Synthetic Study Toward Angucycline and Resin Glycoside Natural Products

A dissertation presented

by

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ABSTRACT OF DISSERTATION

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Angucycline natural products containing carbohydrate motifs have long been known for their impressive biological activities. Apart from their interesting bioactivities, these complex natural products are challenging synthetic targets. A practical total synthetic approach toward these natural products enables adequate material for Structure Activity Relationship (SAR) studies, which are rather limited from the natural sources. These multi-step syntheses also help uncover the information about the structure reactivity and discovery of important/new organic transformations. The carbohydrate portion of natural products plays a crucial role in the bioactivities they exhibit in parts by improving the pharmacokinetic and physiochemical properties (target binding, solubility, tissue targeting, and membrane transportation). The O’Doherty group has developed a *de novo* asymmetric approach to build the desired functionality and stereochemistry within each sugar starting from an achiral starting material, in contrast to the traditional approaches using known carbohydrates as starting materials. The *de novo* approach relies on a highly diastereoselective palladium(0)-catalyzed glycosylation reaction to control the anomeric stereocenter and post-glycosylation transformation to introduce the corresponding functionality and stereocenters in the sugar moiety. Continuing our group’s long lasting interest in carbohydrate chemistry and the utility of this strategy, attention was turned to the syntheses of the bioactive carbohydrate-based angucycline natural product analogues.

In a related investigation, cyclitols (carbasugars) are studied as a sugar surrogate for the angucycline natural products. Although biologically interesting, a large number of glycosylated angucyclines are unstable rendering limited SAR type analysis. So, having access to the cyclitol...
analogues are very compelling especially for unstable glycosylated angucyclines as this renders metabolic stability, improving the pharmacokinetic properties. Cyclitols are an important subset of the C-glycoside structural motif where the endo-acetal ring oxygen is replaced with a methylene group. In particular, polyhydroxylated cyclohexane cyclitols that mimic pyranosugars are ubiquitous in many biologically important natural products. Total synthesis of jadomycin A and a carbasugar analogue of jadomycin B has been achieved successfully, the route also demonstrated a regioselective 6-endo-dig cyclization.

Inspired by the biological evaluation of a hydrolytically stable C-aryl glycoside from an O-aryl glycoside in case of gilvocarcins, the regioisomeric O-cyclitol analogues of gilvocarin M were synthesized and are being evaluated for their antibacterial activities. Toward the synthesis of more active gilvocarin V analogs, a highly regioselective bromination of 3,5-dihydroxy benzoate was also developed for the synthesis of the D-ring of gilvocartcin V.

Using our group’s de novo approach toward carbohydrates, efforts have been made toward the total synthesis of biologically important and complex oligosaccharides (resin glycosides). Synthesis of the macrolactone subunits and detailed NMR analysis corrected the previous report on the regioselectivity of macrolactonization. Successful glycosylation of the macrolactone subunit with the disaccharide was achieved by employing Schmidt glycosylation conditions. Total synthesis of the natural product merremoside D and a regioisomeric macrolactone analog of merremoside D have been successfully achieved. This synthesis established the route that could be used to synthesize various members and/or analogs of resin glycoside family of natural products.
DEDICATED TO

My family
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<th>Description</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Anal.</td>
<td>Analysis</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>Boc</td>
<td>t-Butoxycarbonyl</td>
</tr>
<tr>
<td>bp</td>
<td>Boiling point</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>n-Butyllithium</td>
</tr>
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<td>Calcd</td>
<td>Calculated</td>
</tr>
<tr>
<td>Cbz</td>
<td>Benzyloxy carbonyl</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical Ionization</td>
</tr>
<tr>
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<td>m-Chloroperbenzoic acid</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic acid</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DBA</td>
<td>trans, trans-dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift (ppm)</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropylazodicarboxylate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminum hydride</td>
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<td>DIEPA</td>
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<td>4-Dimethylaminopyridine</td>
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<td>Dimethyl sulfoxide</td>
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<td>ee</td>
<td>Enantiomeric excess</td>
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<td>EI</td>
<td>Electron ionization</td>
</tr>
<tr>
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<td>Enantiomer</td>
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<td>equiv</td>
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<td>ESI</td>
<td>Electron spray ionization</td>
</tr>
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</tr>
<tr>
<td>g</td>
<td>Gram(s)</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrum</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz (cycles per second)</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>Spin-spin coupling constant</td>
</tr>
<tr>
<td>LAH</td>
<td>Lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>L-selectride</td>
<td>Lithium tri-sec-butylborohydride</td>
</tr>
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<td>mol</td>
<td>Mole(s)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
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<td>Minute(s)</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole(s)</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxy methyl</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrum</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-Iodosuccinimide</td>
</tr>
<tr>
<td>NBSH</td>
<td>o-Nitrobenzenesulfonylhydrazide</td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-Methoxybenzyl</td>
</tr>
<tr>
<td>PNBz</td>
<td>p-Nitrobenzoyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>Py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>$R_f$</td>
<td>Ratio to front</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>TBS</td>
<td>$t$-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TTMSS</td>
<td>Tris(trimethylsilyl)silane</td>
</tr>
<tr>
<td>$p$-TsOH</td>
<td>$p$-toluene sulfonic acid</td>
</tr>
</tbody>
</table>
Chapter 1

Total Synthesis of Jadomycin A and Carbasugar Analog of Jadomycin B

1.1 Background

Jadomycins are novel secondary metabolites produced by the Gram-positive soil bacteria *Streptomyces venezuelae* ISP5230 (ATCC10712) under environmental stresses, nutrient limitation, heat shock, phage infection and exposure to toxic concentrations of ethanol.\(^1,2\) In contrast, chloramphenicol is the only antibiotic currently characterized from *Streptomyces venezuelae* under normal growth conditions.\(^3\) In general, jadomycins are called angucycline natural products because of their angular tetracyclic core (phenanthridine ring). These angucycline polyketide natural products are composed of an unusual 8H-benzo-[\(b\)]-phenanthridine backbone with variously fused nitrogen and oxygen containing heterocycles like oxazolidine, pyrimidine and oxazinane (Figure 1.1). Except for jadomycin A (i.e., jadomycin B aglycon), all jadomycins are glycosylated with a L-digitoxose sugar unit.\(^4\) This sugar moiety plays an important role in the biological activities exhibited by these natural compounds. For example, jadomycin B (the glycosylated natural product) exhibits anti-yeast activity whereas its aglycon (jadomycin A) is inactive.\(^5\) Jadomycins are active against Gram-positive and Gram-negative bacteria and also show anticancer activity. The mechanism of action for anticancer activity has been tentatively attributed to aurora-B kinase inhibition and/or DNA cleavage.\(^6\)
1.2 Biosynthetic studies

Since the early isolation work of Ayer,\textsuperscript{6a} the unique structure and interesting biological activities of the jadomycins have inspired extensive study of their biosynthesis. These initial studies ultimately led to the discovery of related jadomycin secondary metabolites. In 1994, Vining was the first to clone and characterize the polyketide synthase (PKS) genes responsible for jadomycin B biosynthesis in \textit{Streptomyces venezuelae} ISP5230.\textsuperscript{7} Later, more detailed investigations of the gene clusters were carried out by Yang \textit{et al}.\textsuperscript{8} Initial biosynthetic studies suggested that rabelomycin is the intermediate in jadomycin biosynthesis and \textit{jadF} catalyzed the oxygenation of rabelomycin leading to B-ring opening.\textsuperscript{2a} However, subsequent work discovered other intermediates in the pathway, including UWM6 1.1.1 and prejadomycin 1.1.2. These genetic studies, along with important contributions from Vining\textsuperscript{9} and Rohr\textsuperscript{10} led to two plausible biosynthetic pathway for jadomycins (Scheme 1.1).

Figure 1.1: Jadomycin structural congeners
Scheme 1.1: Proposed biosynthetic pathway

Although the exact identity of the enzyme responsible for the B-ring opening of dehydrorabelomycin 1.1.4 is still unknown, it is assumed that some combination of $jadF$, $jadH$ and $jadG$ is responsible for this reaction (1.1.4 to 1.1.5).\textsuperscript{10a} Rohr \textit{et al.} have proposed a mechanism for the C-C bond cleavage of the B-ring by a Baeyer-Villiger type mechanism
(1.1.6 to 1.1.7). Subsequent hydrolysis of lactone intermediate 1.1.8 by jadK would give aldehyde 1.1.5. However at the time of this study, the C-12 oxygenation was incorrectly assigned as performed by jadG.\textsuperscript{10b} Although the exact pathway for its formation is still ambiguous, aldehyde 1.1.5 is believed to be the intermediate that incorporates the amino acids. Initial amino acid condensation, followed by a series of decarboxylation and ring closing sequences, form the pentacyclic skeleton of jadomycin. Early on, Vining \textit{et al.}\textsuperscript{2a} suggested that isoleucine incorporation begins with an intermolecular 1,4-addition across the quinone enone, which is followed by decarboxylation. Subsequent intramolecular addition to the aldehyde and lactonization yield the pentacyclic core. Considering the presence of excess amino acid nucleophile (e.g., isoleucine) and the relative reactivity of the functional groups, Rohr \textit{et al.} proposed an alternative mechanism. Their mechanism begins with the amine of isoleucine condensing with the aldehyde 1.1.5 to form intermediate imine 1.2.1. A subsequent cascade cyclization involving carboxylate addition to the imine, amine addition to the quinone\textsuperscript{11} and decarboxylation leads to the pentacyclic core of jadomycin (Scheme 1.2).

![Scheme 1.2: Biosynthetic incorporation of amino acid](image)

The biological activity exhibited by many naturally occurring antibiotics and antitumor agents strongly depends on their glycosidic components.\textsuperscript{12} Over the past years, it has been demonstrated that the substrate specificity, binding affinity and pharmacokinetic properties depend on the
structure of the sugar moieties. The 2,6-dideoxy pattern is the most common substitution pattern of carbohydrates found in these natural products. For example, the antibiotic Kijanimicin contains four L-digitoxose sugar units, the anticancer drug mithramycin includes both D-olivose and methylated D-mycarose, whereas a rare amino sugar, L-ristosamine is present in the antibiotic ristocetin A. The significance of L-digitoxose (a 2,6-dideoxy sugar) in jadomycin B was demonstrated by Vining et al. In their study, it was found that glycosylated natural product (jadomycin B) exhibit anti-yeast activity whereas the aglycon (jadomycin A) does not. This significant finding led to a detailed biosynthetic study on the sugar unit of jadomycin B. Based on sequence analysis and the gene propagation studies in Escherichia coli, Vining et al. have proposed a biosynthetic pathway for the production of the L-digitoxose sugar unit from glucose-1-phosphate (Scheme 1.3). \[JadQ\] encodes glucose-1-phosphate nucleotidyltransferase, which activates glucose to the nucleotide diphosphate (NDP) derivative. A 4,6-dehydratase encoded by \[jadT\] converts this NDP-glucose to NDP-4-keto-6-deoxy-D-glucose. An NDP-hexose 2,3-dehydratase encoded by \[jadO\] converts to a keto-enol intermediate, which exists in equilibrium with the diketone intermediate. This diketone intermediate is transformed to NDP-2,6-dideoxy-D-threo-4-hexulose by an oxidoreductase encoded by \[jadP\]. Isomerization of this D-threo hexulose to L-erythro form occurs by the \[jadU\] product (NDP-4-keto-2,6-dideoxy-5-epimerase) via intermediate. Finally, the ketone group of NDP-4-keto hexulose is reduced by NDP-4-keto-2,6-dideoxyhexose-4-ketoreductase, encoded by \[jadV\], to give the L-digitoxose moiety in jadomycin B biosynthesis (Scheme 1.3).
It is unclear whether glycosylation occurs on jadomycin A or other intermediates prior to the formation of the phenanthridine and oxazolone rings by incorporation of amino acid. Comparison of the amino acid sequence encoded by jadS shows a resemblance to deoxyglycosyltransferase. So, it was proposed that jadS is involved in installing the L-digitoxose sugar unit in jadomycin B.

1.3 Previous synthetic approaches

The benzo-[b]-phenanthidine ring containing natural products are structurally unique angucyclines isolated from different species of Streptomyces.\textsuperscript{18} Despite many synthetic efforts, there have only been a limited number of successful total syntheses of this type of angucycline antibiotics. The lack of successful syntheses can be attributed to both the structural complexity and instability associated with these structures, in particular the instability of the glycosidic bond. In contrast, there have been several successful approaches to the phenanthridine core.\textsuperscript{19,20,21}
Similarly, there have been many successful approaches to the synthesis of \(L\)-digitoxose sugar. Traditionally, the digitoxose sugar moiety has been prepared from a chiral starting material (e.g., glucose derivatives) by reduction of hydroxyl functional groups.\(^{22,23}\) A less common approach, starting with achiral starting material has been reported by Fronza et al.\(^{24}\) and Braun et al.\(^{25}\)

In 2010, Ishikawa et al.\(^{26}\) reported the synthesis of dimethyl-protected jadomycin A. Their route used a \(\alpha\)-spirolactonyldihydroquinone 1.4.2 as the key intermediate for construction of the jadomycin ring system. Retrosynthetically, they envisioned the construction of the jadomycin skeleton by imine cyclization followed by oxazolone formation of amino-aldehyde 1.4.1. This cyclization precursor was obtained from the spirolactone intermediate 1.4.2, which in turn was prepared from bromobenzene derivative 1.4.4 and tetralone 1.4.5 (Scheme 1.4).

![Scheme 1.4: Retrosynthesis by Ishikawa et al.](image)

Although they had successfully synthesized the pentacyclic core of jadomycin using Snieckus’s oxidative cyclization procedure\(^{27}\) involving the intramolecular condensation of an amine and aldehyde to construct the B ring, the synthesis of the natural product (jadomycin A) was
unsuccessful. The sensitive oxazolone ring did not survive the harsh methoxy deprotection conditions (Scheme 1.5).

![Scheme 1.5: Approach toward jadomycin A](image)

1.4 Our synthetic approach

Although different members of the jadomycin family of natural products have been successfully obtained by fermentation processes and great contributions were made to the understanding of the biosynthetic pathway, there was still ambiguity associated with the amino acid incorporation. To date, no enzyme has been isolated in the jadomycin gene cluster that is responsible for the process by which amino acid is introduced into these natural products. Rohr et al. suggested the possibility of a non-enzymatic incorporation of amino acid based on the fact that jadomycin occurs as an inseparable mixture of diastereomers. In order to better understand this process, we undertook a biomimetic approach toward the synthesis of jadomycin. In our approach, we proposed to synthetically achieve the amino acid incorporation and jadomycin ring formation (1.7.4 to 1.7.1) utilizing intermediate 1.7.4 (Scheme 1.7) that would mimic the biosynthetic precursor 1.1.5 (Scheme 1). A successful synthetic route would ensure adequate material, as well as, allow modifications of the sugar and/or aglycon portion for the synthesis of novel analogs for SAR-type studies.
1.5 Retrosynthetic analysis

Although no prior total synthesis of the jadomycin family of natural products had been reported prior to our synthetic study, several approaches to the benzo[b]-phenanthridine ring system were known (Scheme 1.6).\textsuperscript{19,20,21} The most common approach is by cyclization of a 2-amino-3-phenyl-naphthoquinone to construct the B-ring (e.g., 1.6.4 to 1.6.3), rather than an amine cyclization onto the 2-position of an anthroquinone (e.g., 1.6.2 to 1.6.3). Due to stereoelectronic reasons, the latter approach preferentially forms benzo[c]-phenanthridine ring system 1.6.1 by a 6-exo-trig cyclization. We hypothesized that, by switching to a 6-π-electrocyclic ring closure instead of a Michael type addition of amine nucleophile, the stereoelectronic disadvantage of a 6-endo-trig cyclization could be removed and the benzo[b]-phenanthridine ring system could be selectively achieved (Scheme 1.6).

![Scheme 1.6: Retrosynthetic comparison of phenanthridine ring system](image)

Our approach to jadomycin was based on the biosynthetic incorporation of amino acid to form the pentacyclic ring-system. To ascertain this biosynthetic assumption, we undertook a bio-
mimetic approach (Scheme 1.7). We envisioned that a digitoxose sugar could be installed in a late stage glycosylation onto the aglycon to synthesize jadomycin B. The oxazolone ring of jadomycin could be constructed by acid catalyzed transesterification of aminal 1.7.1. The tetracyclic backbone (phenanthridine core) could be constructed by a 6-\(\pi\)-electrocyclic ring-closure of imine 1.7.2. This key intermediate imine 1.7.2 could be obtained by a chemoselective condensation of reactive aldehyde 1.7.4 with \(t\)-butyl-isolucinate 1.7.3. A Stille cross coupling between stannane 1.7.5 and 2-bromojuglone 1.7.6 would successively construct aldehyde 1.7.2 (Scheme 1.7).

![Scheme 1.7: Retrosynthetic analysis](image)

1.6 Synthesis of coupling partners

By a modification of the literature method,\textsuperscript{28} benzoate 1.8.3 was produced in 42\% overall yield in three steps from ethylacetopyruvate 1.8.1 via Claisen adduct 1.8.2. Protection of the phenol as a TBS ether followed by LiAlH\(_4\) reduction gave benzyl alcohol 1.8.4. Oxidation of the
benzylic alcohol with MnO$_2$ gave aldehyde 1.8.5.$^{29}$ The TBS ether was removed under acidic conditions to afford 3-hydroxyl-5-methyl benzaldehyde 1.8.6.$^{30}$ Benzaldehyde 1.8.6 was first protected as an acetal by reacting with 1,3-propanediol in the presence of $p$-toluenesulfonic acid, and then phenol was protected as MOM ether 1.8.8 or BOM ether 1.8.9 in the presence of DIPEA. The MOM/BOM ethers were converted to stannanes 1.8.10/1.8.11 by a directed lithiation followed by quenching the anion intermediate with tributyltin chloride (Scheme 1.8).

Scheme 1.8: Synthesis of stannane

Synthesis of 2-bromojuglone 1.9.4 started from commercially available starting material 1,5-dihydroxynaphthalene 1.9.1. Following a reported method by Jung et al.,$^{31}$ 1,5-dihydroxynaphthalene 1.9.1 was converted to diacetate 1.9.2 in the presence of acetic anhydride and pyridine. Diacetate 1.9.2 was oxidized with NBS to form 2-bromojuglone acetate 1.9.4. The regioselective bromination proceeds through formation of a tribromide intermediate 1.9.3, which undergoes an oxidation/elimination sequence under aqueous reflux to
regioselectively form 2-bromo acetate. Acetate 1.9.4 was hydrolyzed under acidic conditions to produce 2-bromojuglone 1.9.5, which was further protected as benzyl ether 1.9.6 by treatment with benzylbromide and a weak base, Ag₂O (Scheme 1.9).

![Scheme 1.9: Synthesis of 2-bromojuglone](image)

### 1.7 Total synthesis of jadomycin A

With the 2-bromojuglone and the stannane in hand, their coupling was investigated by following the conditions reported in the literature.²¹ Moderate yield of the coupled products (1.10.1-1.10.4) led us to optimize the Stille coupling conditions. In general, bidentate phosphine ligands performed better than the monodentate ligands. Out of all the palladium catalysts/precatalyst, ligands and co-catalysts screened, the best yield (83%) of the coupled product (1.10.1) was obtained by using Pd₂(dba)₃·CHCl₃ as the palladium catalyst, dppe as ligand and copper iodide as the co-catalyst (Scheme 1.10).
After achieving a successful synthesis of the Stille coupled product, we investigated the selective deprotection of the acetal in the presence of MOM ether in 1.10.3. Acetal 1.10.3 was selectively cleaved in 10 min at room temperature using 50% aqueous TFA. The resultant aldehyde 1.11.1 was then subjected to imine formation by condensation with t-butyl protected isoleucine 1.11.2. As expected, imine formation occurs smoothly (determined by $^1$H NMR) but it did not undergo a spontaneous 6-$\pi$-electrocyclic ring closure to form the tetracyclic core 1.11.4. Heating the reaction after initial imine formation resulted in decomposition. At that point, we surmised that, the steric hindrance between the MOM ether and the carbonyl of quinone probably results in a C-C bond rotation along the A-C ring. This orientation most likely favors a minimum energy conformation in which the imine $\pi$-bonds do not align with the $\pi$-
bonds of A and C ring. Thus, a 6-π-electrocyclic ring closure reaction could not take place (Scheme 1.11).

Scheme 1.11: Attempted synthesis of jadomycin A

In order to obtain the desired 6-π-electrocyclic reaction, we decided to remove steric congestion by deprotecting the MOM ether prior to condensation with amino acid. Deprotection of the MOM/BOM ether along with the acetal was achieved by using concentrated HCl in acetonitrile. The aldehydes 1.12.1/1.12.2, when subjected to imine formation with t-butyl isocitrate 1.11.2, formed the desired B-ring of jadomycin via a 6-π-electrocyclic ring closure of the imine intermediate. It is important to note that deprotecting the MOM/BOM ether removes steric congestion and also introduces the potential for a hydrogen bonding interaction, which would stabilize the desired conformation (Scheme 1.12). We think that it is this critical hydrogen bonding interaction, which brings the imine π-electrons in plane with the π-systems of the aromatic ring. Thus, a 6-π-electrocyclic ring closure occurs forming the phenanthridine core.
1.12.3/1.12.4. Treating the aminals 1.12.3/1.12.4 with concentrated TFA resulted in oxazolone ring formation via trans-esterification. We have also found that the benzyl protection of the D-ring can also be removed in one pot during oxazolone formation with an extended reaction time (1.12.4 to jadomycin A).

Scheme 1.12: Synthesis of jadomycin A

1.8 Plausible mechanism of jadomycin ring formation

Based on the information gained during the total synthesis of jadomycin A, we proposed a mechanism for the formation of the pentacyclic ring system of jadomycin (Schem1.13). First there is a chemoselective imine formation between aldehyde 1.12.1 and t-butyl isoleucinate 1.11.2. Because of the hydrogen bonding interaction (evidence of a strong hydrogen bonding can be found in $^1$H NMR, where a sharp singlet is observed around 10.5 ppm) between the phenol of ring A and the quinone, the imine $\pi$-bond aligns in plane with that of ring A and quinone. This in-plane alignment triggers a 6-$\pi$-electrocyclic ring closure forming the tetracyclic intermediate 1.13.1b. A keto-enol tautomerization results in the intermediate 1.13.1c. This
intermediate undergoes an \textit{in situ} hydration with the water molecule generated upon imine formation in the first step. The hydration reduces quinone \textbf{1.13.1c} to hydroquinone \textbf{1.13.1d}. Since the hydroquinone is very sensitive to oxidation, it oxidizes in presence of air to quinone \textbf{1.12.3} forming the phenanthridine core of jadomycin. Finally, acid catalyzed transesterification of aminal \textbf{1.12.3} forms the oxazolone ring and the pentacyclic ring system of jadomycin. Because of the feasibility of the oxazolone ring opening/closing via aminal \textbf{1.12.3}, jadomycin A was obtained as a 6:1 diastereomeric mixture (Scheme 1.13).

![Scheme 1.13: Plausible mechanism of ring closure](image)
1.9 Synthesis of α-L-digitoxose sugar unit

After a successful synthetic investigation of the aglycon (jadomycin A), we turned our attention to the carbohydrate portion of jadomycin B. Toward this, we applied our group’s de novo approach to carbohydrate for the synthesis of L-digitoxose. Following a three-step procedure, achiral starting material acylfuran 1.14.1 was converted to the key building block (i.e., Boc-pyranone 1.14.2). Our initial plan was to employ a palladium catalyzed glycosylation to introduce the building block onto the aglycon and with post glycosylation transformations, obtain the digitoxose sugar of jadomycin B. Unfortunately, all attempts involving palladium glycosylation failed, even with simpler intermediate such as 1.10.1. The aglycons were found to be unreactive and could be recovered after quenching the reaction. One possible reason could be poor nucleophilicity of phenol and/or sensitive structural features like the oxazolone ring of jadomycin A. Next, we proposed a convergent synthesis in which we planned to synthesize the digitoxose sugar unit 1.14.7 and couple it to aglycon, jadomycin A. Various glycosyl donors (1.14.7-1.14.11) were synthesized from the key intermediate 1.14.2 using our de novo approach (Scheme 1.14). Boc-pyranone 1.14.2 was glycosylated with benzyl alcohol stereoselectively using Pd₂(dba)₃•CHCl₃/PPh₃ to form 1.14.3. Using Luche conditions (CeCl₃/MeOH and NaBH₄), enone 1.14.3 was stereoselectively reduced to allylic alcohol, which was subsequently protected as Boc-carbonate 1.14.4. Treating the alkene 1.14.4 with NIS induced an intramolecular trapping of an intermediate iodonium to give iodide 1.14.5. The iodide in 1.14.5 was then removed under radical conditions (TTMSS/AIBN) to obtain carbonate 1.14.6. Finally, reductive debenzylation gave glycosyl donor 1.14.8. Carbonate 1.14.6 was also hydrolyzed and the subsequent diol was protected as acetonide. Debenzylation gave another glycosyl donor 1.14.7. The anomeric alcohol 1.14.8 was then activated as trichloroacetimidate
1.14.9. The glycosyl donor 1.14.8 was also activated as anomeric acetate 1.14.10 by treating with acetic anhydride and pyridine. A glycosyl donor with anomeric chloride 1.14.11 was also prepared by treating 1.14.10 with methanolic HCl (Scheme 1.14).

![Scheme 1.14: Synthesis of glycosyl donors](image)

1.10 Attempted glycosylations

After synthesizing glycosyl donors 1.14.7-1.14.11, we investigated various glycosylation conditions with aglycons jadomycin A and 1.10.1/1.10.2. Trichloroacetimidate donor 1.14.9 and anomeric acetate 1.14.10, which were activated under Lewis acidic conditions, failed to give any desired product with jadomycin A or simpler aglycons 1.10.1/1.10.2. Glycosylation under basic conditions using anomeric chloride 1.14.11 also failed (Scheme 1.15). All of these failed reactions, including our initial palladium catalyzed glycosylation, point to poor nucleophilicity of the phenol of the aglycons, which is fused to the electron withdrawing
quinone. Although the results of our initial glycosylation were disappointing, they gave us important structural information about the nucleophile (e.g., the phenolic proton should be substantially acidic since it is fused to a strongly electron withdrawing quinone). So, we decided to employ Mitsunobu type glycosylation to install the sugar moiety. Mitsunobu glycosylation conditions (PPh$_3$/DIAD) were explored with glycosyl donors 1.14.6 and 1.14.7. Although the color change which occurred during the glycosylation was a promising sign (from dark green to wine-red, the color of glycosylated natural product), no desired product was isolated. Failure to isolate the glycosylated product could be due to the inherent instability associated with the glycosylated natural product. Since the sugar moiety is attached to a very electron poor quinone ring system, the glycosidic bond is sensitive to hydrolysis (Scheme 1.15).

In a recent report detailing the total synthesis of jadomycin B$^{33}$, Yu et al. demonstrated a successful method for this challenging glycosylation. The successful glycosylation was achieved under a low temperature Mitsunobu reaction using 3,4-di-$O$-acetyl-$L$-digitoxose as the donor and jadomycin A as the acceptor (Scheme 1.16). The best yield of glycosylated product 1.16.2 (64%,
\( \alpha: \beta = 6:1 \) was obtained by using 3 eq. donor \textbf{1.16.1}, 2 eq. PPh\textsubscript{3} and 2.5 eq. DEAD at \(-75 \) °C. It is important to note that the structure of the donor plays a key role in the Mitsunobu glycosylation since the flexible donor 3,4-di-\( O\)-acetyl-L-digitoxose \textbf{1.16.1} forms the desired glycosylated product (Scheme 1.16), whereas our rigid L-digitoxose donors that are installed with 3,4-\( O\)-isopropylidene or 3,4-\( O\)-carbonate could not be coupled (Scheme 1.15).

![Scheme 1.16: Biao Yu’s approach;\textsuperscript{33} Mitsunobu glycosylation](image)

**1.11 Synthesis of carbasugar**

Our inability to successfully install digitoxose sugar for the synthesis of jadomycin B and the inherent instability of the glycosides in jadomycin family of natural products motivated us to look for a stable alternative. We knew that the glycosidic bond in jadomycin B was susceptible to hydrolysis. So, in order to generate a stable analog, we decided to replace the ring oxygen of the digitoxose sugar with a methylene group. This would replace the acid sensitive glycosidic bond with a stable ether linkage. The necessity to obtain a stable analog led us to the synthesis of carbasugar a.k.a cyclitol analog of digitoxose sugar unit.
The synthesis of the carbasugar analog started with commercially available starting material D-quinic acid 1.17.1. Following a previously reported method, quinic acid 1.17.1 was converted into dihydroxy ketone 1.17.2 in nine steps. Enone 1.17.3 was obtained by Boc-protection of 1.17.2 followed by base mediated elimination. This enone was chemo and stereoselectively reduced to allylic alcohol 1.17.4 using LiAlH₄ at low temperature. Myers reductive rearrangement of the allylic alcohol gave alkene 1.17.5. Stereoselective dihydroxylation of the alkene and protection of the resulting diol gave 1.17.6. Finally, the Boc group was removed with LiAlH₄ to obtain the Mitsunobu glycosylation precursor 1.17.7 (Scheme 1.17).

### 1.12 Total synthesis of carbasugar analog of jadomycin B

Having successfully synthesized the carbasugar donor 1.17.7, we tried our planned convergent synthesis (i.e., installing cyclitol onto the aglycon jadomycin A). Mitsunobu conditions were employed, but no cyclitolized product 1.18.3 was obtained. Running the reaction for longer periods of time resulted in decomposition of the aglycon and/or elimination of the hydroxyl in cyclitol 1.17.7. Next we planned to install the cyclitol 1.17.7 before amino acid
incorporation/oxazolone ring formation. When cyclitol acceptors 1.10.1/1.10.2 were used, clean cyclitolized products 1.18.1/1.18.2 were obtained (Scheme 1.18).

Scheme 1.18: Mitsunobu cyclitolization

The protecting groups in 1.18.1/1.18.2 were globally removed using 2.4 M HCl in acetonitrile to obtain aldehyde 1.19.1. As before, aldehyde 1.19.1 was condensed with t-butyl isoleucinate 1.11.2 to obtain the phenanthridine core of jadomycin via a 6-π-electrocyclic ring closure of the intermediate imine. Finally, the oxazolone ring was constructed by acid catalyzed transesterification to yield the carbasugar analog of jadomycin B in a 2.5:1 diastereomeric ratio (Scheme 1.19).\(^{35}\)
1.13 Conclusion

In conclusion, the synthetic study on the jadomycin family of natural products has revealed many important structure reactivity relationships (e.g., a very regioselective formation of benzo-[b]-phenanthridine ring system has been developed by applying a 6-π-electrocyclic ring closure). To the best of our knowledge, this is the first time that switching to an electrocyclic ring closure was used to change the regioselectivity for ring closure. The methodology has been successfully employed for the first total synthesis of jadomycin A with 17% overall yield. Our glycosylation attempts\textsuperscript{35} in combination with the recent report by Yu \textit{et al.}\textsuperscript{33} suggest that the L-digitoxose undergoes Mitsunobu glycosylation only when the donor is flexible (i.e., 3,4-hydroxyl groups in L-digitoxose are protected as diacetate rather than a rigid carbonate or acetonide). A stable cyclitol analogue of jadomycin B has also been successfully achieved in a 20 steps, longest linear sequence in a 2.5% overall yield. This synthesis also supports the conclusions by Rohr \textit{et al.}\textsuperscript{11} that the isoleucine incorporation and consequent formation of the oxazolophenanthridine ring system occur non-enzymatically.
Chapter 2

Synthetic approach toward gilvocarcin analogs

2.1 Background

Gilvocarcins are antitumor antibiotics that were initially from the culture broth of Actinomycetes DO-38. The name “gilvocarcin” was coined after the producing organism, which later was found to be a new species called Streptomyces gilvotanareus. Gilvocarcin V is usually produced along with its minor congeners gilvocarcin M and E, where the letters M, E and V represents methyl, ethyl and vinyl chain at C-8 position respectively (Figure 2.1). Hirayama et al. reported the first isolation of this class of natural compounds\textsuperscript{36} and the structures were later confirmed by Balitz et al.\textsuperscript{37} These compounds exits in yellow crystalline form. All of these compounds contain the characteristic polyketide-derived substituted benzo[d]naphthol[1,2-b]pyran-6-one as the aglycon and a fucose sugar unit. The most interesting structural feature of these natural products is the attachment of the sugar unit to the aglycon through a non-hydrolysable C-glycosidic linkage.

Figure 2.1: Structure of gilvocarcins
Gilvocarcins are active against Gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis*, and weakly active against Gram-negative bacteria, such as *Escherichia coli* and *Klebsiella pneumonia*. They are also good DNA-intercalators. The most potent member of this class of natural compounds is the gilvocarcin V which also exhibits potent antiviral and antitumor activity. One of the mechanisms by which it exhibits antitumor activity is by inhibiting topoisomerase II. It has been reported that the vinyl side chain of gilvocarcin V undergoes a [2+2]-cycloadduct formation with DNA thymidine. Gilvocarcin V can also cause cross-linking between DNA and histone H3.

**2.2 Biosynthetic studies**

Interesting biological activities, coupled with remarkably low *in vivo* cytotoxicity, have led to detailed biosynthetic investigations. The biosynthetic pathway for the gilvocarcins is related to that of jadomycins, in which the oxidatively cleaved B-ring of dehydrorabelomycin M 2.1.8/ dehydrorabelomycin E 2.1.9 or dehydrorabelomycin V 2.1.10 forms lactol 2.1.13/2.1.14 after decarboxylation, quinone reduction and the cyclization sequences (Scheme 2.1). The glycosyl moiety is transferred to the aglycon, pregilvocarcin 2.1.13/2.1.14, by glycosyl transferase. Oxidation of the lactol to lactone forms gilvocarcins. On the other hand, if the oxidation of lactol occurs prior to the glycosylation step, defucogilvocarcins are produced. In a collaborative work with Prof. Rohr, enzymatic synthesis of defucogilvocarcin M has been achieved. The study has also established the previously uncertain role of reductive *O*-methyltransferase GilM and *O*-methyltransferase GilMT in the gilvocarcin biosynthetic pathway.
Scheme 2.1: Proposed biosynthetic pathway of gilvocarcins

Although great efforts have been made to understand the biosynthetic pathway, it is still unclear as to how the glycosyl moiety is transferred to the aglycon and how the stable C-aryl glycoside is formed. It has been suggested that glycosyl transferase first installs the sugar moiety on the
phenol, forming \(O\)-glycoside. Since the \(O\)-glycoside is unstable, it undergoes an \(O\) to \(C\) migration forming a hydrolytically stable \(C\)-aryl glycoside (Scheme 2.2).

![Scheme 2.2: Proposed C-aryl glycoside formation](image)

### 2.3 Our working hypothesis

Although aryl \(O\)-glycosides are not uncommon in bacterial metabolites, why did *Streptomyces gilvetanareus* (producing organism for gilvocarcin) evolve to produce these specific \(C\)-glycosides? Is this an evolutionary adaptation to make more stable secondary metabolites or was there evolutionary pressure to form a more potent product? To obtain a better understanding, we proposed to synthesize stable analog 2.3.1 that would mimic the unstable natural \(O\)-glycoside 2.2.3. Comparing the biological activities of the stable analog with those of the natural compound 2.2.4 would give us some idea about the evolutionary sugar migration. We were also interested in synthesizing the regioisomeric analogs since it could give us the critical information about a possible correlation between sugar position and biological activity. In a recent study by Prof. Rohr, gilvocarcin analogs were biosynthesized with varied sugar substitutions.\(^4\) Biological evaluation of the analogs revealed that the analog containing a C-2 deoxy sugar (D-olivose) was the most potent (even more potent than the natural congener). Based on this finding, we proposed to synthesize stable analogs, the sugar portion of which would mimic a C-2 deoxy...
sugar. Based on our previous experience with the total synthesis of a stable jadomycin B carbasugar analog,\textsuperscript{35a} we proposed to install cyclitol or carbasugar onto gilvocarcin aglycon to generate stable \textit{O}-cyclitol analogs \textbf{2.3.1} and its regioisomers \textbf{2.3.2} (Figure 2.2). We were also interested in finding out the effect of changing the sugar stereochemistry on biological activities. To meet that purpose we proposed to synthesize analogs with enantiomeric cyclitol moieties \textit{ent-2.3.1} and \textit{ent-2.3.2} (Figure 2.2).

![Figure 2.2: Target synthetic analogs](image)

**2.4 Previous synthetic approaches**

The first total synthesis and stereochemical assignment of gilvocarcin M was accomplished by Suzuki.\textsuperscript{44} The notable features in their synthesis were an aryl \textit{C}-glycosylation to install the fucose sugar unit (\textbf{2.3.7} to \textbf{2.3.5}), a Diels-Alder reaction to construct the B-ring (\textbf{2.3.5} to \textbf{2.3.3}) and a Pd-catalyzed lactonization to form the tetracyclic core of gilvocarcin (Scheme 2.3).
In contrast to the total synthesis of gilvocarcin family of natural products containing the carbohydrate moiety,\textsuperscript{44,45} many strategies have been developed toward the synthesis of the aglycon. The synthesis of defucogilvocarcin V has been reported by a number of groups: Danishefsky \textit{et al.}\textsuperscript{46} described the synthesis based on the Meyers coupling of Grignard reagent 2.4.8 with the oxazolidine 2.4.9. The lactonization was achieved under acidic conditions to form the tetracyclic core of gilvocarcin V (Scheme 2.4). The chromium carbene annulation strategy for the synthesis of the B-ring of gilvocarcin (2.4.2 from 2.4.3 and 2.4.4) was developed by Parker \textit{et al.}\textsuperscript{47} The tetracyclic core was constructed by employing Danishefsky’s acid catalyzed lactonization (2.4.2 to 2.4.1, Scheme 2.4). An unique approach to the gilvocarcin M, E and V aglycons has been reported by Snieckus \textit{et al.}\textsuperscript{48} Their method involved a directed remote mettallation/lactonization to synthesize the tetracyclic core of gilvocarcin (2.4.12 to 2.4.11). The precursor for directed remote mettallation/lactonization was obtained by Suzuki cross coupling of 2.4.13 with 2.4.14. The iodine coupling partner 2.4.13 was
synthesized from the amide 2.4.15 by ortho-lithiation/iodination (Scheme 2.4). The alkyl/alkenyl side chains were installed in a late stage metal catalyzed coupling of the triflate 2.4.11.

Scheme 2.4: Previous synthetic approaches toward gilvocarcin aglycon

Other strategies for the synthesis of gilvocarcin aglycon include the cycloaddition approach by Suzuki et al.\textsuperscript{49} and Bodwell et al.,\textsuperscript{50} the double annulation of styryl sulfone with pthalide by Mal et al.\textsuperscript{51} and the free radical addition-cyclization approach by Cordero-Vargas et al.\textsuperscript{52}
Echavarren *et al.* \(^{21}\) reported the first synthesis of naturally occurring angucycline BE-12406X\(_2\). The tetracyclic core was constructed by employing the reductive lactonization of 2.5.1. The lactonization precursor 2.5.1 was obtained by Pd-catalyzed cross coupling of organostannane 2.5.3 and bromojuglone 2.5.2 (Scheme 2.5).

\[
\text{BE-12406X}_2 \quad \xrightarrow{\text{reduction/lactonization}} \quad \text{2.5.1} \quad \xrightarrow{\text{metal-catalyzed cross-coupling}} \quad \text{2.5.2}
\]

\[
\text{2.5.3} \quad \text{Et}_2\text{NOC}_\text{Me}_3\text{Sn} \quad \text{OMe}
\]

Scheme 2.5: Echavarren’s approach to BE-12406X\(_2\)

### 2.5 Retrosynthetic analysis: Our synthetic approach

Our synthesis of regioisomeric defucogilvocarcin M is based on Echavarren’s synthesis of BE-12406X\(_2\).\(^{21}\) The lactone of the tetracyclic core could be prepared by a reductive lactonization sequence on the regioisomeric adduct 2.6.4. The lactonization precursor (i.e., the regioisomeric quinone-amide intermediate 2.6.4) could be obtained by the metal catalyzed cross coupling of benzyl protected 2- or 3-bromojuglones 2.6.5 with stannane 2.6.6. Finally, debenzylation of the lactonized product would generate the regioisomeric defucogilvocarcin M 2.6.3 (Scheme 2.6). Based on our previous experience with the synthesis of the cyclitol analog of jadomycin B,\(^{35a}\) we envisioned that the cyclitols could be installed on the regioisomeric defucogilvocarcin M 2.6.3 through a Mitsunobu-type cyclitolization. Since we had developed a route to the C-2 deoxy carbasugar (carba-digitoxose 1.17.7, Scheme 1.17),\(^{35a}\) we planned to install carba-digitoxose as the cyclitol moiety onto the regioisomeric defucogilvocarcin 2.6.3 to generate the regioisomeric O-cyclitol analogs 2.6.1 and 2.6.2 (Scheme 2.6).
2.6 Synthesis of coupling partners

The synthesis of 2-bromojuglone 1.9.5 was accomplished by the procedure described in chapter 1 (Scheme 1.9).\textsuperscript{31} For the regioisomeric 3-bromojuglone 2.7.3, synthesis began with 1,5-dihydroxy naphthalene 1.9.1. Using CuCl, dihydroxy naphthalene was oxidized to hydroxyl quinone 2.7.1. Bromination of the alkene gave the dibromo-intermediate 2.7.2. Preferential elimination of C-2 bromide under ethanol reflux gave 3-bromojuglone 2.7.3 as the major product along with its regioisomeric C-2 bromide 1.9.5 (Scheme 2.7).\textsuperscript{53} The phenol of the major product 2.7.3 was then benzylated in presence of Ag\textsubscript{2}O to form 2.7.4.
Synthesis of the stannane 2.6.6 started with commercially available starting material ethyl-acetopyruvate 1.8.1. Treatment with aqueous acetic acid promoted a Claisen-type condensation to form adduct 1.8.2. Under basic condition, Claisen adduct underwent rearrangement/aromatization to form hydroxyl benzoic acid 2.8.1. The carboxylate 2.8.1 was then converted to an amide by treatment with diethyl amine and p-TsOH•H2O. The resulting phenol was subsequently protected as methyl ether 2.8.2 (Scheme 2.8).

Scheme 2.7: Synthesis of 3-bromojuglone

Scheme 2.8: Synthesis of stannane
The amide functionality in 2.8.2 was critical in order to achieve regioselective lithiation.\textsuperscript{54} Stannation was performed by modification of the previously reported procedure for directed O-lithiation.\textsuperscript{54} Various organolithium reagents were screened for the lithiation/stannation of 2.8.2. It was observed that sterically demanding alkyl-lithium reagents (e.g., t-BuLi) gave the best yield. Sterically less hindered n-BuLi preferentially underwent nucleophilic addition at the amide carbonyl forming the undesired ketone 2.9.1 (Scheme 2.9).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
R & Solvent & R-Li (eq) & Temp (°C) & \% 2.6.6 & \% 2.9.1 \\
\hline
n-Bu & THF & 1.0 & -78 to 0 & <20 & 65 \\
n-Bu & THF & 1.5 & -78 to 0 & <10 & 70 \\
s-Bu & THF & 1.1 & -78 to 0 & 40-45 & 30-35 \\
t-Bu & THF & 1.1 & -78 to 0 & 75 & <5 \\
t-Bu & THF & 1.5 & -78 to 0 & 70 & 7-10 \\
\hline
\end{tabular}
\caption{Scheme 2.9: Optimization of stannation}
\end{table}

\textbf{2.7 Synthesis of defucogilvocarcin M}

The stannane 2.6.6 and bromojuglone 1.9.6 were coupled using Stille-coupling conditions to obtain 2.10.1. The quinone-amide intermediate 2.10.1 was subjected to a modified reductive lactonization to form the tetracyclic core 2.10.2 of gilvocarcin. Although our modified procedure (reduction of quinone to hydroquinone by sodium dithionate and subsequent acid catalyzed lactonization) had comparable yield to the reported method (Zn/HOAc),\textsuperscript{21} it is important to note that our approach was more time efficient (~1 h vs 24 h). Methylation of the phenol, followed by debenzylation of 2.10.3, gave defucogilvocarcin M (Scheme 2.10).
2.8 Syntheses of carbasugars

In contrast to the α-linked carbasugar of jadomycin, gilvocarcin analogs required a β-linked carbasugar. The desired cyclitols (2.11.6, ent-2.11.6) were synthesized from commercially available starting material D-quinic acid 1.17.1. Following the reaction sequence described in Chapter 1 (Scheme 1.17), quinic acid 1.17.1 was converted to the diastereomeric diols 1.1.7.2 and 2.11.1. The diastereomeric diol 2.11.1 was converted to Boc-enone 2.11.2 by Boc-protection/elimination. Selective reduction of ketone at low temperature, followed by Myers reductive transposition\(^{55}\) on the allylic alcohol 2.11.3, gave alkene 2.11.4. Stereoselective dihydroxylation of alkene, followed by acetonide protection, gave 2.11.5. Reductive removal of the Boc-protection generated the desired cyclitol donor 2.11.6 (Scheme 2.11).
As a control to measure the effect of sugar stereochemistry on biological activity, we decided to synthesize the enantiomeric cyclitol \textit{ent-2.11.6}. This enantiomeric cyclitol \textit{ent-2.11.6} was obtained from the cyclitol \textit{1.17.7} (used in the synthesis of carbasugar analog of jadomycin B)\textsuperscript{35a} by the Mitsunobu inversion of the C-1 hydroxyl stereocenter (\textit{1.17.7} to \textit{ent-2.11.6}, Scheme 2.12).

\textbf{2.9 Attempted cyclitolization}

Once we had synthetic access to the aglycon defucogilvocarcin M and the cyclitols \textit{2.11.6} and \textit{ent-2.11.6}, we attempted Mitsunobu-like cyclitolization to install the carbasugar (Scheme 2.13). Unfortunately, no cyclitolylated product was observed under Mitsunobu conditions. Prolonged reaction time caused the opening of the lactone and subsequent oxidation to quinone. The low
reactivity of defucogilvocarcin M was attributed to several facts: 1) the high pKₐ (less acidic) of the phenolic proton in defucogilvocarcin M, 2) poor solubility of defucogilvocarcin M and 3) the susceptibility of the lactone ring to open and undergo subsequent oxidation to quinone.

Scheme 2.13: Attempted Mitsunobu cyclitolization

Next, we planned to investigate the use of the quinone intermediates 1.9.5 and 2.7.3 as the nucleophile in Mitsunobu cyclitolization. The new regioisomeric aglycons were prepared by a Stille coupling of the stannane 2.6.6 with unprotected 2-and 3-bromojuglones 1.9.5 and 2.7.3 respectively. We expected that the phenolic proton in these intermediates would be sufficiently acidic, since it is fused with a highly electron withdrawing quinone (Scheme 2.14).

Scheme 2.14: Synthesis of regioisomeric aglycon
2.10 Syntheses O-cyclitol analogs of gilvocarcin M

As expected, the Mitsunobu reaction with the new aglycon 2.14.1 went smoothly to provide the cyclitolized product 2.15.1. The quinone-amide intermediate was then subjected to a reductive lactonization with sodium dithionate/acetic acid to form the tetracyclic core of gilvocarcin 2.15.2. The phenol was then converted to the methyl ether 2.13.1. Finally acetonide deprotection using 10% aqueous HCl gave the desired O-cyclitol analog of gilvocarcin M 2.6.2. The acetonide in the intermediate 2.15.2 was also removed to obtain a triol analog 2.15.3 (Scheme 2.15).

Scheme 2.15: Synthesis of O-cyclitol analogs of gilvocarcin M
We then set out to use the same route to synthesize the regioisomeric O-cyclitol analogs of gilvocarcin M, 2.6.1 and 2.18.4. Although initially our route seemed promising, the installation of cyclitol on the regioisomeric aglycon 2.14.2 via a Mitsunobu reaction proved difficult. We thought that the complication associated with this regioisomer could be associated with the substitution pattern across the quinone ring rendering the quinone more susceptible to reduction. This concern was based upon the Mukaiyama’s report on a Mitsunobu inversion using substituted quinone 2.16.3 instead of DIAD or DEAD. He showed that quinone 2.16.3 can be reduced in situ to hydroquinone intermediate 2.16.5 by phosphine, activating the alcohol.

The resulting phenolate deprotonates the nucleophile (phenol 2.16.5), which then attacks in an $S_N2$ fashion, inverting the stereochemistry (Scheme 2.16).

![Scheme 2.16: Mukaiyama’s Mitsunobu variant](image)

A similar mechanistic analogy can explain the complications associated with our regioisomeric aglycon. Unlike 2.14.1, its regioisomer 2.14.2 has one of the carbonyl groups sterically accessible to PPh$_3$. The steric accessibility, coupled with the quinone activation by hydrogen bonding of the phenol, makes the quinone susceptible to reduction by PPh$_3$. The phenolate intermediate 2.17.1 thus generated could activate the cyclitol 2.11.6, and exists in equilibrium between three phenoxide species 2.17.4a, 2.17.4b and 2.17.4c. All of these species could
independently react with activated cyclitol 2.17.5 to form at least three different products, generating a complex reaction mixture (Scheme 2.17).

Scheme 2.17: Plausible mechanistic illustration for the complicated Mitsunobu reaction

Recognizing the potential problems associated with the quinone reduction, we designed a low temperature protocol in which a mixture of quinone, cyclitol and excess DIAD (3 eq.) was cooled to −78 °C. Then a THF solution of PPh₃ (1-1.5 eq.) was added slowly over a longer period of time (25-30 min). Performing the reaction at low temperature and having excess DIAD lessened the chance of quinone reduction. Quenching of the reaction at low temperature was critical since at ambient temperature reduced DIAD would add across the enone (1,4-Michael-type addition across the quinone).
2.11 Syntheses of regioisomeric \(O\)-cyclitol analogs of gilvocarcin M

Using this modified procedure, cyclitol 2.11.6 was installed onto the aglycon 2.14.2 to obtain 2.18.1. The quinone-amide 2.18.1 was then converted to tetracyclic lactone 2.18.2 by reductive lactonization. The phenol was then protected as a methyl ether 2.18.3. Subsequent acetonide deprotection using aqueous acid provided the regioisomeric \(O\)-cyclitol analog of gilvocarcin M 2.6.1. A triol analog 2.18.4 was also prepared by removing the acetonide of the intermediate 2.16.2 using aqueous hydrochloric acid (Scheme 2.18).

Scheme 2.18: Synthesis of regioisomeric analogs of gilvocarcin M
After syntheses of the regioisomeric analogs, the analogs were tested against Gram-positive and Gram-negative bacterial strains. All of the analogs were inactive against Gram-negative bacteria (*Escherichia coli*), but showed minimal inhibition against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*). The triol analogs of both regioisomers (2.15.3 and 2.18.4) were the least active. One reason could be associated with their poor aqueous solubility. The measured activities against Gram-(+)-bacteria *S. aureus* HG003 were: analog 2.6.2, MIC >150 µg/mL and analog 2.6.1, MIC = 150 µg/mL whereas the natural gilvocarcin M has MIC = 60 µg/mL. \(^{57}\) Antibacterial activities for the analogs were disappointing compared to that of natural gilvocarcin M. Nonetheless, the initial screening gave us valuable information about the correlation between the position of the sugar and antibacterial activity. From the initial screening results, we summarized that a methyl ether is better compared to a free phenol and the position of cyclitol plays an important role in terms of biological activity. Since gilvocarcin M and its cyclitol analogs are weakly active against cancer cells or topoisomerase activities, we undertook the analog synthesis of the more active member gilvocarcin V. Apart from antibacterial activity, gilvocarcin V also exhibits potent anticancer agent and strong topoisomerase II inhibitory activities.\(^{39,40}\)

2.12 Retrosynthetic analysis for gilvocarcin V analogs

For the synthesis of gilvocarcin V O-cyclitol analogs 2.19.1, we envisioned either a late-stage installation of the vinyl group by transition metal catalyzed coupling on the triflate 2.19.2 or the installation of the vinyl group on the D-ring 2.19.4 at the beginning of the synthesis. The latter was synthetically more attractive since it did not require a phenol protecting group to be carried throughout the synthesis to an advanced stage, as would be required for the late stage vinylation.
For the synthesis of the tetracyclic core 2.19.3, we envisioned using the same approach used in the synthesis of gilvocarcin M analogs (i.e., metal catalyzed coupling of 2.6.5 and 2.19.4 followed by a reductive lactonization, Scheme 2.19).

Scheme 2.19: Retrosynthetic analysis

We first investigated the installation of the vinyl group on the D-ring at the beginning of the synthesis. Although installation of the vinyl group on the D-ring at the beginning of the synthesis was straightforward (2.20.1 to 2.20.2), the subsequent transformation to stannane 2.20.3 was problematic. The vinyl group was not compatible with strongly basic reaction conditions, which were required for stannation (Scheme 2.20). So, we planned to proceed through our initial plan of late-stage vinylation.

Scheme 2.20: Attempted stannation
The need for late-stage installation of a vinyl group led us to redesign our approach to the D-ring of gilvocarcin. We envisioned carrying either a silyl or benzyl ether as the phenol protection on D-ring, which could be orthogonally deprotected. Since we intended to carry two ether functionalities (methyl- and benzyl- or silyl-ethers) on the D-ring 2.21.3, we could not use an amide as a directing group for regioselective lithiation. To overcome this challenge, we envisioned that, if we could have access to aromatic bromide 2.21.1, we would be able to convert it into the desired coupling partner by either a stannation or boration 2.21.2 (Scheme 2.21).

Scheme 2.21: D-ring of gilvocarcin V

2.13 Study on regioselective bromination

For a regioselective bromination, we chose to carry out a protecting group manipulation study. Various protecting groups and substrates were studied under different bromination conditions (Scheme 2.22). From this study, it was found that, except for 3,5-dihydroxy methylbenzoate 2.22.1, all symmetrical substrates (2.22.4 and 2.22.6) could be easily mono brominated by controlling the equivalents of the brominating reagent. With one equivalent of brominating reagent, only ortho-bromination products were observed (2.22.4 to 2.22.5 and 2.22.6 to 2.22.7). Although ortho-bromination on these symmetrical substrates (2.22.4 and 2.22.6) occurred smoothly, differentiations of the phenolic substituents of the bromination products (2.22.5 and 2.22.7) based on selective protection or deprotection were unsuccessful. To our
delight, we found that when one of the phenol groups in 2,5-dihydroxy methylbenzoate 2.22.1 was protected as an ether 20.22.8 or 2.22.10, selective bromination was achieved at the ortho-position (2.22.8 to 2.22.9 and 2.22.10 to 2.20.11). Unlike the bromination products of symmetrical substrates (2.22.5 and 2.22.7), the free phenol in products 2.22.9 and 2.22.11 could be orthogonally protected and were thus synthetically useful. Although silyl protections (2.22.10) were our initially preferred choice, they were not very compatible with the bromination conditions (Scheme 2.22).

Scheme 2.22: Protecting group manipulation for regioselective bromination
The regioselective outcome of the bromination reaction (2.22.8 to 2.22.9) was confirmed by NOE experiments. In the starting material 2.22.8, phenolic proton corresponded to two NOE enhancements at the ortho-protons H_A and H_B. In the brominated product however, there was no NOE enhancement to H_B (Figure 2.3).

![Figure 2.3: Schematic representation of NOE enhancement](image)

Extensive screening of reagents and solvents was carried out to find the optimum bromination conditions. Optimizations of brominating reagents were carried out initially in CCl_4. It was found that NBS performed better over bromine in our studied system. Additives such as HOAc did not improve the yield of bromination. Although good yields (up to 75%) were achievable, reaction times were longer (>8h). After the optimum-brominating reagent was found, solvent screening was carried out. It was observed that CHCl_3 outperforms all the solvents screened in terms of product yield and reaction time. Up to 97% of regioselective bromination was achieved by using 1.05 eq. NBS in CHCl_3 at 0 °C in just 7 minutes (Scheme 2.23).
After successful regioselective bromination, we undertook the syntheses of the coupling partners (2.24.2 and 2.24.3). Phenol 2.22.9 was first converted to methyl ether 2.24.1. The aromatic bromide was subsequently subjected to either palladium catalyzed stannation (2.22.9 to 2.24.2) or boration (2.22.9 to 2.24.3). Although the yields of boration were superior compared to stannation, the subsequent Suzuki cross couplings with bromojuglones 1.9.5 or 2.7.3 were low yielding (Scheme 2.25). The low yields of the Suzuki reaction were probably because of hydrolysis of methyl ester and less tendency of pinacol borane to undergo hydrolysis.
to form boronic acid (the active coupling partner). For this reason we decided to optimize the palladium catalyzed stannation reaction (Scheme 2.24). The best condition for stannation was obtained by using \( \text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 \), \( \text{PCy}_3 \) and \( \text{LiCl} \) in dioxane. The moderate yield (~65%) of stannation was presumably due to an \textit{in situ} protodestannylation of the oxidatively added Pd(II) species or the labile stannane 2.24.2.

![Scheme 2.24: Synthesis of coupling partners](image)

<table>
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<tr>
<th>Pd-cat.</th>
<th>Ligand</th>
<th>Additive</th>
<th>Solvent</th>
<th>Time</th>
<th>% yield of 2.24.2</th>
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<tr>
<td>( \text{Pd}(\text{PPh}_3)_4 )</td>
<td>THF</td>
<td>24 h</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{Pd}(\text{PPh}_3)_4 )</td>
<td>benzene</td>
<td>20 h</td>
<td>40</td>
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<td></td>
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<tr>
<td>( \text{Pd}(\text{PPh}_3)_4 )</td>
<td>toluene</td>
<td>18 h</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{Pd}(\text{PPh}_3)_4 )</td>
<td>dioxane</td>
<td>16 h</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{PdCl}_2(\text{PhCN})_2 )</td>
<td>PPh$_3$</td>
<td>toluene</td>
<td>24 h</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>( \text{Pd}_2(\text{dba})_2 \cdot \text{CHCl}_3 )</td>
<td>PPh$_3$</td>
<td>toluene</td>
<td>18 h</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>( \text{Pd}_2(\text{dba})_2 \cdot \text{CHCl}_3 )</td>
<td>( \text{PCy}_3 )</td>
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<td>50</td>
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<tr>
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<td>36 h</td>
<td>40</td>
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</tr>
<tr>
<td>( \text{Pd}_2(\text{dba})_2 \cdot \text{CHCl}_3 )</td>
<td>P(tBu)$_3$</td>
<td>toluene</td>
<td>18 h</td>
<td>30</td>
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<tr>
<td>( \text{Pd}_2(\text{dba})_2 \cdot \text{CHCl}_3 )</td>
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<td>( \text{LiCl} )</td>
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<td>10 h</td>
<td>65</td>
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<tr>
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<td>( \text{PCy}_3 )</td>
<td>( \text{LiCl} )</td>
<td>toluene</td>
<td>12 h</td>
<td>51</td>
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</table>

Regioisomeric aglycons 2.25.1 and 2.25.2 for gilvocarcin V analogs were synthesized by employing either the Stille or the Suzuki coupling (Scheme 2.25). Considering the yield of the cross coupling reactions, the Stille coupling protocol was preferred for the generation of the coupled products.
Scheme 2.25: Synthesis of gilvocarcin V aglycon

Cyclitol 2.11.6 was installed onto the regioisomeric aglycons to obtain the corresponding cyclitolized products 2.26.1 and 2.26.2 by means of a Mitsunobu reaction. As observed in the case of gilvocarcin M analogs, cyclitolization on 2.25.1 went smoothly at 0 °C but for aglycon 2.25.2, the reaction had to be performed at low temperature with excess DIAD and slow addition of minimal PPh₃ (Scheme 2.26).

Scheme 2.26: Mitsunobu cyclitolization
The cyclitol product 2.26.1 was subjected to reductive lactonization with Zn-dust/HOAc. After filtration and aqueous washing, the crude phenol was protected as a methyl ether 2.27.1. The benzyl protection was removed by hydrogenolysis to obtain phenol 2.27.2. The phenol 2.27.2 was then activated as a triflate 2.27.3 for the installation of vinyl group (Scheme 2.27).

Scheme 2.27: Approach toward gilvocarcin V analogs
2.15 Conclusion

In conclusion, our synthetic studies toward the gilvocarcins has led to the successful syntheses of several $O$-cyclitol analogs of gilvocarcin M. A synthetic route toward the more potent gilvocarcin V analogs has also been developed, which could be used in the future for the syntheses of regioisomeric analogs and for the installation of other cyclitol stereoisomers (Scheme 2.27, future directions). The successful synthesis of the advanced intermediate triflate 2.27.3 also added versatility to our synthetic route, as it would allow a late stage installation of alkynes or other conjugates on to the gilvocarcin aglycon for rapid syntheses of analogs for SAR type studies. The alkyne derivative would be interesting since it is known that the strong topoisomerase II inhibitory activity of gilvocarcin V arises due to the participation of the vinyl group in the formation of $[2+2]$ cycloadduct with DNA thymidine.\(^{40}\) The synthetic approach toward gilvocarcin V analogs has also led to the development of a highly regioselective ortho-bromination of methyl-1,4-dihydroxy benzoate derivatives. This regioselective bromination strategy should be applicable for the syntheses of other related natural products/analogs.
Chapter 3

Synthetic approach toward resin glycosides: merremoside C & D

3.1 Background

Resin glycosides are the constituents of morning glory species e.g., Ipomoea genus (Convolvulaceae family). Plants belonging to this family are known as rich sources of alkaloids and resin glycosides and are widely distributed from tropical to subtropical regions. Although chemical investigations on resin glycosides began as early as the middle of the 19th century, the complete structure elucidation of these glycolipids was possible only after the advent of modern spectroscopic techniques. Resin glycosides are amphiphilic glycosyl derivatives of monohydroxy and dihydroxy fatty acids composed of either 14 or 16 carbon linear chains. The sugar core (hydrophilic moiety) is made up of homo- or heteropolysaccharides, which connect to the hydrophobic aglycon (aliphatic sidechain). The sugar units found in these metabolites are usually the diastereomers of hexose (mainly D-glucose) and deoxy hexose (L-rhamnose, D-fucose and D-quinovose). The hydrophobic aglycon in most cases is found to be jalapinolic acid, 11-(S)-hydroxyhexadecanoic acid, which forms a macrolactone ring connecting two, three or more sugar units in the macrolactone backbone. Additional carboxylic acids may complement the peripheral acylation patterns on the sugar moieties. Thus, a sophisticated molecular array is formed, which exhibits a well-balanced hydrophilicity and hydrophobicity profile. Although most resin glycosides have been isolated from plants, several literature reports indicate that some related glycolipids have also been isolated from bacteria, fungi and yeasts. Some of the isolated glycolipids have a hydrophobic aglycon which is different from jalapinolic acid. The structures of different classes of resin glycosides are shown in Figure 3.1.
Several biological activities have been reported for convolvulaceous resins, including microbial toxicity, mammalian cytotoxicity, plant cytotoxicity etc. The crude methanol-soluble extracts from several Mexican *Ipomoea* species (commonly known as jalaps) have been traditionally used for purgative remedies. It has been also demonstrated that the biological activities exhibited by these complex oligosaccharides are due to the macrolactone moiety, since the glycosidic acid (seco acid) obtained from the saponification is devoid of any activity.\(^{59b}\) The merremoside-type resin glycosides were isolated by Kitagawa *et al.*\(^{59c}\) from the fresh tuber of *Merremia mammosa* (Lour.) Hall. f. (convolvulaceae), a plant traditionally used for the treatment of illnesses associated with the throat and respiratory systems.\(^{59c,d}\) These structurally complex
oligosaccharides consist of a macrolactone (20 or 21-membered) formed by the esterification of jalapinolic acid at the C-2’ or C-3’ hydroxyl of the α-1,4-linked tetramerhamnoside (Figure 3.1). Biological investigations showed that merremoside A-G, H₁ and H₂ display ionophoretic activities (i.e., they have the ability to transport Na⁺, K⁺ and Ca²⁺ across human erythrocyte membranes).⁶² Among the other members, merremoside B and D exhibit significant antiserotonic activity [ED₈₀ (mice): 10 μg/mL for B and 2 μg/mL for D].⁵⁹c

3.2 Previous synthetic approaches

No member of merremoside family of natural products has succumbed to total synthesis, although over the years there have been various strategies developed toward the total synthesis of resin glycosides. Reported synthetic studies revealed that the major challenges involved are the construction of the macrolide unit and the stereoselective glycosylation. Conventionally the macrolactone was constructed by intramolecular esterification between the aglycon carboxylic acid and sugar hydroxyl group under high dilution.⁶³,⁶⁴ This macrolactonization approach has been utilized in the total synthesis of tricolorin F and the macrolide subunits of merremoside-type resin glycosides (Scheme 3.1).⁶⁵,⁶⁶
Furstner et al. developed a ring-closing olefin metathesis approach for the construction of the macrolide unit, which was successfully used in the total synthesis of several resin glycoside natural products,\textsuperscript{67,68} and a formal synthesis of tricolorin A (Scheme 3.2).\textsuperscript{69}

Scheme 3.1: Intramolecular esterification approach

Scheme 3.2: Ring-closing metathesis approach, formal synthesis of tricolorin A
In contrast to the aforementioned approaches, Sakairi *et al.* reported the construction of oligosaccharide containing macrolide structures by intramolecular glycosylation.\textsuperscript{70} Using this concept, a formal synthesis of tricolorin A and total synthesis of tricolorin F were achieved (Scheme 3.3).

![Scheme 3.3: Intramolecular glycosylation approach](image)

### 3.3 Our synthetic approach

In addition to being synthetically challenging targets, the resin glycoside natural products were of synthetic interest to us due to the fact that no detailed structure activity relationship (SAR) has been carried out on these natural products despite their interesting biological activities. To probe these promising and diverse biological activities of resin glycosides, a synthesis driven mapping of their structure-activity relationships was planned. We decided to first target the merremoside family of resin glycosides for their promising biological activities\textsuperscript{59c} and simple oligosaccharide backbone (1,4-\(\alpha\)-linked-L-rhamnosides). Unlike traditional approaches, our *de novo* approach to carbohydrates allows us to fine-tune the systematic incorporation of the stereochemistry on a carbohydrate motif. Thus the desired analogs could be synthesized for a detailed SAR study.
3.4 Retrosynthetic analysis

In our proposed effort toward the synthesis of merremoside C/D, we envisioned maximizing our use of atomless protecting groups. In this synthesis, a double bond could be carried to an advanced intermediate 3.4.2, which then could be dihydroxylated employing Upjohn condition to obtain the desired syn-diol 3.4.1 (Scheme 3.4).

Scheme 3.4: De novo approach to merremosides

Tetrasaccharide 3.4.2 could be obtained by a Schmidt glycosylation using macrolactone disaccharide 3.2.9 and trichloroacetimidate 3.2.3. The macrolactone subunit could be obtained by following Yang’s reported macrolactonization of 3.4.8. The disaccharide units in both the
key fragments (3.4.3 and 3.4.9) could be obtained from achiral starting material acylfural 3.4.6 by employing our group’s de novo approach. The use of our group’s de novo approach toward merremoside is particularly intriguing because all of the 21 stereocenters in the final compound could be derived from achiral starting materials.

3.5 Synthesis of jalapinolic ester (hydrophobic side chain)\textsuperscript{71}

The synthesis of jalapinolic methyl ester started with the commercially available undecyne 3.5.1 and hexanal 3.5.2. Base promoted addition of alkyne 3.5.1 to the aldehyde 3.5.2 resulted in the formation of racemic alkynol, which was oxidized to alkynone 3.5.3 using Parikh Doering oxidation.\textsuperscript{72} The alkynone was then stereoselectively reduced by Noyori asymmetric hydrogenation (3.5.3 to 3.5.4).\textsuperscript{73} Using an alkyne-zipper reaction, the internal alkyne was converted to a terminal alkyne (3.5.4 to 3.2.5).\textsuperscript{74} The hydroxyl of alkynol 3.5.5 was subsequently protected as a TBS ether 3.5.6.

Scheme 3.5: Synthesis of jalapinolic ester
Oxidation of alkyne $\text{3.5.6}$ to the corresponding carboxylic acid by KMnO$_4$ followed by an acid catalyzed esterification, formed the methyl ester and removed the silyl ether to give jalapinolic ester ($\text{3.5.6}$ to $\text{3.5.7}$, Scheme 3.5).

### 3.6 Synthesis of saccharide units (*de novo* approach)

The synthesis of the carbohydrate portion was obtained by using our *de novo* approach.$^{75}$ The inexpensive, achiral acyl furan $\text{3.4.6}$ was reduced to the corresponding enantiomerically enriched alcohols by Noyori asymmetric hydrogenations ($\text{3.6.1}$ using Noyori $S,S$ and $\text{3.6.6}$ using Noyori $R,R$ catalysts). The furan alcohols were subjected to Achmatowicz oxidation, which upon subsequent rearranged formed pyranones $\text{3.6.3}$ and $\text{3.6.7}$. The anomeric alcohols of the rearranged products $\text{3.6.3}$ and $\text{3.6.7}$ were protected with $t$-butyl carbonate to form Boc-pyranones $\text{3.6.3}$, $\text{3.4.5}$ and $\text{3.6.8}$, $\text{3.6.9}$ respectively (Scheme 3.6). Thus, in three steps, we can access all of the building blocks required for the synthesis of a desired sugar motif (e.g., in the synthesis of merremoside D, the rhamnoside unit was obtained from $\alpha$-$L$-Boc-pyranone $\text{3.4.5}$). These building blocks could be stereoselectively glycosylated using very mild/functional group tolerant palladium-catalyzed glycosylation. The $t$-butyl carbonate at the anomeric position of the key intermediates ($\text{3.6.3}$, $\text{3.4.5}$, $\text{3.6.8}$ and $\text{3.6.9}$) served as a good leaving group allowing ionization to form the Pd-$\pi$-allyl complex $\text{3.6.10}$ with inversion of stereochemistry. Nucleophilic attack from the face opposite to the Pd-complex again inverts the stereochemistry, resulting in a net retention of stereochemistry at the anomeric position $\text{3.3.11}$ (Scheme 3.6). Post glycosylation transformations on the glycosylated product lead to the desired sugar moiety.
Scheme 3.6: Synthesis of sugar building blocks

Ruthenium (R,R) Noyori

(97% yield)

NBS, NaOAc, NaHCO₃

98% yield

Boc₂O, DMAP

82% yield

α-L

β-L

(α:β = 4:1)

3.4.5

3.6.3

3.6.6

NBS, NaOAc, NaHCO₃

98% yield

Boc₂O, DMAP

82% yield

α-D

β-D

(α:β = 4:1)

3.6.8

3.6.9

Stereoselective Pd-glycosylation

Boc₅O

3.4.5

Pd(0)

3.6.10

3.6.11

Scheme 3.6: Synthesis of sugar building blocks
3.7 Synthesis of the macrolactone disaccharide

The key building block required for the synthesis of the merremoside family of natural products was α-L-Boc-pyranone 3.4.5. Glycosylation of 3.4.5 using jalapinolic ester 3.5.7 as the nucleophile in presence of catalytic Pd(2dba)3•CHCl3/PPh3 formed glycosylated product 3.7.1 in high yield and complete stereoselectivity. Enone 3.7.1 was then reduced to allylic alcohol 3.7.2 by employing a Luche reduction (Scheme 3.7). 76

Scheme 3.7: Synthesis of macrolactone disaccharide
The alkene \(3.7.2\) was dihydroxylated using Upjohn conditions and the syn-diol was subsequently protected as acetonide \(3.7.4\). The C-4 hydroxy group of \(3.7.4\) served as the nucleophile for the next glycosylation with another unit of Boc-pyranone (\(3.7.4\) to \(3.7.5\)). The enone \(3.7.5\) was subjected to a Luche reduction and the allylic alcohol was subsequently protected as a benzyl ether \(3.7.7\). Dihydroxylation of the alkene \(3.7.7\), followed by saponification of the methyl ester gave the desired macrolactone precursor, diol-acid \(3.1.4\), (Scheme 3.7).

### 3.8 Macrolactonization

Macrolactonization of the diol acid \(3.1.4\) was carried out using the method reported by Yang et al. with an overall yield of 50% (combined for C-2 macrolactone \(3.1.2\) and C-3 macrolactone \(3.1.3\)). The yield of macrolactonization was improved to \(~66\%\) by slight modification of the reported protocol (slow addition of the thioester intermediate generated from diol-acid \(3.1.4\), to boiling toluene over a period of 4 days). Extensive NMR studies on the regioisomeric macrolactones revealed that the major product was a C-2 macrolactone \(3.1.2\), which was obtained in a 4.7:1 ratio with the minor C-3 macrolactone \(3.1.3\). This finding was opposite to the report by Yang et al. (i.e., \(3.1.2\): \(3.1.3\) = 1:5.3). Attempts to reverse the regioselective outcome in the macrolactonization using tin-oxide or boronate ester \(3.8.1\) failed. Macrolactonization under Steglich conditions\(^77\) and Yamaguchi conditions\(^63\) also failed (Scheme 3.8). The results of the macrolactonization were disappointing since we found that our desired product was the minor isomer \(3.1.2\). At that point, we decided to use the major isomer \(3.1.2\) for the synthesis of a tetrasccharide analog of the natural compound merremoside D. This analog synthesis would be an ideal model system to establish the synthetic route, which would be applicable for the synthesis of natural compound, merremoside D.
Separation of the regioisomeric macrolactones 3.1.2 and 3.1.3 was difficult because of their similar polarity. Conversion of the mixture to the corresponding chloroacetic esters, followed by debenzylation, led to easily separable products 3.9.1 and 3.9.2. Thus the desired glycosyl acceptors 3.9.1 and 3.9.2 were obtained (Scheme 3.9).
3.9 Synthetic approach to di-rhamnose disaccharide

We envisioned the synthesis of 1,4-linked disaccharide 3.10.1 through our de novo approach. We proposed to obtain the desired C-3 esterification by employing the tin-mediated regioselective esterification (3.10.4 to 3.10.3). The glycosyl acceptor 3.7.2 could be obtained by orthogonal protection of the C-2 hydroxyl of 3.10.3 followed by desilylation. A Pd-catalyzed glycosylation and subsequent post glycosylation transformations (enone reduction/esterification) would generate the desired disaccharide (3.10.2 to 3.10.1, Scheme 3.10).
Scheme 3.10: Approach to di-rhamnoside

The desired syn-diol 3.10.4 was synthesized from the key building block 3.4.5 in four steps: Pd-catalyzed glycosylation, Luche reduction, TBS-protection and Upjohn dihydroxylation. Regioselective esterification of 3.4.5 at the C-3 hydroxyl was carried out using Bu$_2$SnO and boronate ester 3.8.1. Unfortunately, preferential esterification of the C-2 hydroxyl was observed (3.10.3: 3.11.3 = 1:10). Esterification with DCC/DMAP yielded exclusively the C-2 ester 3.11.3 in good yield (Scheme 3.11). The regioselective outcome was probably due to the steric effect of the bulky TBS-group at C-4. Although the expected regioselectivity was not obtained, this study showed an efficient method of regioselective esterification at the C-2 hydroxyl.
Scheme 3.11: Attempted regioselective esterification

### 3.10 Synthesis of the di-rhamnose disaccharide

In order to achieve a regioselective C-3 esterification, the bulky TBS-protection at the C-4 hydroxyls had to be replaced with a less sterically hindered group. A second pyranone unit was chosen to serve this purpose. In addition to being less sterically hindered, it removed the need for a protecting group. PMB-glycosylated pyranone 3.11.1 was reduced stereoselectively and subsequently dihydroxylated to form triol 3.12.2. The syn-diol was then protected as acetonide 3.12.3. The glycosyl acceptor 3.12.3 was treated with donor 3.4.5 using our Pd-catalyzed glycosylation conditions to form the disaccharide 3.12.4. Removal of the acetonide protection (3.12.4 to 3.12.5) was achieved in good yield using aqueous TFA in CH₂Cl₂ at low temperature. Other deprotection conditions (e.g., HCl(aq), HOAc(aq)) resulted in decomposition of starting materials or cleavage of the glycosidic bond. As expected, when diol 3.12.5 was subjected to regioselective glycosylation using Bu₂SnO, 78 C-3 esterified product 3.12.6 was obtained in 81% yield (Scheme 3.12).
After a successful regioselective esterification, the C-2 hydroxyl group of \( \text{3.12.6} \) was protected as a chloroacetic ester \( \text{3.13.1} \). This orthogonal protecting group would also function as a C-2 anomeric directing group for \( \alpha \)-selectivity in the glycosylation of the macrolactone \( \text{3.9.1} \) (Scheme 3.9) with disaccharide \( \text{3.13.4} \) (Scheme 3.13). The enone \( \text{3.13.1} \) was reduced with NaBH\(_4\) and was subsequently esterified with isobutyryl chloride to form \( \text{3.13.2} \). The PMB-ether of \( \text{3.13.2} \) was oxidatively cleaved with DDQ to form anomeric alcohol \( \text{3.13.3} \), which was then activated as trichloroacetimidate \( \text{3.13.4} \) upon treating with trichloroacetonitrile and catalytic NaH (Scheme 3.13).
3.11 Attempted glycosylations

After the successful syntheses of the glycosyl donor 3.13.4 and glycosyl acceptor 3.9.1, their coupling was performed using Schmidt’s glycosylation conditions. Unfortunately, no glycosylated product was observed even after screening several Lewis acids [BF₃•OEt, TMSOTf, Sc(OTf)₃] and by changing the reaction temperature (−78 °C to rt). To investigate the compatibility of glycosyl donor 3.13.4 in Schmidt glycosylation conditions, a model reaction was studied using a much simpler glycosyl acceptor 3.14.1 (Scheme 3.14). Careful analysis of the model reaction revealed that the acceptor 3.14.1 remained unreacted under the glycosylation conditions, whereas the glycosyl donor 3.13.4 completely decomposed. It was surmised that the allylic glycosidic bond on the glycosyl donor 3.13.4 was probably not compatible with the acidic conditions due to the possible formation of a stable allylic cation resulting in the decomposition of 3.14.4.
3.12 Revised synthesis of glycosyl donor

To overcome the potential problem caused by the generation of a stable allylic cation during Schmidt glycosylation, we undertook the synthesis of a new glycosyl donor 3.16.7, in which the double bonds were dihydroxylated and protected. Boc-pyranone 3.4.5 was glycosylated with benzyl alcohol and subsequently reduced to form allylic alcohol 3.15.1. The alkene of the allylic alcohol 3.15.1 was stereoselectively dihydroxylated and the syn-diol was protected as acetonide (3.15.1 to 3.14.1). The C-4 hydroxyl of 3.14.1 served as a nucleophile for the next glycosylation with Boc-pyranone 3.4.5, forming disaccharide 3.15.2. Aqueous TFA was used for the deprotection of the acetonide 3.15.2 to give diol 3.15.3. Regioselective esterification using dibutyltinoxide (Bu₂SnO) provided C-3 ester 3.15.4 (Scheme 3.15).
The C-2 hydroxyl of 3.15.4 was protected as a chloroacetic ester 3.16.1. A 1,2-reduction of enone 3.16.1 with NaBH₄/CeCl₃•MeOH gave allylic alcohol 3.16.2, which was subsequently esterified as isobutyric ester 3.16.3. Stereoselective dihydroxylation of the double bond in 3.16.3 and acetonide protection of the resulting syn-diol gave fully functionalized disaccharide 3.16.5. Reductive removal of the benzyl group gave anomeric alcohol 3.16.6 in high yield. Finally, the disaccharide was activated as trichloroacetimidate 3.16.7 by treating with trichloroacetonitrile in CH₂Cl₂ using catalytic sodium hydride (NaH) at 0 °C (Scheme 3.16).
Scheme 3.16: Synthesis of new glycosyl donor

3.13 Synthesis of tetrasaccharide (merremoside D analog)

Toward the synthesis of the tetrasaccharide, we designed a model reaction system to optimize the glycosylation conditions. The new glycosyl donor 3.16.7 was subjected to glycosylation conditions with our model glycosyl acceptor 3.14.1. The effects of temperature, solvent and Lewis acid were evaluated in this model reaction (Scheme 3.17). Of all solvents screened, CH₂Cl₂ performed the best and TMSOTf was found to be the reagent of choice. Glycosylation proceeded smoothly at −78 °C to 0 °C with complete α-selectivity forming product 3.14.1 (Scheme 3.17).
Neither ortho-ester formation nor β-glycosylated products were observed during glycosylation. These findings emphasize the possible role of the chloroacetic ester at the C-2 position in neighboring group participation leading to exclusive α-glycosylation (Scheme 3.18).

After optimization of the glycosylation conditions on the model system, the macrolactone disaccharide 3.6.1 was glycosylated with 3.16.7 using 12% TMSOTf in dry CH₂Cl₂. The desired glycosylated product 3.19.1 was obtained in 65% yield. The byproduct
trichloroacetamide was removed by trituration from hexane followed by silica gel chromatography. The tetrasaccharide 3.19.1 was then subjected to bis-dechloroacylation using thiourea, which cleanly produced the tetrasaccharide diol 3.19.2. Finally, bis-acetonide deprotection of 3.19.2 was achieved using aqueous TFA in CH₂Cl₂ at 0 °C to obtain the desired merremoside D analog 3.19.3 (Scheme 3.19).

Scheme 3.19: Synthesis of merremoside D analog

After the synthesis of the tetrasaccharide analog 3.19.3, we turned our attention toward the synthesis of the natural compound merremoside D. We investigated isomerization of the C-2 macrolactone 3.1.2. Using 1 eq. of DBU, 3.1.2 was isomerized to a mixture of C-2 macrolactone 3.1.2 and C-3 macrolactone 3.1.3 in a 2:1 ratio (Scheme 3.20).
3.14 Total synthesis of merremoside D

Next, the desired glycosyl acceptor 3.9.2 was glycosylated with glycosyl donor 3.16.7 to obtain the tetrasaccharide 3.21.1. The bis-acetonide protection was cleaved using aqueous TFA to obtain tetrol 3.21.2. Finally, the bis-chloroacetate was removed using thiourea to obtain the natural compound merremoside D (Scheme 3.21).

Scheme 3.20: Macrolactone isomerization

Scheme 3.21: Total synthesis of merremoside D
3.15 Conclusion

In conclusion, the total synthesis of merremoside D was achieved in 22 steps, longest linear sequence with 2.57% overall yield. A tetrasaccharide analog of merremoside D was also synthesized from the regioisomeric macrolactone 3.1.2 (3.04% overall yield, 22 longest linear steps). Although initially we proposed to use a double bond as an atomless protecting group, its incompatibility in acid catalyzed glycosylation required us to prefunctionalize the alkene. Dihydroxylation of the alkene followed by acetonide protection of the diol in the donor precluded the possibility for the formation of a stable allylic cation. Thus, the glycosylation occurred smoothly. Studies on regioselective esterification showed that the regioselective esterification at the C-2 or C-3 hydroxyl group was largely affected by the nature of the protecting group at C-4 hydroxyl in a rhamnoside. A sterically hindered group like TBS possibly blocked the C-3 hydroxyl, directing esterification at the C-2 hydroxyl even if tin or boronate chemistry was used. Successful synthesis of the merremoside D and its analog led to an optimal route, which could be used to synthesize other members of resin glycosides and their analogs for SAR type studies.
Chapter 4

Experimental section

4.1 General methods and materials

$^1$H and $^{13}$C spectra were recorded on 400 MHz, 500 MHz and 600 Mz spectrometers. Chemical shifts were reported according to NMR solvent data chart (Cambridge Isotope Laboratories, Inc.). Optical rotations were measured at room temperature ($[^\alpha]_D^{25}$) using JASCO P2000 digital polarimeter in the solvent specified. Infrared (IR) spectra were obtained on a Nicolet iS5 FT-IR spectrometer. Melting points (mp) were recorded on Mel-Temp 3.0. Flash column chromatography was performed on 60-200 mesh silica gel. To determine retardation values ($R_f$), analytical thin-layer chromatography was performed with the specified solvent on precoated glass-backed plates and visualized by quenching of fluorescence and by charring after treatment with p-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. Ether, THF, methylene chloride, toluene and triethylamine were dried by passing through activated alumina column with argon gas pressure using solvent purification system. Commercial reagents were used without purification unless otherwise noted. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven/flamed-dried glassware and standard syringe/septum techniques.

For the known compounds which were prepared by modification of reported procedure, experimental procedure and spectroscopic data ($^1$H and $^{13}$C NMR) are reported. All new compounds were fully characterized and their analytical data ($^1$H, $^{13}$C, IR, HRMS, mp, $[^\alpha]_D^{25}$ and $R_f$) are provided.
4.2 Experimental for chapter 1

**Ethyl 3-acetyl-4-hydroxy-5-oxo-2-(2-oxopropyl)-2,5-dihydrofuran-2-carboxylate 1.8.2.**  

To a sample of ethyl acetopyruvate 1.8.1 49.5 g (0.313 mol) in a 500 mL flask, was added a solution of 25.7 g NaOAc (0.312 mol) in 54 mL HOAc and 71 mL H₂O at 0 °C. The bath was removed after addition was complete, and the mixture was stirred at rt 24 h. Then it was poured into a mixture of 165 g ice and 26 mL concentrated H₂SO₄. Gentle shaking of the mixture resulted in formation of precipitate. Then it was cooled down at 0 °C for 15 min. The mixture was filtered under vacuum and the solid was washed with ice-cold water (100 mL X 3). The crude product was directly used for next step except that small amount of solid was dried and used for NMR analysis. White solid: ¹H NMR (CDCl₃, 270 MHz): δ 4.54 (brs, 1H), 4.21 (q, J = 6.9 Hz, 2H), 3.66 (d, J = 17.8 Hz, 1H), 3.29 (d, J = 17.8 Hz, 1H), 2.50 (s, 1H), 2.15 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 67.5 MHz): δ 203.7, 194.0, 167.7, 166.8, 149.5, 123.5, 82.9, 63.1, 44.1, 31.1, 30.0, 13.8.

**Methyl 3-hydroxy-5-methylbenzoate 1.8.3.**

The crude product 1.8.2 from previous reaction was suspended in 500 mL H₂O and 45 g (0.77 mol) Mg(OH)₂ was slowly added at rt while stirring. The mixture was then stirred at reflux for
1.5 h. The hot solution was filtered under reduced pressure and the precipitate was rinsed with warm water. The mother liquor was concentrated under reduced pressure to remove the water to afforded crude solid product, which was then suspended in 270 mL methanol at RT. 13 mL concentrated H₂SO₄ was added into the mixture while stirring. After addition, the mixture was heated up and stirred under reflux for 12 h. Then it was cooled down to 0 ºC and slowly 400 mL saturated aqueous NaHCO₃ was added followed by addition of another 20 g solid NaHCO₃. The mixture was extracted with EtOAc (400 mL X 3). The organic layer was washed with saturated brine and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (8:1,v/v) afforded methyl ester 1.8.3, 14.5 g (56% over three steps) as white solid: ¹H NMR (CDCl₃, 270 MHz): δ 7.41 (s, 2H), 6.9 (s, 1H), 6.20 (brs, 1H), 3.90 (s, 3H), 2.33 (s, 3H); ¹³C NMR (CDCl₃, 67.5 MHz): δ167.7, 155.8, 140.0, 130.9, 122.6, 121.1, 113.5, 52.4, 21.2.

**Methyl 3-(tert-butyldimethylsilyloxy)-5-methylbenzoate 1.8.3a**

![Methyl 3-(tert-butyldimethylsilyloxy)-5-methylbenzoate](image)

To a solution of 4 g (24.1 mmol) methyl ester 1.8.3 in 24 ml CH₂Cl₂, was added 2.46 g (36.2 mmol) imidazole at 0 ºC followed by addition of 3.99 g (26.5 mmol) TBSCl. The ice bath was removed and the mixture was then stirred at rt for 2 h. It was diluted with 150 mL hexane-EtOAc (2:1, v/v) and cooled down to 0 ºC, and then 70 mL H₂O was added. The aqueous layer was extracted with hexane-EtOAc (2:1, v/v) (100 mL X 2). The pooled organic layer was subsequently washed with saturated aqueous NaHCO₃, saturated brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was subjected to silica gel flash
column chromatography. Elution with hexane-EtOAc (50:1, v/v) afforded TBS ether 1.8.3a, 6.7 g (100%) as clear oil: $R_f$ (hexanes/EtOAc, 3.5:1 v/v) = 0.62; IR (thin film, cm$^{-1}$) $\nu$ 2954, 2931, 2898, 2859, 1724, 1594, 1454, 1435, 1322, 1252, 1226, 1160, 1105, 1035, 982; $^1$H NMR (CDCl$_3$, 270 MHz): $\delta$ 7.46 (s, 1H), 7.29 (s, 1H), 6.85 (s, 1H), 3.89 (s, 3H), 2.33 (s, 3H), 0.99 (s, 9H), 0.20 (s, 6H); $^{13}$C NMR (CDCl$_3$, 67.5 MHz): $\delta$ 167.1, 155.5, 139.5, 131.1, 125.5, 123.3, 118.0, 52.0, 25.6, 21.2, 18.1, −4.5; HRMS (ESI): Cacl. for [C$_{15}$H$_{24}$O$_3$Si + H]$^+$: 281.1568, Found: 281.1569.

(3-(tert-butyldimethylsilyloxy)-5-methylphenyl)methanol 1.8.4

To a solution of 6.7 g (24.1 mmol) ester 1.8.3a in 48 mL THF, was slowly added 1.83 g (48.2 mmol) LiAlH$_4$ in several portions at 0 ºC. After addition, the ice bath was removed and the mixture was then stirred at rt for 3 h. It was cooled down to 0 ºC and diluted with 400 mL Et$_2$O, then carefully 3.6 mL 2 M NaOH was added dropwise, followed by the addition of 5.4 mL H$_2$O. The mixture was stirred at 0 ºC for 15 min, and then the precipitate was rinsed with ether. The mother liquor was subsequently washed with saturated aqueous NaHCO$_3$, saturated brine and dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the residue was subjected to silica gel flash column chromatography. Elution with hexane-EtOAc (10:1, v/v) afforded benzyl alcohol 1.8.4, 5.4 g (89%) as clear oil: $R_f$ (hexanes/EtOAc, 3:1 v/v) = 0.40; IR (thin film, cm$^{-1}$) $\nu$ 3306 (broad), 2956, 2930, 2886, 2859, 1595, 1462, 1315, 1253, 1161, 1042, 1019, 947; $^1$H NMR (CDCl$_3$, 270 MHz): $\delta$ 6.77 (s, 1H), 6.65 (s, 1H), 6.59 (s, 1H), 4.59 (s, 2H), 2.30 (s, 3H), 1.72 (s, 1H), 0.99 (s, 9H), 0.20 (s, 6H); $^{13}$C NMR (CDCl$_3$, 67.5 MHz): $\delta$ 155.7,
142.1, 139.6, 120.6, 120.0, 115.5, 65.2, 25.6, 21.4, 18.1, −4.4; HRMS (ESI): Caclcd. for 
\[C_{14}H_{24}O_2Si + H\]^+: 253.1618, Found: 253.1620.

3-(tert-butyldimethylsilyloxy)-5-methylbenzaldehyde 1.8.5\textsuperscript{29}

\[
\begin{align*}
\text{H}_3\text{C} & \text{-} \\
\text{OTBS} & \text{-} \\
\text{CHO} & 
\end{align*}
\]

To a solution of 5.4 g (21.4 mmol) benzyl alcohol 1.8.4 in 33 mL hexane, was added 18.6 g 
(214 mmol) activated MnO\textsubscript{2} at rt. It was stirred at rt for 10 h. The mixture was filtered and the 
precipitate was rinsed with ether. After removal of the solvent under reduced pressure, the 
residue was subjected to silica gel flash column chromatography. Elution with hexane-EtOAc 
(25:1, v/v) afforded aldehyde 1.8.5, 4.5 g (84%) as clear oil: 

$R_f$ (hexanes/EtOAc, 3:1 v/v) = 0.62; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 270 MHz): \textit{δ} 9.90 (s, 1H), 7.29 (s, 1H), 7.12 (s, 1H), 6.92 (s, 1H), 2.37 
(s, 3H), 0.99 (s, 9H), 0.21 (s, 6H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 67.5 MHz): \textit{δ} 192.4, 156.2, 140.4, 137.7, 

3-hydroxy-5-methylbenzaldehyde 1.8.6\textsuperscript{30}

\[
\begin{align*}
\text{H}_3\text{C} & \text{-} \\
\text{OH} & \text{-} \\
\text{CHO} & 
\end{align*}
\]

To a solution of 3.94 g (15.8 mmol) TBS ether 1.8.5 in 20 mL MeOH, was added 898 mg (4.73 
mmol) solid \textit{p}-TsOH•H\textsubscript{2}O while stirring at rt. The mixture was stirred at rt for 24 h. Then it was 
diluted with 200 mL EtOAc and cooled down to 0 ºC. To this solution, 20 mL saturated aqueous 
NaHCO\textsubscript{3} was slowly added. The mixture was stirred at 0 ºC for 10 min. After separation of the 
two phases, the aqueous layer was extracted with EtOAc and the combined organic layer was
washed with saturated brine and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (5:1,v/v) afforded phenol 1.8.6 2.0 g (93%) as white solid: \( R_f \) (hexanes/EtOAc, 2:1 v/v) = 0.42; \(^1\)H NMR (CDCl₃, 270 MHz): \( \delta \) 9.90 (s, 1H), 7.26 (s, 1H), 7.19 (s, 1H), 6.98 (s, 1H), 2.38 (s, 3H); \(^{13}\)C NMR (CDCl₃, 67.5 MHz): \( \delta \) 192.9, 156.4, 140.8, 137.6, 124.2, 122.8, 112.2, 21.1.

3-(1,3-dioxan-2-yl)-5-methylphenol 1.8.7

A solution of 1.77 g (13.0 mmol) benzaldehyde 1.8.6 in 70 mL benzene was placed in a 100 mL flask, which was equipped with a distillation assembly. To this solution solution was added 1.88 mL (26.0 mmol) 1,3-propanediol and 123 mg (0.65 mmol) solid \( p \)-TsOH•H₂O. The mixture was then gradually heated up under Ar. The distillation was allowed to proceed until all starting material was consumed. Then it was cooled down to 0 °C and diluted with Et₂O 130 mL. 50 mL saturated aqueous NaHCO₃ was added to the mixture. The aqueous layer was extracted with Et₂O and the pooled organic layer was washed with saturated brine and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (5:1,v/v) afforded acetal 1.8.7 2.11 g, (84%) as white solid: \( R_f \) (hexanes/EtOAc, 2:1 v/v) = 0.31; \(^1\)H NMR (CDCl₃, 270 MHz): \( \delta \) 6.86 (s, 1H), 6.75 (s, 1H), 6.59 (s, 1H), 6.06 (brs, 1H), 5.42 (s, 1H), 4.25 (dd, \( J = 11.6, 4.9 \) Hz, 2H), 3.96 (ddd, \( J = 12.2, 10.2, 2.0 \) Hz, 2H), 2.23 (s, 3H), 2.17 (m, 1H), 1.43 (d, 13.6 Hz, 1H); \(^{13}\)C NMR (CDCl₃, 67.5 MHz): \( \delta \) 155.6, 139.7, 139.3, 118.7, 116.7, 110.3, 101.6, 67.3, 25.5, 21.2.
2-(3-(methoxymethoxy)-5-methylphenyl)-1,3-dioxane 1.8.8\textsuperscript{30}

To a solution of 172 mg (0.89 mmol) phenol 1.8.7 in 1.5 mL CH\(_2\)Cl\(_2\) at 0 °C, was added 0.55 mL (3.33 mmol) DIPEA, followed by addition of 150 µL (1.98 mmol) MOMCl. It was stirred at rt for 8 h. The mixture was cooled down to 0 °C and diluted with hexane-Et\(_2\)O (1:1, v/v) 50 mL. Then 10 mL water was added and it was then stirred at 0 °C for 20 min. The aqueous layer was extracted with hexane-Et\(_2\)O (1:1, v/v) and the pooled organic layer was subsequently washed with saturated aqueous NaHCO\(_3\), saturated brine and dried over Na\(_2\)SO\(_4\). After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (6:1, v/v) afforded MOM ether 1.8.8 150 mg (68\%) and elution with hexane-EtOAc (3:1, v/v) recovered 42 mg starting material (20\%). White solid; \(R_f\) (hexanes/EtOAc, 2:1 v/v) = 0.49; \(^1\)H NMR (CDCl\(_3\), 600 MHz): \(\delta\) 6.93 (s, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 5.45 (s, 1H), 5.14 (s, 2H), 4.19 (dddd, \(J = 10.2, 4.8, 1.2, 1.2\) Hz, 2H); 4.00 (ddddd, \(J = 12.0, 10.2, 2.4, 1.2\) Hz, 2H), 3.43 (s, 3H), 2.30 (s, 3H), 2.13 (dtt, \(J = 13.8, 12.6, 5.4\) Hz, 1H), 1.46 (dtt, \(J = 13.8, 2.4, 1.2\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz): \(\delta\) 158.7, 141.7, 140.5, 121.7, 118.5, 112.4, 102.9, 95.7, 68.5, 56.3, 27.1, 21.6.
2-(3-(benzylloxymethoxy)-5-methylphenyl)-1,3-dioxane 1.8.9

To a solution of phenol 1.8.7 (884 mg, 4.56 mmol) and diisopropylethylamine (DIPEA) (3.7 mL, 22.8 mmol) in CH2Cl2 (9 mL) at 0 °C, was added dropwise benzylloxymethyl chloride (BOMCl) (1.26 mL, 9.11 mmol). It was stirred at rt for 12 h. The mixture was cooled down to 0 °C, and diluted with Et2O. Then water was added and the mixture was stirred at 0 °C for 30 min. After separation of the two phases, aqueous layer was extracted with Et2O twice. The combined organic layer was subsequently washed with saturated aqueous NaHCO3, saturated brine and dried over Na2SO4. After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography. Elution with hexane-EtOAc (5:1, v/v) afforded BOM ether 1.8.9 (958 mg, 70%) and elution with hexane-EtOAc (2:1, v/v) recovered starting material (250 mg, 28%). Colorless oil; Rf (hexanes/EtOAc, 2:1 v/v) = 0.48; IR (thin film, cm⁻¹) ν 3072, 3037, 2960, 2929, 2853, 1617, 1599, 1456, 1376, 1291, 1236, 1164, 1146, 1104, 1043, 992; ¹H NMR (CD3OD, 600 MHz): δ 7.33-7.24 (m, 5H), 6.98 (brs, 1H), 6.92 (brs, 1H), 6.86 (brs, 1H), 5.45 (s, 1H), 5.26 (s, 2H), 4.68 (s, 2H), 4.19 (ddddd, J = 10.8, 5.4, 1.8, 1.2 Hz, 2H); 3.99 (ddddd, J = 12.0, 10.2, 2.4, 1.2 Hz, 2H), 2.30 (s, 3H), 2.13 (dtt, J = 13.8, 12.6, 5.4 Hz, 1H), 1.46 (dtt, J = 13.8, 2.4, 1.2 Hz, 1H); ¹³C NMR (CD3OD, 150 MHz): δ 158.7, 141.7, 140.5, 139.1, 129.5, 129.2, 128.9, 121.8, 118.6, 112.5, 102.9, 93.6, 71.1, 68.5, 27.1, 21.7. HRMS (ESI): calcd for [C19H22O4+H]+ 315.1591, found 315.1592.
(2-(1,3-dioxan-2-yl)-6-(methoxymethoxy)-4-methylphenyl)-tributylstannane

1.8.10

To a solution of 1.82 g (7.65 mmol) MOM ether 1.8.8 in 23 mL hexane at 0 °C, was added 4.9 mL 2.34 M (11.5 mmol) n-BuLi. The mixture was stirred at 0 °C for 1 h. Then 3.3 mL Bu₃SnCl was slowly added into the reaction mixture at 0 °C. It was stirred at 0 °C for another 1 h and subsequently diluted with hexane-Et₂O (1:1, v/v) 200 mL. To this dilute solution 60 mL saturated aqueous NaHCO₃ was added and stirred at 0 °C for 1 h. The organic layer was separated and the aqueous layer was extracted with hexane-Et₂O (1:1, v/v). The pooled organic layer was subsequently washed with saturated brine and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (25:1,v/v) afforded phenylstannane 1.8.10 1.94 g (49%). Elution with hexane-EtOAc (5:1,v/v) recovered 650 mg starting material (36%). Clear oil; \( R_f \) (hexanes/EtOAc, 2:1 v/v) = 0.78; \(^1\)H NMR (benzene-\( d_6 \), 600 MHz): \( \delta \) 7.68 (s, 1H), 7.06 (s, 1H), 5.55 (s, 1H), 4.93 (s, 2H), 3.96 (dd, \( J = 12.0, 5.4 \) Hz, 2H), 3.69 (ddd, \( J = 12.6, 12.0, 2.4 \) Hz, 2H), 3.24 (s, 3H), 2.14 (s, 3H), 1.94 (dtt, \( J = 12.6, 12.6, 4.8 \) Hz, 1H); 1.74 (m, 6H); 1.48 (m, 6H); 1.29 (m, 6H), 0.98 (t, \( J = 7.2 \) Hz, 9H); 0.75 (d, \( J = 13.2 \) Hz, 1H); \(^{13}\)C NMR (benzene-\( d_6 \), 150 MHz): \( \delta \) 162.9, 148.1, 140.4, 125.9, 122.6, 114.4, 103.0, 95.2, 67.5, 56.0, 30.1, 28.3, 26.4, 21.9, 14.4, 13.0.
(2-(benzyloxymethoxy)-6-(1,3-dioxan-2-yl)-4-methylphenyl)tributylstannane

1.8.11

![Chemical Structure Image]

To a solution of BOM ether 1.8.9 (2.77 g, 9.23 mmol) in hexane (37 mL) at 0 ºC, was added dropwise a solution of n-BuLi in hexane (2.38 M, 5.82 mL, 13.85 mmol). The mixture was stirred at 0 ºC for 1 h. Then Bu$_3$SnCl (3.76 mL, 13.85 mmol) was slowly added into the reaction mixture at 0 ºC. The mixture was stirred at 0 ºC for another 1 h. It was then diluted Et$_2$O (70 mL) followed by addition of saturated aqueous NaHCO$_3$ (60 mL). The mixture was stirred at 0 ºC for 45 min. The aqueous layer was extracted with Et$_2$O twice. The combined organic layer was washed with saturated brine, and dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography. Elution with hexane-EtOAc-Et$_3$N (100:1:1, v/v/v) afforded phenylstannane 1.8.11 (2.91 g, 54%). Elution with hexane-EtOAc (5:1, v/v) recovered starting material (780 mg, 28%). Colorless oil; $R_f$ (hexanes/EtOAc, 4:1 v/v) = 0.58; IR (thin film, cm$^{-1}$) $\nu$ 3076, 3037, 2954, 2920, 2850, 1603, 1569, 1456, 1372, 1283, 1270, 1237, 1169, 1148, 1113, 1048, 1002, 932; $^1$H NMR (CD$_3$OD + two drops of CD$_3$CN, 600 MHz): $\delta$ 7.35-7.25 (m, 5H), 7.18 (s, J(Sn-H) = 5.4 Hz, 1H), 6.99 (s, J(Sn-H) = 6.6 Hz, 1H), 5.39 (s, J(Sn-H) = 2.4 Hz, 1H), 5.25 (s, 2H), 4.70 (s, 2H), 4.18 (dddd, J = 11.4, 4.8, 1.2, 1.2 Hz, 2H), 3.96 (dddd, J = 12.0, 12.0, 2.4, 1.2 Hz, 2H), 2.32 (s, 3H), 2.15 (dtt, J = 13.8, 12.6, 4.8 Hz, 1H); 1.54 (m, 6H); 1.46 (dddd, J = 13.8, 2.4, 1.2, 1.2 Hz, 1H), 1.34 (m, 6H); 1.11 (m, 6H), 0.88 (t, J = 7.2 Hz, 9H); $^{13}$C NMR (CD$_3$OD + two drops of CD$_3$CN, 150 MHz): $\delta$ 163.4, 148.2, 141.2, 138.9, 129.6, 129.1, 129.0, 126.8, 122.3 ($^3$J$_{Sn}^{13}$C = 16.5 Hz), 114.8
\(^{3}J_{\text{Sn}-^{13}C} = 10.4 \text{ Hz}), 103.9 \left( ^{3}J_{\text{Sn}-^{13}C} = 11.6 \text{ Hz} \right), 93.6, 71.2, 68.5, 30.5 \left( ^{2}J_{\text{Sn}-^{13}C} = 9.8 \text{ Hz} \right), 28.6 \left( ^{2}J_{\text{Sn}-^{13}C} = 30.6 \text{ Hz} \right), 27.0, 21.8, 14.2, 13.3 \left( ^{1}J_{\text{Sn}-^{13}C} = 176.0 \text{ Hz} \right), 11.8 \left( ^{1}J_{\text{Sn}-^{13}C} = 168.3 \text{ Hz} \right);

HRMS (ESI): calcd for [C\text{\textsubscript{31}}H\text{\textsubscript{48}}O\text{\textsubscript{4}}Sn + H]^+ 605.2647, found 605.2647.

**Naphthalene-1,5-diyl diacetate 1.9.2\textsuperscript{31}**

\[
\begin{align*}
\text{OAc} & \\
\text{OAc} & \\
\end{align*}
\]

To a solution of 5 g (31.2 mmol) naphthalenediol 1.9.1 in 40 mL pyridine at 0 °C, was slowly added 8.9 mL (125 mmol) AcCl dropwise. It was stirred at rt for 10 min, then it was poured into a 500 mL water when stirring. The solid was collected by filtration and subsequently washed several times with water. After being dried by using vacuum, 7.4 g (97%) diacetate 1.9.2 was afforded as brown solid: \(R_f\) (hexanes/EtOAc, 1:1 v/v) = 0.55; \(^{1}\text{H NMR (CDCl}_3, 270 \text{ MHz)}: \delta 7.80 (d, \(J = 8.4 \text{ Hz}, 2 \text{ H})\), 7.52 (dd, \(J = 8.2, 7.7 \text{ Hz}, 2\text{H})\), 7.31 (d, \(J = 7.4 \text{ Hz}, 2\text{H})\), 2.46 (s, 6H); \(^{13}\text{C NMR (CDCl}_3, 67.5 \text{ MHz)}: \delta 169.2, 146.6, 128.0, 126.0, 119.2, 118.7, 20.9.\)

**6-bromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate 1.9.4\textsuperscript{31}**

\[
\begin{align*}
\text{Br} & \\
\text{OAc} & \\
\text{OAc} & \\
\end{align*}
\]

2.44 g (10.0 mmol) diacetate 1.9.2 was suspended in 100 mL HOAc at 50-60 °C, a solution of 7.12 g (40 mmol) NBS in 100 mL HOAc and 200 mL H\textsubscript{2}O was added into the mixture dropwise over 1 h. After addition, the reaction mixture was stirred at 60 °C for 2 h. It was cooled down to rt. The yellow precipitate that formed was filtered and washed with water. After drying, 1.9 g 2-
bromojuglone acetate **1.9.4** was obtained (66%). Yellow crystal: $R_f$ (hexanes/EtOAc, 2:1 v/v) = 0.46; $^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ 8.14 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.77 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.42 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.39 (s, 1H), 2.44 (s, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ 180.9, 177.4, 169.2, 149.9, 141.4, 138.5, 134.9, 132.6, 130.3, 126.3, 123.1, 21.0.

**2-bromo-5-hydroxynaphthalene-1,4-dione 1.9.5**$^{31}$

![Naphthalene Dione](image)

To a solution of 765 mg (2.59 mmol) acetate **1.9.4** in 26 mL 95% ethanol, was added 8.5 mL 1.5 M aqueous H$_2$SO$_4$. The solution was stirred under reflux conditions for 3 h. It was then cooled down to rt and diluted with 100 mL EtOAc and washed with 150 mL water twice. The organic layer was subsequently washed with saturated aqueous NaHCO$_3$, saturated brine and then dried over Na$_2$SO$_4$. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (15:1,v/v) afforded 2-bromojuglone **1.9.5**, 459 mg (70%). Orange solid: $R_f$ (hexanes/EtOAc, 2:1 v/v) = 0.51; $^1$H NMR (CDCl$_3$, 270 MHz): $\delta$ 11.75 (s, 1H), 7.72 (dd, $J = 7.2, 1.2$ Hz, 1 H), 7.63 (ddd, $J = 7.8, 7.2, 0.6$ Hz, 1H), 7.45 (s, 1H), 7.30 (dd, $J = 8.4, 1.2$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 67.5 MHz): $\delta$ 187.5, 177.2, 161.7, 140.9, 140.3, 136.4, 130.7, 125.1, 121.0, 114.7.
**5-(benzyloxy)-2-bromonaphthalene-1,4-dione 1.9.6**

![Chemical Structure](image)

To a solution of **1.9.5** (3.17 g, 12.5 mmol) in CH$_2$Cl$_2$ (42 mL) at rt, was added BnBr (3 mL, 25.1 mmol), followed by addition of solid Ag$_2$O (3.78 g, 16.3 mmol). The suspension was stirred at rt for 36 h, then it was filtered and rinsed with EtOAc. The eluent was concentrated under reduced pressure to give a residue, which was subjected to silica gel column chromatography. Elution with Hexane-EtOAc (10:1) gave product **1.9.6** (3.9 g, 91%): Yellow solid; $R_f$ (hexanes/EtOAc, 3:1 v/v) = 0.57; $^1$H NMR (CDCl$_3$, 600 MHz): δ 7.83 (d, $J$ = 7.8 Hz, 1H); 7.64 (dd, $J$ = 8.4, 7.8 Hz, 1H), 7.55 (d, $J$ = 7.8 Hz, 2H), 7.43-7.39 (m, 3H), 7.36 (d, $J$ = 8.4 Hz, 1H), 7.33 (dd, $J$ = 7.8, 7.2 Hz, 1H), 5.30 (s, 2H); $^{13}$C NMR (CDCl$_3$, 150 MHz): δ 181.2, 178.2, 158.9, 142.3, 136.9, 135.8, 134.9, 133.1, 128.7, 128.1, 126.7, 120.9, 120.2, 119.9, 71.0.

**2-(2-(1,3-dioxan-2-yl)-6-(methoxymethoxy)-4-methylphenyl)-5-(benzyloxy)naphthalene-1,4-dione 1.10.3**

![Chemical Structure](image)

To a suspension of juglone **1.9.6** (2.82 g, 8.23 mmol), stannane **1.8.10** (4.33 g, 8.23 mmol), and CuI (313 mg, 1.65 mmol) in THF (60 mL) at rt, was added a solution of Pd$_2$(dba)$_3$•CHCl$_3$ (425.5 mg, 0.412 mmol) and PPh$_3$ (431.3 mg, 1.65 mmol) in THF (22 mL). The mixture was stirred at 75 °C for 12 h. It was then cooled down to 0 °C and diluted with EtOAc (200 mL). Saturated aqueous NaHCO$_3$ (120 mL) was added and it was stirred at 0 °C for 30 min. The
aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (2:1, v/v) afforded coupled product **1.10.3**, (3.0 g, 73%): Brown solid, mp: 140-142 °C; R₉ (hexanes/EtOAc, 2:1 v/v) = 0.29; IR (thin film, cm⁻¹) ν 3063, 2985, 2923, 2903, 2868, 2846, 1654, 1588, 1448, 1379, 1344, 1290, 1258, 1245, 1147, 1096, 1053, 1005, 969; ¹H NMR (CD₃CN, 600 MHz): δ 7.74 (dd, J = 8.4, 7.8 Hz, 1 H), 7.70 (dd, J = 7.8, 1.2 Hz, 1H), 7.64-7.61 (m, 2H), 7.53 (dd, J = 8.4, 1.2 Hz, 1H), 7.46-7.42 (m, 2H), 7.35 (dd, J = 7.8, 7.2 Hz, 1H), 7.12 (brs, 1H), 7.00 (brs, 1H), 6.74 (s, 1H), 5.38 (s, 1H), 5.31 (m, 2H), 5.05 (d, J = 6.6 Hz, 1H), 5.03 (d, J = 6.6 Hz, 1H), 3.97 (dddd, J = 11.4, 4.8, 1.8, 1.8 Hz, 1H), 3.94 (dddd, J = 11.4, 4.8, 1.8, 1.2 Hz, 1H), 3.78 (ddd, J = 12.0, 11.8, 2.4 Hz, 1H), 3.71 (ddd, J = 12.0, 11.8, 2.4 Hz, 1H), 3.28 (s, 3H), 2.38 (s, 3H), 1.91 (dddddd, J = 13.2, 12.6, 12.6, 4.8, 4.8 Hz, 1H), 1.29 (dddddd, J = 13.2, 2.4, 2.4, 1.2, 1.2 Hz, 1H); ¹³C NMR (CD₃OD, 150 MHz): δ 184.9, 184.9, 159.4, 155.4, 145.6, 141.2, 140.2, 139.3, 137.9, 136.0, 135.9, 129.6, 129.0, 128.3, 121.4, 121.2, 120.8, 120.4, 116.3, 100.7, 95.6, 71.7, 67.9, 67.8, 56.7, 26.5, 21.8; HRMS (ESI): calcd for [C₃₀H₂₈O₇ + H]⁺ 501.1785, found 501.1773.
2-(2-(benzyloxymethoxy)-6-(1,3-dioxan-2-yl)-4-methylphenyl)-5-hydroxynaphthalene-1,4-dione 1.10.2

To a suspension of juglone 1.9.5 (1.25 g, 4.95 mmol), stannane 1.8.11 (2.91 g, 4.95 mmol), and CuI (188 mg, 0.99 mmol) in 30 mL THF at rt, was added a solution of Pd$_2$(dba)$_3$$\cdot$CHCl$_3$ (256 mg, 0.248 mmol) and PPh$_3$ (259 mg, 0.248 mmol) in THF (20 mL). The mixture was stirred at 80 °C for 12 h. It was then cooled down to 0 °C, diluted with EtOAc (100 mL), and quenched by adding saturated aqueous NaHCO$_3$ (60 mL). The mixture was stirred at 0 °C for 30 min. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na$_2$SO$_4$. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (5:1, v/v) afforded coupled product 1.10.2, (1.30 g, 54%): Brown viscous oil; $R_f$ (hexanes/EtOAc, 2:1 v/v) = 0.46; IR (thin film, cm$^{-1}$) $\nu$ 3068, 3037, 2964, 2929, 2860, 1671, 1639, 1603, 1580, 1454, 1366, 1329, 1307, 1279, 1247, 1155, 1118, 1098, 1078, 1051, 1000, 964; $^1$H NMR (CD$_3$OD, 600 MHz): $\delta$ 7.71 (dd, $J$ = 8.4, 7.8 Hz, 1 H), 7.62 (dd, $J$ = 7.8, 1.2 Hz, 1H), 7.32 (dd, $J$ = 8.4, 1.2 Hz, 1H), 7.26-7.19 (m, 5H), 7.14 (brs, 1H), 7.09 (brs, 1H), 6.84 (s, 1H), 5.39 (s, 1H), 5.21 (d, $J$ = 6.6 Hz, 1H), 5.19 (d, $J$ = 6.6 Hz, 1H), 4.59 (d, $J$ = 11.4 Hz, 1H), 4.53 (d, $J$ = 11.4 Hz, 1H); 4.01 (dddd, $J$ = 10.2, 5.4, 1.8, 1.2 Hz, 1H), 4.00 (dddd, $J$ = 9.6, 4.8, 1.8, 1.2 Hz, 1H), 3.81 (ddd, $J$ = 12.0, 12.0, 2.4 Hz, 1H), 3.78 (ddd, $J$ = 12.0, 12.0, 2.4 Hz, 1H), 2.38 (s, 3H), 1.95 (dddd, $J$ = 13.8, 12.0, 12.0, 5.4, 4.8 Hz, 1H), 1.32 (dddd, $J$ = 13.2, 2.4, 4.2, 1.2 Hz, 1H); $^{13}$C NMR (CD$_3$OD, 150 MHz): $\delta$ 191.6, 184.5, 162.5, 155.8, 150.4, 141.7, 139.2, 138.8, 138.5, 137.8, 134.0, 129.5, 129.2,
128.9, 125.0, 121.9, 121.2, 120.4, 116.5, 116.4, 101.8, 93.7, 71.5, 68.4, 68.3, 26.9, 21.9; HRMS (ESI): calcd for [C_{29}H_{26}O_{7} + H]^+ 487.1751, found 487.1754.

2-(5-(benzylloxy)-1,4-dixo-1,4-dihydranaphthalen-2-yl)-3-(methoxymethoxy)-5-methylbenz aldehyde 1.11.1

A sample of 1.10.3 (297 mg, 0.593 mmol) was dissolved in 4 ml THF at rt. Then added a stirred cool solution of 2.8 ml TFA in 2.8 ml H2O. The reaction mixture was stirred at rt for 10 min. Diluted with EtOAc and quenched with 16g solid NaHCO3. Extracted with EtOAc (50 ml x 3). The combined organic layer was washed with brine, dried over Na2SO4 and concentrated under reduced pressure. The crude product was purified with silica gel chromatography eluting with 2:1 (EtOAc: Hex) to get 225.8 mg 1.11.1, (86%) as a brown solid, mp = 55-57 °C; Rf (hexanes/EtOAc, 1:1 v/v) = 0.51; IR (thin film, cm\(^{-1}\)) \( \nu \) 3068, 2963, 2828, 2739, 152, 1348,1284, 1239, 1036, 1026, 970, 923; \(^1\)H NMR (CDCl\(_3\), 600 MHz): \( \delta \) 9.89 (s, 1H), 7.78 (dd, \( J = 7.8, 1.2 \) Hz, 1H), 7.64 (dd, \( J = 8.4, 7.8 \) Hz, 1H), 7.63-7.60 (dd, \( J = 8.1, 1.2 \) Hz, 2H), 7.44-7.41 (m, 2H), 7.37- 7.32 (m, 2H), 7.31 (s, 1H), 6.80 (s, 2H), 5.33 (s, 2H), 5.14 (d, \( J = 6.6 \) Hz, 1H), 5.1 (d, \( J = 6.6 \) Hz, 1H),  3.39 (s, 3H), 2.48 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz): \( \delta \) 191.2, 191.1, 183.9, 183.8, 158.5, 141.1, 139.4, 136.2, 135.5, 135.4, 134.8, 134.6, 128.6, 127.9, 126.7, 125.9, 121.4, 120.9, 120.7, 120.0, 119.5, 94.6, 70.9, 56.3, 21.5; HRMS (ESI): calcd for [C_{27}H_{22}O_{6} + H]^+ 423.1416, found 423.1421.
2-(5-(benzyloxy)-1,4-dioxo-1,4-dihyronaphthalen-2-yl)-3-hydroxy-5-methylbenzaldehyde 1.12.2

A sample of 1.10.3 (191 mg, 0.380) was placed in a 500 mL flask. A solution of concentrated HCl (aq.) (6.0 mL) in MeCN (30 mL) was added to the flask when stirring at rt. The mixture was stirred at rt for 4 min, then saturated aqueous NaHCO₃ (150 mL) was added while stirring followed by addition of EtOAc (75 mL). After separation, the aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (1.5:1, v/v) afforded deprotected product 1.12.2 (116 mg, 77%): Yellow solid, mp: 185-187 ºC; Rₚ(hexanes/EtOAc, 2:1 v/v) = 0.25; IR (thin film, cm⁻¹) ν 3281 (broad), 3037, 3013, 2924, 2827, 1689, 1649, 1581, 1499, 1446, 1393, 1313, 1287, 1240, 1165, 1093, 1023, 971; ¹H NMR (DMSO-d₆, 600 MHz): δ 9.94 (s, 1H), 9.83 (s, 1H), 7.82 (dd, J = 8.4, 7.8 Hz, 1 H), 7.67 (d, J = 8.4 Hz, 1H), 7.64-7.60 (m, 3H), 7.43 (dd, J = 7.8, 7.8 Hz, 2H), 7.34 (dd, J = 7.8, 7.2 Hz, 1H), 7.31 (s, 1H), 7.08 (s, 1H), 6.78 (s, 1H), 5.38 (s, 2H), 2.38 (s, 3H); ¹³C NMR (DMSO-d₆, 150 MHz): δ 183.7, 183.2, 181.9, 157.9, 155.2, 143.4, 140.1, 138.7, 136.7, 135.5, 135.1, 134.3, 128.4, 127.6, 126.9, 124.0, 122.1, 120.1, 119.8, 119.0, 117.8, 70.1, 20.7; HRMS (ESI): calcd for [C₂₅H₁₈O₅ + H]⁺ 399.1227, found 399.1230.
(2S,3S)-tert-butyl-2-(8-(benzyl oxy)-1,5-dihydroxy-3-methyl-7,12-dioxobenzo-[b]-phenanthridine-6(5H,7H,12H)-yl)-3-methylpentanoate 1.12.4

A sample of 1.12.2 (390 mg, 0.98 mmol) was placed in a 50 ml flask, into which was added a solution of aminoester 1.11.2 (1.46 g, 7.81 mmol) in toluene (10 mL). The mixture was stirred at rt for 24 h with the flask loosely capped so that air could get in. The mixture was directly loaded onto silica gel column. Elution with hexane-EtOAc (5:1, v/v) afforded title compound 1.12.4, (440 mg, 91%): Dark color amorphous solid; $R_f$ (hexanes/EtOAc, 2:1 v/v) = 0.45; IR (thin film, cm$^{-1}$) $\nu$ 3458 (broad), 3014, 2970, 2947, 1739, 1742, 1438, 1365, 1228, 1216, 1206, 900, 770; $^1$H NMR showed that it was a diastereomeric mixture with dr ratio about 4:1; For the major diastereomer: $^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ 10.42 (s, OH), 7.88 (dd, $J = 7.8$ Hz, 1 H), 7.61 (dd, $J = 8.4$, 7.8 Hz, 1H), 7.58 (d, $J = 7.2$ Hz, 2H), 7.42 (dd, $J = 7.8$, 7.2 Hz, 2H), 7.35 (dd, $J = 7.8$, 7.2 Hz, 1H), 7.28 (d, $J = 9.0$ Hz, 1H), 6.90 (brs, 1H), 6.68 (d, $J = 1.2$ Hz, 1H), 6.06 (d, $J = 2.4$ Hz, 1H), 5.30 (d, $J = 12.0$ Hz, 1H), 5.22 (d, $J = 12.0$ Hz, 1H), 4.62 (d, $J = 9.6$ Hz, 1H), 4.45 (d, $J = 3.0$ Hz, 1H), 2.35 (s, 3H), 2.05 (ddqd, $J = 9.6$, 9.0, 6.6, 3.0 Hz, 1H), 1.59 (s, 9H), 1.10 (ddqd, $J = 15.0$, 7.2, 2.4 Hz, 1H), 0.97 (d, $J = 6.6$ Hz, 1H); 0.84 (ddq, $J = 14.4$, 8.4, 7.2 Hz, 1H); 0.63 (dd, $J = 7.2$, 7.2 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ 185.0, 180.8, 173.1, 157.9, 154.2, 147.2, 141.3, 136.2, 135.7, 134.9, 132.6, 128.6, 128.0, 127.0, 126.7, 120.4, 120.3, 119.6, 118.9, 118.5, 82.9, 78.5, 71.2, 69.1, 37.0, 28.1, 26.4, 21.0, 16.3, 10.6; HRMS (ESI): calcd for [C$_{35}$H$_{37}$NO$_7$ + H]$^+$ 584.2643, found 584.2648.
(2S,3S)-tert-buty1-3-methyl-2-(1,5,8-trihydroxy-3-methyl-7,12-dioxobenzo-[b]-phenanthridi ne-6(5H,7H,12H)-yl)pentanoate 1.12.3

![Chemical structure](image)

To a solution of 1.12.1 (48.7 mg, 0.158 mmol) in THF (3 mL), was added aminoester 1.11.2 (236 mg, 1.26 mmol) in THF (5 mL). The mixture was stirred for 48 h at rt with the flask loosely capped so that air could get in. The solvent was concentrated under reduced pressure and then the mixture was directly subjected to silica gel column chromatography. Elution with hexane-EtOAc (8:1, v/v) afforded title compound 1.12.3, (42.8 mg, 55%). Dark color amorphous solid; 

$R_f$ (hexanes/EtOAc, 2:1 v/v) = 0.57; IR (thin film, cm$^{-1}$) $\nu$ 3390 (broad), 3100, 2896, 1834, 1756, 1432, 1412, 1229, 1262, 956, 864; $^1$H NMR showed that it was a diatereomeric mixture with dr ratio of about 12:1; For major isomer: $^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ 11.79 (s, OH), 10.51 (s, OH), 7.78 (dd, $J = 7.2$, 1.2 Hz, 1 H), 7.61 (dd, $J = 7.8$, 7.8 Hz, 1H), 7.21 (dd, $J = 8.4$, 0.6 Hz, 1H), 6.92 (m, 1H), 6.68 (d, $J = 1.2$ Hz, 1H), 6.08 (d, $J = 2.4$ Hz, 1H), 4.87 (d, $J = 9.0$ Hz, 1H), 4.23 (d, $J = 2.4$ Hz, 1H), 2.36 (s, 3H), 2.02 (m, 4H), 1.62 (s, 9H), 1.04 (dq, $J = 15.6$, 7.8, 3.0 Hz, 1H), 0.97 (d, $J = 6.6$ Hz, 1H); 0.80 (dq, $J = 14.4$, 7.8, 7.2 Hz, 1H); 0.60 (dd, $J = 7.8$, 7.2 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ 187.3, 185.0, 173.0, 161.5, 154.4, 143.6, 142.4, 137.0, 133.3, 133.2, 124.0, 123.3, 120.5, 120.4, 118.5, 114.3, 112.4, 83.2, 78.6, 69.3, 37.5, 28.2, 26.6, 21.1, 16.5, 10.5; HRMS (ESI): calcd for [C$_{28}$H$_{31}$O$_7$N + H]$^+$ 494.2173, found 494.2177.
(3aS,4S,6R,7R,7aS)-6-(benzyloxy)-7-iodo-4-methyltetrahydro-3aH[1,3]dioxolo-[4,5-c]pyran-2-one 1.14.5

Alkene 1.14.4 (5.6 g, 17.73 mmol) was dissolved in 100 mL HOAc at rt. Flushed the reaction vessel with Ar three times. Then NIS (7.99 g, 35.53 mmol) was added at rt. The reaction mixture was stirred for 3 h. Diluted with Et₂O, quenched with NaHCO₃, extracted with Et₂O (3 x 200 mL), washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel chromatography eluting with 10% EtOAc/Hexane to give 6.35 g (92%) of 1.14.5 as a colorless solid; mp = 75 °C, Rf = 0.36 (30% EtOAc/Hexane); [α]D²⁵ = −42.62 (c = 1.1, CH₂Cl₂); IR (thin film, cm⁻¹) 2934, 1810, 1497, 1454, 1347, 1149, 1088, 1055, 1024, 920; ¹H NMR (600 MHz, CDCl₃) δ 7.38-7.31 (m, 5H), 5.16 (d, J = 5.4 Hz, 1H), 4.95 (t, J = 7.8 Hz, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.1, Hz, 1H), 4.44 (dd, J = 9.3, 8.4 Hz, 1H), 4.21 (dd, J = 8.7, 6.0 Hz, 1H), 4.05 (dq, J = 9.6, 6.0 Hz, 1H), 1.34 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 152.9, 136.6, 128.5, 128.0, 127.9, 101.0, 78.7, 77.1, 70.2, 64.0, 21.0, 18.6; HRMS (ESI): [C₁₄H₁₅IO₅+Na]⁺ 412.9865, Found: 412.9792.
(3aS,4S,6R,7aR)-6-(benzyloxy)-4-methyltetrahydro-3aH-[1,3]dioxolo-[4,5-c]-pyran-2-one 1.14.6

Iodide 1.14.5 (110 mg, 0.28 mmol) was dissolved in toluene and TTMSS (104.9 mg, 0.42 mmol) was added at −20 °C under Ar. Then AIBN (8.18 mg, 0.06 mmol) was added quickly and freez-pump thaw three times. Slowly raised temperature to 75 °C. After 3 h, heating was stopped. Reaction mixture was concentrated under pressure and the crude product was purified using silica gel chromatography eluting with 30% EtOAc/Hexane to give 48.0 mg (65%) of 1.14.6 as a colorless oil; \( R_f = 0.46 \) (30% EtOAc/Hexane); \([\alpha]_D^{25} = -106.43 \) (c = 2.2, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) \( \nu 2935, 1794, 1497, 1454, 1352, 1152, 1064, 1036, 1024, 920, 739\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta 7.33-7.25 \) (m, 5H), 4.90 (t, \( J = 5.4 \) Hz, 1H), 4.75 (dt, \( J = 6.0, 6.0, 1H\)), 4.68 (d, \( J = 12.0 \) Hz, 1H), 4.49 (d, \( J = 12.0, \) Hz, 1H), 4.23 (dd, \( J = 9.0, 7.8 \) Hz, 1H), 3.98 (dq, \( J = 9.0, 6.6 \) Hz, 1H), \( 2.30 \) (dt, \( J = 15.0, 6.0 \) Mz, 1H), 2.1 (m, 1H), 1.27 (d, \( J = 6.0 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta 154.2, 137.3, 128.4, 127.8, 127.6, 94.1, 72.4, 69.3, 30.6, 18.5\); HRMS (ESI): [C\(_{14}\)H\(_{16}\)O\(_5\) + Na\(^+\)] 287.0889, Found: 287.0889.
(3aS,4S,7aR)-6-hydroxy-4-methyltetrahydro-3aH-[1,3]dioxolo-[4,5-c]-pyran-2-one 1.14.8

Benzyl ether 1.14.6 (75 mg, 0.284 mmol) was dissolved in MeOH (5 mL). To this added 10% Pd-C (40 mg, 10 mol%). The reaction mixture was vacuum degassed three timed and refilled with Ar. Finally degassed and filled with H₂. The reaction was stirred at rt over night under balloon pressure. Filtered of the catalyst to get 1.14.8 as a colorless oil in quantitative yield (1.8:1 diastereomeric mixture). $R_f = 0.09$ (30% EtOAc/Hexane); IR (thin film, cm⁻¹) $\nu$ 3415 (broad), 2924, 2857, 1790, 1456, 1356, 1161, 1062, 1039, 856, 778; $^1$H NMR for the major diastereomer (600 MHz, CDCl$_3$) $\delta$ 5.1 (ddd, $J = 12.0, 10.1, 3.0$ Hz 1H), 4.97 (m, 1H), 4.27 (dt, $J = 9.6, 3.0, 1$H), 3.7 (dq, $J = 9.3, 6.0$ Hz, 1H), 2.96 (d, $J = 4.2$, Hz, 1H), 2.47 (dt, $J = 15.0, 3.0$, Hz, 1H), 2.01 (dd, $J = 12.2, 9.6, 2.4$ Hz, 1H), 1.47 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 154.0, 91.9, 76.1, 72.4, 63.5, 32.6, 18.6; HRMS (ESI): $[C_7H_{10}O_5 + Na]^+$ 197.0420, Found: 197.0420.
(3aS,4S,7aR)-4-methyl-2-oxotetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl-2,2,2-trichloro acetimidate 1.14.9

![Diagram](https://via.placeholder.com/150)

To a solution of anomeric alcohol 1.14.8 (100 mg, 0.57 mmol) in dry dichloromethane (1 mL) at 0 ºC, was added DBU (0.094 mL, 0.63 mmol) under argon. The reaction mixture was stirred for five min at 0 ºC then CCl₃CN (0.085 mL, 0.85 mmol) was added. The reaction temperature was slowly raised to room temp and progress of the reaction was monitored with TLC. Upon consumption of starting material (~1h), the in situ formed imidate product was used for glycosylation without further purification.

(2S,3R,4R,6R)-6-(benzyloxy)-2-methyltetrahydro-2H-pyran-3,4-diol 1.14.6a

![Diagram](https://via.placeholder.com/150)

57.9 mg (0.219 mmol) of carbonate 1.14.6 was dissolved in 5 mL THF at rt. To this 3.5 mL (2M) NaOH was added and stirred at rt for 1 h. The reaction mixture was then passed through a celite pad and washed with EtOAc. Eluent was neutralized with HCl (1N, 5mL x 2), dried over Na₂SO₄ and concentrated under reduced pressure to get pure 1.14.6a in near quantitative yield.

\[ R_f = 0.19 \text{ (30\% EtOAc/Hexane); [\alpha]_D^{25} = -112.41 (c = 2.2, CH}_2Cl}_2; \]  
IR (thin film, cm⁻¹) \( \nu \) 3497 (broad), 2932, 1455, 1404, 1375, 1119, 1100, 1056, 1011, 872, 697; ¹H NMR (600 MHz, CDCl₃) \( \delta \) 7.36-7.29 (m, 5H), 4.95 (d, \( J = 3.0 \) Hz 1H), 4.72 (d, \( J = 12.0, 1H \)), 4.49 (d, \( J = 12.0, 1H \)), 3.94 (dd, \( J = 9.1, 4.3 \) Hz, 1H), 3.78 (ddd, \( J = 12.1, 8.6, 2.0, Hz, 1H \)), 3.15 (dd, \( J = 9.9, 3.0, Hz, 1H \)),
3.01-2.90 (brs, 1H), 2.19 (ddd, $J = 12.0, 9.1, 1.5$ Hz, 1H), 1.92 (dt, $J = 14.4, 3.6$ Hz, 1H), 1.33 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 136.8, 128.5, 127.9, 127.8, 96.3, 72.6, 69.3, 67.3, 64.6, 35.1, 17.7; HRMS (ESI): [C$_{13}$H$_{18}$O$_4$ + Na]$^+$ 261.10973, Found: 261.1084.

**(3aS,4S,6R,7aR)-6-(benzyloxy)-2,2,4-trimethyltetrahydro-3aH-[1,3]-dioxolo[4,5-c]pyran 1.14.6b**

Diol **1.14.6a** (50 mg, 0.21 mmol) was dissolved in 0.5 mL DMP and $p$-TsOH•H$_2$O (0.12 mg, 0.0006 mmol) was added to the solution at 0 °C. The reaction mixture was stirred for 1 h under argon atmosphere. Diluted with EtOAc and quenched with NaHCO$_3$. Organic layer was extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified using silica gel chromatography eluting with 12% EtOAc/Hexane to give 52.6 mg (90%) of **1.14.6b** as a colorless oil; $R_f = 0.68$ (25% EtOAc/Hexane); [$\alpha$]$_D^{25} = -127.52$ (c = 0.92, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) ν 2985, 1794, 2932, 1455, 1370, 1244, 1210, 1044, 1026, 867, 736; $^1$H NMR (600 MHz, CDCl$_3$) δ 7.43-7.21 (m, 5H), 4.87 (t, $J = 5.4$ Hz, 1H), 4.73 (d, $J = 12.1$, 1H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.25 (q, $J = 6.0$, Hz, 1H), 3.85 (ddd, $J = 12.0, 9.3, 3.2$ Hz, 1H), 3.75 (dd, $J = 6.0, 3.0$ Hz, 1H), 2.20 (dt, $J = 14.4, 5.4$ Mz, 1H), 2.1 (ddd, $J = 11.5, 8.5, 3.2$ Hz, 1H), 1.47 (s, 3H), 1.34 (s, 3H), 1.25 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 138.1, 128.3, 127.8, 127.5, 101.1, 95.0, 77.7, 70.9, 69.0, 64.9, 32.3, 27.9, 25.5, 18.6; HRMS (ESI): [C$_{16}$H$_{22}$O$_6$ + H]$^+$ 279.1519, Found: 279.1520.
(3aS,4S,7aR)-2,2,4-trimethyltetrahydro-3aH-[1,3]-dioxolo[4,5-c]pyran-6-ol

1.14.7

The benzyl ether 1.14.6b (100 mg, 0.36 mmol) was dissolved in MeOH (5 mL). To this added 10% Pd-C (50 mg, 10 mol%). The reaction mixture was vacuum degassed three times and refilled with Ar. Finally degassed and filled with H\textsubscript{2}. The reaction was stirred at rt over night under balloon pressure. Filtered of the catalyst to get 1.14.7 as colorless oil in quantitative yield (1:1 diastereomeric mixture). \(R_f=0.2\) (25% EtOAc/Hexane); IR (thin film, cm\(^{-1}\)) 3424 (broad), \(\nu\) 2985, 2934, 1456, 1244, 1217, 1074, 1054, 843; \(^1\)H NMR for the one diastereomer (600 MHz, CDCl\(_3\)) \(\delta\) 5.0 (d, \(J=8.4\) Hz, 1H), 4.36 (q, \(J=4.8\) Hz, 1H), 3.96 (ddd, \(J=12.0, 9.6, 3.0\) Hz, 1H), 3.70 (dd, \(J=6.3, 2.4\) Hz, 1H), 3.51 (ddd, \(J=10.6, 8.4, 2.2\) Hz, 1H), 2.31 (dt, \(J=14.8, 3.0, 2.2\) Hz, 1H), 1.86 (ddd, \(J=12.0, 9.2, 2.2\) Hz, 1H), 1.52 (s, 3H), 1.36 (s, 3H), 1.28 (d, \(J=6.4\) Hz, 3H); \(^1\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 101.5, 92.6, 76.9, 72.8, 64.2, 31.9, 28.2, 25.8, 18.4; HRMS (ESI): \([\text{C}_9\text{H}_{16}\text{O}_4+\text{Na}]^+\) 211.09408, Found: 211.0931.

Tert-butyl (1S,5R)-5-methyl-4-oxocyclohex-2-enyl carbonate 1.17.3\(^{34b}\)

To a solution of diol 1.17.2 (102 mg, 0.71 mmol) and DMAP (5 mg, 0.041 mmol) in CH\(_2\)Cl\(_2\) (3 mL), was added a solution of Boc\(_2\)O (463 mg, 2.12 mmol) in CH\(_2\)Cl\(_2\) (2 mL) at 0 °C while stirring. The mixture was stirred at rt for 1 h, then cooled down to 0 °C. It was first diluted with
EtOAc and quenched by adding saturated aqueous NaHCO₃. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na₂SO₄. The solution was concentrated under reduced pressure to afford a crude product, which was redissolved in CH₂Cl₂ (4 mL) at rt. Et₃N (1 mL) was added slowly to this solution at rt and stirred at rt for 1 h. Then it was cooled down to 0 °C, and diluted with hexane-Et₂O (1:1 v/v). The mixture was subsequently washed with aqueous HCl (1 M), saturated aqueous NaHCO₃, saturated brine and dried over Na₂SO₄. The solution was concentrated under reduced pressure to afford a residue, which was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (10:1, v/v) gave Boc-enone 1.17.3 (141 mg, 88% for two steps). White solid; mp: 62-64 °C, Rᶠ = 0.52 (2:1 (v/v) hexane/EtOAc); [α]D²⁵ = −45.7 (c 1.68, CHCl₃); IR (thin film, cm⁻¹) ν 3044, 2986, 2943, 2885, 1731, 1682, 1618, 1482, 1459, 1366, 1337, 1275, 1252, 1152, 1097, 1082, 974; ¹H NMR (CDCl₃, 600 MHz) δ 6.83 (ddd, J = 10.2, 2.4, 1.8 Hz, 1H), 6.02 (dd, J = 10.2, 2.4 Hz, 1H), 5.47 (dddd, J = 10.8, 4.8, 2.4, 2.4 Hz, 1H), 2.45 (m, 2H), 1.86 (ddd, J = 14.4, 12.6, 10.2 Hz, 1H), 1.51 (s, 9H), 1.17 (d, J = 6.0 Hz, 3H), ¹³C NMR (CDCl₃, 150 MHz) δ 200.1, 152.7, 147.9, 130.1, 83.0, 71.8, 40.0, 37.5, 27.7, 14.9.

**Tert-butyl (1S,4S,5R)-4-hydroxy-5-methylcyclohex-2-enyl carbonate 1.17.4**

![Structure](image)

To a solution of Boc-enone 1.17.3 (293 mg, 1.30 mmol) in THF (8 mL) at -78 °C, was added LiAlH₄ (98 mg, 2.59 mmol) in several portions while stirring. The reaction mixture was stirred at -78 °C for 1 h, then acetone (3 mL) was added dropwise, and the mixture was stirred at -78 °C
for another 20 min to quench excess LiAlH₄. The mixture was diluted with EtOAc and saturated aqueous NaHCO₃ was added. The mixture was stirred at 0 °C for 10 min. The aqueous layer was extracted with EtOAc twice. The combined organic layer was washed with saturated brine, and dried over Na₂SO₄. The solution was concentrated under reduced pressure to give a crude product. Crude ¹H NMR showed that the diastereomeric ratio is about 12:1. The crude product was purified by chromatography on silica gel column, elution with hexane-EtOAc (5:1, v/v) afforded allylic alcohol 1.17.4 (totally 279mg, 94%). White solid; mp: 82.5-84.5 °C; ᵦᵥ = 0.42 (2:1 v/v hexane/EtOAc); [α]D²⁵ = −97.1 (c 4.50, CHCl₃); IR (thin film, cm⁻¹) υ 3517, 3021, 2982, 2947, 2885, 1711, 1460, 1398, 1366, 1352, 1335, 1282, 1256, 1151, 1076, 1055, 958; ¹H (CDCl₃, 600 MHz) δ 5.79 (ddd, J = 10.2, 2.4, 1.8 Hz, 1H), 5.72 (ddddd, J = 10.2, 1.8, 1.8, 1.8 Hz, 1H), 5.20 (ddddd, J = 9.0, 7.8, 2.4, 1.8 Hz, 1H), 3.83 (m, 1H), 2.11 (ddddd, J = 12.6, 5.4, 2.4, 1.8 Hz, 1H), 1.69 (d, J = 6.0 Hz, OH), 1.64 (ddddd, J = 11.4, 9.0, 6.6, 2.4 Hz, 1H), 1.48 (s, 9H), 1.45 (dd, J = 12.6, 12.6, 10.2 Hz, 1H), 1.11 (d, J = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 153.1, 134.5, 128.3, 82.2, 73.2, 72.8, 37.3, 35.8, 27.8, 18.2.

*Tert*-butyl (1R,5R)-5-methylcyclohex-3-enyl carbonate 1.17.5³⁴b

![struct1.17.5](image)

To a solution of allylic alcohol 1.17.4 (279 mg, 1.22 mmol) and PPh₃ (962 mg, 3.67 mmol) in N-methylmorpholine (NMM) (5.4 mL) at −25 °C, was added dropwise DIAD (0.72 mL, 3.67 mmol). The mixture was stirred at −25 °C for 12 min, then o-nitrobenezenesulfonylhydrazide (NBSH) (796 mg, 3.67 mmol) was added. It was stirred at −25 °C for 1.5 h and then was warmed up and stirred at rt for another 2 h. The reaction mixture was diluted with hexane-Et₂O
(1:1 v/v) and washed at 0 °C with aqueous HCl (1M). The aqueous layer was extracted with hexane-Et₂O (1:1 v/v) twice. The combined organic layer was subsequently washed with saturated aqueous NaHCO₃, saturated brine, and dried over Na₂SO₄. The organic layer was concentrated under reduced pressure to give crude product, which was then subjected to chromatography on silica gel. Elution with hexane-EtOAc (20:1, v/v) gave olefin 1.17.5 (226 mg, 87%). Colorless oil; \( R_f = 0.73 \) (4:1 v/v hexane/EtOAc); \( [\alpha]_D^{25} = +50.8 \) (c 2.35, CHCl₃); IR (thin film, cm⁻¹) \( \nu 3029, 2954, 2881, 1736, 1396, 1368, 1313, 1301, 1275, 1250, 1161, 1097, 1066, 980; ^1H NMR (CDCl₃, 600 Mz): d 5.51 (dd, \( J = 9.6, 4.8, 2.4, 2.4 \) Hz, 1H), 5.45 (ddd, \( J = 10.2, 3.0, 3.0, 1.2 \) Hz, 1H), 4.74 (dddd, \( J = 12.0, 9.6, 6.6, 3.0 \) Hz, 1H), 2.41 (m, 2H), 2.09 (m, 2H), 1.47 (s, 9H), 1.27 (dd, \( J = 12.0, 12.0, 12.0 \) Hz, 1H), 1.00 (d, \( J = 7.2 \) Hz, 3H); \(^{13}C\) NMR (CDCl₃, 150 MHz): \( \delta 153.1, 133.1, 122.6, 81.7, 73.4, 37.2, 31.0, 30.9, 27.8, 21.3. \)

**Tert-butyl-(3aR,5S,7R,7aS)-2,2,7-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl-carbonate 1.17.6**

To a solution of olefin 1.17.5 (225 mg, 1.06 mmol) in t-BuOH-acetone-50% NMO (aq.) (3 mL, 1:1:1 v/v/v), was added a small piece of crystalline OsO₄ at 0 °C. The reaction mixture was stirred at 0 °C for 8 h, then was diluted with EtOAc followed by addition of saturated aqueous Na₂S₂O₄ (3 mL). The mixture was stirred at 0 °C for another 30 min and passed through a pad of celite, rinsing with EtOAc. The eluent was dried over Na₂SO₄ and concentrated under reduced pressure to give a residue. Crude \(^1\)H-NMR showed that the diastereoselectivity is about 11:1. The
residue was subjected to chromatography on silica gel column, eluting with hexane-EtOAc (1:1.5, v/v) gave inseparable mixture of diol. The resulted diol mixture was treated with dimethoxypropane (DMP) (1 mL) in the presence of $p$-TsOH•H$_2$O (4.5 mg, 0.025 mmol) at 0 °C for 2h. It was diluted with EtOAc and quenched by addition of saturated aqueous NaHCO$_3$ at 0 °C. The aqueous layer was extracted with EtOAc twice. The combined organic layer was washed with saturated brine, dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure to give a residue, which was subjected to silica gel column chromatography. Elution with hexane-EtOAc (20:1, v/v) afforded acetonide 1.17.6 (243 mg, 80%) with the minor diastereomer removed. Colorless oil; $R_f = 0.74$ (1:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25} = -29.7$ (c 1.86, CHCl$_3$); IR (thin film, cm$^{-1}$) $\nu$ 2986, 2940, 2874, 1737, 1461, 1368, 1305, 1276, 1243, 1218, 1158, 1102, 1066, 1040, 976; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 4.80 (dddd, $J = 10.8, 10.8, 4.8, 4.8$ Hz, 1H), 4.27 (ddd, $J = 4.8, 4.8, 3.0$ Hz, 1H), 3.51 (dd, $J = 9.0, 5.4$ Hz, 1H), 2.40 (dddd, $J = 14.4, 4.8, 2.4, 2.4$ Hz, 1H), 1.92 (dddd, $J = 12.6, 3.6, 3.0, 3.0$ Hz, 1H), 1.74 (ddd, $J = 15.0, 10.8, 4.8$ Hz, 1H), 1.69 (ddqd, $J = 10.2, 10.2, 6.6, 3.6$ Hz, 1H), 1.45 (s, 9H), 1.41 (s, 3H), 1.29 (s, 3H), 1.06 (ddd, $J = 12.6, 12.6, 10.8$ Hz, 1H), 0.99 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 152.8, 108.3, 81.9, 80.3, 73.9, 71.7, 36.4, 33.5, 32.5, 28.4, 27.7, 26.0, 18.6.

(3a$R$,5$S$,7$R$,7a$S$)-2,2,7-trimethylhexahydrobenzo[4][1,3]dioxol-5-ol 1.17.7$^{34b}$

To a solution of carbonate 1.17.6 (240 mg, 0.84 mmol) in THF (8 mL) at 0 °C, was added LiAlH$_4$ (96 mg, 2.52 mmol). The reaction mixture was warmed up and stirred at rt for 4 h, then
the mixture was cooled down to 0 °C, and saturated aqueous NaHCO$_3$ was slowly added to quench the reaction. The mixture was passed through a pad of celite, rinsing with EtOAc. The eluent was dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure to give a residue, which was subjected to chromatography on silica gel column, elution with hexane-EtOAc (1:1, v/v) afforded alcohol 1.17.7 (151 mg, 97%). Colorless needle crystal; mp: 63-64 °C; $R_f = 0.24$ (1:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25} = -78.9$ (c 4.88, CHCl$_3$); IR (thin film, cm$^{-1}$) $\nu$
3273 (broad), 2994, 2889, 1462, 1378, 1364, 1241, 1214, 1197, 1151, 1129, 1064, 1042, 1026, 960; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 4.26 (ddd, $J = 4.2, 4.2, 2.4$ Hz, 1H), 3.94 (ddd, $J = 10.8, 4.2, 4.2$ Hz, 1H), 3.50 (dd, $J = 9.6, 4.8$ Hz, 1H), 2.37 (dddd, $J = 14.4, 4.8, 2.4, 2.4$ Hz, 1H), 2.13 (s, OH), 1.76 (dddd, $J = 13.2, 3.6, 3.6, 3.0$ Hz, 1H), 1.63 (ddqd, $J = 9.6, 9.6, 6.6, 3.0$ Hz, 1H), 1.58 (ddd, $J = 14.4, 10.8, 4.2$ Hz, 1H), 1.42 (s, 3H), 1.30 (s, 3H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.99 (ddd, $J = 13.2, 13.2, 10.8$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 108.1, 80.7, 74.5, 65.9, 40.4, 36.2, 33.7, 28.5, 26.1, 18.7.

2-(2-(1,3-dioxan-2-yl)-6-(methoxymethoxy)-4-methylphenyl)-5-((3aR,5R,7R,7aS)-2,2,7-trimethylhexahydrobenzo[d][1,3]dioxol-5-yloxy)naphthalene-1,4-dione 1.18.1

To a solution of 1.10.1 (64.6 mg, 0.158 mmol), 1.17.7 (29.3 mg, 0.158 mmol) and PPh$_3$ (124.2 mg, 0.474 mmol) in THF (1 mL), was added DIAD (93 µL, 0.474 mmol) at rt. The mixture was stirred at rt for 30 min, then it was diluted with EtOAc and quenched by addition of saturated
aqueous NaHCO$_3$. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, dried over Na$_2$SO$_4$. Concentration under reduced pressure afforded a residue, which was subjected to silica gel column chromatography. Elution with hexane-EtOAc (1:1, v/v) gave an atropisomeric mixture of **1.18.1** (82.7 mg, 91%). Brown viscous oil; $R_f = 0.31$ (hexane/EtOAc, 1:1 (v/v)); $^1$H NMR showed that it was an atropisomeric mixture with a ratio of 1:1; HRMS (ESI): calcd for [C$_{33}$H$_{38}$O$_9$ + H]$^+$ 579.2589, found 579.2592.

**2-(2-(benzyloxy)methoxy)-6-(1,3-dioxan-2-yl)-4-methylphenyl)-5-((3aR,5R,7R,7aS)-2,2,7-trimethylhexahydrobenzo[d][1,3]dioxol-5-yloxy)naphthalene-1,4-dione 1.18.2**

To a solution of **1.10.2** (180 mg, 0.37 mmol), **1.17.7** (68.8 mg, 0.37 mmol) and PPh$_3$ (291 mg, 1.11 mmol) in THF (3 mL), was added DIAD (218 µL, 1.11 mmol) at rt. The mixture was stirred at rt for 30 min, then it was diluted with EtOAc and quenched by addition of saturated aqueous NaHCO$_3$. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, dried over Na$_2$SO$_4$. Concentration under reduced pressure afforded a residue, which was subjected to silica gel column chromatography. Elution with hexane-EtOAc (1.5:1, v/v) gave an atropisomeric mixture of **1.18.2** (203 mg, 84%). Brown viscous oil; $R_f = 0.29$ and 0.33, respectively (hexane/EtOAc, 1:1 (v/v)); $^1$H NMR showed that it was an atropisomeric mixture with a ratio of 1:1; HRMS (ESI): calcd for [C$_{39}$H$_{42}$O$_9$ + H]$^+$ 655.2902, found 655.2905.
A sample of **1.18.1** (79.7 mg, 0.138 mmol) was placed in a 250 mL flask. A solution of concentrated HCl (aq.) (2.2 mL) in MeCN (11.0 mL) was added to the flask while stirring at rt. The mixture was stirred at rt for 4 min, then saturated aqueous NaHCO₃ (55 mL) was added when stirring followed by addition of EtOAc (30 mL). The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with EtOAc:MeOH (50:1, v/v) afforded deprotected product **1.19.1** (35.4 mg, 59%). Yellow solid, mp: 158-161 ºC; R_f (EtOAc/MeOH, 10:1 v/v) = 0.43; IR (thin film, cm⁻¹) v 3418 (broad), 2958, 2929, 2878, 1691, 1647, 1584, 1465, 1315, 1262, 1246, 1160, 1110, 1087, 1055, 985; ¹H NMR (acetone-d₆, 600 MHz): d 9.91 (s, 1H), 8.81 (brs, OH), 7.82 (dd, J = 9.0, 7.8 Hz, 1H), 7.70 (dd, J = 7.8, 1.2 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.37 (q, J = 1.2 Hz, 1H), 7.17 (q, J = 0.6 Hz, 1H), 6.85 (s, 1H), 5.14 (dddd, J = 3.0, 3.0, 3.0, 2.4 Hz, 1H), 4.92 (dd, J = 28.8, 10.8 Hz, 1H), 3.87 (m, 1H), 3.10 (brs, OH), 2.98 (brs, OH), 2.42 (s, 3H), 2.40 (m, 1H), 2.14 (d, J = 15.0 Hz, 1H), 2.06 (m, 1H), 1.90 (m, 1H), 1.42 (dd, J = 13.8, 13.2 Hz, 1H), 0.99 (m, 3H); ¹³C NMR (acetone-d₆, 150 MHz): δ 192.8, 185.4, 184.4, 157.9, 156.1, 145.5, 141.8, 140.1, 137.3, 136.3, 136.2, 125.8, 123.3, 120.9, 120.2, 120.0, 118.9, 77.4, 73.8, 70.0, 36.1, 36.0, 36.0, 21.1, 18.5; HRMS (ESI): calcd for [C₂₅H₂₄O₇ + H]⁺ 437.1595, found 437.1598.
Second approach to 1.19.1

A sample of 1.18.2 (190 mg, 0.29 mmol) was placed in a 250 mL flask. A solution of concentrated HCl (aq.) (4.52 mL) in MeCN (22.6 mL) was added to the flask while stirring at rt. The mixture was stirred at rt for 8 min, then saturated aqueous NaHCO₃ (110 mL) was added, followed by addition of EtOAc (50 mL). The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with EtOAc:MeOH (50:1, v/v) afforded deprotected product 1.19.1 (71 mg, 56%). The spectroscopic and analytical data were consistent with 1.19.1 as found above.

Jadomycin B carbasugar analogue

A sample of 1.19.1 (52 mg, 0.122 mmol) was placed in a 50 ml flask, into which was added a solution of aminoester 1.11.2 (228 mg, 1.22 mmol) in toluene (7 mL). The mixture was stirred at rt for 24 h with the flask loosely capped so that air could get in. The mixture was directly loaded onto silica gel column. Elution with hexane-EtOAc (1:1.5, v/v) afforded a mixture of aminal 1.19.2, a dark color amorphous solid; $R_f$ (EtOAc/MeOH, 10:1 v/v) = 0.69 and 0.62 for each diastereomer, respectively; HRMS (ESI): calcd for [C₃₅H₄₃NO₉ + H]⁺ 622.3011, found 622.3017. These diastereomeric mixtures were then treated with TFA (0.7 mL) at rt for 2.5 h. The reaction was diluted with EtOAc at rt, and then subsequently washed with H₂O (three times),
saturated aqueous NaHCO₃, saturated brine and dried over Na₂SO₄. The solvent was removed under reduced pressure to afford crude product of jadomycin B carbasugar analog (30 mg, 55% over two steps). Dark color amorphous solid; mp: 120-125 °C \( R_f \) (hexanes/EtOAc, 1:1 v/v) = 0.15; IR (thin film, cm⁻¹) \( \nu \) 3497, 2965, 2929, 2879, 1803, 1663,1574, 1514, 1376, 1273, 1234, 1195, 1108, 982, 730; \(^1\)H NMR showed that it was a diastereomeric mixture with a ratio of about 2.5:1. Analytical data for the major diastereomer is provided below; \(^1\)H NMR (CDCl₃, 600 MHz): \( \delta \) 10.15 (s, 1H), 7.92 (d, \( J = 7.86 \) Hz, 1H), 7.70 (d, \( J = 8.4 \) Hz, 1H), 7.34 (s 1H), 7.23 (d, \( J = 9.2 \) Hz, 1H), 6.88 (s, 1H), 6.79 (s 1H), 6.42 (s, 1H), 6.13 (s, 1H), 5.38 (d, \( J = 3.1 \) Hz, 1H), 4.94 (dd, \( J = 7.1 \), 1.2 Hz, 1H), 4.1 (br s, 1H), 3.12 (dd, \( J = 10.2 \), 10.1 Hz, 2H), 2.50 (dt, \( J = 15.6 \), 3.0 Hz, 1H), 2.35 (s, 3H), 2.25 (s, 1H), 2.15 (s, 1H), 2.11 (dq, \( J = 14.7 \), 3.1 Hz, 2H), 2.03 (s 1H), 1.94 (ddd, \( J = 15.3 \), 7.6, 4.2 Hz, 1H), 1.83-1.78 (m, 2H), 1.54-1.48 (m, 2H), 1.33 (td, \( J = 10.8 \), 2.4 Hz, 1H), 1.1-1.0 (m, 1H), 0.43 (d, \( J = 6.7 \) Hz, 3H); \(^{13}\)C NMR (CDCl₃, 150 MHz): \( \delta \) 183.4, 180.4, 170.1, 157.2, 154.0, 145.7, 143.6, 136.3, 135.1, 129.8, 120.9, 120.8, 120.7, 118.1, 118.0, 115.3, 114.5, 87.3, 76.8, 76.6, 73.1, 68.7, 62.6, 39.8, 35.3, 28.9, 25.3, 21.2, 17.9, 14.0, 11.8; HRMS (ESI): calcd for [C₃₁H₃₃N₈O₉ + H]⁺ 548.2279, found 548.2284.
4.3 Experimental for chapter 2

5-hydroxynaphthalene-1,4-dione 2.7.1\textsuperscript{53}

\begin{center}
\includegraphics[width=0.2\textwidth]{5-hydroxynaphthalene.png}
\end{center}

A suspension of fresh CuCl (12.0 g, 0.121 mol) in acetonitrile (500 mL) was placed in a 2 L three-neck flask fitted with a mechanical stirrer and a gas inlet tube and a strong current of air was bubbled through it. A suspension of 1,5-dihydroxynaphthalene 1.9.1 (30.0 g, 0.187 mol) in acetonitrile (500 mL) was added with vigorous stirring at rt in the dark over 30 min. The resulting mixture was stirred for 8 h and then the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography. Elution with hexane-CH\textsubscript{2}Cl\textsubscript{2} (7:3, v/v) afforded 2.7.1 (16.3 g, 50 %) as orange-brown solid. \( R_f \) (hexanes/EtOAc, 9:1 v/v) = 0.48; mp: 155 °C; IR (thin film, cm\(^{-1}\)) \( \upsilon = 3386, 3070, 1665, 1644, 1600, 1486, 1451, 1364, 1338, 1290, 1226; \) \( ^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 11.93 \) (s, 1H), \( \delta = 7.69-7.60 \) (m, 2H), \( \delta = 7.30 \) (dd, \( J = 7.2, 2.4 \) Hz, 1H), \( \delta = 6.98 \) (s, 2H); \( ^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta = 190.2, 184.2, 161.4, 139.5, 138.6, 136.5, 131.7, 124.4, 119.1, 114.9. \)

2-bromo-8-hydroxynaphthalene-1,4-dione 2.7.3\textsuperscript{53}

\begin{center}
\includegraphics[width=0.2\textwidth]{2-bromo-8-hydroxynaphthalene.png}
\end{center}

To a suspension of 3.0 g (17.2 mmol) juglone 2.7.1 in 45 mL HOAc, was added 0.9 mL (17.2 mmol) Br\textsubscript{2} and stirred at rt for 15 min. Then it was poured into 50 g ice followed by addition of 150 mL H\textsubscript{2}O. After stirring for 10 min, the mixture was filtered and the solid was washed with
cold water, which was then transferred to flask followed by addition of 20 mL ethanol. The mixture was stirred at a preheated oil bath (100-110 °C) for 10 min and then cooled down to rt. The solid was collected by filtration. Chromatography of the crude product on silica gel column using hexane-CH₂Cl₂ (1:1, v/v), afforded a 3.5 g orange solid mixture (80% total yield), which contained 81% 3-bromojuglone 1.9.5 and 19% 2-bromojuglone 2.7.3. 3-bromojuglone 2.7.3: 

\[ R_f (\text{hexanes/EtOAc, 3:1 v/v}) = 0.54; \]

\[ ^1H \text{NMR (CDCl}_3, 270 MHz): \delta 11.73 (s, 1H), \delta 7.68 (dd, J = 7.7, 7.4 Hz, 1H), \delta 7.64 (dd, J = 6.5, 1.0 Hz, 1H), \delta 7.49 (s, 1H), 7.31 (dd, J = 7.4, 2.2 Hz, 1H); \]

\[ ^{13}C \text{NMR (CDCl}_3, 67.5 MHz): \delta 182.9, 181.6, 162.1, 141.2, 139.3, 137.2, 131.7, 124.7, 119.9, 114.0. \]

\[ N,N-\text{diethyl-3-methoxy-5-methylbenzamide 2.8.2}^{54} \]

\[ \text{Hydroxy benzoic acid 2.8.1 (10.0 g, 65.72 mmol) was dissolved in dry CH}_2\text{Cl}_2 (120 mL), to this added Et}_2\text{NH (10.15 mL, 98.65 mmol) and p-TsOH (1.13 g, 6.57 mmol). The resulting solution was refluxed overnight. After cooling the reaction to 0 °C, it was quenched with saturated NaHCO}_3. After separation of the two phases, the aqueous layer was extracted with CH}_2\text{Cl}_2 (300 mL X 2). The pooled organic layer was subsequently washed with saturated brine and dried over Na}_2\text{SO}_4. After removal of the solvent under reduced pressure, the crude amide was carried to next step without further purification. The residue was dissolved in 100 mL acetone and to this mixture, added solid K}_2\text{CO}_3 (18.19 g, 131.52 mmol). After stirring for 10 min at rt under argon, MeI (8.62 mL, 131.52 mmol) was added slowly and refluxed for 3h. Acetone was removed under reduced pressure and the crude residue was partitioned between Et}_2\text{O and water. After} \]
separation of the two phases, the aqueous layer was extracted with Et₂O (300 mL X 3). The pooled organic layer was subsequently washed with saturated brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was subjected to silica gel flash column chromatography. Elution with hexane-EtOAc (7:3, v/v) afforded the desired compound 2.8.2, 12.2 g (84%, 2-steps) as clear oil: \( R_f \) (hexanes/EtOAc, 3:2 v/v) = 0.22; IR (thin film, cm⁻¹) \( \nu \) 2930, 2886, 2859, 1646, 1595, 1462, 1315, 1253, 1161, 1042, 1019, 947; \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 6.62 (s, 1H), 6.60 (s, 1H), 6.58 (s, 1H), 3.64 (s, 3H), 3.85 (m, 2H), 3.12 (m, 2H), 2.19 (s, 3H), 1.13-0.97 (m, 6H); \(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta \) 170.8, 159.2, 139.4, 138.1, 118.8, 115.2, 108.3, 54.9, 42.9, 38.8, 21.1, 13.9, 12.6.

**N,N-diethyl-3-methoxy-5-methyl-2-(tributylstannyl)benzamide 2.6.6**

\[
\text{ \text{H}_3\text{C}} \quad \text{\text{OMe}} \quad \text{CONEt}_2 \quad \text{CONEt}_2 \quad \text{SnBu}_3
\]

A solution of 5.22 g (23.59 mmol) amide 2.8.2 in 77 mL dry THF was cooled to –78 0 ºC and vacuum degassed and back filled with argon. After stirring for 15 min at this temperature, \( t\)-BuLi 16.2 mL (25.95 mmol) was added slowly by syringe pump. The resultant reaction mixture was stirred for 45 min at –78 ºC under argon. As the reaction proceeded, yellowish-white precipitate started to form. After 45 min, 8.2 ml (30.67 mmol) Bu₃SnCl was added. The reaction mixture was slowly warmed up to 0 ºC. After 1 h, the reaction mixture was diluted with Et₂O and quenched with saturated NH₄Cl. The aqueous layer was extracted with Et₂O (100 mL X 2). The pooled organic layer was subsequently washed with saturated brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was subjected to flash column chromatography using silica gel neutralized with Et₃N. Elution with hexane-Et₂O (19:1, v/v)
afforded stannane **2.6.6**, 9.0 g (75%) as clear oil: $R_f$ (hexanes/EtOAc, 9:1 v/v) = 0.42; IR (thin film, cm$^{-1}$) $\nu$ 3076, 3037, 2954, 2920, 2850, 1603, 1569, 1456, 1372, 1283, 1270, 1237, 1169, 1148, 1113, 1048, 1002, 932; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.61 (s, $J_{\text{Sn-H}}$ = 5.6 Hz, 1H), 6.58 (s, $J_{\text{Sn-H}}$ = 6.4 Hz, 1H), 3.72 (s, 3H), 3.49 (m, 2H), 3.49 (m, 2H), 3.45 (q, $J$ = 7.2 Hz, 1H), 3.23 (q, $J$ = 7.2 Hz, 1H), 2.30 (s, 3H), 1.5-1.4 (m, 6H), 1.34-1.19 (m, 13H), 1.05 (t, $J$ = 12.6 Hz, 3H), 0.97 (m, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 172.0, 164.4, 145.9, 139.5, 124.6, 119.6 ($^3J_{\text{Sn-}^{13}\text{C}}$ = 15.2 Hz), 110.0 ($^3J_{\text{Sn-}^{13}\text{C}}$ = 17.5 Hz), 55.1, 43.6, 39.1, 29.1 ($^3J_{\text{Sn-}^{13}\text{C}}$ = 13.7 Hz), 27.4 ($^2J_{\text{Sn-}^{13}\text{C}}$ = 32.7 Hz), 21.6, 14.2, 13.7, 13.6, 10.8 ($^1J_{\text{Sn-}^{13}\text{C}}$ = 174.2 Hz); HRMS (ESI): calcd for [C$_{25}$H$_{45}$NO$_2$Sn + H]$^+$ 512.2550, found 512.2556.

**2-(5-(benzyloxy)-1,4-dioxo-1,4-dihyronaphthalen-2-yl)-N,N-diethyl-3methoxy-5-methyl benzamide 2.10.1**

![Chemical Structure](image)

To a suspension of juglone **1.9.6** (475 mg, 1.38 mmol), stannane **2.6.6** (710 mg, 1.39 mmol), and CuI (105.2 mg, 0.55 mmol) in 12 mL THF at rt, was added a solution of Pd$_2$(dba)$_3$•CHCl$_3$ (71.6 mg, 0.069 mmol) and PPh$_3$ (72.5 mg, 0.276 mmol) in THF (3 mL) under Ar. The mixture was stirred at 80 °C for 12 h. It was then cooled down to 0 °C, diluted with EtOAc (10 mL), and quenched by adding saturated aqueous NaHCO$_3$ (20 mL). The mixture was stirred at 0 °C for 30 min. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine and dried over Na$_2$SO$_4$. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (13:7, v/v). The
eluted product was recrystallized from hexane/EtOAc to afforded coupled product 2.10.1, (400 mg, 60%). Redish-brown solid, exits a mixture of rotomer; mp: 210-214 °C; $R_f$ (hexanes/EtOAc, 7:3 v/v) = 0.14; IR (thin film, cm$^{-1}$) $\nu$ 3063, 2985, 2923, 2903, 2868, 2846, 1654, 1588, 1448, 1379, 1344, 1290, 1258, 1245, 1147, 1096, 1053, 1005, 969; $^1$H NMR (CHCl$_3$, 400 MHz): $\delta$ 7.73 (d, $J = 7.2$ Hz, 1H), 7.58 (dd, $J = 8.0, 6.0$ Hz, 1H), 7.56-7.54 (m, 2H), 7.38 (dd, $J = 7.6, 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 6.92 (brs, 1H), 6.78 (s, 1H), 6.76 (s, 1H), 5.27 (s, 2H), 3.72 (s, 3H), 3.62 (m, 1H), 3.26 (dq, $J = 8.0, 6.8$ Hz, 1H), 3.12-3.02 (m, 2H), 2.39 (s, 3H), 1.02 (t, $J = 7.2$ Hz, 3H), 0.94 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CHCl$_3$, 100 MHz): $\delta$ 183.9, 183.6, 169.2, 158.3, 157.2, 143.5, 140.9, 139.6, 138.1, 136.3, 134.6, 128.9, 128.4, 128.1, 126.8, 126.5, 120.6, 119.7, 118.7, 117.4, 112.3, 70.9, 56.0, 42.8, 38.4, 21.9, 14.0, 12.5; HRMS (ESI): calcd for [C$_{30}$H$_{29}$NO$_5$ + H]$^+$ 484.2124, found 484.2118.

1-(benzyloxy)-12-hydroxy-10-methoxy-8-methyl-6H-dibenzo[c,h]chromen-6-one

2.10.2

Quinone 2.10.1 (660 mg, 1.36 mmol) was dissolved in 20 mL THF and degassed by bubbling argon through the solution. In a separate flask, $n$-Bu$_4$NBr (34 mg, 0.34 mmol) and Na$_2$S$_2$O$_4$ (354 mg, 20.37 mmol) was dissolved in distilled H$_2$O (40 mL). The aqueous solution was degased by bubbling argon and transferred to the flask containing quinone via cannula. The reaction mixture was stirred for 1h. Reduction of quinone to hydroquinone was monitored with the disappearance of orange color (color of quinone). Degassed Et$_2$O was added and the organic phase was
extracted via cannula. The organic extract was concentrated under reduced pressure without exposure to air. The crude residue of hydroquinone was dissolved in HOAc (20 mL) and refluxed under argon for 2h. Light yellow precipitate of the lactonized product starts to form after 1h. The reaction was then cooled to 0 °C and added 10 mL H$_2$O. The precipitate was collected using a Hirsch funnel and washed with H$_2$O and hexane to obtain 2.10.2 (410 mg, 73%). Light yellow amorphous solid; mp: 233 °C; $R_f$ (30% hexanes/EtOAc) = 0.57; IR (thin film, cm$^{-1}$) $\nu$ 3486, 2932, 2864, 1714, 1564, 1534, 1375, 1323, 1287, 1254, 1164, 1011. $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 9.39 (s, 1H), $\delta$ 8.23 (s, 1H), $\delta$ 7.94 (d, $J = 8.8$ Hz, 1H), $\delta$ 7.76 (s, 1 H), $\delta$ 7.61 (d, $J = 7.6$ Hz, 2H), $\delta$ 7.54 (dd, $J = 8.4$, 8.0 Hz, 1H), $\delta$ 7.47-7.37 (m, 4H), $\delta$ 7.24 (d, $J = 8.0$ Hz, 1H), $\delta$ 5.43 (s, 2H), $\delta$ 4.05 (s, 3H), $\delta$ 2.47 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 162.5, 157.6, 156.3, 153.8, 141.9, 141.6, 139.6, 130.2, 129.1, 129.0, 128.7, 128.0, 124.4, 122.9, 122.1, 119.8, 119.2, 115.4, 109.1, 107.7, 71.5, 57.1, 21.8; HRMS (ESI): calcd for [C$_{25}$H$_{20}$O$_5$ + H]$^+$ 413.1389, found 413.1397.

1-(benzyloxy)-10,12-dimethoxy-8-methyl-6H-dibenzo[c,h]chromen-6-one 2.10.3

Phenol 2.10.2 (100 mg, 0.24 mmol) was dissolved in 4.1 mL dry THF. The mixture was cooled to 0 °C and added MeI (151.3 µL, 2.4 mmol). After 5 min at this temperature, added a THF solution of t-BuOK (32.7 mg, 0.29 mmol in 1.0 mL THF). The reaction was stirred under argon from 0 °C to rt over 1h. Diluted with Et$_2$O and quenched with saturated NH$_4$Cl. The aqueous layer was extracted with Et$_2$O twice and the combined organic layer was washed with saturated
brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica
gel column chromatography, eluting with 15% hexane-EtOAc gave 2.10.3, (85 mg, 82%).
Light yellow color amorphous solid; mp: 220 °C; R_f (20% hexanes/EtOAc) = 0.57; IR (thin film,
cm⁻¹) ν 2872, 2844, 1716, 1564, 1506, 1395, 1342, 1275, 1231, 1164, 1096, 1023. ¹H NMR
(CDCl₃, 400 MHz): δ 8.30 (s, 1H), δ 8.21 (d, J = 8.0 Hz, 1H), δ 7.88 (s, 1H), δ 7.61 (d, J = 7.2
Hz, 2H), δ 7.41-7.49 (m, 3H), δ 7.34 (dd, J = 7.6, 7.2 Hz, 1H), δ 7.06 (s, 1H), δ 7.03 (d, J = 7.6
Hz, 1H), δ 5.19 (s, 2H), δ 4.03 (s, 3H), δ 3.96 (s, 3H), δ 2.44 (s, 3H); ¹³C NMR (CDCl₃, 100
MHz): δ 161.6, 157.2, 155.7, 152.9, 140.5, 139.8, 137.6, 128.5, 127.7, 127.2, 127.1, 126.8, 123.2,
122.8, 122.0, 118.1, 115.4, 110.2, 104.3, 71.5, 56.5, 56.3, 21.7; HRMS (ESI): calcd for
[C₂₇H₂₂O₅ + H]⁺ 427.1545, found 427.1541.

**1-hydroxy-10,12-dimethoxy-8-methyl-6H-dibenzo[c,h]chromen-6-one (defucogilv ocarcin M)**

![Chemical structure](image)

Benzyl ether 2.10.3 (50 mg, 0.12 mmol) was dissolved in 2.0 mL CH₂Cl₂ and added 2-3 drops
of MeOH. To this added 20 mg 10% Pd/C. Vacuum degased at –78 °C and the reaction was
stirred at rt for 3h under H₂ balloon pressure. The debenzylated product was filtered through a
short pad of celite. After removal of the solvent, the residue was subjected to silica gel column
chromatography, eluting with 40% CH₂Cl₂/hexane gave defucogilvocarcin M, (33 mg, 80%).
Faint yellow crystalline needle-like solid; mp: 290-294 °C; R_f (50% hexanes/EtOAc) = 0.50; IR
(thin film, cm⁻¹) ν 3350, 3008, 2854, 1741, 1564, 1395, 1340, 1243, 1117, 1096, 866. ¹H NMR
(CDCl$_3$, 400 MHz): δ 9.36 (s, 1H), δ 8.32 (s, 1H), δ 8.01 (d, $J = 8.8$ Hz, 1H), δ 7.94 (s, 1H), δ 7.49 (dd, $J = 8.4$, 8.0 Hz, 1H), δ 7.13 (s, 1H), δ 7.01 (d, $J = 8.0$ Hz, 1H), δ 4.12 (s, 3H), δ 4.07 (s, 3H), δ 2.50 (s, 3H), 1.51 (s, H$_2$O); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 161.3, 156.9, 154.3, 151.7, 141.1, 139.9, 128.4, 126.2, 122.9, 122.6, 121.5, 117.9, 114.6, 113.3, 112.9, 112.4, 101.6, 56.1, 55.9, 21.7; HRMS (ESI): calcd for [C$_{20}$H$_{16}$O$_5$ + H]$^+$ 337.1076, found 337.1075.

(3a$R$,5$R$,7$R$,7a$S$)-2,2,7-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl-4-nitrobenzoate 2.12.1

Alcohol 1.17.7 (200 mg, 1.10 mmol), PPh$_3$ (360.3 mg, 1.37 mmol) and p-NBzOH (230 mg, 1.37 mmol) was dissolved in 12 mL dry THF and cooled to 0 ºC. To this cold reaction mixture was added DIAD (0.28 mL, 1.43 mmol) drop wise. The reaction mixture was stirred at this temperature for 1h and diluted with 10 mL Et$_2$O. The reaction was quenched with saturated NaHCO$_3$ and the aqueous layer was extracted with Et$_2$O (50 mL X 3). Combined organic layer was washed with saturated brine, and dried over Na$_2$SO$_4$. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 10% hexane/EtOAc afforded product 2.12.1 (354 mg, 96%). Colorless oil; $R_f$ = 0.35 20% hexane/EtOAc; [α]$_D$$^{25}$ –22.5 (c 1.2, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) ν 2986, 2943, 1737, 1682, 1453, 1367, 1300, 1276, 1241, 1218, 1150, 1102, 1064, 975; $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.24 (m, 4H), δ 8.10 (dd, $J =$
7.2, 5.4, 3.0 Hz, 1H), δ 4.30 (dd, J = 8.4, 5.2 Hz, 1H), δ 3.71 (dd, J = 8.0, 4.8 Hz, 1H), δ 2.42 (dddd, J = 14.2, 4.8, 2.4, 2.6 Hz, 1H), δ 2.05-2.20 (m, 2H), δ 1.99 (dddd, J = 14.6, 8.8, 4.2, 3.6 Hz, 1H), 1.56 (s, 3H), δ 1.42 (J = 12.6, 12.6, 10.6 Hz, 1H), δ 1.38 (s, 3H), 1.01 (d, J = 7.2 Hz, 3H); 13C NMR (CDCl3, 100 MHz) δ 164.2, 150.6, 136.2, 130.9, 123.6, 108.3, 80.4, 76.9, 72.2, 69.3, 34.4, 32.6, 28.9, 26.2, 18.6; HRMS (ESI): calcd for [C17H21NO6 + H]+ 336.1447, found 336.1446.

(3aR,5R,7R,7aS)-2,2,7-trimethylhexahydrobenzo[d][1,3]dioxol-5-ol ent-2.11.6

To a solution of benzoate ester 2.12.1 (355 mg, 1.06 mmol) in THF (10 mL) at 0 °C, was added an aqueous solution of LiOH (38 mg, 1.6 mmol in 1.5 mL H2O). The reaction mixture was warmed up to rt and stirred at rt for 2h, then the mixture was cooled down to 0 °C, and saturated aqueous NaH4Cl was slowly added to quench the reaction. Aqueous phase was extracted with Et2O and the combined organic layer was washed with brine and dried over Na2SO4. The solution was concentrated under reduced pressure to give a residue, which was subjected to chromatography on silica gel column, elution with 25% hexane-EtOAc afforded alcohol ent-2.11.6 (170 mg, 86%). Colorless oil; Rf = 0.41 in 30% hexane/EtOAc; [α]D25 = -72.5 (c 1.16, CH2Cl2); IR (thin film, cm−1) ν 3273 (broad), 2982, 2920, 2888, 1454, 1391, 1364, 1236, 1182, 1151, 1130, 1054, 1037, 1026, 966; 1H NMR (CDCl3, 400 MHz) δ 4.27 (ddd, J = 4.4, 4.2, 2.4 Hz, 1H), δ 3.98 (m, 1H), 3.62 (dd, J = 9.6, 4.6 Hz, 1H), δ 2.80 (d, J = 8.8 Hz, 1H), δ 2.31 (dddd, J = 14.2, 4.6, 2.4, 2.2 Hz, 1H), δ 2.08 (ddqd, J = 9.6, 9.4, 6.6, 3.2 Hz, 1H), δ 1.79-1.88 (m, 1H), 132
$\delta$ 1.53 (s, 3H), 1.35 (s, 3H), $\delta$ 1.58 (ddd, $J = 14.6, 12.2, 2.0$ Hz, 1H), $\delta$ 1.06 (d, $J = 6.4$ Hz, 3H), $\delta$
0.99 (ddd, $J = 13.2, 13.2, 10.8$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 108.4, 80.7, 73.8, 65.5, 37.8, 33.5, 28.9, 28.4, 26.3, 18.8. HRMS (ESI): calcd for [C$_{10}$H$_{18}$O$_3$ + Na]$^+$ 209.1154, found 209.1152.

_Tert-butyl (1S,5S)-5-methyl-4-oxocyclohex-2-enyl carbonate 2.11.2_

Diol _2.11.1_ (250 mg, 1.74 mmol) was dissolved in 15 mL CH$_2$Cl$_2$ at rt, into which 24 mg DMAP (0.2 mmol) was added, followed by addition of a solution of 1.2 g Boc$_2$O (5.6 mmol) in 5 mL CH$_2$Cl$_2$. The mixture was stirred at rt for 2 h, then it was cooled down to 0 °C, diluted with Et$_2$O 30 mL and was then quenched with 10 mL saturated aqueous NaHCO$_3$. The mixture was stirred at 0 °C for another 1 h and then was extracted with Hexane-Et$_2$O (1:2 v/v) 50 mL x 2. The pooled organic layer was washed with 15 mL saturated aqueous NaCl and dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure to afford a residue. The residue was redissolved in 9 mL CH$_2$Cl$_2$ at 0 °C. To this solution, 1.8 mL Et$_3$N (12.9 mmol) was slowly added. The mixture was then stirred at 0 °C overnight and continued to be stirred at rt for another 2 h. Then it was cooled back to 0 °C, diluted with hexane-Et$_2$O (1:1 v/v) 50 mL and was quenched by adding 30 mL 0.5 M NaHSO$_4$ at 0 °C. The aqueous layer was extracted with hexane-Et$_2$O (1:1 v/v) 100 mL X 2. The pooled organic layer was washed with 20 mL saturated aqueous NaHCO$_3$, 20 mL saturated aqueous NaCl and dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure to afford a residue, which was purified by silica gel column. Elution with hexane-EtOAc (10:1 v/v) gave enone _2.11.2_ (325 mg, 83% for two steps) as white
solid; mp: 36.8-38.2 °C; $R_f = 0.49$ (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25} = -175$ (c 1.54, CHCl$_3$); IR (thin film, cm$^{-1}$) $\nu$ 2991, 2969, 2930, 2879, 1731, 1686, 1627, 1454, 1369, 1343, 1274, 1252, 1195, 1156, 1121, 1079, 1067, 1046, 1035, 1026, 1013, 1004, 965; $^1$H NMR (CDCl$_3$, 270 MHz) $\delta$ 6.86 (dd, $J = 10.2$, 4.2 Hz, 1H), $\delta$ 6.04 (dd, $J = 9.9$, 1.0 Hz, 1H), $\delta$ 5.29 (ddd, $J = 4.5$, 4.5, 4.2 Hz, 1H), $\delta$ 2.77 (dqd, $J = 9.6$, 7.2, 4.9 Hz, 1H), $\delta$ 2.25 (ddddd, $J = 13.9$, 4.9, 4.9, 1.0 Hz, 1H), $\delta$ 2.06 (ddd, $J = 13.9$, 9.4, 4.5 Hz, 1H), 1.49 (s, 9H), $\delta$ 1.15 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 67.5 MHz) $\delta$ 201.0, 152.8, 143.3, 131.2, 82.9, 68.1, 37.7, 35.4, 27.7, 14.9. HRMS (ESI): calcd for [C$_{12}$H$_{18}$O$_4$ + H]$^+$: 227.1277, Found: 227.1278.

_Tert-butyl (1S,4R,5S)-4-hydroxy-5-methylcyclohex-2-enyl carbonate 2.11.3_

To a solution of 69 mg enone 2.11.2 (0.30 mmol) in 6 mL THF at $-78$ °C, was added 40 mg LiAlH$_4$ (0.92 mmol) in several portions. The reaction mixture was stirred at $-78$ °C for 30 min, then 2 mL acetone was added dropwise at $-78$ °C and the mixture was stirred for another 20 min to quench the excess LiAlH$_4$. Then it was diluted with 30 mL EtOAc and 6 mL saturated aqueous NH$_4$Cl was added. The mixture was warmed up and stirred at 0 °C for 15 min and then aqueous layer was extracted with EtOAc (30 mL X 2). The pooled organic layer was washed with 5 mL saturated aqueous NH$_4$Cl, 5 mL saturated brine, dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure to give a residue, which was purified by chromatography on silica gel column. Elution with hexane-EtOAc (5:1) afforded allylic alcohol 2.11.3 (60 mg, 90%) as white solid; mp: 81.6-83.6 °C; $R_f = 0.27$ (4:1 v/v hexane/EtOAc); $[\alpha]_D^{25} = -131$ (c 1.05,
CHCl₃; IR (thin film, cm⁻¹) ν 3354, 2974, 1732, 1455, 1370, 1340, 1281, 1256, 1155, 1058, 1035, 945; ¹H (CDCl₃, 600 MHz) δ 5.95 (ddd, J = 9.6, 1.8 Hz, 1H), δ 5.85 (ddddd, J = 10.2, 4.2, 1.8, 1.8 Hz, 1H), δ 4.99 (m, 1H), δ 3.70 (ddd, J = 9.0, 3.6, 1.8 Hz, 1H), δ 1.91 (ddddd, J = 14.4, 3.0, 3.0, 1.8 Hz, 1H), δ 1.82 (ddddd, J = 12.0, 9.6, 6.6, 3.0 Hz, 1H), δ 1.57 (dd, J = 15.0, 12.0, 4.8 Hz, 1H), δ 1.48 (s, 9H), δ 1.07 (d, J = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 153.2, 136.9, 125.4, 82.1, 73.2, 69.1, 34.2, 32.8, 27.8, 18.0; HRMS (ESI) calcd. for [C₁₂H₂₀O₄⁺Na]⁺: 251.1254, Found: 251.1254. HRMS (ESI): calcd for [C₁₂H₂₀O₄⁺Na]⁺: 251.1253, Found: 251.1255.

_Tert-butyl ((1R,5S)-5-methylcyclohex-3-en-1-yl) carbonate 2.11.4_

![Tert-butyl ((1R,5S)-5-methylcyclohex-3-en-1-yl) carbonate](image)

To a solution of allylic alcohol 2.11.3 (5 g, 21.91 mmol) and PPh₃ (17.25 g, 65.84 mmol) in N-methylmorpholine (NMM) (68 mL) at −28 °C, was added dropwise DIAD (10.5 mL, 51.93 mmol). The mixture was stirred at −28 °C for 15 min, then o-nitrobenzenesulfonylhydrazide (NBSH) (14.5 g, 66.8 mmol) was added. It was stirred at −28 °C for 1.5 h and then was warmed up and stirred at rt for another 2 h. The reaction mixture was diluted with hexane-Et₂O (1:1 v/v) and added (1N) aqueous HCl at 0 °C. The aqueous layer was extracted with hexane-Et₂O (1:1 v/v) twice. The combined organic layer was subsequently washed with saturated aqueous NaHCO₃, saturated brine, and dried over Na₂SO₄. The organic layer was concentrated under reduced pressure to give crude product, which was then subjected to chromatography on silica gel. Elution with hexane-EtOAc (20:1, v/v) gave olefin 2.11.4 (4.51 g, 97%). Colorless oil; Rₛ = 0.72 (4:1 v/v hexane/EtOAc); [α]_D²⁵ +25.3 (c 1.3, CH₂Cl₂); IR (thin film, cm⁻¹) ν 3028, 2964,
2880, 1724, 1462, 1394, 1356, 1300, 1264, 1251, 1163, 1098, 1065, 863; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 Mz): δ 5.60 (dddd, J = 9.4, 4.6, 2.4, 2.2 Hz, 1H), δ 5.50 (dddd, J = 10.0, 3.2, 3.0, 1.2 Hz, 1H), δ 4.89 (dddd, J = 12.2, 9.4, 6.6, 2.8 Hz, 1H), δ 2.39-2.43 (m, 1H), δ 2.34 (dddd, J = 12.4, 10.6, 6.4, 3.0 Hz, 1H), δ 2.14 (dddd, J = 12.6, 10.6, 6.2, 2.8 Hz, 1H), δ 1.94 (dddd, J = 12.0, 12.0, 10.6 Hz, 1H), δ 1.49-1.53 (m, 1H), δ 1.46 (s, 9H), δ 1.02 (d, J = 7.2 Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) δ 153.5, 133.2, 122.3, 81.9, 71.2, 34.8, 30.9, 28.1, 27.9, 21.5. HRMS (ESI): calcd for [C\textsubscript{12}H\textsubscript{20}O\textsubscript{3} + Na]\textsuperscript{+}: 235.1304, Found: 235.1304.

\textit{Tert-buty1 ((3aS,5S,7S,7aR)-2,2,7-trimethylhexahydrobenzol\textsubscript{d}[1,3]dioxol-5-yl) carbonate 2.11.5}

To a solution of olefin 2.11.4 (225 mg, 1.06 mmol) in \textit{t}-BuOH-acetone-50% NMO (aq.) (3 mL, 1:1:1 v/v/v), was added a small piece of crystalline OsO\textsubscript{4} at 0 °C. The reaction mixture was stirred at 0 °C for 8 h, then was diluted with EtOAc followed by addition of saturated aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{4} (3 mL). The mixture was stirred at 0 °C for another 30 min and passed through a pad of celite, rinsing with EtOAc. The eluent was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure to give a residue. Crude \textsuperscript{1}H-NMR showed that the diastereoselectivity is about 11:1. The residue was subjected to chromatography on silica gel column, eluting with hexane-EtOAc (1:1.5, v/v) gave inseparable mixture of diol. The resulted diol mixture was treated with dimethoxypropane (DMP) (1 mL) in the presence of \textit{p}-TsOH•H\textsubscript{2}O (4.5 mg, 0.025 mmol) at 0 °C for 2h. It was diluted with EtOAc and quenched by addition of saturated aqueous NaHCO\textsubscript{3} at
0 °C. The aqueous layer was extracted with EtOAc twice. The combined organic layer was washed with saturated brine and dried over Na₂SO₄. The solution was concentrated under reduced pressure to give a residue, which was subjected to silica gel column chromatography. Elution with hexane-EtOAc (20:1, v/v) afforded acetonide 2.11.5 (243 mg, 80%) with the minor diastereomer removed. Colorless oil; R⃗ f = 0.68 (1:1 (v/v) hexane/EtOAc); [α]D25 +2.3 (c 0.86, CH₂Cl₂); IR (thin film, cm⁻¹) ν 2871, 1732, 1460, 1326, 1276, 1254, 1217, 1153, 1100, 1023, 986; ¹H NMR (CDCl₃, 400 MHz) δ 4.72 (dddd, J = 10.6, 10.4, 4.8, 4.8 Hz, 1H), δ 4.20 (dd, J = 13.2, 6.0 Hz, 1H), δ 3.71 (dd, J = 6.0, 5.4 Hz, 1H), δ 2.09-2.21 (m, 2H), δ 2.00 (dd, J = 14.2, 12.6, 3.2 Hz, 1H), δ 1.84 (dddd, J = 12.6, 3.6, 3.2, 3.0 Hz, 1H), δ 1.49 (s, 9H), 1.48 (s, 3H), δ 1.43-1.46 (m, 1H), δ 1.34 (s, 3H), δ 1.06 (d, J = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 153.3, 108.5, 82.1, 79.5, 72.3, 70.2, 33.8, 33.1, 29.3, 28.5, 28.0, 26.2, 18.6. HRMS (ESI): calcd for [C₁₅H₂₆O₅ + Na]⁺ 309.1672, Found: 309.1673.

(3aS,5S,7S,7aR)-2,2,7-trimethylhexahydrobenzo[d][1,3]dioxol-5-ol 2.11.6

To a solution of carbonate 2.11.5 (5.1 g, 17.81 mmol) in THF (150 mL) at 0 °C, was added LiAlH₄ (1.35 g, 35.6 mmol). The reaction mixture was warmed up and stirred at rt for 4 h, then the mixture was cooled down to 0 °C, and saturated aqueous Na₂SO₄ was slowly added while stirring to quench excess LiAlH₄. The mixture was passed through a pad of celite, rinsing with EtOAc. The eluent was dried over Na₂SO₄. The solution was concentrated under reduced pressure to give a residue, which was subjected to chromatography on silica gel column, elution
with 30-35% hexane-EtOAc afforded alcohol \textbf{2.11.6} (3.2 mg, 96.5%). Colorless oil; \(R_f = 0.25\) (20% hexane/EtOAc); \([\alpha]_D^{25} +125.4\ (c 1.2, \text{CH}_2\text{Cl}_2)\); IR (thin film, cm\(^{-1}\)) \(\nu 3300\) (broad), 2981, 2920, 2888, 1436, 1373, 1364, 1213, 1179, 1150, 1064, 1040, 1026, 966; \(^1^H\) NMR (CDCl\(_3\), 400 MHz) \(\delta 4.27\) (dd, \(J = 7.2, 4.4\) Hz, 1H), \(\delta 3.98\) (ddd, \(J = 11.6, 10.8, 3.6\) Hz, 1H), \(\delta 3.60\) (dd, \(J = 8.8, 4.4\) Hz, 1H), \(\delta 2.79\) (d, \(J = 8.8\) Hz, 1H), \(\delta 2.32\) (dddd, \(J = 14.6, 10.8, 3.2, 2.8\) Hz, 1H), \(\delta 2.02-2.13\) (m, 1H), \(\delta 1.79-1.88\) (m, 2H), \(\delta 1.53\) (s, 3H), \(\delta 1.35\) (s, 3H), \(\delta 1.55\) (ddd, \(J = 14.2, 10.8, 3.8\) Hz, 1H), \(\delta 1.06\) (d, \(J = 6.4\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta 108.5, 80.8, 73.9, 65.7, 37.9, 33.4, 29.1, 28.4, 26.4, 18.9\). HRMS (ESI): calcd. for [C\(_{10}\)H\(_{18}\)O\(_3\) + Na]\(^+\) 209.1154, found 209.1152.

\(N,N\)-diethyl-2-(8-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3-methoxy-5-methylbenz amide \textbf{1.14.2}

A suspension of juglone \textbf{2.7.3} (422 mg, 1.67 mmol), stannane \textbf{2.6.6} (936 mg, 1.84 mmol), and CuI (63.5 mg, 0.33 mmol) in 7 mL dry THF at RT was vacuum degassed and backfilled with Ar. To this mixture, added a solution of Pd\(_2\)(dba)\(_3\)•CHCl\(_3\) (86.4 mg, 0.084 mmol) and PPh\(_3\) (88 mg, 0.334 mmol) in THF (2 mL) under Ar. The mixture was stirred at 80 °C for 12 h. It was then cooled down to 0 °C, diluted with EtOAc (10 mL), and quenched with saturated aqueous NaHCO\(_3\) (20 mL). The mixture was stirred at 0 °C for 30 min. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine and dried over Na\(_2\)SO\(_4\). After removal of the solvent, the residue was subjected to silica gel column
chromatography, eluting with hexane/EtOAc (3:1, v/v) afforded coupled product **1.14.2** (498 mg, 75.6%). Redish-brown solid, exits a mixture of rotomer; mp: 159 ºC; \( R_f \) (hexanes/EtOAc, 3:1 v/v) = 0.09; IR (thin film, cm\(^{-1}\)) \( \nu \) 3470, 3065, 2975, 2919, 2903, 2866, 2842, 1654, 1578, 1446, 1379, 1342, 1290, 1258, 1244, 1146, 1096, 1053, 1014; \(^1\)H NMR for the major rotomer (CDCl\(_3\), 400 MHz): \( \delta \) 12.05 (s, 1H), \( \delta \) 7.63 (s, 1H), \( \delta \) 7.62 (s, 1H), \( \delta \) 7.27 (dd, \( J = 8.2, 8.1 \) Hz 1H), \( \delta \) 6.93 (s, 1H), \( \delta \) 6.82 (s, 1H), \( \delta \) 6.79 (s, 1H), \( \delta \) 3.77 (s, 3H), \( \delta \) 3.56 (m, 1H), \( \delta \) 3.27 (dq, \( J = 2.1, 7.2 \) Hz, 1H), \( \delta \) 3.19-3.05 (m, 2H), \( \delta \) 2.42 (s, 3H), \( \delta \) 1.06 (t, \( J = 7.6 \) Hz, 3H), \( \delta \) 0.94 (t, \( J = 7.2 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 189.0, 184.1, 169.1, 161.7, 157.3, 141.5, 138.6, 138.1, 136.5, 132.3, 124.3, 124.1, 118.9, 118.7, 116.9, 115.2, 112.3, 55.9, 42.9, 38.5, 21.9, 14.1, 12.3; HRMS (ESI): calcd for \([C_{23}H_{23}NO_5 + H]^+\) 394.1654, found 394.1646.

\[ 2-(1,4\text{-dioxo-5-((((3aS,5R,7S,7aR)-2,2,7-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)oxy)-1,4-dihydronaphthalen-2-yl}-N,N-diethyl-3-methoxy-5-methylbenzamide 2.15.1 \]

Phenol **2.14.1** (90 mg, 0.23 mmol) and cyclitol **2.11.6** (47 mg, 0.25 mmol) was dissolved in 2.0 mL dry THF. To this added PPh\(_3\) (202 mg, 0.69 mmol), after forming a homogeneous solution, it was cooled to 0 ºC and a THF solution of DIAD (135.3 \( \mu \)L, 0.69 mmol in 0.2 mL THF) was added drop wise. The reaction was stirred at 0 ºC for 2h. Diluted with EtOAc (5.0 mL), and quenched by saturated aqueous NaHCO\(_3\) (20 mL). The mixture was stirred at 0 ºC for 30...
min and the aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na$_2$SO$_4$. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 25% hexane/EtOAc afforded product **2.15.1** (105 mg, 81%). Redish-brown solid, exits a mixture of rotomer; mp: 186 °C; $R_f$ 30% hexanes/EtOAc = 0.31; $[\alpha]_D^{25}$ −10.5 ($c$ 2.1, CH$_2$Cl$_2$), IR (thin film, cm$^{-1}$) ν 2866, 2842, 1741, 1654, 1578, 1379, 1342, 1290, 1278, 1244, 1148, 1096, 1053, 1010; $^1$H NMR for the major rotomer (CDCl$_3$, 400 MHz): δ 7.73 (d, $J$ = 7.2 Hz, 1H), δ 7.61 (dd, $J$ = 8.0, 7.2 Hz, 1H), δ 7.34 (d, $J$ = 8.0 Hz 1H), δ 6.86 (s, 1H), δ 6.78 (s, 1H), δ 6.76 (s, 1H), δ 4.68 (dddd, $J$ = 6.0, 6.0, 4.4, 4.4 Hz, 1H), δ 4.41 (dd, $J$ = 5.2, 2.8 Hz, 1H), δ 3.74 (s, 3H), δ 3.69-3.67 (m, 2H), δ 3.26 (ddd, $J$ = 7.2, 7.2, 6.8 Hz, 1H), δ 3.01-3.11 (m, 2H), δ 2.60 (dd, $J$ = 14.8, 2.1 Hz, 1H), δ 2.39 (s, 3H), δ 1.54-1.85 (m, 2H), δ 1.49 (s, 3H), δ 1.36 (s, 3H), δ 1.18-1.33 (m, 1H), δ 1.07 (d, $J$ = 6.4 Hz, 3H), δ 1.02 (t, $J$ = 7.2 Hz, 3H), δ 0.93 (t, $J$ = 7.4 Hz, 3H), 0.92 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 184.0, 183.6, 169.4, 157.82, 157.4, 141.2, 139.9, 138.3, 135.1, 134.4, 121.6, 120.3, 118.9, 117.7, 112.9, 112.4, 108.5, 80.7, 74.3, 56.1, 42.9, 38.6, 36.8, 33.7, 32.9, 28.7, 26.3, 24.9, 22.0, 18.9, 14.1, 12.6; HRMS (ESI): calcd for [C$_{33}$H$_{39}$NO$_7$ + H]$^+$ 562.2805, found 562.2825.

**12-hydroxy-10-methoxy-8-methyl-1-(((3aS,5R,7S,7aR)-2,2,7-trimethylhexahydrobenzo[d]-[1,3]dioxol-5-yloxy)-6H-dibenzo[c,h]chromen-6-one 2.15.2**

![Image](https://via.placeholder.com/150)

Quinone **2.15.1** (90 mg, 0.16 mmol) was dissolved in 2.4 mL THF and degassed by bubbling
argon through the solution. In a separate flask, \( n \)-Bu\(_4\)NBr (15 mg, 0.04 mmol) and Na\(_2\)S\(_2\)O\(_4\) (279 mg, 1.6 mmol) was dissolved in distilled H\(_2\)O (4.7 mL). The aqueous solution was degased by bubbling argon and transferred to the flask containing quinone via cannula. The reaction mixture was stirred for 1h. Reduction of quinone to hydroquinone was monitored with the disappearance of orange color (color of quinone). Degassed Et\(_2\)O was added and the organic phase was extracted via cannula. The organic extract was concentrated under reduced pressure without exposure to air. The crude residue of hydroquinone was dissolved in HOAc (2.5 mL) and refluxed under argon for 2h. Light yellow precipitate of the lactonized product starts to form after 1h. The reaction was then cooled to 0 °C and added 10 mL H\(_2\)O. The precipitate was collected using a Hirsch funnel and washed with H\(_2\)O and hexane to obtain \( \mathbf{2.15.2} \) (49 mg, 62%). Yellow solid; mp: 268 °C; \( R_f \) (0% hexanes/EtOAc) = 0.78; \([\alpha]_D^{25} \) = −24.5, (c 0.4, CH\(_2\)Cl\(_2\)). IR (thin film, cm\(^{-1}\)) \( \nu \) 3415, 3122, 2927, 2854, 1724, 1655, 1638, 1455, 1368, 1240, 1151, 951, 875, 801; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 9.34 (s, 1H), \( \delta \) 8.37 (s, 1H), \( \delta \) 8.23 (d, \( J = 8.8 \) Hz, 1H), \( \delta \) 7.96 (s, 1H), \( \delta \) 7.46 (dd, \( J = 8.0, 8.0 \) Hz, 1H), \( \delta \) 7.16 (s, 1H), \( \delta \) 7.04 (d, \( J = 7.2 \) Hz, 1H), \( \delta \) 4.91 (dddd, \( J = 6.0, 6.0, 4.4, 3.8 \) Hz, 1H), \( \delta \) 4.42 (dd, \( J = 6.8, 4.4 \) Hz, 1H), \( \delta \) 4.08 (s, 3H), \( \delta \) 3.68 (dd, \( J = 8.8, 4.4 \) Hz, 1H), \( \delta \) 2.83 (dq, \( J = 9.0, 6.4 \) Hz, 1H), \( \delta \) 2.50 (s, 3H), \( \delta \) 2.19 (ddd, \( J = 12.8, 6.8, 3.6 \) Hz, 1H), \( \delta \) 1.98 (ddd, \( J = 14.2, 10.6, 4.4 \) Hz, 1H), \( \delta \) 1.79-1.89 (m, 1H), \( \delta \) 1.59 (s, 3H), \( \delta \) 1.36-1.40 (m, 1H), \( \delta \) 1.39 (s, 3H), \( \delta \) 1.17 (d, \( J = 6.4 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 161.6, 157.7, 153.5, 150.1, 140.1, 139.5, 126.7, 126.2, 123.4, 122.8, 121.9, 118.2, 116.6, 117.7, 115.2, 109.0, 108.8, 107.7, 80.5, 75.0, 74.2, 56.1, 36.9, 33.9, 33.2, 28.7, 26.3, 21.8, 18.8; HRMS (ESI): calcd for [C\(_{29}\)H\(_{30}\)O\(_7\) − H\(^+\)]\(^+\) 489.1913, found 489.1915.
Phenol 2.15.2 (60 mg, 0.12 mmol) was dissolved in 1.5 mL dry THF. The mixture was cooled to 0 °C and added MeI (76.2 µL, 1.22 mmol). After 5 min at this temperature, added a THF solution of t-BuOK (16.5 mg, 0.15 mmol in 0.5 mL THF). The reaction was stirred under argon from 0 °C to rt over 1h. Diluted with Et₂O and quenched with saturated NH₄Cl. The aqueous layer was extracted with Et₂O twice and the combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 25-30% hexane-EtOAc gave 2.13.1 (46 mg, 76%). Light yellow color amorphous solid; mp: 145-146 °C;  

\[ \alpha_D^{25} -9.3, (c 0.3, \text{CH}_2\text{Cl}_2) \]

IR (thin film, cm⁻¹) ν 2930, 2850, 1741, 1635, 1541, 1368, 1244, 1151, 951, 866; ¹H NMR (CDCl₃, 400 MHz): δ 8.43 (s, 1H), δ 8.28 (d, J = 8.8 Hz, 1H), δ 7.97 (s, 1H), δ 7.49 (dd, J = 8.4, 8.0 Hz, 1H), δ 7.18 (s, 1H), δ 7.11 (d, J = 8.0 Hz, 1H), δ 4.63 (dddd, J = 6.4, 6.0, 4.4, 3.2 Hz, 1H), δ 4.45 (dd, J = 8.0, 5.2 Hz, 1H), δ 4.09 (s, 3H), δ 4.02 (s, 3H), δ 3.68 (dd, J = 9.2, 5.2 Hz, 1H), δ 2.63-2.66 (m, 1H), δ 2.51 (s, 3H), δ 2.02-2.12 (m, 2H), δ 1.70-1.75 (m, 1H), δ 1.57 (s, 3H), δ 1.37 (s, 3H), δ 1.35-1.37 (m, 1H), δ 1.07 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 161.7, 157.4, 154.2, 152.8, 140.9, 139.9, 127.2, 123.0, 122.2, 119.4, 118.3, 116.3, 114.7, 113.7, 108.4, 107.9, 105.0, 80.9, 74.9, 74.3, 56.9, 56.4, 36.6, 33.6, 33.2, 28.7, 26.2, 21.8, 18.9; HRMS (ESI): calcd for [C₃₀H₃₂O₇ + H]⁺ 505.2226, found 505.2216.
**1-(((1R,3S,4R,5S)-3,4-dihydroxy-5-methylcyclohexyl)oxy)-10,12-dimethoxy-8-methyl-6H-dibenzo[c,h]chromen-6-one 2.6.2**

Acetonide **2.13.1** (40 mg, 0.08 mmol) was dissolved in 3.0 mL THF. The mixture was cooled to 0 °C and added a 10% (v/v) aqueous solution of HCl (3.0 mL). The reaction was allowed to warm up from 0 °C to rt over 1h. Diluted with EtOAc and quenched with saturated NaHCO₃. The aqueous layer was extracted with EtOAc (3 X 10 mL) and the combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to recrystallization from CH₂Cl₂/hexane to get pure **2.6.2** (26 mg, 70%). Light yellow color amorphous solid; mp: 250 °C; *R*<sub>f</sub> (50% hexanes/EtOAc) = 0.15; [α]_<sub>D</sub><sup>25</sup> −12.5, (c 0.4, CH₂Cl₂), IR (thin film, cm<sup>−1</sup>) <i>υ</i> 3429, 3300, 2945, 2781, 1741, 1654, 1368, 1236, 1150, 1070, 805; <sup>1</sup>H NMR (CDCl₃, 400 MHz): δ 8.42 (s, 1H), δ 8.27 (d, <i>J</i> = 8.4 Hz, 1H), δ 7.97 (s, 1H), δ 7.49 (dd, <i>J</i> = 8.8, 7.6 Hz, 1H), δ 7.18 (s, 1H), δ 7.13 (d, <i>J</i> = 8.4 Hz, 1H), δ 4.69 (dddd, <i>J</i> = 6.4, 6.2, 4.4, 2.8 Hz, 1H), δ 4.18 (dd, <i>J</i> = 8.0, 3.2 Hz, 1H), δ 4.09 (s, 3H), δ 4.01 (s, 3H), δ 3.36 (d, <i>J</i> = 9.6 Hz, 1H), δ 2.59 (dd, <i>J</i> = 8.6, 2.8 Hz, 1H), δ 2.51 (s, 3H), δ 2.19-2.23 (m, 2H), δ 1.91-1.95 (m, 1H), δ 1.78 (ddd, <i>J</i> = 14.0, 10.8, 3.2 Hz, 1H), δ 1.40 (dd, <i>J</i> = 11.2, 10.2 Hz, 1H), δ 1.09 (d, <i>J</i> = 6.8 Hz, 3H); <sup>13</sup>C NMR (CDCl₃, 100 MHz): δ 161.9, 157.6, 154.2, 151.9, 141.2, 139.9, 132.0, 131.1 127.2, 126.3, 125.4, 122.2, 119.4, 118.3, 117.2, 109.8, 107.9, 80.0, 74.9, 74.8, 56.9, 56.5, 38.2, 36.1, 28.8, 24.2, 21.7. HRMS (ESI): calcd for [C<sub>27</sub>H<sub>28</sub>O<sub>7</sub> + H]<sup>+</sup> 465.1913, found 465.1914.

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1-(((1R,3S,4R,5S)-3,4-dihydroxy-5-methylcyclohexyl)oxy)-12-hydroxy-10-methoxy-8-methyl-6H-dibenzo[c,h]chromen-6-one 2.15.3

Acetonide 2.15.2 (15 mg, 0.03 mmol) was dissolved in 2.0 mL THF. The mixture was cooled to 0 °C and added 10% (v/v) aqueous solution of HCl (2.0 mL). The reaction was allowed to warm up from 0 °C to rt over 30 min. Diluted with EtOAc and quenched with saturated NaHCO₃. The aqueous layer was extracted with EtOAc (2 X 10 mL) and the combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to recrystallization from CH₂Cl₂/hexane to get pure 2.15.3 (9.5 mg, 70%). Light yellow color amorphous solid; mp: 268 °C; R_f (70% hexanes/EtOAc) = 0.14; [α]D²⁵ −7.2, (c 0.6, CH₂Cl₂), IR (thin film, cm⁻¹) ν 3430, 3316, 3298 2941, 2780, 1765, 1694, 1226, 1070, 868; ¹H NMR (CDCl₃, 400 MHz): δ 8.42 (s, 1H), δ 8.37 (s, 1H), δ 8.22 (d, J = 8.8 Hz, 1H), δ 7.96 (s, 1H), δ 7.45 (dd, J = 8.0, 8.0 Hz, 1H), δ 7.17 (s, 1H), δ 7.06 (d, J = 7.2 Hz, 1H), δ 5.01 (dddd, J = 6.0, 6.0, 3.6, 2.8 Hz, 1H), δ 4.19 (s, 1H), δ 4.08 (s, 3H), δ 3.36 (dd, J = 9.6, 1.8 Hz, 1H), δ 2.68 (dd, J = 8.6, 2.8 Hz, 1H), δ 2.51 (s, 3H), δ 2.41 (bs, 1H), δ 2.33 (dd, J = 8.4, 3.0 Hz, 1H), δ 2.02 (m, 2H), δ 1.74 (dddd, J = 14.2, 10.6, 3.2 Hz, 1H), δ 1.41 (dd, J = 11.4, 9.8 Hz, 1H), δ 1.12 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 161.8, 157.9, 154.6, 151.2, 141.0, 140.1, 132.2, 130.9 126.8, 125.4, 122.3, 119.5, 118.2, 117.4, 117.1, 109.9, 107.9, 81.8, 73.6, 71.2, 56.2, 36.4, 36.2, 26.9, 22.3, 19.8; HRMS (ESI): calcd for [C₂₆H₂₆O₇ + H]^+ 451.1757, found 451.1749.
2-(1,4-dioxo-8-(((3aS,5R,7S,7aR)-2,2,7-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)oxy)-1,4-dihyronaphthalen-2-yl)-N,N-diethyl-3-methoxy-5-methylbenzamidide 2.18.1

Phenol 2.14.2 (77 mg, 0.20 mmol) was dissolve in 0.9 mL dry THF and cooled to −30 °C. To this added a 0.7 mL THF solution of cyclitol 2.11.6 (40 mg, 0.22 mmol) and 115 μL, 0.58 mmol DIAD dissolved in 1.2 mL THF. To this cooled solution, added a 1.2 mL THF solution of PPh₃ (103 mg, 0.39 mmol) very slowly over 1 h (second drop of PPh₃ solution was not added until the dark color faded). The reaction was stirred at this temperature for 2 h and quenched with saturated aqueous NaHCO₃ (5 mL). After separation of the two layers, the aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 26% hexane/EtOAc afforded product 2.18.1 (80 mg, 73%). Redish-brown solid, exits a mixture of rotomer; mp: 190 °C; $R_f$ (30% hexanes/EtOAc) = 0.35; $[\alpha]_D^{25} = -33.2$, (c 2.5, CH₂Cl₂), IR (thin film, cm⁻¹) ν 2930, 2840, 1743 1690, 1329, 1310, 1290, 1164, 1096, 1053, 866; ¹H NMR for the major rotomer (CDCl₃, 400 MHz): δ 7.73 (d, $J = 7.2$ Hz, 1H), δ 7.61 (dd, $J = 8.4, 8.0$ Hz, 1H), δ 7.33 (d, $J = 8.0$ Hz 1H), δ 6.94 (s, 1H), δ 6.77 (s, 1H), δ 6.76 (s, 1H), δ 4.66 (dddd, $J = 6.2, 6.0, 4.4, 3.2$ Hz, 1H), δ 4.38 (dd, $J = 5.4, 2.8$ Hz, 1H), δ 3.74 (s, 3H), δ 3.69 (m, 1H), δ 3.62 (dd, $J = 9.2, 4.8$ Hz, 1H), δ 3.27 (dddd, $J = 7.2, 7.0, 6.8$ Hz, 1H), δ 2.94-3.06 (m, 2H), δ 2.59 (m, 1H), δ 2.39 (s, 3H), δ 2.00-2.04 (m, 1H), δ 1.70-1.74 (m, 2H), δ 1.48 (s, 3H), δ 1.34 (s, 3H), 1.24 (m, 1H), δ 1.05 (d, $J = 6.4$ Hz, 3H), δ 0.98 (t, $J = 7.4$ Hz, 3H).
Hz, 3H ), δ 0.94 (t, J = 7.4 Hz, 3H); 13C NMR (CDCl3, 100 MHz): δ 184.9, 183.8, 169.2, 157.7, 157.2, 147.8, 141.4, 138.1, 135.2, 134.7, 134.4, 122.2, 121.6, 119.5, 112.4, 112.3, 108.5, 80.6, 74.1, 56.0, 42.8, 38.5, 36.7, 33.5, 32.9, 28.6, 26.2, 24.8, 22.0, 18.8, 14.0, 12.4; HRMS (ESI): calcd for [C33H39NO7 + H]⁺ 562.2805, found 562.2809.

12-hydroxy-10-methoxy-8-methyl-4-(((3aS,5R,7S,7aR)-2,2,7-trimethylhexahydrobenzo[d]-[1,3]-dioxol-5-yl)oxy)-6H-dibenzo-[c,h]-chromen-6-one 2.18.2

Quinone 2.18.1 (94.7 mg, 0.17 mmol) was dissolved in 3.5 mL THF and degassed by bubbling argon through the solution. In a separate flask, n-Bu₄NBr (30 mg, 0.08 mmol) and Na₂S₂O₄ (296 mg, 1.7 mmol) was dissolved in distilled H₂O (7 mL). The aqueous solution was degassed by bubbling argon and transferred to the flask containing quinone via cannula. The reaction mixture was stirred for 1h. Reduction of quinone to hydroquinone was monitored with the disappearance of orange color (color of quinone). Degassed Et₂O was added and the organic phase was extracted via cannula. The organic extract was concentrated under reduced pressure without exposure to air. The crude residue of hydroquinone was dissolved in HOAc (3.5 mL) and refluxed under argon for 2h. Light yellow precipitate of the lactonized product started to form after 1h. The reaction was then cooled to 0 °C and added 10 mL H₂O. The precipitate was collected using a Hirsch funnel and washed with H₂O and hexane to obtain 2.18.2 (54 mg, 65%). Yellow solid; mp: 244 °C; Rf (30% hexanes/EtOAc) = 0.65; [α]D²⁵ = −3.21, (c 1.1, CH₂Cl₂), IR (thin film, cm⁻¹) ν 3416, 3060, 2930, 2854, 1721, 1652, 1627, 1496, 1368, 1241, 1154, 826,
1,12-dimethoxy-8-methyl-4-(((3aS,5R,7S,7aR)-2,2,7-trimethylhexahydrobenzo-[d]-[1,3]-dioxol-5-yl)oxy)-6H-dibenzo-[c,h]-chromen-6-one 2.18.3

Phenol 2.18.2 (50 mg, 0.1 mmol) was dissolved in 3 mL dry THF. The mixture was cooled to 0 ºC and added MeI (62 µL, 0.99 mmol). After 5 min at this temperature, added a THF solution of t-BuOK (13.45 mg, 0.12 mmol in 1.0 mL THF). The reaction was stirred under argon from 0 ºC to rt over 1h. Diluted with Et₂O and quenched with saturated NH₄Cl. The aqueous layer was extracted with Et₂O twice and the combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 25-30% hexane-EtOAc gave 2.18.3 (40.3 mg, 80%). Light yellow color amorphous solid; mp: 149 ºC; Rf (30% hexanes/EtOAc) = 0.5; [α]D²⁵ = +19.5, (c 1.00, CH₂Cl₂), IR (thin film, cm⁻¹) ν 2898, 2850, 1743, 1715, 1493, 1368, 1242, 1157, 1035, 866; ¹H NMR (Acetone-d₆, 400 MHz): δ 9.06 (s, 1H), δ 8.73 (s, 1H), δ 7.93 (d, J = 8.0 Hz, 1H), δ 7.85 (s, 1H), δ 7.52 (dd, J = 8.0, 8.0 Hz, 1H), δ 7.44 (s, 1H), δ 7.22 (d, J = 7.6 Hz, 1H), δ 4.81 (dddd, J = 6.4, 6.2, 4.0, 3.8 Hz, 1H), δ 4.65 (dd, J = 5.2, 1.6 Hz, 1H), δ 4.11 (s, 3H), δ 3.76 (dd, J = 9.6, 5.2 Hz, 1H), δ 2.51 (s, 3H), δ 2.08 (m, 1H); ¹³C NMR (Acetone-d₆, 100 MHz): δ 163.7, 161.3, 158.3, 155.6, 149.4, 149.1, 148.2, 140.8, 127.7, 122.5, 119.2, 115.8, 113.8, 108.4, 107.2, 81.3, 74.9, 74.6, 56.9, 34.1, 33.6, 28.9, 26.3, 21.5, 19.1; HRMS (ESI): calcd for [C₂₉H₃₀O₇]⁺ 490.1991, found 490.1987.
NMR (CDCl$_3$, 400 MHz): $\delta$ 8.46 (s, 1H), $\delta$ 7.91 (s, 1H), $\delta$ 7.92 (d, $J = 8.8$ Hz, 1H), $\delta$ 7.47 (dd, $J = 8.0$, 7.4 Hz, 1H), $\delta$ 7.16 (d, $J = 7.2$ Hz, 1H), $\delta$ 7.13 (s, 1H), $\delta$ 4.76 (dddd, $J = 6.4$, 6.2, 4.2, 3.6 Hz, 1H), $\delta$ 4.55 (dd, $J = 8.8$, 5.2 Hz, 1H), $\delta$ 4.06 (s, 3H), $\delta$ 4.05 (s, 3H), $\delta$ 3.74 (dd, $J = 9.6$, 5.2 Hz, 1H), $\delta$ 2.67-2.73 (m, 1H), $\delta$ 1.54 (ddd, $J = 12.0$, 6.4, 2.8, 1H), $\delta$ 1.38 (s, 3H), $\delta$ 1.08 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 161.4, 157.1, 154.8, 150.9, 141.8, 139.5, 128.4, 127.2, 122.9, 122.7, 122.5, 118.1, 117.5, 114.9, 113.6, 108.2, 102.8, 80.9, 74.7, 74.4, 56.4, 55.7, 36.5, 33.7, 32.9, 28.7, 26.2, 21.8, 18.9; HRMS (ESI): calcd for $[C_{30}H_{32}O_7 + H]^+$ 505.2226, found 505.2217.

4-(((1$R$,3$S$,4$R$,5$S$)-3,4-dihydroxy-5-methylcyclohexyl)oxy)-10,12-dimethoxy-8-methyl-6H-dibenzo[c,h]chromen-6-one 2.6.1

Acetonide 2.18.3 (19 mg, 0.04 mmol) was dissolved in 2.5 mL THF. The mixture was cooled to 0 ºC and added 10% (v/v) aqueous solution of HCl (2.5 mL). The reaction was allowed to warm up from 0 ºC to rt over 1h. Diluted with EtOAc and quenched with saturated NaHCO$_3$. The aqueous layer was extracted with EtOAc (3 X 10 mL) and the combined organic layer was washed with saturated brine, and dried over Na$_2$SO$_4$. After removal of the solvent, the residue was subjected to recrystallization from CH$_2$Cl$_2$/hexane to get pure 2.6.1 (13.3 mg, 72%). Light yellow amorphous solid; mp: 250 ºC; $R_f$ (50% hexanes/EtOAc) = 0.25; $\lbrack \alpha \rbrack_D^{25}$ =−23.1, (c 0.8, CH$_2$Cl$_2$), IR (thin film, cm$^{-1}$) $\nu$ 3430, 3310, 2928, 2781, 1740, 1658, 1413, 1232, 1187, 1023, 866; $^1$H NMR (Acetone-$d_6$, 400 MHz): $\delta$ 8.55 (s, 1H), $\delta$ 7.87 (d, $J = 8.0$ Hz, 1H), $\delta$ 7.81 (s, 1H), $\delta$ 7.81 (s, 1H), $\delta$ 7.81 (s, 1H), $\delta$ 7.81 (s, 1H).
δ 7.52 (dd, J = 8.0, 8.0 Hz, 1H), δ 7.39 (s, 1H), δ 7.24 (d, J = 8.4 Hz, 1H), δ 4.69 (dddd, J = 6.2, 6.2, 4.2, 3.6 Hz, 1H), δ 4.14 (s, 3H), δ 4.10 (m, 1H), δ 4.06 (s, 3H), δ 2.27 (dd, J = 10.0, 2.8 Hz, 1H), δ 2.85 (d, J = 13.6 Hz, 1H), δ 2.57 (dddd, J = 10.2, 7.2, 3.6 Hz, 1H), δ 4.69 (dddd, J = 6.2, 6.2, 4.2, 3.6 Hz, 1H), δ 2.85 (d, J = 13.6 Hz, 1H), δ 2.57 (dddd, J = 10.2, 7.2, 3.6 Hz, 1H), δ 2.49 (s, 3H), δ 1.78 (ddd, J = 10.0, 7.6, 3.2 Hz, 1H), δ 2.06 (s, 3H), δ 1.78 (ddd, J = 10.0, 7.6, 3.2 Hz, 1H), δ 2.06 (s, 3H), δ 1.52 (dd, J = 12.8, 12.2 Hz, 1H), δ 1.07 (d, J = 6.4 Hz, 3H); 13C NMR (Acetone-d6, 100 MHz): δ 160.2, 156.9, 154.7, 150.2, 140.9, 139.9, 127.2, 127.5, 121.9, 121.4, 121.1, 118.8, 116.5, 114.0, 113.4, 112.9, 102.4, 76.2, 74.2, 69.4, 56.6, 55.6, 38.2, 37.2, 30.9, 21.2, 18.9; HRMS (ESI): calcd for [C27H28O7 + H]+ 465.1913, found 465.1914.

4-(((1R,3S,4R,5S)-3,4-dihydroxy-5-methylcyclohexyl)oxy)-12-hydroxy-10-methoxy-8-methyl-6H-dibenzo[c,h]chromen-6-one 2.18.4

Acetonide 2.18.2 (10 mg, 0.02 mmol) was dissolved in 1.0 mL THF. The mixture was cooled to 0 ºC and added 10% (v/v) aqueous solution of HCl (1.0 mL). The reaction was allowed to warm up from 0 ºC to rt over 30 min. Diluted with EtOAc and quenched with saturated NaHCO3. The aqueous layer was extracted with EtOAc (2 X 10 mL) and the combined organic layer was washed with saturated brine, and dried over Na2SO4. After removal of the solvent, the residue was subjected to recrystallization from CH2Cl2/hexane to get pure 2.18.4 (7.2 mg, 80%). Light yellow amorphous solid; mp: 290 ºC; Rf (50% hexanes/EtOAc) = 0.25; [α]D25 −7.6, (c 0.5, CH2Cl2), IR (thin film, cm−1) ν 3424, 3330, 3300, 2916, 2854, 1741, 1685, 1443, 1228, 946; 1H NMR (DMSO-d6, 400 MHz): δ 10.11 (s, 1H), δ 8.57 (s, 1H), δ 7.80 (d, J = 8.8 Hz, 1H), δ 7.77
(s, 1H), δ 7.49 (dd, J = 8.2, 8.0 Hz, 1H), δ 7.48 (s, 1H), δ 7.17 (d, J = 8.0 Hz, 1H), δ 4.69 (dddd, J = 6.4, 6.0, 3.6, 2.8 Hz, 1H), δ 4.43 (d, J = 2.8 Hz, 1H), δ 4.36 (d, J = 6.8 Hz, 1H), δ 4.08 (s, 3H), δ 3.91 (m, 2H), δ 3.06 (ddd, J = 9.6, 6.4, 2.8 Hz, 1H), δ 4.43 (d, J = 2.8 Hz, 1H), δ 4.36 (d, J = 6.8 Hz, 1H), δ 4.08 (s, 3H), δ 3.91 (m, 2H), δ 3.06 (ddd, J = 9.6, 6.4, 2.8 Hz, 1H), δ 2.23 (ddd, J = 10.2, 6.8, 3.2 Hz, 1H), δ 0.97 (d, J = 6.4 Hz, 3H); 13C NMR (DMSO-d6, 100 MHz): δ 160.0, 157.1, 154.4, 150.2, 148.3, 142.1 139.8, 128.1, 127.8, 121.9, 121.4, 121.1, 119.2, 116.0, 114.2, 113.2, 105.6, 76.1, 74.2, 69.3, 56.4, 38.1, 37.1, 30.8, 21.1, 18.7; HRMS (ESI): calcd for [C26H26O7 + H]+ 451.1757, found 451.1749.

N,N-diethyl-3-methoxy-5-vinylbenzamide 2.20.2

Triflate 2.20.1 (355 mg, 1.0 mmol) and vinyltrifluoroborate (134 mg, 1.0 mmol) was dissolved in 2.0 mL THF/H2O (9:1). To this added Cs2CO3 (977.5 mg, 3.0 mmol), PdCl2 (9.0 mg, 0.05 mmol) and PPh3 (40 mg, 0.15 mmol). The reaction mixture was vacuum degassed and refluxed under argon overnight. Diluted with EtOAc (5.0 mL), and quenched by saturated aqueous NH4Cl (10 mL). The mixture was stirred at 0 ºC for 30 min. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na2SO4. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 10% hexane/EtOAc afforded product 2.20.2 (186 mg, 80%). Viscus oil; Rf (20% hexanes/EtOAc) = 0.71; IR (thin film, cm⁻¹) ν 2842, 1654, 1630, 1379, 1342, 1290, 1278, 1053, 864; 1H NMR (CDCl3, 400 MHz): δ 7.97 (s, 1H), δ 7.93 (s, 1H), δ 7.77 (s, 1H), δ 7.66 (dd, J = 18.0, 11.2 Hz, 1H), δ 5.76 (d, J = 17.6 Hz, 1H), δ 5.27 (d, J = 10.4 Hz, 1H),

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\[ \delta 3.80 \text{ (s, 3H)}, \delta 3.53 \text{ (m, 2H)}, \delta 3.25 \text{ (m, 2H)}, \delta 1.27 \text{ (t, } J = 6.8 \text{ Hz, 3H)}, \delta 1.09 \text{ (t, } J = 7.0 \text{ Hz, 3H)}; \]

\[ ^{13} \text{C NMR (CDCl}_3, \text{ 100 MHz): } \delta 170.9, 159.8, 139.4, 138.7, 136.2, 129.6, 116.6, 115.1, 112.6, 55.5, 43.3, 39.3, 14.3, 12.9; \] HRMS (ESI): calcd for \([\text{C}_{14}\text{H}_{19}\text{NO}_2 + \text{H}]^+\) 234.1494, found 234.1496.

**Methyl 2-bromo-5-((tert-butyldimethylsilyl)oxy)-3-hydroxybenzoate 2.22.11**

Phenol 2.22.10 (110.3 mg, 0.39 mmol) was dissolved in 3.9 mL dry CCl\(_4\) and cooled to 0 °C. To this cold solution added \(N\)-bromosuccinimide (73 mg, 0.41 mmol) and stirred for 3h, gradually rising to ambient temperature. Diluted with Et\(_2\)O (10 mL), and quenched by adding saturated aqueous NaHCO\(_3\) (10 mL). The aqueous layer was extracted with Et\(_2\)O twice and the combined organic layer was washed with saturated brine, and dried over Na\(_2\)SO\(_4\). After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 5% hexane/EtOAc afforded product 2.22.11 (63.5 mg, 45%); viscous oil; \(R_f\) (15% hexanes/EtOAc) = 0.55; IR (thin film, cm\(^{-1}\)) \(\nu\) 3410, 3300, 2842, 1724, 1680, 1412, 1264, 1033, 866; \(^1\text{H NMR (CDCl}\_3, \text{ 400 MHz): } \delta 6.89 \text{ (d, } J = 3.2\text{ Hz, 1H)}, \delta 6.68 \text{ (d, } J = 3.2 \text{ Hz, 1H)}, \delta 3.90 \text{ (s, 3H)}, \delta 0.96\text{(s, 9H)}, \delta 0.19 \text{ (s, 6H)}; \]

\[ ^{13} \text{C NMR (CDCl}_3, \text{ 100 MHz): } \delta 166.4, 156.0, 154.0, 132.5, 115.8, 110.9, 101.7, 52.7, 25.7, 18.3, -4.3; \] HRMS (ESI): calcd for \([\text{C}_{14}\text{H}_{21}\text{BrO}_4\text{Si} + \text{H}]^+\) 361.0471, found 361.0474.
Methyl 2-bromo-3,5-dimethoxybenzoate 2.22.5

Dimethoxy benzoate 2.22.4 (100 mg, 0.51 mmol) was dissolved in 1.2 mL dry CHCl₃ and cooled to 0 °C. To this cold solution added N-bromosuccinimide (115.7 mg, 0.65 mmol) in one portion and stirred for 2h and gradually warmed up to rt. The reaction was diluted with CH₂Cl₂ and added saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ thrice. Combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 5% hexane/EtOAc afforded product 2.22.5 (126.3 mg, 90%). Colorless solid; ¹H NMR (CDCl₃, 400 MHz): δ 6.77 (d, J = 2.8 Hz, 1H), δ 6.55 (d, J = 2.8 Hz, 1H), δ 3.90 (s, 3H), δ 3.85 (s, 3H), δ 3.78 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 167.3, 159.6, 157.2, 134.8, 106.2, 102.4, 102.0, 56.6, 55.8, 52.7.

Methyl 5-(benzyloxy)-2-bromo-3-hydroxybenzoate 2.22.9

Phenol 2.22.8 (1.0 g, 3.87 mmol) was dissolved in 40 mL dry CHCl₃ and cooled to 0 °C. To this cold solution added N-bromosuccinimide (723.5 mg, 4.07 mmol) in one portion and stirred for 7 min. After exactly 7 min, saturated aqueous NaHCO₃ (50 mL) was added and the aqueous layer was extracted with CH₂Cl₂. Combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, elution with 6-8% hexane/EtOAc afforded product 2.29.9 (1.26 g, 97%).
Colorless solid; mp: 72 °C; \( R_f \) (10% hexanes/EtOAc) = 0.65; IR (thin film, cm\(^{-1}\)) \( \nu \) 3368, 3310, 2842, 1724, 1680, 1412, 1264, 1033, 866; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.33-7.42 (m, 5H), \( \delta \) 7.10 (d, \( J = 2.8 \) Hz, 1H), \( \delta \) 6.82 (d, \( J = 2.8 \) Hz, 1H), \( \delta \) 5.05 (s, 2H), \( \delta \) 3.92 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 166.3, 158.9, 154.1, 136.2, 132.4, 128.9, 128.5, 127.7, 111.0, 105.8, 101.3, 70.6, 52.8; HRMS (ESI): calcd for [C\(_{15}\)H\(_{13}\)BrO\(_4\) + H]\(^+\) 337.0075, found 337.0075.

**Methyl 5-(benzyloxy)-2-bromo-3-methoxybenzoate 2.24.1**

Bromophenol 2.22.9 (4.14 g, 12.28 mmol) was dissolved in 25 mL acetone. After forming a homogeneous solution, added K\(_2\)CO\(_3\) (3.4 g, 24.56 mmol) and MeI (3.8 mL, 61.4 mmol). The reaction mixture was refluxed under argon for 1h. Cooled to room temperature and acetone was removed under reduced pressure. The residue was redissolved in 100 mL Et\(_2\)O and H\(_2\)O. The aqueous layer was extracted with Et\(_2\)O thrice. Combined organic layer was washed with saturated brine, and dried over Na\(_2\)SO\(_4\). After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 8-10% hexane/EtOAc afforded product 2.22.1 (4.1 g, 95%). Colorless solid: mp: 60-61 °C; \( R_f \) 10% hexanes/EtOAc = 0.85; IR (thin film, cm\(^{-1}\)) \( \nu \) 2842, 1736, 1680, 1434, 1254, 1029, 872; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.33-7.43 (m, 5H), \( \delta \) 6.91 (d, \( J = 2.8 \) Hz, 1H), \( \delta \) 6.65 (d, \( J = 2.8 \) Hz, 1H), \( \delta \) 5.05 (s, 2H), \( \delta \) 3.92 (s, 3H), \( \delta \) 3.84 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 167.2, 158.9, 157.3, 136.1, 134.8, 128.8, 128.4, 127.7, 107.2, 103.1, 102.4, 70.6, 56.6, 52.7; HRMS (ESI): calcd for [C\(_{16}\)H\(_{15}\)BrO\(_4\) + H]\(^+\) 351.0232, found 351.0225.
Methyl 5-(benzyloxy)-3-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate 2.24.3

Aromatic bromide 2.24.1 (20 mg, 0.06 mmol) was dissolved in 1.0 mL THF and cooled to −78 °C and vacuum degased and back filled with argon. To this degassed reaction mixture, added bis(pinacolato)diborane (28.95 mg, 0.11 mmol) and Pd(dppf)₂•Cl₂•CH₂Cl₂. The reaction mixture was refluxed overnight under argon. Cooled to 0 °C and was diluted with Et₂O and quenched with saturated saturated NaHCO₃. The organic layer was extracted with Et₂O (20 mL X 2). The pooled organic layer was subsequently washed with saturated brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was subjected to flash column chromatography using silica gel. Elution with 8-10% hexane-EtOAc gave borate 2.24.3 (17 mg, 75%) as a colorless solid: R_f (10% hexanes/EtOAc) = 0.30; mp: 134 °C; IR (thin film, cm⁻¹) ν 2910, 1741, 1680, 1429, 1320, 1154, 864; ¹H NMR (CDCl₃, 400 MHz): δ 7.31-7.44 (m, 5H), δ 7.19 (d, J = 2.0 Hz, 1H), δ 6.64 (d, J = 1.2 Hz, 1H), δ 5.08 (s, 2H), δ 3.89 (s, 3H), δ 3.76 (s, 3H), δ 1.42 (s, 12H); ¹³C NMR (CDCl₃, 100 MHz): δ 167.9, 163.9, 160.8, 136.6, 135.1, 128.8, 128.3, 127.9, 105.9, 103.4, 84.0, 70.4, 55.9, 52.6, 29.9, 25.1; HRMS (ESI): calcd for [C₂₂H₂₇BO₆ + H]⁺ 399.1979, found 399.1982.
Methyl 5-(benzyloxy)-3-methoxy-2-(tributylstannyl)benzoate 2.24.2

Aromatic bromide 2.24.1 (1.5 g, 4.27 mmol) was dissolved in 85 mL dry dioxane and added LiCl (362.1 mg, 8.54 mmol). The reaction mixture was then cooled to –78 ºC, vacuum degassed and back filled with argon. To this degassed reaction mixture, added hexabutylditin (4.3 mL, 8.54 mmol), a premixed solution of Pd₂(dba)₃•CHCl₃ (155 mg, 0.11 mmol) and PCy₃ (180.8 mg, 0.43 mmol) in 5 mL dioxane. The reaction mixture was refluxed for 10h under argon. Cooled to 0 ºC and was diluted with Et₂O and quenched with saturated NaHCO₃. The organic layer was extracted with Et₂O (100 mL X 2). The pooled organic layer was subsequently washed with saturated brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was subjected to flash column chromatography using silica gel neutralized with Et₃N. Elution with 10% hexane-Et₂O gave stannane 2.24.2 (1.56 g, 65%) as a colorless oil: \( R_f \) (10% hexanes/EtOAc) = 0.80; IR (thin film, cm\(^{-1}\)) \( \nu \) 2950, 2920, 2854, 1740, 1684, 1456, 1378, 1280, 1237, 1169, 1146, 1138, 1048, 1023, 862; \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 7.34-7.48 (m, 5H), \( \delta \) 7.26 (d, \( J = 2.0 \) Hz, \( J_{\text{Sn-H}} = 6.4 \) Hz, 1H), \( \delta \) 6.65 (d, \( J = 2.4 \) Hz, \( J_{\text{Sn-H}} = 6.0 \) Hz, 1H), \( \delta \) 5.11 (s, 2H), \( \delta \) 3.89 (s, 3H), \( \delta \) 3.75 (s, 3H), \( \delta \) 1.46-1.54 (m, 6H), \( \delta \) 1.29-1.38 (m, 6H), \( \delta \) 1.02-1.06 (m, 6H), \( \delta \) 0.91 (t, \( J = 6.4 \) Hz, 9H); \(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta \) 169.1, 166.0, 160.0, 139.3, 136.9, 128.8, 128.3, 127.9, 125.8, 107.2 (\( ^3J_{\text{Sn-C}} = 11.8 \) Hz), 102.1 (\( ^3J_{\text{Sn-C}} = 12.0 \) Hz), 70.4, 55.4, 52.5, 29.4 (\( ^3J_{\text{Sn-C}} = 10.8 \) Hz), 27.6 (\( ^2J_{\text{Sn-C}} = 32.4 \) Hz), 13.9, 12.9 (\( ^1J_{\text{Sn-C}} = 182.6 \) Hz); HRMS (ESI): calcd for [C₂₈H₄₂O₄Sn+H]⁺ 563.2183, found 563.2182.
Methyl-5-(benzyloxy)-2-(5-hydroxy-1,4-dioxo-1,4-dihyronaphthalen-2-yl)-3-methoxy benzoate 2.25.1

A suspension of juglone 1.9.5 (398.73 mg, 1.58 mmol), stannane 2.24.2 (1.15 g, 2.05 mmol), and CuI (60.04 mg, 0.32 mmol) in 18 mL dry THF at rt was vacuum degased and backfilled with argon. To this mixture, added a solution of Pd₂(dba)₃•CHCl₃ (81.8 mg, 0.08 mmol) and PPh₃ (83.1 mg, 0.32 mmol) in THF (2 mL) under argon. The mixture was stirred at 80 °C for 4 h. It was then cooled down to 0 ºC, diluted with EtOAc (50 mL), and quenched by adding saturated aqueous NaHCO₃ (20 mL). The mixture was stirred at 0 ºC for 30 min. After separation of the two phases, the aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 8-10% hexane/EtOAc afforded coupled product 2.25.1 (548 mg, 78%).

**Alternative method:** Bromojuglone 1.9.5 (16.8 mg, 0.07 mmol) and borate 2.24.3 (32 mg, 0.08 mmol) was dissolved in 0.8 mL THF/H₂O (9:1). To this added Cs₂CO₃ (65 mg, 0.2 mmol), Pd(dppf)₂•Cl₂•CH₂Cl₂ (3.0 mg, 0.003 mmol). The reaction mixture was vacuum degassed and refluxed under argon overnight. Diluted with EtOAc (5.0 mL), and quenched by adding saturated aqueous NH₄Cl (10 mL). The mixture was stirred at 0 ºC for 30 min. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 8-10% hexane/EtOAc afforded product 2.25.1 (9.3 mg,
Methyl-5-(benzyloxy)-2-(8-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3-methoxy benzoate 2.25.2

A suspension of juglone 2.7.3 (1.08 g, 4.26 mmol), stannane 2.24.2 (2.4 g, 4.28 mmol), and CuI (163 mg, 0.85 mmol) in 40 mL dry THF at rt was vacuum degassed and backfilled with Ar. To this mixture, added a solution of Pd$_2$(dba)$_3$•CHCl$_3$ (221.3 mg, 0.21 mmol) and PPh$_3$ (225 mg, 0.86 mmol) in THF (3 mL) under Ar. The mixture was stirred at 80 ºC for 5 h. It was then cooled down to 0 ºC, diluted with EtOAc (50 mL), and quenched by adding saturated aqueous NaHCO$_3$ (50 mL). The mixture was stirred at 0 ºC for 30 min. After separation of the two phases, the aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na$_2$SO$_4$. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 10% hexane/EtOAc afforded coupled product 2.25.2 (1.5 g, 80%). Orange solid; mp: 134 ºC; $R_f$ (10% hexane/EtOAc = 0.40; IR (thin film,
cm\(^{-1}\) ν 3300, 2990, 2930, 2864, 2832, 1741, 1684, 1576, 1448, 1342, 1291, 1212, 1120, 966; \(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 12.10 (s, 1H), δ 7.62-7.68 (m, 2H), δ 7.35-7.48 (m, 5H), δ 7.31 (d, \(J = 2.4\) Hz, 1H), δ 7.28 (s, 1H), δ 6.82 (d, \(J = 2.8\) Hz, 1H), δ 6.81 (s, 1H), δ 5.15 (s, 2H), δ 3.75 (s, 3H), δ 3.74 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): δ 190.0, 184.7, 166.6, 161.9, 160.5, 158.4, 147.3, 137.1, 136.5, 136.3, 132.7, 132.2, 128.9, 128.6, 127.9, 124.3, 118.9, 116.4, 115.5, 107.1, 103.8, 70.7, 56.3, 52.7; HRMS (ESI): calcd for [C\(_{26}\)H\(_{20}\)O\(_7\) + H]\(^+\) 445.1287, found 445.1279.

**Methyl-5-(benzyloxy)-2-(1,4-dioxo-5-(((3aS,5R,7S,7aR)-2,2,7-trimethylhexahydrobenzo-[d]-[1,3]-dioxol-5-yl)oxy-1,4-dihydro-2-naphthalenyl)-3-methoxybenzoate 2.26.1**

Phenol 2.25.1 (150 mg, 0.34 mmol) and cyclitol 2.11.6 (75.4 mg, 0.41 mmol) was dissolved in 3.0 mL dry THF. To this added PPh\(_3\) (203.4 mg, 0.77 mmol), after forming a homogeneous solution, it was cooled to 0 °C and a THF solution of DIAD (166 µL, 0.84 mmol in 0.8 mL THF) was added drop wise. The reaction was stirred at 0 °C for 2h. Diluted with EtOAc (10 mL), and quenched by adding saturated aqueous NaHCO\(_3\) (20 mL). The mixture was stirred at 0 °C for 30 min. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na\(_2\)SO\(_4\). After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 20% hexane/EtOAc afforded product 2.26.1 (161 mg, 78%). Redish-brown solid; mp: 102 °C; \(R_f\) (20% hexanes/EtOAc) =
0.25; \([\alpha]_D^{25} -9.6, (c 2.0, CH_2Cl_2), IR \text{ (thin film, cm}^{-1}) \nu 2869, 2812, 1741 1684, 1660, 1571, 1347, 1290, 1282, 1154, 1096, 1026, 892; ^1H NMR for the major rotomer (CDCl_3, 400 MHz): \delta 7.79 (d, \(J = 7.6 \text{ Hz, 1H}), \delta 7.63 (dd, \(J = 8.0, 8.0 \text{ Hz, 1H}), \delta 7.33-7.47 (m, 7H), \delta 6.78 (d, \(J = 2.4 \text{ Hz, 1H}), \delta 6.74 (d, \(J = 1.6 \text{ Hz, 1H}), \delta 5.13 (s, 2H), \delta 4.69 (dddd, \(J = 6.4, 6.2, 4.2, 3.8 \text{ Hz, 1H}), \delta 4.37 (dd, \(J = 6.8, 2.8 \text{ Hz, 1H}), \delta 3.72 (s, 3H), \delta 3.70 (s, 3H), \delta 3.59-3.62 (m, 1H), \delta 2.59 (m, 1H), \delta 1.94-2.04 (m, 2H), \delta 1.74 (m, 1H), \delta 1.49 (s, 3H), \delta 1.35 (s, 3H), \delta 1.25-1.27 (m, 1H), \delta 1.04 (d, \(J = 6.2 \text{ Hz, 3H}); ^13C NMR (CDCl_3, 100 MHz): \delta 185.5, 183.3, 166.7, 160.2, 158.4, 158.2, 149.4, 136.4, 135.1, 134.4, 133.8, 131.9, 128.9, 128.5, 127.9, 122.1, 121.4, 119.4, 118.3, 108.5, 107.0, 103.8, 80.7, 74.3, 73.9, 70.6, 56.2, 52.5, 36.7, 33.6, 33.0, 28.7, 26.3, 18.9; HRMS (ESI): calcd for \([C_{36}H_{36}O_9 + H]^+ \) 613.2438, found 613.2441.

**Methyl-5-(benzyloxy)-2-(1,4-dioxo-8-(((3aS,5R,7S,7aR)-2,2,7-trimethylhexahydronaphthalen-2-yl)-3-methoxybenzo[d]-[1,3]-dioxol-5-yl)oxy-1,4-dihydronaphthalen-2-yl)-3-methoxybenzoate 2.26.2**

Phenol 2.25.2 (200 mg, 0.45 mmol) was dissolve in 3.0 mL dry THF and cooled to \(-30 \text{ °C}. To this added a 1.0 mL THF solution of cyclitol 2.11.6 (108.96 mg, 0.59 mmol) and DIAD (265 \(\mu \text{L}, 1.35 \text{ mmol}) dissolved in 1.0 mL THF. To this cooled solution, added a 1.0 mL THF solution of PPh_3 (242 mg, 1.31 mmol) very slowly over 1h (second drop of PPh_3 solution was not added until the dark color faded). The reaction was stirred at this temperature for 2h at that temperature and quenched with saturated aqueous NaHCO_3 (10 mL). After separation of the two layers, the
aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 17% hexane/EtOAc afforded product 2.26.2 (179.2 mg, 65%). Orange solid; mp: 91 ºC; Rf (20% hexanes/EtOAc) = 0.25; [α]D²⁵ = −9.5 (c 2.4, CH₂Cl₂), IR (thin film, cm⁻¹) ν 2870, 2834, 1728 1674, 1652, 1520, 1392, 1281, 1037, 866; ¹H NMR for the major rotomer (CDCl₃, 400 MHz): δ 7.79 (d, J = 7.6 Hz, 1H), δ 7.63 (dd, J = 8.0, 8.0 Hz, 1H), δ 7.34-7.47 (m, 7H), δ 6.79 (d, J = 2.0 Hz, 1H), δ 6.70 (s, 1H), δ 5.13 (s, 2H), δ 4.72 (dddd, J = 6.4, 6.0, 4.2, 4.0 Hz, 1H), δ 4.37 (dd, J = 7.2, 2.8 Hz, 1H), δ 3.72 (s, 3H), δ 3.69 (s, 3H), δ 2.61-2.64 (m, 2H), δ 2.05-2.11 (m, 2H), δ 1.77-1.80 (m, 1H), δ 1.51 (s, 3H), δ 1.38 (s, 3H), δ 1.21-1.27 (m, 1H), δ 1.10 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 184.6, 184.5, 166.8, 160.2, 158.4, 157.8, 144.7, 138.4, 136.4, 135.2, 134.4, 132.1, 128.9, 128.5, 127.9, 121.3, 121.1, 120.3, 117.2, 108.5, 107.0, 103.7, 80.7, 74.2, 73.9, 70.6, 56.2, 52.5, 36.7, 33.7, 33.0, 28.7, 26.3, 18.9; HRMS (ESI): calcd for [C₃₆H₃₆O₉ + H]+ 613.2438, found 613.2429.

8-(benzyloxy)-10,12-dimethoxy-1-(((3aS,5R,7S,7aR)-2,2,7-trimethylhexahydro benzo-[d]-[1,3]-dioxol-5-yl)oxy)-6H-dibenzo[c,h]chromen-6-one 2.27.1

Quinone 2.26.1 (150 mg, 0.24 mmol) was dissolved in 9.0 mL glacial acetic acid. The mixture was cooled to −78 ºC and vacuum degassed. To the reaction, added Zn-dust (80 mg, 1.22 mmol)
and p-TsOH (7 mg, 0.03 mmol). The reaction was stirred at room temperature under argon for 24 h. When all quinone was consumed, added H2O (5 mL) and stirred at 0 °C for 30 min. The filtrate formed was collected in Hirsch funnel and washed with cold H2O and hexane. The residue was dried azeotropically using toluene and used in next step without further purification. This crude lactone was dissolved in 5.5 mL dry THF and cooled to 0 °C. To this cold solution, added MeI (87 µL, 1.39 mmol) and a THF solution of t-BuOK (18.72 mg, 0.17 mmol in 0.5 mL THF). After 30 min, it was quenched with 10 mL saturated NH4Cl and aqueous phase was extracted with CH2Cl2 (50 mL × 2). The combined organic layer was washed with brine and dried over Na2SO4. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 18% hexane-EtOAc gave 2.27.1 (67 mg, 46%, 2-steps). Light yellow amorphous solid; mp: 82 °C; Rf (30% hexanes/EtOAc) = 0.50; [α]D25 = −26.4, (c 0.2, CH2Cl2), IR (thin film, cm⁻¹) ν 2850, 1740, 1680, 1668, 1520, 1432, 1368, 1258, 1164, 942, 877; 1H NMR (CDCl3, 400 MHz): δ 8.35 (s, 1H), δ 7.89 (d, J = 8.0 Hz, 1H), δ 7.61 (d, J = 2.8 Hz, 1H), δ 7.37-7.50 (m, 6H), δ 7.14 (d, J = 7.2 Hz, 1H), δ 6.91 (d, J = 3.2 Hz, 1H), δ 5.16 (s, 2H), δ 4.76 (dddd, J = 6.2, 6.0, 3.2, 3.2 Hz, 1H), δ 4.55 (dd, J = 8.8, 5.2 Hz, 1H), δ 4.02 (s, 3H), δ 3.74 (dd, J = 8.8, 4.8 Hz, 1H), δ 2.69-2.73 (m, 1H), δ 2.30 (ddd, J = 9.6, 4.4, 4.4 Hz, 1H) δ 2.21-2.25 (m, 1H), δ 1.74-1.80 (m, 1H), δ 1.55 (dd, J = 13.2, 9.2 Hz, 1H), δ 1.50 (s, 3H), δ 1.39 (s, 3H), δ 1.08 (d, J = 6.8 Hz, 3H); 13C NMR (CDCl3, 100 MHz): δ 161.3, 159.1, 158.7, 154.7, 150.9, 141.1, 136.2, 128.9, 128.5, 128.1, 128.0, 127.0, 123.9, 119.6, 117.5, 115.0, 113.6, 108.3, 106.9, 103.9, 102.4, 80.9, 74.7, 74.4, 70.6, 56.4, 55.7, 36.5, 33.7, 33.0, 28.7, 26.3, 18.9; HRMS (ESI): calcd for [C36H36O8 + H]+ 597.2488, found 597.2477.
Benzyl ether 2.27.1 (43 mg, 0.07 mmol) was dissolved in 2.0 mL EtOAc and added 2-3 drops of MeOH. To this added 10 mg 10% Pd/C. The reaction was Vacuum degassed at −78 °C and stirred at rt for 3h under H₂ balloon pressure. The debenzylated product was filtered through a short pad of celite. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 40-50% EtOAc/hexane gave 2.27.2 (30 mg, 83%). Light yellow amorphous solid; mp: 142-144 °C; \( R_f \) (50% hexanes/EtOAc) = 0.50; \([\alpha]_D^{25} = -6.6 \) (c 0.1, CH₂Cl₂), IR (thin film, cm⁻¹) \( \nu \) 3320, 1741, 1664, 1534, 1451, 1368, 1247, 1123, 951, 876; \(^1\)H NMR (Acetone-\( d_6 \), 400 MHz): δ 9.28 (brs, 1H), δ 8.50 (s, 1H), δ 7.85 (d, \( J = 8.0 \) Hz, 1H), δ 7.49 (d, \( J = 8.0 \) Hz, 1H), δ 7.47 (d, \( J = 7.2 \) Hz, 1H), δ 7.19 (d, \( J = 7.6 \) Hz, 1H), δ 7.04 (d, \( J = 2.4 \) Hz, 1H), δ 4.78 (dddd, \( J = 6.2, 6.0, 3.2, 3.0 \) Hz, 1H), δ 4.63 (dd, \( J = 9.6, 5.2 \) Hz, 1H), δ 4.12 (s, 3H), δ 4.05 (s, 3H), δ 3.73 (dd, \( J = 9.6, 5.2 \) Hz, 1H), δ 2.55 (ddd, \( J = 14.8, 3.6, 1.6 \) Hz, 1H), δ 2.21-2.30 (m, 2H), δ 1.74-1.82 (m, 1H), δ 1.44 (dd, \( J = 13.2, 9.6 \) Hz, 1H), δ 1.40 (s, 3H), δ 1.31 (s, 3H), δ 1.04 (d, \( J = 6.8 \) Hz, 3H); \(^{13}\)C NMR (Acetone-\( d_6 \), 100 MHz): δ 160.7, 159.7, 158.8, 155.0, 151.1, 140.9, 128.1, 127.2, 124.3, 117.6, 114.9, 114.1, 113.5, 108.0, 106.8, 106.6, 102.8, 80.8, 74.5, 74.2, 56.4, 55.6, 36.5, 33.6, 33.2, 28.4, 25.9, 18.7; HRMS (ESI): calcd for [C₂₉H₃₀O₈ + H]⁺ 507.2019, found 507.2006.
10,12-dimethoxy-6-oxo-1-(((3aS,5R,7S,7aR)-2,2,7-trimethylhexahydrobenzo[d]-[1,3]-dioxol-5-yl)oxy)-6H-dibenzo[c,h]chromen-8-yl-trifluoromethanesulfonate 2.27.3

Phenol 2.27.2 (30 mg, 0.06 mmol) was dissolved in 1.2 mL dry CH₂Cl₂ and cooled to −78 °C. To this cooled solution, added Et₃N (50 µL, 0.35 mmol) and Tf₂O (14 µL, 0.08 mmol). The reaction mixture was stirred at −78 °C for 30 min and added saturated NaHCO₃ (2 mL) at that temperature. After stirring for 5 min, it was diluted with CH₂Cl₂ and raised to rt. The aqueous phase was extracted with CH₂Cl₂ (20 mL X 3). The combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 10% hexane-EtOAc gave 2.27.3 (32.2 mg, 84%). Light yellow amorphous solid; mp: 90-94 °C; R_f (30% hexanes/EtOAc) = 0.85; [α]D²⁵ −45.0 (c 0.02, CH₂Cl₂), IR (thin film, cm⁻¹) ν 2834, 2729, 1736, 16673, 1544, 1326, 1239, 1177, 923, 866; ¹H NMR (CDCl₃, 400 MHz): δ 8.21 (s, 1H), δ 7.91 (d, J = 2.8 Hz, 1H), δ 7.85 (d, J = 8.0 Hz, 1H), δ 7.48 (dd, J = 8.0, 8.0 Hz, 1H), δ 7.14 (d, J = 8.4 Hz, 1H), δ 7.08 (d, J = 2.4 Hz, 1H), δ 4.77 (dddd, J = 6.4, 6.2, 3.2, 3.2 Hz, 1H), δ 4.55 (dd, J = 9.6, 5.2 Hz, 1H), δ 4.06 (s, 3H), δ 3.99 (s, 3H), δ 3.74 (dd, J = 9.6, 5.4 Hz, 1H), δ 2.67-2.71 (m, 1H), δ 2.28 (dd, J = 9.6, 4.4 Hz, 1H), δ 2.02-2.26 (m, 1H), δ 1.75-1.83 (m, 1H), δ 1.51 (s, 3H), δ 1.49 (dd, J = 12.6, 9.6 Hz, 1H), δ 1.39 (s, 3H), δ 1.11 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.8, 158.7, 155.0, 151.1, 148.5, 142.6, 128.9, 128.1, 125.6, 123.9, (123.7, 120.5, 117.3, 114.1, q, J φ-CF₃ = 320 Hz), 116.9, 116.9
114.8, 113.9, 113.2, 112.1, 109.9, 108.4, 101.8, 80.9, 74.5, 74.3, 56.9, 55.7, 36.5, 33.7, 33.0, 28.7, 26.3, 18.9; HRMS (ESI): calcd for [C\(_{30}\)H\(_{29}\)F\(_{3}\)O\(_{10}\)S + Na]\(^+\) 661.1331, found 661.1332.
4.4 Experimental for chapter 3

Heptadec-7-yn-6-one 3.5.3

A solution of n-BuLi in hexane (30.4 mL, 0.076 mol) was added to a precooled solution of 1-undecyne 3.5.1 (11.5 g, 0.076 mol) in dry THF (138 mL) at −78 °C under argon. After 30 min at this temperature slowly added hexanal 3.5.2 (6.9 g, 0.07 mol) and the resulting mixture was raised to room temperature over a period of 5 h. The reaction mixture was diluted with dichloromethane and quenched with saturated NH₄Cl at 0 °C. The aqueous phase was extracted with CH₂Cl₂ (300 mL X 3). Combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 4% ethylacetate/hexane gave the racemic alkynol. The racemic alkynol was then dissolved in 173 mL DMSO and added Et₃N (57 mL, 41.9 mol). Cooled the mixture to −25 °C and dropwise added a 173 mL DMSO solution of Py•SO₃ (33.2 g, 0.207 mol) via cannula. The reaction mixture was slowly raised to room temperature over 3h. Diluted with CH₂Cl₂ and quenched with 1N HCl at 0 °C. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layer was washed with saturated NaHCO₃ and brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 4% Et₂O/hexane gave 3.5.3 (13.7g, 78% over 2 steps). Faint yellow oil: \( R_f \) (5% hexanes/EtOAc) = 0.28, \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 0.84 (t, \( J = 6.5 \) Hz, 3H), \( \delta \) 0.86 (t, \( J = 6.5 \) Hz, 3H), \( \delta \) 1.23-1.38 (m, 18H), \( \delta \) 1.53 (tt, \( J = 7.2, 7.2 \) Hz, 2H), \( \delta \) 1.62 (tt, \( J = 7.2, 7.2 \) Hz, 2H), \( \delta \) 2.31 (t, \( J = 7.6 \) Hz, 2H), \( \delta \) 2.47 (t, \( J = 7.2 \) Hz, 2H); \(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta \) 188.6, 94.3, 81.0, 45.6, 31.9, 31.3, 29.5, 29.4, 29.2, 28.9, 27.8, 23.9, 22.8, 22.5, 19.0, 14.2, 13.9.
(S)-heptadec-7-yne-6-ol 3.5.4

Propargyl ketone 3.5.3 (6.61 g, 26.4 mmol) was dissolved in 10 mL CH₂Cl₂ and added to a 1:1 mixture of HCOOH : Et₃N (45 mL). The reaction mixture was then degassed by bubbling argon through the solution for 15 min. Noyori-(S,S) catalyst (136 mg, 0.224 mmol) was added and the reaction mixture was stirred vigorously at room temperature for 12 h. The reaction mixture was diluted with Et₂O and quenched with saturated NaHCO₃. The aqueous layer was extracted with Et₂O (100 mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 3% EtOAc/hexane gave propargyl alcohol 3.5.4 (6.0 g, 90%). Light yellow oil: \( R_f \) (10% hexanes/EtOAc) = 0.54, [α]D\text{25} = -0.11 (c 1.14, CH₂Cl₂), \(^1\)H NMR (CDCl₃, 400 MHz): δ 0.88 (t, \( J = 7.6 \) Hz, 3H), δ 0.96 (t, \( J = 6.4 \) Hz, 3H), δ 1.25-1.72 (m, 21H), δ 1.89 (brs, 1H), δ 1.18 (ddd, \( J = 1.2, 5.2, 7.2 \) Hz, 2H), δ 4.33 (ddd, \( J = 2.0, 2.4, 6.8 \) Hz, 1H); \(^{13}\)C NMR (CDCl₃, 100 MHz): δ 85.7, 81.6, 62.9, 38.4, 32.1, 31.7, 29.7, 29.4, 29.3, 29.0, 28.9, 25.1, 22.9, 22.8, 18.9, 14.3, 14.2.

(S)-heptadec-16-yne-6-ol 3.5.5

A dry round-bottom flask was charged with KH (7.6 g, 190 mmol). Hexane was removed by flowing argon through the flask. 1,3-diaminopropane (110 mL, 1.3 mol) was added dropwise and stirred for 90 min to give a homogeneous brown solution. Propargyl alcohol 3.5.4 (9.6 g, 38 mmol) in 54 mL dry THF was added dropwise to the reaction mixture at 0 ºC and allowed to
warm up to room temperature. After stirring for 2h at room temperature, the reaction mixture was cooled to 0 °C and quenched by adding H₂O. The aqueous layer was extracted with CH₂Cl₂ (300 mL X 3) and the combined organic layer was washed with saturated NaHCO₃ and brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 5% EtOAc/hexane gave 3.5.5 (6.7 g, 70%). White solid: \( R_f \) (5% hexanes/EtOAc) = 0.32, [\( \alpha \)]\(_D\)\(^{25} \) = +1.1 (c 0.14, CH₂Cl₂), \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 0.84 (t, \( J = 6.6 \) Hz, 3H), \( \delta \) 1.16-1.50 (m, 23H), \( \delta \) 1.78 (brs, 1H), \( \delta \) 1.89 (t, \( J = 2.8 \) Hz, 1H), \( \delta \) 2.12 (ddd, \( J = 2.4, 6.8, 7.2 \) Hz, 2H), \( \delta \) 3.52 (m, 1H); \(^1\)C NMR (CDCl₃, 100 MHz): \( \delta \) 84.8, 72.0, 68.2, 37.6, 37.5, 32.1, 29.8, 29.7, 29.6, 29.2, 28.9, 28.6, 25.8, 25.5, 22.8, 18.5, 14.2.

\( (S)\)-\textit{tert}-butyl(heptadec-16-yn-6-yl)oxy)dimethylsilane 3.5.6\(^{71} \)

Alcohol 3.5.5 (4.32 g, 17.2 mmol) was dissolved in 34 mL dry CH₃CN. DMAP (2.09 g, 17.2 mmol) was added to this solution and cooled to 0 °C. At 0 °C under argon, added DBU (7.7 mL, 51.4 mmol) followed by TBSCl (10.3 g, 68.5 mmol). The reaction mixture was raised up to room temperature over 2h. After consumption of starting material, reaction mixture was diluted with Et₂O and quenched with 1N HCl at 0 °C. The aqueous layer was extracted with Et₂O (200mL X 3) and the combined organic layer was washed with saturated NaHCO₃ and brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 2-5% Et₂O/hexane gave 3.5.6 (6.3g, quantitative). Colorless oil: \( R_f \) (1% hexanes/EtOAc) = 0.72, [\( \alpha \)]\(_D\)\(^{25} \) = -0.04 (c 5.0, CH₂Cl₂), \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 0.03 (s, 6H), \( \delta \) 0.86 (t, \( J = 6.4 \) Hz, 3H), \( \delta \) 0.88 (s, 12H), \( \delta \) 1.28-1.56 (m, 23H), \( \delta \) 1.89 (t, \( J = 3.2 \) Hz, 1H), \( \delta \) 2.16 (ddd, \( J = 2.8, 4.4 \),
6.8 Hz, 2H), δ 3.61 (m, 1H); 13C NMR (CDCl₃, 100 MHz): δ 84.7, 72.5, 68.3, 37.4, 32.4, 30.1, 29.8, 29.7, 29.4, 29.0, 28.7, 26.1, 25.5, 25.2, 22.9, 18.6, 14.3, −4.2.

(S)-methyl 11-hydroxyhexadecanoate 3.5.7

![Methyl 11-Hydroxyhexadecanoate](image)

Alkyne 3.5.6 (7.23 g, 19.7 mmol) was dissolved in 65 mL benzene and 20 mL HOAc. The resulting solution was cooled to 0 °C and added an aqueous solution of KMnO₄ (12.5 g, 79 mmol in 100 mL H₂O) dropwise via a dropping funnel. To this reaction mixture, added CTAB (1.44 g, 4.0 mmol) and stirred vigorously without replenishing ice over a period of 24h. Upon consumption of starting material, cooled the reaction to 0 °C and slowly added 20 g Na₂SO₃ followed by 26 mL 1N HCl. Stirred for approximately 10 min until white precipitate formed and reaction turned colorless. The precipitate was dissolved by adding H₂O and the aqueous layer was subsequently extracted with CH₂Cl₂ (300mL X 3). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude reaction mixture was passed through a pad of celite to obtain the corresponding carboxylic acid, which was carried to the next step without further purification. The crude carboxylic acid was dissolved in 300 mL MeOH and added 9.0 mL conc. H₂SO₄. The resulting reaction mixture was refluxed at 65 °C for 2h. The reaction was then cooled 0 °C and added 10 g solid NaHCO₃. MeOH was removed under reduced pressure and the resulting ester was partitioned between EtOAc and H₂O. The aqueous layer was extracted with EtOAc (300mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 5-10% EtOAc/hexane gave jalapinolic ester 3.5.7 (3.36, 61%, 2 steps).

White solid: mp: 38-40 °C, Rₜ (10% hexanes/EtOAc) = 0.45, [α]D²⁵ = +1.0 (c 1.07, CH₂Cl₂), ¹H
NMR (CDCl$_3$, 400 MHz): δ 0.88 (t, $J = 6.8$ Hz, 3H), δ 1.20-1.45 (m, 22H), δ 1.60 (m, 2H), δ 2.29 (t, $J = 7.6$ Hz, 2H), δ 3.57 (m, 1H), 3.65 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 174.3, 72.0, 51.4, 72.0, 51.4, 37.5, 37.4, 34.1, 34.1, 29.6, 29.5, 29.5, 29.3, 29.4, 29.1, 25.6, 25.3, 24.9, 22.6, 14.0.

(S)-methyl-11-(((2R,6S)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl)oxy)-hexadecanoate 3.7.1

Jalapinolic ester 3.5.7 (236 mg, 0.82 mmol) was dissolved in 2.7 mL dry CH$_2$Cl$_2$. To this added α-L-Boc-pyranone 3.4.5 (282 mg, 1.24 mmol). The reaction mixture was cooled to 0 °C and added a premixed solution of Pd$_2$(dba)$_3$•CHCl$_3$ (21.3 mg, 0.02 mmol) and PPh$_3$ (21.6 mg, 0.08 mmol) in CH$_2$Cl$_2$ via cannula under argon. The reaction mixture was stirred under argon at 0 °C over night. Concentrated the reaction mixture under reduced pressure and flash chromatography with 12-14% Et$_2$O/hexane yielded the desired product 3.7.1 (318 mg, 97%). Colorless oil: $R_f$ (10% hexanes/EtOAc) = 0.62; [α]$_D^{25}$ = +13.8 (c 0.98, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) $\nu$ 2928, 2855, 1739, 1700, 1158, 1079, 1025; $^1$H NMR (CDCl$_3$, 400 MHz): δ 0.85 (t, $J = 7.2$ Hz, 3H), δ 1.17-1.29 (m, 18H), δ 1.32 (d, $J = 6.8$ Hz, 3H), δ 1.44-1.58 (m, 6H), δ 2.25(t, $J = 7.2$ Hz, 2H), δ 3.64 (s, 3H), δ 3.68 (p, $J = 5.6$ Hz, 1H), δ 4.56 (q, $J = 6.4$ Hz, 1H), δ 5.21 (d, $J = 3.6$ Hz, 1H), δ 6.02 (d, $J = 10.4$ Hz, 1H), δ 6.76 (dd, $J = 3.2$, 10.4 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 196.4, 174.6, 142.9, 128.1, 89.8, 72.2, 71.1, 51.7, 37.7, 37.6, 34.3, 32.1, 30.0, 29.9, 29.6, 29.4, 29.3, 25.8, 25.5, 25.1, 22.9, 15.6, 14.3; HRMS (ESI): calcd for [C$_{23}$H$_{40}$O$_5$ + Na]$^+$ 419.27734, found 419.27680.
(S)-methyl-11-(((2R,5R,6S)-5-hydroxy-6-methyl-5,6-dihydro-2H-pyran-2-yl)oxy)-hexa-decanoate 3.7.2

Enone 3.7.1 (258 mg, 0.65 mmol) was dissolved in 1.3 mL dry CH₂Cl₂ and cooled to –78 °C. To this cooled solution, added a 0.4 M solution of CeCl₃•MeOH (1.3 mL). After stirring for 10 min at this temperature, added solid NaBH₄ (37 mg, 0.98 mmol) in portions. The reaction mixture was stirred at –78 °C for 2h. Quenched with saturated NaHCO₃ at low temperature, diluted with CH₂Cl₂ and warmed to 0 °C. The aqueous layer was extracted with CH₂Cl₂ (50mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 15-20% EtOAc/hexane gave enol 3.7.2 (255 mg, 98%). Colorless oil: Rₜ (10% hexanes/EtOAc) = 0.20; [α]D²⁵ = −29.5 (c 1.08, CH₂Cl₂); IR (thin film, cm⁻¹) ν 3460, 29.27, 28.55, 17.41, 1635, 1457, 1034, 668, 526; ¹H NMR (CDCl₃, 400 MHz): δ 0.86 (t, J = 7.2 Hz, 3H), δ 1.18-1.30 (m, 21H), δ 1.34-1.48 (m, 4H, δ 1.61 (m, 2H), δ 2.27 (t, J = 8.0 Hz, 2H), δ 3.60 (p, J = 5.6 Hz, 1H), δ 3.63 (s, 3H), δ 3.69 (dq, J = 2.4, 6.6 Hz, 1H), δ 3.77 (dd, J = 1.6, 7.2 Hz, 1H), δ 4.95 (s, 1H), δ 5.67 (dd, J = 2.4, 5.2, 10.4 Hz, 1H), δ 5.89 (d, J = 10.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 174.5, 133.6, 127.0, 93.5, 78.8, 69.4, 68.2, 51.6, 35.3, 34.6, 34.2, 29.9, 29.7, 29.5, 29.4, 29.3, 25.5, 25.4, 25.1, 22.8, 18.0, 14.2; HRMS (ESI): calcd for [C₂₃H₴₂O₅ + Na]⁺ 421.29245, found 421.29226.
(S)-methyl-11-(((2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexadecanoate 3.7.3

Allylic alcohol 3.7.2 (234 mg, 0.59 mmol) was dissolved in a 1:1 mixture of t-BuOH/acetone (0.6 mL) and the mixture was cooled to 0 °C. To this added a 50% (v/v) solution of NMO/H₂O (0.6 mL). The reaction mixture was stirred at that temperature for 15 min and added OsO₄ (7.5 mg, 0.03 mmol). The resulting reaction mixture was stirred over night without replenishing ice from 0 °C to rt. After consumption of starting material, the reaction was cooled back to 0 °C, diluted with EtOAc and reduced the excess OsO₄ with saturated Na₂SO₃. The reaction mixture was then concentrated to remove acetone. The aqueous layer was extracted with EtOAc (30mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 65-70% EtOAc/hexane gave triol 3.7.3 (212 mg, 83%). White solid: Rf (70% hexanes/EtOAc) = 0.21; mp: 56 °C; [α]D²⁵ = −41.5 (c 0.66, CH₂Cl₂); IR (thin film, cm⁻¹) ν 3391, 2926, 2854, 1741, 1456, 1048, 668; ¹H NMR (CDCl₃, 400 MHz): δ 0.86 (t, J = 7.2 Hz, 3H), δ 1.18-1.28 (m, 21H), δ 1.45 (m, 4H), δ 1.60 (p, J = 7.6 Hz, 2H), δ 2.29 (t, J = 7.2 Hz, 2H), δ 2.49 (brs, 1H), ), δ 3.47 (m, 1H), δ 3.57 (p, J = 6.0 Hz, 1H), δ 3.65 (s, 3H), δ 3.69-3.89 (m, 3H), δ 4.21 (brs, 1H), δ 4.82 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 174.7, 98.7, 78.1, 73.3, 72.2, 71.9, 68.4, 51.7, 34.6, 34.3, 44.3, 32.1, 30.0, 29.7, 29.5, 29.4, 29.3, 25.3, 25.1, 25.0, 22.8, 17.6, 14.3; HRMS (ESI): calcd for [C₂₅H₄₄O₇+Na]⁺ 455.29847, found 455.29792.
(S)-methyl-11-(((3aR,4R,6S,7S,7aR)-7-hydroxy-2,2,6-trimethyltetrahydro-3aH-[1,3]-dioxolo [4,5-c]pyran-4-yl)oxy)hexadecanoate 3.7.4

Triol 3.7.3 (175 mg, 0.40 mmol) was dissolved in dry acetone (1.3 mL) and the mixture was cooled to 0 °C. To this added 2,2-DMP (98 µL, 0.80 mmol) and p-TsOH (0.76 mg, 0.004 mmol). The reaction was stirred under argon from 0 °C to rt over 2h. Then the reaction was quenched by adding few drops of Et₃N at 0 °C. The mixture was oncentrated under reduced pressure and purified by silica gel chromatography. Elution with 20-25% EtOAc/hexane gave 3.7.4 (170 mg, 90%). Colorless oil: $R_f$ (20% hexanes/EtOAc) = 0.34; [$\alpha$]$_{D}^{25}$ = $-$23.38 ($c$ 1.65, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) $\nu$ 3459, 2928, 2855, 1741, 1457, 1380, 1219, 1071, 1051, 996, 861; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.87 (t, $J$ = 7.4 Hz, 3H), $\delta$ 1.12-1.30 (m, 21H), $\delta$ 1.35 (s, 3H), $\delta$ 1.46 (m, 4H), 1.52 (s, 3H), $\delta$ 1.62 (p, $J$ = 6.8 Hz, 2H), $\delta$ 2.29(t, $J$ = 7.2 Hz, 2H), $\delta$ 2.64 (d, $J$ = 3.6 Hz, 1H), $\delta$ 3.38 (m, 1H), $\delta$ 3.62 (p, $J$ = 5.6 Hz, 1H), $\delta$ 3.64 (s, 3H), $\delta$ 3.74 (dq, $J$ = 6.0, 7.8 Hz, 1H), $\delta$ 3.09 (dd, $J$ = 8.8, 7.8 Hz, 1H), $\delta$ 4.09 (d, $J$ = 3.2 Hz, 1H), $\delta$ 5.02 (s, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 174.6, 109.5, 95.7, 78.6, 76.6, 74.6, 66.2, 51.7, 34.6, 34.3, 33.1, 32.1, 30.0, 29.9, 29.7, 29.6, 29.4, 29.3, 28.2, 26.4, 25.4, 25.1, 25.0, 22.8, 17.5, 14.3; HRMS (ESI): calcd for [C$_{26}$H$_{48}$O$_7$ + Na]$^+$ 495.32922, found 495.32900.
(S)-methyl-11-(((3aR,4R,6S,7S,7aR)-2,2,6-trimethyl-7-(((2R,6S)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl)oxy)tetrahydro-3aH-[1,3]-dioxolo[4,5-c]pyran-4yl)-oxy)hexadecanoate 3.7.5

Glycosyl acceptor 3.7.4 (2.11 g, 4.47 mmol) was dissolved in 15 mL dry CH₂Cl₂. To this added α-L-Boc-pyranone 3.4.5 (2.04 g, 8.95 mmol). The reaction mixture was cooled to 0 °C and added a premixed solution of Pd₂(dba)₃•CHCl₃ (115.7 mg, 0.11 mmol) and PPh₃ (117.2 mg, 0.45 mmol) in CH₂Cl₂ via cannula under argon. The reaction mixture was stirred under argon at 0 °C overnight. Concentrated the reaction mixture under reduced pressure and flash chromatography with 10% EtOAc/hexane yielded the desired product 3.7.5 (2.60 g, quantitative). Colorless oil: 

$R_f$ (20% hexanes/EtOAc) = 0.35; $[\alpha]_D^{25} = -13.52$ (c 1.07, CH₂Cl₂); IR (thin film, cm⁻¹) $\nu$ 2928, 2855, 1734, 1700, 1669, 1576, 1540, 1457, 1045, 1020, 668; 

$^1$H NMR (CDCl₃, 400 MHz): 

δ 0.86 (t, $J = 6.8$ Hz, 3H), δ 1.19-1.32 (m, 22H), δ 1.35 (s, 3H), δ 1.37-1.51 (m, 6H), 1.56 (s, 3H), δ 1.59 (m, 2H), δ 2.87 (t, $J = 7.6$ Hz, 2H), δ 3.58-3.67 (m, 5H), δ 3.75 (p, $J = 5.6$ Hz, 1H), δ 4.09 (d, $J = 5.2$ Hz, 1H), δ 4.21 (dq, $J = 6.0$, 8.2 Hz, 1H), δ 4.54 (q, $J = 6.8$, 1H), δ 5.05 (s, 1H), δ 5.77(d, $J = 3.6$ Hz, 1H), δ 6.08 (d, $J = 10.4$ Hz, 1H), δ 6.87 (dd, $J = 3.6$, 10.0 Hz, 1H); 

$^{13}$C NMR (CDCl₃, 100 MHz): δ 197.2, 174.5, 143.8, 127.2, 109.5, 95.5, 92.5, 79.1, 79.0, 76.9, 70.6, 64.4, 51.6, 34.6, 34.3, 33.2, 32.1, 29.9, 29.8, 29.7, 29.6, 29.4, 29.3, 28.2, 26.6, 25.4, 25.1, 25.0, 22.8, 17.7, 15.3, 14.3; HRMS (ESI): calcd for [C₃₂H₅₄O₉ + Na]⁺ 605.36600, found 605.36590.
Enone 3.7.5 (158 mg, 0.27 mmol) was dissolved in 0.5 mL dry CH$_2$Cl$_2$ and cooled to –78 °C. To this added a 0.4 M solution of CeCl$_3$•MeOH (0.5 mL). After stirring for 10 min at this temperature, added solid NaBH$_4$ (15.4 mg, 0.41 mmol) in portions. The reaction mixture was stirred at to –78 °C for 2h. Quenched with saturated NaHCO$_3$ at low temperature, diluted with CH$_2$Cl$_2$ and warmed to 0 °C. The aqueous layer was extracted with CH$_2$Cl$_2$ (20mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Silica gel chromatography with 20% EtOAc/hexane gave enol 3.7.6 (140 mg, 89%). Colorless oil: $R_f$ (10% hexanes/EtOAc) = 0.21; $[\alpha]_D^{25} = -44.81$ (c 1.69, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) $\nu$ 3479, 2931, 2856, 1741, 1381, 1133, 1050, 1022, 987, 862; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.86 (t, $J = 7.6$ Hz, 3H), $\delta$ 1.16-1.29 (m, 22H), $\delta$ 1.33 (s, 3H), $\delta$ 1.42-1.49 (m, 6H), 1.52 (s, 3H), $\delta$ 1.59 (p, $J = 7.5$ Hz, 2H), $\delta$ 1.91 (d, $J = 8.0$ Hz, 1H), $\delta$ 2.28 (t, $J = 7.6$ Hz, 2H), $\delta$ 3.56-3.75 (m, 7H), $\delta$ 3.82 (dd, $J = 8.0$, 8.0 Hz, 1H), $\delta$ 4.05 (d, $J = 6.2$ Hz, 1H), 4.17 (dd, $J = 1.6$, 6.2 Hz, 1H), $\delta$ 5.03 (s, 1H), $\delta$ 5.44 (s, 1H), $\delta$ 5.77 (ddd, $J = 2.4$, 4.4, 10.0 Hz, 1H), $\delta$ 5.92 (d, $J = 10.4$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 174.6, 133.7, 126.8, 109.3, 95.5, 93.8, 79.2, 78.4, 77.3, 76.9, 69.6, 68.2, 64.5, 51.6, 34.6, 43.3, 33.1, 32.1, 29.9, 29.7, 29.5, 29.4, 29.3 28.2, 26.7, 25.4, 25.1, 25.0, 22.8, 17.9, 17.5, 14.3; HRMS (ESI): calcd for [C$_{32}$H$_{56}$O$_9$ + Na]$^+$ 607.38165, found 607.38145.
(11S)-methyl-11-(((3aR,4R,6S,7S,7aR)-7-(((2S,6S)-5-(benzyloxy)-6-methyl-5,6-dihydro-2H-pyran-2-yl)oxy)-2,2,6-trimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)oxy)hexadecanoate 3.7.7

Allylic alcohol 3.7.6 (53.9 mg, 0.09 mmol) was dissolved in 0.5 mL dry DMF and cooled to 0 °C. To this added BnBr (22.0 µL, 0.184 mmol) followed NaH (3.3 mg, 0.138 mmol). Ice bath was removed after addition of NaH and the reaction was stirred at rt for 2h. Upon consumption of starting material, the reaction was diluted with Et₂O and quenched with saturated NaHCO₃ at 0 °C. The aqueous layer was extracted with Et₂O (20mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na₂SO₄ and concentrated under reduced pressure.

Silica gel chromatography with 7-8 % EtOAc/hexane gave benzyl ether 3.7.7 (58.3 mg, 96%).

Faint yellowish oil: R_f (20% hexanes/EtOAc) = 0.50; [α]_D^25 = −1.50 (c 0.10, CH₂Cl₂); IR (thin film, cm⁻¹): ν 2934, 2860, 1741, 1478, 1397, 1381, 1130, 1049, 981, 866; ¹H NMR (CDCl₃, 400 MHz): δ 0.88 (t, J = 7.6 Hz, 3H), δ 1.24-1.28 (m, 22H), δ 1.35 (s, 3H), δ 1.44-1.47 (m, 6H), 1.54 (s, 3H), δ 1.61 (p, J = 7.62 Hz, 2H), δ 2.30 (t, J = 8.0 Hz, 2H), δ 3.58-3.77 (m, 8H), δ 4.04 (d, J = 5.2 Hz, 1H), δ 4.20 (dd, J = 1.2, 7.2 Hz, 1H), δ 4.67, 4.55 (ABq, J_AB = 11.6 Hz, 2H), δ 5.04 (s, 1H), δ 5.46 (s, 1H), δ 5.81 (ddd, J = 2.4, 4.4, 10.8 Hz, 1H), δ 6.09 (d, J = 10.4 Hz, 1H), δ 7.28-7.34 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 174.5, 138.2, 130.9, 128.6, 128.1, 128.0, 126.9, 109.3, 95.4, 93.9, 79.3, 78.2, 77.0, 76.4, 71.2, 66.1, 64.6, 51.7, 43.6, 34.3, 33.2, 32.1, 30.0, 29.7, 29.6, 29.4, 29.3, 28.2, 26.7, 25.4, 25.1, 25.0, 22.8, 18.2, 17.5, 14.3; HRMS (ESI): calcd for [C₃₀H₆₂O₉ + Na]^+ 697.4292, found 697.4292.
(S)-methyl-11-(((3aR,4R,6S,7S,7aR)-7-(((2S,3R,4S,5R,6S)-5-(benzyloxy)-3,4-dihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2,2,6-trimethyltetrahydro-3aH-[1,3]dioxolo-[4,5c]-pyran-4-yl)oxy)hexadecanoate 3.7.8

Alkene 3.7.7 (125.5 mg, 0.186 mmol) was dissolved in a 1:1 mixture of t-BuOH/acetone (0.5 mL) and the mixture was cooled to 0 °C. To this added a 50% (v/v) solution of NMO/H2O (0.5 mL). The reaction mixture was stirred at that temperature for 15 min and added OsO4 (2.4 mg, 0.009 mmol). The reaction mixture was stirred overnight without replenishing ice from 0 °C to rt. After consumption of starting material, cooled the reaction to 0 °C, diluted with EtOAc and reduced the excess OsO4 with saturated Na2SO3. The reaction mixture was then concentrated to remove acetone. The aqueous layer was extracted with EtOAc (20mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na2SO4 and concentrated under reduced pressure. Silica gel chromatography with 27-30 % EtOAc/hexane gave diol 3.7.8 (115 mg, 87%). Colorless oil: Rf (30% hexanes/EtOAc) = 0.23; [α]D25 = −76.50 (c 0.40, CH2Cl2); IR (thin film, cm⁻¹) ν 3391, 2920, 2854, 1741, 1387, 1393, 1130, 1047, 986, 866; ¹H NMR (CDCl3, 400 MHz): δ 0.88 (t, J = 7.2 Hz, 3H), δ 1.22-1.33 (m, 22H), δ 1.34 (s, 3H), δ 1.46 (m, 6H), 1.53 (s, 3H), δ 1.60 (p, J = 7.4 Hz, 2H), 1.75 (brs, 1H), δ 2.29 (t, J = 8.0 Hz, 2H), δ 2.43 (d, J = 5.2 Hz, 1H), δ 2.55 (brs, 1H), δ 3.36 (dd, J = 8.8, 9.2 Hz, 1H), δ 3.50 (dd, J = 2.0, 9.6 Hz, 1H), δ 3.62 (p, J = 6.0 Hz, 1H), 3.66 (s, 3H), δ 3.67-3.75 (m, 1H), δ 3.84 (dq, J = 6.0, 8.2 Hz, 1H), δ 3.96 (brs, 1H), δ 4.05 (d, J = 3.2, 1H), δ 4.15 (dd, J = 3.0, 7.6 Hz, 1H), δ 4.74 (s, 2H),
δ 5.03 (s, 1H), δ 5.10 (s, CH₂Cl₂), δ 5.35 (s, 1H), δ 7.29-7.36 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 174.6, 138.4, 128.8, 128.4, 128.3, 128.2, 109.5, 98.4, 95.6, 81.7, 78.8, 75.3, 71.6, 71.5, 67.9, 64.3, 51.7, 34.6, 34.3, 33.2, 32.1, 30.0, 29.7, 29.6, 29.4, 29.3, 28.1, 26.7, 25.4, 25.1, 22.8, 18.1, 18.0, 14.3; HRMS (ESI): calcd for [C₃₉H₆₄O₁₁ + Na]⁺ 731.4312, found 731.4324.

(S)-11-(((3aR,4R,6S,7S,7aR)-7-(((2S,3R,4S,5R,6S)-5-(benzyloxy)-3,4-dihydroxy-6-methyltetrahdro-2H-pyran-2-yl)oxy)-2,2,6-trimethyltetrahydro-3aH-[1,3]-dioxolo[4,5-c]pyran-4-yl)oxy)hexadecanoic acid 3.1.4

Methyl ester 3.7.8 (114.9 mg, 0.162 mmol) was dissolved in a 9:1 mixture of MeOH/H₂O (1.6 mL). To the resulting mixture, added KOH (90.9 mg, 1.62 mmol) and refluxed at 55 °C for 3h. Cooled the reaction mixture to 0 °C, diluted with CH₂Cl₂ and quenched with 1N HCl. The aqueous layer was extracted with CH₂Cl₂ (30mL X 3) and the combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 30-35 % acetone/hexane gave diol-acid 3.1.4 (109 mg, 97%). Colorless oil: Rf (30% acetone/hexane) = 0.35; IR (thin film, cm⁻¹) ν 3469, 2986, 2864, 1741, 1715, 1470, 1383, 1038, 981, 862; ¹H NMR (CDCl₃, 400 MHz): δ 0.88 (t, J = 7.2 Hz, 3H), δ 1.21-1.32 (m, 22H), δ 1.33 (s, 3H), δ 1.46 (m, 6H), 1.53 (s, 3H), δ 1.61 (p, J = 7.6 Hz, 2H), δ 2.32 (t, J = 7.2 Hz, 2H), δ 3.38 (dd, J = 9.2, 9.6 Hz, 1H), δ 3.50 (dd, J = 7.3, 10.0 Hz, 1H), δ 3.62 (p, J = 6.0, 1H), δ 3.66-3.77 (m, 2H), δ 3.86 (dd, J = 2.8, 8.8 Hz, 1H), δ 3.96 (d, J = 2.8 Hz, 1H), δ 4.06 (d, J = 4.8 Hz, 1H), δ 4.16 (dd, J =
4.8, 7.6 Hz, 1H), δ 4.77, 4.73 (ABq, J_AB = 11.6 Hz, 2H), δ 5.04 (s, 1H), δ 5.36 (s, 1H), δ 7.28-7.34 (m, 5H); 13C NMR (CDCl3, 100 MHz): δ 179.2, 138.3, 128.7, 128.2, 128.1, 109.5, 98.4, 95.6, 81.6, 78.8, 77.6, 77.5, 76.9, 75.3, 71.6, 68.0, 64.3, 34.6, 34.1, 33.1, 32.0, 29.9, 29.6, 29.5, 29.3, 29.2, 28.0, 26.5, 25.3, 25.0, 24.8, 22.7, 18.0, 17.9, 14.2.

**Macrolactone disaccharides 3.1.2 and 3.1.3**

Diol acid 3.1.4 (150 mg, 0.22 mmol) was dissolved in dry/degassed toluene (5.4 mL). To the resulting mixture was added Py2S2 (228 mg, 1.13 mmol) and PPh3 (295.6 mg, 1.13 mmol). The reaction was stirred at rt under argon for 5h. Upon consumption of starting material, it was diluted to 20 mL with dry/degassed toluene and loaded into a syringe. Using a syringe-pump, the mixture is added to boiling dry/degassed toluene (230 mL) over a period of 4 days. The reaction was then concentrated under reduced pressure and loaded directly on a column. Gradient elution with 12-13 % EtOAc/hexane gave C-2-macrolactone 3.1.2 (80.9 mg, 54.3%) and elution with 14-15 % EtOAc/hexane C-3-macrolactone 3.1.3 (17.2 mg, 11.5%).

**C-2-macrolactone 3.1.2**: Colorless oil; Rf (30% EtOAc/hexane) = 0.32; [α]D^25 = −24.6 (c 0.5, CHCl3); IR (thin film, cm−1) ν 3448, 2980, 2876, 1741, 1710, 1490, 1036, 980, 861; 1H NMR (CDCl3, 400 MHz): δ 0.88 (t, J = 6.4 Hz, 3H), δ 1.23 (d, J = 5.6 Hz, 3H), δ 1.24-1.47 (m, 27H), δ 1.52 (s, 3H), δ 1.66-1.72 (m, 2H), δ 2.32-2.39 (m, 1H), δ 2.45-2.52 (m, 1H), δ 3.36 (dd, J = 3.2, 8.4 Hz, 1H), δ 3.46-3.51 (m, 1H), δ 3.53 (dd, J = 7.6, 8.8 Hz, 1H), δ 3.85-3.94 (m, 2H),
δ 4.02 (d, J = 5.2 Hz, 1H), δ 4.16 (d, J = 2.8 Hz, 1H), δ 4.20 (dd, J = 4.8, 6.4 Hz, 1H), δ 4.52, 4.71 (ABq, J_{AB} = 11.6 Hz, 2H), δ 4.98 (s, 1H), δ 5.10 (dd, J = 2.8, 5.2 Hz, 1H), δ 5.30 (d, J = 5.2 Hz, 1H), δ 7.27-7.35 (m, 5H); 13C NMR (CDCl₃, 100 MHz): δ 173.2, 137.9, 128.7, 128.2, 128.1, 109.7, 96.7, 95.7, 83.7, 81.2, 78.1, 77.9, 76.0, 73.6, 72.6, 69.9, 68.1, 64.5, 35.2, 34.1, 33.0, 32.2, 29.9, 29.6, 29.5, 28.3, 28.2, 27.9, 26.9, 25.9, 25.2, 23.2, 22.8, 19.2, 17.9, 14.3. HRMS (ESI): calcd for [C₃₈H₆₀O₁₀ + Na]⁺ 699.4084, found 699.4079.

**C-3 macrolactone 3.1.3:** Colorless oil; R_f (20% EtOAc/hexane) = 0.31; [α]_D^{25} = −9.1 (c 0.7, CHCl₃); IR (thin film, cm⁻¹) ν 3446, 2986, 2872, 1740, 1710, 1486, 1038, 984, 866; ¹H NMR (CDCl₃, 400 MHz): δ 0.88 (t, J = 7.2 Hz, 3H), δ 1.23-1.32 (m, 26H), δ 1.34 (s, 3H), δ 1.39-1.48 (m, 2H), 1.50 (s, 3H), δ 1.65 (m, 2H), δ 2.04 (d, J = 5.2 Hz, 1H) δ 2.35 (t, J = 7.2 Hz, 2H), δ 3.36-3.46 (m, 1H), δ 3.54-3.60 (m, 2H), δ 3.95-4.01 (m, 2H), δ 4.02-4.08 (m, 2H), δ 4.22 (t, J = 5.2 Hz, 1H), δ 4.62, 4.69 (ABq, J_{AB} = 10.8 Hz, 2H), δ 4.91 (s, 1H), δ 5.13 (s, 1H), δ 5.35 (dd, J = 2.4, 8.8 Hz, 1H), δ 7.27-7.36 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 173.5, 148.2, 128.6, 128.1, 127.9, 109.9, 98.1, 96.7, 80.4, 79.1, 78.5, 76.8, 74.9, 74.3, 74.1, 71.2, 69.4, 66.3, 34.5, 43.2, 34.1, 32.2, 30.0, 28.6, 27.9, 27.8, 27.7, 27.0, 26.3, 26.1, 25.1, 23.9, 22.8, 19.7, 18.1, 14.3. HRMS (ESI): calcd for [C₃₈H₆₀O₁₀ + Na]⁺ 699.4084, found 699.4079.
**Lactone isomerization:**

The C-2 macrolactone 3.1.2 (291 mg, 0.43 mmol) was dissolved in 25 mL dry toluene and cooled to 0 °C. To this cold solution, 64.2 µL DBU was added and stirred under argon, slowly rising to ambient temperature. After 12h, the reaction mixture was cooled back to 0 °C and diluted with Et₂O. A cold solution of 1N HCl was added and the aqueous layer was extracted with Et₂O. The combined organic layer was washed with NaHCO₃ and brine. Dried over Na₂SO₄ and concentrated under reduced pressure. ¹H NMR of the crude reaction mixture showed a 2:1 mixture of C-2 macrolactone 3.1.2 and C-3 macrolactone 3.1.3. The mixture was taken to next step without further purification.

**Glycosyl acceptors 3.9.1 and 3.9.2**

A mixture of C-2 macrolactone 3.1.2 and C-3 macrolactone 3.1.3 (300 mg, 0.44 mmol) was dissolved in dry CH₂Cl₂ (1.0 mL). The mixture was then cooled to 0 °C and added pyridine (75 µL, 0.92 mmol) and chloroacetic anhydride (151 mg, 0.88 mmol). The resulting mixture was stirred under argon from 0 °C to rt over 2h. Diluted with CH₂Cl₂ and quenched with 1N HCl at 0 °C. The aqueous layer was extracted with CH₂Cl₂ (50mL X 3) and the combined organic layer was washed with saturated NaHCO₃ and brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Passed through a short pad of silica gel to obtain crude chloroacetic ester, which was dissolved in EtOAc (5 mL) and few drops of MeOH. Pd/C (50 mg) was added and under H₂ balloon pressure the reaction was stirred for 3h. The solid Pd/C catalyst was removed by filtration through a celite pad. Filtrate was concentrated under reduced pressure and purified by silica gel chromatography. The C-3 macrolactone 3.9.1 (43 mg) was obtained using 12%
EtOAc/hexane and the C-2 macrolactone 3.9.2 (202 mg) was obtained by using 18-20% EtOAc/hexane. The combined yield for 2 steps was 84%.

3.9.1: Colorless oil: \( R_f \) (20% acetone/hexane) = 0.45; \([\alpha]_D^{25} = -44.81 \) (c 1.69, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) \( \nu \) 3456, 3018, 2864, 1780, 1736, 1470, 1030, 976, 856; \(^1\)H NMR (C\(_6\)D\(_6\), 400 MHz): \( \delta \) 0.90 (t, \( J = 7.2 \text{ Hz}, 3\text{H} \)), \( \delta \) 1.19-1.32 (m, 28H), \( \delta \) 1.41 (d, \( J = 6.6 \text{ Hz}, 3\text{H} \)), 1.46 (s, 3H), \( \delta \) 1.71 (m, 2H), \( \delta \) 1.94 (d, \( J = 5.2 \text{ Hz}, 1\text{H} \)), \( \delta \) 2.16-2.23 (m, 1H), \( \delta \) 2.28-2.35 (m, 1H), \( \delta \) 3.26 (brs, 1H), \( \delta \) 3.41 (s, 2H), \( \delta \) 3.47-3.52 (m, 1H), \( \delta \) 3.96 (dd, \( J = 8.0, 9.6 \text{ Hz}, 1\text{H} \)), \( \delta \) 4.02 (dd, \( J = 6.0, 8.0 \text{ Hz}, 1\text{H} \)), \( \delta \) 4.18-4.23 (m, 2H), \( \delta \) 4.63 (dd, \( J = 6.0, 6.4 \text{ Hz}, 1\text{H} \)), \( \delta \) 5.16 (s, 1H), \( \delta \) 5.49 (dd, \( J = 2.8, 3.6 \text{ Hz}, 1\text{H} \)), \( \delta \) 5.54 (dd, \( J = 3.6, 5.2 \text{ Hz}, 1\text{H} \)), \( \delta \) 5.67 (d, \( J = 5.20 \text{ Hz}, 1\text{H} \)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 173.4, 167.6, 109.7, 96.1, 94.5, 80.8, 79.2, 76.6, 76.1, 75.3, 73.6, 70.6, 68.7, 64.1, 41.1, 34.9, 33.8, 33.1, 32.2, 29.9, 29.6, 29.3, 28.4, 28.3, 28.1, 26.9, 25.5, 25.2, 23.4, 22.8, 18.3, 18.0, 14.3; HRMS (ESI): calcd for \([\text{C}_{33}\text{H}_{55}\text{ClO}_{11} + \text{Na}]^+\) 685.3331, found 685.3315.
3.9.2: Colorless oil: $R_f$ (20% acetone/hexane) = 0.26; $[\alpha]_D^{25} = -34.12$ (c 1.69, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) $\nu$ 3426, 3020, 2864, 1781, 1754, 1491, 1024, 976, 831, 659; $^1$H NMR (CD$_6$D$_6$, 400 MHz): $\delta$ 0.90 (t, $J$ = 7.2 Hz, 3H), $\delta$ 1.21-1.42 (m, 29H), $\delta$ 1.47 (s, 3H), $\delta$ 1.49 (s, 3H), $\delta$ 1.64-1.74 (m, 1H), $\delta$ 2.08 (ddd, $J$ = 4.4, 7.2, 14.6 Hz, 1H), $\delta$ 2.18 (ddd, $J$ = 4.4, 7.0, 14.8 Hz, 1H), $\delta$ 2.57 (d, $J$ = 5.2 Hz, 1H), $\delta$ 3.25 (m, 1H), $\delta$ 3.32, 3.43 (ABq, $J_{AB}$ = 14.8 Hz, 2H), $\delta$ 3.78-3.87 (m, 2H), $\delta$ 4.06 (dq, $J$ = 6.0, 9.8 Hz, 1H), $\delta$ 4.19 (d, $J$ = 6.0 Hz, 1H), 4.24 (dq, $J$ = 6.8, 6.8 Hz, 1H), $\delta$ 4.44 (dd, $J$ = 5.2, 6.0 Hz, 1H), $\delta$ 5.11 (s, 1H), $\delta$ 5.46 (dd, $J$ = 2.8, 10.2 Hz, 1H), $\delta$ 5.48 (s, 1H), $\delta$ 5.68 (s, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 176.7, 166.6, 110.2, 96.2, 95.7, 80.0, 79.4, 74.2, 73.5, 73.2, 71.7, 70.5, 65.8, 41.0, 34.4, 34.2, 33.9, 32.3, 29.9, 29.6, 28.9, 28.8, 28.5, 27.9, 27.8, 26.3, 25.4, 25.1, 25.0, 22.8, 19.8, 17.7, 14.3; HRMS (ESI): calcd for [C$_{33}$H$_{55}$ClO$_{11}$ + Na]$^+$ 685.3331, found 685.3315.
**Tert-butyl((((2S,3R,6R)-6-((4-methoxybenzyl)oxy)-2-methyl-3,6-dihydro-2H-pyran-3-yl)oxy) dimethylsilane 3.11.2**

Allylic alcohol **3.11.1a** (1.85 g, 7.39 mmol) was dissolved in 15 CH$_3$CN and cooled to 0 °C. To this cooled mixture, added DBU (5.3 mL, 36.96 mmol), DMAP (90 mg, 0.74 mmol) and TBSCl (5.57 g, 36.96 mmol). The reaction was stirred under argon from 0 °C to rt for 3h. Water was added and the aqueous phase extracted with Et$_2$O (100 mL X 3). The combined organic layer was washed with 1N HCl, saturated NaHCO$_3$ brine. Dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Silica gel chromatography with 5% EtOAc/hexane gave TBS ether **3.11.2** (2.66 g, 99%). Oily liquid: $R_f$ (10% EtOAc/hexane) = 0.81; $[\alpha]_D^{25} = -64.32$ (c 1.23, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) $\nu$ 2855, 1535, 1168, 1071, 866; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.08 (s, 3H), $\delta$ 0.09 (s, 3H), $\delta$ 0.89 (s, 9H), $\delta$ 1.26 (d, $J = 6.0$ Hz, 3H), $\delta$ 3.79-3.89 (m, 4H), $\delta$ 4.50, 4.73 (ABq, $J_{AB} = 12.0$ Hz, 2H), $\delta$ 5.00 (s, 1H), $\delta$ 5.67 (dd, $J = 2.8$, 10.4 Hz, 2H), $\delta$ 5.85 (d, $J = 8.8$ Hz, 1H), $\delta$ 6.89 (d, $J = 8.0$ Hz, 2H), $\delta$ 7.30 (d, $J = 8.8$ Hz, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 159.4, 134.9, 130.4, 129.8, 125.7, 113.9, 93.6, 70.4, 69.6, 67.9, 25.9, 18.4, −4.0, −4.5; HRMS (ESI): calcd for [C$_{20}$H$_{32}$O$_4$Si + Na]$^+$ 387.1968, found 387.1971.
(2R,3R,4S,5R,6S)-5-(
(tert-butyldimethylsilyl)oxy)-2-
((4-methoxybenzyl)oxy)-6-
methyltetrahydro-2H-pyran-3,4-diol 3.10.4

Alkene 3.11.2 (3.31 g, 9.10 mmol) was dissolved in a 1:1 mixture of t-BuOH/acetone (10.0 mL) and the mixture was cooled to 0 °C. To this added a 50% (v/v) solution of NMO/H2O (10.0 mL). The reaction mixture was stirred at that temperature for 15 min and added OsO4 (50 mg, 0.19 mmol). The reaction mixture was stirred overnight without replenishing ice from 0 °C to rt. After consumption of starting material the reaction was cooled back to 0 °C, diluted with EtOAc and reduced the excess OsO4 with saturated Na2SO3. The reaction mixture was then concentrated to remove acetone. The aqueous layer was extracted with EtOAc (100mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na2SO4 and concentrated under reduced pressure. Silica gel chromatography with 25-30 % EtOAc/hexane gave diol 3.10.4 (3.11 g, 86%). Colorless oil: Rf (30% hexanes/EtOAc) = 0.25; [α]D25 = −62.91 (c 1.54, CH2Cl2); IR (thin film, cm−1) ν 3400, 3310, 2834, 2805, 1464, 1168, 1075; 1H NMR (CDCl3, 400 MHz): δ 0.11 (s, 3H), δ 0.13 (s, 3H), δ 0.91 (s, 9H), δ 1.29 (d, J = 6.2 Hz, 3H), δ 2.54 (brs, 1H), δ 3.47 (dd, J = 8.8, 8.8 Hz, 1H), δ 3.68 (dq, J = 6.2, 8.8 Hz, 1H), δ 3.75 (dd, J = 3.2, 8.8 Hz, 1H), δ 3.80 (s, 3H), δ 3.91 (dd, J = 1.6, 3.2 Hz, 1H), δ 4.43, 4.64 (ABq, JAB = 12.0 Hz, 2H), δ 4.81 (s, 1H), δ 6.89 (d, J = 8.4 Hz, 2H), δ 7.26 (d, J = 8.8 Hz, 2H); 13C NMR (CDCl3, 100 MHz): δ 159.5, 129.8, 129.5, 114.0, 98.5, 74.9, 72.3, 71.5, 68.8, 68.6, 55.4, 26.1, 18.4, 18.3, −4.1, −4.2; HRMS (ESI): calcd for [C20H34O6Si + Na]+ 421.2022, found 421.2012.
(2R,3R,4S,5R,6S)-5-((tert-butyldimethylsilyl)oxy)-4-hydroxy-2-((4-methoxybenzyl)oxy)-6-methyltetrahydro-2H-pyran-3-yl isobutyrate 3.11.3

Diol 3.10.4 (216 mg, 0.54 mmol) was dissolved in dry CH₂Cl₂ (18.0 mL) and the mixture was cooled to 0 °C. To this added isobutyric acid (49.2 µL), DCC (133.2 mg, 0.65 mmol) and DMAP (33 mg, 0.27 mmol). The reaction mixture was stirred at 0 °C for 3h under argon then quenched with saturated NaHCO₃ at 0 °C. The aqueous layer was extracted with EtOAc (50 mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 10 % EtOAc/hexane gave isobutyryl ester 3.11.3 (181.6 mg, 72%). Colorless oil: Rf (15% hexanes/EtOAc) = 0.50; [α]D²⁵ = −45.68 (c 0.57, CH₂Cl₂); IR (thin film, cm⁻¹) ν 3310, 2864, 1754, 1514, 1168, 862; ¹H NMR (CDCl₃, 400 MHz): δ 0.11 (s, 3H), δ 0.12 (s, 3H), δ 0.90 (s, 9H), δ 1.19 (d, J = 6.8 Hz, 3H), δ 1.21 (d, J = 6.8 Hz, 3H), δ 1.30 (d, J = 6.4 Hz, 3H), δ 1.91 (brs, 1H), δ 2.63 (septet, J = 6.4 Hz, 1H), δ 3.47 (dd, J = 8.8, 8.8 Hz, 1H), δ 3.68 (dq, J = 6.4, 9.2 Hz, 1H), δ 3.80 (s, 3H), δ 3.94 (dd, J = 3.0, 8.8 Hz, 2H), δ 4.44, 4.64 (ABq, JAB = 12.0 Hz, 2H), δ 4.77 (s, 1H), δ 5.15 (dd, J = 1.2, 3.0 Hz, 1H), δ 6.89 (d, J = 8.4 Hz, 2H), δ 7.27 (d, J = 8.8 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 177.0, 159.5, 129.9, 129.3, 114.0, 96.9, 75.1, 72.6, 70.9, 69.1, 68.9, 55.4, 34.2, 26.1, 19.4, 18.9, 18.5, 18.4, −3.7, −4.3; HRMS (ESI): calcd for [C₂₄H₄₀O₇Si + Na]⁺ 491.2441, found 491.2450.
Glycosyl acceptor 3.12.3 (486 mg, 1.50 mmol) was dissolved in 3.0 mL dry CH$_2$Cl$_2$. To this added α-L-Boc-pyranone 3.4.5 (514 mg, 2.25 mmol). The reaction mixture was cooled to 0 °C and added a premixed solution of Pd$_2$(dba)$_3$•CHCl$_3$ (77.6 mg, 0.075 mmol) and PPh$_3$ (78.9 mg, 0.03 mmol) in CH$_2$Cl$_2$ via cannula under argon. The reaction mixture was stirred overnight under argon at 0 °C. Concentrated the reaction mixture under reduced pressure and flash chromatography with 7% EtOAc/hexane yielded the desired product 3.12.4 (626 mg, 96%). Colorless solid: $R_f$ (15% hexanes/EtOAc) = 0.43; mp: 98 °C; $[\alpha]_{D}^{25}$ = −12.84 (c 2.32, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) ν 2855, 1740, 1709, 1168, 1071, 866; $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.29 (d, $J = 6.0$ Hz, 3H), δ 1.33 (s, 3H), δ 1.38 (d, $J = 6.8$ Hz, 3H), δ 1.55 (s, 3H), δ 3.67 (dd, $J = 7.2$, 9.2 Hz, 1H), δ 3.74 (dq, $J = 6.0$, 9.6 Hz, 1H), δ 3.79 (s, 3H), δ 4.14 (d, $J = 3.2$ Hz, 1H), δ 4.20 (dd, $J = 3.0$, 7.4 Hz, 1H) δ 4.51, 4.63 (ABq, $J_{AB} = 11.6$ Hz, 2H), δ 4.54 (q, $J = 7.2$ Hz, 1H), δ 5.04 (s, 1H), δ 5.77 (d, $J = 3.6$ Hz, 1H), δ 6.07 (d, $J = 9.6$ Hz, 1H), δ 6.85 (dd, $J = 3.8$, 10.4 Hz, 1H), δ 6.89 (d, $J = 8.8$ Hz, 2H), δ 7.27 (d, $J = 8.6$ Hz, 2H), $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 197.2, 159.6, 143.8, 130.2, 129.1, 127.2, 114.1, 109.7, 95.9, 92.4, 78.9, 78.8, 76.5, 70.6, 68.9, 64.3, 55.5, 28.2, 26.5, 17.9, 15.3; HRMS (ESI): calcd for [C$_{23}$H$_{30}$O$_8$ + Na]$^+$ 457.1838, found 457.1830.
(2S,6R)-6-(((2S,3R,4S,5R,6R)-4,5-dihydroxy-6-((4-methoxybenzyl)oxy)-2-methyl tetrahydro-2H-pyran-3-yl)oxy)-2-methyl-2H-pyran-3-(6H)-one 3.12.5

Acetonide protected syn-diol 3.12.4 (912 mg, 2.09 mmol) was dissolved in 45 mL CH₂Cl₂. Cooled to 0 °C and slowly added 3.9 mL aqueous solution TFA (10:1). The reaction mixture was stirred at 0 °C for 10 min and quenched with Et₃N. Water was added and the aqueous phase extracted with CH₂Cl₂ (100 mL X 3). The combined organic layer was washed with 1N HCl, saturated NaHCO₃ and brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 50 % EtOAc/hexane gave diol 3.12.5 (659 mg, 80%). Colorless oil: $R_f$ (50% hexanes/EtOAc) = 0.45; $[\alpha]_D^{25} = -22.56$ (c 1.03, CH₂Cl₂); IR (thin film, cm⁻¹) ν 3469, 3305, 2950, 1741, 1680, 1168, 954, 864; $^1$H NMR (CDCl₃, 400 MHz): δ 1.34 (d, $J = 6.0$ Hz, 3H), δ 1.37 (d, $J = 6.4$ Hz, 3H), δ 2.69 (brs, 1H), δ 3.66 (dd, $J = 8.8$, 9.6 Hz, 1H), δ 3.75 (dq, $J = 6.0$, 9.6 Hz, 1H), δ 3.79 (s, 3H), δ 3.87 (dd, $J = 1.6$, 3.2 Hz, 1H), δ 3.96 (dd, $J = 2.8$, 8.8 Hz, 1H), δ 4.42, 4.62 (ABq, $J_{AB} = 11.6$ Hz, 2H), δ 4.57 (q, $J = 7.6$ Hz, 1H), δ 4.82 (s, 1H), δ 5.74 (d, $J = 3.6$ Hz, 1H), δ 6.07 (d, $J = 10.4$ Hz, 1H), δ 6.86 (d, $J = 8.8$ Hz, 2H), δ 6.85 (dd, $J = 4.0$, 9.6 Hz, 1H), δ 7.24 (d, $J = 8.0$ Hz, 2H); $^{13}$C NMR (CDCl₃, 100 MHz): δ 197.2, 159.6, 143.8, 129.9, 129.1, 127.0, 114.0, 98.5, 94.2, 79.7, 72.5, 71.8, 70.8, 69.1, 66.7, 55.5, 18.1, 15.5; HRMS (ESI): calcd for [C₂₀H₂₆O₈ + Na]⁺ 417.1525, found 417.1526.

The syn-diol 3.12.5 (300 mg, 0.76 mmol) was dissolved in 12.7 mL toluene. The reaction mixture was stirred at rt for 10 min until all starting material dissolved. Bu$_2$SnO (227.2 mg, 0.913 mmol) was added and refluxed for 3h under argon. During reflux, the reaction turned faint orangish in color. Toluene was removed under reduced pressure and the residue was dried under high vacuum for 30 min. The residue was redissolved in dry CH$_3$CN (7.6 mL) and cooled to 0 ºC. DIPEA (0.19 mL, 1.06 mmol) was added followed by slow addition of isobutyrylchloride (0.11mL, 1.06 mmol). The reaction mixture was stirred at this temperature for 1h. Diluted with CH$_2$Cl$_2$ and quenched with saturated NaHCO$_3$. The aqueous phase extracted with CH$_2$Cl$_2$ (100 mL X 2). The combined organic layer was washed with saturated brine. Dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Silica gel chromatography with 27% EtOAc/hexane gave isobutyric ester 3.12.6 (286 mg, 81%). Colorless oil: $R_f$ (40% hexanes/EtOAc) = 0.62; [$\alpha$]$_D^{25}$ = –14.34(c 0.97, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) ν 3340, 2950, 2848, 1814, 1741, 1684, 1168, 1073, 864, 684; $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.21 (d, $J$ = 6.4 Hz, 6H), δ 1.33 (d, $J$ = 6.4 Hz, 3H), δ 1.37 (d, $J$ = 6.2 Hz, 3H), δ 2.04 (brs, 1H), δ 2.62 (septet, $J$ = 6.8 Hz, 1H), δ 3.79 (s, 3H), δ 3.85 (dq, $J$ = 6.0, 9.2 Hz, 1H), δ 3.90 (dd, $J$ = 8.0, 9.2 Hz, 1H), δ 4.05 (s, 1H), δ 4.47, 4.65 (ABq, $J_{AB}$ = 11.6 Hz, 2H), 4.54 (q, $J$ = 5.6 Hz, 1H), δ 4.80 (s, 1H), δ 5.19 (dd, $J$ = 2.5, 9.0 Hz, 1H), δ 5.41 (d, $J$ = 1.5 Hz, 1H), δ 6.01 (d, $J$ = 7.6 Hz, 1H), δ 6.62 (dd, $J$ = 1.6, 8.4 Hz, 1H), δ 6.86 (d, $J$ = 6.4 Hz, 2H), δ 7.24 (d, $J$ = 6.2 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 196.7, 176.1, 159.6,
189.6, 129.9, 129.1, 127.5, 114.0, 98.3, 94.3, 75.0, 70.8, 69.8, 69.1, 67.2, 55.5, 34.4, 19.3, 19.2, 18.1, 15.1; HRMS (ESI): calcd for $[C_{24}H_{32}O_9 + Na]^+$ 487.1944, found 487.1955.

$(2R,3R,4R,5S,6S)-3$-(2-chloroacetoxy)-2-((4-methoxybenzyl)oxy)-6-methyl-5
($(2R,6S)-6$-methyl-5-oxo-$2H$-pyran-2-yl)oxy)-tetrahydro-$2H$-pyran-
4-yl isobutyrate 3.13.1

Alcohol 3.12.6 (400 mg, 0.86 mmol) was dissolved in dry CH$_2$Cl$_2$ (9.0 mL). The mixture was then cooled to 0 °C and added pyridine (139 µL, 136.23 mmol), chloroacetic anhydride (295 mg, 1.72 mmol) and DMAP (52 mg, 0.43 mmol). The resulting mixture was stirred under argon from 0 °C to rt over 2h. Diluted with CH$_2$Cl$_2$ and quenched with 1N HCl at 0 °C. The aqueous layer was extracted with CH$_2$Cl$_2$ (50mL X 3) and the combined organic layer was washed with saturated NaHCO$_3$ and brine. Dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Silica gel chromatography using 10% EtOAc/hexane to obtain 3.13.1 (461 mg, 99%). Colorless solid: $R_f$ (30% acetone/hexane) = 0.82; mp: 118 °C; $[\alpha]_D^{25} = -22.66$ (c 0.48, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) $\nu$ 2954, 2864, 1768, 1736, 1682, 1534, 1030, 976, 866; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.16 (d, $J = 6.4$ Hz, 6H), $\delta$ 1.35 (d, $J = 6.4$ Hz, 3H), $\delta$ 1.39 (d, $J = 7.2$ Hz, 3H), $\delta$ 2.51 (septet, $J = 7.2$ Hz, 1H), $\delta$ 3.80 (s, 3H), $\delta$ 3.86-3.88 (m, 2H), $\delta$ 4.06, 4.13 (ABq, $J_{AB} = 15.2$ Hz, 2H), $\delta$ 4.48, 4.64 (ABq, $J_{AB} = 11.8$ Hz, 2H), 4.55 (q, $J = 6.4$ Hz, 1H), $\delta$ 4.76 (s, 1H), $\delta$ 5.32-5.35 (m, 2H), $\delta$ 5.40 (d, $J = 3.6$ Hz, 1H), $\delta$ 6.01 (d, $J = 10.4$ Hz, 1H), $\delta$ 6.62 (dd, $J = 4.0$, 10.4 Hz, 1H), $\delta$ 6.88 (d, $J = 8.4$ Hz, 2H), $\delta$ 7.26 (d, $J = 8.8$ Hz, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 196.4, 175.7, 166.7, 159.7, 142.2, 130.0, 128.6, 114.1, 95.9, 94.5, 72.4, 72.0, 70.8, 69.3, 67.3, 55.5, 40.8, 34.2,
29.9, 18.9, 18.0, 15.1; HRMS (ESI): calcd for [C\textsubscript{26}H\textsubscript{33}ClO\textsubscript{10} + Na]\textsuperscript{+} 563.1660, found 563.1671.

\((2S,3R,6S)-6\-((2S,3S,4R,5R,6R)-5\-(2\text{-chloroacetoxy})\-4\-(\text{isobutyryloxy})\-6\-((4\text{-methoxybenzyl})\text{oxy})\-2\text{-methyltetrahydro-2H-pyran-3-yl})\text{oxy})\-2\text{-methyl-3,6-dihydro-2H-pyran-3-yl-isobutyrate} 3.13.2

Enone \textbf{3.13.1} (436 mg, 0.81 mmol) was dissolved in 8.1 mL dry CH\textsubscript{2}Cl\textsubscript{2} and cooled to \(-78 ^\circ\text{C}\). To this added a 0.4 M solution of CeCl\textsubscript{3}•MeOH (1.5 mL). After stirring for 10 min at this temperature, added solid NaBH\textsubscript{4} (46.17 mg, 1.22 mmol) in portions. The reaction mixture was stirred at to \(-78 ^\circ\text{C}\) for 2h. Quenched with saturated NaHCO\textsubscript{3} at low temperature, diluted with CH\textsubscript{2}Cl\textsubscript{2} and warmed to 0 °C. The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (50mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Crude allylic alcohol was passed through a pad of celite and carried to next step without further purification. The allylic alcohol thus obtained was dissolved in dry CH\textsubscript{2}Cl\textsubscript{2} (9.0 mL). The mixture was then cooled to 0 °C and added DIPEA (240 µL, 1.38 mmol), isobutyralchloride (135 µL, 1.28 mmol) and DMAP (10.5 mg, 0.086 mmol). The resulting mixture was stirred under argon from 0 °C to rt over 2h. Diluted with CH\textsubscript{2}Cl\textsubscript{2} and quenched with 1N HCl at 0 °C. Organic layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (50mL X 3) and the combined organic layer was washed with saturated NaHCO\textsubscript{3} and brine. Dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Silica gel chromatography using 10% EtOAc/hexane to obtain \textbf{3.13.2} (427 mg, 86%, 2 steps). Colorless solid: \(R_f\) (30% acetone/hexane) = 0.86; mp: 76 °C; \([\alpha]_D^{25} = -92.24\) (c 0.55, CH\textsubscript{2}Cl\textsubscript{2}); IR (thin film, cm\textsuperscript{-1}) \(\nu\) 2962, 1864, 1790, 1764, 1652, 1537, 1117, 1029, 964,
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.12 (d, $J = 6.8$ Hz, 3H), $\delta$ 1.14 (d, $J = 6.4$ Hz, 3H), $\delta$ 1.16 (d, $J = 6.2$ Hz, 3H), $\delta$ 1.18 (d, $J = 6.0$ Hz, 3H), $\delta$ 1.22 (d, $J = 6.8$ Hz, 3H), $\delta$ 1.34 (d, $J = 6.4$ Hz, 3H), $\delta$ 2.45 (septet, $J = 7.6$ Hz, 1H), $\delta$ 2.56 (septet, $J = 7.2$ Hz, 1H), $\delta$ 3.80 (s, 3H), $\delta$ 3.82-3.94 (m, 3H), $\delta$ 4.09, 4.13 (ABq, $J_{AB} = 14.8$ Hz, 2H), $\delta$ 4.44, 4.63 (ABq, $J_{AB} = 12.0$ Hz, 2H), $\delta$ 4.78 (s, 1H), $\delta$ 5.04 (d, $J = 8.4$ Hz, 1H), $\delta$ 5.17 (s, 1H), $\delta$ 5.30 (dd, $J = 2.8, 8.6$ Hz, 1H), $\delta$ 5.32 (s, 1H), $\delta$ 5.60 (dd, $J = 2.0, 10.4$ Hz, 1H), $\delta$ 5.84 (d, $J = 10.4$ Hz, 1H), $\delta$ 6.87 (d, $J = 8.8$ Hz, 2H), $\delta$ 7.25 (d, $J = 8.8$ Hz, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 176.7, 175.8, 166.7, 159.6, 130.9, 129.9, 128.7, 126.7, 114.1, 95.9, 95.5, 76.5, 72.4, 70.2, 69.2, 67.4, 65.5, 55.5, 40.8, 34.2, 19.1, 19.0, 18.9, 17.8, 17.7; HRMS (ESI): calcd for [C$_{30}$H$_{41}$ClO$_{11}$ + Na]$^+$ 635.2235, found 635.2230.


PMB ether 3.13.2 (528 mg, 0.86 mmol) was dissolved in 3.0 mL aqueous CH$_2$Cl$_2$ (20:1) and cooled to 0 ºC. To this added solid DDQ (586.5 mg, 2.58 mmol) in portions. The reaction was allowed to rise to room temperature and stirred overnight at ambient temperature. Upon consumption of starting material, reaction was filtered through a short celite pad and subsequently washed with saturated NaHCO$_3$ at 0 ºC. The aqueous layer was extracted with CH$_2$Cl$_2$ (50mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Silica gel chromatography using 18-20% EtOAc/hexane to obtain glycosyl donor 3.13.3 (348 mg, 82%) as a mixture of diastereomers
(9:1, α:β). Colorless solid: $R_f$ (20% EtOAc/hexane) = 0.25; mp: 114-118 °C; $[\alpha]_D^{25} = -65.54$ (c 0.53, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) ν 3454, 3110, 2973, 1851, 1780, 1598, 1220, 1136, 1029, 866; $^1$H NMR for the major diastereomes (CDCl$_3$, 400 MHz): δ 1.13 (d, $J = 6.6$ Hz, 3H), δ 1.15 (d, $J = 6.2$ Hz, 3H), δ 1.16 (d, $J = 6.0$ Hz, 3H), δ 1.18 (d, $J = 7.0$ Hz, 3H), δ 1.22 (d, $J = 6.0$ Hz, 3H), δ 1.37 (d, $J = 6.0$ Hz, 3H), δ 1.38 (d, $J = 6.0$ Hz, 3H), δ 2.50 (septet, $J = 6.4$ Hz, 1H), δ 2.56 (septet, $J = 6.4$ Hz, 1H), δ 3.13 (d, $J = 3.6$ Hz, 1H), δ 3.81 (dd, $J = 9.6, 9.6$ Hz, 1H), δ 3.92 (dq, $J = 6.4, 9.6$ Hz, 1H), δ 4.09 (dq, $J = 6.4, 6.8$ Hz, 1H), δ 4.12 (s, 2H), δ 5.04 (dd, $J = 3.0, 9.2$ Hz, 1H), δ 5.15 (d, $J = 3.2$ Hz, 1H), δ 5.19 (s, 1H), δ 5.33-5.35 (m, 2H), δ 5.64 (d, $J = 10.0$ Hz, 1H), δ 5.85 (d, $J = 10.4$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 176.8, 175.9, 166.9, 130.9, 126.8, 95.6, 91.9, 76.4, 72.3, 71.9, 70.3, 67.4, 65.6, 40.8, 34.3, 19.1, 19.0, 18.9, 17.9, 17.7; HRMS (ESI): calcd for [C$_{22}$H$_{33}$ClO$_{10}$ + Na]$^+$ 515.1660, found 515.1662.

(2S,3R,6S)-6-(((2S,3S,4R,5R,6S)-5-(2-chloroacetoxy)-4-(isobutyryloxy)-2-methyl-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2H-pyran-3-yl)oxy)-2-methyl-3,6-dihydro-2H-pyran-3-yl isobutyrate 3.13.4

Glycosyl donor 3.13.3 (50 mg, 0.10 mmol) was dissolved in 1.0 mL dry CH$_2$Cl$_2$ and cooled to 0 °C. To this added CNCCl$_3$ (102 µL, 1.04 mmol) and NaH (0.24 mg, 0.01 mmol). The reaction was stirred at 0 °C under argon for 3h. Upon consumption of starting material, reaction was directly loaded to a column (column diameter: 0.5 cm, packed with 2 cm celite and 3 cm silica gel). Elution with 5-10% EtOAc/hexane gave trichloroacetimidate 3.13.4 (56 mg, 88%) as a
mixture of diastereomers (10:1, α:β). Colorless oil: \( R_f (20\% \text{ EtOAc/hexane}) = 0.75; [\alpha]_D^{25} = -20.46 \) (c 0.05, benzene); IR (thin film, cm\(^{-1}\)) \( \nu \) 3430, 3120, 2964, 1851, 1780, 1652, 1556, 1136, 1031, 864; \(^1\)H NMR for the major diastereomes (C\(_6\)D\(_6\), 400 MHz): \( \delta \) 0.99-1.03 (m, 9H), \( \delta \) 1.07 (d, \( J = 6.4 \) Hz, 3H), \( \delta \) 1.18 (d, \( J = 6.0 \) Hz, 3H), \( \delta \) 1.44 (d, \( J = 5.6 \) Hz, 3H), \( \delta \) 2.29-2.37 (m, 2H), \( \delta \) 3.25, 3.35 (ABq, \( J_{AB} = 14.8 \) Hz, 2H), \( \delta \) 4.07 (dq, \( J = 2.8, 5.6 \) Hz, 1H), \( \delta \) 4.14 (dd, \( J = 9.6, 9.6 \) Hz, 1H), \( \delta \) 4.29 (dq, \( J = 4.0, 5.6 \) Hz, 1H), \( \delta \) 5.27 (d, \( J = 8.8 \) Hz, 1H), \( \delta \) 5.41 (s, 1H), \( \delta \) 5.63 (d, \( J = 10.4 \) Hz, 1H), \( \delta \) 5.71 (dd, \( J = 2.8, 10.0 \) Hz, 1H), \( \delta \) 5.79 (d, \( J = 10.4 \) Hz, 1H), \( \delta \) 5.85 (s, 1H), \( \delta \) 6.39 (s, 1H), \( \delta \) 8.47 (s, 1H); \(^{13}\)C NMR (C\(_6\)D\(_6\), 100 MHz): \( \delta \) 176.2, 175.7, 166.6, 160.3, 131.3, 127.5, 96.2, 95.6, 91.4, 76.2, 72.9, 71.2, 70.8, 70.3, 66.2, 40.5, 34.5, 19.3, 19.2, 19.1, 18.4, 18.0; HRMS (ESI): calcd for [C\(_{24}\)H\(_{33}\)Cl\(_4\)NO\(_{10}\) + Na]\(^+\) 658.0756, found 658.0767.

\((2S,6R)-6-(((3aR,4R,6S,7S,7aR)-4-(benzyloxy)-2,2,6-trimethyltetrahydro-3aH-[1,3]-dioxolo-[4,5-c]-pyran-7-yl)oxy)-2-methyl-2H-pyran-3(6H)-one 3.15.2\)

Glycosyl acceptor 3.14.1 (2.17 g, 7.4 mmol) was dissolved in 15 mL dry CH\(_2\)Cl\(_2\). To this added α-L-Boc-pyranone 3.4.5 (2.53 g, 11.1 mmol). The reaction mixture was cooled to 0 °C and added a premixed solution of Pd\(_2\)(dba)\(_3\)•CHCl\(_3\) (574 mg, 0.55 mmol) and PPh\(_3\) (584 mg, 2.2 mmol) in CH\(_2\)Cl\(_2\) via cannula under argon. The reaction mixture was stirred under argon at 0 °C overnight. Concentrated the reaction mixture under reduced pressure and flash chromatography with 10% EtOAc/hexane yielded the desired product 3.15.2 (3.02 g, 94%). Colorless oil: \( R_f (20\% \text{ hexanes/EtOAc}) = 0.6; [\alpha]_D^{25} = -12.16 \) (c 1.09, CH\(_2\)Cl\(_2\); IR (thin film, cm\(^{-1}\)) \( \nu \) 2854, 1741, 1680, 1531, 1462, 1371, 1267, 1197, 1036; \( \delta \) 0.85-1.03 (m, 9H), \( \delta \) 1.04-1.18 (m, 3H), \( \delta \) 1.20 (d, \( J = 6.4 \) Hz, 3H), \( \delta \) 1.42 (d, \( J = 5.6 \) Hz, 3H), \( \delta \) 2.28-2.35 (m, 2H), \( \delta \) 3.28, 3.35 (ABq, \( J_{AB} = 14.8 \) Hz, 2H), \( \delta \) 4.08 (dq, \( J = 2.8, 5.6 \) Hz, 1H), \( \delta \) 4.14 (dd, \( J = 9.6, 9.6 \) Hz, 1H), \( \delta \) 4.29 (dq, \( J = 4.0, 5.6 \) Hz, 1H), \( \delta \) 5.26 (d, \( J = 8.8 \) Hz, 1H), \( \delta \) 5.40 (s, 1H), \( \delta \) 5.62 (d, \( J = 10.4 \) Hz, 1H), \( \delta \) 5.70 (d, \( J = 10.4 \) Hz, 1H), \( \delta \) 5.84 (s, 1H), \( \delta \) 6.36 (s, 1H), \( \delta \) 8.47 (s, 1H); HRMS (ESI): calcd for [C\(_{24}\)H\(_{33}\)Cl\(_4\)NO\(_{10}\) + Na]\(^+\) 658.0756, found 658.0767.
\[ \text{1H NMR (CDCl}_3, 400 \text{ MHz): } \delta 1.29 (d, J = 6.6 \text{ Hz, 3H}), \delta 1.34 (s, 3H), \delta 1.38 (d, J = 6.8 \text{ Hz, 3H}), \delta 1.56 (s, 3H), \delta 3.67-3.79 (m, 2H), \delta 4.18 (d, J = 3.2 \text{ Hz, 1H}), \delta 4.25 (dd, J = 8.0, 8.4 \text{ Hz, 1H}), \delta 4.71 (d, J = 11.6 \text{ Hz, 1H}), \delta 5.08 (s, 1H), \delta 5.77 (s, 1H), \delta 6.75 (d, J = 9.6 \text{ Hz, 1H}), \delta 6.85 (dd, J = 3.0, 9.4 \text{ Hz, 1H}), \delta 7.29-7.34 \text{ (m, 5H)}; \]

\[ \text{13C NMR (CDCl}_3, 100 \text{ MHz): } \delta 196.9, 143.7, 137.1, 128.6, 128.1, 127.1, 109.6, 96.2, 92.4, 78.9, 76.4, 70.5, 69.3, 64.3, 28.1, 26.5, 17.8, 15.2; \]

HRMS (ESI): calcd for [C\text{22}H\text{28}O\text{7} + Na]\text{]}^+ 427.1733, found 427.1720.

\[(2S,6R)-6-(((2S,3R,4S,5R,6R)-6-(benzyloxy)-4,5-dihydroxy-2-methyltetrahydro-2H-pyran-3-yl)oxy)-2-methyl-2H-pyran-3(6H)-one 3.15.3\]

Acetonide protected \textit{syn}-diol \textbf{3.15.2} (1.0 g, 2.3 mmol) was dissolved in 24.7 mL CH\textsubscript{2}Cl\textsubscript{2}. Cooled to 0 °C and slowly added 2.5 mL aqueous solution TFA (10:1). The reaction mixture was stirred at 0 °C for 10 min and quenched with Et\textsubscript{3}N. Water was added and the aqueous phase extracted with CH\textsubscript{2}Cl\textsubscript{2} (100 mL X 3). The combined organic layer was washed with 1N HCl, saturated NaHCO\textsubscript{3} and brine. The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Silica gel chromatography with 50% EtOAc/hexane gave diol \textbf{3.15.3} (788 mg, 94%). Colorless oil: \( R_f \) (50% hexanes/EtOAc) = 0.31; [\( \alpha \)]\textsubscript{D}\textsuperscript{25} = −15.42 (c 1.95, CH\textsubscript{2}Cl\textsubscript{2}); IR (thin film, cm\textsuperscript{-1}) \( \nu \) 3460, 3320, 2950, 1741, 1681, 1023, 964, 866; \textbf{1H NMR (CDCl}_3, 400 \text{ MHz):}\]

\[ \delta 1.33 (d, J = 6.0 \text{ Hz, 3H}), \delta 1.37 (d, J = 6.8 \text{ Hz, 3H}), \delta 3.0 (d, J = 8.0 \text{ Hz, 1H}), \delta 3.1 (d, J = 4.4 \text{ Hz, 1H}), \delta 3.68 (dd, J = 9.6, 9.6 \text{ Hz, 1H}), \delta 3.75 (dq, J = 6.6, 9.6 \text{ Hz, 1H}), \delta 3.91 (s, 1H), \delta 3.97 (dd, J = 3.2, 8.4 \text{ Hz, 1H}), \delta 4.46, 4.69 (\text{ABq, } J_{\text{AB}} = 11.6 \text{ Hz, 2H}), \delta 4.57 (q, J = 6.8 \text{ Hz, 1H}), \]
δ 4.84 (s, 1H), δ 5.74 (d, J = 3.2 Hz, 1H), δ 6.06 (d, J = 10.0 Hz, 1H), δ 6.89 (dd, J = 2.0, 9.6 Hz, 1H), δ 7.29-7.35 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 197.3, 143.8, 137.1, 128.6, 128.2, 128.1, 126.9, 98.8, 94.2, 79.6, 76.9, 72.5, 71.7, 70.7, 69.4,18.1, 15.2; HRMS (ESI): calcd for [C₁₀H₂₄O₇ + Na]⁺ 387.1420, found 387.1418.

(2R,3R,4S,5S,6S)-2-(benzyloxy)-3-hydroxy-6-methyl-5-(((2R,6S)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-4-yl isobutyrate 3.15.4

The syn-diol 3.15.3 (1.8 g, 4.94 mmol) was dissolved in 82.3 mL toluene. The reaction mixture was stirred at rt for 10 min until all starting material dissolved. Bu₂SnO (1.48 g, 5.93 mmol) was added and refluxed for 3h under argon. During reflux, the reaction turned faint yellowish in color. Toluene was removed under reduced pressure and the residue was dried under high vacuum for 30 min. dissolved the residue in dry CH₃CN (49 mL) and cooled to 0 °C. DIPEA (1.2 mL, 6.92 mmol) was added followed by slow addition of isobutyrylchloride (0.73 mL, 6.91 mmol). The reaction mixture was stirred at this temperature for 1h then diluted with CH₂Cl₂ and quenched with saturated NaHCO₃. The aqueous phase extracted with CH₂Cl₂ (100 mL X 2). The combined organic layer was washed with saturated brine, dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 25% EtOAc/hexane gave isobutyric ester 3.15.4 (1.72 g, 80%). Colorless oil: R_f (40% hexanes/EtOAc) = 0.65; [α]D²⁵ = −20.10 (c 1.43, CH₂Cl₂); IR (thin film, cm⁻¹) v 3327, 2930, 1814, 1756, 1638, 1168, 1071, 864; ¹H NMR (CDCl₃, 400 MHz): δ 1.20 (d, J = 6.4 Hz, 6H), δ 1.35 (d, J = 6.2 Hz, 3H), δ 1.36 (d, J = 6.2 Hz, 3H), δ 2.19 (brs, 1H), δ 2.63 (septet, J = 6.8 Hz, 1H), δ 3.86 (dq, J = 6.4, 8.6 Hz, 1H), δ 3.94 (dd, J =
9.6, 9.6 Hz, 1H), δ 4.09 (s, 1H), δ 4.50, 4.72 (ABq, J_{AB} = 11.6 Hz, 2H), 4.53 (q, J = 6.8 Hz, 1H), δ 4.81 (s, 1H), δ 5.25 (dd, J = 2.0, 9.2 Hz, 1H), δ 5.41 (d, J = 2.4 Hz, 1H), δ 6.07 (d, J = 10.4 Hz, 1H), δ 6.63 (dd, J = 3.2, 10.4 Hz, 1H), δ 7.27-7.33 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): δ 196.7, 176.1, 142.6, 137.1, 128.6, 128.1, 127.4, 98.6, 94.3, 74.9, 70.7, 69.7, 69.4, 67.2, 34.3, 19.2, 19.1, 18.1, 15.0; HRMS (ESI): calcd for [C\(_{23}\)H\(_{30}\)O\(_8\) + Na\(^+\)] 457.1838, found 457.1833.

(2R,3R,4R,5S,6S)-2-(benzyloxy)-3-(2-chloracetoxy)-6-methyl-5-(((2R,6S)-6-methyl-5-oxo-5,6-dihydro-2\(H\)-pyran-2-yl)oxy)tetrahydro-2\(H\)-pyran-4-yl-isobutyrate 3.16.1

![Structure](image_url)

Alcohol 3.15.4 (1.1 g, 2.53 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (9.0 mL). The mixture was then cooled to 0 °C and added pyridine (0.51 mL, 6.33 mmol), chloroacetic anhydride (866 mg, 5.06 mmol) and DMAP (154 mg, 1.26 mmol). The resulting mixture was stirred under argon from 0 °C to rt over 2h. Diluted with CH\(_2\)Cl\(_2\) and quenched with 1N HCl at 0 °C. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (50 mL x 3) and the combined organic layer was washed with saturated NaHCO\(_3\) and brine. Dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Silica gel chromatography using 10-12% EtOAc/hexane to obtain 3.16.1 (1.25 g, 97%). Colorless oil: R\(_f\) (20% acetone/hexane) = 0.60; [\(\alpha\)]\(_D\)\(^{25}\) = −60.89 (c 1.05, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) ν 2954, 2861, 1768, 1741, 1672, 1534, 1129, 1030, 866; \(^{1}\)H NMR (CDCl\(_3\), 400 MHz): δ 1.17 (d, J = 6.4 Hz, 6H), δ 1.37 (d, J = 6.4 Hz, 3H), δ 1.39 (d, J = 6.4 Hz, 3H), δ 2.52 (septet, J = 7.2 Hz, 1H), δ 3.89 (m, 2H), δ 4.07, 4.15 (ABq, J\(_{AB}\) = 15.2 Hz, 2H), δ 4.52, 4.72 (ABq, J\(_{AB}\) = 12.4 Hz, 2H), δ 4.55 (q, J = 6.4 Hz, 1H), δ 4.79 (s, 1H), δ 5.35-5.40 (m, 3H), δ 6.08 (d, J = 9.6 Hz,
$^1$H NMR (CDCl$_3$, 400 MHz): δ 1.13 (d, $J = 7.0$ Hz, 3H), δ 1.15 (d, $J = 6.2$ Hz, 3H), δ 1.33 (d, $J = 6.0$ Hz, 3H), δ 1.36 (d, $J = 6.0$ Hz, 3H), δ 1.65 (d, $J = 5.2$ Hz, 1H), δ 2.49 (septet, $J = 7.6$ Hz, 1H), δ 2.56 (dq, $J = 6.4$, 9.2 Hz, 1H), δ 3.78-3.89 (m, 3H), δ 4.06, 4.14 (ABq, $J_{AB} = 14.8$ Hz, 2H), δ 4.54, 4.71 (ABq, $J_{AB} = 12.0$ Hz, 2H), δ 5.78 (s, 1H), δ 5.14 (s, 1H), δ 6.59 (dd, $J = 3.2$, 9.6 Hz, 1H), 7.29-7.34 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 196.3, 175.7, 166.6, 142.2, 136.6, 128.7, 128.2, 128.1, 127.5, 96.2, 94.5, 72.4, 71.9, 70.8, 69.6, 67.3, 40.8, 34.2, 18.9, 17.9, 15.0; HRMS (ESI): calcd for [C$_{25}$H$_{31}$ClO$_9$ + Na]$^+$ 533.1654, found 533.1660.


Enone 3.16.1 (1.5 g, 2.94 mmol) was dissolved in 29.4 mL dry CH$_2$Cl$_2$ and cooled to −78 °C. To this added a 0.4 M solution of CeCl$_3$•MeOH (5.9 mL). After stirring for 10 min at this temperature, added solid NaBH$_4$ (223 mg, 5.87 mmol) in portions. The reaction mixture was stirred at −78 °C for 2h. Quenched with saturated NaHCO$_3$ at low temperature, diluted with CH$_2$Cl$_2$ and warmed up to 0 °C. The aqueous layer was extracted with CH$_2$Cl$_2$ (100mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Silica gel chromatography using 20% EtOAc/hexane to obtain allylic alcohol 3.16.2 (1.4 g, 93%). Colorless solid: $R_f$ (20% acetone/hexane) = 0.25; mp: 146 °C; [$\alpha$]$_D^{25}$ = −66.92 (c 0.80, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) ν 3420, 3300, 2962, 1790, 1751, 1682, 1537, 1215, 1027, 966; $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.13 (d, $J = 7.0$ Hz, 3H), δ 1.15 (d, $J = 6.2$ Hz, 3H), δ 1.33 (d, $J = 6.0$ Hz, 3H), δ 1.36 (d, $J = 6.0$ Hz, 3H), δ 1.65 (d, $J = 5.2$ Hz, 1H), δ 2.49 (septet, $J = 7.6$ Hz, 1H), δ 2.56 (dq, $J = 6.4$, 9.2 Hz, 1H), δ 3.78-3.89 (m, 3H), δ 4.06, 4.14 (ABq, $J_{AB} = 14.8$ Hz, 2H), δ 4.54, 4.71 (ABq, $J_{AB} = 12.0$ Hz, 2H), δ 5.78 (s, 1H), δ 5.14 (s, 1H).
1H), δ 5.34 (dd, J = 3.2, 8.8 Hz, 1H), δ 5.36 (s, 1H), δ 5.58 (dd, J = 2.0, 10.4 Hz, 1H), δ 5.94 (d, J = 10.4 Hz, 1H), 7.29-7.34 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 175.8, 166.7, 136.9, 134.3, 128.7, 128.2, 128.1, 125.8, 96.3, 95.5, 76.3, 72.4, 72.0, 69.5, 69.4, 68.5, 67.6, 40.8, 34.2, 18.9, 17.8, 17.7; HRMS (ESI): calcd for [C₂₅H₃₃ClO₉ + Na]⁺ 535.1711, found 535.1704.


Allylic alcohol 3.16.2 (1.45 g, 2.83 mmol) was dissolved in dry CH₂Cl₂ (28.3 mL). The mixture was then cooled to 0 °C and added pyridine (0.75 mL, 7.1 mmol), isobutyralchloride (0.59 mL, 5.65 mmol) and DMAP (173 mg, 1.42 mmol). The resulting mixture was stirred under argon from 0 °C to rt over 2h. Diluted with CH₂Cl₂ and quenched with 1N HCl at 0 °C. The aqueous layer was extracted with CH₂Cl₂ (50mL X 3) and the combined organic layer was washed with saturated NaHCO₃ and brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography using 10-15% EtOAc/hexane to obtain 3.16.3 (1.6 g, 97%). Colorless solid: Rₜ (20% acetone/hexane) = 0.51; mp: 96 °C; [α]D²⁵ = −88.54 (c 0.70, CH₂Cl₂); IR (thin film, cm⁻¹) ν 2954, 1864, 1786, 1741, 1682, 1463, 11129, 1024, 864; ¹H NMR (CDCl₃, 400 MHz): δ 1.13 (d, J = 6.2 Hz, 3H), δ 1.15 (d, J = 6.2 Hz, 3H), δ 1.16 (d, J = 6.0 Hz, 3H), δ 1.18 (d, J = 6.0 Hz, 3H), δ 1.22 (d, J = 6.0 Hz, 3H), δ 1.34 (d, J = 6.2 Hz, 3H), δ 2.45 (septet, J = 7.2 Hz, 1H), δ 2.56 (septet, J = 7.2 Hz, 1H), δ 3.79-3.94 (m, 3H), δ 4.06, 4.14 (ABq, JAB = 14.4 Hz, 2H), δ 4.55, 4.71 (ABq, JAB = 12.0 Hz, 2H), δ 4.79 (s, 1H), δ 5.04 (d, J = 3.0 Hz, 1H), δ 5.18 (s, 1H), δ 5.32
(dd, \( J = 3.0, 9.6 \text{ Hz}, 1\text{H} \)), \( \delta \) 5.36 (s, 1H), \( \delta \) 5.62 (d, \( J = 10.4 \text{ Hz}, 1\text{H} \)), \( \delta \) 5.84 (d, \( J = 10.4 \text{ Hz}, 1\text{H} \)), 7.29-7.34 (m, 5H); \(^{13}\text{C} \) NMR (CDCl\(_3\), 100 MHz): \( \delta \) 176.6, 175.5, 166.6, 136.7, 130.9, 128.7, 128.2, 128.1, 96.3, 95.6, 76.5, 72.4, 72.0, 70.2, 69.6, 67.5, 65.5, 40.8, 34.2, 19.1, 19.0, 18.9, 17.8, 17.7; HRMS (ESI): calcd for \( [\text{C}_{29}\text{H}_{39}\text{ClO}_{10} + \text{Na}]^{+} \) 605.2129, found 605.2134.

\((2R,3R,4R,5S,6S)-2-(\text{benzyloxy})-3-(2\text{-chloroacetoxy})-5-(((2S,3R,4S,5R,6S)-3,4\text{-dihydroxy}-5-(\text{isobutyryloxy})-6\text{-methyltetrahydro-2H-pyran}-2\text{-yl})\text{oxy})-6\text{-methyltetrahydro-2H-pyran}-4\text{-yl-isobutyrate 3.16.4}\)

Alkene 3.16.3 (1.65 g, 2.83 mmol) was dissolved in a 1:1 mixture of \( t\text{-BuOH}/\text{acetone} \) (6.0 mL) and the mixture was cooled to 0 \(^\circ\)C. To this added a 50% (v/v) solution of NMO/H\(_2\)O (6.0 mL). The reaction mixture was stirred at that temperature for 15 min and added OsO\(_4\) (50 mg, 0.19 mmol). Stirred over night without replenishing ice from 0 \(^\circ\)C to rt. Cooled the reaction to 0 \(^\circ\)C, diluted with EtOAc and reduced the excess OsO\(_4\) with saturated Na\(_2\)SO\(_3\). The reaction mixture was then concentrated to remove acetone. The aqueous layer was extracted with EtOAc (50mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Silica gel chromatography with 35-40 \% EtOAc/hexane gave diol 3.16.4 (1.47 g, 84\%). White solid: \( R_f \) (40\% hexanes/EtOAc) = 0.25; mp: 140-144 \(^\circ\)C; \([\alpha]_{D}^{25} = -117.40 \) (c 1.64, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) \( \nu \) 3390, 3054, 2864, 1741, 1680, 1624, 1478, 1391, 1130, 1042, 987, 866; \(^1\text{H} \) NMR (CDCl\(_3\), 400 MHz): \( \delta \) 1.14-1.21 (m, 15H), \( \delta \) 1.36 (d, \( J = 6.0 \text{ Hz}, 3\text{H} \)), \( \delta \) 2.51 (septet, \( J = 7.2 \text{ Hz}, 1\text{H} \)), \( \delta \) 2.60 (septet, \( J = 7.2 \text{ Hz}, 1\text{H} \)), \( \delta \) 2.79 (d, \( J = 2.4 \text{ Hz}, 2\text{H} \)).
Hz, 1H), δ 3.12 (d, $J = 4.4$ Hz, 1H), δ 3.73 (dd, $J = 9.0, 9.2$ Hz, 1H), δ 3.76-3.91 (m, 4H), δ 4.05, 4.13 (ABq, $J_{AB} = 15.6$ Hz, 2H), δ 4.55, 4.72 (ABq, $J_{AB} = 11.6$ Hz, 2H), δ 4.75 (dd, $J = 9.2, 9.2$ Hz, 1H), δ 4.77 (s, 1H), δ 5.02 (s, 1H), δ 5.31 (dd, $J = 3.2, 9.2$ Hz, 1H), δ 5.35 (s, 1H), 7.29-7.33 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 178.6, 176.0, 166.7, 136.6, 128.7, 128.3, 128.1, 101.3, 96.2, 78.3, 75.1, 71.9, 91.8, 71.2, 70.3, 69.5, 67.3, 66.7, 40.7, 34.3, 34.2, 19.2, 19.0, 18.9, 18.8, 18.2, 17.4; HRMS (ESI): calcld for [C$_{29}$H$_{41}$ClO$_{12}$ + Na]$^+$ 639.2150, found. 639.2169.


The syn-diol 3.16.4 (700 mg, 1.13 mmol) was dissolved in dry CH$_2$Cl$_2$ (3.0 mL) and the mixture was cooled to 0 °C. To this added 2,2-DMP (0.28 mL, 2.27 mmol) and p-TsOH (2.15 mg, 0.01 mmol). The reaction was stirred under argon from 0 °C to rt over 2h. Diluted with CH$_2$Cl$_2$ and quenched by adding saturated NaHCO$_3$ at 0 °C. The aqueous layer was extracted with CH$_2$Cl$_2$ (50mL X 3) and the combined organic layer was washed with saturated brine. Dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The product 3.16.5 was obtained by silica gel chromatography using 10% (683 mg, 92%). Colorless solid: $R_f$ (40% hexanes/EtOAc) = 0.25; mp: 132 °C; [α]$_D^{25}$ = −61.10 (c 1.05, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) ν 2943, 2864, 1864, 1740, 1663, 1624, 1456, 1147, 1042, 978; $^1$H NMR (CDCl$_3$, 500 MHz): δ 1.14 (d, $J = 7.0$ Hz, 3H), δ 1.14 (d, $J = 6.2$ Hz, 3H), δ 1.15 (d, $J = 6.0$ Hz, 3H), δ 1.17 (d, $J = 6.0$ Hz, 3H), δ 1.18 (d, $J$
= 6.6 Hz, 3H), δ 1.26 (s, 3H), δ 1.33 (d, J = 6.8 Hz, 3H), δ 1.52 (s, 3H), δ 2.52 (septet, J = 7.0 Hz, 1H), δ 2.57 (septet, J = 7.2 Hz, 1H), δ 3.73-3.87 (m, 3H), δ 3.99 (d, J = 3.2 Hz, 1H), δ 4.05-4.11 (m, 3H), δ 4.52, 4.71 (ABq, J_{AB} = 12.0 Hz, 2H), δ 4.78 (d, J = 1.0 Hz, 1H), δ 4.83 (dd, J = 8.0, 9.0 Hz, 1H), δ 5.19 (s, 1H), δ 5.34-5.36 (m, 2H), 7.28-7.33 (m, 5H); 13C NMR (CDCl3, 100 MHz): δ 176.2, 176.0, 166.6, 136.7, 128.7, 128.2, 128.1, 109.7, 99.2, 96.3, 77.8, 76.3, 75.7, 73.8, 72.1, 71.9, 69.6, 67.3, 65.1, 40.7, 34.2, 27.7, 26.5, 19.2, 19.0, 18.9, 18.8, 17.9, 16.7; HRMS (ESI): calcd for [C_{32}H_{45}ClO_{12}+Na]^+ 679.2507, found 679.2521.

(2R,3R,4R,5S,6S)-3-(2-chloroacetoxy)-2-hydroxy-5-(((3aR,4S,6S,7S,7aR)-7-(isobutyryloxy)-2,2,6-trimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-oxy)-6-methyltetrahydro-2H-pyran-4-yl isobutyrate 3.16.6

Benzyl ether 3.16.5 (800 mg, 1.22 mmol) was dissolved in EtOAc (10 mL) and few drops of MeOH. To this solution, Pd/C (60 mg) was added and under H2 balloon pressure the reaction was stirred for 3h at rt. The solid Pd/C catalyst was removed by filtration using a celite pad. Filtrate was concentrated under reduced pressure and purified by silica gel chromatography using 30-35% EtOAc/hexane to obtain 3.16.6 (650 mg, 94%) as a mixture of diastereomers (10:1, α:β). White solid: Rf (30% hexanes/EtOAc) = 0.31; mp: 164 ºC; [α]_D^{25} = −22.80 (c 0.50, CH2Cl2); IR (thin film, cm⁻¹) ν 3360, 2985, 2833, 1851, 1741, 1663, 1456, 1147, 1040, 866; 1H NMR of the major diastereomer in (CDCl3, 400 MHz): δ 1.11-1.80 (m, 15H) δ 1.26 (s, 3H), δ 1.33 (d, J = 6.6 Hz, 3H), δ 1.51 (s, 3H), δ 2.48-2.62 (m, 2H), δ 3.73-3.87 (m, 3H), δ 3.99-
3.4.17 (m, 5H), δ 4.82 (dd, J = 8.8, 8.8 Hz, 1H), δ 5.12 (s, 1H), δ 5.19 (s, 1H), δ 5.32-5.36 (m, 2H); \(^{13}\text{C}\) NMR (CDCl\(_3\), 100 MHz): δ 176.5, 176.3, 109.8, 99.1, 91.8, 77.8, 76.3, 75.7, 73.9, 72.3, 71.8, 67.1, 65.1, 40.8, 34.2, 27.8, 26.5 19.2, 19.0, 18.9, 18.8, 18.1, 16.7; HRMS (ESI): calcd for [C\(_{25}\)H\(_{39}\)ClO\(_{12}\) + Na]\(^{+}\) 589.2008, found 589.2028.

(3aR,4S,6S,7S,7aR)-4-(((2S,3S,4R,5R,6S)-5-(2-chloroacetoxy)-4-(isobutyryloxy)-2-methyl-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2H-pyran-3-yl)oxy)-2,2,6-trimethyltetrahydro-3aH-[1,3]-dioxolo-[4,5-c]-pyran-7-yl-isobutyrate 3.16.7

Glycosyl donor 3.16.6 (64 mg, 0.11 mmol) was dissolved in 1.1 mL dry CH\(_2\)Cl\(_2\) and cooled to 0 °C. To this added CNCCl\(_3\) (113 μL, 1.13 mmol) and NaH (0.3 mg, 0.01 mmol). The reaction was stirred at 0 °C under argon for 3h. Upon consumption of starting material, reaction was directly loaded to a column (column diameter: 0.5 cm, packed with 3 cm silica gel topped with a 2 cm celite pad). Elution with 10-15% EtOAc/hexane gave trichloroacetimidate 3.16.7 (55 mg, 70%) as a mixture of diastereomers (12:1, α:β). Colorless oil: \(R_f\) (20% EtOAc/hexane) = 0.50; [\(\alpha\)]\(_{D}^{25}\) = −224.80 (c 0.50, benzene); IR (thin film, cm\(^{-1}\)) ν 3415, 3206, 2837, 1846, 1781, 1652, 1523, 1158, 866; \(^1\text{H}\) NMR for the major diastereomes (C\(_6\)D\(_6\), 400 MHz): δ 1.03-1.13 (m, 15H) δ 1.17 (d, J = 6.0 Hz, 3H), δ 1.39 (d, J = 6.6 Hz, 3H), δ 1.55 (s, 3H), δ 2.39 (septet, J = 6.8 Hz, 1H), δ 2.47 (septet, J = 7.6 Hz, 1H), δ 3.27, 3.26 (ABq, \(J_{AB} = 14.8\) Hz, 2H), δ 3.84 (dq, J = 6.6, 9.4 Hz, 1H), δ 4.04-4.14 (m, 3H), δ 4.29 (dq, J = 6.4, 9.2 Hz, 1H), δ 5.27 (dd, J = 9.6, 10.4 Hz, 1H),
δ 5.53 (s, 1H), δ 5.73 (dd, J = 2.8, 10.4 Hz, 1H), δ 5.84 (s, 1H), δ 6.40 (s, 1H), δ 8.51 (s, 1H);

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ 176.0, 166.5, 160.2, 110.2, 100.2, 95.5, 91.4, 77.7, 77.0, 76.5, 74.4, 72.7, 70.9, 70.2, 65.9, 43.6, 34.5, 28.2, 26.9, 19.4, 19.3, 19.2, 19.1, 18.6, 17.1; HRMS (ESI): calcd for [C$_{27}$H$_{39}$Cl$_4$NO$_{12}$ + Na]$^+$ 732.1124, found 732.1118.

(2S,3R,4R,5S,6S)-2-(((3aR,4R,6S,7S,7aR)4-(benzyloxy)-2,2,6trimethyltetrahydro-3aH-[1,3]-dioxolo[4,5c]pyran-7-yl)oxy)-3-(2-chloroacetoxy)-5(((3aR,4S,6S,7S,7aR)7-(isobutryloxy)-2,2,6-trimethyltetrahydro-3aH-[1,3]dioxolo-[4,5c]-pyran-4-yl)oxy)-6-methyltetrahydro-2H-pyran-4-yl-isobutyrate 3.17.1

Glycosyl acceptor 1.14.1 (15.2 mg, 0.05 mmol) and glycosyl donor 3.16.7 (55 mg, 0.08 mmol) were separately dried azeotropically with benzene and under high vacuum for 3h. Acceptor 1.14.1 was dissolved in dry CH$_2$Cl$_2$(0.5 mL) and transferred to the flask containing the donor 3.16.7 via cannula. Freshly activated molecular sieves (30 mg) was added and stirred under argon for 15 min. The reaction mixture was then cooled to −78 ºC and dropwise added a CH$_2$Cl$_2$ solution of TMSOTf (1.7 µL, 0.009 mmol in 0.15 mL CH$_2$Cl$_2$). The reaction was stirred from −78 ºC to 0 ºC over 1.5h and subsequently quenched with Et$_3$N. Water was added and the aqueous phase extracted with CH$_2$Cl$_2$ (20 mL X 3). The combined organic layer was washed with 1N HCl, saturated NaHCO$_3$ and brine. Dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Silica gel chromatography with 10-12% EtOAc/hexane gave tetrasaccharide 1.17.1
(34 mg, 80%). Colorless oil: $R_f$ (20% EtOAc/hexane) = 0.55; $[\alpha]_D^{25} = -44.43$ (c 0.28, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) $\nu$ 2854, 11781, 1740, 1706, 1684, 1485, 1156, 1023, 1011, 954, 860; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.12-1.19 (m, 15H), $\delta$ 1.25-1.30 (m, 9H), $\delta$ 1.34 (d, $J = 5.6$ Hz, 3H), $\delta$ 1.51 (s, 3H), $\delta$ 1.52 (s, 3H), $\delta$ 2.48-2.63 (m, 2H), $\delta$ 3.52 (dd, $J = 8.4$, 9.2 Hz, 1H), $\delta$ 3.75-3.80 (m, 4H), $\delta$ 4.01 (d, $J = 5.2$ Hz, 1H), $\delta$ 4.08-4.14 (m, 4H), $\delta$ 4.21 (dd, $J = 6.0$, 7.2 Hz, 1H), 4.52, 4.71 (ABq, $J_{AB} = 12.0$ Hz, 2H), $\delta$ 4.83 (dd, $J = 8.8$, 8.8 Hz, 1H), $\delta$ 5.04 (s, 1H), $\delta$ 5.19 (s, 1H), $\delta$ 5.22 (dd, $J = 3.2$, 9.6 Hz, 1H), $\delta$ 5.33 (s, 1H), $\delta$ 5.36 (brs, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 176.4, 176.2, 166.7, 137.1, 128.7, 128.4, 128.2, 109.7, 99.2, 96.2, 95.5, 78.2, 77.4, 77.3, 76.3, 76.2, 75.7, 73.9, 72.1, 71.9, 69.4, 67.7, 65.2, 64.1, 40.8, 34.2, 34.1, 28.0, 27.8, 26.6, 26.5, 19.2, 19.0, 18.9, 18.8, 18.3, 18.0, 16.7; HRMS (ESI): calcd for [C$_{41}$H$_{59}$ClO$_{16}$ + Na]$^+$ 865.3389, found 865.3397.

**Glycosylated tetrasaccharide 3.19.1**

Glycosyl acceptor 3.9.1 (40 mg, 0.06 mmol) and glycosyl donor 3.16.7 (86 mg, 0.12 mmol) were separately dried azeotropically with benzene and under high vacuum for 3h. Acceptor 3.9.1 was dissolved in dry CH$_2$Cl$_2$ (1.0 mL) and transferred to the flask containing the donor 3.16.7 via cannula. Freshly activated molecular sieves (60 mg) was added and stirred under argon for 15 min. The reaction mixture was then cooled to −78 °C and dropwise added a CH$_2$Cl$_2$
solution of TMSOTf (2.6 µL, 0.01 mmol in 0.26 mL CH₂Cl₂). The reaction was stirred from −78 °C to 0 °C over 1.5h and subsequently quenched with Et₃N. Water was added and the aqueous phase extracted with CH₂Cl₂ (20 mL X 3). The combined organic layer was washed with 1N HCl, saturated NaHCO₃ and brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 10-12% EtOAc/hexane gave tetrasaccharide 3.19.1 (52 mg, 72%). Colorless oil: Rf (20% EtOAc/hexane) = 0.50; [α]D²⁵ = −66.42 (c 0.80, CH₂Cl₂); IR (thin film, cm⁻¹) ν 2981, 2866, 1741, 1706, 1680, 1490, 1158, 1036, 1026, 947, 866; ¹H NMR (CDCl₃, 400 MHz): δ 0.88 (t, J = 6.4 Hz, 3H), δ 1.28-1.22 (m, 12H), δ 1.25-1.37 (m, 35H), δ 1.43 (s, 3H), δ 1.53 (s, 3H), δ 1.57 (s, 3H), δ 1.64-1.71 (m, 4H), δ 2.27-2.41 (m, 2H), δ 2.50-2.61 (m, 2H), δ 3.52 (brs, 1H), δ 3.54 (dd, J = 8.8, 9.2 Hz, 1H), δ 3.66 (dd, J = 3.4, 8.8 Hz, 1H), δ 3.76-3.80 (m, 2H), δ 3.83-3.96 (m, 3H), δ 4.01 (d, J = 3.2 Hz, 1H), δ 4.04 (d, J = 3.2 Hz, 1H), δ 4.09-4.18 (m, 5H), δ 4.29 (dd, J = 8.0, 8.8 Hz, 1H), δ 4.83 (dd, J = 8.0, 9.6 Hz, 1H), δ 4.99 (s, 1H), δ 5.10-5.16 (m, 3H), δ 5.19 (s, 1H), δ 5.21-5.27 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 176.3, 176.0, 173.1, 166.9, 166.7, 109.8, 109.7, 99.1, 96.7, 96.1, 94.8, 80.9, 79.1, 78.9, 76.8, 76.3, 76.1, 75.8, 73.9, 73.3, 72.1, 71.4, 70.4, 68.2, 66.8, 65.3, 64.1, 41.0, 40.7, 34.8, 34.2, 34.1, 33.8, 33.2, 32.2, 30.5, 29.9, 29.3, 29.2, 28.5, 28.4, 28.1, 27.8, 26.9, 26.6, 25.7, 25.2, 23.5, 22.8, 19.2, 19.0, 18.9, 18.8, 18.8, 18.0, 17.9, 16.7, 14.3; HRMS (ESI): calcd for [C₅₈H₉₂Cl₂O₂₂ + H]⁺ 1211.5536, found 1211.5582.
Glycosylated tetrasaccharide **3.19.1** (30 mg, 0.025 mmol) was dissolved in THF (1.0 mL). To this added thiourea (23 mg, 0.30 mmol), NaHCO$_3$ (12.6 mg, 0.15 mmol) and TBAI (9.2 mg, 0.03 mmol). The reaction mixture was then refluxed at 55 °C under argon for 3h. Upon consumption of starting material, the reaction was cooled to 0 °C and diluted with EtOAc and H$_2$O. The aqueous phase extracted with EtOAc (20 mL X 3) and combined organic layer was washed with saturated brine. Dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Silica gel chromatography with 40-45% EtOAc/hexane gave tetrasaccharide diol **3.19.2** (24 mg, 91%). Colorless oil: $R_f$ (50% EtOAc/hexane) = 0.45; $[\alpha]_{D}^{25} = -44.8$ (c 1.0, CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) $\nu$ 3448, 3310, 2980, 1741, 1710, 1686, 1677, 1490, 10323, 980, 866; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 0.88 (t, $J = 6.4$ Hz, 3H), $\delta$ 1.21 (d, $J = 6.5$ Hz, 3H), $\delta$ 1.17-1.33 (m, 40 H), $\delta$ 1.35 (s, 3H), $\delta$ 1.36-1.53 (m, 6H), 1.54 (d, $J = 6.6$ Hz, 3H), $\delta$ 1.62-1.75 (m, 4H), $\delta$ 1.95-2.33 (m, 2H), $\delta$ 2.34 (ddd, $J = 3.0$, 5.6, 14.0 Hz, 1H), $\delta$ 2.46 (ddd, $J = 2.5$, 6.0, 13.5 Hz, 1H), $\delta$ 2.57 (septet, $J = 7.5$ Hz, 1H), $\delta$ 2.63 (septet, $J = 7.0$ Hz, 1H), $\delta$ 3.48-3.54 (m, 2H), $\delta$ 3.61 (dd, $J = 3.5$, 7.5 Hz, 1H), $\delta$ 3.77 (dq, $J = 6.0$, 8.5 Hz, 1H), $\delta$ 3.73-3.79 (m, 2H), $\delta$ 3.88-3.94 (m, 2H), $\delta$ 4.01-4.06 (m, 4H), $\delta$ 4.10 (dd, $J = 3.0$, 8.0 Hz, 1H), $\delta$ 4.27 (dd, $J = 3.5$, 9.0 Hz, 1H), $\delta$ 4.83 (dd, $J = 8.8$, 10.0 Hz, 1H), $\delta$ 4.95 (dd, $J = 2.0$, 3.2 Hz, 1H), $\delta$ 4.98 (s, 1H), $\delta$ 5.01 (d, $J = 2.0$, 1H), $\delta$ 5.17 (dd, $J = 3.0$, 8.0 Hz, 1H), $\delta$ 5.19 (s, 1H), $\delta$ 5.22 (brs, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 176.4,
176.4, 173.9, 109.7, 109.6, 98.8, 98.7, 96.3, 95.0, 80.9, 80.7, 78.9, 76.4, 76.1, 75.8, 74.2, 73.9, 73.7, 69.9, 67.9, 67.5, 65.1, 64.2, 36.8, 35.0, 34.3, 34.2, 33.9, 33.1, 29.9, 29.4, 29.3, 28.4, 28.3, 28.0, 27.8, 26.8, 26.6, 25.8, 25.2, 24.9, 23.5, 23.4, 22.8, 19.3, 19.0, 18.1, 18.0, 16.7, 14.3; HRMS (ESI): calcd for [C_{54}H_{90}O_{20} + H]^+ 1059.6104, found 1059.6138.


Bis-acetonide protected tetrasaccharide 3.19.2 (18 mg, 0.017 mmol) was dissolved in CH$_2$Cl$_2$ and cooled to 0 °C. The reaction mixture was stirred for 10 min at this temperature and dropwise added 41 µL aqueous solution TFA (10:1). The reaction mixture was stirred at 0 °C for 40 min and quenched with saturated NaHCO$_3$. Water was added and the aqueous phase extracted with CH$_2$Cl$_2$ (20 mL X 3). The combined organic layer was washed with brine and dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Silica gel chromatography with 5% MeOH/CH$_2$Cl$_2$ gave 3.19.3 (11.6 mg, 70%). White solid: $R_f$ (7% MeOH/CH$_2$Cl$_2$) = 0.5; mp: 152 °C; [$\alpha$]$_D^{25} = -44.8$ (c 1.0, MeOH); IR (thin film, cm$^{-1}$) $\nu$ 3424, 3380, 2910, 2856, 1740, 1768, 1491, 1026, 980, 866; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 0.82 (t, $J = 6.5$ Hz, 3H), $\delta$ 1.12-1.15 (m, 15H), $\delta$ 1.19-
1.26 (m, 18H), δ 1.27 (d, J = 6.5 Hz, 3H), δ 1.28 (d, J = 6.0 Hz, 3H), δ 1.33-1.37 (m, 4H),
δ 1.55-1.69 (m, 4H), δ 2.29 (ddd, J = 2.5, 5.5, 13.5 Hz, 1H), δ 2.34 (ddd, J = 3.0, 6.2, 14.0 Hz,
1H), δ 3.43 (bres, 1H), δ 2.54 (septet, J = 7.5 Hz, 1H), δ 2.56 (septet, J = 7.2 Hz, 1H), δ 2.72 (bres,
1H), δ 2.86 (bres, 1H), 2.91 (d, J = 3.0 Hz, 1H), δ 2.95 (bres, 1H), δ 3.08 (bres, 1H), δ 3.39-3.41 (m,
1H), 3.49 (dd, J = 8.6, 8.8 Hz, 1H), 3.53 (dd, J = 10.0, 10.0 Hz, 1H), δ 3.69-3.91 (m, 8H), δ 4.00-
4.04 (m, 3H), 4.71 (dd, J = 10.0, 10.0 Hz, 1H), 4.72 (d, J = 2.0 Hz, 1H), 4.89 (dd, J = 3.0, 3.2 Hz,
1H), δ 4.96 (s, 1H), δ 4.97 (s, 1H), 5.02 (dd, J = 3.0, 8.5 Hz, 1H), 5.12 (d, J = 3.0 Hz, 1H); ¹³C
NMR (CDCl₃, 100 MHz): δ 178.5, 176.9, 173.9, 100.8, 100.3, 98.7, 94.1, 81.4, 81.2, 79.8, 78.3,
75.0, 74.1, 73.8, 71.9, 71.3, 70.3, 69.6, 69.5, 69.0, 68.1, 67.9, 66.8, 65.8, 34.7, 34.4, 33.9, 32.2,
29.9, 28.8, 28.7, 28.2, 28.2, 27.6, 26.7, 25.5, 25.2, 23.6, 22.8, 19.3, 19.2, 19.0, 18.9, 18.5, 18.0,
17.4, 14.3; HRMS (ESI): calcd for [C₄₈H₈₂O₂₀ + H]⁺ 979.5478, found 979.5517.

**Glycosylated tetrasaccharide 3.22.1**

Glycosyl acceptor **3.9.2** (45 mg, 0.07 mmol) and glycosyl donor **3.16.7** (91 mg, 0.13 mmol)
were separately dried azeotropically with benzene and under high vacuum for 3h. Acceptor
**3.9.2** was dissolved in dry CH₂Cl₂ (1.0 mL) and transferred to the flask containing the donor
**3.16.7** via cannula. Freshly activated molecular sieves (60 mg) was added and stirred under
argon for 15 min. The reaction mixture was then cooled to −78 ºC and dropwise added a CH₂Cl₂
solution of TMSOTf (2.8 µL, 0.02 mmol in 0.3 mL CH₂Cl₂). The reaction was stirred from −78 °C to 0 °C over 1.5h and subsequently quenched with Et₃N. Water was added and the aqueous phase extracted with CH₂Cl₂ (20 mL X 3). The combined organic layer was washed with 1N HCl, saturated NaHCO₃ and brine. Dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 10-12% EtOAc/hexane gave tetrasaccharide 3.22.1 (60 mg, 71%). Colorless oil: \( R_f \) (20% EtOAc/hexane) = 0.5; \([\alpha]_D^{25} = -26.34 \) (c 2.4, CH₂Cl₂); IR (thin film, cm⁻¹) \( \nu \): 2864, 1781, 1740, 1680, 1666, 1485, 1213, 1156, 1036, 948, 866, 788; \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \): 0.87 (t, \( J = 6.6 \) Hz, 3H), \( \delta \): 1.12-1.14 (m, 9H), \( \delta \): 1.17 (d, \( J = 7.2 \) Hz, 3H), \( \delta \): 1.19 (d, \( J = 6.4 \) Hz, 3H), \( \delta \): 1.25-1.36 (m, 34H), \( \delta \): 1.47 (s, 3H), \( \delta \): 1.52 (s, 3H), \( \delta \): 1.54-1.61 (m, 3H), \( \delta \): 1.70 (m, 2H), \( \delta \): 2.21 (ddd, \( J = 4.2, 7.2, 14.2 \) Hz, 1H), \( \delta \): 2.39 (ddd, \( J = 4.4, 7.0, 14.2 \) Hz, 1H), \( \delta \): 2.47-2.61 (m, 2H), \( \delta \): 3.45 (brs, 1H), \( \delta \): 3.49 (dd, \( J = 5.2, 7.2 \) Hz, 1H), \( \delta \): 3.69 (dd, \( J = 9.6, 9.6 \) Hz, 1H), \( \delta \): 3.74-3.79 (m, 2H), \( \delta \): 3.89-3.95 (m, 2H), \( \delta \): 3.98-4.04 (m, 2H), \( \delta \): 4.08 (m, 4H), \( \delta \): 4.12 (s, 2H), \( \delta \): 4.22 (dd, \( J = 5.2, 6.0 \) Hz, 1H), \( \delta \): 4.83 (dd, \( J = 8.8, 8.8 \) Hz, 1H), \( \delta \): 4.91 (s, 1H), \( \delta \): 4.94 (s, 1H), \( \delta \): 5.13 (s, 1H), \( \delta \): 5.15 (brs, 1H), \( \delta \): 5.18 (s, 1H), \( \delta \): 5.25 (dd, \( J = 3.2, 9.6 \) Hz, 1H), \( \delta \): 5.32 (brs, 1H), \( \delta \): 5.45 (dd, \( J = 2.8, 10.4 \) Hz, 1H); \(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta \): 176.3, 175.8, 173.4, 166.5, 166.4, 110.1, 109.8, 99.1, 98.9, 96.4, 95.8, 80.3, 80.2, 78.7, 77.6, 76.8, 76.3, 75.8, 74.4, 73.9, 73.3, 72.2, 71.5, 71.4, 68.5, 68.1, 65.8, 65.2, 40.9, 40.7, 34.6, 34.2, 34.1, 33.1, 32.3, 30.1, 29.9, 28.6, 27.9, 27.8, 27.7, 27.6, 26.6, 26.4, 26.1, 25.1, 22.8, 19.5, 19.2, 19.0, 18.8, 18.3, 17.9, 16.7, 14.3; HRMS (ESI): calcd for [C₅₈H₉₂Cl₂O₂₂ + H]⁺ 1211.5536, found 1211.5582.

The bis-acetonide protected tetrasaccharide 3.22.1 (35 mg, 0.029 mmol) was dissolved in 0.4 mL of CH₂Cl₂ and cooled to 0 °C. The reaction mixture was stirred for 10 min at this temperature and dropwise added 60 µL aqueous solution TFA (10:1). The reaction mixture was stirred at 0 °C for 30 min and quenched with saturated NaHCO₃. Water was added and the aqueous phase extracted with CH₂Cl₂ (20 mL X 3). The combined organic layer was washed with brine and dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel chromatography with 35-40% EtOAc/hexane gave 3.22.2 (23.5 mg, 72%). Colorless oil: $R_f$ (40% EtOAc/hexane) = 0.32; $[\alpha]_D^{25} = -54.3 \ (c \ 0.4, \ CH₂Cl₂); \ IR \ (\text{thin film, cm}^{-1}) \ \nu 3350, 3300, 2912, 1764, 1741, 1684, 1536, 1491, 1216, 1026, 951, 866; \ ^1H \text{NMR (CDCl₃, 500 MHz): } \delta 0.89 (t, J = 7.0 Hz, 3H), \delta 1.14 (d, J = 7.0 Hz, 3H), \delta 1.15 (d, J = 7.0 Hz, 3H), 1.89 (d, J = 7.0 Hz, 3H), 1.20 (d, J = 6.5, 3H), 1.21 (d, J = 6.5 Hz, 3H), \delta 1.25-1.33 (m, 22H), \delta 1.35 (d, J = 6.5 Hz, 3H), \delta 1.36 (d, J = 6.0 Hz, 3H), \delta 1.45-1.54 (m, 5H), \delta 2.43 (ddd, J = 2.5, 8.0, 16.5 Hz, 1H), \delta 2.34 (ddd, J = 3.0, 9.0, 16.7 Hz, 1H), \delta 2.44 (d, J = 5.5 Hz, 1H), \delta 2.51 (septet, J = 7.0 Hz, 1H), \delta 2.61 (septet, J = 6.5 Hz,
1H), δ 2.68 (s, 1H), δ 2.86 (d, J = 8.0 Hz, 1H), δ 3.10 (d, J = 4.5 Hz, 1H), δ 3.42 (dd, J = 9.0, 9.0 Hz, 1H), δ 3.47 (m, 1H), δ 3.68 (dd, J = 9.5, 9.5 Hz, 1H), δ 3.75-3.79 (m, 4H), δ 3.85-3.99 (m, 5H), δ 4.09 (s, 2H), δ 4.11 (s, 2H), δ 4.75 (dd, J = 9.5, 9.5 Hz, 1H), δ 4.82 (d, J = 2.0 Hz, 1H), δ 4.92 (d, J = 1.5 Hz, 1H), δ 5.0 (s, 1H), δ 5.18 (dd, J = 2.5, 2.5 Hz, 1H); δ 5.22 (dd, J = 3.0, 9.5 Hz, 1H) δ 5.24 (d, J = 2.0 Hz, 1H), δ 5.41 (dd, J = 3.0, 10.5 Hz, 1H), δ 5.53 (dd, J = 2.0, 2.6 Hz, 1H); 13C NMR (CDCl3, 100 MHz): δ 178.7, 175.8, 173.9, 167.0, 166.5, 101.2, 99.0, 98.9, 97.2, 82.1, 81.2, 78.7, 78.1, 75.3, 73.4, 72.2, 72.1, 72.0, 71.4, 71.3, 71.1, 70.4, 68.5, 68.1, 66.8, 66.7, 41.0, 40.7, 34.3, 34.2, 33.7, 33.1, 32.3, 30.3, 29.9, 28.6, 27.7, 27.6, 26.6, 25.6, 25.2, 22.8, 22.6, 19.2, 10.0, 18.8, 18.5, 18.4, 18.1, 17.4, 14.2; HRMS (ESI): calcd for [C52H84Cl2O22 + Na]+ 1153.4724, found 1153.4744.

Merremoside D

The bis-chloroacetate 3.22.2 (23.5 mg, 0.02 mmol) was dissolved in THF (1.0 mL). To this added thiourea (19.0 mg, 0.25 mmol), NaHCO3 (11.0 mg, 0.13 mmol) and TBAI (4.0 mg, 0.01 mmol). The reaction mixture was then refluxed at 55 ºC under argon for 3h. Upon consumption of starting material, the reaction was cooled 0 ºC and diluted with EtOAc and H2O. The aqueous phase extracted with EtOAc (10 mL X 3) and combined organic layer was washed with water (7-10 times to remove thiourea and TBAI) and saturated brine. Dried over Na2SO4 and concentrated
under reduced pressure. Silica gel chromatography with 5% MeOH/CHCl₃ gave merremoside D (16 mg, 78%). White solid, mp: 140 °C; Rₛ (5% MeOH/CHCl₃) = 0.3; [α]₀⁺²⁵ = −64.6 (c 0.83, CH₂Cl₂); IR (thin film, cm⁻¹) ν 3330, 3300, 2910, 2850, 1741, 1730, 1864, 1514, 1236, 1026, 941, 866;¹H NMR (CDCl₃, 500 MHz): δ 0.89 (t, J = 7.0 Hz, 3H), δ 1.18-1.20 (m, 15H), δ 1.24-1.32 (m, 22H), 1.35 (d, J = 6.0 Hz, 3H), δ 1.43-1.79 (m, 8H), δ 2.32-2.43 (m, 2H), δ 2.49 (brs, 1H), δ 2.50 (brs, 1H), δ 2.58-2.63 (m, 2H), δ 2.85 (brs, 1H), δ 2.94 (brs, 1H), δ 3.10 (d, J = 5.5 Hz, 1H), δ 3.27 (brs, 1H), δ 3.44 (dd, J = 8.5, 8.5 Hz, 1H), δ 3.48 (m, 1H), δ 3.72 (dd, J = 9.0, 9.0 Hz, 1H), δ 3.77-3.96 (m, 10H), δ 4.21 (s, 1H), δ 4.76 (dd, J = 9.5, 9.5 Hz, 1H), δ 4.81 (s, 1H), δ 4.95 (d, J = 2.5 Hz, 1H), δ 5.03 (s, 1H), δ 5.08 (dd, J = 3.0, 8.5 Hz, 1H), δ 5.16 (d, J = 3.0 Hz, 1H), δ 5.21 (dd, J = 2.0, 8.5 Hz, 1H);¹³C NMR (CDCl₃, 100 MHz): δ 178.7, 176.3, 174.1, 100.7, 100.4, 98.8, 98.7, 81.7, 81.2, 78.3, 77.8, 76.7, 75.3, 74.6, 73.9, 71.5, 71.2, 70.6, 70.4, 70.0, 68.6, 67.9, 66.7, 66.5, 34.3, 34.1, 34.0, 33.7, 32.2, 29.9, 29.8, 28.9, 28.2, 27.9, 27.5, 25.2, 23.8, 22.8, 19.3, 19.2, 19.0, 18.9, 18.7, 18.3, 18.2, 17.4, 14.3; HRMS (ESI): calcd for [C₄₈H₇₂O₂₀ + H]⁺ 979.5478, found 979.5517.
References and notes

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