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

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SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

2013
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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 Lorpithaya, 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. Bai Yaguang, 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.
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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$_3$·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.

![Chemical diagram]

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$_3$·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.

![Chemical diagram]
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 activities. Hence, this concept possesses potential contribution in addressing the synthesis of bioactive small-molecule libraries as well as drug discovery.

![Synthesis Scheme](image)

The potent inhibitory effects on the proliferation of Jurkat cells with IC$_{50}$ values up to 7.05 µM

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.
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<td>δ</td>
<td>chemical shift</td>
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<tr>
<td>Δ</td>
<td>reflux or heat</td>
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<td>Boron trifluoride etherate</td>
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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. In particular, antibiotics containing this moiety have been recognized to possess potent bioactivities against a wide range of human tumors. Since the first isolation of rhodosamine 1 in the 1960s, 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. 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
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 analogues 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.\textsuperscript{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.
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, Sztarickai’s group developed a divergent synthetic route to synthesize 3-amino-2,3,6-trideoxyhexoses, namely, daunosamine and its derivatives (Scheme 1).

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. 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.\textsuperscript{13} The D isomer, D-daunosamine (3), is the unnatural enantiomorph which was first prepared by Richardson group.\textsuperscript{14} The L-amino hexoses bearing \textit{xylo} configuration, which the C-3 epimers of L- and D-daunosamine, have often referred as L- and D-3-\textit{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\textsubscript{3}). Following the same sequence of reactions beginning from 2,3-\textit{O}-isooropylidene-D-glucose mercaptal 56, N-acetyl-D-daunosamine 57 and its D-\textit{xylo} isomer 58 (N-acetyl-D-3-\textit{epi}-daunosamine) were synthesized (Scheme 2).

![Scheme 1](image1)

![Scheme 2](image2)

Using similar strategy as described above, Lomakina and coworkers proceeded to synthesize N-benzoxy-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).

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 \(\alpha,\beta\)-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-dideoxyhexopyranoses 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 6). Hydrogenation of the proamine group in 3-azido-2,3-dideoxy derivatives provided diverse 3-amino and 3-acetamidosugars with poor selectivities. 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).
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. As the most well-known branched aminosugars, vancosamine is a constituent of various antibiotics such as vancomycin, all of which produced by different strains of *Amycolatopsis orientalis*. Other related antibiotics containing L-vancosamine skeleton includes sporaviridine, aculeximycin and UK-68597. L-Vancosamine in the form of its C-3 epimer bearing xyllo configuration, L-3-epi-vancosamine (18), was also found from the gram-positive antibiotic A35512B, which is related to vancomycin, ristocetin, and avoparcin. Normally, it is obtained as a minor product in the syntheses of vancosamine (13).

In 1995, Scharf’s group 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 methylcerium reagent 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).

![Figure 4](image)

Chmielewski \textit{et al.}\textsuperscript{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 8](image)

Akita \textit{et al.}\textsuperscript{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.\textsuperscript{32}

Davies’ group disclosed an entirely different strategy for selective introduction of amino group en route to aminodeoxysugars.\textsuperscript{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.\textsuperscript{34}

Scheme 11

Recently, the same group reported a similar strategy for concise and highly selective asymmetric synthesis of \(N,O\)-diacetyl-L-acosaminide \textsuperscript{126} in 7 steps with 15\% overall yield from sorbic acid \textsuperscript{120}.\textsuperscript{35} However, they presented another possible alternative strategy incorporating diastereoselective oxidation of the olefin using peracid \(\text{F}_3\text{CCO}_3\text{H}\)\textsuperscript{36} in the presence of \(\text{F}_3\text{CCO}_2\text{H}\), resulting in complete conversion to epoxide \textsuperscript{124} with 95:5 \(dr\) in nearly quantitative yield. The stereochemical outcome of the epoxidation of \(\beta\)-amino ester \textsuperscript{122} is therefore

Scheme 12
consistent with an ammonium-directed epoxidation step proceeding \textit{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-daunomycin 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 \((2R,3R)\)-dibenzoyltartaric acid for the introduction of chirality into \(\beta\)-amino ester 127.

![Scheme 13](image)

Another example for the stereoselective synthesis of 3-amino-2,3-dideoxy sugars 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 \(\alpha,\beta\)-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](image)

### 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; 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.
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. 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 is explicable on the basis of allylic strain. The preferred conformation of the transition state A also satisfies the required trajectory of the nitrogen nucleophile for 5-exo-trig cyclization. For path b, the origin of the diastereofacial 1,3-selectivity in the kinetically controlled conjugate addition of the homoallylic carbamates is quite intriguing when considering the steric and stereoelectronic factors. 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. On the other hand, in the case of path c where X = H, Y = OSiR3, 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.

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).

Scheme 15

Scheme 16
Recently, Matsushima’s group described an extremely concise route to optically active D-daunosamine, D-acosamine, D-ristogramine and 3-epi-D-daunosamine precursors by an intramolecular conjugate addition of \( \gamma \)-trichloro acetimidoyloxy-\( \alpha,\beta \)-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](image)

![Fig. 7](image)

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 ristogramine
The strategy proceeded through silica gel promoted intramolecular conjugate addition of $\gamma$-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. The chiral starting material 8 was also known to be derived from ethyl sorbate 148 by Shi’s asymmetric epoxidation and epoxide ring opening. Subsequently, the key intermediates 172 and its epimer 178 were prepared from compounds 170 and 176 respectively via hydrolysis, $\delta$-lactonization and oxidative cleavage.

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. 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 vancomycin 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 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.](image)

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.](image)

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-vanosamine 13 to date and presents an efficient methodology for amino sugar construction.

![Scheme 22]

Scheme 22.

In 2000, Giuliano et al.\textsuperscript{58} reported the synthesis of methyl α-L-vanosaminide (1) via electrophilic cyclization of allylic isoureas as the key step (Scheme 24).

![Scheme 23]

Scheme 23.
1.2.2.3 Cyclizations with nitrene-CH insertion

Parker et al. 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 to a lactaldehyde ether (Marshall reaction) resulted in alkynol. Treatment with trichloroacetyl isocyanate and methanolysis afforded alkynol, which would undergo tungsten-catalyzed alkynol cycloisomerization (McDonald reaction) to form 3-deoxy glycal. Then, the protected L-vancosamine glycal was obtained by rhodium-catalyzed C-H insertion of a carbamate nitrogen (Du Bois reaction) of 34. At a later stage, reaction of protected glycal with sodium hydride and dimethyl sulfate provided N-methyl oxazolidinone 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](image)

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.

![Scheme 26](image)

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).

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).
The above mentioned tungsten-catalyzed alkynol cycloisomerization was developed by McDonald and co-workers. It provided a rapid entry to both
vancosamine and saccharosaminoglycals, as shown in Scheme 29. 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. The key steps in the synthesis include a photochemically induced acylnitrene aziridination reaction followed by a regioselective hydrogenolytic cleavage of 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.
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. Hamada’s group reported a stereocontrolled synthesis of N-benzoyl-L-daunosamine 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](image)

Another example of total synthesis of L-acosamine was proposed by Kametani and co-workers, with the synthesis commencing from chiral natural product-derived starting material such as carvone (Scheme 33).
Shioiri and co-workers\textsuperscript{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 acid 290 by the use of diphenylphosphoryl azide (DPPA), as summarized in Scheme 34.

A concise approach to synthesize \( N \)-acyl derivatives of L-daunomycin 303 and
L-acosamine 153 was reported by Hatanaka’s group in 1991. 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).

Barco et al. 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.

Another example for the construction of L-daunosamine and D-ristosamine derivatives was developed by Sibi and co-workers. 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).

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. 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). These vancosamine donors are key intermediates which could be further applied to the stereoselective total synthesis of vancomycin.

An elegant route for the stereoselective synthesis of N-acetyl-L-daunosamine was developed by Effenberger and co-workers in 2000, 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).
A simple and divergent asymmetric synthesis of all four configurational isomers of 2,3,6-trideoxy-3-aminohexoses (lyxo, arabino, ribo, and xylo) from the racemic 3,6-heotadien-2-ol 337 was described by Dai and co-workers (Scheme 41).\(^81\)

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 1-\(N,O\)-diacetylgulosamine 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).

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).

Scheme 42

Scheme 43

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.

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).
Avenoza and co-workers\textsuperscript{89} reported a diastereoselective synthetic route to form methyl \(N,O\)-dibenzoyl-\(L\)-\(epi\)-vancosamine \textbf{384} (15 steps, 11\% yield from \textbf{379}) through Sharpless’ asymmetric dihydroxylation of a \(Z\) olefin \textbf{380} (derived from aldehyde \textbf{379}) which is analogous to aldehyde \textbf{373} (Scheme 48). Sharpless’ asymmetric dihydroxylation converted the olefin to an inseparable mixture of \textit{anti}}
and syn-diol with a 1:4 ratio.

Recently, Trost’s group\textsuperscript{91} proposed asymmetric synthesis of the L-vanosamine derivative via the Pd-catalyzed regio- and enantioselective ring opening of isoprene monoxide 385 with primary amines as pro-nucleophiles (Scheme 49).

Zhang’s group\textsuperscript{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 Cycloaddition 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. 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\textsuperscript{94} reported a very efficient approach to (±)-methyldi-acetyldaunosamine \textsuperscript{99} and (±)-methyldi-\textit{epi}-3,4-di-acetyldaunosamine \textsuperscript{378}. Diels-Alder reaction between \textsuperscript{403} and acetaldehyde using ZnCl\textsubscript{2} as the Lewis acid enabled the formation of sugar ring \textsuperscript{404} (\textit{syn:anti}=4:1). The dihydropyrones \textsuperscript{404} was then subjected to a series of reactions to afford formoxim \textsuperscript{405} which was further converted to \textsuperscript{99} and \textsuperscript{378} in a ratio of 2:1 (Scheme 51).

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

Larsen’s group\textsuperscript{96} have developed a stereoselective approach to synthesize L-daunosamine \textsuperscript{426} and L-acosamine \textsuperscript{423} from a common starting material \textsuperscript{419} (Scheme 53). Through a hetero-Diels-Alders reaction between vinylogous imide \textsuperscript{420} and ethyl vinyl ether,\textsuperscript{97} a pyranose ring system of these carbohydrate analogues (cycloadduct \textsuperscript{421}) was produced in a 40% yield.
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).
An example for this approach to the synthesis of L-daunosamine 2 from the known 1,2-acetonide derivative\(^9^9\) have been provided by Gurjar and co-workers (Scheme 55).\(^1^0^0\)

An alternative route to 3-amino-2,3-dideoxy sugars had been developed by Monneret and co-workers,\(^1^0^1\) 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-\(\alpha\)-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-\(\alpha\)-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 NaN₃ as the key step (6 steps and 12% overall yield).
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. 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\textsuperscript{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 thiy 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, thiy 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 hydrazone. 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),\textsuperscript{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.

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.\textsuperscript{105} In the first system, haloacetal 6-\textit{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 \textit{via} diastereoselective

\begin{align*}
\text{Haloborad method} & \quad \text{Si-esterified ethynyl method} \\
\begin{array}{c}
\text{HO} \\
\text{OH}
\end{array}
& \quad \begin{array}{c}
\text{OH} \\
\text{CH}
\end{array}
& \quad \begin{array}{c}
\text{OH} \\
\text{CH}
\end{array}
& \quad \begin{array}{c}
\text{OH} \\
\text{CH}
\end{array}
\end{align*}

\text{L-daunosamine}
tin-free radical addition to α-hydroxyhydrazones through 5-exo cyclization of a silicon tethered ethynyl 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.\textsuperscript{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 conditions 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](image)

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).
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.\textsuperscript{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)\textsubscript{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-\textit{epi}-daunosamine derivative 469.
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-\textit{cis} or 1,3-\textit{trans}-3-amino glycosidic bonds have drawn increasing interest, due to their wide range of applications in medicine, pharmaceutical and chemistry fields.\textsuperscript{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.\textsuperscript{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 \(\alpha\)- and \(\beta\)-deoxyglycosides remains an exciting and challenging area of research. Despite the \(\alpha\)-deoxyglycosides being more accessible than the \(\beta\)-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-\textit{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.\textsuperscript{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
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


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


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


397.


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


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, Tetrahedron 1989, 45, 1283 – 1292.


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-\textit{cis} or 1,3-\textit{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 \(\alpha\)- and \(\beta\)-deoxyglycosides remains a challenging area of research. The \(\alpha\)-deoxyglycosides are relatively more accessible than the \(\beta\)-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-\textit{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, 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 (Figure 1).

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 (1H, 13C, COSY, HMQC, HMBC, NOESY). The $J_{H1-H2a}$ 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 (Fig. 2).

![Figure 2. Selected data of 1H NMR, and NOESY for 4a](image)

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, H3PO4, 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, ZnCl2, and (C6F5)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 \( \text{BF}_3\cdot\text{OEt}_2 \) (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
d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Promoter</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFOH (1.1)</td>
<td>toluene</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Amberlyst-15 (1.1)</td>
<td>toluene</td>
<td>180</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TFA (1.1)</td>
<td>toluene</td>
<td>120</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>H$_3$PO$_4$ (1.1)</td>
<td>toluene</td>
<td>180</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>CSA (1.1)</td>
<td>toluene</td>
<td>180</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>( \rho )-TsOH (1.1)</td>
<td>toluene</td>
<td>180</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)$_2$ (1.1)</td>
<td>toluene</td>
<td>180</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>ZnCl$_2$ (1.1)</td>
<td>DCM</td>
<td>180</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>(C$_6$F$_5$)$_3$B (1.1)</td>
<td>toluene</td>
<td>180</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>BF$_3$OEt$_2$ (1.1)</td>
<td>toluene</td>
<td>120</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>BF$_3$OEt$_2$ (2.2)</td>
<td>toluene</td>
<td>30</td>
<td>90</td>
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<td>12</td>
<td>BF$_3$OEt$_2$ (2.2)</td>
<td>DMF</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>BF$_3$OEt$_2$ (2.2)</td>
<td>THF</td>
<td>30</td>
<td>-</td>
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<td>15</td>
<td>BF$_3$OEt$_2$ (2.2)</td>
<td>DCM</td>
<td>30</td>
<td>91</td>
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<tr>
<td>16</td>
<td>BF$_3$OEt$_2$ (2.2)</td>
<td>DCE</td>
<td>30</td>
<td>93</td>
</tr>
<tr>
<td>17</td>
<td>TMSOTf (2.2)</td>
<td>DCE</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>18</td>
<td>SnCl$_4$ (2.2)</td>
<td>DCE</td>
<td>30</td>
<td>92</td>
</tr>
</tbody>
</table>

$^a$ 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 SnCl₄ (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 BF₃·OEt₂, at room temperature 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$_3$·OEt$_2$-promoted one-pot three-component α-selective tandem hydroamination/glycosylation reaction$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>R-NH$_2$</th>
<th>NuH</th>
<th>Product $^b$</th>
<th>Yield (%)$^c$</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>la</td>
<td>2a</td>
<td>TsNH$_2$</td>
<td>n=2 (4b)</td>
<td>88 (4b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n=4 (4c)</td>
<td>84 (4c)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>n=16 (4d)</td>
<td>66 (4d)</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2a</td>
<td>=CH$_2$OH</td>
<td>3e</td>
<td>95</td>
</tr>
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<td>2a</td>
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<td>3h</td>
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</tr>
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<td>2a</td>
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<td>n=1 (4b)</td>
<td>85 (4i)</td>
</tr>
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<td></td>
<td></td>
<td>n=2 (4b)</td>
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<td>88 (4j)</td>
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<td>11</td>
<td>1a</td>
<td>2a</td>
<td>=OH</td>
<td>3o</td>
<td>71</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: BF$_3$·OEt$_2$ (cat.), 0.5 equiv. TsNH$_2$, 2 equiv. R-NH$_2$, 2.5 equiv. 1, 13 mL CH$_2$Cl$_2$, r.t., 30 min

$^b$ Yields by NMR integration.

$^c$ Isolated yields.
<table>
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<tr>
<th></th>
<th>1a</th>
<th>2a</th>
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<td></td>
<td>1a</td>
<td>2a</td>
<td>L-Menthol, 3q</td>
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<td>2a</td>
<td>4q</td>
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<td>R = NO2 (2e)</td>
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<td>1a</td>
<td>R = OMe (2f)</td>
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<td>2g</td>
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<td>1a</td>
<td>CbzNH2</td>
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<td>BocNH2</td>
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<tr>
<td></td>
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<td>2a</td>
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<tr>
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<td>1b</td>
<td>2a</td>
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<tr>
<td></td>
<td>1b</td>
<td>2a</td>
<td>4v</td>
<td></td>
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</table>

*Reaction conditions: 1 (0.18 mmol, 1.0 equiv), 2 (1.1 equiv), 3 (1.1 equiv), BF3·OEt2 (2.2 equiv), DCE (2 mL). All new products were characterized by IR, HRMS, 1H NMR and 13C NMR. 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 $\alpha$ 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.
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$_3$·OEt$_2$ promotes this reaction, we performed simple $^{19}$F NMR spectroscopic studies. Careful scrutiny of the NMR data suggests that BF$_3$·OEt$_2$ is coordinated to the oxygen atom of the glycal. In our control NMR experiments, BnOH and TsNH$_2$ were combined with BF$_3$·OEt$_2$, and as predicted, BF$_3$·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$_3$·OEt$_2$. 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$_3$·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
TMSN₃ which lacks acidic hydrogen did not result in desired product formation. Additionally, when secondary sulfonamide (TsNHCH₃) 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 ion.

![Fig. 3](image-url)

**Fig. 3** ¹⁹F NMR spectra of a) BF₃·OEt₂, b) BF₃·OEt₂ and BnOH, c) BF₃·OEt₂ and TsNH₂, and d) BF₃·OEt₂, BnOH, TsNH₂, and tri-O-acetyl-D-glucal in CD₂Cl₂.

![Scheme 2](image-url)

**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. 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. 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 Conclusions

In summary, a highly stereoselective BF₃·OEt₂-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](image-url)
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$_3$·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 $J_{H1-H2a}$ of 3.2 Hz for anomeric proton H-1 signal at $\delta$ 4.93 in $^1$H NMR is diagnostic for $\alpha$-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). To our delight, in all
Table 3. Substrate scope studies for BF₃·OEt₂-promoted three-component α–selective tandem hydroamination/glycosylation reaction.α

<table>
<thead>
<tr>
<th>entry</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
<th>entry</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
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<td>87 (10a)</td>
<td>8</td>
<td>Ph₂N⁺CH₃&lt;sup&gt;2&lt;/sup&gt;\text{CH} \text{Ph} \text{ClzNH₂} \text{OAc} \text{OAc} \text{ClzNH₃} \text{NuH}</td>
<td>55 (10b)</td>
</tr>
<tr>
<td>2</td>
<td>MeOH \text{3r}</td>
<td>71</td>
<td>9</td>
<td>MeOH \text{3r}</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
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<td>68 (10d)</td>
<td>10</td>
<td>\text{PhCH₂OH} \text{ClzNH₂} \text{OAc} \text{AcO} \text{OAc} \text{ClzNH₃} \text{NuH}</td>
<td>83 (10e)</td>
</tr>
<tr>
<td>4</td>
<td>\text{PhCH₂OH} \text{ClzNH₂} \text{OAc} \text{AcO} \text{OAc} \text{ClzNH₃} \text{NuH}</td>
<td>81 (10f)</td>
<td>11</td>
<td>\text{PhCH₂OH} \text{ClzNH₂} \text{OAc} \text{AcO} \text{OAc} \text{ClzNH₃} \text{NuH}</td>
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<td>72 (10h)</td>
<td>12</td>
<td>\text{PhCH₂OH} \text{ClzNH₂} \text{OAc} \text{AcO} \text{OAc} \text{ClzNH₃} \text{NuH}</td>
<td>75 (10i)</td>
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<tr>
<td>6</td>
<td>\text{PhCH₂OH} \text{ClzNH₂} \text{OAc} \text{AcO} \text{OAc} \text{ClzNH₃} \text{NuH}</td>
<td>86</td>
<td>13</td>
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<td>86 (10j)</td>
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<td>7</td>
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<td>72</td>
<td>14</td>
<td>\text{PhCH₂OH} \text{ClzNH₂} \text{OAc} \text{AcO} \text{OAc} \text{ClzNH₃} \text{NuH}</td>
<td>72 (10k)</td>
</tr>
</tbody>
</table>

αSee Experimental Section for a detailed experimental procedure. βAll products were characterized by ¹H NMR, ¹³C NMR, IR and HRMS. γIsolated 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 NsNH₂, TsNH₂ or MsNH₂, the corresponding aminosugars were isolated in high yields with exclusive stereoselectivities (Table 4, entries 1-3, 10rd, 10rf and 10s). In comparison to sulfonamides, reaction with 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 (TMSN₃) 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

![Scheme 4. Synthesis of l-ristosamine glycosides 11a and 11b.](image)

**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-\textit{O}-acetyl-6-deoxy-L-galactal (1e) was synthesized from ethyl sorbate according to a literature reported procedure.\textsuperscript{10}

Intermediary carbamate protected L-epi-daunosamine (10u) was obtained in 79% yield \textit{via} a three-component reaction involving benzyl carbamate (CbzNH\textsubscript{2}) (2h), cyclohexanol (3j) and 3,4-di-\textit{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\textsubscript{2} provided cyclohexyl L-epi-daunosamine (11c) in 83% with exclusive stereo- and regio-selection. The spectroscopic data (\textsuperscript{1}H and \textsuperscript{13}C NMR, IR) and optical rotation of 11c were identical to those reported in the literature.\textsuperscript{11}

![Scheme 5. Synthesis of L-epi-daunosamine derivative (11c).](image)

### 2.3.1.3 Conclusions

In summary, a stereocontrolled one pot BF\textsubscript{3}OEt\textsubscript{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).
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 12b and 12c, 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 glucosides 12d 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 TsNH₂, NsNH₂ and MsNH₂ 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 (CbzNH₂) proceeded smoothly to afford the corresponding 3-benzyloxycarbonylamino-2,3-dideoxydisaccharide 13t in moderate yields (Table 5, entry 8). Hydrogenolysis of the benzyloxy carbonyl (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 H₂ 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 BF₃·OEt₂-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-dideoxydisaccharide 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$_3$·OEt$_2$-promoted three-component α-selective glycosylation.$^a$

![Diagram of the reaction](image)

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<td>15</td>
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\(^a\) Reaction conditions: donor 1 (1 equiv), acceptor 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\(_3\)-Et\(_2\)O (2.2 equiv) was added, 25 °C, 15 min. \(^b\)All products were characterized by \(^1\)H 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 BF₃·OEt₂-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](image)

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

### 2.3.2.3 Conclusions

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](image)

**Scheme 7.** Synthesis of aminodeoxyysaccharide 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$_3$-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. Specifically, enone N-glycosides have emerged with potential applications in the development of antitumor-cancer oriented ketonucleosides and optically active bicyclic lactams (Fig. 7). 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. 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, have inspired many studies, the structural diversity and approaches toward N-pseudoglycals remain limited. Moreover, there are only few methods available for the synthesis of enoside O-glycosides or enone N-glycosides. 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-dideoxsugars via regio- and stereoselective tandem hydroamination/glycosylation of glycal (Fig. 8, eqn (1)). In conjunction with our previous work, herein, we report a novel design for the stereoselective synthesis of enone N-glycosides through BF₃·Et₂O-promoted glycal rearrangement (Fig. 8, eqn (2)).
2.3.3.2 Results and discussion

Initially, a systematic screening was executed using 1j and p-toluenesulfonamide 2a (TsNH₂) in the presence of BF₃·Et₂O to establish the ideal reaction conditions (Table 6). The first evaluation was conducted with different concentration of BF₃·Et₂O as promoter at room temperature, whereby DCM was employed as reaction solvent. We found that 4.4 equiv. of BF₃·Et₂O 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 BF₃·Et₂O led to a promising anomeric selectivity with α:β ratio of 84:16. Subsequently, the use of other Lewis acids as promoter (TMSOTf, TESOTf, SnCl₄, TiCl₄ and Sc(OTf)₃) also afforded the desired products of enone N-glycosides.
Table 1 Optimization for synthesis of enone N-glycosides

<table>
<thead>
<tr>
<th>entry</th>
<th>promoter (equiv.)</th>
<th>solvent</th>
<th>yield(^d)(%)</th>
<th>(\alpha/\beta) ((15ab))</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>BF(_3)-OEt(_2) (0.5)</td>
<td>DCM</td>
<td>20</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>BF(_3)-OEt(_2) (1.1)</td>
<td>DCM</td>
<td>26</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>BF(_3)-OEt(_2) (2.2)</td>
<td>DCM</td>
<td>31</td>
<td>48</td>
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<tr>
<td>4</td>
<td>BF(_3)-OEt(_2) (3.3)</td>
<td>DCM</td>
<td>57</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>BF(_3)-OEt(_2) (4.4)</td>
<td>DCM</td>
<td>89</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>TMSOTf (4.4)</td>
<td>DCM</td>
<td>44</td>
<td>ND(^d)</td>
</tr>
<tr>
<td>7</td>
<td>TESOTf (4.4)</td>
<td>DCM</td>
<td>55</td>
<td>ND(^d)</td>
</tr>
<tr>
<td>8</td>
<td>SnCl(_2) (4.4)</td>
<td>DCM</td>
<td>52</td>
<td>ND(^d)</td>
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<tr>
<td>9</td>
<td>TiCl(_4) (4.4)</td>
<td>DCM</td>
<td>trace</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OTf)(_2) (4.4)</td>
<td>DCM</td>
<td>NR(^e)</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Sc(OTf)(_3) (4.4)</td>
<td>DCM</td>
<td>72</td>
<td>ND(^d)</td>
</tr>
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<td>12</td>
<td>TfOH (4.4)</td>
<td>DCM</td>
<td>complex</td>
<td>-</td>
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<tr>
<td>13</td>
<td>BF(_3)-OEt(_2) (4.4)</td>
<td>THF</td>
<td>NR(^e)</td>
<td>-</td>
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<tr>
<td>14</td>
<td>BF(_3)-OEt(_2) (4.4)</td>
<td>ACN</td>
<td>78</td>
<td>ND(^d)</td>
</tr>
<tr>
<td>15</td>
<td>BF(_3)-OEt(_2) (4.4)</td>
<td>toluene</td>
<td>67</td>
<td>ND(^d)</td>
</tr>
<tr>
<td>16</td>
<td>BF(_3)-OEt(_2) (4.4)</td>
<td>DMF</td>
<td>complex</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield of anomic mixtures after purification. \(^b\) The anomic ratio was determined on the crude \(^1\)H NMR spectra. \(^c\) NR = no data. \(^d\) ND = 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$_3$·Et$_2$O 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$_3$·Et$_2$O 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

![Diagram of the reaction](image)

<table>
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<tr>
<th>entry</th>
<th>RNH$_2$</th>
<th>product$^b$</th>
<th>yield (%)$^c$</th>
<th>$\alpha/\beta$$^d$</th>
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<td>75 (15a)</td>
<td>84'16 (15a)</td>
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<td>86'14 (15b)</td>
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<td><img src="image" alt="AcO" /></td>
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<td>89'11 (15c)</td>
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<td><img src="image" alt="AcO" /></td>
<td>86 (15d)</td>
<td>91'12 (15d)</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="AcO" /></td>
<td><img src="image" alt="AcO" /></td>
<td>70 (15e)</td>
<td>81'10 (15e)</td>
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<td><img src="image" alt="AcO" /></td>
<td>73 (15f)</td>
<td>84'16 (15f)</td>
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<td>74/26</td>
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<td>89/11</td>
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<td><img src="image" alt="AcO" /></td>
<td>42</td>
<td>68/32</td>
</tr>
</tbody>
</table>

$^a$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 benzyloxy carbonyl (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.\(^\text{10}\)

The selectivity for the \( \alpha \) 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 \( ^4 \)H\(_1\) conformation, 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 \( \alpha \)-anomeric configuration. This intermediate II undergoes a \( \beta \)-elimination affording the dihydropyranones 15a.

![Scheme 7. Proposed mechanism.](image)

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).\(^\text{30}\) 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 adjacent to the carbonyl
group.\textsuperscript{31} Chemical structure determination and stereochemical characterization of 16a
were achieved by extensive and detailed 1D and 2D NMR studies. The subsequent
dihydroxylation\textsuperscript{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.\textsuperscript{33}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_8.png}
\end{center}

\textbf{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).\textsuperscript{34}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_9.png}
\end{center}

\textbf{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.\textsuperscript{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). 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$_3$·Et$_2$O 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 °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 13C NMR spectra in CDCl3, 2.5 ppm for 1H NMR spectra and 39.5 ppm for 13C NMR spectra in MeOD). TMS signal at 0.0 ppm was used an internal standard for partial 1H 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™ 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™ 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$_3$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-\textit{O}-acetyl-\textit{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$_3$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$_2$Cl$_2$ (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.
Benzyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4a): 93% yield, [α]_D^{20} = +41.9 (c 1.0 CHCl₃); \(^1\)H NMR (CDCl₃, 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), 2.05 (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 (CDCl₃, 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 (CHCl₃): 3280, 1738, 1539, 1367, 1236, 1170, 1031, 743 cm\(^{-1}\); HRMS (ESI) m/z [M + H]+ calcd for C₂₄H₃₀NO₅S 492.1692, found 492.1701.

Butyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4b): 88% yield, [α]_D^{20} = +54.8 (c 0.5 CHCl₃); \(^1\)H NMR (CDCl₃, 400 MHz): 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 (CDCl₃, 100 MHz): 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
(CHCl₃): 3420, 1740, 1643, 1229, 1161, 1055, 754 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₂₁H₃₁NO₅SNa 480.1668, found 480.1676.

**Hexyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4c):** 84% yield, [α]D₂₀ = +54.7 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 400MHz): δ 7.61 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.08 (d, J = 8.8 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), 2.34 (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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3327, 2926, 1742, 1342, 1240, 1163, 1055, 735 cm⁻¹; HRMS (ESI) m/z [M + H]⁺ calcd for C₂₃H₃₆NO₅S 486.2162, found 486.2161.

**Octadecyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4d):** 66% yield, [α]D₂₀ = +44.9 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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), 4.17-4.30 (m, 2H), 3.85 (q, J = 3.6 Hz, 1H), 3.69-3.71 (m, 1H), 3.36-3.38 (m, 1H), 2.34 (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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3327, 2926, 1742, 1342, 1240, 1163, 1055, 735 cm⁻¹; HRMS (ESI) m/z [M + H]⁺ calcd for C₂₃H₃₆NO₅S 486.2162, found 486.2161.
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): \(\delta 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, 29.6, 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, 498 cm$^{-1}$; HRMS (ESI) m/z [M + Na]$^+$ calcd for C$_{35}$H$_{59}$NO$_8$SNa 676.3859, found 676.3857.

Propargyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-$\alpha$-D-glucopyranose (4e): 95% yield, \([\alpha]_D^{20} = +51.5\) (c 1.0 CHCl$_3$); $^1$H NMR (CDCl$_3$, 400MHz): \(\delta 7.72\) (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): \(\delta 170.7, 170.4, 143.4, 137.8, 129.8, 126.9, 95.7, 78.1, 75.5, 66.8, 64.7, 62.6, 54.8, 47.8, 32.7, 21.5, 21.0, 20.8;\) IR (CHCl$_3$): 3306, 2922, 1738, 1339, 1242, 1161, 1042, 758 cm$^{-1}$; HRMS (ESI) m/z [M + Na]$^+$ calcd for C$_{20}$H$_{25}$NO$_8$SNa 462.1199, found 462.1201.

![Diagram of compound 4e](image-url)
Allyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4f): 82% yield, [α]D^20 = +115.5 (c 1.0 CHCl₃); ^1H NMR (CDCl₃, 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); ^13C NMR (CDCl₃, 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 (CHCl₃): 3265, 2955, 1742, 1339, 1238, 1163, 1035, 656 cm⁻¹; HRMS (ESI) m/z [M + Na]^+ calcd for C₂₀H₂₇NO₇SNa 464.1355, found 464.1367.

Isopropyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4g): 85% yield, [α]D^20 = +53.9 (c 1.0 CHCl₃); ^1H NMR (CDCl₃, 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); ^13C NMR (CDCl₃, 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 (CHCl₃): 3323, 2970, 1741, 1369, 1230, 1163, 1091, 987, 665 cm⁻¹; HRMS (ESI) m/z [M + Na]^+ calcd for C₂₀H₂₉NO₇SNa 466.1512, found 466.1501.
Isopentanyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4h): 90% yield, [α]D²⁰ = +47.2 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3304, 2935, 1742, 1342, 1229, 1163, 989cm⁻¹; HRMS (ESI) m/z [M + Na]+ calcd for C₂₉H₃₃NO₈SNa 494.1825, found 494.1811.

Cyclopentyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4i): 85% yield, [α]D²⁰ = +43.6 (c 0.5 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3422, 1740, 1340, 1228, 1161, 485 cm⁻¹; HRMS (ESI) m/z \([M + Na]^+\) calcd for C₂₂H₃₁NO₅SNa 492.1668, found 492.1669.

![Diagram](image)

**Cyclohexyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4j):** 88% yield, \([\alpha]_D^{20} = +63.4\) (c 0.25 CHCl₃); \(^1H\) NMR (CDCl₃, 400MHz): \(\delta\) 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); \(^13C\) NMR (CDCl₃, 100MHz): \(\delta\) 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 (CHCl₃): 3419, 1638, 1340, 1230, 1163, 517 cm⁻¹; HRMS (ESI) m/z \([M + Na]^+\) calcd for C₂₅H₃₃NO₅SNa 506.1825, found 506.1830.

![Diagram](image)

**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 CHCl₃); \(^1H\) NMR (CDCl₃, 400MHz): \(\delta\) 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): $\delta$ 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$_2$O$_{10}$SNa 497.1206, found 497.1193.

$^2$-(Allyloxy)ethyl 3-$p$-toluenesulfonamido-4,6-di-$O$-acetyl-2,3-dideoxy-$\alpha$-D-gluco

pyranoside (4l): 76% yield, $[\alpha]_D^{20} = +49.9$ (c 1.0 CHCl$_3$); $^1$H NMR (CDCl$_3$

400MHz): $\delta$ 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): $\delta$ 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$_{25}$NO$_9$SNa 494.1461, found 494.1435.
Phenethyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4m): 91% yield, [α]_D^{20} = +48.2 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 400 MHz): 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), 3.65-3.69 (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); ¹³C NMR (CDCl₃, 100 MHz): 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 (CHCl₃): 3421, 1740, 1647, 1340, 1240, 1163, 752, 492 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₂₅H₃₁NO₅SNa 528.1668, found 528.1664.

(E)-But-2-enyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4n): 83% yield, [α]_D^{20} = +118.4 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 300 MHz): 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); ¹³C NMR (CDCl₃, 100 MHz): 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, 669 cm\(^{-1}\); HRMS (ESI) m/z [M + Na\(^+\)] calcd for C\(_{21}\)H\(_{29}\)NO\(_8\)SNa 478.1512, found 478.1526.

**Benzylthio 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-\(\alpha\)-D-glucopyranoside (4o):** 71% yield, \([\alpha]_{D}^{20} = +8.8\) (c 0.5 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) 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, 2H), 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): \(\delta\) 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, 524 cm\(^{-1}\); HRMS (ESI) m/z [M+Na\(^+\)] calcd for C\(_{24}\)H\(_{28}\)NO\(_7\)S\(_2\)Na 530.1283, found 530.1285.

** tert-Butyl hydrosulfide 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-\(\alpha\)-D-glucopyranoside (4p):** 75% yield, \([\alpha]_{D}^{20} = +54.9\) (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) 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): \(\delta\)
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 (CHCl₃): 3421, 1740, 1636, 1334, 1238, 1163, 1057, 492 cm⁻¹;

HRMS (ESI) m/z [M+ Na]⁺ calcd for C₂₁H₂₁NO₇SNa 496.1440, found 496.1436.

L-menthol 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4q): 77% yield, [α]D²⁰ = +38.9 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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, 561 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₂₇H₄₁NO₈SNa 562.2451, found 562.2471.

Benzyl 3-benzenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4rb): 85% yield, [α]D²⁰ = +70.1 (c 0.25 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3420, 1740, 1647, 1217, 1165, 505 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₂₃H₂₇NO₈SNa 500.1355, found 500.1354.

Benzyl 3-p-fluorophenylsulfonylamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4rc): 91% yield, [α]D²⁰ = +69.1 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3404, 1740, 1494, 1344, 1234, 1169, 1051, 754, 498 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₂₃H₂₆NO₈SFNa 518.1261, found 518.1253.
Benzyl 3-p-chlorophenylsulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4rd): 85% yield, [α]D20 = +64.3 (c 1.0 CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 (CHCl3): 3422, 1740, 1647, 1344, 1240, 1165, 1051, 754, 497 cm⁻¹; HRMS (ESI) m/z [M + Na]+ calcd for C23H26NO8SClNa 534.0965, found 534.0958.

Benzyl 3-p-nitrophenylsulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4re): 88% yield, [α]D20 = +68.4 (c 0.5 CHCl3); 1H NMR (CDCl3, 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): $\delta$ 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, 503 cm$^{-1}$; HRMS (ESI) m/z [M + Na]$^+$ calcld for C$_{23}$H$_{26}$N$_2$O$_{10}$SNa 545.1206, found 545.1207.

Benzyl 3-p-methoxyphenylsulfonamido-4,6-di-O-acetyl-2,3-dideoxy-$\alpha$-D-gluco pyranoside (4rf): 74% yield, $[\alpha]_D^{20} = +102.4$ (c 1.0 CHCl$_3$); $^1$H NMR (CDCl$_3$, 400MHz): $\delta$ 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): $\delta$ 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, 1157 cm$^{-1}$; HRMS (ESI) m/z [M + Na]$^+$ calcld for C$_{24}$H$_{28}$NO$_6$SNa 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 CHCl₃); 

\(^1\)H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3421, 1740, 1647, 1327, 1232, 1153, 1049, 754, 499 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₈H₂₅NO₆SNa 438.1199, found 438.1193.

Benzyl 3-benzzyloxycarbonylamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4t): 72% yield, \([\alpha]_D^{20} = +43.3\) (c 1.0 CHCl₃); 

\(^1\)H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3420, 1734, 1638, 1508, 1223,
1047, 752, 513 cm\(^{-1}\); HRMS (ESI) m/z [M + Na]\(^+\) calcd for C\(_{25}\)H\(_{29}\)NO\(_{6}\)Na 494.1791, found 494.1795.

**Benzyl 3-amido-4,6-di-O-acetyl-2,3-dideoxy-\(\alpha\)-D-glucopyranoside (4u):** 54% yield, \([\alpha]\)\(_D\)\(^{20}\) = +82.0 (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) 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): \(\delta\) 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, 1038 cm\(^{-1}\); HRMS (ESI) m/z [M + H]\(^+\) calcd for C\(_{17}\)H\(_{24}\)NO\(_6\) 338.1604, found 338.1605.

**Benzyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-\(\alpha\)-D-glucopyranoside (4v):** 87% yield, \([\alpha]\)\(_D\)\(^{20}\) = +41.6 (c 0.5 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\) 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): \(\delta\) 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, 665 cm⁻¹;
HRMS (ESI) m/z [M + Na]⁺ calcd for C₂₃H₂₀NO₅Sn 514.1512, found 514.1516.

**Isopentanyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4w):** 83% yield, [α]D²⁰ = +38.0 (c 0.5 CHCl₃); ¹H NMR (CDCl₃, 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 (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,

**Cyclopentyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-glucopyranoside (4x):** 78% yield, [α]D²⁰ = +29.7 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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): \( \delta \) 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, 665 cm\(^{-1}\); HRMS (ESI) m/z [M + Na]\(^+\) calcd for C\(_{22}\)H\(_{31}\)NO\(_8\)SNa 492.1668, found 492.1659.

Cyclohexyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-\( \alpha \)-D-glucopyranoside (4y): 77% yield, \([\alpha]_D^{20} = +34.5 \) (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400MHz): \( \delta \) 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): \( \delta \) 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, 714 cm\(^{-1}\); HRMS (ESI) m/z [M + Na]\(^+\) calcd for C\(_{23}\)H\(_{33}\)NO\(_8\)SNa 506.1825, found 506.1815.

(E)-But-2-enyl 3-p-toluenesulfonamido-4,6-di-O-acetyl-2,3-dideoxy-\( \alpha \)-D-glucopyranoside (4z): 87% yield, \([\alpha]_D^{20} = +32.2 \) (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 300MHz): \( \delta \) 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): \(\delta\) 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, 645 cm\(^{-1}\), HRMS (ESI) m/z [M + Na]\(^+\) calcd for C\(_{21}\)H\(_{29}\)NO\(_3\)SNa 478.1512, found 478.1518.

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

To a solution of 3,4-di-O-acetyl-6-deoxy-L-gulcal 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\(_3\)-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\(_2\)Cl\(_2\) (3 \(\times\) 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-trideoxsugars 10a-10t

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

87% yield, [α]D21 = 100.2 (c 1.0 CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 (CHCl3): 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, [α]D21 = 82.7 (c 1.0 CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 (CHCl₃): 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-benzylxycarbonylamido-4-O-acetyl-2,3,6-trideoxy-α-L-ribo-hexopyranoside (10c):**

\[
\begin{array}{c}
\text{Cbz} \quad \text{NH} \\
\text{AcO} \\
\end{array}
\]

71% yield, \([\alpha]_D^{21} = 90.9\) (c 1.0 CHCl₃); \(^1\)H NMR (CDCl₃, 400 MHz): \(\delta\) 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); \(^1\)C NMR (CDCl₃, 100 MHz): \(\delta\) 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 (CHCl₃): 3475, 2937, 1735, 1510, 1232, 1051 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C17H23NO6Na 360.1423, found 360.1422.

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

\[
\begin{array}{c}
\text{Cbz} \quad \text{NH} \\
\text{AcO} \\
\end{array}
\]

68% yield, \([\alpha]_D^{21} = 100.6\) (c 1.0 CHCl₃); \(^1\)H NMR (CDCl₃, 400 MHz): \(\delta\) 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); \(^1\)C NMR (CDCl₃, 100 MHz): \(\delta\) 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 (CHCl₃): 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-benzylxycarbonylamido-4-acetyl-2,3,6-trideoxy-α-L-ribo-hexopyranoside (10e):

83% yield, [α]D²⁰ = 74.5 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3416, 1726, 1634, 1508, 1230, 1049 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₂₂H₃₁NO₆Na 428.2049, found 428.2051.

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

81% yield, [α]D²¹ = 66.0 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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
Octyl 3-benzyloxycarbonylamido-4-acyl-2,3,6-trideoxy-α-L-ribo-hexopyranoside (10g):

73% yield, [α]D21 = 76.1 (c 1.0 CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 100 MHz): δ 170.4, 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 (CHCl3): 3419, 2928, 1730, 1506, 1230, 1051 cm⁻¹; HRMS (ESI) m/z [M + Na]+ calcd for C22H33NO6Na 430.2206, found 430.2206.

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

72% yield, [α]D21 = 67.2 (c 1.0 CHCl3); 1H NMR (CDCl3, 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,
Isopentanyl 3-benzyloxycarbonylamido-4-O-acetyl-2,3,6-trideoxy-\(\alpha\)-L-ribo-hexopyranoside (10i):

\[
\text{[Diagram of the molecule]}
\]

75% yield, \([\alpha]_D^{21} = 76.7\) (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 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); \(^1^3\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 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, 997 cm\(^{-1}\); HRMS (ESI) m/z [M + H]\(^+\) calcd for C21H31NO6Na 416.2049, found 416.2047.

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

\[
\text{[Diagram of the molecule]}
\]

86% yield, \([\alpha]_D^{21} = 76.2\) (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 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); \(^{13}\text{C}\) NMR (CDCl\(_3\), 100 MHz): \(\delta\) 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 C\(_{21}\)H\(_{31}\)NO\(_6\)Na 416.2049, found 416.2043.

**Allyl 3-benzyloxy carbonylamido-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): \(\delta\) 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); \(^{13}\text{C}\) NMR (CDCl\(_3\), 100 MHz): \(\delta\) 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 C\(_{19}\)H\(_{25}\)NO\(_6\)Na 386.1580, found 386.1577.

**-(E)-But-2-enyl 3-benzyloxy carbonylamido-4-O-acetyl-2,3,6-trideoxy-α-L-ribo-hexopyranoside (10l):**
76% yield, [α]_D^{20} = 49.9 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 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-benzoxycarbonylamido-4-O-acetyl-2,3,6-trIDEOxy-α-L-ribo-hexopyranoside (10m):**

62% yield, [α]_D^{21} = 84.0 (c 0.5 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 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-benzoxycarbonylamido-4-O-acetyl-2,3,6-trIDEOxy-α-L-**
*ribo*-hexopyranoside (10n):

![Chemical Structure](attachment:image)

69% yield, $[\alpha]_D^{21} = 85.1$ (c 1.0 CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 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): $\delta$ 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-$\alpha$-L-ribo-hexopyranoside (10o):

![Chemical Structure](attachment:image)

67% yield, $[\alpha]_D^{21} = 29.4$ (c 1.0 CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 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): $\delta$ 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-benzyloxy carbonylamido-4-\(\text{O}\)-acetyl-2,3,6-trideoxy-\(\alpha\)-L-ribo-hexopyranoside (10p):

68% yield, \([\alpha]_D^{21}\) = 69.5 (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 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); \(^1^3\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 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-benzyloxy carbonylamido-4-\(\text{O}\)-acetyl-2,3,6-trideoxy-\(\alpha\)-L-ribo-hexopyranoside (10q):

55% yield, \([\alpha]_D^{21}\) = 97.4 (c 0.5, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 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); \(^1^3\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 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.

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

54% yield, [α]D²¹ = 35.8 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 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, [α]D²¹ = 66.4 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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): \( \delta \) 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, 1001, 966 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-\( \alpha \)-L-ribo-hexopyranoside (10rb):**

\[
\begin{array}{c}
\text{F} \\
\text{AcO} \\
\text{NH} \\
\text{OBn}
\end{array}
\]

91% yield, \([\alpha]_D^{21} = 79.7 \text{ (c 1.0 CHCl}_3\)); \(^1\)H NMR (CDCl \(_3\), 400 MHz): \( \delta \) 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): \( \delta \) 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-\( \alpha \)-L-ribo-hexopyranoside (10rc):**

\[
\begin{array}{c}
\text{Cl} \\
\text{AcO} \\
\text{NH} \\
\text{OBn}
\end{array}
\]

85% yield, \([\alpha]_D^{21} = 109.6 \text{ (c 1.0 CHCl}_3\)); \(^1\)H NMR (CDCl \(_3\), 400 MHz): \( \delta \) 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): \(\delta\) 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,
1738, 1635, 1529, 1236, 1167, 1049 cm\(^{-1}\); HRMS (ESI) m/z [M + Na]\(^+\) calcd for
C\(_{21}\)H\(_{24}\)N\(_2\)O\(_8\)SNa 487.1151, found 487.1136.

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

\[
\text{O}_2\text{N} \quad \text{S} \\
\text{AcO} \\
\text{O} \\
\text{Bn}
\]

88% yield, \([\alpha]_D^{21}\) = 87.3 (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 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): \(\delta\) 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
C\(_{21}\)H\(_{24}\)N\(_2\)O\(_8\)SNa 487.1151, found 487.1136.

Benzyl 3-p-methoxyphenylsulfonamido-4-O-acetyl-2,3,6-trideoxy-\(\alpha\)-L-ribo-
hexopyranoside (10re):
74% yield, $[\alpha]_{D}^{21} = 68.8$ (c 1.0 CHCl$_3$); $^{1}$H NMR (CDCl$_3$, 400 MHz): $\delta$ 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): $\delta$ 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 C$_{22}$H$_{27}$NO$_7$SNa 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): $\delta$ 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): $\delta$ 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 C$_{22}$H$_{27}$NO$_6$SNa...
446.1546, found 446.1538.

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

\[
\begin{align*}
\text{NO}_2 & \quad \text{S} \\
\text{Ac} & \quad \text{O} \\
\text{NH} & \quad \text{OBn}
\end{align*}
\]

92% yield, \([\alpha]_D^{21} = 239.8\) (c 1.0 CHCl₃); \(^1\)H NMR (CDCl₃, 400 MHz): \(\delta\) 8.05-8.08 (m, 1H), 7.86-7.88 (m, 1H), 7.69-7.71 (m, 1H), 7.18-7.23 (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 (CDCl₃, 100 MHz): \(\delta\) 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 (CHCl₃): 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):**

\[
\begin{align*}
\text{Ms} & \quad \text{O} \\
\text{Ac} & \quad \text{O} \\
\text{NH} & \quad \text{OBn}
\end{align*}
\]

72% yield, \([\alpha]_D^{21} = 65.5\) (c 1.0 CHCl₃); \(^1\)H NMR (CDCl₃, 400 MHz): \(\delta\) 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 (CDCl₃, 100 MHz): \(\delta\) 170.3, 136.7, 128.7, 128.2, 128.0, 95.7, 72.8, 69.5, 62.1, 48.6, 41.6, 34.4,
Benzyl 3-ethoxycarbonylamido-4-O-acetyl-2,3,6-trideoxy-α-L-ribo-hexopyranoside (10t):

\[
\text{AcO} \quad \text{NH} \quad \text{O} \quad \text{Bn}
\]

54% yield, \([\alpha]_D^{21} = 65.0 \) (c 1.0 CHCl₃); \(^1^H\) NMR (CDCl₃, 400 MHz): \(\delta\) 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); \(^1^3^C\) NMR (CDCl₃, 100 MHz): \(\delta\) 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 (CHCl₃): 3421, 1722, 1508, 1232, 1120, 1072, 1049, 660 cm\(^{-1}\); HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₁H₂₃NO₆Na 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 N₂ 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 H₂. 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, CHCl₃-MeOH = 6:1) to obtain methyl L-ristosamine 11a (two-step yield: 82%). [α]D₀ = -42 (c 0.5 CHCl₃); ¹H NMR (CD₃OD, 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); ¹³C NMR (CD₃OD, 100 MHz): δ 97.7, 71.0, 62.9, 53.9, 32.9, 29.3, 16.8; IR (CHCl₃): 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. [α]D₀ = -110.7 (c 1.0 CHCl₃), ([α]D₀ = -131.6 (c 1.0, CH₃OH))²; ¹H NMR (CD₃OD, 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); ¹³C NMR (CD₃OD, 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 (CHCl₃): 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-benzylloxycarbonylamido-4-O-acetyl-2,3,6-trideoxy-α-L-lyxo-**
hexopyranoside (10u).

The title compound 4u was prepared according to the general procedure. 
\[\alpha\] \text{D}_{20} = -10.8 (c 0.5 CHCl₃); \text{¹H NMR (CDCl₃, 400 MHz)}: \delta 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); \text{¹C NMR (CDCl₃, 100 MHz)}: \delta 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 (CHCl₃): 3525, 3070, 2855, 1743, 1381, 1141, 1041, 856 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcld 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. \[\alpha\] \text{D}_{20} = -59.8 (c 1.0 CHCl₃); \text{¹H NMR (CDCl₃, 400 MHz)}: \delta 5.62 (br, 3 H), 5.10 (s, 1 H), 4.17 (d, \(J = 6.0\) Hz, 1H), 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, 1H), 1.32-1.90 (m, 9 H), 1.27 (d, \(J = 6.0\) Hz, 3 H); \text{¹C NMR (CD₃OD, 100 MHz)}: \delta 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 (CHCl₃): 3371, 2932, 2854, 1620, 1365, 1103, 1041, 987 cm⁻¹; HRMS (ESI) m/z [M + H]⁺ calcld for C12H23NO3Na 252.1576, found
2.4.6 General Procedure for Synthesis of 1,3-cis-3-Arylsulphonaminodeoxydisaccharides and Oligosaccharides 13.

![Chemical structure](image)

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 N₂ atmosphere. BF₃·OEt₂ (2.2 equiv) was then added to this mixture. The reaction mixture was stirred for 15 min at room temperature, quenched with saturated NaHCO₃ (3 mL) and subsequently extracted with CH₂Cl₂ (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.

**Characterization of 1,3-cis-3-tosylaminodeoxydisaccharide (13a).** 68% yield, [α]₀⁰⁰ = +45.2 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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, 127.9, 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.

1,3-cis-3-tosylaminodeoxydisaccharide (13b). 69% yield, [α]$^D_{20} = +46.3$ (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, 20.05, 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.
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): $\delta$ 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): $\delta$ 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.

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): $\delta$ 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): \(\delta\) 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\(_7\)SNa 754.1951, found 754.1954.

![Chemical structure of 1,3-cis-3-tosylaminodeoxydisaccharide (13e).](image)

**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): \(\delta\) 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): \(\delta\) 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}Na 870.3133, found 870.3135.

1,3-cis-3-tosylaminodeoxydisaccharide (13f). 47% yield, [α]D_{20}^0 = +98.6 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 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}Na 912.2505, found 912.2513.

1,3-cis-3-tosylaminodeoxydisaccharide (13g). 53% yield, [α]D_{20}^0 = -1.5 (c 0.5 CHCl₃); ¹H NMR (CDCl₃, 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); 13C NMR (CDCl3, 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 (CHCl3): 3271, 2955, 1744, 1435, 1373, 1335, 1157, 1041, 910, 817, 756, 671, 586 cm⁻¹; HRMS (ESI) m/z [M + Na]+ calcd for C31H41NO16S2Na 770.1764, found 770.1764.

1,3-cis-3-tosylaminodeoxydisaccharide (13ha). 51% yield, [α]D²₀ = +40.9 (c 1.0 CHCl₃); 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 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 (CHCl₃): 3310, 2932, 2832, 1744, 1373, 1335, 1227, 1157,
1096, 1049 cm\(^{-1}\); HRMS (ESI) m/z [M + Na\(^+\)] calcld for C\(_{27}H_41NO_{13}\)SNa 642.2195, found 642.2196.

**1,3-cis-3-tosylaminodeoxydisaccharide (13hb).** 56\% yield, [\(\alpha\)]\(^D\)\(_{20}\) = +29.3 (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) 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); \(^1^3\)C NMR (CDCl\(_3\), 100MHz): \(\delta\) 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\(^+\)] calcld for C\(_{45}H_53NO_{13}\)SNa 870.3144, found 870.3135.

**1,3-cis-3-tosylaminodeoxydisaccharide (13i).** 81\% yield, [\(\alpha\)]\(^D\)\(_{20}\) = +9.0 (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 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),
4.01-4.07 (m, 2H), 3.90-3.94 (m, 1H), 3.83 (dd, \( J = 4.72-4.81 \) (m, 5H), 3.49 (t, \( J = 8.8 \) Hz, 1H), 3.40 (s, 3H), 3.30 (dd, \( J = 12.0, 3.6 \) Hz, 1H), 3.17 (d, \( J = 12.4, 4.0 \) Hz, 1H), 1.17 (dd, \( J = 14.4, 3.6 \) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 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 \( \text{C}_{45}\text{H}_{53}\text{NO}_{13}\text{Na} \) 870.3132, found 870.3135.

**1,3-cis-3-tosylaminodeoxydisaccharide (13ja).** 75% yield, [\( \alpha \)]\(^D\)\(_{20}\) = -5.28 (c 1.0 CHCl\(_3\) ); \(^1\)H NMR (CDCl\(_3\), 400MHz): \( \delta \) 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): \( \delta \) 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 (CHCl₃): 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 C₄₃H₅₁NO₁₁SNa
812.3082, found 812.3081.

1,3-cis-3-benzyloxycarbonylaminoxydisaccharide (13jb). 64% yield, [α]D²₀ =
-12.2 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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
(CHCl₃): 3402, 2931, 1728, 1512, 1430, 1366, 127, 1065, 910, 748 cm⁻¹; HRMS (ESI)
m/z [M + Na]⁺ calcd for C₄₄H₅₁NO₁₁Na 792.3356, found 792.3360.

1,3-cis-3-tosylaminodeoxydisaccharide (13k). 58% yield, [α]D²₀ = -17.8 (c 1.0
CHCl₃); ¹H NMR (CDCl₃, 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): $\delta$ 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.

1,3-cis-3-mesyloxyaccharide (13la). 69% yield, $[\alpha]^D_{20} = +44.0$ (c 1.0 CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 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): $\delta$ 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 (CHCl₃): 3309, 2932, 1744, 1527, 1350, 1234, 1056, 856, 740, 694, 617 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₄₄H₅₀N₂O₁₅SNa 901.2827, found 901.2835.

1,3-cis-3-nosylaminodeoxydisaccharide (13lb). 61% yield, [α]D₂₀ = +47.3 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3332, 2924, 1744, 1450, 1365, 1334, 1234, 1149, 1056, 910, 748, 702 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₃₉H₄₀NO₁₅SNa 794.2825, found 794.2822.

1,3-cis-3-tosylaminodeoxydisaccharide (13ma). 71% yield, [α]D₂₀ = +105.2 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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,
1.3-cis-3-tosylaminodeoxydisaccharide (13mb). 62% yield, \([\alpha]^{20}_D = +79.1\) (c 1.0 CHCl₃); \(^1\)H NMR (CDCl₃, 400 MHz): \(\delta\) 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 (CDCl₃, 100 MHz): \(\delta\) 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 (CHCl₃): 3309, 2916, 1751, 1435, 1373, 1334, 1226, 1165, 1041, 910, 756, 671 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₃₆H₄₅NO₁₆SNa 802.2357, found 802.2359.
910, 817, 756, 678 cm\(^{-1}\); HRMS (ESI) m/z [M + Na]\(^+\) calcd for C\(_{32}\)H\(_{43}\)NO\(_{16}\)Sn 752.2200, found 752.2197.

1,3-cis-3-tosylaminodeoxydisaccharide (13mc). 67% yield, \([\alpha]\)\(^D\)\(_{20}\) = +67.4 (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 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): \(\delta\) 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\(_{16}\)Sn 750.2044, found 750.2042.

1,3-cis-3-tosylaminodeoxydisaccharide (13n). 55% yield, \([\alpha]\)\(^D\)\(_{20}\) = +83.4 (c 1.0 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 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, 2.4 Hz, 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 = 10.0, 4.0 Hz, 1H), 1.10-1.28 (m, 4H), 0.85-0.98 (m, 8H), 0.63 (d, J = 6.8 Hz, 3H); 13C NMR (CDCl3, 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 (CHCl3): 3302, 2924, 2870, 1751, 1435, 1373, 1334, 1226, 1165, 1041, 910, 756, 671, 555 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calecd for C39H57NO16SNa 850.3309, found 850.3296.

1,3-cis-3-tosylaminodeoxydisaccharide (13o). 48% yield, [α]D 20 = +108.1 (c 1.0 CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 (CHCl₃): 3294, 2916, 2854, 1751, 1435, 1372, 1226, 1165, 1041, 756, 678 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₃₉H₅₃NO₁₆SNa 846.2980, found 846.2983.

**1,3-cis-3-tosylaminodeoxytrisaccharide (13p).** 46% yield, [α]D²₀ = +61.6 (c 1.0 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3417, 1751, 1643, 1365, 1226, 1041, 740, 555 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₅₇H₆₉NO₂₁SNa 1158.3986, found 1158.3981.
1,3-cis-3-tosylanideoxytrisaccharide (13q). 44% yield, [α]D20 = +44.3 (c 1.0 CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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, 70.0, 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 (CHCl3): 3433, 2945, 1746, 1447, 1241, 1040, 765 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C57H60NO21SNa 1158.3975, found 1158.3972.

1,3-cis-3-tosylanideoxytrisaccharide (13r). 43% yield, [α]D20 = +104.2 (c 1.0 CHCl3); 1H NMR (CDCl3, 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 = 10.8, 3.6 Hz, 1H), 5.55 (d, J = 9.6, 4.0 Hz, 1H), 3.58 (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 = 2.0 Hz, 1H), 3.49 (s, 3H), 3.44 (dd, J = 14.4, 2.8 Hz, 1H); 13C NMR (CDCl3, 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, 133.1, 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 (CHCl3): 3317, 2954, 1728, 1597, 1450, 1365, 1226, 1165, 1103, 1041, 910, 756, 709 cm⁻¹; HRMS (ESI) m/z [M + Na]+ calcd for C57H63NO24SNa 1200.3357, found 1200.3358.

1,3-cis-3-tosylaminodeoxytrisaccharide (13s). 54% yield, [α]D20 = +2.38 (c 1.0
CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 (CHCl3): 3302, 2924, 1751, 1450, 1365, 1334, 1226, 1157, 1072, 910, 817, 748, 702, 601 cm⁻¹; HRMS (ESI) m/z [M + Na]+ calcd for C37H59NO21SNa 1158.3975, found 1158.3981.

**2.4.7 Procedure for Deprotection of 3-Benzylxycarbonylamino-2,3-dideoxydisaccharide 13ib to Synthesize 3-Amino-2,3-dideoxydisaccharide 14.**

![Chemical structure](image)

To a solution of 3-benzylxycarbonylamino-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 N₂ 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 H₂. 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, CHCl₃-MeOH = 1:1) to obtain 3-amino-2,3-dideoxydisaccharide 14 (two-step yield: 74%).
1,3-cis-3-benzyloxycarbonylaminodeoxydisaccharide (14a). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 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): \(\delta\) 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.

1,3-cis-3-aminodeoxydisaccharide (14). \([\alpha]_D^{20} = 2.02\) (c 1.0 MeOH); \(^1\)H NMR (CD\(_3\)OD, 400 MHz): \(\delta\) 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\(_3\)OD, 100 MHz): \(\delta\) 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\(_{28}\)NO\(_8\) 324.1658, found 324.1653.
2.4.8 General procedure for the synthesis of enone N-glycosides 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 BF₃·OEt₂ (62 µL, 0.53 mmol, 4.4 equiv) under N₂ atmosphere. The reaction mixture was stirred at room temperature for 20 min, subsequently quenched with saturated NaHCO₃ (3 mL) and extracted with DCM (3 x 10 mL). The extract was then washed with brine (2 x 20 mL), dried over Na₂SO₄ and was concentrated. The residue was separated using column chromatography (silica gel, hexane/EtOAc system) to obtain pure enone N-glycosides 15a-15o.

N-(p-Methylphenylsulfonylamo)-6-O-acetyl-3,4-dideoxy-a-D-glycero-hex-3-eno-pyranoside-2-ulose (15a). 75% yield, [α]D²¹ = -9.16 (c 0.5 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃) 3429, 1739, 1701, 1327, 1153, 1041, 976 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₅H₁₇NO₆SNa 362.0674, found 362.0681.
N-(p-nitrophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (15b). 56% yield, [α]D 21 = -7.80 (c 0.5 CHCl3); 1H NMR (CDCl3, 400 MHz) δ 8.39 (d, J = 8.8 Hz, 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); 13C NMR (CDCl3, 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 (CHCl3): 3422, 1643, 1350, 1169, 1042, 945 cm⁻¹; HRMS (ESI) m/z [M + Na]^+ calcd for C14H14N2O6SNa 393.0369, found 393.0370.

N-(o-nitrophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (15c). 83% yield, [α]D 21 = -6.35 (c 0.4 CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 C14H18N2O8S 371.0549, found 371.0529.
N-(p-chlorophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (3d). 86% yield, [α]D 21 = -45.0 (c 0.5 CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 (CHCl3): 3020, 1744, 1701, 1215, 1088 cm⁻¹; HRMS (ESI) m/z [M + Na]+ calcd for C14H14NO6SClNa 382.0128, found 382.0125.

N-(p-fluorophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (15e). 76% yield, [α]D 21 = -17.0 (c 0.5 CHCl3); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 (CHCl3): 3429, 1740, 1697, 1339, 1157, 1042, 841 cm⁻¹; HRMS (ESI) m/z [M + Na]+ calcd for C14H14NO6SFNa 366.0424, found 366.0415.
N-(p-methoxyphenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulse (15f). 73% yield, [α]D21 = -28 (c 0.5 CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.88 (d, J = 9.0 Hz, 2H), 6.90–7.02 (m, 3H), 6.21 (dd, J = 10.5, 2.4 Hz, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3422, 1728, 1643, 1339, 1157, 1034 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₅H₁₇NO₃SNa 378.0623, found 378.0632.

N-(phenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulse (15g). 44% yield, [α]D21 = -9.16 (c 0.5 CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CHCl₃): 3429, 1740, 1701, 1450, 1165, 1042 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₄H₁₅NO₆SNa 348.0518, found 348.0514.
N-(methylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-\(\beta\)-ulose (15h). 68% yield, \([\alpha]^{\circ}_{D} = -11.0\) (c 0.5 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 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) \(\delta\) 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\(_9\)H\(_{13}\)NO\(_6\)SNa 286.0361, found 286.0360.

N-(2',2',2'-trichloroethylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-enopyranoside-2-ulose (15i). 71% yield, \([\alpha]^{\circ}_{D} = -27.7\) (c 0.5 CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 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) \(\delta\) 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\(_6\)SCl\(_3\)Na 401.9349, found 401.9350.
N-(benzyloxy carbonylamino)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (15j). 54% yield, [α]$_{21}^{D}$ = -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$_6$Na 342.0954, found 342.0959.

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, [α]$_{21}^{D}$ = -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$_6$Na 430.1267, found 430.1270.
**N-(ethoxycarbonylamino)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (15i).** 55% yield, [α]_D^{21} = -20.0 (c 0.5 CHCl₃); _¹H_ NMR (CDCl₃, 400 MHz) δ 6.98 (dd, J = 10.4, 2.4 Hz, 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); _¹³C_ NMR (CDCl₃, 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 (CHCl₃): 2924, 1736, 1373, 1242, 1034 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₁H₁₅NO₆Na 280.0797, found 280.0798.

**N-(N-allyl-p-methylphenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (15m).** 42% yield, [α]_D^{21} = -64.4 (c 0.5 CHCl₃); _¹H_ NMR (CDCl₃, 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); _¹³C_ NMR (CDCl₃, 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 (CHCl₃): 1730, 1705, 1311, 1183, 1045, 956 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₈H₂₁NO₆SNa 402.0987, found 402.0988.
N-(p-methylphenylsulfonamido)-6-methyl-3,4-dideoxy-\(\beta\)-rhamnal-hex-3-eno-pyranosi de-2-ulose (15n and 15nb).

**15n**: 68% yield, \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 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) \(\delta\) 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\(_4\)SNa 304.0619, found 304.0614.

**15nb**: 22% yield, \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 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) \(\delta\) 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\(_4\)SNa 304.0619, found 304.0617.

\((S)-4\text{-}methyl-N\text{-}(3\text{-}oxo\text{-}3,6\text{-}dihydro}2H\text{-}pyran}2\text{-}yl\text{)benzenesulfonamide}(150)\). 78% yield, \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 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) \( \delta \) 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]\(^+\) calcld for C\(_{13}\)H\(_{15}\)NO\(_4\)SNa 304.0619, found 304.0617.

### 2.4.9 Synthetic procedure and characterization for 16 and 17.

![Reaction Scheme]

To a solution of compound 15a (50 mg, 0.15 mmol) in dry MeOH (1 mL) was added CeCl\(_3\)-7H\(_2\)O (15 mg, 0.04 mmol). After stirring for 10 min at room temperature, the solution was cooled down to 0\(^\circ\)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 \( \mu \)L) and water (25 \( \mu \)L) and N-methylmorpholine N-oxide was added (12 mg, 0.12 mmol). The resulting solution, cooled to 0\(^\circ\)C, was treated with 2\% (w/v) OsO\(_4\) in tert-butyl alcohol (10 \( \mu \)L). 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: 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 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 C₁₅H₁₉NO₆SNa 364.0831, found 364.0833. 17: 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 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 C₁₅H₂₁NO₈SNa 398.0886, found 398.0884.

2.4.10 Synthetic procedure and characterization for cycloaducts 18.

The compound 1₅₀ (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 BF₃·OEt₂ (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 CH₂Cl₂ in which case the same solvent was used for the dilution. The resulting solution was washed with satd aq NaHCO₃, satd aq NaCl, dried (MgSO₄), 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%): 

1H NMR (CDCl₃, 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);

13C NMR (CDCl₃, 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 C₁₈H₂₃NO₄SNa 372.1245, found 372.1241.

2.5 References


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.


20.  

21.  

22.  
(a) F. Louerat, K. Bougrin, A. Loupy, A. M. Ochoa de Retana, J. Pagalday, F. Palacios,  

23.  
(b) O. M. Rodríguez, P. A. Colinas, R. D. Bravo,  

24.  

25.  

26.  
(d) C. H. Wong, *Carbohydrate-Based Drug Discovery*, Wiley-VCH: Weinheim, Germany, **2003**.

27.  
2001, 215, 153. (c) B. K. Gorityala, S. Cai, R. Lorpithaya, J. Ma, K. K. Pasunooti, X. W. Liu, 


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. However, despite their
myriad natural sources, all pyridone aljiukaloids are unified by the presence of a characteristic fused 3,5-disubstitued-4-hydroxy-pyridone structure (I, 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 \(\text{C}=\text{C}\) to give militarinone E or (b) nucleophilic cyclization to afford militarinone F.

![Figure 2. Proposed biogenetic relationship of militarinones](image-url)
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-disubstituted-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. All preceding work toward 3,5-disubstituted-4-hydroxy-pyridone core preparation has been previously summarized in a review by Gademann and co-workers, which can be consulted for further detail. In this section, some selective approaches to 3,5-disubstituted-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).
In 1989, Rigby, J. H. and co-worker reported the first total synthesis of natural pyridone alkaloid \textit{rac}-tenilin by the reaction between isocyanate and enolate, named Rigby’s annulation (Scheme 2).\(^5\)

![Scheme 2.](image)

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.](image)

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).\(^7\)
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 4.

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).  

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).

![Scheme 6](image)

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).
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).\(^\text{11}\)

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).\textsuperscript{12}

At the same year, the same group reported another new pyridone alkaloid natural product torrubiellone C via the same approach.\textsuperscript{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).
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.

![Chemical Reaction Diagram]

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. 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.
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. In addition, research have shown that pyridone exhibit various biological activities ranging from antifungal, antibacterial, insecticidal, cytotoxic activities to the neuritogenic activity. 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. 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.

![Pyridone Alkaloids](image)

**Figure 4.** Selected members of the pyridone alkaloids family

![Convergent and Divergent Total Synthesis](image)

**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.
Our synthetic approach start from commercially available 4-bromophenol 15, which was readily protected under reported conditions\textsuperscript{21} to generate the corresponding benzyl ether in good yield (Scheme 11). Metal-halogen exchange and treatment with boron triisopropoxide\textsuperscript{22} followed by hydrolysis proceeded to afford the desired boronic acid 16, a known compound previously reported by Baldwin.\textsuperscript{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.\textsuperscript{23} Protection of 11 with methyl group in the presence of Ag\textsubscript{2}CO\textsubscript{3} in toluene provided methyl protected pyridine, which upon treatment with NBS in MeCN afford bromo-pyridine 12 in 40\% yield over two steps. According 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\textsubscript{2}CO\textsubscript{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. Unfortunately, problem arises during attempts to scale up synthesis 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. 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) BuBr, TBAI, NaH, THF; b) (i) n-BuLi, B(OiPr)3, THF; (ii) sat. NH3Cl, 45% over 2 steps; c) MeI, Ag2CO3, PhMe, 80 °C, overnight, 79%; d) NBS, MeCN, RT, 8 h, 64%; e) Pd(PPh3)4, Na2CO3, PhMe/EtOH (4:1), 100 °C, overnight, 86%; f) NBS, MeCN, 80 °C, 2 h; g) MeI, Ag2CO3, CHCl3, RT, 3 days, 42% over 2 steps; h) Acetaldehyde, n-BuLi, THF, -78 °C, 88%; i) NMO, TPAP, 4Å molecular sieves, CH2Cl2, 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 R¹. 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) TiCl₄, DIPEA, DCM; or c) TiCl₄, 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 (2R, 4R)-22 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, successive 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) LiBH₄, Ether-MeOH, THF, -78 °C, 2 h, 73%. c) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C. d) 30, Bu₂BOTf, TEA, CH₂Cl₂, -78 °C, 67% (over 2 steps). e) TsCl, DMAP, Py., RT, 8 h, 83%. f) LiBH₄, Ether-MeOH, THF, -78 °C, 2 h, 70%. g) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C. h) (EtO)₂POCH(CH₂)CO₂Et, NaH, THF, -78 °C, 8 h, 73% (over 2 steps, E/Z = 3/1). i) Dibal-H, CH₂Cl₂, -78 °C, 2 h, 89%. j) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C, 95%. k) Ph₃PCHCO₂Et, PhMe, 80 °C, 8 h, 88%. l) Dibal-H, CH₂Cl₂, -78 °C, 2 h, 87%. m) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C, 91%. n) Ph₃P(CH₂)CO₂Et, DCM, RT, overnight, 72%. o) Dibal-H, CH₂Cl₂, -78 °C, 2 h, 94%. p) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C, 92%. q) Ph₃PCHCO₂Et, PhMe, 80 °C, 8 h, 68%. r) Dibal-H, CH₂Cl₂, -78 °C, 2 h, 88%. s) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C, 85%. t) Ph₃PCHCO₂Et, PhMe, 80 °C, 8 h, 82%. u) Dibal-H, CH₂Cl₂, -78 °C, 2 h, 91%. v) (COCl)₂, DMSO, TEA, CH₂Cl₂, -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) TBSCI, n-BuLi, THF, -78 °C to -30 °C, 2 h, 77%. c) (COCl)\(_2\), DMSO, TEA, CH\(_2\)Cl\(_2\), -78 °C. d) Ph\(_3\)PC(CH\(_3\))CO\(_2\)Et, DCM, RT, overnight, 85% (over 2 steps). e) DIBAL-H, CH\(_2\)Cl\(_2\), -78 °C, 2 h, 91%. f) (COCl)\(_2\), DMSO, TEA, CH\(_2\)Cl\(_2\), -78 °C, 88%. g) Ph\(_3\)PCHCO\(_2\)Et, DCM, RT, overnight, 77%. h) DIBAL-H, CH\(_2\)Cl\(_2\), -78 °C, 2 h, 95%. i) (COCl)\(_2\), DMSO, TEA, CH\(_2\)Cl\(_2\), -78 °C; j) Ph\(_3\)PCHCO\(_2\)Et, DCM, RT, overnight, 69% (over 2 steps). k) DIBAL-H, CH\(_2\)Cl\(_2\), -78 °C, 2 h, 86%. l) (COCl)\(_2\), DMSO, TEA, CH\(_2\)Cl\(_2\), -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. 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 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.
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$_2$Cl$_2$, -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 R¹ 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 IC₅₀ 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 IC₅₀ 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)

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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<sup>1</sup> 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 IC₅₀ 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, 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

\[\text{3-Acetyl-2,4-dimethoxypyridine (14)}\]

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): $\delta$ 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): $\delta$ 200.6, 164.1, 161.5, 148.9, 112.7, 101.8, 56.0, 53.9, 32.0; HRMS (ESI) m/z [M+Na]$^+$ calcld for C$_9$H$_{11}$NO$_3$Na 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): $\delta$ 8.22 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 2.53 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 199.6, 161.5, 160.9, 149.8, 119.1, 107.2, 62.4, 54.3, 32.0; HRMS (ESI) m/z [M+Na]$^+$ calcld for C$_{10}$H$_{10}$NO$_3$BrNa 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 (Na₂SO₄). 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%). ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₂H₂₁NO₄Na 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\textsubscript{3}, 400
MHz): \( \delta 7.99 \) (d, \( J = 6.0 \) Hz, 1H), 6.52 (d, \( J = 6.0 \) Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H);
\(^{13}\text{C} \) NMR (CDCl\textsubscript{3}, 100 MHz): \( \delta 167.9, 166.1, 147.5, 106.3, 94.0, 55.2, 53.6; \) HRMS
(ESI) \text{m/z [M+Na]} \text{calcd} \text{for C}_{7}\text{H}_{8}\text{NO}_{2}\text{BrNa 239.9636, found 239.9637.}

\[
\begin{align*}
\text{3-(1-Ethanol)-2,4-dimethoxypyridine (19a)}
\end{align*}
\]

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 \( \times \) 20 mL). The combined organic
layers were washed with brine (25 mL) and dried (Na\textsubscript{2}SO\textsubscript{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\textsubscript{3}, 400 MHz): \( \delta 8.00 \) (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); \(^{13}\text{C} \) NMR (CDCl\textsubscript{3}, 100 MHz): \( \delta 163.7, 162.2, 146.3, 113.7, 102.1,\)
63.0, 55.8, 53.6, 23.1; HRMS (ESI) m/z [M+Na]$^+$ calcd for C$_9$H$_{13}$NO$_3$Na 206.0793, found 206.0801.

![Chemical structure](image)

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%).

![Chemical structure](image)

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

To the solution of (R)-4-benzylazolidin-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$_2$SO$_4$ 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%): ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₄H₁₇NO₃Na 270.1106, found 270.1110.

(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 CH₂Cl₂, dried (Na₂SO₄), 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%): ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 LiBH₄ (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 Na₂SO₄ 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%): ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 CH₂Cl₂ (40 mL) was added a solution of DMSO (6.76 g, 6.1 mL, 86.5 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (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 CH₂Cl₂. The combined organic phase was washed with aqueous HCl (2%), aqueous Na₂CO₃ solution (5%) and brine successively. After drying over Na₂SO₄ 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.

\[
\text{O} \quad \begin{array}{c}
\text{H}
\end{array}
\quad \text{Bn}
\]

\[
\text{O} \quad \begin{array}{c}
\text{H}
\end{array}
\quad \text{Bn}
\]

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

To a solution of (R)-4-benzylloxazolidin-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 N₂ 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 CH₂Cl₂. The organic extract was washed with aq. 1N NaOH solution, dried over Na₂SO₄ 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%): \([\alpha]^{D}_{20} = -97.0 \text{ (c = 1.10, EtOH); } ^1\text{H NMR (400 MHz, CDCl}_3\text{) }\delta 7.35-7.20 \text{ (m, 5H), 4.70-4.64 \text{ (m, 1H), 4.22-4.31 \text{ (m, 2H), 3.29 \text{ (dd, J = 13.4, 3.0 Hz, 1H), 3.04-2.87 \text{ (m, 2H), 2.77 \text{ (dd, J = 13.3, 9.6 Hz, 1H), 1.20 \text{ (t, J = 7.3 Hz, 3H); } ^13\text{C NMR (100 MHz, CDCl}_3\text{) }\delta 174.0, 153.4, 135.3, 129.3,}\)}\]

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\(_{11}\)H\(_{15}\)NO\(_3\)Na [M+Na]\(^{+}\) 256.0950; found 256.0951.

![Chemical structure](image)

**(4R)-4-Benzyl-3-((2R,3S,4R)-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\(_2\)Cl\(_2\) at 0 °C was added dropwise Bu\(_3\)BOTf 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 30 min 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\(_2\)O\(_2\) (50 mL, 2:1). The reaction was extracted with DCM. The combined extract was dried over Na\(_2\)SO\(_4\) 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\(_3\)) \(\delta\) 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, \(J = 6.9, 3.9 \text{ Hz}, 1\text{H}\)), 3.26 (dd, \(J = 13.5, 3.3 \text{ Hz}, 1\text{H}\)), 2.79 (dd, \(J = 13.5, 9.6 \text{ Hz}, 1\text{H}\)), 2.64 (d, \(J = 4.0 \text{ Hz}, 1\text{H}\)), 1.56-1.43 (m, 2H), 1.27 (d, \(J = 6.9 \text{ Hz}, 3\text{H}\)), 1.22-1.10 (m, 1H), 0.98 (d, \(J = 6.6 \text{ Hz}, 3\text{H}\)), 0.91 (t, \(J = 7.5 \text{ Hz}, 3\text{H}\)). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 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)
\[ m/z \text{ calcd for C}_{13}H_{26}NO_4 [M+H]^+ 320.1862; \text{ found } 320.1837. \]

\[
\begin{align*}
\text{TsCl, DMAP} & \quad \text{Pyridine} \\
\text{25} & \quad \text{25a}
\end{align*}
\]

\((2R,3S,4R)-1-((R)-4-Benyl-2-oxooxazolidin-3-yl)-2,4-dimethyl-1-oxohexan-3-yl-4\)

-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 NH₄Cl, extracted with Et₂O. The organic extract was washed with CuSO₄ solution, water, dried over Na₂SO₄ 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\text{20} = -54.4 (c =2.0, CHCl₃).\(\text{1H}^\text{1H}\) NMR (300 MHz, CDCl₃) \(\delta\) 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).\(\text{13C}\) NMR (100 MHz, CDCl₃) \(\delta\) 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\(^{-1}\), CHCl₃): 1774 (C=O), 1701 (C=O). HRMS (ESI) \(m/z \text{ calcd for C}_{25}H_{31}NO_6SNa [M+Na]^+ 496.1770; \text{ found } 496.1776.\)
(2R,4R)-2,4-Dimethylhexan-1-ol (26)

To a solution of tosylate 25a (5.0 g, 10.6 mmol) in Et₂O (50 mL) and MeOH (1.7 g, 1.34 mL, 53.0 mmol) was added portionwise LiBH₄ (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 Na₂SO₄ 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%). [α]D₂₂.₅ = +3.8 (c = 1.64, CHCl₃). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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 C₈H₁₈ONa [M+Na]⁺ 153.1255; found 153.1259.

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

To a solution of oxalyl chloride (1.03 g, 0.69 mL, 8.1 mmol) in anhydrous CH₂Cl₂ (10 mL) was added dropwise DMSO (1.05 g, 0.96 mL, 13.5 mmol) in CH₂Cl₂ (2 mL) at -78 °C in 5 min. After 30 min stirring, the solution of alcohol 26 (700 mg, 5.4 mmol) in CH₂Cl₂ (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 Na₂CO₃ solution (5%) successively. After drying over MgSO₄ 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.

(4R,6R)-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, (2R,4R)-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 Na₂SO₄ 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-(4R,6R)-Ethyl 2,4,6-trimethyloct-2-enoate: ¹H NMR (400 MHz, CDCl₃) 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$_3$) $\delta$ 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$_{22}$O$_2$Na $[M+Na]^+$ 235.1674; found 235.1682. **E-(4R,6R)-Ethyl 2,4,6-trimethyloct-2-enoate**: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_{22}$O$_2$Na $[M+Na]^+$ 235.1674; found 235.1682.

![Reaction Scheme](image)

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

To a solution of ethyl ester 28 (836 mg, 3.9 mmol) in anhydrous CH$_2$Cl$_2$ (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$_2$O, 5 mL) at $-78$ °C. The mixture was stirred for 1 h at room temperature before extracting with EtOAc. The organic layers were washed with brine and dried over Na$_2$SO$_4$. 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-(4R,6R)-2,4,6-Trimethyloct-2-en-1-ol**: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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-(4R,6R)-2,4,6-Trimethylloct-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.

![Reaction Diagram]

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

To a solution of oxalyl chloride (661 mg, 0.44 mL, 5.21 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) was added dropwise DMSO (678 mg, 0.62 mL, 8.68 mmol) in CH$_2$Cl$_2$ (1.5 mL) at -78 °C. After 30 min stirring, a solution of alcohol 28a (590 mg, 3.47 mmol) in CH$_2$Cl$_2$ (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$_2$CO$_3$ 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). \([\alpha]^{D}_{22.5} = -26.0 (c =2.0, \text{CHCl}_3)\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.38\) (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\(_3\)) \(\delta 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\(_{13}\)H\(_{21}\)O [M+H]\(^+\) 169.1592; found 169.1593.

\[\text{(2E,4E,6R,8R)-Ethyl 4,6,8-trimethyldeca-2,4-dienoate (30)}\]

The mixture of aldehyde 29 (554 mg, 3.3 mmol) and EtO\(_2\)CCH=PH\(_3\) (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:** \([\alpha]^{D}_{22.5} = -41.8 (c =1, \text{CHCl}_3)\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.29\) (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\(_3\)) \(\delta 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.
(2E,4E,6R,8R)-4,6,8-Trimethyldeca-2,4-dien-1-ol (30a)

To the ethyl ester 32 (180 mg, 0.76 mmol) in anhydrous CH₂Cl₂ (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%−H₂O, 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 Na₂SO₄. 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: [α]²⁰⁺ = -37.1 (c = 1, CHCl₃). H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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, CHCl₃): 3325 (OH). HRMS (ESI) m/z calc for C₁₃H₂₄ONa [M+Na]⁺ 219.1725; found 219.1728.

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

To a solution of oxalyl chloride (127 mg, 85 μL, 1.0 mmol) in anhydrous CH₂Cl₂ (2 mL) was added dropwise a solution of DMSO (129 mg, 117 μL, 1.65 mmol) in
CH₂Cl₂ (0.1 mL) at -78 °C. After 30 min stirring, the solution of alcohol 30a (130 mg, 0.66 mmol) in CH₂Cl₂ (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 Na₂CO₃ solution (5%). After drying over MgSO₄ 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); [α]D²².⁵ = -61.4 (c = 1, CHCl₃).

¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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, CHCl₃): 1687 (C=O); HRMS (ESI) m/z calcd for C₁₃H₂₁O [M+H]⁺ 195.1749; found 195.1736.

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

A mixture of aldehyde 24 (crude from swern oxidation of alcohol 23, 17.3 mmol) and Ph₃P=C(CH₃)₂CO₂Et (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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$Na [M+Na]$^+$ 193.1204; found 193.1210.

(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$_2$Cl$_2$ (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$_2$O, 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$_2$SO$_4$. 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$_3$) $\delta$ 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$_3$) $\delta$ 132.7, 69.1, 33.7, 30.2, 22.6, 20.6, 14.1, 11.9; HRMS (ESI) m/z calcd for C$_8$H$_{16}$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 CH₂Cl₂ (12 mL) was added dropwise a solution of DMSO (2.75 mL, 3.36 mmol) in CH₂Cl₂ (4 mL) at −78 °C. After 30 min stirring, a solution of alcohol 31a (1.5 g, 11.7 mmol) in CH₂Cl₂ (8 mL) was added at −78 °C. After 30 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 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 Na₂CO₃ solution (5%). After drying over MgSO₄ 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%); [α]²².₅°D = -20.2 (c =1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 195.7, 160.4, 138.2, 35.2, 29.5, 19.5, 11.8, 9.4; HRMS (ESI) m/z calcld for C₉H₁₄O₂Na [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 EtO₂CCH=PPh₃ (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%); [α]²⁰/²⁵ = -53.0 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₂H₂₀O₂Na [M+Na]⁺ 219.1361; found 219.1359.

(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 CH₂Cl₂ (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%-H₂O, 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 Na₂SO₄. 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%); [α]²⁰/²⁵ = -67.9 (c =1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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$_{13}$ONa [M+Na]$^+$ 177.1255; found 177.1252.

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

To a solution of oxalyl chloride (550 µL, 6.5 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) was added dropwise a solution of DMSO (700 µL, 9.75 mmol) in CH$_2$Cl$_2$ (2.5 mL) at -78 °C. After 30 min, a solution of alcohol 33a (500 mg, 3.25 mmol) in CH$_2$Cl$_2$ (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 water and separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na$_2$CO$_3$ 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%); $\left[\alpha\right]_{22.5}^{D} = -34.3$ (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%); [α]^D_{22.5} = -54.5 (c =0.5, CHCl_3); ^1H 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); ^13C 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$_2$SO$_4$. 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$_3$) $\delta$ 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, $J = 7.2$ Hz, 3H); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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.

(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$_2$Cl$_2$ (3 mL) was added dropwise a solution of DMSO (160 µL, 2.25 mmol) in CH$_2$Cl$_2$ (1 mL) at -78 °C. After 30 min, a solution of alcohol 35a (134 mg, 0.75 mmol) in CH$_2$Cl$_2$ (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$_2$CO$_3$ 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, CHCl₃); \(^1^H\) NMR (400 MHz, CDCl₃) \(\delta 9.54\) (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); \(^1^C\) NMR (100 MHz, CDCl₃) \(\delta 193.7, 153.3, 148.4, 146.9, 132.7, 130.4, 123.9, 34.9, 30.1, 20.3, 12.5, 12.0\); HRMS (ESI) \(m/z\) calcd for C₁₂H₁₈ONa \([M+Na]^+ 201.1255; found 201.1248.

![](image)

**2-(Hydroxymethyl) butanol (40)**

A three-necked round bottomed flask equipped with a pressure equalizing addition funnel, reflux condenser and drying tube was flushed with N₂ and LiAlH₄ (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 CH₂Cl₂ (3x30 mL). The volume of the combined organic layers was partially reduced to 100 mL under vacuum and washed with sat. NaHCO₃ and sat.
NaCl solutions. After drying over MgSO₄ 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%); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 66.1; 43.6; 20.6; 11.7; HRMS (ESI) m/z calcd for C₅H₁₂O₂Na [M+Na]⁺ 127.0735; found 127.0733.

![Diagram](image)

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

To a suspension of 60% sodium hydride (261 mg, 6.54 mmol) in THF (10 mL) at 0 °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 (Na₂SO₄) 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 desired titled product 41 as a clear oil; ¹H NMR (400 MHz, CDCl₃) 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\(_3\)) \(\delta\) 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\(_2\)SiNa \([\text{M+Na}]^+\) 241.1600; found 241.1607.

\[
\begin{align*}
\text{HO} & \quad \left(\text{COCl}\right)\_2\text{DMSO, TEA, CH}_2\text{Cl}_2, -78^\circ\text{C} & \quad \text{O} \\
\text{41} & \quad \text{42}
\end{align*}
\]

**2-(Tert-butyldimethylsilanyloxymethyl) butyraldehyde (42)**

To a solution of oxalyl chloride (854 µL, 10.1 mmol) in anhydrous CH\(_2\)Cl\(_2\) (6 mL) was added dropwise a solution of DMSO (1.07 mL, 15.12 mmol) in CH\(_2\)Cl\(_2\) (2 mL) at -78 °C. After 30 min, a solution of alcohol 41 (1.1 g, 5.04 mmol) in CH\(_2\)Cl\(_2\) (4 mL) was added at -78°C and the mixture was stirred for 30 min. Then triethylamine (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 water and separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na\(_2\)CO\(_3\) 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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_{2}SiNa [M+Na]^+ 239.1443; found 239.1438.

![Chemical structure](image)

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

A mixture of aldehyde 42 (crude from swern 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\textsubscript{3}) \(\delta\) 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\textsubscript{3}) \(\delta\) 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_{2}SiNa [M+Na]^+ 323.2010; found 323.2010.

![Chemical structure](image)

**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\textsubscript{2}Cl\textsubscript{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\textsubscript{2}O, 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 Na₂SO₄. 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%); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₄H₃₂O₃SiNa [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 CH₂Cl₂ (1.5 mL) was added dropwise a solution of DMSO (181 µL, 1.68 mmol) in CH₂Cl₂ (0.5 mL) at -78 °C. After 30 min, a solution of alcohol (119 mg, 0.56 mmol) in CH₂Cl₂ (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 then separated. The aqueous layer was extracted with ether. The combined organic layers were washed with aqueous HCl (2%) and then aqueous Na₂CO₃ solution (5%). After drying over MgSO₄ 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$SiNa [M+Na]$^+$ 279.1756; found 279.1762.

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

A mixture of aldehyde 42 (crude from sw erm oxidation of alcohol 41, 3.0 mmol) and EtO$_2$CCH=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$_3$) $\delta$ 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$_3$) $\delta$ 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$_{13}$H$_{30}$O$_3$SiNa [M+Na]$^+$ 309.1862; found 309.1862.
4-(Tert-butyldimethylsilyloxymethyl)-2-hexene-1-ol (45a)

To a solution of ethyl ester 45 (637 mg, 2.23 mmol) in anhydrous CH₂Cl₂ (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%-H₂O, 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 Na₂SO₄. 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%); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₃H₂₈O₂SiNa [M+Na]⁺ 267.1756; found 267.1766.

(2E)-4-(tert-butyldimethylsilyloxymethyl)-hex-2-enal (46)

To a solution of oxalyl chloride (357 μL, 4.22 mmol) in anhydrous CH₂Cl₂ (3 mL) was added dropwise a solution of DMSO (450 μL, 6.33 mmol) in CH₂Cl₂ (1 mL) at -78 °C. After 30 min, a solution of alcohol 45a (514 mg, 2.11 mmol) in CH₂Cl₂ (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 2 h. 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 Na₂CO₃ solution (5%). After drying over MgSO₄ 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.

\[ \text{OHC} \quad \text{O} \quad \text{SiNa} \]

(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 EtO₂CCH=PPh₃ (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, CDCl₃) \(\delta\) 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, CDCl₃) \(\delta\) 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 C₁₇H₃₂O₃SiNa [M+Na]⁺ 335.2018; found 335.2016.
(2E,4E)-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 CH₂Cl₂ (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%-H₂O, 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 Na₂SO₄. 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%); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₃H₃₀O₂SiNa [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 CH₂Cl₂ (2 mL) was added dropwise a solution of DMSO (170 µL, 2.4 mmol) in CH₂Cl₂ (0.5 mL) at -78 °C. After 30 min, a solution of alcohol 47a (160 mg, 0.59 mmol) in CH₂Cl₂ (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 Na₂CO₃ solution (5%). After drying over MgSO₄ 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₅H₂₈O₂SiNa [M+Na]⁺ 291.1756; found 291.1760.

2,4-Dimethoxy-5-(4-(benzyloxy)phenyl)-3-((2E,4E,6R,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$_2$SO$_4$ 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$_4$Na [M+Na]$^+$ 562.2933; found 562.2939.

(2E,4E,6E,8R,10R)-6,8,10-trimethyl-1-[5-(p-benzyloxy-phenyl)-2,4-dihydroxypyrindine-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\textsubscript{2}SO\textsubscript{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, \textit{49a}, as a yellow solid; [\alpha]\textsuperscript{D}\textsubscript{22.5} = -45.3 (c = 0.5, CHCl\textsubscript{3}); \textit{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 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); \textit{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 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\textsubscript{33}H\textsubscript{37}NO\textsubscript{4}Na [M+Na]\textsuperscript{+} 534.2620; found 534.2605.

(2\textit{E},4\textit{E},6\textit{E},8\textit{R},10\textit{R})-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, \textit{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$_2$SO$_4$) 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; $[\alpha]_{22.5}^D = -38.4$ (c = 0.5, MeOH); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_4$Na [M+Na]$^+$ 444.2151; found 444.2160.

\[
\begin{array}{c}
\text{B} & \text{N} \\
\text{O} & \text{C} & \text{Me} & \text{O} & \text{Me} \\
\text{17} & \text{18} & \text{22} & \text{24} & \text{25} \\
\end{array}
\]

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 Na₂SO₄ 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);

\[ \alpha_D^{22.5} = -18.6 \ (c = 1.0, \ \text{CHCl}_3); \]

\(^1\text{H} \ \text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta 8.10 \ (s, 1H), 7.34-7.47 \ (m, 7H), 7.02-7.06 \ (m, 3H), 6.40 \ (d, J = 11.6 \text{ Hz}, 1H), 5.70 \ (d, J = 9.6 \text{ 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 \text{ Hz}, 3H), 0.84 \ (t, J = 7.2 \text{ Hz}, 3H); \]

\(^{13}\text{C} \ \text{NMR} \ (100 \text{ MHz, CDCl}_3) \delta 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 C₃₀H₃₃NO₄Na [M+Na]⁺ 494.2307; found 494.2315.

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

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 (Na₂SO₄) 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; [α]D = -12.8 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₈H₂₉NO₄Na [M+Na]⁺ 466.1994; found 466.1992.

(R,2E,4E)-4,6-dimethyl-1-[5-(p-hydroxyphenyl)-2,4-dihydropyridine-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 (Na₂SO₄) 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; [α]D²².₅ = -35.2 (c = 0.5, MeOH); ³¹H NMR (400 MHz, CD₃OD) 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); ¹³C NMR (100 MHz, CD₃OD) 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 C₂₁H₂₃NO₄Na [M+Na]⁺ 376.1525; found 376.1532.

2,4-Dimethoxy-5-(4-(benzyloxy)phenyl)-3-((R,E,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-dimethoxypyr idine 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 Na₂SO₄ 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); [α]²².₅ = -16.9 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₂H₃₅N⁴O₄Na [M+Na]⁺ 520.2464; found 520.2462.

(R,2E,4E,6E)-6,8-dimethyl-[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 (Na₂SO₄) 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; [α]D²².⁵ = -24.7 (c = 1.0, CHCl₃); ¹H
NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₀H₃₁NO₄Na [M+Na]^+ 492.2151; found 492.2151.

(R,R,E,4E,6E)-6,8-dimethyl1-[5-(p-hydroxyphenyl)-2,4-dihydroxypyridine-3-yl]-d
eca-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 (\(\text{Na}_2\text{SO}_4\)) 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; \([\alpha]_{D}^{22.5} = -37.7 \ (c = 1.0, \text{MeOH}); \) \^1\text{H} NMR (400 MHz, CD3OD) \(\delta 7.87 \ (d, J = 14.8 \text{ Hz, 1H}), 7.52 \ (dd, J = 14.8, 11.2 \text{ Hz, 1H}), 7.35 \ (s, 1H), 7.19 \ (d, J = 8.4 \text{ Hz, 2H}), 6.71 \ (d, J = 8.4 \text{ Hz, 2H}), 6.66 \ (d, J = 15.2 \text{ Hz, 1H}), 6.36 \ (dd, J = 15.2, 11.2 \text{ Hz, 1H}), 5.48 \ (d, J = 9.6 \text{ Hz, 1H}), 2.34-2.45 \ (m, 1H), 1.74 \ (s, 3H), 1.29-1.37 \ (m, 1H), 1.16-1.25 \ (m, 1H), 0.91 \ (d, J = 6.0 \text{ Hz, 3H}), 0.79 \ (t, J = 7.2 \text{ Hz, 3H}); \) \(^{13}\text{C} \) NMR (100 MHz, CD3OD) \(\delta 193.9, 176.7, 163.0, 156.9, 148.0, 145.8, 145.5, 138.9, 133.1, 129.9, 127.2, 125.1, 123.9, 114.9, 114.7, 106.3, 34.7, 29.9, 19.3, 11.3, 11.0; \) HRMS (ESI) \(m/z \) calcd for \(\text{C}_{23}\text{H}_{25}\text{NO}_{4}\text{Na} \ [\text{M+Na}]^{+} \) 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-dimethoxypyrine 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 Na₂SO₄ 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); [α]D²₂.⁵ = -19.4 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₄H₃₇NO₄Na [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-dimethyldec a-2,4,6-trienoyl)-4-hydroxyp yridin-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 (Na₂SO₄) 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: [α]D 22.5 = -20.4 (c = 0.25, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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 C₃₂H₃₃NO₄Na [M+Na]⁺ 518.2307; found 518.2300. 52b: ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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$_{4}$Na [M+Na]$^+$ 520.2464; found 520.2445.

(R,E,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$_2$SO$_4$) 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$_3$OD) $\delta$ 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$_3$OD) $\delta$ 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$_{4}$Na [M+Na]$^+$ 428.1838; found 428.1831.
3-((2E,4E,6E,10R)-8,10-dimethyldec-2,4,6-trienyl)-4-hydroxy-5-(4-hydroxyphenyl)pyridin-2(1H)-one, 9-H-farinose 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$_2$SO$_4$) 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-farinose A 5a, as a yellow solid; $^1$H NMR (400 MHz, CD$_3$OD) 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$_3$OD) 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$_4$Na [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 Na₂SO₄ 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, CDCl₃) 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, CDCl₃) 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 \( \text{C}_{36}\text{H}_{47}\text{NO}_5\text{SiNa} \ [\text{M+Na}]^+ \) 624.3121; found 624.3114.
(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 (Na₂SO₄) 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₉H₂₉NO₅Na [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\(_2\)SO\(_4\)) 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\(_3\)OD) \(\delta\) 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\(_3\)OD) \(\delta\) 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\(_{23}\)H\(_{24}\)NO\(_3\) [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 Na₂SO₄ 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₇H₄₇NO₂SiNa [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 (Na₂SO₄) 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 calc for C_{29}H_{29}NO_{3}Na [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)\textsuperscript{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$_2$SO$_4$) 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$_3$OD) 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$_3$OD) 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 and 10% (v/v) FBS. The cells were cultured in humidified 95% O\(_2\)/5% CO\(_2\) atmosphere incubator at 37 \(^\circ\)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 10\(^3\) 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 10\(^3\) 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 \(\mu\)M. After incubating for 48 h, inherent cells with DMEM were removed, washed with PBS followed by addition of 100 \(\mu\)L of DMEM and 15 \(\mu\)L of MTS while suspension cells were added directly with 15 \(\mu\)L 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% O₂/ 5% CO₂ 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

Montagnon, *Molecules that Changed the World*, Wiley-VCH: Weinheim, 2008; (c) P. Va, E. L.


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


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 apiopsoramide 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.

\[\text{Figure 1. Selected members of the pyridone alkaloids family}\]

### 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. 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. 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). 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.](image)

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 OCONEt₃, 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 ortho-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. 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°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

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Temp. (°C)</th>
<th>Yield[a]</th>
<th>Syn:anti[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-BuLi (4 equiv.)</td>
<td>-78 to r.t.</td>
<td>trace</td>
<td>n.d.</td>
</tr>
<tr>
<td>s-BuLi (4 equiv.)</td>
<td>-78 to r.t.</td>
<td>trace</td>
<td>n.d.</td>
</tr>
<tr>
<td>t-BuLi (4 equiv.)</td>
<td>-78 to r.t.</td>
<td>trace</td>
<td>n.d.</td>
</tr>
<tr>
<td>MESLi (4 equiv.)</td>
<td>-78 to r.t.</td>
<td>trace</td>
<td>n.d.</td>
</tr>
<tr>
<td>i-PrMgCl</td>
<td>-78 to r.t.</td>
<td>trace</td>
<td>n.d.</td>
</tr>
<tr>
<td>n-BuLi (4 equiv.) + TMEDA (4 equiv.)</td>
<td>-78 to r.t.</td>
<td>23</td>
<td>6:1</td>
</tr>
<tr>
<td>n-BuLi (4 equiv.) + HMPA (4 equiv.)</td>
<td>-78 to r.t.</td>
<td>11</td>
<td>5:1</td>
</tr>
<tr>
<td>s-BuLi (4 equiv.) + TMEDA (4 equiv.)</td>
<td>-78 to r.t.</td>
<td>34</td>
<td>9:1</td>
</tr>
<tr>
<td>t-BuLi (4 equiv.) + TMEDA (4 equiv.)</td>
<td>-78 to r.t.</td>
<td>18</td>
<td>10:1</td>
</tr>
<tr>
<td>s-BuLi (4 equiv.) + TMEDA (4 equiv.)</td>
<td>-30 to r.t.</td>
<td>complex</td>
<td>n.d.</td>
</tr>
<tr>
<td>s-BuLi (4 equiv.) + TMEDA (4 equiv.)</td>
<td>-60 to r.t.</td>
<td>41</td>
<td>10:1</td>
</tr>
</tbody>
</table>

[a] Isolated yield. [b] The ration determined by crude 1H 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 [α]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-H2O, 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, TiCl₄, TEA, DCM, 0 °C, 3 h; b) Pd/C, H₂, RT, 24 h, 84%, for 2 steps; c) TBSCI, DMAP, TEA, DCM, 0 °C to RT, 12 h, 97%; d) LiBH₄, Ether-MeOH, THF, -78 °C, 2 h, 86%; e) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C; f) Ph₃PCHCO₂Et, DCM, RT, overnight, 77% (over 2 steps); g) DIBAL-H, CH₂Cl₂, -78 °C, 2 h, 95%; h) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C; i) Ph₃PCHCO₂Et, DCM, RT, overnight, 69% for 2 steps; j) DIBAL-H, CH₂Cl₂, -78 °C, 2 h, 86%; k) (COCl)₂, DMSO, TEA, CH₂Cl₂, -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-H₂O, 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](image)

**Scheme 6.** Route to the total synthesis of Militarinone E.

![Scheme 7](image)

**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

![Chemical Structure](image)

**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 Na₂SO₄ 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%): R₆ = 0.4 (ethyl acetate/hexane = 5:1); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₉H₁₃NO₄Na 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 (Na2SO4). 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%): Rf = 0.35 (ethyl acetate/hexane = 2:1), 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 C11H17NO5Na 266.1004, found 266.1011.

4-((tert-butyldimethylsilyl)oxy)-1-(5-(1-hydroxyethyl)-4,6-bis(methoxymethoxy)pyridin-3-yl)ethanol (15)
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 (Na₂SO₄). 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): Rᵣ = 0.30 (ethyl acetate/hexane = 2:1), ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₃H₄₁NO₇SiNa 494.2550, found 494.2554.
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 °C. The reaction mixture was stirred at ambient temperature for 3 h. A solution of Na₂S₂O₃ and NaHCO₃ (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 NH₄Cl (10 mL), NaHCO₃ (10 mL), brine (10 mL) and dried (Na₂SO₄). 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%): Rf = 0.30 (ethyl acetate/hexane = 4:1), ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₃H₃₉NO₇SiNa 492.2393, found 492.2389.

(2E,4E,6E,8R,10R)-1-(5-((J₅,4S)-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 Na₂SO₄ 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): Rf = 0.4 (ethyl acetate/hexane = 3:1), [α]D²².₅ = -8.3 (c =
0.7, CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₃₆H₅₉NO₇SiNa [M + Na]⁺ 668.3959; found
668.3957.

N-deoxymilitarinone A (8)

To the compound 30 (19 mg, 0.03 mmol) in THF/H₂O (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 (Na₂SO₄) 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: Rₜ = 0.25 (CHCl₃/MeOH = 10:1), [α]²².₅ = -19.4 (c = 0.1, MeOH), ¹H 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); ¹³C 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 C₂₆H₃₇NO₅Na [M + Na]⁺ 466.2570; found 466.2567.

(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 TiCl₄ (1.8 mL, 16.3 mmol) via syringe. The mixture was stirred at 0 °C for 10 min and then Et₃N (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 NaHCO₃ solution. The mixture was extracted with CH₂Cl₂ (30 mL×3). The combined organic layers were washed with saturated aqueous NaHCO₃ (20 mL×2), saturated aqueous NH₄Cl (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.

![Chemical structure](image)

(4R)-4-Benzyl-3-[(2S)-2-(hydroxymethyl)butanoyl]oxazolidin-2-one (19a)

To a stirred solution of the mixture of 19 and (R)-4-benzyl-3-butyryloxazolidin-2-one obtained above in EtOH/CH₂Cl₂ (12:1, 65 mL) was added 10% Pd on carbon (1.0 g) under argon and then the vessel was filled with atmospheric H₂ using a balloon. The mixture was stirred for 23 h under H₂, 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: Rf = 0.35 (ethyl acetate/hexane = 2:1), [α]D₂₂.₅ = -52.1 (c =1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃)
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_{3}Na [M + Na]^+ 300.1212; found 300.1217.

(4R)-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 CH₂Cl₂ (23 mL) were added TBSCl (2.586 g, 17.25 mmol), DMAP (142 mg, 1.15 mmol) and Et₃N (3.26 mL, 23 mmol). The mixture was stirred at room temperature for 5.5 h, diluted with saturated aqueous NH₄Cl (30 mL) at 0 °C, and extracted with CH₂Cl₂ (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: Rᵣ = 0.65 (ethyl acetate/hexane = 5:1), [α]D 22.5 = -26.9 (c =0.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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_{3}SiNa [M + Na]^+ 414.2076; found 414.1080.
(2R)-2-(tert-Butyldimethylsilyloxyethyl)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 LiBH₄ (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 Na₂SO₄ 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%): Rₜ = 0.5 (ethyl acetate/hexane = 5:1), [α]D 22.5 = -25.1 (c = 1.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₁H₂₆O₃SiNa [M + Na]⁺ 241.1600; found 241.1603.

2-(Tert-butyldimethylsilyloxyethyl) butyraldehyde (21a)

To a solution of oxalyl chloride (854 µL, 10.1 mmol) in anhydrous CH₂Cl₂ (6 mL) was added dropwise a solution of DMSO (1.07 mL, 15.12 mmol) in CH₂Cl₂ (2 mL) at -78 °C. After 30 min, a solution of alcohol 21 (1.1 g, 5.04 mmol) in CH₂Cl₂ (4 mL)
was added at –78°C and the mixture was stirred for 30 min. Then triethyl 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 water and separated. The aqueous layer was extracted with ether. The combined organic phase was washed with aqueous HCl (2%) and then aqueous Na₂CO₃ solution (5%). After drying over MgSO₄ and filtration, the solvent was removed in vacuo to afford 1.1 g (100%) of the known 2-(tert-butyldimethylsilanyloxymethyl) butyraldehyde 21a, as a clear oil, which was used for next step without further purification; ¹H NMR (400 MHz, CDCl₃)  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); ¹³C NMR (100 MHz, CDCl₃)  δ 204.8, 61.6, 55.8, 25.8, 18.5, 18.2, 11.4, -5.6; HRMS (ESI) m/z calcd for C₁₁H₂₄O₂SiNa [M + Na]⁺ 239.1443; found 239.1438.

**Ethyl-(2E)-4-(tert-butyldimethylsilanyloxy-methyl)-2-hexenoate (22)**

A mixture of aldehyde 21a (crude from swern oxidation of alcohol 21, 3.0 mmol) and EtO₂CCH=PPh₃ (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: [α]D²².₅ = -14.4 (c = 1.5, CHCl₃), ¹H NMR (400 MHz, CDCl₃)  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$_3$) $\delta$ 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) $m/z$ calcld for C$_{13}$H$_{30}$O$_3$SiNa [M + Na]$^+$ 309.1862; found 309.1862.

4-(Tert-butyldimethylsilanyloxyethyl)-2-hexene-1-ol (22a)

To a solution of ethyl ester 22 (637 mg, 2.23 mmol) in anhydrous CH$_2$Cl$_2$ (7 mL) was added dropwise DIBAL-H (6.68 mL, 6.68 mmol, 1 M in hexane) at $-78^\circ$C. After 2 h, MeOH (1 mL) was added dropwise at $-78^\circ$C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-$\text{H}_2\text{O}$, 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$_2$SO$_4$. 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$_3$) $\delta$ 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$_3$) $\delta$ 134.3, 130.1, 66.3, 63.9, 46.7, 25.9, 23.8, 18.3, 11.6, -5.3; HRMS (ESI) $m/z$ calcld for C$_{13}$H$_{28}$O$_2$SiNa [M + Na]$^+$ 267.1756; found 267.1766.
(2E)-4-(tert-butyldimethylsilyloxymethyl)-hex-2-enal (22b)

To a solution of oxalyl chloride (357 µL, 4.22 mmol) in anhydrous CH₂Cl₂ (3 mL) was added dropwise a solution of DMSO (450 µL, 6.33 mmol) in CH₂Cl₂ (1 mL) at -78 °C. After 30 min, a solution of alcohol 22a (514 mg, 2.11 mmol) in CH₂Cl₂ (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 Na₂CO₃ solution (5%). After drying over MgSO₄ 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 EtO₂CCH=PPPh₃ (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: [α]D²²⁵ = -19.8 (c = 1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃) 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\(_3\)) \(\delta\) 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\(_3\)SiNa [M + Na]\(^+\) 335.2018; found 335.2016.

(2\(E\),4\(E\))-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\(_2\)Cl\(_2\) (3 mL) was added dropwise DIBAL-H (2.1 mL, 2.1 mmol, 1 M in hexane) at \(-78^\circ\)C. After 2 h, MeOH (1 mL) was added dropwise at \(-78^\circ\)C followed by EtOAc (10 mL) and sodium potassium tartrate (20%-H\(_2\)O, 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\(_2\)SO\(_4\). 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_3\)SiNa [M + Na]\(^+\) 293.1913;
found 293.1918.

(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 CH₂Cl₂ (2 mL) was added dropwise a solution of DMSO (170 µL, 2.4 mmol) in CH₂Cl₂ (0.5 mL) at -78 °C. After 30 min, a solution of alcohol 23a (160 mg, 0.59 mmol) in CH₂Cl₂ (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 Na₂CO₃ solution (5%). After drying over Na₂SO₄ 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: [α]D²².₅ = -23.6 (c = 1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₅H₂₈O₂SiNa [M + Na]⁺ 291.1756; found 291.1760.
(R,2E,4E,6E)-1-(5-((1S,4S)-4-((tert-butylidimethylsilyl)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 Na₂SO₄ 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): Rₜ = 0.4 (ethyl acetate/hexane = 3:1), [α]D²₂.₅ = -20.4 (c = 0.6, CHCl₃), ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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_{63}NO_{10}Si_{2}Na [M + Na]^+ 742.4147; found 742.4150.

**Torrubiellones B (10)**

To the compound 25 (22 mg, 0.03 mmol) in THF/H_{2}O (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_{2}SO_{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), [α]_{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_{20}NO_{6}Na [M + Na]^+ 426.1893; found 426.1895.
4.5 References


9 C5-substituted alcohol 16a was observed when the reaction was treated with 3.0 equiv. of t-BuLi.

![Diagram](image_url)

10 See Experimental Section for the details.


PUBLICATIONS

1. “Ferrier-Type N-Glycosylation: Synthesis of N-Glycosides of Enone Sugars”


2. “Synthesis of (R)-Mellein by a Partially Reducing Iterative Polyketide Synthase”


4. “Direct and Stereoselective Synthesis of 1,3-cis-3-Arylsulphonaminodeoxy-disaccharides and Oligosaccharides”


5. “Ready access to 3-amino-2,3-dideoxysugars via regio- and stereo-selective tandem hydroamination/glycosylation of glycols”


6. “A Short and Highly Efficient Synthesis of L-Ristosamine and L-epi-Daunosamine Glycosides”

7. “A mild and efficient synthetic protocol for Ferrier azaglycosylation promoted by ZnCl$_2$/Al$_2$O$_3$”


8. “Pathways Leading to 3-Amino- and 3-Nitro-2,3-dideoxy Sugars: Strategies and Synthesis”


**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, “6$^{th}$ 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)


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”