De Novo Asymmetric Synthesis of C-linked and O-linked Aryl Natural Products

by Qi Zhang

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Dissertation directed by
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Professor of Chemistry and Chemical Biology
DEDICATED to

My father Hemin Zhang

& My mother Fenglan Chen
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ABSTRACT

The carbohydrate portion of many natural products play an important role in their biological activities, such as target binding, solubility, tissue targeting, and membrane transportation. A review of carbohydrate containing natural products leads to the realization that nature uses a myriad of rare carbohydrate structural motifs. In order to explore and exploit these structural motifs for medicinal chemistry structure-activity relationship (SAR) studies, chemists have desired new synthetic approaches that allow for the preparation of unnatural rare sugars and analogous structural motifs. In this regard, the O’Doherty group has developed a divergent de novo methodology to build the desired sugar functionality and stereochemistry from simple achiral 2-keto-furanyl starting materials, which stands in contrast to the traditional method that use the limited number of known carbohydrates as starting materials. Outlined in Chapter 1 Section I is the O’Doherty approach to carbohydrates, which relies on a highly enantioselective Noyori asymmetric reduction reaction, a highly diastereoselective palladium (0)-catalyzed glycosylation reaction to install the stereochemistry. Subsequent post-glycosylation transformations are then used to introduce the remaining sugar functionality.

Digitoxin is a naturally occurring cardiac glycoside, which has been used for the treatment of congestive heart failure, via enhancing cardiac contraction. More recently, digitoxin has been shown to possess anticancer activity. Chapter 1 Section II shows our synthetic and biological studies into the structure activity relationship (SAR) effects on C5’-alkyl substitution on the α-L-sugar (steric effect). The results revealed an inverse relationship between size of the group and cytotoxicity.
The natural product SL0101 is the first specific inhibitor of p90 ribosomal kinase (RSK). We corporately developed a diastereoselective approach for the synthesis of both L- and D-sugar analogues with different degree of acylation. Further, studies involved substitution of the C5’ position (methyl, ethyl, n-propyl, i-butyl). In this regard, a series of analogues were synthesized and evaluated for biological activity. Based on the success of the C5’-alkyl substitution of SL0101, we continued our investigation of C4’-amido and C4’-keto modifications to improve the resistance to ester hydrolysis. Four targets of C4’-amido analogues were made. The C4’-keto series is still undergoing.

The nanaomycins and griseusins are structurally related antibiotic natural products from a family of pyranonaphthoquinone. This family contain a naphtho[2,3-c]pyran-5,10-dione core, with griseusins possessing an additional spiroketal 1,7-dioxaspiro[5,5]undecane ring. The nanaomycins displayed biological activity against a variety of gram-positive bacteria, pathogenic fungi, yeasts, as well as, antiviral activity. A 12-step synthesis of nanaomycin A was completed starting from simple achiral 1,5-dihydroxynaphthalene. Several typical reactions such as Claisen rearrangement of the allyl group, quinone-dimethoxy quinonol interconversion, Sharpless dihydroxylation to install the first stereocenter, 1,3-trans pyran ring formation, nitrile hydrolysis were researched and utilized to finish the total synthesis of natural product (–)-nanaomycin A and (–)-nanaomycin D. Griseusin A was envisioned as resulting from the coupling of a key intermediate β-hydroxy nitrile from the nanaomycin synthesis with a carboxylic acid with protected 1,3-cis-diol. This carboxylic acid was made via a 9-step sequence starting from achiral ethyl sorbate. The route began with a Sharpless dihydroxylation to secure a 1,2-cis-diol, which was converted into a cyclic carbonate and then reduced to give an
allylic alcohol. A second Sharpless dihydroxylation provided the 1,3,4-cis-triol. Benzylidene protection of the 1,3-cis-diol allowed the subsequent Mitsunobu inversion of the C4 stereochemistry. Mom-protection of the hydroxyl and a final saponification should give the desired carboxylic acid for coupling. The practical routes for completing the total synthesis of enantiomeric griseusin A and B are still under investigation.
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<th>Abbreviation</th>
<th>Meaning</th>
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<td>Ac</td>
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<tr>
<td>Ac$_2$O</td>
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<td>AcOH</td>
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<td>Agly</td>
<td>aglycon</td>
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<td>ATP</td>
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<td>Bn</td>
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Chapter 1. *De novo* methods towards various carbohydrates and its applications on SAR study of digitoxin as anticancer agent

Section 1. *De novo* methods towards various carbohydrates

1.1.1. Introduction

Over the past two decades, the O’Doherty group has gradually established new methods towards the synthesis of natural and unnatural carbohydrates.\(^1\) Compared to the traditional approach in which a carbohydrate containing starting material is needed,\(^2\) this *de novo* method starts with simple achiral starting materials to install any desired sugar’s functionality with well-defined stereochemistry. This ‘*de novo*’ approach broadens the range of SAR-amenable research of various carbohydrate containing natural products.

The principal idea of this strategy involves utilizing an asymmetric transition metal catalyst to design any of the desired stereocenters in either monosaccharides or oligosaccharides.\(^3\) To summarize the results of the successful *de novo* approach to carbohydrates, there are three fundamental steps: (1) asymmetric synthesis of pyranone as a glycosyl donor; (2) palladium catalyzed diastereoselective glycosylation; (3) post-glycosylation transformations (Scheme 1.1.1).

**Scheme 1.1.1. *De novo* synthesis of carbohydrate sugars**

![Scheme 1.1.1](image)

**1.1.2. Pyranone synthesis**

The installation of the desired final D- and L-sugar stereoschemistry of the Boc-protected pyranone as glycosyl donors relies on the success of a highly enantioselective
Noyori asymmetric reduction of furan ketone 1-1a and its modified derivatives (Scheme 1.1.2). Highly enantiomerically pure furfural alcohol (S)-1-5a and (R)-1-5a can be achieved in either form of stereoselectivity using different catalyst, which was then rearranged into a diastereomeric mixture of pyranyl alcohols L-1-6a and D-1-6a via Achmatowicz oxidative rearrangement reactions. Different reaction conditions were used to provide different selectivity of α or β isomers: giving α-Boc-pyranone (α-L-1-7a and α-D-1-7a) as the major isomer at −78 ºC or β-Boc-pyranone (β-L-1-7a and β-D-1-7a) as the major isomer at 80 ºC (Not shown in Scheme). Remarkably, the simplest R = Me structures of these Boc-pyranones are naturally occurring and recognized as the hexose pyranoside aculose.

**Scheme 1.1.2. De novo synthesis of Boc-pyranones**

To expand upon our ability to perform SAR studies, other furfural alcohol derivatives bearing different R¹ functional groups (i.e., R¹ = Et, n-Pr, i-Pr, i-Bu, CH₂OH, CH₂NH₂, etc.) were synthesized (Scheme 1.1.3). The four-step synthesis broadens the versatility and diversity of the Boc-pyranone based glycosyl donors.
Scheme 1.1.3. Synthesis of C5'-substituted Boc-pyranones via organolithium

1) NBS, THF/H2O
NaOAc·3H2O
NaHCO3, 0 ºC, 1 h
2) Boc2O, DMAP
CH2Cl2, –78 ºC, 12 h

1-1b: R1 = Et (64%)
1-1c: R1 = n-Pr (72%)
1-1d: R1 = i-Pr (68%)
1-1e: R1 = i-Bu (70%)
1-5b: R1 = Et (65%)
1-5c: R1 = n-Pr (81%)
1-5d: R1 = i-Pr (61%)
1-5e: R1 = i-Bu (81%)

1.1.3. Palladium-catalyzed glycosylation

Glycosylation is a typical method that could couple partially protected sugar moieties with a nucleophile (typically an alcohol) via the formation of a glycosidic bond (Scheme 1.1.4). The glycosidic bond is formed via a nucleophilic substitution of the leaving group (LG) on the anomeric carbon of the sugar moiety (glycosyl donor) by a nucleophile (glycosyl acceptor, e.g. R2OH) through the oxocarbenium intermediate under the catalytic assistance of certain promoters (e.g. E+X–). Generally, this method encounters issues with facial selectivity and thus forms both possible isomers (i.e. α- or β-isomer).

Traditional glycosylation coupling to form carbohydrates has some disadvantages such as sensitivity to moisture, temperature, solvent and structures of substrates and, most importantly, stereoselectivity control. The facial selectivity is mainly based on the substrates and the nucleophiles. Due to the anomeric effect, the α-glycosides are usually formed majorly for gluco- or manno- sugars. The absolute control of anomeric

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1 H.-Y. L. Wang, B. Wu, Q. Zhang, S.-W. Kang, Y. Rojanasakul, G. A. O’Doherty, ACS Med. Chem. Lett., 2011, 2, 259. Dr. Hua-Yu Leo Wang made the pyranone 1-1c and Dr. Bulan Wu provided the NMR spectra for pyranone 1-1c, Qi Zhang made the pyranones 1-1b, 1-1d and 1-1e and provided the NMR spectra.
configuration of the product is challenging when the reaction occurs via a S_N1 mechanism.

**Scheme 1.1.4.** Representative classical glycosylation methods

![Scheme 1.1.4. Representative classical glycosylation methods](image)

Over the past two decades, the O’Doherty group has developed new methodologies for the *de novo* carbohydrate synthesis of natural and unnatural products. Palladium-catalyzed glycosylation successfully coupled glycosyl donor and glycosyl acceptor with both highly regio- and diastereoselectively. For example, the reaction with α-Boc-protected pyranone gives only the α-anomer while the reaction with β-Boc-protected pyranone gives only the β-anomer under mild conditions (from 0 °C to room temperature in a variety of solvents such as CH_2Cl_2, THF, CH_3CN, Et_2O) in good yields. The catalyst loading, of 0.5-5 mol % and the ratio of palladium source to PPh₃ of 1 to 2, seem to be ideal.

Mechanistically, the glycosylation reaction proceeds through a π-allyl palladium intermediate. The whole process occurs via two inversions of configuration and thus keeps in overall retention of configuration. The displacement of Boc-group by Pd(0) catalyst gives a π-allyl complex with the first inversion. Nucleophilic attack onto this complex arises from the opposite face of bulky PdL₂ as a second inversion thus resulting an overall net retention of configuration.
Scheme 1.1.5. Regio- and diastereoslective palladium catalyzed glycosylation via Pd-π-allyl intermediate

1.1.4. Post-glycosylation transformations

After palladium-catalyzed glycosylation, the enone could be furnished by several post-glycosylation reactions to approach the final targets without excessive use of protecting groups that are generally required in the classical glycosylation methods. For example, the enone could be reduced highly stereoselectively under the Luche reduction conditions (NaBH₄/CeCl₃) to install the C4-equatorial stereochemistry. The consequential allylic alcohol would transform to rhamno-sugar under Upjohn dihydroxylation conditions, or undergo a Mitsunobu inversion to convert the C4-equatorial stereochemistry to C4-axial. Particularly, depending on the C4 stereochemistry (equatorial or axial), the dihydroxylation product diol could be installed with rhamno-, manno-, gulo- and talo-stereochemistry. Similarly, diimide reduction of the double bond would produce C2/C3-dideoxy sugars (i.e., amicetose or rhodinose) (Scheme 1.1.6).
Scheme 1.1.6. Post-glycosylation transformations of α-L-Boc-pyranosides

Section 2. Application of Boc-pyranones on SAR study of digitoxin as anticancer agent

1.2.1. Introduction

Cardiotonic steroids (CTSs) such as digitoxin and digoxin are known to be potent inhibitors of enzyme Na/K-ATPase. Na/K-ATPase (a.k.a., Na/K-pump) is a P-type ATP driven cation transporter which pumps three Na cations out of the cell while pumping two K cations into the cell. The imbalanced exchange creates a working potential across the plasma membrane within the cell. This potential gradient is essential to neuronal signaling, muscle contraction and solute/substrate co-transportation.

In cardiac myocytes, the Na/K-ATPase binds drug cardiotonic steroid to inhibit the sodium pump and accumulate high concentration gradient of Na⁺ and thus trigger Ca²⁺ influx. The positive inotropic effect (myocardial contraction) can be enhanced via the increased diastolic Ca²⁺ levels, which triggers additional calcium release. However, there is a potential fatal side effect of this inhibition, which is calcium overload giving rise to arrhythmia (an irregular heartbeat). Even with this deadly side effect, cardiotonic steroids are still widely recognized as useful treatment for congestive heart failure.
1.2.2. Structures of cardiac glycosides

Structurally, cardiotonic steroids contain a basic steroidal skeleton and an unsaturated lactone ring substituted on the D-ring at C17. Compounds with an A-ring free alcohol at C3 are classified as genins, whereas most of these naturally occurring products usually are glycosylated with a mono-, di-, tri- and tetra-saccharide to the hydroxyl group (Figure 1.2.1). Two typical types of lactone rings are unsaturated $\gamma$-butyrolactone or $\alpha$-pyrone rings, which define the two families of aglycons of cardenolides (unsaturated $\gamma$-butyrolactone) and bufadienolides ($\alpha$-pyrone). Other alterations at the C1, C5, C11, C12 and/or C16 positions of the steroidal core with different functional groups (i.e., ester, aldehyde and alcohol) are also found.\textsuperscript{13} On the other side, the carbohydrate portion includes various sugars with different stereochemistries, such as manno-, gluco-, galacto-, allo-, and gulo-, in either $\alpha$-L or $\beta$-D configurations, as well as some deoxy sugar patterns.
Many Na/K-ATPase inhibitors (natural products or chemically modified natural products) are under investigation as therapeutic drugs for cancers and heart failure diseases. Among those, the family of cardiac glycosides especially digitoxins and digoxins drew much attention due to their potency of inhibition of Na/K-ATPase as well as its effective results in the treatment of cancers.

1.2.3. SAR study – C5’-substitution effect in rhamnosyl and amicetosyl digitoxins

1.2.3.1. Introduction

Thorson et al. revealed the first SAR study of digitoxins for comparison of anticancer activities in 2005.14 Previously, Dr. Hua-Yu Leo Wang finished a series of synthetic SAR
studies on the sugar part of digitoxin for apoptotic cytotoxicity against NCI-H460. His studies included (1) O- versus N-glycosidic linkage; (2) mono-, di-, and tri-saccharide forms; (3) O-linked monosaccharide stereochemistry; (4) sugar-chain length effect in rhamnosyl and amicetosyl digitoxin; (5) C5’-substitution effect in rhamnosyl and amicetosyl digitoxin; (6) stereochemical effect of α-L-rhamno-C3’/C4’-deoxy sugar congeners of SAR study of digitoxin analogues as anticancer agent. The following section will focus on the C5’-alkyl modifications in rhamnosyl and amicetosyl digitoxin, which was contributed by me and other coworkers.

From his studies, Dr. Wang concluded that the O-glycosides were more active than MeON-neoglycosides (N-glycosides), and the sugars with β-D-digitoxo-, α-L-amiceto, and α-L-rhamno stereochemistry were the most active. The monosaccharides were better than the di- or tri-saccharides regardless of O- and N-glycosidic linkage, or the α- and β-stereochemistry. We chose to synthesize and test the significance of the C5’-alkyl position to investigate the roles of the sugar part of the α-L-digitoxin glycoside and complete the synthetic SAR studies. Herein our successful chemical synthesis and biological evaluation of five digitoxin α-L-rhamnosides (1-9a to 1-9e) and four digitoxin α-L-amicetosides (1-10a to 1-10b, 1-10d to 1-10e) are reported (Figure 1.2.2).

**Figure 1.2.2.** Digitoxin and related C5’-alkyl substituted analogues

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<tr>
<th>The β-D-digitoses</th>
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<td>Digitoxin di-O-digitoxoside</td>
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<td>Digitoxin (natural)</td>
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<tr>
<td>1-9a: R¹ = Me</td>
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<tr>
<td>1-9b: R¹ = Et</td>
</tr>
<tr>
<td>1-9c: R¹ = n-Pr</td>
</tr>
<tr>
<td>1-9d: R¹ = i-Pr</td>
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<tr>
<td>1-9e: R¹ = i-Bu</td>
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<table>
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</thead>
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<tr>
<td>1-10a: R¹ = Me</td>
</tr>
<tr>
<td>1-10b: R¹ = Et</td>
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<tr>
<td>1-10c: N/A</td>
</tr>
<tr>
<td>1-10d: R¹ = i-Pr</td>
</tr>
<tr>
<td>1-10e: R¹ = i-Bu</td>
</tr>
</tbody>
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1.2.3.2. Synthesis of C5'-alkyl modifications of rhamno-/amiceto-digitoxin analogues

The retrosynthetic analysis of the synthesis of diverse C5’-modified alkyl analogues is outlined in Scheme 1.2.1. We proposed that the targeted rhamno- (with $R^2$, $R^3 = \text{OH}$) or amiceto- (with $R^2$, $R^3 = \text{H}$) functionality and stereochemistry could be completed by several post-glycosylation transformations including a diastereoselective NaBH$_4$ reduction and an Upjohn dihydroxylation, or a diimide reduction of the stereoselective palladium catalyzed glycosylation product digitoxin pyranone precursors (1-11a to 1-11e). The glycosylation couples digitoxigenin (DigOH) with various $\alpha$-L-Boc pyranones ($\alpha$-L-1-7a to $\alpha$-L-1-7e). These desired glycosyl donors could be prepared by applying our group’s de novo asymmetric carbohydrate synthesis from the achiral starting material furan and carboxylic acids ($R^1\text{CO}_2\text{H}$) with different chain length and substitution patterns.

**Scheme 1.2.1.** Retrosynthetic analysis of C5’-subsstituted digitoxin monosaccharide analogues

As shown in Scheme 1.1.3, the C5’-substituted Boc-pyranones $\alpha$-L-1-7b to $\alpha$-L-1-7e were achieved by coupling of the achiral furan with propionic acid ($R^1 = \text{Et}$), butyric acid ($R^1 = \text{n-Pr}$), iso-butyric acid ($R^1 = \text{i-Pr}$), iso-valeric acid ($R^1 = \text{i-Bu}$) respectively. This
one-pot two-step procedure begins with the addition of furan to a hexane-stabilized solution of \( n\)-BuLi, which \textit{in situ} generated the 2-lithiofuran. To this mixed solution was added a THF solution of corresponding carboxylic acid to produce 1-1b to 1-1e in good yields. Noyori (S,S) asymmetric reduction (Noyori (S,S), HCO\(_2\)Na (aq.), 10 mol % CTAB) successfully converted the acetylfurans (furan ketones) into the desired enantiomerically enriched furfural alcohols 1-5b to 1-5e with excellent >98% enantiomeric excess in good yields. Then Achmatowicz rearrangement conditions (NBS/H\(_2\)O) oxidized the functionalized furfural alcohols to a diastereomeric mixture of pyranyl alcohols 1-5b to 1-5e. Subsequent protection of those \( \alpha \) and \( \beta \) diastereomers with Boc\(_2\)O provided the \( \alpha \)-Boc-pyranones a-L-1-7b to a-L-1-7e with modest selectivity (1.8:1 to 2.7:1). Careful chromatography afforded the pure \( \alpha \)-Boc-pyranones. With all desired C5’-alkyl substituted \( \alpha \)-L-Boc-pyranone as glycosyl donors (a-L-1-7a to a-L-1-7e) in hand, we then moved forward to the palladium catalyzed glycosylation reactions (5 mol % Pd(PPh\(_3\))\(_2\)) with aglycon digitoxigenin. This procedure generated the key intermediate \( \alpha \)-L-digitoxin pyranones 1-11a to 1-11e (82-98%) as single diastereomers due to the absolute stereocontrol at anomeric center by the \( \pi \)-allyl intermediates (See Scheme 1.1.5). Luche reduction (NaBH\(_4\)/CeCl\(_3\)) introduced the C4’-equatorial hydroxyl group selectively as allylic alcohols 1-12a to 1-12e (77-99%). The double bonds of the allylic alcohols were easily dihydroxylated under Upjohn conditions (NMO/OsO\(_4\)) to give the C5’-alkyl-substitued \textit{rhamno}-digitoxin analogues 1-9a to 1-9e (74-93%) (See Scheme 1.2.2). Alternatively, reactions with diimide reduction conditions (NBSH/NMM) yielded the C5’-alkyl-substitued \textit{amiceto}-digitoxin analogues 1-10a to 1-10b, 1-10d to 1-10e (85-92%) (See Scheme 1.2.3).
Scheme 1.2.2. Synthesis of C5’-substituted *rhamno*-digitoxin analogues

Scheme 1.2.3. Synthesis of C5’-substituted *amiceto*-digitoxin analogues

1.2.3.3. Biological evaluation of C5’-alkyl substituted digitoxin analogues

With all the available *rhamno*- and *amiceto*-glycosides in hand, Dr. Wang started to evaluate the apoptotic cytotoxicity against NCI-H460 human lung cancer cells. The total of nine analogues were tested using the Hoechst 33342 nuclear stain and propidium iodide method at a fixed single concentration (50 nM) for 12 hours when the degree and
the mechanism of cell death was determined (apoptosis versus necrosis) (Figure 1.2.3).

All nine analogues exhibited different degrees of cytotoxicity with the shortest chain length of alkyl substitution C5'-Me analogues being most cytotoxic (Figure 1.2.3. A and B). Apoptosis was considered the principal mechanism of cell death regardless of potency for all of the analogues. Interestingly, with the increasing chain length/size of the C5' alkyl substituents, the apoptosis activity was decreased significantly. The reasons are still not fully understood. The cells with condensed and fragmented nuclei were stained by the blue Hoechst 33342 are indicative of apoptosis, while the ruptured cells underwent necrosis were stained red with propidium iodide (Figure 1.2.3. C and D).

**Figure 1.2.3.** Apoptotic cell death as effect of steric hindrance at C5'-stereocenter. A. & B. Apoptotic cell death (%) was compared for each C5'-alkyl substituted digitoxin rhamnoside and amicetoside at 50 nM (One-way ANOVA; N = 6; ***, P < 0.001). C. & D. Hoechst stained apoptotic cells appear in blue and propidium iodide stained necrotic cells in red at 50 nM.
**Figure 1.2.4.** Dose-dependent cytotoxicity in the comparison of C5’-alkyl substitution.

Dose response curve of total cell death (apoptosis/necrosis) mediated by digitoxin analogs in a 12 h treatment at increasing concentration (10 nM to 10 µM). All the data were analyzed by two-way ANOVA (N = 6; *, P < 0.05; **, P < 0.01; ***, P < 0.001).

Subsequently, the cytotoxicity was examined under the treatment of increasing concentration (10 nM to 10 µM) in 12 hours session. Outlined in Figure 1.2.4, the results revealed the dose-dependent manner of the apoptotic cell death for all the analogues. The non-linear regressed IC$_{50}$ values were detailed in Table 1.2.1. As seen in single dose experiments, the IC$_{50}$ values boosted correspondingly with the chain length/size of C5’-substituent, although the potency of the C5’-Et-rhamno-analogue 1-9b (IC$_{50}$ ~ 57 nM) was only marginally weaker than the C5’-Me-rhamno-analogue 1-9a (IC$_{50}$ ~ 52 nM). Remarkably, this steric effect seemed to be more obvious on the amiceto-series, in which there was a more substantial increment in the IC$_{50}$ values with the gradually modified larger size of the C5’-alkyl groups.
Table 1.2.1. IC_{50} (nM) and GI_{50} (nM) of digitoxin analogues against NCI-H460 cells.

The IC_{50} value was measured by a 12 h treatment in Hoechst and propidium iodide stain assays. The GI_{50} value was measured by a 48 h treatment in an MTT assay. All values represent the standard error of the mean value of three independent experiments with duplicate determinations.

<table>
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<th>Compound</th>
<th>IC_{50}</th>
<th>GI_{50}</th>
<th>Compound</th>
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<td>(α-L-amicetosides)</td>
<td>(α-L-rhamnosides)</td>
<td>(α-L-amicetosides)</td>
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<td></td>
</tr>
<tr>
<td>C5'-Me 1-9a</td>
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<td>2</td>
<td>C5'-Me 1-10a</td>
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<td>2</td>
</tr>
<tr>
<td>C5'-Et 1-9b</td>
<td>57</td>
<td>2</td>
<td>C5'-Et 1-10b</td>
<td>87</td>
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<tr>
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<td>5</td>
<td>C5'-n-Pr 1-10c</td>
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</tr>
<tr>
<td>C5'-i-Pr 1-9d</td>
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<td>6</td>
<td>C5'-i-Pr 1-10d</td>
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<td>13</td>
<td>C5'-i-Bu 1-10e</td>
<td>458</td>
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To determine if this steric effect was not specific to apoptosis, we decided to test the cytotoxicity with a different assay. The MTT assay was chosen for comparison. The MTT assay evaluated the cell viability based on the measurement of mitochondrial enzymatic activity after 48 hours exposure. The cell viability results (Figure 1.2.5 and Table 1.2.1) indicated that the dose-dependent anticancer activity of any single analogue was similar to that of in the apoptosis assay. With the increasing chain length/size of C5'-substituent, the decrease in cytotoxicity was also observed and this tendency was consistent across both rhamnosides and amicetosides series. However, the greater sensitivity to steric effect of the amiceto- series than the rhamno- series in the apoptosis was not found in the MTT assay.

Figure 1.2.5. Dose-dependent cell viability in the comparison of C5’-alkyl substitution. The dose response curve of cell viability in a 48 h treatment at increasing concentrations (1 nM to 10 µM). All the data were analyzed by two-way ANOVA (N = 6; *, P < 0.05; **, P < 0.01; ***, P < 0.001).

A) α-L-rhamnoside
- C5'-Me 1-9a
- C5'-Et 1-9b
- C5'-n-Pr 1-9c
- C5'-i-Pr 1-9d
- C5'-i-Bu 1-9e

B) α-L-amicetoside
- C5'-Me 1-10a
- C5'-Et 1-10b
- C5'-n-Pr 1-10c
- C5'-i-Pr 1-10d
- C5'-i-Bu 1-10e
1.2.4. Conclusion

In summary, the SAR study of C5’-alkyl substitution on α-L-rhamno-digitoxins (1-9a to 1-9e) and α-L-amiceto-digitoxins (1-10a to 1-10b, 1-10d to 1-10e) were fully examined. The biological results suggested that both series of the rhamno- and amiceto-analogues occupy a very similar binding site and orientation in its targets holding a small hydrophobic pocket for the C5’-alkyl group. As in the single dose experiments, the IC_{50} values increased greatly with the size of C5’-substituent. The sensitivity to this negative steric effect greatly increased as subsequent methylene groups were added. Our flexible divergent de novo approach to the synthesis of carbohydrates eased the systematic SAR study. Further research for optimizing cytotoxicity and revelation of mechanism are needed.
Reference:


Chapter 2. De novo asymmetric syntheses of SL0101 and its analogues

Section I. De novo asymmetric synthesis of SL0101 and analogues and its D-sugar enantiomer analogues

2.1.1. Introduction

P90 Ribosomal S6 Kinase (P90-RSK) is one of the subfamily of RSK family of kinases and has an important downstream effect on mitogen-activated protein kinase (MAPK). In human cells, four distinct RSK isoforms were identified. The isoforms have an amino-terminal kinase domain (NTKD) and a carboxyl-terminal kinase domain (CTKD). The NTKD is responsible for the phosphorylation of exogenous substrates and preferentially phosphorylates at serine/threonine residues, whereas the CTKD is only known for autophosphorylation of the linker region.\(^1\) The mechanism of RSK activation is still not well understood. Some studies show that the docking site for MAPK at the extreme carboxyl terminus of RSK is one of the requirements for specific MAPK phosphorylation of RSK.\(^2\) For the past decade, Smith, Hecht and Lannigan have been working on finding RSK-specific inhibitors. They have screened extensive amounts of botanical extracts derived from rare plants and found that only one extract can inhibit the RSK2 isoform without inhibiting the tyrosine kinase (FAK). This extract was from a South American rainforest dogbane plant named Forsteronia refracta, and was isolated, identified, characterized and named as SL0101. It inhibited 90% RSK activity, and at the same time did not inhibit PKA, p70 S6K or MSK1 to a better extent than FAK thus showing it had a specific inhibitory feature for RSK2 compared to these other AGC kinase family members. Subsequent biological testing revealed that SL0101 could inhibit
proliferation of the human breast cancer cell line MCF-7 without affecting proliferation of the normal human breast cancer cell line MCF-10A, although it inhibits RSK in these cells (Figure 2.1.1). The kaempferol glycosides like other flavonoids are believed to be active in many biological activities. Structurally, SL0101 is a diaecylated kaempferol L-rhamnoside, one of a class of multi-acylated kaempferol L-rhamnosides (2-1a-A to 2-1a-E).

**Figure 2.1.1.** Structure and RSK2 inhibitory activities of natural product SL0101 (2-1a-A) for breast cancer cell line MCF-7. SL0101 selectively inhibits MCF-7 cell proliferation. MCF-7 (solid dots) and MCF-10A (hollow squares) cells were treated with vehicle or indicated concentration of SL0101, and cell viability was measured after 48 hours of treatment. Values are fold proliferation as a percentage of that observed with vehicle-treated cells. Points, mean (n = 3 in quadruplicate); bars, SD.

Our interest in chemically synthesizing SL0101 (2-1a-A) was piqued by the literature report that natural SL0101 showed about 150 times greater activity than the simple kaempferol. In addition, we realized the importance of the displacement of acetyl groups on different positions on the α-L-rhamnose for the SAR study of SL0101 (2-1a-A) (Figure 2.1.2).
Figure 2.1.2. RSK2 inhibitory activities of SL0101 (2-1a-A) and its analogues (2-1a-B to 2-1a-E) and kaempferol aglycon 2-2a

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>R³</th>
<th>IC₅₀ (RSK2)</th>
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<tbody>
<tr>
<td>2-1a-A</td>
<td>Ac</td>
<td>Ac</td>
<td>H</td>
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<tr>
<td>2-1a-B</td>
<td>H</td>
<td>H</td>
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<tr>
<td>2-1a-C</td>
<td>Ac</td>
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<tr>
<td>2-1a-D</td>
<td>Ac</td>
<td>H</td>
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</tr>
<tr>
<td>2-1a-E</td>
<td>Ac</td>
<td>H</td>
<td>Ac</td>
</tr>
<tr>
<td>2-2a</td>
<td></td>
<td></td>
<td>15 µM</td>
</tr>
</tbody>
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2.1.2. Hecht’s method of synthesis of SL0101 (2-1a-A)

In 2005 Prof. Hecht reported the first total synthesis of SL0101. This synthesis was based on using rhamnosyl bromide as a glycosyl donor and flavonol aglycon as a glycosyl acceptor under the catalysis of silver (II) oxide. Rhamnosyl bromide was derived from L-rhamnose via intermediate thioglycoside. The absolute and relative stereochemistry was all derived from this specific L-rhamnose.

In contrast, we were interested in the viability of preparation of SL0101 and its analogues of this class of kaempferol glycosides for different variations. We were not only interested in roles the specific sugar part play in the biological performance but also the roles of different acetyl groups on the sugar part play in the SAR study of SL0101. In our initial effort at elucidating the roles of the sugar and various acetyl groups, we decided to synthesize both SL0101 (L-rhamnose) and its enantiomer (D-rhamnose) and their analogues for biological investigation (Figure 2.1.3).
2.1.3. Retrosynthetic analysis of L- and D-sugar kaempferol rhamno-pyranosides

Retrosynthetically, we proposed that all final compounds could be derived from a glycosylated pyranone 2-3a and (ent)-2-3a via several steps of post-glycosylation transformations (Scheme 2.1.1). Applying our *de novo* palladium-catalyzed glycosylation could couple the flavonol aglycon 2-2 with both $\alpha$-L-1-7a and $\alpha$-D-1-7a Boc-pyranones, which could be prepared from achiral acetylfuran 1-1a. Post-glycosylation transformations include Luche reduction ($\text{NaBH}_4$) and Upjohn dihydroxylation ($\text{OsO}_4$/NMO), which sequentially installed the *manno*-stereochemistry.\(^5\) C4’-acyl group introduction could be achieved in between the reduction and dihydroxylation by an acylation reaction. Originally, Dr. Shan and Dr. Wu utilized a combination of selective orthoester hydrolysis\(^6\) and acyl migration reactions to differentiate the C2’-hydroxyl group from C3’-hydroxyl group. Dr. Shan successfully synthesized SL0101 and four L-rhamnose analogues and one D-rhamnose analogue,\(^7\) Dr. Wu made three D-rhamnose analogues.\(^8\) To replenish materials for biological studies, I made both of the natural SL0101 (2-1a-A) and its D-enantiomer (ent)-2-1a-A by a synthesis which used for
improving selective installation of the 3'-acetate using Taylor’s catalyst borinic acid methodology. Our method for preparing both L- and D-pyranones showed the advantages of being amenable to the divergent preparation of diverse analogues in either L- or D-enantiomers (See Figure 2.1.3).

**Scheme 2.1.1.** Retrosynthetic analysis of α-L- and α-D-sugar kaempferol rhamnosides

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### 2.1.4. Synthesis of Boc-pyranones as glycosyl donors

Our synthesis of started with achiral acetylfuran and used a Noyori asymmetric reduction to establish the L- or D-stereochemistry (Scheme 1.1.2). In the presence of Noyori (S,S) catalyst, HCO₂H and Et₃N (hydrde source) were added at room temperature for more than 24 hours. Alternatively, HCO₂Na as hydrde source can be used with surfactant CTAB (see Chapter 1, Section II). Under these conditions, the achiral acetylfurans were converted to furfural alcohol in high yields with high enantiomeric excess (e.e. > 96%), which could be transformed to hemiacetal via an Achmatowiz
rearrangement reaction in high yields. Following t-butyl carbonate (Boc) protection would differentiate both α- and β-isomers of furfural alcohol and predominantly give α-Boc pyranone at low temperature (i.e. –78 °C) with a range of 1.8:1 to 2.7:1 diastereomeric ratio of α-Boc pyranone versus β-Boc pyranone. Simply using Noyori (R,R) catalyst would switch the stereocenter of the furfural alcohol and in turn lead to the D-sugar precursor.

2.1.5. Glycosylation and post-glycosylation transformations to synthesize targets

Flavonol aglycon 2-2 was provided by Dr. Shan and Dr. Wu who prepared it using Hecht’s method. With both Boc-pyranones and aglycon in hand, Dr. Shan utilized the Pd-glycosylation method (2.5 mol % Pd2(DBA)3⋅CHCl3 and 10 mol % PPh3 in CH2Cl2 at 0 °C) to get glycosylated pyranone 2-3a in 85% yield with complete α-selectivity. Luche reduction (NaBH4) of the enone 2-3a at –78 °C in MeOH/CH2Cl2 (v/v 1:3) gave acid sensitive allylic alcohol 2-4a in 73% yield with exceptional diastereoselectivity (d.r. >20:1). Upjohn dihydroxylation (OsO4/NMO, t-BuOH/acetone) introduced the rhamno-stereochemistry into the protected triol 2-5a in excellent yield (96%). After careful purification, global deprotection of the three benzyl groups occurred under hydrogenolysis conditions (H2, 10% Pd/C) to afford the kaempferol-3-α-L-rhamnoside 2-1a-B in 80% yield. Compared to the unacylated rhamnose sugar, fully acylated sugar 2-1a-C was also easily obtained with two more steps from the protected triol 2-5a. Per-acylation of the triol 2-5a with excess amount of acetic anhydride in the presence of DMAP and pyridine provided triacetate 2-6a in 86% yield. Similar debenzylation of
triacetate 2-6a using catalyst of 10 % Pd/C in the presence of H₂ gave kaempferol-3-α-L-2’,3’,4’-O-triacetyl-rhamno-pyranoside 2-1a-C in 86% yield (Scheme 2.1.2 and 2.1.3).

Scheme 2.1.2. Synthesis of kaempferol-3-α-L-rhamno-pyranoside 2-1a-B

Scheme 2.1.3. Synthesis of kaempferol-3-α-L-2’,3’,4’-O-triacetyl-rhamno-pyranoside 2-1a-C

Selective C4’-acetate installation was completed by a simple acylation of the previously prepared allylic alcohol 2-4a without additional protecting groups. The two-step NaBH₄ reduction of enone 2-2a and following acylation of the resulting allylic alcohol with acetic anhydride under the catalysis of DMAP and pyridine afforded C4’-
Selective acylation to the C2’-axial hydroxyl group of 2’,3’-diol-4’-monoacetate 2-8a was attained using orthoester chemistry (exposure of 2-8a to trimethyl orthoacetate in the presence of 10% p-TsOH in CH$_2$Cl$_2$ followed by hydrolysis with excess 90% HOAc/H$_2$O) in excellent yield (99%). Once again, global reductive debenzylation of 2-9a with H$_2$ and 10% Pd/C produced kaempferol-3-α-L-2’,4’-O-diacetyl-rhamno-pyranoside 2-1a-E in 88% yield (Scheme 2.1.5).
**Scheme 2.1.5.** Synthesis of kaempferol-3-α-L-2’,4’-O-diacetyl-rhamno-pyranoside 2-1a-E

Selective C3’-acylation to the equatorial free alcohol encountered many difficulties. Unfortunately, all attempts using acetic anhydride/pyridine at numerous conditions could only give mixtures of 3’,4’-diacetate 2-10a, 2’,4’-diacetate 2-9a and 2’, 3’, 4’-triacetate 2-6a with the ratio of about 1:1:1. Then our attention turned to the acetyl group shift from less stable C2’-axial position to more stable C3’-equatorial position. The orthoester chemistry combined with acetyl group shift strategy under basic condition (DBU in toluene) successfully moved the C2’-axial acetate to the C3’-equatorial position. Good yields (62%) of 3’,4’-diacetate 2-10a could be achieved along with 34% recovered starting material 2’,4’-diacetate 2-9a after silica chromatography. SL0101 (2-1a-A) was finally obtained in 91% yield after global debenzylation (Scheme 2.1.6).

**Scheme 2.1.6.** Synthesis of kaempferol-3-α-L-3’,4’-O-diacetyl-rhamno-pyranoside SL0101 (2-1a-A)
2.1.6. Taylor’s borinic acid catalyzed regioselective acylation for C3’-acetate selectivity

The regioselective protection of carbohydrates has been studied extensively for preparation of functionalized sugar building blocks for oligosaccharide synthesis. Methods ranged from enzyme-catalyzed methods, organo-catalytic methods, Lewis acid-induced processes and tandem catalytic reactions of persilylated sugar moieties. Taylor et al. identified the organoboron catalysts being powerful promoter for selective acylation of cis-1,2-diol functionality in sugar moieties. 9

As part of my research program, I used Taylor’s catalyst borinic acid (2-11) to assist with C3’-acetate selectivity, which preferably gave 3’,4’-diacetate in good yield (84%) with trace amount of 2’,4’-diacetate (Scheme 2.1.7). This improvement made the synthesis of SL0101 (2-1a-A) (6-step, 32% yield in total) significantly more efficient as compared to the orthoester chemistry with the acetate shift strategy. 1

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1 Qi Zhang made compounds of α-1-7a, 2-3a, 2-4a, 2-5a, 2-8a, 2-10a and SL0101 (2-1a-A) shown in Scheme 2.1.7. The synthesis of SL0101 (2-1a-A) resupplied the biological studies. Dr. Mingde Shan provided the spectra.
Scheme 2.1.7. Borinic acid coordinated selective 3',4'-diacetate route for SL0101 (2-1a-A)

For the D-sugar series of SL0101 and its analogues,\(^2\) we simply used Noyori (\(R,R\)) catalyzed product \(\alpha\)-D-Boc-pyranone (\(\alpha\)-D-1-7a) as the glycosylation donor (Scheme 2.1.8). Pd-catalyzed glycosylation coupled the \(\alpha\)-D-Boc-pyranone (\(\alpha\)-D-1-7a) with

\(^2\) Dr. Shan synthesized the kaempferol-3-\(\alpha\)-D-rhamnoside (\textit{ent})-2-1a-B via the shortest steps in 38% yield and Dr. Wu expanded the synthesis of other three D-sugar analogues, kaempferol-3-\(\alpha\)-D-4'-O-acetylhamnoside (\textit{ent})-2-1a-D, kaempferol-3-\(\alpha\)-D-2',4'-O-diacylhamnoside (\textit{ent})-2-1a-E, kaempferol-3-\(\alpha\)-D-3',4'-O-diacylhamnoside (\textit{ent})-2-1a-A.
aglycon 2-2 and yielded the enone (ent)-2-3a in 82% yield. Subsequent reactions of Luche reduction and Upjohn dihydroxylation provided the protected triol (ent)-2-5a in 60% yield for the two steps. Global debenzylation produced the kaempferol-3-α-D-rhamnoside (ent)-2-1a-B in 90% yield (Scheme 2.1.8).

**Scheme 2.1.8. Synthesis of kaempferol-3-α-D-rhamno-pyranoside (ent)-2-1a-B**

Similarly, the two-step reaction sequence of Luche reduction and acylation provided the C4'-monoacetate (ent)-2-7a in 83% yield for the two steps. Subsequent Upjohn dihydroxylation produced the monoacetate (ent)-2-8a in 73% yield. Again, the final debenzylation yielded the desired (ent)-2-1a-D in 77% yield (Scheme 2.1.9).
Scheme 2.1.9. Synthesis of kaempferol-3-α-D-4’-O-acetyl-rhamno-pyranoside (ent)-2-1a-D

Exposure of (ent)-2-8a to trimethyl orthoacetate in the presence of 10% p-TsOH followed by aq. HOAc hydrolysis produced the protected 2’,4’-diacetate (ent)-2-9a in 82% yield. Once again, global hydroygenation of (ent)-2-9a under hydrogenation conditions (H₂ and 10% Pd/C) gave kaempferol-3-α-D-2’,4’-O-diacyl-rhamno-pyranoside (ent)-2-1a-E in 88% yield (Scheme 2.1.10).

Scheme 2.1.10. Synthesis of kaempferol-3-α-D-2’,4’-O-diacyl-rhamno-pyranoside (ent)-2-1a-E
The orthoester chemistry combined with acetyl group shift strategy under basic condition (DBU in toluene) successfully moved the C2’-axial acetate to the C3’-equatorial position with 61% yield of 3’,4’-diacetate (ent)-2-10a along with 29% recovered starting material 2’,4’-diacetate (ent)-2-9a after silica chromatography. Kaempferol-3-α-D-3’,4’-O-diacetylhamnoside SL0101 ((ent)-2-1a-A) was finally obtained in 85% yield after global debenzylation (Scheme 2.1.11).

**Scheme 2.1.11.** Synthesis of kaempferol-3-α-D-3’,4’-O-diacetyl-rhamno-pyranoside (ent)-SL0101 ((ent)-2-1a-A)

By utilizing the borinic acid coordination method again, the (ent)-SL0101 ((ent)-2-1a-A) was also prepared in a similar method as the natural SL0101 (2-1a-A).³ Pd(0)-catalyzed glycosylation (82%), Luche reduction (78%), acylation (73%), Upjohn dihydroxylation (73%), borinic acid coordinated C3’-acetate selective reaction (74%), global debenzylation (86%) furnished the (ent)-SL0101 ((ent)-2-1a-A) in a total 21% yield for biological activity tests (Scheme 2.1.12).

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³ Qi Zhang made compounds of α-D-1-7a, (ent)-2-3a, (ent)-2-4a, (ent)-2-5a, (ent)-2-8a, (ent)-2-10a and (ent)-SL0101 ((ent)-2-1a-A) shown in Scheme 2.1.12. The synthesis of (ent)-SL0101 ((ent)-2-1a-A) resupplied the biological studies. Dr. Bulan Wu provided the spectra.
2.1.7. Conclusion

In conclusion, our group developed a divergent and highly enantio- and
disastereoselective route to prepare natural product SL0101 as well as other four
kaempferol rhamnoside analogues and four enantiomeric analogues. The routes provided
all the kaempferol glycosides without the use of any protecting group for the sugar
hydroxyl groups. Our method based upon diastereoselective Palladium-catalyzed
glycosylation, Luche reduction, and different combination of dihydroxylation, acylation
and the final hydrogenation. Selective acylation of the axial as well as equatorial hydroxyl group of a cis-diol was also achieved via different conditions. All five L-sugar SL0101 (2-1a-A to 2-1a-E) analogues and three D-sugar analogues ((ent)-2-1a-A, (ent)-2-1a-D and (ent)-2-1a-E) were sent to Prof. Lannigan at University of Virginia (Later at Vanderbilt University). Biological testing showed D-sugar analogues had no effects on the cancer cell lines. (See Figure 2.2.1).

Section II. De novo asymmetric synthesis and biological evaluation of C5'-alkyl-modification of SL0101

2.2.1. Introduction

After the discovery of SL0101 as the first specific RSK inhibitor by Smith, Hecht, Lannigan et al., Hecht published the first total synthesis of SL0101.\(^4\) SL0101 showed significant potency and specificity for RSK2, however, the EC\(_{50}\) of SL0101 as a RSK inhibitor in intact cells increased \(~50\)-fold than its dissociation constant, which indicated that the efficacy of SL0101 might be affected by cellular uptake or \textit{in vivo} instability. Hecht and Lannigan proposed that the loss of efficacy could be the result of ester hydrolysis, which triggered the synthesis of butyl-ether substitutes instead of acetates with increased hydrophobic properties, but these modifications led to loss of selectivity.\(^10\)

To solve these difficulties, our group developed the \textit{de novo} methodology to produce SL0101 and numerous multi-acylated analogues in either enantiomeric (L and D) form. We attempted to explore the role of the sugar part plays and the significance of the particular position of acetyl group(s) for SAR studies. Thus, we have studied, prepared and tested above mentioned both enantiomers of diverse analogues of SL0101,\(^7\) in
addition to the corresponding cyclitol carbasugar analogues made by Dr. Shan.\textsuperscript{11} The \textit{in vitro} assays testing the RSK inhibitory ability revealed that the L-sugars were active and all the D-sugars were inactive for both $O$-glycosides and $C$-glycosides (cyclitols), which indicated that the sugar portion is essential for the binding. Remarkably, the cyclitols exhibited improved activity (increased affinity by ~4-fold) compared to their corresponding $O$-glycosides indicating the possible reasons of increased hydrophobicity and/or loss of anomeric effect.

To further explore these findings, our group decided to make the C5'-alkyl modifications onto SL0101. Dr. Wu first finished the whole series of C5'-n-Pr SL0101 analogues (R = n-Pr). When I joined the Prof. O’Doherty’s group, I started to expand the scope of different C5'-alkyl substitution for the SAR study for SL0101 with R = Et and R = i-Bu.

2.2.2. Retrosynthetic analysis of C5'-alkyl analogues of SL0101

Retrosynthetic strategy of this C5'-modification followed a similar route as that we previously described. The only difference is the acetylfuran starting from achiral furan and corresponding carboxylic acid, which would yield the different side chain for the C5’ position (See Scheme 1.1.3). With substituted acetylfuran in hand, various C5'-alkyl substituted Boc-pyranone could be made via the three-step sequence, Noyori diastereoselective reduction, Achmatowicz oxidative rearrangement and Boc-protection reactions. The C5'-alkyl substituted glycosylated enone could be prepared by our palladium-catalyzed glycosylation between flavonol aglycon and C5'-alkyl-substituted Boc-pyranone. Sequential post-glycosylation reactions including Luche reduction,
Upjohn dihydroxylation would set the *rhamno*-chemistry. Subsequent application of acylation, orthoester hydrolysis, acyl migration reactions and final hydrogenation could produce various acylated products.

**Scheme 2.2.1.** Retrosynthetic analysis of C5’-alkyl analogues of SL0101

2.2.3. Synthesis of C5’-alkyl substituted Boc-pyranones

The new series of our C5’-modification strategy started with the reaction of furan in THF with *n*-BuLi, which gave the 2-lithiofuran (See Scheme 1.1.3). Then the reaction mixture was mixed with corresponding carboxylic acid (*i.e.* propionic acid, *n*-butyric acid, *iso*-butyric acid, *iso*-valeric acid) to form different acetylfurans with various modified side chains 1-1b, 1-1c and 1-1e in good yields (64%-72%). Noyori (S,S) asymmetric reduction of acetylfurans 1-1b, 1-1c and 1-1e using sodium formate (HCO2Na) as hydride source in the presence of phase transfer catalyst cetyltrimethylammonium bromide (CTAB) formed the furfuryl alcohol 1-5b, 1-5c and 1-5e in 61%-81% yields with high enantiomeric excess (>96% e.e., by Mosher ester). The subsequent Achmatowicz reaction rearranged the furfuryl alcohol 1-5b, 1-5c and 1-5e to...
a mixture of hemiacetal, which were filtered through silica gel and ready for the protection of the free alcohol. The \( t \)-butyl carbonate (Boc) protection group was discovered as good leaving group for the following glycosylation step. The \( \alpha \)- and \( \beta \)-Boc-pyranone 1-5b, 1-5c and 1-5e were separated by careful silica gel chromatography with a good diastereomeric ratio (\( \alpha:\beta \) 1.8:1 to 2.7:1) in good yields (44%-54%).

2.2.4. Synthesis of kaempferol-C5’-alkyl-\( \alpha \)-L-rhamno-pyranosides

The kaempferol-C5’-alkyl-\( \alpha \)-L-rhamno-pyranosides without the acetyl groups are the easiest \( rhamno \)-pyranosides to synthesize with shortest four steps of post-glycosylation reactions. Thus, we started with the synthesis of this type of compounds for testing of biological activities. With the known perbenzylated flavonol aglycon 2-2 and the C5’-alkyl substituted \( \alpha \)-Boc-pyranone 1-7b, 1-7c and 1-7e in hand, we ran the Pd(0)-catalyzed glycosylation again to produce the glycosylated enones 2-3b, 2-3c and 2-3e. Exposure of aglycon and \( \alpha \)-Boc-pyranone to 2.5 mol % \( \text{Pd}_2(\text{DBA})_3\cdot\text{CHCl}_3 \) and 10 mol % \( \text{PPh}_3 \) in \( \text{CH}_2\text{Cl}_2 \) at 0 °C resulted in the glycosylated enones in 78%-95% yields with complete \( \alpha \)-selectivity. Reduction with \( \text{NaBH}_4 \) at \(-78 \) °C in \( \text{CH}_2\text{Cl}_2/\text{MeOH} \) converted the enones to allylic alcohols in 68%-88% yields with excellent diastereoselectivity (\( d.r. >20:1 \)). The Upjohn dihydroxylation (\( \text{OsO}_4/\text{NMO}, \ t\text{-BuOH}/\text{Acetone} \)) diastereoselectively installed the two free hydroxyl groups with \( rhamno \)-chemistry in high yields (80%-95%). The global deprotection of the three of benzyl groups using catalyst of 10% Pd/C in the presence of \( \text{H}_2 \) resulted in kaempferol-C5’-alkyl-\( \alpha \)-L-rhamno-pyranosides 2-1b-B, 2-1c-B, 2-1e-B in 54%-66% yields. Since the biological results showed that the \( n \)-Pr series had the best inhibitory effects in comparison with Et and \( i \)-Bu
series (see below Biological results), I did not further synthesize the other acylation analogues 2',3',4'-triacetate, 2',4'-diacetate, 3', 4'-diacetate for C5’-ethyl or C5’-i-Bu series but finished the chemical synthesis of C5’-i-Bu-C4’-monoacetate. Although more recent research showed when R = i-Bu, the analogue kaempferol-C5’-i-Bu-α-L-rhamno-pyranoside 2-1e-B exhibited a slightly better inhibition of RSK compared to kaempferol-C5’-n-Pr-α-L-rhamno-pyranoside 2-1c-B with no statistical difference (See Table 2.2.2).

**Scheme 2.2.2.** Synthesis of kaempferol-C5’-alkyl-α-L-rhamno-pyranosides 2-1b-B, 2-1c-B, 2-1e-B

Dr. Wu completed the synthesis of the series of C5’-n-Pr-α-L-rhamno-pyranosides with similar conditions as did for the C5’-Me-α-L-rhamno-pyranosides in Section 1. The
synthesis of kaempferol-C5’-n-Pr-2’,3’,4’-α-L-rhamno-pyranoside 2-1c-C with 74% yield in two steps from 2-5c, kaempferol-C5’-n-Pr-4’-α-L-rhamno-pyranoside 2-1c-D with a low 11% yield in four steps from 2-3c, kaempferol-C5’-n-Pr-2’,4’-α-L-rhamno-pyranoside 2-1c-E with 54% yield in two steps from 2-8c and kaempferol-C5’-n-Pr-3’,4’-α-L-rhamno-pyranoside 2-1c-A with 39% yield in two steps from 2-9c. Additionally, I made the kaempferol-C5’-i-Bu-4’-α-L-rhamno-pyranosides 2-1e-D starting from the enone 2-3e with standard reduction, acylation of the free alcohol, dihydroxylation and hydrogenation steps with 22% yield (See Schemes 2.2.3, 2.2.4, 2.2.5 and 2.2.6).

**Scheme 2.2.3.** Synthesis of kaempferol-C5’-n-Pr-2’,3’,4’-α-L-rhamno-pyranoside 2-1c-C
Scheme 2.2.4. Synthesis of kaempferol-C5’-n-Pr-4’-α-L-rhamno-pyranoside 2-1c-D and Kaempferol-C5’-i-Bu-4’-α-L-rhamno-pyranoside 2-1e-D

Scheme 2.2.5. Synthesis of kaempferol-C5’-n-Pr-2’,4’-α-L-rhamno-pyranoside 2-1c-E

Scheme 2.2.6. Synthesis of kaempferol-C5’-n-Pr-3’,4’-α-L-rhamno-pyranoside 2-1c-A
2.2.5. Biological evaluation of various SL0101 and its analogues

Hecht and Lannigan in 2005 reported that SL0101 (with *rhamno*-sugar) showed a ~40-fold greater affinity for RSK than kaempferol aglycon, which implied that the sugar moiety of SL0101 plays a very important role in the inhibitory behavior of RSK. For further elucidation of the role of the sugar played, our group synthesized twenty-three SL0101 analogues in total and they were all sent to our collaborator Prof. Lannigan’s lab at University of Virginia (Later in Vanderbilt University) to test for RSK inhibitory cytotoxicity on the breast cancer cell line MCF-7. These compounds ranged from normal *O*-sugars and cyclitol *C*-sugars with R = Me in both L- and D-sugar enantiomeric forms, L-sugars with R = Et, *n*-Pr, *i*-Bu. Shown below are the structure details. The RSK inhibitory activities of these compounds were compared (Figure 2.2.1, data for cyclitol *C*-sugars not shown).
Figure 2.2.1. Assessing the ability of the compounds to inhibit RSK activity at the concentration of 500 nM. Kinase activity data for the *rhamno*-pyranosides were tested and provided by J. Smith at Luna Innovation Incorporated in 2009. RSK was incubated in the presence of 500 nM of each compound. The ability of the compound to inhibit RSK was quantified using phosphor-specific antibodies against the RSK substrate. Data are presented as the percent of RSK activity measured in the presence of the compound relative to that measured in the presence of vehicle alone. Bars = SD of 5 data points.

Previously Hecht and Lannigan found SL0101 (2-1a-A) was a specific RSK inhibitor.\textsuperscript{3a} To investigate the *in vivo* RSK inhibitory activity and assist the structure design for better suitability for *in vivo* use, they reported the improvement of affinity of SL0101 for RSK inhibitory activity in 2013 with the samples synthesized by us.\textsuperscript{12} They analyzed the pharmacokinetic behavior of SL0101 by administrated of a single dose into male CD-1 mice via both intravenous (iv) and intraperitoneal (ip) methods (See Table 2.2.1). The half-life ($t_{1/2}$) of SL0101 (2-1a-A) was less than 30 minutes regardless of the
iv or ip dosing method used (See Table 2.2.1). Even more notably, the extrapolated maximum concentration could only achieved ~10-fold lower than that required for inhibiting the breast cancer cell line MCF-7 proliferation in culture, which implied that SL0101 (2-1a-A) is not suitable for in vivo testing. The identification and synthesis of suitable analogues of SL0101 (2-1a-A) with improved pharmacokinetic properties as well as potency and selectivity is required.

Table 2.2.1. Pharmacokinetic property analysis of SL0101 (2-1a-A) in male CD-1 mice.

<table>
<thead>
<tr>
<th>iv dose (mg/kg)</th>
<th>AUC/D (ng•h•kg/mL/mg)</th>
<th>C₀ (ng/mL)</th>
<th>C_max (ng/mL)</th>
<th>t₁/₂ (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (iv)</td>
<td>38.7</td>
<td>291</td>
<td>—</td>
<td>9</td>
</tr>
<tr>
<td>2.5 (ip)</td>
<td>1023</td>
<td>—</td>
<td>1851</td>
<td>24</td>
</tr>
</tbody>
</table>

A crystal structure of the interaction of NTKD of RSK2 with SL0101 binding pocket has been reported (Figure 2.2.2).\textsuperscript{12,13} Previously, Hecht and Lannigan have found that acylation of the rhamno-sugar moiety is important for the specificity as well as the three phenolic hydroxyl groups are required for affinity due to their hydrogen bond donation. The affinity ability of SL0101 greatly dropped due to the loss of any of these phenolic hydroxyl groups. Additionally, the methylation to these phenolic hydroxyl groups resulted the O-methylated analogue, which showed no inhibition to RSK.\textsuperscript{10}
Figure 2.2.2. X-ray crystallographic structure of SL0101 in complex with RSK2.
A hydrophobic pocket within the RSK2 NTKD allows for an extended C5’-aliphatic chain on the rhamnose.

The crystallographic picture of NTKD of RSK2 binding with SL0101 suggested that the C5’-methyl group of the rhamno-pyranoside only partially occupies the hydrophobic pocket. On the basis of this finding, we designed, synthesized and tested a set of C5’-alkyl substitution analogues bearing longer aliphatic chains (Table 2.2.2).

Table 2.2.2. In vitro RSK inhibitory potency of SL0101 and the analogues. IC_{50}: concentration needed for 50% inhibition of RSK2; the 95% confidence interval (CI) is shown in parentheses; n > 2 in quadruplicate. p (1): Student’s t test compared to SL0101 (2-1a-A). p (3): Student’s t test compared to analogue (2-1c-B).

<table>
<thead>
<tr>
<th>Analogues</th>
<th>RSK2 IC_{50} (µM)</th>
<th>LogP</th>
<th>p (1)</th>
<th>p (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1a-A</td>
<td>0.99 (0.74-1.32)</td>
<td>2.11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-1c-A</td>
<td>0.02 (0.01-0.04)</td>
<td>3.17</td>
<td>0.007</td>
<td>0.005</td>
</tr>
<tr>
<td>2-1c-C</td>
<td>1.77 (1.24-2.53)</td>
<td>3.87</td>
<td>0.008</td>
<td>0.008</td>
</tr>
<tr>
<td>2-1c-D</td>
<td>1.50 (0.90-2.48)</td>
<td>2.90</td>
<td>0.183</td>
<td>0.183</td>
</tr>
<tr>
<td>2-1c-E</td>
<td>0.62 (0.18-2.15)</td>
<td>3.39</td>
<td>0.232</td>
<td>0.804</td>
</tr>
<tr>
<td>2-1b-B</td>
<td>1.51 (0.45-5.09)</td>
<td>2.20</td>
<td>0.211</td>
<td>—</td>
</tr>
<tr>
<td>2-1c-B</td>
<td>0.71 (0.47-1.09)</td>
<td>1.64</td>
<td>0.917</td>
<td>—</td>
</tr>
<tr>
<td>2-1e-B</td>
<td>0.48 (0.17-1.09)</td>
<td>2.41</td>
<td>0.073</td>
<td>—</td>
</tr>
</tbody>
</table>
Since preliminary results showed analogue kaempferol-C5’-n-Pr-3’,4’-α-L-rhamnopyranoside 2-1c-A exhibited extraordinary RSK inhibition activity compared to natural SL0101, it was further evaluated for its ability of inhibiting the proliferation of human breast cancer cell line MCF-7 in parallel with SL0101 (2-1a-A). The concentration of 2-1c-A was limited to ≤ 25 µM due to its poor aqueous solubility. It showed ~50% more potency on inhibiting proliferation of MCF-7 at the concentration of 25 µM than SL0101.

**Figure 2.2.3.** Efficacy of SL0101 (2-1a-A) and kaempferol-C5’-n-Pr-3’,4’-α-L-rhamnopyranoside (2-1c-A) in MCF-7 cells. Various concentrations of inhibitors were added at time 0, and ATP content was measured after 48 h of treatment. Values are the fold proliferation as a percentage of that obtained with vehicle-treated cells (n = 3 in quadruplicate; bars = SD; *p < 0.05 in a Student’s t test compared to the vehicle. †p < 0.05 in a Student’s t test compared to SL0101 (2-1a-A)).

Lannigan previously found that SL0101 (2-1a-A) inhibited proliferation of the MCF-7 line with no effect on the growth of normal breast cell line MCF-10A although SL0101 (2-1a-A) inhibits RSK activity in MCF-10A. The growth of MCF-7 recovered after removal of SL0101 (2-1a-A) after 72-hours treatment. To determine whether C5’-n-Pr analogue 2-1c-A was also specific for RSK, we tested 2-1c-A for inhibiting
proliferation of MCF-7 versus MCF-10A and compared to SL0101 (Figure 2.2.4). The results showed C5’-n-Pr analogue 2-1c-A has similar RSK inhibition specificity to natural SL0101 (2-1a-A).

**Figure 2.2.4.** Specificity of analogue kaempferol-C5’-n-Pr-3’,4’-α-L-rhamno-pyranoside (2-1c-A) for inhibition of RSK activity. Various concentrations of 2-1c-A were added to MCF-7 or MCF-10A cells, and the assay was performed as described in Figure 2.2.4 (n = 3 in quadruplicate; bars = SD; *p < 0.05 in a Student’s t test compared to the vehicle).

2.2.6. Conclusion

In summary, based on the structure-based design method, O’Doherty and Lannigan’s group jointly synthesized and tested the natural product SL0101 and its C5’-alkyl substitution analogues in order to improve on the *in vitro* affinity as well as potency. Results showed that the analogue kaempferol-C5’-n-Pr-3’,4’-α-L-rhamno-pyranoside 2-1c-A improved the affinity for RSK by ~40-fold compared to SL0101 2-1a-A though analogue 2-1c-A only inhibited 2-fold better inhibition the proliferation of the breast cancer cell line MCF-7 compared to SL0101 2-1a-A. It is probably due to the
limited membrane permeability. The studies would provide valuable guidance in designing new analogues to improve the potency for \textit{in vivo} use.

Section III. \textit{De novo} asymmetric synthesis of C4’-azido-modification analogues of SL0101

2.3.1. Introduction

Based on our successful C5’-alkyl substitution of SL0101, we planned to expand the scope of structure modifications to improve the resistance to ester hydrolysis. The decrease of RSK inhibition activity of SL0101 \textit{in vivo} was probably because the acetyl groups in SL0101 were removed rapidly and thus transformed into Kaempferol L-rhamnoside 2-1a-B, which is not a good RSK inhibitor. The modification of C4’-acetamide substitution on the C5’-n-Pr and C5’-i-Bu substituted analogues was investigated and produced by a group of Dr. Bulan Wu, Dr. Rajender Vemula and me. The four targeted C4’-acetamide-C5’-n-Pr-α-L-sugar analogues and two C4’-acetamide-C5’-i-Bu-α-L-sugar analogues were listed in Figure 2.3.1.

\textbf{Figure 2.3.1.} Targeted C4’-acetamide-α-L-sugar analogues of SL0101

\begin{table}[h]
\centering
\begin{tabular}{l}
2-11c-A: R\textsubscript{1} = n-Pr, R\textsubscript{2} = Ac, R\textsubscript{3} = H \\
2-11c-C: R\textsubscript{1} = n-Pr, R\textsubscript{2} = Ac, R\textsubscript{3} = Ac \\
2-11c-D: R\textsubscript{1} = n-Pr, R\textsubscript{2} = H, R\textsubscript{3} = H \\
2-11c-E: R\textsubscript{1} = n-Pr, R\textsubscript{2} = H, R\textsubscript{3} = Ac \\
2-11e-A: R\textsubscript{1} = i-Bu, R\textsubscript{2} = Ac, R\textsubscript{3} = H \\
2-11e-D: R\textsubscript{1} = i-Bu, R\textsubscript{2} = H, R\textsubscript{3} = H \\
\end{tabular}
\end{table}

\[\text{4}\] Dr. Bulan Wu developed the methodology and made four C4’-acetamide-C5’-n-Pr analogues. Dr. Rajender Vemula applied the methodology and made two C4’-acetamide-C5’-i-Bu analogues. Qi Zhang provided the partial α-L-i-Bu-Boc pyranone and the spectrum.
Retrosynthetically, we envisioned that C4'-acetamide-α-L-sugar analogues 2-11c and 2-11e would arise from a glycosylated C4'-azido intermediate 2-12c and 2-12e, which in turn could be prepared from several post-glycosylation transformations such as Luche reduction, Upjohn dohydroxylation, orthoester hydrolysis and acetyl shift from the enones 2-3c and 2-3e. The enones 2-3c and 2-3e could be obtained from our previously described de novo asymmetric synthesis and the palladium-catalyzed reaction of aglycon 2-2 and with 1-7c and 1-7e (Scheme 2.3.1).

Scheme 2.3.1. Retrosynthesis of C4'-acetamide-α-L-sugar analogues of SL0101

2.3.2. Initial approach to targeted C4'-acetamide-α-L-sugar analogues of SL0101

The synthesis started from the same key intermediate allylic alcohol 2-4c available from previous synthesis. For the goal of C4'-acetamide-/azido- sugar analogues, the C4'-carbonate 2-13c with a methyl carbonate leaving group was achieved by reacting of 2-4c with methyl chloroformate in 75% yield. However, the expected conversion of this C4'-carbonate to C4'-azide under the Sinou conditions\textsuperscript{15} (TMSN\textsubscript{3}, [Pd(allyl)Cl]\textsubscript{2}/1,4-
bis(diphenylphosphino)-butane) failed to provide the desired allylic azide 2-12c. A possible reason for the lack of azidation is that the phenolic aglycon is a competitive leaving group (Scheme 2.3.2).

**Scheme 2.3.2.** Initial approach to targeted C4’-acetamide-α-L-sugar analogues of SL0101

2.3.3. The successful approach via Pd-catalyzed glycosylation

In consideration of the fact that the aglycon is sensitive to Sinou conditions, we switched our strategy that introducing the aglycon after the azido group was installed. Consequently, treatment of the Boc-pyranone α-L-1-7c and α-L-1-7e with p-methoxybenzyl alcohol under the conditions of palladium-catalyzed glycosylation (Pd(0)/PPh₃, 1:2) gave the PMB-pyranones 2-14c and 2-14e as a single diastereomer in excellent yield (95% and 92% respectively). Diastereoselective Luche reduction (NaBH₄/CeCl₃) of enones 2-14c and 2-14e yielded PMB-allylic alcohols 2-15c and 2-15e in 92% and 84% yields, which were treated with methyl chloroformate under the
catalysis of DMAP to generate PMB-allylic carbonate 2-16c and 2-16e in 94% and 90% yields. The Sinou conditions (TMSN₃, [Pd(allyl)Cl]₂/1,4-bis(diphenylphosphino)-butane) afforded the desired regio- and stereoisomeric PMB-allylic azides 2-17c and 2-17e in 73% and 75% yields. Conversion of PMB group to Boc group for subsequent glycosylation was completed by an oxidative PMB deprotection (DDQ/H₂O) of 2-17c and 2-17e and the Boc protection of the resulting anomeric alcohol 2-18c and 2-18e (in a 13:1 mixture of (α/β) anomers) in 61% and 64% yields in two steps (Scheme 2.3.3).

**Scheme 2.3.3.** Synthesis of glycosyl donor C4'-azide sugars 2-19c and 2-19e

With Boc-allylic azides 2-19c and 2-19e in hand, we put our efforts into the palladium-catalyzed glycosylation (Scheme 2.3.4). As expected, our typical Pd(0)-catalyzed glycosylation condition coupled the sugar donor Boc-allylic azides 2-19c and 2-19e with accepter aglycon 2-2 successfully to provide desired glycosylated allylic azides 2-20c and 2-20e in excellent yield (98% and 90%) with complete α-selectivity. Similarly, Upjohn dihydroxylation conditions (OsO₄/NMO) stereoselectively converted
the glycosylated allylic azides 2-20c and 2-20e into the rhamno-azole diol 2-21c and 2-21e in 91% and 87% yields.

**Scheme 2.3.4.** Synthesis of key intermediates 2-21c and 2-21e

With the key intermediates rhamno-azole diols 2-21c and 2-21e in hand, we tried to convert the C4’-azole group into C4’-acetamide group, generating 2-23c and 2-23e (Scheme 2.3.4). To our surprise, reduction of azide 2-21c and 2-21e with Zn dust in the presence of Ac₂O and AcOH not only gave the desired C4’-acetamide 2-23c in 29% yield (2-23e in 36% yield), but also provided C4’-acetamide-C3’-acetate 2-22c (SL0101-type) in 27% (2-22e in 32% yield). It is probably because the C3’-equatorial hydroxyl group is active and more accessible compared to C2’-axial hydroxyl group.
Scheme 2.3.5. Synthesis of C4’-acetamide-C3’-acetate (2-16c/e-A) and C4’-acetamide-C2’, C3’-diol (2-16c/e-D)

Two more intermediates 2-24c and 2-25c were prepared on the basis of intermediates 2-22c and 2-23c (Scheme 2.3.6). Acylation of C2’-axial hydroxyl group of 2-22c with Ac₂O in the presence of pyridine and DMAP produced C4’-acetamide-C2’, C3’-diacetate 2-24c in 97% yield. Selective acylation of the C2’-axial hydroxyl group of diol 2-23c was achieved by using orthoester chemistry. Treatment of diol 2-23c with trimethyl orthoacetate in the presence of 10% p-TsOH followed by hydrolysis with excess 90% aq. AcOH yielded C4’-acetamide-C2’-acetate 2-16c-E in 85% yield. Finally, global deprotection of the two benzyl-protected intermediates 2-24c and 2-25c under the typical procedure (Pd/C, H₂), provided the desired products 2-16c-C and 2-16c-E in good yields (94% and 91% respectively).
Scheme 2.3.6. Synthesis of C4′-acetamide-C2′, C3′-diacetate (2-16c-C) and C4′-acetamide-C2′-acetate (2-16c-E)

2.3.4. Conclusion

In summary, four targeted C4′-acetamide-C5′-n-Pr-α-L-sugar analogues of SL0101 2-16c-A, 2-16c-B, 2-16c-C and 2-16c-E as well as two C4′-acetamide-C5′-i-Bu-α-L-sugar analogues 2-16e-A and 2-16e-D have been synthesized via a highly enantio- and diastereoselective de novo asymmetric approach and sent to our collaborator Dr. Lannigan at Vanderbilt University for biological testing. The highly diastereoselective formation of Boc-allylic azide with the subsequent highly diastereoselective Pd(0)-catalyzed glycosylation are the key steps for the success. Post-glycosylation reactions such as Upjohn dihydroxylation, Zn/AcOH reduction of the azide to acetamide and concurrent regioselective acylation provided the desired analogues. The biological testing results are still underway.
Reference:

8. Dr. Bulan Wu’s dissertation, “De Novo Asymmetric Synthesis of SL0101 Analogues, Methymycin Analogues and Cleistriosides/Cleistetrosides” at West Virginia University, Morgantown, WV, 26506.
Chapter 3. Total synthesis of natural naphthalene products nanaomycins and griseusins

3.1. Introduction

The family of pyranonaphthoquinone antibiotics consist of naphtho[2,3-c]pyran-5,10-dione ring containing natural compounds, some with an additional γ-lactone ring while others with a carboxylic acid side chain resulting from ring opening of the γ-lactone. They have been shown to display biological activity against a variety of gram-positive bacteria, pathogenic fungi, yeasts and also antiviral activity. Additionally, they have been shown to be potent bioreductive alkylating agents, which could be their mode of action.

Figure 3.1. General pyranonaphthoquinone skeleton

Psychorubrin 3-1 is probably the simplest naphthopyrandione-containing compound, which processes a hydroxyl group at C3 position. It was isolated from a Chinese plant Psychotria rubar and showed significant inhibitory cytotoxicity against KB tumor cells (ED$_{50}$ = 3µg/mL).

Eleutherin 3-2 and isoeleutherin 3-3 were isolated from the rhizomes of Eleutherin bulbosa (a member of the iris family), and the structures were determined and confirmed later by different groups. Isoeleutherin 3-3 has a pseudo-axial methyl group at C-1 position versus that both methyl groups pseudo-equatorial in eleutherin 3-2, which makes

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1 Michael Royce Naim’s dissertation, Synthetic studies towards griseusin A, Massey University, New Zealand, Spring, 1995.
isoleutherin 3-3 more stable.\(^5\) Eleutherin 3-2 showed some activity\(^{4b}\) against bacterium *Pyococcus aureus* and *Streptococcus haemolyticus A* as well as weak activity\(^6\) against *Bacillus subtilis Bacillus subtilis*. Other similar compounds to the eleutherins were also isolated from different natural plants and identified as 7-methoxyeleutherin and 6-hydroxy-7-methoxyeleutherin.\(^7\)

Fusarubin 3-4 is a red pigment isolated from soil fungus *Fusarium solani* in citrus groves, which was isolated from *F. martii*.\(^8\) Fusarubin 3-4 was reported as a metabolite of several strains of *F. solani*.\(^9\) Two other diastereomeric dihydrofusarubin A 3-5 and dihydrofusarubin B 3-6 were also isolated from *F. solani*. They could be considered as the precursor of fusarubin 3-4 and related co-metabolites since they are not strictly pyranonaphthoquinones.\(^10\) Fusarubin 3-4 was reported to be an antimicrobial agent with activity against several gram-positive bacteria\(^{11}\) such as *Streptomycyes albus*, *Mycobacterium phlei*, *Bacillus subtilis* and *Staphylococcus ayreus* and the yeast\(^{11a}\) *Saccharomyces cerevisiae* and has also phytotoxic\(^{12}\) and antitumor\(^{13}\) properties, but was not active against fungi.\(^{12b}\)

Herbarin 3-7 and anhydroherbarin 3-8, isolated from *Torula herbarum* cultures, are different from the compounds derived from *Fusaria* in the quinol-quinone arrangement around the naphthoquinone core.\(^{14}\) Anhydroherbarin 3-8 can be transformed from herbarin 3-7 via dehydration.

Marticin 3-9 and isomarticin 3-10, also isolated from *F. martii*,\(^{8b}\) have different structural features compared with fusarubins by the presence of an extra C\(_3\) chain forming a carboxylic acid substituted 1,3-dioxane. Marticin 3-9 and isomarticin 3-10 are diastereomers at C2 and C4. Under acidic conditions, isomarticin 3-10 will form marticin
3-9 via protonation and ketonization.\textsuperscript{15} The 1,3-dioxane ring of 3-9 and 3-10, which differs from other members of naphthazarin family, was proposed to provide the phytotoxicity.\textsuperscript{11c, 15b, 16}

Kalafungin 3-11 was isolated\textsuperscript{17} from the fermentation broth of \textit{Streptomyces tanashiensis} and also from actinomyces \textit{Nocardia dassonvillei}. Its structure was determined by X-ray crystallography\textsuperscript{18} and further confirmed by chemically modified methods\textsuperscript{19} and comparison of \textsuperscript{1}H NMR data\textsuperscript{4d} with eleutherin 3-2 and isoeleutherin 3-3. Kalafungin 3-11 showed inhibitory activities in vitro against both gram-positive and gram-negative bacteria, pathogenic fungi, yeasts and protozoa\textsuperscript{20} as well as strong cytotoxicity against mouse leukemic cells L5178Y \textit{in vitro}.\textsuperscript{17b} It also showed antithelminic activity, which potency was increased by different natural sugars especially glucose.\textsuperscript{21} Tetrahydrokalafungin 3-12, with a reduced C4a-C10a quinone double bond, is a variant of kalafungin 3-11. It was isolated from a wild type strain of \textit{Streptomyces tanashiensis} and also some bacterial mutants that do not yield kalafungin 3-11.\textsuperscript{22}

Frenolicins 3-13 to 3-16 are structurally similar to kalafungin 3-11 with an \textit{n}-propyl group substituting the methyl group at C1 position, which were isolated from numerous \textit{Streptomyces} species. Frenolin 3-13 was isolated\textsuperscript{23} from \textit{Streptomyces fradiae} and found to be an epoxide. Frenolin B 3-16 and deoxyfrenolin 3-15 were isolated from \textit{S. roseofulvus},\textsuperscript{24} among which deoxyfrenolin 3-15 was previously synthesized from frenolin 3-13.\textsuperscript{25} Frenolin B 3-16 was found less polar than frenolin 3-13 and missing a carboxylic acid group in IR spectrum, thus the lactone ring was postulated. Oxidation of Frenolin B 3-16 to frenolin 3-13 in pyridine confirmed the proposed lactone structure. The absolute configuration of Frenolin 3-13 being (1S, 3R) was
suggested by the coproduction of nanaomycin A 3-18 and deoxyfrenolicin 3-15 in spite of the contrary signs of their separate Cotton effects.\textsuperscript{26,32}

Figure 3.2. Library of pyranonaphthoquinone antibiotics

Frenolicin 3-13 exhibited weak antibacterial activity. Deoxyfrenolicin 3-15 was reported to be a significant inhibitor against a variety of fungi (e.g. ringworm infections in guinea pigs).\textsuperscript{25a} Both deoxyfrenolicin 3-15 and frenolicin B 3-16 are active against mycoplasmas and fungi with 3-15 showing better inhibition against mycoplasmas whereas 3-16 showing better inhibition of fungi. Frenolicin B 3-16 has been used as a growth promotant in swine due to its excellent anticoccidial property in poultry.\textsuperscript{27} 3-16 also showed strong inhibitory activity to platelet aggregation.\textsuperscript{28} Deoxyfrenolicin 3-15 showed no anticoccidial activity, but it showed great inhibitory activity against tyrosine hydroxylase in rats.\textsuperscript{29}
Medermycins 3-17 was isolated\textsuperscript{30} as a monohydrochloride salt from \textit{Streptomyces tanashiensis}. Its structure was shown to include the identical skeleton displayed in kalafungin 3-11 but with an amino sugar (D-angolosamines) linked to the naphthoquinone core assigned at C8.\textsuperscript{27, 31} This initial structure was revised\textsuperscript{32} to C6 position about 25 years later. \textit{Morin et. al.} corrected the structure of medermycin A/B, lactoquinomycin A/B, menoxymycin A/B, G15-F, and G15-G. They argued that the synthetic works which introduced the C-glycoside at C8 was wrong as there are many (naphtho)quinone antibiotics with C6-glycosylation (ortho to the phenolic group).\textsuperscript{29}

\textbf{Figure 3.3.} Structure of original medermycin and revised medermycin

Ten years after the isolation of medermycin 3-17, Tanaka et. al. announced the isolation of lactoquinomycin A, which showed similarities to medermycin 3-17.\textsuperscript{33} Tanaka et. al. then compared the natural and synthetic medermycin 3-17 directly with lactoquinomycin and the results of the totally identical physiochemical and spectral data confirmed the structural identification of those two antibiotics.\textsuperscript{34}

Medermycin 3-17 showed notably active against gram-positive organisms especially the antibiotic-resistant strains of \textit{Staphylococci} and \textit{Bacillus}. Medermycin 3-17 was also effective against neoplastic cells \textit{in vitro}, antibiotic-resistant cell lines such as L5178Y lymphoblastoma and Ehrlich carcinoma in mice but showed nearly no activity on fungi nor gram-negative bacteria. Medermycin/lactoquinomycin A showed noteworthy
antineoplastic, antibiotic, and platelet aggregation inhibition activities as well as 50% inhibition of human leukemia cells at low concentration.\textsuperscript{27,30} Thus a succinct and flexible synthetic route for the C8-glycosylation was extensively studied.\textsuperscript{35}

As part of the whole screening program for antimycoplasmal antibiotics, Omura \textit{et al.} first explored and isolated nanaomycin families of A \textsuperscript{3-18}, B \textsuperscript{3-19}, C \textsuperscript{3-20}, D \textsuperscript{3-21}, and E \textsuperscript{3-22} from a soil borne bacterium \textit{Streptomyces rosa} var. \textit{notoensis}, which was collected at Nanao-Shi in Japan in the 1970s. Nanaomycin A was found to be an inhibitory agent for gram-positive bacteria, mycoplasma and fungi as well as a platelet aggregation agent.\textsuperscript{28} Structurally, its relative stereochemistry was determined by extensive NMR analysis and comparison of proton NMR data with eleutherin \textsuperscript{3-2}. It showed that the methyl group at C1 is axial and the ester side chain at C3 is equatorial.\textsuperscript{36a,40} The IR spectrum implied the presence of a quinone group in the A and B and it was also found that the two compounds are inter-convertible under basic conditions.\textsuperscript{33a} The UV spectrum of nanaomycin A \textsuperscript{3-18} indicated a juglone fragment, which revealed a hydrogen-bonded quinone carbonyl group as well as a free carboxylic acid. Chemically methylation of nanaomycin A \textsuperscript{3-18} produced the dimethyl derivative, which helped to confirm the presence of the phenolic alcohol group and the carboxyl acid group. By comparison the proton NMR data again with eleutherin \textsuperscript{3-2},\textsuperscript{4d} the C1 methyl and the C3 acetic acid group were assigned as axial and equatorial respectively.\textsuperscript{40} The phenolic alcohol group was identified to be at C9 rather than C6 based on a \textsuperscript{13}C NMR labeling experiment.\textsuperscript{40}
**Figure 3.4.** Structures of members of nanaomycin family

Nanaomycin D 3-21 was shown to possess the identical spectral properties as kalafungin 3-11 but the circular dichroism (CD) spectrum displayed a negative Cotton effect,\(^\text{41}\) thus nanaomycin D 3-21 was identified as the enantiomer of kalafungin 3-11 by comparison of spectroscopic and optical rotatory dispersion (ORD) data.\(^\text{35}\) Synthetically, nanaomycin D 3-21 can be envisioned as the oxidation product from closing of the –CH\(_2\)CO\(_2\)H side chain of nanaomycin A 3-18.

Nanaomycin B 3-19 and E 3-22 are derivatives of A 3-18 with C4a-C10a bond saturated shown in UV spectrum, while \(^{13}\text{C}\) NMR showed chemical shifts of C4a and C10a moved significantly upfield. Nanaomycin B 3-19 could be converted to A 3-18 in cold dilute sodium hydroxide, which confirmed that A 3-18 results from the anti addition of water across the double bond of C4a-C10a. Nanaomycin E 3-22 is the epoxy derivative of A 3-18 with C4a-C10a double bond saturated. The HRMS indicated the molecular formula included one extra oxygen compared to A 3-18, meanwhile the \(^{13}\text{C}\)
NMR showed upfield signals of C4a-C10a like nanaomycin B 3-19. Combination with higher wavenumbers of quinone in IR spectrum proposed a 2,3-epoxy version of nanaomycin A. Many other chemical transformations confirmed the structure its epoxide functionality (Scheme 3.1).

**Scheme 3.1.** Interconversion transformations of nanaomycin family

Nanaomycin C 3-20 was found as an amide derivative of nanaomycin A 3-18 instead of a carboxylic acid. Elemental analysis and mass spectrometry indicated the presence of an extra nitrogen atom and being neutral as well as $^1$H NMR spectrum showed a broad NH$_2$ signal instead of a CO$_2$H proton compared to nanaomycin A 3-18.$^{37}$ The enantiomer of nanaomycin A 3-18, produced by fermentation of a *Nocardi*a species, was named as YS-02931K-β 3-22, also known as dihydrokalafungin. It showed similar high antimicrobial properties against gram-positive bacteria (*i.e.*, *Bacillus subtilis*), dermatophytes and fungi.$^{42}$
Five structurally related new nanaomycin type antibiotics OM-173 \(\alpha A\) 3-24, OM-173 \(\alpha B\) 3-25, OM-173 \(\alpha E\) 3-26, OM-173 \(\beta A\) 3-27, OM-173 \(\beta E\) 3-28, were produced by a soil isolate in Japan.\(^{43}\) They were isolated from a train of Streptomyces rosa var. notoenesis (Strain OM-173), which only differed from the original bacterium in culture characteristics. These compounds were all active against mycoplasmas and fungi, but weaker activity than nanaomycin A 3-18. The change of the carboxyl group (−COOH) to the methyl ester (−COOMe) lowered the antimicrobial activity.

Biologically, nanaomycin A 3-18 and B 3-19 principally inhibit gram-positive bacteria and mycoplasmas, especially at low concentrations when active against *Trichophyton* among fungi, *Mycoplasma gallisepticum* and *M. pneumonia* among mycoplasmas.\(^{36a}\) Nanaomycin B 3-19 seemed no activity itself but being transformed to nanaomycin A 3-18 rapidly under non-enzymatic alkaline conditions.\(^{36b}\)

Nanaomycin A 3-18 was found to be the first DNMT3B-selective inhibitor which induced genomic demethylation.\(^{44}\) DNMT3B is one of the three active DNA methyltransferases in human genome, which (as well as DNMT3A) is responsible for embryonic growth and the creation of genomic imprints.\(^{45}\) It also showed anti-proliferative effects in three different tumor cell lines originating from different tissues.\(^{34}\) The nanaomycin A mode of action as antibiotics against gram-positive bacteria is based on its reduction by the respiratory chain-linked NADH or flavin dehydrogenase (enzyme systems) of the organism. The reduction product from nanaomycin A is then spontaneously autooxidized by molecular \(O_2\) generating singlet molecular oxygen (\(O_2^*\)). This mechanism suggests the ability of nanaomycin A and D producing \(O_2^*\) at the cell membrane as the mechanism of their antibacterial activities.
The postulated pyranonaphthoquinone reduction mechanism is shown below (Scheme 3.2). It may undergo the reduction of the naphthoquinone core to a dihydroxy quinol (a.k.a. hydroquinone), followed by a γ-lactone ring opening, triggered by the neighboring hydroxyl group on the naphthoquinone core. The subsequent pyran ring opening produces the bis-enone, which is easily accessible for Michael addition by any suitable nucleophiles. Interestingly when the nucleophiles a nucleic acid, these quinone antibiotics may form adducts with DNA, which makes these antibiotics worth of synthetic challenges.

**Scheme 3.2.** Possible pyranonaphthoquinone reduction mechanism

Griseusins A 3-29 and B 3-30 are very unique structures among natural pyranonaphthoquinone antibiotics family with the presence of the 1,7-dioxaspiro[5,5]undecane ring system attached to the juglone core at C1 position (Figure 3.5). Griseusins A 3-29 and B 3-30 were isolated from the species of Streptomyces griseus K-63. The γ-lactone ring was indicated from IR and 1H NMR spectra. Their structures and the stereochemistry were established with extensive NMR works especially 1H J coupling constant values.
Similar to the relationship between nanaomycin A 3-18 and D 3-21, griseusin B 3-30 is the γ-lactone ring product of griseusin A 3-29. Griseusin B 3-30 was more polar than A 3-29 and IR spectra showed a carboxylic acid group, and the oxidation of griseusin B 3-30 with pyridine in air further confirmed the relationship of these two griseusins. Under the works of Yoshii et al.48 and Tsuji et al.,49 the absolute configuration of (1R, 3R, 4R, 3'R, 5'R, 6'R) was determined. The synthesis of deoxy analogue 90 of griseusin B 3-30 by Yoshii provided CD spectrum being the mirror image (opposite signs) of natural griseusin B 3-30. After this, Tsuji confirmed the structure by synthesis of a dibromo analogue of griseusin A 3-29, which helped identified the absolute configuration of griseusins.

Griseusin C 3-31 was isolated from fungus *Penicillium sp.* derived from marine cultures by Li et al. in 2006.50 Based on elaborative 1D- and 2D-NMR, HRMS as well as other spectroscopic analysis methods, they determined the structure and relative stereochemistries. Similar to griseusins A 3-29 and B 3-30, C 3-31 showed strong antimicrobial activities against gram-positive bacteria (*i.e.* MRSA) and also some gram-
negative bacteria. One year after, Wen et al. reported the isolation\cite{51} of Griseusin D \textbf{3-32} from the culture of the alkaphilic \textit{Nocardiopsis} sp. YIM 80133. By comparison reported data with related griseusin family members and single-crystal X-ray spectra, the structure was determined as 5’-one-4-hydroxy-12-methoxygriseusin. Griseusin D \textbf{3-32} exhibited high cytotoxicity against human leukemia cell line HL-60 and moderate activity against human lung adenocarcinoma cell lines AGZY.

Griseusin F \textbf{3-33} and G \textbf{3-34} were reported being isolated\cite{52} from the alkophilic \textit{Nocardiopsis} sp. YIM DT 266 by Wen in 2012. Griseusin F \textbf{3-33} and G \textbf{3-34} showed strong cytotoxicity against human cancer cell lines, such as B16, MDA-MB-435S, CFPAC-1, ACHN and HCT-116, as well as antibacterial activities against \textit{Staphylococcus aureus} ATCC 29213, \textit{Micrococcus luteus}, \textit{Bacillus subtilis}.

\subsection{3.2. Previous syntheses of nanaomycins}

Li \textit{et al.} reported the first total synthesis of racemic nanaomycin A and nanaomycin D/kalafungin were reported in 1978 (Scheme 3.3).\cite{53} Started with the reduction and dimethylation of 2-allyl-5-methoxynaphthoquinone \textbf{3-35} giving 2-allyl-1,4,5-trimethoxynaphthalene \textbf{3-36}. The sequence of osmium tetroxide dihydroxylation and periodate cleavage converted \textbf{3-36} to the aldehyde \textbf{3-37}. The following reaction of the aldehyde with ketene ethyl \textit{t}-butyldimethylsilyl acetal generated the hydroxyl ester (+/−)-\textbf{3-38}. The sequence of Ce(NH$_3$)$_2$(NO$_3$)$_6$ oxidation of the dimethyl ether of the quinol, Zn/HCl reduction and pyran ring formation using CH$_3$CHO/HCl, Ag$_2$O oxidation and deprotection of the methyl group using AlCl$_3$ gave 1,3-\textit{cis}-tricyclic product (+/−)-\textbf{3-41}. Epimerization at C9 of the 1,3-\textit{cis}-\textbf{3-41} was achieved by treatment of concentrated H$_2$SO$_4$ giving a 2:1 \textit{trans}:\textit{cis} mixture of isomers \textbf{3-42}. Concentrated HCl hydrolysis of finally
yielded racemic nanaomycin A 3-18. Treatment of nanaomycin A 3-18 with air in MeOH gave a mixture of racemic nanaomycin D and kalafungin.

**Scheme 3.3.** Li’s first total synthesis of racemic nanaomycin A and D

Semmelhack *et al.* developed a strategy including two critical steps: cycloaddition of an alkyne with a carbene-chromium complex and the intramolecular alkoxy-carbonylation of a hydroxyl alkene forming the pyran ring (Scheme 3.4). 54 Reaction of o-bromonisole 3-43 with n-BuLi generated the o-lithio-anisole, which subsequently reacted with chromium complex Cr(CO)$_6$ to form the known carbene-chromium complex 3-44. Heating 3-44 with allylacetylene and oxidation of the resulting crude product led to 2-allyl-5-methoxy-1,4-naphthoquinone 3-45. Since the direct addition of a carbon substituent at C3 in 3-45 failed, an alternative multistep route was established, in which a sequence of reduction of quinone to quinol and monoalkylation made compound 3-45.
Bromination with NBS followed by methylation yielded 3-46, which was lithiated with \( n\)-BuLi. Quenching the resulting anion with CH\(_3\)CHO gave a mixture of 3-47. Under the conditions of \( \text{PdCl}_2/\text{CuCl}_2 \) in MeOH with 1.1 atm of CO, the diastereomeric pyranone products \( \text{cis-3-48} \) and \( \text{trans-3-48} \) were achieved. After separation, direct CAN oxidation generated quinones \( \text{cis-3-49} \) and \( \text{trans-3-49} \), respectively. For \( \text{trans-3-49} \), another 3-step sequence formally yielded\(^{55} \) racemic nanaomycin A 3-18.

Scheme 3.4. Semmelhack’s total synthesis of racemic nanaomycin A

Yoshii et al. in 1983 reported an efficient route to \( (+/-)\)-nanaomycin A.\(^{56} \) This method consists a significant improvement for the multigram preparation of nanaomycin A as compared to previous syntheses (Scheme 3.5).\(^{57} \) This new method relied on the regiospecific installation of the 2-butenoate side chain to the juglone by a modified Claisen rearrangement (3-53 to 3-54). The synthesis started with readily available juglone 3-50, which can be obtained by oxidation of naphthalene-1,5-diol. Juglone 3-50 was readily transformed to 3-52 via the following sequence of reactions: (1) \( \text{Na}_2\text{S}_2\text{SO}_4 \) reduction; (2) acetonide protection; (3) treatment with \( \alpha\)-bromo-\( \gamma\)-butyro-lactone without
purification of the intermediates. Treatment of 3-52 with PhSeNa provided phenylselenide 3-53. Unstable naphthylbutenoate 3-54 was obtained via the oxidative elimination of phenylseleno group of 3-53. Conversion of 3-54 to the key intermediate dihydrofuran 3-55 was achieved readily. Oxidative removal of the acetonide group produced the precursor for nanaomycin A. Zn/HCl reduction of the quinone with addition of CH$_3$CHO and Ag$_2$O oxidation of the resulting quinol generated the cis-isomer of nanaomycin A methyl ester, which was transformed to the racemic nanaomycin A (3-18) via routes of isomerization of the cis-isomer to trans-isomer followed by saponification. Yoshii et al. in 1984 reported an additional example of this methodology using different protecting group for the phenolic alcohols and thus more steps for the synthesis of (+/−)-nanaomycin A.\textsuperscript{58}

**Scheme 3.5.** Yoshii’s total synthesis of racemic nanaomycin A

Liebeskind et al. developed an organotransition metal catalyzed methodology for the synthesis of nanaomycin A in 1984 and 1985 (Scheme 3.6).\textsuperscript{59} This methodology based on
the construction of the quinone core via the formation of an squarate dione 3-60 with a functionalized alkyl under the catalysis of organotransition-metal chemistry. Starting from propargyl alcohol 3-58, highly functionalized benzocyclobutenedione 3-61 was obtained readily. Insertion of cobalt into the dione ring of 3-61 formed the phthaloylcobalt complex 3-62. Intramolecular naphthoquinone ring construction was achieved selectively to yield only one macrocyclic quinone regioisomer 3-63. Zn/HCl reduction followed by Ag₂O work-up provided the desired pyran ring products with a mixture of 3:1 ratio of trans:cis isomers. Removal of the phenolic substituent with AlCl₃, followed by the hydrolysis of the nitrile to the carboxylic acid generated a mixture of 3:1 ratio of trans:cis isomers of nanaomycin A (3-18) and epi-nanaomycin A (epi-3-18).
Scheme 3.6. Liebeskind’s approach to the total synthesis of (+/−)-nanaomycin A (3-18) and (+/−)-epi-nanaomycin A (epi-3-18)

Tatsuta et al. reported the first enantiospecific total synthesis of (−)-nanaomycin D and its enantiomer (+)-kalafungin in 1985 (Scheme 3.7). The divergent synthesis relied on the common optically active intermediate 3-71 to synthesize both enantiomers. Condensation of 3-67 and 3-66 with lithium t-butoxide produced hydroquinone 3-68, which was methylated subsequently to give 3-69. Stereoselective NaBH₄ reduction followed by an acid hydrolysis to selective remove the anomeric methyl group without
epimerization at C1 and C4 generated the mixture of the key intermediate 3-71. Then exposure to Wittig reagent ethoxycarbonylmethylenephosphorane, 3-71 was converted into a mixture of 3-72 and 3-73. Compound 3,4-cis-lactone 3-72 was then oxidized using aq. CAN to give the quinone 3-74, which was transformed to (–)-nanaomycin D (3-21) with AlCl3 demethylation. On the other hand, the 3,4-trans-ester 3-73 was converted to quinone 3-75, which was demethylated, epimerized and lactonized to generate (+)-kalafungin 3-21.

**Scheme 3.7.** Tatsuta’s approach to the total synthesis of enantiomeric (–)-nanaomycin D 3-21 and (+)-kalafungin 3-11

Uno reported another efficient approach to the synthesis of racemic nanaomycin A
in 1986 (Scheme 3.8). The Uno route was based on the addition of an allyl or a 3-(methoxy-carbonyl)allyl group at the vicinal position of 2-alkanoyl-1,4-quinone. Functionalized acetyljuglone 3-76 reacted with butenoate under the catalysis of SnCl₄ provided the conjugated compound 3-77, which was aromatized to mono-TBDMS protected quinol 3-78. Reduction of ketone 3-78, followed by a base-catalyzed Miahcel addition to form the pyran ring products 3-79 as a ca. 1:1 mixture of trans:cis isomers. After separation, treatment with aq. CAN oxidized 3-79 respectively to produce trans-quinone (+/-)-3-80 and cis-quinone (+/-)-3-80. A final saponification provided the racemic nanaomycin A (+/-)-3-18 and the racemic epimers (+/-)-(epi)-3-18.

Scheme 3.8. Uno’s approach to the total synthesis of (+/-)-nanaomycin A (3-18) and (+/-)-epi-nanaomycin A (epi-3-18)

Yamaguchi et al. published the biomimetic synthesis of (+/-)-nanaomycin A in 1990 (Scheme 3.9). This approach relied on the biosynthetic synthesis of intermediate isochromanequinone. The Claisen condensation of the lithiated t-butyl acetate with
naphthalenediol 3-81 yielded selective extended aliphatic t-butyl ketoester 3-82. NaBH₄ reduction, lactonization and MOM protection produced the lactone 3-84. The Claisen condensation of lithiated acetate followed by the removal of alkoxy carbonyl group by palladium catalyzed reaction provided the methyl ketone 3-85. Anhydrous acid treatment of 3-85 deprotected the MOM group and dehydrated to form 3-86. Oxidation of 3-86 with 1,2-dioxirane yielded the para-quinone 3-87, which without purification was reduced to cis-pyran product 3-88. Finally cis-3-88 was epimerized to trans-3-18 nanaomycin A under acidic condition.

**Scheme 3.9.** Yamaguchi’s biomimetic synthesis of (+/−-nanaomycin A

Brimble et al. reported a methodology involving an oxidative rearrangement of a furonaphthofuran, which was prepared via the addition of 2-trimethylsilyloxyfuran 3-90 to the naphthoquinone core to synthesize (−)-nanaomycin D/(+)-kalafungin in 1994
The furofuran annulation was completed with the coupling of naphthoquinone 3-89 and the 2-trimethylsilyloxyfuran 3-90, producing the annulated adduct 3-91. Subsequent CAN oxidative rearrangement of 3-91 to furonaphthopyran 3-92 was completed. Reductively removed the hydroxyl group of the hemeacetal 3-92 generated the precursor 3-93 for the final synthesis of nanomycin D/kalafungin. Treatment of 3-93 with excess BBr₃ deprotected the methoxyl group as well as epimerized at C5 position and resulted in the synthesis of a mixture of nanomycin D 3-21 and kalafungin 3-11. Additionally, treatment of 3-93 under hydrogenation conditions (H₂, Pd/C) was used to form the ester 3-94 from the γ-lactone 3-93. Excess of BBr₃ treatment deprotected the methoxyl group and epimerized at C5 position producing the 1,3-cis-pyran product 3-93, which was transformed to racemic nanaomycin A under KOH hydrolysis.
Scheme 3.10. Brimble’s approach for the synthesis of racemic nanaomycin D (3-21) with kalafungin 3-21

Moore reported another efficient route to the enantiospecific synthesis of (−)-nanaomycin D (Scheme 3.11). This synthesis based on a new methodology involving a ring expansion of iminocyclobutenones to aminophenols. Commercially available L-rhamnose was used to prepare compound 3-96 as reported. Swern oxidation, selective bromination, Luche reduction and direct mesylation transformed 3-96 to compound 3-100, which was ready to form the lactone ring. LiOH hydrolysis followed by treatment with Et₃N in the presence of refluxing benzene provided the butenolide 3-101. DIBAL reduction followed by triisopropylsilyl triflate protection of the resulting hemeketal prepared the substrate for vinyl-lithiation. Ring expanded hydroquinone 3-103 was achieved by treatment of the lithium reagent 3-103 with squarate dione under the
thermolysis in refluxing \( p \)-xylene followed by treatment with HCl and PCC oxidation. Final demethylation produced the \((-\)-nanaomycin D 3-21.

**Scheme 3.11.** Moore’s approach for the enantiospecific \((-\)-nanaomycin D (3-21)

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3.3. Previous syntheses of griseusins-1.7-dioxaspiro[5,5]undecane conformations and the enantiomeric griseusins

Griseusin A 3-31 bears a 1.7-dioxaspiro[5,5]undecane skeleton, which conformation has been studied extensively.\(^6^6\) Yoshii *et al.* published a spiroketal synthesis related to griseusin A in 1981 (Scheme 3.12).\(^6^7\) Alkylation of compound 2-allyl-3-bromo-1,4-dimethoxynaphthalene 3-106 with MOM ether of 5-hydroxylhexanal 3-107 provided the carbinol 3-108, which was oxidized to ketone 3-109 using PCC. Bromination of the 3-
allyl with the addition of hypobromous acid (in situ generated) produced a crude product of bromohydrin 3-110, which was treated with 10% HCl with heating deprotected the MOM group and concomitantly spiro-ketalized to form compound 3-112 and its epimer at C3 position of ca. 1:1 ratio. Nitrile 3-113 and its epimer formed as a 3:2 ratio by treatment of the bromide mixture with NaCN. Hydrolysis of nitrile 3-113 afforded acid 3-114, which was oxidized using aq. CAN to quinone 3-115. Air oxidation in pyridine produced the targeted γ-lactone product 3-116. The methodology was established for the total synthesis (+)-9-deoxygriseusin B.48 (+)-griseusin A and B48 were later synthesized based on this methodology.
Scheme 3.12. Yoshii’s methodology for synthesis of 1,7-dioxaspiro[5,5]undecane conformation

In 1983, based on the above methodology, Yoshii et al. published the first total synthesis of (+)-griseusin A (ent)-3-31, the enantiomer of the naturally occurring (−)-griseusin A 3-31 (Scheme 3.13). Allylation of the 3-bromojuglone 3-117 with 3-butenoic afforded the 2-allyl-3-bromojuglone 3-118, which was sequentially reduced with Na2S2SO4, acetonide protection of the resulting unstable hydroquinone and O-methylation gave compound 3-119. Coupling of this functionalized naphthalene 3-119 with a L-gulose derivative 3-120 generated the epimeric carbinol 3-121, which was oxidized with PCC to form ketone 3-122 ready for the spiroketal-pyran ring formation in one step. Addition of HClO4 and N-bromoacetamide (NBA) to ketone 3-122 followed by
treatment with HCl to deprotect the acetonide provided the desired bromo ketals 3-123a and 3-123b with a mixture of ca. 1:2. The diastereomers were separated to determine the stereostructures and the mixture was subjected to the cyanide substitution of the bromide to form the diastereomeric nitriles 3-124a and 3-124b (ca. 1:2). Hydrolysis with KOH and H$_2$O$_2$, the mixture of nitriles were converted to the single stereoisomer 3-125. Generation of precursor acid 3-126 was achieved via the acetylation of 3-125 followed by the removal of the MOM group. Oxidation with Ag$_2$O in the presence of HNO$_3$ afforded (+)-griseusin B (ent)-3-30. Finally, aerial oxidation in pyridine formed (+)-griseusin A (ent)-3-31, which showed identical spectral properties with natural (−)-griseusin A 3-31 but the CD spectra were mirror images in shape and amplitude.
Scheme 3.13. Yoshii’s total synthesis of (+)-griseusin A and (+)-griseusin B

On the other hand, Brimble *et al.* utilized the same methodology described above (CAN induced oxidative rearrangement of the furonaphthofuran 3-134 via the addition of 2-trimethylsilyloxyfuran 3-90 to the naphthoquinone core) for the synthesis of (−)-nanaomycin D/(+)-kalafungin for the construction of the 1,7-dioxaspiro[5,5]undecane framework in griseusins, produced the γ-lactone product 3-116. 69

In 2000, Brimble *et al.* published a titanium naphtholate approach for the synthesis of analogues of griseusin A (Scheme 3.14). 70 This strategy was based on work by Bigi *et al.*71 and Casiraghi *et al.*72 The desired benzylic alcohol 3-129 was produced by addition
of a titanium naphtholate generated from naphthol 3-127 using Lewis acid TiCl$_3$(Oi-Pr) to the fully functionalized aldehyde 3-128. The alcohol 3-129 was oxidized with MnO$_2$ provided ketone, which was transformed to acetate 3-130 with two other major side products. The key naphthol 3-130 was demethylated with CAN offering unstable naphthoquinone, which was subjected to addition of 2-trimethylsilyloxyfuran 3-90 generated 1:1 ratio of inseparable mixture of furonaphthofuran 3-131a/3-131b. Treatment of 3-131a/3-131b with excess CAN followed by addition of 5% HF yielded only one isomer of lactol 3-132a or 3-132b. CSA catalyzed cyclization of lactol 3-132 produced a 3.2:1 mixture of epimerized pyranonaphthoquinone spiroketal 3-133a and 3-133b.
Scheme 3.14. Brimble’s application of addition of 2-trimethylsilyloxyfuran to form analogues of griseusins

More recently, in 2013, Brimble reported another synthesis for the framework of girsuesin B (Scheme 3.15).\textsuperscript{73} This route relied on a Hauser-Kraus annulation strategy in a convergent way to fulfill the synthesis of the natural product and other analogues. The key step is the Hauser-Kraus annulation of the stabilized phthalide 3-134 with

\[ \text{Scheme 3.15.} \]
functionalized chiral enone 3-135. The stabilized anion of phthalide 3-134 underwent Michael addition to enone 3-135, followed by a Dieckmann type condensation and oxidation produced the naphthaquinone bicyclic skeleton 3-136. Reduction of quinone 3-136 and trapped with Me$_2$SO$_4$ under H$_2$ formed a dimethoxyl intermediate with TBS groups. Subsequent TBS deprotection under the same atmosphere provided the spirocyclization precursor 3-137. Spiroketal 3-137 was then debenzylated and double oxidized to generate the carboxylic acid 3-139, which transformed to the target griseusin B framework 3-140 via an oxidative demethylation reaction using freshly prepared AgO. The stereochemistry of 3-140 proved to be identical to that of the natural griseusin B.

**Scheme 3.15.** Brimble’s methodology for the synthesis of griseusin B framework 3-140
3.4. My work towards the total syntheses of pyranonaphthoquinone nanaomycin A and griseusin A

Based on the importance of the pyranonaphthoquinone antibiotic properties and the interest in the one-step formation of the spiroketal skeleton shown in the progress of synthesizing the griseusins, we started to establish our methodology to approach the total synthesis of nanaomycin A and griseusin A. As illustrated above, there were various methods towards the synthesis of racemic nanaomycin A and D but few practical enantiomeric version of the synthesis. We planned to establish a divergent enantiomeric route for both the enantiomers via the key intermediate 3-144 (later revised to dimethoxyl version 3-163) by applying Sharpless dihydroxylation using either (DHQD)$_2$PHAL or (DHQ)$_2$PHAL as ligands to control the stereochemistry.

Retrosynthetically, we envisioned that (−)-griseusin A 3-29 could be produced from spiroketal with a nitrile group 3-141, which in turn could be prepared from the DCC coupling product 3-142. This precursor would be coupled with a L-gulose derivative carboxylic acid 3-143 and an enantiomeric β-hydroxyl nitrile naphthanoquinone 3-144 (later revised to dimethoxyl version 3-163), which is an important intermediate for the synthesis of nanaomycins.
Scheme 3.16. Retrosynthesis of (–)-griseusin A 3-29

The synthesis of carboxylic acid 3-143 started with the Sharpless dihydroxylation of achiral \((2E,4E)\)-dienolate ethyl sorbate 3-145 under the conditions of catalytic OsO\(_4\) (1 mol %) with \((\text{DHQD})_2\text{PHAL}\) (1.1 mol %) as ligands regio- and enantioselectively generated a 1,2-\(\text{cis}\)-dil 3-146. To this 1,2-\(\text{cis}\)-dil 3-146 was reacted with triphosgene to produce the cyclic carbonate 3-147. The palladium-catalyzed elimination of the allylic hydroxyl generating homoallylic alcohol 3-148 was activated by the cyclic carbonate. The homoallylic alcohol 3-148 was then ready for the second Sharpless dihydroxylation. Under the same dihydroxylation conditions, homoallylic alcohol 3-148 was transformed to the 1,3,4-\(\text{cis}\)-triol 3-149. The 1,3-\(\text{cis}\)-dil of 3-148 was preferentially protected with \(p\)-anisaldehyde dimethyl acetal. The benzyldine-protected \(\text{cis}\)-triol 3-150 was then subjected to the Mitsunobu reaction to convert the stereochemistry of the free alcohol, generating 3-151. Removal of PNB group using \(\text{Et}_3\text{N}\) in MeOH formed the stereochemistry-inverted alcohol 3-152. Protection of the inverted free alcohol using MOMCl yielded benzyldine-protected MOM ether 3-153. However, the LiOH catalyzed hydrolysis of 3-153 has not been successfully completed to produce the desired
carboxylic acid 3-143.

Scheme 3.17. Synthesis of coupling partner 3-143 for griseusin A

At the same time, I started to synthesize another part for the coupling. Monobenzylation of the achiral 1,5-dihydroxynaphthalene 3-154 with limited equivalents of BnBr provided compound 3-155 in 52% yield, which was then subjected to the allylation conditions (reflux in acetone with allyl bromide and K₂CO₃, 90% yield) to form the O-linked allyl product 3-156 for the subsequent Claisen rearrangement (reflux in DMF) to transfer the allyl group to the C-linked allyl product 3-157 in 76% yield. Oxidation of allyl phenol 3-157 was then carried out with different reagents such as Fremy’s salt and hypervalent iodine reagents but did not get satisfactory quinone product. Attention was then focused on the ceric ammonium nitrate aqueous oxidation. Good yield (74%) of the oxidation could be reached with an immediate reaction of CAN in H₂O with allyl phenol 3-157 in MeCN followed by basic work up conditions.
Scheme 3.18. Synthesis of allyl naphthoquinone 3-158

With this quinone 3-158 in hand, I started to use it as the substrate for the Sharpless dihydroxylation reaction. Dihydroxylation was slow and the diol product was not very stable, meanwhile the epoxidation with \textit{m}-CPBA failed to transform the unstable quinone to epoxide as preferred. Thus the idea of transforming this quinone to its dimethoxylated quinol version to enhance the stability came up.

Reduction of allyl quinone 3-158 with aq. Na$_2$S$_2$SO$_4$ in the presence of \textit{n}-Bu$_4$NBr generated the air-sensitive quinol, which \textit{in situ} was methylated under basic conditions (50% KOH). The crude products showed there was a monomethylated product, which was transformed to the dimethylated product 3-159 with a second methylation, which resulted in a 92% yield in total. With the stable allyl dimethoxyl quinol 3-159 in hand, I turned my attention to the Sharpless dihydroxylation again. Normally, 60% conversion of the starting material at room temperature for more than 24 hours can be obtained. Longer reaction did not provide better conversion. Based on the recovered starting material, 87%-93% yield of the dihydroxylation was achieved. Selective tosylation of diol 3-160 was conducted to form primary tosylate 3-161 with TsCl under the catalysis of Bu$_2$SnO. The regioisomer was carefully removed by silica gel chromatography. Substitution of the tosyl group in 3-161 with KCN in DMSO at 60 ºC was achieved (93%) to give β-nitrile
An intermediate of epoxide 3-162 was observed with incomplete reaction. Direct epoxidation to the tosylate 3-161 produced clean epoxide 3-162 in 90% yield.

**Scheme 3.19.** Synthesis of key intermediate enantiomeric β-hydroxyl nitrile 3-163

In literature, the pyran ring formation normally used the quinone as the substrate. It underwent a Zn/HCl (g) reduction of the quinone to quinol first. Then the corresponding aldehyde was added subsequently to form the pyran ring followed by an oxidation to generate the only isomer that could be isolated in either 1,3-*trans* or 1,3-*cis* product. The dimethoxyl quinol was also found to react with the aldehyde directly and produced the desired 1,3-*trans* pyran ring for the desired stereochemistry. Thus, reaction of the dimethoxyl β-hydroxyl nitrile with acetaldehyde in the presence of HCl in dioxane at room temperature overnight securely generated the expected 1,3-*trans* pyran ring product 3-164 in 70% yield. Oxidative demethylation with aq. CAN gave the pyranonaphthaquinone 3-165, which is also unstable. Direct debenzylation under 10% Pd/C in the presence of H₂ generated the nitrile precursor 3-166. Hydrolysis of the nitrile 3-166 in 9 N H₂SO₄ at 90 ºC finally produced the (−)-nanaomycin A in 50% yield. The
yield has not been optimized.

**Scheme 3.20.** Synthesis of natural (−)-nanaomycin A 3-18

Additionally, epoxide 3-162 was utilized to undergo a Coates carbonylation reaction to form the β-lactone 3-167. The β-lactone 3-167 could be opened up generating a β-hydroxyl ester 3-168, which could cyclized to yield the 1,3-cis-pyran product 3-169. Similar manipulations to this ester 3-169 as shown in Scheme 3.19 would produce nanaomycin A in a different way.

**Scheme 3.21.** Alternative route for the synthesis of (−)-nanomycin A 3-18
Divergently, using (DHQ)$_2$PHAL as ligands would prepare another enantiomeric diol suitable for the synthesis of kalafungin 3-11, or deoxyfrenolicin 3-15, frenolicin B 3-16 while using $n$-butyaldehyde to form the pyran ring, which have opposite stereochemistry to natural nanaomycin A 3-18.

We envisioned that a DCC coupling would couple the dimethoxyl $\beta$-hydroxyl nitrile 3-163 with the PMP-MOM-carboxylic acid 3-143 to give the precursor for the synthesis of griseusins. However, the attempts have not been completed. The process is still promising.

**3.5. Conclusion**

A divergent enantiomeric route has been established to synthesize the natural (−)-nanaomycin A and (−)-griseusin A. It is a 12-step synthesis (2.5% yield in total) that based on an enantiomeric Sharpless dihydroxylation reaction to introduce the first stereocenter. The second introduction of the stereocenter was obtained due to the thermodynamic stability. To prepare the precursor for the dihydroxylation, a sequence of monobenzylation, allylation, Claisen rearrangement, CAN oxidation and aq. $\text{Na}_2\text{S}_2\text{SO}_4$ reduction was utilized. Post- dihydroxylation reactions include the selective tosylation, cyanide substitution, CAN oxidation, debenzylation and the final hydrolysis reaction. The total synthesis of the first enantiomeric pure (−)-grisuesin A is still challenging.
References:


Appendix A – Experimental procedures

Section A: General methods

Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon or nitrogen using oven-dried glassware and standard syringe/septa techniques. Ether, tetrahydrofuran, methylene chloride and methanol were dried by passing through activated alumina column with argon. Hexanes refer to the petroleum fraction of boiling point 40-60 °C. Commercial reagents were used without purification unless otherwise noted. Flash chromatography was performed using the indicated solvent system on silica gel standard grade 60 (230-400 mesh). \( R_f \) values are reported for analytical TLC using the specified solvents and 0.25 mm silica gel 60 F254 plates that were visualized by UV irradiation (254 nm) or by KMnO₄ or anisaldehyde staining. Optical rotations were obtained using a digital polarimeter at sodium D line (589 nm) and were reported in concentration of g/100 mL at 25 °C. \(^1\)H and \(^{13}\)C spectra were recorded on 270 MHz, 600 MHz and 400 MHz spectrometer. Chemical shifts are reported relative to CHCl₃ (δ 7.26 ppm) for \(^1\)H and CHCl₃ (δ 77.0 ppm) for \(^{13}\)C. IR was recorded on FT-IR spectrometer; thin film was formed in CHCl₃ solution. Melting points are uncorrected.
Section B: Synthetic Procedures

(S)-1-(furan-2-yl)ethanol ((S)-1-5a): \(^1\)

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To a solution of 15 g acylfuran 1-1a (136.4 mmol) in 20 mL CH\(_2\)Cl\(_2\) was added a freshly prepared solution of HCO\(_2\)H/Et\(_3\)N (40 mL, 2:1 mol:mol) and Noyori asymmetric transfer hydrogenation catalyst \((R)-\text{Ru}(\eta^6\text{-mesitylene})-(S,S)\text{-TsDPEN} (0.2 \text{ g}, 0.25 \text{ mol }\%).\) The resulting solution was stirred at room temperature for 24 h. Then it was diluted with water (90 mL) and extracted with Et\(_2\)O (200 mL x 3). The pooled organic layer was washed with 50 mL saturated aqueous NaHCO\(_3\), 50 mL saturated brine, dried over Na\(_2\)SO\(_4\) and then concentrated under reduced pressure to give a residue. Flash chromatography on silica gel eluting with Et\(_2\)O/Hexane (1:1) gave furfural alcohol (S)-1-5a (14 g, 92%): Colorless oil; \(R_f = 0.45\) (3:7 (v/v) EtOAc/Hexane); \([\alpha]_D^{25} = -21\) (c 1.0, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (600 MHz CDCl\(_3\)) \(\delta 7.30\) (d, \(J = 1.8, 1\text{H}\)), 6.26 (dd, \(J = 3.0, 1.8\text{ Hz, 1H}\)), 6.15 (d, \(J = 3.0, 1\text{H}\)), 4.78 (dq, \(J = 6.6, 6.6\text{ Hz, 1H}\)), 3.11 (s, 1\text{H}\)), 1.46 (d, \(J = 6.6\text{ Hz, 3H}\)); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta 157.7, 141.6, 109.9, 104.9, 63.3, 21.1\).

(2S)-6-hydroxy-2-methyl-2\text{H}-pyran-3(6\text{H})-one (\(\alpha/\beta\text{-1-1-6a}\)): \(^1\)

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To a solution of 14 g furfural alcohol \((S)-1-5a\) (125 mmol) in 416 mL THF/H\(_2\)O (3:1) was added 21 g NaHCO\(_3\) (250 mmol), 17 g NaOAc·3H\(_2\)O (125 mmol), and 22.3 g NBS (125 mmol) at 0 °C. The reaction mixture was kept stirring at this temperature for 1 hour, then at 0 °C 200 mL saturated aqueous NaHCO\(_3\) was added to quench the reaction. The reaction mixture was directly extracted with Et\(_2\)O (300 mL × 3) and the organic layer was pooled, washed by 100 mL saturated brine, dried over Na\(_2\)SO\(_4\) and then concentrated reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with EtOAc/Hexane (1:1) afforded pyranone alcohols \(\alpha\)-\(L\)-1-6a and \(\beta\)-\(L\)-1-6a (14.4 g, 90%, \(\alpha:\beta = 2.8:1\)): White solid; \(R_f = 0.25\) (3:7 (v/v) EtOAc/Hexane); \([\alpha]_D^{25} = +44\) (c 1.0, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (600 MHz, CDCl\(_3\)) major isomer \(\delta 6.82\) (dd, \(J = 10.2, 3.0\) Hz, 1H), 5.96 (d, \(J = 10.2, 1\)H), 5.48 (d, \(J = 3.0\) Hz, 1H), 3.99 (q, \(J = 7.2\) Hz, 1H), 1.23 (d, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) major isomer \(\delta 197.6, 145.3, 126.6, 87.2, 74.8, 15.1\).

**tert-butyl((2S,6S)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl)carbonate (\(\alpha\)-\(L\)-1-7a):**

![tert-butyl((2S,6S)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl)carbonate](image)

To a solution of 7.4 g pyranone alcohols \(\alpha/\beta\)-\(L\)-1-6a (57.8 mmol) in 80 mL CH\(_2\)Cl\(_2\) was added 528 mg DMAP (4.33 mmol) at −78 °C. A pre-cooled solution of 25.2 g (Boc)\(_2\)O (115.6 mmol) in 30 mL CH\(_2\)Cl\(_2\) was added dropwise into the reaction mixture via a cannula. The reaction mixture was stirred at −78 °C for 12 hours. The reaction was
quenched by 100 mL saturated aqueous NaHCO₃ and then extracted with Et₂O (300 mL × 3). The organic layers were pooled, then washed by saturated brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a residue. Flash chromatography on silica gel eluting with Et₂O/Hexane (7:93) gave Boc protected α-pyranone α-L-1-7a (7.8 g, 60%). Elution with Et₂O/Hexane (10:90) gave β-isomer β-L-1-7a (2.5g, 19%) in 3:1.

α-L-1-7a: Rf = 0.60 (3:7 (v/v) EtOAc/Hexane); [α]D²⁵ = +98 (c 1.0, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 6.78 (dd, J = 10.2, 3.6 Hz, 1H), 6.22 (d, J = 3.6 Hz, 1H), 6.09 (d, J = 10.2 Hz, 1H), 4.53 (q, J = 6.6 Hz, 1H), 1.40 (s, 9H), 1.28 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 195.5, 151.7, 140.9, 128.2, 89.1, 83.3, 72.0, 27.5, 15.1.

1-(furan-2-yl)-propan-1-one (1-1b):³

![Structure](image)

To 62 mL of furan 1-8 (860 mmol) was slowly dropped n-BuLi (2.4 M in hexane) (100 mL, 240 mmol) at 0 °C. The solution was then warmed up to room temperature and the resulting solution was stirred at room temperature for 3 h. Then 75 mL of anhydrous THF was added to dissolve the solid mixture at room temperature, which was then transferred to propionic acid (5.9 mL, 79 mmol) in 50 mL of THF at 0 °C. Then resulting solution was stirred 30 min at 0 °C followed by warming up and stirring at room temperature for 3 h. Then into the reaction mixture 300 mL of Et₂O was added to dilute the solution, followed by addition of 300 mL of distilled water at 0 °C. Into the flask, 200 mL of 2M NaOH and 200 mL sat. NaHCO₃ were added to wash the organic layer. The aqueous layer was extracted with Et₂O (300 ml x2). The pooled organic layer was washed with
200 mL saturated brine solution, dried over Na$_2$SO$_4$ and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with EtOAc/Hexane (2:98) gave furan ketone 1-1b (6.31 g, 64%): Light yellow oil; $R_f = 0.83$ (1:4 (v/v) EtOAc/Hexane); IR (thin film, cm$^{-1}$) 3131, 2980, 2939, 1672, 1569, 1469, 1394, 1158, 1010, 882, 758; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 7.56 (dd, $J = 1.7$, 0.8 Hz, 1H), 7.16 (dd, $J = 3.5$, 0.8 Hz, 1H), 6.51 (dd, $J = 3.5$, 1.8 Hz, 1H), 2.64 (q, $J = 7.2$ Hz, 2H), 0.98 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (67.5 MHz, CDCl$_3$) $\delta$ 190.1, 152.5, 146.0, 116.6, 112.0, 31.5, 7.9.

(S)-1-(furan-2-yl)-propan-1-ol (1-5b):$^2$

![Image of furan ketone 1-1b](image_url)

To a solution of aqueous HCO$_2$Na (17.7 g, 130 mL, 2.0 M) was added furan ketone 1-1b (9.63 g, 77.6 mmol) in 6 mL CH$_2$Cl$_2$, followed by the addition of surfactant CTAB (2.83 g, 7.76 mmol). The mixture was stirred for 5 min, then was added Noyori asymmetric transfer hydrogenation catalyst (R)-Ru(η$^6$-mesitylene)-(S,S)-TsDPEN (0.047 g, 0.1 mol %). The resulting solution was stirred at room temperature under argon for 24 h. Then the mixture was added with 300 mL H$_2$O to dilute and extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with 40 mL saturated aqueous NaHCO$_3$, 40 mL saturated brine, dried over Na$_2$SO$_4$ and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with EtOAc/Hexane (8:92) gave furfural alcohol 1-5b (6.4 g, 65%): Colorless oil; $R_f = 0.42$ (1:4 (v/v) EtOAc/Hexane); $[\alpha]_D^{25} = \text{-}13.0$ (c 0.8, CHCl$_3$); IR (thin film, cm$^{-1}$) 3371, 2966, 2935, 2877, 1507, 1461, 1151, 1009, 793, 733; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.35 (dd, $J = 1.8$, 0.6 Hz 1H), 6.31 (dd, $J = 3.0$, 1.8 Hz, 1H), 6.21 (d, $J = 3.0$ Hz, 1H), 4.56 (dd, $J = 6.6$, 6.6
Hz, 1H), 2.32 (s, 1 H), 1.85 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 156.9, 142.0, 110.2, 106.0, 69.3, 28.7, 10.0.

(2S)-2-ethyl-6-hydroxy-2H-pyran-3(6H)-one (α/β-L-1-6b):

To a solution of furfural alcohol 1-5b (3.06 g, 24.3 mmol) in 82 mL THF/H2O (3:1) was added NaHCO3 (4.08 g, 48.6 mmol), NaOAc·3H2O (3.30 g, 24.3 mmol), and 4.32 g NBS (24.3 mmol) at 0 °C. The reaction mixture was kept stirring at this temperature for 1 h. Then at 0 °C 80 mL saturated NaHCO3 solution was added to quench the reaction. The reaction mixture was directly extracted with Et2O (3 x 80 mL) and the organic layer was pooled, washed by 30 mL saturated brine, dried over Na2SO4 and then concentrated reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with EtOAc/Hexane (15:85) afforded mixture of pyranone alcohols α/β-L-1-6b (3.04 g, 88 %): Colorless oil; Rf = 0.44 (1:2 (v/v) EtOAc/Hexane); 1H NMR (400 MHz, CDCl3) major isomer δ 6.89 (dd, J = 10.2, 3.6 Hz, 1H), 6.08 (d, J = 10.2 Hz, 1H), 5.64 (m, 1H), 4.49 (dd, J = 7.6, 4.0 Hz, 1H), 3.87 (d, J = 5.2 Hz, 1H), 1.97-1.87 (m, 1H), 1.85-1.69 (m, 1H), 0.95 (dd, J = 7.2, 7.2 Hz, 3H); 13C NMR (100 MHz, CDCl3) major isomer δ 197.1, 144.9, 127.7, 87.7, 75.4, 23.1, 9.5.
tert-butyl ((2S,6S)-6-ethyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (α-L-1-7b):

To a solution of pyranone alcohol α/β-L-1-6b (3.04 g, 21.4 mmol) in 10 mL CH₂Cl₂ was added DMAP (261.40 mg, 2.14 mmol) at −78 ºC. A pre-cooled solution of (Boc)₂O (5.60 g, 25.68 mmol) in 10 mL CH₂Cl₂ was added drop-wise into the reaction mixture via a cannula. The reaction mixture was stirred at −78 ºC for 12 h. The reaction was quenched by 75 mL saturated NaHCO₃ and then extracted with Et₂O (150 mL x 3). The organic layers were pooled, then washed by 25 mL saturated brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with EtOAc/Hexane (5:95) gave two diastereomers of Boc-protected pyranones α-L-1-7b and β-L-1-7b (4.61 g, 89%) in 1.8:1.

α-L-1-7b: Rᵣ = 0.69 (1:4 (v/v) EtOAc/Hexane); [α]D²⁵ = +62.9 (c 1.0, CHCl₃); IR (thin film, cm⁻¹) 2981, 2885, 1751, 1701, 1462, 1371, 1276, 1256, 1159, 1104, 1057, 1030, 940, 847; ¹H NMR (600 MHz, CDCl₃) δ 6.85 (dd, J = 10.2, 3.6 Hz, 1H), 6.33 (d, J = 3.6 Hz, 1H), 6.16 (d, J = 10.2 Hz, 1H), 4.43 (dd, J = 7.2, 4.2 Hz, 1H), 1.97-1.90 (m, 1H), 1.79-1.72 (m, 1H), 1.49 (s, 9H), 0.93 (dd, J = 7.2, 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 195.3, 151.8, 140.9, 128.9, 89.3, 83.4, 76.6, 27.6 (3), 22.8, 8.9; HRMS (ESI): Calcd. [C₁₂H₁₈O₅+Na]⁺: 65.1047, Found: 265.1050.

β-L-1-7b: Light yellow solid; Rᵣ = 0.61 (1:4 (v/v) EtOAc/Hexane); M.P. 65-66 ºC; [α]D²⁵ = −73.5 (c 1.0, CHCl₃); IR (thin film, cm⁻¹) 2983, 2877, 1740, 1684, 1461, 1397, 1292, 1254, 1160, 1053, 946, 846, 732; ¹H NMR (600 MHz, CDCl₃) δ 6.85 (dd, J = 10.2, 3.0
Hz, 1H), 6.37 (dd, J = 3.0, 1.2 Hz, 1H), 6.20 (dd, J = 10.2, 1.2 Hz, 1H), 4.14 (dd, J = 9.6, 4.8 Hz, 1H), 1.96-1.83 (m, 2H), 1.53 (s, 9H), 1.03 (dd, J = 7.8, 7.2 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 195.7, 151.9, 141.9, 128.3, 89.5, 83.5, 81.0, 31.0, 27.7 (2), 26.7, 9.9; HRMS (ESI): Calcd. [C$_{12}$H$_{18}$O$_5$+Na]$^+$: 265.1047, Found: 265.1051.

1-(furan-2-yl)-2-methylpropan-1-one (1-1d):$^2$

![furan-ketone](image)

To 62 mL of furan 1-8 (860 mmol) was slowly dropped n-BuLi (100 mL, 240 mmol) at 0 ºC. The solution was then warmed up to room temperature and the resulting solution was stirred at room temperature for 3 h. Then 75 mL of anhydrous THF was added to dissolve the solid mixture at room temperature, which was then transferred to $\textit{iso}$-butyric acid (8.8 mL, 79 mmol) in 50 mL of THF at 0 ºC. Then resulting solution was stirred 30 min at 0 ºC followed by warming and stirring at room temperature for 3 h. Then into the reaction mixture 300 mL of Et$_2$O was added to dilute the solution, followed by addition of 300 mL of distilled water at 0 ºC. Into the flask, 200 mL of 2 M NaOH and 200 mL sat. NaHCO$_3$ was added to wash the organic layer. The aqueous layer was extracted with Et$_2$O (300 mL x2). The pooled organic layer was washed with 200 mL saturated brine, dried over Na$_2$SO$_4$ and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with EtOAc/Hexane (3:97) gave furan ketone 1-1d (7.4 g, 68%): Light yellow oil; $R_f$ = 0.80 (1:4 (v/v) EtOAc/Hexane); IR (thin film, cm$^{-1}$) 3138, 2974, 2880, 1669, 1568, 1465, 1396, 1252, 1017, 884, 759; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.58 (dd, J = 1.8, 0.6 Hz, 1H), 7.18 (d, J = 3.6 Hz, 1H), 6.53 (dd, J = 3.6, 1.8 Hz, 1H), 1.96-1.83 (m, 2H), 1.53 (s, 9H), 1.03 (dd, J = 7.8, 7.2 Hz, 3H).
Hz, 1H), 3.33 (hep, J = 6.6 Hz, 1H), 1.21 (d, J = 6.6 Hz, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 193.7, 152.3, 146.3, 117.2, 112.2, 36.4, 18.9 (2).

$(S)$-$1$-(furan-2-yl)-2-methylpropan-1-ol (1-5d):$^2$

![Structure](image)

To a solution of aqueous HCO$_2$Na (6.8 g, 50 mL, 2.0 M) was added furan ketone 1-1d (4.22 g, 0.031 mol) in 2 mL CH$_2$Cl$_2$, followed by the addition of surfactant CTAB (1.12 g, 0.0031 mmol). The mixture was stirred for 5 min, then added Noyori asymmetric transfer hydrogenation catalyst $(R)$-Ru($\eta^6$-mesitylene)-(S,S)-TsDPEN (0.019 g, 0.1 mol %). The resulting solution was stirred at room temperature under argon for 24 h. The mixture was added with 100 mL H$_2$O to dilute and extracted with EtOAc (3 x 70 mL). The combined organic layer was washed with 15 mL saturated aqueous NaHCO$_3$, 15 mL saturated brine, dried over Na$_2$SO$_4$ and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with EtOAc/Hexane (8:92) gave furfural alcohol 1-5d (2.6 g, 61%): Colorless oil; $R_f$ = 0.56 (1:4 (v/v) EtOAc/Hexane); [α]$_D^{25}$ = −22.1 (c 1.0, CHCl$_3$); IR (thin film, cm$^{-1}$) 3387, 2961, 2873, 1505, 1469, 1150, 1007, 807, 730; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.33 (dd, J = 1.8, 0.6 Hz 1H), 6.30 (dd, J = 3.0, 1.8 Hz, 1H), 6.19 (d, J = 3.0, 1H), 4.33 (d, J = 7.2 Hz, 1H), 2.29 (s, 1H), 2.10 (hepd, J = 7.2, 6.6 Hz, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 156.4, 141.7, 110.1, 106.5, 73.6, 33.5, 18.8, 18.4.
(2S)-6-hydroxy-2-isopropyl-2\(H\)-pyran-3(6\(H\))-one (\(\alpha/\beta\)-L-1-6d):

To a solution of furfural alcohol 1-5d (1.93 g, 13.8 mmol) in 44 mL THF/H\(2\)O (3:1) was added NaHCO\(3\) (2.32 g, 27.6 mmol), NaOAc\(\cdot\)3H\(2\)O (1.87 g, 13.8 mmol) and NBS (2.45 g, 13.8 mmol) at 0 °C. The reaction mixture was kept stirring at this temperature for 1 h, then at 0 °C 40 mL saturated NaHCO\(3\) was added to quench the reaction. The reaction mixture was directly extracted with Et\(2\)O (3 x 40 mL) and the organic layer was pooled, washed by 15 mL saturated brine, dried over Na\(2\)SO\(4\) and then concentrated reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with EtOAc/Hexane (15:85) afforded pyranone alcohols \(\alpha/\beta\)-L-1-6d (1.87 g, 87 %): Colorless oil; \(R_f\) = 0.44 (1:2 (v/v) EtOAc/Hexane); \(^1\)H NMR (270 MHz, CDCl\(3\)) major isomer \(\delta\) 6.90 (dd, \(J = 10.2, 3.6\) Hz, 1H), 6.09 (d, \(J = 10.2\) Hz, 1H), 5.66 (d, \(J = 3.0\) Hz, 1H), 4.40 (d, \(J = 3.0\) Hz, 1H), 3.90 (dd, \(J = 3.6, 1.2\) Hz, 1H), 2.51-2.34 (m, 1H), 1.01 (d, \(J = 7.0\) Hz, 3H), 0.86 (d, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (67.5 MHz, CDCl\(3\)) major isomer \(\delta\) 197.1, 144.7, 128.2, 87.7, 78.5, 28.7, 19.2, 16.4.

tert-butyl-((2S,6S)-6-isopropyl-5-oxo-5,6-dihydro-2\(H\)-pyran-2-yl) carbonate (\(\alpha\)-L-1-7d):

O

\[\text{Boc} \]
To a solution of pyranone alcohol $\alpha/\beta$-L-1-6d (1.87 g, 12.0 mmol) in 5 mL CH$_2$Cl$_2$ was added DMAP (146.2 mg, 1.20 mmol) at –78 ºC. A pre-cooled solution of (Boc)$_2$O (5.24 g, 24.0 mmol) in 7 mL CH$_2$Cl$_2$ was added drop-wise into the reaction mixture via a cannula. The reaction mixture was stirred at –78 ºC for 12 h. The reaction was quenched by 30 mL saturated NaHCO$_3$ and then extracted with Et$_2$O (50 mL x 3). The organic layers were pooled, then washed by 15 mL saturated brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with EtOAc/Hexane (5.5: 94.5) gave two diastereomers of Boc-protected pyranone $\alpha$-L-1-7d and $\beta$-L-1-7d (2.67 g, 87%) in 2.5:1;

$\alpha$-L-1-7d: $R_f$ = 0.78 (1:4 (v/v) EtOAc/Hexane); [$\alpha$]$_D^{25}$ = +50.8 (c 1.0, CHCl$_3$); IR (thin film, cm$^{-1}$) 2974, 2878, 1751, 1698, 1463, 1370, 1274, 1255, 1157, 1099, 1056, 943, 846, 736; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.86 (dd, $J$ = 10.2, 3.6 Hz, 1H), 6.35 (d, $J$ = 3.6 Hz, 1H), 6.17 (d, $J$ = 10.2 Hz, 1H), 4.34 (d, $J$ = 3.0 Hz, 1H), 1.92 (dq, $J$ = 6.6, 6.6, 3.0 Hz, 1H), 1.50 (s, 9H), 1.01 (d, $J$ = 6.6 Hz, 3H), 0.86 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 195.6, 152.0, 141.0, 129.6, 89.6, 83.6, 79.9, 28.8, 27.9 (3), 18.8, 16.1; HRMS (ESI): Calcd. [C$_{13}$H$_{20}$O$_5$+Na]$^+$: 279.1203, Found: 279.1207.

$\beta$-L-1-7d: $R_f$ = 0.59 (1:4 (v/v) EtOAc/Hexane); M.P. 70-71 ºC; [$\alpha$]$_D^{25}$ = –65.6 (c 0.7, CHCl$_3$); IR (thin film, cm$^{-1}$) 2971, 2876, 1743, 1683, 1470, 1369, 1287, 1252, 1159, 1055, 944, 847; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.82 (dd, $J$ = 10.2, 3.0 Hz, 1H), 6.35 (dd, $J$ = 2.4, 1.2 Hz, 1H), 6.19 (dd, $J$ = 10.2, 1.8 Hz, 1H), 3.88 (d, $J$ = 7.2 Hz, 1H), 2.32 (dq, $J$ = 7.2, 6.6, 6.6 Hz, 1H), 1.53 (s, 9H), 1.01 (d, $J$ = 6.6 Hz, 3H), 0.95 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 195.5, 152.1, 142.4, 129.2, 90.1, 84.6, 83.8, 31.0, 27.9 (3), 18.9, 18.4; HRMS (ESI): Calcd. [C$_{13}$H$_{20}$O$_5$+Na]$^+$: 279.1203, Found: 279.1206.
1-(furan-2-yl)-3-methylbutan-1-one (1-1e):

To 62 mL of furan 1-8 (860 mmol) was slowly dropped n-BuLi (100 mL, 240 mmol) at 0 °C. The solution was then warmed up to room temperature and the resulting solution was stirred at room temperature for 3 h. Then 75 mL of anhydrous THF was added to dissolve the solid mixture at room temperature, which was then transferred to iso-valeric acid (8.8 mL, 79 mmol) in 50 mL of THF at 0 °C. Then resulting solution was stirred 30 min at 0 °C followed by warming and stirring at room temperature for 3 h. Then into the reaction mixture 300 mL of Et₂O was added to dilute the solution, followed by addition of 300 mL of distilled water at 0 °C. Into the flask, 200 mL of 2 M NaOH and 200 mL saturated NaHCO₃ were added to wash the organic layer. The aqueous layer was extracted with Et₂O (300 ml x2). The pooled organic layer was washed with 200 mL saturated brine, dried over Na₂SO₄ and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with EtOAc/Hexane (3:97) gave furan ketone 1-1e (8.4 g, 70%): Light yellow oil; R_f = 0.71 (1:5 (v/v) EtOAc/Hexane); IR (thin film, cm⁻¹) 3133, 2959, 2872, 1670, 1569, 1467, 1395, 1165, 1026, 883, 757; ¹H NMR (600 MHz, CDCl₃): δ 7.54 (dd, J = 1.8, 0.6 Hz, 1H), 7.14 (dd, J = 3.6, 1.2 Hz, 1H), 6.49 (dd, J = 3.6, 1.8 Hz, 1H), 2.66-2.64 (m, 2H), 2.25 (hepd, J = 7.2, 1.8 Hz, 1H), 0.953 (d, J = 6.6 Hz, 3H), 0.949 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃): δ 190.0, 153.4, 146.4, 117.0, 112.3, 47.5, 25.5, 22.8 (2). HRMS (ESI): Calcd. [C₉H₁₂O₂+H]⁺: 153.0910, Found: 153.0910.
(S)-1-(furan-2-yl)-3-methylbutan-1-ol (1-5e):

To a solution of aqueous HCO$_2$Na (9.7 g, 70 mL, 2.0 M) was added furan ketone 1-1e (6.5 g, 42 mmol) in 3 mL CH$_2$Cl$_2$, followed by the addition of surfactant CTAB (1.56 g, 4.2 mmol). The mixture was stirred for 5 min, and added Noyori asymmetric transfer hydrogenation catalyst ($R$)-Ru($\eta^6$-mesitylene)-(S,S)-TsDPEN (26 mg, 0.1 mol %). The resulting solution was stirred at room temperature under argon for 24 h. Then the mixture was added with 100 mL H$_2$O to dilute and extracted with EtOAc (3 x 70 mL). The combined organic layer was washed with 15 mL saturated aqueous NaHCO$_3$, 15 mL saturated brine, dried over Na$_2$SO$_4$ and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with EtOAc/Hexane (8:92) gave furfural alcohol 1-5e (5.3 g, 61%): Colorless oil; $R_f = 0.54$ (1:4 (v/v) EtOAc/Hexane); $[\alpha]_D^{25} = -22.1$ (c 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3349, 2956, 2870, 1506, 1468, 1150, 1010, 806, 731; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.36 (dd, $J = 1.8, 0.6$ Hz 1H), 6.32 (dd, $J = 3.6, 1.8$ Hz, 1H), 6.20 (d, $J = 3.0$, 1H), 4.74 (dd, $J = 7.8, 5.4$ Hz, 1H), 1.97 (s, 1H), 1.80-1.65 (m, 3H), 0.95 (d, $J = 6.0$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H), $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 157.3, 142.0, 110.3, 105.9, 66.2, 44.7, 24.8, 23.2, 22.3. HRMS (ESI): Calcd. [C$_9$H$_{14}$O$_2$+Na]$^+$: 177.0886, Found: 177.0889.
(2S)-6-hydroxy-2-isobutyl-2H-pyran-3(6H)-one (α/β-L-1-6e):

To a solution of furfural alcohol 1-5e (5.00 g, 32.4 mmol) in 108 mL THF/H₂O (3:1) was added NaHCO₃ (5.44 g, 64.8 mmol), NaOAc·3H₂O (4.41 g, 32.4 mmol) and NBS (5.76 g, 32.4 mmol) at 0 °C. The reaction mixture was kept stirring at this temperature for 1 h. Then at 0 °C 100 mL saturated NaHCO₃ was added to quench the reaction. The reaction mixture was directly extracted with Et₂O (3 x 100 mL) and the organic layer was pooled, washed by 50 mL saturated brine, dried over Na₂SO₄ and then concentrated reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with EtOAc/Hexane (15:85) afforded pyranone alcohols α/β-L-1-6e (4.35 g, 79 %): Colorless oil; Rᵣ = 0.60 (1:2 (v/v) EtOAc/Hexane); ¹H NMR (400 MHz, CDCl₃): major isomer δ 6.87 (dd, J = 10.0, 3.6 Hz, 1H), 6.11 (d, J = 10.4 Hz, 1H), 5.61 (s, 1H), 4.58 (dd, J = 9.6, 3.2 Hz, 1H), 3.92 (s, 1H), 1.92-1.83 (m, 1H), 1.78-1.71 (m, 1H), 1.59-1.52 (m, 1H), 0.91 (d, J = 6.4, Hz, 3H), 0.89 (d, J = 6.8, Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): major isomer δ 197.7, 144.8, 127.6, 87.7, 72.9, 38.2, 24.3, 23.5, 21.5.

tert-butyl ((2S, 6S)-6-isobutyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (α-L-1-7e):
To a solution of pyranone alcohols $\alpha/\beta$-L-1-6e (4.35 g, 25.6 mmol) in 15 mL CH$_2$Cl$_2$ was added DMAP (313.8 mg, 2.56 mmol) at $-78^\circ$C. A pre-cooled solution of (Boc)$_2$O (6.70 g, 30.7 mmol) in 15 mL CH$_2$Cl$_2$ was added drop-wise into the reaction mixture via a cannula. The reaction mixture was stirred at $-78^\circ$C for 12 h. The reaction was quenched by 100 mL saturated NaHCO$_3$ and then extracted with Et$_2$O (150 mL x 3). The organic layers were pooled, then washed by 40 mL saturated brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give a residue. Eluting with EtOAc/Hexane (6.5:93.5) on silica gel gave two diastereomers of Boc-protected pyranones $\alpha$-L-1-7e and $\beta$-L-1-7e (5.33 g, 77%) in 2.5:1;

$\alpha$-L-1-7e: $R_f = 0.68$ (1:4 (v/v) EtOAc/Hexane); $[\alpha]_D^{25} = +32.5$ (c 0.9, CHCl$_3$); IR (thin film, cm$^{-1}$) 2959, 2877, 1751, 1701, 1470, 1370, 1275, 1252, 1156, 1104, 1055, 1029, 939, 844; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.79 (dd, $J = 10.2$, 3.6 Hz, 1H), 6.25 (d, $J = 3.6$ Hz, 1H), 6.12 (d, $J = 10.2$ Hz, 1H), 4.47 (dd, $J = 9.6$, 3.0 Hz, 1H), 1.78 (m, 3H), 1.44 (s, 9H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.82 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 195.8, 151.9, 140.7, 128.9, 89.2, 83.4, 74.0, 37.6, 27.7 (3), 24.1, 23.3, 21.3; HRMS (ESI): Calcd. [C$_{14}$H$_{22}$O$_5$+Na]$^+$: 293.1359, Found: 293.1363.

$\beta$-L-1-7e: $R_f = 0.61$ (1:4 (v/v) EtOAc/Hexane); M.P. 53-58 $^\circ$C; $[\alpha]_D^{25} = -65.3$ (c 1.1, CHCl$_3$); IR (thin film, cm$^{-1}$) 2959, 2873, 1750, 1695, 1471, 1396, 1282, 1251, 1159, 1059, 938, 851, 791, 738; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.83 (dd, $J = 10.2$, 3.0 Hz, 1H), 6.35 (d, $J = 3.0$ Hz, 1H), 6.19 (d, $J = 10.8$ Hz, 1H), 4.29 (dd, $J = 11.4$, 3.6 Hz, 1H), 1.90 (m, 2H), 1.82 (hepd, $J = 6.6$, 4.2 Hz, 1H), 1.50 (s, 9H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 196.5, 152.1, 141.7, 128.3, 89.4, 83.6, 78.2, 42.4, 27.8 (3), 24.3, 23.5, 21.3; HRMS (ESI): Calcd. [C$_{14}$H$_{22}$O$_5$+Na]$^+$: 293.1359, Found:
5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-((2S,6S)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (2-3a):^{3}

To a solution of perbenzylated flavonol 2-2 (265.1 mg, 0.48 mmol) and pyranone α-L-1-7a (217.4 mg, 0.95 mmol) in 4 mL CH₂Cl₂ was added a solution of Pd₂(DBA)₃·CHCl₃ (24.7 mg, 0.024 mmol) and PPh₃ (25.0 mg, 0.095 mmol) in 0.5 mL CH₂Cl₂ at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours and then quenched by 15 mL saturated aqueous NaHCO₃, followed by extraction with Et₂O (25 mL×3). The organic layer was pooled, then washed by 15 mL saturated aqueous brine, dried over Na₂SO₄ and concentrated under reduced pressure to give crude product. Eluting with EtOAc/Hexane (15:85) on silica gel gave glycosylated pyranone 2-3a (289.0 mg, 91%): Yellow solid, M.P. 75-77 °C; Rₕ = 0.50 (1:2 (v/v) EtOAc/Hexane); [α]D²⁵ = −63 (c 0.93, CHCl₃); IR (thin film, cm⁻¹) 3063, 2921, 1699, 1636, 1607, 1574, 1509, 1454, 1375, 1355, 1300, 1252, 1198, 1178, 1162, 1103, 1013, 937. ¹H NMR (CDCl₃, 600 MHz) δ 7.87 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 7.8 Hz, 2H), 7.46-7.29 (m, 13H), 7.27 (dd, J = 10.2, 3.6 Hz, 1H), 7.06 (d, J = 9.0 Hz, 2H), 6.58 (d, J = 1.8 Hz, 1H), 6.47 (d, J = 1.8 Hz, 1H), 6.13 (d, J = 10.2 Hz, 1H), 5.92 (d, J = 3.6 Hz, 1H), 5.27 (s, 2H), 5.15 (s, 2H), 5.08 (d, J = 12 Hz, 1H), 5.08 (d, J = 12 Hz, 1H), 4.02 (q, J = 6.0 Hz, 1H), 0.93 (d, J = 6.6Hz, 3H); ¹³C NMR
A solution of pyranone 2-3a (153.5 mg, 0.23 mmol) in 2.0 mL CH₂Cl₂/MeOH (3:1) was cooled to −78 °C, then NaBH₄ (17.4 mg, 0.46 mmol) was added. The reaction mixture was kept stirring at −78 °C for 3 hours. The reaction was quenched with saturated aq. NaHCO₃, followed by extraction with Et₂O. The organic layer was washed by saturated brine, dried over Na₂SO₄ and concentrated under reduced pressure to give crude product. Crude ¹H NMR showed a d.r. > 20:1. Eluting with EtOAc/Hexane (33:67) on silica gel gave allylic alcohol 2-4a (123.1 mg, 80%): Amorphous yellow solid; Rᵣ = 0.29 (1:1 (v/v) EtOAc/Hexane); [α]D²⁵ = −83 (c 0.85, CHCl₃); IR (thin film, cm⁻¹) 3361, 2927, 1604, 1509, 1453, 1354, 1298, 1251, 1176, 1098, 1013, 916; ¹H NMR (CDCl₃, 600 MHz) δ 7.95 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.45-7.27 (m, 13H), 7.06 (d, J = 9.0 Hz, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.20 (ddd, J = 10.2, 2.4, 2.4 Hz, 1H), 5.97 (d, J = 10.2 Hz, 1H), 5.60 (s, 1H), 5.26 (s, 2H), 5.15 (s, 2H), 5.07 (d, J = 12
Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 3.74 (dd, J = 7.2, 6.6 Hz, 1H), 3.31 (dq, J = 8.4, 6.0 Hz, 1H), 0.71 (d, J = 6.6 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 67.5 MHz) δ 173.8, 162.8, 160.3, 159.9, 159.0, 154.8, 138.3, 136.5, 136.4, 135.7, 133.9, 130.7, 128.8, 128.7, 128.6, 128.5, 128.2, 127.8, 127.7, 127.5, 126.7, 126.6, 123.8, 114.6, 110.2, 98.3, 95.7, 94.0, 70.8, 70.5, 70.1, 69.6, 69.4, 17.0; HRMS (CI): Calcd. [C$_{42}$H$_{36}$O$_8$+Na$^+$]: 691.2302, Found: 691.2296.

(2S,3R,6S)-6-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)-2-methyl-3,6-dihydro-2H-pyran-3-yl acetate (2-5a): 4

A solution of allylic alcohol 2-4a (122.4 mg, 0.18 mmol) in 1.5 mL CH$_2$Cl$_2$ was cooled to 0 °C, then 0.2 mL pyridine, catalytic amount of DMAP and 0.2 mL Ac$_2$O were added. After stirring for 1 hour, the mixture was diluted by Et$_2$O. The organic layer was sequentially washed with H$_2$O, saturated aq. NaHCO$_3$, saturated brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford crude product. Eluting with EtOAc/Hexane (15:85) on silica gel gave 4'-monoacetate 2-5a (106.1 mg, 84%): Amorphous yellow solid; $R_f$ = 0.52 (2:3 (v/v) EtOAc/Hexane); [α]$_D^{25}$ = −146 (c 1.1, CHCl$_3$); IR (thin film, cm$^{-1}$) 3052, 2927, 1736, 1636, 1608, 1509, 1454, 1375, 1355, 1298, 1240, 1178, 1104, 1023, 936; $^1$H NMR (CDCl$_3$, 600 MHz) δ 7.96 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.47-7.27 (m, 13H), 7.09 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.20 (ddd, J = 10.2, 2.4, 2.4 Hz, 1H), 5.90 (d, J =
10.2 Hz, 1H), 5.60 (brs, 1H), 5.27 (s, 2H), 5.17 (s, 2H), 5.08 (d, J = 11.4 Hz, 1H), 5.07 (d, J = 11.4 Hz, 1H), 4.96 (ddd, J = 9.6, 1.8, 1.8 Hz, 1H), 3.60 (dq, J = 9.6, 6.6 Hz, 1H), 2.08 (s, 3H), 0.61 (d, J = 6.0 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 173.5, 170.3, 162.8, 160.2, 159.8, 154.5, 138.4, 138.4, 138.5, 136.4, 135.7, 130.6, 130.3, 128.7, 128.6, 128.5, 128.4, 128.1, 127.6, 127.5, 127.3, 126.6, 123.8, 114.5, 110.0, 98.2, 95.8, 94.0, 70.8, 70.7, 70.4, 70.1, 66.5, 21.1, 17.0; HRMS (CI): Calcd. [C₄₄H₃₈O₉+Na]⁺: 733.2408, Found: 733.2405.

(2S,3R,4S,5R,6S)-6-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)-4,5-dihydroxy-2-methyltetrahydro-2H-pyran-3-yl acetate (2-8a):⁴  

A solution of 4’-monoacetate 2-5a (106.3 mg, 0.15 mmol) in 1 mL acetone/⁻-BuOH (1:1) was cooled to 0 °C. To the solution was added 1 mL NMO/H₂O (w/w 1:1), and a catalytic amount of crystalline OsO⁴ was added into the mixture. The reaction mixture was stirred at 0 °C for 24 hours. The reaction was quenched with saturated aqueous Na₂S₂O₃ and stirred overnight. Then the mixture was passed through a small pad of celite and silica gel, washed with EtOAc/MeOH (1:1), the organic solution was dried over Na₂SO₄ and concentrated under reduced pressure to give a residue. Eluting with EtOAc/Hexane (40:60) on silica gel gave 4’-acetate-2’,3’-diol 2-8a (90.4 mg, 78%): Pale yellow solid, M.P. 91-93 °C; Rᶠ = 0.67 (1:10 (v/v) MeOH/Et₂O); [α]D⁰²⁵ = −116 (c 0.8,
CHCl₃); IR (thin film, cm⁻¹) 3424 (broad), 3066, 3035, 2928, 1741, 1605, 1574, 1509, 1498, 1486, 1454, 1375, 1354, 1299, 1251, 1199, 1177, 1144, 1102, 1049, 1004, 955; ¹H NMR (acetone-d₆, 600 MHz) δ 7.82 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.46-7.27 (m, 13H), 7.09 (d, J = 9.0 Hz, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 5.51 (d, J = 1.8 Hz, 1H), 5.27 (s, 2H), 5.15 (s, 2H), 5.07 (s, 2H), 4.78 (dd, J = 9.6, 9.0 Hz, 1H), 4.51 (ddd, J = 3.6, 3.6, 2.4 Hz, 1H), 3.93 (ddd, J = 8.4, 7.8, 3.0 Hz, 1H), 3.45 (d, J = 4.2 Hz, 1H), 3.40 (dq, J = 9.6, 6.6 Hz, 1H), 2.91 (d, J = 7.8 Hz, 1H), 2.05 (s, 3H), 0.81 (d, J = 6.6 Hz, 3H); ¹³C NMR (acetone-d₆, 150 MHz) δ 173.5, 171.2, 163.0, 160.5, 159.8, 158.9, 154.6, 137.8, 136.4, 136.3, 135.6, 130.5, 128.8, 128.7, 128.6, 128.4, 128.2, 127.8, 127.6, 127.3, 126.8, 123.3, 114.7, 109.9, 101.4, 98.4, 94.0, 74.7, 70.8, 70.7, 70.5, 70.2, 69.9, 67.8, 21.0, 17.1; HRMS (ESI): Calcd. [C₄₄H₄₀O₁₁+H]⁺: 745.2649, Found: 745.2642.

(2S,3S,4S,5R,6S)-6-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)-5-hydroxy-2-methyltetrahydro-2H-pyran-3,4-diyl diacetate (2-10a):⁴

![Chemical Structure](image)

To a solution of 4’-acetate-2’,3’-diol 2-8a (90.4 mg, 0.12 mmol) and 2-aminoethyl diphenylborinate 2-11 (2.6 mg, 0.012 mmol) in 1 mL dry MeCN was added DIPEA (22.6 mg, 30.5 µL, 0.18 mmol) and CH₃COCl (13.8 mg, 12.6 µL, 0.18 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 3 h. After completion, the mixture was diluted
with EtOAc. The organic layer was sequentially washed with H2O, saturated aq. NaHCO3, saturated brine, dried over Na2SO4 and concentrated under reduced pressure to afford crude product. Eluting with EtOAc/Hexane (40:60) gave 3’,4’-diacetate 2-10a (77.2 mg, 84%): White solid, M. P. 93-95 °C; Rf = 0.59 (3:2 v/v) EtOAc/Hexane; [α]D25 = −151.0 (c 1.3, CHCl3); IR (thin film, cm⁻¹) 3394 (broad), 3064, 2924, 1741, 1604, 1509, 1453, 1432, 1369, 1353, 1296, 1249, 1222, 1172, 1100, 1043, 1004, 958; 1H NMR (CDCl3, 600 MHz) δ 7.86 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.46-7.27 (m, 13H), 7.12 (d, J = 9.0 Hz, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 5.53 (d, J = 2.4 Hz, 1H), 5.31 (dd, J = 9.0, 3.0 Hz, 1H), 5.26 (s, 2H), 5.15 (s, 2H), 5.08 (s, 2H), 4.98 (dd, J = 9.6, 9.0 Hz, 1H), 4.57 (ddd, J = 6.6, 3.6 Hz, 1H), 3.46 (dq, J = 9.6, 6.6 Hz, 1H), 2.87 (brs, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 0.82 (d, J = 6.0 Hz, 3H); 13C NMR (CDCl3, 150 MHz) δ 173.3, 169.9, 169.8, 163.0, 160.5, 159.9, 158.9, 154.5, 137.6, 136.4, 136.3, 135.6, 130.5, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 127.6, 127.3, 126.7, 123.2, 114.8, 109.9, 101.9, 98.3, 94.0, 74.7, 71.2, 70.8, 70.5, 70.1, 69.5, 67.9, 20.9, 20.8, 17.2; HRMS (ESI): Calcd. [C₄₆H₄₂O₁₂±Na]⁺: 809.2574, Found: 809.2569.

(2S,3S,4S,5R,6S)-6-((5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yl)oxy)-5-hydroxy-2-methyltetrahydro-2H-pyran-3,4-diyl diacetate (SL0101) (2-1a-A).4
To a solution of 3',4'-diacetate 2-10a (44.4 mg, 0.056 mmol) in 2 mL THF/EtOH (1:1) was added 24 mg Pearlman’s catalyst (Pd-C, 10%). The reaction mixture was degassed using vacuum at –78 °C and refilling with H₂. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H₂ atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and elution with EtOAc/Hexane (3:2) to give SL0101 (2-1a-A) (23.0 mg, 79%): Yellow solid, M.P. 147-149 °C; R_f = 0.26 (2:1 (v/v) EtOAc/Hexane); [α]_D^{25} = –163 (c 1.6, MeOH); IR (thin film, cm⁻¹) 3211 (broad), 2980, 2930, 1722, 1650, 1607, 1502, 1444, 1361, 1206, 1171, 1045, 1005, 970; ¹H NMR (acetone-d₆, 600 MHz) δ 7.86 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 6.48 (d, J = 1.8 Hz, 1H), 6.28 (d, J = 1.8 Hz, 1H), 5.56 (d, J = 1.8 Hz, 1H), 5.17 (dd, J = 10.2, 3.0 Hz, 1H), 5.07 (dd, J = 10.2, 9.6 Hz, 1H), 4.42 (dd, J = 3.0, 1.8 Hz, 1H), 3.49 (dq, J = 9.6, 6.0 Hz, 1H), 2.02 (s, 3H), 1.96 (s, 3H), 0.82 (d, J = 6.0 Hz, 3H); ¹³C NMR (acetone-d₆, 150 MHz) δ 179.2, 170.7, 170.4, 165.1, 163.0, 161.1, 158.7, 158.2, 135.5, 131.8, 122.4, 116.5, 105.8, 102.2, 99.7, 99.6, 94.7, 72.3, 71.2, 69.3, 69.2, 21.0, 20.8, 17.6; HRMS (ESI): Calcd. [C₂₅H₂₄O₁₂+Na]⁺: 539.1166, Found: 539.1161.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(((6S)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one ((ent)-2-3a):⁴
To a solution of perbenzylated flavonol 2-2 (112.4 mg, 0.20 mmol) and pyranone a-d-1-7a (92.2 mg, 0.40 mmol) in 1.5 mL CH₂Cl₂ was added a solution of Pd₂(DBA)₃·CHCl₃ (5.2 mg, 0.0051 mmol) and PPh₃ (5.3 mg, 0.020 mmol) in 0.3 mL CH₂Cl₂ at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours and loaded directly onto silica gel column, eluting with EtOAc/Hexane (15:85) gave glycosylated pyranone (ent)-2-3a (110.5 mg, 82%): Light yellow solid, M.P. 75-77 °C; Rf = 0.34 (1:2 (v/v) EtOAc/Hexane); [α]D²⁰ = +72 (c 2.22, CHCl₃); IR (thin film, cm⁻¹) 3064, 3032, 2985, 2918, 2871, 1698, 1634, 1604, 1573, 1509, 1452, 1374, 1353, 1299, 1250, 1196, 1175, 1161, 1100, 1002, 934. ¹H NMR (CDCl₃, 600 MHz) δ 7.86 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 7.8 Hz, 2H), 7.47-7.29 (m, 13H), 7.27 (dd, J = 10.2, 3.6 Hz, 1H), 7.06 (d, J = 9.0 Hz, 2H), 6.58 (d, J = 1.8 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 10.2 Hz, 1H), 5.91 (d, J = 3.6 Hz, 1H), 5.28 (s, 2H), 5.15 (s, 2H), 5.09 (s, 2H), 4.01 (q, J = 7.2 Hz, 1H), 0.92 (d, J = 6.6Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 196.7, 173.3, 163.0, 160.4, 159.9, 159.0, 154.9, 143.1, 137.6, 136.3, 136.2, 135.6, 130.4, 128.8, 128.7, 128.6, 128.4, 128.3, 127.7, 127.6, 127.4, 126.7, 123.2, 114.7, 110.0, 98.3, 94.3, 94.1, 71.5, 70.8, 70.5, 70.1, 14.6; HRMS (ESI): Calcd. [C₄₂H₃₄O₈⁺Na]⁺: 689.2151, Found: 689.2149.

(2S,3S)-6-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)-2-methyl-3,6-dihydro-2H-pyran-3-yl acetate (ent)-2-5a:⁵
A solution of pyranone (ent)-2-3a (106 mg, 0.16 mmol) in 1.6 mL CH$_2$Cl$_2$-MeOH (3:1) was cooled to –78 °C, then NaBH$_4$ (12 mg, 0.32 mmol) was added. The reaction mixture was stirred at –78 °C for 3 hours. The reaction was quenched with saturated NaHCO$_3$, followed by extraction with Et$_2$O. The organic layer was washed by saturated brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give a residue. All residual solvent was removed by applying a high vacuum produced by oil pump for half an hour. The dry residue was re-dissolved in CH$_2$Cl$_2$ and cooled to 0 °C. To the solution was added 0.2 mL pyridine, catalytic amount of DMAP, and 0.2 mL Ac$_2$O. After stirring for 1 hour, the mixture was diluted by EtOAc. The organic layer was sequentially washed with H$_2$O, saturated aq. NaHCO$_3$, saturated brine, dried over Na$_2$SO$_4$ and then concentrated under reduced pressure to afford crude product. Eluting with EtOAc/Hexane (15:85) on silica gel gave (ent)-4'-monoacetate (ent)-2-5a (82.5 mg, 57% in two steps): Amorphous yellow solid; $R_f = 0.52$ (2:3 (v/v) EtOAc/Hexane); [α]$_D^{25} = +142$ (c 0.9, CHCl$_3$); IR (thin film, cm$^{-1}$) 3063, 2927, 1736, 1634, 1606, 1508, 1453, 1374, 1355, 1297, 1240, 1178, 1102, 1024, 934; $^1$H NMR (CDCl$_3$, 600 MHz) δ 7.96 (d, $J =$ 9.0 Hz, 2H), 7.56 (d, $J =$ 7.8 Hz, 2H), 7.57-7.27 (m, 13H), 7.09 (d, $J =$ 9.0 Hz, 2H), 6.57 (d, $J =$ 2.4 Hz, 1H), 6.44 (d, $J =$ 2.4 Hz, 1H), 6.26 (ddd, $J =$ 10.2, 2.4, 2.4 Hz, 1H), 5.90 (d, $J =$ 10.2 Hz, 1H), 5.60 (brs, 1H), 5.27 (s, 2H), 5.17 (s, 2H), 5.08 (d, $J =$ 11.4 Hz, 1H), 5.07 (d, $J =$ 11.4 Hz, 1H), 4.96 (ddd, $J =$ 9.6, 1.2, 1.2 Hz, 1H), 3.60 (dq, $J =$ 9.0, 6.0 Hz, 1H), 2.08 (s, 3H), 0.61 (d, $J =$ 6.0 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 173.7, 170.6, 163.0, 160.5, 160.0, 159.2, 154.8, 138.6, 136.7, 136.6, 135.9, 130.8, 130.6, 129.0, 128.9, 128.8, 128.6, 128.4, 127.9, 127.8, 127.5, 126.9, 124.1, 114.8, 110.3, 98.5, 96.1, 94.2, 71.0, 70.9, 70.7, 70.3, 66.7, 21.3, 17.1; HRMS (Cl): Calcd. [C$_{44}$H$_{38}$O$_9$+Na]$^+$: 733.2408, Found: 733.2405.
(2S,4S,5R)-6-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)-4,5-dihydroxy-2-methyltetrahydro-2H-pyran-3-yl acetate (ent)-2-8a.5

A solution of 4'-monoacetate (ent)-2-5a (57.0 mg, 0.08 mmol) in 1 mL acetone/t-BuOH (1:1) was cooled to 0 °C. To the solution was added 0.5 mL NMO-H₂O (w/w 1:1), and a catalytic amount of crystalline OsO₄ was added into the mixture. The reaction mixture was stirred at 0 °C for 24 hours. The reaction was quenched with saturated aq. Na₂S₂O₃. Then the mixture was passed through a small pad of celite and silica gel, washed with EtOAc/MeOH (1:1), the organic solution was dried over Na₂SO₄, and concentrated under reduced pressure to give a residue. Eluting with EtOAc/Hexane (3:2) on silica gel gave (ent)-4'-acetate-2',3'-diol (ent)-2-8a (45.3 mg, 73%): Pale yellow solid, M.P. 90-92 °C; Rᵣ = 0.38 (3:2 (v/v) EtOAc/Hexane); [α]D²⁵ = +118 (c 1.1, CHCl₃); IR (thin film, cm⁻¹) 3429 (broad), 3064, 3034, 2935, 1739, 1602, 1573, 1509, 1498, 1486, 1453, 1374, 1353, 1248, 1222, 1197, 1174, 1144, 1100, 1047, 1003, 952; ¹H NMR (CDCl₃, 600 MHz) δ 7.82 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.46-7.27 (m, 13H), 7.09 (d, J = 9.0 Hz, 2H), 6.54 (d, J = 2.4 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 5.52 (d, J = 1.8 Hz, 1H), 5.27 (s, 2H), 5.15 (s, 2H), 5.06 (s, 2H), 4.80 (dd, J = 9.6, 9.0 Hz, 1H), 4.53 (dd, J = 3.0, 2.4 Hz, 1H), 3.93 (d, J = 7.8 Hz, 1H), 3.71 (brs, 1H), 3.37 (dq, J = 9.6, 6.0 Hz, 1H), 3.02 (brs, 1H), 2.04 (s, 3H), 0.80 (d, J = 6.0 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 173.6, 171.1, 163.0, 159.8, 158.9, 154.6, 137.7, 136.4, 136.3, 135.6, 130.5, 128.7, 128.7,
128.6, 128.4, 128.2, 127.7, 127.5, 127.3, 126.8, 123.3, 114.7, 109.9, 101.4, 98.3, 93.9, 74.6, 70.8, 70.7, 70.5, 70.1, 69.8, 67.8, 21.0, 17.1; HRMS (ESI): Calcd. [C_{44}H_{40}O_{11}+H]^+:
745.2649, Found: 745.2642.

\((2S,4S,5R)-6-((5,7\text{-bis(benzyloxy)}-2-(4-(benzyloxy)phenyl)-4\text{-oxo-4H-chromen-3-yl})\text{oxy})-5\text{-hydroxy-2-methyltetrahydro-2H-pyran-3,4-diyl diacetate (}(\text{ent})-2-10a):^5\)

To a solution of (ent)-4'-acetate-2',3'-diol (ent)-2-8a (26 mg, 0.034 mmol) and 2-aminoethyl diphenylborinate 2-11 (0.755 mg, 0.0034 mmol) in 0.5 mL dry MeCN was added DIPEA 6.5 mg, 8.8 µL, 0.050 mmol and CH₃COCl (4.0 mg, 3.6 µL, 0.050 mmol) at 0 ºC, and the resulting mixture was stirred at 0 ºC for 3 h. After completion, the mixture was diluted with EtOAc. The organic layer was sequentially washed with H₂O, saturated aq. NaHCO₃, saturated brine, dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. Eluting with EtOAc/Hexane (40:60) gave (ent)-3',4'-diacetate (ent)-2-10a (19.3 mg, 74%): White solid, M.P. 93-95 ºC; \(R_f = 0.67\) (v/v) EtOAc/Hexane; \([\alpha]_D^{25} = +156\) (c 1.7, CHCl₃); IR (thin film, cm⁻¹) 3393 (broad), 3034, 2935, 1741, 1605, 1509, 1453, 1436, 1369, 1354, 1297, 1250, 1222, 1175, 1101, 1047, 1005, 958; \(^1\)H NMR (CDCl₃, 600 MHz) \(\delta\) 7.86 (d, \(J = 8.4\) Hz, 2H), 7.55 (d, \(J = 7.2\) Hz, 2H), 7.46-7.27 (m, 13H), 7.12 (d, \(J = 9.0\) Hz, 2H), 6.56 (d, \(J = 1.8\) Hz, 1H), 6.46 (d, \(J = 2.4\) Hz, 1H), 5.54 (d, \(J = 2.4\) Hz, 1H), 5.31 (dd, \(J = 9.0, 3.0\) Hz, 1H), 5.26 (s, 2H), 5.15
To a solution of (ent)-3',4'-diacetate (ent)-2-10a (10.0 mg, 0.013 mmol) in 1 mL THF/EtOH (1:1) was added 5 mg Pearlman’s catalyst (Pd-C, 10%). The reaction mixture was degassed using vacuum at –78 °C and refilling with H2. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H2 atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and elution with EtOAc/Hexane (3:2) to give ent-SL0101 ((ent)-2-1a-A) (5.6 mg, 86%): Yellow solid, M.P. 147-149 °C; Rf = 0.39 (2:1 (v/v) EtOAc/Hexane); [α]D25 = +203 (c 0.4, MeOH); IR (thin film, cm⁻¹) 3243
(broad), 2980, 2926, 1723, 1654, 1608, 1502, 1443, 1361, 1207, 1173, 1047, 1005, 972;

$^1$H NMR (CD$_3$OD, 600 MHz) δ 7.78 (d, $J = 9.0$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 6.40 (d, $J = 2.4$ Hz, 1H), 6.22 (d, $J = 2.4$ Hz, 1H), 5.61 (d, $J = 1.8$ Hz, 1H), 5.16 (dd, $J = 10.2$, 3.0 Hz, 1H), 5.00 (dd, $J = 10.2$, 9.6 Hz, 1H), 4.34 (dd, $J = 3.0$, 1.8 Hz, 1H), 3.28 (dq, $J = 9.6$, 6.0 Hz, 1H), 2.07 (s, 3H), 1.98 (s, 3H), 0.81 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR (CD$_3$OD, 150 MHz) δ 179.5, 172.2, 171.9, 166.2, 163.4, 161.9, 159.5, 158.8, 135.3, 132.1, 122.6, 116.8, 106.1, 102.0, 100.1, 95.0, 72.9, 72.0, 69.8, 69.6, 21.0, 20.8, 17.7; HRMS (ESI): Calcd. [C$_{25}$H$_{24}$O$_{12}$+Na$^+$]: 539.1166, Found: 539.1161.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(((2S,6S)-6-ethyl-5-oxo-5,6-dihydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (2-3b):

![Chemical Structure](image)

To a solution of perbenzylated flavonol 2-2 (231.1 mg, 0.954 mmol) and pyranone α-L-1-7b (353.8 mg, 0.636 mmol) in 2.5 mL CH$_2$Cl$_2$ was added a solution of Pd$_2$(DBA)$_3$·CHCl$_3$ (24.7 mg, 0.0238 mmol) and PPh$_3$ (25.0 mg, 0.0954 mmol) in 1 mL CH$_2$Cl$_2$ at 0 ºC. The reaction mixture was stirred at 0 ºC for 4 hours and quenched with saturated NaHCO$_3$, followed by extraction with Et$_2$O. The organic layer was pooled, then washed by saturated brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give crude product. Eluting with EtOAc/Hexane (20:80) on silica gel gave glycosylated pyranone 2-3b (359.1 mg, 83%): Yellow solid, M.P. 70-72 ºC; $R_f$ = 0.39 (1:2 (v/v) EtOAc/Hexane); $[\alpha]_D^{25}$ = –42.4 (c 0.5, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3064, 2927, 1696,
\[1607, 1574, 1509, 1454, 1376, 1354, 1303, 1253, 1179, 1099, 1015, 945, 736, 696;\]

\[^1\]H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.89 (d, \(J = 8.8\) Hz, 2H), 7.56 (d, \(J = 7.2\) Hz, 2H), 7.46-7.29 (m, 14H), 7.06 (d, \(J = 8.8\) Hz, 2H), 6.58 (d, \(J = 2.0\) Hz, 1H), 6.47 (d, \(J = 2.0\) Hz, 1H), 6.15 (d, \(J = 10.4\) Hz, 1H), 6.03 (d, \(J = 3.6\) Hz, 1H), 5.29 (s, 2H), 5.14 (s, 2H), 5.08 (s, 2H), 3.85 (dd, \(J = 7.2, 4.0\) Hz, 1H), 1.55-1.45 (m, 1H), 1.45-1.33 (m, 1H), 0.49 (dd, \(J = 7.6, 7.2\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 196.8, 173.6, 163.2, 160.6, 160.0, 159.2, 154.7, 143.5, 137.8, 136.5, 135.8, 130.7, 129.0, 128.9, 128.7, 128.4, 128.2, 128.0, 127.8, 127.7, 126.8, 123.4, 115.0, 110.1, 98.6, 94.2, 76.2, 71.0, 70.7, 70.3, 22.9, 8.9; HRMS (ESI): Calcd. [C\(_{43}\)H\(_{36}\)O\(_8\)+Na]\(^{+}\): 703.2302, Found: 703.2313.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(((2S,5R,6S)-6-ethyl-5-hydroxy-5,6-dihydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (2-4b):

A solution of glycosylated pyranone 2-3b (92.7 mg, 0.136 mmol) in 3.6 mL CH\(_2\)Cl\(_2\)/MeOH (5:1) was cooled to −78 °C, and then NaBH\(_4\) (10.3 mg, 0.272 mmol) was added. The reaction mixture was kept stirring at −78 °C for 4 hours. The reaction was then quenched with saturated NaHCO\(_3\), followed by extraction with Et\(_2\)O. The organic layer was washed by saturated brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure to give crude product. Crude \(^1\)H-NMR showed a d.r. > 20:1. Eluting with EtOAc/Hexane (33:67) on silica gel gave allylic alcohol 2-4b (81.8 mg, 88%): Yellow solid, M.P. 59-61 °C; \(R_f = 0.38\) (1:1 (v/v) EtOAc/Hexane); \([\alpha]_{D}^{25} = -85.3\) (c 1.0, CHCl\(_3\));
IR (thin film, cm\(^{-1}\)) 3379, 2925, 1605, 1498, 1356, 1297, 1253, 1178, 1104, 1002, 920, 835, 736, 697; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.00 (d, \(J = 8.8\) Hz, 2H), 7.55 (d, \(J = 8.0\) Hz, 2H), 7.46-7.29 (m, 13H), 7.06 (d, \(J = 8.8\) Hz, 2H), 6.57 (d, \(J = 2.0\) Hz, 1H), 6.43 (d, \(J = 2.0\) Hz, 1H), 6.22 (ddd, \(J = 10.0, 2.4, 2.4\) Hz, 1H), 5.98 (d, \(J = 10.0\) Hz, 1H), 5.86 (s, 1H), 5.27 (s, 2H), 5.15 (s, 2H), 5.07 (s, 2H), 3.84 (m, 1H), 3.21 (m, 1H), 1.35-1.10 (m, 2H), 0.41 (dd, \(J = 7.6, 7.2\) Hz, 3H); \(^{13}\)C NMR (Benzene, 150 MHz) \(\delta\) 173.3, 162.9, 160.6, 160.3, 159.2, 153.4, 139.0, 137.2, 137.1, 136.5, 134.7, 131.0, 128.8, 128.7, 128.65, 128.4, 128.3, 128.1, 127.9, 127.7, 127.0, 126.5, 124.6, 114.8, 110.7, 98.1, 95.2, 94.0, 73.9, 70.6, 70.3, 70.0, 67.3, 25.1, 9.0; HRMS (ESI): Calcd. \([\text{C}_{43}\text{H}_{38}\text{O}_8+\text{Na}]^+\): 705.2459, Found: 705.2464.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(((2S,3R,4R,5R,6S)-6-ethyl-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (2-5b):

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

A solution of allylic alcohol 2-4b (40.3 mg, 0.059 mmol) in 1 mL acetone/\(t\)-BuOH (1:1) was cooled to 0 \(^\circ\)C. To the solution was added 0.25 mL NMO-H\(_2\)O (w/w 1:1), and then catalytic amount of crystalline OsO\(_4\) was added into the mixture when stirring. The reaction mixture was kept stirring at 0 \(^\circ\)C overnight. The reaction mixture was then quenched with saturated Na\(_2\)S\(_2\)O\(_3\). After stirring for another 15 min, all the staff was passed through a small pad of celite and silica gel, washed by EtOAc-MeOH (5:1) then

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EtOAc-MeOH (3:1). The organic layer was dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give crude product. Eluting with Et$_2$O/MeOH (20:1) on silica gel gave triol **2-5b** (33.9 mg, 80%): White solid, M.P. 97-99 ºC; $R_f = 0.38$ (20:1 EtOAc/MeOH); $[\alpha]_D^{25} = -97.0$ ($c$ 0.54, CHCl$_3$); IR (thin film, cm$^{-1}$) 3407 (broad), 2923, 2869, 1605, 1509, 1455, 1376, 1296, 1256, 1178, 1080, 946, 736; $^1$H NMR (CD$_3$OD, 600 MHz) $\delta$ 7.85 (d, $J = 9.0$ Hz, 2H), 7.53 (d, $J = 7.2$ Hz, 2H), 7.44-7.26 (m, 13H), 7.11 (d, $J = 9.0$ Hz, 2H), 6.65 (d, $J = 1.8$ Hz, 1H), 6.50 (d, $J = 2.4$ Hz, 1H), 5.56 (d, $J = 1.2$ Hz, 1H), 5.18 (s, 2H), 5.14 (d, $J = 12.0$ Hz, 1H), 5.12 (d, $J = 12.0$ Hz, 1H), 5.10 (d, $J = 12.0$ Hz, 1H), 5.07 (d, $J = 12.0$ Hz, 1H), 4.29 (dd, $J = 3.6$, 1.8 Hz, 1H), 3.75 (dd, $J = 9.6$, 3.6 Hz, 1H), 3.40 (dd, $J = 9.6$, 9.6 Hz, 1H), 3.05 (ddd, $J = 9.6$, 9.0, 2.4 Hz, 1H), 1.53-1.46 (m, 1H), 1.21-1.13 (m, 1H), 0.48 (dd, $J = 7.8$, 7.2 Hz, 3H); $^{13}$C NMR (CD$_3$OD, 150 MHz) $\delta$ 175.3, 164.8, 162.2, 160.8, 160.1, 155.8, 138.4, 138.2, 138.0, 137.5, 131.8, 129.62, 129.57, 129.5, 129.2, 129.0, 128.84, 128.75, 128.6, 128.1, 124.3, 116.0, 110.5, 102.6, 99.3, 95.2, 76.6, 72.4, 71.8, 71.7, 71.6, 71.4, 71.1, 25.2, 9.7; HRMS (ESI): Calcd. [C$_{43}$H$_{40}$O$_{10}$+Na]$^+$: 739.2514, Found: 739.2519.

3-(((2S,3R,4R,5R,6S)-6-ethyl-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (2-1b-B):

![Chemical Structure](image)

A solution of triol **2-5b** (24.0 mg, 0.034 mmol) in 1 mL THF/EtOH (1:1) was added 10 mg Pearlman’s catalyst (Pd-C, 10%). The solution was degassed using vacuum at –78 ºC
and refilling with H₂. This procedure was repeated three times, and then the bath was removed. The reaction was warmed up to room temperature and stirred under a H₂ atmosphere for 3.5 hours. The reaction mixture was loaded onto silica gel and eluted with EtOAc/MeOH (20:1) gave kaempferol-3-α-L-rhamnoside 2-1b-B (8.1 mg, 54%): Pale yellow solid, M.P. 150-151 ºC; \( R_f = 0.26 \) (20:1 (v/v) EtOAc/MeOH); \([\alpha]_D^{25} = -119.1 \) (c 1.0, MeOH); IR (thin film, cm\(^{-1}\)) 3342 (broad), 2931, 1655, 1507, 1456, 1361, 1284, 1208, 1176, 1085, 970; \(^1\)H NMR (CD\(_3\)OD, 400 MHz) \( \delta \) 7.82 (d, \( J = 8.8 \) Hz, 2H), 6.94 (d, \( J = 8.8 \) Hz, 2H), 6.38 (d, \( J = 2.4 \) Hz, 1H), 6.20 (d, \( J = 1.6 \) Hz, 1H), 5.57 (d, \( J = 1.2 \) Hz, 1H), 4.22 (dd, \( J = 3.2, 1.6 \) Hz, 1H), 3.73 (dd, \( J = 9.6, 3.2 \) Hz, 1H), 3.39 (dd, \( J = 9.6, 9.6 \) Hz, 1H), 3.13 (ddd, \( J = 9.2, 9.2, 2.4 \) Hz, 1H), 1.61-1.51 (m, 1H), 1.25-1.14 (m, 1H), 0.54 (dd, \( J = 7.6, 7.2 \) Hz, 3H); \(^{13}\)C NMR (CD\(_3\)OD, 150 MHz) \( \delta \) 179.6, 165.9, 163.2, 161.7, 158.6, 158.5, 135.9, 132.0, 122.7, 116.6, 105.9, 102.9, 99.8, 94.7, 76.7, 72.3, 71.8, 71.4, 25.2, 9.7; HRMS (ESI): Calcd. [C\(_{22}\)H\(_{22}\)O\(_{10}\)H\(^+\)]\(^+\): 447.1286, Found: 447.1289.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-((2S,6S)-6-isobutyl-5-oxo-5,6-dihydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (2-3e):

![diagram](image)

To a solution of perbenzylated flavonol 2-2 (218.7 mg, 0.393 mmol) and pyranone \( \alpha \)-L-1-7e (212.5 mg, 0.786 mmol) in 2 mL CH\(_2\)Cl\(_2\) was added a solution of Pd\(_2\)(DBA)\(_3\)-CHCl\(_3\) (10.2 mg, 0.00983 mmol) and PPh\(_3\) (10.3 mg, 0.0393 mmol) in 1 mL CH\(_2\)Cl\(_2\) at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours and then quenched with saturated
NaHCO₃, followed by extraction with Et₂O. The organic layer was pooled, then washed with saturated brine, dried over Na₂SO₄ and concentrated under reduced pressure to give crude product. Eluting with EtOAc/Hexane (15:85) on silica gel gave glycosylated pyranone 2-3e (231.2 mg, 83%): Yellow solid, M.P. 71-72 °C; R₇ = 0.61 (1:2 (v/v) EtOAc/Hexane); [α]D²⁵ = −23.9 (c 1.00, CHCl₃); IR (thin film, cm⁻¹) 3065, 2956, 2926, 1693, 1631, 1605, 1509, 1453, 1377, 1354, 1298, 1254, 1196, 1178, 1161, 1102, 1012, 930, 736; ¹H NMR (400 MHz, CDCl₃): δ 7.95 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 7.6 Hz, 2H), 7.45-7.29 (m, 14H), 7.05 (d, J = 8.8 Hz, 2H), 6.59 (d, J = 2.0 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.23 (d, J = 3.6 Hz, 1H), 6.18 (d, J = 10.4 Hz, 1H), 5.29 (s, 2H), 5.12 (s, 2H), 5.09 (s, 2H), 3.99 (dd, J = 8.4, 3.6 Hz, 1H), 1.64-1.48 (m, 1H), 1.42-1.27 (m, 2H), 0.66 (d, J = 6.4 Hz, 3H), 0.47 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 196.9, 173.4, 162.9, 160.5, 159.8, 158.8, 153.6, 143.5, 137.5, 136.3, 135.6, 130.4, 128.76, 128.7, 128.64, 128.5, 128.2, 127.7, 127.6, 127.5, 126.6, 123.1, 114.8, 109.8, 98.2, 93.9, 93.0, 74.7, 70.7, 70.5, 70.1, 39.0, 29.8 (grease), 24.4, 23.2, 21.8. HRMS (ESI): Calcd. [C₄₅H₄⁰O₈⁺H]⁺: 709.2796, Found: 709.2803.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(((2S,5R,6S)-5-hydroxy-6-isobutyl-5,6-dihydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (2-4e):

![Pyranone Structure](image)

A solution of pyranone 2-3e (164.0 mg, 0.23 mmol) in 2 mL CH₂Cl₂/MeOH (3:1) was cooled to −78 °C, and then NaBH₄ (17.5 mg, 0.46 mmol) was added. The reaction
mixture was kept stirring at –78 °C for 4 hours. The reaction was then quenched with saturated NaHCO₃, followed by extraction with Et₂O. The organic layer was washed by saturated brine, dried over Na₂SO₄, and concentrated under reduced pressure to give crude product. Crude ¹H-NMR showed a d.r. > 20:1. Eluting with EtOAc/Hexane (30:70) on silica gel gave allylic alcohol 2-4e (111.8 mg, 68%): Yellow solid, M.P. 59-61 °C; R_f = 0.26 (1:2 (v/v) EtOAc/Hexane); [α]_D²⁵ = –77.9 (c 0.92, MeOH); IR (thin film, cm⁻¹) 3415, 2952, 2868, 1604, 1508, 1453, 1355, 1297, 1253, 1178, 1102, 913; ¹H NMR (CDCl₃, 400 MHz) δ 8.05 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 7.6 Hz, 2H), 7.46-7.29 (m, 13H), 7.06 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 6.21 (ddd, J = 10.4, 2.4, 2.0 Hz, 1H), 6.05 (brs, 1H), 5.98 (d, J = 10.4 Hz, 1H), 5.27 (s, 2H), 5.13 (s, 2H), 5.08 (s, 2H), 3.82-3.77 (m, 1H), 3.31 (ddd, J = 8.4, 8.4, 3.2 Hz, 1H), 1.34-1.27 (m, 1H), 1.19-1.09 (m, 2H), 0.65 (d, J = 6.4 Hz, 3H), 0.51 (d, J = 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 173.7, 162.7, 160.3, 159.7, 158.7, 153.1, 138.0, 136.42, 136.40, 135.7, 133.2, 130.5, 128.7, 128.64, 128.57, 128.4, 128.1, 127.6, 127.5, 126.6, 126.5, 126.4, 123.8, 114.6, 109.9, 98.1, 94.1, 93.8, 72.0, 70.7, 70.4, 70.0, 68.0, 41.9, 29.7 (grease), 24.5, 24.0, 23.3; HRMS (ESI): Calcd. [C₄₅H₄₂O₈+Na]⁺: 733.2772, Found: 733.2778.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-propyltetrahydro-2H-pyran-2-yl oxy)-4H-chromen-4-one (2-5e):
A solution of allylic alcohol 2-4e (68.0 mg, 0.0957 mmol) in 1 mL acetone/t-BuOH (1:1) was cooled to 0 °C. To the solution was added 0.5 mL NMO/H$_2$O (w/w 1:1), and then catalytic amount of OsO$_4$ was added into the mixture with stirring. The reaction mixture was stirred at 0 °C for overnight. The reaction mixture was then quenched with saturated Na$_2$S$_2$O$_3$. After stirring for another 30 min, all the staff was passed through a small pad of celite and silica gel, washed by EtOAc/MeOH (1:1). The organic effluent was dried by Na$_2$SO$_4$, and concentrated under reduced pressure to give crude product. Eluting with Et$_2$O/MeOH (20:1) on silica gel gave triol 2-5e (63.4 mg, 89%): White solid, M.P. 84-86 °C; $R_f = 0.40$ (5:1 (v/v) EtOAc/Hexane); $[\alpha]_D^{25} = -90.1$ (c 0.93, CHCl$_3$); IR (thin film, cm$^{-1}$) 3421 (broad), 2927, 2859, 1610, 1510, 1455, 1350, 1304, 1254, 1177, 1140, 1107, 1010, 948; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.91 (d, $J = 8.8$ Hz, 2H), 7.50 (d, $J = 8.0$ Hz, 2H), 7.43-7.28 (m, 13H), 7.06 (d, $J = 9.6$ Hz, 2H), 6.55 (d, $J = 2.4$ Hz, 1H), 6.41 (d, $J = 1.6$ Hz, 1H), 5.85 (d, $J = 0.8$ Hz, 1H), 5.27 (s, 2H), 5.09 (s, 2H), 5.05 (s, 2H), 4.52 (m, 1H), 3.92 (m, 1H), 3.69 (brs, 1H), 3.45 (dd, $J = 9.6, 8.8$ Hz, 1H), 3.39 (brs, 1H), 3.27 (dd, $J = 8.8, 8.0$ Hz, 1H), 2.66 (brs, 1H), 1.42-1.18 (m, 3H), 0.64 (d, $J = 6.0$ Hz, 3H), 0.42 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 174.1, 163.2, 160.9, 159.8, 158.9, 153.8, 137.5, 136.53, 136.45, 135.7, 130.7, 129.0, 128.9, 128.7, 128.4, 128.0, 127.9, 127.8, 127.0, 123.2, 115.0, 109.8, 100.4, 98.4, 93.9, 73.0, 72.1, 71.7, 70.9, 70.7, 70.4, 70.3, 41.3, 24.8, 23.8, 22.1; HRMS (ESI): Calcd. [C$_{45}$H$_{44}$O$_{10}$+H]$^+$: 745.3007, Found: 745.3013.
5,7-dihydroxy-2-(4-hydroxyphenyl)-3-(((2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-isobutyltetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (2-1e-B):

A solution of triol 2-5e (20.1 mg, 0.027 mmol) in 1 mL THF/EtOH (1:1) was added 15 mg Pearlman’s catalyst (Pd-C, 10%). The solution was degassed using vacuum at –78 °C and refilling with H₂. This procedure was repeated three times, and then the bath was removed. The reaction was warmed up to room temperature and stirred under a H₂ atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and eluted with EtOAc/Hexane (55:45) gave kaempferol-3-α-L-rhamnoside 2-1e-B (7 mg, 58%): Pale yellow solid, M.P. 150-152 °C; R_f = 0.28 (20:1 (v/v) EtOAc/MeOH); [α]_D^{25} = −79.2 (c 0.25, MeOH); IR (thin film, cm⁻¹) 3259 (broad), 2959, 2858, 1717, 1650, 1613, 1513, 1453, 1368, 1273, 1207, 1172, 1072, 996, 713; ¹H NMR (CD₃OD, 400 MHz): δ 7.86 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.37 (d, J = 1.6 Hz, 1H), 6.19 (d, J = 1.6 Hz, 1H), 5.82 (d, J = 0.8 Hz, 1H), 4.16 (dd, J = 3.2, 1.6 Hz, 1H), 3.73 (dd, J = 9.6, 3.2 Hz, 1H), 3.34-3.31 (m, 1H), 3.24 (ddd, J = 9.6, 9.6, 1.2 Hz, 1H), 1.45-1.40 (m, 1H), 1.38-1.26 (m, 1H), 1.21-1.13 (m, 1H), 0.67 (d, J = 6.4 Hz, 3H), 0.52 (d, J = 6.4 Hz, 3H); ¹³C NMR (CD₃OD, 100 MHz) δ 179.6, 165.9, 163.2, 161.8, 158.4, 157.7, 135.4, 131.9 (2), 122.5, 116.6 (2), 105.8, 101.8, 99.8, 94.6, 74.6, 72.0 (2), 71.5, 42.3, 25.9, 24.2, 22.4; HRMS (ESI): Calcd. [C₂₄H₂₆O₁₀+H]⁺: 475.1599, Found: 475.1605.
A solution of allylic alcohol 2-4e (102.8 mg, 0.145 mmol) in 1.5 mL CH₂Cl₂ was cooled to 0 °C, then pyridine (58 µL, 0.725 mmol), Ac₂O (27 µL, 0.290 mmol) and DMAP (1.8 mg, 0.0145 mmol) was added via syringe. After stirring for 2 hours, the mixture was diluted with EtOAc and washed with 0.5 M aqueous NaHSO₄. The organic layer was separated and the aqueous layer was extracted with EtOAc. The pooled organic layer was sequentially washed with saturated aq. NaHCO₃, saturated brine, dried over Na₂SO₄. Elution with EtOAc/Hexane (15:85) on silica gel gave 4'-monoacetate 2-7e (78.6 mg, 72%): Pale yellow solid, M.P. 68-69 ºC; R_f = 0.53 (1:2 (v/v) EtOAc/Hexane); [α]_D²⁵ = −88.6 (c 1.19, CH₂Cl₂); IR (thin film, cm⁻¹) 3065, 3035, 2956, 2926, 1738, 1605, 1602, 1509, 1453, 1434, 1372, 1356, 1297, 1246, 1178, 1120, 1028, 1014, 927, 835, 736, 697; ¹H NMR (CDCl₃, 400 MHz) δ 8.06 (d, J = 9.6 Hz, 2H), 7.56 (d, J = 7.2 Hz, 2H), 7.47-7.27 (m, 13H), 7.09 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 6.28 (ddd, J = 10.4, 2.4, 2.0 Hz, 1H), 6.04 (s, 1H), 5.90 (d, J = 10.4 Hz, 1H), 5.27 (s, 2H), 5.14 (s, 2H), 5.08 (s, 2H), 5.03-4.90 (m, 1H), 3.62-3.57 (m, 1H), 2.07 (s, 3H), 1.61 (m, 1H), 1.12-1.03 (m, 2H), 0.64 (d, J = 6.0 Hz, 3H), 0.50 (d, J = 6.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 173.6, 170.4, 162.7, 160.3, 159.7, 158.7, 153.1, 138.1, 136.40, 136.37, 135.6, 130.5, 129.6, 128.7, 128.64, 128.56, 128.4, 128.1, 127.61, 127.57, 127.4,
126.6, 123.8, 114.6, 109.9, 98.1, 94.3, 93.8, 70.7, 70.4, 70.0, 69.6, 68.6, 41.8, 24.3, 23.1, 21.1. HRMS (ESI): Calcd. [C_{47}H_{44}O_9+H]^+: 753.3058, Found: 753.3060.

(2S,3R,4S,5R,6S)-6-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)-4,5-dihydroxy-2-isobutyltetrahydro-2H-pyran-3-yl acetate (2-8e):

![Chemical Structure Image]

A solution of 4'-monoacetate 2-7e (44.0 mg, 0.0584 mmol) in 0.5 mL acetone-\text{-}t\text{-}BuOH (1:1) was cooled to 0 °C. To the solution was added 0.25 mL NMO-H_2O (w/w 1:1), and then catalytic amount of OsO_4 was added into the mixture when stirring. The reaction mixture was stirred at 0 °C for 24 hours. The reaction was quenched with saturated aq. Na_2S_2O_3. Then the mixture was passed through a small pad of celite and silica gel, washed with EtOAc/MeOH (1:1), the organic solution was dried over Na_2SO_4, and concentrated under reduced pressure to give a residue. Eluting with EtOAc/Hexane (40:60) on silica gel gave diol 2-8e (34.5 mg, 75%): Pale yellow solid, M.P. 91-92 °C; R_f = 0.28 (100% EtOAc); [\alpha]_D^{25} = -91.0 (c 0.80, CHCl_3); IR (thin film, cm\(^{-1}\)) 3412 (broad), 3064, 3034, 2954, 2929, 2869, 1737, 1602, 1509, 1372, 1245, 1174, 1142, 1044, 1010, 948, 835, 735, 696; ^1H NMR (CDCl_3, 400 MHz) δ 7.93 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.46-7.28 (m, 13H), 7.09 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 5.86 (d, J = 2.0 Hz, 1H), 5.28 (s, 2H), 5.14 (s, 2H), 5.07 (s, 2H), 4.84 (dd, J = 9.2, 8.8 Hz, 1H), 4.51-4.43 (m, 1H), 4.04-3.93 (m, 2H, with one OH), 3.39 (ddd, J = 9.2, 8.8, 2.4 Hz, 1H), 3.04 (d, J = 4.4 Hz, 1H, OH), 2.04 (s, 3H), 1.32-1.28 (m, 1H),
1.04-0.96 (m, 2H), 0.64 (d, \( J = 6.0 \) Hz, 3H), 0.44 (d, \( J = 6.4 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 173.6, 171.1, 162.9, 160.6, 159.7, 158.7, 153.4, 137.2, 136.32, 136.27, 135.6, 130.5, 128.73, 128.67, 128.6, 128.4, 128.2, 127.7, 127.6, 127.4, 126.7, 123.1, 114.7, 109.7, 100.0, 98.3, 93.8, 73.7, 70.7, 70.6, 70.5, 70.2, 70.1, 69.8, 40.9, 29.7, 24.4, 23.4, 21.8, 21.1; HRMS (ESI): Calcd. \([\text{C}_{47}\text{H}_{46}\text{O}_{11}]^+\): 787.3113, Found: 787.3110. 

\((2S,3R,4S,5R,6S)-6-((5,7\text{-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yl})\text{oxy})-4,5\text{-dihydroxy-2-propyltetrahydro-2H-pyran-3-yl acetate (2-1e-D)}:\)

To a solution of diol 2-8e (25.4 mg, 0.032 mmol) in 1.0 mL THF/EtOH (1:1) was added 13 mg Pearlman’s catalyst (Pd-C, 10%). The reaction mixture was degassed using vacuum at –78 °C and refilling with H\(_2\). This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under H\(_2\) atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and elution with EtOAc/Hexane (60:40) to give product (10.0 mg, 60%): Amorphous yellow solid; \( R_f = 0.31 \) (19:1 (v/v) EtOAc/MeOH); \( [\alpha]_D^{25} = -89.6 \) (c 0.72, MeOH); IR (thin film, cm\(^{-1}\)) 3380 (broad), 2965, 2927, 2870, 1730, 1642, 1607, 1509, 1461, 1362, 1276, 1239, 1210, 1181, 1086, 1041, 970, 829, 750; \(^1\)H NMR (CD\(_3\)OD, 400 MHz) \( \delta \) 7.85 (d, \( J = 8.8 \) Hz, 2H), 6.95 (d, \( J = 8.4 \) Hz, 2H), 6.39 (d, \( J = 2.0 \) Hz, 1H), 6.21 (d, \( J = 2.0 \) Hz, 1H), 5.92 (d, \( J = 0.8 \) Hz, 1H), 4.84 (dd, \( J = 10.0, 10.0 \) Hz, 1H), 4.17 (dd, \( J = 3.2, 1.6 \) Hz, 1H), 3.89 (dd, \( J = 9.6, 3.2 \) Hz, 1H), 3.16 (ddd, \( J = 8.0, 8.0, 2.0 \) Hz, 1H),
2.00 (s, 3H), 1.37-1.27 (m, 1H), 1.20 (ddd, J = 14.0, 9.6, 4.4 Hz, 1H), 0.95 (ddd, J = 14.0, 8.8, 2.4 Hz, 1H), 0.66 (d, J = 6.8 Hz, 3H), 0.51 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (CD\(_3\)OD, 100 MHz) \(\delta\) 179.5, 172.4, 166.0, 163.2, 161.9, 158.4, 157.9, 134.9, 132.0, 122.4, 116.6, 105.8, 101.1, 99.9, 94.6, 74.0, 72.1, 71.4, 70.0, 42.3, 25.8, 23.9, 22.4, 21.0; HRMS (ESI): Calcd. \([C_{26}H_{28}O_{11}+H]^+\): 517.1704, Found: 517.1706.

\((4R,5R,E)\)-ethyl 4,5-dihydroxyhex-2-enoate (3-146):\(^5\)

\[\text{EtO} \quad \begin{array}{c} \text{O} \\ \text{OH} \\ \text{OH} \end{array} \]

Into a 1 liter round bottom flask was added 150 mL of \(t\)-BuOH, 150 mL of H\(_2\)O, K\(_3\)Fe(CN)\(_6\) (140.8 g, 0.42 mol), K\(_2\)CO\(_3\) (59 g, 0.42 mol), MeSO\(_2\)NH\(_2\) (13.5 g, 0.14 mol), (DHQD)\(_2\)PHAL (667 mg, 8.5 mmol, 0.6 mol %), and OsO\(_4\) (181 mg, 7.1 mmol, 0.5 mol %). The mixture was stirred at room temperature for about 15 minutes and then cooled to 0 °C. To this solution was added (2\(E\),4\(E\))-dienoate 3-145 (20 g, 0.14 mol) and the reaction was stirred vigorously at 0 °C overnight using mechanical stirrer. The reaction was quenched with solid sodium sulfite (700 mg) at room temperature. Ethyl acetate was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent. The combined organic layers were washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvents \textit{in vacuo}, flash chromatography on silica gel EtOAc/Hexane (60:40) afforded 1,2-cis-diol 3-146 (18.6 g, 75%): Light yellow oil, \(R_f = 0.19\) (2:3 (v/v) EtOAc/Hexane); \([\alpha]_{D}^{25} = +63\) (c 1, EtOH); IR (thin film, cm\(^{-1}\)) 3399, 2979, 2906, 1699, 1657, 1448, 1394, 1369, 1268, 1176, 1130, 1040, 981, 913, 866, 809, 710; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 6.88 (dd, \(J = 16.0, 4.8\) Hz, 1H), 6.09 (dd, \(J = 15.6, 1.6\) Hz, 1H), 4.16 (q, \(J = 7.2\) Hz, 2H), 4.03-3.99 (m,
1H), 3.71 (d, J = 4.4 Hz, 1H, OH), 3.69-3.64 (m, 1H), 3.41 (d, J = 4.4 Hz, 1H, OH), 1.26 (t, J = 7.2 Hz, 3H), 1.19 (d, J = 6.4 Hz, 3H); 13C NMR (CDCl₃, 100 MHz): δ 166.5, 146.7, 122.2, 75.5, 70.2, 60.6, 19.0, 14.1.

(E)-ethyl 3-((4R,5R)-5-methyl-2-oxo-1,3-dioxolan-4-yl)acrylate (3-147):⁶

\[ \text{EtO} \begin{array}{c} \text{O} \\ \text{O} \end{array} \text{O} \]

Into a 250 mL round-bottom flask was placed 1,2-cis-diol 3-146 (7.0 g, 40.2 mmol) in 30 mL CH₂Cl₂ and 10 mL pyridine. The solution was cooled to 0 °C and triphosgene (13.1 g, 44.2 mmol) in 40 mL CH₂Cl₂ was added slowly with an addition funnel. The reaction was stirred for 1.5 h and quenched with saturated aq. NH₄Cl. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with saturated aq. NaHCO₃, saturated brine and dried over Na₂SO₄. After removal of the solvents in vacuo, flash chromatography on silica gel EtOAc/Hexane (30:70) afforded cyclic carbonate 3-147 (7.2 g, 90%): Clear colorless oil, Rf = 0.24 (3:7 (v/v) EtOAc/Hexane); [α]D²⁵ = +20.7 (c 1.7, CH₂Cl₂); IR (thin film, cm⁻¹) 2983, 2872, 1806, 1721, 1454, 1369, 1304, 1272, 1174, 1190, 1032 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.82 (dd, J = 15.6, 5.6 Hz, 1 H), 6.17 (dd, J = 16.4, 1.6 Hz, 1H), 4.76 (ddd, J = 7.2, 6.0, 1.2 Hz, 1H), 4.48 (dq, J = 6.4, 1.2 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 1.52 (t, J = 6.8 Hz, 3H), 1.28 (d, J = 6.4 Hz, 3H); 13C NMR (CDCl₃, 100 MHz): δ 164.8, 153.4, 138.6, 125.1, 81.2, 77.8, 61.1, 18.3, 14.1.
(R,E)-ethyl 5-hydroxyhex-2-enoate (3-148):\(^7\)

\[
\begin{align*}
\text{EtO} & \quad \text{O} \\
\text{OH} \quad & \\
\end{align*}
\]

Into a 100 mL, round bottomed flask fitted with a condenser and maintained under N\(_2\) was placed the cyclic carbonate 3-147 (4.0 g, 20 mmol), Pd\(_2\)(DBA)\(_3\)·CHCl\(_3\) (103 mg, 1 mmol, 0.5 mol %), PPh\(_3\) (52 mg, 2 mmol, 1 mol %) and 20 mL of THF. Then Et\(_3\)N (8 mL, 60 mmol) and HCO\(_2\)H (2.3 mL, 60 mmol) were added and the mixture was allowed to reflux for 20 minutes. The reaction was cooled to room temperature and quenched with saturated aq. NaHCO\(_3\). The aqueous layer was extracted with ether and the organic layer was washed with saturated brine and dried with anhydrous Na\(_2\)SO\(_4\). After removal of the solvents \textit{in vacuo}, flash chromatography on silica gel EtOAc/Hexane (30:70) afforded homoallylic alcohol 3-148 (2.81 g, 89 %): Yellow oil, \(R_f = 0.32\) (2:3 (v/v) EtOAc/Hexane); \([\alpha]_D^{25} = -15\) (c 1.0, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) 3425, 2976, 2933, 2906, 2867, 1721, 1656, 1449, 1370, 1321, 1267, 1217, 1177, 1043, 982; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 6.95\) (ddd, \(J = 15.2, 8.0, 7.2\) Hz, 1H), 5.89 (ddd, \(J = 16.0, 1.6, 1.2\) Hz, 1H), 4.13 (q, \(J = 7.2\) Hz, 2H), 3.95-3.86 (m, 1H), 2.52 (brs, 1H), 2.31 (ddd, \(J = 7.2, 6.0, 1.2\) Hz, 2H), 1.28 (t, \(J = 7.2\) Hz, 3H), 1.17 (d, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta 166.4, 145.2, 123.6, 66.5, 60.2, 41.7, 23.0, 14.1\).

(2S,3R,5R)-ethyl 2,3,5-trihydroxyhexanoate (3-149):\(^7\)

\[
\begin{align*}
\text{EtO} & \quad \text{O} \\
\text{OH} & \quad \text{O} \\
\text{OH} \quad & \\
\end{align*}
\]

Into a 250 mL round bottom flask was added 20 mL of t-BuOH, 20 mL of H\(_2\)O, K\(_3\)Fe(CN)\(_6\) (17.5 g, 53.1 mmol), K\(_2\)CO\(_3\) (7.3 g, 53.1 mmol), NaHCO\(_3\) (4.5 g, 53.1 mmol),
MeSO₂NH₂ (1.7 g, 17.7 mmol), (DHQD)₂PHAL (152 mg, 1.95 mmol, 1.1 mol %), and OsO₄ (45 mg, 1.77 mmol, 1 mol %). The mixture was stirred at room temperature for about 15 minutes and then cooled to 0 °C. To this solution was added homoallylic alcohol 3-148 (2.8 g, 17.7 mmol) in 3 mL CH₂Cl₂ and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid Na₂SO₃ (200 mg) at room temperature. Then the reaction mixture was filtered through a pad of celite and eluted with EtOAc/MeOH (1:1). The combined organic layers were dried over Na₂SO₄. After removal of the solvents in vacuo, flash chromatography on silica gel EtOAc/Hexane (90:10) afforded 1,3,4-cis-triol 3-149 (2.65 g, 78 %): Viscous oil, R_f = 0.3 (100% EtOAc); [α]D²⁵ = −6.4 (c 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3459, 2971, 2931, 1738, 1507, 1448, 1374, 1301, 1261, 1214, 1140, 1079, 1028, 939; ¹H NMR (CDCl₃, 400 MHz) δ 4.28 (q, J = 7.2 Hz, 2H), 4.18 (ddd, J = 10.4, 2.8, 2.4 Hz, 1H), 4.13–4.08 (m, 1H), 4.05 (d, J = 2.4 Hz, 1H), 3.36 (brs, 3H), 1.82 (ddd, J = 14.4, 10.0, 10.0 Hz, 1H), 1.67 (ddd, J = 14.8, 2.8, 2.8 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 173.0, 73.7, 72.8, 68.0, 62.1, 41.2, 24.1, 14.1; HRMS (ESI): Calcd. for [C₈H₁₀O₅+Na]⁺: 215.0889, Found: 215.0892.

(S)-ethyl 2-hydroxy-2-((2R,4R,6R)-2-(4-methoxyphenyl)-6-methyl-1,3-dioxan-4-yl)acetate (3-150):

To a stirred solution of 1,3,4-cis-triol 3-149 (1.0 g, 5.2 mmol) in 10 mL CH₂Cl₂ at room temperature was added 1-(dimethoxymethyl)-4-methoxybenzene (1.77 ml, 10.4 mmol)
and camphorsulfonic acid (CSA) (24.2 mg, 2 mol %). The reaction was stirred for 3 h and quenched with saturated aq. NaHCO₃ and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated brine, and dried over Na₂SO₄. After removal of the solvents in vacuo, flash chromatography on silica gel EtOAc/Hexane (25:75) afforded benzylidine-protected cis-triol 3-150 (1.10 g, 68%): White crystalline solid: M.P. 110-111 °C; Mosher ester analysis of this alcohol shows > 98% e.e.; Rᵣ = 0.39 (1:2 (v/v) EtOAc/Hexane); [α]D²⁵ = −6.4 (c 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3516, 2975, 2934, 2871, 1741, 1616, 1588, 1518, 1463, 1443, 1399, 1374, 1337, 1250, 1172, 1154, 1100, 1055, 1030, 949, 922, 832, 774, 750; ¹H NMR (CDCl₃, 400 MHz) δ 7.37-7.35 (m, 2H), 6.87-6.85 (m, 2H), 5.49 (s, 1H), 4.28 (q, J = 7.2 Hz, 1H), 4.27 (q, J = 7.2 Hz, 1H), 4.21 (ddd, J = 11.6, 2.8, 2.4 Hz, 1H), 4.13 (dd, J = 8.8, 2.4 Hz, 1H), 4.03-3.95 (m, 1H), 3.79 (s, 3H), 2.94 (d, J = 8.8 Hz, 1H), 1.90 (ddd, J = 13.2, 11.6, 11.6 Hz, 1H), 1.57 (ddd, J = 13.2, 2.4, 2.4 Hz, 1H), 1.34 (d, J = 6.0 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 172.2, 159.8, 130.7, 127.3 (2), 113.5 (2), 100.3, 73.0, 72.6, 61.7, 55.29, 55.24, 33.4, 21.7, 14.2; HRMS (ESI): Calcd. for [C₁₆H₂₂O₆+Na⁺]: 333.1309, Found: 333.1309.

(R)-2-ethoxy-1-((2R,4R,6R)-2-(4-methoxyphenyl)-6-methyl-1,3-dioxan-4-yl)-2-oxoethyl 4-nitrobenzoate (3-151):

![Chemical Structure](image)

Into a round bottom flask was added PPh₃ (845.1 mg, 3.22 mmol) in 4 mL dry THF and then cooled to 0 °C. To this solution, DIAD (0.64 mL, 3.22 mmol) was added drop-wise
and stirred for 5 min. Then benzyldiene-protected cis-triol 3-150 (500.0 mg, 1.61 mmol) in 4 ml THF and p-nitrobenzoic acid (PNBA) (538.5 mg, 3.22 mmol) was added to the solution. The reaction mixture was allowed to stir for 12 h, quenched with saturated aq. NaHCO₃, extracted with EtOAc three times and dried over Na₂SO₄. After removal of the solvents in vacuo, flash chromatography on silica gel EtOAc/Hexane (20:80) afforded nitrobenzoate 3-151 (350.0 mg, 65%): Yellow solid, M.P. 70-71 °C; Rᵢ = 0.56 (1:2 (v/v) EtOAc/Hexane); IR (thin film, cm⁻¹) 2975, 2932, 2870, 1735, 1614, 1529, 1462, 1443, 1375, 1346, 1269, 1130, 1104, 1032, 873, 830, 781, 717; [α]D²⁵ = −1.8 (c 2.02, MeOH); ¹H NMR (CDCl₃, 400 MHz) δ 8.32-8.25 (m, 4H), 7.40-7.38 (m, 2H), 6.87-6.85 (m, 2H), 5.58 (s, 1H), 5.47 (d, J = 4.0 Hz, 1H), 4.44 (ddd, J = 11.6, 3.2, 2.8 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 4.06-3.98 (m, 1H), 3.78 (s, 3H), 1.93 (ddd, J = 12.8, 11.6, 11.6 Hz, 1H), 1.65 (ddd, J = 13.2, 2.4, 2.0 Hz, 1H), 1.39 (d, J = 5.6 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 167.1, 164.0, 160.0, 150.7, 134.6, 131.0, 130.4, 127.4, 123.6, 113.5, 101.0, 75.25, 75.19, 72.7, 62.0, 55.3, 55.2, 33.0, 21.6, 14.1; HRMS (ESI): Calcd. for [C₂₃H₂₅NO₉+Na]⁺: 482.1422, Found: 482.1424.

(R)-ethyl 2-hydroxy-2-((2R,4R,6R)-2-(4-methoxyphenyl)-6-methyl-1,3-dioxan-4-yl)acetate (3-152):

![chemical_structure]

To a stirred solution of nitrobenzoate 3-151 (526.0 mg, 1.14 mmol) in 5 mL MeOH at room temperature was added Et₃N (0.48 ml, 3.43 mmol). The reaction was stirred for 3 h and after removal of the solvents in vacuo, flash chromatography on silica gel
EtOAc/Hexane (20:80) afforded \((R)\)-alcohol 3-152 (277.1 mg, 78%): White crystalline solid, M.P. 64-66 °C; \(R_f = 0.26\) (1:3 (v/v) EtOAc/Hexane); \([\alpha]_D^{25} = -30.6\) (c 2.06, MeOH); IR (thin film, cm\(^{-1}\)) 3485, 2972, 2925, 2875, 1736, 1616, 1518, 1464, 1444, 1400, 1377, 1340, 1249, 1173, 1151, 1115, 1030, 830, 776; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 7.40\) (m, 2H), 6.87 (m, 2H), 5.50 (s, 1H), 4.32-4.26 (m, 2H), 4.15-4.12 (m, 1H), 3.98-3.91 (m, 1H), 3.79 (s, 3H), 3.05 (s, 1H), 1.77 (ddd, \(J = 12.4, 11.6, 11.6\) Hz, 1H), 1.49 (ddd, \(J = 13.2, 2.0, 2.0\) Hz, 1H), 1.33-1.30 (m, 6H); \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 171.6, 159.9, 130.7, 127.4, 113.5, 100.8, 77.9, 73.0, 72.7, 61.8, 55.2, 32.5, 21.6, 14.2;\) HRMS (MALDI): Calcd. \([C_{16}H_{22}O_6Na]^+\): 333.1309, Found: 333.1278.

\((R)\)-ethyl 2-(methoxymethoxy)-2-((2R,4R,6R)-2-(4-methoxyphenyl)-6-methyl-1,3-dioxan-4-yl) acetate (3-153):

To a stirred solution of \((R)\)-alcohol 3-152 (360 mg, 1.16 mmol) in 3 mL CH\(_2\)Cl\(_2\) at 0 °C was added DIPEA (0.40 ml, 2.32 mmol) and MOMCl (0.13 mL, 1.74 mmol). The reaction was stirred for 12 h and after removal of the solvents in vacuo, flash chromatography on silica gel EtOAc/Hexane (10:90) afforded \((R)\)-MOM ether 3-153 (287.8 mg, 70%): Clear viscous oil, \(R_f = 0.42\) (3:7 (v/v) EtOAc/Hexane); \([\alpha]_D^{25} = +3.2\) (c 1.4, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) 2972, 2932, 2851, 1744, 1616, 1589, 1518, 1463, 1444, 1375, 1342, 1302, 1247, 1216, 1186, 1149, 1112, 1026, 979, 920, 828, 777, 736; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 7.40-7.38\) (m, 2H), 6.87-6.85 (m, 2H), 5.50 (s, 1H), 4.76 (d, \(J = 6.8\) Hz, 1H), 4.73 (d, \(J = 6.0\) Hz, 1H), 4.28 (d, \(J = 5.2\) Hz, 1H), 4.25-4.16 (m, 3H), 3.99-
3.91 (m, 1H), 3.79 (s, 3H), 3.40 (s, 3H), 1.71 (ddd, $J = 24.0, 12.4, 11.6$ Hz, 1H), 1.65-1.62 (m, 1H), 1.32 (d, $J = 8.0$ Hz, 3H), 1.28 (t, $J = 8.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 170.4, 159.8, 130.9, 127.4 (2), 113.4 (2), 100.7, 96.5, 77.6, 76.8, 72.7, 61.2, 56.0, 55.3, 33.4, 21.7, 14.2; HRMS (MALDI): Calcd. [C$_{18}$H$_{26}$O$_7$Na$^+$$]$: 377.1571, Found: 377.1551.

5-(benzyloxy)naphthalen-1-ol (3-155):$^8$

![Chemical Structure](image)

A suspension of 1,5-dihydroxy naphthalene 3-154 (20.0 g, 124.8 mmol) and pellets NaOH (10.0 g, 249.7 mmol) in acetone 250 ml was stirred for 30 min at room temperature under Ar. Then benzyl bromide (7.5 ml, 62.4 mmol) was added. The mixture was stirred at room temperature for 4 h. After acidification with 10% HCl solution and removed of acetone under reduced pressure, the mixture was extracted with EtOAc. The organic solution was then washed by sat. NaHCO$_3$ and sat. brine. The organic solution was dried over solid Na$_2$SO$_4$ and concentrated under reduced pressure. Eluting with EtOAc/Hexane (5:95) on silica gel gave monobenzylated naphthalene 3-155 (8.1 g, 52%): Yellow needle; $R_f = 0.29$ (1:5 (v/v) EtOAc/Hexane); IR (thin film, cm$^{-1}$) 3343 (broad), 3066, 3037, 2965, 2868, 1646, 1595, 1518, 1454, 1415, 1377, 1273, 1209, 1163, 1070, 1039, 921, 776, 750, 697; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.95 (dd, $J = 8.0, 0.4$ Hz, 1H), 7.77 (dd, $J = 8.4, 0.4$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 2H), 7.45-7.29 (m, 5H), 6.93 (d, $J = 7.2$ Hz, 1H), 6.86 (d, $J = 7.2$ Hz, 1H), 5.31 (brs, 1H), 5.26 (s, 2H); $^{13}$C NMR (CDCl$_3$,}
100 MHz): δ 154.4, 151.2, 137.1, 128.6 (2), 127.9, 127.3 (2), 127.1, 125.4, 125.21, 125.18, 114.9, 113.9, 109.5, 105.9, 70.1.

1-(allyloxy)-5-(benzyloxy)naphthalene (3-156):

A suspension of monobenzylated naphthalene 3-155 (8.0 g, 31.96 mmol) and K₂CO₃ (8.84 g, 63.92 mmol) in acetone 60 ml was refluxed under Ar for 3 h. The reaction was quenched by 10% HCl solution. After acidification with 10% HCl solution and removal of acetone under reduced pressure, the mixture was extracted with EtOAc. The organic solution was then washed by sat. NaHCO₃ and sat. brine. The organic solution was dried over Na₂SO₄ and concentrated under reduced pressure. Eluting with EtOAc/Hexane (3:97) on silica gel gave allyloxy naphthalene 3-156 (9.28 g, 90%): White solid, M.P. 77-79 ºC; Rf = 0.62 (1:9 (v/v) EtOAc/Hexane); IR (thin film, cm⁻¹) 3080, 3064, 3034, 2984, 2914, 2866, 1649, 1592, 1509, 1456, 1410, 1377, 1267, 1209, 1172, 1076, 1038, 994, 918, 896, 775, 750, 695; ¹H NMR (CDCl₃, 400 MHz) δ 7.97-7.92 (m, 2H), 7.56-7.54 (m, 2H), 7.45-7.36 (m, 5H), 6.94 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.24-6.15 (m, 1H), 5.57 (dd, J = 17.6, 0.8 Hz, 1H), 5.38 (dd, J = 10.4, 0.8 Hz, 1H), 5.26 (s, 2H), 4.73 (dd, J = 4.8, 0.8 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 154.3, 154.1, 137.2, 133.3, 128.5 (2), 127.9 (2), 127.3 (2), 126.8, 125.13, 125.10, 117.3, 114.6 (2), 105.92, 105.85, 70.1, 68.9; HRMS (ESI): Calcd. [C₂₀H₁₈O₂+H]⁺: 291.1380, Found: 291.1394.
2-allyl-5-(benzyloxy)naphthalen-1-ol (3-157):

A solution of allyloxy naphthalene 3-156 (8.0 g, 27.6 mmol) in 60 ml DMF was refluxed at 170 ºC for 12 h. The reaction was quenched by 10% HCl solution. The mixture was extracted with EtOAc. The organic solution was then washed by sat. NaHCO₃ and sat. brine, dried over solid Na₂SO₄ and concentrated under reduced pressure. Eluting with EtOAc/Hexane (5:95) on silica gel gave allyl naphthalenol 3-157 (6.1 g, 76%): White needle, M.P. 107-108 ºC; \( R_f = 0.54 \) (1:5 (v/v) EtOAc/Hexane), IR (thin film, cm⁻¹) 3334 (broad), 3068, 3034, 2975, 2914, 2864, 1637, 1600, 1592, 1509, 1455, 1426, 1374, 1287, 1261, 1210, 1172, 1076, 1042, 993, 915, 897, 850, 821, 796, 736, 695; \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 7.91 (d, \( J = 8.8 \) Hz, 1H), 7.76 (d, \( J = 8.8 \) Hz, 1H), 7.54 (d, \( J = 7.6 \) Hz, 1H), 7.45-7.34 (m, 5H), 7.22 (d, \( J = 8.8 \) Hz, 1H), 6.88 (d, \( J = 8.4 \) Hz, 1H), 6.14-6.04 (m, 1H), 5.52 (s, 1H), 5.28-5.27 (m, 1H), 5.25 (s, 2H), 5.24-5.23 (m, 1H), 3.59 (dd, \( J = 6.0, 1.6 \) Hz, 2H); \(^1^3\)C NMR (CDCl₃, 100 MHz): 6154.4, 149.4, 137.2, 136.1, 128.5 (2), 127.9, 127.7, 127.3 (2), 126.1, 125.9, 125.3, 118.6, 116.9, 114.7, 113.8, 105.2, 70.1, 35.7. HRMS (ESI): Calcd. [C₂₀H₁₈O₂⁺H]⁺: 291.1380, Found: 291.1391.

2-allyl-5-(benzyloxy)naphthalene-1,4-dione (3-158):
To a solution of allyl naphthalenol 3-157 (700 mg, 2.4 mmol) in 10 ml MeCN was added the aqueous solution of CAN (2907 mg, 5.3 mmol) in 5 ml H₂O. After stirring for 5 min, the solution was quenched with sat. NaHCO₃, then concentrated under reduced pressure, extracted with EtOAc, washed with sat. brine, dried over Na₂SO₄. Eluting with EtOAc/Hexane (3:97) on silica gel gave allyl quinone 3-158 (542.9 mg, 74 %): Yellow solid, M.P. 91-92 ºC; Rᵢ = 0.43 (1:4 (v/v) EtOAc/Hexane); IR (thin film, cm⁻¹) 3067, 3033, 2983, 2911, 1656, 1629, 1585, 1499, 1471, 1452, 1382, 1334, 1290, 1256, 1240, 1187, 1168, 1082, 1052, 983, 923, 877, 829, 771, 737, 696; ¹H NMR (CDCl₃, 400 MHz): δ 7.76 (dd, J = 8.0, 0.8 Hz, 1H), 7.61 (dd, J = 8.4, 8.0 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.43-7.30 (m, 5H), 6.93 (dd, J = 1.6, 1.2 Hz, 1H), 5.93-5.83 (m, 1H), 5.30 (s, 2H), 5.23-5.21 (m, 1H), 5.20-5.19 (dd, J = 6.0, 1.8 Hz, 1H), 3.30 (dd, J = 6.8, 1.2 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 185.1, 184.3, 158.2, 147.1, 137.4, 136.1, 134.53, 134.43, 133.1, 128.7 (2), 127.9, 126.6 (2), 120.4, 119.7, 119.5, 118.7, 70.8, 33.0. HRMS (ESI): Calcd. [C₂₀H₁₆O₃+H]⁺: 305.1172, Found: 305.1174.

2-allyl-5-(benzyloxy)-1,4-dimethoxynaphthalene (3-159):

A solution of Na₂S₂O₄ (54.8 g, 314.5 mmol) in degassed H₂O (150 mL) was added to a suspension of allyl quinone 3-158 (9.6 g, 31.5 mmol) and n-Bu₄NBr (2.6 g, 7.9 mmol) in degassed THF (75 mL). After stirring for 30 min at room temperature, degassed 50% aqueous KOH (90 mL) was added to the mixture, which was stirred for 30 min. Then to
the solution was added Me₂SO₄ (8.95 mL, 94.34 mmol) and stirred for 2 h. The reaction mixture was diluted by H₂O and extracted with EtOAc. The combined organic extracts were washed with sat. NaHCO₃, sat. brine, dried over Na₂SO₄, and concentrated under reduced pressure. Eluting with EtOAc/Hexane (1:99) on silica gel gave allyl dimethoxynaphthalene 3-159. Further elution with EtOAc/Hexane (3:97) gave monomethylated product, to which was added 50% aqueous KOH and Me₂SO₄ again to transform monomethylated product to dimethylated product allyl dimethoxynaphthalene 3-159 with combined yield (10.65 g, 92%): White solid, M.P. 68-69 ºC; Rf = 0.60 (1:9 (v/v) EtOAc/Hexane); IR (thin film, cm⁻¹) 3066, 3031, 2989, 2934, 2905, 2840, 1619, 1598, 1581, 1508, 1446, 1375, 1346, 1264, 1197, 1129, 1079, 1062, 1030, 1007, 913, 868, 835, 810, 753, 736, 696; ¹H NMR (CDCl₃, 400 MHz) δ 7.72 (d, J = 8.4, 1.2 Hz, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.45-7.32 (m, 4H), 6.94 (d, J = 7.2 Hz, 1H), 6.68 (s, 1H), 6.12-6.02 (m, 1H), 5.22 (s, 2H), 5.16 (dd, J = 8.8, 1.6 Hz, 1H), 5.13 (dd, J = 1.6, 1.6 Hz, 1H), 3.93 (s, 3H), 2.87 (s, 3H), 3.59 (ddd, J = 6.4, 1.6, 1.2 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 156.3, 153.3, 146.8, 137.6, 137.0, 131.5, 128.31 (2), 128.25, 127.5, 126.9 (2), 126.5, 117.9, 116.0, 115.2, 108.4, 108.1, 71.4, 61.9, 56.6, 34.0. HRMS (EI): Calcd. [C₂₂H₂₂O₃]: 334.1569, Found: 334.1567.

(R)-3-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)propane-1,2-diol (3-160):

Into a 250 mL round bottom flask was added 25 mL of t-BuOH, 25 mL of water, K₃Fe(CN)₆ (12.2 g, 36.9 mol), K₂CO₃ (5.1 g, 36.9 mol), (DHQD)₂PHAL (958 mg, 1.23
mmol, 10 mol %), and OsO₄ (156 mg, 0.62 mmol, 5 mol %). The mixture was stirred at room temperature for 30 minutes. To this solution was added allyl dimethoxynaphthalene 3-159 (4.3 g, 12.3 mol) and the reaction was stirred vigorously for two nights. The reaction was quenched with solid Na₂SO₃ (100 mg) at room temperature. The reaction mixture was diluted by water and extracted with EtOAc. The combined organic extracts were washed with sat. NaHCO₃, sat. brine, dried over Na₂SO₄, and concentrated under reduced pressure. Eluting with EtOAc/Hexane (2:3) on silica gel gave (R)-diol 3-160 (2.45 g, 54%, brsm 91%): White solid, M.P. 97-98 °C; Rₛ = 0.30 (100% EtOAc); [α]D²⁵ = −0.92 (c 1.93, CH₂Cl₂); IR (thin film, cm⁻¹) 3395 (broad), 3066, 3030, 2934, 2843, 1620, 1599, 1581, 1508, 1453, 1376, 1266, 1199, 1128, 1080, 1064, 1029, 1005, 907, 872, 809, 753, 696; ¹H NMR (CDCl₃, 400 MHz): δ 7.65 (dd, J = 8.4, 0.8 Hz, 1 H), 7.58 (d, J = 7.2 Hz, 2 H), 7.44-7.31 (m, 4H), 6.94 (d, J = 8.0 Hz, 1H), 6.66 (s, 1H), 5.21 (s, 2H), 4.05-3.97 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.68-3.49 (m, 2H), 3.00 (ddd, J = 20.4, 13.6, 6.8 Hz, 2H), 2.74-2.71 (m, 1H, OH), 2.48-2.43 (m, 1H, OH); ¹³C NMR (CDCl₃, 100 MHz): δ 156.4, 153.7, 147.2, 137.4, 131.1, 128.3 (2), 127.9, 126.9 (2), 126.8, 126.5, 118.1, 114.9, 108.5, 108.3, 72.6, 71.3, 65.7, 61.7, 56.5, 34.3. HRMS (EI): Calcd. [C₂₂H₂₄O₅]: 368.1624, Found: 368.1631.

(R)-3-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)-2-hydroxypropyl 4-methylbenzenesulfonate (3-161):
To a solution of (R)-dol 3-160 (514 mg, 1.4 mmol) in dry CH$_2$Cl$_2$ (7 mL) was added Bu$_2$SnO (0.14 mg), p-TsCl (399 mg, 2.1 mmol), Et$_3$N (0.29 mL, 2.1 mmol) and reaction was stirred at 0 ºC for 1 h. After completion of reaction the mixture was quenched with water. The reaction mixture was extracted with EtOAc. The combined organic extracts were washed with sat. brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Eluting with EtOAc/Hexane (18:92) on silica gel gave (R)-tosylate 3-161 (583.7 mg, 80 %): White sticky solid, M.P. 38-40 ºC; $R_f = 0.28$ (1:2 (v/v) EtOAc/Hexane); $\left[\alpha\right]_D^{25} = -0.42$ (c 4.03, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3481(broad), 3066, 3032, 2989, 2936, 2844, 1620, 1598, 1581, 1509, 1497, 1452, 1374, 1357, 1264, 1188, 1173, 1128, 1079, 1062, 971, 912, 873, 809, 754, 734, 696, 665; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.77 (d, $J = 8.8$ Hz, 1 H), 7.63-7.59 (m, 4 H), 7.43-7.33 (m, 4 H), 7.31-7.29 (m, 2H), 6.94 (d, $J = 7.6$ Hz, 1H), 6.64 (s, 1H), 5.21 (s, 2H), 4.19-4.13 (m, 1H), 4.00-3.98 (m, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 3.08 (s, 1H, OH), 3.00-2.99 (m, 2H), 2.42 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 156.4, 153.8, 147.3, 145.0, 137.4, 132.5, 131.2, 129.9 (2), 128.4 (2), 127.9 (2), 127.5 (2), 126.9 (2), 125.3, 118.3, 114.9, 108.6, 108.2, 72.6, 71.4, 69.9, 61.5, 56.5, 34.4, 21.6. HRMS (MALDI-TOF): Calcd. [C$_{29}$H$_{30}$SO$_7$+H]$^+$: 523.1785, Found: 523.1761.

(R)-2-((5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)methyl)oxirane (3-162):

To a solution of (R)-tosylate 3-161 (510 mg, 0.98 mmol) in dry THF (5 mL) was added 60% NaH (195 mg, 4.9 mmol) and reaction was stirred at room temperature for 30 min. After completion of reaction the mixture was quenched with water. The reaction mixture
was extracted with EtOAc. The combined organic extracts were washed with sat. brine, dried over Na₂SO₄ and concentrated under reduced pressure. Eluting with EtOAc/Hexane (15:85) on silica gel gave (R)-epoxide 3-162 (307.7 mg, 90 %): Light yellow solid, M.P. 79-80 °C; Rᵣ = 0.29 (1:4 (v/v) EtOAc/Hexane); [α]D²⁵ = 0.74 (c 1.00, CH₂Cl₂); IR (thin film, cm⁻¹) 3058, 3034, 2988, 2934, 2843, 1620, 1599, 1582, 1509, 1453, 1383, 1347, 1266, 1198, 1129, 1080, 1064, 1030, 1007, 980, 932, 912, 871, 834, 810, 753, 697, 660; ¹H NMR (CDCl₃, 400 MHz): δ 7.73 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.46-7.33 (m, 4H), 6.95 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 5.22 (s, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.31-3.25 (m, 1 H), 3.12 (dd, J = 14.0, 4.4 Hz, 1H), 3.05 (dd, J = 14.0, 6.0 Hz, 1H), 2.84 (dd, J = 4.4, 4.4 Hz, 1H), 2.66 (dd, J = 4.4, 2.4 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 156.3, 153.4, 147.2, 137.4, 131.3, 128.2 (2), 127.4, 126.8 (2), 126.6, 125.9, 118.1, 115.0, 108.4, 108.0, 71.2, 61.8, 56.5, 52.0, 46.8, 32.7. HRMS (ESI): Calcd. [C₂₂H₂₂O₄+H]⁺: 351.1591, Found: 351.1602.

(R)-4-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)-3-hydroxybutanenitrile (3-163):

To a solution of (R)-tosylate 3-161 (1.52 g, 2.9 mmol) in DMSO (15 mL) were added KCN (947 mg, 14.5 mmol), KI (48 mg, 0.29 mmol), 4 Å MS (5 g) and reaction was stirred at 60 °C for 4 h. After completion of reaction the mixture was quenched with H₂O and extracted with EtOAc. The combined organic layers were washed with sat. NaHCO₃, sat. brine, dried over Na₂SO₄ and concentrated under reduced pressure. Eluting with EtOAc/Hexane (25:75) on silica gel gave (R)-nitrile 3-163 (1.02 g, 93 %): White solid,
69-70 °C; $R_f = 0.29$ (1:2 (v/v) EtOAc/Hexane); $[\alpha]_D^{25} = 1.29$ (c 2.31, MeOH); IR (thin film, cm$^{-1}$) 3442 (broad), 3067, 3030, 2991, 2934, 2844, 2252, 1620, 1599, 1582, 1509, 1454, 1384, 1266, 1200, 1128, 1080, 1064, 1004, 870, 810, 754, 697; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.65 (d, $J = 6.8$ Hz, 1H), 7.59 (d, $J = 6.0$ Hz, 2H), 7.46-7.32 (m, 4H), 6.96 (d, $J = 6.4$ Hz, 1H), 6.65 (s, 1H), 5.21 (s, 2H), 4.32-4.27 (m, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.15-3.08 (m, 2H), 2.59-2.49 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.5, 154.1, 147.3, 137.3, 131.2, 128.4 (2), 127.6, 127.2, 126.9 (2), 124.9, 118.4, 117.7, 114.9, 108.7, 108.1, 71.3, 68.5, 61.6, 56.6, 37.8, 25.3; HRMS (ESI): Calcd. [C$_{23}$H$_{23}$NO$_4$+H]$^+$: 378.1700, Found: 378.1707.

2-((1S,3R)-9-(benzyloxy)-5,10-dimethoxy-1-methyl-3,4-dihydro-1H-benzo[g]isochromen-3-yl)acetonitrile (3-164):

![Chemical Structure](image)

To a solution of (R)-nitrile 3-163 (805.0 mg, 2.1 mmol) in dry Et$_2$O (5 mL) were added 4 M HCl in dioxane (10 ml) and the reaction was stirred at room temperature for 24 h. After completion of reaction the mixture was slowly quenched with sat. NaHCO$_3$ and extracted with EtOAc. The combined organic layers were washed with sat. brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Eluting with EtOAc/Hexane (10:90) on silica gel gave (1S,3R)-isochromen dimethoxy nitrile 3-164 (598.8 mg, 70 %): White solid, M.P. 90-92 °C; $R_f = 0.46$ (1:2 (v/v) EtOAc/Hexane); $[\alpha]_D^{25} = 0.24$ (c 1.82, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2979, 2933, 2903, 2870, 2844, 2253, 1618, 1595, 1570, 1500, 1443, 1373, 1336, 1265, 1217, 1183, 1139, 1111, 1079, 1057, 1008, 971, 854, 813,
766, 749, 699; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.71 (d, \(J = 8.8\) Hz, 1H), 7.56 (d, \(J = 7.6\) Hz, 2H), 7.44-7.34 (m, 4H), 6.94 (d, \(J = 7.6\) Hz, 1H), 5.32 (dd, \(J = 12.4, 6.6\) Hz, 1H), 5.28 (d, \(J = 11.6\) Hz, 1H), 5.18 (d, \(J = 11.6\) Hz, 1H), 3.89 (s, 3H), 3.88-3.84 (m, 1H), 3.67 (s, 3H), 3.23 (d, \(J = 15.6\) Hz, 1H), 2.76 (d, \(J = 6.0\) Hz, 2H), 2.72 (d, \(J = 11.6\) Hz, 1H), 1.67 (d, \(J = 6.0\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 155.2, 149.3, 148.7, 137.0, 130.0, 129.1, 128.5 (2), 127.8, 127.4 (2), 126.1, 123.7, 120.0, 117.3, 115.0, 108.1, 71.6, 71.4, 68.9, 61.9, 61.4, 29.3, 24.7, 23.2; HRMS (MALDI-TOF): Calcd. [C\(_{25}\)H\(_{25}\)NO\(_4\)]\(^+\): 404.1856, Found: 404.1858.

2-((1S,3R)-9-(benzylxy)-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1\(H\)-benzo[g]isochroman-3-yl)acetonitrile (3-165):

To a solution of (1S,3R)-isochromen dimethoxy nitrile 3-164 (104.3 mg, 0.26 mmol) in CH\(_3\)CN (1 mL) were added CAN (311.8 mg, 0.57 mmol) in H\(_2\)O (1 mL), and reaction was stirred at room temperature for 5 min. After completion of reaction the mixture was slowly quenched with sat. NaHCO\(_3\) and extracted with EtOAc. The combined organic layers were washed with sat. brine, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Eluting with EtOAc/Hexane (15:85) on silica gel gave (1S,3R)-isochromen quinone nitrile 3-165 (63.8 mg, 66 %): Yellow solid, M.P. 158-159 °C; \(R_f = 0.29\) (1:2 (v/v) EtOAc/Hexane); [\(\alpha\)]\(_D\)\(^{25}\) = –20.3 (c 1.33, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) 2956, 2923, 2871, 2854, 2250, 1662, 1639, 1615, 1457, 1377, 1276, 1247, 1171, 1109, 1082, 1058, 1011, 972, 837, 750, 707; \(^1\)H NMR (400 MHz, acetone-d\(_6\)): \(\delta\) 7.77-7.73 (m, 1H), 7.68-
7.66 (m, 3H), 7.60-7.58 (m, 1H), 7.45-7.42 (m, 2H), 7.36-7.33 (m, 1H), 5.38 (d, $J = 12.8$ Hz, 1H), 5.32 (d, $J = 12.4$ Hz, 1H), 4.95-4.88 (m, 1H), 3.89 (d, $J = 4.4$ Hz, 1H), 2.98-2.84 (ddd, $J = 12.8$ Hz, 3H), 2.37-2.28 (m, 1H), 1.51 (d, $J = 6.4$ Hz, 1H); $^{13}$C NMR (100 MHz, acetone-d$_6$): 184.2, 183.6, 159.3, 148.5, 139.4, 137.9, 135.7, 134.9, 129.4 (2), 128.6, 127.8 (2), 121.6, 120.9, 119.7, 118.4, 71.44, 71.38, 69.3, 28.0, 24.2, 21.0. HRMS (MALDI-TOF): Calcd. [C$_{23}$H$_{19}$NO$_4$+H]$^+$: 374.1387, Found: 374.1385.

To a solution of (1S,3R)-isochromen quinone nitrile 3-165 (146.7 mg, 0.39 mmol) in 4mL THF/EtOH (1:1) was added 75.0 mg Pearlman’s catalyst (Pd-C, 10%). The solution was degassed using vacuum at −78 ºC and refilling with H$_2$. This procedure was repeated three times, and then the bath was removed. The reaction was warmed up to room temperature and stirred under a H$_2$ atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and elution with EtOAc/Hexane (10:90) gave (1S,3R)-hydroxyisochromen nitrile 3-166 (72.9 mg, 80%): Orange solid, M.P. 201-202 ºC; $R_f$ = 0.51 (1:2 (v/v) EtOAc/Hexane); [α]$^D_{25}$ = +1.26 (c 1.03, CHCl$_3$); IR (thin film, cm$^{-1}$) 2957, 2922, 2853, 2250, 1662, 1639, 1614, 1510, 1457, 1378, 1364, 1317, 1276, 1249, 1171, 1109, 1057, 1011, 971, 837, 796, 764, 750, 708; $^1$H NMR (400 MHz, CDCl$_3$): δ 11.93 (s, 1H), 7.62-7.58 (m, 2H), 7.25 (m, 1H), 4.98-4.85 (m, 1H), 3.84-3.73 (m, 1H), 2.95-2.90 (m, 1H), 2.73-2.72 (m, 2H), 2.47-2.36 (m, 1H), 1.59 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR (100

2-((1S,3R)-9-hydroxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1H-benzo[g]isochromen-3-yl)acetic acid ((-)3-18):

![Chemical Structure](image)

To a solution of (1S,3R)-hydroxy-isochromen nitrile 3-166 (10.5 mg, 0.037 mmol) in 1 mL 9 N H₂SO₄ was heated to 90 °C and stirred for 5 h. Eluting with EtOAc/Hexane (30:70) gave (−)-nanaomycin 3-18 (5.6 mg, 50%). Analytical amount of (−)-nanaomycin 3-18 was obtained by recrystallization; Orange solid, M.P. 177-178 ºC; Rᵣ = 0.28 (1:1 (v/v) EtOAc/Hexane); [α]𝐃²⁵ = −18.6 (c 0.057, CH₂Cl₂); IR (thin film, cm⁻¹) 2923, 2850, 1703, 1641, 1620, 1577, 1460, 1424, 1369, 1339, 1275, 1246, 1225, 1168, 1107, 1072, 1056, 1022, 1006, 906, 856, 833, 790, 731, 702; ¹H NMR (400 MHz, CDCl₃): δ 12.0 (s, 1H), 7.65-7.59 (m, 2H), 7.27-7.25 (m, 1H), 5.05 (q, J = 6.8 Hz, 1H), 4.37-4.29 (m, 1H), 2.86 (d, J = 19.2 Hz, 1H), 2.72 (d, J = 6.0 Hz, 2H), 2.37 (dd, J = 19.2, 10.4 Hz, 1H), 1.59 (d, J = 6.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 188.6, 183.3, 173.6, 161.9, 146.5, 142.2, 136.6, 131.9, 124.9, 119.5, 77.5, 67.6, 63.5, 40.2, 28.0, 19.7. HRMS (MALDI-TOF): Calcd. [C₁₆H₁₄O₆+Na]⁺: 325.0683, Found: 325.0653.
(R)-4-((5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)methyl)oxetan-2-one (3-167):

To a solution of (R)-epoxide 3-162 (197.9 mg, 0.565 mmol) was added Coates catalyst [CITPPAl][Co(CO)4]9 (7.4 mg, 0.0068 mmol, 1.2 mol %) and THF (1.5 mL). Eluting with EtOAc/Hexane (40:60) on silica gel gave (R)-β-lactone 3-167 (208.6 mg, 97.6%): Pale white solid. M. P. 103-105 °C; Rf = 0.24 (1:3 (v/v) EtOAc/Hexane); [α]D²⁵ = –0.24 (c 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3068, 2932, 2846, 1824, 1599, 1582, 1510, 1453, 1377, 1364, 1313, 1267, 1201, 1130, 1107, 1079, 1062, 1029, 988, 956, 873, 811, 755, 738; ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.45-7.31 (m, 4H), 6.96 (d, J = 7.6 Hz, 1H), 6.67 (s, 1H), 5.21 (s, 2H), 4.88-4.82 (m, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.48 (dd, J = 16.8, 6.0 Hz, 1H), 3.32 (ddd, J = 22.4, 14.0, 6.0 Hz, 1H), 3.25 (dd, J = 14.0, 6.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.4, 156.7, 154.0, 147.8, 137.6, 131.5, 128.6 (2), 127.8, 127.2, 127.1 (2), 123.8, 118.7, 115.3, 109.0, 107.9, 71.6, 70.9, 62.1, 56.8, 42.9, 35.2. HRMS (MALDI-TOF): Calcd. [C₂₃H₂₂O₅+Na]⁺: 401.1359, Found: 401.1382.
References:

1 These known compounds were characterized based on the comparison with authentic samples that our group prepared before: (a) Guo, H.; O’Doherty, G. A. *Org. Lett*. 2005, 7, 3921. (b) Li, M.; Scott, J. G.; O’Doherty, G. A. *Tetrahedron Lett.* 2004, 45, 1005.


4 Dr. Bulan Wu’s dissertation, “De Novo Asymmetric Synthesis of SL0101 Analogues, Methymycin Analogues and Cleistriosides/Cleistetriosides” at West Virginia University, Morgantown, WV, 26506.

5 This known compound was characterized based on the comparison with authentic sample: (a) D. Gao and G. A. O’Doherty, *J. Org. Chem.*, 2005, 70, 9932.


Appendix B – $^1$H and $^{13}$C NMR spectrum

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<td>251</td>
</tr>
<tr>
<td>3-159</td>
<td>253</td>
</tr>
<tr>
<td>3-160</td>
<td>255</td>
</tr>
<tr>
<td>3-161</td>
<td>257</td>
</tr>
<tr>
<td>3-162</td>
<td>259</td>
</tr>
<tr>
<td>3-163</td>
<td>261</td>
</tr>
<tr>
<td>3-164</td>
<td>263</td>
</tr>
<tr>
<td>3-165</td>
<td>265</td>
</tr>
<tr>
<td>3-166</td>
<td>267</td>
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<tr>
<td>(--)3-18</td>
<td>269</td>
</tr>
<tr>
<td>3-167</td>
<td>271</td>
</tr>
</tbody>
</table>
$^1$H NMR (CDCl$_3$, 270 MHz)

1-1b
$^{13}$C NMR (CDCl$_3$, 67.5 MHz)

1-1b
$^1$H NMR (CDCl$_3$, 600 MHz)

1-5b
$^{13}$C NMR (CDCl$_3$, 150 MHz)

1-5b
$^1$H NMR (CDCl$_3$, 400 MHz)

$\text{a/b-L-1-6b}$
$^{13}$C NMR (CDCl$_3$, 100 MHz)

$a/b$-L-1-6b
$^1$H NMR (CDCl$_3$, 600 MHz)
a-1-1-7b
$^{13}$C NMR (CDCl$_3$, 150 MHz)
a-1-1-7b
$\text{H NMR (CDCl}_3, 600 \text{ MHz)}$

b-L-1-7b
$^{13}$C NMR (CDCl$_3$, 150 MHz)

b-1-7b
$^1$H NMR (CDCl$_3$, 600 MHz)

I-1d
$^{13}$C NMR (CDCl$_3$, 150 MHz)

1-1d
$^1$H NMR (CDCl$_3$, 600 MHz)

1-5d
$^{13}$C NMR (CDCl$_3$, 150 MHz)
1-5d
$^1$H NMR (CDCl$_3$, 270 MHz)

[a/b-L-1-6d]
$^{13}$C NMR (CDCl$_3$, 67.5 MHz)

$\textbf{a/b-L-1-6d}$
$^1$H NMR (CDCl$_3$, 600 MHz)

a-L-1-7d
$^{13}$C NMR (CDCl$_3$, 150 MHz)

a-L-1-7d
$^1$H NMR (CDCl$_3$, 600 MHz)

b-L-1-7d
\[ ^{13}\text{C NMR (CDCl}_3, 150\ \text{MHz)} \]

b-L-1-7d
$^1$H NMR (CDCl$_3$, 600 MHz)

1-1e
$^{13}$C NMR (CDCl$_3$, 150 MHz)
$\text{H NMR (CDCl}_3, 600 \text{ MHz)}$
$^{13}$C NMR (CDCl$_3$, 150 MHz)

1-5e
$^1$H NMR (CDCl$_3$, 400 MHz)

a/b-L-1-6e
$^{13}$C NMR (CDCl$_3$, 100 MHz)

\[ a/b - L-1-6e \]
\(^1\)H NMR (CDCl\(_3\), 600 MHz)

a-L-1-7e
$^{13}$C NMR (CDCl$_3$, 150 MHz)

\textit{a-L-1-7e}
$^1$H NMR (CDCl$_3$, 600 MHz)
b-L-1-7e
$\text{C NMR (CDCl}_3, 150 \text{ MHz)}$

b-L-1-7e
$^1$H NMR (CDCl$_3$, 600 MHz)

2-3a
$^1^3$C NMR (CDCl$_3$, 150 MHz)

2-3a
$^1$H NMR (CDCl$_3$, 270 MHz)

2-4a

X: parts per Million: 1H
$^{13}$C NMR (CDCl$_3$, 67.5 MHz)

2-4a
$^1$H NMR (CDCl$_3$, 600 MHz)

2-7a
$^{13}$C NMR (CDCl$_3$, 150 MHz)

2-7a
$^1$H NMR (CDCl$_3$, 600 MHz)

2-8a
$^{13}$C NMR (CDCl$_3$, 150 MHz)

2-8a
$^1$H NMR (CDCl$_3$, 600 MHz)

2-10a
$^{13}$C NMR (CDCl$_3$, 150 MHz)

2-10a
$^{1}H$ NMR (acetone-$d_6$, 600 MHz)

2-la-A
$^{13}C$ NMR (acetone-\textit{d}_6, 150 MHz)

2-1a-A
$^{1}H$ NMR (600MHz, CDCl$_3$) 
(ent)-2-3a
$^{13}$C NMR (150 MHz, CDCl$_3$)
(ent)-2-3a
$^{1}H$ NMR (600 MHz, CDCl$_3$)
(ent)-2-7a
^1^H NMR (150 MHz, CDCl$_3$)
(ent)-2-7a
$^1$H NMR (600MHz, CDCl$_3$)

(1nt) -2-8a
$^{13}$C NMR (150 MHz, CDCl$_3$) (ent)-2-8a
$^1$H NMR (600MHz, CDCl$_3$)

(ent)-2-10a
$^{13}$C NMR (150 MHz, CDCl$_3$) (ent)-2-10a
\(^{1}H\) NMR (600MHz, CD\(_3\)OD)
(ent)-2-1a-A
$^{13}$C NMR (150 MHz, CD$_3$OD)
(ent)-2-1a-A
$^1$H NMR (CDCl$_3$, 400 MHz)
$^{13}$C NMR (CDCl$_3$, 100 MHz)

2-3b
$^1$H NMR (CDCl$_3$, 400 MHz)

2-4b
$^{13}$C NMR (benzene, 150 MHz)

2-4b
$^1$H NMR (CD$_3$OD, 600 MHz)

2-5b
$^{13}$C NMR (CD$_3$OD, 150 MHz)

2-5b
$^1$H NMR (CD$_3$OD, 400 MHz)

2-1b-8
$\text{C NMR (CD}_3\text{OD, 100 MHz)}$

$2-1b-8$
$^1$H NMR (CDCl$_3$, 400 MHz)
$^{13}$C NMR (CDCl$_3$, 100 MHz)

2-3e
\(^1\)H NMR (CDCl\(_3\), 400 MHz) 

2-4e
$^{13}$C NMR (CDCl$_3$, 100 MHz)

2-4e
$^1$H NMR (CDCl$_3$, 400 MHz)

2–5e
$^{13}$C NMR (CDCl$_3$, 100 MHz)

2-5e
$^1$H NMR (CD$_3$OD, 400 MHz)
$^{13}$C NMR (CD$_3$OD, 100 MHz)

2-1e-B
$^1$H NMR (CDCl$_3$, 400 MHz)
$^{13}$C NMR (CDCl$_3$, 100 MHz)

2–7e
$^1$H NMR (CDCl$_3$, 400 MHz)

2–8e
$^{13}$C NMR (CDCl$_3$, 100 MHz)
$^1$H NMR (CD$_3$OD, 400 MHz)

2-1e-D
$^{13}$C NMR ($\text{CD}_3\text{OD}, 100 \text{ MHz}$)

2-1e-D
$^1$H NMR (CDCl$_3$, 400 MHz)

3–146
$\text{EtO}$

\begin{align*}
\text{C NMR (CDCl}_3, 100 \text{ MHz)} \\
3-146
\end{align*}
$^1$H NMR (CDCl$_3$, 400 MHz)
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3-147
$^1$H NMR (CDCl$_3$, 400 MHz)
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3–148
$^1$H NMR (CDCl$_3$, 400 MHz)

3-149
$^{13}$C NMR (CDCl$_3$, 100 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)
3–150
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3-150
$^1$H NMR (CDCl$_3$, 400 MHz)

3-151
$^{13}$C NMR (CDCl$_3$, 100 MHz) 3-151
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3-152
$^1$H NMR (CDCl$_3$, 400 MHz)

3-153
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3–153
$^1$H NMR (CDCl$_3$, 400 MHz)
$^{13}$C NMR (CDCl$_3$, 100 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$\text{OBn}$

$\text{O}$

$3-156$
^1H NMR (CDCl$_3$, 400 MHz)
$\text{f}$ 1-157
$^{13}$C NMR (CDCl$_3$, 100 MHz)
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3-158
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3–158
$^{1}H$ NMR (CDCl$_3$, 400 MHz)

3–159
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3-159
$^1$H NMR (CDCl$_3$, 400 MHz)

3-160
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3–160
$^1$H NMR (CDCl$_3$, 400 MHz)

3-161
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3-161
$^1$H NMR (CDCl$_3$, 400 MHz)

3–162
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3-162
$^1$H NMR (CDCl$_3$, 400 MHz)

3-163

$^1$H NMR (CDCl$_3$, 400 MHz)

3-163
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3–163
$^1$H NMR (CDCl$_3$, 400 MHz)

3-164
$^\text{13}C$ NMR (CDCl$_3$, 100 MHz)

3–164
$^1\text{H NMR (acetone-d}_6^6$, 400 MHz)

$3-165$
$^{13}$C NMR (acetone-d$_6$, 100 MHz)

3-165
$^1$H NMR (CDCl$_3$, 400 MHz)
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3-166
$^1$H NMR (CDCl$_3$, 400 MHz)
3-18 (-)-nanaomycin
$^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz)}$

3-18 (-)-nanaomycin
$^1$H NMR (CDCl$_3$, 400 MHz)

3-167
$^{13}$C NMR (CDCl$_3$, 100 MHz)

3-167