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The use of the palladium-catalyzed glycosylation for the synthesis of C- and O-linked glycosylated natural products

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**The Use of the Palladium-catalyzed Glycosylation for the
Synthesis of *C*- and *O*-linked Glycosylated Natural Products**

Xiaomei Yu

**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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2010**

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ABSTRACT

The Use of the Palladium-catalyzed Glycosylation for the Synthesis of C- and O-linked Glycosylated Natural Products

Xiaomei Yu

The carbohydrate portions of natural products play a crucial role in their pharmacological properties. These properties can vary from improved water solubility, improved membrane transport properties, improved tissue targeting, as well as improved target binding. Herein we describe our efforts to use de novo synthesis to help elucidate the various roles carbohydrates play in biologically active glycosylated natural products.

The O'Doherty group has developed a method that uses asymmetric synthesis for the de novo synthesis of carbohydrates. In contrast to traditional carbohydrate methods, this de novo approach builds the desired functionality and stereochemistry within each sugar. This methodology relies on a highly diastereoselective palladium(0)-catalyzed glycosylation reaction to control the stereochemistry at the anomeric center and post-glycosylation transformation to introduce the corresponding functionality in the sugar moiety.

This de novo approach was first used in a highly enantio- and diastereoselective synthesis of Vineomycin C and PI-080. The trisaccharide was made up of three rare sugars, an α -L-aculose, an α -L-rhodinose and a β -D-olivose. The key transformations

include: the palladium-catalyzed glycosylation, Myers' reductive rearrangement, diastereoselective dihydroxylation, and regioselective Mitsunobu inversion. Material from this synthetic effort was used in several biological studies, such as 60-cell line cytotoxicity screens and apoptosis/necrosis mechanism of cell death studies. Significant apoptotic antitumor activity was found for this trisaccharide, which has implication for Vineomycin C and PI-080's structure-activity relationship. To further elucidate the structural activity relationship for this trissacharide, we also prepared the enantiomeric D/D/L-trisaccharide, which is made up of α -D-aculose, α -D-rhodinose and β -L-olivose sugars.

To further study the structure activity relationship of these *C*-aryl glycoside natural products, an effort was undertaken to develop a selective method for the installation of a β -*C*-aryl glycoside bond to an intact di- and tri-saccharides. This began with a de novo synthesis of the disaccharide portion of two new *C*-aryl glycoside natural products, SCH-47554 and SCH-47555. Unfortunately, despite the exhaustive screening of Lewis acid, no method was found for the formation of the desired β -*C*-aryl glycoside bond that did not occur with hydrolysis of the di- and tri-saccharide glycosidic bonds.

In the final chapter, an effort was described that was aimed at the synthesis of hydroxyl-substituted analogues of two biologically important natural products for further glycosylation. The two natural products that were chosen for these studies were the poly-aromatic alkaloids ellipticine and camptothecin. This effort was aimed at trying to improve the water solubility/membrane transport properties of these anticancer

natural products. While the efforts to prepare the required hydroxy-substituted aza-ellipticin failed, a glycosylated camptothecin was prepared. Unfortunately, the acid sensitivity of the glycosylated camptothecin limits its use in biological studies.

DEDICATED TO

My husband, George O'Doherty and my parents, Guohui Yu, Mingying Liu

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List of Abbreviations

Ac	acetyl		-phino)butane
Anal.	Analysis	dr	diastereomeric ratio
Bn	benzyl	ee	enantiomeric excess
Boc	<i>tert</i> -Butyloxycarbonyl	EI	electron impact
bp	boiling point	<i>ent</i>	enantiomer
Bz	benzoyl	equiv	equivalent(s)
calc	calculated	ESI	electrospray ionization
CI	chemical ionization	Et	ethyl
δ	chemical shift (ppm)	EtOAc	ethyl acetate
d	doublet	Et ₂ O	diethyl ether
dba	dibenzylidene acetone	g	gram(s)
DEAD	diethyl azodicarboxylate	h	hour(s)
DIAD	diisopropyl azodicarboxylate	Hex	hexanes
Dibal-H	diisobutylaluminium hydride	HMDS	hexamethyldisilane
DMAP	4-(dimethylamino) pyridine	HPLC	high pressure liquid chromatography
DMF	dimethylformamide	Hz	hertz (cycles per second)
dppb	1,4-bis(diphenylphos	IR	infrared
		<i>J</i>	spin-spin coupling constant

L-selectride	lithium tri-sec-	R _f	ratio to front
	butylborohydride		room temperature
Me	methyl	t	triplet
MHz	megahertz	TBAF	tetrabutylammonium
min	minute(s)		fluoride
mol	mole(s)	TBS	<i>t</i> -butyldimethylsilyl
mmol	millimole(s)	THF	tetrahydrofuran
mp	melting point	TLC	thin layer
NBS	<i>N</i> -Bromosuccinimide		chromatography
NBSH	o-nitrobenzene	TMS	trimethylsilyl
	sulfonylhydrazide	T _f	trifluoromethanesulfonyl
NMR	nuclear magnetic	<i>p</i> -TsOH	<i>para</i> -toluenesulfonic
	resonance		acid
NMO	<i>N</i> -methylmorpholine- <i>N</i> -		
	-oxide		
Ph	phenyl		
PMB	<i>para</i> -methoxybenzyl		
PNBz	<i>para</i> -nitrobenzoyl		
PABz	<i>para</i> -aminobenzoyl		
ppm	parts per million		
py	pyridine		
q	quartet		

Chapter I. De Novo Asymmetric Syntheses of the Carbohydrate Portion of PI080 and Vineomycin C and its Enantiomer ^{*,1}

Two of the more structurally interesting classes of the anthracycline antibiotic are the angucycline and the vineomycins.² Both families of antibiotics have been of particular interest to both the synthetic and biological communities due to their unique structures and potent antitumor and antibacterial activities.³ The structural diversity of these classes of natural products are typified by two different types of glycosylated aglycon ring systems.⁴ Examples of the angucycline aglycones are the natural products WP-3688-2 and SS-22BY,⁵ as well as the urdamycinone aglycon (Figure 1). Of the angucycline aglycons, SS-22BY can be viewed as a dehydrated version of WP-3688-2 and both are oxidized forms of the urdamycinone aglycon. While it is also not an isolated natural product, the vineomycin aglycon is represented by the synthetic Vineomycinone B₂ methyl ester aglycon.⁶ Both types of natural products share the anthraquinone ring system, with the angucycline ring systems having a D-ring annulated.

Figure 1: *The angucycline/vineomycin aglycones*

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The two types of angucycline/vineomycin aglycone ring systems can be related by a D-ring hydrolysis/methanolysis. This is exemplified by the conversion of WP-3688-2 to give the Vineomycin B₂ methyl ester aglycon, which is outlined in Scheme 1. Similarly, the three types of angucycline type of aglycons are related by an oxidative dihydroxylation of the Urdamycinone aglycon to form the WP-3688-2 ring system and a dehydration of WP-3688-2 to form the SS-22BY ring system.

Scheme 1: *Hydrolytic conversion of angucycline to the vineomycin ring systems*

Most of the members of these two classes of natural products are glycosylated at the position ortho to the A-ring phenol (C-6 for vinomycins and C-9 angucyclines). Examples of these monosaccharide C-glycosides are antibiotics Aquayamycin,⁷ Urdamycinone B⁸ and Vineomycinine B₂ (Figure 2).⁹ In addition to having antibiotic properties, Aquayamycin is known to inhibit tyrosine hydroxylase and Vineomycin B₂ has been shown to have antitumor activity. All three of these natural products have succumbed to total synthesis.

Figure 2: *The angucycline/vineomycin monosaccharides*

Outlined in Figure 3 is a list of the structures of the known vineomycin type antibiotics. It is interesting to note that Vineomycin A₁ has the Urdamycinone ring system, which is consistent with the biosynthetic pathway that relates the two ring systems (Scheme 1). This exception to the above classification probably resulted from the fact that the structures were named before the structures were elucidated. Hence the names that were chosen were based on the microbial species from which the natural products were isolated. With the exception of Vineomycin A₁, the various vineomycins vary in degrees of glycosylation, with mono-, di-, and tri-saccharides at the C-6 position via a β -C-glycoside attachment and α -linked O-glycosides on the side chain.

Figure 3: *The vineomycins*

Like the vineomycins, the angucyclines consist of members with varying degrees of glycosylation. With mono-, di-, and trisaccharides at both the C-9 position (via a β -C-glycoside) and at the tertiary alcohol (via an α -O-glycoside).

Figure 4: *Other glycosylated angucycline antibiotics*

Of all these structurally diverse C-glycoside natural products, the O'Doherty group became interested in PI-080 (**1**)¹⁰ and Vineomycin C (**2**).¹¹ Both PI-080¹² and Vineomycin C share a β -C-glycoside link α -L-aculose, α -L-rhodinose (**4**), and β -D-olivose trisaccharide subunit, whereas PI-080 has an additional α -L-aculose-bis- α -L-rhodinose trisaccharide (**3**). In addition to representing a range of structures, the angucycline family of antibiotics possesses a range of biological activities. The antibiotic Vineomycin C displays potent antitumor activity,¹³ whereas PI-080 strongly inhibits blood coagulation.

Figure 5: Structures of PI-080 and vineomycin C

While the antitumor activity of the angucyclines has been attributed to the anthraquinone portion of natural products,¹³ the anticoagulant activity of PI-080 appears to be associated with one of the trisaccharide portions of the molecule (i.e., the trisaccharide **3**). As part of a larger effort to use the *de novo* synthesis of carbohydrates for medicinal chemistry, the O'Doherty group became interested in elucidating the structural origins of the anticancer activity of Vineomycin C. In particular, we were interested in determining whether any of the antitumor activity associated with Vineomycin C could be attributed to the trisaccharide subunit **4** (R = OPMB).

While there is no report of the total synthesis of PI-080 and Vineomycin B2,¹⁴ the synthesis of the trisaccharide portion **3** has been completed by Sulikowski.¹⁵ While the trisaccharide **3** could be obtained from natural sources, access to the trisaccharide subunit **4** (R = OPMB) required synthesis. Recently, the O'Doherty group had some success using a Pd-catalyzed glycosylation and post-glycosylation reactions for the synthesis of several naturally occurring rare sugar structural motifs.¹⁶ In this chapter, my efforts towards the *de novo* synthesis of trisaccharide subunit **4** from commercially available acylfuran will be described, along with its

antiproliferative activity toward 60 tumor cells lines and apoptosis vs necrosis studies cell death mechanism studies.

Scheme 2. Structures of *PI-080* and *vineomycin C* and their trisaccharide motifs **3** and **4**

Retrosynthetically, it was envisioned that the α -L-aculose and α -L-rhodinose subunits of trisaccharide **4** would come from two α -L-pyranones **5**. Similarly, it was conceived the β -D-olivose ring of **4** would come from β -D-pyranone **6** (Scheme 3). Previously, it was shown in the O'Doherty group that the two pyranones could be prepared from the corresponding enantiomeric furyl alcohols, which in turn could be prepared by a Noyori reduction of 2-acylfuran **8** (Scheme 3).^{18,19} The 2-acylfuran is a rather inexpensive commodity chemical used in the food industry (from the Sigma-Aldrich at \$0.07/g for a 10 Kg scale).

Scheme 3: Retrosynthetic analysis of the vineomycin C trisaccharide

Previously, we have shown that the required Pd-glycosyl donors α -L-pyranones **5** and β -D-pyranones **6**, as well as their enantiomers, could be prepared from 2-acetylfuran **8** (Scheme 4). The stereodivergent route employed an enantioselective Noyori reduction (**8** to **7**/*ent*-**7**),^{17,18} an Achmatowicz oxidation and a diastereoselective *t*-butyl carbonate formation (Scheme 4).^{16,19} The β -pyranone **6** could be isolated in 50% yield when the Boc-protection step was performed at elevated temperature ((Boc)₂O/NaOAc in benzene at 80 °C). Alternatively, α -pyranone **5** could be selectively prepared in 62% (α : β = 3:1) yield at low temperature ((Boc)₂O/DMAP in CH₂Cl₂ at -78 °C).

Scheme 4: De novo approach to D/L-, α / β -Boc-pyranones **5** and **6**

With a practical route to the desired pyranone glycosyl donors, we next turned our attention toward the preparation of 2-deoxy- β -L-olivose ring of the trisaccharide **4**. Previously, we reported an approach to 2-deoxy- β -glycoside associated with *allo*- and *gluco*-stereochemistry.^{16,20} Key to the successful implementation of this strategy is the selective Mitsunobu-like inversion of the *allo*-stereochemistry of the digitoxose sugar **12** into olivose sugar **13** (Scheme 5).

Scheme 5: *Synthesis of a protected β -D-olivose 13*

In practice, we began with the palladium-catalyzed glycosylation (5 mol% $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 / 10\% \text{PPh}_3$)[†] of PMBOH with the β -D-pyranone **6** to form the β -benzyloxy pyranone **9** in 95% yield as a single diastereomer (Scheme 4). Ketone reduction of pyranone **9** with $\text{NaBH}_4/\text{CeCl}_3$ gave a mixture of allylic alcohols **10a/b** in 99% yield (dr ~ 1.5 to 1). Fortunately, both diastereomers **10a/b** could be used in the next reaction. Applying the Myers' reductive rearrangement conditions (NBSH, PPh_3/DEAD , NMM, -30°C to rt)²¹ to the mixture of

[†] To save space in the schemes these typical palladium glycosylation conditions (5 mol% $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 / 10\% \text{PPh}_3$) will be referred to as (5 mol% Pd(0)/2PPh_3) to indicate the percentage of catalyst used in a 1:2 Pd/Ligand ratio.

allylic alcohols **10a/b** cleanly provided olefin **11** in 95% yield. Finally, exposing olefin **11** to the Upjohn conditions (OsO_4/NMO)²² gave exclusively the diol **12** with *allo*-stereochemistry in 85% yield. We then turned to our selective diol inversion, subjecting **12** to the typical Mitsunobu conditions (*p*- $\text{NO}_2\text{PhCO}_2\text{H}/\text{PPh}_3/\text{DIAD}$) cleanly converted it into the protected β -D-olivose **13** in 70% yield. A nice feature of this approach is that the nitrobenzoate group also serves as a temporary protecting group.

Scheme 6: *Synthesis of a β -D-olivose/ α -L-rhodinose disaccharide **17***

With a viable route to the protected β -D-*olivo*-sugar **13** in hand, our efforts turned to the installation of the α -L-rhodinose portion (Scheme 5). The *olivo*-sugar **13** and α -L-pyranone **5** were coupled using our typical palladium-catalyzed glycosylation conditions (5 mol% $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3/10\%$ PPh_3 , 98% yield) to form **14** with complete stereocontrol at the anomeric center. Luche reduction of the keto-group in pyranone **14** stereoselectively provided allylic alcohol **15** (97%). At this stage, a Mitsunobu reaction ($\text{PPh}_3/\text{DIAD}/p\text{-NO}_2\text{PhCO}_2\text{H}$, 74%) was used to afford bis-nitrobenzoate **16** with inverted stereochemistry at C-4. Unfortunately, all

efforts to differentiate the two *p*-nitrobenzoate groups in **16** were unsuccessful. As a result, we opted for hydrolyses of both benzoates with excess LiOH which afford diol **17** (80%) and then turned to the selective introduction of the α -L-aulose at *C*-4.

Scheme 7: *Synthesis of the vineomycin C/PI-080 trisaccharide 19*

Our investigations of the selective introduction of the α -L-aulose at *C*-4 were performed on both diol **17** and diol **18** (Scheme 7), which could easily be prepared by hydrogenation with excess diimide (NBSH/Et₃N, 80%). The Pd-catalyzed glycosylation (5 mol% Pd₂(dba)₃•CHCl₃/10% PPh₃) of alcohol **18** with α -L-pyranone **5** proved to be the better selective method. This was most conveniently performed at low conversion using a slight excess of α -L-pyranone **5** under dilute condition to provide 35% yield of the desired trisaccharide **19**, along with 61% recovered starting material **18** (89% yield, based on recovered starting material). To confirm the regioselectivity of glycosylation, **19** was acylated with Ac₂O/DMAP to form **20**

(82%). Analysis of the one and two-dimensional NMR data of acetate **20** indicated that the glycosylation of **18** occurred selectively at the C-4 position of the α -L-rhodinose sugar. Overall, the trisaccharide **19** was prepared from the achiral 2-acylfuran **8** in 14 steps and 17% overall yield.

Figure 6: Proof of the regioselective glycosylation by NMR structural assignment of **20**

With significant quantities of trisaccharide **19** in hand, we decided to screen it against two types of cancer cell lines from nine different tissue types (Table 1). While we were motivated to test **19** primarily as a control experiment for future studies, we were delighted to find it had wide-ranging cytotoxicity, displaying significant growth inhibition (GI₅₀ from 0.1 to 11 μ M) and cytotoxicity (LC₅₀ from 5.1 to 100 μ M) against these various cell lines. Indeed, at 50 μ M, the trisaccharide **19** showed greater cytotoxicity against NCI-H460 Non-Small Cell Lung cancer cells than Cisplatin at 300 μ M (Figure 7). Interestingly, this level of cytotoxicity is in the range of that found for other glycosylated angucycline antibiotics.²³ Outlined in Tables 2-10 are the results from the screening against the panel of the NCI's 60 cancer cell lines for the same tissue types. While good to moderate GI₅₀ (1 to 20 μ M) values were found across the board,

significant variation was found for the LC₅₀ values (5 to >100 nM).

Table 1: *Comparitive cytotoxicity evaluation of trisaccharide 19 across the cell lines*

<i>cell type</i>	<i>panel/cell line</i>	<u>19 (μM)</u>		
		GI₅₀	TGI	LC₅₀
Leukemia	RPMI-8226	0.12	2.80	> 100
	SR	0.60	19.0	> 100
Non-Small Cell Lung	NCI-H23	1.98	4.59	12.0
	NCI-H460	11.0	23.7	51.0
Colon	COLO-205	1.66	3.02	5.50
	SW-620	1.35	2.64	5.13
CNS	SF-268	3.09	9.54	31.5
	U251	1.82	4.10	9.26
Melanoma	LOX IMVI	1.53	2.87	5.40
	SK-MEL-28	1.82	3.22	5.71
Ovarian	IGROV1	1.62	3.32	6.81
	OVCAR-3	1.60	2.95	5.43
Renal	TK-10	2.32	6.46	23.1
	UO-31	1.49	2.81	5.30
Prostate	PC-3	1.74	3.99	9.16
	DU-145	1.81	3.20	5.66
Breast	MCF7	1.63	3.38	7.04
	T-47D	1.42	2.77	54.1

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

Of all nine tissue types from the NCI panel of 60 cell lines, the trisaccharide **19** showed the worst potency against the leukemia cell line types. While this poor activity was not so obvious from the GI₅₀ growth inhibitory concentrations (ranging from 0.12 μ M to 7.6 μ M), the trend was most clear in the values of LC₅₀ (> 100 μ M). The complete leukemia cell line data for trisaccharide **19** is outlined in Table 2.

Table 2: *Leukemia cell cytotoxicity evaluation of trisaccharide 19*

Leukemia cell type	panel/cell line	<u>19 (μM)</u>		
		GI₅₀	TGI	LC₅₀
	CCRF-CEM	0.30	> 100	> 100
	HL-60(TB)	0.65	> 100	> 100
	K-562	7.6	> 100	> 100
	MOLT-4	4.8	> 100	> 100
	RPMI-8226	0.12	2.80	> 100
	SR	0.60	19.0	> 100

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

The trisaccharide **19** showed much better potency against the Non-Small Cell Lung cancer cell line than the leukemia cell line. The best activities came against the NCI-H23 (GI₅₀ = 1.98 μ M and LC₅₀ = 12.0 μ M) and NCI-H522 (GI₅₀ = 1.10 μ M and LC₅₀ = 5.41 μ M) cell lines and the poorest activity came against the A459/ATCC (GI₅₀ = 16.9 μ M and LC₅₀ = 60.8 μ M) and HOP-62 (GI₅₀ = 20.6 μ M and LC₅₀ = 61.7 μ M) cell lines. The complete Non-Small Cell Lung (NSCL) cell line data for trisaccharide **19** is outlined in Table 3.

Table 3: NSCL cancer cell cytotoxicity evaluation of trisaccharide **19**

Non-Small Cell Lung <i>cell type</i>	<i>panel/cell line</i>	<u>19 (μM)</u>		
		GI₅₀	TGI	LC₅₀
	A459/ATCC	16.9	32.0	60.8
	HOP-62	20.6	35.6	61.7
	HOP-92	1.58	4.44	19.1
	NCI-H226	13.7	26.6	51.6
	NCI-H23	1.98	4.59	12.0
	NCI-H322M	16.2	30.1	56.0
	NCI-H460	11.0	23.7	51.0
	NCI-H522	1.10	2.44	5.41

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

The trisaccharide **19** showed excellent potency across the board against the colon cancer cell lines, with only the HC-2998 cell line showing LC₅₀ values above 10 μ M. All the other cell lines had GI₅₀ values between 1-2 μ M concentrations and LC₅₀ values between 5-7 μ M concentrations. The complete colon cancer cell line data for trisaccharide **19** is outlined in Table 4.

Table 4: Colon Cancer cell cytotoxicity evaluation of trisaccharide **19**

Colon Cancer cell type	panel/cell line	19 (μM)		
		GI₅₀	TGI	LC₅₀
	COLO-205	1.66	3.02	5.50
	HC-2998	3.56	11.8	34.4
	HCT-116	1.18	2.53	5.46
	HCT-15	1.50	3.04	6.15
	HT29	1.53	2.86	5.46
	KM12	1.67	3.30	6.55
	SW-620	1.35	2.64	5.13

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

The trisaccharide **19** showed lesser potency against the panel of central nervous system cancer cell lines than the colon cell lines. The best inhibitory activities came against the U251 ($\text{GI}_{50} = 1.82 \mu\text{M}$ and $\text{LC}_{50} = 9.26 \mu\text{M}$) and the poorest activity came against the SF295 ($\text{GI}_{50} = 13.7 \mu\text{M}$ and $\text{LC}_{50} = 54.7 \mu\text{M}$) cell lines. The complete central nervous system (CNS) cell line data for trisaccharide **19** is outlined in Table 5.

Table 5: CNS Cancer cell cytotoxicity evaluation of trisaccharide **19**

CNS <i>cell type</i>	<i>panel/cell line</i>	<u>19 (μM)</u>		
		GI₅₀	TGI	LC₅₀
	SF-268	3.09	9.54	31.5
	SF295	13.7	27.4	54.7
	SF-539	3.33	13.7	37.1
	SNB-19	12.2	24.6	49.6
	SNB-75	1.11	12.2	34.9
	U251	1.82	4.10	9.26

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

The trisaccharide **19** showed lesser potency against the panel of Melanoma cancer cell lines than the CNS cell lines. The best inhibitory activities came against the LOXIMVI (GI₅₀ = 1.53 μ M and LC₅₀ = 5.40 μ M) and SK-MEL-28 (GI₅₀ = 1.82 μ M and LC₅₀ = 5.71 μ M), with the poorest activity came against the UACC-257 (GI₅₀ = 13.9 μ M and LC₅₀ = 53.8 μ M) cell lines. The complete melanoma cancer cell line data for trisaccharide **19** is outlined in Table 6.

Table 6: *Melanoma Cancer cell cytotoxicity evaluation of trisaccharide 19*

Melanoma cell type	panel/cell line	<u>19 (μM)</u>		
		GI ₅₀	TGI	LC ₅₀
	LOX IMVI	1.53	2.87	5.40
	MALME-3M	2.0	5.23	20.9
	M14	2.74	10.9	33.0
	SK-MEL-2	2.58	6.97	24.5
	SK-MEL-28	1.82	3.22	5.71
	SK-MEL-5	8.19	20.6	45.4
	UACC-257	13.9	27.3	53.8
	UACC-62	3.89	14.4	38.0

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

The trisaccharide **19** showed the best across the board potency against the panel of ovarian cancer cell lines, with all but the OVCAR-4 and OVACR-8 LC₅₀ values being below 10 μM . The best activities were for the OVACR-3 (GI₅₀ = 1.60 μM and LC₅₀ = 5.43 μM) and SK-OV-3 (GI₅₀ = 1.60 μM and LC₅₀ = 5.43 μM), with the poorest activity against the OVACR-4 (GI₅₀ = 1.80 μM and LC₅₀ = 28.5 μM) and OVACR-8 (GI₅₀ = 3.08 μM and LC₅₀ = 33.8 μM) cell lines. The complete ovarian cancer cell line data for trisaccharide **19** is outlined in Table 7.

Table 7: Ovarian Cancer cell cytotoxicity evaluation of trisaccharide **19**

Ovarian Cancer <i>cell type</i>	<i>panel/cell line</i>	<u>19 (μM)</u>		
		GI₅₀	TGI	LC₅₀
	IGROV1	1.62	3.32	6.81
	OVCAR-3	1.60	2.95	5.43
	OVCAR-4	1.80	7.83	28.5
	OVCAR-5	1.89	3.73	7.38
	OVACR-8	3.08	11.2	33.8
	SK-OV-3	1.60	2.95	5.43

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

The trisaccharide **19** showed variable potency against the panel of renal cancer cell lines, with LC₅₀ values ranging from 10 μ M to 51.5 μ M. The best activities were for the UO-31 (GI₅₀ = 1.49 μ M and LC₅₀ = 5.30 μ M), with the poorest activity against the 786-0 (GI₅₀ = 5.10 μ M and LC₅₀ = 40.6 μ M) and A498 (GI₅₀ = 1.37 μ M and LC₅₀ = 51.5 μ M) cell lines. The complete Renal cancer cell line data for trisaccharide **19** is outlined in Table 8.

Table 8: Renal Cancer cell cytotoxicity evaluation of trisaccharide **19**

Renal Cancer cell type	panel/cell line	19 (μM)		
		GI₅₀	TGI	LC₅₀
	786-0	5.10	16.5	40.6
	A498	1.37	2.66	51.5
	ACHN	1.83	3.92	8.39
	CAKI-1	1.97	5.98	22.3
	RXF-393	1.53	3.44	7.74
	SN12C	1.94	4.53	11.5
	TK-10	2.30	6.46	23.1
	UO-31	1.49	2.81	5.30

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

Although it only contains two cell lines, the trisaccharide **19** showed excellent potency against the panel of prostate cancer cell lines, with LC₅₀ values below 10 μM . The best inhibitory activities were found for the DU-145 (GI₅₀ = 1.81 μM and LC₅₀ = 5.66 μM) cell lines, with the excellent although lower activity against the PC-3 (GI₅₀ = 1.74 μM and LC₅₀ = 9.16 μM) cell lines. The complete prostate cancer cell line data for trisaccharide **19** is outlined in Table 9.

Table 9: Prostate Cancer cell cytotoxicity evaluation of trisaccharide **19**

Prostate Cancer <i>cell type</i>	<i>panel/cell line</i>	19 (μM)		
		GI₅₀	TGI	LC₅₀
	PC-3	1.74	3.99	9.16
	DU-145	1.81	3.20	5.66

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

The trisaccharide **19** showed the most variable potency against the panel of breast cancer cell lines, with LC₅₀ values ranging from 5 μM to > 100 μM . The best activities were for the MDA-MB-468 (GI₅₀ = 1.24 μM and LC₅₀ = 4.99 μM), with the poorest activity against the NCI/ADR-RES (GI₅₀ = 2.53 μM and LC₅₀ > 100 μM) and HS 578T (GI₅₀ = 2.51 μM and LC₅₀ > 100 μM) cell lines. The complete breast cancer cell line data for trisaccharide **19** is outlined in Table 10.

Table 10: Breast Cancer cell cytotoxicity evaluation of trisaccharide **19**

Breast Cancer <i>cell type</i>	<i>panel/cell line</i>	19 (μM)		
		GI ₅₀	TGI	LC ₅₀
	MCF7	1.63	3.38	7.04
	NCI/ADR-RES	2.53	6.61	>100
	MDA-MB-231/ATCC	2.61	7.26	25.5
	HS 578T	2.51	8.0	>100
	MDA-MB-435	3.74	15.1	39.7
	BT-549	10.9	23.3	49.6
	T-47D	1.42	2.77	54.1
	MDA-MB-468	1.24	2.49	4.99

GI₅₀: the drug concentration resulting in a 50% reduction in the net protein increase in control cells.

TGI: the drug concentration resulting in no increase in the measured protein as compared to control cells.

LC₅₀: the drug concentration resulting in a 50% reduction in the measured protein as compared to control cells.

We decided to further study the mechanism of cytotoxicity of **19** towards human H460 lung epithelial cancer cells (Figure 7). H460 human lung epithelial cells were treated with trisaccharide **19** at a range of concentrations (50, 100 and 200 μ M) and compared to Cisplatin at 300 μ M as a control. To ascertain the mechanism of cell death (Figure 8), the samples were then stained with two dyes, propidium iodide (PI, 30 mg/ml) and 1 μ g/ml Hoechst (HT, 1 mg/ml). Apoptotic cells appeared shrunken with condensed nuclei and stain only with Hoechst, whereas cells that have undergone apoptosis-dependent or apoptosis-independent necrosis stained with both PI and Hoechst. By comparing these staining differences, the level of total cell death and percent cell death by apoptosis can be determined.

Figure 7: Cytotoxicity of **19**/Cisplatin towards H460

Graph denotes total cell death (apoptosis+necrosis) observed upon treatment of H460 cells with either no drug (NTX), 300 uM cisplatin (CP300), 50 uM of **19** (PI-50), 100 uM of **19** (PI-100), 200 uM of **19** (PI-200).

At 50 μ M of trisaccharide **19**, the H460 cells stained mainly for Hoechst and displayed condensed nuclear bodies without significant uptake of propidium iodide, suggesting that cell death was due primarily to apoptosis. However, at higher concentrations of **19** (100 μ M and 200 μ M), cell death predominantly occurred via necrosis, which was indicated by PI staining without nuclear bodies.

Figure 8: *Mechanism of cell death apoptosis/necrosis*

H460 lung epithelial cancer cells were treated with either Cisplatin (300 μ M) or **19** (50, 100 and 200 μ M) for 8 h in serum free medium, following which each well was incubated in 30 μ g/ml propidium iodide (PI) and 1 μ g/ml Hoechst (HT) for 30 min.

Images show cells stained for Hoechst alone (top panel, blue), PI alone (middle panel, red), or both.

In summary, a practical route to vineomycin C/PI-080 trisaccharide **19** has been developed. This route provided significant amounts of material for biological testing. The trisaccharide **19** was shown to suppress the proliferation of several human cancer cell lines via an apoptotic mechanism at 50 μ M. Although it should be noted that when **19** was tested at higher concentrations (100 and 200 μ M) a significant amount of necrosis was also detected. This synthetic/biological study establishes for the first time the importance of the trisaccharide portion to the SAR to these molecules. To gain a better understanding of how the 3-D structure of **19** relates to its biological activity, we decided to synthesize and test the (L,L,D)-enantiomer of **19** (Figure 9), which we believed would allow us to determine if the cytotoxicity toward the cancer

cells were due to specific interactions with **19** or the general toxicity of various functional groups like pyranones and/or PMB-ethers.

Figure 9: The (D,D,L)-trisaccharide **19** and the (L,L,D)-trisaccharide *ent*-**19**

Retrosynthetically, *ent*-**19** was envisioned as coming from two units of *ent*-**5**(α -D) and one unit of *ent*-**6**(β -L). Thus, by an identical process as described above, *ent*-**6**(β -L) can be converted into *ent*-**13**, which can be coupled with *ent*-**5**(α -D) to form *ent*-**18**. Finally, *ent*-**18** can be coupled with *ent*-**5**(α -D) to give *ent*-**19**, the (L,L,D)-enantiomer of trisaccharide **19**.

Scheme 8: Retrosynthesis the enantiomer of trisaccharide *ent*-**19**

In practice, the synthesis of the enantiomeric series began with the glycosylation of PMBOH with **ent-6** to give **ent-9** (99% yield). The Luche reduction of **ent-9** gave a good yield of a mixture of allylic alcohols **ent-10a/b** (99% yield). The mixture of diastereomeric alcohols **ent-10a/b** were reductively rearranged using the Myer's procedure to give alcohols **ent-11** (99% yield). UpJohn dihydroxylation of **ent-11** cleanly gave diol **ent-12** (86% yield). Finally the L-olivose sugar **ent-13** was prepared by the regioselective Mitsunobu inversion of diol **ent-12** (70% yield).

Scheme 9: Retrosynthesis the enantiomer of monosaccharide **ent-13**

Similarly, the synthesis of the of D,L-disaccharide **ent-18** began with the glycosylation of **ent-13** with **ent-6** (87% yield). The Luche reduction of **ent-14** gave the allylic alcohols **ent-15** (97% yield). Mitsunobu inversion of **ent-15** with *p*-nitrobenzoic acid gave the bis-nitrobenzoate **ent-16** (74% yield). The two esters were hydrolyzed with excess LiOH (80%) and the double bond was hydrogenated with excess diimide (NBSH/Et₃N) to give the D,L-disaccharide **ent-18**.

Scheme 10: Retrosynthesis the enantiomer of D,L-disaccharide **ent-18**

Finally the disaccharide **ent-18** was regioselectively glycosylated with **ent-5**(α -D) at low conversion to give 40% of the desired trisaccharide **ent-19** along with 50% recovered starting material. Material from this synthesis was sent to NCI for evaluation in their 60 cell line screen.

Scheme 11: Retrosynthesis the enantiomer of trisaccharide **ent-19**

In conclusion, a highly enantioselective *de novo* route to vineomycin C/PI-080 trisaccharide **19** and its enantiomer (*ent*-**19**) has been achieved. The trisaccharide **19** was extensively studied as an anti-cancer agent as well as mechanism of action studies. These studies demonstrated **19**'s ability to suppress the proliferation of several human cancer cell lines via an apoptotic mechanism at 50 μ M, which demonstrated for the first time that the sugar portion of these type of natural products can contribute to its anti-cancer activity. It should be noted that when **19** was tested at higher concentrations (100 and 200 μ M), a significant amount of necrosis was also detected, which may suggest its cancer cell toxicity may occur via multiple modes of action. To further explore the mechanism of action a synthesis of *ent*-**19** was undertaken. The synthesis of the *ent*-**19** was also completed and samples were submitted to NCI for biological evaluation. The preparation of the other diastereomers and further biological investigation are ongoing.

Chapter II. Application of De Novo Synthesis Towards the Synthesis of

C-Aryl Glycoside Natural Products

Building on the successful synthesis of the trisaccharide portion of PI-080/Vineomycin C, we decided to next try to explore new methods for installing the *C*-Aryl glycoside portion of PI-080 and Vineomycin C. This was initially envisioned as being a model study, however, it was hoped that these efforts would eventually lead to the first synthesis of Vineomycin C. At the outset, we were aware of the successful syntheses of Vineomycinone B2 methyl ester by others and believed that our previously described methodology could be used to install the remaining two sugars (Scheme 12).⁶⁻⁹ Instead, we decided to focus on trying to develop a method for constructing the crucial β -linked glycosidic bond between the fully constructed trisaccharide and the aglycon.

Scheme 12: Retrosynthetic analysis for vineomycin C

This approach, if successful, in addition to being more efficient due to convergency, would also be more amenable for the synthesis of a larger range of natural products from this family (e.g., both Vineomycin C and PI-080).^{10,11} As outlined in Scheme 13, we envisioned direct coupling of the Vineomycin C/PI-080 trisaccharide **21** with an anomeric leaving group,

with a suitably protected aglycon **22**. We imagined this step would be promoted by a Lewis acid. The exact nature of the right Lewis acid and protecting groups would need to be explored, but there were significant precedents from the syntheses of Vineomycinone B2 methyl ester that we thought we could build upon.^{6,9}

Scheme 13: *Retrosynthetic analysis for vineomycin C*

By a related route, the syntheses of more complicated angucycline structures could also be accomplished (Schemes 14 and 15). Our synthesis of PI-080 was imagined as being completed by an annulation of the naphthalene trisaccharide **23** with **24**. In turn, **23** was envisioned as coming from the above described convergent glycosylation between trisaccharide **25** and naphthalene **26**. Similarly, the slightly simpler angucycline natural products SCH-47554 and SCH-47555²⁴ could be derived by an annulative coupling of the naphthalene disaccharide **27** with **24**, where once again the disaccharide **27** was seen as coming from a Lewis acid mediated coupling between **26** and a disaccharide **28**. Recently a route to a molecule similar to disaccharide **27** was reported by Barrett.²⁵ The Barrett route prepared its disaccharide in 21 total steps from D-glucose and L-rhamnose. Thus as a goal we set out to try to prepare a similar disaccharide to **27** via our de novo methodology in significantly less steps from 2-acylfuran.

Scheme 14: Retrosynthetic analysis for PI-080

For simplicity sake, we decided to focus our methodology on the development of this latter coupling reaction between **26** and **28** (Scheme 15). Because we already had access to trisaccharide **19**, the investigation of the coupling between **25** and **26** was also planned. In addition to the development of a new more convergent coupling strategy, it was also imagined that materials from these studies would lead to important SAR studies of the biological activity of the vineomycin and PI-080 type natural products.

Scheme 15: Retrosynthetic analysis for SCH-47554 and SCH-7555

Our first synthetic target became the known bromonaphthalene **33**, which we hoped can be prepared by a benzyne Diels-Alder reaction/acid catalyzed ring opening reaction sequence (Scheme 16).^{25,26} While **33** was known in the literature, the literature synthesis was reported to occur via an unselective bromination of juvalone.²⁷

Scheme 16: Synthesis of key Bromoanthracene coupling partner

We decided to explore the route outlined in Scheme 16. This was accomplished by treating 2,5-dibromo-1,4-dimethoxybenzene **31** with LDA followed by furan at $-78\text{ }^{\circ}\text{C}$, which led to the formation of Diels-Alder adduct **32** in a near quantitative. Acid-catalyzed rearrangement of **32** cleanly gave **33** in an excellent yield (94%). Key to the success of this strategy was the ability of the bromine atom to direct the furan ring opening reaction. There had been precedent in the literature of methoxy-groups and fluorides but not bromines.

Scheme 17: *Synthesis of the D-amiceto-sugar of the desired disaccharide 38*

We next turned to the synthesis of the desired D,L-disaccharide **38**, with a pivaloate ester as the anomeric leaving group (Scheme 17). We initially looked into using a *t*-butyl carbonate as the anomeric leaving group but it proved to be too unstable. Because we were concerned about the potential instability of the pyranone ring system to the proposed Lewis acid β -C-glycoside forming conditions, we also planned on making the allylic acetate **39**, which in turn can be deprotected and oxidized to the pyranone.

The synthesis of **38** began with the synthesis of α -pyranone **35**. As before, the Achmatowicz oxidation of (*ent*)-**7** formed hemi-acetal **34** as a mixture of diastereomers (Scheme 17), which was diastereoselectively acylated with pivaloyl chloride to give **35** (82% yield).

Luche reduction ($\text{NaBH}_4/\text{CeCl}_3$) of pyranone **35** diastereoselectively gave allylic alcohol **36** (68% yield), which was followed by a diimide reduction (excess NBSH/ Et_3N) of the pyran double bond to give **37** (80%). Our investigation into a cobalt catalyzed one-pot concomitant 1,4-/1,2-reduction of the enone of **35** to the equatorial alcohol of **37** led only to decomposition.

Scheme 18: *Synthesis of the D,L-disaccharides 38 and 39*

We returned to the palladium glycosylation condition to install the L-sugar of the desired disaccharides **38** and **39** (Scheme 18). Exposure of **37** to a slight excess of Boc-pyranone **5(α-L)** and Pd-catalysis (2.5% $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ /10% PPh_3) gave good yield of **38** (70% yield). Finally, another Luche reduction ($\text{NaBH}_4/\text{CeCl}_3$) of pyranone **38** followed by acylation ($\text{Ac}_2\text{O}/\text{DMAP}$) gave the backup disaccharide **39** in 70% for the two steps.

Scheme 19: Attempted Lewis coupling of **38** and **39** with **33**

With the model naphthanol **33** and the two D,L-diassacharides **38** and **39** in hand, we explored the use of various Lewis acid (TiCl_4 , $\text{Ti}(\text{Oi-Pr})_4$, SiCl_4 , BF_3 , and TMSOTf) to promote coupling (Scheme 19). Unfortunately, all the Lewis acids used for the coupling of **33** and the D,L-diassacharides **38** led to decomposition of the disaccharide **38**. Similarly, when the D,L-diassacharides **39** was used, the only coupling products detected were of mono-saccharides with **33**.

Despite these frustrations, we decided to go ahead and explore the coupling of **33** with the vineomycin trisaccharide **19** (Scheme 20). In an attempt to address the problems associated with the instability of the glycosidic bonds to the harsh Lewis acid conditions that are required for the coupling reactions, we decided to first preassociate the two coupling partners via an *O*-glycoside bond (**44**) and pursue condition for migration of the trisaccharide from oxygen to carbon (**44** to **45**), which we hoped would allow for the use of milder Lewis acids.

Scheme 20: *Synthesis of the vineomycin C/PI-080 trisaccharide **43** coupling partner*

To prepare the trisaccharide **19** for the coupling reaction, we first protected the C-3 olivose sugar alcohol as an acetate and deprotected the C-1 OPMB group. This was accomplished by using acetic anhydride and DMAP to give **20** (82%). To our surprise the deprotection of the anomeric PMB group with ceric ammonium nitrate occurred with concomitant acetate deprotection. Fortunately, this problem was easily solved by switching to DDQ condition. These modified conditions led to clean conversion of **20** to **43** (82%) as a mixture of anomeric isomers.

With **43** in hand, we turned our attention to its coupling with **33** to initially form the *O*-glycoside **44**, and eventually its conversion to the desired *C*-glycoside **45**.²⁸ The efforts to assemble the bond began with the attempts to in situ convert the anomeric alcohol to a good

leaving group (tosylate) followed by an S_N2 type displacement with the phenoxide anion from **33**. While we attempted with several bases (Py, Et₃N, NaH, KO^t-Bu), unfortunately no desired product was detected. In contrast, the desired *O*-glycoside **44** was formed as a mixture of anomeric diastereomers in good yield when we turned to typical Mitsunobu conditions (PPh₃/DIAD). Unfortunately, all attempts to use Lewis acids to isomerize the *O*-glycoside **44** into the desired β -link *C*-glycoside led to either no reaction or decomposition of **44**.

Scheme 21: Attempted coupling of **33** with **43**

In conclusion, a new synthesis of the disaccharide portion of the *C*-aryl glycoside natural products SCH-47554 and SCH-47555 was accomplished. In addition, two methods were explored for the Lewis acid directed formation of β -linked *C*-aryl di- and tri-saccharides. The

first was the direct Lewis acid coupling and the second was the Lewis acid promoted migration of *O*- to *C*-glycosides. Unfortunately neither method led to the desired product. It is worth noting that if we were successful in our coupling strategy to make disaccharide **40** we would have achieved our goal to beat the Barrett route by 11 steps (10 vs 21 total steps). Future efforts will focus on the use of other aromatic rings in the Lewis acid promoted migration of *O*- to *C*-glycosides.

Chapter III. Attempted Synthesis of Glycosylated Poly-Aromatic Natural Products

In contrast to the focus of the previous chapters, the focus of this chapter is the development of a new method for installing natural and unnatural sugars onto known poly-aromatic natural products. In the previous chapters, we demonstrated that the sugar portion of glycosylated natural products can also be part of the natural product's pharmacophore, as opposed to a water solubility enhancer. Returning to this previously believed mantra, we imagined installing sugars onto relatively insoluble natural products to improve its solubility. In addition, we hoped that this would improve the overall activity. The biologically active natural products we chose for these efforts were ellipticines²⁹ and camptothecins³⁰ (Figure 10).

Figure 10: *Ellipticine and related compounds*

Both ellipticines and camptothecins are angular, albeit flat poly-aromatic alkaloids that contain a pyridine ring.^{31,32} The structural similarity also shows up in their biological mechanism of action. Both natural products intercalate into DNA and have basic groups that hydrogen bond to DNA. This DNA binding causes the inhibition of the DNA-repair enzymes, topoisomerase I or topoisomerase II.^{29,30,33} Inhibition of topoisomerase I and topoisomerase II has been linked to selective toxicity to various cancer cells, and could possibly lead to a new treatment for cancer.

While neither ellipticine nor camptothecin has become an approved drug, two related camptothecins (topotecan and irinotecan, Figure 12) have been approved for use as cancer chemotherapeutics.^{29,30} For our first foray into the synthesis of glycosylated variants of these types of natural products, we decided to look into the synthesis of glycosylated ellipticines because of the overall simpler structure. These glycosylation studies required the preparation of various hydroxy-substituted aza-ellipticines.³⁴

Figure 11: *Ellipticine and related compounds*

Ellipticine (5,11-Dimethyl-6*H*-pyrido[4,3-*b*]carbazole) is a tetracyclic indole/pyridine containing natural product that has attracted significant attention for its potential as an antineoplastic agent.³⁵ Structurally related natural products, like 9-methoxy-ellipticine³³ and 5-aza-ellipticine,³⁶ have also been isolated and show significant anti-cancer activities (Figure 11). The mode of action for the ellipticines has been found to occur by binding to the DNA repair enzyme topoisomerase II. Unfortunately, issues associated with overall toxicity have limited the interest in the use of these natural products as drugs. That being stated, significant interest in synthesizing and testing of analogue structures of ellipticine still remains active. In this regard,

we felt that glycosylated ellipticines, in addition to having better water solubility (lowering its effective dose), may lead to selective uptake by cancer cells.

Scheme 22: *The Wang cyclization approach to ellipticine*

In a similar effort to prepare more active ellipticine analogues, the Wang group has developed a route to related 5-aza-ellipticines (Scheme 22).³⁷ This route utilizes a Wang or bis-aza-Schmitt type cyclization (**46** to **48**)^{38,39} to establish the aza-ellipticine ring system. The Wang approach to the ellipticine replaces the allene portion of the Schmitt substrate with a carbodiimide functional group, and is believed to occur via a bi-radical intermediate, like **47**. We decided to use this approach to prepare aza-ellipticine substrates for glycosylation.

Scheme 23: *Hydroxylated 5-aza-ellipticines for potential glycosylation*

To allow for glycosylation, we need access to aza-ellipticines substituted with hydroxyl group. To maximize the range of reactivity in the glycosylation reaction, we planned to install both phenolic and benzylic hydroxyl groups. We desired aza-ellipticines **52** and **53** for our glycosylation studies and targeted their syntheses with the appropriate protecting groups (Scheme 23). Our retrosynthetic plan for the target molecule **54**, with R_1 being a protected phenol and R_2 being either a hydrogen or a protected alcohol, is outlined in Scheme 24. We chose to use a benzyl ether and a trialkyl silyl ether as orthogonal protecting groups. Because we were more confident with the stability of the benzyl ether to the thermal conditions of the Wang cyclization, we chose to make aza-ellipticines with $R_1 = \text{BnO}$ and $R_2 = \text{H}$ or R_3SiO (**54**, Scheme 24).

Scheme 24: Retrosynthesis for a Hydroxylated aza-ellipticines

Our first effort to prepare a hydroxylated aza-ellipticine is outlined in Scheme 25 and was based on a route previously developed by Quan Zhang, Chongsheng Shi, Hai-Ren Zhang, and Prof. Wang.³⁷ The synthesis began with protection of the more reactive C-4 phenol in commercially available methyl 2,4-dihydroxybenzoate **60**. Using the Williamson ether conditions ($K_2CO_3/BnBr$), the C-4 phenol was converted to the benzyl ether **61** in an 86% yield. The remaining C-2 phenol was converted into the aryltriflate **62** with Tf_2O/Py in near quantitative yield. Sonogashira coupling of triflate **62** with excess propyne gave **63** in good yield. Base-catalyzed hydrolysis of the methyl ester **63** gave the desired carboxylic acid **64** after acidification. It should be noted that the ester hydrolysis reaction needed to be carefully monitored because of a competing alkyne hydrolysis reaction giving ketone **65**, which at times could be quite significant. The optimal reaction condition was to carefully monitor the reaction by TLC and to quench the reaction at the first sign of ketone formation.

Scheme 25: *Synthesis of the key alkynyl acid*

With the alkynyl acid **64** in hand, we next looked into the conversion of it to isocyanate **67** via Curtius rearrangement (Scheme 26). Exposure of carboxylic acid **64** to phosphoryl azide **66** cleanly gave **67** in good yields without the use of silica gel chromatography. It should be noted that using pH 7 water in the aqueous work up of the reaction is important to prevent hydrolysis of the acyl azide **67** back to the carboxylic acid **64**. Finally, thermolysis of the acyl azide **67** in refluxing toluene cleanly gave isocyanate **68**, which in turn could be used without further purification.

Scheme 26: *Synthesis of the key isocyanate*

Finally, the isocyanate **68** was converted into the desired 9-benzyloxy-5-aza-ellipticine **71** via the Wang cyclization (Scheme 27). Isocyanate **68** was treated with freshly prepared phosphoryl imine **69**.⁴⁰ After the evidence of carbodiimide **70** formation was indicated by TLC, the reaction was heated at 138 °C for 15 h to give the desired aza-ellipticine **71** in 25% overall yield. Pure aza-ellipticine **71** was isolated by a cumbersome extraction/precipitation sequence, instead of silica gel chromatography, due to its poor solubility.

Scheme 27: *Synthesis of a Hydroxylated aza-ellipticines*

The final hydrogenolysis deprotection of benzyl-protected hydroxy-aza-ellipticine failed in many solvents (Scheme 28). The same solubility problem that made the purification of **71** quite difficult also limited our ability to further functionalize **71**. Ellipticine **71** was only soluble in polar protic solvent like acidic acid. In fact, the hydrogenolysis of **71** in acetic acid may have worked. The starting material disappeared by TLC, but no recognizable products were isolated from the reaction. This may have been due to the limited solubility of the product, but also potentially due to the instability of the product **72** (i.e., oxidation of the phenol **72** to an aza-quinone). Thus, we desired an alternative route to different aza-ellipticine.

Scheme 28: Attempted deprotection of the benzyl ether

Our next route envisioned the installation of a TBS-protected benzylic alcohol for eventual glycosylation. The addition of this large lipophilic functional group may also improve the solubility of the product. Once again, this route ran into problems with protecting group chemistry. In particular, problems were experienced with the instability of a TBS-group during the ester hydrolysis step. Later on in this chapter, a similar problem was encountered with a TIPS-group falling off during a Wang cyclization (Scheme 30).

This revised route returned to the Sonogashira coupling of triflate **62**, but now with TBS-protected propargyl alcohol instead of propyne (Scheme 29). While a Sonogashira reaction worked to give an 81% yield of the desired alkynyl ester **74**, all our attempts to hydrolysis the methyl ester **74** occurred with concomitant hydrolysis of the TBS-ether.

Scheme 29: Synthesis of a Hydroxylated aza-ellipticines

Thus, we decided to switch to the bulkier TIPS-protecting group (Scheme 30). Although

the Sonogashira coupling between triflate **62** and TIPS-protected propargyl alcohol failed, we were able to couple the triflate **62** with the unprotected propargyl alcohol to give **75** in good overall yield, which then was protected with TIPS-chloride in near quantitative yield to give TIPS-ether **76**.

Scheme 30: *Synthesis of a Hydroxylated aza-ellipticines*

Now with the TIPS group in place (Scheme 30), we were able to selectively hydrolyze the methyl ester **76** with LiOH and isolate the carboxylic acid **77** in 55% yield after acidification. As before, we were able to convert the carboxylic acid **77** to the acylazide **78** with the phosphoryl azide reagent. Similarly thermolysis of acyl azide **78** cleanly gave isocyanate **79** in good yield. However, the reaction failed when we preformed the typical Wang cyclization procedure on isocyanate **79**. When we treated isocyanate **79** with the phosphoryl imide **69** reagent until a new spot appeared, and then heated the reaction mixture to 138 °C for several

hours, we were not able to isolate any product that looked like the desired aza-ellipticine **80**. Only TIPSOH was detected, which led us to believe that the TIPS ether was falling apart under these high temperatures.

These difficulties associate with the poor solubility of the aza-ellipticines convinced us to switch our starting natural product of focus to the camptothecins. We chose the camptothecins because they share many similar features with the ellipticines. These similarities include: 1) both are poly-aromatic anti-cancer agent, 2) both cytotoxicities result from the inhibition of topoisomerase (I and II), and 3) both potential as a drug candidate suffer from poor solubility. Evidence in the literature suggests that camptothecins display a slightly better solubility profile in aprotic solvents. It should be noted that much of this evidence was collected from the patent literature, which more often than not, did not report experimental procedures and/or spectral data.

Figure 12: *Camptothecin and related structures*

Camptothecin is a naturally occurring highly conjugated polycyclic quinoline that has been attracting a tremendous amount of attention from both the academia and the pharmaceutical industry.⁴¹ Since its initial isolation in 1966 from the Chinese plant *Camptotheca acuminata*,⁴² the alkaloid has shown excellent antitumor activity. In fact, several camptothecin analogues are being used clinically for treatment of various cancers (Figure 12).⁴³

It is worth noting that in the 1970s camptothecin was entered into clinical trials in the form of its water-soluble sodium salt of the hydrolyzed ester; however, the trials failed and the interest in camptothecin subsided. Revived interest in camptothecin came from the discovery of its mechanism of action.⁴⁴ In the late 1980s, it was discovered that camptothecin interacts with DNA topoisomerase I, an enzyme that is essential for DNA replication.⁴⁵ The topoisomerases are enzymes that catalyze the topo-isomerization reactions (relaxation/supercoiling, knotting/unknotting and catenation/decatenation) of DNA.⁴⁶ In fact, the structure of the cleavable ternary complex is of great interest for the elucidation of the mechanism of action and development of new topoisomerase inhibitors. The discovery of topoisomerases as new targets for cancer chemotherapy and the mechanism of action of camptothecin put camptothecin back on the frontlines of anticancer drug development.⁴⁷ As the result of these renewed efforts, two FDA approved drugs have appeared on the market topotecan (ovarian cancer and small-cell lung cancer) and irinotecan (colorectal cancer).⁴⁸

Besides ongoing studies on topotecan and irinotecan, significant effort has also been spent on the development of new anticancer drugs from this family, with a particular effort towards producing compounds with better solubility and tissue-targeting properties.⁴⁹ To these ends, we proposed to take advantage of the inherent water solubility of carbohydrates, along with

the fact that they are actively transported across cell membranes to make new carbohydrate-linked camptothecin analogues. It should be noted that the problems associated with the use of camptothecins are primarily related to its poor solubility in both organic solvents and water.

Scheme 31: *The Wang approach to camptothecin*

More recently, the Wang group developed a new synthetic pathway to the camptothecin ABCD ring system (Scheme 31).⁵⁰ The Wang approach begins with the *N*-alkylation of 1,6-dihydro-6-oxo-2-pyridinecarbonitrile **81** to provide **82**. Treatment of **82** with a catalytic amount of DBU (5 mol %) at 110 °C for 12 hours produced the desired ABCD ring core of camptothecin **85**. Key to the Wang approach is the recognition that a base-catalyzed isomerization of alkyne **82** to **83**, which in turn will undergo a cycloaddition to give **84**, followed by a 1,5-proton migration to give **85**. While there are many approaches to this natural product,⁵¹ none of these approaches could compare to the Wang route in terms of overall efficiency and flexibility.

As a prelude to the eventual glycosylation of synthetic hydroxy-substituted camptothecins from the above route, we decided to work with the natural product instead. We could do this because camptothecin already has a hydroxyl group and is commercially available,

albeit expensive. This idea was drawn from the fact that nature already produced a glycosylated camptothecin (see *gluco*-camptothecin, Figure 12), which had also shown improved biological activity, presumably as a pro-drug. That is to say, the glucose must be hydrolyzed before the camptothecin can bind to DNA.

Scheme 32: Attempted glycosylation of the tertiary hydroxyl of Camptothecin

Encouraged by the fact that the tertiary alcohol of camptothecin can be glycosylated in nature, we began our efforts with the attempt to use our palladium-catalyzed glycosylation reaction on the tertiary alcohol of camptothecin (Scheme 32). Unfortunately, these reactions failed. We believed this was primarily due to the poor solubility of camptothecin in most organic solvents. The only non-protic solvent we were able to get camptothecin to dissolve into was refluxing acetic anhydride, which could not be used in the glycosylation reaction.

We attributed this lack of reactivity to solubility, instead of reactivity, because the related camptothecin SN-38 (Scheme 33) has a much more reactive phenol that also did not react, presumably due to the poor solubility in DMF. This poor solubility also inhibited our efforts to

functionalize the pyridine ring in camptothecin by an *N*-oxide to pyridone rearrangement reagent (e.g., **88** to **89**, X = OH, Scheme 34).

Scheme 33: Attempted glycosylation of the phenolic OH of SN-38

Based on these results, we decided to install sugars via a Sonogashira reaction with glycosylated propargyl alcohols (Scheme 34). We chose to prepare a camptothecin with a *C*-11 leaving group for palladium cross coupling partner (e.g., **89**, X = Cl, Br, I, OTf). This effort began with the attempted synthesis of known *C*-11-substituted camptothecins with either a hydroxyl or triflate group. Unfortunately, this effort failed with our inability to purify the highly insoluble and unstable camptothecin *N*-oxide **88**.

Improved solubility of the camptothecins came with the acylation of the tertiary alcohol, which after acylation could be oxidized and rearranged to the desired *C*-11 chloro-pyridine.⁵² Acylation of the *C*-4 tertiary hydroxyl group of camptothecin was accomplished by exposing camptothecin with 1 equiv of LiBr in refluxing acetic anhydride to provide good yield of camptothecin acetate **90** (92% yield).⁵³ This more soluble substrate could be oxidized with excess mCPBA in refluxing EtOAc/CH₂Cl₂ to give a good yield of the *N*-oxide **91** (quantitative yield). The *N*-oxide **91** was unstable to silica gel chromatography, however, reasonably pure

material could be prepared by aqueous base extraction of the excess acid and re-crystallization. The *N*-oxide **91** was converted to the C-11 chloride **92** by exposure of a DMF/CH₂Cl₂ solution to oxalyl chloride in 76% yield.⁵⁴

Scheme 34: Attempted synthesis of 11-substituted Camptothecin for Sonogashira coupling[‡]

With chloride **92** in hand, we next investigated its use in the Sonogashira coupling reaction with various propargyl alcohols (Scheme 35). This effort built on the work of Lu and co-workers,⁵⁵ who demonstrated the use of 7-chloro-camptothecin **92** in the Buchwald copper-free Sonogashira coupling reaction.⁵⁶ Exposing 7-chloro camptothecin **92** with THP-protected propargyl alcohol to catalytic Pd(OAc)₂/BINAP in refluxing toluene gave good yields of alkyne **94** (75% yield).

[‡] While the compounds in Scheme 34 are known compounds in the patent literature, their experimental and spectral details were not included, see, ref. 52.

While this route worked for very simple substrates like THP-protected propargyl alcohol **93**, it failed to give adequate amount of pure products for our desired glycosylated propargylic alcohol coupling partners. When we exposed our glycosylated propargyl alcohols **95-97** to the same Sonogashira coupling conditions, only trace amount of the desired product was detected for the coupling reaction with **97**. Evidence of the slightly successful coupling reaction between **92** and **97** was seen when the crude reactions products were compared to authentic material (**99**, Scheme 36).

Scheme 35: Attempted synthesis of glycosylated Camptothecin via Sonogashira coupling

With the lack of success with the more convergent Sonogashira coupling strategy, we turned to an alternative protocol for the synthesis of glycosylated camptothecin, like **99**. This began with the acid-catalyzed deprotection of the THP-group to give propargyl alcohol **98** (95% yield). Using our palladium catalyzed glycosylation of propargyl alcohol **98** with the β -pyranone

6, we were able to convert **98** in to pyranone **99**. Unfortunately, the less stable β -pyranone isomerized upon silica gel chromatography, which caused difficulty in separating the mixture of diastereomers at the anomeric position (65%).

Scheme 36: *Attempted synthesis of glycosylated Camptothecin via Sonogashira coupling*

Finally, a successful effort to prepare a glycosylated camptothecin came when we acylated the tertiary alcohol of SN-38 (Scheme 37). This acetate group imparted improved solubility to the camptothecin substrate. Unfortunately, due to the greater reactivity of phenol groups, a two-step acylation/deacylation sequence was needed to acylate the less reactive tertiary alcohol (Scheme 37). Thus both the phenol and tertiary alcohol were acylated with acetic anhydride to give diacetate **101** (65% yield). The more reactive phenol was then removed with

MeOH/Et₃N to give the desired mono-acetate **102** (50% yield). Alternatively, the more reactive phenol could be protected with a TBS group to give **103** in excellent yield (83%). Then the tertiary alcohol was acylated to form **104** (92%). Finally, a TBS deprotection with HF/Py gave the desired phenol **102** (92%). On small scale this later route was the higher yielding, but upon scale up, problem occurred with the formation of diacetate under the acylation conditions.⁵⁴

Scheme 37: *Synthesis of a more soluble analogue of SN-38*

Finally, with the acylated SN-38 **102** in hand, we were able to perform the desired Pd-catalyzed glycosylation. This was performed with both the pyranone **5** and allylic alcohol **106** as π -allyl-precursors. Unfortunately, the pyranone glycosylation product **105** was not very stable, and had to be reduced to allylic alcohol **107** without further purification (~50%). Alternatively, the allylic alcohol product **107** could be prepared in better overall yield when **102** was

glycosylated with **106** (83%). While more stable than **105**, the allylic alcohol **107** was still unstable to acidic conditions. Allylic alcohol **107** smoothly underwent dihydroxylation when it was exposed to the typical Upjohn conditions to provide *rhanno*-SN-38 **108** (85%). While the glycosylated camptothecin **108** was significantly more stable than **105** and **107**, it slowly underwent methanolysis to form the free aglycon **102** and methyl *rhanno*-pyranoside upon standing in methanol. Because of the expense of the SN-38 and overall instability of glycosylated product **108**, we decided not to pursue the synthesis of further glycosylated camptothecin analogues.

Scheme 38: Successful synthesis of a glycosylated Camptothecin SN-38

Scheme 39: Reason for potential instability of glycosylated SN-38

While it was not thought to be a major problem at the outset, the base instability of pyranone **105** and the acid instability of **107** and **108** were not without precedent (Scheme 39). For instance, it is well known that pyranones, like **105**, with good leaving groups at the C-1 position, decomposes in the presence of a base to give 1,3-dipole intermediates like **110**. The basic nature of the pyridine ring in the camptothecin aglycon can lead to its protonation, making it a much better leaving group, which makes both **107** and **108** more prone to acid-catalyzed

hydrolysis (**107** to **112** and **108** to **113**). Due to the presence of the double bond, it is not surprising that **107** is more sensitive to acid hydrolysis than **108**.

In conclusion, we have shown that glycosylated camptothecin can be made, but their syntheses can be complicated by issues associated with poor solubility of the ring system. This solubility problem was a bigger issue in synthesis of aza-ellipticines, such that it prevented the synthesis of the desired hydroxy-aza-ellipticine substrates for our proposed glycosylation studies.

Scheme 40: *Future goals*

While the acid sensitivity of glycosylated SN-38 (**108**) will limit its use as a drug, we believe that future efforts in this regard could include the synthesis of cyclictol analogues like **114**.

Chapter IV. Experimental Section

A. General methods and materials:

^1H and ^{13}C spectra were recorded on 270 MHz and 600 MHz spectrometers. Chemical shifts were reported relative to benzene- d_6 (δ 7.16 ppm), CDCl_3 (δ 7.26 ppm), CD_3OD (δ 3.31 ppm), acetone- d_6 (δ 2.05 ppm), D_2O (δ 4.80 ppm) for ^1H , and benzene- d_6 (δ 127.68 ppm), CDCl_3 (δ 77.0 ppm), CD_3OD (δ 49.15 ppm), and acetone- d_6 (δ 29.92 ppm) for ^{13}C . Optical rotations were measured with a digital polarimeter in the solvent specified. Infrared (IR) spectra were obtained on a FT-IR spectrometer. Flash column chromatography was performed on 60-200 mesh silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates and visualized by quenching of fluorescence and by charring after treatment with 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, toluene and triethylamine were dried by passing through activated alumina (8 x 14 mesh) column with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven/flamed-dried glassware and standard syringe/septum techniques.

B: Experimental Procedures for Chapter I:

(*R*)-1-(furan-2-yl) ethanol (**7(R)**)[§]

To a 250 mL flask was added furan ketone **8** (22 g, 0.2 mol), CH₂Cl₂ (100 mL), formic acid/triethylamine (1:1, 108 mL) and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6 -mesitylene)-(*R,R*)-TsDPEN (585 mg, 0.5 mol%). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (150 mL) and extracted with Et₂O (3 x 150 mL). The combined organic layers were washed with satd. aq. NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% Et₂O/hexanes to give furan alcohol **7(R)** (21.5 g, 0.19 mmol, 96%) as a colorless oil; *R_f*(30% Et₂O/hexanes) = 0.24; $[\alpha]_D^{21} + 20.8$ (*c* 1.20, CHCl₃); IR (thin film, cm⁻¹) 3361, 2979, 2934, 1669, 1504, 1465, 1371, 1230, 1148, 1008, 878, 735; ¹H NMR (270 MHz CDCl₃) δ 7.37 (d, *J* = 1.8 Hz, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.22 (ddd, *J* = 3.2 Hz, 1H), 4.87 (q, *J* = 6.5 Hz, 1H), 2.25 (bs, 1H), 1.53 (d, *J* = 8.0 Hz, 3H); ¹³C NMR (67.5 MHz, CDCl₃) δ 158.0, 142.3, 110.5, 105.5, 64.0, 21.7.

[§] Spectral data matches that for previously reported material, see: Shan, M.; O'Doherty, G. A. *Org. Lett.* **2006**, 8, 5149-5152.

(S)-1-(2-Furyl)-ethanol (7(S)):[§]

To a 250 mL flask was added furan ketone **8** (8 g, 72.7 mmol), CH₂Cl₂ (37 mL), formic acid/triethylamine (1:1, 100 mL) and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6 -mesitylene)-(*S,S*)-TsDPEN (222 mg, 0.5 mol%). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (100 mL) and extracted with Et₂O (3 x 100 mL). The combined organic layers were washed with satd. aq. NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% Et₂O/hexanes to give furan alcohol **7(S)** (7.82 g, 69.8 mmol, 96%) as a colorless oil; R_f (30% Et₂O/hexanes) = 0.24; $[\alpha]_D^{21}$ -20.1 (c 1.0, CHCl₃); IR (thin film, cm⁻¹) 3360, 2980, 2935, 1668, 1505, 1467, 1370, 1229, 1149, 1007, 877, 734; ¹H NMR (270 MHz CDCl₃) δ 7.37 (dd, J = 1.6, 0.8 Hz, 1H), 6.32 (dd, J = 3.2, 1.8 Hz, 1H), 6.23 (ddd, J = 3.2, 0.8, 0.8 Hz, 1H), 4.78 (dq, J = 3.4, 6.1 Hz, 1H), 2.07 (bs, 1H), 1.54 (d, J = 6.5 Hz, 3H); ¹³C NMR (67.5 MHz, CDCl₃) δ 157.7, 141.6, 109.9, 104.9, 63.3, 21.1.

(2*R*)-6-Hydroxy-2-methyl-2*H*-Pyran-3 (6*H*)-one (34): §

Furan alcohol **7(R)** (9.0 g, 79.5 mmol), 100 mL of THF, and 25 mL of H₂O were added to a round bottom flask and cooled to 0 °C. Solid NaHCO₃ (13.4 g, 159 mmol), NaOAc•3H₂O (10.8 g, 79.5 mmol), and NBS (14.9 g, 83.48 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 200 mL) with Et₂O, dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel chromatography eluting with 35% EtOAc/hexanes to give pyranone **34** (9.67 g, 75.5 mmol, 95%, α : β = 2.6 :1): R_f (60% EtOAc/hexanes) = 0.29; IR (thin film, cm⁻¹) 3381, 2988, 2942, 1692, 1447, 1373, 1232, 1021, 937; ¹H NMR (600 MHz, CDCl₃) major isomer (α): δ 6.86 (dd, J = 10.2, 3.0 Hz, 1H), 6.04 (d, J = 10.2 Hz, 1H), 5.57 (dd, J = 4.2, 3.6 Hz, 1H), 4.66 (q, J = 6.6 Hz, 1H), 4.36 (d, J = 5.4 Hz, 1H), 1.32 (d, J = 6.6 Hz, 3H); minor isomer (β): δ 6.91 (dd, J = 10.2, 1.8 Hz, 1H), 6.09 (dd, J = 10.2, 1.8 Hz, 1H), 5.62 (dd, J = 7.2, 1.2 Hz, 1H), 4.71 (d, J = 7.2 Hz, 1H), 4.18 (dq, J = 1.2, 6.6 Hz, 1H), 1.39 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) major isomer (α): δ 197.4, 144.9, 126.9, 87.4, 70.3, 15.2. Minor isomer (β): δ 196.8, 148.5, 128.2, 87.2, 90.8, 75.1, 16.1.

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

To a benzene solution (300 mL) of (5*R*)-1-Hydroxy-5-*tert*-butyl dimethylsilanyloxymethyl-5*H*-pyran 4-(1*H*)-one **A** (18.5 g, 0.144 mol) and (Boc)₂O (47.3 g, 0.22 mol) was added sodium acetate (13.2 g, 0.16 mol). After stirring at 80 °C for 2 h, the mixture was cooled down to room temperature. The reaction was quenched by adding of 300 mL of satd. aq. NaHCO₃ solution, extracted (3 x 300 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 6 and 8% EtOAc/hexanes to give two diastereomers of *tert*-butyl 5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (29.0 g, 0.127 mol, 88%) of (*ent*)-5(α -D) and 6(β -D) (d.r. = 1:1.3).

(*ent*)-5(α -D): *R*_f (20% Et₂O/hexanes) = 0.43; [α]_D²¹ = -97.1 (c 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2986, 1752, 1703, 1633, 1278, 1258, 1159, 1090, 1058, 1029, 944; ¹H NMR (600 MHz, CDCl₃) δ 6.795 (dd, *J* = 10.2, 4.2 Hz, 1H), 6.24 (d, *J* = 4.2 Hz, 1H), 6.10 (d, *J* = 10.2 Hz, 1H), 4.55 (q, *J* = 6.6 Hz, 1H), 1.40 (s, 9H), 1.30 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 195.4, 151.7, 140.9, 128.1, 89.0, 83.2, 71.9, 27.4(3C), 15.0; HRCIMS Calcd for [C₁₁H₁₆O₅Na]⁺: 251.0890, Found 251.0884.

** Spectral data matches that for previously reported material, see: Zhou and G. A. O'Doherty, *J. Org. Chem.* **2007**, 72, 2485-2493.

6(β -D): R_f (20% EtOAc/hexanes) = 0.50; mp: 43-43.5 °C; $[\alpha]_D^{21} = +42.3$ (c 1.3, CHCl₃); IR (thin film, cm⁻¹) 2986, 1752, 1703, 1633, 1278, 1258, 1159, 1090, 1058, 1029, 944; ¹H NMR (600 MHz, CDCl₃) δ 6.82 (dd, J = 10.2, 2.4 Hz, 1H), 6.28 (dd, J = 2.4, 1.2 Hz, 1H), 6.11 (dd, J = 10.2, 1.2 Hz, 1H), 4.27 (q, J = 6.6 Hz, 1H), 1.42 (s, 9H), 1.39 (d, J = 6.9 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 195.6, 151.6, 142.7, 128.0, 89.7, 83.3, 75.5, 27.4(3C), 18.3; HRCIMS Calcd for [C₁₁H₁₆O₅Na]⁺: 251.0890, Found 251.0883.

(2*S*,6*S*)-*trans*-butyl -5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (5(α -L))^{**}

Alcohol (*ent*)-**34** (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 μ mol) was added to the reaction mixture. The reaction was stirred for 1 h at -78 °C, and quenched with 100 mL of satd. aq. NaHCO₃, extracted with Et₂O (3 x 100 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc/hexanes to give 8.02 g (35.2 mmol, 82%) of two diastereomers of Boc-protected pyranone **5(α -L)** and (*ent*)-**6(β -L)** in a ratio of 3:1. **5(α -L)**: *R_f* (20% Et₂O/hexanes) = 0.58; $[\alpha]_D^{21} = +98$ (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 MHz, CDCl₃) δ 195.5, 151.7, 140.9, 128.2, 89.1, 83.3, 72.0, 27.5, 15.1; ClHRMS Calculated for [C₁₁H₁₆O₅Na⁺]: 251.0890, Found: 251.0883.

(2*R*,6*R*)-6-(4-methoxybenzyloxy)-2-methyl-2*H*-pyran-3(6*H*)-one (9):

A CH_2Cl_2 (2 mL) solution of *tert*-butyl (2*S*,6*R*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl carbonate **6(β-D)** (2.28 g, 10 mmol) and 4-methoxybenzyl alcohol (2.76 g, 20 mL) was cooled to 0 °C, $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (260 mg, 2.5 mol%) and PPh_3 (226 mg, 10 mol%) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched by adding 10 mL of satd. aq. NaHCO_3 , extracted three times with ether, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexanes to give pyranone **9** (2.32 g, 9.5 mmol, 95%) as a yellow oil: R_f (10% EtOAc/hexanes) = 0.15; $[\alpha]_{\text{D}}^{21} = -22.4$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 2938, 2837, 1696, 1513, 1246, 1054, 1008, 818, 802; ^1H NMR (600 MHz, CDCl_3) δ 7.23 (d, $J = 8.4$, 2H), 6.88 (d, $J = 8.4$, 2H), 6.83 (dd, $J = 10.2$, 1.2, 1H), 6.03 (d, $J = 10.2$, 1H), 5.29 (d, $J = 1.2$, 1H), 4.79 (d, $J = 11.4$, 1H), 4.54 (d, $J = 11.4$, 1H), 4.15 (q, $J = 6.6$, 1H), 3.71 (s, 3H), 1.45 (d, $J = 6.6$, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 196.5, 159.2, 146.5, 129.5, 128.7, 127.7, 113.6, 93.9, 74.9, 69.5, 54.9, 16.9; CIHRMS Calcd for $[\text{C}_{14}\text{H}_{16}\text{O}_4\text{H}]^+$: 249.1127. Found 249.1122.

(2*R*,6*R*)-6-(4-methoxybenzyloxy)-3,6-dihydro-2-methyl-2*H*-pyran-3-ol (10a/b):

Pyranone **9** was dissolved in 24 mL CH₂Cl₂, resulting solution was cooled to -78 °C, 24 mL of 0.4 M CeCl₃ in methanol solution was added in a dropwise fashion, followed by adding 540 mg of NaBH₄. By TLC tracking, the reaction was done after 1.5 h. The reaction mixture was diluted with 2 mL diethyl ether, then quenched with 2 mL water, extracted with 3 x 20 mL diethyl ether, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 80% EtOAc/Hexane to give allylic alcohol **10a/b** as a mixture of diastereomers (2.40 g, 9.5 mmol, 99%) as a colorless oil: *R_f* (30% EtOAc/hexanes) = 0.45; $[\alpha]_D^{21} = -58.5$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3421, 2977, 2871, 1612, 1513, 1244, 1172, 1031, 818, 788;

10a ¹H NMR (600 MHz, CDCl₃) δ 7.26 (d, *J* = 8.4, 2H), 6.85 (d, *J* = 8.4, 2H), 6.11 (ddd, *J* = 10.2, 5.4, 1.8, 1H), 5.81 (d, *J* = 10.2, 1H), 5.09 (m, 1H), 4.80 (d, *J* = 11.4, 1H), 4.56 (d, *J* = 11.4, 1H), 3.77 (s, 3H), 3.68 (m, 1H), 3.64 (m, 1H), 2.00 (m, 1H), 1.30 (d, *J* = 6.6, 3H);

10b ¹H NMR (600 MHz, CDCl₃) δ 7.26 (d, *J* = 8.4, 2H), 6.85 (d, *J* = 8.4, 2H), 5.92 (d, *J* = 10.2, 1H), 5.75 (d, *J* = 10.2, 1H), 5.09 (m, 1H), 4.76 (d, *J* = 11.4, 1H), 4.52 (d, *J* = 11.4, 1H), 3.77 (s, 3H), 3.71 (m, 1H), 3.68 (m, 1H), 2.00 (m, 1H), 1.35 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) major isomer δ 159.3 (2C), 131.2 (2C), 129.7, 129.6, 113.8, 96.7, 71.5, 69.6, 68.4, 64.8, 55.3, 16.6; CIHRMS Calcd for [C₁₄H₁₈O₄Na]⁺: 273.1103. Found 273.1100.

(2*R*,6*R*)-2-(4-methoxybenzyloxy)-3,6-dihydro-6-methyl-2H-pyran (11):

A flask charged with dry *N*-Methyl morpholine (NMM) 20 mL, triphenyl phosphine (6.86 g, 30.36 mmol) was cooled to -30 °C under argon atmosphere. Diethylazodicarboxylate (4.35 mL, 27.6 mmol) was added and the reaction was stirred for 5 min, allylic alcohol **10a/b** (2.3 g, 9.2 mmol) was added to in a 1 M of NMM (9.2 mL), the resulting reaction mixture was stirred for 10 min, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (5.99 g, 27.6 mmol). The reaction was stirred at -30 °C for 2 h and was monitored by TLC. Upon consumption of **10a/b**, the reaction was warmed to room temperature and stirred for another 2 h. The reaction mixture was diluted with ether (20 mL) and was quenched with 10 mL of satd. aq. NaHCO₃, extracted (3 x 50 mL) with ether, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 95% EtOAc/hexanes to give product **11** (2.10 g, 8.7 mmol, 95%) as a yellow oil. *R_f* (20% EtOAc/hexanes) = 0.55; $[\alpha]_{\text{D}}^{21} = -106$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3034, 2909, 1612, 1512, 1365, 1245, 1155, 1075, 1045, 879, 818; ¹H NMR (600 MHz, CDCl₃) δ 7.30 (d, *J* = 7.8, 2H), 6.88 (d, *J* = 7.8, 2H), 5.67 (dddd, *J* = 9.6, 2.4, 1.2, 1.2, 1H), 5.58 (dddd, *J* = 9.6, 5.4, 2.4, 2.4, 1H), 4.86 (d, *J* = 11.4, 1H), 4.72 (dd, *J* = 8.4, 3.0, 1H), 4.55 (d, *J* = 11.4, 1H), 4.33 (m, 1H), 3.78 (s, 3H), 2.22 (m, 1H), 2.13 (m, 1H), 1.32 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 159.0, 130.8, 129.8, 129.4, 122.3, 113.6, 97.3, 70.4, 69.2, 55.0, 30.8, 21.0; CIHRMS Calcd for [C₁₄H₁₈O₃Na]⁺: 257.1154. Found 257.1148.

(2*R*,3*S*,4*S*,6*R*)-6-(4-methoxybenzyloxy)-2-methyl-tetrahydron-2*H*-pyran-3,4-diol (12):

To a *t*-butanol, acetone (4.3 mL each, 1:1) solution of pyran **11** (1 g, 4.3 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (4.3 mL). Crystalline OsO₄ (1.1 mg, 1 mol %) was added and the reaction was stirred for 12 h. The reaction was quenched by adding EtOAc and satd. aq. NaHCO₃. The organic layer was separated and concentrated. The crude product was purified by silica gel flash chromatography eluting with 50% EtOAc/hexanes to give diol **12** (0.97 g, 3.6 mmol, 85%) as a colorless oil. *R_f* (50% EtOAc/hexanes) = 0.20; $[\alpha]_D^{21} = -53.9$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3411, 2933, 1612, 1513, 1245, 1161, 1032, 997, 819; ¹H NMR (600 MHz, CDCl₃) δ 7.23 (d, *J* = 8.4, 2H), 6.83 (d, *J* = 8.4, 2H), 4.84 (dd, *J* = 9.6, 1.8, 1H), 4.77 (d, *J* = 11.4, 1H), 4.45 (d, *J* = 11.4, 1H), 3.98 (d, *J* = 3.0, 1H), 3.75 (s, 3H), 3.68 (dq, *J* = 9.0, 6.0, 1H), 3.22 (dd, *J* = 3.6, 1H), 3.05 (s, 1H), 2.98 (s, 1H), 2.02 (ddd, *J* = 15, 2.4, 2.4, 1H), 1.69 (ddd, *J* = 14, 11.4, 3.0, 1H), 1.28 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 159.1, 129.6, 129.5, 113.7, 96.6, 72.8, 70.1, 69.4, 67.7, 55.1, 37.5, 18.0; CIHRMS Calcd for [C₁₄H₂₀O₅Na]⁺: 291.1208, Found 291.1205.

(2*R*,3*R*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-tetrahydro-3-hydroxy-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (13**):**

A THF (16 mL) solution of diol **12** (920 mg, 3.43 mmol) at 0 °C was added PPh₃ (1.16 g, 5.15 mmol) and *p*-nitrobenzoic acid (1.15 g, 6.87 mmol), DIAD (1.11 g, 5.49 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred for three days. The reaction mixture was diluted with 50 mL EtOAc, quenched with 40 mL of satd. aq. NaHCO₃, extracted (3 x 50 mL) with ether, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/Hexanes to give nitrobenzoate **13** (1.00 g, 2.4 mmol, 70%) as a yellow solid. *R_f* (30% EtOAc/hexanes) = 0.40; mp: 38-40 °C; [α]_D²¹ = -40.4 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3477, 2939, 1722, 1609, 1513, 1347, 1269, 1166, 1100, 987; ¹H NMR (600 MHz, CDCl₃) δ 8.15 (d, *J* = 9.0, 2H), 8.10 (d, *J* = 9.0, 2H), 7.21 (d, *J* = 8.4, 2H), 6.82 (d, *J* = 8.4, 2H), 5.02 (ddd, *J* = 11.4, 8.4, 4.8, 1H), 4.78 (d, *J* = 11.4, 1H), 4.61 (dd, *J* = 10.2, 2.4, 1H), 4.51 (d, *J* = 11.4, 1H), 3.74 (s, 3H), 3.36 (dq, *J* = 9.0, 6.0, 1H), 3.41 (dd, *J* = 9.0, 9.0, 1H), 2.93 (s, 1H), 2.35 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 1.78 (ddd, *J* = 12, 12, 9.6, 1H), 1.19 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 164.5 (2C), 159.1 (2C), 150.4 (2C), 135.0 (2C), 130.6, 129.4, 129.1, 123.3, 113.7, 97.3, 75.4, 74.5, 71.8, 70.0, 55.0, 36.3, 17.7; CIHRMS Calcd for [C₂₁H₂₃NO₈Na]⁺: 440.1321, Found 440.1317.

(2*R*,3*R*,4*R*,6*R*)-3-((2*R*,6*S*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (14**):**

A CH₂Cl₂ (1.0 mL) solution of Boc pyranone **5**(α -**L**) (2.62 g, 11.5 mmol) and alcohol **13** (960 mg, 2.3 mmol) was cooled to 0 °C. Pd₂(DBA)₃•CHCl₃ (60 mg, 2.5 mol%) and PPh₃ (52 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with 10 mL of satd. aq. NaHCO₃, extracted (3 x 10 mL) with Et₂O, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give pyranone **14** (1.18 g, 2.24 mmol, 98%) as a yellow solid: *R_f* (30% EtOAc/hexanes) = 0.40; mp: 52-54 °C; $[\alpha]_D^{21} = -87.4$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2937, 1723, 1697, 1609, 1527, 1514, 1272, 1101, 979, 832; ¹H NMR (600 MHz, CDCl₃) δ 8.26 (d, *J* = 8.4, 2H), 8.18 (d, *J* = 8.4, 2H), 7.24 (d, *J* = 8.4, 2H), 6.85 (d, *J* = 8.4, 2H), 6.75 (dd, *J* = 10.2, 3.6, 1H), 5.97 (d, *J* = 10.2, 1H), 5.30 (d, *J* = 3.6, 1H), 5.26 (ddd, *J* = 11.4, 9.0, 6.0 1H), 4.81 (d, *J* = 11.4, 1H), 4.66 (d, *J* = 9.6, 1H), 4.53 (d, *J* = 11.4, 1H), 4.29 (q, *J* = 6.6, 1H), 3.77 (s, 3H), 3.62 (dd, *J* = 9.0, 9.0, 1H), 3.47 (dq, *J* = 9.0, 6.6, 1H), 2.38 (dd, *J* = 12.6, 5.4, 1H), 1.80 (ddd, *J* = 12.6, 12, 12, 1H), 1.41 (d, *J* = 6.6, 3H), 0.88 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 196.3, 163.9, 159.4, 150.6, 142.5, 135.4, 130.7, 129.6, 129.1, 126.8, 123.5, 113.9, 97.3, 94.4, 82.6, 73.2, 71.0, 71.0, 70.2, 55.2, 36.7, 18.3, 15.0; CIHRMS Calcd for [C₂₇H₂₉NO₁₀Na]⁺: 550.1689, Found 550.1690.

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

Pyranone **14** (1.14 g, 2.2 mmol) was dissolved in 5.38 mL CH₂Cl₂, resulting solution was cooled to -78 °C, 5.38 mL of 0.4 M CeCl₃ in methanol solution was added dropwise, followed by the addition of 123 mg of NaBH₄. By TLC tracking, the reaction was completed after 1.5 h. The reaction mixture was diluted with 10 mL diethyl ether, and quenched with 2 mL water. Extraction by 3 x 50 mL diethyl ether, dried over Na₂SO₄ and concentrated under reduced pressure to give allylic alcohol **15** (1.11 g, 2.10 mmol, 97%) as a white solid. *R_f* (30% EtOAc/hexanes) = 0.20; mp: 159.5-160.5 °C; $[\alpha]_D^{21} = -114.8$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3384, 1718, 1527, 1513, 1282, 1104, 996, 717; ¹H NMR (600 MHz, CDCl₃) δ 8.26 (d, *J* = 11.0, 2H), 8.19 (d, *J* = 11.0, 2H), 7.25 (d, *J* = 9.0, 2H), 6.86 (d, *J* = 9.0, 2H), 5.84 (d, *J* = 10.2, 1H), 5.66 (ddd, *J* = 10.2, 2.4, 2.4, 1H), 5.21 (ddd, *J* = 12.0, 8.4, 5.4, 1H), 5.04 (d, *J* = 2.4, 1H), 4.81 (d, *J* = 11.4, 1H), 4.62 (dd, *J* = 9.6, 2.4, 1H), 4.53 (d, *J* = 11.4, 1H), 3.79 (s, 3H), 3.60 (ddd, *J* = 9.0, 9.0, 1.8, 1H), 3.53 (dd, *J* = 9.0, 9.0, 1H), 3.46 (dq, *J* = 9.0, 6.0, 1H), 3.42 (dq, *J* = 9.0, 6.0, 1H), 2.36 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 1.80 (ddd, *J* = 12.6, 12, 10.2, 1H), 1.60 (s, 1H), 1.41 (d, *J* = 6.6, 3H), 0.81 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 164.0, 159.4, 150.5, 135.8, 133.2, 130.8, 129.7, 129.2, 126.2, 123.5, 113.9, 97.4, 95.5, 81.8, 73.4, 71.3, 70.2, 69.1, 68.6, 55.3, 36.7, 18.4, 17.6; CIHRMS Calcd for [C₂₇H₃₁NO₁₀Na]⁺: 552.1846, Found 552.1841.

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

A THF (0.7 mL) solution of alcohol **15** (106 mg, 0.2 mmol) at 0 °C was added PPh₃ (90.4 mg, 0.4 mmol) and *p*-nitrobenzoic acid (66.8 mg, 0.4 mmol), DIAD (80.9 mg, 0.4 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred for three days. The reaction mixture was diluted with 5 mL EtOAc, quenched with 1 mL of satd. aq. NaHCO₃, extracted (3x10 mL) with methylene chloride, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give product **16** (101 mg, 0.15 mmol, 74%) as a light yellow solid. *R_f* (30% EtOAc/hexanes) = 0.40; mp: 174-175 °C; [α]_D²¹ = 88.2 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2930, 1723, 1609, 1519, 1342, 1266, 1069, 1040, 987, 834, 754; ¹H NMR (600 MHz, CDCl₃) δ 8.22 (d, *J* = 9, 2H), 8.17 (d, *J* = 9, 2H), 8.16 (d, *J* = 9, 2H), 8.02 (d, *J* = 9, 2H), 7.20 (d, *J* = 9.0, 2H), 6.81 (d, *J* = 9.0, 2H), 6.06 (dd, *J* = 10.2, 5.4, 1H), 5.96 (dd, *J* = 10.2, 3.0, 1H), 5.21 (ddd, *J* = 12.0, 9.0, 5.4 1H), 5.15 (d, *J* = 3, 1H), 4.91 (dd *J* = 9.6, 2.4, 1H), 4.76 (d, *J* = 11.4, 1H), 4.58 (dd *J* = 9.6, 1.8, 1H), 4.49 (d, *J* = 11.4, 1H), 4.03 (dq, *J* = 6.6, 3, 1H), 4.03 (dq, *J* = 9.0, 6.2, 1H), 3.74 (s, 3H), 3.55 (dd, *J* = 8.4, 8.4, 1H), 2.32 (ddd, *J* = 12, 6.0, 1.8, 1H), 1.79 (ddd, *J* = 15, 9.6, 9.6, 1H), 1.38 (d, *J* = 6.6, 3H), 0.71 (d, *J* = 6.6, 3H); ¹³C (150 MHz, CDCl₃) 164.1, 164.0, 159.5, 150.7, 150.6, 135.7, 135.0, 130.9, 130.7, 130.6, 129.7, 129.2, 125.1, 123.5, 123.5, 113.9,

97.3, 95.3, 81.8, 73.2, 71.3, 70.2, 66.1, 65.3, 55.3, 36.7, 18.5, 15.8; CIHRMS Calcd for $[\text{C}_{34}\text{H}_{34}\text{N}_2\text{O}_{13}\text{Na}]^+$: 701.1959, Found 701.1961.

(2*S*, 3*S*, 6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (17):

Bis-nitrobenzoate **16** (723 mg, 1.07 mmol) was dissolved in a mixed solvent of THF/H₂O (15 mL/3 mL) at room temperature, LiOH (102 mg, 4.28 mmol) was added and the reaction was stirred for 24 h. The reaction was quenched by adding 5 mL of satd. aq. NaHCO₃, extracted (3 x 50 mL) with methylene chloride, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give product **17** (324 mg, 0.85 mmol, 80%) as a white solid. *R_f* (50% EtOAc/hexanes) = 0.15; mp: 118-119 °C; [α]_D²¹ = 14.0 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3420, 3390, 2922, 1611, 1513, 1456, 1360, 1246, 1094, 1000, 897, 823; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, *J* = 8.4, 2H), 6.87 (d, *J* = 8.4, 2H), 6.22 (dd, *J* = 10.2, 5.4, 1.2, 1H), 5.87 (dd, *J* = 10.2, 3.6, 1H), 5.07 (dd, *J* = 2.4, 0.6, 1H), 4.82 (d, *J* = 12.0, 1H), 4.60 (m, 1H), 4.53 (d, *J* = 12.0, 1H), 4.52 (dd, *J* = 9.6, 2.4, 1H), 4.22 (qd, *J* = 6.6, 2.4, 1H), 3.80 (s, 3H), 3.63 (m, 1H), 3.60 (ddd, *J* = 12.0, 8.4, 5.4, 1H), 3.32 (dq, *J* = 9, 6.0, 1H), 3.04 (dd, *J* = 8.4, 8.4, 1H), 2.25 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 1.67 (ddd, *J* = 12.6, 12.0, 9.6, 1H), 1.51 (m, 1H), 1.35 (d, *J* = 6.6, 3H), 1.33 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) 159.3, 130.3, 129.6, 129.5, 127.2, 113.8, 98.1, 96.6, 88.9, 70.4, 70.1, 70.0, 67.8, 63.5, 55.3, 38.2, 18.0, 15.9; CIHRMS Calcd for [C₂₀H₂₈O₇Na]⁺: 403.1733, Found 403.1728.

(2*S*, 3*S*, 6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-ol (18**):**

Allylic alcohol **17** (415 mg, 1.09 mmol) was dissolved in CH₂Cl₂ (11 mL) at room temperature, then NBSH (1.33 g, 6.55 mmol) and Et₃N (0.88 g, 8.74 mmol) were added while stirring. The reaction was tracked by TLC, after 12 h, the reaction was quenched by adding 10 mL of satd. aq. NaHCO₃, extracted (3 x 50 mL) with methylene chloride, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give diol **18** (420 mg, 1.09 mmol, 80%) as a yellow oil. *R_f* (50% EtOAc/hexanes) = 0.15; $[\alpha]_D^{21} = -98.2$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3390, 2933, 1612, 1514, 1443, 1368, 1246, 1166, 1114, 1066, 1011, 940, 818; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, *J* = 9.0, 2H), 6.87 (d, *J* = 9.0, 2H), 4.92 (d, *J* = 3, 1H), 4.91 (d, *J* = 3, 1H), 4.81 (d, *J* = 11.4, 1H), 4.79 (d, *J* = 1.2, 1H), 4.52 (d, *J* = 11.4, 1H), 4.50 (dd, *J* = 10.2, 2.4, 1H), 3.79 (s, 3H), 4.14 (qd, *J* = 6.6, 1.2, 1H), 3.62 (m, 1H), 3.56 (m, 1H), 3.31 (dq, *J* = 9, 6.0, 1H), 2.98 (dd, *J* = 8.4, 8.4, 1H), 2.21 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 2.06 (ddd, *J* = 13.8, 13.8, 3.6, 3.6, 1H), 1.98 (ddd, *J* = 13.8, 13.8, 3, 3, 1H), 1.76 (ddd, *J* = 13.2, 7.2, 3.6, 1H), 1.68-1.58 (m, 2H), 1.32 (d, *J* = 6.6, 3H), 1.21 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) 159.3, 129.7, 129.5, 113.8, 99.6, 98.0, 88.7, 70.4, 70.3, 69.9, 68.0, 67.1, 55.3, 38.2, 25.4, 24.2, 18.1, 16.9; CIHRMS Calcd for [C₂₀H₃₀O₇Na]⁺: 405.1889, Found 405.1885.

(2*S*,6*R*)-6-((2*S*,3*S*,6*S*)-6-((2*R*,3*S*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-2*H*-3(6*H*)-one (19):

A CH₂Cl₂ (0.1 mL) solution of Boc pyranone **5(α-L)** (32.23 mg, 0.14 mmol) and alcohol **18** (18 mg, 0.047 mmol) was cooled to 0 °C. Pd₂(DBA)₃•CHCl₃ (1.22 mg, 2.5 mol%) and PPh₃ (1.06 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with 1 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with CH₂Cl₂, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone **19** (8 mg, 0.016 mmol, 35%) as a white solid along with 61% of recovered starting material **18** (11 mg, 0.029 mmol): *R_f* (50% EtOAc/hexanes) = 0.50; mp: 112-113 °C; [α]_D²¹ = -16.7 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3417, 2920, 1698, 1612, 1514, 1457, 1371, 1247, 1067, 1030, 810; ¹H NMR (600 MHz, CDCl₃) δ 7.21 (d, *J* = 9.0, 2H), 6.82 (d, *J* = 9.0, 2H), 6.79 (dd, *J* = 10.2, 3.6, 1H), 6.03 (d, *J* = 10.2, 1H), 5.16 (d, *J* = 3.6, 1H), 4.87 (m, 1H), 4.75 (d, *J* = 11.4, 1H), 4.48 (q, *J* = 6.6, 1H), 4.46 (d, *J* = 11.4, 1H), 3.73 (s, 3H), 4.68 (m, 1H), 4.45 (dd, *J* = 10, 5, 1H), 4.09 (qd, *J* = 6.6, 1.2, 1H), 3.60 (m, 1H), 3.50 (m, 1H), 3.25 (dq, *J* = 9, 6.0, 1H), 2.91 (dd, *J* = 9, 9, 1H), 2.15 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 2.02-1.95 (m, 2H), 1.90-1.85 (m, 1H), 1.60-1.54 (m, 2H), 1.35 (d, *J* = 6.6, 3H), 1.30 (d, *J* = 6.6, 3H), 1.16 (d, *J* = 6.6, 3H);

^{13}C NMR (150 MHz, CDCl_3) 196.5, 159.3, 142.7, 129.6, 129.5, 127.4, 113.8, 98.3, 98.0, 95.2, 88.6, 76.1, 70.6, 70.4, 70.3, 69.9, 67.7, 55.2, 38.2, 25.1, 24.3, 18.1, 16.9, 15.1; CIHRMS Calcd for $[\text{C}_{26}\text{H}_{36}\text{O}_9\text{Na}]^+$: 515.2257, Found 515.2253.

(2*R*,3*S*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (20**):**

Alcohol **19** (75 mg, 0.152 mmol) was dissolved in CH₂Cl₂ (0.2 mL) at room temperature, then acetic anhydride (46.7 mg, 0.457 mmol), pyridine (42.1 mg, 0.532 mmol) and a catalytic amount of DMAP were added in above order. The reaction mixture was stirred at room temperature for 12 h. Reaction mixture was washed with 1 mL 1M HCl solution, followed by washing with 2 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with CH₂Cl₂, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give **20** (67 mg, 0.13 mmol, 82%) as a yellow oil: *R_f* (50% EtOAc/hexanes) = 0.60; $[\alpha]_D^{21} = -47.7$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2928, 1733, 1699, 1613, 1514, 1363, 1239, 1122, 1068, 1030, 962, 734; ¹H NMR (600 MHz, CDCl₃) δ 7.25 (d, *J* = 8.3, 2H), 6.87 (d, *J* = 8.3, 2H), 6.86 (dd, *J* = 10.1, 3.5, 1H), 6.09 (d, *J* = 10.2, 1H), 5.22 (d, *J* = 3.4, 1H), 4.95 (d, *J* = 2.1, 1H), 4.88 (ddd, *J* = 9.0, 8.0, 2, 1H), 4.80 (d, *J* = 11.6, 1H), 4.54 (dd, *J* = 9.7, 5.4, 1H), 4.52 (d, *J* = 11.6, 1H), 4.13 (q, *J* = 7.1, 1H), 4.00 (qd, *J* = 6.6, 1.2, 1H), 3.81 (s, 3H), 3.58 (ddd, *J* = 3.5, 3.0, 1.6, 1H), 3.36 (dd, *J* = 8.0, 7.0, 1H), 3.36 (dq, *J* = 7, 6.6, 1H), 2.27 (ddd, *J* = 12.5, 5.4, 2.0, 1H), 2.01 (ddd, *J* = 13.0, 3.5, 2.9, 0.7, 1H), 2.01 (s, 3H), 1.96 (ddd, *J* =

13.1, 3.5, 3.3, 0.7, 1H), 1.89 (ddd, $J = 13.1, 3.8, 3.5, 3.0, 1\text{H}$), 1.63 (ddd, $J = 12.5, 9.7, 9, 1\text{H}$), 1.55 (ddd, $J = 13.0, 3.8, 3.3, 1.2, 1\text{H}$), 1.37 (d, $J = 6.8, 3\text{H}$), 1.35 (d, $J = 6.6, 3\text{H}$), 1.16 (d, $J = 6.6, 3\text{H}$); ^{13}C NMR (150 MHz, CDCl_3) 196.7, 170.5, 159.4, 143.0, 129.6, 129.3, 127.3, 113.8, 98.2, 97.4, 95.3, 80.5, 76.6, 72.2, 71.5, 70.5, 70.1, 66.6, 55.3, 36.7, 24.8, 24.2, 21.3, 18.4, 17.1, 15.1; CIHRMS Calcd for $[\text{C}_{28}\text{H}_{38}\text{O}_{10}\text{Na}]^+$: 557.2363, Found 557.2358.

(2*R*,3*S*,4*R*,6*R*)-6-(hydroxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (43**):**

PMB ether **20** (100 mg, 0.187 mmol) was dissolved in CH₂Cl₂ (0.2 mL) and water (0.1 mL) at 0 °C, then excess DDQ (85 mg, 0.374 mmol) was added. The reaction mixture was stirred at 0 °C for 5h, at which time the reaction was filtered to remove precipitates, and washed with 2 mL of satd. aq. NaHCO₃. Resulting solution was extracted (3 x 5 mL) with CH₂Cl₂, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give **43** (67 mg, 0.13 mmol, 82%) as a yellow oil:

As an equilibrating mixture of stereo- and regio-isomers:

R_f (30% EtOAc/hexanes) = 0.20; $[\alpha]_D^{21} = 40.7$ ($c = 1.0$, CH₂Cl₂); IR (thin film, cm⁻¹) 2928, 1733, 1699, 1613, 1514, 1363, 1239, 1122, 1068, 1030, 962, 734; ¹H NMR (600 MHz, CDCl₃) δ 6.87/6.86 (m, 1H), 6.09 (d, $J = 10.2$), 5.29 (s)/5.25 (ddd, $J = 13.8, 9.0, 4.8$), 5.21 (m), 4.96 (m)/4.91 (ddd)/4.87 (d), 4.55 (m, 1H), 4.02 (m, 2H), 3.58 (m, 1H), 3.45 (m)/3.35(m), 3.16 (m), 2.66 (m), 2.49 (m), 2.38 (ddd, $J = 12.6, 5.4, 1.8$), 2.25 (ddd, $J = 13.2, 5.4, 1.8$), 2.15-1.80 (m), 2.06/2.05 (s, 3H), 1.73-1.4 (m), 1.4-1.16 (m); ¹³C NMR (150 MHz, CDCl₃) 196.84/196.78,

170.5/170.4, 143.03/142.98, 127.3, 98.3/98.2, 95.4/95.3, 93.43/93.39, 91.39/91.37, 81.0, 80.2, 72.0/ 71.7, 70.6/70.2, 67.3/66.6, 38.1/35.6, 29.8, 24.8, 24.3, 21.4/21.3, 18.4, 17.2, 15.1;
CIHRMS Calcd for $[\text{C}_{20}\text{H}_{30}\text{NaO}_9]^+$: 437.8, Found 437.1786.

(2*S*,6*S*)-6-(4-methoxybenzyloxy)-2-methyl-2*H*-pyran-3(6*H*)-one (*ent*-9):^{††}

A CH₂Cl₂ (10 mL) solution of *tert*-butyl (2*S*,6*R*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl carbonate **6(β-D)** (11.4 g, 50 mmol) and 4-methoxybenzyl alcohol (13.8 g, 100 mL) was cooled to 0 °C, Pd₂(DBA)₃•CHCl₃ (260 mg, 1.0 mol%) and PPh₃ (226 mg, 2 mol%) were added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, and was quenched by adding 50 mL of satd. aq. NaHCO₃. Resulting solution was extracted three times with ether, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexanes to give pyranone *ent*-9 (12.1 g, 50 mmol, 99%) as a yellow oil: *R*_f(10% EtOAc/hexanes) = 0.15; [*α*]_D²¹ = 22.9 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2938, 2837, 1696, 1513, 1246, 1054, 1008, 818, 802; ¹H NMR (600 MHz, CDCl₃) δ 7.23 (d, *J* = 8.4, 2H), 6.88 (d, *J* = 8.4, 2H), 6.83 (dd, *J* = 10.2, 1.2, 1H), 6.03 (d, *J* = 10.2, 1H), 5.29 (d, *J* = 1.2, 1H), 4.79 (d, *J* = 11.4, 1H), 4.54 (d, *J* = 11.4, 1H), 4.15 (q, *J* = 6.6, 1H), 3.71 (s, 3H), 1.45 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 196.5, 159.2, 146.5, 129.5, 128.7, 127.7, 113.6, 93.9, 74.9, 69.5, 54.9, 16.9; CIHRMS Calcd for [C₁₄H₁₆O₄H]⁺: 249.1127. Found 249.1122.

^{††} For compounds in the enantiomeric series only ¹H NMR, ¹³C NMR and optical rotations were recorded.

(2*S*,6*S*)-6-(4-methoxybenzyloxy)-3,6-dihydro-2-methyl-2*H*-pyran-3-ol (*ent*-10a/b):^{††}

Pyranone **9** (12 g, 50 mmol) was dissolved in 100 mL CH₂Cl₂, and resulting solution was cooled to -78 °C. 100 mL of 0.4 M CeCl₃ in methanol solution was added in a dropwise fashion, followed by adding 1 g of NaBH₄. By TLC tracking, the reaction was done after 1.5 h. The reaction mixture was diluted with 10 mL diethyl ether, and quenched with 10 mL water. Resulting solution was extracted with 3 x 20 mL diethyl ether, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 80% EtOAc/Hexane to give allylic alcohol *ent*-**10a/b** as a mixture of diastereomers (12.0 g, 49 mmol, 99%) as a colorless oil: *R_f* (30% EtOAc/hexanes) = 0.45; [α]_D²¹ = 59 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3421, 2977, 2871, 1612, 1513, 1244, 1172, 1031, 818, 788;

10a ¹H NMR (600 MHz, CDCl₃) δ 7.26 (d, *J* = 8.4, 2H), 6.85 (d, *J* = 8.4, 2H), 6.11 (ddd, *J* = 10.2, 5.4, 1.8, 1H), 5.81 (d, *J* = 10.2, 1H), 5.09 (m, 1H), 4.80 (d, *J* = 11.4, 1H), 4.56 (d, *J* = 11.4, 1H), 3.77 (s, 3H), 3.68 (m, 1H), 3.64 (m, 1H), 2.00 (m, 1H), 1.30 (d, *J* = 6, 3H); **10b** ¹H NMR (600 MHz, CDCl₃) δ 7.26 (d, *J* = 8.4, 2H), 6.85 (d, *J* = 8.4, 2H), 5.92 (d, *J* = 10.2, 1H), 5.75 (d, *J* = 10.2, 1H), 5.09 (m, 1H), 4.76 (d, *J* = 11.4, 1H), 4.52 (d, *J* = 11.4, 1H), 3.77 (s, 3H), 3.71 (m, 1H), 3.68 (m, 1H), 2.00 (m, 1H), 1.35 (d, *J* = 6, 3H); ¹³C NMR (150 MHz, CDCl₃) major isomer δ 159.3 (2C), 131.2 (2C), 129.7, 129.6, 113.8, 96.7, 71.5, 69.6, 68.4, 64.8, 55.3, 16.6; CIHRMS Calcd for [C₁₄H₁₈O₄Na]⁺: 273.1103. Found 273.1100.

(2*S*,6*S*)-2-(4-methoxybenzyloxy)-3,6-dihydro-6-methyl-2H-pyran (*ent*-11):^{††}

A flask charged with dry *N*-Methyl morpholine (NMM) 80 mL, triphenyl phosphine (27.5 g, 120 mmol) was cooled to -30 °C under argon atmosphere. Diethylazodicarboxylate (20 mL, 150 mmol) was added and the reaction was stirred for 5 min, allylic alcohol (10 g, 41 mmol) was added in a solution of 1 M NMM (50 mL), the resulting reaction mixture was stirred for 10 min, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (30 g). The reaction was stirred at -30 °C for 2 h and monitored by TLC. Upon consumption of **10a/b**, the reaction was warmed to room temperature and stirred for another 2 h. The reaction mixture was diluted with ether (100 mL) and was quenched with 50 mL of satd. aq. NaHCO₃, extracted (3 x 50 mL) with ether, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 95% EtOAc/hexanes to give ***ent*-11** product (9.10 g, 40 mmol, 98%) as a yellow oil. R_f (20% EtOAc/hexanes) = 0.55; $[\alpha]_D^{21} = 107$ ($c = 1.0$, CH₂Cl₂); IR (thin film, cm⁻¹) 3034, 2909, 1612, 1512, 1365, 1245, 1155, 1075, 1045, 879, 818; ¹H NMR (600 MHz, CDCl₃) δ 7.30 (d, $J = 7.8$, 2H), 6.88 (d, $J = 7.8$, 2H), 5.67 (dddd, $J = 9.6, 2.4, 1.2, 1.2$, 1H), 5.58 (dddd, $J = 9.6, 5.4, 2.4, 2.4$, 1H), 4.86 (d, $J = 11.4$, 1H), 4.72 (dd, $J = 8.4, 3.0$, 1H), 4.55 (d, $J = 11.4$, 1H), 4.33 (m, 1H), 3.78 (s, 3H), 2.22 (m, 1H), 2.13 (m, 1H), 1.32 (d, $J = 7.2$, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 159.0, 130.8, 129.8, 129.4, 122.3, 113.6, 97.3, 70.4, 69.2, 55.0, 30.8, 21.0; CIHRMS Calcd for [C₁₄H₁₈O₃Na]⁺: 257.1154. Found 257.1148.

(2*S*,3*R*,4*R*,6*S*)-6-(4-methoxybenzyloxy)-2-methyl-tetrahydron-2*H*-pyran-3,4-diol (*ent*-12):^{††}

To a t-butanol/acetone (25 mL each, 1:1) solution of pyran ***ent*-11** (5 g, 22 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (25 mL). Crystalline OsO₄ (5 mg, 5 mol %) was added and the reaction was stirred for 12 h. The reaction was quenched by adding EtOAc and satd. aq. NaHCO₃. The organic layer was separated and concentrated. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give diol ***ent*-12** (5.1 g, 19 mmol, 86%) as a colorless oil. *R_f* (50% EtOAc/hexanes) = 0.20; $[\alpha]_{\text{D}}^{21} = 53.5$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3411, 2933, 1612, 1513, 1245, 1161, 1032, 997, 819; ¹H NMR (600 MHz, CDCl₃) δ 7.23 (d, *J* = 8.4, 2H), 6.83 (d, *J* = 8.4, 2H), 4.84 (dd, *J* = 9.6, 1.8, 1H), 4.77 (d, *J* = 11.4, 1H), 4.45 (d, *J* = 11.4, 1H), 3.98 (d, *J* = 8.4, 2H), 4.84 (dd, *J* = 9.6, 1.8, 1H), 4.77 (d, *J* = 11.4, 1H), 4.45 (d, *J* = 11.4, 1H), 3.98 (d, *J* = 8.4, 2H), 3.75 (s, 3H), 3.68 (dq, *J* = 9.0, 6.0, 1H), 3.22 (dd, *J* = 3.6, 1H), 3.05 (s, 1H), 2.98 (s, 1H), 2.02 (ddd, *J* = 15, 2.4, 2.4, 1H), 1.69 (ddd, *J* = 14, 11.4, 3.0, 1H), 1.28 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 159.1, 129.6, 129.5, 113.7, 96.6, 72.8, 70.1, 69.4, 67.7, 55.1, 37.5, 18.0; CIHRMS Calcd for [C₁₄H₂₀O₅Na]⁺: 291.1208, Found 291.1205.

(2*S*,3*S*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-tetrahydro-3-hydroxy-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (*ent*-13):^{††}

A THF (16 mL) solution of diol *ent*-12 (5.0 g, 18.6 mmol) at 0 °C was added PPh₃ (5.8 g, 26 mmol), *p*-nitrobenzoic acid (5.8 g, 26 mmol), and DIAD (5.6 g, 28 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and stirred for three days. The reaction mixture was diluted with 100 mL EtOAc, quenched with 100 mL of satd. aq. NaHCO₃, extracted (3 x 50 mL) with ether, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 15% EtOAc/Hexanes to give nitrobenzoate *ent*-13 (4.98 g, 12 mmol, 65%) as a yellow solid. *R*_f (30% EtOAc/hexanes) = 0.40; mp: 38-40 °C; [α]_D²¹ = 40.0 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3477, 2939, 1722, 1609, 1513, 1347, 1269, 1166, 1100, 987; ¹H NMR (600 MHz, CDCl₃) δ 8.15 (d, *J* = 9.0, 2H), 8.10 (d, *J* = 9.0, 2H), 7.21 (d, *J* = 8.4, 2H), 6.82 (d, *J* = 8.4, 2H), 5.02 (ddd, *J* = 11.4, 8.4, 4.8, 1H), 4.78 (d, *J* = 11.4, 1H), 4.61 (dd, *J* = 10.2, 2.4, 1H), 4.51 (d, *J* = 11.4, 1H), 3.74 (s, 3H), 3.36 (dq, *J* = 9.0, 6.0, 1H), 3.41 (dd, *J* = 9.0, 9.0, 1H), 2.93 (s, 1H), 2.35 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 1.78 (ddd, *J* = 12, 12, 9.6, 1H), 1.19 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 164.5 (2C), 159.1 (2C), 150.4 (2C), 135.0 (2C), 130.6, 129.4, 129.1, 123.3, 113.7, 97.3, 75.4, 74.5, 71.8, 70.0, 55.0, 36.3, 17.7; CIHRMS Calcd for [C₂₁H₂₃NO₈Na]⁺: 440.1321, Found 440.1317.

(2*S*,3*S*,4*S*,6*S*)-3-((2*R*,6*S*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (*ent*-14):^{††}

A CH₂Cl₂ (1.0 mL) solution of Boc pyranone **5(α-L)** (5.0 g, 22 mmol) and alcohol *ent*-13 (2.0 mg, 4.8 mmol) was cooled to 0 °C. Pd₂(DBA)₃•CHCl₃ (60 mg, 1.3 mol%) and PPh₃ (52 mg, 5 mol%) were added to the reaction mixture at 0 °C. After 8 hours stirring, the reaction mixture was quenched with 20 mL of satd. aq. NaHCO₃, extracted (3 x 20 mL) with Et₂O, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give pyranone *ent*-14 (2.2 g, 4.2 mmol, 87%) as a yellow solid: *R_f* (30% EtOAc/hexanes) = 0.40; mp: 52-54°C; [α]_D²¹ = 88 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2937, 1723, 1697, 1609, 1527, 1514, 1272, 1101, 979, 832; ¹H NMR (600 MHz, CDCl₃) δ 8.26 (d, *J* = 8.4, 2H), 8.18 (d, *J* = 8.4, 2H), 7.24 (d, *J* = 8.4, 2H), 6.85 (d, *J* = 8.4, 2H), 6.75 (dd, *J* = 10.2, 3.6, 1H), 5.97 (d, *J* = 10.2, 1H), 5.30 (d, *J* = 3.6, 1H), 5.26 (ddd, *J* = 11.4, 9.0, 6.0 1H), 4.81 (d, *J* = 11.4, 1H), 4.66 (d, *J* = 9.6, 1H), 4.53 (d, *J* = 11.4, 1H), 4.29 (q, *J* = 6.6, 1H), 3.77 (s, 3H), 3.62 (dd, *J* = 9.0, 9.0, 1H), 3.47 (dq, *J* = 9.0, 6.6, 1H), 2.38 (dd, *J* = 12.6, 5.4, 1H), 1.80 (ddd, *J* = 12.6, 12, 12, 1H), 1.41 (d, *J* = 6.6, 3H), 0.88 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 196.3, 163.9, 159.4, 150.6, 142.5, 135.4, 130.7, 129.6, 129.1, 126.8, 123.5, 113.9, 97.3, 94.4, 82.6, 73.2, 71.0, 71.0, 70.2, 55.2, 36.7, 18.3, 15.0; CIHRMS Calcd for [C₂₇H₂₉NO₁₀Na]⁺: 550.1689, Found 550.1690.

(2*S*,3*S*,4*S*,6*S*)-3-((2*S*, 5*R*, 6*R*)-5,6-dihydro-5-hydroxy-6-methyl-2*H*-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (*ent*-15):^{††}

Pyranone ***ent*-14** (2.0 g, 3.9 mmol) was dissolved in 10 mL CH₂Cl₂, resulting solution was cooled to -78 °C, 10 mL of 0.4 M CeCl₃ in methanol solution was added dropwise, followed by 200 mg of NaBH₄. By TLC tracking, the reaction was completed after 1.5 h. The reaction mixture was diluted with 50 mL diethyl ether, and quenched with 2 mL water. Extraction by 3 x 50 mL diethyl ether, drying over Na₂SO₄ and concentration under reduced pressure gave allylic alcohol ***ent*-15** (2.0 g, 3.8 mmol, 97%) as a white solid. *R_f* (30% EtOAc/hexanes) = 0.20; mp: 159.5-160.5 °C; [α]_D²¹ = 114 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3384, 1718, 1527, 1513, 1282, 1104, 996, 717; ¹H NMR (150 MHz, CDCl₃) δ 8.26 (d, *J* = 11, 1H), 8.19 (d, *J* = 11, 1H), 7.25 (d, *J* = 9.0, 2H), 6.86 (d, *J* = 9.0, 2H), 5.84 (d, *J* = 10.2, 1H), 5.66 (ddd, *J* = 10.2, 2.4, 2.4, 1H), 5.21 (ddd, *J* = 12.0, 8.4, 5.4 1H), 5.04 (d, *J* = 2.4, 1H), 4.81 (d, *J* = 11.4, 1H), 4.62 (dd, *J* = 9.6, 2.4, 1H), 4.53 (d, *J* = 11.4, 1H), 3.79 (s, 3H), 3.60 (ddd, *J* = 9.0, 9.0, 1.8, 1H), 3.53 (dd, *J* = 9.0, 9.0, 1H), 3.46 (dq, *J* = 9.0, 6.0, 1H), 3.42 (dq, *J* = 9.0, 6.0, 1H), 2.36 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 1.80 (ddd, *J* = 12.6, 12, 10.2, 1H), 1.60(s, 1H), 1.41 (d, *J* = 6.6, 1H), 0.81 (d, *J* = 6.0, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 164.0, 159.4, 150.5, 135.8, 133.2, 130.8, 129.7, 129.2, 126.2, 123.5, 113.9, 97.4, 95.5, 81.8, 73.4, 71.3, 70.2, 69.1, 68.6, 55.3, 36.7, 18.4, 17.6; CIHRMS Calcd for [C₂₇H₃₁NO₁₀Na]⁺: 552.1846, Found 552.1841.

(2*S*,3*S*,4*S*,6*S*)-3-((2*S*, 5*S*, 6*R*)-5,6-dihydro-5-(4-nitrobenzoate)-6-methyl-2*H*-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (*ent*-16):^{††}

A THF (0.7 mL) solution of alcohol ***ent*-15** (1 g, 2.0 mmol) at 0 °C was added PPh₃ (910 mg, 4.0 mmol) and *p*-nitrobenzoic acid (670 mg, 4.0 mmol). DIAD (8.0 g, 4.0 mmol) was added dropwise and the reaction mixture was warmed up to room temperature and stirred for three days. The reaction mixture was diluted with 5 mL EtOAc, quenched with 10 mL of satd. aq. NaHCO₃, extracted (3 x 20 mL) with methylene chloride, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give ***ent*-16** product (550 mg, 82 mmol, 41%) as a light yellow solid. *R_f* (30% EtOAc/hexanes) = 0.40; mp: 174-175 °C; [α]_D²¹ = -89.9 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2930, 1723, 1609, 1519, 1342, 1266, 1069, 1040, 987, 834, 754; ¹H NMR (600 MHz, CDCl₃) δ 8.22 (d, *J* = 9.0, 2H), 8.17 (d, *J* = 9.0, 2H), 8.16 (d, *J* = 9.0, 2H), 8.02 (d, *J* = 9.0, 2H), 7.20 (d, *J* = 9.0, 2H), 6.81 (d, *J* = 9.0, 2H), 6.06 (dd, *J* = 10.2, 5.4, 1H), 5.96 (dd, *J* = 10.2, 3.0, 1H), 5.21 (ddd, *J* = 12.0, 9.0, 5.4 1H), 5.15 (d, *J* = 3, 1H), 4.91 (dd *J* = 9.6, 2.4, 1H), 4.76 (d, *J* = 11.4, 1H), 4.58 (dd *J* = 9.6, 1.8, 1H), 4.49 (d, *J* = 11.4, 1H), 4.03 (dq, *J* = 6.6, 3, 1H), 4.03 (dq, *J* = 9.0, 6.2, 1H), 3.74 (s, 3H), 3.55 (dd, *J* = 8.4, 8.4, 1H), 2.32 (ddd, *J* = 12, 6.0, 1.8, 1H), 1.79 (ddd, *J* = 15, 9.6, 9.6, 1H), 1.38 (d, *J* = 6.6, 3H), 0.71 (d, *J* = 6.6, 3H); ¹³C (150 MHz, CDCl₃) 164.1, 164.0, 159.5, 150.7, 150.6, 135.7, 135.0, 130.9, 130.7, 130.6, 129.7, 129.2, 125.1,

123.5, 123.5, 113.9, 97.3, 95.3, 81.8, 73.2, 71.3, 70.2, 66.1, 65.3, 55.3, 36.7, 18.5, 15.8;

CIHRMS Calcd for $[\text{C}_{34}\text{H}_{34}\text{N}_2\text{O}_{13}\text{Na}]^+$: 701.1959, Found 701.1961.

(2*R*, 3*R*, 6*R*)-6-((2*S*,3*S*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (*ent*-17):^{††}

Bis-nitrobenzoate ***ent*-16** (500 mg, 0.74 mmol) was dissolved in a mixed solvent of THF/H₂O (15 mL/3 mL) at room temperature, LiOH (100 mg, 4.20 mmol) was added and the reaction stirred for 24 h. The reaction was quenched by adding 5 mL of satd. aq. NaHCO₃, extracted (3 x 50 mL) with methylene chloride, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give product ***ent*-17** (265 mg, 0.70 mmol, 70%) as a white solid. *R_f* (50% EtOAc/hexanes) = 0.15; mp: 118-119 °C; [α]_D²¹ = -15.0 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3420, 3390, 2922, 1611, 1513, 1456, 1360, 1246, 1094, 1000, 897, 823; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, *J* = 8.4, 2H), 6.87 (d, *J* = 8.4, 2H), 6.22 (dd, *J* = 10.2, 5.4, 1.2, 1H), 5.87 (dd, *J* = 10.2, 3.6, 1H), 5.07 (dd, *J* = 2.4, 0.6, 1H), 4.82 (d, *J* = 12.0, 1H), 4.60 (m, 1H), 4.53 (d, *J* = 12.0, 1H), 4.52 (dd, *J* = 9.6, 2.4, 1H), 4.22 (qd, *J* = 6.6, 2.4, 1H), 3.80 (s, 3H), 3.63 (m, 1H), 3.60 (ddd, *J* = 12.0, 8.4, 5.4, 1H), 3.32 (dq, *J* = 9, 6.0, 1H), 3.04 (dd, *J* = 8.4, 8.4, 1H), 2.25 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 1.67 (ddd, *J* = 12.6, 12.0, 9.6, 1H), 1.51 (m, 1H), 1.35 (d, *J* = 6.6, 3H), 1.33 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) 159.3, 130.3, 129.6, 129.5, 127.2, 113.8, 98.1, 96.6, 88.9, 70.4, 70.1, 70.0, 67.8, 63.5, 55.3, 38.2, 18.0, 15.9; CIHRMS Calcd for [C₂₀H₂₈O₇Na]⁺: 403.1733, Found 403.1728.

(2*R*, 3*R*, 6*R*)-6-((2*S*,3*S*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-ol (*ent*-18):^{††}

Allylic alcohol ***ent*-17** (250 mg, 66 mmol) was dissolved in CH₂Cl₂ (11 mL) at room temperature. NBSH (1.33 g, 6.55 mmol) and Et₃N (0.88 g, 8.74 mmol) were added while stirring. The reaction was tracked by TLC. The reaction was quenched by adding 10 mL of satd. aq. NaHCO₃ after 12 hours, extracted (3 x 50 mL) with methylene chloride, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give diol ***ent*-18** (250 mg, 66 mmol, 99%) as a yellow oil. *R*_f(50% EtOAc/hexanes) = 0.15; [α]_D²¹ = 95 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3390, 2933, 1612, 1514, 1443, 1368, 1246, 1166, 1114, 1066, 1011, 940, 818; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, *J* = 9.0, 2H), 6.87 (d, *J* = 9.0, 2H), 4.92 (d, *J* = 3, 1H), 4.91 (d, *J* = 3, 1H), 4.81 (d, *J* = 11.4, 1H), 4.79 (d, *J* = 1.2, 1H), 4.52 (d, *J* = 11.4, 1H), 4.50 (dd, *J* = 10.2, 2.4, 1H), 3.79 (s, 3H), 4.14 (qd, *J* = 6.6, 1.2, 1H), 3.62 (m, 1H), 3.56 (m, 1H), 3.31 (dq, *J* = 9, 6.0, 1H), 2.98 (dd, *J* = 8.4, 8.4, 1H), 2.21 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 2.06 (ddd, *J* = 13.8, 13.8, 3.6, 3.6, 1H), 1.98 (ddd, *J* = 13.8, 13.8, 3, 3, 1H), 1.76 (ddd, *J* = 13.2, 7.2, 3.6, 1H), 1.68-1.58 (m, 2H), 1.32 (d, *J* = 6.6, 3H), 1.21 (d, *J* = 6.6, 3H); ¹³C NMR (150 MHz, CDCl₃) 159.3, 129.7, 129.5, 113.8, 99.6, 98.0, 88.7, 70.4, 70.3, 69.9, 68.0, 67.1, 55.3, 38.2, 25.4, 24.2, 18.1, 16.9; CIHRMS Calcd for [C₂₀H₃₀O₇Na]⁺: 405.1889, Found 405.1885.

(2*R*,6*S*)-6-((2*R*,3*R*,6*R*)-6-((2*S*,3*R*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-2*H*-3(6*H*)-pyran-3-one (*ent*-19):^{††}

A CH₂Cl₂ (0.1 mL) solution of Boc pyranone **5(α-L)** (65 mg, 29 mmol) and alcohol (50 mg, 0.13 mmol) was cooled to 0 °C. Pd₂(DBA)₃•CHCl₃ (1.22 mg, 1.3 mol%) and PPh₃ (1.06 mg, 5 mol%) were added to the reaction mixture at 0 °C. After stirring at room temperature for 12 h, the reaction mixture was quenched with 1 mL of satd. aq. NaHCO₃, extracted (3 x 5 mL) with CH₂Cl₂, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/Hexanes to give pyranone *ent*-**19** (25 mg, 0.05 mmol, 40%) as a white solid along with 50% recovered starting material *ent*-**18** (25 mg, 0.065 mmol): *R_f* (50% EtOAc/hexane) = 0.50; mp: 112-113 °C; [α]_D²¹ = 18 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3417, 2920, 1698, 1612, 1514, 1457, 1371, 1247, 1067, 1030, 810; ¹H NMR (600 MHz, CDCl₃) δ 7.21 (d, *J* = 9.0, 2H), 6.82 (d, *J* = 9.0, 2H), 6.79 (dd, *J* = 10.2, 3.6, 1H), 6.03 (d, *J* = 10.2, 1H), 5.16 (d, *J* = 3.6, 1H), 4.87 (m, 1H), 4.75 (d, *J* = 11.4, 1H), 4.48 (q, *J* = 6.6, 1H), 4.46 (d, *J* = 11.4, 1H), 3.73 (s, 3H), 4.68 (m, 1H), 4.45 (dd, *J* = 10, 5, 1H), 4.09 (qd, *J* = 6.6, 1.2, 1H), 3.60 (m, 1H), 3.50 (m, 1H), 3.25 (dq, *J* = 9, 6.0, 1H), 2.91 (dd, *J* = 9, 9, 1H), 2.15 (ddd, *J* = 12.6, 5.4, 1.8, 1H), 2.02-1.95 (m, 2H), 1.90-1.85 (m, 1H), 1.60-1.54 (m,

2H), 1.35 (d, $J = 6.6$, 3H), 1.30 (d, $J = 6.6$, 3H), 1.16 (d, $J = 6.6$, 3H); ^{13}C NMR (150 MHz, CDCl_3) 196.5, 159.3, 142.7, 129.6, 129.5, 127.4, 113.8, 98.3, 98.0, 95.2, 88.6, 76.1, 70.6, 70.4, 70.3, 69.9, 67.7, 55.2, 38.2, 25.1, 24.3, 18.1, 16.9, 15.1; CIHRMS Calcd for $[\text{C}_{26}\text{H}_{36}\text{O}_9\text{Na}]^+$: 515.2257, Found 515.2253.

(2S,6R)-6-((2S,3S,6S)-6-((2R,3S,4R,6R)-6-(4-methoxybenzyloxy)-4-acetoxy-2-methyl-tetrahydro-2H-pyran-3-yloxy)-2-methyl-tetrahydro-2H-pyran-3-yloxy)-2-methyl-2H-3(6H)-one (20):

C: Experimental Procedures for Chapter II:

(6R)-6-pivaloyl-(2R)-2-methyl 2H-pyran-3(6H)-one (35).

Compound **7a** (2.22 g, 8.59 mmol), 30 mL of CH₂Cl₂, and 1.5 mL of Et₃N were added to a round bottom flask and cooled to -78 °C. A catalytic amount (53 mg, 0.43 mmol) of DMAP and pivaloyl chloride (1.06 mL, 8.59 mmol) were added and the solution was stirred for 3 h at -78 °C. The reaction was quenched with 50 mL of sat. aq. NaHCO₃, extracted (3 x 50 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10 % EtOAc/hexanes to give 2.41 g (7.04 mmol, 82 %) of **35**. *R_f* (20 % EtOAc/hexanes) = 0.4; [α]²¹_D = -66 (c = 0.1, CH₂Cl₂); IR (thin film, cm⁻¹) 2935, 2910, 2855, 1738, 1692, 1461, 1399, 1279; ¹H NMR (600 MHz, CDCl₃) δ 6.88 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.46 (d, *J* = 3.6 Hz, 1H), 6.19 (d, *J* = 10.2 Hz, 1H), 4.57 (q, *J* = 6.6 Hz, 1H), 1.40 (d, *J* = 6.6 Hz, 3H), 1.23 (s, 9H), ¹³C NMR (150 MHz, CDCl₃) δ 195.9, 177.0, 141.8, 128.2, 86.9, 72.3, 39.2, 27.0, 15.4; CI HRMS calcd for [C₁₁H₁₆O₄]⁺: 212.1049, Found 212.1045.

((2*R*,5*S*,6*R*)-5,6-dihydro-5-hydroxy-6-methyl-2H-pyran-2-yl pivalate (36**).**

A solution of pyranone **35** (580 mg, 2.74 mmol) in CH₂Cl₂ (1.5 mL) and 0.4 M CeCl₃/MeOH (1.5 mL) was cooled to -78 °C. NaBH₄ (58.4 mg, 1.54 mmol) was added and the reaction mixture was stirred for 4 h at -78 °C. The resulting solution was diluted with ether (10 mL), quenched with 5 mL of saturated NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel chromatography eluting with 40% EtOAc/hexane to give enol **36** (400 mg, 1.90 mmol, 68%) as a white solid, mp: 62.5-64.0 °C; *R*_f = 0.30 (40% EtOAc/Hexane); $[\alpha]_D^{21} = 21$ (*c* = 0.55, CH₂Cl₂); IR (thin film, cm⁻¹) 3391, 2972, 2933, 2837, 1720, 1612, 1513, 1246, 1029, 999, 819; ¹H NMR (600 MHz, CDCl₃) 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), 2.20 (s, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.20 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 177.7, 134.7, 125.1, 88.4, 70.3, 69.2, 39.1, 27.1, 18.0; CIHRMS: Calculated for [C₁₁H₁₈O₄Na⁺]: 237.1102. Found: 237.1099.

((2*R*,5*S*,6*R*)-3,4,5,6-tetrahydro-5-hydroxy-6-methyl-2H-pyran-2-yl pivalate (37**)).**

A solution of allylic alcohol **36** (370 mg, 1.73 mmol) was dissolved in CH₂Cl₂ (11 mL) at room temperature. NBSH (1.33 g, 6.55 mmol) and Et₃N (0.88 g, 8.74 mmol) were added while stirring. The reaction was tracked by TLC. After 12 h, the reaction was quenched by adding 10 mL of satd. aq. NaHCO₃, extracted (3 x 50 mL) with methylene chloride, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 30% EtOAc/hexanes to give **37** (420 mg, 1.09 mmol, 80%) as a yellow oil. R_f (50% EtOAc/hexanes) = 0.15; $[\alpha]_D^{21} = -105$ ($c = 1.0$, CH₂Cl₂); IR (thin film, cm⁻¹) 3390, 2933, 1724, 1443, 1368, 1246, 1166, 1114, 1066, 1011, 940, 818; ¹H NMR; ¹H NMR (600 MHz, CDCl₃) δ 6.01 (s, 1H), 6.04 (d, $J = 9.6$ Hz, 1H), 3.65 (dq, $J = 9, 6.6$, 1H), 3.30 (ddd, $J = 10.2, 5.4, 1.8$, 1H), 1.98-1.65 (m, 4H), 1.23 (d, $J = 6.6$ Hz, 3H), 1.20 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 177.0, 90.7, 71.8, 71.5, 39.1, 28.5, 27.2, 27.0, 17.9; CIHRMS: Calculated for [C₁₁H₂₀O₄Na⁺]: 239.1259. Found: 239.1264

((2*R*,5*S*,6*R*)-4-((2'*S*,6'*R*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yloxy)-3,4,5,6-tetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl pivalate (38).

A CH₂Cl₂ (1.0 mL) solution of Boc pyranone **5(α-L)** (422 mg, 1.85 mmol) and alcohol **37** (200 mg, 0.93 mmol) was cooled to 0 °C. Pd₂(DBA)₃•CHCl₃ (24 mg, 2.5 mol%) and PPh₃ (21 mg, 10 mol%) were added to the reaction mixture at 0 °C. After stirring at room temperature for 8 h, the reaction mixture was quenched with 10 mL of satd. aq. NaHCO₃, extracted (3 x 10 mL) with Et₂O, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give pyranone **38** (210 mg, 0.65 mmol, 70%) as a yellow oil: *R_f* (30% EtOAc/hexanes) = 0.5; [α]_D²¹ = -105 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2933, 1731, 1701, 1443, 1368, 1246, 1166, 1114, 1066, 1011, 940, 818; ¹H NMR; ¹H NMR (600 MHz, CDCl₃) δ 6.75 (dd, *J* = 10.2, 3.6, 1H), 6.04 (d, *J* = 10.2, 1H), 5.98 (s, 1H), 5.25 (d, *J* = 9.6 Hz, 1H), 4.55 (q, *J* = 6.6, 1H), 3.73 (dq, *J* = 9, 6.6, 1H), 3.30 (m, 1H), 2.09-2.01 (m, 2H), 1.89-1.79 (m, 2H), 1.33 (d, *J* = 6.6 Hz, 3H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.20 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 196.4, 176.6, 142.7, 127.2, 94.7, 90.4, 80.2, 70.2, 69.8, 38.9, 28.2, 26.9, 25.8, 17.9, 15.0; CIHRMS: Calculated for [C₁₇H₂₆NaO₆⁺]:349.3745. Found: 349.3750.

((2*R*,5*S*,6*R*)-4-((2'*S*,6'*R*)-5,6-dihydro-5-(4-acetate)-6-methyl-2*H*-pyran-2-yloxy)-3,4,5,6-tetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl pivalate (39**).**

A solution of pyranone **38** (50 mg, 2.74 mmol) in CH₂Cl₂ (1.5 mL) and 0.4 M CeCl₃/MeOH (1.5 mL) was cooled to -78 °C. NaBH₄ (58.4 mg, 1.54 mmol) was added and the reaction mixture was stirred for 4 h at -78 °C. The resulting solution was diluted with ether (10 mL), quenched with 5 mL of saturated NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was dissolved in CH₂Cl₂ (1.5 mL) and DMAP (10 mg) and acetic anhydride (2 mL) was added. After 10 min the reaction was quenched by adding of Et₂O (5 mL) and 10 mL of satd. aq. NaHCO₃. Resulting mixture was extracted (3 x 10 mL) with Et₂O, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give allylic acetate **39** (65 mg, 0.65 mmol, 70%) as a yellow oil: *R_f* (30% EtOAc/hexanes) = 0.5; $[\alpha]_D^{21} = -65$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2933, 1731, 1725, 1443, 1368, 1246, 1166, 1114, 1066, 1011, 940, 818; ¹H NMR; ¹H NMR (600 MHz, CDCl₃) δ 6.02 (s, 1H), 5.85 (d, *J* = 10.2, 1H), 5.77 (ddd, *J* = 10.2, 2.4, 2.4 1H), 5.05 (m, 1H), 5.03 (m, 1H), 3.99 (dq, *J* = 9.6, 6.6, 1H), 3.76 (dq, *J* = 9.6, 6.6, 1H), 3.30 (m, 1H), 2.06 (s, 3H), 1.89-1.79 (m, 2H), 1.20 (d, *J* = 6.6 Hz, 3H), , 1.21 (s, 9H) 1.19 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz,

CDCl₃) δ 177.1, 170.7, 130.2, 127.6, 96.3, 91.0, 80.1, 71.0, 70.5, 65.0, 39.3, 28.7, 27.3, 26.6, 21.2, 18.3, 18.1; CIHRMS: Calculated for [C₁₉H₃₀NaO₇⁺]:393.4271. Found: 393.4269.

2-Bromo-8-hydroxy-1,4-dimethoxynaphthalene **33**^{‡‡}

To a solution of LDA in THF at $-78\text{ }^{\circ}\text{C}$ was added furan (**1**), and 2,5-dibromo-1,4-dimethoxybenzene **31** was slowly added. The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, quenched by the addition of 10 mL of satd. aq. NaHCO_3 , extracted (3 x 10 mL) with Et_2O , dried over Na_2SO_4 and concentrated under reduced pressure.

^1H NMR (600 MHz, CDCl_3) δ 7.06 (dd, $J = 6, 1.8\text{ Hz}$, 1H), 7.01 (dd, $J = 6, 1.8\text{ Hz}$, 1H), 6.78 (s, 1H), 5.97 (dd, $J = 6, 1.8\text{ Hz}$, 1H), 5.87 (dd, $J = 1, 1\text{ Hz}$, 1H), 3.84 (s, 3H), 3.76 (s, 3H).

The crude cyclo-adduct **32** was dissolved in $\text{MeOH}/\text{H}_2\text{O}$ at RT and then HCl (6M) was added. After the reaction was refluxed for 8 hr, it was cooled to room temperature. The reaction was quenched with 10 mL of satd. aq. NaHCO_3 , extracted (3 x 10 mL) with Et_2O , dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford **12** (356 mg, 94%) as a tan solid.

^{‡‡} G. M. L. Cragg, R. G. F. Giles and G. H. P. Roos J. Chem. Soc., Perkin Trans. 1, 1975, 1339 – 1342.

^1H NMR (600 MHz, CDCl_3) δ 9.37 (s, 1H), 7.68 (dd, $J = 8.4, 0.6$ Hz, 1H), 7.40 (dd, $J = 8.1, 8.1$ Hz, 1H), 6.94 (dd, $J = 7.8, 0.6$ Hz, 1H), 6.82 (s, 1H), 4.00 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 153.2, 153.0, 146.3, 127.7, 127.7, 118.3, 113.9, 112.6, 110.7, 108.4, 62.8, 56.2.

(2*R*,3*S*,4*R*,6*R*)-6-(7-bromo-5,8-dimethoxynaphthalenyloxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (44 α):

(2*R*,3*S*,4*R*,6*S*)-6-(7-bromo-5,8-dimethoxynaphthalenyloxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (44 β):

To a THF (0.5 mL) solution of alcohol **43** (50 mg, 0.121 mmol), phenol **33** (68 mg, 0.242 mmol) and PPh₃ (54.7 mg, 0.242 mmol) was added DIAD (48 μ L) at room temperature. The reaction mixture was stirred at room temperature for 48 h. Reaction mixture was washed with 2 mL of satd. aq. NaHCO₃, extracted with CH₂Cl₂ (3 x 5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give **40** (67 mg, 0.13 mmol, 82%) as a mixture of diastereomers: *R_f* (30% EtOAc/hexanes) = 0.20; $[\alpha]_D^{21} = -26.8$ (*c* = 1.0, CH₂Cl₂);

As an inseparable mixture of stereo-isomers:

IR (thin film, cm^{-1}) 2934, 1737, 1701, 1579, 1508, 1335, 1238;

Major α -isomer: ^1H NMR (600 MHz, CDCl_3) δ 7.94 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.40 (dd, $J = 8.1, 8.1$ Hz, 1H), 7.25 (m, 1H), 6.94 (m, 1H), 6.87 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.10 (d, $J = 10.2$ Hz, 1H), 5.56 (d, $J = 3.0$ Hz, 1H), 5.23 (d, $J = 3.6$ Hz, 1H), 5.00 (d, $J = 0.5$ Hz, 1H), 4.56 (d, $J = 6.6$, 1H), 4.11 (q, $J = 6.6$, 1H), 4.06 (m, 1H), 3.963 (s, 3H), 3.96 (s, 3H), 3.73-3.58 (m 2H), 3.52-3.45 (m 2H), 2.70 (dd, $J = 13.2, 5.4$, Hz, 1H), 2.2-1.80 (m, 2H), 2.10 (s, 3H), 1.4-1.19 (m, 2H), 1.32 (d, $J = 6.6$, 3H), 1.26 (d, $J = 6.6$, 3H), 1.21 (d, $J = 6.6$, 3H);

^{13}C NMR for the Major α -isomer could not be determined:

CIHRMS Calcd for $[\text{C}_{32}\text{H}_{39}\text{BrNaO}_{11}]^+$: 701.1573, Found 701.1570.

D: Experimental Procedures for Chapter III:

Methyl 4-(benzyloxy)-2-hydroxybenzoate (**61**)^{§§}

Methyl 2,4-dihydroxy-benzoate **60** (20.0 g, 119 mmol) was dissolved in 240 ml of acetone, followed by adding tetrabutylammonium iodide (0.132 g, 0.357 mmol), potassium carbonate (16.4 g, 119 mmol) and benzyl bromide (22.4 g, 131 mol). Resulting solution was heated up to reflux for 5 hours. After cooling off to room temperature, the reaction solution was filtered and concentrated under reduced pressure to give a light yellow solid, which was dissolved again in ethyl acetate. This ethyl acetate solution was washed with water (3 x 200 ml) and brine (200 ml), and concentrated to give white solid. The resulting solid was purified by recrystallization from methanol to give a white solid **61** (26.3 g, 102 mmol). Yield: 86%. mp 103–105 °C. ¹H NMR (270 MHz, CDCl₃): δ 11.0 (s, 1H), 7.74 (d, *J* = 9.4 Hz, 1H), 7.37–7.40 (m, 5H), 6.48–6.53 (m, 2H), 5.07 (s, 2H), 3.90 (s, 3H).

^{§§} This procedure provided material with melting point and ¹H NMR that matched that reported in the literature, see: K. Tangdenpaisal, S. Sualek, S. Ruchirawat and P. Ploypradith *Tetrahedron* **2009**, 65, 4316-4325.

Methyl 4-(benzoyloxy)-2-(trifluoromethylsulfonyloxy)benzoate (**62**)

To a solution of 8.31 g (32.2 mmol) of methyl 4-(benzyloxy)-2-hydroxybenzoate **61** and 16.55 ml of pyridine (16.6 mmol) at -10 °C was added dropwise 10.0 g (35.4 mmol) of trifluoromethanesulfonic anhydride. After 10 min of stirring at -10 °C followed by an additional 2 h of stirring at room temperature, the reaction mixture was heated up to 40 °C for 24 hours. The reaction mixture was then poured into a mixture of 200 ml water and 200 ml ether. The organic layer was separated, washed with water (200 ml x 2), 10% HCl solution (200 ml x 2) and brine (200 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (5% ether in hexane) to give **62** as a white solid (11.91 g, 30.3 mmol, 95%): mp 56-57 °C; IR 1729, 1616, 1426, 1134, 862; ¹H NMR (600 MHz, CDCl₃) δ 8.06 (d, *J* = 9.0 Hz, 1H), 7.39 (m, 5H), 7.03 (dd, *J* = 9.0, 1.8 Hz, 1H), 6.87 (d, *J* = 1.8 Hz, 1H), 5.13 (s, 2H), 3.93 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) 163.9, 163.0, 149.5, 135.1, 134.1, 128.8, 128.6, 127.5, 119.8, 116.5, 114.2, 109.7, 70.9, 52.3; HRCIMS Calcd for [C₁₁H₁₆O₅H⁺]: 391.0458, Found 391.0455.

Methyl 4-(benzyloxy)-2-(prop-1-ynyl)benzoate (**63**)

A mixture of triflate **62** (13.8 g, 35.4 mmol), Pd(PPh₃)₂Cl₂ (2.48 g, 3.54 mmol) and CuI (1.35 g, 7.08 mmol) was combined in a flask topped with dry ice trap and was vacuumed for 10 min, 18.5 ml of *N,N*-diisopropylethylamine (106.3 mmol) was added via a syringe followed by adding 110 ml DMF. The dry-ice trap was filled with dry ice to cool down the system, and large excess of gaseous propyne was added using balloons. After 24 hours at room temperature, the DMF was removed by vacuum. The residue was purified by flash chromatography (5% ether in hexane) to give product **63** (8.95 g, 32 mmol, 90%) as a white solid: mp 75-77 °C; IR 2944, 1718, 1591, 1248, 752; ¹H NMR (600 MHz, CDCl₃) 7.89 (d, *J* = 9.0 Hz, 1H), 7.37 (m, 5H), 7.10 (d, *J* = 3.0 Hz, 1H), 6.90 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.09 (s, 2H), 3.88 (s, 3H), 2.13 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) 166.3, 161.1, 136.1, 132.4, 128.7, 128.2, 127.5, 126.7, 124.2, 119.7, 114.4, 91.6, 78.5, 70.1, 51.8, 4.8; CIHRMS Calcd for [C₁₈H₁₆O₃H]⁺: 281.1172. Found 281.1171.

4-(benzyloxy)-2-(prop-1-ynyl) benzoic acid (**64**)

Ester **63** (3.03 g, 10.82 mmol) was dissolved in 325 ml of methanol at room temperature, stirred until the solution was clear. 108 ml water was added followed by the addition of LiOH monohydrate (4.54 g, 108.2 mmol). Track the reaction by TLC. After 14 hours, the reaction was diluted with ammonium chloride until the pH reached ~8, followed by adding 10% HCl solution until the pH reached ~4. Leave the flask in iced bath for about 20 minutes. Collect the white solid appeared during acidification by filtration. The solid was purified by flash chromatography (50% ethyl acetate in hexane) to give product **64** (2.06 g, 7.74 mmol, 72%) as a white solid: mp 175-176 °C; IR 3840, 2971, 1686, 1367, 1217; ¹H NMR (600 MHz, CDCl₃) 8.06 (d, *J* = 9.0 Hz, 1H), 7.39 (m, 5H), 7.13 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.12 (s, 2H), 2.16 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) 168.0, 161.8, 135.9, 133.7, 128.7, 128.3, 127.5, 126.1, 123.0, 119.7, 114.9, 93.7, 78.1, 70.2, 4.8; CIHRMS Calcd for [C₁₇H₁₄O₃H]⁺: 267.1016. Found 267.1015.

(4-benzyloxy)-2-(prop-1-ynyl)benzoyl azide (67)

The solution of carboxylic acid **64** (200 mg, 0.75 mmol) in 2 ml benzene was cooled down to 0 °C, triethylamine (0.11 mL, 0.79 mmol) and DPPA **66** (0.163 mL, 0.752 mmol) were added. After 2 hours of stirring at room temperature, the reaction mixture was poured into 10 ml cold water, extracted with ether (3 x 20 ml). The organic layers were combined, dried over sodium sulfate anhydrous and concentrated. The resulting light yellow solid **67** was dried under a vacuum for 1-2 hours and used in the next step without further purification. mp 104-106 °C; IR 2921, 2142, 1683, 1523, 1292, 1186, 877; ¹H NMR (600 MHz, CDCl₃) 8.05 (d, *J* = 9.0 Hz, 1H), 7.34 (m, 5H), 6.96 (d, *J* = 3.0 Hz, 1H), 6.92 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.00 (s, 2H), 2.11 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) 154.6, 153.5, 136.6, 131.7, 128.6, 128.0, 127.4, 119.8, 117.5, 115.9, 114.2, 93.6, 74.5, 70.3, 4.5; CIHRMS Calcd for [C₁₇H₁₃N₃O₂H]⁺: 292.1081. Found 292.1082.

4-(benzyloxy-1-isocyanato-2-ynyl) benzene (68)

A solution of compound **67** (146 mg, 0.5 mmol) in 4 ml toluene was heated up to 95 °C for around 4 hours (TLC was used to track the reaction). The toluene was removed by vacuum. The residue was dissolved in ether with the remaining solid being filter off. The solution was concentrated to give **68** as a light yellow solid (132 mg, 0.5 mmol). The crude isocyanate was used without further purification. mp 104-106 °C; IR 2280, 1193, 834, 758, 698; ¹H NMR (600 MHz, CDCl₃) 7.35 (m, 5H), 6.96 (d, *J* = 3.0 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 6.80 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.00 (s, 2H), 2.10 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) 156.0, 136.5, 128.6, 128.5, 128.1, 127.4, 127.3, 124.2, 122.2, 117.5, 115.8, 95.2, 75.7, 70.4, 4.4; CIHRMS Calcd for [C₁₇H₁₃NO₂H]⁺: 264.1019. Found 292.1019.

9-(benzyloxy)-11-methyl-6*H*-indolo(2,3-*b*)(1,6)naphthyridine (71)

Isocyanate **68** (130 mg, 0.49 mmol) was dissolved in 20 ml of dry p-xylene, followed by addition of iminophosphorane **69** (192 mg, 0.54 mmol). Resulting solution was heated up under reflux for 15 hours after was stirred at room temperature under argon protection for 2 hours. Para-xylene was removed by vacuum, after three cycles of washing the concentrated residue with diethyl ether, centrifugation, and decanting the supernatant liquid, the residual solid was heated under reflux in 100 ml of benzene for 1 hour. The mixture was allowed to cool to room temperature followed by centrifugation and decanting the supernatant liquid. The remaining solid was pumped to dryness in vacuo to afford **71** (40 mg, 0.12 mmol, 24%) as a yellow solid: compound turned black without melting at 311 °C; IR 2645, 1602, 1480, 1219, 820; ¹H NMR (600 MHz, DMSO) 11.83 (s, 1H), 9.68 (s, 1H), 8.61 (d, *J* = 6.0 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 6.0 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.43 (m, 5H), 7.30 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.26 (s, 2H), 3.25 (s, 3H); ¹³C NMR (150 MHz, DMSO) 155.2, 153.4, 150.2, 149.3, 145.8, 141.0, 137.9, 136.3, 128.9, 128.3, 128.2, 121.9, 120.7, 119.8, 117.7, 117.2, 112.2, 110.1, 70.8, 14.7; CIHRMS Calcd for [C₂₂H₁₇N₃OH]⁺: 340.1444. Found 340.1443.

Methyl 4-(benzyloxy)-2-(3-hydroxyprop-1-ynyl)benzoate (75)

To a solution of triflate **62** (195 mg, 0.5 mmol), diethylamine (1.03 ml, 10 mmol) and tetra-*n*-butylammonium iodide (554 mg, 1.5 mmol) in DMF (1 ml) were added dichlorobis(triphenylphosphine) palladium (14 mg, 0.02 mmol) and copper iodide (11.4 mg, 0.06 mmol). The reaction mixture was stirred for 5 min at room temperature, and propargyl alcohol (0.058 ml, 1 mmol) was added at same temperature. Temperature was raised to 70 °C, and the reaction was stirred for 4 hours. After the mixture was cooled down to room temperature, 20 ml saturated ammonium chloride was added to reaction mixture, and extracted with ether (3 x 50 ml). Organic layers were combined, washed with brine (100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ether in hexane) to give **75** as a white solid (117 mg, 0.40 mmol, 79%): mp 90-91 °C; IR 1708, 1594, 1198, 1006, 784; ¹H NMR (600 MHz, CDCl₃) 7.90 (d, *J* = 9.0 Hz, 1H), 7.36 (m, 5H), 7.10 (d, *J* = 3.0 Hz, 1H), 6.91 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.06 (s, 2H), 4.53 (s, 2H), 3.96 (s, 3H); 2.26 (s, 1H) ¹³C NMR (150 MHz, CDCl₃) 166.0, 161.2, 135.8, 132.4, 128.6, 128.2, 127.4, 125.4, 123.9, 119.5, 115.0, 93.0, 84.0, 70.1, 51.9, 51.5; CIHRMS Calcd for [C₁₈H₁₆O₄H]⁺: 297.1121. Found 297.1122.

Methyl 4-(benzyloxy)-2-(3-(tert-butyldimethylsilyloxy)prop-1-ynyl)benzoate (74)

To a solution of triflate **62** (195 mg, 0.5 mmol), diethylamine (1.03 ml, 10 mmol) and tetra-*n*-butylammonium iodide (554 mg, 1.5 mmol) in DMF (1 ml) were added dichlorobis(triphenylphosphine) palladium (14 mg, 0.02 mmol) and copper iodide (11.4 mg, 0.06 mmol). The reaction mixture was stirred for 5 min at room temperature, and TBS protected propargyl alcohol (0.20 ml, 1 mmol) was added at same temperature. After being stirred at 70°C for 4 hours, the mixture was cooled down to room temperature, and 20 ml saturated ammonium chloride was added to reaction mixture, extracted with ether (3x50 ml). Organic layers were combined, washed with brine (100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ether in hexane) to give **74** as a light yellow liquid (165 mg, 0.40 mmol, 81%): IR 2953, 2252, 1721, 1597, 1251, 905, 695; ¹H NMR (600 MHz, CDCl₃) 7.89 (d, *J* = 9.0 Hz, 1H), 7.36 (m, 5H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.91 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.07 (s, 2H), 4.60 (s, 2H), 3.86 (s, 3H), 0.93 (s, 9H), 0.16 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) 166.0, 161.0, 135.9, 132.4, 128.6, 128.2, 127.4, 125.4, 124.3, 119.7, 114.9, 93.0, 83.3, 70.1, 52.4, 51.8, 25.8, 18.3, -5.14; CIHRMS Calcd for [C₂₄H₃₀O₄SiH]⁺: 411.1986. Found 411.1989.

Methyl 4-(benzyloxy)-2-(3-(triisopropylsilyloxy)prop-1-ynyl)benzoate (76)

Compound **75** (148 mg, 0.5 mmol) was dissolved in 1 ml methylene chloride, TIPS chloride (116 mg, 0.6 mmol), triethylamine (0.14 ml, 1 mmol) and DMAP (6 mg, 0.05 mmol) were added. The reaction mixture was poured into 10 ml of water after stirring overnight at room temperature, and was extracted by ether (3x50 ml). The residue was purified by flash chromatography (10% ether in hexane) to give **76** as a light yellow liquid (226 mg, 0.50 mmol, 100%): IR 2924, 1694, 1593, 1365, 1216, 882; ^1H NMR (600 MHz, CDCl_3) 7.89 (d, $J = 9.0$ Hz, 1H), 7.36 (m, 5H), 7.11 (d, $J = 3.0$ Hz, 1H), 6.91 (dd, $J = 9.0, 3.0$ Hz, 1H), 5.07 (s, 2H), 4.66 (s, 2H), 3.86 (s, 3H), 1.10 (s, 18H), 1.09 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) 166.1, 161.1, 136.0, 132.4, 128.7, 128.2, 127.5, 125.5, 124.3, 119.7, 114.9, 93.2, 83.1, 70.2, 52.7, 51.8, 17.9, 12.0; CIHRMS Calcd for $[\text{C}_{27}\text{H}_{36}\text{O}_4\text{SiH}]^+$: 453.2456. Found 453.2460.

4-(benzyloxy)-2-(3-(triisopropylsilyloxy)prop-1-ynyl)benzoic acid (77)

Compound **76** (928 mg, 2.05 mmol) was dissolved in 60 ml methanol/20 ml water, and lithium hydroxide monohydrate (1.29 g, 30.8 mmol) was added after all solid dissolved. The resulting reaction mixture was stirred at room temperature for 15 hours. The solvent was removed by reduced pressure, the solid left behind was dissolved in 100 ml of water, 10% HCl solution was used to adjust PH to about 3. Extracted the water solution with ether (3x200 ml), ether was combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The solid was purified by flash chromatography (20 % ether in hexane) to give **77** as a white solid (264 mg, 0.60 mmol, 55% based on reacted starting material): m.p. 112-114 °C; IR 2944, 1727, 1597, 1328, 1283, 1190, 1068, 882; ¹H NMR (600 MHz, CDCl₃) 8.02 (d, *J* = 9.0 Hz, 1H), 7.36 (m, 5H), 7.13 (d, *J* = 3.0 Hz, 1H), 6.95 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.10 (s, 2H), 4.66 (s, 2H), 1.10 (s, 18H), 1.09 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) 169.8, 161.7, 135.9, 133.5, 128.7, 128.3, 127.5, 125.9, 123.2, 119.9, 115.1, 94.4, 82.8, 70.3, 52.7, 17.9, 12.1; CIHRMS Calcd for [C₂₆H₃₄O₄SiH]⁺: 439.2299. Found 453.2302.

Camptothecin Acetate (90):**

CPT (500 mg) and LiBr (500 mg) was dissolved in Ac_2O (5 mL), then the resulting mixture was stirred for 48 h at 80 °C. After cooling to room temperature, 30 mL of hexane was added to the reaction mixture while stirring. The product precipitated from hexane was collected by filtration and washed with 45 mL of hexane (15 mL $\times$ 3). After drying under air for 1 h, a gray-white powder **90** (515 mg, 92%) was obtained. mp 273 °C; IR (thin film, cm^{-1}) 3011, 1748, 1668, 1657, 1618, 1229, 1047, 751, 744, 723; ^1H NMR (CDCl_3 , 600 MHz) δ 8.42 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 7.2 Hz, 1H), 7.69 (dd, J = 7.2 Hz, 1H), 7.29 (s, 1H), 5.67 (d, J = 17.4 Hz, 1H), 5.41 (d, J = 17.4 Hz, 1H), 5.29 (d, J = 17.4 Hz, 2H), 2.29 (m, 1H), 2.23 (s, 3H), 2.15 (m, 1H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 170.1, 167.7, 157.6, 152.5, 148.9, 146.2, 146.1, 131.6, 131.0, 129.7, 128.7, 128.5, 128.3, 120.7, 96.4, 76.1, 67.3, 50.1, 32.1, 21.0, 7.8. CIHRMS: Calculated for $[\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_5\text{Na}^+]$: 413.1113. Found: 413.1109.

*** This procedure provided material with melting point, IR, ^1H NMR, and ^{13}C NMR that matched that reported in the literature, see: N. Ravindranath, C. Ramesh, M. R. Reddy, K. V. N. S. Srinivas, and B. Das *Syn. Commun.* **2003**, 33, 4029–4035.

Camptothecin Acetate *N*-oxide (91**):**

A solution of compound **90** (500 mg) in EtOAc (15 mL) and CH₂Cl₂ (15 mL) was added excess 75% mCPBA (2 g), and the reaction mixture was stirred at 80 °C for 24 h. After cooling to room temperature, the reaction was washed with 1N NaOH (2 x 15 mL), then saturated NaHCO₃ (15 mL). The organic layer was washed with H₂O and brine, dried with Na₂SO₄ and evaporated to dryness. The crude oxide product **91** (540 mg) was used without further purification. mp 239 °C; IR (thin film, cm⁻¹) 3563, 3022, 1748, 1660, 1619, 1609, 1231, 1049, 749; ¹H NMR (CDCl₃, 600 MHz) δ 8.76 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.85 (dd, *J* = 7.8 Hz, 1H), 7.74 (dd, *J* = 7.8 Hz, 1H), 5.63 (d, *J* = 17.4 Hz, 1H), 5.36 (d, *J* = 17.4 Hz, 1H), 5.27 (d, *J* = 19.8 Hz, 2H), 2.26 (m, 1H), 2.19 (s, 3H), 2.14 (m, 1H), 0.96 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 170.2, 167.6, 157.0, 146.2, 142.5, 141.0, 137.6, 131.2, 130.5, 130.3, 130.0, 128.8, 121.5, 119.9, 119.3, 101.4, 75.9, 67.1, 50.6, 31.9, 20.8, 7.7; CIHRMS: Calculated for [C₂₂H₁₈N₂O₆Na⁺]: 429.1063. Found: 429.1066.

7-Chloro Camptothecin Acetate (**92**):

The crude oxide product **91** (540 mg) in DMF (10 mL) was added oxalyl chloride (0.5 mL) dropwise. After the reaction mixture was stirred at room temperature for 2 h, saturated NaHCO₃ aqueous and CH₂Cl₂ were added. The organic layer was washed with H₂O and brine, dried with Na₂SO₄ and concentrated under reduced pressure to give a residue, which was purified by column chromatography (silica; chloroform/acetone, 50:1~20:1) to afford the desired compound **92** (410 mg, 76%) as a yellow solid. mp 267 °C; IR (thin film, cm⁻¹) 3003, 1762, 1745, 1664, 1618, 1231, 749; ¹H NMR (CDCl₃, 600 MHz) δ 8.31 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.88 (dd, *J* = 7.8 Hz, 1H), 7.76 (dd, *J* = 7.8 Hz, 1H), 7.25 (s, 1H), 5.27 (d, *J* = 17.4 Hz, 2H), 2.25 (m, 1H), 2.20 (s, 3H), 2.12(m, 1H), 0.96 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 169.9, 167.3, 157.1, 151.8, 149.4, 146.0, 145.6, 138.6, 131.5, 129.7, 129.0, 127.5, 126.2, 123.9, 121.1, 96.9, 75.8, 67.0, 50.0, 31.7, 20.7, 7.5; HRMS (ESI) calcd. For [C₂₂H₁₇ClN₂O₅+Na]⁺: 447.0724, Found: 447.0718.

7-(3-Tetrahydropyranyloxy)prop-1-ynyl Camptothecin Acetate (94):

To a mixture of compound **92** (43 mg, 0.1 mmol), Pd(OAc)₂ (0.01 mmol), *rac*-BINAP (0.02 mmol) and potassium carbonate (56 mg, 0.4 mmol), under an argon atmosphere, was added a solution of tetrahydro-2-(2-propynloxy)-2H-pyran **93** (0.4 mmol) in degassed toluene (9 mL). After the reaction mixture was stirred at 100 °C for 6 h, the solvent was evaporated to give a residue, which was purified by flash column chromatography on silica gel (chloroform/acetone, 50:1~20:1) to furnish compound **94** (40 mg, 75%) as a yellow oil solid. MP **X**; IR (thin film, cm⁻¹) 2947, 1751, 1668, 1615, 1230, 1020, 768. ¹H NMR (CDCl₃, 600 MHz) δ 8.34 (d, *J* = 7.8 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.84 (dd, *J* = 7.8 Hz, 1H), 7.71 (dd, *J* = 7.8 Hz, 1H), 7.21 (s, 1H), 5.67 (d, *J* = 16.8 Hz, 1H), 5.40 (d, *J* = 16.8 Hz, 1H), 5.30 (d, *J* = 19.2 Hz, 2H), 4.96 (t, *J* = 3.6 Hz, 1H), 4.71 (d, *J* = 16.2 Hz, 2H), 3.95 (m, 1H), 3.63 (m, 1H), 2.27 (m, 1H), 2.21 (s, 3H), 2.15 (m, 1H), 1.90-1.58 (m, 6H), 0.97 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 170.1, 167.7, 157.5, 151.8, 148.9, 146.3, 146.1, 131.2, 131.1, 130.1, 128.8, 127.9, 126.2, 125.5, 120.9, 101.4, 97.9, 96.5, 78.6, 76.1, 67.3, 62.5, 55.0, 50.5, 32.0, 30.5, 25.5, 20.9, 19.2, 7.8; HRMS (ESI) calcd. For [C₃₀H₂₈N₂O₇+Na]⁺: 551.1794, Found: 551.1791.

7-(3-Hydroxy)prop-1-ynyl Camptothecin Acetate (98):

To a solution of compound **94** (50 mg) in methanol (1 mL) and chloroform (1 mL) was added *p*-toluenesulfonic acid (5 mg). The reaction mixture was stirred at room temperature for 1 h and evaporated to dryness. The residue was added saturated aq. NaHCO₃, extracted with CH₂Cl₂, and purified by flash column chromatography on silica gel (chloroform/methanol, 80:1~50:1) to furnish compound **98** (40 mg, 95%) as a yellow solid. mp 280 °C; IR (thin film, cm⁻¹) 3267 (broad), 1744, 1658, 1228, 1049, 1019, 771, 723; ¹H NMR (CDCl₃, 600 MHz) δ 8.32 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 7.8 Hz, 1H), 7.71 (dd, *J* = 7.8 Hz, 1H), 7.27 (s, 1H), 5.68 (d, *J* = 17.4 Hz, 1H), 5.41 (d, *J* = 17.4 Hz, 1H), 5.29 (d, *J* = 19.2 Hz, 2H), 4.75 (s, 2H), 2.27 (m, 1H), 2.23 (s, 3H), 2.15 (m, 3H), 0.99 (t, *J* = 7.8 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 170.1, 167.7, 157.5, 151.6, 148.6, 146.3, 146.1, 131.4, 131.2, 129.9, 128.9, 127.8, 126.2, 121.0, 97.0, 89.5, 78.4, 76.1, 67.2, 51.8, 50.6, 32.0, 20.9, 7.8; HRMS (ESI) calcd. For [C₂₅H₂₀N₂NaO₆+Na]⁺: 467.1219, Found: 467.1223.

***O*-*t*-butyldimetylsilyl SN38 (**103**):**

A DMF (1 mL) solution of SN-38 (43 mg, 0.1 mmol) was cooled to 0 °C, and Et₃N and TBSCl (50 mg) were added. After stirring at 0 °C for 2 h, the reaction was quenched by adding 5 mL saturated aq. NaHCO₃, extracted with CH₂Cl₂, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with CH₂Cl₂/MeOH = 80:1~50:1 to give 44 mg (83%) of compound **103** as a white solid. mp °C; IR (thin film, cm⁻¹) 3003, 1762, 1745, 1664, 1618, 1231, 749; ¹H NMR (CDCl₃, 600 MHz) δ 8.11 (d, *J* = 8.4 Hz 1H), 7.65 (s, 1H), 7.38 (m, 2H), 5.64 (d, *J* = 16.2, 1H), 5.30 (d, *J* = 16.2, 1H), 5.23 (s, 2H), 3.81 (s, 1H), 3.12 (q, *J* = 7.8 Hz, 2H), 1.92 (dq, *J* = 15.0, 7.8 Hz, 1H), 1.86 (dq, *J* = 15.0, 7.8 Hz, 1H), 1.64 (s, 1H), 1.39 (t, *J* = 7.8 Hz, 3H), 1.05 (s, 9H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.31 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ 174.1, 157.9, 155.4, 150.6, 150.1, 147.5, 145.7, 143.9, 132.3, 128.4, 127.2, 126.2, 118.2, 110.7, 97.8, 76.1, 73.1, 49.6, 31.9, 25.8, 23.3, 18.6, 13.9, 8.0, -4.0; HRMS (ESI) calcd. For [C₂₈H₃₄N₂O₅Si + H]⁺: 507.2315, Found: 507.2311.

***O*-*t*-butyldimetylsilyl SN38 Acetate (**104**):**

The TBS ether **103** (500 mg) and LiBr (500 mg) was dissolved in Ac₂O (5 mL), and the resulting mixture was stirred for 48 h at 80 °C. After cooling to room temperature, 30 mL of hexane was added to the reaction mixture while stirring. The product precipitated from hexane was collected by filtration and washed with 45 mL of hexane (15 mL × 3). After drying under air for 1 h, a gray-white powder **104** (515 mg, 92%) was obtained. mp 212 °C; IR (thin film, cm⁻¹) 3005, 1762, 1755, 1750, 1664, 1618, 1231, 749; ¹H NMR (CDCl₃, 600 MHz) δ 8.09 (d, *J* = 8.4 Hz 1H), 7.50 (s, 1H), 7.48 (m, 2H), 5.67 (d, *J* = 16.2, 1H), 5.50 (d, *J* = 16.2, 1H), 5.30 (m, 2H), 3.21 (q, *J* = 7.8 Hz, 2H), 2.37 (dq, *J* = 15.0, 7.8 Hz, 1H), 2.30 (s, 3H), 2.24 (dq, *J* = 15.0, 7.8 Hz, 1H), 1.49 (t, *J* = 7.8 Hz, 3H), 1.15 (s, 9H), 1.08 (t, *J* = 7.2 Hz, 3H), 0.42 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ 170.0, 167.9, 157.7, 155.4, 150.0, 147.3, 146.2, 145.6, 144.1, 132.0, 128.5, 127.1, 126.4, 119.7, 110.8, 95.7, 76.1, 67.3, 49.5, 32.0, 25.9, 23.3, 20.9, 18.5, 13.9, 7.74, -4.1; HRMS (ESI) calcd. For [C₃₀H₃₆N₂O₆Si + H]⁺: 549.2421, Found: 549.2426.

SN38 acetate (102):^{†††}

A CH₂Cl₂ (5 mL) solution of compound **104** (550 mg) was cooled to 0 °C and a solution of HF•2Py. After cooling to room temperature, 30 mL of hexane was added to the reaction mixture while stirring. The product precipitated from hexane was collected by filtration and washed with 45 mL of hexane (15 mL × 3). After drying under air for 1 h, a gray-white powder (515 mg, 92%) was obtained. Decomposes > 250 °C; IR (thin film, cm⁻¹) 3350, 3005, 1762, 1755, 1750, 1664, 1618, 1231, 749; ¹H NMR (CDCl₃/CD₃OD, 600 MHz) δ 8.22 (d, *J* = 9.1 Hz, 1H), 7.83 (d, *J* = 2.7 Hz, 1H), 7.58 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.18 (s, 1H), 5.68 (d, *J* = 17.0, 1H), 5.41 (d, *J* = 17.0, 1H), 5.23 (m, 2H), 3.16 (q, *J* = 7.6 Hz, 2H), 2.32 (m, 2H), 2.20 (s, 3H), 1.38 (t, *J* = 7.8 Hz, 3H), 0.99 (t, *J* = 7.2 Hz); HRMS (ESI) calcd. For [C₂₄H₂₂N₂O₆+H]⁺: 434.1478, Found: 434.1472.

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^{†††} This sample was not soluble enough in any mixture of CDCl₃/CD₃OD to get a good ¹³C NMR data.

**(4*R*,1'*S*,6'*S*)-4,11-diethyl-4-acetoxy-9-(6-methyl-5-oxo-6*H*-pyranyloxy)-1*H*-
Pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (105):**

A CH₂Cl₂ (5 mL) solution of compound **102** (43 mg, 0.1 mmol) and compound **5(α-L)** (35 mg, 0.15 mmol) was cooled to 0 °C. A CH₂Cl₂ (1 mL) solution of Pd₂(DBA)₃•CHCl₃ (3 mg, 2.5 mol%) and PPh₃ (4 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with 5 mL of saturated aq NaHCO₃, extracted with CH₂Cl₂, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with CHCl₃/MeOH = 80:1~50:1 to give 44 mg (83%) of compound **105**.

This product was unstable and only crude ¹H NMR was obtained.

**(4*R*,1'*S*,5'*R*,6'*S*)-4,11-diethyl-4-acetoxy-9-(6-methyl-5-hydroxy-6*H*-pyranyloxy)-1*H*-
Pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (107)**

Pyranone **105** (40 mg) was dissolved in 2 mL CH₂Cl₂, resulting solution was cooled to -78 °C, 2 mL of 0.4 M CeCl₃ in methanol solution was added in a dropwise fashion, followed by adding 10 mg of NaBH₄. By TLC tracking, the reaction was done after 1.5 h. The reaction mixture was diluted with 2 mL diethyl ether, quenched with 2 mL water, extracted with 3 x 20 mL diethyl ether, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 80% EtOAc/Hexane. At this stage only a crude ¹H NMR was taken.

Alternatively:

A CH₂Cl₂ (5 mL) solution of compound **102** (43 mg, 0.1 mmol) and compound **106** (35 mg, 0.15 mmol) was cooled to 0 °C. A CH₂Cl₂ (1 mL) solution of Pd₂(DBA)₃•CHCl₃ (3 mg, 2.5 mol%) and PPh₃ (4 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with 5 mL of saturated aq NaHCO₃, extracted with CH₂Cl₂, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with CHCl₃/MeOH =

80:1~50:1 to give 44 mg (83%) of compound **107** as an oil. R_f (50% MeOH/EtOAc) = 0.20; $[\alpha]_D^{21} = -50$ ($c = 0.1$, CD₃OD); IR (thin film, cm⁻¹) 3411, 3050, 2933, 1740, 1612, 1513, 1245, 1161, 1032, 997, 819; ¹H NMR (600 MHz, CD₃OD) δ 8.05 (d, $J = 9.0$, 1H), 7.75 (d, $J = 2.4$ Hz, 1H), 7.56 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.30 (s, 1H), 5.67 (d, $J = 1.2$ Hz, 1H), 5.56 (d, $J = 16.5$ Hz, 1H), 5.45 (d, $J = 16.5$ Hz, 1H), 5.21 (d, $J = 18.0$ Hz, 1H), 5.18 (d, $J = 18.0$ Hz, 1H), 4.12 (dd, $J = 3.0$, 1.8 Hz, 1H), 3.92 (dd, $J = 9.0$, 3.6 Hz, 1H) 3.70 (dd, $J = 4.2$, 4.2 Hz, 1H), 3.65 (m, 1H), 3.51 (m, 2H), 3.2-3.1 (m, 4H), 2.24 (s, 3H), 1.37 (dd, $J = 7.8$, 7.8 Hz, 3H), 1.24 (d, $J = 6.6$ Hz, 3H), 1.04 (dd, $J = 7.5$, 7.5 Hz, 3H); ¹³C NMR (150 MHz, CD₃OD) δ 171.6, 169.7, 159.1, 157.0, 151.3, 148.6, 148.3, 146.7, 146.4, 132.3, 129.6, 129.4, 124.4, 120.2, 107.9, 100.3, 97.5, 77.7, 73.9, 72.4, 72.1, 67.9, 66.6, 50.9, 30.8, 24.1, 20.7, 18.3, 14.1, 8.2; CIHRMS Calcd for [C₃₀H₃₂N₂O₁₀Na]⁺: 603.1955, Found 603.1961.

(4*R*)-4,11-diethyl-4-acetoxy-9-oxy-1H-Pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dionyl- α -L-rhamno-pyranoside (108**):**

To a *t*-butanol/acetone (4.3 ml, 1:1) solution of pyran **107** (20 mg, 4.3 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (4.3 mL). Crystalline OsO₄ (1.1 mg, 1 mol %) was added and the reaction was stirred for 12 h. The reaction was quenched by adding EtOAc and satd. aq. NaHCO₃. The organic layer was separated and concentrated. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give triol **108** (21 mg, 85%) as a colorless oil. *R_f* (50% MeOH/EtOAc) = 0.20; $[\alpha]_D^{21} = -50$ (*c* = 0.1, CD₃OD); IR (thin film, cm⁻¹) 3411, 3050, 2933, 1740, 1612, 1513, 1245, 1161, 1032, 997, 819; ¹H NMR (600 MHz, CD₃OD) δ 8.05 (d, *J* = 9.0, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.56 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.30 (s, 1H), 5.67 (d, *J* = 1.2 Hz, 1H), 5.56 (d, *J* = 16.5 Hz, 1H), 5.45 (d, *J* = 16.5 Hz, 1H), 5.21 (d, *J* = 18.0 Hz, 1H), 5.18 (d, *J* = 18.0 Hz, 1H), 4.12 (dd, *J* = 3.0, 1.8 Hz, 1H), 3.92 (dd, *J* = 9.0, 3.6 Hz, 1H) 3.70 (dd, *J* = 4.2, 4.2 Hz, 1H), 3.65 (m, 1H), 3.51 (m, 2H), 3.2-3.1 (m, 4H), 2.24 (s, 3H), 1.37 (dd, *J* = 7.8, 7.8 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.04 (dd, *J* = 7.5, 7.5 Hz, 3H); ¹³C NMR (150 MHz, CD₃OD) δ 171.6, 169.7, 159.1, 157.0, 151.3, 148.6, 148.3, 146.7, 146.4, 132.3, 129.6, 129.4, 124.4, 120.2, 107.9, 100.3, 97.5, 77.7, 73.9, 72.4,

72.1, 67.9, 66.6, 50.9, 30.8, 24.1, 20.7, 18.3, 14.1, 8.2; CIHRMS Calcd for $[\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_{10}\text{Na}]^+$:
603.1955, Found 603.1961.

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Appendix: Spectra Graphs

C4.072

(*R*)-1-(furan-2-yl) ethanol (7(*R*))

¹H NMR (CDCl₃, 600 MHz)

(R)-1-(furan-2-yl) ethanol (7(*R*))

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

(S)-1-(2-Furyl)-ethanol (7(S)):

^1H NMR (CDCl_3 , 600 MHz)

(S)-1-(2-Furyl)-ethanol (7(S)):

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

(2*R*)-6-Hydroxy-2-methyl-2H-Pyran-3(6*H*)-one (34):

^1H NMR (CDCl_3 , 600 MHz)

(2*R*)-6-Hydroxy-2-methyl-2H-Pyran-3(6*H*)-one (34):

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

(2*S*)-6-Hydroxy-2-methyl-2*H*-Pyran-3(6*H*)-one (34):

¹H NMR (CDCl₃, 600 MHz)

(2*S*)-6-Hydroxy-2-methyl-2*H*-Pyran-3 (6*H*)-one (34):

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

Tert-butyl (2*S*,6*S*)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (6(β -L))

^1H NMR (CDCl_3 , 600 MHz)

Tert-butyl (2*R*,6*R*)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (6(β -D))

^1H NMR (CDCl_3 , 600 MHz)

Tert-butyl (2R,6R)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (6(β-D))

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

Tert-butyl (2*S*,6*S*)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (6(β -L))

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

(2*R*,6*R*)-*t*-butyl -5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbon

¹H NMR (CDCl₃, 600 MHz)

(2*R*,6*R*)-*t*-butyl -5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (5(α -D))

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

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

5(α -L)

^1H NMR (CDCl_3 , 600 MHz)

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

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

(2*R*,6*R*)-6-(4-methoxybenzyloxy)-2-methyl-2*H*-pyran-3(6*H*)-one (9):

(2*R*,6*R*)-6-(4-methoxybenzyloxy)-2-methyl-2*H*-pyran-3(6*H*)-one (9):

(2*R*,6*R*)-6-(4-methoxybenzyloxy)-3,6-dihydro-2-methyl-2*H*-pyran-3-ol (10a/b):

¹H NMR (CDCl₃, 600 MHz)

(2*R*,6*R*)-6-(4-methoxybenzyloxy)-3,6-dihydro-2-methyl-2*H*-pyran-3-ol (10a/b):

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

11c71

✓ (2*R*,6*R*)-2-(4-methoxybenzyloxy)-3,6-dihydro-6-methyl-2H-pyran (11):

(2*R*,6*R*)-2-(4-methoxybenzyloxy)-3,6-dihydro-6-methyl-2H-pyran (11):

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

C₁₂H₁₈O₄ OH 1.0M

(2*R*,3*S*,4*S*,6*R*)-6-(4-methoxybenzyloxy)-2-methyl-tetrahydron-2*H*-pyran-3,4-diol (12):

¹H NMR (CDCl₃, 600 MHz)

(2*R*,3*S*,4*S*,6*R*)-6-(4-methoxybenzyloxy)-2-methyl-tetrahydron-2*H*-pyran-3,4-diol (12):

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

(2*R*,3*R*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-tetrahydro-3-hydroxy-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (13):

^1H NMR (CDCl_3 , 600 MHz)

(2*R*,3*R*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-tetrahydro-3-hydroxy-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (13):

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

(2*R*,3*R*,4*R*,6*R*)-3-((2*R*,6*S*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (14):

^1H NMR (CDCl_3 , 600 MHz)

(2*R*,3*R*,4*R*,6*R*)-3-((2*R*,6*S*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (14):

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

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

¹H NMR (CDCl₃, 600 MHz)

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

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

(2*R*,3*R*,4*R*,6*R*)-3-((2*R*, 5*R*, 6*S*)-5,6-dihydro-5-(4-nitrobenzoate)-6-methyl-2*H*-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-

tetrahydro-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (16):

¹H NMR (CDCl₃, 600 MHz)

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

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

(2*S*, 3*S*, 6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (17):

^1H NMR (CDCl_3 , 600 MHz)

(2*S*, 3*S*, 6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (17):

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

(2*S*, 3*S*, 6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-ol (18):

^1H NMR (CDCl_3 , 600 MHz)

(2*S*, 3*S*, 6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-ol (18):

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

19-
 (2*S*,6*R*)-6-((2*S*,3*S*,6*S*)-6-((2*R*,3*S*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-

methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-2*H*-3(6*H*)-one (19):

¹H NMR (CDCl₃, 600 MHz)

(2*S*,6*R*)-6-((2*S*,3*S*,6*S*)-6-((2*R*,3*S*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-2*H*-3(6*H*)-one (19):

¹³C NMR (CDCl₃, 100 MHz)

(2*R*,3*S*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (20):

¹H NMR (CDCl₃, 600 MHz)

20

(2*R*,3*S*,4*R*,6*R*)-6-(4-methoxybenzyloxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (20):

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

(2*S*,6*S*)-6-(4-methoxybenzyloxy)-2-methyl-2*H*-pyran-3(6*H*)-one (*ent*-9)

(2*S*,6*S*)-6-(4-methoxybenzyloxy)-2-methyl-2*H*-pyran-3(6*H*)-one (*ent*-9)

(2*S*,6*S*)-6-(4-methoxybenzyloxy)-3,6-dihydro-2-methyl-2*H*-pyran-3-ol (*ent*-10a/b):

(2*S*,6*S*)-6-(4-methoxybenzyloxy)-3,6-dihydro-2-methyl-2*H*-pyran-3-ol (*ent*-10a/b):

¹³C NMR (CDCl₃, 150 MHz)

(2*S*,6*S*)-2-(4-methoxybenzyloxy)-3,6-dihydro-6-methyl-2H-pyran (*ent*-11):

(2*S*,6*S*)-2-(4-methoxybenzyloxy)-3,6-dihydro-6-methyl-2H-pyran (*ent*-11):

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

(2*S*,3*R*,4*R*,6*S*)-6-(4-methoxybenzyloxy)-2-methyl-tetrahydron-2*H*-pyran-3,4-diol (*ent*-12):

^1H NMR (CDCl_3 , 600 MHz)

(2*S*,3*R*,4*R*,6*S*)-6-(4-methoxybenzyloxy)-2-methyl-tetrahydropyran-3,4-diol (*ent*-12):

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

(2*S*,3*S*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-tetrahydro-3-hydroxy-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (*ent*-13):

^1H NMR (CDCl_3 , 600 MHz)

(2*S*,3*S*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-tetrahydro-3-hydroxy-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (*ent*-13):

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

(2*S*,3*S*,4*S*,6*S*)-3-((2*R*,6*S*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (*ent*-14):

¹H NMR (CDCl₃, 600 MHz)

(2*S*,3*S*,4*S*,6*S*)-3-((2*R*,6*S*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yloxy)-6-(4-methoxybenzyloxy)-tetrahydro-2-methyl-2*H*-pyran-4-yl 4-nitrobenzoate (*ent*-14):

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

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

¹H NMR (CDCl₃, 600 MHz)

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

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

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

^1H NMR (CDCl_3 , 600 MHz)

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

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

(2*R*, 3*R*, 6*R*)-6-((2*S*,3*S*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (*ent*-17):

¹H NMR (CDCl₃, 600 MHz)

(2*R*, 3*R*, 6*R*)-6-((2*S*,3*S*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (*ent*-17):

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

(2*R*, 3*R*, 6*R*)-6-((2*S*, 3*S*, 4*S*, 6*S*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-ol (*ent*-18):

^1H NMR (CDCl_3 , 600 MHz)

(2*R*, 3*R*, 6*R*)-6-((2*S*,3*S*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-ol (*ent*-18):

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

(2*R*,6*S*)-6-((2*R*,3*R*,6*R*)-6-((2*S*,3*R*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-2*H*-3(6*H*)-pyran-3-one (*ent*-19):

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

(2*R*,6*S*)-6-((2*R*,3*R*,6*R*)-6-((2*S*,3*R*,4*S*,6*S*)-6-(4-methoxybenzyloxy)-4-hydroxy-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-tetrahydro-2*H*-pyran-3-yloxy)-2-methyl-2*H*-3(6*H*)-pyran-3-one (*ent*-19):

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

(6R)-6-pivaloyl-(2R)-2-methyl 2H-pyran-3(6H)-one (35).

^1H NMR (CDCl_3 , 600 MHz)

(6R)-6-pivaloyl-(2R)-2-methyl 2H-pyran-3(6H)-one (35).

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

STANDARD SPECTRA
((2*R*,5*S*,6*R*)-5,6-dihydro-5-hydroxy-6-methyl-2H-pyran-2-yl pivalate (36).

¹H NMR (CDCl₃, 600 MHz)

Width 9594.6 Hz
6 repetitions
OBSERVE H1, 599.6670078 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 0 min, 30 sec

((2*R*,5*S*,6*R*)-5,6-dihydro-5-hydroxy-6-methyl-2H-pyran-2-yl pivalate (36).

¹³C NMR (CDCl₃, 150 MHz)

DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 32 min, 34 sec

((2*R*,5*S*,6*R*)-3,4,5,6-tetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl pivalate (37).

¹H NMR (CDCl₃, 600 MHz)

X : parts per Million : ¹H

((2*R*,5*S*,6*R*)-3,4,5,6-tetrahydro-5-hydroxy-6-methyl-2H-pyran-2-yl pivalate (37).

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

xy-55.3

((2*R*,5*S*,6*R*)-4-((2'*S*,6'*R*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yloxy)-3,4,5,6-tetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl pivalate (38).

^1H NMR (CDCl_3 , 600 MHz)

X : parts per Million : ^1H

((2*R*,5*S*,6*R*)-4-((2'*S*,6'*R*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yloxy)-3,4,5,6-tetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl pivalate (38).

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

((2*R*,5*S*,6*R*)-4-((2'*S*,6'*R*)-5,6-dihydro-5-(4-acetate)-6-methyl-2*H*-pyran-2-yloxy)-3,4,5,6-tetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl pivalate (39).

^1H NMR (CDCl_3 , 600 MHz)

((2*R*,5*S*,6*R*)-4-((2'*S*,6'*R*)-5,6-dihydro-5-(4-acetate)-6-methyl-2*H*-pyran-2-yloxy)-3,4,5,6-tetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl pivalate (39).

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

File size 131072
Total time 32 min, 34 sec

Bm-57

2-Bromo-8-hydroxy-1,4-dimethoxynaphthalene 33

^1H NMR (CDCl_3 , 600 MHz)

USSRV F1, 599.66/00/1 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 0 min, 5 sec

2-Bromo-8-hydroxy-1,4-dimethoxynaphthalene 33

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

DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 32 min, 34 sec

-TMB

(2*R*,3*S*,4*R*,6*R*)-6-(hydroxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (43):

^1H NMR (CDCl_3 , 600 MHz)

As an equilibrating mixture of stereo- and regio-isomers:

(2*R*,3*S*,4*R*,6*R*)-6-(hydroxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (43):

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

(2*R*,3*S*,4*R*,6*R*)-6-(7-bromo-5,8-dimethoxynaphthalenyloxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (44 α):

(2*R*,3*S*,4*R*,6*S*)-6-(7-bromo-5,8-dimethoxynaphthalenyloxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (44 β):

As an inseparable mixture of stereo-isomers:

(2*R*,3*S*,4*R*,6*R*)-6-(7-bromo-5,8-dimethoxynaphthalenyloxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (44 α):

(2*R*,3*S*,4*R*,6*S*)-6-(7-bromo-5,8-dimethoxynaphthalenyloxy)-2-methyl-3-((2*S*,5*S*,6*S*)-6-methyl-5-((2*R*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-2*H*-pyran-4-yl acetate (44 β):