Synthetic approaches to a ribonucleotide, a folic acid analog, fucose/iodose sugars and
gilvocarcins

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Dissertation directed by

George A. O’Doherty
Professor of Chemistry and Chemical Biology
Dedication

*My family, my teachers & women in science*
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The decision to come to the USA for pursuing my doctoral studies was not an easy one. Looking back I feel very glad that I made that decision because it has not just helped me earn my degree, everything about living on my own has been a learning experience. As I prepare to start a new chapter in life, I would like to thank my advisor Prof. George O’Doherty and Northeastern University for giving me the opportunity to pursue my Ph.D. at the Department of Chemistry. I cannot thank George enough for his mentorship, guidance and support. His influence will undoubtedly be the strongest influence on me for years to come. I would also like to sincerely thank my committee members Prof. Penny J. Beuning, Prof. Roman Manestch and Prof. Ganesh Thakur for their guidance and support. I would like to thank the entire faculty and staff at Northeastern University for their guidance and help. I would like to thank Prof. Penny J. Beuning and Prof. Mary Jo Ondrechen for entrusting me with collaborative projects. I am very thankful for the mentorship of my group members, Dr. Ehesan U. Sherif and Dr. Sumit O. Bajaj during the early years. Fellow researcher Lisa Ngu at Prof. Beuning’s Lab deserves special acknowledgement for bringing the collaborative projects to reality. I would like to thank all of my former and present group members Dr. Michael Cuccurese, Dr. Qian Chen, Dr. Hongyan Li, Dr. Mingzong Li, Dr. Yuzhi Ma, Dr. Pei Shi, Dr. Rajender Vemula, Dr. Hua-yu Leo Wang, Dr. Yanping Wang, Dr. Qi Zhang, Dr. Yashan Zhong, Dr. Jiamin Zheng, Yu Li, Xiaofan Liu, Chao Liang, Alhanouf Aljahdali for their support and friendship. I would like to thank my mentees Olivia Capotorto and Curtis Gong for putting in sincere efforts in the projects. I am also thankful to Dr. Jason Guo and Brian D’amico for their help with NMR techniques. I am thankful for the opportunity to work
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Abstract of Dissertation

Glycinamide Ribonucleotide (GAR) and Formyldideazafolic acid (FDDF) were sought as substrates for the study of the biochemical functions of Glycinamide ribonucleotide transformylase (GART enzyme). Since these compounds are not commercially available we took upon the challenge to synthesize both compounds in-house. We chose to develop our own method to synthesize GAR. Although GAR is typically prepared as a mixture of anomers only the beta-form is the active substrate. In this context we also developed a route to synthesize β-GAR selectively. Previously only formylated β-GAR has been prepared biosynthetically. FDDF was synthesized by following literature procedures but different techniques were adopted from different articles and merged together.

We envisioned the development of a very short, asymmetric, practical synthesis of D-/L-fucose from achiral starting materials by employing iterative asymmetric dihydroxylation strategies. In this regard we have developed a novel one-pot procedure for the generation of fucose stereochemistry. For simplicity sake, we chose to work on L-fucose, but the same strategy can be employed for the synthesis of D-fucose and further extrapolated to the synthesis of idose. Gilvocarcins belong to the angucycline group of natural products having antibiotic activities and are structurally characterized by a tetracyclic ring system with a D-fucose sugar attached by a C-glycosidic bond. Our objective is to develop a divergent, de novo asymmetric synthetic approach to gilvocarcins and various unnatural sugar stereoisomers. This synthetic access will allow hitherto unexplored structure activity relationship studies of this class of biologically important natural product.
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List of Abbreviations:

Ac  Acetyl
AD-mix  Asymmetric dihydroxylation mixture
AIBN  Azobisisobutyronitrile
Bu  n-Butyl
$t$-Bu  tertiarybutyl
Bn  Benzyl
Bz  Benzoyl
Bu  Butyl
Calcd  Calculated
Cbz  Benzyloxy carbonyl
Co-ox.  Co-oxidant(s)
Cp  Cyclopentyl
mCPBA  meta-Chloroperoxybenzoic acid
CSA  Camphorsulfonic acid
d  Doublet
DCC  Dicyclohexylcarbodiimide
de  Diastereoisomeric excess
δ  Chemical shift
DIIAMB  Diisoamylborane
DIPEA  Diisopropylethylamine
DMAP  4-Dimethylaminopyridine
DMSO  Dimethyl sulfoxide
ee  Enantiomeric excess
ent  Enantiomer
equiv  Equivalent(s)
Et  Ethyl
EtOAc  Ethyl acetate
g  Gram(s)
h  Hour(s)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrum</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>$J$</td>
<td>Spin-spin coupling constant</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>min</td>
<td>Minute(s)</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole(s)</td>
</tr>
<tr>
<td>mol</td>
<td>Mole(s)</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxy methyl</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrum</td>
</tr>
<tr>
<td>NBS</td>
<td>$N$-Bromosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>$N$-Iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>$N$-Methylmorpholine $N$-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Pd-C</td>
<td>Palladium on carbon</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>$i$Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>Py/Pyr</td>
<td>Pyridine</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>$R_f$</td>
<td>Ratio to front</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBS</td>
<td>t-Butyldimethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflyl, CF₃SO⁻</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
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Chapter 1A

Synthesis of Glycinamide Ribonucleotide (GAR) and Formyldideazafolic acid (FDDF) as substrates for GART assay

1.1 Background

Glycinamide ribonucleotide transformylase (GART) is an enzyme crucial to the de novo purine biosynthesis pathway, as it catalyzes the formation of N-formylglycinamide ribonucleotide (FGAR) from glycinamide ribonucleotide (GAR).\textsuperscript{1,2,3} FGAR undergoes further enzyme-catalyzed transformations to form inosine monophosphate, a nucleotide that serves as a source for purine bases adenine and guanine. Thus effective inhibition of GART can adversely affect nucleic acid building block formation, making it a target for the development of novel cancer therapy.

In humans GART forms part of a multi-enzyme complex called purinosome. However, in \textit{E. coli}, GART exists as an isolated protein. Thus it is easier to develop an assay to study the formyl transfer activity of \textit{E. coli} GART. For the formation of FGAR from GAR, GART utilizes \textit{N}-formyltetrahydrofolate (FTHF) as a formyl-group donor (Figure 1.1A and 1.1B). \textit{N}-10-formyl tetrahydrofolate (FTHF) can exist as (6\textit{R}) or (6\textit{S}) form (Stereochemistry at the 6 position). The (6\textit{R}) form is the natural isomer. The pure natural form of FTHF is difficult to prepare\textsuperscript{4} and also highly susceptible to oxidative aromatization.\textsuperscript{5} Thus, it needs to be constantly reduced back during synthesis and enzyme assays. \textit{N}-10-formyl dideazafolate (FDDF) was first synthesized by Hynes \textit{et al}. as part of a study to evaluate the inhibitory activity of a series of compounds against dihydrofolate reductase (DHFR) enzymes from rat liver and \textit{Streptococcus faecium}.\textsuperscript{6}
These compounds were quinazoline analogues of folic and isofolic acid. FDDF was designed as an analog of N-10-formyl folate, which was known to be the most potent naturally occurring inhibitor of mammalian dihydrofolate reductase. In comparison with the other non-N-10-formylated compounds in the series, the formylated-compounds generally demonstrated a modest enhancement of inhibitory activity against both the DHFR enzymes. Upon testing against L1 210 Leukemia in mice FDDF displayed increase in survival rate by up to 25%. Later, when FDDF was used against GART by Smith et al. as a possible inhibitor, surprisingly they observed it function as a substrate with 77% relative rate compared to (6R)-FTHF. FDDF is routinely used in current GART assays as the standard substrate, the key advantage being its stability to oxidative degradation.

As part of a study of the biochemical function of GART, our collaborators Prof. Penny J. Beuning and Prof. Mary Jo Ondrechen sought GAR and FDDF to develop an assay of GART. As both compounds are not commercially available they needed to be synthesized. We took upon the challenge to synthesize these compounds. GAR has two anomeric forms, only the beta-anomeric form is formylated by GART, whereas the alpha-anomeric form remains untouched. At the outset of this project there were no reports of a diastereoselective synthesis of β-GAR. Thus GART is always assayed with a 1:1 mixture of anomers.

![Figure 1.1A: Formylation of GAR catalyzed by GART with FDDF as formyl-donor](image-url)
1.2 Prior synthetic attempts towards Glycinamide Ribonucleotide (GAR)

There have been several successful chemical syntheses of FGAR and GAR, the earliest dating back to 1965. All of these methods provide FGAR or GAR as 1:1 mixture of alpha and beta anomers. As a result of the era from which these articles were published, there is a dearth of characterization data and experimental details. In one case, the process involved a single step crystallization of amino ribo-pyranose, which lasted over two weeks and involved the use of anhydrous ammonia gas. This is a toxic gas and as such, its use requires special equipment to handle this hazardous material.

Taking inspiration from all the known routes to GAR, we came up with our own unique approach to α/β-GAR. Our method is more practical, economical, reliable and less time consuming. Each step of the synthetic process was optimized, all the intermediates were fully characterized, wherever possible. The details of our synthetic
route to \(\alpha/\beta\)-GAR has been published.\(^{18}\) Of the previous syntheses, some of the most relevant routes are described here.

### 1.2.1 Synthesis of Formylglycinamide Ribonucleotide by Chu and Henderson\(^{11}\)

Chu et al.’s synthesis started with 2,3,5-tri-O-benzoyl-\(\beta\)-D-ribofuranosylazide \(1.1.1\) (Scheme 1.1). Azide \(1.1.1\) was hydrogenated over Pt\(_2\)O to give the corresponding amine \(1.1.2\) as a mixture of anomers. The DCC mediated coupling of \(1.1.2\) with formyl glycine resulted in the formation of tribenzoylated formylglycylyribosylamine \(1.1.3\), as a mixture of anomers. The benzoyl groups were deprotected using NaOMe in MeOH and the product was purified using ion exchange chromatography and lyophilized to give formylglycylyribosylamine \(1.1.4\) (Scheme 1.1). The amide \(1.1.4\) was phosphorylated directly to the corresponding 5’-phosphorodichloridate \(1.1.5\), which was collected by centrifugation and converted to the Ba\(^{2+}\), H\(^+\), NH\(_4\)^+ and finally the Li\(^+\) form of formylglycinamide ribonucleotide \(1.1.6\).

An analysis of Chu’s synthesis identified several issues, starting from \(1.1.1\) to the final product \(1.1.6\), this process involved four synthetic steps and several lyophilization cycles and ion exchange steps at the end. The yields were not high. The lyophilization of the material at step three was key to the success of the phosphorylation at step four. Since we lacked lyophilization capabilities we decided to explore an alternative route. In addition, the starting material was also not commercially available, it can be prepared from ribose in three steps or in a single step from the much more expensive 2,3,5-tri-O-benzoyl-\(\beta\)-D-ribofuranosylacetate.
1.2.2 Synthesis of Glycinamide Ribonucleotide by Boschelli et al.\textsuperscript{12}

In the 1989 Tetrahedron Letters article by Boschelli et al. few details regarding the procedures or characterization data were provided beyond the information depicted in the following scheme (Scheme 1.2). The synthesis began with the commercially available 2,3,5-tri-\textit{O}-benzoyl-\textit{\beta}-\textit{D}-ribofuranosylacetate 1.2.1. The acetate was treated with trimethylsilylazide in presence of SnCl\textsubscript{4} and converted to the corresponding azide 1.1.1. Reduction of the azide to amine under hydrogen over PtO\textsubscript{2} followed by DCC mediated coupling of the amine with Cbz-Glycine afforded tribenzoyl protected carboxybenzylglycylribofuranosylamine 1.2.2 as a mixture of anomers majoring in the alpha diastereomer. The anomers were separated and the alpha anomer was subjected to NaOMe catalyzed debenzoylation to the carboxybenzylglycylribofuranosylamine 1.2.3.
Scheme 1.2: Glycinamide ribonucleotide (GAR) synthesis by Boschelli et al.

An acid catalyzed acetonide protection of the 2,3-hydroxyl groups of 1.2.3 (Scheme 1.2) with the 2,2-dimethoxypropane reagent resulted in anomerization of the resulting acetonide 1.2.4, which was isolated as a mixture majoring in the alpha-anomer. The anomers were again separated and only the alpha anomer 1.2.4 was carried forward and converted to the phosphoramidate by using N,N-diisopropyl dibenzyl phosphoramidite and oxidized to the corresponding phosphate 1.2.5 in situ. Reductive debenzylation and TFA mediated acetonide deprotection gave glycinamide ribonucleotide (GAR) 1.2.6 as the free acid as a 1:1 mixture of anomers.

There are other synthetic routes to GAR and related compounds but the above two methods are most relevant to our work. Carrington et al. were the first to prepare formyl-GAR (FGAR) in 1965. Chettur and Benkovic prepared barium salt of GAR using their
synthetic route in 1977. Shown below in Figure 1.2 are the various syntheses of GAR and FGAR.

**Figure 1.2:** Glimpse at the various synthesis of GAR and FGAR

### 1.3 Our Approach Towards GAR

Starting with d-Ribose 1.3.1 (Scheme 1.3.1), we protected the C-2, C-3 hydroxyl groups as the acetonide giving 1.3.2. The hydroxyl groups at the C-5 and anomic positions were protected as acetates giving 1.3.3. Treating 1.3.3 with trimethylsilylazide in presence of stannic chloride resulted in the conversion of the anomic acetate into the corresponding azide, the major isomer was the beta-anomer 1.3.4. The azide was hydrogenated over palladium on carbon, the reduction resulted in a mixture of anomic amines 1.3.5. This amine mixture, without further purification was subjected to a DCC mediated coupling with Cbz-glycine to provide the carboxybenzylglycyl-ribofuranosylamine derivative 1.3.6 also as a mixture of anomers (1.3.6a for alpha and 1.3.6b for beta), with the alpha-anomer being the major isomer. Separation of the anomers by regular flash column chromatography was not possible at this stage.
Scheme 1.3.1: Synthesis of key carboxybenzylglycylribofuranosylamine derivative

The C-5 acetate 1.3.6 was subjected to NaOMe catalyzed acetate deprotection to give the corresponding C-5-hydroxy product, again as a mixture of anomers in the crude state. Fortunately at this stage, the anomers can be separated by flash column chromatography giving the alpha-anomeric product 1.3.7a in slight excess over the beta-anomeric product 1.3.7b (Scheme 1.3.2). The separation of anomers is not essential for the synthesis of GAR by this method since the last step involves an acetonide deprotection and the acetonide deprotection conditions, which results in a 1:1 anomeric mixture of GAR. Importantly, this mixture is usable for the assay. However, the ability to separate the anomers helped us analyze and assign the spectra more easily. Both the pure anomers are synthetic precursors to GAR, because of the anomerization in the ultimate step. The anomers 1.3.7a and 1.3.7b were separately converted to the corresponding phosphates 1.3.8a and 1.3.8b in good yield by reacting with \(N,N\)-diisopropylidibenzyl phosphoramidite followed by hydrogen peroxide oxidation of the generated phosphite intermediate in situ.
Scheme 1.3.2: Synthesis of Phosphate of Cbz-glycylribofuranosylamine

The anomerically pure phosphates upon reductive debenzylation separately gave the acetonide of glycinamideribonucleotide without scrambling of the anomic center. Thus dibenzyl phosphate 1.3.8a gave the free phosphate 1.3.9a and likewise 1.3.8b gave 1.3.9b in good yields (Scheme 1.3.3). The acetonide GAR precursor, 1.3.9a and 1.3.9b when treated with trifluoroacetic acid separately at ambient temperature resulted in deprotection of the acetonide group, accompanied by anomerization generating a 1:1 mixture of alpha and beta anomers of glycinamide ribonucleotide. Thus we were able to successfully procure glycinamide ribonucleotide for the GART assays by this method described in Scheme 1.3.1-1.3.3. We were also interested in finding a strategy, which can help avoid the anomerization issue and help us procure anomerically pure GAR. To this end we were successful at synthesizing beta-GAR selectively. A short subchapter (Chapter 1B) on the synthesis of beta-GAR follows this main chapter.
Scheme 1.3.3: Synthesis of anomic mixture of glycinamide ribonucleotide (GAR)

1.4 Prior synthetic attempts towards Formyldideazafolic acid (FDDF)

The key contributors in the synthesis of quinazoline analogs (i.e., 5,8-dideaza analogs) of folic acid and isofolic acid are Davoll et al.\textsuperscript{13} and Hynes et al.\textsuperscript{14}. Diethyl-5,8-dideazafolate is a key intermediate for the synthesis of FDDF, hydrolysis of the diester to the dicarboxylic acid followed by formylation of N-10 of the resulting dicarboxylic acid gives formyl dideazafolic acid (FDDF). Hynes et al. followed Davoll et al.’s procedure to synthesize diethyl 5,8-dideazafolate. They were also able to purify the diethyl dideazafolate by flash column chromatography and perform ester hydrolysis followed by N-formylation of the product to obtain FDDF (Scheme 1.4). Subsequently Caperelli\textsuperscript{15} and co-workers followed Hynes et al.’s procedures with slight modifications of the final two steps to obtain FDDF from diethyl dideazafolate.
Synthesis of FDDF by Davoll and Johnson\textsuperscript{3}

The first key intermediate for Davoll and Johnson’s synthesis of FDDF was 2,4-diamino-6-nitroquinazoline \textbf{1.5.2} (Scheme 1.5). They laid out three different methods to prepare \textbf{1.5.2} from three different starting materials namely 2,4-diaminoquinazoline, 2-chloro-5-nitrobenzonitrile and 5-nitroanthranilonitrile \textbf{1.5.1} (only one method has been depicted in the scheme below). Diaminonitroquinazoline \textbf{1.5.2} was hydrogenated over palladium on carbon to give 2,4,6-triaminoquinazoline \textbf{1.5.3}. The amino-group at the 6-position of \textbf{1.5.3} was converted to the nitrile \textbf{1.5.4} by first diazotizing the 6-amino group in \textbf{1.5.3} and then adding the diazotized solution to a solution of CuSO\textsubscript{4}.5H\textsubscript{2}O with excess KCN. Treating the nitrile \textbf{1.5.4} with 1 N HCl under refluxing conditions results in hydrolysis and conversion of the 4-amino-group to the 4-hydroxy-group, which can tautomerize to the corresponding carbonyl compound \textbf{1.5.5}. This compound was reduced with hydrogen over Raney-nickel in presence of diethyl \textit{N-(p-aminobenzoyl-L-glutamate}}
1.5.6. The aldehyde generated *in situ* from the nitrile 1.5.5 was thus made to undergo a subsequent reductive amination. The resultant imine underwent further reduction *in situ* to the secondary amine yielding diethyl dideazafolate 1.4.1. The aminobenzoylglutamate derivative 1.5.6 was prepared by hydrogenation of the corresponding nitrobenzoylglutamate derivative 1.5.9, over palladium on carbon following procedure known in the literature. The nitrobenzoyl glutamate was prepared from reaction of *p*-nitrobenzoyl chloride 1.5.7 with diethyl l-glutamate hydrochloride 1.5.8 in presence of triethylamine.5

Scheme 1.5: Davoll and Johnson’s synthesis of Diethyl 5,8-dideazafolate (DDF)

1.5 Our approach towards Formylideazafolic acid (FDDF)

Most articles on FDDF in the literature are from the late 1960’s or early 1970’s and contain limited modern characterization data, which hinder the reproduction of this work. Several of these methods suffer from poor overall yields, and in some cases, we
found it hard to reproduce the yields for the already low yielding steps. Unfortunately, we could not come up with any obvious solution to improve these yields. Once sufficient material was obtained, we did not invest more time in modifying the overall route towards FDDF. The route we settled upon is a composite of the procedures described by several authors. Davoll and Johnson’s route was followed to synthesize diethyl-5,8-dideazafolate (1.4.1). We decided to push forward more material through the synthetic route and target for 5-10 times more FDDF than we desired, because of the struggles with the poor yields. Once we made the diethyl-5,8-dideazafolate, hydrolysis of the diester to the corresponding dicarboxylic acid was accomplished following Hynes’ procedure. Formylation at N-10 of the resulting dicarboxylic acid following Caperelli’s procedure gave formyl didazafolic acid (FDDF).

1.6 GART Assay

Fellow researcher Lisa Ngu in Prof. Beuning’s research lab is currently conducting GART assays with the GAR and FDDF we prepared. Kinetic studies so far with GART and synthesized GAR/FDDF (Figure 1.3) has revealed the assay to be performing as one would expect from the likely values. These initial experiments helped develop the standards for further kinetics study. Assays are currently underway with the GART variants. The GAR variants are enzymes with an alanine mutated distal residue. These residues are POOL (Partial Order Optimum Likelihood) predicted residues that participate in the enzyme catalysis, an outcome of the computational studies at Prof. Ondrechen’s Research lab at Northeastern University.
1.7 Conclusion

A new synthetic route to an anomeric mixture of glycinamide ribonucleotide (GAR) has been developed. GAR synthesized by this method is currently utilized along with the synthesized FDDF to study GART.
Chapter 1B

Synthesis of beta-Glycinamide Ribonucleotide (β-GAR)

1.8 Background and Working Hypothesis

In Chapter 1A we have discussed the role of glycinamide ribonucleotide transformylase (GART) in catalyzing key transformations in the de novo purine biosynthesis pathway. Specifically, GART catalyzes the formylation of glycinamide ribonucleotide (GAR) to form N-formylglycinamide ribonucleotide (FGAR). FGAR eventually undergoes a number of enzymatic transformations to produce purine bases, which are essential for nucleic acid synthesis. GAR is a D-ribose sugar derivative that can exist as alpha and beta anomers. However, only the beta isomer is the substrate for GART enzyme. Synthetically GAR has always been prepared as a 1:1 mixture of anomers. After enzymatic formylation the alpha isomer remains behind as it is inactive to enzyme.

Although α-GAR is not a substrate, it might have a noticable albeit subtle inhibitory effect on GART. A simple way to determine this is to compare GART assays run using GAR-mixture and pure β-GAR. If the difference in rate increases more than 2 fold with pure β-GAR, one can attribute that difference to the inhibitory effect of α-GAR. We have previously prepared GAR as a mixture of anomers for GART assays and the entire synthetic process has been described earlier (Scheme 1.3.1-1.3.3).18

In our synthetic attempt we prepared the mixture of GAR (1.3.10a and 1.3.10b) from 1.3.8 in two steps. In the first step a reductive debenzylation of alpha-anomer of 1.3.8 (1.3.8a) gave the alpha anomer of 1.3.9 (1.3.9a) selectively and that of the beta anomer of 1.3.8 (1.3.8b) gave the beta anomer of 1.3.9 (1.3.9b) selectively. Hence for the
conversion of 1.3.8 to 1.3.9, no anomerization was observed (Figure 1.4). But when deprotecting the acetonide in 1.3.9 with trifluoroacetic acid (TFA), both the pure alpha and beta anomers (1.3.9a and 1.3.9b) gave an anomic mixture of GAR. Thus the strongly acidic condition in the final step actually caused anomerization. Unfortunately we were not able to find milder acetonide deprotection conditions that worked in this case.

**Figure 1.4**: Final deprotection steps for GAR synthesis

We hypothesized that by changing the acetonide protecting group to the benzylidene protecting group in the final step, we can perform one reductive debenzylolation instead of two deprotection steps and that should give us beta-GAR selectively (Figure 1.5).

**Figure 1.5**: Benzylidene protecting group instead of acetonide for β-GAR synthesis
1.9 Efforts to synthesize beta-glycinamide ribonucleotide

The azide-acetonide intermediate 1.3.4, from the synthesis of anomeric mixture of GAR (Scheme 1.3.1) was refluxed with 3:1 acetic acid in water to provide the 5-O-acetyl-β-D-ribofuranosyl azide 1.6.1 (Scheme 1.6.1). The hydroxyl groups in 1.6.1 were protected as the benzylidene group to give 1.6.3 using dimethoxybenzaldehyde 1.6.2 in presence of catalytic amount of camphorsulfonic acid.

Scheme 1.6.1: Synthesis of benzylidene protected acetylribofuranosyl azide

Previously we used hydrogen over palladium on carbon to reduce azide to amine, prior to coupling with Cbz-glycine. A similar treatment of benzylidene protected azide 1.6.3 was not feasible, as it would lead to the deprotection of the benzylidene group. A Staudinger reduction\(^\text{19}\) seemed to be a better option. We also sought an in situ coupling of the amine in situ in a one-pot manner using Corey-Nicolaou’s macrolactonization condition\(^\text{20}\). Thus by treating 1.6.3 with PPh\(_3\) in presence of 2,2'-dipyridyl disulfide and Cbz-glycine the azide was reduced to the amine, which further coupled with Cbz-glycine in situ to give Cbz-glycylribofuranosyl amide derivative 1.6.4 as a mixture of anomers (1.6.4a and 1.6.4b). The anomers were not easily separable at this stage as a result 1.6.4 was subjected to NaOMe mediated deprotection of the 5-O-acetyl group to give 1.6.5, again as a mixture of anomers. At this stage the anomers can be fairly easily separated by
silica gel column chromatography. However the alpha anomer 1.6.5a was the major product isolated (with 44% yield over 2 steps) and the beta anomer 1.6.5b was the minor product (with 27% yield over 2 steps) (Scheme 1.6.2).

Scheme 1.6.2: Conversion of azide to glycylamide and acetate deprotection

Once we had 1.6.5b, as a pure beta anomer, it was treated with N,N-diisopropyl dibenzyl phosphoramidite in presence of tetrazole to give the phosphite intermediate, which was oxidized in situ with hydrogen peroxide to give the phosphate 1.6.6b as the pure beta anomer. Hydrogenation of 1.6.6b over palladium on carbon resulted in global debenzylolation selectively giving GAR in the pure beta isomer 1.6.7b.

Scheme 1.6.3: Synthesis of β-GAR

An alternative route to beta-GAR was previously pursued (Scheme 1.7), where the phosphate was installed at the C-5 of 1.7.1 to give 1.7.2 and then the azide was
reduced and coupled with glycine to give 1.7.3 as a mixture of anomers. In this case the purification of 1.7.3 from by-products as well as separation of anomers proved difficult specially since highly pure anomeric product was required at this penultimate stage to obtain pure beta-GAR.

Scheme 1.7: Alternative approach to synthesis of beta-GAR

In the following figure (Figure 1.6) NMR spectra of beta-GAR and that of mixture of GAR anomers has been compared.

Figure 1.6: $^1$HNMR of anomeric mixture of GAR on left and beta-GAR on right
1.10 Conclusion

A synthetic route to β-GAR was developed. Synthesis of pure β-GAR has not been published before. We are in the process of procuring and purifying sufficient β-GAR, which will eventually also be used in a GART assay and compared against the anomeric GAR mixture.
Chapter 2

Short stereoselective synthetic approach towards fucose and iodoce

2.1 Background

Monosachcharides are useful synthetic chiral building blocks for both oligosaccharide synthesis and the synthesis of polyol natural products. As the name suggests, rare sugars are particularly valuable as they have to be synthesized. L-fucose and D-fucose are both expensive monosaccharides but D-fucose is roughly 2-3 times more expensive that L-fucose.\textsuperscript{21} Both forms of iodoce are also rare and expensive. The O’Doherty reseach group has had a long-standing interest in the development of enantioselective synthetic routes towards natural and unnatural sugars, ranging from simple monosaccharide targets to more complicated oligosaccharides.\textsuperscript{22} These synthetic routes are designed with vision for stereochemical divergence and applicability towards the synthesis and medicinal chemistry study of naturally occurring carbohydrate-containing structure. In this regard, we wanted to apply our group’s de novo approach towards the stereoselective synthesis of fucose monosaccharides from ethyl sorbate, an inexpensive achiral starting material.

2.2 Hypothesis

The pyranose form of L-fucose and D-fucose are depicted in Scheme 2.1 by structures 2.1.1 and 2.1.2 respectively. Translating these structures to the open chain sugar form, gives 2.1.3 for L- and 2.1.4 for D-fucose. Viewing these sugars in their open chain form, it becomes more evident how ethyl sorbate 2.1.5 can be viewed as a precursor to fucose. In theory, an asymmetric syn-dihydroxylation of the terminal alkene of ethyl sorbate followed by a second asymmetric syn-dihydroxylation of the remaining
alkene in 2.1.6 from the opposite face to the first diol would stereoselectively give the 2.1.7 in the ester oxidation state.

Scheme 2.1: Hypothesis for synthesis of fucose from ethyl sorbate

2.3 Dihydroxylation of Alkenes

2.3.1 Syn- and anti-dihydroxylation

The double bonds in ethyl sorbate are trans in nature. Syn-dihydroxylation of trans-alkene gives syn-diol and anti-dihydroxylation of trans-alkenes gives anti-diol. However, when achiral reagents react with achiral starting materials there is no facial-selectivity, thus resulting in racemic products. Thus achiral trans-alkene 2.2.1 when subjected to the achiral Upjohn dihydroxylation\(^{23}\) (Os\(_4\)/NMO) condition gives syn-diol as a racemic mixture 2.2.2 and when subjected to epoxidation and hydrolysis (\(m\)-CPBA then H\(_3\)O\(^+\)) gives anti-diol also as a racemic mixture 2.2.3 (Scheme 2.2).
2.3.2 Substrate controlled asymmetric dihydroxylation

Presence of chirality in the starting material undergoing dihydroxylation, can make one face of the double-bond more accessible to the reagent than the other. In such a situation even an achiral dihydroxylating agent can provide product diol in a stereoselective manner (i.e., substrate controlled). Shown below (Scheme 2.3) is a great example of substrate controlled asymmetric dihydroxylation from work previously performed in our group. In this example, the substrate 2.3.1 has seven double-bonds which undergo OsO₄/NMO catalyzed facial selective dihydroxylation simultaneously to give the heptasaccharide 2.3.2 in excellent yield.

Scheme 2.3: Classic example of substrate controlled asymmetric dihydroxylation
2.3.3 Upjohn dihydroxylation (OsO₄/NMO) of ethyl sorbate

In our group, we have previously subjected ethyl sorbate to Upjohn dihydroxylation conditions. This results in the terminal alkene reacting first without facial selectivity to give a racemic mixture of enantiomers 2.4.1a and 2.4.1b (Scheme 2.4). These intermediates still have an unreacted double bond which undergoes further dihydroxylation. Diols 2.4.1a and 2.4.1b, although present as a mixture at this stage, are individually chiral substrates. As a result the second dihydroxylation should occur with some desired diastereoselectivity. Thus instead of a 1:1 ratio, diol 2.4.1a is transformed into 2.4.2a and 2.4.3a and diol 2.4.1b is transformed into 2.4.2b and 2.4.3b in a 6:1 ratio. These four intermediates (two sets of enantiomers) are not isolated, rather in the presence of methanol and a base, cyclization to the gamma-lactone occurs. Specifically, the tetrols 2.4.2a and 2.4.2b cyclize to give a racemic mixture of fuconolactone 2.4.4, whereas 2.4.3a and 2.4.3b likewise cyclize to give racemic idolactone 2.4.5. This explains why at the end of this reaction we observe the two diastereoisomers 2.4.4 and 2.4.5 in a 6:1 ratio. Fuconolactone is a potential precursor to fucose, but a racemic fuconolactone will lead to a mixture of D- and L-fucose. While in reality racemic fucose is more rare than D- and L-fucose, synthetically it is less desirable. Thus for the practical reality of asymmetric synthesis we needed to develop a method to obtain optically pure fuconolactone free of any diastereoisomers.
2.3.4 Sharpless Asymmetric dihydroxylation

In 2001 K. Barry Sharpless was awarded the Nobel Prize in Chemistry for developing among other things asymmetric dihydroxylation reaction.\textsuperscript{26} Use of a catalytic amount of enantiomERICALLY pure chiral ligand (quinine or quinidine type) along with catalytic amount OsO\textsubscript{4} brought about an oxidative dihydroxylation of trans- alkenes stereoselectively to produce enantiomERICALLY enriched chiral diols. The reduced catalyst (OsO\textsubscript{3}) in this process was reoxidized back into OsO\textsubscript{4} to complete the catalytic cycle by 2 equivalents of potassium ferricyanide (K\textsubscript{3}Fe(CN)\textsubscript{6}) in the medium. The coordination of the chiral ligands to OsO\textsubscript{4} gives chirality to the complex, which when interacting with an achiral alkene imparts a facial selectivity resulting ultimately in the enantioselectivity of the product diol. The catalytic asymmetric dihydroxylation cycle is depicted in the Figure 2.1.

Scheme 2.4: Upjohn dihydroxylation of ethyl sorbate
The most popular ligands developed by Sharpless were 1,4-bis-dihydroquinine phthalazine (DHQ)$_2$PHAL and its psuedoenantioemic 1,4-dihydroquinidine phthalazine (DHQD)$_2$PHAL (Figure 2.2). These ligands (0.01 mmol) are premixed with K$_2$OsO$_2$(OH)$_4$ (0.002 mmol), K$_3$Fe(CN)$_6$ (3 mmol), K$_2$CO$_3$ (3 mmol), such that 1.4 g will oxidize 1 mmol olefin and these mixtures are commercially available and are commonly known as AD-mix-α and AD-mix-β respectively.

Sharpless developed a mnemonic to help predict the outcome of the asymmetric dihydroxylation as depicted in the below figure (Figure 2.3).
2.4 Sharpless asymmetric dihydroxylation of ethyl sorbate and application to D- and L-fucose synthesis

Treatment of ethyl sorbate (2.1.5) with AD-mix-β by Sharpless et al.\textsuperscript{27} show that the terminal alkene reacts enantioselectively to give the chiral diol 2.4.1b (Scheme 2.5) in good yield. The ligand-catalyst complex, approaches and interacts with the alkene in a face selective manner, and forms the diol on the same face. After the diol is formed the remaining alkene face becomes too crowded and the resulting substrate facial selectivity is in conflict with the catalysts’s inherent facial selectivity. This mismatch in reactivity between the ligand/OsO₄ complex and the substrate, causes the reaction to stall at this stage. Thus 2.4.1b does not undergo further dihydroxylation to 2.4.3b.

This issue of double diastereoselectivity provided us with the inspiration for an enantioselective fucose synthesis. A mismatch in configuration meant that treatment of 2.4.1b with the psuedoenantiomeric AD-mix-α might result in a matched configuration and push the second dihydroxylation forward stereoselectively to give the tetrol 2.4.2b with D-fucose configuration. This mismatch should also improve the diastereoselectivity and enantioselectivity of the overall process. If this works it then also suggests that
treatment of 2.1.5 with AD-mix-α, followed by treatment of the resulting diol 2.4.1a with AD-mix-β would result in the tetrol 2.4.2a with L-fucose configuration albeit with a slight different enantioselectivity.

Scheme 2.5: Inspiration for D- and L-fucose synthesis

2.5 Our efforts towards L-Fucose synthesis

2.5.1 Initial attempts

We envisioned that even if we prepare the tetrol 2.4.2a as a precursor to L-fucose via Sharpless dihydroxylation, the high water solubility of the tetrol would make its isolation from the aqueous reaction medium and separation from the water soluble inorganics not feasible. So we tried to use a pyrrolidine amide analog and thioester analogs of ethyl sorbate (Figure 2.4), in an attempt to decrease the hydrophilic nature of the tetrol derived from these analogs. Also, we envisioned that the possibility of direct reduction of amide or thioester to aldehyde will eventually make it easier to obtain fucose.
Figure 2.4: Pyrrolidine amide and thioester analogs of ethyl sorbate

Interestingly the pyrrolidine amide analog 2.6.1 (Scheme 2.6) when treated with AD-mix-α gave diol 2.6.2 in good yields but the second dihydroxylation resulted in a mixture of diastereoisomers 2.6.3.

Scheme 2.6: Attempted iterative dihydroxylation of the pyrrolidine amide analog

The thioester analog 2.7.1 when treated with AD-mix-α gave diol 2.7.2. In presence of phenyl boronic acid 2.7.1 reacted with AD-mix-α to give the boronate 2.7.3. Upon treatment of 2.7.2 and 2.7.3 with AD-mix-β the second dihydroxylation did not proceed, so we subjected 2.7.2 to Upjohn dihydroxylation condition, this time the product decomposed and we were not able to isolate either any tetrol or any starting material.

Scheme 2.7: Attempted iterative dihydroxylation of the thioester analogs
2.5.2  Latter attempts

After the initial attempts were not successful, we switched our efforts back to working with ethyl sorbate. We realized that the product diols could be trapped *in situ* in the form of boronates in the dihydroxylation reactions. The advantage of this is that it improves the yield, enantioselectivity\(^{28}\) and helps in the isolation of the product. It has been suggested that the boronate is formed directly from the osmate without hydrolysis to the corresponding diol\(^{28}\) (Figure 2.5). The mechanism for this proposed transformation is laid out in Scheme 2.8.

![Conversion of osmate to boronate in situ](image)

**Figure 2.5:** Conversion of osmate to boronate *in situ*

![Mechanism for osmate to boronate conversion](image)

**Scheme 2.8:** Mechanism for osmate to boronate conversion.

We subjected ethyl sorbate to the Sharpless asymmetric dihydroxylation (with chiral ligand \((\text{DHQ})_2\text{PHAL}\)) in presence of phenyl boronic acid and obtained the monoboronate \(2.9.1\). We isolated \(2.9.1\) from the reaction medium, flashed it through a silica gel column and resubjected it to a second matched Sharpless dihydroxylation (with
chiral ligand (DHQD)$_2$PHAL) again in presence of phenyl boronic acid to obtain the bisboronate 2.9.2 as masked L-fucose. Bis-boronate 2.9.2 was also easily isolable from the reaction medium.

**Scheme 2.9: Bisboronate as masked fucose**

2.5.3 **One-pot iterative dihydroxylation approach towards fucose**

We modified the process described above and were able to obtain the bisboronate 2.9.2 in a one-pot procedure. Ethyl sorbate when treated with catalytic OsO$_4$ (1%) and (DHQ)$_2$PHAL (1.5%) in presence of excess co-oxidants and excess phenyl boronic acid got consumed to give the monoboronate 2.9.1. At that point the addition of a catalytic amount of (DHQD)$_2$PHAL (8%) along with some more OsO$_4$ (4%) helped covert 2.9.1 directly to the bisboronate 2.9.2. The bisboronate was easily extracted from the reaction mixture.

**Scheme 2.10: One-pot iterative dihydroxylation approach towards fucose**

2.5.4 **L-fucose from bisboronate**

In section 2.3.3 we mentioned that fuconolactone is a precursor to fucose. In the scheme below we have shown how the ester in triacetate of L-fuconolactone 2.11.1 can be reduced by freshly prepared diisoamylborane to triacetate protected L-fucose 2.11.3 (Scheme 2.11). The bisboronate 2.9.2 isolated from the one-pot procedure was carried
forward without further purification and treated with diethanolamine in MeOH or KHF$_2$ in acetone. This resulted in the cleavage of the boronates and cyclization of the resulting tetrol into a lactone. In either case the boronate salts were removed by filtration and the solution concentrated to the crude lactone 2.11.1, which was taken up in DCM and per-acetylated to give the triacetylated L-fuconolactone 2.11.2. With this protocol we were able to achieve a short stereoselective synthesis of L-fucose. We are currently exploring different protecting groups for L-fuconolactone or possible direct reduction to L-fucose (Scheme 2.12).

**Scheme 2.11: Bisboronate to L-fucose**

**Scheme 2.12: Current attempts and future direction**
2.6 Efforts towards Iodose synthesis

2.6.1 Retrosynthetic approach towards Idose

Once we developed the fucose synthesis, we realized we could employ similar strategies to the synthesis of idose. The fully protected iodo-furanose derivative 2.13.1 (Scheme 2.13) can be obtained by the diisoamylborane mediated reduction from the corresponding L-idolactone derivative 2.13.2. The acetylation of the triol in L-idolactone 2.13.3 can be affected by treating with acetic anhydride and pyridine. Triol 2.13.3 is a mere pyridinium tosylate catalyzed cyclization product of 2.13.4. Thus the tetrol 2.13.4 was defined as a precursor to L-iodose and the enantiomer of 2.13.4 was a precursor to D-iodose.

Scheme 2.13: Retrosynthesis of L-Iodose derivative

2.6.2 Synthesis of dienoate starting material

Drawing comparison with ethyl sorbate, it meant the sugar backbone providing starting material needed was the 6-benzyloxy analog of ethyl sorbate 2.14.1 (Scheme 2.14). Unlike ethyl sorbate, this analog is not commercially available and had to be synthesized. Pent-4-ynol 2.14.2 was benzylated to 2.14.3. The 5-benzyloxypentyne 2.14.3 was treated with BuLi followed by the addition of ethyl chloroformate to give the alkynyl ester product 2.14.4. When alkyne ester when treated with the Rychnovsky variation of the Trost isomerization (PPh₃/PhOH in refluxing toluene) it was converted into the 6-benzyloxydieneoate (2.14.1).
Scheme 2.14: Synthesis of ethyl 6-benzyloxy-2E, 4E-hexadienoate or 6-benzyloxy ethyl sorbate

2.6.3 Iterative asymmetric dihydroxylation approach to Idose

It was known from earlier studies\(^{25}\) that treating 2.14.1 with AD-mix-\(\alpha\) would give the diol 2.15.1 and treating with AD-mix-\(\beta\) will give the enantiomer \(\text{ent-2.15.1}\) stereoselectively (Scheme 2.15). At this stage due to mismatch in configuration between the substrate and the osmate-ligand complex the reaction will not proceed further. However several new chiral ligands have been developed, both of the monodentate and bidentate varieties. Of these new ligands, Corey’s pseudoenantiomeric ligands 1,4-bis-dihydroquinine pyradazine (DHQ)\(_2\)PYDZ and 1,4-bis-dihydroquinidine pyradazine (DHQD)\(_2\)PYDZ were promising. These ligands being less hindered (Scheme 2.16) the mismatch is generally not\(^{30}\) as pronounced so as to stall the reaction (2.15.1 to 2.13.4).

Thus we envisioned that treating 2.15.1 with modified AD-mix-\(\alpha\) containing (DHQ)\(_2\)PYDZ instead of (DHQ)\(_2\)PHAL and \(\text{ent-2.15.1}\) with modified AD-mix-\(\beta\) containing (DHQD)\(_2\)PYDZ instead of (DHQD)\(_2\)PHAL would give us the L-ido- 2.13.4 and D-ido- \(\text{ent-2.13.4}\) respectively.
**Scheme 2.15:** Asymmetric dihydroxylation approach to Idose

### 2.6.4 Model reaction

We tried this model reaction before we had access to the benzyloxyhexadienoate 2.14.1. We prepared 2.16.1 (Scheme 2.16) by acetonide protection of the diol 2.4.1b. The diol was obtained by Sharpless dihydroxylation of ethyl sorbate 2.1.5 with AD-mix-β.

![Scheme 2.16: Model study for obtaining Ido-sugar](image)

The acetonide 2.16.1 was treated with a modified AD-mix-β containing (DHQD)$_2$PYDZ as the chiral ligand. We had previously treated 2.16.1 with AD-mix-α and found that it had given us the fuco-derivative 2.16.2 as the major diastereoisomer. Upon treating with the modified AD-mix-β we obtained the ido-derivative 2.16.3, which was
diastereoisomeric to 2.16.2 as the major diastereoisomer. The structures of the Corey ligands are shown in Scheme 2.16 as well. This showed that our theory should work for ido-synthesis.

2.6.5 Current Attempts

With 2.14.1 now in hand we are now proceeding to work on the iterative dihydroxylation approach to idose.

2.7 Conclusion

A novel, short stereoselective synthesis of fucose has been developed. Work is currently underway to screen ligand variations to maximize diastereoselectivity. Application of the synthetic strategy for the synthesis of idose is also pursued.
Chapter 3
Synthetic approach towards gilvocarcins

3.1 Background

**Isolation and Biological Activity:** Gilvocarcins namely gilvocarcin V and gilvocarcin M were first isolated from the culture broth of *Actinomycete* DO-38 in 1980 by Tomita and coworkers. The gilvocarcins are potent against Gram-positive bacteria (e.g., *Staphylococcus aureus, Bacillus subtilis*) and weakly active against Gram-negative bacteria (e.g. *Escherichia coli, Klebsiella pneumonia*) with gilvocarcin V being more potent than gilvocarcin M. Gilvocarcin V is also known to have minimal toxicity in mice and displayed impressive antitumor activity in experimental tumor models such as mouse sarcoma 180 and mouse leukemia P388.31-32

**Structure:** Tomita and coworkers determined the structures of the gilvocarcins, using chemical degradation studies complemented by NMR, mass and IR spectral studies.33 Soon after, Clardy (with Bristol Laboratories) isolated gilvocarcins E. In addition, Clardy discovered gilvocarcins V and M and further elucidated their structure using NMR and X-ray crystallographic studies.34 Hirayama and coworkers also independently published the crystal structure of gilvocarcin M.35

Structure elucidation of the gilvocarcins revealed a tetracyclic aromatic core, which has a fucose sugar in furanose form attached to the C-4 by a C-glycosidic bond, forming a β-stereocenter at the anomeric position. The alkyl substituent at C-8 is a methyl in gilvocarcin M, vinyl in gilvocarcin V and ethyl in gilvocarcin E (See Figure 3.1). The biosynthesis is believed to proceed via glycosylation of the tetracyclic aromatic core known as defucogilvocarcin.36,37
The interesting biological activities along with the complex structural features make the gilvocarcins a worthy challenge for synthesis. In this regard, we decided to develop a novel route to the gilvocarcins, which allows us access to diverse unnatural sugar analogs as part of the SAR studies of the natural product.

3.2 Prior synthetic attempts

**Defucogilvocarcins:** In the mid 80’s, several groups started pursuing gilvocarcin synthesis. The synthetic routes chosen by these research groups, while widely different from each other, focused mostly on the aglycone portion of gilvocarcins. Via different routes, several groups were successful in synthesizing defucogilvocarcins, however none of these groups were successful at installing the fucose sugar in a regio- and stereoselective manner for gilvocarcin synthesis. McKenzie *et al.*, Jung *et al.* and Hart *et al.* synthesized defucogilvocarcin M; Danishefsky *et al.*, Findlay *et al.*, McGee *et al.* and Parker *et al.* synthesized defucogilvocarcin V while Martin *et al.* synthesized defucogilvocarcin E and M. Some of the more notable syntheses, which were all unique and versatile are described in detail below.
3.2.1 Synthesis of defucogilvocarcin M by McKenzie et al.\textsuperscript{38}

McKenzie’s synthesis started with the reduction of nitroanisole 3.1.1 (Scheme 3.1) and protecting the resulting amine to form pivamide 3.1.2. Treatment with \textit{n}-BuLi then CO\textsubscript{2} generated the acid 3.1.3, which was converted into the methyl ester with simultaneous cleavage of amide to generate the free amine. The amine was further diazotized and coupled with 2,6-dichlorobenzoquinone to afford the bicyclic quinone core 3.1.4.

![Scheme 3.1: Defucogilvocarcin M synthesis by McKenzie et al.](image)

A key step of the McKenzie route involved Diels-Alder reaction with 1-trimethylsilyloxybutadiene followed by HF promoted TMS deprotection and subsequent MnO\textsubscript{2} oxidation lead to the quinone 3.1.5. The OH- group was acetylated and the chloride was converted to thiophenyl group 3.1.6, which was removed by reduction and
the resulting hydroquinone oxidized back to the naphthaquinone 3.1.7. A one step Zn/AcOH reductive lactonization and methylation afforded the acetylated defucogilvocarcin 3.1.8. Finally acetate deprotection afforded the desired defucogilvocarcin M.

3.2.2 Synthesis of defucogilvocarcin V by Danishefsky et al.\(^{39}\)

Danishefsky et al. started their synthesis from 1,5-diacetoxynaphthol 3.2.1 (Scheme 3.2.1). Following known literature procedure\(^{40}\) they were able to obtain the 2-bromojuglone 3.2.2, which was converted to the methoxymethylether 3.2.3. Reduction of 3.2.3 with hydrogen over palladium on carbon gave the bromo-naphthohydroquinone 3.2.4. Protection of hydroxyl groups with methoxymethylchloride (MOMCl) gave the monoprotected ether 3.2.5 selectively. The remaining 4-hydroxy group was then methylated to give 3.2.6, which was one of the prime building blocks.

![Scheme 3.2: Synthesis of naphthol derived building block.](image)

The second building block was derived from vanillin 3.3.1 (Scheme 3.3). The bromo-derivative of vanillin 3.3.2 was again prepared following known procedures.\(^{41}\) A Wittig reaction enabled the conversion of aldehyde to alkene to generate 3.3.3. Upon treatment with \(n\)-BuLi followed by the bubbling of carbon dioxide the bromide was
converted to carboxylate to produce 3.3.4. Treatment of 3.3.4 with oxallyl chloride and 2-amino-2-methylpropanol gave the amide 3.3.5, which cyclized readily in presence of thionyl chloride to give the oxazoline 3.3.6, which serves as the other key building block.

**Scheme 3.3:** Vanillin derived synthon

With both the building blocks in hand, the naphthol type building block 3.2.6 was converted to the corresponding Grignard reagent 3.4.1, which was coupled with 3.3.6 to give 3.4.2. Treatment of the product 3.4.2 with hydrochloric acid resulted in the cleavage of the MOM-protecting groups, hydrolysis of the oxazoline ring and lactonization to give defucogilvocarcin V 3.4.3.

**Scheme 3.4:** Synthesis of defucogilvocarcin V from the two building blocks
3.2.3 Synthesis of Defucogilvocarcin E by Martin et al.\textsuperscript{42}

The D-ring precursor of defucogilvocarcin E (Scheme 3.5) was obtained by Martin et al. by the saponification of the methyl ester (3.5.4). This o-iodoester was obtained from regioselective iodination of (3.5.3), which was obtained from (3.5.1) via benzylic bromination followed by alkylation of the bromide to form the homologue (3.5.5).

![Scheme 3.5](image)

Scheme 3.5: D-ring precursor for defucogilvocarcin E by Martin et al.

For the synthesis of defucogilvocarcin core, benzylated juglone (3.6.1) (Scheme 3.6) was converted through a selective-reductive acetylation, conversion of the hydroxyl to methyl ether and deacetylation to afford the naphthol (3.6.2).

![Scheme 3.6](image)

Scheme 3.6: Defucogilvocarcin E synthesis by Martin et al.
DCC mediated coupling of the benzoate 3.5.5 with the naphthol 3.6.2 gave the intermediate 3.6.3, which readily underwent internal C-H activation and cross coupling that was readily catalyzed by bis(triphenylphosphine)palladium(II) dichloride to afford defucogilvocarcin E.

3.2.4 Synthetic strategy employed towards gilvocarcin M and V by Suzuki et al.

Thus far, Suzuki and coworkers were the only group who have been successful at synthesizing the enantiomer of gilvocarcin M\textsuperscript{43} and gilvocarcin V.\textsuperscript{44} Suzuki’s approach to gilvocarcins was rather different. Instead of a late stage glycosylation of the defucogilvocarcin, their route involved the installation of the fucose sugar much early in the synthesis.

The route was divergent in the sense that the same common naphthalene core bearing key intermediate 3.7.8 (Scheme 3.7) was used for synthesis of gilvocarcin M and then gilvocarcin V.

Suzuki’s Key Intermediate:

In a key step the fucose derivative 3.7.2 (Scheme 3.7) was coupled in an \( \alpha \)-stereoselective manner with the iodoresorcinol 3.7.1. The \( C \)-glycosidic bond formation was brought about by the use of a 1:2 equivalents of \( \text{Cp}_2\text{HfCl}_2 \) and \( \text{AgClO}_4 \) reagent mixture to give 3.7.3. The free phenol was converted into the triflate 3.7.4. When treated with \( n \)-butyllithium in presence of 2-methoxyfuran 3.7.5, the iodo-triflate underwent elimination to form the benzyne intermediate 3.7.6. In another pivotal step in this synthesis, demonstrating incredible route design, the benzyne underwent a regioselective Diels-Alder adduct formation \textit{in situ} as shown in 3.7.7, which rearranged readily to 3.7.8.
to regain aromaticity. Thus, the fucosylated naphthol core 3.7.8 was obtained as the key intermediate for synthesis of gilvocarcins.

**Scheme 3.7:** Suzuki’s novel strategy for regio- and stereoselective glycosylation

**Gilvocarcin M and V from the fucosylated naphthol core:**

Gilvocarcin M 3.8.1 can be obtained by global reductive debenzylation of 3.8.2 (Scheme 3.8), which was obtained in a minimal 3 steps from the key intermediate 3.7.8 via a DCC mediated coupling with the acid chloride 3.8.3, following by a Pd-catalyzed intramolecular biaryl coupling.

Gilvocarcin V 3.8.4 was obtained in 8 steps from the intermediate 3.7.8. Gilvocarcin V was obtained from 3.8.5 via an oxidative deselenation of the arylselenylethyl side chain on ring D, followed by a global acetate deprotection. The arylselenylethyl side chain was obtained by MOM-deprotection of the methoxymethyloxyethyl side chain in 3.8.6, followed by a selenylation. The gilvocarcin precursor 3.8.6 was obtained by reductive tetra-debenzylation and acetylation of 3.8.7. This was done to avoid reducing the vinyl group while attempting debenzylation in the last step, whereas acetate removal did not pose any such threat. The fucosylated
tetracyclic core of gilvocarcin V 3.8.7 was obtained by a DCC mediated coupling of 3.7.8 with the carboxylic acid 3.8.8 followed by Pd-catalyzed intramolecular biaryl coupling.

Scheme 3.8: Retrosynthetic analysis of Suzuki’s divergent gilvocarcin synthesis

3.3 Our synthetic strategy

3.3.1 De Novo approach to sugar Building Blocks

Previously the O’Doherty group demonstrated the construction of D- and L-galacto-γ-lactones starting from simple dienoates through dihydroxylations. Starting with ethyl 6-benzyloxy-2,4-dienoate 2.14.1 a Sharpless asymmetric dihydroxylation with
modified AD-mix α (2% OsO₄, 2.1% (DHQ)₂PHAL, 3 eq K₃Fe(CN)₆, 3 eq K₂CO₃, and 1 eq CH₃SO₂NH₂) gave the alkene diol 2.15.1 stereoselectively. During the first dihydroxylation the terminal double bond forms the diol while the second double bond (alpha to the ester) remains unreacted. At this stage, the mismatch in facial selectivity between the ligand and the diol prevents the reaction from proceeding further. Upon subjecting the diol to Upjohn dihydroxylation conditions (OsO₄/NMO) the second double bond also started to react. Thus treated, 2.15.1 generated the tetrol 3.9.1 as the major diastereoisomer (5:1). If methanol is chosen as the solvent for the reaction, the tetrol 3.9.1 underwent ready in situ cyclization to give the O-Bn-protected L-galaco-γ-lactone 3.9.2 as the favored diastereoisomer.

Scheme 3.9: Iterative Sharpless dihydroxylation towards synthesis of galacto-lactones

3.3.2 Iterative dihydroxylation approach to aryl sugar formation

Papulacandins are naturally occurring glycolipids that contain a lactose disaccharide. The gluco-sugar is linked to an aromatic ring through a glycosidic bond, which forms part of a spiroketal. Previously the O’Doherty group synthesized the gluco-, allo- and manno-analogs of the C-arylglycoside spiroketal core of papulacandins from 5-aryl-2-vinylfurans via Sharpless dihydroxylation. This achievement then inspired the
desire to synthesize the \textit{galacto}-analog \textbf{3.10.6a} and \textbf{3.10.6b}. The \textit{galacto}-analog of this spirocyclic arylglycoside moiety was prepared via an iterative dihydroxylation approach. For this purpose the dienone \textbf{3.10.1} was synthesized from 3,5-dibenzylxyloxy benzyl alcohol in five steps. Sharpless dihydroxylation with AD-mix-\(\beta\) gave the diol \textbf{3.10.2} with high enantioselectivity. An OsO₄/NMO dihydroxylation gave the tetrol \textbf{3.10.3}, which was acetylated to give the tetra-acetate \textbf{3.10.4} in the diastereoisomeric ratio of 4:1. An HCl-mediated TBS-deprotection of \textbf{3.10.4} lead to formation of the mixed ketal \textbf{3.10.5}. Treatment of \textbf{3.10.5} with LiOH resulted in deprotection of all four acetyl groups. The crude product was treated with HCl, which brought about the spiroketalization giving the \textit{galacto}-pyranose moiety \textbf{3.10.6a} and \textit{galacto}-furanose moiety \textbf{3.10.6b} in 2:1 ratio.

\begin{center}
\textbf{Scheme 3.10}: Iterative dihydroxylation approach towards \textit{galacto}-papulacandin moiety
\end{center}
3.4 Current attempts

3.4.1 Application of *de novo* approach to Gilvocarcin Synthesis and retrosynthetic analysis

We envisioned that the gilvocarcins 3.11.8 (Scheme 3.11), where the R-group at the C-9 position varies between methyl, ethyl and vinyl groups, could be obtained by manipulation of the corresponding phenol at C-9 in the protected form as in 3.11.7. The tetracyclic core of 3.11.7 can be obtained from coupling of 3.11.5 with 3.11.6, followed by an intramolecular biaryl coupling. The naphthalene core 3.11.5 can be obtained from 3.11.4 via deprotection, oxidation and protection steps. Our *de novo* approach to sugars can be utilized to build the fucosylated aromatic core 3.11.4 from the achiral dienone side chain bearing aromatic core 3.11.2 through iterative asymmetric dihydroxylations.

Scheme 3.11: Retrosynthesis of gilvocarcins, showing application of de novo approach to sugar construction
3.4.2 Synthesis of diaryl core with achiral side chain as a masked sugar and attempts at sugar construction

Initially we tried to build the naphthalene core with the achiral side chain in the desired position through rearrangement of the side chain as shown in Figure 3.2. For this purpose 1,5-naphthadiol 3.11.1 was monobenzylated to 3.12.1. The free hydroxyl group in 3.12.1 was protected as the sorbate giving 3.12.3 in a DCC/DMAP mediated coupling reaction with sorbic acid 3.12.2. Attempted rearrangement conditions for direct conversion of 3.12.3 to 3.12.5 were not successful, mostly resulting in decomposition. The bromo analog 3.12.4 can be obtained either by bromination of 3.12.3 or by DCC mediated coupling of naphthol 3.12.8 with sorbic acid 3.12.2. We subjected the bromo analog to halogen/metal exchange conditions hoping the arylanion generated after exchange would react in situ and add to the ester carbonyl, thus initiating the transfer of the dienoate side chain eventually resulting in 3.12.5. These attempts mostly led to dehalogenated product, giving 3.12.3 instead.

![Figure 3.2: Intramolecular rearrangement to naphthalene core](image)

At this point we started working on an alternative route to the desired naphthalene core, which also started from 3.12.1. The remaining hydroxy-group in 3.12.1 was either acetylated or chloroacetylated to give 3.12.6 (a and b respectively). A NBS mediated bromination of 3.12.6 gave the corresponding para-bromo naphthol 3.12.7. A base
catalyzed deprotection of 3.12.7 gave naphthol 3.12.8. The naphthol 3.12.8 was not very stable and was readily protected as the methoxymethyl ether to give 3.12.9.

Scheme 3.12: Synthesis of naphthalene core with achiral side chain

Treatment of 3.12.9 with n-BuLi and 2E,4E-hexadienal gave the allylic alcohol 3.13.1. MnO₂ oxidation of the allyl alcohol gave the aryl dienone 3.13.2. A Sharpless dihydroxylation with AD-mix-β, gave the diol 3.13.3 and a successive dihydroxylation with AD-mix-α containing the pseudo-enantiomeric ligand gave the tetrol 3.13.4. Current attempts are focused at the reductive cyclization of the tetrol to get the fucosylated aromatic core 3.13.5, so far we have not succeeded in achieving the desired outcome.
Scheme 3.13: Attempts at synthesis of key intermediate

The goal of this effort is to find a reductive cyclization that installs the sugar ring without the use of selective protection. This is an ongoing project and we have not yet exhausted our options for the cyclization step. We do recognize the challenges associated with this step. Specifically, we are concerned with the issues with five- versus six-membered ring formation. In contrast, control of the anomeric stereochemistry should not be a problem as they are known to isomerize to the β-isomer. The above unsuccessful example represents our initial attempts. Ultimately, we hope to find conditions that use cyclic boronates that will avoid the need of protecting-groups. In advance of this, we explored the use of protecting groups. In this regard the diol 3.13.3 was protected as the acetonide, the resulting acetonide-alkene was converted to the diol via asymmetric dihydroxylation and further diacetylated. Attempts to monobenzylate the diol 3.13.3 for instance results in a 50:50 mixture of γ- and δ-monobenzylated compound. We are also exploring alternative approaches for installing fucose using the protected fuconolactone 3.14.7 (synthesized by our method). This work is in progress and we will need several trial and error runs to eventually rich the finish line.
Scheme 3.14: Alternative approach to Gilvocarcins

**Verification of the para bromination**

NMR experiments provided evidence that the bromination of 3.12.6a occurred at the para-position with respect to the OBn group. However to be certain we prepared the ortho-bromo analog of 3.12.7a. A monoacetylation of dinaphthol 3.11.1 gave 3.15.1. Ortho-bromination of the monoacetate 3.15.1 was affected following known ortho-bromination conditions from literature to form 3.15.2. Protection of the remaining hydroxyl as the benzyl protecting group gave the ortho-bromo analog 3.15.3. Following the preparation of 3.15.3 we compared the proton and carbon NMR spectra of 3.12.7a and 3.15.3, which did not match, proving that the bromination of 3.12.6a occurred para-to the OBn group and the structure for 3.12.7a has been correctly assigned.

Scheme 3.15: Verification of para bromination
Model studies towards oxidation of phenol to quinone and reduction of quinone to quinol

Once naphthol 3.12.8 was obtained a model oxidation/reduction study was conducted to explore the feasibility of conversion of 3.11.4 to 3.11.5 (Scheme 3.11). Naphthol 3.12.1 and its bromo-analog 3.12.8 could both be converted to the corresponding naphthaquinones 3.14.1 and 3.16.1 respectively, using diacetoxyiodobenzene reagent. The quinone 3.16.1 could be reduced and selectively monoprotected in situ to either the methyl ether 3.16.2 or the acetate 3.16.3. Interestingly the OH-group closest to the bromide gets protected first as demonstrated by these examples. The OH-group closest to the benzyloxy group shows strong hydrogen bonding (i.e., the proton appears further downfield than other similar OH-proton) which prevent it from being deprotonated.

![Scheme 3.16: Model oxidation/reduction studies](image)

3.5 Conclusion

Synthetic attempts towards gilvocarcins were conducted. This work is in-progress. Significant contribution has been made which going forward will help develop the divergent route we are seeking.
Chapter 4

Experimental Section

4.1 General methods and materials

$^1$H and $^{13}$C spectra were recorded on 400 MHz, 500 MHz Varian spectrophotometers. Optical rotations were measured ($[\alpha]_D^{25}$) using JASCO P2000 digital polarimeter at room temperature in the mentioned solvents. Nicolet iS5 FT-IR spectrometer was used to obtain IR spectra. Melting points were recorded on Digimelt MP161. Flash chromatography was performed on 60-200 mesh silica gel. $p$-Anisaldehyde or KMnO$_4$ stain was used for staining TLC plates. Solvents were dried using a drying solvent system. Air/moisture sensitive reactions were performed under inert atmosphere in oven or flame dried apparatus. Spectroscopic data for known compounds with unpublished data or modified procedure are provided. New compounds were fully characterized whenever possible and the data provided.

4.2 Experimental for Chapter 1

2,3-O-Isopropyldene-D-ribofuranose 1,5-diacetate (1.3.3)

![Chemical Structure](image)

To a solution of D-ribose (5 g, 33.3 mmol) \textbf{1.3.1} in acetone (50 mL) was slowly added conc. H$_2$SO$_4$ (0.25 mL) at room temperature and the reaction mixture was stirred for 2.5 h. To the reaction mixture was added solid NaHCO$_3$ (10 g) and the solution was filtered. The residue was washed with acetone (2 x 10 mL). The filtrate and washings were
combined and concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 35% EtOAc/Hexanes to obtain 2,3-O-isopropylidene-ribose 1.3.2 as clear colorless viscous liquid (5.56 g, 29.3 mmol, 88%). $R_f$ (40% EtOAc/Hexanes) = 0.25. This compound was dissolved in dry DCM (72 mL) and the solution was cooled to 0 °C and pyridine (10.4 mL, 10.21 g, 129 mmol) was added dropwise with stirring. After 10 min, anhydrous acetic anhydride (11 mL, 11.95 g, 117 mmol) was added dropwise followed by DMAP (355 mg, 2.9 mmol) at 0 °C. The resulting mixture was stirred for 1 h while allowing to gradually warm to room temperature. The reaction mixture was diluted with DCM (120 mL) and poured over ice cold water (50 mL) in a separatory funnel and washed with ice cold dilute HCl (1 N, 50 mL, 2-3 times, until all pyridine is removed). The organic layer was further washed with sat. aq. NaHCO$_3$ followed by brine and dried over Na$_2$SO$_4$. The organic layer was filtered off. The filtrate was concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 12% EtOAc/Hexanes to yield clear colorless viscous liquid 1.3.3 (6.72 g, 24.3 mmol, 83%); $R_f$ (20% EtOAc/Hexanes) = 0.45; IR (neat): ν 2989, 2942, 1739, 1436, 1372, 1209 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.21 (s, 1H), 4.71 (s, 2H), 4.46 (m, 1H), 4.12 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 1.49 (s, 3H), 1.33 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.8, 169.6, 113.6, 102.5, 85.7, 85.4, 81.9, 64.4, 26.8, 25.4, 21.5, 21.1; HRMS calculated for [C$_{12}$H$_{18}$O$_7$Na$^+$] 297.0945, found 297.0945; [$\alpha$]$_D^{22}$ –60 (c 1.98, CH$_2$Cl$_2$).
2,3-O-Isopropyldene-5-O-acetyl-β-D-ribofuranosyl azide ((β) 1.3.4)

The diacetate 1.3.3 (5 g, 18.1 mmol) was dissolved in dry DCM (50 mL), TMSN₃ (2.62 mL, 2.29 g, 19.9 mmol) was added to it at room temperature with stirring. Neat SnCl₄ (18 mL, 1 M in DCM) was diluted with dry DCM (20 mL) and added to the reaction mixture at room temperature and stirred for 5 h. The reaction mixture was diluted with Et₂O and washed with water, sat. aq. NaHCO₃ and brine. The Et₂O extract was dried over Na₂SO₄ and concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 9% EtOAc/Hexanes to give a clear colorless liquid 1.3.4 (2.25 g, 8.8 mmol, 48.2%); R_f (30% EtOAc/Hexane) = 0.65; IR (neat): ν 2989, 2944, 2110, 1743, 1457, 1374, 1210 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 5.49 (s, 1H), 4.63 (d, J = 6 Hz, 1H), 4.40 - 4.45 (m, 2H), 4.10 - 4.19 (m, 2H), 2.05 (s, 3H), 1.44 (s, 3H), 1.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 113.7, 97.2, 85.8, 85.4, 82.3, 64.1, 26.8, 25.2, 21.1; HRMS Calculated for [C₁₀H₁₅N₃O₅Na⁺] 280.0904, found 280.0885; [α]D²⁴ –286 (c 0.43, CH₂Cl₂).
2,3-O-Isopropylidene-5-O-acetyl-D-ribofuranosylamine (1.3.5)

The 2,3-O-isopropylidene-5-O-acetyl-β-D-ribofuranosyl azide 1.3.4 (1 g, 3.9 mmol) was dissolved in MeOH (16 mL). Catalytic Pd-C was added and stirred under H₂ for 6 - 8 h at atmospheric pressure. Upon completion the reaction mixture was filtered through celite, the filtrate was concentrated under reduced pressure, dried at pump and subjected to the following step without further purification. The product 1.3.5 was a thick colorless liquid (0.9 g, quantitative); Rₓ(50% EtOAc/Hexanes) = 0.2. The product was a mixture of both anomers as revealed by NMR.

¹H NMR (400 MHz, CDCl₃) δ 5.01 (dd, J = 9.6, 3.6 Hz, 1H), 4.91 (d, J = 2.8 Hz, 1H), 4.50-4.67 (m, 4H), 4.00-4.27 (m, 6H), 2.02-2.14 (m, 6H), 1.45-1.57 (m, 6H), 1.27-1.42 (m, 6H).

2,3-O-Isopropylidene-5-O-acetyl-1-N-(benzyloxy carbonylglycyl)-D-ribofuranosylamine (1.3.6a and 1.3.6b)

In a reaction flask Cbz-glycine (1.22 g, 5.8 mmol) was dissolved in dry DCM (20 mL). The solution was cooled to 0 °C and DCC (1.2 g, 5.8 mmol) was added followed by DMAP (71.2 mg, 0.6 mmol) with stirring. The reaction was stirred at 0 °C for 30 min.
The amine from the previous step was dissolved in dry DCM (18 mL) and added to the reaction mixture and stirred overnight. The reaction mixture was cooled to 0 °C and filtered through celite and washed with cold DCM. The filtrate and washings were collected and concentrated under reduced pressure. The 5-O-acetyl derivative was purified by silica gel chromatography eluting with 60% EtOAc/Hexanes to obtain the coupling product as a mixture of α (1.3.6a) and β (1.3.6b) anomers as a sticky, syrupy, clear liquid (1.2 g, 2.8 mmol, 73.0%); \( R_f(70\% \text{ EtOAc/Hexanes}) = 0.4 \); IR (neat): \( \nu \ 2937, 1715, 1694, 1514, 1455, 1374, 1268, 1207 \ \text{cm}^{-1} \); HRMS Calculated for \([C_{20}H_{26}N_2O_8Na]^+\) 445.1581, found 445.1556.

**2,3-O-Isopropylidene-5-hydroxy-1-N-(benzyloxycarbonylglycyl)-D-ribofuranosylamine (1.3.7a and 1.3.7b)**

The 5-O-acetyl derivative (1.3.6a and 1.3.6b mixture) (650 mg, 1.5 mmol) was dissolved in MeOH (12 mL) and cooled to 0 °C. NaOMe (3.4 mL, 1.7 mmol, 0.5 N in MeOH) was then added dropwise with stirring at 0 °C. The reaction was stirred for 30 min. The reaction was quenched by adding ice-cold 1 N HCl (10 mL) and the mixture was extracted with \( \text{Et}_2\text{O} \) (40 mL, twice). The combined \( \text{Et}_2\text{O} \) layer was washed with sat. \( \text{NaHCO}_3 \), brine and dried over \( \text{Na}_2\text{SO}_4 \). The \( \text{Et}_2\text{O} \) extract was then concentrated under reduced pressure. The product, a mixture of α and β anomers, was purified by silica gel chromatography eluting with 75% EtOAc/Hexanes to provide the less polar β anomer as
a white solid (200 mg, 0.53 mmol, 34.1%). The α anomer has a smaller $R_f$ value, elutes at 90% EtOAc/Hexanes and is a low-melting solid (253 mg, 0.67 mmol, 43%).

Data for alpha anomer **1.3.7a**:

$R_f$ (EtOAc) = 0.20; IR (neat): ν 3324, 2932, 2360, 2340, 1682, 1506, 1455, 1416, 1381, 1270, 1209 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.32 (m, 4H), 7.19 (m, 1H), 5.91 (m, 1H), 5.80 (dd, $J = 8.4$, 4 Hz, 1H), 5.10 (s, 2H), 4.72 (d, $J = 5.6$ Hz, 1H), 4.66 (m, 1H), 4.1 (s, 1H), 3.82 - 4.02 (m, 3H), 3.52 - 3.74 (m, 2H), 2.73 (s, 1H), 1.46 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.5, 156.9, 136.4, 128.8, 128.5, 128.4, 113.3, 83.1, 82.1, 80.7, 79.6, 67.4, 63.6, 44.8, 26.3, 24.9; HRMS Calculated for [C$_{18}$H$_{24}$N$_2$O$_7$Na$^+$] 403.1476, found 403.1475; [α]$_D^{24}$ –7.6 (c 0.55, CH$_2$Cl$_2$).

Data for beta anomer (**1.3.7b**):

$R_f$ (EtOAc) = 0.22; IR (neat): ν 3323, 2359, 2340, 2320, 1691, 1652, 1520, 1455, 1378, 1335, 1270, 1207 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.74 (d, $J = 7.6$ Hz, 1H), 7.36 (bs, 4H), 5.75 (d, $J = 8.8$ Hz, 1H), 5.67 (m, 1H), 5.10 (s, 2H), 4.77 (d, $J = 5.6$ Hz, 1H), 4.55 (d, $J = 4.4$ Hz, 1H), 4.25 (s, 1H), 3.70 - 3.90 (m, 2H), 3.55 - 3.70 (m, 2H), 2.88 (bs, 1H), 1.51 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.3, 157.0, 136.5, 129.0, 128.8, 128.7, 113.2, 87.1, 86.6, 86.4, 82.1, 67.6, 63.8, 45.1, 27.0, 25.4; HRMS Calculated for [C$_{18}$H$_{24}$N$_2$O$_7$Na$^+$] 403.1476, found 403.1471; [α]$_D^{24}$ –37 (c 0.14, CH$_2$Cl$_2$).
2,3-O-Isopropylidene-1-N-(benzylxycarbonylglycyl)-D-ribofuranosylamine-5-dibenzylphosphate ((α) 1.3.8a)

To a solution of 2,3-O-isopropylidene-1-N-(benzylxycarbonylglycyl)-D-ribofuranosylamine 1.3.7a (430 mg, 1.1 mmol) in dry DCM (5.6 mL) was added a solution of dibenzyl N,N-diisopropylphosphoramidite (0.76 mL, 780.9 mg, 2.3 mmol) in dry DCM (3.75 mL) with stirring. Tetrazole (5 mL, 2.3 mmol, 0.45 M in MeCN) was then added and stirred for 1 h. The reaction mixture was cooled to 0 ºC, H₂O₂ (4 mL, 35% in H₂O) was added and stirred at 0 ºC for 45 min, TLC was checked. Upon complete conversion of the intermediates to product, the reaction was quenched by dropwise addition of sat. aq. Na₂SO₃ with stirring for 5-10 min. The reaction mixture was then extracted with EtOAc (10 mL, twice). The EtOAc extract was washed with sat. aq. NaHCO₃ and brine and dried over Na₂SO₄. The product was purified by silica gel chromatography eluting with 70% EtOAc/Hexanes to obtain the product 1.3.8a as a viscous translucent liquid (637 mg, 1 mmol, 88%); Rₜ (70% EtOAc/Hexanes) = 0.4; IR (neat): ν 3308, 2926, 2854, 2360, 2337, 1692, 1514, 1455, 1377, 1268, 1210, 1158, 1079 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.25 - 7.37 (m, 14H), 7.06 - 7.12 (m, 1H), 5.98 (m, 1H), 5.73 (dd, J = 8.8, 4.4 Hz, 1H), 4.98 - 5.12 (m, 6H), 4.57 (d, J = 6 Hz, 1H), 4.39 (m, 1H), 4.07 (bs, 1H), 3.90 - 3.98 (m, 2H), 3.78 - 3.90 (m, 3H), 1.42 (s, 3H), 1.25 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.5, 156.7, 136.3, 135.6 (m, 2Cs), 128.82, 128.77,
128.6, 128.3, 128.2, 128.2, 113.2, 81.7, 81.0, 80.1 (d, $J = 8$ Hz), 79.1, 69.74 (d, $J = 3$ Hz), 69.70 (d, $J = 3$ Hz), 68.4 (d, $J = 6$ Hz), 67.1, 44.7, 26.1, 24.7; HRMS Calculated for [C$_{32}$H$_{37}$N$_2$O$_{10}$PNa$^+$] 663.2078, found 663.2073; [$\alpha$]$_{D}^{24} - 14$ (c 0.135, CH$_2$Cl$_2$).

2,3-[$\alpha$]-Isopropylidene-$\delta$-ribofuranosylamine-5-phosphate ((\(\alpha\)) 1.3.9a)

2,3-[$\alpha$]-Isopropylidene-1-$N$-(benzyloxy carbonyl glycyl)-$\delta$-ribofuranosylamine-5- dibenzyl phosphate ((\(\alpha\)) 1.3.8a) (180 mg, 0.28 mmol) was dissolved in 4.5 mL EtOH and reduced with Pd-C under hydrogen overnight. Water (2 mL) was added with stirring and the Pd-C was filtered off. The filtrate was concentrated under reduced pressure, water was removed azeotropically with toluene to yield (83 mg, 0.25 mmol, 91%) debenzylated product as a colorless syrupy liquid; $R_f$ (70\% EtOAc/Hexanes) = < 0.1; IR (neat): $\nu$ 3327, 2930, 1690, 1652, 1520, 1206, 1156, 1089, 1037 cm$^{-1}$. $^1$H NMR (400 MHz, D$_2$O) $\delta$ 5.94 (d, $J = 4.4$ Hz, 1H), 5.03 (d, $J = 6.4$ Hz, 1H), 4.91 (dd, $J = 5.6$, 4.4 Hz, 1H), 4.29 (d, $J = 2.8$ Hz, 1H), 3.90 - 3.92 (m, 4H), 1.55 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR (100 MHz, D$_2$O) $\delta$ 168.0, 113.5, 81.9, 81.8, 81.3 (d, $J = 8.3$ Hz), 79.0, 65.7 (d, $J = 5.3$ Hz), 40.8, 25.1, 23.5; HRMS Calculated for [C$_{10}$H$_{19}$N$_2$O$_8$PNa$^+$] 349.0771, found 349.0774; [$\alpha$]$_{D}^{24} - 38$ (c 0.17, H$_2$O).
Glycinamide ribonucleotide (GAR) as a mixture of alpha and beta anomer (1:1) (1.3.10a and 1.3.10b)

The acetonide of glycinamide ribonucleotide 1.3.9a (75 mg, 0.23 mmol) was dissolved in 2.5 mL water. TFA (0.35 mL) was added. The reaction mixture was stirred for 5 h at room temperature. The water and TFA was evaporated off under reduced pressure to afford (39 mg, 0.14 mmol, 60%) glycinamide ribonucleotide as a colorless syrupy liquid.

$R_f$ (100% EtOAc/Hexanes) = < 0.1; IR (neat): $\nu$ 3216, 2930, 1674, 1536, 1434, 1130, 1028 cm$^{-1}$. $^1$H NMR (400 MHz, D$_2$O) $\delta$ 5.65 (d, $J$ = 4 Hz), 5.36 (d, $J$ = 4.2 Hz), 4.13 - 4.18 (m), 3.96 - 4.04 (m), 3.75 - 3.92 (m), 3.75 (s), 3.72 (s); $^{13}$C NMR (100 MHz, D$_2$O) $\delta$ 168.18, 168.16, 83.6, 82.8 (d, $J$ = 9 Hz), 81.0 (d, $J$ = 8 Hz), 80.5, 74.0, 70.8, 70.7, 70.2, 65.0 (d, $J$ = 5 Hz), 64.8 (d, $J$ = 5 Hz), 40.8, 40.7; HRMS Calculated for [C$_7$H$_{15}$N$_2$O$_8$PH]$^+$ 287.0639, found 287.0645; [$\alpha$]$_D^{24}$ −21 (c 0.10, H$_2$O).
Diethyl N-(4-nitrobenzoyl)-L-glutamate (1.5.9)

L-Glutamic acid hydrochloride 1.5.8 (0.40 g, 1.67 mmol) and p-nitrobenzoyl chloride 1.5.7 (0.34 g, 1.83 mmol) were dissolved in dry CH₂Cl₂ (3.5 mL) and cooled to 0 °C. Triethylamine (0.5 mL, 0.34 g, 3.34 mmol) was added dropwise and the reaction was allowed to warm to r.t. The reaction was stirred for 24 hrs. The reaction was quenched with water, extracted with CH₂Cl₂ (20 mL). The CH₂Cl₂ extract was further washed with water, sat. NaHCO₃ and brine. The product was dried over Na₂SO₄, concentrated under reduced pressure and purified by silica gel chromatography, eluting with 25% EtOAc/Hexanes to obtain white solid 1.5.9 (0.52 g, 1.48 mmol, 88%); m.p. 93 °C; Rf (30% EtOAc/hexane) = 0.33; ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, J = 8.4 Hz, 2 H), 7.99 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 6.4 Hz, 1H), 4.74 (d, J = 5.2 Hz, 1 H), 4.23 (q, J = 6.8 Hz, 2 H), 4.11 (q, J = 6.8 Hz, 2 H), 2.48 (m, 2 H), 2.29 (m, 1 H), 2.17 (m, 1 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.22 (t, J = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 171.8, 165.4, 150.0, 139.5, 128.7, 124.1, 62.2, 61.4, 53.2, 30.8, 26.9, 14.5, 14.4. [α]D²³ +6.6 (c 0.25, CH₂Cl₂).
Diethyl N-(4-aminobenzoyl)-L-glutamate (1.5.6)

![Chemical structure of Diethyl N-(4-aminobenzoyl)-L-glutamate](image)

Diethyl N-(4-nitrobenzoyl)-L-glutamate **1.5.9** (0.50 g, 1.42 mmol) was dissolved in ethanol. Pd-C (0.05 g) was added and the reaction mixture was stirred under nitrogen overnight. Once all the starting material is consumed, the Pd-C is filtered off by passing the reaction mixture through celite. The filtrate was then concentrated under reduced pressure and purified by silica gel chromatography, eluting with 50% EtOAc/hexane to afford white crystalline solid **1.5.9** (0.375 g, 1.163 mmol, 82%); m.p. 141 °C; \( R_f \) (70% EtOAc/hexane) = 0.4; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.64 (d, \( J = 8.8 \) Hz, 2 H), 6.78 (d, \( J = 7.2 \) Hz, 1 H), 6.66 (d, \( J = 8.8 \) Hz, 2 H), 4.78 (dd, \( J = 12.8 \) Hz, 7.6 Hz, 1 H), 4.18-4.27 (m, 2 H), 4.05-4.16 (m, 2 H), 3.99 (bs, 2 H), 2.35-2.55 (m, 2 H), 2.23-2.35 (m, 1 H), 2.06-2.16 (m, 1 H), 1.29 (t, \( J = 7.2 \) Hz, 3 H), 1.21 (t, \( J = 7.2 \) Hz, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 173.6, 172.6, 167.1, 150.2, 129.3, 123.5, 114.4, 62.0, 61.1, 52.5, 30.9, 27.8, 14.53, 14.49. [\( \alpha \)]\(_D\)^{24} +12.5 (c 0.32, CH\(_2\)Cl\(_2\)).
**2,4-diamino-6-nitroquinazoline (1.5.2)**

![Chemical Structure](image)

NaOMe (11.9 g, 0.22 mol) was dissolved in a dry MeOH (150 mL) solution at 0 °C. Guanidine hydrochloride (20.1 g, 0.21 mol) was added to the solution and stirred for 0.5 h. The solution was filtered through celite and the residue was washed with 50 ml MeOH. The combined filtrate was transferred into a 500 ml round bottomed flask, and 5-nitroanthranilonitrile (32.6 g, 0.2 mol) was added and the solution refluxed for 5 h. The reaction mixture was allowed to stand overnight and filtered to yield the orange-brown solid **1.5.2** (36 g, 176 mmol, 88%); \( R_f \) (20% MeOH/CHCl₃) = 0.3; mp > 360 °C; IR (neat): 3456, 3435, 3315, 3096, 2359, 2326, 1690, 1651, 1614, 1574, 1557, 1514, 1456, 1325, 1293 cm⁻¹. \(^1\)H NMR (400 MHz, C₂D₆SO) \( \delta \) 9.11 (s, 1 H), 8.25 (d, \( J = 9.6 \) Hz, 1 H), 7.77 (bs, 2 H), 7.25 (d, \( J = 9.2 \) Hz, 1 H), 6.80 (bs, 2H); \(^1^3\)C NMR (100 MHz, C₂D₆SO) \( \delta \) 164.2, 163.9, 158.2, 140.0, 127.5, 125.8, 109.8. (seven peaks only); HRMS Calculated for [C₈H₈N₅O₂⁺] 206.0673, found 206.0673.

**2,4,6-Triaminoquinazoline (1.5.3)**

2,4-diamino-6-nitroquinazoline (18 g, 88 mmol) was stirred in DMF (144 mL) resulting in a suspension, AcOH (1.44 mL) was added along with 10% Pd/C (1.8 g) and the reaction mixture was stirred vigorously under \( \text{H}_2 \) balloon at room temperature overnight. \( \text{H}_2 \) balloon was refilled and stirring continued until all starting material had been
consumed, at which point the reaction mixture turned into a dark greyish brown solution with very little to no suspended material other than the Pd-catalyst. The catalyst was then filtered off the filtrate concentrated to ~90 ml and added to 1.5 L of cold ethyl acetate with vigorous stirring while greyish brown crystals crashed out of solution. The solution was kept stirring overnight, cooled to 0 ºC, stirred at cold for another 2 hrs and filtered to yield small needle like brown crystalline residue 1.5.3 (5.2 g, 29.7 mmol, 34%); \( R_f \) (20\% DMF/EtOAc) = 0.4; mp: 253 ºC; IR (neat): 3292, 3081, 2957, 2932, 2353, 2337, 1680, 1651, 1632, 1590, 1518, 1487, 1454, 1401, 1334, 1291 cm\(^{-1}\); \(^1\)H NMR (400 MHz, D\(_2\)O) \( \delta \) 7.13 (dd, \( J = 8.8, 2.4 \) Hz, 1H), 6.96 (d, \( J = 8.8 \) Hz, 1H), 6.90 (d, \( J = 2.4 \) Hz, 1 H); \(^{13}\)C NMR (100 MHz, D\(_2\)O) \( \delta \) 181.6, 162.6, 153.7, 143.7, 125.8, 118.4, 109.3, 107.2; HRMS Calculated for \([C_8H_9N_5Na]^+\) 198.0750, found 198.0766.

2,4-diamino-6-cyanoquinazoline (1.5.4)

\[
\begin{align*}
\text{NH}_2 & \quad \text{CN} \\
\text{N} & \quad \text{H}_2\text{N} \\
\text{N} & \quad \text{H}_2\text{N}
\end{align*}
\]

2,4,6-triaminoquinazoline (5.2 g, 29.7 mmol) was dissolved in aqueous HCl (62 mL, 2 N), cooled to 5 ºC, diazotized by adding a solution of NaNO\(_2\) (2.15 g, 31.2 mmol) in H\(_2\)O (15 mL) with stirring. In a separate flask, a solution of copper sulfate pentahydrate (7.05 g, 28.2 mmol) in water (23 mL) was added a solution of KCN (8.3 g, 127.7 mmol) in water (15 mL) with vigorous stirring. To this solution was added the crude solution of the diazo intermediate with stirring. The reaction mixture was stirred at 55 ºC for 1 hr. The reaction mixture was cooled to 40 ºC and 30 mL concentrated ammonia was added. The resulting mixture was allowed to cool to room temperature and stirred for 1 hr then filtered. The residue was filtered and extracted with 85 mL boiling 15\% AcOH and
filtered while still hot. The hot filtrate was diluted with 65 mL ethoxy-ethanol and basified with 25 mL concentrated ammonia with stirring. The product 1.5.4 precipitated as greenish yellow needles (0.74 g, 3.95 mmol, ); \( R_f \) (20% MeOH/CHCl₃) = 0.2; mp >360 °C; IR (neat): 3418, 3144, 3091, 2223, 1615, 1556, 1514, 1446, 1405, 1373, 1289 cm⁻¹; \(^1\)H NMR (400 MHz, C₆D₆SO) \( \delta \) 8.55 (s, 1H), 7.76 (dd, \( J = 8.8, \ 1.6 \) Hz, 1H), 7.63 (bs, 2H), 7.25 (d, \( J = 8.8 \) Hz, 1H), 6.57 (s, 2H); \(^{13}\)C NMR (100 MHz, C₆D₆SO) \( \delta \) 163.3, 162.7, 162.0, 152.3, 133.6, 127.3, 124.8, 123.8, 112.0; HRMS Calculated for \([C₉H₈N₅]^+\] 186.0774, found 186.0776.

2-amino-4-hydroxy-6-cyanoquinazoline (1.5.5)

\[
\text{HN} \quad \text{O} \\
\text{H₂N} \quad \text{N} \quad \text{CN} \\
\text{HN} \quad \text{N} \quad \text{CN}
\]

To 2,4-diamino-6-cyanoquinazoline (0.74 g, 4 mmol) was added aqueous HCl (10 mL, 1 N) and refluxed overnight. The dark amber solution was treated with charcoal while still hot and filtered. The filtrate upon neutralization by dropwise addition of concentrated aqueous ammonia gave yellow precipitate of the product. The precipitate was filtered, washed with water and dried to give yellow solid, which was used in the next step without further purification (0.735 g, 3.97 mmol, 99%); \( R_f \) (20% MeOH/CHCl₃) = 0.35 m.p. 360 °C; IR (neat): 3163, 2228, 1651, 1602, 1575, 1557, 1455, 1394, 1334, 1241 cm⁻¹; \(^1\)H NMR (400 MHz, C₆D₆SO) \( \delta \) 8.24 (d, \( J = 2 \) Hz, 1 H), 7.90 (dd, \( J = 8.8, \ 2 \) Hz, 1 H), 7.29 (d, \( J = 8.8 \) Hz, 1H), 6.97 (bs, 2H); \(^{13}\)C NMR (125 MHz, C₆D₆SO) \( \delta \) 163.3, 162.7, 162.0, 152.3, 133.6, 127.3, 124.8, 123.8, 112.0; HRMS Calculated for \([C₉H₇N₄O]^+\] 187.0614, found 187.0638.
Diethyl dideazafolate (1.4.1)

2-amino-4-hydroxy-6-cyanoquinazoline (735 mg, 3.95 mmol) was stirred in 20 mL 70% AcOH with warming until a homogeneous solution formed. The solution was cooled to room temperature and diethyl N-(p-aminobenzoyl)-l-glutamate (1.53 g, 4.74 mmol) and Raney nickel was added and the reaction mixture was stirred under hydrogen from a balloon at room temperature overnight. The stirring was stopped and the Raney nickel was allowed to settle down. The supernatant brown liquid was then filtered through a small plug of glass wool and the residue was washed with ethanol (2 x 1 mL) and filtered through the plug and combined with the crude solution. This crude solution was slowly added with stirring to a cold solution of excess Na$_2$CO$_3$ (2 N), all the acid was quenched, off-white precipitate began to form at this point. The solution was kept stirring for 3-4 hrs and the precipitate was allowed to settle down. The buff colored precipitate was filtered and washed with water to yield product as a buff colored solid. This crude product was purified by flash column chromatography. The product was dissolved in CHCl$_3$ and loaded onto a silica gel column eluting first with CHCl$_3$ to remove the non-polar impurities and unreacted starting materials. The column was then eluted with 1-10% MeOH in CHCl$_3$, the product eluted with 10% MeOH in CH$_2$Cl$_2$, to yield the diethyl ester of dideazafolate (910 mg, 1.84 mmol, 46%). $R_f$ (20% MeOH/CHCl$_3$) = 0.45, mp 210 ºC; IR (neat): 3302, 3280, 2922, 2852, 1715, 1682, 1651, 1633, 1604, 1574, 1556,
1504, 1454, 1398, 1332, 1294 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \(\delta\) 8.01 (s, 1 H), 7.62-7.65 (m, 3 H), 7.25 (d, \(J = 8.5\) Hz, 1H), 6.63 (d, \(J = 8.5\) Hz, 2H), 4.57 (dd, \(J = 9.4, 5.2\) Hz, 1H), 4.43 (s, 2H), 4.18 (q, \(J = 7.2\) Hz, 1H), 4.09 (q, \(J = 7.2\) Hz, 2H), 2.45 (t, \(J = 7.2\) Hz, 2H), 2.20-2.28 (m, 1H), 2.02-2.13(m, 1H), 1.26 (t, \(J = 7.0\) Hz, 3H), 1.21(t, \(J = 7.2\) Hz, 3H). [\(\alpha\)]\(_D\)\(^{25}\) = -2.4 (c 0.05, CH\(_2\)Cl\(_2\)).

Dideazafolic acid (1.4.2)

Diethyl dideazafolate (910 mg, 1.84 mmol) was dissolved in 20 mL EtOH with warming and cooled to room temperature, a solution of aqueous NaOH (2 mL, 2 N, 4.05 mmol) was added and the reaction mixture was stirred for 24 hrs. TLC indicated complete consumption of starting material. The reaction mixture was diluted with 20 mL water and the pH was adjusted to 4 by dropwise addition of 0.5 N HCl with stirring. The solution was cooled for 3-4 hours and the off-white precipitate was filtered off. The residue was washed with water, ether and dried at the vacuum to yield the product as an off-white powder (580 mg, 1.32 mmol, 72%). \(R_f\) (CH\(_3\)Cl : MeOH : NH\(_4\)OH : AcOH = 19 : 4 : 1 : 1) = 0.38, m.p. 230 °C. IR (neat): 3037, 2921, 2856, 2579, 1841, 1694, 1682, 1651, 1601, 1566, 1556, 1538, 1504, 1454, 1398, 1330, 1294 cm\(^{-1}\).\(^1\)H NMR (400 MHz, C\(_2\)D\(_6\)SO) \(\delta\) 7.89 (d, \(J = 2.0\) Hz, 1H), 7.65 (d, \(J = 8.4\) Hz, 2H), 7.58 (d, \(J = 8\) Hz, 1H), 7.20 (d, \(J = 8.4\) Hz, 1H), 6.88-6.94 (m, 1H, NH), 6.63 (d, \(J = 8.8\) Hz, 2H), 6.28-6.40 (m, 2H, NH\(_2\)) 4.37 (s, 2H), 4.27-4.35 (m, 1H), 2.30-2.39 (m, 2H), 1.99-2.09 (m, 1H), 1.89-1.99 (m, 1H).
10-Formyl-5, 8-dideazafolic acid (1.4.3)

Dideazafolic acid (500 mg, 1.15 mmol) was dissolved in 88% formic acid (2.3 mL). Acetic anhydride (0.80 g, 7.8 mmol) was added to the solution and stirred at room temperature for 24 hrs. The solution was diluted with 15 mL water and acidified with 0.5 N HCl to pH = 4. The solution was cooled for 3-4 hrs and the off-white precipitate was isolated by filtration. The residue was washed with water, ether and dried at the vacuum to yield the product as a pale buff powder (470 mg, 1.00 mmol, 87%); $R_f$ (CHCl$_3$ : MeOH : NH$_4$OH : AcOH = 19 : 4 : 1 : 1) = 0.35; m.p. 230 ºC; $^1$H NMR (400 MHz, C$_2$D$_6$SO) δ 8.8 (s, 1H), 7.83 (d, $J$ = 8.8 Hz, 1H), 7.70 (s, 1H), 7.45 (d, $J$ = 8.4 Hz, 1H), 7.37 (dd, $J$ = 8.4, 2 Hz, 1H), 7.20 (d, $J$ = 8.4 Hz, 1H), 7.0-7.2 (m, 3H), 6.63 (d, $J$ = 8.8 Hz, 2H), 6.25-6.40 (m, 2H, NH$_2$), 5.09 (s, 2H), 4.26-4.37 (m, 1H), 2.26-2.34 (m, 2H), 1.96-2.08 (m, 1H), 1.83-1.96 (m, 1H).
4.3 Experimental for Chapter 1B

1-azido-β-D-ribofuranosyl-5-acetate (1.6.1)

\[
\begin{align*}
\text{AcO} & \quad \text{N}_3 \\
\text{HO} & \quad \text{OH}
\end{align*}
\]

2,3-\textit{O}-Isopropyliden-5-\textit{O}-acetyl-β-D-ribofuranosyl azide \textbf{1.3.4} (257 mg, 1 mmol) was dissolved in 6 mL 3:1 AcOH:H\textsubscript{2}O and refluxed for 5 hrs. The reaction was quenched by adding solid NaHCO\textsubscript{3}, diluted with 50 mL DCM and the DCM layer washed with sat. NaHCO\textsubscript{3} solution (5mL x 3). The DCM layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The crude product was purified by flash column chromatography using silica gel, eluting with 50\% EtOAc/Hexane to yield diol \textbf{1.6.1} (169 mg, 0.78 mmol, 78\%) as a syrupy clear liquid. \(R_f\) (70\% EtOAc/Hexane) = 0.33; IR (neat) \(\nu\) 3404, 2946, 2108, 1715, 1434, 1368, 1223 cm\textsuperscript{-1}. \(^1\text{H}\) NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.30 (s, 1H), 4.42 (dd, \(J=12, 3\) Hz, 1H), 4.20-4.29 (m, 2H), 4.14-4.19 (m, 1H), 3.97 (d, \(J=4.5\) Hz, 1H), 2.93 (s, 1H), 2.79 (s, 1H), 2.13 (s, 3H); \(^{13}\text{C}\) NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 179.0, 94.8, 81.7, 75.6, 71.3, 64.1, 21.1; HRMS Calculated for [C\textsubscript{7}H\textsubscript{11}N\textsubscript{3}O\textsubscript{5}] 217.0699, found 217.0702. \([\alpha]\)\textsubscript{D}\textsuperscript{24} = -279 (c 0.66, CH\textsubscript{2}Cl\textsubscript{2}).
**2,3-O-Benzylidene-5-O-acetyl-β-D-ribofuranosyl azide (β) (1.6.3)**

The starting material 1.6.1 (1.1 g, 5.1 mmol) was dissolved in 12.5 mL dry acetonitrile at r.t. under nitrogen. Camphor sulfonic acid (116 mg, 0.5 mmol) was added and stirred. Benzaldehyde dimethyl acetal (0.84 mL, 5.6 mmol) was added and the reaction mixture was stirred for 1 hr. The reaction was quenched by the addition of 5 mL water. The product was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 10 mL sat. NaHCO₃ and 10 mL brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel eluting with 8% EtOAc/Hexane to yield benzylidene azide product (1.36 g, 4.46 mmol, 88%) as a clear viscous oil as the major isomer.

\[ R_f \text{ (70\% EtOAc/Hexane) } = 0.8; \text{ IR (neat) } \nu 2949, 2110, 1740, 1452, 1402, 1371, 1314, 1219 \text{ cm}^{-1}. \] ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.52 (m, 2 H), 7.36-7.45 (m, 3H), 5.81 (s, 1H), 5.71 (s,1H), 4.79 (d, J = 6 Hz, 2H), 4.56-4.7 (m, 2H), 4.17-4.33 (m, 2H), 2.12 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 135.7, 130.4, 128.9, 127.2, 107.0, 96.8, 86.4, 85.1, 83.1, 64.0, 21.1; HRMS Calculated for [C₁₄H₁₅N₃O₅Na⁺] 328.0904, found 328.0927. \[ [\alpha]_D^{24} \text{ (c 0.12, CH}_2\text{Cl}_2) = -153.11. \]
2,3-\textit{O}-Benzyldiene-5-\textit{O}-acetyl-1-\textit{N}-(benzyloxycarbonylglycyl)-\textit{D}-ribofuranosylamine (1.6.4a and 1.6.4b)

![Chemical Structure]

Benzylidene azide (200 mg, 0.66 mmol), PPh\(_3\) (450 mg, 1.72 mmol), Cbz-glycine (153 mg, 0.73 mmol) and Py\(_2\)S\(_2\) (148 mg, 0.67 mmol) were added to a round bottom flask. The flask was sealed with septa and placed in an ice bath. Under nitrogen dry toluene (1.65 mL) was added to the flask slowly with stirring. The solution was allowed to stir overnight. The reaction was quenched by adding water, the product was extracted with EtOAc, dried over Na\(_2\)SO\(_4\), concentrated under reduced pressure and purified by flash column chromatography eluting with 55 \% EtOAc/Hexane to yield coupled product along with some by-product; \(R_f\) (70\% EtOAc/Hexane) = 0.4; IR (neat) \(\nu\) 3419, 3349, 3052, 2922, 2357, 2337, 1736, 1703, 1681, 1539, 1505, 1455, 1437, 1267, 1217 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.28-7.58 (m, 10 H), 5.93 (d, \(J = 9.0\) Hz, 1H), 5.26 (bs, 1H), 5.02 (m, 2H), 4.81 (s, 2H), 4.50 (t, \(J = 4.0\) Hz, 1H), 4.22 (ddd, \(J = 26.7, 12.0, 4.0\) Hz, 2H), 3.85 (d, \(J = 5.0\) Hz, 1H), 2.12 (s, 3H) (major peaks); HRMS Calculated for [\(\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_8\text{Na}\)] \(493.1581\), found 493.1592. [\(\alpha\)]\(_D\)\(^{24}\) \(-23\) (c 0.1, CH\(_2\)Cl\(_2\)).
The product obtained from the previous step was dissolved in 2.5 mL MeOH. NaOMe (1.25 mL, 0.5 N in MeOH) was added at 0 °C and stirred for 30 mins. MeOH was removed by evaporation and the product was extracted in ether. The organic layer was dried over Na2SO4 and concentrated under reduced pressure. The β-anomer was purified by silica gel column chromatography and eluted out at 80 % EtOAc/Hexane. The pure product fractions were combined and concentrated to give white solid, (76 mg, 0.18 mmol, 27% beta-anomer only); Rf (70% EtOAc/Hexane) = 0.2; IR (neat) ν 2357, 2336, 1679, 1651, 1549, 1504, 1453, 1405 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl3/CD3OD) δ 7.35-7.42 (m, 2 H), 7.16-7.31 (m, 8H), 5.80 (s, 1H), 5.69 (s, 1H), 4.98 (s, 2H), 4.76 (d, J =6.4 Hz, 1H), 4.54 (d, J =6.0 Hz, 1H), 4.29 (bs, 2H), 3.55-3.77 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl3) δ 169.7, 157.3, 136.3, 135.9, 130.0, 128.9, 128.6, 128.5, 128.3, 128.1, 127.0, 106.5, 86.8, 86.4, 86.2, 83.1, 67.2, 62.8, 44.4. HRMS Calculated for [C\(_{22}\)H\(_{25}\)N\(_2\)O\(_7\)]\(^+\) 429.1656, found 429.1645. [α]\(^D\)\(_{25}\) = -1.7 (c 0.26, CH\(_2\)Cl\(_2\)).

\(^a\) Melting point data pending
\(^b\) Specific rotation data pending
2,3-\textit{O}-Benzyldiene-1-\textit{N}-(benzyloxy carbonylglycyl)-\textit{D}-ribofuranosylamine-5-
dibenzyllphosphate (\((\alpha)\) 1.6.6a)

\[
\begin{align*}
\text{BnO} & \text{P} \\
\text{O} & \text{O} \\
\text{NHCOCH}_2\text{NHCOOBn} & \text{O} \\
\text{O} & \text{O} \\
\text{BnO} & \text{BnO} \\
\end{align*}
\]

2,3-\textit{O}-Benzyldiene-1-\textit{N}-(benzyloxy carbonylglycyl)-\textit{D}-ribofuranosylamine (\((\beta)\) (108 mg, 0.25 mmol) was dissolved in dry DCM (2.5 mL). Dibenzyl \textit{N},\textit{N}-
diisopropylphosphoramidite (0.33 mL, 348 mg, 1.01 mmol) was dissolved in dry DCM (3.75 mL) and added to the solution of starting material with stirring. Tetrazole (2.2 mL, 1 mmol, 0.45 M in CH\textsubscript{3}CN) was then added and stirred for 1 h. The reaction mixture was cooled to 0 \textdegree C, H\textsubscript{2}O\textsubscript{2} (0.65 mL, 35\% in H\textsubscript{2}O) was added and stirred at 0 \textdegree C for 45 mins, TLC was checked. Upon complete conversion of the intermediate the reaction was quenched by adding sat. NaSO\textsubscript{3} dropwise with stirring for 5-10 mins. The reaction mixture was then extracted with EtOAc (10 mL x 2). The EtOAc extract was washed with sat. NaHCO\textsubscript{3} and brine and dried over Na\textsubscript{2}SO\textsubscript{4}. The product was purified by silica gel chromatography eluting with 45-50\% EtOAc/hexanes to obtain the product as a viscous translucent liquid (144 mg, 1 mmol, 83\%). \(R_f\) (70\% EtOAc/Hexane) = 0.8; IR (neat) \(\nu\) 3305, 3035, 2927, 1723, 1693, 1498, 1455, 1437, 1393, 1264, 1216 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.67 (dd, \(J\) =12, 7.2 Hz, 2 H), 7.23-7.58 (m, 18 H), 5.87 (d, \(J\) =7.2 Hz, 1H) 5.79 (s, 1H), 4.93-5.20 (m, 6H), 4.48-4.59 (m, 2H), 4.42 (s, 1H), 3.94-4.13 (m, 2H), 3.75-3.84 (m, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 169.5, 156.8, 136.7, 135.9,
135.6, 133.4, 132.5, 132.4, 132.3 (2Cs), 130.3, 129.1 (2Cs), 128.9 (2Cs), 128.8 (2Cs), 128.6 (2Cs), 128.5, 127.2, 107.1, 88.9, 86.8, 84.7, 82.3, 70.4 (2Cs), 68.8, 67.3, 44.8;
HRMS Calculated for \([\text{C}_{36}\text{H}_{37}\text{N}_2\text{O}_{10}\text{P}]\) 711.2078, found 711.2054. \([\alpha]_D^{25} \approx -8.4 \text{ (c 0.09, CH}_2\text{Cl}_2)\).

*beta*-Glycinamide ribonucleotide (\(\beta\text{GAR}\)) (1.6.7b)*

\[
\begin{align*}
\text{HO}_3\text{P}_\text{O}_\text{HO} & \quad \text{O} \quad \text{NHCOCH}_2\text{NH}_2 \\
\text{HO}_\text{O}_\text{P}_\text{O}_\text{HO} & \quad \text{O} \\
\text{HO} & \quad \text{OH}
\end{align*}
\]

2,3-\(O\)-Benzyldene-1-N-(benzyloxy carbonylglycyl)-D-ribofuranosylamine-5-dibenzylphosphate (\(\beta\)) (16 mg, 0.023 mmol) was dissolved in 0.15 mL MeOH and 0.5 mL water. Pd-C was added and the reaction mixture was stirred under hydrogen overnight. Pd-C was filtered off. The filtrate was concentrated under reduced pressure, at room temperature to give \(\beta\text{GAR}\) (5.7 mg, 0.02 mmol, 86%) debenzylation product as a colorless syrupy liquid. \(R_f\) (70% EtOAc/Hexane) = < 0.1; \(^1\text{H NMR} (500 \text{ MHz, D}_2\text{O}) \delta 5.32 \text{ (d, } J = 5.5 \text{ Hz, 1H), 4.06-4.12 \text{ (m, 1H), 3.92-3.99 \text{ (m, 2H), 3.71-3.78 (m, 2H), 3.67 (s, 2H).} ^{13}\text{C NMR} (100 \text{ MHz, D}_2\text{O}) \delta 168.3, 83.7, 83.0, 74.1, 70.1, 64.7, 40.8.}

\[^b\] Specific rotation data pending
2,3-\textit{O}-Benzyldiene-5-\textit{O}-hydroxy-\textit{\beta}-\textit{D}-ribofuranosyl azide (\textit{\beta}) (1.7.1)

The azide acetate 1.6.3 (150 mg, 0.49 mmol) was dissolved in 4 mL MeOH. 1.2 mL 0.5 N NaOMe in MeOH was added at 0 °C and stirred for 30 mins. The reaction was quenched at 0 °C by adding MeOH was removed by evaporation and the product was extracted in ether. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The \textit{\beta}-anomer was purified by silica gel column chromatography and eluted out with 15 % EtOAc/Hexane. The pure product fractions were combined and concentrated to give clear oil, (95 mg, 0.36 mmol, 74% beta-anomer only); $R_f$ (30% EtOAc/Hexane) = 0.27; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 (m, 2 H), 7.41 (m, 3 H), 5.82 (s, 1 H), 5.70 (s, 1 H), 4.88 (d, $J$ = 5.6 Hz, 1 H), 4.65 (d, $J$ = 6.0 Hz, 1 H), 4.6 (t, $J$ = 4.0 Hz, 1 H), 3.7-3.85 (m, 2 H), 2.35 (m, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.76, 130.27, 128.77, 127.05, 106.71, 98.06, 88.56, 86.70, 82.92, 63.91.
2,3-\textit{O}-Benzylidene-5-dibenzylphosphate-\beta-d-ribofuranosyl azide (\textit{\beta}) 1.7.2

\begin{center}
\includegraphics[width=0.2\textwidth]{structure.png}
\end{center}

Benzylidene azide 1.7.1 (90 mg, 0.34 mmol) was dissolved in dry DCM (1.8 mL). Dibenzyl N,N-diisopropylphosphoramidite (0.23 mL, 236 mg, 0.68 mmol) was dissolved in dry DCM (1 mL) and added to the solution of starting material with stirring. Tetrazole (1.5 mL, 0.68 mmol, 0.45 M in CH₃CN) was then added and stirred for 1 h. The reaction mixture was cooled to 0 °C, H₂O₂ (1.3 mL, 35% in H₂O) was added and stirred at 0 °C for 45 mins, TLC was checked. Upon complete conversion of the intermediate the reaction was quenched by adding sat. NaSO₃ dropwise with stirring for 5-10 mins. The reaction mixture was then extracted with EtOAc (10 mL x 2). The EtOAc extract was washed with sat. NaHCO₃ and brine and dried over Na₂SO₄. The product was purified by silica gel chromatography eluting with 10-12% EtOAc/hexanes to obtain the product 1.7.2 as a viscous translucent liquid (140 mg, 0.27 mmol, 78%); \textit{R}_f (70\% EtOAc/Hexane) = 0.85; IR (neat) \nu 2969, 2932, 1723, 1455, 1254, 1208 cm\textsuperscript{-1}. \textit{\textsuperscript{1}}H NMR (400 MHz, CDCl₃) \delta 7.31-7.49 (m, 15 H), 5.75 (s, 1H), 5.66 (s,1H), 5.03-5.12 (m, 4H), 4.71 (d, \textit{J} = 6 Hz, 1H), 4.48-4.56 (m, 2H), 4.0-4.12 (m, 2H).\textit{\textsuperscript{13}}C NMR (100 MHz, CDCl₃) \delta 135.95, 135.88, 135.72, 130.33, 129.76, 129.00, 128.96, 128.79, 128.59, 128.40, 127.10, 106.87, 96.90, 86.10, 85.32 (d, \textit{J} = 8.3 Hz), 82.68, 69.98, 69.93, 66.39 (d, \textit{J} = 5.3 Hz).
4.4 Experimental for Chapter 2

\((2E,4E)-1-(\text{pyrrolidin-1-yl})\text{hexa-2,4-dien-1-one (2.6.1)}\)\(^c\)

\[
\begin{align*}
&\text{(2E,4E)-Hexa-2,4-dienoic acid (1.12g, 10 mmol) was dissolved in THF (50 mL) in a} \\
&\text{flask fitted with a mechanical stirrer. The solution was cooled to \(-78 \, \text{ºC}. \text{ A solution of} } \\
&PivCl (1.35 mL, 11 \text{ mmol) was prepared in THF (50 mL) and added dropwise to the acid} \\
&\text{solution at \(-78 \, \text{ºC}. \text{ Et}_3\text{N (2.8 mL, 20 mmol) was added dropwise and stirred for 1 hr at \(-78 \, \text{ºC}. \text{ TLC was checked for complete} } \\
&\text{conversion of acid to pivaloate ester. Pyrrolidine} \\
&\text{(1.7 mL, 20 mmol) was added dropwise to the reaction mixture and stirring was} \\
&\text{continued for additional 2 h at \(-78 \, \text{ºC}. \text{ The residue in the reaction mixture was removed} } \\
&\text{by passing the solution through celite, the filtrate was diluted with ether (200 mL),} \\
&\text{washed with water (50 mL), 1 N HCl (50 mL), sat. NaHCO}_3\text{ (50 mL) and brine (50 mL).} \\
&\text{The organic layer was concentrated and chromatographed on a silica gel column. The} \\
&\text{desired amide eluted with 15% Ethyl Acetate in Hexane, and was collected as a pure} \\
&\text{white solid (1.58 g, 9.6 mmol, 96%); } R_f\text{ (30% EtOAc/Hexane) = 0.4; m.p: 74-76 \, \text{ºC}; IR} \\
&\text{(thin film) } \nu\text{ 2971, 2877, 1651, 1626, 1599, 1588, 1561, 1425, 1404, 1392, 1376, 1357,} \\
&1336, 1295, 1223, 1194, 1170, 1115, 1065, 1005 \text{ cm}^{-1} \text{. } ^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta \\
&\text{7.22 (dd, } J=14.4 \text{ Hz, 11.2 Hz, 1H), 6.15 (t, } J=11.2 \text{ Hz, 1H), 5.97-6.10 \text{ (m, 2H), 3.48} \\
&\text{(dd, } J=14 \text{ Hz, 7.6 Hz, 4H), 1.91 (m, 2H), 1.81 (m, 2H), 1.79 (d, } J=6.4 \text{ Hz, 3H).} ^{13}\text{C} \\
&\text{NMR (100 MHz, CDCl}_3\text{) } \delta 165.4, 142.1, 137.7, 130.4, 119.9, 46.6, 46.0, 26.3, 24.5, 18.8.}
\end{align*}
\]

\(^c\) Mass data pending
(4S,5S,E)-4,5-dihydroxy-1-(pyrrolidin-1-yl)hex-2-en-1-one (2.6.2)

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{OH} & \quad \text{N}
\end{align*}
\]

In a flask was added 2.5 mL water, $K_3[\text{Fe(CN)}_6]$ (0.478 g, 1.45 mmol), $K_2\text{CO}_3$ (0.201 g, 1.45 mmol), CH$_3$SO$_2$NH$_2$ (46 mg, 0.48 mmol), (DHQ)$_2$PHAL (7.5 mg, 9.7 µmol, 2 mol %), OsO$_4$ (1.2 mg, 5 µmol, 1 mol %) and stirred followed by addition of 2.5 mL tBuOH at room temperature and stirred until clear. This solution was cooled to 0 ºC and (2E,4E)-1-(pyrrolidin-1-yl)hexa-2,4-dien-1-one 2.6.1 (80 mg, 0.48 mmol) was added and stirred overnight at 0 ºC. The reaction was quenched with solid Na$_2$SO$_3$ (20 mg) at room temperature. The reaction mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulphate and DCM was removed in vacuo and flash chromatography on silica gel (10% MeOH/DCM) afforded (4S,5S,E)-4,5-dihydroxy-1-(pyrrolidin-1-yl)hex-2-en-1-one 2.6.2 (84 mg, 0.42 mmol, 87%) as a clear oil; $R_f$ (10% MeOH/DCM) = 0.8. IR (thin film) 3345, 3328, 3302, 3273, 3262, 3235, 3210, 2972, 1662, 1599, 1583, 1444, 1325, 1229, 1190, 1147, 1084, 1065, 1007 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.80 (dd, $J$ = 15.2 Hz, 4.8 Hz, 1H), 6.38 (dd, $J$ = 15.6 Hz, 1H), 4.32 (bs, 1H), 4.09 (bs, 1H), 4.00 (t, $J$ = 5.2 Hz, 1H), 3.65 (m, 1H), 3.43-3.51 (m, 4H), 1.91 (m, 2H), 1.82 (m, 2H), 1.15 (d, $J$ = 6Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.1, 144.6, 122.3, 76.1, 70.6, 47.0, 46.3, 26.2, 24.5, 19.2. HRMS Calculated for [C$_{16}$H$_{17}$NNaO$_3$] $^{2+}$ 222.1101, found 222.1184. $[\alpha]_D^{25}$ = -41 (c 0.09, CH$_2$Cl$_2$).
(4R,5S)-2,3,4,5-tetrahydroxy-1-(pyrrolidin-1-yl)hexan-1-one (2.6.3)

In a flask was added 1.5 mL water, K$_3$[Fe(CN)$_6$] (0.593 g, 1.8 mmol), K$_2$CO$_3$ (0.250 g, 1.8 mmol), CH$_3$SO$_2$NH$_2$ (58 mg, 0.61 mmol), (DHQD)$_2$PHAL (47 mg, 60 µmol, 10 mol %), OsO$_4$ (12 mg, 48 µmol, 8 mol %) and stirred followed by addition of 1.5 mL tBuOH at room temperature and stirred until solid dissolved. This solution was cooled to 0 ºC and diol 2.6.2 (120 mg, 0.60 mmol) was added and stirred overnight at 0 ºC. The reaction was quenched with solid sodium thiosulfite (20 mg) at room temperature. The reaction mixture was extracted with EtOAc (6 x 20 mL). The combined organic layers were dried over anhydrous sodium sulphate and solvent was removed in vacuo and flash chromatography on silica gel (10% MeOH/DCM) afforded tetrol as a mixture, as a clear oil 2.6.3 (63 mg, 0.27 mmol, 45%). $R_f = 0.4$ (10% MeOH/DCM). IR (thin film) 3350, 3335, 3318, 3308, 3300, 3261, 3245, 3222, 3203, 2970, 2953, 2935, 1622, 1601, 1556, 1470, 1435, 1404, 1390, 1377, 1354, 1328, 1304, 1227 cm$^{-1}$. HRMS Calculated for [C$_{10}$H$_{20}$NO$_5$]$^+$ 234.1336, Found 234.1313. (Hard to report NMR data since not a pure diastereoisomer)
**S-(**tert-**butyl) (2E,4E)-hexa-2,4-dienethioate (2.7.1a) (R = t-Bu)**

![Chemical Structure](attachment:structure.png)

(2E,4E)-Hexa-2,4-dienoic acid (673 mg, 6 mmol) was dissolved in 20 mL dry DCM and the solution was cooled to 0 ºC, dicyclohexylcarbodiimide (1.545 g, 7.5 mmol) and dimethyl amino pyridine (61 mg, 0.5 mmol) was added and the solution stirred vigorously at 0 ºC for 45 mins. t-Butyl thiol (0.56 mL, 5 mmol) was then added carefully dropwise and stirred overnight while allowing to slowly warm to room temperature. The reaction mixture was concentrated under reduced pressure and loaded onto a silica gel column inside the fume hood. The thioester was eluted with 3-4% ethyl acetate in hexane as a viscous colorless oil (1.069 g, 5.8 mmol, 97%), $R_f = 0.85$ (10% EtOAc/Hexane)

IR (thin film) 2929, 2117, 1665, 1637, 1596, 1363, 1321, 1161, 1122, 1029, 1007 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.11 (dd, $J = 15.6$ Hz, 10.0 Hz, 1H), 6.06-6.23 (m, 2H), 5.97 (d, $J = 15.2$ Hz, 1H), 1.85 (d, $J = 5.6$ Hz, 3H), 1.50 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 191.3, 140.8, 140.1, 130.0, 127.3, 48.3, 30.3, 19.2. HRMS Calculated for [C$_{10}$H$_{17}$OS$^+$] 185.0995, Found 185.0945.
$S$-ethyl (2$E,4E$)-hexa-2,4-dienethioate 2.7.1b

(2$E,4E$)-Hexa-2,4-dienoic acid (673 mg, 6 mmol) was dissolved in 20 mL dry DCM and the solution was cooled to 0 °C, dicyclohexylcarbodiimide (1.545 g, 7.5 mmol) and dimethyl amino pyridine (61 mg, 0.5 mmol) was added and the solution stirred vigorously at 0 °C for 45 mins. Ethane thiol (0.36 mL, 5 mmol) was then added carefully dropwise and stirred overnight while allowing to slowly warm to room temperature. The reaction mixture was concentrated under reduced pressure and loaded onto a silica gel column inside the fume hood. The thioester was eluted with 3-4% ethyl acetate in hexane as a viscous colorless oil (928 mg, 99%), $R_f$=0.83 (10% EtOAc/Hexane).

IR (thin film) 2931, 1667, 1654, 1637, 1598, 1323, 1226, 1170, 1130, 1049, 1016 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.18 (dd, $J$ = 15.2 Hz, 10.0 Hz, 1H), 6.08-6.25 (m, 2H), 6.06 (d, $J$ = 15.6 Hz, 1H), 2.95 (q, $J$ = 7.2 Hz, 2H), 1.86 (d, $J$ = 6 Hz, 3H), 1.28 (t, $J$ = 7.2 Hz, 3H).$^{13}$C NMR (100 MHz, CDCl$_3$) δ 190.6, 141.2, 141.1, 130.0, 126.6, 23.5, 19.2, 15.2.
**S-(**tert-**butyl)** (**4S,5S,E**)−4,5-dihydroxyhex-2-enethioate (2.7.2a) (**R** = **t-Bu**)

![Structure of S-(tert-butyl) (4S,5S,E)-4,5-dihydroxyhex-2-enethioate (2.7.2a)](image_url)

In a flask OsO₄ (0.5 mg, 0.002 mmol), (DHQ)₂PHAL (3 mg, 0.004 mmol), K₃[Fe(CN)₆] (198 mg, 0.6 mmol), K₂CO₃ (83 mg, 0.6 mmol) and methylsulfonamide (23 mg, 0.24 mmol) were stirred in 1 mL tBuOH/water (1:1) at room temperature until dissolved. This mixture was cooled to 0 °C, S-**t**butyl (**2E,4E**)−hexa-2,4-dienethioate **2.7.1a** (37 mg, 0.2 mmol) was added and stirred for 24 hours or until TLC shows complete conversion to diol **2.7.2a**. The reaction was quenched with solid sodium sulfite at room temperature.

Water was added to the reaction mixture and extracted with ether (3 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed *in vacuo* and flash chromatography on silica gel (20 % EtOAc/Hexane) afforded crude diol as a clear syrup (18 mg, 0.082 mmol, 40%), Rₜ = 0.3 (30% EtOAc/Hexane). IR (thin film) 3324, 2926, 2850, 1660, 1625, 1573, 1455, 1364, 1307, 1269, 1242, 1160, 1113, 1067, 1037, 1008 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 6.75 (dd, J = 15.6 Hz, 4.8 Hz, 1H), 6.32 (dd, J = 15.6 Hz, 1.6 Hz, 1H), 4.03 (m, 1H), 3.71 (m, 1H), 2.95 (s, 1H), 2.64 (bs, 1H), 1.49 (s, 9H), 1.24 (d, J = 6.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 191.0, 141.2, 130.2, 76.0, 70.7, 48.7, 30.2, 19.5. HRMS Calculated for [C₁₀H₁₈O₃SNa⁺] 241.0869, Found 241.0860. [α]ᵢ₂⁵ −35 (c 0.11, CH₂Cl₂).
S-(tert-butyl) (E)-3-((4S,5S)-5-methyl-2-phenyl-1,3,2-dioxaborolan-4-yl)prop-2-enethioate 2.7.3a (R = t-Bu)

In a flask OsO₄ (0.5 mg, 0.002 mmol), (DHQ)₂PHAL (3 mg, 0.004 mmol), K₃[Fe(CN)]₆ (198 mg, 0.6 mmol), K₂CO₃ (83 mg, 0.6 mmol) and phenyl boronic acid (29 mg, 0.24 mmol) were stirred in 1 mL tBuOH/water (1:1) at room temperature until dissolved. To this was added S-tbutyl (2E,4E)-hexa-2,4-dienethioate 2.7.1a (37 mg, 0.2 mmol) and stirred for 24 hrs or until complete conversion of starting material to monoboronate is observed by TLC. The reaction was quenched with solid sodium sulfite at room temperature. Water was added to the reaction mixture and extracted with ether (3 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed in vacuo and flash chromatography on silica gel (3-6% EtOAc/Hexane) afforded crude boronate as a clear syrup (20 mg, 0.65 mmol, 33%). \( R_f = 0.55 \) (10% EtOAc/Hexane). IR (thin film, cm⁻¹) 2965, 2924, 1666, 1636, 1603, 1500, 1455, 1440, 1404, 1371, 1349, 1316, 1286, 1213, 1161, 1141, 1096, 1067, 1028, 1009. \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.83 (d, \( J = 6.8 \) Hz, 2H), 7.50 (t, \( J = 7.4 \) Hz, 1H), 7.4 (t, \( J = 7.4 \) Hz, 2H), 6.80 (dd, \( J = 15.4 \) Hz, 5.0 Hz, 1H), 6.33 (dd, \( J = 15.2 \) Hz, 1.6 Hz, 1H), 4.58-4.65 (m, 1H), 4.32-4.42 (m,1H), 1.51 (s, 9H), 1.49 (d, \( J = 6.4 \) Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl₃) \( \delta \) 190.6, 139.4, 135.2 (2C), 132.1, 129.5 (2C), 83.2, 79.0, 48.8, 30.1, 21.5. HRMS Calculated for [C₁₆H₂₁BO₃S] 304.1304, Found 304.1304. \([\alpha]_D^{25} +44 \) (c 0.12, CH₂Cl₂).
$S$-ethyl ($E$)-3-((4S,5S)-5-methyl-2-phenyl-1,3,2-dioxaborolan-4-yl)prop-2-enethioate (2.7.3b) ($R = Et$)\(^d\)

\[
\text{Ph} \quad \text{B} \quad \text{O} \\
\text{S} \\
\text{O} \quad \text{=}_{\text{O}} \quad \text{O}
\]

In a flask OsO$_4$ (2 mg, 0.008 mmol), (DHQ)$_2$PHAL (12 mg, 0.016 mmol), K$_3$[Fe(CN)$_6$] (396 mg, 1.2 mmol), K$_2$CO$_3$ (166 mg, 1.2 mmol) and Phenyl boronic acid (58 mg, 0.48 mmol) were stirred in 2 mL t-BuOH/water (1:1) at room temperature until dissolved. To this was added $S$-ethyl ($2E,4E$)-hexa-2,4-dienethioate (62 mg, 0.4 mmol) and stirred for 24 hours or until complete conversion of starting material to monoboronate is observed by TLC. The reaction was quenched with solid sodium sulfite at room temperature. Water was added to the reaction mixture and extracted with ether (3 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed \textit{in vacuo} and flash chromatography on silica gel (3-6\% EtOAc/Hexane) afforded crude boronate as a clear syrup (34 mg, 0.12 mmol, 31\%); $R_f = 0.5$ (10\% EtOAc/Hexane). IR (thin film, cm$^{-1}$) 2971, 2931, 1668, 1638, 1603, 1500, 1440, 1404, 1371, 1349, 1315, 1288, 1260, 1213, 1159, 1145, 1094, 1066, 10231598, 1323, 1226, 1170, 1130, 1049, 1016; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.84 (d, $J = 7.6$, 1.2 Hz, 2H), 7.46-7.55 (m, 1H), 7.40 (t, $J = 7.4$ Hz, 2H), 6.88 (dd, $J = 15.6$ Hz, 5.2 Hz, 1H), 6.43 (dd, $J = 15.2$ Hz, 1.6 Hz 1H), 4.58-4.72 (m, 1 H), 4.38 (m, 1H), 2.97 (q, $J = 7.4$ Hz, 1H), 1.49 (d, $J = 6.4$ Hz, 3H), 1.29 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$

\(^d\) Optical rotation data pending
190.0, 140.4, 135.2 (2C), 132.1, 128.6, 128.2 (2C), 83.2, 79.0, 23.8, 21.5, 15.0. HRMS Calculated for $[\text{C}_{14}\text{H}_{18}\text{BO}_{3}\text{S}^+]$ 277.1064, Found 277.1139.

**Ethyl (E)-3-((4S,5S)-5-methyl-2-phenyl-1,3,2-dioxaborolan-4-yl)acrylate (2.9.1)**

![Chemical Structure]

In a flask OsO$_4$ (25 mg, 0.1 mmol), (DHQ)$_2$PHAL (390 mg, 0.5 mmol), K$_3$[Fe(CN)$_6$] (9.87 g, 30 mmol), K$_2$CO$_3$ (4.150 g, 30 mmol) and phenyl boronic acid (1.465 g, 12 mmol) were stirred in 50 mL $t$-BuOH/water (1:1) at room temperature until dissolved. To this was added ethyl sorbate (1.4 g, 10 mmol) and for 24 hrs or until complete conversion of ethyl sorbate was observed by TLC. The reaction was quenched with solid sodium sulfite at room temperature. Water was added to the reaction mixture and extracted with ether (3 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed in vacuo and flash chromatography on silica gel (10% EtOAc/Hexane) afforded monoboronate (1.99 g, 0.765 mmol, 76%) as a clear oil: $R_f$ (20% EtOAc/Hexane) = 0.60, m.p. < 0 °C. IR (thin film, cm$^{-1}$) 2975, 1717, 1440, 1405, 1371, 1350, 1322, 1294, 1268, 1214, 1176, 1093, 1027. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.84 (d, $J = 6.2$ Hz, 2H), 7.46-7.61 (m, 1H), 7.40 (t, $J = 7.4$ Hz, 2H), 6.98 (dd, $J = 15.6$ Hz, 5.2 Hz, 1H), 6.18 (dd, $J = 15.6$ Hz, 1.6 Hz 1H), 4.63-4.68 (m, 1 H), 4.37 (m, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 1.49 (d, $J = 6.0$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz, 3H ); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.2, 145.0, 135.2 (2C), 132.0, 128.2 (2C), 122.2, 83.2, 79.0, 61.0, 21.4, 14.5; HRMS Calculated for [C14H17BO4Na+]
283.1112, found 283.1152. [α]_D^25 +62 (c 0.13, CH₂Cl₂).

**Ethyl (4R,4'R,5S,5'S)-5'-methyl-2,2'-diphenyl-[4,4'-bi(1,3,2-dioxaborolane)]-5-carboxylate (2.9.2)**

From Monoboronate: In a flask OsO₄ (250 mg, 1 mmol), (DHQD)₂PHAL (1.145 g, 1.5 mmol), K₃[Fe(CN)₆] (9.9 g, 30 mmol), K₂CO₃ (4.150 g, 30 mmol) and phenyl boronic acid (2.4 g, 24 mmol) were stirred in 50 mL t-BuOH/water (1:1) at room temperature until dissolved. To this was added monoboronate of ethyl sorbate 2.9.1 (1.99 g, 0.76 mmol) and stirred for 24 hours or until complete conversion of monoboronate to bisboronate is indicated by TLC. The reaction was quenched with solid sodium sulfite at room temperature. Water was added to the reaction mixture and extracted with ether (3 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed in vacuo and flash chromatography on silica gel (10% EtOAc/Hexane) afforded 6.6 g of crude bisboronate as clear syrup. This bisboronate can be directly used in the next step. A small portion of this material (300 mg) when chromatographed more carefully gives pure bisboronate (120 mg), thus yield at this stage was ~2.64 g (90%). Rf (20% EtOAc/Hexane) = 0.30, m.p. < 0 °C. IR (thin film) 2980, 2973, 1749, 1604, 1441, 1394, 1374, 1352, 1299, 1254, 1213 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 7.2 Hz, 2H), δ 7.83 (d, J = 6.8 Hz, 2H), 7.49-7.56 (m, 2H), 7.41 (dt, J = 12.0, 7.6 Hz, 4H), 5.00 (d, J = 4.8 Hz, 1H), 4.69 (p, J = 6.2 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H).
4.61 (dd, $J = 6.6$ Hz, 5.0 Hz, 1 H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.19 (dd, $J = 6.4$, 6.4 Hz, 1H), 1.51 (d, $J = 6.0$ Hz, 3H), 1.29 (t, $J = 7.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) 170.8, 136.0, 135.5, 135.3, 133.0, 132.4, 132.1, 128.33, 128.28, 128.2, 84.8, 82.0, 76.7, 62.3, 22.6, 14.5. HRMS Calculated for [C$_{20}$H$_{22}$B$_2$O$_6$] 380.1602, found 380.1602. [$\alpha$]$_D^{25}$ +13 (c 0.1, CH$_2$Cl$_2$).

**One pot from Ethyl sorbate:** In a flask OsO$_4$ (1.27 mg, 0.005 mmol), (DHQ)$_2$PHAL (6 mg, 0.0075 mmol), K$_3$[Fe(CN)$_6$] (494 mg, 1.5 mmol), K$_2$CO$_3$ (207.3 mg, 1.5 mmol) and Phenyl boronic acid (219 mg, 1.8 mmol) were stirred in 2.5 mL $\tau$-BuOH/water (1:1) at room temperature until dissolved. To this was added ethyl sorbate (70 mg, 0.5 mmol) and stirred for 24 hrs or until TLC shows complete conversion of ethyl sorbate to monoboronate. In a separate vial OsO$_4$ (5 mg, 0.02 mmol), (DHQD)$_2$PHAL (31 mg, 0.04 mmol), K$_3$[Fe(CN)$_6$] (494 mg, 1.5 mmol), K$_2$CO$_3$ (207.3 mg, 1.5 mmol) was dissolved in 2.5 mL $\tau$-BuOH/water (1:1) and this solution was added to the reaction mixture and the stirring continued at room temperature until all the monoboronate is converted into the bisboronate. The reaction was quenched with solid sodium sulfite at room temperature. Water was added to the reaction mixture and extracted with ether (3 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed *in vacuo* and flash chromatography on silica gel (20% EtOAc/Hexane) afforded bisboronate (135 mg, 0.35 mmol, 71%) as a clear syrup, which solidified in the freezer. $R_f$ (20% EtOAc/Hexane) = 0.30. IR (thin film) 2980,
2973, 1749, 1604, 1441, 1394, 1374, 1352, 1299, 1254, 1213 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 7.2 Hz, 2H), δ 7.83 (d, J = 6.8 Hz, 2H), 7.49-7.56 (m, 2H), 7.41 (dt, J = 12.0, 7.6 Hz, 4H), 5.00 (d, J = 4.8 Hz, 1H), 4.69 (p, J = 6.2 Hz, 1H), 4.61 (dd, J = 6.6 Hz, 5.0 Hz, 1 H), 4.27 (q, J = 7.2 Hz, 2H), 4.19 (dd, J = 6.4, 6.4 Hz, 1H), 1.51 (d, J = 6.0 Hz, 3H), 1.29 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 170.8, 136.0, 135.5, 135.3, 133.0, 132.4, 132.1, 128.33, 128.28, 128.2, 84.8, 82.0, 76.7, 62.3, 22.6, 14.5.

HRMS Calculated for [C₂₀H₂₂B₂O₆] 380.1602, found 380.1602. [α]ᵤ⁺¹₃ +13 (c 0.1, CH₂Cl₂).

(3S,4S,5R)-dihydro-3,4-dihydroxy-5-((1'S)-1'-hydroxyethyl)furan-2(3H)-one (4a): (2.12.1)

Pure bisboronate 2.9.2 (15 mg, 0.04 mmol) was dissolved in ether (0.2 mL). Diethanolamine (15 µL) was added with vigorous stirring. A white precipitate formed as reaction proceeded. Reaction completed in 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was triturated with 20% EtOAc/Hexane (5 mL X 2) and the resulting solution passed through a small column of silica. The remaining residue was dissolved in 10% MeOH/EtOAc (2 mL X 5) and the solution passed through the silica column, collecting fractions. The lactone containing fractions were collected and concentrated. The lactone 2.12.1 was white crystalline in nature (4.5 mg, 0.028 mmol, 69%), m.p. 75 °C; Rₛ (10% MeOH/EtOAc) = 0.45, [α]ᵤ⁺²⁴ 31.4º (c 1.5, MeOH). IR (thin
film) 3365, 2965, 2923, 2867, 1785, 1315, 1236 cm
\(^{-1}\); \(^1\)H NMR (CD\(_3\)OD, 400 MHz): \(\delta\) 4.34 (d, \(J = 8.8\) Hz, 1H), 4.17 (dd, \(J = 8.8, 7.8\) Hz, 1H), 3.92 (m, 2H), 3.30 (s, 3H), 1.31 (d, \(J = 6.4\) Hz, 3H); \(^{13}\)C NMR (CD\(_3\)OD, 100 MHz): \(\delta\) 175.1, 84.05, 74.7, 73.9, 65.4, 18.3.

HRMS: Calculated for [C\(_6\)H\(_9\)O\(_5\)+Na\(^+\)]: 207.0239, Found: 207.0278 (Matches data in reference 19).

\((3S,4R,5R)-5-((1'S)-1'-acetoxy-ethyl)-3,4-diacetoxy-dihydro-furan-2-one (5a):

\((2.11.1)\)

\begin{center}
\includegraphics[width=0.2\textwidth]{latex/5a.png}
\end{center}

Lactone \(2.12.1\) (60 mg, 0.37 mmol) was dissolved in 1 mL dry DCM, and cooled to 0 °C. Pyridine (0.24 mL) followed by Acetic anhydride (0.14 mL) was added dropwise and stirred in cold for 3 h. Reaction was quenched by adding water, the reaction mixture was extracted with DCM (2 mL x 3). The organic layer was washed with 1 N HCl (3 mL), brine (3 mL), dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The crude was purified by flash chromatography on silica gel, eluting with 30% EtOAc/Hexane to give triacetate \(2.11.1\) (99 mg, 0.34 mmol, 93%), m.p. 108-110 °C. \(R_f\) (70% EtOAc/ hexanes ) = 0.7. 

\([\alpha]_D^{25}\) 14.5° (c 2, CH\(_2\)Cl\(_2\)). IR (thin film, cm-1) 2953, 2922, 2876, 2863, 1808, 1749, 1373, 1234, 1179, 1100, 1069, 1044; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.62 (d, \(J = 7.2\) Hz, 1H), 5.40 (dd, \(J = 7.2, 7.2\) Hz, 1H), 5.13 (dd, \(J = 6.4, 3.6\) Hz, 1H), 4.37 (dd, \(J = 6.8, 3.6\) Hz, 1H), 2.18 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 1.37 (d, \(J = 5.6\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz): \(\delta\) 169.8, 169.6, 169.3, 168.3, 80.4, 72.5, 72.1, 67.7, 20.8, 20.5, 20.3, 15.8.

HRMS Calculated for [C\(_{12}\)H\(_{16}\)O\(_8\)+Na\(^+\)]: 311.0737, found: 311.0745 (Matches data in...
1-Benzylol-pent-4-yn (2.14.3)

To a solution of 4-pentyn-1-ol 2.14.2 (2 g, 23.78 mmol) in toluene (24 mL) was added NaOH (1.9 g, 47.56 mmol). The reaction was heated to 110 °C and benzyl bromide (4.24 mL, 35.67 mmol) was added dropwise. The reaction refluxed and stirred overnight after which toluene was removed under reduced pressure. Ether was added and washed with water. The aqueous layer was further extracted with ether. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (5% EtOAc/Hexane) to yield 2.14.3 (3.9 g, 94%). $R_f$(10% EtOAc/hexane) = 0.6; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.33-7.48 (m, 5H), 4.58 (s, 2H), 3.64 (t, $J$ = 6.2 Hz, 2H), 2.40 (td, $J$ = 7.2, 2.8 Hz, 2H), 2.04 (d, $J$ = 2.8 Hz, 1H), 1.87-1.96 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 138.6, 128.6, 127.8, 127.7, 84.1, 73.3, 72.4, 68.9, 29.0, 15.5.

Ethyl 6-(benzyloxy)hex-2-ynoate (2.14.4)$^e$

To a solution of 2.13.4 (3.9 g, 22.4 mmol) in anhydrous THF was added butyllithium (11.65 mL, 29.12 mmol) dropwise at −78 °C. The reaction was stirred for an hour and

$^e$ IR and mass data pending
ethyl chloroformate (3.13 mL, 29.12 mmol) was added. The reaction stirred overnight at −78 °C after which water was added to quench. THF was removed under reduced pressure and the aqueous layer was extracted with ether. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (5% EtOAc / Hexane) to yield 2.14.4 (1.7 g, 7 mmol, 31%); Rf (20 % EtOAc/hexane) = 0.65. Some unreacted starting material (1.8 g, 46%) was recovered. ¹H NMR (CDCl₃, 400 MHz): δ 7.25-7.38 (m, 5H), 4.51 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.56 (t, J = 6.0 Hz, 2H), 2.48 (t, J = 7.2 Hz, 2H), 1.83-1.92 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 165.9, 138.6, 128.8, 128.0, 89.1, 73.7, 73.4, 68.7, 62.2, 28.2, 16.0, 14.4.

Ethyl (2E,4E)-6-(benzyloxy)hexa-2,4-dienoate (2.14.1)

To a solution of 2.14.4 (1.2 g, 4.87 mmol) in anhydrous toluene (28 mL) was added Ph₃P (1.28 g, 4.87 mmol) and PhOH (458 mg, 4.87 mmol). The reaction was stirred and heated to 50 °C and refluxed overnight. Toluene was removed under reduced pressure. The crude product was redissolved in ethyl acetate and washed with 1 N KOH (aq.) (8 mL) at 0 °C, followed by a wash with water. This process was repeated 3 times. The product was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The product was then dissolved in 10 mL ether and to it was added CH₃I (0.61 mL, 9.74 mmol). The reaction stirred at room temperature for 2.5 hrs. The product was filtered over celite, washed with ether and concentrated under reduced pressure to yield 2.14.1
(2.0 g crude), which was used in the next step without further purification. \( R_f \) (20 % EtOAc/hexane) = 0.59. A small sample was purified for analysis. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.24-7.41 (m, 5H), 6.42 (dd, \( J = 13.4 \) Hz, 1H), 6.18 (dt, \( J = 15.6, 5.2 \) Hz, 2H), 5.89 (d, \( J = 15.6 \) Hz, 1H), 4.55 (s, 2H), 4.21 (q, \( J = 7.2 \) Hz, 2H), 4.14 (d, \( J = 5.2 \) Hz, 2H), 1.30 (t, \( J = 7.2 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 167.3, 144.0, 138.9, 138.2, 129.5, 128.8, 128.14, 128.09, 121.9, 73.0, 70.0, 60.7, 14.6. (Matches known reference)

**Ethyl (4\( R \),5\( R \),E)-4,5-dihydroxyhex-2-enoate (2.4.1b)**

![Chemical Structure](attachment:image.png)

In a flask was added 10 mL \( t \)-BuOH, 10 mL water, K\(_3\)[Fe(CN)\(_6\)] (9.88 g, 30 mmol), K\(_2\)CO\(_3\) (4.15 g, 30 mmol), CH\(_3\)SO\(_2\)NH\(_2\) (971 mg, 12 mmol), (DHQD\(_2\))PHAL (94 mg, 0.12 mmol), OsO\(_4\) (25 mg, 0.1 mmol) and stirred at room temperature until clear. This solution was cooled to 0 ℃ and ethyl sorbate (1.4 g, 10 mmol) was added and stirred overnight at 0 ℃. The reaction was quenched with solid sodium sulfite (0.2 g) at room temperature. The reaction mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed *in vacuo* and flash chromatography on silica gel (50% EtOAc/Hexane) afforded \((E,4R,5R)-\)ethyl 4,5-dihydroxyhex-2-enoate **2.4.1b** as a clear oil (1.4 g, 8 mmol, 80%), \( R_f \) (70% EtOAc/Hexane) = 0.40; IR (thin film, cm\(^{-1}\)) 3503, 3490, 3444, 3345, 3261, 2983, 1747, 1715, 1442, 1373, 1298, 1166, 1089, 1062, 1030. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.92 (dd, \( J = 15.6, 5.2 \) Hz, 1H), 6.14 (dd, \( J = 16, 1.8 \) Hz, 1H), 4.20 (q, \( J = 7.2 \) Hz, 2H), 4.02 (d, \( J = 4.4 \) Hz, 1 H), 3.68-3.78 (m, 1H), 2.64 (d, \( J \) 

105
= 4.4 Hz, 1H), 2.35 (d, \( J = 4.4 \) Hz, 1H), 1.29 (t, \( J = 7.2 \) Hz, 3H), 1.25 (d, \( J = 6.4 \) Hz, 3H);

\( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 166.6, 146.6, 123.0, 76.0, 70.6, 70.0, 19.5, 14.6. \([\alpha]_D^{25} - 18 \) (c 0.1, CH\(_2\)Cl\(_2\)). (Matches known reference)

Ethyl \((E)-3-((4R,5R)-2,2,5\text{-trimethyl-1,3-dioxolan-4-yl})\text{-acrylate (2.16.1)}\)

\( (E,4R,5R)\)-ethyl 4,5-dihydroxyhex-2-enoate 2.4.1b (1.2 g, 6.9 mmol) was dissolved in 14 mL DCM and cooled to 0 °C. Camphor sulphonic acid (32 mg, 2 mol%) and 2,2-dimethoxypropane (1.3 mL, 10.5 mmol) were added and stirred at 0 °C for 1.5 hrs. The reaction was quenched with saturated sodium bicarbonate and extracted with ether (100 mL x 2). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed \textit{in vacuo} and flash chromatography on silica gel (10% EtOAc/Hexane) afforded \((E)\)-ethyl 3-((4R,5R)-5-(methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate 2.16.1 as a clear oil (1.4 g, 6.7 mmol, 97%); \( R_f \) (70\% EtOAc/Hexane) = 0.90; \([\alpha]_D^{25} -6.5^\circ \) (c 2.2, CH\(_2\)Cl\(_2\)). IR (thin film) 2983, 1715, 1371, 1302, 1280, 1173, 1114, 1090, 1066, 1031 cm\(^{-1}\). \(^1H\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.80 (dd, \( J = 15.2, 5.6 \) Hz, 1H), 6.06 (dd, \( J = 15.2, 1.6 \) Hz, 1H), 4.15 (q, \( J = 7.2 \) Hz, 2H), 4.02 (ddd, \( J = 8.4 \) Hz, 5.8, 1.4 Hz 1 H), 3.78 (dq, \( J = 8.4, 6.0 \) Hz, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 1.21-1.28 (m, 6H); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 166.2, 143.7, 123.1, 109.5, 81.9, 76.7, 60.8, 27.5, 26.8, 16.9, 14.4. HRMS: Calculated for [C\(_{11}\)H\(_{18}\)O\(_4\)Na]+: 237.1097, Found: 237.0995.
**Ethyl (2R,3R)-2,3-dihydroxy-3-((4R,5R)-2,2,5-trimethyl-1,3-dioxolan-4-yl)propanoate (2.16.2)**

In a flask was added 13.5 mL tBuOH, 13.5 mL water, K₃[Fe(CN)₆] (6.65 g, 20 mmol), K₂CO₃ (2.8 g, 20 mmol), CH₃SO₂NH₂ (701 mg, 7.4 mmol), (DHQ)₂PHAL (115 mg, 0.15 mmol), OsO₄ (25 mg, 0.1 mmol) and stirred at room temperature until clear. This solution was cooled to 0 ºC and acetonide 2.16.1 (1.4 g, 6.7 mmol) was added and stirred overnight at 0 ºC. The reaction was quenched with solid sodium sulfite (0.2 g) at room temperature. The reaction mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed in vacuo and flash chromatography on silica gel (50% EtOAc/Hexane) afforded (E,4R,5R)-ethyl 4,5- dihydroxyhex-2-enoate 2.16.2 (10:1 dr) as a white solid (1.6 g, 6.5 mmol, 97%), mp 81-83 ºC; Rᶠ (70% EtOAc/Hexane) = 0.65. IR (thin film, cm⁻¹) 2986, 1749, 1730, 1285, 1192, 1173, 1116, 1085. ¹H NMR (400 MHz, CDCl₃) δ 4.42 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 4.11 (dq, J = 7.2, 6.0 Hz, 1H), 3.87 (d, J = 6.4 Hz, 1H), 3.60 (dd, J = 8.8, 7.2 Hz, 1H), 3.36 (bs, 1H), 2.51 (bs, 1H), 1.33-1.42 (m, 9H), 1.31 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 173.7, 109.0, 81.1, 76.9, 74.3, 71.1, 62.6, 27.8, 27.3, 19.8, 14.5. [α]D²⁵ −36 (c 0.14, CH₂Cl₂). (Matches known reference)
Ethyl (2S,3S)-2,3-dihydroxy-3-((4R,5R)-2,2,5-trimethyl-1,3-dioxolan-4-yl)propanoate (2.16.3)\(^f\)

\[
\begin{align*}
\text{O} & \quad \text{OH} & \quad \text{OEt} \\
\text{OH} & \quad \text{O} & \quad \text{Et}
\end{align*}
\]

In a flask was added 1.25 mL tBuOH, 1.25 mL water, K\(_3\)[Fe(CN)\(_6\)] (0.25 g, 0.75 mmol), K\(_2\)CO\(_3\) (0.100 g, 0.75 mmol), CH\(_3\)SO\(_2\)NH\(_2\) (24 mg, 0.25 mmol), (DHQD\(_2\))PYDZ (9 mg, 0.0125 mmol), OsO\(_4\) (1.3 mg, 0.005 mmol) and stirred at room temperature until clear. This solution was cooled to 0 °C and acetonide 2.16.1 (53 mg, 0.25 mmol) was added and stirred overnight at 0 °C. The reaction was quenched with solid sodium sulfite at room temperature. The reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed \textit{in vacuo} and flash chromatography on silica gel (50% EtOAc/Hexane) afforded acetonide diol diastereoisomeric mixture majoring in 2.16.3 (4:1 dr) as a clear oil (60 mg, 0.24 mmol, 97%), \(R_f\) (70% EtOAc/Hexane) = 0.65. IR (thin film, cm\(^{-1}\)) 2986, 1749, 1730, 1285, 1192, 1173, 1116, 1085. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.27 (q, \(J = 7.2\) Hz, 2H), 4.21 (bs, 1H), 4.06-4.15 (m, 1H), 3.84 (s, 1H), 3.71 (dd, \(J = 8.4, 2.4\) Hz, 1H), 3.34 (bs, 1H), 2.88 (bs, 1H), 1.27-1.43 (m, 12H)(Major peaks). \(^1\)\(^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.8, 109.4, 82.7, 73.6, 72.5, 70.6, 62.5, 27.7, 27.0, 17.9, 14.4 (Major peaks).

\(^f\) Mass and optical rotation data pending
4.5 Experimental for Chapter 3

5-(benzyloxy)naphthalen-1-yl hexa-2,4-dienoate (3.12.3)

5-Benzyl邻-萘酚 3.12.1 (1 g, 3.99 mmol) was taken in a reaction flask and dissolved in dry DCM (8 mL). The solution was cooled to 0 °C and 2E,4E-hexadienoic acid 3.12.2 (0.673 g, 6 mmol) was added with stirring. DCC (1.32 g, 6.41 mmol) and DMAP (45 mg, 0.37 mmol) were added consecutively at 0 °C. The resulting mixture was stirred for 1 h while the temperature was allowed to gradually attain room temperature. After 1 hr the solution was filtered and the filtrate was concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 8% EtOAc/hexanes to obtain 3.12.3 as pale brown solid (1.11 g, 3.22 mmol, 81%). mp: 120 °C; $R_f$ (30% EtOAc/Hexane) = 0.8; IR (neat) 1728.6, 1638.6, 1404.4, 1324.2, 1260.8, 1234.5, 1111.8, 1079.4 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.30 (d, $J = 8$ Hz, 1H), 7.33-7.62 (m, 10H), 6.93 (d, $J = 7.2$ Hz, 1H), 6.24-6.39 (m, 2H), 6.15 (d, $J = 15.2$ Hz, 1H), 5.27 (s, 2H), 1.94 (d, $J = 5.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.9, 154.7, 147.4, 146.7, 141.1, 137.1, 129.9, 128.8, 128.3, 128.1, 127.5, 127.3, 126.6, 124.9, 120.4, 119.0, 117.9, 114.0, 105.9, 70.3, 19.0; HRMS Calculated for [C$_{23}$H$_{20}$O$_3$Na$^+$] 367.1305, found 367.1284.
5-(benzyloxy)-8-bromonaphthalen-1-yl hexa-2, 4-dienoate (3.12.4)

![Chemical Structure](image)

5-(benzyloxy)-8-bromonaphthalen-1-ol 3.12.8 (1 g, 3.03 mmol) was taken in a round bottom flask and dissolved in dry CH₂Cl₂ (30 mL). The solution was cooled to 0 °C and 2,4-hexadienoic acid or sorbic acid (0.680 g, 6.06 mmol) was added with stirring. DCC (1.25 g, 6.07 mmol) and DMAP (74 mg, 0.61 mmol) were added consecutively at 0 °C. The resulting mixture was stirred for 1 h while the temperature was allowed to gradually attain room temperature. After 1 hr the solution was cooled, filtered and the filtrate was concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 45% CH₂Cl₂/hexanes to obtain 3.12.4 as fluffy white crystalline solid (0.4 g, 0.9 mmol, 31%). mp: 177 °C; Rₚ (30% EtOAc/Hexane) = 0.8; IR (neat) 2926.5, 1722.3, 1621.1, 1566.4, 1323.0, 1233.2, 1175.3, 1128.0, 1082.2, 1013.9 cm⁻¹; §H NMR (400 MHz, CDCl₃) δ 8.36 (dd, J = 8.4, 1.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.47-7.55 (m, 5H), 7.44 (t, J = 8 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.21-6.36 (m, 2H), 6.13 (d, J = 15.2 Hz, 1H), 5.23 (s, 2H), 1.91 (d, J = 6.0 Hz, 3H); §C NMR (100 MHz, CDCl₃) δ 166.7, 154.5, 147.6, 146.2, 141.0, 136.8, 133.4, 130.3, 129.4, 129.0, 128.5, 127.7, 126.1, 125.9, 122.7, 121.7, 119.1, 106.7, 106.5, 70.8, 19.2; HRMS Calculated for [C₂₃H₁₉BrO₃Na⁺] 445.0410, found 446.0402.
5-(benzyloxy)naphthalenyl-1-acetate (3.12.6a)

5-Benzylxynaphthol 3.12.1 (0.50 g, 2.00 mmol) was dissolved in dry DCM (5 mL), the solution was cooled to 0 °C and pyridine (0.35 mL, 0.34 g, 4.34 mmol) was added and after 10 mins acetic anhydride (0.37 mL, 0.40 g, 3.92 mmol) was added dropwise with stirring. Catalytic amount of DMAP (0.024 g, 0.196 mmol) was added to the reaction mixture and the temperature was slowly raised to rt. After 1 h the reaction was complete. The reaction mixture was extracted with ether (10 mL), the extract was washed with ice cold HCl (0.5 N), sat. NaHCO₃, brine and finally dried over Na₂SO₄. The ether extract was then concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 7% EtOAc/hexanes to obtain 3.12.6a as off-white solid (0.46 g, 16.68 mmol, 79%), m.p. 137-139 °C; Rf (30% EtOAc/Hexane) = 0.45; IR (neat) 1757, 1406, 1373, 1263, 1200, 1146, 1022, 1012 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.35-7.51 (m, 7H), 7.31 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 5.27 (s, 2H), 2.48 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 154.9, 146.7, 137.2, 128.9, 128.3, 128.2, 127.7, 127.4, 126.9, 125.0, 120.8, 119.1, 113.9, 106.1, 70.5, 21.3; HRMS Calculated for [C₁₉H₁₆O₃Na⁺] 315.0992, found 315.0988.
5-(benzyloxy)naphthalen-1-yl 2-chloroacetate (3.12.6b)

5-Benzyl-
noxy-naphthol 3.12.1 (5 g, 19.98 mmol) was dissolved in dry DCM (40 mL), the solution was cooled to 0 °C and pyridine (2.5 mL, 2.445 g, 30.91 mmol) was added followed by chloroacetyl chloride (2.4 mL, 3.41 g, 30.19 mmol) with stirring. Catalytic amount of DMAP (0.037 g, 0.30 mmol) was added to the solution and the temperature was slowly raised to rt. After 4 h the reaction was complete. The reaction mixture was extracted with EtOAc (80 mL), the extract was washed with ice cold HCl (0.5 N), sat. NaHCO₃, brine and finally dried over Na₂SO₄. The EtOAc extract was then concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 8% EtOAc/hexanes to obtain 3.12.6b as crystalline white solid (5.45 g, 16.68 mmol, 85%). mp: 102 °C; R₇ (30% EtOAc/Hexane) = 0.78; IR (neat) 1767.6, 1655.2, 1402.4, 1259.7, 1141.8, 1026.8 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.30 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.41-7.50 (m, 5H), 7.38 (d, J = 7.2 Hz, 1H), 7.33 (dd, J = 7.6, 0.8 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 5.26 (s, 2H), 4.46 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.2, 154.9, 146.2, 137.1, 130.0, 128.4, 127.8, 127.7, 127.5, 127.3, 124.9, 121.4, 118.8, 113.5, 106.3, 70.4, 41.2; HRMS Calculated for [C₁₉H₁₅ClO₃Na⁺] 349.0602, found 349.0587.
5-(benzyloxy)-8-bromonaphthalenyl-1-acetate 3.12.7a

5-(benzyloxy) naphthalen-1-yl 2-acetate 3.12.6a (0.5 g, 1.71 mmol) was dissolved in dry DMF (3 mL) in a flask with stirring. NBS (0.335 g, 1.88 mmol) was dissolved in dry DMF (6 mL) and added drop-wise to the former solution at room temperature. After 45 mins diethyl ether (60 mL) was added. The reaction mixture was repeatedly washed with water (7-8 times) to remove traces of DMF. The ether layer was dried over Na₂SO₄ and concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 8% EtOAc/hexanes to obtain 3.12.7a as light brown crystalline solid (0.59 g, 1.59 mmol, 93%). m.p: 144 ºC; R_f (30% EtOAc/Hexane) = 0.45; IR (neat) 1758.4, 1350.5, 1199.5, 1168.21, 1033.6, 1024.7, 1013.8 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.32-7.57 (m, 6H), 7.25 (d, J = 7.2 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.22 (s, 2H), 2.46 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.7, 154.5, 146.0, 136.7, 133.6, 129.4, 129.0, 128.5, 127.7, 125.8, 122.7, 121.9, 106.7, 106.2, 70.8, 22.4. HRMS Calculated for [C₁₉H₁₃BrO₃Na⁺] 393.009, found 393.0082.
5-(benzyloxy)-8-bromonaphthalen-1-yl 2-chloroacetate 3.12.7b

5-(benzyloxy)naphthalen-1-yl 2-chloroacetate 3.12.6b (1 g, 3.06 mmol) was dissolved in dry DMF (7 mL) in a flask with stirring. N-Bromosuccinimide (0.6 g, 3.37 mmol) was dissolved in dry DMF (8 mL) and added drop-wise to the former solution at room temperature. After 1 hr diethyl ether (60 mL) was added. The reaction mixture was repeatedly washed with water (7-8 times) to remove traces of DMF. The ether layer was dried over Na₂SO₄ and concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 45% CH₂Cl₂/hexanes to obtain 3.12.7b as fluffy white crystalline solid (0.95 g, 2.34 mmol, 81%). mp: 161 °C; Rₚ (30% EtOAc/Hexane) = 0.78; IR (neat) 1752.5, 1591.2, 1505.2, 1415.8, 1348.8, 1306.4, 1242.3, 1158.12, 1006.05 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.40 (dd, J = 8.4, 0.8 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 7.35-7.55 (m, 6H), 7.28 (dd, J = 7.6, 0.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 5.22 (s, 2H), 4.50 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 154.4, 145.3, 136.4, 133.7, 129.3, 128.9, 128.4, 127.6, 125.7, 125.3, 122.4, 122.2, 106.8, 105.7, 70.7, 41.9.
5-(benzyl oxy)-8-bromonaphthalen-1-ol (3.12.8)

To a solution of 5-(benzyl oxy)-8-bromonaphthalen-1-yl 2-chloroacetate 3.12.7b (0.49 g, 1.21 mmol) in THF (10.8 mL) and water (1.2 mL) was added KOH (0.678 g, 12.08 mmol) with stirring at rt. Reaction was completed in 15 mins and the solution color changed from greenish to dark brown. The reaction mixture was extracted with ether (50 mL) and washed with water, ice cold HCl, NaHCO₃ and brine. The ether extract was dried over Na₂SO₄ and concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to obtain 3.12.8 as clear syrupy liquid (0.35 g, 1.06 mmol, 88%). \( R_f \) (30% EtOAc/Hexane) = 0.75; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 8.11 (s, 1H), 8.01 (d, \( J = 8.4 \) Hz, 1H), 7.34-7.52 (m, 6H), 7.12 (d, \( J = 7.6 \) Hz, 1H), 6.66 (d, \( J = 8.4 \) Hz, 1H), 5.20 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl₃) 154.9, 152.8, 136.8, 131.2, 129.4, 129.0 (2C), 128.5, 127.7 (2C), 127.3, 121.2, 115.4, 114.3, 106.1, 70.7. (Compound not very stable, never stored for long as napthol).
1-(benzyloxy)-4-bromo-5-(methoxymethoxy)naphthalene (3.12.9)

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5-(benzyloxy)-8-bromonaphthalen-1-ol 3.12.8 (47 mg, 0.142 mmol) was weighed out in a vial. Chloromethyl methyl ether (25 µL, 26.5 mg, 0.329 mmol) was dissolved in toluene (0.14 mL) in a separate vial and cooled to 5-10 °C. The solution was added to the naphthol at 5-10 °C with stirring. Diisopropylethylamine (30 µL, 23 mg, 0.178 mmol) was then added and the solution was stirred at room temperature for 24 hrs. The reaction mixture was diluted with EtOAc (5 mL) and to remove any residual chloromethyl ether sat. NH₄Cl solution (2 mL) was added and the reaction mixture was stirred for 5 mins. The organic layer was then washed with water (2 mL), brine (2 mL) and dried over Na₂SO₄. The product was purified by silica gel chromatography eluting with 4% EtOAc/Hexanes to obtain a pale wine colored liquid. Yield: 72% (2 steps). mp: 63-65 °C; \( R_f \) (10% EtOAc/Hexane) = 0.5; IR (neat) 1591.2, 1504.9, 1416.0, 1346.0, 1317.4, 1253.4, 1206.1, 1151.1, 1077.0, 1039.9, 1028.7 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl₃) δ 8.09 (d, \( J = 8.8 \) Hz, 1H), 7.66 (d, \( J = 8.0 \) Hz, 1H), 7.50 (d, \( J = 7.6 \) Hz, 2H), 7.32-7.46 (m, 4H), 7.23 (m, 1H), 6.71 (d, \( J = 8.4 \) Hz, 1H), 5.32 (s, 2H), 5.22 (s, 2H), 3.60 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl₃) δ 154.2, 153.1, 137.0, 132.8, 129.4, 129.0, 128.4, 127.7, 126.4, 124.9, 117.0, 112.9, 107.4, 106.7, 95.6, 70.7, 32.0. HRMS Calculated for [C₁₉H₁₇BrO₃] 372.0361, found 372.0369.
(2E,4E)-1-(4-(benzyloxy)-8-(methoxymethoxy)naphthalen-1-yl)hexa-2,4-dien-1-ol (3.13.1)

1-(benzyloxy)-4-bromo-5-(methoxymethoxy) naphthalene 3.12.9 (1g, 2.68 mmol) was dissolved in 4 mL THF and the solution was cooled to −78 °C. n-BuLi (2 mL 1.5 M in ether, 3 mmol) was added dropwise and stirred for 30 mins at −78 °C. Hexadienal (0.6 mL, 515 mg, 5.36 mmol) was then added dropwise and the reaction stirred at −78 °C for another 3 hrs. The reaction was allowed to warm to room temperature slowly and stirred until complete consumption of lithiated starting material is indicated by TLC. The mixture was again cooled to −78 °C, diluted with 10 mL DCM and quenched by adding 5 mL sat. NH₄Cl dropwise, with slow warming to 0 °C. The reaction mixture was then extracted with slightly cold DCM (20 mL, 3 times). The combined organic layers were dried over sodium sulfate, filtered and the filtrate concentrated under reduced pressure at room temperature. The compound was purified by flash column chromatography using neutralized silica gel and eluting with 30% Ether in Hexane to give the diene alcohol 3.13.1 (950 mg, 2.43 mmol, 91%) as an yellow oil. Rᵢ (40% Et₂O/Hexane) = 0.4; IR (neat) 3460, 2950, 2937, 2884, 1727, 1675, 1599, 1514, 1465, 1422, 1375, 1328, 1272, 1218 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (dd, J = 8.4, 1.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 3H), 7.32-7.45 (m, 4 H), 7.29 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1 H), 6.03-6.24 (m, 3H), 5.99 (dd, J = 15.6, 4.8 Hz, 1H), 5.64 (td, J = 13.6, 6.8 Hz 1H), 5.36 (s, 2H), 5.24
(s, 2H), 3.55 (s, 3H), 3.38 (bs, 1H), 1.73 (d, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.4, 153.8, 137.3, 134.2, 131.5, 131.4, 130.1, 129.5, 129.0, 128.8, 128.3, 127.7, 125.5, 124.8, 117.5, 111.5, 105.5, 96.1, 70.5, 57.0, 18.5.

\((2E,4E)-1-(4-(benzylxy)-8-(methoxymethoxy)naphthalen-1-yl)hexa-2,4-dien-1-one\) (3.13.2)

![Structure](image)

The allylic alcohol 3.13.1 (740 mg, 1.89 mmol) was dissolved in 7.5 mL dry DCM. MnO\(_2\) (2.47 g, 28.43 mmol) was added and stirred for 24 h at room temperature. MnO\(_2\) was filtered-off through celite, and the residue washed thoroughly with DCM. The combined filtrate was concentrated under reduced pressure and residue purified by flash column chromatography. The product eluted with 12% ethyl acetate in hexanes as yellow oil 3.13.2 (730 mg, 1.88 mmol, 99%) which solidified upon freezing. IR (neat) 1649.0, 1632.2, 1585.7, 1511.6, 1422.3, 1374.3, 1324.7, 1295.9, 1281.9, 1235.4, 1196.2, 1182.4, 1162.0, 1117.3, 1090.4, 1022.0 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.07 (dd, \(J = 8.4, 0.8\) Hz, 1H), 7.53 (d, \(J = 7.6\) Hz, 2H), 7.31-7.45 (m, 4 H), 7.16-7.23 (m, 2H), 6.90 (d, \(J = 8.0\) Hz, 1H), 6.68 (dd, \(J = 15.2, 10.8\) Hz, 1H), 6.40 (d, \(J = 15.6\) Hz, 1H), 6.21 (ddd, \(J = 14.8, 10.8, 1.2\) Hz, 1H), 5.96 (td, \(J = 13.6, 6.8\) Hz, 1H), 5.27 (s, 2H), 5.17 (s, 2H), 3.42 (s, 3H), 1.79 (d, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 199.3, 155.4, 152.7, 144.5, 139.7, 137.0, 131.0, 130.6, 129.8, 129.0, 128.4, 127.7, 127.4, 126.4, 125.7, 124.2, 116.3, 110.4, 105.0, 95.0, 70.6, 56.8, 19.1. HRMS Calculated for [C\(_{25}\)H\(_{24}\)O\(_4\)Na\(^+\)] 411.1567, found 411.1581
(4R,5R,E)-1-(4-(benzylxy)-8-(methoxymethoxy)naphthalen-1-yl)-4,5-dihydroxyhex-2-en-1-one (3.13.3)\(^g\)

![Chemical Structure](image)

In a flask was added 0.7 mL \(\tau\)-BuOH, 0.7 mL water, \(\text{K}_3[\text{Fe(CN)}_6]\) (168 mg, 0.51 mmol), \(\text{K}_2\text{CO}_3\) (71 mg, 0.51 mmol), \(\text{CH}_3\text{SO}_2\text{NH}_2\) (17 mg, 0.18 mmol), (DHQD)\(_2\)PHAL (6.2 mg, 8 \(\mu\)mol), OsO\(_4\) (1.5 mg, 6 \(\mu\)mol) and stirred at room temperature until clear. This solution was cooled to 0 °C and dienone (67 mg, 0.17 mmol) was added and stirred overnight at 0 °C. The reaction was quenched with solid sodium sulfite (20 mg) at room temperature. The reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvents were removed \textit{in vacuo} and flash chromatography on silica gel (80% EtOAc/Hexanes) afforded 31 mg (0.07 mmol, 43%) as a white solid. 24 mg starting material recovered (36%): \(R_f\) (70% EtOAc/Hexane) = 0.20. \(\text{mp: 115-125 °C; IR (neat) 3430.6, 3057.5, 2926.0, 1652.7, 1588.3, 1509.6, 1454.3, 1421.0, 1402.2, 1374.2, 1326.5, 1239.9, 1151.9, 1078.2, 1023.5 cm}^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.06 (d, \(J = 8.4\) Hz, 1H), 7.52 (d, \(J = 6.8\) Hz, 2H), 7.34-7.46 (m, 4 H), 7.24 (d, \(J = 7.6\) Hz, 1H), 7.13 (d, \(J = 7.6\) Hz, 1 H), 6.89 (d, \(J = 8.0\) Hz, 1H), 6.69 (dd, \(J = 16.0, 1.2\) Hz, 1H), 6.31 (dd, \(J = 16.0, 5.2\) Hz, 1H), 5.27 (s, 2H), 5.16 (s, 2H), 4.01 (bs, 1H), 3.58-3.68 (m, 1H), 3.46 (s, 3H), 2.57 (bs, 1H), 2.36

\(^g\) Mass data pending
(bs, 1H), 1.14 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 198.2, 155.8, 152.3, 144.5, 136.9, 133.4, 129.4, 129.0, 128.5, 127.7, 127.4, 126.6, 126.0, 124.1, 116.6, 110.6, 105.1, 95.4, 76.0, 70.6, 70.5, 57.1, 19.4. [α]$_D$$^{24}$ = 4.7 (c 0.14, CH$_2$Cl$_2$).

$(2R,3S,4S,5R)$-1-(4-(benzyloxy)-8-(methoxymethoxy)naphthalen-1-yl)-2,3,4,5-tetrahydroxyhexan-1-one (3.13.4)$^h$

In a flask was added 0.25 mL t-BuOH, 0.25 mL water, K$_3$[Fe(CN)$_6$] (49 mg, 0.15 mmol), K$_2$CO$_3$ (21 mg, 0.15 mmol), CH$_3$SO$_2$NH$_2$ (5 mg, 0.05 mmol), (DHQ)$_2$PHAL (8 mg, 10 µmol), OsO$_4$ (1.3 mg, 5 µmol) and stirred at room temperature until clear. This solution was cooled to 0 ºC and diol (21 mg, 0.05 mmol) was added and stirred overnight at 0 ºC. The reaction was warmed to room temperature and left running for a day at room temperature. The reaction was quenched with solid sodium sulfite (20 mg) at room temperature. The reaction mixture was filtered through celite, the celite was washed with EtOAc and then 50% EtOAc/MeOH. The combined organic layers were dried over anhydrous sodium sulphate. The solvents were removed in vacuo and flash chromatography on silica gel (90 % EtOAc/Hexane) afforded 10 mg (0.02 mmol, 40%) as a white solid, $R_f$ (70% EtOAc/Hexane) = 0.1. m.p. 134-141º C

IR (neat) ν 3308, 1699, 1590, 1511, 1376, 1328, 1233 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.08 (dd, $J = 8.4, 0.8$ Hz, 1H) 7.51 (d, $J = 7.2$ Hz, 2H), 7.33-7.47 (m, 4H), 7.21 (d, $J =

$^h$ Mass data pending
7.6 Hz, 1H), 6.91 (d, J = 8 Hz, 1H), 5.14-5.32 (m, 5H), 4.12 (m, 1H), 4.01 (bs, 1H), 3.68 (m, 1H), 3.49 (s, 3H), 1.14 (d, J = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 184.5, 156.3, 151.8, 137.0, 136.6, 128.9, 128.4, 127.7, 126.6, 125.9, 123.1, 119.2, 116.8, 111.0, 105.0, 95.8, 94.6, 75.7, 70.6, 67.1, 57.1, 19.9. [α]$_D$ ~33 (c 0.06, CH$_2$Cl$_2$).

5-Acetoxynaphthol 3.15.1

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\text{OH} \quad \text{OAc} \]

In pyridine (10 mL) 1,5-dihydroxynaphthalene 3.11.1 (2.0 g, 12.5 mmol) was dissolved and the solution was cooled to 0 °C. AcCl (1 mL, 1.08 g, 13.75 mmol) was added dropwise with stirring. Reaction was stirred for 1 h. A large amount of the starting material converted to the diacetylated product and a significant amount remained unreacted. The reaction mixture was extracted with EtOAc (75 mL) and the organic layer was washed with 1 N HCl (25 mL x 3). The organic layer was washed with brine (25 mL), dried over Na$_2$SO$_4$. The organic layer was then concentrated under reduced pressure. The product was purified by silica gel chromatography, eluting at 12% EtOAc/hexanes. The monoacetylated product 3.14.1 was obtained as a white solid (230 mg, 1.1 mmol, 9%, minor product); m.p: 159 °C; R$_f$ (20% EtOAc/Hexane) = 0.22; IR (neat) 1730.2, 1600.7, 1577.5, 1519.2, 1405.2, 1358.6, 1273.4, 1232.7, 1216.1, 1131.7, 1061.9, 1012.2 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.99 (d, J = 7.6 Hz, 1H), 7.34-7.42 (m, 2 H), 6.61 (d, J = 7.2 Hz, 1H), 5.89 (s, 1H), 2.46 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.6, 152.0, 146.6, 128.2, 126.9, 126.1, 124.7, 120.5, 118.8, 113.5, 109.5, 21.3. HRMS Calculated for [C$_{12}$H$_{10}$O$_3$] 202.0630, found 202.0626.
2-Bromo-5-acetoxy-2-naphthol 3.15.2

In a long reaction tube, 5-Acetoxy-2-naphthol 3.14.1 (75 mg, 0.37 mmol) was dissolved in 1.06 mL dry dichloromethane. N-Bromosuccinimide (63.4 mg, 0.36 mmol) was added and the reaction tube was sealed and the contents were allowed to reflux for 18 h (some starting material remained unreacted). The reaction mixture was cooled to room temperature and quenched by adding 1 mL 2 N H2SO4 and extracted with dichloromethane (1 mL x 3). The combined organic layers were washed with water (1 ml), brine (1 mL), then dried over Na2SO4 before concentrating under reduced pressure. The product was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to obtain 3.14.2 as brown oil (64 mg, 0.23 mmol, 61%). Rf (20% EtOAc/Hexane) = 0.42; IR (neat) 3459.6, 1750.8, 1741.7, 1407.5, 1373.4, 1275.3, 1235.2, 1211.1, 1161.9, 1121.6 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, J = 8.8 Hz, 1H), 7.47-7.51 (m, 2 H), 7.33 (d, J = 9.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1 H), 6.03 (s, 1H), 2.45 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.6, 148.6, 146.7, 129.2, 127.4, 126.1, 125.9, 120.7, 119.4, 114.9, 105.1, 21.2. HRMS Calculated for [C₁₂H₁₀BrO₃⁺] 280.9808, found 280.9820.
in a reaction tube fitted with a screw-cap, 2-Bromo-5-acetoxy-1-benzyloxynaphthol (64 mg, 0.23 mmol) was dissolved in 1.15 mL acetone, K$_2$CO$_3$ (47 mg, 0.34 mmol) was added to the reaction mixture and stirred at room temperature for 15 mins. Then benzyl bromide (0.085 mL, 117 mg, 0.68 mmol) was added and the reaction mixture heated to reflux in the sealed tube for 1 hr. Acetone was evaporated off. Reaction mixture was extracted with EtOAc, washed with water, brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 3% EtOAc/hexanes to obtain white crystalline solid (70 mg, 0.19 mmol, 83%), m.p. 83 °C; $R_f$ (20% EtOAc/Hexane) = 0.58; IR (thin film cm$^{-1}$) 1757.9, 1582.6, 1408.6, 1355.8, 1296.2, 1211.3, 1198.2, 1161.2, 1124.8, 1085.3, 1059.9, 1008.1. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.04 (d, $J$ = 8.0 Hz, 1H), 7.58-7.68 (m, 3 H), 7.57 (d, $J$ = 9.6 Hz, 1H), 7.36-7.54 (m, 4 H), 7.30 (d, $J$ = 7.6 Hz, 1H), 5.14 (s, 2H), 2.47 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.7, 152.5, 147.2, 137.0, 131.1, 129.0, 128.7, 128.6, 127.7, 126.9, 120.7, 119.3, 119.2, 114.4, 76.2, 21.4. HRMS Calculated for [C$_{19}$H$_{15}$BrO$_3$Na$^+$] 393.0097, found 393.0085.
5-(benzyloxy)-8-bromonaphthalene-1, 4-dione 3.16.1

(Diacetoxyiodo)benzene (0.87 g, 2.7 mmol) was dissolved in 4 mL MeCN/water (2:1).
5-(benzyloxy)-8-bromonaphthalen-1-ol 3.12.8 (0.40 g, 1.215 mmol) was dissolved in 8 mL MeCN/water (2:1) and added dropwise to the (Diacetoxyiodo)benzene solution at 0 °C with stirring. Reaction was quenched after 1 hr 30 mins by adding NaHCO₃. The reaction mixture was extracted with EtOAc. The EtOAc extract was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The product was purified by silica gel chromatography eluting with 12% EtOAc/hexanes to obtain 3.15.2 as yellow solid (0.28g, 0.82 mmol, 67%). mp: 120 °C; Rₚ (20% EtOAc/Hexane) = 0.45; IR (neat) 1654.9, 1554.0, 1438.3, 1319.6, 1282.3, 1242.9, 1139.5, 1108.6, 1026.7 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, J = 9.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.42 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 10.4 Hz, 1H), 5.29 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 184.3, 183.7, 158.6, 158.0, 142.0, 139.3, 137.7, 135.9, 129.1, 128.5, 127.1, 120.7, 113.2, 78.8, 71.6, 64.7; HRMS Calculated for [C₁₇H₁₁BrO₃Na⁺] 364.9784, Found 364.9757.
8-(benzyloxy)-5-bromo-4-methoxynaphthalen-1-ol 3.16.2

Quinone 3.15.2 (34 mg, 0.1 mmol) and nBu₄NBr (8 mg, 0.025 mmol) was taken up in THF (0.25 mL) and vacuum degassed. Na₂S₂O₄ dissolved in degassed water (1.25 mL) was added under N₂ and stirred for 30 min. 50% KOH in water (0.28 mL) was degassed and added to reaction mixture and stirred for 30 mins. MeI (10 µL, 0.15 mmol) was added and stirred for 2 h. Reaction was extracted in ether and washed with dilute HCl. Organic layer was dried over Na₂SO₄ and concentrated and purified by eluting through silica gel with 15% EtOAc/Hexane to give 3.15.3 (10 mg, 0.028 mmol, 28%); R<sub>f</sub> (15% EtOAc/Hexane) = 0.35. Significant amount of quinone 3.15.2 recovered, which resulted from oxidation of unmethylated quinol.

<sup>1</sup>H NMR (400 MHz, CDCl₃) δ 9.352 (s, 1H), 7.624 (d, J = 8 Hz, 1H), 7.38-7.54 (m, 5H), 6.965 (d, J = 8 Hz, 1H), 6.822 (d, J = 8 Hz, 1H), 6.712 (d, J = 8.4 Hz, 1H), 5.242 (s, 3H), 3.874 (s, 3H).

5-(benzyloxy)-8-bromo-4-hydroxynaphthalen-1-yl acetate 3.16.3

Quinone 3.15.2 (14 mg, 0.04 mmol) was dissolved in CHCl₃ (0.2 mL) in a tube and zinc dust (5 mg), pyridine (12 µL) and acetic anhydride (12 µL) was added at room

<sup>1</sup> Not completely characterized
temperature. The tube was sealed, vacuum degassed and flushed with N\textsubscript{2} and the reaction mixture was gently boiled at 40 °C with stirring under N\textsubscript{2} for 30 mins. Disappearance of yellow color of naphthaquinone indicated consumption of starting material. The reaction mixture was diluted with DCM (5 mL) and filtered into water (2 mL). The organic layer was washed with dil. HCl (2 mL), brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated to give

**3.15.4** (12 mg, 0.31, 77%); \( R_f \) (20% EtOAc/Hexane) = 0.35. IR (thin film cm\textsuperscript{-1}) 3344.4, 1754.0, 1601.4, 1579.3, 1542.3, 1426.1, 1406.1, 1331.0, 1280.1, 1197.6, 1113.4, 1065.2, 1006.1. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.273 (s, 1H), 7.35-7.6 (m, 5H), 7.269 (d, \( J = 8.8 \) Hz, 1H), 7.021 (d, \( J = 8.8 \) Hz, 1H), 6.843 (d, \( J = 8.8 \) Hz, 1H), 6.678 (d, \( J = 8.8 \) Hz, 1H), 5.247 (s, 2H), 1.552 (s, 3H).
References


