Synthesis and Evaluation of DPA Analogs as Substrates for Arabinofuranosyltransferases

by

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Abstract

Mycobacteria have a complex and robust cell wall that is important for its survival. Two major components of the cell wall are arabinogalactan (AG) and lipoarabinomannan (LAM). Both AG and LAM contain an arabinan domain, which is composed of arabinofuranose (Ara*f*) residues. Decaprenylphosphoryl-β-D-arabinofuranose (DPA) serves as the only Ara*f* donor and is used by mycobacteria to assemble the arabinan domain. This process is catalyzed by a group of enzymes termed arabinofuranosyltransferases (AraTs), which have been identified as potential drug targets. To investigate the biosynthetic pathway of the arabinan, scientists have used chemical methods to synthesize DPA and analogs, including (*Z*,*Z*)-farnesylphosphoryl-β-D-arabinofuranose (FPA), which is a known substrate for AraTs.

In this thesis, the first investigation focuses on synthesizing six derivatives of FPA, in which different hydroxyl groups are replaced with either a fluorine atom or an azido group. The synthesis of these target molecules was achieved from their corresponding thioglycoside building blocks, which were converted into glycosyl bromides before being phosphorylated. Deprotection of the glycosyl phosphates, followed by the coupling with (*Z*,*Z*)-farnesol and the final deprotection afforded the target compounds. The second investigation centers on the evaluation of these DPA analogs as substrates for AraTs using an *in vitro* cell-free assay. Although the six target molecules have not been tested, I describe the evaluation of the known compound FPA as a substrate for AraTs.

Preface

The work described in this thesis was done solely by me and has not been published.

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Table of Contents

List of Figures

List of Schemes

List of Abbreviations

$[\alpha]_D$	specific rotation (sodium D line)
Å	angstrom(s)
Ac	acetyl
AcOH	acetic acid
AG	arabinogalactan
All	allyl
AMP	adenosine monophosphate
APPI	atmospheric pressure photoionization
aq	aqueous
Ar	aromatic
Ara4	tetraarabinofuranoside
Ara6	hexaarabinofuranoside
Ara*f*	arabinofuranose
AraT	arabinofuranosyltransferase
ATP	adenosine triphosphate
BF_3•OEt_2	boron trifluoride etherate
Bn	benzyl
br	broad (NMR spectra)
BTZ	benzothiazinone
Bz	benzoyl
ºC	degrees Celsius
calcd	calculated

COSY	correlation spectroscopy
d	day(s); doublet (NMR spectra)
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	diethylaminosulfur trifluoride
DAT	diacyltrehalose
deg	degree(s)
DIPEA	*N*,*N*-diisopropylethylamine
dm	decimeter(s)
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNB	dinitrobenzamide
DP	decaprenyl phosphate
DPA	decaprenylphosphoryl-β-D-arabinofuranose
DPPR	decaprenylphosphoryl-β-D-5-phosphoribofuranose
DPR	decaprenylphosphoryl-β-D-ribofuranose
DprE1	decaprenylphosphoryl-β-D-ribofuranose oxidase
DprE2	decaprenylphosphoryl-2-keto-β-D-*erythro*-pentofuranose reductase
DPX	decaprenylphosphoryl-2-keto-β-D-*erythro*-pentofuranose
DTBS	di-*tert*-butylsilylene
EMB	ethambutol
ESI	electrospray ionization
Et	ethyl

Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FPA	(*Z*,*Z*)-farnesylphosphoryl-β-D-arabinofuranose
g	gram(s)
g	gravitational force equivalent
G6P	glucose-6-phosphate
Gal*f*	galactofuranose
gem	geminal
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
i-Pr	*iso*-propyl
LAM	lipoarabinomannan
LC	liquid chromatography
LM	lipomannan
M	molar
m	multiplet (NMR spectra)
M. smegmatis	*Mycobacterium smegmatis*
M. tuberculosis	*Mycobacterium tuberculosis*
m/*z*	mass-to-charge ratio

mAG	mycolyl–arabinogalactan
MALDI	matrix-assisted laser desorption ionization
ManLAM	mannosylated lipoarabinomannan
Man*p*	mannopyranose
MDR	multidrug-resistant
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mM	millimolar
mmol	millimole(s)
mol	mole(s)
MOPS	3-(*N*-morpholino)propanesulfonic acid
MPI	mannosylated phosphatidyl-*myo*-inositol
MS	mass spectrometry
MTX	5-deoxy-5-methylthio-xylofuranose
$NADP^+$	nicotinamide adenine dinucleotide phosphate
nm	nanometer(s)
NMR	nuclear magnetic resonance
p-TsOH	*p*-toluenesulfonic acid
PAT	polyacyltrehalose

PBTZ	piperazine-containing benzothiazinone
$Pd(OH)_2/C$	palladium hydroxide on carbon
Pd/C	palladium on carbon
PDIM	phthiocerol dimycocerosate
Ph	phenyl
P_i	inorganic phosphate
PI	phosphatidyl-*myo*-inositol
PIM	phosphatidyl-*myo*-inositol mannoside
PP_i	inorganic pyrophosphate
ppm	parts per million
pRpp	phospho-α-D-ribofuranosyl-1-pyrophosphate
PrsA	phospho-α-D-ribofuranosyl-1-pyrophosphate synthetase
R5P	ribose-5-phosphate
R_f	retention factor
rpm	revolutions per minute
rt	room temperature
s	singlet (NMR spectra)
SAX	strong anion exchanger
SGL	sulfoglycolipid
S_N2	bimolecular nucleophilic substitution
t-Bu	*tert*-butyl
TB	tuberculosis
TBAF	tetrabutylammonium fluoride

TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TDM	trehalose dimycolate
Tf	trifluoromethanesulfonyl
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMM	trehalose monomycolate
TMS	trimethylsilyl
TOF	time-of-flight
Tol	*p*-tolyl
Tr	triphenylmethyl (trityl)
Ts	*p*-toluenesulfonyl (tosyl)
UbiA	decaprenylphosphoryl-β-D-5-phosphoribofuranosyltransferase
UV	ultraviolet
v/v	volume per unit volume (volume-to-volume ratio)
XDR	extensively drug-resistant
µL	microliter(s)
µm	micrometer(s)

Chapter 1: Introduction

1.1 The Mycobacterial Cell Wall

Many microorganisms, such as bacteria, viruses, parasites or fungi, are pathogens that cause infectious diseases, and many of these diseases can be transmitted from human to human.[1] *Mycobacterium tuberculosis*, the most successful pathogen in the world,[2] is the causative agent of tuberculosis (TB). In 2019, there were an estimated 10 million new cases, and 1.4 million people died from TB.[3] This makes TB one of the top ten causes of death worldwide.[3] The current treatment relies on a six-month regimen of four front-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide (**Figure 1.1**).[3] However, drug-resistant TB, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), remains a public health threat and the treatment for drug-resistant TB is longer and sometimes unmanageable.[3]

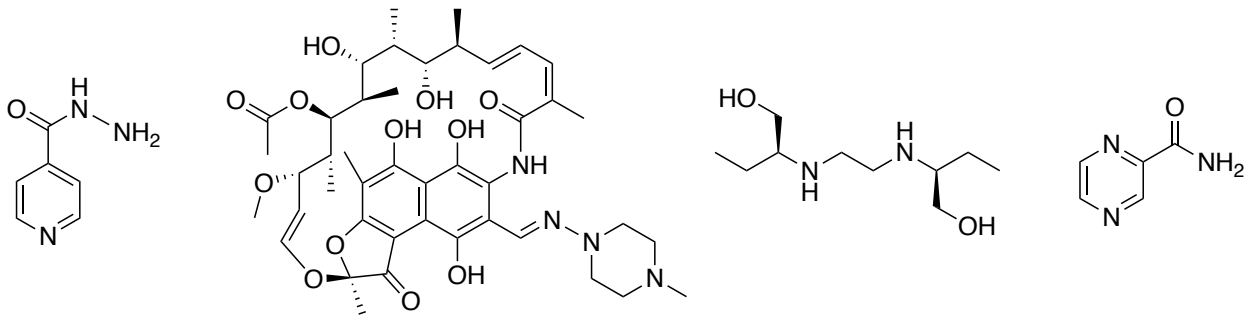


Figure 1.1 Chemical structures of the four front-line anti-TB drugs.

Mycobacteria have a robust and highly complex cell wall that plays a vital role in their survival, and this structure is a well-recognized drug target.[4–8] For example, the biosynthesis of two components on the cell surface, mycolic acids and the arabinan, is inhibited by isoniazid and ethambutol, respectively.[4–7] Many other antibiotics can also kill *M. tuberculosis* by blocking cell

wall synthesis.[4,7] Therefore, to discover and develop new anti-TB drugs, it is essential to understand the structure and biosynthesis of the mycobacterial cell wall.

The predominant structural features of the cell wall are peptidoglycan, arabinogalactan (AG), phosphatidyl-*myo*-inositol mannosides (PIMs), lipomannan (LM), lipoarabinomannan (LAM) and mycolic acids (**Figure 1.2**).[4–9] A series of extractable glycolipids with acyl chains can be found in the inner and outer membranes of the cell envelope, including trehalose monomycolates (TMMs), trehalose dimycolates (TDMs), phthiocerol dimycocerosates (PDIMs), diacyltrehaloses (DATs), polyacyltrehaloses (PATs) and sulfoglycolipids (SGLs).[4,5,7,9]

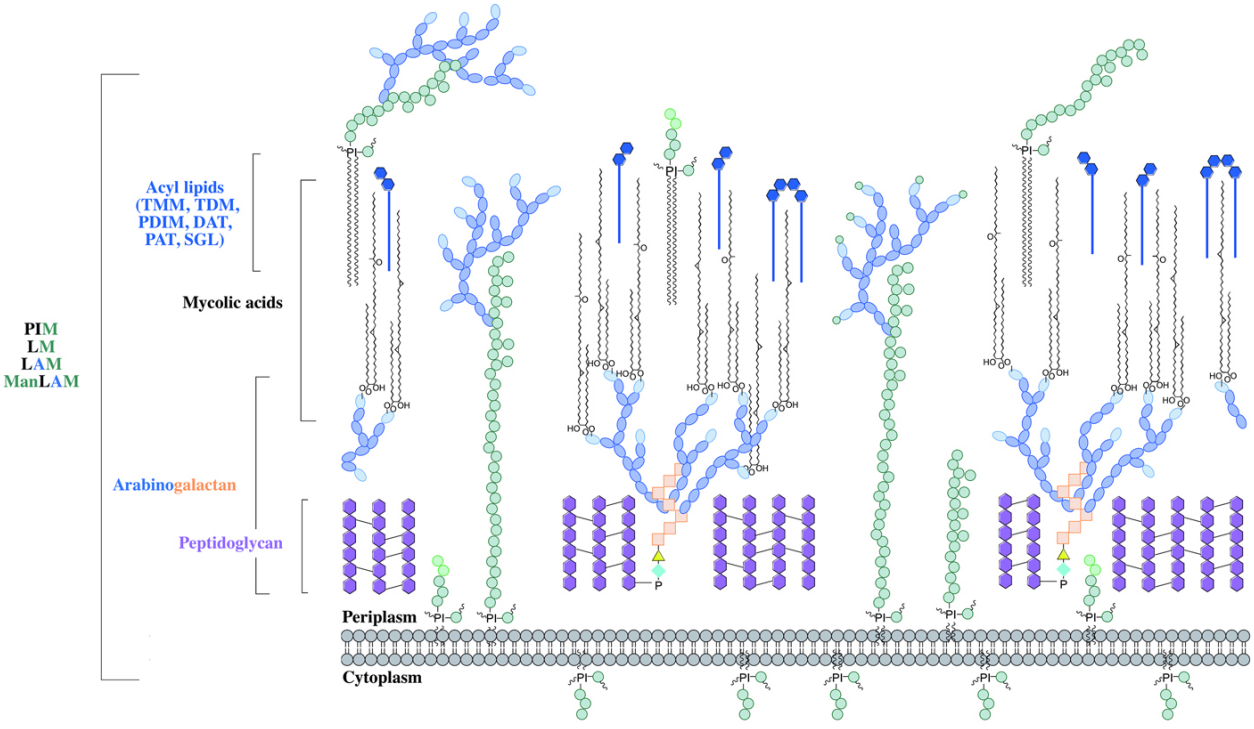
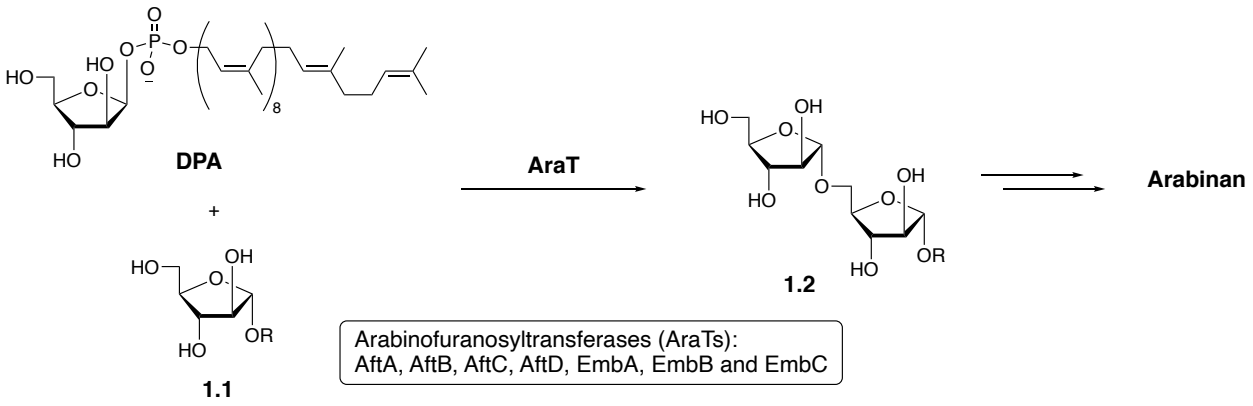


Figure 1.2 The mycobacterial cell wall. PIM, phosphatidyl-*myo*-inositol mannoside; LM, lipomannan; LAM, lipoarabinomannan; ManLAM, mannosylated lipoarabinomannan; TMM, trehalose monomycolate; TDM, trehalose dimycolate; PDIM, phthiocerol dimycocerosate; DAT, diacyltrehalose; PAT, polyacyltrehalose; SGL, sulfoglycolipid. Reproduced with permission from Abrahams, K. A.; Besra, G. S. *Parasitology* **2018**, *145*, 116–133. Copyright Cambridge University Press 2016.

Two major structures of the mycobacterial cell wall, AG and LAM, contain an arabinan domain, which is composed exclusively of a unique sugar residue in the five-membered ring form: arabinofuranose (Ara*f*).[4–9] The arabinan is assembled by seven arabinofuranosyltransferases (AraTs) that use decaprenylphosphoryl-β-D-arabinofuranose, or DPA, as the Ara*f* donor (**Scheme 1.1**).[4,5,7,8,10–13] Three of the AraTs can be inhibited by ethambutol (EMB), and thus they are called Emb proteins: EmbA, EmbB and EmbC.[4–8,11,12] The other four AraTs are Aft enzymes (AftA, AftB, AftC and AftD), which are not inhibited by ethambutol.[4–8,11,12] In the following section, I will discuss the chemical structure and biosynthesis of AG and LAM.



Scheme 1.1 Prototypical AraT-catalyzed reaction.[13] DPA, decaprenylphosphoryl-β-D-arabinofuranose.

1.1.1 Arabinogalactan (AG)

AG has two domains (the arabinan and galactan domains), which are composed of Ara*f* and galactofuranose (Gal*f*) residues (**Figure 1.3**).[4,5,9] Attached to peptidoglycan via a disaccharide linker unit containing L-rhamnose and *N*-acetylglucosamine, the galactan is a linear chain of 23–35 alternating β-(1→5)- and β-(1→6)-linked Gal*f* residues.[5,9] The arabinan domain has two highly branched arabinan chains made of approximately 26 Ara*f* residues each,[5] which are connected to

the galactan chain through α-(1→5) linkages.[7,9] The internal region of the arabinan domain consists of α-(1→5)-linked Ara*f* units with some branching sites introduced by 3,5-linked Ara*f* residues.[5,7,9] Mycolic acids can be found at the non-reducing termini of the arabinan chains forming the mycolyl–arabinogalactan (mAG) complex.[4,5,7–9] Furthermore, galactosamine residues can be present on O-2 of the internal 3,5-linked Ara*f* units in the mAG.[5] For non-mycolylated AG, succinate groups are attached to O-2 of the internal Ara*f* residues.[5]

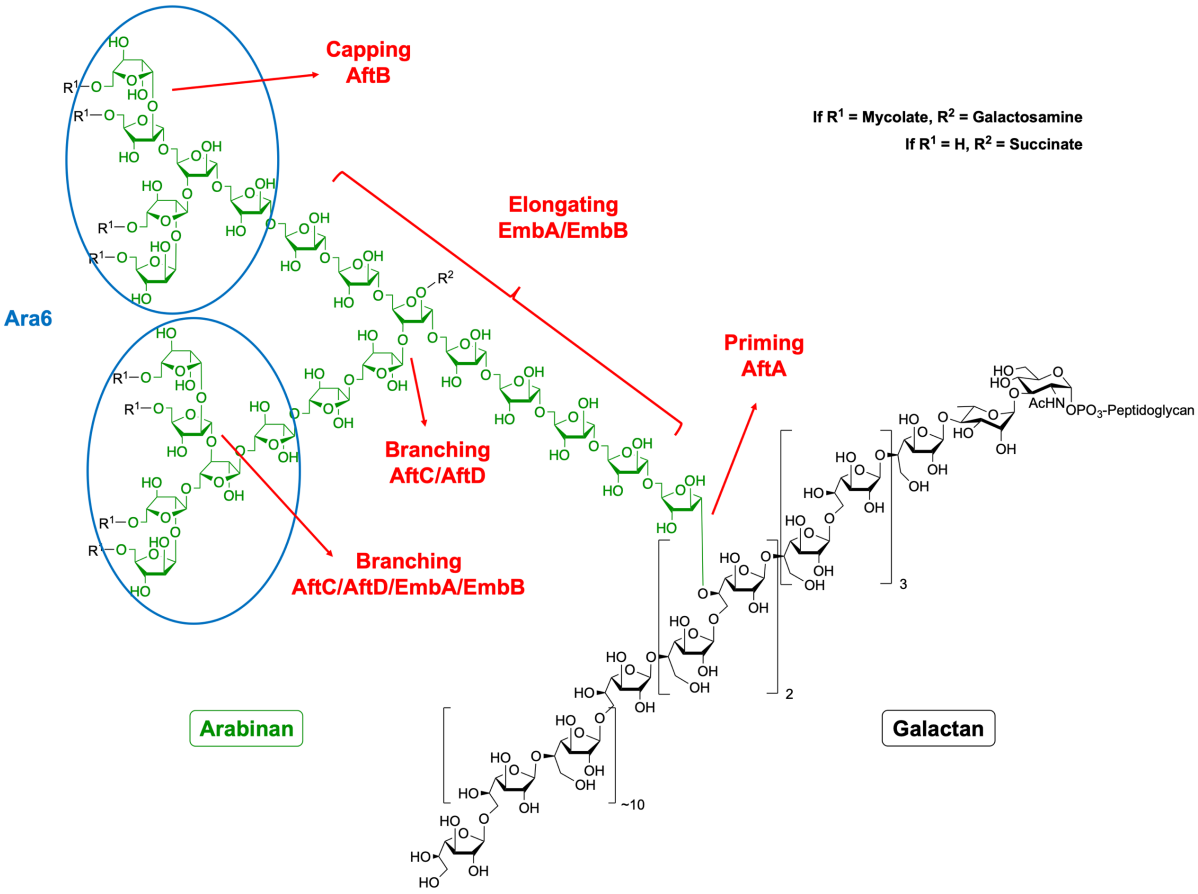


Figure 1.3 Structure of mycobacterial AG.[9] The AraTs involved in the biosynthesis of the arabinan domain are shown in red. Ara6, hexaarabinofuranoside.

The enzymes involved in the biosynthesis of the AG arabinan domain are included in **Figure 1.3**. AftA is a priming AraT that starts the addition by transferring the very first Ara*f* from DPA onto the galactan chain.[4,5,7,8,11,12] EmbA and EmbB are responsible for the following α-(1→5) glycosylation of Ara*f* residues; AftC and AftD perform α-(1→3) Ara*f* branching.[4,5,7,8,11,12] AftB is a capping AraT that adds the terminal β-(1→2) Ara*f* residues.[4,5,7,8,11,12] Additionally, a structurally well-defined hexaarabinofuranoside (Ara6) motif, which can be found at the non-reducing terminus of AG, is constructed by EmbA, EmbB, AftC, AftD and AftB.[4,5,7–9,12] The function of these enzymes have largely been determined by making knock-out mutants and then characterizing the effect on the arabinan structure. Detailed biochemical characterization of these AraTs is, in general, lacking. However, crystal structures of EmbA, EmbB, EmbC and AftD have been reported recently,[14–16] which have provided new insights into the function and specificity of these enzymes.

1.1.2 Lipoarabinomannan (LAM)

LAM is a lipoglycan that has both arabinan and mannan domains, which contain Ara*f* and mannopyranose (Man*p*) residues, respectively (**Figure 1.4**).[4–9,17] The reducing end of the mannan domain is linked to O-6 of a phosphatidyl-*myo*-inositol (PI) unit, which is glycosylated with a single Man*p* residue at the O-2 position and with an acyl chain at the O-3 position.[4–8,17] These units are collectively referred to as the mannosylated phosphatidyl-*myo*-inositol (MPI) anchor, which is non-covalently attached to the inner and outer membranes of the cell envelope.[4,5]

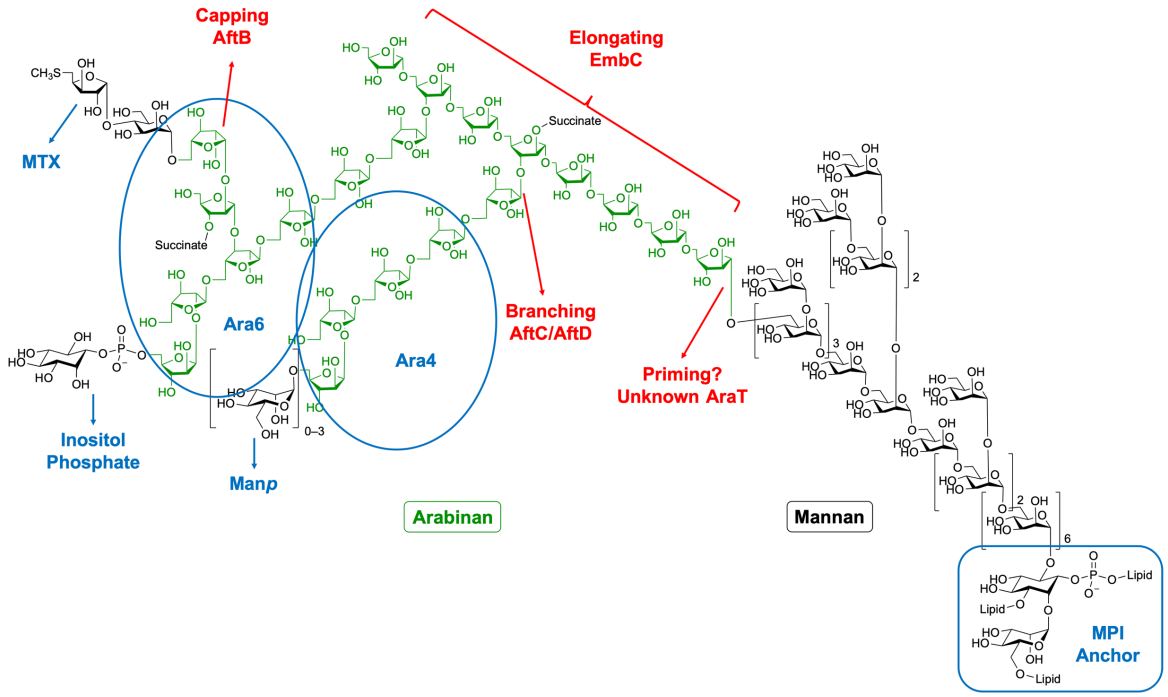


Figure 1.4 Structure of mycobacterial LAM.[9] The AraTs involved in the biosynthesis of the arabinan domain are shown in red. Ara4, tetraarabinofuranoside; Ara6, hexaarabinofuranoside; MTX, 5-deoxy-5-methylthio-xylofuranose; Man*p*, mannopyranose; MPI, mannosylated phosphatidyl-*myo*-inositol.

The mannan backbone is composed of 20–25 α-(1→6)-linked Man*p* units.[4–9,17] Attached to the MPI anchor, the first 5–7 Man*p* residues at the reducing end of the mannan domain are unbranched; nevertheless, the other residues are frequently branched with α-(1→2)-linked Man*p* units.[4–9,17] Recently, Jackson and co-workers demonstrated the possible presence of a secondary mannan side chain with five Man*p* residues, which is attached to the primary mannan backbone through an α-(1→2) linkage.[17] Furthermore, they also revised the understanding in both the regio- and stereochemistry of the linkage between the arabinan and mannan domains. It was believed that the LAM arabinan was connected to the internal mannan region via an α-(1→2) linkage.[4,5]

However, their findings suggested that this arabinan is attached to the non-reducing end of the mannan domain through an α-(1→6) linkage.[17] In contrast to AG, which has two arabinan chains, LAM has only one arabinan chain composed of approximately 50–80 Ara*f* residues.[4,5]

In addition to the Ara6 motif, a linear tetraarabinofuranoside (Ara4) can also be found at the termini of LAM.[5–8] In slow-growing mycobacterial species, *e.g.*, *M. tuberculosis*, the non-reducing arabinan termini are capped with one to three α-(1→2)-linked Man*p* units, yielding mannosylated lipoarabinomannan (ManLAM).[4–9,11,17] In comparison, the LAM termini of the fast-growing mycobacteria can either be capped with inositol phosphates as in *M. smegmatis* or not carry any capping motifs.[5–7] Moreover, the unusual 5-deoxy-5-methylthio-xylofuranose (MTX) residues are linked α-(1→4) to some of the Man*p* caps.[4–7,11,17] The succinate groups are found on O-2 of the internal 3,5-linked Ara*f* residues and on O-3 of the terminal 2-linked Ara*f* units.[5,17]

There are at least four AraTs that participate in the biosynthesis of the LAM arabinan domain.[4–8,11,18] An unknown AraT transfers the first Ara*f* onto the non-reducing end of the mannan backbone.[4,5,11,17,18] Subsequently, EmbC elongates the arabinan chain by adding α-(1→5)-Ara*f* residues.[4–8,11,18] AftC and AftD operate in the same manner as in AG biosynthesis and are responsible for branching by introducing α-(1→3)-linked Ara*f* units.[4–6,8,11,18] AftB terminates the biosynthesis of the arabinan domain by installing β-(1→2)-Ara*f* residues.[4,5,8,11,18] Finally, the Ara4 and Ara6 motifs in LAM are constructed by AftB, AftC, AftD and EmbC.[4] As is the case for AG, the biochemical characterization of these enzymes with regard to LAM arabinan biosynthesis remains quite poorly investigated.

1.2 Decaprenylphosphoryl-β-D-arabinofuranose (DPA)

DPA is a phosphodiester that contains three components: an Ara*f* residue, a phosphate and a lipid (**Scheme 1.1**).[10] The anomeric carbon of the Ara*f* is connected to the lipid phosphate via a 1,2-*cis*-β linkage; the lipid is a decaprenyl moiety, which has ten isoprene units.[10] Mycobacteria use DPA as the only Ara*f* donor to build the arabinan domains in their cell wall.[10–12] DPA reacts with a glycosyl acceptor (*e.g.*, **1.1**) under the catalysis of an AraT to generate the product **1.2**, which will undergo further glycosylation steps in the same way to form the longer and branched arabinan chains.[13] During this process, the lipid phosphate acts as a leaving group for glycosylation to take place. The corresponding α-anomer of DPA, decaprenylphosphoryl-α-D-arabinofuranose (**Figure 1.5**), was shown to be inactive with AraTs.[19]

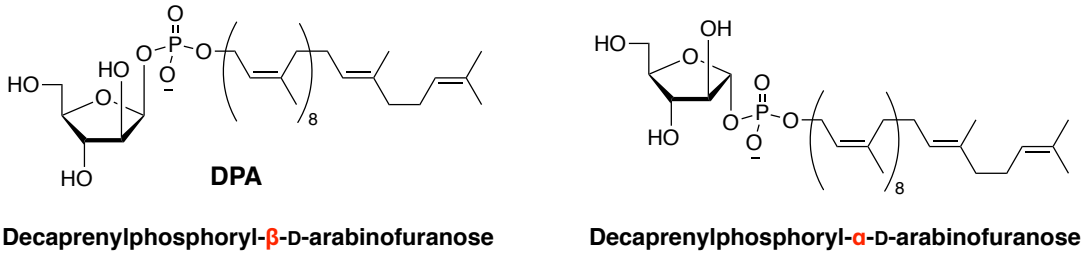
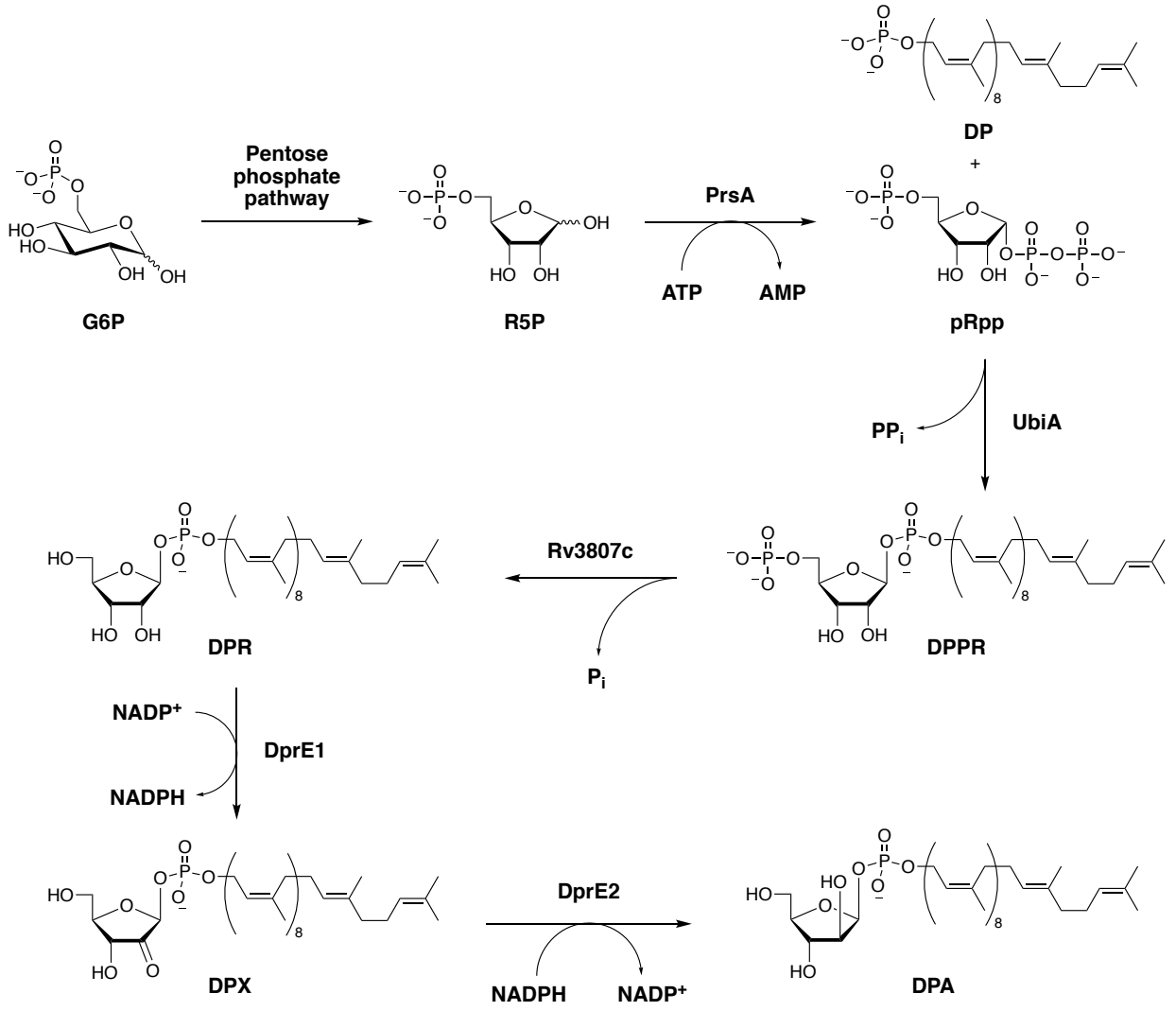


Figure 1.5 Structures of DPA and decaprenylphosphoryl-α-D-arabinofuranose.

1.2.1 Biosynthesis of DPA

DPA biosynthesis begins in the cytosol starting from phospho-α-D-ribofuranosyl-1-pyrophosphate (pRpp), an essential and high-energy biosynthetic precursor (**Scheme 1.2**).[4,7,20,21] PrsA (phospho-α-D-ribofuranosyl-1-pyrophosphate synthetase) catalyzes the formation of pRpp and AMP by transferring pyrophosphate from ATP to the C-1 position of ribose-5-phosphate (R5P), which is generated from glucose-6-phosphate (G6P) through the pentose phosphate

pathway.[4,21] The addition of decaprenyl phosphate (DP) to pRpp is catalyzed by UbiA (decaprenylphosphoryl-β-D-5-phosphoribofuranosyltransferase, or DPPR synthase) giving decaprenylphosphoryl-β-D-5-phosphoribofuranose (DPPR) and pyrophosphate (PP_i).[4,7,20,21] After transfer to the extracellular space, the C-5 position of DPPR is subjected to dephosphorylation by a putative phosphatase (encoded by Rv3807c) affording decaprenylphosphoryl-β-D-ribofuranose (DPR).[4,7,21] Finally, the C-2 position of DPR is oxidized by DprE1 (decaprenylphosphoryl-β-D-ribofuranose oxidase) to obtain decaprenylphosphoryl-2-keto-β-D-*erythro*-pentofuranose (DPX), which is then reduced by DprE2 (decaprenylphosphoryl-2-keto-β-D-*erythro*-pentofuranose reductase) to yield DPA.[4,5,7,21]



Scheme 1.2 Biosynthesis of DPA.[21] G6P, glucose-6-phosphate; R5P, ribose-5-phosphate; PrsA, phospho-α-D-ribofuranosyl-1-pyrophosphate synthetase; ATP, adenosine triphosphate; AMP, adenosine monophosphate; DP, decaprenyl phosphate; pRpp, phospho-α-D-ribofuranosyl-1-pyrophosphate; UbiA, decaprenylphosphoryl-β-D-5-phosphoribofuranosyltransferase; PP_i, inorganic pyrophosphate; DPPR, decaprenylphosphoryl-β-D-5-phosphoribofuranose; P_i, inorganic phosphate; DPR, decaprenylphosphoryl-β-D-ribofuranose; DprE1, decaprenyl-phosphoryl-β-D-ribofuranose oxidase; $NADP^+$, nicotinamide adenine dinucleotide phosphate; DPX, decaprenylphosphoryl-2-keto-β-D-*erythro*-pentofuranose; DprE2, decaprenylphosphoryl-2-keto-β-D-*erythro*-pentofuranose reductase; DPA, decaprenylphosphoryl-β-D-arabinofuranose.

The DPA biosynthetic pathway is recognized as a drug target. Benzothiazinones (BTZs) are a class of antitubercular agents that kill *M. tuberculosis* by inhibiting the function of DprE1.[22] One of the most potent inhibitors in this series, BTZ043 (**Figure 1.6**), has a minimum inhibitory concentration (MIC) of 1 ng/mL against *M. tuberculosis* H37Rv and is effective against MDR and XDR strains of *M. tuberculosis* with low toxicity.[22] Furthermore, a new group of BTZ compounds, the piperazine-containing benzothiazinones (PBTZs), are also inhibitors of DprE1.[23] PBTZ169, which has an MIC of 0.3 ng/mL against *M. tuberculosis* H37Rv, is the most attractive drug candidates in this family to treat TB.[23] In addition, the dinitrobenzamide (DNB) derivatives, such as DNB1, can block DprE1 and have shown potency against *M. tuberculosis*, including XDR strains.[24] To identify other potential targets in the DPA synthetic pathway, conditional knock-down mutants of *dprE1*, *dprE2*, *ubiA*, *prsA* and *rv3807c* were generated, which confirmed that *rv3807c* is not required, but all of other genes are essential for survival.[25] Moreover, BTZ043 and KRT2029 are effective inhibitors of DprE1 and UbiA, respectively.[25]

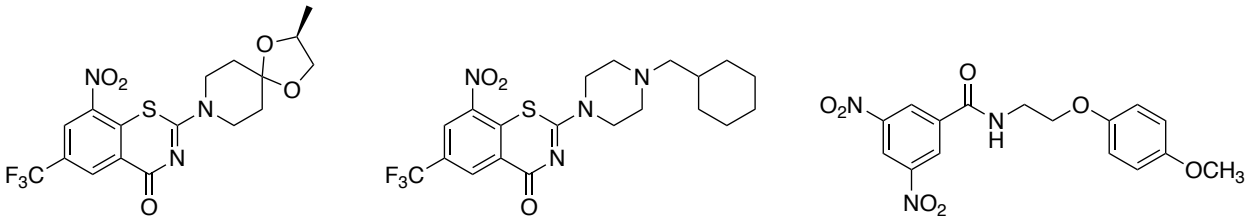
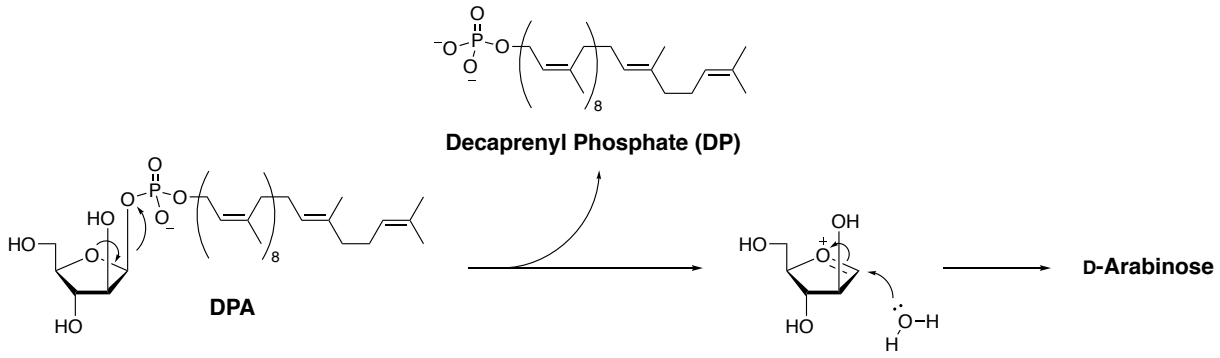


Figure 1.6 Chemical structures of BTZ043, PBTZ169 and DNB1.[22–24]

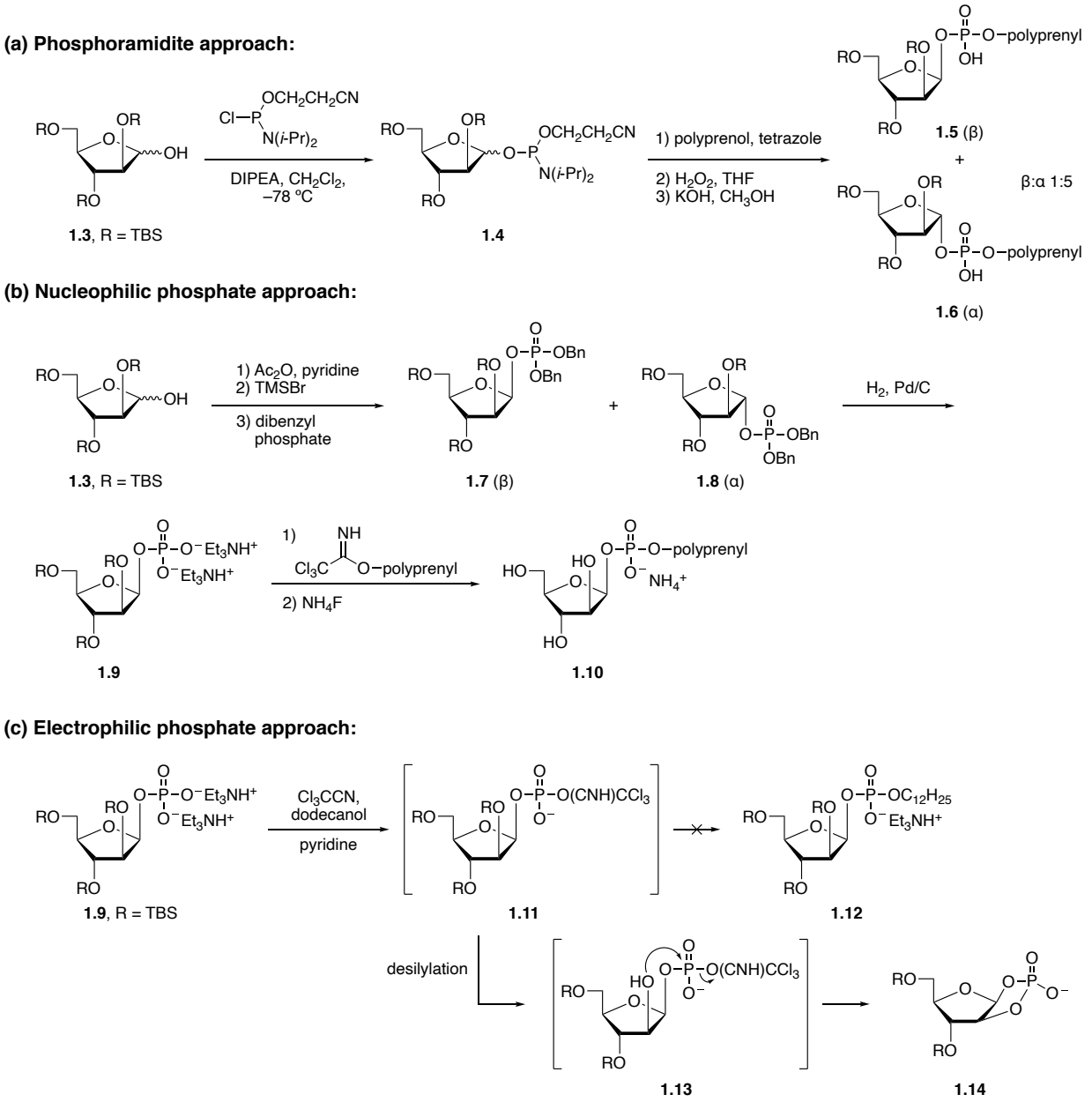
1.2.2 Chemical Synthesis of DPA

There are several challenges to synthesize DPA chemically. First, DPA is very labile.[19] The lipid phosphate of DPA serves as a good leaving group. When water is present, DPA can be hydrolyzed into D-arabinose (**Scheme 1.3**). Secondly, there is a 1,2-*cis*-β linkage, which is one of the most challenging linkages to synthesize in glycosylation reactions, between an Ara*f* residue and the lipid phosphate. It is difficult to install the phosphoryl group at the C-1 position of the sugar with high β-selectivity. Finally, the coupling reaction of the sugar phosphate and the lipid moiety (*i.e.*, the formation of the phosphodiester) is also problematic, which usually leads to a poor yield.



Scheme 1.3 Hydrolysis of DPA.

There have been three methods to chemically synthesize DPA and its analogs.[26] The first approach (**Scheme 1.4a**), published by Lee and co-workers, relies on converting a reducing sugar, the *tert*-butyldimethylsilyl (TBS)-protected Ara*f* **1.3**, to a phosphoramidite (**1.4**), which is then linked to a polyprenol before being oxidized to the phosphate (**1.5** and **1.6**).[19,27] However, a disadvantage of this method is that the phosphodiester anomers are generated as a mixture in which the desired β-anomer (**1.5**) is the minor product (β:α 1:5).[27]



Scheme 1.4 Chemical synthetic approaches to DPA and analogs.[12,26–30]

In the second approach (**Scheme 1.4b**), reported by Liav and Brennan, the anomeric phosphates (**1.7** and **1.8**) are synthesized, and the β-anomer (**1.7**) predominates by a 4:1 (β:α) ratio.[28] After the removal of the benzyl groups on **1.7**, monophosphate salt **1.9** is formed, which behaves as a nucleophile in the following coupling reaction with a polyprenyl trichloroacetimidate

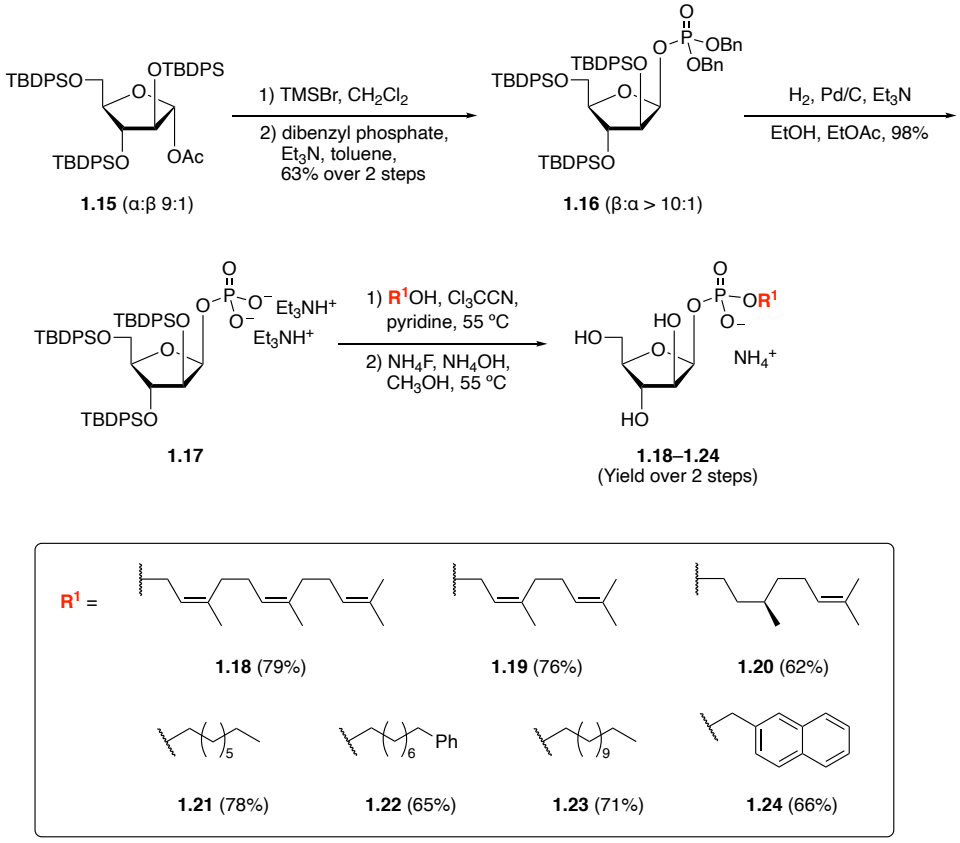
intermediate.[12,28–30] Although this method produces the β-anomer (**1.7**) as the major product, it takes one additional step to synthesize the lipid-linked trichloroacetimidate derivative from the lipid moiety.[12,28–31]

The third approach (**Scheme 1.4c**), developed by Kiessling and co-workers, relies on using a coupling agent, trichloroacetonitrile, to join alcohols with phosphoryl groups to afford phosphodiesters.[26] When this method was applied to **1.9** and dodecanol, they found **1.9** to be very unstable due to the lability of the TBS groups.[26] They assumed the electrophilic iminophosphate intermediate **1.11** was produced, but it was not attacked by dodecanol to generate the desired product **1.12**.[26] Instead, the unwanted cleavage of the TBS group on O-2 in **1.11** gave the desilylated intermediate **1.13**, and the following intramolecular cyclization yielded the undesired cyclic phosphate **1.14**.[26]

This issue may be solved by changing the protecting groups; however, silyl groups still provide a good functional group tolerance and can be easily, and chemoselectively, removed.[26] For instance, benzyl groups could be used, but the conditions to remove them are not tolerated by unsaturated lipids. Furthermore, the use of ester protecting groups will lead to unwanted neighboring-group participation in the glycosylation step, which precludes the production of the β-phosphate.

To circumvent the formation of the cyclic phosphate, the more robust *tert*-butyldiphenylsilyl (TBDPS) protecting group was used.[26] The arabinofuranosyl acetate **1.15** was converted into the corresponding glycosyl bromide, which underwent nucleophilic attack by dibenzyl phosphate to generate the sugar phosphate **1.16** (**Scheme 1.5**).[26] It is notable that the desired β-anomer (**1.16**) was synthesized with high stereoselectivity (β:α > 10:1).[26] Subsequent hydrogenolysis gave the monophosphate salt **1.17**.[26] Finally, applying the electrophilic phosphate

approach to **1.17**, a variety of DPA analogs (**1.18–1.24**) were generated in good yields.[26] This strategy not only offered high β-selectivity in the phosphorylation step but also provided an efficient way to couple the phosphate salt with different types (both saturated and unsaturated) of lipid alcohols.[26]



Scheme 1.5 Synthesis of DPA analogs **1.18**–**1.24** by the electrophilic phosphate approach.[26]

1.3 Statement of Research Purpose

To investigate the biosynthetic pathway of the arabinan domains of AG and LAM, an *in vitro* cell-free assay[11,12,18] is commonly used to monitor the AraT-catalyzed reactions. This assay requires glycosyl donors (DPA or its analogs), acceptors (oligosaccharides), enzymes (AraTs) and

effective ways (*e.g.*, LC–MS[11,18] or MALDI–MS[12] techniques) to probe the reactions. To obtain enough quantity of the donors, the use of organic synthesis is inevitable because DPA is sparingly isolated from mycobacteria.[10,12] Moreover, as detailed above, DPA is difficult to synthesize and is very labile; thus, it is often an arduous task to study these enzymatic reactions.

Previously, Joe and Lowary completed the synthesis of 2-deoxy-2-fluoro-DPA (**1.25**, **Figure 1.7**) and analogs (**1.26–1.28**),[31] and found these molecules to be more stable than DPA. This stability can be attributed to the inductive effect of the fluorine atom. The presence of a strong electron-withdrawing group (*e.g.*, F or N_3) on the sugar phosphate (**1.29**, **Scheme 1.6**) can destabilize the corresponding oxocarbenium ion **1.30**. In other words, the formation of **1.30** from **1.29** is disfavored, and the anomeric C–O bond is therefore stabilized.

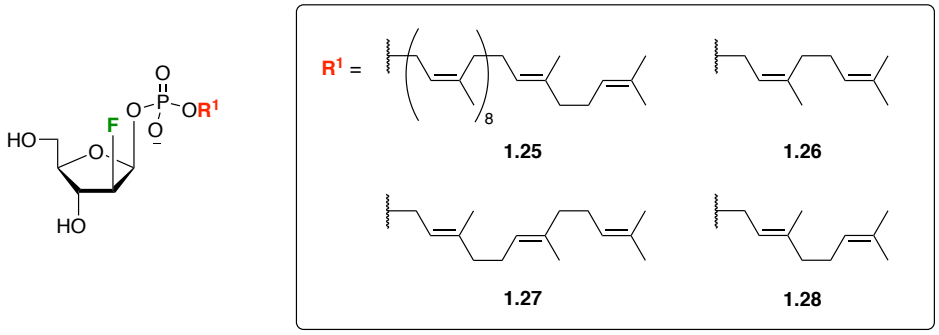
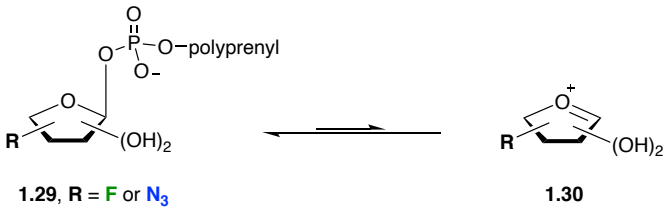


Figure 1.7 Structures of 2-deoxy-2-fluoro-DPA (**1.25**) and analogs (**1.26–1.28**).[31]



Scheme 1.6 Equilibrium between a fluorine- or azide-containing sugar phosphate (**1.29**) and the corresponding oxocarbenium ion (**1.30**).

As a first goal, my project focuses on synthesizing six DPA analogs (**1.31**–**1.36**, **Figure 1.8**), in which different hydroxyl groups are replaced with either a fluorine atom or an azido group. Given that (*Z*,*Z*)-farnesylphosphoryl-β-D-arabinofuranose (FPA, **1.18**) is a known substrate for AftC[12] and other AraTs,[32] we choose to install (*Z*,*Z*)-farnesol, which can be synthesized from nerol in seven steps (**Scheme 1.7**).[33] This was done as this lipid moiety is more accessible than decaprenol and the water solubility of the resulting products higher, which facilitates purification and handling in the assays.

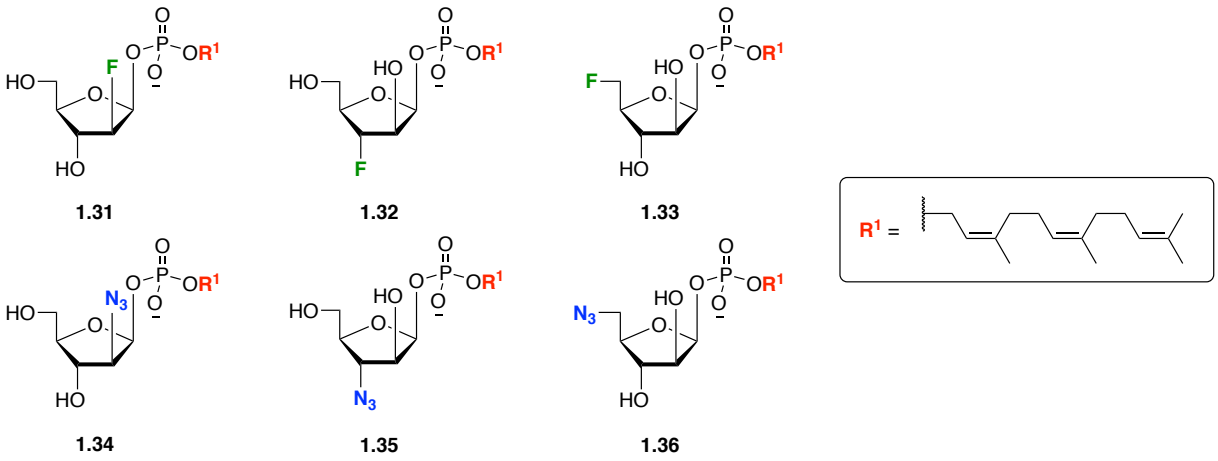
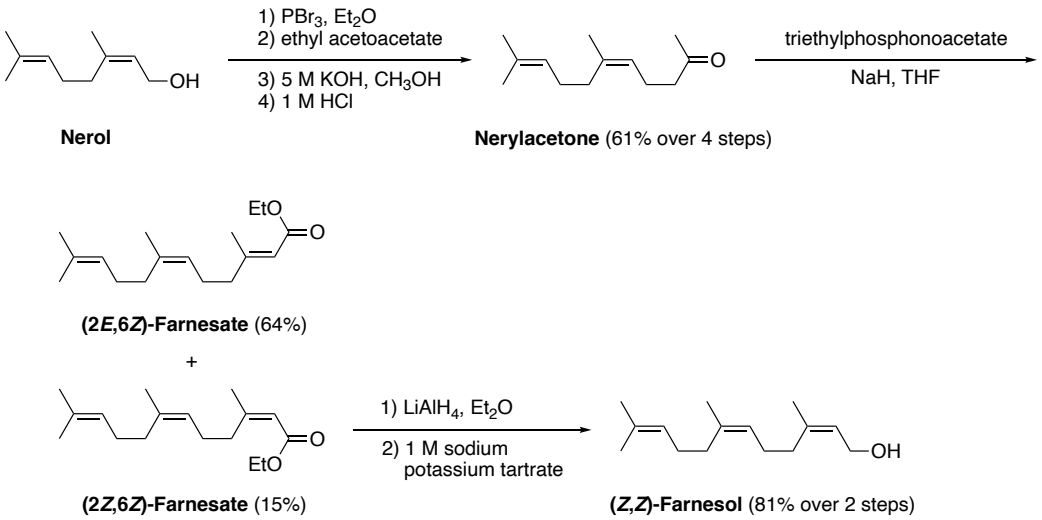
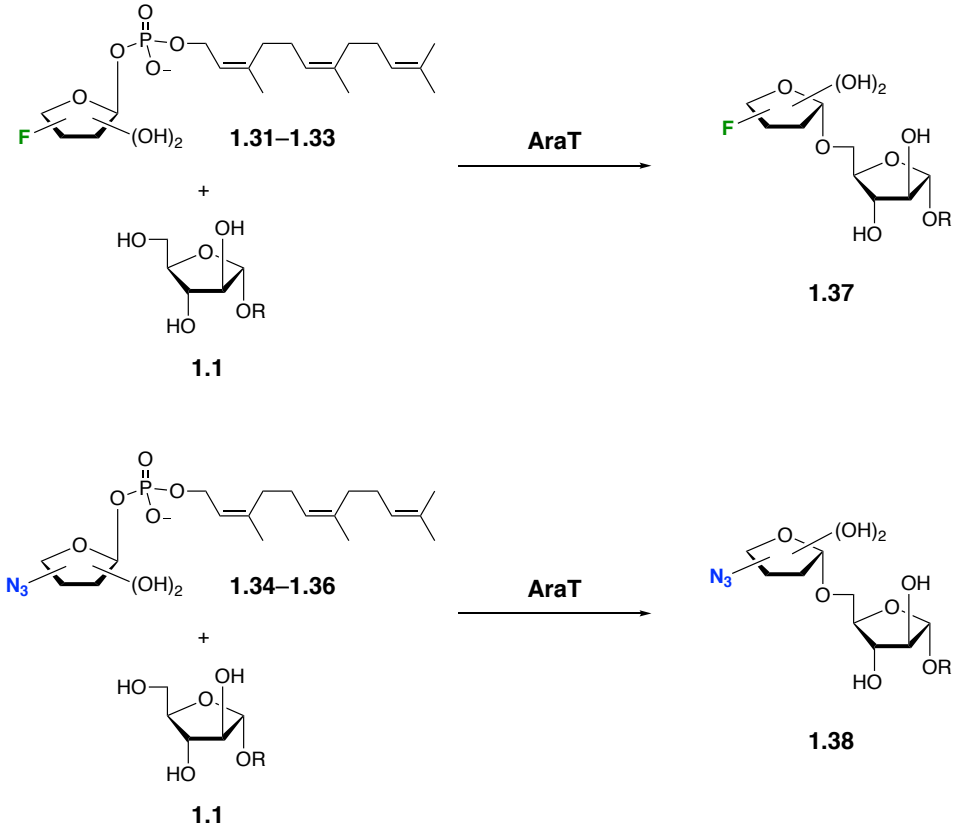


Figure 1.8 Structures of six target DPA analogs **1.31**–**1.36**.



Scheme 1.7 Synthesis of (*Z*,*Z*)-farnesol from nerol.[33]

The second goal is to evaluate whether DPA analogs **1.31**–**1.36** can be accepted as substrates by AraTs. To do this, I will conduct *in vitro* studies using the above-mentioned cell-free AraT assay. If the fluoro-FPA derivatives **1.31**–**1.33** are substrates for these glycosyltransferases, both the enzymatic reactions and products (*e.g.*, **1.37**, **Scheme 1.8**) generated by the assay can be monitored via ^{19}F NMR spectroscopy. In addition, the azido derivatives of FPA **1.34**–**1.36** can be used to incorporate azide-containing Ara*f* residues into their enzymatic products (*e.g.*, **1.38**), which will serve as potential click probes[34,35] of the AraT-catalyzed reactions.



Scheme 1.8 Evaluation of the fluoro- and azido-FPA derivatives **1.31**–**1.36** using the AraT assay.

1.4 References

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Chapter 2: Synthesis and Attempted Evaluation of DPA Analogs as Substrates for Arabinofuranosyltransferases

2.1 Background

To elucidate the biosynthetic pathway of the mycobacterial arabinan, six analogs (**1.31**–**1.36**, **Figure 2.1**) of the Ara*f* donor, DPA, were designed as tools to investigate AraT-catalyzed reactions. An established cell-free assay[1,2] will be carried out to see if these target molecules can be accepted as substrates by the AraTs. To perform control experiments, the known substrate, FPA (**1.18**),[2,3] was also synthesized. In this chapter, I describe the retrosynthetic analysis and chemical synthesis of these compounds.

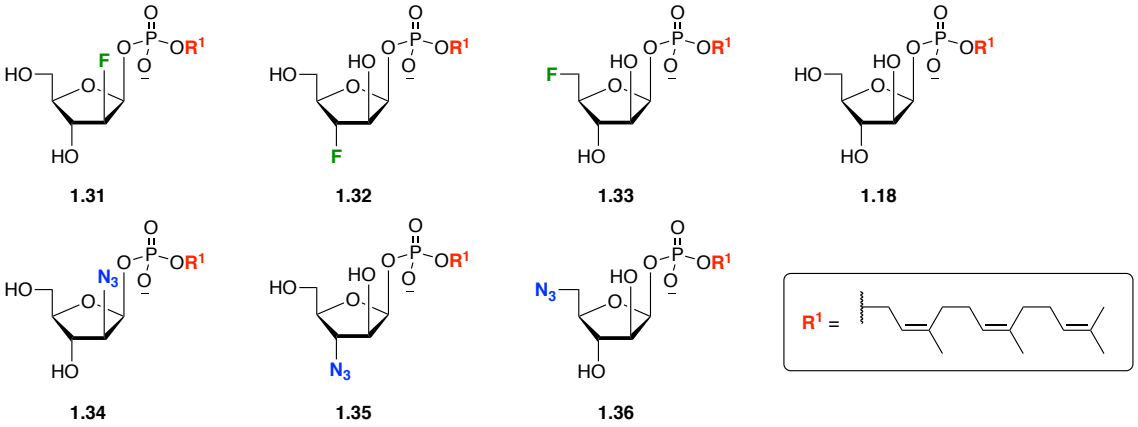
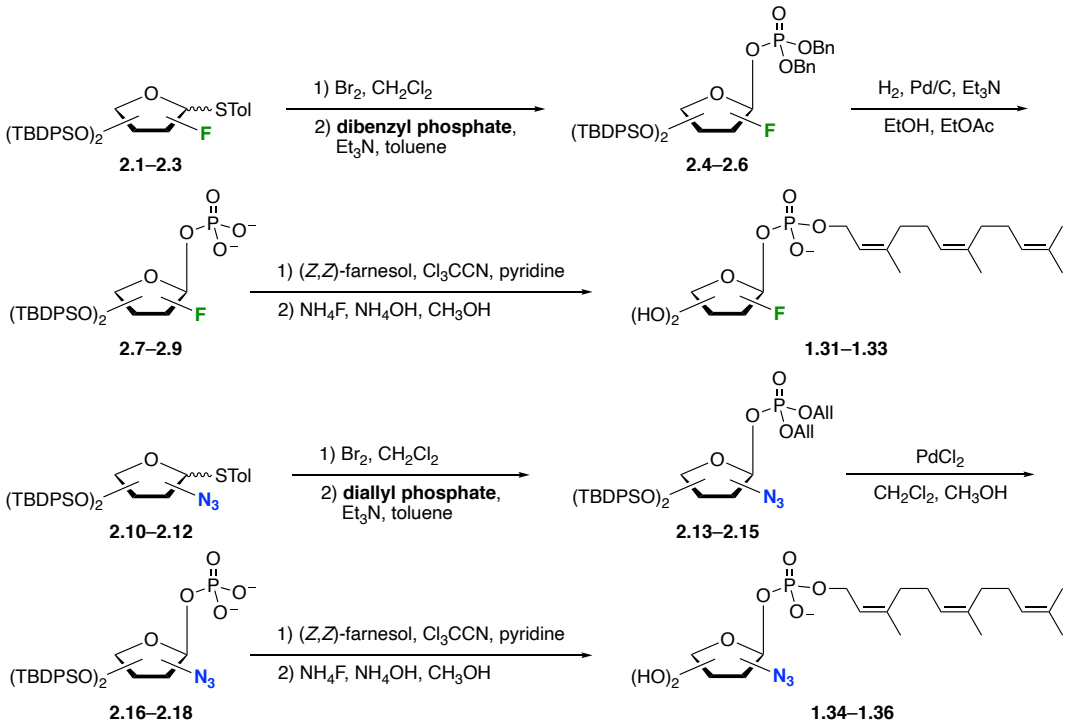


Figure 2.1 Structures of target molecules **1.31**–**1.36** and FPA **1.18**.

As discussed in Chapter 1, there are three chemical methods (**Scheme 1.4**) to synthesize DPA and analogs.[4] The electrophilic phosphate approach (**Scheme 1.5**) using a TBDPS-protected sugar provides excellent β-selectivity in the phosphorylation step and offers an efficient method to couple the monophosphate salt and lipid alcohols with good yields.[4] Thus, I decided to apply this approach to the synthesis of target compounds.

2.1.1 Synthetic Plan for Target Molecules 1.31–1.36

To synthesize the fluoro derivatives of FPA **1.31**–**1.33**, fluorine-containing thioglycosides with TBDPS protecting groups (**2.1**–**2.3**, **Scheme 2.1**) were targeted as the important building blocks. The conversion of **2.1**–**2.3** into their corresponding glycosyl bromide intermediates prior to the reaction with dibenzyl phosphate would generate arabinofuranosyl phosphates **2.4**–**2.6**. Subsequent hydrogenolysis could give monophosphate salts **2.7**–**2.9**, which were used to afford the target compounds **1.31**–**1.33** by the coupling reaction with (*Z*,*Z*)-farnesol,[5] followed by the removal of TBDPS groups.



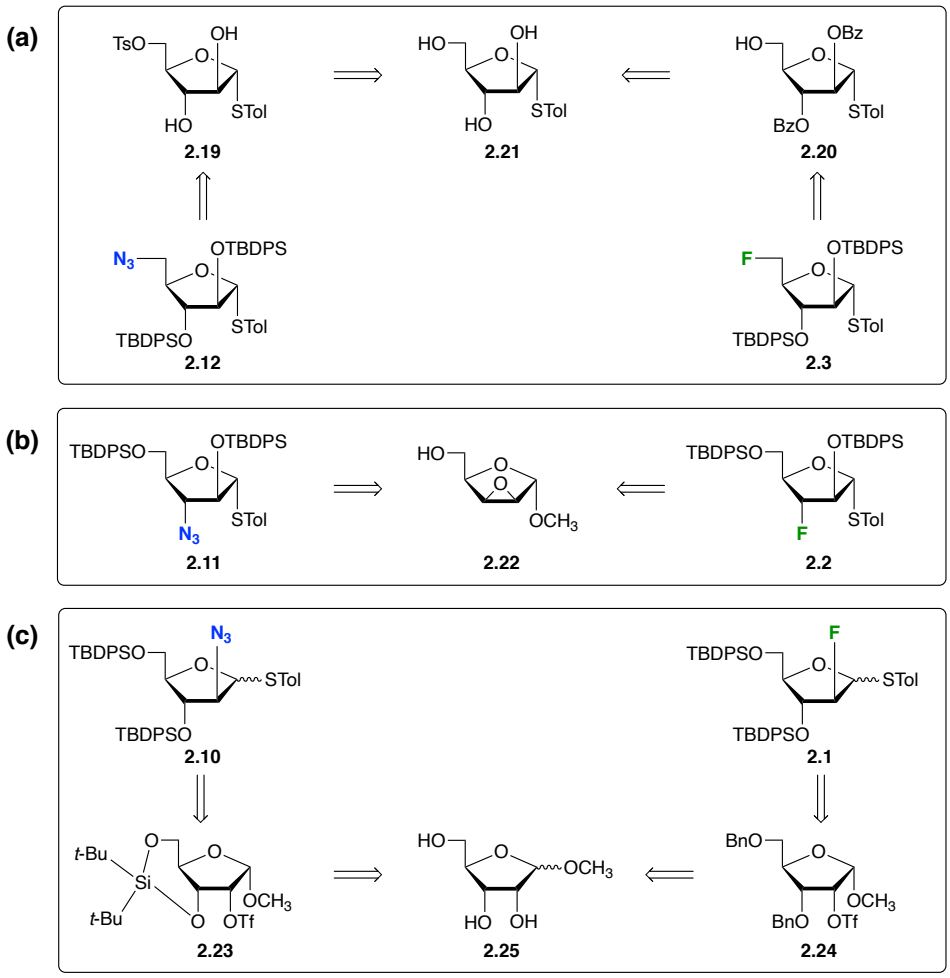
Scheme 2.1 Synthetic plan for the target compounds **1.31**–**1.36**.

The synthesis of azido-FPA derivatives **1.34**–**1.36** could be accomplished via a similar approach (**Scheme 2.1**). Instead of installing dibenzyl phosphate on the sugar, diallyl phosphate[6]

would be used to yield glycosyl phosphates **2.13**–**2.15**. The allyl groups could be removed by the catalysis of palladium(II) chloride[7] to give phosphate salts **2.16**–**2.18**, which were converted into azide-containing FPA **1.34**–**1.36** using the same electrophilic phosphate method as in the synthesis of fluoro-FPA derivatives.

2.1.2 Retrosynthetic Analysis of Thioglycosides 2.1–2.3 and 2.10–2.12

We hypothesized that the key step to synthesize 5-azido-thioglycoside **2.12** (**Scheme 2.2a**) could be replacing the tosyl group in thioglycoside **2.19**[8] with an azido group via a nucleophilic displacement reaction. The synthesis of 5-fluoro-thioglycoside **2.3** could include the conversion of the C-5 hydroxyl group in thioglycoside **2.20**[8] into a fluorine atom. Both **2.19** and **2.20** could be prepared from the known thioglycoside **2.21**.[9] The strategy used to access the C-3-modified glycosides **2.11** and **2.2** (**Scheme 2.2b**) could involve the introduction of an azido group[10] or a fluorine atom[11] via nucleophilic ring opening reactions, in which methyl 2,3-anhydro-α-D-lyxofuranoside (**2.22**)[12] served as an important precursor. The C-2-midofied sugars, 2-azido- and 2-fluoro-arabinofuranosides (**2.10** and **2.1**, **Scheme 2.2c**), could be synthesized from the triflate-containing ribofuranosides **2.23** and **2.24**,[13] respectively, via S_N2 reactions. The synthesis of both **2.23** and **2.24** could be attained from methyl D-ribofuranoside (**2.25**).[14]



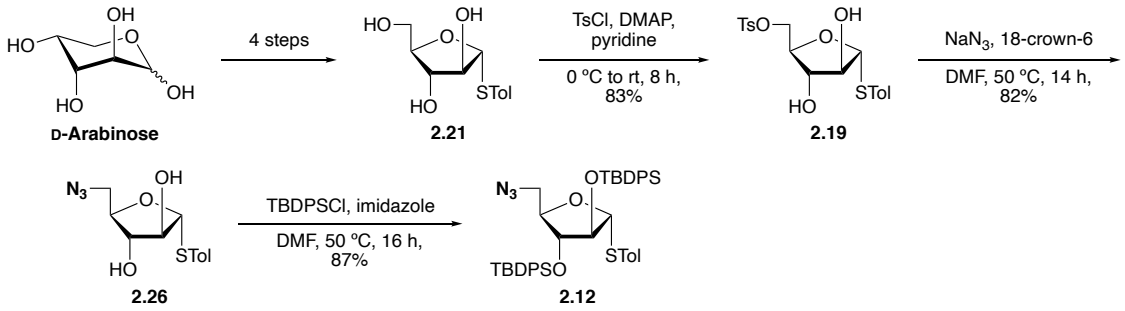
Scheme 2.2 Retrosynthetic analysis of thioglycosides **2.1**–**2.3** and **2.10**–**2.12**.

2.2 Results and Discussion

2.2.1 Synthesis of 5-Azido- and 5-Fluoro-Thioglycosides (2.12 and 2.3)

The synthesis of 5-azido-sugar **2.12** (**Scheme 2.3**) began with D-arabinose, which was used to prepare thioglycoside **2.21** in four steps via a known method.[9] Selective tosylation of the C-5 hydroxyl group in **2.21** gave tosylate **2.19** in 83% yield.[8] The displacement reaction with sodium azide[8] in DMF at 50 ºC afforded 5-azido-arabinofuranoside **2.26** in 82% yield. In the ^{13}C NMR spectrum for **2.26**, the resonance for C-5 appeared at 51.9 ppm, which was consistent with that for

a primary alkyl azide. Additionally, both H-5a and H-5b in **2.26** appeared as doublet of doublets at 3.64 and 3.54 ppm, respectively, which were considerably upfield in comparison with the resonances (4.25–4.23 ppm) of these hydrogens in the starting material **2.19**[8] (**Figure 2.2**). The protection of **2.26** with TBDPS groups in DMF at 50 ºC provided **2.12** in 87% yield.



Scheme 2.3 Synthesis of 5-azido-thioglycoside **2.12**.

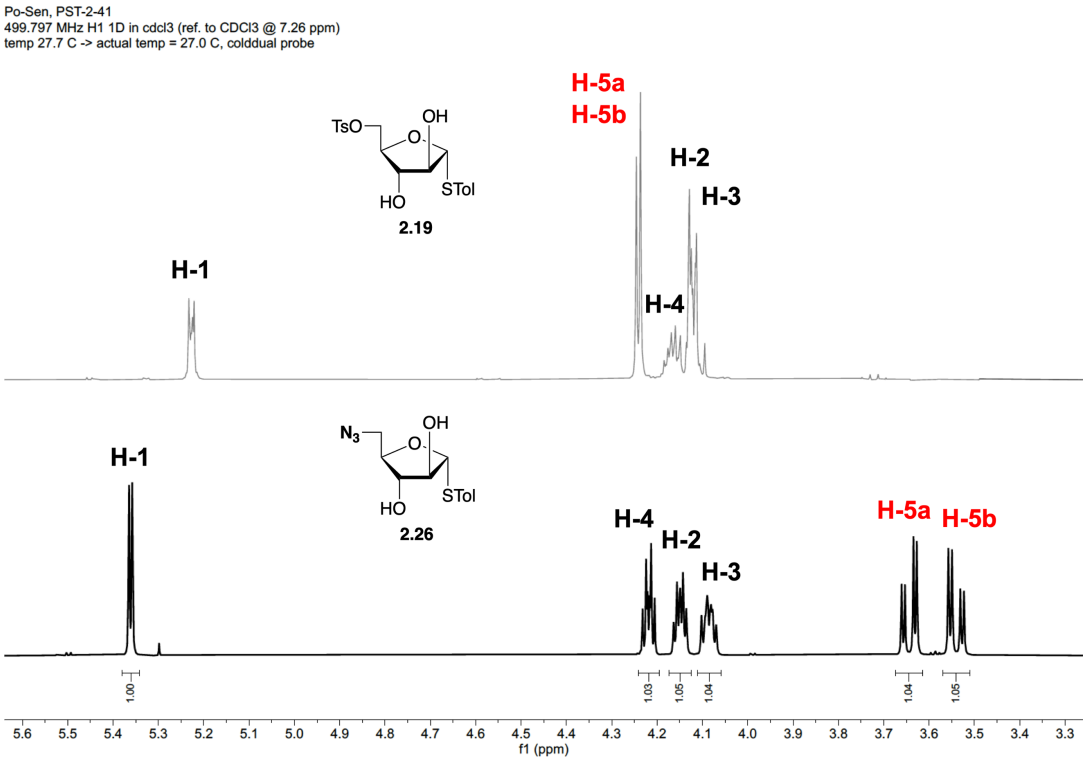


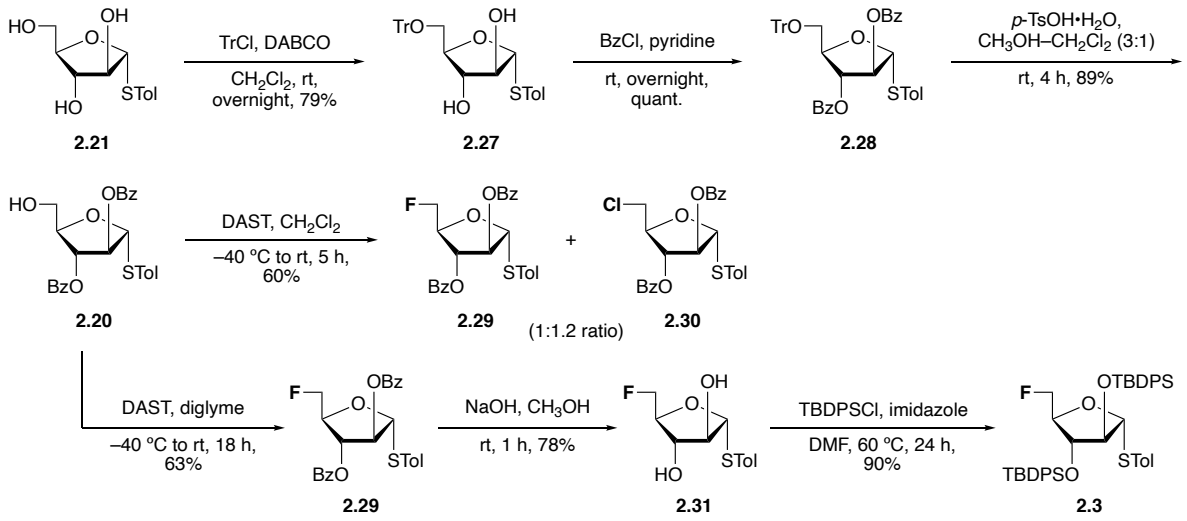
Figure 2.2 Partial ^{1}H NMR spectra of tosylate **2.19**[8] (top) and 5-azido-sugar **2.26** (bottom).

To synthesize 5-fluoro-arabinofuranoside **2.3** (**Scheme 2.4**), a conventional tritylation–benzoylation protocol was employed to convert thioglycoside **2.21** into fully-protected sugar **2.28** in 79% yield over two steps.[8] The trityl group in **2.28** was then cleaved with *p*-toluenesulfonic acid monohydrate to afford alcohol **2.20** in 89% yield.[8] Treatment of **2.20** with diethylaminosulfur trifluoride (DAST) in dichloromethane gave an inseparable mixture of 5-fluoro- and 5-chloro-arabinofuranosides (**2.29** and **2.30**). The formation of fluoro-sugar **2.29** was noticeable by NMR analysis. In the ^{1}H NMR spectrum (**Figure 2.3**), the resonances for H-5a and H-5b were found at 4.87 and 4.81 ppm as two sets of doublet of doublet of doublets with $^{2}J_{H,F}$ values of 46.5 and 47.7 Hz, respectively. Moreover, the resonance for C-5 of **2.29** in the ^{13}C NMR spectrum appeared at 81.9 ppm as a doublet with a $^{1}J_{C,F}$ value of 174.6 Hz. Long-range couplings to the resonances for C-4 at 82.3 ppm ($^{2}J_{C,F}$ = 18.7 Hz) and for C-3 at 77.3 ppm ($^{3}J_{C,F}$ = 6.5 Hz) were also apparent. These NMR data for **2.29** were consistent with those reported.[8] Furthermore, in the ^{19}F NMR spectrum, the resonance for the fluorine was found at –230.29 ppm as a doublet of doublet of doublets with the coupling constants ($J_{5b,F}$ = 47.7 Hz, $J_{5a,F}$ = 46.5 Hz, $J_{4,F}$ = 26.3 Hz) reciprocal to those in the ^{1}H NMR spectrum.

An undesired product, 5-chloro-glycoside **2.30**, could also be found in the same ^{1}H and ^{13}C NMR spectra. The resonance for C-5 of **2.30** in the ^{13}C NMR spectrum appeared at 43.9 ppm as would be expected for a primary alkyl chloride. In addition, both H-5a and H-5b of **2.30** were found as doublet of doublets at 4.02 and 3.97 ppm, which were distinct from those hydrogens of the fluoro-sugar **2.29** in the ^{1}H NMR spectrum (**Figure 2.3**). The generation of the chloro-sugar as a side-product in the reaction with DAST in dichloromethane has not yet been described in any literature. A proposed mechanism for the formation of this product is shown in **Scheme 2.5**. In this reaction, a naked fluoride ion could be generated from DAST, and the by-product cation could

activate the alcohol **2.20** to afford intermediate **2.20a** (**Scheme 2.5a**). The C-5 position of **2.20a** could undergo nucleophilic attack from the fluoride ion to give 5-fluoro-glycoside **2.29**. However, a possible side reaction could happen, in which the fluoride ion could react with dichloromethane to provide a chloride ion (**Scheme 2.5b**). This chloride could then participate in a nucleophilic displacement reaction with **2.20a** to generate 5-chloro-glycoside **2.30**.

To remove the only possible source of the chloride and to circumvent the formation of **2.30**, I followed the same conditions as those reported in the literature[15] and carried out the reaction of **2.20** with DAST in diglyme instead of dichloromethane. This reaction afforded **2.29** in 63% yield. Subsequent removal of benzoyl groups and protection with TBDPS groups provided 5-fluoro-thioglycoside **2.3** in 70% yield over two steps.



Scheme 2.4 Synthesis of 5-fluoro-thioglycoside **2.3**.

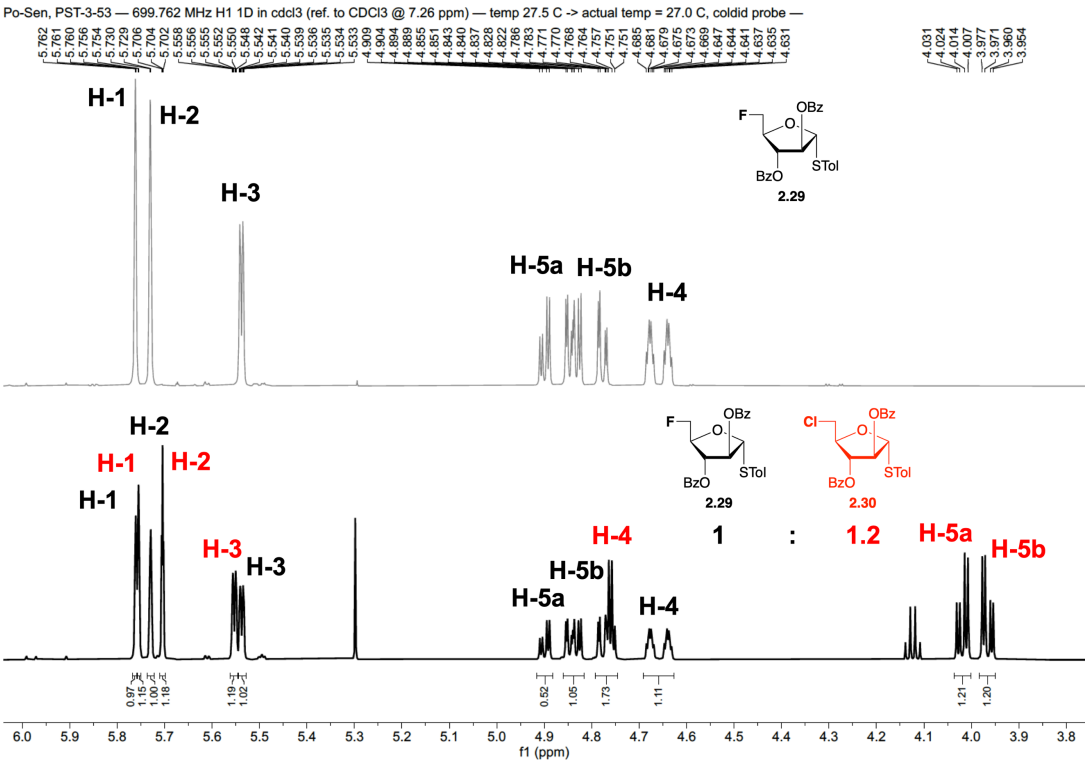
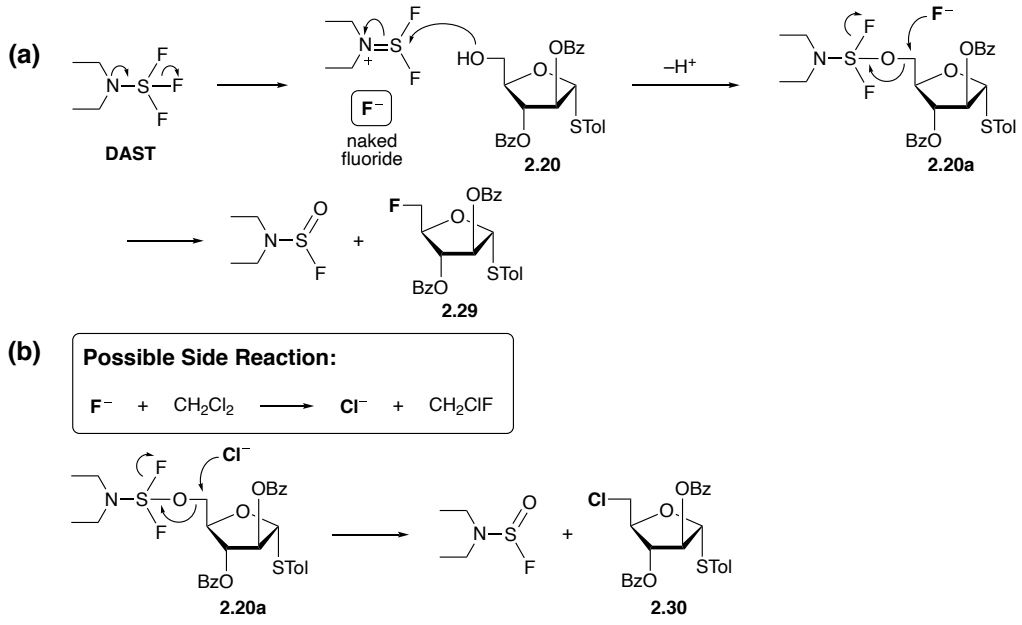


Figure 2.3 Partial ^{1}H NMR spectra of the pure compound **2.29** (top) and the mixture of **2.29** and **2.30** (bottom). In the bottom spectrum, the quartet at 4.12 ppm and the singlet at 5.30 ppm are residual ethyl acetate and dichloromethane, respectively.



Scheme 2.5 Proposed mechanisms for the formation of glycosides **2.29** and **2.30**.

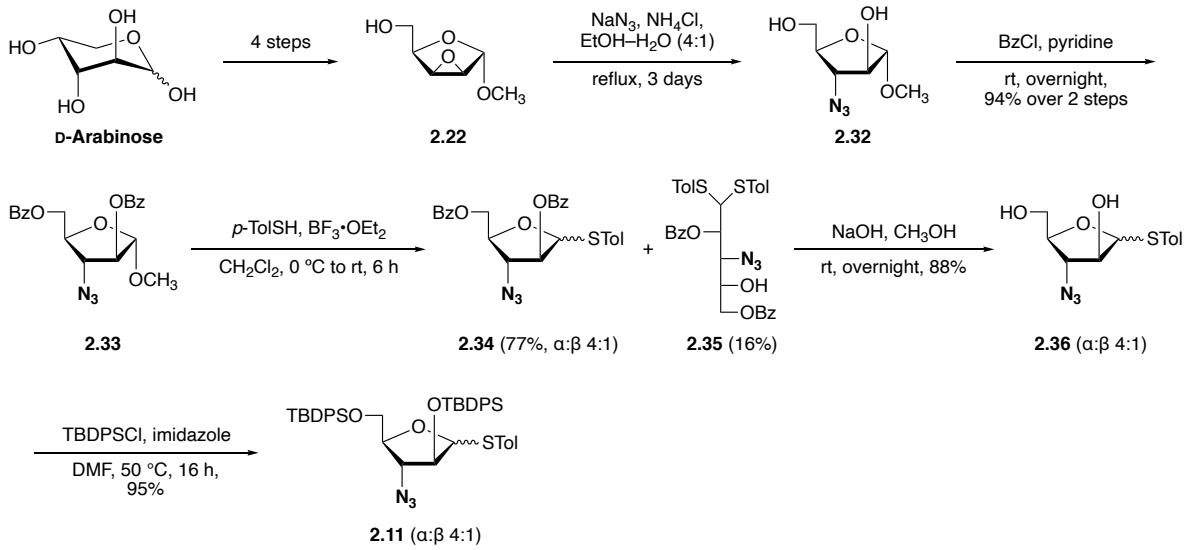
2.2.2 Synthesis of 3-Azido- and 3-Fluoro-Thioglycosides (2.11 and 2.2)

The synthesis of 3-azido-thioglycoside **2.11** (**Scheme 2.6**) started with D-arabinose, which was used to generate 2,3-anhydro-sugar **2.22** in four steps using a published protocol.[12] The nucleophilic ring opening of **2.22** with sodium azide gave 3-azido-arabinofuranoside **2.32**,[10] which was then protected with benzoyl groups to obtain fully-protected sugar **2.33** in 94% yield over two steps. The addition of the nucleophile happened exclusively at the C-3-position of epoxide **2.22**. Presumably due to the steric hindrance caused by the anomeric α-OCH_3 group, attack of the azide at the 2-position was not observed. In the ^{1}H NMR spectrum for **2.33**, the anomeric hydrogen appeared at 5.18 ppm as a singlet. This was consistent with what would be expected for a 1,2-*trans*-furanoside system and could thus confirm the D-*arabino* stereochemistry. Had attack occurred at C-2, a 1,2-*cis*-furanoside (with the D-*xylo* stereochemistry) would have been produced. The installation of the azido group at the C-3-position could also be verified by comparing the ^{1}H NMR spectrum of **2.33** and that of the known compound **2.33a**[16] (**Figure 2.4**). The resonance for H-3 of the fully-protected sugar **2.33a** appeared at 5.59 ppm as a doublet of doublets. In contrast, the resonance for the same hydrogen of 3-azido-sugar **2.33** was found at 4.07 ppm, which was considerably upfield.

Methyl glycoside **2.33** was then converted into a 4:1 mixture of α- and β-thioglycosides (**2.34**) in 77% yield by the reaction with *p*-thiocresol.[10] In this reaction, dithioacetal **2.35** was formed as a side-product in 16% yield. The generation of dithioacetals is not common under these conditions. Thus, I provide a possible mechanism (**Scheme 2.7**). Activation of methyl glycoside **2.33** by boron trifluoride could give the intermediate **2.33b**, which could form the oxocarbenium ion **2.33c**. The addition of *p*-thiocresol to **2.33c**, followed by the loss of a proton could provide thioglycosides **2.34** as a mixture of α- and β-anomers. The formation of the α-anomer would be

favored (α:β 4:1) due to the presence of the O-2 benzoyl protecting group, which could lead to the generation of intermediate **2.33d**. Nucleophilic attack of *p*-thiocresol could only be achieved from the bottom of **2.33d**, which could afford the α-anomer **2.33e**. The remaining Lewis acid, boron trifluoride, could further activate the ring oxygen of **2.34** to generate **2.34a**, which could then be subjected to ring-opening to give the open-chain intermediate ion **2.34b**. The nucleophilic attack of the remaining *p*-thiocresol and the loss of a proton could afford dithioacetal **2.35**.

Thioglycoside **2.34** could be isolated and was then subjected to the removal of benzoyl groups to provide diol **2.36**, which was protected with TBDPS groups to give **2.11** in 84% yield over two steps.



Scheme 2.6 Synthesis of 3-azido-thioglycoside **2.11**.

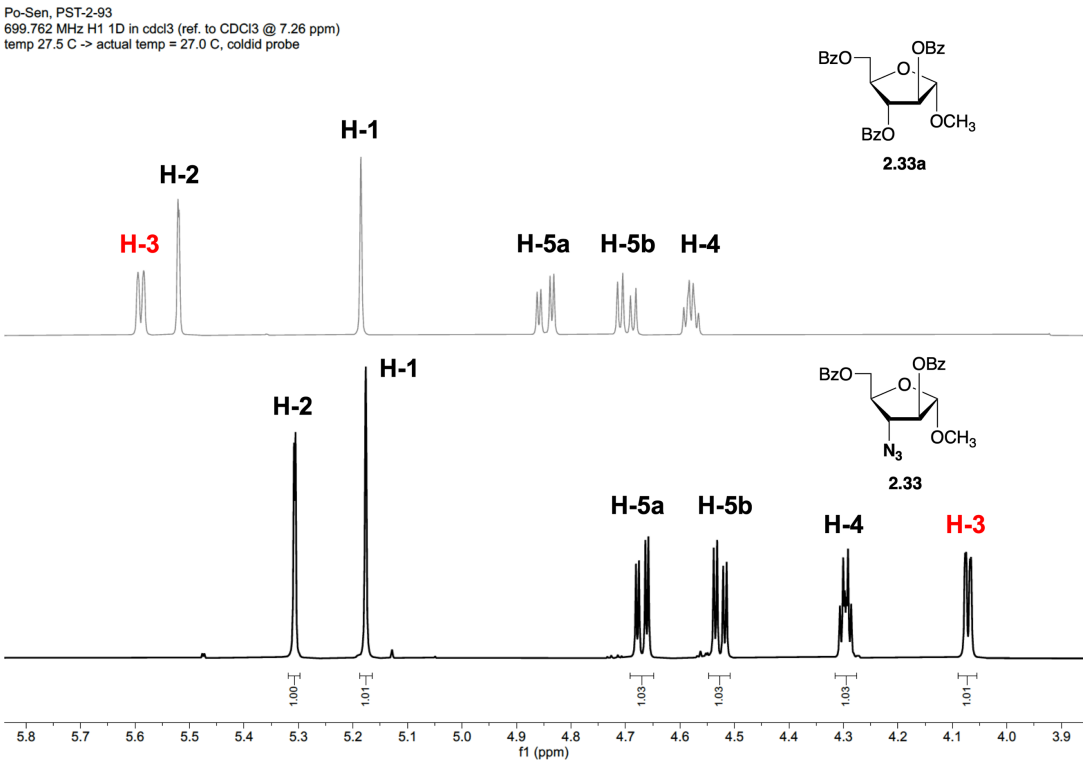
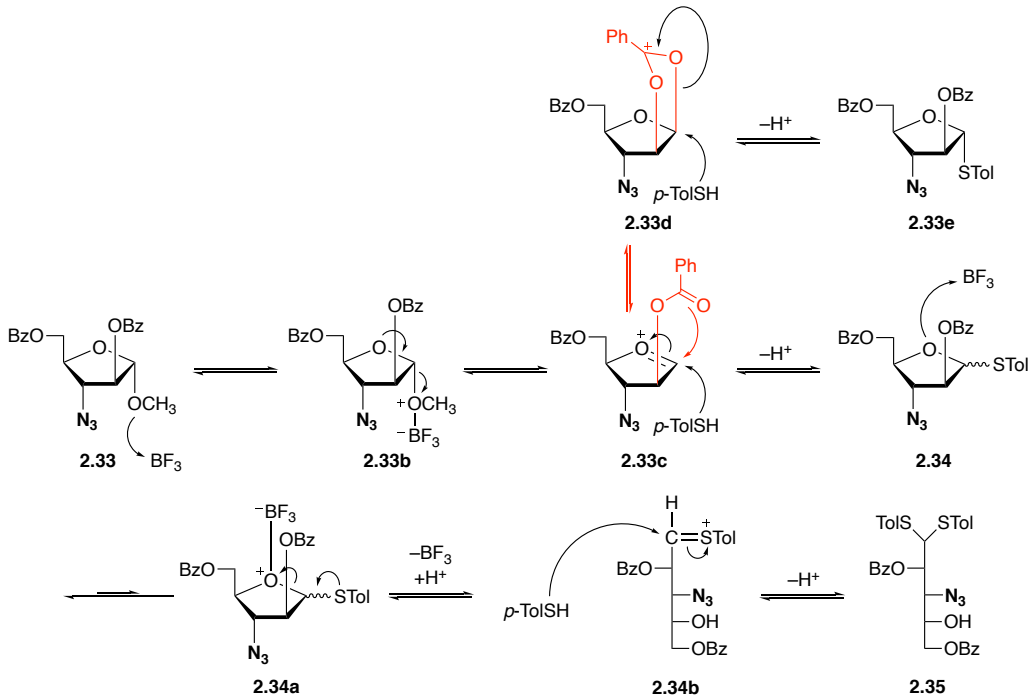


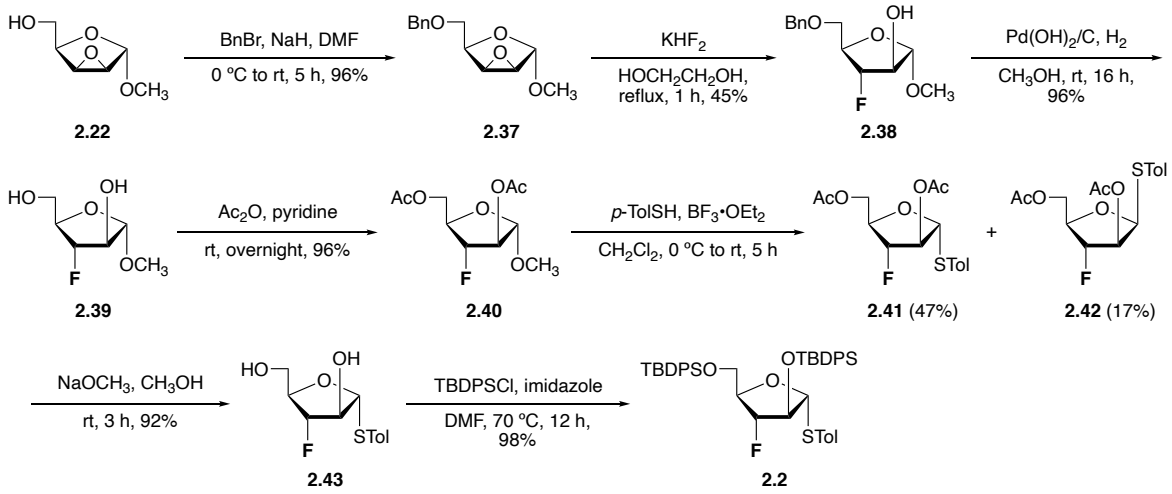
Figure 2.4 Partial ^{1}H NMR spectra of the known compound **2.33a**[16] (top) and 3-azido-sugar **2.33** (bottom).



Scheme 2.7 Proposed mechanism for the formation of thioglycoside **2.34** and dithioacetal **2.35**.

To obtain 3-fluoro-thioglycoside **2.2** (**Scheme 2.8**), the C-5 hydroxyl group in 2,3-anhydro-sugar **2.22** was protected with a benzyl group to give 5-*O*-benzyl glycoside **2.37** in 96% yield.[17] The following epoxide opening reaction of **2.37** with potassium hydrogen difluoride was carried out by heating at reflux in ethylene glycol to provide 3-fluoro-arabinofuranoside **2.38** in 45% yield.[11] The nucleophilic attack of the fluoride at the C-3-position of epoxide **2.37** was also highly selective with no substitution at the 2-position observed. In the ^{1}H NMR spectrum for **2.38** (**Figure 2.5**), the resonance for H-1 appeared at 4.95 ppm as a singlet, which could confirm the D-*arabino* stereochemistry based on the same analysis of 3-azido-sugar **2.33**. Moreover, the resonance for H-3 was found at 4.88 ppm as a doublet with a large $^{2}J_{H,F}$ value of 52.5 Hz. The resonance for C-3 of **2.38** in the ^{13}C NMR spectrum appeared at 97.3 ppm with a $^{1}J_{C,F}$ value of 186.8 Hz. These observations could be used to confirm that the fluorine atom was incorporated at the 3-position.

The subsequent debenzylation of **2.38** using palladium hydroxide on carbon under an atmosphere of hydrogen,[13] followed by acetylation generated fully-protected glycoside **2.40**, which was reacted with *p*-thiocresol to afford separable α- and β-thioglycosides (**2.41** and **2.42**). Compound **2.41** was subjected to Zemplén deacetylation and was protected with TBDPS groups to synthesize **2.2** in 90% yield over two steps.



Scheme 2.8 Synthesis of 3-fluoro-thioglycoside **2.2**.

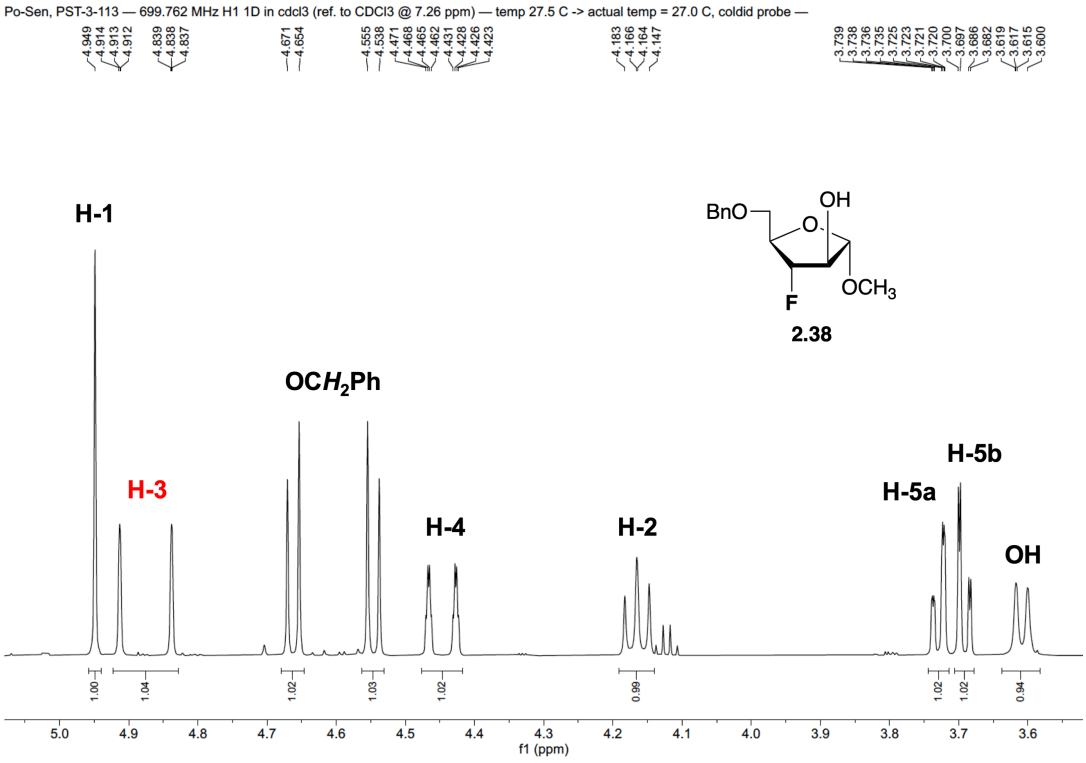
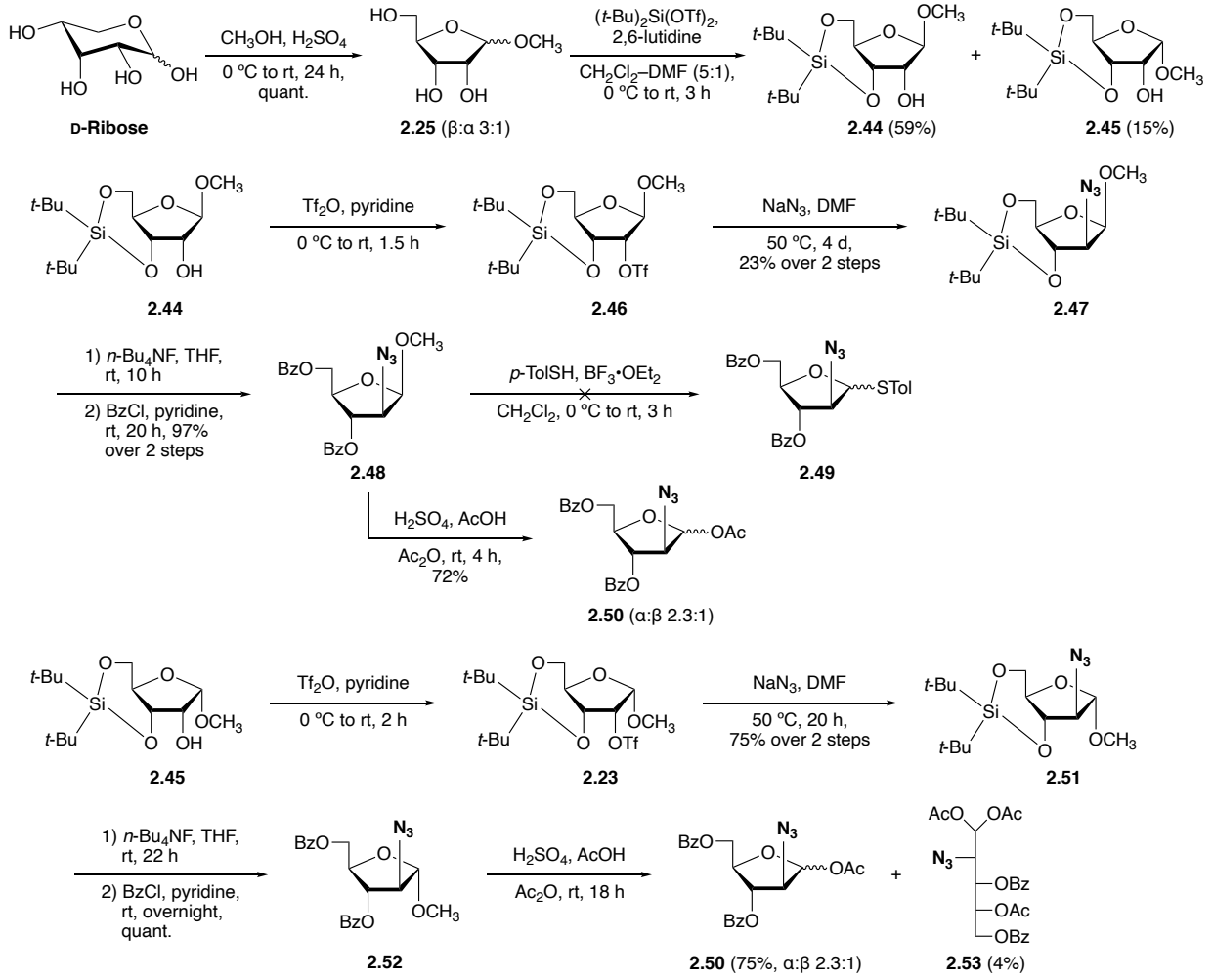


Figure 2.5 Partial ^{1}H NMR spectrum of 3-fluoro-arabinofuranoside **2.38**.

2.2.3 Synthesis of 2-Azido- and 2-Fluoro-Thioglycosides (2.10 and 2.1)

The synthesis of the 2-azido-sugar target began with D-ribose, which was converted into a 3:1 mixture of β- and α-ribofuranosides (**2.25**, **Scheme 2.9**) in quantitative yield using the Fischer glycosylation.[14] Protection of **2.25** with di-*tert*-butylsilylene (DTBS) group[18] gave a separable mixture of β- and α-glycosides (**2.44** and **2.45**). The C-2 hydroxyl group in the major isomer **2.44** was activated as a triflate ester, followed by the nucleophilic displacement with sodium azide[19] to provide 2-azido-arabinofuranoside **2.47** in 23% yield over two steps. Based on the results from the thin-layer chromatography (TLC), all the glycoside **2.44** was converted into triflate **2.46**. The following S_N2 reaction of **2.46** and sodium azide went to completion after heating at 50 ºC for four days but generated more than six spots on the TLC. Only the desired product **2.47** was isolated. This low yield may be due to the presence of the anomeric β-OCH_3 group, which hindered the attack of the nucleophile, through both steric hindrance and electrostatic repulsion of the azide. Subsequent removal of the DTBS group and protection with benzoyl groups generated **2.48** in 97% yield over two steps. However, attempts to synthesize thioglycoside **2.49** from methyl glycoside **2.48** were not successful. No reaction occurred between **2.48** and *p*-thiocresol when using boron trifluoride etherate as the promotor, and compound **2.48** was recovered. We postulated that after the activation of **2.48** by boron trifluoride, the corresponding oxocarbenium ion could not be generated due to the inductive effect of the azido group, which could destabilize the oxocarbenium ion. Therefore, methyl glycoside **2.48** was converted into glycosyl acetate **2.50** in 72% yield using a mixture of sulfuric acid and acetic acid in acetic anhydride.[20] We envisioned that acetate **2.50** would be more reactive than methyl glycoside **2.48** and treatment with *p*-thiocresol and boron trifluoride etherate would provide thioglycoside **2.49**.



Scheme 2.9 Synthesis of 2-azido-arabinofuranosyl acetate **2.50**.

In addition, the DTBS-protected α-ribofuranoside **2.45** could also afford glycosyl acetate **2.50** using the same strategy (**Scheme 2.9**). Alcohol **2.45** was activated as the triflate **2.23**, followed by the nucleophilic attack of sodium azide[19] to generate 2-azido-arabinofuranoside **2.51** in 75% yield over two steps. It should be noted that this yield (75% over two steps) was much better than that (23% over two steps) of synthesizing the corresponding β-glycoside **2.47**. This observation supported the previous assumption: that the β-OCH_3 group interfered the attack of azide. The formation of 2-azido-sugar **2.51** could be confirmed by comparing the NMR data of

2.51 with that of the known alcohol **2.51a**.[21] In the ^{1}H NMR spectra (**Figure 2.6**), the resonance for H-2 in **2.51a** was found at 4.10 ppm. In contrast, the H-2 in azido-sugar **2.51** appeared at 3.83 ppm. In the ^{13}C NMR spectra, the resonances for C-2 in **2.51a** (81.6 ppm) and in **2.51** (70.9 ppm) were also distinct.

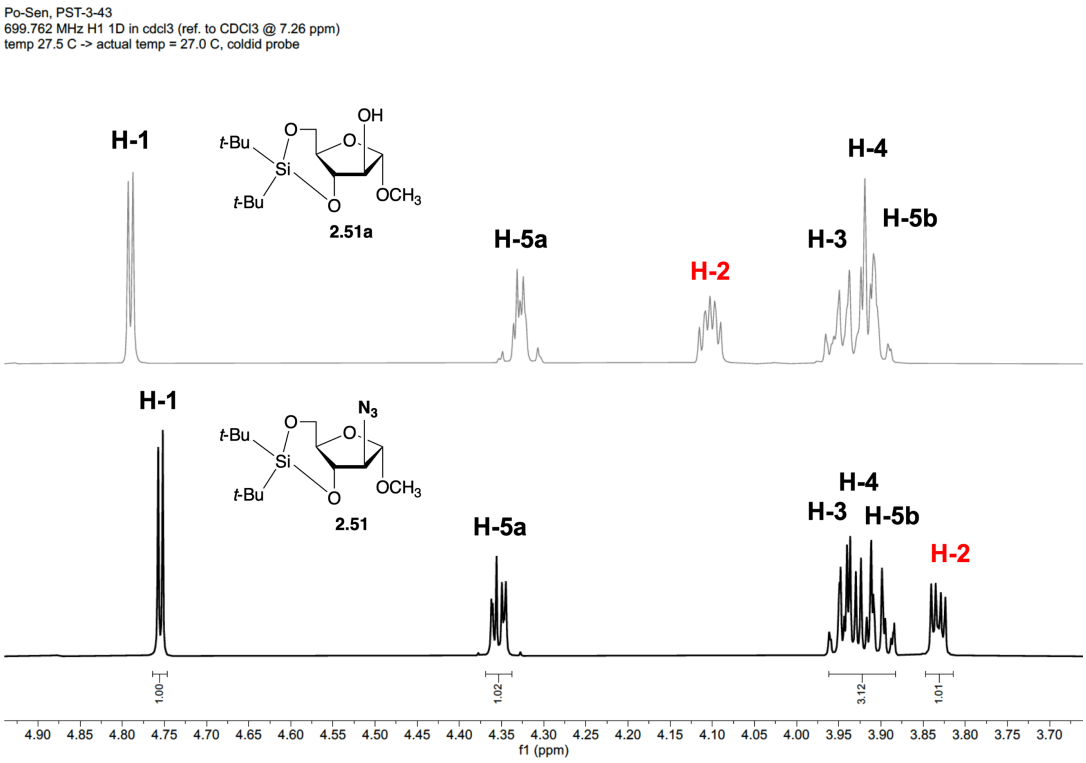
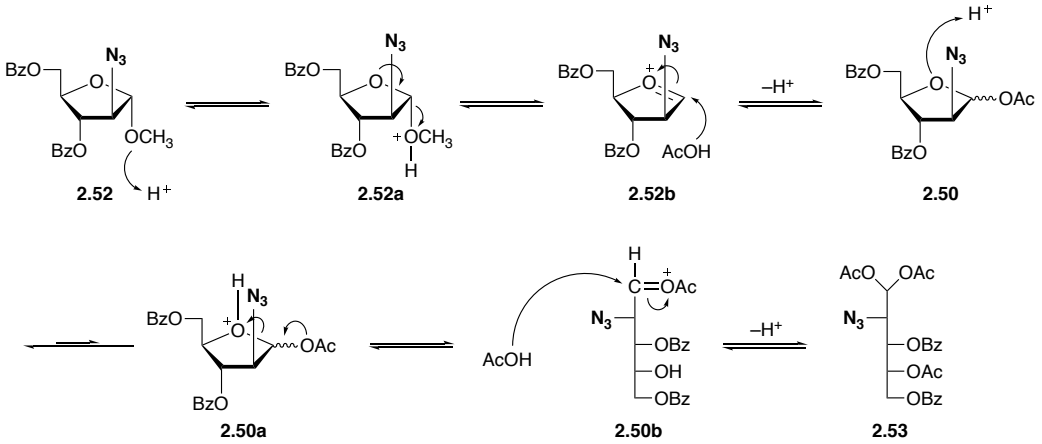


Figure 2.6 Partial ^{1}H NMR spectra of the known alcohol **2.51a**[21] (top) and 2-azido-sugar **2.51** (bottom).

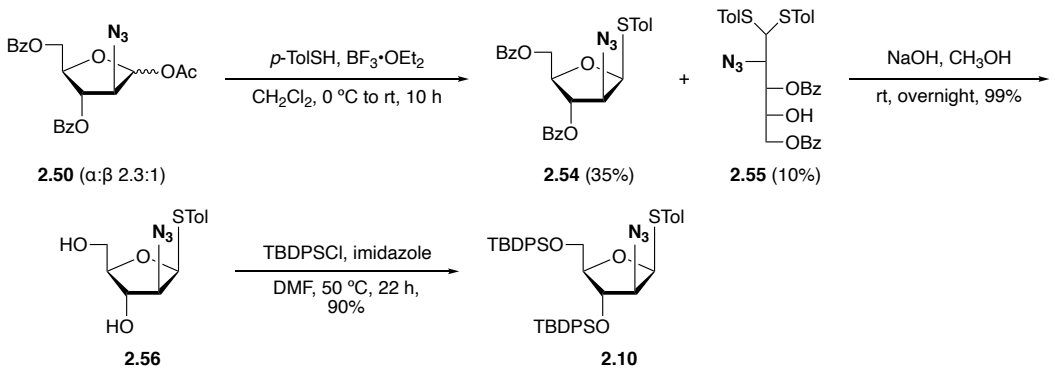
Azido-sugar **2.51** was then subjected to deprotection of the DTBS group and protection with benzoyl groups to give **2.52** in quantitative yield (**Scheme 2.9**). Methyl glycoside **2.52** was converted into a 2.3:1 mixture of α- and β-glycosyl acetates **2.50** in 75% yield. In this reaction, aldehydrol diacetate **2.53** was formed as a side-product in 4% yield. I hypothesized (**Scheme 2.10**) that the mechanism for the generation of **2.53** could be analogous to that for the dithioacetal **2.35**.

That is, protonation of the methoxy group of the acetal **2.52**, followed by loss of methanol could give the oxocarbenium ion **2.52b**. The addition of acetic acid to **2.52b** and loss of a proton could provide glycosyl acetate **2.50**. The ring oxygen of **2.50** could then be protonated to generate **2.50a**, which could be subjected to ring-opening to form the oxocarbenium ion **2.50b**. Acetic acid could add to **2.50b** and the C-4 hydroxyl group could be acetylated by acetic anhydride to yield fully-protected aldehydrol **2.53**.



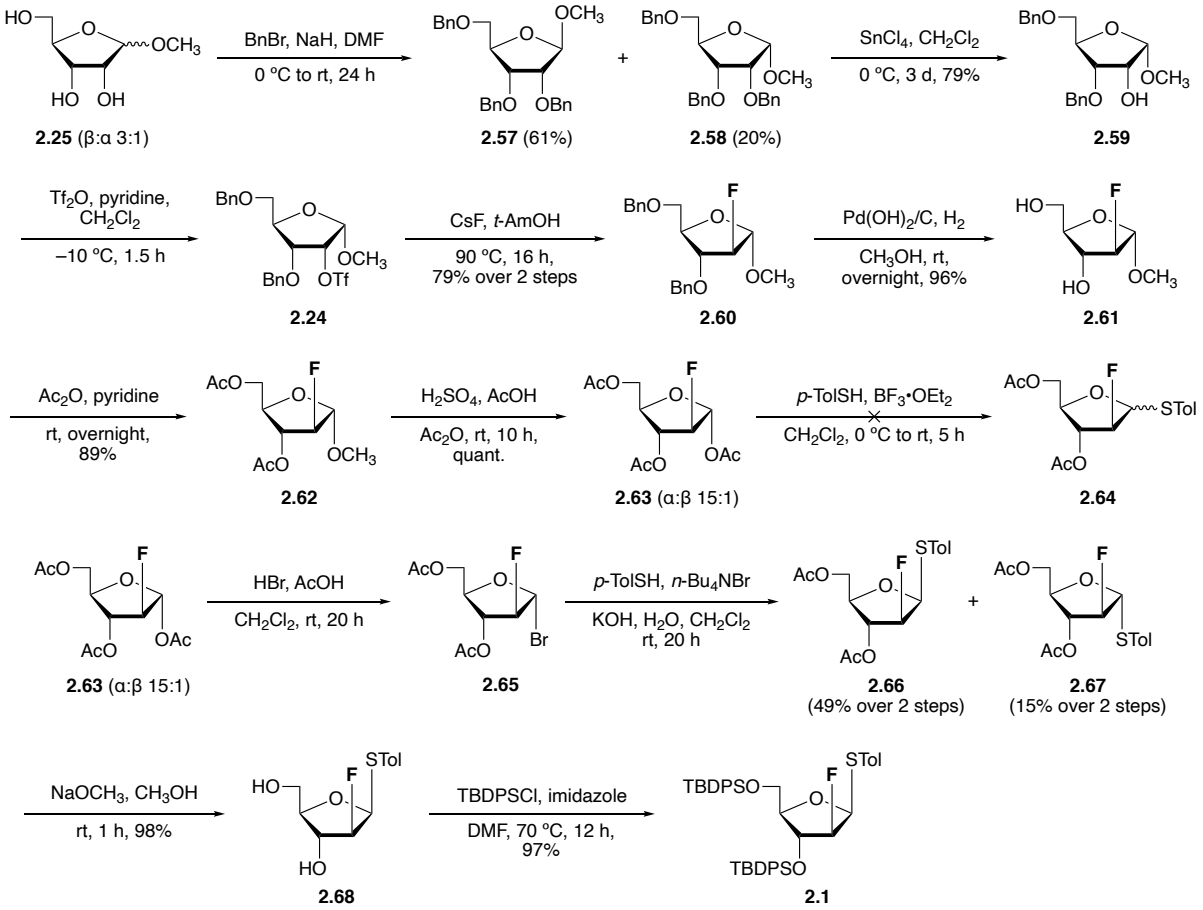
Scheme 2.10 Proposed mechanism for the formation of glycosyl acetate **2.50** and aldehydrol **2.53**.

The conversion of glycosyl acetate **2.50** into thioglycoside **2.54** was achievable, but in a poor (35%) yield (**Scheme 2.11**). Only the β-anomer (**2.54**) was observed after purification by column chromatography, and dithioacetal **2.55** was generated as a side-product in 10% yield. Both the formation of **2.55** and the low yield of thioglycoside **2.54** could be due to the presence of the C-2 azido group, which could interfere the generation of the oxocarbenium ion. Compound **2.54** was subjected to deprotection of the benzoyl groups to afford diol **2.56**, which was protected with TBDPS groups to provide 2-azido-thioglycoside **2.10** in 89% yield over two steps.



Scheme 2.11 Synthesis of 2-azido-thioglycoside **2.10** from glycosyl acetate **2.50**.

To synthesize 2-fluoro-thioglycoside **2.1** (**Scheme 2.12**), methyl ribofuranoside **2.25** was protected with benzyl groups to provide fully-protected β- and α-glycosides (**2.57** and **2.58**).[14] Selective removal of the benzyl group on O-2 in both glycosides using tin(IV) chloride generated alcohol **2.59** in 79% yield.[22] Activation of the hydroxyl group in **2.59** as a triflate ester, followed by the nucleophilic displacement with cesium fluoride introduced the fluorine atom at the C-2 position and gave arabinofuranoside **2.60** in 79% yield over two steps.[13] The ^{1}H, ^{13}C and ^{19}F NMR data for 2-fluoro-sugar **2.60** were identical to those reported previously for this compound.[13] Subsequent hydrogenolysis and acetylation provided **2.62** in 85% yield over two steps. Based on the previous synthesis of 2-azido-sugar **2.10**, preparation of the C-2-modified thioglycoside required the conversion of methyl glycoside into glycosyl acetate, which could be reacted with *p*-thiocresol. Thus, glycoside **2.62** was used to form glycosyl acetate **2.63** in quantitative yield. However, the attempted synthesis of thioglycoside **2.64** from **2.63** failed, and the starting material **2.63** was recovered. To solve this problem, triacetate **2.63** was converted into arabinofuranosyl bromide **2.65**,[23] which was reacted with *p*-thiocresol under phase-transfer conditions[24] to generate β- and α-thioglycosides (**2.66** and **2.67**). The following Zemplén deacetylation of **2.66** provided alcohol **2.68**, which was protected with TBDPS groups to afford **2.1** in 95% yield over two steps.



Scheme 2.12 Synthesis of 2-fluoro-thioglycoside **2.1**.

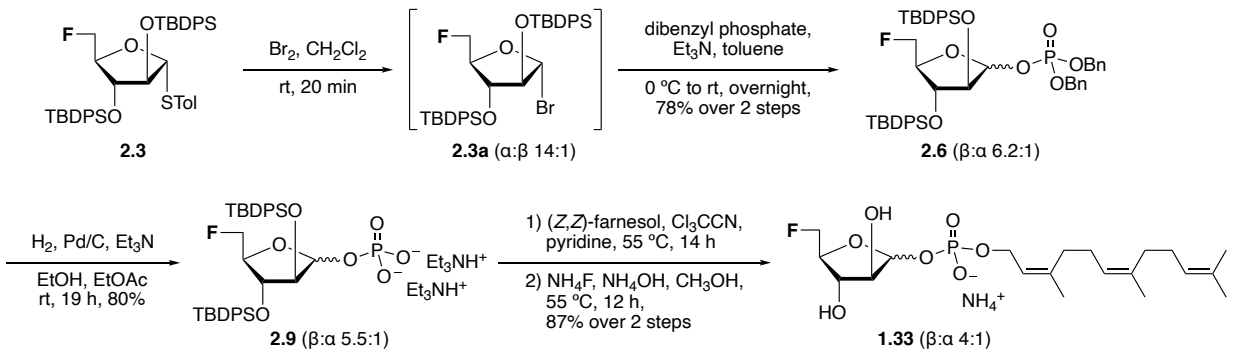
2.2.4 Synthesis of Fluoro Derivatives of FPA 1.31–1.33

With all of the fluoro- and azido-thioglycosides (**2.1**–**2.3** and **2.10**–**2.12**) in hand, the next step was to perform phosphorylation and to couple the resulting arabinofuranosyl phosphates with the lipid alcohol to generate the six target molecules.

To synthesize 5-fluoro-FPA **1.33** (**Scheme 2.13**), thioglycoside **2.3** was treated with bromine in dichloromethane to generate a mixture of α- and β-glycosyl bromides **2.3a**, in which the α-anomer was the major component (α:β 14:1). The following phosphorylation of **2.3a** with dibenzyl phosphate afforded a 6.2:1 mixture of β- and α-arabinofuranosyl phosphates **2.6** in 78%

yield over two steps. The formation of β-phosphate could be confirmed by comparing the ^{1}H NMR and ^{31}P-decoupled ^{1}H NMR spectra of phosphates **2.6**. In the ^{1}H NMR spectrum (bottom of **Figure 2.7**), the H-1 of β-arabinofuranosyl phosphate was coupled to both of the H-2 and the phosphorus and appeared at 5.26 ppm as a doublet of doublets (apparent triplet) with the $J_{1,P}$ of 4.1 Hz and the $J_{1,2}$ of 3.5 Hz. In the ^{31}P-decoupled ^{1}H NMR spectrum (top of **Figure 2.7**), all couplings due to phosphorus were silenced, and the H-1 of β-phosphate became a doublet with the $J_{1,2}$ of 3.5 Hz. In contrast, the resonance for H-1 of the α-anomer was found at 5.79 ppm as a doublet with the $J_{1,P}$ of 4.1 Hz in the ^{1}H NMR spectrum but turned into a singlet in the ^{31}P-decoupled ^{1}H NMR spectrum. The assignments of all the following β- and α-phosphates were attained in the same manner. Moreover, by comparing the α:β ratio of bromides **2.3a** and that of phosphates **2.6**, it should be noted that this glycosylation reaction does proceed through not only an S_N2 mechanism but also via a competing S_N1-like pathway. That is, the ratio of the starting bromides does not correlate with those (inverted) in the phosphates. This observation is consistent with earlier reports.[4]

Palladium-catalyzed hydrogenolysis of **2.6** provided monophosphate salts **2.9** in 80% yield. The subsequent reaction with (*Z*,*Z*)-farnesol in the presence of trichloroacetonitrile[4] generated the corresponding phosphodiester, which was subjected to deprotection by ammonium fluoride to give **1.33** as a 4:1 mixture of β- and α-anomers in 87% yield over two steps. The change of these β:α ratios during the synthesis suggested that isomerization of the molecules happened under the reaction conditions and/or during the purification steps. Although it was not clearly stated in the literature,[2] others seem to have the same difficulty synthesizing DPA analogs as the pure β-anomers.



Scheme 2.13 Synthesis of 5-fluoro-FPA **1.33**.

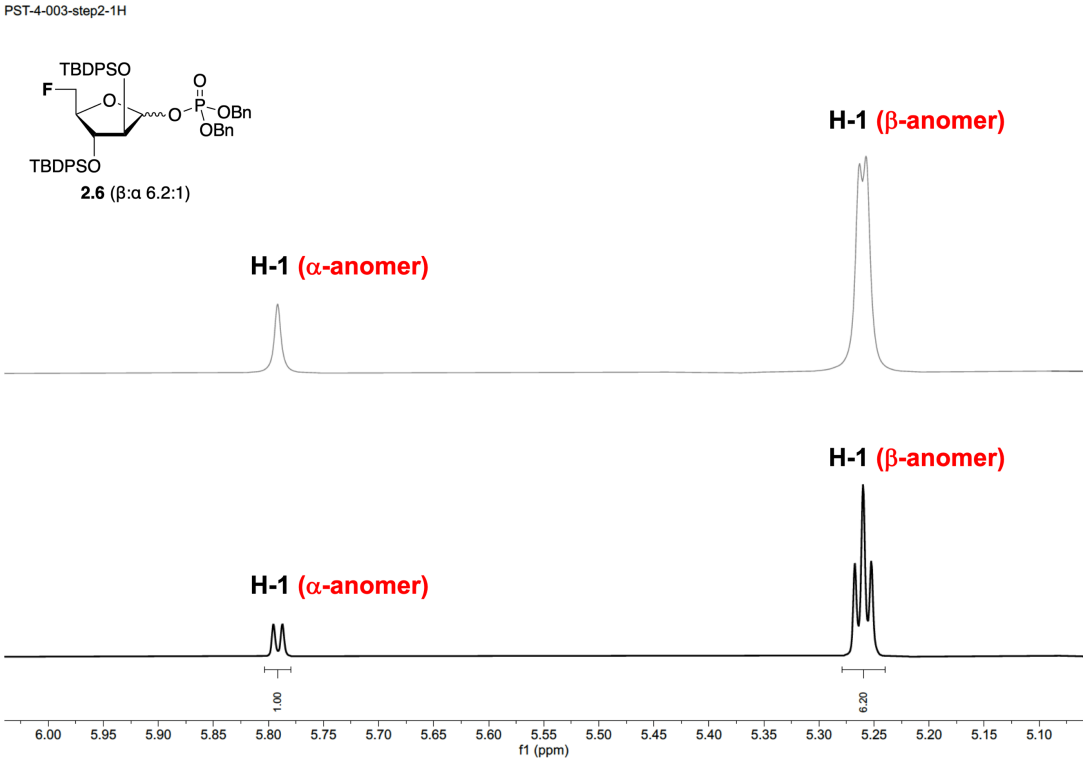
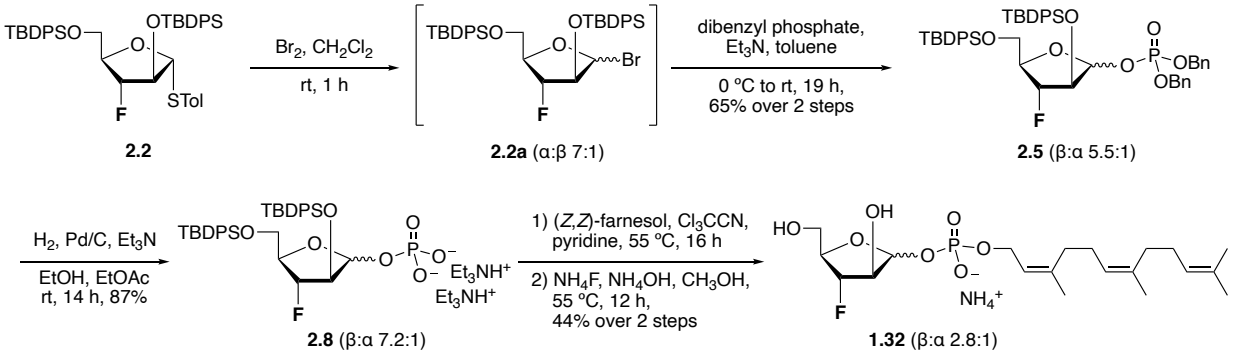


Figure 2.7 Partial ^{31}P-decoupled ^{1}H NMR spectrum (top) and ^{1}H NMR spectrum (bottom) of glycosyl phosphates **2.6**.

The synthesis of 3-fluoro-FPA **1.32** (**Scheme 2.14**) could be accomplished using the same strategy. Thioglycoside **2.2** was converted into bromides **2.2a** as a 7:1 mixture of α- and β-anomers,

which underwent phosphorylation to afford a 5.5:1 mixture of β- and α-glycosyl phosphates **2.5** in 65% yield over two steps. Removal of benzyl groups in **2.5** gave phosphate salts **2.8** in 87% yield. After the coupling reaction with the lipid alcohol and the following desilylation, compound **1.32** was generated as a 2.8:1 mixture of β- and α-phosphodiesters in 44% yield over two steps.

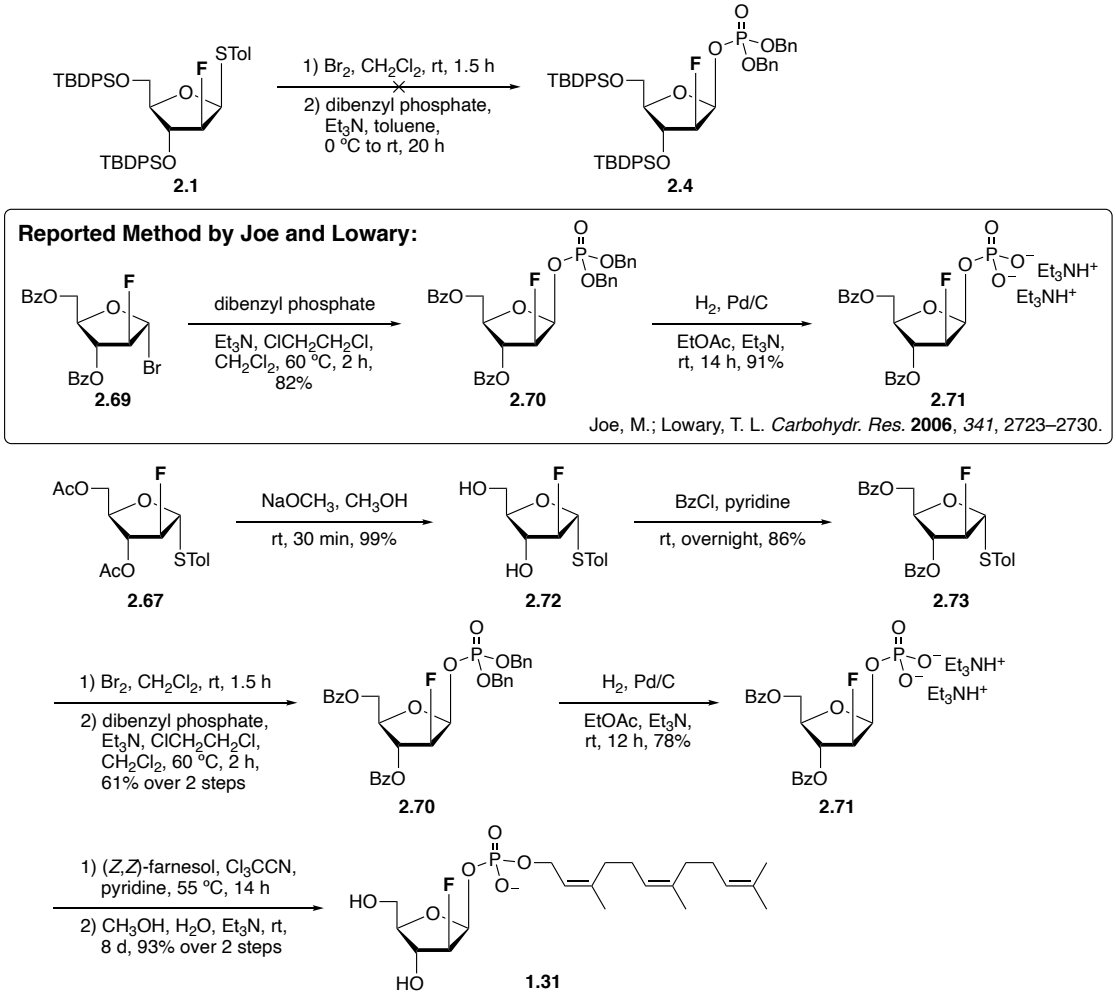


Scheme 2.14 Synthesis of 3-fluoro-FPA **1.32**.

However, the attempted synthesis of 2-fluoro-FPA **1.31** (**Scheme 2.15**) from thioglycoside **2.1** was not successful. After performing the bromination of **2.1**, I was not able to tell whether the corresponding glycosyl bromides were formed by the NMR analysis of the product mixture. I decided to carry out the following phosphorylation step using this mixture, but the desired glycosyl phosphate **2.4** was not observed after purification by column chromatography. Therefore, I turned my attention to a reported method, in which the benzoyl-protected glycosyl bromide **2.69** was used to react with dibenzyl phosphate in a solution of 1,2-dichloroethane and dichloromethane at 60 ºC to give β-phosphate **2.70** in 82% yield.[24] Removal of the benzyl groups provided deprotected phosphate **2.71** in 91% yield.[24]

To follow this strategy, I synthesized the benzoyl-protected 2-fluoro-thioglycoside **2.73**, which was prepared from **2.67** in 85% yield over two steps by Zemplén deacetylation and

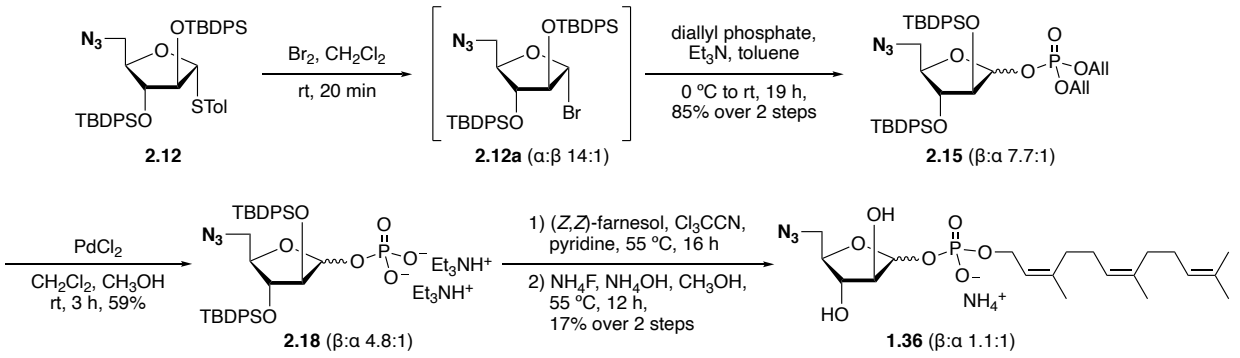
protection with benzoyl groups. Thioglycoside **2.73** was converted into the corresponding glycosyl bromide, and the following glycosylation was carried out under the above-mentioned conditions to generate arabinofuranosyl phosphate **2.70** in 61% yield over two steps. Debenzylation of **2.70** gave monophosphate salt **2.71** in 78% yield. The coupling of **2.71** with (*Z*,*Z*)-farnesol, followed by the cleavage of benzoate esters under mild conditions[24] using a 5:2:1 mixture of methanol–water–triethylamine provided 2-fluoro-FPA **1.31** as the pure β-phosphodiester in 93% yield over two steps.



Scheme 2.15 Synthesis of 2-fluoro-FPA **1.31**.

2.2.5 Synthesis of Azido Derivatives of FPA 1.34–1.36

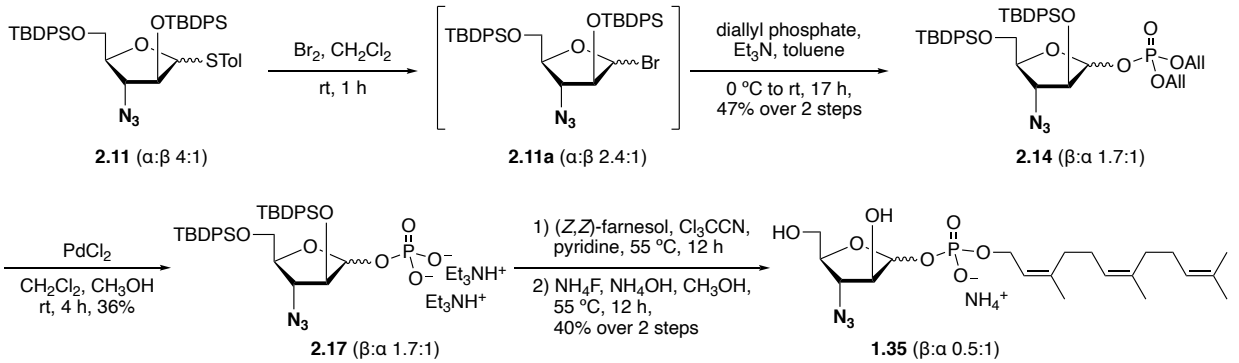
To synthesize 5-azido-FPA **1.36** (**Scheme 2.16**), thioglycoside **2.12** was converted into glycosyl bromides **2.12a**, in which the α-anomer was the major component (α:β 14:1). This α:β ratio was almost the same as that of 5-fluoro-arabinofuranosyl bromides **2.3a** possibly due to the similarity of their ring conformations. Bromides **2.12a** were then reacted with diallyl phosphate to afford arabinofuranosyl phosphates **2.15** as a 7.7:1 mixture of β- and α-anomers in 85% yield over two steps. Deprotection of allyl groups was done by the use of palladium(II) chloride[6] to generate phosphate salts **2.18** in 59% yield. The subsequent coupling reaction with the lipid alcohol and desilylation by ammonium fluoride provided **1.36** as a 1.1:1 mixture of β- and α-phosphodiesters in 17% yield over two steps.



Scheme 2.16 Synthesis of 5-azido-FPA **1.36**.

The same protocol could be employed to synthesize 3-azido-FPA **1.35** (**Scheme 2.17**). Conversion of thioglycosides **2.11** into a 2.4:1 mixture of α- and β-glycosyl bromides **2.11a**, followed by phosphorylation generated phosphates **2.14** in 47% yield over two steps as a 1.7:1 mixture of β- and α-anomers. The poor stereoselectivity in this glycosylation step could be due to the poor α:β (2.4:1) ratio of bromides **2.11a**. The allyl groups in **2.14** were removed to provide

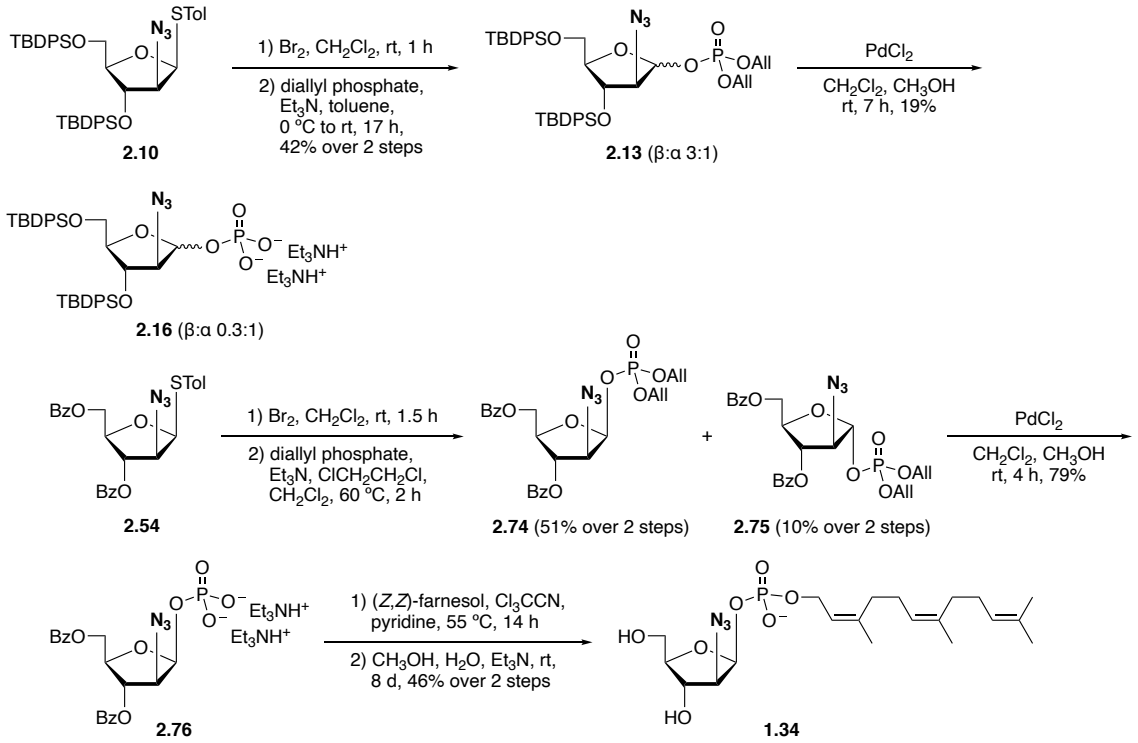
monophosphate salts **2.17** in 36% yield. Coupling of **2.17** with (*Z*,*Z*)-farnesol and deprotection of the TBDPS groups gave **1.35** in 40% yield over two steps. However, the desired β-anomer was the minor component of the product mixture (β:α 0.5:1).



Scheme 2.17 Synthesis of 3-azido-FPA **1.35**.

To synthesize 2-azido-FPA **1.34** (**Scheme 2.18**), thioglycoside **2.10** was reacted with bromine to yield glycosyl bromides. The α:β ratio of these bromides was not able to be determined from the ^{1}H NMR spectrum because of the presence of unknown impurities in the product mixture. The crude glycosyl bromides underwent glycosylation with diallyl phosphate to generate a 3:1 mixture of β- and α-arabinofuranosyl phosphates **2.13** in 42% yield over two steps. Removal of the allyl groups gave monophosphate salts **2.16** in 19% yield. This deprotection step resulted in not only the poor yield but also a low β:α (0.3:1) ratio. Thus, I turned my attention to the protocol[24] mentioned previously in the synthesis of 2-fluoro-FPA **1.31**. Benzoyl-protected thioglycoside **2.54** was converted into glycosyl bromide before the reaction with diallyl phosphate in a solution of 1,2-dichloroethane and dichloromethane at 60 ºC to afford β- and α-glycosyl phosphates (**2.74** and **2.75**). Cleavage of the allyl ethers in **2.74** gave phosphate salt **2.76** in 79% yield. Compound **2.76**

was reacted with the lipid alcohol, followed by deprotection of the benzoyl groups to provide **1.34** as the pure β-anomer in 46% yield over two steps.

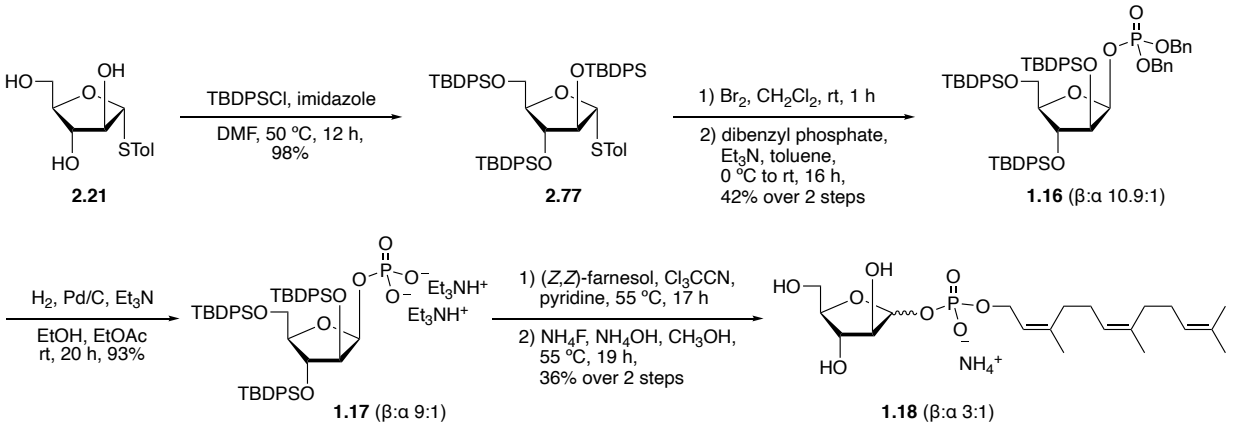


Scheme 2.18 Synthesis of 2-azido-FPA **1.34**.

2.2.6 Synthesis of FPA 1.18

To synthesize FPA **1.18** (**Scheme 2.19**), I began with thioglycoside **2.21**, which was protected with TBDPS groups to give fully-protected sugar **2.77** in 98% yield. Compound **2.77** was converted into the corresponding bromide and was phosphorylated with dibenzyl phosphate in toluene to generate a 10.9:1 mixture of β- and α-arabinofuranosyl phosphates **1.16** in 42% yield over two steps.[4] Debenzylation of **1.16** gave monophosphate salts **1.17** in 93% yield.[4] The

subsequent coupling reaction with (*Z*,*Z*)-farnesol and desilylation provided **1.18** as a 3:1 mixture of β- and α-anomers.[4] The ^{1}H and ^{13}C NMR data for FPA **1.18** were identical to those reported.[4]



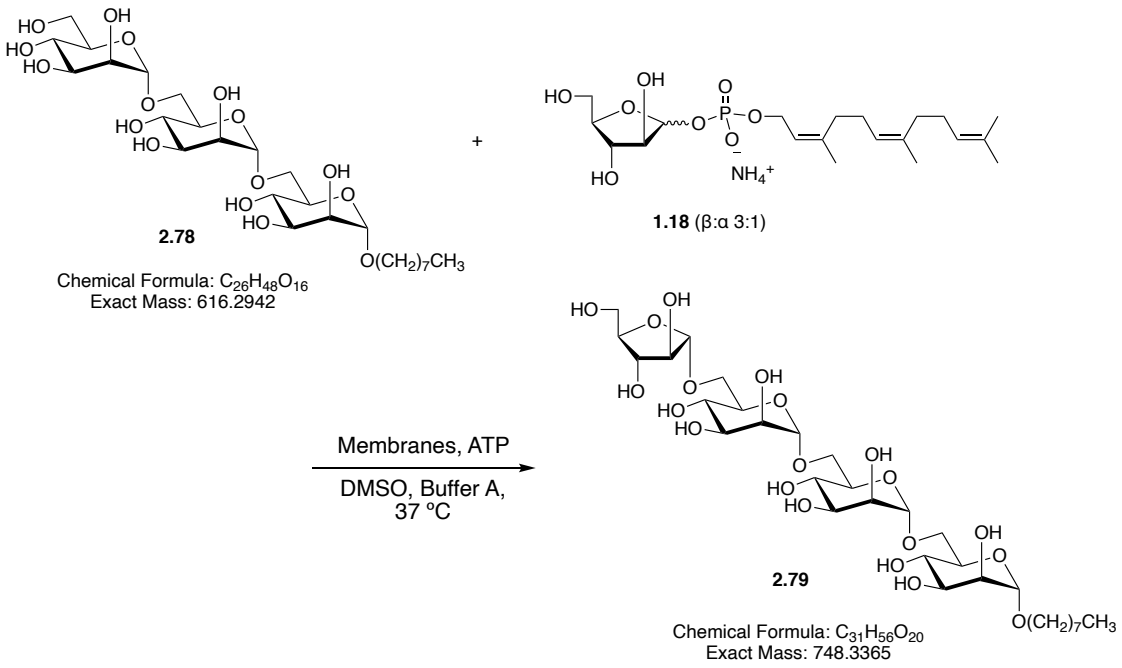
Scheme 2.19 Synthesis of FPA **1.18**.

2.2.7 Evaluation of FPA 1.18 as a Substrate for AraTs

With all of the target molecules **1.31**–**1.36** and FPA **1.18** in hand, I proceeded to evaluate the effectiveness of these compounds as substrates for mycobacterial AraTs using the *in vitro* cell-free assay. A typical AraT assay reaction mixture[1,2] contained DPA or analogs (0.5 mM), synthetic acceptor (0.1 mM), ATP (1 mM), DMSO (2% v/v), buffer A [50 mM MOPS (pH 7.9), 5 mM 2-mercaptoethanol and 10 mM $MgCl_2$] and membranes (0.5 mg) in a total volume of 200 μL. The cell membranes, which were the source of AraTs, were isolated from *Mycobacterium smegmatis*.[1,2]

I first used the known substrate FPA **1.18**[2,3] as the arabinofuranosyl donor (**Scheme 2.20**). Synthetic trimannoside **2.78**, which has shown the acceptor capability in this AraT assay system,[1] was employed as the glycosyl acceptor. The reaction mixture was incubated with shaking at 37 ºC overnight and was then terminated by the addition of 200 μL of ethanol. Upon centrifugation at 14,000 rpm (20,000 × *g*) for 15 minutes, the resulting supernatant was analyzed directly by LC–

MS. Both the enzymatic product **2.79** and the unreacted acceptor **2.78** were detected by this method although the peaks for product **2.79** were very small (**Figure 2.8**).



Scheme 2.20 The AraT assay reaction using FPA **1.18** as the donor and trimannoside **2.78** as the acceptor.

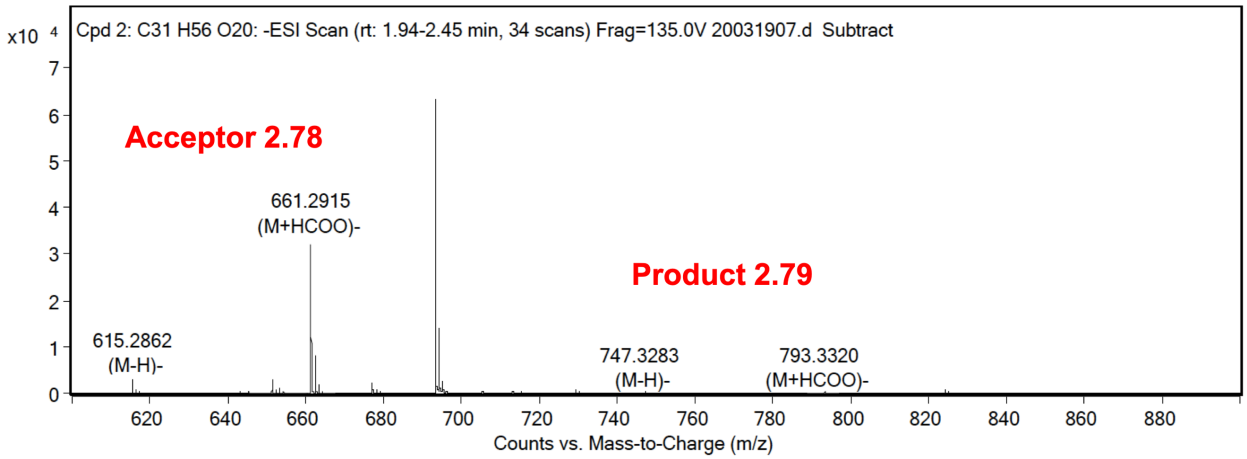


Figure 2.8 LC–MS analysis of the AraT assay reaction products (first attempt). Both the product **2.79** and acceptor **2.78** were detected.

However, when I tried to perform this assay again, it was not successful. I used the same donor FPA **1.18** and acceptor **2.78** as the starting materials and prepared the membrane fractions according to the same procedure. After carrying out the AraT assay reaction and purification by the strong anion exchanger (SAX) cartridge, only the unreacted acceptor **2.78** was detected by LC–MS (**Figure 2.9**). In addition, I also tried derivatizing the enzymatic products by per-*O*-acetylation before the analysis by MALDI–MS and ESI–MS techniques. Nevertheless, only the acceptor **2.78** could be found by these methods. I thought the first possible reason could be that something went wrong when preparing the membrane fractions. The second reason could be that FPA **1.18**, which could be labile, had degraded.

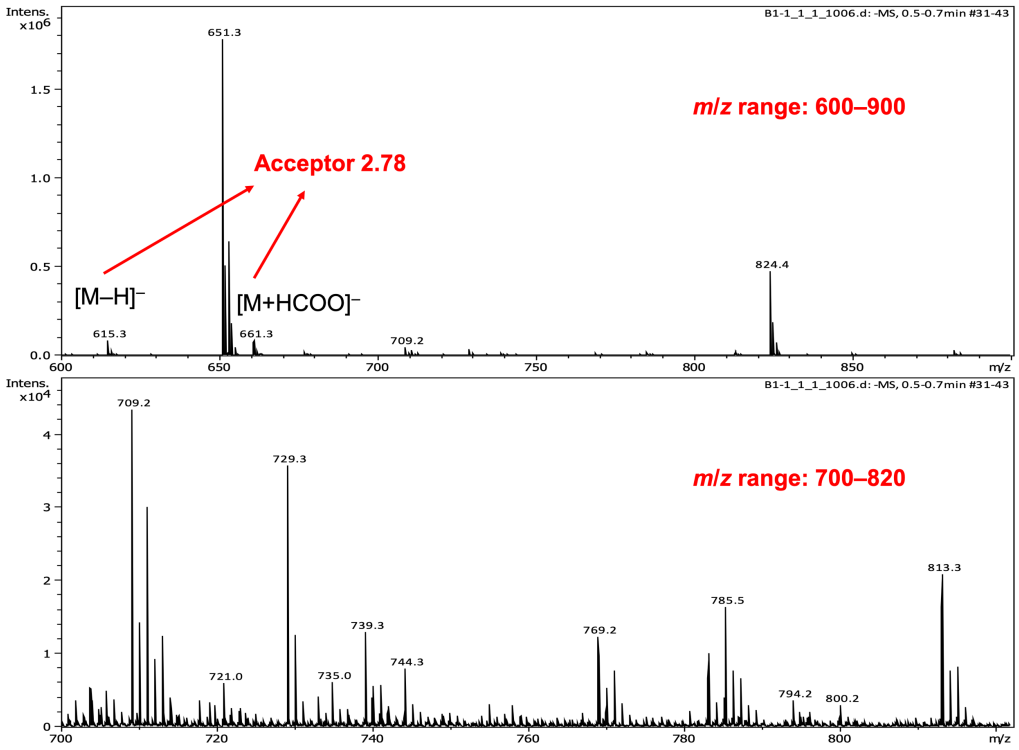
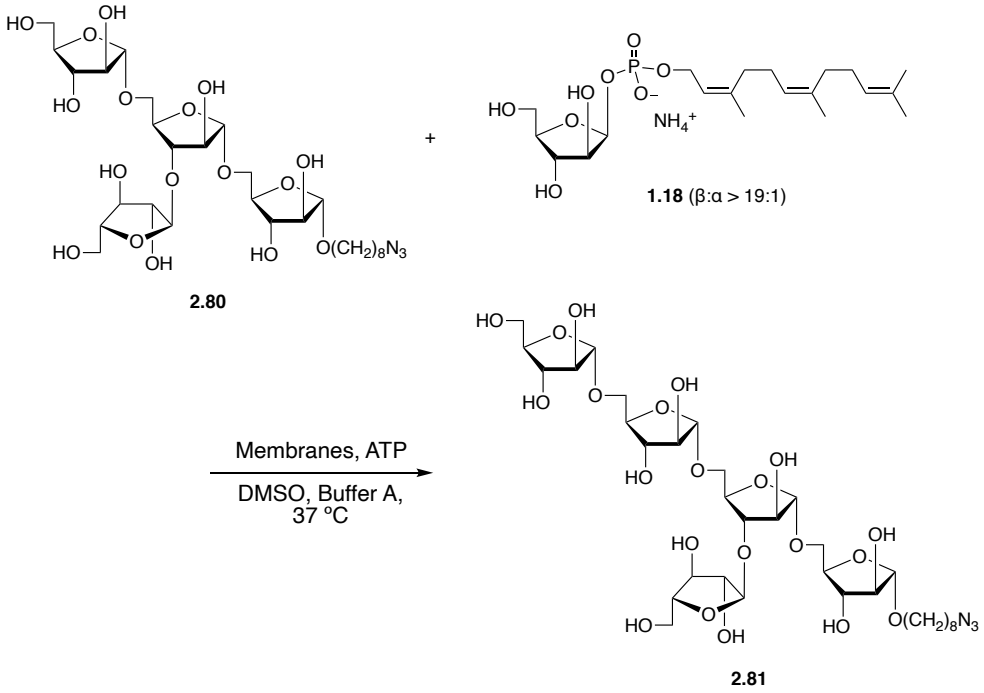


Figure 2.9 LC–MS analysis of the AraT assay reaction products (second attempt). Only the acceptor **2.78** was detected.

Therefore, I repeated the synthesis of FPA **1.18** and I was able to obtain this compound with an excellent β to α ratio (β:α > 19:1). I carried out the assay using **1.18** as the donor and tetraarabinofuranoside **2.80** as the acceptor and treated them with the freshly prepared membrane fractions (**Scheme 2.21**). After purification by the SAX cartridge, the desired enzymatic product **2.81** and the unconsumed acceptor **2.80** were detected using LC–MS technique. The product mixture was per-*O*-acetylated and was analyzed again by LC–MS. Both the acetylated product and the acetylated acceptor were found in the mass spectrum (**Figure 2.10**).



Scheme 2.21 The AraT assay reaction using FPA **1.18** as the donor and tetraarabinofuranoside **2.80** as the acceptor.

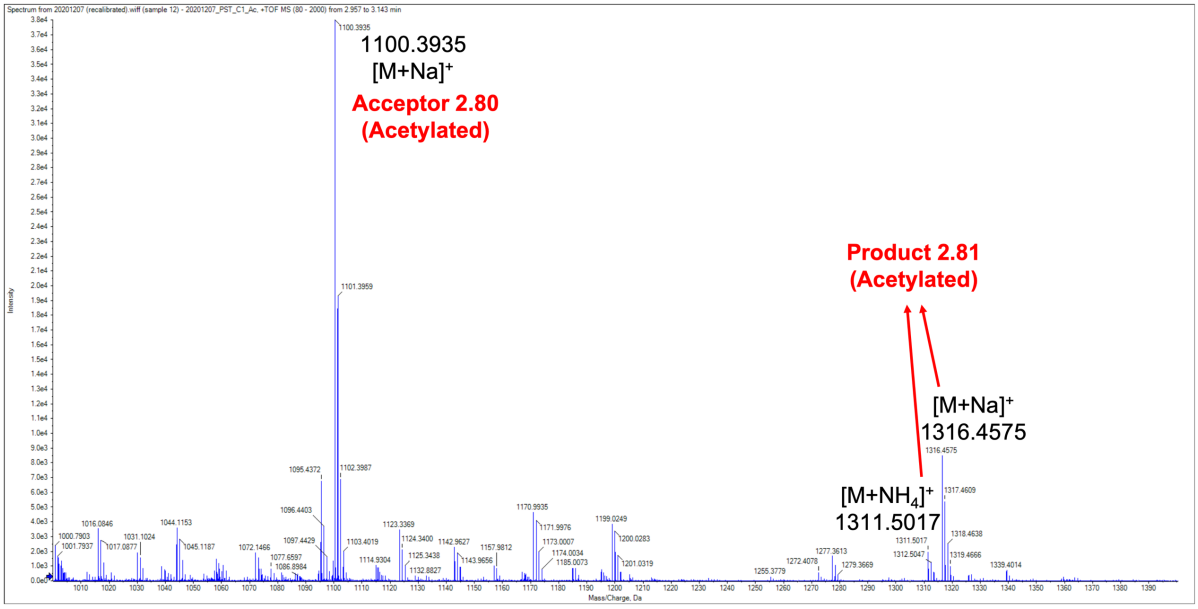


Figure 2.10 LC–MS analysis of the AraT assay reaction products (third attempt). Both the acetylated product **2.81** and the acetylated acceptor **2.80** were detected.

2.3 Summary and Future Work

In conclusion, I synthesized all of the target DPA analogs, including fluoro derivatives **1.31**–**1.33**, azido derivatives **1.34**–**1.36** and FPA **1.18**. Only 2-fluoro- and 2-azido-FPAs (**1.31** and **1.34**) could be generated as the pure β-phosphodiesters. Other FPA derivatives (**1.32**, **1.33**, **1.35** and **1.36**) and the known compound **1.18** were obtained as mixtures of β- and α-anomers. When I first performed the cell-free AraT assay using the known substrate FPA **1.18**, the desired enzymatic product **2.79** could be detected by LC–MS although the peaks were small in the mass spectrum. My second attempt at the same AraT assay reaction was not successful. After I prepared both FPA **1.18** and the membrane fractions again, I carried out the assay using acceptor **2.80**, and this reaction was successful.

Future work will be evaluating the six target molecules (**1.31**–**1.36**) to see if they can be accepted as substrates by AraTs. If any of these compounds is accepted by these enzymes, it can be further used as a tool as discussed previously in Chapter 1 to investigate the biosynthetic pathway of the mycobacterial cell wall.

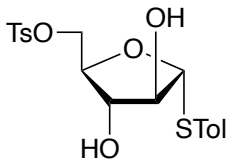
2.4 Experimental Section

2.4.1 General Methods

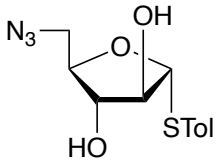
All reagents were purchased from commercial sources and used without further purification unless noted. Dichloromethane, *N*,*N*-dimethylformamide, tetrahydrofuran and toluene used in reactions were taken from a solvent purification system, in which the solvents were purified by successive passage through columns of alumina and copper under argon. Unless stated otherwise, all reactions were carried out in oven-dried round-bottom flasks and were performed under a positive pressure of argon. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} (0.25 mm; Merck) glass plates. TLC spots were detected under UV light and by charring with a solution of *p*-anisaldehyde (7.5 mL) in ethanol (350 mL), acetic acid (10 mL) and sulfuric acid (10 mL). In the reaction work-up involving extractions, solutions of organic solvents were washed with equal amounts of aqueous solutions. Organic solvents were removed under reduced pressure at 40 ºC on a rotary evaporator. All column chromatography was performed on silica gel 60 (40–60 μm). Optical rotations were measured on a PerkinElmer 241 or 341 polarimeter at 22 ± 2 ºC at the sodium D line (589 nm) and are in units of (deg·mL)/(dm·g). NMR spectra were acquired on Agilent/Varian 400, 500 or 700 MHz spectrometers or on a Bruker AVANCE™ 500 MHz spectrometer. ^{1}H NMR spectra were recorded at 500 or 700 MHz, and chemical shifts are referenced to residual $CHCl_3$ (7.26 ppm, $CDCl_3$) or CD_2HOD (3.30 ppm, CD_3OD). ^{13}C NMR spectra were ^{1}H decoupled and were recorded at 126 or 176 MHz, and chemical shifts are referenced to internal $CDCl_3$ (77.06 ppm, $CDCl_3$) or CD_3OD (49.00 ppm, CD_3OD). ^{19}F NMR spectra were collected at 376 or 470 MHz. ^{31}P NMR spectra were ^{1}H decoupled and were acquired at 202 MHz. Peak assignments were based on two-dimensional NMR (COSY, HSQC and HMBC) experiments, and the stereochemistry of the anomeric centers was confirmed by measuring the

value of $^{3}J_{H\text{-}1,H\text{-}2}$. High-resolution electrospray ionization (ESI) and atmospheric pressure photoionization (APPI) mass spectrometry spectra were recorded on an Agilent Technologies 6220 (Santa Clara, California, U.S.A.) time-of-flight (TOF) mass spectrometer or on a Waters LCT (Manchester, U.K.) TOF mass spectrometer with samples dissolved in an appropriate solvent.

2.4.2 Experimental Procedures and Characterization Data

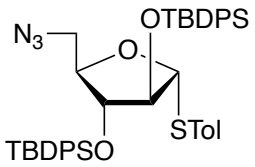


***p*-Tolyl 5-*O*-*p*-toluenesulfonyl-1-thio-α-D-arabinofuranoside (2.19).**[8] To a solution of **2.21**[9] (5.41 g, 21.1 mmol) in dry pyridine (100 mL) at 0 ºC were added *p*-toluenesulfonyl chloride (6.04 g, 31.7 mmol) and DMAP (1.29 g, 10.6 mmol). The reaction mixture was stirred at rt for 8 h and was then diluted with EtOAc. The organic layer was washed with 1 N $HCl_{(aq)}$, H_2O, saturated $NaHCO_{3(aq)}$ and brine before being dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (35% EtOAc–hexanes) to yield **2.19** (7.15 g, 83%) as a colorless oil. The spectroscopic data for **2.19** were identical to those reported.[8]



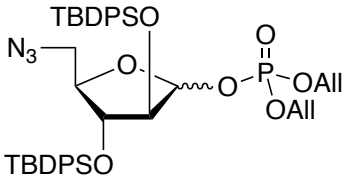
***p*-Tolyl 5-azido-5-deoxy-1-thio-α-D-arabinofuranoside (2.26).** To a solution of **2.19** (1.52 g, 3.70 mmol) in dry DMF (30 mL) were added NaN_3 (722 mg, 11.1 mmol) and 18-crown-6 (2.93 g, 11.1 mmol). The reaction mixture was stirred at 50 ºC for 14 h before being poured into ice-cold water and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column

chromatography (1:1 hexanes–EtOAc) to yield **2.26** (852 mg, 82%) as a colorless oil. R_f 0.60 (1:2 hexanes–EtOAc); $[\alpha]_D$ +179 (*c* 4.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.42–7.38 (m, 2 H, ArH), 7.16–7.12 (m, 2 H, ArH), 5.36 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 4.22 (ddd, $J_{3,4}$ = 5.6 Hz, $J_{4,5b}$ = 4.0 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-4), 4.15 (ddd, $J_{2,2\text{-OH}}$ = 6.8 Hz, $J_{2,3}$ = 3.9 Hz, $J_{1,2}$ = 3.6 Hz, 1 H, H-2), 4.09 (ddd, $J_{3,3\text{-OH}}$ = 6.8 Hz, $J_{3,4}$ = 5.6 Hz, $J_{2,3}$ = 3.9 Hz, 1 H, H-3), 3.64 (dd, $J_{5a,5b}$ = 13.1 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-5a), 3.54 (dd, $J_{5a,5b}$ = 13.1 Hz, $J_{4,5b}$ = 4.0 Hz, 1 H, H-5b), 2.77 (d, $J_{2,2\text{-OH}}$ = 6.8 Hz, 1 H, 2-OH), 2.47 (d, $J_{3,3\text{-OH}}$ = 6.8 Hz, 1 H, 3-OH), 2.34 (s, 3 H, Ar$\underline{C}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 138.2 (Ar), 132.6 (Ar), 129.9 (Ar), 129.2 (Ar), 92.1 (C-1), 82.3 (C-4), 81.6 (C-2), 78.3 (C-3), 51.9 (C-5), 21.1 (Ar$\underline{C}H_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{15}N_3NaO_3S$, 304.0726; found, 304.0726.



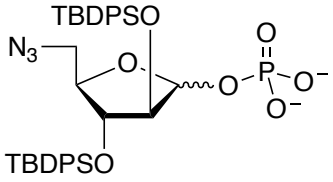
***p*-Tolyl 5-azido-2,3-di-*O*-*tert*-butyldiphenylsilyl-5-deoxy-1-thio-α-D-arabinofuranoside (2.12).** To a solution of **2.26** (731 mg, 2.60 mmol) in dry DMF (11 mL) was added imidazole (2.65 g, 39.0 mmol), followed by TBDPSCl (3.38 mL, 13.0 mmol). The reaction mixture was stirred at 50 ºC for 16 h. After cooling to rt, excess TBDPSCl was quenched by the addition of ice-cold water and the solution was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (50:1 hexanes–EtOAc) to yield **2.12** (1.72 g, 87%) as a colorless oil. R_f 0.60 (10:1 hexanes–EtOAc); $[\alpha]_D$ +27 (*c* 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.70–7.66 (m, 2 H, ArH), 7.60–7.54 (m, 4 H, ArH), 7.51–7.48 (m, 2 H, ArH), 7.47–7.28 (m, 12 H, ArH), 7.16–7.12 (m, 2 H, ArH), 7.05–7.01 (m, 2 H, ArH), 5.29 (s, 1 H, H-1), 4.53 (s, 1 H, H-2), 4.28

(ddd, $J_{4,5a}$ = 7.6 Hz, $J_{4,5b}$ = 4.5 Hz, $J_{3,4}$ = 2.0 Hz, 1 H, H-4), 4.01 (d, $J_{3,4}$ = 2.0 Hz, 1 H, H-3), 3.06 (dd, $J_{5a,5b}$ = 12.5 Hz, $J_{4,5a}$ = 7.6 Hz, 1 H, H-5a), 2.76 (dd, $J_{5a,5b}$ = 12.5 Hz, $J_{4,5b}$ = 4.5 Hz, 1 H, H-5b), 2.31 (s, 3 H, ArC$\underline{H}_3$), 1.03 (s, 9 H, SiC$(CH_3)_3$), 0.96 (s, 9 H, SiC$(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 136.9 (Ar), 135.9 (Ar), 135.8 (Ar), 135.7 (Ar), 133.1 (Ar), 132.9 (Ar), 132.7 (Ar), 132.5 (Ar), 132.3 (Ar), 131.8 (Ar), 130.1 (Ar), 130.0 (Ar), 129.5 (Ar), 127.8 (Ar), 95.7 (C-1), 86.5 (C-4), 84.7 (C-2), 80.9 (C-3), 52.1 (C-5), 26.82 (SiC($\underline{C}H_3)_3$), 26.79 (SiC($\underline{C}H_3)_3$), 21.1 (Ar$\underline{C}H_3$), 19.2 (Si$\underline{C}(CH_3)_3$), 19.0 (Si$\underline{C}(CH_3)_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{44}H_{51}N_3NaO_3SSi_2$, 780.3082; found, 780.3080.



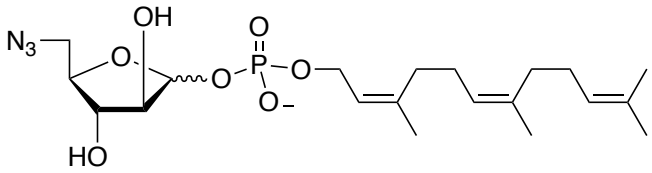
Diallyl (5-azido-2,3-di-*O*-*tert*-butyldiphenylsilyl-5-deoxy-α/β-D-arabinofuranosyl) phosphate (2.15). To a stirred solution of **2.12** (191 mg, 0.252 mmol) in CH_2Cl_2 (3 mL) was added Br_2 (19 μL, 0.37 mmol). The reaction mixture was stirred at rt for 20 min before being concentrated. The crude glycosyl bromide was azeotropically dried with toluene and then used immediately. To a stirred solution of azeotropically dried diallyl phosphate[6] (100 mg, 0.561 mmol) in toluene (1 mL) were added powdered 4 Å molecular sieves (250 mg) and Et_3N (101 μL, 0.728 mmol). The mixture was cooled to 0 ºC, and a solution of the aforementioned glycosyl bromide in toluene (1 mL) was added slowly via a cannula. The transfer was completed by rinsing the flask twice with toluene (2 × 0.5 mL). The reaction mixture was warmed slowly to rt and stirred for 19 h before being filtered through a pad of Celite®, rinsed with EtOAc, and the filtrate was concentrated. The crude residue was purified by column chromatography (15% EtOAc–hexanes) to yield **2.15** (174 mg, 85% over two steps, β:α 7.7:1, inseparable) as a colorless oil. R_f 0.40 (3:1 hexanes–EtOAc);

Data for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.73–7.67 (m, 6 H, ArH), 7.64–7.61 (m, 2 H, ArH), 7.47–7.42 (m, 4 H, ArH), 7.41–7.32 (m, 8 H, ArH), 5.88–5.75 (m, 2 H, 2 × $OCH_2C\underline{H}=CH_2$), 5.29–5.14 (m, 5 H, 2 × $OCH_2CH=C\underline{H_2}$ and H-1), 4.49–4.30 (m, 5 H, 2 × $OC\underline{H_2}CH=CH_2$ and H-2), 4.28 (dd, $J_{2,3}$ = 5.3 Hz, $J_{3,4}$ = 4.5 Hz, 1 H, H-3), 3.83 (ddd, $J_{4,5a}$ = 9.4 Hz, $J_{3,4}$ = 4.5 Hz, $J_{4,5b}$ = 3.3 Hz, 1 H, H-4), 3.05 (dd, $J_{5a,5b}$ = 12.8 Hz, $J_{4,5a}$ = 9.4 Hz, 1 H, H-5a), 2.08 (dd, $J_{5a,5b}$ = 12.8 Hz, $J_{4,5b}$ = 3.3 Hz, 1 H, H-5b), 1.10 (s, 9 H, $SiC(CH_3)_3$), 1.02 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 136.0 (Ar), 135.84 (Ar), 135.80 (Ar), 135.7 (Ar), 133.5 (Ar), 132.8 (Ar), 132.6 (d, $J_{C,P}$ = 7.1 Hz, $OCH_2\underline{C}H=CH_2$), 132.4 (d, $J_{C,P}$ = 7.7 Hz, $OCH_2\underline{C}H=CH_2$), 132.1 (Ar), 130.4 (Ar), 130.11 (Ar), 130.07 (Ar), 128.1 (Ar), 128.0 (Ar), 127.91 (Ar), 127.90 (Ar), 118.0 (2 × $OCH_2CH=\underline{C}H_2$), 99.7 (d, $J_{C,P}$ = 6.6 Hz, C-1), 83.4 (C-4), 79.2 (d, $J_{C,P}$ = 9.0 Hz, C-2), 78.0 (C-3), 68.1 (d, $J_{C,P}$ = 5.2 Hz, $O\underline{C}H_2CH=CH_2$), 68.0 (d, $J_{C,P}$ = 5.1 Hz, $O\underline{C}H_2CH=CH_2$), 52.8 (C-5), 27.1 ($SiC(\underline{C}H_3)_3$), 27.0 ($SiC(\underline{C}H_3)_3$), 19.4 ($Si\underline{C}(CH_3)_3$), 19.1 ($Si\underline{C}(CH_3)_3$); ^{31}P NMR (202 MHz, $CDCl_3$, δ): –0.70; HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{43}H_{54}N_3NaO_7PSi_2$, 834.3130; found, 834.3134.



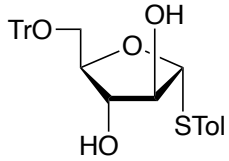
5-Azido-2,3-di-*O-tert*-butyldiphenylsilyl-5-deoxy-α/β-D-arabinofuranosyl phosphate (2.18). To a solution of **2.15** (63.1 mg, 0.0777 mmol) in a mixture of CH_2Cl_2 (0.6 mL) and CH_3OH (0.4 mL) was added $PdCl_2$ (6.9 mg, 0.039 mmol). The reaction mixture was stirred at rt for 3 h and was then filtered through a pad of Celite® with 1:1 CH_2Cl_2–CH_3OH. The filtrate was concentrated to a crude residue that was purified by column chromatography (gradient of 4:1 to 3:7 $CHCl_3$–CH_3OH, containing 2% v/v of Et_3N) to yield **2.18** (as the triethylammonium salt, 42.5 mg, 59%, β:α 4.8:1,

inseparable) as a colorless oil. R_f 0.36 (5:1 EtOAc–CH_3OH); Data for the β-anomer: ^{1}H NMR (500 MHz, CD_3OD, δ): 7.63–7.60 (m, 4 H, ArH), 7.51–7.47 (m, 4 H, ArH), 7.43–7.33 (m, 8 H, ArH), 7.28–7.23 (m, 4 H, ArH), 5.70 (dd, $J_{1,P}$ = 7.0 Hz, $J_{1,2}$ = 3.1 Hz, 1 H, H-1), 4.28 (dd, $J_{2,3}$ = 3.3 Hz, $J_{1,2}$ = 3.1 Hz, 1 H, H-2), 4.05 (dd, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 2.3 Hz, 1 H, H-3), 3.71 (ddd, $J_{4,5a}$ = 7.9 Hz, $J_{4,5b}$ = 5.1 Hz, $J_{3,4}$ = 2.3 Hz, 1 H, H-4), 3.28 (dd, $J_{5a,5b}$ = 12.4 Hz, $J_{4,5a}$ = 7.9 Hz, 1 H, H-5a), 2.52 (dd, $J_{5a,5b}$ = 12.4 Hz, $J_{4,5b}$ = 5.1 Hz, 1 H, H-5b), 1.05 (s, 9 H, $SiC(CH_3)_3$), 0.90 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (126 MHz, CD_3OD, δ): 136.3 (Ar), 135.6 (Ar), 135.55 (Ar), 135.5 (Ar), 133.5 (Ar), 133.0 (Ar), 132.4 (Ar), 132.2 (Ar), 129.8 (Ar), 129.7 (Ar), 129.6 (Ar), 129.5 (Ar), 129.4 (Ar), 127.6 (Ar), 127.50 (Ar), 127.47 (Ar), 127.4 (Ar), 99.2 (d, $J_{C,P}$ = 5.3 Hz, C-1), 82.9 (C-4), 78.6 (C-3), 78.5 (d, $J_{C,P}$ = 8.6 Hz, C-2), 52.8 (C-5), 26.3 ($SiC(\underline{C}H_3)_3$), 26.0 ($SiC(\underline{C}H_3)_3$), 18.8 ($Si\underline{C}(CH_3)_3$), 18.4 ($Si\underline{C}(CH_3)_3$); ^{31}P NMR (202 MHz, CD_3OD, δ): 0.52; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{37}H_{45}N_3O_7PSi_2$, 730.2539; found, 730.2534.



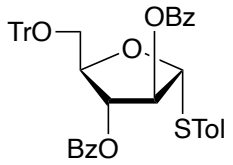
(*Z*,*Z*)-Farnesylphosphoryl-5-azido-5-deoxy-α/β-D-arabinofuranose (1.36). Compound **2.18** (60.2 mg, 0.0644 mmol) and (*Z*,*Z*)-farnesol[5] (57.3 mg, 0.258 mmol) were azeotropically dried with toluene. The mixture was dissolved in pyridine (1 mL) and Cl_3CCN (65 μL, 0.65 mmol) was added. The resulting solution was stirred for 16 h at 55 ºC before being cooled to rt and concentrated. The crude phosphodiester was dissolved in a 15% solution of concentrated NH_4OH in CH_3OH (1.5 mL), and NH_4F (71.6 mg, 1.93 mmol) was added. After stirring for 12 h at 55 ºC, the reaction mixture was cooled to rt, and CH_2Cl_2 (2 mL) was added to precipitate any remaining NH_4F. The solution was filtered through a pad of Celite® and the filtrate was concentrated to a crude residue

that was purified by column chromatography (1:1 EtOAc–CH_3OH). Residual colored impurities were removed by the addition of activated charcoal to the product in CH_3OH, followed by the filtration through a syringe filter (0.45 μm). The filtrate was concentrated to give **1.36** (5.2 mg, 17% over two steps, β:α 1.1:1, inseparable) as a colorless oil. R_f 0.45 (3:2 EtOAc–CH_3OH); Data for the β-anomer: ^{1}H NMR (500 MHz, CD_3OD, δ): 5.53 (dd, $J_{1,P}$ = 6.2 Hz, $J_{1,2}$ = 3.4 Hz, 1 H, H-1), 5.45–5.39 (m, 1 H, OCH_2CH=C), 5.16–5.08 (m, 2 H, 2 × CH_2CH=C), 4.48–4.40 (m, 2 H, OCH_2CH=C), 3.99–3.93 (m, 2 H, H-2 and H-3), 3.85–3.79 (m, 1 H, H-4), 3.55–3.42 (m, 2 H, H-5a and H-5b), 2.14–1.99 (m, 8 H, 4 × allylic CH_2), 1.74 (s, 3 H, CH_3), 1.67 (s, 6 H, 2 × CH_3), 1.61 (s, 3 H, CH_3); ^{13}C NMR (126 MHz, CD_3OD, δ): 139.0 (CH=C), 135.0 (CH=C), 131.0 (CH=C), 124.4 (CH=C), 124.0 (CH=C), 122.1 (d, $J_{C,P}$ = 8.2 Hz, CH=C), 98.2 (d, $J_{C,P}$ = 5.0 Hz, C-1), 81.4 (C-4), 77.7 (d, $J_{C,P}$ = 6.7 Hz, C-2), 75.9 (C-3), 61.9 (d, $J_{C,P}$ = 5.2 Hz, OCH_2CH=C), 54.0 (C-5), 31.9 (allylic CH_2), 31.5 (allylic CH_2), 26.3 (allylic CH_2), 26.2 (allylic CH_2), 24.5 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 16.3 (CH_3); ^{31}P NMR (202 MHz, CD_3OD, δ): 0.43; HRMS–ESI–TOF (*m*/*z*): $[M–H]^–$ calcd for $C_{20}H_{33}N_3O_7P$, 458.2062; found, 458.2059.

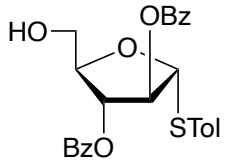


***p*-Tolyl 5-*O*-triphenylmethyl-1-thio-α-D-arabinofuranoside (2.27).**[8] To a solution of **2.21**[9] (1.01 g, 3.94 mmol) in dry CH_2Cl_2 (20 mL) were added DABCO (884 mg, 7.88 mmol) and triphenylmethyl chloride (1.65 g, 5.91 mmol). The reaction mixture was stirred overnight at rt before being concentrated. The crude product was purified by column chromatography (20:1 CH_2Cl_2–CH_3OH) to yield **2.27** (1.55 g, 79%) as a light-yellow solid. R_f 0.55 (10:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ +136 (*c* 1.25, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.43–7.39 (m, 8 H, ArH),

7.33–7.29 (m, 6 H, ArH), 7.27–7.24 (m, 3 H, ArH), 7.16–7.13 (m, 2 H, ArH), 5.50 (d, $J_{1,2}$ = 2.6 Hz, 1 H, H-1), 4.23 (dd, $J_{4,5a}$ = 3.8 Hz, $J_{4,5b}$ = 3.0 Hz, 1 H, H-4), 4.17–4.13 (m, 1 H, H-2), 4.09–4.05 (m, 1 H, H-3), 3.56 (dd, $J_{5a,5b}$ = 10.4 Hz, $J_{4,5a}$ = 3.8 Hz, 1 H, H-5a), 3.45 (d, $J_{2,2\text{-OH}}$ = 8.3 Hz, 1 H, 2-OH), 3.31 (dd, $J_{5a,5b}$ = 10.4 Hz, $J_{4,5b}$ = 3.0 Hz, 1 H, H-5b), 2.50 (d, $J_{3,3\text{-OH}}$ = 7.4 Hz, 1 H, 3-OH), 2.35 (s, 3 H, ArC$\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 143.0 (Ar), 137.9 (Ar), 132.6 (Ar), 129.9 (Ar), 129.6 (Ar), 128.7 (Ar), 128.0 (Ar), 127.4 (Ar), 92.7 (C-1), 87.9 (O$\underline{C}(C_6H_5)_3$), 84.4 (C-4), 81.4 (C-2), 79.0 (C-3), 63.7 (C-5), 21.1 (Ar$\underline{C}H_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{31}H_{30}NaO_4S$, 521.1757; found, 521.1759.

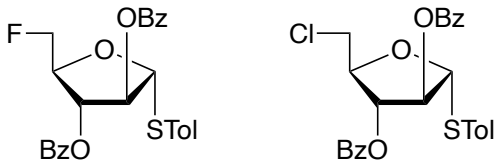


***p*-Tolyl 2,3-di-*O*-benzoyl-5-*O*-triphenylmethyl-1-thio-α-D-arabinofuranoside (2.28).**[8] To a solution of **2.27** (1.55 g, 3.10 mmol) in dry pyridine (10 mL) was added BzCl (1.08 mL, 9.30 mmol) dropwise. The reaction mixture was stirred at rt overnight. Excess BzCl was quenched by the addition of water and the solution was diluted with EtOAc. The organic layer was washed with 1 N $HCl_{(aq)}$, H_2O, saturated $NaHCO_{3(aq)}$ and brine before being dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (gradient of 6:1→4:1 hexanes–EtOAc) to yield **2.28** (2.19 g, quantitative) as a colorless oil. The spectroscopic data for **2.28** were identical to those reported.[8]



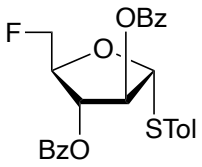
***p*-Tolyl 2,3-di-*O*-benzoyl-1-thio-α-D-arabinofuranoside (2.20).**[8] To a solution of **2.28** (2.19 g, 3.10 mmol) in 3:1 CH_3OH–CH_2Cl_2 (120 mL) was added *p*-toluenesulfonic acid monohydrate (649

mg, 3.41 mmol). The reaction mixture was stirred at rt. After 4 h, Et_3N (1.5 mL) was added, and the solution was concentrated. The crude residue was purified by column chromatography (4:1 hexanes–EtOAc) to give **2.20** (1.28 g, 89%) as a colorless oil. The spectroscopic data for **2.20** were identical to those reported.[8]



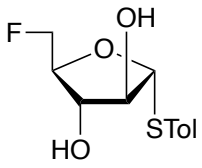
***p*-Tolyl 2,3-di-*O*-benzoyl-5-deoxy-5-fluoro-1-thio-α-D-arabinofuranoside (2.29)[8] and *p*-Tolyl 2,3-di-*O*-benzoyl-5-chloro-5-deoxy-1-thio-α-D-arabinofuranoside (2.30).** Compound **2.20** (227 mg, 0.489 mmol) was stirred in dry CH_2Cl_2 (11 mL) at rt for 5 min under an atmosphere of argon before cooling to –40 ºC. DAST (120 μL, 0.977 mmol) was added and the mixture was stirred for 30 min. The reaction vessel was then warmed to rt and allowed to stir for 5 h. The reaction was carefully neutralized with saturated $NaHCO_{3(aq)}$ and the resultant solution was extracted with Et_2O three times. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (9:1 hexanes–EtOAc) to give an inseparable mixture of **2.29** and **2.30** (139 mg, 60%, **2.29**:**2.30** 1:1.2) as a colorless oil. R_f 0.71 (2:1 hexanes–EtOAc); Data for **2.29**: ^{1}H NMR (700 MHz, $CDCl_3$, δ): 8.14–8.11 (m, 2 H, ArH), 8.07–8.04 (m, 2 H, ArH), 7.64–7.61 (m, 1 H, ArH), 7.61–7.57 (m, 1 H, ArH), 7.52–7.48 (m, 2 H, ArH), 7.48–7.43 (m, 4 H, ArH), 7.16–7.13 (m, 2 H, ArH), 5.76 (s, 1 H, H-1), 5.73 (s, 1 H, H-2), 5.54 (d, $J_{3,4}$ = 4.5 Hz, 1 H, H-3), 4.87 (ddd, $J_{5a,F}$ = 46.5 Hz, $J_{5a,5b}$ = 10.3 Hz, $J_{4,5a}$ = 3.9 Hz, 1 H, H-5a), 4.81 (ddd, $J_{5b,F}$ = 47.7 Hz, $J_{5a,5b}$ = 10.3 Hz, $J_{4,5b}$ = 2.5 Hz, 1 H, H-5b), 4.66 (dddd, $J_{4,F}$ = 26.3 Hz, $J_{3,4}$ = 4.5 Hz, $J_{4,5a}$ = 3.9 Hz, $J_{4,5b}$ = 2.5 Hz, 1 H, H-4), 2.34 (s, 3 H, ArC$\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 165.7 (C=O), 165.2 (C=O), 138.1

(Ar), 133.7 (Ar), 133.6 (Ar), 132.7 (Ar), 130.0 (Ar), 129.91 (Ar), 129.88 (Ar), 129.7 (Ar), 129.0 (Ar), 128.9 (Ar), 128.6 (Ar), 128.5 (Ar), 91.9 (C-1), 82.3 (d, $J_{C,F}$ = 18.7 Hz, C-4), 81.9 (d, $J_{C,F}$ = 174.6 Hz, C-5), 81.7 (C-2), 77.3 (d, $J_{C,F}$ = 6.5 Hz, C-3), 21.1 (Ar<u>C</u>H$_3$); ^{19}F NMR (376 MHz, $CDCl_3$, δ): –230.29 (ddd, $J_{5b,F}$ = 47.7 Hz, $J_{5a,F}$ = 46.5 Hz, $J_{4,F}$ = 26.3 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{23}FNaO_5S$, 489.1142; found, 489.1146. Data for **2.30**: ^{1}H NMR (700 MHz, $CDCl_3$, δ): 8.14–8.11 (m, 2 H, ArH), 8.07–8.04 (m, 2 H, ArH), 7.64–7.61 (m, 1 H, ArH), 7.61–7.57 (m, 1 H, ArH), 7.52–7.48 (m, 2 H, ArH), 7.48–7.43 (m, 4 H, ArH), 7.16–7.13 (m, 2 H, ArH), 5.76 (s, 1 H, H-1), 5.70 (d, $J_{2,3}$ = 1.4 Hz, 1 H, H-2), 5.55 (dd, $J_{3,4}$ = 4.4 Hz, $J_{2,3}$ = 1.4 Hz, 1 H, H-3), 4.76 (ddd, $J_{4,5a}$ = 4.7 Hz, $J_{3,4}$ = 4.4 Hz, $J_{4,5b}$ = 4.2 Hz, 1 H, H-4), 4.02 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 4.7 Hz, 1 H, H-5a), 3.97 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5b}$ = 4.2 Hz, 1 H, H-5b), 2.34 (s, 3 H, ArC<u>H</u>$_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 165.6 (C=O), 165.2 (C=O), 138.2 (Ar), 133.7 (Ar), 133.6 (Ar), 132.8 (Ar), 130.0 (Ar), 129.91 (Ar), 129.88 (Ar), 129.6 (Ar), 129.0 (Ar), 128.9 (Ar), 128.6 (Ar), 128.5 (Ar), 91.9 (C-1), 82.6 (C-4), 82.0 (C-2), 78.7 (C-3), 43.9 (C-5), 21.1 (Ar<u>C</u>H$_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{23}ClNaO_5S$, 505.0847; found, 505.0860.

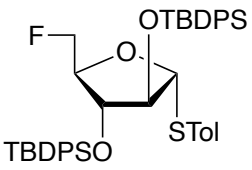


***p*-Tolyl 2,3-di-*O*-benzoyl-5-deoxy-5-fluoro-1-thio-α-D-arabinofuranoside (2.29).**[8] Compound **2.20** (782 mg, 1.68 mmol) was stirred in dry diglyme (8.4 mL) at rt for 5 min under an atmosphere of argon before cooling to –40 ºC. DAST (1.03 mL, 8.42 mmol) was added and the mixture was stirred for 30 min. The reaction vessel was then warmed to rt and allowed to stir for 18 h. The reaction was carefully neutralized with saturated $NaHCO_{3(aq)}$ and the resultant solution was extracted with Et_2O three times. The combined organic layers were dried with $MgSO_4$, filtered,

and the filtrate was concentrated. The crude residue was purified by column chromatography (9:1 hexanes–EtOAc) to yield **2.29** (492 mg, 63%) as a colorless oil. The spectroscopic data for **2.29** were identical to those reported.[8]

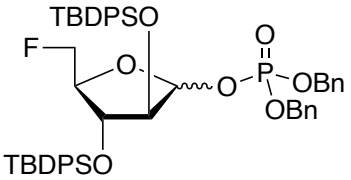


***p*-Tolyl 5-deoxy-5-fluoro-1-thio-α-D-arabinofuranoside (2.31).** Compound **2.29** (491 mg, 1.05 mmol) was treated with 200 mM NaOH in CH_3OH (5 mL), and stirred for 1 h at rt. The reaction mixture was neutralized with Amberlite® IR-120 (H^+) resin, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (gradient of 2:1→1:1 hexanes–EtOAc) to give **2.31** (212 mg, 78%) as a white solid. R_f 0.21 (1:1 hexanes–EtOAc); $[\alpha]_D$ +214 (*c* 1.18, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.42–7.39 (m, 2 H, ArH), 7.15–7.13 (m, 2 H, ArH), 5.36 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 4.64 (ddd, $J_{5a,F}$ = 48.1 Hz, $J_{5a,5b}$ = 10.4 Hz, $J_{4,5a}$ = 2.6 Hz, 1 H, H-5a), 4.61 (ddd, $J_{5b,F}$ = 46.9 Hz, $J_{5a,5b}$ = 10.4 Hz, $J_{4,5b}$ = 3.3 Hz, 1 H, H-5b), 4.26–4.19 (m, 2 H, H-4 and H-3), 4.18–4.16 (m, 1 H, H-2), 2.34 (s, 3 H, ArC$\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 138.2 (Ar), 132.6 (Ar), 129.9 (Ar), 129.1 (Ar), 92.0 (C-1), 82.3 (d, $J_{C,F}$ = 18.8 Hz, C-4), 82.0 (d, $J_{C,F}$ = 172.2 Hz, C-5), 81.6 (C-2), 76.9 (C-3), 21.1 (Ar$\underline{C}H_3$); ^{19}F NMR (376 MHz, $CDCl_3$, δ): –230.53 (ddd, $J_{5a,F}$ = 48.1 Hz, $J_{5b,F}$ = 46.9 Hz, $J_{4,F}$ = 28.9 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{15}FNaO_3S$, 281.0618; found, 281.0613.



***p*-Tolyl 2,3-di-*O*-*tert*-butyldiphenylsilyl-5-deoxy-5-fluoro-1-thio-α-D-arabinofuranoside (2.3).** To a solution of **2.31** (197 mg, 0.763 mmol) in dry DMF (4 mL) was added imidazole (1.56 g, 22.9

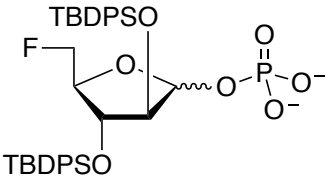
mmol), followed by TBDPSCl (1.96 mL, 7.63 mmol). The reaction mixture was stirred at 60 ºC for 24 h. After cooling to rt, excess TBDPSCl was quenched by the addition of ice-cold water and the solution was extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (50:1 hexanes–EtOAc) to yield **2.3** (502 mg, 90%) as a white solid. R_f 0.48 (10:1 hexanes–EtOAc); $[\alpha]_D$ +35.2 (*c* 1.38, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.72–7.70 (m, 2 H, ArH), 7.63–7.60 (m, 2 H, ArH), 7.58–7.56 (m, 2 H, ArH), 7.51–7.49 (m, 2 H, ArH), 7.48–7.30 (m, 12 H, ArH), 7.18–7.15 (m, 2 H, ArH), 7.06–7.03 (m, 2 H, ArH), 5.31 (s, 1 H, H-1), 4.55 (s, 1 H, H-2), 4.45 (dddd, $J_{4,F}$ = 17.1 Hz, $J_{4,5a}$ = 6.7 Hz, $J_{4,5b}$ = 4.6 Hz, $J_{3,4}$ = 1.9 Hz, 1 H, H-4), 4.18 (ddd, $J_{5a,F}$ = 47.2 Hz, $J_{5a,5b}$ = 9.6 Hz, $J_{4,5a}$ = 6.7 Hz, 1 H, H-5a), 4.10 (d, $J_{3,4}$ = 1.9 Hz, 1 H, H-3), 4.01 (ddd, $J_{5b,F}$ = 46.7 Hz, $J_{5a,5b}$ = 9.6 Hz, $J_{4,5b}$ = 4.6 Hz, 1 H, H-5b), 2.32 (s, 3 H, ArC$\underline{H}_3$), 1.06 (s, 9 H, SiC$(CH_3)_3$), 0.97 (s, 9 H, SiC$(CH_3)_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 136.9 (Ar), 136.0 (Ar), 135.8 (Ar), 135.71 (Ar), 135.69 (Ar), 133.1 (Ar), 132.9 (Ar), 132.7 (Ar), 132.6 (Ar), 132.4 (Ar), 132.0 (Ar), 130.0 (Ar), 129.93 (Ar), 129.92 (Ar), 129.5 (Ar), 127.83 (Ar), 127.81 (Ar), 95.9 (C-1), 86.0 (d, $J_{C,F}$ = 19.9 Hz, C-4), 84.3 (C-2), 82.3 (d, $J_{C,F}$ = 171.9 Hz, C-5), 79.7 (d, $J_{C,F}$ = 5.7 Hz, C-3), 26.79 (SiC($\underline{C}H_3$)$_3$), 26.76 (SiC($\underline{C}H_3$)$_3$), 21.1 (Ar$\underline{C}H_3$), 19.2 (Si$\underline{C}$(CH$_3$)$_3$), 19.0 (Si$\underline{C}$(CH$_3$)$_3$); ^{19}F NMR (376 MHz, $CDCl_3$, δ): –224.47 (ddd, $J_{5a,F}$ = 47.2 Hz, $J_{5b,F}$ = 46.7 Hz, $J_{4,F}$ = 17.1 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{44}H_{51}FNaO_3SSi_2$, 757.2974; found, 757.2972.



Dibenzyl (2,3-di-*O*-*tert*-butyldiphenylsilyl-5-deoxy-5-fluoro-α/β-D-arabinofuranosyl) phosphate (2.6). To a stirred solution of **2.3** (196 mg, 0.267 mmol) in CH_2Cl_2 (3 mL) was added

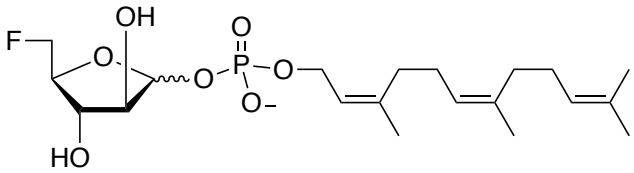
Br_2 (18 μL, 0.35 mmol). The reaction mixture was stirred at rt for 20 min before being concentrated. The crude glycosyl bromide was azeotropically dried with toluene and then used immediately. To a stirred solution of azeotropically dried dibenzyl phosphate (149 mg, 0.534 mmol) in toluene (1 mL) were added powdered 4 Å molecular sieves (250 mg) and Et_3N (96 μL, 0.69 mmol). The mixture was cooled to 0 ºC, and a solution of the aforementioned glycosyl bromide in toluene (1 mL) was added slowly via a cannula. The transfer was completed by rinsing the flask twice with toluene (2 × 0.5 mL). The reaction mixture was warmed slowly to rt and stirred overnight before being filtered through a pad of Celite®, rinsed with EtOAc, and the filtrate was concentrated. The crude residue was purified by column chromatography (15% EtOAc–hexanes) to yield **2.6** (185 mg, 78% over two steps, β:α 6.2:1, inseparable) as a colorless oil. R_f 0.44 (3:1 hexanes–EtOAc); Data for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.72–7.61 (m, 8 H, ArH), 7.46–7.15 (m, 22 H, ArH), 5.26 (dd, $J_{1,P}$ = 4.1 Hz, $J_{1,2}$ = 3.5 Hz, 1 H, H-1), 4.96 (dd, J_{gem} = 11.9 Hz, J_{H-P} = 7.0 Hz, 1 H, OC$\underline{H}_2$Ph), 4.87 (dd, J_{gem} = 11.9 Hz, J_{H-P} = 7.7 Hz, 1 H, OC$\underline{H}_2$Ph), 4.82 (dd, J_{gem} = 8.8 Hz, J_{H-P} = 7.0 Hz, 2 H, OC$\underline{H}_2$Ph), 4.44 (ddd, $J_{2,3}$ = 5.7 Hz, $J_{1,2}$ = 3.5 Hz, $J_{2,P}$ = 2.4 Hz, 1 H, H-2), 4.39 (dd, $J_{2,3}$ = 5.7 Hz, $J_{3,4}$ = 4.6 Hz, 1 H, H-3), 3.99 (dddd, $J_{4,F}$ = 18.5 Hz, $J_{4,5a}$ = 7.5 Hz, $J_{3,4}$ = 4.6 Hz, $J_{4,5b}$ = 3.4 Hz, 1 H, H-4), 3.84 (ddd, $J_{5a,F}$ = 47.5 Hz, $J_{5a,5b}$ = 10.0 Hz, $J_{4,5a}$ = 7.5 Hz, 1 H, H-5a), 3.50 (ddd, $J_{5b,F}$ = 46.2 Hz, $J_{5a,5b}$ = 10.0 Hz, $J_{4,5b}$ = 3.4 Hz, 1 H, H-5b), 1.07 (s, 9 H, SiC(CH_3)$_3$), 1.02 (s, 9 H, SiC(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 136.0 (Ar), 135.85 (Ar), 135.81 (Ar), 135.7 (Ar), 133.4 (Ar), 132.7 (Ar), 132.6 (Ar), 132.2 (Ar), 130.3 (Ar), 130.09 (Ar), 130.07 (Ar), 130.0 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.94 (Ar), 127.88 (Ar), 127.85 (Ar), 127.8 (Ar), 99.6 (d, $J_{C,P}$ = 6.5 Hz, C-1), 82.9 (d, $J_{C,F}$ = 19.3 Hz, C-4), 82.5 (d, $J_{C,F}$ = 172.6 Hz, C-5), 79.3 (d, $J_{C,P}$ = 8.9 Hz, C-2), 76.1 (d, $J_{C,F}$ = 7.0 Hz, C-3), 69.0 (d, $J_{C,P}$ = 4.6 Hz, O$\underline{C}H_2$Ph), 68.9 (d, $J_{C,P}$ = 4.2 Hz, O$\underline{C}H_2$Ph), 27.1 (SiC($\underline{C}H_3$)$_3$), 27.0 (SiC($\underline{C}H_3$)$_3$), 19.4 (Si$\underline{C}$(CH_3)$_3$),

19.1 (Si<u>C</u>$(CH_3)_3$); ^{19}F NMR (470 MHz, $CDCl_3$, δ): –223.65 (ddd, $J_{5a,F}$ = 47.5 Hz, $J_{5b,F}$ = 46.2 Hz, $J_{4,F}$ = 18.5 Hz); ^{31}P NMR (202 MHz, $CDCl_3$, δ): –0.67; HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{51}H_{58}FNaO_7PSi_2$, 911.3335; found, 911.3332.



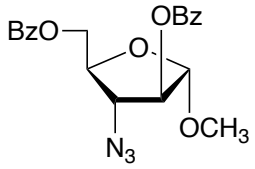
2,3-Di-*O-tert*-butyldiphenylsilyl-5-deoxy-5-fluoro-α/β-D-arabinofuranosyl phosphate (2.9). To a stirred solution of **2.6** (175 mg, 0.197 mmol) in 10% EtOH–EtOAc (7 mL) were added Et_3N (683 μL, 4.92 mmol) and 5% palladium on carbon (419 mg, 0.197 mmol). The reaction vessel was purged with argon and then equipped with a hydrogen-filled balloon. The reaction mixture was stirred at rt for 19 h before being filtered through a pad of Celite® with 10% EtOH–EtOAc. The filtrate was concentrated to yield **2.9** (as the triethylammonium salt, 144 mg, 80%, β:α 5.5:1, inseparable) as a colorless oil. R_f 0.37 (6:1 CH_2Cl_2–CH_3OH); Data for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.79–7.67 (m, 4 H, ArH), 7.62–7.54 (m, 4 H, ArH), 7.41–7.24 (m, 12 H, ArH), 5.39 (br s, 1 H, H-1), 4.30–4.27 (m, 1 H, H-2), 4.25 (ddd, $J_{5a,F}$ = 48.0 Hz, $J_{5a,5b}$ = 9.2 Hz, $J_{4,5a}$ = 7.5 Hz, 1 H, H-5a), 4.19 (dd, $J_{2,3}$ = 4.3 Hz, $J_{3,4}$ = 4.3 Hz, 1 H, H-3), 3.86 (dddd, $J_{4,F}$ = 16.1 Hz, $J_{4,5a}$ = 7.5 Hz, $J_{3,4}$ = 4.3 Hz, $J_{4,5b}$ = 3.3 Hz, 1 H, H-4), 3.25 (ddd, $J_{5b,F}$ = 45.6 Hz, $J_{5a,5b}$ = 9.2 Hz, $J_{4,5b}$ = 3.3 Hz, 1 H, H-5b), 1.07 (s, 9 H, SiC$(CH_3)_3$), 0.95 (s, 9 H, SiC$(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 136.5 (Ar), 135.9 (Ar), 135.79 (Ar), 135.76 (Ar), 133.8 (Ar), 133.6 (Ar), 132.8 (Ar), 132.6 (Ar), 130.0 (Ar), 129.8 (Ar), 129.7 (Ar), 129.5 (Ar), 127.9 (Ar), 127.80 (Ar), 127.77 (Ar), 127.7 (Ar), 127.6 (Ar), 98.3 (d, $J_{C,P}$ = 4.4 Hz, C-1), 84.2 (d, $J_{C,F}$ = 168.5 Hz, C-5), 82.5 (d, $J_{C,F}$ = 18.9 Hz, C-4), 79.4 (d, $J_{C,P}$ = 8.4 Hz, C-2), 77.4 (d, $J_{C,F}$ = 8.8 Hz, C-3), 27.2 (SiC(<u>C</u>$H_3)_3$), 27.0 (SiC(<u>C</u>$H_3)_3$), 19.3 (Si<u>C</u>$(CH_3)_3$), 19.1 (Si<u>C</u>$(CH_3)_3$); ^{19}F NMR (470 MHz, $CDCl_3$, δ): –220.73

(br s); ^{31}P NMR (202 MHz, $CDCl_3$, δ): 1.61; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{37}H_{45}FO_7PSi_2$, 707.2431; found, 707.2427.



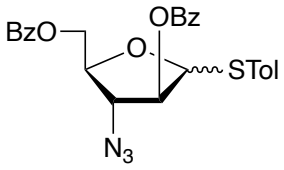
(*Z*,*Z*)-Farnesylphosphoryl-5-deoxy-5-fluoro-α/β-D-arabinofuranose (1.33). Compound **2.9** (144 mg, 0.158 mmol) and (*Z*,*Z*)-farnesol[5] (141 mg, 0.632 mmol) were azeotropically dried with toluene. The mixture was dissolved in pyridine (2.1 mL) and Cl_3CCN (158 μL, 1.58 mmol) was added. The resulting solution was stirred for 14 h at 55 ºC before being cooled to rt and concentrated. The crude phosphodiester was dissolved in a 15% solution of concentrated NH_4OH in CH_3OH (3.2 mL), and NH_4F (176 mg, 4.74 mmol) was added. After stirring for 12 h at 55 ºC, the reaction mixture was cooled to rt, and CH_2Cl_2 (4 mL) was added to precipitate any remaining NH_4F. The solution was filtered through a pad of Celite® and the filtrate was concentrated to a crude residue that was purified by column chromatography (1:1 EtOAc–CH_3OH). Residual colored impurities were removed by the addition of activated charcoal to the product in CH_3OH, followed by the filtration through a syringe filter (0.45 μm). The filtrate was concentrated to give **1.33** (62.4 mg, 87% over two steps, β:α 4:1, inseparable) as a colorless oil. R_f 0.23 (2:1 EtOAc–CH_3OH); Data for the β-anomer: ^{1}H NMR (500 MHz, CD_3OD, δ): 5.55 (dd, $J_{1,P}$ = 6.7 Hz, $J_{1,2}$ = 3.3 Hz, 1 H, H-1), 5.42–5.37 (m, 1 H, $OCH_2C\underline{H}$=C), 5.14–5.09 (m, 2 H, 2 × $CH_2C\underline{H}$=C), 4.51 (dd, $J_{5a,F}$ = 47.5 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-5a), 4.51 (dd, $J_{5b,F}$ = 47.9 Hz, $J_{4,5b}$ = 5.5 Hz, 1 H, H-5b), 4.45–4.41 (m, 2 H, $OC\underline{H}_2CH$=C), 4.02–3.99 (m, 2 H, H-3 and H-2), 3.92 (dddd, $J_{4,F}$ = 19.8 Hz, $J_{3,4}$ = 7.2 Hz, $J_{4,5b}$ = 5.5 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-4), 2.13–1.99 (m, 8 H, 4 × allylic CH_2), 1.72 (s, 3 H, CH_3), 1.67 (s, 6 H, 2 × CH_3), 1.60 (s, 3 H, CH_3); ^{13}C NMR (126 MHz, CD_3OD, δ): 139.2

(CH=C), 135.1 (CH=C), 131.0 (CH=C), 124.4 (CH=C), 124.0 (CH=C), 122.0 (d, $J_{C,P}$ = 8.9 Hz, CH=C), 98.0 (d, $J_{C,P}$ = 5.8 Hz, C-1), 83.4 (d, $J_{C,F}$ = 172.1 Hz, C-5), 81.2 (d, $J_{C,F}$ = 19.1 Hz, C-4), 77.5 (d, $J_{C,P}$ = 5.8 Hz, C-2), 73.4 (d, $J_{C,F}$ = 7.2 Hz, C-3), 61.9 (d, $J_{C,P}$ = 5.2 Hz, OCH$_2$CH=C), 31.9 (allylic CH$_2$), 31.5 (allylic CH$_2$), 26.3 (allylic CH$_2$), 26.2 (allylic CH$_2$), 24.6 (CH$_3$), 22.33 (CH$_3$), 22.28 (CH$_3$), 16.3 (CH$_3$); ^{19}F NMR (470 MHz, CD$_3$OD, δ): –227.01 (ddd, $J_{5b,F}$ = 47.9 Hz, $J_{5a,F}$ = 47.5 Hz, $J_{4,F}$ = 19.8 Hz); ^{31}P NMR (202 MHz, CD$_3$OD, δ): 0.30; HRMS–ESI–TOF (*m*/*z*): [M–H]$^-$ calcd for $C_{20}H_{33}FO_7P$, 435.1953; found, 435.1946.



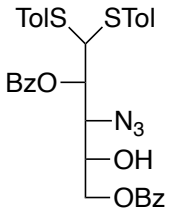
Methyl 3-azido-2,5-di-*O*-benzoyl-3-deoxy-α-D-arabinofuranoside (2.33). A suspension of **2.22**[12] (427 mg, 2.92 mmol), NaN_3 (380 mg, 5.84 mmol) and NH_4Cl (344 mg, 6.42 mmol) in EtOH (9.6 mL) and H_2O (2.1 mL) was heated at a gentle reflux. After 72 h, the reaction mixture was cooled to rt and concentrated to give **2.32**, which was used in the next step without further purification. To a solution of crude **2.32** in dry pyridine (5 mL) was added BzCl (1.02 mL, 8.76 mmol) dropwise. The reaction mixture was stirred at rt overnight. Excess BzCl was quenched by the addition of water and the solution was diluted with EtOAc. The organic layer was washed with 1 N $HCl_{(aq)}$, H_2O, saturated $NaHCO_{3(aq)}$ and brine before being dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (gradient of 8:1→5:1 hexanes–EtOAc) to yield **2.33** (1.09 g, 94% over two steps) as a colorless oil. R_f 0.43 (4:1 hexanes–EtOAc); $[\alpha]_D$ +18.5 (*c* 2.08, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 8.02–7.97 (m, 4 H, ArH), 7.61–7.57 (m, 1 H, ArH), 7.51–7.47 (m, 1 H, ArH), 7.44–7.39 (m, 2 H, ArH), 7.29–7.24 (m, 2 H, ArH), 5.31 (d, $J_{2,3}$ = 1.6 Hz, 1 H, H-2), 5.18 (s, 1 H, H-1), 4.67 (dd, $J_{5a,5b}$ = 12.1 Hz,

$J_{4,5a}$ = 4.0 Hz, 1 H, H-5a), 4.53 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5b}$ = 4.3 Hz, 1 H, H-5b), 4.30 (ddd, $J_{3,4}$ = 6.3 Hz, $J_{4,5b}$ = 4.3 Hz, $J_{4,5a}$ = 4.0 Hz, 1 H, H-4), 4.07 (dd, $J_{3,4}$ = 6.3 Hz, $J_{2,3}$ = 1.6 Hz, 1 H, H-3), 3.46 (s, 3 H, OCH_3); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 166.1 (C=O), 165.5 (C=O), 133.6 (Ar), 133.2 (Ar), 129.8 (Ar), 129.7 (Ar), 129.4 (Ar), 128.9 (Ar), 128.6 (Ar), 128.3 (Ar), 106.5 (C-1), 82.9 (C-2), 80.0 (C-4), 66.3 (C-3), 63.2 (C-5), 54.9 (OCH_3); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{19}N_3NaO_6$, 420.1166; found, 420.1166.



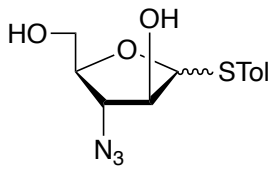
***p*-Tolyl 3-azido-2,5-di-*O*-benzoyl-3-deoxy-1-thio-α/β-D-arabinofuranoside (2.34).** To a solution of **2.33** (1.09 g, 2.73 mmol) and *p*-thiocresol (407 mg, 3.28 mmol) in dry CH_2Cl_2 (15 mL) at 0 ºC was added BF_3•OEt_2 (510 μL, 4.10 mmol) dropwise. The reaction mixture was warmed slowly to rt. After 6 h, Et_3N (140 μL) was added, and the solution was concentrated. The crude residue was purified by column chromatography (9:1 hexanes–EtOAc) to give **2.34** (1.03 g, 77%, α:β 4:1, inseparable) as a colorless oil. R_f 0.48 (4:1 hexanes–EtOAc); Data for the α-anomer: ^1H NMR (700 MHz, $CDCl_3$, δ): 8.04–8.01 (m, 2 H, ArH), 8.01–7.98 (m, 2 H, ArH), 7.62–7.59 (m, 1 H, ArH), 7.54–7.51 (m, 1 H, ArH), 7.46–7.42 (m, 4 H, ArH), 7.33–7.29 (m, 2 H, ArH), 7.14–7.11 (m, 2 H, ArH), 5.70 (d, $J_{1,2}$ = 1.9 Hz, 1 H, H-1), 5.46 (dd, $J_{2,3}$ = 2.6 Hz, $J_{1,2}$ = 1.9 Hz, 1 H, H-2), 4.66 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-5a), 4.57 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5b}$ = 4.5 Hz, 1 H, H-5b), 4.54 (ddd, $J_{3,4}$ = 6.9 Hz, $J_{4,5b}$ = 4.5 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-4), 4.18 (dd, $J_{3,4}$ = 6.9 Hz, $J_{2,3}$ = 2.6 Hz, 1 H, H-3), 2.33 (s, 3 H, Ar$C\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 166.0 (C=O), 165.5 (C=O), 138.4 (Ar), 133.7 (Ar), 133.3 (Ar), 133.1 (Ar), 129.89 (Ar), 129.87 (Ar), 129.7 (Ar), 129.4 (Ar), 129.0 (Ar), 128.8 (Ar), 128.6 (Ar), 128.4 (Ar), 90.7 (C-1), 83.3 (C-2), 79.6 (C-4), 66.9 (C-

3), 62.9 (C-5), 21.1 (Ar<u>C</u>H$_3$); Data for the β-anomer: ^{1}H NMR (700 MHz, CDCl$_3$, δ): 8.14–8.11 (m, 2 H, ArH), 8.09–8.06 (m, 2 H, ArH), 7.65–7.62 (m, 1 H, ArH), 7.56–7.53 (m, 1 H, ArH), 7.52–7.48 (m, 2 H, ArH), 7.40–7.36 (m, 4 H, ArH), 7.10–7.08 (m, 2 H, ArH), 5.73 (d, $J_{1,2}$ = 5.4 Hz, 1 H, H-1), 5.54 (dd, $J_{1,2}$ = 5.4 Hz, $J_{2,3}$ = 5.4 Hz, 1 H, H-2), 4.66 (dd, $J_{5a,5b}$ = 11.8 Hz, $J_{4,5a}$ = 5.0 Hz, 1 H, H-5a), 4.62 (dd, $J_{5a,5b}$ = 11.8 Hz, $J_{4,5b}$ = 5.0 Hz, 1 H, H-5b), 4.43 (dd, $J_{3,4}$ = 6.4 Hz, $J_{2,3}$ = 5.4 Hz, 1 H, H-3), 4.18–4.15 (m, 1 H, H-4), 2.31 (s, 3 H, ArC<u>H</u>$_3$); ^{13}C NMR (176 MHz, CDCl$_3$, δ): 166.2 (C=O), 165.6 (C=O), 138.2 (Ar), 133.8 (Ar), 133.2 (Ar), 132.8 (Ar), 130.0 (Ar), 129.9 (Ar), 129.8 (Ar), 129.5 (Ar), 129.4 (Ar), 128.8 (Ar), 128.7 (Ar), 128.4 (Ar), 89.3 (C-1), 79.4 (C-4), 78.9 (C-2), 65.8 (C-3), 64.0 (C-5), 21.1 (Ar<u>C</u>H$_3$); HRMS–ESI–TOF (*m*/*z*): [M+Na]$^+$ calcd for $C_{26}H_{23}N_3NaO_5S$, 512.1251; found, 512.1248.



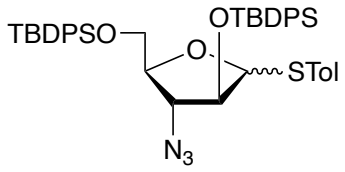
3-Azido-2,5-di-*O*-benzoyl-3-deoxy-D-arabinose di-*p*-tolyl dithioacetal (2.35). Compound **2.35** is a colorless oil and was isolated as a side-product (262 mg, 16%) in the conversion of **2.33** into **2.34**. R_f 0.26 (4:1 hexanes–EtOAc); $[\alpha]_D$ +61.5 (*c* 1.62, CHCl$_3$); ^{1}H NMR (700 MHz, CDCl$_3$, δ): 8.10–8.07 (m, 2 H, ArH), 8.03–8.00 (m, 2 H, ArH), 7.62–7.57 (m, 2 H, ArH), 7.48–7.42 (m, 6 H, ArH), 7.32–7.29 (m, 2 H, ArH), 7.12–7.09 (m, 2 H, ArH), 7.07–7.04 (m, 2 H, ArH), 5.72 (dd, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 2.4 Hz, 1 H, H-2), 4.82 (d, $J_{1,2}$ = 8.1 Hz, 1 H, H-1), 4.69 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5a}$ = 2.5 Hz, 1 H, H-5a), 4.48 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5b}$ = 5.1 Hz, 1 H, H-5b), 4.36 (dd, $J_{3,4}$ = 9.4 Hz, $J_{2,3}$ = 2.4 Hz, 1 H, H-3), 3.90 (dddd, $J_{3,4}$ = 9.4 Hz, $J_{4,OH}$ = 5.2 Hz, $J_{4,5b}$ = 5.1 Hz, $J_{4,5a}$ = 2.5 Hz, 1 H, H-4), 3.53 (d, $J_{4,OH}$ = 5.2 Hz, 1 H, OH), 2.32 (s, 3 H, ArC<u>H</u>$_3$), 2.31 (s, 3 H, ArC<u>H</u>$_3$); ^{13}C NMR (176 MHz, CDCl$_3$, δ): 166.71 (C=O), 166.69 (C=O), 139.0 (Ar), 138.4 (Ar), 133.9 (Ar), 133.8

(Ar), 133.3 (Ar), 133.2 (Ar), 130.3 (Ar), 130.0 (Ar), 129.84 (Ar), 129.78 (Ar), 129.7 (Ar), 129.6 (Ar), 128.9 (Ar), 128.55 (Ar), 128.50 (Ar), 128.47 (Ar), 74.4 (C-2), 68.8 (C-4), 66.1 (C-5), 62.3 (C-3), 61.3 (C-1), 21.20 (Ar<u>C</u>H$_3$), 21.17 (Ar<u>C</u>H$_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{33}H_{31}N_3NaO_5S_2$, 636.1597; found, 636.1596.



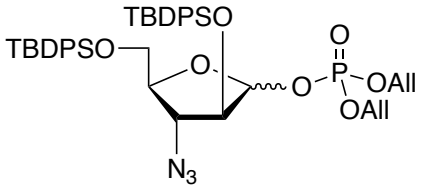
***p*-Tolyl 3-azido-3-deoxy-1-thio-α/β-D-arabinofuranoside (2.36).** Compound **2.34** (991 mg, 2.02 mmol) was treated with 200 mM NaOH in CH_3OH (10 mL). The reaction mixture was stirred overnight at rt before being neutralized with Amberlite® IR-120 (H^+) resin, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (gradient of 2:1→1:1 hexanes–EtOAc) to give **2.36** (499 mg, 88%, α:β 4:1, inseparable) as a colorless oil. R_f 0.08 (4:1 hexanes–EtOAc); Data for the α-anomer: ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.41–7.38 (m, 2 H, ArH), 7.15–7.12 (m, 2 H, ArH), 5.33 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H-1), 4.24 (dd, $J_{2,3}$ = 4.5 Hz, $J_{1,2}$ = 3.8 Hz, 1 H, H-2), 4.09 (ddd, $J_{3,4}$ = 6.5 Hz, $J_{4,5a}$ = 2.6 Hz, $J_{4,5b}$ = 2.6 Hz, 1 H, H-4), 4.03 (dd, $J_{3,4}$ = 6.5 Hz, $J_{2,3}$ = 4.5 Hz, 1 H, H-3), 3.94 (dd, $J_{5a,5b}$ = 12.3 Hz, $J_{4,5a}$ = 2.6 Hz, 1 H, H-5a), 3.73 (dd, $J_{5a,5b}$ = 12.3 Hz, $J_{4,5b}$ = 2.6 Hz, 1 H, H-5b), 2.34 (s, 3 H, ArC<u>H</u>$_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 138.1 (Ar), 132.7 (Ar), 129.9 (Ar), 129.6 (Ar), 93.1 (C-1), 81.5 (C-4), 80.5 (C-2), 66.1 (C-3), 61.5 (C-5), 21.1 (Ar<u>C</u>H$_3$); Data for the β-anomer: ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.41–7.38 (m, 2 H, ArH), 7.15–7.12 (m, 2 H, ArH), 5.47 (d, $J_{1,2}$ = 4.5 Hz, 1 H, H-1), 4.36 (dd, $J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 4.1 Hz, 1 H, H-2), 4.08 (dd, $J_{3,4}$ = 4.4 Hz, $J_{2,3}$ = 4.1 Hz, 1 H, H-3), 3.98 (ddd, $J_{3,4}$ = 4.4 Hz, $J_{4,5a}$ = 2.7 Hz, $J_{4,5b}$ = 2.6 Hz, 1 H, H-4), 3.93 (dd, $J_{5a,5b}$ = 12.3 Hz, $J_{4,5a}$ = 2.7 Hz, 1 H, H-5a), 3.73 (dd, $J_{5a,5b}$ = 12.3 Hz, $J_{4,5b}$ = 2.6 Hz, 1 H, H-5b), 2.34 (s, 3 H, ArC<u>H</u>$_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 137.9

(Ar), 131.9 (Ar), 130.0 (Ar), 129.6 (Ar), 93.0 (C-1), 83.2 (C-4), 77.0 (C-2), 67.1 (C-3), 62.3 (C-5), 21.1 (Ar<u>C</u>H$_3$); HRMS–ESI–TOF (*m*/*z*): [M+Na]$^+$ calcd for $C_{12}H_{15}N_3NaO_3S$, 304.0726; found, 304.0725.



***p*-Tolyl 3-azido-2,5-di-*O*-*tert*-butyldiphenylsilyl-3-deoxy-1-thio-α/β-D-arabinofuranoside (2.11).** To a solution of **2.36** (483 mg, 1.72 mmol) in dry DMF (5 mL) was added imidazole (1.76 g, 25.8 mmol), followed by TBDPSCl (2.21 mL, 8.60 mmol). The reaction mixture was stirred at 50 ºC for 16 h. After cooling to rt, excess TBDPSCl was quenched by the addition of ice-cold water and the solution was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (50:1 hexanes–EtOAc) to give **2.11** (1.24 g, 95%, α:β 4:1, inseparable) as a colorless oil. R_f 0.60 (10:1 hexanes–EtOAc); Data for the α-anomer: ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.69–7.66 (m, 6 H, ArH), 7.48–7.33 (m, 14 H, ArH), 7.18–7.16 (m, 2 H, ArH), 7.04–7.02 (m, 2 H, ArH), 5.29 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1), 4.20 (dd, $J_{2,3}$ = 3.6 Hz, $J_{1,2}$ = 3.5 Hz, 1 H, H-2), 4.07–4.03 (m, 2 H, H-3 and H-4), 3.87 (dd, $J_{5a,5b}$ = 11.3 Hz, $J_{4,5a}$ = 4.1 Hz, 1 H, H-5a), 3.82 (dd, $J_{5a,5b}$ = 11.3 Hz, $J_{4,5b}$ = 3.7 Hz, 1 H, H-5b), 2.31 (s, 3 H, ArC<u>H</u>$_3$), 1.09 (s, 9 H, SiC(CH$_3$)$_3$), 1.07 (s, 9 H, SiC(CH$_3$)$_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 137.4 (Ar), 136.3 (Ar), 135.9 (Ar), 135.8 (Ar), 135.63 (Ar), 135.57 (Ar), 133.10 (Ar), 133.07 (Ar), 132.61 (Ar), 132.55 (Ar), 132.4 (Ar), 132.0 (Ar), 130.4 (Ar), 130.1 (Ar), 130.0 (Ar), 129.8 (Ar), 129.7 (Ar), 129.6 (Ar), 129.5 (Ar), 127.85 (Ar), 127.79 (Ar), 127.76 (Ar), 127.7 (Ar), 93.2 (C-1), 82.4 (C-2), 81.6 (C-4), 68.2 (C-3), 63.2 (C-5), 26.84 (SiC(<u>C</u>H$_3$)$_3$), 26.78 (SiC(<u>C</u>H$_3$)$_3$), 21.1 (Ar<u>C</u>H$_3$), 19.3 (Si<u>C</u>(CH$_3$)$_3$), 19.1

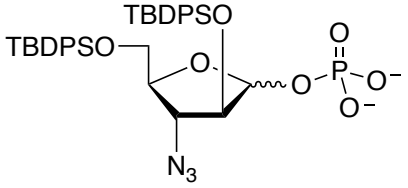
(Si<u>C</u>$(CH_3)_3$); Data for the β-anomer: ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.81–7.78 (m, 2 H, ArH), 7.76–7.73 (m, 2 H, ArH), 7.70–7.69 (m, 4 H, ArH), 7.69–7.67 (m, 6 H, ArH), 7.65–7.63 (m, 2 H, ArH), 7.48–7.46 (m, 4 H, ArH), 7.24–7.22 (m, 2 H, ArH), 7.04–7.02 (m, 2 H, ArH), 5.11 (d, $J_{1,2}$ = 5.2 Hz, 1 H, H-1), 4.40 (dd, $J_{2,3}$ = 5.4 Hz, $J_{1,2}$ = 5.2 Hz, 1 H, H-2), 4.00 (dd, $J_{2,3}$ = 5.4 Hz, $J_{3,4}$ = 5.4 Hz, 1 H, H-3), 3.93 (dd, $J_{5a,5b}$ = 10.4 Hz, $J_{4,5a}$ = 7.5 Hz, 1 H, H-5a), 3.86 (dd, $J_{5a,5b}$ = 10.4 Hz, $J_{4,5b}$ = 6.5 Hz, 1 H, H-5b), 3.81 (ddd, $J_{4,5a}$ = 7.5 Hz, $J_{4,5b}$ = 6.5 Hz, $J_{3,4}$ = 5.4 Hz, 1 H, H-4), 2.29 (s, 3 H, Ar<u>C</u>H_3), 1.16 (s, 9 H, SiC$(CH_3)_3$), 1.06 (s, 9 H, SiC$(CH_3)_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 137.4 (Ar), 136.3 (Ar), 135.9 (Ar), 135.8 (Ar), 135.63 (Ar), 135.57 (Ar), 133.10 (Ar), 133.07 (Ar), 132.61 (Ar), 132.55 (Ar), 132.4 (Ar), 132.0 (Ar), 130.4 (Ar), 130.1 (Ar), 130.0 (Ar), 129.8 (Ar), 129.7 (Ar), 129.6 (Ar), 129.5 (Ar), 127.85 (Ar), 127.79 (Ar), 127.76 (Ar), 127.7 (Ar), 91.5 (C-1), 81.8 (C-4), 78.5 (C-2), 68.7 (C-3), 60.4 (C-5), 26.9 (SiC(<u>C</u>$H_3)_3$), 26.8 (SiC(<u>C</u>$H_3)_3$), 21.0 (Ar<u>C</u>H_3), 19.3 (Si<u>C</u>$(CH_3)_3$), 19.2 (Si<u>C</u>$(CH_3)_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{44}H_{51}N_3NaO_3SSi_2$, 780.3082; found, 780.3081.



Diallyl (3-azido-2,5-di-*O*-*tert*-butyldiphenylsilyl-3-deoxy-α/β-D-arabinofuranosyl) phosphate (2.14). To a stirred solution of **2.11** (214 mg, 0.282 mmol) in CH_2Cl_2 (3 mL) was added Br_2 (19 μL, 0.37 mmol). The reaction mixture was stirred at rt for 1 h before being concentrated. The crude glycosyl bromide was azeotropically dried with toluene and then used immediately. To a stirred solution of azeotropically dried diallyl phosphate[6] (100 mg, 0.564 mmol) in toluene (1 mL) were added powdered 4 Å molecular sieves (250 mg) and Et_3N (102 μL, 0.733 mmol). The mixture was cooled to 0 ºC, and a solution of the aforementioned glycosyl bromide in toluene (1

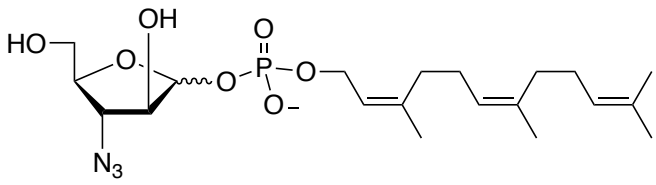
mL) was added slowly via a cannula. The transfer was completed by rinsing the flask twice with toluene (2 × 0.5 mL). The reaction mixture was warmed slowly to rt and stirred for 17 h before being filtered through a pad of Celite®, rinsed with EtOAc, and the filtrate was concentrated. The crude residue was purified by column chromatography (4:1 hexanes–EtOAc) to yield **2.14** (108 mg, 47% over two steps, β:α 1.7:1, inseparable) as a colorless oil. R_f 0.42 (3:1 hexanes–EtOAc); Data for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.73–7.60 (m, 8 H, ArH), 7.49–7.35 (m, 12 H, ArH), 5.89–5.67 (m, 2 H, 2 × $OCH_2C\underline{H}=CH_2$), 5.36 (dd, $J_{1,P}$ = 4.5 Hz, $J_{1,2}$ = 3.9 Hz, 1 H, H-1), 5.30–5.05 (m, 4 H, 2 × $OCH_2CH=C\underline{H}_2$), 4.51–4.30 (m, 4 H, 2 × $OC\underline{H}_2CH=CH_2$), 4.06 (ddd, $J_{2,3}$ = 8.5 Hz, $J_{1,2}$ = 3.9 Hz, $J_{2,P}$ = 3.0 Hz, 1 H, H-2), 4.00 (dd, $J_{2,3}$ = 8.5 Hz, $J_{3,4}$ = 6.6 Hz, 1 H, H-3), 3.83–3.71 (m, 3 H, H-4, H-5a and H-5b), 1.12 (s, 9 H, $SiC(CH_3)_3$), 1.06 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 135.9 (Ar), 135.7 (Ar), 135.6 (Ar), 135.5 (Ar), 133.0 (Ar), 132.9 (Ar), 132.5 (Ar), 132.4 (d, $J_{C,P}$ = 8.1 Hz, 2 × $OCH_2\underline{C}H=CH_2$), 130.19 (Ar), 130.17 (Ar), 129.9 (Ar), 128.1 (Ar), 127.9 (Ar), 127.85 (Ar), 127.81 (Ar), 118.1 ($OCH_2CH=\underline{C}H_2$), 118.0 ($OCH_2CH=\underline{C}H_2$), 98.9 (d, $J_{C,P}$ = 6.2 Hz, C-1), 80.9 (C-4), 77.4 (d, $J_{C,P}$ = 8.7 Hz, C-2), 68.2 (d, $J_{C,P}$ = 5.7 Hz, $O\underline{C}H_2CH=CH_2$), 67.9 (d, $J_{C,P}$ = 5.1 Hz, $O\underline{C}H_2CH=CH_2$), 66.9 (C-3), 65.7 (C-5), 26.82 ($SiC(\underline{C}H_3)_3$), 26.80 ($SiC(\underline{C}H_3)_3$), 19.3 ($Si\underline{C}(CH_3)_3$), 19.2 ($Si\underline{C}(CH_3)_3$); ^{31}P NMR (202 MHz, $CDCl_3$, δ): –0.36; Data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.73–7.60 (m, 8 H, ArH), 7.47–7.36 (m, 12 H, ArH), 5.89–5.67 (m, 3 H, 2 × $OCH_2C\underline{H}=CH_2$ and H-1), 5.30–5.05 (m, 4 H, 2 × $OCH_2CH=C\underline{H}_2$), 4.51–4.30 (m, 4 H, 2 × $OC\underline{H}_2CH=CH_2$), 4.28 (d, $J_{2,3}$ = 1.9 Hz, 1 H, H-2), 4.20 (ddd, $J_{4,5b}$ = 6.5 Hz, $J_{4,5a}$ = 5.0 Hz, $J_{3,4}$ = 4.7 Hz, 1 H, H-4), 3.90 (dd, $J_{3,4}$ = 4.7 Hz, $J_{2,3}$ = 1.9 Hz, 1 H, H-3), 3.87 (dd, $J_{5a,5b}$ = 10.7 Hz, $J_{4,5a}$ = 5.0 Hz, 1 H, H-5a), 3.78 (dd, $J_{5a,5b}$ = 10.7 Hz, $J_{4,5b}$ = 6.5 Hz, 1 H, H-5b), 1.07 (s, 9 H, $SiC(CH_3)_3$), 1.04 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 135.9 (Ar), 135.7 (Ar), 135.6 (Ar), 135.5 (Ar), 132.95 (Ar), 132.93 (Ar), 132.5 (Ar), 132.4 (d,

$J_{C,P}$ = 8.1 Hz, 2 × $OCH_2\underline{C}H{=}CH_2$), 130.32 (Ar), 130.25 (Ar), 129.9 (Ar), 128.1 (Ar), 127.9 (Ar), 127.85 (Ar), 127.81 (Ar), 118.2 ($OCH_2CH{=}\underline{C}H_2$), 118.0 ($OCH_2CH{=}\underline{C}H_2$), 105.5 (d, $J_{C,P}$ = 6.2 Hz, C-1), 84.8 (C-4), 82.4 (d, $J_{C,P}$ = 11.3 Hz, C-2), 68.10 (d, $J_{C,P}$ = 5.8 Hz, $O\underline{C}H_2CH{=}CH_2$), 68.07 (d, $J_{C,P}$ = 5.4 Hz, $O\underline{C}H_2CH{=}CH_2$), 67.8 (C-3), 63.7 (C-5), 26.80 ($SiC(\underline{C}H_3)_3$), 26.78 ($SiC(\underline{C}H_3)_3$), 19.3 ($Si\underline{C}(CH_3)_3$), 19.0 ($Si\underline{C}(CH_3)_3$); ^{31}P NMR (202 MHz, $CDCl_3$, δ): –1.95; HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{43}H_{54}N_3NaO_7PSi_2$, 834.3130; found, 834.3129.



3-Azido-2,5-di-*O*-*tert*-butyldiphenylsilyl-3-deoxy-α/β-D-arabinofuranosyl phosphate (2.17). To a solution of **2.14** (108 mg, 0.133 mmol) in a mixture of CH_2Cl_2 (0.9 mL) and CH_3OH (0.6 mL) was added $PdCl_2$ (11.8 mg, 0.0665 mmol). The reaction mixture was stirred at rt for 4 h and was then filtered through a pad of Celite® with 1:1 CH_2Cl_2–CH_3OH before the filtrate was concentrated. The crude residue was dissolved in CH_3OH (10 mL) and was stirred with a palladium scavenger (QuadraPure® TU, 100 mg) for 2 h at rt. The solution was filtered and the filtrate was concentrated to a residue that was purified by column chromatography (3:7 $CHCl_3$–CH_3OH, containing 2% v/v of Et_3N) to yield **2.17** (as the triethylammonium salt, 45.0 mg, 36%, β:α 1.7:1, inseparable) as a colorless oil. R_f 0.60 (6:1 EtOAc–CH_3OH); Data for the β-anomer: ^{1}H NMR (500 MHz, CD_3OD, δ): 7.79–7.74 (m, 2 H, ArH), 7.68–7.63 (m, 6 H, ArH), 7.48–7.34 (m, 12 H, ArH), 5.35 (dd, $J_{1,P}$ = 5.9 Hz, $J_{1,2}$ = 3.9 Hz, 1 H, H-1), 4.00 (dd, $J_{2,3}$ = 7.9 Hz, $J_{3,4}$ = 6.3 Hz, 1 H, H-3), 3.96–3.90 (m, 3 H, H-2, H-5a and H-5b), 3.69 (ddd, $J_{4,5b}$ = 8.9 Hz, $J_{3,4}$ = 6.3 Hz, $J_{4,5a}$ = 5.4 Hz, 1 H, H-4), 1.10 (s, 9 H, $SiC(CH_3)_3$), 1.03 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (126 MHz, CD_3OD, δ): 135.9 (Ar), 135.7 (Ar), 135.5 (Ar), 135.3 (Ar), 133.0 (Ar), 132.8 (Ar), 132.6 (Ar), 132.2 (Ar), 129.9 (Ar), 129.8 (Ar),

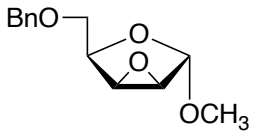
129.64 (Ar), 129.56 (Ar), 127.72 (Ar), 127.70 (Ar), 127.51 (Ar), 127.46 (Ar), 97.0 (d, $J_{C,P}$ = 6.1 Hz, C-1), 79.9 (C-4), 77.6 (d, $J_{C,P}$ = 8.8 Hz, C-2), 69.0 (C-3), 66.5 (C-5), 26.1 (SiC($\underline{C}H_3)_3$), 26.0 (SiC($\underline{C}H_3)_3$), 18.7 (Si$\underline{C}(CH_3)_3$), 18.6 (Si$\underline{C}(CH_3)_3$); ^{31}P NMR (202 MHz, CD_3OD, δ): 0.53; Data for the α-anomer: ^{1}H NMR (500 MHz, CD_3OD, δ): 7.79–7.74 (m, 2 H, ArH), 7.68–7.63 (m, 6 H, ArH), 7.48–7.34 (m, 12 H, ArH), 5.80 (d, $J_{1,P}$ = 5.9 Hz, 1 H, H-1), 4.30 (d, $J_{2,3}$ = 1.4 Hz, 1 H, H-2), 4.23 (ddd, $J_{4,5b}$ = 7.3 Hz, $J_{4,5a}$ = 4.7 Hz, $J_{3,4}$ = 4.3 Hz, 1 H, H-4), 3.88 (dd, $J_{5a,5b}$ = 10.4 Hz, $J_{4,5a}$ = 4.7 Hz, 1 H, H-5a), 3.85 (dd, $J_{3,4}$ = 4.3 Hz, $J_{2,3}$ = 1.4 Hz, 1 H, H-3), 3.74 (dd, $J_{5a,5b}$ = 10.4 Hz, $J_{4,5b}$ = 7.3 Hz, 1 H, H-5b), 1.03 (s, 18 H, 2 × SiC($CH_3)_3$); ^{13}C NMR (126 MHz, CD_3OD, δ): 135.9 (Ar), 135.7 (Ar), 135.5 (Ar), 135.3 (Ar), 133.1 (Ar), 132.9 (Ar), 132.6 (Ar), 132.2 (Ar), 129.9 (Ar), 129.8 (Ar), 129.6 (Ar), 129.5 (Ar), 127.72 (Ar), 127.70 (Ar), 127.5 (Ar), 127.4 (Ar), 104.2 (d, $J_{C,P}$ = 5.6 Hz, C-1), 83.5 (C-4), 82.8 (d, $J_{C,P}$ = 10.4 Hz, C-2), 68.4 (C-3), 63.9 (C-5), 26.05 (SiC($\underline{C}H_3)_3$), 25.96 (SiC($\underline{C}H_3)_3$), 18.7 (Si$\underline{C}(CH_3)_3$), 18.5 (Si$\underline{C}(CH_3)_3$); ^{31}P NMR (202 MHz, CD_3OD, δ): –0.14; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{37}H_{45}N_3O_7PSi_2$, 730.2539; found, 730.2530.



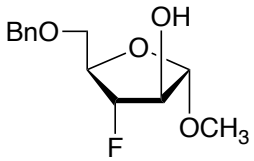
(*Z*,*Z*)-Farnesylphosphoryl-3-azido-3-deoxy-α/β-D-arabinofuranose (1.35). Compound **2.17** (42.9 mg, 0.0459 mmol) and (*Z*,*Z*)-farnesol[5] (40.8 mg, 0.184 mmol) were azeotropically dried with toluene. The mixture was dissolved in pyridine (1 mL) and Cl_3CCN (46 μL, 0.46 mmol) was added. The resulting solution was stirred for 12 h at 55 ºC before being cooled to rt and concentrated. The crude phosphodiester was dissolved in a 15% solution of concentrated NH_4OH in CH_3OH (1.5 mL), and NH_4F (51.0 mg, 1.38 mmol) was added. After stirring for 12 h at 55 ºC, the reaction mixture was cooled to rt, and CH_2Cl_2 (2 mL) was added to precipitate any remaining NH_4F. The

solution was filtered through a pad of Celite® and the filtrate was concentrated to a crude residue that was purified by column chromatography (gradient of 20%→30% CH_3OH–EtOAc). Residual colored impurities were removed by the addition of activated charcoal to the product in CH_3OH, followed by the filtration through a syringe filter (0.45 μm). The filtrate was concentrated to give **1.35** (8.7 mg, 40% over two steps, β:α 0.5:1, inseparable) as a colorless oil. R_f 0.59 (3:2 EtOAc–CH_3OH); Data for the β-anomer: ^{1}H NMR (500 MHz, CD_3OD, δ): 5.46 (dd, $J_{1,P}$ = 4.8 Hz, $J_{1,2}$ = 4.2 Hz, 1 H, H-1), 5.43–5.38 (m, 1 H, $OCH_2C\underline{H}$=C), 5.14–5.09 (m, 2 H, 2 × $CH_2C\underline{H}$=C), 4.45–4.37 (m, 2 H, $OC\underline{H}_2CH$=C), 4.06–4.03 (m, 1 H, H-2), 4.00 (dd, $J_{2,3}$ = 8.7 Hz, $J_{3,4}$ = 7.8 Hz, 1 H, H-3), 3.76–3.73 (m, 1 H, H-4), 3.63–3.58 (m, 2 H, H-5a and H-5b), 2.12–2.00 (m, 8 H, 4 × allylic CH_2), 1.73 (s, 3 H, CH_3), 1.67 (s, 6 H, 2 × CH_3), 1.60 (s, 3 H, CH_3); ^{13}C NMR (126 MHz, CD_3OD, δ): 139.3 (CH=$\underline{C}$), 135.2 (CH=$\underline{C}$), 131.0 (CH=$\underline{C}$), 124.3 ($\underline{C}$H=C), 124.0 ($\underline{C}$H=C), 121.8 (d, $J_{C,P}$ = 8.0 Hz, $\underline{C}$H=C), 97.2 (d, $J_{C,P}$ = 5.7 Hz, C-1), 81.2 (C-4), 76.9 (d, $J_{C,P}$ = 7.7 Hz, C-2), 64.0 (C-3), 62.4 (C-5), 62.0 (d, $J_{C,P}$ = 5.6 Hz, O$\underline{C}H_2CH$=C), 31.9 (allylic CH_2), 31.7 (allylic CH_2), 26.3 (allylic CH_2), 26.2 (allylic CH_2), 24.6 (CH_3), 22.32 (CH_3), 22.28 (CH_3), 16.3 (CH_3); ^{31}P NMR (202 MHz, CD_3OD, δ): 0.52; Data for the α-anomer: ^{1}H NMR (500 MHz, CD_3OD, δ): 5.51 (d, $J_{1,P}$ = 5.9 Hz, 1 H, H-1), 5.43–5.38 (m, 1 H, $OCH_2C\underline{H}$=C), 5.14–5.09 (m, 2 H, 2 × $CH_2C\underline{H}$=C), 4.45–4.37 (m, 2 H, $OC\underline{H}_2CH$=C), 4.19 (dd, $J_{2,3}$ = 3.6 Hz, $J_{2,P}$ = 1.4 Hz, 1 H, H-2), 4.07 (ddd, $J_{3,4}$ = 6.7 Hz, $J_{4,5b}$ = 4.6 Hz, $J_{4,5a}$ = 3.6 Hz, 1 H, H-4), 3.77 (dd, $J_{3,4}$ = 6.7 Hz, $J_{2,3}$ = 3.6 Hz, 1 H, H-3), 3.72 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5a}$ = 3.6 Hz, 1 H, H-5a), 3.65 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5b}$ = 4.6 Hz, 1 H, H-5b), 2.12–2.00 (m, 8 H, 4 × allylic CH_2), 1.73 (s, 3 H, CH_3), 1.67 (s, 6 H, 2 × CH_3), 1.60 (s, 3 H, CH_3); ^{13}C NMR (126 MHz, CD_3OD, δ): 139.3 (CH=$\underline{C}$), 135.2 (CH=$\underline{C}$), 131.0 (CH=$\underline{C}$), 124.3 ($\underline{C}$H=C), 124.0 ($\underline{C}$H=C), 122.0 (d, $J_{C,P}$ = 8.6 Hz, $\underline{C}$H=C), 103.9 (d, $J_{C,P}$ = 5.4 Hz, C-1), 82.7 (C-4), 81.4 (d, $J_{C,P}$ = 8.7 Hz, C-2), 66.8 (C-3), 61.9 (d, $J_{C,P}$ = 5.6 Hz, O$\underline{C}H_2CH$=C), 61.2 (C-5), 31.9 (allylic CH_2), 31.5

(allylic CH_2), 26.3 (allylic CH_2), 26.2 (allylic CH_2), 24.6 (CH_3), 22.34 (CH_3), 22.32 (CH_3), 16.3 (CH_3); ^{31}P NMR (202 MHz, CD_3OD, δ): –0.40; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{20}H_{33}N_3O_7P$, 458.2062; found, 458.2060.

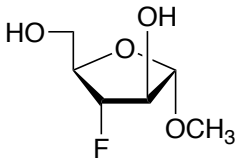


Methyl 2,3-anhydro-5-*O*-benzyl-α-D-lyxofuranoside (2.37).[17] To a stirred solution of **2.22**[12] (241 mg, 1.65 mmol) in dry DMF (3 mL) at 0 ºC were added NaH (60% dispersion in mineral oil; 79.2 mg, 1.98 mmol) and BnBr (235 μL, 1.98 mmol). The reaction mixture was stirred at rt for 5 h before being poured into ice-cold water and the solution was extracted with EtOAc. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (4:1 hexanes–EtOAc) to yield **2.37** (374 mg, 96%) as a colorless oil. The spectroscopic data for **2.37** were identical to those reported.[17]



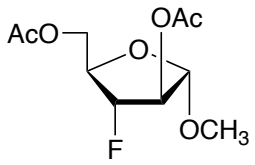
Methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-arabinofuranoside (2.38).[11] Compound **2.37** (5.62 g, 23.8 mmol) and KHF_2 (11.1 g, 143 mmol) in ethylene glycol (110 mL) were heated at reflux gently for 1 h. After being cooled to rt, the solution was poured into saturated $NaHCO_{3(aq)}$ at 0 ºC with stirring and extracted with CH_2Cl_2 three times. The combined organic layers were dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (3:2 hexanes–EtOAc) to yield **2.38** (2.74 g, 45%) as a colorless oil. R_f 0.26 (2:1 hexanes–EtOAc); $[\alpha]_D$ +84.0 (*c* 1.69, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$, δ): 7.39–7.35 (m, 2 H,

ArH), 7.34–7.29 (m, 3 H, ArH), 4.95 (s, 1 H, H-1), 4.88 (d, $J_{3,F}$ = 52.5 Hz, 1 H, H-3), 4.66 (d, J_{gem} = 11.8 Hz, 1 H, OC<u>H</u>$_2$Ph), 4.55 (d, J_{gem} = 11.8 Hz, 1 H, OC<u>H</u>$_2$Ph), 4.45 (ddd, $J_{4,F}$ = 27.4 Hz, $J_{4,5a}$ = 2.2 Hz, $J_{4,5b}$ = 2.0 Hz, 1 H, H-4), 4.17 (dd, $J_{2,F}$ = 13.1 Hz, $J_{2,OH}$ = 11.7 Hz, 1 H, H-2), 3.73 (dd, $J_{5a,5b}$ = 10.5 Hz, $J_{4,5a}$ = 2.2 Hz, 1 H, H-5a), 3.69 (dd, $J_{5a,5b}$ = 10.5 Hz, $J_{4,5b}$ = 2.0 Hz, 1 H, H-5b), 3.61 (d, $J_{2,OH}$ = 11.7 Hz, 1 H, OH), 3.41 (s, 3 H, OCH_3); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 136.5 (Ar), 128.7 (Ar), 128.4 (Ar), 128.0 (Ar), 110.1 (C-1), 97.3 (d, $J_{C,F}$ = 186.8 Hz, C-3), 83.3 (d, $J_{C,F}$ = 27.2 Hz, C-4), 77.5 (d, $J_{C,F}$ = 24.2 Hz, C-2), 74.0 (O<u>C</u>H$_2$Ph), 69.2 (d, $J_{C,F}$ = 9.8 Hz, C-5), 55.2 (OCH_3); ^{19}F NMR (376 MHz, $CDCl_3$, δ): –181.94 (ddd, $J_{3,F}$ = 52.5 Hz, $J_{4,F}$ = 27.4 Hz, $J_{2,F}$ = 13.1 Hz); HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{13}H_{16}FO_4$, 255.1038; found, 255.1041.

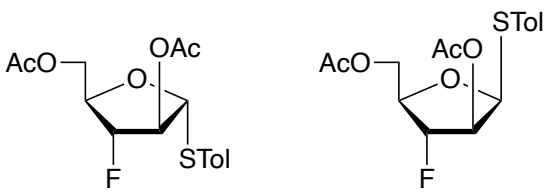


Methyl 3-deoxy-3-fluoro-α-D-arabinofuranoside (2.39). To a solution of **2.38** (2.74 g, 10.7 mmol) in CH_3OH (100 mL) was added 50% palladium hydroxide on carbon (803 mg, 2.86 mmol). The reaction vessel was equipped with a hydrogen-filled balloon. The reaction mixture was stirred at rt for 16 h before being filtered through a pad of Celite® and the filtrate was concentrated to give **2.39** (1.70 g, 96%) as a colorless oil. R_f 0.18 (1:1 hexanes–EtOAc); $[\alpha]_D$ +107 (*c* 1.01, $CHCl_3$); ^{1}H NMR (700 MHz, CD_3OD, δ): 4.82 (s, 1 H, H-1), 4.71 (ddd, $J_{3,F}$ = 53.3 Hz, $J_{3,4}$ = 3.8 Hz, $J_{2,3}$ = 1.5 Hz, 1 H, H-3), 4.16 (dddd, $J_{4,F}$ = 23.0 Hz, $J_{4,5a}$ = 5.0 Hz, $J_{4,5b}$ = 5.0 Hz, $J_{3,4}$ = 3.8 Hz, 1 H, H-4), 4.13 (dd, $J_{2,F}$ = 16.4 Hz, $J_{2,3}$ = 1.5 Hz, 1 H, H-2), 3.69–3.67 (m, 2 H, H-5a and H-5b), 3.36 (s, 3 H, OCH_3); ^{13}C NMR (176 MHz, CD_3OD, δ): 109.1 (d, $J_{C,F}$ = 4.5 Hz, C-1), 97.4 (d, $J_{C,F}$ = 183.5 Hz, C-3), 83.1 (d, $J_{C,F}$ = 26.0 Hz, C-4), 79.1 (d, $J_{C,F}$ = 24.9 Hz, C-2), 61.2 (d, $J_{C,F}$ = 6.3 Hz, C-5), 53.7

(OCH_3); ^{19}F NMR (469 MHz, CD_3OD, δ): –190.42 (ddd, $J_{3,F}$ = 53.3 Hz, $J_{4,F}$ = 23.0 Hz, $J_{2,F}$ = 16.4 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_6H_{11}FNaO_4$, 189.0534; found, 189.0534.

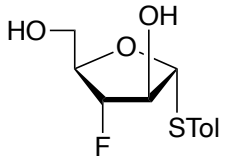


Methyl 2,5-di-*O*-acetyl-3-deoxy-3-fluoro-α-D-arabinofuranoside (2.40). To a solution of **2.39** (1.70 g, 10.2 mmol) in dry pyridine (35 mL) at 0 ºC was added Ac_2O (9.58 mL, 102 mmol) dropwise. The reaction mixture was stirred at rt overnight. Excess Ac_2O was quenched by the addition of CH_3OH at 0 ºC, and the solution was diluted with EtOAc. The organic layer was washed with 1 N $HCl_{(aq)}$, H_2O, saturated $NaHCO_{3(aq)}$ and brine before being dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (3:2 hexanes–EtOAc) to yield **2.40** (2.44 g, 96%) as a colorless oil. R_f 0.33 (2:1 hexanes–EtOAc); $[\alpha]_D$ +43.3 (*c* 1.64, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$, δ): 5.17 (dd, $J_{2,F}$ = 16.1 Hz, $J_{2,3}$ = 1.0 Hz, 1 H, H-2), 4.94 (s, 1 H, H-1), 4.82 (ddd, $J_{3,F}$ = 51.9 Hz, $J_{3,4}$ = 4.1 Hz, $J_{2,3}$ = 1.0 Hz, 1 H, H-3), 4.42 (dddd, $J_{4,F}$ = 22.3 Hz, $J_{4,5b}$ = 5.6 Hz, $J_{4,5a}$ = 4.8 Hz, $J_{3,4}$ = 4.1 Hz, 1 H, H-4), 4.32 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 4.8 Hz, 1 H, H-5a), 4.25 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5b}$ = 5.6 Hz, 1 H, H-5b), 3.42 (s, 3 H, OCH_3), 2.11 (s, 6 H, $C(O)CH_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 170.5 (C=O), 169.5 (C=O), 106.7 (d, $J_{C,F}$ = 3.7 Hz, C-1), 95.5 (d, $J_{C,F}$ = 187.4 Hz, C-3), 80.7 (d, $J_{C,F}$ = 28.1 Hz, C-2), 80.0 (d, $J_{C,F}$ = 28.1 Hz, C-4), 62.8 (d, $J_{C,F}$ = 6.0 Hz, C-5), 55.1 (OCH_3), 20.74 ($C(O)\underline{C}H_3$), 20.69 ($C(O)\underline{C}H_3$); ^{19}F NMR (469 MHz, $CDCl_3$, δ): –189.42 (ddd, $J_{3,F}$ = 51.9 Hz, $J_{4,F}$ = 22.3 Hz, $J_{2,F}$ = 16.1 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{10}H_{15}FNaO_6$, 273.0745; found, 273.0753.



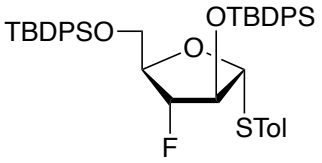
***p*-Tolyl 2,5-di-*O*-acetyl-3-deoxy-3-fluoro-1-thio-α-D-arabinofuranoside (2.41)** and ***p*-Tolyl 2,5-di-*O*-acetyl-3-deoxy-3-fluoro-1-thio-β-D-arabinofuranoside (2.42).** To a solution of **2.40** (784 mg, 3.13 mmol) and *p*-thiocresol (467 mg, 3.76 mmol) in dry CH_2Cl_2 (40 mL) at 0 ºC was added BF_3•OEt_2 (590 μL, 4.70 mmol) dropwise. The reaction mixture was warmed slowly to rt. After 5 h, excess BF_3•OEt_2 was quenched by the addition of saturated $NaHCO_{3(aq)}$ and the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (9:1 hexanes–EtOAc) to yield **2.41** (501 mg, 47%) and **2.42** (182 mg, 17%) as colorless oils. Data for **2.41**: R_f 0.40 (2:1 hexanes–EtOAc); $[\alpha]_D$ +117 (*c* 2.35, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.42–7.39 (m, 2 H, ArH), 7.15–7.11 (m, 2 H, ArH), 5.45 (d, $J_{1,2}$ = 1.6 Hz, 1 H, H-1), 5.36 (ddd, $J_{2,F}$ = 16.4 Hz, $J_{2,3}$ = 1.7 Hz, $J_{1,2}$ = 1.6 Hz, 1 H, H-2), 4.90 (ddd, $J_{3,F}$ = 52.3 Hz, $J_{3,4}$ = 4.5 Hz, $J_{2,3}$ = 1.7 Hz, 1 H, H-3), 4.63 (dddd, $J_{4,F}$ = 21.8 Hz, $J_{4,5b}$ = 5.3 Hz, $J_{4,5a}$ = 4.9 Hz, $J_{3,4}$ = 4.5 Hz, 1 H, H-4), 4.31 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5a}$ = 4.9 Hz, 1 H, H-5a), 4.28 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5b}$ = 5.3 Hz, 1 H, H-5b), 2.33 (s, 3 H, ArC$\underline{H}_3$), 2.11 (s, 3 H, C(O)CH_3), 2.10 (s, 3 H, C(O)CH_3); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 170.5 (C=O), 169.4 (C=O), 138.3 (Ar), 132.9 (Ar), 129.9 (Ar), 129.3 (Ar), 95.6 (d, $J_{C,F}$ = 187.7 Hz, C-3), 90.8 (d, $J_{C,F}$ = 3.7 Hz, C-1), 81.1 (d, $J_{C,F}$ = 28.2 Hz, C-2), 79.6 (d, $J_{C,F}$ = 27.4 Hz, C-4), 62.3 (d, $J_{C,F}$ = 5.6 Hz, C-5), 21.1 (Ar$\underline{C}H_3$), 20.73 (C(O)$\underline{C}H_3$), 20.70 (C(O)$\underline{C}H_3$); ^{19}F NMR (469 MHz, $CDCl_3$, δ): –188.71 (ddd, $J_{3,F}$ = 52.3 Hz, $J_{4,F}$ = 21.8 Hz, $J_{2,F}$ = 16.4 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{19}FNaO_5S$, 365.0829; found, 365.0833. Data for **2.42**: R_f 0.50 (2:1 hexanes–EtOAc); $[\alpha]_D$ –145 (*c* 0.970, $CHCl_3$); ^{1}H NMR (700

MHz, $CDCl_3$, δ): 7.40–7.37 (m, 2 H, ArH), 7.14–7.11 (m, 2 H, ArH), 5.63 (d, $J_{1,2}$ = 5.1 Hz, 1 H, H-1), 5.55 (ddd, $J_{2,F}$ = 16.3 Hz, $J_{1,2}$ = 5.1 Hz, $J_{2,3}$ = 3.2 Hz, 1 H, H-2), 5.04 (ddd, $J_{3,F}$ = 52.3 Hz, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 3.1 Hz, 1 H, H-3), 4.41–4.35 (m, 1 H, H-5a), 4.33–4.27 (m, 2 H, H-4 and H-5b), 2.33 (s, 3 H, ArC$\underline{H}_3$), 2.19 (s, 3 H, C(O)CH_3), 2.11 (s, 3 H, C(O)CH_3); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 170.5 (C=O), 169.5 (C=O), 138.2 (Ar), 132.6 (Ar), 129.9 (Ar), 129.5 (Ar), 95.2 (d, $J_{C,F}$ = 186.0 Hz, C-3), 89.6 (d, $J_{C,F}$ = 3.4 Hz, C-1), 80.0 (d, $J_{C,F}$ = 25.9 Hz, C-4), 77.0 (d, $J_{C,F}$ = 27.9 Hz, C-2), 63.0 (d, $J_{C,F}$ = 7.5 Hz, C-5), 21.1 (Ar$\underline{C}H_3$), 20.8 (C(O)$\underline{C}H_3$), 20.6 (C(O)$\underline{C}H_3$); ^{19}F NMR (469 MHz, $CDCl_3$, δ): –188.19 (ddd, $J_{3,F}$ = 52.3 Hz, $J_{4,F}$ = 25.5 Hz, $J_{2,F}$ = 16.3 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{19}FNaO_5S$, 365.0829; found, 365.0827.



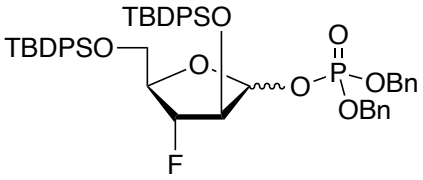
***p*-Tolyl 3-deoxy-3-fluoro-1-thio-α-D-arabinofuranoside (2.43).** To a solution of **2.41** (469 mg, 1.37 mmol) in CH_3OH (7 mL) was added $NaOCH_3$ (111 mg, 2.05 mmol). The reaction mixture was stirred for 3 h at rt before being neutralized with Amberlite® IR-120 (H^+) resin, filtered, and the filtrate was concentrated to give **2.43** (324 mg, 92%) as a white solid. R_f 0.31 (1:1 hexanes–EtOAc); $[\alpha]_D$ +105 (*c* 0.930, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.43–7.40 (m, 2 H, ArH), 7.15–7.12 (m, 2 H, ArH), 5.49 (d, $J_{1,2}$ = 1.3 Hz, 1 H, H-1), 4.98 (ddd, $J_{3,F}$ = 52.8 Hz, $J_{3,4}$ = 1.9 Hz, $J_{2,3}$ = 1.6 Hz, 1 H, H-3), 4.54 (dddd, $J_{4,F}$ = 25.8 Hz, $J_{4,5a}$ = 2.7 Hz, $J_{4,5b}$ = 2.2 Hz, $J_{3,4}$ = 1.9 Hz, 1 H, H-4), 4.44 (ddd, $J_{2,F}$ = 14.4 Hz, $J_{2,3}$ = 1.6 Hz, $J_{1,2}$ = 1.3 Hz, 1 H, H-2), 3.95 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 2.7 Hz, 1 H, H-5a), 3.86 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5b}$ = 2.2 Hz, 1 H, H-5b), 2.34 (s, 3 H, ArC$\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 137.9 (Ar), 132.5 (Ar), 130.4 (Ar), 129.9 (Ar), 97.4 (d, $J_{C,F}$ = 185.8 Hz, C-3), 94.4 (d, $J_{C,F}$ = 1.8 Hz, C-1), 83.3 (d, $J_{C,F}$ = 26.1 Hz, C-4), 79.4 (d, $J_{C,F}$ = 24.9 Hz,

C-2), 61.8 (d, $J_{C,F}$ = 8.6 Hz, C-5), 21.1 (Ar<u>C</u>H$_3$); ^{19}F NMR (469 MHz, CDCl$_3$, δ): –183.45 (ddd, $J_{3,F}$ = 52.8 Hz, $J_{4,F}$ = 25.8 Hz, $J_{2,F}$ = 14.4 Hz); HRMS–ESI–TOF (*m*/*z*): [M+Na]$^+$ calcd for $C_{12}H_{15}FNaO_3S$, 281.0618; found, 281.0615.



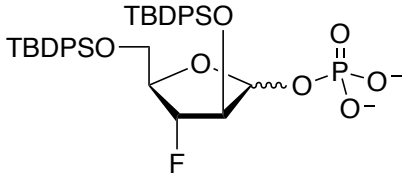
***p*-Tolyl 2,5-di-*O*-*tert*-butyldiphenylsilyl-3-deoxy-3-fluoro-1-thio-α-D-arabinofuranoside (2.2).** To a solution of **2.43** (315 mg, 1.22 mmol) in dry DMF (6 mL) was added imidazole (2.49 g, 36.6 mmol), followed by TBDPSCl (3.13 mL, 12.2 mmol). The reaction mixture was stirred at 70 ºC for 12 h. After cooling to rt, excess TBDPSCl was quenched by the addition of ice-cold water and the solution was extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (50:1 hexanes–EtOAc) to yield **2.2** (881 mg, 98%) as a white solid. R_f 0.40 (10:1 hexanes–EtOAc); $[\alpha]_D$ +11.1 (*c* 1.72, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.70–7.65 (m, 8 H, ArH), 7.48–7.36 (m, 12 H, ArH), 7.22–7.19 (m, 2 H, ArH), 7.06–7.03 (m, 2 H, ArH), 5.32 (d, $J_{1,2}$ = 2.8 Hz, 1 H, H-1), 5.10 (ddd, $J_{3,F}$ = 53.5 Hz, $J_{3,4}$ = 3.9 Hz, $J_{2,3}$ = 2.4 Hz, 1 H, H-3), 4.48 (ddd, $J_{2,F}$ = 16.8 Hz, $J_{1,2}$ = 2.8 Hz, $J_{2,3}$ = 2.4 Hz, 1 H, H-2), 4.39 (dddd, $J_{4,F}$ = 22.1 Hz, $J_{4,5a}$ = 5.6 Hz, $J_{4,5b}$ = 5.6 Hz, $J_{3,4}$ = 3.9 Hz, 1 H, H-4), 3.89–3.87 (m, 2 H, H-5a and H-5b), 2.32 (s, 3 H, ArC<u>H</u>$_3$), 1.10 (s, 9 H, SiC(CH$_3$)$_3$), 1.08 (s, 9 H, SiC(CH$_3$)$_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 137.5 (Ar), 135.9 (Ar), 135.8 (Ar), 135.63 (Ar), 135.62 (Ar), 133.24 (Ar), 133.21 (Ar), 132.7 (Ar), 132.5 (Ar), 130.6 (Ar), 130.11 (Ar), 130.05 (Ar), 129.81 (Ar), 129.76 (Ar), 129.6 (Ar), 127.90 (Ar), 127.85 (Ar), 127.79 (Ar), 127.75 (Ar), 97.9 (d, $J_{C,F}$ = 185.4 Hz, C-3), 93.5 (d, $J_{C,F}$ = 5.2 Hz, C-1), 82.5 (d, $J_{C,F}$ = 25.4 Hz, C-4), 81.8 (d, $J_{C,F}$ = 26.3 Hz, C-2), 63.1 (d, $J_{C,F}$ = 6.2 Hz, C-5), 26.9 (SiC(<u>C</u>H$_3$)$_3$),

26.8 (SiC($\underline{C}H_3)_3$), 21.1 (Ar$\underline{C}H_3$), 19.3 (Si$\underline{C}(CH_3)_3$), 19.1 (Si$\underline{C}(CH_3)_3$); ^{19}F NMR (469 MHz, $CDCl_3$, δ): –188.11 (ddd, $J_{3,F}$ = 53.5 Hz, $J_{4,F}$ = 22.1 Hz, $J_{2,F}$ = 16.8 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{44}H_{51}FNaO_3SSi_2$, 757.2974; found, 757.2980.



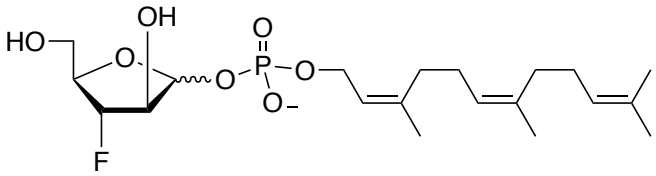
Dibenzyl (2,5-di-*O*-*tert*-butyldiphenylsilyl-3-deoxy-3-fluoro-α/β-D-arabinofuranosyl) phosphate (2.5). To a stirred solution of **2.2** (215 mg, 0.292 mmol) in CH_2Cl_2 (3 mL) was added Br_2 (19 μL, 0.38 mmol). The reaction mixture was stirred at rt for 1 h before being concentrated. The crude glycosyl bromide was azeotropically dried with toluene and then used immediately. To a stirred solution of azeotropically dried dibenzyl phosphate (162 mg, 0.584 mmol) in toluene (1 mL) were added powdered 4 Å molecular sieves (250 mg) and Et_3N (105 μL, 0.759 mmol). The mixture was cooled to 0 ºC, and a solution of the aforementioned glycosyl bromide in toluene (1 mL) was added slowly via a cannula. The transfer was completed by rinsing the flask twice with toluene (2 × 0.5 mL). The reaction mixture was warmed slowly to rt and stirred for 19 h before being filtered through a pad of Celite®, rinsed with EtOAc, and the filtrate was concentrated. The crude residue was purified by column chromatography (15% EtOAc–hexanes) to yield **2.5** (169 mg, 65% over two steps, β:α 5.5:1, inseparable) as a colorless oil. R_f 0.25 (4:1 hexanes–EtOAc); Data for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.69–7.59 (m, 8 H, ArH), 7.45–7.13 (m, 22 H, ArH), 5.45 (dd, $J_{1,P}$ = 5.0 Hz, $J_{1,2}$ = 4.2 Hz, 1 H, H-1), 5.09 (ddd, $J_{3,F}$ = 56.6 Hz, $J_{2,3}$ = 6.5 Hz, $J_{3,4}$ = 5.3 Hz, 1 H, H-3), 4.96–4.81 (m, 4 H, 2 × OC$\underline{H}_2$Ph), 4.39 (dddd, $J_{2,F}$ = 20.9 Hz, $J_{2,3}$ = 6.5 Hz, $J_{1,2}$ = 4.2 Hz, $J_{2,P}$ = 2.7 Hz, 1 H, H-2), 4.06 (dddd, $J_{4,F}$ = 20.9 Hz, $J_{4,5b}$ = 7.9 Hz, $J_{4,5a}$ = 5.7 Hz, $J_{3,4}$ = 5.3 Hz, 1 H, H-4), 3.81–3.75 (m, 2 H, H-5a and H-5b), 1.08 (s, 9 H, SiC($CH_3)_3$), 1.03 (s,

9 H, SiC(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 135.9 (Ar), 135.8 (Ar), 135.6 (Ar), 133.2 (Ar), 133.1 (Ar), 132.6 (Ar), 132.4 (Ar), 130.14 (Ar), 130.11 (Ar), 129.9 (Ar), 129.8 (Ar), 128.49 (Ar), 128.45 (Ar), 128.42 (Ar), 128.3 (Ar), 128.1 (Ar), 127.89 (Ar), 127.87 (Ar), 127.83 (Ar), 127.81 (Ar), 127.77 (Ar), 99.5 (dd, $J_{C,F}$ = 11.0 Hz, $J_{C,P}$ = 6.3 Hz, C-1), 97.4 (d, $J_{C,F}$ = 186.8 Hz, C-3), 81.0 (d, $J_{C,F}$ = 24.9 Hz, C-4), 77.6 (dd, $J_{C,F}$ = 22.5 Hz, $J_{C,P}$ = 8.5 Hz, C-2), 69.2 (d, $J_{C,P}$ = 5.3 Hz, O$\underline{C}$H$_2$Ph), 69.0 (d, $J_{C,P}$ = 5.2 Hz, O$\underline{C}$H$_2$Ph), 64.7 (d, $J_{C,F}$ = 4.2 Hz, C-5), 26.8 (2 × SiC($\underline{C}$H$_3$)$_3$), 19.3 (Si$\underline{C}$(CH$_3$)$_3$), 19.2 (Si$\underline{C}$(CH$_3$)$_3$); ^{19}F NMR (470 MHz, $CDCl_3$, δ): –196.44 (ddd, $J_{3,F}$ = 56.6 Hz, $J_{4,F}$ = 20.9 Hz, $J_{2,F}$ = 20.9 Hz); ^{31}P NMR (202 MHz, $CDCl_3$, δ): –0.65; HRMS–ESI–TOF (*m*/*z*): [M+Na]$^+$ calcd for $C_{51}H_{58}FNaO_7PSi_2$, 911.3335; found, 911.3330.



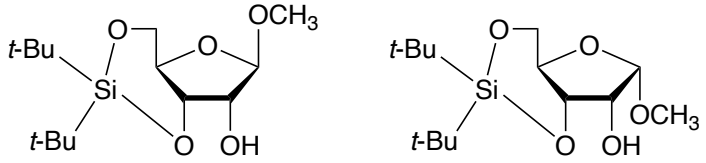
2,5-Di-*O*-*tert*-butyldiphenylsilyl-3-deoxy-3-fluoro-α/β-D-arabinofuranosyl phosphate (2.8). To a stirred solution of **2.5** (168 mg, 0.189 mmol) in 10% EtOH–EtOAc (6.8 mL) were added Et_3N (657 μL, 4.73 mmol) and 5% palladium on carbon (402 mg, 0.189 mmol). The reaction vessel was purged with argon and then equipped with a hydrogen-filled balloon. The reaction mixture was stirred at rt for 14 h before being filtered through a pad of Celite® with 10% EtOH–EtOAc. The filtrate was concentrated to yield **2.8** (as the triethylammonium salt, 150 mg, 87%, β:α 7.2:1, inseparable) as a colorless oil. R_f 0.50 (6:1 CH_2Cl_2–CH_3OH); Data for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.80–7.72 (m, 4 H, ArH), 7.67–7.61 (m, 4 H, ArH), 7.41–7.30 (m, 12 H, ArH), 5.44 (dd, $J_{1,P}$ = 6.8 Hz, $J_{1,2}$ = 4.1 Hz, 1 H, H-1), 5.13 (ddd, $J_{3,F}$ = 56.5 Hz, $J_{2,3}$ = 5.5 Hz, $J_{3,4}$ = 3.4 Hz, 1 H, H-3), 4.25 (dddd, $J_{2,F}$ = 20.7 Hz, $J_{2,3}$ = 5.5 Hz, $J_{1,2}$ = 4.1 Hz, $J_{2,P}$ = 1.7 Hz, 1 H, H-2), 3.98–3.83 (m, 3 H, H-4, H-5a and H-5b), 1.08 (s, 9 H, SiC(CH_3)$_3$), 1.02 (s, 9 H, SiC(CH_3)$_3$);

^{13}C NMR (126 MHz, $CDCl_3$, δ): 136.2 (Ar), 135.9 (Ar), 135.6 (Ar), 135.5 (Ar), 133.6 (Ar), 133.5 (Ar), 133.2 (Ar), 133.0 (Ar), 129.8 (Ar), 129.68 (Ar), 129.65 (Ar), 127.79 (Ar), 127.76 (Ar), 127.7 (Ar), 98.9 (d, $J_{C,F}$ = 184.4 Hz, C-3), 97.7 (dd, $J_{C,F}$ = 9.3 Hz, $J_{C,P}$ = 5.6 Hz, C-1), 80.1 (d, $J_{C,F}$ = 24.0 Hz, C-4), 77.5 (dd, $J_{C,F}$ = 22.6 Hz, $J_{C,P}$ = 8.4 Hz, C-2), 65.2 (d, $J_{C,F}$ = 5.7 Hz, C-5), 26.9 (SiC($\underline{C}H_3)_3$), 26.8 (SiC($\underline{C}H_3)_3$), 19.3 (Si$\underline{C}(CH_3)_3$), 19.2 (Si$\underline{C}(CH_3)_3$); ^{19}F NMR (470 MHz, $CDCl_3$, δ): –192.34 (ddd, $J_{3,F}$ = 56.5 Hz, $J_{4,F}$ = 22.5 Hz, $J_{2,F}$ = 20.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$, δ): 1.71; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{37}H_{45}FO_7PSi_2$, 707.2431; found, 707.2433.



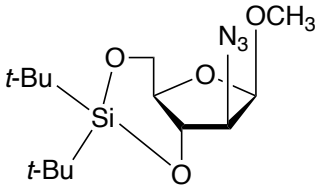
(*Z*,*Z*)-Farnesylphosphoryl-3-deoxy-3-fluoro-α/β-D-arabinofuranose (1.32). Compound **2.8** (147 mg, 0.161 mmol) and (*Z*,*Z*)-farnesol[5] (144 mg, 0.646 mmol) were azeotropically dried with toluene. The mixture was dissolved in pyridine (2.1 mL) and Cl_3CCN (161 μL, 1.61 mmol) was added. The resulting solution was stirred for 16 h at 55 ºC before being cooled to rt and concentrated. The crude phosphodiester was dissolved in a 15% solution of concentrated NH_4OH in CH_3OH (3.2 mL), and NH_4F (179 mg, 4.83 mmol) was added. After stirring for 12 h at 55 ºC, the reaction mixture was cooled to rt, and CH_2Cl_2 (4 mL) was added to precipitate any remaining NH_4F. The solution was filtered through a pad of Celite® and the filtrate was concentrated to a crude residue that was purified by column chromatography (1:1 EtOAc–CH_3OH). Residual colored impurities were removed by the addition of activated charcoal to the product in CH_3OH, followed by the filtration through a syringe filter (0.45 μm). The filtrate was concentrated to give **1.32** (32.0 mg, 44% over two steps, β:α 2.8:1, inseparable) as a colorless oil. R_f 0.64 (3:2 EtOAc–CH_3OH); Data for the β-anomer: ^{1}H NMR (500 MHz, CD_3OD, δ): 5.54 (dd, $J_{1,P}$ = 5.3 Hz, $J_{1,2}$ =

4.5 Hz, 1 H, H-1), 5.43–5.38 (m, 1 H, $OCH_2C\underline{H}$=C), 5.14–5.09 (m, 2 H, 2 × $CH_2C\underline{H}$=C), 4.94 (ddd, $J_{3,F}$ = 57.3 Hz, $J_{2,3}$ = 6.1 Hz, $J_{3,4}$ = 5.3 Hz, 1 H, H-3), 4.44–4.40 (m, 2 H, $OC\underline{H}_2CH$=C), 4.36–4.27 (m, 1 H, H-2), 4.08 (dddd, $J_{4,F}$ = 21.4 Hz, $J_{4,5b}$ = 6.2 Hz, $J_{3,4}$ = 5.3 Hz, $J_{4,5a}$ = 4.7 Hz, 1 H, H-4), 3.74 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5a}$ = 4.7 Hz, 1 H, H-5a), 3.68 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5b}$ = 6.2 Hz, 1 H, H-5b), 2.13–2.00 (m, 8 H, 4 × allylic CH_2), 1.73 (s, 3 H, CH_3), 1.67 (s, 6 H, 2 × CH_3), 1.61 (s, 3 H, CH_3); ^{13}C NMR (126 MHz, CD_3OD, δ): 139.6 (CH=$\underline{C}$), 135.2 (CH=$\underline{C}$), 131.0 (CH=$\underline{C}$), 124.3 ($\underline{C}$H=C), 124.0 ($\underline{C}$H=C), 121.8 (d, $J_{C,P}$ = 8.3 Hz, $\underline{C}$H=C), 97.9 (dd, $J_{C,F}$ = 10.2 Hz, $J_{C,P}$ = 6.5 Hz, C-1), 96.5 (d, $J_{C,F}$ = 182.9 Hz, C-3), 81.5 (d, $J_{C,F}$ = 25.3 Hz, C-4), 76.4 (dd, $J_{C,F}$ = 22.1 Hz, $J_{C,P}$ = 7.3 Hz, C-2), 62.4 (d, $J_{C,F}$ = 3.8 Hz, C-5), 62.1 (d, $J_{C,P}$ = 5.3 Hz, $O\underline{C}H_2CH$=C), 31.9 (allylic CH_2), 31.5 (allylic CH_2), 26.3 (allylic CH_2), 26.2 (allylic CH_2), 24.6 (CH_3), 22.32 (CH_3), 22.27 (CH_3), 16.3 (CH_3); ^{19}F NMR (470 MHz, CD_3OD, δ): –200.93 (ddd, $J_{3,F}$ = 57.3 Hz, $J_{4,F}$ = 21.4 Hz, $J_{2,F}$ = 16.8 Hz); ^{31}P NMR (202 MHz, CD_3OD, δ): –0.48; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{20}H_{33}FO_7P$, 435.1953; found, 435.1944.



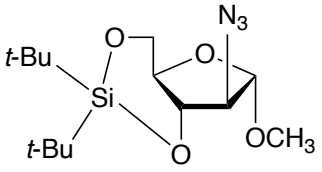
Methyl 3,5-*O*-di-*tert*-butylsilylene-β-D-ribofuranoside (2.44) and **Methyl 3,5-*O*-di-*tert*-butylsilylene-α-D-ribofuranoside (2.45).** To a solution of **2.25**[14] (3.65 g, 22.2 mmol) in a mixture of CH_2Cl_2 (100 mL) and DMF (20 mL) at 0 ºC were added 2,6-lutidine (10.3 mL, 88.8 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (7.23 mL, 22.2 mmol). After stirring for 3 h at rt, the reaction mixture was concentrated, diluted with EtOAc, and washed with H_2O and brine. The organic layer was dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (9:1 hexanes–EtOAc) to yield **2.44** (3.98 g, 59%) and

2.45 (1.02 g, 15%) as light-yellow solids. Data for **2.44**: R_f 0.62 (2:1 hexanes–EtOAc); $[\alpha]_D$ –86.7 (*c* 3.07, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$, δ): 4.89 (s, 1 H, H-1), 4.40 (dd, $J_{5a,5b}$ = 9.0 Hz, $J_{4,5a}$ = 4.9 Hz, 1 H, H-5a), 4.08–4.05 (m, 2 H, H-3 and H-2), 4.05–4.00 (m, 1 H, H-4), 3.94 (dd, $J_{4,5b}$ = 10.2 Hz, $J_{5a,5b}$ = 9.0 Hz, 1 H, H-5b), 3.40 (s, 3 H, OCH_3), 2.30 (s, 1 H, OH), 1.06 (s, 9 H, $SiC(CH_3)_3$), 1.01 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 109.2 (C-1), 76.3 (C-2), 74.3 (C-3), 74.1 (C-4), 68.4 (C-5), 56.0 (OCH_3), 27.4 ($SiC(\underline{C}H_3)_3$), 27.3 ($SiC(\underline{C}H_3)_3$), 22.6 ($Si\underline{C}(CH_3)_3$), 20.3 ($Si\underline{C}(CH_3)_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{28}NaO_5Si$, 327.1598; found, 327.1608. Data for **2.45**: R_f 0.35 (2:1 hexanes–EtOAc); $[\alpha]_D$ +55.8 (*c* 1.22, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$, δ): 5.07 (d, $J_{1,2}$ = 3.9 Hz, 1 H, H-1), 4.40 (dd, $J_{5a,5b}$ = 9.3 Hz, $J_{4,5a}$ = 5.1 Hz, 1 H, H-5a), 4.30 (ddd, $J_{1,2}$ = 3.9 Hz, $J_{2,OH}$ = 1.8 Hz, $J_{2,3}$ = 1.4 Hz, 1 H, H-2), 4.09 (ddd, $J_{3,4}$ = 9.3 Hz, $J_{4,5b}$ = 7.1 Hz, $J_{4,5a}$ = 5.1 Hz, 1 H, H-4), 3.87 (dd, $J_{3,4}$ = 9.3 Hz, $J_{2,3}$ = 1.4 Hz, 1 H, H-3), 3.86 (dd, $J_{5a,5b}$ = 9.3 Hz, $J_{4,5b}$ = 7.1 Hz, 1 H, H-5b), 3.53 (s, 3 H, OCH_3), 2.64 (d, $J_{2,OH}$ = 1.8 Hz, 1 H, OH), 1.06 (s, 9 H, $SiC(CH_3)_3$), 1.02 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 103.9 (C-1), 77.7 (C-3), 72.7 (C-4), 69.6 (C-2), 67.6 (C-5), 56.5 (OCH_3), 27.3 ($SiC(\underline{C}H_3)_3$), 27.2 ($SiC(\underline{C}H_3)_3$), 22.7 ($Si\underline{C}(CH_3)_3$), 20.4 ($Si\underline{C}(CH_3)_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{28}NaO_5Si$, 327.1598; found, 327.1597.



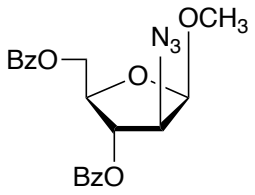
Methyl 2-azido-3,5-*O*-di-*tert*-butylsilylene-2-deoxy-β-D-arabinofuranoside (2.47). To a solution of **2.44** (510 mg, 1.68 mmol) in dry pyridine (9 mL) at 0 ºC was added Tf_2O (410 µL, 2.52 mmol). The reaction mixture was stirred for 1.5 h at rt before water and EtOAc were added. The organic layer was washed with H_2O, dried with $MgSO_4$, filtered, and the filtrate was

concentrated to yield crude methyl 3,5-*O*-di-*tert*-butylsilylene-2-*O*-trifluoromethanesulphonyl-β-D-ribofuranoside (**2.46**) as a light-yellow oil that was co-evaporated twice with toluene. The residue was dissolved in dry DMF (6 mL), and then NaN_3 (437 mg, 6.72 mmol) was added. The reaction mixture was stirred at 50 ºC for 4 days before being poured into ice-cold water and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (19:1 hexanes–EtOAc) to yield **2.47** (126 mg, 23% over two steps) as a colorless oil. R_f 0.58 (4:1 hexanes–EtOAc); $[\alpha]_D$ –150 (*c* 1.04, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 4.93 (d, $J_{1,2}$ = 5.3 Hz, 1 H, H-1), 4.35 (dd, $J_{5a,5b}$ = 9.3 Hz, $J_{4,5a}$ = 5.1 Hz, 1 H, H-5a), 4.33 (dd, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 9.1 Hz, 1 H, H-3), 3.92 (dd, $J_{4,5b}$ = 10.6 Hz, $J_{5a,5b}$ = 9.3 Hz, 1 H, H-5b), 3.75 (ddd, $J_{4,5b}$ = 10.6 Hz, $J_{3,4}$ = 9.1 Hz, $J_{4,5a}$ = 5.1 Hz, 1 H, H-4), 3.66 (dd, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 5.3 Hz, 1 H, H-2), 3.44 (s, 3 H, OCH_3), 1.08 (s, 9 H, $SiC(CH_3)_3$), 1.00 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 102.2 (C-1), 76.7 (C-3), 74.8 (C-4), 68.4 (C-5), 65.0 (C-2), 56.1 (OCH_3), 27.4 ($SiC(\underline{C}H_3)_3$), 27.1 ($SiC(\underline{C}H_3)_3$), 22.5 ($Si\underline{C}(CH_3)_3$), 20.1 ($Si\underline{C}(CH_3)_3$); HRMS–APPI–TOF (*m*/*z*): $[M+H-N_2]^+$ calcd for $C_{14}H_{28}NO_4Si$, 302.1782; found, 302.1781.



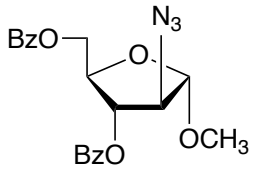
Methyl 2-azido-3,5-*O*-di-*tert*-butylsilylene-2-deoxy-α-D-arabinofuranoside (2.51). To a solution of **2.45** (1.02 g, 3.35 mmol) in dry pyridine (10 mL) at 0 ºC was added Tf_2O (820 µL, 5.03 mmol). The reaction mixture was stirred for 2 h at rt before water and EtOAc were added. The organic layer was washed with H_2O, dried with $MgSO_4$, filtered, and the filtrate was concentrated to yield crude methyl 3,5-*O*-di-*tert*-butylsilylene-2-*O*-trifluoromethanesulphonyl-α-

D-ribofuranoside (**2.23**) as a light-yellow oil that was co-evaporated twice with toluene. The residue was dissolved in dry DMF (10 mL), and then NaN_3 (871 mg, 13.4 mmol) was added. The reaction mixture was stirred at 50 ºC for 20 h before being poured into ice-cold water and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (19:1 hexanes–EtOAc) to yield **2.51** (833 mg, 75% over two steps) as a colorless oil. R_f 0.57 (5:1 hexanes–EtOAc); $[\alpha]_D$ +54.6 (*c* 1.02, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 4.75 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H-1), 4.35 (dd, $J_{5a,5b}$ = 9.2 Hz, $J_{4,5a}$ = 3.3 Hz, 1 H, H-5a), 3.97–3.88 (m, 3 H, H-3, H-4 and H-5b), 3.83 (dd, $J_{2,3}$ = 8.0 Hz, $J_{1,2}$ = 3.8 Hz, 1 H, H-2), 3.41 (s, 3 H, OCH_3), 1.06 (s, 9 H, $SiC(CH_3)_3$), 1.00 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 107.2 (C-1), 80.1 (C-3), 74.0 (C-4), 70.9 (C-2), 67.4 (C-5), 56.1 (OCH_3), 27.3 ($SiC(\underline{C}H_3)_3$), 27.0 ($SiC(\underline{C}H_3)_3$), 22.6 ($Si\underline{C}(CH_3)_3$), 20.1 ($Si\underline{C}(CH_3)_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{27}N_3NaO_4Si$, 352.1663; found, 352.1664.



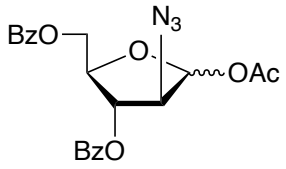
Methyl 2-azido-3,5-di-*O*-benzoyl-2-deoxy-β-D-arabinofuranoside (2.48). A solution of **2.47** (110 mg, 0.333 mmol) in THF (2 mL) was treated with 1 M TBAF in THF (1 mL). The solution was stirred for 10 h at rt before being concentrated to yield crude methyl 2-azido-2-deoxy-β-D-arabinofuranoside, which was dissolved in dry pyridine (2 mL) and then BzCl (390 µL, 3.33 mmol) was added dropwise. The reaction mixture was stirred at rt for 20 h. Excess BzCl was quenched by the addition of water and the solution was diluted with EtOAc. The organic layer was washed with 1 N $HCl_{(aq)}$, H_2O, saturated $NaHCO_{3(aq)}$ and brine before being dried with $MgSO_4$, filtered,

and the filtrate was concentrated. The crude residue was purified by column chromatography (15% EtOAc–hexanes) to yield **2.48** (128 mg, 97% over two steps) as a colorless oil. R_f 0.28 (4:1 hexanes–EtOAc); $[\alpha]_D$ –92.0 (*c* 1.09, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 8.07–8.03 (m, 4 H, ArH), 7.62–7.59 (m, 1 H, ArH), 7.55–7.52 (m, 1 H, ArH), 7.48–7.45 (m, 2 H, ArH), 7.41–7.38 (m, 2 H, ArH), 5.80 (dd, $J_{2,3}$ = 8.1 Hz, $J_{3,4}$ = 5.9 Hz, 1 H, H-3), 5.06 (d, $J_{1,2}$ = 4.5 Hz, 1 H, H-1), 4.71 (dd, $J_{5a,5b}$ = 11.7 Hz, $J_{4,5a}$ = 4.1 Hz, 1 H, H-5a), 4.56 (dd, $J_{5a,5b}$ = 11.7 Hz, $J_{4,5b}$ = 6.1 Hz, 1 H, H-5b), 4.46 (ddd, $J_{4,5b}$ = 6.1 Hz, $J_{3,4}$ = 5.9 Hz, $J_{4,5a}$ = 4.1 Hz, 1 H, H-4), 4.00 (dd, $J_{2,3}$ = 8.1 Hz, $J_{1,2}$ = 4.5 Hz, 1 H, H-2), 3.45 (s, 3 H, OCH_3); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 166.2 (C=O), 165.8 (C=O), 133.7 (Ar), 133.1 (Ar), 129.8 (Ar), 129.7 (Ar), 129.1 (Ar), 128.9 (Ar), 128.5 (Ar), 128.3 (Ar), 103.2 (C-1), 79.5 (C-4), 75.7 (C-3), 65.6 (C-2), 65.4 (C-5), 55.5 (OCH_3); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{19}N_3NaO_6$, 420.1166; found, 420.1166.



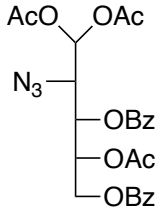
Methyl 2-azido-3,5-di-*O*-benzoyl-2-deoxy-α-D-arabinofuranoside (2.52). A solution of **2.51** (828 mg, 2.51 mmol) in THF (8 mL) was treated with 1 M TBAF in THF (7.5 mL). The solution was stirred for 22 h at rt before being concentrated to yield crude methyl 2-azido-2-deoxy-α-D-arabinofuranoside, which was dissolved in dry pyridine (8 mL) and then BzCl (5.83 mL, 50.2 mmol) was added dropwise. The reaction mixture was stirred at rt overnight. Excess BzCl was quenched by the addition of water and the solution was diluted with EtOAc. The organic layer was washed with 1 N $HCl_{(aq)}$, H_2O, saturated $NaHCO_{3(aq)}$ and brine before being dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (9:1 hexanes–EtOAc) to yield **2.52** (998 mg, quantitative) as a colorless oil. R_f

0.35 (4:1 hexanes–EtOAc); $[\alpha]_D$ +59 (*c* 0.56, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$, δ): 8.09–8.04 (m, 4 H, ArH), 7.61–7.53 (m, 2 H, ArH), 7.47–7.40 (m, 4 H, ArH), 5.34 (dd, $J_{3,4}$ = 5.2 Hz, $J_{2,3}$ = 2.2 Hz, 1 H, H-3), 5.00 (s, 1 H, H-1), 4.71 (dd, $J_{5a,5b}$ = 11.8 Hz, $J_{4,5a}$ = 3.6 Hz, 1 H, H-5a), 4.60 (dd, $J_{5a,5b}$ = 11.8 Hz, $J_{4,5b}$ = 4.7 Hz, 1 H, H-5b), 4.57 (ddd, $J_{3,4}$ = 5.2 Hz, $J_{4,5b}$ = 4.7 Hz, $J_{4,5a}$ = 3.6 Hz, 1 H, H-4), 4.18 (d, $J_{2,3}$ = 2.2 Hz, 1 H, H-2), 3.44 (s, 3 H, OCH_3); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 166.2 (C=O), 166.0 (C=O), 133.6 (Ar), 133.1 (Ar), 129.9 (Ar), 129.7 (Ar), 129.6 (Ar), 129.0 (Ar), 128.5 (Ar), 128.4 (Ar), 107.1 (C-1), 80.1 (C-4), 78.4 (C-3), 70.5 (C-2), 63.5 (C-5), 55.1 (OCH_3); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{19}N_3NaO_6$, 420.1166; found, 420.1166.



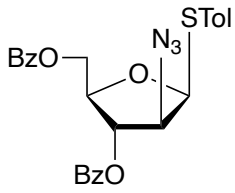
1-*O*-Acetyl-2-azido-3,5-di-*O*-benzoyl-2-deoxy-α/β-D-arabinofuranose (2.50). From **2.48**: To a solution of **2.48** (117 mg, 0.295 mmol) in a mixture of AcOH (1 mL) and Ac_2O (1 mL) was added dropwise concentrated H_2SO_4 (0.1 mL) in AcOH (1 mL). The reaction mixture was stirred at rt for 4 h before being diluted with EtOAc. The resulting solution was washed with saturated $NaHCO_{3(aq)}$ and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (gradient of 4:1→3:1 hexanes–EtOAc) to give **2.50** (90.5 mg, 72%, α:β 2.3:1, inseparable) as a colorless oil. From **2.52**: To a solution of **2.52** (497 mg, 1.25 mmol) in a mixture of AcOH (4 mL) and Ac_2O (4 mL) was added dropwise concentrated H_2SO_4 (0.4 mL) in AcOH (4 mL). The reaction mixture was stirred at rt for 18 h before being diluted with EtOAc. The resulting solution was washed with saturated $NaHCO_{3(aq)}$ and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (gradient of 4:1→3:1 hexanes–EtOAc) to give **2.50** (399 mg, 75%, α:β 2.3:1,

inseparable) as a colorless oil. R_f 0.41 (2:1 hexanes–EtOAc); Data for the α-anomer: ^{1}H NMR (700 MHz, $CDCl_3$, δ): 8.10–8.04 (m, 4 H, ArH), 7.64–7.60 (m, 1 H, ArH), 7.57–7.54 (m, 1 H, ArH), 7.50–7.46 (m, 2 H, ArH), 7.44–7.41 (m, 2 H, ArH), 6.26 (s, 1 H, H-1), 5.38 (dd, $J_{3,4}$ = 4.2 Hz, $J_{2,3}$ = 1.3 Hz, 1 H, H-3), 4.75–4.72 (m, 1 H, H-4), 4.67 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5a}$ = 4.1 Hz, 1 H, H-5a), 4.61 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5b}$ = 5.1 Hz, 1 H, H-5b), 4.33 (d, $J_{2,3}$ = 1.3 Hz, 1 H, H-2), 2.13 (s, 3 H, $C(O)CH_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 169.4 (C=O), 166.2 (C=O), 165.7 (C=O), 133.8 (Ar), 133.2 (Ar), 129.9 (Ar), 129.78 (Ar), 129.77 (Ar), 128.6 (Ar), 128.39 (Ar), 128.37 (Ar), 100.3 (C-1), 82.7 (C-4), 77.9 (C-3), 70.0 (C-2), 63.4 (C-5), 21.0 ($C(O)\underline{C}H_3$); Data for the β-anomer: ^{1}H NMR (700 MHz, $CDCl_3$, δ): 8.07–8.04 (m, 4 H, ArH), 7.64–7.60 (m, 1 H, ArH), 7.55–7.52 (m, 1 H, ArH), 7.50–7.46 (m, 2 H, ArH), 7.41–7.38 (m, 2 H, ArH), 6.44 (d, $J_{1,2}$ = 4.7 Hz, 1 H, H-1), 5.81 (dd, $J_{2,3}$ = 8.1 Hz, $J_{3,4}$ = 6.1 Hz, 1 H, H-3), 4.75 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 4.0 Hz, 1 H, H-5a), 4.56 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5b}$ = 5.8 Hz, 1 H, H-5b), 4.52 (ddd, $J_{3,4}$ = 6.1 Hz, $J_{4,5b}$ = 5.8 Hz, $J_{4,5a}$ = 4.0 Hz, 1 H, H-4), 4.24 (dd, $J_{2,3}$ = 8.1 Hz, $J_{1,2}$ = 4.7 Hz, 1 H, H-2), 2.03 (s, 3 H, $C(O)CH_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 169.3 (C=O), 165.9 (C=O), 165.7 (C=O), 133.9 (Ar), 133.2 (Ar), 129.9 (Ar), 129.78 (Ar), 129.77 (Ar), 128.6 (Ar), 128.39 (Ar), 128.37 (Ar), 95.1 (C-1), 80.4 (C-4), 74.8 (C-3), 65.2 (C-2), 64.4 (C-5), 20.9 ($C(O)\underline{C}H_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{19}N_3NaO_7$, 448.1115; found, 448.1112.



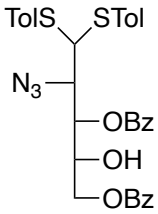
1,1,4-Tri-*O*-acetyl-2-azido-3,5-di-*O*-benzoyl-2-deoxy-D-arabinose aldehydrol (2.53). Compound **2.53** is a colorless oil and was isolated as a side-product (24.4 mg, 4%) in the conversion of **2.52** into **2.50**. R_f 0.25 (2:1 hexanes–EtOAc); $[\alpha]_D$ +14.8 (*c* 1.43, $CHCl_3$); ^{1}H NMR

(700 MHz, $CDCl_3$, δ): 8.07–8.01 (m, 4 H, ArH), 7.62–7.55 (m, 2 H, ArH), 7.48–7.42 (m, 4 H, ArH), 6.97 (d, $J_{1,2}$ = 5.7 Hz, 1 H, H-1), 5.85 (dd, $J_{3,4}$ = 7.8 Hz, $J_{2,3}$ = 2.4 Hz, 1 H, H-3), 5.57 (ddd, $J_{3,4}$ = 7.8 Hz, $J_{4,5b}$ = 5.2 Hz, $J_{4,5a}$ = 3.0 Hz, 1 H, H-4), 4.81 (dd, $J_{5a,5b}$ = 12.5 Hz, $J_{4,5a}$ = 3.0 Hz, 1 H, H-5a), 4.32 (dd, $J_{5a,5b}$ = 12.5 Hz, $J_{4,5b}$ = 5.2 Hz, 1 H, H-5b), 3.82 (dd, $J_{1,2}$ = 5.7 Hz, $J_{2,3}$ = 2.4 Hz, 1 H, H-2), 2.14 (s, 3 H, C(O)CH_3), 2.04 (s, 3 H, C(O)CH_3), 2.01 (s, 3 H, C(O)CH_3); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 169.6 (C=O), 168.1 (C=O), 168.0 (C=O), 166.0 (C=O), 164.9 (C=O), 133.9 (Ar), 133.3 (Ar), 130.0 (Ar), 129.7 (Ar), 129.4 (Ar), 128.7 (Ar), 128.5 (Ar), 128.4 (Ar), 87.7 (C-1), 69.8 (C-4), 68.4 (C-3), 61.9 (C-5), 61.3 (C-2), 20.9 (C(O)<u>C</u>H_3), 20.51 (C(O)<u>C</u>H_3), 20.50 (C(O)<u>C</u>H_3); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{25}N_3NaO_{10}$, 550.1432; found, 550.1431.

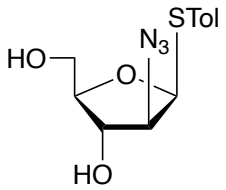


***p*-Tolyl 2-azido-3,5-di-*O*-benzoyl-2-deoxy-1-thio-β-D-arabinofuranoside (2.54).** To a solution of **2.50** (763 mg, 1.79 mmol) and *p*-thiocresol (535 mg, 4.31 mmol) in dry CH_2Cl_2 (23 mL) at 0 ºC was added BF_3•OEt_2 (670 μL, 5.37 mmol) dropwise. The reaction mixture was warmed slowly to rt. After 10 h, Et_3N (190 μL) was added, and the solution was concentrated. The crude residue was purified by column chromatography (9:1 hexanes–EtOAc) to give **2.54** (307 mg, 35%) as a colorless oil. R_f 0.40 (3:1 hexanes–EtOAc); $[\alpha]_D$ +74 (*c* 0.77, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 8.09–8.05 (m, 4 H, ArH), 7.64–7.60 (m, 1 H, ArH), 7.57–7.54 (m, 1 H, ArH), 7.50–7.46 (m, 2 H, ArH), 7.45–7.40 (m, 4 H, ArH), 7.15–7.12 (m, 2 H, ArH), 5.50 (d, $J_{1,2}$ = 3.3 Hz, 1 H, H-1), 5.41 (dd, $J_{3,4}$ = 4.9 Hz, $J_{2,3}$ = 3.2 Hz, 1 H, H-3), 4.74 (ddd, $J_{3,4}$ = 4.9 Hz, $J_{4,5b}$ = 4.9 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-4), 4.68 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-5a), 4.63 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5b}$ = 4.9

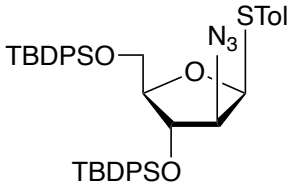
Hz, 1 H, H-5b), 4.26 (dd, $J_{1,2}$ = 3.3 Hz, $J_{2,3}$ = 3.2 Hz, 1 H, H-2), 2.34 (s, 3 H, ArC$\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 166.1 (C=O), 165.7 (C=O), 138.5 (Ar), 133.8 (Ar), 133.2 (Ar), 133.0 (Ar), 130.0 (Ar), 129.9 (Ar), 129.7 (Ar), 129.6 (Ar), 129.0 (Ar), 128.8 (Ar), 128.6 (Ar), 128.4 (Ar), 90.9 (C-1), 80.2 (C-4), 78.3 (C-3), 70.4 (C-2), 63.5 (C-5), 21.1 (Ar$\underline{C}H_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{23}N_3NaO_5S$, 512.1251; found, 512.1251.



2-Azido-3,5-di-*O*-benzoyl-2-deoxy-D-arabinose di-*p*-tolyl dithioacetal (2.55). Compound **2.55** is a colorless oil and was isolated as a side-product (109 mg, 10%) in the conversion of **2.50** into **2.54**. R_f 0.17 (3:1 hexanes–EtOAc); $[\alpha]_D$ +31.0 (*c* 1.19, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 8.06–8.02 (m, 4 H, ArH), 7.60–7.56 (m, 2 H, ArH), 7.46–7.42 (m, 4 H, ArH), 7.40–7.38 (m, 2 H, ArH), 7.34–7.32 (m, 2 H, ArH), 7.10–7.07 (m, 2 H, ArH), 7.04–7.02 (m, 2 H, ArH), 5.92 (dd, $J_{3,4}$ = 7.9 Hz, $J_{2,3}$ = 2.8 Hz, 1 H, H-3), 4.54 (dd, $J_{5a,5b}$ = 11.8 Hz, $J_{4,5a}$ = 2.7 Hz, 1 H, H-5a), 4.51 (d, $J_{1,2}$ = 6.8 Hz, 1 H, H-1), 4.36 (dd, $J_{5a,5b}$ = 11.8 Hz, $J_{4,5b}$ = 6.0 Hz, 1 H, H-5b), 4.33 (ddd, $J_{3,4}$ = 7.9 Hz, $J_{4,5b}$ = 6.0 Hz, $J_{4,5a}$ = 2.7 Hz, 1 H, H-4), 4.10 (dd, $J_{1,2}$ = 6.8 Hz, $J_{2,3}$ = 2.8 Hz, 1 H, H-2), 2.32 (s, 3 H, ArC$\underline{H}_3$), 2.28 (s, 3 H, ArC$\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 167.1 (C=O), 165.5 (C=O), 138.8 (Ar), 138.6 (Ar), 134.0 (Ar), 133.8 (Ar), 133.62 (Ar), 133.58 (Ar), 133.4 (Ar), 130.2 (Ar), 130.1 (Ar), 130.0 (Ar), 129.9 (Ar), 129.8 (Ar), 128.54 (Ar), 128.51 (Ar), 128.48 (Ar), 72.9 (C-3), 70.1 (C-4), 66.2 (C-5), 64.0 (C-2), 62.3 (C-1), 21.21 (Ar$\underline{C}H_3$), 21.19 (Ar$\underline{C}H_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{33}H_{31}N_3NaO_5S_2$, 636.1597; found, 636.1591.

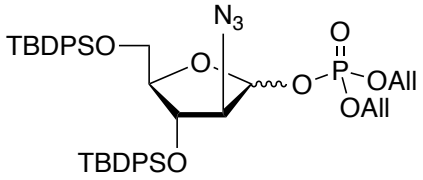


***p*-Tolyl 2-azido-2-deoxy-1-thio-β-D-arabinofuranoside (2.56).** Compound **2.54** (307 mg, 0.627 mmol) was treated with 200 mM NaOH in CH_3OH (10 mL). The reaction mixture was stirred overnight at rt before being neutralized with Amberlite® IR-120 (H^+) resin, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (1:1 hexanes–EtOAc) to give **2.56** (175 mg, 99%) as a colorless oil. R_f 0.21 (1:1 hexanes–EtOAc); $[\alpha]_D$ +98 (*c* 0.79, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.44–7.41 (m, 2 H, ArH), 7.17–7.14 (m, 2 H, ArH), 5.22 (d, $J_{1,2}$ = 5.8 Hz, 1 H, H-1), 4.13 (dd, $J_{3,4}$ = 7.6 Hz, $J_{2,3}$ = 6.5 Hz, 1 H, H-3), 3.99 (ddd, $J_{3,4}$ = 7.6 Hz, $J_{4,5b}$ = 3.4 Hz, $J_{4,5a}$ = 3.3 Hz, 1 H, H-4), 3.87 (dd, $J_{2,3}$ = 6.5 Hz, $J_{1,2}$ = 5.8 Hz, 1 H, H-2), 3.86 (dd, $J_{5a,5b}$ = 12.4 Hz, $J_{4,5a}$ = 3.3 Hz, 1 H, H-5a), 3.73 (dd, $J_{5a,5b}$ = 12.4 Hz, $J_{4,5b}$ = 3.4 Hz, 1 H, H-5b), 2.35 (s, 3 H, Ar$\underline{C}H_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 138.7 (Ar), 133.5 (Ar), 130.0 (Ar), 128.5 (Ar), 89.2 (C-1), 82.1 (C-4), 74.6 (C-3), 71.0 (C-2), 61.0 (C-5), 21.2 (Ar$\underline{C}H_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{15}N_3NaO_3S$, 304.0726; found, 304.0726.



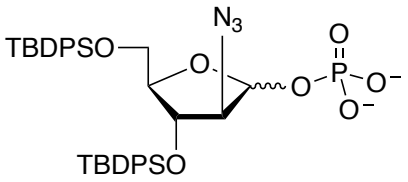
***p*-Tolyl 2-azido-3,5-di-*O*-*tert*-butyldiphenylsilyl-2-deoxy-1-thio-β-D-arabinofuranoside (2.10).** To a solution of **2.56** (164 mg, 0.582 mmol) in dry DMF (3 mL) was added imidazole (594 mg, 8.73 mmol), followed by TBDPSCl (750 μL, 2.91 mmol). The reaction mixture was stirred at 50 ºC for 22 h. After cooling to rt, excess TBDPSCl was quenched by the addition of ice-cold water and the solution was extracted with EtOAc. The organic layer was washed with H_2O and

brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (50:1 hexanes–EtOAc) to yield **2.10** (398 mg, 90%) as a colorless oil. R_f 0.58 (10:1 hexanes–EtOAc); $[\alpha]_D$ +68 (*c* 0.78, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.67–7.63 (m, 4 H, ArH), 7.57–7.52 (m, 4 H, ArH), 7.46–7.44 (m, 2 H, ArH), 7.43–7.39 (m, 4 H, ArH), 7.38–7.35 (m, 2 H, ArH), 7.33–7.29 (m, 6 H, ArH), 7.14–7.12 (m, 2 H, ArH), 5.24 (d, $J_{1,2}$ = 5.7 Hz, 1 H, H-1), 4.28–4.24 (m, 2 H, H-3 and H-4), 3.91 (dd, $J_{1,2}$ = 5.7 Hz, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 3.65 (dd, $J_{5a,5b}$ = 11.6 Hz, $J_{4,5a}$ = 2.3 Hz, 1 H, H-5a), 3.42 (dd, $J_{5a,5b}$ = 11.6 Hz, $J_{4,5b}$ = 3.9 Hz, 1 H, H-5b), 2.36 (s, 3 H, ArC<u>H</u>$_3$), 1.08 (s, 9 H, SiC(C<u>H</u>$_3$)$_3$), 0.94 (s, 9 H, SiC(C<u>H</u>$_3$)$_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 137.8 (Ar), 135.8 (Ar), 135.63 (Ar), 135.58 (Ar), 135.3 (Ar), 133.2 (Ar), 133.1 (Ar), 132.8 (Ar), 132.7 (Ar), 132.6 (Ar), 130.2 (Ar), 130.03 (Ar), 130.00 (Ar), 129.7 (Ar), 129.55 (Ar), 129.53 (Ar), 127.81 (Ar), 127.79 (Ar), 127.58 (Ar), 127.55 (Ar), 90.0 (C-1), 84.4 (C-4), 76.4 (C-3), 72.5 (C-2), 63.0 (C-5), 26.8 (SiC(<u>C</u>H$_3$)$_3$), 26.7 (SiC(<u>C</u>H$_3$)$_3$), 21.1 (Ar<u>C</u>H$_3$), 19.2 (Si<u>C</u>(CH$_3$)$_3$), 19.1 (Si<u>C</u>(CH$_3$)$_3$); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{44}H_{51}N_3NaO_3SSi_2$, 780.3082; found, 780.3086.

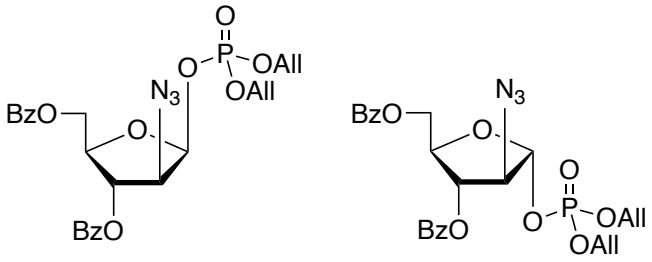


Diallyl (2-azido-3,5-di-*O-tert*-butyldiphenylsilyl-2-deoxy-α/β-D-arabinofuranosyl) phosphate (2.13). To a stirred solution of **2.10** (58.9 mg, 0.0777 mmol) in CH_2Cl_2 (1.6 mL) was added Br_2 (5.0 μL, 0.10 mmol). The reaction mixture was stirred at rt for 1 h before being concentrated. The crude glycosyl bromide was azeotropically dried with toluene and then used immediately. To a stirred solution of azeotropically dried diallyl phosphate[6] (27.7 mg, 0.155 mmol) in toluene (0.3 mL) were added powdered 4 Å molecular sieves (80 mg) and Et_3N (28 μL, 0.20

mmol). The mixture was cooled to 0 ºC, and a solution of the aforementioned glycosyl bromide in toluene (0.3 mL) was added slowly via a cannula. The transfer was completed by rinsing the flask twice with toluene (2 × 0.2 mL). The reaction mixture was warmed slowly to rt and stirred for 17 h before being filtered through a pad of Celite®, rinsed with EtOAc, and the filtrate was concentrated. The crude residue was purified by column chromatography (4:1 hexanes–EtOAc) to yield **2.13** (26.5 mg, 42% over two steps, β:α 3:1, inseparable) as a colorless oil. R_f 0.42 (3:1 hexanes–EtOAc); Data for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.58–7.50 (m, 8 H, ArH), 7.42–7.37 (m, 4 H, ArH), 7.34–7.25 (m, 8 H, ArH), 5.91 (dd, $J_{1,P}$ = 5.5 Hz, $J_{1,2}$ = 4.4 Hz, 1 H, H-1), 5.88–5.68 (m, 2 H, 2 × $OCH_2C\underline{H}=CH_2$), 5.29–5.07 (m, 4 H, 2 × $OCH_2CH=C\underline{H_2}$), 4.47–4.32 (m, 4 H, 2 × $OC\underline{H_2}CH=CH_2$), 4.22 (ddd, $J_{4,5b}$ = 7.1 Hz, $J_{3,4}$ = 6.2 Hz, $J_{4,5a}$ = 3.3 Hz, 1 H, H-4), 4.12 (dd, $J_{2,3}$ = 7.4 Hz, $J_{3,4}$ = 6.2 Hz, 1 H, H-3), 3.86 (ddd, $J_{2,3}$ = 7.4 Hz, $J_{1,2}$ = 4.4 Hz, $J_{2,P}$ = 1.8 Hz, 1 H, H-2), 3.49 (dd, $J_{5a,5b}$ = 11.4 Hz, $J_{4,5a}$ = 3.3 Hz, 1 H, H-5a), 3.43 (dd, $J_{5a,5b}$ = 11.4 Hz, $J_{4,5b}$ = 7.1 Hz, 1 H, H-5b), 1.01 (s, 9 H, $SiC(CH_3)_3$), 0.95 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 135.8 (Ar), 135.7 (Ar), 135.5 (Ar), 133.2 (Ar), 133.0 (Ar), 132.4 (Ar), 132.26 (d, $J_{C,P}$ = 7.4 Hz, $OCH_2\underline{C}H=CH_2$), 132.25 (d, $J_{C,P}$ = 7.4 Hz, $OCH_2\underline{C}H=CH_2$), 130.13 (Ar), 130.09 (Ar), 129.6 (Ar), 127.9 (Ar), 127.8 (Ar), 127.73 (Ar), 127.66 (Ar), 118.2 ($OCH_2CH=\underline{C}H_2$), 118.1 ($OCH_2CH=\underline{C}H_2$), 100.1 (d, $J_{C,P}$ = 4.6 Hz, C-1), 85.9 (C-4), 74.0 (C-3), 68.6 (d, $J_{C,P}$ = 6.7 Hz, C-2), 68.3 (d, $J_{C,P}$ = 5.3 Hz, $O\underline{C}H_2CH=CH_2$), 68.1 (d, $J_{C,P}$ = 5.3 Hz, $O\underline{C}H_2CH=CH_2$), 64.6 (C-5), 26.8 ($SiC(\underline{C}H_3)_3$), 26.7 ($SiC(\underline{C}H_3)_3$), 19.2 ($Si\underline{C}(CH_3)_3$), 19.1 ($Si\underline{C}(CH_3)_3$); ^{31}P NMR (202 MHz, $CDCl_3$, δ): –1.27; HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{43}H_{54}N_3NaO_7PSi_2$, 834.3130; found, 834.3123.

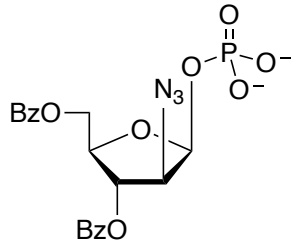


2-Azido-3,5-di-*O-tert*-butyldiphenylsilyl-2-deoxy-α/β-D-arabinofuranosyl phosphate (2.16). To a solution of **2.13** (70.2 mg, 0.0864 mmol) in a mixture of CH_2Cl_2 (0.6 mL) and CH_3OH (0.4 mL) was added $PdCl_2$ (7.7 mg, 0.043 mmol). The reaction mixture was stirred at rt for 7 h and was then filtered through a pad of Celite® and a syringe filter (0.45 μm) with 1:1 CH_2Cl_2–CH_3OH. The filtrate was concentrated to a crude residue that was purified by column chromatography (4:1 $CHCl_3$–CH_3OH, containing 2% v/v of Et_3N) to yield **2.16** (as the triethylammonium salt, 15.1 mg, 19%, β:α 0.3:1, inseparable) as a colorless oil. R_f 0.69 (3:1 EtOAc–CH_3OH); Data for the α-anomer: ^{1}H NMR (500 MHz, CD_3OD, δ): 7.67–7.62 (m, 4 H, ArH), 7.56–7.50 (m, 4 H, ArH), 7.42–7.38 (m, 4 H, ArH), 7.33–7.29 (m, 8 H, ArH), 5.62 (dd, $J_{1,P}$ = 6.4 Hz, $J_{1,2}$ = 1.3 Hz, 1 H, H-1), 4.34 (ddd, $J_{3,4}$ = 6.4 Hz, $J_{4,5b}$ = 4.4 Hz, $J_{4,5a}$ = 2.6 Hz, 1 H, H-4), 4.26 (dd, $J_{3,4}$ = 6.4 Hz, $J_{2,3}$ = 3.2 Hz, 1 H, H-3), 4.13 (dd, $J_{2,3}$ = 3.2 Hz, $J_{1,2}$ = 1.3 Hz, 1 H, H-2), 3.62 (dd, $J_{5a,5b}$ = 11.6 Hz, $J_{4,5a}$ = 2.6 Hz, 1 H, H-5a), 3.42 (dd, $J_{5a,5b}$ = 11.6 Hz, $J_{4,5b}$ = 4.4 Hz, 1 H, H-5b), 1.04 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (126 MHz, CD_3OD, δ): 135.7 (Ar), 135.6 (Ar), 135.4 (Ar), 135.3 (Ar), 133.1 (Ar), 132.9 (Ar), 132.7 (Ar), 132.4 (Ar), 129.9 (Ar), 129.8 (Ar), 129.39 (Ar), 129.37 (Ar), 127.59 (Ar), 127.57 (Ar), 127.4 (Ar), 127.3 (Ar), 102.2 (d, $J_{C,P}$ = 4.4 Hz, C-1), 85.5 (C-4), 77.1 (C-3), 74.6 (d, $J_{C,P}$ = 6.8 Hz, C-2), 62.4 (C-5), 26.0 ($SiC(\underline{C}H_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 18.62 ($Si\underline{C}(CH_3)_3$), 18.58 ($Si\underline{C}(CH_3)_3$); ^{31}P NMR (202 MHz, CD_3OD, δ): –0.30; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{37}H_{45}N_3O_7PSi_2$, 730.2539; found, 730.2548.



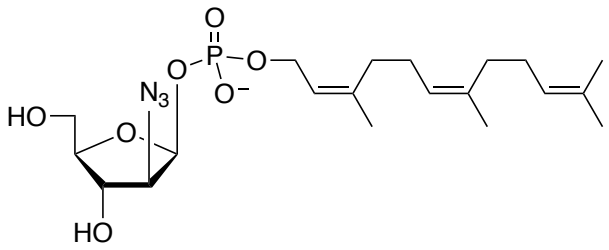
Diallyl (2-azido-3,5-di-*O*-benzoyl-2-deoxy-β-D-arabinofuranosyl) phosphate (2.74) and **Diallyl (2-azido-3,5-di-*O*-benzoyl-2-deoxy-α-D-arabinofuranosyl) phosphate (2.75).** To a stirred solution of **2.54** (108 mg, 0.220 mmol) in CH_2Cl_2 (3 mL) was added Br_2 (15 μL, 0.29 mmol). The reaction mixture was stirred at rt for 1.5 h before being concentrated, azeotropically dried with toluene, and used immediately. A solution of the crude glycosyl bromide in 1,2-dichloroethane (1.5 mL) containing powdered 4 Å molecular sieves (50 mg) was stirred for 20 min at rt. In a separate flask, a solution of diallyl phosphate[6] (51 mg, 0.29 mmol) in CH_2Cl_2 (1.5 mL) was stirred with powdered 4 Å molecular sieves (50 mg) for 20 min at rt and then Et_3N (52 μL, 0.37 mmol) was added. After stirring for another 3 min, this solution was added to the mixture containing the glycosyl bromide. The resulting reaction mixture was stirred at 60 ºC for 2 h before being cooled to rt, filtered through a pad of Celite®, and the filtrate was concentrated. The crude residue was purified by column chromatography (35% EtOAc–hexanes) to yield **2.74** (60.6 mg, 51% over two steps) and **2.75** (12.4 mg, 10% over two steps) as colorless oils. Data for **2.74**: R_f 0.30 (3:2 hexanes–EtOAc); $[\alpha]_D$ –57 (*c* 0.61, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.04–8.01 (m, 4 H, ArH), 7.63–7.59 (m, 1 H, ArH), 7.54–7.50 (m, 1 H, ArH), 7.48–7.44 (m, 2 H, ArH), 7.39–7.35 (m, 2 H, ArH), 6.05 (dd, $J_{1,P}$ = 5.5 Hz, $J_{1,2}$ = 4.4 Hz, 1 H, H-1), 5.99–5.90 (m, 1 H, $OCH_2C\underline{H}=CH_2$), 5.88–5.78 (m, 2 H, $OCH_2C\underline{H}=CH_2$ and H-3), 5.40–5.14 (m, 4 H, 2 × $OCH_2CH=C\underline{H}_2$), 4.75–4.70 (m, 1 H, H-5a), 4.65–4.48 (m, 6 H, 2 × $OC\underline{H}_2CH=CH_2$, H-5b and H-4), 4.22 (ddd, $J_{2,3}$ = 8.2 Hz, $J_{1,2}$ = 4.4 Hz, $J_{2,P}$ = 2.3 Hz, 1 H, H-2); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 166.0 (C=O), 165.6 (C=O), 133.9

(Ar), 133.2 (Ar), 132.1 (d, $J_{C,P}$ = 7.5 Hz, $OCH_2\underline{C}H=CH_2$), 132.0 (d, $J_{C,P}$ = 7.4 Hz, $OCH_2\underline{C}H=CH_2$), 129.9 (Ar), 129.8 (Ar), 129.5 (Ar), 128.7 (Ar), 128.5 (Ar), 128.4 (Ar), 118.6 ($OCH_2CH=\underline{C}H_2$), 118.5 ($OCH_2CH=\underline{C}H_2$), 99.6 (d, $J_{C,P}$ = 5.0 Hz, C-1), 80.5 (C-4), 74.6 (C-3), 68.6 (d, $J_{C,P}$ = 5.4 Hz, $O\underline{C}H_2CH=CH_2$), 68.4 (d, $J_{C,P}$ = 5.2 Hz, $O\underline{C}H_2CH=CH_2$), 66.0 (d, $J_{C,P}$ = 7.7 Hz, C-2), 64.9 (C-5); ^{31}P NMR (202 MHz, $CDCl_3$, δ): –0.89; HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{26}N_3NaO_9P$, 566.1299; found, 566.1292. Data for **2.75**: R_f 0.39 (3:2 hexanes–EtOAc); $[\alpha]_D$ +41.5 (*c* 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.09–8.03 (m, 4 H, ArH), 7.63–7.54 (m, 2 H, ArH), 7.48–7.41 (m, 4 H, ArH), 5.97–5.84 (m, 3 H, 2 × $OCH_2C\underline{H}=CH_2$ and H-1), 5.38–5.30 (m, 3 H, $OCH_2CH=C\underline{H}_2$ and H-3), 5.25–5.19 (m, 2 H, $OCH_2CH=C\underline{H}_2$), 4.81 (ddd, $J_{4,5b}$ = 5.1 Hz, $J_{3,4}$ = 4.3 Hz, $J_{4,5a}$ = 3.8 Hz, 1 H, H-4), 4.70 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5a}$ = 3.8 Hz, 1 H, H-5a), 4.63–4.54 (m, 5 H, 2 × $OC\underline{H}_2CH=CH_2$ and H-5b), 4.43 (dd, $J_{2,3}$ = 1.5 Hz, $J_{2,P}$ = 1.4 Hz, 1 H, H-2); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 166.1 (C=O), 165.9 (C=O), 133.9 (Ar), 133.3 (Ar), 132.1 (d, $J_{C,P}$ = 7.2 Hz, $OCH_2\underline{C}H=CH_2$), 132.0 (d, $J_{C,P}$ = 7.2 Hz, $OCH_2\underline{C}H=CH_2$), 129.9 (Ar), 129.8 (Ar), 129.5 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 118.7 (2 × $OCH_2CH=\underline{C}H_2$), 103.3 (d, $J_{C,P}$ = 5.2 Hz, C-1), 82.9 (C-4), 77.7 (C-3), 70.9 (d, $J_{C,P}$ = 9.5 Hz, C-2), 68.6 (d, $J_{C,P}$ = 5.4 Hz, $O\underline{C}H_2CH=CH_2$), 68.5 (d, $J_{C,P}$ = 5.4 Hz, $O\underline{C}H_2CH=CH_2$), 63.2 (C-5); ^{31}P NMR (202 MHz, $CDCl_3$, δ): –2.13; HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{26}N_3NaO_9P$, 566.1299; found, 566.1300.



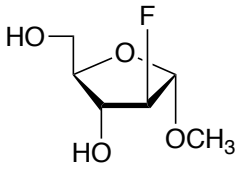
2-Azido-3,5-di-*O*-benzoyl-2-deoxy-β-D-arabinofuranosyl phosphate (2.76). To a solution of **2.74** (54.6 mg, 0.100 mmol) in a mixture of CH_2Cl_2 (0.6 mL) and CH_3OH (0.4 mL) was added

$PdCl_2$ (8.9 mg, 0.050 mmol). The reaction mixture was stirred at rt for 4 h and was then filtered through a pad of Celite® and a syringe filter (0.45 μm) with 1:1 CH_2Cl_2–CH_3OH before the filtrate was concentrated. The crude residue was dissolved in CH_3OH (5 mL) and was stirred with a palladium scavenger (QuadraPure® TU, 90 mg) for 1 h at rt. The solution was filtered and the filtrate was concentrated to give **2.76** (36.7 mg, 79%) as a colorless oil that was sufficiently pure for the use in the next step. R_f 0.26 (3:2 $CHCl_3$–CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ): 8.05–7.95 (m, 4 H, ArH), 7.65–7.61 (m, 1 H, ArH), 7.55–7.46 (m, 3 H, ArH), 7.37–7.32 (m, 2 H, ArH), 5.93 (dd, $J_{1,P}$ = 5.8 Hz, $J_{1,2}$ = 4.2 Hz, 1 H, H-1), 5.79 (dd, $J_{2,3}$ = 8.6 Hz, $J_{3,4}$ = 6.0 Hz, 1 H, H-3), 4.62–4.55 (m, 3 H, H-5a, H-5b and H-4), 4.37 (ddd, $J_{2,3}$ = 8.6 Hz, $J_{1,2}$ = 4.2 Hz, $J_{2,P}$ = 2.0 Hz, 1 H, H-2); ^{13}C NMR (126 MHz, CD_3OD, δ): 166.2 (C=O), 165.7 (C=O), 133.5 (Ar), 132.9 (Ar), 129.45 (Ar), 129.37 (Ar), 128.8 (Ar), 128.4 (Ar), 128.1 (Ar), 99.0 (d, $J_{C,P}$ = 5.0 Hz, C-1), 79.3 (C-4), 74.9 (C-3), 65.4 (d, $J_{C,P}$ = 7.6 Hz, C-2), 65.1 (C-5); ^{31}P NMR (202 MHz, CD_3OD, δ): –0.68; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{19}H_{17}N_3O_9P$, 462.0708; found, 462.0697.



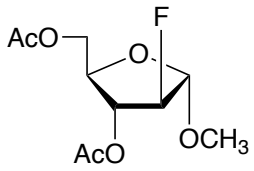
(*Z*,*Z*)-Farnesylphosphoryl-2-azido-2-deoxy-β-D-arabinofuranose (1.34). Compound **2.76** (36.7 mg, 0.0792 mmol) and (*Z*,*Z*)-farnesol[5] (70.5 mg, 0.317 mmol) were azeotropically dried with toluene. The mixture was dissolved in pyridine (1.2 mL) and Cl_3CCN (79 μL, 0.79 mmol) was added. The resulting solution was stirred for 14 h at 55 ºC before being cooled to rt and concentrated. The crude phosphodiester was dissolved in a solution of 5:2:1 CH_3OH–H_2O–Et_3N (2 mL) and stirred for 8 days before being concentrated to a residue that was purified by column

chromatography (gradient of 50%→70% CH_3OH–EtOAc). Residual colored impurities were removed by the addition of activated charcoal to the product in CH_3OH, followed by the filtration through a syringe filter (0.45 μm). The filtrate was concentrated to give **1.34** (16.9 mg, 46% over two steps) as a colorless oil. R_f 0.50 (3:2 EtOAc–CH_3OH); $[\alpha]_D$ –10.2 (*c* 1.28, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ): 5.60 (dd, $J_{1,P}$ = 4.6 Hz, $J_{1,2}$ = 4.4 Hz, 1 H, H-1), 5.43–5.38 (m, 1 H, OCH_2CH=C), 5.14–5.09 (m, 2 H, 2 × CH_2CH=C), 4.45–4.41 (m, 2 H, OCH_2CH=C), 4.38 (dd, $J_{2,3}$ = 8.9 Hz, $J_{3,4}$ = 7.1 Hz, 1 H, H-3), 3.87–3.83 (m, 1 H, H-4), 3.78 (dd, $J_{5a,5b}$ = 12.4 Hz, $J_{4,5a}$ = 2.9 Hz, 1 H, H-5a), 3.67–3.62 (m, 2 H, H-2 and H-5b), 2.13–2.00 (m, 8 H, 4 × allylic CH_2), 1.73 (s, 3 H, CH_3), 1.67 (s, 6 H, 2 × CH_3), 1.61 (s, 3 H, CH_3); ^{13}C NMR (126 MHz, CD_3OD, δ): 139.3 (CH=C), 135.2 (CH=C), 131.0 (CH=C), 124.3 (CH=C), 124.0 (CH=C), 121.9 (d, $J_{C,P}$ = 8.3 Hz, CH=C), 97.6 (d, $J_{C,P}$ = 5.7 Hz, C-1), 84.1 (C-4), 71.0 (C-3), 67.3 (d, $J_{C,P}$ = 8.3 Hz, C-2), 62.1 (C-5), 62.0 (d, $J_{C,P}$ = 5.7 Hz, OCH_2CH=C), 31.9 (allylic CH_2), 31.5 (allylic CH_2), 26.3 (allylic CH_2), 26.2 (allylic CH_2), 24.5 (CH_3), 22.32 (CH_3), 22.27 (CH_3), 16.3 (CH_3); ^{31}P NMR (202 MHz, CD_3OD, δ): –0.04; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{20}H_{33}N_3O_7P$, 458.2062; found, 458.2065.



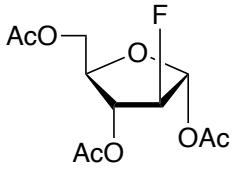
Methyl 2-deoxy-2-fluoro-α-D-arabinofuranoside (2.61). To a solution of **2.60**[13] (5.06 g, 14.6 mmol) in CH_3OH (100 mL) was added 50% palladium hydroxide on carbon (1.10 g, 3.92 mmol). The reaction vessel was equipped with a hydrogen-filled balloon. The reaction mixture was stirred overnight at rt before being filtered through a pad of Celite® and the filtrate was concentrated to give **2.61** (2.33 g, 96%) as a colorless oil. R_f 0.18 (1:1 hexanes–EtOAc); $[\alpha]_D$ +125 (*c* 1.54, $CHCl_3$);

^{1}H NMR (700 MHz, CD_3OD, δ): 4.97 (dd, $J_{1,F}$ = 12.0 Hz, $J_{1,2}$ = 0.7 Hz, 1 H, H-1), 4.73 (ddd, $J_{2,F}$ = 51.9 Hz, $J_{2,3}$ = 2.5 Hz, $J_{1,2}$ = 0.7 Hz, 1 H, H-2), 4.07 (ddd, $J_{3,F}$ = 26.0 Hz, $J_{3,4}$ = 6.6 Hz, $J_{2,3}$ = 2.5 Hz, 1 H, H-3), 3.91 (ddd, $J_{3,4}$ = 6.6 Hz, $J_{4,5b}$ = 5.4 Hz, $J_{4,5a}$ = 3.3 Hz, 1 H, H-4), 3.75 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5a}$ = 3.3 Hz, 1 H, H-5a), 3.64 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5b}$ = 5.4 Hz, 1 H, H-5b), 3.37 (s, 3 H, OCH_3); ^{13}C NMR (176 MHz, CD_3OD, δ): 106.1 (d, $J_{C,F}$ = 36.3 Hz, C-1), 101.9 (d, $J_{C,F}$ = 180.5 Hz, C-2), 83.8 (d, $J_{C,F}$ = 4.8 Hz, C-4), 75.3 (d, $J_{C,F}$ = 25.7 Hz, C-3), 61.1 (C-5), 53.5 (OCH_3); ^{19}F NMR (469 MHz, CD_3OD, δ): –192.45 (ddd, $J_{2,F}$ = 51.9 Hz, $J_{3,F}$ = 26.0 Hz, $J_{1,F}$ = 12.0 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_6H_{11}FNaO_4$, 189.0534; found, 189.0536.



Methyl 3,5-di-*O*-acetyl-2-deoxy-2-fluoro-α-D-arabinofuranoside (2.62). To a solution of **2.61** (2.33 g, 14.0 mmol) in dry pyridine (50 mL) at 0 ºC was added Ac_2O (13.1 mL, 140 mmol) dropwise. The reaction mixture was stirred at rt overnight. Excess Ac_2O was quenched by the addition of CH_3OH at 0 ºC, and the solution was diluted with EtOAc. The organic layer was washed with 1 N $HCl_{(aq)}$, H_2O, saturated $NaHCO_{3(aq)}$ and brine before being dried with $MgSO_4$. The solution was filtered and the filtrate was concentrated to give a crude residue that was purified by column chromatography (30% EtOAc–hexanes) to yield **2.62** (3.13 g, 89%) as a colorless oil. R_f 0.35 (2:1 hexanes–EtOAc); $[\alpha]_D$ +81.8 (*c* 1.54, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 5.10 (d, $J_{1,F}$ = 10.7 Hz, 1 H, H-1), 5.08 (ddd, $J_{3,F}$ = 23.4 Hz, $J_{3,4}$ = 5.0 Hz, $J_{2,3}$ = 0.7 Hz, 1 H, H-3), 4.90 (dd, $J_{2,F}$ = 49.4 Hz, $J_{2,3}$ = 0.7 Hz, 1 H, H-2), 4.47 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 3.2 Hz, 1 H, H-5a), 4.25 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5b}$ = 5.3 Hz, 1 H, H-5b), 4.21 (ddd, $J_{4,5b}$ = 5.3 Hz, $J_{3,4}$ = 5.0 Hz, $J_{4,5a}$ = 3.2 Hz, 1 H, H-4), 3.41 (s, 3 H, OCH_3), 2.12 (s, 3 H, $C(O)CH_3$), 2.10 (s, 3 H, $C(O)CH_3$); ^{13}C NMR

(176 MHz, $CDCl_3$, δ): 170.7 (C=O), 170.1 (C=O), 106.2 (d, $J_{C,F}$ = 35.4 Hz, C-1), 98.1 (d, $J_{C,F}$ = 181.5 Hz, C-2), 80.6 (d, $J_{C,F}$ = 1.9 Hz, C-4), 76.9 (d, $J_{C,F}$ = 30.4 Hz, C-3), 63.1 (C-5), 54.9 (OCH_3), 20.8 (C(O)$\underline{C}H_3$), 20.7 (C(O)$\underline{C}H_3$); ^{19}F NMR (469 MHz, $CDCl_3$, δ): –190.69 (ddd, $J_{2,F}$ = 49.4 Hz, $J_{3,F}$ = 23.4 Hz, $J_{1,F}$ = 10.7 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{10}H_{15}FNaO_6$, 273.0745; found, 273.0745.

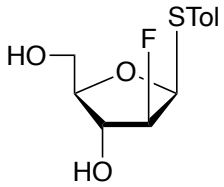


1,3,5-Tri-*O*-acetyl-2-deoxy-2-fluoro-α/β-D-arabinofuranose (2.63). To a solution of **2.62** (3.13 g, 12.5 mmol) in a mixture of AcOH (10 mL) and Ac_2O (10 mL) was added dropwise concentrated H_2SO_4 (1 mL) in AcOH (10 mL). The reaction mixture was stirred at rt for 10 h before being diluted with EtOAc. The resulting solution was washed with saturated $NaHCO_{3(aq)}$ and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (3:2 hexanes–EtOAc) to give **2.63** (3.48 g, quantitative, α:β 15:1, inseparable) as a colorless oil. R_f 0.23 (2:1 hexanes–EtOAc); Data for the α-anomer: ^1H NMR (700 MHz, $CDCl_3$, δ): 6.35 (d, $J_{1,F}$ = 10.5 Hz, 1 H, H-1), 5.16 (ddd, $J_{3,F}$ = 21.4 Hz, $J_{3,4}$ = 4.3 Hz, $J_{2,3}$ = 0.9 Hz, 1 H, H-3), 5.02 (dd, $J_{2,F}$ = 48.8 Hz, $J_{2,3}$ = 0.9 Hz, 1 H, H-2), 4.42 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-5a), 4.38 (ddd, $J_{4,5b}$ = 5.3 Hz, $J_{3,4}$ = 4.3 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-4), 4.26 (dd, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5b}$ = 5.3 Hz, 1 H, H-5b), 2.14 (s, 3 H, C(O)CH_3), 2.12 (s, 3 H, C(O)CH_3), 2.09 (s, 3 H, C(O)CH_3); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 170.6 (C=O), 169.8 (C=O), 169.1 (C=O), 99.0 (d, $J_{C,F}$ = 37.5 Hz, C-1), 97.5 (d, $J_{C,F}$ = 184.3 Hz, C-2), 83.0 (C-4), 76.4 (d, $J_{C,F}$ = 30.6 Hz, C-3), 62.9 (C-5), 20.9 (C(O)$\underline{C}H_3$), 20.7 (C(O)$\underline{C}H_3$), 20.6 (C(O)$\underline{C}H_3$); ^{19}F NMR (469 MHz, $CDCl_3$, δ): –190.29

(ddd, $J_{2,F}$ = 48.8 Hz, $J_{3,F}$ = 21.4 Hz, $J_{1,F}$ = 10.5 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{11}H_{15}FNaO_7$, 301.0694; found, 301.0691.

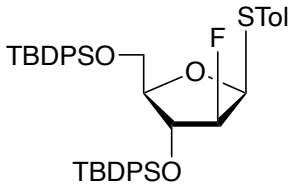
***p*-Tolyl 3,5-di-*O*-acetyl-2-deoxy-2-fluoro-1-thio-β-D-arabinofuranoside (2.66)** and ***p*-Tolyl 3,5-di-*O*-acetyl-2-deoxy-2-fluoro-1-thio-α-D-arabinofuranoside (2.67).** A solution of **2.63** (3.48 g, 12.5 mmol) in CH_2Cl_2 (30 mL) was treated with 33% HBr in AcOH (4.32 mL). The reaction mixture was stirred for 20 h at rt before being concentrated. The residue was dissolved in CH_2Cl_2, washed with H_2O and saturated $NaHCO_{3(aq)}$, dried with $MgSO_4$, filtered, and the filtrate was concentrated to give 3,5-di-*O*-acetyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**2.65**), which was not further purified. A solution of crude **2.65** and *p*-thiocresol (2.33 g, 18.8 mmol) in CH_2Cl_2 (125 mL) was treated with *n*-Bu_4NBr (806 mg, 2.50 mmol) in H_2O (17 mL), and then a solution of KOH (1.40 g, 25.0 mmol) in H_2O (17 mL) was added dropwise. The reaction mixture was stirred for 20 h at rt before being diluted with CH_2Cl_2. The organic layer was separated, washed with H_2O and brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (4:1 hexanes–EtOAc) to yield **2.66** (2.09 g, 49% over two steps) and **2.67** (641 mg, 15% over two steps) as colorless oils. Data for **2.66**: R_f 0.45 (2:1 hexanes–EtOAc); $[\alpha]_D$ –106 (*c* 1.25, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.46–7.43 (m, 2 H, ArH), 7.15–7.13 (m, 2 H, ArH), 5.39 (dd, $J_{1,F}$ = 27.4 Hz, $J_{1,2}$ = 3.3 Hz, 1 H, H-1), 5.27 (ddd, $J_{3,F}$ = 15.8 Hz, $J_{3,4}$ = 2.6 Hz, $J_{2,3}$ = 1.3 Hz, 1 H, H-3), 5.11 (ddd, $J_{2,F}$ = 50.0 Hz, $J_{1,2}$ = 3.3 Hz, $J_{2,3}$ = 1.3 Hz, 1 H, H-2), 4.35–4.33 (m, 2 H, H-5a and H-5b), 4.14 (ddd, $J_{4,5a}$ = 5.8 Hz, $J_{4,5b}$ = 5.8 Hz, $J_{3,4}$ = 2.6 Hz, 1 H, H-4), 2.34 (s, 3 H, ArC$\underline{H}_3$), 2.10 (s, 3 H, C(O)CH_3), 2.08 (s, 3 H, C(O)CH_3);

^{13}C NMR (176 MHz, $CDCl_3$, δ): 170.7 (C=O), 169.4 (C=O), 138.1 (Ar), 132.3 (Ar), 130.0 (Ar), 129.9 (Ar), 95.5 (d, $J_{C,F}$ = 188.6 Hz, C-2), 89.9 (d, $J_{C,F}$ = 18.7 Hz, C-1), 81.8 (C-4), 77.2 (d, $J_{C,F}$ = 30.5 Hz, C-3), 63.3 (d, $J_{C,F}$ = 2.4 Hz, C-5), 21.1 (Ar$\underline{C}H_3$), 20.8 (C(O)$\underline{C}H_3$), 20.7 (C(O)$\underline{C}H_3$); ^{19}F NMR (376 MHz, $CDCl_3$, δ): –193.12 (ddd, $J_{2,F}$ = 50.0 Hz, $J_{1,F}$ = 27.4 Hz, $J_{3,F}$ = 15.8 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{19}FNaO_5S$, 365.0829; found, 365.0835. Data for **2.67**: R_f 0.58 (2:1 hexanes–EtOAc); $[\alpha]_D$ +204 (*c* 1.46, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$, δ): 7.41–7.38 (m, 2 H, ArH), 7.16–7.13 (m, 2 H, ArH), 5.65 (dd, $J_{1,F}$ = 19.1 Hz, $J_{1,2}$ = 1.3 Hz, 1 H, H-1), 5.17 (ddd, $J_{3,F}$ = 21.0 Hz, $J_{2,3}$ = 1.3 Hz, $J_{3,4}$ = 1.0 Hz, 1 H, H-3), 5.08 (ddd, $J_{2,F}$ = 50.9 Hz, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 1.3 Hz, 1 H, H-2), 4.47 (ddd, $J_{4,5b}$ = 5.2 Hz, $J_{4,5a}$ = 3.7 Hz, $J_{3,4}$ = 1.0 Hz, 1 H, H-4), 4.40 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-5a), 4.31 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5b}$ = 5.2 Hz, 1 H, H-5b), 2.34 (s, 3 H, Ar$C\underline{H}_3$), 2.15 (s, 3 H, C(O)CH_3), 2.09 (s, 3 H, C(O)CH_3); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 170.6 (C=O), 169.9 (C=O), 138.4 (Ar), 132.8 (Ar), 130.0 (Ar), 129.1 (Ar), 99.0 (d, $J_{C,F}$ = 191.5 Hz, C-2), 91.0 (d, $J_{C,F}$ = 27.7 Hz, C-1), 80.6 (d, $J_{C,F}$ = 2.0 Hz, C-4), 77.2 (d, $J_{C,F}$ = 29.8 Hz, C-3), 62.7 (C-5), 21.1 (Ar$\underline{C}H_3$), 20.74 (C(O)$\underline{C}H_3$), 20.70 (C(O)$\underline{C}H_3$); ^{19}F NMR (376 MHz, $CDCl_3$, δ): –178.13 (ddd, $J_{2,F}$ = 50.9 Hz, $J_{3,F}$ = 21.0 Hz, $J_{1,F}$ = 19.1 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{19}FNaO_5S$, 365.0829; found, 365.0825.



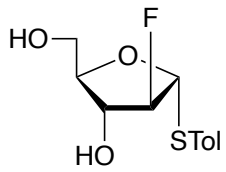
***p*-Tolyl 2-deoxy-2-fluoro-1-thio-β-D-arabinofuranoside (2.68).** To a solution of **2.66** (978 mg, 2.86 mmol) in CH_3OH (14 mL) was added $NaOCH_3$ (77.2 mg, 1.43 mmol). The reaction mixture was stirred for 1 h at rt before being neutralized with Amberlite® IR-120 (H^+) resin, filtered, and the filtrate was concentrated to give **2.68** (722 mg, 98%) as a white solid. R_f 0.28 (1:2 hexanes–

EtOAc); $[\alpha]_D$ –68.9 (*c* 1.06, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$, δ): 7.44–7.41 (m, 2 H, ArH), 7.15–7.13 (m, 2 H, ArH), 5.48 (dd, $J_{1,F}$ = 22.4 Hz, $J_{1,2}$ = 4.0 Hz, 1 H, H-1), 5.08 (ddd, $J_{2,F}$ = 52.1 Hz, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 2.7 Hz, 1 H, H-2), 4.49 (ddd, $J_{3,F}$ = 18.1 Hz, $J_{3,4}$ = 4.4 Hz, $J_{2,3}$ = 2.7 Hz, 1 H, H-3), 3.94 (ddd, $J_{4,5b}$ = 5.0 Hz, $J_{3,4}$ = 4.4 Hz, $J_{4,5a}$ = 4.0 Hz, 1 H, H-4), 3.84 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5a}$ = 4.0 Hz, 1 H, H-5a), 3.79 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5b}$ = 5.0 Hz, 1 H, H-5b), 2.34 (s, 3 H, Ar$C\underline{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 138.0 (Ar), 132.0 (Ar), 130.0 (Ar), 97.9 (d, $J_{C,F}$ = 189.9 Hz, C-2), 89.0 (d, $J_{C,F}$ = 18.8 Hz, C-1), 85.2 (d, $J_{C,F}$ = 3.7 Hz, C-4), 75.3 (d, $J_{C,F}$ = 26.2 Hz, C-3), 62.0 (C-5), 21.1 (Ar$\underline{C}H_3$); ^{19}F NMR (376 MHz, $CDCl_3$, δ): –192.29 (ddd, $J_{2,F}$ = 52.1 Hz, $J_{1,F}$ = 22.4 Hz, $J_{3,F}$ = 18.1 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{15}FNaO_3S$, 281.0618; found, 281.0619.



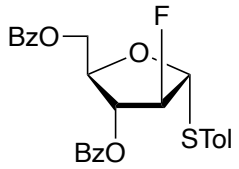
***p*-Tolyl 3,5-di-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-fluoro-1-thio-β-D-arabinofuranoside (2.1).** To a solution of **2.68** (711 mg, 2.75 mmol) in dry DMF (14 mL) was added imidazole (5.62 g, 82.5 mmol), followed by TBDPSCl (7.06 mL, 27.5 mmol). The reaction mixture was stirred at 70 ºC for 12 h. After cooling to rt, excess TBDPSCl was quenched by the addition of ice-cold water and the solution was extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (50:1 hexanes–EtOAc) to yield **2.1** (1.96 g, 97%) as a white solid. R_f 0.51 (10:1 hexanes–EtOAc); $[\alpha]_D$ –13.2 (*c* 1.82, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$, δ): 7.63–7.58 (m, 8 H, ArH), 7.46–7.30 (m, 14 H, ArH), 7.14–7.11 (m, 2 H, ArH), 5.51 (dd, $J_{1,F}$ = 29.0 Hz, $J_{1,2}$ = 3.1 Hz, 1 H, H-1), 4.89 (ddd, $J_{2,F}$ = 51.0 Hz, $J_{1,2}$ = 3.1 Hz, $J_{2,3}$ = 1.0 Hz, 1 H, H-2), 4.48 (ddd, $J_{3,F}$ = 14.8

Hz, $J_{3,4}$ = 2.1 Hz, $J_{2,3}$ = 1.0 Hz, 1 H, H-3), 4.18 (ddd, $J_{4,5b}$ = 6.3 Hz, $J_{4,5a}$ = 6.0 Hz, $J_{3,4}$ = 2.1 Hz, 1 H, H-4), 3.61 (dd, $J_{5a,5b}$ = 10.9 Hz, $J_{4,5a}$ = 6.0 Hz, 1 H, H-5a), 3.50 (dd, $J_{5a,5b}$ = 10.9 Hz, $J_{4,5b}$ = 6.3 Hz, 1 H, H-5b), 2.34 (s, 3 H, ArC$\underline{H}_3$), 1.07 (s, 9 H, SiC$(CH_3)_3$), 0.97 (s, 9 H, SiC$(CH_3)_3$); ^{13}C NMR (176 MHz, $CDCl_3$, δ): 137.5 (Ar), 135.73 (Ar), 135.68 (Ar), 135.66 (Ar), 135.64 (Ar), 133.3 (Ar), 132.8 (Ar), 132.6 (Ar), 131.9 (Ar), 130.2 (Ar), 130.1 (Ar), 129.8 (Ar), 129.6 (Ar), 129.5 (Ar), 128.0 (Ar), 127.9 (Ar), 127.60 (Ar), 127.57 (Ar), 98.1 (d, $J_{C,F}$ = 189.0 Hz, C-2), 89.3 (d, $J_{C,F}$ = 18.3 Hz, C-1), 87.6 (C-4), 77.0 (d, $J_{C,F}$ = 27.6 Hz, C-3), 63.3 (d, $J_{C,F}$ = 3.6 Hz, C-5), 26.9 (SiC($\underline{C}H_3)_3$), 26.7 (SiC($\underline{C}H_3)_3$), 21.1 (Ar$\underline{C}H_3$), 19.2 (Si$\underline{C}(CH_3)_3$), 19.1 (Si$\underline{C}(CH_3)_3$); ^{19}F NMR (469 MHz, $CDCl_3$, δ): –190.37 (ddd, $J_{2,F}$ = 51.0 Hz, $J_{1,F}$ = 29.0 Hz, $J_{3,F}$ = 14.8 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{44}H_{51}FNaO_3SSi_2$, 757.2974; found, 757.2966.



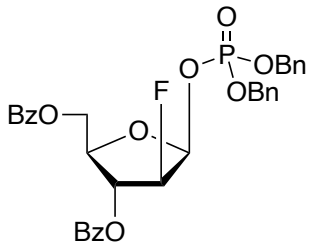
***p*-Tolyl 2-deoxy-2-fluoro-1-thio-α-D-arabinofuranoside (2.72).** To a solution of **2.67** (628 mg, 1.83 mmol) in CH_3OH (9 mL) was added $NaOCH_3$ (49.5 mg, 0.917 mmol). The reaction mixture was stirred for 30 min at rt before being neutralized with Amberlite® IR-120 (H^+) resin, filtered, and the filtrate was concentrated to give **2.72** (470 mg, 99%) as a white solid. R_f 0.40 (1:1 hexanes–EtOAc); $[\alpha]_D$ +262 (*c* 1.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.42–7.38 (m, 2 H, ArH), 7.17–7.13 (m, 2 H, ArH), 5.58 (dd, $J_{1,F}$ = 18.6 Hz, $J_{1,2}$ = 1.0 Hz, 1 H, H-1), 4.97 (ddd, $J_{2,F}$ = 52.4 Hz, $J_{2,3}$ = 2.3 Hz, $J_{1,2}$ = 1.0 Hz, 1 H, H-2), 4.36 (ddd, $J_{3,F}$ = 22.2 Hz, $J_{3,4}$ = 6.1 Hz, $J_{2,3}$ = 2.3 Hz, 1 H, H-3), 4.23 (ddd, $J_{3,4}$ = 6.1 Hz, $J_{4,5b}$ = 4.2 Hz, $J_{4,5a}$ = 3.5 Hz, 1 H, H-4), 3.88 (dd, $J_{5a,5b}$ = 12.3 Hz, $J_{4,5a}$ = 3.5 Hz, 1 H, H-5a), 3.77 (dd, $J_{5a,5b}$ = 12.3 Hz, $J_{4,5b}$ = 4.2 Hz, 1 H, H-5b), 2.34 (s, 3 H, ArC$\underline{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 138.5 (Ar), 133.1 (Ar), 130.0 (Ar), 128.7 (Ar), 101.2 (d,

$J_{C,F}$ = 191.2 Hz, C-2), 90.0 (d, $J_{C,F}$ = 28.2 Hz, C-1), 84.0 (d, $J_{C,F}$ = 3.9 Hz, C-4), 75.7 (d, $J_{C,F}$ = 25.7 Hz, C-3), 61.4 (C-5), 21.2 (Ar<u>C</u>H$_3$); ^{19}F NMR (470 MHz, $CDCl_3$, δ): –179.77 (ddd, $J_{2,F}$ = 52.4 Hz, $J_{3,F}$ = 22.2 Hz, $J_{1,F}$ = 18.6 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{15}FNaO_3S$, 281.0618; found, 281.0612.

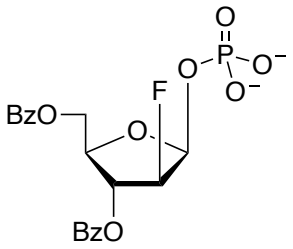


***p*-Tolyl 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-1-thio-α-D-arabinofuranoside (2.73).** To a solution of **2.72** (443 mg, 1.71 mmol) in dry pyridine (6 mL) at 0 ºC was added BzCl (1.99 mL, 17.1 mmol) dropwise. The reaction mixture was stirred at rt overnight. Excess BzCl was quenched by the addition of CH_3OH at 0 ºC, and the solution was diluted with EtOAc. The organic layer was washed with 1 N $HCl_{(aq)}$, H_2O, saturated $NaHCO_{3(aq)}$ and brine before being dried with $MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (9:1 hexanes–EtOAc) to yield **2.73** (690 mg, 86%) as a colorless oil. R_f 0.55 (5:1 hexanes–EtOAc); $[\alpha]_D$ +156 (*c* 1.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.13–8.04 (m, 4 H, ArH), 7.65–7.53 (m, 2 H, ArH), 7.52–7.40 (m, 6 H, ArH), 7.15–7.12 (m, 2 H, ArH), 5.79 (dd, $J_{1,F}$ = 18.9 Hz, $J_{1,2}$ = 1.0 Hz, 1 H, H-1), 5.58 (ddd, $J_{3,F}$ = 20.3 Hz, $J_{3,4}$ = 4.4 Hz, $J_{2,3}$ = 1.1 Hz, 1 H, H-3), 5.31 (ddd, $J_{2,F}$ = 50.5 Hz, $J_{2,3}$ = 1.1 Hz, $J_{1,2}$ = 1.0 Hz, 1 H, H-2), 4.78 (ddd, $J_{4,5b}$ = 4.7 Hz, $J_{3,4}$ = 4.4 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-4), 4.72 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5a}$ = 3.7 Hz, 1 H, H-5a), 4.68 (dd, $J_{5a,5b}$ = 12.0 Hz, $J_{4,5b}$ = 4.7 Hz, 1 H, H-5b), 2.33 (s, 3 H, ArC<u>H</u>$_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 166.2 (C=O), 165.5 (C=O), 138.4 (Ar), 133.8 (Ar), 133.2 (Ar), 132.9 (Ar), 130.0 (Ar), 129.8 (Ar), 129.7 (Ar), 129.1 (Ar), 128.8 (Ar), 128.6 (Ar), 128.4 (Ar), 99.0 (d, $J_{C,F}$ = 191.5 Hz, C-2), 91.4 (d, $J_{C,F}$ = 27.3 Hz, C-1), 81.3 (C-4), 77.8 (d, $J_{C,F}$ = 30.5 Hz, C-3), 63.4 (C-5), 21.2 (Ar<u>C</u>H$_3$); ^{19}F NMR

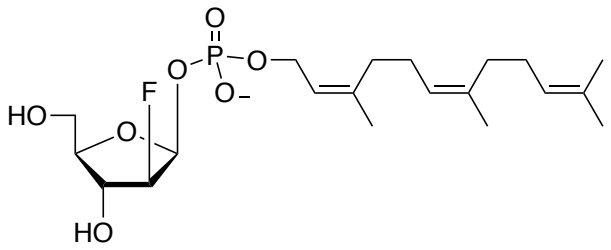
(470 MHz, $CDCl_3$, δ): –177.35 (ddd, $J_{2,F}$ = 50.5 Hz, $J_{3,F}$ = 20.3 Hz, $J_{1,F}$ = 18.9 Hz); HRMS–ESI–TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{23}FNaO_5S$, 489.1142; found, 489.1138.



Dibenzyl (3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl) phosphate (2.70).[24] To a stirred solution of **2.73** (129 mg, 0.275 mmol) in CH_2Cl_2 (3 mL) was added Br_2 (18 μL, 0.35 mmol). The reaction mixture was stirred at rt for 1.5 h before being concentrated, azeotropically dried with toluene, and used immediately. A solution of the crude glycosyl bromide in 1,2-dichloroethane (1.5 mL) containing powdered 4 Å molecular sieves (50 mg) was stirred for 20 min at rt. In a separate flask, a solution of dibenzyl phosphate (100 mg, 0.358 mmol) in CH_2Cl_2 (1.5 mL) was stirred with powdered 4 Å molecular sieves (50 mg) for 20 min at rt and then Et_3N (65 μL, 0.47 mmol) was added. After stirring for another 3 min, this solution was added to the mixture containing the glycosyl bromide. The resulting reaction mixture was stirred at 60 ºC for 2 h before being cooled to rt, filtered through a pad of Celite®, and the filtrate was concentrated. The crude residue was purified by column chromatography (35% EtOAc–hexanes) to yield **2.70** (104 mg, 61% over two steps) as a colorless oil. The spectroscopic data for **2.70** were identical to those reported.[24]

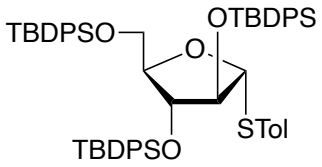


3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl phosphate (2.71).[24] To a solution of **2.70** (103 mg, 0.165 mmol) in 10:1 EtOAc–Et_3N (6.6 mL) was added 5% palladium on carbon (352 mg, 0.165 mmol). The reaction vessel was purged with argon and then equipped with a hydrogen-filled balloon. The reaction mixture was stirred at rt for 12 h before being filtered through a pad of Celite® with 3:7 EtOAc–CH_3OH. The filtrate was concentrated to yield **2.71** (as the triethylammonium salt, 82.8 mg, 78%) as a colorless oil. The spectroscopic data for **2.71** were identical to those reported.[24]



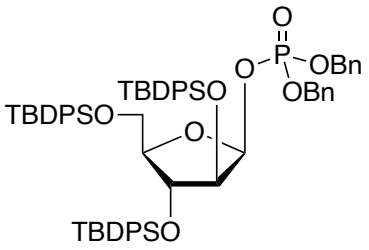
(*Z*,*Z*)-Farnesylphosphoryl-2-deoxy-2-fluoro-β-D-arabinofuranose (1.31). Compound **2.71** (82.8 mg, 0.129 mmol) and (*Z*,*Z*)-farnesol[5] (115 mg, 0.515 mmol) were azeotropically dried with toluene. The mixture was dissolved in pyridine (1.7 mL) and Cl_3CCN (129 μL, 1.29 mmol) was added. The resulting solution was stirred for 14 h at 55 ºC before being cooled to rt and concentrated. The crude phosphodiester was dissolved in a solution of 5:2:1 CH_3OH–H_2O–Et_3N (2 mL) and stirred for 8 days before being concentrated to a residue that was purified by column chromatography (gradient of 30%→50%→70% CH_3OH–EtOAc). Residual colored impurities were removed by the addition of activated charcoal to the product in CH_3OH, followed by the filtration through a syringe filter (0.45 μm). The filtrate was concentrated to give **1.31** (52.3 mg,

93% over two steps) as a colorless oil. R_f 0.53 (3:2 EtOAc–CH_3OH); $[\alpha]_D$ –14 (*c* 0.58, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ): 5.64 (dd, $J_{1,P}$ = 5.2 Hz, $J_{1,2}$ = 4.3 Hz, 1 H, H-1), 5.41–5.37 (m, 1 H, OCH_2CH=C), 5.14–5.09 (m, 2 H, 2 × CH_2CH=C), 4.83 (dddd, $J_{2,F}$ = 53.7 Hz, $J_{2,3}$ = 7.2 Hz, $J_{1,2}$ = 4.3 Hz, $J_{2,P}$ = 1.9 Hz, 1 H, H-2), 4.42–4.37 (m, 2 H, OCH_2CH=C), 4.35 (ddd, $J_{3,F}$ = 17.5 Hz, $J_{2,3}$ = 7.2 Hz, $J_{3,4}$ = 6.8 Hz, 1 H, H-3), 3.84 (ddd, $J_{3,4}$ = 6.8 Hz, $J_{4,5b}$ = 6.5 Hz, $J_{4,5a}$ = 3.3 Hz, 1 H, H-4), 3.77 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5a}$ = 3.3 Hz, 1 H, H-5a), 3.66 (dd, $J_{5a,5b}$ = 12.1 Hz, $J_{4,5b}$ = 6.5 Hz, 1 H, H-5b), 2.12–1.99 (m, 8 H, 4 × allylic CH_2), 1.73 (s, 3 H, CH_3), 1.67 (s, 6 H, 2 × CH_3), 1.60 (s, 3 H, CH_3); ^{13}C NMR (126 MHz, CD_3OD, δ): 139.6 (CH=C), 135.2 (CH=C), 131.0 (CH=C), 124.3 (CH=C), 124.0 (CH=C), 121.7 (d, $J_{C,P}$ = 8.4 Hz, CH=C), 95.3 (dd, $J_{C,F}$ = 18.0 Hz, $J_{C,P}$ = 5.4 Hz, C-1), 95.0 (dd, $J_{C,F}$ = 200.1 Hz, $J_{C,P}$ = 7.8 Hz, C-2), 82.9 (d, $J_{C,F}$ = 9.6 Hz, C-4), 71.8 (d, $J_{C,F}$ = 21.3 Hz, C-3), 62.6 (C-5), 62.0 (d, $J_{C,P}$ = 5.6 Hz, OCH_2CH=C), 31.9 (allylic CH_2), 31.5 (allylic CH_2), 26.3 (allylic CH_2), 26.2 (allylic CH_2), 24.6 (CH_3), 22.34 (CH_3), 22.28 (CH_3), 16.4 (CH_3); ^{19}F NMR (470 MHz, CD_3OD, δ): –208.23 (dd, $J_{2,F}$ = 53.7 Hz, $J_{3,F}$ = 17.5 Hz); ^{31}P NMR (202 MHz, CD_3OD, δ): –0.73; HRMS–ESI–TOF (*m*/*z*): $[M–H]^-$ calcd for $C_{20}H_{33}FO_7P$, 435.1953; found, 435.1961.



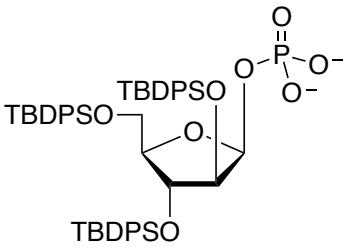
***p*-Tolyl 2,3,5-tri-*O*-*tert*-butyldiphenylsilyl-1-thio-α-D-arabinofuranoside (2.77).** To a solution of **2.21**[9] (280 mg, 1.09 mmol) in dry DMF (5 mL) was added imidazole (1.34 g, 19.6 mmol), followed by TBDPSCl (1.68 mL, 6.55 mmol). The reaction mixture was stirred at 50 ºC for 12 h. After cooling to rt, excess TBDPSCl was quenched by the addition of ice-cold water and the solution was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried with

$MgSO_4$, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography (40:1 hexanes–EtOAc) to yield **2.77** (1.04 g, 98%) as a colorless oil. R_f 0.65 (10:1 hexanes–EtOAc); $[\alpha]_D$ +24 (*c* 0.72, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.66–7.62 (m, 2 H, ArH), 7.59–7.52 (m, 6 H, ArH), 7.49–7.20 (m, 22 H, ArH), 7.15–7.12 (m, 2 H, ArH), 7.02–6.98 (m, 2 H, ArH), 5.25 (s, 1 H, H-1), 4.51 (ddd, $J_{4,5a}$ = 6.5 Hz, $J_{4,5b}$ = 6.0 Hz, $J_{3,4}$ = 2.1 Hz, 1 H, H-4), 4.43 (s, 1 H, H-2), 4.27 (d, $J_{3,4}$ = 2.1 Hz, 1 H, H-3), 3.59 (dd, $J_{5a,5b}$ = 10.5 Hz, $J_{4,5a}$ = 6.5 Hz, 1 H, H-5a), 3.52 (dd, $J_{5a,5b}$ = 10.5 Hz, $J_{4,5b}$ = 6.0 Hz, 1 H, H-5b), 2.30 (s, 3 H, Ar$C\underline{H}_3$), 1.01 (s, 9 H, $SiC(CH_3)_3$), 0.95 (s, 9 H, $SiC(CH_3)_3$), 0.83 (s, 9 H, $SiC(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 136.5 (Ar), 136.0 (Ar), 135.9 (Ar), 135.77 (Ar), 135.75 (Ar), 135.62 (Ar), 135.58 (Ar), 133.7 (Ar), 133.48 (Ar), 133.45 (Ar), 133.1 (Ar), 132.91 (Ar), 132.89 (Ar), 132.6 (Ar), 131.6 (Ar), 129.78 (Ar), 129.75 (Ar), 129.71 (Ar), 129.68 (Ar), 129.5 (Ar), 129.44 (Ar), 129.41 (Ar), 127.71 (Ar), 127.67 (Ar), 127.63 (Ar), 127.57 (Ar), 127.5 (Ar), 95.2 (C-1), 88.1 (C-4), 84.9 (C-2), 80.2 (C-3), 64.4 (C-5), 26.83 ($SiC(\underline{C}H_3)_3$), 26.81 ($SiC(\underline{C}H_3)_3$), 26.7 ($SiC(\underline{C}H_3)_3$), 21.1 ($Ar\underline{C}H_3$), 19.23 ($Si\underline{C}(CH_3)_3$), 19.18 ($Si\underline{C}(CH_3)_3$), 18.9 ($Si\underline{C}(CH_3)_3$); HRMS–ESI–TOF (*m*/*z*): $[M+NH_4]^+$ calcd for $C_{60}H_{74}NO_4SSi_3$, 988.4641; found, 988.4631.

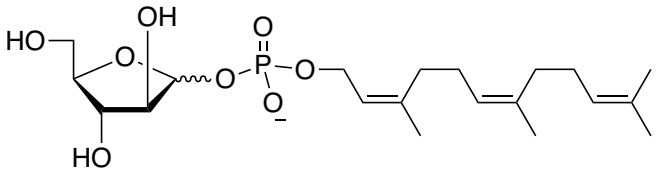


Dibenzyl (2,3,5-tri-*O*-*tert*-butyldiphenylsilyl-α/β-D-arabinofuranosyl) phosphate (1.16).[4] To a stirred solution of **2.77** (207 mg, 0.213 mmol) in CH_2Cl_2 (3.2 mL) was added Br_2 (14 μL, 0.27 mmol). The reaction mixture was stirred at rt for 1 h before being concentrated. The crude glycosyl bromide was azeotropically dried with toluene and then used immediately. To a stirred solution of

azeotropically dried dibenzyl phosphate (119 mg, 0.426 mmol) in toluene (1.2 mL) were added powdered 4 Å molecular sieves (160 mg) and Et_3N (77 μL, 0.55 mmol). The mixture was cooled to 0 ºC, and a solution of the aforementioned glycosyl bromide in toluene (0.4 mL) was added slowly via a cannula. The transfer was completed by rinsing the flask twice with toluene (2 × 0.2 mL). The reaction mixture was warmed slowly to rt and stirred for 16 h before being filtered through a pad of Celite®, rinsed with EtOAc, and the filtrate was concentrated. The crude residue was purified by column chromatography (15% EtOAc–hexanes) to yield **1.16** (102 mg, 42% over two steps, β:α 10.9:1, inseparable) as a colorless oil. The spectroscopic data for **1.16** were identical to those reported.[4]



2,3,5-Tri-*O-tert*-butyldiphenylsilyl-α/β-D-arabinofuranosyl phosphate (1.17).[4] To a stirred solution of **1.16** (102 mg, 0.0904 mmol) in 10% EtOH–EtOAc (3.1 mL) were added Et_3N (313 μL, 2.26 mmol) and 10% palladium on carbon (192 mg, 0.181 mmol). The reaction vessel was purged with argon and then equipped with a hydrogen-filled balloon. The reaction mixture was stirred at rt for 20 h before being filtered through a pad of Celite® with 10% EtOH–EtOAc. The filtrate was concentrated to yield **1.17** (as the triethylammonium salt, 96.2 mg, 93%, β:α 9:1, inseparable) as a white powder. The spectroscopic data for **1.17** were identical to those reported.[4]



(*Z*,*Z*)-Farnesylphosphoryl-α/β-D-arabinofuranose (1.18).[2,4] Compound **1.17** (67.4 mg, 0.0587 mmol) and (*Z*,*Z*)-farnesol[5] (52.2 mg, 0.235 mmol) were azeotropically dried with toluene. The mixture was dissolved in pyridine (1 mL) and Cl_3CCN (59 μL, 0.59 mmol) was added. The resulting solution was stirred for 17 h at 55 ºC before being cooled to rt and concentrated. The crude phosphodiester was dissolved in a 15% solution of concentrated NH_4OH in CH_3OH (1 mL), and NH_4F (65.2 mg, 1.76 mmol) was added. After stirring for 19 h at 55 ºC, the reaction mixture was cooled to rt, and CH_2Cl_2 (2 mL) was added to precipitate any remaining NH_4F. The solution was filtered through a pad of Celite® and the filtrate was concentrated to a crude residue that was purified by column chromatography (gradient of 30%→50% CH_3OH–EtOAc). Residual colored impurities were removed by the addition of activated charcoal to the product in CH_3OH, followed by the filtration through a syringe filter (0.45 μm). The filtrate was concentrated to give **1.18** (9.5 mg, 36% over two steps, β:α 3:1, inseparable) as a colorless oil. The spectroscopic data for **1.18** were identical to those reported.[4]

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