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Asymmetric Synthesis of SL0101, Cyclitol and Jadomycin

Mingde Shan

**Dissertation submitted to the
Eberly College of Arts and Sciences
at West Virginia University
in partial fulfillment of the requirements
for the degree of**

**Doctor of Philosophy
In
Organic Chemistry**

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**Morgantown, West Virginia
2009**

Keywords: SL0101, Cyclitol and Jadomycin

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ABSTRACT

Asymmetric Synthesis of SL0101, Cyclitol and Jadomycin

Minde Shan

The carbohydrate portion of natural products plays a crucial role in biology, such as target binding, solubility, tissue targeting, and membrane transportation. The O'Doherty group has developed a *de novo* methodology to build the desired functionality and stereochemistry within each sugar, in contrast to the traditional approach using known carbohydrates as starting materials. This methodology relies on a highly diastereoselective palladium(0)-catalyzed glycosylation reaction to control the stereochemistry at the anomeric center and post-glycosylation transformation to introduce the corresponding functionality in the sugar moiety.

Continuing our investigations on the utility of this strategy, we turned our attention to the syntheses of the bioactive carbohydrate-based natural product analogues. The targets we chose are the p90 ribosomal S6 kinase (RSK) inhibitors SL0101 and its analogues. We developed a practical 7-10 step diastereoselective route for the syntheses of six different analogues of SL0101 in either enantiomeric form without using any protecting groups in the sugar moieties.

C-glycosides are carbohydrates where one of the acetal oxygens has been replaced with a methylene group. These non-hydrolyzable sugar mimics have long been recognized as an important pharmacophore. Cyclitols/Carbasugars are an important subset of the C-glycoside structural motif where the endo-acetal ring oxygen has been replaced with a methylene group. In particular, polyhydroxylated cyclohexane cyclitols that mimic pyrano-sugars are ubiquitous in many biologically important natural products. We successfully developed a practical route to achieve rhamno-carbasugars in either enantiomeric and diastereomeric form (*e.g.*, α -L, β -L, α -D, β -D) starting with quinic acid. Three cyclitol/carbasugar monosaccharides and five carbasugar C-1 phosphates have been synthesized.

In order to further facilitate the medicinal structure-activity relationship (SAR) study of SL0101, we also turned our attention to the synthesis of carbasugar glycoside analogues of

SL0101. A practical palladium(0)-catalyzed cyclitolization/C-in ring-glycosylation and a post-cyclitolization transformation has been successfully developed. This methodology has been utilized to synthesize six carbasugar analogues of SL0101 in either enantiomeric form.

Efforts have been made toward the synthesis of biologically important jadomycin A and B. A practical approach has been successfully developed to achieve α -digitoxose, the sugar moiety of jadomycin B by employing a new post-glycosylation reactions following palladium(0)-catalyzed glycosylation reaction. Jadomycin A, the aglycone part of jadomycin B, has been successfully synthesized. The key transformations included an oxidative ring closure of dihydropyridine followed by acid induced lactonization to form an oxazolone ring.

DEDICATED TO

**My wife Huihua Lu, My son Kevin L. Shan
My mother Xinying Wu**

IN MEMORY OF

My father Yuanxi Shan

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List of Abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Anal.	Analysis
Bn	Benzyl
Bz	Benzoyl
Boc	<i>t</i> -Butoxycarbonyl
bp	Boiling point
Bu	Butyl
BuLi	<i>n</i> -Butyllithium
Calcd	Calculated
Cbz	Benzyloxyl carbonyl
CI	Chemical Ionization
<i>m</i> CPBA	<i>m</i> -Chloroperbenzoic acid
CSA	Camphorsulfonic acid
d	Doublet
DBA	<i>trans, trans</i> -dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
δ	Chemical shift (ppm)
DIAD	Diisopropylazodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIEPA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess

EI	Electron ionization
<i>ent</i>	Enantiomer
equiv	Equivalent(s)
ESI	Electron spray ionization
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram(s)
h	Hour(s)
HRMS	High resolution mass spectrum
Hz	Hertz (cycles per second)
IR	Infrared
<i>J</i>	Spin-spin coupling constant
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
L-selectride	Lithium tri-sec-butylborohydride
mol	Mole(s)
m	Multiplet
Me	Methyl
MHz	Megahertz
min	Minute(s)
mmol	Millimole(s)
MOM	Methoxy methyl
mp	Melting point
MS	Mass spectrum
NBS	N-Bromosuccinimide
NIS	N-Iodosuccinimide
NBSH	<i>o</i> -Nitrobenzenesulfonylhydrazide
NMO	N-Methylmorpholine N-oxide
NMR	Nuclear magnetic resonance
Ph	Phenyl

PMB	<i>p</i> -Methoxybenzyl
PNBz	<i>p</i> -Nitrobenzoyl
ppm	Parts per million
Py	Pyridine
q	Quartet
R_f	Ratio to front
rt	Room temperature
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBS	<i>t</i> -Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TTMSS	Tris(trimethylsilyl)silane
<i>p</i> -TsOH	<i>p</i> -toluene sulfonic acid

Chapter I. De Novo Asymmetric Syntheses of SL0101 and Its Analogues^{*,1}

In an effort to find specific inhibitors of p90 Ribosomal S6 Kinase (RSK), Smith and Hecht screened an extensive collection of botanical extracts derived from rare plants.² Using a dual high-throughput screen they found only one extract, which inhibited the RSK2 isoform (RSK2) without inhibiting the tyrosine kinase (FAK). The active extract was from a South American dogbane plant named *Forsteronia refracta*. More detailed bioactive fractionation revealed the active constituent to be a kaempferol glycoside, which was given the name SL0101 (Figure 1).² SL0101 (**I-1a**) is a member of a class of acylated kaempferol L-rhamnosides which occur naturally with various degrees of acylation (e.g., **I-1a** to **I-1e**).³ SL0101 sans acetyl groups (**I-1b**) is also known as afzelin.^{3a} The kaempferol glycosides, like most flavonoids, have received a great deal of attention because they are believed to induce many positive biological effects.⁴

	R ₁	R ₂	R ₃	IC ₅₀ (RSK2)
I-1a	Ac	Ac	H	89 nM
I-1b	H	H	H	-----
I-1c	Ac	Ac	Ac	-----
I-1d	Ac	H	H	189 nM
I-1e	Ac	H	Ac	580 nM

Figure 1. *Rsk2* inhibitory activities of SL0101 (**I-1a**) and its analogues (**I-1b** to **I-1e**)

In addition to this unique activity, our interest in SL0101 (**I-1a**) was peaked by the report that it displayed some 150 times greater activity than the simple aglycon, kaempferol. Similarly, we

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were intrigued by the importance of the specific placement of acetyl groups on the L-rhamnose and its effect on the structure-activity relationship (SAR) of SL0101 (Figure 1).⁵ As part of an effort to elucidate the role of the sugar and acetyl portion of SL0101 to its activity, we decided to prepare both enantiomers of SL0101 (**I-1a**) and its analogues **I-1b** to **I-1e** (Figure 1).

Not long after the isolation and structure elucidation of SL0101 (**I-1a**), its first synthesis was reported by Professor Hecht.⁵ The Hecht synthesis derived the absolute and relative stereochemistry from L-rhamnose. In contrast, we were interested in the possibility of preparing all five members of this class of kaempferol glycosides (**I-1a** to **I-1e**) via asymmetric catalysis. This *de novo* approach would have the additional advantage of preparing both the D- and the L-enantiomers for biological testing.

Recently we reported a diastereoselective palladium-catalyzed glycosylation reaction that used alcohols as nucleophiles and Boc-pyranones such as **I-4a** as glycosyl donors.⁶ We have also found several post glycosylation transforms, which subsequently install the desired sugar stereochemistry.⁷ This methodology also works well for other *N*- and *O*-nucleophiles, such as 6-chloropurine/benzimidazole and phenol.⁸ In order to produce this class of interesting compounds for activity studies, we decided to apply this methodology toward the syntheses of the flavone glycosides, SL0101 (**I-1a**) and its analogues (**I-1b** to **I-1e**). In addition to providing material for biological study, this effort should also allow us to study flavon-3-ol as a nucleophile in the palladium-catalyzed glycosylation.

Scheme 1. Retrosynthetic analysis of kaempferol rhamnosides (**I-1a** to **I-1e**)

Retrosynthetically, we envisioned that pyranone **I-2** could be derived from a palladium(0)-catalyzed glycosylation between flavonol **I-3** and pyranone **I-4α** (Scheme 1). Subsequent application of NaBH_4 reduction and Upjohn dihydroxylation (OsO_4/NMO)⁹ would install the *manno*-stereochemistry.¹⁰ The selective introduction of the C-4 acetyl group should occur by introducing an acylation reaction between the NaBH_4 reduction and dihydroxylation. All that would remain would be to differentiate the C-2 hydroxyl group from the C-3 hydroxyl group. For this, we planned to use a combination of selective orthoester hydrolysis¹¹ and acyl migration reactions.¹² Since pyranone **I-4α** has been prepared in either enantiomeric form, this procedure should be amenable to the preparation of both enantiomers of **I-1a** to **I-1e**. In this chapter, we will describe our successful efforts at the implementation of this strategy to this class of kaempferol glycosides (**I-1a** to **I-1e**), which is noteworthy in that the various acetyl groups in **I-1a** to **I-1e** are installed without any hydroxyl protecting groups on the sugar.

Scheme 2. Synthesis of aglycone

Our synthesis started with the known perbenzylated kaempferol **I-3**, which was synthesized from naringin **I-6** in three steps (Scheme 2).⁵ Benzylation of naringin **I-6** by BnBr in the $\text{K}_2\text{CO}_3/\text{acetone}$ reflux condition with concomitant β -elimination afforded enone **I-7**, which was subjected to oxidative cyclization to enone **I-8** under I_2/DMSO condition. The cyclic enone was oxidized to epoxide by *in situ* produced DMDO in a basic buffer, which underwent acid-induced rearrangement to give aglycone flavonol **I-3**.

Scheme 3. Synthesis of Boc-pyranones as sugar donors

For the synthesis of the Boc-pyranone, we started with the achiral acylfuran (Scheme 3). Noyori reduction of acetylfruan **I-5** by using Noyori (*S,S*) catalyst in the presence of complex of formic acid and triethylamine as hydride source produced the furfuryl alcohol **I-9** in 93% yield with high enantiomeric excess (> 96% ee). An Achmatowiz rearrangement transformed the furfuryl alcohol to hemi-acetal **I-10** in 91% yield. The hemiacetal was then protected as *t*-butyl carbonate **I-4 α** and **I-4 β** at low temperature in 78% yield with 3:1 (α/β) diastereomeric ratio, which could be easily separated to give the L-sugar precursor. It is worth noting that by simply switching the catalyst Noyori (*S,S*) to Noyori (*R,R*), we are able to synthesize the D-sugar precursor.

Scheme 4. Synthesis of kaempferol-3- α -L-rhamnoside (**I-1b**)

The glycosylation was carried out with flavonol **I-3** and L-Boc-pyranone **I-4a** under catalysis of 2.5 mol% $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and 10 mol% of PPh_3 in CH_2Cl_2 at 0 °C, which afforded glycosylated pyranone **I-2** in 85% yield with complete α -selectivity (Scheme 4). Reduction of the enone **I-2** by NaBH_4 at -78 °C in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ resulted in allylic alcohol **I-11** in 73% yield with excellent diastereoselectivity ($\text{dr} > 20:1$). The *rhamno*-stereochemistry in **I-1b** was diastereoselectively introduced upon exposure of **I-11** to the Upjohn conditions (OsO_4/NMO , 96%). Debenzylation of resulted **I-12** using Pearlman's catalyst (10% Pd/C) in the presence of hydrogen gave kaempferol-3- α -L-rhamnoside (**I-1b**) in 80% yield.

In addition to the unacylated *rhamno*-sugar **I-1b**, the peracylated sugar **I-1c** could also be easily prepared in two steps from triol **I-12** (Scheme 5). Exhaustive acylation of the triol **I-12** with the excess acetic anhydride in presence of pyridine and 10 mol% DMAP gave triacetate **I-13** in 86% yield. Debenzylation of triacetate **I-13** by hydrogen using Pearlman's catalyst (10% Pd/C) again produced kaempferol-3- α -L-2'',3'',4''-O-triacetylramnoside (**I-1c**) in 86% yield.

Scheme 5. Synthesis of kaempferol-3- α -L-2'',3'',4''-O-triacetylramnoside (**I-1c**)

The selective installation of the C-4 acetyl group in **I-1d** was easily achieved without the need of additional protecting groups from the previously described allylic alcohol **I-11** (Scheme 4). In this route (Scheme 6), the NaBH_4 reduction of enone **I-2** was followed by an acylation of the resulting allylic alcohol with acetic anhydride in the presence of pyridine and DMAP. This two-step procedure afforded acetate **I-14** in 70% overall yield. Once again, dihydroxylation using the Upjohn condition stereoselectively converted allylic acetate **I-14** into the *rhamno*-diol **I-15** in 77% yield. Global deprotection was accomplished under hydrogenolysis conditions by

exposure of diol **I-15** to 1 atm of H₂ in the presence of Pearlman's catalyst (Pd/C), which furnished kaempferol-3- α -L-4''-O-acetylramnoside (**I-1d**) in 87% yield.

Scheme 6. *Synthesis of kaempferol-3- α -L-4''-O-acetylramnoside (**I-1d**)*

Acylation of the C-2 axial hydroxyl group of diol **I-15** was selectively achieved by using orthoester chemistry in excellent yield (99%) (Scheme 7).¹¹ Exposure of diol **I-15** to trimethyl orthoacetate in the presence of 10% *p*-TsOH in CH₂Cl₂ followed by hydrolysis with excess 90% HOAc/H₂O afforded diacetate **I-16** (Scheme 5). Once again, reductive debenzoylation of **I-16** with hydrogen and 10% Pd/C produced kaempferol-3- α -L-2'',4''-O-diacetylramnoside (**I-1e**) in 88% yield.

Scheme 7. Synthesis of kaempferol-3- α -L-2'',4''-O-diacetylramnoside (**I-1e**)

In contrast to the selective C-2 acylation of the axial alcohol in **I-15** (Scheme 7), our synthesis of SL0101 required the selective acylation of the C-3 equatorial alcohol (Scheme 8). Unfortunately, all of our attempts with $\text{Ac}_2\text{O}/\text{Py}$ at various temperature only furnished mixtures of diacetate **I-17** and **I-16**, as well as triacetate **I-13** (~1:1:1). Since we could achieve **I-16** with high regioselectivity, we turned our attention to the acetyl group shift from the less stable axial C-2 acetate in **I-16** to the more stable equatorial C-3 acetate in **I-17**.

All attempts to shift the axial acetyl group of diacetate **I-16** to the equatorial position by using 10 mol% $p\text{-TsOH}$ in CH_2Cl_2 at room temperature failed to give desired diacetate **I-17** (Scheme 8). In contrast, more promising results were seen with basic conditions. For instance, analysis of crude ^1H NMR of dilute toluene solutions of **I-16** with one equiv of DBU showed clean conversion to a 2:1 mixture of **I-17** and **I-16**. In practice good yields of **I-17** (62%) could be obtained along with recovered starting material (34%) after SiO_2 chromatography. Finally, debenzoylation of **I-17** under the similar condition as before produced SL0101 (**I-1a**) in 91% yield.

Scheme 8. Synthesis of SL0101 (I-1a**)**

To synthesize the D-sugar analogue of SL0101, we started our synthesis by simply switching the α -L-Boc-pyranone to α -D-Boc-pyranone (Scheme 9). Palladium(0)-catalyzed glycosylation of perbenzylated aglycone **I-3** with α -D-Boc-pyranone (*ent*)-**I-4a** afforded glycosylated pyranone (*ent*)-**I-2** in 71% yield and absolute stereocontrol. NaBH₄ reduction of (*ent*)-**I-2** followed by the dihydroxylation of the resulted allylic alcohol upon Upjohn condition furnished triol (*ent*)-**I-8** in 60% yield over two steps. Debenzylation of the triol (*ent*)-**8** under Pd/C hydrogenation condition produced SL0101 α -D-sugar analogue (*ent*)-**1b** in 90% yield. Our synthetic products (**I-1a** to **I-1e**) were physically and spectroscopically identical to the isolated natural materials in terms of melting point, optical rotation, *R_f*, ¹H NMR, ¹³C NMR and MS.^{3,5}

Scheme 9. *Synthesis of SL0101 D-sugar analogue*

In conclusion, a divergent and highly enantio- and diastereoselective procedures for the preparation of naturally occurring SL0101 (**I-1a**) as well as four kaempferol rhamnoside analogues (**I-1b** to **I-1e**) and one enantiomeric analogue (**(ent)-1b**) has been developed. This approach provides all the kaempferol glycosides without protecting any of the sugar hydroxyl groups. Our approach relied upon a diastereoselective palladium(0)-catalyzed glycosylation followed by a sequence of reduction/dihydroxylation reaction, as well as acylation. An acetyl group shift from an axial position to an equatorial position provided an alternative way for selective acylation of the equatorial hydroxyl group of a *cis*-diol in carbohydrate chemistry.

Chapter II. Asymmetric Synthesis of Cyclitol/Carbasugar

II.1. Cyclitol/Carbasugar monosaccharide^{†,13}

C-glycosides are carbohydrates where one of the acetal oxygens has been replaced with a methylene group.¹⁴ These non-hydrolyzable sugar mimics have long been recognized as an important pharmacophore.¹⁵ Cyclitols are an important subset of the C-glycoside structural motif where the endo-acetal ring oxygen has been replaced with a methylene group.¹⁶ In particular, polyhydroxylated cyclohexane cyclitols that mimic pyrano-sugars are ubiquitous in biologically important natural products (e.g., aminoglycosides, validamycins, acarbose, pyralomicins, pancratistatin).¹⁶

Scheme 10. Existing routes to cyclitol pyranose sugar

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Because of their pharmacological importance, there has been a myriad of approaches to the cyclitols (Scheme 10).^{16,17} These various routes have used both chiral (e.g., sugars and quinic acid) and achiral (e.g., arenes, furans, dienes) molecules as starting materials, with carbohydrates dominating this list of starting materials.^{16,17}

Scheme 11. *Our approach to normal pyranose carbohydrates*

For the last ten years, we have been interested in developing *de novo* approaches to pyranose sugars using dienoates and furans as starting materials.¹⁸ The dienoate route uses an iterative Sharpless asymmetric dihydroxylation to prepare *galacto*-lactones. The furan route uses asymmetric catalysis to a furan alcohol **II-3**, followed by an Achmatowicz rearrangement to a pyranone **II-2**, which in turn can be converted into various pyranose sugars **II-1** (Scheme 11).¹⁹ Of these two approaches, the route that uses furans as starting materials has the advantage of being more flexible in terms of substitution pattern and stereochemistry.

Scheme 12. *Pseudoenantiomeric enones from quinic acid*

As part of our continuing efforts to develop new approaches to biologically important carbohydrates, we desired a new approach to cyclitol sugars. In particular, we were interested in developing an approach to the cyclitols that had the same structural flexibility as our furan

approach. In particular, we desired a route that uses enones as cyclitol pyranones analogues that could similarly be converted into various cyclitol stereoisomers. While we ultimately want to develop a *de novo* asymmetric approach, we chose to use quinic acid **II-5** as our starting material, because it was already known to be easily converted into pseudoenantiomeric enones **II-4** and **II-6** (Scheme 12).²⁰ Herein, we describe our approach to cyclitol sugars **II-7**, **II-8**, (*ent*)-**II-7** from known enones **II-4** and **II-6** (Figure 2).

Figure 2. Targeted carbasugar monosaccharide

Our initial plan to install the methyl group for these target molecules was to use enolate chemistry to introduce a methyl group at the α -position of α,β -unsaturated ketone either through *in situ* generated enolate or silylenol ether. We envisioned the stereochemistry of methylation could be controlled by the other substituents in the ring. Finally, the desired sugar stereochemistry could be established by subsequent transformation, akin to our pyranone to sugar chemistry.^{18,19}

Our synthesis started with enone **II-4**, which was easily prepared from D-quinic acid **II-5** in 4 steps with 60% overall yield.²⁰ Unfortunately, all attempts at 1,4-reduction and direct alkylation of enone **II-4** were unsuccessful. For instance, the Tsuda-Saegusa catalytic copper hydride 1,4-reduction proceeded smoothly, but *in situ* alkylation of the enolate intermediate with methyl iodide failed to cleanly give the desired α -methyl ketones **II-11a/II-11b** (Scheme 13).²¹ The *in situ* use of Stryker's reagent for 1,4-hydrosilylation of **II-4** also proved to be problematic.²²

Alternatively, we envisioned that a cyclopropanation and ring opening process could lead to the formation of α -methyl ketone.²³ Thus, one pot hydrosilylation of enone **II-4** ($\text{RhCl}(\text{PPh}_3)_3/\text{PhMe}_2\text{SiH}$, 60 °C)²⁴ followed by Simmons-Smith cyclopropanation ($\text{ZnEt}_2/\text{CH}_2\text{I}_2$)²⁵ of the resulting silylenol ether at 0 °C gave an inseparable mixture of

cyclopropanol silyl ethers, which when desilylated under acidic conditions (*p*-TsOH/MeOH) furnished two readily separable diastereoisomers **II-9a/II-9b** in 83% overall yield with dr ~1:1 (Scheme 13). With the cyclopropanol in hand, we next turned our attention to the ring opening of cyclopropanol.

Scheme 13. Cyclopropanation and attempts to ring-opening

Unfortunately, all attempts to open the three membered ring using acid or base failed to give the desired α -methyl ketone.²⁶ The ring opening promoted by Pd(OAc)₂ in the presence of pyridine at 80 °C resulted in a mixture of separable *exo*- and *endo*- α,β -unsaturated ketone (**II-10a/II-10b** 1:2) in 86% yield.²⁷ When this reaction was carried out under similar conditions with

the addition of two equivalents of quinone, **II-10a** was the only enone product produced in 70% yield along with 10% recovered starting material, which could prevent palladium(0) catalyzed isomerization of **II-10a** to **II-10b**. Interestingly, the cyclopropanol could also be opened by stoichiometric Pd/C at RT to afford **II-10a** exclusively. With access to enones **10a** and **10b**, we next explored their hydrogenation to prepare the α -methyl ketones **II-11a/II-11b**. Thus, hydrogenation of **II-10a** under typical conditions (H_2 , Pd/C) afforded an inseparable diastereomeric mixture of α -methyl ketone **II-11a/II-11b** in 88% yield (dr 3:1), while hydrogenation of **II-10b** under the same conditions produced **II-11a/II-11b** in 89% yield with opposite diastereoselectivity (dr 1:10). In order to skirt the separation problem at this point, we continued our synthesis with the diastereomeric mixture of **II-11a/II-11b**. Base promoted β -elimination of **II-11a/II-11b** (dr 3:1) (0.5 M NaOH/THF, 0 °C) furnished a mixture of allylic alcohol **II-12a/II-12b** (dr 2:3) in 85% yield,²⁸ which were also difficult to separate. These results forced us to reinvestigate the cyclopropanol ring opening process.

Scheme 14. *Synthesis of α -D-5a-carba-rhamnose*

We thought a direct hydrogenation with Pd/C of the cyclopropanol ring could avoid

formation of the enone intermediate **II-10a** by preventing β -hydride elimination. That is to say, we hoped the Pd-homoenolate intermediate might be trapped by the Pd-bound hydrogen.²⁹ To our delight, hydrogenation of **II-9a** with Pd/C under balloon pressure of H₂ resulted in **II-11a** as a single diastereomer (dr >100:1) in 80% yield (Scheme 14). Deprotection of **II-11a** under acidic conditions (10% HCl/THF) produced diol **II-13**. Alternatively, the diol could be achieved as a single diastereomer by first deprotection of acetonide in **9a** (10% HCl/THF, 82%), then followed by the isomerization of the resulted triol **14** under the same hydrogenation condition (Pd/C, H₂, 82%).

With the methyl group having been set, we next tried to install the α -D-rhamnose stereochemistry. Thus, the diol **II-13** was acylated with Boc-anhydride followed by β -elimination to afford enone **II-15** in 83% yield over two steps. The carbonyl group of **II-15** was diastereoselectively reduced with LiAlH₄ at -78 °C to provide allylic alcohol **II-16** in 91% yield (dr 11:1) with easy removal of the minor diastereomer by column chromatography. Dihydroxylation of cyclohexene **II-16** under Upjohn conditions produced triol **II-17** as a single diastereomer with good yield (87%). Reductive removal of the *t*-butyl carbonate group with LiAlH₄ resulted in 5a-carba- α -D-rhamnopyranose **II-7** in 83% yield.

In order to prepare the β -D-carbasugar, we switched the starting material to enone **II-6** (Scheme 15). Enone **II-6** could also be readily prepared from D-quinic acid **II-5** in 5 steps in 50% yield.³⁰ As with enone **II-4** (c.f. Scheme 13), a one pot hydrosilylation and cyclopropanation of **II-6**, followed by desilylation under acidic conditions gave a diastereomeric mixture of cyclopropanol **II-18a**/ **II-18b** (dr ~1:1) in 85% overall yield. Although these two cyclopropanol isomers were inseparable, a direct cyclopropanol ring opening of this mixture by Pd/C under hydrogenation conditions (balloon pressure of H₂, 6 h, RT) afforded a diastereomeric mixture of α -methyl ketones **II-19a**/**II-19b** (63% yield, dr 2:1) along with some recovered cyclopropanol **II-18b** (20%, as a single diastereomer). The mixture of **II-19a** and **II-19b** could be separated by a combination of crystallization and silica gel chromatography resulting in a diastereomerically enriched mixture of **II-19a** (dr >13:1) and diastereomerically pure **II-19b**. X-ray crystallography analysis of **II-19b** confirmed its stereochemistry.

Scheme 15. *Synthesis of β -D-5a-carba-digitoxose*

X-ray of II-19b

With the **II-19b** in hand, we next turned our attention to install the β -D-digitoxose stereochemistry. Thus, deprotection of **II-19b** in acidic condition (90% TFA/H₂O) gave crude diol (albeit with some C-5 epimerization, dr ~15:1), which underwent acylation with Boc-anhydride, and subsequent β -elimination to afford enone **II-20** (79% yield from **II-19b**, dr ~15:1). While pure isomer **II-20** could be obtained by careful chromatography, the diastereomeric mixture of **II-20** could be directly used in the diastereoselective reduction (LiAlH₄ at -78 °C), resulting in an allylic alcohol in 82 % yield, with the minor diastereomers readily removed by chromatography, which was then treated in Meyer's reductive rearrangement condition to provide olefin **II-21** in good yield (73%, two steps).³¹ Dihydroxylation of the olefin **II-21** under the Upjohn dihydroxylation conditions (OsO₄/NMO) afforded an inseparable diastereomeric mixture of diol (dr 11:1), which was derivatized as an acetonide **II-22** (81% for two steps), with the minor diastereomer removed by chromatography. Finally, reduction of the Boc-carbonate by LiAlH₄ and removal of acetonide in acid condition (10% HCl/THF) afforded 5a-carba- β -D-digitoxopyranose **II-8** in 85% yield.

Our efforts toward the L-carbasugars, commenced with the synthesis of α -methyl ketone **II-19a** (Scheme 16). Acid hydrolysis of the bis-ketal in **II-19a** (dr ~10:1) afforded diol **II-23** in 70% yield. It was difficult to prevent some epimerization of the axial methyl group in **II-23** under the reaction conditions (dr ~8:1 for crude **II-23**). However, the minor diastereomer could be removed by silica gel chromatography. Then the diol **II-23** subsequently underwent acylation with Boc-anhydride and β -elimination under basic condition to furnish enone (*ent*)-**II-15** (90% overall yield, two steps). Thus, this enantiomer of **II-15** could be converted into 5a-carba- α -L-rhamnopyranose (*ent*)-**II-7** using the same 3-step reaction sequence for the conversion of **II-15** to **II-7**.

Scheme 16. *Synthesis of α -L-5a-carba-rhamnose*

Alternatively, the L-series of carbasugar could be prepared from cyclopropanol **II-9b** (Scheme 4). We first deprotected the acetonide of **II-9b** under acidic conditions (10% HCl/THF) to give triol **II-24** in 82% yield (Scheme 16). Exposure of the cyclopropanol **II-24** to similar hydrogenation conditions (Pd/C, H₂) as before afforded the α -methyl ketone **II-25** in 80% yield

as a single diastereomer. An X-ray crystallography analysis of **II-25** clearly confirmed the formation of α -methyl ketone and its stereochemistry. Dehydration of diol **II-25** through carbonate formation and β -elimination furnished allylic alcohol **II-12b** in 73% yield over two steps. In order to prepare the α -sugar, we need to invert the stereochemistry of the C-1 hydroxyl group. Thus, Mitsunobu reaction of **II-12b** with *p*-nitrobenzoic acid in the presence of DIAD and PPh₃ gave the ester **II-26** in excellent yield (95%) with desired inverted stereochemistry.³² Diastereoselective reduction of the enone **II-26** (LiAlH₄, -78 °C) afforded allylic alcohol **II-27** in 90% yield (dr 11:1) with the minor isomer easily removed by chromatography. Dihydroxylation of the allylic alcohol **II-27** produced triol **II-28** in 94% yield with complete stereocontrol. Saponification of ester **II-28** under basic conditions (LiOH/MeOH) afforded 5a-carba- α -L-rhamnopyranose (*ent*)-**II-7** in 85% yield.³³

In conclusion, three carbasugars in D/L and α/β forms have been successfully synthesized starting with D-(–)-quinic acid. This synthesis highlights a novel diastereospecific Pd/C catalyzed cyclopropanol ring opening, diastereoselective reduction and dihydroxylation. Mitsunobu reaction and Myers' reductive rearrangement were also used to install the desired carbasugar stereochemistry.

II.2. Carbasugar C-1 Phosphate^{‡,34}

Carbohydrates are a recurring structural motif in many bioactive natural products (e.g., antimicrobial and anticancer agents).³⁵ Often the sugar portion of the molecule is a crucial element for the activities of these compounds; for instance, many aglycons of biologically active natural products are void of activity.³⁶ A cursory structure activity relationship analysis of the carbohydrate containing natural products points to the use of rare and deoxysugars (Scheme 17).³⁷ The removal or stereochemical inversion of the various sugar hydroxyl groups can impart significant *in vitro*-stability by lessening the abilities of naturally occurring glycosidase enzymes to degrade the structure. In fact, our ongoing interest in the de novo synthesis of carbohydrates is aimed at being able to provide new glycosylated natural products for medicinal chemistry studies.³⁸ An alternative approach is to alter the biosynthesis of the glycosylated natural products.³⁹

Scheme 17. *Biosynthesis of glycosyltransferase inhibitors*

In an effort to understand and ultimately alter the microbial biosynthesis of rare/deoxy-sugar containing natural products various C-glycoside analogues of the NDP-sugars have been prepared.⁴⁰ Most of these efforts have been focused on the synthesis and use of C-glycoside analogues with exo-acetal oxygen replaced with a methylene group (Y = CH₂).⁴⁰ In contrast, there is only one report that describes the use of the endo-acetal oxygen C-glycoside (X = CH₂, cyclitol).⁴¹ To these ends, we have initiated an effort to develop an approach to these cyclitol sugar phosphates (X = CH₂) in a manner that would mimic our de novo approach to carbohydrates (i.e., one that is amenable to both enantiomers of either α- or β-isomers). Herein

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we described our successful efforts towards these aims.

Figure 3. *The target cyclitol sugar phosphates*

To address these aims, we targeted the synthesis of four α -sugars and one β -sugar. These structures are outlined in Figure 3: 2,3-dideoxy-4-oxo-5a-carba- α -D-rhamnopyranose phosphate (**II-31**), 2,3-dideoxy-5a-carba- α -D-rhamnopyranose phosphate (**II-32**), 5a-carba- α -D-rhamnopyranose phosphate (**II-33**), 5a-carba- β -D-digitoxopyranose phosphate (**II-34**) and 5a-carba- α -L-rhamnopyranose phosphate (**(ent)-II-33**).

Scheme 18. *Retrosynthetic analysis*

Retrosynthetically, we envisioned that the desired carbasugar phosphates stereoisomers **II-35** could be achieved from both enantiomers of the cis- and trans-diastereomers of the enone γ -phosphate **II-36** (Scheme 18). We thought **II-36** could be derived from corresponding allylic alcohol **II-37** which are readily available or could be easily synthesized from suitable intermediates we already achieved during the synthesis of carbasugar monosaccharide.

Scheme 19. Synthesis of 2,3-dideoxy-4-oxo-5a-carba- α -D-rhamnopyranose 1-phosphate (**II-32**)

We started the synthesis of the D-carbasugar phosphates with diol **II-13**. Carbonate formation of **II-13** using triphosgene followed by β -elimination in basic condition resulted in allylic alcohol **II-38** in 73% yield (Scheme 19). Phosphorylation of the alcohol **II-38** with *N,N*-diethyl dibenzylphosphoramidite in the presence of 1*H*-tetrazole gave a phosphite intermediate which was oxidized by addition of 30% H_2O_2 to form dibenzyl phosphate **II-39** in 76% yield. Debenzylation and reduction of double bond under hydrogenation condition (H_2 , Pd/C) failed to give the desired dihydrogen phosphate **II-31**, presumably due to hydrogenolysis of the allylic phosphate. Attempts at hydrogenation of **II-39** with diimide (NBSH/ Et_3N) proved unsuccessful. Thus we decided reduce the double bond before introduction of the phosphate functional group. Hydrogenation of **II-38** (H_2 , Pd/C) gave saturated alcohol **II-40** in 72% yield. Phosphorylation of **II-40** in the same condition described before gave dibenzyl phosphate **II-41** in 70% yield. Then debenzylation under typical hydrogenation condition (H_2 , Pd/C) afforded the 2,3-dideoxy-4-oxo-5a-carba- α -D-rhamnopyranose phosphate (**II-31**) in 73% yield. While analysis of the crude product showed diastereomerically clean material, upon sitting the product slowly epimerized to a ~2:1 of methyl diastereomers.

Scheme 20. Synthesis of 2,3-dideoxy-5a-carba- α -D-rhamnopyranose 1-phosphate (**II-32**), 5a-carba- α -D-rhamnopyranose 1-phosphate (**II-33**)

To synthesize the phosphate **II-32** and **II-33**, we returned to enone **II-39** (Scheme 20). A diastereoselective reduction with LiAlH_4 at -78°C gave the equatorial alcohol **II-42** in good yield (87%) and diastereoselectivity (dr 11:1). Diimide reduction ($\text{NBSH}/\text{Et}_3\text{N}$) of **II-42** resulted in saturated alcohol **II-43** in 60% yield with 20% starting material back. Hydrogenation of **II-43** on Pd/C furnished 2,3-dideoxy-5a-carba- α -D-rhamnopyranose phosphate (**II-32**) in 83% yield. Alternatively, dihydroxylation of allylic alcohol **II-42** under Upjohn condition⁴² resulted in a single diastereomeric triol **II-44** in 86% yield, which similarly underwent hydrogenolysis to afford 5a-carba- α -D-rhamnopyranose phosphate (**II-33**) in 87% yield.

In order to achieve the β -D-digitoxose phosphate **II-34**, we started with Boc-carbonate **II-22** (Scheme 21). Reduction of Boc-carbonate **II-22** by LiAlH_4 gave alcohol **II-45** in 93% yield which was then phosphorylated to give dibenzyl phosphate **II-46** in 74% yield. The acetonide deprotection of **II-46** in acid condition produced diol **II-47** with excellent yield (95%), which under typical hydrogenation conditions (H_2 , Pd/C) resulted in 5a-carba- β -D-digitoxopyranose phosphate (**II-34**) in 78% yield.

Scheme 21. Synthesis of 5a-carba- β -D-digitoxopyranose 1-phosphate (**II-34**)

In order to access the L-series of carbasugar phosphate, we started with the intermediate **II-27**. TBS-protection and ester hydrolysis of **II-27** gave alcohol allylic alcohol **II-48** in good overall yield (85% for 2 steps) (Scheme 22). Phosphorylation of alcohol **II-48** afforded dibenzyl phosphate **II-49** in 66% yield. Dihydroxylation of **II-49** under Upjohn conditions produced diol in 81% yield as a single diastereomer, which after acid deprotection (*p*-TsOH/MeOH) provided triol **II-50** in excellent overall yield (79% for two steps). Finally hydrogenation of dibenzylphosphate **II-50** resulted in 5a-carba- α -L-rhamnopyranose phosphate (*(ent)*-**II-33**) in 81% yield.

Scheme 22. *Synthesis of 5a-carba- α -L-rhamnopyranose 1-phosphate ((ent)-5)*

In conclusion, five carbasugar phosphates have been successfully synthesized in either D or L, α or β form from D-(–)-quinic acid. This synthesis includes a novel highly diastereospecific Pd/C catalyzed cyclopropanol ring opening, which may be a useful alternative for the introduction of methyl groups alpha to ketones. Diastereoselective reduction, dihydroxylation, Mitsunobu reaction and Myers' reductive rearrangement were also used to install the desired sugar stereochemistry. The biological evaluation of these cyclitol phosphates is ongoing.

Chapter III. Methodology and Synthesis of Carbasugar Analogues of SL0101

III.1. Methodology development of carbasugar glycoside

In order to facilitate the medicinal structure-activity relationship (SAR) study of SL0101, we turned our attention to the carbasugar glycoside analogues of SL0101 (Figure 4). The advantage is that because these carbasugar analogues are not hydrolyzable because the ring oxygen has been replaced with a methylene group, and the biological activities of these carbasugar analogues will provide very important information to the structure-activity relationship (SAR) study of SL0101, particularly it may help us to understand the function of the sugar moiety.

Figure 4. Carbasugar glycoside analogues of SL0101

Over these years, O'Doherty group has successfully developed a de novo approach to synthesize carbohydrates by using a palladium(0)-catalyzed glycosylation to introduce the glycosidic bond and post-glycosylation transformations to install corresponding stereochemistry of all kinds of glycosides.⁴³ We want to develop a practical method to synthesize carbasugar or cyclitol glycoside, which is compatible to our method in the synthesis of normal carbohydrates (Scheme 23). To do this, we have two problems that need to be addressed. First, we want to know whether or not the palladium(0)-catalyzed glycosylation (i.e. Palladium(0)-catalyzed cyclitolization) from **III-4** to **III-5** would still work well without a ring oxygen. Second, we want to know whether or not a post-glycosylation (i.e. post-cyclitolization) could be developed to convert enone **III-5** to the corresponding carbasugar **III-6** accordingly as we did for normal

carbohydrates, since the anomeric effect no longer exists when the ring oxygen was replaced by a methylene group.

Scheme 23. *Proposed carbasugar synthesis*

As we mentioned in chapter II of this dissertation, we already synthesized both α -L-Boc-enone (**III-4**) and α -D-Boc-enone ((*ent*)-**III-4**) from quinic acid. Our carbasugar synthesis was carried out by first testing the palladium(0)-catalyzed cyclitolization. In practice, α -D-Boc-enone ((*ent*)-**III-4**) was reacted with BnOH in CH_2Cl_2 in the presence of 10 mol% $\text{Pd}(\text{PPh}_3)_2$ at 0 °C for 10 hours. As a result, the reaction afforded glycosylated enone **III-7** in a reasonable 60% yield (Scheme 24).

Scheme 24. *Palladium(0)-catalyzed cyclitolization or C-in ring glycosylation*

In order to produce SL0101 carbasugar analogues we next examined the cyclitolization reaction of SL0101 aglycone (Scheme 25). Reaction between flavonol aglycone **III-8** and α -D-Boc-enone ((*ent*)-**III-4**) went smoothly in CH_2Cl_2 in the presence of $\text{Pd}(\text{PPh}_3)_2$ catalyst to afford desired glycosylated enone (*ent*)-**III-9** in 84% yield. In reality, this reaction finished in half an hour at 0 °C with only 5 mol% Pd loading.

Scheme 25. Palladium(0)-catalyzed cyclitolization of the SL0101 aglycone

Since the palladium(0)-catalyzed cyclitolization reaction between flavonol **III-8** and the Boc-enone (ent)-**III-4** worked very well, we believe a testing of the substrate scope will be useful for us to understand this reaction in terms of the electronic and steric effect from the substrates, which also would broaden its application to the synthesis of carbasugar glycoside analogues of many biologically important natural glycosides. For this purpose, a number of phenols and enols with different substitution patterns were chosen for testing (Scheme 26). From the experiments, the palladium(0)-catalyzed cyclitolization overall gave reasonable to excellent yields including phenols such as **III-10** to **III-17** and coumarin **III-19**, enols such as naphthaquinone-2-ol (**III-20**) and flavonol **III-8**. Tentatively, we could conclude that (1) Phenols with electron donating groups tend to give higher yield for the cyclitolization than those with electron withdrawing groups, and for the extreme case, highly electron deficient *p*-nitrophenol did not react at all; (2) Steric hinderance did not greatly affect those phenols with electron donating groups even with a *t*-butyl group in ortho position such as **III-14**; but for those with electron withdrawing groups such as **III-16**, the steric hinderance might be responsible for the lower yield; (3) Highly electron deficient enol such as **III-20** also gave high yield of cyclitolization, which we did not expect that before.

Scheme 26. Palladium(0)-catalyzed cyclitolization for phenols and enols

Entry	ROH	Products	Yield
1	(III-10)	(III-21)	88%
2	(III-11)	(III-22)	96%
3	(III-12)	(III-23)	86%
4	(III-13)	(III-24)	89%
5	(III-14)	(III-25)	88%
6	(III-15)	(III-26)	76%
7	(III-16)	(III-27)	66%

8	(III-17)	(III-28)	84%
9	(III-18)	-----	NR
10	(III-19)	(III-29)	98%
11	(III-20)	(III-30)	83%
12	(III-8)	((ent)-III-9)	85%

Once the palladium(0)-catalyzed cyclitolization has been developed, we next turned our attention to the post-cyclitolization transformation to install desired stereochemistry of the carbasugars. In particular, we hope to develop a practical way to the rhmannose stereochemistry since the sugar moiety in SL0101 and its analogues are rhmannose. The first thing we wanted to do was the reduction of the glycosylated enone such as **III-7** to allylic alcohol with high diastereoselectivity (Scheme 27). NaBH₄ reduction with or without CeCl₃ at -78 °C, which are usual conditions we used to reduce pyranones in our normal carbohydrate synthesis, had some selectivity of **III-31** over **III-32** but not that satisfying. We next examined DIBAL-H, which gave a 1:1 ratio of these two allylic alcohols. The more bulky lithium tri-*t*-butoxyaluminumhydride did not increase the selectivity too much. Fortunately, LiAlH₄ reduction at -78 °C resulted in a reasonable diastereoselectivity of 11:1 to afford allylic alcohol **III-31** with 85% yield, when the temperature was lowered down to -100 °C, the selectivity slightly increased to 12:1.

Scheme 27. *Reduction of glycosylated enone*

Entry	Reduction condition	Ratio of III-31 / III-32
1	NaBH ₄ /-78 °C	3 : 1
2	NaBH ₄ /CeCl ₃ /-78 °C	1.5 : 1
3	DIBAL-H/-78 °C	1 : 1
4	LiAlH(<i>t</i> -BuO) ₃ /-78 °C	3.5 : 1
5	LiAlH ₄ /-78 °C	11 : 1
6	LiAlH ₄ /-100 °C	12 : 1

To install the rhmannose stereochemistry, olefin **III-31** was then converted to diol **III-33** (Scheme 28). In practice, dihydroxylation of the allylic alcohol **III-31** upon Upjohn condition (OsO₄/NMO) condition at 0 °C afforded triol **III-33** in 90% yield with complete stereocontrol.

Scheme 28. *Dihydroxylation of allylic alcohol III-31*

III.2. Synthesis of carbasugar glycoside analogues of SL0101

Once the methodology of palladium(0)-catalyzed cyclitolization and post-cyclitolization transformation had been successfully developed, we next started the synthesis of carbasugar analogues of SL0101. Treatment of tribenzylated kaempferol **III-8** with α -L-Boc-enone **III-4** in the presence of 5 mol% Pd catalyst in CH_2Cl_2 at 0 °C for 30 minutes furnished the glycosylated enone **III-9** with 84% yield (Scheme 29).

Scheme 29. Palladium(0)-catalyzed cyclitolization of SL0101 aglycone

Reduction of the enone **III-9** by LiAlH_4 at -78 °C afforded allylic alcohol **III-34** in 89% yield with the diastereoselectivity of 11:1 (Scheme 30). Acylation of the resulted allylic alcohol gave allylic acetate **IV-24** in 93% yield. Dihydroxylation of the olefin in **IV-24** furnished the diol **IV-25** in 73% yield as a single diastereomer. The diol **IV-25** was then converted to one of our desired carbasugar analogues of SL0101, C-4 monoacetate **IV-1** after debenzylation on Pd/C hydrogenation condition in 68% yield.

Scheme 30. Synthesis of α -L carbasugar analogue of SL0101 (C-4 monoacetate)

In order to achieve the diacetate carbasugar analogues of SL0101, we thought a selective acylation could be carried out on intermediate diol **III-36** by an orthoacetate formation and kinetic hydrolysis just like what we did in the synthesis of SL0101 (Scheme 31). Treatment of diol with trimethyl orthoacetate in the presence of catalytical amount of *p*-toluenesulfonic acid followed by the hydrolysis by using 90% aqueous acetic acid furnished a mixture of 2,4-diacetate **III-37** and 3,4-diacetate **III-38** in a 1.5:1 ratio, which was in contrast to the completely regioselective acylation of the axial hydroxy group in the synthesis of SL0101. This result clearly indicated the ring flip of cyclohexane ring is much easier due to the loss of anomeric effect which helps control the sugar conformation. Fortunately, we could separate these two regioisomers on silica gel column chromatography. Then, debenzoylation of **III-37** and **III-38** was carried out by hydrogenation to produce SL0101 C-2,C-4-diacetate carbasugar analogue **III-2** and C-3,C-4-diacetate carbasugar analogue **III-3** respectively.

Scheme 31. *Synthesis of diacetate carbasugar analogues of SL0101*

In order to access D-series of carbasugar analogues of SL0101, we first coupled the aglycone kaempferol **III-8** with the α -D-Boc-enone (*ent*)-**III-4** by using palladium(0)-catalyzed cyclitolization condition to furnish glycosylated enone (*ent*)-**III-9** in 85% yield (Scheme 32).

Scheme 32. *Palladium(0)-catalyzed cyclitolization of SL0101 aglycone with α -D-Boc-enone*

Reduction of enone (*ent*)-**III-9** by LiAlH₄ at -78 °C afforded allylic alcohol (*ent*)-**III-34** in 89% yield with the diastereoselectivity 11:1 (Scheme 33). Acylation of the resulted allylic

alcohol gave allylic acetate (*ent*)-**III-35** in 98% yield. Dihydroxylation of the olefin (*ent*)-**III-35** upon Upjohn condition furnished the diol (*ent*)-**III-36** in 82% yield as a single diastereomer. The diol (*ent*)-**III-36** was then converted to one of α -D carbasugar analogues of SL0101, C-4 monoacetate (*ent*)-**III-1** after debenzylation on Pd/C hydrogenation condition in 73% yield.

Scheme 33. Synthesis of monoacetate of α -D-carbasugar analogue of SL0101

To synthesize the diacetate of α -D carbasugar analogues of SL0101, an orthoacetate formation and kinetic hydrolysis was performed on the diol intermediate (*ent*)-**III-36** (Scheme 34). Treatment of diol with trimethyl orthoacetate in the presence of catalytic amount of *p*-toluenesulfonic acid followed by hydrolysis using 90% aqueous acetic acid furnished 2,4-diacetate (*ent*)-**III-37** and 3,4-diacetate (*ent*)-**III-38** in about 1:1 ratio. After separation of these two regioisomers, (*ent*)-**III-37** and (*ent*)-**III-38** were debenzylated by the hydrogenation to produce SL0101 C-2,C-4-diacetate of α -D carbasugar analogue (*ent*)-**III-2** and C-3,C-4-diacetate of α -D carbasugar analogue (*ent*)-**III-3**, respectively.

Scheme 34. *Synthesis of diacetate of α -D-carbasugar analogues of SL0101*

In conclusion, a palladium(0)-catalyzed cyclitolization and post-cyclitolization transformation have been successfully developed. Six carbasugar analogues of SL0101 including three α -L and three α -D forms have been synthesized by utilizing this methodology.

Chapter IV. Efforts toward the Total Synthesis of Jadomycin A and B

IV.1. Introduction

Jadomycins are a group of angucycline-derived antibiotics that were produced by *Streptomyces venezuelae* following heat shock, ethanol shock or phage infection.⁴⁴ The unique structural feature of these class of antibiotics is the pentacyclic 8*H*-benz[*b*]oxazolo[3,2-*f*]-phenanthridine backbone, which consists of a dihydropyridine ring and an oxazolone ring. The formation of these two unique rings are believed to arise from the condensation of a biosynthetic aldehyde intermediate, which is derived from anguclinone, with amino acid followed by a series of transformations.⁴⁵ The jadomycins exhibited a multitude of activities such as antibacterial, antiyeast, cytotoxicity against cancer cell lines, antiviral, and enzyme inhibitory activities.^{44,46}

Figure 5. Structural Features of Jadomycin A and Jadomycin B

Jadomycin A and B (Figure 5) were the first jadomycins that were isolated from *Streptomyces venezuelae* ISP5230 when grown in an isoleucine containing medium under stress conditions by Prof. Ayer in 1991 and 1993 respectively.⁴⁴ Jadomycin A is the aglycone of jadomycin B, which is an α -L-digitoxoside. The sugar moiety, α -L-digitoxose in jadomycin B is believed of great importance for some biological activities such as anti-yeast, which jadomycin A does not have.^{44c,47} Since the discovery of jadomycin A and B, many analogues of jadomycin B have been produced by the fermentation in medium with variant non-natural and natural aminoacids. All these jadomycin analogues were called jadomycins and their biological activities, as well as their biosynthetic pathway have been broadly investigated.^{45,48,49}

Although they are structurally unique and biologically important, so far no total synthesis of jadomycins including jadomycin A, B and their analogues have been reported. We believe a practical synthetic approach to these structures as well as the ease to incorporate different aminoacid and sugar moiety would significantly enhance the medicinal structure-activity relationship (SAR) studies of this class of antibiotics.

Scheme 35. Retrosynthetic analysis of jadomycin B

Retrosynthetically, we think the jadomycin B (**IV-2**) could be disconnected on the glycosidic bond between the sugar moiety and aglycone (Scheme 35). The successful synthesis of the aglycone of jadomycin B could be used to determine the structure of jadomycin A (**IV-1**), which was not clearly identified in the isolation paper in terms of the stereochemistry of the methyl group in the amino acid. We envisioned that the glycosidic bond could be installed via our palladium(0)-catalyzed glycosylation reaction between jadomycin A (**IV-1**) and Boc-pyranone (**IV-3**), while a post-glycosylation transformation from glycosylated pyranone to α -digitoxose need to be developed. We believed the aglycone part could be achieved from three components juglone **IV-4**, benzaldehyde **IV-5**, and the amino acid **IV-6**. The connection between juglone part and benzaldehyde part could be achieved by using some sort of cross coupling reactions or direct

nucleophilic addition reactions. The aminoacid part could be introduced at due course, although we don't know the stereochemistry of the methyl group, it is reasonable for us to start with natural isoleucine.

IV.2. De novo asymmetric synthesis of α -digitoxose

Scheme 36. *Limitation of our current methodology to digitoxose*

In order to synthesize the sugar moiety of jadomycin B, first we need to develop a practical method to achieve α -digitoxose in terms of installation of the correct stereochemistry. As part of efforts to search for more potent digitoxin analogues for the anti-cancer agents, we successfully developed a route to β -digitoxose (Scheme 36).⁵⁰ The approach features a palladium(0)-glycosylation to a β -pyranone **IV-7**, which subsequently underwent reduction to allylic alcohol **IV-8**, Myers' 1,3-transposition to olefin **IV-9**, and dihydroxylation of the resulted olefin. This approach afforded exclusively the desired β -digitoxose **IV-10**. When it comes to the α -digitoxose case, after reduction of an α -pyranone **IV-11** to allylic alcohol **IV-12**, 1,3-transposition of the double bond and dihydroxylation of the resulted olefin **IV-13** will produce a diastereomeric mixture of desired α -digitoxose **IV-14** and undesired sugar **IV-15** with the undesired diastereomer as the major product. This limitation clearly indicated that a new practical post-glycosylation transformation should be needed to prepare α -digitoxose.

Scheme 37. *Proposed approach to α -digitoxose*

We envisioned that since the reduction of the α -pyranone gave an allylic alcohol **IV-12** which has the same stereochemistry as required in jadomycin B (**IV-2**), the hydroxyl group could possibly direct the introduction of adjacent hydroxy group by a cyclic carbonate formation from **IV-16** to **IV-17** to set up the second hydroxy group which after suitable transformation could be converted to α -digitoxose (scheme 37). After searching in the literature, similar transformations could be seen.⁵¹ But all these transformations from allyl carbonate to cyclic carbonate involved the use of very strong electrophile such as $I(\text{Collidine})_2\text{ClO}_4$, which limited the compatibility of this approach. We started to investigate more general electrophiles that could promote the formation of cyclic carbonate **IV-17** from a mixed carbonate **IV-16**, at the same time it might be compatible with the aromatic ring such as aglycone in jadomycin B.

Scheme 38. *Asymmetric Synthesis of Boc-pyranone*

We started the synthesis with the achiral acylfuran (Scheme 38). Noyori reduction of acylfuran **IV-18** by using Noyori (*R,R*) catalyst in the presence of complex of formic acid and triethylamine as hydride source produced the furyl alcohol **IV-19** in 93% yield with high enantiomeric excess (> 96% ee). An Achmatowicz rearrangement transformed the furyl alcohol to hemiacetal **IV-20** in 91% yield. The hemiacetal was then protected as *t*-butyl carbonate **IV-22a** and **IV-22b** at low temperature in 78% yield with 3:1 (α/β) diastereomeric ratio, which could be easily separated to give the D-sugar precursor.⁵² It worth noting that by simply switching the catalyst Noyori (*R,R*) to Noyori (*S,S*), we are able to synthesize the L-sugar precursor.

Scheme 39. *Synthesis of the allyl carbonate*

Palladium(0)-catalyzed glycosylation reaction developed in our lab diastereoselectively installed glycosidic bond at the anomeric center with complete α selectivity (**IV-22a** to **IV-23**) (Scheme 39). NaBH₄ reduction of the enone **IV-23** at -78 °C resulted in the allylic alcohol **IV-24** with high diastereoselectivity (dr > 20:1). Acylation of the allylic alcohol **IV-24** with either CbzCl or Boc₂O afforded carbonate **IV-25** and **IV-26** respectively, which are ready for the screening of iodo-carbonation.

Scheme 40. Screening for the halo-carbonation of allyl carbonate

Entry	R	Solvent	Electrophile	Lewis Acid	Yield
1	Boc	CH ₂ Cl ₂	NBS		NR
2	Boc	CH ₂ Cl ₂	NIS		NR
3	Boc	CH ₂ Cl ₂	I ₂		NR
4	Boc	CH ₂ Cl ₂	PhNMe ₃ Br ₃		NR
5	Boc	CH ₂ Cl ₂	NIS	LiClO ₄	Trace amount
6	Boc	CH ₂ Cl ₂	NIS	MgBr ₂ •Et ₂ O	26%
7	Boc	CH ₂ Cl ₂	NIS	ZnI ₂	NR
8	Boc	CH ₂ Cl ₂	NIS	Zn(OTf) ₂	decompose
9	Boc	CH ₂ Cl ₂	NIS	Sc(OTf) ₃	decompose
10	Boc	CH ₂ Cl ₂	NIS	BF ₃ •Et ₂ O	decompose
11	Cbz	CH ₂ Cl ₂	NIS	LiClO ₄	NR
12	Cbz	CH ₂ Cl ₂	NIS	MgBr ₂ •Et ₂ O	NR
13	Cbz	CH ₂ Cl ₂	NIS	ZnI ₂	NR
14	Cbz	CH ₂ Cl ₂	NIS	Zn(OTf) ₂	NR
15	Cbz	CH ₂ Cl ₂	NIS	Sc(OTf) ₃	Not clean reaction
16	Cbz	CH ₂ Cl ₂	NIS	BF ₃ •Et ₂ O	decompose
17	Boc	HOAc	NIS		96%
18	Cbz	HOAc	NIS		51%

At the beginning, we screened this cyclic carbonate formation in CH₂Cl₂ by using halogen sources such as NBS, NIS, I₂, and PhNMeBr₃ as electrophiles and *t*-butyl allyl mixed carbonate **IV-25** as substrate (Scheme 40). No reaction was observed by TLC as shown in entry 1-4. Next, we tried to use Lewis acid to promote the cyclization reactions. Therefore, a number of Lewis acid such as LiClO₄, MgBr₂•Et₂O, ZnI₂, Zn(OTf)₂, Sc(OTf)₃, BF₃•Et₂O were used as the

promoters in term of their attenuated Lewis acidity. The screening was carried out in a 0.05 M solution of substrate in CH₂Cl₂ with one equivalent NIS as electrophile and 30 mol% Lewis acid as promoter. As a result, MgBr₂•Et₂O was found having some activity in promoting the conversion of mixed carbonate **IV-25** to cyclic carbonate **IV-27**, while LiClO₄ case also gave trace amount of desired product, although both conversions were not complete, and most substrate remained untouched. ZnI₂ showed no reactivity probably due to its poor Lewis acidity. The stronger Lewis acid such as Zn(OTf)₂, Sc(OTf)₃, BF₃•Et₂O caused the decomposition of the substrate. We also examined the substrate of benzyl allyl mixed carbonate **IV-26**. This time the LiClO₄, MgBr₂•Et₂O, ZnI₂, Zn(OTf)₂ did not give any conversion, instead, Sc(OTf)₃ afforded some products but the reaction was not clean. Once again, the BF₃•Et₂O caused the decomposition of substrate.

Fortunately, when we switched the solvent from CH₂Cl₂ to HOAc without any Lewis acid, the *t*-butyl allyl mixed carbonate **IV-25** was converted to the desired iodo-carbonate **IV-27** cleanly with high yield. When the benzyl allyl mixed carbonate **IV-26** was used as the substrate, the reaction also had reasonable conversion in the same condition as used for **IV-25**.

Scheme 41. *Synthesis of α-digitoxose*

Encouraged by the preliminary results, we next carried out our synthesis of α-digitoxose (Scheme 41). The iodocarbonate **IV-27** could be obtained from carbonate **IV-25** with NIS/HOAc

condition in 96% yield or NIS/MgBr₂/CH₂Cl₂ condition in 25%. And also the carbonate **IV-26** could be converted to **IV-27** in 51% yield. Iodine in iodocarbonate **IV-27** was reductively removed by tris(trimethylsilyl)silane upon heating in the presence of AIBN as a radical initiator to afford cyclic carbonate **IV-28**,⁵³ which was subjected to basic hydrolysis to furnish benzyl α -digitoxoside (**IV-29**)

To sum up this part, a highly diastereoselective route to α -digitoxose has been developed. The route relies on a palladium(0)-catalyzed glycosylation reaction and post-glycosylation transformation. The asymmetry of α -digitoxose originated from Noyori reduction of acylfuran and subsequent introduction of other stereogenic centers. An iodo-carbonate formation is the key step for the construction of α -digitoxose stereochemistry.

IV.3. Synthesis of Jadomycin A

With the approach to α -digitoxose having been successfully developed, we next turned our attention to synthesize jadomycin A, the aglycone part of the jadomycin B. Our first strategy to the jadomycin A (**IV-1**) was shown in Scheme 42, which features an oxazolone ring formation as the key step to connect the three building blocks together (i.e. from **IV-32** or **IV-33** and **IV-34** to **IV-30** or **IV-31** respectively). Once the oxazolone ring was formed, the dihydropyridine ring formation could be achieved via direct Michael addition or Heck reaction (i.e. from **IV-30** or **IV-31** to **IV-1**).

Scheme 42. First strategy to jadomycin A

We started the synthesis with the benzaldehyde part **IV-34** (Scheme 43). By a modification of the reported method in the literature,⁵⁴ benzoate **IV-37** was produced in 56% overall yield in three steps from acetopyruvate (**IV-35**). Protection of phenol **IV-37** as TBS ether followed by LiAlH_4 reduction delivered benzyl alcohol **IV-38** in 89% yield over two steps, which upon MnO_2 oxidation to aldehyde **IV-39** (84%) and deprotection of TBS ether in acid condition afforded 3-hydroxyl-5-methyl benzaldehyde (**IV-34**) in 93% yield.

Scheme 43. *Synthesis of 3-hydroxyl-5-methyl benzaldehyde*

Our next synthetic intermediate is the juglone part **IV-43** (Scheme 44). Isoleucine (**IV-6**) was first protected as *t*-butyl ester **IV-40**. 3-bromojuglone (**IV-42**) was synthesized from juglone **IV-41** according to the reported method in 80% yield.⁵⁵ Introducing the aminoacid into the 3-position of the juglone was successfully achieved in 67% yield by mixing **IV-40** and **IV-42** in CH_2Cl_2 in the presence of triethylamine.⁵⁶ The resulted aminojuglone **IV-43** was then brominated by Br_2 in ethanol to afford 2-bromo-3-aminojuglone **IV-44** in 87% yield.⁵⁷

Scheme 44. *Synthesis of bromojuglone IV-44*

With the two building blocks in hand, we turned our attention to the investigation of the oxazolone ring formation (Scheme 45). Bromoaminojuglone **IV-44** was first chosen to test this reaction. The *t*-butyl ester was deprotected by exposure to trifluoroacetic acid, which afforded free carboxylic acid **IV-33**. The carboxylic acid was then heated with benzaldehyde **IV-34** in benzene in the presence of *p*-toluenesulfonic acid by using Dean-Stark trap technique, or direct distillation. Unfortunately, no desired oxazolone was formed. We thought it might be due to the steric hinderance from the bromine. Therefore, we examined the reaction between benzaldehyde **IV-34** and the free acid **IV-32**, which came from the deprotection of *t*-butyl ester **IV-43**, by using the same technique of Dean-Stark trap. Once again, no reaction was observed.

Scheme 45. *Tries on oxazolone ring formation*

Due to the difficulty we ran into during the synthesis of the aglycone by forming oxazolone ring, we next examined the possibility of direct coupling of the two components, which will significantly facilitate the formation of the dihydropyridine ring and oxazolone ring as well (Scheme 46). Therefore, benzaldehyde **IV-34** was first protected as acetal by 1,3-propanediol in the presence of acid (84%), which was then further protected as MOM ether in the condition of MOMCl/DIPEA (68%). The MOM ether **IV-45** was converted to stannane **IV-46** by a directed lithiation followed by reacting the anion intermediate with tributyltin chloride in 49% yield with the recovery of 35% starting material. A Stille coupling was carried out between bromojuglone **IV-44** and stannane **IV-46** in the presence of palladium(0) and cocatalyst CuI,⁵⁸ but unfortunately, no desired product was observed.

Scheme 46. First try of Stille coupling

The failure of the Stille coupling between aminobromojuglone **IV-44** and stannane **IV-46** suggested that the steric hinderance should be an important factor here. We now believed that a coupling between the juglone part and benzaldehyde should be needed before the introduction of the aminoacid part. Therefore, we turned our attention to the synthesis of 2-bromojuglone (**IV-50**) by following the reported method.⁵⁹ Naphthalenediol **IV-47** was converted to diacetate **IV-48** in the presence of acetic chloride/pyridine in 92% yield (Scheme 47). Diacetate **IV-48** was oxidized by NBS to 2-bromojuglone acetate **IV-49** in 80% yield, which was hydrolyzed in acid condition to produce 2-bromojuglone (**IV-50**) in 75% yield. With the 2-bromojuglone in hand, the coupling between it and stannane **IV-46** was then tested by following the conditions reported in the literature.⁵⁸ In practice, the coupling was carried out in the presence of 5 mol% palladium(0) and 20 mol% CuI as cocatalyst in THF at elevated temperature, which afforded the coupled product **IV-51** in 76% yield.

Scheme 47. Stille coupling between 2-bromojuglone and stannane

With the juglone part and benzaldehyde having been coupled. We then investigated the introduction of the aminoacid (Scheme 48). A direct aza-Michael addition to achieve **IV-52** proved to be not successful by mixing the juglone part **IV-51** and aminoacid **IV-40**. We next tried to knock off the protecting group to produce aldehyde, which then possibly help introduction of the aminoacid part. To our surprise, deprotection of the acetal and MOM ether by treatment of **IV-51** with TFA caused the decomposition of the starting material. Upon a short time heating of **IV-51** in aqueous HCl/THF, around 20% yield of aldehyde **IV-53** was obtained. Mixing the aldehyde **IV-53** with aminoacid **IV-40** in toluene at RT, over two days, the starting material disappeared. After passing the mixture through a short column, a crude product was obtained, which was then treated with TFA furnished jadomycin A (**IV-1**). The crude NMR data showed that the product was a mixture of diastereomers at a ratio of 6 to 1 with the major isomer matching very well with the reported data of jadomycin A. This also confirmed that the stereochemistry of the methyl group is the same as it is in natural isoleucine.

Scheme 48. Synthesis of jadomycin A

In conclusion, a model study for synthesis of α -digitoxose, the sugar moiety of jadomycin B has been successfully carried out by preparing benzyl α -digitoxoside, which relies upon a palladium(0) catalyzed glycosylation, post-glycosylation featuring an iodo-carbonation and corresponding transformations. Jadomycin A, the aglycone part of jadomycin B, has also been successfully synthesized and structurally defined by the comparison of our spectral data with the reported one from isolation. This synthesis features a Stille cross coupling reaction, a tandem imine formation/dihydropyridine ring formation during the incorporation of the aminoacid. Efforts toward the synthesis of the jadomycin B will be continued by applying the newly developed methodology for installation of α -digitoxose to the jadomycin A.

Chapter V. Experimental Section

V.1. General methods and materials

^1H and ^{13}C spectra were recorded on 270 MHz and 600 MHz spectrometers. Chemical shifts were reported relative to benzene- d_6 (δ 7.16 ppm), CDCl_3 (δ 7.26 ppm), CD_3OD (δ 3.31 ppm), acetone- d_6 (δ 2.05 ppm), D_2O (δ 4.80 ppm) for ^1H , and benzene- d_6 (δ 127.68 ppm), CDCl_3 (δ 77.0 ppm), CD_3OD (δ 49.15 ppm), acetone- d_6 (δ 29.92 ppm) for ^{13}C , and H_3PO_4 in D_2O (δ 0.00 ppm) as external reference for ^{31}P . Optical rotations were measured with a digital polarimeter in the solvent specified. Infrared (IR) spectra were obtained on a FT-IR spectrometer. Flash column chromatography was performed on 60-200 mesh silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates and visualized by quenching of fluorescence and by charring after treatment with panisaldehyde or phosphomolybdic acid or potassium permanganate stain. R_f values were obtained by elution in the stated solvent ratios (v/v). Ether, THF, methylene chloride, toluene and triethylamine were dried by passing through activated alumina (8 x 14 mesh) column with argon gas pressure. 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.

V.2. Chapter I experimental

(*E*)-1-(2,4-bis(benzyloxy)-6-hydroxyphenyl)-3-(4-(benzyloxy)phenyl)prop-2-en-1-one (I-7)⁵

To a solution of 4.0 g 4', 5, 7-trihydroxyflavanone **I-6** (14.7 mmol) in 50 mL acetone was added 5.3 mL BnBr (44.4 mmol) and 12.2 g K₂CO₃ (88.2 mmol). The reaction mixture was heated under reflux for 6 hours, then cooled down to room temperature. The mixture was concentrated under reduced pressure to give a residue which was then partitioned between 150 mL EtOAc and 80 mL H₂O. The water layer was extracted by EtOAc (100 mL × 3). The organic layer was pooled, then washed by saturated brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a crude product. Recrystallization and further chromatography for the mother liquid eluting with hexane-EtOAc (6:1) gave pure phenol **I-7** (6 g, 75%): Yellow solid; *R_f* = 0.51 (3:1 (v/v) hexane/EtOAc); ¹H NMR (CDCl₃, 270 MHz) δ 7.75 (dd, *J* = 15.6, 15.3 Hz, 2H), 7.53-7.30 (m, 15H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.22 (d, *J* = 2.5 Hz, 1H), 6.17 (d, *J* = 2.5 Hz, 1H), 6.13 (d, *J* = 10.2 Hz, 1H), 5.10 (s, 2H), 5.08 (s, 2H), 5.05 (s, 2H); ¹³C NMR (CDCl₃, 67.5 MHz) δ 192.6, 168.8, 165.1, 161.7, 160.3, 142.7, 136.5, 135.9, 135.5, 130.1, 128.9, 128.8, 128.7, 128.6, 128.6, 128.5, 128.3, 128.1, 127.7, 127.4, 125.2, 115.0, 106.3, 95.0, 92.5, 71.4, 70.3, 70.0.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4H-chromen-4-one (I-8)⁵

2.76 g phenol **I-7** (5.09 mmol) was dissolved in 6 mL dry DMSO, and a catalytic amount of I₂ (41 mg, 0.16 mmol) was added into the solution. The reaction mixture was heated to 110 °C and kept stirring at this temperature for 24 hours. Then it was cooled down to the room temperature. 10 mL saturated aqueous NaHCO₃ was added to quench the reaction. The water layer was extracted with EtOAc (30 mL × 3). The organic layer was pooled, then washed by 10 mL saturated brine, dried over Na₂SO₄, and concentrated the organic layer under reduced pressure to give a crude product. Chromatography eluting with hexane-EtOAc (2:1) afforded desired flavone **I-8** (2.10 g, 76%): Yellow solid; *R*_f = 0.20 (2:1 (v/v) Hexane/EtOAc); ¹H NMR (CDCl₃, 600 MHz) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.46-7.28 (m, 13H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 1.8 Hz, 1H), 6.58 (s, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 5.23 (s, 2H), 5.14 (s, 2H), 5.11 (s, 2H); ¹³C NMR (CDCl₃, 67.5 MHz) δ 177.3, 162.8, 161.1, 160.6, 159.6, 136.4, 136.2, 135.7, 128.7, 128.6, 128.5, 128.4, 128.2, 127.6, 127.4, 126.5, 124.0, 118.0, 115.2, 109.7, 107.7, 98.3, 94.2, 70.7, 70.4, 70.1.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-hydroxy-4H-chromen-4-one (I-3)⁵

150 mL solution of freshly generated DMDO in acetone (~ 0.1 M) was dried by 3 Å MS at -20 °C under the protection of argon, and into this solution was added a solution of 2.3 g flavone **I-8** (4.26 mmol) in 20 mL dry CH₂Cl₂ at this temperature via a cannula. Then allow it warm up to 0 °C and keep stirring at 0 °C overnight. The solvent was evaporated under reduced pressure to give brown-yellowish solid, which was then redissolved in 20 mL CH₂Cl₂. Into this solution was added 2 mg TsOH·H₂O and it was then kept stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to a residue, which was then subjected to chromatography. Elution with hexane-EtOAc (5:1) gave perbenzylated flavonol **I-3** (1.2 g, 50%) and elution with hexane-EtOAc (2:1) recovered 0.7 g starting material.

Alternative procedure:

A solution of 1.5 g (2.77 mmol) enone **I-8** in 54 mL CH₂Cl₂ and 27 mL acetone was added a buffer solution of 3.6 g NaHCO₃ and 7.5 g Na₂CO₃ in 189 mL H₂O at RT. When vigorous stirring, the mixture was slowly added a solution of 16.2 g (26.4 mmol) oxone (2KHSO₅•KHSO₄•K₂SO₄) in 189 mL H₂O over 2 hour. Then it was stirred for another 10 min. Then it was separated and the aqueous layer was extracted with CH₂Cl₂ 80 mL X 2. The combined organic layer was washed subsequently with 120 mL aqueous solution of Na₂S₂O₃ (30 mL saturated aqueous Na₂S₂O₃ plus 90 mL H₂O), 120 mL saturated brine and then was dried over Na₂SO₄. Into the solution, 9 mg (0.05 mmol) *p*-TsOH•H₂O was added at RT, and the mixture was stirred for 20 min. It was then diluted with 200 mL Et₂O followed by washing with saturated aqueous NaHCO₃, saturated brine, and dried over Na₂SO₄. After removal of the solvent, a viscous residue was obtained. Then addition of several mL of CH₂Cl₂ into the mixture and stirring resulted in solid formation, which was filtered and rinsed with hexane-EtOAc (1:1, v/v) to afford 380 mg product **I-3** (25%). The mother liquid was concentrated and once again addition of CH₂Cl₂ induced the solid formation, which after filtration delivered another 140 mg product **I-3** (9%).

Perbenzylated flavonol **I-3**: Yellow solid; *R*_f = 0.35 (3:1 (v/v) Hexane/EtOAc); ¹H NMR (CDCl₃, 600 MHz) δ 8.17 (d, *J* = 9.6 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.47-7.30 (m, 13H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.64 (d, *J* = 1.8 Hz, 1H), 6.49 (d, *J* = 1.8 Hz, 1H), 5.24 (s, 2H), 5.15 (s, 2H), 5.12 (s, 2H); ¹³C NMR (CDCl₃, 67.5 MHz) δ 171.8, 163.2, 159.8, 159.4, 158.7, 142.2, 137.6, 136.5, 136.2, 135.6, 128.9, 128.8, 128.6, 128.5, 128.1, 127.8, 127.6, 127.5, 126.7, 123.8, 114.9, 106.8, 97.6, 93.7, 70.7, 70.6, 70.0.

(*S*)-1-(furan-2-yl)ethanol (**I-9**)⁶⁰

To a solution of 15 g acylfuran **I-5** (136.4 mmol) in 20 mL CH₂Cl₂ was added a prepared solution of formic acid/triethylamine (40 mL, 2:1(mol/mol)) and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6 -mesitylene)-(*S*, *S*)-TsDPEN (0.2 g, 0.25 mol%).⁶¹ The resulting solution was stirred at room temperature for 24 h. Then it was diluted with water (90 mL) and extracted with Et₂O (200 mL x 3). The pooled organic layer was washed with 50 mL saturated aqueous NaHCO₃, 50 mL saturated brine, dried over Na₂SO₄ and then concentrated under reduced pressure to give a residue. Flash chromatography on silica gel eluting with hexane-Et₂O (1:1) gave furan alcohol **I-9** (14 g, 92%): Colorless oil; *R*_f = 0.45 (7:3 (v/v) Hexane/EtOAc); [α]_D²⁵ = -21 (c = 1.0, CH₂Cl₂); ¹H NMR (600 MHz CDCl₃) δ 7.30 (d, *J* = 1.8, 1H), 6.26 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.15 (d, *J* = 3.0, 1H), 4.78 (dq, *J* = 6.6, 6.6 Hz, 1H), 3.11 (s, 1H), 1.46 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 157.7, 141.6, 109.9, 104.9, 63.3, 21.1.

(2*S*, 6*R*)-6-hydroxy-2-methyl-2H-pyran-3(6H)-one (I-10**)**⁶⁰

To a solution of 14 g furan alcohol **I-9** (125 mmol) in 416 mL THF-H₂O (3:1) was added 21 g NaHCO₃ (250 mmol), 17 g NaOAc•3H₂O (125 mmol), and 22.3 g NBS (125 mmol) at 0 °C. The reaction mixture was kept stirring at this temperature for 1 hour, then at 0 °C 200 mL saturated aqueous NaHCO₃ was added to quench the reaction. The reaction mixture was directly extracted with Et₂O (300 mL x 3) and the organic layer was pooled, washed by 100 mL saturated brine, dried over Na₂SO₄ and then concentrated reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with hexane-EtOAc (1:1) afforded pyranone alcohol **I-10** (14.4 g, 90%, α : β =2.8:1): White solid; *R*_f = 0.25 (7:3 (v/v) hexane/EtOAc); [α]_D²⁵ = +44 (c = 1.0, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃, α isomer) δ 6.82 (dd, *J* = 10.2, 3.0

Hz, 1H), 5.96 (d, $J = 10.2$, 1H), 5.48 (d, $J = 3.0$ Hz, 1H), 3.99 (q, $J = 7.2$ Hz, 1H), 1.23 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3 , α isomer) δ 197.6, 145.3, 126.6, 87.2, 74.8, 15.1.

(2*S*,6*S*)-*t*-butyl -5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (I-4 α)⁶⁰

To a solution of 7.4 g pyranone alcohol **I-10** (57.8 mmol) in 80 mL CH_2Cl_2 was added 528 mg DMAP (4.33 mmol) at -78°C . A pre-cooled solution of 25.2 g $(\text{Boc})_2\text{O}$ (115.6 mmol) in 30 mL CH_2Cl_2 was dropwisely into the reaction mixture via a cannula. The reaction mixture was stirred at -78°C for 12 hours. The reaction was quenched by 100 mL saturated aqueous NaHCO_3 and then extracted with Et_2O (300 mL $\times$ 3). The organic layers were pooled, then washed by 70 mL saturated aqueous NaCl , dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. Flash chromatography on silica gel eluting with hexane- Et_2O (100:7) gave Boc protected α -pyranone **I-4 α** (7.8 g, 60%). Elution with hexane- Et_2O (10:1) gave β -isomer **I-4 β** (2.5g, 19%).

α -pyranone **I-4 α** : $R_f = 0.60$ (7:3 (v/v) hexane/ EtOAc); $[\alpha]_D^{25} = +98$ (c 1.0, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3) δ 6.78 (dd, $J = 10.2$, 3.6 Hz, 1H), 6.22 (d, $J = 3.6$ Hz, 1H), 6.09 (d, $J = 10.2$ Hz, 1H), 4.53 (q, $J = 6.6$ Hz, 1H), 1.40 (s, 9H), 1.28 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150.8 MHz, CDCl_3) δ 195.5, 151.7, 140.9, 128.2, 89.1, 83.3, 72.0, 27.5, 15.1;

3-((2*S*,6*S*)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yloxy)-5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4H-chromen-4-one (2)

To a solution of 875 mg perbenzylated flavonol **I-3** (1.6 mmol) and 537 mg pyranone **I-4a** (2.4 mmol) in 8 mL CH₂Cl₂ was added a solution of 41 mg Pd₂(DBA)₃•CHCl₃ (0.04 mmol) and 41 mg PPh₃ (0.16 mmol) in 1 mL CH₂Cl₂ at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours and then quenched by 15 mL saturated aqueous NaHCO₃, followed by extraction with Et₂O (25 mL×3). The organic layer was pooled, then washed by 15 mL saturated aqueous NaCl, dried over Na₂SO₄ and concentrated under reduced pressure to give crude product. Chromatography on silica gel, eluting with hexane-EtOAc (3:1) gave glycosylated pyranone **I-2** (888 mg, 85%): Yellow solid, mp: 75-77 °C; *R_f* = 0.50 (2:1 (v/v) hexane/EtOAc); [α]_D²⁵ -63 (*c* 0.93, CHCl₃); IR (thin film, cm⁻¹) 3063, 2921, 1699, 1636, 1607, 1574, 1509, 1454, 1375, 1355, 1300, 1252, 1198, 1178, 1162, 1103, 1013, 937. ¹H NMR (CDCl₃, 600 MHz) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.46-7.29 (m, 13H), 7.27 (dd, *J* = 10.2, 3.6 Hz, 1H), 7.06 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 1.8 Hz, 1H), 6.47 (d, *J* = 1.8 Hz, 1H), 6.13 (d, *J* = 10.2 Hz, 1H), 5.92 (d, *J* = 3.6 Hz, 1H), 5.27 (s, 2H), 5.15 (s, 2H), 5.08 (d, *J* = 12 Hz, 1H), 5.08 (d, *J* = 12 Hz, 1H), 4.02 (q, *J* = 6.0 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 196.7, 173.3, 163.0, 160.4, 159.8, 159.0, 154.9, 143.1, 137.6, 136.3, 136.2, 135.6, 130.4, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 127.6, 127.4, 126.6, 123.2, 114.7, 109.9, 98.3, 94.3, 94.0, 71.5, 70.8, 70.5, 70.1, 14.6; HRMS (CI): calcd. for [C₄₂H₃₄O₈+Na]⁺: 689.2146, Found: 689.2153.

3-((2*S*,5*R*,6*S*)-5,6-dihydro-5-hydroxy-6-methyl-2H-pyran-2-yloxy)-5,7 bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4H-chromen-4-one (I-11)

A solution of 87 mg pyranone **I-2** (0.13 mmol) in 3.5 mL CH₂Cl₂-MeOH (5:1) was cooled down to -78 °C, then 10 mg NaBH₄ (0.26 mmol) was added in. The reaction mixture was kept stirring at -78 °C for 3 hours. The reaction was then quenched by 2 mL saturated aqueous NaHCO₃, followed by extraction with Et₂O (10 mL × 3). The organic layer was washed by 2 mL saturated aqueous NaCl, dried over Na₂SO₄, and concentrated under reduced pressure to give crude product. Crude ¹H NMR showed a dr > 20:1. Chromatography on silica gel eluting with hexane-EtOAc (2:1) gave allylic alcohol **I-11** (63 mg, 73%): Amorphous yellow solid; *R_f* = 0.29 (1:1 (v/v) hexane/EtOAc); [α]_D²⁵ -83 (*c* 0.85, CHCl₃); IR (thin film, cm⁻¹) 3361, 2927, 1604, 1509, 1453, 1354, 1298, 1251, 1176, 1098, 1013, 916; ¹H NMR (CDCl₃, 600 MHz) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.45-7.27 (m, 13H), 7.06 (d, *J* = 9.0 Hz, 2H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.20 (ddd, *J* = 10.2, 2.4, 2.4 Hz, 1H), 5.97 (d, *J* = 10.2 Hz, 1H), 5.60 (s, 1H), 5.26 (s, 2H), 5.15 (s, 2H), 5.07 (d, *J* = 12 Hz, 1H), 5.07 (d, *J* = 12 Hz, 1H), 3.74 (dd, *J* = 7.2, 6.6 Hz, 1H), 3.31 (dq, *J* = 8.4, 6.0 Hz, 1H), 0.71 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 67.5 MHz) δ 173.8, 162.8, 160.3, 159.9, 159.0, 154.8, 138.3, 136.5, 136.4, 135.7, 133.9, 130.7, 128.8, 128.7, 128.6, 128.5, 128.2, 127.8, 127.7, 127.5, 126.7, 126.6, 123.8, 114.6, 110.2, 98.3, 95.7, 94.0, 70.8, 70.5, 70.1, 69.6, 69.4, 17.0; HRMS (CI): calcd. for [C₄₂H₃₆O₈+Na]⁺: 691.2302, Found: 691.2296.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(α -L-rhamnopyranosyloxy)-4H-chromen-4-one (I-12**)**

A solution of 80 mg allylic alcohol **I-11** (0.12 mmol) in 2 mL acetone-*t*-BuOH (1:1) was cooled down to 0 °C. To the solution was added 0.5 mL NMO-H₂O (w/w 1:1), and then catalytic amount of crystalline OsO₄ was added into the mixture when stirring. The reaction mixture was kept stirring at 0 °C for 3 hours. The reaction mixture was then quenched by 0.5 mL saturated aqueous Na₂S₂O₃. After stirring for another 5 hours, all the stuff was passed through a small pad of celite and silica gel, washed by EtOAc-MeOH (1:1) (10 mL×3). The organic effluent was dried by Na₂SO₄, and concentrated under reduced pressure to give crude product. Chromatography on silica gel eluting with Et₂O-MeOH (20:1) gave triol **I-12** (80 mg, 96%): White solid, mp: 105-107 °C; *R*_f = 0.56 (10:1 (v/v) Et₂O/MeOH); [α]_D²⁵ -112 (*c* 1.3, MeOH); IR (thin film, cm⁻¹) 3418 (broad), 2924, 1606, 1506, 1453, 1354, 1299, 1255, 1177, 1141, 1102, 1058, 998, 953; ¹H NMR (acetone-*d*₆, 600 MHz) δ 7.91 (d, *J* = 9.0 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 4H) 7.43-39 (m, 6H), 7.38-7.29 (m, 3H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 1.8 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 5.57 (d, *J* = 1.8 Hz, 1H), 5.29 (d, *J* = 13.2 Hz, 1H), 5.28 (d, *J* = 13.2 Hz, 1H), 5.24 (s, 2H), 5.23(s, 2H), 4.28 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.70 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.33 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.21 (dq, *J* = 9.6, 6.0 Hz, 1H), 2.91 (brs, 1H), 0.87 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (acetone-*d*₆, 150 MHz) δ 173.5, 164.1, 161.5, 160.8, 159.8, 154.8, 138.4, 138.1, 138.0, 137.4, 131.4, 129.5, 129.4, 129.3, 129.1, 128.9, 128.7, 128.5, 128.4, 127.9, 124.4, 115.7, 110.6, 102.2, 98.9, 95.1, 73.2, 72.2, 71.5, 71.4, 71.3, 71.2, 70.8, 17.9; HRMS (ESI) calcd. for [C₄₂H₃₈O₁₀+H]⁺: 703.2543, Found: 703.2537.

Kaempferol-3-*α*-L-rhamnoside (**I-1b**)⁶²

A solution of 50 mg triol **I-12** (0.07 mmol) in 2 mL THF-EtOH (1:1) was added 20 mg Pearlman's catalyst (Pd-C, 10%). The solution was degassed using vacuum at -90 °C and refilling with H₂. This procedure was repeated three times, and then the bath was removed. The reaction was warmed up to room temperature and stirred under a H₂ atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and elution with Et₂O-MeOH (20:1) gave kaempferol-3- α -L-rhamnoside (**I-1b**) (24mg, 80%): Pale yellow solid, mp: 140-142 °C; R_f = 0.71 (5:1 (v/v) Et₂O/MeOH); $[\alpha]_D^{25}$ -96 (c 1.3, MeOH); IR (thin film, cm⁻¹) 3259 (broad), 2924, 2855, 1653, 1607, 1442, 1360, 1251, 1207, 1172, 1057, 996; ¹H NMR (CD₃OD, 600 MHz) δ 7.72 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 6.30 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 1.8 Hz, 1H), 5.33 (d, J = 1.8 Hz, 1H), 4.18 (dd, J = 3.0, 1.8 Hz, 1H), 3.67 (dd, J = 9.0, 2.4 Hz, 1H), 3.30-3.27 (m, 4H), 0.88 (d, J = 6.0 Hz, 3H); ¹³C NMR (CD₃OD, 150 MHz) δ 179.5, 163.2, 161.6, 159.1, 158.7, 136.1, 131.9, 122.7, 116.6, 105.5, 103.5, 100.4, 95.2, 73.2, 72.2, 72.2, 71.9, 17.6; HRMS (ESI) calcd. for [C₂₁H₂₀O₁₀+Na]⁺: 455.0954, Found: 455.0949.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(2,3,4-*O*-triacetyl- α -L-rhamnopyranoyloxy)-4H-chromen-4-one (I-13**)**

A solution of 63 mg triol **I-12** (0.09 mmol) in 2.5 mL CH₂Cl₂ was cooled down to 0 °C, then sequentially 0.4 mL pyridine, catalytic amount of DMAP and 0.4 mL Ac₂O were added. The reaction mixture was stirred at 0 °C overnight. The reaction mixture was diluted by 15 mL Et₂O and then the reaction was quenched by 1.5 mL H₂O, the organic layer was washed by 2 mL saturated aqueous NaHCO₃, 2 mL saturated aqueous NaCl, dried over Na₂SO₄, and concentrated under reduced pressure to give a residue which was subjected to chromatography on silica gel. Elution with hexane-EtOAc (2:1) afforded triacetate **I-13** (63 mg, 86%): White solid, mp: 90-92 °C; *R_f* = 0.58 (1:1 (v/v) hexane/EtOAc); [α]_D²⁵ -175 (*c* 1.3, CHCl₃); IR (thin film, cm⁻¹) 3035, 2982, 2938, 1746, 1632, 1605, 1574, 1509, 1498, 1486, 1453, 1432, 1368, 1298, 1247, 1217, 1174, 1136, 1101, 1044, 1019, 968; ¹H NMR (CDCl₃, 600 MHz) δ 7.86 (d, *J* = 9.0 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.46-7.27 (m, 13H), 7.14 (d, *J* = 9.0 Hz, 2H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 5.73 (d, *J* = 1.8 Hz, 1H), 5.72 (dd, *J* = 3.6, 1.8 Hz, 1H), 5.32 (dd, *J* = 10.2, 3.0 Hz, 1H), 5.26 (s, 2H), 5.15 (s, 2H), 5.08 (s, 2H), 4.92 (dd, *J* = 10.2, 9.6 Hz, 1H), 3.37 (dq, *J* = 10.2, 6.6 Hz, 1H), 2.11 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 0.85 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 172.9, 169.9, 169.8, 169.5, 162.9, 160.6, 159.9, 158.8, 154.2, 136.5, 136.4, 136.3, 135.6, 130.4, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 127.5, 127.4, 126.6, 123.1, 114.9, 110.1, 98.4, 97.9, 94.0, 70.8, 70.7, 70.5, 70.2, 69.3, 69.1, 68.1, 20.9, 20.8, 20.7, 17.1; HRMS (ESI) calcd. for [C₄₈H₄₄O₁₃+Na]⁺: 851.2679, Found: 851.2678.

Kaempferol-3- α -L-3'',4'',5''-O-triacetylrrhamnoside (**I-1c**)⁶³

To a solution of 60 mg triacetate **I-13** (0.07 mmol) in 3 mL THF-EtOH (1:1) was added 30 mg Pearlman's catalyst (Pd-C, 10%). The reaction mixture was degassed using vacuum at -90 °C

and refilling with H₂. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H₂ atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (1:1) gave kaempferol-3- α -L-3'',4'',5''-O-triacetylrrhamnoside (**I-1c**) (35 mg, 86%): Yellow solid, mp: 152-154 °C; *R_f* = 0.42 (1:2 (v/v) hexane/EtOAc); [α]_D²⁵ -128 (*c* 1.4, CHCl₃); IR (thin film, cm⁻¹) 3372 (broad), 2982, 1749, 1654, 1609, 1504, 1364, 1207, 1174, 1085, 1043, 971; ¹H NMR (CDCl₃, 600 MHz) δ 12.5 (s, 1H), 7.77 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 1.8 Hz, 1H), 6.25 (d, *J* = 2.4 Hz, 1H), 5.62 (dd, *J* = 3.6, 1.8 Hz, 1H), 5.55 (d, *J* = 1.8 Hz, 1H), 5.32 (dd, *J* = 10.2, 3.6 Hz, 1H), 4.97 (dd, *J* = 10.2, 9.6 Hz, 1H), 3.54 (dq, *J* = 10.2, 6.0 Hz, 1H), 2.13 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 177.9, 170.8, 170.3, 170.1, 162.5, 162.1, 158.6, 157.4, 156.9, 134.1, 130.7, 122.1, 115.7, 105.7, 99.3, 98.2, 94.1, 70.4, 69.4, 69.2, 68.4, 20.9, 20.8, 20.7, 17.1; HRMS (ESI) calcd. for [C₂₇H₂₆O₁₃+Na]⁺: 581.1271, Found: 581.1266.

6-(5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yloxy)-3,6-dihydro-2-methyl-2H-pyran-3-yl acetate (I-14)

A solution of 210 mg pyranone **I-2** (0.32 mmol) in 3.5 mL CH₂Cl₂-MeOH (5:1) was cooled down to -78 °C, then 25 mg NaBH₄ (0.64 mmol) was added. The reaction mixture was stirred at -78 °C for 3 hours. Then the reaction was quenched by 3 mL saturated aqueous NaHCO₃, followed by extraction with Et₂O (15 mL $\times$ 3). The organic layer was washed by 3 mL saturated aqueous NaCl, dried over Na₂SO₄, and concentrated under reduced pressure to give a residue. All residual solvent was removed by applying a high vacuum produced by oil pump for half an

hour. The dry residue was redissolved in CH_2Cl_2 and cooled down to $0\text{ }^\circ\text{C}$. To the solution was added 0.4 mL pyridine, catalytic amount of DMAP, and 0.3 mL Ac_2O . After stirring for 1 hour, the mixture was diluted by 20 mL Et_2O . The organic layer was sequentially washed with 2 mL H_2O , 2 mL saturated aqueous NaHCO_3 , 2 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to afford crude product. Chromatography on silica gel eluting with hexane-EtOAc (5:1) gave pure acetate **I-14** (156 mg, 70%): Amorphous yellow solid; $R_f = 0.52$ (3:2 (v/v) hexane/EtOAc); $[\alpha]_D^{25} -146$ (c 1.1, CHCl_3); IR (thin film, cm^{-1}) 3052, 2927, 1736, 1636, 1608, 1509, 1454, 1375, 1355, 1298, 1240, 1178, 1104, 1023, 936; ^1H NMR (CDCl_3 , 600 MHz) δ 7.96 (d, $J = 9.0$ Hz, 2H), 7.55 (d, $J = 7.2$ Hz, 2H), 7.47-7.27 (m, 13H), 7.09 (d, $J = 8.4$ Hz, 2H), 6.56 (d, $J = 2.4$ Hz, 1H), 6.44 (d, $J = 2.4$ Hz, 1H), 6.20 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.90 (d, $J = 10.2$ Hz, 1H), 5.60 (brs, 1H), 5.27 (s, 2H), 5.17 (s, 2H), 5.08 (d, $J = 11.4$ Hz, 1H), 5.07 (d, $J = 11.4$ Hz, 1H), 4.96 (ddd, $J = 9.6, 1.8, 1.8$ Hz, 1H), 3.60 (dq, $J = 9.6, 6.6$ Hz, 1H), 2.08 (s, 3H), 0.61 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 173.5, 170.3, 162.8, 160.2, 159.8, 154.5, 138.4, 136.5, 136.4, 135.7, 130.6, 130.3, 128.7, 128.6, 128.6, 128.5, 128.4, 128.1, 127.6, 127.5, 127.3, 126.6, 123.8, 114.5, 110.0, 98.2, 95.8, 94.0, 70.8, 70.7, 70.4, 70.1, 66.5, 21.1, 17.0; HRMS (CI): calcd. for $[\text{C}_{44}\text{H}_{38}\text{O}_9 + \text{Na}]^+$: 733.2408, Found: 733.2405.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(4-*O*-acetyl- α -L-rhamnopyranoyloxy)-4H-chromen-4-one (I-15)

A solution of 142 mg acetate **I-14** (0.20 mmol) in 3 mL acetone-*t*-BuOH (1:1) was cooled down to $0\text{ }^\circ\text{C}$. To the solution was added 1 mL NMO- H_2O (w/w 1:1), and a catalytic amount (~ 5 mg) of crystalline OsO_4 was added into the mixture. The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for 24

hours. The reaction was quenched with 1 mL saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (aq.) and stirred overnight. Then the mixture was passed through a small pad of celite and silica gel, washed with EtOAc-MeOH (1:1) (15 mL $\times$ 3), the organic solution was dried over Na_2SO_4 , and concentrated under reduced pressure to give a residue. Chromatography on silica gel eluting with hexane-EtOAc (2:3) gave diol **I-15** (115 mg, 77%): Pale yellow solid, mp: 90.5-92.5 °C; R_f = 0.67 (10:1 (v/v) Et_2O /MeOH); $[\alpha]_{\text{D}}^{25}$ -116 (c 0.8, CHCl_3); IR (thin film, cm^{-1}) 3424 (broad), 3066, 3035, 2928, 1741, 1605, 1574, 1509, 1498, 1486, 1454, 1375, 1354, 1299, 1251, 1199, 1177, 1144, 1102, 1049, 1004, 955; ^1H NMR (acetone- d_6 , 600 MHz) δ 7.82 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.46-7.27 (m, 13H), 7.09 (d, J = 9.0 Hz, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 5.51 (d, J = 1.8 Hz, 1H), 5.27 (s, 2H), 5.15 (s, 2H), 5.07 (s, 2H), 4.78 (dd, J = 9.6, 9.0 Hz, 1H), 4.51 (ddd, J = 3.6, 3.6, 2.4 Hz, 1H), 3.93 (ddd, J = 8.4, 7.8, 3.0 Hz, 1H), 3.45 (d, J = 4.2 Hz, 1H), 3.40 (dq, J = 9.6, 6.6 Hz, 1H), 2.91 (d, J = 7.8 Hz, 1H), 2.05 (s, 3H), 0.81 (d, J = 6.6 Hz, 3H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 173.5, 171.2, 163.0, 160.5, 159.8, 158.9, 154.6, 137.8, 136.4, 136.3, 135.6, 130.5, 128.8, 128.7, 128.6, 128.4, 128.2, 127.8, 127.6, 127.3, 126.8, 123.3, 114.7, 109.9, 101.4, 98.4, 94.0, 74.7, 70.8, 70.7, 70.5, 70.2, 69.9, 67.8, 21.0, 17.1; HRMS (ESI) calcd. for $[\text{C}_{44}\text{H}_{40}\text{O}_{11}+\text{H}]^+$: 745.2649, Found: 745.2642.

Kaempferol-3- α -L-4''-O-acetylramnoside (**1d**)^{62c}

To a solution of 54.8 mg diol **I-15** (0.07 mmol) in 3 mL THF-EtOH (1:1) was added 30 mg Pearlman's catalyst (Pd-C , 10%). The reaction mixture was degassed using vacuum at -90 °C and refilling with H_2 . This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H_2

atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (1:2) to give kaempferol-3- α -L-4''-*O*-acetylramnoside (**I-1d**) (30 mg, 87%): Yellow solid, mp: 150-152 °C; R_f = 0.18 (1:3 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ -145 (c 1.3, MeOH); IR (thin film, cm^{-1}) 3317 (broad), 2927, 1721, 1651, 1607, 1500, 1446, 1359, 1253, 1207, 1172, 1141, 1085, 1047, 1004, 970, 952; ^1H NMR (acetone- d_6 , 600 MHz) δ 7.84 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 6.47 (d, J = 1.8 Hz, 1H), 6.28 (d, J = 1.8 Hz, 1H), 5.53 (d, J = 1.2 Hz, 1H), 4.82 (dd, J = 9.6, 9.6 Hz, 1H), 4.23 (dd, J = 3.6, 1.8 Hz, 1H), 3.85 (dd, J = 9.6, 3.6 Hz, 1H), 3.40 (dq, J = 9.6, 6.0 Hz, 1H), 2.87 (brs, 1H), 1.97 (s, 3H), 0.78 (d, J = 6.6 Hz, 3H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 179.3, 170.9, 165.1, 163.1, 161.1, 158.7, 158.2, 135.7, 131.8, 122.5, 116.4, 105.9, 102.4, 99.6, 94.7, 74.6, 71.5, 69.8, 69.1, 21.0, 17.6; HRMS (ESI) calcd. for $[\text{C}_{23}\text{H}_{22}\text{O}_{11} + \text{Na}]^+$: 497.1060, Found: 497.1054.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(2,4-*O*-triacetyl- α -L-rhamnopyranoyloxy)-4H-chromen-4-one (I-16)

To a solution of 75 mg diol **I-15** (0.10 mmol) in 1.6 mL CH_2Cl_2 was added 0.6 mg (3 μmol) p -TsOH $\cdot\text{H}_2\text{O}$, 38 μL trimethylorthoacetate (0.30 mmol) at 0 °C. After stirring at 0 °C for 15 min, 0.5 mL 90% HOAc (aq.) was added and the reaction mixture was stirred for another 15 min. The reaction mixture was diluted with 25 mL EtOAc and washed at 0 °C by 3 mL saturated aqueous NaHCO_3 two times, then it was washed by 3 mL saturated brine, and dried over Na_2SO_4 . 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 (1:1) gave diacetate **12** (78 mg, 99%): White solid, mp: 99.5-101.5 °C; R_f = 0.58 (1:2 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ -115 (c 1.1, CHCl_3); IR (thin film, cm^{-1}) 3430 (broad), 3032, 2927, 1741, 1628, 1604, 1575, 1509, 1499, 1486, 1453, 1433, 1373, 1299, 1225, 1196, 1174, 1136, 1099, 1047, 1017, 963; ^1H NMR

(CDCl₃, 600 MHz) δ 7.81 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 7.2 Hz, 2H), 7.46-7.27 (m, 13H), 7.11 (d, J = 9.0 Hz, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 5.58 (d, J = 1.2 Hz, 1H), 5.57 (dd, J = 3.6, 1.8 Hz, 1H), 5.26 (s, 2H), 5.16 (s, 2H), 5.07 (s, 2H), 4.76 (dd, J = 10.2, 9.6 Hz, 1H), 4.11 (ddd, J = 9.6, 6.6, 3.0 Hz, 1H), 3.50 (dq, J = 10.2, 6.6 Hz, 1H), 2.28 (d, J = 6.6 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 0.89 (d, J = 6.0 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 173.0, 171.2, 170.5, 162.9, 160.6, 159.9, 158.8, 154.3, 136.9, 136.3, 135.6, 130.3, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 127.6, 127.3, 126.7, 123.1, 114.9, 110.0, 98.4, 98.3, 94.0, 74.1, 72.1, 70.8, 70.5, 70.2, 68.8, 67.9, 21.0, 20.9, 17.1; HRMS (ESI) calcd. for [C₄₆H₄₂O₁₂+Na]⁺: 809.2574, Found: 809.2567.

Kaempferol-3- α -L-2'',4''-O-diacetylramnoside (**I-1e**)⁶⁴

To a solution of 66.8 mg diacetate **I-16** (0.08 mmol) in 3 mL THF-EtOH (1:1) was added 30 mg Pearlman's catalyst (Pd-C, 10%). The reaction mixture was degassed using vacuum at -90 °C and refilling with H₂. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H₂ atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (2:3) to give kaempferol-3- α -L-2'',4''-O-diacetylramnoside (**I-1e**) (38 mg, 88%): Yellow solid, mp: 127-129 °C; R_f = 0.24 (1:2 (v/v) hexane/EtOAc); [α]_D²⁵ -93 (c 0.96, MeOH); IR (thin film, cm⁻¹) 3311 (broad), 2925, 1721, 1653, 1608, 1502, 1445, 1362, 1205, 1171, 1144, 1129, 1085, 1047, 1007, 970; ¹H NMR (acetone-d₆, 600 MHz) δ 7.85 (d, J = 9.0 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.48 (d, J = 1.8 Hz, 1H), 6.28 (d, J = 1.8 Hz, 1H), 5.60 (s, 1H), 5.47 (dd, J = 3.6, 1.8 Hz, 1H), 4.76 (dd, J = 10.2, 9.6 Hz, 1H), 4.04 (dd, J = 9.6, 3.6 Hz, 1H), 3.38 (dq, J = 10.2, 6.0

Hz, 1H), 2.06 (s, 3H), 1.99 (s, 3H), 0.81 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 179.0, 170.8, 170.3, 165.2, 163.0, 161.2, 158.8, 158.1, 134.8, 131.8, 122.3, 116.5, 105.8, 99.7, 99.3, 94.7, 74.4, 72.4, 69.2, 68.0, 21.0, 20.9, 17.7; HRMS (ESI) calcd. for $[\text{C}_{25}\text{H}_{24}\text{O}_{12} + \text{Na}]^+$: 539.1166, Found: 539.1159.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-(3,4-*O*-triacetyl- α -L-rhamnopyranoyloxy)-4H-chromen-4-one (I-17)

To a solution of 50 mg diacetate **I-16** (0.064 mmol) in 4 mL toluene was added a solution of 10 μl DBU in 1 mL toluene at 0 $^{\circ}\text{C}$. The reaction mixture was stirred at 0 $^{\circ}\text{C}$ for 1 hour, then diluted with 20 mL Et₂O-EtOAc (1:1). The mixture was sequentially washed with 2 mL saturated aqueous NH₄Cl, 2 mL saturated aqueous NaHCO₃, dried over Na₂SO₄. The organic layer was concentrated under reduced pressure to give a residue. Crude ^1H -NMR showed this residue contains 64% diacetate **I-17** vs. 36% diacetate **I-16**. Chromatography on silica gel eluting with hexane-EtOAc (1.6:1) gave desired diacetate **I-17** (31 mg, 62%) and further elution with hexane-EtOAc (1.4:1) gave 17 mg (34%) starting material **I-16** back. Diacetate **I-17** : White solid, mp: 93-95 $^{\circ}\text{C}$; $R_f = 0.59$ (2:3 (v/v) hexane/EtOAc); $[\alpha]_D^{25} -151$ (c 1.3, CHCl₃); IR (thin film, cm^{-1}) 3394 (broad), 3064, 2924, 1741, 1604, 1509, 1453, 1432, 1369, 1353, 1296, 1249, 1222, 1172,

1100, 1043, 1004, 958; ^1H NMR (CDCl_3 , 600 MHz) δ 7.86 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.46-7.27 (m, 13H), 7.12 (d, J = 9.0 Hz, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 5.53 (d, J = 2.4 Hz, 1H), 5.31 (dd, J = 9.0, 3.0 Hz, 1H), 5.26 (s, 2H), 5.15 (s, 2H), 5.08 (s, 2H), 4.98 (dd, J = 9.6, 9.0 Hz, 1H), 4.57 (ddd, J = 6.6, 3.6 Hz, 1H), 3.46 (dq, J = 9.6, 6.6 Hz, 1H), 2.87 (brs, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 0.82 (d, J = 6.0 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 173.3, 169.9, 169.8, 163.0, 160.5, 159.9, 158.9, 154.5, 137.6, 136.4, 136.3, 135.6, 130.5, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 127.6, 127.3, 126.7, 123.2, 114.8, 109.9, 101.9, 98.3, 94.0, 74.7, 71.2, 70.8, 70.5, 70.1, 69.5, 67.9, 20.9, 20.8, 17.2; HRMS (ESI) calcd. for $[\text{C}_{46}\text{H}_{42}\text{O}_{12}+\text{Na}]^+$: 809.2574, Found: 809.2569.

SL0101 (**I-1a**)^{3d,5}

To a solution of 46 mg diacetate **I-17** (0.058 mmol) in 2.5 mL THF-EtOH (1:1) was added 25 mg Pearlman's catalyst (Pd-C, 10%). The reaction mixture was degassed using vacuum at -90 °C and refilling with H_2 . This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H_2 atmosphere for 3 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (2:3) to give SL0101 (**I-1a**) (28 mg, 91%): Yellow solid, mp: 147-149 °C; R_f = 0.26 (1:2 (v/v) hexane/EtOAc); $[\alpha]_{\text{D}}^{25}$ -163 (c 1.6, MeOH); IR (thin film, cm^{-1}) 3211 (broad), 2980, 2930, 1722, 1650, 1607, 1502, 1444, 1361, 1206, 1171, 1045, 1005, 970; ^1H NMR (acetone- d_6 , 600 MHz) δ 7.86 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 6.48 (d, J = 1.8 Hz, 1H), 6.28 (d, J = 1.8 Hz, 1H), 5.56 (d, J = 1.8 Hz, 1H), 5.17 (dd, J = 10.2, 3.0 Hz, 1H), 5.07 (dd, J = 10.2, 9.6 Hz, 1H), 4.42 (dd, J = 3.0, 1.8 Hz, 1H), 3.49 (dq, J = 9.6, 6.0 Hz, 1H), 2.02 (s, 3H), 1.96 (s, 3H), 0.82

(d, $J = 6.0$ Hz, 3H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 179.2, 170.7, 170.4, 165.1, 163.0, 161.1, 158.7, 158.2, 135.5, 131.8, 122.4, 116.5, 105.8, 102.2, 99.7, 99.6, 94.7, 72.3, 71.2, 69.3, 69.2, 21.0, 20.8, 17.6; HRMS (ESI) calcd. for $[\text{C}_{25}\text{H}_{24}\text{O}_{12} + \text{Na}]^+$: 539.1166, Found: 539.1161.

3-((2*R*,6*R*)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yloxy)-5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4H-chromen-4-one ((*ent*)-I-2**)**

To a solution of 44 mg (0.079 mmol) perbenzylated flavonol **I-3** and 45 mg (0.197 mmol) α -D-pyranone (*ent*)-**I-4a** in 1 mL CH_2Cl_2 was added a solution of 3 mg (0.0029 mmol) $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ and 3 mg PPh_3 (0.011 mmol) in 0.3 mL CH_2Cl_2 at 0°C . The reaction mixture was stirred at 0°C for 3 hours and loaded directly onto silica gel column, eluting with hexane-EtOAc (2.5:1) gave glycosylated pyranone (*ent*)-**I-2** (37.4 mg, 71%): Light yellow solid, mp: 75-77 $^\circ\text{C}$; $R_f = 0.34$ (2:1 (v/v) hexane/EtOAc); $[\alpha]_{\text{D}}^{20} +72$ (c 2.22, CHCl_3); IR (thin film, cm^{-1}) ν 3064, 3032, 2985, 2918, 2871, 1698, 1634, 1604, 1573, 1509, 1452, 1374, 1353, 1299, 1250, 1196, 1175, 1161, 1100, 1002, 934. ^1H NMR (CDCl_3 , 600 MHz) δ 7.86 (d, $J = 9.0$ Hz, 2H), 7.57 (d, $J = 7.8$ Hz, 2H), 7.47-7.29 (m, 13H), 7.27 (dd, $J = 10.2, 3.6$ Hz, 1H), 7.06 (d, $J = 9.0$ Hz, 2H), 6.58 (d, $J = 1.8$ Hz, 1H), 6.47 (d, $J = 2.4$ Hz, 1H), 6.13 (d, $J = 10.2$ Hz, 1H), 5.91 (d, $J = 3.6$ Hz, 1H), 5.28 (s, 2H), 5.15 (s, 2H), 5.09 (s, 2H), 4.01 (q, $J = 7.2$ Hz, 1H), 0.92 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 196.7, 173.3, 163.0, 160.4, 159.9, 159.0, 154.9, 143.1, 137.6,

136.3, 136.2, 135.6, 130.4, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 127.6, 127.4, 127.4, 126.7, 123.2, 114.7, 110.0, 98.3, 94.3, 94.1, 71.5, 70.8, 70.5, 70.1, 14.6; HRMS (ESI): calcd. for $[C_{42}H_{34}O_8+Na]^+$: 689.2151, Found: 689.2149.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-((2*R*,3*S*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-methyltetrahydro-2*H*-pyran-2-yloxy)-4*H*-chromen-4-one ((*ent*)-I-12**)**

A solution of 135.5 mg pyranone (*ent*)-**I-2** (0.203 mmol) in 2.5 mL CH_2Cl_2 -MeOH (5:1) was cooled down to $-78\text{ }^{\circ}C$, then 19 mg (0.50 mmol) $NaBH_4$ was added in. The reaction mixture was stirred at $-78\text{ }^{\circ}C$ for 3 hours. The reaction was then quenched by 2 mL saturated aqueous $NaHCO_3$, followed by extraction with EtOAc (20 mL $\times$ 3). The organic layer was washed by 2 mL saturated aqueous NaCl, dried over Na_2SO_4 , and concentrated under reduced pressure to give crude product. The crude product was redissolved in a mixture of 1 mL *t*-BuOH, 1 mL acetone and 1 mL NMO (50% w/w aqueous) at $0\text{ }^{\circ}C$. Then catalytic amount of crystalline OsO_4 was added into the mixture. The reaction mixture was stirred at $0\text{ }^{\circ}C$ overnight, then was quenched by addition of 0.5 mL saturated aqueous $Na_2S_2O_3$. After stirring for another 0.5 hour at $0\text{ }^{\circ}C$, all the stuff was passed through a small pad of celite and silica gel, washed by EtOAc-MeOH (10:1) (10 mL $\times$ 3). The organic effluent was dried by Na_2SO_4 , and concentrated under reduced pressure to give crude product. Chromatography on silica gel column, eluting with Et_2O -MeOH (20:1), gave

triol (*ent*)-**I-12** (85 mg, 60% over two steps): White solid, mp: 103-105 °C; R_f = 0.27 (20:1 (v/v) Et₂O/MeOH); $[\alpha]_D^{20}$ +121 (c 1.0, MeOH); IR (thin film, cm⁻¹) ν 3386 (broad), 3063, 2931, 1602, 1509, 1453, 1352, 1299, 1252, 1198, 1174, 1102, 1098, 1055, 998, 993; ¹H NMR (acetone-d₆, 600 MHz) δ 7.91 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 4H) 7.43-7.39 (m, 6H), 7.38-7.29 (m, 3H), 7.19 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 1.8 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 5.57 (d, J = 1.8 Hz, 1H), 5.29 (d, J = 13.2 Hz, 1H), 5.28 (d, J = 13.2 Hz, 1H), 5.24 (s, 2H), 5.23(s, 2H), 4.28 (dd, J = 3.6, 1.8 Hz, 1H), 3.70 (dd, J = 9.0, 3.6 Hz, 1H), 3.33 (dd, J = 9.6, 9.6 Hz, 1H), 3.21 (dq, J = 9.6, 6.0 Hz, 1H), 2.91 (brs, 1H), 0.87 (d, J = 6.0 Hz, 3H); ¹³C NMR (acetone-d₆, 150 MHz) δ 173.5, 164.1, 161.5, 160.8, 159.8, 154.8, 138.4, 138.1, 138.0, 137.4, 131.4, 129.5, 129.4, 129.3, 129.1, 128.8, 128.8, 128.5, 128.4, 127.9, 124.4, 115.7, 110.6, 102.2, 98.9, 95.1, 73.2, 72.2, 71.5, 71.4, 71.3, 71.2, 70.8, 17.9; HRMS (ESI) calcd. for [C₄₂H₃₈O₁₀+H]⁺: 703.2543, Found: 703.2541.

Kaempferol-3- α -D-rhamnoside ((*ent*)-**I-1b**)

A solution of 24 mg triol (*ent*)-**I-12** (0.034 mmol) in 2 mL THF-EtOH (1:1) was added 14 mg Pd/C (10% w/w). The solution was degassed using vacuum at -50 to -40 °C and refilling with H₂. This procedure was repeated three times, and then the bath was removed. The reaction was warmed up to room temperature and stirred under a H₂ atmosphere for 5 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (1:3) gave kaempferol-3- α -D-rhamnoside ((*ent*)-**I-1b**) (14 mg, 93%): Pale yellow solid, mp: 148-150 °C; R_f = 0.71 (5:1 (v/v) Et₂O/MeOH); $[\alpha]_D^{20}$ +118 (c 1.0, MeOH); IR (thin film, cm⁻¹) ν 3290 (broad), 2922, 2853, 1654, 1607, 1500, 1448, 1359, 1261, 1207, 1173, 1056, 947; ¹H NMR (acetone-d₆, 600 MHz) δ 7.85 (d,

$J = 9.0$ Hz, 2H), 7.01 (d, $J = 8.4$ Hz, 2H), 6.47 (d, $J = 1.8$ Hz, 1H), 6.27 (d, $J = 2.4$ Hz, 1H), 5.53 (d, $J = 1.8$ Hz, 1H), 4.21 (dd, $J = 3.0, 1.8$ Hz, 1H), 3.68 (dd, $J = 9.0, 3.6$ Hz, 1H), 3.33 (dd, $J = 9.6, 8.4$ Hz, 1H), 3.30 (dd, $J = 9.6, 6.0$ Hz, 1H), 0.89 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 179.4, 165.1, 163.0, 161.0, 158.5, 158.1, 135.9, 131.8, 122.6, 116.3, 105.8, 102.8, 99.6, 94.6, 73.0, 72.2, 71.5, 71.4, 17.9; HRMS (ESI) calcd. for $[\text{C}_{21}\text{H}_{20}\text{O}_{10} + \text{Na}]^+$: 455.0954, Found: 455.0949.

V.3. Chapter II Experimental

(3a*R*,4a*S*,5a*R*,6a*S*)-hexahydro-2,2-dimethyl-3aH-bicyclo[4.1.0]hept-1(6)-eno[3,4-d][1,3]dioxol-4a-ol (II-9a)

(3a*R*,4a*R*,5a*S*,6a*S*)-hexahydro-2,2-dimethyl-3aH-bicyclo[4.1.0]hept-1(6)-eno[3,4-d][1,3]dioxol-4a-ol (II-9b)

To a solution of 17.0 g enone **II-4** (101.2 mmol) in 185 mL toluene was added 155 mg $\text{RhCl}(\text{PPh}_3)_3$ (0.34 mmol) and 17.0 mL phenyldimethylsilane (111.3 mmol), the mixture was stirred at 60 °C for 1 hour. Then the reaction mixture was cooled down to 0 °C, into which a

solution of 18.7g ZnEt₂ (151.8 mmol) was slowly added followed by addition of 18.4 ml CH₂I₂ (228.0 mmol). The reaction mixture was stirred at 0 °C overnight. Then it was diluted with 800 mL hexane-ether (v/v 1:1) and quenched with 150 mL saturated aqueous NH₄Cl. The aqueous layer was extracted with Et₂O with hexane-ether (v/v 1:1) 500 mL X 2. The combined organic layer was washed with 100 mL saturated aqueous Na₂S₂O₃, 100 mL saturated brine and dried over Na₂SO₄. The solution was then concentrated to a residue, which was redissolved in 360 mL MeOH at 0 °C and 546 mg (2.87 mmol) *p*-TsOH was added in portions. It was stirred at 0 °C for 15 min, then quenched with 50 mL saturated aqueous NaHCO₃. The mixture was concentrated under reduced pressure to remove most of the MeOH, and then extracted with hexane-EtOAc (v/v 1:5) 800 mL X 3. The organic layer was washed with saturated brine 300 mL and dried over Na₂SO₄. Concentration of the solution gave a residue, which was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (3:1) afforded cyclopropanol **II-9a** (9.3 g, 50 %) and elution with hexane-EtOAc (3:2) afforded **II-9b** (3.7 g, 20%).

II-9a: Colorless oil; *R_f* = 0.44 (1:1 (v/v) hexane/EtOAc); [α]_D²⁰ +19 (*c* 2.50, CHCl₃); IR (thin film, cm⁻¹) ν 3433, 2987, 2933, 1453, 1371; ¹H NMR (600 MHz, CDCl₃) δ 4.48 (ddd, *J* = 7.8, 3.0, 2.4 Hz, 1H), 4.32 (ddd, *J* = 7.8, 3.0, 2.4 Hz, 1H), 2.72 (s, 1H), 2.50 (dd, *J* = 15.6, 3.0 Hz, 1H), 2.30 (dddd, *J* = 15.6, 4.8, 2.4, 1.8 Hz, 1H), δ 1.48 (s, 3H), 1.33 (s, 3H), 1.25 (dd, *J* = 15.6, 2.4 Hz, 1H), 1.08 (m, 2H), 0.62 (m, 1H); 0.18 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 107.1, 74.0, 73.6, 52.0, 34.4, 29.9, 26.4, 23.4, 20.6, 14.8. HRMS (ESI): calcd. for [C₁₀H₁₆O₃+Na]⁺: 207.09917, Found: 207.09916.

II-9b: Colorless oil; *R_f* = 0.26 (1:1 (v/v) hexane/EtOAc); [α]_D²⁰ +11 (*c* 2.36, CHCl₃); IR (thin film, cm⁻¹) ν 3371, 2988, 2915, 1463, 1371; ¹H NMR (600 MHz, CDCl₃) δ 4.45 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 4.29 (ddd, *J* = 8.4, 6.0, 6.0 Hz, 1H), 2.35 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.24 (ddd, *J* = 15.0, 5.4, 5.4 Hz, 1H), 2.05 (brs, 1H), 1.82 (dd, *J* = 15.0, 6.0 Hz, 1H), δ 1.44 (s, 3H), 1.39 (ddd, *J* = 15.0, 6.0, 6.0 Hz, 1H), 1.30 (s, 3H), 1.06 (dddd, *J* = 9.6, 6.0, 6.0, 5.4 Hz, 1H), 0.92 (dd, *J* = 9.6, 5.4 Hz, 1H), 0.88 (dd, *J* = 6.0, 5.4 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 107.2, 72.0, 71.8, 53.4, 34.6, 27.6, 26.4, 23.1, 20.4, 17.1. HRMS (ESI): calcd. for [C₁₀H₁₆O₃+H]⁺: 185.11722, Found: 185.11719. ¹H-¹H COSY and NOE as follow:

^1H - ^1H COSY of **13b**

NOE of **13b**

(3a*R*,7a*S*)-tetrahydro-2,2-dimethyl-6-methylenebenzo[d][1,3]dioxol-5(6*H*)-one (II-10a)

(3a*R*,7a*S*)-3a,4-dihydro-2,2,6-trimethylbenzo [d][1,3]dioxol-5(7a*H*)-one (II-10b)

To a solution of 139 mg **II-9a** (0.76 mmol) in 6 mL toluene was added 128 μL pyridine (1.59 mmol) and 178 mg $\text{Pd}(\text{OAc})_2$ (0.79 mmol). The reaction mixture was heated up to 80 $^\circ\text{C}$ and kept stirring for 3 h. Then it was cooled to RT, and was filtered through filter paper, rinsing with Et_2O -hexane (1:1, v/v) 50 mL. The solution was washed with 1 mL 0.5 M NaHSO_4 at 0 $^\circ\text{C}$, then was washed with 1 mL saturated aqueous NaHCO_3 , and 1 mL saturated aqueous NaCl , dried over Na_2SO_4 . The solution was concentrated under reduced pressure to give a residue, which was

purified by silica gel column. Elution with hexane-EtOAc (7:1) afforded two pure compounds **II-10a** (42 mg, 31%) and **II-10b** (75 mg, 55%).

To a solution of 10 mg **II-9a** (0.05 mmol) in 0.5 mL toluene was added 8.7 μ L pyridine (0.11 mmol), 12 mg quinone (0.10 mmol) and 14 mg Pd(OAc)₂ (0.06 mmol). The reaction mixture was heated up to 80 °C and kept stirring for 3 h. Then it was cooled to RT, and was filtered through filter paper, rinsing with Et₂O-hexane (1:1, v/v) 5 mL. The solution concentrated under reduced pressure and directly loaded onto a silica gel column. Elution with hexane-EtOAc (5:1) afforded compounds **II-10a** (7 mg, ~70%) and **II-9a** (1 mg, ~10% recovery).

To a solution of 1.6 mg **II-9a** (0.009 mmol) in 0.6 mL THF-EtOH (1:1 v/v) was added 11 mg 10% Pd/C (0.01 mmol Pd). The reaction mixture was stirred at RT for 24 h and the mixture was then filtered through filter paper. The solution was concentrated under reduced pressure to give a residue, which was shown by crude ¹H NMR that it was exclusively **II-10a**.

II-10a: White solid; mp: 58.3-60.3 °C; *R_f* = 0.45 (1:1 (v/v) hexane/EtOAc); [α]_D²⁰ +16 (*c* 0.33, CHCl₃); IR (thin film, cm⁻¹) ν 2991, 2917, 1709, 1671, 1627, 1431, 1384, 1363, 1286, 1274, 1243, 1207, 1163, 1081, 1062, 1038, 950; ¹H NMR (CDCl₃, 270 MHz) δ 6.17 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.32 (dd, *J* = 2.2, 1.7 Hz, 1H), 4.69 (ddd, *J* = 6.7, 3.2, 3.2 Hz, 1H), 4.60 (ddd, *J* = 7.4, 3.2, 3.2 Hz, 1H), 2.79 (dd, *J* = 15.3, 2.7 Hz, 1H), 2.77 (dd, *J* = 15.8, 3.0 Hz, 1H), 2.64 (dddd, *J* = 15.3, 3.7, 2.2, 2.2 Hz, 1H), 2.58 (dd, *J* = 15.8, 3.5 Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H); ¹³C NMR (CDCl₃, 67.5 MHz) δ 197.3, 138.9, 123.5, 108.0, 73.1, 72.4, 42.0, 34.9, 26.0, 24.1; HRMS (ESI) calcd. for [C₁₀H₁₄O₃+H]⁺: 183.1016, Found: 183.1016.

II-10b: Colorless oil; *R_f* = 0.55 (1:1 (v/v) hexane/EtOAc); [α]_D²⁰ +71 (*c* 1.89, CHCl₃); IR (thin film, cm⁻¹) ν 2986, 2926, 1679, 1450, 1380, 1368, 1243, 1223, 1155, 1063, 1038, 1012, 967; ¹H NMR (CDCl₃, 270 MHz) δ 6.39 (dq, *J* = 4.7, 1.5 Hz, 1H), 4.69 (dddd, *J* = 4.5, 3.0, 3.0, 1.5 Hz, 1H), 4.63 (ddq, *J* = 4.9, 3.0, 2.0 Hz, 1H), 2.92 (dd, *J* = 17.3, 2.7 Hz, 1H), 2.65 (dd, *J* = 17.3, 3.9 Hz, 1H), 1.80 (dd, *J* = 1.5, 1.5 Hz, 3H), 1.36 (s, 3H), 1.34 (s, 3H); ¹³C NMR (CDCl₃, 67.5 MHz)

δ 195.7, 140.6, 135.5, 109.6, 73.6, 71.6, 39.1, 27.8, 26.6, 15.8; HRMS (ESI) calcd. for $[\text{C}_{10}\text{H}_{14}\text{O}_3+\text{H}]^+$: 183.1016, Found: 183.1016.

Hydrogenation of **II-10a** and **II-10b**

To a solution of 40 mg enone **II-10a** (or **II-10b**) (0.22 mmol) in 3 mL THF-EtOH (1:1 v/v) was added 20 mg 10% Pd/C. The reaction mixture was degassed using vacuum and refilled with H_2 at $\sim -30^\circ\text{C}$ for three times and then was stirred under balloon pressure of H_2 at RT for 2 h. The mixture was filtered through filter paper and the solution was concentrated under reduced pressure to give a residue. A crude ^1H NMR showed that it was a diastereomeric mixture of α -methyl ketone **II-11a/II-11b** with $\text{dr}_{(11a/11b)}$ 3:1 for **II-10a** (or $\text{dr}_{(11a/11b)}$ 1:10 for **II-10b**). The two isomers **II-11a** and **II-11b** were inseparable on silica gel column and the mixture of isomers **II-11a/II-11b** were obtained in 88% yield for **II-10a** (or 89% for **II-10b**).

β -elimination of **II-11a/II-11b**

To a solution of 18 mg mixture of **II-11a/II-11b** (dr 3:1) (0.1 mmol) in 6 mL THF at 0°C was added 5 drops of 0.5 M $\text{NaOH}_{(\text{aq.})}$ and the mixture was stirred at 0°C for 30 h. Then into the mixture was added 10 drops of saturated aqueous NH_4Cl and diluted with 20 mL EtOAc. The organic layer was washed with 1 mL saturated aqueous NH_4Cl , 1 mL saturated aqueous NaCl and dried over Na_2SO_4 . The solution was concentrated under reduced pressure to give a residue which by crude ^1H NMR was shown that it was a mixture of **II-12a/II-12b** ($\text{dr}_{(12a/12b)}$ 2:3). The two isomers **II-12a** and **II-12b** were inseparable on silica gel column and the mixture of **II-12a/II-12b** was obtained in 85% yield.

(3a*R*,6*S*,7a*S*)-tetrahydro-2,2,6-trimethylbenzo[d][1,3]dioxol-5(6*H*)-one (II-11a)

To a solution of 660 mg cyclopropanol **II-9a** (3.6 mmol) in 30 mL THF-EtOH (v/v 1:1) was added 350 mg 10% Pd/C. The solution was degassed using vacuum and refilled with H₂ three times at low temperature (~ -30 °C). Then at room temperature, the solution was stirred overnight under balloon pressure of H₂. It was filtered through a filter paper and rinse with ethyl acetate. The solution was concentrated under reduced pressure to a small volume, which was then subjected to chromatography on silica gel column. Elution with Hexane-EtOAc (7:2) gave product **II-11a** (530 mg, 80%).

II-11a: Colorless oil; R_f = 0.55 (1:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ +105 (c 2.7, CHCl₃); IR (thin film, cm⁻¹) ν 2989, 2937, 1702, 1458, 1378, 1204, 1164, 1017; ¹H NMR (CDCl₃, 600 MHz) δ 4.63 (ddd, J = 7.2, 4.2, 3.0 Hz, 1H), 4.52 (ddd, J = 7.2, 3.0, 2.4 Hz, 1H), 2.67 (dd, J = 17.4, 3.0 Hz, 1H), 2.53 (dq, J = 13.8, 6.6, 4.2 Hz, 1H), 2.44 (dd, J = 16.8, 3.6 Hz, 1H), 2.06 (ddd, J = 15.0, 4.2, 2.4 Hz, 1H), 1.65 (ddd, J = 16.2, 13.2, 3.0 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 1.09 (d, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 211.7, 107.6, 72.9, 71.9, 41.1, 37.4, 34.3, 26.0, 23.8, 14.8; HRMS (ESI): calcd. for [C₁₀H₁₆O₃+H]⁺: 185.11722, Found: 185.11723.

(2S,4S,5R)-4,5-dihydroxy-2-methylcyclohexanone (**II-13**)

1.0 g acetone **II-11a** (5.4 mmol) was placed in 250 mL flask at 0 °C, a pre-cooled 40 mL solution of THF-10% HCl (v/v 1:1) was added into the flask when stirring. Then the ice bath was removed and the mixture was allowed to warm up to room temperature over 1 hour when stirring.

The mixture was cooled down to 0 °C and diluted with 120 mL EtOAc, into which 10 g NaHCO₃ (s) was slowly added to quench the reaction. The mixture was extracted with EtOAc 200 mL X 3 and the organic layer was washed with 40 mL saturated aqueous NaCl, dried over Na₂S₂O₄. The solution was concentrated under reduced pressure to a residue which was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (1:3) gave product diol **II-13** (600 mg, 77%).

II-13: Colorless oil; R_f = 0.53 (10:1 (v/v) EtOAc/MeOH); $[\alpha]_D^{20}$ +35 (c 1.32, CHCl₃); IR (thin film, cm⁻¹) ν 3391, 2969, 2932, 1701, 1455, 1430, 1376, 1355, 1243, 1215, 1105, 1066, 1031, 963, 915; ¹H NMR (CDCl₃, 270 MHz) δ 4.15 (ddd, J = 2.7, 2.7, 2.7 Hz, 1H), 3.94 (ddd, J = 11.6, 5.4, 3.0 Hz, 1H), 2.78 (m, 2H), 2.55 (dd, J = 13.1, 5.2 Hz, 1H), 2.22 (ddd, J = 14.4, 5.9, 4.0 Hz, 1H), 1.42 (ddd, J = 14.6, 13.1, 2.5 Hz, 1H), 1.01 (d, J = 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 210.1, 72.0, 68.3, 45.1, 37.6, 36.2, 13.6; HRMS (ESI): calcd. for [C₇H₁₂O₃+Na]⁺: 167.06787, Found: 167.06781.

(1S,3R,4S,6R)-bicyclo[4.1.0]heptane-1,3,4-triol (II-14)

A solution of 2.8 g of **II-9a** was dissolved in 10 mL THF-10%HCl (v/v, 1:1) and stirred at room temperature for 20 min. The mixture was cooled down to 0 °C, and diluted with 100 mL EtOAc, then ~7 g NaHCO₃ was slowly added to quench the reaction. The mixture was filtered through a glass wool and the liquid was concentrated to a residue which was loaded to a silica gel column. Elution with EtOAc-MeOH (10:1 v/v) gave triol **II-14** (1.8g, 82%).

II-14: White solid; mp: 148-149 °C; R_f = 0.19 (10:1 (v/v) EtOAc/MeOH); $[\alpha]_D^{20}$ +26 (c 4.99, MeOH); IR (thin film, cm⁻¹) ν 3368, 3245, 2928, 2911, 1434, 1363, 1276, 1213, 1172; ¹H NMR (CD₃OD, 600 MHz) δ 3.56 (ddd, J = 6.6, 4.8, 1.8 Hz, 1H), 3.38 (ddd, J = 9.0, 4.8, 1.8 Hz, 1H),

2.23 (ddd, $J = 13.2, 13.2, 5.4$ Hz, 1H), 2.19 (m, 2H), 1.56 (ddd, $J = 15.0, 4.8, 1.8$ Hz, 1H), 1.03 (dddd, $J = 10.2, 7.8, 6.0, 1.8$ Hz, 1H), 0.84 (ddd, $J = 10.2, 5.4, 1.2$ Hz, 1H), 0.18 (dd, $J = 6.0, 6.0$ Hz, 1H); ^{13}C NMR (CD_3OD , 150 MHz) δ 70.1, 69.7, 55.4, 36.2, 31.5, 20.0, 18.1; HRMS (ESI): calcd. for $[\text{C}_7\text{H}_{12}\text{O}_3 + \text{Na}]^+$: 167.06787, Found: 167.06783.

Alternatively preparation of **II-13** from **II-14**

Into a solution of 300 mg (2.08 mmol) cyclopropanol **II-14** in 13 mL THF-EtOH (1:1 v/v) was added 150 mg 10% Pd/C. The solution was degassed using vacuum and refilled with H_2 three times at low temperature (~ -30 °C). Then at room temperature, the solution was stirred 4 hr under balloon pressure of H_2 . It was filtered through a filter paper and rinsed with ethyl acetate. The solution was concentrated under reduced pressure to a small volume (some of the solution was taken out and concentrated to dry, then a crude NMR was taken to show that NO diastereomer was seen). The residue was subjected to chromatography on silica gel column. Elution with Hexane-EtOAc (1:3) gave product **II-13** (246 mg, 82%).

t-Butyl (1*S*,5*S*)-5-methyl-4-oxocyclohex-2-enyl carbonate (**II-15**)

Diol **II-13** (250 mg, 1.74 mmol) was dissolved in 15 mL CH_2Cl_2 at RT, into which 24 mg DMAP (0.2 mmol) was added, followed by addition of a solution of 1.2 g Boc_2O (5.6 mmol) in 5 mL CH_2Cl_2 . The mixture was stirred at RT for 2 h, then it was cooled down to 0 °C, diluted with Et_2O 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_2O (1:2 v/v) 50 mL x 2. The pooled organic layer was washed with 15 mL saturated aqueous NaCl and dried over Na_2SO_4 .

The solution was concentrated under reduced pressure to afford a residue. The residue was redissolved in 9 mL CH₂Cl₂ at 0 °C. Into the solution 1.8 mL Et₃N (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-Et₂O (1:1 v/v) 50 mL and it was then quenched by 30 mL 0.5 M NaHSO₄ at 0 °C. The aqueous layer was extracted with hexane-Et₂O (1:1 v/v) 100 mL x 2. The pooled organic layer was washed with 20 mL saturated aqueous NaHCO₃, 20 mL saturated aqueous NaCl and dried over Na₂SO₄. 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 **II-15** (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); [*α*]_D²⁰ -175 (*c* 1.54, CHCl₃); IR (thin film, cm⁻¹) *ν* 2991, 2969, 2930, 2879, 1731, 1686, 1627, 1454, 1369, 1343, 1274, 1252, 1195, 1156, 1121, 1079, 1067, 1046, 965; ¹H NMR (CDCl₃, 270 MHz) *δ* 6.86 (dd, *J* = 10.2, 4.2 Hz, 1H), 6.04 (dd, *J* = 9.9, 1.0 Hz, 1H), 5.29 (ddd, *J* = 4.5, 4.5, 4.2 Hz, 1H), 2.77 (dq, *J* = 9.6, 7.2, 4.9 Hz, 1H), 2.25 (dddd, *J* = 13.9, 4.9, 4.9, 1.0 Hz, 1H), 2.06 (ddd, *J* = 13.9, 9.4, 4.5 Hz, 1H), 1.49 (s, 9H), 1.15 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 67.5 MHz) *δ* 201.0, 152.8, 143.3, 131.2, 82.9, 68.1, 37.7, 35.4, 27.7, 14.9;

***t*-Butyl (1*S*,4*R*,5*S*)-4-hydroxy-5-methylcyclohex-2-enyl carbonate (**II-16**)**

To a solution of 69 mg enone **II-15** (0.30 mmol) in 6 mL THF at -78 °C was added 40 mg LiAlH₄ (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 reaction. Then it was diluted with 30 mL EtOAc and 6 mL saturated aqueous NH₄Cl 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_4Cl , 5 mL saturated brine, dried over Na_2SO_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 **II-16** (60 mg, 90%) as white solid; mp: 81.6-83.6 °C; R_f = 0.27 (4:1 v/v hexane/EtOAc); $[\alpha]_D^{20}$ -131 (c 1.05, CHCl_3); IR (thin film, cm^{-1}) ν 3354, 2974, 1732, 1455, 1397, 1370, 1340, 1281, 1256, 1155, 1058, 1035, 945; ^1H (CDCl_3 , 600 MHz) δ 5.95 (ddd, J = 9.6, 1.8 Hz, 1H), 5.85 (dddd, J = 10.2, 4.2, 1.8, 1.8 Hz, 1H), 4.99 (m, 1H), 3.70 (ddd, J = 9.0, 3.6, 1.8 Hz, 1H), 1.91 (dddd, J = 14.4, 3.0, 3.0, 1.8 Hz, 1H), 1.82 (ddqd, J = 12.0, 9.6, 6.6, 3.0 Hz, 1H), 1.57 (ddd, J = 15.0, 12.0, 4.8 Hz, 1H), 1.48 (s, 9H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 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 $[\text{C}_{12}\text{H}_{20}\text{O}_4 + \text{Na}]^+$: 251.1254, Found: 251.1254.

***t*-Butyl (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-trihydroxy-5-methylcyclohexyl carbonate (II-17)**

To a solution of 37 mg olefin **II-16** (0.16 mmol) in 1.5 mL *t*-BuOH-actone-50% $\text{NMO}_{(\text{aq.})}$ (1:1:1 v/v/v) was added a small piece of crystalline OsO_4 at 0 °C. The reaction mixture was stirred at 0 °C for overnight, then 1.5 mL saturated aqueous $\text{Na}_2\text{S}_2\text{O}_4$ was added and it was stirred at 0 °C for another 2 h. The reaction mixture was passed through a pad of sand-silica gel-celite, rinsing with EtOAc-MeOH (10:1, v/v). The effluent was dried over Na_2SO_4 and concentrated under reduced pressure to give a residue, which was purified by silica gel column. Elution with hexane-EtOAc (1:2) gave triol **II-17** (37 mg, 87%) as colorless oil: R_f = 0.27 (1:3 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ +10 (c 1.9, MeOH); IR (thin film, cm^{-1}) ν 3388, 2933, 1740, 1457, 1369, 1277, 1255, 1157, 1051, 960; ^1H NMR (CD_3OD , 600 MHz) δ 4.69 (ddd, J = 3.6, 3.0, 1.8 Hz, 1H), 3.92 (ddd, J = 3.6, 3.6, 1.2 Hz, 1H), 3.48 (dd, J = 9.6, 3.6 Hz, 1H), 3.29 (ddd, J = 9.0, 9.0, 1.8 Hz, 1H), 1.67 (m, 3H), 1.46 (s, 9H), 1.02 (d, J = 5.4 Hz, 3H); ^{13}C NMR (CD_3OD , 150 MHz) δ 154.4, 83.1, 76.4,

76.3, 74.5, 72.2, 33.8, 33.2, 28.2, 18.4; HRMS (ESI) calcd. for $[C_{12}H_{22}O_6+Na]^+$: 285.1309, Found: 285.1309.

5a-Carba- α -D-rhamnopyranose (II-17)

To a solution of 26 mg carbonate **II-17** (0.10 mmol) in 2 mL THF at 0 °C was added 26 mg $LiAlH_4$ (0.68 mmol). The reaction mixture was warmed up and stirred at RT for 1 h, then it was diluted with 10 mL EtOAc and 2 mL saturated aqueous $NaHCO_3$ was added. It was stirred for another 20 min to quench the reaction and then the mixture was passed through a pad of sand-silica gel-celite, eluting with EtOAc-MeOH (10:1 v/v). The effluent was dried over Na_2SO_4 . The solution was concentrated under reduced pressure to give a residue, which was purified by silica gel column. Elution with EtOAc-MeOH (10:1) afforded cyclitol **II-7** (13 mg, 83%) as colorless oil; $R_f = 0.24$ (5:1 (v/v) EtOAc/MeOH); $[\alpha]_D^{20} -17$ (c 0.58, MeOH); IR (thin film, cm^{-1}) ν 3315, 2922, 1404, 1377, 1281, 1240, 1186, 1154, 1052, 1003, 964; 1H NMR (CD_3OD , 600 MHz) δ 3.87 (dd, $J = 3.6, 3.0$ Hz, 1H), 3.83 (ddd, $J = 3.6, 3.0, 3.0$ Hz, 1H), 3.61 (dd, $J = 9.6, 3.0$ Hz, 1H), 3.26 (dd, $J = 9.6, 9.6$ Hz, 1H), 1.78 (ddqd, $J = 10.2, 9.6, 6.6, 6.6$ Hz, 1H), 1.59 (m, 2H), 1.01 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3OD , 150 MHz) δ 76.9, 75.0, 74.3, 71.1, 35.9, 33.1, 18.6;

(2*S*,3*S*,4*aR*,5*aS*,7*aR*)-octahydro-2,3-dimethoxy-2,3-dimethyl-2H-bicyclo[4.1.0]hept-1(6)-eno[3,4-*b*][1,4]dioxin-5a-ol (II-18b)

To a solution of 5.2 g enone **II-6** (21.5 mmol) in 74 mL toluene was added 30 mg $\text{RhCl}(\text{PPh}_3)_3$ (0.065 mmol) and 4.1 mL phenyldimethylsilane (26.9 mmol), the mixture was stirred at 60 °C for 1 hour. Then the reaction mixture was cooled down to 0 °C, into which a solution of 5.96 g ZnEt_2 (48.3 mmol) was slowly added followed by addition of 4.9 mL CH_2I_2 (60.7 mmol). The reaction mixture was stirred at 0 °C overnight. Then it was diluted with 300 mL hexane-ether (v/v 1:1) and quenched with 120 mL saturated aqueous NH_4Cl . The aqueous layer was extracted with hexane-ether (v/v 1:1) 300 mL X 2. The combined organic layer was washed with 10 mL saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, 100 mL saturated brine, dried over Na_2SO_4 . The solution was then concentrated to a residue, which was redissolved in 215 mL MeOH at 0 °C and 326 mg (1.72 mmol) *p*-TsOH was added in portions. It was stirred at 0 °C for 15 min, and then quenched with 10 mL saturated aqueous NaHCO_3 and 1 g NaHCO_3 . The mixture was concentrated under reduced pressure to remove most of solvent, then 50 mL EtOAc was added and concentrated again to remove more solvent. The residue (~10 mL) was directly loaded onto a silica gel column. Elution with hexane-EtOAc (3:2, v/v) afforded cyclopropanol (4 g, 73 %) as diastereomeric mixture (dr ~1:1).

To a solution of 2.0 g diastereomeric mixture (7.75 mmol, dr ~1:1) in 300 mL EtOAc was added 700 mg 10% Pd/C. The solution was degassed using vacuum and refilled with H_2 three times at low temperature (~-30 °C). Then at room temperature, the solution was stirred for 6 hr under balloon pressure of H_2 . It was then filtered through a filter paper and rinse with ethyl acetate. The solution was washed with 30 mL saturated aqueous NaHCO_3 , 30 mL saturated aqueous NaCl , dried over Na_2SO_4 and then concentrated under reduced pressure to a small volume, which was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (2.5:1) gave product diastereomeric mixture of **II-19** (1.26g, 63%, dr(**II-19a**/**II-19b**) ~2:1) and elution with hexane-EtOAc (1:1) gave pure cyclopropanol **II-18b** (420 mg, 21%). **II-18b**: Colorless oil; R_f = 0.48 (1:2 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ = +159 (*c* 1.0, CHCl_3); IR (thin film, cm^{-1}) ν 3405, 2992,

2933, 2833, 1456, 1377, 1218, 1200, 1123, 1050, 1038; ^1H NMR (600 MHz, CDCl_3) δ 3.61 (ddd, $J = 11.4, 10.8, 7.2$ Hz, 1H), 3.25 (s, 3H), 3.23 (s, 3H), 3.22 (ddd, $J = 11.4, 10.2, 5.4$ Hz, 1H), 2.51 (ddd, $J = 12.6, 5.4, 0.6$ Hz, 1H), 2.31 (ddd, $J = 16.2, 9.6, 7.2$ Hz, 1H), 2.03 (ddd, $J = 12.0, 10.8, 1.2$ Hz, 1H), 1.36 (ddd, $J = 13.8, 11.4, 2.4$ Hz, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 1.12 (dddd, $J = 9.6, 9.6, 6.6, 1.2$ Hz, 1H), 1.01 (ddd, $J = 10.8, 6.0, 1.8$ Hz, 1H), 0.38 (dd, $J = 6.0, 5.4$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 99.2, 99.0, 68.9, 67.1, 55.9, 47.9, 47.8, 36.0, 29.6, 20.9, 18.0, 17.8. HRMS (ESI): calcd. for $[\text{C}_{13}\text{H}_{22}\text{O}_5 + \text{Na}]^+$: 281.13594, Found: 281.13599.

(2*S*,3*S*,4*aR*,7*R*,8*aR*)-hexahydro-2,3-dimethoxy-2,3,7-trimethylbenzo[*b*][1,4]dioxin-6(7H)-one (II-19a)

(2*S*,3*S*,4*aR*,7*S*,8*aR*)-hexahydro-2,3-dimethoxy-2,3,7-trimethylbenzo[*b*][1,4]dioxin-6(7H)-one (II-19b)

Separation of **II-19a** and **II-19b**

Diastereomeric mixture of **II-19a/II-19b** (6.5g, dr ~2:1) was recrystallized from hexane-ether multiple times, which resulted in diastereomerically enriched **II-19a** (~3.3g, dr_(19a/19b) ~10:1) from the mother solutions and **II-19b** (~2.0g, dr_(II-19b/II-19a) >20:1) from the crystal form, as well as other small amount of mixtures (dr ratio range from 4:1 to 1:4). The **II-19a** enriched part and the **II-19b** enriched part were further purified respectively by silica gel column chromatography, eluting with hexane-EtOAc (6:1) to give more enriched **II-19a** (2.6 g, dr ~18:1, 40% recovery from original mixture) and the pure **II-19b** (1.8g, 28% recovery from original mixture).

II-19a (dr_(II-19b/II-19a) 18:1): White solid; mp: 92.0-93.0 °C; R_f = 0.31 (4:1 (v/v) hexane/EtOAc); IR (thin film, cm⁻¹) ν 3016, 2949, 2911, 2840, 1731, 1461, 1430, 1364, 1277, 1204, 1108, 1073, 1039, 1025, 971; ¹H NMR (CDCl₃, 600 MHz) δ 4.00 (ddd, J = 12.0, 9.6, 4.8 Hz, 1H), 3.74 (ddd, J = 13.2, 10.2, 5.4 Hz, 1H), 3.28 (s, 3H), 3.21 (s, 3H), 2.61 (dd, J = 15.0, 12.6 Hz, 1H), 2.58 (m, 1H), 2.48 (ddd, J = 15.0, 5.4, 1.2 Hz, 1H), 1.84 (ddd, J = 13.2, 12.0, 6.6 Hz, 1H), 1.74 (ddd, J = 13.8, 6.6, 3.0 Hz, 1H), 1.29 (s, 3H), 1.28 (s, 3H), 1.20 (d, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 210.7, 99.7, 99.3, 68.8, 66.3, 48.0, 47.9, 43.3, 41.5, 32.2, 17.9, 17.7, 17.6; HRMS (ESI) calcd. for [C₁₃H₂₂O₅+Na]⁺: 281.1359, Found: 281.1360.

II-19b: White crystal; mp: 174-175 °C; R_f = 0.33 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ = +145 (c 0.37, CHCl₃); IR (thin film, cm⁻¹) ν 2987, 2951, 2913, 2884, 2833, 1703, 1468, 1444, 1431, 1377, 1277, 1231, 1220, 1202, 1156, 1112, 1081, 1054, 1037, 928; ¹H NMR (600 MHz, CDCl₃) δ 3.96 (ddd, J = 12.0, 9.6, 4.8 Hz, 1H), 3.71 (ddd, J = 13.2, 9.6, 5.4 Hz, 1H), 3.32 (s, 3H), 3.23 (s, 3H), 2.60 (dd, J = 13.8, 5.4 Hz, 1H), 2.53 (ddd, J = 13.2, 13.2, 1.2 Hz, 1H), 2.41 (ddqd, J = 12.6, 6.6, 6.6, 1.2 Hz, 1H), 2.08 (ddd, J = 12.6, 6.6, 4.2 Hz, 1H), 1.43 (ddd, J = 13.2, 12.6, 12.0 Hz, 1H), 1.32 (s, 3H), 1.31 (s, 3H), 1.07 (d, J = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 208.0, 99.6, 99.4, 69.6, 69.4, 48.0, 47.9, 44.5, 43.0, 34.5, 17.7, 17.6, 14.0. HRMS (ESI): calcd. For [C₁₃H₂₂O₅+H]⁺: 259.1540, Found: 259.1540.

A 2.03 g sample of bisketal **II-19b** (7.86 mmol) was placed in 250 mL flask, a 5 mL solution of TFA/H₂O (5:1 v/v) was added into the flask at RT when stirring. The mixture was continued to be stirred at RT for 15 min, then cooled down to 0 °C and diluted with 50 mL EtOAc, into which 20 mL saturated aqueous NaHCO₃, as well as 10 g NaHCO₃ (s) was slowly added to quench the reaction. The mixture was run through a pad of sand-silica gel-celite, rinsing with EtOAc-MeOH (10:1, v/v), and the effluent was dried over Na₂SO₄. The solution was concentrated under reduced pressure to give a residue. Crude ¹H NMR showed that a little isomerization on the α-methyl group happened with dr ratio 25:1. The residue was then subjected to chromatography on silica gel column. Elution with hexane-EtOAc (1:3) gave product diol (930 mg, 88%, dr ~15:1).

930 mg diol (6.46 mmol, dr ~15:1) was dissolved in 32 mL THF-CH₂Cl₂ (v/v 1:1) at RT, into which 73 mg DMAP was added in, followed by addition of a solution of 5.0 g Boc₂O (22.9 mmol) in 5 mL CH₂Cl₂. The mixture was stirred at RT for 2 hr, then it was cooled down to 0 °C, diluted with Et₂O 30 mL and quenched by 15 mL saturated aqueous NaHCO₃. The mixture was stirred at 0 °C for another 2 hr and then was extracted with Hexane-Et₂O (1:2 v/v) 150 mL X 2. The pooled organic layer was washed with 15 mL saturated aqueous NaCl and dried over Na₂SO₄. The solution was concentrated under reduced pressure to afford a residue.

The residue was redissolved in 35 mL CH₂Cl₂ at 0 °C. Into the solution 5.5 mL Et₃N was slowly added in. The mixture was then stirred at 0 °C overnight and continued to be stirred at RT for another 2 hr. Then it was cooled down to 0 °C, diluted with hexane-Et₂O (1:1 v/v) 130 mL and quenched by 50 mL 0.5 M NaHSO₄. The aqueous layer was then extracted with hexane-Et₂O (1:1 v/v) 150 mL X 2. The pooled organic layer was washed with 20 mL 0.5 M NaHSO₄, 20 mL saturated aqueous NaHCO₃, 20 mL saturated aqueous NaCl 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 enone **II-20** (1.23g, 84% overall for two steps, 40% with dr >25:1 and 44% with dr ~8:1).

II-20: White solid; mp: 64.7-66.1 °C, $R_f = 0.45$ (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20} +42$ (c 4.23, CHCl₃); IR (thin film, cm⁻¹) ν 2982, 2948, 1733, 1683, 1618, 1479, 1457, 1366, 1336, 1275, 1252, 1153, 1098, 1082, 974; ¹H NMR (CDCl₃, 270 MHz) δ 6.81 (ddd, $J = 10.2, 2.4, 1.8$ Hz, 1H), 5.99 (dd, $J = 9.0, 2.4$ Hz, 1H), 5.46 (dddd, $J = 10.8, 5.4, 2.4, 2.4$ Hz, 1H), 2.43 (m, 2H), 1.84 (ddd, $J = 14.4, 12.6, 10.4$ Hz, 1H), 1.5 (s, 9H), 1.15 (d, $J = 6.0$ Hz, 3H), ¹³C NMR (CDCl₃, 67.5 MHz) δ 200.0, 152.7, 147.9, 130.0, 82.9, 71.7, 39.9, 37.5, 27.7, 14.8; HRMS (ESI) calcd. for [C₁₂H₁₈O₄+H]⁺: 227.12779, Found: 227.12780.

***t*-Butyl (1*R*,4*R*,5*S*)-4-hydroxy-5-methylcyclohex-2-enyl carbonate (II-20a)**

To a solution of 545 mg enone **II-20** (2.41mmol, dr 10:1) in 35 mL THF at -78 °C was added 200 mg LiAlH₄ (5.26 mmol) in several portions. The reaction mixture was stirred at -78 °C for 30 min, then 2 mL acetone was added dropwise in at -78 °C and the mixture was stirred for another 20 min to quench the reaction. Then it was diluted with Et₂O 150 mL and 50 mL saturated aqueous NH₄Cl was added. The mixture was stirred at 0 °C for 15 min then aqueous layer was extracted with Et₂O 200 mL X 2. The pooled organic layer was washed with 20 mL saturated aqueous NH₄Cl, 20 mL saturated brine, dried over Na₂SO₄. The solution was concentrated under reduced pressure to give a residue. Crude ¹H NMR showed that there was three isomers with diastereomeric ratio 11:1:1.1. The two minor isomers were easily removed by chromatography on silica gel column, elution with hexane-EtOAc (5:1) afforded allylic alcohol **II-20a** (450 mg, 82%).

II-20a: White solid; mp: 100.2-101.7 °C; $R_f = 0.15$ (4:1 v/v hexane/EtOAc); $[\alpha]_D^{20} +95$ (c 1.90, CHCl₃); IR (thin film, cm⁻¹) ν 3515, 2977, 2941, 2878, 1713, 1458, 1396, 1351, 1366, 1334, 1284, 1257, 1153, 1076, 1054, 956; ¹H (CDCl₃, 600 MHz) δ 5.80 (ddd, $J = 10.2, 2.4, 1.8$ Hz, 1H), 5.73 (ddd, $J = 10.2, 3.6, 1.8$ Hz, 1H), 5.04 (dddd, $J = 9.6, 7.2, 2.4, 1.8$ Hz, 1H), 3.85 (ddd, J

= 9.0, 4.8, 2.4 Hz, 1H), 2.13 (dddd, J = 12.6, 5.4, 2.4, 1.8 Hz, 1H), 1.65 (dddd, J = 12.0, 9.6, 6.6, 3.0 Hz, 1H), 1.49 (s, 9H), 1.45 (ddd, J = 13.2, 13.2, 10.2 Hz, 1H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 153.1, 134.4, 128.4, 82.2, 73.3, 72.8, 37.3, 35.8, 27.8, 18.2; HRMS (ESI) calcd. for $[\text{C}_{12}\text{H}_{20}\text{O}_4+\text{Na}]^+$: 251.12538, Found: 251.12550.

***t*-Butyl (1*S*,5*S*)-5-methylcyclohex-3-enyl carbonate (**II-21**)**

To a solution of 312 mg allylic diol **II-20a** (1.37 mmol) in 6 mL *N*-methylmorpholine at -25 °C was added 1.07 g (4.1 mmol) PPh_3 , followed by dropwise addition of 0.81 mL DIAD, the mixture was stirred at -25 °C for 10 min, then 889 mg NBSH (4.1 mmol, *o*-nitrobenzenesulfonylhydrazide) was added in. It was stirred at -25 °C for 2 hr and then was warmed up and stirred at RT for another 2 hr. The reaction mixture was diluted with 120 mL hexane-Et₂O (1:1 v/v) and washed at 0 °C with 30 mL 0.5 M NaHSO_4 . The aqueous layer was extracted with hexane-Et₂O (1:1 v/v) 120 mL X 2. The pooled organic layer was washed with 30 mL 0.5 M NaHSO_4 again, then with 20 mL saturated aqueous NaHCO_3 , 20 mL saturated brine, dried over Na_2SO_4 . 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 **II-21** (260 mg, 89%).

II-21: Colorless oil; R_f = 0.69 (4:1 v/v hexane/EtOAc); $[\alpha]_D^{20}$ -55 (c 0.89, CHCl_3); IR (thin film, cm^{-1}) ν 3024, 2958, 2934, 2873, 1736, 1476, 1457, 1393, 1368, 1313, 1300, 1275, 1249, 1159, 1097, 1066, 983; ^1H NMR (CDCl_3 , 600 M): 5.53 (dddd, J = 9.6, 4.8, 2.4, 2.4 Hz, 1H), 5.47 (dddd, J = 10.2, 3.0, 3.0, 1.2 Hz, 2H), 4.77 (dddd, J = 12.0, 9.6, 6.0, 3.6 Hz, 1H), 2.41 (m, 2H), 2.10 (m, 1H), 1.49 (s, 9H), 1.29 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.02 (d, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 153.1, 133.2, 122.7, 81.8, 73.4, 37.2, 31.0, 30.9, 27.8, 21.3; HRMS (ESI) calcd. for $[\text{C}_{12}\text{H}_{20}\text{O}_3+\text{Na}]^+$: 235.13047, Found: 235.13049.

***t*-Butyl (3a*R*,4*S*,6*R*,7a*S*)-hexahydro-2,2,4-trimethylbenzo[d][1,3]dioxol-6-yl carbonate (II-22)**

To a solution of 138 mg olefin **II-21** (0.65 mmol) in 3 mL *t*-BuOH-Actone-50% NMO (aq.) (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 overnight, then 3 mL saturated aqueous Na₂S₂O₄ was added and it was stirred at 0 °C for another 3 hr. The reaction mixture was passed through a pad of sand-silica gel-celite, rinsing with EtOAc. The effluent was dried over Na₂SO₄ and concentrated under reduced pressure to give a residue. Crude ¹H-NMR showed that the diastereoselectivity is 11:1. The residue was subjected to chromatography on silica gel column, eluting with hexane-EtOAc (1:1.5) gave inseparable mixture of diol (156 mg, 95%, dr 11:1).

A 160 mg sample of diol (0.65 mmol, dr 11:1) was treated with 1 mL dimethoxypropane in the presence of 6.3 mg *p*-TsOH (0.033 mmol) at 0 °C for 2hr. It was diluted with 40 mL hexane-Et₂O (1:1 v/v) and quenched with 3 mL saturated aqueous NaHCO₃ at 0 °C. The aqueous layer was extracted with hexane-Et₂O (1:1 v/v) 40 mL X 2. The pooled organic layer was washed with 3 mL saturated brine, dried over Na₂SO₄. The solution was concentrated under reduced pressure to give a residue. The minor diastereomer was easily removed by chromatography on silica gel column, elution with hexane-EtOAc (25:1) afforded acetone **II-22** (155 mg, 83%).

II-22: Colorless oil; *R*_f = 0.51 (4:1 (v/v) hexane-EtOAc); [α]_D²⁰ +23 (*c* 1.74, CHCl₃); IR (thin film, cm⁻¹) ν 2982, 2933, 2874, 1736, 1459, 1368, 1276, 1242, 1218, 1156, 1101, 1065, 1042, 975; ¹H NMR (CDCl₃, 600 MHz) δ 4.84 (dddd, *J* = 10.8, 10.8, 4.2, 4.2 Hz, 1H), 4.31 (ddd, *J* = 4.8, 4.8, 2.4 Hz, 1H), 3.55 (dd, *J* = 9.0, 4.8 Hz, 1H), 2.44 (dddd, *J* = 14.4, 5.4, 3.0, 3.0 Hz, 1H), 1.96 (ddd, *J* = 12.6, 6.6, 3.6 Hz, 1H), 1.78 (ddd, *J* = 15.0, 10.8, 4.8 Hz, 1H), 1.73 (ddqd, *J* = 10.2,

10.2, 6.6, 3.6 Hz, 1H), 1.48 (s, 9H), 1.45 (s, 3H), 1.33 (s, 3H), 1.09 (ddd, $J = 12.6, 12.6, 10.2$ Hz, 1H), 1.03 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3OD , 150 MHz) δ 152.9, 108.4, 82.1, 80.4, 73.9, 71.8, 36.5, 33.5, 32.6, 28.5, 27.8, 26.1, 18.7; HRMS (ESI) calcd. for $[\text{C}_{15}\text{H}_{26}\text{O}_5\text{P}+\text{Na}]^+$: 309.16725, Found: 309.16729.

5a-Carba- β -D-digitoxopyranose (**II-8**)

To a solution of 16 mg carbonate **II-22** (0.06 mmol) in 2 mL THF at 0 °C was added 16 mg LiAlH_4 (0.42 mmol). The reaction mixture was warmed up and stirred at RT for 1 h, then it was diluted with 5 mL EtOAc and 1.5 mL saturated aqueous NaHCO_3 was added. It was stirred for another 20 min to quench the reaction and then the mixture was passed through a pad of sand-silica gel-celite, eluting with EtOAc. The effluent was dried over Na_2SO_4 . The solution was concentrated under reduced pressure to give a residue. The residue was redissolved in 1.5 mL THF-10% HCl (1:1 v/v) and the mixture was stirred at room temperature for 30 min. It was then cooled down to 0 °C, and diluted with 5 mL EtOAc, then 1 mL saturated aqueous NaHCO_3 and 250 mg NaHCO_3 (s) was slowly added to quench the reaction. The mixture was concentrated to a residue, which was directly loaded to a silica gel column. Elution with EtOAc-MeOH (20:1) gave cyclitol **II-8** (7 mg, 85%) as colorless oil; $R_f = 0.44$ (5:1 (v/v) EtOAc-MeOH); $[\alpha]_D^{20} +33$ (c 0.64, CHCl_3); IR (thin film, cm^{-1}) ν 3353, 2975, 2950, 2930, 1454, 1417, 1370, 1307, 1184, 1141, 1094, 1047, 980; ^1H NMR (CD_3OD , 600 MHz) δ 3.95 (ddd, $J = 3.0, 3.0, 2.4$ Hz, 1H), 3.94 (dddd, $J = 11.4, 11.4, 4.2, 4.2$ Hz, 1H), 3.06 (dd, $J = 10.2, 3.0$ Hz, 1H), 2.11 (dddd, $J = 13.2, 3.6, 3.6, 3.0$ Hz, 1H), 1.88 (dddd, $J = 12.0, 3.6, 3.6, 2.4$ Hz, 1H), 1.83 (ddqd, $J = 10.2, 10.2, 6.6, 3.6$ Hz, 1H), 1.39 (ddd, $J = 13.2, 11.4, 2.4$ Hz, 1H), 1.01 (ddd, $J = 12.6, 12.6, 11.4$ Hz, 1H), 1.00 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3OD , 150 MHz) δ 78.3, 71.7, 66.1, 43.4, 41.5, 32.4, 19.2; HRMS (ESI) calcd. for $[\text{C}_7\text{H}_{14}\text{O}_3-\text{H}]^-$: 145.0870, Found: 145.0871.

(2*R*,4*R*,5*R*)-4,5-dihydroxy-2-methylcyclohexanone (II-23)

A 500 mg sample of bisketal **II-19a** (1.94 mmol, dr ~10:1) was placed in 250 mL flask at 0 °C, and 3.7 mL solution of TFA/H₂O (5:1 v/v) was added into the flask at 0 °C when stirring. The mixture was stirred at 0 °C for 20 min, then was diluted with 30 mL EtOAc, into which 10 mL saturated aqueous NaHCO₃, as well as 6 g NaHCO₃ (s) was slowly added to quench the reaction. The mixture was run through a pad of sand-silica gel-celite, rinsing with EtOAc-MeOH (10:1, v/v), and the effluent was dried over Na₂SO₄. The solution was concentrated under reduced pressure to give a residue. Crude ¹H NMR showed that a little isomerization on the α-methyl group happened, which lower the dr to ~8:1. The residue was then purified by silica gel column. Elution with hexane-EtOAc (1:3) gave pure diol **II-23** (195 mg, 70%) with the minor isomer removed.

II-23: White solid; mp: 67.9-69.2 °C; *R*_f = 0.50 (10:1 (v/v) EtOAc/MeOH); [α]_D²⁰ -13 (*c* 2.6, CHCl₃); IR (thin film, cm⁻¹) ν 3373, 3280, 2969, 2924, 1694, 1437, 1421, 1399, 1380, 1276, 1229, 1165, 1123, 1094, 1071, 1032, 967; ¹H NMR (CDCl₃, 600 MHz) δ 4.19 (dddd, *J* = 4.8, 4.2, 3.6, 3.2 Hz, 1H), 4.02 (dddd, *J* = 4.2, 3.6, 3.6, 3.6 Hz, 1H), 2.91 (ddd, *J* = 14.4, 3.6, 0.6 Hz, 1H), 2.78 (ddq, *J* = 7.8, 7.2, 6.6 Hz, 1H), 2.42 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.14 (d, *J* = 3.0 Hz, 1H), 2.07 (d, *J* = 3.6 Hz, 1H), 2.00 (dd, *J* = 8.4, 4.2 Hz, 1H), 1.99 (dd, *J* = 8.4, 3.6 Hz, 1H), 1.08 (d, *J* = 6.6 Hz, 1H); ¹³C NMR (CDCl₃, 150 MHz) δ 211.9, 74.0, 69.0, 44.5, 40.1, 36.9, 14.7; HRMS (ESI) calcd. for [C₇H₁₂O₃+H]⁺: 145.0859, Found: 145.0859.

***t*-Butyl (1*R*,5*R*)-5-methyl-4-oxocyclohex-2-enyl carbonate ((*ent*)-II-15)**

142 mg diol **II-23** (1.0 mmol) was dissolved in 7.5 mL THF-CH₂Cl₂ (1:2 v/v) at RT, into which 12 mg DMAP (0.1 mmol) was added in, followed by addition of a solution of 870 mg Boc₂O (4 mmol) in 2.5 mL CH₂Cl₂. The mixture was stirred at RT for 2 h, then it was cooled down to 0 °C, diluted with Et₂O 30 mL and was then quenched with 7 mL saturated aqueous NaHCO₃. The mixture was stirred at 0 °C for another 2 h and then was extracted with Hexane-Et₂O (1:2 v/v) 30 mL x 2. The pooled organic layer was washed with 7 mL saturated aqueous NaCl and dried over Na₂SO₄. The solution was concentrated under reduced pressure to afford a residue. The residue was redissolved in 6.5 mL CH₂Cl₂ at 0 °C. Into the solution 1.0 mL Et₃N (5 mmol) was slowly added in. 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-Et₂O (1:1 v/v) 40 mL and it was then quenched by 10 mL 0.5 M NaHSO₄ at 0 °C. The aqueous layer was extracted with hexane-Et₂O (1:1 v/v) 40 mL x 2. The pooled organic layer was washed with 10 mL 0.5 M NaHSO₄ at 0 °C, then was washed with 10 mL saturated aqueous NaHCO₃, 10 mL saturated aqueous NaCl and dried over Na₂SO₄. 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 (*ent*)-**II-15** (200 mg, 90%) as white solid; mp: 37.5-38.9 °C; *R*_f = 0.44 (4:1 (v/v) hexane/EtOAc); [α]_D²⁰ +168 (*c* 1.0, CHCl₃); IR (thin film, cm⁻¹) *ν* 2980, 2935, 2875, 1735, 1684, 1459, 1369, 1341, 1272, 1252, 1155, 1080, 1044, 965; ¹H NMR (CDCl₃, 600 MHz) δ 6.86 (dd, *J* = 10.2, 4.2 Hz, 1H), 6.03 (d, *J* = 10.2 Hz, 1H), 5.29 (ddd, *J* = 4.8, 4.8, 4.2 Hz, 1H), 2.76 (dq, *J* = 10.2, 7.2, 5.4 Hz, 1H), 2.25 (dddd, *J* = 14.4, 4.8, 4.8, 0.6 Hz, 1H), 2.06 (ddd, *J* = 14.4, 9.6, 4.8 Hz, 1H), 1.49 (s, 9H), 1.15 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 200.9, 152.9, 143.3, 131.2, 82.9, 68.1, 37.7, 35.4, 27.7, 14.9; HRMS (ESI) calcd. for [C₁₂H₁₈O₄+Na]⁺: 249.1097, Found: 249.1097.

(1*R*,3*R*,4*S*,6*S*)-bicyclo[4.1.0]heptane-1,3,4-triol (II-24)

A solution of 1.39 g (7.5 mmol) of **II-9b** was dissolved in 6 mL THF-10% HCl (1:1 v/v) and stirred at room temperature for 15 min. The mixture was cooled down to 0 °C, and diluted with 70 mL EtOAc, then ~5 g NaHCO_3 (s) was slowly added to quench the reaction. The mixture was filtered through a glass wool and the liquid was concentrated to a residue which was loaded to a silica gel column. Elution with EtOAc-MeOH (10:1 v/v) gave triol **II-24** (1.0 g, 82%).

II-24: Colorless oil; R_f = 0.38 (5:1 (v/v) EtOAc/MeOH); $[\alpha]_D^{20}$ 0.71 (c 7.03, MeOH); IR (thin film, cm^{-1}) ν 3304, 3009, 2924, 1432, 1362, 1276, 1218, 1183, 1093, 1045, 914; ^1H NMR (CD_3OD , 600 MHz) δ 3.82 (ddd, J = 5.4, 5.4, 2.4 Hz, 1H), 3.70 (ddd, J = 7.8, 5.4, 1.8 Hz, 1H), 2.36 (ddd, J = 14.4, 6.0 Hz, 1H), 2.11 (dd, J = 14.4, 5.4 Hz, 1H), 2.09 (ddd, J = 13.8, 8.4, 6.0 Hz, 1H), 1.64 (ddd, J = 14.4, 8.4, 1.8 Hz, 1H), 0.97 (dddd, J = 10.2, 8.4, 8.4, 2.4 Hz, 1H), 0.80 (m, 2H); ^{13}C NMR (CD_3OD , 150 MHz) δ 70.5, 70.3, 53.5, 38.3, 29.7, 21.9, 18.9; HRMS (ESI): calcd. for $[\text{C}_7\text{H}_{12}\text{O}_3 + \text{Na}]^+$: 167.06787, Found: 167.06785.

(2*R*,4*S*,5*R*)-4,5-dihydroxy-2-methylcyclohexanone (**II-25**)

Into a solution of 200 mg (1.39 mmol) cyclopropanol **II-24** in 4.5 mL THF-EtOH (1:1 v/v) was added 80 mg 10% Pd/C. The solution was degassed using vacuum and refilled with H_2 three times at low temperature (~-30 °C). Then at room temperature, the solution was stirred 5 hr under balloon pressure of H_2 . It was filtered through a filter paper and rinsed with ethyl acetate. The solution was concentrated under reduced pressure to a small volume (some of the solution

was taken out and concentrated to dry, then a crude NMR was taken to show that NO diastereomer was seen). The residue was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (1:4) gave product **II-25** (160 mg, 80%).

II-25: White solid; mp: 76-78 °C; R_f = 0.55 (5:1 (v/v) EtOAc/MeOH); $[\alpha]_D^{20}$ -19 (c 1.47, MeOH); IR (thin film, cm^{-1}) ν 3366, 2940, 2918, 2863, 1696, 1447, 1405, 1380, 1315, 1244, 1213, 1160, 1097, 1036, 1008, 973, 937; ^1H NMR (CDCl_3 , 600 MHz) δ 4.26 (ddd, J = 5.4, 3.0, 3.0 Hz, 1H), 4.13 (ddd, J = 11.4, 4.2, 2.4 Hz, 1H), 3.83 (brs, 1H), 3.66 (brs, 1H), 2.55 (ddd, J = 14.4, 3.0, 0.6 Hz, 1H), 2.51 (dd, J = 15.0, 3.6 Hz, 1H), 2.43 (dq, J = 12.6, 6.6, 6.0 Hz, 1H), 2.03 (dddd, J = 12.0, 6.0, 4.8, 1.8 Hz, 1H), 1.82 (ddd, J = 12.6, 12.6, 12.0 Hz, 1H), 0.99 (d, J = 6.0 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 211.3, 72.1, 70.0, 45.8, 41.8, 36.3, 14.2; HRMS (ESI): calcd. for $[\text{C}_7\text{H}_{12}\text{O}_3 + \text{H}]^+$: 145.08592, Found: 145.08589.

X-Ray Crystal data: Empirical formula $\text{C}_7\text{H}_{12}\text{O}_3$; formula weight 144.17; Temperature 293(2) K; wavelength 0.71073 Å; crystal system monoclinic; space group $P2_1$; unit cell dimensions $a=5.7707(9)\text{Å}$, $b=8.6125(13)\text{Å}$, $c=7.7163(12)\text{Å}$, $\alpha=90^\circ$, $\beta=105.997(3)^\circ$, $\gamma=90^\circ$; volume $368.6(1)\text{Å}^3$; $Z=2$; density (calculated) 1.299 g/cm^3 ; absorption coefficient 1.01cm^{-1} ; $F(000)$ 156; crystal size 0.16 X 0.18 X 0.50 mm; θ range for data collection 3.63 to 27.50° ; index ranges $-7 \leq h \leq 7$, $-11 \leq k \leq 10$, $-9 \leq l \leq 10$; reflections collected 2356; independent reflections 1230 [$R(\text{int})=0.0318$]; completeness to $\theta=27.50^\circ$ 96.7%; refinement method Full-matrix least-squares on F^2 ; data/restraints/parameters 1230/1/94; goodness-of-fit on F^2 1.022; final R indices [$I > 2\sigma(I)$] $R1=0.0460$, $wR2=0.1213$; R indices (all data) $R1=0.0494$, $wR2=0.1253$; absolute structure parameter -0.3(15); largest diff. peak and hole 0.364 and -0.178 e/Å^3 .

(4*S*,6*R*)-4-hydroxy-6-methylcyclohex-2-enone (**II-12b**)

A solution of 1.88 g diol **II-25** (13.1 mmol) in 70 mL CH₂Cl₂ was added 159 mg (1.31 mmol) DMAP at 0 °C, then 7.9 mL (9.80 mmol) pyridine was injected in. Then a solution of 3.8 g (13.1 mmol) triphosgene in 20 mL CH₂Cl₂ was slowly injected in at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr. The solution was then diluted with 150 mL hexane-EtOAc (1:2 v/v), and added 25 mL 0.5 M NaHSO₄, it was stirred for ~10 min at 0 °C. The aqueous layer was then extracted with hexane-EtOAc (1:2 v/v) 150 mL X 2. The pooled organic layer was washed with 25 mL 0.5 M NaHSO₄ at 0 °C, then washed with 20 mL saturated aqueous NaHCO₃, 20 mL saturated aqueous NaCl, dried over Na₂SO₄. Concentration of the solution under reduced pressure gave a residue. Then the residue was redissolved in 50 mL CH₂Cl₂ at 0 °C, into which 7.2 mL (52.2 mmol) Et₃N was added slowly. The mixture was stirred overnight at 0 °C and continued to be stirred at room temperature for another 1 hour. Then the mixture was diluted with hexane-EtOAc (1:1 v/v) 200 mL and cooled down to 0 °C, then was quenched with 25 mL 0.5 M NaHSO₄ at 0 °C. The aqueous layer was then extracted with hexane-EtOAc (1:1 v/v) 150 mL X 2. The pooled organic layer was washed with 25 mL 0.5 M NaHSO₄ at 0 °C again, then it was washed with 25 mL saturated aqueous NaHCO₃, 25 mL saturated aqueous NaCl, dried over Na₂SO₄. Concentration of the solution under reduced pressure gave a residue, which was purified by silica gel column. Elution with hexane-EtOAc (2:3, v/v) gave product allylic alcohol **II-12b** (1.2 g, 73%).

II-12b: Colorless oil; R_f = 0.40 (1:2 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -65 (c 2.38, CHCl₃); IR (thin film, cm⁻¹) ν 3406, 3036, 2968, 2934, 2870, 1668, 1457, 1376, 1252, 1214, 1182, 1100, 1067, 1027, 952; ¹H NMR (CDCl₃, 270 MHz) δ 6.87 (ddd, J = 10.2, 1.8, 1.8 Hz, 1H), 5.96 (dd, J = 10.2, 2.4 Hz, 1H), 4.64 (d, J = 8.4 Hz, 1H), 2.40 (dq, J = 13.2, 6.6, 4.8 Hz, 1H), 2.37 (dddd, J = 12.0, 5.4, 4.8, 2.4 Hz 1H), 1.73 (ddd, J = 13.8, 13.2, 10.8 Hz 1H), 1.16 (d, J = 6.6 Hz, 3H), ¹³C NMR (CDCl₃, 150 MHz) δ 201.2, 152.9, 128.7, 67.4, 41.4, 40.1, 14.9; HRMS (ESI) calcd. for [C₇H₁₀O₂+H]⁺: 127.07536, Found: 127.07535.

(1*R*,5*R*)-5-methyl-4-oxocyclohex-2-enyl 4-nitrobenzoate (II-26)

To a solution of 710 mg allylic diol **II-12b** (5.6 mmol) in 40 mL THF at 0 °C was injected a solution of 1.14 g (6.8 mmol) *p*-nitrobenzoic acid in 10 mL THF, followed by a injection of a solution of 1.79 g PPh₃ (6.8 mmol) in 10 mL THF. Then at 0 °C 1.65 mL (7.1 mmol) DIAD was added dropwise. The mixture was stirred at 0 °C for 1 hr. The mixture was diluted with 150 mL hexane-Et₂O (1:2 v/v) and was washed with 15 mL 0.5 M NaHSO₄ at 0 °C. The aqueous layer was extracted with hexane-Et₂O (1:2 v/v) 120 mL X 2 at 0 °C. The pooled organic layer was washed with 20 mL saturated aqueous NaHCO₃, 20 mL saturated brine, dried over Na₂SO₄. The organic layer was concentrated under reduced pressure to give crude product, which was then subjected to chromatography on silica gel column. Elution with hexane-EtOAc (7:1 v/v) gave ester **II-26** (1.28g, 95%).

II-26: Pale yellow solid; mp: 119-120.5 °C; *R*_f = 0.42 (3:1 (v/v) hexane/EtOAc); [α]_D²⁰ +265 (*c* 6.24, CHCl₃); IR (thin film, cm⁻¹) ν 3112, 3086, 2992, 2970, 2933, 2874, 1718, 1676, 1607, 1523, 1343, 1321, 1274, 1222, 1205, 1099, 1063, 1045, 1009, 931; ¹H NMR (CDCl₃, 600 MHz) δ 8.31 (d, *J* = 9.0 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 6.95 (dd, *J* = 10.2, 4.2 Hz, 1H), 6.16 (d, *J* = 10.2 Hz, 1H), 5.78 (ddd, *J* = 4.8, 4.2, 4.2 Hz, 1H), 2.85 (dq, *J* = 12.0, 7.2, 2.4 Hz, 1H), 2.37 (ddd, *J* = 13.8, 4.8, 4.8 Hz 1H), 1.73 (ddd, *J* = 14.4, 10.2, 4.2 Hz 1H), 1.25 (d, *J* = 7.2 Hz, 3H), ¹³C NMR (CDCl₃, 150 MHz) δ 200.6, 164.1, 150.8, 142.6, 135.1, 132.0, 130.9, 123.7, 67.3, 37.9, 35.5, 15.0; HRMS (ESI) calcd. for [C₁₄H₁₃NO₅+Na]⁺: 298.06859, Found: 298.06865.

(1*R*,4*S*,5*R*)-4-hydroxy-5-methylcyclohex-2-enyl 4-nitrobenzoate (II-27)

To a solution of 1.28 g ester **II-26** (4.64 mmol) in 60 mL THF at -78 °C was slowly added 330 mg (8.68 mmol) LiAlH₄ in portions. The reaction mixture was stirred at -78 °C for 30 min, then 6 mL acetone was added dropwise in at -78 °C to quench the reaction, which was stirred at -78 °C for 30 min. It was then diluted with 360 mL hexane-EtOAc (1:5 v/v) and slowly 30 mL saturated aqueous NH₄Cl was added in. It was then allowed to stir at 0 °C for 20 min. The organic layer was washed again with 30 mL saturated aqueous NH₄Cl, then washed with 30 mL saturated brine, dried over Na₂SO₄. The solution was concentrated under reduced pressure to give a residue. A crude ¹H NMR showed that the diastereoselectivity is 11:1. The residue was subjected to chromatography on silica gel column and elution with hexane-EtOAc (4:1) afforded allylic alcohol **II-27** (1.16 g, 91%).

II-27: White solid; mp: 77.2-78.5 °C; *R*_f = 0.55 (1:1 (v/v) hexane/EtOAc); [α]_D²⁰ +197 (*c* 3.52, CHCl₃); IR (thin film, cm⁻¹) *ν* 3272, 3113, 3039, 2959, 2909, 2889, 1717, 1607, 1521, 1460, 1338, 1270, 1116, 1101, 1056, 1038, 1009, 958, 903; ¹H NMR (CDCl₃, 600 MHz) δ 8.30 (d, *J* = 9.0 Hz, 1H), 8.20 (d, *J* = 9.6 Hz, 1H), 6.05 (dd, *J* = 10.2, 2.4 Hz, 1H), 5.92 (dddd, *J* = 10.2, 4.2, 1.8, 1.8 Hz, 1H), 5.47 (ddd, *J* = 6.0, 4.2, 1.8 Hz, 1H), 3.81 (ddd, *J* = 9.0, 3.6, 2.4 Hz, 1H), 2.01 (dddd, *J* = 15.0, 3.0, 1.8, 1.8 Hz 1H), 1.92 (ddqd, *J* = 12.0, 9.0, 6.6, 3.0 Hz 1H), 1.71 (ddd, *J* = 14.4, 12.0, 4.2 Hz 1H), 1.14 (d, *J* = 6.6 Hz, 3H), ¹³C NMR (CDCl₃, 150 MHz) δ 164.2, 150.5, 137.5, 135.8, 130.7, 125.0, 123.5, 73.1, 68.2, 34.3, 32.9, 18.1; HRMS (ESI) calcd. for [C₁₄H₁₅NO₅+Na]⁺: 300.08424, Found: 300.08421.

(1R,2R,3R,4S,5R)-2,3,4-trihydroxy-5-methylcyclohexyl-4-nitrobenzoate (II-28)

To a solution of 30 mg olefin **II-27** (0.11 mmol) in 1.5 mL *t*-BuOH-actone-50% NMO_(aq.) (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 overnight, then 1.5 mL saturated aqueous Na₂S₂O₃ was added and it was stirred at 0 °C for another 2 h. The reaction mixture was passed through a pad of sand-silica gel-celite, rinsing with EtOAc-MeOH (10:1, v/v). The effluent was dried over Na₂SO₄ and concentrated under reduced pressure to give a residue, which was purified by silica gel column. Elution with EtOAc-MeOH (20:1) gave triol **II-28** (32 mg, 94%) as white solid; mp: 203-204 °C; *R_f* = 0.20 (1:2 (v/v) hexane/EtOAc); [α]_D²⁰ -33 (*c* 0.54, MeOH); IR (thin film, cm⁻¹) ν 3351, 2925, 1715, 1608, 1525, 1408, 1346, 1314, 1275, 1159, 1122, 1102, 1078, 1052, 1009, 952; ¹H NMR (CD₃OD, 600 MHz) δ 8.33 (d, *J* = 9.0 Hz, 2H); 8.22 (d, *J* = 9.0 Hz, 2H); 5.20 (ddd, *J* = 4.2, 2.4, 2.4 Hz, 1H), 4.05 (dd, *J* = 3.0, 3.0 Hz, 1H), 3.65 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.39 (dd, *J* = 9.6, 9.6 Hz, 1H), 1.82 (m, 3H), 1.07 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (CD₃OD, 150 MHz) δ 165.2, 152.3, 137.0, 131.9, 124.9, 76.3, 75.4, 74.8, 72.0, 34.1, 33.1, 18.5; HRMS (ESI) calcd. for [C₁₄H₁₇O₇+Na]⁺: 334.0897, Found: 334.0896.

5a-Carba- α -L-rhamnopyranose ((*ent*)-**II-7**)

To a solution of 25 mg ester **II-28** (0.08 mmol) in 1.5 mL MeOH was added 3.0 mg LiOH (0.12 mmol) at RT. The reaction mixture was stirred at RT for 4 h. Then 0.5 mL saturated aqueous NH₄Cl was added. This small amount of mixture was directly loaded onto a silica gel column. Elution with EtOAc-MeOH (10:1) afforded cyclitol (*ent*)-**II-7** (11 mg, 85%) as colorless oil; *R_f* =

0.28 (5:1 (v/v) EtOAc/MeOH); $[\alpha]_D^{20} +11$ (c 0.65, MeOH); IR (thin film, cm^{-1}) ν 3297, 2922, 1455, 1406, 1377, 1296, 1239, 1186, 1153, 1050, 1002, 964; ^1H NMR (CD_3OD , 600 MHz) δ 3.87 (dd, $J = 3.6, 3.6$ Hz, 1H), 3.83 (ddd, $J = 3.0, 3.0, 3.0$ Hz, 1H), 3.62 (dd, $J = 9.6, 3.0$ Hz, 1H), 3.26 (dd, $J = 10.2, 9.6$ Hz, 1H), 1.78 (ddqd, $J = 9.6, 9.6, 6.6, 6.6$ Hz, 1H), 1.59 (m, 2H), 1.01 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3OD , 150 MHz) δ 76.9, 75.0, 74.3, 71.1, 35.9, 33.1, 18.6; HRMS (ESI) calcd. for $[\text{C}_7\text{H}_{14}\text{O}_4 + \text{Na}]^+$: 185.0784, Found: 185.0784.

(4*S*,6*S*)-4-hydroxy-6-methylcyclohex-2-enone (II-38)

A solution of 234 mg diol **II-13** (1.63 mmol) in 8.5 mL CH_2Cl_2 was added 19 mg (0.16 mmol) DMAP at 0 °C, then 0.46 mL (5.69 mmol) pyridine was slowly added via syringe. Then a solution of 250 mg (0.81 mmol) triphosgene in 2 mL CH_2Cl_2 was slowly injected in at 0 °C. The reaction mixture was stirred at 0 °C for 2 hr. The solution was then diluted with 80 mL EtOAc, and quenched with 8 mL 0.5 M NaHSO_4 . The aqueous layer was then extracted with EtOAc 50 mL X 2. The pooled organic layer was washed with 10 mL saturated aqueous NaHCO_3 , 10 mL saturated aqueous NaCl , dried over Na_2SO_4 . Concentration of the solution under reduced pressure gave a residue. Then the residue was redissolved in 6.5 mL CH_2Cl_2 at 0 °C, into which 0.8 mL (5.8 mmol) Et_3N was added. The mixture was stirred overnight at 0 °C and continued to be stirred at room temperature for another 1 hour. Then the mixture was diluted with EtOAc 120 mL EtOAc, and cooled down to 0 °C then was quenched with 20 mL 0.5 M NaHSO_4 at 0 °C. The aqueous layer was then extracted with EtOAc 50 mL X 2. The pooled organic layer was washed with 15 mL saturated aqueous NaHCO_3 , 15 mL saturated aqueous NaCl , dried over Na_2SO_4 . Concentration of the solution under reduced pressure gave a residue, which was purified by silica gel column. Elution with hexane-EtOAc (3:2, v/v) gave product allylic alcohol **II-38** (150 mg, 73%)

II-38: Colorless oil; $R_f = 0.40$ (1:2 (v/v) hexane/EtOAc); $[\alpha]_D^{20} -145$ (c 1.72, CHCl_3); IR (thin film, cm^{-1}) ν 3412, 3036, 2967, 2934, 2875, 1664, 1454, 1380, 1252, 1056; ^1H NMR (CDCl_3 , 270 MHz) δ 6.86 (dd, $J = 10.1, 3.9$ Hz, 1H), 5.96 (dd, $J = 10.1, 1.0$ Hz, 1H), 4.55 (ddd, $J = 4.7, 4.7, 4.5$ Hz, 1H), 2.76 (ddd, $J = 7.4, 7.4, 5.2$ Hz, 1H), 2.11 (m, 2H), 1.17 (d, $J = 7.2$ Hz, 3H), ^{13}C NMR (CDCl_3 , 67.5 MHz) δ 201.9, 148.3, 129.2, 63.5, 38.8, 37.8, 15.3; HRMS (ESI) calcd. for $[\text{C}_7\text{H}_{10}\text{O}_2 + \text{H}]^+$: 127.07536, Found: 127.07535.

Dibenzyl (1S,5S)-5-methyl-4-oxocyclohex-2-enyl phosphate (II-39)

Into a solution of 54 mg allylic alcohol **II-38** (0.43 mmol) in 1.8 mL CH_2Cl_2 was added a solution of 0.36 mL 85% N,N -diethyl dibenzylphosphoramidite (1.1 mmol) in 1.5 mL CH_2Cl_2 at room temperature followed by addition of 2.5 mL 0.45 M 1*H*-tetrazole in acetonitrile (1.1 mmol). The mixture was stirred at RT for 1 hr. Then it was cooled down to 0 °C, and added 1.5 mL 30% H_2O_2 . It was stirred at 0 °C for 15 min. Into the mixture 2 mL saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ was added and it was then stirred 0 °C for 2 hr. The mixture was extracted with EtOAc 30 mL X 2. The organic layer was washed with 4 mL saturated aqueous NaHCO_3 , 4 mL saturated aqueous NaCl, dried over Na_2SO_4 , and concentrated under reduced pressure to give a residue which was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (1:1) afforded phosphate **II-39** (126 mg, 76%).

II-39: Colorless oil; $R_f = 0.48$ (1:2 (v/v) hexane/EtOAc); $[\alpha]_D^{20} -43$ (c 3.09, CHCl_3); IR (thin film, cm^{-1}) ν 3035, 2965, 1683, 1498, 1456, 1381, 1269, 1215, 981; ^1H NMR (CDCl_3 , 600 MHz) δ 7.36 (m, 10H), 6.69 (ddd, $J = 10.2, 4.8, 1.2$ Hz, 1H), 5.96 (d, $J = 10.2$ Hz, 1H), 5.09 (ddd, $J = 11.4, 8.4, 5.4$ Hz, 2H), 5.04 (ddd, $J = 12.0, 9.0, 3.6$ Hz, 2H), 4.99 (dddd, $J = 7.8, 4.2, 4.2, 4.2$ Hz, 1H), 2.64 (dq, $J = 9.6, 7.2, 4.8$ Hz, 1H), 2.18 (dddd, $J = 14.4, 4.8, 4.8, 1.2$ Hz, 1H), 1.94 (dddd, $J = 14.4, 10.2, 4.2, 1.2$ Hz, 1H), 1.08 (d, $J = 6.6$ Hz, 1H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 200.7,

143.2 (d, $J = 4.6$ Hz), 135.6 (d, $J = 5.2$ Hz), 131.0, 128.7, 128.6, 128.0 (d, $J = 5.2$ Hz), 69.6 (d, $J = 5.7$ Hz), 69.5 (d, $J = 5.2$ Hz), 37.3, 36.7 (d, $J = 4.5$ Hz), 14.7; HRMS (ESI) calcd. for $[\text{C}_{21}\text{H}_{23}\text{O}_5\text{P}+\text{Na}]^+$: 409.11753, Found: 409.11727.

(2*S*,4*R*)-4-hydroxy-2-methylcyclohexanone (II-40)

To a solution of 52 mg allylic alcohol **II-38** (0.41 mmol) in 4 mL MeOH was added 30 mg 10% Pd/C. The reaction mixture was degassed using vacuum and refilled with H_2 at ~ -30 °C three times. The reaction was stirred under balloon pressure of H_2 at room temperature for 3 hr. The reaction mixture was filtered and rinsed with EtOAc and concentrated under reduced pressure to give a residue, which was loaded onto silica gel column. Elution with hexane-EtOAc (3:2) gave saturated alcohol **II-40** (43 mg, 72%). **II-40**: Colorless oil; $R_f = 0.43$ (1:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20} +6$ (c 1.7, CHCl_3); IR (thin film, cm^{-1}) ν 3407, 2966, 2931, 1697, 1436, 1349, 1318, 1257, 1138, 1111, 1011, 950; ^1H NMR (CDCl_3 , 600 MHz) δ 4.25 (dddd, $J = 3.6, 3.0, 2.4, 2.4$ Hz, 1H), 2.90 (m, 1H), 2.76 (ddd, $J = 13.2, 13.2, 6.0$ Hz, 1H), 2.27 (ddd, $J = 13.8, 4.8, 2.4$ Hz, 1H), 2.15 (m, 2H), 1.92 (dddd, $J = 13.8, 13.8, 5.4, 3.0$ Hz, 1H), 1.63 (ddd, $J = 12.6, 12.6, 2.4$ Hz, 1H), 1.03 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 213.1, 65.3, 42.5, 39.2, 36.2, 34.3, 14.3; HRMS (ESI) calcd. for $[\text{C}_7\text{H}_{12}\text{O}_2+\text{H}]^+$: 129.09101, Found: 129.09102.

Dibenzyl (1*R*,3*S*)-3-methyl-4-oxocyclohexyl phosphate (II-41)

Into a solution of 20 mg alcohol **II-40** (0.16 mmol) in 0.5 mL CH₂Cl₂ was added a solution of 0.14 mL 85% N,N-diethyl dibenzylphosphoramidite (0.43 mmol) in 0.5 mL CH₂Cl₂ at room temperature followed by addition of 0.95 mL 0.45 M 1*H*-tetrazole in acetonitrile (0.43 mmol). The mixture was stirred at RT for 1 hr. Then it was cooled down to 0 °C, and slowly added 0.75 mL 30% H₂O₂. It was stirred at 0 °C for 15 min. Into the mixture, 2 mL saturated aqueous Na₂S₂O₃ was added and it was then stirred at 0 °C for 2 hr. The mixture was extracted with EtOAc 30 mL X 2. The organic layer was washed with 4 mL saturated aqueous NaHCO₃, 4 mL saturated aqueous NaCl, dried over Na₂SO₄, and concentrated under reduced pressure to give a residue which was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (1:1) afforded phosphate **II-41** (42 mg, 70%).

II-41: Colorless oil; R_f = 0.36 (1:2 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -3 (*c* 2.2, MeOH); IR (thin film, cm⁻¹) ν 3035, 2934, 1712, 1497, 1455, 1270, 990; ¹H NMR (CD₃OD, 600 MHz) δ 7.38 (m, 10H), 5.13 (dd, *J* = 12.0, 9.6 Hz, 2H), 5.09 (dd, *J* = 12.0, 10.2 Hz, 2H), 4.73 (m, 1H), 2.58 (ddd, *J* = 19.8, 12.6, 6.6 Hz, 1H), 2.52 (ddd, *J* = 14.4, 14.4, 5.4 Hz, 1H), 2.19 (m, 1H), 2.13 (ddd, *J* = 14.4, 4.8, 2.4 Hz, 1H), 1.87 (dddd, *J* = 11.8, 11.8, 4.8, 2.4, 2.4 Hz, 1H), 1.58 (dddd, *J* = 11.8, 11.8, 2.4, 2.4 Hz, 1H), 0.89 (d, *J* = 6.6 Hz, 1H); ¹³C NMR (CD₃OD, 150 MHz) δ 213.6, 137.5 (d, *J* = 5.7 Hz), 137.4 (d, *J* = 5.7 Hz), 130.0, 129.9, 129.4 (d, *J* = 2.2 Hz), 75.6 (d, *J* = 5.7 Hz), 71.1 (d, *J* = 5.7 Hz), 41.4 (d, *J* = 1.6 Hz), 40.3, 37.0, 33.5 (d, *J* = 4.6 Hz), 14.4; HRMS (ESI) calcd. for [C₂₁H₂₅O₅P+H]⁺: 389.15124, Found: 389.15117.

(1*R*,3*S*)-3-methyl-4-oxocyclohexyl dihydrogen phosphate (**II-31**)

38 mg 10% Pd/C was first washed with HPLC grade MeOH 2 mL X 2, then it was transferred with another 2 mL HPLC grade MeOH to 25 mL flask which contained 22 mg dibenzyl phosphate **II-41** (0.06 mmol). The mixture was degassed using vacuum and refilled with H₂ at ~-

30 °C three times. The reaction was stirred under balloon pressure of H₂ at room temperature for 3 hr. The reaction mixture was filtered and rinsed with HPLC grade MeOH and concentrated under reduced pressure to give a residue, which was then treated under vacuum at RT overnight to afford phosphate **II-31** (8.5 mg, 73%). ¹H and ³¹P NMR show it is a mixture of two epimers on the α-methyl group (dr α:β 2:1).

II-31 (dr α:β 2:1): Colorless oil; [α]_D²⁰ -4 (c 0.74, MeOH); IR (thin film, cm⁻¹) ν 3500-2500 (broad), 2936, 1702, 1456, 1378, 1150, 1013, 990; HRMS (ESI) calcd. for [C₇H₁₃O₅P-H]⁻: 207.04278, Found: 207.04273.

II-31α: (α isomer) ¹H NMR (D₂O, 600 MHz) δ 3.01 (ddd, *J* = 18.6, 12.6, 6.0 Hz, 1H), 2.85 (ddd, *J* = 13.8, 13.8, 6.0 Hz, 1H), 2.36 (m, 3H), 2.02 (dd, *J* = 14.4, 13.8 Hz, 1H), 1.77 (dd, *J* = 13.8, 13.2 Hz, 1H), 1.03 (d, *J* = 6.6 Hz, 1H); ¹³C NMR (D₂O, 150 MHz) δ 220.0, 71.1 (d, *J* = 5.1 Hz), 40.6 (d, *J* = 3.8 Hz), 39.6, 36.2, 32.7 (d, *J* = 4.5 Hz), 13.6; ³¹P NMR (D₂O, 242 MHz) δ 0.66;

II-31β: (β epimer) ¹H NMR (D₂O, 600 MHz) δ 2.75 (ddd, *J* = 19.8, 13.2, 6.6 Hz, 1H), 2.63 (ddd, *J* = 14.4, 14.4, 7.8 Hz, 1H), 2.36 (m, 3H), 1.89 (dd, *J* = 15.0, 15.0, 4.8 Hz, 1H), 1.68 (dd, *J* = 13.8, 13.2 Hz, 1H), 1.05 (d, *J* = 6.6 Hz, 1H); ¹³C NMR (D₂O, 150 MHz) δ 218.4, 72.8 (d, *J* = 5.7 Hz), 41.7, 40.8 (d, *J* = 4.5 Hz), 37.8, 33.0 (d, *J* = 3.9 Hz), 13.9; ³¹P NMR (D₂O, 242 MHz) δ 0.46;

Dibenzyl (1*S*,4*R*,5*S*)-4-hydroxy-5-methylcyclohex-2-enyl phosphate (**II-42**)

To a solution of 89 mg phosphate **II-39** (0.23 mmol) in 3.5 mL THF at -78 °C was added 20 mg LiAlH₄ (0.50 mmol). The reaction mixture was stirred at -78 °C for 30 min, then 1 mL acetone was added at -78 °C to quench the reaction. Then 6 mL saturated aqueous NH₄Cl was added and the reaction was stirred at 0 °C for 15 min. The mixture was passed through a pad of sand-silica

gel-celite, eluting with EtOAc-MeOH (10:1) and the effluent was dried over Na₂SO₄. The solution was concentrated under reduced pressure to give a residue. Crude ¹H NMR showed that the diastereoselectivity is 11:1. The residue was subjected to silica gel chromatography and elution with hexane-EtOAc (2:3) afforded allylic alcohol **II-42** (67 mg, 87%).

II-42: colorless oil; *R_f* = 0.71 (10:1 v/v EtOAc/MeOH); [α]_D²⁰ -6 (*c* 2.50, CHCl₃); IR (thin film, cm⁻¹) ν 3412, 3034, 2954, 1498, 1456, 1380, 1252, 1215, 1034, 982; ¹H (CDCl₃, 600 MHz) δ 7.34 (m, 10H), 5.90 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.76 (dddd, *J* = 10.2, 4.2, 1.8, 1.8 Hz, 1H), 5.04 (ddd, *J* = 12.0, 8.4, 3.0 Hz, 2H), 5.01 (ddd, *J* = 11.4, 8.4, 3.0 Hz, 2H), 4.78 (dddd, *J* = 7.2, 4.2, 3.6, 3.0 Hz, 1H), 3.66 (ddd, *J* = 9.0, 3.0, 1.8 Hz, 1H), 1.90 (dddd, *J* = 14.4, 2.4, 2.4, 1.2 Hz, 1H), 1.77 (ddqd, *J* = 12.6, 12.6, 6.6, 3.0 Hz, 1H), 1.48 (dddd, *J* = 14.4, 12.0, 3.6, 1.8 Hz, 1H), 1.02 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 136.9, 135.9 (d, *J* = 7.0 Hz), 128.5, 128.4 (d, *J* = 1.2 Hz), 127.9 (d, *J* = 4.4 Hz), 125.8 (d, *J* = 4.4 Hz), 73.0, 70.9 (d, *J* = 6.0 Hz), 69.1 (d, *J* = 5.4 Hz), 35.6 (d, *J* = 4.8 Hz), 32.2, 17.9; HRMS (ESI) calcd. for [C₂₁H₂₅O₅P+Na]⁺: 411.13318, Found: 411.13294.

Dibenzyl (1*R*,3*S*,4*S*)-4-hydroxy-3-methylcyclohexyl phosphate (**II-43**)

To a solution of 30 mg allylic alcohol **II-42** (0.077 mmol) in 0.35 mL *N*-methylmorpholine was added 167 mg (0.77 mmol) *o*-nitrobenzenesulfonylhydrazide and 128 μ L Et₃N. It was stirred at RT for 18 hr, then the reaction mixture was diluted with 30 mL EtOAc and washed at 0 °C by 8 mL 0.5 M NaHSO₄. The aqueous layer was extracted with EtOAc 30 mL X 2. The organic layer was washed with 5 mL saturated aqueous NaHCO₃, 5 mL 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 column. Elution with hexane-EtOAc (1:1.5-1:2) gave saturated alcohol **II-43** (18 mg, 60%) and recovered starting material **II-42** (6 mg, 20% recovery).

II-43: Colorless oil; R_f = 0.19 (1:3 v/v hexane/EtOAc); $[\alpha]_D^{20}$ +0.3 (c 0.76, CHCl_3); IR (thin film, cm^{-1}) ν 3420, 3064, 2977, 2934, 1498, 1456, 1256, 1213, 997; ^1H NMR (CDCl_3 , 600 MHz) δ 7.35 (m, 10H), 5.06 (dd, J = 12.0, 8.4 Hz, 2H), 5.02 (ddd, J = 12.0, 8.4, 1.2 Hz, 2H), 4.61 (dddd, J = 6.0, 3.6, 3.0, 3.0, 2.4 Hz, 1H), 3.13 (ddd, J = 10.2, 10.2, 4.2 Hz, 1H), 1.97 (dddd, J = 13.8, 6.6, 3.6, 3.0 Hz, 1H), 1.91 (ddd, J = 14.4, 7.2, 3.6 Hz, 1H), 1.74 (ddd, J = 12.0, 7.2, 3.6 Hz, 1H), 1.67 (ddqd, J = 13.2, 12.6, 6.6, 3.0 Hz, 1H), 1.53 (m, 2H), 1.18 (dddd, J = 14.4, 12.0, 2.4, 1.8 Hz, 1H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 136.0 (d, J = 5.4 Hz), 128.5, 128.4, 127.8, 75.1, 74.2 (d, J = 6.0 Hz), 69.1 (d, J = 5.4 Hz), 38.1 (d, J = 4.4 Hz), 34.0, 30.2 (d, J = 4.4 Hz), 20.1, 17.8; ^{31}P NMR (CD_3OD , 242 MHz) δ -0.419; HRMS (ESI) calcd. for $[\text{C}_{21}\text{H}_{27}\text{O}_5\text{P}+\text{H}]^+$: 391.16687, Found: 391.16685.

(1R,3S,4S)-4-hydroxy-3-methylcyclohexyl dihydrogen phosphate (II-32)

38 mg 10% Pd/C was first washed with HPLC grade MeOH 2 mL X 2, then it was transferred with another 2 mL HPLC grade MeOH to 25 mL flask which contained 21 mg dibenzyl phosphate **II-43** (0.05 mmol). The mixture was degassed using vacuum and refilled with H_2 at $\sim$ 30 $^\circ\text{C}$ three times. The reaction was stirred under balloon pressure of H_2 at room temperature for 3 hr. The reaction mixture was filtered and rinsed with HPLC grade MeOH and concentrated under reduced pressure to give a residue, which was then treated under vacuum at RT overnight to afford phosphate **II-32** (9.5 mg, 85%).

II-32: Colorless oil; $[\alpha]_D^{20} +14$ (c 0.95, MeOH); IR (thin film, cm^{-1}) ν 3500-2500 (broad), 3254, 2935, 2872, 1654, 1446, 1377, 1162, 1001, 980; ^1H NMR (D_2O , 600 MHz) δ 4.50 (m, 1H), 3.29 (ddd, $J = 10.2, 10.2, 4.2$ Hz, 1H), 2.00 (m, 1H), 1.97 (m, 2H), 1.79 (m, 2H), 1.65 (m, 2H), 1.35 (dddd, $J = 13.8, 12.6, 1.2, 1.2$ Hz, 1H), 1.00 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (D_2O , 150 MHz) δ 75.2, 72.8 (d, $J = 5.6$ Hz), 38.0 (d, $J = 4.4$ Hz), 33.4, 29.9 (d, $J = 4.4$ Hz), 28.3, 17.6; ^{31}P NMR (D_2O , 242 MHz) δ -0.492; HRMS (ESI) calcd. for $[\text{C}_7\text{H}_{15}\text{O}_5\text{P}-\text{H}]^-$: 209.05843, Found: 209.05843.

Dibenzyl (1S,2S,3S,4R,5S)-2,3,4-trihydroxy-5-methylcyclohexyl phosphate (II-44)

To a solution of 60 mg allylic alcohol **II-42** (0.154 mmol) in 1.5 mL t-BuOH-Actone-50% NMO (aq.) (1:1:1 v/v/v) was added a small piece of crystalline OsO_4 at 0 °C. The reaction mixture was stirred at 0 °C for overnight, then 1.5 mL saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ was added and it was stirred at 0 °C for another 2 hr. The reaction mixture was passed through a pad of sand-silica gel-celite, washing with EtOAc-MeOH (1:1, v/v). The solution was dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. Crude ^1H -NMR showed only one single diastereomer was formed. The residue was subjected to chromatography on silica gel column, eluting with EtOAc-MeOH (20:1) gave triol **II-44** (50 mg, 77%).

II-44: Colorless oil: $R_f = 0.77$ (10:1 (v/v) EtOAc/MeOH); $[\alpha]_D^{20} +6$ (c 1.84, MeOH); IR (thin film, cm^{-1}) 3378, 3066, 3035, 2952, 2926, 1498, 1456, 1378, 1247, 1215, 995, 970; ^1H NMR (CD_3OD , 600 MHz) δ 7.37 (m, 10H), 5.06 (ddd, $J = 11.4, 8.4, 1.2$ Hz, 2H), 5.03 (ddd, $J = 11.4, 9.0, 4.2$ Hz, 2H), 4.46 (dddd, $J = 6.6, 4.2, 3.0, 2.4$ Hz, 1H), 3.95 (dd, $J = 3.6, 3.6$ Hz, 1H), 3.49 (dd, $J = 9.6, 3.6$ Hz, 1H), 3.25 (dd, $J = 9.6, 9.6$ Hz, 1H), 1.64 (m, 3H), 0.96 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3OD , 150 MHz) δ 137.3 (d, $J = 5.8$ Hz), 129.9 (d, $J = 2.8$ Hz), 129.8 (d, $J = 1.2$ Hz), 129.3 (d, $J = 7.5$ Hz), 78.9 (d, $J = 6.3$ Hz), 76.2, 74.0, 72.8 (d, $J = 5.8$ Hz), 71.1 (d, $J = 6.4$ Hz).

Hz), 71.0 (d, $J = 6.4$ Hz), 34.2 (d, $J = 4.0$ Hz), 33.2, 18.2; ^{31}P NMR (CD_3OD , 242 MHz) δ -1.003; HRMS (ESI) calcd. for $[\text{C}_{21}\text{H}_{27}\text{O}_7\text{P}+\text{H}]^+$: 423.15672, Found: 423.15630.

(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-trihydroxy-5-methylcyclohexyl dihydrogen phosphate (II-33)

39 mg 10% Pd/C was first washed with HPLC grade MeOH 2 mL X 2, then it was transferred with another 2 mL HPLC grade MeOH to 25 mL flask which contained 24 mg dibenzyl phosphate **II-44** (0.06 mmol). The mixture was degassed using vacuum and refilled with H_2 at ~ 30 °C three times. The reaction was stirred under balloon pressure of H_2 at room temperature for 4 hr. The reaction mixture was filtered and rinsed with HPLC grade MeOH and concentrated under reduced pressure to give a residue, which was then treated with vacuum at RT overnight to afford phosphate **II-33** (12 mg, 87%).

II-33: Colorless oil; $[\alpha]_{\text{D}}^{20} +4$ (c 1.13, MeOH); IR (thin film, cm^{-1}) ν 3283, 2918, 1376, 1011, 972; ^1H NMR (D_2O , 600 MHz) δ 4.37 (ddd, $J = 9.0, 6.0, 3.0$, 1H), 4.12 (ddd, $J = 3.6, 3.6, 1.2$ Hz, 1H), 3.73 (dd, $J = 9.6, 3.0$ Hz, 1H), 3.35 (dd, $J = 10.2, 10.2$ Hz, 1H), 1.89 (dddd, $J = 14.4, 3.0, 2.4, 1.8$ Hz, 1H), 1.83 (ddqd, $J = 13.2, 10.8, 6.6, 4.2$ Hz, 1H), 1.63 (dddd, $J = 13.2, 13.2, 2.4, 1.2$ Hz, 1H), 1.05 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (D_2O , 150 MHz) δ 75.1, 74.5 (d, $J = 5.6$ Hz), 72.2, 71.9 (d, $J = 5.4$ Hz), 32.8 (d, $J = 3.4$ Hz), 31.6, 17.1; ^{31}P NMR (D_2O , 242 MHz) δ -0.612; HRMS (ESI) calcd. for $[\text{C}_7\text{H}_{15}\text{O}_7\text{P}-\text{H}]^-$: 241.04826, Found: 241.04805.

(3*aS*,5*R*,7*S*,7*aR*)-hexahydro-2,2,7-trimethylbenzo[d][1,3]dioxol-5-ol (II-45)

To a solution of 130 mg carbonate **II-22** (0.45 mmol) in 5 mL THF at 0 °C was added 48 mg LiAlH_4 (1.26 mmol). The reaction mixture was warmed up and stirred at RT for 2 hr, then it was diluted with 30 mL EtOAc and cooled down to 0 °C, and 4 mL saturated aqueous NaHCO_3 was added and it was stirred for another 20 min to quench the reaction. The mixture was passed through a pad of sand-silica gel-celite, rinsing with EtOAc. The effluent was dried over Na_2SO_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 (5:1) afforded alcohol **II-45** (78 mg, 93%).

II-45: White solid; mp: 61.5-62.0 °C; R_f = 0.28 (1:2 (v/v) hexane-EtOAc); $[\alpha]_D^{20}$ +54 (c 0.66, CHCl_3); IR (thin film, cm^{-1}) ν 3257, 2990, 2940, 2923, 2884, 1458, 1433, 1378, 1364, 1242, 1214, 1197, 1151, 1130, 1064, 1042, 1024, 960; ^1H NMR (CDCl_3 , 600 MHz) δ 4.28 (ddd, J = 4.8, 4.8, 2.4 Hz, 1H), 3.96 (ddd, J = 10.8, 10.8, 4.2, 4.2 Hz, 1H), 3.51 (dd, J = 9.6, 5.4 Hz, 1H), 2.39 (dddd, J = 14.4, 4.8, 2.4, 2.4 Hz, 1H), 1.85 (s, OH), 1.77 (ddd, J = 12.6, 6.6, 3.6 Hz, 1H), 1.65 (ddqd, J = 10.2, 10.2, 6.6, 3.6 Hz, 1H), 1.59 (ddd, J = 15.0, 10.8, 6.4 Hz, 1H), 1.43 (s, 3H), 1.32 (s, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.00 (ddd, J = 13.2, 13.2, 10.8 Hz, 1H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 108.2, 80.7, 74.5, 66.0, 40.5, 36.2, 33.7, 28.5, 26.1, 18.7; HRMS (ESI) calcd. for $[\text{C}_{10}\text{H}_{18}\text{O}_3+\text{H}]^+$: 187.13287, Found: 187.13288.

Dibenzyl (3a*R*,4*S*,6*R*,7a*S*)-hexahydro-2,2,4-trimethylbenzo[d][1,3]dioxol-6-yl phosphate (II-46)

Into a solution of 74 mg alcohol **II-45** (0.40 mmol) in 1.8 mL CH₂Cl₂ was added a solution of 0.39 mL 85% N,N-diethyl dibenzylphosphoramidite (1.2 mmol) in 1.8 mL CH₂Cl₂ at room temperature followed by addition of 2.6 mL 0.45 M 1*H*-tetrazole in acetonitrile (1.2 mmol). The mixture was stirred at RT for 1 hr. Then it was cooled down to 0 °C, and added 1.8 mL 30% H₂O₂. It was stirred at 0 °C for 30 min. To the mixture was added 3 mL saturated aqueous Na₂S₂O₃ and it was then stirred 0 °C for 2 hr. The mixture was extracted with EtOAc 30 mL X 3. The organic layer was washed with 5 mL saturated aqueous NaHCO₃, 5 mL saturated aqueous NaCl, dried over Na₂SO₄, and concentrated under reduced pressure to give a residue which was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (3:1) afforded phosphate **II-46** (131 mg, 74%).

II-46: Colorless oil: R_f = 0.38 (1:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ +14 (c 2.95, CHCl₃); IR (thin film, cm⁻¹) ν 3034, 2955, 2934, 1497, 1456, 1370, 1264, 1243, 1216, 1065, 993; ¹H NMR (CDCl₃, 600 MHz) δ 7.35 (m, 10H), 5.03 (m, 4H), 4.60 (dddd, J = 10.8, 10.8, 7.2, 4.2, 4.2 Hz, 1H), 4.24 (ddd, J = 4.8, 4.8, 2.4 Hz, 1H), 3.49 (dd, J = 9.6, 5.4 Hz, 1H), 2.45 (dddd, J = 14.4, 4.8, 2.4, 2.4 Hz, 1H), 1.90 (ddd, J = 13.2, 6.6, 3.6 Hz, 1H), 1.76 (ddd, J = 14.4, 10.2, 4.2 Hz, 1H), 1.60 (ddqd, J = 10.2, 10.2, 6.6, 3.6 Hz, 1H), 1.43 (s, 3H), 1.31 (s, 3H), 1.12 (ddd, J = 12.6, 12.6, 10.8 Hz, 1H); 0.98 (d, J = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 135.9 (d, J = 7.0 Hz), 128.5 (d, J = 2.7 Hz), 128.4 (d, J = 1.6 Hz), 127.9, 80.1, 73.9, 73.7 (d, J = 6.0 Hz), 69.2 (d, J = 5.6 Hz), 37.9 (d, J = 3.9 Hz), 34.1 (d, J = 6.0 Hz), 33.3, 28.4, 26.1, 18.5; HRMS (ESI) calcd. for [C₂₄H₃₁O₆P+H]⁺: 447.19310, Found: 447.19283.

Dibenzyl (1*R*,3*S*,4*R*,5*S*)-3,4-dihydroxy-5-methylcyclohexyl phosphate (II-47)

A solution of 100 mg (0.22 mmol) of acetone **II-46** was dissolved in 1.4 mL THF-10% HCl (v/v, 1:1) and stirred at room temperature for 30 min. The mixture was cooled down to 0 °C, and diluted with 50 mL EtOAc, then 2 mL saturated aqueous NaHCO_3 and 400 mg NaHCO_3 (s) was slowly added to quench the reaction. The mixture was filtered through a pad of sand-silica gel-celite, rinsing with EtOAc-MeOH (10:1 v/v). The effluent was dried over Na_2SO_4 and concentrated to a residue, which was loaded to a silica gel column. Elution with hexane-EtOAc (1:7 v/v) gave diol **II-47** (93mg, 95%).

II-47: White solid; mp: 122-123 °C; $R_f = 0.13$ (1:2 (v/v) hexane/EtOAc); $[\alpha]_D^{20} +4$ (c 0.91, MeOH); IR (thin film, cm^{-1}) ν 3454, 3394, 3038, 2956, 2926, 2869, 1605, 1497, 1456, 1377, 1251, 1215, 1057, 1007; ^1H NMR (CD_3OD , 600 MHz) δ 7.36 (m, 10H), 5.03 (dd, $J = 12.6, 8.0$ Hz, 1H), 5.01 (ddd, $J = 12.0, 8.4, 1.8$ Hz, 1H), 4.60 (dddd, $J = 11.4, 11.4, 7.2, 4.8, 4.8$ Hz, 1H), 3.93 (ddd, $J = 3.6, 3.0, 3.0$ Hz, 1H), 3.06 (dd, $J = 10.8, 3.0$ Hz, 1H), 2.24 (dddd, $J = 13.2, 4.2, 3.0, 3.0$ Hz, 1H), 1.92 (dddd, $J = 12.6, 4.2, 3.6, 3.6$ Hz, 1H); 1.82 (ddqd, $J = 13.2, 10.2, 6.6, 3.6$ Hz, 1H), 1.59 (ddd, $J = 13.8, 11.4, 3.0$ Hz, 1H), 1.17 (ddd, $J = 12.6, 12.6, 12.6$ Hz, 1H); 0.97 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3OD , 150 MHz) δ 137.4 (d, $J = 6.0$ Hz), 129.8, 129.7, 129.3, 77.5, 75.9 (d, $J = 6.6$ Hz), 71.1, 70.8 (d, $J = 5.4$ Hz), 41.0 (d, $J = 4.5$ Hz), 39.9 (d, $J = 4.8$ Hz), 33.2, 18.9; ^{31}P NMR (CD_3OD , 242 MHz) δ -1.003; HRMS (ESI) calcd. for $[\text{C}_{21}\text{H}_{27}\text{O}_6\text{P}+\text{H}]^+$: 407.1618, Found: 407.1617.

(1R,3S,4R,5S)-3,4-dihydroxy-5-methylcyclohexyl dihydrogen phosphate (II-34)

A 37 mg sample of 10% Pd/C was first washed with HPLC grade MeOH 2 mL X 2, then it was transferred with another 2 mL HPLC grade MeOH to 25 mL flask which contained 21 mg dibenzyl phosphate **II-47** (0.05 mmol). The mixture was degassed using vacuum and refilled with H₂ at ~-30 °C three times. The reaction was stirred under balloon pressure of H₂ at room temperature for 3 hr. The reaction mixture was filtered and rinsed with HPLC grade MeOH and concentrated under reduced pressure to give a residue, which was then treated with vacuum at RT overnight to afford phosphate **II-34** (9.0 mg, 78%).

II-34: Colorless oil; $[\alpha]_D^{20} +14$ (*c* 0.85, MeOH); IR (thin film, cm⁻¹) ν 3311, 2933, 1653, 1459, 1379, 1158, 1124, 1088, 1005, 960, 917; ¹H NMR (D₂O, 600 MHz) δ 4.49 (dddd, *J* = 11.4, 11.4, 9.0, 4.8, 4.8 Hz, 1H), 4.12 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 3.32 (dd, *J* = 10.8, 3.0 Hz, 1H), 2.29 (dddd, *J* = 13.2, 4.2, 3.6, 3.6 Hz, 1H), 2.12 (dddd, *J* = 12.6, 4.2, 3.6, 3.6 Hz, 1H); 1.90 (ddqd, *J* = 13.2, 10.2, 6.6, 3.6 Hz, 1H), 1.71 (ddd, *J* = 13.8, 12.0, 2.4 Hz, 1H), 1.30 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H); 1.05 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (D₂O, 150 MHz) δ 76.2, 71.7 (d, *J* = 5.4 Hz), 70.0, 39.4 (d, *J* = 4.1 Hz), 38.2 (d, *J* = 4.4 Hz), 30.6, 17.8; ³¹P NMR (D₂O, 242 MHz) δ -0.413; HRMS (ESI) calcd. for [C₇H₁₅O₆P-H]⁻: 225.05335, Found: 225.05335.

(1*R*,4*S*,5*R*)-4-*t*-butyldimethylsilyloxy-5-methylcyclohex-2-enyl 4-nitrobenzoate (II-27a**)**

A solution of 1.15 g allylic alcohol **II-27** (4.18 mmol) in 42 mL CH₂Cl₂ was added 1.14 g (16.7 mmol) imidazole when stirring, followed by addition of 1.30 g TBSCl (16.7 mmol) in portions. It was stirred at RT overnight, then it was diluted with 200 mL hexane-Et₂O (1:3 v/v) and cooled down to 0 °C, and 25 mL saturated aqueous NaHCO₃ was added. It was stirred at 0 °C for 30 min, and then the aqueous layer was extracted with Et₂O 60 mL x 2. The pooled organic layer was washed with 50 mL saturated aqueous NaCl, dried over Na₂SO₄. Concentration of the

solution under reduced pressure gave crude product which will be used directly for next step reaction. For characterization, small amount of the crude product was subjected to chromatography on silica gel column, eluting with hexane-EtOAc (20:1, v/v) gave product silylether **II-27a**.

II-27a: White solid; mp: 77.3-78.3 °C; R_f = 0.51 (6:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20} +97$ (c 4.12, CHCl₃); IR (thin film, cm⁻¹) ν 3039, 2953, 2929, 2898, 2857, 1713, 1609, 1600, 1522, 1462, 1390, 1338, 1271, 1249, 1101, 1081, 1008, 932; ¹H NMR (CDCl₃, 600 MHz) δ 8.27 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 5.95 (dd, J = 10.2, 1.8 Hz, 1H), 5.84 (dddd, J = 10.2, 3.6, 1.8, 1.2 Hz, 1H), 5.45 (ddd, J = 6.0, 3.0, 1.2 Hz, 1H), 3.80 (ddd, J = 8.4, 3.6, 1.8 Hz, 1H), 1.98 (ddd, J = 14.4, 4.2, 3.2 Hz 1H), 1.94 (ddqd, J = 12.0, 9.6, 6.6, 3.0 Hz 1H), 1.68 (ddd, J = 16.2, 12.0, 4.8 Hz 1H), 1.05 (d, J = 6.6 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 164.2, 150.5, 138.7, 136.0, 130.8, 124.0, 123.4, 73.8, 68.4, 34.5, 32.8, 25.8, 18.5, 18.1, -4.2, -4.6; HRMS (ESI) calcd. for [C₂₀H₂₉NO₅Si+Na]⁺: 414.17072, Found: 414.17035.

***t*-Butyldimethylsilyl (1*S*,4*R*,6*R*)-4-hydroxy-6-methylcyclohex-2-enyl ether (II-48)**

The crude product of **II-27a** obtained from last step was redissolved in 45 mL MeOH at 0 °C. Then 115.4 mg LiOH (4.81 mmol) was slowly added into the solution. The reaction mixture was stirred at 0 °C for 2 hr. It was then diluted with 450 mL hexane-EtOAc (1:2 v/v) and 35 mL saturated aqueous NH₄Cl was added in. The aqueous layer was extracted with hexane-EtOAc (1:2 v/v) 100 mL X 2. The pooled organic layer was washed with 50 mL saturated aqueous NaCl, dried over Na₂SO₄. Concentration of the solution under reduced pressure gave a residue, then washed with 30 mL saturated brine, dried over Na₂SO₄. The solution was concentrated under reduced pressure to give ~5 mL residue, which was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (8:1) afforded allylic alcohol **II-48** (873 mg, 85% for two

steps). **II-48**: Colorless oil; $R_f = 0.49$ (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20} -21$ (c 1.74, CHCl_3); IR (thin film, cm^{-1}) ν 3335, 3032, 2953, 2929, 2896, 2858, 1472, 1462, 1388, 1251, 1098, 1078, 1061, 989; ^1H NMR (CDCl_3 , 600 MHz) δ 5.75 (dddd, $J = 10.2, 3.0, 1.2, 1.2$ Hz, 1H), 5.71 (dd, $J = 10.2, 1.8$ Hz, 1H), 4.10 (ddd, $J = 6.6, 3.0$ Hz, 1H), 3.70 (ddd, $J = 7.8, 3.0, 1.8$ Hz, 1H), 1.80 (m, 2H), 1.50 (ddd, $J = 16.8, 12.6, 4.8$ Hz, 1H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 135.5, 128.7, 74.0, 64.0, 37.4, 32.0, 25.8, 18.5, 18.1, -4.2, -4.7; HRMS (ESI) calcd. for $[\text{C}_{13}\text{H}_{26}\text{O}_2\text{Si}+\text{H}]^+$: 243.17748, Found: 243.17744.

Dibenzyl (1S,4R,5S)-4-*t*-butyldimethylsiloxy-5-methylcyclohex-2-enyl phosphate (II-49)

Into a solution of 36.7 mg allylic alcohol **II-48** (0.15 mmol) in 0.5 mL CH_2Cl_2 was added a solution of 0.15 mL 85% *N,N*-diethyl dibenzylphosphoramidite (0.46 mmol) in 0.5 mL CH_2Cl_2 at room temperature, followed by addition of 1.0 mL 0.45 M 1*H*-tetrazole in acetonitrile (0.45 mmol). The mixture was stirred at RT for 1 hr. Then it was cooled down to 0 °C, and added 0.75 mL 30% H_2O_2 . It was stirred at to 0 °C for 30 min. Into the mixture 1 mL saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ was added and it was then stirred 0 °C for 20 min. The mixture was extracted with EtOAc 15 mL X 3. The organic layer was washed with 4 mL saturated aqueous NaHCO_3 , 4 mL saturated aqueous NaCl , dried over Na_2SO_4 , and concentrated under reduced pressure to give a residue which was subjected to chromatography on silica gel column. Elution with hexane-EtOAc (4:1) afforded phosphate **II-49** (49 mg, 66%).

II-49: Colorless oil; $R_f = 0.30$ (2:1 v/v EtOAc/MeOH); $[\alpha]_D^{20} +18$ (c 2.0, CHCl_3); IR (thin film, cm^{-1}) ν 3035, 2955, 2929, 2857, 1498, 1456, 1394, 1252, 1214, 1082, 985; ^1H (CDCl_3 , 600 MHz) δ 7.34 (m, 10H), 5.82 (dd, $J = 10.2, 1.8$ Hz, 1H), 5.76 (dddd, $J = 10.2, 4.2, 1.8, 1.8$ Hz, 1H), 5.04 (ddd, $J = 11.4, 7.8, 2.4$ Hz, 2H), 5.02 (ddd, $J = 11.4, 7.8, 3.0$ Hz, 2H), 4.79 (m, 1H), 3.66 (ddd, $J = 8.4, 2.4, 1.8$ Hz, 1H), 1.91 (dddd, $J = 14.4, 4.2, 2.4$ Hz, 1H), 1.85 (ddqd, $J = 13.2, 9.0, 6.6, 2.4$

Hz, 1H), 1.48 (dddd, $J = 14.4, 12.6, 4.2, 1.8$ Hz, 1H), 0.95 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 138.0, 136.0 (d, $J = 6.9$ Hz), 128.5, 128.4, 127.8 (d, $J = 8.7$ Hz), 124.9 (d, $J = 4.0$ Hz), 73.7, 71.1 (d, $J = 5.8$ Hz), 69.1 (d, $J = 5.8$ Hz), 35.7 (d, $J = 5.2$ Hz), 32.0, 25.8, 18.3, 18.1, -4.3, -4.7; HRMS (ESI) calcd. for $[\text{C}_{27}\text{H}_{39}\text{O}_5\text{PSi}+\text{H}]^+$: 503.23771, Found: 503.23769.

Dibenzyl (1*S*,2*S*,3*S*,4*R*,5*S*)-4-*t*-butyldimethylsilyloxy-2,3-dihydroxy-5-methylcyclohexyl phosphate (II-49a)

To a solution of 72 mg olefin **II-49** (0.146 mmol) in 1.5 mL *t*-BuOH-Actone-50% NMO (aq.) (1:1:1 v/v/v) was added a small piece of crystalline OsO_4 at 0 °C. The reaction mixture was stirred at 0 °C for overnight, then 1 mL saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ was added and it was stirred at 0 °C for another 2 hr. The reaction mixture was passed through a pad of sand-silica gel-celite, washing with EtOAc-MeOH (1:1, v/v). The solution was dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. Crude ^1H -NMR showed only one single diastereomer was formed. The residue was subjected to chromatography on silica gel column, eluting with hexane-EtOAc (1:1) gave diol **II-49a** (62 mg, 81%).

II-49a: Colorless oil: $R_f = 0.36$ (1:2 (v/v) hexane-EtOAc); $[\alpha]_{\text{D}}^{20} -8$ (c 2.43, CHCl_3); IR (thin film, cm^{-1}) ν 3380, 3066, 3036, 2953, 2928, 2893, 2856, 1498, 1457, 1386, 1361, 1247, 1215, 1096, 997; ^1H NMR (CDCl_3 , 600 MHz) δ 7.34 (m, 10H), 5.04 (m, 2H), 5.01 (m, 2H), 4.52 (dddd, $J = 8.4, 5.4, 5.4, 3.0$ Hz, 1H), 3.95 (dd, $J = 4.2, 4.2$ Hz, 1H), 3.60 (dd, $J = 7.2, 5.0$ Hz, 1H), 3.45 (dd, $J = 7.8, 7.2$ Hz, 1H), 3.2 (brs, 1H), 2.34 (brs, 1H), 1.72 (m, 2H), 1.58 (d, $J = 10.8, 10.8, 3.6, 3.0$ Hz, 1H), 0.93 (d, $J = 7.2$ Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 135.7 (d, $J = 6.3$ Hz), 128.6, 128.0, 127.9, 76.3 (d, $J = 5.8$ Hz), 76.0, 73.7, 71.9 (d, $J = 5.1$ Hz), 69.5 (d, $J = 4.6$ Hz), 71.0 (d, $J = 6.4$ Hz), 33.0 (d, $J = 4.6$ Hz), 32.9, 25.9, 18.2, 18.0, -

4.1, -4.4; ^{31}P NMR (CD_3OD , 242 MHz) δ -1.003; HRMS (ESI) calcd. for $[\text{C}_{27}\text{H}_{41}\text{O}_7\text{PSi}+\text{H}]^+$: 537.24319, Found: 537.24241.

Dibenzyl (1*R*,2*R*,3*R*,4*S*,5*R*)-2,3,4-trihydroxy-5-methylcyclohexyl phosphate (II-50)

A 60 mg sample of diol **II-49a** (0.114 mmol) was dissolved in 1.2 mL MeOH at 0 °C and 4.4 mg (0.023 mmol) *p*-TsOH•H₂O was added. It was stirred at 0 °C for 24 hr, then was diluted with 10 mL EtOAc and quenched with 0.4 mL saturated aqueous NaHCO₃. The mixture was concentrated under reduced pressure to give a residue, which was subjected to chromatography on silica gel column. Elution with EtOAc-MeOH (20:1) afforded triol **II-50** (46 mg, 98%).

II-50: Colorless oil: R_f = 0.31 (10:1 (v/v) EtOAc-MeOH); $[\alpha]_D^{20}$ -6 (c 1.57, MeOH); IR (thin film, cm^{-1}) ν 3376, 3065, 3036, 2953, 2926, 1498, 1456, 1379, 1247, 1215, 995, 970; ^1H NMR (CD_3OD , 600 MHz) δ 7.37 (m, 10H), 5.06 (ddd, J = 12.0, 9.0, 1.2 Hz, 2H), 5.03 (ddd, J = 11.4, 9.0, 4.2 Hz, 1H), 4.46 (dddd, J = 6.6, 4.2, 3.6, 3.0 Hz, 1H), 3.96 (dd, J = 3.0, 3.0 Hz, 1H), 3.50 (dd, J = 9.6, 3.0 Hz, 1H), 3.26 (dd, J = 9.6, 9.0 Hz, 1H), 1.64 (m, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CD_3OD , 150 MHz) δ 137.3 (d, J = 6.3 Hz), 129.9 (d, J = 2.2 Hz), 129.8 (d, J = 1.2 Hz), 129.3 (d, J = 6.9 Hz), 78.9 (d, J = 6.3 Hz), 76.2, 73.9, 72.8 (d, J = 5.8 Hz), 71.1 (d, J = 5.8 Hz), 71.0 (d, J = 5.8 Hz), 34.1 (d, J = 4.0 Hz), 33.2, 18.2; HRMS (ESI) calcd. for $[\text{C}_{21}\text{H}_{27}\text{O}_7\text{P}+\text{H}]^+$: 423.15672, Found: 423.15655.

(1*R*,2*R*,3*R*,4*S*,5*R*)-2,3,4-trihydroxy-5-methylcyclohexyl dihydrogen phosphate ((*ent*)-II-33)

A 37 mg sample of 10% Pd/C was first washed with HPLC grade MeOH 2 mL x 2, then it was transferred with another 2 mL HPLC grade MeOH to 25 mL flask which contained 22 mg dibenzyl phosphate **II-50** (0.05 mmol). The mixture was degassed using vacuum and refilled with H₂ at ~ -30 °C three times. The reaction was stirred under balloon pressure of H₂ at room temperature for 4 hr. The reaction mixture was filtered and rinsed with HPLC grade MeOH and concentrated under reduced pressure to give a residue, which was then treated with vacuum at RT overnight to afford phosphate (*ent*)-**II-33** (10 mg, 81%).

(*ent*)-**II-33**: Colorless oil; $[\alpha]_D^{20}$ -6 (*c* 0.73, MeOH); IR (thin film, cm⁻¹) ν 3278, 2933, 1440, 1376, 1137, 1010, 972; ¹H NMR (D₂O, 600 MHz) δ 4.37 (ddd, *J* = 9.0, 6.6, 3.0, 1H), 4.12 (ddd, *J* = 3.0, 3.0, 1.2 Hz, 1H), 3.74 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.35 (dd, *J* = 10.2, 9.6 Hz, 1H), 1.89 (dddd, *J* = 14.4, 3.0, 2.4, 1.8 Hz, 1H), 1.83 (ddqd, *J* = 13.2, 10.2, 6.6, 3.0 Hz, 1H), 1.63 (dddd, *J* = 13.2, 13.2, 2.4, 1.2 Hz, 1H), 1.05 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (D₂O, 150 MHz) δ 75.1, 74.4 (d, *J* = 5.6 Hz), 72.2, 71.9 (d, *J* = 5.4 Hz), 32.8 (d, *J* = 3.9 Hz), 31.6, 17.1; ³¹P NMR (D₂O, 242 MHz) δ -0.594; HRMS (ESI) calcd. for [C₇H₁₅O₇P-H]⁻: 241.04826, Found: 241.04805.

V.4. Chapter III Experimental

(4*S*,6*S*)-4-(benzyloxy)-6-methylcyclohex-2-enone (**III-7**)

A solution of 832 mg (3.68 mmol) α -D-Boc-enone (*ent*)-**III-4** and 0.70 mL (6.77 mmol) BnOH in 3 mL CH₂Cl₂ at 0 °C was added a solution of 95 mg (0.092 mmol) Pd₂(dba)₃•CHCl₃ and 96 mg (0.368 mmol) PPh₃ in 2 mL CH₂Cl₂. It was stirred at 0 °C for 2 h and another solution of 95 mg (0.092 mmol) Pd₂(dba)₃•CHCl₃ and 96 mg (0.368 mmol) PPh₃ in 2 mL CH₂Cl₂ was added. The reaction mixture was stirred at 0 °C for another 3 h. The mixture was directly loaded onto silica gel column. Elution with hexane-EtOAc (15:1, v/v) afforded glycosylated enone **III-7** (475 mg 60%) as colorless oil. R_f = 0.35 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -146 (*c* 2.56, CHCl₃); IR (thin film, cm⁻¹) ν 3033, 2964, 2931, 2872, 1678, 1497, 1454, 1377, 1331, 1250, 1205, 1220, 1087, 1068, 1027, 946; ¹H NMR (CDCl₃, 600 MHz) δ 7.38-7.35 (m, 4H), 7.31 (m, 1H), 6.89 (dd, J = 10.2, 3.6 Hz, 1H), 5.99 (d, J = 9.6 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.20 (ddd, J = 4.8, 4.2, 4.2 Hz, 1H), 2.80 (dq, J = 9.0, 7.2, 4.8 Hz, 1H), 2.55 (dddd, J = 13.8, 6.0, 4.8, 1.2 Hz, 1H), 1.98 (ddd, J = 13.8, 9.0, 4.2 Hz, 1H), 1.15 (d, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 201.9, 146.2, 138.0, 129.9, 128.5, 127.9, 127.7, 71.3, 69.8, 37.8, 35.6, 15.2; HRMS (ESI): calcd. for [C₁₄H₁₆O₂+H]⁺: 217.1223, Found: 217.1223.

General procedure of palladium(0)-catalyzed cyclitolization for phenols

A solution of 0.1 mmol phenol and 27 mg (0.12 mmol) α -D-Boc-enone (*ent*)-**III-4** in 1.5 mL CH₂Cl₂ at 0 °C was added a solution of 2.6 mg (0.0025 mmol Pd₂(dba)₃•CHCl₃ and 2.6 mg (0.010 mmol) PPh₃ in 0.5 mL CH₂Cl₂. The reaction mixture was stirred at 0 °C for 0.5-2 h, then the mixture was directly subjected to silica gel column chromatography to afford the corresponding glycosylated product.

(4*S*,6*S*)-6-methyl-4-phenoxy-cyclohex-2-enone (**III-21**)

Colorless oil, $R_f = 0.43$ (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20} -150$ (c 1.2, CHCl_3); IR (thin film, cm^{-1}) ν 3039, 2932, 1683, 1596, 1492, 1455, 1384, 1290, 1227, 1054, 980; ^1H NMR (CDCl_3 , 600 MHz) δ 7.32 (dd, $J = 7.2, 7.2$ Hz, 2H), 7.01 (t, $J = 7.2$ Hz, 1H), 6.96 (m, 3H), 6.08 (d, $J = 10.2$ Hz, 1H), 5.04 (ddd, $J = 4.8, 4.2, 4.2$ Hz, 1H), 2.87 (dq, $J = 9.6, 7.2, 4.8$ Hz, 1H), 2.39 (ddd, $J = 13.8, 4.8, 4.8$ Hz, 1H), 2.11 (ddd, $J = 13.8, 9.6, 4.8$ Hz, 1H), 1.20 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 201.5, 157.3, 144.6, 130.7, 129.8, 121.7, 115.9, 68.6, 37.7, 35.5, 15.1; HRMS (ESI): calcd. for $[\text{C}_{13}\text{H}_{14}\text{O}_2 + \text{H}]^+$: 203.1066, Found: 203.1066.

(4S,6S)-4-(4-methoxyphenoxy)-6-methylcyclohex-2-enone (III-22)

Colorless oil, $R_f = 0.31$ (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20} -233$ (c 0.07, CHCl_3); IR (thin film, cm^{-1}) ν 3042, 2933, 1680, 1591, 1504, 1463, 1441, 1383, 1289, 1212, 1033, 980; ^1H NMR (CDCl_3 , 600 MHz) δ 6.95 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 6.06 (d, $J = 10.2$ Hz, 1H), 4.90 (ddd, $J = 4.8, 4.8, 4.2$ Hz, 1H), 2.86 (dq, $J = 9.0, 7.2, 4.8$ Hz, 1H), 2.36 (ddd, $J = 13.8, 5.4, 4.8$ Hz, 1H), 2.07 (ddd, $J = 13.8, 9.0, 4.2$ Hz, 1H), 1.19 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 201.6, 154.7, 151.3, 144.9, 130.5, 117.6, 114.9, 70.0, 55.7, 37.7, 35.6, 15.1; HRMS (ESI): calcd. for $[\text{C}_{14}\text{H}_{16}\text{O}_3 + \text{H}]^+$: 233.1172, Found: 233.1173.

(4S,6S)-4-(7-bromo-5,8-dimethoxynaphthalen-1-yloxy)-6-methylcyclohex-2-enone (III-23)

Brown solid, mp: 85.0-86.5 °C; R_f = 0.36 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -138 (c 1.51, CHCl₃); IR (thin film, cm⁻¹) ν 3074, 2963, 2931, 2834, 1680, 1576, 1505, 1453, 1441, 1430, 1408, 1329, 1259, 1209, 1178, 1057, 1041, 975; ¹H NMR (CDCl₃, 600 MHz) δ 7.94 (dd, J = 8.4, 1.2 Hz, 1H), 7.40 (dd, J = 8.4, 7.2 Hz, 1H), 7.06 (ddd, J = 9.6, 4.2, 0.6 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.96 (s, 1H), 6.12 (dd, J = 9.6, 0.6 Hz, 1H), 5.09 (ddd, J = 4.8, 4.2, 4.2 Hz, 1H), 3.97 (s, 3H), 3.82 (s, 3H), 3.01 (dq, J = 9.6, 7.2, 5.4 Hz, 1H), 2.50 (dddd, J = 14.4, 5.4, 4.8, 0.6 Hz, 1H), 2.11 (ddd, J = 13.8, 9.6, 4.2 Hz, 1H), 1.21 (d, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 201.7, 152.5, 152.0, 146.3, 144.6, 130.8, 128.6, 125.8, 122.3, 117.1, 114.7, 114.0, 109.1, 71.1, 61.8, 56.0, 37.8, 35.4, 15.1; HRMS (ESI): calcd. for [C₁₉H₁₉BrO₄+Na]⁺: 413.0359, Found: 413.0361.

(4S,6S)-6-methyl-4-(o-tolyloxy)cyclohex-2-enone (III-24)

Colorless oil, R_f = 0.42 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -190 (c 1.0, CHCl₃); IR (thin film, cm⁻¹) ν 3024, 2966, 2931, 2874, 1681, 1601, 1589, 1490, 1460, 1438, 1380, 1232, 1188, 1117, 1048, 980; ¹H NMR (CDCl₃, 600 MHz) δ 7.17 (m, 2H), 6.97 (dd, J = 10.2, 3.6 Hz, 1H), 6.92 (m, 2H), 6.08 (d, J = 10.2 Hz, 1H), 5.03 (ddd, J = 4.8, 4.2, 4.2 Hz, 1H), 2.89 (dq, J = 9.0, 7.2, 4.8 Hz, 1H), 2.41 (ddd, J = 13.8, 5.4, 4.8 Hz, 1H), 2.23 (s, 3H), 2.12 (ddd, J = 13.8, 9.0, 4.2 Hz, 1H), 1.21 (d, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 201.5, 155.5, 144.9, 131.3, 130.5, 128.1, 126.8, 121.4, 112.9, 68.9, 37.8, 35.8, 16.3, 15.1; HRMS (ESI): calcd. for [C₁₄H₁₆O₂+H]⁺: 217.1223, Found: 217.1223.

(4S,6S)-4-(2-*t*-butylphenoxy)-6-methylcyclohex-2-enone (III-25)

Colorless oil; R_f = 0.42 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -218 (c 1.85, CHCl_3); IR (thin film, cm^{-1}) ν 3005, 2985, 2960, 2950, 2940, 2895, 1689, 1593, 1484, 1441, 1378, 1290, 1249, 1222, 1200, 1125, 1091, 1051, 985; ^1H NMR (CDCl_3 , 600 MHz) δ 7.34 (dd, J = 7.8, 1.8 Hz, 1H), 7.20 (ddd, J = 9.0, 7.2, 1.8 Hz, 1H), 7.01 (dd, J = 10.2, 4.2 Hz, 1H), 6.93 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 6.91 (ddd, J = 7.8, 1.2, 0.6 Hz, 1H), 6.10 (dd, J = 10.2, 1.2 Hz, 1H), 5.18 (ddd, J = 4.8, 4.8, 4.2 Hz, 1H), 2.87 (dq, J = 9.0, 7.2, 4.8 Hz, 1H), 2.48 (dddd, J = 13.8, 5.4, 4.8, 1.2 Hz, 1H), 2.19 (ddd, J = 13.8, 9.0, 4.2 Hz, 1H), 1.24 (d, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 201.4, 155.7, 144.6, 138.6, 130.6, 127.3, 127.0, 120.8, 111.7, 67.5, 38.1, 35.6, 34.9, 29.9, 15.2; HRMS (ESI): calcd. for $[\text{C}_{17}\text{H}_{22}\text{O}_2 + \text{H}]^+$: 259.1692, Found: 259.1693.

(4S,6S)-4-(4-bromophenoxy)-6-methylcyclohex-2-en-1-one (III-26)

Colorless oil, R_f = 0.54 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -148 (c 1.78, CHCl_3); IR (thin film, cm^{-1}) ν 3040, 2970, 2931, 2875, 1680, 1578, 1384, 1280, 1230, 1173, 1148, 978; ^1H NMR (CDCl_3 , 600 MHz) δ 7.41 (d, J = 9.0 Hz, 2H), 6.92 (dd, J = 10.2, 4.2 Hz, 1H), 6.84 (d, J = 9.0 Hz, 2H), 6.08 (dd, J = 10.2, 1.2 Hz, 1H), 4.98 (ddd, J = 4.8, 4.2, 4.2 Hz, 1H), 2.85 (dq, J = 9.0, 7.2, 4.8 Hz, 1H), 2.36 (dddd, J = 14.4, 5.4, 4.8, 1.2 Hz, 1H), 2.09 (ddd, J = 13.2, 9.0, 4.2 Hz, 1H), 1.20 (d, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 201.2, 156.4, 143.9, 132.6, 131.0, 117.7, 113.9, 69.0, 37.6, 35.4, 15.1.

Methyl 2-((1S,5S)-5-methyl-4-oxocyclohex-2-enyloxy)benzoate (III-27)

Colorless oil, R_f = 0.33 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -194 (c 1.42, CHCl_3); IR (thin film, cm^{-1}) ν 3040, 2951, 2875, 1725, 1680, 1599, 1485, 1450, 1299, 1240, 1126, 1081, 1045; ^1H NMR (CDCl_3 , 600 MHz) δ 7.82 (ddd, J = 8.4, 2.4, 0.6 Hz, 1H), 7.48 (ddd, J = 7.8, 7.8, 1.8, 0.6 Hz, 1H), 7.07 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 6.98 (dd, J = 10.2, 4.2 Hz, 1H), 6.09 (d, J = 10.2 Hz, 1H), 5.04 (ddd, J = 4.8, 4.2, 4.2 Hz, 1H), 3.86 (s, 3H), 2.97 (dq, J = 9.6, 7.2, 4.8 Hz, 1H), 2.44 (ddd, J = 13.8, 4.8, 4.8 Hz, 1H), 2.10 (ddd, J = 13.8, 9.6, 4.2 Hz, 1H), 1.20 (d, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 201.5, 166.4, 156.9, 144.0, 133.3, 132.0, 131.0, 122.5, 121.9, 116.6, 70.9, 52.0, 37.6, 35.8, 15.0; HRMS (ESI): calcd. for $[\text{C}_{15}\text{H}_{16}\text{O}_4 + \text{Na}]^+$: 283.0941, Found: 283.0942.

(4S,6S)- 4-(4-acetylphenoxy)-6-methylcyclohex-2-enone (III-28)

Colorless oil; R_f = 0.27 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -194 (c 1.79, CHCl_3); IR (thin film, cm^{-1}) ν 3075, 3040, 2975, 2965, 2935, 2870, 1677, 1597, 1576, 1506, 1359, 1271, 1242, 1174, 954; ^1H NMR (CDCl_3 , 600 MHz) δ 7.96 (d, J = 9.0 Hz, 2H), 6.98 (dd, J = 9.0 Hz, 2H), 6.94 (dd, J = 10.2, 4.2 Hz, 1H), 6.11 (dd, J = 10.2, 0.6 Hz, 1H), 5.14 (ddd, J = 4.8, 4.2, 4.2 Hz, 1H), 2.85 (dq, J = 9.6, 7.2, 4.8 Hz, 1H), 2.56 (s, 3H), 2.40 (dddd, J = 13.8, 4.8, 4.8, 0.6 Hz, 1H), 2.14 (ddd, J = 14.4, 9.6, 4.8 Hz, 1H), 1.21 (d, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 200.9, 196.5, 161.1, 143.3, 131.3, 131.0, 130.8, 115.1, 68.6, 37.6, 35.4, 26.3, 15.0; HRMS (ESI): calcd. for $[\text{C}_{15}\text{H}_{16}\text{O}_3 + \text{H}]^+$: 245.1172, Found: 245.1173.

7-((1S,5S)-5-methyl-4-oxocyclohex-2-enyloxy)-2H-chromen-2-one (III-29)

White solid, mp: 137.2-137.8 °C; R_f = 0.36 (1:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -104 (c 1.97, CHCl₃); IR (thin film, cm⁻¹) ν 3075, 3055, 2980, 2970, 2920, 2890, 1703, 1683, 1608, 1501, 1403, 1352, 1403, 1276, 1232, 1211, 1196, 1124, 1079, 1031, 1005, 985; ¹H NMR (CDCl₃, 600 MHz) δ 7.64 (d, J = 9.6 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 6.94 (dd, J = 10.2, 4.2 Hz, 1H), 6.88 (m, 2H), 6.28 (d, J = 9.6 Hz, 1H), 6.12 (d, J = 10.2 Hz, 1H), 5.11 (ddd, J = 4.8, 4.8, 4.2 Hz, 1H), 2.86 (dq, J = 9.6, 7.2, 5.4 Hz, 1H), 2.40 (ddd, J = 13.8, 4.8, 4.8 Hz, 1H), 2.16 (ddd, J = 13.8, 9.6, 4.8 Hz, 1H), 1.21 (d, J = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 200.8, 160.8, 160.4, 155.8, 143.1, 142.9, 131.4, 129.1, 113.7, 113.5, 113.1, 102.4, 69.1, 37.6, 35.2, 15.0; HRMS (ESI): calcd. for [C₁₆H₁₄O₄+H]⁺: 271.0965, Found: 271.0966.

2-((1S,5S)-5-methyl-4-oxocyclohex-2-enyloxy)naphthalene-1,4-dione (III-30)

Red brown solid, mp: 60-62 °C; R_f = 0.58 (10:1 (v/v) CH₂Cl₂/MeOH); $[\alpha]_D^{20}$ -97 (c 0.55, CHCl₃); IR (thin film, cm⁻¹) ν 3280, 2975, 2925, 2870, 1740, 1720, 1664, 1642, 1595, 1460, 1368, 1340, 1273, 1246, 1214, 1153; ¹H NMR (CDCl₃, 600 MHz) δ 8.15 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.80 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H), 7.73 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H), 7.54 (s, 1H), 6.87 (ddd, J = 10.2, 1.8, 1.2 Hz, 1H), 6.07 (dd, J = 10.2, 2.4 Hz, 1H), 4.32 (dddd, J = 10.2, 5.4, 2.4, 2.4 Hz, 1H), 2.68 (dq, J = 12.0, 7.2, 4.8 Hz, 1H), 2.45 (ddd, J = 13.8, 9.6, 4.8 Hz, 1H), 1.94 (dddd, J = 13.2, 4.8, 4.8, 1.2 Hz, 1H), 1.29 (d, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 202.2, 183.7, 181.2, 153.7, 151.0, 135.4, 133.3, 132.7, 129.2, 127.7, 127.1, 126.4, 123.4, 40.2, 34.2, 29.4, 15.6; HRMS (ESI): calcd. for [C₁₇H₁₄O₄+H]⁺: 283.0965, Found: 283.0966.

(1*R*,4*S*,6*S*)-4-(benzyloxy)-6-methylcyclohex-2-enol (III-31)

A solution of 528 mg (2.44 mmol) enone **III-7** in 10 mL THF at -78 °C was added 93 mg (2.44 mmol) LiAlH₄ in one portion. It was stirred at -78 °C for 1 h and then diluted with 50 mL EtOAc and quenched with 16 mL saturated aqueous NaHCO₃. The mixture was stirred at 0 °C for 15 min. The organic layer was separated and the aqueous layer was extracted with EtOAc. The pooled organic layer was washed with 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 (4:1, v/v) afforded allylic alcohol **III-31** (454 mg 85%). *R_f* = 0.48 (1:1 (v/v) hexane/EtOAc); [α]_D²⁰ -90 (*c* 1.33, CHCl₃); IR (thin film, cm⁻¹) ν 3357 (broad), 3064, 3029, 2952, 2928, 2908, 2869, 1497, 1454, 1390, 1375, 1326, 1305, 1196, 1067, 1037, 1026, 971; ¹H NMR (CDCl₃, 600 MHz) δ 7.37-7.32 (m, 4H), 7.30-7.26 (m, 1H), 5.88 (m, 2H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 3.87 (m, 1H), 3.68 (d, *J* = 9.0 Hz, 1H), 1.94 (dddd, *J* = 14.4, 3.6, 3.0, 1.2 Hz, 1H), 1.68 (ddqd, *J* = 11.4, 8.4, 6.6, 3.0 Hz, 1H), 1.43 (dddd, *J* = 13.8, 11.4, 4.2 Hz, 1H), 1.08 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 138.8, 134.9, 128.4, 127.7, 127.6, 127.5, 73.6, 70.8, 70.3, 38.9, 32.8, 18.2; HRMS (ESI): calcd. for [C₁₄H₁₈O₂+Na]⁺: 241.1199, Found: 241.1199.

(1*R*,2*S*,3*S*,4*S*,6*S*)-4-(benzyloxy)-6-methylcyclohexane-1,2,3-triol (III-33)

To a solution of 22 mg olefin **III-31** (0.10 mmol) in 0.9 mL *t*-BuOH-actone-50% NMO_(aq.) (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 2h, and then it was diluted with EtOAc 20 mL and 1.5 mL saturated aqueous Na₂S₂O₃ was added at 0 °C. It was stirred at 0 °C for 30 min. The mixture was passed through a pad of sand-silica gel-celite, eluting with EtOAc-MeOH (3:1, v/v). The effluent was dried over Na₂SO₄ and concentrated under reduced pressure to give a residue, which was purified by silica gel column. Elution with EtOAc-MeOH (20:1) gave triol **III-33** (25 mg, 98%) as viscous colorless oil: *R_f* = 0.46 (10:1 (v/v) EtOAc/MeOH); [α]_D²⁰ +14 (*c* 2.58, MeOH); IR (thin film, cm⁻¹) ν 3357 (broad), 3060, 3025, 2920, 2870, 1497, 1453, 1055, 1027, 976; ¹H NMR (CD₃OD, 600 MHz) δ 7.35-7.30 (m, 4H), 7.28-7.23 (m, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.01 (dd, *J* = 3.0, 3.0 Hz, 1H), 3.61 (m, 1H), 3.60 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.27 (dd, *J* = 9.6, 9.6 Hz, 1H), 1.77 (m, 1H), 1.73 (ddqd, *J* = 13.2, 10.2, 6.6, 3.6 Hz, 1H), 1.52 (ddd, *J* = 14.4, 12.6, 1.8 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CD₃OD, 150 MHz) δ 140.3, 129.5, 128.8, 128.7, 78.6, 76.8, 74.7, 72.9, 71.9, 33.4, 33.0, 18.6; HRMS (ESI): calcd. for [C₁₄H₂₀O₄+Na]⁺: 275.1254, Found: 275.1255.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-((1*R*,5*R*)-5-methyl-4-oxocyclohex-2-enyloxy)-4H-chromen-4-one (III-9)

133 mg (0.24 mmol) perbenzylated flavonol **III-8** and 65 mg (0.29 mmol) α -L-Boc-enone (**III-4**) was suspended in 2.5 mL CH_2Cl_2 at 0 °C. A solution of 6.2 mg (0.006 mmol) $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and 6.3 mg PPh_3 (0.024 mmol) in 1 mL CH_2Cl_2 was added via a syringe at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then directly loaded onto a silica gel column, elution with hexane-EtOAc (3:1) gave glycosylated enone **III-9** (133 mg, 84%): yellow solid, mp: 59-61 °C; R_f = 0.60 (1:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20} + 57$ (c 3.1, CHCl_3); IR (thin film, cm^{-1}) ν 3063, 3034, 2931, 2872, 1734, 1681, 1626, 1602, 1572, 1508, 1452, 1436, 1375, 1355, 1296, 1248, 1195, 1173, 1100, 1043, 1003, 972. ^1H NMR (CDCl_3 , 600 MHz) δ 7.96 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 7.8 Hz, 2H), 7.46-7.29 (m, 13H), 7.04 (d, J = 9.0 Hz, 2H), 7.04 (dd, J = 10.2, 4.2 Hz, 1H), 6.59 (d, J = 1.8 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 5.92 (dd, J = 9.6, 1.2 Hz, 1H), 5.29 (s, 2H), 5.14 (s, 2H), 5.09 (s, 2H), 5.07 (ddd, J = 4.8, 4.2, 4.2 Hz, 1H), 2.60 (dq, J = 10.2, 6.6, 4.8 Hz, 1H), 2.11 (ddd, J = 13.8, 4.8, 4.2 Hz, 1H), 1.86 (ddd, J = 14.4, 10.2, 4.8 Hz, 1H), 0.94 (d, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 201.9, 173.7, 162.9, 160.4, 159.8, 158.8, 154.1, 145.6, 138.7, 136.3, 135.6, 130.4, 130.0, 128.7, 128.6, 128.6, 128.4, 128.2, 127.7, 127.5, 127.4, 126.6, 123.3, 114.6, 109.9, 98.3, 94.0, 72.8, 70.8, 70.5, 70.1, 37.8, 35.8, 14.7; HRMS (ESI): calcd. for $[\text{C}_{43}\text{H}_{36}\text{O}_7 + \text{H}]^+$: 665.2534, Found: 665.2530.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-((1R,4S,5R)-4-hydroxy-5-methylcyclohex-2-enyloxy)-4H-chromen-4-one (III-34)

A solution of 115 mg (0.17 mmol) enone **III-9** in 14 mL THF at -78 °C was added 13 mg (0.35 mmol) LiAlH₄ in two portions. It was stirred at -78 °C for 1 h and then 3 mL acetone was slowly added via syringe into the reaction mixture at -78 °C. The mixture was stirred at -78 °C for 20 min and diluted with 20 mL hexane-EtOAc (1:1, v/v) and quenched with 6 mL saturated aqueous NaHCO₃. The mixture was stirred at 0 °C for 20 min. The organic layer was separated and the aqueous layer was extracted with EtOAc. The pooled organic layer was washed with 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 (1.5:1, v/v) afforded allylic alcohol **III-34** (97 mg, 89%). *R_f* = 0.38 (1:1 (v/v) hexane/EtOAc); [α]_D²⁰ + 10 (*c* 3.7, CHCl₃); IR (thin film, cm⁻¹) ν 3507, 3035, 2949, 2900, 2862, 1626, 1597, 1507, 1447, 1379, 1361, 1303, 1245, 1179, 1103, 1038, 947; ¹H NMR (CDCl₃, 600 MHz) δ 7.99 (d, *J* = 9.0 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.46-7.27 (m, 13H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 1.8 Hz, 1H), 6.03 (dddd, *J* = 9.6, 4.2, 1.8, 1.8 Hz, 1H), 5.80 (dd, *J* = 9.6, 1.8 Hz, 1H), 5.28 (s, 2H), 5.15 (s, 2H), 5.08 (s, 2H), 4.73 (m, 1H), 3.59 (d, *J* = 8.4 Hz, 1H), 1.73 (ddd, *J* = 14.4, 4.2, 2.4 Hz, 1H), 1.63 (ddqd, *J* = 13.2, 9.6, 6.6, 3.0 Hz, 1H), 1.29 (ddd, *J* = 15.0, 12.6, 4.8 Hz, 1H), 0.79 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 174.0, 162.6, 160.2, 159.8, 158.8, 154.0, 139.3, 136.5, 136.4, 135.7, 135.4, 130.6, 128.7, 128.7, 128.6, 128.4, 128.1, 127.7, 127.6, 127.5, 127.4, 126.7, 123.8, 114.4, 110.1, 98.2, 94.0, 73.7, 73.5, 70.8, 70.4, 70.1, 34.5, 33.0, 17.8; HRMS (ESI): calcd. for [C₄₃H₃₈O₇+H]⁺: 667.2696, Found: 667.2678.

(1*S*,4*R*,6*R*)-4-(5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yloxy)-6-methylcyclohex-2-enyl acetate (III-35)

A solution of 95 mg (0.14 mmol) enone **III-34** and 1.7 mg (0.014 mmol) DMAP in 2.5 mL CH_2Cl_2 at 0 °C was added 250 μL (3.09 mmol) pyridine and 150 μL (1.59 mmol) Ac_2O via syringe. It was stirred at 0 °C for 2 h and diluted with 20 mL hexane-EtOAc (1:1, v/v) and washed with 6 mL 0.5 M aqueous NaHSO_4 . The organic layer was separated and the aqueous layer was extracted with EtOAc. The pooled organic layer was washed with saturated aqueous NaHCO_3 and saturated brine subsequently and then dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography. Elution with hexane-EtOAc (3:1, v/v) afforded allylic acetate **III-35** (94 mg, 93%). Pale yellow solid, mp: 68-70 °C; R_f = 0.30 (hexane/EtOAc 2:1, v/v); $[\alpha]_D^{20}$ -33 (c 3.15, CHCl_3); IR (thin film, cm^{-1}) ν 3063, 3033, 2930, 1729, 1625, 1602, 1508, 1453, 1434, 1372, 1356, 1295, 1243, 1172, 1100, 1021, 920; ^1H NMR (CDCl_3 , 600 MHz) δ 8.02 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 7.2 Hz, 2H), 7.47-7.27 (m, 13H), 7.06 (d, J = 9.6 Hz, 2H), 6.58 (d, J = 1.8 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.13 (dddd, J = 10.2, 4.2, 1.8, 1.2 Hz, 1H), 5.71 (dd, J = 10.2, 1.8 Hz, 1H), 5.28 (s, 2H), 5.15 (s, 2H), 5.08 (s, 2H), 4.88 (dddd, J = 9.0, 2.4, 1.8, 1.2 Hz, 1H), 4.74 (m, 1H), 2.09 (s, 3H), 1.94 (ddqd, J = 13.2, 9.6, 6.6, 3.0 Hz, 1H), 1.77 (m, 1H), 1.40 (ddd, J = 14.4, 12.6, 4.8 Hz, 1H), 0.70 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 173.9, 171.0, 162.7, 160.2, 159.8, 158.8, 153.8, 139.4, 136.5, 136.4, 135.7, 131.1, 130.5, 129.2, 128.7, 128.7, 128.6, 128.4, 128.1, 127.6, 127.5, 127.4, 126.6, 123.8, 114.4, 110.1, 98.2, 94.0, 75.2, 73.5, 70.8, 70.4, 70.1, 34.3, 29.5, 21.2, 17.6; HRMS (ESI): calcd. for $[\text{C}_{45}\text{H}_{40}\text{O}_8+\text{H}]^+$: 709.2796, Found: 709.2782.

(1*S*,2*S*,3*R*,4*R*,6*R*)-4-(5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yloxy)-2,3-dihydroxy-6-methylcyclohexyl acetate (III-36)

A solution of 92 mg (0.13 mmol) allylic acetate (**III-35**) in 1 mL acetone-*t*-BuOH (1:1) was cooled down to 0 °C. To the solution was added 0.5 mL NMO-H₂O (w/w 1:1), and a small piece of crystalline OsO₄ was added into the mixture. The reaction mixture was stirred at 0 °C for 20 hours. The reaction was diluted with 20 mL EtOAc and then quenched with 1 mL saturated Na₂S₂O₃ (aq.) and stirred for 1 h at 0 °C. Then the mixture was passed through a small pad of celite/silica gel/sand and washed with EtOAc-MeOH (3:1). The effluent was dried over Na₂SO₄, and concentrated under reduced pressure to give a residue. Chromatography on silica gel eluting with hexane-EtOAc (1.5:1) gave diol **III-36** (70 mg, 73%): White solid, mp: 97-99 °C; *R*_f = 0.24 (1:2 (v/v), hexane/EtOAc); [α]_D²⁰ -47 (*c* 2.7, CHCl₃); IR (thin film, cm⁻¹) ν 3404, 3064, 2932, 1727, 1601, 1508, 1453, 1433, 1373, 1297, 1247, 1196, 1172, 1099, 1036, 959; ¹H NMR (CDCl₃, 600 MHz) δ 7.90 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.47-7.27 (m, 13H), 7.08 (d, *J* = 9.0 Hz, 2H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 5.26 (s, 2H), 5.15 (s, 2H), 5.07 (s, 2H), 4.79 (dd, *J* = 7.8, 7.2 Hz, 1H), 4.28 (ddd, *J* = 5.4, 5.4, 3.0 Hz, 1H), 4.17 (dd, *J* = 3.6, 4.8 Hz, 1H), 3.85 (dd, *J* = 7.2, 3.0 Hz, 1H), 2.85 (brs, 1H), 2.08 (s, 3H), 1.80 (m, 1H), 1.69 (ddd, *J* = 14.4, 5.4, 4.8 Hz, 1H), 1.41 (ddd, *J* = 13.8, 9.6, 3.6 Hz, 1H), 0.81 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 174.2, 171.3, 163.0, 160.5, 159.8, 158.8, 154.4, 139.3, 136.4, 136.3, 135.6, 130.6, 128.7, 128.7, 128.6, 128.4, 128.2, 127.7, 127.5, 127.4, 126.7, 123.4, 114.6, 109.8, 98.4, 94.0, 80.6, 76.9, 72.0, 71.9, 70.9, 70.5, 70.1, 32.7, 31.1, 21.1, 17.3; HRMS (ESI) calcd. for [C₄₅H₄₂O₁₀+H]⁺: 743.2851, Found: 743.2835.

(1*S*,2*S*,3*R*,4*R*,6*R*)-4-(5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yloxy)-2,3-dihydroxy-6-methylcyclohexyl acetate (III-1**)**

To a solution of 17 mg (0.023 mmol) diol **III-36** in 2.5 mL THF-EtOH (1:1) was added 21 mg Pd/C (10%). The reaction mixture was degassed at -50 to -40 °C using vacuum and refilled with H₂. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H₂ atmosphere for 12 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (1.5:1) to give product (**III-1**) (7.3 mg, 68%): Yellow solid, mp: 161-163 °C; R_f = 0.24 (1:4 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -31 (c 0.49, MeOH); IR (thin film, cm⁻¹) ν 3283, 2923, 1710, 1649, 1607, 1499, 1436, 1360, 1259, 1208, 1170, 1085, 1039, 971; ¹H NMR (CD₃OD, 600 MHz) δ 7.78 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 6.38 (d, J = 1.8 Hz, 1H), 6.21 (d, J = 1.8 Hz, 1H), 4.76 (dd, J = 10.2, 10.2 Hz, 1H), 4.31 (ddd, J = 3.0, 3.0, 3.0 Hz, 1H), 4.08 (dd, J = 3.0, 3.0 Hz, 1H), 3.72 (dd, J = 9.6, 3.0 Hz, 1H), 2.07 (s, 3H), 1.70 (ddqd, J = 12.6, 10.2, 6.0, 3.0 Hz, 1H), 1.64 (dddd, J = 15.0, 4.2, 3.0, 1.2 Hz, 1H), 1.50 (ddd, J = 15.0, 12.6, 2.4 Hz, 1H), 0.70 (d, J = 5.4 Hz, 3H); ¹³C NMR (CD₃OD, 150 MHz) δ 180.2, 173.5, 166.0, 163.4, 161.8, 159.4, 158.7, 137.7, 132.2, 123.0, 116.6, 106.2, 99.9, 94.9, 82.1, 79.0, 72.9, 72.3, 33.3, 32.1, 21.2, 18.0; HRMS (ESI) calcd. for [C₂₄H₂₄O₁₀+H]⁺: 473.1442, Found: 473.1441.

(1*S*,2*R*,3*R*,4*R*,6*R*)-4-(5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yloxy)-2-hydroxy-6-methylcyclohexane-1,3-diyl diacetate (III-37**)**

(1*S*,2*S*,3*S*,4*R*,6*R*)-4-(5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yloxy)-3-hydroxy-6-methylcyclohexane-1,2-diyl diacetate (III-38)

To a solution of 46 mg (0.062 mmol) diol **III-36** in 1.3 mL CH₂Cl₂ at 0 °C was added 1.0 mg (5.5 μmol) *p*-TsOH•H₂O, 48 μL trimethylorthoacetate (0.36 mmol). After stirring at 0 °C for 20 min, 0.5 mL 90% HOAc (aq.) was added at 0 °C, and the reaction mixture was stirred for another 15 min at 0 °C. The reaction mixture was diluted with 30 mL EtOAc and washed at 0 °C with 15 mL saturated aqueous NaHCO₃. It was then washed by 10 mL 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 (1:1) gave diacetate **III-37** (26 mg, 54%) and **III-38** (16.5 mg, 34%):

III-37: White solid, mp: 99-101 °C; *R*_f = 0.36 (1:1.5 (v/v) hexane/EtOAc); [*α*]_D²⁰ +26 (*c* 1.23, CHCl₃); IR (thin film, cm⁻¹) *ν* 3471, 3030, 2932, 1731, 1626, 1603, 1574, 1509, 1453, 1432, 1370, 1298, 1228, 1172, 1101, 1039, 963; ¹H NMR (CDCl₃, 600 MHz) *δ* 7.85 (d, *J* = 9.0 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.47-7.27 (m, 13H), 7.11 (d, *J* = 9.0 Hz, 2H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 5.28 (s, 2H), 5.15 (s, 2H), 5.07 (s, 2H), 5.06 (ddd, *J* = 3.6, 3.6, 1.2 Hz, 1H), 4.70 (dd, *J* = 10.8, 10.2 Hz, 1H), 4.39 (dddd, *J* = 3.0, 3.0, 2.4 Hz, 1H), 3.76 (ddd, *J* =

9.6, 6.0, 3.6 Hz, 1H), 2.18 (dddd, $J = 14.4, 4.2, 3.0, 1.8$ Hz, 1H), 2.11 (s, 3H), 2.01 (s, 3H), 1.97 (ddqd, $J = 13.2, 10.2, 6.0, 3.6$ Hz, 1H), 1.85 (d, $J = 5.4$ Hz, 1H), 1.49 (ddd, $J = 15.0, 13.2, 3.0$ Hz, 1H), 0.88 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 173.5, 171.9, 170.1, 162.8, 160.6, 159.8, 158.8, 154.1, 139.1, 136.4, 135.7, 130.5, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 127.5, 127.4, 126.7, 123.3, 114.8, 110.1, 98.4, 94.0, 77.7, 73.1, 70.8, 70.5, 70.3, 70.2, 33.5, 30.4, 21.1, 21.0, 17.4; HRMS (ESI) calcd. for $[\text{C}_{47}\text{H}_{44}\text{O}_{11}+\text{H}]^+$: 785.2956, Found: 785.2940.

III-38: White solid, mp: 89-91 °C; $R_f = 0.47$ (1:1.5 (v/v) hexane/EtOAc); $[\alpha]_{\text{D}}^{20} -63$ (c 1.32, CHCl_3); IR (thin film, cm^{-1}) ν 3426, 3031, 2930, 1735, 1623, 1603, 1573, 1508, 1453, 1432, 1367, 1297, 1249, 1224, 1173, 1101, 1040, 962; ^1H NMR (CDCl_3 , 600 MHz) δ 7.90 (d, $J = 9.0$ Hz, 2H), 7.56 (d, $J = 7.8$ Hz, 2H), 7.47-7.27 (m, 13H), 7.11 (d, $J = 9.0$ Hz, 2H), 6.57 (d, $J = 2.4$ Hz, 1H), 6.45 (d, $J = 2.4$ Hz, 1H), 5.26 (s, 2H), 5.22 (dd, $J = 9.0, 3.0$ Hz, 1H), 5.16 (d, $J = 11.4$ Hz, 1H), 5.15 (d, $J = 12.0$ Hz, 1H), 5.08 (s, 2H), 4.92 (dd, $J = 9.6, 9.0$ Hz, 1H), 4.41 (ddd, $J = 4.2, 3.6, 3.6$ Hz, 1H), 4.31 (dd, $J = 3.6, 3.6$ Hz, 1H), 2.93 (brs, 1H), 2.02 (s, 3H), 2.02 (s, 3H), 1.81 (ddqd, $J = 13.2, 10.8, 6.6, 3.6$ Hz, 1H), 1.73 (ddd, $J = 14.4, 4.2, 4.2$ Hz, 1H), 1.52 (ddd, $J = 14.4, 10.8, 3.0$ Hz, 1H), 0.74 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 173.8, 170.5, 169.5, 162.8, 160.5, 159.8, 158.8, 154.1, 139.3, 136.5, 136.3, 135.6, 130.5, 128.8, 128.7, 128.6, 128.4, 128.1, 127.7, 127.6, 127.4, 126.7, 123.3, 114.8, 110.0, 98.3, 94.0, 79.7, 74.5, 73.4, 70.9, 70.8, 70.5, 70.1, 32.3, 31.0, 20.9, 20.9, 17.2; HRMS (ESI) calcd. for $[\text{C}_{47}\text{H}_{44}\text{O}_{11}+\text{H}]^+$: 785.2956, Found: 785.2942.

(1*S*,2*R*,3*R*,4*R*,6*R*)-4-(5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yloxy)-2-hydroxy-6-methylcyclohexane-1,3-diyl diacetate (III-2)

To a solution of 19 mg (0.024 mmol) diol **III-37** in 2.5 mL THF-EtOH (1:1) was added 23 mg Pd/C (10%). The reaction mixture was degassed at -50 to -40 °C using vacuum and refilled with H₂. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H₂ atmosphere for 12 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (1:1) to give product (**III-2**) (7.7 mg, 63%): Yellow solid, mp: 165-167 °C; R_f = 0.31 (1:3 (v/v) hexane/EtOAc); $[\alpha]_D^{20} +4$ (c 0.51, MeOH); IR (thin film, cm⁻¹) ν 3220, 2961, 1717, 1650, 1607, 1505, 1441, 1366, 1248, 1210, 1174, 1108, 1084, 1040, 1008, 972; ¹H NMR (CD₃OD, 600 MHz) δ 7.78 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.38 (d, J = 2.4 Hz, 1H), 6.21 (d, J = 1.8 Hz, 1H), 5.22 (ddd, J = 3.6, 3.6, 1.2 Hz, 1H), 4.73 (dd, J = 10.2, 10.2 Hz, 1H), 4.28 (ddd, J = 3.0, 3.0, 3.0 Hz, 1H), 3.91 (dd, J = 9.6, 3.0 Hz, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 1.83 (ddqd, J = 13.2, 10.2, 6.6, 3.6 Hz, 1H), 1.82 (ddd, J = 15.6, 3.6, 3.0, 1.2 Hz, 1H), 1.44 (ddd, J = 16.2, 13.8, 3.0 Hz, 1H), 0.78 (d, J = 6.6 Hz, 3H); ¹³C NMR (CD₃OD, 150 MHz) δ 179.9, 173.2, 172.0, 166.0, 163.4, 161.9, 159.4, 158.7, 137.4, 132.1, 122.8, 116.7, 106.1, 100.0, 94.9, 78.8, 78.8, 74.5, 70.4, 34.1, 32.0, 21.2, 21.0, 18.0; HRMS (ESI) calcd. for [C₂₆H₂₆O₁₁+H]⁺: 515.1548, Found: 515.1547.

(1*S*,2*S*,3*S*,4*R*,6*R*)-4-(5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yloxy)-3-hydroxy-6-methylcyclohexane-1,2-diyl diacetate (III-3**)**

To a solution of 20 mg (0.0255 mmol) diol **III-38** in 2.5 mL THF-EtOH (1:1) was added 21.6 mg Pd/C (10%). The reaction mixture was degassed at -50 to -40 °C using vacuum and refilled with H₂. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H₂ atmosphere for 7 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (1.5:1) to give product (**III-3**) (9.8 mg, 75%): Yellow solid, mp: 127-129 °C; *R_f* = 0.36 (1:3 (v/v) hexane/EtOAc); [α]_D²⁰ -93 (*c* 0.75, MeOH); IR (thin film, cm⁻¹) ν 3342, 2927, 1716, 1650, 1607, 1505, 1437, 1364, 1208, 1171, 1084, 1042, 1008, 972; ¹H NMR (CD₃OD, 600 MHz) δ 7.79 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.38 (d, *J* = 1.8 Hz, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 5.06 (dd, *J* = 10.2, 3.0 Hz, 1H), 4.94 (dd, *J* = 10.8, 10.2 Hz, 1H), 4.47 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.26 (ddd, *J* = 4.2, 4.2, 1.2 Hz, 1H), 2.02 (s, 3H), 1.99 (s, 3H), 1.65 (ddqd, *J* = 12.6, 10.2, 6.0, 3.6 Hz, 1H), 1.62 (ddd, *J* = 15.6, 4.2, 3.0, 1.2 Hz, 1H), 1.50 (ddd, *J* = 15.0, 13.2, 2.4 Hz, 1H), 0.67 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CD₃OD, 150 MHz) δ 180.1, 172.7, 172.2, 166.0, 163.4, 161.7, 159.5, 158.7, 137.2, 132.2, 122.9, 116.6, 106.2, 99.9, 94.9, 81.3, 75.9, 75.1, 70.8, 32.7, 32.2, 21.0, 20.9, 17.9; HRMS (ESI) calcd. for [C₂₆H₂₆O₁₁+H]⁺: 515.1548, Found: 515.1547.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-((1S,5S)-5-methyl-4-oxocyclohex-2-enyloxy)-4H-chromen-4-one ((*ent*)-III-9)

85 mg (0.15 mmol) perbenzylated flavonol **III-8** and 50 mg (0.22 mmol) α -D-Boc-enone (*ent*)-**III-4** was suspended in 1.5 mL CH_2Cl_2 at 0 °C. A solution of 4.0 mg (0.004 mmol) $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ and 4.0 mg PPh_3 (0.015 mmol) in 0.5 mL CH_2Cl_2 was added via a syringe at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then directly loaded onto a silica gel column, elution with hexane-EtOAc (3:1) gave glycosylated enone (*ent*)-**III-9** (86 mg, 84%). Off white powder, mp: 63-65 °C; R_f = 0.60 (1:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -63 (*c* 2.2, CHCl_3); IR (thin film, cm^{-1}) ν 3033, 2931, 1731, 1681, 1625, 1602, 1572, 1508, 1452, 1433, 1375, 1354, 1297, 1250, 1171, 1100, 1002, 972. ^1H NMR (CDCl_3 , 600 MHz) δ 7.96 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.2 Hz, 2H), 7.46-7.29 (m, 13H), 7.04 (d, J = 9.0 Hz, 2H), 7.04 (dd, J = 10.2, 4.2 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 5.92 (d, J = 9.6 Hz, 1H), 5.28 (s, 2H), 5.14 (s, 2H), 5.09 (s, 2H), 5.07 (ddd, J = 4.8, 4.2, 4.2 Hz, 1H), 2.60 (dq, J = 10.2, 7.2, 4.8 Hz, 1H), 2.11 (ddd, J = 13.8, 4.2, 4.2 Hz, 1H), 1.86 (ddd, J = 14.4, 10.2, 4.8 Hz, 1H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 201.9, 173.7, 162.9, 160.5, 159.8, 158.8, 154.1, 145.6, 138.7, 136.3, 135.6, 130.4, 130.0, 128.7, 128.7, 128.6, 128.4, 128.2, 127.7, 127.5, 127.4, 126.6, 123.3, 114.6, 110.0, 98.3, 94.0, 72.8, 70.9, 70.5, 70.1, 37.8, 35.8, 14.7.

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-((1S,4R,5S)-4-hydroxy-5-methylcyclohex-2-enyloxy)-4H-chromen-4-one ((*ent*)-III-34**)**

A solution of 135 mg (0.20 mmol) enone (*ent*)-**III-9** in 15 mL THF at -78 °C was added 15 mg (0.4 mmol) LiAlH₄ in two portions. It was stirred at -78 °C for 1 h and then 3 mL acetone was slowly added via syringe into the reaction mixture at -78 °C. The mixture was stirred at -78 °C for 20 min and diluted with 20 mL hexane-EtOAc (1:1, v/v) and quenched with 6 mL saturated aqueous NaHCO₃. The mixture was stirred at 0 °C for 20 min. The organic layer was separated and the aqueous layer was extracted with EtOAc. The pooled organic layer was washed with 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 (1.5:1, v/v) afforded allylic alcohol (*ent*)-**III-34** (118 mg, 89%). Pale yellow solid, mp: 72-74 °C; R_f = 0.38 (1:1 (v/v) hexane/EtOAc); $[\alpha]_D^{20}$ -12 (*c* 2.1, CHCl₃); IR (thin film, cm⁻¹) ν 3422, 3064, 3032, 2927, 1735, 1620, 1601, 1508, 1452, 1373, 1355, 1296, 1249, 1172, 1100, 1041, 1013, 966; ¹H NMR (CDCl₃, 600 MHz) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.46-7.27 (m, 13H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.03 (dddd, *J* = 9.6, 3.6, 1.8, 1.2 Hz, 1H), 5.80 (dd, *J* = 9.6, 1.8 Hz, 1H), 5.28 (s, 2H), 5.15 (s, 2H), 5.08 (s, 2H), 4.73 (m, 1H), 3.59 (dd, *J* = 7.8, 7.2 Hz, 1H), 1.73 (ddd, *J* = 14.4, 4.2, 3.0 Hz, 1H), 1.63 (ddqd, *J* = 13.2, 9.6, 6.6, 3.0 Hz, 1H), 1.29 (ddd, *J* = 14.4, 12.0, 4.2 Hz, 1H), 0.79 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 174.0, 162.7, 160.2, 159.8, 158.8, 154.0, 139.3, 136.5, 136.4, 135.7, 135.4, 130.6, 128.7, 128.7, 128.6, 128.4, 128.1, 127.7, 127.6, 127.6, 127.4, 126.7, 123.8, 114.4, 110.1, 98.2, 94.0, 73.6, 73.5, 70.8, 70.4, 70.1, 34.5, 33.0, 17.8.

(1*R*,4*S*,6*S*)-4-(5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yloxy)-6-methylcyclohex-2-enyl acetate ((*ent*)-III-35**)**

A solution of 99 mg (0.15 mmol) enone (*ent*)-**III-34** and 1.8 mg (0.015 mmol) DMAP in 2.0 mL CH₂Cl₂ at 0 °C was added 200 μL (2.0 mmol) pyridine and 94 μL (1.0 mmol) Ac₂O via syringe. It was stirred at 0 °C for 2 h and diluted with 20 mL hexane-EtOAc (1:1, v/v) and washed with 5 mL 0.5 M aqueous NaHSO₄. The organic layer was separated and the aqueous layer was extracted with EtOAc. The pooled organic layer was washed with saturated aqueous NaHCO₃ and saturated brine subsequently and then dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography. Elution with hexane-EtOAc (3:1, v/v) afforded allylic acetate (*ent*)-**III-35** (103 mg, 98%). Pale yellow solid, mp: 61-63 °C, *R*_f = 0.30 (hexane/EtOAc 2:1, v/v); [α]_D²⁰ +31 (*c* 3.25, CHCl₃); IR (thin film, cm⁻¹) ν 3065, 3034, 2958, 2931, 2873, 1732, 1626, 1602, 1508, 1452, 1434, 1372, 1356, 1295, 1242, 1173, 1101, 1022, 920; ¹H NMR (CDCl₃, 600 MHz) δ 8.02 (d, *J* = 9.0 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.47-7.27 (m, 13H), 7.06 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 1.8 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.13 (dddd, *J* = 10.2, 4.8, 1.8, 1.8 Hz, 1H), 5.71 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.28 (s, 2H), 5.15 (s, 2H), 5.08 (s, 2H), 4.88 (dddd, *J* = 9.0, 1.8, 1.8, 1.8 Hz, 1H), 4.74 (m, 1H), 2.09 (s, 3H), 1.94 (ddqd, *J* = 13.2, 9.6, 6.6, 3.0 Hz, 1H), 1.77 (m, 1H), 1.40 (ddd, *J* = 14.4, 12.6, 4.8 Hz, 1H), 0.70 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 173.9, 171.0, 162.7, 160.2, 159.8, 158.8, 153.8, 139.4, 136.5, 136.4, 135.7, 131.1, 130.5, 129.2, 128.7, 128.7, 128.6, 128.4, 128.1, 127.7, 127.6, 127.4, 126.7, 123.8, 114.4, 110.1, 98.2, 94.0, 75.2, 73.5, 70.8, 70.4, 70.1, 34.3, 29.5, 21.2, 17.6.

(1*R*,2*R*,3*S*,4*S*,6*S*)-4-(5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yloxy)-2,3-dihydroxy-6-methylcyclohexyl acetate ((*ent*)-III-36**)**

A solution of 103 mg (0.145 mmol) allylic acetate ((*ent*)-**III-35**) in 2 mL acetone-*t*-BuOH (1:1) was cooled down to 0 °C. To the solution was added 1 mL NMO-H₂O (w/w 1:1), and a small piece of crystalline OsO₄ was added into the mixture. The reaction mixture was stirred at 0 °C for 12 hours. The reaction was diluted with 20 mL EtOAc and then quenched with 2 mL saturated Na₂S₂O₃ (aq.) and stirred for 2 h at 0 °C. Then the mixture was passed through a small pad of celite/silica gel/sand and washed with EtOAc-MeOH (3:1). The effluent was dried over Na₂SO₄, and concentrated under reduced pressure to give a residue. Chromatography on silica gel eluting with hexane-EtOAc (1:1.5) gave diol (*ent*)-**III-36** (89 mg, 82%): White solid, mp: 91-93 °C; R_f = 0.12 (1:1 (v/v), hexane/EtOAc); $[\alpha]_D^{20}$ +47 (*c* 2.95, CHCl₃); IR (thin film, cm⁻¹) ν 3418, 3032, 2929, 1727, 1602, 1508, 1452, 1432, 1372, 1357, 1298, 1247, 1197, 1172, 1099, 1036, 959; ¹H NMR (CDCl₃, 600 MHz) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.47-7.27 (m, 13H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 1.8 Hz, 1H), 5.26 (s, 2H), 5.15 (s, 2H), 5.08 (s, 2H), 4.80 (dd, *J* = 7.8, 7.2 Hz, 1H), 4.28 (ddd, *J* = 5.4, 5.4, 3.0 Hz, 1H), 4.17 (ddd, *J* = 5.4, 3.0, 3.0 Hz, 1H), 3.85 (ddd, *J* = 7.2, 4.2, 4.2 Hz, 1H), 2.86 (d, *J* = 4.2 Hz, 1H), 2.08 (s, 3H), 1.80 (m, 1H), 1.69 (ddd, *J* = 13.8, 5.4, 4.8 Hz, 1H), 1.41 (ddd, *J* = 13.8, 9.6, 3.6 Hz, 1H), 0.81 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 174.1, 171.3, 162.9, 160.5, 159.8, 158.8, 154.4, 139.2, 136.3, 136.2, 135.6, 130.6, 128.7, 128.7, 128.6, 128.4, 128.2, 127.7, 127.5, 127.4, 126.7, 123.4, 114.6, 109.8, 98.3, 94.0, 80.6, 76.9, 72.0, 71.9, 70.8, 70.5, 70.1, 32.7, 31.0, 21.1, 17.3.

(1*R*,2*R*,3*S*,4*S*,6*S*)-4-(5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yloxy)-2,3-dihydroxy-6-methylcyclohexyl acetate ((*ent*)-III-1**)**

To a solution of 26 mg (0.035 mmol) diol (*ent*)-**III-36** in 2 mL THF-EtOH (1:1) was added 26 mg Pd/C (10%). The reaction mixture was degassed at -50 to -40 °C using vacuum and refilled with H₂. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H₂ atmosphere for 7 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (1:1.5) to give product (*ent*)-(**III-1**) (12 mg, 73%): Yellow solid, mp: 148-150 °C; *R_f* = 0.24 (1:4 (v/v) hexane/EtOAc); [α]_D²⁰ +34 (*c* 0.78, MeOH); IR (thin film, cm⁻¹) ν 3217, 2927, 1709, 1650, 1607, 1497, 1440, 1361, 1258, 1207, 1171, 1085, 1037, 970; ¹H NMR (CD₃OD, 600 MHz) δ 7.78 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 1.8 Hz, 1H), 4.76 (dd, *J* = 10.8, 9.6 Hz, 1H), 4.31 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.08 (ddd, *J* = 3.6, 3.0, 1.2 Hz, 1H), 3.72 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.07 (s, 3H), 1.70 (ddqd, *J* = 13.2, 10.8, 7.2, 3.6 Hz, 1H), 1.64 (dddd, *J* = 15.0, 4.2, 3.0, 1.8 Hz, 1H), 1.50 (ddd, *J* = 15.0, 12.6, 2.4 Hz, 1H), 0.69 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CD₃OD, 150 MHz) δ 180.1, 173.5, 166.0, 163.4, 161.8, 159.4, 158.7, 137.7, 132.2, 123.0, 116.6, 106.2, 99.9, 94.9, 82.1, 79.0, 72.9, 72.3, 33.3, 32.1, 21.2, 18.0.

(1*R*,2*S*,3*S*,4*S*,6*S*)-4-(5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yloxy)-2-hydroxy-6-methylcyclohexane-1,3-diyl diacetate ((*ent*)-III-37**)**

(1*R*,2*R*,3*R*,4*S*,6*S*)-4-(5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4*H*-chromen-3-yloxy)-3-hydroxy-6-methylcyclohexane-1,2-diyl diacetate ((*ent*)-III-38)

To a solution of 59 mg (0.080 mmol) diol (*ent*)-III-36 in 1 mL CH₂Cl₂ at 0 °C was added 0.6 mg (3.2 μmol) *p*-TsOH·H₂O, 35 μL (0.27 mmol) trimethylorthoacetate. After stirring at 0 °C for 20 min, 0.5 mL 90% HOAc (aq.) was added at 0 °C, and the reaction mixture was stirred for another 20 min at 0 °C. The reaction mixture was diluted with 20 mL EtOAc and washed at 0 °C with 15 mL saturated aqueous NaHCO₃. It was then washed with 15 mL 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 (1:1) gave diacetate (*ent*)-III-37 (28 mg, 45%) and elution with hexane-EtOAc (1:1.25) gave (*ent*)-III-38 (27.5 mg, 44%):

(*ent*)-III-37: White solid, mp: 99-101 °C; *R*_f = 0.27 (1:1.5 (v/v) hexane/EtOAc); [α]_D²⁰ -28 (*c* 1.46, CHCl₃); IR (thin film, cm⁻¹) ν 3474, 3066, 2930, 1732, 1626, 1603, 1574, 1509, 1453, 1433, 1370, 1298, 1225, 1172, 1100, 1039, 963; ¹H NMR (CDCl₃, 600 MHz) δ 7.85 (d, *J* = 9.0 Hz,

2H), 7.56 (d, $J = 7.2$ Hz, 2H), 7.47-7.27 (m, 13H), 7.11 (d, $J = 9.0$ Hz, 2H), 6.56 (d, $J = 2.4$ Hz, 1H), 6.44 (d, $J = 2.4$ Hz, 1H), 5.28 (s, 2H), 5.15 (s, 2H), 5.07 (s, 2H), 5.06 (ddd, $J = 3.0, 3.0, 1.8$ Hz, 1H), 4.70 (dd, $J = 10.8, 10.2$ Hz, 1H), 4.39 (ddd, $J = 3.0, 3.0, 3.0$ Hz, 1H), 3.75 (m, 1H), 2.18 (ddd, $J = 15.0, 3.6, 2.4, 1.2$ Hz, 1H), 2.10 (s, 3H), 2.01 (s, 3H), 1.97 (ddqd, $J = 13.2, 10.8, 6.6, 4.2$ Hz, 1H), 1.85 (d, $J = 5.4$ Hz, 1H), 1.49 (ddd, $J = 15.0, 12.6, 3.0$ Hz, 1H), 0.88 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 173.5, 171.9, 170.1, 162.8, 160.6, 159.8, 158.8, 154.1, 139.1, 136.4, 135.6, 130.5, 128.7, 128.7, 128.6, 128.4, 128.2, 127.7, 127.5, 127.4, 126.6, 123.3, 114.8, 110.1, 98.4, 94.0, 77.7, 73.1, 70.8, 70.5, 70.3, 70.2, 33.5, 30.3, 21.1, 21.0, 17.4.

(*ent*)-**III-38**: White solid, mp: 98-100 °C; $R_f = 0.38$ (1:1.5 (v/v) hexane/EtOAc); $[\alpha]_{\text{D}}^{20} +66$ (c 1.95, CHCl_3); IR (thin film, cm^{-1}) ν 3436, 3033, 2932, 1735, 1603, 1573, 1508, 1453, 1432, 1366, 1298, 1248, 1223, 1172, 1100, 1039, 962; ^1H NMR (CDCl_3 , 600 MHz) δ 7.90 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 7.2$ Hz, 2H), 7.47-7.27 (m, 13H), 7.11 (d, $J = 9.0$ Hz, 2H), 6.56 (d, $J = 2.4$ Hz, 1H), 6.45 (d, $J = 2.4$ Hz, 1H), 5.26 (s, 2H), 5.22 (dd, $J = 9.0, 3.6$ Hz, 1H), 5.16 (d, $J = 11.4$ Hz, 1H), 5.15 (d, $J = 12.0$ Hz, 1H), 5.08 (s, 2H), 4.93 (dd, $J = 9.6, 9.0$ Hz, 1H), 4.42 (ddd, $J = 4.2, 3.6, 3.6$ Hz, 1H), 4.32 (dd, $J = 4.2, 4.2$ Hz, 1H), 2.98 (brs, 1H), 2.02 (s, 3H), 2.02 (s, 3H), 1.80 (ddqd, $J = 13.8, 10.8, 6.6, 4.2$ Hz, 1H), 1.73 (ddd, $J = 14.4, 4.2, 3.6$ Hz, 1H), 1.52 (ddd, $J = 14.4, 11.4, 3.0$ Hz, 1H), 0.73 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 173.7, 170.4, 169.5, 162.8, 160.4, 159.8, 158.8, 154.1, 139.2, 136.5, 136.3, 135.6, 130.5, 128.7, 128.6, 128.6, 128.4, 128.1, 127.7, 127.5, 127.4, 126.7, 123.3, 114.7, 110.0, 98.3, 93.9, 79.7, 74.5, 73.4, 70.8, 70.8, 70.5, 70.1, 32.3, 31.0, 20.9, 20.9, 17.2.

(1*R*,2*S*,3*S*,4*S*,6*S*)-4-(5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4*H*-chromen-3-yl)-2-hydroxy-6-methylcyclohexane-1,3-diyl diacetate ((*ent*)-III-2**)**

To a solution of 26 mg (0.033 mmol) diol (*ent*)-**III-37** in 1.5 mL THF-EtOH (1:1) was added 26 mg Pd/C (10%). The reaction mixture was degassed at -50 to -40 °C using vacuum and refilled with H₂. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H₂ atmosphere for 5 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (1:1.5) to give product (*ent*)-**III-2** (11 mg, 65%): Yellow solid, mp: 167-169 °C; *R_f* = 0.11 (1:1.5 (v/v) hexane/EtOAc); [α]_D²⁰ -5 (*c* 0.76, MeOH); IR (thin film, cm⁻¹) ν 3200, 2926, 1717, 1650, 1607, 1503, 1441, 1361, 1248, 1208, 1171, 1109, 1083, 1038, 1008, 972; ¹H NMR (CD₃OD, 600 MHz) δ 7.78 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.38 (d, *J* = 1.8 Hz, 1H), 6.21 (d, *J* = 1.8 Hz, 1H), 5.22 (ddd, *J* = 3.6, 3.6, 1.2 Hz, 1H), 4.73 (dd, *J* = 10.2, 10.2 Hz, 1H), 4.28 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 3.91 (dd, *J* = 10.2, 3.6 Hz, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 1.83 (ddqd, *J* = 13.2, 10.2, 6.6, 3.0 Hz, 1H), 1.82 (ddd, *J* = 15.6, 4.2, 3.0, 1.8 Hz, 1H), 1.44 (ddd, *J* = 15.6, 13.8, 3.0 Hz, 1H), 0.78 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CD₃OD, 150 MHz) δ 179.9, 173.2, 172.0, 166.0, 163.4, 161.9, 159.4, 158.7, 137.4, 132.1, 122.8, 116.7, 106.1, 100.0, 94.9, 78.8, 78.8, 74.5, 70.4, 34.1, 32.0, 21.2, 21.0, 18.0.

(1*R*,2*R*,3*R*,4*S*,6*S*)-4-(5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yloxy)-3-hydroxy-6-methylcyclohexane-1,2-diyl diacetate ((*ent*)-III-3**)**

To a solution of 26 mg (0.033 mmol) diol (*ent*)-**III-38** in 3 mL THF-EtOH (1:1) was added 23 mg Pd/C (10%). The reaction mixture was degassed at -50 to -40 °C using vacuum and refilled with H₂. This procedure was repeated three times, then the bath was removed and the reaction was warmed up to room temperature. The reaction mixture was stirred under a H₂ atmosphere for 7 hours. The reaction mixture was loaded onto silica gel and elution with hexane-EtOAc (1:1) to give product (*ent*)-**III-3** (12 mg, 70%): Yellow solid, mp: 147-149 °C; *R_f* = 0.47 (1:3 (v/v) hexane/EtOAc); [α]_D²⁰ +114 (*c* 0.74, MeOH); IR (thin film, cm⁻¹) ν 3335, 2931, 1716, 1653, 1608, 1499, 1440, 1363, 1207, 1170, 1085, 1041, 972; ¹H NMR (CD₃OD, 600 MHz) δ 7.79 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.38 (d, *J* = 1.8 Hz, 1H), 6.20 (d, *J* = 1.8 Hz, 1H), 5.06 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.94 (dd, *J* = 10.8, 10.2 Hz, 1H), 4.47 (ddd, *J* = 3.0, 3.0, 2.4 Hz, 1H), 4.26 (ddd, *J* = 3.6, 3.6, 1.2 Hz, 1H), 2.02 (s, 3H), 1.99 (s, 3H), 1.66 (ddqd, *J* = 12.6, 10.2, 6.0, 3.6 Hz, 1H), 1.62 (ddd, *J* = 15.0, 3.6, 2.4, 1.2 Hz, 1H), 1.50 (ddd, *J* = 15.0, 12.6, 2.4 Hz, 1H), 0.67 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CD₃OD, 150 MHz) δ 180.1, 172.7, 172.2, 165.9, 163.4, 161.7, 159.4, 158.7, 137.2, 132.2, 122.9, 116.6, 106.2, 99.9, 94.9, 81.3, 75.9, 75.1, 70.8, 32.7, 32.1, 21.0, 21.0, 17.9.

V.5. Chapter IV Experimental

(2R,3S,6S)-6-(benzyloxy)-2-methyl-3,6-dihydro-2H-pyran-3-yl tert-butyl carbonate (IV-25)

A solution of 519 mg (2.38 mmol) allylic alcohol **IV-24** and 14.5 mg (0.119 mmol) DMAP in 8 mL CH₂Cl₂ at 0 °C was added a solution of 778 mg (3.57 mmol) Boc₂O in 2.5 mL CH₂Cl₂. Then the reaction mixture was stirred at RT for 1 h. It was diluted with 20 mL EtOAc and quenched with saturated aqueous NaHCO₃ at 0 °C. The mixture was stirred at 0 °C for 20 min, then was extracted with 100 mL Et₂O and the aqueous layer was extracted again with 50 mL Et₂O. The pooled organic layer was subsequently washed with saturated aqueous NH₄Cl, NaHCO₃, 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 (20:1, v/v) afforded the carbonate **IV-25** 663 mg (87%) as white solid: mp 60-62 °C; *R_f* (hexanes/EtOAc, 3:1 v/v) = 0.60; [α]_D²⁰ +89 (*c* 2.99, CHCl₃); IR (thin film, cm⁻¹) ν 2982, 2935, 1732, 1455, 1370, 1336, 1317, 1286, 1269, 1254, 1154, 1094, 1049, 1028, 969; ¹H NMR (CDCl₃, 600 MHz): δ 7.38-7.32 (m, 4H), 7.29 (m, 1H), 5.93 (d, *J* = 10.2 Hz, 1 H), 5.82 (ddd, *J* = 10.8, 2.4, 1.8 Hz, 1 H), 5.06 (brs, 1H), 4.86 (ddd, *J* = 9.0, 3.0, 1.8 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.01 (dq, *J* = 9.0, 6.0 Hz, 1H), 1.50 (s, 9H), 1.22 (d, *J* = 6.0 Hz, 3 H); ¹³C NMR (CDCl₃, 150 MHz): δ 153.1, 138.1, 129.7, 128.4, 127.9, 127.8, 127.6, 93.7, 82.6, 73.5, 70.1, 64.9, 27.7, 17.8; HRESIMS: Calcd. for [C₁₈H₂₄O₅+Na]⁺: 343.1516, Found: 343.1517.

Benzyl (2R,3S,6S)-6-(benzyloxy)-2-methyl-3,6-dihydro-2H-pyran-3-yl carbonate (IV-26)

A solution of 224 mg (1.03 mmol) allylic alcohol **IV-24** in 4 mL CH₂Cl₂ at RT was added 220 mg 60% NaH (5.5 mmol) in 2 mL CH₂Cl₂ which was washed with hexane before use. Then 369 mg *n*-Bu₄NI (1 mmol) was added to the mixture followed by the addition of 61 mg DMAP (0.5 mmol). The reaction mixture was stirred at RT for 2 h. It was then diluted with Et₂O and washed with saturated aqueous NH₄Cl and the aqueous layer was extracted with Et₂O twice and the pooled organic layer was then washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was subjected silica gel column chromatography, elution with hexane-EtOAc (15:1, v/v) afforded the carbonate **IV-26** 270 mg (74%) as colorless viscous oil: *R*_f (hexanes/EtOAc, 3:1 v/v) = 0.44; [α]²⁰_D +96 (*c* 4.48, CHCl₃); IR (thin film, cm⁻¹) ν 3032, 2979, 2936, 1747, 1497, 1456, 1382, 1250, 1049, 1020, 962; ¹H NMR (CDCl₃, 600 MHz): δ 7.41-7.34 (m, 9H), 7.31 (m, 1H), 5.96 (d, *J* = 10.2 Hz, 1 H), 5.85 (ddd, *J* = 9.6, 12.4, 1.8 Hz, 1 H), 5.21 (d, *J* = 12.6 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.08 (brs, 1H), 4.94 (ddd, *J* = 9.0, 3.0, 1.8 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.05 (dq, *J* = 9.6, 6.6 Hz, 1H), 1.24 (d, *J* = 6.0 Hz, 3 H); ¹³C NMR (CDCl₃, 150 MHz): δ 154.7, 137.9, 135.0, 129.1, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.6, 93.6, 74.7, 70.1, 69.8, 64.7, 17.8; HRESIMS: Calculated for [C₂₁H₂₂O₅+Na]⁺: 377.1359, Found: 377.1362.

(3a*R*,4*R*,6*S*,7*S*,7a*R*)-6-(benzyloxy)-7-iodo-4-methyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-2-one (IV-27)

A solution of 285 mg (0.90 mmol) allyl carbonate **IV-25** in 3 mL HOAc was added 320 mg NIS

(1.42 mmol) at RT. It was stirred at RT 12 h, then another 230 mg (1.0 mmol) NIS was added and continued stirring at RT for another 12 h. The reaction mixture was diluted with EtOAc and cooled down to 0 °C and quenched by addition of saturated aqueous NaHCO₃. The mixture was extracted with EtOAc and the organic layer was washed subsequently with saturated aqueous Na₂S₂O₃, 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 the iodo-carbonate **IV-27** 335 mg (95%) as white solid: mp 80.5-82.5 °C; *R_f* (hexanes/EtOAc, 3:1 v/v) = 0.38; [α]_D²⁰ + 52 (*c* 2.65, CHCl₃); IR (thin film, cm⁻¹) ν 3030, 2980, 2935, 1839, 1806, 1497, 1454, 1347, 1331, 1147, 1087, 1053, 1021, 970; ¹H NMR (CDCl₃, 600 MHz): δ 7.39-7.34 (m, 4H), 7.32 (m, 1H), 5.16 (d, *J* = 5.4 Hz, 1 H), 4.96 (dd, *J* = 8.4, 7.8 Hz, 1 H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.40 (dd, *J* = 9.0, 7.8 Hz, 1H), 4.21 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.05 (dq, *J* = 9.0, 6.6 Hz, 1H), 1.35 (d, *J* = 6.0 Hz, 3 H); ¹³C NMR (CDCl₃, 150 MHz): δ 152.9, 136.6, 128.5, 128.1, 127.9, 101.0, 78.7, 77.1, 70.2, 64.0, 21.0, 18.6; HRESIMS: Calculated for [C₁₄H₁₅IO₅+Na]⁺: 412.9856, Found: 412.9859.

MgBr₂•Et₂O catalyzed iodo-carbonation of Boc-carbonate **IV-25**

A solution of 31.8 mg (0.1 mmol) allyl carbonate **IV-25** and 33.8 mg (0.15 mmol) NIS in 0.8 mL CH₂Cl₂ was added 25.8 mg (0.1 mmol) MgBr₂•Et₂O at RT. It was stirred at RT 12 h, then another 22.5 mg (0.1 mmol) NIS was added and continued stirring at RT for another 24 h. The reaction mixture was diluted with EtOAc and cooled down to 0 °C and quenched by addition of saturated aqueous NaHCO₃. The mixture was extracted with EtOAc and the organic layer was washed subsequently with saturated aqueous Na₂S₂O₃, brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure, a crude ¹H NMR experiment showed that the ratio of product and remaining starting material is 2:1. Then the residue was subjected to silica gel column chromatography, elution with hexane-EtOAc (7:1, v/v) afforded 10.1 mg iodo-carbonate **IV-27** (26%).

Iodo-carbonation of Cbz-carbonate **IV-26**

A solution of 35.4 mg (0.10 mmol) allyl carbonate **IV-26** in 3 mL HOAc was added 33.8 mg NIS (0.15 mmol) at RT. It was stirred at RT 12 h, then another 22.5 mg (0.1 mmol) NIS was added and continued stirring at RT for another 24 h. Once again 22.5 mg (0.1 mmol) NIS was added and continued stirring at RT for another 24 h. The reaction mixture was diluted with EtOAc and cooled down to 0 °C and quenched by addition of saturated aqueous NaHCO₃. The mixture was extracted with EtOAc and the organic layer was washed subsequently with saturated aqueous Na₂S₂O₃, 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 (7:1, v/v) afforded the iodo-carbonate **IV-27** 20 mg (51%)

(3*aR*,4*R*,6*S*,7*aS*)-6-(benzyloxy)-4-methyltetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyran-2-one (**IV-28**)

A solution of 59 mg (0.15 mmol) iodo-carbonate **IV-27** in 2 mL toluene was added 70 µL (0.22 mmol) TMSS and then quickly 5 mg (0.03 mmol) solid AIBN was added in one portion at 0 °C. The system was then cooled down to ~-50 °C and degassed with vacuum and refilled with Ar. This procedure was repeated three times and then the mixture was heated up to 75 °C for 40 min. The reaction mixture was cooled down to RT, and then directly loaded onto silica gel column. Elution with hexane-EtOAc (3:1, v/v) afforded carbonate **IV-28** 17.8 mg (45%) as colorless viscous oil; R_f (hexanes/EtOAc, 2:1 v/v) = 0.29; $[\alpha]_D^{20} +129$ (*c* 0.93, CHCl₃); IR (thin film, cm⁻¹) ν 3035, 2975, 2940, 1798, 1454, 1356, 1175, 1152, 1066, 1036, 1023, 919; ¹H NMR (CDCl₃, 600 MHz): δ 7.36-7.27 (m, 5H), 4.92 (dd, *J* = 5.4, 4.8 Hz, 1 H), 4.78 (ddd, *J* = 7.2, 7.2, 6.0 Hz, 1 H), 4.71 (d, *J* = 12.6 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.26 (dd, *J* = 9.0, 7.8 Hz, 1H), 4.01 (dq, *J* = 9.0, 6.0 Hz, 1H), 2.31 (ddd, *J* = 15.0, 5.4, 5.4 Hz, 1H), 2.19 (ddd, *J* = 15.0, 7.2, 4.8 Hz, 1 H), 1.31 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz): δ 154.3, 137.2, 128.5, 127.8, 127.7, 94.2,

77.0, 72.5, 69.3, 63.3, 30.7, 18.5; HRESIMS: Calculated for $[C_{14}H_{16}O_5+Na]^+$: 287.0890, Found: 287.0890.

(2*R*,3*S*,4*S*,6*S*)-6-(benzyloxy)-2-methyltetrahydro-2H-pyran-3,4-diol (IV-29)⁶⁵

A solution of 16 mg (0.06 mmol) carbonate **IV-28** in 2 mL THF was added 1 mL 2 M NaOH. The mixture was stirred at RT for 1 h. It was then diluted with EtOAc and passed through a pad of celite-silica gel-sand, eluting with EtOAc-MeOH (3:1, v/v). The effluent was dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography, elution with hexane-EtOAc (1.5:1, v/v) afforded the α -digitoxoside **IV-29** 12 mg (84%) as colorless oil; R_f (hexanes/EtOAc, 1:1 v/v) = 0.25; $[\alpha]_D^{20} + 107$ (c 1.2, $CHCl_3$); IR (thin film, cm^{-1}) ν 3461 (broad), 3090, 3065, 3033, 2975, 2918, 1497, 1454, 1407, 1235, 1148, 1120, 1101, 1054, 1010, 970; 1H NMR ($CDCl_3$, 600 MHz): δ 7.39-7.35 (m, 2H), 7.34-7.30 (m, 3H), 4.97 (d, J = 3.6 Hz, 1 H), 4.72 (d, J = 12.0 Hz, 1 H), 4.50 (d, J = 11.4 Hz, 1H), 3.96 (brs, 1 H), 3.77 (dq, J = 9.6, 6.0 Hz, 1H), 3.45 (brs, OH), 3.16 (dd, J = 10.2, 3.6 Hz, 1H), 2.48 (brs, OH), 2.22 (ddd, J = 15.0, 3.0, 1.2 Hz, 1H), 1.94 (ddd, J = 15.0, 3.6, 3.6 Hz, 1H), 1.33 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 136.9, 128.6, 128.1, 127.9, 96.4, 72.6, 69.5, 67.3, 64.7, 35.1, 17.8.

Ethyl 3-acetyl-4-hydroxy-5-oxo-2-(2-oxopropyl)-2,5-dihydrofuran-2-carboxylate (IV-36)⁵⁴

A sample of 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 complete addition, and the mixture was stirred at RT 24 h. Then it was poured into a mixture of 165g 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 reduced pressure 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 test. 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 (**IV-37**)⁵⁴

The crude product **IV-36** from last reaction was suspended in 500 mL H₂O and 45 g (0.77 mol) Mg(OH)₂ was slowly added at RT when stirring. The mixture was 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 afford crude solid product, which was then suspended in 270 mL methanol at RT. 13 mL concentrated H₂SO₄ was added into the mixture when stirring. After addition, the mixture was heated up and stirred under reflux for 12 h. Then it was cooled down to 0 °C 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 **IV-37** 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): δ 167.7, 155.8, 140.0, 130.9,

122.6, 121.1, 113.5, 52.4, 21.2.

Methyl 3-(tert-butyldimethylsilyloxy)-5-methylbenzoate (IV-37a)

A solution of 4 g (24.1 mmol) methyl ester **IV-37** in 24 ml CH_2Cl_2 was added 2.46 g (36.2 mmol) imidazole at 0 °C followed by a 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 °C, and then 70 mL H_2O was added. After separation, 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 NaHCO_3 , saturated brine and dried over Na_2SO_4 . 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 **IV-37a** 6.7 g (100%) as clear oil: R_f (hexanes/EtOAc, 3.5:1 v/v) = 0.62; IR (thin film, cm^{-1}) ν 2954, 2931, 2898, 2859, 1724, 1594, 1454, 1435, 1322, 1252, 1226, 1160, 1105, 1035, 982; ^1H NMR (CDCl_3 , 270 MHz): δ 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): δ 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): Calcd. for $[\text{C}_{15}\text{H}_{24}\text{O}_3\text{Si}+\text{H}]^+$: 281.1568, Found: 281.1569.

(3-(tert-butyldimethylsilyloxy)-5-methylphenyl)methanol (IV-38)

A solution of 6.7 g (24.1 mmol) ester **IV-37a** in 48 mL THF was slowly added 1.83 g (48.2 mmol) LiAlH_4 in several portions at 0 °C. After addition, the ice bath was removed and the mixture was then stirred at RT for 3 h. It was cooled down to 0 °C and diluted with 400 mL Et_2O , then carefully 3.6 mL 2 M NaOH was added dropwise, followed by the addition of 5.4 mL H_2O . The mixture was stirred at 0 °C 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_2SO_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 **IV-38** 5.4 g (89%) as clear oil: R_f (hexanes/EtOAc, 3:1 v/v) = 0.40; IR (thin film, cm^{-1}) ν 3306 (broad), 2956, 2930, 2886, 2859, 1595, 1462, 1315, 1253, 1161, 1042, 1019, 947; ^1H NMR (CDCl_3 , 270 MHz): δ 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): δ 155.7, 142.1, 139.6, 120.6, 120.0, 115.5, 65.2, 25.6, 21.4, 18.1, -4.4; HRMS (ESI): Calcd. for $[\text{C}_{14}\text{H}_{24}\text{O}_2\text{Si}+\text{H}]^+$: 253.1618, Found: 253.1620.

3-(tert-butyldimethylsilyloxy)-5-methylbenzaldehyde (**IV-39**)⁶⁶

A solution of 5.4 g (21.4 mmol) benzyl alcohol **IV-38** in 33 mL hexane was added 18.6 g (214 mmol) activated MnO_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 **IV-39** 4.5 g (84%) as clear oil: R_f (hexanes/EtOAc, 3:1 v/v) = 0.62; ^1H NMR (CDCl_3 , 270 MHz): 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); ^{13}C NMR (CDCl_3 , 67.5 MHz): δ 192.4, 156.2, 140.4, 137.7, 127.3, 124.2, 117.2, 25.6, 21.2, 18.2, -4.4.

3-hydroxy-5-methylbenzaldehyde (IV-34)⁶⁷

A solution of 3.94 g (15.8 mmol) TBS ether **IV-39** in 20 mL MeOH was added 898 mg (4.73 mmol) solid *p*-TsOH•H₂O when 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 °C. Into the solution, 20 mL saturated aqueous NaHCO₃ was slowly added. The mixture was stirred at 0 °C for 10 min. After separation, 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 **IV-34** 2.0 g (93%) as white solid: *R_f* (hexanes/EtOAc, 2:1 v/v) = 0.42; ¹H NMR (CDCl₃, 270 MHz): δ 9.90 (s, 1H), 7.26 (s, 1H), 7.19 (s, 1H), 6.98 (s, 1H), 2.38 (s, 3H); ¹³C NMR (CDCl₃, 67.5 MHz): δ 192.9, 156.4, 140.8, 137.6, 124.2, 122.8, 112.2, 21.1.

(2*S*,3*S*)-tert-butyl 2-amino-3-methylpentanoate (IV-40)

A sample of 2.62 g (20.0 mmol) isoleucine **IV-6** was placed in a 40 mL pressure vessel, into which a premixed 20 mL THF and 5 mL concentrated H₂SO₄ was added when stirring. The suspension was cooled down to -78 °C under Ar. Then the inlet of Ar was closed, and isobutene was allowed to bubble through the solution via a needle. The bubbling was stopped until about 3 mL liquid of isobutene was seen floating on the solution. Quickly switch the septum to a pressure gauge and the pressure vessel was sealed. The mixture was stirred at RT for 15 h. The solution was cooled down to 0 °C, and then the pressure was released and quickly the mixture was poured into a suspension of 100 g ice in 200 mL 1.25 M aqueous NaOH when stirring. The

mixture was stirred at 0 °C for 15 min and extracted with EtOAc twice. The organic layer was subsequently washed with saturated aqueous NaHCO₃ and brine, then was dried over Na₂SO₄. Concentration of the solution resulted in isoleucine *t*-butyl ester **IV-40** 2.0 g (54%) as clear oil: ¹H NMR (CDCl₃, 270 MHz): δ 3.25 (d, *J* = 4.70 Hz, 1H), 2.03 (brs, 2H), 1.72 (m, 1H), 1.45 (s, 9H), 1.21 (m, 2H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 67.5 MHz): δ 174.5, 80.9, 59.3, 39.2, 28.1, 24.8, 15.6, 11.8.

2-Bromo-8-hydroxynaphthalene-1,4-dione (**IV-42**)⁵⁵

A suspension of 3.0 g (17.2 mmol) juglone (**IV-41**) in 45 mL HOAc was added 0.9 mL (17.2 mmol) Br₂ when stirring at RT. The mixture was stirred at RT for 15 min. Then it was poured into 50 g ice followed by addition of 150 mL H₂O. It was stirred at RT 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, eluting with hexane-CH₂Cl₂ (1:1, v/v), afforded a 3.5 g orange solid mixture (80% total yield), in which contained 81% 3-bromojuglone (**IV-42**) and 19% 2-bromojuglone.

3-bromojuglone (**IV-42**): *R_f* (hexanes/EtOAc, 3:1 v/v) = 0.54; ¹H NMR (CDCl₃, 270 MHz): δ 11.73 (s, 1H), 7.68 (dd, *J* = 7.7, 7.4 Hz, 1H), 7.64 (dd, *J* = 6.5, 1.0 Hz, 1H), 7.49 (s, 1H), 7.31 (dd, *J* = 7.4, 2.2 Hz, 1H); ¹³C NMR (CDCl₃, 150 MHz): δ 182.9, 181.6, 162.1, 141.2, 139.3, 137.2, 131.7, 124.7, 119.9, 114.0.

(2*S*,3*S*)-tert-butyl
methylpentanoate (**IV-43**)

2-(8-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)-3-

A solution of 253 mg (1.0 mmol) juglone mixture which contain 81% 2-bromojuglone (**IV-42**) in 1 mL CH₂Cl₂ at 0 °C was added a solution of 234 mg (1.25 mmol) isoleucine *t*-butyl ester in 1 mL CH₂Cl₂ when stirring, followed by addition of 139 μL Et₃N (1.0 mmol) in 1 mL CH₂Cl₂. The mixture was stirred at 0 °C for 15 min and then diluted with 30 mL hexane-EtOAc (1:1, v/v) and washed with 6 mL water. The aqueous layer was extracted with hexane-EtOAc (1:1, v/v) 20 mL. The pooled organic layer was subsequently washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography. Elution with hexane-EtOAc (10:1, v/v) afforded aminojuglone **IV-43** 240 mg (67%) as dark red oil: *R*_f (hexanes/EtOAc, 3:1 v/v) = 0.60; [α]_D²⁰ -60 (*c* 0.59, CHCl₃); IR (thin film, cm⁻¹) *ν* 3361, 2967, 2934, 1731, 1680, 1624, 1604, 1509, 1469, 1385, 1368, 1293, 1247, 1227, 1156, 1041, 918; ¹H NMR (CDCl₃, 600 MHz): δ 12.95 (s, 1H), 7.61 (dd, *J* = 7.2, 1.2 Hz, 1 H), 7.47 (dd, *J* = 8.4, 7.8 Hz, 1 H), 7.24 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 3.87 (dd, *J* = 8.4, 5.4 Hz, 1H), 1.97 (dqdd, *J* = 9.0, 7.2, 5.4, 5.4 Hz, 1H), 1.58 (dq, *J* = 13.8, 7.2, 5.4 Hz, 1H), 1.50 (s, 9H), 1.35 (ddq, *J* = 14.4, 9.0, 7.2 Hz, 1 H); 1.00 (dd, *J* = 7.8, 7.8 Hz, 3 H); 0.98 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR (CDCl₃, 150 MHz): δ 189.2, 180.7, 169.1, 161.1, 147.7, 134.0, 130.5, 125.8, 119.1, 114.8, 100.5, 83.1, 59.7, 37.5, 28.1, 25.9, 15.2, 11.6; HRESIMS: Calcd. for [C₂₀H₂₅NO₅+H]⁺: 360.1806, Found: 360.1807.

(2*S*,3*S*)-*t*-butyl 2-(3-bromo-8-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)-3-methylpentanoate (IV-44)[§]

A solution of 152 mg (0.42 mmol) aminojuglone **IV-43** in 4 mL CH₂Cl₂ at 0 °C was added a solution of 24 µL (0.46 mmol) Br₂ and 38 µL (0.46 mmol) pyridine in 4 mL CH₂Cl₂. It was stirred at 0 °C for 10 min, then it was diluted with hexane-EtOAc (1:1, v/v) 80 mL followed by addition of 15 mL H₂O. The organic layer was separated and subsequently washed with saturated aqueous NaHCO₃, saturated brine and dried over Na₂SO₄. After removal of the solvent, the residue was subjected to silica gel column chromatography. Elution with hexane-EtOAc (20:1,v/v) afforded 2-bromo-3-aminojuglone **IV-44** 140 mg (76%) as dark red oil: *R_f* (hexanes/EtOAc, 1:1 v/v) = 0.78; [α]_D²⁰ +20 (*c* 2.9, CHCl₃); IR (thin film, cm⁻¹) ν 3300, 2965, 2930, 2875, 1725, 1680, 1620, 1605, 1586, 1458, 1237, 1214, 1151, 1131, 1108, ; ¹H NMR (CDCl₃, 600 MHz): δ 12.56 (s, 1H), 7.56 (brs, 1H), 7.46 (dd, *J* = 8.4, 7.8 Hz, 1 H), 7.22 (dd, *J* = 8.4 Hz, 1 H), 5.18 (brs, 1H), 1.98 (brs, 1H), 1.62 (dq, *J* = 12.6, 7.2, 4.8 Hz, 1H), 1.49 (s, 9H), 1.37 (ddq, *J* = 14.4, 9.6, 7.2 Hz, 1 H); 1.01 (dd, *J* = 7.8, 7.2 Hz, 3 H); 0.96 (d, *J* = 7.2 Hz, 3 H); HRESIMS: Calculated for [C₂₀H₂₄BrNO₅+H]⁺: 438.0906, Found: 438.0913.

3-(1,3-dioxan-2-yl)-5-methylphenol (IV-34a)⁵⁸

[§] An average optical rotation was given due to the unstable data that was obtained. The ¹³C NMR data was not given due to the broadening of most signals of carbons on the quinone part, a copy of the spectra was enclosed in the spectra section.

A solution of 1.77 g (13.0 mmol) benzaldehyde **IV-34** in 70 mL benzene was placed in a 100 mL flask which was equipped with a distillation assembly. Into the 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 the total volume of solution was about 5-10 mL. 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 **IV-34a** 2.11 g (84%) as white solid: *R_f* (hexanes/EtOAc, 2:1 v/v) = 0.31; ¹H NMR (CDCl₃, 270 MHz): δ 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); ¹³C NMR (CDCl₃, 67.5 MHz): δ 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 (**IV-45**)⁵⁸

A solution of 172 mg (0.89 mmol) phenol **IV-34a** in 1.5 mL CH₂Cl₂ at °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-Et₂O (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 hexan-Et₂O (1:1, v/v) and the pooled organic layer was subsequently washed with saturated aqueous NaHCO₃, saturated brine and dried over Na₂SO₄. 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 **IV-45** 150 mg (68%) and elution with hexane-EtOAc (3:1, v/v) recovered 42 mg starting material (20%). MOM ether **IV-45**: White solid; *R_f* (hexanes/EtOAc,

2:1 v/v) = 0.49; ^1H NMR (CDCl_3 , 600 MHz): δ 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 (dddd, 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): δ 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-(1,3-dioxan-2-yl)-6-(methoxymethoxy)-4-methylphenyl)tributylstannane (IV-46)⁵⁸

A solution of 1.82 g (7.65 mmol) MOM ether **IV-45** in 23 mL hexane at $^{\circ}\text{C}$ was added 4.9 mL 2.34 M (11.5 mmol) *n*-BuLi. The mixture was stirred at $^{\circ}\text{C}$ for 1 h. Then 3.3 mL Bu_3SnCl was slowly added in to the reaction mixture at $^{\circ}\text{C}$. It was stirred at $^{\circ}\text{C}$ for another 1 h. It was then diluted with hexane- Et_2O (1:1, v/v) 200 mL followed by addition of 60 mL saturated aqueous NaHCO_3 . The mixture was stirred at $^{\circ}\text{C}$ for 1 h. The organic layer was separated and the aqueous layer was extracted with hexane- Et_2O (1:1, v/v). The pooled organic layer was subsequently washed with saturated brine and dried over Na_2SO_4 . After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (25:1, v/v) afforded phenylstannane **IV-46** 1.94 g (49%). Elution with hexane-EtOAc (5:1, v/v) recovered 650 mg starting material (36%). Phenylstannane **IV-46**: clear oil; R_f (hexanes/EtOAc, 2:1 v/v) = 0.78; ^1H NMR (benzene- d_6 , 600 MHz): δ 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): δ 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.

Naphthalene-1,5-diyl diacetate (**IV-48**)⁵⁹

A solution of 5 g (31.2 mmol) naphthalenediol **IV-47** 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, washing with water several times. After being dried by using vacuum, 7.4 g (97%) diacetate **IV-48** was afforded as brown solid: R_f (hexanes/EtOAc, 1:1 v/v) = 0.55; ^1H NMR (CDCl_3 , 270 MHz): δ 7.80 (d, J = 8.4 Hz, 2 H), 7.52 (dd, J = 8.2, 7.7 Hz, 2H), 7.31 (d, J = 7.4 Hz, 2H), 2.46 (s, 6H); ^{13}C NMR (CDCl_3 , 67.5 MHz): δ 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 (**IV-49**)⁵⁹

2.44 g (10.0 mmol) diacetate **IV-48** 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_2O 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. Yellow precipitate started to form. Filtration and washing with water. After drying, 1.9 g 2-bromojuglone acetate (**IV-49**) was obtained (66%). Yellow crystal: R_f (hexanes/EtOAc, 2:1 v/v) = 0.46; ^1H NMR (CDCl_3 , 600 MHz): δ 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): δ 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 (IV-50)⁵⁹

A solution of 765 mg (2.59 mmol) acetate **IV-49** in 26 mL 95% ethanol was added 8.5 mL 1.5 M aqueous H₂SO₄. The solution was stirred under reflux condition for 3 h. It was then cooled down to RT and diluted with EtOAc 100 mL and washed with water 150 mL twice. The organic layer was subsequently washed with saturated aqueous NaHCO₃, saturated brine and then dried over Na₂SO₄. 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 (**IV-50**) 459 mg (70%). Orange solid: *R_f* (hexanes/EtOAc, 2:1 v/v) = 0.51; ¹H NMR (CDCl₃, 270 MHz): δ 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); ¹³C NMR (CDCl₃, 67.5 MHz): δ 187.5, 177.2, 161.7, 140.9, 140.3, 136.4, 130.7, 125.1, 121.0, 114.7.

2-(2-(1,3-dioxan-2-yl)-6-(methoxymethoxy)-4-methylphenyl)-5-hydroxynaphthalene-1,4-dione (IV-51)

A suspension of 253 mg (1.0 mmol) juglone **IV-50**, 526 mg (1.0 mmol) stannane **IV-46**, and 19.0 mg (0.10 mmol) CuI in 8 mL THF at RT was added a solution of 25.9 mg (0.025 mmol) Pd₂(dba)₃•CHCl₃ and 26.2 mg (0.10 mmol) PPh₃ in 2 mL THF. The mixture was stirred at 75 °C for 5 h. It was then cooled down to 0 °C and diluted with 100 mL EtOAc and washed with saturated aqueous NaHCO₃, saturated brine, then 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 coupled product **IV-51** 310 mg (76%). Orange solid, mp: 44-46 °C; R_f (hexanes/EtOAc, 2:1 v/v) = 0.47; IR (thin film, cm^{-1}) ν 2955, 2925, 2850, 1639, 1455, 1247, 1148, 1050, 999; ^1H NMR (CD_3OD , 600 MHz): δ 7.70 (dd, J = 8.4, 7.8 Hz, 1 H), 7.61 (dd, J = 7.2, 1.2 Hz, 1H), 7.31 (dd, J = 8.4, 1.2 Hz, 1H), 7.12 (brs, 1H), 7.04 (brs, 1H), 6.86 (s, 1H), 5.38 (s, 1H), 5.08 (d, J = 6.6 Hz, 1H), 5.07 (d, J = 7.2 Hz, 1H), 3.99 (m, 2H); 3.80 (ddd, J = 12.0, 12.0, 3.0 Hz, 1H), 3.76 (ddd, J = 12.0, 12.0, 2.4 Hz, 1H), 3.33 (s, 3H), 2.38 (s, 3H), 1.94 (dddd, J = 13.2, 12.0, 12.0, 4.8, 4.8 Hz, 1H), 1.30 (dddd, J = 13.2, 2.4, 2.4, 1.2, 1.2 Hz, 1H); ^{13}C NMR (CD_3OD , 150 MHz): δ 191.7, 184.5, 162.5, 155.9, 150.4, 141.7, 139.2, 138.4, 137.8, 134.0, 125.0, 121.8, 121.2, 120.4, 116.5, 101.8, 95.9, 68.4, 68.3, 56.6, 26.8, 21.9; HRESIMS: Calculated for $[\text{C}_{23}\text{H}_{22}\text{O}_7+\text{H}]^+$: 411.1438, Found: 411.1440.

3-hydroxy-2-(5-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-5-methylbenzaldehyde (IV-53)

A sample of 80 mg (0.20 mmol) MOM ether **IV-51** was placed in a 50 mL flask. A premixed solution of 5 mL 4.5 M $\text{HCl}_{(\text{aq})}$ /THF (1:1, v/v) was added at RT. The solution was stirred on preheated oil bath (65 °C) for 10 min under Ar. The reaction mixture was then quickly cooled down to 0 °C, and diluted with 20 mL EtOAc, followed by addition of 20 mL saturated aqueous NaHCO_3 . After separation, the aqueous layer was extracted with EtOAc and the pooled organic layer was washed with saturated brine and dried over Na_2SO_4 . After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with hexane-EtOAc (2:1, v/v) afforded deprotected product **IV-53** 14 mg (23%). Orange solid, mp: 144-150 °C; R_f (hexanes/EtOAc, 2:1 v/v) = 0.28; IR (thin film, cm^{-1}) ν 3250 (brs), 2925, 2860, 1670, 1637, 1604, 1453, 1363, 1310, 1244, 1162, 1047, 900; ^1H NMR (CD_3OD , 600 MHz): δ 9.8 (s, 1H), 7.71 (dd,

$J = 8.4, 7.8$ Hz, 1 H), 7.60 (ddd, $J = 7.2, 1.2$ Hz, 1H), 7.33 (q, $J = 1.2$ Hz, 1H), 7.32 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.09 (d, $J = 1.2$ Hz, 1H), 6.87 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (CD_3OD , 150 MHz): δ 194.1, 191.6, 184.8, 162.5, 156.8, 149.9, 142.6, 137.9, 137.8, 137.6, 134.4, 127.2, 124.9, 123.6, 120.3, 118.7, 116.7, 21.3; HRESIMS: Calculated for $[\text{C}_{18}\text{H}_{12}\text{O}_5 + \text{H}]^+$: 309.0758, Found: 309.0759.

Jadomycin A (**IV-1**)^{44a}

A suspension of 14 mg (0.045 mmol) aldehyde **IV-53** in 3 mL toluene was added 51 μL (0.14 mmol) isoleucine *t*-butyl ester. The mixture was stirred for 2 days at RT with The flask only loosely capped in order that air could get in. The mixture was directly subjected to silica gel column chromatography. Elution with hexane-EtOAc (8:1,v/v) afforded a crude product, which was then treated with 0.15 mL TFA at RT for 1 h. Then it was diluted with 20 mL EtOAc and subsequently washed with saturated aqueous NaHCO_3 and saturated brine, then dried over Na_2SO_4 . After removal the solvent, a NMR experiment showed it's a mixture of two isomers with 6:1 ratio with the *cis* product as major. The two isomers can't be separated with silica gel column chromatography. Jadomycin A (**IV-1**): R_f (hexanes/EtOAc, 2:1 v/v) = 0.65; ^1H NMR (CDCl_3 , 600 MHz): δ 11.72 (s, 1H), 10.18 (s, 1H), 7.81 (d, $J = 7.8$ Hz, 1 H), 7.67 (dd, $J = 8.4, 7.2$ Hz, 1H), 7.25 (d, $J = 7.2$ Hz, 1H), 6.91 (s, 1H), 6.82 (s, 1H), 6.16 (s, 1H), 5.30 (d, $J = 3.0$ Hz, 1H), 2.37 (s, 3H), 1.83 (m, 2H), 1.56 (m, 1H), 1.04 (t, $J = 7.2$ Hz, 1H), 0.45 (d, $J = 6.6$ Hz, 1H); ^{13}C NMR (CDCl_3 , 150 MHz): δ 185.7, 183.5, 170.0, 162.0, 154.1, 143.3, 142.1, 137.7, 133.1, 129.9, 124.4, 122.1, 120.9, 120.9, 114.5, 113.3, 111.1, 87.2, 62.6, 40.0, 25.2, 21.3, 13.8, 11.9; HRESIMS: Calculated for $[\text{C}_{24}\text{H}_{21}\text{NO}_6 + \text{H}]^+$: 420.1442, Found: 420.1443.

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Supporting Spectra

For

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Mingde Shan

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^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 270 MHz)

X : parts per Million : ^1H

¹³C NMR (CDCl₃, 67.5 MHz)

^1H NMR (acetone- d_6 , 600 MHz)

^{13}C NMR (acetone- d_6 , 150 MHz)

^{13}C NMR (CD_3OD , 150 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (acetone- d_6 , 600 MHz)

^{13}C NMR (acetone- d_6 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (acetone- d_6 , 600 MHz)

^{13}C NMR (acetone- d_6 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (acetone- d_6 , 600 MHz)

^{13}C NMR (acetone- d_6 , 150 MHz)

¹³C NMR (acetone-d₆, 150 MHz)

^{13}C NMR (acetone- d_6 , 150 MHz)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (270 MHz)

CDCl_3

7.2783
7.2600

6.1734
6.1661

5.3223

4.6892
4.6764
4.6086

2.7726
2.7469
2.6141
2.6003

2.1706
2.0442

1.5852
1.5669
1.3378
1.3259

X : parts per Million : 1H

^{13}C NMR (67.5 MHz)

CDCl_3

^1H NMR (270 MHz)

CDCl_3

^{13}C NMR (67.5 MHz)

CDCl_3

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (270 MHz, CDCl₃)

^{13}C NMR (67.5 MHz, CDCl_3)

^1H NMR (600 MHz, CD_3OD)

^{13}C NMR (150 MHz, CD_3OD)

^1H NMR (270 MHz)

CDCl_3

7.2600
6.8706
6.8486
6.8330

6.0552
6.0515
6.0176

5.4899
5.2966
5.2801

2.7780
2.7515
2.2311
2.2274
2.1092
2.0927
2.0735
2.0570
1.5155
1.4899
1.4578
1.1665
1.1408

X : parts per Million : ^1H

^{13}C NMR (67.5 MHz)

CDCl_3

^1H NMR (600 MHz)

CDCl_3

¹³C NMR (150 MHz)

CDCl₃

¹H NMR (600 MHz)

CD₃OD

¹³C NMR (150 MHz)

CD₃OD

¹H NMR (600 MHz)

CD₃OD

^{13}C NMR (150 MHz)

CD_3OD

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

CDCl₃

^{13}C NMR (150 MHz)

CDCl_3

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz)

CD_3OD

^{13}C NMR (150 MHz)

CD_3OD

^1H NMR (600 MHz)

CDCl_3

^{13}C NMR (150 MHz)

CDCl_3

^1H NMR (600 MHz)

CDCl_3

^{13}C NMR (150 MHz)

CDCl_3

^1H NMR (600 MHz, CD_3OD)

^{13}C NMR (150 MHz, CD_3OD)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz)

CD_3OD

^{13}C NMR (150 MHz)

CD_3OD

¹³C NMR (150 MHz)

CD₃OD

^1H NMR (600 MHz)

CD_3OD

¹H NMR (270 MHz, CDCl₃)

^{13}C NMR (67.5 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

¹³C NMR (150 MHz, CDCl₃)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CD_3OD)

^{13}C NMR (150 MHz, CD_3OD)

¹H NMR (600 MHz, D₂O) (dr >15:1)

(2:1)

¹H NMR (600 MHz, D₂O)

(2:1)

^{13}C NMR (150 MHz, D_2O)

³¹P NMR (242 MHz, D₂O)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, D_2O)

^{13}C NMR (150 MHz, D_2O)

^{31}P NMR (242 MHz, D_2O)

^1H NMR (600 MHz, CD_3OD)

^{13}C NMR (150 MHz, CD_3OD)

¹H NMR (600 MHz, D₂O)

^{13}C NMR (150 MHz, D_2O)

^{31}P NMR (242 MHz, D_2O)

-0.612

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CD_3OD)

^{13}C NMR (150 MHz, CD_3OD)

^1H NMR (600 MHz, D_2O)

^{13}C NMR (150 MHz, D_2O)

^{31}P NMR (242 MHz, D_2O)

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

¹³C NMR (150 MHz, CDCl₃)

¹H NMR (600 MHz, CDCl₃)

¹³C NMR (150 MHz, CDCl₃)

^1H NMR (600 MHz, CD_3OD)

^{13}C NMR (150 MHz, CD_3OD)

^1H NMR (600 MHz, D_2O)

^{13}C NMR (150 MHz, D_2O)

^{31}P NMR (242 MHz, D_2O)

-0.594

¹H NMR (CDCl₃, 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

¹H NMR (CD₃OD, 600 MHz)

¹³C NMR (CD₃OD, 150 MHz)

$^1\text{H NMR}$ (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

¹H NMR (CDCl₃, 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

¹H NMR (CDCl₃, 600 MHz)

^1H NMR (CDCl_3 , 600 MHz)

¹H NMR (CD₃OD, 600 MHz)

¹H NMR (CDCl₃, 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

¹H NMR (CDCl₃, 270 MHz)

¹³C NMR (CDCl₃, 67.5 MHz)

^1H NMR (CDCl_3 , 270 MHz)

¹³C NMR (CDCl₃, 67.5 MHz)

¹H NMR (CDCl₃, 270 MHz)

^{13}C NMR (CDCl_3 , 67.5 MHz)

¹H NMR (CDCl₃, 270 MHz)

X : parts per Million : 1H

^{13}C NMR (CDCl_3 , 67.5 MHz)

¹H NMR (CDCl₃, 270 MHz)

X : parts per Million : 1H

¹³C NMR (CDCl₃, 67.5 MHz)

¹H NMR (CDCl₃, 270 MHz)

7.2600

4.1193
4.0928
4.0662

3.3974
3.2609
3.2435

2.0295
2.0259
1.4551
1.4505
0.9466
0.9265
0.9210
0.8999
0.8724

X : Parts per Million : 1H

^{13}C NMR (CDCl_3 , 67.5 MHz)

^1H NMR (CDCl_3 , 600 MHz)

¹H NMR (CDCl₃, 600 MHz)

¹³C NMR (CDCl₃, 150 MHz)

^1H NMR (CDCl_3 , 270 MHz)

^{13}C NMR (CDCl_3 , 67.5 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

¹H NMR (benzene-d₆, 600 MHz)

^{13}C NMR (benzene- d_6 , 150 MHz)

¹H NMR (CDCl₃, 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

¹³C NMR (CDCl₃, 150 MHz)

^1H NMR (CDCl_3 , 600 MHz)

^{13}C NMR (CDCl_3 , 150 MHz)

^1H NMR (CD_3OD , 600 MHz)

^{13}C NMR (CD_3OD , 150 MHz)

¹H NMR (CD₃OD, 600 MHz)

^{13}C NMR (CD_3OD , 150 MHz)

dr 6:1 (cis:trans)
 ^1H NMR (CDCl_3 , 600 MHz)

dr 6:1 (*cis:trans*)
 ^{13}C NMR (CDCl_3 , 150 MHz)