Diverse reactivity of glycals with arylamines and sulfonamides : synthesis of 4-aminocyclopentenones, cyclopentanone fused indolines and sialic acid

Wang, Siming

2013

Wang, S. (2013). Diverse reactivity of glycals with arylamines and sulfonamides : synthesis of 4-aminocyclopentenones, cyclopentanone fused indolines and sialic acid. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/53522>

<https://doi.org/10.32657/10356/53522>

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**DIVERSE REACTIVITY OF GLYCALS WITH
ARYLAMINES AND SULFONAMIDES: SYNTHESIS
OF 4-AMINOCYCLOPENTENONES,
CYCLOPENTANONE FUSED INDOLINES AND
SIALIC ACID**

WANG SIMING

SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

2013

**DIVERSE REACTIVITY OF GLYCALS WITH ARYLAMINES AND
SULFONAMIDES: SYNTHESIS OF 4-AMINOCYCLOPENTENONES,
CYCLOPENTANONE FUSED INDOLINES AND SIALIC ACID**

WANG SIMING

School of Physical and Mathematical Sciences

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

2013

*"Don't only practice your art,
but force your way into its secrets, for
it and knowledge can raise men to the
divine."*

Ludwig Van Beethoven

ACKNOWLEDGEMENTS

Seven years ago, I was a process chemist at Lonza Guangzhou R&D center. My job involves developing safe, efficient and robust chemical processes, which will enable the long-term manufacture of the APIs. Process development is not simply a matter of taking existing chemistry and doing it on a larger scale. It requires a good understanding of chemistry--understanding mechanisms of reactions and how the chemistry works. After working several years, it is clear to me that I wanted to pursue a PhD degree in synthetic chemistry.

Fortunately, I got a chance.

First and foremost, I would like to thank my main supervisor, Dr. Steve Zhou for providing me the opportunity to pursue my PhD degree in Singapore. His enthusiastic efforts towards research inspire me a lot.

I am also very grateful for my co-supervisor Assoc. Prof. Liu Xuewei for offering me the opportunity to explore sugar chemistry in his group. His continuous encouragement, enduring patience and constructive criticism allowed my research to achieve a level that I would have never envisioned. All of my PhD research work is completed under his supervision.

I will always remember all my lab-mates whom I have had the honor to share the bench with over the years. Special thanks are extended to Dr. Rujee, Dr. Ma, Dr. Kalyan, Dr. Kishan, Dr. Biswajit, Dr. Wu, Dr. Fu, Dr. Song, Dr. Sharad, Ding Feiqing, Ge Xin, Ji Li, Ronny William, Cai hua, Kim Kui Georgina Estelle Seah, Liao hongze, Seenuvasan Vedachalam, Minli Leow, Shuting Cai, Zeng Jing, Bai Yaguang, Xiang Shaohua, Huang Jie, Le Mai Hoang Kim, Toh Dewei Joel, Adhitya Mangala Putra Moeljadi, Heng Guang Wei

Evan.

I am thankful to Dr. Li Yongxin for the X-ray crystallographic analysis. I also thank technical staff Goh Ee Ling, Zhu Wenwei, for their support for NMR, mass spectroscopy.

My biggest personal challenge is to maintain a healthy work-family balance. I would like to thank my wife, Qiongxia, for her sacrifice throughout. For almost single-handedly raising our daughter so I can accomplish my goal, I am truly grateful. I also acknowledge my parents for the support and encouragement over the past years. Without them, it is impossible for me to finish my PhD study.

Wang Siming

SUMMARY

The diverse class of *N*-containing compounds, which comprises various biologically important natural and unnatural substances with complex molecular architecture, has challenged synthetic chemists to devise imaginative strategies towards their construction.

This thesis discusses salient synthetic methodologies to access *N*-containing compounds including 4-aminocyclopentenones, cyclopentanone-fused indolines and sialic acid from readily available glycals.

By judicious choice of the reaction solvent, an array of 4-aminocyclopentenones or cyclopentanone fused indolines was synthesized from common glycals and secondary arylamines. This novel methodology involves an interrupted Nazarov process in which the cyclopentenyl cation intermediate is captured by water or aryl moieties.

In addition, we have developed a methodology that allows facile synthesis of common and uncommon sialic acids. This methodology employs a tandem Rh-catalyzed nitrene insertion and Barbier allylation as the key step.

INDEX OF ABBREVIATIONS

δ	chemical shift	HRMS	high resolution mass spectroscopy
$^{\circ}\text{C}$	degree celsius		
Ac	acetyl	Hz	hertz
Aq	aqueous	IR	infrared
Bn	benzyl	<i>i</i> Pr	isopropyl
Boc	<i>tert</i> -butoxycarbonyl	<i>J</i>	coupling constants
brs	broad singlet	M	concentration (mol/L)
Bz	benzoyl	M ⁺	parent ion peak (mass spectrum)
calcd.	calculated	m	multiplet
cat.	catalytic	<i>m</i>	<i>mata</i>
cm ⁻¹	inverse centimeter	Me	methyl
d	doublet	mg	milligram
dd	doublet of doublets	MHz	megahertz
DMAP	4-(<i>N, N</i> -dimethylamino)pyridine	min	minute
DMF	<i>N, N</i> -dimethylformamide	mL	milliliter
DMSO	dimethyl sulfoxide	mmol	millimoles
EI	electron ionization	mol	moles
equiv	equivalent	MS	molecular sieve
Et	ethyl	<i>n</i> Bu	<i>n</i> -butyl
ether	diethyl ether	NMR	nuclear magnetic resonance
FTIR	fourier transfer infrared spectroscopy	NOE	nuclear overhauser effect
g	gram	Nu	nucleophile
h	hour (time)	OTf	trifluoromethane sulfonate
Hex	hexane	<i>o</i>	<i>ortho</i>
HMBC	heteronuclear multiple bond Correlation	<i>p</i>	<i>para</i>
HMQC	heteronuclear multiple quantum correlation	Pd/C	palladium on carbon
		PG	protecting group
		Ph	phenyl
		ppm	parts per million

Py	pyridine
q	quartet
RT	room temperature
RBF	round bottom flask
s	singlet
sat	saturated
t	triplet
td	triplet of doublets
TBS	tert-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl
v	volume

TABLE OF CONTENTS**CHAPTER 1 --- Introduction: Diverse Reactivity of Glycals with Sulfonamides and Arylamines**

1.1 Background of glycals	1
1.2 Ferrier azaglycosylation of glycals with sulfonamides	2
1.3 Sulfonamidoglycosylation of glycals with sulfonamides and I(sym-colidine) ₂ ClO ₄	4
1.4 Hydroamination of glycals with sulfonamides	5
1.5 Regio- and stereo-selective tandem hydroamination–glycosylation of glycals	6
1.6 Aziridination and ring-opening of glycals	8
1.7 Cyclization of glycals with arylamines	10
1.8 Glycosidation of glycals with arylamines	16
1.9 Conclusion	19

CHAPTER 2 ---- InBr₃-Catalyzed Cascade Reaction of Glycals with Secondary Arylamines

2.1 Background of 4-aminocyclopentenones	21
2.2 A serendipitous discovery	24
2.3 Results and discussion	26

2.4 Conclusion.....	57
2.5 Experimental section	59
2.5.1 General considerations	59
2.5.2 General procedure	60
2.5.3 Characterization Data for the Isolated Products	64

CHAPTER 3 ----Synthesis of Sialic Acid from Glycal

3.1 Background of sialic acids	101
3.2 Results and discussion.....	107
3.3 Conclusion.....	111
3.4 Experimental Section	112
3.4.1 General considerations	112
3.4.2 General procedure and characterization data for the isolated products.....	113
References	122

CHAPTER 1

Introduction: Diverse Reactivity of Glycals with Sulfonamides and Arylamines

1.1 Background of glycals

Sugars are readily available and highly functionalized molecules bearing multiple functional groups and stereocenters. As a consequence, these molecules are extremely useful as chiral starting materials in organic chemistry. The transformation of sugars to sugar derivatives or nonsugar molecules has been extensively studied as a versatile methodology to prepare useful compounds ranging from novel chiral building blocks to complex natural products.

Glycals are cyclic enol ether derivatives of sugars having a double bond between C1 and C2 of the ring. The term “glycal” is only used as a general name for all sugars with a double bond between C1 and C2. Several frequently encountered glycals are shown in Figure 1.1. D-glucal was first synthesized from D-glucose by Fischer and Zach in 1913.¹

Figure 1.1 Some frequently encountered glycals.

Glycals not only act as glycosyl donors in oligosaccharide synthesis, but also serve as very useful building blocks in synthetic organic chemistry. Like an alkene, a

glycal can allow many other functional groups to be introduced into the sugar moieties. In addition, the presence of the ring oxygen strongly influences the reactivity of this double bond, so the glycals will have different properties from those normal alkenes.

The present chapter mainly highlights some of the recent approaches to biologically important *N*-containing compounds, including our own achievements, which utilize readily available glycals as starting materials and sulfonamides or arylamines as nitrogen sources.

1.1 Ferrier azaglycosylation of glycals with sulfonamides

In the presence of Lewis acid catalysts, glycals can undergo nucleophilic substitution reaction with various *O*-, *S*-, *C*-, *N*- and *P*- nucleophiles to produce 2,3-unsaturated glycosides. This rearrangement reaction has been referred to as the “Ferrier rearrangement”.²

Besides azide, *N*- nucleophiles have not been investigated extensively in the Ferrier rearrangement. In addition, there are only two prior reports of the Ferrier azaglycosylation of glycals with sulfonamides in the presence of $\text{B}(\text{C}_6\text{F}_5)_3$ ³ or $\text{BF}_3\cdot\text{OEt}_2$ ⁴ as catalysts (Scheme 1.1).

Scheme 1.1 Ferrier azaglycosylation of glycals with sulfonamides.

However, there are very limited examples of Ferrier rearrangement with arylamines for the production of *N*-pseudoglycals (Scheme 1.2).^{3,5} It should be noted that the synthetic utility of these two examples is rather limited, by the fact that the arylamine needs to be protected with a Ts group or the glycal needs to be protected with an Ac group together with the requirement of a C3 alkyl substituent.

Scheme 1.2 Ferrier azaglycosylation of glycals with arylamines.

1.2 Sulfonamidoglycosylation of glycals with sulfonamides and

I(sym-colidine)₂ClO₄

Aziridino sugars are very useful synthetic intermediates. The pioneering work by Danishefsky⁶ showed the method of aminoglycoside synthesis which involve 1,2-aziridinohexose as key intermediate. In this process, glycal was first converted to 1,2-iodosulfonamide via treatment with iodonium collidine perchlorate and sulfonamide (Scheme 1.3). The *in situ* generated aziridine underwent a ring opening reaction with the *O*-nucleophile to give the 2-aminoglycoside.

Scheme 1.3 Danishefsky's iododisulfonamidation methodology.

While this is a useful methodology for preparing 2-aminoglycosides, there are still several limitations. *Trans*-1,2-iodosulfonamides are prone to isomerization when electron withdrawing groups, such as acetyl group, are used as the protecting group. Also other disadvantages including the use of a stoichiometric amount of silver salts

and the problematic iodine source render this method less attractive in terms of practicability.

1.3 Hydroamination of glycals with sulfonamides

Colinas reported the first example of hydroamination of glycals with sulfonamides catalyzed by $\text{HBr} \cdot \text{PPh}_3$.⁷ This process proceeded in a highly stereoselective fashion to give the β -sulfonamidoglycosides in good yields (Scheme 1.4).

Scheme 1.4 Hydroamination of glycals with sulfonamides.

Notably, when $\text{BF}_3 \cdot \text{OEt}_2$ was used as a catalyst for this reaction, a 3-arylsulphonamino-2,3-dideoxy sugar product was obtained (Scheme 1.5). They suggested that this product could be formed by the reaction of sulfonamide with the carbenium ion at C3 followed by the nucleophilic addition of the benzyl alcohol to the double bond.

Scheme 1.5 $\text{BF}_3 \cdot \text{OEt}_2$ catalyzed hydroamination of glycals with sulfonamides.

1.4 Regio- and stereo-selective tandem hydroamination–glycosylation of glycals

Well-defined 3-arylsulphonamino-2,3-dideoxy sugars have stimulated tremendous research interest, due to their prevalence in pharmaceuticals such as L-epi-daunosamine, L-ristoamine, L-vancosamine. Our group has reported a robust and concise method for preparing 3-arylsulphonamino-2,3-dideoxy sugars from easily available glycals and sulfonamides (Scheme 1.6).⁸

Scheme 1.6 Tandem hydroamination–glycosylation of glycals.

The stereochemical outcome could be a result of diastereofacial selective attack of the *N*-nucleophile at C3 position followed by *O*-nucleophile at C1 position through possible hydrogen bonding between the nitrogen (Scheme 1.7). In addition, the anomeric effect also favors the formation of α anomeric product.

Scheme 1.7 Proposed mechanism for tandem hydroamination–glycosylation.

The synthetic utility of this practical method has been further demonstrated by a concise and highly efficient synthesis of L-ristosamine and L-epi-daunosamine glycosides (Scheme 1.8).

Scheme 1.8 Synthesis of L-ristosamine and L-epi-daunosamine.

1.5 Aziridination and ring-opening of glycals

Recently, our group reported the stereoselective preparation of 2-amino-2-deoxy sugars by application of rhodium-catalyzed nitrene insertion to glycals. Glycals, bearing a sulfamate moiety on C4 or C6, gave optically pure β -aminoglycosides or α -aminoglycosides, respectively.⁹ However, it was found that a sulfamate moiety on C3 did not result in stereoselective aminoglycosylation (Scheme 1.9). Moreover, the sulfamate moiety can be further displaced by a second nucleophile to give additional substituted aminoglycosides. This methodology has been successfully used for the synthesis of natural and unnatural *mono*-, *di*-, and *tri*- aminoglycosides with unique stereochemistry.

Scheme 1.9 Intramolecular amidoglycosylation of glucal sulfamates.

The crucial step in this novel process is the Rh-catalyzed nitrene transfer to the double bond of the glycal, which is supported by the DFT calculations.¹⁰ The resulting aziridine-rhodium species was highly reactive and the regioselectivity of the polyfunctionalization would be the consequence of the S_N2-type nucleophilic ring opening of the aziridine. The anomeric aminoglycosides mixtures obtained from C3 sulfamoyl glucal could be consequence of less stable aziridine that would undergo ring opening process to generate oxocarbenium intermediates (Scheme 1.10).

Scheme 1.10 Intramolecular *N* insertion of glucal bearing a sulfamate moiety on C4.

Interestingly, the glucal having C4 sulfamate moiety underwent *N*-insertion on the allylic C-H when C3 hydroxyl group was protected by a more electron-rich *O*-silyl group (Scheme 1.11).

Scheme 1.11 Intramolecular C-H insertion of glucal sulfamates.

1.6 Cyclization of glycols with arylamines

In 2003, Yadav *et al.* reported the first example of synthesis of tetrahydroquinolines from glycols and primary arylamines using a catalytic amount of InBr_3 or a stoichiometric amount of TMSOTf (Scheme 1.12).¹¹ A series of tetrahydroquinolines were formed in good yields with high stereoselectivity. However, in the absence of InBr_3 , the reaction did not proceed even with a prolonged reaction time.

Scheme 1.12 The first example of synthesis of tetrahydroquinolines from glycols and primary arylamines.

In the course of mechanism studies, they carried out the reaction of deuterated aniline with 3,4,6-tri-*O*-acetyl-D-glucal, and no deuterium was incorporated in the product. However, deuterated products were observed when the reaction was carried in D_2O , indicating that protons were abstracted from the solvent. Based on this investigation, they proposed the reaction proceed by a Friedel-Crafts reaction to give C-glycoside product (In^{III} species I) followed by an intramolecular amination to afford *N*-glycoside product (In^{III} species II) (Scheme 1.13). Finally, the In^{III} species II abstracted proton from solvent to form the deuterated tetrahydroquinoline product.

Scheme 1.13 The proposed mechanism by Yadav.

Subsequently, they developed a related reaction catalyzed by stoichiometric amount of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and NaI in water (Scheme 1.14).¹² The reaction proceeded efficiently in water at 80 °C and the corresponding tetrahydroquinoline products were obtained with high stereoselectivity. Also the reactions could proceed with hydrochloric acid, but low conversions were obtained even after long reaction times.

Scheme 1.14 $\text{CeCl}_3 \cdot \text{H}_2\text{O}$ /NaI promoted stereoselective synthesis of tetrahydroquinolines.

As opposed to their previous proposed mechanism, they suggested that the cascade reaction proceeds through a 1,4-addition of arylamine to the α,β -unsaturated aldehyde (known as Perlin aldehyde), which is generated *in situ* from

3,4,6-tri-*O*-acetyl-D-glucal and water (Scheme 1.15). The initially formed 1,4-adduct underwent an intramolecular cyclization to afford the fused tetrahydroquinoline. However, they didn't explain the high level of stereoselectivity observed in their reactions.

Scheme 1.15 The proposed mechanism by Yadav.

In 2009, Zhang *et al.* attempted to apply Yadav's methodology for the total synthesis of Marmycin A (Scheme 1.16).⁵ However, the final synthesis of Marmycin A was unsuccessful due to the failure to obtain the C3 methyl substituted glycal fragment.

Scheme 1.16 Retrosynthetic analysis of Marmycin A.

Instead, several desmethyl analogues of Marmycin A were prepared by using C3 H substituted glycals and tricyclic aminoquinones as probe substrates. Interestingly, as opposed to Yadav's report, a pair of diastereomeric tetrahydroquinolines was obtained in 2:1 ratio as major products (Scheme 1.17).

Scheme 1.17 Synthesis of C3- desmethyl analogues of Marmycin A.

The poor diastereoselectivity may be due to the presence of two carbonyl groups in aniline derivative. As shown in scheme 1.18, they proposed the reaction proceeded by a Friedel-Crafts reaction first to give C-glycoside product (In^{IV} species I). The subsequent deacetylated product would then undergo intramolecular amination from both α - (path b) and β - (path a) face to afford two diastereomers.

Scheme 1.18 The proposed mechanism by Zhang.

Snider also reported a similar synthesis of desmethyl analogue of Marmycin A based on Yadav's methodology. In their hands, the use of $\text{In}(\text{OTf})_3$ as catalyst was proved to be less moisture sensitive than InBr_3 in Yadav's reaction (Scheme 1.19).¹³ Based on their works, a 2:1 mixture of diastereomers is similarly obtained.

Scheme 1.19 Synthesis of C3-desmethyl analogue of Marmycin A by Snider.

However, Snider proposed another mechanism which involves C3 amino substituted glycal as key intermediate, in view of the ample precedent for the formation of these compounds from glycals and other nucleophiles (Scheme 1.20). Protonation of the resulting glycal followed by an intramolecular Friedel-Crafts reaction would then furnished a mixture of diastereomeric tetrahydroquinolines.

Scheme 1.20 The proposed mechanism by Snider.

Zhang's group further investigated the cyclization reactions of arylamines with glycals. They found that high diastereomeric selectivity can be achieved only when C5 substituted glycal was used as substrate in this reaction.¹⁴ In addition, the diastereoselectivity of the product was controlled by the configuration of C5 substituted group (Scheme 1.21).

Scheme 1.21 Cyclization reactions of arylamines with glycals.

To rationalize this result, they proposed that the reaction proceeded via the Friedel-Crafts reaction first to give *C*-glycoside product (In^{III} species). Subsequently, the amino group can attack the C3 carbon from both α - (path b) and β - (path a) face to afford two diastereomers. However, the steric effect between the C5 substituent ($\text{X} = \text{CH}_2\text{OH}$ or CH_3) and the In^{III} complex would disfavor the attack from β - face (path a), and thus, only one diastereomer was formed resulting from addition from the opposite face of C5 substituent (Scheme 1.22).

Scheme 1.22 The proposed mechanism by Zhang.

1.7 Glycosidation of glycals with arylamines

A novel process for 4-aminocyclopent-2-enones was discovered when Zhang's group was studying total synthesis of Marmycin A.¹⁵ They found that glycosidation of tetracyclic aminoquinone with 3,4,6-tri-*O*-acetyl-D-glucal yielded a pair of

diastereomeric tetrahydroquinolines as major products in 42% and 35% yields, respectively. Interestingly, a 4-aminocyclopent-2-enone side product was obtained in 4% yield (Scheme 1.23).

Scheme 1.23 Synthesis of C3- desmethyl ananlogues of Marmycin A.

Later, they tried to suppress the formation of tetrahydroquinolines products by replacing the acetyl group with free hydroxyl group. However, the model reaction led to a complex mixture containing several inseparable products, with no desired 4-aminocyclopentenone product isolated at all (Scheme 1.24).

Scheme 1.24 Unsuccessful trial to produce 4-aminocyclopent-2-enone from L-rhamnal.

Subsequently, they found that sterically encumbered glycal, which bears a C3 methyl group, showed better activities than the normal glycals. The expected 4-aminocyclopent-2-enone with *trans* configuration was obtained whereas tetrahydroquinolines products were not observed (Scheme 1.25).

Scheme 1.25 InBr₃ catalyzed synthesis of 4-aminocyclopent-2-enone from glycal.

In contrast to their previous report,⁵ they proposed that the reaction proceed *via* a Ferrier rearrangement reaction first to give *N*-pseudoglycal product. Subsequent ring-opening followed by a 4π conrotatory electrocyclozation¹⁶ yielded cyclopentenone product (Scheme 1.26).

Scheme 1.26 Mechanistic rationalization by Zhang.

1.8 Conclusion

There is a continuing interest and appreciation for developing novel stereoselective and versatile methodologies for synthesis of natural products from easily available glycals. In recent years, the discovery of several methods for the formation of biologically important *N*-containing compounds from glycals has reinforced the synthetic utility of these unsaturated compounds.

Scheme 1.27 Reactions illustrating the synthetic utility of glycals.

Many reactions are focused on the functionalization of the double bond with different nitrogen sources, but extension that includes multiple transformations may provide new scaffolds which are not yet directly attainable.

The high synthetic potential of glycals for the synthesis of *N*-containing compounds ranging from simple *N*-glycosides to *N*-containing scaffolds has been highlighted in this chapter. While many mechanisms are proposed, few are supported by detailed mechanistic studies. On the basis of improved mechanistic understanding, there remains promising opportunity for discovery of new variants of such transformations that would ultimately provide us with highly advanced synthetic chiral intermediates.

The development of novel methods for the synthesis of *N*-containing compounds from readily available glycals has been of long-standing interest to organic chemists due to their great importance in chemistry and biology. A number of remarkable syntheses of tetrahydroquinolines from glycals, such as employing arylamines as the nitrogen sources, have been reported. However, significant challenges still exist in exploring the detailed mechanism. On the other hand, Zhang' group has reported a novel synthetic pathway for the syntheses of 4-aminocyclopent-2-enones from glycals and arylamines. However, their method is limited to unprotected C-3 alkyl substituted glycals. We therefore aim to develop a new variant of such transformation on the basis of improved mechanistic study.

CHAPTER 2

InBr₃-Catalyzed Cascade Reaction of Glycals with Secondary Arylamines

2.1 Background of 4-aminocyclopentenones

Functionalized cyclopentenones are members of a diverse class of fascinating molecules in organic synthesis.¹⁷ Particularly 4-aminocyclopentenones are important building blocks that provide ever-increasing opportunities for access to densely functionalized aminocyclopentitols with potential antiviral and anticancer activities, such as Mannostatin A, Trehazolamine, Aristeromycin and Bacteriohopanetetrol (Figure 2.1).¹⁸

Figure 2.1 Some biologically important aminocyclopentitols.

Accordingly, this molecular motif has challenged organic chemists to devise imaginative strategies towards its synthesis since the earlier methods generally suffer from long sequences or substrate limitation.¹⁹

In 2003, Li *et al.* reported the first endocyclic enamine cyclopentenone annulation, which was rationalized as an *azo*-Nazarov-type cyclization (Scheme 2.1).²⁰

Scheme 2.1 *Azo*-Nazarov-type cyclization reported by Li.

Later, Batey reported the Ln(III) catalyzed formation of 4,5-diaminocyclopentenones from furfuraldehyde and secondary amines through a “Nazarov-like” mechanism (Scheme 2.2).²¹

Scheme 2.2 Formation of 4,5-diaminocyclopent-2-enones from 2-furaldehyde.

Encouraged by their results, De Alaniz *et al.* developed a useful process for the preparation of 4-aminocyclopentenones that utilizes *aza*-Piancatelli rearrangement catalyzed by Dy(OTf)₃ (Scheme 2.3).²²

Scheme 2.3 Aza-Piancatelli reaction reported by De Alaniz.

More recently, Yao and Zhang described a novel InBr_3 -catalyzed glycosidation of glycols with anilines to form 4-aminocyclopent-2-enones (Scheme 2.4).¹⁵

Scheme 2.4 Formation of 4-aminocyclopent-2-enone from glycol.

Despite the different strategies to prepare 4-aminocyclopentenones, a 4π conrotatory electrocyclicization of pentadienyl cation, a process similar to the Nazarov cyclization, is believed to be the crucial step in these cascade transformations (Scheme 2.5). Furthermore, this cyclization may proceed in either a clockwise or counterclockwise manner, generating a mixture of enantiomers.

Scheme 2.5 Preparation of 4-aminocyclopentenone.

2.2 A serendipitous discovery

In our continuing effort to develop novel methodologies for the synthesis of biologically important compounds employing readily available glycals,²³ we observed that the InBr_3 -catalyzed reaction of 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) with *N*-benzyl-4-methoxyaniline (**2.2a**) in refluxing aqueous acetonitrile proceeded through an unprecedented cascade transformation to give **2.3a** as a single diastereomer in 65% yield and no tetrahydroquinoline or *N*-glycoside product was observed at all (Scheme 2.6). No reaction occurred when the reaction was performed in anhydrous organic solvent indicating that water plays an important role for this transformation.

Scheme 2.6 Initial discovery.

More interestingly, by the addition of 1.2 equiv of water, the same reaction gave solely cyclopentanone-fused indoline **2.4a**, a structural motif, which is embedded in

many biologically important compounds, such as Suspendole, Polyveoline and WAY-163909 (Figure 2.2).²⁴ Therefore, it is apparent that there is great interest in developing new methods to efficiently access these key molecular frameworks.

Figure 2.2 Some biologically important molecules that contain aminocyclopentane motif.

However, when D-glucal **2.1aa** was used as substrate, the reaction did not give **2.4aa**. Thus, we reasoned that this novel domino reaction may involve an interrupted Nazarov process²⁵ (Scheme 2.7) in which the cyclopentenyl cation I intermediate was captured by water²⁶ (path a) or aryl moieties²⁷ (path b).

Scheme 2.7 Possible interrupted Nazarov process.

The interrupted Nazarov process has been extensively developed and refined in recent years through the efforts of the West group.²⁵ West has shown the cyclopentenyl cation intermediate can be trapped by many nucleophilic species such as alkenes, arenes and halides.^{25b} For a very recent example, Romo reported a diastereoselective synthesis of Agelastatin A, which proceeds through the Nazarov cyclization and the resulting *N*-acyliminium intermediate was captured by addition of water (Scheme 2.8).²⁸

Scheme 2.8 A recent example of interrupted Nazarov process.

2.3 Results and discussion

We noticed that the synthetic utility of the method reported by Zhang and Yao¹⁵ is limited to unprotected C3 substituted glycals (Scheme 2.4). In our hands, commercially available 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) and *N*-benzyl-4-methoxyaniline (**2.2a**) were chosen as probe substrates with the following two salient

features. (a) Hydroxymethyl group (-CH₂OH) is a commonly encountered moiety in nucleoside analogues and could also be used for further transformations, and (b) Conventional methods to remove benzyl (Bn) or *p*-methoxyphenyl (PMP) group are well documented. It should be noted that the condensation of primary arylamines with glycals, which contain only hydrogen on C3, to form tetrahydroquinolines have been extensively studied.^{5,11,12,13}

In addition, the utilization of water as solvent to mimic nature's way of making chemical bonds is of preeminent importance to the realization of economic, safe, and environmentally benign organic transformations.²⁹ However, water is not commonly considered as a solvent for organic reactions because of the limited solubility of most organic compounds in water. One of the effective methods of increasing solubility is by using surfactants. Inspired by Kobayashi's pioneering work in Lewis acid-surfactant-combined catalyst,³⁰ we became interested in developing green processes, which is more attractive to the pharmaceutical industry,³¹ to improve the synthesis of 4-aminocyclopentenones by eliminating organic solvents.

Our initial optimization studies were conducted by treating **2.1a** with **2.2a** in refluxing water using different Lewis acids and sodium dodecylbenzene sulfonate (SDBS). This revealed that heating a mixture of **2.1a** (1 equiv) and **2.2a** (1.1 equiv) with 10 mol% of SDBS and 30 mol% of InBr₃ in water at 100 °C for 24 h gave the best yield of **2.3a** (**Standard condition A**, Table 2.1, entry 17). Notably, no reaction took place when a condition identical to Zhang's¹⁵ was used for this reaction, showing that water plays a significant role in this transformation.

Table 2.1 Lewis catalysts screening for the reaction of glycal with secondary arylamine in water.^[a]

Entry	Catalyst (mol%)	Temp [°C]	Yield [%] ^[b]
1	AgOTf (10)	100	47
2	AlCl ₃ (10)	100	39
3	AuCl ₃ (10)	100	53
4	Cu(OTf) ₂ (10)	100	19
5	Dy(OTf) ₃ (10)	100	0
6	Yb(OTf) ₃ (10)	100	0
7	FeCl ₃ (10)	100	46
8	Sc(OTf) ₃ (10)	100	51
9	NaOTf (10)	100	0
10	NiCl ₂ (10)	100	0
11	ZnCl ₂ (10)	100	8
12	TiCl ₄ (10)	100	0
13	InCl ₃ (10)	100	44
14	In(OTf) ₃ (10)	100	29
15	InBr ₃ (10)	100	57
16	InBr ₃ (20)	100	76
17	InBr ₃ (30)	100	81
18	InBr ₃ (30)	80	43

19	InBr ₃ (30)	25	0
20 ^[c]	InBr ₃ (30)	100	0
21 ^[d]	InBr ₃ (30)	100	79
22	HOTf (10)	100	4
23	HCl (10)	100	trace

[a] Unless otherwise specified, these reactions were carried out at **Standard condition A** --- glycal **2.1a** (0.3 mmol, 1 equiv) and arylamine **2.2a** (0.3 mmol, 1.1 equiv) with catalyst and SDBS (0.03 mmol, 0.1 equiv) in 8 mL of H₂O. [b] Isolated yield. [c] In the absence of SDBS. [d] The reaction was carried out in 8 mL CH₃CN/H₂O (9:1 v/v).

This protocol was applied to a variety of secondary arylamines, and the desired 4-aminocyclopentenones were obtained in 33-84% yield (Table 2.2). The reaction of electron-rich or electron-neutral arylamines gave moderate to good yields and the electron-poor arylamines gave somewhat low yields (**2.3f**, **2.3q**). Sterically hindered arylamines also gave low yields (**2.3k**, **2.3l**), due to the steric effect. To our delight, many of the useful substitution patterns can be introduced with efficiency (**2.3o**, **2.3p**, **2.3u**, **2.3v**). The tolerance of the free hydroxyl group (**2.3r**) for this reaction is remarkable since no other *O*-glycoside product has been observed. To further explore the substrate scope, 3,4-di-*O*-methyl-L-rhamnal (**2.1b**) and 3,4-di-*O*-methyl-D-xylal (**2.1c**) were also tested. The corresponding 4-amino cyclopentenones were obtained in 73-82% yield.

High *trans* diastereoselectivity was observed in every case, as determined by the small coupling constant between H4 and H5 ($J_{\text{H4-H5}} = 2.4 \text{ Hz}$). The *trans* stereochemistry of **2.3d** was further confirmed by a single crystal X-ray structural determination.

Figure 2.3 X-ray structure of **2.3d**.

Table 2.2 InBr₃-catalyzed cascade reaction of glycols with secondary arylamines in water.^[a,b]

[a] The reaction was carried out using glycal **2.1a** (0.3 mmol, 1 equiv) and arylamine **2.2** (0.3 mmol, 1.1 equiv) with InBr₃ (0.09 mmol, 0.3 equiv) and SDBS (0.03 mmol, 0.1 equiv) in H₂O (8 mL) at 100 °C. [b] Isolated yield. [c] Glycal **2.1b** = 3, 4-di-*O*-methyl-L-rhamnal. [d] Glycal **2.1c** = 3,4-di-*O*-methyl-D-xylal.

It should be noted that the reaction of arylamine **2.5** did not give the corresponding 4-aminocyclopentenones. However, oxazine fused cyclopentanone **2.6** was obtained in 47% yield, after removing the benzyl protecting group, as a single diastereomer which was unambiguously established by a single crystal X-ray diffraction determination. This product may arise from an interrupted Nazarov process in which the cyclopentenyl cation is captured by *O*- nucleophiles.³²

Scheme 2.9 Reaction of glycal **2.1a** with arylamine **2.5** in water and X-ray structure of product **2.6**.

Since a variety of metal salts, which may act as precatalysts for the formation of protic acid catalysts via interaction with water, were found to be able to catalyze this reaction, we hypothesized that Brønsted acids would also promote this reaction.

Inspired by Kobayashi's pioneering work in Brønsted acid-surfactant-combined catalyst,³³ we conducted the initial studies by treating 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) with *N*-benzyl-4-methoxyaniline (**2.2a**) in refluxing water using different Brønsted acids and SDBS (sodium dodecylbenzene sulfonate). Among the Brønsted acids studied, MeSO₃H is found to be a cheap and efficient catalyst for this transformation (**Standard condition B**, Table 2.3, entry 10).

Table 2.3 Brønsted catalysts screening for the reaction of glycal with secondary arylamine.^[a]

<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> 2.1a </div> <div style="text-align: center;"> 2.2a </div> <div style="text-align: center;"> 2.3a </div> </div>				
Entry	Catalyst	Catalyst load (mol%)	Temp [°C]	Yield [%] ^[b]
1	H ₂ SO ₄	10	100	15
2	HCl	10	100	22
3	(+) CSA	10	100	27
4	TsOH.H ₂ O	10	100	30
5	CH ₃ COOH	10	100	18
6	CF ₃ SO ₃ H	10	100	25
7	Amberlyst-15	10	100	3
8	MeSO ₃ H	10	100	32

9	MeSO ₃ H	50	100	56
10	MeSO ₃ H	100	100	78
11	MeSO ₃ H	200	100	76
12	MeSO ₃ H	100	25	0
13	MeSO ₃ H	100	40	0
14	MeSO ₃ H	100	80	64
15	MeSO ₃ H	100	90	71
16	MeSO ₃ H	100	110	75

[a] Unless otherwise specified, these reactions were carried out at **standard condition B** --- glycal **2.1a** (0.3 mmol, 1 equiv.) and aniline **2.2a** (0.3 mmol, 1.1 equiv.) with MeSO₃H (0.3 mmol, 1 equiv.) and SDBS (0.03 mmol, 0.1 equiv.) in 2 mL of H₂O. [b] Isolated yield.

This optimized **standard condition B** (100 mol% MeSO₃H and 10 mol% SDBS) could be used in gram-scale synthesis of **2.3a** (Figure 2.4). After the reaction is finished, the water-insoluble colored product was collected by filtration. This simple workup procedure is one of the advantages of the present reaction condition.

Reaction profile

Figure 2.4 Gram-scale synthesis of **2.3a**.

We next turn our attention to finding the optimal condition for the selective formation of cyclopentanone-fused indolines **2.4a** through the reaction of 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) and *N*-benzyl-4-methoxyaniline (**2.2a**). We found that InBr₃ and CH₃NO₂ were the optimal catalyst and solvent, respectively, for this interrupted Nazarov process (Table 2.4). Heating a mixture of **2.1a** (1 equiv) and **2.2a** (1.1 equiv) with 30 mol% of InBr₃ in CH₃NO₂ at 100 °C for 4 h gave the best yield of **2.4a** (Standard condition C, Table 2.4, entry 11).

Table 2.4 Optimization of the reaction of glycal with secondary arylamine in organic solvent. ^[a]

Entry	Catalyst (mol%)	Solvent	Temp[°C]	Yield ^[b] [%]
1	AgOTf (30)	CH ₃ CN	100	49
2	AlCl ₃ (30)	CH ₃ CN	100	0
3	Cu(OTf) ₂ (30)	CH ₃ CN	100	8
4	Dy(OTf) ₃ (30)	CH ₃ CN	100	29
5	Yb(OTf) ₃ (30)	CH ₃ CN	100	26

6	FeCl ₃ (30)	CH ₃ CN	100	0
7	NiCl ₂ (30)	CH ₃ CN	100	0
8	Sc(OTf) ₃ (30)	CH ₃ CN	100	55
9	ZnCl ₂ (30)	CH ₃ CN	100	35
10	InCl ₃ (30)	CH ₃ CN	100	52
11	InBr ₃ (30)	CH ₃ CN	100	58
12	InBr ₃ (30)	Toluene	100	0
13	InBr ₃ (30)	DMF	100	0
14	InBr ₃ (30)	DMSO	100	0
15	InBr ₃ (30)	DCE	100	12
16	InBr ₃ (30)	CH ₃ NO ₂	100	62
17	InBr ₃ (30)	Dioxane	100	0
18	InBr ₃ (30)	CH ₃ NO ₂	80	29
19	InBr ₃ (30)	CH ₃ NO ₂	25	0

[a] Unless otherwise specified, these reactions were carried out under **standard condition C** --- glycol **2.1a** (0.3 mmol, 1 equiv) and arylamine **2.2a** (0.3 mmol, 1.1 equiv) with catalyst in 8 mL of organic solvent. [b] NMR yield determined using 1,1,2,2- tetrachloroethane as internal standard.

We observed that product **2.4a** was unstable and, thus, was isolated as the corresponding *trans,trans,cis*-aminocyclopentitols product **2.7a**, as the major isomer in 52% yield after reduction with NaBH₄ *in situ*.

We further probe the scope of this interrupted Nazarov reaction, and found that the use of electron-rich and electron-neutral arylamines give the desired product in moderate yields (Table 2.5). Failure to obtain the corresponding product **2.7d** from electron-poor arylamine was probably due to inadequate nucleophilicity of the aryl moiety, in analogy to the earlier report by West.^{27c} It is noteworthy to mention that the reaction of *N*-benzyl-2-methoxyaniline, under this condition, did not give the expected interrupted Nazarov product **2.7e**. This result may due to the steric and electronic effects of the ortho substituent. In addition, this interrupted Nazarov process for the *meta*- and *para*-substituted arylamine gave the sterically favored product **2.7f** with high regioselectivity.

Table 2.5 InBr₃-catalyzed cascade reaction of glycols with secondary arylamines in

CH₃NO₂.^[a,b,c]

[a] The reaction was carried out using glycol **2.1a** (0.3 mmol, 1 equiv) and arylamine **2.2** (0.3 mmol, 1.1 equiv) with InBr_3 (0.09 mmol, 0.3 equiv) in CH_3NO_2 (8 mL) at 100 °C. [b] Diastereomeric ratio determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Combined yield after column chromatography.

The relative *trans,trans,cis*-configurations of these compounds were determined by NOE effects of products **2.7a**, **2.7g** (Figure 2.6, Figure 2.8).

4124-r, cosy AV500MHz CDCl₃

Figure 2.5 COSY of compound 2.7a.

4124-r, noesy AV500MHz CDCl₃

Figure 2.6 NOESY of compound 2.7a.

4131-r cosy bbfo2-400

Figure 2.7 COSY of compound 2.7g.

4131-r noesy bbfo2-400

Figure 2.8 NOESY of compound 2.7g.

It is noteworthy that the interrupted Nazarov product **2.4a** was converted to **2.4a'** under prolonged heating. This transformation can be further enhanced by changing catalyst to $\text{Dy}(\text{OTf})_3$ (Scheme 2.10). By using $\text{Dy}(\text{OTf})_3$ as catalyst, compound **2.4a'** can be trapped by CH_3NO_2 *via* a Michael addition.

Scheme 2.10 Degradative transformation of **2.4a**.

More interestingly, by replacing the solvent from CH_3NO_2 to CH_3CN , the same reaction gave a cyclopentenone-fused tetrahydroquinoline **2.8a** as a single diastereomer which was unambiguously established by a single crystal X-ray diffraction determination (Scheme 2.11).

Scheme 2.11 $\text{Dy}(\text{OTf})_3$ -catalyzed reaction of glycols with secondary arylamines **2.2a**.

Similar result was observed when arylamines **2.2g** was used for this reaction (Scheme 2.12). In addition, this reaction gave the sterically favored product **2.8b** with high regioselectivity. Although additional study is needed to settle the exact mechanism, a tentative reaction pathway was proposed in scheme 2.25.

Scheme 2.12 $\text{Dy}(\text{OTf})_3$ -catalyzed reaction of glycols with secondary arylamines **2.2g**.

Mechanism investigation

During our investigation of this cascade reaction, we made several interesting observations which provided useful insight into the mechanism.

(a) Treatment of 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) with 4-methoxyaniline (**2.9**) in refluxing CH_3NO_2 , using 30 mol% of InBr_3 as catalyst, gave tetrahydroquinoline **2.10** in 46% yield (Scheme 2.13). However, using water as solvent resulted in a decrease of the yield of **2.10**.

Scheme 2.13 Reaction of glycal **2.1a** with 4-methoxyaniline **2.9**.

The condensation of primary arylamines with glycals, which only contain hydrogen on C-3, to form tetrahydroquinolines have been extensively studied by Yadav's group^{11, 12} and others^{13,14,15}. Our result was consistent with their reports. The discussions for the mechanisms are shown in scheme 1.13, scheme 1.15, scheme 1.18 and scheme 1.22.

(b) No reaction occurred when the reaction was carried in anhydrous organic solvent, showing that water plays a significant role in this transformation (Scheme 2.14). Also, no reaction took place when condition identical to Zhang's¹⁵ was used for this reaction, showing that our reaction does not proceed via a Ferrier rearrangement reaction first to give *N*-pseudoglycal product.

Scheme 2.14 Control experiment I.

However, by the addition of 10 equiv of water, the same reaction gave a mixture of **2.3a** and **2.4a** (Figure 2.9), which mean that the cyclopentenyl cation I was trapped by the water and aryl moiety (Scheme 2.15).

Scheme 2.15 Control experiment II.

Figure 2.9 ^1H NMR of the reaction crude mixture.

(c) The result of isotope labeling experiment using H_2^{18}O as solvent demonstrated that water is involved in the reaction (Figure 2.10). Upon Nazarov cyclization, pentadienyl cation **I** generates cyclopentenyl cation **I** which reacts with water to form the 4-aminocyclopentenone **2.3a**.

Figure 2.10 Isotope labeling experiment.

(d) Control experiment indicated that 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) react with water under **standard condition A** to afford tri-*O*-benzyl-2-deoxy-D-glucose (**2.11**) (Scheme 2.16), along with a trace amount of α,β -unsaturated aldehyde **2.12** (known as Perlin aldehyde³⁴).

Scheme 2.16 Control experiment III.

Figure 2.10 ^1H NMR of the reaction crude mixture.

These two compounds (**2.11**, **2.12**) were identified as alternative reactants to 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) for this cascade reaction (**standard condition A**, Scheme 2.17).

Scheme 2.17 Control experiment IV.

Interestingly, the reaction of α,β -unsaturated aldehyde **2.12** with *N*-benzyl-4-methoxyaniline (**2.2a**) in the presence of 30 mol% InBr_3 takes place smoothly at room temperature to give dienamine **2.18**. Heating dienamine **2.18** at 100 $^\circ\text{C}$ give **2.3a** in 85% yield (Scheme 2.18).

Scheme 2.18 Control experiment V.

In addition, using anhydrous CH_3CN as solvent and 30 mol% InBr_3 as catalyst, tri-*O*-benzyl-2-deoxy-D-glucose (**2.11**) react with *N*-benzyl-4-methoxyaniline (**2.2a**) to afford solely **2.4a**, albeit with a low conversion (Scheme 2.19).

Scheme 2.19 Control experiment VI.

(e) When α,β -unsaturated aldehyde **2.12** and 4-methoxyaniline (**2.9**) were subjected to the **standard condition A**, tetrahydroquinoline **2.10** was isolated in 48% yield (Scheme 2.20).

Scheme 2.20 Control experiment VII.

The cyclization of primary arylamine with Perlin aldehyde in the presence of a catalytic amount of InCl_3 or $\text{Bi}(\text{OTf})_3$ has been reported by Yadav's group (Scheme 2.21). They suggested that this transformation involves a tandem Michael and intramolecular Friedel-Crafts type cyclization. Furthermore, simple α,β -unsaturated

aldehydes without a δ -hydroxyl group did not afford the tetrahydroquinoline product under their condition.

Scheme 2.21 Cyclization of primary arylamine with Perlin aldehyde.

(f) In the presence of 10 mol % of SDBS and 30 mol % of InBr_3 , 3,4,6-tri-*O*-benzyl-D-galactal (**2.1d**) also reacted with *N*-benzyl-4-methoxyaniline (**2.2a**) in water to provide **2.3a** in 83% yield (Scheme 2.22). Therefore, a cyclic, planar, conjugated cyclopentadienyl cation should be produced in our reaction.

Scheme 2.22 Reaction of glycals **2.1d** with *N*-benzyl-4-methoxyaniline **2.2a** in water.

(g) When D-glucal **2.1aa** or 3,4,6-tri-*O*-acetyl-D-glucal (**2.1e**) was subjected to the **standard condition C**, none of the corresponding cyclopentanone-fused indolines product was isolated, instead the 4-aminocyclopentenone product was afforded as major product (Scheme 2.21). These results indicated that the stability and the lifetime of the cyclopentenyl cation intermediate are the key factors for the interrupted Nazarov process.

Scheme 2.21 Reaction of glycols **2.1aa**, **2.1e** with *N*-benzyl-4-methoxyaniline **2.2a** in CH_3NO_2 .

When tri-*O*-benzyl-2-deoxy-D-glucose (**2.11**) and *N*-benzyl-4-methoxyaniline (**2.2a**) were subjected to the **standard condition C**, **2.4a** was isolated in 43% yield. However, in the case of 2-deoxy-D-glucose **2.11a** as substrate, the only isolated product is **2.3aa** (Scheme 2.22). These results indicated that the choice of appropriate

protecting groups for glycals is one of the decisive factors in successful realization of the interrupted Nazarov process.

Scheme 2.22 Reaction of 2-deoxy-D-glucoses **2.11a**, **2.11** with *N*-benzyl-4-methoxyaniline **2.2a** in CH_3NO_2 .

(h) In the presence of 30 mol% of $\text{Dy}(\text{OTf})_3$, a selective transformation of **2.4a** to **2.7a'** or **2.8a** at 100°C was observed, when CH_3NO_2 or CH_3CN was used as solvent respectively (Scheme 2.23).

Scheme 2.23 Selective transformation of **2.4a** to **2.7a'** and **2.8a**.

Although the exact mechanism of these cascade transformations are not completely understood, a mechanistic rationalization of our results was proposed on the basis of isotope-labeling, as well as control and trapping experiments.

The proposed overall transformation is depicted in Scheme 2.24, and proceeds through a 4π conrotatory electrocyclization as the key step. Initially, in the absence of arylamine, the 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) reacts with water to give mixture of tri-*O*-benzyl-2-deoxy-D-glucose (**2.11**) and α,β -unsaturated aldehyde **2.12**. In the presence of primary arylamine **2.9**, α,β -unsaturated aldehyde **2.12** undergoes a tandem Michael and intramolecular Friedel-Crafts type cyclization to form tetrahydroquinoline **2.10**. However, when secondary arylamine is added as a reactant, iminium **2.17** can be produced by condensation of secondary arylamine with α,β -unsaturated aldehyde **2.12**, which is generated from hemiacetal **2.13** (**Pathway A**). Iminium **2.17** cannot be generated through **Pathway B** since no *N*-Glycoside product **2.16** has been observed. On the other hand, iminium **2.17** can also be generated from glycosylamine **2.19**, which is formed by condensation with tri-*O*-benzyl-2-deoxy-D-glucose **2.11** and secondary arylamine (**Pathway C**). Iminium **2.17** can be further converted to dienamine **2.18**, which produce the corresponding pentadienyl cation **2.22** via the elimination of water. Upon cyclization, pentadienyl cation **2.22** generates cyclopentenyl cation **2.23** which reacts with water to form the 4-aminocyclopentenone **2.3a**. If this reaction is performed in organic solvent, cyclopentenyl cation **2.23** can be trapped by the aryl moiety, generating **2.25** which react with water to form **2.4a**.

Scheme 2.24 A possible mechanism.

In addition, a tentative reaction pathway for the conversion of **2.4a** to **2.8a** was proposed in scheme 2.25. The interrupted Nazarov product **2.4a** can be converted to **2.4a'** via the elimination of BnOH. We speculated that **2.4a'** represents ideal acceptor moieties that are susceptible to activation by a Lewis acid catalyst. This activation is expected to increase the hydride acceptor capability of the conjugated double bond. **2.4a'** may undergo a tandem 1, 5-hydride shift^{35a}, which could be attributed to the

superior hydride donor capability of benzylic C–H bond, and Mannich reaction to afford cyclopentenone-fused tetrahydroquinoline product **2.8a**.

cheme 2.25 A possible mechanism.

The deuterium-labeling study unambiguously indicated that this reaction involves a 1,5-H shift process (Scheme 2.26).

Scheme 2.26 Isotope labeling experiment.

However, previously reported 1,5-H shift process^{35a,35b} seldom followed by a C–N bond cleavage. Xi' group^{35c} reported a base-mediated ring expansion of 2,4-diiminoazetidines via cleavage of C–N and 1,5-H shift process (Scheme 2.27). The mechanism is well confirmed by the trapping experiments of two key intermediates and deuterium labeling studies.

Scheme 2.27 A possible retro-ene reaction mechanism.

Also, an alternative mechanism, which involves a retro-ene reaction, for this transformation cannot be ruled out at this time (Scheme 2.28).

Scheme 2.28 Possible retro-ene reaction.

Cadogan's group^{35d} reported a gas-phase rearrangement reaction of 2-allyl-1,2,3,4-tetrahydroisoquinoline. They suggested that this reaction involves a retro-ene reaction (Scheme 2.29).

Scheme 2.29 Gas-phase rearrangement reaction of 2-allyl-1,2,3,4-tetrahydroisoquinoline.

However, the exact mechanism of our 1,5-H shift process is not completely understood. Further mechanistic studies are still underway in our laboratory.

2.4 Conclusion

In conclusion, we have developed a versatile and practical method for the chemoselective preparation of an array of 4-aminocyclopentenones and cyclopentanone-fused indolines from common glycals and secondary arylamines (Scheme 2.26). Preliminary mechanism studies revealed that a 4π conrotatory electrocyclicization is the crucial step in these cascade transformations. By judicious choice of the reaction solvent, the Nazarov intermediate can be trapped with water or aryl moieties.

Scheme 2.26 InBr_3 -catalyzed cascade reaction of glycals with secondary arylamines.

Most importantly, these cascade reactions for the synthesis of 4-aminocyclopentenones can tolerate various functional groups and perform in water under aerobic conditions, making this method suitable for applications in the pharmaceutical industry. Also, the new approach for the synthesis of cyclopentanone-fused indolines complements previously reported interrupted Nazarov process.

In addition, further developments on the tandem 1, 5-hydride shift and Mannich reaction are currently underway in our laboratory (Scheme 2.27). On the basis of detailed mechanistic study, there remains promising opportunity for discovery of new variants of such transformations. It would further enhance the diverse chemistry of glycols and provide a variety of novel alkaloids that are of significant synthetic and biological interest.

Scheme 2.27 $Dy(OTf)_3$ -catalyzed cascade reaction of glycols with secondary arylamines.

2.5 Experimental section

2.5.1 General considerations

Unless otherwise specified, these reactions were performed under air atmosphere. 3,4-di-*O*-methyl-L-rhamnal (**2.1b**), 3,4-di-*O*-methyl-D-xylal (**2.1c**) and α,β -unsaturated aldehyde **2.12** were prepared according to the known procedure.³⁴ Reactions were monitored through thin layer chromatography [Merck 60 F254 TLC plate (0.2 mm thickness)]. Later, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by using basic solution of KMnO₄ or acidic solution of Ceric molybdate as stain. Flash chromatography was carried out using silica gel 60. HRMS spectra were recorded on a Waters Q-ToF premierTM mass Spectrometer. ¹H NMR and ¹³C NMR spectra were performed by Bruker Avance 300, 400 and 500 MHz spectrometers. Chemical shifts for ¹H NMR spectra are recorded as δ in units of ppm downfield from SiMe₄ (δ 0.0) and relative to the signal of CDCl₃ (δ 7.260, singlet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); td (triplet of doublet); m (multiplets); ddt (doublet of doublet of triplet) and *etc.* Coupling constants are recorded as a *J* value in Hz. Carbon NMR spectra (¹³C NMR) are recorded as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of CDCl₃ (δ 77.00, triplet).

2.5.2 General procedure

General procedure A for preparation of 4-aminocyclopentenones

2.3a

To a suspension of 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) (124.8 mg, 1.0 equiv, 0.3 mmol) and *N*-benzyl-4-methoxyaniline (**2.2a**) (70.3 mg, 1.1 equiv, 0.33 mmol) in H₂O (8 mL) was added InBr₃ (32.0 mg, 0.3 equiv, 0.09 mmol) and sodium dodecylbenzene sulfonate (10.4 mg, 0.1 equiv, 0.03 mmol). The reaction was stirred at RT for 10mins. The reaction was then heated to 100 °C with good stirring for 24 h. Then the crude mixture was extracted with EtOAc (3 × 50 mL), washed with 10% NaHCO₃ (2 × 50 mL) and brine (2 × 50 mL). The organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to yield the crude residue as dark yellow oil. The crude product was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:20 to 1:4) to afford **2.3a** (100.4 mg, 81% yield) as a yellow oil.

General procedure B for preparation of 4-aminocyclopentenones

2.3a

To a suspension of 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) (124.8 mg, 0.3 mmol) and *N*-benzyl-4-methoxyaniline (**2.2a**) (70.3 mg, 1.1 equiv, 0.33 mmol) in H₂O (8 mL) was added MeSO₃H (19.5 μ L, 1.0 equiv, 0.3 mmol) and sodium dodecylbenzene sulfonate (10.4 mg, 0.1 equiv, 0.03 mmol). The reaction was stirred at 100 °C for 24 h, then extracted with EtOAc (2 $\times$ 50 mL), washed with 10% NaHCO₃ (2 $\times$ 50 mL) and brine (2 $\times$ 50 mL). The organic layers were dried over anhydrous Na₂SO₄, and concentrated to yield the crude residue as dark yellow oil. The crude residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:15 to 1:4) to afford **2.3a** (96.6 mg, 78%) as a yellow oil.

General procedure C for preparation of *trans,trans,cis*-aminocyclopentitols

2.7a

To a suspension of 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) (124.8 mg, 1.0 equiv, 0.3 mmol) and **2.2a** (70.3 mg, 1.1 equiv, 0.33 mmol) in CH₃NO₂ (8 mL) was added InBr₃ (32.0 mg, 0.3 equiv, 0.09 mmol) and H₂O (6.5 μL, 1.2 equiv, 0.36 mmol). The reaction was stirred at 100 °C for 4 h, and then concentrated to yield the crude residue as brown oil. The crude residue was dissolved in CH₃OH (8 mL). To the solution was added NaBH₄ (13.7 mg, 1.2 equiv, 0.36 mmol) portionwise. The reaction mixture was stirred at rt for 1 h. The reaction was quenched with water (5 mL), then concentrated under reduced pressure and extracted with EtOAc (50 mL). The organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to yield the crude residue as yellow oil. The crude residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:20 to 1:3) to afford *trans,trans,cis*-**2.7a** (64.7 mg, 52% yield) as a major isomer.

General procedure D for preparation **2.7a'**

To a suspension of 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) (124.8 mg, 1.0 equiv, 0.3 mmol) and **2.2a** (70.3 mg, 1.1 equiv, 0.33 mmol) in CH₃NO₂ (8 mL) was added Dy(OTf)₃ (55.0 mg, 0.3 equiv, 0.09 mmol) and H₂O (6.5 μL, 1.2 equiv, 0.36 mmol). The mixture was stirred at 100 °C for 24 h, and then concentrated to yield the crude residue as brown oil. Then the oil was extracted with EtOAc (3 × 50 mL), washed with 10% NaHCO₃ (2 × 50 mL) and brine (2 × 50 mL). The crude residue was purified by flash column chromatography (solvent: EtOAc:hexane = 1:3 to 1:1) to afford **2.7a'** (71.4 mg, 65% yield).

General procedure E for preparation 2.8a

To a suspension of 3,4,6-tri-*O*-benzyl-D-glucal (**2.1a**) (124.8 mg, 1.0 equiv, 0.3 mmol) and **2.2a** (70.3 mg, 1.1 equiv, 0.33 mmol) in CH₃CN (8 mL) was added Dy(OTf)₃ (55.0 mg, 0.3 equiv, 0.09 mmol) and H₂O (6.5 μL, 1.2 equiv, 0.36 mmol). The reaction mixture was stirred at 100 °C for 24 h, and then concentrated under reduced pressure to yield the crude residue as brown oil. Then the oil was extracted with EtOAc (3 × 50 mL), washed with 10% NaHCO₃ (2 × 50 mL) and brine (2 × 50

mL). The crude residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:3 to 1:1) to afford **2.8a** (59.5 mg, 65% yield).

2.5.3 Characterization Data for the Isolated Products

4-(Benzyl(4-methoxyphenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone (**2.3a**)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 81%. **¹H NMR** (400 MHz, CDCl₃): δ 7.65 (dd, *J*=6.0, 2.0 Hz, 1H), 7.36-7.20 (m, 10H), 6.79 - 6.77 (m, 2H), 6.72-6.70 (m, 2H), 6.28 (dd, *J*=5.6, 2.0 Hz, 1H), 5.27 (q, *J*=2.4 Hz, 1H), 4.55 (d, *J*=12.0, 1H), 4.46 (d, *J*=12.0, 1H), 4.32-4.25 (m, 2H), 3.92 (dd, *J*=9.6, 3.6 Hz, 1H), 3.72 (s, 3 H), 3.71 (dd, *J*=9.2, 3.6 Hz, 1H), 2.47 (q, *J*=3.2 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 206.3, 163.9, 153.1, 142.5, 139.4, 138.0, 135.2, 128.6, 128.4, 127.8, 127.7, 127.0, 126.7, 117.4, 114.6, 73.4, 67.2, 63.3, 55.6, 51.7, 50.9; **HRMS** (ESI):*m/z*. calcd for C₂₇H₂₈NO₃ [M+H]⁺ 414.2069; found: 414.2067.

4-(Benzyl(4-methoxyphenyl)amino)-5-(hydroxymethyl)cyclopent-2-enone (2.3aa)

The product was obtained as yellow oil. Yield: 64%. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.72 (dd, $J=5.6, 1.6$ Hz, 1H), 7.33-7.21 (m, 5H), 6.89 (d, $J=8.8$, 2H), 6.80 (d, $J=8.8$, 2H), 6.29 (dd, $J=5.6, 2.1$ Hz, 1H), 5.08 (s, 1 H), 4.35 (d, $J=16.4$, 1H), 4.30 (d, $J=16.4$, 1H), 4.10 (dd, $J=10.8, 3.2$ Hz, 1H), 3.83 (dd, $J=11.2, 5.2$ Hz, 1H), 3.73 (s, 3H), 2.54 (q, $J=4.0$ Hz, 1H), 2.43 (brs, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 207.9, 164.6, 153.5, 142.4, 139.2, 135.1, 128.7, 127.1, 126.8, 118.1, 114.7, 63.3, 60.3, 55.6, 52.3, 52.0; **HRMS** (ESI): m/z calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 324.1600; found: 324.1596.

2-(Benzyl(4-methoxyphenyl)amino)-5-oxocyclopent-3-en-1-yl)methyl acetate (2.3ab)

The product was obtained as yellow oil. Yield: 8%. **¹H NMR** (300 MHz, CDCl₃): δ 7.75 (dd, *J*=5.7, 2.1 Hz, 1H), 7.34-7.27 (m, 5H), 6.91-6.80 (m, 4H), 6.35 (dd, *J*=6.0, 2.1 Hz, 1H), 4.98 (s, 1H), 4.43 (m, 2H), 4.34 (d, *J*=5.1, 2H), 3.78 (s, 3H), 2.54 (q, *J*=3.9 Hz, 1H), 1.99 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃): δ 204.8, 170.8, 163.6, 154.0, 142.2, 139.0, 135.1, 128.6, 127.2, 126.9, 118.9, 114.7, 64.4, 61.8, 55.6, 52.4, 49.0, 20.7; **HRMS** (ESI):*m/z* calcd for C₂₀H₂₄NO₄ [M+H]⁺ 366.1705; found: 366.1700.

N-(4-(benzyl(5-((benzyloxy)methyl)-4-oxocyclopent-2-en-1-yl)amino)phenyl)acetamide (2.3b)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 71%. **¹H NMR** (500 MHz, CDCl₃): δ = 7.61 (dd, *J*=6.0, 2.0 Hz, 1H), 7.36-7.18 (m, 12H), 6.75-6.73 (m, 2H), 6.31 (dd, *J*=5.5, 2.0 Hz, 1H), 5.43 (d, *J*=2.0 Hz, 1H), 4.56 (d, *J*=12.0, 1H), 4.47 (d, *J*=12.0, 1H), 4.36 (d, *J*=12.0, 1H), 3.96 (dd, *J*=9.5, 3.0 Hz, 1H), 3.73 (dd, *J*=9.5, 3.5 Hz, 1H), 2.46 (q, *J*=3.0 Hz, 1 H), 2.12 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃): δ = 206.1, 168.2, 163.4, 145.6, 139.0, 137.9, 135.4, 129.0, 128.7, 128.5, 127.8, 127.0, 126.2, 122.1, 114.6, 73.5, 66.9, 62.0, 51.3, 50.7, 24.3; **HRMS** (ESI):*m/z* calcd for C₂₈H₂₉N₂O₃ [M+H]⁺ 441.2178; found: 441.2173.

4-(Benzyl(4-chlorophenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone (2.3c)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 73%. **¹H NMR** (400 MHz, CDCl₃): δ 7.59 (dd, $J=5.6, 2.0$ Hz, 1H), 7.38-7.18 (m, 10H), 7.07-7.04 (m, 2H), 6.70-6.68 (m, 2H), 6.33 (dd, $J=5.6, 2.0$ Hz, 1H), 5.45 (d, $J=2.4$ Hz, 1H), 4.59 (d, $J=12.0$ Hz, 1H), 4.47 (d, $J=12.0$ Hz, 1H), 4.37 (d, $J=17.2$ Hz, 1H), 4.29 (d, $J=17.6$ Hz, 1H), 3.97 (dd, $J=9.2, 3.2$ Hz, 1H), 3.74 (dd, $J=9.6, 3.6$ Hz, 1H), 2.44 (q, $J=3.2$ Hz, 1 H); **¹³C NMR** (100 MHz, CDCl₃): δ 205.7, 162.9, 147.1, 138.5, 137.8, 135.6, 129.1, 128.8, 128.5, 127.9, 127.2, 126.1, 122.9, 115.1, 73.5, 66.8, 61.7, 51.4, 50.3; **HRMS** (ESI): m/z calcd for C₂₆H₂₅ClNO₂ [M+H]⁺ 418.1574; found: 418.1570.

4-(Benzyl(4-iodophenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone (2.3d)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 77%. **¹H NMR** (400 MHz, CDCl₃): δ 7.57 (dd, *J*=6.0, 2.0 Hz, 1H), 7.38-7.17 (m, 14H), 6.56-6.54 (m, 2H), 6.33 (dd, *J*=6.8, 2.0 Hz, 1H), 5.46 (d, *J*=2.4 Hz, 1H), 4.58 (d, *J*=12.0, 1H), 4.47 (d, *J*=12.0 Hz, 1H), 4.36 (d, *J*=17.6, 1H), 4.28 (d, *J*=17.6Hz, 1H), 3.97 (dd, *J*=9.2, 3.2 Hz, 1H), 3.74 (dd, *J*=9.2, 3.2 Hz, 1H), 2.45 (q, *J*=3.2 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 205.6, 162.7, 148.1, 138.4, 137.9, 137.8, 135.7, 128.8, 128.5, 127.9, 127.2, 126.0, 116.0, 79.2, 73.5, 66.8, 61.3, 51.4, 50.1; **HRMS** (ESI):*m/z* calcd for C₂₆H₂₅INO₂ [M+H]⁺ 510.0930; found: 510.0928.

4-(Benzyl(4-(tert-butyl)phenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone (2.3e)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 69%. **¹H NMR** (400 MHz, CDCl₃): δ 7.61 (dd, *J*=5.6, 2.0 Hz, 1H), 7.38 - 7.20 (m, 10H), 7.17-7.13 (m, 2H), 6.75-6.71 (m, 2H), 6.31 (dd, *J*=6.0, 2.0 Hz, 1H), 5.49 (d, *J*=2.4 Hz, 1H), 4.59 (d, *J*=12.0, 1H), 4.48 (d, *J*=12.4, 1H), 4.37 (d, *J*=17.6 Hz, 1H), 4.30 (d, *J*=17.6 Hz, 1H), 3.97 (dd, *J*=9.2, 2.8 Hz, 1H), 3.77 (dd, *J*=9.2, 3.2 Hz, 1H), 2.45 (q, *J*=3.2 Hz, 1H), 1.26 (s, 9H); **¹³C NMR** (100

MHz, CDCl₃): δ 206.3, 163.7, 146.3, 140.8, 139.6, 138.0, 135.4, 128.7, 128.5, 127.9, 127.8, 127.0, 126.2, 126.2, 113.5, 73.5, 66.7, 61.3, 51.3, 50.8, 33.8, 31.5;

HRMS (ESI): m/z calcd for C₃₀H₃₄NO₂ [M+H]⁺ 440.2590; found: 440.2584.

Methyl 4-(benzyl(5-((benzyloxy)methyl)-4-oxocyclopent-2-en-1-yl)amino) benzoate (2.3f)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 36%. **¹H NMR** (400 MHz, CDCl₃): δ 7.83 (d, J =9.2 Hz, 2H), 7.57 (dd, J =6.0, 2.4 Hz, 1H), 7.39-7.24 (m, 8H), 7.19 (d, J =7.2 Hz, 2H), 6.78 (d, J =9.2 Hz, 2H), 6.36 (dd, J =5.6, 2.0 Hz, 1H), 5.64 (q, J =2.4 Hz, 1H), 4.60 (d, J =12.0, 1H), 4.50 (d, J =12.0, 1H), 4.43-4.41 (m, 2H), 4.01 (dd, J =9.6, 3.2 Hz, 1H), 3.85 (s, 3H), 3.77 (dd, J =9.6, 3.6 Hz, 1H), 2.48 (q, J =3.2 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 205.4, 167.0, 162.2, 152.0, 137.9, 137.7, 135.9, 131.5, 128.9, 128.5, 127.9, 127.3, 125.9, 119.0, 112.2, 73.6, 66.6, 60.8, 51.7, 51.6, 49.9; **HRMS** (ESI): m/z calcd for C₂₈H₂₈NO₄ [M+H]⁺ 442.2018; found: 442.2015.

4-(Benzyl(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone (2.3g)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 73%. ¹H NMR (400 MHz, CDCl₃): δ 7.64 (dd, *J*=6.0, 2.0 Hz, 1H), 7.36-7.20 (m, 10H), 6.68 (d, *J*=8.8, 1H), 6.42 (d, *J*=2.8, 1H), 6.37 (dd, *J*=8.8, 3.2 Hz, 1H), 6.29 (dd, *J*=6.0, 2.0 Hz, 1H), 5.29 (d, *J*=2.0 Hz, 1H), 4.56 (d, *J*=12.0 Hz, 1H), 4.49 (d, *J*=12.0 Hz, 1H), 4.31-4.17 (m, 6H), 3.95 (dd, *J*=9.2, 3.2 Hz, 1H), 3.74 (dd, *J*=9.2, 3.2 Hz, 1H), 2.47 (q, *J*=3.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 206.3, 163.7, 143.9, 143.5, 139.3, 138.0, 136.7, 135.2, 128.6, 128.4, 127.8, 127.7, 127.0, 126.5, 117.5, 109.0, 104.7, 73.4, 67.0, 64.7, 64.2, 62.8, 51.5, 51.0; HRMS (ESI): *m/z* calcd for C₂₈H₂₈NO₄ [M+H]⁺ 442.2018; found: 442.2013.

4-(Benzyl(3-bromo-4-methylphenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone (2.3h)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 70%. **¹H NMR** (400 MHz, CDCl₃): δ 7.57 (dd, *J*=5.6, 2.0 Hz, 1H), 7.36-7.19 (m, 10H), 7.13 (d, *J*=2.8, 1H), 6.96 (d, *J*=8.4 Hz, 1H), 6.62 (dd, *J*=8.4, 2.8 Hz, 1H), 6.30 (dd, *J*=5.6, 2.0 Hz, 1H), 5.44 (d, *J*=2.4 Hz, 1H), 4.54 (s, 2H), 4.35 (d, *J*=17.2, 1H), 4.28 (d, *J*=17.6, 1H), 3.98 (dd, *J*=9.6, 3.2 Hz, 1H), 3.74 (dd, *J*=9.6, 3.6 Hz, 1H), 2.45 (q, *J*=3.2 Hz, 1H), 2.26 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 205.7, 162.9, 147.8, 138.7, 137.9, 135.5, 131.1, 128.8, 128.4, 127.8, 127.8, 127.2, 127.1, 126.2, 125.7, 117.7, 113.4, 73.5, 67.0, 61.8, 51.4, 50.4, 21.6; **HRMS** (ESI): *m/z* calcd for C₂₇H₂₇BrNO₂ [M+H]⁺ 476.1225; found: 476.1220.

4-(Benzyl(mesityl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone
(2.3i)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 71%. **¹H NMR** (400 MHz, CDCl₃): δ 7.37 (dd, *J*=6.0, 2.4 Hz, 1H), 7.30 - 7.10 (m, 10H), 6.78 (s, 2H), 6.12 (dd, *J*=5.6, 1.6 Hz, 1H), 4.61 (q, *J*=2.0 Hz, 1H), 4.45 (d, *J*=12.4 Hz, 1H), 4.37 (d, *J*=12.4 Hz, 1H), 4.24 (d, *J*=14.0 Hz, 1H), 4.19 (d, *J*=14.4 Hz, 1H), 3.76 (dd, *J*=9.2, 4.0 Hz, 1H), 3.50 (dd, *J*=9.2, 3.2 Hz, 1H), 2.60 (dd, *J*=6.0, 3.6 Hz, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 2.10 (s, 3H); **¹³C NMR**

NMR (100 MHz, CDCl_3): δ 207.5, 164.6, 144.2, 140.6, 138.1, 137.5, 137.0, 135.2, 133.8, 130.0, 129.7, 128.9, 128.3, 128.2, 127.5, 127.0, 73.2, 67.9, 66.2, 56.3, 52.9, 20.8, 20.0, 19.9; **HRMS** (ESI): m/z calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 426.2433; found: 426.2429.

4-(Benzyl(3,5-dimethylphenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-en-1-one (2.3j)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 80%. **^1H NMR** (400 MHz, CDCl_3): δ 7.60 (dd, $J=5.6, 2.0$ Hz, 1H), 7.34-7.22 (m, 10H), 6.50 (s, 2H), 6.45 (s, 1H), 6.30 (dd, $J=6.0, 2.0$ Hz, 1H), 5.53 (d, $J=2.4$ Hz, 1H), 4.55 (d, $J=12.0$ Hz, 1H), 4.52 (d, $J=12.0$ Hz, 1H), 4.39 (d, $J=17.6$ Hz, 1H), 4.31 (d, $J=17.6$ Hz, 1H), 3.99 (dd, $J=9.6, 3.2$ Hz, 1H), 3.76 (dd, $J=9.6, 3.6$ Hz, 1H), 2.47 (q, $J=3.6$ Hz, 1 H), 2.20 (s, 6 H); **^{13}C NMR** (100 MHz, CDCl_3): δ 206.2, 163.6, 149.0, 139.6, 139.0, 138.0, 135.3, 128.7, 128.4, 127.7, 127.6, 127.0, 126.2, 120.2, 111.8, 73.5, 67.1, 61.3, 51.4, 50.6, 21.8; **HRMS** (ESI): m/z calcd for $\text{C}_{28}\text{H}_{30}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 412.2277; found: 412.2275.

5-((Benzyloxy)methyl)-4-(ethyl(naphthalen-1-yl)amino)cyclopent-2-enone (2.3k)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 33%. **¹H NMR** (400 MHz, CDCl₃): δ 8.38 (d, *J*=8 Hz, 1H), 7.86-7.80 (m, 2H), 7.65-7.48 (m, 1H), 7.46-7.40 (m, 2H), 7.40-7.36 (m, 1H), 7.20-7.19 (m, 3H), 6.96-6.95 (m, 2H), 6.27 (d, *J*=6.0 Hz, 1H), 4.76 (s, 1H), 4.31 (d, *J*=12.0 Hz, 1H), 4.19 (d, *J*=12.0 Hz, 1H), 3.77 (dd, *J*=9.2, 3.6 Hz, 1H), 3.40 (brs, 1H), 3.26-3.19 (m, 1H), 3.17-3.08 (m, 1H), 2.61 (d, *J*=3.2 Hz, 1H), 1.01 (t, *J*=14, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 207.1, 164.2, 145.3, 137.9, 135.0, 134.9, 131.8, 128.3, 128.2, 127.4, 127.4, 126.0, 125.8, 125.3, 124.9, 123.8, 119.7, 73.2, 67.8, 67.3, 49.5, 42.8, 13.4; **HRMS** (ESI):*m/z* calcd for C₂₅H₂₆NO₂ [M+H]⁺ 372.1964; found: 372.1958.

5-((Benzyloxy)methyl)-4-(3,4-dihydroquinolin-1(2H)-yl)cyclopent-2-enone (2.3l)

The title compound was prepared according to the general procedure A. The product was obtained as brown oil. Yield: 39%. **¹H NMR** (400 MHz, CDCl₃): δ 7.64 (dd, *J*=5.6, 2.0 Hz, 1H), 7.36-7.26 (m, 5H), 6.98-6.93 (m, 2H), 6.80 (d, *J*=8.4 Hz, 1H), 6.64-6.62 (m, 1H), 6.36 (dd, *J*=6.0, 2.0 Hz, 1H), 5.43 (d, *J*=2.4 Hz, 1H), 4.61 (d, *J*=12.0, 1H), 4.48 (d, *J*=12.0, 1H), 4.02 (dd, *J*=9.2, 2.8 Hz, 1H), 3.75 (dd, *J*=9.2, 3.2 Hz, 1H), 3.09-3.04 (m, 2H), 2.78-2.74 (m, 2H), 2.51 (q, *J*=3.2 Hz, 1H), 1.93-1.89 (m, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ 206.4, 164.7, 144.9, 137.9, 135.1, 129.7, 128.4, 127.9, 127.8, 127.2, 123.2, 116.9, 111.3, 73.5, 67.1, 60.3, 49.9, 43.7, 28.1, 22.3; **HRMS** (ESI): *m/z* calcd for C₂₂H₂₄NO₂ [M+H]⁺ 334.1807; found: 334.1800.

4-(Benzyl(2-methoxyphenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone (2.3m)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 67%. **¹H NMR** (400 MHz, CDCl₃): δ 7.71 (dd, *J*=6.0, 2.4 Hz, 1H), 7.29-7.12 (m, 10H), 7.00-6.96 (m, 2H), 6.83 (d, *J*=7.6, 1H), 6.78-6.74 (m, 1H), 6.16 (dd, *J*=6.0, 2.0 Hz, 1H), 4.91 (q, *J*=2.4 Hz, 1H), 4.41 (d, *J*=12.4, 1H), 4.35 (d, *J*=12.4, 1H), 4.41 (d, *J*=15.2, 1H), 4.25 (d, *J*=15.2, 1H), 3.83-3.79 (m, 4H), 3.55 (dd, *J*=9.2, 3.6 Hz, 1H), 2.59 (q, *J*=3.2 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 207.3, 165.1, 154.7, 139.6, 138.2, 137.7, 134.1, 128.3, 128.2,

127.9, 127.4, 126.8, 125.0, 124.5, 120.6, 111.9, 73.2, 67.6, 65.7, 55.3, 52.8, 50.4;

HRMS (ESI): m/z calcd for $C_{27}H_{28}NO_3$ $[M+H]^+$ 414.2069; found: 414.2064.

5-((Benzyloxy)methyl)-4-((4-methoxyphenyl)(methyl)amino)cyclopent-2-enone (2.3n)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 78%. **1H NMR** (500 MHz, $CDCl_3$): δ 7.65 (dd, $J=5.5$, 2.0 Hz, 1H), 7.36-7.26 (m, 5H), 6.84-6.78 (m, 4H), 6.33 (dd, $J=6.0$, 2.0 Hz, 1H), 5.18 (d, $J=2.0$ Hz, 1H), 4.54 (d, $J=12.5$, 1H), 4.42 (d, $J=12.5$, 1H), 3.92 (dd, $J=9.0$, 3.0 Hz, 1H), 3.75 (s, 3H), 3.58 (dd, $J=9.5$, 3.5 Hz, 1H), 2.44 (q, $J=3.5$ Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 206.5, 164.3, 153.0, 143.9, 138.0, 135.0, 128.4, 127.8, 127.7, 116.7, 114.7, 73.3, 67.2, 64.2, 55.7, 49.2, 33.6; **HRMS** (ESI): m/z calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$ 338.1756; found: 338.1752.

4-(Allyl(4-methoxyphenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone (2.3o)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 75%. **¹H NMR** (400 MHz, CDCl₃): δ 7.64 (dd, *J*=6.0, 2.4 Hz, 1H), 7.36-7.25 (m, 5H), 6.81-6.74 (m, 4H), 6.31 (dd, *J*=6.0, 2.0 Hz, 1H), 5.86-5.77 (m, 1H), 5.22-5.17 (m, 2H), 5.16-5.10 (m, 1H), 4.56 (d, *J*=12.0, 1H), 4.46 (d, *J*=12.0, 1H), 3.94 (dd, *J*=9.2 3.2 Hz, 1H), 3.77 (s, 3H), 3.69-3.65 (m, 3H), 2.45 (q, *J*=3.2 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 206.5, 164.0, 153.0, 142.4, 138.0, 135.8, 135.0, 128.4, 127.8, 127.7, 117.2, 116.4, 114.6, 73.4, 67.0, 63.0, 55.7, 50.9, 50.3; **HRMS** (ESI):*m/z* calcd for C₂₃H₂₆NO₃ [M+H]⁺ 364.1913; found: 364.1907.

5-((Benzyloxy)methyl)-4-((4-methoxyphenyl)(prop-2-yn-1-yl)amino)cyclopent-2-enone (2.3p)

The title compound was prepared according to the general procedure A. The product was obtained as brown oil. Yield: 70%. **¹H NMR** (400 MHz, CDCl₃): δ 7.75 (dd, *J*=6.0, 2.4 Hz, 1H), 7.38-7.26 (m, 5H), 6.97 - 6.93 (m, 2H), 6.81 - 6.78 (m, 2H), 6.34 (dd, *J*=5.6, 2.0 Hz, 1H), 5.15 (q, *J*=2.4 Hz, 1H), 4.57 (d, *J*=12.0 Hz, 1H), 4.45 (d, *J*=12.0 Hz, 1H), 3.92 (dd, *J*=9.6 Hz, 3.6 Hz, 1H), 3.87 (d, *J*=2.4 Hz, 1H), 3.85 (d, *J*=2.4 Hz, 1H), 3.77 (s, 3H), 3.69 (dd, *J*=9.2, 3.6 Hz, 1H), 2.65 (q, *J*=3.2 Hz, 1H), 2.23 (t, *J*=2.4 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 206.4, 163.5, 154.0, 141.4, 138.0, 135.3, 128.4, 127.9, 127.7, 118.8, 114.6, 81.2, 73.4, 73.0, 67.2, 63.5, 55.6,

50.6, 38.4; **HRMS** (ESI): m/z calcd for $C_{23}H_{24}NO_3$ $[M+H]^+$ 362.1756; found: 362.1751.

4-((5-((Benzyloxy)methyl)-4-oxocyclopent-2-en-1-yl)(methyl)amino)benzonitrile (2.3q)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 42%. **1H NMR** (400 MHz, $CDCl_3$): δ 7.54 (dd, $J=5.6, 2.0$ Hz, 1H), 7.40-7.32 (m, 5H), 7.28-7.25 (m, 2H), 6.77 (d, $J=9.2$, 2H), 6.41 (dd, $J=6.0, 2.0$ Hz, 1H), 5.41 (d, $J=2.4$ Hz, 1H), 4.59 (d, $J=12.0$, 1H), 4.43 (d, $J=12.0$, 1H), 3.97 (dd, $J=9.2, 3.2$ Hz, 1H), 3.68 (dd, $J=9.2, 3.6$ Hz, 1H), 2.77 (s, 3H), 2.40 (q, $J=3.6$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 205.1, 162.3, 151.9, 137.5, 135.9, 133.6, 128.5, 128.0, 120.1, 112.3, 99.2, 73.6, 66.4, 60.8, 50.8, 32.3; **HRMS** (ESI): m/z calcd for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1603; found: 333.1597.

4-(Benzyl(2-(2-hydroxyethyl)phenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone (2.3r)

The title compound was prepared according to the general procedure A. The product was obtained as brown oil. Yield: 52%. **¹H NMR** (400 MHz, CDCl₃): δ 7.77(dd, *J*=6.0, 2.4 Hz, 1H), 7.31-7.01 (m, 14H), 6.27 (dd, *J*=5.6, 1.6 Hz, 1H), 4.60 (q, *J*=2.4 Hz, 1H), 4.42 (d, *J*=12.0, 1H), 4.33 (d, *J*=12.0, 1H), 4.16 (m, 2H), 3.82 (dd, *J*=9.6, 4.0 Hz, 1H), 3.69 - 3.65 (m, 2H), 3.53 (dd, *J*=9.2, 3.6 Hz, 1H), 3.02- 2.97 (m, 1H), 2.94-2.89 (m, 1H), 2.62 (q, *J*=3.6 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 206.7, 163.5, 148.0, 138.5, 137.8, 136.2, 135.0, 130.4, 128.8, 128.3, 128.3, 127.6, 127.2, 126.9, 125.5, 124.8, 73.3, 67.8, 67.3, 63.0, 54.0, 49.7, 33.7; **HRMS** (ESI):*m/z* calcd for C₂₈H₃₀NO₃ [M+H]⁺ 428.2226; found: 428.2220.

4-(Benzyl(phenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone

(2.3s)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 72%. **¹H NMR** (400 MHz, CDCl₃): δ 7.61 (dd, *J*=5.6, 2.0 Hz, 1H), 7.36-7.27 (m, 7H), 7.24-7.22 (m, 3H), 7.19-7.12 (m, 2H), 6.80 (d, *J*=8.0 Hz, 2H), 6.76 (t, *J*=7.2 Hz, 1H), 6.31 (dd, *J*=6.0, 2.0 Hz, 1H), 5.52 (q, *J*=2.4 Hz, 1H), 4.58 (d, *J*=12.0 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 4.40 (d, *J*=17.2 Hz, 1H), 4.32 (d, *J*=17.2 Hz, 1H), 3.97 (dd, *J*=9.2, 3.2 Hz, 1H), 3.76 (dd, *J*=9.6, 3.6 Hz, 1H), 2.47 (q, *J*=3.2 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 206.1, 163.4, 148.6, 139.2, 137.9, 135.5, 129.4, 128.7, 128.5, 127.9, 127.8, 127.0, 126.2, 118.1, 113.9,

73.5, 66.9, 61.4, 51.4, 50.5; **HRMS** (ESI): m/z calcd for $C_{26}H_{26}NO_2$ $[M+H]^+$ 384.1964; found: 384.1961.

5-((Benzyloxy)methyl)-4-(methyl(phenyl)amino)cyclopent-2-enone

(2.3t)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 84%. **1H NMR** (400 MHz, $CDCl_3$): δ 7.61 (dd, $J=6.0, 2.0$ Hz, 1H), 7.36-7.26 (m, 5H), 7.24-7.18 (m, 2H), 6.86 - 6.83 (m, 2H), 6.79 - 6.75 (m, 1H), 6.35 (dd, $J=6.0, 2.0$ Hz, 1H), 5.39 (d, $J=2.0$ Hz, 1H), 4.56 (d, $J=12.0$, 1H), 4.45 (d, $J=12.0$, 1H), 3.97 (dd, $J=9.2, 3.2$ Hz, 1H), 3.66 (dd, $J=9.6, 3.6$ Hz, 1H), 2.70 (s, 3H), 2.43 (q, $J=3.2$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.3, 164.2, 149.5, 137.9, 135.2, 129.4, 128.4, 127.9, 127.8, 118.0, 113.7, 73.4, 66.9, 62.1, 50.0, 32.5; **HRMS** (ESI): m/z calcd for $C_{20}H_{22}NO_2$ $[M+H]^+$ 308.1651; found: 308.1645.

5-((Benzyloxy)methyl)-4-(cyclohexyl(phenyl)amino)cyclopent-2-enone

e (2.3u)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 66%. **¹H NMR** (400 MHz, CDCl₃): δ 7.75 (dd, *J*=5.6, 1.6 Hz, 1H), 7.40-7.26 (m, 5H), 7.15-7.11 (m, 2H), 6.79-6.75 (m, 3H), 6.30 (dd, *J*=6.0, 2.4 Hz, 1H), 4.92 (m, 1H), 4.59 (d, *J*=12.0 Hz, 1H), 4.45 (d, *J*=12.0 Hz, 1H), 3.94 (dd, *J*=9.2, 2.4 Hz, 1H), 3.63 (dd, *J*=9.2, 2.8 Hz, 1H), 3.43 (m, 1H), 2.75 (d, *J*=3.2 Hz, 1H), 1.91-1.76 (m, 5H), 1.50-1.31 (m, 5H); **¹³C NMR** (100 MHz, CDCl₃): δ 206.0, 169.3, 147.8, 138.0, 133.6, 129.0, 128.3, 128.0, 127.7, 119.2, 117.7, 73.5, 65.6, 59.4, 58.5, 49.9, 32.3, 31.7, 26.3, 26.0, 25.7; **HRMS** (ESI): *m/z* calcd for C₂₅H₃₀NO₂ [M+H]⁺ 376.2277; found: 376.2270.

5-((Benzyloxy)methyl)-4-(butyl(phenyl)amino)cyclopent-2-enone

(2.3v)

The title compound was prepared according to the general procedure A. The product was obtained as brown oil. Yield: 73%. **¹H NMR** (400 MHz, CDCl₃): δ 7.66 (dd, *J*=6.0, 2.4 Hz, 1H), 7.40-7.27 (m, 5H), 7.20 (dd, *J*=8.8, 7.2 Hz, 2H), 6.83 (d, *J*=8.4 Hz, 2H), 6.77 (dd, *J*=5.6, 2.0 Hz, 1H), 6.35 (dd, *J*=5.6, 2.0 Hz, 1H), 5.29 (d, *J*=2.4, 1H), 4.57 (d, *J*=12.0 Hz, 1H), 4.45 (d, *J*=12.0 Hz, 1H), 3.97 (dd, *J*=9.2, 3.2 Hz, 1H), 3.69 (dd, *J*=9.6, 3.6 Hz, 1H), 3.15 - 2.96 (m, 2H), 2.46 (q, *J*=3.6 Hz, 1H), 1.60-1.44 (m, 2H), 1.31 (m, 2H), 0.92 (t, *J*=7.6 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 206.4, 164.5, 148.2, 138.0, 134.9, 129.3, 128.4, 127.8, 127.7, 117.9, 114.5, 73.4, 66.9,

62.6, 51.2, 46.3, 31.0, 20.3, 13.9; **HRMS** (ESI): m/z calcd for $C_{23}H_{28}NO_2$ $[M+H]^+$ 350.2120; found: 350.2115.

4-(Benzyl(4-chlorophenyl)amino)-5-methylcyclopent-2-enone (2.3w)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 73%. **1H NMR** (500 MHz, $CDCl_3$): δ 7.55 (dd, $J=6.0, 2.0$ Hz, 1H), 7.34 -7.31 (m, 2H), 7.26-7.22 (m, 3H), 7.15-7.13 (m, 2H), 6.75-6.72 (m, 2H), 6.34 (dd, $J=5.5, 2.0$ Hz, 1H), 4.85 (d, $J=2.5$ Hz, 1H), 4.38 (d, $J=17.5$, 1H), 4.32 (d, $J=17.5$, 1H), 2.42 (qd, $J=7.0, 3.0$ Hz, 1H), 1.32 (d, $J=7.5$ Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 208.1, 161.2, 147.2, 138.5, 135.5, 129.2, 128.8, 127.2, 126.1, 123.3, 115.5, 67.5, 50.6, 45.7, 14.4; **HRMS** (ESI): m/z calcd for $C_{19}H_{19}ClNO$ $[M+H]^+$ 312.1155; found: 312.1150.

4-(Benzyl(4-methoxyphenyl)amino)-5-methylcyclopent-2-enone (2.3x)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 80%. **1H NMR** (500 MHz, $CDCl_3$): δ 7.62 (dd, $J=5.5, 2.0$ Hz, 1H), 7.31-7.26 (m, 4H), 7.25-7.23 (m, 1H), 6.86 - 6.78 (m, 4H),

6.28 (dd, $J=6.0, 2.0$ Hz, 1H), 4.66 (q, $J=2.5$ Hz, 1H), 4.34 (d, $J=16.5$, 1H), 4.29 (d, $J=16.0$, 1H), 3.74 (s, 3H), 2.43 (qd, $J=7.0, 3.0$ Hz, 1H), 1.28 (d, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 208.8, 162.2, 153.4, 142.7, 139.4, 134.9, 128.6, 127.0, 126.8, 118.2, 114.7, 69.2, 55.6, 52.1, 45.2, 14.4; HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 308.1651; found: 308.1644.

4-(Benzyl(4-chlorophenyl)amino)cyclopent-2-enone (2.3y)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 78%. ^1H NMR (400 MHz, CDCl_3): δ 7.56 (dd, $J=5.6, 2.4$ Hz, 1H), 7.34-7.26 (m, 2H), 7.25-7.22 (m, 3H), 7.16-7.13 (m, 2H), 6.72-6.68 (m, 2H), 6.30 (dd, $J=6.0, 2.0$ Hz, 1H), 5.21 (dd, $J=6.4, 2.4$ Hz, 1H), 4.36 (q, $J=17.6$ Hz, 2H), 2.90 (dd, $J=18.8, 6.4$ Hz, 1H), 2.30 (dd, $J=18.8, 2.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 206.3, 162.4, 147.4, 138.8, 136.4, 129.2, 128.9, 127.2, 126.1, 123.4, 115.3, 59.4, 50.7, 39.7; HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{17}\text{ClNO}$ $[\text{M}+\text{H}]^+$ 298.0999; found: 298.0991.

4-(Benzyl(4-methoxyphenyl)amino)cyclopent-2-enone (2.3z)

The title compound was prepared according to the general procedure A. The product was obtained as yellowish oil. Yield: 82%. **¹H NMR** (400 MHz, CDCl₃): δ 7.60 (dd, *J*=5.6, 2.4 Hz, 1H), 7.33-7.21 (m, 5 H), 6.79 (s, 4H), 6.24 (dd, *J*=5.6, 2.0 Hz, 1H), 5.08-5.03 (m, 1H), 4.30 (q, *J*=16.8 Hz, 2H), 3.74 (s, 3H), 2.80 (dd, *J*=18.8, 6.4 Hz, 1H), 2.34 (dd, *J*=18.8, 2.8 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 206.9, 163.6, 153.4, 142.8, 139.6, 135.9, 128.6, 127.0, 126.7, 117.7, 114.7, 60.6, 55.6, 52.2, 39.2; **HRMS** (ESI):*m/z* calcd for C₁₉H₂₀NO₂ [M+H]⁺ 294.1494; found: 294.1489.

1-(Hydroxymethyl)-9-methyl-3,3a,9,9a-tetrahydrobenzo[b]cyclopent a[e][1,4]oxazin-2(1H)-one (2.6)

The product was obtained as white solid. Yield: 49%. **¹H NMR** (400 MHz, CDCl₃): δ 6.96 (m, 1H), 6.85 (dd, *J*=8.0, 1.6 Hz, 1H), 6.71 (m, 2H), 4.56 (t, *J*=4.0 Hz, 1H), 4.25 (dd, *J*=11.2, 2.0 Hz, 1H), 4.06 (dd, *J*=10.4, 3.2 Hz, 1H), 3.86 (dd, *J*=11.2, 4.0 Hz, 1H), 3.13 (s, 3H), 2.77 (dd, *J*=19.2, 1.6 Hz, 1H), 2.52 (dd, *J*=19.2, 4.0 Hz, 1H), 2.40 (d, *J*=10.4 Hz, 1H), 1.97 (brs, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 215.2, 142.3, 132.7, 122.5, 117.6, 116.4, 111.8, 70.2, 59.1, 59.1, 52.7, 45.5, 38.5; **HRMS** (ESI):*m/z* calcd for C₁₃H₁₆NO₃ [M+H]⁺ 234.1130; found: 234.1124.

4-Benzyl-3-((benzyloxy)methyl)-7-methoxy-1,3a,4,8b-tetrahydrocyclopenta[b]indol-2(3H)-one (2.4a)

The product was obtained as yellowish oil. ^1H NMR (500 MHz, CDCl_3): δ = 7.34-7.21 (m, 10H), 6.73 (d, $J=2.5$, 1H), 6.61 (dd, $J=8.5$, 2.5 Hz, 1H), 6.33 (d, $J=8.5$, 1H), 4.45-4.37 (m, 2H), 4.28-4.21 (m, 3H), 3.89 (q, $J=8.5$, 1H), 3.73 (s, 3H), 3.69 (dd, $J=9.0$, 4.5 Hz, 1H), 3.48 (dd, $J=9.0$, 3.5 Hz, 1H), 2.77 (dd, $J=19.0$, 10.0 Hz, 1H), 2.55 (s, 1H), 2.44 (dd, $J=19.0$, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ = 218.7, 153.2, 145.7, 138.3, 137.9, 134.2, 128.6, 128.4, 127.7, 127.5, 127.2, 112.5, 111.7, 108.5, 73.4, 71.9, 69.6, 56.0, 54.0, 52.8, 44.4, 41.5; HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{28}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 414.2069; found: 414.2061.

4-Benzyl-3-((benzyloxy)methyl)-7-methoxy-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indol-2-ol (2.7a)

The title compound was prepared according to the general procedure B. The product was obtained as yellowish oil. Yield: 52%. ^1H NMR (500 MHz, CDCl_3): δ

7.32-7.21 (m, 10H), 6.68 (d, $J=2.0$, 1H), 6.57 (dd, $J=8.5$, 2.5 Hz, 1H), 6.30 (d, $J=8.5$, 1H), 4.42-4.37 (m, 2H), 4.30-4.22 (m, 2H), 4.08-4.05 (m, 1H), 3.79 (dd, $J=9.0$, 3.0 Hz, 1H), 3.70 (s, 3H), 3.62-3.57 (m, 1H), 3.31 (d, $J=6.5$ Hz, 2H), 2.89 (d, $J=6.0$ Hz, 1H), 2.42-2.34 (m, 2H), 1.84-1.79 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 153.2, 145.2, 138.7, 138.1, 134.6, 128.6, 128.5, 127.9, 127.6, 127.1, 112.4, 111.5, 108.2, 77.2, 73.2, 72.5, 71.5, 56.0, 53.7, 53.6, 43.7, 41.5; HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{30}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 416.2226; found: 416.2220.

4-Benzyl-7-methoxy-3-(2-nitroethyl)-1,3a,4,8b-tetrahydrocyclopenta[b]indol-2(3H)-one (2.7a')

The product was obtained as yellowish oil. ^1H NMR (500 MHz, CDCl_3): δ 7.29-7.19 (m, 5H), 6.68 (d, $J=2.5$, 1H), 6.60 (dd, $J=8.5$, 2.5 Hz, 1H), 6.37 (d, $J=8.5$, 1H), 4.38-4.31 (m, 2H), 4.30-4.19 (m, 2H), 3.86-3.78 (m, 2H), 3.66 (s, 3H), 2.74 (dd, $J=9.0$, 4.5 Hz, 1H), 3.48 (dd, $J=19.0$, 9.5 Hz, 1H), 2.45 (dd, $J=19.5$, 6.5 Hz, 1H), 2.36-2.34 (m, 1H), 2.04-2.01 (m, 1H), 1.98-1.93 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 217.6, 153.6, 145.3, 137.8, 133.6, 128.8, 127.9, 127.6, 112.9, 111.6, 109.1, 72.6, 56.0, 52.9, 49.4, 42.9, 40.6, 27.1; HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 367.1658; found: 367.1660.

4-Benzyl-3-((benzyloxy)methyl)-2-hydroxy-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indol-7-yl acetamide (2.7b)

The title compound was prepared according to the general procedure B. The product was obtained as yellowish oil. Yield: 42%. $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.34-7.21 (m, 11H), 6.98 (s, 1H), 6.57 (dd, $J=8.0, 2.0$ Hz, 1H), 6.32 (d, $J=8.5$, 1H), 4.46-4.42 (m, 2H), 4.41-4.29 (m, 2H), 4.09-4.06 (m, 1H), 3.85 (dd, $J=9.5, 3.5$ Hz, 1H), 3.67-3.61 (m, 1H), 3.38-3.36 (m, 2H), 2.64 (d, $J=5.5$ Hz, 1H), 2.45-2.41 (m, 1H), 2.40-2.35 (m, 1H), 2.12 (s, 3H), 1.84-1.79 (m, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 168.2, 148.1, 138.3, 138.0, 133.4, 128.6, 128.5, 128.5, 127.7, 127.6, 127.6, 127.1, 120.8, 118.3, 106.9, 76.9, 73.3, 71.6, 71.5, 53.9, 52.0, 43.3, 41.5, 24.3; **HRMS** (ESI): m/z calcd for $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_3[\text{M}+\text{H}]^+$ 443.5568; found: 443.5564.

4-Benzyl-3-((benzyloxy)methyl)-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indol-2-ol (2.7c)

The title compound was prepared according to the general procedure B. The product was obtained as light yellow oil. Yield: 40%. **¹H NMR** (400 MHz, CDCl₃): δ 7.38-7.27 (m, 10H), 7.11-7.04 (m, 2H), 6.71 (t, *J*=7.6, 1H), 6.44 (d, *J*=7.6 Hz, 1H), 4.47-4.36 (m, 4H), 4.13-4.10 (m, 1H), 3.89 (dd, *J*=9.6, 4.0 Hz, 1H), 3.71-3.68 (m, 1H), 3.45-3.41 (m, 2H), 2.65 (d, *J*=5.6 Hz, 1H), 2.52-2.45 (m, 1H), 2.41-2.39 (m, 1H), 1.89-1.86 (m, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 150.8, 138.5, 138.0, 132.7, 128.6, 128.4, 127.9, 127.7, 127.6, 127.1, 124.2, 117.7, 107.1, 77.1, 73.3, 71.8, 71.2, 53.9, 51.8, 43.3, 41.6; **HRMS** (ESI):*m/z* calcd for C₂₆H₂₈NO₂ [M+H]⁺ 386.2120; found: 386.2115.

6-Benzyl-7-((benzyloxy)methyl)-2,3,6,6a,7,8,9,9a-octahydrocyclopenta[b][1,4]dioxino[2,3-f]indol-8-ol (2.7f)

The title compound was prepared according to the general procedure B. The product was obtained as yellowish oil. Yield: 44%. **¹H NMR** (500 MHz, CDCl₃): δ 7.34-7.22 (m, 10H), 6.61 (s, 1H), 5.94 (s, 1H), 4.45-4.39 (m, 2H), 4.30-4.21 (m, 2H), 4.18-4.15 (m, 4H), 4.09-4.04 (m, 1H), 3.80 (dd, *J*=9.0, 3.0 Hz, 1H), 3.58 (q, *J*=9.0 Hz, 1H), 3.36-3.31 (m, 2H), 2.79 (d, *J*=6.5 Hz, 1H), 2.40-2.34 (m, 2H), 1.83-1.78 (m, 1H);

^{13}C NMR (125 MHz, CDCl_3): δ 145.6, 142.9, 138.5, 138.1, 135.8, 128.6, 128.4, 127.8, 127.7, 127.6, 127.1, 126.0, 113.3, 97.2, 77.0, 73.2, 72.4, 71.5, 64.7, 64.2, 53.7, 53.2, 43.1, 41.6; **HRMS** (ESI): m/z calcd for $\text{C}_{28}\text{H}_{30}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 444.2175; found: 444.2167.

4-Benzyl-3-((benzyloxy)methyl)-6,8-dimethyl-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indol-2-ol (2.7g)

The title compound was prepared according to the general procedure B. The product was obtained as yellowish oil. Yield: 38%. **^1H NMR** (500 MHz, CDCl_3): δ 7.34-7.23 (m, 10H), 6.33 (s, 1H), 6.10 (s, 1H), 4.45-4.39 (m, 2H), 4.35 (s, 2H), 4.09-4.05 (m, 1H), 3.81 (dd, $J=9.5, 4.0$ Hz, 1H), 3.61 (q, $J=9.0$ Hz, 1H), 3.41 (m, 2H), 2.76 (d, $J=5.5$ Hz, 1H), 2.51-2.46 (m, 1H), 2.36-2.31 (m, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 1.78-1.72 (m, 1H); **^{13}C NMR** (125 MHz, CDCl_3): δ 151.1, 138.7, 138.0, 137.9, 133.5, 128.5, 128.4, 128.1, 127.7, 127.6, 127.6, 127.0, 120.0, 105.6, 77.1, 73.2, 71.8, 71.6, 53.7, 52.2, 42.0, 40.4, 21.6, 18.5; **HRMS** (ESI): m/z calcd for $\text{C}_{28}\text{H}_{32}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 414.2433; found: 414.2428.

3-((Benzyloxy)methyl)-4-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indol-2-ol (2.7h)

The title compound was prepared according to the general procedure B. The product was obtained as yellowish oil. Yield: 55%. **¹H NMR** (500 MHz, CDCl₃): δ 7.38 - 7.29 (m, 5H), 7.11-7.06 (m, 2H), 6.71 (t, 1H), 6.46 (d, *J*=7.5 Hz, 1H), 4.59- 4.54 (m, 2H), 4.15-4.12 (m, 1H), 3.69 (dd, *J*=9.0, 2.5 Hz, 1H), 3.62-3.59 (m, 1H), 3.57-3.47 (m, 2H), 2.98 (s, 1H), 2.76 (s, 3H), 2.49 (brs, 1H), 2.45-2.39 (m, 1H), 1.83-1.78 (m, 1H); **¹³C NMR** (125 MHz, CDCl₃): δ 151.3, 138.1, 133.3, 128.5, 127.8, 127.8, 127.6, 124.1, 118.2, 107.2, 77.5, 74.5, 73.3, 71.5, 52.9, 43.4, 41.5, 34.3; **HRMS** (ESI):*m/z* calcd for C₂₀H₂₄NO₂ [M+H]⁺ 310.1807; found: 310.1801.

(2S,3S,4R,6S)-3-(benzyloxy)-4-((benzyloxy)methyl)-8-methoxy-2,3,4,6-tetrahydro-1H-2,6-methanobenzo[c][1,5]oxazocine (2.10)

The product was obtained as brown oil. **¹H NMR** (500 MHz, CDCl₃): δ 7.34-7.22 (m, 10H), 6.75 (dd, *J*=8.5, 3.0 Hz, 1H), 6.70 (d, *J*=3.0, 1H), 6.55 (d, *J*=8.5, 1H), 4.72 (brs, 1H), 4.63 (d, *J*=12.5, 1H), 4.56 (d, *J*=11.5, 1H), 4.46 (d, *J*=7.0, 1H), 4.44 (d,

$J=6.0$, 1H), 3.73 (s, 3H), 3.71 (brs, 1H), 3.66-3.63 (m, 2H), 3.54 (dd, $J=6.0$, 2.0 Hz, 1H), 3.40 (dd, $J=3.5$, 2.0 Hz, 1H), 3.38 (dd, $J=3.5$, 2.5 Hz, 1H), 2.20 (dt, $J=13.5$, 3.0 Hz, 1H), 2.01 (ddd, $J=13.5$, 4.5, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 151.8, 139.8, 138.3, 138.1, 128.5, 128.3, 128.0, 127.9, 127.9, 127.6, 120.8, 116.6, 115.1, 114.7, 77.2, 73.5, 71.7, 70.0, 69.2, 68.6, 55.8, 46.2, 28.3; HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{30}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 432.2175; found: 432.2169.

(4R,5S,6R)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-ol (2.11)

The product was obtained as white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.37-7.28 (m, 13H), 7.21-7.20 (m, 2H), 5.40 (s, 1H), 4.93 (d, $J=11.5$ Hz, 1H), 4.70-4.51 (m, 6H), 4.09-4.04 (m, 2H), 3.73-3.61 (m, 2H), 3.52-3.46 (m, 1H), 3.35 (s, 1H), 2.31 (d, $J=12.5$, 5.0 Hz, 1H), 1.72 (dt, $J=12.5$, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 138.7, 138.5, 137.9, 128.4, 128.4, 128.4, 128.1, 128.0, 127.8, 127.7, 127.7, 92.1, 78.6, 75.0, 73.5, 71.8, 70.7, 69.4, 35.6; HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{31}\text{O}_5$ $[\text{M}+\text{H}]^+$ 435.2171; found: 435.2164.

(4S,5R,Z)-4,6-bis(benzyloxy)-5-hydroxyhex-2-enal (2.12)

The title compound was prepared according to the ref 34a. The product was obtained as colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 9.61 (d, *J*=7.6 Hz, 1H), 7.38-7.29 (m, 10H), 6.91 (dd, *J*=15.6, 6.0 Hz, 1H), 6.37 (dd, *J*=16.0, 8.0 Hz, 1H), 4.63 (d, *J*=11.2 Hz, 1H), 4.52 (s, 2H), 4.43 (d, *J*=11.2 Hz, 1H), 4.21 (t, *J*=5.6, 1H), 3.95-3.90 (m, 1H), 3.64-3.56 (m, 2H), 2.51 (d, *J*=5.6 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ 193.3, 153.7, 137.5, 137.2, 133.9, 128.6, 128.5, 128.4, 128.1, 128.0, 128.0, 127.9, 78.5, 73.6, 72.3, 72.0, 70.1; **HRMS** (ESI):*m/z* calcd for C₂₀H₂₃O₄ [M+H]⁺ 327.1596; found: 327.1591.

8-Methoxy-2-methyl-4-phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-3-one (2.8a)

The title compound was prepared according to the general procedure C. The product was obtained as colorless solid. **¹H NMR** (400 MHz, CDCl₃): δ 7.37-7.24 (m, 5H), 6.82 (d, *J*=2.4 Hz, 1H), 6.65 (dd, *J*=8.8, 2.8 Hz, 1H), 6.52 (d, *J*=8.4 Hz, 1H), 4.46 (d, *J*=4.8 Hz, 1H), 4.09-4.07 (m, 1H), 3.77 (s, 3H), 3.09 (dd, *J*=6.4, 4.8 Hz, 1H), 1.81 (t,

$J=1.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 208.5, 159.4, 153.1, 142.8, 139.6, 138.0, 128.6, 127.5, 127.3, 123.1, 116.6, 113.9, 113.2, 57.2, 55.7, 52.8, 40.1, 10.2; HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 306.1494; found: 306.1496.

2-Methyl-4-phenyl-3a,4,5,8,9,11b-hexahydro-3H-cyclopenta[c][1,4]dioxino[2,3-g]quinolin-3-one (2.8b)

The title compound was prepared according to the general procedure C. The product was obtained as colorless solid. ^1H NMR (400 MHz, CDCl_3): δ 7.31-7.22 (m, 5H), 6.73 (s, 1H), 6.09 (s, 1H), 4.46 (d, $J=4.8$ Hz, 1H), 4.21-4.17 (m, 4H), 4.01-4.00 (m, 1H), 3.77 (s, 1H), 3.05 (dd, $J=6.8, 4.8$ Hz, 1H), 1.81 (t, $J=1.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 208.6, 159.7, 142.8, 139.2, 138.4, 128.6, 127.4, 127.2, 116.4, 115.2, 103.9, 64.7, 64.3, 56.9, 52.7, 39.2, 10.2; HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 334.1443; found: 334.1446.

Deuterium-labeled-2-methyl-4-phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-3-one (2.8c)

The title compound was prepared according to the general procedure C. The product was obtained as colorless solid. **¹H NMR** (400 MHz, CDCl₃): δ 7.40-7.12 (m, 6H), 7.05 (t, *J*=5.2 Hz, 1H), 6.8 (t, *J*=5.2 Hz, 1H), 6.60 (d, *J*=8.0 Hz, 1H), 4.01-4.00 (m, 1H), 3.1 (d, *J*=5.6 Hz, 1H), 1.81 (t, *J*=2.0 Hz, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ 208.4, 160.7, 143.8, 141.2, 133.4, 128.6, 127.4, 127.2, 115.4, 114.2, 105.9, 77.5, 74.6, 71.3, 70.0; **HRMS** (ESI):*m/z* calcd for C₁₉H₁₆D₂NO [M+H]⁺ 278.1508; found: 278.1510.

X-Ray data for 4-(benzyl(4-iodophenyl)amino)-5-((benzyloxy)methyl)cyclopent-2-enone 2.3d

Crystal data and structure refinement for 2.3d.

Identification code	2.3d
Empirical formula	C ₂₆ H ₂₄ INO ₂
Formula weight	509.36
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	P2(1)/c
Unit cell dimensions	$a = 11.4974(4) \text{ \AA}$ $= 90^\circ$ $b = 10.8284(4) \text{ \AA}$ $= 93.080(2)^\circ$ $c = 17.7117(6) \text{ \AA}$ $= 90^\circ$
Volume	$2201.89(13) \text{ \AA}^3$
Z	4
Density (calculated)	1.537 Mg/m^3
Absorption coefficient	1.477 mm^{-1}
F(000)	1024
Crystal size	$0.40 \times 0.30 \times 0.24 \text{ mm}^3$
Theta range for data collection	2.21 to 29.75°
Index ranges	$-15 \leq h \leq 15$, $-15 \leq k \leq 13$, $-23 \leq l \leq 24$
Reflections collected	33406
Independent reflections	6183 [R(int) = 0.0356]
Completeness to theta = 29.75°	98.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7182 and 0.5896
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6183 / 0 / 271
Goodness-of-fit on F^2	1.051
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0278$, $wR2 = 0.0647$
R indices (all data)	$R1 = 0.0370$, $wR2 = 0.0688$

Largest diff. peak and hole 1.185 and -0.551 e.Å⁻³

X-Ray data for 1-(hydroxymethyl)-9-methyl-3,3a,9,9a-tetrahydrobenzo[b]cyclopenta[e][1,4] oxazin-2(1H)-one 2.6

Crystal data and structure refinement for 2.6

Identification code	2.6	
Empirical formula	C ₁₃ H ₁₅ NO ₃	
Formula weight	233.26	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 17.2388(8) Å	= 90 °
	b = 9.0530(5) Å	= 96.162(3) °
	c = 7.3181(3) Å	= 90 °
Volume	1135.49(9) Å ³	
Z	4	
Density (calculated)	1.364 Mg/m ³	
Absorption coefficient	0.097 mm ⁻¹	

F(000)	496
Crystal size	0.40 x 0.38 x 0.22 mm ³
Theta range for data collection	2.54 to 29.11 °
Index ranges	-23<= <i>h</i> <=23, -12<= <i>k</i> <=11, -8<= <i>l</i> <=9
Reflections collected	10949
Independent reflections	3029 [R(int) = 0.0328]
Completeness to theta = 29.11 °	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9789 and 0.9621
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3029 / 0 / 156
Goodness-of-fit on F ²	1.045
Final R indices [<i>I</i> >2σ(<i>I</i>)]	R1 = 0.0427, wR2 = 0.1104
R indices (all data)	R1 = 0.0535, wR2 = 0.1180
Largest diff. peak and hole	0.448 and -0.194 e.Å ⁻³

X-Ray data for 8-methoxy-2-methyl-4-phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-3-one 2.8a

Crystal data and structure refinement for 2.8a.

Identification code	2.8a	
Empirical formula	C ₂₀ H ₁₉ NO ₂	
Formula weight	305.36	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.3067(3) Å	= 90 °
	b = 8.0232(3) Å	= 99.909(2) °
	c = 23.4518(9) Å	= 90 °
Volume	1539.66(10) Å ³	
Z	4	
Density (calculated)	1.317 Mg/m ³	
Absorption coefficient	0.085 mm ⁻¹	
F(000)	648	
Crystal size	0.20 x 0.16 x 0.14 mm ³	
Theta range for data collection	2.49 to 27.90 °	
Index ranges	-10 ≤ h ≤ 9, -10 ≤ k ≤ 10, -30 ≤ l ≤ 30	
Reflections collected	16405	
Independent reflections	3673 [R(int) = 0.0474]	
Completeness to theta = 27.90 °	99.6 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9882 and 0.9832
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3673 / 0 / 213
Goodness-of-fit on F^2	1.095
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0514$, $wR2 = 0.1432$
R indices (all data)	$R1 = 0.0698$, $wR2 = 0.1543$
Largest diff. peak and hole	0.358 and $-0.237 \text{ e.}\text{\AA}^{-3}$

**X-Ray data for 2-methyl-4-phenyl-3a, 4, 5, 8, 9, 11b-hexahydro-3H-cyclopenta[c]
[1,4]dioxino [2,3-g]quinolin-3-one 2.8b**

Crystal data and structure refinement for 2.8b.

Identification code	2.8b
Empirical formula	$\text{C}_{21}\text{H}_{19}\text{NO}_3$
Formula weight	333.37
Temperature	103(2) K
Wavelength	$0.71073 \text{ \AA}$

Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	$a = 8.0178(17) \text{ \AA}$ $= 95.780(17)^\circ$ $b = 8.915(2) \text{ \AA}$ $= 108.076(15)^\circ$ $c = 12.540(3) \text{ \AA}$ $= 90.264(16)^\circ$
Volume	$847.2(3) \text{ \AA}^3$
Z	2
Density (calculated)	1.307 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	352
Crystal size	$0.40 \times 0.30 \times 0.08 \text{ mm}^3$
Theta range for data collection	$1.72 \text{ to } 28.31^\circ$
Index ranges	$-10 \leq h \leq 10, -11 \leq k \leq 11, 0 \leq l \leq 16$
Reflections collected	4090
Independent reflections	4090 [R(int) = 0.0000]
Completeness to theta = 25.00°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9930 and 0.9659
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4090 / 0 / 231
Goodness-of-fit on F^2	1.000
Final R indices [I > 2sigma(I)]	R1 = 0.0968, wR2 = 0.2349

R indices (all data)

$R1 = 0.1651$, $wR2 = 0.2751$

Largest diff. peak and hole

0.405 and -0.410 e.Å⁻³

CHAPTER 3

Synthesis of Sialic Acid from Glycal

3.1 Background of sialic acids

Sialic acids are *N*- or *O*-substituted derivatives of naturally occurring 2-keto-3-deoxynononic acids, with a nine-carbon backbone. There are over 40 different sialic acid derivatives in nature.³⁶ The most ubiquitous member of the neuraminic acid family is *N*-acetylneuraminic acid (Neu5Ac), which is used as a synonym for sialic acid. The other two important sialic acids are *N*-glycolylneuraminic acid (Neu5Gc) and 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN).³⁷

Figure 3.1 Important derivatives of sialic acids.

Sialic acids are the most abundant terminal sugar on mammalian glycoconjugates and play pivotal roles in many significant biological events, including cell-cell recognition. In bacterial systems, Neu5Ac is biosynthesized by an aldolase enzyme. This enzyme uses a mannose derivative as a substrate, inserting three carbons from pyruvate into the resulting sialic acid structure (Scheme 3.1).³⁸

The realization of the vital roles sialic acids play in various disease states and physiological processes has promoted the discovery of anti-influenza drugs such as Zanamivir³⁹ and Oseltamivir⁴⁰. Moreover, development of a more practical and efficient synthetic method to sialic acids remains urgent. Since the first reported synthesis of sialic acid (Neu5Ac) by Cornforth *et al* in 1958,⁴¹ there has been an accompanying effort to develop effective syntheses of sialic acid as well as their analogues.⁴²

The first total synthesis of Neu5Ac from non-carbohydrate precursors was reported by Danishefsky *et al.* in 1988.^{42c} However, it's not cost effective because the synthetic route is lengthy and the overall yield is low (Scheme 3.2).

Most of the works for the syntheses of Neu5Ac has focused on the enzymatic or chemical elongation of D-mannose or its derivatives.^{42d-j}

The application of indium-mediated allylation strategy for the synthesis of the sialic acid analogue has been utilized mainly by Whitesides and Chan's group.^{42d,e}

Chan's group further found that the carboxylic acid function is compatible with the indium-mediated reaction condition. They developed an indium-mediated coupling reaction of acrylic acid with D-mannose in aqueous media.^{42r} The reaction has been applied to the syntheses of Neu5Ac and KDN (Scheme 3.3). However, this method involved a non-selective reaction.

Scheme 3.3 Indium-mediated allylation strategy for the synthesis of the sialic acid analogue.

Therefore, a great demand in this area is the development of an efficient method for the synthesis of sialic acids and analogues with a high degree of flexibility in structural and stereochemical alteration. Working toward this goal, Wong's group provided a efficient method for the synthesis of Neu5Ac from D-galactose (Scheme 3.4).^{42k} A key element of this method is a stereoselective Petasis coupling reaction, 1,3-dipolar cycloaddition, and base-catalyzed β elimination. Neu5Ac was successfully obtained with an overall yield of 29 %.

Scheme 3.4 Three-step synthesis of salicylic acid.

In addition, approaches toward structurally modified Neu5Ac derivatives usually start with Neu5Ac itself. However, these approaches need the expensive Neu5Ac as starting material.

This situation prompted Sugai's group to develop an expeditious route toward Neu5Ac derivative with allylic substituent at C-7 (Scheme 3.5).^{42t} Carbamate and alkyl substituents were first introduced at C-3 and at C-4 position of D-glucal respectively. Then a rhodium-nitrene complex was generated and simultaneously delivered to the 1,2- π -system of the glucal, leading to a putative aziridine. The aziridine ring-opening occurred in a regioselective manner at the C-1 position, using *tert*-butyl alcohol as a nucleophile. Subsequent deprotection under mild conditions furnished the ManNAc derivative, which was the substrate for aldolase-catalyzed reactions. Finally, sialic derivative with allylic substituent at C-7 hydroxyl group was successfully obtained with an overall yield of 36 %.

Scheme 3.5 Chemo-enzymatic route towards the synthesis of sialic derivative with alkyl group at C-7 hydroxyl group.

Our group has developed a methodology for stereoselective preparation of 2-amino-2-deoxy sugars by application of rhodium-catalyzed nitrene insertion to glycals.^{9,10} Specifically, the diastereofacial preference of the nitrene insertion is controlled by installation of the sulfamate moiety on C4 or C6 position. Based on this methodology, we further develop a protocol for C-aminoglycosylation by a tandem rhodium-catalyzed nitrene insertion and Barbier allylation. This reaction proceeded selectively to [1,2,3]-oxathiazocane-2,2-dioxide **3.5** in a single step (Scheme 3.6).

Scheme 3.6 One-pot, rhodium-catalyzed nitrene insertion and indium-mediated allylation.

We envisage that the values of this protocol would become enhanced significantly if this 8-membered oxathiazepane product **3.5** could be used for the library synthesis of biologically active sialic acids. To obtain sialic acids, the sulfamoyloxy moiety of oxathiazocane **3.5** can be displaced by a nucleophile to give an acyclic methylene compound. Subsequent ozonolysis and saponification will allow the pyranose ring of sialic acid to re-form (Scheme 3.7).

Scheme 3.7 Proposed strategies for sialic acid synthesis.

3.2 Results and discussion

Our initial investigation was focused on searching the suitable conditions to displace the sulfamoyloxy group of oxathiazepane **3.5**. Unfortunately, all efforts to achieve this transformation failed (Scheme 3.8).

Scheme 3.8 Attempts to cleave the sulfamoyloxy moiety oxathiazepane **3.5**.

Upon treatment with aqueous HCl, the desired ring-opening product could not be observed by LCMS. Instead, a butyrolactone product **3.6** was isolated in 95% yield. Attempt to remove the sulfamoyloxy functionality under basic condition also proved unproductive. In addition, treatment of oxathiazepane **3.5** with sodium acetate (NaOAc) in hot DMF gave several unidentified products.

We reasoned that the electrophilic reactivity of the 8-member oxathiazocane **3.5** can be improved by introducing an electron-withdrawing group to the nitrogen atom.⁴³ Thus, oxathiazocane **3.5** was treated with Ac_2O in a mixture of CH_2Cl_2 and Et_3N to give reactive triacetate **3.7** which could be observed by LCMS (peak at 790,

$M^+ + Et_3N$). Attempts to purify the reactive triacetate **3.7** by column chromatography on silica were unsuccessful due to rapid degradation. Accordingly, after removing solvents, the crude product was treated with diluted H_2SO_4 in THF at room temperature overnight. Cleavage of the sulfamoyloxy moiety was achieved, and the resulting crude product **3.8** was treated with Ac_2O to afford a stable tetraacetate **3.9**. However, attempt to directly convert the triacetate **3.5** to tetraacetate **3.9** using NaOAc as nucleophile was not successful (Scheme 3.9).

Scheme 3.9 Cleavage of the sulfamoyloxy moiety.

Benzoyl (Bz) group was also employed to protect oxathiazocane **3.5**. Interestingly, the only isolated product was a chlorinated product **3.11** resulting from ring opening of sulfamoyloxy moiety by Cl^- (Scheme 3.10).

Scheme 3.10 Cleavage of the sulfamoyloxy moiety by Cl^- .

With stable tetraacetate **3.9** in hand, the focus shifted to the preparation of sialic acid (Neu5Ac). To achieve this transformation, deprotection of the Ac and Bz groups and ozonolysis of the methylene group would be required. Upon treatment with NaOMe in methanol, hydrolysis product of tetraacetate could be observed by LCMS, and then the resulted crude product was subjected to ozonolysis condition. The corresponding ozonolysis product was purified by flash column chromatography to give methyl ester product **3.12** as viscous oil (Scheme 3.11). However, if tetraacetate **3.9** was subjected to ozonolysis first and followed by saponification, a mixture of unidentified polar products was obtained instead.

Scheme 3.11 Attempts to convert tetraacetate **3.9** to sialic acid.

Methyl ester product **3.12** was treated with 1 equiv. LiOH in aqueous MeOH to form sialic acid **3.13** which could be purified by ion-exchange chromatography (Dowex 1X8-100 resin, formate form). The analytical data obtained for sialic acid **3.13** was consistent with previous literature reported.^{42b} In addition, the conversion of sialic acid **3.13** into penta-acetyl-methyl ester **3.14** was achieved by acetylation and methylation in a simple operation. Alternatively, methyl ester product **3.12** could be converted to **3.14** by a single transformation (Scheme 3.12).

Scheme 3.12 Synthesis of sialic acid **3.13** and its derivative **3.14**.

3.3 Conclusion

In the present study we have developed a novel, efficient method for the synthesis of sialic acid and derivatives through three one-pot syntheses from glycal **3.1** bearing sulfamate moiety on C6 position. Neu5Ac was successfully obtained with an overall yield of 40 %.

Scheme 3.9 Three one-pot syntheses of sialic acid.

The uses of other nucleophiles to replace the sulfamoyloxy moiety or reaction starting from different glycals are still under investigation in our laboratory. This method is expected to allow a rapid synthesis of common and uncommon sialic acids.

3.4 Experimental Section

3.4.1 General considerations

General methods: All air and moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware unless otherwise indicated. All anhydrous solvents were distilled prior to use. Commercial reagents were used without purification. 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). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using base solution of potassium permanganate. Technical grade solvents were used for chromatography and were distilled prior to use. IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 300 MHz Bruker ACF 300, 400 MHz Bruker DPX 400, 500 MHz Bruker AMX 500, and 400 MHz NMR spectrometers. The residual solvent signals were taken as the reference (7.26 ppm for ^1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in CDCl_3 , 4.79 ppm for ^1H NMR spectra in D_2O). Chemical shift is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal. High Resolution Mass (HRMS) spectra were obtained using Finnigan MAT95XP GC/HRMS (Thermo Electron Corporation).

3.4.2 General procedure and characterization data for the isolated products

General procedure for rhodium catalyzed nitrene insertion and indium-mediated allylation.

A mixture of sulfamate ester **3.1** (30 mg, 0.0692 mmol), 5 mole percent of $\text{Rh}_2(\text{tfacam})_4$ (2.5 mg, 0.00383 mmol), PhIO (22 mg, 0.0999 mmol, 1.5equiv), MgO (14 mg, 0.347 mmol, 5 equiv) in DCM (3 mL for 30 mg of sulfamate **3.1**) was stirred at RT for 1 h under argon atmosphere. In another round bottom flask, suspension of indium powder (16 mg, 0.138 mmol, 2 equiv) and potassium iodide (12 mg, 0.0722 mmol, 1 equiv) were refluxed in THF (2 mL for 30 mg of sulfamate **3.1**) and allyl bromide (39 mg, 0.205 mmol, 3 equiv) was added. Refluxing was continued for 15 min to form clear solution and cooled to room temperature. Indium reagent at room temperature was added to the above mixture and suspension was stirred for 1 h. The resulted mixture was filtered through the silica gel and then washed with CH_2Cl_2 and combined filtrate was concentrated under reduced pressure. The crude product was

purified by silica gel column chromatography (eluent: 30~40 % ethyl acetate in hexane) to afford [1,2,3]-oxathiazocane-2,2-dioxide **3.5** (36 mg, 92%).

$[\alpha]_D^{23} = -8.8$ (*c* 0.3, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.87 (d, $J = 7.5$ Hz, 2H), 7.83 (d, $J = 7.5$ Hz, 2H), 7.40–7.48 (m, 2H), 7.23–7.32 (m, 4H), 6.24 (s, 1H), 6.14 (t, $J = 9.7$ Hz, 1H), 5.66 (d, $J = 9.0$ Hz, 1H), 5.73 (s, 1H), 4.63 (dd, $J = 13.5, 1.6$ Hz, 1H), 4.57 (dd, $J = 13.5, 4.2$ Hz, 1H), 4.49 (m, 1H), 4.01 (q, $J = 7.2$, 3H), 3.92 (dd, $J = 7.8, 4.4$ Hz, 1H), 3.74 (d, $J = 10.3$ Hz, 1H), 3.53 (br s, 1H, OH), 2.73 (dd, $J = 14.1, 8.2$ Hz, 1H), 2.64 (dd, $J = 14.1, 3.7$ Hz, 1H), 1.11 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 167.7 (s), 166.2 (s), 166.0 (s), 136.5 (s), 133.7 (s), 133.5 (s), 129.8 (2d), 129.7 (2d), 129.2 (t), 128.6 (d), 128.5 (d), 128.4 (2d), 128.4 (2d), 77.2 (d), 75.8 (d), 72.9 (t), 72.6 (d), 68.6 (d), 61.1 (t), 57.6 (d), 36.9 (t), 13.9 (q); **IR** (CHCl_3): 3439, 3420, 3018, 1717, 1634, 1450, 1373, 1115, 1096 cm^{-1} ; **HRMS** (ESI) m/z calcd for: $\text{C}_{26}\text{H}_{30}\text{NO}_{11}\text{S}$; 564.1540 $[\text{M}+\text{H}]^+$; found: 564.1533.

(2R,3R,4R,5R)-2-hydroxy-1-(4-methylene-5-oxotetrahydrofuran-2-yl)-3,4-di-O-benzoyl-[1,2]thiazepane-1,1-dioxide (3.6)

Starting material **3.5** (4 mg, 0.0071 mmol) was dissolved in a mixture solution 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 5 % NaHCO₃, and brine, dried over Na₂SO₄. Solvents were removed under vacuum to give a crude product. The crude product was purified by silica gel column chromatography to afford **3.6** (3.7 mg, 95 %).

¹H NMR (CDCl₃, 400 MHz): δ 8.09 (d, J = 7.1 Hz, 2H), 8.03 (d, J = 7.1 Hz, 2H), 7.58 (t, J = 7.3 Hz, 2H), 7.48-7.43 (m, 4H), 5.95 (ddd, J = 17.5, 10.7, 1.0 Hz, 1H), 5.55 (dd, J = 4.5, 1.5 Hz, 1H), 5.27 (dd, J = 4.8, 1.5 Hz, 1H), 5.15 (d, J = 3.2 Hz, 1H), 5.05 (dd, J = 17.5, 1.1 Hz, 1H), 5.00 (dd, J = 10.7, 1.1 Hz, 1H), 4.60 (q, J = 11.5 Hz, 2H), 3.64 (q, J = 6.2 Hz, 1H), 3.50 (dd, J = 4.8, 3.2 Hz, 1H), 2.21 (br s, 1H), 1.95 (s, 3H), 1.33 (s, 9H), 1.14 (s, 3H), 1.10 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz): δ 170.1, 166.0, 165.1, 133.7, 133.6, 133.5, 129.7, 129.6, 128.5, 128.4, 128.3, 123.3, 77.3, 75.9, 73.0, 72.7, 69.3, 56.9, 28.9; **HRMS** (ESI): m/z : calcd for C₂₄H₂₃NO₁₀SNa: 540.0940 [M+Na]⁺; found: 540.0936.

(2R,3S,4R,5R,6S)-5-acetamido-3,4-bis(benzoyloxy)-8-(ethoxycarbonyl)non-8-ene-1,2,6-triyltriacetate 3.9

A solution of compound **3.5** (140 mg, 0.261 mmol) in $\text{CH}_2\text{Cl}_2\text{:Et}_3\text{N}$ (1.5 mL, 1:1) was cooled to 0 °C and treated with Ac_2O (0.15 mL, 1.507 mmol). The progress of reaction was monitored by LCMS showing peak at 790 ($\text{M}^+ + \text{Et}_3\text{N}$). Solvents were removed under reduced pressure. Crude product was dissolved in water (0.1 mL) and THF (2 mL), cooled to 0 °C. conc. H_2SO_4 (0.2 mL) was added and the reaction mixture was kept stirring at RT for overnight. Reaction mixture was quenched by sat. NaHCO_3 and extracted with EA, then the organic layer was dried with Na_2SO_4 , concentrated under reduced pressure. Crude product was further used without purification. The crude product was dissolved in CH_2Cl_2 (1.5 mL) and Et_3N (0.5 mL), followed by addition of Ac_2O (0.1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After completion, the reaction mixture was diluted with 0.2 N HCl and extracted in ethyl acetate. The organic layer was washed with sat. NaHCO_3 , brine, and dried over Na_2SO_4 . Solvents were removed under vacuum. Purification was done by silica gel column chromatography to give tetra-acetate derivative **3.9** (53 mg, 74% yield) as colorless viscous oil.

$[\alpha]_{\text{D}}^{23} = +3.58$ (c 0.6, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.99 – 8.06 (m, 4H), 7.54 – 7.59 (m, 2H), 7.42 – 7.48 (m, 4H), 6.10 (dd, $J = 5.0, 1.3$ Hz, 1H), 5.84 (d, $J = 10.2$ Hz, 1H), 5.71 (dd, $J = 6.7, 2.6$ Hz, 1H), 5.60 (dd, $J = 8.8, 2.7$ Hz, 1H), 5.48 (s, 1H), 5.24 – 5.32 (m, 2H), 4.68 (ddd, $J = 10.3, 8.7, 1.5$ Hz, 1H), 4.43 (dd, $J = 12.4, 3.7$ Hz, 1H), 3.99 – 4.06 (m, 2H), 2.55 (dd, $J = 13.8, 4.6$ Hz, 1H), 2.40 (dd, $J = 13.9, 8.5$ Hz, 1H), 2.06 (s, 1H), 1.99 (s, 1H), 1.98 (s, 3H), 1.95 (s, 3H), 1.08 (t, $J =$

7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 170.7, 169.8, 169.7, 169.4, 166.2, 165.4, 165.3, 135.9, 133.5, 133.4, 129.8, 129.3, 129.1, 128.6, 128.5, 128.1, 70.0, 69.6, 69.5, 69.3, 62.0, 60.7, 50.3, 35.1, 23.2, 20.8, 20.7, 20.6, 13.8; IR (CHCl_3): ν 3431, 3018, 1717, 1603, 1452, 1373, 1277, 1215, 1180, 1096 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{34}\text{H}_{40}\text{NO}_{13}$: 670.2500 $[\text{M}+\text{H}]^+$; found: 670.2504.

(2S,3S,4R,5R,6S)-5-benzamido-1-chloro-8-(ethoxycarbonyl)non-8-ene-2,3,4,6-tetrayl tetrabenzoate 3.11

A solution of compound **3.5** (14 mg, 0.026 mmol) in $\text{CH}_2\text{Cl}_2:\text{Et}_3\text{N}$ (1.5 mL, 1:1) was cooled to 0 $^\circ\text{C}$ and treated with BzCl (0.16 mL, 0.157 mmol). The progress of reaction was monitored by LCMS. Reaction mixture was quenched with sat. NaHCO_3 and extracted with ethyl acetate, then the organic layer was dried over Na_2SO_4 , concentrated under reduced pressure. Purification was done by silica gel column chromatography to give tetra-acetate derivative **3.11** (15 mg, 73% yield) as colorless viscous oil.

^1H NMR (CDCl_3 , 400 MHz): δ 8.21 – 8.01 (m, 11H), 7.84 – 7.53 (m, 15H), 6.21 (dd, J = 5.1, 1.2 Hz, 1H), 5.82 (d, J = 10.1 Hz, 1H), 5.24 – 5.12 (m, 2H), 4.62 (ddd, J = 10.1, 8.4, 1.2 Hz, 1H), 4.63 (dd, J = 12.4, 3.2 Hz, 1H), 3.90 – 4.02 (m, 2H),

2.58 (dd, $J = 13.3, 4.2$ Hz, 1H), 2.37 (dd, $J = 13.2, 8.4$ Hz, 1H), 1.09 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 171.7, 169.7, 169.6, 169.3, 166.1, 165.3, 165.1, 135.2, 133.1, 132.4, 129.9, 129.1, 129.1, 128.5, 128.3, 128.0, 71.0, 69.6, 69.4, 69.1, 62.1, 60.1, 55.3, 34.1, 4.1; **IR** (CHCl_3): ν 3425, 3009, 1719, 1602, 1447, 1367, 1277 cm^{-1} ; **HRMS** (ESI): m/z : calcd for $\text{C}_{47}\text{H}_{43}\text{ClNO}_{11}$: 832.2525 $[\text{M}+\text{H}]^+$; found: 832.2532.

Methyl ester product 3.12

A cool solution of tetra-acetate **3.9** (120 mg, 0.179 mmol) in methanol (1 mL) was added NaOMe (3 mg, 0.054 mmol), and stirred at room temperature for 12 h. The progress of reaction was monitored by silica gel TLC (MeOH : CH_2Cl_2 (1:4)). Ozone was bubbled through reaction mixture at -78°C for 10 min followed by purging of oxygen for 5 min and 0.5 mL of Me_2S was added. Solvent was removed under vacuum. The resulted residue was purified by silica gel column chromatography to give methyl ester derivative **3.12** as colorless viscous oil.

^1H NMR (MeOD, 400 MHz): δ 4.03 (dd, $J = 10.3, 4.6$ Hz, 1H), 3.99 (dd, $J = 10.3, 1.2$ Hz, 1H), 3.83 (m, 2H), 3.77 (s, 3H), 3.72-3.68 (m, 1H), 3.62 (dd, $J = 11.2,$

5.6 Hz, 1H), 3.48 (dd, $J=13.1$, 5.0 Hz, 1H), 2.05 (s, 3H), 1.86 (dd, $J=13.1$, 11.4 Hz, 1H); ^{13}C NMR (MeOD, 100 MHz): δ 173.7, 170.4, 95.3, 70.7, 70.2, 68.8, 66.5, 63.4, 52.9, 51.7, 39.3, 21.2; IR (KBr): ν 3490, 3343, 3306, 2934, 1722, 1656, 1530, 1437, 1370, 1126 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_9\text{Na}$: 346.1114 $[\text{M}+\text{Na}]^+$; found: 346.1119.

Sialic acid (Neu5Ac), **3.13**

A solution of compound **3.12** in H_2O (1 mL) and MeOH (1 mL) was added LiOH (7 mg, 0.179 mmol). The reaction was stirred at RT for 6 h. The mixture was then purified by ion-exchange chromatography (Dowex 1X8-100 resin, formate form) to afford pure Sialic acid **3.13** (33 mg, 60% for three steps) as a white powder.

^1H NMR (D_2O , 400 MHz): δ 4.02 – 4.08 (m, 2H), 3.91 (t, $J=10.2$ Hz, 1H), 3.82 (dd, $J=11.8$, 2.6 Hz, 1H), 3.73 (ddd, $J=9.1$, 6.3, 2.6 Hz, 1H), 3.60 (dd, $J=11.8$, 6.3 Hz, 1H), 3.54 (dd, $J=9.3$, 1.0 Hz, 1H), 2.29 (dd, $J=13.1$, 5.0 Hz, 1H), 2.05 (s, 3H), 1.86 (dd, $J=13.1$, 11.4 Hz, 1H); ^{13}C NMR (D_2O , 100 MHz): δ 175.0, 173.6, 95.5, 70.5, 70.3, 68.4, 66.9, 63.3, 52.2, 39.0, 22.2; IR (KBr): ν 3491, 3462, 3340,

[α]_D²³ = -3.97 (c 0.6, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 5.37 (dd, *J* = 5.2, 1.4 Hz, 1H), 5.32 (dd, *J* = 7.1, 2.6 Hz, 1H), 5.22 – 5.28 (m, 1H), 5.07 (ddd, *J* = 7.5, 5.2, 2.5 Hz, 1H), 4.49 (dd, *J* = 12.3, 2.5 Hz, 1H), 4.12 (dd, *J* = 12.3, 6.8 Hz, 1H), 4.10 – 4.13 (m, 2H), 3.78 (s, 3H), 2.55 (dd, *J* = 13.3, 5.0 Hz, 1H), 2.15 (s, 3H), 2.14 (s, 3H), 2.09 (dd, *J* = 13.3, 10.4 Hz, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.89 (s,

3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 171.0, 170.6, 170.3, 170.2, 168.2, 166.3, 97.5, 72.9, 71.3, 68.3, 67.8, 62.1, 53.2, 49.4, 35.9, 23.2, 20.83, 20.77; IR (CHCl_3): ν 3426, 3019, 1746, 1371, 1215, 1040 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{22}\text{H}_{32}\text{NO}_{14}$: 534.1823 $[\text{M}+\text{H}]^+$; found: 534.1813.

References

1. E. Fischer, K. Zach, *Chem. Zentralblatt.*, **1913**, *1*, 1968.
2. a) R. J. Ferrier, *J. Chem. Soc., Perkin Trans, 1*, **1979**, *0*, 1455-1458. b) J. Ferrier, Robert, A. Zubkov, *Org. React.*, **2003**, 62.
3. S. Chandrasekhar, C. R. Reddy, G. Chandrashekar, *Tetrahedron Lett.*, **2004**, *45*, 6481-6484.
4. P. A. Colinas, R. D. Bravo, *Carbohydr. Res.*, **2007**, *342*, 2297-2302.
5. C. Ding, S. Tu, F. Li, Y. Wang, Q. Yao, W. Hu, H. Xie, L. Meng, A. Zhang, *J. Org. Chem.*, **2009**, *74*, 6111-6119.
6. a) D. A. Griffith, S. J. Danishefsky, *J. Am. Chem. Soc.*, **1990**, *112*, 5811-5819; b) T. K. Park, I. J. Kim, S. Hu, M. T. Bilodeau, J. T. Randolph, O. Kwon, S. J. Danishefsky, *J. Am. Chem. Soc.*, **1996**, *118*, 11488-11500; c) O. Kwon, S. J. Danishefsky, *J. Am. Chem. Soc.*, **1998**, *120*, 1588-1599.
7. P. A. Colinas, R. D. Bravo, *Org. Lett.*, **2003**, *5*, 4509-4511.
8. a) F. Ding, R. William, F. Wang, J. Ma, L. Ji, X.-W. Liu, *Org. Lett.*, **2011**, *13*, 652-655; b) F. Ding, R. William, S. Wang, B. Gorityala, X.-W. Liu, *Org. Biomol. Chem.*, **2011**, *9*, 3929-3939.
9. R. Lorpitthaya, Z.-Z. Xie, J.-L. Kuo, X.-W. Liu, *Chem. Eur. J.*, **2008**, *14*, 1561-1570. b) R. Lorpitthaya, K. B. Sophy, J.-L. Kuo, X.-W. Liu, *Org. Biomol. Chem.*, **2009**, *7*, 1284-1287.
10. R. Lorpitthaya, Z.-Z. Xie, K. B. Sophy, J.-L. Kuo, X.-W. Liu, *Chem. Eur. J.*,

- 2010**, *16*, 588-594.
11. J. S. Yadav, B. V. S. Reddy, K. V. Rao, K. S. Raj, A. R. Prasad, S. K. Kumar, A. C. Kunwar, P. Jayaprakash, B. Jagannath, *Angew. Chem. Int. Ed.*, **2003**, *42*, 5198-5201.
12. J. S. Yadav, B. V. S. Reddy, M. Srinivas, B. Padmavani, *Tetrahedron*, **2004**, *60*, 3261-3266.
13. N. Mangel, B. B. Snider, *Org. Lett.*, **2009**, *11*, 4926-4929.
14. C. Du, F. Li, X. Zhang, W. Hu, Q. Yao, A. Zhang, *J. Org. Chem.*, **2011**, *76*, 8833-8839.
15. F. Li, C. Ding, M. Wang, Q. Yao, A. Zhang, *J. Org. Chem.*, **2011**, *76*, 2820-2827.
16. R. Hoffmann, R. B. Woodward, *Acc. Chem. Res.*, **1968**, *1*, 17-22.
17. For reviews on the synthesis of cyclopentenones through Pauson–Khand reaction, see: a) P. L. Pauson, *Tetrahedron.*, **1985**, *41*, 5855; b) N. E. Schore, *Chem. Rev.*, **1988**, *88*, 1081-1119; c) N. E. Schore, *Org. React.*, **1991**, *40*, 1; d) O. Geis, H.-G. Schmalz, *Angew. Chem. Int. Ed.*, **1998**, *37*, 911-914; e) K. M. Brummond, J. L. Kent, *Tetrahedron*, **2000**, *56*, 3263-3283; f) J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. Dominguez, J. Perez-Castells, *Chem. Soc. Rev.*, **2004**, *33*, 32-42; g) H.-W. Lee, F. Kwong, *Eur. J. Org. Chem.*, **2010**, 789-811; For reviews on the synthesis of cyclopentenones through Nazarov reactions, see: a) H. Pellissier, *Tetrahedron*, **2005**, *61*, 6479-6517; b) M. A. Tius, *Eur. J. Org. Chem.*, **2005**, 2193-2206; c) W. Nakanishi, F. G. West, *Curr. Opin. Drug Discov.*, **2009**, *12*, 732-751. d) N. Shimada, C. Stewart, M. A. Tius, *Tetrahedron*, **2011**, *67*,

- 5851-5870; e) T. Vaidya, R. Eisenberg, A. J. Frontier, *ChemCatChem*, **2011**, *3*, 1531-1548.
18. a) A. Berecibar, C. Grandjean, A. Siriwardena, *Chem. Rev.*, **1999**, *99*, 779-844; b) V. B. Kurteva, C. A. M. Afonso, *Chem. Rev.*, **2009**, *109*, 6809-6857; c) S. P. Kawatkar, D. A. Kuntz, R. J. Woods, D. R. Rose, G.-J. Boons, *J. Am. Chem. Soc.*, **2006**, *128*, 8310-8319.
19. a) F. J. A. D. Bakkeren, N. G. Remesh, D. de Groot, A. J. H. Klunder, B. Zwanenburg, *Tetrahedron Lett.*, **1996**, *37*, 8003-8006; b) N. G. Ramesh, A. J. H. Klunder, B. Zwanenburg, *J. Org. Chem.*, **1999**, *64*, 3635-3641; c) J. Dauvergne, A. M. Happe, V. Jadhav, D. Justice, M.-C. Matos, P. J. McCormack, M. R. Pitts, S. M. Roberts, S. K. Singh, T. J. Snape, J. Whittall, *Tetrahedron*, **2004**, *60*, 2559-2567; d) F. A. Davis, Y. Wu, *Org. Lett.*, **2004**, *6*, 1269-1272.
20. W.-D. Z. Li, Y.-Q. Wang, *Org. Lett.*, **2003**, *5*, 2931-2934.
21. S.-W. Li, R. A. Batey, *Chem. Commun.*, **2007**, 3759-3761.
22. a) G. K. Veits, D. R. Wenz, J. Read de Alaniz, *Angew. Chem. Int. Ed.*, **2010**, *49*, 9484-9487; b) L. I. Palmer, J. R. de Alaniz, *Angew. Chem. Int. Ed.*, **2011**, *50*, 7167-7170.
23. a) J. Zeng, S. Vedachalam, S. Xiang, X.-W. Liu, *Org. Lett.*, **2010**, *13*, 42-45; b) S. Cai, B. Kishan Gorityala, J. Ma, M. L. Leow, X.-W. Liu, *Org. Lett.*, **2011**, *13*, 1072-1075; c) F. Ding, R. William, F. Wang, J. Ma, L. Ji, X.-W. Liu, *Org. Lett.*, **2011**, *13*, 652-655; d) R. Lorpitthaya, S. B. Suryawanshi, S. Wang, K. K. Pasunooti, S. Cai, J. Ma, X.-W. Liu, *Angew. Chem. Int. Ed.*, **2011**, *50*,

- 12054-12057; e) S. Xiang, S. Cai, J. Zeng, X.-W. Liu, *Org. Lett.*, **2011**, *13*, 4608-4611; f) F. Ding, R. William, S. Cai, J. Ma, X.-W. Liu, *J. Org. Chem.*, **2012**, *77*, 5245-5254; g) F. Ding, R. William, X.-W. Liu, *J. Org. Chem.* **2013**, jo302619b.
24. a) G. S. Welmaker, J. E. Sabalski, *Tetrahedron Lett.*, **2004**, *45*, 4851-4854; b) I. Ngantchou, B. Nyasse, C. Denier, C. Blonski, V. Hannaert, B. Schneider, *Bioorg. Med. Chem.*, **2010**, *20*, 3495-3498; c) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.*, **2010**, *110*, 4489-4497.
25. Review of the interrupted Nazarov reactions: a) T. N. Grant, C. J. Rieder, F. G. West, *Chem. Commun.*, **2009**, 5676-5688. Examples of halides trapping b) T. D. White and F. G. West, *Tetrahedron Lett.*, **2005**, *46*, 5629-5632.
26. M. Kokubo, S. Kobayashi, *Chem. Asian J.*, **2009**, *4*, 526-528.
27. Examples of intramolecular arene trapping: a) J. A. Bender, A. M. Arif, F. G. West, *J. Am. Chem. Soc.*, **1999**, *121*, 7443-7444; b) C. C. Browder, F. P. Marmsater, F. G. West, *Org. Lett.*, **2001**, *3*, 3033-3035; c) C. C. Browder, F. P. Marmsäter, F. G. West, *Can. J. Chem.*, **2004**, *82*, 375-385; d) T. N. Grant, F. G. West, *Org. Lett.*, **2007**, *9*, 3789-3792. Examples of intermolecular arene trapping: e) C. J. Rieder, R. J. Fradette, F. G. West, *Chem. Commun.*, **2008**, 1572-1574; f) A. K. Basak, M. A. Tius, *Org. Lett.*, **2008**, *10*, 4073-4076; g) V. M. Marx, F. M. LeFort, D. J. Burnell, *Adv. Synth. Catal.*, **2011**, *353*, 64-68.
28. J. C. P. Reyes, D. Romo, *Angew. Chem. Int. Ed.*, **2012**, *51*, 6870-6873.
29. a) C. J. Li, *Chem. Rev.*, **1993**, *93*, 2023-2035; b) C.-J. Li, *Chem. Rev.*, **2005**, *105*,

- 3095-3166; c) C.-J. Li, L. Chen, *Chem. Soc. Rev.*, **2006**, 35, 68-82; d) C.-J. Li, T.-H. Chan, *Comprehensive organic reactions in aqueous media*, 2nd ed., Wiley-Interscience, Hoboken, N.J., **2007**; e) A. Chanda, V. V. Fokin, *Chem. Rev.*, **2009**, 109, 725-748; f) R. N. Butler, A. G. Coyne, *Chem. Rev.*, **2010**, 110, 6302-6337.
30. a) K. Manabe, Y. Mori, T. Wakabayashi, S. Nagayama, S. Kobayashi, *J. Am. Chem. Soc.*, **2000**, 122, 7202-7207; b) S. Kobayashi, K. Manabe, *Acc. Chem. Res.*, **2002**, 35, 209-217; c) S. Azoulay, K. Manabe, S. Kobayashi, *Org. Lett.*, **2005**, 7, 4593-4595.
31. Selected example for the Nazarov reaction in water: T. Leikoski, J. Kaunisto, M. Alkio, O. Aaltonen, J. Yli-Kauhaluoma, *Org. Process Res. Dev.*, **2005**, 9, 629-633.
32. Alternative mechanisms cannot be ruled out at this time. Examples of oxygen trapping for the interrupted Nazarov reaction: a) A. R. de Lera, J. García Rey, D. Hrovat, B. Iglesias, S. López, *Tetrahedron Lett.*, **1997**, 38, 7425-7428; b) V. Nair, S. Bindu, V. Sreekumar, A. Chiaroni, *Org. Lett.*, **2002**, 4, 2821-2823; c) V. M. Marx, D. J. Burnell, *Org. Lett.*, **2009**, 11, 1229-1231.
33. a) K. Manabe, Y. Mori and S. Kobayashi, *Synlett.*, **1999**, 1401-1402; b) K. Manabe and S. Kobayashi, *Org. Lett.*, **1999**, 1, 1965-1967; c) K. Manabe, Y. Mori and S. Kobayashi, *Tetrahedron.*, **2001**, 57, 2537-2544; d) K. Manabe, X.-M. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, **2001**, 123, 10101-11102; e) K. Manabe, S. Iimura, X.-M. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, **2002**, 124,

11971-11978.

34. a) F. Gonzalez, S. Lesage, A. S. Perlin, *Carbohydr. Res.*, **1975**, 42, 267-274.

Recent report for the synthesis of Perlin aldehyde using InCl_3 as catalyst, see: b) P.

Nagaraj, M. Ganesan, N. G. Ramesh, *Tetrahedron.*, **2011**, 67, 769-776.

35. a) For a recent review on hydride shifts, see: C. I. F. Watt. *Adv. Phys. Org. Chem.*,

1988, 24, 57-112; b) For a recent report about 1, 5 hydride shift process, see: M.

C. Haibach, I. Deb, C. K. De and D. Seidel, *J. Am. Chem. Soc.*, **2011**, 133,

2100-2103; c) For a recent report about 1, 5 hydride shift process with C–N bond

cleavage, see: Y. Wang, Y. Chi, W.-X. Zhang, Z. Xi, *J. Am. Chem. Soc.*, **2012**,

134, 2926-2929; d) J. I. Cadogan, C. L. Hickson, H. McNab, *J. Chem. Res.* **1983**,

243,2247-2259.

36. *Biology of the Sialic Acids*; A. Rosenberg; Plenum Press: New York, **1995**.

37. R. Schauer, *Adv. Carbohydr. Chem. Biochem.*, **1982**, 40, 131-234.

38. W. Fitz, J. -R. Schwark, C. -H. Wong, *J. Org. Chem.*, **1995**, 60, 3663-3670.

39. M. Vonitzstein, W. Y. Wu, G. B. Kok, M. S. Pegg, J. C. Dyason, B. Jin, T. V.

Phan, M. L. Smythe, H. F. White, S. W. Oliver, P. M. Colman, J. N. Varghese, D.

M. Ryan, J. M. Woods, R. C. Bethell, V. J. Hotham, J. M. Cameron, C. R. Penn,

Nature., **1993**, 363, 418-423.

40. C. U. Kim, W. Lew, M. A. Williams, H. T. Liu, L. J. Zhang, S. Swaminathan, N.

Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver, R. C. Stevens,

J. Am. Chem. Soc., **1997**, 119, 681-690.

41. J. W. Cornforth, M. E. Firth, A. Gottschalk, *J. Biol. Chem.*, **1958**, 68, 57-61.

42. a) C. Auge, S. David, C. Gautheron, *Tetrahedron Lett.*, **1984**, 25, 4663-4664; b) S. J. Danishefsky, W. H. Pearson, B. E. Segmuller, *J. Am. Chem. Soc.*, **1985**, 107, 1280-1285; c) S. J. Danishefsky, M. P. DeNinno, S. H. Chen, *J. Am. Chem. Soc.*, **1988**, 110, 3929-3940; d) T. H. Chan, C. J. Li, *J. Chem. Soc. Chem. Commun.*, **1992**, 747-748; e) D. M. Gordon, G. M. Whitesides, *J. Org. Chem.*, **1993**, 58, 7937-7938; f) A. Dondoni, A. Marra, P. Merino, *J. Am. Chem. Soc.*, **1994**, 116, 3324-3336; g) M. Banwell, C. Desavi, K. Watson, *J. Chem. Soc. Perkin Trans. I*, **1998**, 2251-2252; h) T. Takahashi, H. Tsukamoto, M. Kurosaki, H. Yamada, *Synlett.*, **1997**, 1065 -1066; i) W. Fitz, M. J. Kim, W. J. Hennen, H. M. Sweers, C.-H. Wong, *J. Am. Chem. Soc.*, **1988**, 110, 6481-6486; j) M. Banwell, C. Desavi, K. Watson, *J. Chem. Soc. Perkin Trans. I*, **1998**, 2251-2252; k) Z. Hong, L. Liu, C.-C. Hsu, C.-H. Wong, *Angew. Chem. Int. Ed.*, **2006**, 45, 7417-7421; l) S. H. Kang, H.W. Choi, J. S. Kim, J. H. Youn, *Chem. Commun.*, **2000**, 227-228; m) E. A. Voight, C. Rein, S. D. Burke, *J. Org. Chem.*, **2002**, 67, 8489-8499; h) A. Dondoni, A. Marra, A. Boscarato, *Chem. Eur. J.*, **1999**, 5, 3562-3572; n) M. Banwell, C. Desavi, K. Watson, *J. Chem. Soc. Perkin Trans. I*, **1998**, 2251-2252; o) L. S. Li, Y. L. Li, Y. Wu, *Org. Lett.*, **2000**, 2, 891-894; p) E. A. Voight, C. R. Rein, S. D. Burke, *Tetrahedron Lett.*, **2001**, 42, 8747-8749; q) K. G. Liu, S. Yan, Y. L. Wu, Z. J. Yao, *J. Org. Chem.*, **2002**, 67, 6758-6763; r) T. H. Chan, M. C. Lee, *J. Org. Chem.*, **1995**, 60, 4228-4232; s) M. Warwel, W. Fessner, *Synlett.*, **2000**, 865-867; t) J. Calveras, Y. Nagai, I. Sultana, Y. Ueda, T. Higashi, M. Shoji, T. Sugai, *Tetrahedron.*, **2010**, 66, 4284-4291.

43. a) B. Aguilera, A. Fernandez-Mayoralas, *J. Org. Chem.*, **1998**, 63, 2719-2723; b) H. M. Chen, S. G. Withers, *Carbohydr. Res.*, **2007**, 342, 2212-2222; c) C. G. Espino, P. M. Wehn, J. Chow, J. Du Bois, *J. Am. Chem. Soc.*, **2001**, 123, 6935-6936; d) S. Toumieux, P. Compain, O. R. Martin, *J. Org. Chem.*, **2008**, 73, 2155-2162.

Siming Wang, Ph. D. (candidate)

Division of Chemistry and Biological Chemistry
Nanyang Technological University
21 Nanyang Link, Singapore 637371
Email: wang0558@ntu.edu.sg;

EDUCATION:

2009-present

Graduate Student
Division of Chemistry and Biological Chemistry
Nanyang Technological University

2002-2005

Master of Science Degree in Medicinal Chemistry
College of Pharmacy
Wuhan University

1998-2002

Bachelor of Science Degree in Pharmacy Engineering
School Material Science and Engineering
Wuhan Institute of Technology

PROFESSIONAL EXPERIENCE:

2005-2006

Research Chemist
Shanghai ChemPartner Co., Ltd

2006-2009

Process Chemist
Lonza Guangzhou Research & Development Center Ltd

PUBLICATIONS:

- 1 A Mild and Efficient Synthetic Protocol for Ferrier Azaglycosylation Promoted by $\text{ZnCl}_2/\text{Al}_2\text{O}_3$. F. Q. Ding, R. William, B. K. Gorityala, J. M. Ma, **S. M. Wang**, X. W. Liu, *Tetrahedron Lett.*, **2010**, 51, 3146-3148.
- 2 A Microwave-assisted, Copper-catalyzed Three-component Synthesis of Dihydropyrimidinones Under Mild Conditions. K. K. Pasunooti, H. Chai, C. N. Jensen, B. K. Gorityala, **S. M. Wang**, X. W. Liu, *Tetrahedron Lett.*, **2011**, 52, 80-84.
- 3 Ready Access to 3-amino-2,3-dideoxysugars via Regio- and Stereo-selective Tandem Hydroamination-glycosylation of Glycals. F. Q. Ding, R. William, **S. M. Wang**, B. K. Gorityala, X. W. Liu, *Org. Biomol. Chem.*, **2011**, 9, 3929-3939;
- 4 Total Synthesis of Sialic Acid by a Sequential Rhodium-Catalyzed Aziridination and Barbier Allylation of D-Glycal R. Lorpitthaya, S. B. Suryawanshi, **S. M. Wang**, K. K. Pasunooti, S. T. Cai, J. M. Ma, X. W. Liu, *Angew. Chem. Int. Ed.*, **2011**, 50, 12054-12057;
- 5 N-Heterocyclic Carbene Catalyzed Homoenolate-Addition Reaction of Enals and Nitroalkenes: Asymmetric Synthesis of 5-Carbon-Synthon δ -Nitroesters. B. Maji, L. Ji, **S. M. Wang**, S. Vedachalam, R. Ganguly, X. W. Liu, *Angew. Chem. Int. Ed.*, **2012**, 51, 8276-8280
- 6 Brønsted Acid-surfactant-combined Catalyzed Synthesis of 4-Aminocyclopentenones From Glycals in Water. **S. M. Wang**, X. W. Liu, *Submitted*.
- 7 InBr_3 -Catalyzed Cascade Reaction of Glycals with Secondary Arylamines: Trapping the Nazarov Intermediate with Water or Aryl Moieties. **S. M. Wang**, R.

William, K. K. G. E. Seah, and X. W. Liu, *Manuscript in preparation*.

CONFERENCES:

- 1 C-Aminoglycosylation via Barbier-type Allylation of Glycal: An Approach to Sialic Acids (Neu5Ac). **S. M. Wang**, R. Lorpitthaya, K. K. Pasunooti, X. W. Liu, *the 6th Asian-European Symposium on Metal Mediated Efficient Reactions*. June 7-9 2010, Nanyang Technological University, Singapore (**Poster** Presentation).
- 2 Green Synthesis of Cyclopentenones from Glycals. **S. M. Wang**, *the 3rd Asia-Oceania Conference on Green and Sustainable Chemistry (AOC-3)*. December 4 - 7, 2011, Melbourne, Australia (**Oral** Presentation).
- 3 InBr₃-Catalyzed Cascade Reaction of Glycals with Secondary Arylamines. **S. M. Wang**, X. W. Liu, *Asian Network for Natural and Unnatural Materials*. October 3-5 2012, Nanyang Technological University, Singapore (**Poster** Presentation).
- 4 InBr₃-Catalyzed Cascade Reaction of Glycals with Secondary Arylamines. **S. M. Wang**, *2nd Junior International Conference on Cutting-edge Organic Chemistry in Asia (ICCEOCA.)* December 8-10, 2012 University of Malaya, Kuala Lumpur, Malaysia (**Poster** Presentation).

PATENTS:

- 1 D. M. Dai, W. Zhu, **S. M. Wang**. Process For Preparing 2-Aminothiazol -4-yl-Acetic Acid Derivates, **WO2011029596**.