), 129.72 (Ph), 128.7 (Ph), 128.5 (Ph), 128.4 (Ph), 117.9 (=CH_2), 76.7 (C3), 73.1 (C2), 72.4 (C4), 72.0 (CH_2OSO_2), 69.6 (C6), 54.6 (C5), 40.5 (CH), 16.2 (CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3500, 3307, 3018, 1714, 1602, 1452, 1278 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{24}H_{29}NO_{10}S_1Na$: 528.1299 [M+Na]$^+$; found: 528.1266.

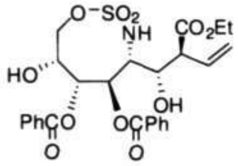


14

(2*R*,3*R*,4*R*,5*R*,6*S*,7*S*)-2,6-Dihydroxy-7-ethyl-8-ene-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (14)

Yield: 72 %; colourless solid. Diastereomeric ratio: 1.5:1 of two inseparable diastereomers; **^{1}H NMR (500 MHz, $CDCl_3$) of the major diastereomer**: δ (ppm): 7.92 (d, J = 7.6 Hz, 2H, Ph), 7.87 (d, J = 7.6 Hz, 2H, Ph), 7.53-7.44 (m, 2H, Ph), 7.36 (t, J = 7.6 Hz, 2H, Ph), 7.30 (t, J = 7.6 Hz, 2H, Ph), 6.13 (dd, J = 9.6, 8.5 Hz, 1H, H4), 5.94 (br d, J = 8.5 Hz, 1H, NH), 5.85 (br s, 1H, OH), 5.61 (d, J = 8.5 Hz, 1H, H3), 5.48 (ABX system, J_{AX} = 17.0, J_{BX} = 9.9, J_{AB} = 1.8 Hz, 1H, CH=CH_2), 5.29 (dd, J =

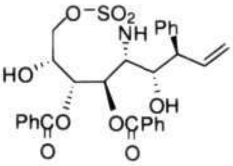
9.9, 1.8 Hz, 1H, CH=CH_2), 5.24 (dd, J = 17.0, 1.8 Hz, 1H, CH=CH_2), 4.58 (m, 2H, CH_2OSO_2), 4.51 (m, 1H, H2), 3.92 (m, 1H, H5), 3.63 (br s, 1H, OH), 3.39 (dd, J = 9.6, 2.2 Hz, 1H, H6), 2.39 (m, 1H, CH), 1.70 (m, 1H, CH_2CH_3), 1.16 (m, 1H, CH_2CH_3), 0.87 (t, d, J = 7.4 Hz, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$) of the major diastereomer:** δ (ppm): 166.4 (CO), 165.6 (CO), 138.4 (=CH), 133.8 (Ph), 133.78 (Ph), 133.70 (Ph), 129.8 (Ph), 129.7 (Ph), 128.8 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 120.4 (=CH_2), 77.3 (C3), 72.4 (CH_2OSO_2), 71.8 (C2), 70.6 (C4), 69.6 (C6), 54.8 (C5), 48.2 (CH), 23.0 (CH_2CH_3), 11.2 (CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3018, 2929, 1718, 1649, 1388, 1269 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{25}H_{31}NO_{10}SNa$: 542.1455 [M+Na]$^+$; found: 542.1335.



15

(2*R*,3*R*,4*R*,5*R*,6*S*,7*S*)-2,6-Dihydroxy-7-ethoxycarbonyl-8-ene-3,4-di-*O*-benzoyl-[1,2] thiazepane-1,1-dioxide (15)

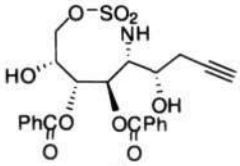
Yield: 53 %; colourless solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 7.88 (d, J = 7.6 Hz, 2H, Ph), 7.83 (d, J = 7.6 Hz, 2H, Ph), 7.48 (m, 2H, Ph), 7.36-7.26 (m, 4H, Ph), 6.17 (d, J = 3.2 Hz, 1H, NH), 6.11 (t, J = 9.5 Hz, 1H, H4), 5.75 (dt, J = 17.2, 10.4, 1H, CH=CH_2), 5.61 (d, J = 8.8 Hz, 1H, H3), 5.45 (d, J = 17.2 Hz, 1H, CH=CH_2), 5.34 (d, J = 10.4, 1H, CH=CH_2), 4.61 (dd, J = 12.9, 2.0 Hz, 1H, CH_2OSO_2), 4.52 (dd, J = 12.9, 4.0 Hz, 1H, CH_2OSO_2), 4.49 (m, 1H, H2), 4.15 (m, 2H, CH_2), 3.94 (m, 2H, CH and H6), 3.83 (br d, J = 9.8 Hz, 1H, OH), 3.59 (t, , J = 9.2 Hz, 1H, H5), 3.50 (br d, J = 5.5 Hz, 1H, OH), 1.23 (t, J = 7.2 Hz, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 172.9 (CO), 166.1 (CO), 165.9 (CO), 152.6 (=CH), 133.8 (Ph), 133.6 (Ph), 131.1 (Ph), 129.9 (Ph), 129.7 (Ph), 129.6 (Ph), 128.5 (Ph), 128.4 (Ph), 121.7 (=CH_2), 75.9 (C3), 72.1 (C2), 70.3 (CH_2OSO_2), 69.2 (C6 and C4), 61.3 ($\mathit{C}H_2CH_3$), 54.7 (C5), 51.7 ($\mathit{C}HCO_2Et$), 14.0 ($CH_2\mathit{C}H_3$); **IR ($CHCl_3$):** $\tilde{\nu}$ = 2956, 1712, 1629, 1450, 1278 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{25}NO_{10}SNa$: 586.1354 $[M+Na]^+$; found: 586.1373.



16

(2*R*,3*R*,4*R*,5*R*,6*S*,7*S*)-2,6-Dihydroxy-7-phenyl-8-ene-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (16)

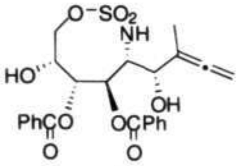
Yield: 74 %; colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 7.84 (d, J = 7.9 Hz, 2H, Ph), 7.77 (d, J = 7.9 Hz, 2H, Ph), 7.61 (t, J = 7.4 Hz, 1H, Ph), 7.54 (t, J = 7.4 Hz, 1H, Ph), 7.47 (t, J = 7.8 Hz, 2H, Ph), 7.36 (t, J = 7.8 Hz, 2H, Ph), 7.30 (t, J = 7.4 Hz, 3H, Ph), 7.19 (m, 2H, Ph), 6.07 (m, 2H, H4 and NH), 5.92 (dt, J = 16.9, 9.6 Hz, 1H, $C\mathit{H}=CH_2$), 5.41 (d, J = 8.6 Hz, 1H, H3), 5.27 (d, J = 16.9 Hz, 1H, $CH=C\mathit{H}_2$), 5.18 (d, J = 9.6 Hz, 1H, $CH=C\mathit{H}_2$), 4.58 (dd, J = 13.5, 2.3, 1H, CH_2OSO_2), 4.48 (dd, J = 13.5, 4.0, 1H, CH_2OSO_2), 4.40 (m, 1H, H2), 3.90 (br d, J = 10.4 Hz, 1H, OH), 3.67 (t, J = 9.7 Hz, 1H, H6), 3.54 (t, J = 10.0 Hz, 1H, H5), 3.52 (br d, 1H, OH); **^{13}C NMR (75 MHz, $CDCl_3$):** δ (ppm): 166.1 (CO), 165.6 (CO), 139.4 (Ph), 138.4 (=CH), 133.7 (Ph), 133.67 (Ph), 133.61 (Ph), 130.1 (Ph), 129.9 (Ph), 129.7 (Ph), 128.8 (Ph), 128.5 (Ph), 128.48 (Ph), 128.45 (Ph), 127.2 (Ph), 118.8 (=CH_2), 76.1 (C3), 72.5 (C2), 72.0 (CH_2OSO_2), 71.4 (C6), 69.7 (C4), 54.4 (C5), 52.9 (CH); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3485, 3294, 3064, 1715, 1601, 1492, 1274 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{29}H_{31}NO_{10}SNa$: 590.1461 $[M+Na]^+$; found: 590.1487.



17

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,6-Dihydroxy-8-yne-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (17)

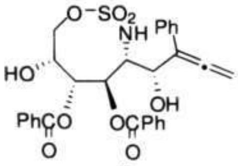
Yield: 90 %; colourless oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 7.89 (d, J = 7.4 Hz, 2H, Ph), 7.82 (d, J = 7.4 Hz, 2H, Ph), 7.50-7.40 (m, 2H, Ph), 7.34-7.25 (m, 4H, Ph), 6.12 (t, J = 9.8 Hz, 1H, H4), 5.67 (d, J = 9.0 Hz, 1H, H3), 4.63 (dd, J = 13.6, 1.5 Hz, 1H, CH$_2$OSO$_2$), 4.57 (dd, J = 13.6, 4.2 Hz, 1H, CH$_2$OSO$_2$), 4.50 (m, 1H, H2), 3.94 (t, J = 6.8 Hz, 1H, H6), 3.83 (d, J = 10.5 Hz, 1H, H5), 2.67 (dd, J = 7.8, 2.5 Hz, 1H, CH$_2$), 2.54 (dd, J = 5.8, 2.5 Hz, 1H, CH$_2$), 2.05 (t, J = 2.5 Hz, 1H, ≡CH); **^{13}C NMR (75 MHz, CDCl$_3$):** δ (ppm): 166.3 (CO), 166.0 (CO), 133.9 (Ph), 133.6 (Ph), 130.1 (Ph), 129.8 (Ph), 129.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 80.1 (≡Cq), 75.8 (C3), 73.0 (C2), 72.3 (CH$_2$OSO$_2$), 71.0 (≡CH), 68.1 (C4 and C6), 56.8 (C5), 23.6 (CH$_2$); **IR (CHCl$_3$):** $\tilde{\nu}$ = 3487, 3305, 3018, 2434, 1716, 1381, 1215 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for C$_{23}$H$_{25}$NO$_{10}$SNa: 512.0986 [M+Na]$^+$; Found: 512.096.



18

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,6-Dihydroxy-7-methy-7,8-diene-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (18)

Yield: 89 %; colourless solid. **^{1}H NMR (300 MHz, CDCl$_3$):** δ (ppm): 7.90 (d, J = 7.5 Hz, 2H, Ph), 7.85 (d, J = 7.5 Hz, 2H, Ph), 7.50-7.43 (m, 2H, Ph), 7.34-7.27 (m, 4H, Ph), 6.15 (t, *J* = 9.5 Hz, 1H, H4), 6.01 (br s, 1H, NH), 5.65 (d, *J* = 8.8 Hz, 1H, H3), 5.03 (m, 2H, =CH_2), 4.56 (dd, *J* = 13.5, 4.2 Hz, 1H, CH_2OSO_2), 4.55 (d, *J* = 13.5 Hz, 1H, CH_2OSO_2), 4.48 (m, 1H, H2), 4.10 (s, 1H, H6), 3.93 (br s, 1H, OH), 3.87 (d, *J* = 9.7 Hz, 1H, H5), 2.64 (br s, 1H, OH), 1.76 (t, *J* = 2.8 Hz, 3H, CH_3); **^{13}C NMR (75 MHz, $CDCl_3$):** δ (ppm): 205.1 (=C_q), 166.1 (CO), 165.9 (CO), 133.7 (Ph), 133.6 (Ph), 129.75 (Ph), 129.71 (Ph), 128.58 (Ph), 128.53 (Ph), 128.4 (Ph), 99.2 (=CH_2), 80.1 (*C*(CH_3)), 75.9 (C3), 72.7 (C2), 72.1 (CH_2OSO_2), 69.2 (C4), 69.1 (C6), 55.9 (C5), 15.0 (CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 1720, 1689, 1635 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{24}H_{27}NO_{10}SNa$: 526.1141 $[M+Na]^+$; found: 526.1141.

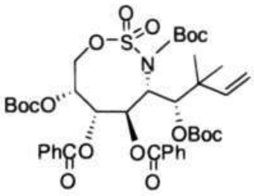


19

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,6-Dihydroxy-7-pheny-7,8-diene-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (19)

Yield: 77%; colourless solid. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm): 7.97 (d, *J* = 7.7 Hz, 2H, Ph), 7.89 (d, *J* = 7.7 Hz, 2H, Ph), 7.57 (t, *J* = 7.7 Hz, 1H, Ph), 7.51 (t, *J* = 7.7 Hz, 1H, Ph), 7.44-7.20 (m, 9H, Ph), 6.22 (t, *J* = 9.5 Hz, 1H, H4), 6.13 (br s, 1H, NH), 5.57 (d, *J* = 8.6 Hz, 1H, H3), 5.49 (dd, *J* = 11.7, 2.7 Hz, 1H, =CH_2), 5.42 (dd, *J* = 11.7, 3.2 Hz, 1H, =CH_2), 4.76 (br s, 1H, OH), 4.62 (dd, *J* = 13.4, 2.0 Hz, 1H, CH_2OSO_2), 4.50 (dd, *J* = 13.4, 4.0 Hz, 1H, CH_2OSO_2), 4.39 (m, 1H, H2), 4.00 (d, *J* = 5.0 Hz, 1H, H6), 3.86 (t, *J* = 9.7 Hz, 1H, H5), 2.75 (br d, *J* = 7.1 Hz, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 207.4 (=C_q), 166.1 (CO), 165.7 (CO), 133.9 (Ph), 133.6 (Ph), 133.2 (Ph), 129.8 (Ph), 129.7 (Ph), 128.7 (Ph), 128.6 (Ph), 128.4 (Ph), 127.7 (Ph), 126.8 (Ph), 106.7 (=CH_2), 83.0 (*C*(CH_3)), 76.1 (C3), 72.7 (C2), 72.1 (CH_2OSO_2), 69.4

(C4), 66.4 (C6), 56.6 (C5); **IR ($CHCl_3$):** $\tilde{\nu}$ = 3406, 3018, 1710, 1419, 1363, 1215 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{29}H_{2}9NO_{9}SNa$: 588.1299 $[M+Na]^+$; found: 588.1294.



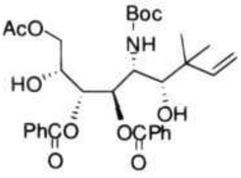
25

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,6-Di-(tert-butoxycarbonyloxy)-7,7-dimethyl-8-ene-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (25)

Di-tert-butyl dicarbonate (88 μL, 0.37 mmol) and DMAP (0.7 mg, 5.7×10^{-3} mmol) were added to a solution of oxathiazepane **12** (32 mg, 6.2×10^{-5} mmol) in CH_2Cl_2 (1 mL) and Et_3N (11 μL, mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h and then quenched with sat. aq. NH_4Cl. The mixture was extracted with EtOAc (2 ×). The combined organic layers were dried over anh. Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (eluent 20 % ethyl acetate in hexane).

Yield: 88 %; colourless solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 7.92 (m, 2H, Ph), 7.85 (m, 2H, Ph), 7.49-7.45 (m, 2H, Ph), 7.36-7.27 (m, 4H, Ph), 5.88 (ABX system, J_{AX} = 17.5, J_{BX} = 10.7, J_{AB} = 1.0 Hz, 1H, C*H*=CH_2), 5.72 (m, 1H, H4), 5.65 (m, 1H, H3), 5.28 (br t, *J* = 4.0 Hz, 1H, H5), 5.13 (dd, *J* = 17.5 Hz, 1H, CH=CH_2), 5.12 (d, *J* = 10.7 Hz, 1H, CH=CH_2), 4.77 (s, 1H, H1), 4.60 (m, 2H, CH_2OSO_2), 4.17 (t, *J* = 9.9 Hz, 1H, H2), 1.50 (s, 18H, CH_3), 1.42 (s, 9H, CH_3), 1.16 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); **^{13}C NMR (75 MHz, $CDCl_3$):** δ (ppm): 164.7 (CO), 152.6 (CO), 152.0 (CO), 143.1 (=CH), 133.5 (Ph), 133.4 (Ph), 129.9 (Ph), 129.7 (Ph), 128.5 (Ph), 128.47 (Ph), 128.44 (Ph), 114.7 (=CH_2), 84.1 (Cq), 82.9 (Cq), 78.7 (C6), 75.6 (C2), 72.8 (C3 and C4), 69.0

(CH_2), 54.3 (C2), 41.3 (Cq), 27.7 (CH_3), 27.6 (CH_3), 23.7 (CH_3), 23.1 (CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 2977, 2929, 1735, 1451, 1253 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{35}H_{45}NO_{13}SNa$: 743.2503 $[M+Na+H]^+$; found: 743.2576.

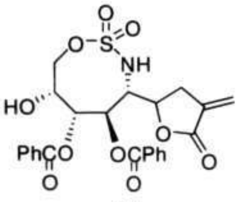


26

(2*R*,3*R*,4*R*,5*R*,6*S*)-1-Acetoxy-5-(*tert*-butoxycarbonylamino)-2,6-dihydroxy-7,7-dimethylnon-8-ene-3,4-diyl dibenzoate (26)

Sodium acetate (30 mg, 0.36 mmol) was added to a solution of oxathiazepane **25** (25 mg, 3.1 × 10^{-2} mmol) in dry DMF (0.6 mL) in the presence of 4 Å molecular sieves. The mixture was stirred at 90 °C for 12 h under nitrogen. After cooling the reaction to room temperature, 1N NaH_2PO_4 (0.5 mL) was added and the mixture was stirred for another hour. The mixture was filtered and the filtrate was washed with water (3 ×), dried over anh. Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by chromatography on silica gel (eluent 50 % ethyl acetate in hexane).

Yield: 91 %; colourless solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.09 (d, J = 7.1 Hz, 2H, Ph), 8.03 (d, J = 7.1 Hz, 2H, Ph), 7.58 (t, J = 7.3 Hz, 2H, Ph), 7.48-7.43 (m, 4H, Ph), 5.95 (ABX system, J_{AX} = 17.5, J_{BX} = 10.7, J_{AB} = 1.0 Hz, 1H, C*H*=CH_2), 5.55 (dd, J = 4.5, 1.5 Hz, 1H, H5), 5.27 (dd, J = 4.8, 1.5 Hz, 1H, H4), 5.15 (d, J = 3.2 Hz, 1H, H1), 5.05 (dd, J = 17.5, 1.1 Hz, 1H, CH=CH_2), 5.00 (dd, J = 10.7, 1.1 Hz, 1H, CH=CH_2), 4.60 (ABq, J = 11.5, 2H, CH_2OSO_2), 3.64 (q, J = 6.2 Hz, 1H, H5), 3.50 (dd, J = 4.8, 3.2 Hz, H2), 2.21 (br s, 1H, NH), 1.95 (s, 3H, CH_3), 1.33 (s, 9H, CH_3), 1.14 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 170.7 (CO), 165.4 (CO), 166.3 (CO), 153.7 (CO), 144.3 (=CH), 133.4 (Ph), 133.3 (Ph), 130.1 (Ph), 129.8 (Ph), 129.6 (Ph), 128.5 (Ph), 128.6 (Ph), 128.5 (Ph), 113.3 (=CH_2), 82.2 (Cq), 81.9 (C3), 80.8 (C1), 77.7 (C5), 64.2 (C2), 62.4 (CH_2OSO_2), 59.3 (C5), 41.3 (C_q), 27.6 (CH_3), 24.3 (CH_3), 23.0 (CH_3), 20.8 (CH_3); **IR ($CHCl_3$):** $\tilde{\nu}$ = 2977, 1742, 1724, 1254 cm^{-1}; **HRMS (ESI):** *m/z*: calcd for $C_{32}H_{40}NO_9$: 582.2704 $[M-OH]^+$; found: 582.2703.

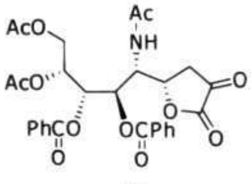


27

(2*R*,3*R*,4*R*,5*R*)-2-hydroxy-1-(4-methylene-5-oxotetrahydrofuran-2-yl)-3,4-di-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (27)

Starting material **11** or **23** (7.5×10^{-4} mmol) was dissolved in a mixture of HCl (4M aq, 1.6 mL) in dioxane (1.6 mL). The reaction mixture was stirred at room temperature until complete conversion was observed by TLC. The mixture was then diluted with EtOAc, washed with aq. 5% $NaHCO_3$, and brine, dried over anh. Na_2SO_4. Solvents were removed under vacuum to give a crude product, which was further purified by chromatography on silica gel (eluent 30 % ethyl acetate in hexane).

Yield: 95 %; colourless solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm): 8.09 (d, J = 7.1 Hz, 2H, Ph), 8.03 (d, J = 7.1 Hz, 2H, Ph), 7.58 (t, J = 7.3 Hz, 2H, Ph), 7.48-7.43 (m, 4H, Ph), 5.95 (ABX system, J_{AX} = 17.5, J_{BX} = 10.7, J_{AB} = 1.0 Hz, 1H, C*H*=CH_2), 5.55 (dd, J = 4.5, 1.5 Hz, 1H, H5), 5.27 (dd, J = 4.8, 1.5 Hz, 1H, H4), 5.15 (d, J = 3.2 Hz, 1H, H1), 5.05 (dd, J = 17.5, 1.1 Hz, 1H, CH=CH_2), 5.00 (dd, J = 10.7, 1.1 Hz, 1H, CH=CH_2), 4.60 (ABq, J = 11.5, 2H, CH_2OSO_2), 3.64 (q, J = 6.2 Hz, 1H, H5), 3.50 (dd, J = 4.8, 3.2 Hz, 1H, H2), 2.21 (br s, 1H, NH), 1.95 (s, 3H, CH_3), 1.33 (s, 9H, CH_3), 1.14 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm): 170.1 (CO), 166.0 (CO), 165.1 (CO), 133.7 (Ph), 133.6 (Ph), 133.5 (Ph), 129.7 (Ph), 129.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 123.3 (=CH_2), 77.3 (C3), 75.9 (C6), 73.0 (C2), 72.7 (CH_2), 69.3 (C4), 56.9 (C5), 28.9 (CH_2); **HRMS (ESI):** *m/z*: calcd for $C_{24}H_{23}NO_{10}SNa$: 540.0940 $[M+Na]^+$; found: 540.0936.



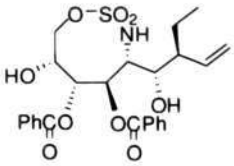
29

(2*R*,3*R*,4*R*,5*R*)-1,2-Di-acetoxy-5-(acetylamino)-1-(4,5-di-oxo-tetrahydrofuran-2-yl)-3,4-diyl benzoate (29)

O_3 in O_2 was bubbled through a solution of **11** (170 mg, 0.30 mmol) in methanol (17 mL) for 5 min at −78 °C. Na_2SO_3 (170 mg, 1.4 mmol) was then added, and the solution was stirred overnight. After filtration and evaporation of the solvent until about 2/3 of the origin volume remaining, 1N NaH_2PO_4 (2.0 mL) was added and the mixture was stirred for another hour. The mixture was filtered and the solvent was removed under reduced pressure to dryness. The resulting residue was washed with diethyl ether (3 ×) and used for next step without purification. The residue was dissolved in CH_2Cl_2 (20 mL) and pyridine (0.1 mL), and acetyl chloride (88 μL, 1.2 mmol) was added. After being stirred at ambient temperature for 4 h, the reaction was washed with water, brine, dried over anh. Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by chromatography on silica gel (eluent 50 % ethyl acetate in hexane).

Yield: 62 %; colourless solid. **^{1}H NMR (400 MHz, CDCl$_3$):** δ (ppm): 8.09 (d, J = 7.2 Hz, 2H, Ph), 7.99 (d, J = 7.2 Hz, 2H, Ph), 7.63 (t, J = 7.5 Hz, 1H, Ph), 7.56 (t, J = 7.5 Hz, 1H, Ph), 7.50-7.40 (m, 4H, Ph), 6.23 (d, J = 9.6 Hz, 1H, NH), 5.90 (dd, J = 9.7, 1.9 Hz, 1H, CH), 5.53 (dd, J = 9.4, 1.9 Hz, 1H, CH), 5.22 (t, J = 1.6 Hz, 1H, CH), 4.87 (t, J = 9.7, 1.3 Hz, 1H, CH), 4.17 (dd, J = 11.9, 3.1 Hz, 1H, CH$_2$), 4.13 (dd, J = 11.3, 5.4 Hz, 1H, CH$_2$), 4.10 (t, J = 2.7 Hz, 1H, CH), 4.02 (m, 1H, CH), 2.23 (s, 3H, CH$_3$), 1.99 (s, 3H, CH$_3$), 1.96 (s, 3H, CH$_3$); **HRMS (ESI):** *m/z*: calcd for $C_{29}H_{29}NO_{12}Na$: 606.1587 [M+Na]$^+$; found: 606.1584.

Table 1 Crystal data and structure refinement for a major diastereomer **14**.



14

Empirical formula	$C_{25}H_{29}NO_9S$	
Formula weight	519.55	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 14.2985(4) Å	α = 90°
	b = 8.2394(2) Å	β = 91.610(2)°
	c = 22.1560(7) Å	γ = 90°
Volume	2609.19(13) $Å^3$	
Z	4	
Density (calculated)	1.323 Mg/m^3	
Absorption coefficient	0.176 mm^{-1}	
F(000)	1096	
Crystal size	0.30 x 0.24 x 0.18 mm^3	
The range for data collection	1.42 to 26.83°	
Index ranges	-18<=h<=18, -10<=k<=10, -28<=l<=28	
Reflections collected	34296	
Independent reflections	10776 [R(int) = 0.0377]	
Completeness to theta = 26.83°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9690 and 0.9490	
Refinement method	Full-matrix least-squares on F^2	

Table 1 Crystal data and structure refinement for a major diastereomer **14**. (*continued*)

Data / restraints / parameters	10776 / 72 / 687
Goodness-of-fit on F^2	1.061
Final R indices [I>2sigma(I)]	R1 = 0.0435, wR2 = 0.1041
R indices (all data)	R1 = 0.0669, wR2 = 0.1297
Absolute structure parameter	-0.03(6)
Largest diff. peak and hole	0.468 and -0.365 e.Å^{-3}

4.2 Computational Studies

DFT calculations were carried out with the Gaussian 03 package.[24] The energy profiles of the reaction were computed at the B3LYP level.[25] Effective core potentials (ECPs) with double-ξ valence basis (LANL2DZP)[26] were used to describe the indium atom and the standard 6-31+G(d) basis set was used for all other atoms (*C*, *O*, *H*, *S* and *N*). Analytical second derivatives (normal modes) were also calculated for zero point energy correction and estimation of the Gibbs free energy at room temperature.

Table 1 Select bond distances (Å) for complexes **20a-b** and **21a-b** at the allylation step

complex	O1-C1	C1-C3'	O1-In	In-C1'	O1-C2'
20a (R = Me)	1.324	2.551	2.676	2.387	3.028
20b (R = Me)	1.321	2.643	2.708	2.355	3.182
21a (R = Me)	1.498	1.535	2.228	2.904	3.012
21b (R = Me)	1.498	1.534	2.215	3.034	2.896
20a (R = Et)	1.324	2.553	2.689	2.389	2.888
20b (R = Et)	1.322	2.637	2.711	2.355	3.180
21a (R = Et)	1.498	1.536	2.241	2.868	3.015
21b (R = Et)	1.498	1.536	2.217	3.044	2.887

O1 = anomeric oxygen, C1 = anomeric carbon, C1' = carbon atom on the allyl moiety that binds with indium metal, C2' = carbon atom at the second position on the allyl moiety, and C3' = carbon atom at the third postion on the allyl moiety

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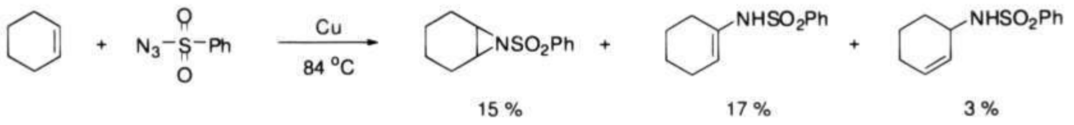
CHAPTER 4

Additional studies

1. INTRODUCTION

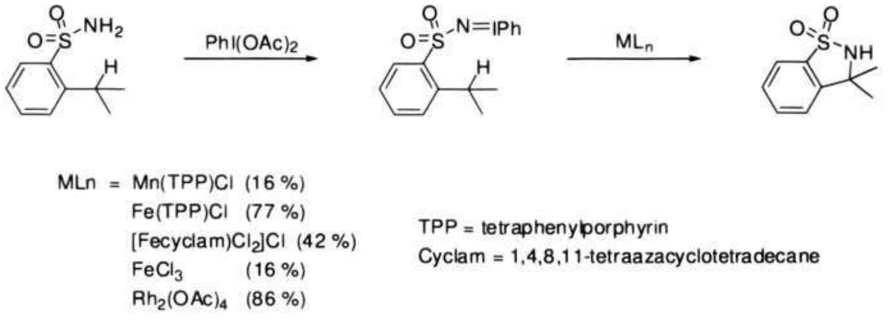
Our research theme is focused on developing new efficient methodologies that are of broad utility to synthetic chemistry. A range of molecules of interest is carbohydrates due to their importance in the biological systems, in roles of cell regulation, recogination and growth. Moreover, various stereochemical centers presented in the carbohydrate molecules have shown high potential in controlling the stereochemical outcomes of products. Particularly, a wide range of aminoglycosides have been successfully synthesized by the intramolecular *N*-insertion into the carbon-carbon double bond of glycal scaffold as shown in previous chapters. The powerful uses of carbohydrates as well as reactive nitrene species have inspired us to extend our research topic to the functionalization of the carbon-carbon single bond on glucose based molecule. We believe that the C–H amination would be more stereospecific on the sugar template and, moreover, offer an alternative route towards α-hydroxyamines and unusual amino acids.

The early work done using nitrenes in this way was in the late 1960's by Kwart and Kahn.[1] Their work was regarded as the first use of a C–H insertion using a nitrene intermediate under the influence of a transition metal. They used a copper catalyst to cause benzenesulfonyl azides and select hydrocarbons to undergo C–H insertion and alkane aziridation. This was never confirmed however as azides were rarely used as nitrogen sources in metal directed aminations and it was seen that reactions of this type were more likely to follow a non stereospecific radical reaction pathway.



Scheme 1 Copper-catalyzed C–H insertion investigated by Kwart and Kahn.

Roughly 20 years later, Breslow and Gellman[2] found a metal-nitrene amination. Their early work took inspiration from natural cytochrome p450 enzyme systems which used iron tetraphenylporphyrin (TPP) catalysis. They applied this porphyrin metal catalyst to a reaction of oxygen in iodosyl benzene to certain hydrocarbons Scheme 2. Initial results showed that in reactions using *N*-arenesulfonyliminiodinane ($ArSO_2N{=}IPh$) nitrene precursors in *N* atom insertion worked well with Mn(III)(TPP)Cl and $[Rh_2(OAc)_4]$ catalysis being used as well as Fe(III) based catalysts.

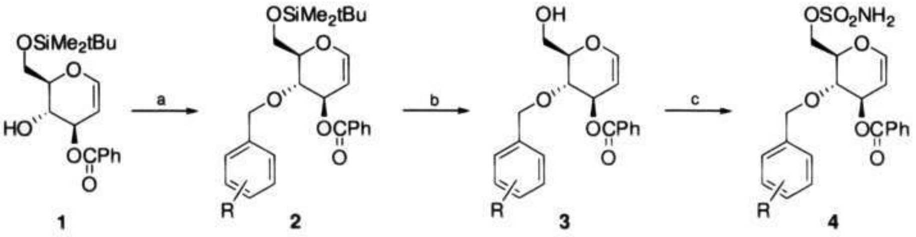


Scheme 2 Metal-catalyzed intramolecular C–H insertion investigated by Breslow and Gellman.

More work by Du Bois involved the use of sulfamate esters as nitrogen precursor. These substrates undergo selective C–H amination to give [1,2,3]-oxathi azinane-2,2-dioxides, where further reaction with a suitable nucleophile causes ring opening to obtain 1,3-difunctionalized amines.[3] Sulfamate esters were also found to be much more efficient in amination than carbamates. The improvement of the catalytic turnover was observed for the reaction of sulfamate ester with the metal nitrene, comparing with the carbamate substrate. The sulfamate requires only 1-2 mol% rhodium(II) loading compared to the 5% catalytic loading for carbamate reactions.

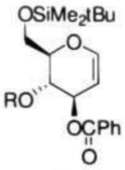
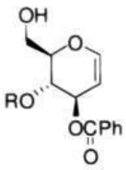
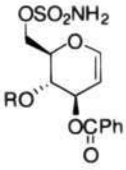
2. RESULTS AND DISCUSSION

In order to examine the hypothesis of selective nitrogen insertion at the benzylic site, we planned to synthesize the starting material from commercially available D-glycal. Synthesis involved the use of D-glycal's varying reactivity of different hydroxyl sites allowing for selective protection. With common protective group methodology, benzyl derivatives were synthesized as shown in general scheme 3 and yields of each step were shown in Table 1.



Scheme 3 Synthesis of sulfamate-protected glycal derivatives. a) benzyl bromide/NaH/THF/DMF/0 °C. b) TBAF/THF/0 °C. c) $ClSO_2NCO/HCO_2H$/DMA/0 °C.

Table 1 Yields of benzylated, desilylated, and sulfamoylated products

R substituent	% isolated yield		
	 **2**	 **3**	 **4**
a: benzyl	84	90	48
b: 4-methoxybenzyl	82	69	92
c: 4-methylthiobenzyl	86	76	71
d: 4-isopropylbenzyl	79	93	74
e: 4-nitrobenzyl	47	74	67
f: 3-methoxybenzyl	83	91	94
g: 2-trifluoromethylbenzyl	76	82	62
h: 2-bromobenzyl	67	89	76
i: 2-methoxy-2-oxoethoxy	80	55	76

The structural characterization of each compound was thoroughly made by using ^1H and ^{13}C NMR, and mass spectroscopy. For example, sulfamate esters **4a-h** in ^1H NMR show two characteristic peaks which are a broad singlet of sulfamoyloxy group ($-SO_2NH_2$) and two doublets of two geminal protons at the benzylic site (11-13 Hz).

Finally, we investigated the C–H insertion reaction started as shown in Table 2. The reaction was catalyzed by dimeric rhodium catalyst, $Rh_2(OAc)_4$, and employed iodosobenzene diacetate ($PhI(OAc)_2$) as oxidant.

Table 2 The rhodium-catalyzed C–H insertion of the glycal

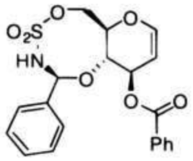
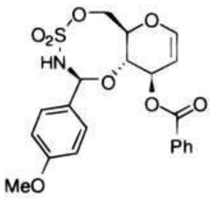
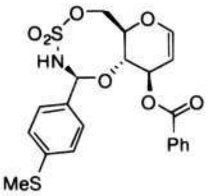
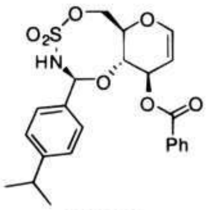
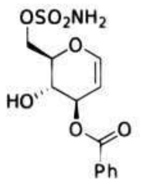
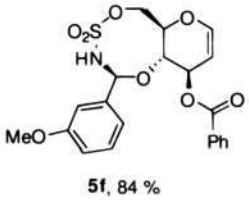
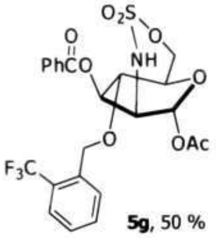
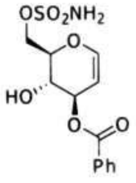
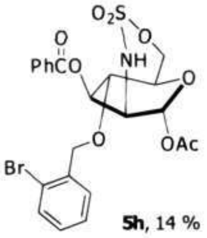
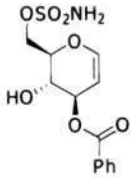
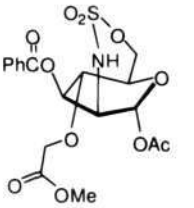
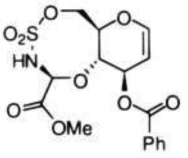
starting material	product (% isolated yield)
4a	 **5a**, 78 %
4b	 **5b**, 92 %
4c	 **5c**, 54 %
4d	 **5d**, 83 %
4e	 **6**, 75 %
4f	 **5f**, 84 %

Table 2 ***(continued)***

starting material	product (% isolated yield)		
4g	 **5g**, 50 %	+	 **6**, 15 %
4h	 **5h**, 14 %	+	 **6**, 76 %
4i	 **5i''**, 79 %	+	 **5i**, 7 %

Analysis of ^{1}H NMR spectra indicated the formation of a highly shifted singelt of instensity equal to one hydrogen at the region of 8.94-9.03 ppm for compounds **5a-f** and a doublet at 5.20 ppm for compound **5i**. This was assigned to be a methine proton on the newly formed *N-C* bond, whereas the others are belong to proton signals of hydropyran ring. Moreover, the NMR spectroscopic data of each product indicated a pure diastereomer, which meant the insertion reaction was stereoselective. The stereochemistry at a benzylic carbon was assigned based on the approaching direction of the nitrogen atom. Sulfamate substrates (**4a-i**) bear the nitrogen atom on the top face of glycal molecule. We thus assume that the nitrene delivery onto a C–H bond occurs on the top face providing insertion products as shown in Table 2. Additionally, The presence of the double bond on the sugar ring gave the competitive reaction between C=C and C–H insertions. We observed that the C–H insertion reaction predominates by having an electron-donating substituent on the benzene ring. On the contrary, having an electron-withdrawing group and a substituent on the *ortho*-postion of the benzene ring was not able to promote the C–H insertion but gave compound **6**, **5g** and **5i''** as side products.

To overcome these side reactions, we moved to a new synthetic plan by introducing a benzyl or keto group on C1 and a sulfamate ester group on C2 as shown in Figure 1. We hope that new starting materials would provide a good stereo- and regioselectivity of C–H insertion and, moreover, the sulfamoyloxy protective group and the aminobenzylic part would be easier to cleave to provide α-hydroxy aminobenzenes as final products. We have been investigating the C–H insertion on this new template and results are in progress.

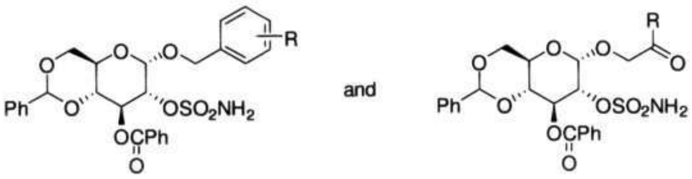
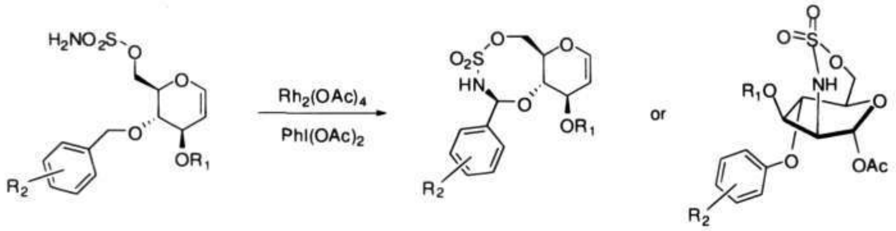


Figure 1 New starting materials for studies of C-H insertion on the sugar template.

3. CONCLUSION

The possibility of intramolecular rhodium-nitrene insertion of the carbon-hydrogen bond has been investigated. We found that C–H insertion could occur in preference to the C=C bond aziridination in glycal molecules. Having an electron donating group on the benzyl moiety could promote C–H insertion, while the electron withdrawing groups could not deliver any C–H insertion products. Significantly, the ^{1}H NMR showed good purity of products and only the diastereomer of the desired product was observed.



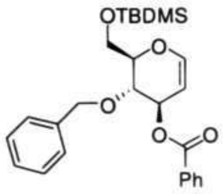
Scheme 4 General strategy for the C-H amination of D-glycal-derived sulfamate ester.

Moreover, this type of reaction could be applied with ester and carbonyl derivatives, which is an application to synthesize aminobenzyl alcohols and amino esters. The method proposed here can be a new way of providing nitrogen group functionalization in good yield and potential stereoselectivity.

4. EXPERIMENTAL

4.1 General procedure for benzylation

To a solution of glycal (1.1 mmol) in THF (2.0 mL) and DMF (1.0 mL) was added benzyl bromide (1.3 mmol) and Bu_4NI (0.55 mmol) at 0 °C. A suspension of NaH (1.6 mmol) was added portionwise to the above mixture and the reaction mixture was left to stir at 0 °C for 2 hours. The reation mixture was quenched with sat. aq. NH_4Cl in ice bath and EtOAc (15 mL) was added. The resulting solution was washed with H_2O (2 ×), brine, dried over anh. Na_2SO_4, and filtered. The solvents were removed under reduced pressure to give a colourless liquid, which was purified by flash column chromatography eluting with 20 % EtOAc in hexane.

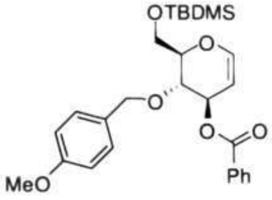


2a

(2*R*,3*S*,4*R*)-2-((tert-butyldimethylsilyloxy)methyl)-3-(benzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (2a)

Yield: 84 %; colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm): 7.99 (d, *J* = 7.7 Hz, 2H, Ph), 7.56 (t, *J* = 7.44 Hz, 1H, Ph), 7.34-7.21 (m, 5H, Ph), 6.49 (d, *J* = 6.1 Hz, 1H, H1), 5.67 (d, *J* = 4.1 Hz, 1H, H3), 4.87 (dd, *J* = 6.1, 4.8 Hz, 1H, H2), 4.77 (ABq, *J* = 11.3 Hz, 2H, CH_2Ph), 4.1-3.99 (m, 3H, H4, H5, and 1 × CH_2), 3.94 (dd, *J* = 10.9, 2.8 Hz, 1H, CH_2); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm): 166.1 (CO), 146.0 (C1), 137.9 (Ph), 133.0 (Ph), 130.2 (Ph), 129.6 (Ph), 128.3 (Ph), 127.9 (Ph), 127.7 (Ph), 98.7 (C2), 77.9 (C5), 73.5 (CH_2), 72.8 (C4), 70.6 (C3), 61.2 (CH_2), 25.9 (CH_3), 18.4 (Cq), -5.1 (CH_3), -5.3 (CH_3); **HRMS (ESI)**: *m/z*: calcd for

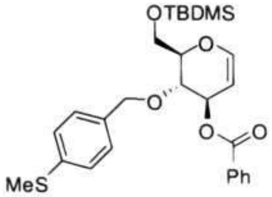
$C_{26}H_{34}O_5SiNa$: 477.2073 [M+Na]$^+$; found: 477.2071.



2b

(2*R*,3*S*,4*R*)-2-((tert-butyldimethylsilyloxy)methyl)-3-(4-methoxybenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (2b)

Yield: 82 %; pale yellow oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.00 (d, *J* = 8.2 Hz, 2H, Ph), 7.57 (t, *J* = 8.2 Hz, 1H, Ph), 7.44 (t, *J* = 7.5 Hz, 1H, Ph), 7.23 (d, *J* = 8.3 Hz, 2H, Ph), 6.78 (d, *J* = 7.7 Hz, 2H, Ph), 6.47 (d, *J* = 6.0 Hz, 1H, H1), 5.64 (m, 1H, H3), 4.86 (dd, *J* = 6.0, 3.1 Hz, 1H, H2), 4.66 (ABq, *J* = 11.1 Hz, 2H, CH_2Ph), 4.00 (m, 2H, H4 and H5), 3.93 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 0.90 (s, 9H, CH_3), 0.09 (s, 3H; CH_3), 0.07 (s, 3H, CH_3); **^{13}C NMR (125 MHz, CDCl$_3$):** δ (ppm): 166.1 (CO), 159.2 (Cq), 146.0 (C1), 133.0 (Ph), 130.2 (Ph), 130.1 (Ph), 129.65 (Ph), 129.63 (Ph), 128.35 (Ph), 128.33 (Ph), 113.8 (CH), 98.7 (C2), 78.0 (C5), 73.1 (CH_2), 72.4 (C4), 70.6 (C3), 61.2 (CH_2), 55.1 (OCH_3), 25.9 (CH_3), 18.3 (Cq), -5.16 (CH_3), -5.17 (CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{36}O_6SiNa$ [M+Na]$^+$: 507.2173; found: 507.2181.

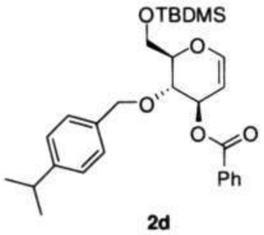


2c

(2*R*,3*S*,4*R*)-2-((tert-butyldimethylsilyloxy)methyl)-3-(4-(methylthio)benzyloxy)-

3,4-dihydro-2H-pyran-4-yl benzoate (2c)

Yield: 86 %; pale yellow oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 7.98 (dd, J = 7.8 Hz, 2H, Ph), 7.57 (t, J = 7.5 Hz, 1H, Ph), 7.44 (t, J = 7.5 Hz, 2H, Ph), 7.21 (d, J = 8.2 Hz, 2H, Ph), 7.13 (d, J = 8.2 Hz, 2H, Ph), 6.47 (dd, J = 6.1, 1.2 Hz, 1H, H1), 5.65 (dd, J = 4.4, 3.1 Hz, 1H, H3), 4.86 (dd, J = 6.1, 3.1 Hz, 1H, H2), 4.72 (ABq, J = 11.5 Hz, 2H, CH$_2$Ph), 4.07 (dd, J = 7.7, 5.7 Hz, 1H, H4), 4.04-4.00 (m, 2H, H5 and CH$_2$), 3.95 (dd, J = 11.1, 1.8 Hz, 1H, CH$_2$), 0.9 (s, 9H, C(CH$_3$)$_2$), 0.07 (s, 3H, SiCH$_3$), 0.06 (s, 3H, SiCH$_3$); **^{13}C (125 MHz, CDCl$_3$):** δ (ppm): 166.1 (CO), 145.9 (C1), 137.9 (Ph), 134.7 (Ph), 133.0 (Ph), 130.1 (Ph), 129.5 (Ph), 128.3 (Ph), 126.5 (Ph), 98.7 (C2), 77.9 (C5), 72.9 (CH$_2$), 72.6 (C4), 70.5 (C3), 61.1 (CH$_2$), 25.7 (CH$_3$), 18.3 (Cq), 15.8 (CH$_3$), -5.2 (CH$_3$), -5.3 (CH$_3$); **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{36}O_5SSiNa$: 523.1950 [M+Na]$^+$; found: 523.1956

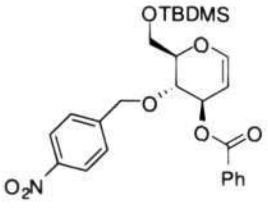


2d

(2*R*,3*S*,4*R*)-2-((tert-butyldimethylsilyloxy)methyl)-3-(4-isopropylbenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (2d)

Yield: 79 %, colourless liquid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.05 (d, J = 7.4 Hz, 2H, Ph), 7.58 (*t*, J = 7.4 Hz, 1H, Ph), 7.45 (t, J = 7.8 Hz, 2H, Ph), 7.25 (d, J = 8.0 Hz, 2H, Ph), 7.15 (d, J = 8.0 Hz, 2H, Ph), 6.49 (d, J = 6.1 Hz, 1H, H1), 5.68 (dd, J = 4.5, 3.4 Hz, 1H, H3), 4.89 (dd, J = 6.1, 3.4 Hz, 1H, H2), 4.75 (ABq, J = 11.2 Hz, 2H, CH$_2$Ph), 4.10 (t, J = 6.6 Hz, 1H, H4), 4.07-4.01 (m, 2H, H5 and CH$_2$), 3.95 (dd, J = 11.1, 3.3 Hz, 1H, CH$_2$), 2.86 (quint, J = 6.9 Hz, 1H, CH), 1.21 (d, J =

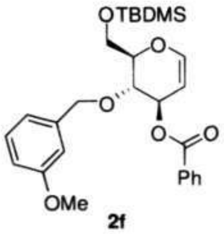
6.9 Hz, 3H, CH_3), 1.20 (d, *J* = 6.9 Hz, 3H, CH_3), 0.91 (s, 9H, $C(CH_3)_3$), 0.09 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$); **^{13}C (125 MHz, $CDCl_3$):** δ (ppm): 166.0 (CO), 148.5 (Cq), 145.9 (C1), 135.2 (Ph), 133.0 (Ph), 130.1 (Ph), 129.6 (Ph), 128.3 (Ph), 128.0 (Ph), 126.4 (Ph), 98.6 (C2), 77.9 (C5), 73.4 (CH_2), 72.6 (C4), 70.6 (C3), 61.2 (CH_2), 33.7 (CH), 25.8 (CH_3), 23.93 (CH_3), 23.90 (CH_3), 18.3 (Cq), -5.2 (CH_3), -5.4 (CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{29}H_{40}O_5SiNa$; 519.2543 $[M+Na]^+$; found; 519.2546.



2e

(2*R*,3*S*,4*R*)-2-((tert-butyldimethylsilyloxy)methyl)-3-(4-nitrobenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (2e)

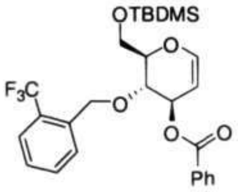
Yield: 47 %; yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.12 (d, *J* = 8.7 Hz, 2H, Ph), 8.00 (dd, *J* = 8.7 Hz, 2H, Ph), 7.55 (t, *J* = 7.5 Hz, 1H, Ph), 7.38-7.25 (m, 4H, Ph), 6.48 (dd, *J* = 6.1, 1.3 Hz, 1H, H1), 5.70-5.68 (m, 1H, H3), 4.89-4.82 (m, 3H, H2 and CH_2Ph), 4.09 (dd, *J* = 7.7, 5.9 Hz, 1H, H4), 4.06-3.95 (m, 3H, H5 and CH_2), 0.89 (s, 9H, $C(CH_3)_3$), 0.07 (s, 3H, CH_3), 0.06 (s, 3H, $SiCH_3$); **^{13}C (125 MHz, $CDCl_3$):** δ (ppm): 166.0 (CO), 147.2 (Cq), 146.1 (C1), 145.6 (Cq), 133.2 (Ph), 129.8 (Ph), 129.4 (Ph), 128.3 (Ph), 127.9 (Ph), 123.5 (Ph), 98.6 (C2), 77.8 (C5), 73.7 (C4), 72.2 (CH_2), 70.4 (C3), 61.1 (CH_2), 25.8 (CH_3), 18.3 (Cq), -5.2 (CH_3), -5.4 (CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{26}H_{33}O_7NSiNa$: 522.1924 $[M+Na]^+$; found: 522.1913.



2f

(2*R*,3*S*,4*R*)-2-((tert-butyldimethylsilyloxy)methyl)-3-(3-methoxybenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (2f)

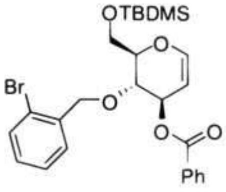
Yield: 83%; colourless liquid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 7.99 (dd, J = 8.1, 1.2 Hz, 2H, Ph), 7.58-7.54 (tt, J = 7.4, 1.2 Hz, 1H, Ph), 7.42 (t, J = 7.7 Hz, 2H, Ph), 7.17 (t, J = 7.7 Hz, 2H, Ph), 6.88-6.84 (m, 2H, Ph), 6.75 (dd, J = 8.1, 2.0 Hz, 1H, Ph), 6.48 (dd, J = 6.1, 1.1 Hz, 1H, H1), 5.667 (m, 1H, H3), 4.87 (dd, J = 6.1, 3.2 Hz, 1H, H2), 4.74 (ABq, J = 11.6 Hz, 2H, CH$_2$Ph), 4.09-4.03 (m, 2H, H4 and H5), 4.02 (dd, J = 11.1, 4.0 Hz, 1H, CH$_2$), 3.94 (dd, J = 11.1, 3.2 Hz, 1H, CH$_2$), 3.70 (s, 3H, OCH$_3$), 0.89 (s, 9H, C(CH$_3$)$_3$), 0.07 (s, 3H, SiCH$_3$), 0.06 (s, 3H, SiCH$_3$); **^{13}C (125 MHz, CDCl$_3$):** δ (ppm): 166.0 (CO), 159.6 (Cq), 145.9 (C1), 139.4 (Ph), 133.0 (Ph), 130.1 (Ph), 129.6 (Ph), 129.3 (Ph), 128.3 (Ph), 120.1 (Ph), 113.6 (Ph), 113.0 (Ph), 98.6 (C2), 77.9 (C5), 73.4 (CH$_2$), 72.9 (C4), 70.5 (C3), 61.2 (CH$_2$), 55.0 (OCH$_3$), 25.8 (CH$_3$), 18.3 (Cq), -5.2 (CH$_3$), -5.4 (CH$_3$); **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{36}O_6SiNa$: 507.2179 [M+Na]$^+$; found: 507.2171.



2g

(2*R*,3*S*,4*R*)-2-((tert-butyldimethylsilyloxy)methyl)-3-(2-(trifluoromethyl)benzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (2g)

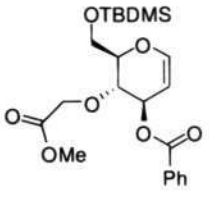
Yield: 76 %; colourless oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 7.99 (d, J = 7.6 Hz, 2H, Ph), 7.65 (d, J = 7.6 Hz, 1H, Ph), 7.58-7.53 (m, 2H, Ph), 7.47-7.40 (m, 4H, Ph), 7.27 (t, J = 7.6 Hz, 1H, Ph), 6.47 (d, J = 6.0 Hz, 1H, H1), 5.75 (m, 1H, H3), 4.99 (br s, 2H, CH$_2$Ph), 4.88 (dd, J = 6.0, 2.8 Hz, 1H, H2), 4.16 (t, J = 7.1 Hz, 1H, H4), 4.08 (t, J = 3.4 Hz, 1H, H5), 4.05 (dd, J = 11.0, 3.4 Hz, 1H, CH$_2$), 3.97 (dd, J = 11.0, 3.4 Hz, 1H, CH$_2$), 0.91 (s, 9H, C(CH$_3$)$_3$), 0.08 (s, 6H, Si(CH$_3$)$_2$); **^{13}C (125 MHz, CDCl$_3$):** δ (ppm): 166.1 (CO), 145.9 (C1), 136.8 (Ph), 133.0 (Ph), 131.8 (Ph), 129.9 (Ph), 129.5 (Ph), 129.0 (Ph), 128.2 (Ph), 127.2 (Ph), 125.5 (Ph), 98.7 (C2), 77.8 (C5), 73.9 (C4), 71.2 (C3), 69.4 (CH$_2$), 61.3 (CH$_2$), 25.8 (CH$_3$), 18.3 (Cq), -5.3 (CH$_3$), -5.5 (CH$_3$); **HRMS (ESI):** *m/z*: calcd for $C_{27}H_{33}O_5F_3SiNa$: 545.1947 [M+Na]$^+$; found: 545.1945.



2h

(2*R*,3*S*,4*R*)-2-((tert-butyldimethylsilyloxy)methyl)-3-(2-bromobenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (2h)

Yield: 67 %; pale yellow liquid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.01 (dd, J = 8.1, 1.0 Hz, 2H, Ph), 7.55 (t, J = 7.3 Hz, 1H, Ph), 7.46-7.38 (m, 4H, Ph), 7.25 (t, J = 7.8 Hz, 1H, Ph), 7.08 (t, J = 7.8 Hz, 1H, Ph), 6.48 (dd, J = 6.1, 1.1 Hz, 1H, H1), 5.71 (dd, J = 5.4, 2.8 Hz, 1H, H3), 4.88 (dd, J = 6.1, 2.8 Hz, 1H, H2), 4.86 (ABq, J = 11.2 Hz, 2H, CH$_2$Ph), 4.15-4.08 (m, 1H, H4 and H5), 4.03 (dd, J = 11.2, 3.2 Hz, 1H, CH$_2$), 3.97 (dd, J = 11.2, 3.2 Hz, 1H, CH$_2$), 0.90 (s, 9H, C(CH$_3$)$_3$), 0.08 (s, 6H; Si(CH$_3$)$_2$); **^{13}C (125 MHz, CDCl$_3$):** δ (ppm): 166.2 (CO), 146.0 (C1), 137.4 (Ph), 133.0 (Ph), 132.4 (Ph), 130.1 (Ph), 129.6 (Ph), 129.3 (Ph), 129.0 (Ph), 128.3 (Ph), 127.3 (Ph), 122.6 (Ph), 98.7 (C2), 77.9 (C5), 73.5 (C4), 73.0 (CH_2), 71.0 (C3), 61.4 (CH_2), 25.9 (CH_3), 18.4 (Cq), -5.2 (CH_3), -5.3 (CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{26}H_{33}O_5SiBrNa$: 557.1158 $[M+Na]^+$; found: 557.1160 (^{81}Br) and 555.1184 (^{79}Br).



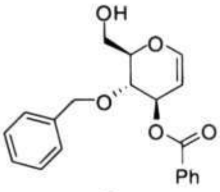
2i

(2*R*,3*S*,4*R*)-2-((tert-butyldimethylsilyloxy)methyl)-3-(2-methoxy-2-oxoethoxy)-3,4-dihydro-2H-pyran-4-yl benzoate (2i)

Yield: 80 %; colourless liquid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.02 (d, *J* = 8.5 Hz, 2H, Ph), 7.54 (m, 1H, Ph), 7.43-7.39 (m, 2H, Ph), 6.44 (dd, *J* = 6.1, 1.0 Hz, 1H, H1), 5.61 (dd, *J* = 5.5, 2.9 Hz, 1H, H3), 4.85 (dd, *J* = 6.1, 3.1 Hz, 1H, H2), 4.35 (Abq, *J* = 16.2 Hz, 2H, CH_2CO_2Me), 4.10 (m, 1H, H5), 4.03-3.97 (m, 2H, H4 and CH_2), 3.94 (dd, *J* = 11.4, 3.6 Hz, 1H, CH_2), 0.87 (s, 9H, $C(CH_3)_3$), 0.06 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$); **^{13}C (125 MHz, $CDCl_3$):** δ (ppm): 170.1 (CO), 165.8 (CO), 145.9 (C1), 133.0 (Ph), 129.7 (Ph), 129.4 (Ph), 128.3 (Ph), 98.3 (C2), 77.4 (C5), 74.7 (C4), 70.5 (C3), 68.9 (CH_2), 61.1 (CH_2), 51.6 (OCH_3), 25.7 (CH_3), 18.1 (Cq), -5.3 (CH_3), -5.2 (CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{22}H_{32}O_7SiNa$: 459.1815 $[M+Na]^+$; found: 459.1814.

4.2 General procedure for desilylation

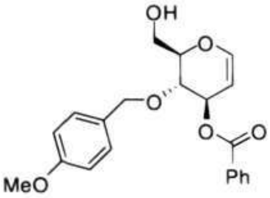
To a solution of glycal (1.5 mmol) in dry THF (2.0 mL) was added 1M solution of TBAF in THF (1.6 mmol) dropwise at 0 °C and kept stirring at that temperature for 3 hours. Water was added to the reaction mixture (5 mL) and, subsequently, washed it with brine, dried over anh. Na_2SO_4. Solvent was removed and the crude product was purified by column chromatography eluting with 20 % EtOAc in hexane.



3a

(2*R*,3*S*,4*R*)-2-(hydroxymethyl)-3-(benzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (3a)

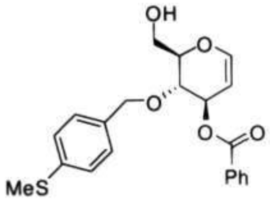
Yield: 90 %; colourless solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.04 (d, J = 7.3 Hz, 2H, Ph), 7.61 (t, J = 7.3 Hz, 1H, Ph), 7.48 (t, J = 7.8 Hz, 2H, Ph), 7.38-7.24 (m, 5H, Ph), 6.49 (d, J = 6.0 Hz, 1H, H1), 5.77 (dd, J = 4.4, 1.4 Hz, 1H, H3), 4.93 (dd, J = 6.1, 2.7 Hz, 1H, H2), 4.78 (ABq, J = 11.4 Hz, 2H, CH_2Ph), 4.12-4.06 (m, 2H, H4 and H5), 4.00 (d, J = 12.3 Hz, 1H, CH_2), 3.95 (d, J = 12.3 Hz, 1H, CH_2), 2.09 (br s, 1H, OH); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 166.0 (CO), 145.5 (C1), 137.5 (Ph), 133.1 (Ph), 129.9 (Ph), 129.6 (Ph), 128.46 (Ph), 128.44 (Ph), 128.0 (Ph), 127.9 (Ph), 99.8 (C2), 77.8 (C5), 73.7 (CH_2), 73.1 (C4), 71.9 (C3), 61.3 (CH_2); **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{21}O_5$: 341.1389 $[M+H]^+$; found: 341.1393.



3b

(2*R*,3*S*,4*R*)-2-(hydroxymethyl)-3-(4-methoxybenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (3b)

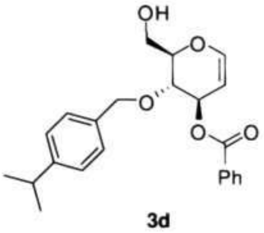
Yield: 69 %; pale yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.00 (d, J = 8.4 Hz Ph), 7.58 (t, J = 7.4 Hz, 1H, Ph), 7.45 (t, J = 7.4 Hz, 2H; Ph), 7.22 (d, J = 8.6 Hz, 2H, Ph), 6.79 (d, J = 8.6, 2H; Ph), 6.45 (dd, J = 6.0, 1.1 Hz, 1H, H1), 5.72 (m, 1H, H3), 4.88 (dd, J = 6.0, 2.6 Hz, 1H, H2), 4.70 (ABq, J = 11.1 Hz, 2H, CH$_2$Ph), 4.10 (m, 2H, CH$_2$), 3.98-3.86 (m, 2H, H4 and H5), 3.74 (s, 3H, OCH$_3$), 1.87 (br s, 1H, OH); **^{13}C (125 MHz, CDCl$_3$):** δ (ppm): 166.1 (CO), 159.4 (Cq), 145.6 (C1), 133.1 (Ph), 130.0 (Ph), 129.78 (Ph), 129.70 (Ph), 129.6 (Ph), 128.4 (Ph), 113.8 (Ph), 99.9 (C2), 77.8 (C5), 73.3 (CH$_2$), 72.8 (C4), 71.9 (C3), 61.3 (CH$_2$), 55.2 (OCH$_3$); **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{22}O_6Na$: $[M+Na]^+$: 393.1309, found: 393.1323.



3c

(2*R*,3*S*,4*R*)-2-(hydroxymethyl)-3-(4-(methylthio)benzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (3c)

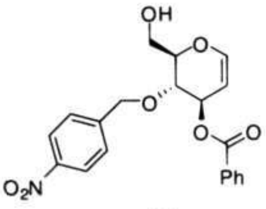
Yield: 76 %; yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 7.97 (d, J = 8.0 Hz, 2H, Ph), 7.56 (t, J = 7.4 Hz, 1H, Ph), 7.43 (t, J = 7.7 Hz, 2H, Ph), 7.19 (d, J = 8.2 Hz, 2H, Ph), 7.11 (d, J = 8.2 Hz, 2H, Ph), 6.44 (d, J = 6.0 Hz, 1H, H1), 5.71 (dd, J = 4.6, 1.3 Hz, 1H, H3), 4.87 (dd, J = 6.0, 2.6 Hz, 1H, H2), 4.69 (ABq, J = 11.5 Hz, 2H, CH$_2$Ph), 4.07-4.01 (m, 2H, H4 and H5), 3.97-3.90 (m, 2H, CH$_2$), 2.54 (br s, 1H, OH), 2.38 (s, 3H, CH$_3$); **^{13}C (125 MHz, CDCl$_3$):** δ (ppm): 165.9 (CO), 145.4 (C1), 138.0 (Ph), 134.2 Ph), 133.0 (Ph), 129.7 (Ph), 129.4 (Ph), 128.4 (Ph), 128.2 (Ph), 126.2 (Ph), 99.5 (C1), 77.7 (C5), 73.0 (CH_2), 72.8 (C4), 71.5 (C3), 60.9 (CH_2), 15.5 (CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{22}O_5SNa$: 409.1086 $[M+Na]^+$; found: 409.1070.



3d

(2*R*,3*S*,4*R*)-2-(hydroxymethyl)-3-(4-isopropylbenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (3d)

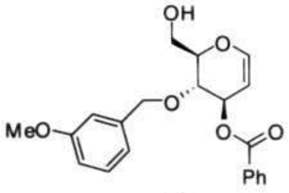
Yield: 93 %; colourless solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.04 (d, J = 7.1 Hz, 2H, Ph), 7.58 (tt, J = 7.5, 1.3 Hz, 1H, Ph), 7.46 (t, J = 7.1 Hz, 2H, Ph), 7.22 (d, J = 8.1 Hz, 2H, Ph), 7.14 (d, J = 8.1 Hz, 2H, Ph), 6.46 (dd, J = 6.0, 1.2 Hz, 1H, H1), 5.74 (ddd, J = 5.9, 2.6, 1.2 Hz, 1H, H3), 4.90 (dd, J = 6.1, 2.6 Hz, 1H, H2), 4.73 (ABq, J = 11.2 Hz, 2H, CH_2Ph), 4.07-4.04 (m, 2H, H4 and H5), 3.97 (dd, J = 12.2, 3.5 Hz, 1H, CH_2), 3.92 (dd, J = 12.2, 3.5 Hz, 1H, CH_2), 2.85 (quint, J = 6.9 Hz, 1H, CH), 2.10 (br s, 1H, OH), 1.21 (d, J = 6.9 Hz, 3H, CH_3), 1.20 (d, J = 6.9 Hz, 3H, CH_3); **^{13}C (125 MHz, $CDCl_3$):** δ (ppm): 166.0 (CO), 148.7 (Cq), 145.5 (C1), 134.8 (Ph), 133.1 (Ph), 130.0 (Ph), 129.6 (Ph), 128.4 (Ph), 128.1 (Ph), 126.5 (Ph), 99.8 (C2), 77.7 (C5), 73.6 (CH_2), 73.0 (C4), 72.0 (C3), 61.3 (CH_2), 33.7 (CH), 23.9 (CH_3), 23.8 (CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{26}O_5Na$: 405.1678 $[M+Na]^+$; found: 405.1674.



3e

(2*R*,3*S*,4*R*)-2-(hydroxymethyl)-3-(4-nitrobenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (3e)

Yield: 74 %; yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.03 (d, J = 8.7 Hz, 2H, Ph), 7.91 (d, J = 8.7 Hz, 2H, Ph), 7.56 (t, J = 7.5 Hz, 1H, Ph), 7.43-7.39 (m, 4H, Ph), 6.47 (dd J = 6.0, 1.3 Hz, 1H, H1), 5.74 (dd, J = 6.0, 1.3 Hz, 1H, H3), 4.86 (ABq, J = 13 Hz, 2H, CH$_2$Ph), 4.85 (dd, J = 6.0, 2.7 Hz, 1H, H2), 4.09-4.07 (m, 2H, H4 and H5), 3.99 (m, 2H, CH$_2$), 1.94 (br s, 1H, OH); **^{13}C (125 MHz, CDCl$_3$):** δ (ppm): 165.9 (CO), 145.6 (C1), 145.2 (Ph), 133.3 (Ph), 129.6 (Ph), 129.4 (Ph), 128.4 (Ph), 127.9 (Ph), 123.5 (Ph), 99.8 (C1), 77.7 (C5), 73.9 (C4), 72.4 (CH$_2$), 71.4 (C3), 60.9 (CH$_2$); **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{19}O_7NNa$: 408.1059 [M+Na]$^+$; found: 408.1059.

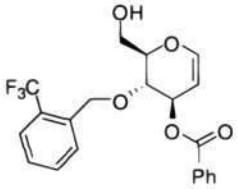


3f

(2*R*,3*S*,4*R*)-2-(hydroxymethyl)-3-(3-methoxybenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (3f)

Yield: 91 %; colourless solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.00 (d, J = 8.3 Hz, 2H, Ph), 7.57 (t, J = 7.4 Hz, 1H, Ph), 7.44 (t, J = 7.8 Hz, 2H, Ph), 7.18 (t, J = 7.8 Hz, 1H, Ph), 6.46 (dd, J = 6.0, 1.0 Hz, 1H, H1), 5.74 (m, 1H, H3), 4.89 (dd, J

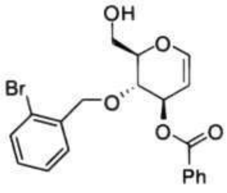
= 6.0, 2.7 Hz, 1H, H2), 4.72 (ABq, *J* = 11.5 Hz, 2H, CH_2Ph), 4.09-4.03 (m, 2H, H4 and H5), 3.98 (dd, *J* = 9.4, 3.3, 1H, CH_2), 3.93 (dd, *J* = 9.4, 2.7 Hz, 1H, CH_2), 3.71 (s, 3H, OCH_3), 2.04 (br s, 1H, OH); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 166.0 (CO), 159.6 (Cq), 145.6 (C1), 139.1 (Ph), 133.1 (Ph), 129.9 (Ph), 129.5 (Ph), 120.1 (Ph), 113.7 (Ph), 113.2 (Ph), 99.8 (C2), 77.8 (C5), 73.6 (CH_2), 73.2 (C4), 71.8 (C3), 61.2 (CH_2), 55.0 (OCH_3); **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{22}O_6Na$: 393.1314 $[M+Na]^+$; found: 393.1312.



3g

(2*R*,3*S*,4*R*)-2-(hydroxymethyl)-3-(2-(trifluoromethyl)benzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (3g)

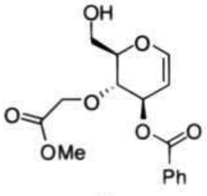
Yield: 82 %; colourless solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 7.98 (dd, *J* = 8.1, 1.0 Hz, 2H, Ph), 7.62 (d, *J* = 7.8 Hz, 1H, Ph), 7.57-7.51 (m, 2H, Ph), 7.46-7.40 (m, 3H, Ph), 7.27 (t, *J* = 7.7 Hz, 1H, Ph), 6.46 (dd, *J* = 6.1, 1.3 Hz, 1H, H1), 5.14 (ddd, *J* = 6.5, 2.7, 1.3 Hz, 1H, H3), 5.00 (ABq, *J* = 12.7 Hz, 2H, CH_2Ph), 4.91 (dd, *J* = 6.1, 2.7 Hz, 1H, H2), 4.15 (d, J= 6.5 Hz, 1H, H4), 4.10 (t, *J* = 3.4 Hz, 1H, H5), 4.01 (dd, *J* = 12.1, 4.1 Hz, 1H, CH_2), 3.97 (dd, *J* = 12.1, 2.9 Hz, 1H, CH_2), 2.28 (br s, 1H, OH); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 166.0 (CO), 145.5 (C1), 136.3 (Ph), 133.1 (Ph), 131.9 (Ph), 129.7 (Ph), 129.5 (Ph), 129.2 (Ph), 128.3 (Ph), 127.4 (Ph), 125.58 (Ph), 125.54 (Ph), 99.7 (C2), 77.6 (C5), 74.2 (C4), 71.9 (C3), 70.0 (CH_2), 61.1 (CH_2); **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{19}O_5F_3Na$: 431.1082 $[M+Na]^+$; found: 431.1084.



3h

(2*R*,3*S*,4*R*)-2-(hydroxymethyl)-3-(2-bromobenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (3h)

Yield: 89 %; pale yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.01 (dd, J = 8.2, 1.1 Hz, 2H, Ph), 7.56 (t, J = 7.4 Hz, 1H, Ph), 7.45-7.39 (m, 4H, Ph), 7.22 (t, J = 7.5 Hz, 1H, Ph), 7.07 (t, J = 7.5 Hz, 1H, Ph), 6.47 (dd, J = 6.0, 1.1 Hz, 1H, H1), 5.77-5.75 (ddd, J = 6.6, 3.8, 2.6 Hz, 1H, H3), 4.91 (dd, J = 6.0, 2.6 Hz, 1H, H2), 4.85 (ABq, J = 12.2 Hz, 2H, CH$_2$Ph), 4.14 (d, J = 6.6 Hz, 1H, H4), 4.08 (t, J = 3.8 Hz, 1H, H5), 4.02 (dd, J = 12.2, 4.2 Hz, 1H, CH$_2$), 3.97 (dd, J = 12.2, 3.8 Hz, 1H, CH$_2$), 2.08 (br s, 1H, OH); **^{13}C (125 MHz, CDCl$_3$):** δ (ppm): 166.0 (CO), 145.5 (C1), 136.9 (Cq), 133.1 (Ph), 132.5 (Ph), 129.8 (Ph), 129.6 (Ph), 129.2 (Ph), 128.3 (Ph), 127.3 (Ph), 122.9 (Ph), 99.7 (C2), 77.6 (C5), 73.7 (C4), 73.0 (CH$_2$), 72.0 (C3), 61.3 (CH$_2$); **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{19}O_5BrNa$: 443.0293 [M+Na]$^+$; found: 441.0319 (^{79}Br) and 443.0299 (^{81}Br).



3i

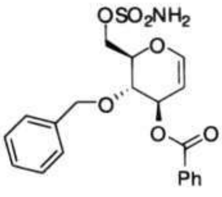
(2*R*,3*S*,4*R*)-2-(hydroxymethyl)-3-(2-methoxy-2-oxoethoxy)-3,4-dihydro-2H-pyran-4-yl benzoate (3i)

Yield: 55 %; colourless solid. **^{1}H NMR (500 MH$_Z$, CDCl$_3$):** δ (ppm): 8.01 (d, J =

7.1 Hz, 2H, Ph), 7.57 (t, *J* = 7.5 Hz, 1H, Ph), 7.45 (t, *J* = 7.5 Hz, 2H, Ph), 6.44 (dd, *J* = 6.0, 1.0 Hz, 1H, H1), 5.73 (dt, *J* = 6.7, 1.8 Hz, 1H, H3), 4.82 (dd, *J* = 6.0, 2.5 Hz, 1H, H2), 4.37 (Abq, *J* = 17.0 Hz, 2H, CH_2CO_2Me), 4.13-4.09 (m, 2H, H5 and CH_2), 3.99 (dt, *J* = 6.7, 2.9 Hz, 1H. H5), 3.90 (dd, *J* = 12.5, 2.9 Hz, 1H, CH_2), 3.66 (s, 3H, OCH_3), 3.46 (br s, 1H, OH); **^{13}C (125 MHz, $CDCl_3$):** δ (ppm): 171.5 (CO), 165.8 (CO), 146.0 (C1), 133.2 (Ph), 129.7 (Ph), 129.5 (Ph), 128.4 (Ph), 99.2 (C2), 77.5 (C5), 74.2 (C4), 73.4 (C3), 67.8 (CH_2), 61.0 (CH_2), 52.1 (OCH_3); **HRMS (ESI):** *m/z*: calcd for $C_{16}H_{18}O_7Na$: 345.0950 $[M+Na]^+$; found: 345.0950.

4.3 General procedure for sulfamoylation

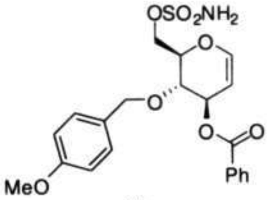
Formic acid (1.6 mmol) was added drop wise to neat chlorosulfonyl isocyanate (1.6 mmol) at 0 °C with rapid stirring. Vigorous gas evolution was observed during the addition process. The resulting vicous suspension was stirred for 5 mins at 0 °C during which time the mixture solidified. Dry CH_3CN (7.8 mmol) was added providing a clear solution and the solution was stirred for 1 h at 0°C then 6 h at room temperature. The mixture was cooled to 0°C, and a solution of glycal (0.77 mmol) in DMA (2.5 mL) was added dropwise. The reaction was stirred at 0 °C over a 2 hour period, and quenched by the successive addition of Et_3N. The mixture was poured into ethyl ether (10 mL) and water (5 mL), the organic phase was collected, and the aqueous layer was extracted with EtOAc (3 ×). The combined organic extracts were washed with brine, dried over anh. $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (30 % EtOAc in hexane).



4a

(2*R*,3*S*,4*R*)-2-(sulfamoyloxymethyl)-3-(benzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (4a)

Yield: 78 %; colourless solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.03 (dd, J = 8.0, 0.9 Hz, 2H, Ph), 7.59 (t, J = 7.8 Hz, 1H, Ph), 7.46 (t, J = 7.8 Hz, 2H, Ph), 7.30-7.28 (m, 5H, Ph), 6.47 (dd, J = 6.1, 1.1 Hz, 1H, H1), 5.73 (ddd, J = 6.0, 2.9, 1.1 Hz, 1H, H3), 4.96 (dd, J = 6.1, 2.9 Hz, 1H, H2), 4.76 (ABq, J = 11.2 Hz, 2H, CH_2Ph), 4.70 (s, 2H, NH_2), 4.61 (dd, J = 11.7, 4.7 Hz, 1H, CH_2), 4.48 (dd, J = 11.1, 2.5 Hz, 1H, CH_2), 4.26 (ddd, J = 8.6, 4.7, 2.5 Hz, 1H, H5), 4.08 (dd, J = 8.6, 6 Hz, 1H, H4); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 165.9 (CO), 145.3 (C1), 137.2 (Ph), 133.3 (Ph), 129.7 (Ph), 129.6 (Ph), 128.5 (Ph), 128.14 (Ph), 128.10 (Ph), 100.0 (C2), 74.9 (C5), 73.6 (CH_2), 72.5 (C4), 70.9 (C3), 68.5 (CH_2); **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{21}O_7NSNa$: 442.0936 $[M+Na]^+$; found: 442.0925.

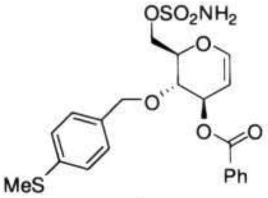


4b

(2*R*,3*S*,4*R*)-2-(sulfamoyloxymethyl)-3-(4-methoxybenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (4b)

Yield: 92 %; colourless solid. **^{1}H NMR (500 MHz, *d_4*-MeOD):** δ (ppm): 7.98 (d, J = 8.2 Hz, 2H, Ph), 7.64 (t, J = 7.6 Hz, 1H, Ph), 7.50 (t, J = 7.6 Hz, 2H, Ph), 7.21

(d, J = 8.0 Hz, 2H, Ph), 6.77 (d, J = 8.0 Hz, 2H, Ph), 6.53 (d, J = 6.0 Hz, 1H, H1), 5.65 (m, 1H, H3), 4.89 (d, J = 6.0 Hz, 1H, H2), 4.68 (ABq, J = 11.0 Hz, 2H, CH_2Ph), 4.52 (dd, J = 11.0, 4.5 Hz, 1H, CH_2), 4.44 (dd, J = 11.0, 1.6 Hz, 1H, CH_2), 4.28 (m, 1H, H5), 4.06 (d, J = 6.8 Hz, 1H, H4), 3.72 (s, 3H, OCH_3); **^{13}C NMR (125 MHz, d_4-MeOD):** δ (ppm): 166.0 (CO), 159.5 (Cq), 145.4 (C1), 133.0 (Ph), 129.8 (Ph), 129.7 (Ph), 129.4 (Ph), 129.2 (Ph), 128.2 (Ph), 113.3 (Ph), 99.0 (C2), 75.1 (C5), 73.0 (CH_2), 72.5 (C4), 71.0 (C3), 66.9 (CH_2), 54.1 (OCH_3); **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{23}NO_8SNa$ $[M+Na]^+$: 472.1037; found: 472.1021.

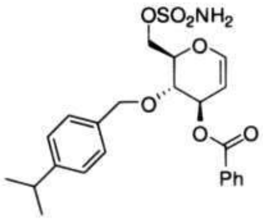


4c

(2*R*,3*S*,4*R*)-2-(sulfamoyloxymethyl)-3-(4-(methylthio)benzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (4c)

Yield: 71 %; yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.00 (dd, J = 8.1, 1.1 Hz, 2H, Ph), 7.58 (tt, J = 7.5, 1.2 Hz, 1H, Ph), 7.46 (t, J = 8.1 Hz, 2H, Ph), 7.20 (d, J = 8.3 Hz, 2H, Ph), 7.14 (d, J = 8.3 Hz, 2H, Ph), 6.45 (dd, J = 6.1, 1.2 Hz, 1H, H1), 5.71 (ddd, J = 6.2, 2.9, 1.4 Hz, 1H, H3), 5.01 (s, 2H, NH_2), 4.93 (dd, J = 6.1, 2.9 Hz, 1H, H2), 4.74 (ABq, J = 11.3 Hz, 2H, CH_2Ph), 4.55 (dd, J = 11.1, 4.6 Hz, 1H, CH_2), 4.45 (dd, J = 11.1, 2.5 Hz, 1H, CH_2), 4.23 (ddd, J = 8.7, 4.6, 2.5 Hz, 1H, H5), 4.04 (dd, J = 8.7, 6.2 Hz, 1H, H4), 2.42 (s, 3H, CH_3); **^{1}H NMR (125 MHz, $CDCl_3$):** δ (ppm): 165.9 (CO), 145.2 (C1), 138.4 (Ph), 133.8 (Ph), 133.3 (Ph), 129.6 (Ph), 129.5 (Ph), 128.7 (Ph), 128.5 (Ph), 126.4 (Ph), 99.9 (C2), 74.9 (C5), 73.2 (CH_2), 72.3 (C4), 70.9 (C3), 68.3 (CH_2), 15.6 (CH_3); **HRMS (ESI):** *m/z*:

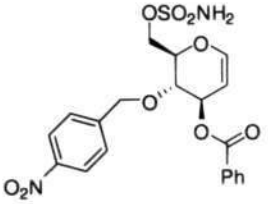
calcd for $C_{21}H_{23}O_7NS_2Na$: 488.0814 $[M+Na]^+$; found: 488.0806.



4d

(2*R*,3*S*,4*R*)-2-(sulfamoyloxymethyl)-3-(4-isopropylbenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (4d)

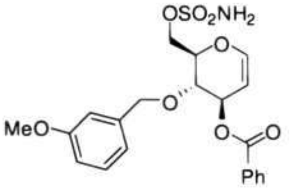
Yield: 74 %; colourless solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.04 (dd, J = 8.0, 1.2 Hz, 2H, Ph), 7.59 (t, J = 7.5 Hz, 1H, Ph), 7.47 (t, J = 8.0 Hz, 2H, Ph), 7.22 (d, J = 8.1 Hz, 2H, Ph), 7.15 (d, J = 8.1 Hz, 2H, Ph), 6.45 (d, J = 6.1 Hz, 1H, H1), 5.73 (ddd, J = 6.2, 2.8, 1.3 Hz, 1H, H3), 4.98 (s, 2H, NH_2), 4.95 (dd, J = 6.1, 2.8 Hz, 1H, H2), 4.72 (ABq, J = 11.0 Hz, 2H, CH_2Ph), 4.59 (dd, J = 11.1, 4.7 Hz, 1H, CH_2), 4.47 (dd J = 11.1, 2.4 Hz, 1H, CH_2), 4.26 (m, 1H, H5), 4.08 (dd, J = 8.7, 6.2 Hz, 1H, H4), 2.88-2.82 (quint, J = 6.9 Hz, 1H, CH), 1.20 (d, J = 6.9 Hz, 3H, CH_3), 1.19 (d, J = 6.9 Hz, 3H, CH_3); **^{13}C NMR (125 MHz, CDCl$_3$):** δ (ppm): 165.9 (CO), 148.9 (Cq), 145.2 (C1), 134.5 (Ph), 133.3 (Ph), 129.69 (Ph), 129.61 (Ph), 128.5 (Ph), 128.2 (Ph), 126.5 (Ph), 99.9 (C2), 74.9 (C5), 73.5 (CH_2), 72.4 (C4), 71.1 (C3), 68.5 (CH_2), 33.8 (CH), 23.8 (CH_3), 23.8 (CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{27}O_7NSNa$: 484.1406 $[M+Na]^+$; found: 484.1410.



4e

(2*R*,3*S*,4*R*)-2-(sulfamoyloxymethyl)-3-(4-nitrobenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (4e)

Yield: 67 %; pale yellow solid. **^{1}H NMR (500 MHz, d_4-MeOD):** δ (ppm): 8.02 (dd, J = 8.7 Hz, 2H, Ph), 7.90 (dd, J = 8.1, 1.1 Hz, 2H, Ph), 7.59 (tt, J = 7.5, 1.1 Hz, 1H, Ph), 7.50 (d, J = 8.7 Hz, 2H, Ph), 7.44 (t, J = 7.5 Hz, 2H, Ph), 6.55 (dd, J = 6.1, 1.3 Hz, 1H, H1), 5.71 (ddd, J = 6.4, 2.7, 1.3 Hz, 1H, H3), 4.91 (ABq, J = 13.1 Hz, 2H, CH_2Ph), 4.90-4.89 (m, 1H, H2), 4.58 (dd, J = 11.0, 4.2 Hz, 1H, CH_2), 4.48 (dd, J = 11.0, 2.4 Hz, 1H, CH_2), 4.36 (ddd, J = 8.8, 4.2, 2.4 Hz, 1H, H5), 4.13 (dd, J = 8.8, 6.4 Hz, 1H, H4), 3.33 (s, 2H, NH_2); **^{13}C NMR (125 MHz, d_4-MeOD):** δ (ppm): 165.8 (CO), 145.6 (Cq), 145.5 (C1), 133.1 (Ph), 129.5 (Ph), 129.1 (Ph), 128.2 (Ph), 127.8 (Ph), 123.0 (Ph), 99.0 (C2), 74.9 (C5), 74.0 (C4), 72.3 (CH_2), 71.0 (C3), 66.8 (CH_2); **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{20}O_9N_2SNa$: 487.0787 [M+Na]$^+$; found: 487.0787.

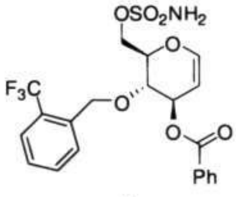


4f

(2*R*,3*S*,4*R*)-2-(sulfamoyloxymethyl)-3-(3-methoxybenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (4f)

Yield: 94 %; colourless solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.02 (dd, J = 8.2, 1.2 Hz, 2H, Ph), 7.59 (tt, J = 7.5, 1.2 Hz, 1H, Ph), 7.46 (t, J = 8.2 Hz, 2H, Ph), 7.20 (t, J = 7.8 Hz, 1H, Ph), 6.87-6.84 (m, 2H, Ph), 6.79 (d, J = 7.6, 1,9 Hz, 1H, Ph), 6.46 (dd, J = 6.1, 1.2 Hz, 1H, H1), 5.74 (ddd, J = 6.2, 2.9, 1.2 Hz, 1H, H3), 4.95 (dd, J = 6.1, 2.9 Hz, 1H, H2), 4.78 (s, 2H, NH_2), 4.72 (ABq, J = 11.5, 2H,

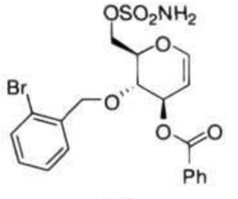
CH_2Ph), 4.60 (dd, *J* = 11.1, 4.5 Hz, 1H, CH_2), 4.48 (dd, *J* = 11.0, 2.5 Hz, 1H, CH_2), 4.25 (ddd, *J* = 8.8, 4.5, 2.5 Hz, 1H, H5), 4.07 (dd, *J* = 8.7, 6.2 Hz, 1H, H4), 3.75 (s, 3Hm OCH_3); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 165.9 (CO), 159.6 (Cq), 145.3 (C1), 138.7 (Ph), 133.3 (Ph), 129.7 (Ph), 129.6 (Ph), 129.5 (Ph), 128.5 (Ph), 120.4 (Ph), 113.6 (Ph), 113.5 (Ph), 100.0 (C2), 74.9 (C5), 73.3 (CH_2), 72.3 (C4), 71.1 (C3), 68.4 (CH_2), 55.2 (OCH_3); **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{23}O_8NSNa$: 472.1042 $[M+Na]^+$; found: 472.1039.



4g

(2*R*,3*S*,4*R*)-2-(sulfamoyloxymethyl)-3-(2-(trifluoromethyl)benzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (4g)

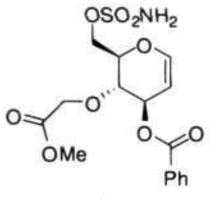
Yield: 62 %; colourless solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 7.99 (dd, *J* = 8.4 Hz, 2H, Ph), 7.61-7.53 (m, 3H, Ph), 7.49-7.41 (m, 3H, Ph), 7.30 (t, *J* = 7.4 Hz, 1H, Ph), 6.45 (dd, *J* = 6.1, 1.1 Hz, 1H, H1), 5.71 (ddd, *J* = 6.2, 2.8, 1.1 Hz, 1H, H3), 5.06 (br s, 2H, NH_2), 4.98 (dd, *J* = 6.1, 2.8 Hz, 1H, H2), 4.96 (ABq, *J* = 12.2 Hz, 2H, CH_2Ph), 4.61 (dd, *J* = 11.1, 4.7 Hz, 1H, CH_2), 4.53 (dd, *J* = 11.1, 2.4 Hz, 1H, CH_2), 4.30 (ddd, *J* = 8.6, 4.7, 2.4 Hz, 1H, H5), 4.14 (dd, *J* = 8.6, 6.2 Hz, 1H, H4); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 165.9 (CO), 145.2 (C1), 135.7 (Ph), 133.3 (Ph), 132.0 (Ph), 129.56 (Ph), 129.50 (Ph), 128.4 (Ph), 127.7 (Ph), 125.7 (Ph), 125.6 (Ph), 99.9 (C2), 74.7 (C5), 73.4 (C4), 71.0 (C3), 69.7 (CH_2), 68.4 (CH_2); **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{20}O_7F_3NSNa$: 510.0810 $[M+Na]^+$; found: 510.0801.



4h

(2*R*,3*S*,4*R*)-2-(sulfamoyloxymethyl)-3-(2-bromobenzyloxy)-3,4-dihydro-2H-pyran-4-yl benzoate (4h)

Yield: 76 %; yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.02 (d, J = 7.3 Hz, 2H, Ph), 7.57 (t, J = 7.5 Hz, 1H, Ph), 7.44, (t, J = 7.8 Hz, 2H, Ph), 7.40 (d, J = 6.6 Hz, 2H, Ph) 7.23 (t, J = 7.5 Hz, 1H, Ph), 7.08 (dt, J = 7.8, 1.4 Hz, 1H, Ph), 6.46 (d, J = 6.1 Hz, 1H, H1), 5.46-5.48 (m, 1H, H3), 5.06 (s, 2H, NH$_2$), 4.95 (dd, J = 6.1, 2.8 Hz, 1H, H2), 4.83 (ABq, J = 11.9 Hz, 2H, CH$_2$Ph), 4.62 (dd, J = 11.1, 4.7 Hz, CH$_2$), 4.53 (dd, J = 11.1, 2.4 Hz, 1H, CH$_2$), 4.29 (m, 1H, H5), 4.12 (dd, J = 6.3, 2.5 Hz, 1H, H4); **^{13}C NMR (125 MHz, CDCl$_3$):** δ (ppm): 165.9 (CO), 145.2 (C1), 136.5 (Ph), 133.3 (Ph), 132.6 (Ph), 129.8 (Ph), 129.6 (Ph), 129.49 (Ph), 128.47 (Ph), 127.5 (Ph), 123.0 (Ph), 99.9 (C2), 74.8 (C5), 73.1 (CH$_2$), 73.0 (C4), 71.2 (C3), 68.5 (CH$_2$); **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{20}O_7BrNSNa$: 520.0042 [M+Na]$^+$; found: 520.0041.



4i

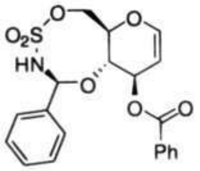
(2*R*,3*S*,4*R*)-2-(sulfamoyloxymethyl)-3-(2-methoxy-2-oxoethoxy)-3,4-dihydro-2H-pyran-4-yl benzoate (4i)

Yield: 76 %; colourless oil. **^{1}H NMR (500 MH$_Z$, CDCl$_3$):** δ (ppm): 8.00 (d, J = 8.4

Hz, 2H, Ph), 7.57 (t, *J* = 7.4 Hz, 1H, Ph), 7.44 (t, *J* = 8.0 Hz, 2H, Ph), 6.43 (dd, *J* = 6.0, 1.1 Hz, 1H, H1), 5.73 (ddd, *J* = 6.4, 2.6, 1.3 Hz, 1H, H3), 5.53 (br s, 2H, NH_2), 4.89 (dd, *J* = 6.0, 2.7 Hz, 1H, H2), 4.66 (dd, *J* = 11.1, 4.6 Hz, 1H, CH_2), 4.53 (dd, *J* = 11.1, 2.5 Hz, 1H, CH_2), 4.35 (Abq, *J* = 16.5 Hz, 2H, CH_2CO_2Me), 4.30 (m, 1H, H5), 4.07 (dd, *J* = 9.0, 6.4 Hz, 1H. H5), 3.55 (s, 3H, OCH_3); **^{13}C (125 MHz, $CDCl_3$):** δ (ppm): 170.7 (CO), 165.7 (CO), 145.3 (C1), 133.4 (Ph), 129.5 (Ph), 129.4 (Ph), 128.5 (Ph), 99.4 (C2), 74.5 (C5), 73.9 (C4), 71.4 (C3), 68.2 (CH_2), 68.1 (CH_2), 51.9 (OCH_3); **HRMS (ESI):** *m/z*: calcd for $C_{16}H_{19}O_9NSNa$: 424.0678 $[M+Na]^+$; found: 424.0674.

4.4 General procedure for rhodium-catalyzed C–H insertion

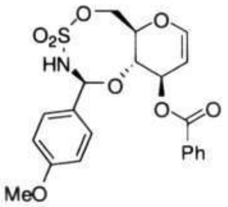
A mixture of sulfamate ester (7.2×10^{-2} mmol), MgO (3.6×10^{2} mmol), $PhI(OAc)_2$ (1.1×10^{2} mmol), 5 mol% of $Rh_2(OAc)_4$ (4×10^{-4} mmol) and 4 Å molecular sieves was in CH_2Cl_2 (3.0 mL) was stirred vigorously at room temperature for 6 hours. The reaction mixture was filtered through a pad of celite. The filtered celite was rinsed with CH_2Cl_2 and the combined filtrates were evaporated under reduced pressure. The residue was purified by chromatography on silica gel (30 % EtOAc in hexane) to afford the oxathiazinane product.



5a

(5*S*,6*R*,9*R*)-3-phenyl-5,6-dihydro-2H-pyran-9-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (5a)

Yield: 78 %; colourless oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 9.03 (s, 1H, CH), 8.02 (dd, J = 8.1, 1.0 Hz, 2H, Ph), 7.95 (dd, J = 7.2, 1.0 Hz, 1H, Ph), 7.65 (t, J = 7.4 Hz, 1H, Ph), 7.60-7.43 (m, 5H, Ph), 7.27 (d, J = 13.6 Hz, 1H, Ph), 6.47 (dd, J = 6.1, 1.4 Hz, 1H, H1), 5.54 (dd, J = 2.5, 1.4 Hz, 1H, H3), 4.86 (dd, J = 6.1, 2.5 Hz, 1H, H2), 4.81 (dd, J = 11.3, 3.7 Hz, 1H, CH$_2$), 4.7 (dd, J = 11.3, 1.7 Hz, 1H, CH$_2$), 4.14 (m, 2H, H4 and H5); **^{13}C NMR (500 MHz, CDCl$_3$):** δ (ppm): 173.4 (CH), 167.8 (CO), 146.1 (C1), 135.6 (Ph), 133.5 (Ph), 131.4 (Ph), 129.8 (Ph), 128.8 (Ph), 128.5 (Ph), 99.4 (C2), 76.0 (C5), 73.7 (C3), 70.3 (CH$_2$), 66.9 (C4); **HRMS (ESI):** *m/z*: calcd for $C_{20}H_{19}O_7NSNa$: 440.0780 $[M+Na]^+$; found: 440.0769.

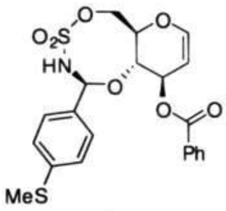


5b

(5*S*,6*R*,9*R*)-3-(4-methoxyphenyl)-5,6-dihydro-2H-pyran-9-*O*-benzoyl-[1,2]thiazepane-1,1-dioxide (5b)

Yield: 92 %; colourless oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.95 (s, 1H, CH), 8.04 (d, J = 7.6 Hz, 2H, Ph), 7.93 (d, J = 8.9 Hz, 2H, Ph), 7.61 (t, J = 7.6 Hz, 1H, Ph), 7.46 (t, J = 7.6 Hz, 2H, Ph), 7.00 (d, J = 8.9 Hz, 2H, Ph), 6.49 (dd, J = 6.0, 1.2 Hz, 1H, H1), 5.57 (m, 1H, H3), 4.88 (dd, J = 6.0, 2.4 Hz, 1H, H2), 4.76 (dd, J = 11.0, 3.0 Hz, 1H, CH$_2$), 4.71 (d, J = 11.0 Hz, 1H, CH$_2$), 4.16 (m, 2H, H4 and H5), 3.91 (s, 3H, OCH$_3$), 3.75 (d, J = 2.0 Hz, 1H, NH); **^{13}C NMR (500 MHz, CDCl$_3$):** δ (ppm): 172.4 (CH), 167.6 (Cq), 165.8 (CO), 146.1 (C1), 134.0 (Ph), 133.5 (Ph), 129.8 (Ph), 129.4 (Ph), 128.4 (Ph), 124.5 (Ph), 114.9 (CH), 99.5 (C2), 76.1 (C5), 73.4 (C3), 69.9 (CH$_2$), 66.7 (C4), 55.7 (OCH$_3$); **HRMS (ESI):** *m/z*:

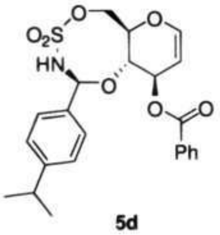
calcd for $C_{21}H_{21}O_8NSNa$: 470.0880 $[M+Na]^+$; found: 470.0870.



5c

(5*S*,6*R*,9*R*)-3-(4-methylthiophenyl)-5,6-dihydro-2H-pyran-9-*O*-benzoyl-[1,2] thiazepane-1,1-dioxide (5c)

Yield: 54 %; pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.94 (s, 1H, CH), 8.03 (d, *J* = 8.1 Hz, 2H, Ph), 7.83 (d, *J* = 8.5 Hz, 2H, Ph), 7.59 (t, *J* = 7.4 Hz, 1H, Ph), 7.46 (m, 2H, Ph), 7.29-7.25 (m, 2H, Ph), 6.47 (dd, *J* = 6.1, 1.4 Hz, 1H, H1), 5.55 (m, 1H, H3), 4.86 (dd, *J* = 6.1, 2.4 Hz, 1H, H2), 4.80 (d, *J* = 11.6 Hz, 1H, CH_2), 4.71 (d, *J* = 11.6 Hz, 1H, CH_2), 4.14 (m, 2H, H4 and H5), 3.75 (d, *J* = 2.5 Hz, 1H, NH); **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{21}O_7NS_2Na$: 486.0657 $[M+Na]^+$; found: 486.0659.

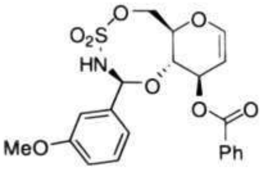


5d

(5*S*,6*R*,9*R*)-3-(4-isopropylphenyl)-5,6-dihydro-2H-pyran-9-*O*-benzoyl-[1,2] thiazepane-1,1-dioxide (5d)

Yield: 83 %; colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.99 (s, 1H, CH), 8.04 (dd, *J* = 7.1, 1.1 Hz, 2H, Ph), 7.89 (d, *J* = 7.1 Hz, 2H, Ph), 7.59 (tt, *J* =

7.4, 1.2 Hz, 1H, Ph), 7.44 (t, *J* = 7.3, 1.5 Hz, 2H, Ph), 7.36 (d, *J* = 8.2 Hz, 2H, Ph), 6.47 (dd, *J* = 6.0, 1.2 Hz, 1H, H1), 5.55 (m, 1H, H3), 4.86 (dd, *J* = 6.1, 2.5 Hz, 1H, H2), 4.78 (dd, *J* = 11.3, 3.7 Hz, 1H, CH_2), 4.71 (dd, *J* = 11.3, 1.2 Hz, 1H, CH_2), 4.15 (m, 2H, H4 and H5), 3.73 (d, *J* = 2.8 Hz, 1H, NH), 2.97 (quint, *J* = 6.9 Hz, 1H. CH), 1.27 (d, *J* = 6.9 Hz, 6H, CH_3); **^{13}C NMR (500 MHz, $CDCl_3$):** δ (ppm): 173.2 (CH), 158.3 (CO), 146.1 (C1), 133.5 (Ph), 131.8 (Ph), 129.8 (Ph), 129.5 (Ph), 129.4 (Ph), 128.4 (Ph), 127.5 (Ph), 99.4 (C2), 76.0 (C5), 73.6 (C3), 70.0 (CH_2), 66.8 (C4), 34.5 (CH), 23.4(CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{25}O_7NSNa$: 482.1249 $[M+Na]^+$; found: 482.1259.

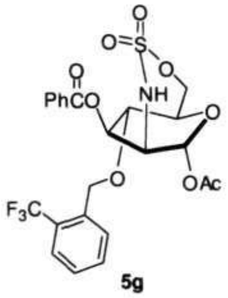


5f

(5*S*,6*R*,9*R*)-3-(3-methoxyphenyl)-5,6-dihydro-2H-pyran-9-*O*-benzoyl-[1,2]thiaze pane-1,1-dioxide (5f)

Yield: 84 %; colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.97 (s, 1H, CH), 8.01 (d, *J* = 7.1 Hz, 2H, Ph), 7.58 (t, *J* = 6.9, 1.2 Hz, 1H, Ph), 7.49-7.40 (m, 5H, Ph), 7.19 (m, 1H, Ph), 6.47 (dd, *J* = 6.1, 1.3 Hz, 1H, H1), 5.54 (m, 1H, H3), 4.87 (dd, *J* = 6.1, 2.5 Hz, 1H, H2), 4.79 (dd, *J* = 11.3, 3.6 Hz, 1H, CH_2), 4.72 (d, *J* = 11.3 Hz, 1H, CH_2), 4.15 (m, 2H, H4 and H5), 3.83 (s, 3H, OCH_3), 1.78 (br s, 1H, NH); **^{13}C NMR (500 MHz, $CDCl_3$):** δ (ppm): 172.4 (CH), 167.8 (Cq), 160.1 (CO), 146.1 (C1), 133.5 (Ph), 133.0 (Ph), 130.2 (Ph), 129.8 (Ph), 129.3 (Ph), 128.4 (Ph), 125.5 (Ph), 122.8 (Ph), 113.4 (CH), 99.5 (C2), 75.9 (C5), 73.7 (C3), 70.2 (CH_2), 66.8 (C4), 55.5 (OCH_3); **HRMS (ESI):** *m/z*: calcd for $C_{21}H_{21}O_8NSNa$: 470.0886

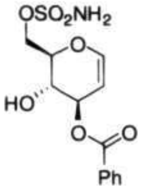
$[M+Na]^+$; found: 470.0877.



5g

9-*O*-Acetyl-7-(2-(trifluoromethyl)benzyloxy)-8-*O*-benzoyl-4,10-dioxa-3-thia-2-aza bicyclo[4.2.2]decane-3,3-dioxide (5g)

Yield: 50 %; colourless liquid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 8.60 (dd, J = 8.2, 1.2 Hz, 2H, Ph), 7.66-7.58 (m, 3H, Ph), 7.50 (t, J = 7.8 Hz, 2H, Ph), 7.44 (t, J = 8.2 Hz, 1H, Ph), 7.37 (t, J = 7.6 Hz, 1H, Ph), 6.79 (d, J = 1.2 Hz, 1H, H1), 5.73 (t, J = 5.0 Hz, 1H, H3), 5.15 (br s, 1H, NH), 4.81 (ABq, J = 12.9 Hz, 2H, CH_2Ph), 4.73 (dd, J = 13.0, 1.0 Hz, 1H, CH_2), 4.59 (m, 1H, H5), 4.28 (dd, J = 13.0, 2.9 Hz, 1H, CH_2), 4.24 (d, J = 4.6 Hz, 1H, H4), 4.98 (m, 1H, H2), 2.13 (s, 3H, CH_3); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 169.0 (CO), 165.1 (CO), 134.1 (Ph), 132.0 (Ph), 130.1 (Ph), 129.9 (Ph), 129.4 (Ph), 128.7 (Ph), 128.4 (Ph), 128.0 (Ph), 125.9 (Ph), 90.5 (C1), 77.9 (C5), 76.3 (C4), 75.7 (CH_2), 71.1 (C3), 68.2 (CH_2), 52.4 (C2), 21.0 (CH_3); **HRMS (ESI):** *m/z*: calcd for $C_{23}H_{22}NO_9SF_3Na$: 568.0865 $[M+Na]^+$; found: 568.0867.

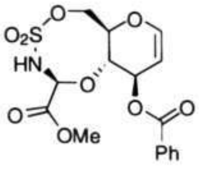


6

(2*R*,3*S*,4*R*)-3-hydroxy-2-(sulfamoyloxymethyl)-3,4-dihydro-2H-pyran-4-yl

benzoate (6)

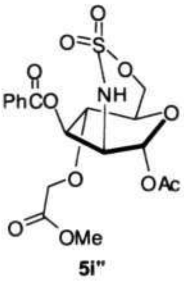
Yield: 76 %; colourless solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.02 (dd, J = 7.3 Hz, 2H, Ph), 7.58 (t, J = 7.4 Hz, 1H, Ph), 7.43 (t, J = 7.7 Hz, 2H, Ph), 6.47 (d, J = 6.1 Hz, 1H, H1), 5.54 (d, J = 6.0 Hz, 1H, H3), 5.31 (br s, 2H, NH$_2$), 4.84 (dd, J = 6.1, 2.4 Hz, 1H, H2), 4.57 (dd, J = 11.4, 3.7 Hz, 1H, CH$_2$), 4.54 (d, J = 11.4 Hz, 1H, CH$_2$), 4.15-4.09 (m, 3H, H4, H5, and OH); **^{13}C NMR (125 MHz, CDCl$_3$):** δ (ppm): 167.9 (CO), 145.9 (C1), 133.6 (Ph), 129.8 (Ph), 129.2 (Ph), 128.5 (Ph), 99.6 (C2), 75.9 (C5), 73.5 (C3), 68.6 (C4), 67.0 (CH$_2$); **HRMS (ESI):** *m/z*: calcd for $C_{13}H_{15}O_7NSNa$: 352.0467 [M+Na]$^+$; found: 352.0471.



5i

(5*S*,6*R*,9*R*)-3-(2-methoxy-2-oxoethoxy)-5,6-dihydro-2H-pyran-9-*O*-benzoyl-[1,2] thiazepane-1,1-dioxide (5i)

Yield: 7 %; colourless oil. **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 8.07 (d, J = 7.1 Hz, 2H, Ph), 7.61 (t, J = 7.4 Hz, 1H, Ph), 7.48 (t, J = 7.4 Hz, 2H, Ph), 7.19 (m, 1H, Ph), 6.42 (dd, J = 6.0, 1.4 Hz, 1H, H1), 6.27 (d, J = 10.4 Hz, 1H, NH), 5.83 (dt, J = 8.3, 1.9 Hz, 1H, H3), 5.20 (d, J = 9.9 Hz, 1H, CH), 4.90 (dd, J = 6.0, 2.0 Hz, 1H, H2), 4.72 (dd, J = 13.2, 3.2 Hz, 1H, CH$_2$), 4.57 (d, J = 13.2 Hz, 1H, CH$_2$), 4.33 (dd, J = 10.3, 8.3 Hz, 1H, H4), 4.18 (dd, J = 10.3, 1.9 Hz, 1H, H5), 3.38 (s, 3H, OCH$_3$); **HRMS (ESI):** *m/z*: calcd for $C_{16}H_{17}O_9NSNa$: 422.0522 [M+Na]$^+$; found: 422.0514.



5i''

9-*O*-Acetyl-7-(2-methoxy-2-oxoethoxy)-8-*O*-benzoyl-4,10-dioxa-3-thia-2-azabicyclo [4.2.2] decane-3,3-dioxide (5i'')

Yield: 79 %; colourless solid. **^{1}H NMR (500 MHz, CDCl$_3$):** δ(ppm): 8.08 (dd, J = 8.2, 1.2 Hz, 2H, Ph), 7.64 (t, J = 7.5 Hz, 1H, Ph), 7.50 (t, J = 7.8 Hz, 2H, Ph), 6.77 (s, 1H, H1), 5.64 (t, J = 5.1 Hz, 1H, H3), 5.24 (br s, 1H, NH), 4.75 (br s, 1H, H5), 4.70 (d, J = 13.0 Hz, 1H, CH$_2$), 4.50 (dd, J = 13.0, 2.8 Hz, 1H, CH$_2$), 4.28 (ABq, J = 17.0 Hz, 2H, CH$_2$Ph), 4.24 (m, 1H, H4), 3.94 (dt, J = 3.8, 1.3 Hz, 1H, H2), 3.67 (s, 3H, OCH$_3$), 2.14 (s, 3H, CH$_3$); **^{13}C NMR (125 MHz, CDCl$_3$):** δ(ppm): 170.7 (CO), 169.1 (CO), 165.2 (CO), 134.1 (Ph), 129.8 (Ph), 128.86 (Ph), 128.83 (Ph), 128.5 (Ph), 90.7 (C1), 78.9 (C5), 77.6 (C4), 75.8 (CH$_2$), 71.8 (C3), 68.1 (CH$_2$), 52.5 (C2), 52.0 (OCH$_3$), 21.0 (CH$_3$); **HRMS (ESI):** *m/z*: calcd for $C_{18}H_{21}NO_{11}SNa$: 482.0733[M+Na]$^+$; found: 482.0733.

5. REFERENCES

1 H. Kwart, A. A. Khan, *J. Am. Chem. Soc.* **1967**, *89*, 1951.

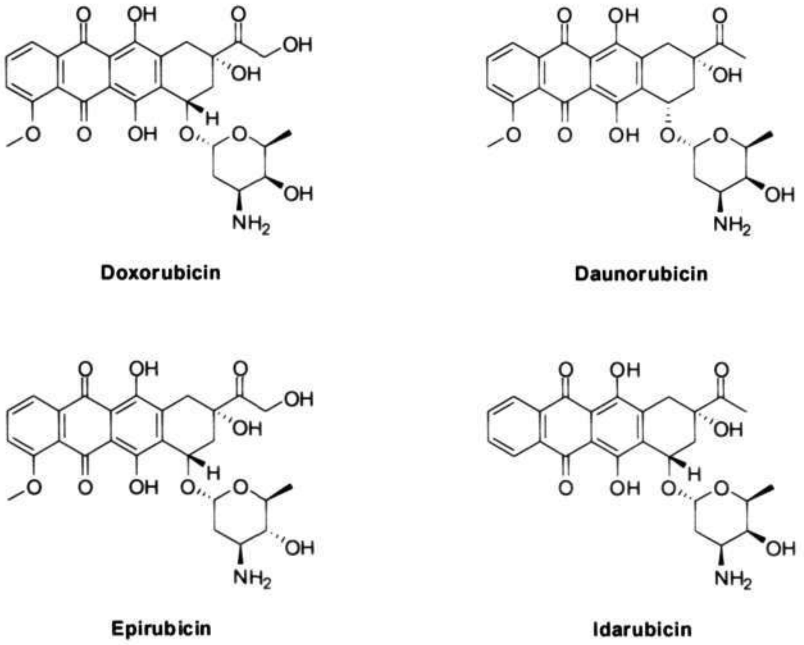
2 R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1983**, *105*, 6728.

3 P. M. Wehn, J. Lee, J. Du Bois, *Org. Lett.* **2003**, *25*, 4823.

1. INTRODUCTION

Carbohydrates present new insights into drug design for targeting specific diseases. Several carbohydrate-based drugs possess many important roles in medical field, for example, anthracycline antibiotics are among the most effective for cancer chemotherapy. This family of compounds is widely used in clinical treatment of breast, uterine, ovarian, and lung cancers, leukemia, and lymphomas.[1] With their high potential against more types of cancer than other classes of chemotherapeutic agents, many researchers have paid attention to developing effective methodologies for the synthesis of the anthracyclines and also have been continuously inspired for the design of new analogs. However, the highly severe adverse effects, which considerably limit their use, are heart failure and antitumor effects. The damage is mainly caused by the cumulative dose.

Anthracycline antibiotics include daunorubicin, doxorubicin, epirubicin, and idarubicin (Figure 1). The structures of naturally occurring anthracyclines are composed of the 3-aminosugar moiety linked with the aglycone skeleton through an *O*-glycosidic bond.



Doxorubicin

Daunorubicin

Epirubicin

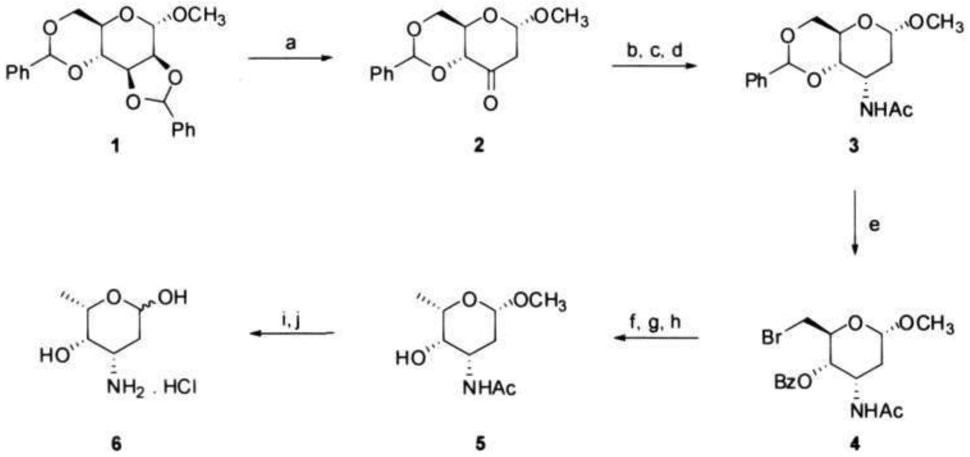
Idarubicin

Figure 1 Examples of anthracycline antibiotics.

The ability to specifically control many stereogenic centers on carbohydrate molecules would have major application both in chemistry, biochemistry and related disciplines. Likewise in daunorubicin, synthesis of analogues in which the stereocenters on carbohydrate were altered is of great biochemical and practical importance. This is even more critical when the analogues produced were able to show enhanced activities against cancer cells or good activities against other diseases.[2]

With prior knowledge in high stereoselective synthesis of aminoglycosides via rhodium catalysis in our research group, we were very much hopeful to be able to provide an alternative pathway to the usual manner in which 3-amino glycosylation are obtained synthetically. Most of the synthetic methodologies started from monosaccharide precursors, followed by the introduction of nitrogen functionality at C-3 as the key step. The common methods include nucleophilic substitution of sulfonate esters with sodium azide, amination of an oxirane ring or 2,3-unsaturated pyranosides, reaction of sugar dialdehydes with nitromethane, halogen promoted cyclization of allylic iminoesters.[3]

Horton reported a new synthetic pathway for daunosamine as outlined in Scheme 1. The synthetic pathway started from D-mannose and could provide daunosamine hydrochloride in 9 steps with an overall yield of 40 %.[4] Introduction of nitrogen functionality at C-3 was achieved by reacting keto **2** with hydroxylamine. The corresponding oxime intermediate was isolated without recourse to chromatographic separation and transformed to acetyl amine **3** with high selectivity.



Scheme 1 Synthetic scheme of daunosamine hydrochloride. a) BuLi b) NH_2OH c) $LiAlH_4$ d) Ac_2O e) NBS f) AgF g) NaOMe h) H_2/Pd/C i) $Ba(OH)_2$ j) aq. HCl.

By observing how D-mannose could potentially be transformed into such useful compounds, we were inspired to examine the possibilities of varying the stereochemistry present in the carbohydrate. In the previous chapter, we have described the possibility of the nitrogen insertion to C–H bonds to form sulfamoyl imine. Considering its structure, we have seen the conjugated system, which is equivalent to Michael acceptor (Figure 2). The addition of a nucleophile is believed to preferably attack on an anomeric carbon due to the electronegativity preference. Moreover, we believe that, through our proposed synthetic scheme, we would be able to control the stereochemistry of the C-1, C-3 and C-4 positions of the pyranose ring effectively.

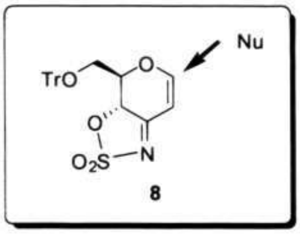
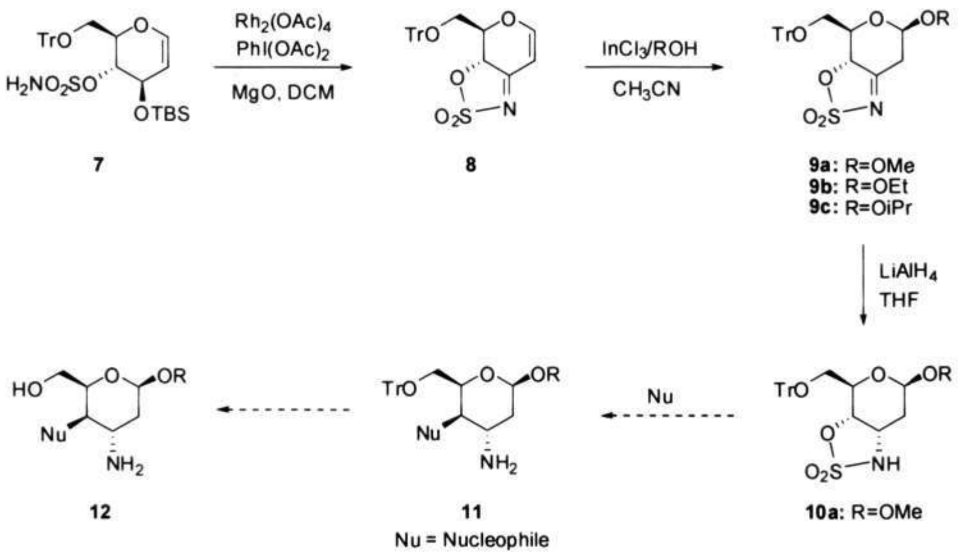


Figure 2 Sulfamoyl imine acts as Michael adduct.

2. RESULTS AND DISCUSSION

The preparation of sulfamoyl imine **8**, which could be easily obtained under the rhodium-catalytic condition, was described in the previous chapter. The stereochemistry at the glycosylation step can be controlled due to the structure of imine **8** and, consequently, β–glycosylation should be more favorable. In order to facilitate the 1,4-nucleophilic addition, a soft metal is required to promote the reaction. We have screened some Lewis acid and solvents, and found that use of indium trichloride in refluxing acetonitrile gave the best yields of products. Different alcoholic neucleophiles such as methanol, ethanol and isopropyl alcohol were examined, yielding glycosylated products **9a**, **9b**, and **9c** in moderate-to-good yields (Scheme 2). Evidence from NMR spectroscopic data suggest that the glycosylation proceeded via 1,4-addition and the product still retains the imine functionality.

Reduction of the imine functional group was carried out by treating **9a** with $LiAlH_4$ in THF, giving a secondary substituted amine **10**. By its ^1H and NOESY NMR spectra, it was determined that the amine moiety is *trans* to the methoxy group at C–1 position. As expected, the nucleophile preferred to attack at the anomeric carbon from the top face of molecule to give β–glycosylated products with high selectivity. Ideally, the sulfamate ester bond can be cleaved through a nucleophilic attack by *O*–, *S*– or *N*–nucleophiles to gain access to complex aminosaccharide conjugates. To overcome this stage, a variety of nucleophiles investigated in our laboratory.



Scheme 2 Reaction pathway towards 3-aminosaccharides.

In order to increase the possibilities of accessing a wider variety of glycosylated complexes, we attempted to invert the stereocenter at the C-4 position to facilitate the α–glycosylation reaction. As such, we proposed an additional synthetic route to access the derivatives required.

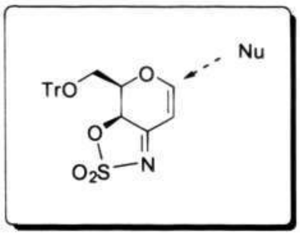


Figure 3 The approach of nucleophile on the bottom face for α–glycosylation.

The inversion of stereocenters was made possible through a 5-step synthetic pathway. Initially, compound **13** was treated with mesyl chloride in CH_2Cl_2 and pyridine to yield **14**. The TBDMS protecting group on the C-3 position of **14** was then deprotected by using 1M solution of TBAF in THF to give **15**. Reaction of compound **15** with *t*-BuOK, followed by the addition of a mixture of Bu_4NBr and Me_3SiOK, which generated tetrabutylammonium trimethylsilanolate ($Bu_4N^+SiO^-$), finally produced diol **17** in a completely regio- and stereoselective way. This reaction proceeded via an epoxide intermediate, where *t*-BuOK functioned to deprotonate the hydroxyl group at C-3 position, releasing –OMs as leaving group. As common method, the TBS-protected gulal was obtained by treating **17** with TBDMSCl and imidazole in dry DMF.

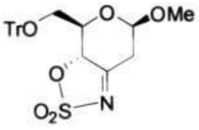
3. CONCLUSION

We have proposed an alternative pathway to construct 3-amino pyranose rings with high stereoselectivity through one-pot rhodium-catalyzed C–H insertion and OTBDMS removal as key step. The resulting sulfamoyl imine acts as a Michael synthon inducing selective glycosylation. The stereochemistry at C-3 seems to be important in controlling the approaching direction of nucleophiles, We have also proven that the pathway designed is viable. With such extensive results, we will continue to work on the project and additional results will be reported in the future.

4. EXPERIMENTAL

General procedure for *O*–glycosylation

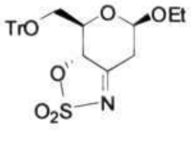
To a solution of sulfamoyl imine **8** (70 mg, 0.16 mmol) in CH_3CN (0.7 mL) was added alcohol (20 equiv) and $InCl_3$ (38 mg, 0.17 mmol). The reaction mixture was heated at 80 °C for 1 hour. After cooling down to room temperature, the reaction mixture was extracted with EtOAc and washed with water. The combined organic layer was washed with brine, dried over anh. Na_2SO_4, filtered and the solvents were removed under reduced pressure. The product was purified by column chromatography eluting with 30 % EtOAc in hexane to yield the corresponding glycosylated product.



9a

1-*O*-Methyl-2-deoxy-3-imino-4-*O*-sulfamate-6-*O*-trityl-hexopyranose (9a)

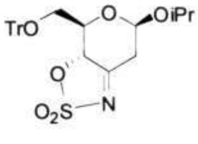
Yield 89 %; colorless viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm): 7.46-7.41 (m, 6H, Ph), 7.34-7.24 (m, 9H, Ph), 5.28-5.24 (m, 2H, 2 × CH), 3.92-3.88 (m, 1H, CH), 4.39 (dd, J = 10.7, 1.84 Hz, 1H, CH_2), 3.39 (s, 3H, CH_3), 3.32 (dd, J = 10.7, 4.1 Hz, 1H, CH_2), 3.08 (d, J = 14.2 Hz, 1H, CH_2), 2.98 (dd, J = 14.2, 4.6 Hz, 1H, CH_2); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm): 181.2 (Cq), 143.5 (Ph), 128.7 (Ph), 128.2 (Ph), 128.1 (Ph), 127.5 (Ph), 98.9 (CH), 87.2 (Cq), 81.5 (CH), 72.1 (CH), 62.6 (CH_2), 55.6 (OCH_3), 37.3 (CH_2); **HRMS (ESI)**: *m/z*: calcd for $C_{26}H_{25}NO_6SNa$: 502.1300 $[M+Na]^+$; found: 502.1304.



9b

1-*O*-Ethyl-2-deoxy-3-imino-4-*O*-sulfamate-6-*O*-trityl-hexopyranose (9b)

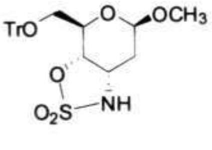
Yield 70 %; colourless viscous oil; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ (ppm): 7.44-7.42 (m, 6H, Ph), 7.34-7.23 (m, 9H, Ph), 5.37 (d, J = 4.6 Hz, 1H, CH), 5.24 (d, J = 9.6 Hz, 1H, CH), 3.94-3.90 (m, 1H, CH), 3.74-3.66 (m, 1H, CH$_2$), 3.56-3.50 (m, 1H, CH$_2$), 3.47 (dd, J = 10.7, 1.8 Hz, 1H, CH$_2$), 3.30 (dd, J = 10.7, 4.1 Hz, 1H, CH$_2$), 3.06 (d, J = 14.2 Hz, 1H, CH$_2$), 2.98 (dd, J = 14.2, 5.0 Hz, 1H, CH$_2$), 1.91 (t, J = 6.8 Hz, 3H, CH$_3$); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ (ppm): 181.4 (Cq), 143.5 (Ph), 128.8 (Ph), 128.3 (Ph), 128.2 (Ph), 127.5 (Ph), 97.5 (CH), 87.2 (Cq), 81.6 (CH), 72.1 (CH), 64.1 (CH$_2$), 62.6 (CH$_2$), 37.6 (CH$_2$), 14.9 (CH$_3$); **HRMS (ESI)**: *m/z*: calcd for $C_{27}H_{27}NO_6SNa$: 516.1457 [M+Na]$^+$; found: 516.1492.



9c

1-*O*-Isopropyl-2-deoxy-3-imino-4-*O*-sulfamate-6-*O*-trityl-hexopyranose (9c)

Yield 89 %; colourless viscous oil; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ (ppm): 7.45-7.42 (m, 6H, Ph), 7.35-7.26 (m, 9H, Ph), 5.49 (br s, 1H, CH), 5.24 (d, J = 12.7 Hz, 1H, CH), 4.01-3.90 (m, 1H, CH), 3.93 (quin, J = 6.2 Hz, 1H, CH), 3.45 (dd, J = 14.2, 2.6 Hz, 1H, CH$_2$), 3.29 (d, J = 14.3, 5.7 Hz, 1H, CH$_2$), 3.01 (m, 2H, CH$_2$), 1.18 (d, J = 6.2 Hz, 3H, CH$_3$), 1.17 (d, J = 6.2 Hz, 3H, CH$_3$); **^{13}C NMR (75 MHz, CDCl$_3$)**: δ (ppm): 181.6 (Cq), 143.5 (Ph), 128.8 (Ph), 128.2 (Ph), 127.5 (Ph), 95.9 (CH), 87.2 (Cq), 81.6 (CH), 72.3 (CH), 70.7 (CH), 62.6 (CH_2), 38.1 (CH_2), 23.2 (CH_3), 21.4 (CH_3); **HRMS (ESI)**: *m/z*: calcd for $C_{28}H_{29}NO_6SNa$: 530.1613 $[M+Na]^+$; found: 530.1605.

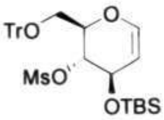


10

1-*O*-Methyl-2-deoxy-3-imino-4-*O*-sulfamate-6-*O*-trityl-hexopyranose (10)

To a solution of methoxy imine **9a** (6 mg, 0.01 mmol) in THF (1 mL), was added $LiAlH_4$ (2 mg, 0.05 mmol) at 0°C. The reaction mixture was left to stir at room temperature for 3 hrs. The reaction was then quenched with 10 % sodium hydroxide at 0 °C. The mixture was extracted with EtOAc, washed with brine, dried over anh. $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by column chromatography eluting with 30 % EtOAc in hexane to yield **10** (2 mg, 42 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm): 7.46-7.41 (m, 6H, ArH), 7.34-7.24 (m, 9H, ArH), 5.52 (d, J = 11.8 Hz, 1H, NH), 4.93 (d, J = 3.4 Hz, 1H, CH), 4.75 (dd, J = 9.9, 5.3 Hz, 1H, CH), 4.21-4.17 (m, 1H, CH), 4.11-4.08 (m, 1H, CH), 3.45 (s, 3H, OCH_3), 3.40 (dd, J = 10.4, 2.1 Hz, 1H, CH_2), 3.27 (d, J = 10.4, 5.1 Hz, 1H, CH_2), 2.26 (d, J = 15.4 Hz, 1H, CH_2), 2.14 (d, J = 15.4, 5.1 Hz, 1H, CH_2); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ(ppm): 143.5 (Cq), 128.8 (Ph), 128.1 (Ph), 127.3 (Ph), 97.4 (CH), 87.2 (Cq), 78.6 (CH), 65.2 (CH), 62.8 (CH_2), 56.0 (CH_3), 52.6 (CH), 29.0 (CH_2). **HRMS (ESI)**: *m/z*: calcd for $C_{26}H_{27}NO_6SNa$: 504.1457 $[M+Na]^+$; found: 504.1451.

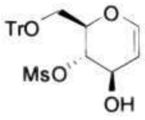


14

3-*O*-(tert-Butyldimethylsilyl)-4-*O*-mesyl-6-*O*-trityl-D-Glucal (14)

Glucal **13** (2.0 g, 3.98 mmol) was dissolved in anhydrous CH_2Cl (12.5 ml) and anhydrous pyridine (35 ml). Methanesulfonyl chloride (0.6 mL, 7.75 mmol) was added dropwise at 0 °C over 2 minutes. The reaction mixture was left to stir at that temperature overnight. The mixture was extracted with CH_2Cl. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by column chromatography eluting with 20 % EtOAc in hexane to yield **14** as colourless viscous oil (1.6 g, 69 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.46-7.44 (m, 5H, Ph), 7.31-7.23 (m, 10H, Ph), 6.40 (d, J = 6.4 Hz, 1H, =CH), 4.74 (dd, J = 6.4, 4.1 Hz, 1H, =CH), 4.65 (t, J = 3.6 Hz, 1H, CH), 4.34 (m, 1H, CH), 4.15 (t, J = 3.6 Hz, 1H, CH), 3.69 (dd, J = 11.0, 8.2 Hz, 1H, CH_2), 3.22 (dd, J = 11.0, 2.8 Hz, 1H, CH_2), 2.91 (s, 3H, CH_3), 0.79 (s, 9H, CH_3), 0.03 (s, 6H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm): 143.8 (Cq), 143.5 (=CH), 128.9 (Ph), 128.0 (Ph), 127.2 (Ph), 101.3 (=CH), 87.0 (Cq), 77.1 (CH), 75.7 (CH), 63.9 (CH), 62.0 (CH_2), 38.9 (CH_3), 25.9 (CH_3), 18.0 (Cq), -4.4 (CH_3), -4.6 (CH_3). **HRMS (ESI)**: *m/z*: calcd for $C_{32}H_{40}O_6SiSNa$: 603.2213 $[M+Na]^+$; found: 603.2219.

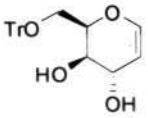


15

4-*O*-Mesyl-6-*O*-trityl-D-Glucal (15)

A solution of glucal **14** (3.26 g, 5.61 mmol) in dry THF (190 mL) was treated with a 1M solution of TBAF in THF (5.6 mL, 5.60 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h. The mixture was diluted with CH_2Cl, washed with brine, dried over anh. $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by column chromatography eluting with 30 % EtOAc in hexane to yield **15** as colourless viscous oil (2.6 g, 99 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.48-7.42 (m, 5H, Ph), 7.31-7.23 (m, 10H, Ph), 6.53 (d, J = 6.0 Hz, 1H, =CH), 4.91 (dd, J = 8.9, 6.2 Hz, 1H, CH), 4.86 (dd, J = 6.0, 2.8 Hz, 1H, =CH), 4.45 (m, 1H, CH), 4.07 (m, 1H, CH), 3.59 (dd, J = 10.9, 2.7 Hz, 1H, CH_2), 3.28 (dd, J = 10.9, 4.1 Hz, 1H, CH_2), 2.99 (d, J = 5.5 Hz, 1H, OH), 2.82 (s, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm): 144.8 (Cq), 143.3 (=CH), 128.8 (Ph), 128.0 (Ph), 127.3 (Ph), 101.5 (=CH), 87.1 (Cq), 79.1 (CH), 74.9 (CH), 67.4 (CH), 61.7 (CH_2), 38.0 (CH_3); **HRMS (ESI)**: *m/z*: calcd for $C_{26}H_{26}O_6SNa$: 489.1348 $[M+Na]^+$; found: 489.1359.

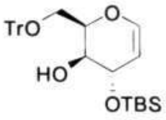


17

6-*O*-Trityl-D-Gulal (17)

A solution of compound **15** (1.0 g, 2.13 mmol) in anhydrous THF (21 mL) was treated with *t*-BuOK (0.23 g, 2.13 mmol). After 30 minutes stirring at room temperature, the reaction was treated with a solution of tetrabutylammonium trimethylsilanoate [prepared from Bu_4NBr (4.14 g, 12.88 mmol) and Me_3SiOK (1.65 g, 12.88 mmol)] in anhydrous THF (43 mL). After 48 hours stirring at the same temperature, the reaction mixture was concentrated under reduced pressure, diluted with diethyl ether and the resulting mixture was stirred for 30 minutes at room temperature in the presence of a small amount of Celite. Filtration of the suspension and evaporation of the collected organic solution afforded a crude product. Purification by column chromatography eluting with 50 % EtOAc in hexane yielded **17** (0.4 g, 48 %) as colourless liquid.

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm): 7.46-7.44 (m. 6H, Ph), 7.31-7.23 (m, 9H, Ph), 6.64 (d, J = 5.9 Hz, 1H, =CH), 4.98 (t, J = 5.5 Hz, 1H, =CH), 3.90 (m, 2H, 2 × CH), 3.82 (s, 1H, CH), 3.65 (dd, J = 10.3, 4.0 Hz, 1H, CH$_2$), 3.40 (dd, J = 10.3, 4.5 Hz,), 2.99 (d, J = 4.1 Hz, 1H, OH), 1.61 (s, 1H, OH). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ (ppm): 147.3 (=CH), 143.4 (Cq), 128.6 (Ph), 128.1 (Ph), 127.3 (Ph), 100.3 (=CH), 87.4 (Cq), 71.8 (CH), 70.0 (CH), 64.6 (CH$_2$), 63.9 (CH). **HRMS (ESI)**: *m/z*: calcd for $C_{25}H_{24}O_4Na$: 411.1572 [M+Na]$^+$; found: 411.1580.



18

3-*O*-(tert-Butyldimethylsilyl)-6-*O*-trityl-D-Gulal (18)

A solution of compound **17** (120 mg, 0.31 mmol) in anhydrous DMF (1 mL) was treated with imidazole (42 mg, 0.62 mmol), DMAP (4 mg, 0.03 mmol) and TBSCl (51 mg, 0.33 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was added EtOAc and washed with water several times. The organic layer was washed with brine, dried over anh. Na$_2$SO$_4$, filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography eluting with 30 % EtOAc in hexane giving rise to compound **18** (145 mg, 93 %) as colourless viscous oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm): 7.48-7.45 (m, 6H, Ph), 7.32-7.23 (m, 9H, Ph), 6.57 (d, J = 6.4 Hz, 1H, =CH), 4.87 (td, J = 6.4, 1.4 Hz, 1H, =CH), 3.99 (t, J = 4.1 Hz, 1H, CH), 3.80 (dd, J = 5.0, 2.3 Hz, 1H, CH), 3.73 (br t, J = 2.3 Hz, 1H, CH), 3.62 (dd, J = 10.1, 4.5 Hz, 1H, CH$_2$), 3.35 (dd, J = 10.1, 4.1 Hz, 1H, CH$_2$), 2.87 (d, J = 5.0 Hz, 1H, OH); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ (ppm): 145.8 (=CH), 143.4 (Cq), 128.6 (Ph), 127.9 (Ph), 127.1 (Ph), 101.6 (=CH), 87.3 (Cq), 71.7 (CH), 70.5 (CH), 64.6 (CH_2), 64.4 (CH), 25.8 (CH_3), 18.0 (Cq), -4.28 (CH_3), -4.66 (CH_3); **HRMS (ESI)**: *m/z*: calcd for $C_{31}H_{38}O_4SiNa$: 525.2437 $[M+Na]^+$; found: 525.2430.

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1. INTRODUCTION

In 1991, Arduengo *et al* introduced the first stable *N*-heterocyclic carbene (NHC), which could be isolated in the laboratory (Figure 1).[1] Ever since then, much interest has developed around the chemistry of NHCs, given their potential as transition m.etal ligands and organocatalysts.

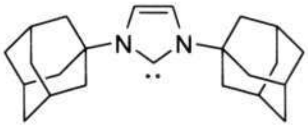


Figure 1 The first NHC isolated by Arduengo's group.

The exceptional catalytic abilities of NHC complexes are mainly due to their rich σ-donating and poor π-accepting characters.[2, 3] Being able to generate a more electron rich metal center upon coordination, NHC complexes tend to make transition metal-catalyzed oxidative addition step more favorable.[4] Also, the strong metal-carbenic bond of NHC complexes promotes tight binding kinetics, thus decreasing ligand dissociation. Additionally, the presence of sterically encumber *N*-bound subunits facilitates reductive elimination of the product from the metal center. These properties result in impressive catalytic reactions, such as Pd-catalyzed cyclisation of bromoanilide (Figure 2).[5]

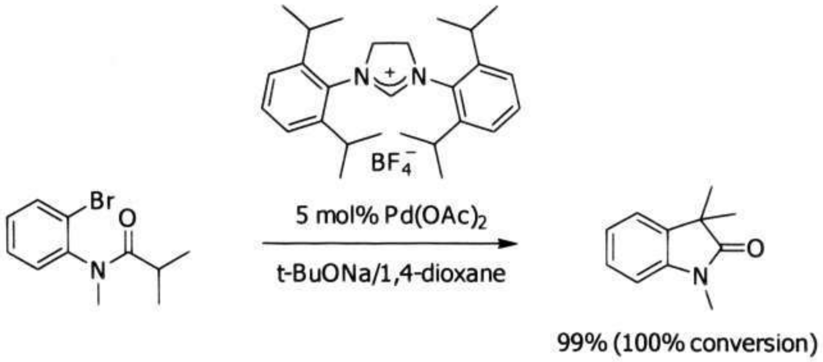


Figure 2 Pd-catalyzed cyclisation of bromoanilide.

Furthermore, NHC complexes were also studied as potential organocatalysts since organocatalyzed reactions are comparatively more economical and environmentally friendly than organometallic catalysts.[6] With so much excitement around the chemistry of NHC complexes, intensive researches were carried out at the same time to increase regio- and stereoselectivity of the catalytic systems.

It is well known that carbohydrates have been identified as a diverse and naturally occurring source of chirality. Therefore, carbohydrate ligands can be systematically modified to give high activity and selectivity in asymmetric catalysis. They can confer advanced properties such as hydrophilicity, which make applications in water possible.[3] The interaction between saccharides is also important for molecular and cell recognition in biological system.[7] Furthermore, they may induce high regio- and stereoselectivity in catalytic system as seen in chiral carbohydrate-incorporated phosphanes used in commercial synthesis of optically pure products. Moreover, we have witnessed the possibilities of incorporating carbohydrate into NHCs from the work of Nishioka (Figure 3).[3]

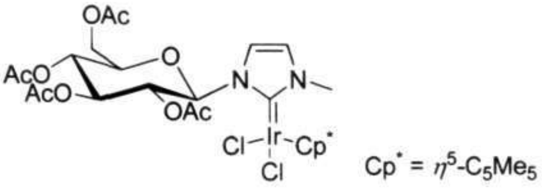


Figure 3 Carbohydrate incorporated NHC by Nishioka's group.

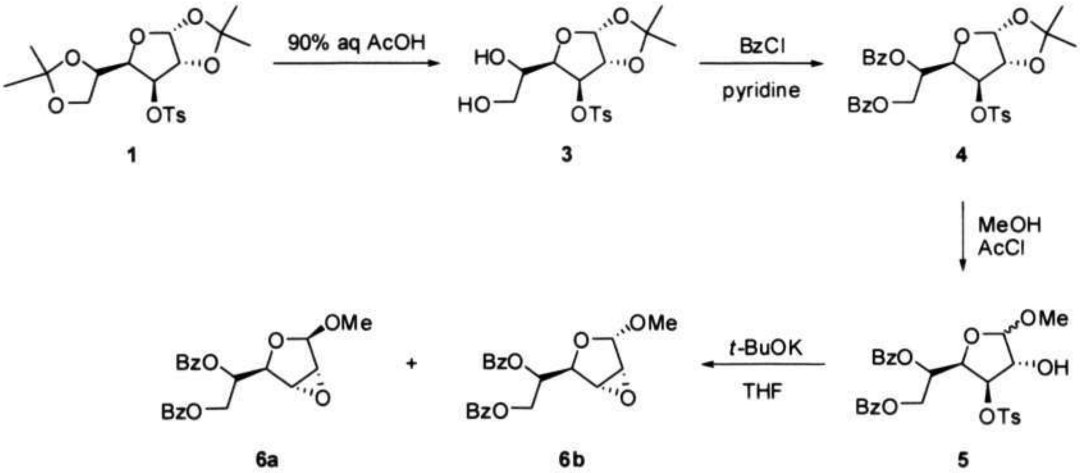
Inspired by these ideas, we decided to focus on the effect of carbohydrate as a chiral scaffold for NHCs in this article. Herein, we wish to report the synthesis of glucofuranoside-incorporated NHCs.

2. RESULTS AND DISCUSSION

To start our research in synthesizing a novel carbohydrate based NHC complex, we first selected furanoside as our starting material due to its relatively significant steric bulk. Commercially available diacetone-D-glucose was used. The first approach taken was to examine the possibility of a S_N2 reaction at the C-3 position which could lead us to the target compound in just two steps. The hydroxyl group of diacetone-D-glucose was substituted by leaving groups such as *p*-toluenesulfonyl and trifluoromethanesulfonyl groups. Unfortunately, treatment of those sulfonyl compounds with imidazole under basic condition (DBU or NaH) failed to give desired products even upon heating at 105 °C for 3 days. Products from E2 elimination were observed instead (Scheme 1). Interestingly, we noted that upon heating the reaction mixture beyond 60 °C, elimination product **2** would form readily, suspecting that the problem may lie on the reactivity of the leaving group. The elimination would proceed faster than the substitution. Another result is possibly due to the conformation of **1**. Since S_N2 reaction requires the nucleophile to attack from a 180° angle, the bulkiness at the C–1, C–2 and C–4 position coupled with the rigidity of the furanose ring make this angle of attack deemed unfavourable.

Scheme 1 Side reaction of sulfonyl compounds with imidazole under basic conditions.

Therefore, we aimed to prevent the elimination reaction by using epoxide **6** as starting material. We postulated that imidazole nucleophile would prefer to attack on the epoxide ring. The synthesis of epoxide **6** is shown in Scheme 1.



Scheme 2 Proposed alternative synthetic scheme.

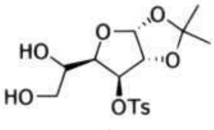
Deprotection of the isopropylidene group in aqueous acetic acid at room temperature nicely provided the diol functionality in good yield. The exposed diol were next protected with benzoyl chloride, followed by heating compound **4** in MeOH at reflux in the presence of a catalytic amount of acetyl chloride (AcCl). The second deprotection of the isopropylidene group was achieved to yield **5**, with a methoxy group on the anomeric position. This reaction afforded **5** as two inseparable diastereomers. The formation of epoxide products was achieved by treatment of the two diastereomers **5** with potassium tert-butoxide (*t*-BuOK) in dry THF. At this step, we could separate two diastereomers of epxides **6a** and **b** in the ratio of 3:1.

The nucleophilic attack of the epoxide with imidazole was attempted under basic conditions. Unfortunately, the desired product could not be obtained when using different bases (K_2CO_3 and DBU) for abstracting a proton from imidazole. Only deprotection of the benzoyl group was observed instead. We then tried to use Lewis acid to promote the substitution reaction. The epoxide ring was opened by water molecule and the benzoyl protective groups were cleaved under $ZnCl_2$-mediated reaction. Even though, the reaction did not proceed as expected, we had some hints that this substitution reaction is very sensitive to moisture and the use of the benzoyl protective group is not suitable in this type of reaction.

3. CONCLUSION

In the attempt to synthesize these glucofuranose-incorporated NHCs, we have met much challenge. Nevertheless, this project will be continued to obtain the proposed NHCs. We believe that our synthesized NHCs would be very efficient in inducing regio- and stereoselectivity in asymmetric and organometallic catalysis reactions.

4. EXPERIMENTAL

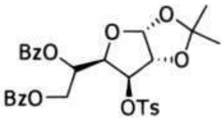


3

Synthesis of 1,2-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (3)

Tolsylate **1** (300 mg, 0.75 mmol) was dissolved in aqueous acetic acid (80 mL, AcOH:H_2O = 9:1). The mixture was left to stir at room temperature over 28 hours. After reaction was observed to be completed by TLC, the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with $NaHCO_3$, brine, dried over anh. $MgSO_4$, filtered. The solvents were removed under reduced pressure. Toluene was added and evaporated under reduced pressure successively to remove excessive acetic acid present. The product was purified by column chromatography eluting with 50 % EtOAc in hexane to yield **3** (156 mg, 56 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.80 (d, J = 7.3 Hz, 2H, Ph), 7.35 (d, J = 8.2 Hz, 2H, Ph), 5.83 (d, J = 3.7 Hz, 1H, CH), 4.95 (d, J = 1.8 Hz, 1H, CH), 4.54 (d, J = 3.7 Hz, 1H, CH), 4.10 (dd, J = 9.2, 1.8 Hz, 1H, CH_2), 3.79-3.73 (m, 1H, CH), 3.59 (dd, J = 11.4, 5.5 Hz, 1H, CH_2), 3.07 (br s, 1H, OH), 2.79 (s, 1H, OH), 2.41 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.20 (s, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm): 145.8 (Ph), 132.4 (Ph), 130.2 (Ph), 128.1 (Ph), 112.7 (Cq), 104.9 (CH), 82.9 (CH), 81.9 (CH), 78.9 (CH), 68.0 (CH), 64.0 (CH_2), 26.5 (CH_3), 26.2 (CH_3), 21.8 (CH_3).

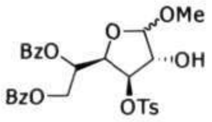


4

Synthesis of 1,2-*O*-isopropylidene-5,6-*O*-dibenzoate-3-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (4)

A solution of diol **3** (132 mg, 0.35 mmol) in pyridine (90 mL) was cooled to 0 °C. Benzoyl chloride (0.9 µL, 0.78 mmol) was added dropwise at 0 °C and the reaction mixture was left to stir at room temperature for 6 hours. The mixture was quenched extracted saturated aqueous NH_4Cl and then extracted with EtOAc. The combined organic layer was washed with brine, dried over anh. $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by column chromatography eluting with 30 % EtOAc in hexane to yield **4** (160 mg, 75 %) as a colourless solid.

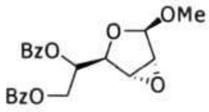
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.91 (dd, *J* = 8.5, 1.4 Hz, 2H, Ph), 7.81 (dd, *J* = 8.5, 1.3 Hz, 2H, Ph), 7.64 (d, *J* = 8.7 Hz, 2H, Ph), 7.53-7.48 (m, 2H, Ph), 7.39-7.35 (m, 2H, Ph), 7.02 (d, *J* = 8.2 Hz, 2H, Ph), 5.98 (d, *J* = 3.7 Hz, 1H, CH), 5.39 (dq, *J* = 3.7, 1.8 Hz, 1H, CH), 4.95 (d, *J* = 3.6 Hz, 1H, CH), 4.91 (m, 1H, CH), 4.89 (dd, *J* = 12.7, 2.7 Hz, 1H, CH_2), 4.67 (dd, *J* = 9.6, 2.7 Hz, 1H, CH_2), 4.41 (dd, *J* = 12.7, 4.1 Hz, 1H, CH), 2.12 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm): 165.9 (CO), 164.8 (CO), 145.4 (Cq), 133.2 (Ph), 133.1 (Ph), 132.0 (Ph), 129.9 (Ph), 129.7 (Ph), 129.6 (Ph), 128.4 (Ph), 128.3 (Ph), 127.9 (Ph), 112.9 (Cq), 104.9 (CH), 83.1 (CH), 80.7 (CH), 76.5 (CH), 68.4 (CH), 63.2 (CH_2), 26.7 (CH_3), 26.4 (CH_3), 21.6 (CH_3). **HRMS (ESI)**: *m/z*: calcd for $C_{30}H_{30}O_{10}SNa$: 605.1457 $[M+Na]^+$; found: 605.1456.


5

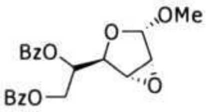
Synthesis of 1-methyl-5,6-*O*-dibenzoate-3-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (5)

To a solution of dibenzoyl compound **4** (1.1 g, 1.88 mmol) in MeOH (5.7 mL) was added acetyl chloride (70 μL) and then heated at 60 °C for 30 hours. The reaction mixture was cooled to room temperature, neutralized with $AgCO_3$, and stirred for 2 hours. The precipitate was filtered off and the filtrate was concentrated under vacuum. The residue was purified by column chromatography eluting with 40 % EtOAc in hexane to give **5a** and **b** as a diastereomeric mixture in the ratio of 3:1 (883 mg, 84 %).

^{1}H NMR (300 MHz, $CDCl_3$) of the major diastereomer 6a: δ (ppm): 7.97-7.94 (m, 2H, Ph), 7.90-7.85 (m, 2H, Ph), 7.67-7.60 (m, 2H, Ph), 7.55-7.51 (m, 2H, Ph), 7.41-7.36 (m, 4H, Ph), 7.07-7.03 (m, 2H, Ph), 5.59-5.49 (m, 1H, CH), 4.98-4.96 (m, 1H, CH), 4.85-4.75 (m, 2H, CH_2), 4.59-4.49 (m, 2H, 2 × CH), 3.41 (s, 3H, OCH_3), 2.47 (s, 3H, CH_3); **^{13}C NMR (75 MHz, $CDCl_3$) of the major diastereomer 6a:** δ (ppm): 166.0 (CO), 164.8 (CO), 145.0 (Cq), 133.0 (Ph), 132.4 (Ph), 129.7 (Ph), 129.6 (Ph), 129.5 (Ph), 128.3 (Ph), 128.2 (Ph), 127.8 (Ph), 127.7 (Ph), 109.5 (CH), 82.0 (CH), 79.4 (CH), 77.3 (CH), 69.3 (CH), 63.5 (CH), 56.0 (OCH_3), 21.6 (CH_3); **HRMS (ESI)**: *m/z*: calcd for $C_{28}H_{28}O_{10}SNa$: 579.1301 $[M+Na]^+$; found: 579.1292.


6a

+


6b

Synthesis of 1-methyl-2,3-anhydro-5,6-*O*-dibenzoate-α-D-glucofuranoses (6a and 6b)

A diastereomeric mixture **5a** and **b** (295 mg, 0.53 mmol) was dissolved in THF (3 mL) at room temperature followed by the addition of *t*-BuOK (59 mg, 0.53 mmol). The reaction mixture was left to stir for 30 minutes and then concentrated under reduced pressure. The residue was added EtOAc and washed with water. The aqueous layer was reextracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried over anh. $MgSO_4$, filtered. The solvents were removed under reduced pressure. The product was purified by column chromatography eluting with 20 % EtOAc in hexane to yield **6a** (100 mg, 53 %) and **6b** (52 mg, 28 %).

^{1}H NMR (400 MHz, $CDCl_3$) of a major diastereomer 6a: δ (ppm): 8.06-8.01 (m, 4H, Ph), 7.60-7.53 (m, 2H, Ph), 7.47-7.41 (m, 4H, Ph), 5.48-5.43 (m, 1H, CH), 5.01 (s, 1H, CH), 4.82 (dd, J = 11.9, 2.7 Hz, 1H, CH_2), 4.57 (dd, J = 11.9, 5.0 Hz, 1H, CH_2), 4.51 (d, J = 8.7 Hz, 1H, CH), 3.87 (d, J = 2.7 Hz, 1H, CH), 3.72 (d, J = 2.7 Hz, 1H, CH), 3.45 (s, 3H, CH_3); **^{13}C NMR (100 MHz, $CDCl_3$) of a major diastereomer 6a:** δ (ppm): 166.3 (CO), 165.7 (CO), 133.6 (Ph), 133.4 (Ph), 130.0 (Ph), 129.9 (Ph), 129.6 (Ph), 128.7 (Ph), 128.6 (Ph), 103.2 (CH), 76.2 (CH), 71.5 (CH), 63.4 (CH_2), 56.4 (CH), 56.3 (CH), 55.4 (OCH_3); **HRMS (ESI)**: *m/z*: calcd for $C_{21}H_{20}O_7Na$: 407.1107 $[M+Na]^+$; found: 407.1110.

^{1}H NMR (400 MHz, $CDCl_3$) of a minor diastereomer 6b: δ (ppm): 8.04-7.98 (m, 4H, Ph), 7.61-7.53 (m, 2H, Ph), 7.47-7.40 (m, 4H, Ph), 5.46-5.42 (m, 1H, CH), 5.17 (s, 1H, CH), 4.80 (dd, J = 11.9, 2.7 Hz, 1H, CH_2), 4.65 (d, J = 6.9 Hz, 1H, CH), 4.55 (dd, J = 11.9, 5.0 Hz, 1H, CH_2), 3.87 (d, J = 2.7 Hz, 1H, CH), 3.82 (d, J = 2.7 Hz, 1H, CH), 3.51 (s, 3H, OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$) of a minor diastereomer 6b:** δ (ppm): 166.2 (CO), 165.7 (CO), 133.8 (Ph), 133.5 (Ph), 129.9 (Ph), 129.8 (Ph), 129.6 (Ph), 129.3 (Ph), 128.8 (Ph), 128.7 (Ph), 102.7 (CH), 76.8 (CH), 71.5 (CH), 62.9 (CH_2), 57.3 (CH), 56.4 (CH), 56.2 (OCH_3); **HRMS (ESI)**: *m/z*: calcd for $C_{21}H_{20}O_7Na$: 407.1107 $[M+Na]^+$; found: 407.1110.

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2 Highly stereoselective synthesis of aminoglycosides *via* rhodium-catalyzed and substrate-controlled aziridination of glycals. Rujee Lorpitthaya, K. B. Sophy, Jer-Lai Kuo, and Xue-Wei Liu; *Organic & Biomolecular Chemistry*, **2009**, *7*, 1284.

3 Mechanistic Insights into the Substrate-Controlled Stereochemistry of Glycals in One-Pot Rhodium-Catalyzed Aziridination and Aziridine Ring Opening. Rujee Lorpitthaya, Zhi-Zhong Xie, K. B. Sophy, Jer-Lai Kuo, and Xue-Wei Liu; *Chemistry: A European Journal*, **2009**, *16*, 588.

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