SYNTHESIS OF 3-AMINO-2,3-DIDEOXYSUGARS WITH THEIR APPLICATIONS AND TOTAL SYNTHESIS OF PYRIDONE ALKALOIDS

NANYANG TECHNOLOGICAL UNIVERSITY

SYNTHESIS OF 3-AMINO-2,3-DIDEOXYSUGARS WITH THEIR APPLICATIONS AND TOTAL SYNTHESIS OF PYRIDONE ALKALOIDS

DING FEIQING

SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

2013

DING FEIQING 2013

SYNTHESIS OF 3-AMINO-2,3-DIDEOXYSUGARS WITH THEIR APPLICATIONS AND TOTAL SYNTHESIS OF PYRIDONE ALKALOIDS

DING FEIQING

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

ACKNOWLEDGEMENTS

It would never be possible to finish this Thesis without the help of a huge number of persons.

On the first place, it is with great respect and immense pleasure that I would like to express my profound gratitude to my supervisor Assoc. Prof. Dr. Liu Xue-Wei for his constant encouragement, intellectual inspiration and constructive criticism during the course of my doctoral studies. I would also like to thank my co-supervisor Assoc. Prof. Dr. Liu Chuan-Fa from SBS, NTU for providing the scholarship, which enabled me to finish my PhD studies.

I have enormous gratitude for my colleagues with whom I have had the pleasure of working alongside over the years. I would like to thank Mr. Ronny William, whom I collaborated with on the most of my projects. His cheer, goodwill and friendship have carried me through many challenging times. I would also like to thank my collaborators, Miss. Wang Fei, Miss. Lee Ruilin, Miss. Liu Zhenlan and Miss. Fong Zi Mei Jacqueline. Furthermore, I am indebted to all the former and present members of the Liu's group, Dr. Rujee Lorpitthaya, Dr. Ma Jimei, Dr. Kalyan Kumar Pasunooti, Dr. Seenuvasan Vedachalam, Dr. Biswajit Maji, Dr. Bala Kishan Gorityala, Dr. Lu Zhiqiang, Dr. Sharad Suryawanshi, Dr. Wu Junliang, Dr. Fu Rui, Mr. Wang Siming, Miss. Cai Shuting, Miss. Leow Min Li, Mr. Zeng Jing, Miss. Ji Li, Miss. Ge Xin, Miss. Chai Hua, Mr. BaiYaguang, Mr. Xiang Shaohua, Mr. Kim Le Mai Hoang, Miss. Tan Yujia, Miss. Seah Kim Kui Georgina Estelle, Mrs. Huang Jie and Mr. Liao Hongze for their help, cooperation and friendly environment.

I appreciate Dr. Li Yongxin and Dr Rakesh Ganguly for the X-ray crystallographic analysis. I also thank Dr Attapol Pina, Ms. Goh Ee Ling and Ms. Zhu Wenwei for their support on NMR and mass spectroscopy. I am grateful to the general office staff from NTU, SPMS (CBC), for providing all the generous help and supports during the different stages of my doctoral studies.

I would like to express my appreciation to Prof. Koichi Naraska, Assoc. Prof. Li Tianhu, Assoc. Prof. Roderick W. Bates, Assoc. Prof. Shunsuke Chiba, Assoc. Prof. Tan Choon Hong , Nanyang Assist Prof. Yoshikai Naohiko and Assist Prof. Garcia Felipe for their valuable comments and suggestion for my PhD studies and PhD thesis.

I would like to thank my friends in CBC, Dr. Rao Weidong, Dr. Lei Maoyi and Mr. Jiang Yaojia since we are friends in Suzhou University, as well as Dr. Chen Ke. I gratefully acknowledge them for their constant support and discussion that made me happy and enjoy everyday in Singapore.

I have the greatest thanks and praise for my parents, sister, brother and friends for all the encouragement and support throughout my career. Finally, I would most of all like to my wife and son for their love and understanding. I am extremely blessed and proud to have such a loving and close family. They have instilled in me the values that have made these studies possible, and I am honored to dedicate this thesis to them.

Table of Contents

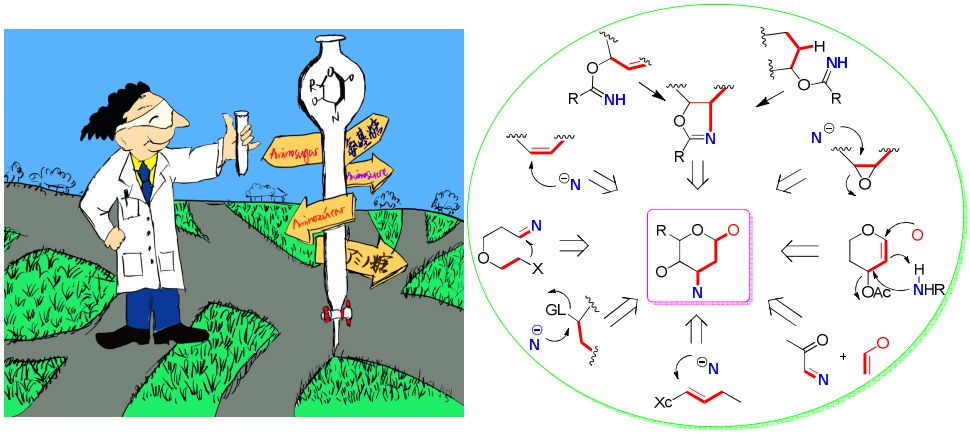
CHAPTER 2: *Synthesis of 3-Amino-2,3-dideoxysugars with Their Applications*

SUMMARY

PART 1: Synthesis of 3-Amino-2,3-dideoxysugars with Their Applications

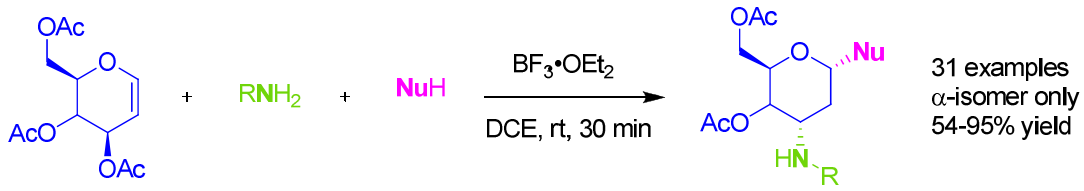
CHAPTER 1: Pathways Leading to 3-Amino- and 3-Nitro-2,3-dideoxy Sugars: Strategies, Synthesis and Their Bioactivities

3-Amino- and 3-nitro-2,3-dideoxy sugars, which are structurally diverse uncommon sugars bearing amino substitution on a sugar scaffold, have been shown to play crucial roles for the biological activities of aminoglycoside antibiotics and aminoglycoside containing natural products. Over the past few decades, there have been continuing efforts on the convenient synthesis of monosaccharides and oligoaccharides containing 3-amino- and 3-nitro-2,3-dideoxysugar motifs, beginning from either carbohydrate or non-carbohydrate precursors. This chapter is intended to provide an updated overview of the most striking contributions in this field, based on the various strategies to construct the 3-amino sugar ring.

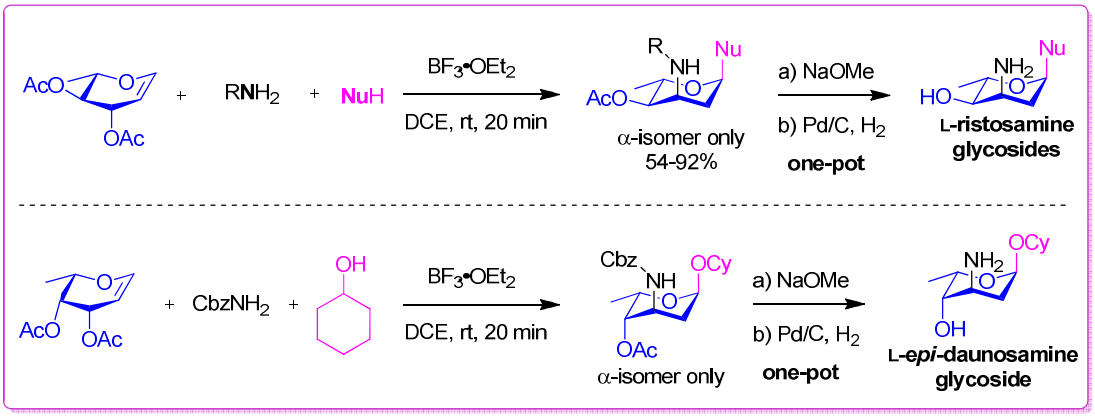


CHAPTER 2: Synthesis of 3-Amino-2,3-dideoxysugars with Their Applications

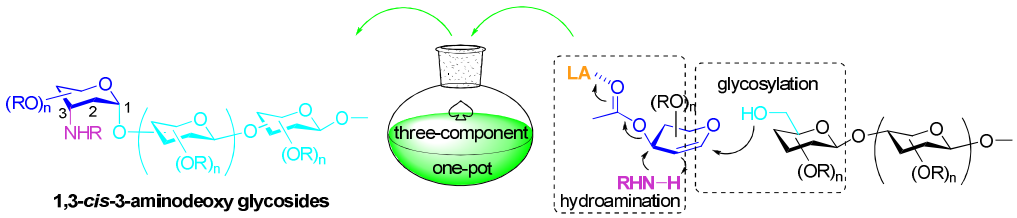
In this chapter, a highly stereoselective $BF_3{\cdot}OEt_2$-promoted tandem hydroamination/ glycosylation on glycal scaffold has been developed to form 3-amino-2,3-dideoxysugars in a one-pot manner. This efficient multicomponent reaction protocol offers simplicity and general applicability to a broad range of variations on each component.



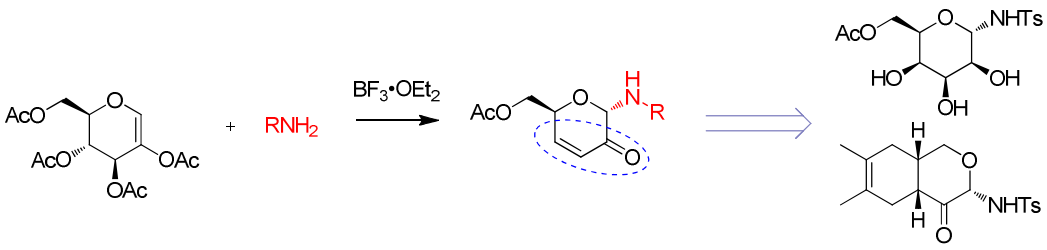
Based on the developed methodology, broad applications were introduced in glycochemistry. Firstly, a highly efficient synthesis of L-ristosamine and L-*epi*-daunosamine glycosides *via* $BF_3{\cdot}OEt_2$ promoted tandem hydroamination/glycosylation of 3,4-di-*O*-acetyl-6-deoxy-L-glucal and galactal has been developed. The method proceeds in a completely stereocontrolled manner within a short reaction time. Preparation of a library of L-ristosamine and L-*epi*-daunosamine glycosides with potential biochemical applications, by varying each component, exemplified the generality of the reaction.



Secondly, the 3-amino glycosides are ubiquitous in biologically important classes of glycoconjugates and naturally occurring oligosaccharides. Despite the rapid growth in the development of synthetic method of 3-amino glycosides, the current state-of-the art suffers from limited substrate scope, low yields, long reaction times, and anomeric mixtures. This work presents a novel direct method for the synthesis of 1,3-*cis*-3-aminodeoxy disaccharides and oligosaccharides via α-selective glycosylation and hydroamination of glycal in one-pot manner. This efficient multicomponent reaction methodology provides ready access to 1,3-*cis*-3-aminodeoxy disaccharides and oligosaccharides, and allows derivatization by variation of each component.



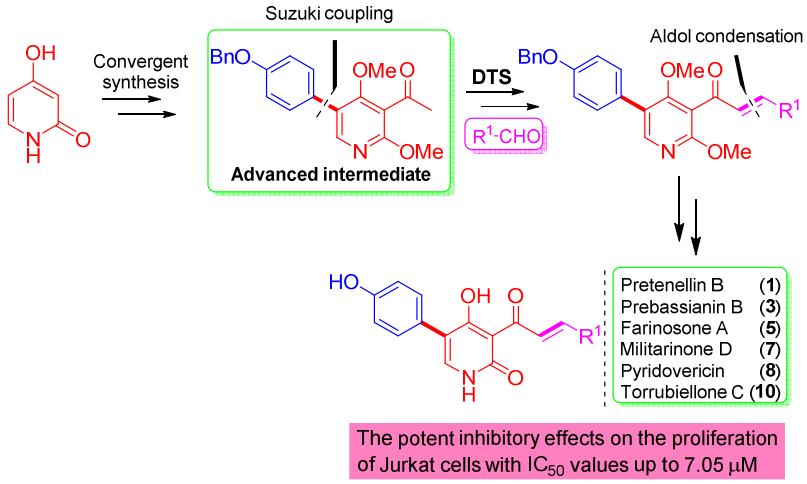
Finally, a mild and efficient protocol for the stereoselective synthesis of *N*-glycosides of enone sugars has been developed. The reaction proceeds to provide *N*-glycosides of enone sugars in moderate to good yields with preferential α-anomeric selectivity. Additionally, the applications of the *N*-glycosides of enone sugar derivatives as precursor to assemble some biochemically functional derivatives have also been explored. This includes the use of *N*-glycosides of enone sugars as reactive dienophile in asymmetric synthesis of bicyclic adduct through Diels-Alder cycloaddition reaction.



PART 2: Total Synthesis of Pyridone Alkaloids

CHAPTER 3. Total Synthesis of Pyridone Alkaloids with Antiproliferation Activities

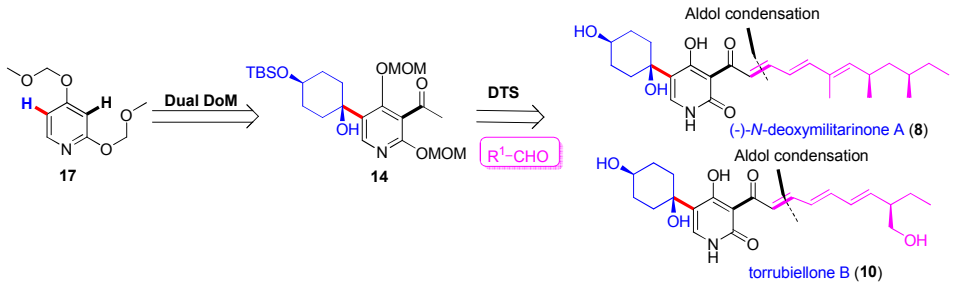
A combination of convergent and divergent total synthesis (DTS) approach presented herein sets stage for an iterative introduction of R^1 chain among structurally diverse pyridone alkaloids (see scheme). Interestingly, among the six tumor cell lines conducted for cell proliferation, Jurkat T-cells was discovered with potent and apoptotic inhibitory activites. Hence, this concept possesses potential contribution in addressing the synthesis of bioactive small-molecule libraries as well as drug discovery.



CHAPTER 4: The Asymmetric Total Synthesis of Torrubiellone B and N-deoxymillilarione A

A diverted total synthesis (DTS) approach to the total syntheses of pyridone alkaloids *N*-deoxymilitarninone A (**8**) and Torrubiellone B (**10**) has been developed. The common intermediate **14** was first assembled by dual Directed ortho Metalation (DoM) process using MOM as Directed Metalation Groups (DMGs) (see scheme). The crucial steps in

our synthesis are the assembly of polyenes under Aldol condensation for DTS using general and concise strategy and diastereoselective synthesis of the syn-dimethyl array by Evans aldol reaction. This concept has the potential to contribute to addressing the synthesis of bioactive small-molecule libraries in drug discovery.



INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux or heat
^{o}C	degree centigrade
Ac	acetyl
AcCl	acetyl chloride
ACN	acetonitrile
AcOH	acetic acid
Aq	aqueous
Bn	benzyl
$BF_3 \cdot Et_2O$	Boron trifluoride etherate
Boc	*tert*-butoxycarbonyl
brs	broad singlet
BSP	1-benzenesulfinyl piperidine
Bu	butyl
calcd.	calculated
cat.	catalytic
Cbz	carbobenzyloxy
$CDCl_3$	deuterated chloroform
CH_2Cl_2/DCM	dichloromethane
$CHCl_3$	chloroform
cm^{-1}	inverse centimeter
Cy	cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1 ,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DHP	dihydropyran
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminiumhydride
DIPEA	diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino) pyridine
DMF	*N*,*N*-dimethylformamide
DIPT	diisopropyl tartrate
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
EDCI	1-ethyl-3-(3-dimethylamino-propyl)carbodiimide
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent
Et	ethyl
ether	diethyl ether
Et_3N	triethylamine
EtOAc	ethylacetate
EtOH	ethanol
Fmoc	fluorenylmethoxycarbonyl
FTIR	fourier transfer infrared spectroscopy

dd	doublet of doublets	g	gram
DBU	1,8-diazabicycloundec-7-ene	h	hour (time)
		MS	mass spectrum
	chromatography	Ms	methane sulfonyl
HRMS	high resolution mass spectroscopy	MVK	methyl vinyl ketone
		NBS	*N*-bromosuccinimide
Hz	hertz	*n*Bu	*n*-butyl
Hex	hexane	N	concentration (normality)
HPLC	high performance liquid	NIS	N-Iodosuccinimide
IBX	2-iodoxybenzoic acid	NMR	nuclear magnetic resonance
IR	infrared	NMO	*N*-methylmorphine *N*-oxide
*i*Pr	isopropyl	Nu	nucleophile
J	coupling constants	kg	kilogram
LDA	lithium diisopropylamide	OTf	trifluromethanesulfonate
LiHMDS	lithium bis(trimethylsilyl) Amide	*p*	para
		PCC	pyridiniumchlorochromate
M	concentration (mol/L)	PDC	pyridinium dichromate
M^+	parent ion peak (mass spectrum)	Pd/C	palladium on carbon
		Ph	phenyl
m	multiplet	PMB	*p*-methoxybenzyl
*m*CPBA	*meta*-chloroperoxybenzoic acid	PMP	*p*-methoxyphenyl
		PNBCl	*p*-nitrobenzyl chloride
Me	methyl	ppm	parts per million
MEMCl chloride	metoxyethoxymethyl	PPTS	pyridinium*p*-tolunesulfonate
		Py	pyridine
MeCN	acetonitrile	q	quartet
MeOH	methanol	rt	room temperature
mg	milligram	RBF	round bottom flask
MHz	megahertz	s	singlet
min	minute	*s*Bu	*s*-butyl
mL	milliliter	sat	saturated

mm	millimeter	t	triplet
mmol	millimoles	TBAF	tetrabutylammonium fluoride
mol	moles	TBS	tert-butyldimethylsilyl
MOMCl	methyl chloromethyl ether	TLC	thin layer chromatography
MPMBr	p-methoxybenzyl bromide	TMS	trimethylsilyl
TBDMSOTf	t-butyldimethylsilyl triflate	TPAP	tetrapropylammonium
TEA	triethlyamine		perruthenate
Tec	trichloromethane	Ts	*p*-toluenesulfone
TFA	trifluoroacetic acid	v	volume
THF	tetrahydrofuran		
THP	tetrahydropyran		

Part 1. Synthesis of 3-Amino-2,3-dideoxysugars with Their Applications

Chapter 1. Pathways Leading to 3-Amino- and 3-Nitro-2,3-dideoxy Sugars: Strategies, Synthesis and Their Bioactivities

1.1 Introduction

Structurally-defined aminosugars such as 3-amino- and 3-nitro-2,3-dideoxy sugars are of great importance and have stimulated tremendous interests for research due to their prevalence in pharmaceuticals such as anthracycline antibiotics, and natural products.[1] In particular, antibiotics containing this moiety have been recognized to possess potent bioactivities against a wide range of human tumors.[2] Since the first isolation of rhodosamine **1** in the 1960s,[3] there has been continual emergence of reports for such antibiotics and over 25 analogues have been documented to date (Figure 1), each of which displaying exceptional potentials. In conjunction with synthetic studies on this class of compounds, numerous naturally occurring 3-amino- and 3-nitro-2,3-dideoxy sugars as well as their configurational isomers were continuously isolated. One of the most significant groups, shown in Figure 2, includes aminosugars which are not found as distinct entities, but as structural components of glycosidic and polysaccharide antibiotics in glycoconjugates.[4] The medicinal and glycobiological studies of the intriguing activities of 3-amino- and 3-nitro-2,3-dideoxy sugars and their derivatives have since gained momentous results. For instance, naturally occurring

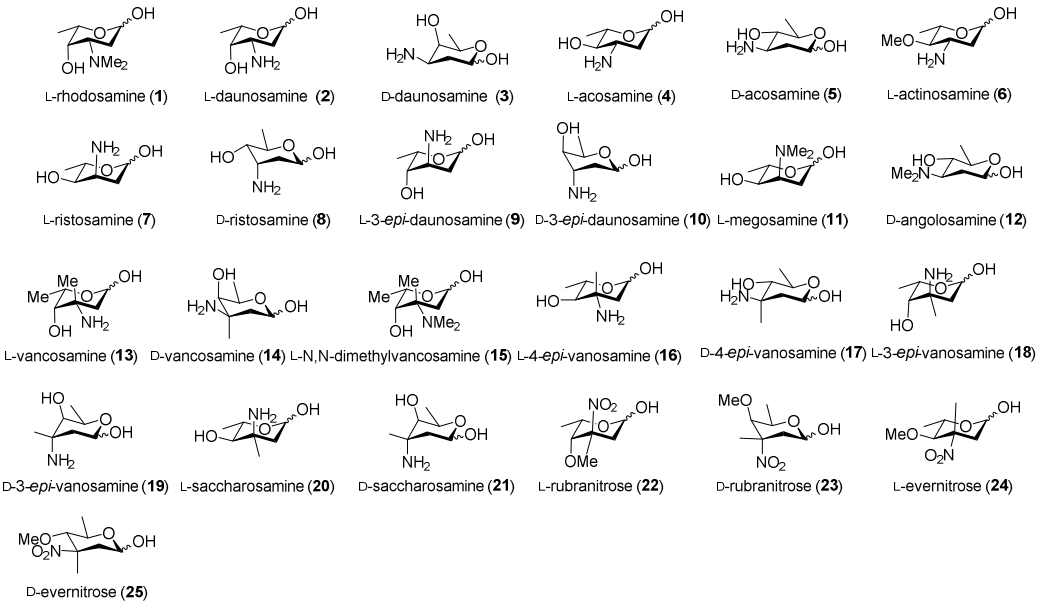


Fig. 1 Naturally occurring 3-amino- and 3-nitro-2,3-dideoxy sugars

daunorubicin **31**[5] and doxorubicin **33**[6] which contain a L-daunosamine residue in their structures are approved as anti-cancer agents[7] whilst the synthetic analogue epirubicin **32** (containing an L-acosamine residue) was marketed by Pfizer as Pharmorubicin for the treatment of breast cancer. Interestingly, two heptadecaglycoside antibiotics (saccharomicins A **48** and B **49**), containing four D-saccharosamine residues and four D-4-*epi*-vancosamine residues in each molecule, were isolated from a new species of *Saccharothrix*.[8] A closer examination of their biological properties revealed that both displayed antimicrobial activity against gram-positive bacteria. Judging from the affirmative biological data generated from the aminosugars and their contribution as important anologues in many pharmacological compounds, it is not surprising that significant attention has been placed on them over the past years.

The importance of such sugars has brought irrefutable attention and demand to devise elegant and expedient strategies for their straightforward access.[9] However, to

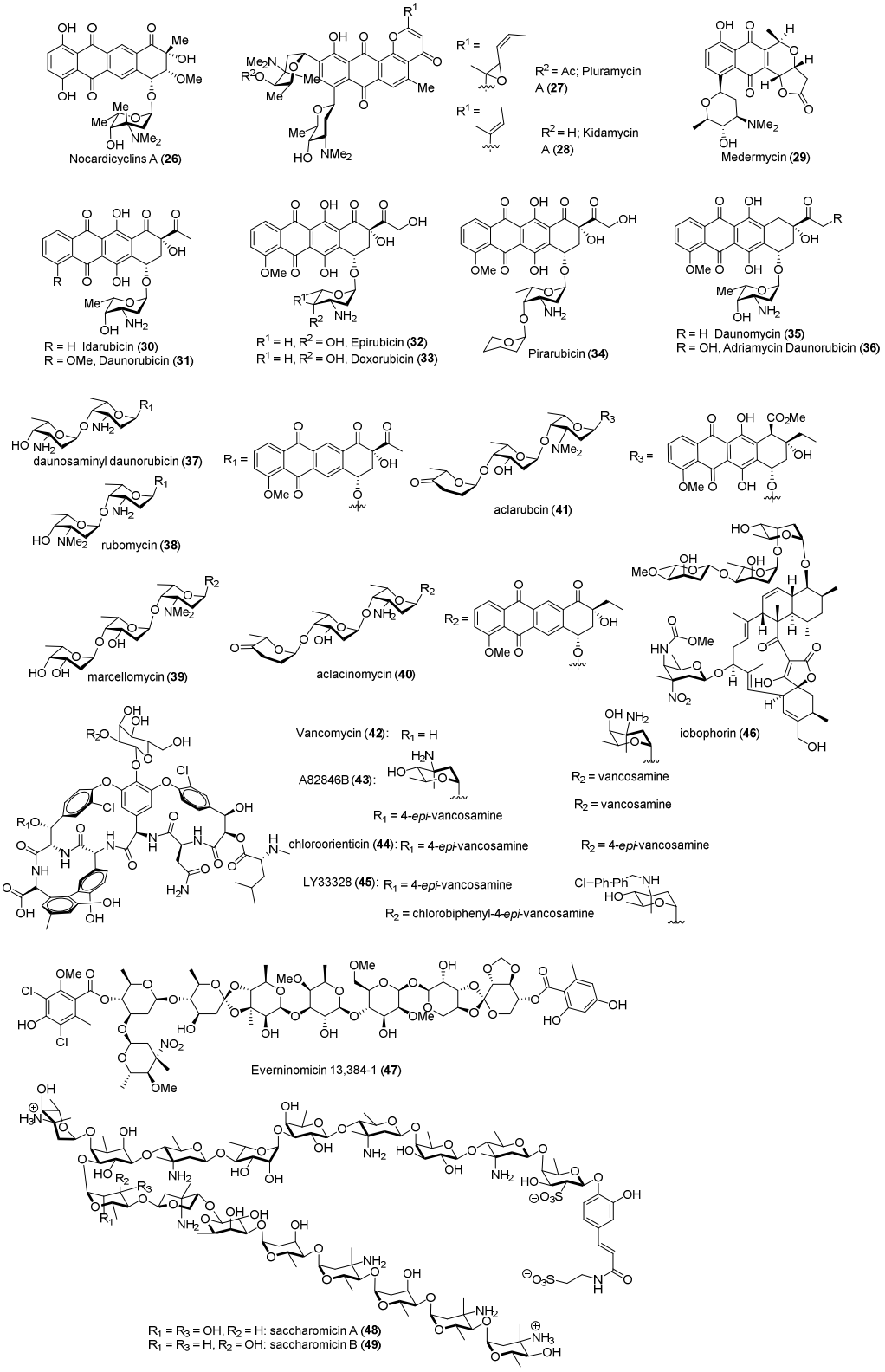


Fig. 2 3-Amino- and 3-nitro-2,3-dideoxy sugars as components of glycosidic and polysaccharide antibiotics

synthesize 3-amino- and 3-nitro-2,3-dideoxyglycosides and their derivatives, there is a contemporary challenge in carbohydrate chemistry because of the lack of stereodirecting substituents at C2, especially in the construction of amine-bearing C-3 quaternary center for the carbon-branched sugars. Considerable attention has therefore been devoted to the syntheses of these monosaccharides, utilizing both carbohydrate and non-carbohydrate starting materials. Extensive efforts have been made on various synthetic strategies to achieve more efficient syntheses of 3-amino- and 3-nitro-2,3-dideoxysugars, all of which hold potential divergent extensions to the syntheses of numerous natural products or their analogues. These preceding works toward 3-amino- and 3-nitro-2,3-dideoxysugar syntheses have been previously outlined in a review by Hauser *et al.*, which can be consulted for earlier account of this area of research.[10] The section below is intended as an updated synthesis review published in 1986. As such, 3-amino- and 3-nitro-2,3-dideoxysugar syntheses published after this year will be summarized.

In this section, we wish to give the reader an overview of the recent achievements on the synthesis of 3-amino- and 3-nitro-2,3-dideoxysugars by using diverse strategies, including: intermolecular and intramolecular conjugate addition, chiral auxiliary-based strategies, asymmetric oxidation; cycloaddition, nucleophilic substitution; radical strategy, solid-phase-based strategy and one-pot strategy (Figure 3). We have focused on the reaction approach in an attempt to categorize the reactions and highlight the key concepts that are emerging on the basis of these studies.

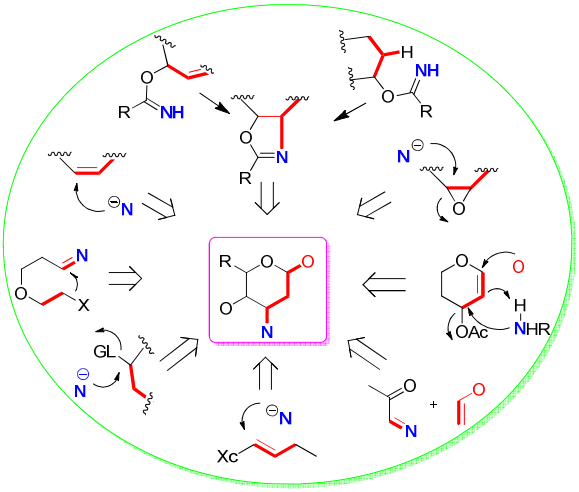


Fig. 3 Summary of strategies in the synthesis of 3-amino- and 3-nitro-2,3-dideoxy sugars.

1.2 Strategies and Synthesis

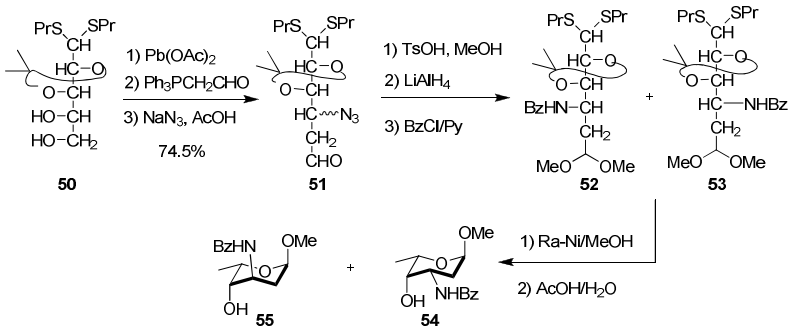
1.2.1 Intermolecular conjugate addition

The strategy of employing intermolecular conjugate addition to synthesize 3-amino-2,3-dideoxy sugars involves nucleophilic addition of nitrogen to the C=C bond directly. This process has wide utility and is considered to be the most direct route for the synthesis of such amino sugars. However, one major drawback is that this method normally results in poor stereoselectivity due to the absence of a stereocontrolled approach. In 1990, Sztaricskai's group developed a divergent synthetic route to synthesize 3-amino-2,3,6-trideoxyhexoses, namely, daunosamine and its derivatives (Scheme 1).[11]

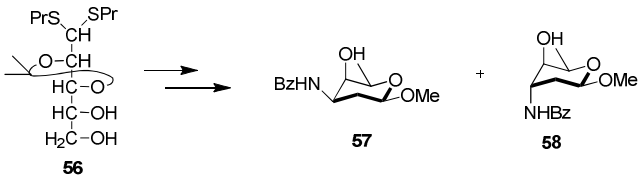
L-Daunosamine (**2**), the most well-known of the trideoxyaminohexoses to date, was first isolated from the antibiotic daunorubicin by Arcamone *et al.* in the 1960s.[12] It is the glycosidic component of a number of important anthracycline antibiotics that exhibit remarkable activity against a broad range of solid tumors

and soft tissue sarcomas.[13] The D isomer, D-daunosamine (**3**), is the unnatural enantiomorph which was first prepared by Richardson group.[14] The L-amino hexoses bearing *xylo* configuration, which the C-3 epimers of L- and D-daunosamine, have often referred as L- and D-3-*epi*-daunosamine (**9** and **10**). They are not naturally occurring isomers, and usually obtained as minor by-products during the synthesis of other amino sugars.

The strategy employed by Sztaricskai and co-workers' involves nucleophilic addition using sodium azide (NaN_3). Following the same sequence of reactions beginning from 2,3-*O*-isooropylidene-D-glucose mercaptal **56**, *N*-acetyl-D-daunosamine **57** and its D-*xylo* isomer **58** (*N*-acetyl-D-3-*epi*-daunosamine) were synthesized (Scheme 2).



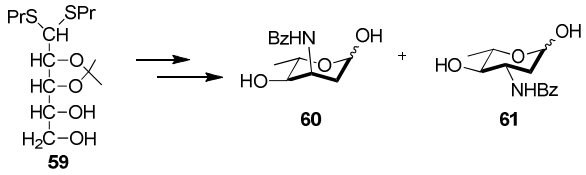
Scheme 1



Scheme 2

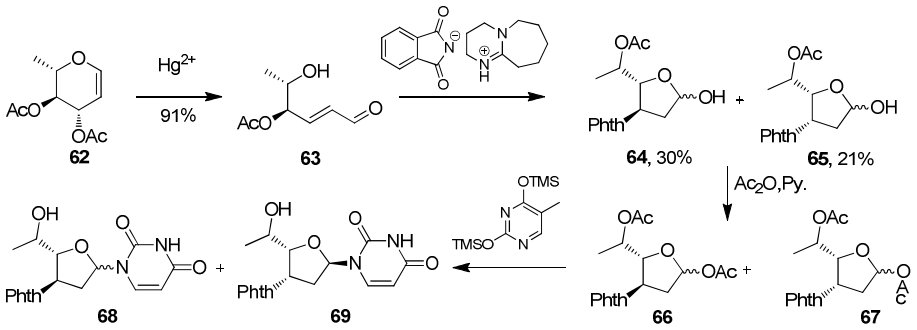
Using similar strategy as described above, Lomakina and coworkers proceeded to synthesize *N*-benzoyl-L-ristosamine **60** and L-acosamine **61** from

2,3-*O*-isopropylidene-D-ribose mercaptal **59** in 8 steps with a 21% overall yield (Scheme 3).[15]



Scheme 3

In 1991, Pedersen *et al.*[16] reported the synthesis of L-acosamine and L-ristosamine nucleosides of furanose configuration from acetylated L-rhamnal **62**, as shown in Scheme 4. The resulting target compounds were then assessed for their antiviral activity against HSV-1 and HIV.[17] Although promising results have yet to be obtained, the biological activities of these compounds still possess great potentials.

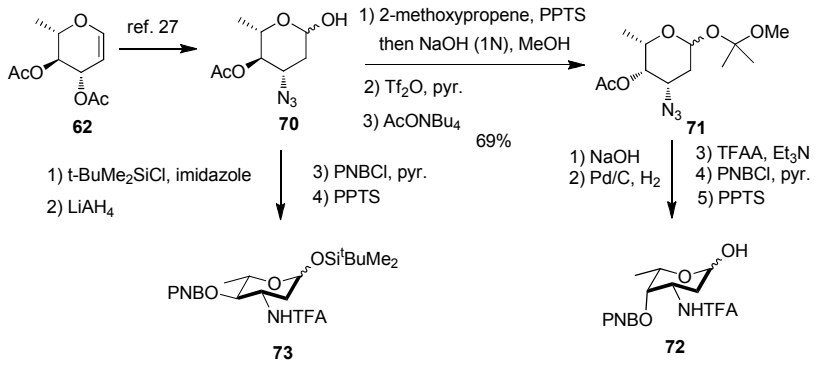


Scheme 4

In another approach, St-Denis *et al.*[18] contributed to the synthesis of protected L-daunosamine and protected L-acosamine by modification of known procedures (Scheme 5).[19] Addition of hydrazoic acid to α,β-unsaturated aldehydes (derived from rhamanal diacetate **62**) gave 3-azido-2,3,6-trideoxyhexopyranoses **70**.[20]

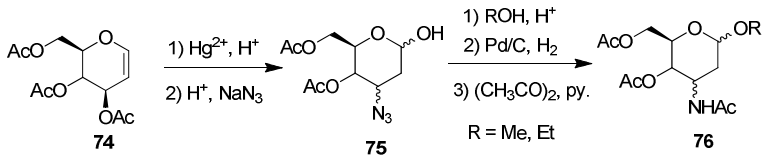
Daunosamine **72** and acosamine **73** could then be conveniently acquired *via* two separate routes from **70**. Through changes to the protecting groups and modification of the reaction conditions, they established that the time for the whole sequence was shortened, the yields were increased and the number of chromatographic operations compared with the known procedure was reduced.

Addition of hydrazoic acid to α,β-unsaturated aldehydes derived from tri-*O*-acetyl-D-glucal and D-galactal **74** provided 3-azido-2,3-dideoxy hexopyranoses **75**. These were converted into 1,4,6-tri-*O*-acetyl-3-azido-2,3-dideoxyhexopyranoses as well as methyl and ethyl glycosides **76** (ratio = 1:1)

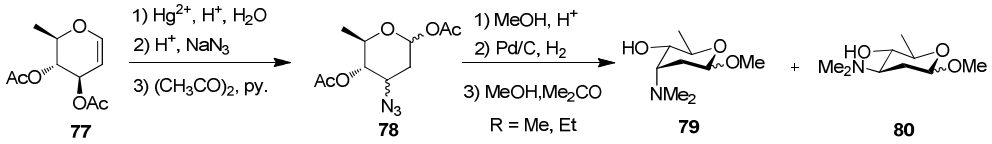


Scheme 5

(Scheme 6). Hydrogenation of the proamine group in 3-azido-2,3-dideoxy derivatives provided diverse 3-amino and 3-acetamidosugars with poor selectivities.[21] Similar results in terms of selectivities were also obtained for D-ristosamine **79** and D-acosamine **80** analogues (ratio = 2:1), both of which originated from 3,4-di-*O*-acetyl-D-rhamnal (**77**) (Scheme 7).[22]



Scheme 6



Scheme 7

L-Vancosamine (**13**), a methyl-branched aminosugar with a 3,4-*cis*-hydroxyamino substructure and an amine-bearing C-3 quaternary center, was isolated by McCormick *et al.* in 1956.[23] As the most well-known branched aminosugars, vancosamine is a constituent of various antibiotics such as vancomycin,[24] all of which produced by different strains of *Amycolatopsis orientalis*. Other related antibiotics containing L-vancosamine skeleton includes sporaviridine[25], aculeximycin[26] and UK-68597[27]. L-Vancosamine in the form of its C-3 epimer bearing *xylo* configuration, L-3-*epi*-vancosamine (**18**), was also found from the gram-positive antibiotic A35512B, which is related to vancomycin, ristocetin, and avoparcin.[28] Normally, it is obtained as a minor product in the syntheses of vancosamine (**13**).

In 1995, Scharf's group[29] investigated 1,2-addition of a methylcerium reagent with imine to the methyl β-glycopyranoside of L-vancosamine (**13**) and L-3-*epi*-vancosamine (**18**). Starting from methyl 2,6-dideoxy-β-L-*lyxo*-hexopyranoside (**81**), the synthesis was completed in eight steps as shown in Scheme 8. It should be noted that the methylceriumreagent in the reaction with

oximino sugar **83** preferentially attacked the C=N bond from the least hindered *re*-face to afford the *lyxo*-product **84** selectively (Figure 4).

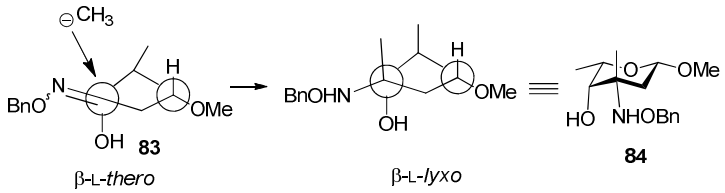
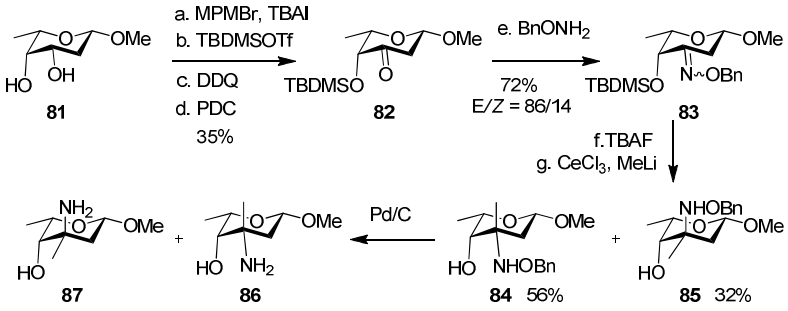
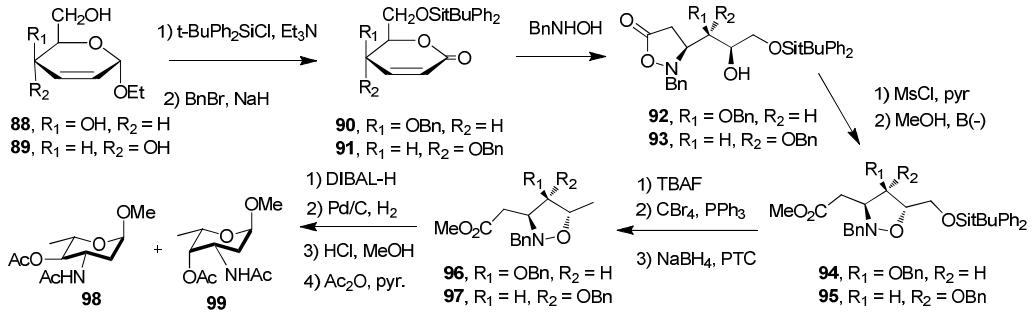


Fig. 4



Scheme 8

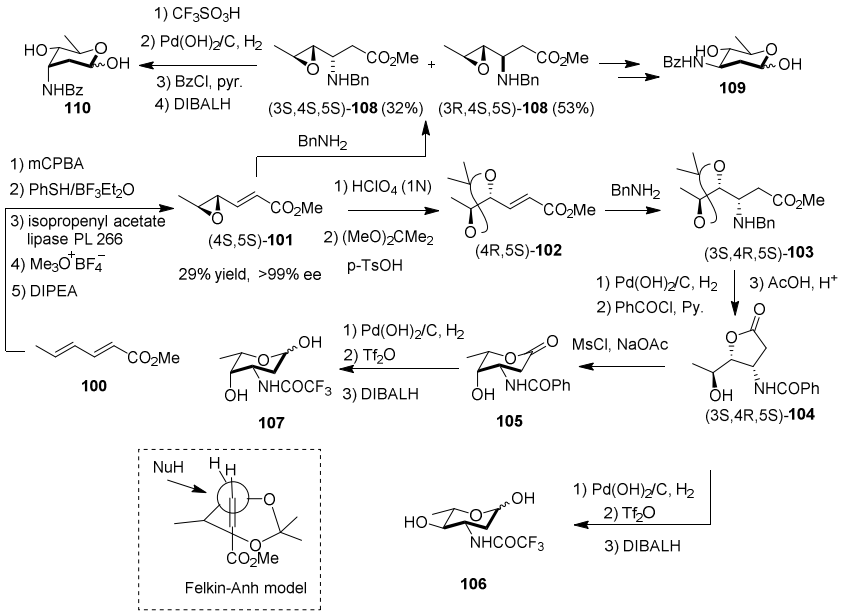
Chmielewski *et al.*[30] developed an efficient approach to switch from sugars of the D-configuration series to those of the L-series, providing an attractive entry to important L-3-amino-2,3-dideoxysugars (Scheme 9).



Scheme 9

Akita *et al.*[31] demonstrated a divergent route for the stereoselective synthesis of

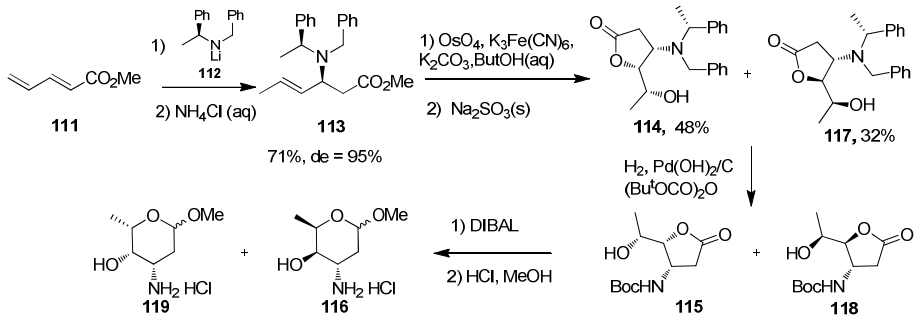
3-amino-2,3-dideoxy sugars from one common α,β-unsaturated ester **100**, providing almost any desired configuration at the three stereogenic centers (Scheme 10). It should be noted that the 3,4-*syn*-selective addition of a nucleophile to α,β-unsaturated ester could be explained by a Felkin-Anh model as depicted in Scheme 10.[32]



Scheme 10

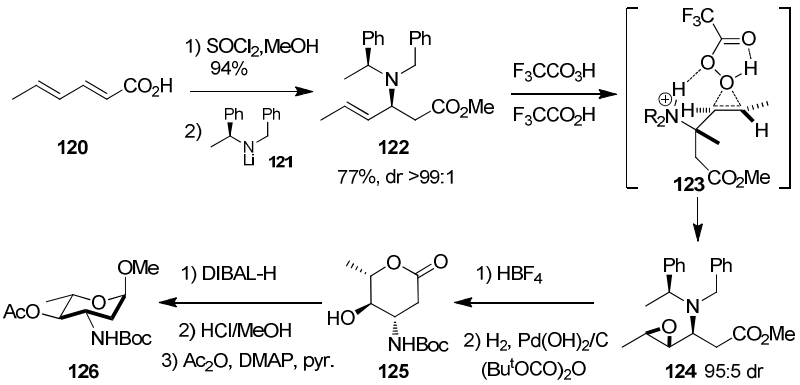
Davies' group disclosed an entirely different strategy for selective introduction of amino group en route to aminodeoxysugars.[33] In this case, it is the conjugate addition of enantiopure lithium amide (*R*)-*N*-benzyl-*N*-(α- methylbenzyl) amide **112** to α,β-unsaturated ester **111** that allowed the creation of a C-N bond in a highly stereoselective manner (Scheme 11). The highly diastereoselective asymmetric conjugate addition of **112** to methyl (*E*,*E*)-hexa-2,4-dienoate **111** yielded the *anti*-addition product **113** (*de* = 95%). This very strategy yields the 2,3,5-trideoxyaminopentose in a remarkably short fashion and should also be

applicable to the synthesis of aminodeoxyhexoses. The low intrinsic selectivity of the key dihydroxylation step can be significantly improved by employing the Sharpless' modified asymmetric dihydroxylation protocol.[34]



Scheme 11

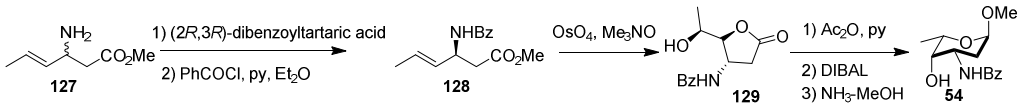
Recently, the same group reported a similar strategy for concise and highly selective asymmetric synthesis of *N,O*-diacetyl-L-acosaminide **126** in 7 steps with 15% overall yield from sorbic acid **120**.[35] However, they presented another possible alternative strategy incorporating diastereoselective oxidation of the olefin using peracid F_3CCO_3H[36] in the presence of F_3CCO_2H, resulting in complete conversion to epoxide **124** with 95:5 *dr* in nearly quantitative yield. The stereochemical outcome of the epoxidation of β-amino ester **122** is therefore



Scheme 12

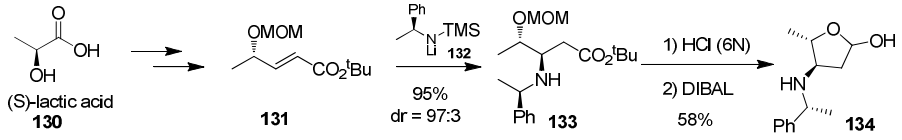
consistent with an ammonium-directed epoxidation step proceeding *via* a transition state model **123**, in which 1,3-allylic strain is minimized (Scheme 12).

Two precedents existed for the synthesis of *N*-benzoyl-L-daunosamine **54** using a substrate-controlled osmium tetroxide-catalyzed dihydroxylation. The approach by Hauser and co-workers[37] (Scheme 13) is most closely related to the current situation, but employs a different strategy by using (2*R*,3*R*)-dibenzoyltartaric acid for the introduction of chirality into β-amino ester **127**.



Scheme 13

Another example for the stereoselective synthesis of 3-amino-2,3-dideoxysugar **134** was disclosed by Sewald and co-workers. Through the same strategy of utilizing the conjugate addition of enantiopure lithium amide-(*S*)-*N*-(1-phenylethyl) trimethyl silylamine **132** to α,β-unsaturated ester **131** which was derived from (*S*)-lactic acid (**130**). The a C-N bond was created in a highly stereoselective manner (*dr* = 97:3) (Scheme 14).[38]



Scheme 14

1.2.2 Intramolecular conjugate addition

A number of different protocols to 3-amino- and 3-nitro-2,3-dideoxy sugars

were established based on intramolecular conjugate addition of nitrene to C=C, as shown in Fig. 6, including: a) conjugate addition of δ-carbamoyloxy-α,β-unsaturated esters **130** with anionic nitrogen for smooth cyclization under basic conditions to 6-membered cyclic carbamates **131** with high 1,3-*syn*-asymmetric induction of **132**;[39] b) cyclizations by nitrene addition to a double bond in which the allylic oxygen of **133** could act as the fulcrum for direct entry to the *cis* nitrogen functionality in **135** by way of intermediate **134**; c) cyclizations with nitrene-CH insertion to effect regio- and stereodirected oxygenation at the adjacent site followed by *cis* oxyamination procedure, providing access to *cis* aminosugars **138**; d) aziridination of a nitrene with an olefin.

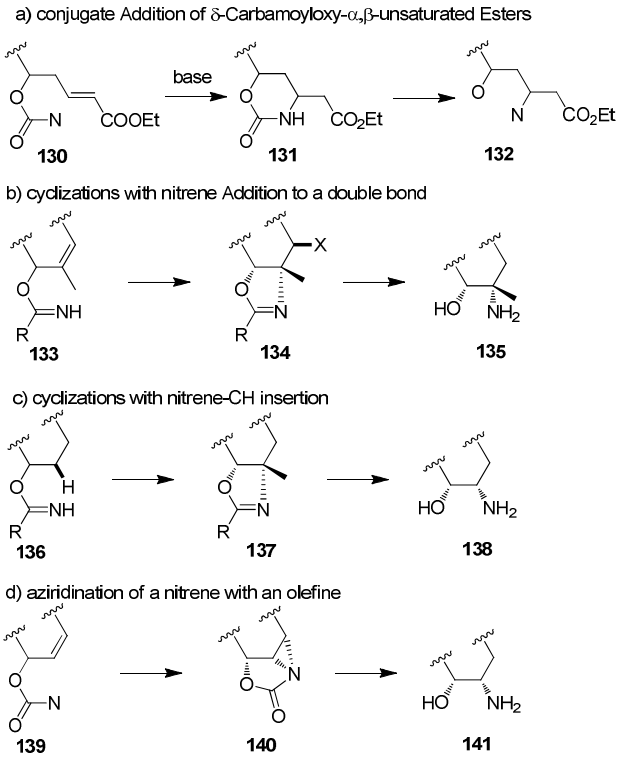
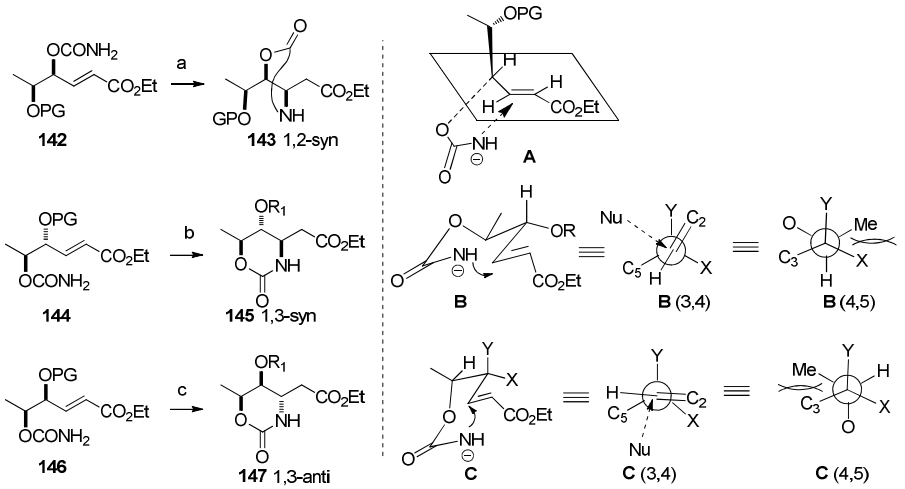


Fig. 6

1.2.2.1 Conjugate addition of δ-carbamoyloxy-α,β-unsaturated esters

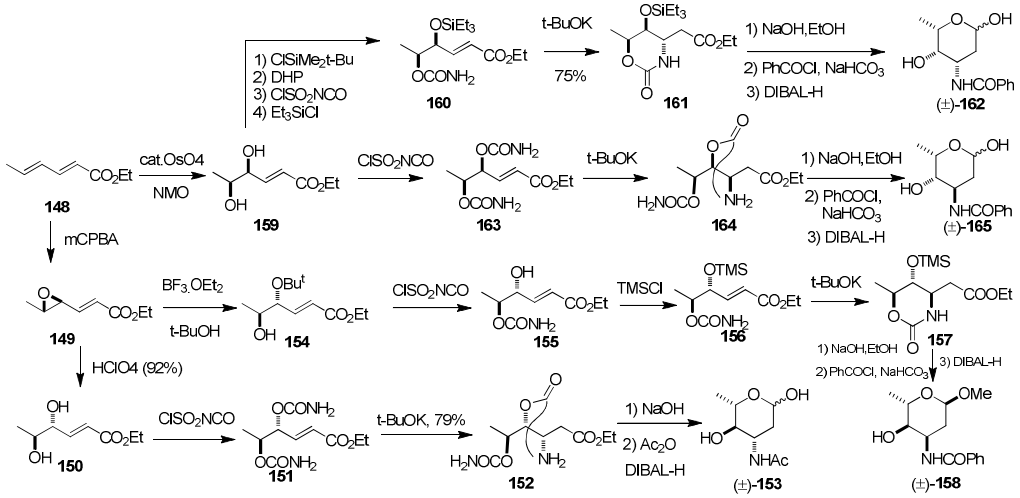
1,2- and 1,3-asymmetric induction in the intramolecular Michael additions of γ-and δ-carbamoyloxy-α,β-unsaturated esters were developed by Hirama and co-workers in earlier years.[40] Since the attack of nitrogen nucleophile to the diastereotopic face of β-carbon is controlled by both the position and the configuration of carbamoyloxy group in these reactions, they provide expedient ways to achieve diastereoselective amination of acyclic systems by varying the site of carbamoyloxy group, as exemplified in Scheme 15. For path a, the 1,2-*syn* selectivity in the reactions of allylic carbamates **142** is explicable on the basis of allylic strain.[41] The preferred conformation of the transition state A also satisfies the required trajectory of the nitrogen nucleophile for 5-*exo-trig* cyclization.[42] For path b, the origin of the diastereofacial 1,3-selectivity in the kinetically controlled conjugate addition of the homoallylic carbamates **144** is quite intriguing when considering the steric and stereoelectronic factors.[43] Introduction of an oxygen functionality in the *erythro* configuration (X = OSiR, Y = H) would cause extra stabilization to the transition state B by stereoelectronic effect, while gauche interaction remains nearly the same: in B, LUMO of the unsaturated ester part would be stabilized by its perturbation with σ* of the C-O bond at C4 and results in a better interaction with HOMO of the nucleophile (antiperiplanar effect). Noteworthy, such an effect cannot be expected in C.[44] On the other hand, in the case of path c where X = H, Y = $OSiR_3$, the two effects counteract each other: while steric effect still favors B, stereoelectronic stabilization operates only in C,

and the 1,3-*syn* selectivity would be decreased in these cases as compared with path b.



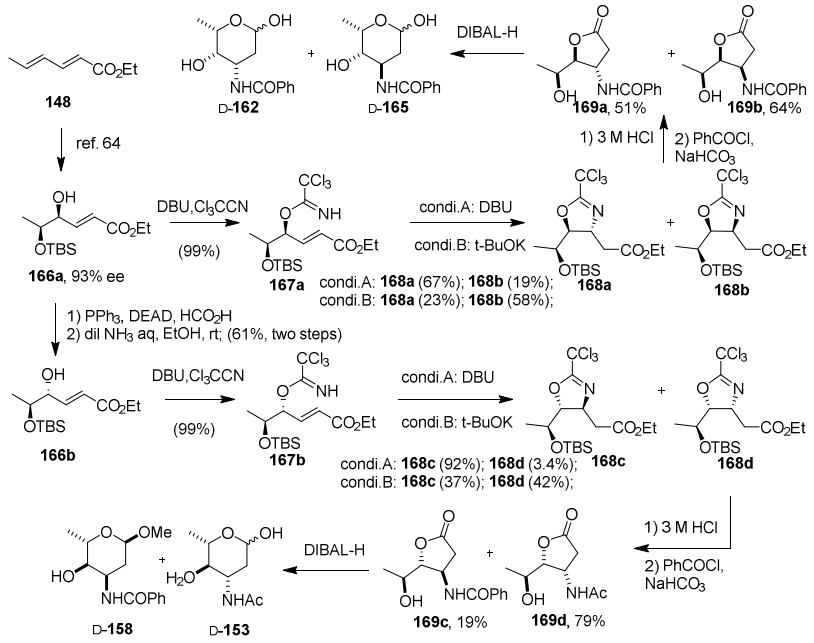
Scheme 15

Hirama's group has made huge contribution using this strategy, developing a general route for the stereoselective syntheses of all four possible diastereomers of racemic *N*-protected-3-amino-2,3,6-trideoxyhexoses (Scheme 16).[45]



Scheme 16

Recently, Matsushima's group[46] described an extremely concise route to optically active D-daunosamine, D-acosamine, D-ristosamine and 3-*epi*-D-daunosamine precursors by an intramolecular conjugate addition of γ-trichloro acetimidoyloxy-α,β-unsaturated esters from the same starting material, ethyl sorbate **148** (Scheme 17). Stereoselectivity in the cyclization can be anticipated using the transition state (TS) models shown in Figure 7.



Scheme 17.

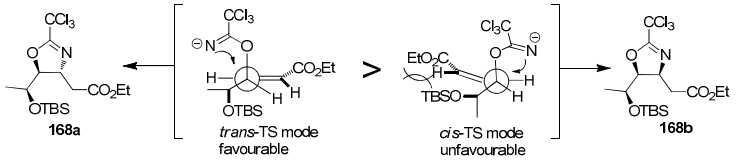
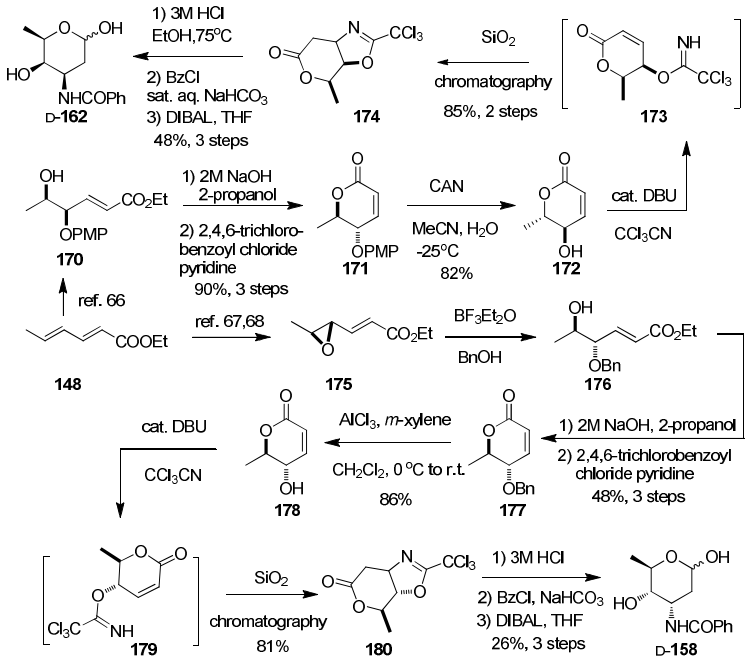


Fig. 7.

The exact group reported their results in developing a brief synthetic route for the synthesis of *N*-Bz-protected daunosamine **162** and *N*-Bz-protected ristosamine

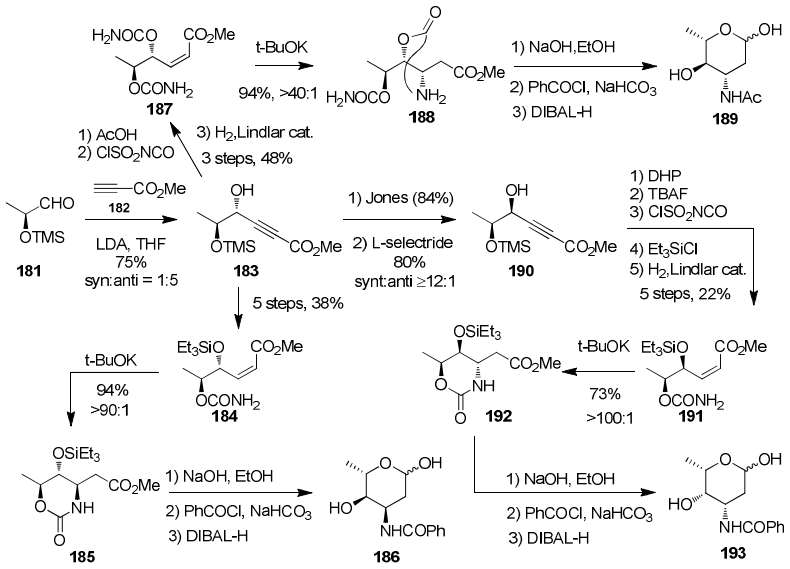
158 (Scheme 18).[47] The strategy proceeded through silica gel promoted intramolecular conjugate addition of γ-trichloroacetimidates, which are obtained from osmundalactone **172** and its epimer **178** respectively. This synthetic strategy began from the known compound **170**, which was prepared from commercially available ethylsorbate **148** by Sharpless' asymmetric dihydroxylation, following palladium (Pd)-catalyzed etheration.[48] The chiral starting material **8** was also known to be derived from ethyl sorbate **148** by Shi's asymmetric epoxidation[49] and epoxide ring opening.[50] Subsequently, the key intermediates **172** and its epimer **178** were prepared from compounds **170** and **176** respectively *via* hydrolysis, δ-lactonization and oxidative cleavage.



Scheme 18.

Another stereodivergent synthetic approach towards optically active

N-acetyl-L-acosamine (**189**), *N*-benzoyl-L-ristosamine **186** and *N*-benzoyl-L-daunosamine **193** was also developed by the same group.[51] The previous strategies were adopted but the synthesis originated from optically active starting materials based on the Cram-selective nucleophilic coupling of metallated methyl propiolate **182** with protected acetaldehyde **181** (Scheme 19).



Scheme 19.

1.2.2.2 Cyclizations with nitrene addition to a double bond

In vancosamine and other amino and nitro sugars in which the nitro or amino group is *cis* to an adjacent hydroxyl group, the electrophilic cyclization of allylic imidates, carbamates, or isoureas to a carbon-carbon double bond has been an effective method for controlling the stereochemistry at the critical C-3 position. Hydrolysis of the resulting oxazoline provides the *cis* amino alcohol functionality. This strategy was introduced by Fraser-Reid's group[52] *via* iodocyclization of allylic imidate in which the allylic oxygen acts as a fulcrum to direct entry of the

cis nitrogen function from **194** through intermediate **195** (Fig. 8). The implementation of this approach for the synthesis of L-ristosmine and L-daunosamine derivatives **199** and **202** is outlined in Scheme 20.

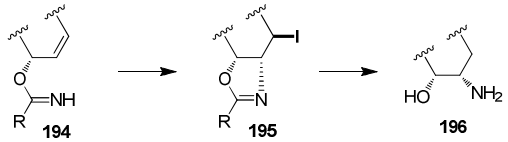
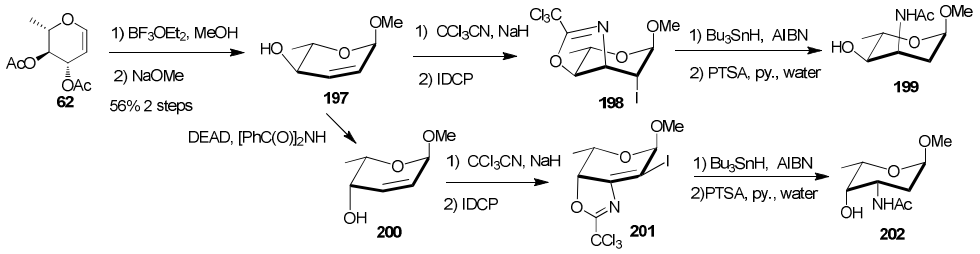


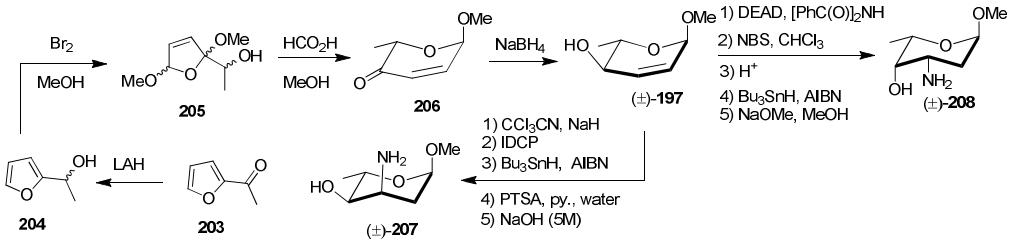
Fig. 8 Strategy to synthesis of *cis* amino alcohol **196**.



Scheme 20

The 1-(2-furyl)ethanol **204**, prepared in quantitative yield from 2-acetylfuran **203** *via* reduction, can be conveniently employed for the total synthesis of deoxysugars. Achmatowics and co-workers[53] demonstrated that bromination in methanol afforded an intermediate dimethoxy derivative **205** which upon acid-catalyzed hydrolysis, gave pyranuloses **206** and its isomer in a 3:1 (α:β) anomeric ratio in an overall yield of 83%. The major pyranulose product **206** was reduced using sodium borohydride ($NaBH_4$) to give the epimeric allylic alcohols (±)-**197** and its isomer in a 13:1 ratio. Similarly, allylic alcohols (±)-**197** has been converted into methyl D/L-daunosaminide (±)-**208** and methyl D/L-ristosaminide (±)-**207** by an intramolecular cyclization of the trichloroacetimidate group (Scheme 21).[54]

A diastereomer of vancosamine, D-saccharosamine **21**, has been recently isolated from a new species of *Saccharothrix* as a component of saccharomicin, an oligosaccharide antibiotic that is active against bacteria resistant to vancomycin.[55] L-Saccharosamine **20** is the 3-C-methyl sugar with the *arabino* configuration and although it has not been isolated from natural sources, the preparation has been reported.

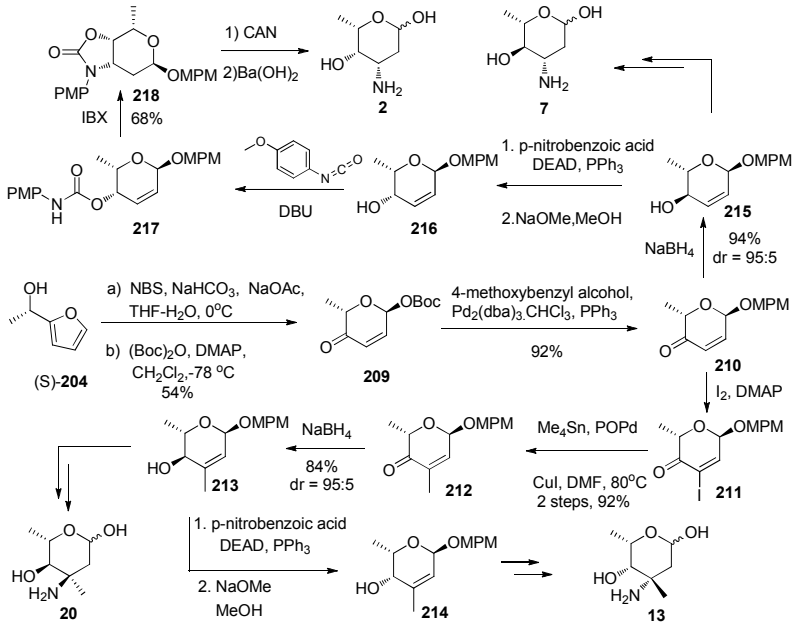


Scheme 21.

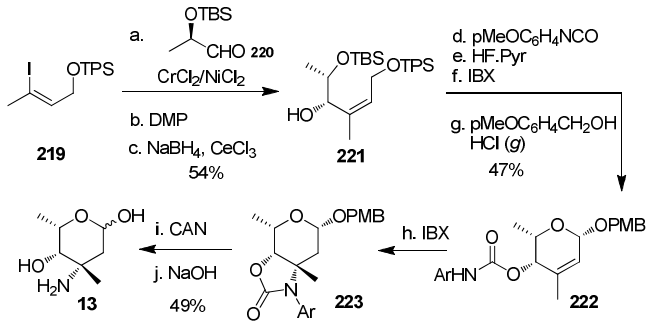
Asymmetric reduction of 2-acetylfuran **203** gave (*S*)**-**1-(2-furyl)ethanol **204** in good enantiomeric excess (Scheme 22). Therefore, this protocol represents a short route to optically active amino sugars, including L-daunosamine **2**, L-ristosamine **7**, L-vancosamine **13** and L-saccharosamine **20**, from an economical, non-carbohydrate precursor as shown in Scheme 22.[56] This method could also be easily applied to the synthesis of their enantiomers from (*R*)-**204**.

Notably, Nicolaou *et al.*[57] exemplified an efficient and general synthetic technology for the rapid and stereoselective preparation of a diverse array of amino sugar building blocks and compound libraries for biological screening. The synthesis proceeded *via* a key step of the cyclization of *N*-arylcarbamates onto olefins, orchestrated by IBX. In conjunction with these studies, they achieved the synthesis of L-vancosamine (**13**), as shown in Scheme 23 (10 steps, 13% yield

from the readily available chiral aldehyde **220**). This sequence constitutes one of the shortest syntheses reported for L-vancosamine **13** to date and presents an efficient methodology for amino sugar construction.

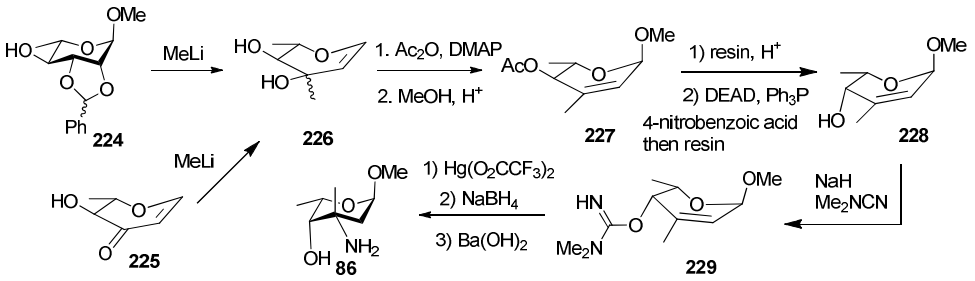


Scheme 22.



Scheme 23.

In 2000, Giuliano *et al.*[58] reported the synthesis of methyl α-L-vancosaminide (**1**) *via* electrophilic cyclization of allylic isoureas as the key step (Scheme 24).

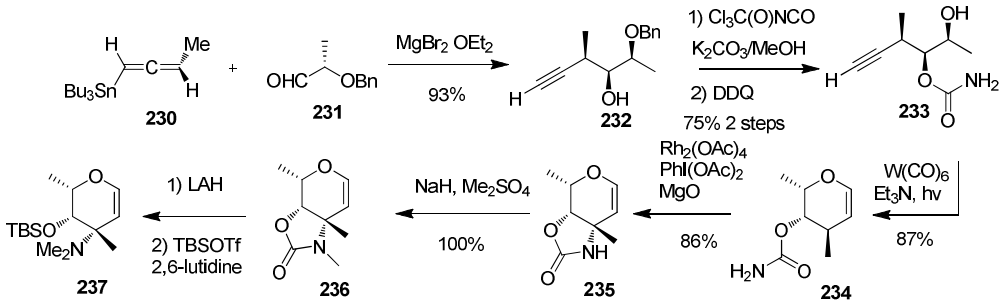


Scheme 24.

1.2.2.3 Cyclizations with nitrene-CH insertion

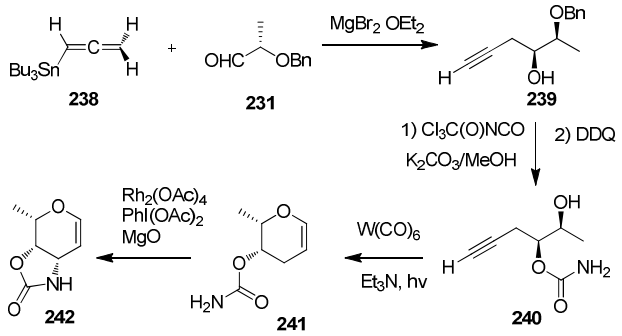
Parker *et al.*[59] discovered an efficient synthetic strategy to prepare the carbamate-protected glycals of L-vancosamine, L-daunosamine, D-saccharosamine, and L-ristosamine in seven steps from non-carbohydrate precursors (Scheme 25). The key steps included oxidation of the appropriate carbamates and subsequent ring closure of the resulting nitrenes. The sequence leading to protected-L-vancosamine glycal is summarized in Scheme 25. The diastereoselective addition of an allenyl stannane **230**[60] to a lactaldehyde ether **231**[61] (Marshall reaction)[62] resulted in alkynol **232**. Treatment with trichloroacetyl isocyanate and methanolysis afforded alkynol **233**, which would undergo tungsten-catalyzed alkynol cycloisomerization (McDonald reaction)[63] to form 3-deoxy glycal **234**. Then, the protected L-vancosamine glycal **235** was obtained by rhodium-catalyzed C-H insertion of a carbamate nitrogen (Du Bois reaction)[64] of **234**. At a later stage, reaction of protected glycal **235** with sodium hydride and dimethyl sulfate provided *N*-methyl oxazolidinone **236** in quantitative yield. Reduction with LAH provided crude *N*,*N*-dimethyl vancosamine glycal, which was directly subjected to silylation. Thus, the *N*,*N*-dimethyl vancosamine glycal

237 was obtained from the key vancosamine synthon **234**.



Scheme 25.

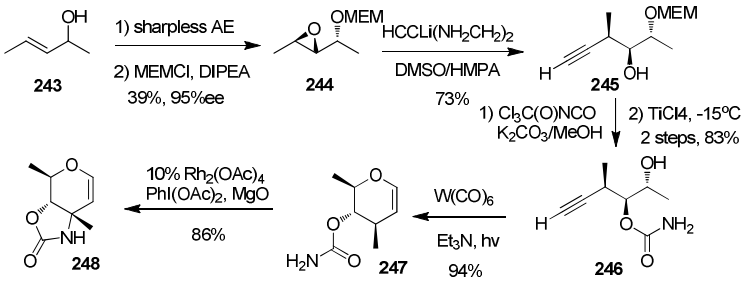
The same strategy to the synthesis of protected glycal of L-daunosamine **242** was further applied by utilizing a different starting material namely allenyl stannate **238**, as shown in Scheme 26.[65]



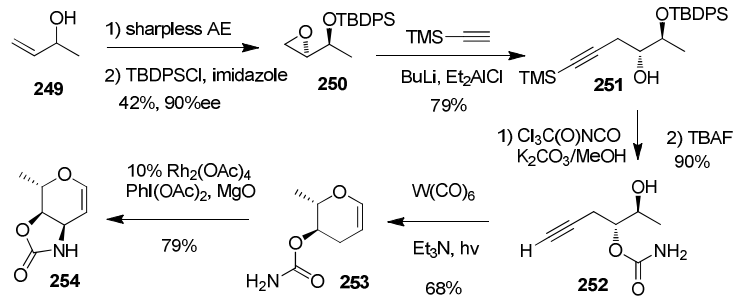
Scheme 26.

Another two successful applications of this strategy to the synthesis of protected glycals of D-saccharosamine and L-ristosamine using similar protocols were also presented by the same group (Scheme 27).[66]

Preparation of protected L-ristosamine glycal **254** began from racemic 3-buten-2-ol **249** through a similar sequence of reactions in 7 steps (Scheme 28).

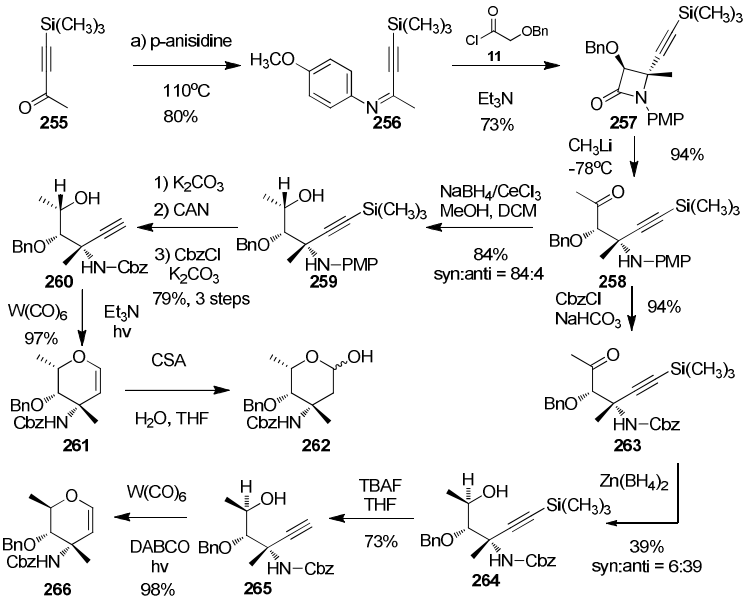


Scheme 27



Scheme 28

The above mentioned tungsten-catalyzed alkynol cycloisomerization was developed by McDonald and co-workers. It provided a rapid entry to both

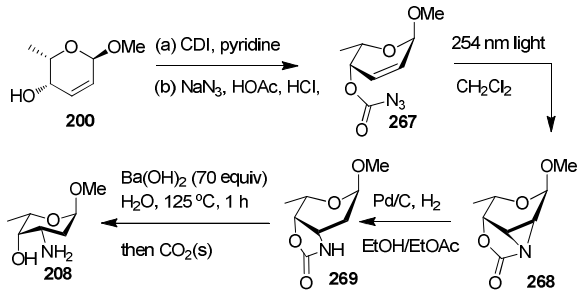


Scheme 29

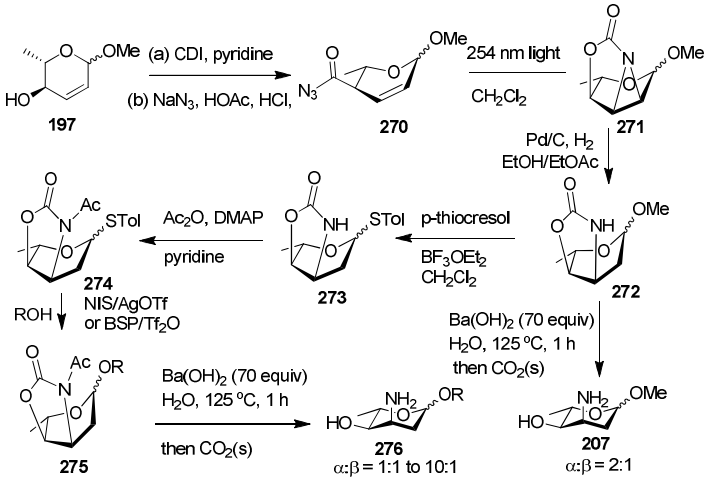
vancosamine and saccharosamineglycals, as shown in Scheme 29.[67] The amino sugars were constructed using an *endo*-cyclization methodology.

1.2.2.4 Aziridination of a nitrene with an olefine

In 2006, Lowary's group reported another new and stereospecific synthesis of methyl glycoside derivatives of daunosamine and ristosamine.[68] The key steps in the synthesis include a photochemically induced acylnitrene aziridination reaction followed by a regioselective hydrogenolytic cleavageof aziridine. The procedure is summarized in Scheme 30. In similar manner, synthesis of methyl L-ristosamine **207** from the known compound **197** has been described, as shown in Scheme 31.



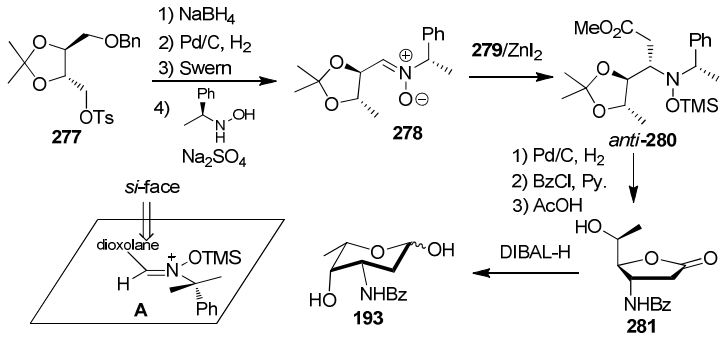
Scheme 30



Scheme 31

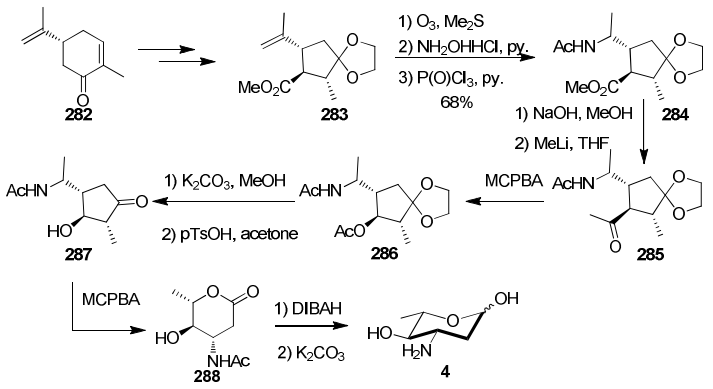
1.2.3 Chiral Auxiliary-Based Strategies

A chiral auxiliary based strategy, beginning from selected chiral synthetic intermediates, to stereoselectively elongate the carbon skeleton is the central point of the aminodeoxy sugars synthesis. From a synthetic viewpoint, it can be valuable to classify and investigate strategies originating from these chiral auxiliary building blocks. The auxiliaries' bulkiness enables control of stereoselectivity in the addition of nucleophiles.[69] Hamada's group[70] reported a stereocontrolled synthesis of *N*-benzoyl-L-daunosamine **193** utilizing a 1,3-addition of ketene methyl *tert*-butyldimethylsilylacetal (**279**) to the chiral nitrone **280** (Scheme 32). Molecular models suggested that the *si*-face attack of the enolate anion is favored due to steric hindrance associated with approach from *re*-face and may explain the high selectivity for the *S*-nitrone rather than the *R*-nitrone as depicted in model **A**.



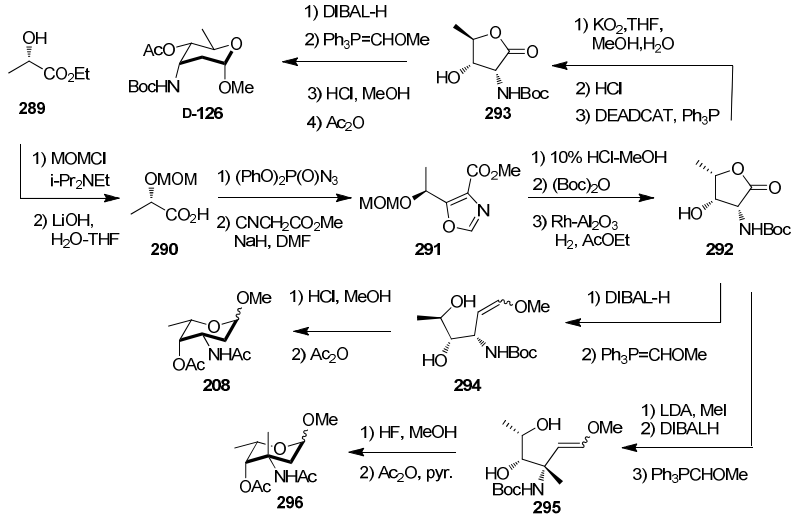
Scheme 32

Another example of total synthesis of L-acosamine was proposed by Kametani and co-workers,[71] with the synthesis commencing from chiral natural product-derived starting material such as carvone (Scheme 33).



Scheme 33

Shioiri and co-workers[72] developed an effective synthetic strategy to synthesize 3-amino-2,3,6-trideoxyhexoses *via* the key intermediate 4-alkoxycarbonyloxazole **291** (Scheme 34). The intermediate **291** can be easily prepared by direct *C*-acylation of isocyanoacetic esters **289** with *O*-protected α-hydroxycarboxylic

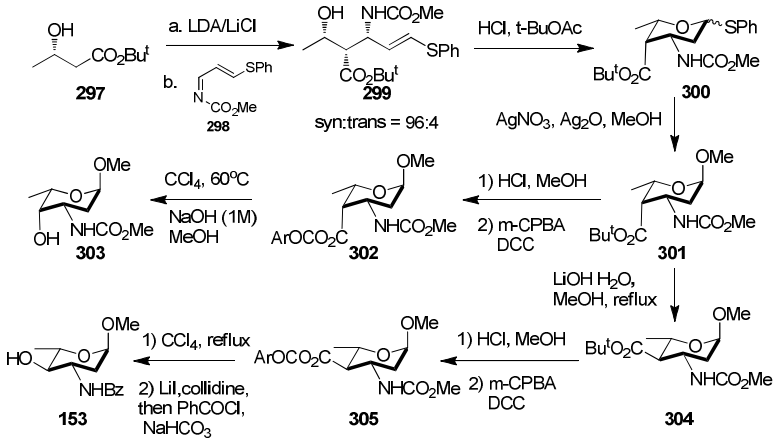


Scheme 34

acid **290** by the use of diphenylphosphoryl azide (DPPA), as summarized in Scheme 34.

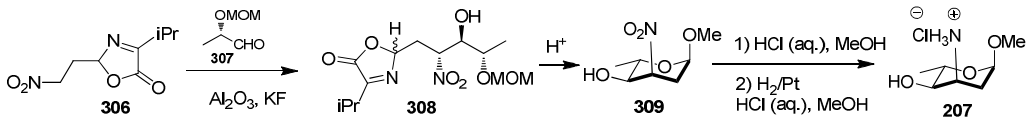
A concise approach to synthesize *N*-acyl derivatives of L-daunosamine **303** and

L-acosamine **153** was reported by Hatanaka's group in 1991.[73] The key steps of this sequence included the highly stereoselective enolate-imine condensation of the lithium dianion of *t*-butyl S-(+)-3-hydroxybutanoate **297** with *N*-acylimine **298**, as well as the transformation of compound **301** to **304** by base-induced inversion (Scheme 35).



Scheme 35

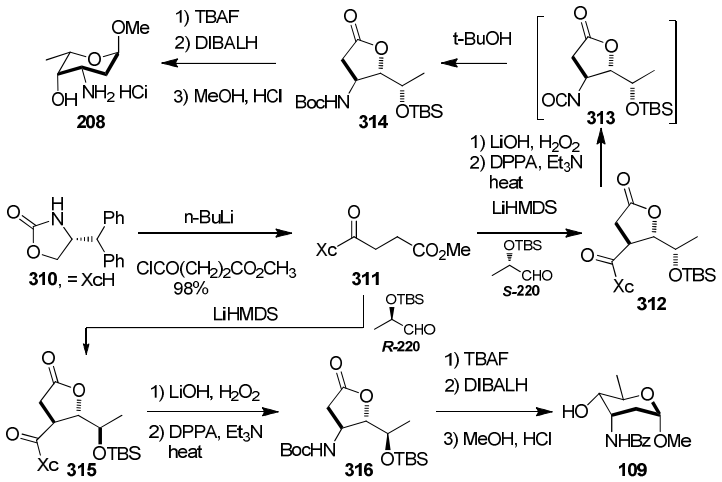
Barco *et al.*[74] reported a total synthesis of methyl L-ristosaminide **207** by utilizing oxazolidinone as the auxiliary (Scheme 36). The complete diastereo- and enantioselectivity of the sequence, in addition to the facile preparation of the starting materials are the main advantages of the synthesis.



Scheme 36

Another example for the construction of L-daunosamine and D-ristosamine derivatives was developed by Sibi and co-workers.[75] The syntheses proceeded *via*

an asymmetric aldol strategy, utilizing non-carbohydrate precursors as the auxiliary. Lithium enolate mediated aldol reactions of **311** with lactaldehydes (*S*)-**220** or (*R*)-**220** gave non-Evans *syn* aldol products with high selectivities which were then cyclized to lactone **312** and **315** respectively (Scheme 37).

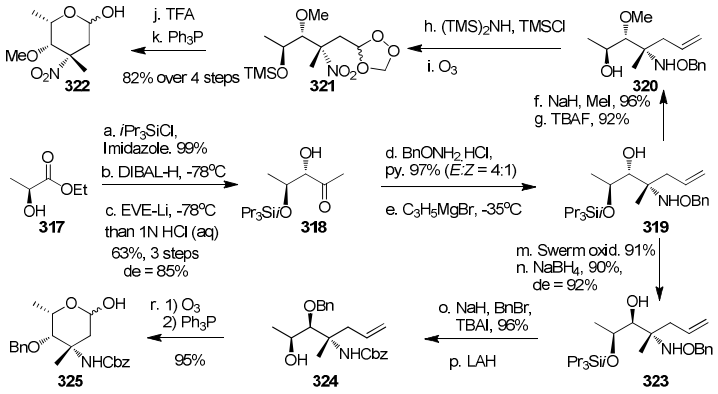


Scheme 37

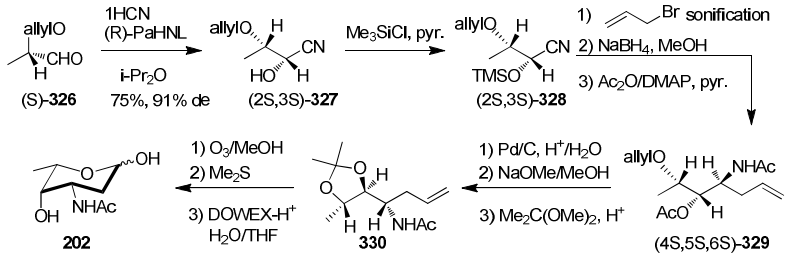
Evernitrose (**24**), with the L-arabino configuration, was the first naturally occurring nitro sugar to be isolated. It is a constituent of the oligosaccharide antibiotics everninomycin B, C, and D and is liberated upon acidic hydrolysis.[76] In 1998, Nicolaou *et al.* synthesized vancosamine derivative **325** (11 steps from **317**, ca. 25% overall yield) and evernitrose **322** (11 steps from **317**, ca. 30% overall yield) from a common chiral intermediate derived from L-lactic acid (Scheme 38).[77] These vancosamine donors are key intermediates which could be further applied to the stereoselective total synthesis of vancomycin.[78]

An elegant route for the stereoselective synthesis of N-acetyl-L-daunosamine was developed by Effenberger and co-workers in 2000,[79] applying a combination

of enzymatic and chemical steps (Scheme 39).



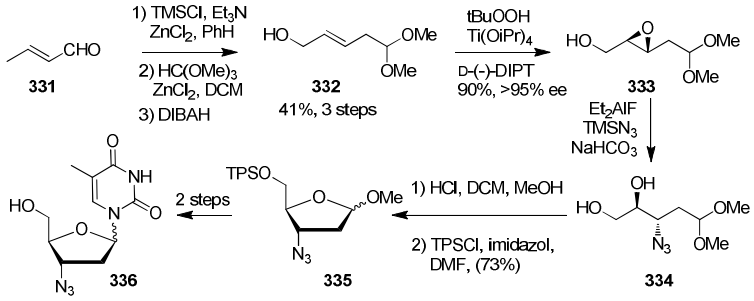
Scheme 38



Scheme 39

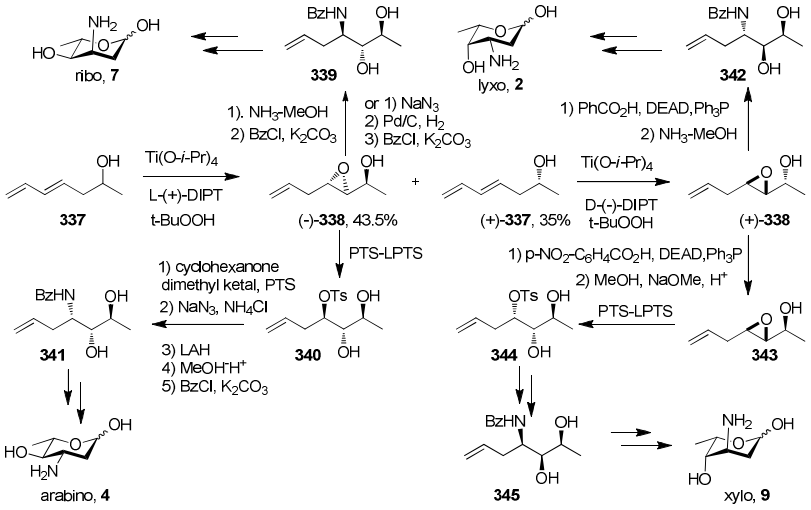
1.2.4 Asymmetric oxidation strategies

The asymmetric Sharpless' epoxidation and later, the asymmetric dihydroxylation have found widespread use in organic chemistry, particularly in the preparation of deoxy sugars. In previous sections, various oxidation strategies were briefly introduced and incorporated in the overall strategy. One former example of utilizing Sharpless' asymmetric epoxidation as key step was demonstrated in the efficient stereospecific total synthesis of D-AZT (9 steps starting from crotonaldehyde **331**) by Arshava, Jung and co-workers (Scheme 40).[80]



Scheme 40

A simple and divergent asymmetric synthesis of all four configurational isomers of 2,3,6-trideoxy-3-aminohexoses (l*yxo*, *arabino*,*ribo*, and *xylo*) from the racemic 3,6-heotadien-2-ol **337** was described by Dai and co-workers (Scheme 41).[81]

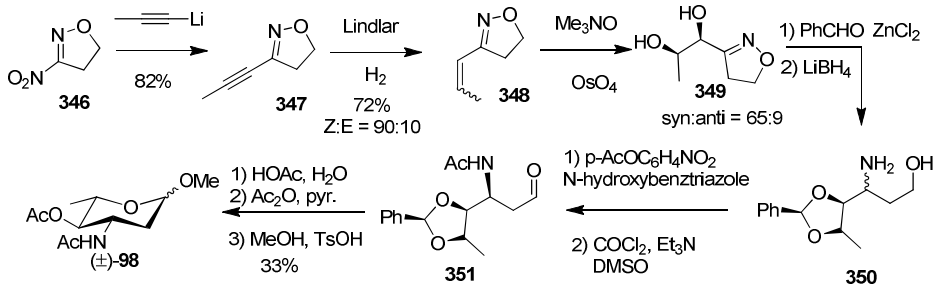


Scheme 41

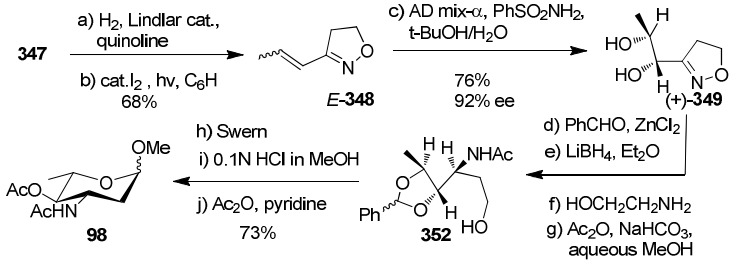
Wade's group reported the synthesis of amino sugar derivatives from dihydroisoxazole precursors through the formation of γ-aminoalcohol (Scheme 42).[82]

Later on, the same group presented the asymmetric synthesis of methyl L-*N*,*O*-diacetylacosamine **98** from the same starting material alkyne **347** in 10 steps with a 8.5% overall yield. The key step of the synthesis involved the

Sharpless' asymmetric dihydroxylation whereby the corresponding diol (+)-**349** was formed in 92% *ee* (Scheme 43).[83]

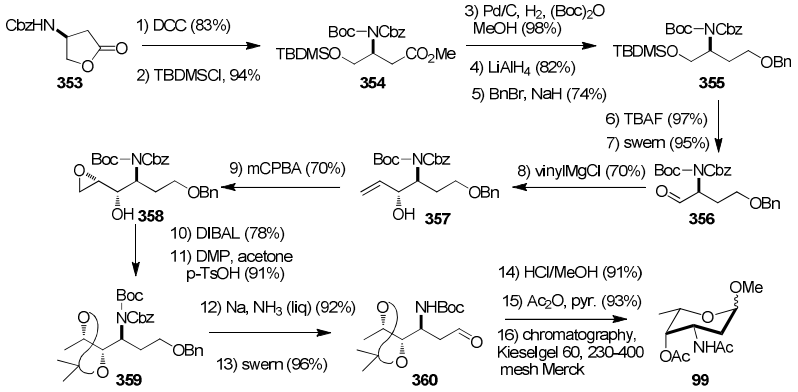


Scheme 42



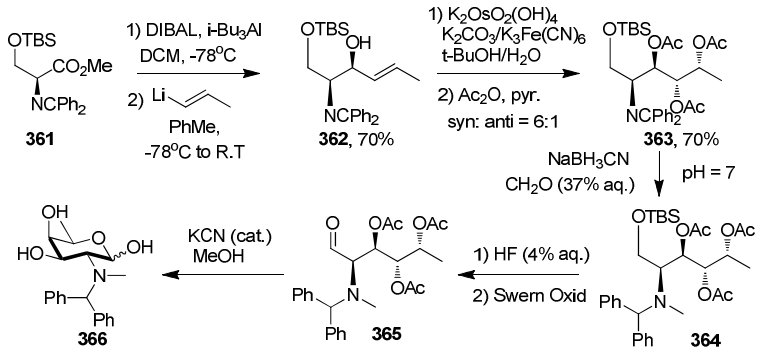
Scheme 43

A total synthesis of L-daunosamine *via* formation of the key intermediate of L-homoserinal derivative through epoxidation was developed by Janusz Jurczak's group (Scheme 44).[84]



Scheme 44

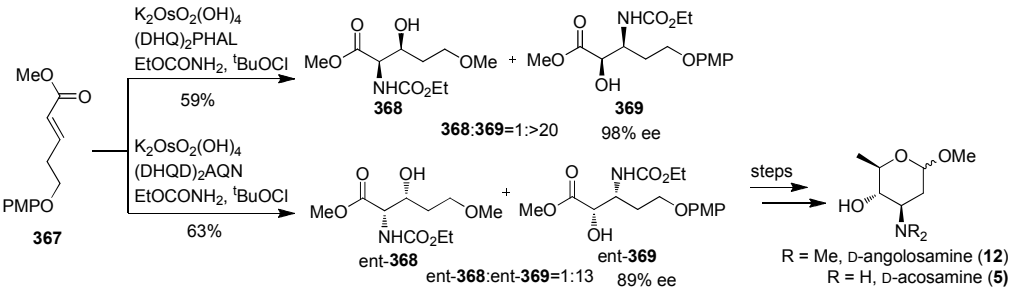
D-(+)-*N*-methylfucosamine **366** could be synthesized *via* Sharpless' dihydroxylation (13% overall yield over 7 steps) (Scheme 45).[85] TBS-protected methyl L-serinate benzophenone Schiff base (O'Donnell's Shiff base)[86] **361** was selected as the starting material to the intermediate **362**, with appropriate stereochemical configuration, through two steps chelation-controlled reduction and alkylation.



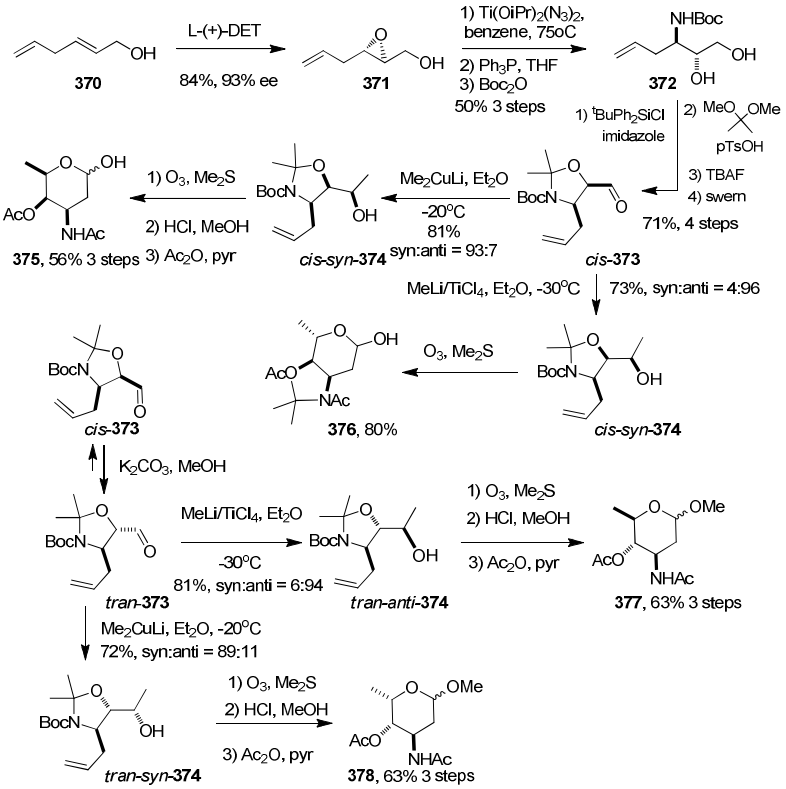
Scheme 45

Asymmetric aminohydroxylation (AA) of α,β-unsaturated ester **367** provided β-amino isomers **369** and *ent*-**369** with optimum regioselectivity in excellent *ee* by employing $(DHQ)_2AQN$ and $(DHQD)_2AQN$ as the chiral ligands and the chloramine salt of ethyl carbamate as the nitrogen source, which will serve as a starting point for the asymmetric synthesis of D-angolosamine **12** and D-acosamine **5** (Scheme 46).[87]

Riera's group[88] demonstrated a divergent and enantioselective approach to the four diastereomers of 3-amino-2,3,6-trideoxyhexoses including daunosamine, ristosamine, acosamine, and *epi*-daunosamine from starting material **9**, which was prepared from propargyl alcohol (Scheme 47).



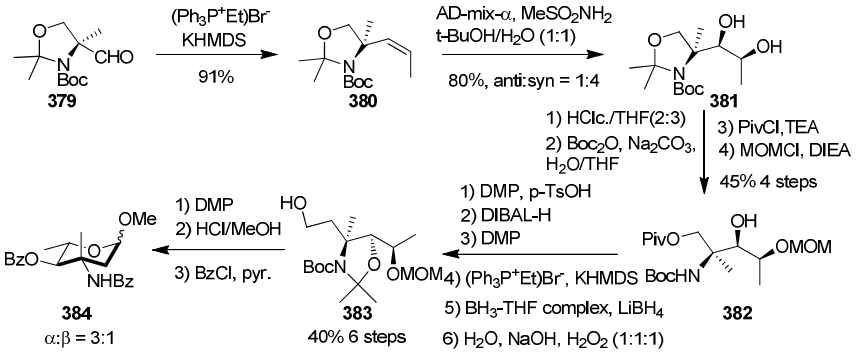
Scheme 46



Scheme 47

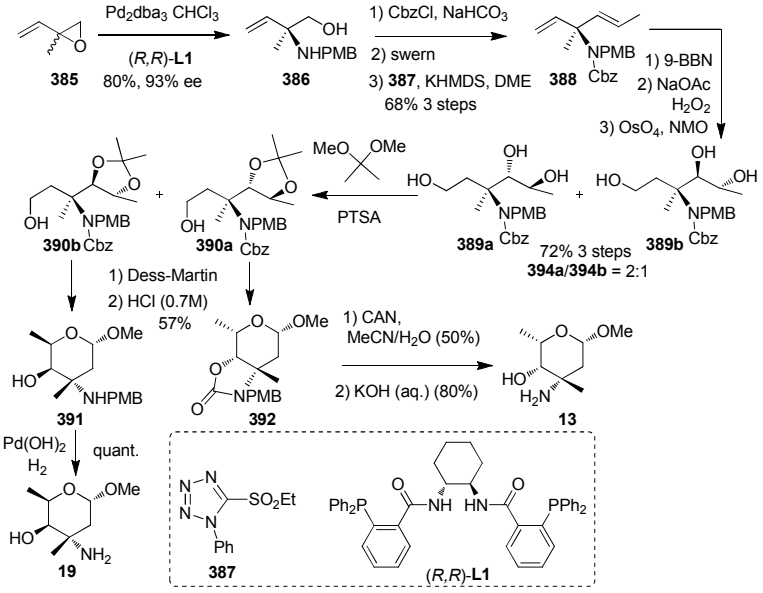
Avenoza and co-workers[89] reported a diastereoselective synthetic route to form methyl *N*,*O*-dibenzoyl-L-*epi*- vancosamine **384** (15 steps, 11% yield from **379**) through Sharpless' asymmetric dihydroxylation of a *Z* olefin **380** (derived from aldehyde **379**[90] which is analogous to aldehyde **373**) (Scheme 48). Sharpless' asymmetric dihydroxylation converted the olefin to an inseparable mixture of *anti*

and *syn*-diol with a 1:4 ratio.



Scheme 48

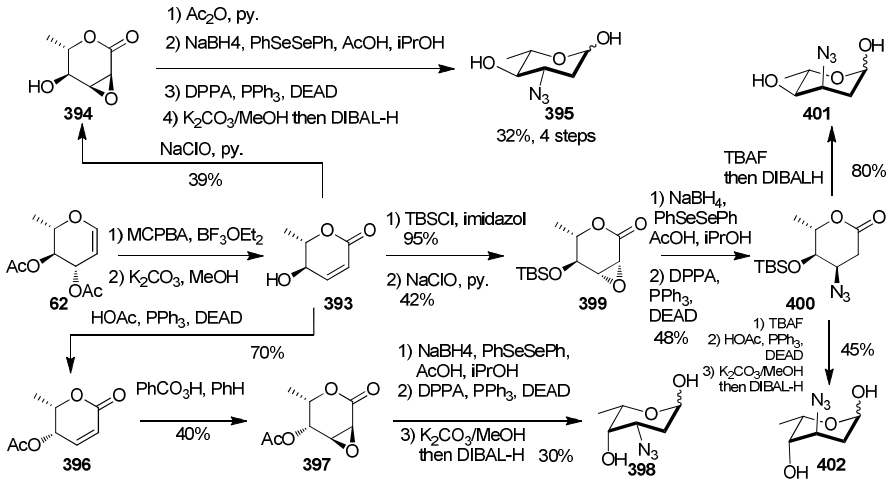
Recently, Trost's group[91] proposed asymmetric synthesis of the L-vancosamine derivative *via* the Pd-catalyzed regio- and enantioselective ring opening of isoprene monoxide **385** with primary amines as pro-nucleophiles (Scheme 49).



Scheme 49

Zhang's group[92] developed a divergent approach for producing 3-azido-2,3,6-trideoxy-L-hexoses; protected forms of daunosamine, ristosamine,

acosamine, and *epi*-daunosamine (Scheme 50). The absolute configuration at C-3 and C-4 was controlled by a chain of reactions; epoxidation occurring at the *anti*-face of the existing hydroxyl group, Mitsunobu reaction and selective reduction of the epoxide.

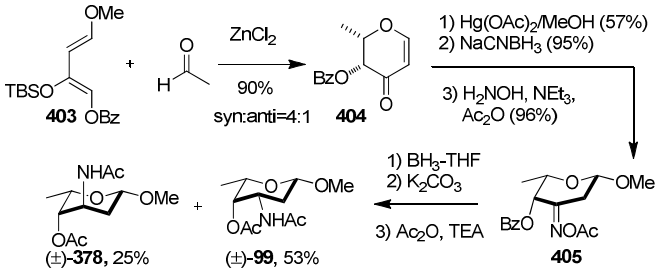


Scheme 50

1.2.5 Cycloaddtion strategies

Among all the strategies to synthesize amino deoxy sugars from non-carbohydrate precursors, cycloaddition is the most popular and competitive. Under ideal conditions, the formation of two bonds in the key step can afford the heterocyclic target which possesses highly controlled stereoselectivity on the newly formed stereocenters. According to the suprafacial-suprafacial model, only one pair of enantiomers is formed because of polarity controlled orientation and *exo*/*endo* selectivity. Frontier orbital overlap can explain the unique selectivity and differentiate the normal and inverse type of Diels-Alder reaction.[93] This field of natural product synthesis often utilizes Diels-Alder reaction which combines C-C

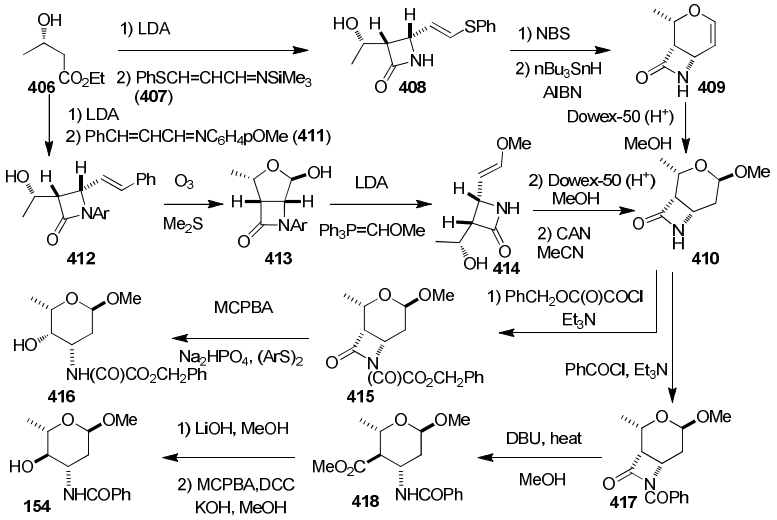
formation with regio- and diastereoselectivity at several centers since all six carbons on the pyranose ring can be potential targets. Danishefsky and co-workers[94] reported a very efficient approach to (±)-methyl 3,4-di-acetyldaunosamine **99** and (±)-methyl 3-*epi*-3,4-di-acetyldaunosamine **378**. Diels-Alder reaction between **403** and acetylaldehyde using $ZnCl_2$ as the Lewis acid enabled the formation of sugar ring **404** (*syn*:*anti*=4:1). The dihydropyrone **404** was then subjected to a series of reactions to afford formoxime **405** which was further converted to **99** and **378** in a ratio of 2:1 (Scheme 51).



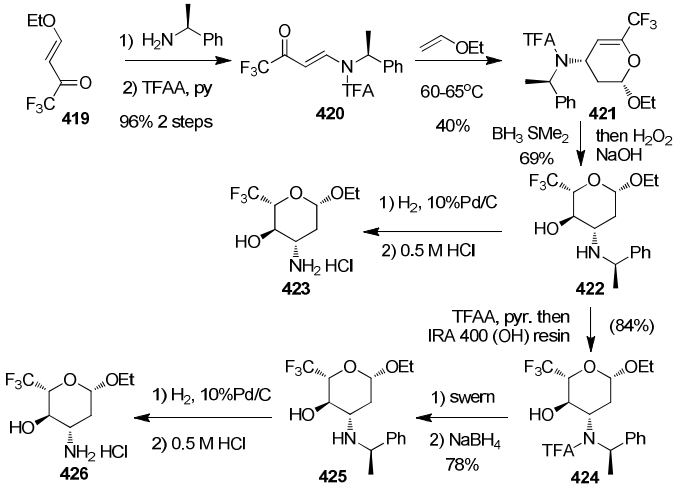
Scheme 51

Hart's group[95] reported a route to the protected analogs of amino-saccharides daunosamine (**414**) (9.8% yield in 8 steps) and acosamine (**154**) (6.6% in 10 steps) from (*S*)-ethyl 3-hydroxybutyrate **406** *via* ester-imine condensation as key step (Scheme 52).

Larsen's group[96] have developed a stereoselective approach to synthesize L-daunosamine **426** and L-acosamine **423** from a common starting material **419** (Scheme 53). Through a hetero-Diels-Alders reaction between vinylogous imide **420** and ethyl vinyl ether,[97] a pyranose ring system of these carbohydrate analogues (cycloadduct **421**) was produced in a 40% yield.



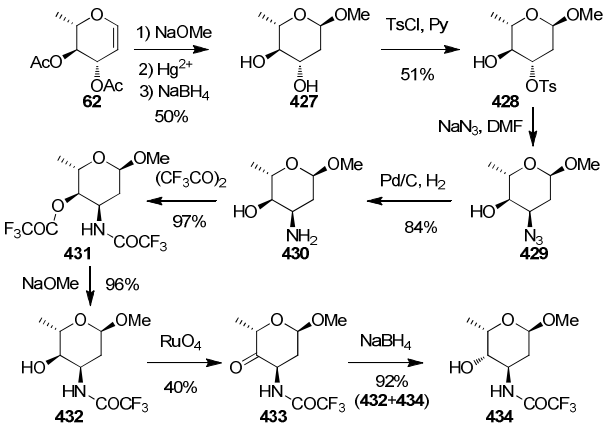
Scheme 52



Scheme 53

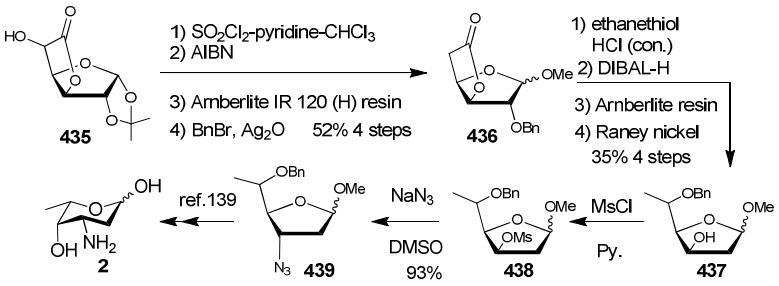
1.2.6 Nucleophilic substitution

The stereoselective nucleophilic substitution by azide at the C-3 position of the hexose ring followed by hydrogenation of the azido, would lead to the corresponding deoxyamino sugars. Earlier examples for this approach to the synthesis of methyl L-ristosamine and methyl D-daunosamine from L-rhamnal were described by Sztaricskai's group (Scheme 54).[98]



Scheme 54

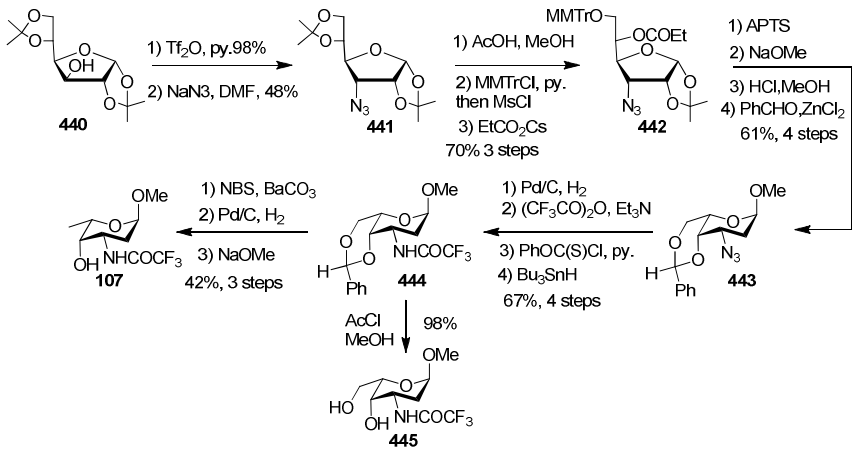
An example for this approach to the synthesis of L-daunosamine **2** from the known 1,2-acetonide derivative[99] have been provided by Gurjara and co-workers (Scheme 55).[100]



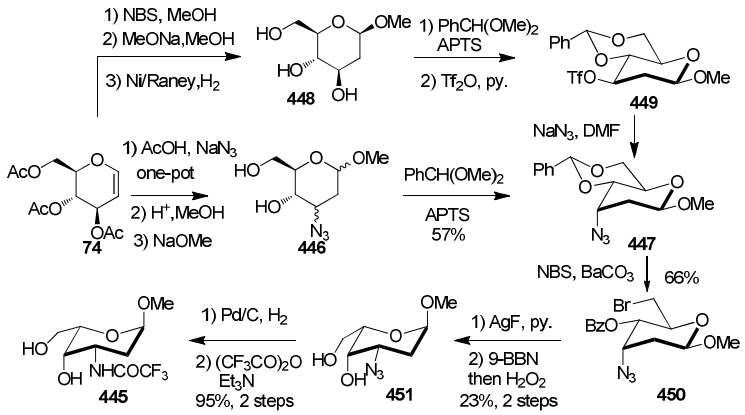
Scheme 55

An alternative route to 3-amino-2,3-dideoxy sugars had been developed by Monneret and co-workers,[101] involving nucleophilic substitution of triflate to azide at C-3 position of the hexose ring as the key step (Scheme 56). In this route, methyl 3-trifluoroacetamido-2,3-dideoxy-α-L-*lyxo*-hexopyranoside **445** was synthesized from derivatives of D-glucose following two pathways. The first one which involves 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose (**440**) as starting material, is mainly based upon azidation at C-3, inversion of configuration at C-5 and then radical deoxygenation at C-2 (13 steps and 12% overall yield). This

pathway also afforded methyl *N*-trifluoroacetyl-α-L-daunosamine **107** (15 steps and 5.2% overall yield). The second pathway, as shown in scheme 57, which started from tri-*O*-acetyl-D-glucal (**74**), relied essentially upon Michael addition of azide onto the corresponding hex-2-enose and further glycosidation to afford azido **446**. After the β-D-*ribo* isomer **446** was subsequently converted into its *p*-methyl glycoside **447**, inversion of configuration at C-5 was carried out *via* the formation of 6-bromo-sugar **450**, followed by construction of the hex-5-enopyranoside. Hydroboration of hex-5-enopyranoside stereoselectively afforded **451**, which upon catalytic hydrogenation and trifluoroacetylation gave **445** (9 steps, but less than 1% overall yield). Another route to synthesize **447** was described from the same starting material tri-*O*-acetyl-D-glucal (**74**), identifying the azide displacement of **449** with NaN_3 as the key step (6 steps and 12% overall yield).



Scheme 56

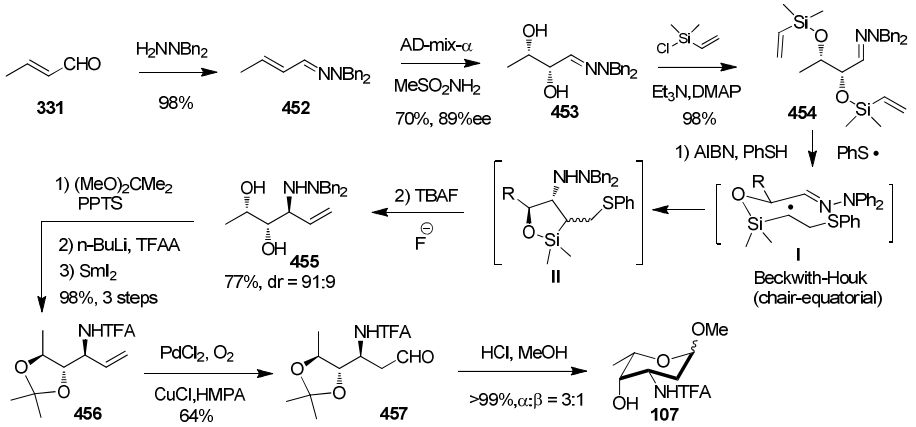


Scheme 57

1.2.7 Radical strategy

Friestad *et al.* reported a silicon-tethered radical addition strategy to access L-daunosamine (**2**), as shown in scheme 58.[102] Condensation of *trans*-crotonaldehyde **331** with dibenzylhydrazine is the first step of the synthesis. The resulting (*E*)-α,β-unsaturated hydrazone **452** was subjected to Sharpless' asymmetric dihydroxylation[103] to form the *syn*-diol **453** with 89% *ee*. The product underwent silylation with chlorodimethylvinylsilane to form the radical cyclization precursor **454**. In the key step, exposure to thiyl radicals generated from benzenethiol and AIBN led to the radical cyclization of dibenzylhydrazone **454** with fluoride, yielding vinyl adduct **455** (*dr* 91:9). During the process, thiyl radical was added to the vinyl group, generating an intermediate alkyl radical which could undergo 5-*exo* cyclization with the C=N functionality of the hydrazine. The temporary tether was removed by treatment with fluoride (**II**) and the benzenethiolate was eliminated, regenerating the vinyl group of an allylic amino alcohol. The *anti*-relative configuration is favored and is consistent to a

chairlike Beckwith-Houk transition state model (**I**),[104] with the exocyclic substituent R adopting an equatorial position. Under mild conditions, a tin-free diastereoselective radical addition of vinyl group may be achieved using the silicon tethering approach.



Scheme 58

Two years later, the same group extended their studies in this area. They developed two alternative methods for the introduction of 2-acetyl fragment by means of radical equivalents in an acetaldehyde Mannich addition reaction.[105] In the first system, haloacetal 6-*exo* radical cyclization in the presence of a 2-benzyloxy substituent will invert the previously established stereochemistry, leading to the L-daunosamine **2** configuration (Fig. 9, eq. 1). In the second process, the 2-(phenylthio)vinyl group can be installed *via* diastereoselective

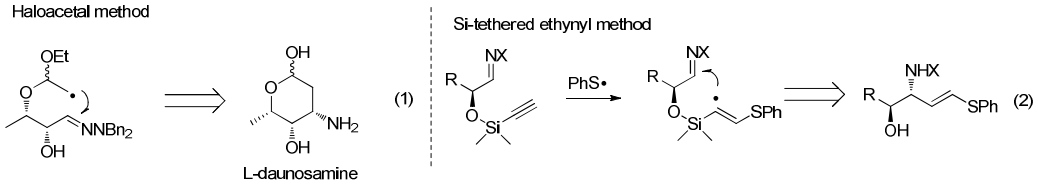
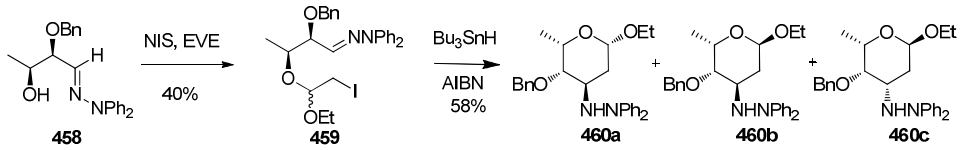


Fig. 9

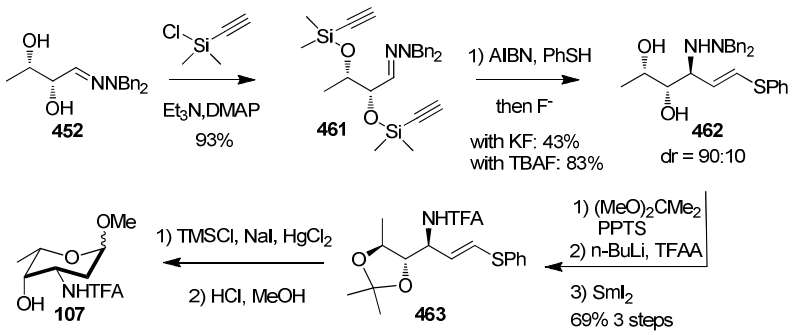
tin-free radical addition to α-hydroxyhydrazones through 5-*exo* cyclization of a silicon tetheredethynyl group (Fig. 9, eq. 2).

Monobenzyl-protected dihydroxyhydrazone **458** was synthesized from *trans*-crotonaldehyde by a three-step method which involved condensation with diphenylhydrazine, Sharpless' asymmetric dihydroxylation (89% *ee*), and stannulene-mediated hydroxyl differentiation.[106] Treatment of **458** with *N*-iodosuccinimide (NIS) in ethyl vinyl ether generated iodoacetal **459** in modest yield with a mixture of diastereomers (Scheme 59). Under typical tin-mediated contions initiated by AIBN, cyclization occurred and resulted in the formation of a mixture of three 3-aminosugars **460a-c** with a ratio of 5:3.8:1 (58% yield).



Scheme 59

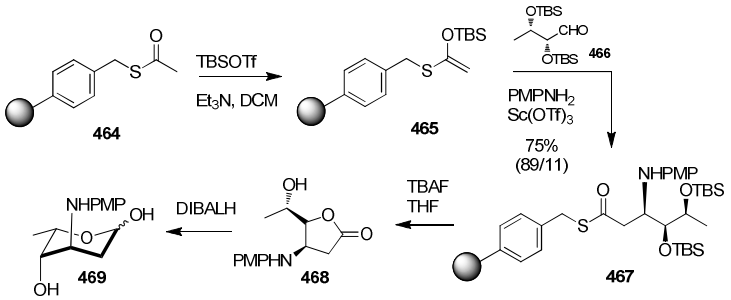
The silicon-tethered strategy was acknowledged as a reliable strategy for generation of the alternative L-daunosamine configuration. From crotonaldehyde **331**, the reaction entailed an *in situ* generation of hydrogen iodide in moist acetonitrile and mercuric chloride to afford *N*-trifluoroacetyl-L-daunosamine **107** with a 17% overall yield (Scheme 60).



Scheme 60

1.2.8 Solid-phase-based strategy

A solid-phase-based strategy towards 3-amino deoxy sugars, with the use of polymeric supports for simplifying purification procedures, was developed by Kobayashi and co-workers in 1998, as shown in Scheme 61.[107] Thioester resin **464** was silylated to give polymer-supported *silyl enol ether* (PSSEE) **465**. The key three-component reaction of an aldehyde **466**, an amine and **465** proceeded smoothly in the presence of catalytic amount of scandium triflate ($Sc(OTf)_3$) to afford the corresponding adduct **467** with good stereoselectivity (89:11). Subsequent deprotection of the TBS group induced a spontaneous cyclization to deliver lactone **468**, which was reduced with DIBAL-H to produce L-3-*epi*-daunosamine derivative **469**.

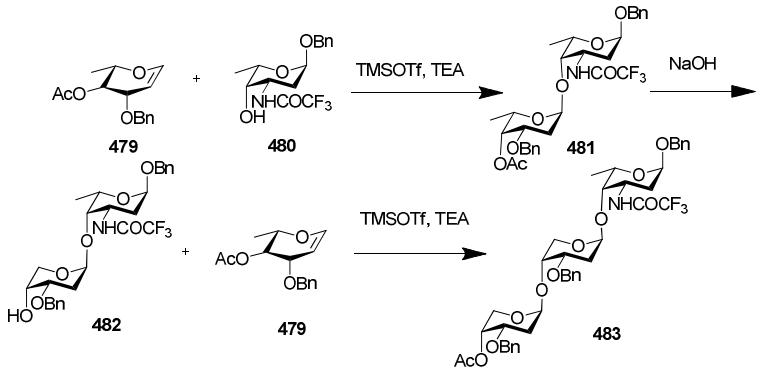


Scheme 61

1.2.9 Synthesis of 3-amino-2,3,6-trideoxy containing disaccharides and oligosaccharides

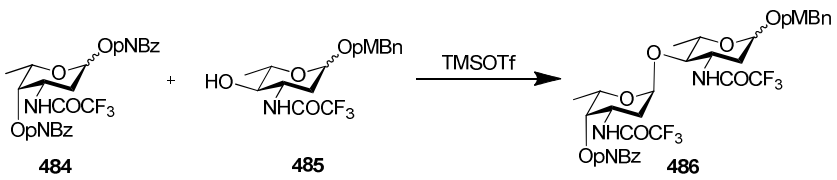
In contrast to 3-amino-2,3,6-trideoxy monosaccharides, there are only limited examples in the reports that describe chemical synthesis of 3-amino-2,3,6-trideoxy containing disaccharides and oligosaccharides. Thus, the construction of 3-amino- and 3-nitro-2,3-dideoxyglycosides with linkages to other residues of sugar *via* either 1,3-*cis* or 1,3-*trans*-3-amino glycosidic bonds have drawn increasing interest, due to their wide range of applications in medicine, pharmaceutical and chemistry fields.[108] Stereocontrolled glycosylation, especially in the assembly of glycosidic bonds in deoxysugar derivatives, is fundamentally difficult to achieve due to the absence of stereodirecting substituents at C-2.[109] Consequently, in the past decades, many progresses in the synthesis of 3-aminodeoxyglycosides have predominantly concentrated on the glycosidic bond's stereoselective formation. However, the development of dependable methods for stereoselective construction of both α- and β-deoxyglycosides remains an exciting and challenging area of research. Despite the α-deoxyglycosides being more accessible than the β-anomers due to the anomeric effect, under acidic conditions, glycosylation of 2-deoxyglycosides commonly provides an anomeric mixture. In addition, the frequently employed methods for the synthesis of 1,3-*cis*-3-aminodeoxydisaccharides and oligosaccharides use an indirect approach; the glycosyl donors bearing a protected heteroatom at C-2 which directs facial selectivity of the reaction. This protecting group can be then cleaved off at a later stage.[110]

Most of the described syntheses include glycosylation of aminodeoxy monosaccharide acceptor with glycosyl donor, accompanied by a suitable activator. In an attempt to synthesize anthracycline antibiotics containing disaccharide residue, glycosylation of 2-deoxy-L-fucose donor **479** with daunosamine acceptor **480** was accomplished in the presence of triethylamine and TMSOTf. *O*-deacetylation and coupling of the resultant aminodeoxy disaccharide **482** with another glycosyl donor delivered aminodeoxy trisaccharide **483** (Scheme 65).[111]



Scheme 65

Synthesis of a disaccharide chain **486** in which the second aminosugar residue (daunosamine) was bound to the first one *via* α (1→4) linkage had also been stated in literature. The glycosylation reaction of suitably protected 2-deoxy-L-rhamnoside **484** with daunosamine donor derivative **485** in the presence of TMSOTf had been reported (Scheme 66).[112]



Scheme 66

1.3 Conclusions

The synthesis of monosaccharides containing 3-amino- and 3-nitro-2,3-dideoxy sugars and their derivatives has been a daunting challenge in carbohydrate research due to the presence of numerous stereogenic centers with diverse functionalities. Despite these existing problems, remarkable progresses have been achieved for the preparation of complex carbohydrates in the past decades. The development in this area is substantial and the problems have been addressed thoroughly, paving a convenient way to the construction of these carbohydrates in high stereoselectivities as well as reasonable yields. Such consequence enables efficient analysis of the biological activities and brought about significant advances in the pharmaceutical fields. Particularly, asymmetric synthesis has allowed the preparation of a variety of amino sugars in an expedient manner, deviating from the pioneer approaches of employing natural carbohydrates as precursors.

In contrast to monosaccharide based 3-amino- and 3-nitro-2,3-dideoxy sugars, the synthesis of glycoconjugates featuring amino sugars in their scaffold has a less comprehensive advancement. Due to importance of these glycoconjugates, many have attempted to deliver concise and economical routes to their synthesis.

However, such glycoconjugates are bulky and possess a bundant stereochemistry thus, devising expedient routes for their synthesis remains difficult. There continues to be vast potentials and interests in producing efficient synthesis for their construction. Therefore, in essence, the development of straightforward synthesis, in terms of productivity and efficiency, for these glycoconjugates will continue to be of immense interests and this potential area will likely see more expansion in the future.

1.4 References

1 (a) F. Barresi and O. Hindsgaul, *Chemically Synthesized Oligosaccharides*; **1994**; A Searchable Table of Glycosidic Linkages, *J. Carbohydr. Chem.* **1995**, *14*, 1043; (b) F. Barresi and O. Hindsgaul, Glycosylation Methods in Oligosaccharide Synthesis. *In Modern Synthetic Methods*; **1995**; 281.

2 (a) A. Kirschning, A. F. W. Bechtold and J. Rohr, *Top. Curr. Chem.* **1997**, *188*, 2.

3 (a) H. Brockmann, E. Spohler and Waehneldt, T. *Chem. Ber.* **1963**, *96*, 2925; (b) H. Brockmann and T. Waeneldt, *Naturwissenschaften* **1963**, *50*, 92.

4 (a) J. F. Kennedy, and C. A. White, *In Bioactive Carbohydrates in Chemistry, Biochemistry, and Biology*; Ellis Horwood Publishers: Chichester, **1983**; (b) A. C. Weymouth-Wilson, *Nat. Prod. Rep*. 1997, *14*, 99.

5 A. Di Marco, M. L. Gaetani, M. Dirogotti and O. Soldati, Bellini, *Nature* **1964**, *201*,706.

6 F. G. Arcamone, G. Cassinelli, A. Fantani, P. Grein, C. Orezzi and C. P. Spalla, *Biotechnol. Bioeng*. **1969**, *11*, 1101.

7 (a) R. Weiss and B. Semin. *Oncol.* **1992**, *19*, 670; (b) M. J. Zaya, R. N. Hines, and J. C. Stevens, *Drug Metab. Dispos.* **2006**, *34*, 2097.

8 F. Kong, N. Zhao, M. M. Siegel, K. Janota, J. S. Ashcroft, F. E. Koehn, D. B. Borders and G. T. Carter, *J. Am. Chem. Soc.* **1998**, *120*, 13301.

9 For some excellent reviews on the approaches to the synthesis of deoxy sugars, see: (a) K.

Toshima and K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503; (b) A. Kirschning, A. F. W. Bechthold and J. Rohr, *In Bioorganic Chemistry: Deoxysugars, Polyketides and Related Classes: Synthesis; Biosynthesis: Enzymes*, **1997**. pp. 1; (c) T. M. Hallis and H. Liu, *Acc. Chem. Res.* **1999**, *32*, 579; (d) C. H. Marzabadi and R. W. Franck, *Tetrahedron* **2000**, *56*, 8385; (e) X. He, G. Agnihotri and Liu, H.-W. *Chem. Rev.* 2000, **100**, 4615; (f) D. Hou and T. L. Lowary, *Carbohydr. Res.,* **2009**, *344*, 1911.

10 F. M. Hauser and S. R. Ellenberger, *Chem. Rev*., **1986**, *86*, 35.

11 P. Herczegh, M. Zsely, I. Kovacs, G. Batta and F. J. Sztaricskai, *Tetrahedron Lett.* **1990**, *31*, 1195-1198.

12 F. Arcamone, G. Franceschi, P. Orezzi, W. Babier and R. Mondelli, *J. Am. Chem. Soc.* **1964**, *86*, 5334. (b) F. Arcamone, G. Cassinelli, P. Orezzi, G. Franceschi and R. Mondelli, *J. Am. Chem. Soc.* **1964**, *86*, 5335.

13 (a) F. Arcamone, G. Franceschi, S. Penco, and A. Selva, *Tetrahedron Lett.* **1969**, 1007; (b) S. K. Carter, *J. Natl. Cancer Inst.* **1975**, *55*, 1265; (c) T. Skovsgaard, and N. I. Nissen, *Dan. Med. Bull.* **1975**, *22*, 62.

14 A. C. Richardson, *J. Chem. Soc., Chem. Commun.* **1965**, 1627.

15 I. Kovacs, P. Herczegh and F. J. Sztaricskai, *Tetrahedron* **1991**, *37*, 7837-7844.

16 J. Lau, E. B. Pedersen and C. M. Mielsen, *Acta Chemica Scandinavica*, **1991**, *45*, 616-620.

17 E. De Clercq, A. Van Aerschot, P. Herdewijn, M. Baba, R. Pauwels and J. Balkzarini, *Nucleosides Nucleotides,* **1989**, *8*, 659; (b) R. Busson, L. Colla and H. Vanderhaeghe, *Nucl. Acid Res.* **1981**, *9*, 49.

18 Y. St- Denis, J. F. Lavallee, D. Nguyen and G. Attardo, *Synlett* **1995**, 272.

19 C. Kolar, K. Dehmel, H. Moldenhauer and M. Gerken, *J. Carbohydrate Chem.* **1990**, *9*, 873.

20 Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe and S. Terashma, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 423.

21 B. Liberek, A. Dabrowska, R. Frankowski, M. Matuszewska and Z. Smiatacz, *Carbohydr. Res.* **2002**, *337*, 1803; (b) A. Dabrowska, P. Dokurno, A. Konitz and Z. Smiatacz, *Carbohydr. Res.* **2000**, *323*, 230.

22 M. A. Brimble, R. M. Davey, M. D. Mcleod and M. Murphy, *Australia J. Chem.* **2003**, *56*, 787.

23 M. H. McCormick, W. M. Stark, G. E. Pittenger, R. C. Pittenger and J. M. McGuire, *"Antibiotics*

Annual"; Medical Encyclopedia, Inc.: New York, **1956**; p 606.

24 (a) D. H. Williams and J. R. Kalman, *J. Am. Chem. Soc.* **1977**, *99*, 66; (b) D. H. Williams, V. Rajananda, M. P. Wiiliamson and G. Bojesen, in P. G. Sammes (Ed.), *Topics in Antibiotic Chemistry*, Vol. 5, Section B, Ellis Horwood, Chichester, **1980**, pp 119.

25 I. Kimura, K. Yamamoto, K. Harada and M. Suzuki, *Tetrahedron Lett.,* **1987**, *28*, 1917; (b) I. Kimura, Y. Ota, R. Kimura, T. Ito, Y. Yamada, Y. Kimura, Y. Sato, H. Watanabe, Y. Mori, K. Harada, and M. Suzuki, *Tetrahedron Lett.,* **1987**, *28*, 1921.

26 H. Murata, K, Harada, M Suzuki, T. Ikemoto, T. Shibuya, T. Haoeishi, and A. Torikata, J. Antibiot., **1989**, *42*, 701.

27 N. J. Skelton, D. H. Williams, R. A. Monday, and J. C. Ruddock, *J. Org. Chem.,* **1990**, *55*, 3718.

28 M. Debono, R. M. Mollov, *J. Org. Chem.* **1980**, *45*, 4685.

29 R. Greven, P. Jiitten and H. D. Scharf, *Carbohydr. Res.* **1995**, *275*, 83.

30 D. Socha, M. Jurczak and M. Chmielewski, *Tetrahedron,* **1997**, *53*, 739.

31 (a) S. Nagumo, I. Umezawa, J. Akiyama, H. Akita, *Chem. Pharm. Bull.* **1995**, *43*, 171; (b) M. Ono, C. Saotome and H. Akita, *Heterocycles,* **1997**, *45*, 1257; (c) M. Ono, C. Saotome and H. Akita, *Tetrahedron: Asymmetry,* **1996**, *7*, 2595; (c) C. Saotome, M. Ono and H. Akita, *Tetrahedron: Asymmetry,* **2000**, *11*, 4137.

32 (a) M. Cherest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, *18*, 2199–2204; (b) N. T. Anh, O. Eisentein, *Nouv. J. Chim.* **1977**, *1*, 61–70.

33 S. G. Davies and G. D. Smyt, Tetrahedron: Asymmetry, **1996**, *7*, 1273; (b) S. G. Davies, G. D. Smyth and A. M. Chippindale, *J. Chem. Soc*., *Perkin Trans. 1*, **1999**, 3089.

34 (a) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu and X.-L. Zhang, *J. Org. Chem.,* **1992**, *57*, 2768; (b) H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.,* **1994**, *94*, 2483.

35 S. K. Bagal, S. G. Davies, A. M. Fletcher, J. A. Lee, P. M. Roberts, P. M. Scott and J. E. Thomson, *Tetrahedron Lett.* **2011**, *52*, 2216.

36 W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.* **1955**, *77*, 89.

37 F. M. Hauser, R. P. Rhee and S. R. Ellenberger, *J. Org. Chem.,* **1984**, *49*, 2236.

38 (a) N. Sewald, K. D. Hiller, M. Körner, M. Findeisen, *J. Org. Chem.* **1998**, *63*, 7263; (b) For a general description of this conjugate addition approach refer to: N. Sewald, *Amino Acids* **1996**, *11*,

397.

39 Review: M. Hirama, and S. Ito, Heterocycles, **1989**, *28*, 1229.

40 M. Hirama, T. Shigemoto, Y. Yamazaki and S. Ito, *J. Am. Chem. Soc.,* **1985**, *107*, 1797.

41 F. Johnson, *Chem. Rev.,* **1968**, *68*, 375.

42 H. B. Burgi, J. M. Lehn and G. Wipff, *J. Am. Chem. Soc.,* **1974**, *96* , 1956.

43 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.,* **1976**, 735.

44 (a) P. Caramella, N. G. Rondan, M. N. Paddon-Row and K. N. Houk, *J. Am. Chem. Soc.,* **1982**, *103*, 2438; (b) M. N. Paddon-Row, N.G. Rondan and K. N. Houk, *ibid*, **1982**, *104*, 7162.

45 (a) M. Hirama, T. Shigemoto, Y. Yamazaki and S. Ito, *Tetrahedron Lett.,* **1985**, *26*, 4133; (b) M. Hirama, T. Shigemoto, and S. Itô, *Tetrahedron Lett.* **1985**. *26*, 4137.

46 Y. Matsushima and J. Kino, *Tetrahedron Lett.* **2006**, *47*, 8777.

47 Y. Matsushima and J. Kino, *Eur. J. Org. Chem.* **2010**, 2206.

48 Y. Matsushima and J. Kino, *Tetrahedron* **2008**, *64*, 3943.

49 (a) M. Frohn, M. Dalkiewicz, Y. Tu, Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1998**, *63*, 2948–2953; (b) K. Uchida, K. Ishigami, H. Watanabe, T. Kitahara, *Tetrahedron* **2007**, *63*, 1281.

50 M. Ono, C. Saotome, H. Akita, *Tetrahedron: Asymmetry* **1996**, *7*, 2595.

51 (a) M. Hirama, T. Shigemoto and S. Ito, *J. Org. Chem.* **1987**, *52*, 3342; (b) M. Hirama, I. Nishizaki, T. Shigemoto, and S. Ito, *J. Chem. Soc., Chem. Commun.,* **1986**, 393; (c) M. Hirama. *J. Synth. Org. Chem. Jpn.,* **1987**, *45*. 346; (d) M. Hirama, H. Hioki, S. Itô, and C. Kabuto, *Tetrahedron Lett.,* **1988**, *29*, 3121; (e) M. Hirama, H. Hioki, and S. Itô, *Ibid.,* **1988**, **29**, 3125. 11; (f) M. Hirama, T. Iwakuma, and S. Itô, *J. Chem. Soc., Chem. Commun.,* **1987**, 1523; (g) M. Hirama, T. Shigemoto and S. Itô, *J. Org. Chem,* **1987**, *52*, 3342.

52 B. Fraser-Reid and J. C. López, *Curr. Org. Chem.,* **2009**, *13*, 532.

53 (a) O. Achmatowics Jr, P. Bukowski, B. Szechner, A. Zwierzchowska, *Tetrahedron* **1971**, *27*, 1973; (b) O. Achmatowics Jr, B. Szechner, *Bull. Acad. Pol. Sc.* **1971**, *31*, 309.

54 P. G. Sammes, D. Thetford, *J. Chem. Soc., Chem. Commun.* **1985**, 352; (b) P. G. Sammes and Dean. Thetford, *J. Chem. Soc. Perkintrans.* I **1988**, 111.

55 F. Kong, N. Zhao, M. M. Siegel, K. Janota, J. S. Ashcroft, F. E. Koehn, D. B. Borders, and G. T. Carter, *J. Am. Chem. Soc.* **1998**, *120*, 13301.

56 T. Doi, K. Shibata, A. Kinbara and T. Takahashi, *Chem. Lett.,* **2007**, *36*, 1372.

57 K. C. Nicolaou, P. S. Baran, Y. L. Zhong and J. A. Vega, *Angew. Chem. Int. Ed.* **2000**, *39*, 2525.

58 G. R. Smith and R. M. Giuliano, *Carbohydr. Res.* **2000**, *323*, 208.

59 K. A. Parker and W. Chang, *Org. Lett.,* **2003**, *5*, 3891-3893.

60 (a) J. A. Marshall, Z.-H. Lu and B. A. Johns, *J. Org. Chem.* **1998**, *63*, 817; (b) J. A. Marshall and C. M. Grant, *J. Org. Chem.* **1999**, *64*, 8214.

61 (a) P. Varelis and B. L. Johnson, *Aust. J. Chem.* **1995**, *48*, 1775; (b) A. Solladie-Cavallo and F. Bonne, *Tetrahedron: Asymmetry* **1996**, *7*, 171.

62 (a) J. A. Marshall and X. J. Wang, *J. Org. Chem.* **1991**, *56*, 3211; (b) J. A. Marshall and X. J. Wang, *J. Org. Chem.* **1992**, *57*, 1242. For a review of this and related stereoselective addition reactions, see: J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31.

63 F. E. McDonald, K. S. Reddy, Y. Diaz, *J. Am. Chem. Soc.* **2000**, *122*, 4304.

64 C. G. Espino, J. Du Bois, *Angew. Chem., Int. Ed.* **2001**, *40*, 598.

65 K. A. Parker and W. Chang, *Org. Lett.,* **2005**, *7*, 1785.

66 W. W. Cutchins and F. E. McDonald, *Org. Lett.,* **2002**, *4*,749.

67 M. T. Mendlik, P. Tao, C. M. Hadad, R. S. Coleman and T. L. Lowary. *J. Org.Chem.* **2006**, *71*, 8059.

68 (a) Y. Kita, F. Itoh, O. Tamura, Y. Y. Ke and Y. Tamura, *Tetrahedron Lett.* **1987**, *28*, 1431; (b) I. F. Pelyves, C. Monneret and P. Herczegh, *Synthetic Aspects of Aminodeoxy Sugars of Antibiotics*, Springer, Heidelberg **1988**.

69 (a) Y. Hamada, A. Kawai, T. Shioiri, *Tetrahedron Lett.* **1984**, **25**, 5413. (b) Y. Hamada, A. Kawai and T. Shioiri, *Tetrahedron Lett*. **1984**, *25*, 5409. (c) A. Kawai, Y. Hamada and T. Shioiri, *Heterocycles* 1986, *24*, 248.

70 T. Kametani, Y. Suzuki, C. Ban and T. Honda, *Heterocycles* **1987**, *26*, 1789.

71 Y. Hamad, A. Kawal, T. Matsul, O. Hara and T. Shioiri, *Tetrahedron,* **1990**, *46*, 4823.

72 M. Hatanaka and I. Udda, *Chem. Lett.* **1991**, 61.

73 A. Barco, S. Benetti, C. De Risi, G. P. Pollini, G. Spalluto and V. Zanirato, *Tetrahedron* **1996**, *52*, 4719.

74 M. P. Sibi, J. Lu and J. Edwards, *J. Org. Chem.* **1997**, *62*, 5864.

75 (a) A. K. Ganguly and A. K. Saksena, *J. Antibiot.* **1975**, *28*, 707; (b) A. K. Ganguly and S. Szmulewicz, *J. Antibiot.* **1975**, *28*, 710.

76 (a) K. C. Nicolaou, H. J. Mitchell, F. L. Van Delft, F. Ruebsam and R. M. Rodriguez, *Angew. Chem., Int. Ed.* **1998**, *37*, 1871; (b) K. C. Nicolaou, H. J. Mitchell, H. Suzuki, R. M. Rodriguez, O. Baudoin and K. C. Fylaktakidou, *Angew. Chem., Int. Ed.* **1999**, *38*, 3340.

77 K. C. Nicolaou, H. J. Mitchell, N. F. Jain, T. Bando, R. Hughes, N. Winssinger, S. Natarajan and A. E. Koumbis, *Chem. Eur. J.* **1999**, *5*, 2648.

78 F. Effenberger and J. Roos, *Tetrahedron: Asymmetry* **2000**, *11*, 1085.

79 S. M. Markin, Y. E. Raifeld, L. L. Zilberg and B. M. Arshava, *J. Org. Chem. USSR* **1984**, *20*, 189; (b) M. E. Jung and J. M. Gardiner, *J. Org. Chem.* **1991**, *56*, 2614.

80 L. X. Dai, B. L. Lou and Y. Z. Zhang, *J. Am. Chem. Soc.* **1988**, *110*, 5195.

81 P. A. Wade, J. A. Rao, J. F. Bereznak, C.-K. Yuan, *Tetrahedron Lett.* **1989**, *30*, 5969; (b) P. A. Wade, *J. Org. Chem.* **1978**, *43*, 2020.

82 P. A. Wade, S. G. Ambrosio, J. A. Rao, S. Shah-Patel, D. T. Cole, J. K. Murray, Jr., and P. J. Carroll *J. Org. Chem.* **1997**, *62,* 3671-3677.

83 Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe, S. Terashima, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 423; (b) J. Jurczak, J. Kozak and A. Coiebiowski, *Tetrahedron* **1992**, *48*, 4231.

84 D. Sames and R. Polt, *J. Org. Chem.* **1994**, *59*, 4596.

85 M. J. O'Donnell, R. L. Polt, *J. Org. Chem.* **1982**, *47*, 2663.

86 R. M. Davey, M. A. Brimble and M. D. McLeod, *Tetrahedron Lett.* **2000**, *41*, 5141.

87 X. Ginesta, M. Pasto, M. A. Pericas and A. Riera, *Org. Lett.,* **2003**, *5*, 3001.

88 A. Avenoza, J. H. Busto, F. Corzana, J. M. Peregrina, D. Sucunza and M. M. Zurbano, T*etrahedron: Asymmetry* **2003**, *14*, 1037;

89 A. Avenoza, C. Cativiela, F. Corzana, J. M. Peregrina and M. M. Zurbano, *J. Org. Chem.* **1999**, *64*, 8220.

90 M .Trost, C. Jiang and K. Hammer, *Synthesis* **2005**, *19*, 3335.

91 G. Zhang, L. Shi, Q. Liu, X. Liu, L. Li and J. Wang *Tetrahedron Lett.* **2007**, *48*, 3413.

92 Reviews: (a) S. J. Danishefsky, *Chemtracts* **1989**, 273; (b) S. J. Danishefsky and M. P. DeNinno, *Angew. Chem., Int. Ed*. **1987**, *26*, 15; (c) D. Hoppe, *Nachr. Chem. Tech. Lab.* **1982**, *30*, 403.

93 S. J. Danishefsky and J. M, Clarence, *J. Am. Chem. Soc.* **1985**, *107*, 1269.

94 (a) D. J. Hart and D.-C. Ha, *Tetrahedron Lett.* **1985**, **26**, 5493; (b) J. C. Gallucci, D.-C. Ha and D. J. Hart, *Terrahedron* **1989**, *45*, 1283 – 1292.

95 C. M. Hayman, D. S. Larsen, J. Simpson, K. B. Bailey and G. S. Gill, *Org. Biomol. Chem.,* **2006**, *4*, 2794.

96 C. M. Hayman, D. S. Larsen and S. Brooker, *Aust. J. Chem.,* **1998**, *51*, 545; (b) C. M. Hayman, L. R. Hanton, D. S. Larsen and J. M. Guthrie, *Aust. J. Chem.,* **1999**, *52*, 921.

97 S. Ferenc, P. István, S. László, B. Rezsö, T. József and N. Andás, *Carbohydr. Res.***1978***, 65*, 193-200.

98 M. E. Muesser and J. Defaye, *Methods Carbohydr. Chem.,* **1980**, *8*, 177.

99 M. K. Gurjara, S. M. Pawara and P. S. Mainkara, *J. Carbohydr. Chem.,* **1989**, *8*, 785-791.

100 L. Daley, P. Roger and C. Monneret, *J. Carbohydr. Chem.,* **1997**, *16*, 25.

101 G. K. Friestad, T. Jiang and A. K. Mathies, *Org. Lett.,* **2007**, *9*, 777.

102 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

103 (a) A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron* **1985**, *41*, 3925. (b) D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.* **1987**, *52*, 959.

104 G. K. Friestad, T. Jiang and G. M. Fioroni, *Tetrahedron* **2008**, *64*, 11549.

105 (a) G. K. Friestad and S. E. Massari, *Org. Lett.* **2000**, *2*, 4237; (b) G. K. Friestad and S. E. Massari, *J. Org. Chem.* **2004**, *69*, 863.

106 S. Kobayashi, T. Wakabayashi and M. Yasuda, *J. Org. Chem.* **1998**, *63*, 4868.

107 (a) C. Temperini, L. Messori, P. Orioli, C. D. Bugno, F. Animati, and G. Ughetto, *Nucleic Acids Res.* **2003**, *31*, 1464; (b) X. M. He and H. W. Liu, *Curr. Opin. Chem. Biol.* **2002**, *6*, 590.

108 (a) A. Varki, R. Cummings, J. Esko, H. Freeze, G. Hart and Marth, J. *Essentials of Glycobiology*; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, **1999**. For recent reviews: (b) R. A. Dwek and T. D. Butters, *Chem. Rev.* **2002**, *102*, 283; (c) C. R. Bertozzi and L. L. Kiessling, *Science* **2001**, *291*, 2357.

109 For reviews, see: (a) A. T. Carmona, A. J. Moreno-Vargas and I. Robina, *Current Organic Synthesis* **2008**, *5*, 33; (b) M. J. Klefel and M. Itzstein, *Chem. Rev.* **2002**, *102,* 471; (c) G. J. Boons and A. V. Demchenko, *Chem. Rev.* **2000**, *100,* 4539.

110 F. Animati, F. Arcamone, M. Berettoni, A. Cipollone, M. Franciotti and P. Lombardi, *J. Chem. Soc. Perkin Trans. I* **1996**, 1327.

111 C. Kolar, G. Kneissl and T. Kampchen, *Carbohydr. Res.* **1990**, *208*, 111.

Chapter 2. Synthesis of 3-Amino-2,3-dideoxysugars with Their Applications

2.1 Introduction

The synthesis of 3-amino- and 3-nitro-2,3-dideoxyglycosides *via* either 1,3-*cis* or 1,3-*trans*-3-amino glycosidic bonds, have attracted growing interest, due to their broad spectrum of applications in chemical, medicinal, and pharmaceutical fields. Stereocontrolled glycosylation in the assembly of glycosidic bonds in deoxysugar derivatives is inherently difficult to achieve because of the lack of stereodirecting substituents at C2. Therefore, many advances in the synthesis of 3-aminodeoxyglycosides in the past decades have predominantly focused on the stereoselective formation of glycosidic bond, as reviewed in Chapter 1. Although results from most of the reports are encouraging, poor stereoselectivities, low yields and multiple synthetic steps are the major impediments of the reported strategies to widespread use. However, the development of reliable methods for stereoselective construction of both α- and β-deoxyglycosides remains a challenging area of research. The α-deoxyglycosides are relatively more accessible than the β-anomers due to the anomeric effect, however, glycosylation of 2-deoxyglycosides under acidic conditions frequently provides a mixture of both anomers. In addition, the routinely used methods for the synthesis of 1,3-*cis*-3-aminodeoxydisaccharides and oligosaccharides employ an indirect approach whereby the glycosyl donors possess a protected heteroatom at C2 that directs facial selectivity of the reaction and the protecting group can be cleaved at later stage.[1]

The following sections describe our new strategy for ready access to 3-amino-2,3-dideoxysugars *via* regio- and stereo-selective tandem hydroamination/glycosylation of glycols in one–pot manner. In continuation of our strong interest in the synthesis of biologically active aminosugars and glycosaminoglycans,[2] herein, we report a concise and robust synthetic approach that provides 3-amino-2,3-dideoxysugars with not only exclusive anomeric stereoselectivity but also with a plethora of structural derivatizatives. Specifically, we envisioned a straightforward synthesis of 3-amino-2,3-dideoxyglycosides by a three-component reaction of 3,4,6-tri-*O*-acetyl-D-glycal with two (*N*-, and *O*-, or *S*-containing) nucleophiles in a one-pot manner. This methodology involves regio- and stereoselective glycosylation and C-3 amination on the protected glycal scaffold (Figure1).

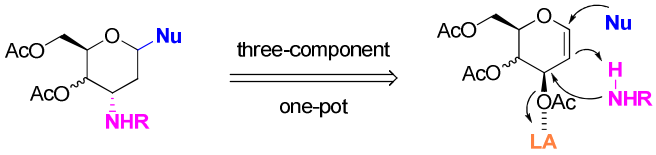


Fig. 1 Our plan for quick access to 3-amino-2,3-dideoxysugars *via* regio- and stereoselective tandem hydroamination/glycosylation of glycols.

2.2 Results and Discussion

2.2.1 Initial Studies

We first determined whether our proposed one-pot three-component reaction was a viable strategy to form the desired products. In fact, when 3,4,6-tri-*O*-acetyl-D-glucal (**1a**), *p*-toluenesulfonamide (**2a**) and benzyl alcohol (**3a**)

were subjected to a one-pot reaction in the presence of 1.1 equiv of triflic acid (TfOH) in toluene at room temperature for 30 min, the desired aminoglycoside **4a** was obtained with exclusive α-stereoselectivity but in a low yield of 31% (Table 1, entry 1). The structural and stereochemical characterization of **4a** was determined by extensive NMR experiments (^{1}H, ^{13}C, COSY, HMQC, HMBC, NOESY). The $J_{H1\text{-}H2a}$ of 3.2 Hz for anomeric proton H-1 signal at δ 4.93 in ^{1}H NMR is diagnostic for α-linked glycosides. The stereochemistry at the C-3 position is assigned by NOESY experiment. The correlation for N-H/H-5 and no correlation for H-1/N-H or H-1/H-3 indicate that the newly introduced sulfonamido group and glycosyl acceptor are in a cis diaxial configuration, adopting $^{1}C_{4}$ conformation in solution (Fig. 2).

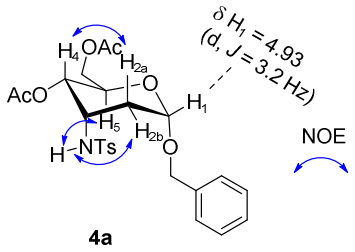
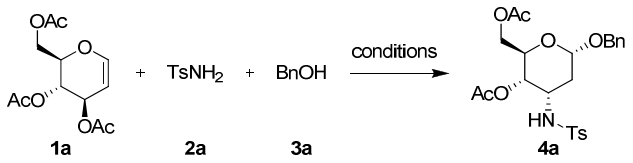


Figure 2. Selected data of ^{1}H NMR, and NOESY for **4a**

To further optimize this process, we conducted a series of experiments to evaluate various promoters and solvents. The results of the preliminary screening are listed in Table 1. For different Brønsted acids tested, such as Amberlyst-15, TFA, H_3PO_4, *p*-TsOH and CSA, the desired product was not detected even after prolonged reaction times (Table 1, entries 2-6). We started to try Lewis acids such as $Cu(OTf)_2$, $ZnCl_2$, and $(C_6F_5)_3B$, but also failed to transform starting materials into the desired 3-amino-2,3-dideoxysugars (Table 1, entries 7-9). However, it is

worthy of note that the reaction was found to proceed with the strong Lewis acid $BF_3{\cdot}OEt_2$ (1.1 equiv), albeit with extended reaction time and with a moderate yield of 45% (Table 1, entry 10). However, an increase in the promoter loading (2.2 equiv) was found to improve the yield to 90% (Table 1, entry 11). Amongst different solvents screened, 1,2-dichloroethane (DCE) was found to be superior

Table 1 Optimization of the one-pot three-component tandem hydroamination/glycosylation reaction[a]



Entry	Promoter	Solvent	Time (min)	Yield (%)[b]
1	TfOH (1.1)	toluene	30	31
2	Amberlyst-15 (1.1)	toluene	180	-
3	TFA (1.1)	toluene	120	trace
4	H_3PO_4 (1.1)	toluene	180	-
5	CSA (1.1)	toluene	180	-
6	*p*-TsOH (1.1)	toluene	180	-
7	$Cu(OTf)_2$ (1.1)	toluene	180	-
8	$ZnCl_2$ (1.1)	DCM	180	-
9	$(C_6F_5)_3B$ (1.1)	toluene	180	-
10	$BF_3{\cdot}OEt_2$ (1.1)	toluene	120	45
11	$BF_3{\cdot}OEt_2$ (2.2)	toluene	30	90
12	$BF_3{\cdot}OEt_2$ (2.2)	DMF	30	-
13	$BF_3{\cdot}OEt_2$ (2.2)	THF	30	-
14	$BF_3{\cdot}OEt_2$ (2.2)	MeCN	30	trace
15	$BF_3{\cdot}OEt_2$ (2.2)	DCM	30	91
16	$BF_3{\cdot}OEt_2$ (2.2)	DCE	30	93
17	TMSOTf (2.2)	DCE	30	90
18	$SnCl_4$ (2.2)	DCE	30	92

[a] Reaction were carried out with 3,4,6-tri-*O*-acetyl-D-glucal **1a** (50 mg, 0.18 mmol), $TsNH_2$ **2a** (1.1 equiv), BnOH **3a** (1.1 equiv) in 2 mL of solvent. [b] Isolated yields. DCE = 1, 2-dichloroethane.

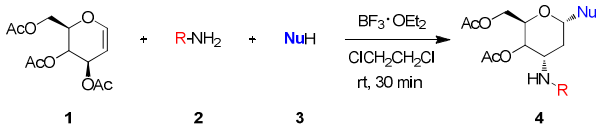
to other solvents in terms of reaction time, percentage yield and activity profile

(entry 16). When the reaction was carried out with other strong Lewis acids TMSOTf (2.2 equiv) and $SnCl_4$ (2.2 equiv), the product could also be obtained in comparable yields (Table 1, entries 17 and 18). It is noteworthy that this tandem hydroamination/ glycosylation reaction is operationally simple, easy to carry out and more importantly, devoid of by-products. When we tested the crude reaction mixture by NMR, there was no indication of a double bond, suggesting that there is no formation of a Ferrier product. Thus, the optimized reaction conditions for the one-pot synthesis were found to be 2.2 equiv of $BF_3{\cdot}OEt_2$, at room temparature with DCE as solvent under nitrogen for 30 min (Table 1, entry 16).

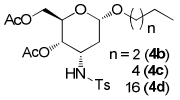
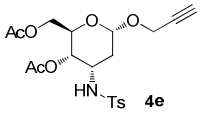
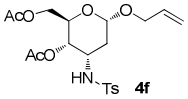
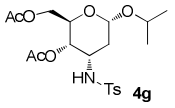
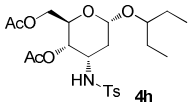
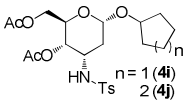
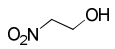
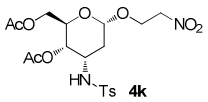
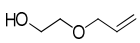
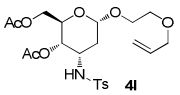
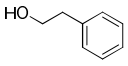
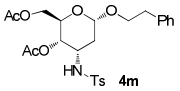
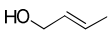
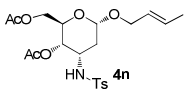
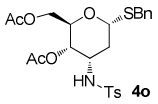
2.2.2 Substrates Scope

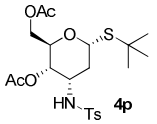
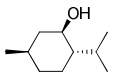
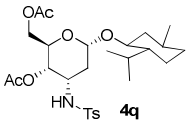
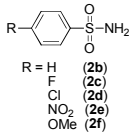
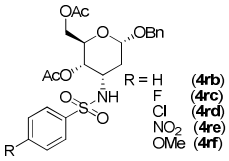
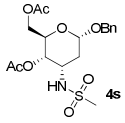
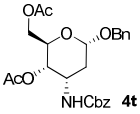
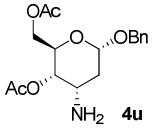
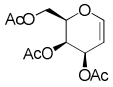
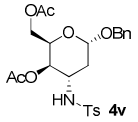
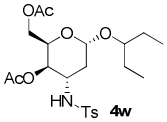
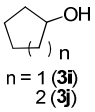
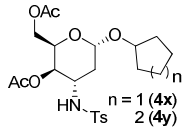
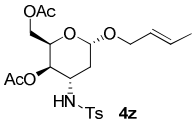
With the optimized reaction conditions in hand, we investigated the substrate scope by carrying out the reaction with various nucleophiles. As shown in Table 2, a wide range of aromatic and aliphatic alcohols and thiols gave the desired aminoglycosides with exclusive α-stereoselectivities in high yields. A series of 3-amino-2,3-dideoxyglucosides **4b-4p** were prepared in good to excellent yields (66–95%) (Table 2, entries 1-12). It was observed that long chain alcohols, alcohols bearing an electron withdrawing group ,aromatic and hindered aliphatic thiols gave products in slightly lower yields (Table 2, entries 1, 7, 11 and 12, **4d**, **4k**, **4o** and **4p**). With this expediated protocol, we synthesized L-menthol glucoside **4q** in 77% yield (Table 2, entry 13), which is a commonly seen 3-amino-2,3-dideoxysugar motif appended to biologically important natural products.[3] To our delight, all of the glycosylation products were obtained as pure

Table 2 Substrate scope studies for $BF_3{\cdot}OEt_2$-promoted one-pot three-component α–selective tandem hydroamination/glycosylation reaction[a]



1 **2** **3** **4**

Entry	**1**	R-NH_2	NuH	Product [b]	Yield (%)[c]
1	 **1a**	$TsNH_2$ **2a**	 n = 2 (**3b**) 4 (**3c**) 16 (**3d**)	 n = 2 (**4b**) 4 (**4c**) 16 (**4d**)	88 (**4b**) 84 (**4c**) 66 (**4d**)
2	**1a**	**2a**	 **3e**	 **4e**	95
3	**1a**	**2a**	 **3f**	 **4f**	82
4	**1a**	**2a**	 **3g**	 **4g**	85
5	**1a**	**2a**	 **3h**	 **4h**	90
6	**1a**	**2a**	 n = 1 (**3i**) 2 (**3j**)	 n = 1 (**4i**) 2 (**4j**)	85 (**4i**) 88 (**4j**)
7	**1a**	**2a**	 **3k**	 **4k**	76
8	**1a**	**2a**	 **3l**	 **4l**	76
9	**1a**	**2a**	 **3m**	 **4m**	91
10	**1a**	**2a**	 **3n**	 **4n**	83
11	**1a**	**2a**	 **3o**	 **4o**	71

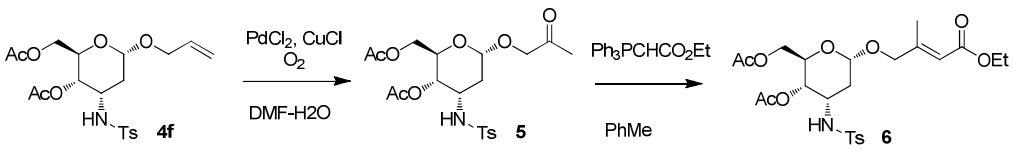
12	**1a**	**2a**	 **3p**	 **4p**	75
13	**1a**	**2a**	 L-Menthol, **3q**	 **4q**	77
14	**1a**	 R = H (**2b**) F (**2c**) Cl (**2d**) NO_2 (**2e**) OMe (**2f**)	**3a**	 R = H (**4rb**) F (**4rc**) Cl (**4rd**) NO_2 (**4re**) OMe (**4rf**)	85 (**4rb**) 91 (**4rc**) 85 (**4rd**) 88 (**4re**) 74 (**4rf**)
15	**1a**	 **2g**	**3a**	 **4s**	92
16	**1a**	$CbzNH_2$ **2h**	**3a**	 **4t**	72
17	**1a**	$BocNH_2$ **2i**	**3a**	 **4u**	54
18	 **1b**	**2a**	**3a**	 **4v**	87
19	**1b**	**2a**	**3h**	 **4w**	83
20	**1b**	**2a**	 n = 1 (**3i**) 2 (**3j**)	 n = 1 (**4x**) 2 (**4y**)	78 (**4x**) 77 (**4y**)
21	**1b**	**2a**	**3n**	 **4z**	87

[a] Reaction conditions: **1** (0.18 mmol, 1.0 equiv), **2** (1.1 equiv), **3** (1.1 equiv), $BF_3{\cdot}OEt_2$ (2.2 equiv), DCE (2 mL). [b] All new products were characterized by IR, HRMS, ^1H NMR and ^{13}C NMR. [c] Isolated yields. DCE = 1, 2-dichloroethane.

diastereomers.

In our protocol, aromatic and aliphatic sulfonamides achieve the best results (Table 2, entries 14 and 15). For instance, $TsNH_2$, $NsNH_2$ and $MsNH_2$ proved to be excellent nucleophiles, providing the corresponding products in high yields and anomeric selectivities. Likewise, the reaction with benzyl carbamate ($CbzNH_2$) gave the corresponding 3-amino-2,3-dideoxyglucoside **4t** in moderate yield (Table 2, entry 16). The benzyloxycarbonyl (Cbz) group in the resulting product could be easily transformed into free amino group. Interestingly, when 3,4-6-tri-*O*-acetyl-D-glucal **1a** was treated with *t*-butyl carbamate ($BocNH_2$) under the same reaction conditions, the deprotected product **4u** was isolated after purification (Table 2, entry 17). In contrast, reaction of trimethylsilyl azide ($TMSN_3$) with tri-*O*-acetyl-D-glucal **1a** proved to be unsuccessful. Finally, the analogous reaction of tri-*O*-acetyl-D-galactal **1b** with $TsNH_2$ and aromatic or aliphatic alcohols also afforded the corresponding 3-amino-2,3-dideoxy galactosides **4v-4z** in good to excellent yields with exclusive α anomeric selectivity (Table 2, entries 18-21).

Further transformation of **4f** to **6** was tested (scheme 1). X-ray crystallography analysis of 3-amino-2,3-dideoxyglucoside **6** further confirmed the structure and stereochemical outcome of the tandem hydroamination/glycosylation (Figure 2).



Scheme 1 Synthesis of 3-amino-2,3-dideoxyglucoside **6**.

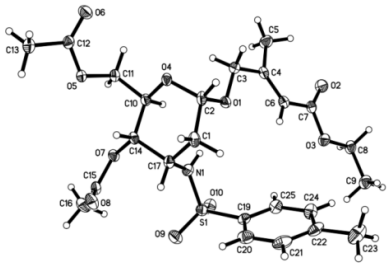


Fig 2 X-ray Structure of 3-amino-2,3-dideoxyglucoside **6**.

2.2.3 Mechanistic Proposal

We felt that the investigation of the mechanisms would be worthwhile due to the diastereoselectivity of the reaction, even in the absence of a neighbouring directing group at C-2. To gain insight into the mechanism by which $BF_3{\cdot}OEt_2$ promotes this reaction, we performed simple ^{19}F NMR spectroscopic studies. Careful scrutiny of the NMR data suggests that $BF_3{\cdot}OEt_2$ is coordinated to the oxygen atom of the glycal. In our control NMR experiments, BnOH and $TsNH_2$ were combined with $BF_3{\cdot}OEt_2$, and as predicted, $BF_3{\cdot}OEt_2$ did not show any observable shift from the original ^{19}F NMR signal, suggesting negligible or no interaction between these nucleophiles and $BF_3{\cdot}OEt_2$.[4] However, upon the addition of glycal to the remaining nucleophiles, shifts of the ^{19}F signal were observed, which indicates the formation of the boron–sugar complex (Fig. 3). This result implies that $BF_3{\cdot}OEt_2$ is coordinated to the glycal. In our initial attempt to probe the reaction mechanism, we found that when C-3 epimer of 3,4,6-*tri*-*O*-acetyl-D-glucal **1c** was reacted under the same reaction conditions, the 3-amino-2,3-dideoxyglucoside formed was of the same configuration as that obtained from the corresponding D-glucal yield (Scheme 2). This observation implies that both acetyl protected D-glucal and its epimer led to a common reactive intermediate that eventually converged to the resulting 3-amino-2,3-dideoxyglucoside. The use of

$TMSN_3$ which lacks acidic hydrogen did not result in desired product formation. Additionally, when secondary sulfonamide ($TsNHCH_3$) was employed as one of the nucleophile, no desired 3-amino-2,3-dideoxyglucoside was obtained as well. The diastereofacial selectivities observed in the absence of a directing group at C2 position is novel and prompted us to look into the mechanistic cause. Though a detailed mechanism of the present protocol still awaits further studies, a plausible pathway is postulated (Scheme 3). One possibility is that the reaction proceeds through allyloxocarbenium ion intermediate **7**. Preferential attack of *N*-nucleophile occurs from stereoelectronically favoured α face of the presumably almost planar conformation of the allyloxocarbenium intermediate to generate **8**. Rapid proton transfer follows to generate the corresponding oxocarbenium ion. Subsequently, nucleophilic addition of carbohydrate oxygen or sulfur nucleophiles to the oxonium

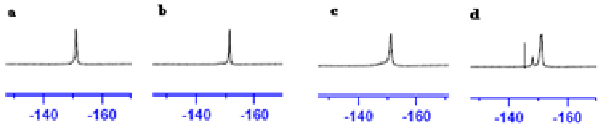
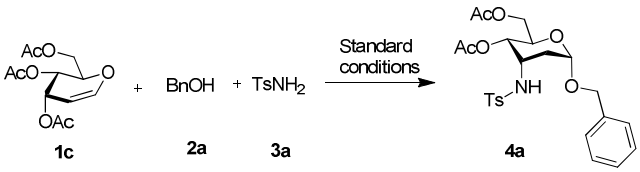
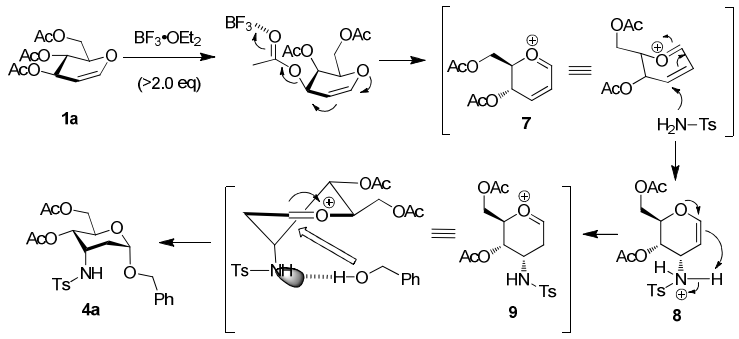


Fig. 3 ^{19}F NMR spectra of a) $BF_3{\cdot}OEt_2$, b) $BF_3{\cdot}OEt_2$ and BnOH, c) $BF_3{\cdot}OEt_2$ and $TsNH_2$, and d) $BF_3{\cdot}OEt_2$, BnOH, $TsNH_2$, and tri-*O*-acetyl-D-glucal in CD_2Cl_2.



Scheme 2. Three-component reaction with donor **1c**.



Scheme 3. Proposed reaction mechanism.

ion proceeds readily to furnish the desired product with high stereo- and regio-selectivity. The observed α-anomeric selectivity can reasonably be explained by considering addition of O-nucleophile to the stereoelectronically preferred face of the more stable conformer.[5] The facial selectivity might be further reinforced by possible effective coordination (hydrogen bonding) between the nitrogen and the incoming *O*-nucleophile (ROH) as shown in structure **9**.[6] In this way, the carbohydrate alcohol or thiol is directed to attack pseudoaxially from the same face of the oxocarbenium ion on the C1 carbon to furnish the thermodynamically favoured 1,3-*cis* α-isomer.

2. 2.4 Conlusions

In summary, a highly stereoselective $BF_3{\cdot}OEt_2$-promoted aminoglycosylation of glucals has been developed in a one-pot manner. This efficient multicomponent reaction protocol offers simplicity and general applicability to a broad range of variations on each component. Because of the aforementioned advantages, the present methodology is believed to be able to find broad applications in glycochemistry.

2.3 Synthetic Applications

2.3.1 Synthesis of L-Ristosamine and L-*epi*-Daunosamine Glycosides

2.3.1.1 Introduction

A wide variety of approaches to racemic and asymmetric syntheses of daunosamine, ristosamine along with their branched analogs have been reported from both sugar and non-sugar precursors, as reviewed in Chapter 1. However, most of the reported approaches suffer from drawbacks such as excessive number of synthetic steps, low yields, poor stereoselectivity and long reaction times. In continuation of our efforts to develop reliable method to prepare aminosugars with potential biological activity, we wish to report a direct and stereospecific synthesis of 3-amino-2,3,6-trideoxyhexoses that include L-ristosamine and L-*epi*-daunosamine glycosides. We envisaged a rapid assembly of 3-amino-2,3,6-trideoxyhexoses *via* a three-component reaction of 3,4-di-*O*-acetyl-6-deoxy-L-glucal with two (*N*- and *O*-, or *S*-containing) nucleophiles in a one-pot manner. Our synthetic strategy involves regio- and stereoselective tandem hydroamination/glycosylation on the protected glycal scaffold (Figure 4). To demonstrate the versatility of the present method, it was applied for facile synthesis of L-ristosamine and L-*epi*-daunosamine glycosides in a

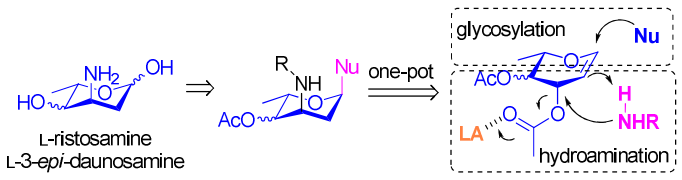


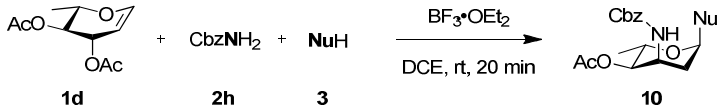
Figure 4. Our synthetic strategy

three step reaction sequences.

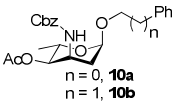
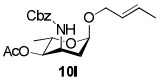
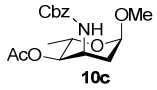
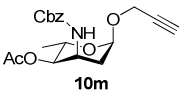
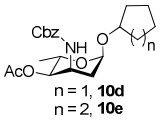
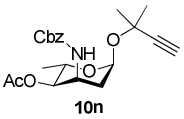
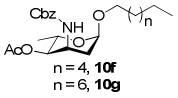
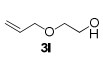
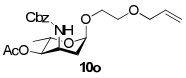
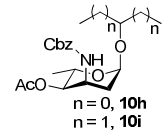
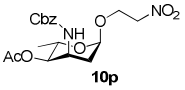
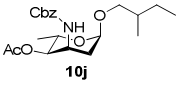
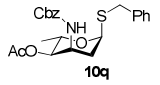
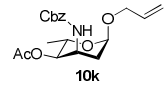
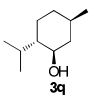
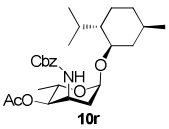
2.3.1.2 Results and discussion

In our initial study, a mixture of 3,4-di-*O*-acetyl-6-deoxy-L-glucal (**1d**), benzyl alcohol (**3a**) and benzyl carbamate (**2h**) in DCE was subjected to treatment with 2.2 equiv of $BF_3{\cdot}OEt_2$ at room temperature under a nitrogen atmosphere for 20 min, to afford **10a** in 87% yield with exclusive stereospecificity (Table 3, entry 1). The exclusive formation of pure diastereomers allowed easy purification of the desired product by SiO_2 flash column chromatography. Chemical structure determination and stereochemical characterization of **10a** was achieved by extensive and detailed 1D and 2D NMR studies. The $J_{H1\text{-}H2a}$ of 3.2 Hz for anomeric proton H-1 signal at δ 4.93 in ^1H NMR is diagnostic for α-linked glycosides. The stereochemistry at the C-3 position is assigned by NOESY experiment. The correlation for N-H/H-5 and no correlation for H-1/N-H or H-1/H-3 indicate that the newly introduced sulfonamido group and glycosyl acceptor are in a cis diaxial configuration, adopting $^1C_4$ conformation in solution. With this gratifying preliminary result, our attention was directed to investigating the substrate scope by varying the nucleophiles. A diverse set of primary, secondary, tertiary alcohols and thiol (**3o**) worked well as nucleophiles to provide the desired *N*-benzyloxycarbonyl-L-ristosamine glycosides with exclusive stereoselectivity in good yield as shown in Table 1. Accordingly, facile syntheses of 3-amino-2,3,6-trideoxyhexoses **10b-10q** were achieved in moderate to good yields (55–86%) (Table 3, entries 2-13). To further exploit this protocol, L-menthol glucoside **10r** was prepared in 54% yield (Table 3, entry 14).[7] To our delight, in all

Table 3. Substrate scope studies for $BF_3{\cdot}OEt_2$-promoted three-component α–selective tandem hydroamination/glycosylation reaction.[a]



1d **2h** **3** **10**

entry	**3**	Product[b]	yield[c] (%)	entry	**3**	Product[b]	yield[c] (%)
1	 n = 0, **3a** n = 1, **3m**	 n = 0, **10a** n = 1, **10b**	87 (**10a**) 55 (**10b**)	8	 **3n**	 **10l**	76
2	MeOH **3r**	 **10c**	71	9	 **3e**	 **10m**	62
3	 n = 1, **3i** n = 2, **3j**	 n = 1, **10d** n = 2, **10e**	68 (**10d**) 83 (**10e**)	10	 **3r**	 **10n**	69
4	 n = 4, **3c** n = 6, **3s**	 n = 4, **10f** n = 6, **10g**	81 (**10f**) 73 (**10g**)	11	 **3l**	 **10o**	67
5	 n = 0, **3g** n = 0, **3h**	 n = 0, **10h** n = 1, **10i**	72 (**10h**) 75 (**10i**)	12	 **3k**	 **10p**	68
6[c]	 **3t**	 **10j**	86	13	 **3o**	 **10q**	55
7	 **3f**	 **10k**	72	14	 **3q**	 **10r**	54

[a]See Experimental Section for a detailed experimental procedure. [b]All products were characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS. [c]Isolated yield.

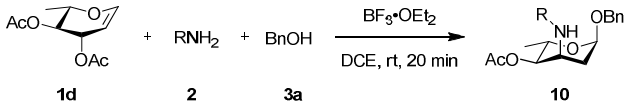
cases, the desired aminosugars were obtained as pure diastereomers with α

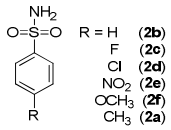
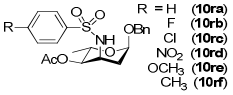
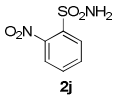
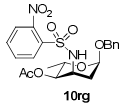
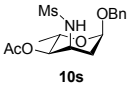
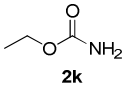
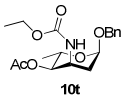
configuration at the C1 position. The stereochemical outcome can presumably be viewed as a result of stereospecific amination at the C3 position followed by possible hydrogen bonding between the nitrogen and the incoming *O*-nucleophile (ROH). Additionally, the anomeric effect also favours the formation of the thermodynamically more stable α anomeric product.[8]

Having established the scope for *O*-nucleophile, we set out to demonstrate the generality of the reaction by using various *N*-nucleophiles. It is noteworthy that the reaction proceeded remarkably well with aromatic and aliphatic sulfonamides. For example, when the reactions were carried out with $NsNH_2$, $TsNH_2$ or $MsNH_2$, the corresponding aminosugars were isolated in high yields with exclusive stereoselectivities (Table 4, entries 1-3, **10rd**, **10rf** and **10s**). In comparison to sulfonamides, reactionwith ethyl carbamate (**2k**) gave the corresponding 3-amino-2,3,6-trideoxyhexoses **10t** in slightly lower yields (Table 4, entry 4). In contrast, reaction of trimethylsilyl azide ($TMSN_3$) with 3,4-di-*O*-acetyl-6-deoxy-L-glucal (**1d**) turned out to be unsuccessful.

As a final step in the sequence, *N*-benzyloxycarbonyl-L-ristosamine glycosides were converted into the desired free L-ristosamine glycosides. For example, one-pot deprotection of the Cbz and acetyl groups resulted in L-ristosamine derivatives (**11a**) and (**11b**) in 82% and 87% yield, respectively (Scheme 4). Overall, the development of this novel one-pot method is of particular significance for the synthesis of L-ristosamine glycosides **11a** and **11b** as it is highly superior to previously described routes that normally comprise 9 to 11 linear steps.[9] X-ray crystallography analysis of

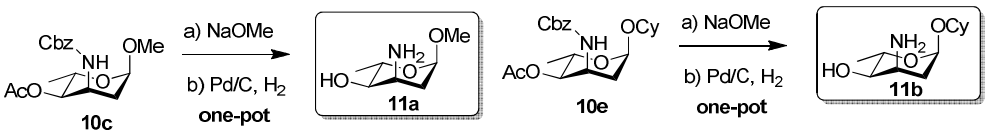
Table 4. Scope of the nitrogenic nucleophiles [a]



entry	RNH_2	Product[b]	yield[c](%)
1			85 (**10ra**) 91 (**10rb**) 85 (**10rc**) 88 (**10rd**) 74 (**10re**) 84 (**10rf**)
2			92
3	$MsNH_2$ (**2g**)		72
4			54

[a]See Experimental Section for a detailed experimental procedure. [b] All products were characterized by IR, HRMS, ^{1}H NMR and ^{13}C NMR. [c]Isolated yield.

L-ristosamine derivative (**11b**) further confirmed the structure and stereochemical outcome of the tandem hydroamination/glycosylation (Figure 5).



Scheme 4. Synthesis of L-ristosamine glycosides **11a** and **11b**.

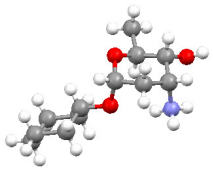
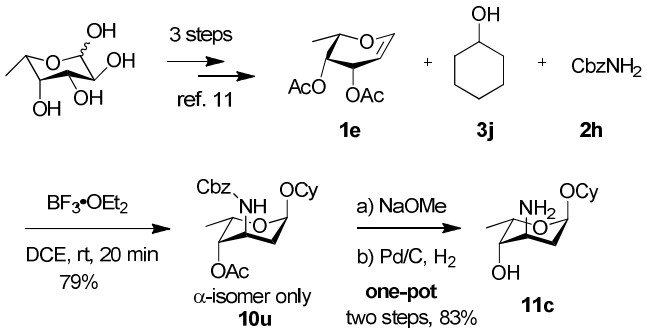


Figure 5. X-ray Structure of L-ristosamine derivative (**5b**); red (O); blue (N).

To prepare another diastereomeric 3-amino-2,3,6-trideoxyhexose, L-*epi*-daunosamine, the starting 3,4-di-*O*-acetyl-6-deoxy-L-galactal (**1e**) was synthesized from ethyl sorbate according to a literature reported procedure.[10] Intermediary carbamate protected L-*epi*-daunosamine (**10u**) was obtained in 79% yield *via* a three-component reaction involving benzyl carbamate ($CbzNH_2$) (**2h**), cyclohexanol (**3j**) and 3,4-di-*O*-acetyl-6-deoxy-L-galactal (Scheme 5). Similarly, removal of the acetyl group by treating **10u** with NaOMe in methanol, followed by direct removal of the Cbz group through treatment with Pd/C under H_2 provided cyclohexyl L-*epi*-daunosamine (**11c**) in 83% with exclusive stereo- and regio-selection. The spectroscopic data (^1H and ^{13}C NMR, IR) and optical rotation of **11c** were identical to those reported in the literature.[11]



Scheme 5. Synthesis of L-*epi*-daunosamine derivative (**11c**).

2.3.1.3 Conlusions

In summary, a stereocontrolled one pot $BF_3{\cdot}OEt_2$-promoted hydroamination/ glycosylation on glycal scaffolds to synthesize 3-amino-2,3,6-trideoxyhexoses has been developed that circumvents the problem of lack of stereoselectivity, and thus laborious isolation of pure diastereomeric products, associated with previously reported strategies. Other attractive features of this multicomponent reaction are a

simple and practical experimental procedure, and its adaptability for the synthesis of a diverse set of aminosugars. The synthetic utility of this novel method has been further illustrated in a concise and highly expedient synthesis of L-ristosamine and L-*epi*-daunosamine glycosides. Thus, the present methodology represents attractive entry to aminosugars and its further application is underway.

2.3.2 Synthesis of 1,3-cis-3-Arylsulphonamino-deoxydisaccharides and Oligosaccharides

2.3.2.1 Introduction

Our interest in drug discovery motivated us to devise new methodologies for the aminosugar syntheses. In section **2.3.1**, we derived a strategy for ready access to 3-arylsulphonamino-2,3-dideoxysugars *via* regio- and stereoselective tandem hydroamination/glycosylation of glycal. In conjunction with our previous work, herein, we wish to report a direct and reliable synthetic approach that provides 1,3-*cis*-3-arylsulphonamino-2,3-deoxydisaccharides and oligosaccharides with not only exclusive anomeric stereoselectivity but also a wide range of derivatization. We envisaged a straightforward synthesis of 1,3-*cis*-3-arylsulphonamino-2,3-dideoxy glycosides by a three-component reaction of the glycosy donor, glycosy acceptor and sulfonamide/carbamate in a one-pot manner. This methodology involves regio- and stereoselective tandem hydroamination/glycosylation on the protected glycal scaffold (Figure 6).

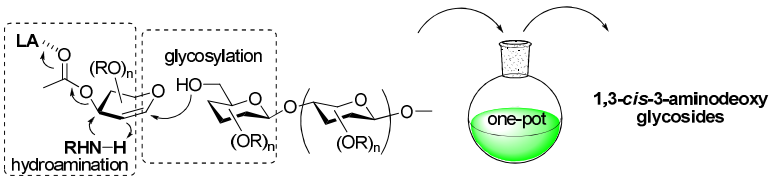


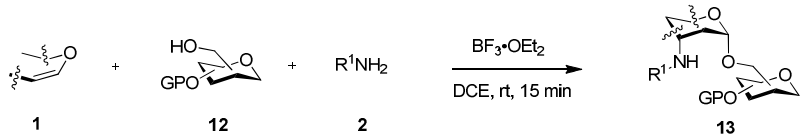
Figure 6. Quick access to 1,3-*cis*-3-arylsulphonaminodeoxy glycosides *via* regio- and stereoselective tandem hydroamination/glycosylation of glycols.

2.3.2.2 Results and discussion

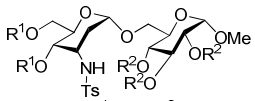
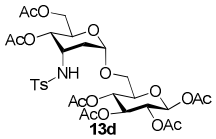
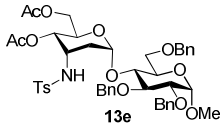
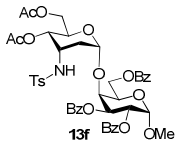
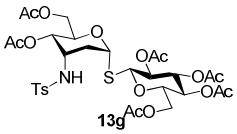
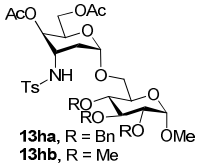
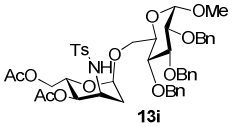
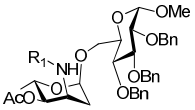
With the optimized condition in hand, we investigated versatility of the method by preparation of α-linked deoxyglycosides composing of various *N*-protected 2,3-dideoxy- and 2,3,6-trideoxy-1,3-*cis*-3- aminodisaccharides and oligo-saccharides **13a-13s** (Table 5). The glycosylation of glucosides 1**2b** and 1**2c**, which possess free hydroxyl groups at C6 position, with 3,4,6-*tri-O*-acetyl-D-glucal (**1a**) and *p*-toluenesulfonamide (**2a**) under the optimized condition afforded the corresponding 1,3-*cis*-3-tosylamino-2,3-deoxydisaccharides **13b** and **13c** in 69% and 86% yield respectively (Table 5, entries 1, 2). Pivaloyl protected glycals glycals also gave the desired product **13c** in moderate yield under standard conditions. The possibility of secondary alcohol as viable nucleophilic glycosyl acceptor was also investigated. Accordingly, glycosylation of glycosides 1**2d** and **12e** possessing hydroxyl groups at C4 with glucal donor (**1a**) and *p*-toluenesulfonamide provided disaccharides **13e** and **13f** as pure α-isomers in poor yields (Table 5, entries 3, 4). When glucose thiol **12f** was employed as the glycosyl acceptor, the corresponding *S*-linked deoxyglycoside **13g** was obtained in slightly lower yield (Table 5, entry 5). Importantly, the α-linked 3-arylsulphonamino-2,3-deoxydisaccharides did not decompose under the reaction conditions. In our protocol, we found that aromatic and aliphatic sulfonamides such

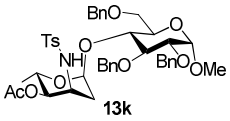
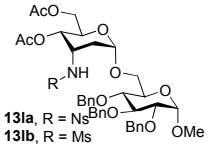
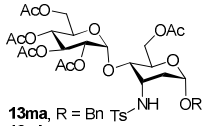
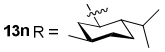
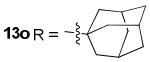
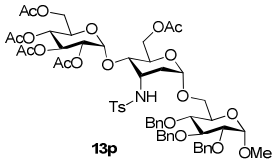
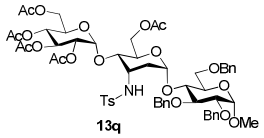
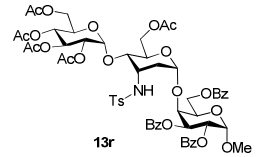
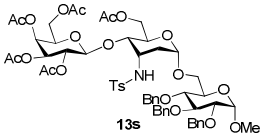
as $TsNH_2$, $NsNH_2$ and $MsNH_2$ worked particularly well for this reaction and provided the corresponding products in good yields and are anomerically pure (Table 5, entry 10). In the same manner, the reaction with benzyl carbamate ($CbzNH_2$) proceeded smoothly to afford the corresponding 3-benzyloxycarbonylamino-2,3-dideoxydisaccharide **13t** in moderate yields (Table 5, entry 8). Hydrogenolysis of the benzyloxycarbonyl (Cbz) group in the resulting product is expected to liberate the amino group. For example, removal of the acetyl group by treating 3-benzyloxycarbonylamino-2,3-dideoxydisaccharide **13jb** with NaOMe in methanol, followed by direct removal of the Cbz group through treatment with Pd/C under H_2 provided 3-amino-2,3-deoxydisaccharide **14** in 74% with exclusive stereo- and regio-selection (Scheme 6). We next examined the glycosylation of **12a** with a variety of glycosyl donors **1b**, **1g** and **1d** under $BF_3{\cdot}OEt_2$-mediated conditions. All the reactions afforded the expected arylsulphonaminodeoxydisaccharides **13h**-**13k** in moderate to good yields with exclusive α-selectivity (Table 5, entries 6–9). Similarly, *N*-protected 3-amino-2,3-dideoxy-disaccharides **13ma** and **13mb** were prepared by the treatment of disaccharides donor **1d** with nucleophiles **3a** and **3f** bearing primary hydroxyl moieties (Table 5, entry 11). With this expedient protocol, we synthesized L-menthol glucoside **13n** in 55% yield (Table 2, entry 11), which exemplifies a common 3-arylsulphonamino-2,3-dideoxydisaccaride motif appended to biologically important natural products. To demonstrate that the current method can be employed for oligosaccharide synthesis, a number of deoxytrisaccharides **13p**-**13s** were

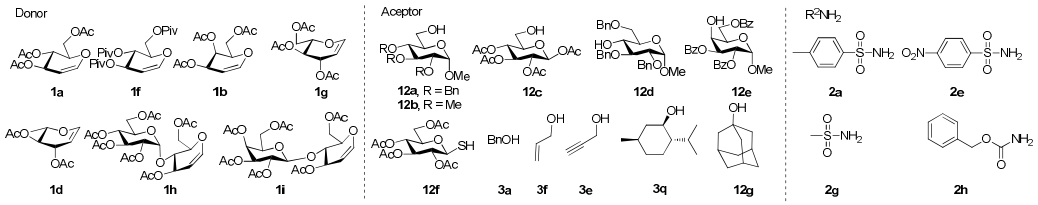
Table 5. Substrate scope studies for $BF_3{\cdot}OEt_2$-promoted three-component α-selective glycosylation.[a]



1 **12** **2** **13**

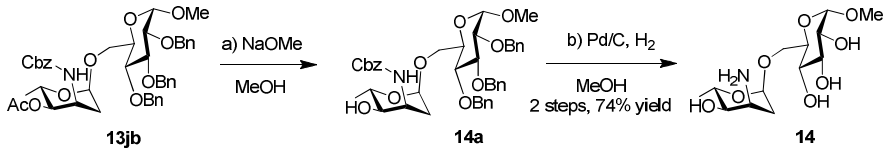
Entry	1	12	2	Product[b]	Yield (%)[c]
1	**1a**	**12a**	**2a**	 **13a**, R^1 = Ac, R^2 = Bn **13b**, R^1 = Ac, R^2 = Me **13c**, R^1 = Piv, R^2 = Bn	68 (**13a**)
	1a	**12b**			69 (**13b**)
	1f	**12a**			59 (**13c**)
2	**1a**	**12c**	**2a**	 **13d**	86
3	**1a**	**12d**	**2a**	 **13e**	54
4	**1a**	**12e**	**2a**	 **13f**	47
5	**1a**	**12f**	**2a**	 **13g**	53
6	**1b**	**12a**	**2a**	 **13ha**, R = Bn **13hb**, R = Me	51 (**13ha**)
		12b			56 (**13hb**)
7	**1g**	**12a**	**2a**	 **13i**	81
8	**1d**	**12a**	**2a**	 **13ja**, R_1 = Ts **13jb**, R_1 = Cbz	75 (**13ja**)
			2h		64 (**13jb**)

9	**1e**	**12d**	**2a**	 **13k**	58
10	**1a**	**12a**	**2e**	 **13la**, R = Ns **13lb**, R = Ms	69 (**13la**)
			2g		61 (**13lb**)
11	**1f**	**3a**	**2a**	 **13ma**, R = Bn **13mb**, R = All **13mc**, R = Propargyl	71 (**13ma**)
		3f			62 (**13mb**)
		3e			67 (**13mc**)
		3q		 **13n** R =	55 (**13o**)
		12g		 **13o** R =	48 (**13p**)
12	**1f**	**12a**	**2a**	 **13p**	46
13	**1f**	**12d**	**2a**	 **13q**	44
14	**1f**	**12e**	**2a**	 **13r**	43
15	**1g**	**12a**	**2a**	 **13s**	54



[a] Reaction conditions: donor **1** (1 equiv), aceptor **12** (1.1 equiv) and **2** (1.1 equiv) were mixed together in 2 mL/0.1 mmol DCE under N_2 atmosphere and finally $BF_3{\cdot}OEt_2$ (2.2 equiv) was added, 25 °C, 15 min. [b]All products were characterized by ^1H NMR, ^{13}C NMR, IR and HRMS. [c]Isolated yield.

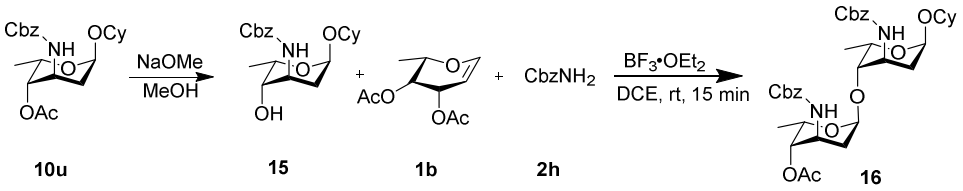
prepared from disaccharide donors hex-*O*-acetyl-D-maltal (**1h**), hex-*O*-acetyl-D-lactal (**1i**) and acceptors (Table 5, entries 12–15). To the best of our knowledge, the $BF_3{\cdot}OEt_2$-promoted one-pot α-selective tandem hydroamination/glycosylation is the first example of a direct and stereoselective synthesis of *N*-protected 2,3-dideoxy- or 2,3,6-trideoxy-1,3- *cis*-3-aminodisaccharides and oligosaccharides.



Scheme 6. Deprotection of 3-benzyloxycarbonylamino-2,3-dideoxydisaccharide **13jb** to synthesize 3-amino-2,3-dideoxydisaccharide **14**.

2.3.2.3 Conlusions

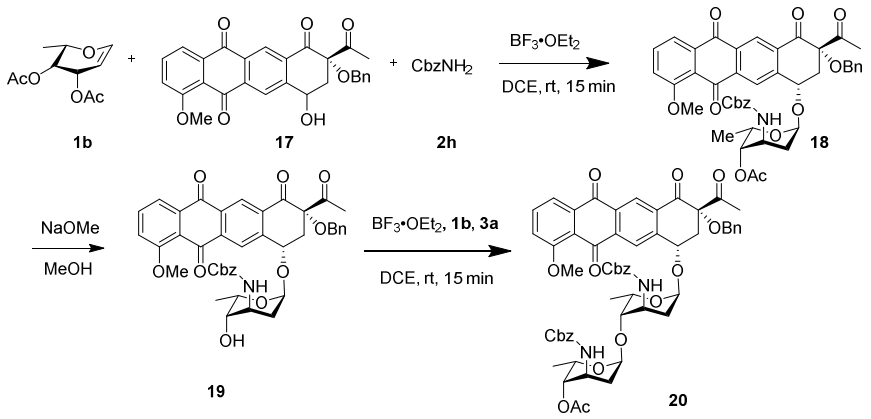
Our future effort will be directed to demonstrate the applicability of the method to synthesis some complex natural products and drug molecules. We envisage that aminosugars containing α-(1→4) linkage such as **16** can be prepared using our multicomponent reaction. Removal of acetal protecting group from previously prepared L-*epi*-daunosamine derivative **10** would provide compound **15** which can serve as glycosyl acceptor in another three-component reaction as depicted in Scheme 18.



Scheme 7. Synthesis of aminodeoxysaccharide **16** containing α-(1→4) linkage

Ultimately, the efficiency of our three-component method can be further exploited in expedient synthesis of anthracycline analogue of daunosaminyl daunorubicin. For instance, a synthetic route to a derivative of anthracycline analogue **20** in which the daunosamine residues are replaced by 3-*epi*-daunosamines can be envisioned

employing our novel reaction methodology (Scheme 8).



Scheme 8. Three-component approach to synthesis of daunosaminyl daunorubicin analogue

In conclusion, we have described a highly efficient direct and stereoselective one-pot procedure for assembly of *N*-protected 1,3-*cis*-3-aminodeoxy disaccharides and oligosaccharides *via* $BF_3{\cdot}OEt_2$-promoted hydroamination and α-selective glycosylation on glycal scaffold. This multicomponent reaction protocol offers simplicity over the conventional indirect method and the exclusive stereoselectivity facilitated the purification to a great extent. Additionally, the method works with a broad range of disarmed sugars and primary amines make derivatization possible. Due to the aforementioned advantages, the present methodology is believed to be able to find broad applications in glycochemistry.

2.3.3 Ferrier-type *N*-Glycosylation: Synthesis of *N*-Glycosides of Enone Sugars

2.3.3.1 Introduction

Structurally-defined nucleosides with *N*-glycosidic linkage have attracted a great deal of interest academically in view of their extensive applicability as pharmacological

agents including antibiotic, antineoplastic and antiviral compounds.[23] Specifically, enone *N*-glycosides have emerged with potential applications in the development of antitumor-cancer oriented ketonucleosides[24] and optically active bicyclic lactams (Fig. 7).[25] It is well established that oligosaccharides and glycoconjugates containing *O*-glycosidic bonds are prone to chemical or enzymatic hydrolysis leading to cleavage of glycosyl linkage and degradation. To address this issue, tremendous efforts have been directed towards structural modification of naturally occurring carbohydrates over the past few decades.[26] Needless to say, the development of more convenient method to access to structurally modified enone *N*-glycosides which are more biologically stable is highly desirable. Although 2,3-unsaturated glycals, which are traditionally obtained by Ferrier rearrangement,[27] have inspired many studies, the structural diversity and approaches toward *N*-pseudoglycals remain limited.[28] Moreover, there are only few methods available for the synthesis of enoside *O*-glycosides or enone *N*-glycosides.[29] Nevertheless, the stereoselective synthesis of enone *N*-glycosides is still inadequate by virtue of the lack of advancement in methodological development for *N*-glycosides. Recently, we derived a strategy for ready access to 3-arylsulphonamino-2,3-dideoxysugars *via* regio- and stereoselective tandem hydroamination/glycosylation of glycal (Fig. 8, eqn (1)).[20] In conjunction with our previous work, herein, we report a novel design for the stereoselective synthesis of enone *N*-glycosides through $BF_3 \cdot Et_2O$-promoted glycal rearrangement (Fig.8, eqn (2)).

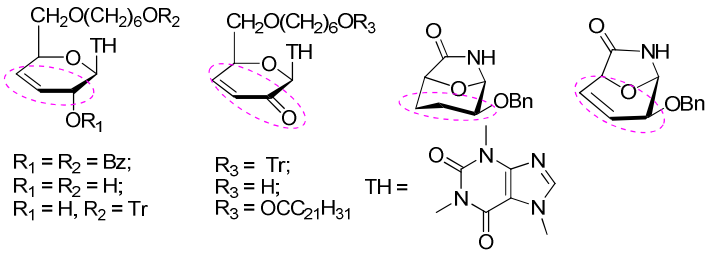


Fig. 7 Structures of cancer oriented ketonucleosides and optically active bicyclic lactams.

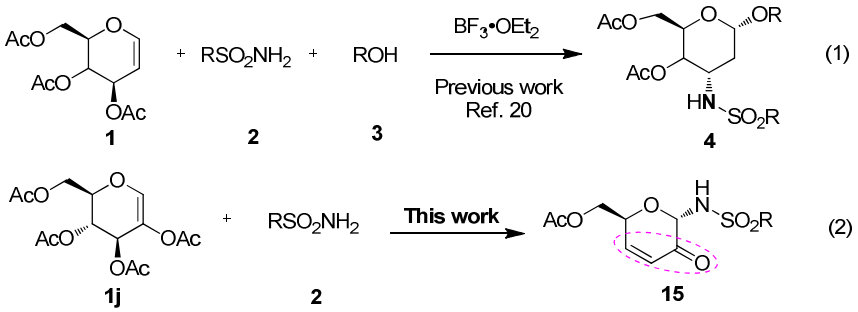
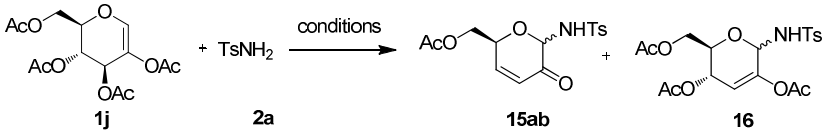


Fig. 8 Our previous work and new design of quick access to enone *N*-glycosides.

2.3.3.2 Results and discussion

Initially, a systematic screening was executed using **1j** and *p*-toluenesulfonamide **2a** ($TsNH_2$) in the presence of $BF_3{\cdot}Et_2O$ to establish the ideal reaction conditions (Table 6). The first evaluation was conducted with different concentration of $BF_3{\cdot}Et_2O$ as promoter at room temperature, whereby DCM was employed as reaction solvent. We found that 4.4 equiv. of $BF_3{\cdot}Et_2O$ was required to promote the reaction and achieve excellent selectivity for the formation of enone *N*-glycosides **15ab** with 89% yield (Table 6, entry 5). It is notable that when promoter loading as low as 0.5-2.2 equivalent was used, the reaction favored the Ferrier rearranged 2,3-unsaturated glycosides **16** as the major product (Table 6, entries 1-3). Furthermore, 4.4 equivalence of $BF_3{\cdot}Et_2O$ led to a promising anomeric selectivity with α:β ratio of 84:16. Subsequently, the use of other Lewis acids as promoter (TMSOTf, TESOTf, $SnCl_4$, $TiCl_4$ and $Sc(OTf)_3$) also afforded the desired products of enone *N*-glycosides

Table 1 Optimization for synthesis of enone *N*-glycosides



1j **2a** **15ab** **16**

entry	promoter (equiv.)	solvent	yield[b](%)		α/β[c] (**15ab**)
			15ab	**16**	
1	$BF_3{\cdot}OEt_2$ (0.5)	DCM	20	63	ND[d]
2	$BF_3{\cdot}OEt_2$ (1.1)	DCM	26	55	ND[d]
3	$BF_3{\cdot}OEt_2$ (2.2)	DCM	31	48	ND[d]
4	$BF_3{\cdot}OEt_2$ (3.3)	DCM	57	24	ND[d]
5	**$BF_3{\cdot}OEt_2$ (4.4)**	**DCM**	**89**	**trace**	**84: 16**
6	TMSOTf (4.4)	DCM	44	ND[d]	60 : 40
7	TESOTf (4.4)	DCM	55	ND[d]	56 : 44
8	$SnCl_4$ (4.4)	DCM	52	ND[d]	58 : 42
9	$TiCl_4$ (4.4)	DCM	trace	83	ND[d]
10	$Cu(OTf)_2$ (4.4)	DCM	NR[e]	-	-
11	$Sc(OTf)_3$ (4.4)	DCM	72	ND[d]	72 : 28
12	TfOH (4.4)	DCM	complex	-	-
13	$BF_3{\cdot}OEt_2$ (4.4)	THF	NR[e]	-	-
14	$BF_3{\cdot}OEt_2$ (4.4)	ACN	78	ND[d]	75 : 25
15	$BF_3{\cdot}OEt_2$ (4.4)	toluene	67	ND[d]	78 : 22
16	$BF_3{\cdot}OEt_2$ (4.4)	DMF	complex	-	-

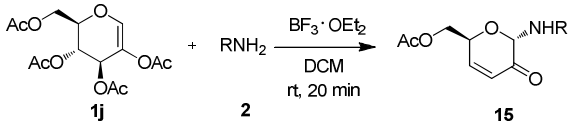
[a] Isolated yield of anomeric mixtures after purification. [b] The anomeric ratio was determined on the crude ^{1}H NMR spectra. [c] ND = no data. [d] NR = no reaction.

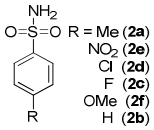
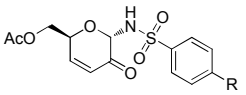
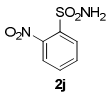
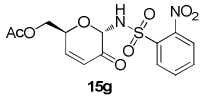
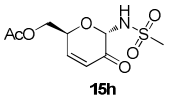
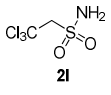
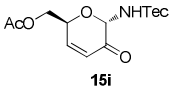
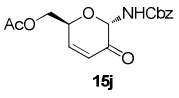
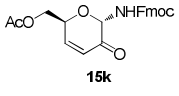
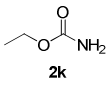
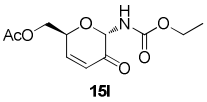
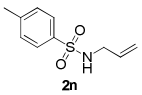
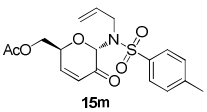
15ab and 2,3-unsaturated glycosides **16**, albeit with incomplete conversion and poor selectivity (Table 6, entries 6-9, 11). In contrast, treatment of the reaction with $Cu(OTf)_2$ exhibited no reaction whereas with TfOH complex mixture of products

were obtained (Table 6, entries 10, 12). Next, screening was performed in various solvents namely THF, toluene, MeCN and DMF. It is found that when DCM was used as solvent, the desired product was produced in the highest yield and selectivity (Table 6, entries 13-16). A decrement in reaction temperature adversely affected the yield and selectivity after prolonged reaction time. Thus, the optimized conditions were found to include the employment of 4.4 equivalence of $BF_3 \cdot Et_2O$ with DCM as the solvent and stirring at room temperature under nitrogen atmosphere for 20 minutes.

Under the optimized conditions obtained, the scope and generality of stereoselective synthesis of enone *N*-glycosides **15a**-**15m** promoted by $BF_3 \cdot Et_2O$ was examined extensively. A range of nitrogen derived nucleophiles with various substituent (R) groups was screened and the results were summarized in Table 7. To our delight, the pure α isomer can be easily separated by purification with flash column chromatography and the isolated yields of the pure isomer ranged from moderate to good. In general, aromatic sulfonamides (**2a**, **2d**, **2c**, **2f** and **2b**) afforded the corresponding enone *N*-glycosides (**15a**, **15c** to **15f**) in moderate yield and good anomeric selectivity (Table 7, entries 1 and 2). The only exception is aromatic sulfonamides bearing nitro group (**2e** and **2j**) which have shown relatively lower reactivity with moderate α to β anomeric selectivity. Interestingly, halogen bearing aromatic sulfonamides (**2c** and **2d**) provided good yield and superior anomeric selectivity with α to β ratio of ~90:10. Subsequently, methanesulfonamide **2g** ($MsNH_2$) and trichloromethane-sulfonamide **2l** ($TecNH_2$) were also exploited as

Table 7. Scope of the stereosynthesis of enone *N*-glycosides



entry	RNH_2	product[b]	yield (%)[c]	α/β[d]
1	 R = Me (**2a**), NO_2 (**2e**), Cl (**2d**), F (**2c**), OMe (**2f**), H (**2b**)	 R = Me (**15a**), NO_2 (**15b**), Cl (**15c**), F (**15d**), OMe (**15e**), H (**15f**)	75 (**15a**) 56 (**15b**) 83 (**15c**) 86 (**15d**) 76 (**15e**) 73 (**15f**)	84/16 (**15a**) 86/14 (**15b**) 89/11 (**15c**) 91/9 (**15d**) 81/19 (**15e**) 84/16 (**15f**)
2	 **2j**	 **15g**	44	74/26
3	$MsNH_2$ **2g**	 **15h**	68	90/10
4	 **2l**	 **15i**	71	78/22
5	$CbzNH_2$ **2h**	 **15j**	54	7/23
6	$FmocNH_2$ **2m**	 **15k**	46	75/25
7	 **2k**	 **15l**	55	89/11
8	 **2n**	 **15m**	42	68/32

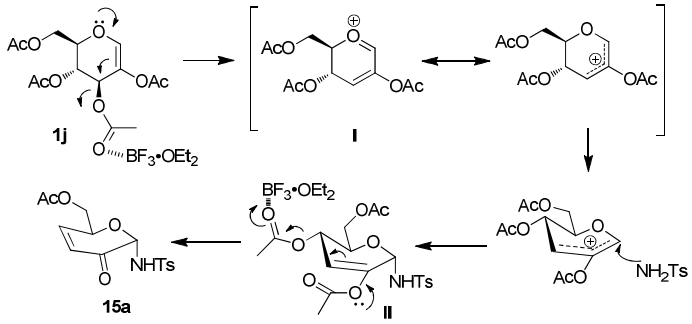
[a] All products were characterized by IR, HRMS, ^{1}H NMR and ^{13}C NMR. [b] Isolated yields of pure isomer after purification. [c] The anomeric ratio was determined on the crude ^{1}H NMR spectra.

viable nucleophile. Reaction of 2-acyloxy glycols with alkylsulfonamide which provides the desired glycoside with moderate yield and high anomeric selectivity illustrated the extended feasibility of our reaction (Table 7, entries 3 and 4).

Encouraged by the results, we further investigated the scope of carbamates (**2h**, **2m** and **2k**) that can serve as efficient nucleophiles (Table 7, entries 5-7). The enone *N*-glycoside **15j** represent a crucial example as benzyloxycarbonyl (Cbz) group could be transformed into amines easily following simple protective group chemistry. Likewise, we have attempted the reaction with allyl-substituted aromatic sulfonamide **15m** which furnished the corresponding enone *N*-glycosides **15m** with moderate yield and selectivity (Table 7, entry 8). The presence of easily functionalized allyl group allows promising application of the resulting *N*-glycosides as precursor in asymmetric synthesis. Overall, this novel synthetic method provides a straightforward access to a wide range of enone *N*-glycosides derivatives, with potential biochemical applications.

In our initial attempt to probe the reaction mechanism, we found that when C-4 epimer of 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glactal (from the corresponding D-glactal) was reacted under the same reaction conditions, the *N*-glycoside of enone sugar formed was of the similar results as that obtained from the corresponding D-glucal. This observation implies that both acetyl protected D-glucal and D-glactal led to a common reactive intermediate that eventually converged to the resulting *N*-glycoside of enone sugar. Additionally, reaction with *p*-toluenesulfonamide **2a** and 2,3-unsaturated glycosides **16**, similar α/β ratio of **15ab** was observed. A plausible

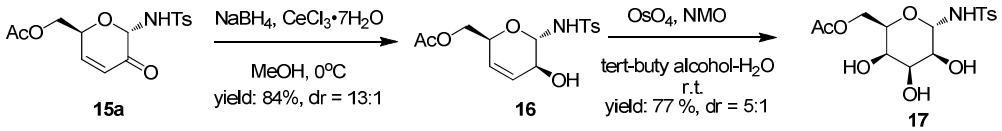
mechanism for the formation of enone *N*-glycosides **15** was depicted in Scheme 7.[10] The selectivity for the α isomer in the formation of **15** can be explained by taking into account the steric course of the glycosylation of **1j** combined with anomeric effect. Our proposed mechanism involves formation of intermediary allyloxocarbenium ion **I** as a result of expulsion of acetoxy group. Assuming that **1j** reacts in the preferred $^4H_1$ conformation, the quasiaxial allylic acetoxy group can be readily eliminated by coordinating with the Lewis acid. Simultaneous migration of thedouble bond (Ferrier's rearrangement) generates a cation at C-1 that can be stabilized by participation of the oxygen-ring lone pair. The quasiaxially oriented alkoxy group at C-4 should induce the attack of the sulfonamide from the opposite face to give the 2-enopyranoside with the α-anomeric configuration. This intermediate **II** undergoes a β-elimination affording the dihydropyranones **15a**.



Scheme 7. Proposed mechanism.

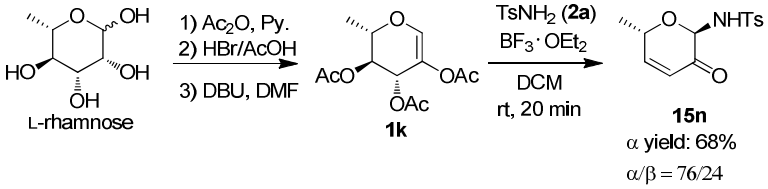
To demonstrate the application of enone *N*-glycosides **15** as precursor to potentially biological active derivatives, compound **15** was subjected to a sequence of reactions that consisted of the reduction of ketone functionality followed by dihydroxylation of the unsaturated double bond (Scheme 8).[30] It is noteworthy that

there was a remarkable diastereoselectivity in the reduction of **15a** to **16**, probably due to steric hindrance imposed by anomeric substituent adhjacent to the carbonyl group.[31] Chemical structure determination and stereochemical characterization of **16a** were achieved by extensive and detailed 1D and 2D NMR studies. The subsequent dihydroxylation[32] of **16** occurred smoothly by diastereofacial selective addition of osmium tetroxide to the double bond from the same side of the ring as the existing allylic hydroxy group to afford *N*-sulfonamidotalose **17**.[33]



Scheme 8. Synthesis of *N*-sulfonamidotalose **17**.

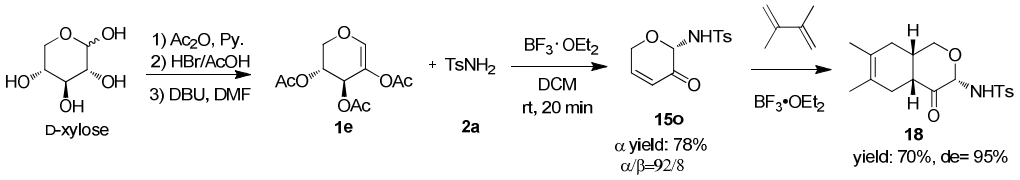
In similar manner, we have prepared the 6-deoxy enone *N*-glycoside derivative **15n** which has various possible synthetic and biochemical applications. The starting 2,3,4-tri-*O*-acetyl-6-deoxy-L-rhamnal **1k** was synthesized from L-rhamnose according to a literature reported procedure (Scheme 9).[34]



Scheme 9. Synthesis of 6-deoxy enone *N*-glycoside **15n**.

Optically active dihydropyranones derived from common sugars are useful chiral templates for the synthesis of natural products and their analogues.[35] To explore the reactivity of enone *N*-glycosides derivatives **15o** as dienophile, optically active pure

2,6-dihydropyran-3-one **18** has been prepared through Diels-Alder cycloaddition with 2,3-dimethylbutadiene (Scheme 10).[36] As expected, the presence of chiral centre at the anomeric position which induces asymmetry during the cycloaddition reaction led to preponderant formation of a diastereomer. The high diastereofacial selectivity in the cycloaddition provides reliable entry to optically active tetrahydrobenzopyranones possessing a number of contiguous stereogenic centers established in a desired manner.



Scheme 10. Synthesis of 2,6-dihydropyran-3-one **18**.

2.3.3.3 Conclusions

In conclusion, we have developed a new protocol for stereoselective synthesis of *N*-glycosides of enone sugars with a wide range of nitrogen nucleophiles utilizing $BF_3 \cdot Et_2O$ as promoter. This method would allow the application of *N*-glycosides of enone sugar derivatives to expeditiously assemble a wide pool of biologically active derivatives through a straightforward manner. *N*-glycosides of enone sugar derivatives also served as dienophile which underwent Diels-Alder cycloaddition with excellent diastereofacial selectivity providing a landmark access to optically active bicyclic adduct, where the multiple stereogenic centered compound could serve as chiral building block for potential synthesis of complex natural products.

2.4 Experimental Section

2.4.1 General experimental

All the reactions were carried out in a flame or oven-dried glassware under an argon or nitrogen atmosphere with freshly distilled solvents under anhydrous conditions unless otherwise indicated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 ^{o}C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 mm). 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 JEOL ECA 400 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 $CDCl_3$, 2.5 ppm for ^{1}H NMR spectra and 39.5 ppm for ^{13}C NMR spectra in MeOD). TMS signal at 0.0 ppm was used an internal standard for partial ^{1}H NMR spectra. Chemical shift (δ) 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. HRMS (ESI) spectra were recorded on a Q-Tof premier^{TM} mass spectrometer. X-ray crystallographic data was collected by using a Bruker X8Apex diffractometer with Mo K/α radiation (graphite monochromator). Microwave

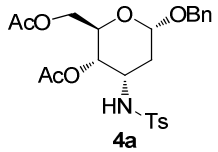
experiments were conducted in a CEM Discover^{TM} system.

2.4.2 Materials

All solvents were distilled under nitrogen from the following drying agents immediately before use: tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl; dichloromethane and 1, 2-dichloroethane were distilled from calcium hydride. Anhydrous acetonitrile (MeCN) was purchased from commercial suppliers and used without further purification. $BF_3{\cdot}OEt_2$ was distilled from calcium hydride before use. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. All the catalysts and additives were purchased from commercial suppliers and used without further purification.

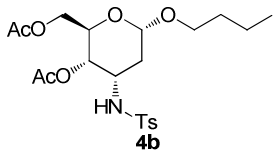
2.4.3 General procedure for synthesis of 3-amino-2,3-dideoxysugars 4

To a solution of 3,4,6-tri-*O*-acetyl-D-glucal **1a** (50 mg, 0.18 mmol) and nitrogen nucleophiles **2** (1.1 equiv) in DCE (2 mL) was added oxygen or sulfur nucleophiles **3** (1.1 equiv) under N_2 atmosphere. $BF_3{\cdot}OEt_2$ (50 μL, 0.4 mmol, 2.2 equiv) was then added to this mixture. The reaction mixture was stirred for 30 min at room temperature, quenched with saturated $NaHCO_3$ (3 mL) and subsequently extracted with CH_2Cl_2 (5 mL). The extract was dried and concentrated. The residue was subjected to column chromatography (silica gel, hexane-EtOAc) to obtain pure 3-amino-2,3-dideoxysugar **4**.



4a

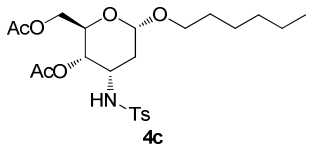
Benzyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4a): 93% yield, $[\alpha]_D^{20}$ = +41.9 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.27-7.41 (m, 7H), 6.03 (d, *J* = 9.2 Hz, 1H), 4.88 (d, *J* = 2.8 Hz, 1H), 4.72 (d, *J* = 12 Hz, 1H), 4.64 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.51 (d, *J* = 12 Hz, 1H), 4.28-4.33 (m, 1H), 4.13-4.28 (m, 2H), 3.92 (q, *J* = 3.6 Hz, 1H), 2.41 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 1.81 (dt, *J* = 9.6, 3.6 Hz, 1H), 1.47 (dd, *J* = 14.4, 2.0Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.4, 143.3, 138.0, 136.4, 129.8, 128.7, 128.3, 127.9, 126.9, 96.2, 69.7, 67.0, 64.6, 62.7, 48.0, 32.9, 21.5, 20.9, 20.8; IR ($CHCl_3$): 3280, 1738, 1539, 1367, 1236, 1170, 1031, 743cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{30}NO_8S$ 492.1692, found 492.1701.



4b

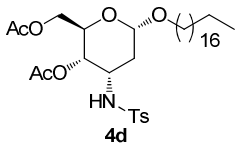
Butyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4b): 88% yield, $[\alpha]_D^{20}$ = +54.8 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.08 (d, *J* = 9.2 Hz, 1H), 4.81 (d, *J* = 3.6 Hz, 1H), 4.62 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.31 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.11-4.21 (m, 2H), 3.89 (q, *J* = 3.6 Hz, 1H), 3.71-3.73 (m, 1H), 3.38-3.40 (m, 1H), 2.43 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.78 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.24-1.45 (m, 5H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.5, 143.3, 138.0, 129.8, 126.9, 97.1, 68.1, 67.0, 64.4, 62.8, 48.1, 32.8, 31.4, 21.5, 21.0, 20.8, 19.4, 13.8; IR

($CHCl_3$): 3420, 1740, 1643, 1229, 1161, 1055, 754cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{31}NO_8SNa$ 480.1668, found 480.1676.



4c

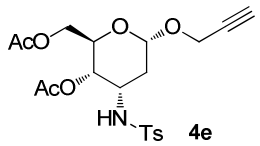
Hexyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4c): 84% yield, $[\alpha]_D^{20}$ = +54.7 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.00 (d, *J* = 8.8 Hz, 1H), 4.72 (d, *J* = 3.2 Hz, 1H), 4.53 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.23 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.03-4.09 (m, 2H), 3.81 (q, *J* = 3.6 Hz, 1H), 3.59-3.64 (m, 1H), 3.27-3.32 (m, 1H), 2.34 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.71 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.25-1.54 (m, 9H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.3, 138.0, 129.7, 126.8, 97.1, 68.4, 67.0, 64.4, 62.8, 48.1, 32.8, 31.4, 29.7, 25.9, 22.6, 21.5, 21.0, 20.8,14.0; IR ($CHCl_3$): 3327, 2926, 1742, 1342, 1240, 1163, 1055, 735cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{36}NO_8S$ 486.2162, found 486.2161.



4d

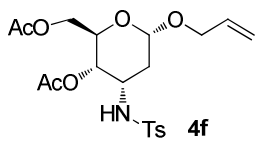
Octadecyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyrano side (4d): 66% yield, $[\alpha]_D^{20}$ = +44.9 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.08 (d, *J* = 8.8 Hz, 1H), 4.81 (d, *J* = 2.8 Hz, 1H), 4.62 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.29 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.17-4.30 (m, 2H), 3.85 (q, *J* = 3.6 Hz, 1H), 3.69-3.71 (m, 1H), 3.36- 3.38 (m, 1H),

2.42 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.77 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.25-1.54 (m, 33H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.3, 138.1, 129.7, 126.8, 97.1, 68.4, 67.0, 64.4, 62.8, 48.1, 36.6, 32.8, 31.9, 29.7, 29.66, 29.65, 29.61, 29.5, 29.4, 29.3, 26.2, 24.7, 22.7, 21.5, 21.0, 20.8, 14.1; IR ($CHCl_3$): 3421, 2924, 1741, 1342, 1240, 1163, 1055, 756, 498cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{35}H_{59}NO_8SNa$ 676.3859, found 676.3857.



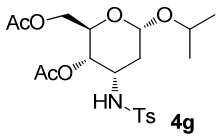
4e

Propargyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4e): 95% yield, $[\alpha]_D^{20}$ = +51.5 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.82 (d, *J* = 8.8 Hz, 1H), 5.05 (d, *J* = 3.2 Hz, 1H), 4.65 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.32 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.09-4.27 (m, 3H), 3.91 (q, *J* = 3.6 Hz, 1H), 3.38-3.40 (m, 1H), 2.46 (s, 1H), 2.42 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.87 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.50 (dd, *J* = 18.4, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.4, 137.8, 129.8, 126.9, 95.7, 78.1, 75.5, 66.8, 64.7, 62.6, 54.8, 47.8, 32.7, 21.5, 21.0, 20.8; IR ($CHCl_3$): 3306, 2922, 1738, 1339, 1242, 1161, 1042, 758cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{20}H_{25}NO_8SNa$ 462.1199, found 462.1201.



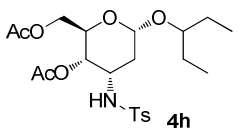
4f

Allyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4f): 82% yield, $[\alpha]_D^{20}$ = +115.5 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.02 (d, *J* = 9.2 Hz, 1H), 5.87-5.93 (m, 1H), 5.25-5.31 (m, 2H), 4.87 (d, *J* = 3.2 Hz, 1H), 4.64 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.32 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.14-4.23 (m, 3H), 3.98 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.91 (q, *J* = 3.6 Hz, 1H), 2.42 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 1.82 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.47 (dd, *J* = 18.4, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.4, 138.0, 133.0, 129.8, 126.9, 118.2, 96.3, 68.6, 66.9, 64.5, 62.7, 48.0, 32.8, 21.5, 21.0, 20.8; IR ($CHCl_3$): 3265, 2955, 1742, 1339, 1238, 1163, 1035, 656cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{27}NO_8SNa$ 464.1355, found 464.1367.



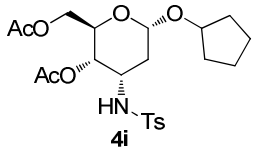
4g

Isopropyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4g): 85% yield, $[\alpha]_D^{20}$ = +53.9 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.16 (d, *J* = 8.8 Hz, 1H), 4.94 (d, *J* = 3.2 Hz, 1H), 4.61 (dd, *J* = 10.8, 4.0 Hz, 1H), 4.31 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.16-4.22 (m, 2H), 3.87-3.92 (m, 2H), 2.42 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.78 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.38 (dd, *J* = 10.8, 2.4 Hz, 1H), 1.30 (d, *J* = 6.0Hz, 3H), 1.16 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.3, 138.0, 129.7, 126.9, 95.3, 70.6, 67.2, 64.5, 62.8, 48.1, 33.2, 23.4, 21.5, 21.4, 21.0, 20.8; IR ($CHCl_3$): 3323, 2970, 1741, 1369, 1230, 1163, 1091, 987, 665cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{29}NO_8SNa$ 466.1512, found 466.1501.



4h

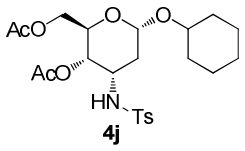
Isopentanyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyran oside (4h): 90% yield, $[\alpha]_D^{20}$ = +47.2 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.18 (d, *J* = 8.8 Hz, 1H), 4.92 (d, *J* = 3.2 Hz, 1H), 4.60 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.17-4.31 (m, 3H), 3.89 (q, *J* = 3.6 Hz, 1H), 3.50-3.53 (m, 1H), 2.42 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.76 (dt, *J* = 14.8, 4.0Hz, 1H), 1.63-1.66 (m, 2H), 1.48-1.54 (m, 2H), 1.39 (dd, *J* = 14.4, 2.8 Hz, 1H), 0.98 (q, *J* = 7.2 Hz, 3H), 0.85 (q, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.5, 143.3, 138.0, 129.7, 126.9, 96.1, 81.4, 67.2, 64.7, 62.9, 48.1, 33.1, 26.7, 25.0, 21.5, 21.0, 20.8, 9.9, 9.0; IR ($CHCl_3$): 3304, 2935, 1742, 1342, 1229, 1163, 989cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{22}H_{33}NO_8SNa$ 494.1825, found 494.1811.



4i

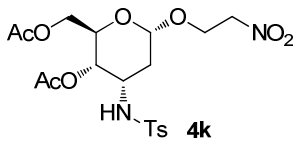
Cyclopentyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyran oside (4i): 85% yield, $[\alpha]_D^{20}$ = +43.6 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.15 (d, *J* = 9.2 Hz, 1H), 4.89 (d, *J* = 3.2 Hz, 1H), 4.62 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.32 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.16-4.21 (m, 3H), 3.86-3.91 (m, 1H), 2.42 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.61-1.86 (m, 9H), 1.36 (dd, *J* = 14.4, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.3, 138.1, 129.7, 126.9, 95.9, 79.9, 67.1, 64.6, 62.8, 48.2, 33.5, 33.1,

31.8, 23.4, 23.0, 21.5, 21.0, 20.8; IR ($CHCl_3$): 3422, 1740, 1340, 1228, 1161, 485cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{22}H_{31}NO_8SNa$ 492.1668, found 492.1669.



4j

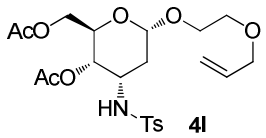
Cyclohexyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyran oside (4j): 88% yield, $[\alpha]_D^{20}$ = +63.4 (c 0.25 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.26 (d, *J* = 8.8 Hz, 1H), 4.89 (d, *J* = 3.2 Hz, 1H), 4.61 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.30 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.18-4.24 (m, 2H), 3.89 (q, *J* = 3.6 Hz, 1H), 3.60-3.65 (m, 1H), 2.42 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.90-1.92 (m, 1H), 1.70-1.80 (m, 4H), 1.41 -1.55 (m, 2H), 1.23-1.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.3, 138.1, 129.7, 126.9, 95.3, 76.0, 67.2, 64.6, 62.8, 48.2, 33.3, 33.2, 31.3, 25.5, 23.9, 23.5, 21.5, 21.0, 20.8; IR ($CHCl_3$): 3419, 1638, 1340, 1230, 1163, 517cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{33}NO_8SNa$ 506.1825, found 506.1830.



4k

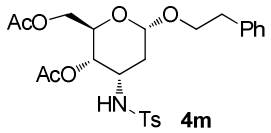
2'-Nitroethyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-gluco pyranoside (4k): 76% yield, $[\alpha]_D^{20}$ = +34.2 (c 0.5 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.66 (d, *J* = 9.2 Hz, 1H), 4.88 (d, *J* = 3.2 Hz, 1H), 4.62-4.69 (m, 3H), 4.22-4.27 (m, 3H), 4.09-4.13 (m,

1H), 3.88-3.99 (m, 2H), 2.42 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.85 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.38 (dd, *J* = 14.2, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.3, 143.4, 138.0, 129.8, 126.8, 97.7, 74.8, 66.7, 65.0, 63.9, 62.6, 47.7, 32.7, 21.5, 20.9, 20.8; IR ($CHCl_3$): 3421, 1734, 1638, 1558, 1340, 1230, 1161, 497cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{26}N_2O_{10}SNa$ 497.1206, found 497.1193.



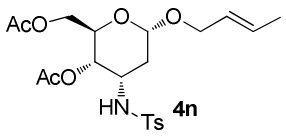
4l

2'-(Allyloxy)ethyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-gluco pyranoside (4l): 76% yield, $[\alpha]_D^{20}$ = +49.9 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.20 (d, *J* = 9.2 Hz, 1H), 5.91-6.02 (m, 1H), 5.32 (dd, *J* = 16.4 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 4.89 (d, *J* = 3.2 Hz, 1H), 4.64 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.30 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.16-4.21 (m, 2H), 4.07-4.09 (m, 2H), 3.93 (q, *J* = 3.6 Hz, 1H), 3.83-3.85 (m, 1H), 3.62-4.65 (m, 2H), 3.57-3.58 (m, 1H), 2.41 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 1.80 (dt, *J* = 10.8, 4.0 Hz, 1H), 1.54 (dd, *J* = 14.2, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.2, 138.3, 134.5, 129.8, 126.8, 117.5, 96.9, 72.4, 68.6, 67.0, 66.4, 64.4, 62.7, 48.1, 32.7, 21.5, 20.9, 20.8; IR ($CHCl_3$): 3325, 2924, 1740, 1340, 1240, 1163, 1057, 499cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{29}NO_9SNa$ 494.1461, found 494.1435.



4m

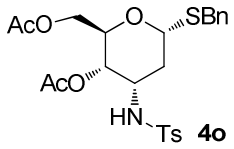
Phenethyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyran oside (4m): 91% yield, $[\alpha]_D^{20}$ = +48.2 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.27-7.38 (m, 7H), 5.85 (d, *J* = 9.2 Hz, 1H), 4.76 (d, *J* = 3.2 Hz, 1H), 4.55 (dd, *J* = 10.8, 4.0 Hz, 1H), 4.18 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.94-4.06 (m, 2H), 3.82-3.84 (m, 1H), 3.65-3.69 (m, 2H), 2.91-2.94 (m, 2H), 2.41 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.71 (dt, *J* = 9.6, 3.6 Hz, 1H), 1.39 (dd, *J* = 14.4, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.3, 138.6, 138.1, 129.7, 128.8, 128.3, 126.9, 126.6, 97.0, 68.9, 68.5, 66.7, 62.6, 47.9, 36.1, 32.9, 21.5, 20.9, 20.8; IR ($CHCl_3$): 3421, 1740, 1647, 1340, 1240, 1163, 752, 492cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{31}NO_8SNa$ 528.1668, found 528.1664.



4n

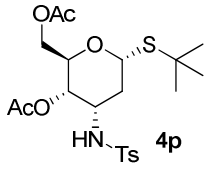
(*E*)-But-2-enyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopy ranoside (4n): 83% yield, $[\alpha]_D^{20}$ =+118.4 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 300MHz): δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.04 (d, *J* = 8.7 Hz, 1H), 5.70-5.75 (m, 1H), 5.54-5.57 (m, 1H), 4.86 (d, *J* = 3.3 Hz, 1H), 4.63 (dd, *J* = 10.5, 3.9 Hz, 1H), 4.32 (dd, *J* = 12.3, 4.5 Hz, 1H), 4.11-4.20 (m, 3H), 3.88-3.94 (m, 2H), 2.42 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 1.82 (dt, *J* = 10.8, 3.9 Hz, 1H), 1.76 (d, *J* = 6.9 Hz, 3H), 1.44 (dd, *J* = 14.4, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.8, 170.5, 143.4, 138.0, 131.2, 129.8, 126.9, 125.9, 95.8, 68.4, 67.1, 64.4, 62.8, 48.1,

32.9, 21.6, 21.1, 20.9, 17.9; IR (neat): 3419, 1741, 1643， 1240, 1163, 1091, 669cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{29}NO_8SNa$ 478.1512, found 478.1526.



4o

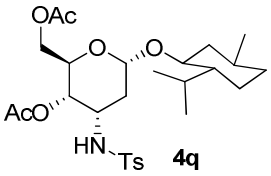
Benzylthio 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4o): 71% yield, $[\alpha]_D^{20}$ = +8.8 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.27-7.32 (m, 7H), 5.18 (d, *J* = 10.0 Hz, 1H), 4.74-4.84 (m, 2 H), 3.99 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.68-3.78 (m, 3H), 3.33-3.48 (m, 1H), 2.70-2.75 (m, 1H), 2.41 (s, 3H), 2.27 (dt, *J* = 6.4, 2.4 Hz, 1H), 2.07 (s, 3H), 2.04 (dd, *J* = 14.4, 2.0 Hz, 1H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.6, 169.8, 143.8, 138.4, 137.2, 129.4, 128.9, 128.7, 127.4, 127.3, 81.6, 75.9, 68.3, 62.6, 44.6, 38.5, 34.7, 21.5, 20.8, 20.7; IR ($CHCl_3$): 3420, 1637, 1238, 1163, 524cm^{-1}; HRMS (ESI) m/z [M+ Na]$^+$ calcd for $C_{24}H_{29}NO_7S_2Na$ 530.1283, found 530.1285.



4p

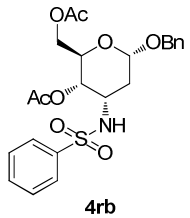
tert-Butyl hydrosulfide 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4p): 75% yield, $[\alpha]_D^{20}$ = +54.9 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.17-5.19 (m, 2H), 4.68 (dd, *J* = 10.0, 4.8 Hz, 1H), 4.03 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.70-3.82 (m, 2H), 3.41 (q, *J* = 3.6 Hz, 1H), 2.41 (s, 3H), 2.12 (dt, *J* = 6.4, 2.4 Hz, 1H), 2.09 (s, 3H), 2.04 (dd, *J* = 14.4, 2.0 Hz, 1H), 2.01 (s, 3H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 100MHz): δ

170.5, 170.1, 143.6, 138.5, 129.3, 127.3, 79.5, 76.7, 72.4, 68.4, 62.7, 44.1, 40.3, 40.2, 21.5, 21.1, 20.7; IR ($CHCl_3$): 3421, 1740, 1636, 1334, 1238, 1163, 1057, 492cm^{-1}; HRMS (ESI) m/z $[M+ Na]^+$ calcd for $C_{21}H_{31}NO_7S_2Na$ 496.1440, found 496.1436.



4q

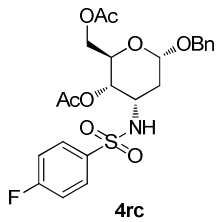
L-menthol 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyran oside (4q): 77% yield, $[\alpha]_D^{20}$ = +38.9 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 300MHz): δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.14 (d, *J* = 9.0 Hz, 1H), 4.88 (d, *J* = 3.3 Hz, 1H), 4.61 (dd, *J* = 10.5, 3.6 Hz, 1H), 4.18-4.32 (m, 3H), 3.89 (q, *J* = 3.6 Hz, 1H), 3.28 (td, *J* = 4.5 Hz, 1H), 2.42 (s, 3H), 2.17-2.21 (m, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 1.87-1.90 (m, 1H), 1.63-1.75 (m, 4H), 1.04-1.39 (m, 5H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.69 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.9, 170.5, 143.4, 138.2, 129.7, 126.8, 99.4, 82.8, 67.3, 64.7, 48.8, 43.0, 34.1, 33.1, 31.7, 26.1, 23.2, 22.3, 21.6, 21.3, 21.1, 20.9, 16.2; IR (neat): 3419, 1743, 1653, 1230, 1172, 1042, 561cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{27}H_{41}NO_8SNa$ 562.2451, found 562.2471.



4rb

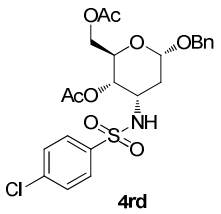
Benzyl 3-benzenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4rb): 85% yield, $[\alpha]_D^{20}$ = +70.1 (c 0.25 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.80

(d, *J* = 10.0 Hz, 2H), 7.27-7.41 (m, 8H), 6.03 (d, *J* = 9.2 Hz, 1H), 4.88 (d, *J* = 2.8 Hz, 1H), 4.72 (d, *J* = 12 Hz, 1H), 4.64 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.51 (d, *J* = 12 Hz, 1H), 4.28-4.33 (m, 1H), 4.13-4.28 (m, 2H), 3.92 (q, *J* = 3.6 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 1.81 (dt, *J* = 9.6, 3.6 Hz, 1H), 1.47 (dd, *J* = 14.4, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 143.3, 138.0, 136.4, 129.8, 128.7, 128.3, 127.9, 126.9, 96.2, 69.7, 67.0, 64.6, 62.7, 48.0, 32.9, 21.0, 20.8; IR ($CHCl_3$): 3420, 1740, 1647, 1217, 1165, 505cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{23}H_{27}NO_8SNa$ 500.1355, found 500.1354.



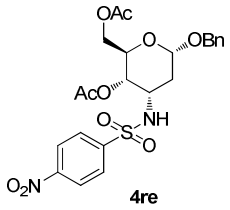
4rc

Benzyl 3-*p*-fluorophenylsulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4rc): 91% yield, $[\alpha]_D^{20}$ = +69.1 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.79-7.82 (m, 2H), 7.30-7.40 (m, 7H), 6.10 (d, *J* = 8.8 Hz, 1H), 4.91 (d, *J* = 3.2 Hz, 1H), 4.73 (d, *J* = 12 Hz, 1H), 4.65 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.52 (d, *J* = 12 Hz, 1H), 4.31 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.13-4.17 (m, 2H), 3.95 (q, *J* = 3.6 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.86 (dt, *J* = 14.4, 4.0 Hz, 1H), 1.49 (dd, *J* = 14.4, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.8, 170.5, 136.4, 129.6, 129.5, 128.9, 128.5, 128.0, 116.5, 116.4, 96.2, 69.9, 67.0, 64.7, 62.7, 48.2, 33.0, 21.0, 20.9; IR ($CHCl_3$): 3404, 1740, 1494, 1344, 1234, 1169, 1051, 754, 498cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{23}H_{26}NO_8SFNa$ 518.1261, found 518.1253.



4rd

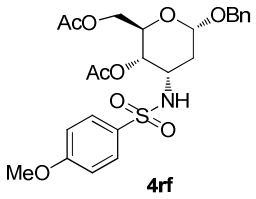
Benzyl 3-*p*-chlorophenylsulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4rd): 85% yield, $[\alpha]_D^{20}$ = +64.3 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.29-7.40 (m, 5H), 6.11 (d, *J* = 8.8 Hz, 1H), 4.91 (d, *J* = 2.8 Hz, 1H), 4.73 (d, *J* = 12 Hz, 1H), 4.65 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.51 (d, *J* = 12 Hz, 1H), 4.30 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.11-4.16 (m, 2H), 3.94 (q, *J* = 3.6 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 1.85 (dt, *J* = 14.4, 4.0 Hz, 1H), 1.49 (dd, *J* = 14.8, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 139.6, 139.1, 136.3, 129.5, 128.8, 128.4, 128.3, 127.9, 96.1, 69.8, 66.9, 64.6, 62.6, 48.2, 32.9, 20.9, 20.8; IR ($CHCl_3$): 3422, 1740, 1647, 1344, 1240, 1165, 1051, 754, 497cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{26}NO_8SClNa$ 534.0965, found 534.0958.



4re

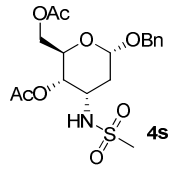
Benzyl 3-*p*-nitrophenylsulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4re): 88% yield, $[\alpha]_D^{20}$ = +68.4 (c 0.5 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 8.33 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.29-7.43 (m, 5H), 6.28 (d, *J* = 8.8 Hz, 1H), 4.93 (d, *J* = 3.2 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.68 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.31 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.13-4.18(m,

2H), 4.01 (q, *J* = 4.0 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 1.90 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.50 (dd, *J* = 14.8, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.3, 147.6, 147.0, 136.2, 128.9, 128.6, 128.0, 127.9, 124.5, 96.0, 69.9, 66.8, 64.6, 62.5, 48.5, 33.0, 20.9, 20.8; IR ($CHCl_3$): 3323, 1740, 1529, 1350, 1240, 1166, 503cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{26}N_2O_{10}SNa$ 545.1206, found 545.1207.

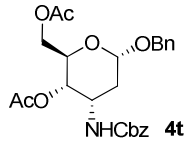


4rf

Benzyl 3-*p*-methoxyphenylsulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-gluco pyranoside (4rf): 74% yield, $[\alpha]_D^{20}$ = +102.4 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.32-7.41 (m, 5H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.00 (d, *J* = 8.8 Hz, 1H), 4.89 (d, *J* = 3.2 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.65 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.32 (dd, *J* = 12.4, 5.2 Hz, 1H), 4.13-4.16 (m, 2H), 3.91 (q, *J* = 4.0 Hz, 1H), 3.89 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.90 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.48 (dd, *J* = 14.8, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.4, 162.8, 136.4, 132.6, 128.9, 128.8, 128.3, 127.9, 114.3, 96.2, 69.8, 67.0, 64.6, 62.7, 55.6, 48.0, 32.9, 21.0, 20.8; IR ($CHCl_3$): 3335, 1740, 1597, 1499, 1257, 1157cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{29}NO_9SNa$ 530.1461, found 530.1454.

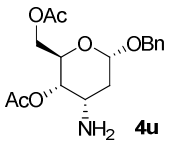


Benzyl 3-methylsulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4s): 92% yield, $[\alpha]_D^{20}$ = +58.6 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.32-7.39 (m, 5H), 5.84 (d, *J* = 8.4 Hz, 1H), 5.01 (d, *J* = 3.2 Hz, 1H), 4.77 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.73 (d, *J* = 12.4 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.32 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.11-4.15 (m, 3H), 2.94 (s, 3H), 2.05-2.17 (m, 8H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 170.1, 136.3, 128.8, 128.4, 128.1, 95.8, 69.7, 67.2, 64.5, 62.6, 48.4, 41.6, 34.0, 21.0, 20.8; IR ($CHCl_3$): 3421, 1740, 1647, 1327, 1232, 1153, 1049, 754, 499cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{25}NO_8SNa$ 438.1199, found 438.1193.



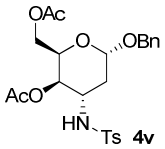
Benzyl 3-benzyloxycarbonylamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyranoside (4t): 72% yield, $[\alpha]_D^{20}$ = +43.3 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.31-7.35 (m, 10H), 6.23 (d, *J* = 8.8 Hz, 1H), 5.07 (q, *J* = 12.4 Hz, 2H), 4.99 (d, *J* = 3.2 Hz, 1H), 4.82 (dd, *J* = 10.8, 4.0 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.42-4.45 (m, 1H), 4.43 (dd, *J* = 10.8, 4.0 Hz, 1H), 4.09-4.16 (m, 2H), 2.10 (s, 3H), 1.95-2.06 (m, 2H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.8, 170.0, 156.2, 136.8, 136.7, 128.7, 128.5, 128.1, 128.0, 127.9, 127.8, 96.0, 69.4, 67.7, 66.5, 64.4, 62.9, 45.2, 33.0, 20.8, 20.7; IR ($CHCl_3$): 3420, 1734, 1638, 1508, 1223,

1047, 752, 513cm^{-1}; HRMS (ESI) m/z [M + Na]$^{+}$ calcd for $C_{25}H_{29}NO_8Na$ 494.1791, found 494.1795.



4u

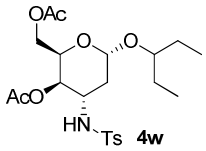
Benzyl 3-amido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glucopyrano-side (4u): 54% yield, $[\alpha]_D^{20}$ = +82.0 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.28-7.37 (m, 5H), 5.75-5.95 (m, 2H), 5.35 (d, *J* = 9.2 Hz, 1H), 5.15-5.31 (m, 2H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.12-4.31 (m, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 1.28-1.44 (m, 1H), 0.87-0.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.8, 170.3, 137.6, 129.3, 128.3, 128.1, 127.9, 127.8, 93.7, 70.3, 67.1, 65.3, 62.9, 41.4, 21.0, 20.9; IR ($CHCl_3$): 3443, 1742, 1643, 1369, 1231, 1153, 1038cm^{-1}; HRMS (ESI) m/z [M + H]$^{+}$ calcd for $C_{17}H_{24}NO_6$ 338.1604, found 338.1605.



4v

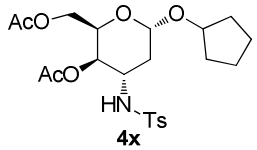
Benzyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glacopyranoside (4v): 87% yield, $[\alpha]_D^{20}$ = +41.6 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.31-7.75 (m, 7H), 6.06 (d, *J* = 8.1 Hz, 1H), 4.92 (d, *J* = 3.0 Hz, 1H), 4.78 (d, *J* = 2.7 Hz, 1H), 4.74 (d, *J* = 12 Hz, 1H), 4.51 (d, *J* = 12 Hz, 1H), 4.26-4.30 (m, 1H), 3.99-4.10 (m, 2H), 3.63 (q, *J* = 2.7 Hz, 1H), 2.42 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.95-2.04 (m, 1H), 1.18-1.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 170.5, 169.5, 143.5, 137.8, 136.5, 129.8, 128.7, 128.3, 128.1, 127.1, 95.7, 69.4, 67.9, 63.4,

62.9, 47.6, 28.6, 21.6, 20.8, 20.7; IR (neat): 3417, 1643, 1214, 1175, 1042, 665cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{24}H_{29}NO_8SNa$ 514.1512, found 514.1516.



4w

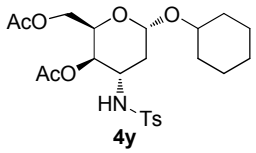
Isopentanyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glacopyranoside (4w): 83% yield, $[\alpha]_D^{20}$ = +38.0 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.21 (d, *J* = 8.1 Hz, 1H), 4.98 (d, *J* = 3.0 Hz, 1H), 4.75 (d, *J* = 3.0 Hz, 1H), 4.32- 4.37 (m, 1H), 4.01- 4.04 (m, 2H), 3.61 (q, *J* = 3.3Hz, 1H), 3.49-3.57 (m, 1H), 2.42 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.96-2.04 (m, 1H), 1.49-1.66 (m, 4H), 1.39 (d, *J* = 14.1, 1H), 1.00 (q, *J* = 7.2 Hz, 1H), 0.88 (q, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 170.5, 169.6, 143.5, 137.9, 129.8, 127.1, 95.9, 81.0, 68.0, 63.5, 63.1, 47.7, 28.9, 26.7, 25.0, 21.6, 20.8, 20.7, 9.9, 9.1; IR (neat): 3419, 1635, 1230, 1161, 1025, 748cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{22}H_{33}NO_8SNa$ 494.1825, found 494.1815.



4x

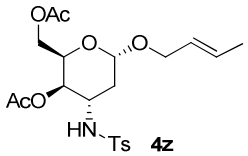
Cyclopentyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glacopyranoside (4x): 78% yield, $[\alpha]_D^{20}$ = +29.7 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.17 (d, *J* = 8.4 Hz, 1H), 4.94 (d, *J* = 3.2 Hz, 1H), 4.76 (d, *J* = 3.2 Hz, 1H), 4.27 (t, *J* = 6.0 Hz, 1H), 4.18-4.20 (m, 1H), 4.03-4.06 (m, 2H), 3.58-3.63 (m, 1H), 2.43 (s, 3H), 2.07 (s, 3H), 2.05 (d, *J* = 1.6 Hz,

1H), 2.03 (s, 3H), 1.71-1.98 (m, 8H), 1.34 (dd, *J* = 13.2, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.5, 169.6, 143.4, 137.9, 129.8, 127.0, 95.9, 79.9, 68.0, 63.3, 62.9, 47.8, 33.4, 31.9, 28.9, 23.4, 23.0, 21.6, 20.8, 20.7; IR (neat): 3419, 1745, 1227, 1161, 1047, 665cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{22}H_{31}NO_8SNa$ 492.1668, found 492.1659.



4y

Cyclohexyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-glacopyran oside (4y): 77% yield, $[\alpha]_D^{20}$ = +34.5 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.27 (d, *J* = 8.0 Hz, 1H), 5.02 (d, *J* = 2.8 Hz, 1H), 4.76 (d, *J* = 2.8 Hz, 1H), 4.28-4.36 (m, 1H), 4.02-4.16 (m, 2H), 2.41 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.90-1.92 (m, 1H), 1.29-2.03 (m, 11H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.6, 170.4, 143.5, 138.0, 129.8, 127.1, 95.4, 76.1, 68.1, 63.4, 63.1, 47.9, 33.4, 31.5, 29.0, 25.5, 24.1, 23.5, 21.6, 20.9, 20.8; IR (neat): 3415, 1742, 1230, 1164, 1032, 714cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{23}H_{33}NO_8SNa$ 506.1825, found 506.1815.

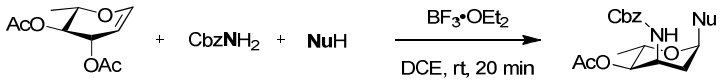


4z

(E)-But-2-enyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glacopy ranoside (**4z**): 87% yield, $[\alpha]_D^{20}$ = +32.2 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.08 (d, *J* = 8.1 Hz, 1H), 5.58-5.75 (m, 1H), 5.52-5.57 (m, 1H), 4.91 (d, *J* = 3.0 Hz, 1H), 4.76 (d, *J* = 2.7 Hz,

1H), 4.11-4.15 (m, 1H), 3.98-4.09 (m, 3H), 3.88-3.94 (m, 1H), 3.59 (q, *J* = 2.7 Hz, 1H), 2.42 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.97-2.00 (m, 1H), 1.76 (d, *J* = 5.4 Hz, 3H), 1.42 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.5, 169.5, 143.5, 137.8, 131.1, 129.8, 127.1, 126.0, 95.6, 68.2, 68.0, 63.2, 62.9, 47.6, 28.6, 21.6, 20.8, 20.7, 17.8; IR (neat): 3419, 1744, 1645, 1228, 1161, 1091, 645cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{29}NO_8SNa$ 478.1512, found 478.1518.

2.4.4 General procedures for the synthesis of 3-amino-2,3,6-trideoxyhexoses 10

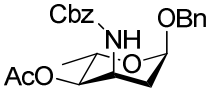


1d **2h** **3** **10**

To a solution of 3,4-di-*O*-acetyl-6-deoxy-L-glucal **1d** (50 mg, 0.24 mmol) and nitrogen nucleophiles **2h** (1.1 equiv) in DCE (2.5 mL, dry) was added *O*- or *S*-nucleophiles **3** (1.1 equiv) under N_2 atmosphere. $BF_3{\cdot}OEt_2$ (2.2 equiv) was then added to this mixture. The reaction mixture was stirred for 20 min at room temperature, quenched with saturated $NaHCO_3$ (3 mL) and subsequently extracted with CH_2Cl_2 (3 × 5 mL). The extract was dried and concentrated. The residue was subjected to column chromatography (silica gel, hexane-EtOAc) to obtain pure 3-amino-2,3,6-trideoxyhexoses **10**.

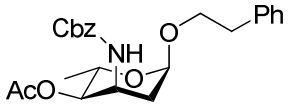
Spectroscopic characterization of 3-amino-2,3,6-trideoxysugars 10a-10t

Benzyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10a):



87% yield, $[\alpha]_D^{21}$ = 100.2 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.38 (m, 10H), 6.29 (d, *J* = 9.2 Hz, 1H), 5.06-5.19 (m, 2H), 4.93 (d, *J* = 3.2 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.52-4.74 (m, 2H), 4.37-4.40 (m, 1H), 4.00-4.07 (m, 1H), 2.11 (dq, *J* = 13.6, 4.0 Hz, 1H), 2.00 (s, 3H), 1.96-1.99 (m, 1H), 1.18 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 156.2, 136.9, 136.8, 128.6, 128.4, 128.0, 127.9, 127.8, 127.7, 96.9, 73.3, 69.1, 66.4, 61.9, 45.3, 33.4, 21.9, 17.5; IR ($CHCl_3$): 3420, 1726, 1510, 1230, 1051 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C23H27NO6Na 436.1736, found 436.1737.

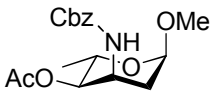
Phenethyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10b):



55% yield, $[\alpha]_D^{21}$ = 82.7 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.44 (m, 5H), 7.16-7.28 (m, 5H), 6.04 (d, *J* = 9.2 Hz, 1H), 5.17 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 4.80 (d, *J* = 3.2 Hz, 1H), 4.45 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.28-4.32 (m, 1H), 3.92-3.97 (m, 1H), 3.65-3.70 (m, 1H), 3.49-3.54 (m, 1H), 2.90-2.93 (m, 2H), 2.02 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.99 (s, 3H), 1.91 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.07 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 156.2, 138.9, 137.0, 128.7, 128.6, 128.5, 128.1, 128.0, 126.3, 96.7, 73.1, 68.7, 66.4, 61.5, 45.2, 36.3, 33.4, 20.8,

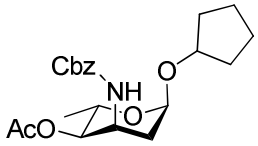
17.4; IR ($CHCl_3$): 3402, 3018, 1734, 1508, 1215, 1053, 756, 669 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C24H29NO6Na 450.1893, found 450.1895.

Methyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10c):



71% yield, $[\alpha]_D^{21}$= 90.9 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.28 (m, 5H), 6.12 (d, *J* = 9.2 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.73 (d, *J* = 3.2 Hz, 1H), 4.53 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.33-4.38 (m, 1H), 3.93-3.99 (m, 1H), 3.38 (s, 3H), 2.04-2.10 (m, 1H), 1.96 (s, 3H), 1.91-1.95 (m, 1H), 1.21 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 156.2, 136.8, 128.5, 128.2, 128.1, 98.0, 73.3, 66.5, 61.5, 55.2, 45.4, 33.4, 20.8, 17.5; IR ($CHCl_3$): 3475, 2937, 1735, 1510, 1232, 1051 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C17H23NO6Na 360.1423, found 360.1422.

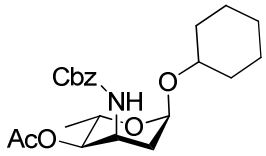
Cyclopentyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10d):



68% yield, $[\alpha]_D^{21}$ = 100.6 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.39 (m, 5H), 6.30 (d, *J* = 9.2 Hz, 1H), 5.13 (d, *J* = 12.8, 4.4 Hz, 1H), 5.09 (d, *J* = 12.8, 4.4 Hz, 1H), 4.92 (d, *J* = 3.2 Hz, 1H), 4.52 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.31-4.39 (m, 1H), 4.21-4.22 (m, 1H), 4.02-4.04 (m, 1H), 2.08 (dt, *J* = 10.4, 4.0 Hz, 1H), 1.96 (s, 3H), 1.88 (dd, *J* = 11.6, 1.6 Hz, 1H), 1.58-1.85 (m, 8H), 1.20 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 156.2, 137.1, 128.4, 127.9, 127.8, 95.3, 79.7, 73.5,

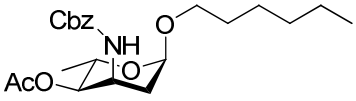
66.2, 61.8, 45.4, 33.7, 33.5, 31.7, 23.4, 23.0, 20.9, 17.5; IR ($CHCl_3$): 3418, 2957, 1728, 1506, 1230, 1120, 1053 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C21H29NO6Na 414.1893, found 414.1896.

Cyclohexyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10e):



83% yield, $[\alpha]_D^{20}$ = 74.5 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.38 (m, 5H), 6.39 (d, *J* = 8.8 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.99 (d, *J* = 3.2 Hz, 1H), 4.51 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.32-4.34 (m, 1H), 4.02-4.06 (m, 1H), 3.61-3.63 (m, 1H), 2.01 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.94 (s, 3H), 1.18-1.85 (m, 11H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 156.2, 137.1, 128.4, 128.1, 127.8, 91.5, 73.6, 66.3, 61.8, 45.5, 35.6, 33.8, 33.4, 31.2, 25.6, 24.1, 23.6, 20.9, 17.5; IR ($CHCl_3$): 3416, 1726, 1634, 1508, 1230, 1049 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C22H31NO6Na 428.2049, found 428.2051.

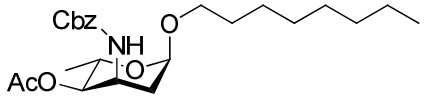
Hexyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10f):



81% yield, $[\alpha]_D^{21}$ = 66.0 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.38 (m, 5H), 6.28 (d, *J* = 8.8 Hz, 1H), 5.13 (d, *J* = 12.8 Hz, 1H), 5.07 (d, *J* = 12.8 Hz, 1H), 4.84 (d, *J* = 3.2 Hz, 1H), 4.52 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.32-4.36 (m, 1H), 3.97-3.99 (m, 1H), 3.69-3.72 (m, 1H), 3.39-3.42 (m, 1H), 2.05 (dt, *J* = 10.4, 4.0 Hz, 1H), 1.98 (s, 3H), 1.94-1.96 (m, 1H), 1.59-1.72 (m, 2H), 1.30-1.40 (m, 6H), 1.20-1.24

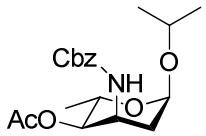
(m, 3H), 0.89-0.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 156.2, 137.0, 129.4, 128.4, 127.9, 96.8, 67.9, 66.3, 61.6, 55.2, 45.4, 33.4, 31.6, 29.5, 26.0, 22.5, 20.8, 17.5, 14.0; IR ($CHCl_3$): 3442, 2950, 1735, 1510, 1230, 1165, 910, 695 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C22H33NO6Na 430.2206, found 430.2206.

Octyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10g):



73% yield, $[\alpha]_D^{21}$ = 76.1 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.39 (m, 5H), 6.28 (d, *J* = 8.8 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 4.85 (d, *J* = 3.2 Hz, 1H), 4.53 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.36-4.37 (m, 1H), 3.97-4.01 (m, 1H), 3.41-3.43 (m, 1H), 2.06 (dt, *J* = 10.4, 4.0 Hz, 1H), 1.99 (s, 3H), 1.94 (dd, *J* = 15.6, 3.2 Hz, 1H), 1.61-1.68(m, 3H), 1.29-1.43 (m, 10H), 1.21 (d, *J* = 6.4 Hz, 3H), 0.89-0.92 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 156.2, 137.1, 128.4, 127.9, 127.8, 96.8, 73.4, 67.9, 66.3, 61.7, 45.4, 33.5, 31.8, 29.5, 29.4, 29.2, 26.3, 22.6, 20.8, 17.5, 14.1; IR ($CHCl_3$): 3419, 2928, 1730, 1506, 1230, 1051 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C24H37NO6Na 458.2519, found 458.2517.

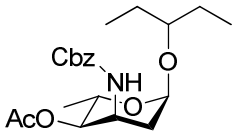
Isopropyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10h):



72% yield, $[\alpha]_D^{21}$ = 67.2 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26-7.37 (m, 5H), 6.29 (d, *J* = 9.0 Hz, 1H), 5.09 (s, 2H), 4.94 (d, *J* = 3.3 Hz, 1H), 4.50 (dd, *J* = 10.2, 3.6 Hz, 1H), 4.31-4.35 (m, 1H), 3.88-4.04 (m, 2H), 2.05 (dt, *J* = 10.5, 3.9 Hz,

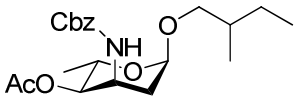
1H), 1.94 (s, 3H), 1.85 (d, *J* = 12.6 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.13-1.18 (m, 6H);); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.2, 137.1, 129.4, 129.0, 128.4, 127.9, 94.5, 73.5, 69.1, 66.3, 61.7, 45.5, 33.7, 23.5, 21.2, 20.8, 17.5; IR ($CHCl_3$): 3418, 3019, 1717, 1508, 1215, 1118, 1053, 1001,756 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for C19H27NO6Na 388.1685, found 388.1679.

Isopentanyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10i):



75% yield, $[\alpha]_D^{21}$ = 76.7 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26-7.36 (m, 5H), 6.35 (d, *J* = 9.2 Hz, 1H), 5.12 (d, *J* = 12.8 Hz, 1H), 5.07 (d, *J* = 12.8 Hz, 1H), 4.95 (d, *J* = 3.6 Hz, 1H), 4.50 (dd, *J* = 10.0, 4.6 Hz, 1H), 4.31-4.39 (m, 1H), 4.06-4.08 (m, 1H), 3.53-3.56 (m, 1H), 2.04 (dt, *J* = 10.4, 4.0 Hz, 1H), 1.94 (s, 3H), 1.91 (d, *J* = 2.0 Hz, 1H), 1.57-1.65 (m, 2H), 1.50-1.54 (m, 2H), 1.17(d, *J* = 6.4 Hz, 3H), 0.97(t, *J* = 7.2 Hz, 3H), 0.86 (t, 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.4, 156.2, 137.1, 128.4, 127.8, 127.7, 95.2, 79.7, 73.6, 66.2, 61.8, 45.4, 33.7, 26.7, 24.8, 20.9, 17.4, 9.8, 9.0; IR ($CHCl_3$): 3584, 2966, 1730, 1506, 1230, 1120, 1064, 997cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C21H31NO6Na 416.2049, found 416.2047.

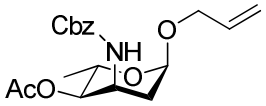
2'-Methylbutyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10j):



86% yield, $[\alpha]_D^{21}$ = 76.2 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.36 (m, 5H), 6.31-6.33 (m, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.81 (d,

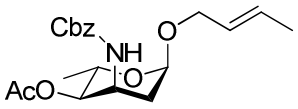
J = 3.2 Hz, 1H), 4.50 (dd, *J* = 10.4, 3.2 Hz, 1H), 4.32-4.35 (m, 1H), 3.93-3.97 (m, 1H), 3.50-3.57 (m,1H), 3.20-3.28 (m, 1H), 2.05 (dt, *J* = 10.4, 4.0 Hz, 1H), 1.95 (s, 3H), 1.90 (d, *J* = 2.0 Hz, 1H), 1.67-1.71 (m, 1H), 1.40-1.50 (m, 1H), 1.17-1.25 (m, 4H), 0.90-0.97 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 156.1, 137.0, 127.8, 127.5, 97.0, 73.4, 73.0, 66.2, 61.7, 45.4, 34.8, 33.4, 26.4, 26.2, 20.9, 17.5, 16.9, 11.5; IR ($CHCl_3$): 3418, 2961, 1732, 1508, 1369, 1230, 1122, 1409 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C21H31NO6Na 416.2049, found 416.2043.

Allyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10k):



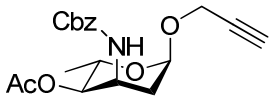
72% yield, $[\alpha]_D^{21}$ = 94.2 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26-7.37 (m, 5H), 6.18 (d, *J* = 9.2 Hz, 1H), 5.82-5.88 (m, 1H), 5.29 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.22 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.88 (d, *J* = 3.2 Hz, 1H), 4.52 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.32-4.36 (m, 1H), 4.20 (dd, *J* = 14.4, 3.2 Hz, 1H), 3.96-4.02 (m, 2H), 2.07 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.94 (s, 3H), 1.92 (d, *J* = 2.0 Hz, 1H), 1.19 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 156.2, 136.9, 133.6, 128.4, 128.2, 128.0, 117.4, 95.9, 73.3, 68.1, 66.4, 61.7, 45.3, 33.4, 20.8, 17.4; IR ($CHCl_3$): 3419, 3018, 1732, 1635, 1215, 1043, 752, 669 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C19H25NO6Na 386.1580, found 386.1577.

(*E*)-But-2-enyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10l):



76% yield, $[\alpha]_D^{20}$ = 49.9 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26-7.37 (m, 5H), 6.20 (d, *J* = 9.0 Hz, 1H), 5.70-5.77 (m, 1H), 5.52-5.59 (m, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.87 (d, *J* = 3.3 Hz, 1H), 4.52 (dd, *J* = 10.2, 3.6 Hz, 1H), 4.32-4.36 (m, 1H), 4.11 (dd, *J* = 12.3, 5.4 Hz, 1H), 3.88-4.00 (m, 2H), 2.05 (dt, *J* = 10.5, 4.2 Hz, 1H), 1.95 (s, 3H), 1.90 (dd, *J* = 14.4, 2.1 Hz, 1H), 1.71 (d, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ170.3, 156.2, 136.9, 130.1, 128.4, 128.0, 127.8, 126.4, 95.4, 73.4, 67.7, 66.4, 61.6, 45.4, 33.4, 20.8, 17.8, 17.4; IR ($CHCl_3$): 3325, 2924, 1740, 1340, 1240, 1163, 1057, 499 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C20H27NO6Na 400.1736, found 400.1730.

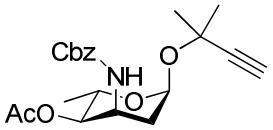
Propargyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10m):



62% yield, $[\alpha]_D^{21}$ = 84.0 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ7.26-7.39 (m, 5H), 5.99 (d, *J* = 8.8 Hz, 1H), 5.05-5.13 (m, 3H), 4.53 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.34-4.39 (m, 1H), 4.26 (d, *J* = 2.4 Hz, 2H), 3.94-4.01 (m, 1H), 2.44 (t, *J* = 2.4 Hz, 1H), 2.11 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.96 (s, 3H), 1.92-1.93 (m, 1H), 1.19 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ170.3, 156.2, 136.8, 128.5, 128.1, 128.0, 95.5, 77.2, 74.9, 73.1, 66.6, 62.1, 54.4, 45.2, 33.2, 20.8, 17.3; IR ($CHCl_3$): 3435, 1645, 1506, 1230, 1039, 665 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C19H23NO6Na 384.1423, found 384.1422.

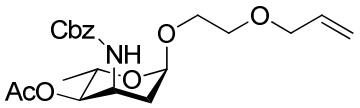
2-Methylbut-3-yn-2-yl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-

***ribo*-hexopyranoside (10n):**



69% yield, $[\alpha]_D^{21}$ = 85.1 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27-7.37 (m, 5H), 6.15 (d, *J* = 8.7 Hz, 1H), 5.44 (d, *J* = 3.0 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.52 (dd, *J* = 9.9, 3.6 Hz, 1H), 4.33-4.37 (m, 1H), 4.09-4.16 (m, 1H), 2.49 (s, 1H), 2.09 (dt, *J* = 14.4, 4.2 Hz, 1H), 1.95 (s, 3H), 1.87 (d, *J* = 12.9 Hz, 1H), 1.56 (d, *J* = 6.0 Hz, 6H), 1.15 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.3, 156.2, 137.0, 128.4, 127.9, 127.8, 93.5, 85.0, 73.4, 73.0, 71.7, 66.3, 62.0, 45.5, 34.3, 30.2, 29.6, 20.8, 17.3; IR ($CHCl_3$): 3423, 1732, 1635, 1508, 1234, 1053, 989, 754 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C21H27NO6Na 412.1736, found 412.1737.

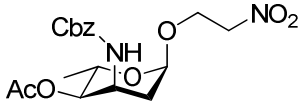
2'-(Allyloxy)ethyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10o):



67% yield, $[\alpha]_D^{21}$ = 29.4 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.40 (m, 5H), 6.34 (d, *J* = 9.2 Hz, 1H), 5.84-5.88 (m, 1H), 5.24 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.05-5.14 (m, 3H), 4.90 (d, *J* = 3.2 Hz, 1H), 4.53 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.33-4.40 (m, 1H), 4.00-4.06 (m, 3H), 3.83-3.86 (m, 1H), 3.54-3.64 (m, 3H), 2.05 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.02 (dd, *J* = 4.0 Hz, 1H), 1.95 (s, 3H), 1.20 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 156.3, 134.6, 128.6, 128.2, 128.0, 127.9, 117.1, 96.6, 73.3, 72.3, 68.8, 67.0, 66.4, 61.7, 45.4, 33.3, 20.8, 17.5; IR ($CHCl_3$): 3464, 1732,

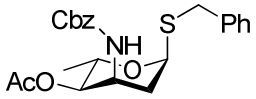
1645, 1508, 1338, 1232, 1057 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C21H29NO7Na 430.1842, found 430.1851.

2-Nitroethyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10p):



68% yield, $[\alpha]_D^{21}$ = 69.5 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.42 (m, 5H), 5.85 (d, *J* = 9.2 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 4.91 (d, *J* = 3.2 Hz, 1H), 4.61-4.65 (m, 2H), 4.52 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.27-4.36 (m, 2H), 3.92-3.98 (m, 2H), 2.04-2.12 (m, 1H), 2.09 (dd, *J* = 12.0, 5.6 Hz, 1H), 1.98 (s, 3H), 1.21 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 156.2, 136.9, 128.4, 127.9, 127.8, 97.4, 74.9, 72.9, 66.4, 63.4, 62.3, 44.9, 33.2, 20.8, 17.4; IR ($CHCl_3$): 3429, 3018, 1732, 1558, 1508, 1373, 1217, 752 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C18H24N2O8Na 419.1430, found 419.1439.

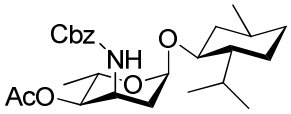
Benzylthio 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10q):



55% yield, $[\alpha]_D^{21}$ = 97.4 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.31 (m, 10H), 5.10 (d, *J* = 5.2 Hz, 1H), 4.66 (d, *J* = 9.6 Hz, 1H), 4.63 (d, *J* = 9.6 Hz, 1H), 4.08-4.15 (m, 1H), 3.63-3.74 (m, 4H), 2.95-3.02 (m, 1H), 2.13-2.18 (m, 1H), 2.09 (s, 3H), 2.03-2.06 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 156.2, 138.1, 137.9, 128.93, 128.89, 128.6, 128.5, 127.1, 127.0, 79.4, 74.9, 67.3, 42.9, 37.4, 34.7, 34.4, 20.9, 17.9; IR ($CHCl_3$): 3015, 1735, 1235, 1090, 1055,

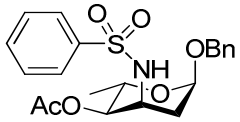
685 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C23H27NO5SNa 452.1508, found 452.1504.

L-Menthol 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10r):



54% yield, $[\alpha]_D^{21}$ = 35.8 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.37 (m, 5H), 6.35 (d, *J* = 8.4 Hz, 1H), 5.04-5.16 (m, 3H), 4.50 (dd, *J* = 10.0, 3.2 Hz, 1H), 4.34 (d, *J* = 4.8 Hz, 1H), 4.00-4.04 (m, 1H), 3.53-3.54 (m, 1H), 2.11-2.26 (m, 1H), 2.07- 2.10 (m, 2H), 1.98 (s, 3H), 1.84 (d, *J* = 14.0 Hz, 1H), 1.69 (d, *J* = 12.4 Hz, 3H), 1.29-1.41 (m, 3H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 13.2 Hz, 1H), 0.93 (d, *J* = 2.8 Hz, 6H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 156.1, 137.0, 128.4, 127.8, 127.6, 92.2, 75.0, 73.7, 66.3, 62.1, 47.9, 45.3, 39.4, 34.3, 33.7, 31.3, 26.2, 22.7, 22.3, 21.2, 20.9, 17.5, 15.3; IR ($CHCl_3$): 3408, 2929, 2224, 1732, 1637, 1506, 1230, 760 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C26H39NO6Na 484.2675, found 484.2669

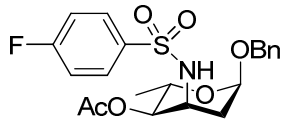
Benzyl 3-phenylsulfonamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10ra):



85% yield, $[\alpha]_D^{21}$ = 66.4 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.50-7.83 (m, 3H), 7.29-7.45 (m, 5H), 6.15 (d, *J* = 9.2 Hz, 1H), 4.85 (d, *J* = 3.2 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.39 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.07-4.11 (m, 1H), 3.90-3.95 (m, 1H), 2.09 (s, 3H), 1.82 (dt, *J* =

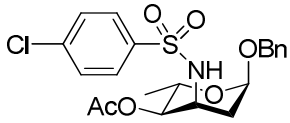
14.4, 4.0 Hz, 1H), 1.49 (dd, *J* = 12.4, 2.0 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 141.3, 136.8, 132.4, 129.1, 128.7, 128.2, 127.8, 126.8, 96.1, 72.5, 69.6, 62.2, 48.2, 33.2, 21.0, 17.4; IR ($CHCl_3$): 3520, 2965, 1710, 1330, 910 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for C21H25NO6SNa 442.1300, found 442.1295.

Benzyl 3-*p*-fluorophenylsulfonamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10rb):



91% yield, $[\alpha]_D^{21}$ = 79.7 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.82 (m, 2H), 7.30-7.41 (m, 5H), 7.14-7.18 (m, 2H), 6.13 (d, *J* = 9.2 Hz, 1H), 4.83 (d, *J* = 3.6 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.36 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.03-4.07 (m, 1H), 3.88-3.90 (m, 1H), 2.07 (s, 3H), 1.81 (dt, *J* = 14.4, 4.0 Hz, 1H), 1.47 (dd, *J* = 14.0, 2.4 Hz, 1H), 1.20 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 136.7, 129.5, 129.4, 128.7, 128.2, 127.8, 116.4, 116.2, 96.0, 72.5, 69.6, 62.2, 48.2, 33.2, 21.0, 17.4; IR ($CHCl_3$): 3400, 1734, 1635, 1236, 1155, 1051, 665 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for C21H24NO6SFNa 460.1206, found 460.1208.

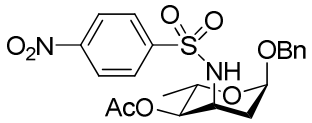
Benzyl 3-*p*-chlorophenylsulfonamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10rc):



85% yield, $[\alpha]_D^{21}$ = 109.6 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* =

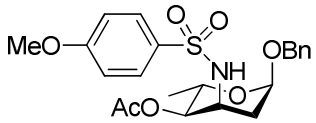
6.4 Hz, 2H), 7.74 (d, *J* = 6.4 Hz, 2H), 7.28-7.42 (m, 5H), 6.17 (d, *J* = 9.2 Hz, 1H), 4.86 (d, *J* = 3.2 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.38 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.03-4.10 (m, 1H), 3.88-3.93 (m, 1H), 2.09 (s, 3H), 1.83 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.50 (dd, *J* = 12.8, 2.0 Hz, 1H), 1.20 (d, *J* = 6.4 Hz, 3H);^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 139.7, 138.9, 136.7, 129.4, 128.7, 128.6, 128.3, 127.8, 96.0, 72.5, 69.6, 62.2, 48.3, 33.2, 21.0, 17.4; IR ($CHCl_3$): 3290, 2950, 1740, 1340, 1240, 1163, 1050, 750 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for C21H24NO6SClNa 476.0911, found 476.0913.

Benzyl 3-*p*-nitrophenylsulfonamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10rd):



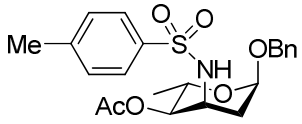
88% yield, $[\alpha]_D^{21}$ = 87.3 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (d, *J* = 9.2 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.36-7.41 (m, 3H), 7.27-7.32 (m, 2H), 6.33 (d, *J* = 9.2 Hz, 1H), 4.86 (d, *J* = 3.6 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.39 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.03-4.07 (m, 1H), 3.94-3.98 (m, 1H), 2.08 (s, 3H), 1.86 (dt, *J* = 14.4, 4.0 Hz, 1H), 1.47 (dq, *J* = 10.8, 2.0 Hz, 1H), 1.22 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 149.9, 147.1, 136.6, 128.8, 128.4, 128.0, 127.9, 124.4, 95.9, 72.3, 69.7, 62.2, 48.6, 33.2, 21.0, 17.4; IR ($CHCl_3$): 3419, 1738, 1635, 1529, 1236, 1167, 1049 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for C21H24N2O8SNa 487.1151, found 487.1136.

Benzyl 3-*p*-methoxyphenylsulfonamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10re):



74% yield, $[\alpha]_D^{21}$ = 68.8 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.29-7.40 (m, 5H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.03 (d, *J* = 9.2 Hz, 1H), 4.81 (d, *J* = 3.2 Hz, 1H), 4.72(d, *J* = 12.0 Hz, 1H), 4.49(d, *J* = 12.0 Hz, 1H), 4.34 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.02-4.14 (m, 2H), 3.86 (s, 3H), 2.08 (s, 3H), 1.77(dt, *J* = 14.4, 4.0 Hz, 1H), 1.45(dd, *J* = 14.8, 2.4 Hz, 1H), 1.19 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 162.7, 136.8, 132.7, 129.0, 128.7, 128.2, 127.8, 114.2, 96.0, 72.6, 69.5, 62.2, 55.6, 48.0, 33.1, 21.1, 17.5; IR ($CHCl_3$): 3400, 2950, 1730, 1595, 1245, 1170, 1030, 565 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C22H27NO7SNa 472.1406, found 472.1409.

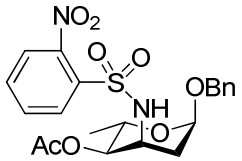
Benzyl 3-*p*-methylphenylsulfonamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10rf):



84% yield, $[\alpha]_D^{21}$ = 150.1 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.28-7.40 (m, 7H), 6.06 (d, *J* = 9.2 Hz, 1H), 4.80 (d, *J* = 3.2 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.34 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.03-4.07 (m, 1H), 3.84-3.87 (m, 1H), 2.40 (s, 3H), 2.06 (s, 3H), 1.76 (dq, *J* = 13.6, 4.0 Hz, 1H), 1.45 (dd, *J* = 14.4, 2.4 Hz, 1H), 1.19 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 143.2, 138.2, 136.8, 129.7, 128.7, 128.2, 127.8, 126.9, 96.0, 72.6, 69.5, 62.2, 48.1, 33.1, 21.5, 21.0, 17.5; IR ($CHCl_3$): 3443, 1738, 1637, 1238, 1163, 1053, 669 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C22H27NO6SNa

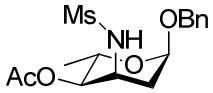
446.1546, found 446.1538.

Benzyl 3-*o*-nitrophenylsulfonamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10rg):



92% yield, $[\alpha]_D^{21}$ = 239.8 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05-8.08 (m, 1H), 7.86-7.88 (m, 1H), 7.69-7.71 (m, 2H), 7.26-7.37 (m, 5H), 7.04 (d, *J* = 8.0 Hz, 1H), 4.83 (d, *J* = 3.2 Hz, 1H), 4.77 (d, *J* = 12.4 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.41 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.07-4.14 (m, 2H), 2.09 (s, 3H), 1.91 (dt, *J* = 14.4, 4.0 Hz, 1H), 1.66 (dd, *J* = 10.8, 1.2 Hz, 1H), 1.19 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 136.6, 135.0, 133.2, 132.8, 130.5, 128.5, 128.4, 128.1, 125.3, 95.0, 78.3, 72.6, 69.4, 62.0, 48.9, 33.5, 21.1, 17.4; IR ($CHCl_3$): 3325, 1740, 1541, 1429, 1362, 1238, 1171, 1115, 1055 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C21H24N2O8SNa 487.1151, found 487.1157.

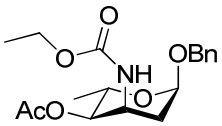
Benzyl 3-methylsulfonamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10s):



72% yield, $[\alpha]_D^{21}$ = 65.5 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.43 (m, 5H), 5.89 (d, *J* = 8.8 Hz, 1H), 4.97 (d, *J* = 3.2 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.58 (s, 1H), 4.50-4.55 (m, 1H), 4.03-4.11 (m, 2H), 2.96 (s, 3H), 2.15-2.17 (m, 1H), 2.14 (s, 3H), 2.02-2.13 (m, 1H), 1.31 (d, *J* = 17.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 136.7, 128.7, 128.2, 128.0, 95.7, 72.8, 69.5, 62.1, 48.6, 41.6, 34.4,

21.1, 17.4; IR ($CHCl_3$): 3430, 2950, 1740, 1240, 1150, 1050, 695 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C16H23NO6SNa 380.1144, found 380.1140.

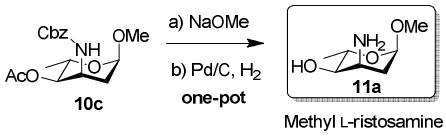
Benzyl 3-ethoxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (10t):



54% yield, $[\alpha]_D^{21}$ = 65.0 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.40 (m, 5H), 6.13 (d, *J* = 8.8 Hz, 1H), 4.93 (d, *J* = 3.2 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.53-4.56 (m, 2H), 4.34- 4.37 (m, 1H), 4.01-4.12 (m, 3H), 2.08 (dt, *J* = 14.0, 4.0 Hz, 1H), 2.05 (s, 3H), 1.96 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.21 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 156.5, 137.2, 128.6, 128.0, 127.7, 95.9, 73.4, 69.2, 61.9, 60.7, 45.1, 33.4, 20.9, 17.5, 14.7; IR ($CHCl_3$): 3421, 1722, 1508, 1232, 1120, 1072, 1049, 660 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C18H25NO6Na 374.1580, found 374.1579.

2.4.5 Synthetic procedure and characterization for methyl L-ristosamine (11a), cyclohexyl L-ristosamine (11b) and cyclohexyl L-*epi*-daunosamine (11c).

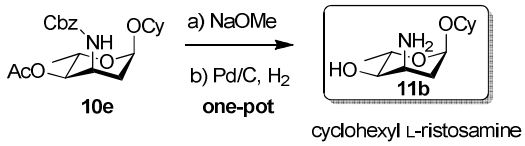
methyl L-ristosamine (11a)



To a solution of compound **10c** (0.1 mmol) in MeOH (2 mL) was added NaOMe (0.3 equiv) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 3 hours, and filtered with silica gel, washed with EtOAc. The filtrate was concentrated. The crude product was dissolved in MeOH (2 mL) and palladium

on carbon (10%, 10 mg) was added. The mixture was degassed and then stirred overnight under H_2. The mixture was filtered through a pad of celite and washed with EtOAc. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography (silica gel, $CHCl_3$-MeOH = 6:1) to obtain methyl L-ristosamine **11a** (two-step yield: 82%). $[\alpha]^D_{20}$ = -42 (c 0.5 $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz): δ 4.58 (t, 1 H, *J* = 1.6 Hz), 3.61-3.68 (m, 1 H), 3.25 (s, 3 H), 3.19-3.23 (m, 1 H), 3.06-3.08 (m, 1 H), 1.86-1.89 (m, 2 H), 1.15 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (CD_3OD, 100 MHz): δ 97.7, 71.0, 62.9, 53.9, 32.9, 29.3, 16.8; IR ($CHCl_3$): 3518, 2924, 2306, 1743, 1535, 1126, 1064, 856 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for C7H15NO3Na 184.0950, found 184.0949.

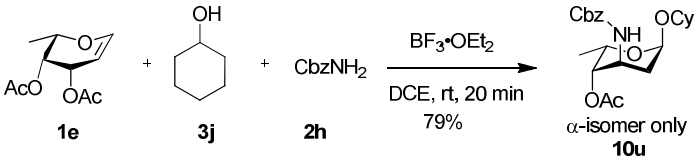
Cyclohexyl L-ristosamine (11b).



The title compound **11b** was prepared from **10e** according to the same procedure of **11a**. $[\alpha]^D_{20}$ = -110.7 (c 1.0 $CHCl_3$), {$[\alpha]^D_{20}$ = -131.6 (c 1.0, CH_3OH)}[2]; ^{1}H NMR (CD_3OD, 400 MHz): δ 5.00 (t, 1 H, *J* = 2.4 Hz), 3.83 (dq, 1 H, *J* = 6.0, 9.6 Hz), 3.62-3.59 (m, 1 H), 3.30-3.35 (m, 2 H), 3.16 (d, *J* = 3.6 Hz, 1 H), 2.03-2.01 (m, 2 H), 1.88-1.98 (m, 2 H), 1.71-1.78 (m, 2 H), 1.25-1.57 (m, 6 H), 1.22 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (CD_3OD, 100 MHz): δ 94.8, 75.0, 71.7, 63.2, 48.7, 33.7, 33.2, 31.0, 25.4, 23.7, 23.4, 17.0; IR ($CHCl_3$): 3430, 2931, 2856, 1634, 1450, 1119, 1055, 1001 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for C12H24NO3 230.1756, found 230.1757.

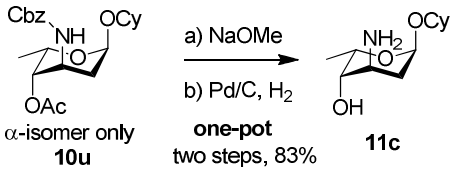
Cyclohexyl 3-benzyloxycarbonylamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*lyxo*-

hexopyranoside (10u).



The title compound **4u** was prepared according to the general procedure. $[\alpha]^{D}_{20}$ = -10.8 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.37 (m, 5H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 5.04-5.07 (m, 2H), 4.82 (s, 1H), 4.20-4.25 (m, 1H), 3.91-3.92 (m, 1H), 3.61-3.63 (m, 1H), 2.18 (dt, *J* = 14.8, 4.0 Hz, 1H), 2.13 (s, 3H), 1.82-1.84 (m, 2H), 1.63 (d, *J* = 10.0 Hz, 1H), 1.21-1.53 (m, 6H), 1.10 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 155.4, 136.7, 128.5, 128.1, 128.0, 95.0, 74.9, 69.8, 66.6, 61.2, 46.3, 33.4, 31.3, 28.9, 25.6, 24.0, 23.7, 20.9, 16.7; IR ($CHCl_3$): 3525, 3070, 2855, 1743, 1381, 1141, 1041, 856 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for C22H31NO6Na 428.2049, found 428.2044.

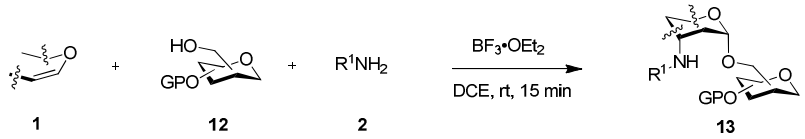
Cyclohexyl L-*epi*-daunosamine (11c)



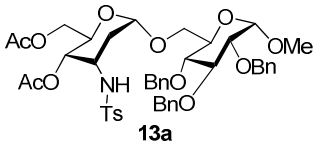
The title compound **11c** was prepared from **10u** according to the same procedure of **11a**. $[\alpha]^{D}_{20}$ = -59.8 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.62 (br, 3 H), 5.10 (s, 1 H), 4.17 (d, *J* = 6.0 Hz, 1 H), 4.02 (s, 1 H), 3.79 (s, 1 H), 3.59-3.61 (m, 1 H), 3.30-3.35 (m, 2 H), 2.34 (d, *J* = 14.4 Hz, 1 H), 1.32-1.90 (m, 9 H), 1.27 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (CD_3OD, 100 MHz): δ 94.8, 71.7, 67.1, 62.4, 49.7, 33.5, 31.3, 29.5, 25.4, 24.3, 23.9, 16.2; IR ($CHCl_3$): 3371, 2932, 2854, 1620, 1365, 1103, 1041, 987 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for C12H23NO3Na 252.1576, found

252.1575.

2.4.6 General Procedure for Synthesis of 1,3-cis-3-Arylsulphonaminodeoxy-disaccharides and Oligosaccharides 13.



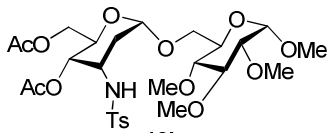
To a solution of glycosyl donor **1** (0.1 mmol, 1.0 equiv) and nitrogen nucleophiles **2** (1.1 equiv) in DCE (2 mL, dry) was added glycosyl acceptor **12** (1.1 equiv) under N_2 atmosphere. $BF_3{\cdot}OEt_2$ (2.2 equiv) was then added to this mixture. The reaction mixture was stirred for 15 min at room temperature, quenched with saturated $NaHCO_3$ (3 mL) and subsequently extracted with CH_2Cl_2 (3 × 5 mL). The extract was dried and concentrated. The residue was subjected to column chromatography (silica gel, hexane-EtOAc) to obtain pure 1,3-*cis*-3-arylsulphonaminodeoxydisaccharides or oligosaccharides **13**.



13a

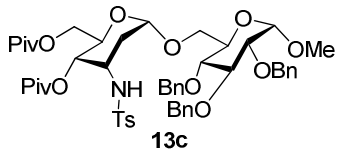
Characterization of 1,3-cis-3-tosylaminodeoxydisaccharide (13a). 68% yield, $[\alpha]^{D}_{20}$ = +45.2 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.23-7.39 (m, 17H), 6.08 (d, *J* = 9.2 Hz, 1H), 5.02 (d, *J* = 11.2 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.77-4.84 (m, 3H), 4.69-4.74 (m,2H), 4.62 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.26 (dd, *J* = 13.6, 4.8 Hz, 1H), 4.15 (m, 2H), 4.05 (t, *J* = 9.2 Hz, 1H), 3.81-3.91 (m, 1H), 3.70-3.75 (m, 1H), 3.72 (m, *J* = 11.2, 4.4 Hz, 1H),

3.55-3.58 (m, 2H), 3.46 (s, 3H), 3.34 (t, *J* = 9.2 Hz, 1H), 2.39 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.80 (td, *J* = 10.4, 3.6 Hz, 1H), 1.52 (dd, *J* = 9.6, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.5, 143.3, 138.6, 138.1, 138.0, 137.9, 129.8, 128.5, 128.4, 128.3, 128.1, 128.01, 127.95, 127.92, 127.8, 127.7, 126.8, 97.9, 97.2, 81.8, 80.0, 78.6, 75.8, 75.3, 73.3, 69.3, 67.2, 66.8, 64.5, 62.6, 55.6, 47.9, 32.6, 21.5, 21.0, 20.8; IR ($CHCl_3$): 3426, 3024, 2932, 1744, 1643, 1450, 1366, 1242, 1157, 1057, 756 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{45}H_{53}NO_{13}SNa$ 870.3142, found 870.3135.



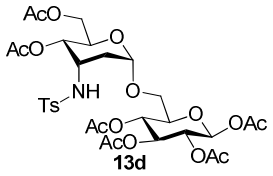
13b

1,3-cis-3-tosylaminodeoxydisaccharide (13b). 69% yield, $[\alpha]^D_{20}$ = +46.3 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.11 (d, *J* = 8.8 Hz, 1H), 4.91 (d, *J* = 2.8 Hz, 1H), 4.87 (d, *J* = 3.6 Hz, 1H), 4.65 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.21-4.33 (m, 3H), 3.90-3.93 (m, 1H), 3.79 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.68-3.72 (m, 1H), 3.64 (s, 3H), 3.62-3.53 (m, 1H), 3.57 (s, 3H), 3.50-3.53 (m, 1H), 3.55 (s, 3H), 3.47 (s, 3H), 3.19 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.97 (t, *J* = 9.2 Hz, 1H), 2.42 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.82 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.52 (dd, *J* = 14.8, 2.4Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.5, 143.3, 138.1, 129.8, 126.8, 97.3, 97.2, 83.3, 81.8, 80.4, 69.4, 67.0, 66.9, 64.5, 62.7, 60.9, 60.7, 59.0, 55.5, 48.0, 32.6, 21.5, 21.05, 20.8; IR ($CHCl_3$): 3426, 2947, 2839, 1744, 1643, 1342, 1242, 1157, 1096, 1049, 903, 579 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{27}H_{41}NO_{13}SNa$ 642.2198, found 642.2196.



13c

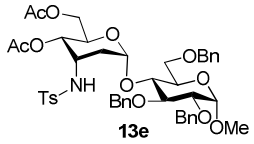
1,3-cis-3-tosylaminodeoxydisaccharide (13c). 59% yield, $[\alpha]^{D}_{20}$ = +55.2 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.28-7.37 (m, 15H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.95 (d, *J* = 9.2 Hz, 1H), 5.02 (d, *J* = 10.8 Hz, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.77-4.84 (m, 3H), 4.69-4.72 (m, 2H), 4.54 (d, *J* = 11.2 Hz, 1H), 3.94-3.96 (m, 1H), 3.84 (t, *J* = 8.0 Hz, 1H), 3.73 (dd, *J* = 10.4, 6.8 Hz, 1H), 3.57 (d, *J* = 10.4 Hz, 1H), 3.51 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.46 (s, 3H), 3.30 (t, *J* = 9.6 Hz, 1H), 2.38 (s, 3H), 1.71 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.33 (dd, *J* = 14.4, 2.4 Hz, 1H), 1.25 (s, 9H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.0, 177.6, 143.2, 138.6, 138.5, 138.0, 137.9, 129.8, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 127.1, 126.7, 97.9, 97.3, 81.8, 80.0, 78.6, 75.8, 75.3, 73.3, 69.7, 67.1, 66.9, 64.7, 62.7, 55.7, 48.4, 38.9, 32.4, 27.2, 27.0, 21.5, 14.2; IR ($CHCl_3$): 3419, 2972, 1732, 1629, 1454, 1346, 1284, 1165, 1091, 981, 752, 667 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{51}H_{66}NO_{13}S$ 932.4255, found 932.4238.



13d

1,3-cis-3-tosylaminodeoxydisaccharide (13d). 86% yield, $[\alpha]^{D}_{20}$ = +81.5 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.34 (d, *J* = 3.6 Hz, 1H), 6.07 (d, *J* = 9.6 Hz, 1H), 5.54 (d, *J* = 10.0 Hz, 1H), 5.13 (d, *J* = 9.6 Hz, 1H), 5.03 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.86 (d, *J* = 3.2 Hz, 1H), 4.64 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.08-4.17 (m, 4H), 3.93-3.97 (m, 1H), 3.59 (dd, *J* =

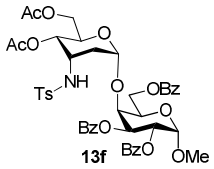
12.4, 2.4 Hz, 1H), 3.57 (dd, *J* = 12.0, 2.0 Hz, 1H), 2.43 (s , 3H), 2.19 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.80 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.55 (dd, *J* = 14.4, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.4, 170.1, 169.8, 169.6, 169.0, 143.2, 138.5, 129.7, 126.9, 97.6, 88.9, 71.0, 69.5, 69.4, 68.2, 66.9, 64.9, 64.5, 62.7, 47.9, 32.9, 21.5, 20.9, 20.85, 20.79, 20.7, 20.67, 20.5; IR ($CHCl_3$): 3317, 2947, 1751, 1435, 1373, 1219, 1157, 1041, 933, 756, 671, 601, 547 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{31}H_{41}NO_{17}SNa$ 754.1951, found 754.1954.



13e

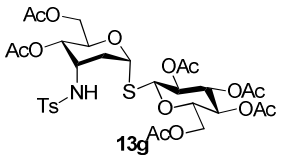
1,3-cis-3-tosylaminodeoxydisaccharide (13e). 54% yield, $[\alpha]^D_{20}$ = +34.3 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.29-7.38 (m, 12H), 7.22-7.25 (m, 3H),7.02-7.04 (m, 2H), 5.89 (d, *J* = 11.2 Hz, 1H), 5.25 (d, *J* = 3.6 Hz, 1H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.72 (d, *J* = 8.8 Hz, 1H), 4.69 (d, *J* = 9.2 Hz, 1H) 4.58-4.62 (m, 3H), 4.50 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 4.08 (dd, *J* = 12.0, 4,4 Hz, 1H), 3.98-4.02 (m, 1H), 3.77-3.89 (m, 4H), 3.56-3.69 (m, 3H), 3.50 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.45 (s, 3H), 2.38 (s, 3H), 2.09 (s, 3H), 1.98 (s, 3H), 1.51 (dt, *J* = 14.8, 4.0 Hz, 1H), 1.20 (dd, *J* = 14.4, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.3, 143.4, 138.3, 138.1, 137.7, 137.6, 129.8, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 126.9, 98.7, 97.7, 82.3, 80.1, 77.2, 75.5, 73.5, 73.2, 69.7, 69.1, 67.0, 64.8, 62.7, 55.6, 47.7, 32.8, 21.5, 21.0, 20.8; IR ($CHCl_3$): 3433, 2924, 1743, 1643, 1450, 1357, 1242, 1157, 1049, 910, 740, 548 cm^{-1}; HRMS

(ESI) m/z $[M + Na]^+$ calcd for $C_{45}H_{53}NO_{13}SNa$ 870.3133, found 870.3135.



13f

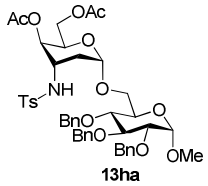
1,3-cis-3-tosylaminodeoxydisaccharide (13f). 47% yield, $[\alpha]^D_{20}$ = +98.6 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, *J* = 7.2 Hz, 2H), 8.00-8.08 (m, 4H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.33-7.46 (m, 11H), 6.03 (d, *J* = 9.2 Hz, 1H), 5.81 (dd, *J* = 11.2, 3.2 Hz, 1H), 5.61 (dd, *J* = 11.2, 3.6 Hz, 1H), 5.33 (d, *J* = 3.6 Hz, 1H), 4.95 (d, *J* = 3.2 Hz, 1H), 4.56 (d, *J* = 3.2 Hz, 1H), 4.49-4.56 (m, 2H), 4.43 (t, *J* = 6.8 Hz, 1H), 4.16-4.21 (m, 2H), 3.95-3.98 (m, 1H), 3.68 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.49 (s, 3H), 3.24 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.43 (s, 3H), 1.98 (s, 3H), 1.90 (s, 3H), 1.80 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.62 (dd, *J* = 14.8, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 170.2, 166.0, 165.8, 143.4, 138.4, 133.7, 133.6, 133.3, 130.0, 129.7, 129.6, 129.3, 129.2, 128.8, 128.7, 128.6, 128.5, 128.4, 127.0, 126.9, 98.0, 97.5, 73.9, 69.4, 68.8, 67.6, 66.5, 64.9, 62.3, 61.9, 55.8, 47.7, 32.7, 21.6, 20.9, 20.6; IR ($CHCl_3$): 3333, 3063, 2955, 1728, 1450, 1265, 1111, 1057, 710 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{45}H_{47}NO_{16}SNa$ 912.2505, found 912.2513.



13g

1,3-cis-3-tosylaminodeoxydisaccharide (13g). 53% yield, $[\alpha]^D_{20}$ = -1.5 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.68 (d, *J* = 10.0 Hz, 1H), 5.21 (t, *J* = 9.2 Hz, 1H), 5.05 (t, *J* = 10.0 Hz, 1H),

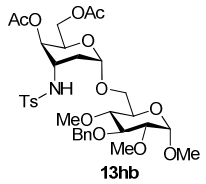
4.96 (t, *J* = 9.2 Hz, 1H), 4.86 (td, *J* = 10.8, 2.0 Hz, 1H), 4.68-4.73 (m, 2H), 4.27 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.16 (dd, *J* = 12.4, 2.0 Hz, 1H), 4.05 (dd, *J* = 12.4, 4.8 Hz, 1H), 3.78 (dd, *J* = 12.4, 2.4 Hz, 1H), 3.68 (dq, *J* = 10.0, 2.0 Hz, 1H), 3.54 (dq, *J* = 8.8, 1.6 Hz, 1H), 3.05 (td, *J* = 12.0, 4.0 Hz, 1H), 2.42 (s, 3H), 2.39-2.41 (m, 1H), 2.06 (s, 3H), 2.05 (s, 6H), 2.03 (s, 3H), 2.01 (s, 3H), 2.00 (s,3H), 1.92-1.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 170.5, 170.1, 169.7, 169.4, 169.2, 143.6, 138.5, 129.4, 127.2, 81.7, 81.3, 77.2, 76.0, 75.8, 73.8, 70.0, 68.3, 66.7, 62.6, 61.9, 44.5, 39.6, 21.5, 20.83, 20.76, 20.62, 20.59, 20.55; IR ($CHCl_3$): 3271, 2955, 1744, 1435, 1373, 1335, 1157, 1041, 910, 817, 756, 671, 586 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{31}H_{41}NO_{16}S_2Na$ 770.1764, found 770.1764.



13ha

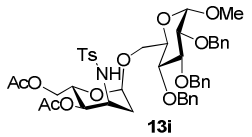
1,3-cis-3-tosylaminodeoxydisaccharide (13ha). 51% yield, $[\alpha]^D_{20}$ = +40.9 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.23 (d, *J* = 8.4 Hz, 1H), 4.96 (d, *J* = 2.8 Hz, 1H), 4.89 (d, *J* = 3.6 Hz, 1H), 4.76 (d, *J* = 2.4 Hz, 1H), 4.30 (t, *J* = 6.4 Hz, 1H), 4.04-4.07 (m, 2H), 3.72-3.80 (m, 2H), 3.65-3.64 (m, 1H), 3.63 (s, 3H), 3.59-3.56 (m, 1H), 3.57 (s, 3H), 3.54 (s, 3H), 3.53-3.50 (m, 1H), 3.49 (s, 3H), 3.22 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.98 (t, *J* = 9.2 Hz, 1H), 2.42 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.99-2.03 (m, 1H), 1.52 (d, *J* = 14.8, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.3, 169.5, 143.4, 138.0, 129.8, 127.0, 97.4, 97.0, 83.3, 81.9, 80.6, 77.2, 69.2, 67.8, 66.9, 63.4, 62.9, 60.9, 60.6, 59.0, 55.6, 47.6, 28.5, 21.5, 20.8; IR ($CHCl_3$): 3310, 2932, 2832, 1744, 1373, 1335, 1227, 1157,

1096, 1049 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{27}H_{41}NO_{13}SNa$ 642.2195, found 642.2196.



13hb

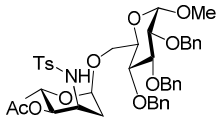
1,3-cis-3-tosylaminodeoxydisaccharide (13hb). 56% yield, $[\alpha]^D_{20}$ = +29.3 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.27-7.40 (m, 14H), 7.23-7.26 (m, 3H), 6.21 (d, *J* = 8.4 Hz, 2H), 5.02 (d, *J* = 10.8 Hz, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.89 (d, *J* = 2.8 Hz, 1H), 4.78-4.83 (m, 2H), 4.70-4.76 (m, 2H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.24 (t, *J* = 6.0 Hz, 1H), 3.94-4.08 (m, 3H), 3.87 (td, *J* = 9.2, 3.6 Hz, 1H), 3.71 (dd, *J* = 10.4, 6.8 Hz, 1H), 3.56-3.64 (m, 3H), 3.48 (s, 3H), 3.32-3.37 (m, 1H), 2.40 (s, 3H), 2.06 (s, 3H), 1.96-2.01 (m, 1H), 1.92 (s, 3H), 1.50 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.4, 169.5, 143.4, 138.6, 138.04, 138.02, 137.97, 129.8, 128.51, 128.48, 128.46, 128.11, 128.05, 127.95, 127.88, 127.71, 127.68, 127.0, 97.9, 97.0, 81.8, 80.0, 78.7, 75.8, 75.2, 73.2, 69.3, 67.7, 66.9, 66.3, 62.8, 55.7, 47.6, 28.4, 21.5, 20.8, 20.7; IR ($CHCl_3$): 3317, 2916, 1744, 1405, 1427, 1366, 1227, 1157, 1087, 1049, 740, 702, 548 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{45}H_{53}NO_{13}SNa$ 870.3144, found 870.3135.



13i

1,3-cis-3-tosylaminodeoxydisaccharide (13i). 81% yield, $[\alpha]^D_{20}$ = +9.0 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.11-7.41 (m, 17H), 6.27 (d, *J* = 9.6 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 4.84 (d, *J* = 3.2 Hz, 1H),

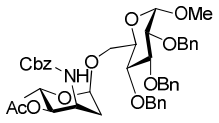
4.72-4.81 (m, 4H), 4.58 (dd, *J* = 10.8, 4.0 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 1.6 Hz, 1H), 4.25 (dd, *J* = 12.0, 3.6 Hz, 1H), 4.17 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.01-4.07 (m, 2H), 3.90-3.94 (m, 1H), 3.83 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.65-3.72 (m, 2H), 3.49 (t, *J* = 8.8 Hz, 1H), 3.40 (s, 3H), 3.83 (dd, *J* = 10.0, 3.6 Hz, 1H), 2.35 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.61 (td, *J* =12.4, 4.0 Hz, 1H), 1.17 (dd, *J* = 14.4, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.4, 143.0, 139.0, 138.9, 138.2, 138.1, 129.8, 128.3-128.4 (m, 5C), 128.1, 127.8, 127.7, 127.6, 126.6, 98.0, 96.1, 81.9, 80.7, 75.9, 75.5, 74.5, 73.4, 68.6, 66.9, 64.4, 63.9, 62.7, 55.4, 48.1, 32.6, 21.4, 21.0, 20.8; IR ($CHCl_3$): 3479, 3032, 2916, 1744, 1450, 1358, 1258, 1196, 1072, 1026, 741, 694 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{45}H_{53}NO_{13}SNa$ 870.3132, found 870.3135.



13ja

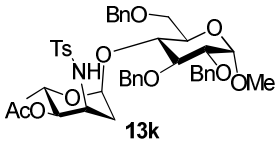
1,3-cis-3-tosylaminodeoxydisaccharide (13ja). 75% yield, $[\alpha]^D_{20}$ = -5.28 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.32-7.41 (m, 7H), 7.25-7.31 (m, 3H), 7.20-7.22 (m, 3H), 7.12-7.16 (m, 4H), 6.29 (d, *J* = 9.6 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 4.72-4.81 (m, 5H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.27-4.31 (m, 2H), 4.04 (t, *J* = 8.8 Hz, 1H), 3.91-3.98 (m, 1H), 3.80-3.87 (m, 2H), 3.66-3.73 (m, 2H), 3.50 (t, *J* = 9.6 Hz, 1H), 3.41 (s, 3H), 3.30 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.34 (s, 3H), 2.08 (s, 3H), 1.59 (dd, *J* = 14.4, 3.2 Hz, 1H), 1.18 (dd, *J* = 14.4, 2.4 Hz, 1H) , 1.16 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 170.7, 142.9, 139.1, 138.9, 138.2, 138.1, 129.8, 128.3-128.4 (m, 5C), 128.1, 127.8, 127.7, 127.6, 126.7, 98.0,

96.1, 81.9, 80.6, 76.2, 75.6, 74.5, 73.4, 72.6, 68.8, 64.1, 62.0, 55.4, 48.1, 32.9, 21.4, 21.1, 17.4; IR ($CHCl_3$): 3302, 2932, 1736, 1450, 1342, 1234, 1157, 1064, 1026, 987, 910, 817, 748,702, 671 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{43}H_{51}NO_{11}SNa$ 812.3082, found 812.3081.



13jb

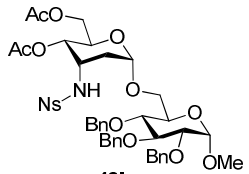
1,3-cis-3-benzyloxycarbonylaminodeoxydisaccharide (13jb). 64% yield, $[\alpha]^D_{20}$ = -12.2 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.34 (m, 20H), 6.32 (d, *J* = 9.6 Hz, 1H), 5.10 (d, *J* = 12.8 Hz, 1H), 4.87-4.98 (m, 3H), 4.80 (d, *J* = 9.6 Hz, 1H), 4.43-4.63 (m, 6H), 4.31-4.34 (m, 1H), 3.91-4.01 (m, 2H), 3.83 (dd, *J* = 2.0, 10.0 Hz, 1H),3.74-3.79 (m, 1H), 3.46-3.52 (m, 2H), 3.38-3.42 (m, 1H), 3.29 (s, 3H), 1.96 (dt, *J* = 10.8, 3.6 Hz, 1H),1.91 (s, 3H), 1.82 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.15 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 156.3, 138.7, 138.2, 138.1, 137.1, 128.5, 128.3-124 (m, 4C), 128.1, 128.0, 127.9, 127.89, 127.8, 127.7, 127.66, 98.0, 96.4, 82.1, 80.6, 75.8, 75.0, 73.2, 73.19, 69.5, 66.2, 65.1, 61.7, 55.2, 45.4, 33.4, 20.8, 17.4; IR ($CHCl_3$): 3402, 2931, 1728, 1512, 1430, 1366, 127, 1065, 910, 748 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{44}H_{51}NO_{11}Na$ 792.3356, found 792.3360.



13k

1,3-cis-3-tosylaminodeoxydisaccharide (13k). 58% yield, $[\alpha]^D_{20}$ = -17.8 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.24-7.33 (m, 15H), 5.84 (d, *J* = 8.8 Hz, 1H), 5.19 (d, *J* = 10.8 Hz, 1H),

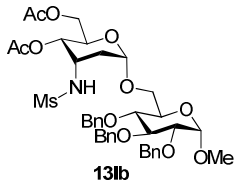
4.73-4.78 (m, 4H), 4.60-4.63 (m, 4H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.15 (d, *J* = 2.4 Hz, 2H), 3.84 (t, *J* = 8.0 Hz, 1H), 3.60-3.69 (m, 2H), 3.53 (dd, *J* = 10.8, 2.0 Hz, 1H), 3.43 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.40 (s, 3H), 2.41 (s, 3H), 1.93 (s, 3H), 1.49 (dt, *J* = 14.4, 4.0 Hz, 1H), 1.28 (dd, *J* = 14.0, 2.8 Hz, 1H), 0.67 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 143.4, 138.7, 138.5, 138.0, 137.3, 129.6, 128.5, 128.4, 128.2, 128.14, 128.10, 128.0, 127.9, 127.3, 127.2, 127.0, 98.0, 96.7, 80.8, 79.6, 75.6, 74.2, 73.6, 73.3, 72.6, 70.1, 68.3, 62.2, 55.5, 48.1, 33.4, 21.5, 20.9, 16.8; IR ($CHCl_3$): 3318, 2932, 2862, 1736, 1450, 1342, 1242, 1165, 1096, 1049 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{43}H_{51}NO_{11}SNa$ 812.3073, found 812.3081.



13la

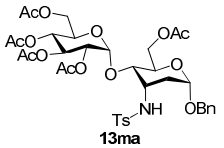
1,3-cis-3-mesylaminodeoxydisaccharide (13la). 69% yield, $[\alpha]^D_{20}$ = +44.0 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.26-7.39 (m, 15H), 6.38 (d, *J* = 9.2 Hz, 1H), 5.01 (d, *J* = 11.2 Hz, 1H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.86 (d, *J* = 2.8 Hz, 1H), 4.80-4.83 (m, 2H), 4.63-4.71 (m, 3H), 4.56 (d, *J* = 8.8 Hz, 1H), 4.25 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.12-4.17 (m, 2H), 4.06 (t, *J* = 9.2 Hz, 1H), 3.97-4.00 (m, 1H), 3.83-3.87 (m, 1H), 3.75 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.60 (dd, *J* = 10.0, 1.6 Hz, 1H), 3.53 (t, *J* = 9.6, 3.6 Hz, 1H), 3.44 (s, 3H), 3.34 (t, *J* = 9.6 Hz, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 1.86 (dt, *J* = 10.8, 3.6 Hz, 1H), 1.51 (dd, *J* = 14.4, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 170.3, 150.0, 147.1, 138.5, 138.1 137.9, 128.53, 128.51, 128.47, 128.2, 128.03, 127.96, 127.9, 127.8, 127.69, 124.4, 98.1, 97.1, 81.6, 80.2, 78.6, 77.2, 75.8, 75.2, 73.4, 69.4, 67.2, 66.7, 64.5, 62.5,

55.7, 48.5, 32.7, 20.9, 20.7; IR ($CHCl_3$): 3309, 2932, 1744, 1527, 1350, 1234, 1056, 856, 740, 694, 617 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{44}H_{50}N_2O_{15}SNa$ 901.2827, found 901.2835.



13lb

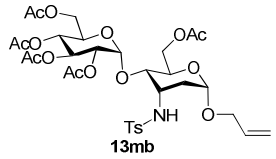
1,3-cis-3-nosylaminodeoxydisaccharide (13lb). 61% yield, $[\alpha]^D_{20}$ = +47.3 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.26-7.38 (m, 15H), 5.95 (d, *J* = 8.8 Hz, 1H), 4.92-5.01 (m, 2H), 4.68-4.82 (m, 4H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.28 (d, *J* = 12.0, 4.4 Hz, 1H), 4.09-4.16 (m, 2H), 4.03 (t, *J* = 9.2 Hz, 1H), 3.85-3.97 (m, 1H), 3.69 (dd, *J* = 10.4, 7.2 Hz, 1H), 3.62 (dd, *J* = 10.4, 2.4 Hz, 1H), 3.54 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.43 (s, 3), 3.31 (t, *J* = 9.2 Hz, 1H), 2.87 (s, 3H), 2.17 (s, 3H), 2.11 (dt, *J* = 12.0, 4.4 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.00 (dd, *J* = 14.4, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.0, 138.6, 138.1, 138.0, 128.5, 128.4, 128.3, 128.04, 128.0, 127.9, 127.88, 127.7, 127.6, 97.9, 97.0, 81.8, 80.1, 78.7, 75.8, 75.1, 69.3, 67.1, 67.05, 64.5, 62.6, 55.5, 48.5, 41.6, 33.8, 30.9, 21.0, 20.7; IR ($CHCl_3$): 3332, 2924, 1744, 1450, 1365, 1334, 1234, 1149, 1056, 910, 748, 702 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{39}H_{49}NO_{13}SNa$ 794.2825, found 794.2822.



13ma

1,3-cis-3-tosylaminodeoxydisaccharide (13ma). 71% yield, $[\alpha]^D_{20}$ = +105.2 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.35-7.42 (m, 3H), 7.27-7.29 (m, 4H), 5.85 (d, *J* = 10.0 Hz, 1H), 5.42-5.47 (m, 2H), 5.25 (dd, *J* = 3.6,

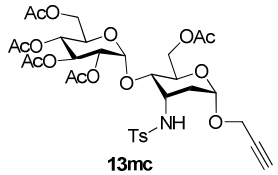
10.4 Hz, 1H), 5.11 (t, *J* = 9.6 Hz, 1H), 4.79 (d, *J* = 2.4 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.49 (dd, *J* = 2.8, 12.0 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.31 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.19 (dd, *J* = 11.6, 4.0 Hz, 1H), 4.09-4.17 (m, 2H), 3.90-3.97 (m, 2H), 3.75 (dd, *J* = 9.6, 4.0 Hz, 1H), 2.43 (s, 3H), 2.18 (s, 3H), 2.10 (s, 6H), 2.03 (s, 3H), 1.99 (s, 3H), 1.55 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.25 (dd, *J* = 14.8, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.4, 170.3, 169.9, 169.5, 143.5, 138.3, 136.6, 129.8, 128.7, 128.3, 127.8, 126.8, 96.2, 91.9, 70.1, 69.8, 68.7, 68.5, 68.4, 68.2, 65.8, 63.1, 61.7, 46.3, 31.6, 21.6, 20.9, 20.8, 20.7, 20.63, 20.61; IR ($CHCl_3$): 3302, 3024, 2954, 1751, 1435, 1373, 1334, 1226, 1165, 1041, 910, 756, 671 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{36}H_{45}NO_{16}SNa$ 802.2357, found 802.2359.



13mb

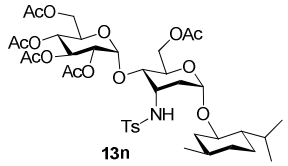
1,3-cis-3-tosylaminodeoxydisaccharide (13mb). 62% yield, $[\alpha]^D_{20}$ = +79.1 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 5.85-5.91 (m, 2H), 5.44-5.49 (m, 2H), 5.25-5.31 (m, 3H), 5.14 (t, *J* = 9.6 Hz, 1H), 4.78 (d, *J* = 2.4 Hz, 1H), 4.51 (dd, *J* = 12.0, 2.8 Hz, 1H), 4.33 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.18-4.25 (m, 2H), 4.12-4.15 (m, 2H), 3.92-3.99 (m, 3H), 3.76 (dd, *J* = 9.6, 4.0 Hz, 1H), 2.45 (s, 3H), 2.22 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.57 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.23-1.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.5, 170.3, 170.0, 169.6, 143.6, 138.2, 133.1, 129.9, 126.8, 117.9, 96.3, 91.6, 77.2, 70.0, 68.6, 68.5, 68.4, 68.2, 68.1, 65.5, 63.0, 61.6, 46.2, 31.6, 21.6, 21.0, 20.8, 20.7, 20.6; IR ($CHCl_3$): 3309, 2916, 1751, 1435, 1373, 1334, 1226, 1165, 1041,

910, 817, 756, 678 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{32}H_{43}NO_{16}SNa$ 752.2200, found 752.2197.



13mc

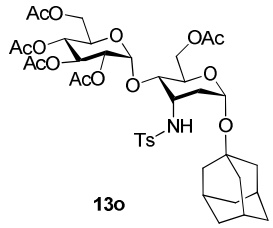
1,3-cis-3-tosylaminodeoxydisaccharide (13mc). 67% yield, $[\alpha]^{D}_{20}$ = +67.4 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.69 (d, *J* = 10.0 Hz, 1H), 5.42-5.46 (m, 1H), 5.24 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.12 (t, *J* = 10.0 Hz, 1H), 4.93 (d, *J* = 1.6 Hz, 1H), 4.47 (dd, *J* = 12.0, 2.4 Hz, 1H), 4.19-4.33 (m, 3H), 4.09-4.17 (m, 4H), 3.95-3.98 (m, 1H), 3.75 (dd, *J* = 9.6, 4.0 Hz, 1H), 2.49 (t, *J* = 2.4 Hz, 1H), 2.43 (s, 3H), 2.20 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.61 (dt, *J* = 14.4, 3.6 Hz, 1H), 1.31 (dd, *J* = 14.8, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.4, 170.3, 170.0, 169.6, 143.6, 138.1, 129.9, 126.8, 95.7, 92.1, 78.2, 75.4, 70.0, 68.6, 68.4, 68.1, 66.1, 62.9, 61.7, 60.4, 54.9, 46.2, 31.5, 21.5, 20.9, 20.8, 20.7, 20.6, 14.2; IR ($CHCl_3$): 3413, 1657, 1542, 1364, 1217, 1154, 1049, 687 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{32}H_{41}NO_{16}SNa$ 750.2044, found 750.2042.



13n

1,3-cis-3-tosylaminodeoxydisaccharide (13n). 55% yield, $[\alpha]^{D}_{20}$ = +83.4 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 5.94 (d, *J* = 10.0 Hz, 1H), 5.42-5.48 (m, 2H), 5.27 (dd, *J* = 10.4, 3.6 Hz, 1H),

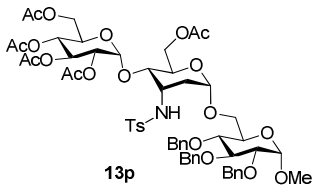
5.11 (t, *J* = 10.0 Hz, 1H), 4.76 (d, *J* = 2.8 Hz, 1H), 4.45 (dd, *J* = 11.6, 2.4Hz, 1H), 4.31 (dd, *J* = 11.6, 4.8 Hz, 1H), 4.20-4.29 (m, 1H), 4.17 (d, *J* = 3.6 Hz, 1H), 4.09-4.13 (m, 1H), 3.87-3.93 (m, 2H), 3.69 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.24 (td, *J* = 9.6, 4.0 Hz, 1H), 2.42 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.73-1.80 (m, 1H), 1.63-1.67 (m, 2H), 1.48 (dt, *J* = 14.4, 3.6 Hz, 1H), 1.38-1.41 (m, 1H), 1.10-1.28 (m, 4H), 0.85-0.98 (m, 8H), 0.63 (d, *J* =6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.5, 170.4, 170.0, 169.6, 143.5, 138.2, 129.7, 126.7, 99.1, 91.2, 82.3, 70.0, 68.5, 68.4, 68.1, 68.0, 65.3, 63.3, 61.7, 48.9, 46.1, 43.1, 34.0, 32.0, 31.7, 25.5, 22.8, 22.3, 21.6, 21.4, 21.0, 20.9, 20.7, 20.66, 20.6, 15.8; IR ($CHCl_3$): 3302, 2924, 2870, 1751, 1435, 1373, 1334, 1226, 1165, 1041, 910, 756, 671, 555 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{39}H_{57}NO_{16}SNa$ 850.3309, found 850.3296.



13o

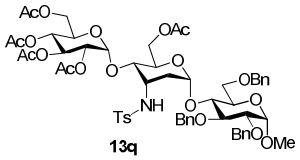
1,3-cis-3-tosylaminodeoxydisaccharide (13o). 48% yield, $[\alpha]^D_{20}$ = +108.1 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.29 (d, *J* = 9.6 Hz, 1H), 5.44-5.51 (m, 2H), 5.29 (dd, *J* = 10.5, 3.9 Hz, 1H), 5.10-5.17 (m, 2H), 4.43-4.46 (m, 1H), 4.30-4.37 (m, 2H), 4.22 (dd, *J* = 12.6, 1.8 Hz, 1H), 4.11-4.15 (m, 1H), 3.88-3.97 (m, 2H), 3.71 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.45 (s, 3H), 2.23 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.61-1.86 (m, 15H), 1.48 (dt, *J* = 14.4, 3.6 Hz, 1H), 0.96-1.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100

MHz): δ 170.6, 170.5, 170.4, 170.0, 169.6, 143.4, 138.4, 129.7, 126.8, 91.2, 90.3, 75.9, 70.1, 68.4-68.5 (m, 4C), 68.0, 67.2, 65.4, 62.8, 61.7, 46.3, 42.5, 36.1, 32.3, 30.6, 21.6, 21.0, 20.8, 20.7, 20.6; IR ($CHCl_3$): 3294, 2916, 2854, 1751, 1435, 1372, 1226, 1165, 1041, 756, 678 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{39}H_{53}NO_{16}SNa$ 846.2980, found 846.2983.



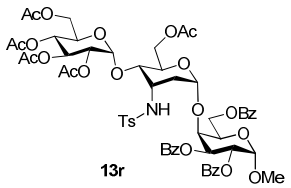
13p

1,3-cis-3-tosylaminodeoxytrisaccharide (13p). 46% yield, $[\alpha]^D_{20}$ = +61.6 (c 1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.28-7.39 (m, 15H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.87 (d, *J* = 11.2 Hz, 1H), 5.43-5.49 (m, 2H), 5.29 (dd, *J* = 12.4, 3.6 Hz, 1H), 5.12 (t, *J* = 9.6 Hz, 1H), 5.04 (d, *J* = 11.2 Hz, 1H), 4.98 (d, *J* = 11.2 Hz, 1H), 4.78-4.86 (m, 2H), 4.70-4.74 (m, 3H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.45 (dd, *J* = 12.4, 4.0 Hz, 1H), 4.19 (dd, *J* = 10.0, 2.4 Hz, 2H), 4.03-4.10 (m, 3H), 3.79-3.92 (m, 3H), 3.70-3.74 (m, 2H), 3.51-3.56 (m, 2H), 3.47 (s, 3H), 3.34 (t, *J* = 8.4 Hz, 1H), 2.39 (s, 3H), 2.17 (s, 3H), 2.10 (s, 3H), 2.03(s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.50-1.54 (m, 1H), 1.20-1.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.4, 170.2, 170.0, 169.5, 143.5, 138.7, 138.3, 138.0, 129.9, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 126.7, 98.0, 97.2, 91.5, 81.8, 80.1, 78.6, 75.6, 75.3, 73.3, 70.2, 69.6, 68.5, 68.4, 68.0, 67.7, 67.2, 65.4, 62.8, 61.6, 55.8, 46.1, 31.6, 30.9, 21.5, 20.9, 20.8, 20.7, 20.6; IR ($CHCl_3$): 3417, 1751, 1643, 1365, 1226, 1041, 740, 555 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{57}H_{69}NO_{21}SNa$ 1158.3986, found 1158.3981.



13q

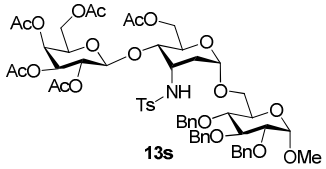
1,3-cis-3-tosylaminodeoxytrisaccharide (13q). 44% yield, $[\alpha]^{D}_{20}$ = +44.3 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, *J* = 6.8 Hz, 2H), 7.22-7.45 (m, 15H), 7.00 (d, *J* = 6.0 Hz, 2H), 6.21 (d, *J* = 10.0 Hz, 1H), 5.51 (t, *J* = 6.0 Hz, 1H), 5.45 (d, *J* = 4.8 Hz, 1H), 5.26-5.28 (m, 1H), 5.14 (d, *J* = 4.8 Hz, 1H), 5.12 (t, *J* = 9.2 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.8 Hz, 1H), 4.57-4.65 (m, 4H), 4.02-4.17 (m, 5H), 3.88-3.91 (m, 2H), 3.37-3.77 (m, 3H), 3.49-3.59 (m, 2H), 3.46 (s, 3H), 2.39 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.95-1.98 (m, 4H), 1.11 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.3, 170.2, 170.0, 169.5, 143.4, 138.9, 137.7, 137.0, 129.9, 128.7, 128.6, 128.4, 128.3, 128.1, 128.2, 127.9, 127.8, 127.7, 127.6, 126.9, 97.8, 97.3, 91.2, 82.7, 79.9, 76.7, 76.5, 75.5, 73.6, 73.3, 70.2, 70.1, 69.0, 68.7, 68.5, 68.1, 68.0, 65.7, 63.0, 61.6, 55.6, 45.6, 31.6, 21.5, 20.8, 20.7, 20.6, 20.5; IR ($CHCl_3$): 3433, 2945, 1746, 1447, 1241, 1040, 765 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{57}H_{69}NO_{21}SNa$ 1158.3975, found 1158.3972.



13r

1,3-cis-3-tosylaminodeoxytrisaccharide (13r). 43% yield, $[\alpha]^{D}_{20}$ = +104.2 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, *J* = 7.2 Hz, 2H), 7.99-8.01 (m, 4H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.70-7.72 (m, 1H), 7.45-7.60 (m, 6H), 7.34-7.38 (m, 4H),

5.92-5.96 (m, 2H), 5.55 (dd, *J* = 10.8, 3.6 Hz,1H), 5.46 (d, *J* = 2.0 Hz, 1H), 5.37 (d, *J* = 3.6 Hz, 1H), 5.28-5.30 (m, 2H), 5.08-5.11 (m, 2H), 4.84 (d, *J* = 2.4 Hz, 1H), 4.40-4.48 (m, 3H), 4.23-4.25 (m, 1H), 4.08 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.98-4.02 (m, 2H), 3.72 (dt, *J* = 14.4, 2.4 Hz, 1H), 3.62 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.58 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.49 (s, 3H), 3.44 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.45 (s, 3H), 2.30 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.88 (s, 3H), 1.54 (dt, *J* = 14.8, 3.6 Hz, 1H), 1.40 (dd, *J* = 14.4, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.5, 170.0, 169.9, 169.5, 165.9, 165.8, 165.7, 143.7, 138.3, 134.5, 133.6, 133.3, 130.1, 129.9, 129.6, 129.3, 129.2, 129.1, 128.7, 128.5, 128.4, 128.3, 127.0, 97.4, 97.3, 91.4, 73.2, 70.2, 69.2, 68.7, 68.6, 68.5, 68.4, 67.8, 67.6, 65.8, 62.3, 62.0, 61.5, 55.8, 45.8, 31.5, 21.6, 21.1, 20.71, 20.68, 20.62, 20.59; IR ($CHCl_3$): 3317, 2954, 1728, 1597, 1450, 1365, 1226, 1165, 1103, 1041, 910, 756, 709 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{57}H_{63}NO_{24}SNa$ 1200.3357, found 1200.3358.

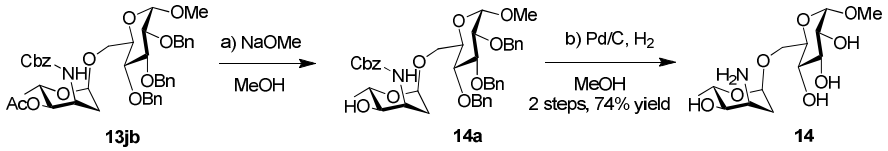


13s

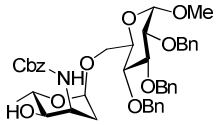
1,3-cis-3-tosylaminodeoxytrisaccharide (13s). 54% yield, $[\alpha]^D_{20}$ = +2.38 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.23-7.39 (m, 17H), 5.37 (d, *J* = 2.8 Hz, 1H), 5.22 (d, *J* = 6.0 Hz, 1H), 5.15 (dd, *J* = 10.4, 7.6 Hz, 1H), 4.97-5.01 (m, 2H), 4.78-4.86 (m, 3H), 4.69-4.73 (m, 2H), 4.65 (d, *J* = 3.6 Hz, 1H), 4.45 (d, *J* = 3.6 Hz, 1H), 4.43 (d, *J* = 8.0 Hz, 1H), 4.15-4.17 (m, 1H), 4.05-4.11 (m, 2H), 3.89-4.00 (m, 5H), 3.66-3.71 (m, 3H), 3.51-3.56 (m, 2H), 3.46 (t, *J* = 9.2 Hz, 1H), 3.35 (s, 3H), 2.28 (s, 3H), 2.11-2.18 (m, 4H), 2.04 (s, 3H), 2.03(s, 6H), 1.99 (s,

3H), 1.46 (dt, J = 13.6, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.33, 170.27, 170.1, 170.0, 169.4, 143.7, 138.8, 138.3, 138.2, 137.4, 129.8, 128.4-128.5 (m, 6C), 128.13, 128.10, 127.9, 127.8, 127.7, 127.6, 127.1, 101.7, 98.2, 97.9, 82.0, 80.0, 75.8, 75.0, 73.3, 72.5, 71.0, 70.5, 69.7, 68.6, 67.3, 66.7, 64.1, 60.9, 55.1, 47.4, 32.3, 21.3, 20.8, 20.7, 20.6, 20.5; IR ($CHCl_3$): 3302, 2924, 1751, 1450, 1365, 1334, 1226, 1157, 1072, 910, 817, 748, 702, 601 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{57}H_{69}NO_{21}SNa$ 1158.3975, found 1158.3981.

2.4.7 Procedure for Deprotection of 3-Benzyloxycarbonylamino-2,3-dideoxy disaccharide 13ib to Synthesize 3-Amino-2,3-dideoxydisaccharide 14.

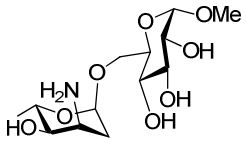


To a solution of 3-benzyloxycarbonylamino- 2,3-dideoxydisaccharide **13jb** (71.0 mg, 0.1 mmol) in MeOH (2 mL) was added NaOMe (3.0 mg, 0.03 mmol, 0.3 equiv) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 5 hours, and filtered with silica gel, washed with MeOH. The filtrate was concentrated. The crude product **14a** was dissolved in MeOH (2 mL) and palladium on carbon (10%, 7 mg) was added. The mixture was degassed and then stirred overnight under H_2. The mixture was filtered through a pad of celite and washed with EtOAc. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography (silica gel, $CHCl_3$-MeOH = 1:1) to obtain 3-amino-2,3-dideoxydisaccharide **14** (two-step yield: 74%).



14a

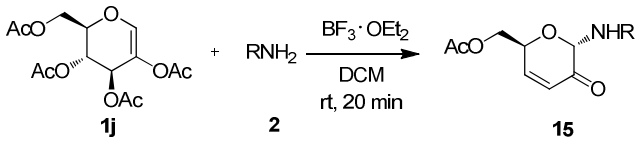
1,3-*cis*-3-benzyloxycarbonylaminodeoxydisaccharide (14a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.33 (m, 20H), 6.42 (d, *J* = 8.0 Hz, 1H), 5.07 (q, *J* = 12.4 Hz, 2H), 5.01 (d, *J* = 12.4 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.79 (d, *J* = 10.8 Hz, 1H), 4.40-4.57 (m, 5H), 4.11-4.18 (m, 1H), 3.98 (t, *J* = 9.2 Hz, 1H), 3.82 (d, *J* = 10.0 Hz, 1H), 3.73-3.75 (m, 2H), 3.45-3.50 (m, 2H), 3.37-3.38 (m, 2H), 3.26 (s, 3H), 3.03-3.05 (m, 1H), 1.81-1.94 (m, 2H), 1.26 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4, 138.7, 138.2, 138.13, 137.08, 136.4, 128.6, 128.49, 128.45, 128.41, 128.23, 128.15, 128.10, 128.05, 127.93, 127.86, 127.8, 127.7, 97.8, 96.1, 82.0, 80.5, 75.8, 75.0, 73.6, 73.2, 69.4, 67.0, 64.9, 64.4, 55.2, 48.7, 33.4, 17.5; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{42}H_{49}NO_{10}Na$ 750.3254, found 750.3259.



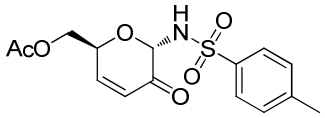
14

1,3-*cis*-3-aminodeoxydisaccharide (14). $[\alpha]^{D}_{20}$ = 2.02 (c 1.0 MeOH); ^{1}H NMR (CD_3OD, 400 MHz): δ 4.59 (d, *J* = 3.6 Hz, 1H), 3.80 (dd, *J* = 2.4, 10.8 Hz, 1H), 3.70-3.76 (m, 1H), 3.45-3.52 (m, 1H), 3.31 (s, 3H), 3.19-3.30 (m, 4H), 3.02-3.07 (m, 1H), 1.80-1.96 (m, 2H), 1.15 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz): δ 100.0, 96.9, 73.7, 72.1, 71.4, 70.7, 69.7, 65.8, 63.0, 54.3, 33.1, 16.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{26}NO_8$ 324.1658, found 324.1653.

2.4.8 General procedure for the synthesis of enone *N*-glycisides 15a-15o.

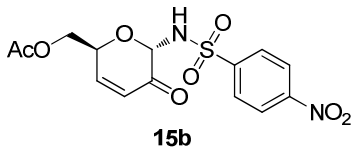


To a solution of 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal **1j** (40 mg, 0.12 mmol) and nitrogen nucleophiles **2** (0.132 mmol, 1.1 equiv) in DCM (4.0 mL) was added $BF_3{\cdot}OEt_2$ (62 µL, 0.53 mmol, 4.4 equiv) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 20 min, subsequently quenched with saturated $NaHCO_3$ (3 mL) and extracted with DCM (3 x 10 mL). The extract was then washed with brine (2 x 20 mL), dried over Na_2SO_4 and was concentrated. The residue was separated using column chromatography (silica gel, hexane/EtOAc system) to obtain pure enone *N*-glycosides **15a-15o**.



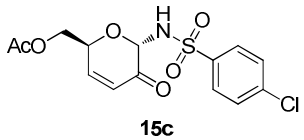
15a

N-(p-Methylphenylsulfonamido)-6-o-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyra noside-2-ulose (**15a**). 75% yield, $[\alpha]^{D}_{21}$ = -9.16 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.95 (dd, *J* = 10.4, 2.0 Hz, 1H), 6.17 (dd, *J* = 10.8, 2.4 Hz, 1H), 5.46 (d, *J* = 7.2 Hz, 1H), 4.45–4.48 (m, 1H), 4.27 (dd, *J* = 11.6, 5.2 Hz, 1H), 4.05 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.43 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.8, 170.6, 148.2, 144.1, 137.4, 129.7, 126.6, 80.7, 68.4, 63.8, 21.6, 20.7; IR ($CHCl_3$) 3429, 1739, 1701, 1327, 1153, 1041, 976 cm^{-1}; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{17}NO_6SNa$ 362.0674, found 362.0681.



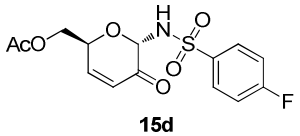
15b

N-(p-nitrophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyrano side-2-ulose (**15b**). 56% yield, $[\alpha]^{D}_{21}$ = -7.80 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, *J* = 8.8Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H), 6.99 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.24 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.80 (br, 1H), 5.65 (s, 1H), 4.56–4.60 (m, 1H), 4.41 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.22 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.2, 170.4, 147.7, 145.4, 128.5, 126.6, 124.4, 80.0, 70.0, 63.3, 30.9, 20.7; IR ($CHCl_3$): 3422, 1643, 1350, 1169, 1042, 945cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{14}N_2O_8SNa$ 393.0369, found 393.0370.



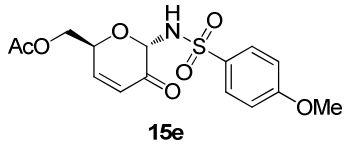
15c

N-(o-nitrophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyrano side-2-ulose (**15c**). 83% yield, $[\alpha]^{D}_{21}$ = -6.35 (c 0.4 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, *J* = 10.0 Hz, 1H), 7.91 (d, *J* = 10.0 Hz, 1H), 7.78–7.82 (m, 2H), 7.00 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.44 (d, *J* = 7.2 Hz, 1H), 6.24 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.58 (d, *J* = 8.4 Hz, 1H), 4.55–4.58 (m, 1H), 4.25 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.05 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.7, 170.5, 163.3, 147.9, 131.8, 129.5, 126.6, 114.3, 80.6, 68.7, 63.8, 55.7, 20.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_8S$ 371.0549, found 371.0529.



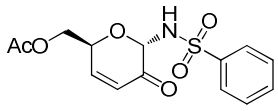
15d

N-(p-chlorophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyran oside-2-ulose (**3d**). 86% yield, $[\alpha]^{D}_{21}$ = -45.0 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 6.97 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.21 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.53 (d, *J* = 7.2 Hz, 1H), 4.52–4.55 (m, 1H), 4.34 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.16 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.5, 170.5, 147.8, 139.7, 139.0, 129.4, 128.7, 126.7, 80.3, 69.2, 63.6, 20.7; IR ($CHCl_3$): 3020, 1744, 1701, 1215, 1088 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{14}NO_6SClNa$ 382.0128, found 382.0125.



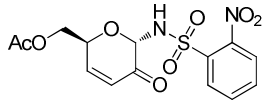
15e

N-(p-fluorophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyran oside-2-ulose (**15e**). 76% yield, $[\alpha]^{D}_{21}$ = -17.0 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94-7.97 (m, 2H), 7.21 (t, *J* = 8.4 Hz, 2H), 6.97 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.20 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.52 (d, *J* = 7.2 Hz, 1H), 4.50–4.54 (m, 1H), 4.33 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.14 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.6, 170.5, 147.9, 140.4, 130.1, 130.0, 126.6, 116.8, 116.3, 80.4, 69.0, 63.6, 20.7; IR ($CHCl_3$): 3429, 1740, 1697, 1339, 1157, 1042, 841 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{14}NO_6SFNa$ 366.0424, found 366.0415.



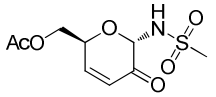
15f

N-(*p*-methoxyphenylsulfonamido)-6-*O*-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**15f**). 73% yield, $[\alpha]^{D}_{21}$ = -28 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (d, *J* = 9.0 Hz, 2H), 6.90–7.02 (m, 3H), 6.21 (dd, *J* = 10.5, 2.4Hz, 1H), 5.48–5.52 (m, 2H), 4.53–4.56 (m, 1H), 4.36 (dd, *J* = 11.7, 5.1 Hz, 1H), 4.14 (dd, *J* = 11.7, 4.5 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.2, 170.4, 147.7, 145.4, 128.5, 126.6, 124.4, 80.0, 70.0, 63.3, 30.9, 20.7; IR ($CHCl_3$): 3422, 1728, 1643, 1339, 1157, 1034 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{17}NO_7SNa$ 378.0623, found 378.0632.



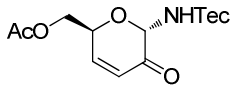
15g

N-(phenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**15g**). 44% yield, $[\alpha]^{D}_{21}$ = -9.16 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, *J* = 4.0 Hz, 2H), 7.54–7.63 (m, 3H), 6.95 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.19 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.69 (d, *J* = 6.8 Hz, 1H), 4.47–4.49 (m, 1H), 4.31 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.09 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.6, 170.5, 147.9, 140.4, 133.2, 129.1, 127.2, 126.6, 80.5, 68.8, 63.7, 20.7; IR ($CHCl_3$): 3429, 1740, 1701, 1450, 1165, 1042cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{15}NO_6SNa$ 348.0518, found 348.0514.



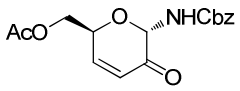
15h

N-(methylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**15h**). 68% yield, $[\alpha]^{D}_{21}$ = -11.0 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.27 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.63 (d, *J* = 6.8 Hz, 1H), 5.51 (d, *J* = 6.0 Hz, 1H), 4.80–4.84 (m, 1H), 4.49 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.35 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.8, 170.5, 147.4, 126.8, 80.0, 70.1, 63.5, 43.3, 20.7; IR ($CHCl_3$): 3418, 1732, 1697, 1327, 1153, 1042, 976 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_9H_{13}NO_6SNa$ 286.0361, found 286.0360.



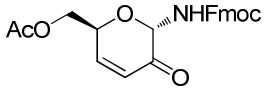
15i

N-(2',2',2'-trichloroethylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**15i**). 71% yield, $[\alpha]^{D}_{21}$ = -27.7 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.29 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.66 (d, *J* = 6.8 Hz, 1H), 4.85–4.90 (m, 1H), 4.67–4.77 (m, 1H), 4.51 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.33 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.5, 170.5, 147.8, 126.6, 80.2, 78.8, 73.3, 70.5, 63.5, 20.8; IR ($CHCl_3$): 3163, 1732, 1701, 1377, 1188, 1045, 961 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{10}H_{12}NO_6SCl_3Na$ 401.9349, found 401.9350.



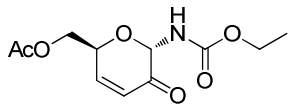
15j

N-(benzyloxycarbonylamino)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranos ide-2-ulose (**15j**). 54% yield, $[\alpha]^{D}_{21}$ = -37.0 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.37 (m, 5H), 6.99 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.25 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.71 (d, *J* = 8.0 Hz, 1H), 5.15 (s, 2H), 4.75–4.79 (m, 1H), 4.51 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.27 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.2, 170.6, 147.5, 135.6, 128.6, 128.4, 128.3, 127.6, 127.1, 78.6, 70.1, 67.7, 63.9, 20.8; IR ($CHCl_3$): 3418, 1732, 1697, 1369, 1169, 1042, 988 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{17}NO_6Na$ 342.0954, found 342.0959.



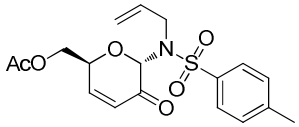
15k

N-(((9H-fluoren-9-yl)methoxy)carbonylamino)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**15k**). 46% yield, $[\alpha]^{D}_{21}$ = -9.56 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 4.4 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 6.99 (dd, *J* = 10.4, 2.8Hz, 1H), 6.25 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.69 (d, *J* = 6.8 Hz, 1H), 4.75–4.82 (m, 1H), 4.47 (d, *J* = 6.8 Hz, 1H), 4.32 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.24 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.2, 170.6, 147.5, 143.6, 141.3, 127.8, 127.1, 125.1, 125.0, 120.0, 78.6, 67.6, 63.9, 47.0, 20.8; IR ($CHCl_3$): 3418, 1694, 1636, 1450, 1161 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{21}NO_6Na$ 430.1267, found 430.1270.



15l

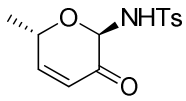
N-(ethoxycarbonylamino)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside -2-ulose (**15l**). 55% yield, $[\alpha]^{D}_{21}$ = -20.0 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (dd, *J* = 10.4, 2. 4Hz, 1H), 6.27 (dd, *J* = 10.4, 2.8 Hz, 1H), 5.68 (d, *J* = 8.0 Hz, 1H), 4.76–4.79 (m, 1H), 4.51 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.34 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.15–4.28 (m, 2H), 2.11 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 170.6, 155.6, 147.5, 127.7, 127.1, 78.6, 73.1, 64.6, 63.9, 61.9, 20.8, 14.2; IR ($CHCl_3$): 2924, 1736, 1373, 1242, 1034 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{11}H_{15}NO_6Na$ 280.0797, found 280.0798.



15m

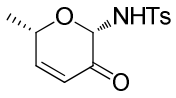
N-(N-allyl-p-methylphenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**15m**). 42% yield, $[\alpha]^{D}_{21}$ = -64.4 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.29 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.58–5.68 (m, 1H), 5.13 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.05 (dd, *J* = 14.4, 1.6 Hz, 1H), 4.82–4.85 (m, 1H), 4.46 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.25 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.79–3.86 (m, 1H), 2.43 (s, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.8, 170.3, 146.4, 143.9, 136.5, 133.2, 129.5, 128.3, 127.9, 118.8, 84.4, 70.4, 64.3, 49.1, 21.6, 20.8; ; IR ($CHCl_3$): 1730, 1705, 1311, 1183, 1045, 956 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{21}NO_6SNa$ 402.0987, found 402.0988.

N-(p-methylphenylsulfonamido)-6-methyl-3,4-dideoxy-D-rhamnal-hex-3-eno-pyranosi de-2-ulose (**15n** and **15nb**).



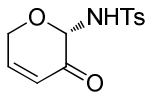
15n

15n: 68% yield, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.91 (dd, *J* = 10.4, 1.6 Hz, 1H), 6.03 (d, *J* = 10.4 Hz, 1H), 5.90 (br, 1H), 5.36 (d, *J* = 8.0 Hz, 1H), 4.34–4.38 (m, 1H), 2.43 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.3, 153.4, 143.9, 137.6, 129.6, 127.3, 124.3, 80.2, 65.8, 21.6, 18.6; IR ($CHCl_3$): 3023, 1746, 1715, 1334, 1176, 1042, 954 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{13}H_{15}NO_4SNa$ 304.0619, found 304.0614.



15nb

15nb: 22% yield, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.90 (dd, *J* = 10.0, 1.6 Hz, 1H), 6.10 (dd, *J* = 10.0, 2.4 Hz, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 5.26 (dd, *J* = 6.0, 1.6 Hz, 1H), 4.63–4.69 (m, 1H), 2.41 (s, 3H), 1.32 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.3, 153.4, 143.7, 138.1, 129.5, 127.2, 125.2, 82.1, 70.9, 21.5, 20.3; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{13}H_{15}NO_4SNa$ 304.0619, found 304.0617.

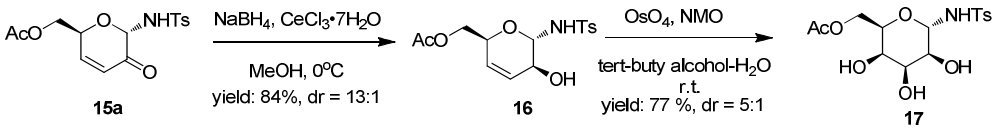


15o

(S)-4-methyl-N-(3-oxo-3,6-dihydro-2H-pyran-2-yl)benzenesulfonamide(**15o**). 78% yield, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz,

2H), 6.90 (dq, *J* = 10.4, 2.4 Hz, 1H), 6.10 (dq, *J* = 10.4, 1.6 Hz, 1H), 5.87 (d, *J* = 6.4 Hz, 1H), 5.27 (dd, *J* = 6.4, 1.6 Hz, 1H), 4.39–4.54 (m, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.7, 149.2, 143.9, 137.8, 129.7, 127.1, 125.6, 82.3, 63.9, 21.6; IR ($CHCl_3$): 3033, 1748, 1356, 1201, 1056 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{13}H_{15}NO_4SNa$ 304.0619, found 304.0617.

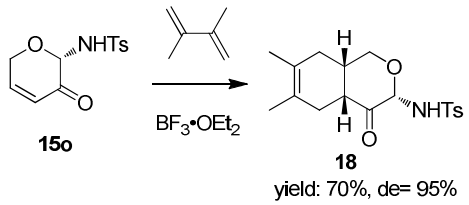
2.4.9 Synthetic procedure and characterization for 16 and 17.



To a solution of compound **15a** (50 mg, 0.15 mmol) in dry MeOH (1 mL) was added $CeCl_3 \cdot 7H_2O$ (15 mg, 0.04 mmol). After stirring for 10min at room temperature, the solution was cooled down to 0°C, and $NaBH_4$ (6 mg, 0.15 mmol) was added with stirring for 30 min. After the workup, the crude syrup, which showed a main product by TLC (R_f = 0.3, DCM/MeOH = 10:1), was purified by flash chromatography (DCM/MeOH = 10:1) to afford the corresponding alcohol **16** (40 mg, yield: 84%). Compound **5** (40 mg, 0.12 mmol) was dissolved in a mixture of tert-butyl alcohol (250 μL) and water (25 μL) and N-methylmorpholine N-oxide was added (12 mg, 0.12 mmol). The resulting solution, cooled to 0°C, was treated with 2% (w/v) OsO_4 in tert-butyl alcohol (10 μL). After stirring at room temperature for 16 h, the mixture was diluted with tert-butyl alcohol and stirred with $NaHSO_3$. After filtration, the residue was washed with tert-butyl alcohol, and the filtrate was concentrated to give the 8:1 mixture of isomers, determined from the 1H NMR spectrum. The crude syrup

was purified by flash chromatography (DCM/MeOH = 10:1) to afford the pure major isomer **17** (14 mg, yield of pure **17**: 64%). **16**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.95 (dq, *J* = 10.4, 2.4 Hz, 1H), 6.17 (dq, *J* = 10.4, 0.8 Hz, 1H), 5.30-5.33 (m, 1H), 4.19–4.21 (m, 1H), 4.09–4.13 (m, 2H), 4.03 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.42 (s, 3H), 2.08 (s, 3H), 1.67 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 143.6, 138.5, 129.5, 128.8, 127.9, 127.2, 78.7, 70.6, 64.4, 63.0, 21.6, 20.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{19}NO_6SNa$ 364.0831, found 364.0833. **17**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 9.2 Hz, 1H), 5.37 (t, *J* = 1.6 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.27 (d, *J* = 0.8 Hz, 1H), 3.76 (t, *J* = 2.4 Hz, 1H), 3.36–3.41 (m, 3H), 3.23 (br, 3H), 2.43 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 143.7, 138.5, 129.6, 129.5, 127.3, 127.2, 81.3, 72.0, 66.5, 65.8, 62.6, 29.7, 21.5, 20.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{21}NO_8SNa$ 398.0886, found 398.0884.

2.4.10 Synthetic procedure and characterization for cycloadducts 18.



The compound **15o** (50 mg, 0.18 mmol) was weighed into a vial equipped with a magnetic stirrer and septum seal. The anhydrous solvent (0.5 mL) was added, and the vial was flushed with dry argon and sealed. The mixture was cooled to -18°C, and $BF_3{\cdot}OEt_2$ (27 mg, 0.18 mmol) was added. The mixture was stirred at -18°C for 5 min, and the flask was placed in a bath at the temperature desired for the cycloaddition. A

solution of the 2,3-dimethyl-1,3-butadiene (26 mg, 0.32 mmol) in the dry solvent (0.6 mL) was then slowly injected, and the temperature was maintained for 20 min. The reaction mixture was diluted with ethyl ether (10 mL), except for the reaction in CH_2Cl_2 in which case the same solvent was used for the dilution. The resulting solution was washed with satd aq $NaHCO_3$, satd aq NaCl, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (10-30% EtOAc in hexane) to afford the pure cycloadducts **18** (41 mg, yield of pure **18**: 67%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.97 (d, *J* = 8.0 Hz, 1H), 5.13 (d, *J* = 6.8 Hz, 1H), 4.10 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.77 (d, *J* = 12.0 Hz, 1H), 2.97 (t, *J* = 6.4 Hz, 1H), 2.44–2.48 (m, 2H), 2.41 (s, 3H), 2.44–2.48 (m, 2H), 2.01–2.14 (m, 3H), 1.79 (dd, *J* = 12.8, 4.8 Hz, 1H), 1.64 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.2, 143.5, 138.3, 129.5, 127.0, 123.4, 122.3, 83.9, 69.4, 47.3, 39.3, 31.3, 29.0, 21.5, 19.1, 18.6; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{23}NO_4SNa$ 372.1245, found 372.1241.

2.5 References

1. For reviews, see: (a) A. T. Carmona, , A. J. Moreno-Vargas, I. Robina*Current Organic Synthesis* **2008**, 5, 33. (b) M. J. Klefel, M. Itzstein, *Chem. Rev.* **2002**, *102,* 471.

2. (a) R. Lorpitthaya, Z. Z. Xie, K. B. Sophy, J. L. Kuo, X.-W. Liu, *Chem. Eur. J.* **2010**, *16*, 588. (b) F. Q. Ding, R. William, B. K. Gorityala, J. M. Ma, S. M. Wang, X.-W. Liu, *Tetrahedron Lett.* **2010**, *51*, 3146 c) H. G. Sudibya, J. M. Ma, X. Dong, S. Ng, L.-J. Li, X.-W. Liu, P. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 2723. (d) R. L. Yang, K. K. Pasunooti, F. X.-W. Li, Liu, C.-F. Liu, *J.*

Am. Chem. Soc. **2009**, *131*, 13592.

3. (a) F. Sztaricskai, U. Hornyak, I. Konaromi, B. G. Gyula, I. F. Pelyvis, *Bioorg. Med. Chem. Lett.* 1992, **3**, 235 (b) F. C. Claudio, P. Grasselli, G. P. Fantoni, *J. Org. Chem.* 1983, **48**, 909 (c) K. Parker, W. Chang, *Org. Lett.* 2005, **7**, 1785.
4. E. L. Myers, C. P. Butts, A. G. Aggarwal, *Chem. Commun.,* 2006, **42**, 4434.
5. (a) P. A. Colinas and R. D. Bravo, *Org. Lett.*, 2003, **5**, 4509 (b) P. A. Colinas, A. N. Nicolás and R. D. Bravo, *J. Carbohydr. Chem.*, 2008, **27**, 141.
6. (a) C. T. Chang, Y. Hui and B. Elchert, *Tetrahedron Lett.*, 2001, **42**, 7019 (b) R. Greven, P. Jutten and H. D. Scharf, *J. Org. Chem.*, 1993, **58**, 3742; (d) M. Brent, P. Daniel and K. Jennifer *J. Carbohydr. Chem.*, 2005, **24**, 161.
7. Noguchi, K. Nakagawa, H. Yoshiyama, M. Shimura, S. Kirimura, K. Usami, S. J. Ferment. *Bioeng.* **1998**, *85*, 436.
8. (a) V. D. Bussolo, M. Caselli, M. R. Romano, M. Pineschi, P. Crotti, *J. Org. Chem.* **2004**, *69*, 7383. (b) V. D. Bussolo, M. R. Romano, M. Pineschi, P. Crotti, *Org. Lett.* **2005**, *7*, 1299.
9. (a) F. Sztaricskai, U. Hornyak, I. Konaromi, B. G. Gyula, I. F. Pelyvis, *Bioorg. Med. Chem. Lett.* **1992**, *3*, 235. (b) T. M. Matthew, T. Peng, M. H. Christopher, S. C. Robert, T. L. Lowary, *J. Org. Chem.* **2006**, *71*, 8059.
10. B. K. Shull, Z. Wu, M. Koreeda, *J. Carbohydr. Chem.* **1996**, *15*, 955.
11. (a) Other efficient syntheses of daunosamine and its derivatives from commercially available achiral or non-carbohydrate precursors range from five to nine steps with 7-34% overall yield; (b) G. K. Friestad, T. Jiang, A. K. Mathies, *Org. Lett.* **2007**, *9*, 777.

12. (a) R. A. Dwek, T. D. Butters, *Chem. Rev.* **2002**, *102*, 491–514 special issue; (b) L. L. Kiessling, J. E. Gestwicki, L. E. Strong, *Angew. Chem., Int. Ed.* **2006**, *45*, 2348-2368. (c) S. A. W. Gruner, E. Locardi, E. Lohof, H. Kessler, *Chem. Rev.* **2002**, *102*, 491–514.

13. (a) V. Rostovtsev, L. Green, V. Fokin, B. Sharpless. *Angew. Chem Int. Ed.* **2002**, *41*, 2596. (b) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467. (c) C. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057.

14. For recent reviews on the applications CuAAC in carbohydrate chemistry, see: (e) S. Dedola, S. A. Nepogodiev, R. A. Field, *Org. Biomol. Chem.,* **2007**, *5*, 1006. (f) A. Dondoni, *Chem.–Asian J.,* **2007**, *2*, 700.

15. (a) A. Varki, *Glycobiology* **1993**, *3*, 97. (b) L. Qiao, B. W. Murray, M. Shimazaki, J. Schultz, C.-H. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 7653. (c) B. Müller, C. Schaub, R. R. Schmidt, *Angew. Chem., Int. Ed.* **1998**, *37*, 2893. (c) R. chwörer, R. R. Schmidt, *J. Am. Chem. Soc.* **2002**, *124*, 1632.

16. (a) P. Compain, O. R. Martin, *Bioorg. Med. Chem.* **2001**, *9*, 3077; (b) K.-H. Jung, R. R. Schmidt, *In Glycosyltransferase Inhibitors*; C.-H. Wong, Ed.; Carbohydrate-Based Drug Discovery; Wiley-VCH Verlag GmbH & Co: KGaA, **2003**; pp 609–659.

17. (a) H. C. Kolb, K. B. Sharpless, *Drug Discov. Today* **2003**, *8*, 1128–1137. (b) M. Whiting, K. B. Sharpless, J. H. Elder, V. V. Fokin, *Angew. Chem., Int. Ed.* **2006**, *45*, 1435. (c) K. Oh, Z. Guan, *Chem. Commun.* **2006**, 3069.

18. (a) S. Pajk, M. Garvas, J. Strancar, S. Pecar, *Org. Biomol. Chem.,* **2011**, *9*, 4150. (b) G. D. K. Kumar, S. Baskaran, *J. Org. Chem.* **2005**, *70*, 4520.

19. (a) F. Santoyo-Gonzalez, F. Hernandez-Mateo, *Top. Heterocyl. Chem.* **2007**, 7, 133–177; For more specific examples, see: (b) Q. Chen, F. Yang, Y. Du, *Carbohydr. Res.* **2005**, *340*, 2476–2482;

(c) S. G. Gouin, L. Bultel, C. Falentin, J. Kovensky, *Eur. J. Org. Chem.* **2006**, 1160–1167 (d) S. Hotha, S. Kashyap, *J. Org. Chem.* **2006**, *71*, 364. (e) M. Ortega-Munoz, J. Lopez-Jaramillo, F. Hernandez-Mateo, F. Santoyo-Gonzalez, *Adv. Synth. Catal.* **2006**, *348*, 2410–2420.

20. (a) F. Q. Ding, R. William, F. Wang, J. Ma, L. Ji, X.-W. Liu, *Org. Lett.* **2011**, *13*, 652-655. (b) F. Q. Ding, R. William, S. M. Wang, B. K. Gorityala, X.-W. Liu, *Org. Biomol. Chem.* **2011**, *9*, **3929-3939.** (c) F. Q. Ding, R. William, S. T. Cai, J. Ma, X.-W. Liu, *J. Org. Chem.* **2012***, 77,* 5245 (d) F. Q. Ding, R. William, X.-W. Liu, *J. Org. Chem.* **2013**, *78*, 1293-1299.
21. (a) F. Perez-Balderas, F. Santoyo-Gonzalez, *Org. Lett.* **2003**, *5*, 1951.
22. (a) F. Louerat, K. Bougrin, A. Loupy, A. M. Ochoa de Retana, J. Pagalday, F. Palacios, *Heterocycles* **1998**, *48*, 161. (b) A. R. Katritzky, A. K. Singh, *J. Org. Chem.* **2002**, *67*, 9077.
23. (a) R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683. (b) O. M. Rodríguez, P. A. Colinas, R. D. Bravo, *Synlett* **2009**, 1154. (c) P. A. Colinas, C. A. Témpera, O. M. Rodríguez, R. D. Bravo, *Synthesis* **2009**, 4143 and references cited therein.
24. (a) B. Fraser-Reid, *Acc. Chem. Res.* **1996**, *29*, 57. (b) B. Fraser-Reid, *Acc. Chem. Res.* **1985**, *18*, 347. (c) N. L. Holder, *Chem. Rev.* **1982**, *82*, 287.
25. a) H. Therese, K. Dimitri, A. Kontas, *Carbohydr. Res.* **1986**, *156*, 256. (b) H. Kazuhiko, M. Kenichi, O. Masahiko, *Chem. Lett.* **1991**, *12*, 2223.
26. (a) B. Fraser-Reid, R. Underwood, M. Osterhout, J. A. Grossman, D. Liotta, *J. Org. Chem.* **1986**, *51*, 2152. (b) O. Varela, G. M. De Fina, R. M. Lederkremer, *Carbohydr. Res.* **1993**, *246*, 371. (c) D. Horton, J. P. Roski, P. Norris, *J. Org. Chem.* **1996**, *61*, 3783. (d) C. H. Wong, *Carbohydrate-Based Drug Discovery*, Wiley-VCH: Weinhemin, Germany, **2003**.
27. (a) R. J. Ferrier, O. A. Zubkov, *Org. React.* **2003**, *62*, 569. (b) R. J. Ferrier, *Top. Curr. Chem.*

2001, *215*, 153. (c) B. K. Gorityala, S. Cai, R. Lorpitthaya, J. Ma, K. K. Pasunooti, X. W. Liu, *Tetrahedron Lett.* **2009**, *50*, 676 and references therein.

28. (a) P. A. Colinas, R. D. Bravo, *Org. Lett.* **2003**, *5*, 4509. (b) P. A. Colinas, R. D. Bravo, *Carbohydr. Res.* **2007**, *342*, 2297. (c) P. A. Colinas, A. N. Nicolas, R. D. Bravo, *J. Carbohydr. Chem.* **2008**, *27*, 141. (d) F. Q. Ding, R.William, B. K. Gorityala, J. M. Ma, S. M. Wang and X.-W. Liu, *Tetrahedron Lett.* **2010**, *51*, 3146.
29. (a) P. Gupta, N. Kumari, A. Agarwal, Y. D. Vankar, *Org. Biomol. Chem.* **2008**, *6*, 3948. (b) R. Crespo, M. G. Bravo, P. A. Colinas, R. D. Bravo, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6469.
30. (a) A. Christian, I. Capaccio, O. Varela. *J. Org. Chem.* **2001**, *66*, 8859. (b) A. Christian, I. Capaccio, O. Varela. *J. Org. Chem.* **2002**, *67*, 7839.
31. a) C. A. Iriarte Capaccio, O. Varela, *Tetrahedron: Asymmetry* **2000**, *11*, 4945. (b) P. A. Zunszain, O. Varela, *Tetrahedron: Asymmetry* **1998**, *9*, 1269. (c) O. Varela, G. M. De Fina, R. M. Lederkremer, *Carbohydr. Res.* **1993**, *246*, 371.
32. S. Jarosz, *Carbohydr. Res.* **1992**, *224*, 73.
33. J. K. Cha, W. J. Christ, Y. Kishi, *Tetrahedron* **1984**, *40*, 2247.
34. a) D. R. Rao, L. M. Lerner, *Carbohydr. Res.* **1972**, *22*, 345-350. (b) F. W. Lichtenthaler, T. Metz, *Eur. J. Org. Chem.* **2003**, 3081.
35. (a) D. Horton, J. P. Roski, P. Norris, *J. Org. Chem.* **1996**, *61*, 3783. (b) D. Horton, J. P. Roski, *J. Chem. Soc., Chem. Commun.* **1992**, 759. (c) W. G. Dauben, B. A. Kowalczyk, F. W. Lichtenthaler, *J. Org. Chem.* **1990**, *55*, 2391.
36. (a) F. Fringuelli, A. Taticchi, T*he Diels–Alder Reaction. Selected Practical Methods* John Wiley & Sons: New York, 2002. (b) I. Fleming, *Pericyclic Reaction*s Oxford University Press: New

York, 1999. (c) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

Part 2. Total Synthesis of Pyridone Alkaloids

Chapt 3. Total Synthesis of Pyridone Alkaloids with Antiproliferation Activities

3.1 Introduction

Pyridone alkaloids, which form a small group of fungal metabolites, possess an expansive repertoire of biological activities intimately mirroring their structural diversity, ranging from antifungal, antibacterial, insecticidal and cytotoxic activity to the induction of neurite outgrowth in different cell assays.[1] However, despite their

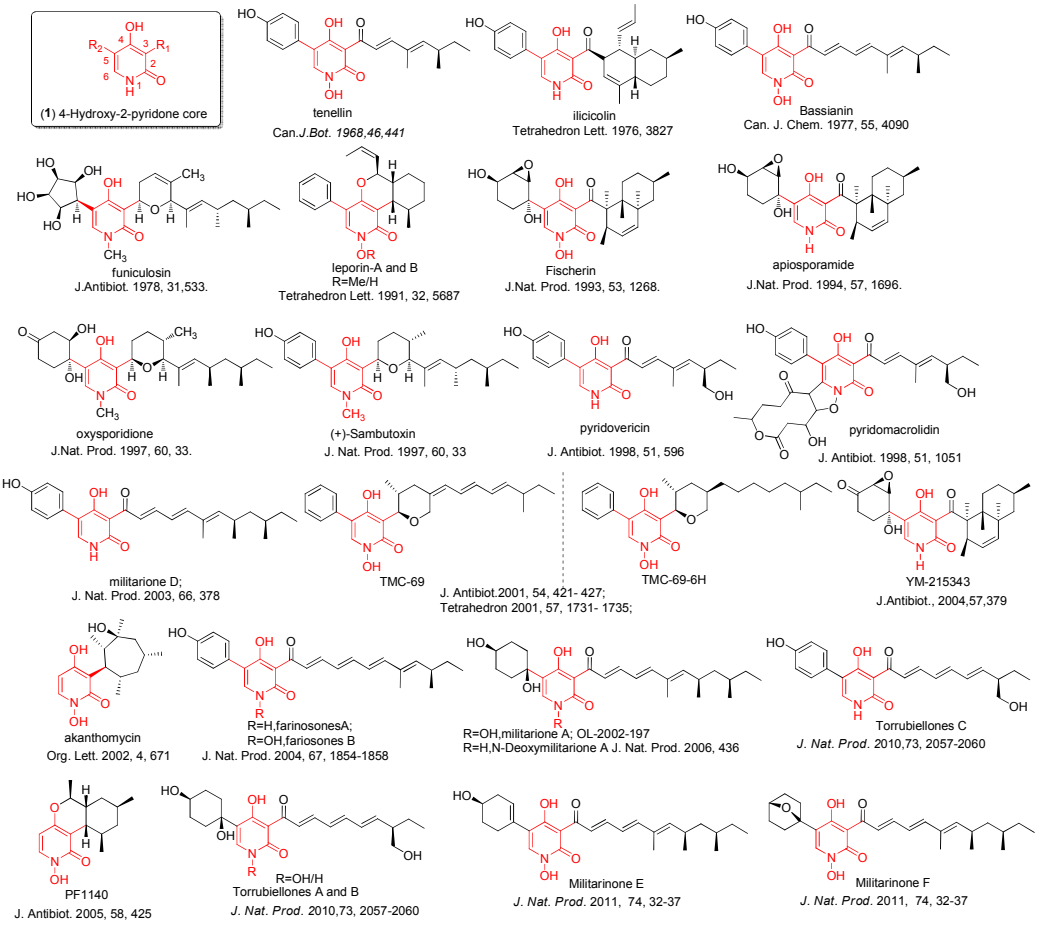


Figure 1. The pyridone alkaloids family

myriad natural sources, all pyridone aljiukaloids are unified by the presence of a characteristic fused 3,5-disubstitued-4-hydroxy-pyridone structure (**1**, Figure 1.1).[2]

Biosynthesis

On the basis of the intriguing structural relationships, several proposed biogenetic relationships connecting the above-mentioned militarinones were revealed in some details that the biosynthetic sequence likely proceeds according to Scheme 1, and as such will only be briefly summarized here.[3] And it was shown that they are derived from a polyketide chain or tyrosine and an aromatic amino acid. While the biosynthesis of militarinone D presumably follows a similar pathway, this compound could undergo further reactions such as *N*-oxidation, and several oxidative and reductive steps in the aromatic ring would lead to the *cis*-(1,4-dihydroxycyclohexyl) moiety of N-deoxymilitarinone A, followed by N-oxidation to give militarinone A. A simple dehydration of militarinone A could enter two different paths: (a) elimination to form C=C to give militarinone E or (b) nucleophilic cyclization to afford militarinone F.

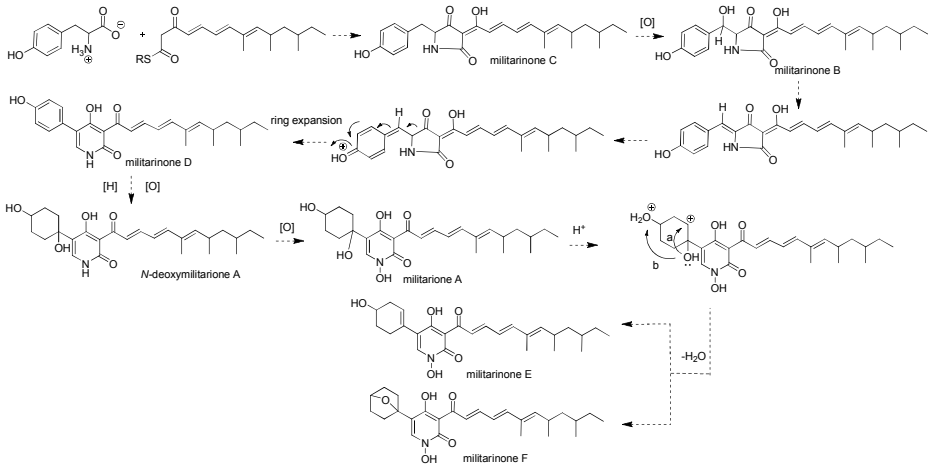
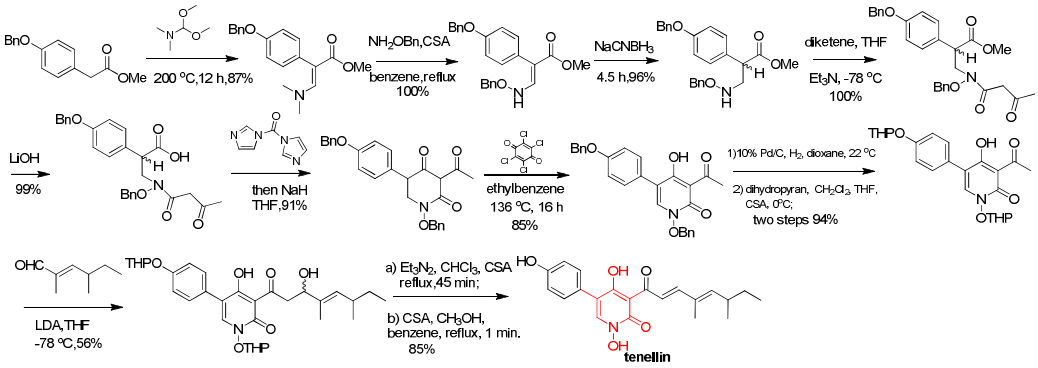


Figure 2. Proposed biogenetic relationship of militarinones

4-Hydroxy-2-pyridone Core Construction

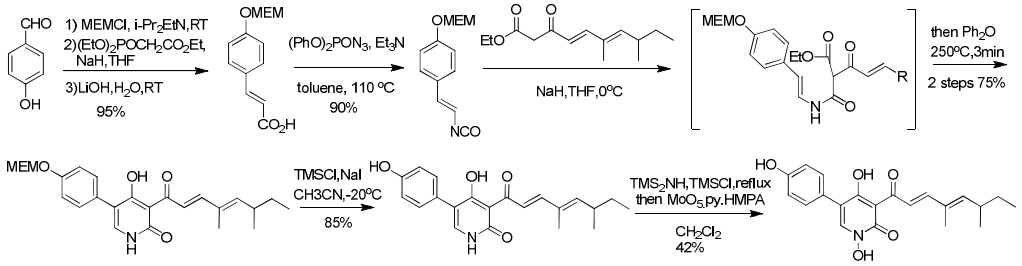
From a general point of view, pyridone alkaloids are attractive targets for total syntheses because of their unique 3,5-disubstitued-4-hydroxy-pyridone structure, their various biological and chemical properties, and the difficulties of obtaining them in pure forms from natural sources. More than 50 pyridone alkaloids with related structures are known, and synthetic pathways to these molecules have been investigated extensively.[2] All preceding work toward 3,5-disubstitued-4-hydroxy-pyridone core preparation has been previously summarized in a review by Gademann and co-workers, which can be consulted for further detail.[2] In this section, some selective approaches to 3,5-disubstitued-4-hydroxy-pyridone alkaloids would be briefly introduced.

One of the first synthetic strategies for the construction of pyridone alkaloids dates back to 1982, and was developed by David Williams and coworkers, who later disclosed other innovative strategies for the synthesis of these compounds. Preparation of rac-tenellin commenced with the condensation of methyl ester and *N,N*-dimethylformamide dimethyl acetal (Scheme 1).[4]



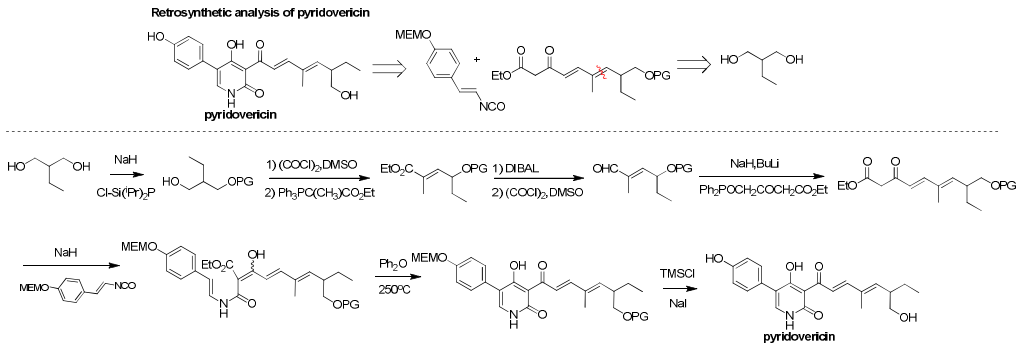
Scheme 1.

In 1989, Rigby, J. H. and co-worker reported the first total synthesis of natural pyridone alkaloid *rac*-tenilin by the reaction between isocyanate and enolate, named Rigby's annulation (Scheme 2).[5]



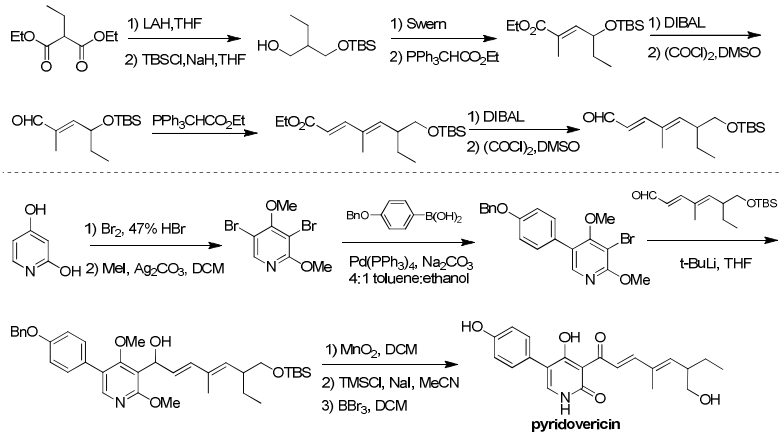
Scheme 2.

In 2002, Curran, D, P. and co-workers reported the total synthesis of Pyridovericin which was isolated from the entomopathogenic fungus BeauVeria bassiana EPF-5 in 1998, and is an inhibitor of the protein tyrosine kinase (Scheme 6).[6]



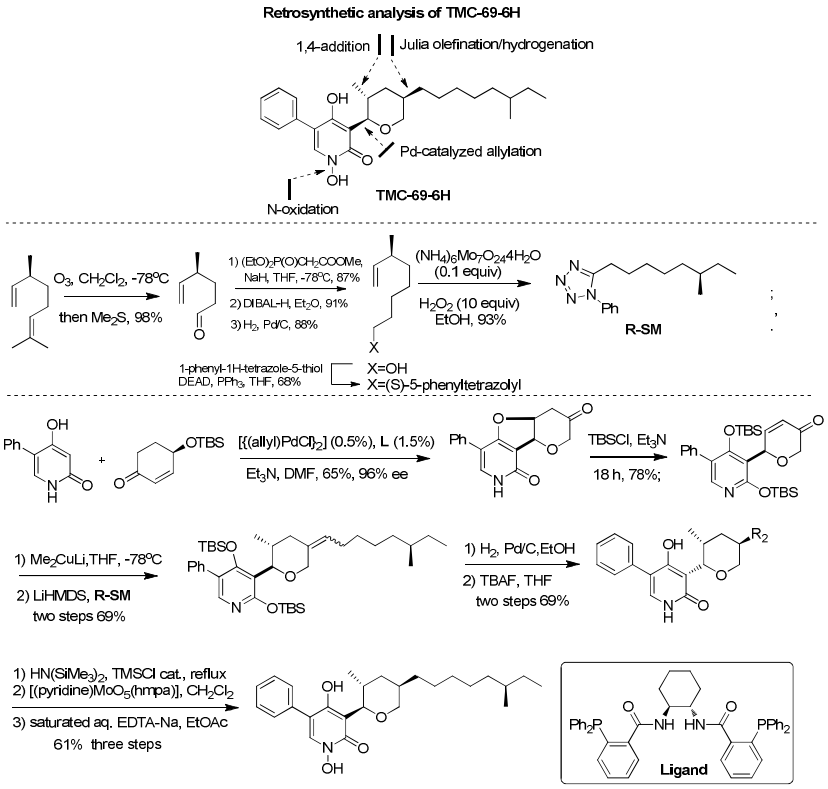
Scheme 3.

In 2004, Baldwin and co-workers reported the total synthesis of the naturally occurring kinase inhibitor Pyridovericin. A flexible and efficient synthesis has been accomplished in good yield from readily available 2,4-dihydroxypyridine (Scheme 7).[7]



Scheme 4.

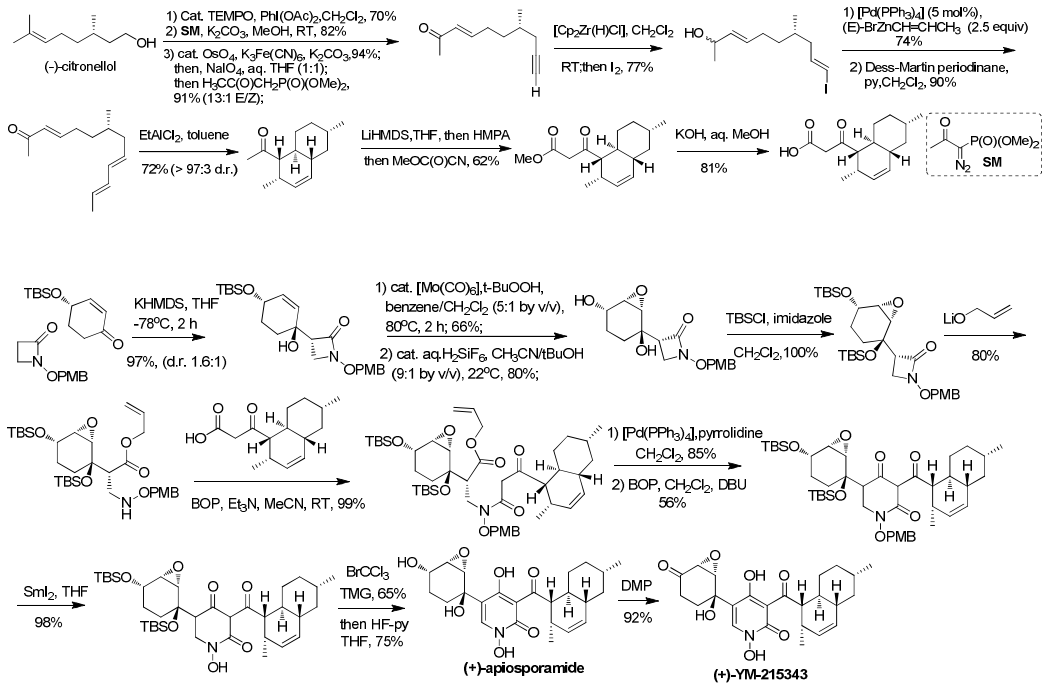
In 2004, Fürstner and co-worker described a concise, efficient and flexible total synthesis of the potent antitumor agent TMC-69-6H. Key steps involve the palladium catalyzed regioselective addition of 4-hydroxy-2-pyridone to pyranyl acetate.



Scheme 5.

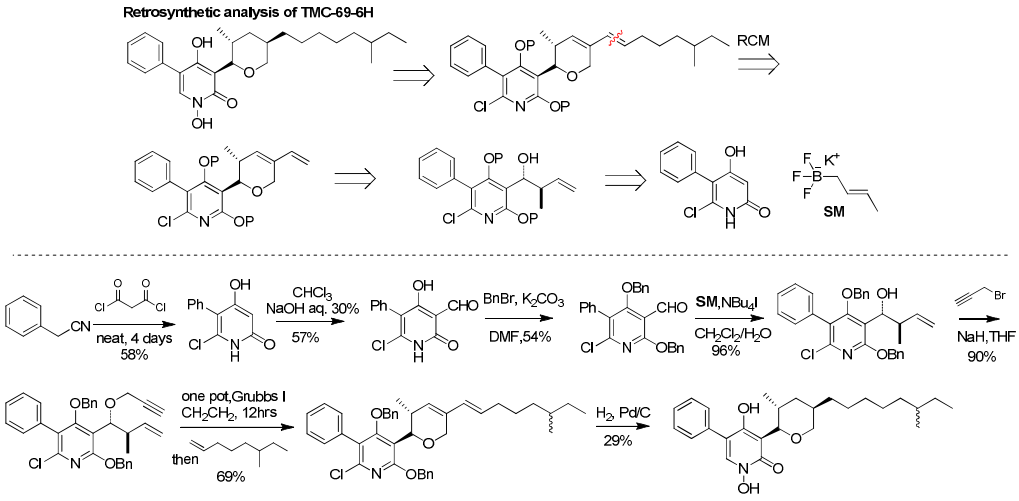
Optically enriched (*S*)-3,7-dimethylocta-1,6-diene was conveniently prepared by a lipase catalyzed kinetic dynamic resolution. The flexibility inherent to this route allows for the preparation of a focused library of analogues for biochemical evaluation (Scheme 5).[8]

In 2005, Williams reported the total synthesis of (+)-Apiosporamide. Activated β-alanine enolate equivalents derived from β-lactams were the key to the synthesis of intermediate alcohol as shown in the first step (Scheme 6).[9]



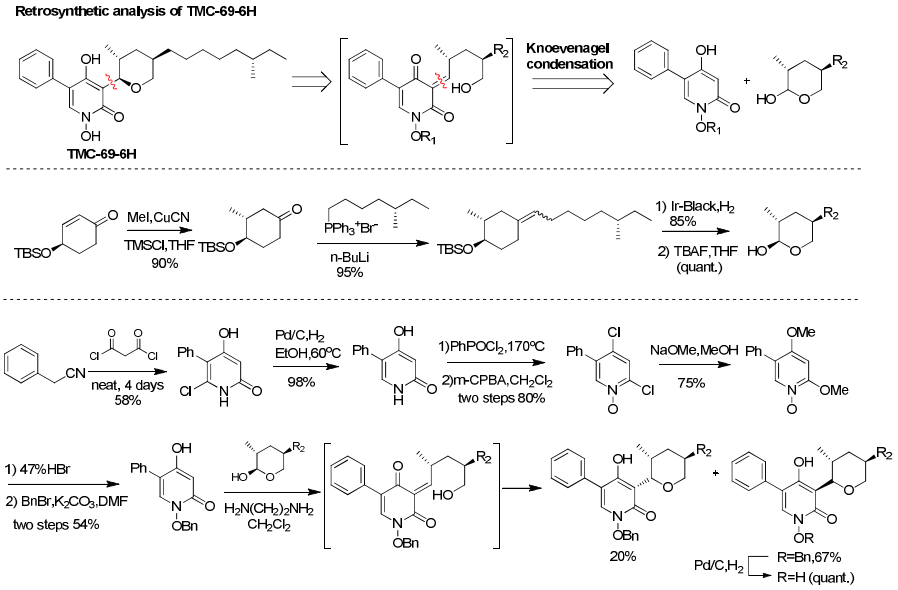
Scheme 6.

In 2006, Renoux, B. and co-workers reported the synthesis of racemic TMC-69-6H. This strategy involves two key steps: a diastereoselective aldol reaction and a one-pot tandem ring-closing and cross metathesis for the construction of the pyran moiety (Scheme 7).[10]



Scheme 7.

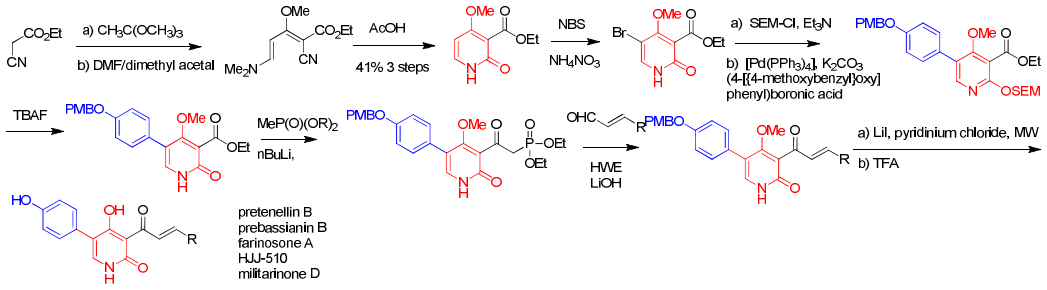
In 2007, Sugawara, K. and co-workers reported the total synthesis of (17S)-TMC-69-6H in a stereoselective manner, starting from an enantiomerically pure pyranone using Knoevenagel condensation as a key step (Scheme 8).[11]



Scheme 8.

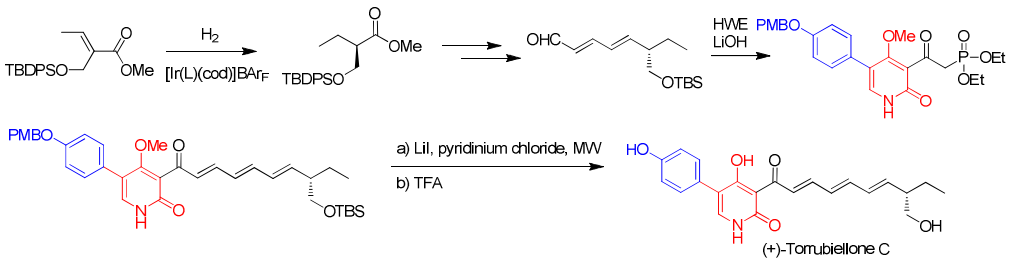
Most recently, Gademann and coworkers reported a unified approach for the stereoselective total synthesis of pyridone alkaloids such as pretenellin B (1) and

militarinone D, farinosone A as well as the putative natural products prebassianin B and HJJ-510 *via* a Horner-Wadsworth-Emmons (HWE) reaction on a densely functionalized pyridone β-ketophosphonate (Scheme 9).[12]



Scheme 9.

At the same year, the same group reported another new pyridone alkaloid natural product torrubiellone C *via* the same approach.[13] Silyl-protected (R)-methyl 2-(hydroxymethyl)butanoate was obtained by an enantioselective Ir-catalyzed hydrogenation in high yield and selectivity. Elaboration of this building block via Takai and Stille reactions gave a protected hydroxy polyene chain, which was coupled to a 5-hydroxyphenyl-4-hydroxy-2-pyridone derivative by a modified Horner–Wadsworth-Emmons reaction. Deprotection gave synthetic (+)-torrubiellone C, which led to the assignment of the configuration of the natural product as (R).



Scheme 10.

Regarding the strategic construction of the pyridone alkaloids outlined above, there are basically two general approaches towards the pyridone alkaloids, viz. the modification of a preformed pyridone core structure with (often) electrophilic reagents, or a linear route with a late-stage cyclization event, as summarized in Figure 3.

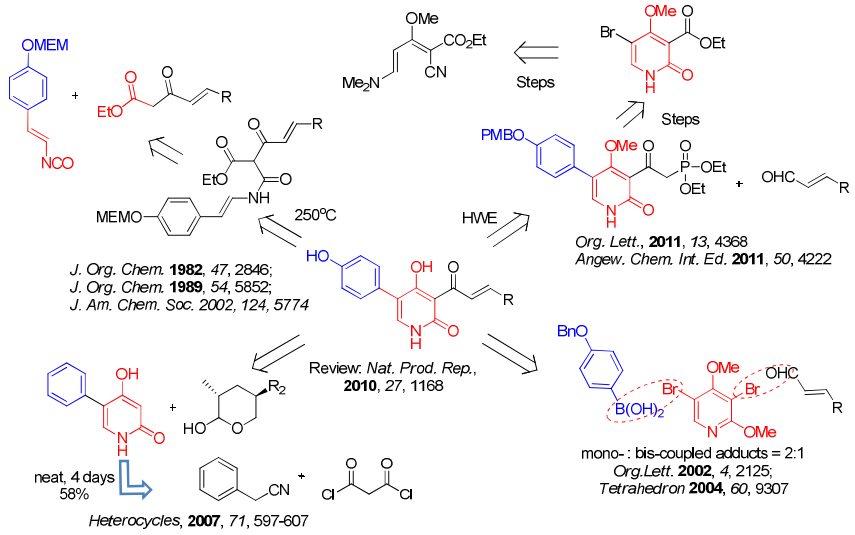


Fig. 3.

3.2 Results and Discussion

In the era of modern drug discovery, understanding nature's biosynthetic pathway, regulation and mechanism, has become an important method for target drug design. Conventional drug discovery process often involves high-throughput screening of small molecules for biological studies. However, this process was repeatedly hindered by the lack of readily available and structural diverse libraries.[14] As a result, over the past decades, “convergent total synthesis” and “diverted total synthesis (DTS)” has been pursued as a more efficient method to increase structural diversity of the natural product as well as finding novel lead compounds for drug discovery.[15-17] Pyridone

alkaloids are a phenotypic class of natural products that are intriguing in biological activities due to their structural diversity. Over the years, new constitutions of pyridone alkaloids with fascinating structures have been disclosed and strategic approach of great diversity to their synthesis has been developed.[2] In addition, research have shown that pyridone exhibit various biological activities ranging from antifungal, antibacterial, insecticidal, cytotoxic activities to the neuritogenic activity.[2] Although there have been increases in knowledge in pyridone alkaloid, many of their biological synthesis, absolute configuration and targets are still unknown. In addition to resistance that often occurs, a challenge for drug discovery is the difficulty of finding new scaffold with potent cytotoxicity and novel mechanistic pathway. Thus, with this objective in mind, a different approach was sought with emphasis on maximum convergency and flexibility for diverted synthesis as well as finding new drug targets. Since pyridone alkaloids possess a similar core structures and differ only in their structure of polyene chain and substitution pattern, we implement strategy that uses a convergent and diverted total synthesis to focus on increasing structural and library diversity in a more efficient manner for future pyridone analogues synthesis for biological studies. Indeed, these targets are perfect for application of a unified approach as recently demonstrated by Gademann and coworkers *via* a Horner-Wadsworth-Emmons (HWE) reaction on a densely functionalized pyridone β-ketophosphonate.[12] Herein, we introduce a strategy to combine a convergent and diverted total synthesis of a family of pyridone alkaloid which includes pretenellin B (**1**), prebassianin B (**3**), farinosone A (**5**), militarinone D (**7**), pyridovericin (**8**) and

torrubiellone C (**10**) (Figure 4).[18] The general concept and synthetic strategy for this total synthesis was illustrated in Figure 5. The expeditious synthetic route affords the key precursor intermediate (Int) through a series of steps in a convergent way, which is then engaged in a divergent total synthesis strategy to provide the target natural products I, II, III and their analogues. In addition, cell proliferation of these analogues was evaluated for source of potent activities.

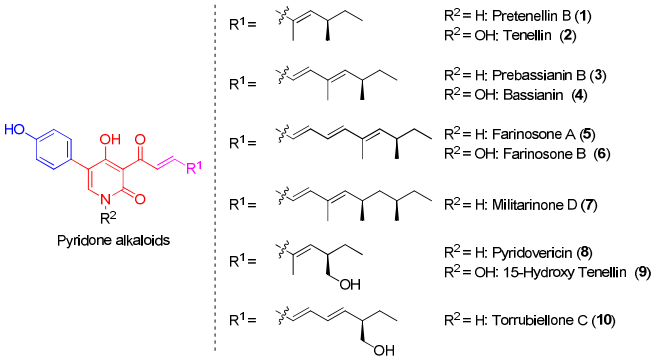


Figure 4. Selected members of the pyridone alkaloids family

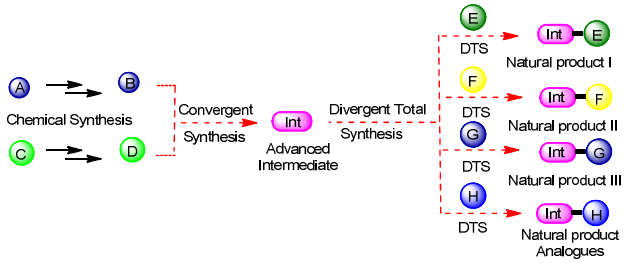


Figure 5. Combination of convergent and divergent total Synthesis.

At the outset of our studies, we realized that a clear distinction between the construction of framework (that is, the 4-hydroxy-2-pyridone core) and polyene chain (the variation of the corresponding R^1 chain) could lead to a conceptually unprecedented and general approach towards pyridone alkaloids. This concept would allow a variation in substitution patterns and polyene chain without substantial

changes in the overall synthetic strategy and assist future endeavour in bioactivity-directed synthesis of structurally defined pyridone alkaloids libraries. Notably, considerable attention was given to ensure the practicability of the synthetic strategy. The current approach consists of a combination of well-established operationally simple methodologies, in which only a small number of classic transformations is necessary to achieve synthesis in an efficient manner. Our synthetic investigation (Figure 6) is directed towards the 4-hydroxy-2-pyridone class of compounds rather than on a specific synthetic target, with the ulterior aim of building a systematically varied library of natural and non-natural products. In view of our interest in developing a step-economy process, we designed a single synthetic route to an advanced intermediate that, on late-stage differential diversifications, would provide access to a number of targets in short parallel sequences. With regard to final construction of target molecules, the key step in the synthesis involves aldol condensation of the key advanced intermediate **17** with appropriately functionalized conjugated aldehydes, which is expected to give high yields of the desired *E* isomers.[19] Importantly, the key advanced intermediate would provide easy access to a majority of pyridone alkaloids and their hitherto unexplored analogues. The key advanced intermediate **17** was in turn assembled convergently *via* a palladium-catalysed Suzuki-Miyaura cross-coupling of protected boronic acid **16** and bromo-pyridine **12**.[20] The brevity of this synthetic approach coupled with the simplicity of the precursors in term of structure compelled us to embark on its implementation.

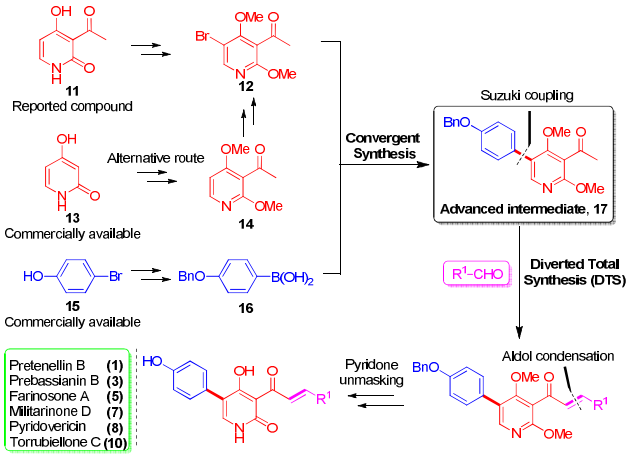
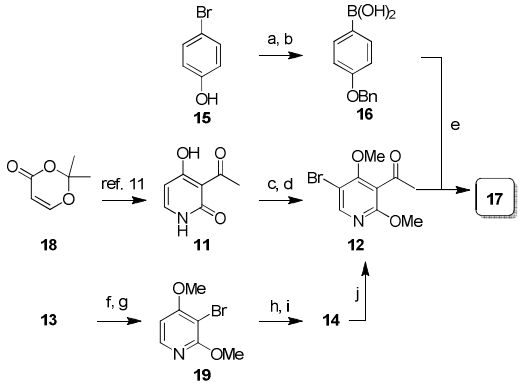


Figure 6. Synthetic strategy for pyridone alkaloids

Our synthetic approach start from commercially available 4-bromophenol **15**, which was readily protected under reported conditions[21] to generate the corresponding benzyl ether in good yield (Scheme 11). Metal-halogen exchange and treatment with boron triisopropoxide[22] followed by hydrolysis proceeded to afford the desired boronic acid **16**, a known compound previously reported by Baldwin.[23] With the required boronic acid coupling partner **16** in hand, our objective is shifted to the synthesis of the crucial precursor pyridone core **17**. In the initial stage, we successfully prepared the requisite intermediate pyridone unit **12** starting from 3-acetyl-4-hydroxy-2-pyridone **11**, which was first synthesized from 2,2-dimethyl-1,3-dioxin-4-one **18** by Sato and coworkers.[23] Protection of **11** with methyl group in the presence of Ag_2CO_3 in toluene provided methyl protected pyridine, which upon treatment with NBS in MeCN afford bromo-pyridine **12** in 40% yield over two steps. Acccording to the plan, the resulting pyridine **12** was subjected to palladium-catalysed Suzuki-Miyaura cross-coupling with 4-(benzyloxy)phenylboronic acid **16** in the presence of Na_2CO_3 in PhMe/EtOH (4:1)

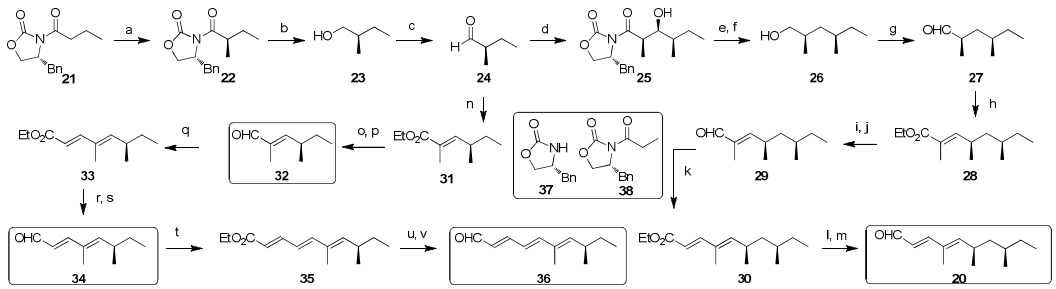
to produce the corresponding key intermediate pyridine core **17** in 86% yield with trace amounts of arylated byproduct formed.[24] Unfortunately, problem arises during attempts to scale up sythesis of **11**. Hence, we turned our attention toward exploration of an alternative route to the synthesis of the pyridine **17**. To our delight, pyridine **19** is readily accessible in a one-pot two-step process from commercially available 2,4-dihydroxypyridine **13** by regioselective bromination and subsequent *O*-methylation in a gram scale synthesis.[25] After extensive experimentation, it was found that metal-halogen exchange of bromo-pyridine **19** followed by nucleophilic attack of the pyridyl anion on acetaldehyde gave the desired alcohol which was further oxidized in good overall yield. Subsequent bromination of **14** afforded the fully protected bromo-pyridine **12** in 64% yield with only trace amounts formation of debromo byproduct observed. This protocol was found reliable for efficiently and gram-scaled preparing the key intermediate **17**.



Scheme 11. Convergent synthesis of the key advanced intermediate pyridone unit **17**. Reagent and conditions: a) BnBr, TBAI, NaH, THF; b) (i) *n*-BuLi, $B(OiPr)_3$, THF; (ii) sat. NH_4Cl, 45% over 2 steps; c) MeI, Ag_2CO_3, PhMe, 80 °C, overnight, 79%; d) NBS, MeCN, RT, 8 h, 64%; e) **12**, $Pd(PPh_3)_4$, Na_2CO_3, PhMe/EtOH (4:1), 100 °C, overnight, 86%; f) NBS, MeCN, 80 °C, 2 h; g) MeI, Ag_2CO_3, $CHCl_3$, RT, 3 days, 42% over 2 steps; h) Acetaldehyde, *n*-BuLi, THF, -78 °C, 88%; i) NMO, TPAP, 4Å molecular sieves, CH_2Cl_2, RT, overnight, 96%; j) NBS, MeCN, RT, 8 h, 64%.

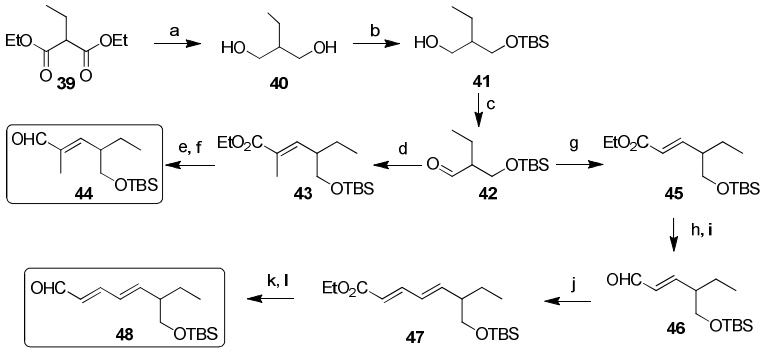
With the key advanced intermediate **17** in hand, we next focused on the synthesis of the aldehydes side-chain with different R^1. For this purpose, we selected aldehyde **20** as our initial synthetic target (Scheme 12). Synthesis of aldehyde **20** began with preparation of auxiliary **21** obtained from treatment of (*R*)-4-benzyl-3-propyloxazolidin-2-one **37** with *n*-BuLi and propionyl chloride followed by diastereoselective alkylation of the corresponding oxazolidinone amide, which introduce chirality at C2 position in 72% yield. Reduction of oxazolidinone **22** with lithium borohydride in a mixture of methanol and ether afforded the desired optically pure alcohol **23** accompanied by around 65% of recovered oxazolidinone **37**. Subsequent Swern oxidation of **23** furnished aldehyde **24**, which was subjected to Evans aldol reaction with propionimide **38** under either one of these three conditions: a) $(BuB)_2OTf$, TEA, DCM; or b) $TiCl_4$, DIPEA, DCM; or c) $TiCl_4$, TMEDA, DCM.[26] Comparison of the yield and diastereoselectivity revealed that boron enolate turned out to be a better choice than chlorotitanium enolate. The diastereomer was readily separable by column chromatography to provide the oxazolidinone **25** in good yield and diastereomeric purity. Further protection of alcohol **25** by Ts group proceeded with high yield. Lithium borohydride reduction ensued in similar manner but accompanied with displacement of OTs group by nucleophilic hydride to give the desired optically pure alcohol **26** along with 70% of the recovered oxazolidinone **37**. Alcohol **26** can be transformed to aldehyde (2*R*, 4*R*)-**22**[27] by Swern oxidation, and the resulting aldehyde was directly involved in Horner-Wadsworth-Emmons (HWE) reaction with triethyl 2-phosphonopropionate to provide ester **28**.[28] Next, ester

reduction using DIBAL-H followed by another Swern oxidation/Wittig olefination sequence gave diene **30** in excellent overall yield. Finally, succesive reduction and oxidation steps converted the ester **30** to the desired dienal **20**, which was ready to be coupled to the pyridine unit. Starting from aldehyde **24**, the same approach (Wittig olefination/ester reduction/Swern oxidation) was applied to prepare aldehydes **32**, **34** and **36**, which would be subjected to aldol condensation (Scheme 12). The described protocols provided the required R-configured all-*E* unsaturated aldehydes efficiently and stereoselectively and found well reproducible on different scales.



Scheme 12. Synthesis of the side-chain aldehydes **20**, **32**, **34** and **36**. Reagent and conditions: a) MeI, NaHMDS, THF, -78 °C, 2 h, 72%. b) $LiBH_4$, Ether-MeOH, THF, -78 °C, 2 h, 73%. c) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C. d) **30**, Bu_2BOTf, TEA, CH_2Cl_2, -78 °C, 67% (over 2 steps). e) TsCl, DMAP, Py., RT, 8 h, 83%. f) $LiBH_4$, Ether-MeOH, THF, -78 °C, 2 h, 70%. g) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C. h) $(EtO)_2POCH(CH_3)CO_2Et$, NaH, THF, -78 °C, 8 h, 73% (over 2 steps, *E/Z* = 3/1). i) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 89%. j) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 95%. k) Ph_3PCHCO_2Et, PhMe, 80 °C, 8 h, 88%. l) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 87%. m) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 91%. n) $Ph_3PC(CH_3)CO_2Et$, DCM, RT, overnight, 72%. o) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 94%. p) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 92%. q) Ph_3PCHCO_2Et, PhMe, 80 °C, 8 h, 68%. r) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 88%. s) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 85%. t) Ph_3PCHCO_2Et, PhMe, 80 °C, 8 h, 82%. u) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 91%. v) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 95%.

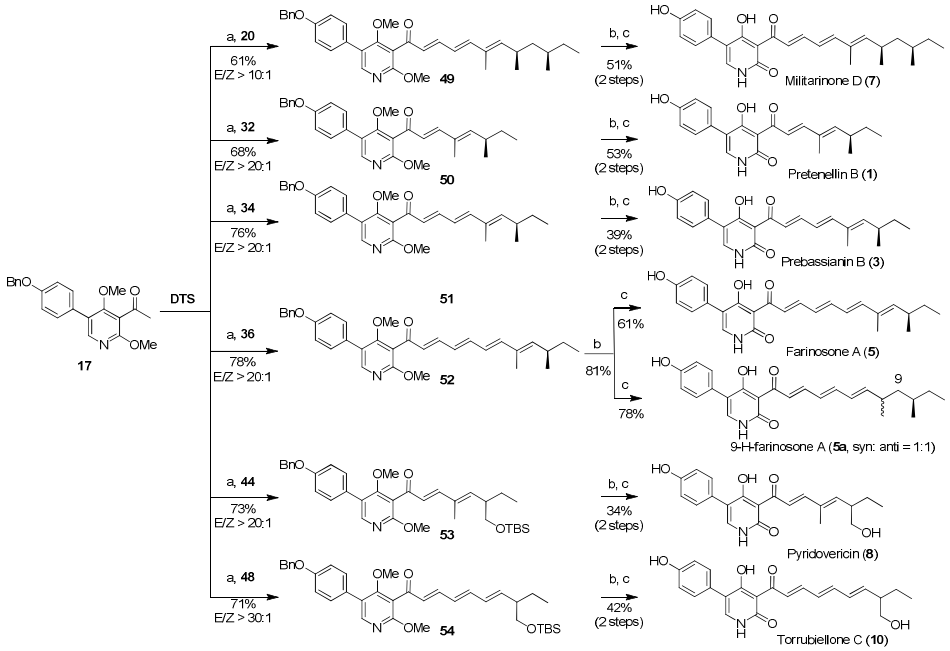
The total synthesis of pyridone alkaloids pyridovericin (**8**) and torrubiellone (**10**) required aldehyde fragments **44** and **48**, respectively (Scheme 13). Preparation of aldehyde **44** has been reported by Baldwin.[23] In accord with the established procedure, the synthesis of these two side-chain aldehydes began with reduction of diethyl 2-ethylmalonate **39** to the corresponding diol **40** which was monoprotected to afford the desired silyl ether **41** in good yield. Swern oxidation and subsequent Wittig olefination of **42** gave ester **43** and **45**, respectively. Ester reduction followed by Swern oxidation gave aldehydes **44** and **46** in excellent overall yield Further wittig olefination of **46** generated pure (*E*,*E*)-diene **47**. Reduction of **47** to the corresponding alcohol followed by oxidation provided the desired aldehyde intermediate **48**, which was ready to be coupled to the pyridine unit.



Scheme 13. Synthesis of the side-chain aldehydes **44** and **48**. Reagent and conditions: a) $LiAlH_4$, THF, 80 °C, 3 days, 65%. b) TBSCl, *n*-BuLi, THF, -78 °C to -30 °C, 2 h, 77%. c) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C. d) $Ph_3PC(CH_3)CO_2Et$, DCM, RT, overnight, 85% (over 2 steps). e) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 91%. f) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 88%. g) Ph_3PCHCO_2Et, DCM, RT, overnight, 77%. h) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 95%. i) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C; j) Ph_3PCHCO_2Et, DCM, RT, overnight, 69% (over 2 steps). k) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 86%. l) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 96%.

With the key advanced intermediate pyridone unit **17** and all side-chain aldehydes

20, **32**, **34**, **36**, **44** and **48** successfully prepared, we next focused on the construction of the C=C *via* coupling of these two fragments to complete the syntheses of pyridone alkaloids (Scheme 14). The assembly of the pyridone core structures with polyene aldehyde chain which constitutes the key step in the synthetic route was accomplished *via* aldol condensation. We found that the aldol condensation step were prone to a range of side reactions. After careful optimization of the reaction parameters, the formation of byproducts is almost completely suppressed. The optimum condition required the use of 3 equivalents of NaH in a degassed THF at 0 °C with a 1:1.2 ratio of ketone **17** to aldehyde. The targeted protected natural products **49**-**54** were finally obtained after few hours with yields ranging from 61 to 78% with good *E/Z* selectivities from 10:1 to 30:1. The subsequent cleavage of the protecting groups at this point proved to be challenging, as most of the methods attempted for removal of the protecting groups either resulted in no reaction or caused complete decomposition of the starting material. To our delight, after numerous attempts, we found that facile removal of the methyl protecting group could be performed by *in-situ* generated trimethylsilyl iodide to afford the desired de-methyl products, with the benzyl group intact.[29] To our surprise, deprotection of **52** following the optimized condition provided the desired product along with an interesting side-product. Finally, the deprotection of benzyl protecting group was effected using boron tribromide[30] to generate the corresponding synthetic natural products (or their analogues), which were isolated in multi-milligram quantities with all-*E* configuration of the double bonds.[31]



Scheme 14. Diverted total synthesis of pyridone alkaloids family. Reagent and conditions: a) NaH, THF, 0 °C to RT, 2 h; b) TMSCl, NaI, MeCN, RT, 3 days; c) BBr_3, CH_2Cl_2, -78 °C, 1 h.

Next, the synthetic pyridone alkaloids were investigated for cell proliferation against six human tumor cell lines namely Jurkat T-cell leukemia, SNU-16 stomach, heLa cervical, MCF-7 breast, A549 lung and HCT-116 colon. The results for the synthesized compounds are summarized in Table 1. From Table 1, compound **3** and **10** have shown to display significant inhibition against Jurkat cell as compared to other cell lines with IC_{50} values of 7.62 and 7.05 μM respectively while positive control etoposide showed IC_{50} values of 3.86 μM. The remaining pyridone alkaloid compound **1**, **3**, **8** and **10** exhibit weak cytotoxicity while compounds **5** and **7** have shown to be almost inactive against the six cell lines. Analysis of pyridone analogue revealed that the length of the carbonyl side chain at R^1 influences the cell proliferation. It was observed that with a side chain of C-9 as shown in compound **5** and **7**, the activity for all the six cell line decreases drastically with an IC_{50} of > 100

μM. More distinct differences regarding the carbon length can be observed in Jurkat cell. From the Jurkat cell line, when there was an increase in carbon length at R^1 from C-5 to C-7, cytotoxicity of **3** and **10** greatly increased by 50 times more active. On the other hand, when C-7 was increased to C-9, cell proliferation of **5** and **7** decreased by 100-fold. However for IC_{50} value of **8** and **10**, we could only infer that either or both absolute configuration have that particular inhibition. These preliminary results deduced that optimum carbon length of carbonyl side chain appear to be essential to this pharmacophore and that C-7 on **3** and **10** exhibited potent inhibitory effects on the proliferation of Jurkat cells with IC_{50} values of 7.62 and 7.05 μM respectively. Next, we investigated whether **3**-treated induces growth inhibition of Jurkat cells was due to an increase in apoptosis. Jurkat cells were treated with DMSO vehicle and **3** (20 μM) for 48 hours, and annexin V-FITC and PI fluorescence was determined by flow cytometry (Figure 7). In the untreated control cells and DMSO-treated groups, only 4.0% (95% CI = 2.7% to 5.3%) and 3.4% (95% CI = 2.5% to 4.3%) of cells were stained positive for annexin V respectively whereas in **3**-treated group, 28.0% (95% CI = 10.7% to 45.3%, $P<0.003$) of cells stained positive for annexin V. Hence, this preliminary study constitutes the foremost report on pyridone alkaloid **3** and **10** having strong inhibition and **3** induces apoptotic cell death in Jurkat cells which might provide 2-pyridone as key lead structure for the development of promising new drug therapeutic treatment for acute lymphoblastic leukemia cells. The exact mechanistic cell proliferation studies of this natural product are on-going.

Table 1: Cell proliferation of pyridone alkaloid in six tumor cell lines (μM)

Compd	Cell lines IC_{50} (μM)					
	Jurkat	SNU-16	Hela	MCF-7	A549	HCT-116
1	43.47	21.01	31.41	41.38	22.23	29.59
3	7.62	12.99	16.22	13.44	34.87	27.65
5	>100	>100	>100	>100	>100	> 100
7	>100	>100	>100	>100	>100	> 100
8	41.72	37.46	64.86	81.77	>100	53.57
10	7.05	23.22	28.13	55.85	68.33	41.98
Etoposide	3.86	28.77	22.46	> 100	69.27	22.56

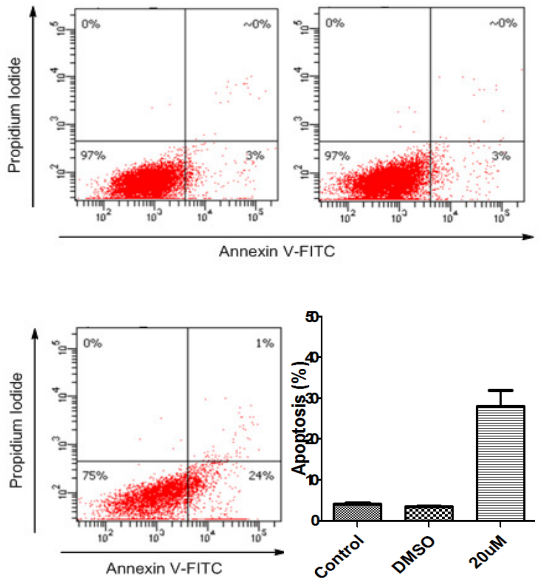


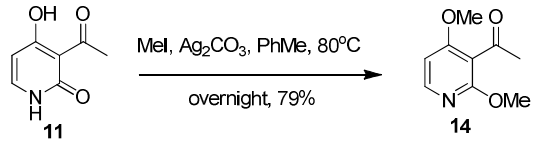
Fig. 7 Annexin V-FLUOS staining test using in vitro Jurkat T cell line co-stained with annexin V-FITC and propidium iodide(PI) followed by examination for apoptosis by flow cytometry. (a) 0 μM., (b) DMSO, (c) Jurkat cells were treated with 20 μM of **3** with incubation for 48 h, (d) Percentage of Jurkat cells undergoing apoptosis after 48 h.

3.3 Conclusion

In conclusion, we have reported a combination of convergent and divergent approach for the total synthesis of a family of pyridone alkaloids, including five natural products and two analogues, which differ in their R^1 chain. The key transformations in our strategy include: 1) convergent formation of densely substituted pyridone

intermediate **17** by Suzuki-Miyaura cross-coupling reactions, 2) iterative synthesis of homologous aldehydes **20**, **32**, **34**, **36**, **44** and **48** with all *trans* polyene backbones *via* an efficient reaction sequence of Wittig olefination, ester reduction, and Swern oxidation, and 3) divergent total synthesis of target molecules under the condition of aldol condensation of pyridone intermediate **17** and the homologous aldehydes above. Interestingly, cell proliferation assay was conducted on six tumor cell lines and discovered that natural products **3** and **10** exhibited potent inhibitory effects on the proliferation of Jurkat cells with IC_{50} values of 7.62 and 7.05 μM respectively. Furthermore, annexin-FITC test was performed and found that **3**-treated induces apoptotic cell death in Jurkat cells. Hence, our synthetic approach can be employed to generate a themic library of pyridone alkaloid analogues as well as recently reported natural products such as Torrubiellones A, and B,[32] and together set up the stage for in-depth structure–activity relationships studies as well as understanding the mechanistic pathway for drug discovery.

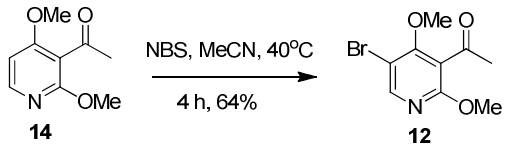
3.4 Experimental Section



3-Acetyl-2,4-dimethoxypyridine (14)

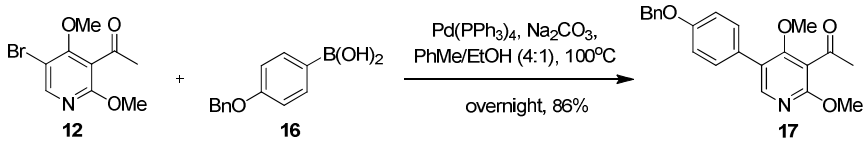
3-Acetyl-4-hydroxypyridone **11**[33] (153 mg, 1.0 mmol) was suspended in toluene (5 mL) to which silver carbonate (690 mg, 2.5 mmol) and iodomethane (513 mg, 246 μL, 3.0 mmol) were added. The suspension was stirred overnight at 80 °C. The reaction mixture was cooled to room temperature and then filtered through Celite. The filtrate was concentrated under reduced pressure. The product was purified by column

chromatography eluting with ethyl acetate in hexane (1:5) to give the title compound **14** as a colourless oil (143 mg, 79%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 6.0 Hz, 1H), 6.55 (d, *J* = 6.0 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.6, 164.1, 161.5, 148.9, 112.7, 101.8, 56.0, 53.9, 32.0; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_9H_{11}NO_3Na$ 204.0637, found 204.0633.



3-Acetyl-5-bromo-2,4-dimethoxypyridine (12)

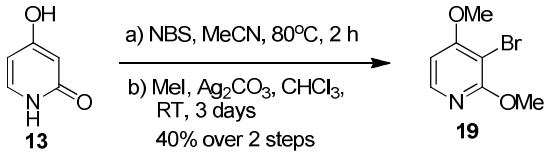
N-Bromosuccinimide (141 mg, 0.79 mmol) was added to a solution of compound **14** (143 mg, 0.79 mmol) in acetonitrile (3 mL). The reaction mixture was stirred at 40 °C for 4 h after which the solvent was removed under reduced pressure. The product was purified by column chromatography eluting with ethyl acetate in hexane (1:10) to give the title compound **12** as a colourless oil (130 mg, 64%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.6, 161.5, 160.9, 149.8, 119.1, 107.2, 62.4, 54.3, 32.0; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_9H_{10}NO_3BrNa$ 281.9742, found 281.9750.



3-Acetyl-5-(4-(benzyloxy)phenyl)-2,4-dimethoxypyridine (17)

A solution of 3-acetyl-5-bromo-2,4-dimethoxy pyridine **12** (130 mg, 0.5 mmol) and p-benzyloxy- phenylboronic acid **16**[34] (171 mg, 0.75 mmol) in a 4:1 mixture of a

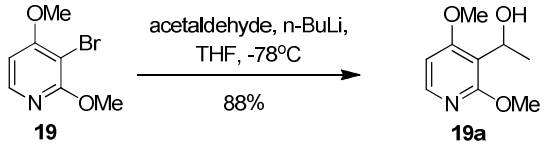
toluene/ethanol (5 mL) was sequentially treated with tetrakis(triphenylphosphine)palladium(0) (3 mg, 0.025 mmol), 2 M sodium carbonate solution (1 mL), and the resulting mixture was refluxed for 12 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate (10 mL). The organic layer was washed with water (5 mL), brine (5 mL) and dried (Na_2SO_4). The solvent was evaporated under vacuum and the crude product purified by flash column chromatography eluting with ethyl acetate in hexane (1:10) to afford the desired titled product **17** as a white solid (156 mg, 86%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.33-7.46 (m, 7H), 7.04 (d, *J* = 8.8 Hz, 2H), 5.10 (s, 2H), 3.98 (s, 3H), 3.48 (s, 3H), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.0, 162.7, 160.5, 158.6, 148.8, 136.8, 130.0, 128.5, 127.5, 127.3, 124.4, 117.8, 116.1, 115.1, 70.1, 63.4, 54.0, 32.2; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{22}H_{21}NO_4Na$ 386.1368, found 386.1375.



3-Bromo-2,4-dimethoxypyridine (19)[25]

N-Bromosuccinimide (7.62 g, 42.8 mmol) was added to a solution of 2,4-dihydroxypyridine **13** (5.00 g, 45.0 mmol) in acetonitrile (100 mL). The reaction mixture was stirred at ambient temperature for 3 h after which the solvent was removed under reduced pressure. The crude intermediate was suspended in chloroform (90 mL) to which silver carbonate (49.60 g, 180.0 mmol) and iodomethane (11.2 mL, 180.0 mmol) were added. The suspension was stirred at ambient temperature for 72 h. The reaction mixture was filtered through Celite and

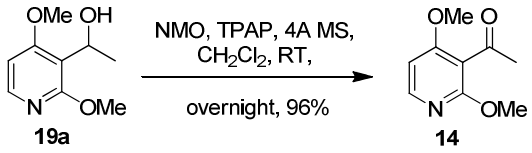
the filtrate was concentrated under reduced pressure. The product was purified by column chromatography eluting with ethyl acetate in hexane (1:9) to give the title compound as a colourless amorphous solid **19** (4.12 g, 42%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 6.0 Hz, 1H), 6.52 (d, *J* = 6.0 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.9, 166.1, 147.5, 106.3, 94.0, 55.2, 53.6; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_7H_8NO_2BrNa$ 239.9636, found 239.9637.



3-(1-Ethanol)-2,4-dimethoxypyridine (19a)

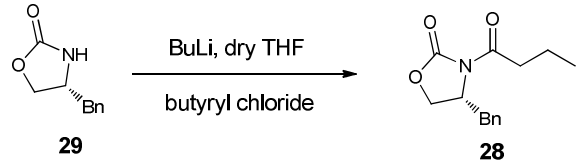
3-Bromo-2,4-dimethoxypyridine **19** (2.18 g, 10 mmol) was dissolved in THF (20 mL) and cooled to -78 °C. *n*-Butyl lithium (2 M, 6.0 mL, 12.0 mmol) was added dropwise after which the solution was stirred for 10 min. Acetaldehyde (484 mg, 617 µL, 11 mmol) was then added dropwise over five minutes and the reaction was allowed to stir at -78 °C for 30 min. Aqueous ammonium chloride solution (10 mL) was added to quench the reaction which was subsequently allowed to warm to ambient temperature and the reaction mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography eluting with ethyl acetate in hexane (1:4) to afford the title compound as a clear white solid (1.61 g, 88%):^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, *J* = 6.0 Hz, 1H), 6.53 (d, *J* = 6.0 Hz, 1H), 5.18-5.26 (m, 1H), 3.98 (s, 3H), 3.87 (s, 3H), 3.56 (br, 1H), 1.48 (d, *J* = 6.80 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.7, 162.2, 146.3, 113.7, 102.1,

63.0, 55.8, 53.6, 23.1; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_9H_{13}NO_3Na$ 206.0793, found 206.0801.



3-Acetyl-2,4-dimethoxypyridine (14)

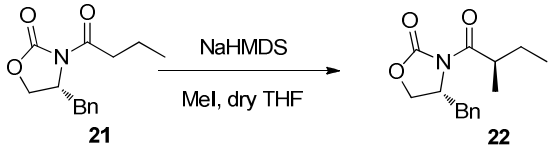
Tetrapropylammonium perruthenate (150 mg, 0.44 mmol), *N*-methylmorpholine-*N*-oxide (1.51 g, 13.2 mmol), and 4Å molecular sieves (4.4 g) were added to a solution of alcohol **19a** (1.61 g, 8.8 mmol) in dichloromethane (60 mL). The mixture was stirred at room temperature for 8 h and then filtered through a Celite pad. The solvent was evaporated in vacuo and the residue was purified by flashing chromatography using 10% ethyl acetate-hexane as eluent afforded the title compound **14** as a clear colourless oil (1.53 g, 96%).



(*R*)-4-Benzyl-3-butyryloxazolidin-2-one (28)

To the solution of (*R*)-4-benzyloxazolidin-2-one **29** (10.0 g, 56.4 mmol) in THF (80 mL) was added dropwise a solution of 2.0 M *n*-BuLi (31.3 mL, 62.6 mmol) at -78 °C under N_2 over 30 min. After 30 min of stirring, butyryl chloride (7.1 mL, 81.3 mmol) was added. The reaction was stirred for 30 min at -78 °C and then allowed to warm to room temperature. After 30 min, the reaction was quenched by saturated aqueous ammonium chloride and extracted with DCM (3 × 50 mL). The extracts were washed with aq. 1N NaOH solution (40 mL), dried over Na_2SO_4 and concentrated under

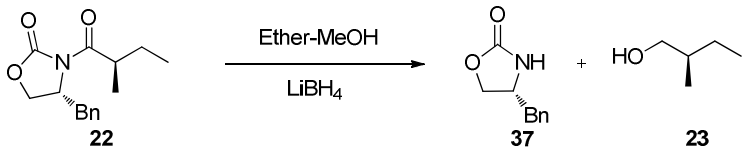
reduced pressure to give the residue, which was purified by column chromatography to afford the title compound **28** as a colorless oil (13.8 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 5H), 4.69 (m, 1H), 4.20 (m, 2H), 3.32 (dd, J = 13.4, 3.3 Hz, 1H), 2.95 (m, 2H), 2.78 (m, 1H), 1.75 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 152.6, 135.3, 129.4, 128.9, 127.3, 66.1, 55.1, 37.9, 37.3, 17.7, 13.6; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{14}H_{17}NO_3Na$ 270.1106, found 270.1110.



21 22

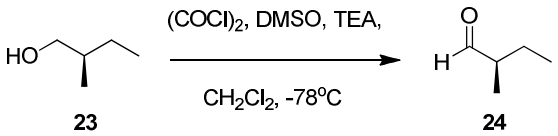
(*R*)-4-Benzyl-3-((R)-2-methylbutanoyl)oxazolidin-2-one (22)

To reaction mixture of (*R*)-4-benzyl-3-butyryloxazolidin-2-one **21** (13.8 g, 55.8 mmol) in THF (80 ml) at -78 °C was added NaHMDS (67.0 mL of 1 M solution in THF, 67.0 mmol) *via* syringe. The mixture was stirred for 30 min, and methyl iodide (8.63 mL g, 140 mmol) was added. After 2 h, the reaction was quenched with 50 ml of saturated NaCl solution. The mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated, and flashed by silica gel chromatography (n-hexane/ EtOAc = 10:1) to furnish the title compound **22** as a colourless oil (10.5 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.34 (m, 5H), 4.65-4.70 (m, 1H), 4.11-4.21 (m, 2H), 3.63 (q, J = 6.8 Hz, 1H), 3.26 (dd, J = 13.6, 3.2 Hz, 1H), 2.77 (dd, J= 13.6, 9.3 Hz, 1H), 1.71-1.81 (m, 1H), 1.44-1.51 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 153.1, 135.4, 129.5, 128.9, 127.3, 66.0, 55.3, 39.2, 37.9, 26.4, 16.9, 11.6.



(*R*)-2-Methylbutan-1-ol (23)

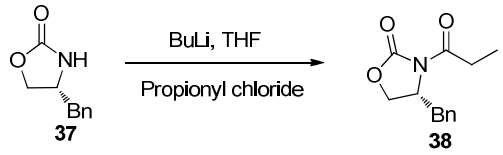
To a solution of (*R*)-4-benzyl-3-((*R*)-2-methylbutanoyl)oxazolidin-2-one **22** (10.5 g, 40.2 mmol) in ether (70 mL) and MeOH (2.6 mL) was added $LiBH_4$ (1.75 g, 28 mmol) at -20 °C. The reaction was stirred at 0 °C for 2 h and then a solution of 1N NaOH (10 mL) was added. After 30 min, the reaction mixture was extracted with ether. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* with cold ice water bath to give the crude product. The residue was purified by column chromatography (ether/pentane =1:3) to give the title compound **23** as colourless liquid (3.04 g, 86%) and Evans chiral auxiliary **37** (5.12 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44–3.53 (m, 2H), 1.44-1.57 (m, 2H), 1.28 (br, 1H), 1.13-1.17 (m, 1H), 0.91-0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.0, 37.4, 25.7, 16.1, 11.3.



(*R*)-2-Methylbutanal (24)

To a stirred solution of oxalyl chloride (6.59 g, 4.39 mL, 51.9 mmol) in CH_2Cl_2 (40 mL) was added a solution of DMSO (6.76 g, 6.1 mL, 86.5 mmol) in CH_2Cl_2 (10 mL) at -78 °C within 20 min. After stirring for 30 min, a solution of (*R*)-2-methyl-1-butanol **23** (3.04 g, 34.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the resulting mixture was stirred for 30 min at -78 °C. Triethylamine (17.51 g, 24.11 mL, 173 mmol) was added dropwise and the resulting mixture was

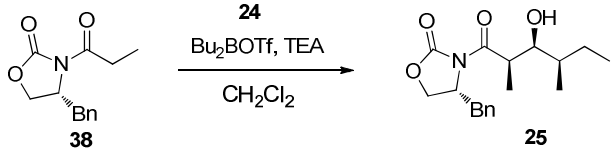
continued stirring for another 30 min. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with water and separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with aqueous HCl (2%), aqueous Na_2CO_3 solution (5%) and brine successively. After drying over Na_2SO_4 and filtration, the reaction mixture was concentrated at cold water bath to afford the crude aldehyde as a colourless liquid, which was directly used for the next step.



(*R*)-4-Benzyl-3-propionyloxazolidin-2-one (38)

To a solution of (*R*)-4-benzyloxazolidin-2-one **37** (4.2 g, 23.7 mmol) in THF (40 mL) was added dropwise a solution of 2.0 M *n-BuLi* (13.2 mL, 26.4 mmol) at -78 °C under N_2 over 10 min. After 10 min of stirring, propionyl chloride (3.26 g, 34.1 mmol) was added. The reaction was stirred for 30 min at -78 °C and then allowed to warm to room temperature. After 30 min, the reaction was quenched by saturated aqueous ammonium chloride, and the mixture was extracted with CH_2Cl_2. The organic extract was washed with aq. 1N NaOH solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc = 4/1) to afford product **38** as a white solid (5.47 g, 99%): $[\alpha]^{D}_{20}$ = -97.0 (c = 1.10, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 4.70-4.64 (m, 1H), 4.22-4.31 (m, 2H), 3.29 (dd, *J* = 13.4, 3.0 Hz, 1H), 3.04-2.87 (m, 2H), 2.77 (dd, *J* = 13.3, 9.6 Hz, 1H), 1.20 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 153.4, 135.3, 129.3,

128.9, 127.2, 66.1, 55.1, 37.8, 29.1, 8.2. IR (cm^{-1}, $CHCl_3$) 1778 (C=O), 1703 (C=O); HRMS (ESI) *m/z* calcd for $C_{13}H_{15}NO_3Na$ $[M+Na]^+$ 256.0950; found 256.0951.

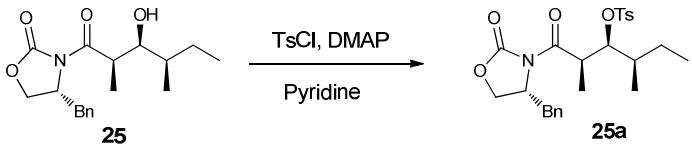


38 25

(4*R*)-4-Benzyl-3-((2*R*,3*S*,4*R*)-3-hydroxy-2,4-dimethylhexanoyl)oxazolidin-2-one[35]

To a solution of (R)-4-benzyl-3-propionyloxazolidin-2-one **38** (4.44 g, 19.03 mmol) in CH_2Cl_2 at 0 °C was added dropwise Bu_2BOTf 1M solution (24.7 mL, 24.7 mmol) and triethyl amine (2.04 mL, 27.8 mmol). Then the red solution was stirred at 0 °C for 45 min and cooled to -78 °C. (*R*)-Methylbutanal **24** (crude from swerm oxidation of alcohol **23**, 17.3 mmol) was added dropwise to the yellow solution. The reaction was stirred at -78 °C for 30min and stirred overnight at 0 °C. Aqueous phosphate buffer (4.0 mL, 1.0 M) and methanol (20 mL) were added followed by the solution of methanol/H_2O_2 (50 mL, 2:1). The reaction was extracted with DCM. The combined extract was dried over Na_2SO_4 and concentrated *in vacuo* to give the residue, which was purified by column chromatography (*n*-hexane/EtOAc = 4/1) to afford the product (4.06 g, 12.75 mmol, 67%). $\alpha]^D_{20}$ = -47.1, (*c* = 1.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 4.74-4.66 (m, 1H), 4.26-4.17 (m, 2H), 4.03-3.94 (m, 1H), 3.69 (dd, *J* = 6.9, 3.9 Hz, 1H), 3.26 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.79 (dd, *J* = 13.5, 9.6 Hz, 1H), 2.64 (d, *J* = 4.0 Hz, 1H), 1.56-1.43 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.22-1.10 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 152.9, 135.0, 129.4, 129.0, 127.4, 75.0, 66.1, 55.1, 39.8, 37.7, 37.2, 25.6, 14.6, 11.2, 11.1. IR (cm^{-1}, $CHCl_3$): 1780 (C=O), 1691 (C=O). HRMS (ESI)

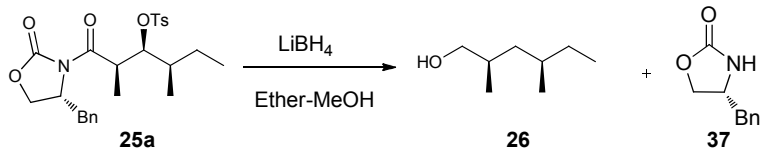
m/z calcd for $C_{18}H_{26}NO_4$ $[M+H]^+$ 320.1862; found 320.1837.



25 **25a**

(2*R*,3*S*,4*R*)-1-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-2,4-dimethyl-1-oxohexan-3-yl-4 -methylbenzenesulfonate (25a)

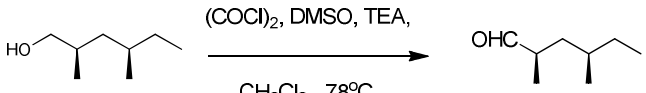
To a solution of alcohol **25** (4.06 g, 12.75 mmol) in pyridine (20 mL) was added TsCl (7.27 g, 38.25 mmol) and DMAP (78 mg, 0.65 mmol) at 0 °C. After 30 min, the reaction was stirred at room temperature for 1 day. The reaction was quenched with saturated solution NH_4Cl, extracted with Et_2O. The organic extract was washed with $CuSO_4$ solution, water, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by column chromatography (*n*-hexane/EtOAc = 10/1) to afford the product as a yellow oil (5.0 g, 10.6 mmol, 83%). $[\alpha]^D_{20}$ = -54.4 (*c* =2.0, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.32-7.24 (m, 7H), 5.00 (dd, *J* = 6.0, 5.1 Hz, 1H), 4.74- 4.66 (m, 1H), 4.29 (t, *J* = 8.3 Hz, 1H), 4.22-4.09 (m, 2H), 3.29 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.79 (dd, *J* = 13.5, 9.6 Hz, 1H), 2.44 (s, 3H), 1.67-1.58 (m, 1H), 1.52-1.43 (m, 1H), 1.22-1.12 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 153.5, 144.5, 135.3, 134.5, 129.6, 129.5, 128.9, 127.7, 127.3, 86.2, 66.5, 55.9, 40.6, 37.7, 37.5, 25.5, 21.6, 14.8, 11.6, 11.6. IR (cm^{-1}, $CHCl_3$): 1774 (C=O), 1701 (C=O). HRMS (ESI) *m/z* calcd for $C_{25}H_{31}NO_6SNa$ $[M+Na]^+$ 496.1770; found 496.1776.



25a **26** **37**

(2*R*,4*R*)-2,4-Dimethylhexan-1-ol (26)

To a solution of tosylate **25a** (5.0 g, 10.6 mmol) in Et_2O (50 mL) and MeOH (1.7 g, 1.34 mL, 53.0 mmol) was added portionwise $LiBH_4$ (1.166 g, 53.0 mmol) at 0 °C. After 30 min, the reaction was stirred overnight at room temperature. 1 N aq. NaOH solution (10 mL) was then added. After 30 min, the reaction mixture was extracted with ether. The combined extract was dried over Na_2SO_4 and concentrated at cold water bath to give the crude product, which was purified by column chromatography (ether/pentane = 2/3) to give alcohol as a colourless liquid (1.17 g, 9.01 mmol, 85%) and Evans chiral auxiliary **37** (1.31 g, 70%). $[\alpha]^{D}_{22.5}$ = +3.8 (*c* = 1.64, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55-3.46 (m, 1H), 3.43-3.35(m, 1H), 1.74-1.65 (m, 1H), 1.42-1.25 (m, 4H), 1.11-1.05(m, 1H), 0.93-0.83(m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.5, 40.6, 33.1, 31.6, 29.0, 19.8, 17.3, 11.2. IR (cm^{-1}, neat): 3348 (OH). HRMS (ESI) *m/z* calcd for $C_8H_{18}ONa$ $[M+Na]^+$ 153.1255; found 153.1259.

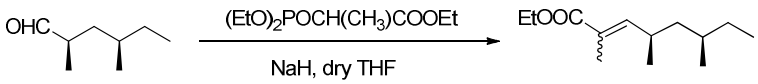


26 **27**

(2*R*,4*R*)-2,4-Dimethylhexanal (27)

To a solution of oxalyl chloride (1.03 g, 0.69 mL, 8.1 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise DMSO (1.05 g, 0.96 mL, 13.5 mmol) in CH_2Cl_2 (2 mL) at -78 °C in 5 min. After 30 min stirring, the solution of alcohol **26** (700 mg, 5.4 mmol) in CH_2Cl_2 (3 mL) was added at -78 °C. Stirring was continued for 30 min, then

triethyl amine (2.73 g, 3.76 mL, 27.0 mmol) was added dropwise and the resulting mixture was stirred for another 30 min. The solution was allowed to warm to room temperature and stirred for 2h. The reaction was quenched with water and separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and aqueous Na_2CO_3 solution (5%) successively. After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo* with an ice-water bath to afford the crude aldehyde as a colourless liquid, which was directly used for the next step without purification.

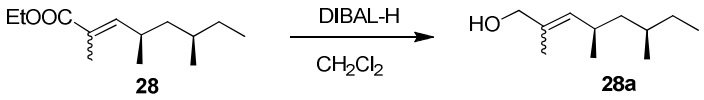


27 **28**

(4*R*,6*R*)-Ethyl 2,4,6-trimethyloct-2-enoate (28)

To a mixture of NaH (432 mg, 60 % in mineral oil, 10.8 mmol) in anhydrous THF (10 mL) was added triethyl 2-phosphonopropionate (1.67 g, 1.5 mL, 7.02 mmol) at 0 °C. After stirring for 1 h, (2*R*,4*R*)-2,4-dimethylhexanal **27**(crude, 5.4 mmol) in anhydrous THF (4 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was seperated between ether and water. The aqueous layer was extracted with ether and the combined extract was dried over Na_2SO_4 and concentrated *in vacuo* with an ice-water bath. The residue was purified by column chromatography (ether/pentane = 1/10) to give the product as a mixture of E/Z isomers with ratio of 1/3 (836 mg, 3.9 mmol, 73%). ***Z*-(4*R*,6*R*)-Ethyl 2,4,6-trimethyloct-2-enoate**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (d, J = 10 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.25-3.22 (m, 1H), 1.89 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.30-1.20 (m, 3H), 1.20-1.00 (m, 2H), 0.95 (d, J = 6.4 Hz, 3H), 0.90-0.80 (m, 6H).

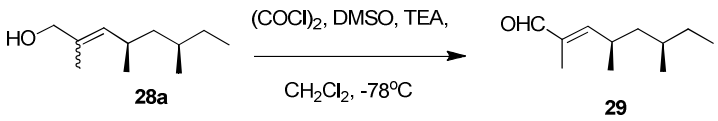
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 148.6, 125.8, 60.1, 44.8, 32.4, 31.1, 30.1, 21.2, 20.9, 19.0, 14.3, 11.4. IR (cm^{-1}, $CHCl_3$): 1722 (C=O). HRMS (ESI) *m/z* calcd for $C_{13}H_{24}O_2Na$ $[M+Na]^+$ 235.1674; found 235.1682. ***E*-(4*R*,6*R*)-Ethyl 2,4,6-trimethyloct-2-enoate**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, *J* = 9 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.65-2.58 (m, 1H), 1.84 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.30-1.20 (m, 3H), 1.20-1.00 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.90-0.80 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 148.6, 125.8, 60.1, 44.8, 32.4, 31.1, 30.1, 21.2, 20.9, 19.0, 14.3, 11.4. IR (cm^{-1}, $CHCl_3$): 1722 (C=O). HRMS (ESI) *m/z* calcd for $C_{13}H_{24}O_2Na$ $[M+Na]^+$ 235.1674; found 235.1682.



(4*R*,6*R*)-2,4,6-Trimethyloct-2-en-1-ol (28a)

To a solution of ethyl ester **28** (836 mg, 3.9 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise DIBAL-H (11.7 mL, 11.7 mmol, 1M in hexane) at –78 °C. After 2 h, MeOH (2 mL) was added dropwise followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H_2O, 5 mL) at –78 °C. The mixture was stirred for 1 h at room temperaturebefore extracting with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure *in vacuo* with ice-water bath gave a crude product, which was purified by flash column chromatography on silica gel (ether/pentane = 1/5) to afford mixture of E/Z alcohol as colorless oil (590 mg, 3.47 mmol, 89%). ***Z*-(4*R*,6*R*)-2,4,6-Trimethyloct-2-en-1-ol**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (d, *J* = 10 Hz, 1H), 4.14 (s, 2H), 2.56-2.48 (m, 1H), 1.79 (s, 3H), 1.33-1.05 (m, 5H), 0.92 (d, *J* = 6.4 Hz,

3H), 0.89-0.80 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 132.6, 62.0, 45.0, 32.1, 30.1, 29.7, 22.4, 21.3, 19.0, 11.3. IR (cm^{-1}, $CHCl_3$): 3240 (OH). HRMS (ESI) *m/z* calcd for $C_{11}H_{22}ONa$ $[M+Na]^+$ 193.1568; found 193.1578. ***E*-(4*R*,6*R*)-2,4,6-Trimethyloct-2-en-1-ol**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, J = 9 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.65-2.58 (m, 1H), 1.84 (s, 3H), 1.30-1.20 (m, 3H), 1.20-1.00 (m, 2H), 0.93 (d, J = 6.4 Hz, 3H), 0.90-0.80 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 148.6, 125.8, 60.1, 44.8, 32.4, 31.1, 30.1, 21.2, 20.9, 19.0, 14.3, 11.4. IR (cm^{-1}, $CHCl_3$): 3240 (OH). HRMS (ESI) *m/z* calcd for $C_{11}H_{22}ONa$ $[M+Na]^+$ 193.1568; found 193.1578.

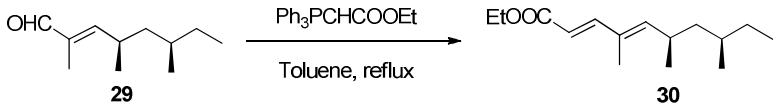


28a **29**

***E*-(4*R*,6*R*)-2,4,6-trimethyloct-2-enal (29)**

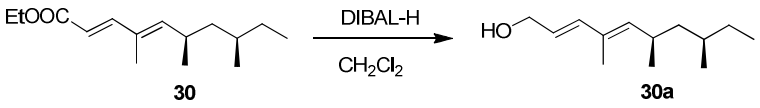
To a solution of oxalyl chloride (661 mg, 0.44 mL, 5.21 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise DMSO (678 mg, 0.62 mL, 8.68 mmol) in CH_2Cl_2 (1.5 mL) at -78 °C. After 30 min stirring, a solution of alcohol **28a** (590 mg, 3.47 mmol) in CH_2Cl_2 (2 mL) was added at -78 °C. After 30 min, triethyl amine (1.76 g, 2.42 mL, 17.35 mmol) was added dropwise and the resulting mixture was stirred for another 30 min. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with water and separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and aqueous Na_2CO_3 solution (5%) successively. After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo* in ice-water bath. The crude product was

purified by column chromatography (ether/pentane = 1/10) to afford product **21** as colorless oil (554 mg, 3.3 mmol, 95%, *E* only). $[\alpha]^{D}_{22.5}$ = -26.0 (*c* =2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 6.22 (d, *J* = 9.9 Hz, 1H), 2.86-2.76 (m, 1H), 1.76 (s, 3H), 1.40-1.10 (m, 5H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.87- 0.83 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 161.0, 137.9, 44.0, 32.5, 31.3, 30.0, 20.4, 19.1, 11.2, 9.4. IR (cm^{-1}, $CHCl_3$): 1687 (C=O). HRMS (ESI) *m/z* calcd for $C_{11}H_{21}O$ $[M+H]^+$ 169.1592; found 169.1593.



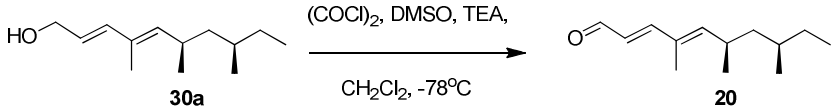
(2*E*,4*E*,6*R*,8*R*)-Ethyl 4,6,8-trimethyldeca-2,4-dienoate (30)

The mixture of aldehyde **29** (554 mg, 3.3 mmol) and $EtO_2CCH{=}PPh_3$ (1.72 g, 4.95 mmol) in toluene (1.42 mL) was refluxed overnight. After reaction was completed, the reaction mixture was loaded to column chromatography (ether/pentane = 1/15) to give the product as a mixture of *Z*/*E* isomers with ratio of 1/5 (691 mg, 2.9 mmol, 88%). ***E*-isomer**: $[\alpha]^{D}_{22.5}$ = -41.8 (*c* =1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 15.6 Hz, 1H), 5.77 (d, *J* = 15.6 Hz, 1H), 5.62 (d, *J* = 10.0 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.67-2.60 (m, 1H), 1.76 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.36-1.16 (m, 3H), 1.16-1.05 (m, 2H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.88-0.79 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 150.0, 148.8, 131.2, 115.5, 60.1, 44.5, 32.2, 30.9, 30.1, 21.1, 19.1, 14.4, 12.3, 11.3. IR (cm^{-1}, $CHCl_3$): 1724 (C=O). HRMS (ESI) *m/z* calcd for $C_{15}H_{27}O_2$ $[M+H]^+$ 239.2011; found 239.2011.



(2*E*,4*E*,6*R*,8*R*)-4,6,8-Trimethyldeca-2,4-dien-1-ol (30a)

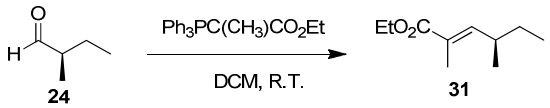
To the ethyl ester **32** (180 mg, 0.76 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise DIBAL-H (2.2 mL, 2.2 mmol, 1 M in hexane) at –78 °C. After 2 h, MeOH (1 mL) was added dropwise at –78 °C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H_2O, 5 mL) . The mixture was stirred for 1 h at room temperature and extracted with ether. The organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure in ice-water bath gave a crude product, which was purified by flash column chromatography on silica gel (ether/pentane = 1/5) to afford a mixture of E/Z (5:1) alcohol as colorless oil (130 mg, 0.66 mmol, 87%); ***E*-isomer:** $[\alpha]^{D}_{22.5}$ = -37.1 (*c* =1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (d, *J* = 16.0 Hz, 1H), 5.70 (m, 1H), 5.22 (d, *J* = 9.7 Hz, 1H), 4.19 (d, *J* = 5.5 Hz, 2H), 2.62-2.52 (m, 1H), 1.76 (s, 3H), 1.32 (s, 1H), 1.30-1.21 (m, 3H), 1.21-1.05 (m, 2H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.91-0.80 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.3, 131.2, 125.0, 64.1, 44.9, 32.3, 30.3, 30.2, 21.6, 19.1, 12.6, 11.3. IR (cm^{-1}, $CHCl_3$): 3325 (OH). HRMS (ESI) *m/z* calcd for $C_{13}H_{24}ONa$ $[M+Na]^+$ 219.1725; found 219.1728.



(2*E*,4*E*,6*R*,8*R*)-4,6,8-Trimethyldeca-2,4-dienal (20)

To a solution of oxalyl chloride (127 mg, 85 µL, 1.0 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise a solution of DMSO (129 mg, 117 µL, 1.65 mmol) in

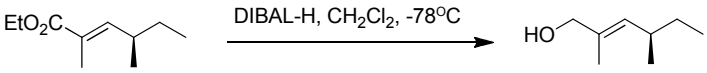
CH_2Cl_2 (0.1 mL) at -78 °C. After 30 min stirring, the solution of alcohol **30**a (130 mg, 0.66 mmol) in CH_2Cl_2 (0.3 mL) was added at -78 °C. After 30 min, triethyl amine (334 mg, 460 μL, 3.3 mmol) was added dropwise and the resulting mixture was stirred for another 5 min. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with water and separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na_2CO_3 solution (5%). After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo* in ice-water bath. The crude product was purified by column chromatography (ether/pentane = 1/15) to afford product **20** as colorless oil (116 mg, 0.6 mmol, 91%, E only); $[\alpha]^{D}_{22.5}$ = -61.4 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 15.6 Hz, 1H), 6.11 (dd, *J* = 15.6, 7.8 Hz, 1H), 5.76 (d, *J* = 10.0 Hz, 1H), 2.72-2.65 (m, 1H), 1.84 (s, 3H), 1.44-1.11 (m, 5H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.87-0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 158.3, 151.2, 131.7, 126.2, 44.4, 32.4, 31.2, 30.1, 20.9, 19.1, 12.5, 11.3; IR (cm^{-1}, $CHCl_3$): 1687 (C=O); HRMS (ESI) *m/z* calcd for $C_{13}H_{23}O$ $[M+H]^+$ 195.1749; found 195.1736.



(*R*)-ethyl 2,4-dimethylhex-2-enoate (31)

A mixture of aldehyde **24** (crude from swerm oxidation of alcohol **23**, 17.3 mmol) and $Ph_3P{=}C(CH_3)CO_2Et$ (9.40 g, 25.95 mmol) in DCM (30 mL) was stirred overnight at room temperature. After reaction was completed, the reaction mixture was loaded to column chromatography (ether/pentane = 1/15) to give the product **31** as a pale

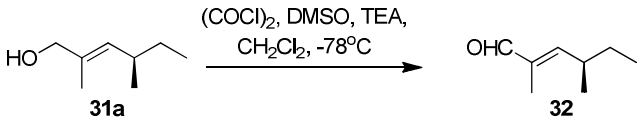
yellow oil (2.12 g, 12.45 mmol, 72%); $[\alpha]^{D}_{22.5}$ = -34.9 (*c* =1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.15 (q, *J* = 6.8 Hz, 2H), 2.35-2.44 (m, 1H), 1.85 (s, 3H), 1.41-1.49 (m, 2H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 147.8, 133.3, 126.5, 60.4, 34.9, 29.6, 19.7, 12.5, 11.9; HRMS (ESI) *m/z* calcd for $C_{10}H_{18}O_2Na$ $[M+Na]^+$ 193.1204; found 193.1210.



31 **31a**

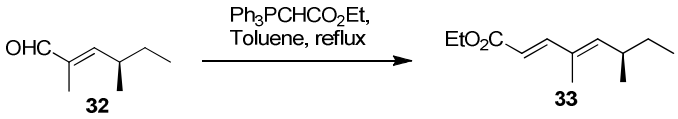
(*R*)-2,4-dimethylhex-2-en-1-ol (31a)

To a solution of ethyl ester **31** (2.12 g, 12.45 mmol) in anhydrous CH_2Cl_2 (35 mL) was added dropwise DIBAL-H (37.35 mL, 37.35 mmol, 1 M in hexane) at –78 °C. After 2 h, MeOH (5 mL) was added dropwise –78 °C followed by EtOAc (20 mL) and sodium potassium tartrate (20%-H_2O, 15 mL). The mixture was stirred at rt for 1 h and the n extracted with ether. The organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure in ice-water bath gave a crude product, which was purified by flash column chromatography on silica gel (ether/pentane = 1/6) to afford title alcohol **31a** as a pale yellow oil (1.5 g, 11.7 mmol, 94%); $[\alpha]^{D}_{22.5}$ = -30.5 (*c* =1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (d, *J* = 9.6 Hz, 1H), 4.00 (s, 2H), 2.25-2.34 (m, 1H), 1.67 (s, 3H), 1.23-1.43 (m, 2H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 69.1, 33.7, 30.2, 22.6, 20.6, 14.1, 11.9; HRMS (ESI) *m/z* calcd for $C_8H_{16}ONa$ $[M+Na]^+$ 151.1099; found 151.1100.



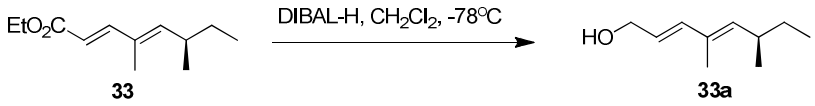
(*R,E*)-2,4-dimethylhex-2-enal (32)

To a solution of oxalyl chloride (2.18 mL, 25.8 mmol) in anhydrous CH_2Cl_2 (12 mL) was added dropwise a solution of DMSO (2.75 mL, 3.36 mmol) in CH_2Cl_2 (4 mL) at –78 °C. After 30 min stirring, a solution of alcohol **31a** (1.5 g, 11.7 mmol) in CH_2Cl_2 (8 mL) was added at –78 °C. After30 min, triethyl amine (9.0 mL, 64.5 mmol) was added dropwise and the mixture was stirred for another 30 min. The solution was allowed to warm to room tempeture and stirred for 2 h. The reaction mixture was quenched with water and separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and thenaqueous Na_2CO_3 solution (5%). After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo* in ice-water bath. The crude product was purified by column chromatography (ether/pentane = 1/10) to afford product **32** as a pale yellow oil (1.35 g, 92%); $[\alpha]^{D}_{22.5}$ = -20.2 (*c* =1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 6.25 (dd, *J* = 10.0, 1.2 Hz, 1H), 2.57-2.65 (m, 1H), 1.75 (s, 3H), 1.38-1.52 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 160.4, 138.2, 35.2, 29.5, 19.5, 11.8, 9.4; HRMS (ESI) *m/z* calcd for $C_8H_{14}ONa$ $[M+Na]^+$ 149.0942; found 149.0942.



(*R,2E,4E*)-ethyl 4,6-dimethylocta-2,4-dienoate (33)

A mixture of aldehyde **32** (1.17 g, 8.9 mmol) and $EtO_2CCH=PPh_3$ (6.17 g, 17.8 mmol) in toluene (15 mL) was refluxed overnight. After reaction was completed, the reaction mixture was loaded to column chromatography (ether/pentane = 1/15) to give the title product **33** as a pale yellow oil (1.19 g, 6.1 mmol, 68%); $[\alpha]^{D}_{22.5}$ = -53.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 15.6 Hz, 1H), 5.77 (d, *J* = 15.6 Hz, 1H), 5.66 (d, *J* = 9.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.38-2.49 (m, 1H), 1.77 (s, 3H), 1.41-1.44 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.20-1.29 (m, 1H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 150.0, 148.3, 131.5, 115.5, 60.1, 34.9, 30.0, 20.1, 14.3, 12.4, 11.9; HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_2Na$ $[M+Na]^+$ 219.1361; found 219.1359.

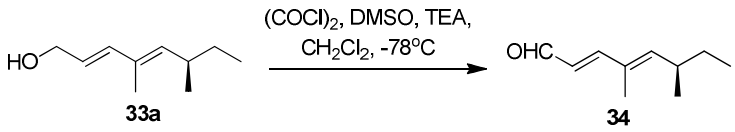


33 **33a**

(R,2E,4E)-4,6-dimethylocta-2,4-dien-1-ol (33a)

To a solution of ethyl ester **33** (761 mg, 3.88 mmol) in anhydrous CH_2Cl_2 (12 mL) was added dropwise DIBAL-H (10.0 mL, 10.0 mmol, 1 M in hexane) at –78 °C. After 2 h, MeOH (2 mL) was added dropwise at –78 °C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H_2O, 10 mL). The mixture was stirred at rt for 1 h before extraction with ether. The organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash column chromatography on silica gel (ether/pentane = 6/1) to afford alcohol **33a** as a pale yellow oil (525 mg, 3.41 mmol, 88%); $[\alpha]^{D}_{22.5}$ = -67.9 (*c* =1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (d, *J* = 16.0 Hz, 1H), 5.71 (dt, *J* = 15.6, 6.4 Hz, 1H), 5.26 (d, *J* = 9.6 Hz, 1H), 4.19 (d, *J* = 6.0

Hz, 2H), 3.40 (d, *J* = 6.4 Hz, 1H), 2.36-2.42 (m, 1H), 1.75 (s, 3H), 1.18-1.38 (m, 2H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 137.2, 125.0, 64.1, 34.3, 30.3, 20.6, 18.9, 12.7, 12.0; HRMS (ESI) *m/z* calcd for $C_{10}H_{18}ONa$ $[M+Na]^+$ 177.1255; found 177.1252.

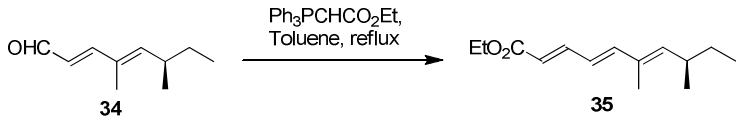


33a **34**

(*R,2E,4E*)-4,6-dimethylocta-2,4-dienal (34)

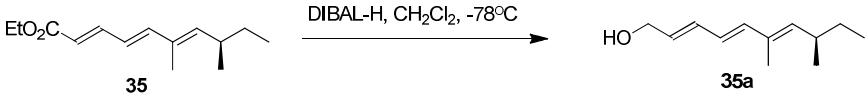
To a solution of oxalyl chloride (550 µL, 6.5 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise a solution of DMSO (700 µL, 9.75 mmol) in CH_2Cl_2 (2.5 mL) at -78 °C. After 30 min, a solution of alcohol **33a** (500 mg, 3.25 mmol) in CH_2Cl_2 (7.5 mL) was added at -78 °C. After 30 min, triethyl amine (2.26 mL, 16.25 mmol) was added dropwise and the mixture was stirred for another 30 min. The solution was allowed to warm to room temperature and stirred for 2h. The reaction was quenched with waterand separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na_2CO_3 solution (5%). After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (ether/pentane = 1/20) to afford product **34** as a pale yellow oil (420 mg, 85%); $[\alpha]^D_{22.5}$ = -34.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 15.6 Hz, 1H), 6.09 (dd, *J* = 15.6, 7.8 Hz, 1H), 5.79 (d, *J* = 10.0 Hz, 1H), 2.44-2.50 (m, 1H), 1.82 (s, 3H), 1.36-1.47 (m, 1H), 1.27-1.34 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 158.3, 150.8, 132.2, 126.8, 35.1,

29.9, 20.0, 12.6, 11.9; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}ONa$ $[M+Na]^+$ 175.1099; found 175.1103.



(*R,2E,4E,6E*)-ethyl 6,8-dimethyldeca-2,4,6-trienoate (35)

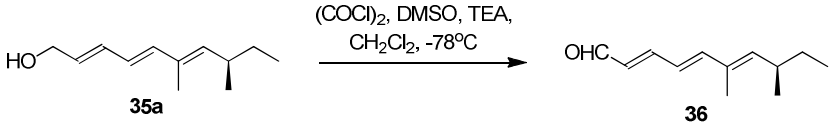
A mixture of aldehyde **34** (152 mg, 1.0 mmol) and $EtO_2CCH{=}PPh_3$ (700 g, 2.0 mmol) in toluene (5 mL) was refluxed overnight. After the reaction was completed, the mixture was loaded to column chromatography (ether/pentane = 1/15) to give the product **35** as a pale yellow oil (182 mg, 0.82 mmol, 82%); $[\alpha]^D_{22.5}$ = -54.5 (*c* =0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 15.2, 7.2 Hz, 1H), 6.56 (d, *J* = 15.2 Hz, 1H), 6.22 (dd, *J* = 14.8, 10.8 Hz, 1H), 5.84 (d, *J* = 9.6 Hz, 1H), 5.47 (d, *J* = 9.6 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.37-2.46 (m, 1H), 1.79 (s, 3H), 1.22-1.44 (m, 5H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 146.2, 145.5, 144.9, 132.5, 123.7, 119.6, 60.1, 34.8, 30.2, 20.4, 14.3, 12.5, 11.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_2Na$ $[M+Na]^+$ 245.1517; found 245.1521.



(*R,2E,4E,6E*)-6,8-dimethyldeca-2,4,6-trien-1-ol (35a)

To a solution of ethyl ester **35** (182 mg, 0.82 mmol) in anhydrous CH_2Cl_2 (4 mL) was added dropwise DIBAL-H (2.46 mL, 2.46 mmol, 1M in hexane) at –78 °C. After 2 h, MeOH (1 mL) was added dropwise at –78 °C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H_2O, 5 mL). The mixture was stirred for 1 h at room temperature and then extracted with ether. The organic layers were washed with brine

and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash column chromatography on silica gel (ether/pentane = 1/5) to afford alcohol **35a** as a pale yellow oil (134 mg, 0.75 mmol, 91%); $[\alpha]^{D}_{22.5}$ = -23.3 (*c* =1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22-6.25 (m, 1H), 6.11-6.17 (m, 2H), 5.81 (dt, *J* = 15.6, 6.4 Hz, 1H), 5.28 (d, *J* = 9.6 Hz, 1H), 4.18 (d, *J* = 6.0 Hz, 2H), 3.40 (d, *J* = 6.4 Hz, 1H), 2.35-2.43 (m, 1H), 1.76 (s, 3H), 1.18-1.38 (m, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 138.7, 132.5, 130.5, 125.2, 63.6, 34.5, 30.3, 20.6, 18.9, 12.6, 12.0; HRMS (ESI) *m/z* calcd for $C_{12}H_{20}ONa$ $[M+Na]^+$ 203.1412; found 203.1409.

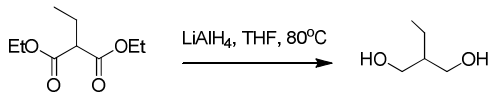


35a **36**

(*R,2E,4E,6E*)-6,8-dimethyldeca-2,4,6-trienal (36)

To a solution of oxalyl chloride (127 µL, 1.5 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise a solution of DMSO (160 µL, 2.25 mmol) in CH_2Cl_2 (1 mL) at -78 °C. After 30 min, a solution of alcohol **35a** (134 mg, 0.75 mmol) in CH_2Cl_2 (2 mL) was added at -78 °C. After 30 min, triethyl amine (523 µL, 3.75 mmol) was added dropwise and the resulting mixture was stirred for another 5 min. The solution was allowed to warm to room temperature and stirred for 2h. The reaction was quenched with water and separated. The aqueous layer was extracted with ether. The combined organic layers were washed with aqueous HCl (2%) and aqueous Na_2CO_3 solution (5%) successively. After drying over $MgSO_4$ and filtration, the solvent was removed

in vacuo. The crude product was purified by column chromatography (ether/pentane = 1/20) to afford product trienal **36** as a pale yellow oil (126 mg, 95%); $[\alpha]^{D}_{22.5}$ = -34.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 15.2, 10.2 Hz, 1H), 6.68 (d, *J* = 15.2 Hz, 1H), 6.35 (dd, *J* = 15.2 Hz, 10.2 Hz, 1H), 6.15 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.57 (d, *J* = 9.6 Hz, 1H), 2.40- 2.50 (m, 1H), 1.82 (s, 3H), 1.36-1.47 (m, 1H), 1.24-1.34 (m, 1H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 153.3, 148.4, 146.9, 132.7, 130.4, 123.9, 34.9, 30.1, 20.3, 12.5, 12.0; HRMS (ESI) *m/z* calcd for $C_{12}H_{18}ONa$ $[M+Na]^+$ 201.1255; found 201.1248.

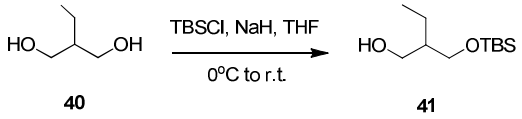


39 **40**

2-(Hydroxymethyl) butanol (40)[36]

A three-necked round bottomed flask equipped with a pressure equalizing addition funnel, reflux condenser and drying tube was flushed with N_2 and $LiAlH_4$ (570 mg, 15 mmol) was added. The flask was loaded with dry THF (10 mL). A solution of diethyl alkyl melonate **39** (1.88 g, 10 mmol) in dry THF (5 mL) was added dropwise over 1 h at room temperature, *via* the pressure equalizing addition funnel, and the reaction mixture was refluxed for 3 days. The mixture was cooled to 0 °C and quenched by 0.5M HCl (5 mL). The white suspension was diluted with water (10 mL) and was adjusted to pH = 7 with concentrated HCl. The aqueous solution was extracted with CH_2Cl_2 (3x30 mL). The volume of the combined organic layers was partially reduced to 100 mL under vacuum and washed with sat. $NaHCO_3$ and sat.

NaCl solutions. After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica gel, 25% ethyl acetate in hexane) to afford the product diol **40** as a clear oil (680 mg, 6.54 mmol; 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (dd, *J* = 10.4, 4.0 Hz, 2H); 3.63 (dd, *J* = 10.8, 7.6 Hz, 2H), 2.80 (bs, 2H, OH), 1.63-1.71 (m, 1H), 1.29 (q, *J* = 7.2 Hz, 2H), 0.94 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.1; 43.6; 20.6; 11.7; HRMS (ESI) *m/z* calcd for $C_5H_{12}O_2Na$ $[M+Na]^+$ 127.0735; found 127.0733.

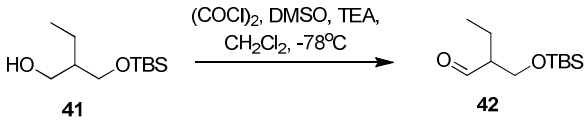


40 **41**

2-(tert-Butyldimethylsilanyloxymethyl)-1-butanol (41)

To a suspension of 60% sodium hydride (261 mg, 6.54 mmol) in THF (10 mL) at0 °C, was added dropwise a solution of 2-ethylpropan-1,3-diol **40** (680 mg, 6.54 mmol) in THF (3 mL). The reaction mixture was stirred at room temperature for 1 h, during which time a large amount of an opaque white precipitate formed. The reaction mixture was cooled to 0 °C and a solution of *tert*-butyldimethylsilyl chloride (981 mg, 6.54 mmol) in THF (3 mL) was added slowly. The reaction was warmed up and stirred overnight at room temperature, and was then quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with water (2 × 10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10% ethyl acetate in hexane) to afford 1.1 g, (77%) of known[24] desired titled product **41** as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57-3.83 (m, 4H), 2.89

(br, 1H), 1.58-1.70 (m, 1H), 1.22-1.33 (m, 2H), 0.92 (t, *J* = 10.0 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.1, 66.3, 43.7, 25.8, 20.6, 18.1, 11.7, -5.59, -5.65; HRMS (ESI) *m/z* calcd for $C_{11}H_{26}O_2SiNa$ $[M+Na]^+$ 241.1600; found 241.1607.

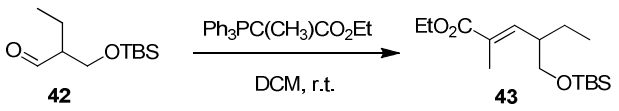


41 **42**

2-(Tert-butyldimethylsilanyloxymethyl) butyraldehyde (42)

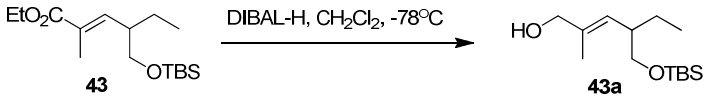
To a solution of oxalyl chloride (854 μL, 10.1 mmol) in anhydrous CH_2Cl_2 (6 mL) was added dropwise a solution of DMSO (1.07 mL, 15.12 mmol) in CH_2Cl_2 (2 mL) at -78 °C. After 30 min, a solution of alcohol **41** (1.1 g, 5.04 mmol) in CH_2Cl_2 (4 mL) was added at –78°C and the mixture waswas stirred for 30 min. Thentriethyl amine (3.5 mL, 25.2 mmol) was added dropwise and the mixture was stirred for another 30 min. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with waterand separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na_2CO_3 solution (5%). After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo* to afford 1.1 g (100%) of the known[6] 2-(tert-butyldimethylsilanyloxymethyl) butyraldehyde **42**, as a clear oil, which was used for next step without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.4 Hz, 1H), 3.84 (d, *J* = 5.2 Hz, 2H), 2.30-2.43 (m, 1H), 1.63-1.74 (m, 1H), 1.48-1.55 (m, 1H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 61.6, 55.8, 25.8, 18.5, 18.2, 11.4, -5.6; HRMS (ESI) *m/z* calcd

for $C_{11}H_{24}O_2SiNa$ $[M+Na]^+$ 239.1443; found 239.1438.



Ethyl-(2E)-4-(tert-butyldimethylsilanyloxy-methyl)-2-methyl-2-hexenoate (43)

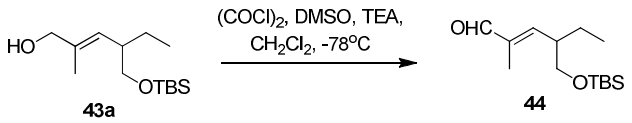
A mixture of aldehyde **42** (crude from swerm oxidation of alcohol **41**, 0.73 mmol) and (carbethoxyethylidene)triphenylphosphorane (529 mg, 1.46 mmol) in DCM (30 mL) was stirred overnight at room temperature. After the reaction was completed, the solvent was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in hexane) to afford 186 mg (85%) of the desired titled product **43** as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 10.6, 1.2 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.49-3.55 (m, 2H), 2.46-2.56 (m, 1H), 1.86 (d, *J* = 1.2 Hz, 3H), 1.60-1.66 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.23-1.25 (m, 1H), 0.87 (s, 9H), 0.85 (t, *J* = 7.6 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 143.8, 128.9, 65.6, 60.3, 43.5, 25.8, 24.0, 18.3, 14.3, 12.9, 11.7, -5.4, -5.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{32}O_3SiNa$ $[M+Na]^+$ 323.2018; found 323.2010.



4-(Tert-butyldimethylsilanyloxymethyl)-2-methyl-2-hexene-1-ol (43a)

To a solution of ethyl ester **43** (186 mg, 0.62 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise DIBAL-H (1.85 mL, 1.85 mmol, 1M in hexane) at -78 °C. After 2 h, MeOH (1 mL) was added dropwise at –78 °C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H_2O, 5 mL). The mixture was stirred at room

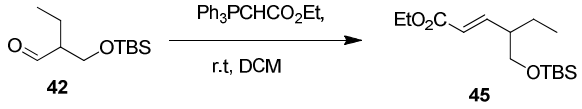
temperature for 1 h and then extracted with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 6/1) to afford the title compound **43a** as colorless oil (145 mg, 0.56 mmol, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (dd, *J* = 10.6, 1.2 Hz, 1H), 4.01 (d, *J* = 4.8 Hz, 2H), 3.41-3.47 (m, 2H), 2.34-2.42 (m, 1H), 1.67 (s, 3H), 1.56-1.64 (m, 1H), 1.41 (br, 1H), 1.10-1.18 (m, 1H), 0.88 (s, 9H), 0.82 (t, *J* = 7.6 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 127.8, 69.1, 66.5, 42.3, 25.9, 24.5, 18.4, 14.3, 11.7, -5.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{30}O_2SiNa$ $[M+Na]^+$ 281.1913; found 281.1914.



(2E)-4-(tert-butyldimethylsilanyloxymethyl)-2-methylhex-2-enal (44)

To a solution of oxalyl chloride (95 µL, 1.12 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added dropwise a solution of DMSO (181 µL, 1.68 mmol) in CH_2Cl_2 (0.5 mL) at -78 °C. After 30 min, a solution of alcohol (119 mg, 0.56 mmol) in CH_2Cl_2 (1 mL) was added at –78 °C and stirred for 30 min. Then triethyl amine (390 µL, 2.8 mmol) was added dropwise and the mixture was stirred for another 30 min. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with water and thenseparated. The aqueous layer was extracted with ether. The combined organic layers were washed with aqueous HCl (2%) and then aqueous Na_2CO_3 solution (5%). After drying over $MgSO_4$ and filtration, the solvent was

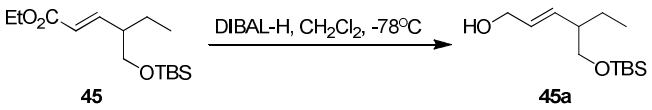
removed *in vacuo*. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 10/1) to afford product as colorless oil (165 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 6.30 (d, *J* = 10.0, 1H), 3.55-3.65 (m, 2H), 2.67-2.73 (m, 1H), 1.77 (s, 3H), 1.62-1.69 (m, 1H), 1.33-1.38 (m, 1H), 0.91 (s, 9H), 0.89 (t, *J* = 7.6 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 156.6, 140.4, 65.4, 43.8, 25.9, 24.0, 18.3, 11.7, 9.8, -5.4; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}O_2SiNa$ $[M+Na]^+$ 279.1756; found 279.1762.



42 45

Ethyl-(2E)-4-(*tert*-butyldimethylsilanyloxy-methyl)-2-hexenoate (45)

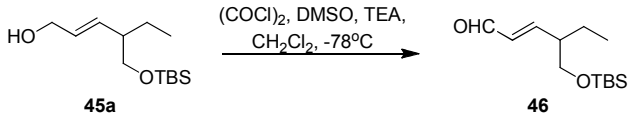
A mixture of aldehyde **42** (crude from swerm oxidation of alcohol **41**, 3.0 mmol) and $EtO_2CCH{=}PPh_3$ (2.01 g, 6.0 mmol) in DCM (10 mL) was stirred overnight at room temperature. After the reaction was completed, the solvent was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in hexane) to afford 637 mg, (77%) of the desired titled product **45** as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.83 (d, *J* = 8.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.56 (dd, *J* = 6.0, 2.0 Hz, 2H), 2.22-2.28 (m, 1H), 1.54-1.64 (m, 1H), 1.33-1.38 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.89 (t, *J* = 7.6 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 150.5, 122.2, 65.3, 60.1, 46.8, 25.8, 23.2, 18.3, 14.3, 11.6, -5.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{30}O_3SiNa$ $[M+Na]^+$ 309.1862; found 309.1862.



45 **45a**

4-(*Tert*-butyldimethylsilanyloxymethyl)-2-hexene-1-ol (45a)

To a solution of ethyl ester **45** (637 mg, 2.23 mmol) in anhydrous CH_2Cl_2 (7 mL) was added dropwise DIBAL-H (6.68 mL, 6.68 mmol, 1 M in hexane) at –78°C. After 2 h, MeOH (1 mL) was added dropwise at –78 °C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H_2O, 5 mL). The mixture was stirred at room temperature for 1 h, extracted with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 6/1) to afford alcohol **45a** as colorless oil (514 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dt, *J* = 11.2, 5.6 Hz, 1H), 5.51 (dd, *J* = 15.6, 8.8 Hz, 1H), 4.11 (t, *J* = 5.2 Hz, 2H), 3.51 (d, *J* = 6.0 Hz, 2H), 2.04-2.10 (m, 1H), 1.32-1.36 (m, 1H), 1.34 (br, 1H), 1.24-1.27 (m, 1H), 0.88 (s, 9H), 0.85 (t, *J* = 7.6 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 130.1, 66.3, 63.9, 46.7, 25.9, 23.8, 18.3, 11.6, -5.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{28}O_2SiNa$ $[M+Na]^+$ 267.1756; found 267.1766.

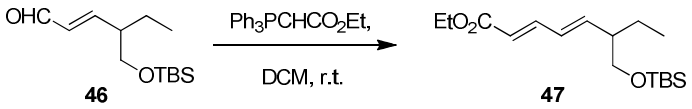


45a **46**

(2*E*)-4-(tert-butyldimethylsilanyloxymethyl)-hex-2-enal (46)

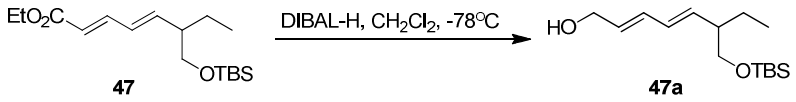
To a solution of oxalyl chloride (357 μL, 4.22 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise a solution of DMSO (450 μL, 6.33 mmol) in CH_2Cl_2 (1 mL) at -78 °C. After 30 min, a solution of alcohol **45a** (514 mg, 2.11 mmol) in CH_2Cl_2 (2 mL)

was added at – 78 °C. Stirring was continued for 30 min, then triethyl amine (1.5 mL, 0.4 mmol) was added dropwise and the mixture was stirred for another 5 min. The solution was allowed to warm to room temperature and stirred for 2h. The reaction was quenched with water. The mixture was separated and the aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na_2CO_3 solution (5%). After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo* with ice-water bath to afford the crude aldehyde **46** as a colourless liquid, which was directly used for the next step without purification.



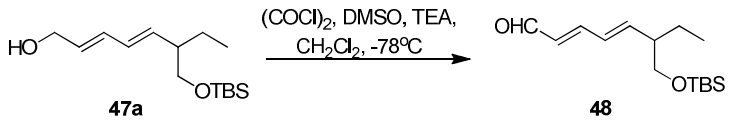
(*2E,4E*)-ethyl 6-(((tert-butyldimethylsilyl)oxy)methyl)octa-2,4-dienoate (47)

A mixture of aldehyde **46** (crude from swerm oxidation of alcohol **45a**, 2.11 mmol) and $EtO_2CCH{=}PPh_3$ (1.4 g, 4.22 mmol) in DCM (10 mL) was stirred overnight at room temperature. After the reaction was completed, the solvent was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in hexane) to afford 454 mg, (69%) of the desired titled product **47** as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 15.6, 11.2 Hz, 1H), 6.19 (dd, *J* = 15.6, 10.8 Hz, 1H), 5.95 (dd, *J* = 15.2, 8.8 Hz, 1H), 5.78 (d, *J* = 15.6 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.50-3.55 (m, 2H), 2.15-2.27 (m, 1H), 1.51-1.62 (m, 1H), 1.28-1.30 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.89 (t, *J* = 7.6 Hz, 3H), 0.03 (s, 6H)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 145.9, 145.0, 129.3, 119.6, 65.8, 60.2, 47.5, 25.9, 23.7, 18.3, 14.3, 11.6, -5.3; HRMS (ESI) *m/z* calcd for $C_{17}H_{32}O_3SiNa$ $[M+Na]^+$ 335.2018; found 335.2016.



(2*E*,4*E*)-6-(((tert-butyldimethylsilyl)oxy)methyl)octa-2,4-dien-1-ol (47a)

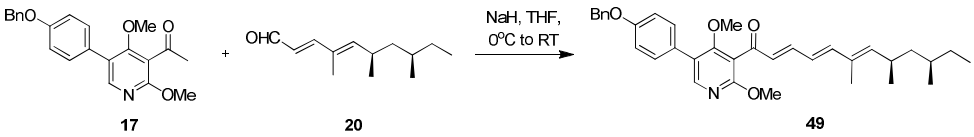
To a solution of ethyl ester **45** (215 mg, 0.69 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise DIBAL-H (2.1 mL, 2.1 mmol, 1 M in hexane) at –78 °°C. After 2 h, MeOH (1 mL) was added dropwise at –78 °C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H_2O, 5 mL). The mixture was stirred at rt for 1 h and then extracted with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 6/1) to afford alcohol as colorless oil (159 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (dd, J = 15.2, 10.4 Hz, 1H), 6.07 (dd, J = 15.2, 10.4 Hz, 1H), 5.74 (dt, J = 15.2, 6.0 Hz, 1H), 5.51 (dd, J = 15.2, 8.8 Hz, 1H), 4.30 (d, J = 7.2 Hz, 2H), 3.47-3.54 (m, 2H), 2.06-2.15 (m, 1H), 1.54-1.60 (m, 1H), 1.20-1.29 (m, 1H), 0.88 (s, 9H), 0.83 (t, J = 7.6 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 132.0, 130.5, 129.8, 66.4, 63.5, 47.2, 25.9, 24.0, 18.3, 11.6, -5.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{30}O_2SiNa$ $[M+Na]^+$ 293.1913; found 293.1918.



(*2E,4E*)-6-(((tert-butyldimethylsilyl)oxy)methyl)octa-2,4-dienal (48)

To a solution of oxalyl chloride (100 μL, 1.18 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise a solution of DMSO (170 μL, 2.4 mmol) in CH_2Cl_2 (0.5 mL) at -78 °C. After 30 min, a solution of alcohol **47a** (160 mg, 0.59 mmol) in CH_2Cl_2 (1.5

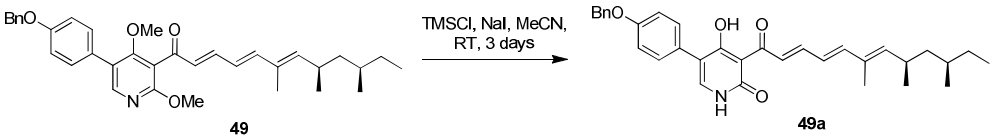
mL) was added at -78 °C. Stirring was continued for 30 min, then triethyl amine (418 µL, 3.0 mmol) was added dropwise and the mixture was stirred for another 30 min. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with water and extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na_2CO_3 solution (5%). After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 20/1) to afford product dienal **48** as colorless oil (152 mg, 96%) as a yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, J = 8.0 Hz, 1H), 7.08 (dd, J = 15.2, 10.8 Hz, 1H), 6.34 (dd, J = 15.2, 10.8 Hz, 1H), 6.06-6.15 (m, 2H), 3.53-3.62 (m, 2H), 2.22-2.26 (m, 1H), 1.55-1.61 (m, 1H), 1.31-1.42 (m, 1H), 0.88 (t, J = 7.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 152.7, 148.7, 130.3, 129.5, 65.6, 47.7, 25.9, 23.7, 18.3, 11.7, -5.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}O_2SiNa$ $[M+Na]^+$ 291.1756; found 291.1760.



2,4-Dimethoxy-5-(4-(benzyloxy)phenyl)-3-((*2E,4E,6E,8R,10R*)-6,8,10-trimethyldeca-2,4,6-trienoyl)pyridine (49)

Sodium hydride (23 mg, 60 % in mineral oil, 0.57 mmol) was added to a solution of 3-Acetyl-5-(4- (benzyloxy)phenyl)-2,4-dimethoxypyridine **17** (65 mg, 0.19 mmol) in dry THF (3 mL) at 0 °C. After 30 min, the appropriate aldehyde **20** (45 mg, 0.23 mmol) in dry THF (2 mL) was added at 0 °C. The reaction mixture was stirred for 30

min and then warmed to room temperature and stirred for 8 h. After that, the reaction was quenched with ice-water and extracted with EtOAc. The combined organic phase was washed with brine. After drying over Na_2SO_4 and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (n-hexane/EtOAc = 10/1) to afford product **49** as yellow oil (60 mg, 61%, E/Z >10:1); $[\alpha]^{D}_{22.5}$ = -18.9 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.34-7.47 (m, 7H), 7.04-7.11 (m, 3H), 6.60 (d, *J* = 15.2 Hz, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.34 (d, *J* = 15.2, 11.2 Hz, 1H), 5.48 (d, *J* = 15.8 Hz, 1H), 5.11 (s, 2H), 3.94 (s, 3H), 3.51 (s, 3H), 2.58-2.65 (m, 1H), 1.82 (s, 3H), 1.24-1.33 (m, 3H), 1.09-1.14 (m, 2H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 163.0, 161.2, 158.4, 148.4, 148.2, 147.5, 146.7, 136.9, 132.4, 131.2, 130.2, 130.1, 128.6, 128.1, 127.5, 127.4, 124.2, 124.1, 115.0, 70.1, 61.0, 54.0, 44.6, 32.4, 30.8, 30.1, 21.3, 19.1, 12.4, 11.2; HRMS (ESI) *m/z* calcd for $C_{35}H_{41}NO_4Na$ $[M+Na]^+$ 562.2933; found 562.2939.

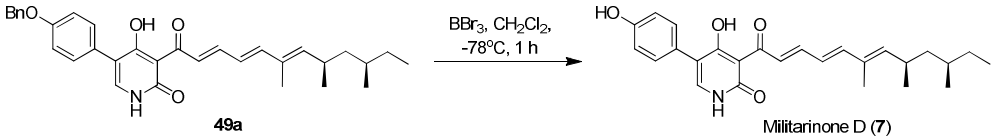


49 49a

(*2E,4E,6E,8R,10R*)-6,8,10-trimethyl-1-[5-(p-benzyloxy-phenyl)-2,4-dihydroxypyridine-3-yl]-dodeca-2,4,6-trien-1-one (49a)

To a -20 °C solution of pyridine, **49** (48 mg, 0.089 mmol) in acetonitrile (11 mL) was added anhydrous sodium iodide (54 mg, 0.36 mmol) and trimethylsilyl chloride (35 µL, 0.27 mmol) and the reaction was slowly brought to room temperature over a period of 4 h. The reaction was stirred for 3 days at room temperature, and then

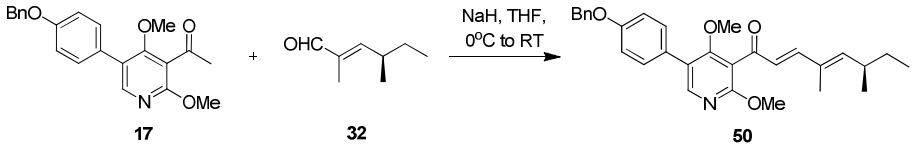
diluted with ethyl acetate (10 mL) and water (5 mL). The solution was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with 5% aq. sodium bicarbonate (10 mL), water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The crude residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 3/1) to afford 27 mg (60%) of the desired pyridone, **49a**, as a yellow solid; $[\alpha]^{D}_{22.5}$ = -45.3 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (br, 1H), 8.02 (d, *J* = 15.2 Hz, 1H), 7.71 (dd, *J* = 14.4, 11.2 Hz, 1H), 7.35-7.46 (m, 7H), 7.32 (d, *J* = 5.2 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 15.2 Hz, 1H), 6.46 (dd, *J* = 14.8, 11.2 Hz 1H), 5.53 (d, *J* = 10.0 Hz, 1H), 5.07 (s, 2H), 2.60-2.69 (m, 1H), 1.84 (s, 3H), 1.26-1.35 (m, 3H), 1.08-1.17 (m, 2H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 177.9, 184.0, 158.6, 148.9, 147.0, 146.8, 138.2, 136.9, 132.7, 132.5, 130.3, 128.6, 128.0, 127.5, 126.2, 125.4, 115.8, 114.9, 106.6, 70.1, 44.7, 32.3, 30.9, 30.1, 21.2, 19.1, 12.5, 11.3; HRMS (ESI) *m/z* calcd for $C_{33}H_{37}NO_4Na$ $[M+Na]^+$ 534.2620; found 534.2605.



(*2E,4E,6E,8R,10R*)-6,8,10-trimethyl-1-[5-(p-hydroxyphenyl)-2,4-dihydroxypyridine-3-yl]-dodeca-2,4,6-trien-1-one, militarinone (7)

A solution of pyridone, **49a** (27 mg, 0.05 mmol) in dichloromethane (10 mL) at -78 °C was treated dropwise with a 1 M solution of boron tribromide in dichloromethane (0.5 mL, 0.5 mmol). The reaction was then stirred at -78 °C for 1 h,

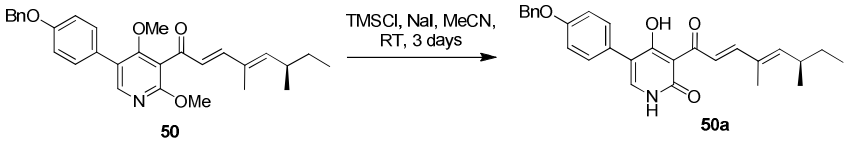
before methanol (0.1 mL) was added, and the mixture was kept at -78 °C for 10 min. The reaction was then further quenched by the sequential addition of water (5 mL), and ethyl acetate (5 mL). The solution was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 5% aq. sodium bicarbonate (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 1/1), to afford 18 mg (84%) of millitarinone D[6] **7**, as a yellow solid; $[\alpha]^{D}_{22.5}$ = -38.4 (c = 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 17.86 (s, 1H), 10.37 (brs, 1H), 8.03 (d, *J* = 14.8 Hz, 1H), 7.71 (dd, *J* = 14.8, 11.2 Hz, 1H), 7.38 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 15.2 Hz, 1H), 6.47 (dd, *J* = 15.2, 11.2 Hz, 1H), 5.53 (d, *J* = 10.0 Hz, 1H), 5.04 (brs, 1H), 2.64-2.67 (m, 1H), 1.83 (s, 3H), 1.23-1.37 (m, 3H), 1.10-1.17 (m, 2H), 0.97 (d, *J* = 6.0 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 178.1, 163.5, 155.4, 148.9, 147.1, 146.8, 137.8, 132.8, 130.5, 126.7, 125.4, 125.2, 115.6, 115.4, 106.7, 44.7, 32.4, 30.9, 30.1, 21.2, 19.1, 12.5, 11.3; HRMS (ESI) *m/z* calcd for $C_{26}H_{31}NO_4Na$ $[M+Na]^+$ 444.2151; found 444.2160.



2,4-Dimethoxy-5-(4-(benzyloxy)phenyl)-3-((*R,2E,4E*)-4,6-dimethylocta-2,4-dienoyl)pyridine (50)

Sodium hydride (23 mg, 60 % in mineral oil, 0.57 mmol) was added to a solution of the key intermediate 3-Acetyl-5-(4-(benzyloxy)phenyl)-2,4-dimethoxypyridine **17**

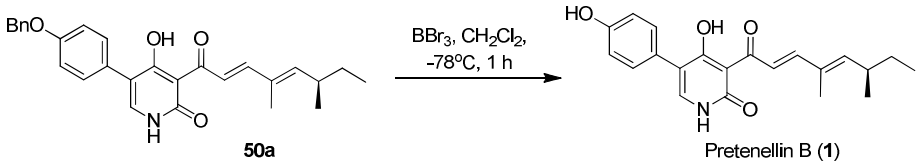
(65 mg, 0.19 mmol) in dry THF (3 mL) at 0 °C. After 30 min, the appropriate aldehyde **32** (29 mg, 0.23 mmol) in dry THF (2 mL) was added at 0 °C. The reaction mixture was stirred for 30 min and then warmed to room temperature and stirred for 8 hours. After that, the reaction was quenched with ice-water, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine. After drying over Na_2SO_4 and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (n-hexane/EtOAc = 5/1) to afford product **56** as yellow oil (61 mg, 68%, E/Z >20:1); $[\alpha]^{D}_{22.5}$ = -18.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.34-7.47 (m, 7H), 7.02-7.06 (m, 3H), 6.40 (d, *J* = 11.6 Hz, 1H), 5.70 (d, *J* = 9.6 Hz, 1H), 5.11 (s, 2H), 3.95 (s, 3H), 3.51 (s, 3H), 2.43-2.52 (m, 1H), 1.84 (s, 3H), 1.37-1.43 (m, 1H), 1.26-1.33 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 163.0, 161.2, 158.5, 151.9, 150.7, 148.4, 136.9, 132.2, 130.1, 128.6, 128.1, 127.5, 127.4, 126.3, 124.2, 115.6, 115.0, 70.1, 61.1, 54.0, 35.2, 29.9, 20.0, 12.6, 12.0; HRMS (ESI) *m/z* calcd for $C_{30}H_{33}NO_4Na$ $[M+Na]^+$ 494.2307; found 494.2315.



(*R,2E,4E*)-4,6-dimethyl-1-[5-(p-benzyloxy-phenyl)-2,4-dihydroxypyridine-3-yl]-octa-2,4-dien-1-one (50a)

To a -20 °C solution of pyridine, **50** (54 mg, 0.115 mmol) in acetonitrile (11 mL) was added anhydrous sodium iodide (69 mg, 0.46 mmol) and trimethylsilyl chloride (44

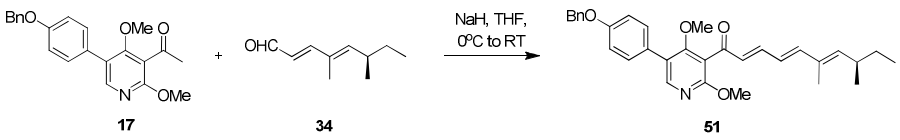
μL, 0.345 mmol) and the reaction was slowly brought to room temperature over a period of 4 h. The reaction was stirred for 3 days at room temperature, and then diluted with ethyl acetate (10 mL) and water (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with 5% aq. sodium bicarbonate (10 mL), water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 3/1) to afford 34 mg (67%) of the desired pyridone, **50a**, as a yellow solid; $[\alpha]^{D}_{22.5}$ = -12.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 17.69 (s, 1H), 11.05 (brs, 1H), 7.96 (d, *J* = 15.2 Hz, 1H), 7.64 (d, *J* = 15.2 Hz, 1H), 7.32-7.46 (m, 8H), 7.04 (d, *J* = 8.4 Hz, 2H), 5.86 (d, *J* = 9.6 Hz, 1H), 5.10 (s, 2H), 2.46-2.53 (m, 1H), 1.91 (s, 3H), 1.36-1.47 (m, 1H), 1.24-1.34 (m, 1H), 1.00 (d, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 177.8, 163.9, 158.6, 151.5, 151.1, 138.0, 136.9, 133.2, 130.3, 128.6, 128.1, 127.5, 126.2, 125.3, 123.0, 114.9, 106.7, 70.1, 35.3, 30.0, 20.1, 12.8, 12.0; HRMS (ESI) *m/z* calcd for $C_{28}H_{29}NO_4Na$ $[M+Na]^+$ 466.1994; found 466.1992.



(*R,2E,4E*)-4,6-dimethyl-1-[5-(p-hydroxyphenyl)-2,4-dihydroxypyridine-3-yl]-octa -2,4-dien-1-one, pretenellin B (1)[37]

A solution of pyridone, **50a** (22 mg, 0.05 mmol) in dichloromethane (10 mL) at -78°C was treated dropwise with a 1 M solution of boron tribromide in dichloromethane (0.5 mL, 0.5 mmol). The reaction was then stirred at -78 °C for 1 h, before methanol

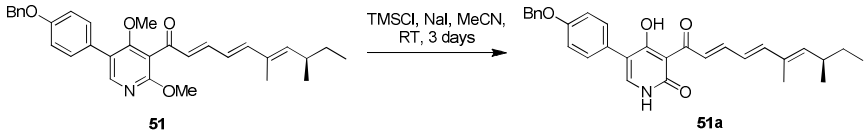
(0.1 mL) was added, and the mixture was kept at -78°C for 10 min. The reaction was then further quenched by the sequential addition of water (5 mL), and ethyl acetate (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 5% aq. sodium bicarbonate (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 1/1), to afford 14 mg (79%) of pretenellin **1**, as a yellow solid; $[\alpha]^{D}_{22.5}$ = -35.2 (c = 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, *J* = 15.2 Hz, 1H), 7.60 (d, *J* = 15.2 Hz, 1H), 7.50 (s, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.87 (d, *J* = 10.0 Hz, 1H), 2.53-2.64 (m, 1H), 1.94 (s, 3H), 1.47-1.53 (m, 1H), 1.34-1.45 (m, 1H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 194.6, 176.7, 163.2, 156.9, 150.3, 149.8, 138.9, 133.2, 130.0, 123.9, 123.3, 115.0, 114.7, 106.3, 35.0, 29.7, 19.1, 11.5, 10.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}NO_4Na$ $[M+Na]^+$ 376.1525; found 376.1532.



2,4-Dimethoxy-5-(4-(benzyloxy)phenyl)-3-((*R,2E,4E,6E*)-6,8-dimethyldeca-2,4,6-trienoyl)pyridine (51)

Sodium hydride (23 mg, 60 % in mineral oil, 0.57 mmol) was added to a solution of the key intermediate 3-Acetyl-5-(4-(benzyloxy)phenyl)-2,4-dimethoxypyridine **17** (65 mg, 0.19 mmol) in dry THF (3 mL) at 0 °C. After 30 min, the appropriate

aldehyde **34** (35 mg, 0.23 mmol) in dry THF (2 mL) was added at 0 °C, and the reaction mixture was stirred for 30 min and then warmed to room temperature stirred for 8 h. After that, the reaction was quenched with ice-water and extracted with EtOAc. The combined organic phase was washed with brine. After drying over Na_2SO_4 and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (n-hexane/EtOAc = 5/1) to afford product **51** as yellow oil (74 mg, 76%, E/Z >20:1); $[\alpha]^{D}_{22.5}$ = -16.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.32-7.44 (m, 7H), 7.04-7.12 (m, 3H), 6.61 (d, *J* = 15.2 Hz, 1H), 6.47 (d, *J* = 15.2 Hz, 1H), 6.35 (dd, *J* = 14.8, 10.8 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.11 (s, 2H), 3.94 (s, 3H), 3.51 (s, 3H), 2.38-2.44 (m, 1H), 1.81 (s, 3H), 1.35-1.40 (m, 1H), 1.24-1.31 (m, 1H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.84 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 163.1, 161.2, 158.4, 148.5, 148.2, 147.5, 146.3, 136.9, 132.8, 130.2, 130.1, 128.6, 128.1, 127.5, 127.4, 124.3, 124.2, 115.4, 115.0, 70.1, 61.0, 54.0, 34.9, 30.1, 20.3, 12.5, 12.0; HRMS (ESI) *m/z* calcd for $C_{32}H_{35}NO_4Na$ $[M+Na]^+$ 520.2464; found 520.2462.

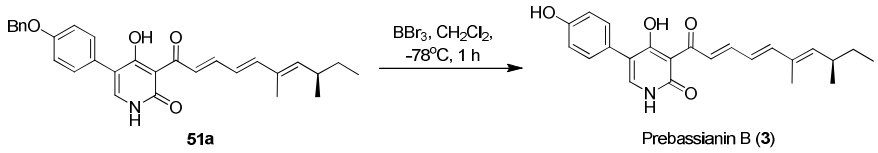


51 **51a**

(R,2E,4E,6E)-6,8-dimethyl1-[5-(p-benzyloxy-phenyl)-2,4-dihydroxypyridine-3-yl]-deca-2,4,6-trien-1-one (51a)

To a -20 °C solution of pyridine, **51** (48 mg, 0.089 mmol) in acetonitrile (11 mL) was added anhydrous sodium iodide (54 mg, 0.36 mmol) and trimethylsilyl chloride (35 µL, 0.27 mmol) and the reaction was slowly brought to room temperature over a

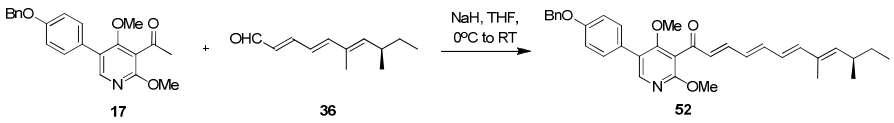
period of 4 h. The reaction was stirred for 3 days at room temperature, and then diluted with ethyl acetate (10 mL) and water (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with 5% aq. sodium bicarbonate (10 mL), water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 3/1) to afford 27 mg (60%) of the desired pyridone, **51a**, as a yellow solid; $[\alpha]^{D}_{22.5}$ = -24.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 17.74 (s, 1H), 11.87 (brs, 1H), 8.05 (d, *J* = 15.2 Hz, 1H), 7.71 (dd, *J* = 14.8, 11.2 Hz, 1H), 7.31-7.49 (m, 8H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 14.8 Hz, 1H), 6.49 (dd, *J* = 14.8, 11.2 Hz 1H), 5.56 (d, *J* = 9.6 Hz, 1H), 5.04 (s, 2H), 2.43-2.47 (m, 1H), 1.89 (s, 3H), 1.38-1.43 (m, 1H), 1.26-1.36 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 177.7, 164.4, 158.6, 148.9, 147.0, 146.4, 138.4, 136.9, 133.1, 130.3, 128.6, 128.0, 127.5, 126.9, 125.4, 125.2, 115.5, 114.8, 106.6, 70.1, 34.9, 30.2, 20.3, 12.5, 12.0; HRMS (ESI) *m/z* calcd for $C_{30}H_{31}NO_4Na$ $[M+Na]^+$ 492.2151; found 492.2151.



(R,2E,4E,6E)-6,8-dimethyl1-[5-(p-hydroxyphenyl)-2,4-dihydroxypyridine-3-yl]-deca-2,4,6-trien-1-one, prebassianin B (3)

A solution of pyridone, **51a** (26 mg, 0.05 mmol) in dichloromethane (10 mL) at -78 °C was treated dropwise with a 1 M solution of boron tribromide in dichloromethane (0.5 mL, 0.5 mmol). The reaction was then stirred at -78 °C for 1 h,

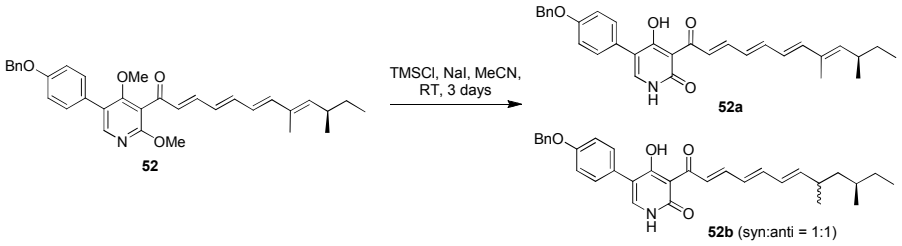
before methanol (0.1 mL) was added, and the mixture was kept at -78 °C for 10 min. The reaction was then further quenched by the sequential addition of water (5 mL), and ethyl acetate (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 5% aq. sodium bicarbonate (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 1/1), to afford 15 mg (64%) of prebassianin B **3**, as a yellow solid; $[\alpha]^{D}_{22.5}$ = -37.7 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, CD3OD) δ 7.87 (d, *J* = 14.8 Hz, 1H), 7.52 (dd, *J* = 14.8, 11.2 Hz, 1H), 7.35 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 15.2 Hz, 1H), 6.36 (dd, *J* = 15.2, 11.2 Hz, 1H), 5.48 (d, *J* = 9.6 Hz, 1H), 2.34-2.45 (m, 1H), 1.74 (s, 3H), 1.29-1.37 (m, 1H), 1.16-1.25 (m, 1H), 0.91 (d, *J* = 6.0 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD3OD) δ 193.9, 176.7, 163.0, 156.9, 148.0, 145.8, 145.5, 138.9, 133.1, 129.9, 127.2, 125.1, 123.9, 114.9, 114.7, 106.3, 34.7, 29.9, 19.3, 11.3, 11.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NO_4Na$ $[M+Na]^+$ 402.1681; found 402.1687.



2,4-Dimethoxy-5-(4-(benzyloxy)phenyl)-3-((R,2E,4E,6E,8E)-8,10-dimethyldodeca-2,4,6,8-tetraenoyl)pyridine (52)

Sodium hydride (23 mg, 60 % in mineral oil, 0.57 mmol) was added to a solution of the key intermediate 3-Acetyl-5-(4-(benzyloxy)phenyl)-2,4-dimethoxypyridine **17** (65 mg, 0.19 mmol) in dry THF (3 mL) at 0 °C. After 30 min, the appropriate

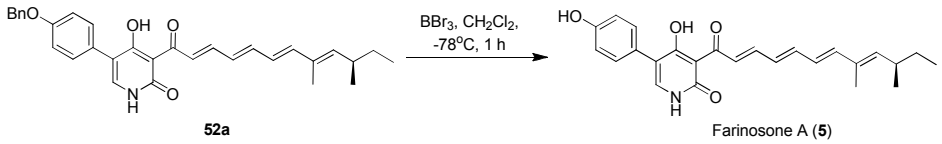
aldehyde **36** (41 mg, 0.23 mmol) in dry THF (2 mL) was added at 0 °C, and the reaction mixture was stirred for 30 min and then warmed to room temperature stirred for 8 h. After that, the reaction was quenched with ice-water and extracted with EtOAc. The combined organic phase was washed with brine. After drying over Na_2SO_4 and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (n-hexane/EtOAc = 5/1) to afford product **52** as yellow oil (78 mg, 78%, E/Z >20:1); $[\alpha]^{D}_{22.5}$ = -19.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.32-7.45 (m, 7H), 7.04-7.13 (m, 3H), 6.65 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.46 (d, *J* = 14.8 Hz, 2H), 6.41 (d, *J* = 13.6 Hz, 1H), 6.25 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.44 (d, *J* = 9.6 Hz, 1H), 5.11 (s, 2H), 3.95 (s, 3H), 3.51 (s, 3H), 2.39-2.46 (m, 1H), 1.79 (s, 3H), 1.36-1.43 (m, 1H), 1.24-1.31 (m, 1H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 163.1, 161.2, 158.5, 148.5, 146.5, 144.2, 143.7, 143.6, 136.9, 132.8, 130.2, 130.1, 129.2, 128.6, 128.1, 127.5, 127.4, 125.9, 124.2, 115.4, 115.0, 70.1, 61.1, 54.0, 34.8, 30.2, 20.4, 12.6, 12.0; HRMS (ESI) *m/z* calcd for $C_{34}H_{37}NO_4Na$ $[M+Na]^+$ 546.2620; found 546.2626.



(R,2E,4E,6E,8E)-8,10-dimethyl-1-[5-(p-benzyloxy-phenyl)-2,4-dihydroxypyridin e-3-yl]-dodeca-2,4,6,8-tetraen-1-one (52a) and 5-(4-(benzyloxy)phenyl)-3-((*2E,4E, 6E,10R*)-8,10-dimethyldodeca-2,4,6-trienoyl)-4-hydroxypyridin-2(1H)-one (52b)

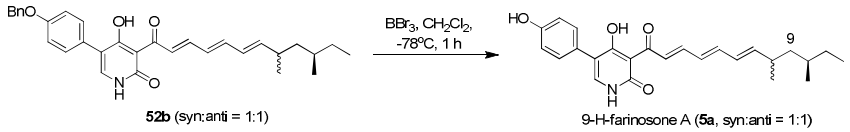
To a -20 °C solution of pyridine, **52** (47 mg, 0.089 mmol) in acetonitrile (11 mL) was added anhydrous sodium iodide (54 mg, 0.36 mmol) and trimethylsilyl chloride (35 μL, 0.27 mmol) and the reaction was slowly brought to room temperature over a period of 4 h. The reaction was stirred for 3 days at room temperature, and then diluted with ethyl acetate (10 mL) and water (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with 5% aq. sodium bicarbonate (10 mL), water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 3/1) to afford 10 mg (23%) of the desired pyridone **52a**, and 26 mg (58%) of the side product pyridone **52b** as a yellow solid; **52a**: $[\alpha]^{D}_{22.5}$ = -20.4 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 17.88 (s, 1H), 10.51 (brs, 1H), 8.06 (d, *J* = 15.2 Hz, 1H), 7.54 (dd, *J* = 14.8, 11.6 Hz, 1H), 7.35-7.58 (m, 8H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.81 (dd, *J* = 14.4, 10.4 Hz, 1H), 6.59 (dd, *J* = 14.8, 11.2 Hz 1H), 6.30 (dd, *J* = 15.2, 11.2 Hz, 1H), 5.14 (s, 2H), 2.46-2.48 (m, 1H), 2.84 (s, 3H), 1.26-1.37 (m, 1H), 1.09-1.16 (m, 1H), 0.87 (t, *J* = 7.2 Hz, 3H); HRMS (ESI) *m/z* calcd for $C_{32}H_{33}NO_4Na$ $[M+Na]^+$ 518.2307; found 518.2300. **52b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 17.66 (s, 1H), 11.67 (brs, 1H), 8.01 (d, *J* = 15.2 Hz, 1H), 7.65 (dd, *J* = 14.8, 11.6 Hz, 1H), 7.32-7.46 (m, 8H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.66 (dd, *J* = 14.4, 10.4 Hz, 1H), 6.46 (dd, *J* = 14.8, 11.2 Hz 1H), 6.17 (dd, *J* = 15.2, 11.2 Hz, 1H), 5.83 (dq, *J* = 15.2, 7.6 Hz, 1H), 5.10 (s, 2H), 2.32-2.36 (m, 1H), 1.26-1.37 (m, 3H), 1.09-1.16 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.80-0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 177.7, 164.2, 158.6, 148.9, 147.0, 146.8, 145.3,

138.4, 136.9, 130.2, 129.5, 128.6, 128.5, 128.0, 127.5, 125.4, 115.5, 114.9, 106.7, 70.1, 44.1, 35.0, 32.0, 29.9, 21.1, 19.3, 11.3; HRMS (ESI) *m/z* calcd for $C_{32}H_{35}NO_4Na$ $[M+Na]^+$ 520.2464; found 520.2445.



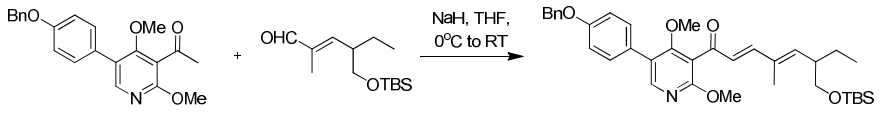
(*R,2E,4E,6E,8E*)-8,10-dimethyl-1-[5-(p-hydroxyphenyl)-2,4-dihydroxypyridine-3-yl]-dodeca-2,4,6,8-tetraen-1-one, farinosone A (5)[18d]

A solution of pyridone, **52a** (10 mg, 0.02 mmol) in dichloromethane (5 mL) at -78 °C was treated dropwise with a 1 M solution of boron tribromide in dichloromethane (0.2 mL, 0.2 mmol). The reaction was then stirred at -78 °C for 1 h, before methanol (0.05 mL) was added, and the mixture was kept at -78 °C for 10 min. The reaction was then further quenched by the sequential addition of water (5 mL), and ethyl acetate (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 5% aq. sodium bicarbonate (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 1/1), to afford 4 mg (61%) of farinosone A **5**, as a yellow solid; $[\alpha]^D_{22.5}$ = -18.0 (c = 0.25, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, J = 14.8, 1H), 7.66 (dd, J = 14.8, 11.6, 1H), 7.49 (s, 1H), 7.31 (d, J = 8.4, 2H), 6.82 – 6.87 (m, 3H), 6.54 – 6.61 (m, 2H), 6.41 (dd, J = 15.2, 10.4, 1H), 5.49 (d, J = 9.6, 1H), 2.52 – 2.55 (m, 1H), 1.84 (d, J = 0.8, 3H),1.44 – 1.53 (m, 1H), 1.33 – 1.38 (m, 1H), 1.01 (d, J = 6.8, 3H), 0.89 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 194.2, 176.9, 163.4, 156.9, 145.3, 144.1, 143.3, 133.1, 130.7, 130.0, 129.9, 128.4, 127.2, 125.9, 123.9, 115.0, 114.7, 36.2, 30.0, 20.0, 11.3, 10.9; HRMS (ESI) *m/z* calcd for $C_{25}H_{27}NO_4Na$ $[M+Na]^+$ 428.1838; found 428.1831.



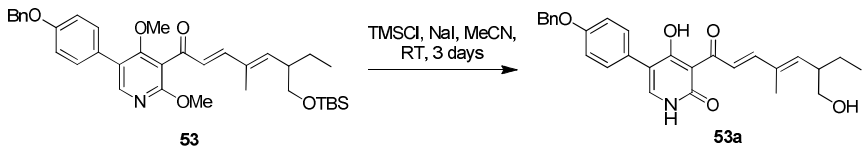
3-((*2E,4E,6E,10R*)-8,10-dimethyldodeca-2,4,6-trienoyl)-4-hydroxy-5-(4-hydroxyphenyl)pyridin-2(1H)-one, 9-H-farinosone A (5a)

A solution of pyridone, **52b** (26 mg, 0.05 mmol) in dichloromethane (10 mL) at -78 °C was treated dropwise with a 1 M solution of boron tribromide in dichloromethane (0.5 mL, 0.5 mmol). The reaction was then stirred at -78 °C for 1 h, before methanol (0.1 mL) was added, and the mixture was kept at -78 °C for 10 min. The reaction was then further quenched by the sequential addition of water (5 mL), and ethyl acetate (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 5% aq. sodium bicarbonate (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc = 1/1), to afford 15 mg (78%) of 9-H-farinosone A **5a**, as a yellow solid; ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, J = 15.2, 1H), 7.60 (dd, J = 15.6, 11.6, 1H), 7.46 (s, 1H), 7.28 (d, J = 8.4, 2H), 6.81 (d, J = 8.4, 2H), 7.31 (dd, J = 15.2, 11.2, 1H), 6.44 (dd, J = 15.6, 11.6, 1H), 6.25 (dd, J = 14.8, 10.8, 1H), 5.83 – 5.95 (m, 1H), 2.52 – 2.55 (m, 1H), 1.28-1.38 (m, 3H), 1.10-1.19 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H), 0.86-0.97 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 194.0, 176.7, 156.9, 147.4, 147.0, 145.2, 143.4, 143.3, 138.9, 129.2, 128.7, 128.3, 127.5, 123.9, 114.7, 43.9, 34.9, 31.9, 29.7, 20.2, 19.2, 18.4, 10.2; HRMS (ESI) *m/z* calcd for $C_{25}H_{29}NO_4Na$ $[M+Na]^+$ 430.1994; found 430.1996.



2,4-Dimethoxy-5-(4-(benzyloxy)phenyl)-3-((2E,4E)-6-(((tert-butyldimethylsilyl)oxy)methyl)-4-methylocta-2,4-dienoyl)pyridine (53)

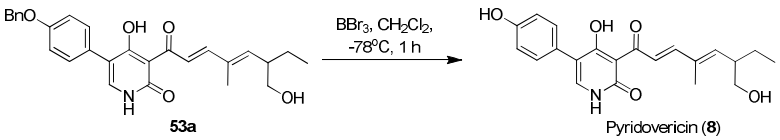
Sodium hydride (23 mg, 60 % in mineral oil, 0.57 mmol) was added to a solution of the key intermediate 3-Acetyl-5-(4-(benzyloxy)phenyl)-2,4-dimethoxypyridine **17** (65 mg, 0.19 mmol) in dry THF (3 mL) at 0°C. After 30 min, the appropriate aldehyde **44** (59 mg, 0.23 mmol) in dry THF (2 mL) was added at 0°C, and the reaction mixture was stirred for 30 min and then warmed up to room temperature stirred for 8 hours. After that, the reaction was quenched with ice-water and extracted with EtOAc. The combined organic phase was washed with brine. After drying over Na_2SO_4 and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (n-hexane/EtOAc = 5/1) to afford product **53** as yellow oil (82 mg, 73%, E/Z >20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.32-7.47 (m, 7H), 7.04-7.08 (m, 3H), 6.41 (d, J = 15.6 Hz, 1H), 5.69 (d, J = 10.0 Hz, 1H), 5.11 (s, 2H), 3.94 (s, 3H), 3.47-3.56 (m, 5H), 2.55-2.62 (m, 1H), 1.87 (s, 3H), 1.58-1.65 (m, 1H), 1.23-1.28 (m, 1H), 0.86 (s, 9H), 0.85 (t, J = 7.2 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 163.0, 161.2, 158.5, 151.6, 148.5, 146.4, 136.9, 134.6, 130.1, 128.6, 128.1, 127.5, 127.4, 126.5, 124.2, 115.5, 115.0, 70.1, 65.9, 61.1, 54.0, 43.8, 25.9, 24.3, 18.3, 13.0, 11.8, -5.4, -5.3; HRMS (ESI) *m/z* calcd for $C_{36}H_{47}NO_2SiNa$ $[M+Na]^+$ 624.3121; found 624.3114.



53 **53a**

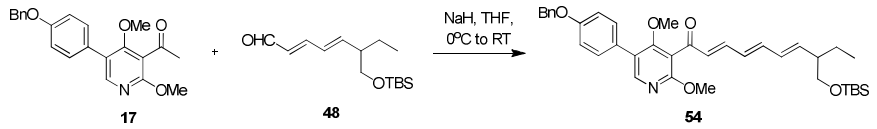
(2E,4E)-6-(Hydroxymethyl)-1-[5-(p-benzyloxy-phenyl)-2,4-dihydroxypyridine-3-yl]-4-methylocta-2,4-dien-1-one (53a)

To a -20°C solution of pyridine, **53** (53 mg, 0.089 mmol) in acetonitrile (11 mL) was added anhydrous sodium iodide (54 mg, 0.36 mmol) and trimethylsilyl chloride (35 µL, 0.27 mmol) and the reaction slowly brought to room temperature over a period of 4 h. The reaction was stirred for 3 days at room temperature, and then diluted with ethyl acetate (10 mL) and water (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with 5% aq. sodium bicarbonate (10 mL), water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 3/1) to afford 19 mg (47%) of the desired pyridone, **53a**, as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 17.58 (s, 1H), 10.81 (brs, 1H), 8.00 (d, J = 15.6 Hz, 1H), 7.65 (d, J = 15.2 Hz, 1H), 7.33-7.47 (m, 8H), 7.05 (d, J = 8.4 Hz, 2H), 5.84 (d, J = 10.0 Hz, 1H), 5.12 (s, 2H), 3.64-3.67 (m, 1H), 3.51-3.56 (m, 1H), 2.63-2.70 (m, 1H), 1.98 (s, 3H), 1.26-1.35 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 163.7, 160.4, 159.6, 158.6, 149.9, 145.5, 140.1, 136.9, 136.8, 130.2, 128.8, 128.6, 128.1, 127.5, 123.9, 115.5, 114.9, 70.1, 66.1, 43.9, 24.4, 13.3, 11.7; HRMS (ESI) *m/z* calcd for $C_{28}H_{29}NO_5Na$ $[M+Na]^+$ 482.1943; found 482.1943.



(*2E,4E*)-6-(Hydroxymethyl)-1-[5-(p-hydroxyphenyl)-2,4-dihydroxypyridine-3-yl] -4-methylocta-2,4-dien-1-one, pyridovericin (8)[38]

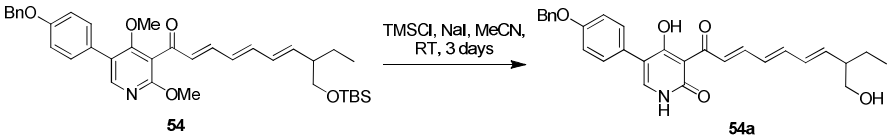
A solution of pyridone, **53a** (19 mg, 0.04 mmol) in dichloromethane (10 mL) at -78 °C was treated dropwise with a 1 M solution of boron tribromide in dichloromethane (0.4 mL, 0.4 mmol). The reaction was then stirred at -78 °C for 1 h, before methanol (0.1 mL) was added, and the mixture kept at -78 °C for 10 min. The reaction was then further quenched by the sequential addition of water (5 mL), and ethyl acetate (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 5% aq. sodium bicarbonate (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The crude residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 1/1), to afford 10 mg (72%) of pyridovericin **8**, as a yellow solid; ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (t, J = 15.6 Hz, 1H), 7.60 (d, J = 15.6 Hz, 1H), 7.47 (s, 1H), 7.29 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 9.6 Hz, 1H), 3.46-3.58 (m, 2H), 2.56-2.67 (m, 1H), 1.95 (s, 3H), 1.65-1.69 (m, 1H), 1.26-1.33 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 194.7, 176.8, 161.7, 156.9, 149.4, 145.9, 138.8, 135.8, 130.0, 124.0, 123.6, 114.7, 114.4, 106.4, 64.7, 43.7, 24.1, 11.9, 10.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{24}NO_5$ $[M+H]^+$ 370.1654; found 370.1658.



2,4-Dimethoxy-5-(4-(benzyloxy)phenyl)-3-((2E,4E,6E)-8-(((tert-butyldimethylsilyl)oxy)methyl)deca-2,4,6-trienoyl)pyridine (54)

Sodium hydride (23 mg, 60 % in mineral oil, 0.57 mmol) was added to a solution of the key intermediate 3-Acetyl-5-(4- (benzyloxy)phenyl)-2,4-dimethoxypyridine **17** (65 mg, 0.19 mmol) in dry THF (80 mL) at 0 °C. After 30 min, the appropriate aldehyde **48** (62 mg, 0.23 mmol) in dry THF (100 mL) was added at 0 °C, and the reaction mixture was stirred for 30 min and then warmed up to room temperature stirred for 8 h. After that, the reaction was quenched with ice-water and extracted with EtOAc. The combined organic phase was washed with brine. After drying over Na_2SO_4 and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (n-hexane/EtOAc = 5/1) to afford product **54** as yellow oil (82 mg, 71%, E/Z >30:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.34-7.47 (m, 7H), 7.02-7.09 (m, 3H), 6.58 (dd, J = 14.8, 10.8 Hz, 1H), 6.44 (d, J = 15.2 Hz, 1H), 6.34 (dd, J = 14.8, 11.2 Hz, 1H), 6.20 (dd, J = 15.2, 10.8 Hz, 1H), 5.80 (dd, J = 14.8, 8.4 Hz, 1H), 5.11 (s, 2H), 3.94 (s, 3H), 3.52-3.55 (m, 2H), 3.51 (s, 3H), 2.17-2.19 (m, 1H), 1.54-1.59 (m, 1H), 1.21-1.29 (m, 1H), 0.88 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 163.1, 161.2, 158.5, 151.6, 148.5, 146.6, 143.0, 136.9, 136.7, 130.9, 130.6, 130.1, 128.6, 128.1, 127.5, 127.4, 124.2, 115.3, 115.0, 70.1, 66.0, 61.1, 54.0, 47.6, 25.9, 23.8, 18.3, 11.7, -5.4, -5.3; HRMS (ESI) *m/z* calcd for $C_{37}H_{47}NO_2SiNa$ $[M+Na]^+$ 636.3121;

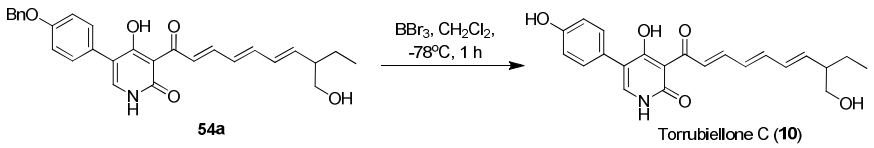
found 636.3122.



(2E,4E,6E)-8-(hydroxymethyl)-1-[5-(p-benzyloxy-phenyl)-2,4-dihydroxypyridine -3-yl]-deca-2,4,6-trien-1-one (54a)

To a -20°C solution of pyridine, **54** (55 mg, 0.089 mmol) in acetonitrile (11 mL) was added anhydrous sodium iodide (54 mg, 0.36 mmol) and trimethylsilyl chloride (35 µL, 0.27 mmol) and the reaction slowly brought to room temperature over a period of 4 h. The reaction was stirred for 3 days at room temperature, and then diluted with ethyl acetate (10 mL) and water (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with 5% aq. sodium bicarbonate (10 mL), water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 3/1) to afford 23 mg (53%) of the desired pyridone, **54a**, as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 17.62 (s, 1H), 10.97 (brs, 1H), 8.02 (d, J = 15.2 Hz, 1H), 7.63 (dd, J = 15.2, 11.6 Hz, 1H), 7.32-7.50 (m, 8H), 7.03 (d, J = 8.4 Hz, 2H), 6.68 (dd, J = 14.4, 10.8 Hz, 1H), 6.49 (dd, J = 15.2, 11.6 Hz, 1H), 6.30 (dd, J = 15.2, 11.2 Hz, 1H), 5.80 (dd, J = 15.2, 7.2 Hz, 1H), 5.10 (s, 2H), 3.63 (brs, 1H), 3.50-3.54 (m, 1H), 3.14-3.20 (m, 1H), 2.25-2.31 (m, 1H), 1.52-1.55 (m, 1H), 1.30-1.37 (m, 1H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 177.8, 168.8, 163.7, 158.6, 145.6, 142.6, 141.7, 138.3, 136.9, 132.4, 130.5, 130.2, 128.6, 128.1, 128.0, 127.5, 115.5, 114.9, 106.7, 70.1, 66.7, 47.6,

23.9, 11.7; HRMS (ESI) *m/z* calcd for $C_{29}H_{29}NO_5Na$ $[M+Na]^+$ 494.1943; found 494.1945.



(2E,4E,6E)-8-(hydroxymethyl)-1-[5-(p-hydroxyphenyl)-2,4-dihydroxypyridine-3-yl]-deca-2,4,6-trien-1-one, torrubiellone C (10)[3, 13]

A solution of pyridone, **54a** (23 mg, 0.05 mmol) in dichloromethane (10 mL) at -78°C was treated dropwise with a 1 M solution of boron tribromide in dichloromethane (0.5 mL, 0.5 mmol). The reaction was then stirred at -78°C for 1 h, before methanol (0.1 mL) was added, and the mixture was kept at -78°C for 10 min. The reaction was then further quenched by the sequential addition of water (5 mL), and ethyl acetate (5 mL). The phase was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 5% aq. sodium bicarbonate (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The crude residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 1/1), to afford 15 mg (78%) of torrubiellone C **10**, as a yellow solid; ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (d, J = 15.2 Hz, 1H), 7.60 (dd, J = 14.8, 11.2 Hz, 1H), 7.46 (s, 1H), 7.28 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 6.76 (dd, J = 14.8, 11.2 Hz, 1H), 6.46 (dd, J = 14.8, 11.2 Hz, 1H), 6.31 (dd, J = 15.2, 11.2 Hz, 1H), 5.86 (dd, J = 15.2, 8.8 Hz, 1H), 3.46-3.55 (m, 2H), 2.18-2.26 (m, 1H), 1.54-1.64 (m, 1H), 1.28-1.35 (m, 1H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 194.0, 176.7, 156.9, 145.0, 143.0, 142.2, 139.0, 131.5, 130.0, 129.5, 127.8, 123.9, 114.9, 114.7, 106.3,

64.7, 60.1, 23.6, 13.1, 10.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{24}NO_5$ $[M+H]^+$ 382.1654; found 382.1655.

Biological Methods

Cell Lines Culture. Jurkat human T-cell acute lymphoblastic leukemia cells, SNU-16 stomach carcinoma, HeLa human cervical carcinoma, MCF-7 human breast carcinoma, A549 human lung carcinoma, HCT-116 human colorectal carcinoma, and were purchased from American Type Cell Collection, ATCC (Rockville, MP). HeLa, MCF-7, A549, HCT-116 and HeLa were cultured in Dulbecco's modified Eagles medium (DMEM) containing 1% (v/v) Penicillin/Streptomycin (PS) and 10% (v/v) fetal bovine serum (FBS) (Hyclone, Logan, UT). Jurkat and SNU-16 was cultured in RPMI-1640 (Hyclone, Logan, UT) supplemented with 1% (v/v) PS and10% (v/v) FBS. The cells were cultured in humidified 95% O2/ 5% CO2 atmosphere incubator at 37 °C. Etoposide was purchased from Sigma Aldrich.

Cell Viability Assays. All assays were performed in triplicate. HeLa, MCF-7, A549 and HCT-116 cells were trypsinized and seeded at a density of 5.0 x 103 per well into 96-well plate and incubated for 24 h while Jurkat and SNU-16 cells were seeded at a density of 10.0 x 103 into 96-well plate. Cells were treated with test compound which have been prepared as stock solution solubilized in DMSO to provide the concentration range of 100 nM to 200 μM. After incubating for 48 h, inherent cells with DMEM were removed, washed with PBS followed by addition of 100 μL of DMEM and 15 μL of MTS while suspension cells were added directly with 15 μL of MTS. Cells were then further incubated until colour change was observed before

reading the absorbance at 490 nm. The absorbance value of control wells where no drug was added was set to 100% cell viability and from this graphs of absorbance versus cell density per well, cell viability were assessed through graphs of percentage cell viability versus log concentration of test compound added and the IC50 values for the various cancer cell line were calculated according to the sigmoidal inhibition curve using software Graphpad prism 5. CellTiter96® Aqueous One Solution Cell Proliferation Assay (MTS) was purchased from Promega Corporation (WI, USA). Absorbance was measured using the BIO-RAD Benchmark Plus microplate reader spectrophotometer at 490nm.

Apoptosis Assays. Jurkat cells control and treated cell were done by using a 6 well plate where cells were seeded and incubated at 37 °C in 95% O_2/ 5% CO_2 for 24 h. It was then treated with test compound at 20 μM and re-incubated for another 48 h. The apoptosis was examined using Annexin-V-FLUOS Staining Kit from Roche (Indianapolis, IN) where treated and control cells were washed with PBS, typsinized and collected and then treated with 100 μL of incubation buffer containing 2 μL of Annexin-V-FLUOS solution and 2 μl of propidium iodide solution. After incubated for 30 min in the dark at room temperature, 500 μL of incubation buffer was added and the cells were analyzed by using BD LSR II flow cytometry.

3.5 References

1. (a) D. J. Newman and G. M. Cragg, *J. Nat. Prod.* 2007, **70**, 461–477; (b) K. C. Nicolaou and T. Montagnon, *Molecules that Changed the World,* Wiley-VCH: Weinheim, 2008; (c) P. Va, E. L.

Campbell, W. M. Robertson and D. L. Boger, *J. Am. Chem. Soc.* 2010, **132**, 8489–8495.

2. Review: H. J. Jessen and K. Gademann, *Nat. Prod. Rep.* 2010, **27**, 1168–1185.
3. M. Isaka, P. Chinthanom, S. Supothina, P. Tobwor and N. L. Hywel-Jones, *J. Nat. Prod.* 2010, **73**, 2057–2060.
4. D. R. Williams and S.-Y. Sit, J. Org. Chem., 1982, 47, 2846–2851.
5. J. H. Rigby and M. Qabar, *J. Org. Chem.* 1989, **54**, 5852–5853.
6. Q. Zhang, A. Rivkin and D. P. Curran, *J. Am. Chem. Soc.* 2002, **124**, 5774–5781.
7. Jack E. Baldwin Org.Lett. 2002, 4, 2125; *Tetrahedron* 60 (2004) 9307–9317.
8. A. Furstner, F. Feyen, H. Prinz and H. Waldmann, *Angew. Chem. Int. Ed.* 2003, **42**, 5361–536; (b) *Tetrahedron* 60 (**2004**) 9543.
9. D. R. Williams, D. C. Kammler, A. F. Donnell and W. R. F. Goundry, *Angew. Chem. Int. Ed.* 2005, **44**, 6715–6718.
10. Brigitte Renoux *Tetrahedron Letters* 47 (**2006**) 9305–9308.
11. Sugawara,K. *Heterocycles*,**2007**,71,597-607
12. H. J. Jessen, A. Schumacher, T. Shaw, A. Pfaltz and K. Gademann, *Angew. Chem. Int. Ed.* 2011, **50**, 4222–4226.
13. H. J. Jessen, A. Schumacher, F. Schmid, A. Pfaltz and K. Gademann, *Org. Lett.* 2011, **13**, 4368–4370.
14. a) G. M. Cragg, D. J. Newman, K. M. Snader, *J. Nat. Prod.* **1997**, *60*, 52–60; b) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461–477; c) A. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477–1489; d) K. C. Nicolaou, T. Montagnon, *Molecules that Changed the World,* Wiley-VCH: Weinheim, 2008; e) K. C. Nicolaou, J. S. Chen, S. M. Dalby, *Bioorg. Med. Chem.* **2009**, *17*,

2290–2303. f) P. Va, E. L. Campbell, W. M. Robertson, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 8489–8495.

15. For recent selected examples following the logic of "convergent total synthesis", see: a) M. Sasaki, H. Fuwa, *Nat. Prod. Rep.* **2008**, *25*, 401–426; b) R. Matsui, K. Seto, Y. Sato, T. Suzuki, A. Nakazaki, S. Kobayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 680–683; c) J. E. DeLorbe, S. Y. Jabri, S. M. Mennen, L. E. Overman, F. L. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 6549–6552; d) K. L. Wu, E. V. Mecado, T. R. R. Pettus, *J. Am. Chem. Soc.* **2011**, *133*, 6114–6117; e) D. H. Wang, J. Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 5767–5769.

16. For examples following the logic of "diverted total synthesis", see: a) C. Gaul, J. T. Njardarson, S. J. Danishefsky, *J. Am. Chem. Soc.* **2003**, *125*, 6042-6043; b) J. T. Njardarson, C. Gaul, D. Shan, X.-Y. Huang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 1038-1040; c) C. Gaul, J. T. Njardarson, D. Shan, D. C. Dorn, K.-D. Wu, W. P. Tong, X.-Y. Huang, M. A. S. Moore, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 11326-11337; d) D. Shan, L. Chen, J. T. Njardarson, C. Gaul, X. Ma, S. Danishefsky, X.-Y. J. Huang, *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 3772-3776; e) R. M. Wilson, S. J. Danishefsky, *J. Org. Chem.* **2006**, *71*, 8329–8351; f) R. M. Wilson, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2010**, *49*, 6032-6056; g) A. M. Szpilman, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 9592–9628; h) A. Furstner, D. Kirk, M. D. B. Fenster, C. Aissa, D. De Souza, O. Muller, *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8103–8108; i) A. Furstner, D. De Souza, L. Turet, M. D. B. Fenster, L. Parra-Rapado, C. Wirtz, R. Mynott, C. W. Lehmann, *Chem. Eur. J.* **2007**, *13*, 115–134; j) A. Furstner, D. Kirk, M. D. B. Fenster, C. Aissa, D. De Souza, C. Nevado, T. Tuttle, W. Thiel, O. Muller, *Chem. Eur. J.* **2007**, *13*, 135–149; k) A. Furstner, E. Kattnig, G. Kelter, H.-H. Fiebig, *Chem. Eur. J.* **2009**, *15*, 4030–4043; l) A. Furstner, *Isr. J. Chem.*

2011, *51*, 329–345.

17. The terms of "gateway synthesis" and "collective synthesis" are often used with the similar meanings, selected examples see: a) P. A. Wender, N. Buschmann, N. B. Cardin, L. R. Jones, C. Kan, J. M. Kee, J. A. Kowalski, K. E. Longcore, *Nature Chem.* **2011**, *3*, 615–619; b) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183–188.

18. (a) S. Takahashi, N. Kakinuma, K. Uchida, R. Hashimoto, T. Yanagisawa and A. Nakagawa, *J. Antibiot.* 1998, **51**, 596–598; (b) K. Schmidt, U. Riese, Z. Li and M. Hamburger, *J. Nat. Prod.* 2003, **66**, 378–383; (c) L. M. Halo, M. N. Heneghan, A. A. Yakasai, Z. Song, K. Williams, A. M. Bailey, R. J. Cox, C. M. Lazarus and T. J. Simpson, *J. Am. Chem. Soc.,* 2008, **130**, 17988–17996; (d) Y. Cheng, B. Schneider, U. Riese, B. Schubert, Z. Li and M. Hamburger, *J. Nat. Prod.*, 2004, **67**, 1854–1858; (e) M. Isaka, P. Chinthanom, S. Supothina, P. Tobwor and N. L. Hywel-Jones, *J. Nat. Prod.* 2010, **73**, 2057–2060.

19. a) D. R. Williams, M. L. Bremmer, D. L. Brown and J. D'Antuono, *J. Org. Chem.*, **1985**, *50*, 2809–2810; b) A. T. Nielsen, W. J. Houlihan, *Org. React.* **1968**, *16*, 1–438; T. Mukaiyama, *Org. React.* **1982**, *28*, 203–331; c) R. Mahrwald, *Modern Aldol Reactions,* Wiley-VCH: Weinheim, 2004.

20. a) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.*, **2003**, *125*, 11818–11819; b) A. Bermejo, A. Ros, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.*, **2008**, *130*, 15798–15799; c) A. S. Guram, X. Wang, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli, *J. Org. Chem.*, **2007**, *72*, 5104–5112; d) S. Li, Y. Lin, J. Cao, S. Zhang, *J. Org. Chem.*, **2007**, *72*, 4067–4072; e) J. Han, Y. Liu, R. Guo, *J. Am. Chem. Soc.*, **2009**, *131*, 2060–2061.

21. K. Kanai, I. Sakamoto, S. Ogawa, T. Suami, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1529-1531.

22. S. R. Piettre, C. Andre, M. C. Chanal, J. B. Ducep, B. Lesur, F. Piriou, P. Raboisson, J. M. Rondeau, C. Schelcher, P. Zimmermann, A. J. Ganzhorn, *J. Med. Chem.* **1997**, *40*, 4208-4221.

23. a) J. E. Baldwin, R. M. Adlington, A. Conte, N. R. Irlapati, R. Marquez, G. J. Pritchard, *Org. Lett.* **2002**, *4*, 2125-212; b). N. R. Irlapati, R. M. Adlington, A. Conte, G. J. Pritchard, R. Marquez, J. E. Baldwin, *Tetrahedron* **2004**, *60*, 9307–9317.

24. D. Adone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem.* **1997**, *62*, 7170-7173.

25. I. L. Jones, F. K. Moore, C. L. L. Chai, *Org. Lett.* **2009**, *11*, 5526–5529.

26. a) D. A. Evans, D. L. Rieger, M. T. Bilodeau, F. Urpi, *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049; b) M. M. Hansen, H. Danda, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 173–181; c) J. D. White, A. T. Johnson; *J. Org. Chem.* **1994**, *59*, 3347–3358.

27. a) J. D. White, A. T. Johnson, *J. Org. Chem.* **1990**, *55*, 5938–5940; b) J. D. White, A. T. Johnson, *J. Org. Chem.* **1994**, *59*, 3347–3358; c) M. G. Organ, Y. V. Bilokin, S. Bratovanov, *J. Org. Chem.* **2002**, *67*, 5176–5183; d) W. R. Leonard, K. M. Belyk, D. R. Bender, D. A. Conlon, D. L. Hughes, P. J. Reider, *Org. Lett.* **2002**, *4*, 4201–4204; e) Negishi, E. I. Tan, Z. Liang, B. Novak, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5782–5787.

28. W. D. Horner, W. S. Wadsworth, *J. Am. Chem. Soc.* **1961**, *83*, 1733– 1738.

29. K. E. Henegar, S. W. Ashford, T. A. Baughman, J. C. Sih, R. L. Gu, *J. Org. Chem.* **1997**, *62*, 6588-6597.

30. D. E. Ward, Y. Gai, B. F. Kaller, *J. Org. Chem.* **1995**, *60*, 7830-7836.

31. The trace of Z-isomers could be removed carefully by the process of chromatography.

32. M. Isaka, P. Chinthanom, S. Supothina, P. Tobwor, N. L. Hywel-Jones, *J. Nat. Prod.* **2010**, *73*, 2057–2060.

33. a) M. Sato, N. Kanuma, T. Kato, *Chem. Pharm. Bull.* **1982**, *30*, 1315-1321; b) M. Sato, N. Yoneda, C. Kaneko, *Chem. Pharm. Bull.* **1986**, *34*, 621-627.

34. a) J. E. Baldwin, R. M. Adlington, A. Conte, N. R. Irlapati, R. Marquez, G. J. Pritchard, *Org. Lett.* **2002**, *4*, 2125-212; b). N. R. Irlapati, R. M. Adlington, A. Conte, G. J. Pritchard, R. Marquez, J. E. Baldwin, *Tetrahedron.* **2004**, *60*, 9307-9317.

35. M. M. Hansen, H. Danda, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 173–181; b) J. D. White, A. T. Johnson; *J. Org. Chem.* **1994**, *59*, 3347-3358.

36. Q. Zhang, A. Rivkin and D. P. Curran, *J. Am. Chem. Soc.*, **2002**, *124*, 5774–5781.

37. L. M. Halo, M. N. Heneghan, A. A. Yakasai, Z. Song, K. Williams, A. M. Bailey, R. J. Cox, C. M. Lazarus, T. J. Simpson, *J. Am. Chem. Soc.,* **2008**, *130*, 17988–17996.

38. S. Takahashi, N. Kakinuma, K. Uchida, R. Hashimoto, T. Yanagisawa, A. Nakagawa, *J. Antibiot.* **1998**, *51*, 596–598.

Chapter 4 The Asymmetric Total Synthesis of Torrubiellone B and *N*-deoxymillilarione A

4.1 Introduction

Pyridone alkaloids, which comprise a small group of fungal metabolites, possess an expansive repertoire of biological activities intimately mirroring their structural diversity, ranging from antifungal, antibacterial, insecticidal and cytotoxic activity to the induction of neurite outgrowth in different cell assays.[1] From a general point of view, pyridone alkaloids are attractive targets for total syntheses because of their unique 3,5-disubstituted-4-hydroxy-pyridone structure, their various biological and chemical properties, and the difficulties in obtaining them in pure forms from natural sources. More than 50 pyridone alkaloids with related structures are known, and synthetic pathways to these molecules have been investigated extensively.[2] Previous targets in this class of natural products, including tenellin (**1**),[3a] bassianin (**2**),[3b] farinosone A and B (**3**, **4**),[3c] militarinone D (**5**),[3d] pyridovericin (**6**)[3e] (Figure 1) have focused on the construction of 4-hydroxy-5-phenyl-2-pyridone skeletons *via* palladium-mediated C-C bond formation at the C5-position. Few examples focused on 4-hydroxy-5-alkyl-2-pyridone skeletons such as those present in N-deoxymilitarinone A (**8**),[4a] militarinone A (**9**),[4b] torrubiellones A and B (**11**, **10**),[4c] militarinone E and F (**12**, **13**)[4d] (Figure 1) and thus syntheses to this sub class of natural products remain a challenge. Notably, the only example of total synthesis of 4-hydroxy-5-alkyl-2-pyridones including apiosporamide and YM-215343 to date was accomplished elegantly by Williams and co-workers in 2005.[5]

N-deoxymilitarinone A, a new pyridone alkaloid member of militarinone family, was initially isolated by bioassay-guided fractionation from the mycelium of the entomogenous fungus Paecilomyces farinosus RCEF 0097 by Hamburger and co-workers in 2006. It displayed neurite sprouting in PC 12 cells when tested at 33 and 100 μM concentrations while a cytotoxic effect was observed in human neurons (IMR-32) at a concentration of 100 μM.[4a] Torrubiellones A and B (**10** and **11**), which are new pyridone alkaloids, were recently isolated from the spider pathogenic fungus Torrubiella sp. BCC 2165 by Isaka and co-workers. Torrubiellone A (1) exhibited antimalarial activity with an IC 50 value of 8.1 μM, while very weak cytotoxic activity was shown.[4c] To date, no total synthesis or synthetic approach to pyridone alkaloids **8**-**13** has been reported.

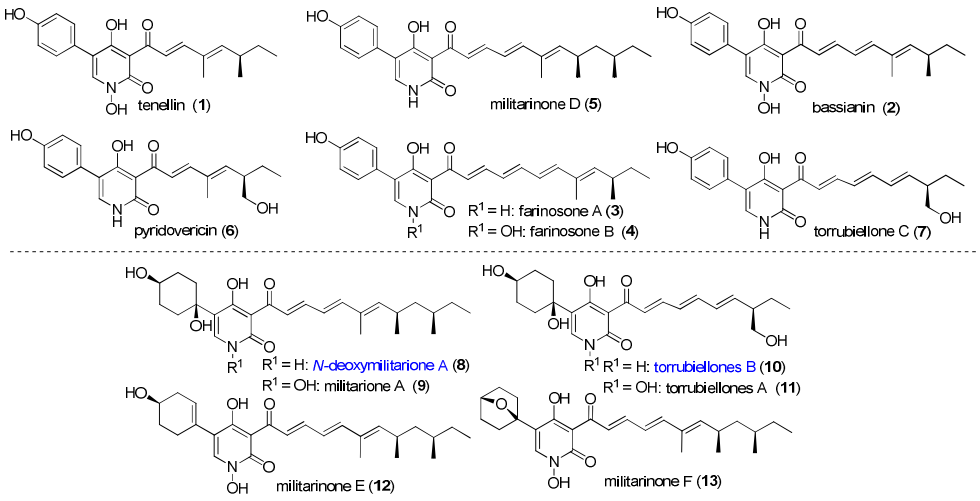


Figure 1. Selected members of the pyridone alkaloids family

4.2 Results and Discussion

Since pyridone alkaloids possess a similar core structure and differ only in their structure of polyene chain and substitution pattern, we implement a strategy that

exploits diverted total synthesis to focus on increasing structural and library diversity in a more efficient manner, constructing future pyridone analogues syntheses for biological studies. Indeed, these targets are perfect for application of a unified approach as recently demonstrated by Gademann and co-workers *via* a Horner-Wadsworth-Emmons (HWE) reaction on a densely functionalized pyridone β-ketophosphonate.[6] Herein we report the successful development of a strategy that has enabled completion of the first asymmetric total synthesis of *N*-deoxymilitarinone A (**8**) and torrubiellones B (**10**), devising the route for maximum flexibility of future forays into analogue synthesis. The general concept and synthetic strategy for this total synthesis was illustrated in Figure 2. With regard to the final construction of target molecules, the key step in this synthesis involves aldol condensation of the key advanced intermediate **14** with appropriately functionalized conjugated aldehydes, which is expected to give the desired *E* isomers in high yields.[7] Importantly, an additional challenge is the stereoselective construction of the core skeleton of 4-hydroxy-5-alkyl-2-pyridone. We envisioned that the key advanced intermediate would be constructed by a stereoselective alkylation at the 5-position of the pyridone *via* Directed ortho Metalation (DoM) process using methoxymethyl group (MOM) as Directed Metalation Groups (DMGs)[8]. To the best of our knowledge, such an approach has never been applied in the numerous reported total syntheses of pyridone alkaloids. Retrosynthetic simplification of alcohol **16** based on a secondary DoM reaction process for regioselective alkylation leads to precursor **17**, which is in turn obtainable by the protection of 4-hydroxy-2- pyridone. The brevity of this synthetic

approach coupled with the simplicity of the precursors in term of structure compelled us to embark on its implementation.

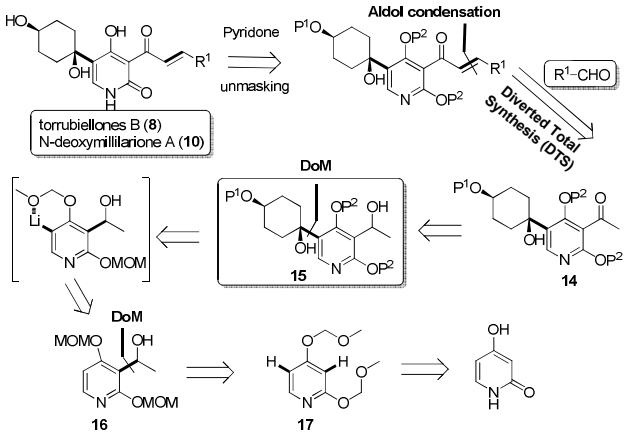
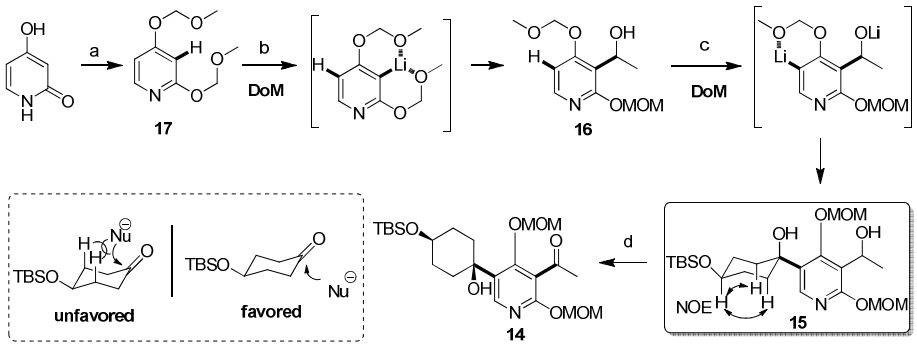


Figure 2. Retrosynthetic strategy for 4-hydroxy-5-alkyl-2-pyridone alkaloids.

In our synthesis, the first challenge was the choice of the appropriate protecting group along with the DMGs for the hydroxy group on the pyridone ring (Scheme 1). Standard silyl protecting groups, such as TBS, as well as alkyl-containing groups, such as Me, Bn or PMB, tertiary amide and carbamate DMGs such as OPiv or $OCONEt_3$, led to decomposition during isolation or on their removal. Finally, we found that the methoxymethyl group (MOM) proved ideal for our purposes. Ultimately, we were able to achieve regioselective orhto-lithiation at C-3 postion without affecting C-5 position of 2,4-protected pyridone in the presence of the MOM as directing group followed by addition to acetaldehyde. We are pleased to find that only C3-substituted alcohol **16** was observed with 45% yield when the reaction mixtures was treated with 1.9 equiv. of *t*-BuLi.[9] The corresponding alcohol **16** obtained, provided another challenge for stereoselective C-C bond formation at C-5

position of 2,4-protected pyridone. Reaction with 4-(*tert*-butyldimethylsilyloxy) cyclohexanone *via* secondary DoM strategy and using MOM as DMGs, is probably the most difficult part in this proposed total synthesis protocol. First, we tried to utilize the same strategy of DoM reaction using MOM as the directing group for the C-C formation on C3 that we have successfully developed in the initial DoM reactions. Not surprisingly, only trace amount of the desired product **15** was detected by treating with different lithium reagents such as *n*-BuLi, *s*-BuLi, *t*-BuLi, PhLi and MESLi, as well as organomagnesium reagent such as *i*-PrMgCl. To enhance the reactivity and stereoselectivity of this reaction, TMEDA was added as ligand in the presence of 4 equiv. of *n*-BuLi. However, the reaction proceeded to give poor yield (23%) of the desired product. Further optimization revealed 4 equiv. of ligand TMEDA coordinated with 4 equiv. of *s*-BuLi at -60 ^{o}C as the ideal condition for this transformation, giving a moderate yield (44%) and good stereoselectivity (syn : anti = 10:1) as determined by 2D NMR spectroscopy studies (Table 1).[10] Notably, around 40% of the starting material was recovered from the reaction which was subjected to the same reaction again. The stereoselectivity can be explained by the steric hindrance due to 1,3-diaxial interactions caused by the bulky incoming nucleophile, resulting in a more preferable attack from the equatorial position rather than axial position. Subsequently, a final oxidation of the alcohol **15** provided the desired key intermediate ketone **14.**



Scheme 1. Synthesis of the key advanced intermediate pyridone unit **14**. Reagent and conditions: a) MOMCl, NaH, THF, 73%; b) acetaldehyde, *t*-BuLi (1.9 equiv.), THF, -78 °C, 45%; c) table 1; d) DMP, py., MeCN, RT, 8 h, 83%. MOM = methoxymethyl, TBS = tert-butyldimethylsilyl, Bu = butyl, DMP = Dess-Martin periodinane, Py. = pyridine, THF = tetrahydrofuran, RT = room temperature.

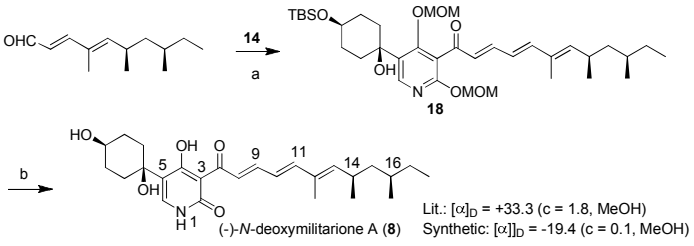
Table 1. Optimization of the DoM reaction with **15** and (tert-butyldimethylsilyloxy) cyclohexanone

Reagents	Temp. (^{o}C)	Yield[a]	Syn:anti[b]
n-BuLi (4 equiv.)	-78 to r.t.	trace	n.d.
s-BuLi (4 equiv.)	-78 to r.t.	trace	n.d.
t-BuLi (4 equiv.)	-78 to r.t.	trace	n.d.
MESLi (4 equiv.)	-78 to r.t.	trace	n.d.
i-PrMgCl	-78 to r.t.	trace	n.d.
n-BuLi (4 equiv.) + TMEDA (4 equiv.)	-78 to r.t.	23	6:1
n-BuLi (4 equiv.)+ HMPA (4 equiv.)	-78 to r.t.	11	5:1
s-BuLi (4 equiv.) + TMEDA (4 equiv.)	-78 to r.t.	34	9:1
t-BuLi (4 equiv.) + TMEDA (4 equiv.)	-78 to r.t.	18	10:1
s-BuLi (4 equiv.) + TMEDA (4 equiv.)	-30 to r.t.	complex	n.d.
s-BuLi (4 equiv.) + TMEDA (4 equiv.)	-60 to r.t.	41	10:1

[a] Isolated yield. [b] The ration determined by crude ^{1}H NMR.

The first step in the late stage of the synthesis focused on the construction of the C=C *via* aldol condensation of the pyridone core structures with polyene aldehyde chain which constitutes the key step in the synthetic route (Scheme 3).[7] We found that the aldol condensation step is prone to a range of side reactions. After careful optimization of the reaction parameters, the formation of byproducts is almost completely suppressed. The optimum condition required the use of 3 equivalents of

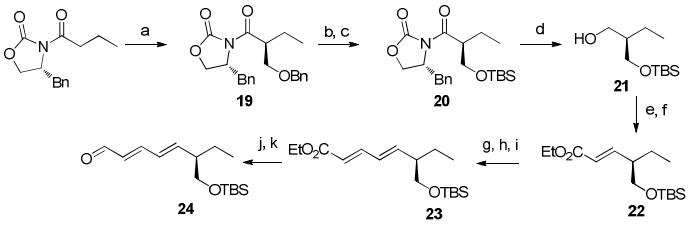
NaH in a degassed THF at 0 °C with a 1:1.2 ratio of ketone **14** to aldehyde. The targeted protected natural product **18** was finally obtained after few hours with good yield and good *E/Z* selectivity (10:1). Notably, this pyridone intermediate has the provision to react with other side chains aldehydes to access to 4-hydroxy-5-phenyl-2-pyridone analogues under similar protocol. Finally, the subsequent cleavage of protecting groups was effected using TsOH to generate the synthetic natural product *N*-deoxymilitarinone A (**8**). The analytical data of the synthetic material were found to be identical in all respects in comparison with the published values,[4a] except for the inverted $[\alpha]_D$ value. The configuration of naturally occurring (+)-*N*-deoxymilitarinone A (**8**) is therefore assigned as (14S, 16S).



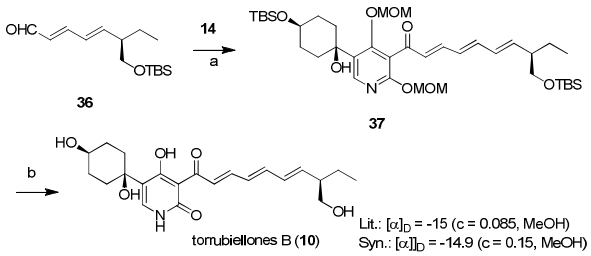
Scheme 3. Completion of the total synthesis of *N*-deoxymilitarinone A (**8**). Reagent and conditions: a) NaH, THF, 0 °C to RT, 2 h, 61%; b) TsOH, THF-H_2O, RT, overnight, 59%.

Synthesis established for *N*-deoxymillitarione A, but using a different side chain aldehyde **24**, was also utilized for the synthesis of torrubiellones B. Starting from auxiliary (*R*)-4-benzyl-3-butyryloxazolidin-2-one, the same approach (diastereoselective alkylation, Wittig olefination, ester reduction, and Swern oxidation) was applied to prepare aldehyde **24**,[15] which would be subjected to aldol condensation (Scheme 4). Coupling the side chain with MOM-protected pyridone **14**

delivered, after deprotection, the expected natural product torrubiellones B (**10**) (Scheme 5). All the spectroscopic data were in good agreement with those obtained from the authentic sample.



Scheme 4. Synthesis of the side-chain aldehyde **24**. Reagent and conditions: a) benzyl chloromethyl ether, $TiCl_4$, TEA, DCM, 0 °C, 3 h; b) Pd/C, H_2, RT, 24 h, 84%, for 2 steps; c) TBSCl, DMAP, TEA, DCM, 0 °C to RT, 12 h, 97%; d) $LiBH_4$, Ether-MeOH, THF, -78 °C, 2 h, 86%; e) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C; f) Ph_3PCHCO_2Et, DCM, RT, overnight, 77% (over 2 steps); g) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 95%; h) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C; i) Ph_3PCHCO_2Et, DCM, RT, overnight, 69% for 2 steps; j) DIBAL-H, CH_2Cl_2, -78 °C, 2 h, 86%; k) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 96%.

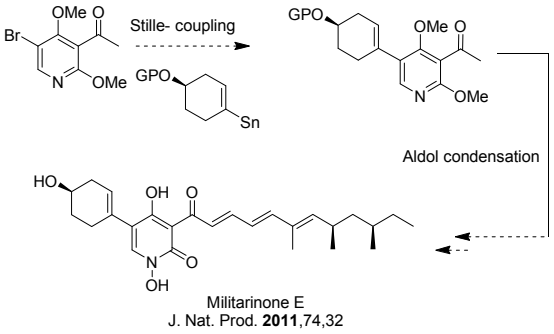


Scheme 5. Completion of the total synthesis of torrubiellones B (**10**). Reagent and conditions: a) NaH, THF, 0 °C to RT, 2 h, 65%; b) TsOH, THF-H_2O, RT, overnight, 47%.

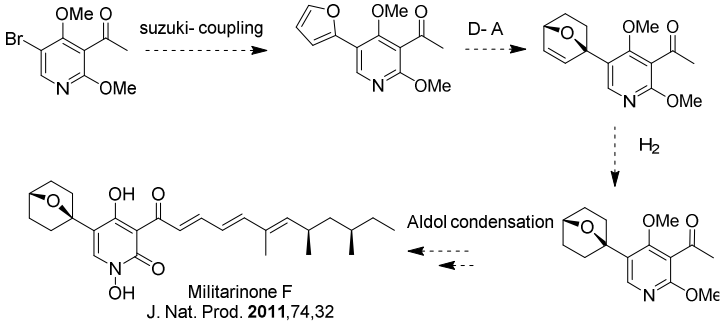
4.3 Conclusion

With this synthetic approach in hand, future work will concentrate on the extension towards the total synthesis of other structurally-similar natural product such as militarione E (scheme 6) and militarinone F (scheme 7). We believed that this work could be used to generate a library of pyridone alkaloid analogues and set up the stage

for in-depth structure–activity relationships studies. The future effort will be focused on the total synthesis directed to demonstrate the applicability of the method to synthesis some complex natural products and drug molecules.



Scheme 6. Route to the total synthesis of Militarinone E.



Scheme 7. Route to the total synthesis of Militarinone F.

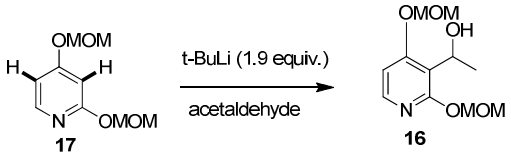
In conclusion, we have reported a modular assembly for the efficient synthesis of a family of sensitive polyene pyridone alkaloids *N*-deoxymilitarinone A (**8**) and torrubiellones B (**10**). Notable elements in this divergent synthetic route include the following: 1) the common intermediate **14** was first assembled by dual Directed ortho Metalation (DoM) process using MOM as Directed Metalation Groups (DMGs), and 2) assembly of the polyenes under aldol condensation for DTS in few general steps.

4.4 Experimental Section

17

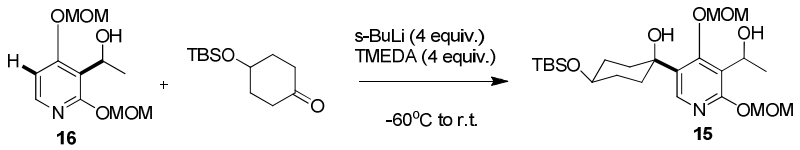
2,4-bis(methoxymethoxy)pyridine (17)

NaH (2.0 g, 50.0 mmol, 5 equiv.) was added to a solution of 2,4-dihydroxypyridone (1.1 g, 10.0 mmol) in DMF (20 mL) at 0 °C. Chloromethyl methyl ether (2.28 mL, 30.0 mmol, 3 equiv.) was added dropwise after which the solution was stirred for 30 min. The reaction mixture was stirred overnight at 0 °C. Aqueous ammonium chloride solution (10 mL) was added to quench the reaction at the same temperature which was subsequently allowed to warm to ambient temperature and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (25 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the residue, which was purified by column chromatography to afford the title compound **17** as a colorless oil (1.45 g, 73%): R_f = 0.4 (ethyl acetate/hexane = 5:1), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, *J* = 5.6 Hz, 1H), 6.58 (dd, *J* = 6.0, 2.0 Hz, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 5.46 (s, 2H), 5.17 (s, 2H), 3.49 (s, 3H), 3.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 164.4, 147.9, 107.3, 97.1, 93.8, 91.9, 57.0, 56.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_9H_{13}NO_4Na$ 222.0742, found 222.0738.



1-(2,4-bis(methoxymethoxy)pyridin-3-yl)ethanol (16)

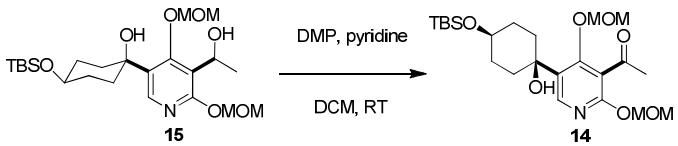
2,4-bis(methoxymethoxy)pyridine **17** (1.31 g, 6.58 mmol) was dissolved in THF (13 mL) and cooled to -78 °C. *t*-Butyl lithium (1.7 M, 7.35 mL, 12.5 mmol, 1.9 equiv.) was added dropwise after which the solution was stirred for 10 min. Acetaldehyde (580 mg, 737 µL, 13.16 mmol, 2 equiv.) in THF (5 mL) was then added dropwise over five minutes and the reaction was allowed to stir at -78 °C for 1 hour. Cooled brine (10 mL) was added dropwise to quench the reaction which was subsequently allowed to warm to ambient temperature and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the residue, which was purified by column chromatography to afford the title compound **16** as white solid (720 mg, 45%): R_f = 0.35 (ethyl acetate/hexane = 2:1), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, *J* = 6.0 Hz, 1H), 6.71 (d, *J* = 6.0 Hz, 1H), 5.60 (d, *J* = 5.6 Hz, 1H), 5.52 (d, *J* = 6.0 Hz, 1H), 5.28-5.22 (m, 1H), 5.20 (s, 2H), 3.52 (d, *J* = 12.0 Hz, 1H), 3.50 (s, 3H), 3.45 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.7, 160.7, 146.3, 114.7, 105.1, 94.0, 91.9, 63.2, 57.3, 56.5, 23.3; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{11}H_{17}NO_5Na$ 266.1004, found 266.1011.



4-((tert-butyldimethylsilyl)oxy)-1-(5-(1-hydroxyethyl)-4,6-bis(methoxymethoxy)p

yridin-3-yl)cyclohexanol (15)

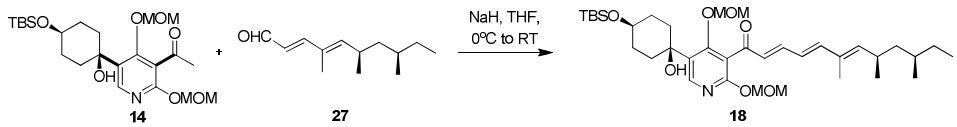
Compound **16** (365 mg, 1.5 mmol) was dissolved in THF (2 mL) and cooled to -60 °C, followed by addition of TMEDA (0.9 mL, 6 mmol, 4 equiv.). *s*-Butyl lithium (1.5 M, 4 mL, 6 mmol, 4 equiv.) was added dropwise after which the solution was stirred for 1 hour. *tert*-Butyldimethylsilyloxy cyclohexanone (684 mg, 3 mmol, 2 equiv.) in THF (2 mL) was then added dropwise over five minutes and the reaction was allowed to stir at -60 °C for 1 hour and warmed up to room temperature to continue for 2 hours. Cooled brine (10 mL) was added dropwise to quench the reaction and the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the residue, which was purified by column chromatography to afford the title compound **15** as a colorless oil (289 mg, 41%, syn/anti = 10:1): R_f = 0.30 (ethyl acetate/hexane = 2:1), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (s, 1H), 5.66 (d, *J* = 6.0 Hz, 1H), 5.53 (d, *J* = 6.0 Hz, 1H), 5.16-5.09 (m, 2H), 5.07-5.01 (m, 1H), 3.62 (s, 3H), 3.53 (s, 3H), 3.55-3.51 (m, 1H), 2.21-2.14 (m, 2H), 1.88-1.77 (m, 6H), 1.60 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.8, 160.9, 143.4, 130.8, 120.1, 101.7, 92.1, 70.4, 63.9, 60.0, 57.7, 35.2, 35.1, 31.1, 25.9, 22.9, 18.2, -4.6; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{41}NO_7SiNa$ 494.2550, found 494.2554.



1-(5-(4-((tert-butyldimethylsilyl)oxy)-1-hydroxycyclohexyl)-2,4-bis(methoxymeth

oxy)pyridin-3-yl)ethanone (14)

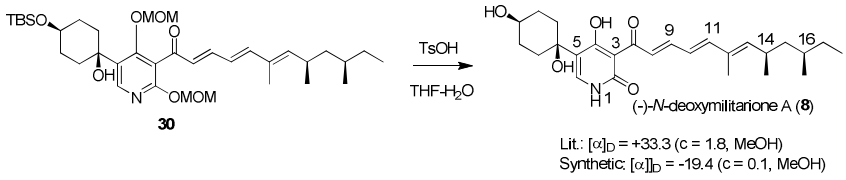
Dess-Martin periodinane (405 mg, 0.955 mmol, 1.5 equiv.) was added to a solution of compound **15** (300 mg, 0.64 mmol) and pyridine (0.5 mL, 7.04 mmol, 11 equiv.) in DCM (5 mL) at 0 ^{o}C. The reaction mixture was stirred at ambient temperature for 3 h. A solution of $Na_2S_2O_3$ and $NaHCO_3$ (1:1) (10 mL) was added dropwise to quench the reaction and the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with NH_4Cl (10 mL), $NaHCO_3$ (10 mL), brine (10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the residue, which was purified by column chromatography to afford the title compound **14** as a colorless oil (250 mg, 83%): R_f = 0.30 (ethyl acetate/hexane = 4:1), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 5.50 (s, 2H), 5.05 (s, 2H), 3.68-3.61 (m, 1H), 3.50 (s, 3H), 3.47 (s, 3H), 2.54 (s, 3H), 2.09-2.06 (m, 2H), 1.88-1.70 (m, 6H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.9, 161.3, 159.3, 145.6, 129.8, 117.6, 100.4, 92.0, 70.6, 70.5, 57.7, 57.4, 35.0, 32.1, 31.1, 25.9, 18.2, -4.6; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{23}H_{39}NO_7SiNa$ 492.2393, found 492.2389.



(*2E,4E,6E,8R,10R*)-1-(5-((*1s,4S*)-4-((tert-butyldimethylsilyl)oxy)-1-hydroxycyclohexyl)-2,4-bis(methoxymethoxy)pyridin-3-yl)-6,8,10-trimethyldodeca-2,4,6-trien-1-one (18)

Sodium hydride (23 mg, 60 % in mineral oil, 0.57 mmol) was added to a solution of

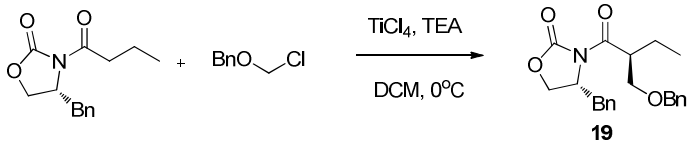
compound **14** (89 mg, 0.19 mmol) in dry THF (3 mL) at 0 °C. After 30 min, the dienal **27** (45 mg, 0.23 mmol) in dry THF (2 mL) was added at 0 °C. The reaction mixture was stirred for 30 min and then warmed to room temperature and stirred for 8 h. After that, the reaction was quenched with ice-water and extracted with EtOAc. The combined organic phase was washed with brine. After drying over Na_2SO_4 and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (n-hexane/EtOAc = 10/1) to afford product **18** as yellow oil (60 mg, 61%, E/Z >10:1): R_f = 0.4 (ethyl acetate/hexane = 3:1), $[\alpha]^D_{22.5}$ = -8.3 (*c* = 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 1H), 7.03 (dd, *J* = 14.6, 11.2 Hz, 1H), 6.59 (d, *J* = 14.4 Hz, 1H), 6.45 (t, *J* = 15.6 Hz, 1H), 6.34 (t, *J* = 10.8 Hz, 1H), 5.51-5.46 (m, 3H), 5.08 (s, 2H), 3.88 (s, 1H), 3.65-3.56 (m, 1H), 3.51 (s, 3H), 3.41 (s, 3H), 2.71-2.69 (m, 1H), 2.16-2.14 (m, 2H), 1.90-1.81 (m, 5H), 1.80 (s, 3H), 1.76-1.74 (m, 2H), 1.33-1.28 (m, 2H), 1.15-1.11 (m, 2H), 0.95 (t, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.80 (t, *J* = 6.0 Hz, 6H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.2, 162.3, 159.8, 148.9, 147.6, 147.3, 145.4, 132.3, 130.2, 129.7, 123.9, 100.5, 91.7, 70.7, 70.6, 58.0, 57.1, 44.6, 35.1, 32.4, 31.1, 30.9, 30.1, 29.3, 25.9, 21.2, 19.1, 18.2, 12.4, 11.3, -4.6; HRMS (ESI) *m/z* calcd for $C_{36}H_{59}NO_7SiNa$ $[M + Na]^+$ 668.3959; found 668.3957.



N-deoxymilitarinone A (8)

To the compound **30** (19 mg, 0.03 mmol) in THF/H_2O (3 mL, *v:v* = 20:1) was added

TsOH (2.2 mg, 2.2 mmol, 1 M in hexane) at room temperature. The reaction was stirred for 12 h and then quenched by the sequential addition of aqueous sodium bicarbonate solution (5 mL), and ethyl acetate (5 mL). The solution was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography, to afford 8 mg (59%) of *N*-deoxymilitarinone A (**8**), as a yellow solid: R_f = 0.25 ($CHCl_3$/MeOH = 10:1), $[\alpha]^D_{22.5}$ = -19.4 (c = 0.1, MeOH), ^{1}H NMR (MeOD, 400 MHz) δ 7.93 (d, *J* = 14.4 Hz, 1H), 7.64 (s, 1H), 7.55 (d, *J* = 14.4 Hz, 1H), 6.78 (d, *J* = 14.8 Hz, 1H), 6.48 (dd, *J* = 15.2, 11.6 Hz, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 3.64 (m, 1H), 2.70 (m, 1H), 2.39 (m, 2H), 1.95-1.60 (m, 9H), 1.35-1.13 (m, 5H), 0.98 (d, *J* = 5.6 Hz, 3H), 0.87 (m, 6H); ^{13}C NMR (MeOD, 100 MHz) δ 195.6, 178.7, 164.8, 149.6, 147.5, 145.0, 139.3, 134.3, 128.5, 126.6, 121.5, 107.6, 71.8, 70.8, 45.9, 34.8, 33.8, 32.1, 31.6, 31.3, 21.7, 19.6, 12.7, 11.8; HRMS (ESI) *m/z* calcd for $C_{26}H_{37}NO_5Na$ $[M + Na]^+$ 466.2570; found 466.2567.

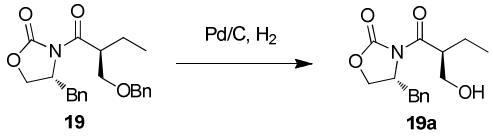


19

(R)-4-benzyl-3-((S)-2-((benzyloxy)methyl)butanoyl)oxazolidin-2-one (19)

To reaction mixture of (*R*)-4-benzyl-3-butyryloxazolidin-2-one (3.64 g, 14.7 mmol) in DCM (20 ml) at 0 °C was dropwise added $TiCl_4$ (1.8 mL, 16.3 mmol) *via* syringe. The mixture was stirred at 0 °C for 10 min and then Et_3N (2.26 mL, 16.3 mmol) was added. The mixture was stirred at 0 °C for 30 min and then BOMCl (2.26 mL, 17.64

mmol) was added. After 3 h, the reaction was quenched with 20 ml of saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (30 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL×2), saturated aqueous NH_4Cl (20 mL) and brine (20 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel to provide 5.1 g of an inseparable mixture of **19** and (*R*)-4-benzyl-3-butyryloxazolidin-2-one as a colorless oil, which was used in the next step.

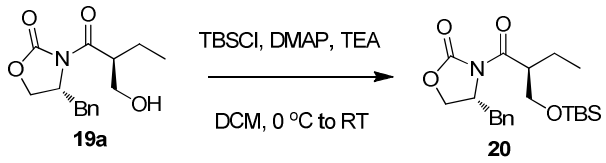


19 **19a**

(4*R*)-4-Benzyl-3-[(2*S*)-2-(hydroxymethyl)butanoyl]oxazolidin-2-one (19a) [2]

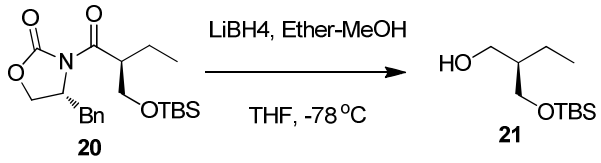
To a stirred solution of the mixture of **19** and (*R*)-4-benzyl-3-butyryloxazolidin-2-one obtained above in EtOH/CH_2Cl_2 (12:1, 65 mL) was added 10% Pd on carbon (1.0 g) under argon and then the vessel was filled with atmospheric H_2 using a balloon. The mixture was stirred for 23 h under H_2, filtered through a pad of Celite, and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7 to 1:1) to provide 3.42 g (84%, for 2 steps) of compound **19a** as a colorless oil: R_f = 0.35 (ethyl acetate/hexane = 2:1), $[\alpha]^{D}_{22.5}$ = -52.1 (*c* =1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H), 4.72-4.68 (m, 1H), 4.24-4.17 (m, 2H), 3.91-3.84 (m, 3H), 3.30 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.82 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.31 (t, *J* = 7.2 Hz, 1H), 1.75-1.59 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 175.8, 153.6, 135.2, 129.5, 129.0, 127.4, 66.2, 63.5, 55.5, 47.0, 37.9, 21.7, 11.7; HRMS (ESI) *m/z* calcd for $C_{15}H_{19}O_4Na$ $[M + Na]^+$ 300.1212; found 300.1217.



(4*R*)-4-Benzyl-3-[(2*S*)-2-(tert-butyldimethylsilyloxymethyl)butanoyl]oxazolidin-2-one (20)

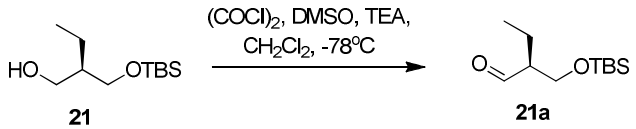
To a cooled (0 °C), stirred solution of compound **19a** (3.18 g, 11.5 mmol) in CH_2Cl_2 (23 mL) were added TBSCl (2.586 g, 17.25 mmol), DMAP (142mg, 1.15 mmol) and Et_3N (3.26 mL, 23 mmol). The mixture was stirred at room temperature for 5.5 h, diluted with saturated aqueous NH_4Cl (30 mL) at 0 °C, and extracted with CH_2Cl_2 (30 mL×2). The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 4.35g (97%) of the title compound **20** as a colorless oil: R_f = 0.65 (ethyl acetate/hexane = 5:1), $[\alpha]^D_{22.5}$ = -26.9 (*c* =0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H), 4.76-4.71 (m, 1H), 4.21-4.14 (m, 2H), 4.01-3.98 (m, 1H), 3.93 (t, *J* = 17.6 Hz, 1H), 3.81 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.32 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.72 (dd, *J* = 13.6, 9.6 Hz, 1H), 1.78-1.70 (m, 1H), 1.60-1.55 (m, 1H), 0.94 (t, *J* = 7.6 Hz, 3H), 0.88 (s, 9 H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 153.2, 135.5, 129.5, 129.0, 127.3, 65.9, 64.1, 55.3, 47.2, 38.1, 25.9, 21.7, 18.3, 11.5, -3.6, -5.45; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}NO_4SiNa$ $[M + Na]^+$ 414.2076; found 414.1080.



20 21

(2*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)butan-1-ol (21)

To a solution of compound **20** (4.3 g, 11 mmol) in ether (25 mL) and MeOH (1 mL) was added $LiBH_4$ (0.5 g, 22 mmol) at -20 °C. The reaction was stirred at 0 °C for 2 h and then a solution of 1N NaOH (10 mL) was added. After 30 min, the reaction mixture was extracted with ether. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* with cold ice water bath to give the crude product. The residue was purified by column chromatography (ether/pentane =1:3) to give the title compound **21** as colourless liquid (2.0 g, 86%) and Evans chiral auxiliary (1.5 g, 75%): R_f = 0.5 (ethyl acetate/hexane = 5:1), $[\alpha]^D_{22.5}$ = -25.1 (*c* = 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.77-3.71 (m, 1H), 3.66-3.58 (m, 2H), 2.93 (dd, *J* = 6.8, 4.4 Hz, 1H), 1.67-1.60 (m, 1H), 1.31-1.24 (m, 1H), 1.29-1.23 (m, 1H), 0.92 (t, *J* = 7.6 Hz, 3H), 0.89 (s, 9 H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.3, 66.7, 43.6, 25.9, 20.6, 18.32, 11.8, -5.5, -5.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{26}O_2SiNa$ $[M + Na]^+$ 241.1600; found 241.1603.

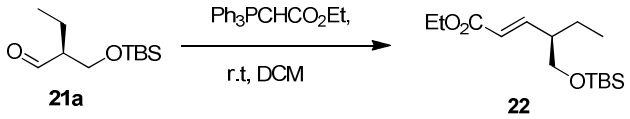


21 21a

2-(Tert-butyldimethylsilanyloxymethyl) butyraldehyde (21a)

To a solution of oxalyl chloride (854 µL, 10.1 mmol) in anhydrous CH_2Cl_2 (6 mL) was added dropwise a solution of DMSO (1.07 mL, 15.12 mmol) in CH_2Cl_2 (2 mL) at -78 °C. After 30 min, a solution of alcohol **21** (1.1 g, 5.04 mmol) in CH_2Cl_2 (4 mL)

was added at –78°C and the mixture waswas stirred for 30 min. Thentriethyl amine (3.5 mL, 25.2 mmol) was added dropwise and the mixture was stirred for another 30 min. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with waterand separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na_2CO_3 solution (5%). After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo* to afford 1.1 g (100%) of the known[6] 2-(tert-butyldimethylsilanyloxymethyl) butyraldehyde **21a**, as a clear oil, which was used for next step without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.4 Hz, 1H), 3.84 (d, *J* = 5.2 Hz, 2H), 2.30-2.43 (m, 1H), 1.63-1.74 (m, 1H), 1.48-1.55 (m, 1H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 61.6, 55.8, 25.8, 18.5, 18.2, 11.4, -5.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{24}O_2SiNa$ $[M + Na]^+$ 239.1443; found 239.1438.

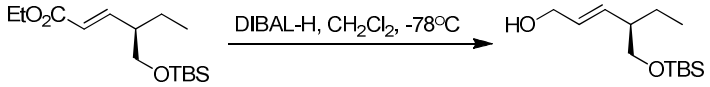


21a **22**

Ethyl-(2E)-4-(*tert*-butyldimethylsilanyloxy-methyl)-2-hexenoate (22)

A mixture of aldehyde **21a** (crude from swerm oxidation of alcohol **21**, 3.0 mmol) and $EtO_2CCH{=}PPh_3$ (2.01 g, 6.0 mmol) in DCM (10 mL) was stirred overnight at room temperature. After the reaction was completed, the solvent was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in hexane) to afford 637 mg, (77%) of the desired titled product **22** as a clear oil: $[\alpha]^D_{22.5}$ = -14.4 (c = 1.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80

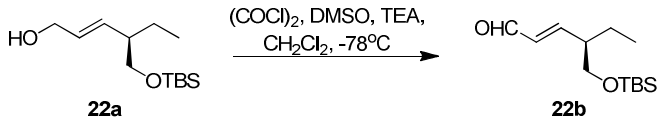
(dd, *J* = 15.6, 8.8 Hz, 1H), 5.83 (d, *J* = 8.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.56 (dd, *J* = 6.0, 2.0 Hz, 2H), 2.22-2.28 (m, 1H), 1.54-1.64 (m, 1H), 1.33-1.38 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.89 (t, *J* = 7.6 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 150.5, 122.2, 65.3, 60.1, 46.8, 25.8, 23.2, 18.3, 14.3, 11.6, -5.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{30}O_3SiNa$ $[M + Na]^+$ 309.1862; found 309.1862.



22 **22a**

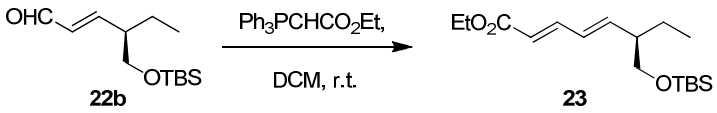
4-(*Tert*-butyldimethylsilanyloxymethyl)-2-hexene-1-ol (22a)

To a solution of ethyl ester **22** (637 mg, 2.23 mmol) in anhydrous CH_2Cl_2 (7 mL) was added dropwise DIBAL-H (6.68 mL, 6.68 mmol, 1 M in hexane) at –78°C. After 2 h, MeOH (1 mL) was added dropwise at –78 °C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H_2O, 5 mL). The mixture was stirred at room temperature for 1 h, extracted with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 6/1) to afford alcohol **22a** as colorless oil (514 mg, 95%): $[\alpha]^D_{22.5}$ = -8.6 (c = 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dt, *J* = 11.2, 5.6 Hz, 1H), 5.51 (dd, *J* = 15.6, 8.8 Hz, 1H), 4.11 (t, *J* = 5.2 Hz, 2H), 3.51 (d, *J* = 6.0 Hz, 2H), 2.04-2.10 (m, 1H), 1.32-1.36 (m, 1H), 1.34 (br, 1H), 1.24-1.27 (m, 1H), 0.88 (s, 9H), 0.85 (t, *J* = 7.6 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 130.1, 66.3, 63.9, 46.7, 25.9, 23.8, 18.3, 11.6, -5.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{28}O_2SiNa$ $[M + Na]^+$ 267.1756; found 267.1766.



(2*E*)-4-(tert-butyldimethylsilanyloxymethyl)-hex-2-enal (22b)

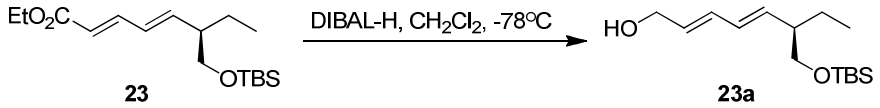
To a solution of oxalyl chloride (357 µL, 4.22 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise a solution of DMSO (450 µL, 6.33 mmol) in CH_2Cl_2 (1 mL) at -78 °C. After 30 min, a solution of alcohol **22a** (514 mg, 2.11 mmol) in CH_2Cl_2 (2 mL) was added at – 78 °C. Stirring was continued for 30 min, then triethyl amine (1.5 mL, 0.4 mmol) was added dropwise and the mixture was stirred for another 5 min. The solution was allowed to warm to room temperature and stirred for 2h. The reaction was quenched with water. The mixture was separated and the aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na_2CO_3 solution (5%). After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo* with ice-water bath to afford the crude aldehyde **22b** as a colourless liquid, which was directly used for the next step without purification.



(*2E,4E*)-ethyl 6-(((tert-butyldimethylsilyl)oxy)methyl)octa-2,4-dienoate (23)

A mixture of aldehyde **22b** (crude from swerm oxidation of alcohol **22a**, 2.11 mmol) and $EtO_2CCH{=}PPh_3$ (1.4 g, 4.22 mmol) in DCM (10 mL) was stirred overnight at room temperature. After the reaction was completed, the solvent was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in hexane) to afford 454 mg, (69%) of the desired titled product **23** as a clear oil: $[\alpha]^{D}_{22.5}$ = -19.8 (c = 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25

(dd, *J* = 15.6, 11.2 Hz, 1H), 6.19 (dd, *J* = 15.6, 10.8 Hz, 1H), 5.95 (dd, *J* = 15.2, 8.8 Hz, 1H), 5.78 (d, *J* = 15.6 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.50-3.55 (m, 2H), 2.15-2.27 (m, 1H), 1.51-1.62 (m, 1H), 1.28-1.30 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.89 (t, *J* = 7.6 Hz, 3H), 0.03 (s, 6H)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 145.9, 145.0, 129.3, 119.6, 65.8, 60.2, 47.5, 25.9, 23.7, 18.3, 14.3, 11.6, -5.3; HRMS (ESI) *m/z* calcd for $C_{17}H_{32}O_3SiNa$ $[M + Na]^+$ 335.2018; found 335.2016.

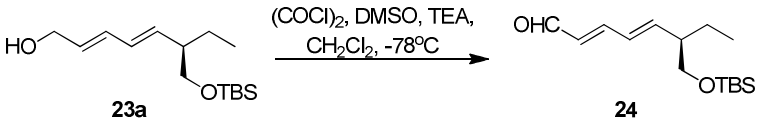


23 **23a**

(2*E,4E*)-6-(((tert-butyldimethylsilyl)oxy)methyl)octa-2,4-dien-1-ol (23a)

To a solution of ethyl ester **23** (215 mg, 0.69 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise DIBAL-H (2.1 mL, 2.1 mmol, 1 M in hexane) at –78 °°C. After 2 h, MeOH (1 mL) was added dropwise at –78 °C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H_2O, 5 mL). The mixture was stirred at rt for 1 h and then extracted with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 6/1) to afford alcohol **23a** as colorless oil (159 mg, 86%): $[\alpha]^D_{22.5}$ = -22.6 (c = 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.21 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.07 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.74 (dt, *J* = 15.2, 6.0 Hz, 1H), 5.51 (dd, *J* = 15.2, 8.8 Hz, 1H), 4.30 (d, *J* = 7.2 Hz, 2H), 3.47-3.54 (m, 2H), 2.06-2.15 (m, 1H), 1.54-1.60 (m, 1H), 1.20-1.29 (m, 1H), 0.88 (s, 9H), 0.83 (t, *J* = 7.6 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 132.0, 130.5, 129.8, 66.4, 63.5, 47.2, 25.9, 24.0, 18.3, 11.6, -5.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{30}O_2SiNa$ $[M + Na]^+$ 293.1913;

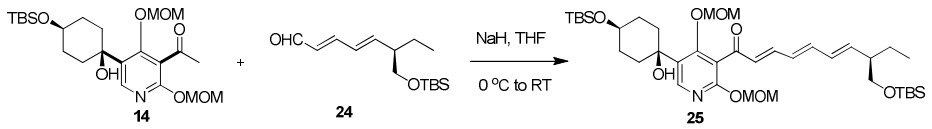
found 293.1918.



23a **24**

(*2E,4E*)-6-(((tert-butyldimethylsilyl)oxy)methyl)octa-2,4-dienal (24)

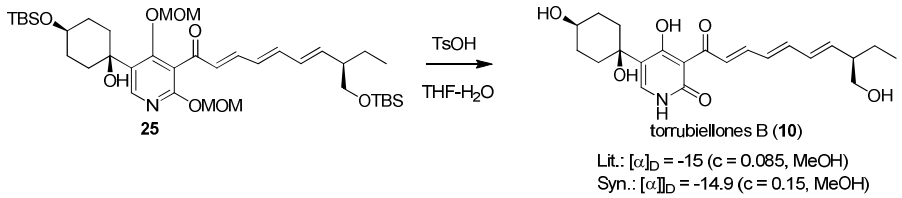
To a solution of oxalyl chloride (100 μL, 1.18 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise a solution of DMSO (170 μL, 2.4 mmol) in CH_2Cl_2 (0.5 mL) at -78 °C. After 30 min, a solution of alcohol **23a** (160 mg, 0.59 mmol) in CH_2Cl_2 (1.5 mL) was added at -78 °C. Stirring was continued for 30 min, then triethyl amine (418 μL, 3.0 mmol) was added dropwise and the mixture was stirred for another 30 min. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with water and extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na_2CO_3 solution (5%). After drying over Na_2SO_4 and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 20/1) to afford product dienal **24** as colorless oil (152 mg, 96%) as a yellowish oil: $[\alpha]^{D}_{22.5}$ = -23.6 (c = 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, J = 8.0 Hz, 1H), 7.08 (dd, J = 15.2, 10.8 Hz, 1H), 6.34 (dd, J = 15.2, 10.8 Hz, 1H), 6.06-6.15 (m, 2H), 3.53-3.62 (m, 2H), 2.22-2.26 (m, 1H), 1.55-1.61 (m, 1H), 1.31-1.42 (m, 1H), 0.88 (t, J = 7.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 152.7, 148.7, 130.3, 129.5, 65.6, 47.7, 25.9, 23.7, 18.3, 11.7, -5.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}O_2SiNa$ $[M + Na]^+$ 291.1756; found 291.1760.



(*R,2E,4E,6E*)-1-(5-((*1s,4S*)-4-((tert-butyldimethylsilyl)oxy)-1-hydroxycyclohexyl)-2,4-bis(methoxymethoxy)pyridin-3-yl)-8-(((tert-butyldimethylsilyl)oxy)methyl)deca-2,4,6-trien-1-one (25)

Sodium hydride (23 mg, 60 % in mineral oil, 0.57 mmol) was added to a solution of compound **14** (47 mg, 0.1 mmol) in dry THF (3 mL) at 0 °C. After 30 min, the dienal **24** (45 mg, 0.23 mmol) in dry THF (2 mL) was added at 0 °C. The reaction mixture was stirred for 30 min and then warmed to room temperature and stirred for 8 h. After that, the reaction was quenched with ice-water and extracted with EtOAc. The combined organic phase was washed with brine. After drying over Na_2SO_4 and filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (n-hexane/EtOAc = 10/1) to afford product **25** as yellow oil (46 mg, 65%, E/Z >10:1): R_f = 0.4 (ethyl acetate/hexane = 3:1), $[\alpha]^D_{22.5}$ = -20.4 (c = 0.6, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (s, 1H), 7.03 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.57 (dd, *J* = 14.8, 4.0 Hz, 1H), 6.43 (d, *J* = 15.2 Hz, 1H), 6.33 (dd, *J* = 14.8, 3.6 Hz, 1H), 6.22 (dd, *J* = 15.2, 4.4 Hz, 1H), 5.85 (dd, *J* = 14.8, 4.0 Hz, 1H), 5.52-5.47 (m, 2H), 5.09 (s, 2H), 3.59-3.53 (m, 1H), 3.52-3.50 (m, 2H), 3.51 (s, 3H), 3.43 (s, 3H), 2.21-2.16 (m, 3H), 1.95-1.76 (m, 6H), 1.63-1.59 (m, 2H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (t, *J* = 6.4 Hz, 3H), 0.09 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.1, 162.4, 159.8, 146.6, 145.5, 143.7, 143.6, 130.8, 130.1, 129.6, 128.3, 100.5, 91.7, 70.7, 70.6, 65.9, 58.0, 57.2, 35.1, 25.9, 25.8, 23.8, 18.3, 18.2, 11.7, -4.5, -4.9;

HRMS (ESI) *m/z* calcd for $C_{38}H_{65}NO_8Si_2Na$ $[M + Na]^+$ 742.4147; found 742.4150.



Torrubiellones B (10)

To the compound **25**(22 mg, 0.03 mmol) in THF/H_2O (3 mL, *v:v* = 20:1) was added TsOH (2.2 mg, 2.2 mmol, 1 M in hexane) at room temperature. The reaction was stirred for 12 h and then quenched by the sequential addition of aqueous sodium bicarbonate solution (5 mL), and ethyl acetate (5 mL). The solution was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash column chromatography, to afford 6 mg (47%) of *N*-deoxymilitarione A (**8**), as a yellow solid: R_f = 0.25 ($CHCl_3$/MeOH = 10:1), $[\alpha]^D_{22.5}$ = -14.9 (c = 0.15, MeOH), ^{1}H NMR (acetone-d_6, 400 MHz) δ 18.35 (brs, 1H), 10.29 (brs, 1H), 8.13 (d, *J* = 15.2 Hz, 1H), 7.79 (brs, 1H), 7.64 (dd, *J* = 11.2, 5.2 Hz, 1H), 6.84 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.53 (dd, *J* = 14.8, 11.6 Hz, 1H), 6.37 (dd, *J* = 14.8, 11.6 Hz, 1H), 5.96 (dd, *J* = 15.2, 7.2 Hz, 1H), 3.99 (s, 1H), 3.61 (brs, 1H), 3.56 (m, 2H), 2.36 (m, 2H), 2.22 (m, 1H), 1.79-1.75 (m, 4H), 1.64-1.62 (m, 2H), 1.33-1.13 (m, 1H), 0.88 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 193.8, 177.8, 162.0, 145.1, 143.4, 143.2, 138.9, 131.3, 129.6, 127.7, 106.1, 70.3, 69.2, 64.8, 47.9, 34.0, 30.9, 29.7, 23.7, 11.1; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}NO_6Na$ $[M + Na]^+$ 426.1893; found 426.1895.

4.5 References

1 Review: H. J. Jessen, K. Gademann, *Nat. Prod. Rep.* **2010**, *27*, 1168–1185.

2 Selected examples for total synthesis of pyridone alkaloids, see: a) D. R. Williams, S.-Y. Sit, *J. Org. Chem.* **1982**, *47*, 2846–2851; b) J. H. Rigby, M. Qabar, *J. Org. Chem.* **1989**, *54*, 5852–5853; c) D. R. Williams, R. A. Turske, *Org. Lett.* **2000**, *2*, 3217–3220; d) Q. Zhang, A. Rivkin, D. P. Curran, *J. Am. Chem. Soc.* **2002**, *124*, 5774–5781; e) J. E. Baldwin, R. M. Adlington, A. Conte, N. R. Irlapati, R. Marquez, G. J. Pritchard, *Org. Lett.* **2002**, *4*, 2125-212; f) A. Furstner, F. Feyen, H. Prinz, H. Waldmann, *Angew. Chem. Int. Ed.* **2003**, *42*, 5361–5364. g) H. J. Jessen, D. Barbaras, M. Hamburger, K. Gademann, *Org. Lett.* **2009**, *11*, 3446–3449; h) H. J. Jessen, A. Schumacher, F. Schmid, A. Pfaltz, K. Gademann, *Org. Lett.* **2011**, *13*, 4368–4370.

3 a) S. H. El Basyouni, D. Brewer, L. C. Vining, *Can. J. Bot.* **1968**, *46*, 441–448; b) A. G. McInnes, D. G. Smith, Chi-Kit Wat, L. C. Vining, J. L. C. Wright, *J. Chem. Soc., Chem. Commun.* **1974**, 281–282; c) Y. Cheng, B. Schneider, U. Riese, B. Schubert, Z. Li, M. Hamburger, *J. Nat. Prod.*, **2004**, *67*, 1854–1858; d) K. Schmidt, U. Riese, Z. Li, M. Hamburger, *J. Nat. Prod.* **2003**, *66*, 378-383.

4 a) Y. Cheng, B. Schneider, U. Riese, B. Schubert, Z. Li, M. Hamburger, *J. Nat. Prod.* **2006**, *69*, 436–438; b) K. Schmidt, W. Gunther, S. Stoyanova, B. Schubert, Z. Li, M. Hamburger, *Org. Lett.* **2002**, *4*, 197–199; c) M. Isaka, P. Chinthanom, S. Supothina, P. Tobwor, N. L. Hywel-Jones, *J. Nat. Prod.* **2010**, *73*, 2057–2060; d) C. Ma, Y. Li, S. Niu, H. Zhang, X. Liu, Y. Che, *J. Nat. Prod.* **2011**, *74*, 32–37.

5 D. R. Williams, D. C. Kammler, A. F. Donnell, W. R. F. Goundry, *Angew. Chem. Int. Ed.* **2005**, *44*, 6715–6718.

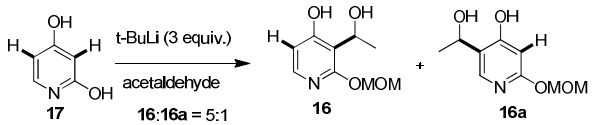
6 H. J. Jessen, A. Schumacher, T. Shaw, A. Pfaltz, K. Gademann, *Angew. Chem. Int. Ed.* **2011**, *50*, 4222–4226.

7 a) D. R. Williams, M. L. Bremmer, D. L. Brown and J. D'Antuono, *J. Org. Chem.*, **1985**, *50*,

2809–2810; b) A. T. Nielsen, W. J. Houlihan, *Org. React.* **1968**, *16*, 1–438; T. Mukaiyama, *Org. React.* **1982**, *28*, 203–331; c) R. Mahrwald, *Modern Aldol Reactions,* Wiley-VCH: Weinheim, 2004.

8 Review: a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933; b) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225.

9 C5-substitued alcohol **16a** was observed when the reaction was treated with 3.0 equiv. of *t*-BuLi.



10 See Experimental Section for the details.

11 a) J. R. Gage, D. A. Evans, *Org. Synth.* **1990**, *68*, 77-82; b) D. A. Evans, D. L. Rieger, M. T. Bilodeau, F. Urpi, *J. Am. Chem. Soc.* **1991**, *113*, 1047-1049.

12 a) D. A. Evans, D. L. Rieger, M. T. Bilodeau, F. Urpi, *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049; b) M. M. Hansen, H. Danda, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 173–181; c) J. D. White, A. T. Johnson; *J. Org. Chem.* **1994**, *59*, 3347–3358.

13] Selected examples for synthesis of aldehyde (2*R*, 4*R*)-**24**, see: a) J. D. White, A. T. Johnson, *J. Org. Chem.* **1990**, *55*, 5938-5940; b) J. D. White, A. T. Johnson, *J. Org. Chem.* **1994**, *59*, 3347-3358; c) M. G. Organ, Y. V. Bilokin, S. Bratovanov, *J. Org. Chem.* **2002**, *67*, 5176-5183; d) W. R. Leonard, K. M. Belyk, D. R. Bender, D. A. Conlon, D. L. Hughes, P. J. Reider, *Org. Lett.* **2002**, *4*, 4201-4204; e) Negishi, E. I. Tan, Z. Liang, B. Novak, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5782-5787..

14 W. D. Horner, W. S. Wadsworth, *J. Am. Chem. Soc.* **1961**, *83*, 1733 – 1738.

15 Selected examples for synthesis of alcohol (2*R*)-**33**, see: a) J. S. Panek, N. F. Jain, *J. Org. Chem.* **2001**, *66*, 2747–2756; b) K. Komatsu, K. Tanino, M. Miyashita, *Angew. Chem. Int. Ed.* **2004**, *43*, 4341 –4345; c) K. Miyashita, T. Tsunemi, T. Hosokawa, M. Ikejiri, T. Imanishi, *J. Org. Chem.* **2008**, *73*, 5360–5370; d) D. Matsumura, T. Toda, T. Hayamizu, K. Sawamura, K. Takao, K. Tadano, *Tetrahedron Lett.* **2009**, *50*, 3356–3358; e) S. Mirilashvili, N. C. Rubinstein, A. Albeck, *Eur. J. Org. Chem.* **2010**, 4671–4686.

PUBLICATIONS

1. " Ferrier-Type N-Glycosylation: Synthesis of N-Glycosides of Enone Sugars"

   Feiqing Ding, Ronny William and Xue-Wei Liu, *J. Org. Chem.*, **2013**, *78*, 1293-1299. (Featured article).

2. "Synthesis of (R)-Mellein by a Partially Reducing Iterative Polyketide Synthase"

   Huihua Sun, Chun Loong Ho, **Feiqing Ding**, Xue-wei Liu and Zhao-Xun Liang, *J. Am. Chem. Soc.,* **2012**, *134*, 11924-11927.

3. "Triflimide-catalyzed allyl–allyl cross-coupling: a metal-free allylic alkylation"

   Feiqing Ding, Ronny William, Fei Wang and Xue-Wei Liu, *Chem. Commun.*, **2012**, *48*, 8709-8711. (Highlighted by *Synfacts* **2012***, 8,* 1142)

4. "Direct and Stereoselective Synthesis of 1,3-cis-3-Arylsulphonaminodeoxy-disaccharides and Oligosaccharides"

   Feiqing Ding, Ronny William, Shuting Cai, Jimei Ma, and Xue-Wei Liu, *J. Org. Chem.* **2012**, *77*, 5245-5254. (Featured article).

5. "Ready access to 3-amino-2,3-dideoxysugars *via* regio- and stereo-selective tandem hydroamination/glycosylation of glycols"

   Feiqing Ding, Ronny William, Siming Wang, Bala Kishan Gorityala, and Xue-Wei Liu, *Org. Biomol. Chem.,* **2011**, *9*, 3929-3939. (Featured article)

6. "A Short and Highly Efficient Synthesis of L-Ristosamine and L-epi-Daunosamine Glycosides"

   Feiqing Ding, Ronny William, Fei Wang, Jimei Ma, Li Ji and Xue-Wei Liu, *Org. Lett.* **2011**, *13*, 652-655.

7. "A mild and efficient synthetic protocol for Ferrier azaglycosylation promoted by $ZnCl_2/Al_2O_3$"

   Feiqing Ding, Ronny William, Bala Kishan Gorityala, Jimei Ma, Siming Wang and Xue-Wei Liu, *Tetrahedron Lett.* **2010**, *51*, 3146-3148. (Highlighted by *Synfacts* **2010**, *8*, 0965)

8. "Pathways Leading to 3-Amino- and 3-Nitro-2,3-dideoxy Sugars: Strategies and Synthesis"

   Feiqing Ding, Shuting Cai, Ronny William and Xue-Wei Liu, *RSC Advance,* **2013**, in press, DOI: 10.1039/C3RA40595H. (Invited Review)

9. "Directed Ortho Metalation and the Total Synthesis of Torrubiellone B and N-Deoxymillilarinone A"

   Feiqing Ding, Ronny William, Min Li Leow, Junliang Wu, Shuting Cai, and Xue-Wei Liu, submitted.

10. "Convergent and Divergent Total Synthesis of Pyridone Alkaloids with Antiproliferation Activities"

    Feiqing Ding, Min Li Leow, Jimei Ma, Ronny William, Jing Zeng, Ho Sup Yoon and Xue-Wei Liu, submitted.

CONFERENCES

1. "A Facile and Efficient One-Pot Synthesis of 3-Amino-2,3-dideoxysugars."

   Ding Feiqing, Ronny William and Xue-Wei Liu, *"6th Asian-European Symposium on Metal Mediated Efficient Reactions"* June 7–9, **2010**, NTU, Singapore (Poster Presentation)

2. "Direct and Stereoselective Synthesis of α-linked 1,3-*cis*-3-Aminodeoxyglycosides." **Ding Feiqing** and Xue-Wei Liu,*"First NTU-TITech Joint Student Symposium*" June 8–10, **2011**, Tokyo Institute of Technology, Ookayama Campus, Tokyo, Japan (Poster, *Won best poster award*)
3. "Direct and Stereoselective Synthesis of α-linked 1,3-*cis*-3-Aminodeoxyglycosides." **Ding Feiqing** and Xue-Wei Liu, "*NTU-JSPS Joint Symposium*" August 16-17, **2011**, NTU, Singapore.
4. "Direct and Stereoselective Synthesis of α-linked 1,3-*cis*-3-Aminodeoxyglycosides." **Ding Feiqing** and Xue-Wei Liu, *"The 6th International Conference on Cutting-Edge Organic Chemistry in Asia (ICCEOCA-6)*" December 11-15, **2011**, Hongkong.
5. "Convergent and Divergent Total Synthesis of Pyridone Alkaloids with Antiproliferation Activities"

   Ding Feiqing, Min Li Leow, Ronny William and Xue-Wei Liu, *"The 2nd International Conference on Molecular and Functional Catalysis (ICMFC-2)*" July 30-31 **2012**, Biopolis, Singapore
6. "Convergent and Divergent Total Synthesis of Pyridone Alkaloids with Antiproliferation Activities"

   Ding Feiqing, Min Li Leow, Ronny William and Xue-Wei Liu, *"Asian Network for Natural and Unnatural Materials II (ANNUM II)*" 3-5 Oct. **2012**, NTU, Singapore.