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De novo asymmetric synthesis of mannopeptimycin-E, novobiocin and methymycin analogues

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**De Novo Asymmetric Synthesis of Mannopeptimycin-E, Novobiocin
and Methymycin Analogues**

Sanjeeva Rao Guppi

**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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**Keywords: Mannopeptimycin-E, Novobiocin and Methymycin
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ABSTRACT

De Novo Asymmetric Synthesis of Mannopectimycin-E, Novobiocin and Methymycin Analogues

Sanjeeva Rao Guppi

The carbohydrate portion of the natural products plays a crucial role in biology, such as target binding, solubility, tissue targeting, and membrane transportation. The O'Doherty group use a de novo methodology to build the desired functionality and stereochemistry within each sugar, in contrast to the traditional approach using known sugar isomers as starting materials. Recently, we have developed a practical and highly diastereoselective palladium catalyzed glycosylation reaction to control the stereochemistry at the anomeric center. 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 mannopectimycin-E, novobiocin, methymycin, ribofuranose-adenosine and coumarin glycosides. All of which we felt were amenable to medicinal SAR studies.

Mannopectimicins are cyclic hexapeptides glycosylated with a disaccharide side chain, which possesses potent antibacterial activity against gram-positive bacteria with good activity against drug resistant (MDR) bacteria. An enantioselective syntheses of the *manno*-disaccharide fragments of mannopectimycin-E and its nine analogues were been achieved in 7-10 steps and 35-40% overall yield via an iterative palladium-glycosylation strategy. Key to the success of this approach was the ease with which the C-4 isovalerate group was introduced, and the high diastereoselectivity of the palladium-catalyzed glycosylation and bis-dihydroxylation reactions.

Recently novobiocin was shown to inhibit Hsp90 protein, which is a promising target for development of cancer chemotherapeutics. We developed a practical 7-10 steps diastereoselective route for the syntheses of nine different analogues of three aglycones all in good yields. This route relies on an alternative pyranol palladium-catalyzed glycosylation reaction, diastereoselective dihydroxylation, regioselective carbamate installation strategy. Currently, the nine-novobiocin analogues are being tested against different cancer cell lines in Prof. Blagg's labs.

Methymycin is a 12-membered macrolactone, an important class of antibiotics used to treat infections caused by Gram-positive bacteria. We have developed divergent and highly enantioselective route to eight various amino/azido/dideoxy methymycin analogues. The key to the success of this method is the iterative use of the palladium-catalyzed glycosylation reaction, Luche reduction and Myers' reductive rearrangement. Currently, a small library of methymycin analogues was under testing on glycosyltransferase assays in Prof. Hung-Wen Liu labs.

DEDICATED TO

**My wife, Supraja Guppi, my mother Parvathi, my father Lakshmi Narayana and
my grand mother Easwaramma.**

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List of Abbreviations

Ac	Acetyl
AD	Asymmetric dihydroxylation
Bn	Benzyl

Boc	<i>N</i> -tert-butoxycarbonyl
BOP	Benzotriazolyloxytris(dimethylamino)phosphonium hexa
bp	Boiling point
Bu	Butyl
BuLi	<i>n</i> -Butyllithium
calc	Calculated
CSA	Camphorsulfonic acid
d	Doublet
DBA	<i>trans,trans</i> -dibenzylideneacetone
DCC	Dicyclohexylcarbodiimide
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DIBAL-H	Diisobutylaluminum hydride
DIEPA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	<i>N, N</i> -Dimethylformamide
DMP	Dess-Martin periodinane

DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EI	Electron impact
Et	Ethyl
EtOAc	Ethyl acetate
	2-(1 <i>H</i> -Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
HBTU	hexafluorophosphate
HKR	Hydrolytic kinetic resolution
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High resolution mass spectrum
IR	Infrared
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
mCPBA	<i>m</i> -Chloroperbenzoic acid
Me	Methyl
MHz	megahertz
mmol	millimole(s)
MS	Mass spectrum

Chapter 1

Studies towards Palladium-Catalyzed Glycosylation Reaction and Syntheses of Biologically Important Glycosides.

1.1. Introduction.

Recently, it has been shown that the carbohydrate portion of the natural products play a crucial role in its biological activities, such as target binding, solubility, tissue targeting, and membrane transportation.¹ For example, the corresponding aglycons of natural products are often devoid of activity. Since the initial discovery of biologically active glycosylated natural products, medicinal chemists have desired the ability to change the carbohydrate structures of natural products to reveal the role the carbohydrate plays. Although nature uses a diverse array of carbohydrate structures in these natural products only a limited number of sugar isomers (glucose, galactose and mannose) are provided in accessible quantities for SAR studies, eventually affecting the ability of chemists to install rare/unnatural sugar isomers. Undoubtedly, synthetic alternative methods are required to address this medicinal chemistry need.

An alternative method would be to not use the carbohydrate based starting materials and prepare the desired carbohydrate functionality and chirality from simple achiral starting materials.^{2,3,4} This de novo methodology should allow the medicinal chemist to install a much broader range of carbohydrate structures amenable for SAR-studies. This new approach is in stark contrast to using known sugar isomers as starting materials where variability is narrow and extensive the protecting group chemistry is required. The term “de novo” approach is used to illustrate the way we built the desired functionality and stereochemistry within each sugar, in contrast to the traditional

carbohydrate approach, which start with known sugars. Herein we describe our efforts towards the development of this methodology and its ongoing application towards the synthesis of various carbohydrate structural motifs.

1.2. De Novo Syntheses of Various Hexose.

Over the past years, significant efforts have been made toward the development of new synthetic routes to monosaccharides.³ Of particular interest is the de novo synthesis of these sugar isomers (i.e., from simple achiral starting materials using asymmetric catalysis). While there are many uses of the term “de novo” in carbohydrate chemistry,⁵ herein the term de novo asymmetric syntheses refer to the use of asymmetric catalysis for the asymmetric synthesis of carbohydrates from achiral compounds (vide infra).

The de novo enantioselective synthesis of the various hexoses stands as a challenge to asymmetric catalysis.³ Despite some seminal efforts toward the hexoses, notably by Masamune/Sharpless (epoxidation),² Danishefsky (Diels-Alder),⁶ Johnson/Hudlicky (enzymatic desymmetrization)⁴ and Wong/Sharpless (osmium/enzyme),⁷ a practical, non-enzymatic route does not exist to all the hexoses.⁸ Recently this task has also been taken up by others like MacMillan (iterative aldol strategy)⁹ and White (allylic oxidation)¹⁰.

For the last ten years O'Doherty group have endeavored to develop practical methods for the de novo synthesis of the hexoses. Our group has resulted in the discovery of two orthogonal approaches to pyrano-hexoses with variable C-6 substitution as -CH₃/-CH₂OH.

Our first generation approach started with furfuraldehyde **I-1**, which when exposed to the Petersen olefination conditions (TMSCH₂MgCl/1N HCl) produced

vinylfuran **I-2** (Scheme 1). We derived the furfuryl alcohol stereochemistry in either enantiomeric form **I-3** and **I-4** by means of the Sharpless asymmetric dihydroxylation (AD-mix- α/β) of vinyl furan **I-2**.¹¹

Scheme 1. O'Doherty group's first-generation approach to furfuryl alcohols.

Because the enantioselectivity of dihydroxylation step was too low (~90% ee), we looked for a better approach and settled on the Noyori reduction of acylfurans (Scheme 2).¹² This improved approach requires the preparation of the acylketone **I-9** in three steps from glycolic acid **I-5** via a 2-lithiofuran addition to the TBS-protected amide **I-7** in 70% overall yield. The furyl alcohols **I-3/I-4** were enantioselectively prepared from Noyori asymmetric reduction of furyl ketone **I-9** catalyst **I-10a/I-10b** in good yields (85-90%) and excellent enantioselectivity (>95% ee).¹³

Scheme 2. O'Doherty group's improved approach to furyl alcohols via Noyori reduction.

The synthesis of pyrano-hexoses relies on the use of the Achmatowicz rearrangement¹⁴ (Scheme 4 for mechanism), which is an oxidative rearrangement of furfuryl alcohols **I-3/I-4** to hemiacetals **I-11/I-12**. Thus, treatment of furyl alcohols **I-3/I-4** with NBS in aqueous THF gave hemiacetals **I-11/I-12** in very good yields (Scheme 3). We have succeeded in developing a short route that is flexible enough for the syntheses of four possible diastereomeric hexoses **I-13**, **I-14**, **I-15** and **I-16** by selectively acylation with Boc anhydride in high yields (86-88%). Depending on the reaction temperature, the acylation step can selectively give the α -Boc pyranones **I-13** and **I-15** at (-78 °C) or a 1:1 ratio of α/β -Boc pyranones at room temperature.

Scheme 3. Syntheses of pyranones.

Scheme 4. Achmatowicz reaction and its mechanism.

1.3. De Novo Synthesis of Coumarin and Flavonol Glycosides.

A related family of interesting natural products are the coumarin and flavonol glycosides, which are used for the treatments of digestive disorders, bronchitis, and inflammation in traditional medicine.^{15,16,17} These active coumarin and flavonol glycosides attracted our attention towards the synthesis of several *manno*-glycoside analogues of these phenols, flavones and coumarins glycosides using our recently developed palladium catalyzed glycosylation reaction.

Recently, we have developed a practical and highly diastereoselective palladium catalyzed glycosylation reaction (coupling of **I-15** and **ROH** to give **I-17**) to control the stereochemistry at the anomeric center (Scheme 4). We have also demonstrated the practical utility of this reaction for the de novo synthesis of oligosaccharides.¹⁸

Scheme 4. Pd-catalyzed reaction and its mechanism.

Herein, we describe our results for the de novo synthesis of α - and β -linked coumarin and flavonol glycosides using this palladium catalyzed glycosylation reaction. In addition, the coumarin and flavone glycosylation products were transformed into *manno*-glycosides using a simple reduction/oxidation sequence.

Since our approach is quite mild and equally amenable to the glycosyl transfer of either a α - and β -linked glycosides. Initially we subjected several substituted phenols to the diastereoselective glycosylation reaction and gave excellent results.¹⁹ With these primary results at hand, we next explored the glycosylation reaction of the coumarins. The palladium-catalyzed glycosylation of coumarin **I-18** with α/β -pyranones **I-15/I-16** gave the respective α/β -glycosides **I-19 α /I-19 β** as a single diastereomers in good yields.

Scheme 5. Syntheses of coumarin glycosides.

The glycosylation reaction worked well with good yields for phenols and simple alcohols¹⁹ but not promising yields for coumarin and flavanol aglycones. A change in solvent from CH_2Cl_2 to THF for glycosylation of coumarins and flavone remarkably improved the yields. The yields of various coumarin α/β -glycosides shown in the table 1.

Table 1. Syntheses of various coumarin glycosides and their yields.

We next turned our attention towards the preparation of α - and β -flavanol-glycosides. Thus, using the same Pd-catalyzed glycosylation conditions (2.5 mol % Pd(0)/10% PPh₃, THF), the α -/ β -pyranones **I-15/I-16** were coupled with flavanol providing α / β - glycosides **I-33 α /I-33 β** respectively. The yields for flavanol glycosides were shown in Scheme 6.

Scheme 6. Syntheses of flavone glycosides.

The flavonol and coumarin α -glycoside products were easily converted into L-hexo-pyranoses by a two-step reduction/oxidation sequence. Thus by exposure of the glycosylated products to NaBH_4 at -78°C in CH_2Cl_2 and CH_3OH (Scheme 7) gave good yields (78-96%) of equatorial alcohols **I-41a-d** with complete stereocontrol (Table 2). Similarly, the resulting allylic alcohols **I-41a-d** could be diastereoselectively oxidized to the *manno*-triols **I-42a-d** in excellent yields (84-92%) with complete stereocontrol under the Upjohn condition (OsO_4/NMO).²⁰ The yields for reduction and dihydroxylation steps were all high and are summarized in table 2.

Scheme 7. Syntheses of various *manno*-sugars.

Table 2 Syntheses of various *manno*-glycosides and their yields

1.4. De Novo Asymmetric Synthesis of Homoadenosine.[†]

1.4.a. Introduction.

The hexopyranosyl nucleosides make up a large and varied class of natural products (e.g., blasticidin,²¹ gougerotin,²² hikizimycin,²³ mildiomycin,²⁴ the bagougeramines,²⁵ SF-2140,²⁶ the pentopyranines,²⁷ and miharamycin²⁸). In addition to the intriguing structures, they also possess distinct biological activities.²⁹ Inspired by these natural products, chemists have made two hexopyranosyl nucleosides 2-deoxy- β -D-*ribo*-hexopyranose adenosine (**I-51**)³⁰ and 2,3-dideoxy- β -D-*ribo*-hexopyranose adenosine (**I-52**).³¹ These homologous nucleosides of adenosine and deoxyadenosine possess obvious structural and configurational similarities to the corresponding ribofuranose adenosines **I-53** and **I-54** (Figure 1).

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Figure 1. Adenosines and hexopyranosyl nucleosides.

Biological studies of these ring-expanded analogues (**I-51** and **I-52**) have led to the discovery of several pyrano-nucleotide analogues with both antitumor and antiviral activity.³²

1.4.b. Project Description and Goals.

While there has been significant synthetic effort toward the synthesis of adenosine analogues,²⁹ we were interested in preparing pyrano-analogues of this class of compounds from an achiral starting material using enantioselective catalysis to set the asymmetry (de novo synthesis). In addition, we were interested in a synthesis that allows for the diastereoselective installation of the base at C-1. To test the breadth of this methodology, we set out to prepare various analogues of pyranose adenosines (**I-51** and **I-52**). To accomplish this goal, we needed to extend the palladium glycosylation reaction to nitrogen nucleophiles (e.g., benzimidazole and purines).³³ Herein, we describe our successful efforts to prepare the homoadenosine analogues (*ent*)-**I-51** and (*ent*)-**I-52**.³⁴

Scheme 8. Pd-catalyzed *N*-glycosylation.

To test the strategy, we carried out a model study using benzimidazole **I-55** and pyranone **I-15α**. The Pd-catalyzed *N*-glycosylation of benzimidazole **I-55** and pyranone **I-15α** successfully gave the desired glycosylated pyranone **I-56α** in good yield with complete stereocontrol (Scheme 8).

Our initial attempts at post-glycosylation modification of the *N*-glycoside with the α-anomers were not encouraging. The pyranone **I-56α** was readily reduced to give the *C*-4 allylic alcohol **I-57α**. This reduction, however, occurred with less stereocontrol at *C*-4 (4:1) as compared to NaBH₄ reduction of pyranone with *C*-1 α-oxygen substituents.³⁵ The post-glycosylation chemistry for these *N*-glycosides diverged with the *O*-glycosides during our attempts to modify the double bond of pyran **I-57α**. To our surprise, all attempts to either dihydroxylate or reduce **I-57α** were unsuccessful (Scheme 8).

Scheme 9. Pd-catalyzed *N*-glycosylation: Synthesis of *N*-glycosylated sugars.

To our relief, our difficulties with the α -anomer did not occur with the β -isomers (Schemes 9). The Pd-catalyzed *N*-glycosylation of benzimidazole **I-55** and pyranone **I-16β** successfully gave the desired glycosylated pyranone **I-58β** in good yield. Reduction of the pyranone **I-58β** using NaBH_4 at $-78\text{ }^\circ\text{C}$ gave exclusively allylic alcohol **I-59β**. Subjecting alcohol **I-59β** to Myers' reductive 1,3-transposition condition³⁶ (NBSH , PPh_3 / DEAD , NMM , $-30\text{ }^\circ\text{C}$ to rt) provided the rearranged olefin **I-60β** in good yield (65%). Dihydroxylation of **I-60β** using the Upjohn conditions (OsO_4 / NMO)²⁰ gave the diol **I-61β** in 85% yield. In contrast to the oxidation chemistry, **I-59β** could also be reduced, although not in high yield. Thus, exposing **I-60β** to excess diimide precursor ($\text{NBSH}/\text{Et}_3\text{N}$) gave the 2,3-dideoxypyranose **I-62β** in low yield (30%) but with good recovery of starting material (50%). While the yield of **I-62β** was low, this procedure was superior to traditional hydrogenation (H_2 , 5% Pd/C in MeOH), which occurred with complete hydrogenolysis of the *C*-1 benzimidazole. These successful model studies inspired us to synthesize the adenosine analogues.³⁴

Scheme 10. Enantioselective synthesis of homoadenosine and 2'-eoxy-homoadenosine.

Our synthesis commenced with the coupling of Boc-protected pyranone **I-16β** and commercially available 6-chloropurine **I-63**. Further subjection to the similar transformations used in model study gave homoadenosine (*ent*)-**I-51** and 2'-deoxyhomoadenosine (*ent*)-**I-52** in good yields.

1.5. Summary.

In conclusion, we have applied our practical palladium-catalyzed *O*-glycosylation reaction for the syntheses of phenol, flavonol and coumarin glycosides. Using our three-step protocol we have demonstrated the syntheses of coumarin and flavonol *L-manno*-pyranoses with excellent stereocontrol and high yields.

We have also developed highly enantio- and diastereoselective procedure for the preparation of hexopyranose adenosine analogues using palladium-catalyzed *N*-glycosylation reaction in five to six steps from Boc-protected pyranone. The synthesis of other potential analogues and evaluation of the biological activity of these compounds are ongoing.

Chapter 2

Asymmetric Synthesis and Medicinal Chemistry Studies of Novobiocin Analogues.

2.1. Introduction and biological activity to novobiocin analogues

The Aminocoumarin antibiotics, like novobiocin **II-1**, clorobiocin **II-2** and Coumermycin A1 **II-3** (Figure 2) are secondary metabolites isolated from several *Streptomyces* strains and show potent activity against Gram-positive bacteria.³⁷ These coumarin antibiotics share a key structural core of a 3-acetamido-4-hydroxy-coumarin and a rare-sugar fragment both of which play critical role in biological activities. These coumarin antibiotics bind to type II topoisomerases and DNA-gyrase B subunit and inhibit the enzyme catalyzed hydrolysis of ATP.³⁸

Figure 2. Naturally occurring aminocoumarin antibiotics.

Recently Novobiocin was shown to inhibit Hsp90 through C-terminal ATP binding site, which is a promising target for development of cancer chemotherapeutics (i.e., antitumor agents capable of inhibiting all six hallmarks of cancer by restraining Hsp90 protein folding machinery).³⁹ This promising biological activity and interesting structural features have inspired researchers to synthesize Novobiocin analogues.

2.2. Previous approaches to novobiocin analogues.

2.2.a. Photolabile novobiocin analogues.

Blagg *et al.* reported a convergent synthesis of four photolabile Novobiocin analogues in 2004.⁴⁰ Their synthesis started with the known compound 4,7- dihydroxy-8-methyl-2H-1-benzopyran-2-one **II-4**,⁴¹ which when treated with diazonium salt **II-5** gave the corresponding diazocoumarin derivative **II-6** (Scheme 11). This diazaphenyl group serves as an amine protecting group in **II-6**. Previously Blagg had prepared 3-sulphone coumarin analogues, which failed to selectively glycosylate (7 vs 4 phenolic positions) under typical Schmidt glycosylation condition.⁴²

Scheme 11. Synthesis of aminocoumarins.

In contrast when the diazocoumarin **II-6** was treated with trichloroacetimidate **II-7** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, it produced the 7-noviose diazocoumarin derivative **II-8** in good yield. Diazacoumarin **II-8** was deprotected by using hydrogenation conditions afford to 3-aminocoumarin **II-9**. Due to the instability of **II-9** to purification conditions, crude **II-9** was subjected to DCC conditions with 3-azido or 4-azidobenzoic acids yielding the desired amides **II-10** and **II-13** (Scheme 12). Previously Vaterlaus had studied the carbonate ring opening reaction to regioselectively form the desired carbamates.⁴³

Scheme 12. Synthesis of photolabile novobiocin analogues.

After careful optimization, Prof. Blagg group came up with a general methanolic ammonia (room temperature) conditions to prepare 3-carbamate noviose products **II-11** and **II-14** from amides **II-10** and **II-13** resulted in good yields respectively. Even under these optimized conditions the ring opening selectivities were less than perfect. Thus, significant amounts of the 2-carbamate isomers **II-12** and **II-15** were also isolated as minor products.

2.2.b. Hsp90 inhibitors

With success achieved in the initial synthesis of photolabile novobiocin analogues, Blagg turns to the preparation of novobiocin libraries with various coumarin substitution (Scheme 13). In 2005, Blagg *et al.* reported the Hsp90 inhibitors identified from a library of novobiocin analogues.⁴⁴ They started the library syntheses with a range of coumarins (**II-A** - **I-E**). These **II-A** - **II-E** coumarins were coupled with trichloroacetimidate-noviose carbonate **II-7** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to yield five coumarin- carbonates (**II-A1** - **II-E1**). These carbonates **II-A1** - **II-E1** were subjected to methanolic ammonia (ring opening conditions) to provide 2'-carbamoyl **II-A2-II-E2**, 3'-carbamoyl **II-A3-II-E3**, and des-carbamoyl compounds **II-A4-II-E4** in good yields.

Scheme 13. Syntheses of novobiocin analogues.

All novobiocin analogues in Scheme 3 were tested against Hsp90 client protein by incubating with SKBr3 breast cancer cells at a concentration of 100 μM . Western blot analysis of protein lysates showed that analogue **II-A4** (Figure 2) was the most active compound.

In 2006, Blagg *et al.* reported two more novobiocin analogues **DHN1** and **DHN2** (Figure 3), which are evaluated against Hsp90 and both analogues were significantly more potent than the natural product novobiocin.⁴⁵ The **DHN2** analogue proved to be more active than **DHN1**.

Figure 3. The DHN1 and DHN2 are selective Hsp90 inhibitors.

2.2.c. Biosynthesis and Glycorandomization of novobiocin analogues

Prof. Thorson's group also investigated the synthesis of Novobiocin analogues using a biosynthetic method. They called their approach *in-vitro* glycorandomization (IVG).⁴⁶ IVG was used for the biosynthesis of sugar libraries of various complex natural products.⁴⁷ In this study they have found a novobiocin specific glycosyl transferase enzyme NovM and screened it for activity with four aglycon coumarin analogues and ~40 sugar nucleotides. With these optimized procedure they used the NovM enzyme for the glycosylation of three nucleotides (**II-16**, **II-20** and **II-22**) with the novobiocin aglycon **II-18** to afford three new coumarin antibiotics (Scheme 14). Out of three novobiocin analogues, compound **II-19** showed the best antibiotic activity (MIC 5 $\mu\text{g mL}^{-1}$) compared with novobiocin **II-1** (MIC 0.06 $\mu\text{g mL}^{-1}$) and was consistent with novobiocin **II-1** mechanism of action.²

Scheme 14. Biosynthesis of new coumarin antibiotics.

Presented herein are two different approaches to glycosylated coumarin antibiotic analogues of the novobiocin. These approaches allowed for the preparation of analogues containing aminocoumarin core with various substituted deoxysugars. Interestingly, each group used modular synthesis with advanced building blocks and successfully addressed the key issues of both synthetic selectivity and biological activity.

2.3. Project Description and Goals

Since inhibitors of Hsp90 are considered to be novel target for anticancer therapeutics, we decided to prepare a small library of novobiocin analogues using our palladium-coupling chemistry. In collaboration with Prof. Blagg's lab, we planned to test our compounds on different cancer cell lines. This we felt was an excellent opportunity

to test our various novobiocin analogue compounds. A continuing theme of using asymmetric catalysis to improve the synthetic efficiency and atom economy of carbohydrate synthesis. The retrosynthetic analysis for our synthesis of novobiocin analogues is shown in Scheme 15. Several coumarin aglycones were coupled with pyranone ester **II-30** using our Pd-catalyzed glycosylation as the key reaction.⁴⁸ The pyranone ester **II-30** can be constructed from commercially available starting material acylfuran **II-24**.

Scheme 15. Retrosynthesis of novobiocin analogues.

2.4. Synthesis of Novobiocin Analogues

In this approach the pyranone asymmetry was derived by the use of a Noyori asymmetric hydrogenation of acylfuran **II-24** to yield furan alcohol **II-25**.⁴⁹ Pyranone **II-27** can easily be prepared from furan alcohol **II-25** by an Achmatowicz rearrangement, followed by hemiacetal protection with Boc anhydride. The more reactive axial anomeric alcohols can be acylated selectively (>20:1, $\alpha:\beta$) at -78°C . Alternatively at room temperature, (1.3:1) mixture of anomers can be produced with excellent enantiomeric excess >96% (Scheme 16).⁵⁰

Scheme 16. Synthesis of Boc-Pyranone.

We next turned our attention toward the preparation of *manno*-sugar linked coumarins. The glycosylation of 7-hydroxy 4-methyl coumarin alcohol **II-28** with the α -L-pyranone **II-27** in the presence of (5 mol% Pd(0)/10% PPh₃) to form the glycosylated pyranone **II-29** in 84% yield as a single diastereomer (Scheme 17). Pyranone **II-29** was subjected to Luche conditions⁵¹ (NaBH₄/CeCl₃, -78 °C) to reduce the ketone but unfortunately it fails to produce the desired allylic alcohol.

Scheme 17. Synthesis of glycosylated pyranol.

After investigating with different reaction conditions in the reduction step, we modified our approach by shifting the glycosylation step to after the reduction and methylation steps (Scheme 18). In this regard, the protecting group of pyranone was changed from carbonate (Boc) to Piv-ester due stability reasons during the reduction step.

Thus, hemiacetal **II-26** were subjected to PivCl to give Piv-protected enone **II-30** in excellent yield. The ketone of pyranone **II-30** was diastereoselectively reduced under Luche conditions forming the equatorial allylic alcohol in excellent yield (90%) followed by alkylation of allylic alcohol as methyl ether in neutral conditions (Ag_2O , MeI,) to give methyl ether **II-32** in 85% yield. We next explored the Pd-catalyzed glycosylation by subjecting allylic pivalate **II-32** to coumarin **II-28** under glycosylation conditions (5 mol % $\text{Pd}(0)/10\%\text{PPh}_3$), which afforded glycosylated coumarin **II-33** with complete stereocontrol in 80% yield.

Scheme 18. Synthesis of Glycosylated Coumarin

After successful completion of the glycosylation step, we move forward with dihydroxylation of **II-33** using the Upjohn conditions²⁰ (OsO_4/NMO), which gave exclusively the diol **II-34** in 85 % yield (Scheme 19). Then we regioselectively protected the C-2 axial alcohol of **II-34** via ortho ester formation, and selective hydrolysis to provide acetate **II-35** in 90% yield.⁵² Finally the C-5 des methyl noviose synthesis was completed by subjecting the free equatorial alcohol with chlorosulfonyl isocyanate,

followed by hydrolysis with $\text{K}_2\text{CO}_3/\text{MeOH}$ gave C3-carbamoyl analogue **II-36** in good yield (80% two steps).⁵³ Alternatively the dideoxy sugar analogue was prepared in excellent yields by exposing the allylic ether **II-33** to excess diimide precursor and base (93% yield).⁵⁴ Thus with this successful model study, we have synthesized three novobiocin analogues **II-34**, **II-36** and **II-37**.

Scheme 19. Synthesis of des-methyl-novobiocin analogues **II-34**, **II-36** and **II-37**.

Encouraged by the above results, we prepared a set of six analogues using the above methodology with two biologically promising aglycones **II-38** & **II-44** provided by Prof. Blagg research group (Scheme 20). Once again a Pd-catalyzed glycosylation of allylic pivalate **II-32** with the acetamido coumarin **II-38**, followed by series of post-glycosylation transformations gave three different analogues **II-40**, **II-41** and **II-43** with similar yields comparing with simple coumarin analogues (Scheme 20 & 21).

In this vein, we next explored the Pd-catalyzed glycosylation by subjecting allylic pivalate **II-32** to coumarin **II-38** under glycosylation conditions (5 mol% Pd(0)/10% PPh₃), which afforded glycosylated coumarin **II-39** in 80% yield (Scheme 10). Dihydroxylation of **II-39** using the Upjohn conditions²⁰ (OsO₄/NMO), which gave exclusively the diol **II-40** in 85 % yield. Alternatively the dideoxy sugar analogue **II-41** was prepared in excellent yields by exposing the allylic ether **II-39** to excess diimide precursor and base (95% yield).

Scheme 20. Syntheses of des-novobiocin analogues **II-40** and **II-41**.

Then we regioselectively protected the C-2 axial alcohol of **II-40** via ortho ester formation, and selective hydrolysis to provide acetate **II-42** in 91% yield (Scheme 21). Finally the C-5 des methyl novobiose synthesis was completed by subjecting the free equatorial alcohol with chlorosulfonyl isocyanate, followed by hydrolysis with K₂CO₃/MeOH gave C-3-carbamoyl analogue **II-43** in good yield (83% two steps).

Scheme 21. Synthesis of des-novobiocin analogue **II-43**.

Using the same chemistry, we explored the Pd-catalyzed glycosylation by subjecting allylic pivalate **II-32** to coumarin **II-44** under glycosylation conditions (5 mol% Pd(0)/10% PPh₃) gave glycosylated coumarin **II-45** in 85% yield (Scheme 22). Dihydroxylation of **II-45** using the Upjohn conditions (OsO₄/NMO) gave exclusively the diol **II-40** in 86 % yield. Alternatively the dideoxy sugar analogue **II-47** was prepared in excellent yields by exposing the allylic ether **II-45** to excess diimide precursor and Et₃N (96% yield).

Then again we regioselectively protected the C-2 axial alcohol of **II-46** via ortho ester formation, and selective hydrolysis to provide acetate **II-48** in 90% yield (Scheme 23). Finally the C-5 des methyl novobiose synthesis was completed by subjecting the free equatorial alcohol with chlorosulfonyl isocyanate, followed by hydrolysis with K₂CO₃/MeOH gave C-3-carbamoyl analogue **II-49** in good yield (81% two steps). After successful syntheses of a small library of nine novobiocin analogues, they were sent for activity testing at Blagg's lab against different cancer cell lines.

Scheme 22. Syntheses of des-novobiocin analogue **II-46** & **II-47**.

Scheme 23. Synthesis of des-novobiocin analogue **II-49**.

We next investigated the removal of the second methyl group at the C-5 center of the sugar position of the molecule. In this connection we have started building di-des-

methyl novobiocin analogues. Our synthetic strategy (Scheme 24) started by taking furyl alcohol **II-50** treating with NBS in aqueous THF (Achmatowicz reaction) gave hemiacetal **II-51** in 85% yield.

Scheme 24. Synthesis of des-*C*-5-methy-novobiocin analogue **II-55**.

Pd(0) glycosylation	% ee*	%yield
PPh ₃ , 0 °C, THF	0	85 %
<i>R,R</i> -Trost ligand, 0 °C, THF	60	75 %

* measured by HPLC

Acylation of hemiacetal **II-51** with PivCl provided the Piv protected pyranone **II-52** in good yield (80%). A reduction of pyranone **II-52** under Luche conditions gave racemic allylic alcohol **II-53** in 86% yield as a single diastereomer. Using 5 mol% palladium/*R,R* Trost ligand, allylic alcohol **II-53** was coupled with coumarin alcohol providing glycoside **II-54** in 75% yield with 60% ee where as racemic material could be

prepared using Ph_3P as the ligand. Exposing allylic alcohol **II-54** to the Upjohn conditions²⁰ (OsO_4/NMO) gave the diol **II-55** in good yield (85%).

2.5. Summary

In conclusion, we developed a practical 7 to 10 step diastereoselective route for the syntheses of nine different analogues of three aglycones all in good yields. This route relies on an alternative pyranol palladium-catalyzed glycosylation reaction, diastereoselective dihydroxylation, regioselective carbamate installation strategy. Currently, the nine-novobiocin analogues are being tested against different cancer cell lines in Prof. Blagg's labs.

Chapter 3

Enantioselective Synthesis of Mannopeptimycin-E analogues.[†]

3.1. Introduction to mannopeptimycins.

The continuing emergence of bacterial resistance to traditional antibiotics has inspired a never-ending search for new antibiotics.⁵⁵ The five mannopeptimycins (**III-1A-E**) were isolated from the fermentation broths of *Streptomyces hygroscopicus* LL-AC98 and related mutant strains.⁵⁶ The key structural features of the mannopeptimycins are a cyclic hexapeptide core with alternating D- and L-amino acids, three of which are rare. Two of the amino acids (β -D-hydroxyenuricididine and D-tyrosine) are glycosylated with mannose sugars. The glycosylated amino acids are an *N*-glycosylated β -hydroxyenuricididine with an α -mannose and an *O*-glycosylated tyrosine with a α -(1,4-linked)-bis-*manno*-pyranosyl pyranoside.

Figure 4. Structure of mannopeptimycin-E **III-1E**.

The unique structure and unprecedented biological activity have inspired both biological⁵⁷ and synthetic studies⁵⁸ from labs at Wyeth Pharmaceuticals. Among the mannopeptimycins, mannopeptimycin-E (**III-1E**, Figure 4) was reported as the most

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active member against methicillin-resistant staphylococci and vancomycin-resistant enterococci (Table 3).⁵⁹

Table 3. Activities of mannopeptimycins.

mannopeptimycins A-E	MIC range (µg/mL)	
	MRSA ^a	Enterococcus faecium ^b
A R =	>128	>128
B R = H	64-128	32->128
C R =	8	16-64
D R =	8	8-64
E R =	4	4-32

^a Methicillin-resistant *S. aureus*. ^b A range of activities four lines of vancomycin resistant. *i-val* = *i*-valerate

A particularly interesting aspect of the SAR for the mannopeptimycins is how the specific placement of the isovalerate group on the bis-*manno*-disaccharide correlates with its antibacterial activity. It has been shown that C-4 isovalerate substitution on the terminal mannose leads to a substantial increase in antibacterial potency. For instance,

mannopeptimycins-C and -D, which have C-2 and C-3 isovalerate groups, respectively, have reduced activity, whereas mannopeptimycins-A and -B, which lack isovalerate substitution, have even lower activity (Table 3).⁵⁹

3.2. Previous Approaches to Mannopeptimycin Analogues.

3.2.a. Synthesis of Mannopeptimycin derivatives

The crisis associated with the capability of organisms to develop resistance mechanisms to antibiotics has fueled the continuous search for new antibacterial agents.⁵⁵ The mannopeptimycins, a tris-*manno*-glycosylated class of cyclic hexapeptides with alternating D and L-amino acids, were isolated as part of this mission. Of the mannopeptimycins, mannopeptimycin-E (**III-1E**) (Figure 4) is the most active member, displaying activity against methicillin-resistant staphylococci and vancomycin-resistant enterococci.⁵⁶ In an effort to identify compounds with improved activity and SAR studies, chemists at Wyeth⁵⁸ have synthesized several derivatives of mannopeptimycins. Retrosynthetically, they envisioned that the ketal derivative **III-4** could be prepared from fully protected linear hexapeptide **III-5** using solid-phase chemistry and anticipated to cyclize the hexapeptide with the amide bond formation between the L-serine and unhindered glycine. Free amine of compound **III-5** was prepared by using D-tyrosine containing disaccharide **III-11** and five commercially available amino acids (Scheme 25). **Scheme 25.** Retrosynthesis of mannopeptimycin derivative **III-4**.

They synthesized the peptide disaccharide derivative **III-11** by coupling bis-*manno*-disaccharide **III-13** and protected tyrosine **III-12** using *N*-iodosuccinimide/trimethylsilyltriflate. Compound **III-13** was prepared from sugar intermediates **III-14** and **III-15** (Scheme 26).

Scheme 26. Retrosynthesis of tyrosine-bis-*mannose* **III-11**.

3.3. Project description and project goals.

This work confirmed the importance of the C-4 isovaleryl group for antibiotic activity. The critical role isovalerate substitution has on the antibacterial activity of the mannopeptimycin-E inspired us to pursue a synthesis of an appropriate *O*-glycosylated D-tyrosine with C-4 isovalerate substitution (e.g., **III-2a** and **III-2b**, Scheme 27).⁶⁰ In addition to our desire to synthesize and test the mannopeptimycin analogues **III-2a** and **III-2b**, we felt that the synthesis of **III-2a** would serve as part of a model study for our synthesis of the natural product. In addition, the preparation of **III-3b**, a fully protected bis-glycosylated tyrosine, would be of use for the synthesis of mannopeptimycin-E. Herein, we report the successful implementation of our palladium-catalyzed glycosylation reaction^{61,62} for the de novo installation of both a D,D- and an L,L-bis-*manno*-disaccharide fragment on a D-tyrosine. The flexibility of the approach is demonstrated by the syntheses of bis-2,3-dideoxy analogues in their D,D- and an L,L-forms.⁶³

Scheme 27. Retrosynthesis of mannopeptimycin-E **III-1E** and its key fragment **III-2a**.

Our retrosynthetic analysis of the disaccharide fragment **III-2a** and its fully protected variant **III-3b** is outlined in Scheme 27. We envisioned that the *manno*-stereochemistry in both **III-2a** and **III-3b** could be installed by a diastereoselective ketone reduction and a bis-dihydroxylation of a 1,4-linked pyran/pyranone **III-16**. Similarly, we believed that the pyran/pyranone **III-16** could be assembled using a diastereoselective palladium-catalyzed glycosylation of tyrosine **III-17**.⁶¹ Recently, we reported a diastereoselective palladium-catalyzed glycosylation reaction that used alcohols as nucleophiles and pyranones such as **III-18** as glycosyl donors. Thus, sequential application of our Pd(0)-glycosylation/NaBH₄ reduction/Pd(0)-glycosylation sequence to tyrosine **III-17** and pyranone **III-18** was expected to allow for the rapid preparation of **III-16**. Replacing the above-mentioned bis-dihydroxylation with a bis-diimide reduction might also allow for the preparation of the deoxy analogue **III-2b**. Previously, we have shown that pyranone **III-18** can be prepared in either enantiomeric

form. Thus, this procedure was expected to allow the incorporation of either D- or L-sugars.⁶⁴

3.4. Synthesis of key fragment of mannopeptimycin-E and its analogues.

Our synthesis studies began with the protected D-tyrosine **III-17** and pyranone **III-18** which, when exposed to 1 mol % $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and 4.0 mol % of PPh_3 , underwent a diastereoselective glycosylation with complete α -selectivity to afford the pyranone **III-20** in 92% yield. A diastereoselective 1,2-reduction of the enone **III-20** occurred, when it was subjected to NaBH_4 in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1) at -24°C , which afforded allylic alcohol **III-21** as a single diastereomer (dr > 20:1). We next investigated the viability of the C-4 alcohol in the Pd-catalyzed glycosylation. Exposing allylic alcohol **III-21** to a second glycosylation using 1.2 equiv of pyranone **III-18** and 1 mol % of Pd catalyst (1:2.5, $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3/\text{PPh}_3$) afforded the 1,4-linked- α -bis pyranone **III-16** in good yield (82%) and virtually complete stereocontrol (Scheme 28).

Scheme 28. De novo synthesis of disaccharide enone **III-16**.

The final post-glycosylation transformation of **III-16** is shown in Scheme 29. Treatment of 1,4-linked pyran/pyranone **III-16** under the same reduction conditions as before (**III-20** to **III-21**, Scheme 4) gave allylic alcohol **III-22** in excellent yield (91%) and diastereoselectivity (>20:1). The isovalerate group was installed by treating allylic

alcohol **III-22** with isovaleric acid and DCC/DMAP in CH₂Cl₂, which provided the C-4 isovalerate disaccharide precursor **III-23** in excellent yield (96%). The *manno*-stereochemistry in **3a** was diastereoselectively introduced⁶⁵ upon exposure of **III-23** to the Upjohn conditions²⁰ (OsO₄/NMO, 85%). Removal of both TBS-ethers was accomplished with TBAF (0 °C in THF) affording the α-1,4-linked-bis-*manno*-disaccharide **III-2a** in good yield (76%).

Scheme 29. Synthesis of tyrosine Bis-*manno*-disaccharide **III-2a**.

Finally the bis-*manno*-sugar **III-3a** could also be converted to the fully protected α-1,4-linked-bis-*manno*-disaccharide **III-3b** without any ester migration (Scheme 30). This was easily accomplished by treating a CH₂Cl₂ solution of tetraol **III-3a** with 2,2-dimethoxypropane and 10 mol % of CSA, which provided the bis-acetonide **III-3b** in good yield (80%).

Scheme 30. Synthesis of fully protected Bis-*manno*-disaccharide **III-3b**.

Replacing pyranone **III-18** with its L-enantiomer (*ent*)-**III-18** resulted in an equally efficient synthesis of the L,L-bis-*manno*-disaccharide diastereomer of **III-2a**, **III-26** (Scheme 31). Thus, in three analogous steps, D-tyrosine was converted into pyran/pyranone **III-24** (69% overall yield). The L,L-1,4-linked pyran/pyranone **III-24** was stereoselectively reduced and acylated to form **III-25** in good overall yield (86%). Once again, two diastereoselective dihydroxylations occurred upon exposure of **III-25** to the Upjohn conditions. This bis-dihydroxylation occurred with near perfect stereocontrol, as with the diastereomeric series (cf. Scheme 29). The tetraol product was converted to the unprotected bis-sugar **III-26** via a TBS group deprotection (TBAF, 78%) or to the fully protected diastereomer **III-27** by means of an acetonide protection (10 mol % of CSA/2,2-DMP, 81%).

Scheme 31. Synthesis of L,L-disaccharide analogues **III-26**.

Having synthesized the key disaccharide fragment of mannopeptimycin-E (**III-2a** and **III-3b**) along with its L,L-diastereomers (**III-26** and **III-27**), we turned our attention to the preparation of deoxy analogues (Scheme 32). The simplest 2,3-deoxy analogue **III-28** was obtained by an exhaustive diimide reduction.⁶⁶ Both double bonds of **III-23** were reduced using an excess of the diimide precursor NBSH in CH₂Cl₂ to afford the 2,3-deoxybis-pyranoside **III-28** in nearly quantitative yield (95%).⁶⁷ Under identical conditions, the diastereomeric L,L-1,4-linked bis bispyran **III-25** was reduced to give an excellent yield of the bis-dideoxy analogue **III-28** (97%).⁶⁷

Scheme 32. Synthesis of Bis-2,3-dideoxydisaccharide analogues **III-2b** and **III-28**.

3.5. Asymmetric synthesis of aza-analogue of mannopeptimycin-E disaccharide portion.[†]

3.5.a. Retrosynthetic analysis of aza-analogue of mannopeptimycin-E key fragment.

In particular, we were interested in the critical role of the C-4' isovaleryl group and its specific location played on antibacterial activity.^{56,59} It has been shown that removal or

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migration of the C-4' isovalerate substitution on the terminal mannose leads to a substantial decrease in antibacterial potency.^{56,59} Along this vein, we became interested in an aza-analogue **III-3** that should be resistant to both hydrolysis and migration (Scheme 33).

Herein, we describe the enantioselective synthesis of the C-4' acylated 1,4-*manno,manno*-4' amino disaccharide analogue **III-29** via the iterative use of highly diastereo- and regioselective palladium-catalyzed allylation reactions. Our retrosynthetic analysis of the aza-disaccharide fragment **III-29** is outlined in Scheme 33. This route begins with allylic alcohol **III-22**, which we have previously prepared enroute to the disaccharide **III-2**, via the sequential application of our Pd(0)-glycosylation/post-glycosylation transformations upon a protected tyrosine **III-17**.⁶¹ Key to this new approach to the C-4' amido analogue **III-29** is the regio- and stereoselective conversion of the allylic alcohol **III-22** to the allylic azide **III-32** by a palladium-catalyzed allylic substitution.⁶⁸ Finally, we envisioned the *manno,manno*-stereochemistry in **III-29** being installed by an azide reduction/acylation and stereoselective bis-dihydroxylation of a 1,4-linked-C-4' amino-bis-pyran **III-30**.⁶⁹ Simply substituting a bis-diimide reduction for the above mentioned bis-dihydroxylation would also allow for the preparation of a deoxy-analogue **III-36** (*vide infra*).

Scheme 33. Retrosynthetic analysis of mannopeptimycin analogue **III-29**.

3.5.b. Synthetic approach of aza-analogue of mannopeptimycin-E key fragment.

Our divergent approach to the aza-analogue **III-29** began with the known bis-pyran **III-22** with the conversion of the allylic alcohol portion into an π -allyl palladium leaving group (Scheme 34). We chose to use the methyl carbonate group as in **III-31**, which was readily prepared by treating **III-22** with methyl chloroformate in excellent yield (90%). Exposing carbonate **III-31** to the conditions developed by Sinou (TMSN_3 , $(\text{Pd}(\text{allyl})\text{Cl})_2/1,4\text{-bis}(\text{diphenylphosphino})\text{butane}$) at room temperature afforded a single regio- and stereoisomeric allylic azide **III-32** in good yield (88%).⁷⁰ To avoid problems with allylic rearrangements, the allylic azide **III-32** was immediately reduced with $\text{P}(n\text{-Bu})_3/\text{THF}$ to give allylic amine **III-30** (80%).⁷¹

Scheme 34. Synthesis of allylic amine **III-30**.

The key isovaleryl group was easily installed by treating allylic amine **III-30** with isovaleric acid and DCC/DMAP in CH₂Cl₂, which provided the C-4 isovaleryl amide disaccharide precursor **III-33** in excellent yield (85%) (Scheme 35). The *manno*-stereochemistry in **III-34** was diastereoselectively introduced upon exposure of **III-33** to the Upjohn conditions (OsO₄/NMO, 80%).^{20,62} To complete the model system both TBS-ethers were easily removed with TBAF (0 °C in THF) affording the 1,4-linked-bis-*manno*-4'-amido-disaccharide **III-29** in good yield (80%). In addition, the fully protected disaccharide **III-35** was also prepared for macrocyclic peptide assembly. This was easily accomplished by converting the bis-*manno*-C-4'-amido disaccharide **III-34** to the bis-acetonide **III-35** (10 mol % CSA/2,2-DMP, 80%).

Scheme 35. Synthesis of tyrosine-bis-*manno*-amido disaccharide **III-29** and **III-35**.

Finally, the 2,3-deoxy analogue **III-36** was readily prepared by an exhaustive diimide reduction (Scheme 36). Both double bonds of **III-33** were reduced with excess diimide precursor (NBSH) in CH₂Cl₂ affording the 2,3-deoxy-C4'-amido bis-pyranoside **III-36** in excellent yield (95%).⁶⁶

Scheme 36. Synthesis of bis-2,3-dideoxyamido disaccharide analogue **III-36**.

3.6. Syntheses of Serine and threonine analogue of mannopeptimycin-E key fragment.

After successfully making the key disaccharide fragment of mannopeptimycin E and its aza-analogues, we turned our attention to synthesize a small library of analogues of the disaccharide fragment of mannopeptimycin-E. In this vein, we replaced pyranone **III-18** with its L-enantiomer (*ent*)-**III-18** resulted in an equally efficient synthesis of the serine-L,L-bis-*manno*-sugar analogues **III-41**, **III-43** (Scheme 37). Thus, in three analogous steps, D-serine was converted into pyran/pyranone **III-39** in 67% overall yield. The L,L-1,4-linked pyran/pyranone **III-39** was stereoselectively reduced and acylated to form **III-40** in good overall yield (77%). Once again, two diastereoselective dihydroxylations occurred upon exposure of **III-25** to the Upjohn conditions. This bis-dihydroxylation occurred with near perfect stereocontrol, as with the diastereomeric series (cf. Scheme 29). The tetraol product was converted to the unprotected bis-sugar **III-41** via a TBS group deprotection (TBAF, 78%) or to the fully protected diastereomer **III-42** by means of an acetonide protection (10 mol % of CSA/2,2-DMP, 75%). Simply substituting a *bis*-diimide reduction for the above mentioned *bis*-dihydroxylation on compound **III-40** will allow for the preparation of a deoxy-analogue **III-36** with excellent yield (94%).

Scheme 37. Syntheses of serine analogues of mannopeptimycin-E key fragment **III-41** and **III-43**.

Because of our motivation to test similar compounds as antibiotics, we synthesized threonine-L,L-bis-*manno*-sugar analogues **III-47**, **III-49** by using L-pyranone **(ent)-III-18** and D-threonine **III-40** in an equally efficient manner (Scheme 38). Thus, in three analogous steps, D-threonine was converted into pyran/pyranone **III-45** in 70% overall yield. The L,L-1,4-linked pyran/pyranone **III-45** was stereoselectively reduced and acylated to form **III-46** in good overall yield (84%). Once again, two diastereoselective dihydroxylations occurred upon exposure of **III-46** to the Upjohn conditions. This bis-dihydroxylation occurred with near perfect stereocontrol, as with the diastereomeric series (cf. Scheme 29). The tetraol product was converted to the unprotected bis-sugar **III-47** via a TBS group deprotection (TBAF, 75%) or to the fully protected diastereomer **III-48** by means of an acetonide protection (10 mol % of

CSA/2,2-DMP, 78%). Simply substituting a *bis*-diimide reduction for the above mentioned *bis*-dihydroxylation on compound **III-46** will allow for the preparation of a deoxy-analogue **III-49** with excellent yield (96%).

Scheme 38. Synthesis of threonine analogues of mannopeptimycin-E key fragment **III-47** and **III-49**.

3.7. Towards asymmetric synthesis of Mannoepitimycin-E analogue.

The key portion of mannopeptimycin-E and its analogues have been prepared successfully with our *de novo* approach towards an idea of activity testing. Further, we turned our attention in developing a strategy to check the compatibility of carbohydrate approach with peptide sequence. In this vein, our proposed retrosynthetic approach was

shown in Scheme 39. Mannopeptimycin analogue **III-50** could be assembled from two linear tripeptide intermediates **III-51** and **III-52** using HBTU coupling conditions (Scheme 39).⁷²

Scheme 39. Retrosynthesis of mannopeptimycin-E analogue **III-50**.

Tripeptide **III-51** could be synthesized from D-/L-serine. We envisioned the other tripeptide **III-52a** could be prepared from coupling of three synthetic peptides glycine, phenylalanine and D-tyrosine (Scheme 40). A related procedure will be used to prepare the *O*-bismannose containing diastereomeric tripeptide **III-52b**.

Scheme 40. Retrosynthesis of tripeptides **III-51** and **III-52a/b**.

Outlined in Scheme 41 is the synthetic approach of L-ser-D-ser-L-ser tripeptide **III-63**. Our synthesis started with the protection of the primary alcohol of D-serine **III-59** as TBS ether **III-60**, followed by hydrolysis of methyl ester with NaOH/MeOH, which gave acid **III-55** in excellent yield (85%). Peptide **III-55** was coupled with L-ser-NH₂ **III-56** using HBTU in presence of Et₃N affording dipeptide **III-61** in 83% yield. Exposing dipeptide **III-61** under catalytic hydrogenolysis condition (Pd/C, H₂, MeOH) afforded the dipeptide amine **III-62** in good yield (90%). Tripeptide **III-63** was prepared by HBTU-mediated coupling between dipeptide amine **III-62** and L-serine-acid **III-54** in good yield (85%).⁷²

Scheme 41. Synthesis of tripeptide **III-63**.

Having synthesized the above tripeptide fragment, we turned our attention to the preparation of Gly-L-Phe-D-Tyr tripeptide **III-52a** (Scheme 42). Treatment of Cbz-Phe-OH **III-58** with trimethylsilyl chloride in presence of methanol gave methyl ester **III-64**. Subsequent treatment of compound **III-64** under hydrolysis condition (Pd/C, H₂, MeOH) afforded amine **III-65** in excellent yield (90%). Coupling of amine **III-65** with Cbz-Gly-OH **III-57** using HBTU gave dipeptide **III-66** in 85% yield. Further, treatment of dipeptide **III-66** under hydrolysis conditions (LiOH/MeOH) gave carboxylic acid **III-67** in 78% yield.

Tyrosine amine precursor **III-69** can be derived from commercially available D-tyrosine **III-68** using four synthetic steps of selective protections and deprotections. D-tyrosine **III-68** was protected as methyl ester with MeOH/SOCl₂, followed by protection of the amino group as its Cbz derivative under standard conditions afforded phenol **III-68a** in 95% yield for two steps.⁷³ Subsequent *O*-silylation of phenol **III-68a** with TBSCl/Et₃N gave fully protected tyrosine **III-53** in good yield (87%). Selective deprotection of Cbz group of compound **III-53** using catalytic hydrogenation (Pd/C, H₂, MeOH) gave the desired amine **III-69** in good yield (89%). Treatment of dipeptide acid **III-67** with amine **III-69** using HBTU gave tripeptide **III-52a** in 80% yield.

Scheme 42. Synthesis of tripeptide **III-52a**.

Having successfully synthesized the Gly-L-Phe-D-Tyr tripeptide in good yield, the next goal was to synthesize the *O*-bis-*manno*-tripeptide **III-52b** using similar procedures (Scheme 43). Thus, we subjected tyrosine-disaccharide fragment **III-3b** to catalytic hydrogenation (Pd/C, H₂, MeOH), which afforded the Bis-*manno*-Tyr-amine **III-70** in 75% yield. There was some concern about deprotection of TBS-ether during the hydrogenation step, but this turned out not to be the case neutral condition and lower reaction times were maintained. Under HBTU coupling conditions, the amine **III-70** and the carboxylic acid **III-67** gave desired *O*-bis-*manno*-tripeptide **III-52b** in good yield as single diastereomer (75%).

Scheme 43. Synthesis of *O*-bis-*manno*-tripeptide **III-52b**.

Completion of the synthesis of mannopeptimycin-E analogue **III-50** requires selective removal of protecting groups, followed by two coupling steps and global deprotection from the two advanced tripeptide intermediates **III-63** and **III-52b** (Scheme 44). These efforts are ongoing in the group.

Scheme 44. Synthesis of mannopeptimycin-E analogue **III-50**.

3.8. Summary

In conclusion, an enantioselective synthesis of the *manno*-disaccharide fragments of mannopeptimycin-E and its five analogues were been achieved in seven steps and 35-40% overall yields from D-tyrosine via an iterative palladium-glycosylation strategy. Key

to the success of this approach was the ease with which the C-4 isovalerate group was introduced, and the high diastereoselectivity of the palladium-catalyzed glycosylation and bis-dihydroxylation reactions. The use of this methodology gave two 1,4-linked-bis-*manno*-4'-amido-disaccharide analogues of mannopeptimycin-E, which have been synthesized in 10 steps with 21% overall yield from D-tyrosine via a palladium-catalyzed azide allylation reaction for the stereoselective installation of the C-4 isovaleramide group. We have synthesized the two advanced intermediate tripeptides using our de novo and traditional peptide chemistry. Further studies on the completion of synthesis of mannopeptimycin analogue **III-50** and their subsequent biological investigation will be reported in due course.

Chapter 4

Syntheses and Biosynthetic Studies of Methymycin Analogues.

4.1. Introduction to 12-membered lactone methymycin

The 12-membered macrolactones are an important class of antibiotics used to treat infections caused by Gram-positive bacteria.⁷⁴ *Streptomyces venezuelae* ATCC 15439 produces these 12-membered ring polyketides methymycin **IV-1**, 10-deoxymethynolide **IV-2** and neomethymycin **IV-3**, (Figure 5).⁷⁵ These polyketides contain a lactone aglycone attached to rare deoxy amino sugar as an important component. The biological activities of these secondary metabolites are dramatically decreases when the sugar is removed. Therefore modifications of these critical deoxy amino sugar substituents are important in order to generate new macrolide antibiotics with promising biological activity.⁷⁶

Figure 5. 12-membered macrolactones antibiotics.

A method for modifying natural products by combining existing biosynthetic genes from diverse allied bacteria to create a pathway for producing unnatural products

known as combinatorial biosynthesis, which has recently become a promising method for the development of new class of antibiotics. The macrolide antibiotic biosynthetic pathways from different species of *Streptomyces* has led to genetic manipulations to combine genes from various pathways for the biosynthesis of new hybrid macrolides with promising bioactivity.⁷⁷

There is a significant interest in the possibility of using combinatorial biosynthesis to generate new macrolactones attached with new deoxy sugar moieties. Recent studies on the flexibility of glycosyltransferases in accepting non-native sugars as substrate for attachment to specific macrolactones has made these enzymes an important tool for combinatorial biosynthesis of novel compounds with altered glycosylation patterns.⁷⁸ It is assumed that this research based on a combinatorial biosynthetic strategy will facilitate the development of new novel antibiotics.

4.2. Previous Approaches to Methymycin Analogues

4.2.a. Biosynthesis of methymycin and neomethymycin via glycosylation using DesVII/DesVIII mutants.

Hung-Wen Liu *et al.* have been making significant progress in using genetic and biochemical methods to develop new class of macrolide antibiotics using glycosyltransferase as their key biosynthetic tool.⁷⁹ They have used different enzyme gene clusters ranging from desI-desVIII of *Streptomyces venezuelae* involved in the biosyntheses of 12-membered macrolide antibiotics like methymycin **IV-1** and neomethymycin **IV-3** (Scheme 45). These polyketides mainly contain the single 3-dimethylamino-3,4,6-trideoxy sugar, desoamine, and different identified gene clusters,

represent a model system to probe the feasibility of making new macrolides containing modified sugar components *in vivo*.⁸⁰

Scheme 45. Biosynthesis of methymycin **IV-1** and neomethymycin **IV-3**.

As shown in Scheme 45, they tried to couple the sugar donor TDP-D-deosamine **IV-5**, and the aglycone acceptor 10-deoxymethynolide **IV-2** with the enzyme pair DesVII to get 10-deoxy methymycin **IV-4**. Unfortunately no products were detected. After exploring various conditions like solvent system/pH range/temperature, then surprisingly discovered that Des VIII as a necessary component in presence of enzyme DesVII at higher pH to produce the desired compound 10-deoxy methymycin **IV-4**. Compound **IV-4** was further modified by another enzyme PikC. They showed the catalytic properties of DesVII/DesVIII pair towards biosynthesis of various donor and acceptor substrates for the development of *in vitro* glycosylation of macrolides and other classes of natural products.⁸⁰

4.3. Project Description and Goals

Since the deoxyaminosugar portion of macrolides is essential for their antimicrobial activity,⁸¹ their modification hold promise as a valuable approach towards

preparing new macrolide antibiotics with improved biological properties.⁸² Many research groups have reported the use of modified biosynthetic pathways for the production of new glycosylated antibiotics;⁸³ however their use of complex sugar nucleotide intermediates and low-moderate yields leave room for improvement of macrolide antibiotics.

The main goal of this project is to develop a diastereoselective route to install different sugar motifs onto complex antibiotic aglycones from simple achiral starting material. In this connection our research group has initiated collaboration with Prof. Hung-Wen Liu's labs and developed the de novo approach, which would allow for facile synthesis of various methymycin analogues and planned to test our compounds in his labs.

Scheme 46. Retrosynthesis of methymycin analogues.

Our retrosynthetic analysis for the synthesis of methymycin analogues is shown in Scheme 46. Our plan was to develop a method for the installation of various amino and deoxy sugars onto 10-deoxymethynolide **IV-2** using our Pd-glycosylation/post glycosylation modification.⁸⁴ As previously discussed, all the required pyranone stereoisomers **IV-6**, **IV-6a**, **IV-27** and **IV-21** can be prepared by employing an enantioselective Noyori *R,R/S,S* reduction⁸⁵ of acyl furan **IV-6b**, followed by Achmatowicz oxidation, and diastereoselective carbonate formation.⁸⁶

4.4. Synthesis of Methymycin analogues

Our synthetic strategy starts with a selective reduction of the double bond in 10-deoxymethynolide **IV-2** by subjecting with excess diimide precursor⁸⁷ which gave the desired dihydro aglycone **IV-7** in 95% yield (Scheme 47). Aglycone **IV-7** underwent a diastereoselective palladium-catalyzed glycosylation with of α -Boc-pyranone **IV-6** producing α -glycoside **IV-8** as a single diastereomer and in good yield (86%). Luche reduction⁸⁸ of enone **IV-8** gave the equatorial allylic alcohol **IV-9** in 82% yield. Diimide reduction of allylic alcohol **IV-9** with excess triethylamine and *O*-nitrophenylsulfonyl hydrazide produced dideoxy analogue **IV-10** in excellent yield (90%).

Scheme 47. Synthesis of methymycin analogue **IV-10** and **IV-11**.

The *rhamnose*-sugar analogue **IV-11** was achieved by diastereoselective dihydroxylation using Upjohn conditions²⁰ (OsO_4/NMO) in 85% yield (Scheme 47).

We next investigated methods for construction of various *C*-4-amino/azido sugar analogues (Scheme 48). To do this, we converted the allylic alcohol **IV-9** into a methyl carbonate leaving group by reaction with methyl chloroformate to form *C*-4-carbonate **IV-12** in 70% yield.

Scheme 48. Synthesis of methymycin analogues **IV-14**, **IV-15** and **IV-16**.

Exposing carbonate **IV-12** to the Sinou conditions⁷⁰ (TMSN_3 , $(\text{Pd}(\text{allyl})\text{Cl})_2/1,4$ -bis(diphenylphosphino)butane) afforded a single regio-, and stereoisomeric allylic azide **IV-13** in 75% yield. As before, diimide reduction of allylic azide **IV-13** gave 2,3-dideoxy analogue **IV-14** in 90% yield. Once again, a diastereoselective dihydroxylation (OsO_4/NMO), followed by reduction of azide (Pd/C , H_2 , MeOH) produced amino-mannose analogue **IV-16** in 80% yield via rhamno-azide **IV-15** in 85%.

Hydrogenolysis (Pd/C , H_2 , MeOH) of allylic azide **IV-13** gave dideoxy amino sugar analogue **IV-17** via one-pot reduction of both azide and allylic double bond in 82% yield (Scheme 49).

With successful syntheses of amino- and deoxy-rhamnose sugar analogues of methymycin, next explored the synthesis of inverted amino sugar analogue **IV-17** at the C-4-position (Scheme 49).

Scheme 49. Synthesis of dideoxy-amino analogues **IV-17** and **IV-20**.

When carbonate **IV-12** was subjected to Mitsunobu conditions using TMS azide as the nucleophile, no desired *C*-4-azido compound **IV-19** was formed. We next turned to a two step $\text{S}_{\text{N}}2$ reaction route. Thus allylic alcohol **IV-9** was converted into mesylate **IV-18** ($\text{MsCl/Et}_3\text{N}$) in excellent yield 88%, followed by treating **IV-18** with NaN_3/THF to give the inverted *C*-4-azido compound **IV-19** in 86% yield. Reduction of the *C*-4-azido group and allylic double bond in compound **IV-19** under hydrogenolysis conditions ($\text{Pd/C, H}_2, \text{MeOH}$) gave *C*-4-deoxy-amino analogue of methymycin **IV-20** in excellent yield 80%.

Figure 6. The reverse glycosyl transferase assay using HPLC chromatogram analysis on our small library of eight compounds.

Reactions with narbonolide

Reactions with ty lactone

Reactions with 10-dml

TLC assay of reverse reaction:

Lx means standard of compound 10d-Lx
 X is reaction of the same compound
 Aglycone product spots are shown with arrows

Prof. Hung-Wen Liu group had tested all eight compounds (Compound **IV-9**, **IV-10**, **IV-11**, **IV-13**, **IV-14**, **IV-15**, **IV-16**, **IV-17**) as sugar donors in the reactions with three different acceptors: 10-deoxymethynolide, narbonolide, and tylactone (Figure 6). They ran assays from 5 h to overnight and analyzed the reactions with narbonolide by HPLC and TLC, and two other sets by HPLC. Then they did the reverse assay only (no aglycone acceptor added, excess of TDP) just to see if the enzyme recognizes the substrates. By TLC assay, it appears that **IV-9**, **IV-10**, **IV-13**, **IV-14**, **IV-17** are de-glycosylated, and **IV-11**, **IV-15**, **IV-16** are not. These initial results imply that some (**IV-9**, **IV-10**, **IV-13**, **IV-14**, **IV-17**) sugars are hydrolyzed but not transformed to the new substrate, which implies L-analogs are not recognized well. There may be better chance of success with D-analogs since they see up to 30% transfer with natural sugar. Thus we plan to investigate the syntheses β -D-sugar methymycin analogues.

In this connection, we next investigated the synthesis of 2,6 dideoxy β -D-*allo*-sugar analogue **IV-25** of methymycin (Scheme 50). The methodology developed by our group for the synthesis of Digitoxin and its analogues has been used in the synthesis of 2,6 dideoxy β -D-*allo*-sugar. Thus taking 10-dideoxymethynolide **IV-7** and β -D-pyranone **IV-21** subjecting to palladium-catalyzed glycosylation gave the β -D-glycoside **IV-22** as single diastereomer and in good yield (90%). Luche reduction of ketone **IV-22** provided a mixture of diastereomeric allylic alcohols **IV-23** in 83% yield.

Scheme 50. Synthesis of *allose*-sugar analogue **IV-25**.

Scheme 51. Mechanism of Myers' reductive rearrangement.

Further, exposing the mixture of allylic alcohols **IV-23** to the Myers' reductive rearrangement conditions⁸⁹ (NBSH, Ph₃/DEAD, NMM, -30 °C to rt) provided olefin **IV-24** in moderate yield (63%) (Scheme 51). Finally, dihydroxylation of olefin **IV-24** using the Upjohn conditions (OsO₄/NMO) gave exclusively the 2,6 dideoxy *allose*-sugar analogue **IV-25** in 90% yield.

Encouraged by the above results, we next investigated our palladium-catalyzed glycosylation reaction to methymycin aglycone **IV-26** with α -D-pyranone **IV-27**. Our

strategy worked well and gave single regioselective glycosylated product **IV-28** in 75% yield with the free tertiary alcohol left unreacted (Scheme 52). The structure of **IV-28** was confirmed using 1D NOE difference, COSY and heterocorrelation HETCOR experiments.

Scheme 52. Synthesis of methynolide- α -D-glycoside **IV-28**.

4.5. Summary

In conclusion, a divergent and highly enantioselective route to eight various amino/azido/dideoxy methymycin analogues have been developed. The key to the success of this method is the iterative use of the palladium-catalyzed glycosylation reaction, Luche reduction/Myers' reductive rearrangement, diastereoselective dihydroxylation, and regioselective reductions. This unique application of our Pd-catalyzed glycosylation efficiently prepares a challenging and important α/β -glycoside target. Currently, a small library of methymycin analogues was under testing on glycosyltransferase assays in Prof. Hung-Wen Liu labs.

Chapter 5

Experimental Section.

General Methods and materials.

General Methods and materials: ^1H and ^{13}C spectra were recorded on Joel 270 and Varian 600 spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00+) or CDCl_3 (δ 7.26) or CD_3OD (δ 4.87) for ^1H and CDCl_3 (δ 77.1) or CD_3OD (δ 49.15) for ^{13}C . Optical rotations were measured with a Jasco DIP-370 digital polarimeter in the solvent specified. Infrared (IR) spectra were obtained on a prospect MIDAC FT-IR spectrometer. Flash column chromatography was performed on ICN reagent 60 (60-200 mesh) silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates (Whatman K6F 60Å, F254) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde 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 and triethylamine were dried by passing through activated alumina (8 x 14 mesh) column with nitrogen 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/septa techniques.

1-(2'-Furyl)-2-trimethylsilanylethan-1-ol (I-2a).¹⁴

Magnesium turnings (10.1 g, 0.415 mol) were placed in a 1 L-3-neck round bottom flask and a condenser along with a side arm addition funnel were attached. The apparatus was flame dried (3x), each time flushing with nitrogen. Chloromethyltrimethylsilane (42.4 g, 0.346 mol) in 200 mL of Et₂O were added slowly to the dry magnesium. After the addition, the solution was refluxed for 1 h. Freshly distilled furfural (25.0 mL, 0.302 mol) and 300 mL of Et₂O were added slowly to the Grignard reagent at 0 °C and the solution was stirred for 3 h at 0 °C and 9 h at room temp. The reaction was quenched with 200 mL of sat. aq. NH₄Cl and extracted (3 x 100 mL) with Et₂O. The organic layer was washed with satd aq NaHCO₃ (2 x 50 mL), brine (2 x 50 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give 1-(2'-furyl)-2-trimethylsilanylethan-1-ol **I-2a** in 90% yield, 50.1 g (0.272 mol): *R_f* (30% Et₂O/hexanes) = 0.58; IR (thin film, cm⁻¹) 3390, 2950, 2895, 1655, 1505, 1250; ¹H NMR (270 MHz, CDCl₃) δ 7.28 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.24 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.13 (d, *J* = 3.3 Hz, 1H), 4.77 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.13 (bs, 1H), 1.28 (dd, *J* = 14.1, 8.8 Hz, 1H), 1.23 (dd, *J* = 14.1, 6.8 Hz, 1H), -0.10 (s, 9H); ¹³C NMR (67.5 MHz, CDCl₃) δ 157.7, 141.6, 110.1, 105.5, 65.6, 24.8, -1.4 (3C); CIHRMS Calcd for [C₉H₁₆O₂Si]⁺: 184.0920. Found 184.0905.

1-(2'-Furyl)-ethan-1R, 2-diol (I-2b).¹⁴

The β-hydroxy silane **I-2a** (44.2 g, 0.240 mol) and 120 mL of Et₂O were added to a 500 mL round bottom flask followed by addition of 120 mL of 1 M HCl and the solution was stirred for 1 h. Phases were separated and the aq layer was extracted (2 x 50 mL) with

Et₂O and combined with the organic layer. The organic layer was washed (2 x 50 mL) with sat. aq. NaHCO₃ and added to a solution of 300 mL of *t*-BuOH, 750 mL of H₂O, 50 g of AD-mix- α , 133 g of K₃Fe(CN)₆, and 56 g of K₂CO₃ at 0 °C. The solution was vigorously stirred with a mechanical stirrer for 12 h at 0 °C. The reaction was slowly quenched with (500 mL) satd aq Na₂SO₃. The phases were separated and the aqueous layer was extracted (6 x 100 mL) with EtOAc. The organic layer was washed with satd aq NaHCO₃ (2 x 100 mL), brine (2 x 100 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 40% Et₂O/hexanes to yield 1-(2'-furyl)-ethan-1*R*,2-diol **I-2b** 25.0 g (0.195 mol, 85%): *R_f* (50% Et₂O/hexanes) = 0.37; [α]_D²¹ = +32.0 (*c* 2.17, CH₂Cl₂); IR (thin film, cm⁻¹) 3390, 2933, 2881, 1684, 1505, 1464, 1228; ¹H NMR (270 MHz, CDCl₃) δ 7.30 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.27 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.23 (dd, *J* = 4.0, 0.6 Hz, 1H), 4.71 (t, *J* = 5.9 Hz, 1H), 4.54 (bs, 2H), 3.74 (d, *J* = 5.9 Hz, 2H); ¹³C NMR (67.5 MHz, CDCl₃) δ 153.9, 142.3, 110.5, 107.0, 68.4, 65.0; CIHRMS Calcd for [C₆H₈O₃ + NH₄]⁺: 146.0817. Found 146.0822; Anal. Calcd for C₆H₈O₃: C, 56.23; H, 6.30. Found: C, 56.04; H, 6.20.

1-(2'-Furyl)-2-*tert*-butyldimethylsilanyloxyethan-1-*R*-ol (I-3).¹⁴

Diol 1-(2'-furyl)-ethan-1*R*,2-diol **I-2b** (0.986 g, 7.70 mmol), 15 mL of CH₂Cl₂, and 5.5 mL of Et₃N were added to a round bottom flask and cooled to 0 °C. A catalytic amount (50 mg, 0.41 mmol) of DMAP was added followed by addition of *tert*-butyldimethylsilyl chloride (1.19 g, 7.89 mmol) and the solution was stirred at 0 °C for 6 h. The reaction

was quenched with 1 M NaHSO₄ and extracted (3 x 25 mL) with Et₂O, washed with satd aq NaHCO₃ (2 x 20 mL), and dried (Na₂SO₄). The crude product was purified by silica gel flash chromatography eluting with 25% Et₂O/hexanes to yield 1-(2'-furyl)-2-*tert*-butyldimethylsilanyloxyethan-1*R*-ol **I-3** 1.69 g (6.97 mmol, 91%): *R_f* (30% Et₂O/hexanes) = 0.55; [α]²¹_D = +15.9 (*c* 1.37, CH₂Cl₂); IR (thin film, cm⁻¹) 3447, 2954, 2930, 2884, 2857, 1471, 1463, 1361; ¹H NMR (270 MHz, CDCl₃) δ 7.37 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.35 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.33 (dd, *J* = 3.3, 0.9 Hz, 1H), 4.75 (dd, *J* = 6.4, 4.6 Hz, 1H), 3.86 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.85 (dd, *J* = 10.1, 6.7 Hz, 1H), 3.04 (bs, 1H), 0.90 (s, 9H), 0.07 (s, 6H); ¹³C NMR (67.5 MHz, CDCl₃) δ 154.0, 142.0, 110.3, 107.1, 68.5, 65.9, 26.0 (3C), 18.4, -5.3 (2C); CIHRMS Calcd for [(C₁₂H₂₂O₃Si)-H₂O]⁺: 225.1310. Found 225.1296; Anal. Calcd for C, 59.47; H, 9.16. Found C, 59.80; H, 9.37.

6-Hydroxy-(2*R*)-2-*tert*-butyldimethylsilanyloxymethyl-2*H*-pyran-3-(6*H*)-one (I-12).¹⁴

Compound 1-(2'-furyl)-2-*tert*-butyldimethylsilanyloxyethan-1*R*-ol **I-4** (1.69 g, 6.97 mmol), 12 mL of THF, and 3 mL of H₂O were added to a round bottom flask and cooled to 0 °C. Solid NaHCO₃ (1.17 g, 13.9 mmol), NaOAc•3H₂O (0.950 g, 6.98 mmol), and NBS (1.24 g, 6.97 mmol) were added to the solution and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with satd aq NaHCO₃ (15 mL), extracted (3 x 25 mL) with Et₂O, dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel chromatography eluting with 20% EtOAc/hexanes to give 6-hydroxy-(2*R*)-2-*tert*-butyldimethylsilanyloxymethyl-2*H*-pyran-3-(6*H*)-one **I-12** 1.71 g (6.62 mmol, 95%):

R_f (40% Et₂O/hexanes) = 0.40; IR (thin film, cm⁻¹) 3388, 2951, 2929, 2884, 2858, 1699, 1464, 1256; ¹H NMR (270 MHz, CDCl₃) major isomer δ 6.93 (dd, J = 10.3, 3.3 Hz, 1H), 6.12 (dd, J = 10.4, 0.6 Hz, 1H), 5.79 (dd, J = 5.1, 3.1 Hz, 1H), 4.59 (dd, J = 5.0, 2.8 Hz, 1H), 4.02 (dd, J = 11.2, 5 Hz, 1H), 3.93 (dd, J = 11.2, 2.0 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C NMR (67.5 MHz, CDCl₃) major isomer δ 194.9, 145.9, 128.1, 88.1, 76.7, 63.5, 25.8 (3C), 18.5, -5.2, -5.3; CIHRMS Calcd for [(C₁₂H₂₂O₄Si)+H]⁺: 259.1366. Found 259.1366; Anal. Calcd for C, 55.79; H, 8.59. Found C, 55.86; H, 8.45.

Carbonic acid *tert*-butyl ester 6-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yl ester (I-15).¹⁴

6-Hydroxy-(2*R*)-2-*tert*-butyldimethylsilanyloxymethyl-2*H*-pyran-3-(6*H*)-one **I-12** (2.58 g, 10 mmol) was dissolved in CH₂Cl₂ (8 mL) and the solution was cooled to -78 °C. A CH₂Cl₂ (2 mL) solution of (Boc)₂O (2.61 g, 12 mmol) and a catalytic amount of DMAP (122 mg, 1 μmol) was added to the reaction mixture. The reaction was stirred for 1 h at -78 °C. The reaction was quenched with 50 mL of satd. aq NaHCO₃, extracted (3 x 50 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc/hexanes to give 2.93 g (8.20 mmol, 82%) of carbonic acid *tert*-butyl ester 6-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yl ester **I-15**: R_f (20% Et₂O/hexanes) = 0.70; $[\alpha]_D^{21}$ = +47.7 (c = 1.5, CH₂Cl₂); IR (thin film, cm⁻¹) 2956, 2932, 2858, 1754, 1703, 1472, 1371, 1277, 1257; ¹H NMR (270 MHz, CDCl₃) δ 6.88 (dd, J =

10.2, 3.7 Hz, 1H), 6.45 (d, $J = 3.5$ Hz, 1H), 6.23 (d, $J = 10.2$ Hz, 1H), 4.54 (dd, $J = 3.5$, 3.3 Hz, 1H), 4.05 (d, $J = 3.5$ Hz, 1H), 4.03 (d, $J = 3.5$ Hz, 1H), 1.51 (s, 9H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 193.6, 151.7, 141.4, 129.2, 89.1, 83.5, 77.7, 62.6, 27.6 (3C), 25.8 (3C), 18.2, -5.3 (2C); CIHRMS Calcd for $[\text{C}_{17}\text{H}_{30}\text{O}_6\text{Si}+\text{Na}]^+$: 381.1716. Found 381.1716.

Carbonic acid *tert*-butyl ester 6-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yl ester (I-16).¹⁴

6-Hydroxy-(2*R*)-2-*tert*-butyldimethylsilanyloxymethyl-2*H*-pyran-3-(6*H*)-one **I-12** (2.58 g, 10 mmol) was dissolved in CH_2Cl_2 (8 mL) and the solution was cooled to 0 °C. A CH_2Cl_2 (2 mL) solution of $(\text{BOC})_2\text{O}$ (2.61 g, 12 mmol) and a catalytic amount of DMAP (122 mg, 1 μmol) was added to the reaction mixture. The reaction was stirred for 1 h at 0 °C. The reaction was quenched with 50 mL of satd. aq NaHCO_3 , extracted (3 x 50 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc /hexanes to give 2.57 g (7.17 mmol, 72%) of two diastereomers of carbonic acid *tert*-butyl ester 6-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yl ester **6c α** and **I-16** in 1:1 ratio R_f (20% Et_2O /hexanes) = 0.70; $[\alpha]_D^{21} = -32.27$ ($c = 1.5$, CH_2Cl_2); IR (thin film, cm^{-1}) 2926, 1742, 1680, 1283, 1252, 1162, 1066; ^1H NMR (270 MHz, CDCl_3) δ 6.86 (dd, $J = 10.4$, 2.7 Hz, 1H), 6.40 (dd, $J = 2.7$, 1.3 Hz, 1H), 6.25 (dd, $J = 10.4$, 1.2 Hz, 1H), 4.33 (dd, $J = 5.9$, 3.7 Hz, 1H), 4.00 (dd, $J = 11.2$, 5.7 Hz, 1H), 3.94

(dd, $J = 11.0, 3.7$ Hz, 1H), 1.51 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 193.6, 152.0, 142.6, 129.2, 89.2, 83.4, 80.7, 64.4, 27.7 (3C), 25.8 (3C), 18.3, -5.4 (2C); CIHRMS Calcd for $[\text{C}_{17}\text{H}_{30}\text{O}_6\text{Si}+\text{Na}]^+$: 381.1716. Found 381.1714.

6-Benzyloxy-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-6*H*-pyran-3-one (I-17).

A CH_2Cl_2 (3.2 mL) solution of compound **I-15** (1.5 g, 4.189 mmol) and benzyl alcohol (543 mg, 5.027 mmol) was cooled to 0 °C. A CH_2Cl_2 (1 mL) solution of $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (54 mg, 2.5 mol%) and PPh_3 (43 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with 5 mL of satd aq NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc /hexanes to give 1.29 g (3.72 mmol, 89%) of **I-17**: R_f (20% EtOAc /hexanes) = 0.56; $[\alpha]_D^{21} = +27.5$ ($c = 1.5$, CH_2Cl_2); IR (thin film, cm^{-1}) 2929, 2359, 1699, 1253, 1133, 1037, 836; ^1H NMR (270 MHz, CDCl_3) δ 7.34 (m, 5H), 6.86 (dd, $J = 10.2, 3.3$ Hz, 1H), 6.10 (d, $J = 10.2$ Hz, 1H), 5.40 (d, $J = 3.3$ Hz, 1H), 4.87 (d, $J = 11.6$ Hz, 1H), 4.67 (d, $J = 11.6$ Hz, 1H), 4.50 (dd, $J = 4.5, 2.9$ Hz, 1H), 4.04 (m, 2H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 194.6, 143.8, 136.9, 128.5, 128.2 (2C), 128.0 (2C), 92.0, 76.1, 70.4, 62.4, 25.8 (3C), 18.2, -5.3 (2C); CIHRMS Calcd for $[\text{C}_{19}\text{H}_{28}\text{O}_4\text{Si}+\text{H}]^+$: 349.1835. Found 349.1819.

6-Benzyloxy-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-3,6-dihydro-2*H*-pyran-3-ol (I-17b).

A CH₂Cl₂ (2.86 mL) solution of compound **I-17** (1 g, 2.86 mmol) and MeOH (2.8 mL) was cooled to -78 °C. NaBH₄ (108 mg, 2.86 mmol) was added and the reaction mixture was stirred at -78°C for 3 hours. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of satd aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give 903 mg (2.58 mmol, 90%) of **I-17b**: *R*_f (40% EtOAc/hexanes) = 0.32; [α]_D²¹ = - 31.0 (c = 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3442, 2929, 1462, 1255, 1043, 838; ¹H NMR (270 MHz, CDCl₃) δ 7.35 (m, 5H), 5.93 (dd, *J* = 10.2, 1.1 Hz, 1H), 5.77 (ddd, *J* = 10.2, 2.5, 2.3 Hz, 1H), 5.74 (dd, *J* = 2.5, 2.3 Hz, 1H), 5.04 (dd, *J* = 2.5, 1.9 Hz, 1H), 4.77 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.18 (m, 1H), 3.80 (dd, *J* = 8.5, 3.9 Hz, 1H), 3.74 (m, 1H), 2.88 (d, *J* = 3.7 Hz, 1H), 0.92 (s, 9H), 0.10 (s, 6H); ¹³C NMR (67.5 MHz, CDCl₃) δ 138.0, 132.9, 128.3 (2C), 127.9 (2C), 127.6, 125.7, 93.4, 70.1, 70.0, 67.0, 65.0, 25.8 (3C), 18.2, -5.4, 5.5; CIHRMS Calcd for [C₁₉H₃₀O₄SiNa⁺]: 373.1811 Found 373.1805.

2-Benzyloxy-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-tetrahydro-pyran-3,4,5-triol (I-17c).

To a *t*-butanol, acetone (0.3 mL, 1:1, 1M) solution of allyl alcohol **I-17b** (100 mg, 0.285 mmol) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (0.1 mL). Crystalline OsO₄ (0.5 mg, 1 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column (1 cm × 4”) using a small amount of CH₂Cl₂ (0.6 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/ether (2:98 to 4:96). Pure fractions were combined and concentrated to afford triol **I-17c** 91 mg (0.238 mmol, 84%): *R_f* (70% EtOAc/hexanes) = 0.32; [α]²¹_D = - 50.1 (c = 2, CH₂Cl₂); IR (thin film, cm⁻¹) 3406, 2929, 1460, 1254, 1098, 838; ¹H NMR (270 MHz, CDCl₃) δ 7.31 (m, 5H), 4.86 (s, 1H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.27 (m, 1H), 4.02 (m, 1H), 3.91-3.61 (m, 7H), 0.89 (s, 9H), 0.07 (s, 6H); ¹³C NMR (67.5 MHz, CDCl₃) δ 137.2, 128.3 (2C), 127.9 (2C), 127.7, 98.7, 71.7, 70.4, 69.6, 68.8, 67.5, 64.2, 25.8 (3C), 18.2, -5.3, 5.4; CIHRMS Calcd for [C₁₉H₃₂O₆SiNa⁺]: 407.1866 Found 407.1882.

7-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy]-chromen-2-one (I-25**).**

A THF (0.3 mL) solution of compound **I-16** (100 mg, 0.28 mmol) and 7-hydroxy coumarin (90 mg, 0.56 mmol) was cooled to 0 °C. A THF (0.3mL) solution of Pd₂(DBA)₃·CHCl₃ (7.2 mg, 2.5 mol%) and PPh₃ (7.3 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with 2 mL of satd aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried

(Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15-20% EtOAc/hexanes to give **I-25** 75 mg (0.18 mmol, 65%) of 10b α : R_f (20% EtOAc/hexanes) = 0.36; $[\alpha]_D^{21} = 129.9$ ($c = 0.7$, CH₂Cl₂); IR (thin film, cm⁻¹) 2927, 1735, 1732, 1696, 1231, 1125, 836; ¹H NMR (600 MHz, CD₃OD) δ 7.83 (d, $J = 9.6$ Hz, 1H), 7.50 (d, $J = 9.6$ Hz, 1H), 7.11 (dd, $J = 10.2, 2.4$ Hz, 1H), 7.10 (d, $J = 2.4$ Hz, 1H), 7.04 (dd, $J = 9.0, 1.8$ Hz, 1H), 6.24 (br s, 1H), 6.23 (d, 2.4 Hz, 1H), 6.21 (dd, $J = 2.4, 1.2$ Hz, 1H), 4.39 (dd, $J = 6.6, 3.0$ Hz, 1H), 3.95 (dd, $J = 11.4, 7.2$ Hz, 1H), 3.88 (dd, $J = 10.8, 3.0$ Hz, 1H), 0.80 (s, 9H), -0.09 (s, 3H), -0.16 (s, 3H); ¹³C NMR (150 MHz, CD₃OD) δ 198.4, 195.3, 162.9, 161.4, 145.8, 145.4, 130.4, 129.8, 115.4(2C), 114.4, 105.1, 94.0, 81.7, 64.9, 26.1 (3C), 19.0, -5.3, -5.5; CIHRMS Calcd for [C₂₁H₂₆O₆Si+Na]⁺: 425.1390. Found 425.1420.

7-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-2H-pyran-2-yloxy]-chromen-2-one (I-23).

A THF (0.3 mL) solution of compound **I-15** (100 mg, 0.28 mmol) and 7-hydroxy coumarin (90 mg, 0.56 mmol) was cooled to 0 °C. A THF (0.3mL) solution of Pd₂(DBA)₃·CHCl₃ (7.2 mg, 2.5 mol%) and PPh₃ (7.3 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with 2 mL of satd aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15-20% EtOAc/hexanes to give 75 mg

(0.18 mmol, 65%) of **I-23**: R_f (20% EtOAc/hexanes) = 0.36; $[\alpha]_D^{21} = -96.10$ ($c = 0.7$, CH_2Cl_2); IR (thin film, cm^{-1}) 2927, 1736, 1702, 1615, 1231, 1125, 836; ^1H NMR (600 MHz, CD_3OD) δ 7.64 (d, $J = 9.6$ Hz, 1H), 7.40 (d, $J = 9.0$ Hz, 1H), 7.14 (d, $J = 1.8$ Hz, 1H), 7.06 (dd, $J = 9.0, 2.4$ Hz, 1H), 7.02 (dd, $J = 10.2, 3.0$ Hz, 1H), 6.30 (d, $J = 9.0$ Hz, 1H), 6.29 (d, $J = 10.2$ Hz, 1H), 6.09 (d, $J = 3.0$ Hz, 1H), 4.50 (dd, $J = 4.8, 3.0$ Hz, 1H), 4.05 (dd, $J = 12.0, 4.2$ Hz, 1H), 3.03 (dd, $J = 12.0, 3.0$ Hz, 1H), 0.71 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 193.8, 160.8, 159.7, 155.4, 143.0, 141.7, 129.6, 128.8, 114.2, 114.0, 113.8(2C), 104.4, 91.7, 62.5, 25.7(3C), 18.1, -5.4(2C); CIHRMS Calcd for $[\text{C}_{21}\text{H}_{26}\text{O}_6\text{Si}+\text{Na}]^+$: 425.1390. Found 425.1373.

7-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-hydroxy-5,6-dihydro-2H-pyran-2-yloxy]-chromen-2-one (I-41a**).**

A THF (0.2 mL) solution of compound **I-23** (100 mg, 0.24 mmol) and MeOH (0.2 mL) was cooled to -78°C . NaBH_4 (9.20 mg, 0.24 mmol) was added and the reaction mixture was stirred at -78°C for 3 hours. The reaction mixture was diluted with ether (5 mL) and was quenched with 5 mL of satd aq NaHCO_3 , extracted (2 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give 90 mg (0.21 mmol, 90.0%) of **I-41a**: R_f (30% EtOAc/hexanes) = 0.42; $[\alpha]_D^{21} = -203.7$ ($c = 1$, CH_3OH); IR (thin film, cm^{-1}) 3557, 2954, 1733, 1615, 1118, 835; ^1H NMR (270 MHz, CDCl_3) δ 7.64 (d, $J = 9.6$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.07 (d, $J = 2.4$ Hz, 1H),

6.97 (dd, $J = 9.0, 2.4$ Hz, 1H), 6.28 (d, $J = 9.0$ Hz, 1H), 6.13 (dd, $J = 10.2, 2.4$ Hz, 1H), 5.90 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.70 (d, $J = 2.4$ Hz, 1H), 4.30 (ddd, $J = 5.4, 3.0, 1.2$ Hz, 1H), 3.88 (dd, $J = 9.6, 5.4$ Hz, 1H), 3.80 (dd, $J = 9.0, 4.2$ Hz, 1H), 3.75 (dd, $J = 10.2, 6.6$ Hz, 1H), 3.10 (d, $J = 3.6$ Hz, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 161.2, 160.3, 155.5, 143.3, 134.5, 128.7, 123.9, 114.1, 113.7, 113.4, 104.1, 92.6, 71.0, 66.5, 65.0, 25.7(3C), 18.1, -5.5, -5.6; CIHRMS Calcd for $[\text{C}_{21}\text{H}_{28}\text{O}_6\text{Si}+\text{Na}]^+$: 427.1547. Found 427.1538.

7-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-2H-pyran-2-yloxy]-chromen-2-one (I-42a).

To a *t*-butanol, acetone (0.4 mL, 1:1, 1M) solution of allyl alcohol **I-41a** (160 mg, 0.363 mmol) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (0.2 mL). Crystalline OsO_4 (1.0 mg, 1 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using a small amount of CH_2Cl_2 (0.6 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/ether (2:98 to 4:96). Pure fractions were combined and concentrated to afford triol **I-42a** 145 mg (0.329 mmol, 84%): R_f (50% EtOAc/hexanes) = 0.29; $[\alpha]_D^{21} = -63.4$ ($c = 2$, CH_2Cl_2); IR (thin film, cm^{-1}) 3449, 3420, 2955, 1742, 1618, 1129, 836; ^1H NMR (600 MHz, CD_3OD) δ 7.91 (d, $J = 9.6$ Hz, 1H), 7.57 (d, $J = 9.0$ Hz, 1H), 7.16 (br s, 1H), 7.09 (d, $J = 7.8$ Hz, 1H), 6.30 (d, $J = 10.2$ Hz, 1H), 5.60 (br s, 1H), 4.05 (br s, 1H), 3.95 (d, $J = 11.4$ Hz, 1H), 3.90 (dd,

$J = 9.0, 3.0$ Hz, 1H), 3.75 (dd, $J = 10.8, 6.0$ Hz, 1H), 3.65 (dd, $J = 10.2, 9.0$ Hz, 1H), 3.33 (m, 3H), 0.78 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 163.2, 161.0, 156.8, 145.7, 130.5, 115.6, 115.3, 114.3, 105.1, 100.0, 76.6, 72.5, 71.6, 68.6, 64.4, 26.4 (3C), 19.1, -5.0, -5.1; CIHRMS Calcd for $[\text{C}_{21}\text{H}_{30}\text{O}_8\text{Si}+\text{Na}]^+$: 461.1602. Found 461.1578.

7-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-4-methyl-2H-pyran-2-yloxy]-chromen-2-one (I-27**).**

A THF (0.3 mL) solution of compound **I-15** (100 mg, 0.28 mmol) and 7-hydroxy coumarin (98.6 mg, 0.56 mmol) was cooled to 0 °C. A THF (0.3 mL) solution of $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (7.2 mg, 2.5 mol%) and PPh_3 (7.3 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with 2 mL of satd aq NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc /hexanes to give 98 mg (0.23 mmol, 82%) of **I-27**: R_f (30% EtOAc /hexanes) = 0.50; $[\alpha]_D^{21} = -75.4$ ($c = 0.7$, CH_2Cl_2); IR (thin film, cm^{-1}) 2928, 1726, 1700, 1611, 1262, 1134, 834; ^1H NMR (600 MHz, CDCl_3) δ 7.52 (d, $J = 2.4$ Hz, 1H), 7.13 (d, $J = 2.4$ Hz, 1H), 7.07 (dd, $J = 9.0, 2.4$ Hz, 1H), 7.02 (dd, $J = 9.6, 3.6$ Hz, 1H), 6.28 (d, $J = 10.8$ Hz, 1H), 6.17 (d, $J = 1.2$ Hz, 1H), 6.10 (d, $J = 3.6$ Hz, 1H), 4.50 (dd, $J = 4.8, 2.4$ Hz, 1H), 4.05 (dd, $J = 11.4, 4.8$ Hz, 1H), 4.02 (dd, $J = 12.0, 3.0$ Hz, 1H), 2.40 (d, $J = 1.2$ Hz, 3H), 0.81 (s, 9H), 0.04 (s, 3H),

0.03 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 193.8, 160.9, 159.6, 154.8, 152.1, 141.7, 129.2(2C), 125.6, 115.1, 113.5, 112.9, 104.4, 91.7, 62.5, 25.7(3C), 18.6, 18.2, -5.4, -5.5; CIHRMS Calcd for $[\text{C}_{22}\text{H}_{28}\text{O}_6\text{Si}+\text{Na}]^+$: 439.1547. Found 439.1535.

7-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-4-methyl-2H-pyran-2-yloxy]-chromen-2-one (I-28).

A THF (0.3 mL) solution of compound **I-16** (100 mg, 0.28 mmol) and 7-hydroxy coumarin (98.6 mg, 0.56 mmol) was cooled to 0 °C. A THF (0.3mL) solution of $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (7.2 mg, 2.5 mol%) and PPh_3 (7.3 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with 2 mL of satd aq NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20-25% EtOAc /hexanes to give 73 mg (0.17 mmol, 61%) of **I-28**: R_f (30% EtOAc /hexanes) = 0.40; $[\alpha]_D^{21} = -49$ ($c = 0.7$, CH_2Cl_2); IR (thin film, cm^{-1}) 2930, 1703, 1732, 1614, 1256, 1118, 836; ^1H NMR (600 MHz, CDCl_3) δ 7.61 (d, $J = 9.0$ Hz, 1H), 7.01(dd, $J = 10.2$, 3.0 Hz, 1H), 6.84 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.72 (d, $J = 3.0$ Hz, 1H), 6.12 (dd, $J = 1.2$, 1.2 Hz, 1H), 6.09 (d $J = 10.8$ Hz, 1H), 5.24 (dd, $J = 3.6$, 1.2 Hz, 1H), 4.42 (dd, $J = 4.8$, 2.4 Hz, 1H), 4.08 (dd, $J = 10.8$, 4.8 Hz, 1H), 4.02 (dd, $J = 11.4$, 2.4 Hz, 1H), 2.44 (d, $J = 1.2$ Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 196.6, 163.8, 162.9, 156.5, 155.9,

146.1, 128.6, 127.4, 114.3, 113.8, 111.2, 103.4, 95.4, 77.1, 63.8, 26.3 (3C), 19.1, 18.6, -5.2, -5.3; CIHRMS Calcd for $[C_{22}H_{28}O_6Si+Na]^+$: 439.1547. Found 439.1554.

7-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-hydroxy-5,6-dihydro-4-methyl-2H-pyran-2-yloxy]-chromen-2-one (I-41b).

A THF (0.2 mL) solution of compound **I-28** (100 mg, 0.23 mmol) and MeOH (0.2 mL) was cooled to -78°C . NaBH_4 (8.70 mg, 0.23 mmol) was added and the reaction mixture was stirred at -78°C for 3 hours. The reaction mixture was diluted with ether (5 mL) and was quenched with 5 mL of satd aq NaHCO_3 , extracted (2 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give 73 mg (0.17 mmol, 73.0%) of **I-41b**: R_f (30% EtOAc/hexanes) = 0.40; $[\alpha]_D^{21} = -110.2$ ($c = 1$, CH_3OH); IR (thin film, cm^{-1}) 3425, 2926, 1710, 1611, 1121, 835; ^1H NMR (600 MHz, CDCl_3) δ 7.50 (d, $J = 8.4$ Hz, 1H), 7.07 (d, $J = 2.4$ Hz, 1H), 6.99 (dd, $J = 9.0, 2.4$ Hz, 1H), 6.14 (m, 2H), 5.89 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.70 (m, 1H), 4.31 (dd, $J = 8.4, 1.2$ Hz, 1H), 3.88 (dd, $J = 9.6, 4.8$ Hz, 1H), 3.81 (ddd, $J = 7.2, 4.8, 4.8$ Hz, 1H), 3.75 (dd, $J = 9.6, 7.2$ Hz, 1H), 3.03 (d, $J = 3.0$ Hz, 1H), 2.04 (d, $J = 0.6$ Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 161.2, 160.1, 154.9, 152.4, 134.4, 125.4, 123.9, 114.5, 113.7, 112.4, 104.1, 92.5, 70.8, 66.8, 65.2, 25.7(3C), 18.7, 18.1, -5.5, -5.6; CIHRMS Calcd for $[C_{22}H_{30}O_6Si+Na]^+$: 441.1703. Found 441.1725.

7-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-oxo-5,6-dihydro-4-methyl-2*H*-pyran-2-yloxy]- chromen-2-one (I-42b**).**

To a *t*-butanol, acetone (0.4 mL, 1:1, 1M) solution of allyl alcohol **I-41b** (160 mg, 0.373 mmol) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (0.2 mL). Crystalline OsO₄ (1.0 mg, 1 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column (1 cm × 4") using a small amount of CH₂Cl₂ (0.6 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/ether (2:98 to 4:96). Pure fractions were combined and concentrated to afford triol **I-42b** 145 mg (0.329 mmol, 84%): *R_f* (50:49:1 EtOAc/hexanes/methanol) = 0.35; [α]_D²¹ = -84 (c = 2, CH₂Cl₂); IR (thin film, cm⁻¹) 3406, 2927, 1729, 1613, 1068, 836; ¹H NMR (600 MHz, CDCl₃) δ 7.52 (d, *J* = 9.0 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.18 (d, *J* = 1.2 Hz, 1H), 5.62 (d, *J* = 1.2 Hz, 1H), 4.17 (d, *J* = 2.4 Hz, 1H), 4.07 (ddd, *J* = 9.0, 3.6, 2.4 Hz, 1H), 3.94 (dd, *J* = 9.6, 9.0 Hz, 1H), 3.87 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.79 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.65 (dddd, *J* = 10.8, 6.6, 4.8, 4.8 Hz, 1H), 3.36 (s, 2H), 2.79 (d, *J* = 3.6 Hz, 1H), 2.67 (d, *J* = 3.0 Hz, 1H), 2.40 (d, *J* = 0.6 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ; ¹³C NMR (150 MHz, CDCl₃) δ 161.1, 158.7, 154.8, 152.4, 125.6, 114.8, 113.3, 112.7, 104.0, 97.6, 76.5, 71.2, 71.1, 69.7, 64.6, 25.7 (3C), 18.6, 18.1, -5.5, -5.6 ; CIHRMS Calcd for [C₂₂H₃₂O₈Si+Na]⁺: 475.1758. Found 475.1778.

Methyl-7-((2*S*,6*S*)-6-((*tert*-butyldimethylsilyloxy)methyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-2-oxo-2*H*-chromene-4-carboxylate (I-30).

A THF (2.0 mL) solution of compound **I-15** (400 mg, 1.11 mmol) and 7-hydroxy coumarin (492.0 mg, 2.22 mmol) was cooled to 0 °C. A THF (1.0 mL) solution of Pd₂(DBA)₃·CHCl₃ (28.7 mg, 2.5 mol%) and PPh₃ (29.0 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with 5 mL of satd aq NaHCO₃, extracted (3 x 10 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30-50% EtOAc/hexanes to give 300 mg (0.64 mmol, 57%) of **I-30**: *R_f* (20% EtOAc/hexanes) = 0.37; [α]_D²¹ = - 68.1 (c = 0.7, CH₂Cl₂); IR (thin film, cm⁻¹) 2927, 1737, 1703, 1613, 1263, 1135, 837; ¹H NMR (600 MHz, CD₃OD) δ 7.59 (d, *J* = 9.0 Hz, 1H), 7.14 (d, *J* = 3.0 Hz, 1H), 7.08 (dd, *J* = 9.6, 2.4 Hz, 1H), 6.26 (d, *J* = 1.8 Hz 1H), 6.23 (d, *J* = 7.2 Hz, 1H), 6.21 (s, 1H), 4.47 (dd, *J* = 4.8, 2.4 Hz, 1H), 3.99 (m, 1H), 3.98 (dd, *J* = 12, 4.2 Hz, 1H), 3.94 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.66 (s, 3H), 0.75 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); ¹³C NMR (150 MHz, CD₃OD) δ 195.5, 171.1, 162.6, 161.4, 150.9, 143.9, 129.7, 127.7, 127.5, 115.3, 115.2, 105.4, 92.4, 78.0, 63.5, 53.0, 38.1, 26.3 (3C), 19.0, -5.2, -5.3; CIHRMS Calcd for [C₂₃H₂₈O₈SiCH₂Na]⁺: 497.1602. Found 497.1621.

Methyl-7-((2*R*,6*S*)-6-((*tert*-butyldimethylsilyloxy)methyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-2-oxo-2*H*-chromene-4-carboxylate (I-31).

A THF (0.1 mL) solution of compound **I-16** (30 mg, 0.096 mmol) and MeOH (0.1 mL) was cooled to -78 °C. NaBH₄ (3.36 mg, 0.096 mmol) was added and the reaction mixture was stirred at -78°C for 3 hours. The reaction mixture was diluted with ether (3 mL) and was quenched with 2 mL of satd aq NaHCO₃, extracted (2 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 100% EtOAc/hexanes to give 39 mg (0.083 mmol, 85%) of **I-31**: R_f (30% EtOAc/hexanes) = 0.31; $[\alpha]_D^{21} = +10$, C 1, CH₂Cl₂; IR (thin film, cm⁻¹) 3384, 3034, 2975, 1656, 1634, 1047, 879; ¹H NMR (600 MHz, CDCl₃) 7.56 (d, J = 9.6 Hz, 1H), 7.09 (dd, J = 10.8, 1.8 Hz, 1H), 6.96 (d, J = 1.8 Hz, 1H), 6.85 (dd, J = 9.0, 2.4 Hz, 1H), 6.47 (br s, 1H), 6.21 (ddd, J = 10.2, 8.4, 1.8 Hz, 1H), 5.05 (m, 1H), 4.32 (d, J = 9.0 Hz, 1H), 4.00 (dd, J = 11.4, 2.4 Hz, 1H), 3.83 (dd, J = 11.4, 6.6 Hz, 1H), 3.75 (s, 3H), 0.76 (s, 9H), -0.09 (s, 3H), -0.11 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 193.5, 169.2, 160.7, 155.2, 149.5, 147.5, 128.4, 125.5, 113.8, 117.7, 103.5, 82.2, 73.8, 62.1, 53.1, 50.0, 37.9, 25.6 (3C), 18.1, -5.63, -5.65; CIHRMS Calcd for [C₂₃H₂₈O₈SiCH₂Na]⁺: 497.1602. Found 497.1618

7-((2S,6S)-6-((tert-butyldimethylsilyloxy)methyl)-5-oxo-5,6-dihydro-2H-pyran-2-yloxy)-2-phenyl-4H-chromen-4-one (I-33).

A THF (0.3 mL) solution of compound **I-15** (100 mg, 0.28 mmol) and 6-hydroxy flavone (133.3 mg, 0.56 mmol) was cooled to 0 °C. A THF (0.3 mL) solution of Pd₂(DBA)₃·CHCl₃ (7.2 mg, 2.5 mol%) and PPh₃ (7.3 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with 2 mL of satd aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give 120.6 mg (0.25 mmol, 90%) of **I-33**: *R*_f (30% EtOAc/hexanes) = 0.66; [α]²¹_D = - 95.1 (c = 0.7, CH₂Cl₂); IR (thin film, cm⁻¹) 2927, 1701, 1637, 1455, 1255, 1129, 835; ¹H NMR (600 MHz, CDCl₃) δ 7.95 (d, *J* = 3.0 Hz, 1H), 7.91-7.93 (m, 2H), 7.54-7.50 (m, 4H), 7.47 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.04 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.80 (s, 1H), 6.28 (d, *J* = 10.2 Hz, 1H), 6.11 (d, *J* = 3.6 Hz, 1H), 4.56 (dd, *J* = 4.2, 3.0 Hz, 1H), 4.06-4.05 (m, 2H), 0.82 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ¹³C NMR (67.5 MHz, CDCl₃) δ 194.1, 177.8, 163.2, 154.0, 151.9, 142.2, 131.7, 131.5, 129.0(3C), 126.2(2C), 124.7, 124.5(2C), 119.5, 110.8, 106.8, 92.2, 62.6, 25.7(3C), 18.2, -5.4, -5.5; CIHRMS Calcd for [C₂₇H₃₀O₆Si+Na]⁺: 501.1703. Found 501.1680.

7-((2*S*,5*R*,6*S*)-6-((*tert*-butyldimethylsilyloxy)methyl)-5-hydroxy-5,6-dihydro-2*H*-pyran-2-yloxy)-2-phenyl-4*H*-chromen-4-one (I-41c).

A THF (0.2 mL) solution of compound **I-33** (100 mg, 0.20 mmol) and MeOH (0.2 mL) was cooled to -78 °C. NaBH₄ (7.90 mg, 0.20 mmol) was added and the reaction mixture was stirred at -78°C for 3 hours. The reaction mixture was diluted with ether (5 mL) and was quenched with 5 mL of satd aq NaHCO₃, extracted (2 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give 73 mg (0.15 mmol, 76.0%) of **I-41c**: *R_f* (30% EtOAc/hexanes) = 0.44; [α]_D²¹ = -113.10 (c = 1, CH₃OH); IR (thin film, cm⁻¹) 3346, 2956, 1738, 1623, 1073, 831; ¹H NMR (600 MHz, CDCl₃) δ 7.92-7.91 (m, 2H), 7.86 (d, *J* = 3.0 Hz, 1H), 7.23-7.50 (m, 3H), 7.40 (dd, *J* = 9.6, 3.0 Hz, 1H), 6.80 (s, 1H), 6.12 (dddd, *J* = 10.2, 3.0, 1.2, 1.2 Hz, 1H), 5.91 (dddd, *J* = 10.2, 4.8, 2.4, 2.4 Hz, 1H), 5.74 (dd, *J* = 2.4, 1.8 Hz, 1H), 4.31-4.29 (m, 1H), 4.11 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.89 (ddd, *J* = 9.0, 5.4, 5.4 Hz, 1H), 3.86 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.78 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.17 (d, *J* = 3.0 Hz, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 178.1, 168.2, 163.2, 1159.5, 154.5, 151.7, 134.1, 131.8, 131.5, 129.0, 126.2, 124.8, 124.6, 124.4, 119.3, 110.2, 106.8, 93.0, 70.8, 66.9, 65.3, 25.7(3C), 18.1, -5.5, -5.6; CIHRMS Calcd for [C₂₇H₃₂O₆Si+Na]⁺: 503.1860. Found 503.1873.

7-((2*S*,3*R*,4*R*,5*R*,6*S*)-6-((*tert*-butyldimethylsilyloxy)methyl)-3,4,5-trihydroxy-tetrahydro-2*H*-pyran-2-yloxy)-2-phenyl-4*H*-chromen-4-one (I-42c).

To a *t*-butanol, acetone (0.4 mL, 1:1, 1M) solution of allyl alcohol **I-41c** (160 mg, 0.333 mmol) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (0.2 mL). Crystalline OsO₄ (1.0 mg, 1 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column (1 cm × 4”) using a small amount of CH₂Cl₂ (0.6 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/ether (2:98 to 4:96). Pure fractions were combined and concentrated to afford triol **I-42c** 144 mg (0.279 mmol, 84%): *R_f* (50:40:10 EtOAc/hexanes/methanol) = 0.24; $[\alpha]_D^{21} = -96.4$ (c = 2, CH₂Cl₂); IR (thin film, cm⁻¹) 3332, 2947, 1739, 1366, 1120, 978; ¹H NMR (600 MHz, CDCl₃) δ 7.92-7.90 (m, 2H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.53-7.51(m, 4H), 7.41 (dd, *J* = 9.6, 3.0 Hz, 1H), 6.80 (s, 1H), 5.64 (d, *J* = 1.2 Hz, 1H), 4.11 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.00 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.86 (dd, *J* = 6.0, 3.0 Hz, 1H), 3.84 (dd, *J* = 5.4, 2.4 Hz, 1H), 3.80 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.65 (ddd, *J* = 9.6, 4.8, 4.8 Hz, 1H), 1.80 (d, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ; ¹³C NMR (150 MHz, CDCl₃) δ 179.2, 164.6, 154.1, 152.2, 132.0, 131.7, 129.2(2C), 126.5(2C), 125.1, 124.3, 119.9, 109.9, 105.9, 99.0, 75.4, 71.4, 70.6, 67.5, 63.3, 25.2 (3C), 18.0, -6.1, -6.2 ; CIHRMS Calcd for [C₂₇H₃₄O₈Si+Na]⁺: 537.1915. Found 537.1894.

7-((2*S*,5*R*,6*S*)-6-((*tert*-butyldimethylsilyloxy)methyl)-5-hydroxy-tetrahydro-2*H*-pyran-2-yloxy)-2-phenyl-4*H*-chromen-4-one (I-43).

The allyl alcohol compound **I-41c** (70 mg, 0.15 mmol), O-NO₂ArSO₂NHNH₂ (236.5 mg, 1.16 mmol) were dissolved in 1.46 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen condition then triethylamine (146.5 mg, 1.5 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion monitored by TLC, reaction mixture is three portions. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give **I-43** 56 mg (0.11 mmol, 80 %): *R_f* (30% EtOAc/Hexane) = 0.44; [α]²¹_D = -95.30 (*c* 2, CH₂Cl₂); IR (thin film, cm⁻¹) 2985, 1737, 1372, 1252, 1097, 846; ¹H NMR (600 MHz, CDCl₃) δ 7.93 (m, 3H), 7.54-7.49 (m, 5H), 6.82 (d, *J* = 1.8 Hz, 1H), 5.62 (d, *J* = 1.8 Hz, 1H), 3.80 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.73 (dd, *J* = 16.8, 7.8 Hz, 1H), 3.68 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.66 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.34 (dd, *J* = 7.8, 7.2 Hz, 1H), 2.08-1.97 (m, 4H), 0.85 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 180.5, 165.7, 155.8, 153.1, 133.1, 133.0, 132.9, 130.4, 127.6, 126.3, 125.5, 124.9, 120.9, 110.8, 107.1, 106.8, 77.0, 66.6, 64.4, 30.2, 28.1, 26.4(3C), 19.2, -5.0, -5.1; CIHRMS Calcd for [C₂₇H₃₄O₆SiNa⁺]: 505.2016. Found 505.2025.

7-((2*R*,6*S*)-6-((*tert*-butyldimethylsilyloxy)methyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-2-phenyl-4*H*-chromen-4-one (I-33).

A THF (0.2 mL) solution of compound **I-15** (50 mg, 0.14 mmol) and 6-hydroxy flavone (65.3 mg, 0.28 mmol) was cooled to 0 °C. A THF (0.2 mL) solution of Pd₂(DBA)₃·CHCl₃

(3.6 mg, 2.5 mol%) and PPh₃ (3.6 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with 2 mL of satd aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give 52.5 mg (0.11 mmol, 80%) of **I-33**: *R_f* (30% EtOAc/hexanes) = 0.60; [α]²¹_D = 70.1 (c = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2929, 1721, 1642, 1456, 1251, 1121, 839; ¹H NMR (600 MHz, CD₃OD) δ 8.04 (d, *J* = 1.8 Hz, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.91 (d, *J* = 3.0 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.60-7.54 (m, 5H), 7.19 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.90 (br s, 1H), 6.25 (dd, *J* = 12.6, 10.2 Hz, 1H), 4.55 (dd, *J* = 4.8, 2.4 Hz, 1H), 4.05 (dd, *J* = 11.4, 4.8 Hz, 1H), 4.01 (dd, *J* = 11.4, 2.4 Hz, 1H), 0.78 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ¹³C NMR (150 MHz, CD₃OD) δ 195.4, 179.4, 164.4, 155.5, 150.6, 144.8, 143.2, 131.9, 131.7 (2C), 129.1, 129.0 (2C), 127.5 (2C), 123.6, 119.5, 107.6, 105.5, 76.0, 62.6, 25.1 (3C), 17.9, -6.4 (2C); CIHRMS Calcd for [C₂₇H₃₀O₆SiNa]⁺: 501.1703. Found 501.1700.

(2*S*,6*S*)-6-(1'*H*-benzimidazol-1'-yl)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-2*H*-pyran-3(6*H*)-one (I-58β):

A CH₂Cl₂ (1.0 mL) solution of pyranone **I-16β** (358 mg, 1.00 mmol) and benzimidazole (141.7 mg, 1.20 mmol) was cooled to 0 °C. A CH₂Cl₂ (1.0 mL) solution of Pd₂(DBA)₃·CHCl₃ (25.8 mg, 2.5 mol %) and PPh₃ (26.2 mg, 10 mol %) was added to the reaction

mixture at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with 5 mL of saturated aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50:40:10 EtOAc/hexanes/methanol to give (2S,6S)-6-(1'H-benzo[d]imidazol-1'-yl)-2-(tert-butyl-dimethyl-silanyloxymethyl)-2H-pyran-3(6H)-one **I-58β** (250 mg, 1.00 mmol, 82%) as viscous oil. *R_f* (50% EtOAc/hexanes) = 0.20; $[\alpha]_D^{26} = -11$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2854, 1702, 1606, 1458, 1251, 1070, 834; ¹H NMR (600 MHz, CDCl₃) δ 8.00 (s, 1H), 7.82 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.54 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.32 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 7.30 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 7.07 (dd, *J* = 10.2, 1.8 Hz, 1H), 6.55 (dd, *J* = 4.2, 1.8 Hz, 1H), 6.46 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.45 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.44 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.06 (dd, *J* = 6.6, 3.0 Hz, 1H), 0.81 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H); ¹³C NMR (150 MHz, DCl₃) δ 192.5, 145.0, 144.0, 141.5, 132.5, 131.0, 123.7, 123.1, 120.6, 111.1, 81.4, 78.7, 62.2, 25.7 (3C), 18.2, -5.4, -5.5; CIHRMS Calcd for [C₁₉H₂₆N₂O₃SiNa]⁺: 381.1604, Found : 381.1599.

(2S,3R,6S)-6-(1'H-benzo[d]imidazol-1'-yl)-3,6-dihydro-2-(tert-butyl-dimethyl-silanyloxymethyl)-2H-pyran-3-ol (I-59β):

A CH₂Cl₂ (0.5 mL) solution of enone **I-58β** (170 mg, 0.454 mmol) and MeOH (0.5 mL) was cooled to -78 °C. NaBH₄ (20.6 mg, 0.544 mmol) was added and the reaction

mixture was stirred at -78°C for 3 h. The reaction mixture was diluted with ether (5 mL) and was quenched with 5 mL of saturated aq NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50:45:5 EtOAc /hexanes/methanol to give (2S,3R,6S)-6-(1'H-benzo[d]imidazol-1'-yl)-3,6-dihydro-2-(tert-butyl-dimethyl-silanyloxymethyl)-2H-pyran-3-ol **I-59 β** (135 mg, 0.37 mmol, 79%) as viscous oil. R_f (50% EtOAc /hexanes) = 0.20; $[\alpha]_D^{26} = -0.23$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3192, 2928, 2856, 1459, 1119, 1087; ^1H NMR (600 MHz, CDCl_3) δ 7.98 (s, 1H), 7.79 (dd, $J = 6.6, 2.4$ Hz, 1H), 7.46 (dd, $J = 6.6, 1.8$ Hz, 1H), 7.29 (ddd, $J = 7.2, 6.6, 2.4$ Hz, 1H), 7.28 (ddd, $J = 6.6, 6.6, 1.8$ Hz, 1H), 6.29 (dd, $J = 2.4, 2.4$ Hz, 1H), 6.27 (dd, $J = 2.4, 1.8$ Hz, 1H), 5.94 (ddd, $J = 9.6, 3.0, 2.4$ Hz, 1H), 4.52 (dd, $J = 8.4, 2.4$ Hz, 1H), 3.97 (dd, $J = 10.2, 4.8$ Hz, 1H), 3.84 (ddd, $J = 11.4, 5.4, 4.2$ Hz, 1H), 3.77 (dd, $J = 10.2, 7.8$ Hz, 1H), 3.33 (s, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 138.0, 133.0, 128.3 (2C), 127.9 (2C), 127.6, 125.7, 93.4, 70.4, 70.0, 66.7, 65.1, 25.8 (3C), 18.2, -5.4, -5.5; CIHRMS Calcd for $[\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_3\text{SiH}]^+$: 361.1942, Found : 361.1984.

((2R,6S)-6-(1'H-benzo[d]imidazol-1'-yl)-5,6-dihydro-2H-pyran-2-yl) tert-butyl-dimethyl-silanyloxymethane (I-60 β).

A flask was charged with dry N-methyl morpholine (NMM) 25 ml, triphenyl phosphine (459 mg, 1.172 mmol) and was cooled to -30°C under Ar atmosphere.

Diethylazodicarboxylate (251.4 μ l, 1.597 mmol) was added and the reaction was stirred for 5 min, allylic alcohol **I-59 β** (200 mg, 0.531 mmol) was added in a 1M solution of NMM and the reaction mixture was stirred for 10 min, followed by addition of o-nitrobenzenesulfonyl hydrazide (NBSH) (323.5 mg, 1.593 mmol). The reaction was stirred at -30 $^{\circ}$ C for 2h and was monitored by TLC, upon consumption of starting material, warm up to room temperature and stirred for another 4h. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of satd. aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give ((2R,6S)-6-(1'H-benzo[d]imidazol-1'-yl)-5,6-dihydro-2H-pyran-2-yl) tert-butyl-dimethyl-silanyloxymethane **I-60 β** (119 mg, 0.345 mmol, 65%) as viscous oil. R_f (50:49:1 % EtOAc/hexanes/methanol) = 0.35; $[\alpha]_D^{26} = +72$ ($c = 1.0$, CH₂Cl₂); IR (thin film, cm⁻¹) 3296, 2929, 1721, 1066, 835; ¹H NMR (600 MHz, CDCl₃) δ 8.04 (m, 1H), 7.79 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.50 (dd, $J = 7.2, 2.4$ Hz, 1H), 7.28 (ddd, $J = 7.2, 7.2, 1.2$ Hz, 1H), 7.27 (ddd, $J = 7.2, 7.2, 1.2$ Hz, 1H), 5.96 (dd, $J = 10.2, 6.0$ Hz, 1H), 5.92 (dd, $J = 10.2, 2.4$ Hz, 1H), 5.77 (dd, $J = 9.6, 3.0$ Hz, 1H), 4.56 (br s, 1H), 3.75 (dd, $J = 9.6, 6.0$ Hz, 1H), 3.61 (dd, $J = 9.6, 6.0$ Hz, 1H), 2.90 (ddd, $J = 10.8, 10.2, 3.0$ Hz, 1H), 2.50 (ddd, $J = 10.8, 9.6, 3.0$ Hz, 1H), 0.86 (s, 9H), 0.02 (s, 3H), -0.002 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 140.3, 127.8, 123.5, 123.2 (2C), 122.9, 122.7, 120.2, 111.0, 80.3, 77.4, 65.3, 30.4, 25.7(3C), 18.2, -3.5, -5.4; CIHRMS Calcd for [C₁₉H₂₈N₂O₂SiNa⁺]: 367.1812, Found : 367.1829.

(2*S*,3*R*,4*R*,6*S*)-6-(1'*H*-benzo[d]imidazol-1'-yl)-tetrahydro-2-(*tert*-butyl-dimethyl-silanyloxymethy)-2*H*-pyran-3,4-diol (I-61 β).

To a solution of olefin **I-60 β** (80 mg, 0.110 mmol) in *t*-butanol/ acetone (0.4 mL, 1:1, 1M) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (0.12 mL) and crystalline OsO₄ (0.6 mg, 1 mol %) was added. The reaction mixture was stirred for 12 hours and the reaction was quenched with adding EtOAc and satd. NaHCO₃. The organic layer was separated and concentrated. It was purified by a silica gel column using 5% methanol/EtOAc. Pure fractions were combined and concentrated to afford (2*S*,3*R*,4*R*,6*S*)-6-(1'*H*-benzo[d]imidazol-1'-yl)-tetrahydro-2-(*tert*-butyl-dimethyl-silanyloxymethy)-2*H*-pyran-3,4-diol **I-61 β** (36 mg, 0.094 mmol, 85%) as viscous oil. R_f (10% methanol/40%EtOAc/50hexanes) = 0.40; $[\alpha]_D^{26} = +22$ ($c = 1.2$, CH₂Cl₂); IR (thin film, cm⁻¹) 3166, 2928, 1615, 1065, 777; ¹H NMR (600 MHz, CDCl₃) δ 8.29 (s, 1H), 7.67 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.66 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.30 (ddd, $J = 7.2, 7.2, 1.8$ Hz, 1H), 7.28 (ddd, $J = 7.2, 7.2, 1.8$ Hz, 1H), 6.09 (dd, $J = 11.4, 1.8$ Hz, 1H), 4.27 (dd, $J = 5.4, 3.6$ Hz, 1H), 4.03 (dd, $J = 10.2, 5.2$ Hz, 1H), 3.97 (dd, $J = 11.4, 2.4$ Hz, 1H), 3.85 (dd, $J = 11.4, 5.4$ Hz, 1H), 3.72 (dd, $J = 10.2, 3.6$ Hz, 1H), 2.52 (ddd, $J = 13.2, 11.4, 2.4$ Hz, 1H), 2.29 (ddd, $J = 13.2, 3.6, 2.4$ Hz, 1H), 0.85 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 144.4, 142.4, 134.4, 124.6,

124.1 (2C), 120.3 (2C), 113.1, 80.3, 78.0, 68.8, 66.3, 64.6, 38.2, 26.5, 19.3, -4.9, -5.0;
 CIHRMS Calcd for $[C_{19}H_{30}N_2O_4SiNa^+]$: 401.1867, Found: 401.1870.

(2S,3R,6S)-6-(1'H-benzo[d]imidazol-1'-yl)-tetrahydro-2-(tert-butyl-dimethyl-silanyloxymethyl)-2H-pyran-3-ol (I-62β).

The allyl alcohol **I-59β** (200 mg, 0.53 mmol), *o*-NO₂ArSO₂NHNH₂ (863 mg, 4.25 mmol) were dissolved in 5.0 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen condition then triethylamine (760 μl, 5.31 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion monitored by TLC. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of saturated NaHCO₃ and aqueous layers were extracted (3 x 10 mL) with Et₂O, dried over sodium sulphate and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50:45:5 EtOAc/hexanes/methanol to give (2S,3R,6S)-6-(1'H-benzo[d]imidazol-1'-yl)-tetrahydro-2-(tert-butyl-dimethyl-silanyloxymethyl)-2H-pyran-3-ol **I-62β** (60 mg, 0.16 mmol, 30 %) as viscous oil. *R_f* (50% EtOAc/Hexane) = 0.25; $[\alpha]_D^{26} = +0.23$ (*c* 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3195, 2952, 2928, 1459, 1252, 1237, 1085, 922, 835; ¹H NMR (600 MHz, CDCl₃) δ 8.0 (s, 1H), 7.79 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.47 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.30 (ddd, *J* = 7.2, 7.2, 1.8 Hz, 1H), 7.29 (ddd, *J* = 7.2, 7.2, 1.8 Hz, 1H), 5.57 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.97 (dd, *J* = 10.2, 4.8 Hz, 1H) 3.80 (dd, *J* = 10.2, 7.8 Hz, 1H), 3.64 (dd, *J* = 4.8,

4.2 Hz, 1H), 2.36 (ddd, $J = 12.0, 9.0, 3.6$ Hz, 1H), 2.28 (ddd, $J = 15.0, 9.6, 3.6$ Hz, 1H), 2.20 (dd, $J = 6.6, 3.0$ Hz, 1H), 2.18 (dd, $J = 6.6, 3.0$ Hz, 1H), 2.04 (s, 1H), 0.91 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 140.1, 123.2, 122.6, 120.5 (2C), 110.6 (2C), 83.0, 79.2, 69.6, 65.9, 30.8, 29.6, 25.7 (3C), 18.1, -5.5, -5.6; CIHRMS Calcd for $[\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}_3\text{SiNa}]^+$: 385.1917, Found : 385.1920.

(2*S*,6*R*)-6-(1'*H*-benzo[d]imidazol-1'-yl)-2-(tert-butyl-dimethyl-silanyloxymethyl)-2H-pyran-3(6*H*)-one (I-56 α) :

A CH_2Cl_2 (0.8 mL) solution of pyranone **I-15 α** (289 mg, 0.807 mmol) and benzimidazole (114 mg, 1.20 mmol) was cooled to 0 °C. A CH_2Cl_2 (0.8 mL) solution of $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (20.8 mg, 2.5 mol%) and PPh_3 (21.1 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with 5 mL of satd aq NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50:45:5 EtOAc /hexanes/methanol to give (2*S*,6*R*)-6-(1'*H*-benzo[d]imidazol-1'-yl)-2-(tert-butyl-dimethyl-silanyloxymethyl)-2H-pyran-3(6*H*)-one **I-56 α** (230 mg, 0.642 mmol, 77%) as viscous oil. R_f (50% EtOAc /hexanes) = 0.35; $[\alpha]_D^{26} = -2$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3309, 2946, 1646, 1459, 1257, 1021, 744; ^1H NMR (600 MHz, CDCl_3) δ 7.96 (s, 1H), 7.82 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.55 (dd, $J = 7.2, 1.8$ Hz, 1H), 7.34 (ddd, $J = 6.6, 6.6,$

1.8 Hz, 1H), 7.33 (ddd, $J = 7.2, 7.2, 1.8$ Hz, 1H), 7.16 (dd, $J = 10.2, 2.4$ Hz, 1H), 6.84 (dd, $J = 2.4, 1.8$ Hz, 1H), 6.53 (dd, $J = 10.2, 1.8$ Hz, 1H), 4.21 (dd, $J = 3.6, 2.4$ Hz, 1H), 4.10 (dd, $J = 11.4, 3.6$ Hz, 1H), 4.05 (dd, $J = 11.4, 2.4$ Hz, 1H), 0.85 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 193.4, 144.1, 142.8, 141.3, 133.0, 131.1(2C), 123.8, 123.1, 120.6, 110.6, 78.8, 64.4, 25.7 (3C), 18.1, -5.5, -5.6; CIHRMS Calcd for $[\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_3\text{SiNa}]^+$: 381.1604. Found : 381.1602.

((2*S*,5*R*,6*S*)-5,6-dihydro-5-hydroxy-6-methyl-2H-pyran-2-yl pivalate (II-30).

A solution of pyranone **II-26** (327 mg, 1.54 mmol) in dry CH_2Cl_2 (1.5 mL) and 0.4 M $\text{CeCl}_3/\text{MeOH}$ (1.5 mL) was cooled to -78°C . NaBH_4 (58.4 mg, 1.54 mmol) was added and the reaction mixture was stirred for 4 h at -78°C . The resulting solution was diluted with ether (10 mL) and was quenched with 5 mL of saturated NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel chromatography eluting with 40% EtOAc /hexane to give enol **II-30** (297 mg, 1.34 mmol, 90%) as a white solid, mp: $62.5\text{--}64.0^\circ\text{C}$; $R_f = 0.30$ (40% EtOAc /Hexane); $[\alpha]_{\text{D}}^{26} = -28$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3391, 2972, 2933, 2837, 1612, 1513, 1246, 1029, 999, 819; ^1H NMR (600 MHz, CDCl_3) δ 6.21 (dd, $J = 2.4, 1.8$ Hz, 1H), 6.04 (d, $J = 9.6$ Hz, 1H), 5.75 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 3.90 (d, $J = 8.4$ Hz, 1H), 3.72 (m, 1H), 1.31 (d, $J = 6.6$ Hz, 3H), 1.20 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.7, 134.7, 125.1, 88.4, 70.3, 69.2, 39.1, 27.1 (3C), 18.0; CIHRMS: Calculated for $[\text{C}_{11}\text{H}_{18}\text{O}_4\text{Na}^+]$: 237.1102. Found: 237.1099

(2*S*,5*R*,6*S*)-5,6-dihydro-5-methoxy-6-methyl-2*H*-pyran-2-yl pivalate (II-32).

To a mixture of allylic alcohol **II-30** (1.7 g, 7.94 mmol) and silver (I) oxide (9.1 g, 39.7 mmol), was added 2.5 ml CH₃I. The reaction suspension was allowed to stirred for 2 days under room temperature, passed a celite pad with 100 ml Et₂O, concentrated under reduced pressure and purified using silica gel flash chromatography eluting with pure 5-7% EtOAc/Hexane to give alcohol 21 (1.6 mg, 6.98 mmol, 88%) alcohol **II-32** as white foam; *R_f* = 0.52 (30% EtOAc/Hexane); $[\alpha]_D^{26} = -128$ (*c* = 2.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2973, 2954, 2111, 1738, 1277, 1130, 1042, 921; ¹H NMR (600 MHz, CDCl₃) δ 6.19 (br s, 1H), 6.15 (d, *J* = 10.2 Hz, 1H), 5.75 (td, *J* = 10.2, 2.4 Hz, 1H), 3.78 (ddd, *J* = 12.0, 9.0, 6.6 Hz, 1H), 3.48 (dd, *J* = 9.0, 1.2 Hz, 1H), 3.42 (s, 3H), 1.29 (d, *J* = 6.0, Hz, 3H), 1.18 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 201.4, 131.2, 124.9, 88.3, 77.7, 68.0, 56.8, 38.9, 26.9 (3C), 18.1; CIHRMS: Calculated for [C₁₂H₂₀O₄Na⁺]: 251.1259, Found: 251.1253.

7-((2*S*,5*R*,6*S*)-5,6-dihydro-5-methoxy-6-methyl-2*H*-pyran-2-yloxy)-4-methyl-2*H*-chromen-2-one (II-33).

A THF (8 mL) solution of Piv-enol **II-32** (953 mg, 4.18 mmol) and 4-methyl coumarin alcohol **5** (882 mg, 6.27 mmol) was cooled to 0 °C. A THF (2.0 mL) solution of

$\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (108 mg, 2.5 mol%) and PPh_3 (110 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 5 hours. The reaction mixture was quenched with 5 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc /hexanes to give coumarin-enol **II-33** (1.07 g, 3.55 mmol, 85%) as viscous oil. R_f (20% EtOAc /hexane) = 0.33; $[\alpha]_{\text{D}}^{26} = -145$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 2950, 2939, 1731, 1613, 1389, 1134, 1067, 951; ^1H NMR (600 MHz, CDCl_3) δ 7.50 (d, $J = 9.0$ Hz, 1H), 7.08 (d, $J = 2.4$ Hz, 1H), 6.98 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.23 (d, $J = 10.2$ Hz, 1H), 6.15 (d, $J = 1.2$ Hz, 1H), 5.91 (ddd, $J = 10.2, 3.0, 1.8$ Hz, 1H), 5.67 (br s, 1H), 3.87 (ddd, $J = 12.6, 9.0, 6.6$ Hz, 1H), 3.54 (dd, $J = 9.6, 1.2$ Hz, 1H), 3.44 (s, 3H), 2.40 (d, $J = 1.2$ Hz, 3H), 1.26 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 161.2, 160.3, 125.9, 152.4, 131.9, 125.4, 125.0, 114.4, 113.7, 112.4, 104.2, 93.0, 77.7, 67.0, 56.6, 18.6, 18.1; CIHRMS: Calculated for $[\text{C}_{17}\text{H}_{18}\text{O}_5\text{H}^+]$: 303.1232, Found: 303.1228.

4-methyl-7-(tetrahydro-3,4-dihydroxy-5-methoxy-6-methyl-2H-pyran-2-yloxy)-2H-chromen-2-one (II-34).

To a CH_2Cl_2 (0.2 mL) solution of diene ester **II-33** (400 mg, 1.32 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (0.7 mL).

Crystalline OsO₄ (17 mg, 5 mol %) was added and the reaction was stirred for 8 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/Hexane (10:40:50). Pure fractions were combined and concentrated to afford diol **II-34** (368 mg, 1.09 mmol, 83%) as viscous oil. *R_f* (60% EtOAc/Hexane) = 0.20; $[\alpha]_D^{26} = -50$ (*c* = 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3412, 2917, 2949, 1708, 1615, 1559, 1372, 1290, 1118, 1071, 849; ¹H NMR (600 MHz, CDCl₃) δ 7.51 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.98 (dd, *J* = 9.0, 2.0 Hz, 1H), 6.15 (d, *J* = 1.2 Hz, 1H), 5.56 (d, *J* = 1.2 Hz, 1H), 4.17 (d, *J* = 1.8 Hz, 1H), 4.05 (ddd, *J* = 9.0, 4.2, 4.2 Hz, 1H), 3.65 (dddd, *J* = 9.6, 6.0, 6.0, 6.0 Hz, 1H), 3.58 (s, 3H), 3.19 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.07 (dd, *J* = 4.2 Hz, 1H), 2.92 (d, *J* = 4.8 Hz, 1H), 2.39 (d, *J* = 1.2 Hz, 3H), 1.27 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 161.2, 158.9, 154.8, 152.5, 125.6, 114.7, 113.2, 112.6, 104.0, 97.5, 82.6, 71.0, 70.6, 68.5, 60.9, 18.6, 17.6; CIHRMS Calcd for [C₁₇H₂₀O₇Na⁺]: 359.1106. Found 359.1102.

4-methyl-7-(tetrahydro-3-hydroxy-4-acetoxy-5-methoxy-6-methyl-2H-pyran-2-yloxy)-2H-chromen-2-one (II-35).

To a solution of diol **II-34** (110 mg, 0.31 mmol) and trimethyl orthoacetate (1.02 ml, 8.1 mmol) mixture in THF (0.6 ml) was added *p*-toluenesulfonic acid monohydrate (2.6 mg,

0.02 mmol), stirring for 0.5 h. The solvent was removed under reduced pressure and residue was dissolved in 1.5 ml THF/H₂O (1:1, v/v) solution. Then *p*-toluenesulfonic acid (26.3 mg 0.15 mmol) was added. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched with adding EtOAc and satd. NaHCO₃. The organic layer was separated, dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel flash chromatography eluting with 70% EtOAc/hexane to give acetate **II-35** (104 mg, 0.28 mmol, 90%) as white foam. *R*_f = 0.35 (50% EtOAc/Hexane); $[\alpha]_{\text{D}}^{26} = -121$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3437, 2938, 1728, 1611, 1389, 1232, 1067, 976, 850; ¹H NMR (600 MHz, CDCl₃) δ 7.51 (d, *J* = 9.0 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 9.0, 4.2 Hz, 1H), 6.17 (d, *J* = 1.2 Hz, 1H), 5.51 (d, *J* = 1.2 Hz, 1H), 5.29 (dd, *J* = 3.6, 1.8 Hz, 1H), 4.21 (ddd, *J* = 9.0, 5.4, 3.6 Hz, 1H), 3.69 (dddd, *J* = 9.0, 6.6, 6.6, 6.6 Hz, 1H), 3.60 (s, 3H), 3.15 (dd, *J* = 9.6, 9.0 Hz, 1H), 2.40 (d, *J* = 1.8 Hz, 3H), 2.28 (d, *J* = 4.8 Hz, 1H), 2.21 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 170.6, 160.9, 158.7, 154.9, 152.1, 125.6, 114.9, 113.2, 112.8, 104.1, 95.6, 82.9, 71.9, 69.6, 68.7, 61.0, 20.9, 18.6, 17.9; CIHRMS: Calculated for [C₁₉H₂₂O₈Na⁺]: 401.1212, Found: 401.1206.

2-(7-hydroxy-4-methyl-2*H*-chromen-2-one)-tetrahydro-3-hydroxy-5-methoxy-6-methyl-2*H*-pyran-4-yl carbamate (II-36).

To a CH_2Cl_2 (1.5 mL, 0.1M) solution of acetate alcohol **II-35** (70 mg, 0.17 mmol) at 0 °C was added trichloro acetyl isocyanate (32 μL , 0.26 mmol) and the reaction was stirred for 1 h. The solvent was removed under reduced pressure and residue was dissolved in 2.0 ml $\text{MeOH}/\text{H}_2\text{O}$ (2:1, v/v) solution. Then potassium carbonate (72.5 mg 0.53 mmol) was added at 0 °C. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched with adding EtOAc and satd. NaHCO_3 . The organic layer was separated, dried (Na_2SO_4), concentrated under reduced pressure and purified by silica gel flash chromatography eluting with $\text{MeOH}/\text{EtOAc}/\text{Hexane}$ (10:40:50). Pure fractions were combined and concentrated to afford carbamate **II-36** (53 mg, 0.14 mmol, 80 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.25; $[\alpha]_{\text{D}}^{26} = -44$ (c 0.5, CH_2Cl_2); IR (thin film, cm^{-1}) 3436, 2852, 1708, 1611, 1376, 1103, 1067, 992, 786; ^1H NMR (600 MHz, CDCl_3) δ 7.68 (d, $J = 9.0$ Hz, 1H), 7.07 (dd, $J = 9.0, 2.4$ Hz, 1H), 7.05 (d, $J = 4.2$ Hz, 1H), 6.17 (d, $J = 1.2$ Hz, 1H), 5.51 (d, $J = 1.8$ Hz, 1H), 5.01 (dd, $J = 9.6, 3.6$ Hz, 1H), 4.15 (dd, $J = 3.6, 1.8$ Hz, 1H), 3.62 (m, 1H), 3.48 (s, 3H), 3.32 (dd, $J = 9.0, 9.0$ Hz, 1H), 2.42 (d, $J = 1.8$ Hz, 3H), 1.21 (d, $J = 6.0$ Hz, 3H); NMR (150 MHz, CDCl_3) δ 163.4, 160.8, 159.1, 156.2, 155.6, 127.6, 116.2, 115.1, 113.1, 104.8, 99.8, 81.5, 75.4, 70.4, 70.2, 61.1, 18.7, 18.2; CIHRMS Calcd for $[\text{C}_{18}\text{H}_{21}\text{NO}_8\text{Na}^+]$: 402.1164. Found 402.1161.

4-methyl-7-(tetrahydro-5-methoxy-6-methyl-2H-pyran-2-yloxy)-2H-chromen-2-one
(II-37).

The ene compound **II-33** (60 mg, 0.20 mmol) and *o*-NO₂C₆H₄SO₂NHNH₂ (322 mg, 1.80 mmol) were dissolved in 2.0 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen atmosphere then triethylamine (288 μL, 2.0 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion, as monitored by TLC. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give deoxy compound **II-37** (54 mg, 0.18 mmol, 90 %) as viscous oil. *R_f* (50% EtOAc/Hexane) = 0.40; [α]_D²⁶ = - 140 (*c* 1, CH₂Cl₂); IR (thin film, cm⁻¹) 2934, 2929, 1729, 1511, 1390, 1104, 1067, 849; ¹H NMR (600 MHz, CDCl₃) δ 7.49 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.98 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.14 (dd, *J* = 2.4, 1.2 Hz, 1H), 5.53 (dd, *J* = 3.6, 1.2 Hz, 1H), 3.39 (s, 3H), 3.64 (ddd, *J* = 12.0, 9.6, 6.6 Hz, 1H), 2.93 (m, 1H), 2.39 (d, *J* = 1.2 Hz, 3H), 2.11 (m, 2H), 1.86 (m, 2H), 1.18 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 161.2, 159.8, 155.0, 152.3, 125.3, 114.2, 113.5, 112.3, 103.9, 94.9, 80.2, 69.2, 56.5, 29.0, 23.0, 18.6, 18.1; CIHRMS Calcd for [C₁₇H₂₀O₅H⁺]: 305.1389. Found 305.1384.

***N*-(7-(5,6-dihydro-5-methoxy-6-methyl-2*H*-pyran-2-yloxy)-8-methyl-2-oxo-2*H*-chromen-3-yl)acetamide (**II-39**).**

A THF (1.5 mL) solution of Piv-enol **II-32** (115 mg, 0.50 mmol) and acetamido coumarin alcohol **5** (128.7 mg, 0.55 mmol) was cooled to 0 °C. A THF (0.5 mL) solution of Pd₂(dba)₃·CHCl₃ (21.4 mg, 2.5 mol%) and PPh₃ (21.8 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 4 hours. The reaction mixture was quenched with 5 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 40% EtOAc/hexanes to give coumarin-enol **II-39** (158 g, 0.44 mmol, 80%) as viscous oil. *R_f* (50% EtOAc/hexane) = 0.373; [α]_D²⁶ = - 132 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2936, 1698, 1671, 1604, 1501, 1365, 1090, 1031, 976, 808; ¹H NMR (600 MHz, CDCl₃) δ 8.62 (s, 1H), 7.97 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 1H), 6.24 (d, *J* = 10.2 Hz, 1H), 5.94 (ddd, *J* = 7.2, 4.8, 2.4 Hz, 1H), 5.65 (d, *J* = 2.4 Hz, 1H), 3.92 (ddd, *J* = 12.0, 9.6, 6.0 Hz, 1H), 3.54 (ddd, *J* = 9.0, 3.0, 1.8 Hz, 1H), 3.45 (s, 3H), 2.30 (s, 3H), 2.22 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 169.1, 159.1, 157.0, 149.0, 131.5, 125.5, 125.4, 124.2, 121.6, 115.5, 114.1, 112.5, 93.6, 77.8, 67.0, 56.7, 24.6, 18.1, 8.3; CIHRMS: Calculated for [C₁₉H₂₁O₆Na⁺]: 382.1266, Found: 382.1262.

***N*-(8-methyl-2-oxo-7-(tetrahydro-3,4-dihydroxy-5-methoxy-6-methyl-2*H*-pyran-2-yloxy)-2*H*-chromen-3-yl)acetamide (**II-40**).**

To a CH₂Cl₂ (1.0 mL) solution of ene compound **II-39** (150 mg, 0.417 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (208 μL). Crystalline OsO₄ (6 mg, 5 mol %) was added and the reaction was stirred for 10 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/Hexane (90:10). Pure fractions were combined and concentrated to afford diol **II-40** (148 mg, 0.35 mmol, 85%) as viscous oil. *R*_f (100% EtOAc) = 0.30; [α]_D²⁶ = - 65 (*c* = 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3336, 2917, 2950, 1714, 1607, 1529, 1376, 1250, 1120, 980; ¹H NMR (600 MHz, CDCl₃) δ 8.61 (s, 1H), 7.98 (s, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 1H), 5.57 (d, *J* = 1.2 Hz, 1H), 4.21 (dd, *J* = 5.4, 3.0 Hz, 1H), 4.06 (ddd, *J* = 9.0, 8.4, 3.0 Hz, 1H), 3.68 (m, 1H), 3.59 (s, 3H), 3.19 (dd, *J* = 9.6, 9.6 Hz, 1H), 2.59 (m, 2H), 2.29 (s, 3H), 2.23 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 161.9, 159.0, 155.3, 149.0, 125.6, 124.1, 121.8, 114.7, 114.3, 111.4, 97.4, 82.9, 71.3, 70.8, 68.5, 61.0, 24.6, 18.0, 8.2; CIHRMS Calcd for [C₁₉H₂₃NO₈Na⁺]: 416.1321. Found 416.1317.

***N*-(8-methyl-2-oxo-7-(tetrahydro-3-acetoxy,4-hydroxy-5-methoxy-6-methyl-2*H*-pyran-2-yloxy)-2*H*-chromen-3-yl)acetamide (**II-42**).**

To a solution of diol **II-40** (80 mg, 0.20 mmol) and trimethyl orthoacetate (130 μ L, 0.30 mmol) mixture in THF (0.4 mL) was added *p*-toluenesulfonic acid monohydrate (1.7 mg, 0.02 mmol), stirring for 0.5 h. The solvent was removed under reduced pressure and residue was dissolved in 1.5 ml THF/H₂O (1:1, v/v) solution. Then *p*-toluenesulfonic acid (18.0 mg 0.15 mmol) was added. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched with adding EtOAc and satd. NaHCO₃. The organic layer was separated, dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel flash chromatography eluting with 75% EtOAc/hexane to give acetate **II-42** (83 mg, 0.19 mmol, 95%) as white foam. R_f = 0.30 (50% EtOAc/Hexane); $[\alpha]_D^{26}$ = -141 (c = 0.5, CH₂Cl₂); IR (thin film, cm⁻¹) 3448, 2937, 1728, 1712, 1611, 1368, 1234, 1067, 990, 851; ¹H NMR (600 MHz, CDCl₃) δ 8.60 (s, 1H), 7.99 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 5.52 (d, J = 1.8 Hz, 1H), 5.31 (dd, J = 3.6, 1.8 Hz, 1H), 4.23 (ddd, J = 9.0, 5.4, 3.0 Hz, 1H), 3.70 (ddd, J = 12.0, 9.6, 6.0 Hz, 1H), 3.61 (s, 3H), 3.16 (dd, J = 9.6, 9.6 Hz, 1H), 2.33 (s, 1H), 2.29 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.30 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 170.6, 169.2, 158.9, 155.2, 149.0, 125.6, 124.0, 121.9, 114.5, 111.4, 95.6, 83.0, 79.9, 72.1, 69.8,

68.8, 61.0, 24.6, 20.9, 17.9, 8.2; CIHRMS: Calculated for $[C_{21}H_{25}NO_9H^+]$: 436.1607.

Found: 436.1604.

2-(*N*-(7-hydroxy-8-methyl-2-oxo-2*H*-chromen-3-yl)acetamide)-tetrahydro-3-hydroxy-5-methoxy-6-methyl-2*H*-pyran-4-yl carbamate (II-43**).**

To a CH_2Cl_2 (0.9 mL, 0.1M) solution of acetate alcohol **II-42** (40 mg, 0.10 mmol) at 0 °C was added trichloro acetyl isocyanate (20 μ L, 0.46 mmol) and the reaction was stirred for 1 h. The solvent was removed under reduced pressure and residue was dissolved in 1.0 ml MeOH/ H_2O (2:1, v/v) solution. Then potassium carbonate (38 mg 0.28 mmol) was added at 0 °C. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched with adding EtOAc and satd. $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), concentrated under reduced pressure and purified by silica gel flash chromatography eluting with MeOH/EtOAc/Hexane (10:40:50). Pure fractions were combined and concentrated to afford carbamate **II-43** (31 mg, 0.07 mmol, 70 %) as viscous oil. R_f (70% EtOAc/Hexane) = 0.35; $[\alpha]_D^{26} = -42$ (c 0.5, CH_2Cl_2); IR (thin film, cm^{-1}) 3397, 3291, 2932, 1718, 1667, 1529, 1111, 1065, 990, 771; 1H NMR (600 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.33 (d, $J = 9.0$ Hz, 1H), 7.14 (d, $J = 8.4$ Hz, 1H), 5.48 (d, $J = 1.8$ Hz, 1H), 5.09 (dd, $J = 9.6, 3.0$ Hz, 1H), 4.50 (br s, 1H), 4.19 (dd, $J = 3.0, 2.4$

Hz, 1H), 3.63 (m, 1H), 3.55 (s, 3H), 3.33 (dd, $J = 9.6, 9.6$ Hz, 1H), 2.28 (s, 3H), 2.16 (s, 3H), 2.11 (br s, 1H), 1.21 (d, $J = 6.0$ Hz, 3H); NMR (150 MHz, CDCl_3) δ 172.6, 159.1, 157.0, 126.9, 123.4, 115.8, 112.8, 99.9, 97.7, 84.2, 81.5, 75.6, 74.5, 70.4, 61.1, 45.9, 23.9, 23.1, 18.2, 8.4; CIHRMS Calcd for $[\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_9\text{Na}^+]$: 459.1379. Found 459.1376.

***N*-(8-methyl-2-oxo-7-(tetrahydro-5-methoxy-6-methyl-2*H*-pyran-2-yloxy)-2*H*-chromen-3-yl)acetamide (II-41).**

The ene compound **II-39** (10 mg, 0.03 mmol) and $o\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_2\text{NHNH}_2$ (33 mg, 0.16 mmol) were dissolved in 0.2 mL of CH_2Cl_2 in a round bottom flask and cooled 0°C under nitrogen atmosphere then triethylamine (39 μL , 0.27 mmol) was added and the reaction mixture was stirred at 0°C for 12 hours and on completion, as monitored by TLC. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 40% EtOAc/hexanes to give deoxy compound **II-41** (9.5 mg, 0.02 mmol, 95 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.35; $[\alpha]_{\text{D}}^{26} = -23$ (c 1, CH_2Cl_2); IR (thin film, cm^{-1}) 3352, 2951, 2929, 1712, 1677, 1374, 1138, 1086, 977, 783; ^1H NMR (600 MHz, CDCl_3) δ 8.61 (s, 1H), 7.96 (s, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 5.56 (br s, 1H), 3.65 (ddd, $J = 12.0, 9.0, 6.6$ Hz, 1H), 3.40 (s, 3H), 2.94 (ddd, $J = 10.8, 9.0, 4.8$ Hz, 1H), 2.33 (s, 3H), 2.22 (s,

3H), 2.14 (m, 2H), 1.90 (m, 2H), 1.19 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.1, 159.2, 156.2, 149.1, 125.5, 124.4, 121.4, 114.7, 113.8, 111.6, 94.8, 80.4, 69.2, 56.5, 29.3, 24.6, 23.2, 18.2, 8.2; CIHRMS Calcd for $[\text{C}_{19}\text{H}_{23}\text{NO}_6\text{Na}^+]$: 384.1423. Found 384.1418.

***N*-(7-(5,6-dihydro-5-methoxy-6-methyl-2*H*-pyran-2-yloxy)-8-methyl-2-oxo-2*H*-chromen-3-yl)-4-methoxy-3,3'-methoxyphenylbenzamide (II-45).**

A THF (0.5 mL) solution of Piv-enol **II-32** (47 mg, 0.28 mmol) and coumarin alcohol **II-44** (60 mg, 0.14 mmol) was cooled to 0 °C. A THF (0.5 mL) solution of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (7.2 mg, 2.5 mol%) and PPh_3 (7.3 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 5 hours. The reaction mixture was quenched with 5 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 35% EtOAc /hexanes to give coumarin-enol **II-45** (64 mg, 0.12 mmol, 83%) as viscous oil. R_f (50% EtOAc /hexane) = 0.30; $[\alpha]_{\text{D}}^{25} = -26$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 2934, 1706, 1669, 1603, 1364, 1088, 939, 817; ^1H NMR (600 MHz, CDCl_3) δ 8.80 (s, 1H), 8.70 (s, 1H), 7.92 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.33 (d, $J = 9.0$ Hz, 1H), 7.20 (d, $J = 9.0$ Hz, 1H), 7.12 (d, $J = 7.8$ Hz, 1H), 7.09 (d, $J = 2.4, 1.2$ Hz, 1H), 7.06

(d, $J = 8.4$ Hz, 1H), 6.93 (dd, $J = 7.8, 3.0$ Hz, 1H), 6.23 (d, $J = 10.2$ Hz, 1H), 5.94 (td, $J = 12.6, 2.4$ Hz, 1H), 5.66 (br s, 1H), 3.93 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.54 (dd, $J = 10.2, 1.8$ Hz, 1H), 3.46 (s, 3H), 2.33 (s, 3H), 1.30 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 165.4, 159.7, 159.4, 159.3, 157.0, 149.0, 138.6, 131.5, 131.0, 129.9, 129.1, 128.1, 126.1, 125.6, 125.4, 124.1, 122.0 (2C), 115.5, 115.2, 114.3, 113.1, 112.6, 111.0, 93.6, 77.8, 67.0, 56.7, 55.8, 55.3, 18.1, 8.3; CIHRMS: Calculated for $[\text{C}_{32}\text{H}_{31}\text{NO}_8\text{H}^+]$: 558.2127, Found: 558.2126.

***N*-(7-(tetrahydro-3,4-dihydroxy-5-methoxy-6-methyl-2*H*-pyran-2-ylloxy)-8-methyl-2-oxo-2*H*-chromen-3-yl)-4-methoxy-3-3'-methoxyphenylbenzamide (II-46).**

To a CH_2Cl_2 (0.8 mL) solution of ene compound **II-45** (50 mg, 0.09 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (45 μL). Crystalline OsO_4 (2 mg, 5 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/Hexane (10:40:50). Pure fractions were combined and concentrated to afford diol **II-46** (43 mg, 0.07 mmol, 80%) as viscous oil. R_f (80% EtOAc/Hexane) = 0.20; $[\alpha]_{\text{D}}^{26} = -25$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3465, 2984, 1737, 1670, 1371, 1291, 1140, 1091, 984; ^1H NMR (600 MHz, CDCl_3) δ 8.80 (s, 1H),

8.70 (s, 1H), 7.92 (dd, $J = 6.0, 2.4$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 7.35 (m, 2H), 7.17 (d, $J = 9.0$ Hz, 1H), 7.12 (d, $J = 9.0$ Hz, 1H), 7.09 (dd, $J = 2.4, 1.8$ Hz, 1H), 7.07 (d, $J = 9.0$ Hz, 1H), 6.93 (dd, $J = 8.4, 1.8$ Hz, 1H), 5.58 (d, $J = 1.2$ Hz, 1H), 4.22 (dd, $J = 3.6, 1.2$ Hz, 1H), 4.09 (dd, $J = 9.0, 3.6$ Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.68 (ddd, $J = 9.6, 6.0, 3.6$ Hz, 1H), 3.60 (s, 3H), 3.20 (dd, $J = 9.6, 9.6$ Hz, 1H), 2.55 (br s, 2H), 2.31 (s, 3H), 1.30 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 165.5, 159.8, 159.3, 155.3, 149.0, 138.6, 131.1, 129.9, 129.1, 128.1, 126.0, 125.7, 124.0, 122.1, 122.0 (2C), 115.2, 114.7, 114.5, 113.1, 111.4, 111.0, 97.4, 82.9, 71.3, 70.5, 68.5, 61.0, 55.8, 55.3, 18.0, 8.2; CIHRMS Calcd for $[\text{C}_{32}\text{H}_{33}\text{NO}_{10}\text{Na}^+]$: 614.2002. Found 614.2002.

***N*-(7-(tetrahydro-3-acetoxy,4-hydroxy-5-methoxy-6-methyl-2*H*-pyran-2-yloxy)-8-methyl-2-oxo-2*H*-chromen-3-yl)-4-methoxy-3,3'-methoxyphenylbenzamide (II-48).**

To a solution of diol **II-46** (65 mg, 0.11 mmol) and trimethyl orthoacetate (71 μL , 0.55 mmol) mixture in THF (0.3 ml) was added *p*-toluenesulfonic acid monohydrate (1.0 mg, 0.01 mmol), stirring for 0.5 h. The solvent was removed under reduced pressure and residue was dissolved in 1.0 ml THF/ H_2O (1:1, v/v) solution. Then *p*-toluenesulfonic acid (10.0 mg 0.05 mmol) was added. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched with adding EtOAc and satd. NaHCO_3 . The organic layer was separated, dried (Na_2SO_4), concentrated under reduced

pressure and purified by silica gel flash chromatography eluting with 65% EtOAc/hexane to give acetate **II-48** (64 mg, 0.10 mmol, 92%) as white foam. $R_f = 0.37$ (10:40:50% MeOH/EtOAc/Hexane); $[\alpha]_D^{26} = -6$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3455, 2980, 1735, 1693, 1382, 1290, 1128, 1042, 978; ^1H NMR (600 MHz, CDCl_3) δ 8.80 (d, $J = 3.0$ Hz, 1H), 8.71 (s, 1H), 7.92 (dd, $J = 9.0, 2.4$ Hz, 1H), 7.89 (d, $J = 1.8$ Hz, 1H), 7.36 (m, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.12 (m, 1H), 7.09 (m, 1H), 6.92 (ddd, $J = 8.4, 2.4, 1.2$ Hz, 1H), 5.54 (br s, 1H), 5.37 (dd, $J = 9.0, 3.0$ Hz, 1H), 4.32 (m, 1H), 4.12 (dd, $J = 13.8, 7.2$ Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.78 (m, 1H), 3.62 (br s, 1H), 3.51 (s, 3H), 3.69 (m, 1H), 2.36 (s, 3H), 2.20 (s, 3H), 2.17 (dd, $J = 13.8, 3.6$ Hz, 1H), 1.32 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.6, 169.8, 165.5, 159.8, 159.3, 155.2, 149.1, 138.6, 131.1, 129.9, 129.1, 128.1, 125.6, 123.9, 122.0, 115.2, 113.1, 111.4, 111.0, 97.6, 65.7, 83.0, 79.9, 73.7, 69.5, 68.8, 60.5, 60.3, 55.8, 55.3, 21.1, 17.8, 14.1, 8.3; CIHRMS: Calculated for $[\text{C}_{34}\text{H}_{35}\text{NO}_{11}\text{Na}^+]$: 656.2107. Found: 656.2105.

***N*-(7-(tetrahydro-3-hydroxy,4-carbamoyl-5-methoxy-6-methyl-2*H*-pyran-2-yloxy)-8-methyl-2-oxo-2*H*-chromen-3-yl)-4-methoxy-3,3'-methoxyphenylbenzamide (II-49).**

To a CH_2Cl_2 (0.5 mL, 0.1M) solution of acetate alcohol **II-48** (35 mg, 0.06 mmol) at 0°C was added trichloro acetyl isocyanate (11 μL , 0.08 mmol) and the reaction was stirred for

1 h. The solvent was removed under reduced pressure and residue was dissolved in 1.0 ml MeOH/H₂O (2:1, v/v) solution. Then potassium carbonate (22.9 mg 0.17 mmol) was added at 0 °C. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched with adding EtOAc and satd. NaHCO₃. The organic layer was separated, dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel flash chromatography eluting with MeOH/EtOAc/Hexane (10:40:50). Pure fractions were combined and concentrated to afford carbamate **II-49** (23 mg, 0.04 mmol, 78 %) as viscous oil. R_f (70% EtOAc/Hexane) = 0.30; $[\alpha]_D^{26} = -43$ (c 0.5, CH₂Cl₂); IR (thin film, cm⁻¹) 3434, 2930, 2852, 1712, 1606, 1366, 1265, 1099, 987, 810; ¹H NMR (600 MHz, CDCl₃) δ 8.80 (s, 1H), 7.92 (dd, J = 6.6, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.35 (m, 3H), 7.15 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.09 (dd, J = 2.4, 1.8 Hz, 1H), 6.93 (dd, J = 8.4, 2.4 Hz, 1H), 5.55 (d, J = 1.8 Hz, 1H), 5.26 (dd, J = 9.0, 3.6 Hz, 1H), 4.36 (br s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.80 (ddd, J = 9.6, 6.0, 5.4 Hz, 1H), 3.52 (s, 3H), 3.36 (m, 2H), 2.36 (s, 3H), 2.17 (s, 1H), 1.32 (d, J = 6.0 Hz, 3H); NMR (150 MHz, CDCl₃) δ 160.0, 159.5, 155.6, 149.2, 138.8, 131.2, 130.1, 129.3, 128.3, 126.1, 125.9, 125.8, 124.3, 122.2 (2C), 115.4, 115.3, 114.7, 113.3, 111.7, 111.2, 98.1, 96.2, 80.2, 74.6, 69.4, 69.0, 60.5, 56.0, 55.5, 29.8, 18.0, 8.4; CIHRMS Calcd for [C₃₃H₃₄N₂O₁₁Na⁺]: 657.2060. Found 657.2057.

***N*-(7-(tetrahydro-5-methoxy-6-methyl-2*H*-pyran-2-yl)-8-methyl-2-oxo-2*H*-chromen-3-yl)-4-methoxy-3-3'-methoxyphenylbenzamide (II-47).**

The ene compound **II-45** (20 mg, 0.03 mmol) and *o*-NO₂C₆H₄SO₂NHNH₂ (59 mg, 0.29 mmol) were dissolved in 0.3 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen atmosphere then triethylamine (53 μL, 0.36 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion, as monitored by TLC. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give deoxy compound **II-47** (19 mg, 0.03 mmol, 92 %) as viscous oil. *R_f* (50% EtOAc/Hexane) = 0.35; [α]_D²⁶ = - 31 (*c* 1, CH₂Cl₂); IR (thin film, cm⁻¹) 2927, 2853, 1708, 1670, 1605, 1392, 1239, 1090, 979, 786; ¹H NMR (600 MHz, CDCl₃) δ 8.80 (s, 1H), 8.70 (s, 1H), 7.92 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.89 (d, *J* = 1.8 Hz, 1H), 7.34 (m, 2H), 7.18 (d, *J* = 9.0 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.09 (dd, *J* = 2.4, 1.8 Hz, 1H), 7.06 (s, 1H), 6.93 (dd, *J* = 7.8, 2.4 Hz, 1H), 5.57 (br s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.67 (ddd, *J* = 9.6, 6.0, 4.8 Hz, 1H), 3.50 (s, 3H), 2.94 (ddd, *J* = 10.2, 9.0, 4.8 Hz, 1H), 2.35 (s, 3H), 2.16 (m, 2H), 1.91 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 165.4, 159.7, 159.5, 156.2, 149.1, 138.6, 131.0, 129.9, 129.1, 128.1, 126.1, 125.5, 124.3, 122.0, 121.8, 115.2, 114.7, 113.9, 113.1, 111.6, 111.0, 94.8, 80.4, 69.2, 56.5, 55.8, 55.3, 29.6, 29.3, 23.2, 18.2, 8.2; CIHRMS Calcd for [C₃₂H₃₃NO₈H⁺]: 560.2284. Found 560.2281

5,6-dihydro-5-oxo-2H-pyran-2-yl pivalate (II-52).

The furfuryl alcohol **II-50** (20.0 g, 203.8 mmol), 326 mL of THF, and 81 mL of H₂O were added to a round bottom flask and cooled to 0 °C. Solid NaHCO₃ (34.2 g, 407.6 mmol), NaOAc•3H₂O (27.7 g, 203.8 mmol), and NBS (36.3 g, 203.8 mmol) were added to the solution and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with satd aq NaHCO₃ (200 mL), extracted (3 x 100 mL) with Et₂O, dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel chromatography eluting with 20% EtOAc/hexanes to give hemiacetal **II-51**. The hemiacetal **II-51** (16.0 g, 140.3 mmol) was dissolved in CH₂Cl₂ (350 mL) and the solution was cooled to -78 °C. A CH₂Cl₂ (50 mL) solution of Piv-Cl (19.2 mL, 154.3 mmol), a catalytic amount of DMAP (856 mg, 7.0 mmol) and Et₃N (21 mL, 154.3 mmol) were added to the reaction mixture. The reaction was stirred for 6 h at -78 °C. The reaction was quenched with 200 mL of satd. aq NaHCO₃, extracted (3 x 150 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10 % EtOAc/hexanes to give Piv-enone **II-52** (33.5 g, 169.1 mmol, 83 %). *R_f* (50% EtOAc/hexanes) = 0.52; IR (thin film, cm⁻¹) 2955, 2928, 2859, 1765, 1713, 1417, 1379, 1265, 950; ¹H NMR (600 MHz, CDCl₃) δ 6.92 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.46 (d, *J* = 3.6 Hz, 1H), 6.25 (d, *J* = 10.8 Hz, 1H), 4.47 (d, *J* = 16.8 Hz, 1H), 4.20 (d, *J* = 16.8 Hz, 1H), 1.22 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 193.4, 176.9, 142.4, 128.6, 86.5, 67.3, 39.2, 26.9 (3C); CIHRMS Calcd for [C₁₀H₁₄O₄Na]⁺: 221.0789. Found 221.0784.

5,6-dihydro-5-hydroxy-2H-pyran-2-yl pivalate (II-52).

A solution of pyranone **II-52** (1.17 g, 5.46 mmol) in dry CH_2Cl_2 (4.5 mL) and 0.4 M $\text{CeCl}_3/\text{MeOH}$ (4.5 mL) was cooled to $-78\text{ }^\circ\text{C}$. NaBH_4 (258 mg, 5.46 mmol) was added and the reaction mixture was stirred for 2 h at $-0\text{ }^\circ\text{C}$. The resulting solution was diluted with ether (50 mL) and was quenched with 25 mL of saturated NaHCO_3 , extracted (3 x 25 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel chromatography eluting with 30% EtOAc /hexane to give enol **II-53** (1.08 g, 5.02 mmol, 92%) as a semi solid; $R_f = 0.38$ (50% EtOAc /Hexane); IR (thin film, cm^{-1}) 3395 2965, 2938, 1674, 1519, 1245, 1054, 987; ^1H NMR (600 MHz, CDCl_3) δ 6.56 (br s, 1H), 6.11 (dd, $J = 10.2, 2.4$ Hz, 1H), 5.75 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 4.35 (m, 1H), 3.90 (m, 1H), 3.61 (m, 1H), 2.05 (d, $J = 7.2$ Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.6, 134.6, 125.1, 87.7, 64.3, 62.5, 38.9, 26.9 (3C); CIHRMS Calcd for $[\text{C}_{10}\text{H}_{16}\text{O}_4\text{Na}]^+$: 223.0946. Found 223.0942.

7-((2S,5R)-5,6-dihydro-5-hydroxy-2H-pyran-2-yloxy)-4-methyl-2H-chromen-2-one (II-54).

Method 1: A THF (1.0 mL) solution of Piv-enol **II-53** (150 mg, 0.69 mmol) and 4-methyl coumarin alcohol **5** (61.1 mg, 0.35 mmol) was cooled to 0 °C. A THF (0.3 mL) solution of Pd₂(dba)₃·CHCl₃ (18 mg, 2.5 mol%) and *R,R*-Trost ligand (27.5 mg, 5 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 4 hours. The reaction mixture was quenched with 3 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give coumarin-enol **II-54** (143 mg, 0.52 mmol, 75%) as viscous oil.

Method 2: A THF (1.0 mL) solution of Piv-enol **II-53** (130 mg, 0.60 mmol) and 4-methyl coumarin alcohol **5** (53 mg, 0.30 mmol) was cooled to 0 °C. A THF (0.6 mL) solution of Pd₂(dba)₃·CHCl₃ (15 mg, 2.5 mol%) and PPh₃ (15.7 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was quenched with 3 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50-60% EtOAc/hexanes to give coumarin-enol **II-54** (140 mg, 0.51 mmol, 85%) as viscous oil. *R_f* (50% EtOAc/hexane) = 0.42; $[\alpha]_{\text{D}}^{26} = -145$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3440, 2950, 2942, 1731, 1613, 1389, 1134, 1067, 961; ¹H NMR (600 MHz, CDCl₃) δ 7.50 (d, *J* = 10.2 Hz, 1H), 7.03 (d, *J* = 2.4, 1.2 Hz, 1H), 6.98 (ddd, *J* = 7.2, 3.6, 1.2 Hz, 1H), 6.19 (m, 1H), 6.14 (dd, *J* = 7.2, 2.4 Hz, 1H), 5.89 (m, 1H), 5.67 (br s, 1H), 4.34 (m, 1H), 3.88 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.69 (ddd, *J* = 18.6, 8.4, 1.8 Hz, 1H), 2.38 (d, *J* = 1.2 Hz, 3H), 2.06 (br s, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 161.4, 160.0, 154.8, 152.5, 135.2, 125.5,

125.0, 114.6, 113.6, 112.4, 104.2, 92.4, 63.7, 62.3, 18.5; CIHRMS: Calculated for $[C_{15}H_{14}O_5Na^+]$: 297.0739, Found: 297.0736.

7-((2S,3R,4R,5S)-tetrahydro-3,4,5-trihydroxy-2H-pyran-2-yloxy)-4-methyl-2H-chromen-2-one (II-55).

To a CH_2Cl_2 (3.6 mL) solution of diene **II-54** (100 mg, 0.36 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (0.2 mL). Crystalline OsO_4 (4.6 mg, 5 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/Hexane (5:45:50). Pure fractions were combined and concentrated to afford diol **II-55** (95 mg, 0.30 mmol, 85%) as viscous oil. R_f (60% EtOAc/Hexane) = 0.25; $[\alpha]_D^{26} = -50$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3420, 2927, 2939, 1728, 1655, 1559, 1371, 1285, 1117, 1071, 862; 1H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, $J = 9.0$ Hz, 1H), 7.07 (dd, $J = 9.0, 2.4$ Hz, 1H), 7.03 (d, $J = 2.4$ Hz, 1H), 6.18 (d, $J = 1.2$ Hz, 1H), 5.49 (d, $J = 3.0$ Hz, 1H), 4.52 (s, 1H), 3.98 (t, $J = 3.0$ Hz, 1H), 3.86 (m, 2H), 3.77 (ddd, $J = 11.5, 3.9, 1.8$ Hz, 1H), 3.48 (m, 1H), 2.43 (d, $J = 1.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3, 161.1, 156.0, 155.4, 127.3, 116.0, 114.8, 112.8, 104.8, 100.2, 72.5, 71.0, 68.4, 65.1, 18.6; CIHRMS Calcd for $[C_{15}H_{16}O_7Na^+]$: 331.0793. Found 331.0791.

(2*S*,6*R*)-6-[(2'*S*)-2'- *N*-Carbobenzyloxy-D-tyrosine methoxycarbonyl]-2-*tert*-butyl-dimethyl-silanyloxymethyl-6*H*-pyran-3-one (III-20).

A CH₂Cl₂ (0.7 mL) solution of compound **III-18** (260 mg, 0.72 mmol) and Cbz-D-tyrosine methyl ester **III-17** (238 mg, 0.726 mmol) was cooled to 0 °C. A CH₂Cl₂ (0.7 mL) solution of Pd₂(dba)₃·CHCl₃ (18 mg, 2.5 mol%) and PPh₃ (16 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was quenched with 5 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 14% EtOAc/hexanes to give enone **III-20** (380 mg, 0.66 mmol, 92%) as viscous oil. *R*_f (30% EtOAc/hexanes) = 0.42; [α]_D²⁶ = + 0.8 (*c* = 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3351, 2952, 1752, 1725, 1509, 1256, 1219, 1151, 995, 836; ¹H NMR (600 MHz, CDCl₃) δ 7.35 (m, 5H), 7.05 (m, 4H), 6.97 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.22 (d, *J* = 10.8 Hz, 1H), 5.93 (d, *J* = 3.6 Hz, 1H), 5.30 (d, *J* = 7.8 Hz, 1H), 5.10 (d, *J* = 12.6 Hz, 1H), 5.07 (d, *J* = 12.6 Hz, 1H), 4.62 (dd, *J* = 13.8, 6.0 Hz, 1H), 4.54 (dd, *J* = 4.8, 3.0 Hz, 1H), 4.05 (dd, *J* = 11.4, 4.8 Hz, 1H), 4.02 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.71 (s, 3H), 3.10 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.04 (dd, *J* = 14.4, 6.0 Hz, 1H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 194.2, 174.8, 156.1, 155.4, 151.6, 150.0, 142.6, 136.0, 130.3(2C), 130.0,

128.6, 128.4(2C), 128.0, 127.9, 117.0, 91.9, 76.6, 66.8, 62.5, 54.7, 52.2, 37.2, 25.7(3C), 18.1, -5.44, -5.48; CIHRMS Calcd for $[C_{30}H_{39}NO_8SiNa^+]$: 592.2337. Found 592.2290.

3-{4-[6-(*tert*-Butyl-dimethylsilanyloxymethyl)-5-hydroxy-5,6-dihydro-2*H*-pyran-2-yloxy]-phenyl}-2- *N*-carbobenzyloxy-D-tyrosine methyl ester (III-21**).**

The enone compound **III-20** (320 mg, 0.562 mmol) was dissolved in 0.5 mL of CH_2Cl_2 and 0.5 mL MeOH in round bottom flask and cooled $-78\text{ }^{\circ}C$ then $NaBH_4$ (21 mg, 0.562 mmol) was added and the reaction mixture was stirred at $-78\text{ }^{\circ}C$ for 3 hours and on completion, monitored by TLC, reaction mixture was diluted with ether and was quenched with 5 mL of satd. aq. $NaHCO_3$, extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 18% EtOAc/hexanes to give **III-21** (300 mg, 0.525 mmol, 87%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.30; $[\alpha]_D^{26} = +29.0$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3386, 2925, 1459, 1255, 1069, 1027, 838; 1H NMR (600 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.98 (m, 4H), 6.08 (d, $J = 10.2$ Hz, 1H), 5.88 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.57 (d, $J = 1.8$ Hz, 1H), 5.21 (d, $J = 7.8$ Hz, 1H), 5.11 (d, $J = 13.2$ Hz, 1H), 5.08 (d, $J = 12.0$ Hz, 1H), 4.62 (dd, $J = 13.2, 5.4$ Hz, 1H), 4.28 (dd, $J = 9.0, 1.8$ Hz, 1H), 3.89 (dd, $J = 10.2, 4.8$ Hz, 1H), 3.84 (dq, $J = 12.0, 7.2, 4.8$ Hz, 1H), 3.75 (dd, $J = 9.6, 6.6$ Hz, 1H), 3.32 (s, 3H), 3.08 (dd, $J = 13.8, 5.4$ Hz, 1H), 3.04 (dd, $J = 13.8, 5.4$ Hz, 1H), 3.02 (d, $J = 3.0$ Hz, 1H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s,

3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.9, 156.5, 133.3, 130.3, 130.2(2C), 128.5(2C), 128.4, 128.1, 128.0, 124.8, 116.9(2C), 115.5, 92.8, 70.7, 66.9, 66.5, 65.1, 54.8, 52.3, 52.2, 37.2, 25.7(3C), 18.1, -5.5, -5.6; CIHRMS Calcd for $[\text{C}_{30}\text{H}_{41}\text{NO}_8\text{SiNa}^+]$: 594.2493 Found 594.2467.

(1'S, 4'S, 5'R, 1S, 5R)-1-[1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5-(tert-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy]-5-(tert-butyl-dimethylsilanyloxymethyl) -1H-pyran-4-one (III-16).

A CH_2Cl_2 (0.5 mL) solution of compound **III-16** (280 mg, 0.49 mmol) and alcohol **III-21** (175 mg, 0.49 mmol) was cooled to 0 °C. A CH_2Cl_2 (0.5 mL) solution of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (12 mg, 2.5 mol%) and PPh_3 (11 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched with 5 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 16% EtOAc /hexanes to give dienone **III-16** (328 mg, 0.40 mmol, 82%) as viscous oil. R_f (30% EtOAc /hexanes) = 0.44; $[\alpha]_{\text{D}}^{26} = +0.15$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3351, 2952, 1752, 1725, 1509, 1256, 1219, 1151, 995, 836; ^1H NMR (600 MHz, CDCl_3) δ 7.35 (m, 5H), 7.05 (m, 4H), 6.84 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.23 (d, $J = 10.8$ Hz, 1H), 6.14 (d, $J = 10.2$ Hz, 1H), 5.95 (ddd, $J =$

10.2, 2.4, 1.8 Hz, 1H), 5.62 (d, $J = 3.6$ Hz, 1H), 5.60 (d, $J = 1.8$ Hz, 1H), 5.26 (d, $J = 8.4$ Hz, 1H), 5.10 (d, $J = 13.2$ Hz, 1H), 5.07 (d, $J = 12.6$ Hz, 1H), 4.62 (dd, $J = 13.8, 6.0$ Hz, 1H), 4.59 (d, $J = 9.0$ Hz, 1H), 4.44 (dd, $J = 3.6, 2.4$ Hz, 1H), 4.13 (d, $J = 3.6$ Hz, 1H), 4.10 (dd, $J = 10.2, 4.2$ Hz, 1H), 3.96 (dd, $J = 10.2, 2.4$ Hz, 1H), 3.86 (dq, $J = 9.6, 1.8$ Hz, 1H), 3.81 (dd, $J = 10.2, 1.8$ Hz, 1H), 3.70 (s, 3H), 3.08 (dd, $J = 13.8, 5.4$ Hz, 1H), 3.03 (dd, $J = 13.8, 6.0$ Hz, 1H), 0.86 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 194.5, 171.8, 156.4, 155.5, 143.8, 136.1, 130.1(2C), 130.0, 129.0, 128.5, 128.4(2C), 128.0, 127.9(2C), 126.4, 116.9, 92.8, 89.7, 76.5, 71.1, 66.8, 66.3, 62.8, 62.4, 60.2, 54.7, 52.1, 37.2, 25.78(3C), 25.76(3C), 18.28, 18.23, -5.4, -5.3, -5.4, -5.2; CIHRMS Calcd for $[\text{C}_{42}\text{H}_{61}\text{NO}_{11}\text{Si}_2\text{Na}^+]$: 834.3675. Found 834.3638.

(1'S,4'S,5'R,1S,4S,5R)-1-[*N*-carbobenzyloxy-D-tyrosine methoxycarbonyl -5'-(*tert*-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy]-5-(*tert*-butyl-dimethylsilanyloxymethyl)-1,4-dihydro-5H-pyran-4-ol (III-22).

The enone compound **III-16** (200 mg, 0.246 mmol) was dissolved in 0.3 mL of CH_2Cl_2 and 0.3 mL MeOH were added to a round bottom flask and cooled to -78°C then (9 mg,

0.246 mmol) NaBH₄ was added and the reaction mixture was stirred at -78°C for 6 hours and on completion, as monitored by TLC, reaction mixture is diluted with ether and was quenched with 5 mL of satd aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give enol **III-22** (182 mg, 0.223 mmol, 91%) as viscous oil. R_f (40% EtOAc/hexanes) = 0.44; $[\alpha]_D^{26} = +49$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 3420, 2930, 2855, 1725, 1717, 1510, 1256, 1219, 1151, 995, 836; ¹H NMR (600 MHz, CDCl₃) δ 7.35 (m, 5H), 7.05 (m, 4H), 6.15 (d, $J = 10.2$ Hz, 1H), 5.96 (d, $J = 10.2$ Hz, 1H), 5.92 (dq, $J = 10.2$, 1.2 Hz, 1H), 5.68 (dd, $J = 10.2$, 2.4 Hz, 1H), 5.59 (d, $J = 1.8$ Hz, 1H), 5.25 (d, $J = 7.8$ Hz, 1H), 5.18 (d, $J = 1.8$ Hz, 1H), 5.10 (d, $J = 12.6$ Hz, 1H), 5.08 (d, $J = 12.6$ Hz, 1H), 4.62 (dd, $J = 13.2$, 5.4 Hz, 1H), 4.37 (d, $J = 9.0$ Hz, 1H), 4.24 (d, $J = 8.4$ Hz, 1H), 3.97 (dd, $J = 9.6$, 4.2 Hz, 1H), 3.89 (ddd, $J = 10.2$, 5.4, 2.4 Hz, 1H), 3.85 (dd, $J = 10.2$, 1.8 Hz, 1H), 3.81 (dd, $J = 12.0$, 5.4 Hz, 1H), 3.75 (dd, $J = 10.2$, 7.2 Hz, 1H), 3.70 (s, 3H), 3.71 (m, 1H), 3.08 (d, $J = 3.0$ Hz, 1H), 3.05 (dd, $J = 8.4$, 6.0 Hz, 1H), 3.02 (d, $J = 6.0$ Hz, 1H), 0.91 (s, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 174.7, 171.8, 156.5, 155.5, 136.1, 133.1, 130.5, 130.0(2C), 128.4(2C), 128.0, 127.9(2C), 126.0, 125.3, 117.1(2C), 92.7, 91.0, 71.3, 70.1, 66.8, 66.6, 66.5, 65.1, 62.6, 54.8, 52.1, 37.2, 25.8(3C), 25.7(3C), 18.3, 18.1, -5.1, -5.2, -5.5, -5.6; CIHRMS Calcd for [C₄₂H₆₃NO₁₁Si₂Na⁺]: 836.3831. Found 836.3818.

(1'S,4'S,5'R,1S,4S,5R)-1-[1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5'-(tert-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy] -5-(tert-

butyl-dimethylsilanyloxymethyl)-1,4-dihydro-5H-pyran-*O*-4'-isovaleric ester (**III-23**).

The alcohol compound **III-22** (140 mg, 0.171 mmol), isovaleric acid (21 mg, 0.206 mmol) and DCC (42 mg, 0.206 mmol) were dissolved in 0.3 mL of CH₂Cl₂ in a round bottom flask and cooled to 0 °C then DMAP (2 mg, 0.01 mmol) was added and the reaction mixture was stirred at 0 °C for 6 hours and on completion, as monitored by TLC, the reaction mixture was diluted with ether and was quenched with 5 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/hexanes to give **III-23** (148 mg, 0.164 mmol, 96%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.62; $[\alpha]_D^{26} = +90$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 2956, 2928, 1738, 1733, 1510, 1253, 1219, 1123, 986, 835; ¹H NMR (600 MHz, CDCl₃) δ 7.34 (m, 5H), 7.00 (m, 4H), 6.20 (dd, $J = 10.2, 2.4$ Hz, 1H), 5.93 (m, 2H), 5.74 (dd, $J = 10.2, 1.8$ Hz, 1H), 5.59 (d, $J = 1.2$ Hz, 1H), 5.42 (dd, $J = 10.2, 1.8$ Hz, 1H), 5.28 (d, $J = 1.2$ Hz, 1H), 5.24 (d, $J = 8.4$ Hz, 1H), 5.10 (d, $J = 12.6$ Hz, 1H), 5.08 (d, $J = 12.6$ Hz, 1H), 4.62 (dd, $J = 13.2, 5.4$ Hz, 1H), 4.42 (d, $J = 9.0$ Hz, 1H), 3.89 (ddd, $J = 10.2, 5.4, 2.4$ Hz, 1H), 3.85 (dd, $J = 10.2, 1.8$ Hz, 1H), 3.81 (dd, $J = 11.4, 5.4$ Hz, 1H), 3.78 (dd, $J = 10.2, 1.8$ Hz, 1H), 3.75 (m, 1H), 3.70 (s, 3H), 3.71 (m, 1H), 3.08 (dd, $J = 13.8,$

5.4 Hz, 1H), 3.04 (dd, $J = 13.8, 6.0$ Hz, 1H), 2.20 (d, $J = 1.2$ Hz, 2H), 2.10 (m, 1H), 0.96 (d, $J = 6.6$ Hz, 6H), 0.89 (s, 9H), 0.85 (s, 9H), 0.05 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.1, 171.8, 156.6, 155.5, 136.2, 130.3, 130.0(2C), 129.8, 128.4(2C), 128.0(2C), 127.9, 127.2, 126.1, 117.2(2C), 92.9, 90.9, 71.4, 69.6, 66.8, 66.3, 64.6, 62.8, 62.1, 54.7, 52.1, 43.3, 37.2, 25.9, 25.8(6C), 25.6, 22.3, 22.2 18.38, 18.36, -5.1, -5.2, -5.41, -5.45; CIHRMS Calcd for $[\text{C}_{47}\text{H}_{71}\text{NO}_{12}\text{Si}_2\text{Na}^+]$: 920.4407. Found 920.4385.

1'- N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(*tert*-butyl-dimethylsilanyloxymethyl)-di-1,4- α -D-mannose -O-4' isovaleric ester (III-3a**).**

To a *t*-butanol-acetone (0.2 mL, 1:1) solution of diene ester **III-23** (100 mg, 0.11 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (0.1 mL). Crystalline OsO_4 (1.4 mg, 5 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/ether (2:98 to 4:96). Pure fractions were combined and concentrated to afford bis- α -D-*manno*-tetrol **III-3a** (91 mg, 0.094 mmol, 85 %) as viscous oil. R_f (90% EtOAc/MeOH) = 0.56; $[\alpha]_{\text{D}}^{26} = +61.9$ ($c = 2$, CH_2Cl_2); IR (thin film, cm^{-1}) 2956, 2928, 1738, 1733, 1510, 1253, 1219, 1123, 986, 835; ^1H NMR (600

MHz, CDCl₃) δ 7.31 (m, 5H), 6.99 (m, 4H), 5.45 (d, J = 1.2 Hz, 1H), 5.36 (d, J = 1.8 Hz, 1H), 5.26 (d, J = 8.4 Hz, 1H), 5.10 (d, J = 12.6 Hz, 1H), 5.07 (d, J = 12.6 Hz, 1H), 5.02 (dd, J = 10.2, 9.0 Hz, 1H), 4.62 (dd, J = 6.0, 1.8 Hz, 1H), 4.22 (ddd, J = 10.2, 6.0, 3.6, Hz, 1H), 4.13 (dd, J = 10.2, 6.6 Hz, 1H), 4.03 (dd, J = 4.2, 1.8 Hz, 1H), 3.97 (ddd, J = 10.8, 7.2, 2.4 Hz, 1H), 3.93 (dd, J = 10.2, 4.2 Hz, 1H), 3.89 (dd, J = 10.2, 9.6 Hz, 1H), 3.86 (dd, J = 11.4, 10.2 Hz, 1H), 3.78 (dd, J = 10.2, 4.8 Hz, 1H), 3.72 (dd, J = 10.2, 4.8 Hz, 1H), 3.70 (s, 3H), 3.70 (m, 2H), 3.45 (d, J = 3.6 Hz, 1H), 3.25 (d, J = 7.2 Hz, 1H), 3.10 (d, J = 1.2 Hz, 1H), 3.06 (dd, J = 13.8, 6.0 Hz, 1H), 3.02 (dd, J = 15.0, 5.4 Hz, 1H), 2.24 (dd, J = 15.0, 7.2 Hz, 1H), 2.20 (dd, J = 13.8, 7.2 Hz, 1H), 2.16 (d, J = 1.8 Hz, 1H), 2.08 (m, 1H), 0.96 (d, J = 6.6 Hz, 6H), 0.89 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 173.5, 171.9, 155.6, 155.4, 136.1, 130.2(2C), 128.4(3C), 128.1(2C), 128.0, 116.8(2C), 98.3, 97.7, 73.7, 71.6, 71.2, 70.8, 70.1, 70.0, 69.8, 66.9, 62.8, 54.8, 52.2, 43.4(2C), 37.2, 25.9, 25.9(3C), 25.8(3C), 25.7, 22.3, 22.2, 18.4, 18.3, -5.2, -5.3, -5.40, -5.47; CIHRMS Calcd for [C₄₇H₇₅NO₁₆Si₂Na⁺]: 988.4516. Found 988.4459.

1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(*tert*-butyl-dimethylsilanyloxymethyl)-2,3,2',3'-di acetonide-bis-1,4- α -D-mannose-*O*-4'-isovaleric ester (III-3b).

To a CH₂Cl₂ (0.1 mL, 1.0M) solution of D-*manno*-tetrol **III-3a** (20 mg, 0.02 mmol) and 2,2-dimethoxypropane (4.6 mg, 0.04 mmol) at 0 °C was added CSA (0.50 mg, 10 mol%) and the reaction was stirred for 6 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/Hexane (40:60). Pure fractions were combined and concentrated to afford **III-3b** (17 mg, 0.02 mmol, 80 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.45; $[\alpha]_D^{26} = +49$ (c 1, CH₂Cl₂); IR (thin film, cm⁻¹) 2955, 2935, 1728, 1511, 1226, 1101, 1017, 833; ¹H NMR (600 MHz, CDCl₃) δ 7.35 (m, 5H), 7.29 (m, 4H), 5.97 (d, $J = 10.2$ Hz, 1H), 5.92 (ddd, $J = 10.2, 3.0, 1.8$ Hz, 1H), 5.40 (br s, 1H), 5.04 (br s, 2H), 4.94 (dd, $J = 9.6, 7.8$ Hz, 1H), 4.79 (d, $J = 12.0$ Hz, 1H), 4.56 (d, $J = 12.0$ Hz, 1H), 4.38 (ddd, $J = 9.0, 4.2, 4.2$ Hz, 1H), 4.26 (d, $J = 6.0$ Hz, 1H), 4.21 (dd, $J = 13.2, 5.4$ Hz, 1H), 4.09 (dd, $J = 11.4, 5.4$ Hz, 1H), 4.01 (m, 1H), 3.78 (d, $J = 5.4$ Hz, 1H), 3.74 (dd, $J = 10.2, 2.4$ Hz, 1H), 3.72 (br s, 1H), 3.68 (d, $J = 6.0$ Hz, 1H), 3.67 (s, 3H), 3.61 (d, $J = 10.2$ Hz, 1H), 3.06 (dd, $J = 7.2, 6.0$ Hz, 1H), 2.95 (s, 1H), 2.88 (s, 1H), 2.26 (dd, $J = 15.0, 6.6$ Hz, 1H), 2.18 (dd, $J = 15.0, 7.2$ Hz, 1H), 1.93 (m, 3H), 1.85 (m, 3H), 1.63 (m, 3H), 1.50 (m, 3H), 0.97 (s, 6H), 0.95 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 6H), 0.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 173.2, 172.6, 154.2, 137.5, 130.3, 128.7, 128.6(2C), 128.5, 128.4(2C), 128.1, 128.0(2C), 127.8, 116.7, 110.0, 92.9(2C), 75.1, 69.9(3C), 69.5(2C), 66.6, 62.8(2C), 58.8(2C), 53.2, 50.4, 40.1, 38.1, 29.3, 28.7(2C), 28.4, 26.0(3C), 25.9(3C), 22.3(2C), 18.6, 18.3(2C), -5.0, -5.2(2C), -5.3; CIHRMS Calcd for [C₅₃H₈₃NO₁₆Si₂Na⁺ - C₃H₆²⁺]: 1028.5142. Found 1028.4585.

1'- *N*-carbobenzyloxy-*D*-tyrosine methoxycarbonyl -5',5-(hydroxy methyl)-di-1,4-*α*-*D*-mannose –*O*-4' isovaleric ester (**III-2a**).

To a THF (0.5 mL, 0.1M) solution of *D-manno*-tetrol **III-3a** (50 mg, 0.05 mmol) at 0 °C was added a solution of TBAF in THF (50 μ L, 1.0M) and the reaction was stirred for 1 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/Hexane (10:40:50). Pure fractions were combined and concentrated to afford **III-2a** (31 mg, 0.04 mmol, 80 %) as viscous oil. R_f (10:50:40% MeOH/EtOAc/Hexane) = 0.20; $[\alpha]_D^{26} = +71$ (c 0.5, CH₃OH); IR (thin film, cm⁻¹) 3337, 2956, 2926, 1738, 1611, 1510, 1228, 1217, 1094, 976, 834; ¹H NMR (600 MHz, CDCl₃) δ 7.36 (m, 5H), 7.17 (m, 4H), 5.48 (d, J = 1.8 Hz, 1H), 5.42 (d, J = 1.8 Hz, 1H), 5.09 (br s, 2H), 4.59 (br s, 1H), 4.45 (ddd, J = 7.8, 6.6, 1.8 Hz, 1H), 4.08 (dd, J = 10.2, 1.8 Hz, 1H), 4.05 (m, 3H), 4.00 (br s, 1H), 3.89 (dd, J = 9.6, 2.4 Hz, 1H), 3.80 (dd, J = 10.2, 2.4 Hz, 1H), 3.74 (m, 4H), 3.68 (m, 1H), 3.62 (m, 1H), 3.36 (m, 3H), 3.15 (ddd, J = 10.2, 4.8, 4.8 Hz, 1H), 2.93 (m, 2H), 2.29 (m, 1H), 2.13 (m, 1H), 1.34 (m, 1H), 1.03 (d, J = 6.6 Hz, 6H); NMR (150 MHz, CDCl₃) δ 172.1, 155.8, 155.3, 136.4, 130.5(2C), 129.9, 128.4(2C), 128.2(2C), 116.6, 103.2, 102.4, 98.1, 71.8, 71.3, 67.1(2C), 61.1, 55.1,

52.5(2C), 43.6, 43.1, 37.5, 36.6, 31.6, 30.5, 29.8, 28.6, 25.9, 23.1, 22.5(2C); CIHRMS Calcd for $[C_{35}H_{47}NO_{16}Na^+]$: 760.2787. Found 760.2798.

(1'S,4'S,5'R,1S,4S,5R)-1-[1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5'-(tert-butyl-dimethylsilanyloxymethyl)-tetrahydro-pyran-4'-yloxy]-5-(tert-butyl-dimethylsilanyloxymethyl) -tetrahydro-pyran-O-4'-isovaleric ester (III-2b).

The dienone ester compound **III-23** (27 mg, 0.03 mmol) and *o*-NO₂C₆H₄SO₂NHNH₂ (20 mg, 0.02 mmol) were dissolved in 0.2 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen atmosphere then triethylamine (17 mg, 0.17 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion, as monitored by TLC. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/hexanes to give **III-2b** (18 mg, 0.02 mmol, 95 %) as viscous oil. R_f (30% EtOAc/Hexane) = 0.46; $[\alpha]_D^{26} = +35$ (c 1, CH₂Cl₂); IR (thin film, cm⁻¹) 2952, 2929, 1735, 1510, 1254, 1220, 1123, 996, 836; ¹H NMR (600 MHz, CDCl₃) δ 7.34 (m, 5H), 6.98 (m, 4H), 5.45 (br s, 1H), 5.24 (d, $J = 7.8$ Hz, 1H), 5.09 (br s, 2H), 5.08 (d, $J = 2.4$ Hz, 1H), 4.73 (ddd, $J = 10.2, 9.6, 4.8$ Hz, 1H), 4.60 (ddd, $J = 7.8, 5.4, 5.4$ Hz, 1H), 3.84 (d, $J = 11.4$ Hz, 1H), 3.79-3.67 (m, 6H), 3.70 (s,

3H), 3.05 (dd, $J = 13.2, 6.0$ Hz, 1H), 3.01 (dd, $J = 13.2, 5.4$ Hz, 1H), 2.15 (m, 3H), 2.06 (m, 1H), 2.00 (m, 2H), 1.80 (m, 3H), 1.71 (m, 2H), 0.89 (d, $J = 6.6$ Hz, 6H), 0.86 (s, 9H), 0.84 (s, 9H), 0.03 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 172.0, 172.2, 156.4, 136.5, 130.2, 128.4(2C), 128.2(2C), 128.1, 128.0(2C), 116.7(2C), 94.8, 90.5, 75.1, 73.4, 71.5, 67.7, 66.8, 66.4, 63.1, 62.6, 54.6, 52.0, 43.6, 37.5, 28.6, 25.8(3C), 25.7(3C), 25.7, 23.6, 22.2(3C), 22.0, 18.4, 18.2, -5.1, -5.3, -5.40, -5.44; CIHRMS Calcd for $[\text{C}_{47}\text{H}_{75}\text{NO}_{12}\text{Si}_2\text{Na}^+]$: 924.4720. Found 924.4702.

3-{4-[6-(*tert*-Butyl-dimethylsilanyloxymethyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy]-phenyl}-2-*N*-carbobenzyloxy-D-tyrosine methyl ester (III-24a).

A CH_2Cl_2 (0.6 mL) solution of compound (*ent*)- **III-18** (200 mg, 0.55 mmol) and Cbz-D-tyrosine methyl ester **III-17** (220 mg, 0.67 mmol) was cooled to 0 °C. A CH_2Cl_2 (0.6 mL) solution of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (14 mg, 2.5 mol%) and PPh_3 (14 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was quenched with 5 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc /hexanes to give **III-24a** (278 mg, 0.50 mmol, 90%) as viscous oil. R_f (40% EtOAc /hexanes) = 0.40; $[\alpha]_{\text{D}}^{26} = (c\ 0.64, \text{CH}_2\text{Cl}_2)$; IR (thin film, cm^{-1}) 3351, 2952,

1752, 1725, 1509, 1256, 1219, 1151, 995, 836; ^1H NMR (270 MHz, CDCl_3) δ 7.35 (m, 5H), 7.05 (m, 4H), 6.97 (dd, $J = 10.2, 3.5$ Hz, 1H), 6.22 (d, $J = 10.2$ Hz, 1H), 5.94 (d, $J = 3.3$ Hz, 1H), 5.33 (dd, $J = 8.5, 4.2$ Hz, 1H), 5.09 (br s, 2H), 4.62 (dd, $J = 13.2, 5.7$ Hz, 1H), 4.53 (dd, $J = 4.1, 3.1$ Hz, 1H), 4.15-4.00 (m, 2H), 3.71 (s, 3H), 3.69 (m, 2H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 194.2, 177.7, 156.1, 155.4, 151.6, 150.0, 142.6, 136.0, 133.1, 130.2, 130.0, 128.5, 128.3, 128.0, 127.9, 121.2, 116.9, 91.8, 83.3, 66.8, 62.4, 54.7, 52.2, 37.1, 25.1(3C), 18.1, -5.46, -5.49; CIHRMS Calcd for $[\text{C}_{30}\text{H}_{39}\text{NO}_8\text{SiNa}^+]$: 592.2343. Found 592.2369.

3-{4-[6-(*tert*-Butyl-dimethylsilanyloxymethyl)-5-hydroxy-5,6-dihydro-2*H*-pyran-2-yloxy]-phenyl}-2- *N*-carbobenzyloxy-D-tyrosine methyl ester (III-24b).

The enone compound **III-24a** (300 mg, 0.527 mmol), dissolved in 0.5 mL of CH_2Cl_2 and 0.5 mL MeOH, was added to a round bottom flask and cooled to -24°C then (20 mg, 0.527 mmol) NaBH_4 was added and the reaction mixture was stirred at -24°C for 1 hour and on completion, as monitored by TLC, the reaction mixture was diluted with ether and was quenched with 5 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give **III-24b** (270 mg, 0.47 mmol, 89%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.30; $[\alpha]_{\text{D}}^{26} = -$

82 (*c* 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3357, 2928, 1722, 1611, 1439, 1225, 1054, 985, 835; ¹H NMR (600 MHz, CDCl₃) δ 7.33 (m, 5H), 6.97 (m, 4H), 6.07 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.85 (ddd, *J* = 10.2, 2.4, 2.4 Hz, 1H), 5.56 (dd, *J* = 2.4, 1.2 Hz, 1H), 5.20 (d, *J* = 7.8 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 4.61 (dd, *J* = 13.2, 5.4 Hz, 1H), 4.26 (dd, *J* = 9.0, 1.8 Hz, 1H), 3.89 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.83 (ddd, *J* = 9.0, 7.2, 4.8 Hz, 1H), 3.73 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.31 (s, 3H), 3.08 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.04 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.01 (d, *J* = 3.0 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.9, 156.6, 136.2, 133.3, 130.2, 130.2(2C), 128.5(2C), 128.1, 128.0, 124.8, 116.9(2C), 116.6, 92.8, 70.7, 66.9, 66.8, 65.3, 54.8, 52.3, 52.2, 37.3, 25.7(3C), 18.1, -5.5, -5.6; CIHRMS Calcd for [C₃₀H₄₁NO₈SiNa⁺]: 594.2493 Found 594.2500.

(1'*R*, 4'*R*, 5'*S*, 1*R*, 5*S*)-1-[1'-*N*-carbobenzyloxy-*D*-tyrosine methoxycarbonyl -5-(*tert*-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'*H*-pyran-4'-yloxy]-5-(*tert*-butyl-dimethylsilanyloxymethyl) -1*H*-pyran-4-one (III-24).

A CH₂Cl₂ (0.5 mL) solution of compound (*ent*)-**III-18** (163 mg, 0.45 mmol) and alcohol **III-24b** (260 mg, 0.45 mmol) was cooled to 0 °C. A CH₂Cl₂ (0.5 mL) solution of Pd₂(dba)₃.CHCl₃ (11.8 mg, 2.5 mol%) and PPh₃ (12 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The

reaction mixture was quenched with 5 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 16% EtOAc/hexanes to give dienone **III-24** (313 mg, 0.38 mmol, 85%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.44; $[\alpha]_D^{26} = -63$ (c 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3341, 2952, 1725, 1700, 1509, 1252, 1226, 1123, 984, 836; ¹H NMR (600 MHz, CDCl₃) δ 7.34 (m, 5H), 7.00 (m, 4H), 6.84 (dd, J = 10.2, 3.6 Hz, 1H), 6.23 (d, J = 10.2 Hz, 1H), 6.14 (d, J = 10.8 Hz, 1H), 5.95 (ddd, J = 10.2, 3.0, 1.2 Hz, 1H), 5.62 (d, J = 3.6 Hz, 1H), 5.61 (d, J = 1.8 Hz, 1H), 5.18 (d, J = 7.8 Hz, 1H), 5.10 (br s, 2H), 4.62 (dd, J = 13.8, 6.0 Hz, 1H), 4.59 (d, J = 9.0 Hz, 1H), 4.44 (dd, J = 3.6, 2.4 Hz, 1H), 4.13 (d, J = 3.6 Hz, 1H), 4.10 (dd, J = 10.2, 4.2 Hz, 1H), 3.96 (dd, J = 10.2, 2.4 Hz, 1H), 3.86 (dq, J = 12.0, 3.6 Hz, 1H), 3.80 (dd, J = 12.0, 4.2 Hz, 1H), 3.72 (s, 3H), 3.07 (dd, J = 13.8, 5.4 Hz, 1H), 3.03 (dd, J = 13.8, 6.0 Hz, 1H), 0.86 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 194.6, 171.9, 156.4, 155.6, 143.9, 136.2, 133.3, 130.2(2C), 130.1, 129.1, 128.6, 128.5(2C), 128.1, 128.0, 126.6(2C), 117.0, 92.9, 89.8, 76.7, 71.3, 66.9, 66.5, 62.9, 62.5, 54.8, 52.2, 37.3, 25.9(3C), 25.8(3C), 18.4, 18.3, -5.1, -5.3(2C), -5.4; CIHRMS Calcd for [C₄₂H₆₁NO₁₁Si₂Na⁺]: 834.3675. Found 834.3648.

(1'*R*,4'*R*,5'*S*,1*R*,4*R*,5*S*)-1-[*N*-carbobenzyloxy-*D*-tyrosine methoxycarbonyl -5'-(*tert*-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'*H*-pyran-4'-yloxy]-5-(*tert*-butyl-dimethylsilanyloxymethyl)-1,4-dihydro-5*H*-pyran-4-ol (III-25a).

The dienone compound **III-24** (300 mg, 0.37 mmol), dissolved in 0.4 mL of CH_2Cl_2 and 0.4 mL MeOH, was added to a round bottom flask and cooled to -24°C then NaBH_4 (14 mg, 0.37 mmol) was added and the reaction mixture was stirred at -24°C for 1 hour and on completion, as monitored by TLC, the reaction mixture is diluted with ether and was quenched with 5 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give **III-25a** (271 mg, 0.333 mmol, 90%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.30; $[\alpha]_{\text{D}}^{26} = -72$ (c 1, CH_2Cl_2); IR (thin film, cm^{-1}) 3433, 2928, 2857, 1724, 1509, 1253, 1226, 1123, 1044, 981, 836; ^1H NMR (600 MHz, CDCl_3) δ 7.34 (m, 5H), 7.00 (m, 4H), 6.15 (d, $J = 10.8$ Hz, 1H), 5.97 (dd, $J = 10.2$, 1.8 Hz, 1H), 5.92 (ddd, $J = 10.2$, 3.0, 1.8 Hz, 1H), 5.68 (ddd, $J = 10.2$, 2.4, 1.8 Hz, 1H), 5.59 (d, $J = 1.8$ Hz, 1H), 5.18 (br s, 2H), 5.09 (br s, 2H), 4.61 (dd, $J = 13.2$, 5.4 Hz, 1H), 4.36 (d, $J = 8.4$ Hz, 1H), 4.24 (d, $J = 8.4$ Hz, 1H), 3.97 (dd, $J = 9.6$, 4.2 Hz, 1H), 3.89 (dddd, $J = 5.4$, 3.6, 1.8, 1.8 Hz, 1H), 3.85 (dd, $J = 11.4$, 2.4 Hz, 1H), 3.80 (dd, $J = 11.4$, 5.4 Hz, 1H), 3.73 (dd, $J = 10.2$, 1.8 Hz, 1H), 3.72 (s, 3H), 3.69 (m, 1H), 3.06 (d, $J = 6.0$ Hz, 1H), 3.05 (d, $J = 5.4$ Hz, 1H), 3.02 (d, $J = 2.4$ Hz, 1H), 0.92 (s, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.9, 156.7, 155.6, 136.2, 133.1, 130.5, 130.1(2C), 130.0, 129.0, 128.4(2C), 128.1, 128.0, 126.1, 125.4, 117.2, 116.9, 92.8, 91.1, 71.4, 70.0, 66.9, 66.9,

66.7, 65.3, 62.6, 54.8, 52.2, 37.3, 25.8(3C), 25.8(3C), 18.3, 18.2, -5.0, -5.1, -5.4, -5.6;

CIHRMS Calcd for $[C_{42}H_{63}NO_{11}Si_2Na]^+$: 836.3831. Found 836.3844.

(1'*R*,4'*R*,5'*S*,1*R*,4*R*,5*S*)-1-[1'- *N*-carbobenzyloxy-*D*-tyrosine methoxycarbonyl -5'-(*tert*-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'*H*-pyran-4'-yloxy] -5-(*tert*-butyl-dimethylsilanyloxymethyl)-1,4-dihydro-5*H*-pyran-*O*-4'-isovaleric ester (III-25).

The alcohol compound **III-25a** (135 mg, 0.17 mmol), isovaleric acid (20 mg, 0.20 mmol) and DCC (41 mg, 0.20 mmol) were dissolved in 0.3 mL of CH_2Cl_2 in a round bottom flask and cooled to 0 °C then DMAP (2 mg, 0.016 mmol) was added and the reaction mixture was stirred at 0 °C for 6 hours and on completion, as monitored by TLC, the reaction mixture was diluted with ether and was quenched with 5 mL of satd. aq. $NaHCO_3$, extracted (3 x 5 mL) with Et_2O , dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% $EtOAc$ /hexanes to give **III-25** (141.5mg, 0.16 mmol, 95%) as viscous oil. R_f (30% $EtOAc$ /hexanes) = 0.60; $[\alpha]_D^{26} = -99$ (c 1, CH_2Cl_2); IR (thin film, cm^{-1})

2956, 2929, 1737, 1509, 1253, 1219, 1123, 986, 835; ^1H NMR (600 MHz, CDCl_3) δ 7.34 (m, 5H), 7.00 (m, 4H), 6.20 (d, $J = 10.2$ Hz, 1H), 5.94 (dd, $J = 2.4, 1.8$ Hz, 1H), 5.92 (dd, $J = 2.4, 1.8$ Hz, 1H), 5.76 (dd, $J = 3.0, 1.8$ Hz, 1H), 5.74 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.59 (d, $J = 1.8$ Hz, 1H), 5.41 (dd, $J = 10.2, 1.8$ Hz, 1H), 5.28 (d, $J = 1.8$ Hz, 1H), 5.17 (d, $J = 7.8$ Hz, 1H) 5.10 (br s, 2H), 4.62 (dd, $J = 13.2, 5.4$ Hz, 1H), 4.41 (d, $J = 9.0$ Hz, 1H), 3.90 (dddd, $J = 10.2, 5.4, 2.4, 2.4$ Hz, 1H), 3.85 (dd, $J = 11.4, 2.4$ Hz, 1H), 3.80 (dd, $J = 11.4, 5.4$ Hz, 1H), 3.77 (dd, $J = 6.0, 2.4$ Hz, 1H), 3.75 (m, 1H), 3.72 (s, 3H), 3.06 (dd, $J = 9.6, 4.2$ Hz, 1H), 3.04 (dd, $J = 9.6, 5.4$ Hz, 1H), 2.20 (d, $J = 1.8$ Hz, 2H), 2.10 (m, 1H), 0.96 (d, $J = 7.6$ Hz, 6H), 0.89 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.2, 171.9, 156.7, 136.2, 130.4, 130.1(2C), 129.9, 128.5(2C), 128.1(2C), 128.0, 127.3, 126.2, 117.3, 117.2(2C), 92.9, 91.0, 71.5, 69.7, 66.9, 66.4, 64.7, 62.9, 62.2, 54.8, 52.2, 43.4, 37.3, 25.94(3C), 25.92(3C), 25.7, 22.4, 22.3, 20.2, 18.45(2C), -5.1, -5.2, -5.4, -5.3; CIHRMS Calcd for $[\text{C}_{47}\text{H}_{71}\text{NO}_{12}\text{Si}_2\text{Na}^+]$: 920.4407. Found 920.4401.

1'- N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(*tert*-butyl-dimethylsilanyloxymethyl)-di-1,4- α -l-mannose-*O*-4'-isovaleric ester (III-26a):

To a CH₂Cl₂ (1.6 mL, 0.1M) solution of dienone **III-25** (148 mg, 0.16 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (0.1 mL). Crystalline OsO₄ (4.2 mg, 10 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/Hexane (10:40:50). Pure fractions were combined and concentrated to afford *manno*-tetrol **III-26a** (137 mg, 0.142 mmol, 86 %) as viscous oil. R_f (60% EtOAc/Hexane) = 0.20; $[\alpha]_D^{26} = -20$ (c 1, CH₃OH); IR (thin film, cm⁻¹) 3441, 2928, 2855, 1726, 1611, 1510, 1252, 1227, 1107, 1020, 835; ¹H NMR (600 MHz, CDCl₃) δ 7.36 (m, 5H), 7.10 (m, 4H), 5.47 (d, J = 1.8 Hz, 1H), 5.44 (d, J = 1.8 Hz, 1H), 5.20 (dd, J = 10.2, 9.6 Hz, 1H), 5.10 (br s, 2H), 4.87 (br s, 4H), 4.59 (m, 1H), 4.45 (dd, J = 9.0, 5.4 Hz, 1H), 4.08 (dd, J = 9.0, 3.0 Hz, 1H), 4.02 (dd, J = 3.0, 2.4 Hz, 1H), 4.00 (d, J = 1.8 Hz, 1H), 3.98 (dd, J = 9.0, 1.8 Hz, 1H), 3.90 (dd, J = 10.2, 9.0 Hz, 1H), 3.88 (ddd, J = 10.2, 6.6, 2.4 Hz, 1H), 3.87 (dd, J = 10.2, 9.6 Hz, 1H), 3.84 (dd, J = 4.8, 1.8 Hz, 1H), 3.83 (m, 1H), 3.75 (m, 3H), 3.74 (dd, J = 4.2, 1.8 Hz, 1H), 3.69 (ddd, J = 9.6, 6.6, 1.8 Hz, 1H), 3.13 (dd, J = 13.8, 5.4 Hz, 1H), 2.92 (dd, J = 13.8, 9.0 Hz, 1H), 2.29 (dd, J = 15.0, 7.2 Hz, 1H), 2.24 (dd, J = 15.0, 7.2 Hz, 1H), 2.13 (m, 1H), 1.03 (d, J = 7.2 Hz, 6H), 0.95 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 173.8, 171.9, 155.6, 136.2, 130.3(2C), 128.5(3C), 128.2, 128.0, 116.6(2C), 97.5, 96.9, 73.9, 71.49, 71.40, 71.0, 70.8, 70.3(2C), 68.8, 66.9, 63.0, 62.9, 54.8, 52.3, 43.4(2C), 37.4, 25.9(3C), 25.8(3C), 25.8, 22.3(2C), 22.3, 18.4, 18.3, -5.2, -5.3, -5.40, -5.46; CIHRMS Calcd for [C₄₇H₇₅NO₁₆Si₂Na⁺]: 988.4516. Found 988.4485.

1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(hydroxy methyl)-di-1,4- α -l-mannose -O-4' isovaleric ester (III-26).

To a THF (0.8 mL, 0.1M) solution of *manno*-tetrol **III-26a** (67 mg, 0.16 mmol) at 0 °C was added a solution of TBAF in THF (138 μ L, 1.0M) and the reaction was stirred for 1 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/Hexane (10:40:50). Pure fractions were combined and concentrated to afford **III-26** (40 mg, 0.054 mmol, 78 %) as viscous oil.

R_f (10:50:40% MeOH/EtOAc/Hexane) = 0.20; $[\alpha]_D^{26} = -110$ (c 0.5, CH₃OH); IR (thin film, cm⁻¹) 3337, 2956, 2926, 1738, 1611, 1510, 1228, 1217, 1094, 976, 834; ¹H NMR (600 MHz, CDCl₃) δ 7.35 (m, 5H), 7.10 (m, 4H), 5.48 (d, J = 1.8 Hz, 1H), 5.42 (d, J = 2.4 Hz, 1H), 5.12 (dd, J = 9.6, 9.6 Hz, 1H), 5.07 (br s, 2H), 4.59 (s, 1H), 4.45 (ddd, J = 12.6, 9.6, 1.2 Hz, 1H), 4.10 (dd, J = 9.0, 3.6 Hz, 1H), 4.02-4.08 (m, 4H), 4.00 (dd, J = 3.6, 1.8 Hz, 1H), 3.89 (dd, J = 9.6, 3.0 Hz, 1H), 3.83 (dd, J = 5.4, 3.0 Hz, 1H), 3.80 (dd, J = 7.2, 5.4 Hz, 1H), 3.77-3.72 (m, 1H), 3.75 (s, 3H), 3.67 (s, 1H), 3.62 (dd, J = 6.0, 3.0 Hz, 1H), 3.35 (br s, 4H), 3.14 (dd, J = 13.8, 4.2 Hz, 1H), 2.92 (dd, J = 13.8, 9.0 Hz, 1H), 2.31 (dd, J = 14.4, 7.2 Hz, 1H), 2.30 (dd, J = 7.2, 2.4 Hz, 1H), 2.27 (dd, J = 14.4, 7.2 Hz,

1H), 2.14 (m, 1H), 1.02 (d, $J = 6.6$ Hz, 6H); NMR (150 MHz, CDCl_3) δ 173.6, 172.0, 155.7, 136.1, 130.3(2C), 128.4(3C), 128.1, 127.9, 116.3(2C), 101.6, 97.9, 73.9, 71.9, 71.6(2C), 71.1, 70.6, 69.3, 66.9, 60.9, 60.6, 60.4, 54.8, 52.2, 43.3, 42.9, 37.2, 29.5, 25.6, 22.23, 22.20; CIHRMS Calcd for $[\text{C}_{35}\text{H}_{47}\text{NO}_{16}\text{Na}^+]$: 760.2787. Found 760.2750.

1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(*tert*-butyl-dimethylsilanyloxymethyl)-2,3,2',3'-bis acetonide-di-1,4- α -l-mannose-*O*-4'-isovaleric ester (III-27).

To a CH_2Cl_2 (0.1 mL, 1.0M) solution of *manno*-tetrol **III-26a** (25 mg, 0.02 mmol) and 2,2-dimethoxypropane (5.7 mg, 0.05 mmol) at 0 °C was added CSA (0.60 mg, 10 mol%) and the reaction was stirred for 6 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/Hexane (40:60). Pure fractions were combined and concentrated to afford **III-27** (22 mg, 0.02 mmol, 81 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.44; $[\alpha]_{\text{D}}^{26} = -31$ (c 1, CH_2Cl_2); IR (thin film, cm^{-1}) 2953, 2928, 1726, 1510, 1220, 1091, 1019, 833; ^1H NMR (600 MHz, CDCl_3) δ 7.31 (m, 5H), 6.96 (m, 4H), 5.51 (d, $J = 1.2$ Hz, 1H), 5.42 (d, $J =$

1.8 Hz, 1H), 5.06 (br s, 2H), 4.96 (dd, $J = 10.2, 7.8$ Hz, 2H), 4.62 (dd, $J = 13.8, 5.4$ Hz, 1H), 4.25 (dd, $J = 9.6, 3.6$ Hz, 1H), 4.16 (dd, $J = 12.6, 5.4$ Hz, 1H), 4.10 (d, $J = 5.4$ Hz, 1H), 4.00 (m, 1H), 3.91 (m, 1H), 3.89 (dd, $J = 10.2, 6.0$ Hz, 1H), 3.86 (dd, $J = 9.6, 4.8$ Hz, 1H), 3.84 (d, $J = 9.0$ Hz, 1H), 3.75 (m, 2H), 3.69 (s, 3H), 3.64 (d, $J = 5.4$ Hz, 1H), 3.02 (m, 2H), 3.03 (d, $J = 6.0$ Hz, 1H), 2.73 (s, 1H), 2.56 (s, 1H), 2.24 (dd, $J = 14.4, 7.2$ Hz, 1H), 2.20 (m, 1H), 2.16 (s, 1H), 2.12 (dd, $J = 13.2, 6.0$ Hz, 1H), 0.94 (d, $J = 6.6$ Hz, 6H), 0.87 (s, 9H), 0.81 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), -0.08 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.0, 171.9, 155.5, 155.4, 130.3(2C), 128.4(3C), 128.1(2C), 128.0, 116.8(2C), 109.9 (2C), 97.7, 95.0, 76.0, 75.8, 73.8, 71.2, 70.8, 69.8, 69.1(2C), 66.9, 63.1, 62.9, 54.8, 54.7, 52.2, 43.3(2C), 37.2, 29.6, 27.4, 26.3, 25.85(3C), 25.81(3C), 25.6, 22.3, 22.2, 18.4, 18.3, -5.3(2C), -5.47, -5.57; CIHRMS Calcd for $[\text{C}_{53}\text{H}_{83}\text{NO}_{16}\text{Si}_2\text{Na}^+ - \text{C}_3\text{H}_6^{2+}]$: 1028.5142. Found 1028.4585.

(1'*R*,4'*R*,5'*S*,1*R*,4*R*,5*S*)-1-[1'-*N*-carbobenzyloxy-*D*-tyrosine methoxycarbonyl -5'-(*tert*-butyl-dimethylsilanyloxymethyl)-tetrahydro-pyran-4'-yloxy]-5-(*tert*-butyl-dimethylsilanyloxymethyl)-tetrahydro-pyran-*O*-4'-isovaleric ester (III-28):

The diene ester **III-25** (27 mg, 0.03 mmol) and $o\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_2\text{NHNH}_2$ (91.6 mg, 0.45 mmol) were dissolved in 0.3 mL of CH_2Cl_2 in a round bottom flask and cooled to 0 °C under nitrogen atmosphere then triethylamine (60.6 mg, 0.60 mmol) was added and the

reaction mixture was stirred at 0 °C for 12 hours and on completion, as monitored by TLC. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/hexanes to give **III-28** (26.2 mg, 0.03 mmol, 97 %) as viscous oil. R_f (30% EtOAc/Hexane) = 0.46; $[\alpha]_D^{26} = -59$ (*c* 2, CH₂Cl₂); IR (thin film, cm⁻¹) 2955, 2928, 1738, 1510, 1252, 1219, 1122, 996, 835; ¹H NMR (600 MHz, CDCl₃) δ 7.33 (m, 5H), 6.97 (m, 4H), 5.44 (br s, 1H), 5.24 (d, *J* = 7.8 Hz, 1H), 5.08 (br s, 2H), 5.07 (d, *J* = 2.4 Hz, 1H), 4.73 (ddd, *J* = 10.2, 9.6, 4.8 Hz, 1H), 4.60 (ddd, *J* = 7.8, 5.4, 5.4 Hz, 1H), 3.85 (d, *J* = 11.4 Hz, 1H), 3.78-3.64 (m, 6H), 3.70 (s, 3H), 3.05 (dd, *J* = 13.2, 6.0 Hz, 1H), 3.01 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.13 (m, 3H), 2.06 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1H), 2.00 (m, 2H), 1.80 (m, 3H), 1.71 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 6H), 0.88 (s, 9H), 0.84 (s, 9H), 0.02 (s, 6H), 0.018 (s, 3H), 0.004 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 172.1, 172.0, 156.2, 136.2, 130.1(2C), 128.6, 128.4(2C), 128.1, 128.0, 116.9(2C), 94.9, 90.5, 75.0, 73.3, 71.5, 67.5, 66.9, 66.3, 63.2, 62.6, 54.8, 52.2, 43.6, 37.3, 28.7, 25.92(3C), 25.91(3C), 25.7, 23.6, 22.3(2C), 22.2(2C), 22.0, 18.4, 18.3, -5.1, -5.3, -5.43, -5.46; CIHRMS Calcd for [C₄₇H₇₅NO₁₂Si₂Na⁺]: 924.4720. Found 924.4717.

(1'S,4'S,5'R,1S,4S,5R)-1-[1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5'-(tert-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy] -5-(tert-butyl-dimethylsilanyloxymethyl)-1,4-dihydro-5H-pyran-O-4-methyl carbonate (III-31).

To a solution of allylic alcohol **III-22** (400 mg, 0.50 mmol) in dry CH_2Cl_2 (1.0 ml) at 0 °C, was added pyridine (237 mg, 3.00 mmol), DMAP (30 mg), and methyl chloroformate (283 mg, 3.00 mmol). After stirring 24 h at room temperature, water (3 ml) was added and then the mixture was extracted with EtOAc (3 x 10 ml), dried (Na_2SO_4), concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/hexane to give carbonate **III-31** (370.6 mg, 0.43 mmol, 85%) as viscous oil. R_f (30% EtOAc/hexane) = 0.65; $[\alpha]_D^{26} = +50$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 2928, 2885, 1748, 1441, 1509, 1266, 1090, 981, 865; ^1H NMR (600 MHz, CDCl_3) δ 7.34 (m, 5H), 7.00 (m, 4H), 6.18 (d, $J = 10.2$ Hz, 1H), 6.01 (d, $J = 10.2$ Hz, 1H), 5.94 (dd, $J = 2.4, 1.8$ Hz, 1H), 5.92 (ddd, $J = 10.8, 2.4, 1.8$ Hz, 1H), 5.77 (ddd, $J = 10.2, 3.0, 1.8$ Hz, 1H), 5.59 (d, $J = 1.8$ Hz, 1H), 5.31 (dd, $J = 3.0, 1.8$ Hz, 1H), 5.29 (dd, $J = 3.0, 2.4$ Hz, 1H), 5.11 (d, $J = 12.6$ Hz, 1H), 5.08 (d, $J = 12.6$ Hz, 1H), 4.61 (ddd, $J = 8.4, 6.0, 5.4$ Hz, 1H), 4.43 (d, $J = 9.6$ Hz, 1H), 3.88 (dd, $J = 5.4, 2.4$ Hz, 1H), 3.86 (dd, $J = 6.0, 2.4$ Hz, 1H), 3.84 (dd, $J = 4.8, 1.8$ Hz, 1H), 3.83 (dd, $J = 4.8, 2.4$ Hz, 1H), 3.81 (dd, $J = 4.8, 1.8$ Hz, 1H), 3.79 (s, 3H), 3.76 (s, 1H), 3.71 (s, 3H), 3.07 (ddd, $J = 8.4, 5.4, 5.4$ Hz, 1H), 3.05 (ddd, $J = 7.8, 6.0, 5.4$ Hz, 1H), 0.89 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 178.3, 171.9, 156.6, 155.6, 155.0, 136.2, 130.3, 130.1, 129.4, 129.0, 128.5 (2C), 128.1,

128.0, 127.6, 126.2, 117.2, 117.0, 109.9, 92.9, 91.0, 71.4, 69.3, 68.4, 66.9, 66.4, 62.7, 62.0, 54.9, 54.8, 52.2, 37.4, 25.93 (3C), 25.91 (3C), 18.43, 18.42, -5.0, -5.2, -5.4 (2C); CIHRMS Calcd for $[C_{44}H_{65}NO_{13}Si_2Na^+]$: 894.3892. Found 894.3890.

(1'S,4'S,5'R,1S,4S,5R)-1-[1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5'-(tert-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy]-5-(tert-butyl-dimethylsilanyloxymethyl)-4-azido-1,4-dihydro-5H-pyran (III-32).

To a mixture of carbonate **III-31** (210 mg, 0.24 mmol), allylpalladium chloride dimer (13.2 mg, 0.03 mmol) and 1,4-bis(diphenylphosphino)butane (61.6 mg, 0.13 mmol) in dry THF (0.25 ml) was added $TMSN_3$ (277 mg, 1.20 mmol) under argon atmosphere. The solution was stirred at room temperature for 3 h. Then the mixture was evaporated with a amount of silica gel under reduced pressure, purified using silica gel flash chromatography eluting with 15% EtOAc/hexane to give allylic azide **III-32** (162 mg, 0.19 mmol, 80%) as viscous oil. R_f (30% EtOAc/hexane) = 0.70; $[\alpha]_D^{26} = +65$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 2952, 2929, 2856, 2103, 1726, 1510, 1253, 1043, 993, 830; 1H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.99 (m, 4H), 6.18 (d, $J = 10.2$ Hz, 1H), 6.00 (d, $J = 10.2$ Hz, 1H), 5.94 (ddd, $J = 10.8, 2.4, 1.8$ Hz, 1H), 5.83 (ddd, $J = 10.2, 3.0, 2.4$ Hz, 1H), 5.59 (d, $J = 2.4$ Hz, 1H), 5.26 (d, $J = 1.8$ Hz, 1H), 5.11 (d, $J = 12.6$ Hz, 1H), 5.08 (d, $J = 12.6$ Hz, 1H), 4.62 (ddd, $J = 7.8, 6.0, 5.4$ Hz, 1H), 4.42 (d, $J = 9.0$ Hz, 1H),

4.14 (dd, $J = 3.8, 1.8$ Hz, 1H), 4.12 (dd, $J = 10.2, 1.8$ Hz, 1H), 3.92 (d, $J = 3.0$ Hz, 1H), 3.90 (d, $J = 3.0$ Hz, 1H), 3.88 (ddd, $J = 4.2, 3.6, 3.0$ Hz, 1H), 3.86 (d, $J = 1.8$ Hz, 1H), 3.80 (dd, $J = 4.2, 2.4$ Hz, 1H), 3.71 (s, 3H), 3.65 (ddd, $J = 9.0, 3.0, 1.8$ Hz, 1H), 3.08 (ddd, $J = 8.4, 6.0, 5.4$ Hz, 1H), 3.04 (ddd, $J = 8.4, 6.0, 5.4$ Hz, 1H), 0.91 (s, 9H), 0.85 (s, 9H), 0.099 (s, 3H), 0.094 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.9, 156.6, 155.6, 136.2, 130.3, 130.1 (2C), 129.0 (2C), 128.5 (2C), 128.1, 128.0 (2C), 126.2, 117.2 (2C), 109.9, 92.9, 90.8, 71.3, 70.5, 66.9, 66.2, 62.6, 62.4, 54.8, 53.4, 52.2, 37.3, 25.9 (6C), 18.4 (2C), -5.0, -5.2 (2C), -5.3; CIHRMS Calcd for $[\text{C}_{42}\text{H}_{62}\text{N}_4\text{O}_{10}\text{Si}_2\text{Na}^+]$: 861.3902. Found 861.3910.

(1'S,4'S,5'R,1S,4S,5R)-1-[1'-N -carbobenzyloxy-D-tyrosine methoxycarbonyl -5'-(*tert*-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy]-5-(*tert*-butyl-dimethylsilanyloxymethyl)-4-amino-1,4-dihydro-5H-pyran-(III-30).

To a solution of Azide **III-32** (140 mg, 0.16 mmol) in THF/ H_2O (9:1, v/v, 0.3 ml) was added (*n*-Bu) $_3\text{P}$ (84 mg, 0.41 mmol), the mixture was stirred at room temperature for 1 h. Then the reaction mixture was dried with a little silica gel under reduced pressure and the crude product was purified using silica gel flash chromatography eluting with MeOH/EtOAc/hexane (10:40:50) to give allylic amine **III-30** (100 mg, 0.12 mmol, 70%) as a colorless oil, $R_f = 0.50$ (10:40:50% MeOH/EtOAc/Hexane); $[\alpha]_{\text{D}}^{26} = +24$ ($c = 1$,

CH₂Cl₂); IR (thin film, cm⁻¹) 3361, 2944, 2833, 1740, 1448, 1374, 1240, 1120, 1040, 981, 847; ¹H NMR (600 MHz, CD₃OD) δ 7.27 (m, 5H), 6.99 (m, 4H), 6.21 (d, *J* = 9.6 Hz, 1H), 5.91 (d, *J* = 10.2 Hz, 1H), 5.84 (ddd, *J* = 10.2, 10.2, 8.4 Hz, 1H), 5.69 (ddd, *J* = 11.4, 10.2, 10.2 Hz, 1H), 5.59 (d, *J* = 2.4 Hz, 1H), 5.22 (br s, 1H), 5.02 (d, *J* = 12.6 Hz, 1H), 4.95 (d, *J* = 12.6 Hz, 1H), 4.36 (m, 1H), 4.27 (d, *J* = 9.0 Hz, 1H), 3.91 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.86 (m, 1H), 3.83 (dd, *J* = 6.0, 3.0 Hz, 1H), 3.80 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.75 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.65 (s, 3H), 3.50 (ddd, *J* = 9.6, 4.2, 3.6 Hz, 1H), 3.46 (ddd, *J* = 9.0, 4.8, 4.2 Hz, 1H), 3.36 (dd, *J* = 11.4, 9.6 Hz, 1H), 3.03 (ddd, *J* = 8.4, 6.0, 5.4 Hz, 1H), 2.85 (ddd, *J* = 8.4, 6.0, 5.4 Hz, 1H), 2.11 (s, 2H), 0.89 (d, *J* = 4.2 Hz, 9H), 0.79 (d, *J* = 5.4 Hz, 9H), 0.77 (d, *J* = 4.2 Hz, 6H), -0.00 (s, 3H), -0.02 (d, *J* = 2.4 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 172.3, 172.0, 156.6, 155.7, 136.2, 131.7, 130.1 (2C), 129.1 (2C), 128.4 (2C), 128.1 (2C), 126.4, 117.3 (2C), 92.9, 90.7, 71.6, 66.9, 63.6, 63.2, 54.8, 52.2, 46.1, 44.0, 37.2, 26.1, 25.9 (3C), 25.8 (3C), 22.3, 18.4, 18.3, -5.1, -5.2, -5.3, -5.4; CIHRMS Calcd for [C₄₂H₆₄N₂O₁₀Si₂H⁺]: 813.4177. Found 813.4177.

(1'*S*,4'*S*,5'*R*,1*S*,4*S*,5*R*)-1-[1'-*N*-carbobenzyloxy-*D*-tyrosine methoxycarbonyl -5'-(*tert*-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'*H*-pyran-4'-yloxy] -5-(*tert*-butyl-dimethylsilanyloxymethyl)-1,4-dihydro-5*H*-pyran-*N*-4-isovaleric amide (III-33).

The amine compound **III-30** (100 mg, 0.12 mmol), isovaleric acid (15 mg, 0.15 mmol) and DCC (30 mg, 0.14 mmol) were dissolved in 0.3 mL of CH₂Cl₂ in a round bottom flask and cooled to 0 °C then DMAP (2 mg, 0.01 mmol) was added and the reaction mixture was stirred at 0 °C for 6 hours and on completion, as monitored by TLC, the reaction mixture was diluted with ether and was quenched with 5 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give amide **III-33** (94 mg, 0.10 mmol, 85%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.70; $[\alpha]_D^{26} = +4$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 2985, 2927, 1736, 1447, 1372, 1253, 1098, 1043, 938, 846; ¹H NMR (600 MHz, CDCl₃) δ 7.33 (m, 5H), 7.00 (m, 4H), 6.20 (d, $J = 10.8$ Hz, 1H), 5.92 (ddd, $J = 10.2, 3.0, 1.8$ Hz, 1H), 5.81 (d, $J = 10.2$ Hz, 1H), 5.71 (ddd, $J = 10.2, 3.0, 2.4$ Hz, 1H), 5.56 (d, $J = 2.4$ Hz, 1H), 5.21 (m, 1H), 5.07 (br s, 2H), 4.58 (dd, $J = 10.2, 5.4$ Hz, 1H), 4.52 (d, $J = 8.4$ Hz, 1H), 4.32 (d, $J = 9.0$ Hz, 1H), 3.90 (m, 1H), 3.86 (d, $J = 11.4$ Hz, 1H), 3.82 (m, 2H), 3.76 (ddd, $J = 11.4, 5.4, 4.8$ Hz, 1H), 3.72 (dd, $J = 11.4, 3.0$ Hz, 1H), 3.69 (s, 3H), 3.66 (dd, $J = 3.0, 2.4$ Hz, 1H), 3.64 (dd, $J = 4.2, 2.4$ Hz, 1H), 3.03 (m, 2H), 2.11 (m, 1H), 2.00 (d, $J = 7.8$ Hz, 2H), 0.93 (d, $J = 6.6$ Hz, 6H), 0.87 (s, 9H), 0.80 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H), -0.02 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.9, 156.6, 155.6, 136.2, 133.1, 130.5, 130.1, 129.0, 128.4 (2C), 128.1 (2C), 128.0 (2C), 126.1, 125.4 (2C), 117.2 (2C), 92.8, 91.1, 71.4, 70.0, 66.9 (2C), 66.8, 66.7, 65.3 (2C), 62.6, 54.8, 52.2, 37.3, 27.3, 25.9 (3C), 25.8 (3C), 24.0, 18.3, 18.2, -5.0, -5.1, -5.4, -5.6; CIHRMS Calcd for [C₄₇H₇₂N₂O₁₁Si₂Na⁺]: 919.4572. Found 919.4543.

1'- N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(tert-butyl-dimethylsilanyloxymethyl)-di-1,4- α -D-mannose -N-4 isovaleric amide (III-34):

To a CH_2Cl_2 (1.3 mL) solution of diene amide **III-33** (120 mg, 0.13 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (0.1 mL). Crystalline OsO_4 (3.4 mg, 10 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/hexanes (10:40:50). Pure fractions were combined and concentrated to afford bis-*manno*-amido-tetrol **III-34** (101 mg, 0.10 mmol, 78 %) as viscous oil. R_f (90% EtOAc/MeOH) = 0.40; $[\alpha]_{\text{D}}^{26} = +12.5$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 2956, 2928, 1738, 1733, 1510, 1253, 1219, 1123, 986, 835; ^1H NMR (600 MHz, CDCl_3) δ 7.30 (m, 5H), 6.98 (m, 4H), 5.45 (d, $J = 1.2$ Hz, 1H), 5.34 (d, $J = 1.8$ Hz, 1H), 5.22 (d, $J = 1.8$ Hz, 1H), 5.01 (d, $J = 12.6$ Hz, 1H), 5.00 (d, $J = 12.6$ Hz, 1H), 4.50 (br s, 1H), 4.37 (dd, $J = 8.4, 5.4$ Hz, 1H), 4.34 (dd, $J = 9.0, 4.8$ Hz, 1H), 4.06 (dd, $J = 14.4, 7.2$ Hz, 1H), 4.02 (dd, $J = 6.6, 6.6$ Hz, 1H), 3.99 (dd, $J = 9.0, 4.2$ Hz, 1H), 3.93 (dd, $J = 6.0, 4.2$ Hz, 1H), 3.91 (m, 1H), 3.85 (d, $J = 11.4$ Hz, 1H), 3.82 (dd, $J = 6.0, 5.4$ Hz, 1H), 3.81 (dd, $J = 9.6, 5.4$ Hz, 1H), 3.73 (dd, $J = 6.6, 3.0$ Hz, 1H), 3.72 (d, $J = 3.0$ Hz, 1H), 3.70 (dd, $J = 3.0, 1.8$ Hz, 1H), 3.68 (dd, $J = 6.0, 1.8$ Hz, 1H), 3.65 (s, 3H), 3.60 (m,

1H), 3.03 (dd, $J = 9.6, 4.8$ Hz, 1H), 3.02 (dd, $J = 9.0, 4.8$ Hz, 1H), 2.86 (dd, $J = 9.0, 4.2$ Hz, 1H), 2.84 (dd, $J = 9.6, 4.2$ Hz, 1H), 2.15 (m, 1H), 2.04 (dd, $J = 5.4, 1.8$ Hz, 1H), 2.02 (dd, $J = 4.8, 1.2$ Hz, 1H), 0.87 (d, $J = 6.0$ Hz, 6H), 0.81 (s, 9H), 0.80 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 173.0, 172.9, 157.3, 155.9, 137.1, 131.1, 130.3 (2C), 128.4 (2C), 127.9, 127.6 (2C), 116.9 (2C), 101.1, 99.0, 73.7, 73.5, 72.5, 72.1, 71.3 (2C), 69.7, 69.4, 66.5, 64.1, 63.3, 56.0, 51.6, 43.5 (2C), 36.81, 30.9, 28.8, 25.8 (2C), 25.5 (3C), 21.8, 18.3, 18.2, -5.7, -5.9, -6.1, -6.3; CIHRMS Calcd for $[\text{C}_{47}\text{H}_{76}\text{N}_2\text{O}_{15}\text{Si}_2\text{Na}^+]$: 987.4682. Found 987.4680.

1'- N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(hydroxy methyl)-di-1,4- α -D-mannose –N-4 isovaleric amide (III-29).

To a THF (0.4 mL, 0.1 M) solution of D-manno-tetrol **III-34** (40 mg, 0.04 mmol) at 0 °C was added a solution of TBAF in THF (85 μL , 0.08 mmol) and the reaction was stirred for 1 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/Hexane (20:40:40). Pure fractions were combined and concentrated to afford hexol **III-29** (31 mg, 0.04 mmol, 80 %) as viscous oil. R_f (10:50:40% MeOH/EtOAc/Hexane) = 0.20; $[\alpha]_{\text{D}}^{26} = +15$ (c 0.5, CH_3OH); IR

(thin film, cm^{-1}) 3330, 2960, 2928, 1735, 1621, 1511, 1232, 1092, 983, 829; ^1H NMR (600 MHz, CDCl_3) δ 7.30 (m, 5H), 6.99 (m, 4H), 5.39 (d, $J = 1.2$ Hz, 1H), 5.33 (d, $J = 1.8$ Hz, 1H), 5.23 (d, $J = 1.8$ Hz, 1H), 5.00 (m, 2H), 4.37 (dd, $J = 5.4, 4.8$ Hz, 1H), 4.35 (dd, $J = 5.4, 4.2$ Hz, 1H), 4.16 (dd, $J = 11.4, 6.6$ Hz, 1H), 4.01 (dd, $J = 9.0, 3.6$ Hz, 1H), 3.96 (dd, $J = 9.6, 6.6$ Hz, 1H), 3.91 (dd, $J = 3.6, 1.8$ Hz, 1H), 3.80 (dd, $J = 9.6, 3.0$ Hz, 1H), 3.74 (dd, $J = 8.4, 4.8$ Hz, 1H), 3.71 (dd, $J = 8.4, 4.2$ Hz, 1H), 3.67 (d, $J = 3.0$ Hz, 1H), 3.65 (m, 3H), 3.60 (dd, $J = 9.0, 4.2$ Hz, 1H), 3.58 (dd, $J = 9.6, 4.2$ Hz, 1H), 3.53 (dd, $J = 5.4, 3.0$ Hz, 1H), 3.15 (dd, $J = 5.4, 2.4$ Hz, 1H), 3.05 (dd, $J = 9.0, 4.8$ Hz, 1H), 3.04 (dd, $J = 9.6, 4.8$ Hz, 1H), 2.84 (m, 2H), 2.22 (dd, $J = 4.8, 1.8$ Hz, 1H), 2.19 (dd, $J = 5.4, 1.8$ Hz, 1H), 2.04 (m, 1H), 0.92 (d, $J = 6.6$ Hz, 6H); NMR (150 MHz, CDCl_3) δ 174.5, 174.0, 158.4, 156.8, 138.2, 132.2, 131.4 (2C), 129.5 (2C), 129.0, 128.7 (2C), 117.8, 102.8, 103.4, 100.1, 75.7, 74.9, 74.0, 73.8, 73.6, 73.0, 72.5, 70.6, 67.6, 65.2, 62.8, 62.4, 57.1, 52.8, 44.4, 37.9, 26.8, 22.9; CIHRMS Calcd for $[\text{C}_{35}\text{H}_{48}\text{N}_2\text{O}_{15}\text{Na}^+]$: 759.2947. Found 759.2940.

1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(tert-butyl-dimethylsilanyloxymethyl)-2,3,2',3'-di acetonide-bis-1,4- α -D-mannose-N-4-isovaleric amide (III-35).

To a CH₂Cl₂ (0.1 mL, 1.0M) solution of D-*manno*-amido-tetrol III-34 (10 mg, 0.01 mmol) and 2,2-dimethoxypropane (2.4 mg, 0.02 mmol) at 0 °C was added CSA (0.23 mg, 10 mol%) and the reaction was stirred for 3 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/Hexane (50:50). Pure fractions were combined and concentrated to afford di-acetonide III-35 (9 mg, 0.01 mmol, 80 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.40; $[\alpha]_D^{26} = +65$ (*c* 1, CH₂Cl₂); IR (thin film, cm⁻¹) 2951, 2930, 1731, 1498, 1228, 1009, 831; ¹H NMR (600 MHz, CDCl₃) 7.34 (m, 5H), 6.98 (m, 4H), 5.77 (d, *J* = 10.8 Hz, 1H), 5.39 (d, *J* = 8.4 Hz, 1H), 5.20 (d, *J* = 7.8 Hz, 1H), 5.09 (br s, 2H), 4.62 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.44 (dd, *J* = 6.0, 1.2 Hz, 1H), 4.32 (d, *J* = 5.4 Hz, 1H), 4.16 (d, *J* = 5.4 Hz, 1H), 4.09 (d, *J* = 4.8 Hz, 1H), 4.08 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.95 (m, 1H), 3.72 (s, 3H), 3.69 (m, 2H), 3.69 (m, 1H), 3.62 (d, *J* = 3.6 Hz, 1H), 3.55 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.09 (dd, *J* = 13.2, 6.0 Hz, 1H), 3.03 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.16 (s, 1H), 2.15 (m, 1H), 2.12 (dd, *J* = 4.8, 1.2 Hz, 1H), 2.09 (m, 1H), 2.05 (d, *J* = 3.6 Hz, 1H), 1.65 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 6H), 0.87 (s, 9H), 0.84 (s, 9H), 0.42 (s, 3H), 0.03 (s, 6H), 0.02 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) 173.1, 171.8, 155.5, 137.5, 130.3, 128.7 (2C), 128.6 (2C), 128.5, 128.4 (2C), 128.0 (2C), 127.8, 116.7, 109.9, 97.5, 92.9 (2C), 76.1, 75.7, 71.4, 70.0, 69.9 (2C), 69.5 (2C), 69.3, 62.7 (2C), 58.8(2C), 56.4, 52.2, 43.3, 38.5, 34.5, 28.8(2C), 28.7 (2C), 27.5, 26.4, 25.9 (2C), 25.7, 18.6, 18.3, -5.1, -5.2 (2C), -5.3; CIHRMS Calcd for [C₅₃H₈₄N₂O₁₅Si₂H⁺]: 1045.5488. Found 1045.5503.

(1'S,4'S,5'R,1S,4S,5R)-1-[1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5'-(*tert*-butyl-dimethylsilanyloxymethyl)-tetrahydro-pyran-4'-yloxy]-5-(*tert*-butyl-dimethylsilanyloxymethyl) -tetrahydro-pyran-*N*-4-isovaleric amide (III-36).

The dieno-amide compound **III-33** (70 mg, 0.07 mmol) and *o*-NO₂C₆H₄SO₂NHNH₂ (170 mg, 1.17 mmol) were dissolved in 0.8 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen atmosphere then triethylamine (112 mg, 1.56 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion, as monitored by TLC. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give di-deoxy pyranoside **III-36** (68 mg, 0.07 mmol, 95 %) as viscous oil. *R_f* (30% EtOAc/Hexane) = 0.50; [α]_D²⁶ = + 37 (*c* 1, CH₂Cl₂); IR (thin film, cm⁻¹) 2932, 2927, 1725, 1509, 1220, 1055, 965, 836; ¹H NMR (600 MHz, CDCl₃) δ 7.33 (m, 5H), 6.98 (m, 4H), 5.43 (br s, 1H), 5.26 (d, *J* = 7.8 Hz, 1H), 5.07 (br s, 2H), 4.58 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.87 (dd, *J* = 9.0, 7.2 Hz, 1H), 3.73 (d, *J* = 3.0 Hz, 1H), 3.72 (m, 2H), 3.69 (m, 3H), 3.65 (dd, *J* = 6.0, 5.4 Hz, 1H), 3.63 (dd, *J* = 6.0, 4.8 Hz, 1H), 3.50 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.47 (m, 1H), 3.03 (dd, *J* = 14.4, 5.4 Hz, 1H), 3.01 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.13 (m, 1H), 2.01 (dd, *J* = 13.2, 7.8 Hz, 1H), 1.99 (dd, *J* = 13.2, 7.8 Hz, 1H), 1.95 (m, 1H), 1.85 (dd, *J* =

8.4, 4.2 Hz, 1H), 1.82 (m, 1H), 1.79 (dd, $J = 8.4, 3.6$ Hz, 1H), 1.76 (dd, $J = 7.8, 3.6$ Hz, 1H), 1.74 (dd, $J = 7.8, 4.2$ Hz, 1H), 1.68 (m, 2H), 1.06 (m, 2H), 0.88 (d, $J = 6.0$ Hz, 6H), 0.81 (s, 9H), 0.80 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H), -0.02 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.0, 156.2, 136.2, 130.0 (2C), 128.6 (2C), 128.4 (2C), 128.1 (2C), 128.0 (2C), 116.9 (2C), 94.9, 90.8, 74.0, 73.5, 72.1, 67.2, 66.9, 64.3, 63.5, 54.8, 54.7, 52.2 (2C), 47.3, 47.2, 37.3, 29.4, 28.7, 26.0 (3C), 25.9 (3C), 25.8, 22.2, 18.36, 18.33, -5.0, -5.1, -5.2, -5.3; CIHRMS Calcd for $[\text{C}_{47}\text{H}_{76}\text{N}_2\text{O}_{11}\text{Si}_2\text{Na}^+]$: 923.4885. Found 923.4886.

(1*R*,5*S*)-1-*N*-Carbobenzyloxy-L-serine methyl ester-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-1*H*-pyran-2-one (III-39a).

A CH_2Cl_2 (1 mL) solution of compound (*ent*)-**III-18** (358 mg, 1 mmol) and *N*-carbobenzyloxy-L-serine methyl ester **9h** (506 mg, 2 mmol) was cooled to 0 °C. A CH_2Cl_2 (1 mL) solution of $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (25 mg, 2.5 mol%) and PPh_3 (26 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was quenched with 5 mL of satd aq NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 14% EtOAc /hexanes to give 430 mg (0.87 mmol, 87%) of **III-39a**: R_f (40%

EtOAc/hexanes) = 0.46; $[\alpha]_D^{26} = -2$ ($c = 1.5$, CH_2Cl_2); IR (thin film, cm^{-1}) 2956, 1726, 1701, 1518, 1213, 1021, 836; ^1H NMR (270 MHz, CDCl_3) δ 7.34 (m, 5H), 6.77 (dd, $J = 10.0, 3.5$ Hz, 1H), 6.06 (d, $J = 10.2$ Hz, 1H), 5.70 (d, $J = 8.7$ Hz, 1H), 5.26 (d, $J = 3.3$ Hz, 1H), 5.12 (br s, 2H), 4.60 (ddd, $J = 8.7, 3.1, 3.1$ Hz, 1H), 4.26 (m, 2H), 4.24 (d, $J = 3.5$ Hz, 1H), 3.99 (m, 2H) 3.84 (dd, $J = 9.8, 3.1$ Hz, 1H), 3.72 (s, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 194.4, 170.2, 156, 143.1, 136, 128.6, 128.5, 128.3, 128.2, 93.1, 76.2, 68.5, 67.2, 62.6, 54.0, 52.7, 25.8 (3C), 18.3, -5.3(2C); CIHRMS Calcd for $[\text{C}_{24}\text{H}_{35}\text{NO}_8\text{Si}+\text{H}]^+$: 494.2210. Found 494.2244.

3-{4-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-hydroxy-5,6-dihydro-2*H*-pyran-2-yloxy]-phenyl}-2- N-Carbobenzyloxy-L-serine methyl ester (III-39b**).**

A CH_2Cl_2 (0.7 mL) solution of compound **III-39a** (352 mg, 0.713 mmol) and MeOH (0.7 mL) was cooled to -78°C . NaBH_4 (26 mg, 0.713 mmol) was added and the reaction mixture was stirred at -78°C for 3 hours. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of satd aq NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give 310 mg (0.685 mmol, 87%) of **III-39b**: R_f (50% EtOAc/hexanes) = 0.34; $[\alpha]_D^{26} = +1$ ($c = 0.7$, CH_2Cl_2); IR (thin film, cm^{-1}) 3437, 2953, 1725, 1517, 1213, 1076, 1009, 838; ^1H

NMR (270 MHz, CDCl₃) δ 7.36 (m, 5H), 5.90 (d, J = 10.1 Hz, 1H), 5.73 (d, J = 8.6 Hz, 1H), 5.64 (ddd, J = 10.1, 2.4, 2.4 Hz, 1H), 5.10 (br s, 2H), 4.87 (s, 1H), 4.55 (ddd, J = 6.6, 3.2, 3.2 Hz, 1H), 4.15 (ddd, J = 9.8, 3.2, 3.2 Hz, 2H), 3.86 (dd, J = 10.3, 5.2 Hz, 1H), 3.78-3.66 (m, 5H), 3.54 (dd, J = 8.9, 5.9 Hz, 1H), 3.12 (s, 1H), 0.89 (s, 9H), 0.89 (s, 6H); ¹³C NMR (67.5 MHz, CDCl₃) δ 170.4, 155.9, 136.0, 133.1, 128.4 (2C), 128.1, 128.0 (2C), 124.9, 93.8, 70.3, 67.6, 66.9, 66.1, 64.7, 54.1, 52.4, 25.7 (3C), 18.1, -5.6 (2C); CIHRMS Calcd for [C₂₄H₃₇NO₈SiNa⁺]: 518.2186 Found 518.2187.

(1'*R*, 4'*R*, 5'*S*, 1*R*, 5*S*)-1-[1'-*N*-Carbobenzyloxy-*L*-serine methyl ester -5-(*tert*-butyl-dimethyl-silanyloxymethyl)-1',4'-dihydro-5'*H*-pyran-4'-yloxy]-5-(*tert*-butyl-dimethyl-silanyloxymethyl) -1*H*-pyran-4-one (III-39).

A CH₂Cl₂ (0.3 mL) solution of compound (*ent*)-**III-18** (120 mg, 0.23 mmol) and alcohol **III-39b** (101 mg, 0.28 mmol) was cooled to 0 °C. A CH₂Cl₂ (0.3 mL) solution of Pd₂(DBA)₃·CHCl₃ (6 mg, 2.5 mol%) and PPh₃ (6.1 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched with 5 mL of satd aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give

III-39 (149 mg, 0.20 mmol, 85%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.30; $[\alpha]_D^{26} = +19$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3350, 2927, 1723, 1700, 1507, 1251, 1015, 830; ^1H NMR (600 MHz, CDCl_3) δ 7.36 (m, 5H), 6.80 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.23 (d, $J = 10.2$ Hz, 1H), 6.06 (d, $J = 10.2$ Hz, 1H), 5.76 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.62 (d, $J = 8.4$ Hz, 1H), 5.55 (d, $J = 3.0$ Hz, 1H), 5.12 (br s, 1H), 4.96 (d, $J = 7.2$ Hz, 1H), 4.56 (ddd, $J = 7.8, 3.0, 3.0$ Hz, 1H), 4.43 (dd, $J = 9.6, 1.8$ Hz, 1H), 4.40 (dd, $J = 4.2, 2.4$ Hz, 1H), 4.19 (dd, $J = 9.6, 3.6$ Hz, 1H), 4.12 (dd, $J = 13.8, 6.6$ Hz, 1H), 4.09 (dd, $J = 11.4, 4.2$ Hz, 1H), 3.95 (dd, $J = 10.8, 2.4$ Hz, 1H), 3.80 (dd, $J = 11.4, 1.8$ Hz, 1H), 3.75 (dd, $J = 11.4, 4.8$ Hz, 1H), 3.73 (s, 3H), 3.63 (dd, $J = 4.8, 1.8$ Hz, 1H), 3.62 (dd, $J = 5.4, 2.4$ Hz, 1H), 0.88 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 194.6, 170.4, 155.9, 143.9 (2C), 136.1, 129.2, 128.5 (2C), 128.5, 128.2, 128.1, 126.8, 94.0, 89.7, 70.5, 67.6, 67.0, 66.8, 62.9, 62.7, 60.3, 54.1, 52.5, 25.9 (3C), 25.8 (3C), 18.4, 18.3, -5.1, -5.3, -5.3, -5.4; CIHRMS Calcd for $[\text{C}_{36}\text{H}_{57}\text{NO}_{11}\text{Si}_2\text{Na}^+]$: 758.3362. Found 758.3378.

(1'R,4'R,5'S,1R,4R,5S)-1-[N-Carbobenzyloxy-L-serine methyl ester -5'-(tert-butyl-dimethyl-silanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy]-5-(tert-butyl-dimethyl-silanyloxymethyl)-1,4-dihydro-5H-pyran-4-ol (III-40a).

The ketone compound **III-39** (328 mg, 0.439 mmol), was dissolved in 0.4 mL of CH₂Cl₂ and 0.4 mL MeOH were added to a round bottom flask and cooled -78 °C then (16.6 mg, 0.439 mmol) NaBH₄ was added and the reaction mixture was stirred at -78°C for 6 hours and on completion monitored by TLC, reaction mixture is diluted with ether and was quenched with 5 mL of satd. aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give **III-40a** (279.6 mg, 0.37 mmol, 85%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.25; $[\alpha]_D^{26} = -5$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 3450, 2929, 1716, 1500, 1249, 1039, 829, 777; ¹H NMR (600 MHz, CDCl₃) δ 7.36 (m, 5H), 5.98 (d, $J = 10.2$ Hz, 1H), 5.95 (dd, $J = 10.2$, 1.2 Hz, 1H), 5.73 (ddd, $J = 9.6$, 3.0, 1.8 Hz, 1H), 5.65 (dd, $J = 2.4$, 1.8 Hz, 1H), 5.64 (dd, $J = 2.4$, 1.8 Hz, 1H), 5.13 (br s, 2H), 5.11 (br s, 1H), 4.91 (d, $J = 1.2$ Hz, 1H), 4.56 (ddd, $J = 7.2$, 3.0, 3.0 Hz, 1H), 4.23 (dd, $J = 9.0$, 2.4 Hz, 1H), 4.23 (dd, $J = 9.6$, 1.8 Hz, 1H), 4.20 (ddd, $J = 10.8$, 1.8, 1.8 Hz, 1H), 3.94 (dd, $J = 9.6$, 4.2 Hz, 1H), 3.87 (dd, $J = 10.2$, 1.8 Hz, 1H), 3.74 (s, 3H), 3.73 (d, $J = 1.8$ Hz, 1H), 3.71 (dd, $J = 6.0$, 2.4 Hz, 1H), 3.69 (dd, $J = 9.6$, 4.2 Hz, 1H), 3.66 (dd, $J = 7.8$, 4.2 Hz, 1H), 3.64 (d, $J = 1.8$ Hz, 1H), 3.03 (d, $J = 2.4$ Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 170.4, 156.0, 136.2, 133.0 (2C), 129.8, 128.5 (2C), 128.2, 128.1, 126.3, 125.4, 93.8, 91.0, 70.5, 69.9, 67.5, 67.1, 67.0, 66.9, 65.4, 62.9, 54.1, 52.5, 25.9 (3C), 25.8 (3C), 18.4, 18.2, -5.1, -5.2, -5.4, -5.6; CIHRMS Calcd for [C₃₆H₅₉NO₁₁Si₂Na⁺]: 760.3518. Found 760.3543.

1'-(2' N-Carbobenzyloxy-L-serine methyl ester -1'-yloxy)- -5',5-(tert-butyl-dimethyl-silanyloxymethyl)-bis-1,4- α -L-mannose (III-40b).

A CH_2Cl_2 (0.7 mL, 1mol) solution of compound of allyl alcohol **III-40a** (55 mg, 0.07 mmol) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (0.05 mL). Crystalline OsO_4 (1.0 mg, 5 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using a small amount of CH_2Cl_2 (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 100 % EtOAc to give **III-40b** (50 mg, 0.06 mmol, 86 %) as viscous oil. R_f (40:10:50 EtOAc/MeOH/Hexane) = 0.20; $[\alpha]_D^{26} = -45$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3419, 2929, 2856, 1720, 1508, 1264, 1094, 1028, 970, 836; ^1H NMR (600 MHz, CDCl_3) δ 7.33 (m, 5H), 5.82 (d, 8.4 Hz, 1H), 5.16 (s, 1H), 5.09 (br s, 2H), 4.72 (d, 1.2 Hz, 1H), 4.55 (dd, $J = 5.4, 2.4$ Hz, 1H), 4.09 (ddd, $J = 10.2, 2.4, 1.8$ Hz, 1H), 3.96 (d, $J = 2.4$ Hz, 1H), 3.84 (d, $J = 6.0$ Hz, 1H), 3.81 (dd, $J = 9.6, 4.8$ Hz, 1H), 3.79 (d, $J = 4.8$ Hz, 1H), 3.75 (br s, 1H), 3.74 (d, $J = 2.4$ Hz, 1H), 3.72 (s, 3H), 3.67 (d, $J = 6.0$ Hz, 1H), 3.64 (dd, $J = 9.0, 5.4$ Hz, 1H), 3.58 (dd, $J = 10.2, 2.4$ Hz, 1H), 3.43 (d, $J = 3.0$ Hz, 1H), 3.38 (dd, $J = 15.6, 7.2$ Hz, 1H), 3.13 (d, $J = 2.4$ Hz, 1H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 172.0, 158.4, 138.0, 129.4 (2C), 129.0, 128.8 (2C), 102.5, 100.9, 75.4, 75.3, 73.9, 72.9, 72.5, 72.2, 72.0, 68.4, 67.7, 67.6,

64.8, 64.6, 55.4, 52.9, 26.6 (3C), 26.5 (3C), 19.4, 19.2, -4.8 (2C), -4.9, -5.0; CIHRMS
Calcd for $[C_{36}H_{63}NO_{15}Si_2Na^+]$: 828.3628. Found 828.3646.

(1'R,4'R,5'S,1R,4R,5S)-1-[1'-N-Carbobenzyloxy-L-serine methyl ester -5'-(tert-butyl-dimethyl-silanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy] -5-(tert-butyl-dimethyl-silanyloxymethyl)-1,4-dihydro-5H-pyran-4-isovaleric ester (III-40).

The alcohol compound **III-40a** (278 mg, 0.371 mmol), isovaleric acid (45.2 mg, 0.445 mmol) and DCC (91.7 mg, 0.445 mmol) were dissolved in 0.7 mL of CH_2Cl_2 in a round bottom flask and cooled $0^\circ C$ then (4.5mg, 0.1 mmol) DMAP was added and the reaction mixture was stirred at $0^\circ C$ for 6 hours and on completion monitored by TLC, reaction mixture is diluted with ether and was quenched with 5 mL of satd aq $NaHCO_3$, extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% $EtOAc$ /hexanes to give **III-40** (280 mg, 0.34 mmol, 91%) as viscous oil. R_f (30% $EtOAc$ /hexanes) = 0.50; $[\alpha]_D^{26} = -76$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 2928, 1738, 1464, 1510, 1254, 1092, 1005, 836; 1H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.03 (d, $J = 10.2$ Hz, 1H), 5.92 (d, $J = 10.2$ Hz, 1H), 5.74 (dd, $J = 10.2$, 3.0 Hz, H), 5.71 (dd, $J = 10.8$, 2.4 Hz, 1H), 5.39 (dd, $J = 9.0$, 1.2 Hz, 1H), 5.21 (d, $J = 2.4$ Hz, 1H), 5.13 (br s, 2H),

4.92 (br s, 1H), 4.55 (dd, $J = 6.6, 3.0$ Hz, 1H), 4.26 (d, $J = 9.6$ Hz, 1H), 4.20 (dd, $J = 9.6, 3.6$ Hz, 1H), 3.88 (d, $J = 1.8.0$ Hz, 1H), 3.86 (dd, $J = 3.0, 1.8$ Hz, 1H), 3.84 (ddd, $J = 7.2, 2.4, 2.4$ Hz, 1H), 3.75 (d, $J = 3.0$ Hz, 1H), 3.73 (s, 3H), 3.72 (dd, $J = 10.2, 3.6$ Hz, 1H), 3.71 (dd, $J = 6.6, 3.6$ Hz, 1H), 3.68 (d, $J = 1.8$ Hz, 1H), 3.67 (dd, $J = 6.0, 3.0$ Hz, 1H), 2.21 (d, $J = 1.8$ Hz, 1H), 2.19 (d, $J = 1.8$ Hz, 1H), 2.10 (m, 1H), 0.96 (d, $J = 7.2$ Hz, 6H), 0.90 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 173.7, 172.1, 158.4, 138.1, 130.5, 130.4, 129.4 (2C), 129.0, 128.9 (2C), 128.8, 127.7, 95.3, 92.3, 72.0, 70.9, 68.4, 68.1, 67.7, 65.9, 64.4, 63.4, 55.6, 52.8, 44.2, 26.9, 26.6 (3C), 26.4 (5C), 22.7, 22.7, 19.4, 19.2, -4.8, -4.9, -5.0, -5.1; CIHRMS Calcd for $[\text{C}_{41}\text{H}_{67}\text{NO}_{12}\text{Si}_2\text{Na}^+]$: 844.4094. Found 844.4116.

1'-N-Carbobenzyloxy-L-serine methyl ester -5',5-(*tert*-butyl-dimethyl-silanyloxymethyl)-bis-1,4- α -L-mannose - isovaleric ester (III-41).

A CH_2Cl_2 (0.3 mL, 1Mol) solution of compound of allyl alcohol **III-40** (106 mg, 0.127 mmol) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (0.10 mL). Crystalline OsO_4 (1.6 mg, 5 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using a small amount of CH_2Cl_2 (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 50:30:20 (EtOAc

: Hexane : Methanol) to give **III-41** (140 mg, 0.16 mmol, 94 %) as viscous oil. R_f (60:40 EtOAc/Hexane) = 0.20; $[\alpha]_D^{26} = -46$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3448, 2954, 2928, 1725, 1517, 1463, 1252, 1210, 1097, 834; ^1H NMR (600 MHz, CDCl_3) δ 7.35 (m, 5H), 5.70 (d, $J = 9.0$ Hz, 1H), 5.28 (br s, 1H), 5.13 (br s, 2H), 4.98 (dd, $J = 9.0, 9.0$ Hz, 1H), 4.76 (d, $J = 3.0$ Hz, 1H), 4.57 (dd, $J = 5.4, 3.0$ Hz, 1H), 4.12 (ddd, $J = 10.2, 3.6, 3.6$ Hz, 1H), 3.91 (d, $J = 4.8$ Hz, 1H), 3.88 (dd, $J = 9.6, 4.8$ Hz, 1H), 3.87 (dd, $J = 9.6, 4.2$ Hz, 1H), 3.84 (d, $J = 10.2, 3.0$ Hz, 1H), 3.82 (d, $J = 6.0, 3.0$ Hz, 1H), 3.74 (s, 3H), 3.69 (d, $J = 4.2$ Hz, 1H), 3.68 (br s, 1H), 3.63 (dd, $J = 9.6, 2.4$ Hz, 1H), 3.46 (ddd, $J = 8.4, 6.0, 3.0$ Hz, 1H), 3.28 (d, $J = 3.0$ Hz, 1H), 3.15 (d, $J = 7.2$ Hz, 1H), 2.82 (d, $J = 3.0$ Hz, 1H), 2.24 (dd, $J = 14.4, 7.2$ Hz, 1H), 2.19 (dd, $J = 14.4, 7.2$ Hz, 1H), 2.11 (m, 1H), 0.96 (d, $J = 7.2$ Hz, 6H), 0.90 (s, 9H), 0.88 (s, 9H), 0.07 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 173.5, 170.4, 155.9, 136.0, 128.5 (3C), 128.2, 128.1, 98.9, 98.0, 73.6, 71.7, 71.4, 70.9, 70.8, 70.1, 70.0, 69.8, 67.1, 67.0, 63.1, 62.9, 53.9, 52.6, 43.4, 25.8 (6C), 25.7, 22.3, 22.3, 18.4, 18.3, -5.2, -5.3, -5.4, -5.5; CIHRMS Calcd for $[\text{C}_{41}\text{H}_{71}\text{NO}_{16}\text{Si}_2\text{Na}^+]$: 912.4203. Found 912.4209.

(1'R,4'R,5'S,1R,4R,5S)-1-[1'-N-Carbobenzyloxy-L-serine methyl ester -5'-(tert-butyl-dimethyl-silanyloxymethyl)-tetrahydro-pyran-4'-yloxy]-5-(tert-butyl-dimethyl-silanyloxymethyl) -tetrahydro-pyran-4-isovaleric ester (III-43).

The allyl alcohol compound **III-40** (49 mg, 0.058 mmol), *O*-NO₂ArSO₂NHNH₂ (71.6 mg, 0.353 mmol) were dissolved in 0.6 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen condition then triethylamine (47.6 mg, 0.471 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion monitored by TLC, reaction mixture is three portions. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give **III-43** (48.3 mg, 0.057 mmol, 98 %) as viscous oil. R_f (30% EtOAc/Hexane) = 0.60; $[\alpha]_D^{26} = -69$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 2953, 2928, 1734, 1508, 1462, 1251, 1205, 1122, 993, 833; ¹H NMR (600 MHz, CDCl₃) δ 7.35 (m, 5H), 5.61 (d, $J = 9.0$ Hz, 1H), 5.14 (br s, 2H), 5.00 (d, $J = 2.4$ Hz, 1H), 4.74 (d, $J = 2.4$ Hz, 1H), 4.70 (ddd, $J = 10.2, 9.6, 4.8$ Hz, 1H), 4.57 (ddd, $J = 6.6, 3.6, 3.0$ Hz, 1H), 4.13 (dd, $J = 10.2, 3.6$ Hz, 1H), 3.92 (dd, $J = 10.2, 1.8$ Hz, 1H), 3.75 (s, 3H), 3.72 (dd, $J = 10.8, 5.4$ Hz, 1H), 3.69 (d, $J = 2.4$ Hz, 1H), 3.68 (dd, $J = 4.8, 1.8$ Hz, 1H), 3.67 (d, $J = 2.4$ Hz, 1H), 3.64 (m, 1H), 3.60 (dd, $J = 10.2, 3.0$ Hz, 1H), 3.55 (ddd, $J = 10.8, 10.2, 4.2$ Hz, 1H), 3.44 (m, 1H), 2.15 (d, $J = 2.4$ Hz, 1H), 2.14 (d, $J = 1.2$ Hz, 1H), 2.12-2.04 (m, 4H), 1.79-1.42 (m, 4H), 0.95 (d, $J = 6.6$ Hz, 6H), 0.91 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 172.0, 170.0, 155.9, 136.1, 128.5 (3C), 128.2, 128.1, 95.9, 90.3, 73.1, 71.6, 67.6, 67.0, 66.4 (2C), 63.4, 62.7, 54.0, 52.3, 43.6 (3C), 28.7, 28.2, 26.0 (3C),

25.9 (3C), 25.7, 23.7, 22.4, 22.3, 22.1, 18.4, 18.3, -5.1, -5.3, -5.3, -5.4; CIHRMS Calcd for $[C_{41}H_{71}NO_{12}Si_2Na^+]$: 848.4407. Found 848.4392.

(1*R*,5*S*)-1-N-Carbobenzyloxy-L-threonine methyl ester-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-1*H*-pyran-2-one (III-45a).

A CH_2Cl_2 (1 mL) solution of compound (*ent*)-**III-18** (716 mg, 1.396 mmol) and *N*-Carbobenzyloxy-L-threonine methyl ester **III-44** (447 mg, 1.675 mmol) was cooled to 0 °C. A CH_2Cl_2 (0.4 mL) solution of $Pd_2(DBA)_3 \cdot CHCl_3$ (36 mg, 2.5 mol%) and PPh_3 (33 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was quenched with 5 mL of satd aq $NaHCO_3$, extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 16% $EtOAc$ /hexanes to give 914 mg (1.802 mmol, 90%) of **III-45a**: R_f (20% $EtOAc$ /hexanes) = 0.34; $[\alpha]_D^{26} = -45$ ($c = 1.5$, CH_2Cl_2); IR (thin film, cm^{-1}) 2953, 1727, 1702, 1514, 1215, 1022, 836; 1H NMR (270 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.72 (dd, $J = 10.3, 3.5$ Hz, 1H), 6.07 (d, $J = 10.3$ Hz, 1H), 5.47 (d, $J = 9.7$ Hz, 1H), 5.36 (d, $J = 3.6$ Hz, 1H), 5.14 (br s, 2H), 4.58 (qd, $J = 6.3, 2.4$ Hz, 1H), 4.44 (dd, $J = 9.7, 2.4$ Hz, 1H), 4.22 (dd, $J = 4.1, 2.7$ Hz, 1H), 4.04 (dd, $J = 11.0, 4.3$ Hz, 1H), 3.92 (dd, $J = 11.0, 2.5$ Hz, 1H), 3.70 (s, 3H), 1.29 (d, $J = 6.3$, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 194.2, 171.1, 156.6, 143.4, 136.0, 128.5 (2C), 128.3,

128.2, 128.1, 89.7, 76.0, 76.1, 72.1, 67.2, 62.5, 58.5, 52.5, 25.8 (3C), 18.3, 15.9, -5.3, -5.4; CIHRMS Calcd for $[C_{25}H_{37}NO_8SiNa^+]$: 530.2186. Found 530.2195.

3-{4-[6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-hydroxy-5,6-dihydro-2*H*-pyran-2-yloxy]-phenyl}-2- N-Carbobenzyloxy-L-threonine methyl ester (III-45b**).**

A CH_2Cl_2 (0.3 mL) solution of compound **III-45a** (120 mg, 0.236 mmol) and MeOH (0.3 mL) was cooled to $-78^\circ C$. $NaBH_4$ (8.5 mg, 0.236 mmol) was added and the reaction mixture was stirred at $-78^\circ C$ for 3 hours. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of satd aq $NaHCO_3$, extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give

111 mg (0.218 mmol, 91%) of **III-45b**: R_f (40% EtOAc/hexanes) = 0.32; $[\alpha]_D^{26} = +2$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3437, 2953, 1725, 1517, 1213, 1076, 1009, 838; 1H NMR (270 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.90 (d, $J = 10.2$ Hz, 1H), 5.58 (dd, $J = 10.2$, 2.3 Hz, 1H), 5.50 (d, $J = 9.7$ Hz, 1H), 5.13 (br s, 2H), 4.96 (s, 1H), 4.46 (qd, $J = 6.3$, 2.3, 1H), 4.38 (dd, $J = 9.7$, 2.3 Hz, 1H), 4.17 (d, $J = 9.3$, 1H), 3.95 (dd, $J = 9.7$, 4.5 Hz, 1H), 3.73 (s, 3H), 3.67 (m, 1H), 3.45 (ddd, $J = 12.8$, 12.8, 4.5 Hz, 1H), 3.08 (s, 1H), 1.22 (d, $J = 6.3$ Hz, 3H), 0.90 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.9, 156.6, 136.2, 132.9, 128.5 (2C), 128.1 (2C), 128.0, 125.2, 90.7, 71.3, 69.4, 67.0 (2C), 65.3, 58.8,

52.3, 25.7 (3C), 18.1, 15.9, -5.6, -5.6; CIHRMS Calcd for $[C_{25}H_{39}NO_8SiNa^+]$: 532.2343
Found 532.2356.

(1'*R*,4'*R*,5'*S*,1*R*,5*S*)-1-[1'-*N*-Carbobenzyloxy-*L*-threonine methyl ester -5-(*tert*-butyl-dimethyl-silanyloxymethyl)-1',4'-dihydro-5'*H*-pyran-4'-yloxy]-5-(*tert*-butyl-dimethyl-silanyloxymethyl) -1*H*-pyran-4-one (III-45).

A CH_2Cl_2 (0.7 mL) solution of compound (*ent*)-**III-18** (574 mg, 1.60 mmol) and alcohol **III-45b** (700 mg, 1.34 mmol) was cooled to 0 °C. A CH_2Cl_2 (0.7 mL) solution of $Pd_2(DBA)_3 \cdot CHCl_3$ (34.5 mg, 2.5 mol%) and PPh_3 (35 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched with 25 mL of satd aq $NaHCO_3$, extracted (3 x 25 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% $EtOAc$ /hexanes to give **10jα** (924 mg, 0.82 mmol, 91%) as viscous oil. R_f (30% $EtOAc$ /hexanes) = 0.50; $[\alpha]_D^{26} = +14$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3444, 2930, 2857, 1729, 1701, 1511, 1254, 1013, 835; 1H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.81 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.12 (d, $J = 10.2$ Hz, 1H), 6.07 (d, $J = 10.2$ Hz, 1H), 5.69 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.56 (d, $J = 3.6$ Hz, 1H), 5.54 (d, $J = 10.2$ Hz, 1H), 5.13 (br s, 2H), 5.01 (d, $J = 2.4$ Hz, 1H), 4.50 (dd, $J = 9.0, 1.2$ Hz, 1H), 4.44 (dddd, $J = 9.6, 6.6, 3.0, 3.0$ Hz, 1H), 4.39

(dd, $J = 6.6, 3.0$ Hz, 1H), 4.37 (d, $J = 3.0$ Hz, 1H), 4.10 (dd, $J = 11.4, 3.6$ Hz, 1H), 3.93 (dd, $J = 11.4, 2.4$ Hz, 1H), 3.78 (dd, $J = 7.8, 2.4$ Hz, 1H), 3.76 (dd, $J = 6.6, 2.4$ Hz, 1H), 3.69 (s, 3H), 3.51 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 1.23 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 194.8, 170.9, 156.6, 144.0, 136.2, 129.2, 128.6, 128.5 (2C), 128.1, 128.0 (2C), 127.0, 90.4, 89.6, 76.6, 70.8, 70.1, 67.1, 66.2, 62.9, 62.2, 58.8, 52.3, 25.9 (3C), 25.8 (3C), 18.4, 18.3, 15.7, -5.1, -5.3 (2C), -5.4; CIHRMS Calcd for $[\text{C}_{37}\text{H}_{59}\text{NO}_{11}\text{Si}_2\text{Na}^+]$: 772.3518. Found 772.3543.

(1'R,4'R,5'S,1R,4R,5S)-1-[N-Carbobenzyloxy-L-threonine methyl ester -5'-(tert-butyl-dimethyl-silanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy]-5-(tert-butyl-dimethyl-silanyloxymethyl)-1,4-dihydro-5H-pyran-4-ol (III-46a).

The ketone compound **III-45** (600 mg, 0.79 mmol), was dissolved in 0.8 mL of CH_2Cl_2 and 0.8 mL MeOH were added to a round bottom flask and cooled -78°C then (44.7 mg, 1.18 mmol) NaBH_4 was added and the reaction mixture was stirred at -78°C for 6 hours and on completion monitored by TLC, reaction mixture is diluted with ether and was quenched with 10 mL of satd. aq NaHCO_3 , extracted (3 x 10 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc /hexanes to give **III-46a**

(529 mg, 0.69 mmol, 88%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.40; $[\alpha]_D^{26} = -16$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3445, 2953, 2930, 1729, 1514, 1254, 1036, 837, 779; ^1H NMR (600 MHz, CDCl_3) δ 7.36 (m, 5H), 5.99 (dd, $J = 10.2, 2.4$ Hz, 1H), 5.95 (dd, $J = 10.2, 1.8$ Hz, 1H), 5.66 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.63 (dd, $J = 4.8, 2.4$ Hz, 1H), 5.58 (d, $J = 9.6$ Hz, 1H), 5.13 (dd, $J = 9.0, 1.8$ Hz, 1H), 5.12 (br s, 2H), 5.00 (d, $J = 2.4$ Hz, 1H), 4.45 (dddd, $J = 9.0, 3.6, 3.0, 3.0$ Hz, 1H), 4.38 (dd, $J = 10.2, 3.0$ Hz, 1H), 4.27 (dd, $J = 10.2, 1.8$ Hz, 1H), 4.23 (dd, $J = 10.8, 3.0$ Hz, 1H), 3.96 (dd, $J = 10.2, 4.2$ Hz, 1H), 3.83 (dd, $J = 6.0, 1.8$ Hz, 1H), 3.81 (d, $J = 1.8$ Hz, 1H), 3.75 (dd, $J = 10.8, 4.8$ Hz, 1H), 3.71 (s, 3H), 3.54 (ddd, $J = 9.0, 5.4, 1.8$ Hz, 1H), 3.08 (d, $J = 3.6$ Hz, 1H), 2.03 (br s, 1H), 1.25 (d, $J = 6.6$ Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.9, 156.6, 136.2, 132.9, 129.7, 128.4 (2C), 128.1, 128.0 (2C), 126.5, 125.5, 90.9, 90.0, 70.5, 70.1, 69.8, 67.0, 66.5, 65.3, 62.5, 60.3, 58.9, 52.3, 25.9 (3C), 25.8 (3C), 18.5, 18.1, 15.5, -5.1, -5.2, -5.4, -5.6; CIHRMS Calcd for $[\text{C}_{37}\text{H}_{61}\text{NO}_{11}\text{Si}_2\text{Na}^+]$: 774.3675. Found 774.3655.

1'-(2' *N*-Carbobenzyloxy-*L*-threonine methyl ester -1'-yloxy)- -5',5-(*tert*-butyl-dimethyl-silanyloxymethyl)-bis-1,4- α -*L*-mannose (III-46b).

A CH_2Cl_2 (0.8 mL, 1mol) solution of compound of allyl alcohol **III-46a** (60 mg, 0.08 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide /

water (0.05 mL). Crystalline OsO₄ (1.0 mg, 5 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using a small amount of CH₂Cl₂ (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 100 % EtOAc to give **III-46b** (54 mg, 0.07 mmol, 83 %) as viscous oil. *R_f* (40:10:50 EtOAc/MeOH/Hexane) = 0.25; $[\alpha]_D^{26} = -30$ (*c* = 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3356, 2929, 2857, 1719, 1529, 1252, 1046, 968, 838; ¹H NMR (600 MHz, CDCl₃) δ 7.36 (m, 5H), 5.68 (d, *J* = 9.6 Hz, 1H), 5.19 (d, *J* = 10.2 Hz, 1H), 5.14 (br s, 2H), 4.85 (d, *J* = 10.8 Hz, 1H), 4.44 (dd, *J* = 10.2, 2.4 Hz, 1H), 4.40 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.06 (d, *J* = 6.0 Hz, 1H), 3.97 (br s, 1H), 3.84 (d, *J* = 5.4 Hz, 1H), 3.81 (br s, 2H), 3.78 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.74 (d, *J* = 3.6 Hz, 1H), 3.71 (s, 3H), 3.69 (br s, 1H), 3.68 (br s, 1H), 3.38 (m, 3H), 3.33 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.08 (br s, 1H), 1.97 (m, 4H), 1.20 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 171.3, 156.6, 136.1, 128.5 (2C), 128.2, 128.1 (2C), 99.8, 94.6, 74.4, 71.9, 71.8, 71.4, 71.3, 70.6, 70.4, 69.8, 69.7, 67.2, 64.6, 62.8, 58.2, 52.5, 25.9 (3C), 25.8 (3C), 18.3, 18.3, 14.3, -5.2, -5.3, -5.4, -5.5; CIHRMS Calcd for [C₃₇H₆₅NO₁₅Si₂Na⁺]: 842.3784. Found 842.3751.

(1'*R*,4'*R*,5'*S*,1*R*,4*R*,5*S*)-1-[1'-*N*-Carbobenzyloxy-*L*-threonine methyl ester -5'-(*tert*-butyl-dimethyl-silanyloxymethyl)-1',4'-dihydro-5'*H*-pyran-4'-yloxy] -5-(*tert*-butyl-dimethyl-silanyloxymethyl)-1,4-dihydro-5*H*-pyran-4-isovaleric ester (III-46).

The alcohol compound **III-46a** (540 mg, 0.71 mmol), isovaleric acid (86.6 mg, 0.85 mmol) and DCC (175 mg, 0.85 mmol) were dissolved in 1.5 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C then (8.6 mg, 0.1 mmol) DMAP was added and the reaction mixture was stirred at 0 °C for 6 hours and on completion monitored by TLC, reaction mixture is diluted with ether and was quenched with 5 mL of satd aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give **III-46** (557 mg, 0.66 mmol, 93%) as viscous oil. R_f (30% EtOAc/hexanes) = 0.60; $[\alpha]_D^{26} = -54$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 3448, 2931, 1736, 1511, 1461, 1254, 1123, 1008, 836; ¹H NMR (600 MHz, CDCl₃) δ 7.36 (m, 5H), 6.04 (d, $J = 10.8$ Hz, 1H), 5.91 (d, $J = 10.2$ Hz, 1H), 5.71 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.67 (ddd, $J = 10.2, 2.4, 1.8$ Hz, 1H), 5.60 (d, $J = 10.2$ Hz, 1H), 5.42 (dd, $J = 9.6, 1.2$ Hz, 1H), 5.22 (d, $J = 2.4$ Hz, 1H), 5.12 (br s, 2H), 5.01 (d, $J = 1.8$ Hz, 1H), 4.44 (dd, $J = 6.0, 3.6$ Hz, 1H), 4.38 (dd, $J = 9.0, 3.6$ Hz, 1H), 4.34 (dd, $J = 9.0, 1.8$ Hz, 1H), 3.84 (dd, $J = 4.2, 1.8$ Hz, 1H), 3.81 (dd, $J = 11.4, 1.8$ Hz, 1H), 3.78 (d, $J = 4.8$ Hz, 1H), 3.76 (d, $J = 4.2$ Hz, 1H), 3.73 (d, $J = 7.8$ Hz, 1H), 3.71 (s, 3H), 3.58 (dddd, $J = 7.2, 5.4, 1.8, 1.8$ Hz, 1H), 2.21 (d, $J = 1.2$ Hz, 1H), 2.19 (d, $J = 1.2$ Hz, 1H), 2.11 (m, 1H), 1.20 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H),

0.03 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.5, 170.9, 156.7, 136.3, 130.0, 129.6, 128.4 (2C), 128.0 (2C), 127.4, 126.6, 90.8, 90.2, 70.7, 70.6, 70.2, 69.6, 67.0, 66.3, 64.7, 62.8, 62.1, 58.9, 52.3, 43.6, 43.4, 26.0, 25.9 (3C), 25.7 (3C), 22.4, 22.3, 18.5, 18.4, 15.6, -5.1, -5.3 (2C), -5.4; CIHRMS Calcd for $[\text{C}_{42}\text{H}_{69}\text{NO}_{12}\text{Si}_2\text{Na}^+]$: 858.4250. Found 858.4267.

1'-N-Carbobenzyloxy-L-threonine methyl ester -5',5-(*tert*-butyl-dimethyl-silanyloxymethyl)-bis-1,4- α -L-mannose - isovaleric ester (III-47).

A CH_2Cl_2 (2.5 mL, 0.5 Mol) solution of compound of diene **III-46** (430 mg, 0.51 mmol) at 0 °C was added a solution of (50% w/v) of N-methyl morpholine N-oxide / water (0.25 mL). Crystalline OsO_4 (13 mg, 10 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using a small amount of CH_2Cl_2 (3 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with 50:30:20 (EtOAc : Hexane : Methanol) to give **III-47** (394 mg, 0.43 mmol, 85 %) as viscous oil. R_f (60:40 EtOAc/Hexane) = 0.20; $[\alpha]_{\text{D}}^{26} = -63$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3443, 2931, 2857, 1730, 1517, 1462, 1100, 1031, 836; ^1H NMR (600 MHz, CDCl_3) δ 7.36 (m, 5H), 5.69 (d, $J = 10.2$ Hz, 1H), 5.18 (br s, 1H), 5.14 (br s, 2H), 4.85 (d, $J = 10.2$ Hz, 1H), 4.44 (d, $J = 10.2$, 2.4 Hz, 1H), 4.40 (dd, $J = 6.0$, 2.4 Hz, 1H), 4.06 (d, $J = 6.6$ Hz, 1H), 3.97 (s, 1H), 3.84 (d, $J = 5.6$ Hz, 1H), 3.82 (dd, $J = 10.2$ Hz, 1H), 3.81-3.73 (m, 6H), 3.74 (d, $J =$

3.6 Hz, 1H), 3.71 (s, 3H), 3.68 (d, $J = 10.2$ Hz, 1H), 3.38 (d, $J = 6.0$ Hz, 1H), 3.33 (dd, $J = 9.6, 6.0$ Hz, 1H), 3.10 (d, $J = 7.8$ Hz, 1H), 2.75 (br s, 1H), 2.23 (dd, $J = 15.0, 7.8$ Hz, 1H), 2.18 (dd, $J = 14.2, 7.2$ Hz, 1H), 2.10 (m, 1H), 1.20 (d, $J = 6.0$ Hz, 3H), 0.94 (d, $J = 7.2$ Hz, 6H), 0.91 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 173.5, 171.2, 156.6, 136.0, 128.5 (2C), 128.2, 128.1 (2C), 97.5, 94.6, 73.5, 71.6, 71.4, 71.3, 71.1, 70.9, 70.1, 69.9, 69.8, 69.3, 67.2, 62.9, 58.5, 52.4, 43.4, 25.9 (3C), 25.8 (3C), 25.7, 22.4, 22.3, 18.4, 18.3, 14.5, -5.2, -5.3, -5.4, -5.5; CIHRMS Calcd for $[\text{C}_{42}\text{H}_{73}\text{NO}_{16}\text{Si}_2\text{Na}^+]$: 926.4360. Found 926.4373.

(1'*R*,4'*R*,5'*S*,1*R*,4*R*,5*S*)-1-[1'-*N*-Carbobenzyloxy-*L*-threonine methyl ester -5'-(*tert*-butyl-dimethyl-silanyloxymethyl)-tetrahydro-pyran-4'-yloxy]-5-(*tert*-butyl-dimethyl-silanyloxymethyl) -tetrahydro-pyran-4-isovaleric ester (III-49).

The allyl alcohol compound **III-46** (85 mg, 0.10 mmol), $\text{O-NO}_2\text{ArSO}_2\text{NHNH}_2$ (305 mg, 1.50 mmol) were dissolved in 1.0 mL of CH_2Cl_2 in a round bottom flask and cooled 0°C under nitrogen condition then triethylamine (203 mg, 2.00 mmol) was added and the reaction mixture was stirred at 0°C for 12 hours and on completion monitored by TLC, reaction mixture is three portions. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give **III-49** (76 mg, 0.09 mmol, 90 %) as viscous oil. R_f (30% EtOAc/Hexane) = 0.60; $[\alpha]_{\text{D}}^{26} = -102$ ($c = 1$, CH_2Cl_2); IR

(thin film, cm^{-1}) 3450, 2955, 2857, 1735, 1510, 1461, 1253, 1124, 995, 836; ^1H NMR (600 MHz, CDCl_3) δ 7.35 (m, 5H), 5.50 (d, $J = 9.6$ Hz, 1H), 5.14 (br s, 2H), 5.00 (d, $J = 2.4$ Hz, 1H), 4.86 (d, $J = 3.0$ Hz, 1H), 4.72 (dd, $J = 10.2, 6.0, 2.4$ Hz, 1H), 4.41 (dd, $J = 8.4, 2.4$ Hz, 1H), 4.40 (dd, $J = 4.2, 2.4$ Hz, 1H), 3.84 (dd, $J = 10.8, 1.8$ Hz, 1H), 3.75 (dd, $J = 11.4, 4.8$ Hz, 1H), 3.72 (s, 3H), 3.70 (dd, $J = 10.2, 2.4$ Hz, 1H), 3.69 (dd, $J = 4.2, 1.8$ Hz, 1H), 3.57 (ddd, $J = 10.2, 1.8, 1.8$ Hz, 1H), 3.34 (m, 2H), 2.14 (dd, $J = 8.4, 3.6$ Hz, 1H), 2.13 (dd, $J = 8.4, 3.6$ Hz, 1H), 2.08 (m, 1H), 1.21 (d, $J = 6.0$ Hz, 3H), 1.75 (ddd, $J = 12.6, 4.2, 4.2$ Hz, 1H), 1.71 (dd, $J = 10.8, 2.4$ Hz, 1H), 1.69 (dd, $J = 12.6, 3.0$ Hz, 1H), 1.63 (dd, $J = 12.0, 6.0$ Hz, 1H), 1.59 (m, 2H), 1.46 (dd, $J = 10.2, 6.0$ Hz, 1H), 1.42 (dd, $J = 10.8, 6.0$ Hz, 1H), 0.90 (d, $J = 6.0$ Hz, 6H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.0, 171.1, 156.7, 136.2, 128.5 (2C), 128.2, 128.1, 91.3, 90.2, 72.9, 71.5, 68.8, 67.6, 67.1, 66.1, 63.1, 62.6, 58.8, 52.1, 43.6, 28.8, 28.4, 26.3, 26.0 (3C), 25.9 (3C), 25.7, 23.7, 22.4, 22.3, 21.9, 18.4, 18.3, 14.8, -5.1, -5.3, -5.4 (2C); CIHRMS Calcd for $[\text{C}_{42}\text{H}_{73}\text{NO}_{12}\text{Si}_2\text{Na}^+]$: 862.4563. Found 862.4522.

1'- N-Carbobenzyloxy-L-threonine methyl ester -5',5-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3,2',3'-bis acetonide-bis-1,4- α -L-mannose-isovaleric ester (III-48).

To a CH_2Cl_2 (0.1mL, 1.0M) solution of tris- α -D-*manno*-tetrol **III-46** (70 mg, 0.07 mmol) and 2,2 dimethoxy propane (9.5 mg, 0.17 mmol) at 0 °C add CSA (1.8 mg, 10 mol%) and the reaction was stirred for 6 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using a small amount of CH_2Cl_2 (2 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/Hexane (40:60). Pure fractions were combined and concentrated to afford **III-48** (66 mg, 0.06 mmol, 82 %): R_f (50% EtOAc/Hexane) = 0.50; $[\alpha]_{\text{D}}^{26} = -38$ (c 1, CH_2Cl_2); IR (thin film, cm^{-1}) 2953, 2934, 1735, 1510, 1253, 1090, 1019, 835; ^1H NMR (600 MHz, CDCl_3) δ 7.34 (m, 5H), 6.61 (d, $J = 10.2$ Hz, 1H), 5.41 (d, $J = 10.2$, 4.8 Hz, 1H), 5.10 (br s, 2H), 4.51 (dd, $J = 12.0$, 3.6 Hz, 1H), 4.38 (ddd, $J = 12.6$, 10.2, 3.6 Hz, 1H), 4.12 (dd, $J = 13.2$, 2.4 Hz, 1H), 4.09 (dd, $J = 6.6$, 2.4 Hz, 1H), 4.06 (d, $J = 10.2$, 6.0 Hz, 1H), 4.01 (d, $J = 7.2$, 6.0 Hz, 1H), 3.96 (dd, $J = 12.6$, 6.0 Hz, 1H), 3.90 (dd, $J = 10.2$, 7.8 Hz, 1H), 3.71 (dd, $J = 8.4$, 2.4 Hz, 1H), 3.67 (d, $J = 16.2$ Hz, 1H), 3.62 (m, 1H), 3.57 (s, 3H), 3.56 (d, $J = 4.2$ Hz, 1H), 3.45 (ddd, $J = 10.2$, 6.6, 3.6 Hz, 1H), 3.28 (ddd, $J = 10.2$, 3.6, 3.6 Hz, 1H), 3.23 (ddd, $J = 10.2$, 3.0, 2.4 Hz, 1H), 2.21 (dd, $J = 10.2$, 3.6 Hz, 1H), 2.21 (d, $J = 10.2$, 3.6 Hz, 1H), 2.19 (dd, $J = 10.8$, 3.6 Hz, 1H), 2.05 (m, 1H), 1.49 (d, $J = 6.0$ Hz, 3H), 1.46 (d, $J = 7.8$ Hz, 3H), 1.30 (d, $J = 5.4$ Hz, 3H), 1.26 (d, $J = 8.4$ Hz, 3H), 1.20 (d, $J = 5.4$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 6H), 0.89 (s, 9H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01

(s, 3H), -0.00 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.7, 170.8, 137.3, 128.5(2C), 128.2(2C), 128.1(2C), 114.2, 113.4, 109.5, 97.0, 92.9, 78.6, 78.3, 75.8, 70.9, 70.7, 70.0, 69.7, 69.0, 67.2 (2C), 62.3, 62.0, 58.5, 52.3, 43.5, 27.7(2C), 26.3 (2C), 25.9 (3C), 25.8 (3C), 22.3, 22.2, 18.4, 18.3, 14.5, -5.1, -5.3, -5.5 (2C); CIHRMS Calcd for $[\text{C}_{48}\text{H}_{81}\text{NO}_{16}\text{Si}_2\text{Na}^+ - \text{C}_3\text{H}_6^{2+}]$: 966.4486. Found 966.4441.

Benzyl (S)-1-(methoxycarbonyl)-2-phenylethylcarbamate (III-64).

To a solution of acid **III-58** (8.6 g, 28.7 mmol) in MeOH (56 mL) was added TMSCl (9.2 mL, 71.5 mmol) at room temperature. After stirring for 24 hr at room temperature, the reaction was quenched by addition of water. The MeOH was removed *in vacuo* and then the mixture was extracted with EtOAc (3 x 25 mL), dried (Na_2SO_4), concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexane to give ester **III-64** (8.6 g, 27.32 mmol, 95%) as viscous oil. R_f (50% EtOAc/hexane) = 0.71; $[\alpha]_{\text{D}}^{26} = +7$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3336, 2953, 2880, 1755, 1516, 1212, 1054, 1038, 744; ^1H NMR (600 MHz, CDCl_3) δ 7.34 (m, 5H), 7.27 (m, 5H), 5.22 (d, $J = 7.8$ Hz, 1H), 5.11 (d, $J = 12.6$ Hz, 1H), 5.09 (d, $J = 12.6$ Hz, 1H), 4.66 (dd, $J = 12.0, 6.6$ Hz, 1H), 3.72 (s, 3H), 3.15 (dd, $J = 13.8, 5.4$ Hz, 1H), 3.09 (dd, $J = 13.8, 5.4$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.9, 155.5, 136.2, 135.6, 129.2 (2C), 128.5 (2C), 128.4 (2C), 128.1 (2C), 128.0, 127.1, 66.9, 54.7, 52.2, 38.2.; CIHRMS Calcd for $[\text{C}_{18}\text{H}_{19}\text{NO}_4\text{H}^+]$: 314.1392. Found 314.1386.

(S)-methyl 2-amino-3-phenylpropanoate (III-65).

To a solution of ester **III-64** (3.8 g, 12.1 mmol) in dry MeOH (24 mL) was added Pd/C (129 mg) and the mixture was stirred under H₂ at a 100-psi pressure for 12 h at room temperature. The catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure. The resulting crude product was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/hexanes (40:60). Pure fractions were combined and concentrated to afford amine **III-65** (5.14 mg, 28.9 mmol, 97 %) as viscous oil. R_f (50% EtOAc/hexane) = 0.30; $[\alpha]_D^{26} = +17$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 3345, 3028, 1745, 1662, 1496, 1204, 1016, 700; ¹H NMR (600 MHz, CDCl₃) δ 7.31 (m, 5H), 3.73 (dd, $J = 7.8, 5.4$ Hz, 1H), 3.70 (s, 3H), 3.07 (dd, $J = 13.2, 5.4$ Hz, 1H), 2.86 (dd, $J = 13.8, 7.8$ Hz, 1H), 1.45 (s, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 175.3, 137.2, 129.2 (2C), 128.5 (2C), 126.7, 55.8, 51.8, 41.0; CIHRMS Calcd for [C₁₀H₁₃NO₂H⁺]: 180.1024. Found 180.1019.

(S)-benzyl (methoxycarbonyl)-methyl-2-amino-3-phenylpropanoate (III-66).

To a solution of amine **III-65** (1.28 g, 7.15 mmol), Cbz-glycin acid **III-57** (1.65 g, 7.86 mmol) in CH₃CN (15 ml) was added HBTU (2.98 g, 7.86 mmol) at 0 °C, and after 5 min, triethylamine (2.0 mL, 15.3 mmol) was added and stirring was continued for 8 h at rt. The mixture was taken up in EtOAc (50 mL) and washed with 5% aqueous KHSO₄ solution, 5% aqueous NaHCO₃ solution, and saturated aqueous NaCl solution. Then the reaction mixture was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with MeOH/EtOAc/hexane (2:48:50) to give dipeptide **III-66** (2.3 g, 6.10 mmol, 85%) as a colorless oil, $R_f = 0.41$ (50% EtOAc/Hexane); $[\alpha]_D^{26} = +49$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 3311, 2953, 1718, 1664, 1516, 1213, 1047, 732; ¹H NMR (600 MHz, CD₃OD) δ 7.36 (m, 5H), 7.25-7.06 (m, 5H), 6.38 (br s, 1H), 5.33 (br s, 1H), 5.12 (br s, 2H), 4.88 (dd, $J = 13.2, 5.4$ Hz, 1H), 3.88 (dd, $J = 10.2, 5.4$ Hz, 1H), 3.81 (dd, $J = 10.2, 5.4$ Hz, 1H), 3.71 (s, 3H), 3.12 (d, $J = 5.4$ Hz, 1H), 3.10 (d, $J = 5.4$ Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 171.6, 168.5, 136.1, 135.5, 129.2, 128.6 (2C), 128.5 (2C), 128.2 (2C), 128.0 (2C), 127.1 (2C), 67.1, 53.0, 52.3, 44.3, 37.8; CIHRMS Calcd for [C₂₀H₂₂N₂O₅H⁺]: 371.1607. Found 371.1601.

(1'S,4'S,5'R,1S,4S,5R)-1-[1'- N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5'- (III-67).

To a solution of methyl ester **III-66** (3.7 g, 9.60 mmol) in CH₃OH (18 mL) was added LiOH (0.46 g, 19.26 mmol) at 0 °C, and the reaction mixture was stirred at rt for 2 hours and on completion, as monitored by TLC, the reaction mixture was diluted with ether and was quenched with 5 mL of satd. aq. NaHCO₃, extracted (3 x 25 mL) with AcOEt. The combined aqueous phases were taken to pH 3 by addition of 2M aqueous KHSO₄ and extracted with AcOEt (3 x 25 mL). The combined organic phases were washed with saturated aqueous NaCl solution (3 x 10 mL), dried, and dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 100% EtOAc to give acid **III-67** (2.84 g, 7.68 mmol, 80%) as viscous oil. R_f (10:40:50% MeOH/EtOAc/hexanes) = 0.20; $[\alpha]_D^{26} = +24$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 3312, 2982, 2935, 1737, 1655, 1556, 1259, 1048, 940, 743; ¹H NMR (600 MHz, CDCl₃) δ 7.30 (m, 5H), 7.16 (m, 5H), 5.05 (br s, 2H), 5.64 (dd, $J = 7.8, 5.4$ Hz, 1H), 3.74 (d, $J = 17.4$ Hz, 1H), 3.70 (d, $J = 17.4$ Hz, 1H), 3.14 (dd, $J = 14.4, 4.8$ Hz, 1H), 2.96 (dd, $J = 13.8, 8.4$ Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) 173.1, 170.6, 157.7, 136.9, 129.1 (2C), 128.27 (2C), 128.29, 127.8 (2C), 127.6 (2C), 126.4, 66.6, 53.7, 53.6, 43.5, 37.1; CIHRMS Calcd for [C₁₉H₂₀N₂O₅H⁺]: 357.1444. Found 357.1450.

Benzyl (S)-1-(methoxycarbonyl)-2-(4-tert-butyl-dimethylsilanyloxy phenyl) ethylcarbamate (III-53).

D-tyrosine **III-68** was first protected as its methyl ester. Thionyl chloride (2.3 mL) was added drop wise to dry methanol (30 mL) at -15 °C, following by addition of D - tyrosine (2.8 g, 16.2 mmol). The resulting mixture was warmed to room temperature for 15 hrs. The solvent was removed under reduced pressure, and the residue was further dried under high vacuum to provide the methyl ester as a white solid. The above methyl ester and Na₂CO₃ (2.2 g, 15.7 mmol) was dissolved in 1:1 mixture 60 mL of acetone/H₂O. Benzyl chloroformate (CbzCl) (4.7 mL, 34.7 mmol) was added drop wise. After 2 hrs at room temperature, the reaction solution was diluted with EtOAc (250 mL). The layers were separated, and the organic layer was washed with H₂O, brine, dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 3:1 to 1:1 hexane/EtOAc) to give N-Cbz protected tyrosine methyl ester **III-68a** (5.0 g, 95%). Phenol **III-68a** (2.47 g, 7.50 mmol), 15 mL of CH₂Cl₂, and 4.2 mL of Et₃N were added to a round bottom flask and cooled to 0 °C. A catalytic amount (92 mg, 0.75 mmol) of DMAP was added followed by addition of *tert*-butyldimethylsilyl chloride (1.35 g, 9.00 mmol) and the solution was stirred at 0 °C for 6 h. The reaction was quenched with 1 M NaHSO₄ and extracted (3 x 50 mL) with Et₂O, washed with satd aq NaHCO₃ (2 x 50 mL), and dried (Na₂SO₄). The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/Hexane (15:85). Pure fractions were combined and concentrated to afford protected tyrosine **III-53** (2.89 g, 6.52 mmol, 87 %) as viscous oil. *R_f* (50%

EtOAc/Hexane) = 0.80; $[\alpha]_D^{26} = -75$ (c 1, CH_2Cl_2); IR (thin film, cm^{-1}) 3337, 2954, 2930, 1720, 1508, 1438, 1225, 1055, 837; ^1H NMR (600 MHz, CDCl_3) δ 7.34 (m, 5H), 6.95 (d, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 8.4$ Hz, 2H), 5.21 (br s, 1H), 5.12 (d, $J = 12.0$ Hz, 1H), 5.09 (d, $J = 12.0$ Hz, 1H), 4.62 (dd, $J = 13.2, 6.0$ Hz, 1H), 3.69 (s, 3H), 3.04 (m, 2H), 1.63 (m, 1H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.2, 155.8, 155.0, 136.5, 130.4 (2C), 128.7 (2C), 128.4, 128.3 (2C), 128.2 (2C), 120.3, 67.1, 55.1, 52.4, 37.7, 25.8 (3C), 18.3, -4.1, -4.2; CIHRMS Calcd for $[\text{C}_{24}\text{H}_{33}\text{NO}_5\text{H}^+]$: 444.2206. Found 444.2201.

(S)-methyl 2-amino-3-(4-tert-butyl-dimethylsilanyloxyphenyl)propanoate (III-69).

To a solution of Cbz-ester **III-53** (3.3 g, 7.45 mmol) in dry MeOH (15 mL) was added Pd/C (79 mg) and the mixture was stirred under H_2 at a 100-psi pressure for 12 h at room temperature. The catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure. The resulting crude product was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/hexanes (40:60). Pure fractions were combined and concentrated to afford amine **III-69** (2.50 g, 6.63 mmol, 89 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.33; $[\alpha]_D^{26} = +8$ (c 1, CH_2Cl_2); IR (thin film, cm^{-1}) 3365, 2953, 2930, 1738, 1509, 1211, 1217, 1015, 914, 839; ^1H NMR (600 MHz, CDCl_3) δ 7.95 (s, 1H), 7.01 (d, $J = 8.4$ Hz, 2H), 7.75 (d, $J = 8.4$ Hz, 2H), 3.68 (s, 3H), 3.66 (m, 2H), 2.97

(dd, $J = 13.8, 5.4$ Hz, 1H), 2.78 (dd, $J = 13.2, 7.8$ Hz, 1H), 0.95 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 175.4, 154.5, 130.3, 130.1 (2C), 120.1 (2C), 115.5, 55.8, 51.8, 40.3, 25.6 (3C), 18.1, -4.4; CIHRMS Calcd for $[\text{C}_{16}\text{H}_{27}\text{NO}_3\text{H}^+]$: 310.1838. Found 310.1833.

1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(tert-butyl-dimethylsilanyloxymethyl)-di-1,4- α -D-mannose -N-4 isovaleric amide (III-52a).

To a solution of amine **III-69** (83.5 mg, 0.27 mmol), acid **III-67** (100 mg, 0.27 mmol) in CH_3CN (0.5 mL) was added HBTU (112.5 mg, 0.29 mmol) at 0 °C, and after 5 min, triethylamine (76 μL , 0.54 mmol) was added and stirring was continued for 5 h at rt. The mixture was taken up in EtOAc (10 mL) and washed with 5% aqueous KHSO_4 solution, 5% aqueous NaHCO_3 solution, and saturated aqueous NaCl solution. Then the reaction mixture was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with EtOAc/hexane (60:40) to give tripeptide **III-52a** (140 mg, 0.22 mmol, 80%) as a colorless oil, $R_f = 0.60$ (100% EtOAc); $[\alpha]_{\text{D}}^{26} = +35$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3275, 2954, 1739, 1696, 1508, 1241, 1218, 915, 838; ^1H NMR (600 MHz, CDCl_3) δ 7.33 (m, 5H), 7.23 (m, 4H), 7.10 (d, $J = 7.2$ Hz, 2H), 6.76 (d, $J = 7.2$ Hz, 2H), 6.69 (m, 3H), 6.50 (br s, 1H), 5.45 (br s, 1H), 5.08 (br s, 2H), 4.70 (m, 2H), 3.80 (d, $J = 5.4$ Hz, 1H), 3.79 (d, $J = 5.4$ Hz, 1H),

3.59 (s, 3H), 2.98 (m, 1H), 2.88 (dd, $J = 13.8, 6.6$ Hz, 1H), 2.79 (dd, $J = 13.8, 6.0$ Hz, 1H), 0.94 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.6, 170.1, 168.8, 156.5, 154.78, 154.73, 136.2, 136.0, 130.1 (2C), 129.3 (2C), 128.6 (2C), 128.5 (2C), 128.2 (2C), 128.1 (2C), 127.0, 120.1, 67.2, 54.2, 53.3, 52.2, 44.4, 38.3, 37.0, 25.6 (3C), 18.1, -4.4 (2C); CIHRMS Calcd for $[\text{C}_{35}\text{H}_{45}\text{N}_3\text{O}_7\text{SiH}^+]$: 648.3105. Found 648.3102.

1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(hydroxy methyl)-di-1,4- - D-mannose –N-4 isovaleric amide (III-70).

To a solution of tyrosine ester **III-3b** (600 mg, 0.62 mmol) in dry MeOH (3.0 mL) was added Pd/C (6.5 mg) and the mixture was stirred under H_2 at a 100-psi pressure for 6 h at room temperature and checked against the completion of the reaction with TLC analysis. The catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure as amine **III-70**, $R_f = 0.35$ (70% EtOAc). To a solution of crude amine **III-70** (100 mg, 0.11 mmol), acid **III-67** (58.6 mg, 0.17 mmol) in CH_3CN (0.2 mL) was added HBTU (45.7 mg, 0.12 mmol) at 0 °C, and after 5 min, $i\text{Pr}_2\text{NEt}$ (31 μL , 0.22 mmol) was added and stirring was continued for 4 h at rt. The mixture was taken up in EtOAc (10 mL) and washed with 5% aqueous KHSO_4 solution, 5% aqueous NaHCO_3 solution, and saturated aqueous NaCl solution. Then the reaction mixture was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel

flash chromatography eluting with EtOAc/hexane (40:60) to give tripeptide **III-52b** (96 mg, 0.07 mmol, 70%) as a colorless oil, $R_f = 0.47$ (70% EtOAc); $[\alpha]_D^{26} = +35$ ($c = 1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3296, 2930, 2857, 1741, 1649, 1510, 1372, 1225, 1140, 986, 835; ^1H NMR (600 MHz, CDCl_3) δ 7.35 (m, 5H), 7.22 (m, 5H), 7.13 (m, 1H), 6.91 (m, 1H), 6.63 (d, $J = 7.2$ Hz, 1H), 6.29 (m, 1H), 5.75 (s, 1H), 5.69 (s, 1H), 5.48 (br s, 1H), 5.10 (m, 2H), 4.97 (dd, $J = 10.2, 7.2$ Hz, 1H), 4.70 (dd, $J = 13.2, 7.8$ Hz, 1H), 4.60 (d, $J = 7.8$ Hz, 1H), 4.40 (dd, $J = 6.6, 6.0$ Hz, 1H), 4.30 (d, $J = 5.4$ Hz, 1H), 4.13 (m, 2H), 4.01 (dd, $J = 10.2, 7.2$ Hz, 1H), 3.83 (d, $J = 6.0$ Hz, 1H), 3.76 (s, 3H), 3.66 (br s, 1H), 3.65 (d, $J = 1.2$ Hz, 1H), 3.65 (br s, 1H), 3.62 (m, 3H), 3.05 (dd, $J = 13.8, 5.4$ Hz, 1H), 2.98 (m, 2H), 2.64 (m, 1H), 2.25 (dd, $J = 15.0, 6.6$ Hz, 1H), 2.16 (dd, $J = 14.4, 7.8$ Hz, 1H), 2.09 (m, 1H), 1.16 (s, 3H), 1.54 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.24 (m, 1H), 0.95 (d, $J = 1.8$ Hz, 3H), 0.94 (d, $J = 1.8$ Hz, 3H), 0.86 (s, 18H), 0.04 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.8, 171.2, 169.9, 169.0, 154.6, 136.2, 130.3 (2C), 129.8, 129.1, 129.2 (2C), 128.69, 128.65 (2C), 128.5 (2C), 128.2 (2C), 128.1 (2C), 127.0, 116.8, 110.0, 109.7, 95.6, 95.4, 78.7, 76.0, 75.87, 75.80, 71.1, 70.0, 69.4, 69.3, 67.2, 62.8, 61.4, 54.1, 53.3, 52.3, 44.4, 43.3, 37.6, 37.0, 37.1, 29.6, 27.8, 27.5, 26.4, 26.3, 25.9 (3C), 25.7 (3C), 27.3, 18.5 (2C), -5.3 (4C); CIHRMS Calcd for $[\text{C}_{64}\text{H}_{95}\text{N}_3\text{O}_{18}\text{Si}_2\text{Na}^+]$: 1272.6227. Found 1272.6400.

Benzyl (*R*)-1-(methoxycarbonyl)-2-(4-*tert*-butyl-dimethylsilanyloxy) ethylcarbamate (III-60).

Alcohol **III-59** (5.0 g, 19.76 mmol), 40 mL of CH_2Cl_2 , and 7.9 mL of Et_3N were added to a round bottom flask and cooled to 0 °C. A catalytic amount (241 mg, 1.97 mmol) of DMAP was added followed by addition of *tert*-butyldimethylsilyl chloride (3.57 g, 23.71 mmol) and the solution was stirred at 0 °C for 10 h. The reaction was quenched with 1 M NaHSO_4 and extracted (3 x 50 mL) with Et_2O , washed with satd aq NaHCO_3 (2 x 50 mL), and dried (Na_2SO_4). The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/Hexane (15:85). Pure fractions were combined and concentrated to afford protected tyrosine **III-60** (6.1 g, 16.9 mmol, 90 %) as viscous oil. R_f (40% EtOAc/Hexane) = 0.75; $[\alpha]_{\text{D}}^{26} = -43$ (c 1, CH_2Cl_2); IR (thin film, cm^{-1}) 3443, 2953, 2857, 1721, 1504, 1203, 1063, 870, 775; ^1H NMR (600 MHz, CDCl_3) δ 7.35 (m, 5H), 5.57 (d, $J = 8.4$ Hz, 1H), 5.14 (d, $J = 12.0$ Hz, 1H), 5.10 (d, $J = 12.0$ Hz, 1H), 4.41 (d, $J = 8.4$ Hz, 1H), 4.04 (dd, $J = 10.2, 1.8$ Hz, 1H), 3.83 (dd, $J = 10.2, 2.4$ Hz, 1H), 3.73 (s, 3H), 0.83 (s, 9H), 0.002 (s, 3H), -0.006 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.8, 155.9, 136.2, 128.4 (2C), 128.1 (2C), 128.0, 69.9, 63.6, 55.9, 52.3, 25.6 (3C), 18.1, -5.5, -5.7; CIHRMS Calcd for $[\text{C}_{18}\text{H}_{29}\text{NO}_5\text{SiH}^+]$: 368.1893. Found 368.1884.

Benzyl (R)-1-((R)-1,2-di-*tert*-butoxyethylcarbamoyl)-2-(4-*tert*-butyl-dimethylsilanyloxy) ethylcarbamate (III-61).

To a solution of amine **III-56** (1.68 g, 7.71 mmol), acid **III-55** (2.88 g, 8.84 mmol) in CH₃CN (15 ml) was added HBTU (3.20 g, 8.84 mmol) at 0 °C, and after 5 min, triethylamine (2.1 mL, 15.4 mmol) was added and stirring was continued for 12 h at rt. The mixture was taken up in EtOAc (50 mL) and washed with 5% aqueous KHSO₄ solution, 5% aqueous NaHCO₃ solution, and saturated aqueous NaCl solution. Then the reaction mixture was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with EtOAc/hexane (20:80) to give dipeptide **III-61** (3.45 g, 6.39 mmol, 83%) as a colorless oil, R_f = 0.65 (50% EtOAc/Hexane); $[\alpha]_D^{26} = +6$ ($c = 4$, CH₂Cl₂); IR (thin film, cm⁻¹) 3348, 2930, 2857, 1732, 1670, 1497, 1249, 1099, 875, 732; ¹H NMR (600 MHz, CD₃OD) δ 7.33 (m, 5H), 7.15 (d, $J = 7.8$ Hz, 1H), 5.69 (br s, 1H), 5.10 (br s, 2H), 4.58 (ddd, $J = 5.4, 3.0, 3.0$ Hz, 1H), 4.24 (br s, 1H), 4.04 (d, $J = 6.6$ Hz, 1H), 3.75 (dd, $J = 8.4, 3.0$ Hz, 1H), 3.69 (dd, $J = 10.2, 6.0$ Hz, 1H), 3.48 (m, 1H), 1.43 (s, 9H), 1.10 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 169.6, 169.4, 168.8, 136.0, 128.3 (2C), 128.0, 127.9 (2C), 81.5, 72.8, 66.8, 63.1, 62.0, 56.1, 53.2, 27.8 (3C), 27.1 (3C), 25.7 (3C), 18.1, -5.5, -5.6; CIHRMS Calcd for [C₂₈H₄₈N₂O₇H⁺]: 553.3309. Found 555.3305.

(2R)-N-((R)-1,2-di-tert-butoxyethyl)-2-amino-3-(4-tert-butyl-dimethylsilanyloxy)propanamide (III-62).

To a solution of Cbz-ester **III-61** (1.89 g, 3.50 mmol) in dry MeOH (7.0 mL) was added Pd/C (37 mg) and the mixture was stirred under H₂ at a 100-psi pressure for 8 h at room temperature. The catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure. The resulting crude product was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/hexanes (50:50). Pure fractions were combined and concentrated to afford amine **III-62** (1.27 g, 3.15 mmol, 90 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.21; $[\alpha]_D^{26} = +7$ (c 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3392, 2971, 2930, 1729, 1672, 1509, 1365, 1230, 837; ¹H NMR (600 MHz, CDCl₃) δ 7.93 (d, J = 8.4 Hz, 1H), 4.45 (ddd, J = 8.4, 3.6, 3.0 Hz, 1H), 3.86 (dd, J = 9.6, 4.8 Hz, 1H), 3.77 (dd, J = 9.0, 3.0 Hz, 1H), 3.71 (dd, J = 9.6, 7.2 Hz, 1H), 3.51 (dd, J = 8.4, 3.6 Hz, 1H), 3.46 (dd, J = 6.6, 4.8 Hz, 1H), 1.65 (br s, 2H), 1.44 (s, 9H), 1.33 (s, 9H), 0.87 (s, 9H), 0.59 (s, 3H), 0.53 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 172.5, 169.3, 81.5, 72.9, 65.3, 62.3, 56.9, 52.9, 27.9 (3C), 27.3 (3C), 25.8 (3C), 18.2, -5.40, -5.44; CIHRMS Calcd for [C₂₀H₄₂NO₅SiH⁺]: 419.2941. Found 419.2936.

(2R)-N-((R)-1,2-di-tert-butoxyethyl)-2-amido-3-(4-tert-butyl-dimethylsilanyloxy)5-amino-fluorenylmethoxycarbonyl-6-(benzyloxy)hexamide (III-63).

To a solution of dipeptide amine **III-62** (860 mg, 2.13 mmol), acid **III-54** (976 mg, 2.34 mmol) in CH₃CN (4.5 mL) was added HBTU (887 mg, 2.34 mmol) at 0 °C, and after 5 min, triethylamine (0.6 mL, 15.3 mmol) was added and stirring was continued for 4 h at rt. The mixture was taken up in EtOAc (50 mL) and washed with 5% aqueous KHSO₄ solution, 5% aqueous NaHCO₃ solution, and saturated aqueous NaCl solution. Then the reaction mixture was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with EtOAc/hexane (35:65) to give tripeptide **III-63** (1.48 g, 1.81 mmol, 85%) as a colorless oil, *R_f* = 0.65 (50% EtOAc/Hexane); $[\alpha]_D^{26} = +8$ (*c* = 3, CH₂Cl₂); IR (thin film, cm⁻¹) 3296, 2954, 2929, 1731, 1645, 1520, 1249, 1152, 1102, 838, 737; ¹H NMR (600 MHz, CD₃OD) δ 7.67 (m, 2H), 7.58 (m, 2H), 7.39 (m, 4H), 7.33 (m, 5H), 7.19 (d, *J* = 8.4 Hz, 1H), 5.71 (br s, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 4.61 (m, 2H), 4.51 (br s, 1H), 4.90 (dd, *J* = 10.2, 4.8 Hz, 1H), 4.41 (d, *J* = 7.8 Hz, 1H), 4.39 (d, *J* = 7.8 Hz, 1H), 4.36 (d, *J* = 7.2 Hz, 1H), 4.21 (dd, *J* = 7.2, 6.6 Hz, 1H), 4.06 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.90 (br s, 1H), 3.77 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.62 (m, 2H), 3.52 (d, *J* = 8.4, 3.6 Hz, 1H), 1.45 (s, 9H), 1.12 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 169.7, 169.3, 168.9, 143.8, 143.6 (2C), 141.25, 141.23 (2C), 137.3, 128.4 (2C), 127.9 (2C), 127.8 (2C), 128.6 (2C), 127.0, 125.1, 119.9 (2C), 81.7, 73.3, 70.0, 69.3, 67.3, 62.9, 62.1, 54.6, 53.4, 47.0,

27.9 (3C), 27.2 (3C), 25.86, 25.81 (3C), 18.1, -5.4, -5.5; CIHRMS Calcd for $[C_{45}H_{63}N_3O_9SiH^+]$: 818.4399. Found 818.4419.

(1'S,4'S,5'R,1S,4S,5R)-1-[1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5'-(tert-dimethylsilanyloxymethyl) -tetrahydro-pyran-N-4-isovaleric amide (IV-7).

The enone compound **IV-2** (100 mg, 0.34 mmol) and *o*-NO₂C₆H₄SO₂NHNH₂ (414 mg, 2.04 mmol) were dissolved in 3.4 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen atmosphere then triethylamine (393 μL, 2.72 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion, as monitored by TLC. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with EtOAc/hexanes (15:85) to give deoxy ketone **IV-7** (96 mg, 0.32 mmol, 95 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.70; $[\alpha]_D^{26} = -19.4$ (*c* 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3481, 2965, 2934, 1726, 1703, 1458, 1170, 992, 898; ¹H NMR (600 MHz, CDCl₃) δ 4.69 (ddd, *J* = 7.8, 5.4, 2.4 Hz, 1H), 3.50 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.10 (ddd, *J* = 18.6, 12.6, 1.2 Hz, 1H), 2.70 (m, 1H), 2.54 (m, 1H), 2.12 (ddd, *J* = 19.2, 5.4, 2.4 Hz, 1H), 1.87 (m, 3H), 1.55 (d, *J* = 5.4 Hz, 1H), 1.53 (m, 2H), 1.44 (m, 1H), 1.36 (dd, *J* = 12.6, 3.6 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (150 MHz, CDCl_3) δ 214.2, 174.5, 80.9, 79.0, 45.9, 43.8, 33.97, 33.94, 33.5, 32.2, 24.2, 20.6, 19.4, 17.9, 16.9, 15.3, 10.8; CIHRMS Calcd for $[\text{C}_{17}\text{H}_{30}\text{O}_4\text{Na}^+]$: 321.2041. Found 321.2037.

(S)-1-(2-Furyl)-ethanol (IV-6a).

To a 25 ml flask was added furan ketone **II-24** (800 mg, 7.27 mmol), CH_2Cl_2 (3.7 ml), formic acid/triethylamine (1:1, 9.71 ml) and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6 -mesitylene)-(*S,S*)-TsDPEN (22.2 mg, 0.5 mol%). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (10 ml) and extracted with EtOAc (3 x 25 ml). The combined organic layers were washed with saturated NaHCO_3 , dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 30% EtOAc/hexane to give furan alcohol **IV-6a** (745 mg, 6.76 mmol, 93%): colorless oil; R_f (30% EtOAc/hexane) = 0.41; $[\alpha]_D^{25} = +21$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3360, 2980, 2935, 1668, 1505, 1467, 1370, 1229, 1149, 1007, 877, 734; ^1H NMR (600 MHz CDCl_3) 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); ^{13}C NMR (150 MHz, CDCl_3) δ 157.7, 141.6, 109.9, 104.9, 63.3, 21.1.

(2S)-6-Hydroxy-2-methyl-2H-Pyran-3 (6H)-one (II-26).

Compound furan alcohol **IV-6a** (8.30 g, 74.1 mmol), 184.5 mL of THF, and 61.5 mL of H₂O were added to a round bottom flask and cooled to 0 °C. Solid NaHCO₃ (12.4 g, 148.2 mmol), NaOAc•3H₂O (10.1 g, 74.1 mmol), and NBS (13.1 g, 74.1 mmol) were added to the solution and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated NaHCO₃ (200 mL), extracted (3 x 200 mL) with Et₂O, dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel chromatography eluting with 25% EtOAc/hexane to give pyranone **II-26** (8.56 g, 67.4 mmol, 91%): *R_f* (60% EtOAc/hexane) = 0.29; [α]_D²⁵ = + 44 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3381, 2988, 2942, 1692, 1447, 1373, 1232, 1021, 937; ¹H NMR (600 MHz, CDCl₃) major 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); ¹³C NMR (150 MHz, CDCl₃) major isomer δ 197.6, 145.3, 126.6, 87.2, 74.8, 15.1.

(2*S*, 6*S*)-*tert*-butyl -5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl carbonate (**IV-6α**).

Pyronone alcohol **II-26** (5.5 g, 42.9 mmol) was dissolved in CH₂Cl₂ (42 mL) and the solution was cooled to -78 °C. A CH₂Cl₂ (2 mL) solution of (Boc)₂O (13.46 g, 51.6 mmol) and a catalytic amount of DMAP (524.2 mg, 4.76 μmol) was added to the reaction mixture. The reaction was stirred for 1 h at -78 °C, and quenched with 200 mL of saturated NaHCO₃, extracted with Et₂O (3 x 200 mL), dried (Na₂SO₄), and concentrated

under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc/hexane to give 7.62 g (33.5 mmol, 78%) of two diastereomers of Boc-protected pyranone **IV-6 α** and **IV-6 β** in 3:1: R_f (20% Et₂O/hexane) = 0.58; $[\alpha]_D^{25} = +98$ ($c = 1.0$, CH₂Cl₂); IR (thin film, cm⁻¹) 2984, 2942, 1752, 1703, 1371, 1273, 1254, 1153, 938, 838; ¹H NMR (600 MHz, CDCl₃) δ 6.78 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.22 (d, $J = 3.6$ Hz, 1H), 6.09 (d, $J = 10.2$ Hz, 1H), 4.53 (q, $J = 6.6$ Hz, 1H), 1.40 (s, 9H), 1.28 (d, $J = 6.6$ Hz, 3H); ¹³C NMR (150.8 MHz, CDCl₃) δ 195.5, 151.7, 140.9, 128.2, 89.1, 83.3, 72.0, 27.5 (3C), 15.1; CIHRMS Calculated for [C₁₁H₁₆O₅Na⁺]: 251.0890, Found: 251.0883.

(2*S*, 6*S*)-tert-butyl -5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl carbonate (IV-6 β).

To a 1000 ml flask was added furan ketone **II-26** (40 g, 363.5 mmol), CH₂Cl₂ (240 ml), formic acid/triethylamine (5:3, 480 ml) and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6 -mesitylene)-(*R*, *R*)-TsDPEN (222 mg, 0.1 mol%). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (500 ml) and extracted with EtOAc (3 x 700 ml). The combined organic layers were washed with saturated NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. The resulted crude compound furan alcohol was dissolve in 603 mL of THF/H₂O (3:1) and cooled down to 0 °C. Solid NaHCO₃ (60.9 g, 727.8 mmol), NaOAc•3H₂O (49.6 g, 363.9 mmol), and NBS (64.3 g, 363.7 mmol) were added to the solution and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with

saturated NaHCO_3 (600 mL), extracted (3 x 800 mL) with Et_2O , dried (Na_2SO_4), concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 (500 mL) and the solution was cooled to $-78\text{ }^\circ\text{C}$. $(\text{Boc})_2\text{O}$ (93 g, 400 mmol) and a catalytic amount of DMAP (4.0 g) was added to the reaction mixture. The reaction was stirred for 12 h at -78 to $-30\text{ }^\circ\text{C}$, and quenched with saturated NaHCO_3 , extracted with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc /hexane to give 61.4 g (269.2 mmol, 80%) of two diastereomers of Boc-protected pyranone **II-26 β** in 3:1: R_f (20% Et_2O /hexane) = 0.58; $[\alpha]_D^{25} = -98$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 2984, 2942, 1752, 1703, 1371, 1273, 1254, 1153, 938, 838; ^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 (3C), 15.1; CIHRMS Calculated for $[\text{C}_{11}\text{H}_{16}\text{O}_5\text{Na}^+]$: 251.0890, Found: 251.0883.

6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-2-methyl-6H-pyran-3-one (IV-8).

A CH_2Cl_2 (0.6 mL) solution of Boc-enone **IV-6** (93 mg, 0.40 mmol) and 10-deoxymethynolide alcohol **5** (60 mg, 0.20 mmol) was cooled to $0\text{ }^\circ\text{C}$. A CH_2Cl_2 (0.2 mL)

solution of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (21 mg, 2.5 mol%) and PPh_3 (22 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 5 hours. The reaction mixture was quenched with 5 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc /hexanes to give enone **IV-8** (75 mg, 0.18 mmol, 90%) as viscous oil. R_f (50% EtOAc /hexanes) = 0.50; $[\alpha]_{\text{D}}^{26} = -65$ ($c = 0.3$, MeOH); IR (thin film, cm^{-1}) 2965, 2930, 1724, 1701, 1459, 1171, 1019, 974; ^1H NMR (600 MHz, CDCl_3) δ 6.85 (dd, $J = 10.8, 3.0$ Hz, 1H), 6.07 (d, $J = 10.2$ Hz, 1H), 5.24 (d, $J = 3.6$ Hz, 1H), 4.70 (ddd, $J = 7.8, 5.4, 2.4$ Hz, 1H), 4.60 (dd, $J = 13.8, 6.6$ Hz, 1H), 3.65 (dd, $J = 10.2, 1.2$ Hz, 1H), 3.09 (ddd, $J = 19.6, 11.4, 2.4$ Hz, 1H), 2.87 (ddd, $J = 16.8, 7.2, 6.6$ Hz, 1H), 2.56 (m, 1H), 2.13 (ddd, $J = 18.6, 5.4, 3.0$ Hz, 1H), 1.88 (d, $J = 13.2$ Hz, 1H), 1.83 (m, 1H), 1.51 (m, 3H), 1.47 (m, 1H), 1.36 (dd, $J = 7.2, 2.4$ Hz, 1H), 1.42 (m, 1H), 1.36 (d, $J = 6.6$ Hz, 3H), 1.24 (d, $J = 7.2$ Hz, 3H), 1.14 (d, $J = 7.2$ Hz, 3H), 1.09 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 7.2$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.1, 196.8, 174.1, 142.5, 126.9, 109.9, 95.8, 88.5, 81.1, 70.6, 45.8, 44.1, 34.7, 34.3, 33.8, 32.3, 24.2, 20.6, 17.9, 17.1, 15.3, 14.9, 10.8; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{36}\text{O}_6\text{Na}^+]$: 431.2409. Found 431.2405.

6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-2-methyl-3, 6-dihydro-2H-pyran-3-ol (IV-9).

The enone compound **IV-8** (60 mg, 0.15 mmol) was dissolved in 0.2 mL of CH_2Cl_2 and 0.2 mL MeOH in round bottom flask and cooled $-78\text{ }^\circ\text{C}$ then NaBH_4 (6.1 mg, 0.15 mmol) was added and the reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 3 hours and on completion, monitored by TLC, reaction mixture was diluted with ether and was quenched with 2 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give allylic alcohol **IV-9** (56 mg, 0.14 mmol, 92%) as viscous oil. R_f (50% EtOAc/hexanes) = 0.35; $[\alpha]_{\text{D}}^{26} = -14$ ($c = 0.25$, MeOH); IR (thin film, cm^{-1}) 3444, 2968, 2934, 1726, 1704, 1460, 1171, 1039, 899; ^1H NMR (600 MHz, CDCl_3) δ 5.94 (d, $J = 10.2$ Hz, 1H), 5.78 (td, $J = 10.2, 2.4$ Hz, 1H), 4.98 (br s, 1H), 4.68 (ddd, $J = 7.2, 4.8, 2.4$ Hz, 1H), 3.81 (d, $J = 8.4$ Hz, 1H), 3.67 (ddd, $J = 12.6, 9.0, 6.0$ Hz, 1H), 3.57 (d, $J = 10.2$ Hz, 1H), 3.10 (ddd, $J = 18.6, 12.6, 2.4$ Hz, 1H), 2.83 (m, 1H), 2.55 (m, 1H), 2.14 (ddd, $J = 18.6, 5.4, 2.4$ Hz, 1H), 2.06 (m, 1H), 1.88 (m, 2H), 1.83 (m, 2H), 1.66 (br s, 1H), 1.51 (td, $J = 14.4, 7.2$ Hz, 1H), 1.29 (d, $J = 6.0$ Hz, 3H), 1.24 (br s, 2H), 1.21 (d, $J = 7.2$ Hz, 3H), 1.14 (d, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.4, 174.4, 133.4, 126.0, 96.4, 86.8, 80.9, 69.2, 68.0, 45.9, 44.3,

34.8, 34.0, 33.8, 32.2, 29.6, 24.2, 20.5, 17.9, 17.6, 17.1, 15.3, 10.8; CIHRMS Calcd for $[C_{23}H_{38}O_6Na^+]$: 433.2566. Found 433.2560.

(2*S*,3*R*,6*R*)-6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-tetrahydro-2-methyl-2*H*-pyran-3-ol (IV-10).

The enol compound **IV-9** (40 mg, 0.10 mmol) and o -NO₂C₆H₄SO₂NHNH₂ (120 mg, 0.60 mmol) were dissolved in 1.0 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen atmosphere then triethylamine (114 μL, 0.80 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion, as monitored by TLC. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with EtOAc/hexanes (30:70) to give deoxy alcohol **IV-10** (40 mg, 0.09 mmol, 96 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.26; $[\alpha]_D^{26} = -34$ (c 0.25, CH₂Cl₂); IR (thin film, cm⁻¹) 3449, 2963, 2928, 1726, 1703, 1459, 1170, 1019, 940, 898; ¹H NMR (600 MHz, CDCl₃) δ 4.74 (d, J = 2.4 Hz, 1H), 4.67 (ddd, J = 8.4, 5.4, 1.8 Hz, 1H), 3.70 (ddd, J = 12.6, 9.0, 6.0 Hz, 1H), 3.48 (d, J = 10.2 Hz, 1H), 3.28 (ddd, J = 10.2, 9.0, 4.2 Hz, 1H), 3.10 (ddd, J = 18.6, 12.6, 2.4 Hz, 1H), 2.79 (ddd, J = 13.2, 10.2, 7.2 Hz, 1H), 2.55 (m, 1H), 2.13 (m, 1H), 1.93 (m, 1H), 1.91 (m, 1H), 1.89

(d, $J = 2.4$ Hz, 1H), 1.87 (d, $J = 1.8$ Hz, 1H), 1.84 (m, 1H), 1.82 (dd, $J = 4.2, 2.4$ Hz, 1H), 1.75 (ddd, $J = 10.2, 7.2, 3.6$ Hz, 1H), 1.73 (m, 1H), 1.69 (dd, $J = 10.2, 3.6$ Hz, 1H), 1.43 (m, 3H), 1.37 (d, $J = 4.8$ Hz, 1H), 1.21 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 7.2$ Hz, 3H), 1.15 (d, $J = 7.2$ Hz, 3H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.91 (d, $J = 7.2$ Hz, 3H), 0.87 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.3, 174.5, 99.2, 80.8, 72.0, 70.2, 45.9, 44.3, 34.7, 34.3, 33.8, 32.2, 29.9, 29.6, 27.6, 24.2, 20.6, 19.2, 18.0, 17.5, 17.0, 15.5, 10.7; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{40}\text{O}_6\text{Na}^+]$: 435.2722. Found 435.2717.

(2*R*,5*R*,6*R*)-2-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-tetrahydro-6-methyl-2*H*-pyran-3,4,5-triol (IV-11).

To a CH_2Cl_2 (0.2 mL) solution of allylic alcohol **IV-9** (10 mg, 0.02 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (10 μL). Crystalline OsO_4 (2.0 mg, 10 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/hexanes (10:40:50). Pure fractions were combined and concentrated to afford triol **IV-11** (9.7 mg, 0.02 mmol, 91 %) as viscous oil. R_f (90% EtOAc/MeOH) = 0.30; $[\alpha]_{\text{D}}^{26} = -39$ ($c = 0.3$, MeOH); IR (thin film, cm^{-1}) 3390, 2965,

2929, 1723, 1702, 1458, 1173, 1062, 899, 735; ^1H NMR (600 MHz, CDCl_3) δ 4.80 (d, J = 1.2 Hz, 1H), 4.67 (ddd, J = 8.4, 4.8, 1.8 Hz, 1H), 4.02 (br s, 1H), 3.78 (ddd, J = 12.6, 9.6, 6.0 Hz, 1H), 3.71 (m, 1H), 3.51 (d, J = 10.2 Hz, 1H), 3.47 (dd, J = 10.2, 9.0 Hz, 1H), 3.09 (ddd, J = 12.0, 9.2, 2.4 Hz, 1H), 2.81 (ddd, J = 13.8, 10.2, 6.6 Hz, 1H), 2.54 (m, 1H), 2.42 (m, 1H), 2.23 (m, 1H), 2.15 (dd, J = 5.4, 3.0 Hz, 1H), 1.85 (m, 2H), 1.52 (dd, J = 12.6, 7.2 Hz, 1H), 1.55 (m, 3H), 1.44 (m, 2H), 1.29 (d, J = 6.0 Hz, 3H), 1.25 (d, J = 1.2 Hz, 1H), 1.22 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H), 1.06 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 7.2 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.1, 174.2, 102.6, 81.1, 73.4, 71.8, 71.2, 68.4, 45.8, 44.1, 34.6, 34.2, 33.8, 32.3, 29.6, 24.2, 20.6, 19.2, 18.0, 17.1, 16.9, 15.5, 10.7; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{40}\text{O}_8\text{Na}^+]$: 467.2620. Found 467.2616.

(2*R*,3*R*,6*R*)-6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-3,6-dihydro-2-methyl-2*H*-pyran-3-yl methyl carbonate (IV-12).

To a solution of allylic alcohol **IV-9** (60 mg, 0.15 mmol) in dry CH_2Cl_2 (1.0 mL) at 0 °C, was added pyridine (59 μL , 0.73 mmol), DMAP (3.6 mg), and methyl chloroformate (57 mg, 0.73 mmol). After stirring 24 h at room temperature, water (1 mL) was added and then the mixture was extracted with EtOAc (3 x 5 mL), dried (Na_2SO_4), concentrated under reduced pressure. The crude product was purified using silica gel flash

chromatography eluting with EtOAc/hexane (20:80) to give carbonate **IV-12** (60.2 mg, 0.13 mmol, 88%) as viscous oil. R_f (50% EtOAc/hexane) = 0.50; $[\alpha]_D^{26} = -12$ ($c = 0.5$, CH_2Cl_2); IR (thin film, cm^{-1}) 2962, 2924, 1752, 1701, 1459, 1261, 1045, 970; ^1H NMR (600 MHz, CDCl_3) δ 5.94 (d, $J = 10.2$ Hz, 1H), 5.85 (ddd, $J = 7.8, 4.8, 2.4$ Hz, 1H), 5.01 (br s, 1H), 4.85 (dd, $J = 9.0, 1.8$ Hz, 1H), 4.69 (ddd, $J = 8.4, 5.4, 1.8$ Hz, 1H), 3.95 (ddd, $J = 12.0, 9.6, 6.0$ Hz, 1H), 3.81 (s, 3H), 3.65 (dd, $J = 10.2, 1.2$ Hz, 1H), 3.10 (ddd, $J = 18.6, 12.6, 2.4$ Hz, 1H), 2.84 (ddd, $J = 13.8, 10.2, 6.6$ Hz, 1H), 2.54 (ddd, $J = 13.2, 7.2, 1.8$ Hz, 1H), 2.12 (ddd, $J = 18.6, 6.0, 2.4$ Hz, 1H), 1.89 (dd, $J = 6.0, 1.2$ Hz, 1H), 1.85 (br s, 1H), 1.83 (m, 2H), 1.52 (dd, $J = 7.2, 6.0$ Hz, 1H), 1.50 (dd, $J = 7.2, 6.6$ Hz, 1H), 1.43 (m, 1H), 1.36 (ddd, $J = 16.8, 9.6, 4.2$ Hz, 1H), 1.24 (d, $J = 6.0$ Hz, 3H), 1.21 (d, $J = 7.2$ Hz, 3H), 1.15 (d, $J = 7.2$ Hz, 3H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.5, 174.5, 155.5, 129.3, 127.8, 96.5, 87.2, 81.1, 74.5, 64.9, 55.2, 46.1, 44.4, 34.9, 34.2, 34.0, 32.4, 24.4, 20.8, 19.5, 18.1, 17.8, 17.3, 15.4, 11.0; CIHRMS Calcd for $[\text{C}_{25}\text{H}_{40}\text{O}_8\text{Na}^+]$: 491.2620. Found 491.2615.

(2*R*,3*R*,6*R*)-3-azido-6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-3,6-dihydro-2-methyl-2*H*-pyran (IV-13).

To a mixture of carbonate **IV-12** (55 mg, 0.12 mmol), allylpalladium chloride dimer (6.4 mg, 0.02 mmol) and 1,4-bis(diphenylphosphino)butane (30 mg, 0.08 mmol) in anhydrous THF (0.20 mL) was added TMSN₃ (77 µg, 0.59 mmol) under argon atmosphere. The solution was stirred at room temperature for 3 h. Then the mixture was evaporated under reduced pressure, purified using silica gel flash chromatography eluting with EtOAc/hexane (15:85) to give allylic azide **IV-13** (43 mg, 0.10mmol, 85%) as viscous oil. R_f (30% EtOAc/hexane) = 0.60; $[\alpha]_D^{26} = -45$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 2968, 2934, 2103, 1725, 1703, 1459, 1170, 1041, 984; ¹H NMR (600 MHz, CDCl₃) δ 5.96 (d, $J = 10.8$ Hz, 1H), 5.93 (ddd, $J = 9.6, 2.4, 2.4$ Hz, 1H), 5.00 (br s, 1H), 4.69 (ddd, $J = 8.4, 6.0, 2.4$ Hz, 1H), 3.74 (ddd, $J = 12.6, 9.0, 6.6$ Hz, 1H), 3.51 (d, $J = 10.2$ Hz, 1H), 3.55 (d, $J = 9.6$ Hz, 1H), 3.10 (ddd, $J = 18.6, 12.6, 2.4$ Hz, 1H), 2.84 (ddd, $J = 13.2, 10.2, 7.2$ Hz, 1H), 2.55 (m, 1H), 2.13 (ddd, $J = 18.6, 6.0, 1.8$ Hz, 1H), 1.88 (m, 2H), 1.83 (m, 1H), 1.51 (m, 2H), 1.43 (m, 1H), 1.35 (m, 2H), 1.30 (d, $J = 6.6$ Hz, 3H), 1.21 (d, $J = 7.2$ Hz, 3H), 1.15 (d, $J = 6.6$ Hz, 3H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 214.5, 174.5, 128.6, 128.2, 94.4, 87.3, 81.1, 66.3, 60.2, 46.1, 44.4, 34.9, 34.2, 34.0, 32.4, 24.4, 20.8, 19.5, 18.3, 18.1, 17.4, 15.5, 11.0; CIHRMS Calcd for [C₂₃H₃₇N₃O₅Na⁺]: 458.2630. Found 458.2625.

(2*R*,3*R*,6*R*)-3-azido-6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-tetrahydro-2-methyl-2*H*-pyran (IV-14).

The allylic azide compound **IV-13** (20 mg, 0.04 mmol) and *o*-NO₂C₆H₄SO₂NHNH₂ (56 mg, 0.27 mmol) were dissolved in 0.4 mL of CH₂Cl₂ in a round bottom flask and cooled 0 °C under nitrogen atmosphere then triethylamine (60 μL, 0.36 mmol) was added and the reaction mixture was stirred at 0 °C for 12 hours and on completion, as monitored by TLC. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. The crude product was purified using silica gel flash chromatography eluting with EtOAc/hexanes (15:85) to give deoxy azide **IV-14** (18 mg, 0.04 mmol, 90 %) as viscous oil. R_f (50% EtOAc/Hexane) = 0.65; $[\alpha]_D^{26} = -13$ ($c = 0.5$, CH₂Cl₂); IR (thin film, cm⁻¹) 2965, 2930, 1724, 1701, 1459, 1171, 1019, 974; ¹H NMR (600 MHz, CDCl₃) δ 4.78 (d, $J = 3.0$ Hz, 1H), 4.68 (ddd, $J = 8.4, 4.2, 2.4$ Hz, 1H), 3.73 (ddd, $J = 12.6, 9.6, 6.6$ Hz, 1H), 3.48 (d, $J = 10.8$ Hz, 1H), 3.10 (m, 1H), 3.04 (m, 1H), 2.80 (ddd, $J = 13.2, 10.2, 7.2$ Hz, 1H), 2.56 (ddd, $J = 11.4, 7.8, 4.2$ Hz, 1H), 2.14 (m, 1H), 1.97 (m, 1H), 1.95 (dd, $J = 4.2, 1.8$ Hz, 1H), 1.88 (br s, 1H), 1.86 (m, 2H), 1.84 (m, 1H), 1.80 (d, $J = 2.4$ Hz, 1H), 1.78 (dd, $J = 9.0, 2.4$ Hz, 1H), 1.75 (d, $J = 3.6$ Hz, 1H), 1.51 (d, $J = 7.2$ Hz, 3H), 1.44 (m, 1H), 1.35 (m, 1H), 1.21 (d, $J = 6.6$ Hz, 3H), 1.17 (t, $J = 6.0$ Hz, 3H), 1.03 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 214.3, 174.4, 99.1, 88.3, 80.9, 68.2, 62.6,

45.9, 44.3, 34.7, 34.5, 33.8, 32.2, 29.5, 24.5, 23.9, 20.6, 19.2, 18.3, 18.0, 17.0, 15.5, 10.7;

CIHRMS Calcd for $[C_{23}H_{39}N_3O_5Na]^+$: 460.2787. Found 460.2783.

(2*R*,5*R*,6*R*)-5-azido-2-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-tetrahydro-6-methyl-2*H*-pyran-3,4-diol (IV-15).

To a CH_2Cl_2 (0.3 mL) solution of allylic azide **IV-13** (15 mg, 0.3 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (17 μ L). Crystalline OsO_4 (1.0 mg, 10 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/hexanes (2:48:50). Pure fractions were combined and concentrated to afford diol **IV-15** (15 mg, 0.03 mmol, 90 %) as viscous oil. R_f (50% EtOAc/hexanes) = 0.20; $[\alpha]_D^{26} = -62$ ($c = 0.5$, MeOH); IR (thin film, cm^{-1}) 3411, 2968, 2933, 2108, 1725, 1703, 1459, 1174, 1051, 997, 900; 1H NMR (600 MHz, $CDCl_3$) δ 4.81 (d, $J = 1.2$ Hz, 1H), 4.67 (ddd, $J = 7.8, 5.4, 2.4$ Hz, 1H), 4.11 (dd, $J = 14.4, 7.2$ Hz, 1H), 4.00 (ddd, $J = 4.8, 3.0, 1.8$ Hz, 1H), 3.78 (ddd, $J = 10.2, 7.2, 3.0$ Hz, 1H), 3.69 (m, 1H), 3.51 (d, $J = 10.2$ Hz, 1H), 3.31 (d, $J = 10.2$ Hz, 1H), 3.07 (ddd, $J = 17.4, 6.6, 2.4$ Hz, 1H), 2.80 (ddd, $J = 13.2, 10.2, 6.6$ Hz, 1H), 2.55 (m, 2H), 2.35 (br s, 1H), 1.16 (br s, 1H), 2.13

(m, 1H), 1.84 (m, 3H), 1.60 (d, $J = 3.0$ Hz, 1H), 1.51 (dd, $J = 14.4, 7.8$ Hz, 1H), 1.44 (m, 1H), 1.32 (d, $J = 6.0$ Hz, 3H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.15 (d, $J = 6.0$ Hz, 3H), 1.03 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.1, 174.1, 102.4, 89.6, 81.1, 70.5, 67.4, 65.8, 60.3, 45.8, 44.1, 34.6, 34.2, 33.7, 32.3, 24.2, 20.5, 19.2, 18.0, 17.0, 15.6, 14.1, 10.7; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{39}\text{N}_3\text{O}_7\text{Na}^+]$: 492.2685. Found 492.2684.

(2*S*,3*R*,6*R*)-6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-tetrahydro-2-methyl-2*H*-pyran-3-amine (IV-17).

To a solution of allylic azide **IV-13** (15 mg, 0.04 mmol) in dry MeOH (0.3 mL) was added Pd/C (10 mg) and the mixture was stirred under H_2 at an 100 psi pressure for 8 h at room temperature. The catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure. The resulting crude product was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/hexanes (200:40:40). Pure fractions were combined and concentrated to afford deoxy amine **IV-17** (13.2 mg, 0.03 mmol, 92 %) as viscous oil. R_f (90% EtOAc/MeOH) = 0.30; $[\alpha]_{\text{D}}^{26} = -38$ ($c = 0.5$, MeOH); IR (thin film, cm^{-1}) 3345, 2964, 2929, 1728, 1705, 1457, 1167, 1016, 983, 897;

^1H NMR (600 MHz, CDCl_3) δ 4.71 (d, $J = 3.0$ Hz, 1H), 4.61 (ddd, $J = 9.0, 4.2, 1.8$ Hz, 1H), 3.92 (ddd, $J = 12.6, 9.6, 6.6$ Hz, 1H), 3.40 (d, $J = 10.2$ Hz, 1H), 3.12 (m, 1H), 2.79 (ddd, $J = 13.2, 10.2, 7.2$ Hz, 1H), 2.48 (m, 1H), 1.95 (d, $J = 10.2$ Hz, 1H), 1.91 (d, $J = 10.2$ Hz, 1H), 1.79 (m, 2H), 1.76 (br s, 1H), 1.68 (m, 3H), 1.53 (m, 3H), 1.50 (m, 1H), 1.48 (dd, $J = 6.0, 2.4$ Hz, 1H), 1.36 (ddd, $J = 15.6, 10.2, 4.2$ Hz, 1H), 1.25 (br s, 2H), 1.15 (d, $J = 7.2$ Hz, 3H), 1.14 (d, $J = 6.0$ Hz, 3H), 1.12 (d, $J = 7.2$ Hz, 3H), 1.03 (d, $J = 6.0$ Hz, 3H), 0.90 (d, $J = 7.2$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 217.1, 176.6, 101.2, 82.6, 68.9, 66.8, 49.7, 47.4, 41.0, 36.3, 35.9, 35.2, 33.7, 31.5, 25.4, 21.7, 19.5, 19.2, 18.5, 17.8, 16.2, 16.1, 11.3; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{41}\text{NO}_5\text{H}^+]$: 412.3063. Found 412.3061.

(2*R*,3*R*,4*R*,5*R*,6*S*)-5-amino-2-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-tetrahydro-6-methyl-2*H*-pyran-3,4-diol (IV-16).

To a solution of dihydroxy azide **IV-15** (10 mg, 0.02 mmol) in dry MeOH (0.2 mL) was added Pd/C (2 mg) and the mixture was stirred under H_2 at an 100 psi pressure for 6 h at room temperature. The catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure. The resulting crude product was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/hexanes (20:40:40). Pure

fractions were combined and concentrated to afford dihydroxy amine **IV-16** (8.5 mg, 0.02 mmol, 90 %) as viscous oil. R_f (90% EtOAc/MeOH) = 0.20; $[\alpha]_D^{26} = -130$ ($c = 0.5$, MeOH); IR (thin film, cm^{-1}) 3373, 2967, 2933, 1721, 1702, 1458, 1366, 1173, 1032, 984; ^1H NMR (600 MHz, CDCl_3) δ 4.71 (d, $J = 2.4$ Hz, 1H), 4.63 (ddd, $J = 8.4, 4.8, 1.8$ Hz, 1H), 3.85 (dd, $J = 3.0, 1.8$ Hz, 1H), 3.69 (ddd, $J = 12.6, 9.6, 5.4$ Hz, 1H), 3.48 (dd, $J = 10.2, 3.0$ Hz, 1H), 3.42 (d, $J = 10.8$ Hz, 1H), 3.13 (ddd, $J = 19.2, 12.0, 2.4$ Hz, 1H), 2.83 (ddd, $J = 13.8, 10.2, 6.6$ Hz, 1H), 2.76 (t, $J = 10.2$ Hz, 1H), 2.49 (m, 1H), 2.21 (m, 2H), 1.88 (ddd, $J = 12.6, 7.8, 4.8$ Hz, 1H), 1.81 (dd, $J = 14.4, 2.4$ Hz, 1H), 1.57 (m, 1H), 1.55 (m, 3H), 1.45 (d, $J = 4.2$ Hz, 1H), 1.43 (dd, $J = 4.2, 1.8$ Hz, 1H), 1.40 (d, $J = 4.2$ Hz, 1H), 1.27 (br s, 1H), 1.24 (m, 1H), 1.20 (d, $J = 7.2$ Hz, 3H), 1.19 (d, $J = 6.0$ Hz, 3H), 1.16 (d, $J = 7.2$ Hz, 3H), 1.04 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 217.1, 176.3, 105.5, 82.7, 72.1, 71.5, 71.1, 55.3, 47.4, 45.8, 35.9, 35.8, 35.1, 33.6, 31.4, 25.4, 21.7, 19.5, 18.3, 18.1, 17.6, 16.0, 11.3; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{41}\text{NO}_7\text{H}^+]$: 444.2961. Found 444.2955.

(2*R*,3*S*,6*R*)-3-azido-6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione))-3,6-dihydro-2-methyl-2*H*-pyran (IV-19).

To a solution of allylic alcohol **IV-9** (15 mg, 0.03 mmol) and methanesulphonyl chloride (4 μ L, 0.05 mmol) in dry CH_2Cl_2 (0.3 mL) at 0 $^\circ\text{C}$, was added triethylamine (6 μ L, 0.04 mmol). After stirring 8 h at room temperature, water (1 mL) was added and then the mixture was extracted with EtOAc (3 x 5 mL), dried (Na_2SO_4), concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with EtOAc/hexane (15:85) to give mesylate **IV-18**. To a solution mesylate **IV-18** (15 mg, 0.12 mmol) in THF (0.3 mL) was added NaN_3 (3.0 mg, 0.05 mmol) under argon atmosphere. The solution was stirred at room temperature for 2 h. Then the mixture was evaporated under reduced pressure, purified using silica gel flash chromatography eluting with EtOAc/hexane (20:80) to give allylic azide **IV-19** (10 mg, 0.02 mmol, 80%) as viscous oil. R_f (30% EtOAc/hexane) = 0.55; $[\alpha]_{\text{D}}^{26} = +73$ ($c = 0.3$, CH_2Cl_2); IR (thin film, cm^{-1}) 2967, 2932, 2100, 1725, 1702, 1460, 1170, 1041, 972; ^1H NMR (600 MHz, CDCl_3) δ 6.16 (dd, $J = 10.2, 3.0$ Hz, 1H), 6.10 (dd, $J = 10.2, 6.0$ Hz, 1H), 5.06 (d, $J = 2.4$ Hz, 1H), 4.69 (ddd, $J = 7.8, 5.4, 2.4$ Hz, 1H), 4.22 (ddd, $J = 13.2, 6.0, 2.4$ Hz, 1H), 3.62 (d, $J = 10.2$ Hz, 1H), 3.13 (dd, $J = 5.4, 2.4$ Hz, 1H), 3.09 (ddd, $J = 12.6, 6.0, 2.4$ Hz, 1H), 2.84 (m, 1H), 2.54 (m, 1H), 2.13 (m, 1H), 1.91 (d, $J = 13.2$ Hz, 1H), 1.87 (d, $J = 13.2$ Hz, 1H), 1.83 (m, 1H), 1.53 (dd, $J = 8.6, 6.0$ Hz, 1H), 1.50 (d, $J = 7.2, 6.6$ Hz, 1H), 1.43 (m, 2H), 1.32 (d, $J = 6.0$ Hz, 3H), 1.25 (d, $J = 6.6$ Hz, 3H), 1.17 (m, 1H), 1.14 (d, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 6.6$ Hz, 3H), 1.07 (d, $J = 7.2$ Hz, 3H), 0.89 (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.2, 174.2, 129.8, 124.9, 96.3, 86.7, 80.9, 66.4, 55.1, 45.9, 44.2, 34.7, 34.1, 33.8, 32.2, 24.2, 20.6, 19.3, 17.9, 17.2, 16.9, 15.3, 10.8; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{37}\text{N}_3\text{O}_5\text{Na}^+]$: 458.2630. Found 458.2631.

(2*R*,3*S*,6*R*)-6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-tetrahydro-2-methyl-2*H*-pyran-3-amine (IV-20).

To a solution of allylic azide **IV-19** (10 mg, 0.02 mmol) in dry MeOH (0.2 mL) was added Pd/C (5 mg) and the mixture was stirred under H₂ at an 100 psi pressure for 7 h at room temperature. The catalyst was filtered off through a short pad of Celite, concentrated under reduced pressure. The resulting crude product was pipetted directly on to a silica gel column using CH₂Cl₂ (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/hexanes (20:60:20). Pure fractions were combined and concentrated to afford deoxy amine **IV-20** (7.1 mg, 0.02 mmol, 87 %) as viscous oil. R_f (90% EtOAc/MeOH) = 0.35; $[\alpha]_D^{26} = +39$ ($c = 0.3$, CH₂Cl₂); IR (thin film, cm⁻¹) 3329, 2942, 2832, 1728, 1705, 1449, 1112, 1021, 856; ¹H NMR (600 MHz, CDCl₃) δ 4.62 (dd, $J = 6.0, 2.4$ Hz, 1H), 4.60 (br s, 1H), 4.30 (m, 1H), 4.18 (dd, $J = 6.0, 2.4$ Hz, 1H), 4.12 (d, $J = 9.6$ Hz, 1H), 3.41 (d, $J = 10.8$ Hz, 1H), 3.38 (m, 1H), 3.15 (dd, $J = 3.6, 1.8$ Hz, 1H), 3.13 (dd, $J = 6.0, 1.8$ Hz, 1H), 3.10 (d, $J = 2.4$ Hz, 1H), 2.84 (dd, $J = 9.0, 3.6$ Hz, 1H), 2.80 (dd, $J = 10.2, 6.6$ Hz, 1H), 2.61 (br s, 1H), 2.47 (m, 1H), 2.46 (dd, $J = 6.0, 5.4$ Hz, 1H), 2.39 (s, 1H), 2.24 (s, 1H), 2.22 (dd, $J = 8.4, 3.0$ Hz, 1H), 2.19 (dd, $J = 5.4, 3.0$ Hz, 1H), 1.74 (m, 1H), 1.53 (m, 1H), 1.24 (br s, 1H), 1.15 (d, $J = 6.6$ Hz, 3H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 6.6$ Hz, 3H), 1.01 (d, $J =$

6.0 Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 216.0, 175.4, 100.3, 81.5, 56.5, 84.5, 48.5, 46.3, 34.9, 34.7, 34.5, 34.0, 32.5, 29.8, 27.5, 24.3, 20.8, 20.6, 18.4, 17.2, 16.5, 14.9, 10.1; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{41}\text{NO}_5\text{H}^+]$: 412.3063. Found 412.3061.

6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-2-methyl-2H-pyran-3(6H)-one (IV-22).

A CH_2Cl_2 (1.5 mL) solution of Boc-enone **IV-21** (366 mg, 1.60 mmol) and 10-deoxymethynolide alcohol **IV-7** (120 mg, 0.41 mmol) was cooled to 0°C . A CH_2Cl_2 (1.5 mL) solution of $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (41 mg, 2.5 mol%) and PPh_3 (42 mg, 10 mol%) was added to the reaction mixture at 0°C . The reaction mixture was stirred at 0°C for 2 hours. The reaction mixture was quenched with 10 mL of satd. aq. NaHCO_3 , extracted (3 x 10 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc /hexanes to give enone **IV-22** (131 mg, 0.32 mmol, 80%) as viscous oil. R_f (50% EtOAc /hexanes) = 0.45; $[\alpha]_{\text{D}}^{26} = -12$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 2967, 2934, 1725, 1703, 1459, 1171, 1018, 899; ^1H NMR (600 MHz, CDCl_3) δ 6.92 (dd, $J = 10.2, 1.2$ Hz, 1H), 6.12 (dd, $J = 10.2, 1.8$ Hz, 1H), 5.34 (d, $J = 1.2$ Hz, 1H), 4.70 (ddd, $J = 9.0, 4.8, 1.8$ Hz, 1H), 4.11 (m, 1H), 3.68 (dd, $J = 10.2, 1.2$ Hz, 1H), 3.11 (ddd, $J = 18.6, 6.6, 2.4$

Hz, 1H), 2.92 (ddd, $J = 13.2, 10.2, 7.2$ Hz, 1H), 2.56 (m, 1H), 2.14 (m, 1H), 1.89 (dd, $J = 6.0, 3.0$ Hz, 1H), 1.86 (br s, 1H), 1.84 (dd, $J = 3.0, 2.4$ Hz, 1H), 1.53 (dd, $J = 13.8, 7.2$ Hz, 1H), 1.45 (m, 2H), 1.42 (d, $J = 6.6$ Hz, 3H), 1.39 (d, $J = 4.2$ Hz, 1H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.17 (m, 1H), 1.13 (d, $J = 6.6$ Hz, 3H), 1.09 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 7.2$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.5, 196.6, 174.4, 147.5, 129.2, 98.6, 88.2, 81.3, 75.3, 46.0, 44.1, 34.6, 34.3, 34.0, 32.4, 24.4, 20.8, 19.4, 18.1, 17.1, 15.9, 15.8, 11.0; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{36}\text{O}_6\text{Na}^+]$: 431.2409. Found 431.2403.

6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-3,6-dihydro-2-methyl-2H-pyran-3-ol (IV-23).

The enone compound **8 IV-22** (90 mg, 0.22 mmol) was dissolved in 0.3 mL of CH_2Cl_2 and 0.3 mL MeOH in round bottom flask and cooled -78°C then NaBH_4 (9.2 mg, 0.24 mmol) was added and the reaction mixture was stirred at -78°C for 3 hours and on completion, monitored by TLC, reaction mixture was diluted with ether and was quenched with 2 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give allylic alcohol **IV-23** (77 mg, 0.19 mmol, 85%) as viscous oil. R_f (50% EtOAc/hexanes) = 0.35;

$[\alpha]_D^{26} = +7$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3329, 2939, 22834, 1721, 1697, 1456, 1172, 1032, 900; ^1H NMR (600 MHz, CDCl_3) δ 5.92 (td, $J = 12.0, 2.4$ Hz, 1H), 5.82 (td, $J = 11.4, 1.2$ Hz, 1H), 5.06 (br s, 1H), 4.70 (dd, $J = 10.8, 2.4$ Hz, 1H), 3.93 (ddd, $J = 10.2, 6.0, 1.8$ Hz, 1H), 3.60 (d, $J = 7.2$ Hz, 1H), 3.50 (m, 1H), 3.10 (ddd, $J = 15.6, 12.6, 2.4$ Hz, 1H), 2.85 (m, 1H), 2.55 (m, 1H), 2.10 (m, 1H), 2.04 (s, 1H), 1.86 (br s, 1H), 1.84 (m, 2H), 1.54 (dd, $J = 8.4, 5.4$ Hz, 1H), 1.50 (dd, $J = 5.4, 1.2$ Hz, 1H), 1.43 (m, 2H), 1.33 (d, $J = 6.0$ Hz, 3H), 1.26 (dd, $J = 7.2, 2.4$ Hz, 1H), 1.23 (d, $J = 6.6$ Hz, 3H), 1.13 (d, $J = 7.2$ Hz, 3H), 1.09 (d, $J = 6.0$ Hz, 3H), 0.93 (d, $J = 7.2$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.5, 174.5, 132.8, 128.9, 99.4, 87.5, 80.9, 74.5, 69.0, 64.5, 45.9, 44.0, 34.5, 34.2, 33.8, 32.2, 24.2, 20.6, 19.2, 18.1, 16.9, 15.5, 10.7; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{38}\text{O}_6\text{Na}^+]$: 433.2566. Found 433.2559.

2-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-3,6-dihydro-6-methyl-2H-pyran (IV-24).

A flask was charged with dry N-methyl morpholine (NMM) 0.8 mL, triphenyl phosphine (126 mg, 0.48 mmol) and was cooled to -30 $^{\circ}\text{C}$ under Ar atmosphere. Diethylazodicarboxylate (69 μL , 0.44 mmol) was added and the reaction was stirred for 25 min, Allylic alcohol **IV-23** (60 mg, 0.15 mmol) was added in a 1M solution of NMM and the reaction mixture was stirred for 10 min, followed by addition of o-

nitrobenzenesulfonyl hydrazide (NBSH) (89 mg, 0.44 mmol). The reaction was stirred at -30 °C for 2h and was monitored by TLC, upon consumption of starting material, warm up to room temperature and stirred for another 4h. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of satd aq NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give **IV-24** (29 mg, 0.07 mmol, 40%) of viscous product: R_f (50% EtOAc/hexanes) = 0.60; $[\alpha]_D^{26} = +20$ ($c = 0.5$, CH₂Cl₂); IR (thin film, cm⁻¹) 2959, 2932, 1756, 1700, 1429, 1131, 1017, 985; ¹H NMR (600 MHz, CDCl₃) δ 5.64 (m, 1H), 5.57 (td, $J = 11.4$, 1.8 Hz, 1H), 4.69 (ddd, $J = 7.8$, 5.4, 2.4 Hz, 1H), 4.60 (dd, $J = 8.4$, 3.6 Hz, 1H), 4.27 (m, 1H), 3.54 (d, $J = 10.2$ Hz, 1H), 3.12 (ddd, $J = 19.2$, 12.0, 2.4 Hz, 1H), 2.85 (m, 1H), 2.57 (m, 1H), 2.18 (dd, $J = 5.4$, 3.6 Hz, 1H), 2.13 (dd, $J = 5.4$, 3.0 Hz, 1H), 2.10 (dd, $J = 5.4$, 3.0 Hz, 1H), 1.86 (br s, 1H), 1.84 (m, 1H), 1.53 (d, $J = 1.8$ Hz, 1H), 1.52 (d, $J = 2.4$ Hz, 1H), 1.51 (br s, 1H), 1.49 (dd, $J = 4.2$, 2.4 Hz, 1H), 1.44 (m, 2H), 1.24 (d, $J = 7.2$ Hz, 3H), 1.22 (d, $J = 6.6$ Hz, 3H), 1.13 (d, $J = 6.6$ Hz, 3H), 1.10 (br s, 3H), 0.94 (d, $J = 7.2$ Hz, 3H), 0.89 (d, $J = 7.2$ Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 214.6, 174.6, 131.3, 122.7, 100.9, 86.4, 80.8, 71.1, 45.9, 44.1, 34.5, 34.1, 33.8, 32.1, 31.0, 24.2, 20.7, 20.6, 19.2, 18.0, 16.9, 15.4, 10.7; CIHRMS Calcd for [C₂₃H₃₈O₅Na⁺]: 417.2617. Found 417.2613.

(3*S*,4*R*,6*R*)-6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-tetrahydro-2-methyl-2*H*-pyran-3,4-diol (IV-25).

To a CH_2Cl_2 (0.5 mL) solution of ene **IV-24** (10 mg, 0.03 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (10 μL). Crystalline OsO_4 (0.3 mg, 10 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/hexanes (10:40:50). Pure fractions were combined and concentrated to afford diol **IV-25** (8 mg, 0.02 mmol, 70 %) as viscous oil. R_f (90% EtOAc/MeOH) = 0.20; $[\alpha]_{\text{D}}^{26} = -12$ ($c = 0.5$, CH_2Cl_2); IR (thin film, cm^{-1}) 3442, 2928, 2919, 1741, 1711, 1459, 1167, 1080, 989, 734; ^1H NMR (600 MHz, CDCl_3) δ 4.78 (dd, $J = 10.2, 1.8$ Hz, 1H), 4.69 (ddd, $J = 12.0, 7.8, 1.8$ Hz, 1H), 4.10 (dd, $J = 6.6, 3.0$ Hz, 1H), 3.68 (m, 1H), 3.52 (d, $J = 10.8$ Hz, 1H), 3.31 (dd, $J = 10.2, 3.0$ Hz, 1H), 3.11 (ddd, $J = 16.8, 12.6, 1.8$ Hz, 1H), 2.81 (m, 1H), 2.56 (m, 1H), 2.25 (m, 1H), 2.12 (m, 2H), 1.96 (m, 1H), 1.88 (d, $J = 2.4$ Hz, 1H), 1.84 (m, 2H), 1.69 (ddd, $J = 13.8, 10.2, 2.4$ Hz, 1H), 1.55 (br s, 2H), 1.46 (d, $J = 6.0$ Hz, 1H), 1.26 (d, $J = 6.0$ Hz, 3H), 1.21 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 7.2$ Hz, 3H), 1.06 (d, $J = 6.0$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.6, 174.6, 99.4, 86.9, 80.8, 73.0, 69.2, 68.3, 45.9, 44.0, 37.8, 34.5, 34.1, 33.8, 32.1, 29.6, 24.2, 20.6, 19.2, 17.9, 16.9, 15.4, 10.7; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{40}\text{O}_7\text{Na}^+]$: 451.2671. Found 451.2665.

6-(11-hydroxy-12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-2,8-dione)-2-methyl-6H-pyran-3-one (IV-28).

A CH₂Cl₂ (0.1 mL) solution of Boc-enone **IV-27** (17 mg, 0.07 mmol) and 11-hydroxy-10-deoxymethynolide alcohol **IV-26** (20 mg, 0.06 mmol) was cooled to 0 °C. A CH₂Cl₂ (0.1 mL) solution of Pd₂(dba)₃·CHCl₃ (2 mg, 2.5 mol%) and PPh₃ (2 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched with 3 mL of satd. aq. NaHCO₃, extracted (3 x 3 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 35% EtOAc/hexanes to give enone **IV-28** (21 mg, 0.05 mmol, 80%) as viscous oil. *R_f* (50% EtOAc/hexanes) = 0.30; [α]_D²⁶ = +44 (*c* = 0.5, CH₂Cl₂); IR (thin film, cm⁻¹) 3401, 2970, 2936, 1725, 1686, 1458, 1280, 1153, 1082, 977; ¹H NMR (600 MHz, CDCl₃) δ 6.85 (dd, *J* = 10.2, 3.6 Hz, 1H), 5.59 (d, *J* = 16.2 Hz, 1H), 6.32 (d, *J* = 16.2 Hz, 1H), 6.07 (d, *J* = 10.2 Hz, 1H), 5.26 (d, *J* = 3.0 Hz, 1H), 4.79 (dd, *J* = 10.8, 1.8 Hz, 1H), 4.58 (dd, *J* = 13.2, 7.2 Hz, 1H), 3.78 (d, *J* = 10.2 Hz, 1H), 2.74 (m, 1H), 2.57 (m, 1H), 1.95 (ddd, *J* = 16.2, 5.4, 1.8 Hz, 1H), 1.66 (m, 1H), 1.51 (m, 2H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.37 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.25 (m, 2H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 203.6, 196.6, 174.7, 148.8, 142.5,

126.9, 125.4, 95.8, 87.4, 76.5, 74.4, 70.7, 44.9, 42.8, 34.2, 33.8, 21.2, 19.4, 18.1, 17.5, 16.5, 14.9, 10.6; CIHRMS Calcd for $[C_{23}H_{34}O_7Na^+]$: 445.2202. Found 445.2201.

6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-9-ene-2,8-dione)-2-methyl-6H-pyran-3-one.

A CH_2Cl_2 (0.2 mL) solution of Boc-enone (31 mg, 0.14 mmol) and 10-methynolide alcohol (20 mg, 0.07 mmol) was cooled to 0 °C. A CH_2Cl_2 (0.2 mL) solution of $Pd_2(dba)_3 \cdot CHCl_3$ (7 mg, 2.5 mol%) and PPh_3 (7 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 5 hours. The reaction mixture was quenched with 3 mL of satd. aq. $NaHCO_3$, extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% $EtOAc$ /hexanes to give enone (24 mg, 0.06 mmol, 88%) as viscous oil. R_f (50% $EtOAc$ /hexanes) = 0.60; $[\alpha]_D^{26} = -32$ ($c = 0.5$, $MeOH$); IR (thin film, cm^{-1}) 2979, 2949, 1718, 1705, 1458, 1171, 1018, 969; 1H NMR (600 MHz, $CDCl_3$) δ 6.83 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.75 (dd, $J = 16.2, 5.4$ Hz, 1H), 6.42 (dd, $J = 16.2, 1.2$ Hz, 1H), 6.06 (d, $J = 10.2$ Hz, 1H), 5.19 (d, $J = 2.4$ Hz, 1H), 4.79 (ddd, $J = 8.4, 5.4, 2.4$ Hz, 1H), 4.60 (dd, $J = 13.8, 6.6$ Hz, 1H), 3.68 (d, $J = 10.8$ Hz, 1H), 2.77 (m, 1H), 2.63 (m, 1H), 2.54 (m, 1H), 1.71 (m, 3H), 1.57 (m, 2H), 1.36

(d, $J = 6.6$ Hz, 3H), 1.27 (d, $J = 7.2$ Hz, 3H), 1.20 (d, $J = 7.2$ Hz, 3H), 1.11 (d, $J = 6.6$ Hz, 3H), 1.05 (d, $J = 6.0$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 204.5, 196.8, 174.3, 147.0, 142.0, 126.9, 125.7, 95.8, 88.1, 74.0, 70.6, 45.0, 43.7, 37.8, 34.1, 33.5, 25.1, 17.6, 17.5, 16.1, 14.9, 10.2, 9.5; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{34}\text{O}_6\text{Na}^+]$: 429.2253. Found 429.2249.

6-(12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-9-ene-2,8-dione)-2-methyl-3, 6-dihydro-2H-pyran-3-ol.

The enone compound (20 mg, 0.05 mmol) was dissolved in 0.2 mL of CH_2Cl_2 and 0.2 mL MeOH in round bottom flask and cooled -78°C then NaBH_4 (2.0 mg, 0.05 mmol) was added and the reaction mixture was stirred at -78°C for 3 hours and on completion, monitored by TLC, reaction mixture was diluted with ether and was quenched with 2 mL of satd. aq. NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give allylic alcohol (18 mg, 0.04 mmol, 90%) as viscous oil. R_f (50% EtOAc/hexanes) = 0.40; $[\alpha]_{\text{D}}^{26} = -62$ ($c = 0.33$, MeOH); IR (thin film, cm^{-1}) 3470, 2951, 2923, 1725, 1711, 1478, 1179, 1045, 890; ^1H NMR (600 MHz, CDCl_3) δ 6.74 (dd, $J = 15.6, 6.0$ Hz, 1H), 6.42 (d, $J = 15.6$ Hz, 1H),

5.94 (d, $J = 10.2$ Hz, 1H), 5.79 (dd, $J = 10.2, 2.4$ Hz, 1H), 4.97 (m, 1H), 4.12 (dd, $J = 14.4, 7.2$ Hz, 1H), 3.82 (m, 1H), 3.69 (m, 1H), 3.62 (d, $J = 10.8$ Hz, 1H), 2.75 (ddd, $J = 14.4, 10.8, 7.2$ Hz, 1H), 2.63 (dd, $J = 6.6, 6.6$ Hz, 1H), 2.55 (m, 1H), 1.90 (m, 1H), 1.73 (dd, $J = 14.4, 6.6$ Hz, 1H), 1.68 (m, 1H), 1.55 (br s, 2H), 1.33 (dd, $J = 13.8, 4.2$ Hz, 1H), 1.30 (d, $J = 6.0$ Hz, 3H), 1.25 (d, $J = 6.0$ Hz, 3H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.10 (d, $J = 6.6$ Hz, 3H), 1.04 (d, $J = 6.6$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 204.8, 174.6, 146.9, 133.3, 126.1, 125.9, 96.4, 86.4, 73.8, 69.5, 68.4, 68.0, 60.3, 45.0, 43.9, 37.8, 34.2, 33.3, 25.1, 17.6, 16.2, 10.2, 9.5; CIHRMS Calcd for $[\text{C}_{23}\text{H}_{36}\text{O}_6\text{Na}^+]$: 431.2409. Found 431.2405.

References:

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- ¹ Gijssen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443-73..
- ² Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A.; Sharpless, K. B. *Science* **1983**, *220*, 949-951.
- ³ a) Zamoiski, A.; Banaszek, A.; Gryniewicz, G. **1982**, *40*, 1. b) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165-176. c) Grapsas, I., K.; Couladouros, E. A.; Georgiadis, M. P. *Pol. J. Chem.* **1990**, *64*, 823-826.
- ⁴ (a) Johnson, C. R.; Golebiowski, A.; Steensma, D. H.; Scialdone, M. A. *J. Org. Chem.* **1993**, *58*, 7185-7194. (b) Hudlicky, T.; Pitzer, K. K.; Stabile, M. R.; Thorpe, A. J.; Whited, G. M. *J. Org. Chem.* **1996**, *61*, 4151-4153.
- ⁵ a) Timmer, M. S. M.; Adibekian, A.; Seeberger, P. H. *Angew. Chem.* **2005**, *117*, 7777-7780; *Angew. Chem. Int. Ed.* **2005**, *44*, 7605-7607. b) Schmidt, R. R. *Pure Appl. Chem.* **1987**, *59*, 415-424. c) Kirschning, A.; Jesberger, M.; Schöning, K. U. *Synthesis* **2001**, 507-540.
- ⁶ a) Danishefsky, S. J. *Chemtracts* **1989**, 273. For improved catalysis see: b) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403-405.
- ⁷ Henderson, I.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 558-561.
- ⁸ Gijssen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443-73.
- ⁹ Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752-1755.
- ¹⁰ Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 8217-8220.
- ¹¹ Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17-36.
- ¹² (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521-2522. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40-73.
- ¹³ Li, M.; Scott, J. G. and G. A. O'Doherty, *Tetrahedron Lett.* **2004**, *45*, 1005-1009.
- ¹⁴ (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165-176. (b) Grapsas, I., K.; Couladouros, E. A.; Georgiadis, M. P. *Pol. J. Chem.* **1990**, *64*, 823-826. (c) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982-2983. (d) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydrate Res.* **2000**, *328*, 17-36.

-
- ¹⁵ (a) Hooper, D. C.; Wolfson, J. S.; McHugh, G. L.; Winters, M. B.; Swartz, M. N. *Antimicrob. Agents Chemother.* **1982**, *22*, 662-671. (b) Maxwell, A. *Mol. Microbiol.* **1993**, *9*, 681-686. (c) Maxwell, A. *Trends Microbiol.* **1997**, *5*, 102-109. (d) Maxwell, A. *Biochem. Soc. Trans.* **1999**, *27*, 48-53.
- ¹⁶ (a) Tsai, F. T.; Singh, O. M.; Skarzynski, T.; Wonacott, A. J.; Weston, S.; Tucker, A.; Pauptit, R. A.; Breeze, A. L.; Poyser, J. P.; O'Brien, R.; Ladbury, J. E.; Wigley, D. B. *Proteins* **1997**, *28*, 41-52. (b) Lewis, R. J.; Singh, O. M.; Smith, C. V.; Skarzynski, T.; Maxwell, A.; Wonacott, A. J.; Wigley, D. B. *EMBO J.* **1996**, *15*, 1412-1420.
- ¹⁷ (a) Stackman, R.W.; Eckenstein, F.; Frei, B.; Kulhanek, D.; Nowlin, J.; Quinn, J.F.; *Exp Neurol*, **2003**, *184*, 510-520. (b) Goh, L.M.; Barlow, P.J.; Yong, C.S.; *Food Chem*, **2003**, *82*, 275-282.
- ¹⁸ Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428-3429
- ¹⁹ Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406-12408.
- ²⁰ VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973-1976.
- ²¹ Onuma, S.; N., Y.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1091. Nomoto, S.; Shimoyama, A. *Tetrahedron Lett.* **2001**, *42*, 1753-1755.
- ²² (a) Fox, J. J.; Kuwada, Y.; Watanabe, K. A.; Ueda, T.; Whipple, E. B. *Antimicrob. Agents Chemother.* **1964**, 518-529. (b) Watanabe, K. A.; Falco, E. A.; Fox, J. J. *J. Am. Chem. Soc.* **1972**, *94*, 3272-3274.
- ²³ (a) Ennifar, S.; Das, B. C.; Nash, S. M.; Nagarajan, R. *J. Chem. Soc., Chem. Commun.* **1977**, 41-42. For its synthesis, see: (b) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657-9659. (c) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524-2536.
- ²⁴ Harada, S.; Mizuta, E.; Kishi, T. *J. Am. Chem. Soc.* **1978**, *100*, 4895-4897.
- ²⁵ Takahashi, A.; Ikeda, D.; Naganawa, H.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1986**, *39*, 1041-1046.
- ²⁶ (a) Ito, T.; Ohba, K.; Koyama, M.; Sezaki, M.; Tohyama, H.; Shomura, T.; Fukuyasu, H.; Kazuno, Y.; Niwa, T.; Kojima, M.; Niida, T. *J. Antibiot.* **1984**, *37*, 931-934. (b) For its synthesis, see: Buchanan, J. G.; Stoddart, J.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, *11*, 1417-1426.
- ²⁷ (a) Watanabe, K. A.; Matsuda, A.; Itoh, T. *Can. J. Chem.* **1981**, *59*, 468-472. (b) Watanabe, K. A.; Matsuda, A.; Itoh, T. *Can. J. Chem.* **1981**, *59*, 468-72.

-
- ²⁸ (a) Seto, H.; Koyama, M.; Ogino, H.; Tsuruoka, T.; Inouye, S.; Otake, N. *Tetrahedron Lett.* **1983**, 24, 1805-1808. (b) Czernecki, S.; Franco, S.; Horns, S.; Valery, J.-M. *Tetrahedron Lett.* **1996**, 37, 4003-4006.
- ²⁹ Recent Advances in Nucleosides: Chemistry and Chemotherapy; Chu, C. K., Ed.; Elsevier Science: Amsterdam, **2002**.
- ³⁰ (a) Nord, L. D.; Dalley, N. K.; McKernan, P. A.; Robins, R. K. *J. Med. Chem.* **1987**, 30, 1044-54. (b) Zorbach, W. W.; Saeki, S. *J. Org. Chem.* **1964**, 29, 2018-2019.
- ³¹ Groebke, K.; Hunziker, J.; Fraser, W.; Peng, L.; Diederichsen, U.; Zimmermann, K.; Holzner, A.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta.* **1998**, 81, 375-474.
- ³² (a) Leutzinger, E. E.; Meguro, T.; Townsend, L. B.; Shuman, D. A.; Schweizer, M. P.; Stewart, C. M.; Robins, R. K. *J. Org. Chem.* **1972**, 37, 3695-3703. (b) Boehringer, M.; Roth, H. J.; Hunziker, J.; Goebel, M.; Krishnan, R.; Giger, A.; Schweizer, B.; Schreiber, J.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta.* **1992**, 75, 1416-1477.
- ³³ For the Pd-catalyzed *N*-glycosylation of indolocarboazoles, see: Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, 4, 2005-2008.
- ³⁴ While our approach has the flexibility to prepare either D- or L-pyranonucleosides, we targeted the L-enantiomers of both **46** and **47** (i.e., (*ent*)-**46** and (*ent*)-**47**), because of our interest in comparing the antitumor activity of (*ent*)-**46** to **46**.
- ³⁵ The differences in the stability and post-glycosylation modification in the a- and b-benzimidazole glycosides as well as the comparison to the *O*-glycosides are not without precedent. Similar phenomena for anomeric imidazoles have been described as a reverse anomeric effect; see: (a) Randell, K. D.; Johnston, B. D.; Green, D. F. and Pinto, B. M. *J. Org. Chem.* **2000**, 65, 220-226. (b) Vaino, A. R.; Szarek, W. A. *J. Org. Chem.* **2001**, 66, 1097-1102.
- ³⁶ (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, 118, 4492-4493. (b) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, 37, 4841-4844. (c) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, 62, 7507.
- ³⁶ (a) Hooper, D. C.; Wolfson, J. S.; McHugh, G. L.; Winters, M. B.; Swartz, M. N. *Antimicrob. Agents Chemother.* **1982**, 22, 662-671. (b) Maxwell, A. *Mol. Microbiol.* **1993**, 9, 681-686. (c) Maxwell, A. *Trends Microbiol.* **1997**, 5, 102-109. (d) Maxwell, A. *Biochem. Soc. Trans.* **1999**, 27, 48-53.
- ³⁸ (a) Tsai, F. T.; Singh, O. M.; Skarzynski, T.; Wonacott, A. J.; Weston, S.; Tucker, A.; Pauptit, R. A.; Breeze, A. L.; Poyser, J. P.; O'Brien, R.; Ladbury, J. E.; Wigley, D. B.

Proteins **1997**, 28, 41-52. (b) Lewis, R. J.; Singh, O. M.; Smith, C. V.; Skarzynski, T.; Maxwell, A.; Wonacott, A. J.; Wigley, D. B. *EMBO J.* **1996**, 15, 1412-1420.

³⁹ Hanahan, D.; Weinberg, R. A. *Cell* **2000**, 100, 57.

⁴⁰ Gang Shen; Xiao Ming Yu; Brian S. J. Blagg. *Bioorg. Med. Chem. Lett.* **2004**, 14, 5903.

⁴¹ Spencer, C. F.; Rodin, J. O.; Walton, E.; Holly, F. W.; Folkers, K. *J. Am. Chem. Soc.* **1958**, 80, 140.

⁴² Peixoto, C.; Laurin, P.; Klich, M.; Dupuis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Tetrahedron Lett.* **2000**, 41, 1741.

⁴³ Vaterlaus, B. P.; Kiss, J.; Spiegelberg, H. *Helv. Chim. Acta* **1964**, 47, 381.

⁴⁴ X Ming Yu, G Shen, L Neckers, H Blake, J Holzbeierlein, B Cronk, and B S. J. Blagg. *J. Am. Chem. Soc.* **2005**, 127, 12778-12779.

⁴⁵ Burlison, J. A.; Neckers, L. M.; Smith, A.; Maxwell, A.; Blagg,* B. S. J. Novobiocin. Redesigning DNA Gyrase Inhibitors for Selective Inhibition of Hsp90. *J. Am. Chem. Soc.* **2006**, 128, 15529-15536.

⁴⁶ Albermann, C.; Soriano, A.; Jiang, J.; Vollmer, H.; Biggins, J. B.; Barton, W. A.; Lesniak, J.; Nikolov, D. B.; Thorson, J. S. *Org. Lett.* **2003**, 5, 933.

⁴⁷ (a) Griffith, B. R.; Langenhan, J. M.; Thorson, J. S. *Curr. Opin. Biotechnol.* **2005**, 16, 622-630. (b) Langenhan, J. M.; Peters, N. R.; Guzei, I. A.; Hoffman, F. M.; Thorson, J. S. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, 102, 12305-12310. (c) Ahmed, A.; Peters, N. R.; Fitzgerald, M. K.; Watson, J. A., Jr.; Hoffman, F. M.; Thorson, J. S. *J. Am. Chem. Soc.* **2006**, 128, 14224-14225.

⁴⁸ (a) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, 126, 3428-3429. (b) Guppi, S. R.; Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, 8, 293-296. (c) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, 125, 12406-12408.

⁴⁹ (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, 118, 2521-2522. (b) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, 45, 1005-1009. (c) Li, M.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, 45, 6407-6411.

⁵⁰ See ref 11. (a) Babu, R. S.; O'Doherty, G. A. *J. Carb. Chem.* **2005**, 24, 169-177. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, 7, 3921-3924.

⁵¹ For the Luche reduction, see: (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, 100, 2226-2227. (b) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, 3, 401-404.

-
- ⁵² a) Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Ed. Engl.* **1988**, 27, 1697-1699. (b) Unverzagt, C.; Kunz, H. *Bioorg. Med. Chem.* **1994**, 2, 1189-1201. (c) McDonald, F. E.; Danishefsky, S. J. *J. Org. Chem.* **1992**, 57, 7001-7002.
- ⁵³ Kocovsky, P. *Tetrahedron Lett.* **1986**, 27, 5521.
- ⁵⁴ Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, 4, 1771-1774.
- ⁵⁵ Walsh, C. T. *Nature* **2000**, 406, 775-781.
- ⁵⁶ He, H.; Williamson, R. T.; Shen, B.; Graziani, E. I.; Yang, H. Y.; Sakya, S. M.; Petersen, P. J.; Carter, G. T. *J. Am. Chem. Soc.* **2002**, 124, 9729-9736.
- ⁵⁷ (a) Petersen, P. J.; Wang, T. Z.; Dushin, R. G.; Bradford, P. A. *Antimicrob. Agents Chemother.* **2004**, 48, 739-746. (b) Sum, P. E.; How, D.; Torres, N.; Petersen, P. J.; Lenoy, E. B.; Weiss, W. J.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **2003**, 13, 1151-1155. (c) He, H.; Shen, B.; Petersen, P. J.; Weiss, W. J.; Yang, H. Y.; Wang, T.-Z.; Dushin, R. G.; Koehn, F. E.; Carter, G. T. *Bioorg. Med. Chem. Lett.* **2004**, 14, 279-282.
- ⁵⁸ (a) Wang, T.-Z.; Wheless, K. L.; Sutherland, A. G.; Dushin, R. G. *Heterocycles* **2004**, 62, 131-135. (b) Dushin, R. G.; Wang, T. Z.; Sum, P. E.; He, H.; Sutherland, A. G.; Ashcroft, J. S.; Graziani, E. I.; Koehn, F. E.; Bradford, P. A.; Petersen, P. J.; Wheless, K. L.; How, D.; Torres, N.; Lenoy, E. B.; Weiss, W. J.; Lang, S. A.; Projan, S. J.; Shlaes, D. M.; Mansour, T. S. *J. Med. Chem.* **2004**, 47, 3487-3490.
- ⁵⁹ Singh, M. P.; Petersen, P. J.; Weiss, W. J.; Janso, J. E.; Luckman, S. W.; Lenoy, E. B.; Bradford, P. A.; Testa, R. T.; Greenstein, M. *Antimicrob. Agents Chemother.* **2003**, 47, 62-69.
- ⁶⁰ We were mindful of Kahne's discovery of simple disaccharide fragments of vancomycin with significant activity toward vancomycin resistance bacteria, see: Sun, B.; Chen, Z.; Eggert, U. S.; Shaw, S. J.; LaTour, J. V.; Kahne, D. *J. Am. Chem. Soc.* **2001**, 123, 12722-12723.
- ⁶¹ Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, 125, 12406-12407.
- ⁶² (a) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, 126, 3428-3429. (b) Babu, R. S.; O'Doherty, G. A. *J. Carbohydr. Chem.* **2005**, 24, 169-177. (c) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. VI, p 342.
- ⁶³ Presumably, the L,L-diastereomer and the bis-2,3-dideoxy analogues of mannopeptimycin-E would have improved stability.

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- ⁶⁴ Pyranones such as **6** can be prepared in three steps from achiral acylfurans such as **7** in either enantiomeric form (D/L). The pyranone asymmetry is derived from a Noyori reduction; see ref 7 and: Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005-1009
- ⁶⁵ The relative stereochemistry of **3a** and **14a** was determined by analysis of various coupling constants from their ¹H NMR spectra; see the Supporting Information.
- ⁶⁶ We have found *o*-nitrophenylsulfonylhydrazide/triethylamine to be an excellent diimide precursor, ideal for reducing pyrans of this type; see ref 8 and: Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771-1774.
- ⁶⁷ To achieve complete conversion, occasionally the crude reaction mixture may need to be resubjected to the diimide conditions.
- ⁶⁸ Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609-1612.
- ⁶⁹ (a) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428-3429. (b) Babu, R. S.; O'Doherty, G. A. *J. Carbohydr. Chem.* **2005**, *24*, 169-177. (c) Guppi, S. R.; Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 293-296.
- ⁷⁰ de Oliveira, R. N.; Cottier, L.; Sinou, D.; Srivastava, R. M. *Tetrahedron* **2005**, *61*, 8271-8281.
- ⁷¹ (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635-646. (b) Chen, J.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 1281-1283.
- ⁷² (a) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219-1222. (b) Dourtoglou, V.; Ziegler, J.-C.; Gross, B. *Tetrahedron Lett.* **1978**, 1269-1272. (c) Fre'rot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259-270. (d) Carpino, L. A.; El-Fahan, A.; Minor, C. A.; Albericio, F. *J. Chem. Soc., Chem. Commun.* **1994**, 201-203.
- ⁷³ Lin, S.; Yang, Z.-Q.; Kowk, B. H. B.; Koldobskiy, M. A.; Crews, C. M.; Danishefsky, S. J. *J. Chem. Soc., Chem. Commun.* **2004**, 6347-6355.
- ⁷⁴ (a) Rawlings, B. J. *Nat. Prod. Rep.* **2001**, *18*, 190-227. (b) Rawlings, B. J. *ibid.* 231-281. (c) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380-416. (d) Walsh, C. *Antibiotics: Actions, Origins, Resistance*; ASM Press: Washington, D.C., 2003. (e) Weissman, K. J. *Philos. Trans. R. Soc. London, Ser. A* **2004**, *362*, 2671-2690.
- ⁷⁵ Xue, Y.; Zhao, L.; Liu, H.-w.; Sherman, D. H. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12111-12116.

-
- ⁷⁶ D. O'Hagan (1991) The polyketide metabolites, Ellis Horwood, Chichester.
- ⁷⁷ Staunton, J. and Weissman, K.J. Polyketide biosynthesis: a millennium review. *Nat. Prod. Rep.* **2001**, *18*, 380-416.
- ⁷⁸ (a) Me'ndez, C. and Salas, J.A. *Trends Biotechnol.* **2001**, *11*, 449-456. (b) Rix, U., Fischer, C., Remsing, L.L. and Rohr, J. *Nat. Prod. Rep.* **2002**, *19*, 542-580.
- ⁷⁹ (a) Borisova, S. A.; Zhao, L.; Melancüon, C. E., III; Kao, C.-L.; Liu, H.-w. *J. Am. Chem. Soc.* **2004**, *126*, 6534-6535. (b) Borisova, S. A.; Zhao, L.; Sherman, D. H.; Liu, H.-w. *Org. Lett.* **1999**, *1*, 133-136. (c) Kao, C.-L.; Borisova, S. A.; Kim, H. J.; Liu, H.-w. *J. Am. Chem. Soc.* **2006**, *128*, 5606-5607.
- ⁸⁰ (a) Rodriguez, E.; McDaniel, R. *Curr. Opin. Microbiol.* **2001**, *4*, 526-534. (b) Rix, U.; Fischer, C.; Remsing, L. L.; Rohr, J. *Nat. Prod. Rep.* **2002**, *19*, 542-580. (c) Walsh, C.; Freel Meyers, C. L.; Losey, H. C. *J. Med. Chem.* **2003**, *46*, 3425-3436.
- ⁸¹ (a) He, X. M.; Liu, H.-w. *Annu. Rev. Biochem.* **2002**, *71*, 701-754. (b) Johnson, D. A.; Liu, H.-w. *Curr. Opin. Chem. Biol.* **1998**, *2*, 642-649. (c) Liu, H.-w.; Thorson, J. S. *Annu. Rev. Microbiol.* **1994**, *48*, 223-256.
- ⁸² (a) Thorson, J. S.; Hosted, T. J., Jr.; Jiang, J.; Biggins, J. B.; Ahlert, J. *Curr. Org. Chem.* **2001**, *5*, 139-167. (b) Kren, V.; Martí'nkova', L. *Curr. Med. Chem.* **2001**, *8*, 1303-1328. (c) Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99-110.
- ⁸³ (a) Hong, J. S. J.; Park, S. H.; Choi, C. Y.; Sohng, J. K.; Yoon, Y. J. *FEMS Microbiology Letters*, **2004**, *238*, 391-399. (b) see the reference: 7
- ⁸⁴ (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406-12407. (b) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714-8715. (c) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336-1337. (d) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428-3429.
- ⁸⁵ (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521-2522. (b) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005-1009. (c) Li, M.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 6407-6411.
- ⁸⁶ (a) Babu, R. S.; O'Doherty, G. A. *J. Carbohydr. Chem.* **2005**, *24*, 169-177. (b) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005-1009.
- ⁸⁷ Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771-1774.
- ⁸⁸ (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227. (b) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401-404.

⁸⁹ (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493. (b) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841-4844. (c) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507. (d) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771-1774.