Application of *De Novo* Methodology for the Synthesis of Vineomycins and Oligosaccharides

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DEDICATED to

My parents Yeping Zhong & Huaxiang Li
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ABSTRACT of DISSERTATION

Vineomycin/Fridamycin antibiotics constitute a class of antitumor antibiotics that have been of particular interest to both the synthetic and biological communities. These natural compounds consist of an anthraquinone nucleus bearing one or more sugar moieties via O- or C-glycosidic bond. Acid-catalyzed methanolysis of biologically active Vineomycin B₂ would afford its aglycone Vineomycinone B₂ methyl ester. Our first project developed an effectively convergent route to successfully synthesize Vineomycinone B₂ methyl ester from commercially available anthrarufin. The key steps of the synthesis included Sharpless dihydroxylation, regio- and stereoselective Coates carbonylation, and Lewis acid catalyzed C-glycosylation.

In the Vineomycin family of natural products, the carbohydrate moiety plays a crucial role in assisting processes such as target binding, membrane transportation and so forth. But nature only makes a limited number of monosaccharides due to the limitation of enzymes. For instance, when a D- sugar is made naturally, then it rarely generates the L-stereoisomer of the sugar. This limitation intrigued our interest in synthesizing stereochemically diverse library of carbohydrate products. The trisaccharide subunit of Vineomycin B₂ was pointed out to possess interesting antitumor and antibacterial activity, and our second project was divergently synthesizing all eight D-/L-stereoisomers of Vineomycin B₂’s trisaccharide portion using our de novo synthesis method. Our synthetic route included de novo asymmetric synthesis of Boc-pyranones, regio- and stereo-selective palladium-catalyzed glycosylation and post-glycosylation modifications from commercially available achiral acetyl furan. From an achiral acetyl furan, two protected monosaccharides were synthesized, which generated four disaccharides and gave the
eight target trisaccharides in the end. A library of in total twelve D-/L-stereoisomer trisaccharides was synthesized, of which the biological evaluation result indicated that the natural trisaccharide subunit didn’t have to be superior to unnatural trisaccharides.

The objective of the last project is to synthesize Vineomycin B₂ and Vineomycin C. We discussed our unsuccessful effort toward the synthesis of Vineomycin B₂ in the last chapter of the thesis, which included catalysts screening, synthetic route optimization as well as new substrates synthesis.
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<tr>
<td>Ac</td>
<td>acetyl</td>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>Ac₂O</td>
<td>acetic anhydride</td>
<td>TLC</td>
<td>thin layer chromatography</td>
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<td>ATP</td>
<td>adenosine triphosphate</td>
<td>SAR</td>
<td>structure activity relationship</td>
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<td>Bn</td>
<td>benzyl</td>
<td>PNBz</td>
<td>para-nitrobenzyl</td>
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<td>Boc</td>
<td>tert-Butyloxy carbonyl</td>
<td>p-TsOH</td>
<td>para-toluenesulfonic acid</td>
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<td>ceric ammonium nitrate</td>
<td>dppb</td>
<td>1.4-bis(diphenylphosphino)butane</td>
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<td>cetyltrimethylammonium bromide</td>
<td>DMSO</td>
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<td>d</td>
<td>doublet</td>
<td>d.r.</td>
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<td>q</td>
<td>quartet</td>
<td>e.e.</td>
<td>enantiomeric excess</td>
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<td>dimethylformamide</td>
<td>Et₂O</td>
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<td>δ</td>
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<td>g</td>
<td>gram(s)</td>
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<tr>
<td>DIAD</td>
<td>diisopropylazodicarboxylate</td>
<td>h</td>
<td>hour(s)</td>
</tr>
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<td>Me</td>
<td>methyl</td>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
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<td>megahertz</td>
<td>IR</td>
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<td>i-Pr</td>
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<td>N-methylmorpholine N-oxide</td>
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<td>PMP</td>
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Chapter 1

Chapter 1. Total Synthesis of Vineomycinone B₂ Methyl Ester

1.1 Introduction:

Vineomycin/Fridamycin antibiotics constitute a class of antitumor antibiotics that have been of particular interest to both the synthetic and biological communities due to their unique structures and potent antitumor and antibacterial activities. From a structural point of view, Vineomycin family compounds consist of an anthraquinone nucleus bearing one or more sugar moieties attached through C-glycosidic bonds. Among them, Fridamycin E (I-1) can be regarded as the aglycon core of the more complex C-glycosidic Fridamycins: Vineomycins B₂ (I-2) and Vineomycin C (I-3) (Figure 1.1).

Figure 1.1: Structures of Fridamycin/Vineomycin Families

Of Vineomycin family, Vineomycin A₁ is a potentially important compound for the treatment of hypertrophic scar tissue and keloid in vivo studies and was proved to possess inhibition activity toward propyl hydroxylase. Propyl hydroxylase is an
oxygenase that catalyzes hydroxylation process of proline residues and results in precursor peptides of collagen to 4-hydroxproline. Through pathological fibrosis, prolyl hydroxylase’s activity could be enhanced.\textsuperscript{5} Vineomycin B\textsubscript{2} is a secondary metabolite of \textit{Streptomyces matensis} subsp. \textit{vineus}, which displays potent antitumor/antibiotic activity with a pharmacologic profile similar to that of the clinically important anthracyclines.\textsuperscript{6,7} Vineomycin B\textsubscript{2} contains a very similar skeleton structure of Vineomycin A\textsubscript{1} and it has been studied for use as a collagen prolyl hydroxylase inhibitor.\textsuperscript{8} Acid-catalyzed methanolysis of Vineomycin B\textsubscript{2} would afford its aglycone Vineomycinone B\textsubscript{2} methyl ester (I-4) which is the result of \textit{ortho}-C-glycosylation (\(\beta\)-D-olivose) of the methyl ester of Fridamycin E (I-1) (Figure 1.2).\textsuperscript{9} Its unique structures rendered Vineomycinone B\textsubscript{2} methyl ester as the representative member of the \(C\)-aryl glycoside natural product family for total synthesis.\textsuperscript{10,11}

\textbf{Figure 1.2: Structures of Vineomycin A\textsubscript{1}/ B\textsubscript{2}/ C, Fridamycin E and Vineomycin B\textsubscript{2}}

\textbf{Methyl Ester}
The total synthesis of Vineomycin B$_2$ methyl ester has been published by several groups.$^{12,13,14,15,16,17}$ Methods used by these groups varied from the use of cycloadditions with siloxydienes, metalation/stannylation reaction, Bradsher cycloaddition, Cp$_2$HfCl$_2$/AgClO$_4$ promoted O- to C-glycosylation to the use of tandem intra-molecular benzyne-furan cycloadditions. Although this molecule has been synthesized via so many methods, we thought that using our *de novo* asymmetric synthesis would efficiently simplify the synthetic process, improve the yield and provide a way to its stereoisomers.

The first total synthesis of Vineomycinone B$_2$ methyl ester was published by Danishefsky in 1985 (Scheme 1.1).$^{13}$ His synthesis featured three Diels-Alder cycloadditions with simple siloxydienes that reacted with excellent regioselectivities. The first two cycloadditions happened among motif I-6, I-7, and I-8 to construct the anthraquinone ring of the molecule I-5. While the third Diels-Alder reaction occurred between ketoaldehyde I-5 and diene I-9 under Eu(fod)$_3$ catalysis condition with (CH$_3$)$_2$S•BH$_3$ to afford C-glycosyl anthraquinone.$^{18,19}$ Followed by subsequent transformations, it gave Vineomycinone B$_2$ methyl ester in the end. This first total synthesis was accomplished within 12 steps with 0.1% yield. During this process HPLC has to be required for the purification.

**Scheme 1.1: Danishefsky’s Synthesis of Vineomycinone B$_2$ Methyl Ester**
Tius envisioned the synthesis in a different way. Tius envisioned Vineomycone B₂ methyl ester as being derived from three subunits: quinol I-11, olivose I-12, and allyl bromide I-14. Quinol I-11 could be achieved after a 4-step modification starting from commercially available anthrarufin. Via a first Negishi coupling, fraction I-11 and I-7 reacted with each other to afford C-glycosyl anthracene I-13. Next, the stannanylated product I-13 reacted with allyl bromide I-14 under palladium-catalyzed coupling. This was followed by removal of all protecting groups, which furnish Vineomycinone B₂ methyl ester in the end. This total synthesis was completed in 22 steps with a yield 0.7% from commercially available material (Scheme 1.2).

**Scheme 1.2: Tius’ Synthesis of Vineomycone B₂ Methyl Ester**

Falck’s synthesis of Vineomycinone B₂ methyl ester included a very important intermediate I-18, which was made from facile Bradsher cyclization between ether I-17 and the salt of pyrido[3,4-g]isoquinoline I-16. Starting material I-17 was readily available from the etherification of tertiary alcohol with p-biphenylmethyl (BPM) bromide of (S)-mevalonolactone. Fraction I-15 and was appended to the anthracycline ring of the molecule through a second Bradsher cyclization. Vineomycone B₂ methyl
ester was prepared in a total of 28 steps from commercially available materials with 0.09% yield via Falcke route (Scheme 1.3).

**Scheme 1.3: Falck’s Synthesis of Vineomycinone B$_2$ Methyl Ester**

In 1991 Suzuki reported his synthesis of Vineomycinone B$_2$ methyl ester in *JACS*. The key part of his synthesis was $O$- to $C$-glycoside rearrangement: at low temperature, Lewis acid catalyzed (CpHfCl$_2$/AgClO$_4$) $O$-glycosylation occurred between I-21 and I-22. With increasing temperature, $O$-glycoside was converted *in situ* to $C$-glycoside I-23. The $C$-glycosylated I-23 was coupled with aldehyde I-24, which constituted the right-hand side chain. By subsequent elaboration, Vineomycinone B$_2$ methyl ester could be accomplished in 32 steps with 0.8% yield from commercially available materials (Scheme 1.4).
The most recent synthesis of Vineomycinone B\textsubscript{2} methyl ester dates back to 2006 by Dr. Martin’s group published\textsuperscript{17,30}. In their synthetic route, they applied the strategy of using silicon tethers as disposable linkers to control the regiochemistry in ring-closure reaction. The first stage of the synthesis was the formation of intermediate I-\textsuperscript{28} through two Mitsunobu reactions (1) between subunits I-\textsuperscript{26} and I-\textsuperscript{27}; (2) product of first Mitsunobu reaction and subunit I-\textsuperscript{25}. By using \textit{n}-BuLi to promote the benzyne-furan cycloaddition in I-\textsuperscript{28}, bis-cycloaddition product I-\textsuperscript{29} could be delivered, which contained the major skeleton of target molecule-Vineomycinone B\textsubscript{2} methyl ester. The bonds between silicon and the bridgehead carbon atoms in I-\textsuperscript{29} were cleaved under modified Rickborn conditions (using KOH in DMF/H\textsubscript{2}O (10:1))\textsuperscript{31} and with following deprotection process, Vineomycinone B\textsubscript{2} methyl ester could be furnished in 27 steps with a yield 0.17\% from commercially available starting materials (Scheme 1.5).
Vineomycinone B₂ methyl ester consists of three parts: (1) an aglycone part which is similar to Fridamycin E (I-1), (2) the left-hand monosaccharide, and (3) the right-hand linear side chain. Our group published the synthesis of Fridamycin E in 2012 and this work was lead by Dr. Qian Chen in collaborate with Prof. Geoffrey Coate.³²,³³ The synthetic route started with commercially available anthrarufin. It went through mono-methallylation, Claisen rearrangement, benzyl protection, Sharpless dihydroxylation, tosylation, deprotonation, Coates carbonylation,³⁴ hydrolysis and the removal of the benzyl protecting group. Fridamycin E was synthesized in 9 steps with a 16% overall yield (Scheme 1.6).
In our group, the synthesis of various oligosaccharides usually started with commercially available acetyl furan via our de novo asymmetric strategy (Scheme 1.7). Through a 3-step reaction sequence (enantioselective Noyori reduction, Achmatowitcz oxidation, and Boc protection) stereoisomer I-40 can be obtained from I-39. Several C-6 substituted glycosyl donors can be synthesized using this approach, which, when combined with a Pd-catalyzed glycosylation and postglycosylation method, provides a generalized approach to sugars.
1.2 Retrosynthesis of Vineomycinone B₂ Methyl Ester

Retrosynthetically, Vineomycinone B₂ methyl ester could be divided into two parts: Fridamycin E methyl ester (I-37) and glycosyl donor. Lewis acid promoted β-C-glycosylation could be used to form the C-glycosidic bond between these two parts. Besides an olivose stereoisomer which is the glycosyl part of target molecule, a digitoxose stereoisomer possesses a directing group effect which could be essential for the selectivity in the C-glycoslation reaction and make digitoxose stereoisomer another suitable glycosyl donor. Through our de novo Achmatowicz strategy, both these two glycosyl donors could be synthesized from commercially available acetyl furan. Thus, in this part of the synthesis, synthetic advantage of the olivose diastereomer presents on the convergent strategy. The aglycone portion of the synthesis could be built based upon our Fridamycin E’s routes (Scheme 1.8).³²,³⁸
1.3 Total Synthesis of Vineomycinone B₂ Methyl Ester

1.3.1 Synthesis of Glycosyl Donors

Through a three-step reaction sequence, β-D-Boc-pyranone I-44 could be obtained with a moderate yield.³⁹ Pd-catalyzed glycosylation was used to give PMB-glycosylated pyranone I-45. It was followed by a Luche reduction and Myers rearrangement to afford olefin I-46. OsO₄ catalyzed Upjohn dihydroxylation was carried out and furnished β-D-digitoxose I-47.⁴⁰ The regioselective acetylating of the two hydroxyl groups of I-47 gave acetyl product I-48. This acetyl protected digitoxose I-48 underwent an oxidative deprotection reaction under ceric ammonium nitrate (CAN) to remove the PMB-group. The resulting lactol I-49 was subsequently acetylated to give glycosyl donor I-50 (Scheme 1.9).
Scheme 1.9: Synthesis of Glycosyl Donor (I-50)

Preparation of another glycosyl donor (I-55) started from β-D-digitoxose I-47. A highly regio- and stereo-selective Mitsunobu reaction was applied on I-47 to provide I-51 in a good yield. Hydrolysis of nitro-benzoate I-51 under LiOH condition gave diol I-52. Per-benzyl protection was used to protect two free hydroxyl groups as starting material for I-55. The following two steps were exactly the same as the last two steps of I-50 synthesis: oxidative deprotection and acetylation. Alternative glycosyl donor I-55 was synthesized, as expected in five steps from I-47 (Scheme 1.10).

Scheme 1.10: Synthesis of Glycosyl Donor (I-55)

1.3.2 Synthesis of Aglycone Precursors

For Vineomycinone B₂ methyl ester synthesis, aglycone’s formation is the critical step. When looking at both Vineomycinone B₂ methyl ester and Fridamycin E’s structures, we found they are sharing the same aglycone motif. Dr Chen has already
developed a practical synthetic route to get Fridamycin E.\textsuperscript{32} Based on Dr. Chen’s method published in 2011, we modified his synthetic route to allow for a convergent route to Vineomycinone B\textsubscript{2} methyl ester aglycone precursor.

With commercially available anthrarufin \textbf{I-30} in hand, a mono-methallylation reaction was performed under KI/DBU condition to afford mono-methallylated \textbf{I-31} with a moderate yield. This was followed by a Claisen rearrangement and benzyl protection to furnish benzyl protected diphenol \textbf{I-33} which was subjected to Sharpless dihydroxylation reaction to produce diol \textbf{I-34} with 88\% ee. This diol was treated under 1.5 eqiv. TsCl and catalytic Bu\textsubscript{2}SnO condition to afford tosylate \textbf{I-35} in the end (Scheme 1.11).

\textbf{Scheme 1.11: Synthesis of Tosylate (I-35)}

Using sodium hydride (NaH) promoted ring-closure condition, epoxide \textbf{I-36} was synthesized. A subsequent Coates carbonylation gave regio- and stereoselective $\beta$-lactone \textbf{I-37}. After methanolysis (K\textsubscript{2}CO\textsubscript{3}/MeOH), $\beta$-hydroxyl carboxylic acid methyl ester \textbf{I-56} could be generated smoothly with a 96\% yield. The deprotection of the benzyl group afforded Fridamycin E methyl ester \textbf{I-57} as one of the aglycone precursors (Scheme 1.12).
Scheme 1.12: Synthesis of Fridamycin E Methyl Ester (I-57)

With both glycosyl donor and aglycon in hand, we explored the possibility of a Lewis acid promoted C-glycosylation of I-57 with I-50 and I-55 (Scheme 13). Unfortunately, efforts at screening for effective Lewis acids and conditions (e.g., BF$_3$•Et$_2$O, TMSOTf and Cp$_2$HfCl$_2$/AgClO$_4$) turned out to be futile. No sign of the desired C-glycoside product was detected during the reaction (Scheme 1.13).

Scheme 1.13: Attempted C-glycosylation between Aglycone Precursor I-57 and Glycosyl Donor I-50, I-55

The failure of at C-glycosylation made us look for alternative substrates. From a review of the success C-glycosylation found in the literature, it occurred to us that an appropriate aglycone precursor should be an electron rich compound rather than an electron deficient one.$^{29}$ Our first generation aglycone precursor: Fridamycin E methyl
ester (I-57) is an electron deficient substrate. We believed the reason behind our failed C-glycosylation between I-57 and those glycosyl donors was due to the low electron density of our aglycone precursor I-57. Thus we turned our attention to make an electron rich aglycone precursor instead.

Starting with methyl ester I-56, via reduction and methylation reaction, dimethylated quinol I-58 could be formed by using Na₂S₂O₄ and Me₂SO₄. Obviously, quinol I-58 met one of C-glycosylation requirement: an electron rich compound. But we still needed to work on it, since there wasn’t a free hydroxyl group to couple with a glycosyl donor. The deprotection of the benzyl groups released free alcohol on quinol aromatic ring, which furnished the appropriate C-glycosylation substrate I-59 (Scheme 1.14). Although it contained a tertiary alcohol on the right-hand side chain of compound I-59, we were counting on the low tendency that tertiary alcohols would react with our glycosyl donors.

Scheme 1.14: Synthesis of Aglycone Precursor I-59

![Scheme 1.14: Synthesis of Aglycone Precursor I-59](image)

With the second generation aglycone precursor I-59 in hand, we began our next attempt at C-glycosylation. Various sets of catalysts such as Cp₂HfCl₂/AgClO₄, TMSOTf/DCM etc. were tried for aglycone I-59 and glycosyl donor I-50/ I-55 coupling. To our delight, when we mixed I-59 and glycosyl donor I-55 under Suzuki’s glycosylation condition (Cp₂HfCl₂/AgClO₄), these two compounds reacted as we expected and formed β-C-glycoside I-60 as a single regio- and diastereo-isomer. The yield for this reaction was 48%. A realiable mechanism for this C-glycosylation was
believed to undergo a formation of O-glycoside with a following O- to C-glycoside migration. With the deprotection of the benzyl groups and oxidation of quinol to quinone under BBr₃ condition in one pot, our desired product Vineomycinone B₂ methyl ester was synthesized successfully (Scheme 1.15).

**Scheme 1.15: End Game of Synthesizing Vineomycinone B₂ Methyl Ester (I-4)**

1.3.4 Improved Synthetic Route to Vineomycinone B₂ methyl ester

We successfully synthesized Vineomycinone B₂ methyl ester. During the process of synthesis, we noticed that when we were synthesizing aglycone precursor I-59 through the route described in Scheme 14, it suffered from irreproducible problem while we were trying to scale it up. When scaling beyond 200 mg of I-56 to the reduction reaction of I-56 to I-58, the reaction yield dropped from 89% to 26%. The reason behind the low yield of the reaction was majorly due to the oxidation side reaction that competed with the dimethylation process. Making Vineomycinone B₂ methyl ester was an early phase project need to synthesize natural product Vineomycin B₂. In order to have enough material later on, we revised our synthetic route and made it more feasible for large scale reaction (Scheme 1.16).
Instead of a benzyl group, MOM protecting group was used in this revised route. MOM was introduced to Fridamycin E methyl ester (I-57) easily under DIPEA condition. By using MOM group, the yield can be kept at 63% even at large reaction scale. Deprotection of MOM occurred in a BF$_3$Et$_2$O/EtSH environment to afford aglycone precursor I-59 with a 90% yield.

Overall, we successfully synthesized Vineomycinone B$_2$ methyl ester in 14 steps in the longest linear sequence with an overall yield of 7% by using our group’s *de novo* asymmetric method, which featured a convergent *de novo* synthesis of coupling partners for a late stage convergent C-glycosylation followed by a single step deprotection/oxidation. It beats the shortest synthetic route (16 steps) published before. Further Vineomycin synthesis and biological evaluations will be discussed later in this thesis.
Chapter 2. Total synthesis of D-/L- stereoisomers of Vineomycin B₂/C Trisaccharide Portion

2.1 Introduction

Vineomycins and angucycline natural products are two classes of the anthracycline antibiotics, which possess an aglycone aromatic backbone as well as one or more saccharide portion. Most structures in this family are either possess antibacterial activity or anticancer activity.¹ ² ⁴¹ Although the mechanism for their biological activities haven’t been clearly illustrated, ⁴² it never decreases scientists’ enthusiasm towards synthesizing these Vineomycins. ²²,²¹,²³,³⁰ All Vineomycin family members vary in degrees by glycosylated with mono-, di-, or tri-saccharides either with β-C-glycosidic bond or α-linked O-glycosidic bond on side chain. Typical structures for this family compounds are represented by Vineomycin B₂, Vineomycin C and PI-080 (Figure 2.1).⁴³

It is of our interest that all these three compounds are sharing an exactly same β-C-glycoside trisaccharide portion.⁴⁴,⁴⁵ This trisaccharide subunit consists of three nature sugars: β-D-olivose (marked as black), α-L-rhodinose (marked as blue) and α-L-aculose (marked as red), whereas Vineomycin B₂ has an additional α-linked O-glycoside: α-L-rhodinose-α-L-aculose and PI-080 contains an extra bis-α-L-rhodinose-α-L-aculose trisaccharide (Figure 2.1).
Figure 2.1: Structures of Vineomycin B₂, Vineomycin C and PI-080

Vineomycin C and its related monosaccharide angucycline Vineomycin B₂ possess antitumor activity against S-180 solid tumors in mice. Their impressive biological activities were attributed to the common anthraquinone portion of the molecules. While most synthetic efforts were focusing on the its anthraquinone ring, the synthesis of the α-linked O-glycosidic trisaccharide portion of PI-080 was completed by Sulikowski in 1996. With the inspiration of Sulikowski’s work, Dr. Xiaomei Yu accomplished the first total synthesis of the β-C-glycoside trisaccharide portion of PI-080/Vineomycin C/Vineomycin B₂ in 14 steps in 2008. Her route featured O’Doherty’s de novo asymmetric synthesis of Boc-pyranones, regio- and stereo-selective palladium-catalyzed glycosylation and post-glycosylation modifications from commercially available achiral...
acetyl furan (Scheme 2.1).46

Scheme 2.1: Dr. Xiaomei Yu’s Synthetic Route to II-1

A set of biological testing were carried out on II-1. Results indicated that at 50 µM, trisaccharide II-1 displayed greater cytotoxicity than cisplatin (chemotherapy drug, which will ultimately trigger apoptosis) at 300 µM. With the fact that this level of cytotoxicity fell into the range of other glycosylated angucycline antibiotics’ cytotoxicity that were found so far, we were inspired with the possibility of the trisaccharide subunit of angucycline compound would functionalize as a potent antitumor drug like complete angucycline molecule (Figure 2.2).

Figure 2.2: Cytotoxicity of Trisaccharide/Cisplatin towards H460*

*Graph denotes total cell death (apoptosis+necrosis) observed upon treatment of H460 cells with either no drug (NTX), 300 µM cisplatin (CP300), 50 µM of trisaccharide II-1 (pI-50), 100 µM of trisaccharide II-1(II-1(pI-100), 200 µM of trisaccharide II-1 (pI-200).
In addition to its antibacterial activity, the trisaccharide subunit (II-1) also possessed wide range cytotoxicity. For instance, it displayed significant growth inhibition ability ($\text{GI}_{50}$ from 0.1 to 11 $\mu$M) and cytotoxicity ($\text{LC}_{50}$ from 5.1 to 100 $\mu$M) against several cancer cell lines (Table 2.1).\(^{46}\)

### Table 2.1: Cytotoxicity Evaluation of Trisaccharide Subunit (II-1) across Cell Lines*

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Reproduced with permission from *Org. Lett.* 2008, 10, 4529-4532. Copyright 2008, American Chemical Society. **GI$_{50}$**: the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells. **TGI**: the drug concentration resulting in no increase in the measured protein as compared to control cells. **LC$_{50}$**: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

These interesting biological results inspired us to conduct more SAR studies for the trisaccharide subunit. Nature made this biologically active trisaccharide for us. While we appreciate the fantasy of nature, we also notice that there are certain structural motifs that nature does not provide. For instance, carbohydrates when provided by nature are only
prevailed in either D- or L- form. In contrast, by using chemistry method we could synthesize both D- and L- unnatural sugar as we need. This is important especially because rare research has been focused on these unnatural sugars so far. It’s entirely possible these unnatural oligosaccharides possess similar or even better biological activities than the natural one. Bringing this hypothesis into the trisaccharide subunit II-1, we targeted our second project at the synthesis of all eight D-/L-stereoisomers (unnatural) of Vineomycin B2/C trisaccharide portion. These eight targeted molecules are listed in Figure 2.3.

**Figure 2.3: Eight Target D-/L-stereoisomers of Vineomycin B2/C Trisaccharide Portion**

![Eight Target D-/L-stereoisomers of Vineomycin B2/C Trisaccharide Portion](image)

O’Doherty’s *de novo* synthetic method of sugars is widely used in this project. Palladium-catalyzed glycosylation in the synthesis was accomplished with high regio- and diastereo- selectivity to guarante the installation of stereoisomer sugars: α-Boc-pyranone gives only α-anomer while β-Boc-pyranone generates only β-anomer. Beside
the advantage of high stereoselectivity, ease of preparation and mild reaction environment also make palladium-catalyzed glycosylation popular: the required catalyst was prepared simply through mixed Pd$_2$(dba)$_3$·CHCl$_3$ and PPh$_3$ with a ratio of 1 : 2 and simply poured into reaction mixture under 0 °C. Mechanistically, the formation of π-allyl palladium intermediate was the key step during the reaction. Two inversion of configuration during the process resulted in the retention of stereochemistry of starting material: first inversion occurs with the formation of π-allyl palladium complex, while the second one occurs during nucleophilic (R$_2$OH) attack from less bulky side of the intermediate (Scheme 2.2).

Scheme 2.2: Mechanism of Retention of Stereochemistry in Palladium-catalyzed Glycosylation

![Scheme 2.2: Mechanism of Retention of Stereochemistry in Palladium-catalyzed Glycosylation](image)

2.2 Divergent Synthetic Strategy to Eight D-/L-trisaccharides Stereoisomers

By applying Dr. Yu’s method to our synthetic route, we developed a highly efficient \textit{de novo} divergent strategy starting from an achiral acetyl furan to the eight stereoisomer targets. To simplify our synthesis, we were able to get two monosaccharide building blocks from one achiral acetyl furan. Then, based on these two monosaccharides, four disaccharides could be synthesized via palladium-catalyzed glycosylation method. At last, these four disaccharides would afford eight target trisaccharides (Scheme 2.3).
This divergent synthetic strategy assures the highest efficiency in synthesizing all eight goal molecules. It also presents the power of our *de novo* synthesis method: from the achiral compounds, we could synthesize a variety of unnatural sugars in as few steps as possible. In this project we started with an achiral acetyl furan, two protected monosaccharides were synthesized, which led to four disaccharides and then the eight target trisaccharides.

**Scheme 2.3: Divergent Synthetic Strategy to Eight Target Trisaccharides**

![Scheme 2.3](image)

2.3 Total Synthesis of D-/L- stereoisomers of Trisaccharide Portion: β-D-olivose-α-L-rhodinose-α-L-aculose (DLL), β-D-olivose-α-L-rhodinose-α-D-aculose (DLD), β-L-olivose-α-D-rhodinose-α-D-aculose (LDD), β-L-olivose-α-D-rhodinose-α-L-aculose (LDL)

2.3.1 Synthesis of β-L-/D-olivose

The synthesis of the first sugar β-L-olivose and its enantiomer started from acetyl furan I-43. Noyori \((R,R)\) and Noyori \((S,S)\) were used to install different stereo-center and afforded furan alcohol II-8 and \((ent)\)-II-8 respectively. These furan alcohols were
subjected to Achmatowitz rearrangement, which was followed by a Boc-anhydride protection to generate α/β-L (II-6/II-7) and α/β-D-Boc-pyranone ((ent)-II-6/(ent)-II-7) with yields 86% and 88% (Scheme 2.4). It’s worth noticing that the ratio of α to β-Boc-pyranone produced in one reaction was able to be controlled by different reaction conditions: under low temperature (−78 °C), the ratio of α: β was around 4:1, while by increasing the temperature to 80 °C this value decreased to 1 to 1 (Scheme 2.4).

Scheme 2.4: Synthesis of α/β-L and α/β-D-Boc-pyranone

Synthesis of the D- and L- β-olivose followed the same protocol of Dr. Yu’s paper. In this thesis, we used the synthesis of β-L-olivose as an example to elucidate the synthetic route. With β-L-Boc-pyranone III-6 in hand, a palladium-catalyzed glycosylation was used to append PMB alcohol with β-L-Boc-pyranone and stereoselectively gave pyranone II-10 with a yield of 92%. Pyranone II-10 was then subjected to a Luche reduction followed by a Myer’s rearrangement to afford olefin II-12. A subsequent Upjohn dihydroxylation reaction was applied later to install two more chiral centers on C-3 and C-4 position on II-13. With a Mitsunobu reaction, the allo-stereochemistry on C-3 position of digitoxose II-13 was inverted to p-nitrobenzoate-olivose II-14 (Scheme 2.5).
Scheme 2.5: Synthesis of β-L-olivose

The enantiomer of II-14: β-D-olivose ((ent)-II-14) was synthesized through the same reaction sequence from the enantiomeric starting material (Scheme 2.6).

Scheme 2.6: Synthesis of β-D-olivose

2.3.2 Synthesis of Disaccharides β-olivose-α-rhodinose

Synthesis of the disaccharide began with a palladium-catalyzed glycosylation between α-L-Boc-pyranone II-7 and β-L-olivose II-14 (Scheme 2.7). Two more steps were needed to install the stereochemistry center on the disaccharide: (1) a Luche reduction was used to afford allylic alcohol II-15 with high diastereoselectivity; (2) this was followed by a Mitsunobu reaction, which occurred under NBSH/DIAD condition and formed β-L-olivose-α-L-rhodinose II-16 with 70% yield.

When using α-D-Boc-pyranone ((ent)-II-7) in the first palladium-catalyzed glycosylation, a β-L-olivose-α-D-rhodinose disaccharide was synthesized. This disaccharide was subjected to the following Luche reduction and Mitsunobu reaction to afford II-18 (Scheme 2.7).
Scheme 2.7: Synthesis of Disaccharides β-L-olivose-α-L/D-rhodinose (II-16 and II-18)

Enantiomers of disaccharide II-16 and II-18 were formed using the same method mentioned above (Scheme 2.8).

Scheme 2.8: Synthesis of Disaccharides β-D-olivose-α-L/D-rhodinose ((ent)-II-16 and (ent)-II-18)

2.3.3 Synthesis of Linear Trisaccharides β-L-olivose-α-D-rhodinose-α-D-/L-aculose and Branched Trisaccharides β-L-olivose-α-L-rhodinose-α-D-/L-aculose as well as their Enantiomers

A set of disaccharides (II-16, II-18, (ent)-II-16, (ent)-II-18) had been synthesized successfully. Our target molecules were eight trisaccharides, which were only one-sugar
away from trisaccharide molecules. Before attached the last sugar to the disaccharide II-16, a LiOH promoted hydrolysis was used to deprotect p-nitrobenzoate group on II-18. Then, the double bond was reduced by NBSH to afford diol II-20. A subsequent palladium-catalyzed glycosylation regioselectively occurred on C-4 position of II-20 to furnish target linear trisaccharides (ent)-II-2 (LDL) and (ent)-II-1 (LDD) respectively (Scheme 2.9).

**Scheme 2.9: Synthesis of Two Target Trisaccharides (LDL, LDD)**

Trisaccharides II-1 (LDL) and II-2 (LDD) were synthesized through a similar reaction sequence (Scheme 2.10). Finally, we divergently got four desired trisaccharides from two disaccharides intermediates. These four molecules were β-L-olivose-α-D-rhodinose-α-D-aculose ((ent)-II-1), β-L-olivose-α-D-rhodinose-α-L-aculose ((ent)-II-2), β-D-olivose-α-L-rhodinose-α-L-aculose (II-1), β-D-olivose-α-L-rhodinose-α-D-aculose (II-2).
To our disappointment, when same chemistry was applied to the synthesis of trisaccharides started with II-16 and (ent)-II-16 disaccharides, the circumstance with regard to the regio-selective glycosylation was dramatically changed (Scheme 2.11). Thus, hydrolysis and reduction of II-16 was carried under similar condition as before. To our surprise, the palladium-catalyzed regio-selective glycosylation of II-21 with either α-L-Boc-pyranone or α-D-Boc-pyranone selectively occurred on the C-3 hydroxyl group of β-olivose rather than C-4 hydroxyl group of α-rhodinose, thus generated branched trisaccharide subunits II-22 and II-23 instead of the linear trisaccharides.
Scheme 2.11: Synthesis of Branched Trisaccharides (LLL, LLD)

Not surprising, the same selectivity was observed for the synthesis of (ent)-II-23, and (ent)-II-22 (Scheme 2.12). Thus, two more branched glycosylated trisaccharides (DDL and DDD) were formed in three steps from disaccharide (ent)-II-16. Although the formation of branched trisaccharides was a windfall of this project in terms of analogue generation, what left for us was that we still need seeking for an effective synthetic route to the four remaining linear target trisaccharides.

Scheme 2.12: Synthesis of Branched Trisaccharides (DDL, DDD)
2.3.4 Revised Route to Linear Trisaccharides β-L-olivose-α-L-rhodinose-α-D/-L-aculose as well as Their Enantiomers

The formation of branched trisaccharides indicated that the hydroxyl group of β-olivose was more reactive than α-rhodinose in the disaccharides β-L-olivose-α-L-rhodinose (II-21) and β-D-olivose-α-D-rhodinose ((ent)-II-21) when compared with other two disaccharide intermediates II-20, (ent)-II-20. A possible reason for the reverse activity of hydroxyl group might due to the different roles of hydrogen bond playing in DD-(or LL-) and DL- (or LD-) disaccharide building blocks. Based on the occurrence of the highly regioselective glycosylation on II-21, we hypothesized that the protection of the hydroxyl groups would also occur with similarly high regio-selectivity. Thus, the selective installation of ester and TBS protecting group were explored for this purpose. Unfortunately, all attempts failed due to poor regio-selectivity or extremely low yields. Thus, the strategy of using protecting group was proved to be futile. We had to develop an alternative synthetic route to surpass the regioselectivity problem.

While scrutinizing our synthetic route, we noticed that the key point to solve the problem was to identify an appropriate place to differentiate the two hydroxyl groups on DD- and LL-disaccharides. Thus, this brought us back to the second Mitsunobu reaction. Instead of using p-nitrobenzoic acid, chloroacetic acid was chosen as the reagent for the Mitsunobu reaction of II-15 which would selectively leave the two hydroxyl groups orthogonally protected. The deprotection of chloroacetyl group on II-24 was smoothly carried out with thiourea and n-Bu₄NI to afford allylic alcohol II-25. Under this deprotection condition, p-nitrobenzoic group on β-L-olivose survived. With an NBSH reduction of the olefin II-25, the hydroxyl group on C-4 position of α-L-rhodinose was
free to undergo linear palladium-catalyzed glycosylation. In this way, we successfully avoided the regioselectivity problem. The following palladium-catalyzed glycosylation lead to the formation of linear trisaccharides precursors II-27 and II-28 with moderate yields (Scheme 2.13).

**Scheme 2.13: Revised Route to Linear Trisaccharides Precursors**

The enantiomers of II-27 and II-28 was synthesized through the same synthetic route and gave linear trisaccharide precursor (ent)-II-27 and linear trisaccharide precursor (ent)-II-28 respectively (Scheme 2.14).
If hydrolysis of $p$-nitrobenzoic group worked well for II-27, it would afford the target trisaccharide. However, when LiOH was used to deprotect the $p$-nitrobenzoic group, no desired product was observed. Starting material II-27 underwent a deprotonation process rather than the $p$-nitrobenzoic deprotection reaction and resulted in the decomposition of the trisaccharide. If we could prevent the deprotonation process, then the trisaccharide should be stable under basic hydrolysis condition. Reduction of $\alpha$-pyranone to allylic alcohol met the expectation: Luche reduction was used to reduce pyranone II-28 to allylic alcohol II-29, which underwent LiOH hydrolysis reaction to give II-30 with 90% yield. Oxidation of the alcohol group of II-30 with MnO$_2$ led to the formation of goal trisaccharide II-3 (Scheme 2.15).
Scheme 2.15: End Game to Target Linear Trisaccharides (LLL)

The remaining three linear trisaccharides II-4, (ent)-II-3, (ent)-II-4 were synthesized in the same way (Scheme 2.16).

Scheme 2.16: End Game to Target Linear Trisaccharides (LLD, DDD, DDL)
Finally, we had successfully synthesized eight desired linear trisaccharides as well as four branched trisaccharides. These twelve molecules are displayed in Figure 2.4.

**Figure 2.4: Structures of Eight Linear Target Trisaccharides and Four Branched Trisaccharides**

2.4 Biological Evaluation of Twelve Trisaccharides

With eight linear trisaccharides and four branched trisaccharides in hand, we began to perform the biological activity evaluation.

2.4.1 Biological Evaluation of Natural Trisaccharide (II-1) vs Its Enantiomer

Natural trisaccharide subunit **II-1** (DLL) and its enantiomer (**ent**)-**II-1** (LLD) were
compared in GI$_{50}$ values over 60 cancer cell lines (this work was finished by NCI). Results are presented in Figure 2.5. There was no considerable difference in antitumor activity between natural trisaccharide subunit II-1 and its enantiomer (ent)-II-1. Although for some specific cell lines such as UO-31, 786-0 the natural trisaccharide displayed a higher activity than the enantiomeric trisaccharide, for other cell likes such as EKVX, the enantiomeric compound was much more active.

**Figure 2.5: Antitumor Activity Comparison between Natural Trisaccharide and Its Enantiomer**

![Antitumor Activity Comparison between Natural Trisaccharide and Its Enantiomer](image)

2.4.2 Biological Evaluation of Natural Trisaccharide (DLL) vs Unnatural Trisaccharides (LDD, LDL, DLD)

Other unnatural trisaccharides were added into the screening process. We compared GI$_{50}$ values of natural DLL (II-1), LDD ((ent)-II-1), DLD (II-2) and LDL ((ent)-II-2).
Some interesting results were observed. Antitumor results indicated that although natural II-1 displayed stronger activity towards some specific cell lines such as RPMI-8226, trisaccharide (ent)-II-2 (LDL) presented a wider range of activity over various cell lines. Especially, for most of these cell lines, unnatural trisaccharide displayed a similar or higher activity than the natural trisaccharide. This result matched with our hypothesis: unnature oligosaccharides could possess even better biological activities.

Figure 2.6: **GI\textsubscript{50} Value Comparisons of DLL (II-1), LDD ((ent)-II-1), DLD (II-2) and LDL ((ent)-II-2) over 60 Cell Lines**

2.4.3 Cytotoxity (IC\textsubscript{50}) of Twelve Trisaccharides against H460 Cell Line

Cytotoxity for all these twelve trisaccharides were tested against human cancer cell
line H460. The complete data is shown in Table 2.2.

Of all the twelve trisaccharides II-1 (DLL, natural one) was not the trisaccharide subunit possessing the highest anticancer activity. Interestingly, some linear stereo-trisaccharide subunits such as II-2 (DLD), (ent)-II-2 (LDL) proved to be more potent than natural trisaccharide II-1 (DLL). For example, its enantiomer (ent)-II-1 (LDD) showed a much better potency against H460 cell line. Even the branched subunit possessed a higher activity, which indicated that the linear skeleton might not be necessary structure for its antitumor ability. The most promising stereo-trisaccharide was found as β-L-olivose-α-D-rhodinose-α-L-aculose ((ent)-II-2), whose cytotoxicity was almost 6 folds (2.2 µM) higher than the natural subunit (11.7 µM).

**Table 2.2: Cytotoxicity Evaluation (IC₅₀) of 12 D-/L-stereoisomer trisaccharides against H460 Cell Line*.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀ (µM)</th>
<th>Compound</th>
<th>IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-1</td>
<td>11.7</td>
<td>(ent)-II-1</td>
<td>3.7</td>
</tr>
<tr>
<td>II-2</td>
<td>6.0</td>
<td>(ent)-II-2</td>
<td>2.2</td>
</tr>
<tr>
<td>II-22</td>
<td>74.0</td>
<td>(ent)-II-22</td>
<td>16.3</td>
</tr>
<tr>
<td>II-23</td>
<td>15.3</td>
<td>(ent)-II-23</td>
<td>8.0</td>
</tr>
<tr>
<td>II-3</td>
<td>49.5</td>
<td>(ent)-II-3</td>
<td>84.9</td>
</tr>
<tr>
<td>II-4</td>
<td>60.0</td>
<td>(ent)-II-4</td>
<td>9.1</td>
</tr>
</tbody>
</table>

**2.4.4 Antibacterial Activity of Twelve Trisaccharides**

Inspired by the interesting antitumor activity result, we kept evaluating the antibacterial activity of these twelve trisaccharides. Three strains *B. subtilis*, *E. faecium* and *E. faecalis*, were chosen for antibacterial activity testing. All the twelve trisaccharides’ MIC values were larger than 80 µM for *E. faecium* and *E. faecalis* strains, which implied the low activity toward these two types of bacterial strains. The complete
data of antibacterial activity against B. subtilis strain was listed in Table 2.3. Altought the antibacterial activity for all of them was not impressive, the natural trisaccharide subunit II-1’s data presented here was not the lowest compared with other unnatural trisaccharide such as II-2, (ent)-II-2, (ent)-II-22, (ent)-II-23 (Table 2.3).

Table 2.3: MIC (µM) values for 12 D-/L-stereoisomer Trisaccharides against B. subtilis

<table>
<thead>
<tr>
<th>Compound</th>
<th>B. subtilis</th>
<th>Compound</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JH642</td>
<td>PY79</td>
<td>3610</td>
</tr>
<tr>
<td>II-1</td>
<td>80</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>II-2</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>II-22</td>
<td>80</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>II-23</td>
<td>80</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>II-3</td>
<td>40</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>II-4</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

*Antibacterial activity was assessed by MIC method, which was performed by the broth dilution method described by the National Committee for Clinical Laboratory Standard Methods (M7-A6, 2003).

To our delight, the biological data supports our hypothesis that the natural trisaccharide was not the most potent compounds especially in antitumor ability. This conclusion inspired us to work on unnatural compound synthesis for the purpose of developing more effective substitutes of natural compound.

In conclusion, we successfully synthesized all twelve D-/L-stereoisomers of trisaccharides portion of Vineomycin B2/C. Our hypothesis had been validated by the biological evaluation results: the natural occurring trisaccharide subunit does not possess the highest antitumor activity or antibacterial activity. We could get more biologically active compounds through chemical synthesis, which are more likely to become potent drugs that will benefit human beings.
Chapter 3

Chapter 3. Progress toward Total Synthesis of Vineomycinone B$_2$ / Vineomycin C

3.1 Introduction

Vineomycin B$_2$ is an angucycline antibiotic, which was first isolated from culture broth of *Streptomyces matensis* subsp. *Vineus* by Omura’s group.$^{43}$ This natural compound was shown to possess activity against Gram-positive bacteria and sarcoma 180 solid tumor cells in mice. Vineomycin C is a new member of the angucycline family, which wasn’t identified until 2000 by Khisal et al. from *Streptomyces* sp.$^{47}$ Like other angucycline compounds, it also displayed interesting antitumor activity.

The structures of these two molecules are shown in Figure 3.1. From the structure of Vineomycin B$_2$ and Vineomycin C, we can easily identify many structural similarities between them, for instance, the C-glycosydic trisaccharide (marked as red) and the Fridamycin E like aglycone ring (marked as black). The only difference between them is the extra $O$-linked disaccharide $\alpha$-L-rhodinose-$\alpha$-L-aculose in Vineomycin B$_2$ (marked as blue).

**Figure 3.1: Structures of Vineomycin B$_2$ and Vineomycin C**
Over last two decades, chemists have focused on the synthesis of various angucycline family compounds.\cite{14,17,23,30,38} Although tremendous effort has been made toward the synthesis of these natural compounds, the total synthesis of Vineomycin B$_2$ and Vineomycin C remain as a big challenge. In 2013, the first total synthesis of Vineomycin B$_2$ was published by Toshima’s group on JACS.\cite{48}

Toshima’s synthesis of Vineomycin B$_2$ was divided into three parts.

1). Synthesis of intermediate III-6 (Scheme 3.1). The synthesis of this part started with the C-glycosylation between the unprotected D-olivose III-5 and 5,9,10-trimethoxyantracen-1-ol III-1 under TMSOTf condition to give C-glycoside III-2.\cite{49,50,51} C-glycoside III-2 was converted into Suzuki’s intermediate arylstannane III-3\cite{16} in three steps: (1) methylation of the phenol hydroxyl group of III-2, (2) followed by the TBS protection of the two hydroxyl groups of the olivose and (3) stannylation in the presence of $n$-BuLi to afford arylstannane III-3. Arylstanne III-3 was then treated with MeLi and coupled with aldehyde III-7 to afford III-4. A subsequent benzylation of alcohol III-4 and oxidation of quinol to quinone using CAN gave its anthraquinone derivative. Of which the benzyl ether were removed by Pd/C catalyzed hydrogenolysis, and a following deoxygenation at the benzylic position in the presence of Na$_2$S$_2$O$_4$ gave quinone III-5 in the end (Scheme 3.1).

Aldehyde III-7 used in the metalation addition step was synthesized from 3-methylbut-3-en-1-ol.\cite{17} With a PMP protection of the primary alcohol and a Sharpless dihydroxylatoin, diol III-8 was formed. III-8 was subjected to a following reaction sequence (1) tetrahydropyranylation in the presence of 3,4-dihydro-2$H$-pyran, (2) benzylation with BnBr, (3) removal of the THP group and (4) oxidation of the terminal
alcohol to afford aldehyde III-7.

Scheme 3.1: Toshima’s Synthesis of Vineomycin B2: Aglycone Precursor

2). Synthesis of glycosyl donor III-14 (Scheme 3.2). The known 2,3-unsaturated sugar III-10 was synthesized from commercially available substrate III-9 using a Mitsunobu reaction. This was followed by a TBDPS protection of the allylic alcohol III-10, CAN oxidative deprotection of PMP group as well as an acetylation of the C-1 position to afford olefin III-11. Thioglycoside III-12 was formed in three steps: (1) hydrogenation of the olefin III-11 using 5% Rh/Al2O3, which was followed by subsequent (2) thiophenylation and (3) deprotection of TBDPS with TBAF. With III-11 and III-12 in hand, the chemoselective glycosylation was carried out under TBSOTf condition. This resulted in the formation of highly α-selective disaccharide III-13. The
disaccharide was subjected to TBAF condition (removal of TBDPS group), and then oxidized by a Dess-Martin reagent to give thiodisaccharide III-14 (Scheme 3.2).

**Scheme 3.2: Toshima’s Synthesis of Vineomycin B₂: Glycosyl Donor Part**

3). End game of total synthesis of Vineomycin B₂ (Scheme 3.3). With both glycosyl donor and aglycone precursor in hand, Toshima screened a couple of glycosylation conditions and found NIS/TfOH to be the superior activator over alternatives such as MeOTf, AgOTf and NBS/TfOH for promoting the glycosylation between III-6 and III-14. In addition, they discovered that the occurrence of bis-glycosylated or monoglycosylated product could be controlled through changing the concentration of glycosyl donor. Synchronical glycosylation with two *equivs* disaccharide III-14 and aglycone precursor III-6 under NIS/TfOH condition worked well to furnish III-15. This was followed by a deprotection of TBDPS group using TASF and a Dess-Martin oxidation of the resulting primary alcohol to afford AcCl-protected Vineomycin B₂. The formation of Vineomycin B₂ was accomplished with the deprotection of AcCl using thiourea (Scheme 3.3).
3.2 Retrosynthesis of Vineomycin B₂

We envisioned a synthetic route to Vineomycin B₂ in a rather different way from Toshima’s synthesis. Instead of attaching β-olivose to the center aromatic ring in the beginning, we preferred to synthesize the aglycone with the carboxylic acid side chain first, and then append the sugars to the aglycone motif. Retrosynthetically, Vineomycin B₂ could be envisioned as consisting of aglycone III-19 and oligosaccharides III-17, III-20. With both these two parts in hand, a successful coupling between them would lead to the formation of the target molecule. We believe both of these two halves could be
synthesized from commercially available materials: anthrarufin I-30 and acetyl furan I-43 by modifying our previously established syntheses (Scheme 3.4).

**Scheme 3.4: Retrosynthesis of Vineomycin B$_2$**

![Scheme 3.4: Retrosynthesis of Vineomycin B$_2$](image)

3.3 Progress toward Synthesis of Vineomycin B$_2$

3.3.1 Revised Route to Aglycone Precursor

In Chapter 1, we introduced the synthetic route to Vineomycinone B$_2$ methyl ester, of which the process of forming intermediate Fridamycin E methyl ester (III-26) was elucidated. In the synthetic route to III-26, tosylate III-22 was converted from commercially available anthrarufin I-30 through a 5-step reaction sequence. This was followed by a NaH promoted ring closure reaction and regio-/stereospecific Coates
carbonylation\textsuperscript{34} to afford $\beta$-lactone III-24. A smooth methanolysis of I-37 gave $\beta$-hydroxyl carboxylic acid methyl ester III-25. Then the deprotection of benzyl group was carried out with 1,4-cyclohexadiene and Pd/C in ethanol to deliver Fridamycin E methyl ester III-26 in the end (Scheme 3.5).

**Scheme 3.5: Original Route to Fridamycin E Methyl Ester III-26**

We developed a more efficient route to aglycone precursor III-30, from which Fridamycin E methyl ester was more easily to be prepared. Using same reaction sequence, tosylate III-22 was synthesized in 5 steps. Instead of the NaH promoted ring-closure reaction, an S\textsubscript{N}2 cyanide substitution was used to form cyanide III-27. Hydrolysis of cyanide III-27 before debenzylation afforded corresponding carboxylic acid in very low yield (<10%). To our delight, when we exchanged the reaction order of hydrolysis and debenzylation, diphenol Fridamycin E I-1 was obtained with a two-step overall yield of 74%. The debenzylation of III-27 was carried out with AcCl/EtOH rather than under harsh Pd/C environment to afford III-28. This was followed by the base hydrolysis of diphenol III-28 to give Fridamycin E I-1. Methylation of Fridamycin E furnished Fridamycin E methyl ester III-26 without any problem. Using the revised route, Fridamycin E methyl ester was synthesized in 9 steps from anthrarufin I-30. The reaction conditions used for this revised synthetic route were milder and easier to operate.
MOMCl was used to protect di-phenol groups of III-26, which was followed by a reductive methylation of quinone to afford quinol III-29 with a 60% yield. A subsequent deprotection of MOM with BF$_3$•Et$_2$O furnished aglycone precursor III-30 in the end (Scheme 3.7).

Scheme 3.6: Revised Route to Fridamycin E Methyl Ester III-26

Scheme 3.7: Synthetic Route to Aglycone Precursor III-30

3.3.2 Synthesis of Glycosyl Donor

Starting from acetyl furan I-43, pyranone III-31 was synthesized through asymmetric Noyori(R,R) reduction and Achmatowicz rearrangement. At –78 °C, pyranone III-32 along with pivaloyl chloride was mixed with DMAP and led to the formation of α- and β-Piv-pyranone with α: β = 3:1. The α-stereoisomer was subjected to Luche reduction and afforded allylic alcohol III-33 in a yield of 97% (Scheme 3.8).
Scheme 3.8: Synthetic Route to Glycosyl Donor

Using the same reaction sequence described in Chapter 2, the β-D-Boc-pyranone III-34 was furnished in 3 steps from acetyl furan I-43: (1) Noyori \((R,R)\) reduction (2) Achmatowicz rearrangement (3) Boc anhydride protection. A subsequent palladium-catalyzed glycosylation was carried out to append a PMB group to the C-1 position of III-34 and gave III-35 in 95% yield (Scheme 3.9). A Luche reduction was used again to form PMB-allylic alcohol III-36, of which Myers rearrangement and Upjohn dihydroxylation were applied to afford diol III-38. Finally, 2,2-dimethoxy propane was used for the protecting of alcohols under acid catalyzed condition, PMB-acetonide III-39 was produced with a yield 99%.

Scheme 3.9: Synthetic Route to Glycosyl Donor (continued)

Another potential glycosyl donor is the natural trisaccharide portion of Vineomycin B₂, which we successfully synthesized in Chapter 2. The conversions from II-1 to III-41 are presented in Scheme 3.10. Using Ac₂O/DMAP, the free hydroxyl of group II-1 was protected with an acetyl group.\(^{53}\) When CAN was used for the oxidative deprotection of
PMB, the acetyl group of III-40 detached from the molecule and resulted in the formation of undesired product. Thus, the deprotection of PMB of III-40 was carried out using DDQ instead of CAN to afford acetyl protected trisaccharide III-41 (Scheme 3.10).

Scheme 3.10: Synthesis of Trisaccharide Glycosyl Donor

3.3.3 Attempted C-glycosylation

With both aglycone precursor and glycosyl donors in hand, we turned our attention to the C-glycosylation coupling. If we could directly attach the trisaccharide portion to the aglycone precursor, it would result in a very succinct synthesis of the Vineomycin family nature products.

With this hope, we tried the C-glycosylation between trisaccharide donors and aglycone precursor III-30 (Scheme 3.11). We tried to assemble the bond between II-1 and III-30 first. TMSOTf was used as a catalyst to prompt the reaction. Unfortunately, only the decomposition of the trisaccharide substrate was observed, which indicated the TMSOTf condition was too harsh for trisaccharide II-1. A similar outcome occurred for trisaccharides III-40 and III-41. Suzuki’s catalyst (CpHfCl2/AgClO4) was also investigated for C-glycosylation of aglycone precursor III-30 and glycosyl donors. To our disappointment, when applying the same catalyst system for all trisaccharide donors (II-1, III-40, III-41) with III-30, no product was observed (Scheme 3.11).
Scheme 3.11: Attempted C-glycosylation between III-30 and Trisaccharide Substrates

Although we failed to directly assembling the bond between trisaccharide substrates and III-30, we kept working on the C-glycosylation between monosaccharides which were sterically less hindered substrate and aglycone precursor. Various catalyst sets (TMSOTf/AgClO4, CpHfCl2/AgClO4, Sc(OTf)3 etc. Table 3.1) were applied over different monosaccharide substrates (eg. III-31, III-32, III-34, III-39 etc.) and glycosyl acceptor III-30. But no desired product was obtained under these conditions (Scheme 3.12).

Scheme 3.12: Attempted C-glycosylation between I-59 and Monosaccharide Substrates

Table 3.1: Lewis Catalysts Used for C-glycosylation Reaction

<table>
<thead>
<tr>
<th>Glycosyl Donors</th>
<th>Aglycone</th>
<th>Glycosyl Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>III-31</td>
<td>III-32</td>
</tr>
<tr>
<td>III-30</td>
<td>TMSOTf/AgClO4</td>
<td>Sc(OTf)3</td>
</tr>
<tr>
<td>III-30</td>
<td>CpHfCl2/AgClO4</td>
<td>CpHfCl2/AgClO4</td>
</tr>
<tr>
<td>III-30</td>
<td></td>
<td>CpTiCl2/AgClO4</td>
</tr>
</tbody>
</table>
Direct C-glycosylation between aglycone precursor **III-30** and sugars proved to be futile. When looking into Suzuki’s C-glycosylation mechanism, it mentioned that Suzuki’s C-glycosylation actually underwent an O- to C-glycoside transfer process: at low temperature, Lewis acid catalyzed (CpHfCl₂/AgClO₄) O-glycosylation occurred between glycosyl donor and acceptor; while with increasing temperature, O-glycoside was converted *in situ* to C-glycoside to afford C-glycosylated product. Palladium-catalyzed O-glycosylation was well developed in our lab. If we could successfully carry out the O-glycosylation reaction between aglycone and sugars, with a subsequent O-glycoside to C-glycoside conversion the C-glycosylated product would be obtainable eventually. However, it was frustrating when we discovered that the aglycone precursor **III-30** remained inactive when exposed to the glycosylation conditions with either Boc-pyranone **III-34** or allylic alcohol **III-33** (Scheme 3.13).

**Scheme 3.13: Attempted O-glycosylation between III-30 and Glycosyl donor**

In conclusion, a more efficient and easier way to get important aglycone intermediate Fridamycin E methyl ester **III-26** has been proposed in this chapter. In addition to the revised synthetic route, various glycosyl donors had been synthesized here by utilizing
our \textit{de novo} asymmetric synthesis. Two strategies of $C$-glycosylation were explored (1) Lewis acid catalyzed $C$-glycosylation and (2) catalyst promoted migration from $O$-glycosides to $C$-glycosides. Although we are still putting efforts in getting the desired $C$-glycosylated product, it’s worth noting that once we surpass the difficulty in coupling sugar and aglycone portion, we should able to achieve the total synthesis of varieties of Vineomycin products. Further effort will focus on carrying out $C$-glycosylation reaction on more aglycone substrates and glycosyl donors.
Section A: General methods

Triethylamine, 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. 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. 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 KMnO$_4$ or anisaldehyde staining. $^1$H and $^{13}$C spectra were recorded on 500 MHz (Inova-500) and 400 MHz (Mercury-400BB) spectrometer. Chemical shifts are reported relative to CDCl$_3$ ($\delta$ 7.26 ppm) for $^1$H and CDCl$_3$ ($\delta$ 77.0 ppm) for $^{13}$C. Optical rotations were obtained using a digital polarimeter at sodium D line (589 nm) and were reported in concentration of g/100 mL at the temperature shown. IR was recorded on a Bruker FT-IR spectrometer. Melting points are uncorrected.
Section B: Experimental Protocol

Chapter 1. Total Synthesis of Vineomycinone B₂ Methyl Ester

Tert-butyl ((2S,6R)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (I-45)

![Chemical Structure](image)

To a 1000 mL flask was added furan ketone I-43 (40 g, 363.5 mmol), CH₂Cl₂ (240 mL), formic acid/triethylamine (5:4 (molar ratio), 480 mL) and Noyori asymmetric transfer hydrogenation catalyst (R)-Ru(η₆-6-mesitylene)-(R, R)-TsDPEN (222 mg, 0.1 mol%). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (500 mL) and extracted with EtOAc (3 x 700 mL). The combined organic layers were washed with saturated NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. The resulting crude furan alcohol 10 was dissolved in 603 mL of THF/H₂O (3:1) and cooled to 0 °C. Solid NaHCO₃ (60.9 g, 727.8 mmol), NaOAc•3H₂O (49.6 g, 363.9 mmol), and NBS (64.3 g, 363.7 mmol) were added to the solution and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated NaHCO₃ (600 mL), extracted (3 x 800 mL) with Et₂O, dried (Na₂SO₄), concentrated under reduced pressure. The crude mixture 11 was dissolved in CH₂Cl₂ (500mL) and the solution was cooled to -78 °C. (Boc)₂O (93 g, 400 mmol) and a catalytic amount of DMAP (1.5 g) was added to the reaction mixture. The reaction was stirred for 12 h at -78 to -30 °C, and quenched with saturated NaHCO₃, extracted with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified...
using silica gel flash chromatography eluting with 6% EtOAc/Hexane to give 46.1 g (201.9 mmol, 60%) of Boc-protected pyranone 1-45: Rf (20% Et₂O/Hexane) = 0.58; [α]₂⁴<sup>D</sup> = -98 (c = 1.0, CH₂Cl₂); <sup>1</sup>H 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); <sup>1</sup>C NMR (150 MHz, CDCl₃) δ 195.5, 151.7, 140.9, 128.2, 89.1, 83.3, 72.0, 27.5, 15.1; CIHRMS: Calculated for [C₁₁H₁₆O₅Na]<sup>+</sup>: 251.0890, Found: 251.0883.

(2R,6R)-6-((4-methoxybenzyl)oxy)-2-methyl-2H-pyran-3(6H)-one (I-45)

A CH₂Cl₂ (34 mL) solution of 1-44 (7.73 g, 33.9 mmol) and 4-methoxybenzyl alcohol (8.48 mL, 67.8 mmol) was cooled to 0 °C, and a solution of Pd₂(dba)₃•CHCl₃ (351 mg, 0.339 mmol, 1 mol %) and PPh₃ (335 mg, 1.36 mmol, 4 mol %) in CH₂Cl₂ (10 mL) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with satd. aqueous NaHCO₃, extracted with ether (3 x 100 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexanes to give pyranone 1-45 (8.00 g, 32.2 mmol, 95%) as a yellow oil: Rf (10% EtOAc/hexanes) = 0.15; [α]₂⁴<sup>D</sup> = -24.7 (c = 1.1, CH₂Cl₂); <sup>1</sup>H NMR (600 MHz, CDCl₃) δ 7.30 (d, J = 7.8 Hz, 2H), 6.90 (J = 7.8 Hz, 2H), 6.86 (dd, J = 10.2, 0.6 Hz, 1H), 6.12 (d, J = 10.2, 0.6 Hz, 1H), 5.37 (d, J = 1.2 Hz, 1H), 4.87 (d, J = 11.4 Hz, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.22 (q, J =
6.6 Hz, 1H), 3.81 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl3) δ 196.8, 159.6, 146.7, 129.9, 128.9, 128.1, 114.0, 94.0, 75.3, 69.8, 55.3, 17.3; CIHRMS Calcd. For [C$_{14}$H$_{16}$O$_4$H]$^+$: 249.1127. Found 249.1122

(2R,6R)-2-((4-methoxybenzyl)oxy)-6-methyl-3,6-dihydro-2H-pyran (I-46)

Pyranone I-45 (7.84 g, 31.6 mmol) was dissolved in CH$_2$Cl$_2$ (31.6 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl$_3$ in methanol solution (12.6 mmol, 31.6 mL) was added in a dropwise fashion, followed by adding NaBH$_4$ (1.20 g, 31.6 mmol). By TLC tracking, the reaction was done after 1.5 h. The reaction mixture was diluted with ether (6 mL), then quenched with water (6 mL), extracted with ether (3 x 60 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give allylic alcohol as a mixture of diastereomers (7.83 g, 31.3 mmol, 99%) as a colorless oil. A flask charged with dry N-Methyl morpholine (NMM) (60 mL), triphenyl phosphine (24.0 g, 91 mmol) was cooled to -30 °C under argon atmosphere. Diisopropyl azodicarboxylate (16.5 mL, 83 mmol) was added and the reaction was stirred for 5 min, allylic alcohol (6.9 g, 27.6 mmol) was added to in a 1 M of NMM (27.6 mL), the resulting reaction mixture was stirred for 10 min, followed by addition of NBSH (18.0 g, 83 mmol). The reaction was stirred at -30 °C for 2 h and was monitored by TLC. Upon consumption of starting material, the reaction was warmed to room temperature and stirred for another 2 h. The reaction mixture was diluted with ether (60 mL) and was quenched with satd. aqueous
NaHCO₃, extracted with ether (3 x 150 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexanes to give product **I-46** (6.07 g, 25.9 mmol, 94%) as a colorless oil: R₇ (20% EtOAc/hexanes) = 0.55; [α]₂⁵⁴ = -106 (c = 1.0, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 7.30 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 7.8 Hz, 2H), 5.67 (dddd, J = 9.6, 2.4, 1.2, 1.2 Hz, 1H), 5.58 (dddd, J = 9.6, 5.4, 2.4, 2.4 Hz, 1H), 4.86 (d, J = 12.0 Hz, 1H), 4.72 (dd, J = 8.4, 3.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.34-4.32 (m, 1H), 3.80 (s, 3H), 2.26-2.20 (m, 1H), 2.16-2.11 (m, 1H), 1.32 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 159.2, 130.9, 130.0, 129.6, 122.5, 113.8, 97.4, 70.6, 69.4, 55.2, 31.0, 21.2; CIHRMS Calcd. For [C₁₄H₁₈O₃Na]⁺: 257.1154. Found 257.1148.

**(2R,3S,4S,6R)-6-((4-methoxybenzyl)oxy)-2-methyltetrahydro-2H-pyran-3,4-diol (I-47)**

![I-47](image)

To a t-butanol, acetone (8.9 mL each, 1:1) solution of pyran **I-46** (2.07 g, 8.85 mmol) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (8.9 mL). Crystalline OsO₄ (22.5 mg, 0.0885 mmol) was added and the reaction was stirred for 12 h. The reaction was quenched with EtOAc and satd. aqueous NaHCO₃. The organic layer was separated and concentrated. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give diol **I-47** (2.17 g, 8.09 mmol, 91%) as a colorless oil: R₇ (50% EtOAc/hexanes) = 0.20; [α]₂¹ = -57.8 (c = 1.0,
\[ \text{CH}_2\text{Cl}_2; \] ¹H NMR (600 MHz, CDCl₃) \( \delta \) 7.27 (d, \( J = 8.4 \) Hz, 2H), 6.87 (d, \( J = 8.4 \) Hz, 2H), 4.88 (dd, \( J = 9.6, 2.4 \) Hz, 1H), 4.81 (d, \( J = 11.4 \) Hz, 1H), 4.50 (d, \( J = 11.4 \) Hz, 1H), 4.11 (d, \( J = 3.0 \) Hz, 1H), 3.80 (s, 3H), 3.74 (dq, \( J = 9.0, 6.6 \) Hz, 1H), 3.33 (dd, \( J = 9.6, 3.6 \) Hz, 1H), 2.15 (brs, 2H), 2.10 (ddd, \( J = 15.0, 2.4, 2.4 \) Hz, 1H), 1.77 (ddd, \( J = 14.0, 11.4, 3.0 \) Hz, 1H), 1.34 (d, \( J = 6.0 \) Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) \( \delta \) 159.3, 129.8, 129.6, 113.8, 96.7, 73.1, 70.2, 69.4, 68.0, 55.3, 37.7, 18.1; CIHRMS Calcd. For [C₁₄H₂₀O₅Na]+: 291.1208. Found 291.1205.

\((2R,3R,4S,6R)-6-((4\text{-methoxybenzyl})\text{oxy})-2\text{-methyltetrahydro-2H-pyran-3,4-diyl diacetate (I-48)}\)

To a solution of I-47 (537 mg, 2.00 mmol) in pyridine (4.5 mL) was added Ac₂O (3.0 mL) at 0 °C. After stirring at room temperature overnight, the reactant was quenched with satd. aqueous NaHCO₃, extracted with EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give I-48 (650 mg, 1.84 mmol, 92%) as a colorless oil: \( R_f \) (20% EtOAc/hexanes) = 0.10; [\( \alpha \)]\( ^{23}_D \) = -14.4 (c = 0.80, CH₂Cl₂); IR (thin film, cm⁻¹) 2937, 1742, 1613, 1514, 1367, 1242, 1224, 1152, 1053, 1007, 820; ¹H NMR (400 MHz, CDCl₃) \( \delta \) 7.27 (d, \( J = 8.8 \) Hz, 2H), 6.88 (d, \( J = 8.0 \) Hz, 2H), 5.46 (dd, \( J = 6.8, 3.2 \) Hz, 1H), 4.88 (dd, \( J = 9.6, 2.8 \) Hz, 1H), 4.84 (d, \( J = 11.2 \) Hz, 1H), 4.62 (dd, \( J = 9.6, 2.8 \) Hz, 1H), 4.50 (d, \( J = 12.0 \) Hz, 1H), 3.95 (dq, \( J = 9.2, 6.4 \) Hz,
1H), 3.80 (s, 3H), 2.08 (s, 3H), 2.05 (ddd, J = 14.0, 2.8, 2.0 Hz, 1H), 2.01 (s, 3H), 1.91 (ddd, J = 14.4, 9.6, 3.2 Hz, 1H), 1.26 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 170.0, 169.9, 159.3, 129.6, 129.5, 113.8, 96.9, 72.5, 70.2, 68.2, 67.3, 55.2, 35.5, 21.0, 20.8, 17.9; ESI-HRMS calc for [C\textsubscript{18}H\textsubscript{24}O\textsubscript{7}Na]\textsuperscript{+}: 375.1414, found 375.1427.

(2R,3R,4S)-6-hydroxy-2-methyltetrahydro-2H-pyran-3,4-diyl diacetate (I-49)

![](image)

To a solution of I-48 (640 mg, 1.82 mmol) in CH\textsubscript{3}CN/H\textsubscript{2}O (18 mL/1.8 mL) was added CAN (2.29 g, 4.18 mmol) at room temperature. After stirring at room temperature for 1 h, the reactant was then poured into satd. aqueous NaHCO\textsubscript{3}, extracted with EtOAc, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give I-49 (405 mg, 1.74 mmol, α:β = 3:1, 96%) as a colorless oil: R\textsubscript{f} (50% EtOAc/hexanes) = 0.32; [α]\textsubscript{D}\textsuperscript{23} = +65.9 (c = 0.90, CH\textsubscript{2}Cl\textsubscript{2}); IR (thin film, cm\textsuperscript{-1}) 3436, 2979, 2938, 1741, 1371, 1247, 1227, 1155, 1054, 947, 859; ^{1}H NMR (400 MHz, CDCl\textsubscript{3}) major isomer (α): δ 5.40-5.37 (m, 1H), 5.09 (dd, J = 9.6, 2.4 Hz, 1H), 4.52 (dd, J = 10.4, 3.2 Hz, 1H), 4.30 (br, 1H), 3.94 (dq, J = 9.6, 6.0 Hz, 1H), 2.05 (s, 3H), 2.03 (ddd, J = 14.0, 3.6, 3.2 Hz, 1H), 1.95 (s, 3H), 1.78 (ddd, J = 14.8, 9.6, 3.2 Hz, 1H), 1.16 (d, J = 6.4 Hz, 3H); minor isomer (β): δ 5.40-5.37 (m, 1H), 5.16 (dd, J = 2.8, 2.8 Hz, 1H), 4.58 (dd, J = 9.6, 3.2 Hz, 1H), 4.30 (br, 1H), 4.28 (dq, J = 8.8, 6.8 Hz, 1H), 2.08 (s, 3H), 2.07-2.03 (m, 1H), 1.95 (s, 3H), 2.00-1.90 (m, 1H), 1.15 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl\textsubscript{3}) major isomer (α): δ
170.0(2C), 92.1, 72.3, 67.9, 67.3, 36.7, 20.7, 20.6, 17.7; minor isomer (β): δ 169.9(2C), 90.4, 72.0, 66.9, 62.0, 33.7, 20.9, 20.8, 17.3; ESI-HRMS calcd for [C₁₀H₁₆O₆Na]⁺: 255.0839, found 255.0850.

(4S,5R,6R)-6-methyltetrahydro-2H-pyran-2,4,5-triyl triacetate (I-50)

To a solution of I-49 (395 mg, 1.70 mmol) in pyridine (3.8 mL) was added DMAP (cat.) and Ac₂O (2.5 mL) at 0 °C. After stirring at room temperature overnight, the reactant was quenched with satd. aqueous NaHCO₃, extracted with EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give I-50 (427 mg, 1.56 mmol, α:β = 1:4, 92%) as a colorless oil: Rₚ(20% EtOAc/hexanes) = 0.17; [α]²⁰D = +55.9 (c = 1.3, CH₂Cl₂); IR (thin film, cm⁻¹) 2982, 2940, 1741, 1434, 1368, 1216, 1145, 1053, 1023, 981; ¹H NMR (400 MHz, CDCl₃) δ major isomer (β): δ 6.04 (dd, J = 9.6, 2.0 Hz, 1H), 5.49 (dd, J = 7.2, 2.8 Hz, 1H), 4.63 (dd, J = 9.6, 2.8 Hz, 1H), 4.09 (dq, J = 8.8, 6.0 Hz, 1H), 2.10 (s, 6H), 2.06-2.04 (m, 1H), 2.02 (s, 3H), 1.99-1.93 (m, 1H), 1.23 (d, J = 5.6 Hz, 3H); minor isomer (α): δ 6.08 (d, J = 3.6 Hz, 1H), 5.32 (dd, J = 6.4, 3.2 Hz), 4.67 (dd, J = 10.4, 3.2 Hz, 1H), 4.30 (dq, J = 9.6, 6.0 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.08-2.06 (m, 1H), 2.04 (s, 3H), 2.00-1.93 (m, 1H), 1.20 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) major isomer (β): δ 170.0(2C), 169.2, 90.5, 71.9, 69.4, 66.6, 34.0, 21.1, 20.9,
20.7, 17.9; minor isomer (α): δ 169.8(2C), 169.4, 90.1, 71.8, 65.8, 64.1, 32.2, 21.1, 21.0, 20.7, 17.4; ESI-HRMS calcd for [C_{12}H_{18}O_7Na]^+: 297.0945, found 297.0961.

(2R,3R,4R,6R)-3-hydroxy-6-((4-methoxybenzyl)oxy)-2-methyltetrahydro-2H-pyran-4-yl 4-nitrobenzoate (I-51)

![I-51](image)

To a THF (45 mL) solution of diol I-47 (2.17 g, 8.09 mmol) at 0 °C was added PPh₃ (3.18 g, 12.2 mmol) and p-nitrobenzoic acid (2.68 g, 16.2 mmol), DIAD (2.6 mL, 13.0 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred for 24 hours. The reaction mixture was diluted with EtOAc (100 mL), quenched with satd. aqueous NaHCO₃, extracted with ether (3 x 100 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/hexanes to give nitrobenzoate I-51 (2.30 g, 5.51 mmol, 68%) as a white solid: Rf (30% EtOAc/hexanes) = 0.40; [α]D²⁴ = -38.2 (c = 0.5, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 8.27 (d, J = 9.0 Hz, 2H), 8.19 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.06 (ddd, J = 11.4, 8.4, 4.8 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.65 (dd, J = 9.6, 1.8 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 3.80 (s, 3H), 3.47 (dd, J = 9.6, 8.4 Hz, 1H), 3.41 (dq, J = 9.0, 6.0 Hz, 1H), 2.39 (ddd, J = 12.6, 5.4, 1.8 Hz, 1H), 1.85 (ddd, J = 12.0, 12.0, 9.6 Hz, 1H), 1.43 (d, J = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 164.8, 159.4, 150.7, 135.0, 130.8, 129.7, 129.2,
To a solution of I-51 (1.25 g, 3.00 mmol) in THF/H$_2$O (35 mL/7 mL) was added LiOH (144 mg, 6.00 mmol) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give I-52 (710 mg, 2.65 mmol, 88%) as a white solid: $R_f$ (50% EtOAc/hexanes) = 0.10; mp: 68–70 °C; [$\alpha$]$^2$D = -60.6 (c = 1.9, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3393, 2933, 1613, 1514, 1453, 1249, 1067, 821; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J$ = 8.4 Hz, 2H), 6.87 (d, $J$ = 8.8 Hz, 2H), 4.80 (d, $J$ = 11.6 Hz, 1H), 4.50 (d, $J$ = 10.8 Hz, 2H), 3.79 (s, 3H), 3.51 (ddd, $J$ = 11.6, 8.0, 4.4 Hz, 1H), 3.29 (br, 2H), 3.22 (dq, $J$ = 8.8, 6.0 Hz, 1H), 3.06 (dd, $J$ = 9.2, 8.8 Hz, 1H), 2.15 (ddd, $J$ = 12.4, 4.8, 1.6 Hz, 1H), 1.63 (ddd, $J$ = 12.4, 11.6, 9.6 Hz, 1H), 1.33 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.3, 129.7, 129.3, 113.8, 98.0, 77.4, 71.6, 71.5, 70.1, 55.2, 38.9, 17.7; EI-HRMS calcd for [C$_{14}$H$_{20}$O$_5$]$^+$: 268.1305, found 268.1308.
(2R,3R,4R,6R)-3,4-bis(benzyloxy)-6-((4-methoxybenzyl)oxy)-2-methyltetrahydro-2H-pyran (I-53)

To a solution of I-52 (623 mg, 2.32 mmol) in dry DMF (12 mL) was added NaH (460 mg, ca. 60% in oil, 11.6 mmol). After stirring at room temperature for 10 min, BnBr (1.0 mL, 5.80 mmol) and TBAI (85 mg, 0.232 mmol) were then added at 0 °C and the mixture was stirred at room temperature for 1 h. The reactant was then poured into satd. aqueous NH₄Cl and extracted with EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10% EtOAc/hexanes to give I-53 (936 mg, 2.09 mmol, 90%) as a colorless oil: Rf (EtOAc/hexanes = 10/1) = 0.21; [α]D²² = -59.3 (c = 1.5, CH₂Cl₂); IR (thin film, cm⁻¹) 2933, 1612, 1513, 1454, 1247, 1092, 1070, 750, 698; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.27 (m, 12H), 6.89 (d, J = 8.8 Hz, 2H), 4.96 (d, J = 10.8 Hz, 1H), 4.83 (d, J = 11.6 Hz, 1H), 4.67 (d, J = 11.2 Hz, 2H), 4.56 (d, J = 11.2 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.48 (ddd, J = 11.2, 8.4, 2.8 Hz, 1H), 3.81 (s, 3H), 3.62 (ddd, J = 14.0, 8.8, 5.2 Hz, 1H), 3.35 (dq, J = 9.6, 6.4 Hz, 1H), 3.17 (dd, J = 8.8, 8.8 Hz, 1H), 2.35 (ddd, J = 12.4, 5.2, 2.0 Hz, 1H), 1.65 (ddd, J = 12.4, 11.6, 9.6 Hz, 1H), 1.38 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.3, 138.5, 138.3, 129.7, 129.5, 128.4(2C), 128.3, 128.0, 127.7, 127.6(2C), 113.8, 98.0, 83.7, 79.3, 75.2, 71.3, 70.0, 55.2, 36.9, 18.2; ESI-HRMS calcd for [C₂₈H₃₂O₅Na]⁺: 471.2142, found 471.2151.
(4R,5R,6R)-4,5-bis(benzyloxy)-6-methyltetrahydro-2H-pyran-2-ol (I-54)

To a solution of I-53 (647 mg, 1.44 mmol) in CH$_3$CN/H$_2$O (14.4 mL/1.44 mL) was added CAN (1.82 g, 3.32 mmol) at room temperature. After stirring at room temperature for 1 h, the reactant was then poured into satd. aqueous NaHCO$_3$ and extracted with EtOAc, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give I-54 (397 mg, 1.21 mmol, α:β = 1.6:1, 84%) as a white solid: R$_f$(20% EtOAc/hexanes) = 0.17; mp: 93~95 °C; [α]$^D_{1}$ = +25.4 (c = 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3354, 2985, 1497, 1397, 1306, 1090, 1029, 997, 750, 694; $^1$H NMR (400 MHz, CDCl$_3$) major isomer (α): δ 7.37-7.28 (m, 10H), 5.33 (d, J = 2.8 Hz, 1H), 4.96 (d, J = 10.4 Hz, 1H), 4.69-4.64 (m, 3H), 4.05-3.96 (m, 2H), 3.15 (dd, J = 9.6, 8.8 Hz, 1H), 2.77 (br, 1H), 2.32 (dd, J = 13.2, 5.6 Hz, 1H), 1.68 (ddd, J = 14.4, 13.2, 3.6 Hz, 1H), 1.28 (d, J = 6.8 Hz, 3H); minor isomer (β): δ 7.37-7.28 (m, 10H), 4.96 (d, J = 10.8 Hz, 1H), 4.75 (dd, J = 9.6, 1.2 Hz, 1H), 4.71-4.60 (m, 3H), 3.64 (ddd, J = 13.2, 8.8, 5.2 Hz, 1H), 3.44 (br, 1H), 3.40 (dq, J = 9.6, 6.0 Hz, 1H), 3.15 (dd, J = 8.8, 8.8 Hz, 1H), 2.41 (ddd, J = 12.8, 5.2, 1.6 Hz, 1H), 1.56 (ddd, J = 12.8, 11.6, 9.6 Hz, 1H), 1.33 (d, J = 5.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) major isomer (α): δ 138.6, 138.5, 128.4, 128.3, 128.0(2C), 127.6(2C), 91.9, 84.2, 76.8, 75.2, 71.8, 67.4, 35.7, 18.2; minor isomer (β): δ 138.3, 138.2, 128.4, 128.3, 128.0(2C), 127.7, 127.6, 93.8, 83.3, 78.9, 75.2, 71.5, 71.4, 38.3, 18.2; ESI-HRMS calcd for [C$_2$$_9$H$_{24}$O$_4$Na]$^+$: 351.1567, found 351.1580.
(4R,5R,6R)-4,5-bis(benzyloxy)-6-methyltetrahydro-2H-pyran-2-ol (I-55)

To a solution of I-54 (460 mg, 1.40 mmol) in pyridine (3.2 mL) was added Ac₂O (2.1 mL) at 0 °C. After stirring at room temperature overnight, the reactant was quenched with satd. aqueous NaHCO₃, extracted with EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10% EtOAc/hexanes to give I-55 (515 mg, 1.39 mmol, α:β = 2.8:1, 99%) as a colorless oil: Rᵋ(EtOAc/hexanes = 10/1) = 0.32; [α]ᵋ²²D = +48.0 (c = 0.9, CH₂Cl₂); IR (thin film, cm⁻¹) 2932, 1750, 1454, 1366, 1275, 1260, 1100, 1028, 971, 750, 698; ¹H NMR (400 MHz, CDCl₃) major isomer (α): δ 7.37-7.30 (m, 10H), 6.18 (d, J = 2.4 Hz, 1H), 4.99 (d, J = 10.0 Hz, 1H), 4.71-4.68 (m, 3H), 3.95 (ddd, J = 13.2, 8.8, 4.8 Hz, 1H), 3.84 (dq, J = 10.0, 6.8 Hz, 1H), 3.21 (dd, J = 9.6, 8.8 Hz, 1H), 2.30 (ddd, J = 14.0, 5.2, 1.6 Hz, 1H), 2.07 (s, 3H), 1.81 (ddd, J = 14.4, 13.2, 3.2 Hz, 1H), 1.32 (d, J = 5.6 Hz, 3H); minor isomer (β): δ 7.37-7.30 (m, 10H), 5.69 (dd, J = 10.0, 1.6 Hz, 1H), 4.97 (d, J = 11.2 Hz, 1H), 4.72-4.62 (m, 3H), 3.71 (ddd, J = 14.0, 8.8, 5.6 Hz, 1H), 3.50 (dq, J = 9.2, 5.6 Hz, 1H), 3.18 (dd, J = 8.8, 8.8 Hz, 1H), 2.39 (ddd, J = 12.4, 4.8, 2.0 Hz, 1H), 2.12 (s, 3H), 1.77 (ddd, J = 12.8, 12.0, 10.0 Hz, 1H), 1.36 (d, J = 5.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) major isomer (α): δ 169.4, 138.3, 138.2, 128.4(2C), 128.0(2C), 127.6, 127.6, 91.7, 83.5, 76.6, 75.3, 71.7, 69.7, 34.4, 21.0, 18.2; minor isomer (β): δ 169.1, 138.2, 138.0, 128.4(2C), 128.0(2C), 127.7, 127.6, 91.8, 83.0, 78.7, 75.2, 72.3, 71.6, 35.6, 21.0, 18.0; ESI-HRMS calcd for [C₂₂H₂₆O₅Na]⁺: 393.1672, found 393.1688.
1-hydroxy-5-((2-methylallyl)oxy)anthracene-9,10-dione (I-31)

A mixture of 1,5-dihydroxyanthracene-9,10-dione (7.20 g, 30.0 mmol), methallyl chloride (4.40 mL, 40.5 mmol), anhydrous potassium carbonate (22.9 g, 166 mmol), and potassium iodide (1.76 g, 10.5 mmol) in DMF (400 mL) was stirred at 75 °C for 7 h under argon. The mixture was filtered and the purple solid was washed with acetone. The solvent removed under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10% EtOAc/hexanes to give ether I-31 (3.70 g, 12.6 mmol, 42%) as an orange solid: Rf (20% EtOAc/hexanes) = 0.50; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 12.45 (s, 1H), 7.94 (dd, \(J = 7.8, 1.2\) Hz, 1H), 7.76 (dd, \(J = 7.8, 1.2\) Hz, 1H), 7.68-7.62 (m, 2H), 7.31 (d, \(J = 8.4\) Hz, 1H), 7.22 (dd, \(J = 8.4, 1.2\) Hz, 1H), 5.35 (s, 1H), 5.09 (s, 1H), 4.63 (s, 2H), 1.92 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 188.6, 181.3, 161.9, 159.5, 139.6, 136.8, 135.3, 135.0, 134.8, 122.8, 121.7, 119.8, 119.5, 119.3, 115.6, 113.3, 72.8, 19.3 CIHRMS Calcd. For [C\(_{14}\)H\(_{16}\)O\(_4\)H]\(^+\): 249.1127. Found 249.1122

1,5-dihydroxy-2-(2-methylallyl)anthracene-9,10-dione (I-32)

![Chemical Structure](image)

A solution of the ether **I-31** (883 mg, 3.00 mmol) in DMF (100 mL) was added to a heated (90 °C) solution of sodium dithionite (1.04 g, 6.00 mmol) in water (200 mL) and DMF (100 mL) under argon, and the mixture was heated under reflux for 3 h. Sodium hydroxide (0.30 g, 7.50 mmol) was added and the refluxing continued for a further 0.75 h. The mixture was cooled to room temperature, and then it was extracted with EtOAc (200 mL) for three times. The combined organic layers were washed with water for five times, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10% EtOAc/hexanes to give diphenol **I-32** (790 mg, 2.68 mmol, 89%) as an orange solid: $R_f$ (10% EtOAc/hexanes) = 0.35; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 13.05 (s, 1H), 12.70 (s, 1H), 7.85 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.81 (d, $J = 7.2$ Hz, 1H), 7.68 (dd, $J = 7.8$, 7.8 Hz, 1H), 7.57 (d, $J = 7.8$ Hz, 1H), 7.32 (dd, $J = 8.4$, 0.6 Hz, 1H), 4.90 (s, 1H), 4.74 (s, 1H), 3.49 (s, 2H), 1.78 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 188.2, 187.8, 162.7, 161.2, 143.0, 137.0, 136.5, 133.3, 131.4, 124.8, 119.3, 119.2, 119.0, 116.1, 115.5, 112.9, 37.4, 22.5.

1,5-bis(benzyloxy)-2-(2-methylallyl)anthracene-9,10-dione (I-33)

Benzyl bromide (1.07 mL, 9.00 mmol) and potassium carbonate (4.15 g, 30.0 mmol) were added to a solution of diphenol I-32 (883 mg, 3.00 mmol) in acetone (150 mL), and the mixture was heated at reflux overnight. The mixture was filtered and concentrated. The crude product was purified using silica gel flash chromatography eluting with 50% CH$_2$Cl$_2$/hexanes to give ether I-33 (1.26 g, 2.66 mmol, 89%) as a yellow solid: $R_f$ (20% EtOAc/hexanes) = 0.52; mp: 109~110 °C; IR (thin film, cm$^{-1}$) 1669, 1584, 1573, 1452, 1261, 1022, 697; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 7.8$ Hz, 1H), 7.94 (dd, $J = 7.8$, 0.6 Hz, 1H), 7.66-7.60 (m, 6H), 7.44-7.30 (m, 7H), 5.34 (s, 2H), 5.04 (s, 2H), 4.88 (s, 1H), 4.65 (s, 1H), 3.44 (s, 2H), 1.70 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 182.9, 182.2, 158.7, 156.9, 143.8, 141.0, 137.3, 137.2, 136.3, 136.1, 135.9, 134.7, 128.7, 128.5, 128.4, 128.1, 127.9, 126.8, 125.4, 123.4, 121.6, 120.1, 119.0, 113.1, 76.2, 71.0, 37.8, 22.6; ESI-HRMS calcd for [C$_{32}$H$_{26}$O$_4$Na]$^+$: 497.1723, found 497.1727.

(R)-1,5-bis(benzyloxy)-2-(2,3-dihydroxy-2-methylpropyl)anthracene-9,10-dione (I-33)
A round-bottom flask was charged with $t$-BuOH (37 mL), water (37 mL), $K_3$Fe(CN)$_6$ (3.65 g, 11.1 mmol), $K_2$CO$_3$ (1.53 g, 11.1 mmol), (DHQ)$_2$DPP (688 mg, 0.738 mmol), and OsO$_4$ (37.0 mg, 0.148 mmol). After the mixture was stirred at room temperature for 5 min, the mixture was cooled to 0 °C. Unsaturated ether I-33 (1.75 g, 3.69 mmol) was added at once, and the heterogeneous slurry was stirred vigorously for 6 h at 0 °C and then at room temperature overnight. Na$_2$SO$_3$ (2.00 g) was added, and the mixture was stirred for 1 h. EtOAc (20 mL) was added, and the aqueous layer was extracted with EtOAc for three times. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give diol I-34 (1.84 g, 3.62 mmol, 98%) as a yellow solid: $R_f$ (50% EtOAc/hexanes) = 0.24; mp: 129~130 °C; $[\alpha]_D^{26} = +6.9$ ($c = 0.83$, CH$_2$Cl$_2$, 88% ee); IR (thin film, cm$^{-1}$) 3453, 1669, 1585, 1570, 1264, 1015, 697; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.12 (d, $J = 7.8$ Hz, 1H), 7.94 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.68-7.60 (m, 6H), 7.46-7.32 (m, 7H), 5.34 (s, 2H), 5.08 (d, $J = 10.2$ Hz, 1H), 5.05 (d, $J = 10.2$ Hz, 1H), 3.29 (d, $J = 10.8$ Hz, 1H), 3.24 (d, $J = 11.4$ Hz, 1H), 2.97 (d, $J = 13.2$ Hz, 1H), 2.83 (d, $J = 13.2$ Hz, 1H), 2.27 (br, 2H), 1.07 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 182.6, 181.9, 158.7, 156.6, 138.7, 138.2, 137.1, 136.4, 136.2, 136.1, 134.9, 128.9, 128.8(2C), 128.7, 127.9, 126.8, 125.2, 123.7, 121.4, 120.2, 119.1, 76.9, 73.6, 71.0, 69.0, 39.2, 23.5; ESI-HRMS calcd for [C$_{32}$H$_{28}$O$_6$Na]$^+$: 531.1778, found 531.1778. The ee value was determined by the use of Mosher’s reagent.
(R)-3-(1,5-bis(benzyloxy)-9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-hydroxy-2-methylpropyl 4-methylbenzenesulfonate (I-35)

To a solution of diol I-34 (1.83 g, 3.60 mmol) in dry CH₂Cl₂ (36.0 mL) were added dibutyltin oxide (~1 mg), p-toluenesulfonyl chloride (1.03 g, 5.40 mmol), triethylamine (0.75 mL, 5.40 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. After completion of reaction the mixture was quenched with water. The layers were separated, and the water layer was extracted with CH₂Cl₂ for 3 times. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 3% EtOAc/CH₂Cl₂ to give I-35 (2.18 g, 3.29 mmol, 91%) as a yellow solid: Rf (20% EtOAc/hexanes) = 0.14; mp: 174~175 °C; [α]ᵢᴰ² = +13.6 (c = 0.95, CH₂Cl₂); IR (thin film, cm⁻¹) 3492, 2930, 1670, 1586, 1265, 1176, 984, 843; ¹H NMR (600 MHz, CDCl₃) δ 8.04 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 7.8, 1.2 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.66 (dd, J = 8.4, 7.8 Hz, 1H), 7.62-7.54 (m, 5H), 7.44-7.30 (m, 9H), 5.35 (s, 2H), 5.07 (d, J = 10.8 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 3.76 (d, J = 9.6 Hz, 1H), 3.69 (d, J = 9.6 Hz, 1H), 3.19 (br, 1H), 2.99 (d, J = 13.8 Hz, 1H), 2.99 (d, J = 13.8 Hz, 1H), 2.76 (d, J = 13.8 Hz, 1H), 2.42 (s, 3H), 1.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 182.6, 181.8, 158.8, 156.7, 145.0, 138.0, 137.4, 137.2, 136.7, 136.3, 136.2, 134.9, 132.5, 129.9, 128.9, 128.8, 128.7, 128.6,
ESI-HRMS calcd for [C\textsubscript{39}H\textsubscript{34}O\textsubscript{8}SNa]\textsuperscript{+}: 685.1867, found 685.1872.

(R)-1,5-bis(benzyloxy)-2-((2-methyloxiran-2-yl)methyl)anthracene-9,10-dione (I-36)

![Chemical Structure](image)

To a solution of I-35 (331 mg, 0.50 mmol) in dry THF (50 mL) was added NaH (100 mg, ca. 60% in oil, 2.50 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. After completion of reaction the mixture was quenched with water. The layers were separated, and the water layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} for three times. The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give epoxide I-36 (227 mg, 0.463 mmol, 92%) as a yellow solid: R\textsubscript{f} (20% EtOAc/hexanes) = 0.26; mp: 114-115 °C; [\alpha]\textsubscript{D}\textsuperscript{21} = -27.9 (c = 0.26, CH\textsubscript{2}Cl\textsubscript{2}); IR (thin film, cm\textsuperscript{-1}) 2932, 1670, 1585, 1452, 1262, 1022, 699; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta\) 8.09 (d, \(J = 8.4\) Hz, 1H), 7.93 (dd, \(J = 7.8, 1.2\) Hz, 1H), 7.72 (d, \(J = 7.8\) Hz, 1H), 7.64 (dd, \(J = 8.4, 7.8\) Hz, 1H), 7.61-7.58 (m, 4H), 7.44-7.31 (m, 7H), 5.34 (s, 2H), 5.09 (d, \(J = 10.8\) Hz, 1H), 5.00 (d, \(J = 10.2\) Hz, 1H), 3.00 (d, \(J = 14.4\) Hz, 1H), 2.96 (d, \(J = 14.4\) Hz, 1H), 2.55 (d, \(J = 4.8\) Hz, 1H), 2.54 (d, \(J = 4.8\) Hz, 1H), 1.25 (s, 3H); \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) \(\delta\) 182.8, 182.0, 158.7, 157.0, 138.3, 137.2, 137.0, 136.9, 136.3, 136.2, 134.8, 128.7, 128.6, 128.5, 128.2, 127.9, 126.8, 125.2, 123.3, 121.5, 120.1, 119.0,
A six-chamber stainless-steel high-pressure reactor was dried overnight under vacuum at 100 °C. In a glove box, 8 mL vials equipped with Teflon-coated magnetic stir bars were charged with 20.0 mg (0.0408 mmol) of epoxide I-36 and 2.0 mL of a 0.0020 M stock solution of [Cl(TPP)Al(THF)]\textsuperscript{+}[Co(CO)\textsubscript{4}]\textsuperscript{-} (4.4 mg, 0.0040 mmol, 10 mol %) in THF. The vials were then placed in a custom-made 6-well high-pressure reactor. The reactor was sealed taken out of the glove box and pressured with carbon monoxide to 900 psi. The reactor was then sealed again and the reaction mixtures were stirred for 20 h at 40 °C. The reactor was then cooled to ambient temperature and carefully vented in a well-ventilated hood. The crude reaction mixtures were concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give β-lactone I-37 as a yellow solid (14.8 mg, 0.0285 mmol, 70%). Residual amounts of ethylacetate and hexanes were removed by suspending the powder in methanol and subsequently removing all volatiles under vacuum at 22 °C. R\textsubscript{f} (20% EtOAc/hexanes) = 0.11; mp: 134–135 °C; [\alpha]\textsubscript{D}\textsuperscript{24} = -10.2 (c = 1.0, CH\textsubscript{2}Cl\textsubscript{2}); IR (thin film, cm\textsuperscript{-1}) 2926, 1818, 1669, 1585, 1261, 734, 696; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 8.11
(d, J = 8.0 Hz, 1H), 7.92 (d, J = 6.8 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 8.4, 8.0 Hz, 1H), 7.61-7.59 (m, 2H), 7.52 (dd, J = 8.0, 1.6 Hz, 2H), 7.44-7.32 (m, 7H), 5.34 (s, 2H), 5.08 (d, J = 10.8 Hz, 1H), 5.04 (d, J = 11.2 Hz, 1H), 3.30 (d, J = 16.4 Hz, 1H), 3.18 (d, J = 14.0 Hz, 1H), 3.10 (d, J = 14.4 Hz, 1H), 3.04 (d, J = 16.8 Hz, 1H), 1.50 (s, 3H);

\( ^{13} \text{C NMR (100 MHz, CDCl}_3 \) \( \delta \) 182.7, 181.7, 167.2, 158.7, 157.0, 137.5, 137.0, 136.9, 136.7, 136.1(2C), 134.9, 128.7(2C), 128.5, 128.4, 127.9, 126.7, 125.2, 123.5, 121.3, 120.0, 119.0, 77.8, 76.9, 70.9, 47.3, 38.5, 24.8; ESI-HRMS calcd for \([\text{C}_{33}\text{H}_{26}\text{O}_6\text{Na}]^+\): 541.1622, found 541.1625.

(R)-methyl 4-(1,5-bis(benzyloxy)-9,10-dioxo-9,10-dihydroanthracen-2-yl)-3-hydroxy-3-methylbutanoate (I-56)

![Structure I-56](image)

To a solution of I-37 (52 mg, 0.10 mmol) in methanol (1 mL) was added \( \text{K}_2\text{CO}_3 \) (18 mg, 0.13 mmol), and the reaction was stirred at room temperature for 1 h. The mixture was quenched with water (5 mL) and extracted with \( \text{CH}_2\text{Cl}_2 \) for three times. The combined organic layers were dried over \( \text{Na}_2\text{SO}_4 \) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give ester I-56 (53 mg, 0.096 mmol, 96%) as a yellow solid: \( \text{R}_f \) (20% EtOAc/hexanes) = 0.10; mp: 34–36 °C; \([\alpha]_{D}^{22} = +0.30 \ (c = 1.1, \text{CH}_2\text{Cl}_2)\); IR (thin film, cm\(^{-1}\)) 3499, 2927, 1731, 1670, 1585, 1452, 1262, 1015; \( ^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta \)
8.10 (d, \( J = 8.0 \) Hz, 1H), 7.92 (d, \( J = 6.8 \) Hz, 1H), 7.76 (d, \( J = 8.0 \) Hz, 1H), 7.66-7.57 (m, 5H), 7.44-7.30 (m, 7H), 5.34 (s, 2H), 5.03 (s, 2H), 3.85 (br, 1H), 3.60 (s, 3H), 2.97 (d, \( J = 13.2 \) Hz, 1H), 2.93 (d, \( J = 13.2 \) Hz, 1H), 2.45 (d, \( J = 16.4 \) Hz, 1H), 2.41 (d, \( J = 16.0 \) Hz, 1H), 1.20 (s, 3H); \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 182.7, 182.0, 173.1, 158.6, 157.0, 138.6, 138.4, 137.2, 136.8, 136.4, 136.2, 134.8, 128.7, 128.6, 128.4, 128.3, 127.9, 126.7, 125.1, 123.2, 121.4, 120.1, 119.0, 76.6, 71.7, 71.0, 51.5, 44.4, 41.3, 27.3; ESI-HRMS calcd for [C\(_{34}\)H\(_{31}\)O\(_7\)]\(^+\): 551.2070, found 551.2072.

\((R)\)-methyl 4-(1,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-3-hydroxy-3 methylbutanoate (I-57)

To a solution of ester I-56 (33 mg, 0.0599 mmol) in ethanol (0.4 mL) were added 1,4-cyclohexadiene (0.1 mL) and 10% Pd-C (10 mg), and the mixture was stirred at reflux for 2 h. The reactant was filtered on a short pad of silica. After concentration under reduced pressure, the crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give I-57 (19 mg, 0.0513 mmol, 86%) as a yellow solid: \( R_f \) (20% EtOAc/hexanes) = 0.33; mp: 107-109 °C; \([\alpha]_{D}^{22} = -11.8 \) (c = 1.0, CHCl\(_3\)); IR (thin film, cm\(^{-1}\)) 3490, 2924, 1726, 1627, 1432, 1372, 1315, 1259, 792; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 13.17 (s, 1H), 12.65 (s, 1H), 7.82 (dd, \( J = 7.6, 1.2 \) Hz, 1H), 7.79 (d, \( J = 8.0 \) Hz, 1H), 7.69 (d, \( J = 7.6 \) Hz, 1H), 7.66 (dd, \( J = 8.0, 8.0 \) Hz, 1H), 7.31 (dd, \( J = 8.4, 1.2 \) Hz,
1H), 3.90 (br, 1H), 3.71 (s, 3H), 3.10 (d, J = 13.6 Hz, 1H), 3.03 (d, J = 13.2 Hz, 1H), 2.59 (d, J = 16.0 Hz, 1H), 2.54 (d, J = 16.0 Hz, 1H), 1.30 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 188.3, 187.7, 173.3, 162.7, 161.3, 139.7, 136.6, 134.6, 133.1, 131.7, 125.0, 119.3, 118.8, 116.1, 115.5, 71.8, 51.8, 44.3, 40.4, 27.2. ESI-HRMS calcd for [C\(_{20}\)H\(_{19}\)O\(_7\)]\(^+\): 371.1125, found 371.1137.

\((R)-\)methyl 4-(1,5-bis(benzyloxy)-9,10-dimethoxyanthracen-2-yl)-3-hydroxy-3-methylbutanoate (I-58)

A solution of Na\(_2\)S\(_2\)O\(_4\) (398 mg, 2.28 mmol) in degassed water (4.60 mL) was added to a suspension of anthraquinone I-56 (63 mg, 0.114 mmol) and nBu\(_4\)NBr (17 mg, 0.057 mmol) in degassed THF (2 mL). After stirring for 30 min at room temperature, 50% degassed aqueous KOH (0.35 mL) was added to the mixture, which was stirred for 10 min. After adding Me\(_2\)SO\(_4\) (0.034 mL, 0.342 mmol) and stirring for 30 min, the reaction was stopped by adding water at 0 °C and the mixture was extracted with CH\(_2\)Cl\(_2\). The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give I-58 (57 mg, 0.0982 mmol, 86%) as a brown oil: R\(_f\) (20% EtOAc/hexanes) = 0.43; [\(\alpha\)]\(_D\)\(^{26}\) = -1.7 (c = 1.5, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) 3495, 2929, 1732, 1619, 1524, 1449, 1357, 1260, 1043; \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 8.18 (d, J = 9.6 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 7.2 Hz,
2H), 7.59 (d, J = 7.2 Hz, 2H), 7.48-7.36 (m, 8H), 6.91 (d, J = 7.6 Hz, 1H), 5.30 (s, 2H), 5.01 (d, J = 10.0 Hz, 1H), 4.96 (d, J = 10.4 Hz, 1H), 4.24 (br, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.57 (s, 3H), 3.15 (d, J = 7.2 Hz, 1H), 2.59 (d, J = 15.6 Hz, 1H), 2.50 (d, J = 15.6 Hz, 1H), 1.33 (s, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 173.1, 155.2, 151.3, 149.2, 146.9, 137.4, 137.0, 129.5, 128.7(2C), 128.5, 128.4, 128.0, 127.9, 127.8, 127.6, 127.0, 125.3, 119.9, 119.4, 118.5, 115.7, 105.8, 76.8, 72.5, 71.2, 63.6, 63.3, 51.4, 44.3, 41.8, 27.5; ESI-HRMS calcd for [C\textsubscript{36}H\textsubscript{36}O\textsubscript{7}Na]+: 603.2353, found 603.2357.

(R)-methyl 4-(1,5-dihydroxy-9,10-dimethoxyanthracen-2-yl)-3-hydroxy-3-methylbutanoate (I-59)

![Chemical Structure](image)

To a solution of I-58 (58 mg, 0.0999 mmol) in ethanol (0.4 mL) were added 1,4-cyclohexadiene (0.1 mL) and 10% Pd-C (10 mg), and the mixture was stirred at reflux for 8 h. The reactant was filtered on a short pad of silica. After concentration under reduced pressure, the crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give I-59 (31 mg, 0.0774 mmol, 77%) as a yellow oil: R\textsubscript{f} (20% EtOAc/hexanes) = 0.20; \([\alpha]^{21}_D = -6.8 (c = 0.70, CHCl\textsubscript{3} ); IR \) (thin film, cm\(^{-1}\)) 3334, 2987, 1730, 1361, 1276, 1261, 1020,764; \textsuperscript{1}H NMR (400 MHz, (CD\textsubscript{3})\textsubscript{2}CO) \( \delta \) 10.14 (s, 1H), 9.75 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.39 (dd, J = 8.8, 7.6 Hz, 1H), 6.82 (d, J = 7.2 Hz, 1H), 4.20 (brs, 1H), 4.12 (s, 3H), 4.11 (s, 3H), 3.64 (s, 3H), 3.13 (d, J = 13.6 Hz, 1H), 3.09 (d, J = 14.0 Hz, 1H), 2.61 (d, J =
15.2 Hz, 1H), 2.55 (d, J = 15.6 Hz, 1H), 1.34 (s, 3H); $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO) δ 173.1, 154.5, 151.5, 148.9, 148.6, 132.3, 127.5, 126.3, 125.4, 118.4, 117.2, 116.9, 113.2, 112.4, 109.0, 73.1, 64.6, 64.5, 51.4, 45.5, 41.7, 27.4; ESI-HRMS calcd for [C$_{22}$H$_{25}$O$_7$]$^+$: 401.1595, found 401.1598.

(R)-methyl 4-(6-((2R,4R,5R,6R)-4,5-bis(benzyl oxy)-6-methyltetrahydro-2H-pyran-2-yl)-1,5-dihydroxy-9,10-dimethoxyanthracen-2-yl)-3-hydroxy-3-methylbutanoate (I-60)

![I-60](image)

To a stirred mixture of Cp$_2$HfCl$_2$ (208 mg, 0.548 mmol), AgClO$_4$ (226 mg, 1.09 mmol) and powdered molecular sieves 4Å (1.60 g) in CH$_2$Cl$_2$ (2.0 mL) was added I-59 (73 mg, 0.182 mmol) in CH$_2$Cl$_2$ (2.0 mL) and I-55 (135 mg, 0.364 mmol) in CH$_2$Cl$_2$ (3.0 mL) at -78 °C. The temperature was then gradually raised to 0 °C during 1 h. The reactant was then quenched with satd. aqueous NaHCO$_3$. The mixture was filtered through Celite, extracted with CH$_2$Cl$_2$, and dried over Na$_2$SO$_4$. After concentration under reduced pressure, the crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give I-60 (62 mg, 0.0872 mmol, 48%) as a yellow oil: $R_f$ (20% EtOAc/hexanes) = 0.13; $[\alpha]_{D}^{20} = +40.4$ (c = 1.2, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3320, 2926, 1732, 1533, 1453, 1417, 1362, 1259, 1112, 1004, 749; $^1$H NMR (400 MHz, CDCl$_3$) δ 10.18 (s, 1H, OH), 10.13 (s, 1H, OH), 7.70 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 9.6 Hz, 1H), 7.41-7.27 (m, 11H), 5.12 (dd, J = 12.0, 2.4 Hz, 1H),
5.05 (d, J = 11.2 Hz, 1H), 4.76 (d, J = 10.4 Hz, 2H), 4.68 (d, J = 12.0 Hz, 1H), 4.10 (s, 3H), 4.07 (s, 3H), 3.92 (dd, J = 14.0, 8.8, 5.2 Hz, 1H), 3.70 (s, 1H, OH), 3.69 (s, 3H), 3.65 (dq, J = 9.6, 6.0 Hz, 1H), 3.30 (dd, J = 8.8, 8.8 Hz, 1H), 3.18 (d, J = 14.0 Hz, 1H), 3.10 (d, J = 14.0 Hz, 1H), 2.66 (d, J = 11.6 Hz, 1H), 2.59 (d, J = 11.6 Hz, 1H), 2.56 (ddd, J = 12.4, 5.2, 2.0 Hz, 1H), 1.78 (ddd, J = 12.4, 11.6, 10.0 Hz, 1H), 1.43 (d, J = 5.6 Hz, 3H), 1.38 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 173.4, 150.8, 148.8, 148.3, 147.8, 138.6, 138.6, 131.4, 128.4(2C), 128.1, 127.7, 127.6(2C), 127.5, 125.0, 124.7, 120.7, 117.1, 116.2, 115.9, 112.8, 112.0, 84.2, 81.2, 75.8, 75.3, 72.7, 71.3, 70.8, 64.1, 64.0, 51.5, 44.4, 41.1, 37.5, 27.4, 18.7; ESI-HRMS calcd for [C42H47O10]+: 711.3164, found 711.3169.

**Vineomycinone B2 methyl ester (I-4)**

![Vineomycinone B2 methyl ester (I-4)](image)

To a solution of I-60 (29 mg, 0.0408 mmol) in CH2Cl2 (5.5 mL) was added BBr3 (275 mg, 1.10 mmol) in CH2Cl2 (0.9 mL) at -78 °C. After stirring at -78 °C for 25 min, the reactant was then quenched with satd. aqueous NaHCO3. After stirring for 5 min, the mixture was acidified with 1N aqueous HCl, extracted with CH2Cl2 and dried over Na2SO4. After concentration under reduced pressure, the crude product was purified using silica gel flash chromatography eluting with EtOAc to give vineomycinone B2 methyl ester I-4 (18 mg, 0.0360 mmol, 88%). Recrystallization from CHCl3-hexanes gave I-4 as orange needles: RF (EtOAc) = 0.52; [α]D20 = +109 (c = 0.27, dioxane); IR (thin film, cm⁻¹) 3392,
2923, 1726, 1626, 1581, 1476, 1374, 1260, 1070, 1020, 792; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 13.22 (s, 1H), 13.10 (s, 1H), 7.92 (d, \(J = 8.4\) Hz, 1H), 7.86 (d, \(J = 8.0\) Hz, 1H), 7.81 (d, \(J = 8.0\) Hz, 1H), 7.69 (d, \(J = 7.2\) Hz, 1H), 4.94 (dd, \(J = 11.6, 1.6\) Hz, 1H), 3.93 (s, 1H, OH), 3.86 (ddd, \(J = 12.0, 8.0, 5.2\) Hz, 1H), 3.72 (s, 3H), 3.53 (dq, \(J = 8.8, 6.0\) Hz, 1H), 3.22 (dd, \(J = 9.2, 8.8\) Hz, 1H), 3.11 (d, \(J = 13.2\) Hz, 1H), 3.02 (d, \(J = 13.2\) Hz, 1H), 2.60 (d, \(J = 16.4\) Hz, 1H), 2.54 (d, \(J = 16.4\) Hz, 1H), 2.52 (ddd, \(J = 12.4, 5.2, 2.0\) Hz, 1H), 2.34 (br, 1H, OH), 2.26 (br, 1H, OH), 1.48 (ddd, \(J = 12.4, 11.6, 11.6\) Hz, 1H), 1.42 (d, \(J = 6.0\) Hz, 3H), 1.30 (s, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 188.2, 188.1, 173.3, 161.3, 158.9, 139.6, 138.2, 134.6, 133.3, 131.8, 131.7, 119.4, 118.9, 115.6, 115.4, 78.1, 76.0, 73.1, 71.8, 71.2, 51.8, 44.3, 40.4, 39.4, 27.2, 18.1; ESI-HRMS calcd for [C\textsubscript{26}H\textsubscript{29}O\textsubscript{10}]\textsuperscript{+}: 501.1755, found 501.1768.

**(R)-methyl 4-(1,5-bis(methoxymethoxy)-9,10-dioxo-9,10-dihydroanthracen-2-yl)-3-(methoxymethoxy)-3-methylbutanoate (I-61)**

To a solution of I-57 (111 mg, 0.300 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (3.0 mL) were added DIPEA (0.522 mL, 3.00 mmol) and MOMCl (0.139 mL, 1.80 mmol), and the mixture was stirred at room temperature for 2 days. The reactant was quenched with satd. NaHCO\textsubscript{3} and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic layer was then washed with 1N aqueous HCl and dried over Na\textsubscript{2}SO\textsubscript{4}. After concentration under reduced pressure, the crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give
I-61 (143 mg, 0.284 mmol, 95%) as a yellow oil: R$_f$ (20% EtOAc/hexanes) = 0.09; $[\alpha]_D^{22}$ = -31.8 (c = 0.73, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2984, 1735, 1670, 1586, 1439, 1264, 1154, 734; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.98 (d, $J = 8.4$ Hz, 1H), 7.90 (d, $J = 7.2$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.65 (dd, $J = 8.4$, 8.0 Hz, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 5.35 (s, 2H), 5.16 (d, $J = 6.8$ Hz, 1H), 5.08 (d, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 8.0$ Hz, 1H), 4.74 (d, $J = 8.0$ Hz, 1H), 3.66 (s, 3H), 3.61 (s, 3H), 3.54 (s, 3H), 3.34 (d, $J = 8.0$ Hz, 1H), 3.28 (s, 3H), 3.20 (d, $J = 13.2$ Hz, 1H), 2.63 (d, $J = 14.0$ Hz, 1H), 2.56 (d, $J = 13.6$ Hz, 1H), 1.34 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 182.7, 182.2, 171.0, 157.1, 156.5, 138.7, 138.3, 136.9, 135.9, 134.7, 124.1, 122.8, 121.8, 121.5, 121.0, 102.2, 95.1, 91.1, 77.6, 57.8, 56.5, 55.4, 51.5, 44.2, 39.5, 23.1. ESI-HRMS calcd for [C$_{26}$H$_{30}$O$_{10}$Na]$^+$: 525.1731, found 525.1744.

(R)-methyl 4-(9,10-dimethoxy-1,5-bis(methoxymethoxy)anthracen-2-yl)-3-(methoxymethoxy)-3-methylbutanoate (I-62)

![Chemical structure of I-62](image)

A solution of Na$_2$S$_2$O$_4$ (2.24 g, 12.9 mmol) in degassed water (49 mL) was added to a suspension of anthraquinone I-61 (650 mg, 1.29 mmol) and nBu$_4$NBr (103 mg, 0.32 mmol) in degassed THF (22 mL). After stirring at room temperature for 2 h, 50% degassed aqueous KOH (1.94 mL) was added to the mixture, which was stirred for 10 min. After adding Me$_2$SO$_4$ (0.33 mL, 3.23 mmol) and stirring for 30 min, the reaction
was stopped by adding water at 0 °C and the mixture was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give I-62 (433 mg, 0.813 mmol, 63%) as a brown oil: Rf (20% EtOAc/hexanes) = 0.18; [α]_D^{23} = -10.8 (c = 0.40, CH₂Cl₂); IR (thin film, cm⁻¹) 2929, 1736, 1449, 1359, 1294, 1152, 1033, 972, 924, 810, 765; ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.35 (dd, J = 8.8, 8.0 Hz, 1H), 7.09 (d, J = 6.4 Hz, 1H), 5.40 (s, 2H), 5.12 (d, J = 6.8 Hz, 1H), 5.09 (d, J = 6.4 Hz, 1H), 4.90 (d, J = 7.2 Hz, 1H), 4.83 (d, J = 8.0 Hz, 1H), 4.01 (s, 3H), 3.90 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H), 3.61 (s, 3H), 3.43-3.30 (m, 2H), 3.35 (s, 3H), 2.77 (d, J = 14.8 Hz, 1H), 2.63 (d, J = 14.8 Hz, 1H), 1.49 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 153.1, 150.1, 148.6, 146.9, 129.6, 128.4, 127.9, 127.3, 125.2, 119.3, 118.6, 118.4, 116.8, 110.0, 101.2, 96.0, 91.2, 78.5, 63.3, 62.7, 58.0, 56.5, 55.3, 51.4, 44.1, 40.0, 23.3. ESI-HRMS calcd for [C₂₈H₃₇O₁₀]⁺: 533.2381, found 533.2391.

(R)-methyl 4-(1,5-dihydroxy-9,10-dimethoxyanthracen-2-yl)-3-hydroxy-3-methylbutanoate (I-59)

![I-59](image)

To a solution of I-62 (74 mg, 0.139 mmol) and EtSH (0.21 mL) in CH₂Cl₂ (1.7 mL) was added BF₃•Et₂O (0.17 mL, 1.39 mmol) at -78 °C. The mixture was stirred at -78 °C for 30
min. Then the temperature was gradually warmed to -30 °C during 30 min. The reactant was quenched with satd. NaHCO₃, extracted with EtOAc and dried over Na₂SO₄. After concentration under reduced pressure, the crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give 1-59 (50 mg, 0.125 mmol, 90%) as yellow oil.
Chapter 2. Total synthesis of D-/L- stereoisomers of Vineomycin B2/C Trisaccharide

Portion

(S)-1-(furan-2-yl)ethanol (II-8)

\[
\text{II-8}
\]

To a solution of aqueous HCO\(_2\)Na (200 mL, 2.0 M) was added furan ketone (12.5 g, 0.11 mol) and CH\(_2\)Cl\(_2\) (10 mL). CTAB (4.2 g, 11 mmol) was then added. The mixture was stirred for 5 minutes. Noyori asymmetric transfer hydrogenation catalyst (R)-Ru(η\(^6\)-mesitylene)-(S,S)-TsDPEN (70 mg, 0.11 mmol) was added to the solution. The mixture was then stirred at room temperature overnight under argon. The reaction mixture was extracted with Et\(_2\)O (3 x 300 mL). The combined organic layers were washed with satd. aqueous NaHCO\(_3\), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% Et\(_2\)O/hexanes to give furan alcohol II-8 (12 g, 0.105 mol, 95%) as a colorless oil: \(R_f\) (30% EtOAc/hexanes) = 0.24; \([\alpha]^{23}_D = -21.0\) (c = 1.0, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.37 (dd, \(J = 1.8, 0.6\) Hz, 1H), 6.32 (dd, \(J = 3.0, 1.8\) Hz, 1H), 6.22 (dd, \(J = 3.0, 2.4\) Hz, 1H), 4.88 (q, \(J = 6.6\) Hz, 1H), 1.97 (brs, 1H), 1.54 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 157.6, 141.9, 110.1, 105.1, 63.6, 21.3.

(R)-1-(furan-2-yl)ethanol ((ent)-II-8)

To a solution of aqueous HCO$_2$Na (200 mL, 2.0 M) was added furan ketone (12.5 g, 0.11 mol) and CH$_2$Cl$_2$ (10 mL). CTAB (4.2 g, 11 mmol) was then added. The mixture was stirred for 5 minutes. Noyori asymmetric transfer hydrogenation catalyst (R)-Ru($\eta^6$-mesitylene)-(R,R)-TsDPEN (70 mg, 0.11 mmol) was added to the solution. The mixture was then stirred at room temperature overnight under argon. The reaction mixture was extracted with Et$_2$O (3 x 300 mL). The combined organic layers were washed with satd. aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% Et$_2$O/hexanes to give furan alcohol (ent)-II-8 (12 g, 0.105 mol, 95%) as a colorless oil: $R_f$ (30% EtOAc/hexanes) = 0.24; $[\alpha]_{D}^{23} = 21.2$ (c = 1.0, CH$_2$Cl$_2$); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.37 (dd, $J = 1.8$, 0.6 Hz, 1H), 6.32 (dd, $J = 3.0$, 1.8 Hz, 1H), 6.22 (dd, $J = 3.0$, 2.4 Hz, 1H), 4.88 (q, $J = 6.6$ Hz, 1H), 1.97 (brs, 1H), 1.54 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 157.6, 141.9, 110.1, 105.1, 63.6, 21.3.

(S)-6-hydroxy-2-methyl-2H-pyran-3(6H)-one (II-9):

Furan alcohol II-8 (12 g, 105 mmol), THF (120 mL), and H₂O (30 mL) were added to a round bottom flask and cooled to 0 ºC. Solid NaHCO₃ (17.8 g, 210 mmol), NaOAc•3H₂O (14.4 g, 105 mmol), and NBS (19.8 g, 110 mmol) were added to the solution and the mixture was stirred for 1 h at 0 ºC. The reaction was quenched with satd. aqueous NaHCO₃, extracted with ether (3 x 200 mL), dried over Na₂SO₄, concentrated under reduced pressure and purified by silica gel chromatography eluting with 35% EtOAc/hexanes to give pyranone II-9 (11.8 g, 92 mmol, 88%, α:β =2.6 :1): Rᵢ (40% EtOAc/hexanes) = 0.29; ¹H NMR (600 MHz, CDCl₃) major isomer (α): δ 6.86 (dd, J = 10.2, 3.0 Hz, 1H), 6.04 (d, J = 10.2 Hz, 1H), 5.57 (dd, J = 4.2, 3.6 Hz, 1H), 4.66 (q, J = 6.6 Hz, 1H), 4.12 (brs, 1H), 1.32 (d, J = 6.6 Hz, 3H); minor isomer (β): δ 6.91 (dd, J = 10.2, 1.8 Hz, 1H), 6.09 (dd, J = 10.2, 1.8 Hz, 1H), 5.62 (dd, J = 7.2, 1.2 Hz, 1H), 4.47 (br, 1H), 4.18 (dq, J = 6.6, 1.2 Hz, 1H), 1.39 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) major isomer (α): δ 197.4, 144.9, 126.9, 87.4, 70.3, 15.2; minor isomer (β): δ 196.8, 148.5, 128.2, 90.8, 75.1, 16.1.

(R)-6-hydroxy-2-methyl-2H-pyran-3(6H)-one ((ent)-II-9)

Furan alcohol (ent)-II-8 (12 g, 105 mmol), THF (120 mL), and H₂O (30 mL) were added to a round bottom flask and cooled to 0 ºC. Solid NaHCO₃ (17.8 g, 210 mmol), NaOAc•3H₂O (14.4 g, 105 mmol), and NBS (19.8 g, 110 mmol) were added to the solution and the mixture was stirred for 1 h at 0 ºC. The reaction was quenched with satd. aqueous NaHCO₃, extracted with ether (3 x 200 mL), dried over Na₂SO₄, concentrated under reduced pressure and purified by silica gel chromatography eluting with 35% EtOAc/hexanes to give pyranone (ent)-II-9 (12 g, 93.6 mmol, 89%, α:β = 2.6 :1): Rᵣ (40% EtOAc/hexanes) = 0.29; ¹H NMR (600 MHz, CDCl₃) major isomer (α): δ 6.86 (dd, J = 10.2, 3.0 Hz, 1H), 6.04 (d, J = 10.2 Hz, 1H), 5.57 (dd, J = 4.2, 3.6 Hz, 1H), 4.66 (q, J = 6.6 Hz, 1H), 3.73 (brs, 1H), 1.32 (d, J = 6.6 Hz, 3H); minor isomer (β): δ 6.91 (dd, J = 10.2, 1.8 Hz, 1H), 6.09 (dd, J = 10.2, 1.8 Hz, 1H), 5.62 (dd, J = 7.2, 1.2 Hz, 1H), 4.18 (dq, J = 6.6, 1.2 Hz, 1H), 3.80 (brs, 1H), 1.39 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) major isomer (α): δ 197.4, 144.9, 126.9, 87.4, 70.3, 15.2; minor isomer (β): δ 196.8, 148.5, 128.2, 90.8, 75.1, 16.1.

Tert-butyl (2S,6S)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (II-7 (α-L)) and tert-butyl (2R,6S)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (II-6 (β-L)):
Alcohol \textbf{II-9} (11.8 g, 92 mmol) was dissolved in \text{CH}_2\text{Cl}_2 (92 mL) and the solution was cooled to -78 °C. A \text{CH}_2\text{Cl}_2 (20 mL) solution of (Boc)_2O (24.8 g, 111 mmol) and a catalytic amount of DMAP (1.14 g, 9.3 mmol) was added to the reaction mixture. The reaction was stirred for 1 h at -78 °C, and quenched with satd. aqueous NaHCO$_3$, extracted with ether (3 x 200 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc/hexanes to give 18.4 g (80.7 mmol, 88%) of two diastereomers of Boc-protected pyranone \textbf{II-7 (α-L)} and \textbf{II-6 (β-L)} in a ratio of 3:1.

\textbf{II-7 (α-L)}: \text{Rf} (20\% \text{EtOAc/hexanes}) = 0.58; [\alpha]_D^{23} = 83.2 (c = 1.0, \text{CH}_2\text{Cl}_2); \text{^1H NMR} (600 MHz, CDCl$_3$) \delta 6.87 (dd, \textit{J} = 10.2, 3.6 Hz, 1H), 6.33 (d, \textit{J} = 3.6 Hz, 1H), 6.20 (d, \textit{J} = 10.2 Hz, 1H), 4.65 (q, \textit{J} = 6.6 Hz, 1H), 1.52 (s, 9H), 1.41 (d, \textit{J} = 7.2 Hz, 3H); \text{^13C NMR} (150 MHz, CDCl$_3$) \delta 195.7, 151.9, 140.9, 128.4, 89.2, 83.6, 72.2, 27.7, 15.3.

\textbf{II-6 (β-L)}: \text{Rf} (20\% \text{EtOAc/hexanes}) = 0.50; [\alpha]_D^{23} = -44.2 (c = 1.0, \text{CH}_2\text{Cl}_2); \text{^1H NMR} (600 MHz, CDCl$_3$) \delta 6.88 (dd, \textit{J} = 10.2, 2.4 Hz, 1H), 6.37 (dd, \textit{J} = 2.4, 1.2 Hz, 1H), 6.21 (dd, \textit{J} = 10.2, 1.2 Hz, 1H), 4.37 (q, \textit{J} = 7.2 Hz, 1H), 1.52 (s, 9H), 1.51 (d, \textit{J} = 6.6 Hz, 3H); \text{^13C NMR} (150 MHz, CDCl$_3$) \delta 195.9, 151.8, 142.8, 128.3, 89.9, 83.6, 75.8, 27.7, 18.6.


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*Tert*-butyl *(2R,6R)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate* (*ent*-II-7 *(α-D)*)) and *tert*-butyl *(2S,6R)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate* (*ent*-II-6 *(β-D)*))

To a benzene solution (200 mL) of *(2R)-6-Hydroxy-2-methyl-2H-Pyran-3 *(6H)-one* (*ent*-II-9 (12 g, 93.6 mmol) and (Boc)$_2$O (30.7 g, 143 mmol) was added sodium acetate (8.4 g, 102 mmol). After stirring at 80 °C for 2 h, the mixture was cooled down to room temperature. The reaction was quenched with satd. aqueous NaHCO$_3$, extracted with ether (3 x 200 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 6% EtOAc/hexanes to give two diastereomers of *tert*-butyl 5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (18.8 g, 82.4 mmol, 88%) of (*ent*-II-7 *(α-D)*) and (*ent*-II-6 *(β-D)*) (d.r. = 1:1.3).

*(ent)-II-7 *(α-D)*: \(R_f\) (20% EtOAc/hexanes) = 0.58; \([\alpha]^{21}_D = -90.0 \ (c = 1.15, \text{CH}_2\text{Cl}_2)\); $^1$H NMR (600 MHz, CDCl$_3$) \(\delta\) 6.87 (dd, \(J = 10.2, 3.6 \text{ Hz}, 1\text{H}\)), 6.33 (d, \(J = 3.6 \text{ Hz}, 1\text{H}\)), 6.20 (d, \(J = 10.2 \text{ Hz}, 1\text{H}\)), 4.65 (q, \(J = 6.6 \text{ Hz}, 1\text{H}\)), 1.52 (s, 9H), 1.41 (d, \(J = 7.2 \text{ Hz}, 3\text{H}\)); $^{13}$C NMR (150 MHz, CDCl$_3$) \(\delta\) 195.7, 151.9, 140.9, 128.4, 89.2, 83.6, 72.2, 27.7, 15.3.

*(ent)-II-6 *(β-D)*: \(R_f\) (20% EtOAc/hexanes) = 0.50; \([\alpha]^{21}_D = 45.8 \ (c = 1.0, \text{CH}_2\text{Cl}_2)\); $^1$H NMR (600 MHz, CDCl$_3$) \(\delta\) 6.88 (dd, \(J = 10.2, 2.4 \text{ Hz}, 1\text{H}\)), 6.37 (dd, \(J = 2.4, 1.2 \text{ Hz}, 1\text{H}\)), 6.21 (dd, \(J = 10.2, 1.2 \text{ Hz}, 1\text{H}\)), 4.37 (q, \(J = 7.2 \text{ Hz}, 1\text{H}\)), 1.52 (s, 9H), 1.51 (d, \(J = 6.6 \text{ Hz}, 1\text{H}\), 1.41 (d, \(J = 7.2 \text{ Hz}, 3\text{H}\)).
$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 195.9, 151.8, 142.8, 128.3, 89.9, 83.6, 75.8, 27.7, 18.6.


(2S,6S)-6-(4-methoxybenzyloxy)-2-methyl-2H-pyran-3(6H)-one (II-10)

A CH$_2$Cl$_2$ (15 mL) solution of tert-butyl (2S,6R)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate II-6 (β-L) (3.57 g, 15.6 mmol) and 4-methoxybenzyl alcohol (3.9 mL, 31.3 mL) was cooled to 0 °C, and a solution of Pd$_2$(dba)$_3$•CHCl$_3$ (160 mg, 0.156 mmol, 1 mol%) and PPh$_3$ (0.16 g, 0.625 mmol, 4 mol%) in CH$_2$Cl$_2$ (5 mL) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with satd. aqueous NaHCO$_3$, extracted with ether (3 x 100 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexanes to give pyranone II-10 (3.55 g, 14.3 mmol, 92%) as a yellow oil: $R_f$ (10% EtOAc/hexanes) = 0.15; [α]$^{23}_D$ = 24.1 (c = 1.05, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2938, 2837, 1697, 1612, 1514, 1463, 1374, 1246, 1055, 1029, 818, 803; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.30 (d, $J$ = 7.8 Hz, 2H), 6.90 ($J$ = 7.8 Hz, 2H), 6.86 (dd, $J$ = 10.2, 0.6 Hz, 1H), 6.12 (d, $J$ = 10.2, 0.6 Hz, 1H), 5.37 (d, $J$ = 1.2 Hz, 1H), 4.87 (d, $J$ = 11.4 Hz, 1H), 4.62 (d, $J$ = 11.4 Hz, 1H), 4.22 (q, $J$ = 6.6 Hz, 1H), 3.81 (s, 3H), 1.52 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 196.8, 159.6, 146.7,
129.9, 128.9, 128.1, 114.0, 94.0, 75.3, 69.8, 55.3, 17.3; CIHRMS calcd for [C_{14}H_{16}NaO_4]^+: 271.0941, found 271.0939.

(2S,6S)-6-(4-methoxybenzyloxy)-3,6-dihydro-2-methyl-2H-pyran-3-ol (II-11)

Pyranone II-10 (3.55 g, 14.3 mmol) was dissolved in CH_2Cl_2 (14.3 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl_3 in methanol solution (5.7 mmol, 14.3 mL) was added in a dropwise fashion, followed by adding NaBH_4 (0.56 g, 14.3 mmol). By TLC tracking, the reaction was done after 1.5 h. The reaction mixture was diluted with ether (6 mL), then quenched with water (6 mL), extracted with ether (3 x 60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexane to give allylic alcohol II-11a/b as a mixture of diastereomers (3.6 g, 14.3 mmol, 99%) as a colorless oil:

\[ R_f (30\% \text{ EtOAc/hexanes}) = 0.45; \alpha^{23}_D = 36.6 (c = 1.1, \text{CH}_2\text{Cl}_2); \text{IR (thin film, cm}^{-1}) 3411, 2977, 2871, 1613, 1514, 1173, 1051, 1032, 1007, 810, 789; \]

II-11a: ^{1}H NMR (600 MHz, CDCl_3) \delta 7.29 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.13 (ddd, J = 10.2, 5.4, 1.8 Hz, 1H), 5.82 (d, J = 10.2 Hz, 1H), 5.10 (brr, 1H), 4.82 (d, J = 11.4 Hz, 1H), 4.58 (d, J = 11.4 Hz, 1H), 3.79 (s, 3H), 3.74-3.70 (m, 1H), 3.66 (brr, 1H), 2.03 (brr, 1H), 1.33 (d, J = 6.6 Hz, 3H); II-11b: ^{1}H NMR (600 MHz, CDCl_3) \delta 7.29 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.92 (d, J = 10.2 Hz, 1H), 5.75 (d, J = 10.2 Hz, 1H), 5.15 (brr, 1H), 4.78 (d, J = 11.4 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H), 3.89 (br, 1H), 3.79 (s, 3H), 3.65-3.61 (m, 1H), 2.24 (brr, 1H), 1.37 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150
MHz, CDCl$_3$) major isomer $\delta$ 159.3, 131.2, 129.7, 129.6, 113.8, 96.7, 71.5, 69.6, 68.4, 64.8, 55.3, 16.6; CIHRMS calcd for [C$_{14}$H$_{18}$O$_4$Na]$^+$: 273.1097, found 273.1095.

$\text{(2S,6S)-2-(4-methoxybenzyloxy)-3,6-dihydro-6-methyl-2H-pyran (II-12)}$

\[
\text{PMBO} \quad \text{O} \quad \text{CH}_3 \\
\text{II-12}
\]

A flask charged with dry N-Methyl morpholine (NMM) (30 mL), triphenyl phosphine (12.5 g, 47.5 mmol) was cooled to -30 °C under argon atmosphere. Diisopropyl azodicarboxylate (8.6 mL, 43.2 mmol) was added and the reaction was stirred for 5 min, allylic alcohol (3.6 g, 14.4 mmol) was added to in a 1 M of NMM (14.4 mL), the resulting reaction mixture was stirred for 10 min, followed by addition of o-nitrobenzenesulfonyl hydrazide (NBSH) (9.4 g, 43.2 mmol). The reaction was stirred at -30 °C for 2 h and was monitored by TLC. Upon consumption of II-11a/b, the reaction was warmed to room temperature and stirred for another 2 h. The reaction mixture was diluted with ether (30 mL) and was quenched with satd. aqueous NaHCO$_3$, extracted with ether (3 x 100 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexanes to give product II-12 (3.12 g, 13.3 mmol, 92%) as a colorless oil: $R_f$ (20% EtOAc/hexanes) = 0.55; $[\alpha]_{D}^{23} = 105.9$ (c = 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3034, 2909, 1613, 1513, 1357, 1245, 1156, 1076, 1026, 880, 819; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.30 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 7.8$ Hz, 2H), 5.67 (dddd, $J = 9.6$, 2.4, 1.2, 1.2 Hz, 1H), 5.58 (ddddd, $J = 9.6$, 5.4, 2.4, 2.4 Hz, 1H), 4.86 (d, $J = 12.0$ Hz, 1H), 4.72 (dd, $J = 8.4$, 3.0 Hz, 1H), 4.55 (d, $J = 12.0$ Hz, 1H), 4.32-4.34 (m, 1H), 3.80 (s, 3H), 2.20-2.26 (m,
1.12-1.6 (m, 1H), 1.32 (d, J = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.2, 130.9, 130.0, 129.6, 122.5, 113.8, 97.4, 70.6, 69.4, 55.2, 31.0, 21.2; CIHRMS calcd for [C$_{14}$H$_{18}$O$_3$Na]$^+$: 257.1148, found 257.1146.

(2S,3R,4R,6S)-6-(4-methoxybenzylxylo)-2-methyl-tetrahydron-2H-pyran-3,4-diol (II-13)

To a $t$-butanol, acetone (13.3 mL each, 1:1) solution of pyran II-12 (3.12 g, 13.3 mmol) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (13.3 mL). Crystalline OsO$_4$ (33.8 mg, 0.133 mmol) was added and the reaction was stirred for 12 h. The reaction was quenched with EtOAc and satd. aqueous NaHCO$_3$. The organic layer was separated and concentrated. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give diol II-13 (2.85 g, 10.6 mmol, 80%) as a colorless oil: R$_f$ (50% EtOAc/hexanes) = 0.20; [α]$_D^{23}$ = 64.4 ($c$ = 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3416, 2933, 1613, 1514, 1246, 1162, 1066, 998, 820, 723; $^1$H NMR (600 MHz, CDCl$_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.88 (dd, J = 9.6, 2.4 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.50 (d, J = 11.4 Hz, 1H), 4.11 (d, J = 3.0 Hz, 1H), 3.80 (s, 3H), 3.74 (dq, J = 9.0, 6.6 Hz, 1H), 3.33 (dd, J = 9.6, 3.6 Hz, 1H), 2.15 (brs, 2H), 2.10 (ddd, J = 15.0, 2.4, 2.4 Hz, 1H), 1.77 (ddd, J = 14.0, 11.4, 3.0 Hz, 1H), 1.34 (d, J = 6.0 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.3, 129.8, 129.6, 113.8, 96.7, 73.1, 70.2, 69.4, 68.0, 55.3, 37.7, 18.1; CIHRMS calcd for [C$_{14}$H$_{26}$O$_5$Na]$^+$: 291.1203, found 291.1200.
To a THF (60 mL) solution of diol II-13 (2.85 g, 10.6 mmol) at 0 °C was added PPh$_3$ (4.2 g, 16.0 mmol) and p-nitrobenzoic acid (3.5 g, 21.2 mmol), DIAD (3.4 mL, 17.0 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred for 24 hours. The reaction mixture was diluted with EtOAc (100 mL), quenched with satd. aqueous NaHCO$_3$, extracted with ether (3 x 100 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/Hexanes to give nitrobenzoate II-14 (2.3 g, 5.5 mmol, 68%) as a white solid: R$_f$ (30% EtOAc/hexanes) = 0.40; mp: 38-40 °C; [α]$_{D}^{23}$ = 38.3 (c = 0.23, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3327, 2939, 1718, 1610, 1515, 1348, 1269, 1243, 1168, 1102, 1063, 988, 720; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.27 (d, $J$ = 9.0 Hz, 2H), 8.19 (d, $J$ = 9.0 Hz, 2H), 7.27 (d, $J$ = 8.4 Hz, 2H), 6.88 (d, $J$ = 8.4 Hz, 2H), 5.06 (ddd, $J$ = 11.4, 8.4, 4.8 Hz, 1H), 4.83 (d, $J$ = 11.4 Hz, 1H), 4.65 (dd, $J$ = 9.6, 1.8 Hz, 1H), 4.56 (d, $J$ = 11.4 Hz, 1H), 3.80 (s, 3H), 3.47 (dd, $J$ = 9.6, 8.4 Hz, 1H), 3.41 (dq, $J$ = 9.0, 6.0 Hz, 1H), 2.39 (ddd, $J$ = 12.6, 5.4, 1.8 Hz, 1H), 1.85 (ddd, $J$ = 12.0, 12.0, 9.6 Hz, 1H), 1.43 (d, $J$ = 6.0 Hz, 3H), 1.24 (d, $J$ = 6.0 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 164.8, 159.4, 150.7, 135.0, 130.8, 129.7, 129.2, 123.5, 113.9, 97.4, 75.7, 74.9, 72.0, 70.2, 55.3, 36.4, 17.8; CIHRMS calcd for [C$_{21}$H$_{23}$NO$_8$Na]$^+$: 440.1316, found 440.1312.
(2R,6R)-6-(4-methoxybenzylxoy)-2-methyl-2H-pyran-3(6H)-one ((ent)-II-10)

A CH$_2$Cl$_2$ (34 mL) solution of tert-butyl (2S,6R)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (ent)-II-6 (β-D) (7.73 g, 33.9 mmol) and 4-methoxybenzyl alcohol (8.48 mL, 67.8 mmol) was cooled to 0 °C, and a solution of Pd$_2$(dba)$_3$•CHCl$_3$ (351 mg, 0.339 mmol, 1 mol%) and PPh$_3$ (335 mg, 1.36 mmol, 4 mol%) in CH$_2$Cl$_2$ (10 mL) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with satd. aqueous NaHCO$_3$, extracted with ether (3 x 100 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexanes to give pyranone (ent)-II-10 (8.0 g, 32.2 mmol, 95%) as a yellow oil: $R_f$ (10% EtOAc/hexanes) = 0.15; $[\alpha]_{23}^D = -24.7$ (c = 1.1, CH$_2$Cl$_2$); $^1$H NMR (600 MHz, CDCl$_3$) δ 7.30 (d, $J$ = 7.8 Hz, 2H), 6.90 ($J$ = 7.8 Hz, 2H), 6.86 (dd, $J$ = 10.2, 0.6 Hz, 1H), 6.12 (d, $J$ = 10.2, 0.6 Hz, 1H), 5.37 (d, $J$ = 1.2 Hz, 1H), 4.87 (d, $J$ = 11.4 Hz, 1H), 4.62 (d, $J$ = 11.4 Hz, 1H), 4.22 (q, $J$ = 6.6 Hz, 1H), 3.81 (s, 3H), 1.52 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 196.8, 159.6, 146.7, 129.9, 128.9, 128.1, 114.0, 94.0, 75.3, 69.8, 55.3, 17.3.

Pyranone (ent)-II-10 (7.84 g, 31.6 mmol) was dissolved in CH$_2$Cl$_2$ (31.6 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl$_3$ in methanol solution (12.6 mmol, 31.6 mL) was added in a dropwise fashion, followed by adding NaBH$_4$ (1.2 g, 31.6 mmol). By TLC tracking, the reaction was done after 1.5 h. The reaction mixture was diluted with ether (6 mL), then quenched with water (6 mL), extracted with ether (3 x 60 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexane to give allylic alcohol (ent)-II-11a/b as a mixture of diastereomers (7.83 g, 31.3 mmol, 99%) as a colorless oil: $R_f$ (30% EtOAc/hexanes) = 0.45; $[\alpha]^{23}_D$ = -64.5 ($c$ = 1.0, CH$_2$Cl$_2$);

(ent)-II-11a: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.29 (d, $J$ = 8.4 Hz, 2H), 6.87 (d, $J$ = 8.4 Hz, 2H), 6.13 (ddd, $J$ = 10.2, 5.4, 1.8 Hz, 1H), 5.82 (d, $J$ = 10.2 Hz, 1H), 5.10 (brs, 1H), 4.82 (d, $J$ = 11.4 Hz, 1H), 4.58 (d, $J$ = 11.4 Hz, 1H), 3.79 (s, 3H), 3.74-3.70 (m, 1H), 3.66 (brs, 1H), 2.03 (brs, 1H), 1.33 (d, $J$ = 6.6 Hz, 3H); (ent)-II-11b: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.29 (d, $J$ = 8.4 Hz, 2H), 6.87 (d, $J$ = 8.4 Hz, 2H), 5.92 (d, $J$ = 10.2 Hz, 1H), 5.75 (d, $J$ = 10.2 Hz, 1H), 5.15 (brs, 1H), 4.78 (d, $J$ = 11.4 Hz, 1H), 4.54 (d, $J$ = 11.4 Hz, 1H), 3.89 (br, 1H), 3.79 (s, 3H), 3.65-3.61 (m, 1H), 2.24 (brs, 1H), 1.37 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) major isomer $\delta$ 159.3, 131.2, 129.7, 129.6, 113.8, 96.7, 71.5, 69.6, 68.4, 64.8, 55.3, 16.6.

\((2R,6R)-2-(4\text{-methoxybenzyloxy})-3,6\text{-dihydro-6-methyl-2H-pyran }((\text{ent})\text{-II-12})\)

A flask charged with dry \(N\)-Methyl morpholine (NMM) (60 mL), triphenyl phosphine (24 g, 91 mmol) was cooled to -30 °C under argon atmosphere. Diisopropyl azodicarboxylate (16.5 mL, 83 mmol) was added and the reaction was stirred for 5 min, allylic alcohol (6.9 g, 27.6 mmol) was added to in a 1 M of NMM (27.6 mL), the resulting reaction mixture was stirred for 10 min, followed by addition of \(o\)-nitrobenzenesulfonyl hydrazide (NBSH) (18 g, 83 mmol). The reaction was stirred at -30 °C for 2 h and was monitored by TLC. Upon consumption of \((\text{ent})\text{-II-11}\), the reaction was warmed to room temperature and stirred for another 2 h. The reaction mixture was diluted with ether (60 mL) and was quenched with satd. aqueous NaHCO₃, extracted with ether (3 x 150 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexanes to give product \((\text{ent})\text{-II-12}\) (6.07 g, 25.9 mmol, 94%) as a colorless oil: \(R_f\) (20% EtOAc/hexanes) = 0.55; [\(\alpha\)]\(\text{D}^{23}\) = -106.2 (c = 1.0, CH₂Cl₂); \(^1\)H NMR (600 MHz, CDCl₃) δ 7.30 (d, \(J = 8.4\) Hz, 2H), 6.88 (d, \(J = 7.8\) Hz, 2H), 5.67 (dddd, \(J = 9.6, 2.4, 1.2, 1.2\) Hz, 1H), 5.58 (dddd, \(J = 9.6, 5.4, 2.4, 2.4\) Hz, 1H), 4.86 (d, \(J = 12.0\) Hz, 1H), 4.72 (dd, \(J = 8.4, 3.0\) Hz, 1H), 4.55 (d, \(J = 12.0\) Hz, 1H), 4.34-4.32 (m, 1H), 3.80 (s, 3H), 2.26-2.20 (m, 1H), 2.16-2.11 (m, 1H), 1.32 (d,
\[ J = 6.6 \text{ Hz}, 3H; \] \[ ^{13}\text{C NMR (150 MHz, CDCl}_3 \delta 159.2, 130.9, 130.0, 129.6, 122.5, 113.8, 97.4, 70.6, 69.4, 55.2, 31.0, 21.2. \]


\((2R,3S,4S,6R)-6-(4\text{-methoxybenzoyloxy})\text{-tetrahydro-2-methyl-2H-pyran-3,4-diol}
\)
\((\text{ent})\text{-II-13})

To a \(t\)-butanol, acetone (8.9 mL each, 1:1) solution of pyran \((\text{ent})\text{-II-12} \) (2.07 g, 8.85 mmol) at 0 °C was added a solution of (50% w/v) of \(N\)-methyl morpholine \(N\)-oxide / water (8.9 mL). Crystalline OsO\(_4\) (22.5 mg, 0.0885 mmol) was added and the reaction was stirred for 12 h. The reaction was quenched with EtOAc and satd. aqueous NaHCO\(_3\). The organic layer was separated and concentrated. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give diol \((\text{ent})\text{-II-13} \) (2.17 g, 8.09 mmol, 91%) as a colorless oil: \(R_f\) (50% EtOAc/hexanes) = 0.20; \([\alpha\] \text{D}^{23} = -57.8 \) (\(c = 1.0, \text{CH}_2\text{Cl}_2\)); \(^1\text{H NMR (600 MHz, CDCl}_3 \delta 7.27 (d, J = 8.4 \text{ Hz}, 2H), 6.87 (d, J = 8.4 \text{ Hz}, 2H), 4.88 (dd, J = 9.6, 2.4 \text{ Hz}, 1H), 4.81 (d, J = 11.4 \text{ Hz}, 1H), 4.50 (d, J = 11.4 \text{ Hz}, 1H), 4.11 (d, J = 3.0 \text{ Hz}, 1H), 3.80 (s, 3H), 3.74 (dq, J = 9.0, 6.6 \text{ Hz}, 1H), 3.33 (dd, J = 9.6, 3.6 \text{ Hz}, 1H), 2.15 (brs, 2H), 2.10 (ddd, J = 15.0, 2.4, 2.4 \text{ Hz}, 1H), 1.77 (ddd, J =
14.0, 11.4, 3.0 Hz, 1H), 1.34 (d, J = 6.0 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.3, 129.8, 129.6, 113.8, 96.7, 73.1, 70.2, 69.4, 68.0, 55.3, 37.7, 18.1.


(2R,3R,4R,6R)-6-(4-methoxybenzyloxy)-tetrahydro-3-hydroxy-2-methyl-2H-pyran-4-yl 4-nitrobenzoate ((ent)-II-14)

To a THF (45 mL) solution of diol (ent)-II-13 (2.17 g, 8.1 mmol) at 0 °C was added PPh$_3$ (3.18 g, 12.2 mmol) and p-nitrobenzoic acid (2.68 g, 16.2 mmol), DIAD (2.6 mL, 13.0 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred for 24 hours. The reaction mixture was diluted with EtOAc (100 mL), quenched with satd. aqueous NaHCO$_3$, extracted with ether (3 x 100 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/Hexanes to give nitrobenzoate (ent)-II-14 (2.3 g, 5.5 mmol, 68%) as a white solid: $R_f$ (30% EtOAc/hexanes) = 0.40; [$\alpha$]$^\circ_{D}$ = -38.2 (c = 0.5, CH$_2$Cl$_2$); $^1$H NMR (600 MHz, CDCl$_3$) δ 8.27 (d, J = 9.0 Hz, 2H), 8.19 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.06 (ddd, J = 11.4, 8.4, 4.8 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.65 (dd, J = 9.6, 1.8 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 3.80 (s, 3H), 3.47 (dd, J = 9.6, 8.4 Hz, 1H), 3.41 (dq, J = 9.0, 6.0 Hz, 1H),
2.39 (ddd, J = 12.6, 5.4, 1.8 Hz, 1H), 1.85 (ddd, J = 12.0, 12.0, 9.6 Hz, 1H), 1.43 (d, J = 6.0 Hz, 3H), 1.24 (d, J = 6.0 Hz, 1H); 

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 164.8, 159.4, 150.7, 135.0, 130.8, 129.7, 129.2, 123.5, 113.9, 97.4, 75.7, 74.9, 72.0, 70.2, 55.3, 36.4, 17.8.


$(2S,3S,4S,6S)$-3-(((2$R,6S$)-5,6-dihydro-6-methyl-5-oxo-$2H$-pyran-2-yloxy)-6-(4-methoxybenzyl oxy)-tetrahydro-2-methyl-$2H$-pyran-4-yl 4-nitrobenzoate (II-15-a)

A CH$_2$Cl$_2$ (10 mL) solution of Boc pyranone II-7(α-L) (4.5 g, 19.7 mmol) and alcohol II-14 (1.6 g, 3.83 mmol) was cooled to 0 °C. A solution of Pd$_2$(dba)$_3$•CHCl$_3$ (105 mg, 0.101 mmol) and PPh$_3$ (106 mg, 0.404 mmol) in CH$_2$Cl$_2$ (10 mL) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at for 8 h. The reaction mixture was quenched with satd. aqueous NaHCO$_3$, extracted with Et$_2$O (3 x 30 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give pyranone II-15-a (1.33 g, 2.52 mmol, 66%) as a yellow solid: $R_f$ (20% EtOAc/hexanes) = 0.30; mp: 134-137 °C; $\left[\alpha\right]_{D}^{23} = -82.4$ (c = 0.30, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2940, 1726, 1701, 1611, 1528, 1515, 1271, 1101, 1049, 985, 834; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.31 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 10.5 Hz, 1H), 7.79 (d, J = 10.5 Hz, 1H), 2.05 (d, J = 10.5 Hz, 1H), 1.98 (d, J = 10.5 Hz, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.23 (s, 3H), 0.98 (t, J = 6.9 Hz, 3H), 0.92 (t, J = 6.9 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H), 0.83 (t, J = 6.9 Hz, 3H), 0.79 (t, J = 6.9 Hz, 3H), 0.75 (t, J = 6.9 Hz, 3H), 0.71 (t, J = 6.9 Hz, 3H), 0.67 (t, J = 6.9 Hz, 3H), 0.63 (t, J = 6.9 Hz, 3H), 0.59 (t, J = 6.9 Hz, 3H), 0.55 (t, J = 6.9 Hz, 3H), 0.51 (t, J = 6.9 Hz, 3H), 0.47 (t, J = 6.9 Hz, 3H), 0.43 (t, J = 6.9 Hz, 3H), 0.39 (t, J = 6.9 Hz, 3H), 0.35 (t, J = 6.9 Hz, 3H), 0.31 (t, J = 6.9 Hz, 3H), 0.27 (t, J = 6.9 Hz, 3H), 0.23 (t, J = 6.9 Hz, 3H), 0.19 (t, J = 6.9 Hz, 3H), 0.15 (t, J = 6.9 Hz, 3H), 0.11 (t, J = 6.9 Hz, 3H), 0.07 (t, J = 6.9 Hz, 3H), 0.03 (t, J = 6.9 Hz, 3H), 0.00 (t, J = 6.9 Hz, 3H), -0.03 (t, J = 6.9 Hz, 3H), -0.07 (t, J = 6.9 Hz, 3H), -0.11 (t, J = 6.9 Hz, 3H), -0.15 (t, J = 6.9 Hz, 3H), -0.19 (t, J = 6.9 Hz, 3H), -0.23 (t, J = 6.9 Hz, 3H), -0.27 (t, J = 6.9 Hz, 3H), -0.31 (t, J = 6.9 Hz, 3H), -0.35 (t, J = 6.9 Hz, 3H), -0.39 (t, J = 6.9 Hz, 3H), -0.43 (t, J = 6.9 Hz, 3H), -0.47 (t, J = 6.9 Hz, 3H), -0.51 (t, J = 6.9 Hz, 3H), -0.55 (t, J = 6.9 Hz, 3H), -0.59 (t, J = 6.9 Hz, 3H), -0.63 (t, J = 6.9 Hz, 3H), -0.67 (t, J = 6.9 Hz, 3H), -0.71 (t, J = 6.9 Hz, 3H), -0.75 (t, J = 6.9 Hz, 3H), -0.79 (t, J = 6.9 Hz, 3H), -0.83 (t, J = 6.9 Hz, 3H), -0.87 (t, J = 6.9 Hz, 3H), -0.92 (t, J = 6.9 Hz, 3H), -0.98 (t, J = 6.9 Hz, 3H).
Hz, 2H), 8.21 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.42 (dd, J = 10.2, 3.0 Hz, 1H), 5.96 (d, J = 10.2 Hz, 1H), 5.42 (d, J = 3.0 Hz, 1H), 5.25 (ddd, J = 11.4, 9.0, 5.4 Hz, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.66 (dd, J = 9.0, 1.8 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.56 (q, J = 6.6 Hz, 1H), 3.81 (s, 3H), 3.76 (dd, J = 9.0, 9.0 Hz, 1H), 3.50 (dq, J = 9.0, 6.0 Hz, 1H), 2.44 (ddd, J = 12.0, 5.4, 1.8 Hz, 1H), 1.85 (ddd, J = 12.0, 12.0, 9.6 Hz, 1H), 1.46 (d, J = 6.6 Hz, 3H), 1.37 (d, J = 6.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 196.0, 163.6, 159.4, 150.9, 142.0, 134.7, 130.6, 129.7, 129.1, 127.3, 123.9, 113.9, 97.3, 94.2, 80.4, 75.6, 70.7, 70.6, 70.3, 55.3, 36.7, 18.2, 14.9; CIHRMS calcd for [C$_{27}$H$_{29}$NO$_{10}$Na]$^+$: 550.1684, found 550.1702.

(2S,3S,4S,6S)-3-((2S,5R,6S)-5,6-dihydro-5-hydroxy-6-methyl-2H-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2H-pyran-4-yl 4-nitrobenzoate (II-15)

Pyranone II-15-a (1.33 g, 2.51 mmol) was dissolved in CH$_2$Cl$_2$ (6.5 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl$_3$ (6.5 mL, 2.60 mmol) in methanol solution was added dropwise, followed by the addition of NaBH$_4$ (175 mg, 4.63 mmol). By TLC tracking, the reaction was completed after 1 h. The reaction mixture was diluted with ether (20 mL), and then quenched with water (5 mL), extracted with ether (3 x 50 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give allylic alcohol II-15 (0.9 g, 1.7 mmol, 68%) as a white solid: $R_f$ (50% EtOAc/hexanes) = 0.35; mp: 118-125 °C; $[\alpha]^{23}_D$ = 42.3 (c = 0.39, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3456, 2940, 1729, 1529,
1274, 1249, 1103, 1057, 985, 722; H NMR (600 MHz, CDCl₃) δ 8.29 (d, J = 9.0 Hz, 2H), 8.18 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.83 (d, J = 10.2 Hz, 1H), 5.40 (ddd, J = 10.2, 2.4, 2.4 Hz, 1H), 5.20 (ddd, J = 12.0, 9.6, 5.4 Hz, 1H), 5.15 (brs, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.64 (dd, J = 9.6, 1.8 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 3.81 (s, 3H), 3.79 (br, 1H), 3.68 (dd, J = 9.0, 9.0 Hz, 1H), 3.66 (dq, J = 8.4, 6.0 Hz, 1H), 3.46 (dq, J = 9.0, 6.0 Hz, 1H), 2.42 (ddd, J = 12.0, 4.8, 1.8 Hz, 1H), 1.81 (ddd, J = 12.6, 12.0, 9.6 Hz, 1H), 1.45 (d, J = 6.6 Hz, 1H), 1.31 (d, J = 6.6 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 163.7, 159.4, 150.8, 135.0, 134.0, 130.6, 129.6, 129.2, 125.7, 123.8, 113.9, 97.4, 95.2, 79.6, 75.7, 70.8, 70.2, 69.2, 68.3, 55.3, 36.7, 18.0, 17.6; CIHRMS calcd for [C₂₇H₃₁NO₁₀Na]⁺: 552.1840, found 552.1921.

(2S,3S,4S,6S)-3-((2S,5S,6S)-5,6-dihydro-5-(4-nitrobenzoate)-6-methyl-2H-pyran-2-yl-oxy)-6-(4-methoxybenzyl-oxy)-tetrahydro-2-methyl-2H-pyran-4-yl 4-nitrobenzoate (II-16)

To a THF (9 mL) solution of alcohol II-15 (0.9 g, 1.7 mmol) at 0 °C was added PPh₃ (0.89 g, 3.4 mmol) and p-nitrobenzoic acid (0.56 g, 3.4 mmol), DIAD (0.69 mL, 3.4 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (20 mL), quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel...
flash chromatography eluting with 20% EtOAc/Hexanes to give product \textbf{II-16} (807 mg, 1.2 mmol, 70%) as a white solid: \( R_f \) (20% EtOAc/hexanes) = 0.22; mp: 215-218 °C; \([\alpha]_{23}^{23} = 85.1 \) (c = 1.0, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) 2937, 1726, 1607, 1520, 1352, 1265, 1061, 1047, 983, 831, 717; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 8.30 (d, \( J = 9.0 \) Hz, 2H), 8.27 (d, \( J = 9.0 \) Hz, 2H), 8.20 (d, \( J = 9.0 \) Hz, 2H), 8.20 (d, \( J = 9.0 \) Hz, 2H), 6.89 (d, \( J = 8.4 \) Hz, 2H), 6.12 (dd, \( J = 9.6, 5.4 \) Hz, 1H), 5.74 (dd, \( J = 10.2, 3.0 \) Hz, 1H), 5.30 (d, \( J = 3.0 \) Hz, 1H), 5.24 (ddd, \( J = 12.0, 9.0, 5.4 \) Hz, 1H), 5.13 (dd, \( J = 5.4, 2.4 \) Hz, 1H), 4.84 (d, \( J = 11.4 \) Hz, 1H), 4.66 (dd, \( J = 9.6, 1.8 \) Hz, 1H), 4.56 (d, \( J = 11.4 \) Hz, 1H), 4.33 (dq, \( J = 6.6, 2.4 \) Hz, 1H), 3.81 (s, 3H), 3.74 (dd, \( J = 9.6, 9.0 \) Hz, 1H), 3.49 (dq, \( J = 9.0, 6.0 \) Hz, 1H), 2.43 (ddd, \( J = 12.0, 4.8, 1.8 \) Hz, 1H), 1.85 (ddd, \( J = 12.0, 12.0, 9.6 \) Hz, 1H), 1.47 (d, \( J = 6.0 \) Hz, 1H), 1.31 (d, \( J = 6.6 \) Hz, 1H); \(^{13}\)C (150 MHz, CDCl\(_3\)) \( \delta \) 164.2, 163.7, 159.5, 150.8, 150.7, 135.0, 134.9, 130.8, 130.7, 130.3, 129.7, 129.2, 125.6, 123.8, 123.6, 113.9, 97.4, 95.3, 80.0, 75.6, 70.8, 70.3, 66.3, 65.4, 55.3, 36.8, 18.0, 16.0; CIHRMS calcd for [C\(_{34}\)H\(_{34}\)N\(_2\)O\(_{13}\)Na]\(^+\): 701.1953, found 701.1890.

\((2S,3S,4S,6S)-3-((2S,6R)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yloxy)-6-(4-methoxybenzyloxy) tetrahydro-2-methyl-2H-pyran-4-yl 4-nitrobenzoate (II-17-a)\)

\[ \text{II-17-a} \]

A CH\(_2\)Cl\(_2\) (13 mL) solution of Boc pyranone (\textit{ent})-\textbf{II-7} (\( \alpha \)-D) (7.5 g, 33 mmol) and alcohol \textbf{II-14} (2.4 g, 5.75 mmol) was cooled to 0 °C. A solution of Pd\(_2\)(dba)\(_3\)•CHCl\(_3\) (172 mg, 0.165 mmol) and PPh\(_3\) (173 mg, 0.66 mmol) in CH\(_2\)Cl\(_2\) (13 mL) was added to the
reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with satd. aqueous NaHCO₃, extracted with ether (3 x 30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give pyranone **II-17-a** (2.8 g, 5.3 mmol, 92%) as a yellow solid: Rₜ (30% EtOAc/hexanes) = 0.40; mp: 52-53 °C; [α]²³_D = 83.4 (c = 0.9, CH₂Cl₂); IR (thin film, cm⁻¹) 2937, 1725, 1698, 1611, 1528, 1276, 1103, 983, 834; ¹H NMR (600 MHz, CDCl₃) δ 8.29 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.76 (dd, J = 10.2, 3.6 Hz, 1H), 6.00 (d, J = 10.2 Hz, 1H), 5.31 (d, J = 3.6 Hz, 1H), 5.28 (ddd, J = 11.4, 9.0, 6.0 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.64 (d, J = 9.6 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.31 (q, J = 6.6 Hz, 1H), 3.81 (s, 3H), 3.63 (dd, J = 9.0, 9.0 Hz, 1H), 3.49 (dq, J = 9.0, 6.0 Hz, 1H), 2.40 (dd, J = 12.6, 5.4 Hz, 1H), 1.84 (ddd, J = 12.6, 12.0, 12.0 Hz, 1H), 1.44 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 196.3, 163.9, 159.5, 150.7, 142.4, 135.4, 130.8, 129.7, 129.1, 126.9, 123.6, 113.9, 97.3, 94.5, 82.6, 73.2, 71.1, 71.0, 70.2, 55.3, 36.7, 18.3, 15.1; CIHRMS calcd for [C₂₇H₂₉NO₁₀Na]+: 550.1684, found 550.1679.

**II-17**

(2S,3S,4S,6S)-3-((2R,5S,6R)-5,6-dihydro-5-hydroxy-6-methyl-2H-pyran-2-yl)oxy)-6-(4-methoxy-benzylxyloxy)-tetrahydro-2-methyl-2H-pyran-4-yl 4-nitrobenzoate (**II-17**):
Pyranone II-17-a (2.7 g, 5.3 mmol) was dissolved in CH$_2$Cl$_2$ (13 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl$_3$ (13 mL, 5.3 mmol) in methanol solution was added dropwise, followed by the addition of NaBH$_4$ (307 mg, 8.0 mmol). By TLC tracking, the reaction was completed after 1.5 h. The reaction mixture was diluted with ether (20 mL), and then quenched with water (5 mL), extracted with ether (3 x 50 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give allylic alcohol II-17 (2.59 g, 4.9 mmol, 92%) as a white solid: R$_f$ (30% EtOAc/hexanes) = 0.20; mp: 158-159 °C; [α]$_{D}^{23}$ = 102.7 (c = 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3384, 2920, 1738, 1531, 1513, 1369, 1282, 1104, 996, 717; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.28 (d, $J$ = 8.4 Hz, 2H), 8.21 (d, $J$ = 8.4 Hz, 2H), 7.27 (d, $J$ = 8.4 Hz, 2H), 6.89 (d, $J$ = 8.4 Hz, 2H), 5.86 (d, $J$ = 10.2 Hz, 1H), 5.68 (ddd, $J$ = 10.2, 2.4, 2.4 Hz, 1H), 5.25 (ddd, $J$ = 12.0, 8.4, 5.4 Hz, 1H), 5.06 (d, $J$ = 2.4 Hz, 1H), 4.83 (d, $J$ = 11.4 Hz, 1H), 4.64 (dd, $J$ = 9.6, 1.8 Hz, 1H), 4.56 (d, $J$ = 11.4 Hz, 1H), 3.81 (s, 3H), 3.62 (ddd, $J$ = 9.0, 9.0, 1.8 Hz, 1H), 3.56 (dd, $J$ = 9.0, 9.0 Hz, 1H), 3.48 (dq, $J$ = 9.0, 6.0 Hz, 1H), 3.44 (dq, $J$ = 9.0, 6.0 Hz, 1H), 2.39 (ddd, $J$ = 12.6, 5.4, 1.8 Hz, 1H), 1.83 (ddd, $J$ = 12.6, 12.0, 10.2 Hz, 1H), 1.43 (d, $J$ = 6.0 Hz, 3H), 0.83 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 164.0, 159.4, 150.5, 135.8, 133.2, 130.8, 129.7, 129.2, 126.2, 123.5, 113.9, 97.4, 95.5, 81.8, 73.4, 71.3, 70.2, 69.1, 68.6, 55.3, 36.7, 18.4, 17.5; CIHRMS calcd for [C$_{27}$H$_{31}$NO$_{10}$Na]$^+$: 552.1840, found 552.1837.
(2S,3S,4S,6S)-3-((2R,5R,6R)-5,6-dihydro-5-(4-nitrobenzoate)-6-methyl-2H-pyran-2-yloxy)-6-(4-methoxybenzyl)oxy)-tetrahydro-2-methyl-2H-pyran-4-yl 4-nitrobenzoate (II-18)

To a THF (12 mL) solution of alcohol II-17 (0.59 g, 1.11 mmol) at 0 °C was added PPh₃ (585 mg, 2.22 mmol) and p-nitrobenzoic acid (368 mg, 2.22 mmol), DIAD (0.44 mL, 2.22 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (10 mL), quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give product II-18 (567 mg, 0.836 mmol, 75%) as a white solid: Rₓ (30% EtOAc/hexanes) = 0.40; mp: 168-169 °C; [α]ᵢ₂³ = -92.5 (c = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2930, 1722, 1609, 1528, 1347, 1270, 1102, 1047, 983, 834, 720; ¹H NMR (600 MHz, CDCl₃) δ 8.28 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.14 (dd, J = 10.2, 5.4 Hz, 1H), 6.03 (dd, J = 10.2, 3.0 Hz, 1H), 5.28 (ddd, J = 12.0, 9.0, 6.0 Hz, 1H), 5.22 (d, J = 2.4 Hz, 1H), 4.98 (dd, J = 5.4, 2.4 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.65 (dd, J = 9.6, 1.2 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.10 (dq, J = 6.6, 2.4 Hz, 1H), 3.80 (s, 3H), 3.62 (dd, J = 9.0, 9.0 Hz, 1H), 3.53-3.49 (m, 1H), 2.39 (ddd, J = 12.0, 5.4, 1.8 Hz, 1H), 1.86 (ddd, J = 15.0, 9.6, 9.6 Hz,
H, 1.45 (d, $J = 6.6$ Hz, 3H), 0.79 (d, $J = 6.6$ Hz, 3H); $^{13}$C (150 MHz, CDCl$_3$) δ 164.1, 164.0, 159.4, 150.7, 150.6, 135.7, 135.0, 130.9, 130.7, 130.6, 129.7, 129.2, 125.1, 123.5, 123.4, 113.9, 97.3, 95.3, 81.8, 73.2, 71.3, 70.2, 66.1, 65.3, 55.3, 36.7, 18.4, 15.8; CIHRMS calcd for [C$_{34}$H$_{34}$N$_2$O$_{13}$Na]$^+_{15}$: 701.1953, found 701.1952.


A CH$_2$Cl$_2$ (12 mL) solution of Boc pyranone (ent)-II-7 ($\alpha$-D) (4.9 g, 21.5 mmol) and alcohol (ent)-II-14 (1.8 g, 4.3 mmol) was cooled to 0 °C. A solution of Pd$_2$(dba)$_3$•CHCl$_3$ (110 mg, 0.11 mmol) and PPh$_3$ (115 mg, 0.44 mmol) in CH$_2$Cl$_2$ (12 mL) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with satd. aqueous NaHCO$_3$, extracted with ether (3 x 30 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give pyranone (ent)-II-15-a (2.15 g, 4.08 mmol, 95%) as a yellow solid: R$_f$ (20% EtOAc/hexanes) = 0.30; mp: 133-135 °C; $[\alpha]^{23}_D$ = -85.0 ($c = 0.52$, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2944, 1726, 1702, 1611, 1528, 1515, 1272, 1102, 1082, 986, 834, 720; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.31 (d, $J = 9.0$ Hz, 2H), 8.21 (d, $J = 8.4$ Hz, 2H),
7.27 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.42 (dd, J = 10.2, 3.0 Hz, 1H), 5.96 (d, J = 10.2 Hz, 1H), 5.42 (d, J = 3.0 Hz, 1H), 5.25 (dd, J = 11.4, 9.0, 5.4 Hz, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.66 (dd, J = 9.0, 1.8 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.56 (q, J = 6.6 Hz, 1H), 3.81 (s, 3H), 3.76 (dd, J = 9.0, 9.0 Hz, 1H), 3.50 (dq, J = 9.0, 6.0 Hz, 1H), 2.44 (ddd, J = 12.0, 5.4, 1.8 Hz, 1H), 1.85 (ddd, J = 12.0, 12.0, 9.6 Hz, 1H), 1.46 (d, J = 6.6 Hz, 3H), 1.37 (d, J = 6.6 Hz, 3H); ^13^C NMR (150 MHz, CDCl$_3$) $\delta$ 196.0, 163.6, 159.4, 150.9, 142.0, 134.7, 130.6, 129.7, 129.1, 127.3, 123.9, 113.9, 97.3, 94.2, 80.4, 75.6, 70.7, 70.6, 70.3, 55.3, 36.7, 18.2, 14.9; CIHRMS calcd for [C$_{27}$H$_{29}$NO$_{10}$Na]$^+$: 550.1684, found 550.1695.


Pyranone (ent)-II-15-a (0.8 g, 1.52 mmol) was dissolved in CH$_2$Cl$_2$ (3.8 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl$_3$ (3.8 mL, 1.52 mmol) in methanol solution was added dropwise, followed by the addition of NaBH$_4$ (86.5 mg, 2.27 mmol). By TLC tracking, the reaction was completed after 1.5 h. The reaction mixture was diluted with ether (10 mL), and then quenched with water (3 mL), extracted with ether (3 x 20 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give allylic alcohol (ent)-II-15 (537 mg, 1.01 mmol, 67%) as a white solid: R$_f$ (50% EtOAc/hexanes) = 0.35;
mp: 124-126 °C; [α]$_D^{23}$ = -40.0 (c = 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2920, 2853, 1738, 1265, 738; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.29 (d, $J$ = 9.0 Hz, 2H), 8.18 (d, $J$ = 9.0 Hz, 2H), 7.27 (d, $J$ = 9.0 Hz, 2H), 6.88 (d, $J$ = 8.4 Hz, 2H), 5.83 (d, $J$ = 10.2 Hz, 1H), 5.40 (ddd, $J$ = 10.2, 2.4, 2.4 Hz, 1H), 5.20 (ddd, $J$ = 12.0, 9.6, 5.4 Hz, 1H), 5.15 (brs, 1H), 4.83 (d, $J$ = 11.4 Hz, 1H), 4.64 (dd, $J$ = 9.6, 1.8 Hz, 1H), 4.55 (d, $J$ = 12.0 Hz, 1H), 3.81 (s, 3H), 3.79 (br, 1H), 3.68 (dd, $J$ = 9.0, 9.0 Hz, 1H), 3.66 (dq, $J$ = 8.4, 6.0 Hz, 1H), 3.46 (dq, $J$ = 9.0, 6.0 Hz, 1H), 2.42 (ddd, $J$ = 12.0, 4.8, 1.8 Hz, 1H), 1.81 (ddd, $J$ = 12.6, 12.0, 9.6 Hz, 1H), 1.45 (d, $J$ = 6.6 Hz, 1H), 1.31 (d, $J$ = 6.6 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 163.7, 159.4, 150.8, 135.0, 134.0, 130.6, 129.6, 129.2, 125.7, 123.8, 113.9, 97.4, 95.2, 79.6, 75.7, 70.8, 70.2, 69.2, 68.3, 55.3, 36.7, 18.0, 17.6; CIHRMS calcd for [C$_{27}$H$_{31}$NO$_{10}$Na]$^+$: 552.1840, found 552.1848.

(2R,3R,4R,6R)-3-((2R,5R,6R)-5,6-dihydro-5-(4-nitrobenzoate)-6-methyl-2H-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2H-pyran-4-yl 4-nitrobenzoate ((ent)-II-16)

![Chemical Structure](image)

To a THF (7 mL) solution of alcohol (ent)-II-15 (651 mg, 1.23 mmol) at 0 °C was added PPh$_3$ (647 mg, 2.46 mmol) and p-nitrobenzoic acid (406 mg, 2.46 mmol), DIAD (0.52 mL, 2.46 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (20 mL),
quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give product (ent)-II-16 (590 mg, 0.87 mmol, 71%) as a white solid: Rf (20% EtOAc/hexanes) = 0.22; mp: 205-207 °C; [α]$_D^{23}$ = -82.4 (c = 1.0, CH₂Cl₂); IR (thin film, cm$^{-1}$) 2937, 1724, 1609, 1528, 1348, 1270, 1102, 1066, 1048, 984, 833, 719; $^1$H NMR (600 MHz, CDCl₃) δ 8.30 (d, $J$ = 9.0 Hz, 2H), 8.27 (d, $J$ = 9.0 Hz, 2H), 8.20 (d, $J$ = 9.0 Hz, 2H), 7.27 (d, $J$ = 8.4 Hz, 2H), 6.89 (d, $J$ = 8.4 Hz, 2H), 6.12 (dd, $J$ = 9.6, 5.4 Hz, 1H), 5.74 (dd, $J$ = 10.2, 3.0 Hz, 1H), 5.30 (d, $J$ = 3.0 Hz, 1H), 5.24 (dd, $J$ = 12.0, 9.0, 5.4 Hz, 1H), 5.13 (dd, $J$ = 5.4, 2.4 Hz, 1H), 4.84 (d, $J$ = 11.4 Hz, 1H), 4.66 (dd, $J$ = 9.6, 1.8 Hz, 1H), 4.56 (d, $J$ = 11.4 Hz, 1H), 4.33 (dq, $J$ = 6.6, 2.4 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, $J$ = 9.6, 9.0 Hz, 1H), 3.49 (dq, $J$ = 9.0, 6.0 Hz, 1H), 2.43 (dd, $J$ = 12.0, 4.8, 1.8 Hz, 1H), 1.85 (ddd, $J$ = 12.0, 12.0, 9.6 Hz, 1H), 1.47 (d, $J$ = 6.0 Hz, 1H), 1.31 (d, $J$ = 6.6 Hz, 1H); $^{13}$C (150 MHz, CDCl₃) δ 164.2, 163.7, 159.5, 150.8, 150.7, 135.0, 134.9, 130.8, 130.7, 130.3, 129.7, 129.2, 125.6, 123.8, 123.6, 113.9, 97.4, 95.3, 80.0, 75.6, 70.8, 70.3, 66.3, 65.4, 55.3, 36.8, 18.0, 16.0; CIHRMS calcd for [C$_{34}$H$_{34}$N$_2$O$_3$Na]$^+$: 701.1953, found 701.1967.
(2R,3R,4R,6R)-3-((2R,6S)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl oxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2H-pyran-4-yl 4-nitrobenzoate((ent)-II-7-a)

A CH₂Cl₂ (15 mL) solution of Boc-pyranone II-7 (a-L) (6.3 g, 27.55 mmol) and alcohol (ent)-II-14 (2.3 g, 5.51 mmol) was cooled to 0 °C. A solution of Pd₂(dba)₃•CHCl₃ (142 mg, 0.138 mmol) and PPh₃ (144 mg, 0.551 mmol) in CH₂Cl₂ (15 mL) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with satd. aqueous NaHCO₃, extracted with ether (3 x 30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give pyranone (ent)-II-17-a (2.7 g, 5.12 mmol, 93%) as a yellow solid: Rᵢ (30% EtOAc/hexanes) = 0.40; mp: 53-54 °C; [α]D²³ = -89.4 (c = 0.5, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 8.29 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.76 (dd, J = 10.2, 3.6 Hz, 1H), 6.00 (d, J = 10.2 Hz, 1H), 5.31 (d, J = 3.6 Hz, 1H), 5.28 (ddd, J = 11.4, 9.0, 6.0 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.64 (d, J = 9.6 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.31 (q, J = 6.6 Hz, 1H), 3.81 (s, 3H), 3.63 (dd, J = 9.0, 9.0 Hz, 1H), 3.49 (dq, J = 9.0, 6.0 Hz, 1H), 2.40 (dd, J = 12.6, 5.4 Hz, 1H), 1.84 (ddd, J = 12.6, 12.0, 12.0 Hz, 1H), 1.44 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 196.3, 163.9, 159.5, 150.7, 142.4,

\((2R,3R,4R,6R)-3-(((2S,5R,6S)-5,6-dihydro-5-hydroxy-6-methyl-2H-pyran-2-yl)oxy)-6-(4-methoxy-benzyl)oxy)-tetrahydro-2-methyl-2H-pyran-4-yl 4-nitrobenzoate (\textit{ent-}\textit{II-17})

Pyranone (\textit{ent-}\textit{II-17-a} (2.7 g, 5.1 mmol) was dissolved in CH\(_2\)Cl\(_2\) (12.8 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl\(_3\) (12.8 mL, 5.1 mmol) in methanol solution was added dropwise, followed by the addition of NaBH\(_4\) (291 mg, 7.7 mmol). By TLC tracking, the reaction was completed after 1.5 h. The reaction mixture was diluted with ether (20 mL), and then quenched with water (5 mL), extracted with ether (3 x 50 mL), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure to give allylic alcohol (\textit{ent-}\textit{II-17} (2.6 g, 4.9 mmol, 96%) as a white solid: R\(_f\) (30% EtOAc/hexanes) = 0.20; mp: 159-160 °C; [\(\alpha\)]\textsubscript{D}\(^{23}\) = -110.2 (c = 0.5, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.28 (d, \(J = 8.4\) Hz, 2H), 8.21 (d, \(J = 8.4\) Hz, 2H), 7.27 (d, \(J = 8.4\) Hz, 2H), 6.89 (d, \(J = 8.4\) Hz, 2H), 5.86 (d, \(J = 10.2\) Hz, 1H), 5.68 (ddd, \(J = 10.2, 2.4, 2.4\) Hz, 1H), 5.25 (ddd, \(J = 12.0, 8.4, 8.4\) Hz, 1H).
5.4 Hz, 1H), 5.06 (d, J = 2.4 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.64 (dd, J = 9.6, 1.8 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 3.81 (s, 3H), 3.62 (ddd, J = 9.0, 9.0, 1.8 Hz, 1H), 3.56 (dd, J = 9.0, 9.0 Hz, 1H), 3.48 (dq, J = 9.0, 6.0 Hz, 1H), 3.44 (dq, J = 9.0, 6.0 Hz, 1H), 2.39 (ddd, J = 12.6, 5.4, 1.8 Hz, 1H), 1.83 (ddd, J = 12.6, 12.0, 10.2 Hz, 1H), 1.43 (d, J = 6.0 Hz, 3H), 0.83 (d, J = 6.0 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 164.0, 159.4, 150.5, 135.8, 133.2, 130.8, 129.7, 129.2, 126.2, 123.5, 113.9, 97.4, 95.5, 81.8, 73.4, 71.3, 70.2, 69.1, 68.6, 55.3, 36.7, 18.4, 17.5.


To a THF (12 mL) solution of alcohol (ent)-II-17 (1.22 g, 2.3 mmol) at 0 °C was added PPh3 (1.21 g, 4.6 mmol) and p-nitrobenzoic acid (0.76 g, 4.6 mmol), DIAD (0.94 mL, 4.6 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (20 mL), quenched with satd. aqueous NaHCO3, extracted with CH2Cl2 (3 x 50 mL), dried over Na2SO4, and concentrated under reduced pressure. The crude product was purified using silica gel
flash chromatography eluting with 20% EtOAc/Hexanes to give product (ent)-II-18 (1.2 g, 1.77 mmol, 77%) as a white solid: R$_f$ (30% EtOAc/hexanes) = 0.40; mp: 169-170 °C; 
$[\alpha]^{23}_D = 93.5$ (c = 1.0, CH$_2$Cl$_2$); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.28 (d, $J$ = 8.4 Hz, 2H), 8.24 (d, $J$ = 8.4 Hz, 2H), 8.23 (d, $J$ = 8.4 Hz, 2H), 8.09 (d, $J$ = 9.0 Hz, 2H), 7.26 (d, $J$ = 8.4 Hz, 2H), 6.88 (d, $J$ = 8.4 Hz, 2H), 6.14 (dd, $J$ = 10.2, 5.4 Hz, 1H), 6.03 (dd, $J$ = 10.2, 3.0 Hz, 1H), 5.28 (ddd, $J$ = 12.0, 9.0, 6.0 Hz, 1H), 5.22 (d, $J$ = 2.4 Hz, 1H), 4.98 (dd, $J$ = 5.4, 2.4 Hz, 1H), 4.83 (d, $J$ = 11.4 Hz, 1H), 4.65 (dd, $J$ = 9.6, 1.2 Hz, 1H), 4.56 (d, $J$ = 11.4 Hz, 1H), 4.10 (dq, $J$ = 6.6, 2.4 Hz, 1H), 3.80 (s, 3H), 3.62 (dd, $J$ = 9.0, 9.0 Hz, 1H), 3.53-3.49 (m, 1H), 2.39 (ddd, $J$ = 12.0, 5.4, 1.8 Hz, 1H), 1.86 (ddd, $J$ = 15.0, 9.6, 9.6 Hz, 1H), 1.45 (d, $J$ = 6.6 Hz, 3H), 0.79 (d, $J$ = 6.6 Hz, 3H); $^{13}$C (150 MHz, CDCl$_3$) $\delta$ 164.1, 164.0, 159.4, 150.7, 150.6, 135.7, 135.0, 130.9, 130.7, 130.6, 129.7, 129.2, 125.1, 123.5, 123.4, 113.9, 97.3, 95.3, 81.8, 73.2, 71.3, 70.2, 66.1, 65.3, 55.3, 36.7, 18.4, 15.8.


(2R,3R,6R)-6-((2S,3R,4S,6S)-6-(4-methoxybenzylxoy)-4-hydroxy-2-methyl-tetrahydro-2H-pyran-3-yloxy)-2-methyl-3,6-dihydro-2H-pyran-3-ol (II-19)

Bis-nitrobenzoate II-18 (563 mg, 0.83 mmol) was dissolved in a mixed solvent of THF/H$_2$O (12 mL/2.4 mL) at room temperature, LiOH•H$_2$O (80 mg, 1.9 mmol) was
added and the reaction stirred for 24 h. The reaction was quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give product **II-19** (280 mg, 0.736 mmol, 89%) as a white solid: Rₜ (50% EtOAc/hexanes) = 0.15; mp: 137-138 °C; [α]̅₂₃⁰ = -33.4 (c = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3414, 3390, 2922, 1611, 1513, 1456, 1360, 1246, 1094, 1000, 897, 823; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.22 (dd, J = 10.2, 6.0 Hz, 1H), 5.87 (dd, J = 9.6, 3.0 Hz, 1H), 5.06 (d, J = 3.0 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.59 (brs, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.52 (dd, J = 9.6, 1.8 Hz 1H), 4.22 (dq, J = 6.6, 1.8 Hz, 1H), 3.80 (s, 3H), 3.63 (br, 1H), 3.60 (ddd, J = 12.0, 8.4, 5.4 Hz, 1H), 3.32 (dq, J = 9, 6.0 Hz, 1H), 3.04 (dd, J = 8.4, 8.4 Hz, 1H), 2.25 (ddd, J = 12.6, 5.4, 1.8 Hz, 1H), 1.67 (ddd, J = 12.6, 12.0, 9.6 Hz, 1H), 1.50 (d, J = 10.2 Hz, 1H), 1.35 (d, J = 6.6 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 159.3, 130.3, 129.6, 129.5, 127.2, 113.8, 98.1, 96.6, 88.9, 70.4, 70.1, 70.0, 67.8, 63.5, 55.3, 38.2, 18.0, 15.9; CIHRMS calcd for [C₂₀H₃₈O₇Na]⁺: 403.1727, found 403.1734.


![II-20](image)

Allylic alcohol **II-19** (274 mg, 0.72 mmol) was dissolved in CH₂Cl₂ (10 mL) at room temperature, then NBSH (0.94 g, 4.32 mmol) and Et₃N (0.80 mL, 5.76 mmol) were
added by stirring. The reaction was tracked by TLC and after 12 h, the reaction was quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give diol **II-20** (220 mg, 0.575 mmol, 80%) as a colorless oil: Rₐ (50% EtOAc/hexanes) = 0.15; [α]²³_D = 83.0 (c = 0.5, CH₂Cl₂); IR (thin film, cm⁻¹) 3395, 2934, 1613, 1515, 1370, 1248, 1167, 1115, 1068, 1011, 979, 821; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 4.92 (d, J = 2.4 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.79 (brs, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.50 (dd, J = 9.6, 1.8 Hz, 1H), 4.14 (dq, J = 6.6, 1.8 Hz, 1H), 3.79 (s, 3H), 3.62 (brs, 1H), 3.58-3.53 (m, 1H), 3.31 (dq, J = 9.0, 6.0 Hz, 1H), 2.98 (dd, J = 9.0, 8.4 Hz, 1H), 2.21 (dd, J = 12.6, 5.4, 1.8 Hz, 1H), 2.08-2.03 (m, 1H), 2.00-1.95 (m, 1H), 1.77-1.74 (m, 1H), 1.68-1.58 (m, 2H), 1.32 (d, J = 6.0 Hz, 3H), 1.21 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 159.3, 129.6, 129.5, 113.8, 99.6, 98.0, 88.7, 70.4, 70.3, 69.9, 68.0, 67.1, 55.3, 38.2, 25.4, 24.2, 18.1, 16.9; CIHRMS calcd for [C₂₀H₃₀O₇Na]⁺: 405.1884, found 405.1884.

A CH₂Cl₂ (3 mL) solution of Boc pyranone II-7 (α-L) (200 mg, 0.80 mmol) and alcohol II-20 (112 mg, 0.29 mmol) was cooled to 0 °C. Pd₂(dba)₃•CHCl₃ (7.6 mg, 0.0073 mmol) and PPh₃ (7.6 mg, 0.029 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone (ent)-II-2 (80 mg, 0.162 mmol, 56%) as a white solid along with recovered starting material II-20 (20 mg, 0.026 mmol, 18%): Rf (50% EtOAc/hexanes) = 0.30; mp: 83-86 °C; [α]蛛₂₃ = 75.8 (c = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3414, 2935, 1698, 1613, 1514, 1370, 1247, 1067, 1026, 1006, 967, 733; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.79 (dd, J = 10.2, 3.6 Hz, 1H), 6.10 (d, J = 10.2 Hz, 1H), 5.27 (d, J = 3.0 Hz, 1H), 4.95 (brs, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.76 (brs, 1H), 4.60 (q, J = 6.6 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.50 (dd, J = 9.6, 1.8 Hz, 1H), 4.23 (dq, J = 5.4, 1.2 Hz, 1H), 3.82 (brs, 1H), 3.80 (s, 3H), 3.59-3.55 (m, 1H), 3.32 (dq, J = 9.0, 6.0 Hz, 1H), 3.00 (dd, J = 9.0, 8.4 Hz, 1H), 2.21 (ddd, J = 12.6, 5.4, 1.8 Hz, 1H), 2.05-2.02 (m, 1H), 1.94-1.88 (m, 2H), 1.67-1.60 (m, 2H), 1.36 (d, J = 7.2 Hz, 3H), 1.32 (d, J = 6.0 Hz, 3H), 1.25 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 196.7, 159.5, 143.4, 129.9, 129.7, 127.8, 114.0, 99.5, 98.2, 90.5, 88.8, 71.8, 70.8, 70.6, 70.5, 70.1, 68.1, 55.5, 38.4, 24.8, 21.4, 18.3, 17.3, 15.3; CIHRMS calcd for [C₂₆H₃₆O₉Na]⁺: 515.2252, found 515.2236.

A CH$_2$Cl$_2$ (3 mL) solution of Boc pyranone (ent)-II-7 (α-D) (100 mg, 0.44 mmol) and alcohol II-20 (56 mg, 0.146 mmol) was cooled to 0 °C. Pd$_2$(dba)$_3$•CHCl$_3$ (3.8 mg, 0.00365 mmol) and PPh$_3$ (3.8 mg, 0.0146 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 5 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone (ent)-II-1 (37 mg, 0.075 mmol, 52%) as a white solid along with recovered starting material II-20 (10 mg, 0.12 mmol, 18%): R$_f$ (50% EtOAc/hexanes) = 0.30; mp: 112-113 °C; [$\alpha$]$^\text{23}_D$ = 26.4 (c = 0.55, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3411, 2925, 2856, 1701, 1614, 1515, 1458, 1376, 1249, 1084, 1035, 1010, 738; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.27 (d, $J$ = 8.4 Hz, 2H), 6.88 (d, $J$ = 8.4 Hz, 2H), 6.86 (dd, $J$ = 10.2, 3.0 Hz, 1H), 6.10 (d, $J$ = 10.2 Hz, 1H), 5.23 (d, $J$ = 3.6 Hz, 1H), 4.94 (brs, 1H), 4.82 (d, $J$ = 12.0 Hz, 1H), 4.74 (brs, 1H), 4.56 (q, $J$ = 6.6 Hz, 1H), 4.53 (d, $J$ = 11.4 Hz, 1H), 4.50 (dd, $J$ = 10.2, 1.8 Hz, 1H), 4.16 (dq, $J$ = 6.6, 1.8 Hz, 1H), 3.80 (s, 3H), 3.67 (brs, 1H), 3.59-3.55 (m, 1H), 3.32 (dq, $J$ = 9.0, 6.0 Hz,
1H), 2.99 (dd, J = 9.0, 8.4 Hz, 1H), 2.21 (ddd, J = 12.6, 5.4, 1.8 Hz, 1H), 2.10-2.03 (m, 2H), 1.96-1.90 (m, 1H), 1.67-1.62 (m, 2H), 1.37 (d, J = 6.6 Hz, 3H), 1.33 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.6 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 196.5, 159.3, 142.7, 129.6, 129.5, 127.4, 113.8, 98.3, 98.0, 95.2, 88.6, 76.1, 70.6, 70.4, 70.3, 69.9, 67.7, 55.2, 38.2, 25.1, 24.3, 18.1, 16.9, 15.1; CIHRSMS calcd for [C26H36O9Na]+: 515.2252, found 515.2233.

(2S,3S,6S)-6-((2R,3S,4R,6R)-6-(4-methoxybenzylloxy)-4-hydroxy-2-methyl-tetrahydro-2H-pyran-3-yloxy)-2-methyl-3,6-dihydro-2H-pyran-3-ol (II-1-a)

Bis-nitrobenzoate (ent)-II-18 (563 mg, 0.83 mmol) was dissolved in a mixed solvent of THF/H2O (12 mL/2.4 mL) at room temperature, LiOH•H2O (80 mg, 1.9 mmol) was added and the reaction stirred for 24 h. The reaction was quenched with satd. aqueous NaHCO3, extracted with CH2Cl2 (3 x 50 mL), dried over Na2SO4, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give product II-1-a (296 mg, 0.78 mmol, 94%) as a white solid: Rf (50% EtOAc/hexanes) = 0.15; mp: 132-134 °C; [α]23D = 31.8 (c = 1.0, CH2Cl2); 1H NMR (600 MHz, CDCl3) δ 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.22 (dd, J = 10.2, 6.0 Hz, 1H), 5.87 (dd, J = 9.6, 3.0 Hz, 1H), 5.06 (d, J = 3.0 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.59 (brs, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.52 (dd, J = 9.6, 1.8 Hz 1H), 4.22 (dq, J = 6.6, 1.8 Hz, 1H), 3.80 (s, 3H), 3.63 (br, 1H), 3.60 (dd, J = 12.0,
8.4, 5.4 Hz, 1H), 3.32 (dq, \( J = 9 \), 6.0 Hz, 1H), 3.04 (dd, \( J = 8.4 \), 8.4 Hz, 1H), 2.25 (ddd, \( J = 12.6 \), 5.4, 1.8 Hz, 1H), 1.67 (ddd, \( J = 12.6 \), 12.0, 9.6 Hz, 1H), 1.50 (d, \( J = 10.2 \) Hz, 1H), 1.35 (d, \( J = 6.6 \) Hz, 3H), 1.33 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta \) 159.3, 130.3, 129.6, 129.5, 127.2, 113.8, 98.1, 96.6, 88.9, 70.4, 70.1, 70.0, 67.8, 63.5, 55.3, 38.2, 18.0, 15.9.


\((2S,3S,6S)-6-((2R,3S,4R,6R)-6-(4-methoxybenzyloxy)-tetrahydro-4-hydroxy-2-methyl-2H-pyran-3-yloxy)-tetrahydro-2-methyl-2H-pyran-3-ol (II-1-b)\)

\[\text{PMBO} \quad \text{CH}_3 \]

Allylic alcohol \( \text{II-1-a} \) (296 mg, 0.78 mmol) was dissolved in CH\(_2\)Cl\(_2\) (12 mL) at room temperature, then NBSH (1.02 g, 4.67 mmol) and Et\(_3\)N (0.86 mL, 6.22 mmol) were added by stirring. The reaction was tracked by TLC and after 12 h, the reaction was quenched with satd. aqueous NaHCO\(_3\), extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give diol \( \text{II-1-b} \) (290 mg, 0.76 mmol, 97%) as a colorless oil: \( R_f \) (50% EtOAc/hexanes) = 0.15; \( [\alpha]^{23}_D = -96.4 \) (c = 0.85, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.27 (d, \( J = 9.0 \) Hz, 2H), 6.87 (d, \( J = 9.0 \) Hz, 2H).

$$\text{D}$$

A CH$_2$Cl$_2$ (3 mL) solution of Boc pyranone (ent)-II-7 ($\alpha$-D) (137 mg, 0.60 mmol) and alcohol II-1-b (76.5 mg, 0.20 mmol) was cooled to 0 °C. Pd$_2$(dba)$_3$•CHCl$_3$ (5.2 mg, 0.005 mmol) and PPh$_3$ (5.2 mg, 0.02 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was
quenched with satd. aqueous NaHCO$_3$ (5 mL), extracted with CH$_2$Cl$_2$ (3 x 5 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone II-2 (53 mg, 0.108 mmol, 54%) as a white solid along with recovered starting material II-1-b (10 mg, 0.026 mmol, 13%): $R_f$ (50% EtOAc/hexanes) = 0.30; mp: 83-86 °C; $[\alpha]_{D}^{23} = -79.8$ (c = 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3404, 2934, 1700, 1613, 1515, 1371, 1266, 1248, 1083, 1067, 1028, 1008, 734, 703; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.27 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 6.79 (dd, $J = 10.2$, 3.6 Hz, 1H), 6.10 (d, $J = 10.2$ Hz, 1H), 5.27 (d, $J = 3.0$ Hz, 1H), 4.95 (brs, 1H), 4.81 (d, $J = 11.4$ Hz, 1H), 4.76 (brs, 1H), 4.60 (q, $J = 6.6$ Hz, 1H ), 4.53 (d, $J = 11.4$ Hz, 1H), 4.50 (dd, $J = 9.6$, 1.8 Hz, 1H), 4.23 (dq, $J = 5.4$, 1.2 Hz, 1H), 3.82 (brs. 1H), 3.80 (s, 3H), 3.59-3.55 (m, 1H), 3.32 (dq, $J = 9.0$, 6.0 Hz, 1H), 3.00 (dd, $J = 9.0$, 8.4 Hz, 1H), 2.21 (ddd, $J = 12.6$, 5.4, 1.8 Hz, 1H), 2.05-2.02 (m, 1H), 1.94-1.88 (m, 2H), 1.67-1.60 (m, 2H), 1.36 (d, $J = 7.2$ Hz, 3H), 1.32 (d, $J = 6.0$ Hz, 3H), 1.25 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 196.7, 159.5, 143.4, 129.9, 129.7, 127.8, 114.0, 99.5, 98.2, 90.5, 88.8, 71.8, 70.8, 70.6, 70.5, 70.1, 68.1, 55.5, 38.4, 24.8, 21.4, 18.3, 17.3, 15.3; CIHRMS calcd for [C$_{26}$H$_{36}$O$_9$Na]$^+$: 515.2252, found 515.2235.

![Chemical Structure]

A CH<sub>2</sub>Cl<sub>2</sub> (3 mL) solution of Boc pyranone II-7 (α-L) (149 mg, 0.66 mmol) and alcohol II-1-b (83 mg, 0.22 mmol) was cooled to 0 °C. Pd<sub>2</sub>(dba)<sub>3</sub>•CHCl<sub>3</sub> (5.7 mg, 0.0055 mmol) and PPh<sub>3</sub> (5.8 mg, 0.022 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with satd. aqueous NaHCO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone II-1 (42 mg, 0.085 mmol, 39%) as a white solid along with recovered starting material II-1-b (45 mg, 0.12 mmol, 54%): R<sub>f</sub> (50% EtOAc/hexanes) = 0.30; mp: 112-113 °C; [α]<sup>23</sup><sub>D</sub> = -29.3 (c = 1.0, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.86 (dd, J = 10.2, 3.0 Hz, 1H), 6.10 (d, J = 10.2 Hz, 1H), 5.23 (d, J = 3.6 Hz, 1H), 4.94 (brs, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.74 (brs, 1H), 4.56 (q, J = 6.6 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.50 (dd, J = 10.2, 1.8 Hz, 1H), 4.16 (dq, J = 6.6, 1.8 Hz, 1H), 3.80 (s, 3H), 3.67 (brs, 1H), 3.59-3.55 (m, 1H), 3.32 (dq, J = 9.0, 6.0 Hz, 1H), 2.99 (dd, J = 9.0, 8.4 Hz, 1H), 2.21 (ddd, J = 12.6, 5.4, 1.8 Hz, 1H), 2.10-2.03 (m, 2H), 1.96-1.90 (m, 1H),...
1.67-1.62 (m, 2H), 1.37 (d, $J = 6.6$ Hz, 3H), 1.33 (d, $J = 6.0$ Hz, 3H), 1.23 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 196.5, 159.3, 142.7, 129.6, 129.5, 127.4, 113.8, 98.3, 98.0, 95.2, 88.6, 76.1, 70.6, 70.4, 70.3, 69.9, 67.7, 55.2, 38.2, 25.1, 24.3, 18.1, 16.9, 15.1.


(2S,3S,6S)-6-((2S,3R,4S,6S)-6-(4-methoxybenzyloxy)-tetrahydro-4-hydroxy-2-methyl-2H-pyran-3-yloxy)-3,6-dihydro-2-methyl-2H-pyran-3-ol (II-21-a)

Bis-nitrobenzoate **II-16** (473 mg, 0.70 mmol) was dissolved in a mixed solvent of THF/H$_2$O (10 mL/2 mL) at room temperature, LiOH•H$_2$O (67 mg, 1.6 mmol) was added and the reaction stirred for 24 h. The reaction was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give product **II-21-a** (237 mg, 0.62 mmol, 89%) as a white solid: $R_f$ (50% EtOAc/hexanes) = 0.10; mp: 123-125 °C; $[\alpha]_{D}^{23} = 126.0$ (c = 0.3, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3399, 2933, 1613, 1515, 1443, 1369, 1248, 1067, 1025, 821; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 6.19 (ddd, $J = 10.2, 4.8, 1.2$ Hz, 1H), 5.92 (dd, $J = 9.6, 3.0$ Hz, 1H), 5.49 (d, $J = 2.4$ Hz, 1H), 4.81 (d,
$J = 11.4 \text{ Hz, 1H}$, 4.51 (d, $J = 11.4 \text{ Hz, 1H}$), 4.50 (dd, $J = 9.6, 1.8 \text{ Hz, 1H}$), 4.12 (dq, $J = 6.6, 2.4 \text{ Hz, 1H}$), 3.80 (s, 3H), 3.72 (brs, 1H), 3.60 (br, 1H), 3.33 (dd, $J = 9.0, 8.4 \text{ Hz, 1H}$), 3.29 (dq, $J = 9.0, 6.0 \text{ Hz, 1H}$), 2.16 (dd, $J = 12.6, 5.4, 1.8 \text{ Hz, 1H}$), 2.01 (brs, 1H), 1.68 (dd, $J = 12.6, 12.0, 9.6 \text{ Hz, 1H}$), 1.64 (brs, 1H), 1.38 (d, $J = 6.0 \text{ Hz, 3H}$), 1.29 (d, $J = 6.6 \text{ Hz, 3H}$); $^{13}\text{C NMR}$ (150 MHz, CDCl$_3$) $\delta$ 159.3, 130.3, 129.7, 129.5, 128.1, 113.8, 97.8, 95.0, 82.2, 72.3, 70.7, 70.0, 67.0, 63.9, 55.3, 40.0, 18.0, 15.9; CIHRMS calcd for [C$_{20}$H$_{28}$O$_7$Na$^+$]: 403.1727, found 403.1744.

(2S,5S,6S)-6-((2S,3R,4S,6S)-6-(4-methoxybenzyloxy)-tetrahydro-4-hydroxy-2-methyl-2H-pyran-3-yl oxy)-tetrahydro-2-methyl-2H-pyran-3-ol (II-21)

![Structure of II-21](image)

Allylic alcohol II-21-a (120 mg, 0.315 mmol) was dissolved in CH$_2$Cl$_2$ (5 mL) at room temperature, then NBSH (0.415 g, 1.9 mmol) and Et$_3$N (0.35 mL, 2.53 mmol) were added by stirring. The reaction was tracked by TLC and after 12 h, the reaction was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes and 1% Et$_3$N to give diol II-21 (115 mg, 0.30 mmol, 95%) as a colorless oil: $R_f$ (50% EtOAc/hexanes) = 0.06; $[\alpha]_{D}^{23} = -16.7$ (c = 0.85, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3363, 2931, 2931, 1613, 1514, 1438, 1248, 1177, 1119, 1067, 1017, 981, 722; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.27 (d, $J = 9.0 \text{ Hz}$,
2H), 6.88 (d, J = 8.4 Hz, 2H), 5.34 (brs, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 7.2 Hz, 1H), 4.04 (dq, J = 6.6, 1.8 Hz, 1H), 3.80 (s, 3H), , 3.74 (burs, 1H), 3.60 (burs, 1H), 3.33 (dq, J = 9.0, 6.0 Hz, 1H), 3.24 (dd, J = 9.0, 8.4 Hz, 1H), 2.19 (ddd, J = 12.6, 5.4, 1.8 Hz, 1H), 2.13 (burs, 1H), 2.00-1.95 (m, 2H), 1.78-1.74 (m, 1H), 1.71-1.65 (m, 1H), 1.39 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 7.2 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 159.4, 129.7, 129.5, 113.8, 97.8, 97.0, 82.1, 71.8, 70.8, 70.0, 67.3, 67.0, 55.3, 39.7, 25.6, 23.8, 18.5, 17.0; CIHRMS calcd for [C20H30O7Na]+: 405.1884, found 405.1890.


A CH2Cl2 (2 mL) solution of Boc pyranone II-7 (α-L) (70 mg, 0.306 mmol) and alcohol II-21 (39 mg, 0.102 mmol) was cooled to 0 °C. Pd2(dba)3•CHCl3 (2.6 mg, 0.00255 mmol) and PPh3 (2.7 mg, 0.0102 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with satd. aqueous NaHCO3, extracted with CH2Cl2 (3 x 5 mL), dried over Na2SO4 and concentrated under reduced pressure. The crude product was purified using
silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone II-22 (14 mg, 0.0284 mmol, 28%) as a colorless oil: Rf (50% EtOAc/hexanes) = 0.27; [α]^23_D = -12.7 (c = 0.5, CH₂Cl₂); IR (thin film, cm⁻¹) 3488, 2930, 1701, 1617, 1516, 1376, 1251, 1069, 1032, 1018, 983; ′H NMR (600 MHz, CDCl₃) δ 7.28 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 6.69 (dd, J = 10.2, 4.2 Hz, 1H), 6.07 (d, J = 10.2 Hz, 1H), 5.28 (d, J = 3.6 Hz, 1H), 5.15 (d, J = 3.6 Hz, 1H), 4.82 (d, J = 11.4 Hz, 1H), 4.53 (dd, J = 9.6, 1.8 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.50 (q, J = 6.6 Hz, 1H), 4.05 (dq, J = 5.4, 1.8 Hz, 1H), 3.81 (s, 3H), 3.74-3.70 (m, 1H), 3.61 (brs, 1H), 3.34 (dd, J = 9.0, 9.0 Hz, 1H), 3.34 (dq, J = 9.0, 6.0, 1H), 2.32 (ddd, J = 12.0, 4.8, 1.8, 1H), 2.03-1.99 (m, 1H), 1.97-1.91 (m, 1H), 1.80-1.75 (m, 2H), 1.52-1.49 (m, 1H), 1.40 (d, J = 5.4 Hz, 3H), 1.34 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H); ′C NMR (150 MHz, CDCl₃) δ 196.5, 159.4, 142.2, 129.8, 129.3, 127.6, 113.9, 98.5, 97.7, 95.2, 81.9, 81.3, 70.9, 70.4, 70.1, 67.2, 66.8, 55.3, 38.8, 25.7, 23.8, 18.4, 16.9, 15.1; CIHRMS calcd for [C₂₆H₃₆O₉Na]^+: 515.2252, found 515.2261.

A CH₂Cl₂ (3 mL) solution of Boc pyranone (ent-II-7 (α-D) (88 mg, 0.384 mmol) and alcohol II-21 (49 mg, 0.128 mmol) was cooled to 0 °C. Pd₂(dba)₃•CHCl₃ (3.3 mg, 0.0032 mmol) and PPh₃ (3.3 mg, 0.013 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone II-22 (35 mg, 0.071 mmol, 56%) as a colorless oil: R_f (50% EtOAc/hexanes) = 0.36; [α]₂₃D = -30.4 (c = 0.70, CH₂Cl₂); IR (thin film, cm⁻¹) 3417, 2934, 1698, 1613, 1514, 1247, 1164, 1064, 1015, 974, 737; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.76 (dd, J = 10.2, 3.6 Hz, 1H), 6.07 (d, J = 10.2 Hz, 1H), 5.31 (d, J = 3.6 Hz, 1H), 5.27 (d, J = 2.4 Hz, 1H), 4.82 (d, J = 11.4 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.53 (dd, J = 9.6, 1.8 Hz, 1H), 4.43 (q, J = 6.6 Hz, 1H), 4.01 (dq, J = 5.4, 1.8 Hz, 1H), 3.95-3.91 (m, 1H), 3.81 (s, 3H), 3.58 (brs, 1H), 3.44 (dd, J = 9.0, 9.0 Hz, 1H), 3.37 (dq, J = 9.0, 6.0 Hz, 1H), 2.38 (dd, J = 12.0, 4.8, 1.8 Hz, 1H), 1.93-1.85 (m, 2H), 1.73-1.70 (m, 1H), 1.62-1.57 (m, 2H), 1.41 (d, J = 6.0 Hz, 3H), 1.38 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 196.5, 159.4, 143.9, 129.8, 129.3, 127.3, 113.9, 97.8, 97.6, 88.1, 78.9, 76.2, 71.1, 70.7, 70.1, 67.2, 66.8, 55.3, 35.4, 25.6, 23.5, 18.6, 17.0, 15.4; CIHRMS calcd for [C₂₆H₃₆O₉Na]⁺: 515.2252, found 515.2262.
Bis-nitrobenzoate (ent)-II-16 (480 mg, 0.707 mmol) was dissolved in a mixed solvent of THF/H$_2$O (10 mL/2.0 mL) at room temperature, LiOH•H$_2$O (119 mg, 2.83 mmol) was added and the reaction stirred for 24 h. The reaction was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give product (ent)-II-23-a (246 mg, 0.65 mmol, 91%) as a white solid: R$_f$ (50% EtOAc/hexanes) = 0.10; mp: 123-125 °C; [$\alpha$]$^D_{23}$ = -119.9 (c = 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3399, 2933, 1613, 1515, 1443, 1368, 1248, 1066, 1025, 901, 821; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 6.19 (ddd, $J = 10.2$, 4.8, 1.2 Hz, 1H), 5.92 (dd, $J = 9.6$, 3.0 Hz, 1H), 5.49 (d, $J = 2.4$ Hz, 1H), 4.81 (d, $J = 11.4$ Hz, 1H), 4.51 (d, $J = 11.4$ Hz, 1H), 4.50 (dd, $J = 9.6$, 1.8 Hz, 1H), 4.12 (dq, $J = 6.6$, 2.4 Hz, 1H), 3.80 (s, 3H), 3.72 (brs, 1H), 3.60 (br, 1H), 3.33 (dd, $J = 9.0$, 8.4 Hz, 1H), 3.29 (dq, $J = 9.0$, 6.0 Hz, 1H), 2.16 (ddd, $J = 12.6$, 5.4, 1.8 Hz, 1H), 2.01 (brs, 1H), 1.68 (ddd, $J = 12.6$, 12.0, 9.6 Hz, 1H), 1.64 (brs, 1H), 1.38 (d, $J = 6.0$ Hz, 3H), 1.29 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.3, 130.3, 129.7, 129.5, 128.1, 113.8, 97.8, 95.0, 82.2, 72.3, 70.7, 70.0, 67.0, 63.9, 55.3, 40.0, 18.0, 15.9; CIHRMS calcd for [C$_{20}$H$_{28}$O$_7$Na]$^+$: 403.1727, found 403.1732.
(2R,3R,6R)-6-((2R,3S,4R,6R)-6-(4-methoxybenzylxylo)-tetrahydro-4-hydroxy-2-methyl-2H-pyran-3-yloxy)-tetrahydro-2-methyl-2H-pyran-3-ol (ent-II-23-b)

Allylic alcohol (ent)-II-23-a (241 mg, 0.634 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) at room temperature, then NBSH (0.83 g, 3.80 mmol) and Et$_3$N (0.70 mL, 5.07 mmol) were added by stirring. The reaction was tracked by TLC and after 24 h, the reaction was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes and 1% Et$_3$N to give diol (ent)-II-23-b (230 mg, 0.60 mmol, 94%) as a colorless oil: R$_f$ (50% EtOAc/hexanes) = 0.06; $[\alpha]^2_{D}$ = 16.7 (c = 0.85, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3370, 2931, 1612, 1514, 1438, 1248, 1177, 1119, 1067, 1017, 981, 722, 695; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.27 (d, $J$ = 9.0 Hz, 2H), 6.88 (d, $J$ = 8.4 Hz, 2H), 5.34 (brs, 1H), 4.81 (d, $J$ = 11.4 Hz, 1H), 4.52 (d, $J$ = 11.4 Hz, 1H), 4.52 (d, $J$ = 7.2 Hz, 1H), 4.04 (dq, $J$ = 6.6, 1.8 Hz, 1H), 3.80 (s, 3H), 3.74 (brs, 1H), 3.60 (brs, 1H), 3.33 (dq, $J$ = 9.0, 6.0 Hz, 1H), 3.24 (dd, $J$ = 9.0, 8.4 Hz, 1H), 2.19 (ddd, $J$ = 12.6, 5.4, 1.8 Hz, 1H), 2.13 (brs, 1H), 2.00-1.95 (m, 2H), 1.78-1.74 (m, 1H), 1.71-1.65 (m, 1H), 1.39 (d, $J$ = 6.6 Hz, 3H), 1.19 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.4, 129.7, 129.5, 113.8, 97.8, 97.0, 82.1, 71.8, 70.8, 70.0, 67.3, 67.0, 55.3, 39.7, 25.6, 23.8, 18.5, 17.0; CIHRMS calcd for [C$_{20}$H$_{30}$O$_7$Na]$^+$: 405.1884, found 405.1885.

A CH$_2$Cl$_2$ (3 mL) solution of Boc pyranone II-7 ($\alpha$-L) (87 mg, 0.381 mmol) and alcohol (ent)-II-23-b (48 mg, 0.127 mmol) was cooled to 0 °C. Pd$_2$(dba)$_3$•CHCl$_3$ (3.3 mg, 0.00318 mmol) and PPh$_3$ (3.3 mg, 0.0127 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 5 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone (ent)-II-23 (19 mg, 0.038 mmol, 30%) as a colorless oil: R$_f$(50% EtOAc/hexanes) = 0.36; [a]$_{D}^{23}$ = 31.2 (c = 0.42, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3417, 2939, 1699, 1440, 1176, 1120, 723; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.27 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 9.0$ Hz, 2H), 6.76 (dd, $J = 10.2$, 3.6 Hz, 1H), 6.07 (d, $J = 10.2$ Hz, 1H), 5.31 (d, $J = 3.6$ Hz, 1H), 5.27 (d, $J = 2.4$ Hz, 1H), 4.82 (d, $J = 11.4$ Hz, 1H), 4.53 (d, $J = 11.4$ Hz, 1H), 4.53 (dd, $J = 9.6$, 1.8 Hz, 1H), 4.43 (q, $J = 6.6$ Hz, 1H), 4.01 (dq, $J = 5.4$, 1.8 Hz, 1H), 3.95-3.91 (m, 1H), 3.81 (s, 3H), 3.58 (brs, 1H), 3.44 (dd, $J = 9.0$, 9.0 Hz, 1H), 3.37 (dq, $J = 9.0$, 6.0 Hz, 1H),
2.38 (ddd, \( J = 12.0, 4.8, 1.8 \) Hz, 1H), 1.93-1.85 (m, 2H), 1.73-1.70 (m, 1H), 1.62-1.57 (m, 2H), 1.41 (d, \( J = 6.0 \) Hz, 3H), 1.38 (d, \( J = 6.6 \) Hz, 3H), 1.16 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta \) 196.5, 159.4, 143.9, 129.8, 129.3, 127.3, 113.9, 97.8, 97.6, 88.1, 78.9, 76.2, 71.1, 70.7, 70.1, 67.2, 66.8, 55.3, 35.4, 25.6, 23.5, 18.6, 17.0, 15.4; CIHRMS calcd for [C\(_{26}\)H\(_{36}\)O\(_9\)Na]\(^+\): 515.2252, found 515.2261.

(2\(R\),6\(S\))-6-((2\(R\),3\(R\),6\(R\))-6-((2\(R\),3\(S\),4\(R\),6\(R\))-6-(4-methoxybenzyloxy)-tetrahydro-4-hydroxy-2-methyl-2\(H\)-pyran-3-yloxy)-tetrahydro-2-methyl-2\(H\)-pyran-3-yloxy)-2-methyl-2\(H\)-pyran-3(\(6\)\(H\)))-one((\(ent\))-II-22)

\[ \text{A CH}_2\text{Cl}_2 (3 \text{ mL}) \text{ solution of Boc pyranone (\(ent\))-II-7 (\(\alpha\)-D) (87 mg, 0.381 mmol) and alcohol (\(ent\))-II-23-b (48 mg, 0.127 mmol) was cooled to 0 °C. Pd}_2(\text{dba})_3\text{•CHCl}_3 (3.3 mg, 0.00318 mmol) and PPh}_3 (3.3 mg, 0.0127 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with satd. aqueous NaHCO\(_3\), extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone (\(ent\))- (\(ent\))-II-22 (20 mg, 0.041 mmol, 32%) as a colorless oil: R\(_f\) (50% EtOAc/hexanes) = 0.27; \([\alpha]_{D}^{25} = 12.4 (c = 1.0, \text{CH}_2\text{Cl}_2)\); IR (thin film, cm\(^{-1}\)) 3491, 2934, 1701, 1615, 1516, 2824, 1371, 1247, 1043, 754, 695.]
1376, 1250, 1068, 1033, 1018, 984; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.28 (d, $J = 9.0$ Hz, 2H), 6.89 (d, $J = 9.0$ Hz, 2H), 6.69 (dd, $J = 10.2$, 4.2 Hz, 1H), 6.07 (d, $J = 10.2$ Hz, 1H), 5.28 (d, $J = 3.6$ Hz, 1H), 5.15 (d, $J = 3.6$ Hz, 1H), 4.82 (d, $J = 11.4$ Hz, 1H), 4.53 (dd, $J = 9.6$, 1.8 Hz, 1H), 4.52 (d, $J = 11.4$ Hz, 1H), 4.50 (q, $J = 6.6$ Hz, 1H), 4.05 (dq, $J = 5.4$, 1.8 Hz, 1H), 3.81 (s, 3H), 3.74-3.70 (m, 1H), 3.61 (brs, 1H), 3.34 (dd, $J = 9.0$, 9.0 Hz, 1H), 3.34 (dq, $J = 9.0$, 6.0, 1H), 2.32 (dd, $J = 12.0$, 4.8, 1.8, 1H), 2.03-1.99 (m, 1H), 1.97-1.91 (m, 1H), 1.80-1.75 (m, 2H), 1.52-1.49 (m, 1H), 1.40 (d, $J = 5.4$ Hz, 3H), 1.34 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 196.5, 159.4, 142.2, 129.8, 129.3, 127.6, 113.9, 98.5, 97.7, 95.2, 81.9, 81.3, 70.9, 70.4, 70.1, 67.2, 66.8, 55.3, 38.8, 25.7, 23.8, 18.4, 16.9, 15.1; CIHRMS calcd for [C$_{26}$H$_{36}$O$_9$Na]$^+$: 515.2252, found 515.2261.

(2S,3S,4S,6S)-3-(((2S,5S,6S)-5-(2-chloroacetoxy)-6-methyl-5,6-dihydro-2H-pyran-2-yl)oxy)-6-((4-methoxybenzyl)oxy)-2-methyltetrahydro-2H-pyran-4-yl 4-nitrobenzoate (II-24)

To a THF (2.25 mL) solution of alcohol II-15 (180 mg, 0.34 mmol) at 0 °C was added PPh$_3$ (178.9 g, 0.68 mmol) and chloroacetic acid (64.13 mg, 0.68 mmol), DIAD (0.41 mL, 2.6 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (20 mL), quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over
Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/Hexanes to give product **II-24** (189.6 mg, 0.31 mmol, 92%) as a white solid: Rₚ (33% EtOAc/hexanes) = 0.70; mp: 140-147 °C; [α]²³° = 145.04 (c = 0.95, CH₂Cl₂); IR (thin film, cm⁻¹) 3296, 2869, 1729, 1529, 1277, 1104, 1067, 984, 720; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.00 (dd, J = 9.6 Hz, 5.2 Hz, 1H), 5.68 (dd, J = 10.4 Hz, 2.8 Hz, 1H), 5.24 (d, J = 2.0 Hz, 1H), 5.22-5.16 (m, 1H), 4.92 (dd, J = 6.0 Hz, 2.0 Hz, 1H), 4.82 (d, J = 11.6 Hz, 1H), 4.63 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.21 (dq, J = 6.4 Hz, 2.0 Hz, 1H), 4.04 (d, J = 6.8 Hz, 2H), 3.79 (s, 3H), 3.69 (t, J = 8.8, 1H), 3.45 (dq, J = 9.6 Hz, 6.4 Hz, 1H), 2.40 (dd, J = 11.6 Hz, 5.2 Hz, 1.2 Hz, 1H), 1.81 (q, J = 11.6 Hz, 1H), 1.42 (d, J = 6.8 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 163.6, 159.3, 150.7, 134.7, 130.6, 130.3, 129.6, 129.0, 125.3, 123.8, 113.8, 97.3, 95.0, 79.6, 75.5, 70.6, 70.2, 66.5, 65.0, 55.2, 40.6, 36.6, 17.9, 16.7; CIHRMS calcd for [C₂₉H₃₂ClNO₁₁Na]⁺: 628.1556, found 628.1566.

(2S,3S,4S,6S)-3-(((2S,5S,6S)-5-hydroxy-6-methyl-5,6-dihydro-2H-pyran-2-yl)oxy)-6-((4-methoxybenzyl)oxy)-2-methyltetrahydro-2H-pyran-4-yl 4-nitrobenzoate (**II-25**)

![II-25](image)

To a THF (24 mL) solution of ester **II-24** (817 mg, 1.35 mmol) was added thiourea (646 mg, 8.48 mmol), NaHCO₃ (711 mg, 8.46 mmol) and n-Bu₄NI (521 mg, 1.41 mmol). The
reaction mixture was stirred at 60 °C for 12 h. The reaction solution was pipetted directly on to a silica gel column and eluted with 10–40% EtOAc/Hexane to afford allylic alcohol II-25 (308 mg, 0.58 mmol, 43%) as a white solid: $R_f$ (33% EtOAc/hexanes) = 0.25; mp: 149-155 °C; $[\alpha]_D^{23} = 87.9$ (c = 0.8, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3432, 2979, 2935, 1726, 1601, 1529, 1350, 1274, 1103, 1049, 981, 720; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.30 (d, $J = 8.8$ Hz, 2H), 8.19 (d, $J = 8.8$ Hz, 2H), 7.27 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 6.09 (dd, $J = 9.6$ Hz, 5.2 Hz, 1H), 5.53 (dd, $J = 9.6$ Hz, 2.8 Hz, 1H), 5.24-5.18 (m, 1H), 5.19 (d, $J = 3.2$ Hz, , 2H), 4.84 (d, $J = 11.2$ Hz, 1H), 4.64 (dd, $J = 9.6$ Hz, 1.6 Hz, 1H), 4.55 (d, $J = 10.8$ Hz, 1H), 4.08 (dq, $J = 6.8$ Hz, 1.6 Hz, 1H), 3.81 (s, 3H), 3.71 (t, $J = 9.6$ Hz, 1H), 3.60-3.56 (m, 1H) 3.46 (dq, $J = 8.8$ Hz, 2.8 Hz, 1H), 2.42 (ddd, $J = 12.4$ Hz, 4.2 Hz, 1.6 Hz, 1H), 1.82 (dq, $J = 9.6$ Hz, 2.4 Hz, 1H), 1.44 (d, $J = 6.0$ Hz, 3H), 1.29 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.7, 159.4, 151.7, 134.9, 130.6, 130.5, 129.7, 129.1, 127.4, 123.8, 113.8, 97.4, 95.4, 79.3, 75.7, 70.8, 70.2, 67.0, 63.6, 55.3, 36.7, 18.0, 15.8; CIHRMS calcd for [C$_{27}$H$_{31}$NNaO$_{10}$]+: 552.1840, found 552.1848.

(2S,3S,4S,6S)-3-(((2S,5S,6S)-5-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-6-((4-methoxybenzyl)oxy)-2-methyltetrahydro-2H-pyran-4-yl 4-nitrobenzoate (II-26)

[Diagram of II-26]

Allylic alcohol II-25 (308 mg, 0.59 mmol) was dissolved in CH$_2$Cl$_2$ (13.7 mL) at room temperature, then NBSH (0.77 g, 3.64 mmol) and Et$_3$N (0.65 mL, 4.52 mmol) were
added by stirring. The reaction was tracked by TLC and after 12 h, the reaction was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes and 1% Et$_3$N to give diol II-26 (292 mg, 0.55 mmol, 93%) as a yellow oil: R$_f$ (33% EtOAc/hexanes) = 0.25; $[\alpha]^{23}_D$ = 11.37 (c = 0.69, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3490, 2935, 1726, 1529, 1274, 1117, 1067, 1017, 984, 833, 721; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.29 (d, $J$ = 8.8 Hz, 2H), 8.17 (d, $J$ = 8.8 Hz, 2H), 7.26 (d, $J$ = 8.8 Hz, 2H), 6.88 (d, $J$ = 8.0 Hz, 2H), 5.21-5.15 (m, 1H), 5.05 (d, $J$ = 2.8 Hz, 1H), 4.83 (d, $J$ = 11.6 Hz, 1H), 4.64 (dd, $J$ = 9.2 Hz, 1.2 Hz, 1H), 4.55 (d, $J$ = 10.8 Hz, 1H), 4.01 (q, $J$ = 6.4 Hz, 1H), 3.81 (s, 3H), 3.61 (t, $J$ = 8.8 Hz, 1H), 3.56 (brs, 1H) 3.51-3.44 (m, 1H), 2.37 (ddd, $J$ = 12.4 Hz, 5.2 Hz, 1.2 Hz, 1H), 1.87-1.61 (m, 6H), 1.45 (d, $J$ = 6.4 Hz, 3H), 1.17 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.7, 159.4, 150.7, 135.0, 130.7, 129.7, 129.1, 123.7, 113.8, 98.2, 97.3, 79.3, 75.7, 70.9, 70.2, 67.0, 66.9, 55.3, 36.6, 25.4, 23.5, 18.4, 17.0; CIHRMS calcd for [C$_{27}$H$_{33}$NO$_{11}$Na]$^+$: 554.1997, found 554.1993.

A CH$_2$Cl$_2$ (0.82 mL) solution of Boc pyranone II-7 (α-L) (342 mg, 1.5 mmol) and alcohol II-26 (125 mg, 0.235 mmol) was cooled to 0°C. Pd$_2$(dba)$_3$•CHCl$_3$ (7.8 mg, 0.0075 mmol) and PPh$_3$ (7.9 mg, 0.3 mmol) were added to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 5 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/Hexanes to give pyranone II-27 (107 mg, 0.17 mmol, 71%) as a yellow solid: R$_f$ (50% EtOAc/hexanes) = 0.50; mp: 65-69 °C [α]$_{D}^{23}$ = 60.48 (c = 0.48, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2937, 2856, 1726, 1529, 1274, 1102, 1071, 1016, 721; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 7.2 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.85 (dd, J = 10.4 Hz, 2.8 Hz, 1H), 6.06 (d, J = 10.4 Hz, 1H), 6.50 (d, J = 3.6 Hz, 2H ), 5.22-5.15 (m, 1H), 5.08 (d, J = 2.4 Hz, 1H), 4.83 (d, J = 11.2 Hz, 1H), 4.64 (dd, J = 9.6 Hz, 2.0 Hz 1H), 4.55 (d, J = 11.6 Hz, 1H), 4.43 (q, J = 6.8 Hz, 1H), 4.01 (q, J = 5.6 Hz, 1H), 3.81 (s, 3H), 3.64-3.59 (m, 2H), 3.51-3.44 (m, 1H), 2.40 (ddd, J = 12.4 Hz, 5.2 Hz, 2.4 Hz, 1H), 1.84-1.72 (m, 4H), 1.45 (d, J = 6.4 Hz, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 196.6, 163.8, 159.4, 150.7, 142.8, 134.9, 130.7, 129.7, 129.1, 127.3, 123.8, 113.9, 98.1, 97.3, 95.3, 79.4, 76.1, 75.7, 70.9, 70.5, 70.2, 66.7, 55.3, 36.6, 24.4, 24.3, 18.4, 17.0, 15.1; CIHRMS calcd for [C$_{33}$H$_{39}$NO$_{12}$Na]$^+$: 664.2364, found 664.2379.

A CH$_2$Cl$_2$ (0.82 mL) solution of Boc pyranone (ent)-II-7 (α-D) (80.0 mg, 0.35 mmol) and alcohol II-26 (44.5 mg, 0.08 mmol) was cooled to 0°C. Pd$_2$(dba)$_3$•CHCl$_3$ (3.1 mg, 0.003 mmol) and PPh$_3$ (3.1 mg, 0.012 mmol) were added to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 5 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/Hexanes to give pyranone II-28 (43.6 mg, 0.07 mmol, 85%) as a white solid: $R_f$ (33% EtOAc/hexanes) = 0.48; mp: 179-181 °C [α]$^2$$_D$ = -34.39 (c = 0.43, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2935, 1727, 1529, 1274, 1070, 1013, 721; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.29 (d, $J$ = 8.8 Hz, 2H), 8.17 (d, $J$ = 8.8 Hz, 2H), 7.27 (d, $J$ = 5.6 Hz, 2H), 6.89 (d, $J$ = 9.2 Hz, 2H), 6.71 (dd, $J$ = 10.0 Hz, 3.6 Hz, 1H), 6.07 (d, $J$ = 10.4 Hz, 1H), 5.18 (d, $J$ = 2.8 Hz, 2H), 5.22-5.15 (m, 1H), 5.09 (d, $J$ = 1.6 Hz, 1H), 4.83 (d, $J$ = 11.2 Hz, 1H), 4.64 (dd, $J$ = 9.6 Hz, 2.0 Hz 1H), 4.60 (d, $J$ = 6.4 Hz, 1H), 4.55 (d, $J$ = 12.0 Hz, 1H), 4.10 (q, $J$ = 7.2 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 1H), 3.62 (t, $J$ = 9.6 Hz, 1H), 3.47 (m, 1H), 2.40 (ddd, $J$ = 12.4 Hz, 5.2 Hz, 1.2 Hz, 1H), 1.83-
1.73 (m, 4H), 1.45 (d, J = 6.0 Hz, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 196.7, 163.8, 159.4, 150.7, 143.4, 134.9, 130.7, 129.7, 129.1, 127.4, 123.7, 113.9, 98.2, 97.3, 90.1, 79.5, 75.8, 71.5, 70.9, 70.6, 70.2, 66.9, 55.3, 36.6, 23.8, 21.1, 18.4, 17.0, 15.1; CIHRMS calcd for [C$_{33}$H$_{39}$NO$_{12}$Na]$^+$: 664.2364, found 664.2366.


To a THF (6.7 mL) solution of alcohol (ent)-II-15 (532.4 g, 1.01 mmol) at 0 °C was added PPh$_3$ (529.1 mg, 2.02 mmol) and chloroacetic acid (189.7 mg, 2.02 mmol), DIAD (1.213 mL, 7.73 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (20 mL), quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/Hexanes to give product (ent)-II-24 (605.9 mg, 0.99 mmol, 91%) as a white solid: $R_f$ (50% EtOAc/hexanes) = 0.83; mp: 138-147 °C; $[\alpha]_{D}^{25}$ = -129.3 (c = 0.73, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2939, 1729, 1529, 1275, 1169, 1104, 1066, 982, 720; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.31 (d, J = 8.8 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.89 (d, J =
8.8 Hz, 2H), 6.02 (dd, J = 9.6 Hz, 5.2 Hz, 1H), 5.56 (dd, J = 10.4 Hz, 2.8 Hz, , 1H), 5.26 (d, J = 2.4 Hz, , 2H), 5.24-5.19 (m, 1H), 4.89 (d, J = 7.6 Hz, 1H), 4.65 (dd, J = 9.2 Hz, 2.0 Hz, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.23 (dq, J = 6.4 Hz, 1.6 Hz, , 1H), 4.07 (d, J = 6 Hz, 2H), 3.81 (s, 3H), 3.71 (t, J = 8.8, 6.0 Hz, 1H), 3.47 (dq, J = 8.8, 6.8 Hz, 1H), 2.42 (dd, J = 12.0, 5.2, Hz, 1H), 1.83 (dd, J = 11.6, 21.2 Hz, 1H), 1.44 (d, J = 6 Hz, 3H), 1.26 (d, J = 6.4 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 167.3, 164.0, 159.7, 151.1, 135.1, 130.9, 130.6, 129.9, 129.4, 125.6, 124.1, 114.1, 97.7, 95.3, 80.0, 75.9, 71.0, 70.5, 66.8, 65.4, 55.5, 40.9, 37.0, 18.2, 16.0; CIHRMS calcd for [C_{29}H_{32}ClNO_{11}Na]^+: 628.1556, found 628.1566.


To a THF (3 mL) solution of ester (ent)-II-24 (22 mg, 0.038 mmol) was added thiourea (17.4 mg, 0.228 mmol), NaHCO3 (19.2 mg, 0.228 mmol) and n-Bu4NI (14 mg, 0.038 mmol). The reaction mixture was stirred at 60 oC for 12 h. The reaction solution was S24pipetted directly on to a silica gel column and eluted with 10~40% EtOAc/Hexane to afford allylic alcohol (ent)-II-25 (13.7 mg, 0.026 mmol, 68%) as a yellow solid: Rf (33% EtOAc/hexanes) = 0.35; mp: 135-140 °C; [α]_{D}^{23} = -94.6 (c = 1.1, CH2Cl2); IR (thin film, cm^{-1}) 3446, 2935, 1726, 1529, 1274, 1103, 1049, 981, 720; 1H NMR (400 MHz, CDCl3) δ 8.30 (d, J = 8.4 Hz, 2H), 8.18 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.88 (d, J =
8.0 Hz, 2H), 6.08 (dd, \( J = 10.4 \) Hz, 6.0 Hz, 1H), 5.53 (dd, \( J = 10.4 \) Hz, 3.2 Hz, 1H), 5.24-5.18 (m, 1H), 5.19 (d, \( J = 2.4 \) Hz, , 2H), 4.83 (d, \( J = 10.8 \) Hz, 1H), 4.64 (dd, \( J = 9.6 \) Hz, 1.6 Hz, 1H), 4.55 (d, \( J = 11.6 \) Hz, 1H), 4.08 (dq, \( J = 4.4 \) Hz, 2.0 Hz, 1H), 3.81 (s, 3H), 3.71 (t, \( J = 8.8 \) Hz, 1H), 3.57 (t, \( J = 7.2 \) Hz, 1H), 3.45 (dq, \( J = 7.2, 2.8 \) Hz, 1H), 2.41 (ddd, \( J = 11.6 \) Hz, 4.2 Hz, 1.2 Hz, 1H), 1.83 (dq, \( J = 9.6 \) Hz, 2.4 Hz, 1H), 1.44 (d, \( J = 6.8 \) Hz, 3H), 1.29 (d, \( J = 6.4 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 164.0, 159.7, 151.0, 135.2, 130.9, 130.8, 129.9, 129.5, 127.6, 124.1, 114.1, 97.7, 95.7, 80.0, 76.0, 71.1, 70.5, 67.3, 63.9, 55.5, 37.0, 18.2, 16.1; CIHRMS calcd for [C\(_{27}\)H\(_{31}\)NO\(_{10}\)Na]\(^+\): 552.1840, found 552.1848.


Allylic alcohol (ent)-II-25 (11 mg, 0.021 mmol) was dissolved in CH\(_2\)Cl\(_2\) (0.6 mL) at room temperature, then NBSH (27.5 mg, 0.13 mmol) and Et\(_3\)N (0.023 mL, 0.16 mmol) were added by stirring. The reaction was tracked by TLC and after 12 h, the reaction was quenched with satd. aqueous NaHCO\(_3\), extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes and 1% Et\(_3\)N to give (ent)-II-26 (10.6 mg, 0.020mmol, 95%) as a yellow oil: \( R_f \) (33% EtOAc/hexanes) = 0.35; \([\alpha]^{23}_D = -11.4643 \) (\( c = 1.15, \) CH\(_2\)Cl\(_2\)\); IR (thin film, cm\(^{-1}\)) 3464, 2936, 1726, 1529, 1275, 139
1117, 1068, 1017, 984, 834, 721; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.29 (d, $J = 8.8$ Hz, 2H), 8.17 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.22-5.15 (m, 1H), 5.05 (s, 1H), 4.83 (d, $J = 11.6$ Hz, 1H), 4.64 (d, $J = 9.6$ Hz, 1H), 4.55 (d, $J = 11.2$ Hz, 1H), 4.08 (q, $J = 6.8$ Hz, 1H), 3.81 (s, 3H), 3.47 (t, $J = 8.8$ Hz, 1H), 3.57 (brs, 1H) 3.50-3.44 (m, 1H), 2.41 (dd, $J = 12.4$ Hz, 5.2 Hz, 1H), 1.90-1.64 (m, 6H), 1.45 (d, $J = 6.0$ Hz, 3H), 1.17 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 163.7, 159.4, 150.7, 135.0, 130.7, 129.7, 129.2, 123.7, 113.9, 98.2, 97.3, 79.3, 75.7, 70.9, 70.2, 67.0, 66.9, 55.3, 36.6, 25.4, 23.5, 18.4, 17.0; CIHRMS calcd for [C$_{27}$H$_{33}$NO$_{10}$Na]$^+$: 554.1997, found 554.1993.


A CH$_2$Cl$_2$ (2.5 mL) solution of Boc pyranone (ent)-II-7 (α-D) (270 mg, 1.2 mmol) and alcohol (ent)-II-26 (150 mg, 0.28 mmol) was cooled to 0°C. Pd$_2$(dba)$_3$•CHCl$_3$ (10.5 mg, 0.01 mmol) and PPh$_3$ (10.5 mg, 0.04 mmol) were added to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 5 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/Hexanes to give pyranone (ent)-II-27 (131 mg, 0.204 mmol, 73%) as a yellow oil: R$_f$ (50% EtOAc/hexanes) = 0.71; [$\alpha$]$_D^{23}$
= -38.32 (c = 0.55, CH₂Cl₂); IR (thin film, cm⁻¹) 2930, 2853, 1726, 1529, 1275, 1016, 721; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 4.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.85 (dd, J = 10.4 Hz, 3.6 Hz, 1H), 6.06 (d, J = 10.4 Hz, 1H), 5.20 (d, J = 3.6 Hz, 2H), 5.22-5.15 (m, 1H), 5.08 (d, J = 2.4 Hz, 1H), 4.83 (d, J = 11.2 Hz, 1H), 4.64 (dd, J = 9.6 Hz, 2.0 Hz 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.43 (q, J = 6.8 Hz, 1H), 4.01 (q, J = 6.4 Hz, 1H), 3.81 (s, 3H), 3.64-3.59 (m, 2H), 3.47 (dq, J = 6.0 Hz, 2.8 Hz 1H), 2.41 (ddd, J = 12.4 Hz, 5.2 Hz, 1.6 Hz, 1H), 1.84-1.72 (m, 4H), 1.45 (d, J = 6.0 Hz, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 196.6, 163.8, 159.4, 150.7, 142.8, 134.9, 130.7, 129.7, 129.1, 127.4, 123.8, 113.9, 98.1, 97.3, 95.3, 79.4, 76.1, 75.7, 70.9, 70.2, 66.7, 55.3, 36.6, 24.4, 24.3, 18.4, 17.0, 15.1; CIHRMS calcd for [C₃₃H₃₉NO₁₂Na]⁺: 664.2364, found 664.2379.


A CH₂Cl₂ (0.76 mL) solution of Boc pyranone II-7(α-L) (319 mg, 1.41 mmol) and alcohol (ent)-II-26 (117 mg, 0.22 mmol) was cooled to 0°C. Pd₂(dba)₃•CHCl₃ (7.23 mg, 0.007 mmol) and PPh₃ (7.35 mg, 0.028 mmol) were added to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was
quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 33% EtOAc/Hexanes to give pyranone (ent)-II-28 (89.8 mg, 0.14 mmol, 65%) as a yellow solid: Rf (33 % EtOAc/hexanes) = 0.71; mp: 159-165 °C, [α]²³[D] = 22.49 (c = 0.70, CH₂Cl₂); IR (thin film, cm⁻¹) 2934, 1727, 1529, 1275, 1103, 1014, 721; ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 10.4 Hz, 4.0 Hz, 1H), 6.06 (d, J = 10.4 Hz, 1H), 5.19 (d, J = 3.6 Hz, 2H), 5.22-5.15 (m, 1H), 5.08 (d, J = 2.4 Hz, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.64 (dd, J = 9.6 Hz, 2.4 Hz 1H), 4.60 (d, J = 7.2 Hz, 1H), 4.55 (d, J = 11.2 Hz, 1H) 4.10 (q, J = 6.8 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 1H), 3.62 (q, J = 9.6 Hz, 1H), 3.47 (dq, J = 8.8 Hz, 2.8 Hz 1H), 2.40 (dd, J = 12.4 Hz, 4.8 Hz, 1.6 Hz, 1H), 1.85-1.73 (m, 4H), 1.45 (d, J = 6.4 Hz, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 196.7, 163.8, 159.4, 150.7, 143.4, 134.9, 130.7, 129.7, 129.1, 127.4, 123.7, 113.9, 98.1, 97.3, 90.1, 79.5, 75.8, 71.5, 70.9, 70.5, 70.2, 66.9, 55.3, 36.6, 23.8, 21.1, 18.4, 17.2, 15.1; CIHRMS calcd for [C₃₃H₃⁹NO₁₂Na]⁺: 664.2364, found 664.2366.

Pyranone **II-27** (107 mg, 0.17 mmol) was dissolved in CH$_2$Cl$_2$ (0.52 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl$_3$ (0.0.52 mL, 0.21 mmol) in methanol solution was added dropwise, followed by the addition of NaBH$_4$ (10.0 mg, 0.27 mmol). By TLC tracking, the reaction was completed after 1 h. The reaction mixture was diluted with ether (20 mL), and then quenched with water (5 mL), extracted with ether (3 x 50 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give allylic alcohol **II-29** (98.5 mg, 0.15 mmol, 90%) as a white solid: R$_f$ (50% EtOAc/hexanes) = 0.48; mp: 140-143 °C; [α]$^2$$^\circ$ = 23.58 (c = 0.86, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2933, 1726, 1529, 1275, 1101, 1017, 721; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.29 (d, $J$ = 8.8 Hz, 2H), 8.17 (d, $J$ = 8.8 Hz, 2H), 7.27 (d, $J$ = 2.4 Hz, 2H), 6.88 (d, $J$ = 8.8 Hz, 2H), 5.88 (d, $J$ = 10.4 Hz, 1H), 5.78 (ddd, $J$ = 10.4 Hz, 2.4 Hz, 2.0 Hz 1H ), 5.21-5.14 (m, 1H), 5.08 ( d, $J$ = 2.0 Hz, 1H), 4.93 (s, 1H), 4.83 (d, $J$ = 11.6 Hz, 1H), 4.63 (dd, $J$ = 9.6 Hz, 2.4 Hz, 1H), 4.55 (d, $J$ = 11.6 Hz, 1H), 3.95 (q, $J$ = 6.4 Hz, 1H), 3.80 (s, 3H) , 3.62 (m, 2H), 3.50-3.44 (m, 2H), 2.39 (ddd, $J$ = 12.4 Hz, 5.2 Hz, 1.6 Hz, 1H), 1.91-1.72 (m, 6H), 1.61 ( brs, 1H), 1.44 (d, $J$ = 6.0 Hz, 3H), 1.21 (d, $J$ = 5.6 Hz, 3H), 1.15 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.8, 159.4, 150.7, 135.0, 133.2, 130.7, 129.7, 129.2, 126.5, 123.8, 113.8, 98.2, 97.3, 96.4, 79.2, 75.8, 75.4, 70.9, 70.2, 69.6, 68.0, 67.0, 55.3, 36.6, 24.7, 24.4, 18.4, 17.8, 17.0; CIHRMS calcd for [C$_{33}$H$_{41}$NO$_{12}$Na]$^+$: 666.2521, found 666.2523.

Nitrobenzoate II-29 (76.6 mg, 0.12 mmol) was dissolved in a mixed solvent of THF/H₂O (1.62 mL/0.32 mL) at room temperature, LiOH•H₂O (11.06 mg, 0.26 mmol) was added and the reaction stirred for 24 h. The reaction was quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give product II-30 (53.4 mg, 0.11 mmol, 90%) as a white solid: Rf (50% EtOAc/hexanes) = 0.1; mp: 137-140 °C; [α]²³_D = -7.76 (c = 0.47, CH₂Cl₂); IR (thin film, cm⁻¹) 3418, 2932, 1515, 1249, 1037; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, J = 5.2 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.92 (d, J = 10.4 Hz, 1H), 5.81 (ddd, J = 10.0 Hz, 2.4 Hz, 2.0 Hz, 1H), 5.34 (s, 1H), 4.97 (s, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.53-4.50 (m, 2H), 3.98 (q, J = 6.4 Hz, 1H), 3.84 (d, J = 12.0 Hz, 1H), 3.80 (s, 3H), 3.77-3.73 (m, 2H), 3.56 (brs, 1H), 3.32 (m, 1H), 3.22 (t, J = 8.8 Hz, 1H), 2.33 (d, J = 5.2 Hz, 1H), 2.19 (ddd, J = 13.2 Hz, 5.2 Hz, 2.4 Hz, 1H), 2.09-1.86 (m, 6H), 1.38 (d, J = 5.6 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H), 1.17 (d, J = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.3, 133.1, 129.7, 129.4, 126.6, 113.8, 97.8, 96.6, 96.4, 82.0, 75.7, 71.5, 70.8, 69.9, 69.7, 68.1,

Allylic alcohol II-30 (46 mg, 0.09 mmol) was dissolved in n CH$_2$Cl$_2$ (4 mL) at room temperature. MnO$_2$ (163 mg, 1.87 mmol) was added, and the resulting solution stir at room temperature overnight. The reaction was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give product II-3 (22.2 mg, 0.045 mmol, 50%) as yellow oil. $R_f$ (50% EtOAc/hexanes) = 0.46; $[\alpha]^{23}_D = 17.0$ (c = 0.5, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2931, 1699, 1514, 1248, 1034, 1014; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.27 (d, $J$ = 8.0 Hz, 2H), 6.87 (d, $J$ = 8.8 Hz, 2H), 6.86 (d, $J$ = 10.4 Hz, 1H), 6.09 (d, $J$ = 10.4 Hz, 1H), 5.34 (s, 1H), 5.23 (d, $J$ = 2.8 Hz, 1H), 4.81 (d, $J$ = 11.6 Hz, 1H), 4.56 (q, $J$ = 6.4 Hz, 1H), 4.51 (d, $J$ = 11.6 Hz, 2H), 4.03 (q, $J$ = 6.4 Hz, 1H), 3.80 (s, 3H), 3.73 (m, 1H), 3.65 (brs, 1H), 3.33 (dq, $J$ = 8.8 Hz, 6.0 Hz, 1H), 3.23 (t, $J$ = 8.8 Hz, 1H), 2.19 (ddd, $J$ = 12.4 Hz, 5.2 Hz, 1.6 Hz, 1H), 2.01-1.98 (m, 2H), 1.92-1.88 (m, 1H), 1.71-1.65 (m, 1H), 1.62-1.59 (m, 2H), 1.39-1.36 (m, 6H), 1.20 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$
196.8, 159.3, 143.0, 129.7, 129.4, 127.3, 113.8, 97.7, 96.7, 95.3, 82.1, 76.4, 71.6, 70.8, 70.5, 70.0, 66.7, 55.3, 42.7, 24.4, 18.4, 17.0, 15.1; [MALDI-TOF] calcd for $[\text{C}_{26}\text{H}_{36}\text{O}_9\text{Na}]^+$: 515.2252, found 515.2261.

$(2S,3S,4S,6S)-3-(((2S,5S,6S)-5-(((2R,5S,6R)-5\text{-hydroxy-6-methyl-5,6-dihydro-2H-pyran-2-yl})\text{oxy})-6\text{-methyltetrahydro-2H-pyran-2-yl})\text{oxy})-6-((4\text{-methoxybenzyl})\text{oxy})-2\text{-methyltetrahydro-2H-pyran-4-yl 4-nitrobenzoate (II-4-a)}$

Pyranone II-28 (85.4 mg, 0.13 mmol) was dissolved in CH$_2$Cl$_2$ (0.42 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl$_3$ (0.42 mL, 0.23 mmol) in methanol solution was added dropwise, followed by the addition of NaBH$_4$ (8.0 mg, 0.29 mmol). By TLC tracking, the reaction was completed after 1 h. The reaction mixture was diluted with ether (20 mL), and then quenched with water (5 mL), extracted with ether (3 x 50 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give allylic alcohol II-4-a (77.0 mg, 0.12 mmol, 92%) as a white solid: $R_f$ (50% EtOAc/hexanes) = 0.55; mp: 172-174 °C; $[\alpha]_D^{23}$ = 9.17 (c = 0.28, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2927, 2875, 1727, 1530, 1275, 1017, 721; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.29 (d, $J = 8.8$ Hz, 2H), 8.17 (d, $J = 8.8$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 6.89 (d, $J = 9.2$ Hz, 2H), 5.91 (d, $J = 10.4$ Hz, 1H), 5.77 (ddd, $J = 9.6$ Hz, 2.4 Hz, 2.0 Hz 1H ), 5.21-5.14 (m, 1H), 5.09 (s, 1H), 4.91 (s, 1H), 4.83 (d, $J = 12.0$ Hz, 1H), 4.63 (dd, $J = 9.6$ Hz, 2.0 Hz 1H), 4.55 (d, $J = 12.0$ Hz, 1H), 4.05 (q, $J = 6.4$ Hz, 1H), 3.81 (s, 3H), 3.62 (m, 1H), 3.65-3.60 (m, 2H), 3.51-3.44 (m,
1H), 2.37 (ddd, \( J = 12.8 \) Hz, 5.2 Hz, 1.6 Hz, 1H), 1.84-1.65 (m, 6H), 1.57 (brs, 1H), 1.45 (d, \( J = 6.0 \) Hz, 3H), 1.29 (d, \( J = 5.6 \) Hz, 3H), 1.20 (d, \( J = 6.4 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 163.8, 159.4, 150.7, 135.0, 133.4, 130.7, 129.7, 129.2, 126.8, 123.7, 113.9, 98.2, 97.3, 91.4, 79.2, 75.9, 71.0, 70.9, 70.1, 69.5, 68.3, 66.9, 55.3, 36.6, 23.9, 21.4, 18.4, 17.8, 17.1; CIHRMS calcd for \([C_{33}H_{41}NO_{12}Na]^+\): 666.2521, found 666.2523.

(2R,3S,6R)-6-(((2S,3S,6S)-6-(((2S,3R,4S,6S)-4-hydroxy-6-((4-methoxybenzyl)oxy)-2-methyltetrahydro-2H-pyran-3-yl)oxy)-2-methyltetrahydro-2H-pyran-3-yl)oxy)-2-methyl-3,6-dihydro-2H-pyran-3-ol (II-4-b)

Nitrobenzoate II-4-a (66.5 mg, 0.10 mmol) was dissolved in a mixed solvent of THF/H\(_2\)O (1.41mL/0.28 mL) at room temperature, LiOH•H\(_2\)O (9.6 mg, 0.22 mmol) was added and the reaction stirred for 24 h. The reaction was quenched with satd. aqueous NaHCO\(_3\), extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give product II-4-b (46.5 mg, 0.09 mmol, 94%) as a white solid: \( R_f \) (50% EtOAc/hexanes) = 0.13; mp: 144-147 °C; \([\alpha]_D^{23} = -13.58 \) (c = 0.34, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) 3421, 2931, 1515, 1250, 1017; \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.27 (d, \( J = 4.4 \) Hz, 2H), 6.88 (d, \( J = 8.8 \) Hz, 2H), 5.95 (d, \( J = 10.0 \) Hz, 1H), 5.72 (ddd, \( J = 9.6 \) Hz, 2.4 Hz, 2.0 Hz, 1H ), 5.34 ( s, 1H), 4.99 (s, 1H), 4.81 (d, \( J = 12.0 \) Hz, 1H), 4.52 (d, \( J = 11.2 \) Hz, 1H), 4.51 (dd, \( J = 9.6 \) Hz, 2.4 Hz, 1H), 4.07 (ddd, \( J = 12.4 \) Hz, 5.6
Hz, 1.2 Hz, 1H 1H), 3.84 (d, J = 8.0 Hz, 1H), 3.80 (s, 3H), 3.78-3.72 (m, 2H), 3.71 (brs, 1H), 3.32 (dq, J = 8.8 Hz, 6.4 Hz, 1H), 3.24 (t, J = 8.8 Hz, 1H), 2.36 (brs, 1H), 2.20 (ddd, J = 12.4 Hz, 5.2 Hz, 1.6 Hz, 1H), 2.00-1.63 (m, 6H), 1.39 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.3, 133.4, 129.7, 129.4, 126.9, 113.8, 97.7, 96.5, 91.5, 81.9, 71.6, 71.2, 70.8, 69.9, 69.6, 68.3, 67.0, 55.3, 39.6, 24.2, 21.5, 18.4, 17.8, 17.1; CIHRMS calcd for \([\text{C}_{26}\text{H}_{38}\text{O}_{9}\text{Na}]^+\): 517.2408, found 517.2411.


Allylic alcohol II-4-b (54 mg, 0.11 mmol) was dissolved in n CH\(_2\)Cl\(_2\) (3.75 mL) at room temperature. MnO\(_2\) (191.3 mg, 2.2 mmol) was added, and the resulting solution stir at room temperature overnight. The reaction was quenched with satd. aqueous NaHCO\(_3\), extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give product II-4 (23.8 mg, 0.048 mmol, 44%) as white solid. \(R_f\) (50% EtOAc/hexanes) = 0.38; mp: 103-106 °C \(\alpha\)\(_{\text{D}}^{23}\) = -23.84 (c = 0.38, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) 2926, 1699, 1514, 1302, 1248, 1119, 1066, 1013; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.27 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.80 (dd, J =
10.4 Hz, 2.8 Hz, 1H), 6.10 (d, J = 10.4 Hz, 1H), 5.35 (s, 1H), 5.27 (d, J = 3.6 Hz, 1H), 4.81 (d, J = 11.6 Hz, 1H), 4.62 (q, J = 6.8 Hz, 1H), 4.52 (d, J = 11.6 Hz, 2H), 4.12 (q, J = 6.8 Hz, 1H), 3.80 (s, 3H), 3.77-3.71 (m, 2H), 3.33 (dq, J = 8.8 Hz, 6.0 Hz, 1H), 3.24 (t, J = 8.8 Hz, 1H), 2.17 (ddd, J = 12.4 Hz, 5.2 Hz, 1.6 Hz, 1H), 1.95-1.89 (m, 3H), 1.71-1.57 (m, 3H), 1.39 (d, J = 5.6 Hz, 3H), 1.37 (d, J = 7.2 Hz, 3H) 1.22 (d, J = 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 196.8, 159.3, 143.5, 129.7, 129.4, 127.4, 113.8, 97.7, 96.7, 90.2, 82.1, 71.7, 70.8, 70.6, 70.0, 66.9, 55.3, 39.6, 27.7, 24.1, 21.2, 18.4, 17.2, 15.1; [MALDI-TOF] calcd for [C26H36O9Na]+: 515.2252, found 515.2264.


Pyranone (ent)-II-27 (118 mg, 0.184 mmol) was dissolved in CH2Cl2 (0.57 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl3 (0.57 mL, 0.23 mmol) in methanol solution was added dropwise, followed by the addition of NaBH4 (10.9 mg, 0.29 mmol). By TLC tracking, the reaction was completed after 1 h. The reaction mixture was diluted with ether (20 mL), and then quenched with water (5 mL), extracted with ether (3 x 50 mL), dried over Na2SO4 and concentrated under reduced pressure to give allylic alcohol (ent)-II-29 (108 mg, 0.17 mmol, 91%) as a white solid: Rf (50% EtOAc/hexanes) = 0.52;
mp: 140-145 °C; [α]_{D}^{23} = -25.11 (c = 1.01, CH₂Cl₂); IR (thin film, cm⁻¹) 3453, 2935, 1725, 1529, 1274, 1101, 1036, 1016, 720; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.87 (d, J = 10.4 Hz, 1H), 5.77 (ddd, J = 10.4 Hz, 2.4 Hz, 2.0 Hz, 1H), 5.21-5.14 (m, 1H), 5.08 (s, 1H), 4.93 (s, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.63 (dd, J = 9.6 Hz, 2.4 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 3.95 (q, J = 6.4 Hz, 1H), 3.80 (s, 3H), 3.62 (dq, J = 8.8 Hz, 4.4 Hz, 2H), 3.50-3.43 (m, 2H), 2.39 (ddd, J = 12.4 Hz, 5.2 Hz, 1.2 Hz, 1H), 1.91-1.72 (m, 6H), 1.61 (brs, 1H), 1.44 (d, J = 6.4 Hz, 3H), 1.20 (d, J = 5.6 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.8, 159.4, 150.7, 135.0, 133.2, 130.7, 129.7, 129.2, 126.4, 123.7, 113.8, 98.2, 97.3, 96.4, 79.2, 75.8, 75.4, 70.9, 70.1, 69.5, 67.9, 67.0, 55.3, 36.6, 24.7, 24.4, 18.4, 17.8, 17.0; CIHRMS calcd for [C₁₇H₂₃NO₄Na]⁺: 666.2521, found 666.2523.


Nitrobenzoate (ent)-II-29 (72.8 mg, 0.11 mmol) was dissolved in a mixed solvent of THF/H₂O (1.53 mL/0.31 mL) at room temperature, LiOH•H₂O (10.52 mg, 0.25 mmol) was added and the reaction stirred for 24 h. The reaction was quenched with satd.
aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give product (ent)-II-30 (38.1 mg, 0.77 mmol, 70%) as a white solid: R_f (50% EtOAc/hexanes) = 0.11; mp: 139-142 °C; [α]²θ = 14.75 (c = 0.4, CH₂Cl₂); IR (thin film, cm⁻¹) 3422, 2931, 1515, 1249, 1037; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.92 (d, J = 10.4 Hz, 1H), 5.81 (ddd, J = 10.0 Hz, 2.4 Hz, 2.0 Hz 1H ), 5.34 ( s, 1H), 4.97 (s, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.53-4.50 (m, 2H), 3.98 (q, J = 6.4 Hz, 1H), 3.84 (d, J = 12.0 Hz, 1H), 3.80 (s, 3H) , 3.78-3.72 (m, 2H), 3.56 (brs, 1H), 3.32 (dq, J = 6.0 Hz, 2.8 Hz, 1H), 3.22 (t, J = 8.8 Hz, 1H), 2.33 (brs, 1H), 2.19 (ddd, J = 13.2 Hz, 5.2 Hz, 2.4 Hz, 1H), 2.06-1.87 (m, 6H), 1.44 (d, J = 6.4 Hz, 3H), 1.20 (d, J = 5.6 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.3, 133.1, 129.7, 129.4, 126.6, 113.8, 97.8, 96.6, 96.4, 82.0, 75.7, 71.5, 70.8, 69.9, 69.7, 68.1, 67.0, 55.3, 39.6, 24.8, 24.7, 18.4, 17.9, 17.0; CIHRMS calcd for [C₂₆H₃₆O₉Na]⁺: 517.2408, found 517.2415.


Allylic alcohol (ent)-II-30 (28.8 mg, 0.058 mmol) was dissolved in n CH₂Cl₂ (0.6 mL) at room temperature. MnO₂ (102 mg, 1.17 mmol) was added, and the resulting solution stir
at room temperature overnight. The reaction was quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give product (ent)-II-3 (20.0 mg, 0.04 mmol, 70%) as yellow oil. Rᵣ (50% EtOAc/hexanes) = 0.49; [α]ᵣ²³ = -3.19 (c = 0.7, CH₂Cl₂); IR (thin film, cm⁻¹) 2922, 1699, 1514, 1249, 1034, 1014; ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 8.8 Hz, 2H), 6.87 (d, J = 10.4 Hz, 1H) 6.09 (d, J = 10.4 Hz, 1H), 5.35 (s, 1H), 5.24 (d, J = 3.2 Hz, 1H), 4.81 (d, J = 11.6 Hz, 1H), 4.57 (q, J = 6.8 Hz, 1H), 4.52 (d, J = 11.6 Hz, 2H), 4.032 (q, J = 6.4 Hz, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.66 (brs, 1H), 3.33 (dq, J = 8.8 Hz, 6.0 Hz, 1H), 3.23 (t, J = 8.8 Hz, 1H), 2.20 (ddd, J = 12.8 Hz, 5.2 Hz, 2.4 Hz, 1H), 2.01-1.98 (m, 2H), 1.91-1.88 (m, 1H), 1.71-1.62 (m, 2H), 1.62-1.60 (m, 1H), 1.40-1.37 (m, 6H), 1.27-1.24 (m, 1H), 1.2 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 196.8, 159.3, 143.0, 129.7, 129.4, 127.3, 113.8, 97.7, 96.7, 95.3, 82.7, 76.4, 71.6, 70.8, 70.5, 70.0, 66.7, 55.3, 39.6, 24.6, 24.4, 18.4, 17.0, 15.1; [MALDI-TOF] calcd for [C₂₆H₃₆O₉Na]⁺: 515.2252, found 515.2261.

Pyranone (ent)-II-28 (89.2 mg, 0.14 mmol) was dissolved in CH₂Cl₂ (0.433 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl₃ (0.433 mL, 0.17 mmol) in methanol solution was added dropwise, followed by the addition of NaBH₄ (8.35 mg, 0.22 mmol). By TLC tracking, the reaction was completed after 1 h. The reaction mixture was diluted with ether (20 mL), and then quenched with water (5 mL), extracted with ether (3 x 50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give allylic alcohol (ent)-II-4-a (83.7 mg, 0.13 mmol, 91%) as a white solid: R_f (50% EtOAc/hexanes) = 0.53; mp: 194-198 °C; [α]$_D^{23}$ = -6.74 (c = 0.57, CH₂Cl₂); IR (thin film, cm⁻¹) 3444, 2933, 1727, 1530, 1275, 1120, 1070, 1017, 721; $^1$H NMR (400 MHz, CDCl₃) δ 8.29 (d, J = 9.6 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 6.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.90 (d, J = 10.4 Hz, 1H), 5.64 (dd, J = 10.0 Hz, 2.4 Hz, 2.0 Hz 1H ), 5.21-5.14 (m, 1H), 5.09 (s, 1H), 4.91 (s, 1H), 4.83 (d, J = 11.2 Hz, 1H), 4.64 (dd, J = 9.2 Hz, 1.2 Hz 1H), 4.55 (d, J = 11.6 Hz, 1H), 4.05 (dq, J = 6.4 Hz, 1.2 Hz, 1H), 3.81 (s, 3H) , 3.74 (dq, J = 8.8 Hz, 6.0 Hz, 1H), 3.63 (t, J = 8.8 Hz, 2H), 3.47 (dq, J = 8.8 Hz, 6.8 Hz, 1H), 2.39 (ddd, J = 12.4 Hz, 5.2 Hz, 2.4 Hz, 1H), 1.84-1.65 (m, 6H), 1.58 ( brs, 1H), 1.45 (d, J = 6.0 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 1.20 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl₃) δ 163.8, 159.4, 150.7, 135.0, 133.4, 130.7, 129.7, 129.2, 126.8, 123.7, 113.8, 98.2, 97.3, 91.4, 79.2, 75.8, 71.0, 70.9, 70.2, 69.5, 68.3, 66.9, 55.3, 36.6, 23.9, 21.4, 18.4, 17.8, 17.1; CIHRMS calcd for [C$_{33}$H$_{41}$NO$_{12}$Na]$^+$: 666.2521, found 666.2523.

Nitrobenzoate (ent)-II-4-a (71.7 mg, 0.11 mmol) was dissolved in a mixed solvent of THF/H₂O (1.52mL/0.31 mL) at room temperature, LiOH•H₂O (10.4 mg, 0.24 mmol) was added and the reaction stirred for 24 h. The reaction was quenched with satd. aqueous NaHCO₃, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give product (ent)-II-4-b (52.8 mg, 0.11 mmol, 97%) as a white solid: Rᶠ (50% EtOAc/hexanes) = 0.09; mp: 146-150 °C; [α]²³_D = -8.39 (c = 0.4, CH₂Cl₂); IR (thin film, cm⁻¹) 3421, 2929, 1514, 1248, 1017; ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 5.93 (d, J = 10.0 Hz, 1H), 5.72 (ddd, J = 10.4 Hz, 2.4 Hz, 2.0 Hz 1H), 5.34 (s, 1H), 5.00 (s, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.53-4.49 (m, 2H), 4.07 (q, J = 6.4 Hz, 1H), 3.83 (d, J = 9.6 Hz, 1H), 3.80 (s, 3H), 3.78-3.74(m, 2H), 3.70 (brs, 1H), 3.32 (dq, J = 8.8 Hz, 2.4 Hz, 1H), 3.24 (t, J = 8.8 Hz, 1H), 2.38 (brs, 1H), 2.20 (ddd, J = 12.8 Hz, 5.2 Hz, 2.4 Hz, 1H), 2.02-1.61 (m, 6H), 1.39 (d, J = 6.0 Hz, 3H), 1.30 (d, J = 6.0 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.3, 133.4, 129.7, 129.4, 126.9, 113.8, 97.7, 96.4, 91.5, 81.8,
71.6, 71.2, 70.8, 69.9, 69.6, 68.3, 67.0, 55.3, 39.7, 24.2, 21.5, 18.4, 17.8, 17.1; CIHRMS calcd for [C$_{26}$H$_{38}$O$_9$Na]$^+$: 517.2408, found 517.2411.


Allylic alcohol (ent)-II-4-b (53.3 mg, 0.011 mmol) was dissolved in CH$_2$Cl$_2$ (4.6 mL) at room temperature. MnO$_2$ (189 mg, 2.17 mmol) was added, and the resulting solution stir at room temperature overnight. The reaction was quenched with satd. aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give product (ent)-II-4 (26.6 mg, 0.054 mmol, 49 %) as white solid. R$_f$ (50% EtOAc/hexanes) = 0.33; mp: 108-112 °C [α]$^2$$_D$ = 25.44 (c = 0.51, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2926, 1699, 1514, 1370, 1247, 1166, 1103, 1066, 1013; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.27 (d, $J$ = 8.8 Hz, 2H), 6.79 (d, $J$ = 8.0 Hz, 2H), 6.80 (dd, $J$ = 10.0 Hz, 3.6 Hz, 1H), 6.10 (d, $J$ = 10.4 Hz, 1H), 5.35 (s, 1H), 5.27 (d, $J$ = 2.8 Hz, 1H), 4.82 (d, $J$ = 10.8 Hz, 1H), 4.62 (q, $J$ = 7.2 Hz, 1H), 4.52 (d, $J$ = 10.8 Hz, 2H), 4.12 (q, $J$ = 6.4 Hz, 1H), 3.81 (s, 3H), 3.78-3.70 (m, 2H), 3.33 (dq, $J$ = 8.8 Hz, 6.4 Hz, 1H), 3.24 (t, $J$ = 8.8 Hz, 1H), 2.20 (ddd, $J$ = 13.2 Hz, 5.2 Hz, 2.0 Hz, 1H), 1.96-1.87 (m, 3H), 1.71-1.57
(m, 3H), 1.39 (d, $J = 5.6$ Hz, 3H), 1.37 (d, $J = 6.4$ Hz, 3H) 1.22 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 196.8, 159.3, 143.5, 129.7, 129.4, 127.4, 113.8, 97.7, 96.7, 90.2, 82.1, 71.7, 70.8, 70.5, 70.0, 66.9, 55.3, 39.6, 29.7, 24.1, 21.2, 18.4, 17.2, 15.1; [MALDI-TOF] calcd for [C$_{26}$H$_{36}$O$_9$Na]$^+$: 515.2252, found 515.2264.
Chapter 3. Progress toward Total Synthesis of Vineomycinone B$_2$ / Vineomycin C

(R)-4-(1,5-bis(benzyloxy)-9,10-dihydro-9,10-dioxoanthracen-6-yl)-3-hydroxy-3-methylbutanenitrile (III-27)

To a solution of III-22 (720 mg, 1.09 mmol) in DMSO (30 mL) were added KCN (378 mg, 5.8 mmol), potassium iodide (19 mg, 0.116 mmol), 4 Å MS (5 g) and reaction was stirred at 60 °C for 16 h. After completion of reaction the mixture was quenched with water. The mixture was extracted with CH$_2$Cl$_2$ for three times. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/CH$_2$Cl$_2$ to give III-27 (502 mg, 0.97 mmol, 89%) as a yellow solid: R$_f$ (50% EtOAc/hexanes) = 0.52; mp: 134-135 °C; [$\alpha$]$^19$ = -20.03 (c = 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 3462, 2928, 1668, 1584, 1453, 1322, 1260, 1070, 1016, 735, 697; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.12 (d, $J$ = 7.8, 1H), 7.93 (d, $J$ = 7.8, 1H), 7.68-7.55 (m, 6H), 7.44-7.32 (m, 7H), 5.34 (s, 2H), 5.10 (s, 2H), 3.37 (br, 1H), 2.93 (AB, $J$ = 13.8 Hz, 2H), 2.40 (AB, $J$ = 16.2 Hz, 2H), 1.28 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 182.5, 181.6, 158.8, 156.7, 137.9, 137.1, 137.0, 136.9, 136.2, 136.1, 135.0, 128.9, 128.8, 128.7, 128.0, 126.8, 125.3, 123.9, 121.3, 120.2, 119.2, 117.5, 77.2, 71.8, 71.0, 41.9, 31.2, 27.2; CIHRMS calcd for [C$_{33}$H$_{27}$O$_5$NNa]$^+$: 540.1781, found 540.1785.
(R)-4-(9,10-dihydro-1,5-dihydroxy-9,10-dioxaanthracen-6-yl)-3-hydroxy-3-methylbutanenitrile (III-28)

To a solution of III-27 (230 mg, 0.444 mmol) in EtOH (10 mL) was added AcCl (4 mL) dropwise at 0 °C and reaction was stirred at room temperature overnight. Then additional AcCl(2 mL) was added dropwise. After completion of reaction, the mixture was quenched with water. The mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 2.5% MeOH/CH₂Cl₂ to give diphenol III-28 (140 mg, 0.415 mmol, 93%) as a yellow solid: R_f (20% EtOAc/hexanes) = 0.10; mp: 176-178 °C; [α]₁⁹ = +3.7 (c = 0.2, CH₂Cl₂/MeOH = 4/1); IR (thin film, cm⁻¹) 3468, 2925, 1629, 1600, 1583, 1429, 1372, 1310, 1258, 1079, 786, 696; ¹H NMR (400 MHz, CDCl₃) δ 13.0 (s, 1H), 12.4 (s, 1H), 7.88-7.85 (m, 2H), 7.73-7.65 (m, 2H), 7.35 (d, J = 8.0 Hz, 1H), 3.11 (AB, J = 13.2 Hz, 2H), 2.60 (s, 2H), 1.45 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 188.4, 187.4, 162.8, 160.8, 139.3, 136.8, 132.9 (2C), 132.4, 125.4, 119.6, 119.3, 117.5, 115.7, 72.0, 41.0, 31.4, 27.2; CIHRMS calcd for [C₁₉H₁₆O₅N]⁺: 338.1023, found 338.1028.
(R)-3-((9,10-dihydro-1,5-dihydroxy-9,10-dioxoanthracen-6-yl)methyl)-3-hydroxybutanoic acid (I-1)

To an aqueous NaOH solution (15 mL, 1.0 M) was added diphenol III-28 (135 mg, 0.4 mmol) and reaction was heated at reflux overnight. The mixture was washed with CH₂Cl₂ for three times. Aqueous HCl (30 mL, 1.0 M) was added. The mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10% MeOH/CH₂Cl₂ to give (R)-Fridamycin E I-1 (114 mg, 0.32 mmol, 80%) as an orange solid: R_f (CH₂Cl₂/MeOH = 10/1) = 0.20; mp: 175-176 °C; [α]²¹ = +8.25 (c = 0.1, CHCl₃); IR (thin film, cm⁻¹) 3400, 2925, 1712, 1627, 1513, 1430, 1373, 1315, 1258, 792; ¹H NMR (400 MHz, CDCl₃) δ 13.3 (s, 1H), 12.6 (s, 1H), 7.86-7.84 (m, 2H), 7.71-7.65 (m, 2H), 7.33 (d, J = 9.6 Hz, 1H), 3.11 (AB, J = 13.2 Hz, 2H), 2.62 (s, 2H), 1.35 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 188.4, 187.6, 162.7, 161.0, 139.6, 136.7, 133.8, 133.0, 132.0, 125.2, 119.5, 119.1, 116.0, 115.8, 72.1, 44.7, 41.2, 27.2; CIHRMS calcd for [C₁₉H₁₀O₇Na]⁺: 379.0788, found 379.0794.

(6R)-6-pivaloyl-(2R)-2-methyl 2H-pyran-3(6H)-one (III-32)
Compound III-31 (2.22 g, 8.59 mmol), 30 mL of CH₂Cl₂, and 1.5 mL of Et₃N were added to a round bottom flask and cooled to -78 °C. A catalytic amount (53 mg, 0.43 mmol) of DMAP and pivaloyl chloride (1.06 mL, 8.59 mmol) were added and the solution was stirred for 3 h at -78 °C. The reaction was quenched with 50 mL of sat. aq. NaHCO₃, extracted (3 x 50 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10 % EtOAc/hexanes to give 2.41 g (7.04 mmol, 82 %) of III-32. Rf (20 % EtOAc/hexanes) = 0.4; [α]²¹ = -66 (c = 0.1, CH₂Cl₂); IR (thin film, cm⁻¹) 2935, 2910, 2855, 1738, 1692, 1461, 1399, 1279; ¹H NMR (600 MHz, CDCl₃) δ 6.88 (dd, J = 10.2, 3.6 Hz, 1H), 6.46 (d, J = 3.6 Hz, 1H), 6.19 (d, J = 10.2 Hz, 1H), 4.57 (q, J = 6.6 Hz, 1H), 1.40 (d, J = 6.6 Hz, 3H), 1.23 (s, 9H), ¹³C NMR (150 MHz, CDCl₃) δ 195.9, 177.0, 141.8, 128.2, 86.9, 72.3, 39.2, 27.0, 15.4; CI HRMS calcd for [C₁₁H₁₆O₄]⁺: 212.1049, Found 212.1045.

((2R,5S,6R)-5,6-dihydro-5-hydroxy-6-methyl-2H-pyran-2-yl pivalate (III-33)

A solution of pyranone III-32 (580 mg, 2.74 mmol) in CH₂Cl₂ (1.5 mL) and 0.4 M CeCl₃/MeOH (1.5 mL) was cooled to -78 °C. NaBH₄ (58.4 mg, 1.54 mmol) was added and the reaction mixture was stirred for 4 h at -78 °C. The resulting solution was diluted with ether (10 mL), quenched with 5 mL of saturated NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel chromatography eluting with 40% EtOAc/hexane to give enol
Pyranone III-35 (7.84 g, 31.6 mmol) was dissolved in CH$_2$Cl$_2$ (31.6 mL), resulting solution was cooled to -78 °C, 0.4 M CeCl$_3$ in methanol solution (12.6 mmol, 31.6 mL) was added in a dropwise fashion, followed by adding NaBH$_4$ (1.2 g, 31.6 mmol). By TLC tracking, the reaction was done after 1.5 h. The reaction mixture was diluted with ether (6 mL), then quenched with water (6 mL), extracted with ether (3 x 60 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexane to give allylic alcohol III-36a/b as a mixture of diastereomers (7.83 g, 31.3 mmol, 99%) as a colorless oil: $R_f$ (30% EtOAc/hexanes) = 0.45; $[\alpha]_{D}^{23} = -64.5$ (c = 1.0, CH$_2$Cl$_2$);

III-36a: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.29 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 6.13 (ddd, $J = 10.2$, 5.4, 1.8 Hz, 1H), 5.82 (d, $J = 10.2$ Hz, 1H), 5.10 (brs, 1H), 4.82 (d, $J$
= 11.4 Hz, 1H), 4.58 (d, \( J = 11.4 \) Hz, 1H), 3.79 (s, 3H), 3.74-3.70 (m, 1H), 3.66 (brs, 1H), 2.03 (brs, 1H), 1.33 (d, \( J = 6.6 \) Hz, 3H); **III-36b:** \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.29 (d, \( J = 8.4 \) Hz, 2H), 6.87 (d, \( J = 8.4 \) Hz, 2H), 5.92 (d, \( J = 10.2 \) Hz, 1H), 5.75 (d, \( J = 10.2 \) Hz, 1H), 5.15 (brs, 1H), 4.78 (d, \( J = 11.4 \) Hz, 1H), 4.54 (d, \( J = 11.4 \) Hz, 1H), 3.89 (br, 1H), 3.79 (s, 3H), 3.65-3.61 (m, 1H), 2.24 (brs, 1H), 1.37 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) major isomer \( \delta \) 159.3, 131.2, 129.7, 129.6, 113.8, 96.7, 71.5, 69.6, 68.4, 64.8, 55.3, 16.6.


\((3\text{aR,4R,6R,7aS})\)-6-((4-methoxybenzyl)oxy)-2,2,4-trimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran (III-39)

![III-39](image)

To a solution of diol **III-38** (0.5 g, 1.86 mmol) in acetone (5 mL) and 2,2-dimethoxypropane (1.14 mL, 9.3 mmol) at 0 °C was added p-Toluenesulfonic acid monohydrate (3.54 mg, 0.0186 mmol). The reaction mixture was stirred for 2 h. The reaction mixture was quenched with water and then was concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 33% EtOAc/Hexane to give **III-39** (0.687 g, 99%): \( R_f \) (50% EtOAc/hexanes) = 0.80; \([\alpha]\)
\( ^{23}D = -11.5 \ (c = 0.71, \text{CH}_2\text{Cl}_2) \); IR (thin film, cm\(^{-1}\)) 3038, 2934, 1613, 1515, 1381, 1370, 1247, 1217, 1171, 1157, 1078, 1056, 1037, 1007, 844, 822; \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\)

7.27 (d, \(J = 7.2 \text{ Hz, } 2\text{H}\)), 6.87 (d, \(J = 7.6 \text{ Hz, } 2\text{H}\)), 4.83-4.79 (m, 2H), 4.49 (d, \(J = 10.8 \text{ Hz, } 1\text{H}\)), 4.42 (d, \(J = 2.0 \text{ Hz, } 1\text{H}\)), 3.80 (s, 3H), 3.68 (dd, \(J = 8.8, 5.2 \text{ Hz, } 1\text{H}\)), 3.47 (dq, \(J = 7.2, 1.6 \text{ Hz, } 1\text{H}\)), 2.23 (d, \(J = 14.8 \text{ Hz, } 1\text{H}\)), 1.98 (ddd, \(J = 13.8, 8.8, 4.4 \text{ Hz, } 1\text{H}\)), 1.45 (s, 3H), 1.34 (s, 3H), 1.31 (d, \(J = 5.6 \text{ Hz, } 3\text{H}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.2, 129.6, 129.6, 113.8, 108.8, 97.1, 76.8, 72.7, 71.3, 70.0, 55.2, 32.9, 28.2, 25.9, 18.4.

\((2R,3S,4R,6R)-6-(4\text{methoxybenzyloxy})-2\text{methyl}-3-((2S,5S,6S)-6\text{methyl-5-oxo-5,6-dihydro-2H-pyran-2-ylxy})\text{-tetrahydro-2H-pyran-2-ylxy})\text{-tetrahydro-2H-pyran-4-yl acetate (III-40)}\)

Alcohol II-1 (75 mg, 0.152 mmol) was dissolved in CH\(_2\)Cl\(_2\) (0.2 mL) at room temperature, then acetic anhydride (46.7 mg, 0.457 mmol), pyridine (42.1 mg, 0.532 mmol) and a catalytic amount of DMAP were added in above order. The reaction mixture was stirred at room temperature for 12 h. Reaction mixture was washed with 1 mL 1M HCl solution, followed by washing with 2 mL of satd. aq. NaHCO\(_3\), extracted (3 x 5 mL) with CH\(_2\)Cl\(_2\), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give III-40 (67 mg, 0.13 mmol, 82%) as a yellow oil: \(R_f\) (50%
EtOAc/hexanes) = 0.60; \[\alpha\]_D \text{= -47.7 (c = 1.0, CH}_2\text{Cl}_2\]; IR (thin film, cm\(^{-1}\)) 2928, 1733, 1699, 1613, 1514, 1363, 1239, 1122, 1068, 1030, 962, 734; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 7.25 (d, J = 8.3, 2H), 6.87 (d, J = 8.3, 2H), 6.86 (dd, J = 10.1, 3.5, 1H), 6.09 (d, J = 10.2, 1H), 5.22 (d, J = 3.4, 1H), 4.95 (d, J = 2.1, 1H), 4.88 (ddd, J = 9.0, 8.0, 2, 1H), 4.80 (d, J = 11.6, 1H), 4.54 (dd, J = 9.7, 5.4, 1H), 4.52 (d, J = 11.6, 1H), 4.13 (q, J = 7.1, 1H), 4.00 (qd, J = 6.6, 1.2, 1H), 3.81 (s, 3H), 3.58 (ddd, J = 3.5, 3.0, 1.6, 1H), 3.36 (dd, J = 8.0, 7.0, 1H), 3.36 (dq, J = 7, 6.6, 1H), 2.27 (ddd, J = 12.5, 5.4, 2.0, 1H), 2.01 (ddd, J = 13.0, 3.5, 2.9, 0.7, 1H), 2.01 (s, 3H), 1.96 (ddd, J = 13.1, 3.5, 3.3, 0.7, 1H), 1.89 (ddd, J = 13.1, 3.8, 3.5, 3.0, 1H), 1.63 (ddd, J = 12.5, 9.7, 9, 1H), 1.55 (ddd, J = 13.0, 3.8, 3.3, 1.2, 1H), 1.37 (d, J = 6.8, 3H), 1.35 (d, J = 6.6, 3H), 1.16 (d, J = 6.6, 3H); \(^1^3\)C NMR (150 MHz, CDCl\(_3\)) 196.7, 170.5, 159.4, 143.0, 129.6, 129.3, 127.3, 113.8, 98.2, 97.4, 95.3, 80.5, 76.6, 72.2, 71.5, 70.5, 70.1, 66.6, 55.3, 36.7, 24.8, 24.2, 21.3, 18.4, 17.1, 15.1; CIHRMS Calcd for \([\text{C}_{28}\text{H}_{38}\text{O}_{10}\text{Na}]^+\): 557.2363, Found 557.2358.

(2\(R\),3\(S\),4\(R\),6\(R\))-6-(hydroxy)-2-methyl-3-((2\(S\),5\(S\),6\(S\))-6-methyl-5-oxo-5,6-dihydro-2\(H\)-pyran-2-yloxy)-tetrahydro-2\(H\)-pyran-4-yl acetate (III-41):

![III-41](image)

PMB ether III-40 (100 mg, 0.187 mmol) was dissolved in CH\(_2\)Cl\(_2\) (0.2 mL) and water (0.1 mL) at 0 °C, then excess DDQ (85 mg, 0.374 mmol) was added. The reaction
mixture was stirred at 0 °C for 5h, at which time the reaction was filtered to remove precipitates, and washed with 2 mL of satd. aq. NaHCO₃. Resulting solution was extracted (3 x 5 mL) with CH₂Cl₂, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give III-41 (67 mg, 0.13 mmol, 82%) as a yellow oil. \( R_f \) (30% EtOAc/hexanes) = 0.20; \([\alpha]^{23}_D = 40.7 \) (c = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2928, 1733, 1699, 1613, 1514, 1363, 1239, 1122, 1068, 1030, 962, 734; \(^1\)H NMR (600 MHz, CDCl₃) \( \delta \) 6.87/6.86 (m, 1H), 6.09 (d, \( J = 10.2 \)), 5.29 (s)/5.25 (dd, \( J = 13.8, 9.0, 4.8 \)), 5.21 (m), 4.96 (m)/4.91 (dd, \( J = 13.8, 9.0, 4.8 \)), 4.55 (m, 1H), 4.02 (m, 2H), 3.58 (m, 1H), 3.45 (m)/3.35 (m), 3.16 (m), 2.66 (m), 2.49 (m), 2.38 (dd, \( J = 12.6, 5.4, 1.8 \)), 2.25 (dd, \( J = 13.2, 5.4, 1.8 \)), 2.15-1.80 (m), 2.06/2.05 (s, 3H), 1.73-1.4 (m), 1.4-1.16 (m); \(^{13}\)C NMR (150 MHz, CDCl₃) 196.84/196.78, 170.5/170.4, 143.03/142.98, 127.3, 98.3/98.2, 95.4/95.3, 93.43/93.39, 91.39/91.37, 81.0, 80.2, 72.0, 71.7, 70.6/70.2, 67.3/66.6, 38.1/35.6, 29.8, 24.8, 24.3, 21.4/21.3, 18.4, 17.2, 15.1; CIHRMS Calcd for [C₂₀H₃₀NaO₉]⁺: 437.8, Found 437.1786.
Section C: Proton Assignments of Chapter 2 Trisaccharides

\[
(2S,6R)-6-((2S,3S,6S)-6-((2R,3S,4R,6R)-6-(4-methoxybenzyl)oxy)-tetrahydro-4-hydroxy-2-methyl-2H-pyr-3-yloxy)-tetrahydro-2-methyl-2H-pyr-3(6H)-one (II-1) (DLL)
\]

![Chemical structure of the trisaccharide]

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<th>Sugar C</th>
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<td>4.94 (brs, 1H)</td>
</tr>
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<td>3pmb (2H)</td>
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<td>2.21 (ddd, ( J = 12.6, 5.4, 1.8 ), 1H)</td>
<td>5.23 (d, ( J = 3.6 ), 1H)</td>
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<td>2b&quot; (1H)</td>
</tr>
<tr>
<td>1pmb (1H)</td>
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<td>3.39-3.55 (m, 1H)</td>
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<td>6a (3H)</td>
<td>1.37 (d, ( J = 6.6, 3H ))</td>
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(2S,6R)-6-((2S,3S,6S)-6-((2S,3R,4S,6S)-6-(4-methoxybenzyloxy)-tetrahydro-4-hydroxy-2-methyl-2H-pyran-3-yloxy)-tetrahydro-2-methyl-2H-pyran-3(6H)-one (II-22) (Branched LLL)

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<td>6b (3H)</td>
<td>1.62-1.59 (m, 2H)</td>
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</table>
Reference:


30. Sparks, S; Martin, S; Tetrahedron. 2007, 63, 8619-8635.
33. For Fridamycin E’s synthesis, I helped with starting material production.

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46. Both vineomycin C and the related monosaccharide angucycline, vineomycinone B2 possess antitumor activity against S-180 solid tumors in mice; thus, associating the antitumor activity with the common anthraquinone portion of the molecules, see: ref.4.5.6


$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}C$ NMR (150 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
(en)-11-23-β

H NMR (500MHz, CDCl3)

PMDO  CH3

CH3  CH3

O

OH

O