Synthesis of 2-*C*-Branched Sugars

by
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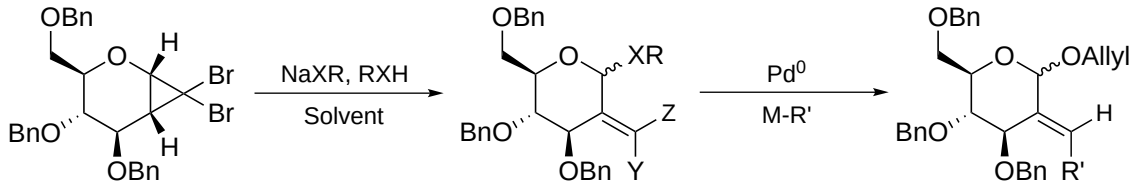
Abstract

A range of unnatural carbohydrates (sugars) with an unusual 2-*C*-bromomethylene branch have been synthesised by reaction of the 1,2-cyclopropanated carbohydrate **52** with different nucleophiles. Initial work to optimise the cyclopropane ring opening in the presence of sodium allyloxide/allyl alcohol provided anomers **140** and **141** in up to 75% yield. Use of sodium thiophenolate/thiophenol provided anomeric thioglycosides **181** and **182** (76% yield, 7:2 ratio), while sodium diethylamide/diethylamine provided anomeric glycosylamines **183** and **184** (50% yield, 1:1 ratio). Further functionalisation of the 2-*C*-branch of **141** was performed using various palladium-catalysed cross-coupling reactions, providing a series of products. Reaction of **140** and **141** under acidic conditions caused *E*-*Z* isomerisation of the bromoalkene forming a single anomer, **194**.



52

H^+

140, **141** XR=OAllyl, Y=Br, Z=H
181, **182** XR=SPh, Y=Br, Z=H,
183, **184** XR=NEt_2, Y=Br, Z=H
194 XR=OAllyl, Y=H, Z=Br

From **141**

Efforts to obtain mechanistic information about the cyclopropane ring opening were made through attempted trapping of a cyclopropene intermediate, deuterium labelling experiments, synthesis of possible stable intermediates and reactions with internal nucleophiles.

Acknowledgments

First and foremost, I would like to thank my supervisor Dr Joanne Harvey. Your enthusiasm of chemistry always left me feeling more cheerful about this project after our discussions. Our at times lengthy conversations trying to confirm the identity of structures or debate of possible mechanisms were hugely beneficial.

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movies rather than revising for math.

Thanks to all the SCPS staff and postgraduate students, it is a wonderfully supportive research environment. Thanks especially to the lab technicians Teresa, Jackie and Jaime-Anne who had to endure having me in their labs as an undergraduate student through to a demonstrator for the last six years.

Finally, thank you to my family, Mum, Dad and Robert. Without your support I could not have dedicated myself to this research.

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Glossary

4Å MS	4 Angstrom molecular sieves
Ac	acetate
Allyl	CH_2CHCH_2-
aq.	aqueous
Ar	aromatic
S-BINAP	(*S*)-(−)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
BOC	-$COOC(CH)_3$
Bn	benzyl
Bz	benzoyl
COD	1,5-cyclooctadiene
m-CPBA	*m*-chloroperbenzoic acid
CSA	(1*S*)-(+)-10-camphorsulfonic acid
CN	cyano
d	doublet
DBA	1,3-dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
d.e.	diastereomeric excess
DME	1,2-dimethoxyethane (a.k.a. ethylene glycol dimethyl ether)
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
DTBPY	4,4′-di-tert-butyl-2,2′-dipyridine
e.e.	enantiomeric excess
eq.	equivalents
Et	ethyl
ESI	electrospray ionisation
gem	geminal
HRMS	high resolution mass spectrometry
i-Pr	-$CH(CH_3)_2$
IR	infrared
Me	methyl
MOM	methoxymethyl ether (-CH_2OCH_3)

m.p.	melting point
Ms	methanesulfonyl (a.k.a. mesyl)
n-BuLi	*normal*-butyllithium
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
PG	protecting group
Ph	phenyl
PIN	pinacolato ligand (-$OC(CH_3)_2C(CH_3)_2O$-)
Py	pyridine
q	quartet
R_f	retention factor
r.t.	room temperature
s	singlet
sat.	saturated
t	triplet
TBS	*t*-butyldimethylsilyl
TEBAC	benzyltriethylammonium chloride
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (a.k.a triflyl)
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tr	trityl
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter 1

Introduction

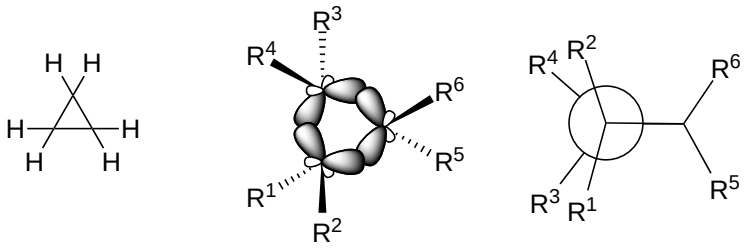
1.1 Cyclopropanes

Cyclopropanes are three–membered carbon rings which represents the smallest ring formation possible. The parent compound, cyclopropane itself (Figure 1.1A), is a highly flammable gas with anaesthetic properties that was first synthesised by August Freund in 1881.[1] The first publication of cyclopropane derivatives was by William Perkin Jr, under the supervision of Adolf von Baeyer.[2,3] At the time of these discoveries, the observed reactivity of cyclopropane and its derivatives was unusual, especially its propensity to undergo ring opening reactions. Adolf von Baeyer published a paper in 1885 on the theory of ring closures which aided in understanding of this unusual reactivity.[4] This publication included the following statement about ring strain:

> "*The four valences of the carbon atom act in the directions that connect the center of a sphere with the corners of a tetrahedron and that form an angle of 109 ° 28' with each other. The direction of the attraction can experience a deviation that will, however, cause an increase in strain correlating with the degree of this deviation.*"[4]
> Translated by Armin de Meijere[5]

Cyclopropane (Figure 1.1A) contains angles of 60° between the carbon atoms, a significant deviation from the 109° for an ideal tetrahedron. von Baeyer's statement above implies that cyclopropane contains significant ring strain which helps explain its propensity to undergo ring opening reactions. Current orbital theories describe a tetrahedrally substituted carbon as an sp^3 hybridised centre, however, the orbitals involved in the carbon-carbon bonds of a cyclopropyl ring has increased 'p' character resulting in reactive bent or 'banana' bonds (Figure 1.1B). Cyclopropane also contains considerable torsional strain due to eclipsing interactions between vicinal substituents (Figure 1.1C). The combined angle and torsional strain in cyclopropane

result in its unusual ring opening properties.



A B C

Figure 1.1 A) Cyclopropane, B) Bent 'Banana' Bonds in the Cyclopropyl Group, C) Newman Projection of the Cyclopropyl Group.

Cyclopropane itself currently holds little interest as its chemical, physical and physiological properties have long been recorded.[6] Of more interest is the cyclopropyl moiety as a functional group in natural products and other target compounds, and as an intermediate in synthetic chemistry.

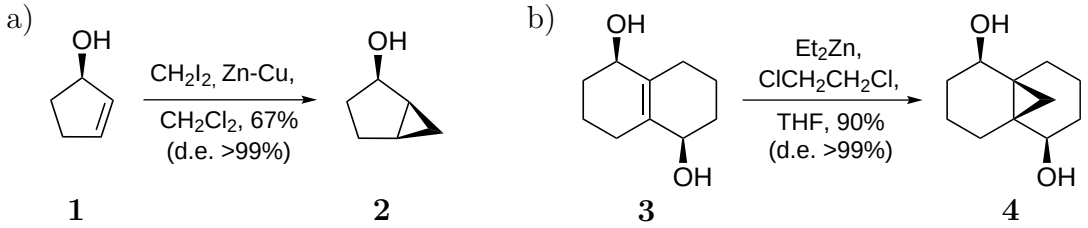
1.1.1 Synthesis of Cyclopropanes

There are many synthetic routes to cyclopropanes most of which involve trapping of a carbene or carbene-type species with an alkene. The two most common methods are the Simmons-Smith and Mąkosza cyclopropanations which will be discussed in more detail below. Other synthetic methods employed use reagents such as trihalomethyl(phenyl)mercury, methyl azide, ethyl trichloroacetate, sodium trichloroacetate and ylide reagents.[7] None of these methods will be discussed further as that are less prevalent.

Simmons-Smith Cyclopropanation

In 1959 Simmons and Smith discovered a procedure that produces cyclopropanes cleanly from alkenes without the side products usually observed in reactions with free carbenes. This procedure involves treatment of an alkene with CH_2I_2 and a zinc-copper couple.[8] The exact structure of the active species is unknown but is thought to be an organozinc intermediate such as $Zn(CH_2I)_2$.[9,10] The stereoselectivity of the Simmons-Smith cyclopropanation is directed by oxygen functionality, usually a hydroxyl group. The oxygen coordinates to the zinc species which directs the cyclopropanation to the same face as the oxygen functionality.[11] This is shown in Scheme 1.1a, where cyclic allylic alcohol **1** is cyclopropanated forming **2** in 67% yield. The high diastereomeric excess in this reaction is attributed to the active zinc species coordinating to the alcohol functionality, which delivers the carbene almost exclusively from above, providing the *syn*-product.[12] The second

example, Scheme 1.1b, uses the common Furukawa modification which employs a diethylzinc species rather than a zinc-copper couple.[13,14] In this example, diol **3** is cyclopropanated from above due to coordination of the active zinc species to either of alcohol functionalities, forming **4** in 90% yield and >99% d.e.[15]



1 **2** **3** **4**

Scheme 1.1 Simmons-Smith Cyclopropanation, A) Zn-Cu Couple,[12] b) Furukawa Modified Method[15]

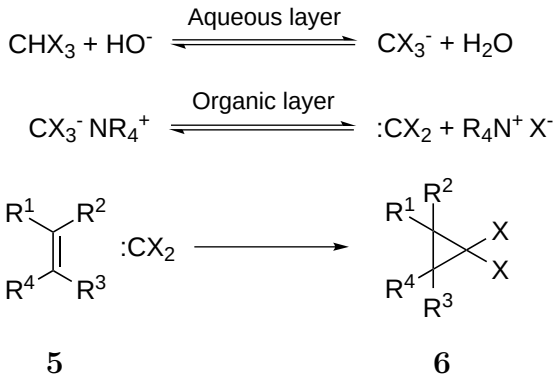
There have been many modifications to the Simmons-Smith method, including the expansion of the method to include a variety of metals including titanium and ruthenium. Enantioselectivity can also be achieved though the use of chiral ligands. This area of research is the subject of several literature reviews.[11,16]

gem-Dihalocyclopropanation

The first synthesis of a geminally dihalogenated cyclopropane was reported in 1954 by Doering and Hoffmann.[17] They showed that a *gem*-dichlorocyclopropane could be synthesised by trapping of a chloroform-derived dichlorocarbene with an alkene under strictly anhydrous conditions.[17] The generation of the dichlorocarbene proceeds through α-elimination of hydrochloric acid from chloroform by a strong base. In 1969, Mąkosza developed a method in which it was possible to generate and trap a dihalocarbene with an alkene (**5**) in a biphasic system under phase transfer-catalysed conditions (Scheme 1.2).[18] This system uses an aqueous solution of sodium hydroxide to remove the haloform proton. The resulting anionic species then complexes to the phase transfer catalyst (a quaternary ammonium salt) which allows its transfer from the aqueous phase to the organic phase, where decomposition of the anion generates the dichlorocarbene. The carbene is then trapped by the alkene (**5**), producing the cyclopropane (**6**), which can be isolated as it resides in the organic layer, unexposed to the harsh basic aqueous conditions that could cause ring opening and other side reactions.[18]

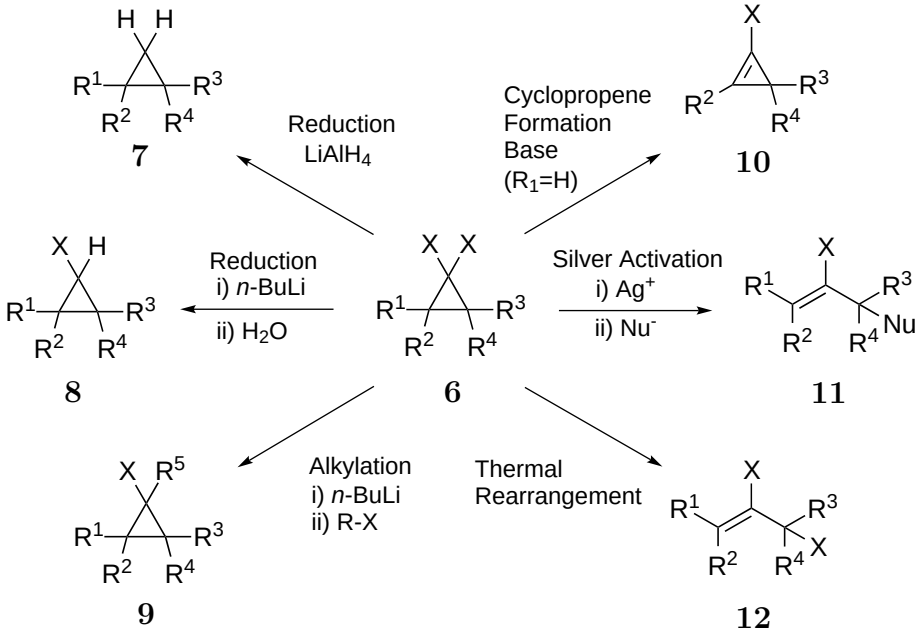
1.1.2 Reactions of *gem*-Dihalocyclopropanes

gem-Dihalocyclopropyl groups are important functional groups in synthetic organic chemistry. They provide facile routes to other functionalised and unfunctionalised cyclopropanes, including those found in natural products and halo-π-allyl interme-



Scheme 1.2 Mąkosza Cyclopropanation[18]

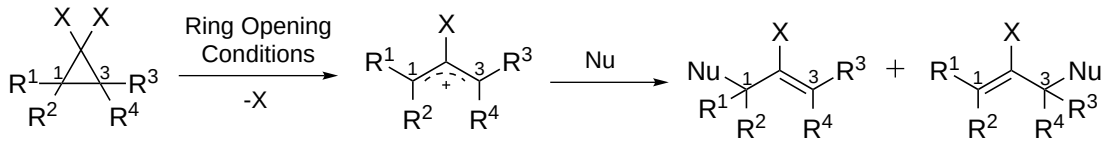
diates. Scheme 1.3 shows a range of reactions of a generic *gem*-dihalocyclopropane, **6**. For example **6** can be converted to the corresponding unfunctionalised cyclopropane (**7**) using $LiAlH_4$, or to the monohalocyclopropane (**8**) using *n*-BuLi in a bromine-for-lithium exchange reaction followed by quenching with water. Alternatively, quenching with an alkyl electrophile produces a substituted bromocyclopropane (**9**).[19]



Scheme 1.3 Reactions of *gem*-Dihalocyclopropane **6**[19]

Reactions of *gem*-dihalocyclopropanes (such as **6**), where at least one other substituent is a hydrogen (R^1), with a strong base such as potassium *tert*-butoxide can lead to cyclopropenes (**10**). Formation of cyclopropenes is highly dependent on the electronic and steric nature of the remaining substituent groups (R^2, R^3, R^4) with aromatic functionalities favouring the elimination. These species are often short-lived species with rearrangement to alkynes or trapping reactions (addition across the double bond) observed regularly.[19] Reactions under thermal conditions or with silver(I) salts led to cyclopropane ring opening, forming halo-π-allyl intermediates. In the presence of an added nucleophile the halo-π-allyl is attacked, forming the

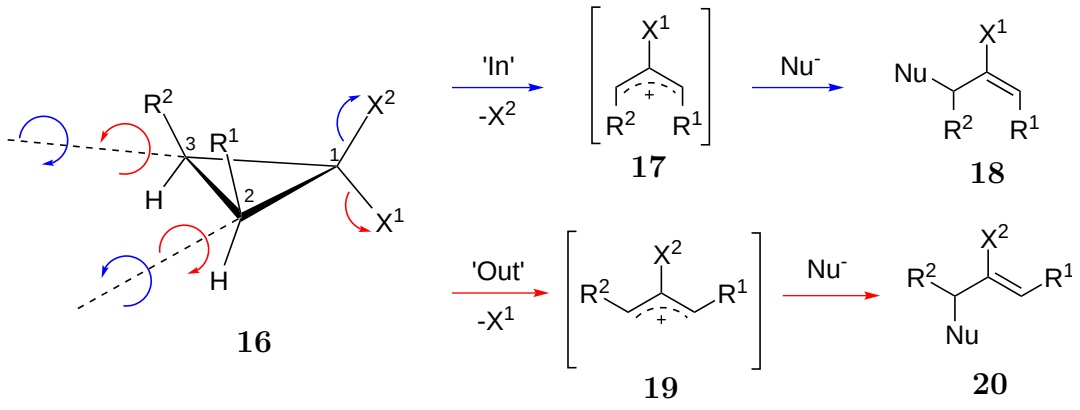
substituted bromoalkene **11**.[19] While reactions under thermal conditions without an added nucleophile produces 2,3-dihaloalkene functionality (i.e. **12** in Scheme 1.3), nucleophilic attack of the halo-π-allyl intermediate **13** can occur at either C-1, providing **14**, or at C-3, providing **15** (Scheme 1.4). The position of nucleophilic attack is dependent on the steric and electronic properties of the nucleophile and the halo-π-allyl intermediate, therefore this may or may not occur regioselectively.



6 **13** **14** **15**

Scheme 1.4 Cyclopropane Ring Opening with Accompanying Nucleophilic Attack

In the 1960's, Woodward and Hoffmann proposed that this electrocyclic ring opening reaction proceeded through a concerted disrotatory mechanism.[20] This was independently confirmed with experimental evidence by DePuy *et al.* who established the "*cis*-in *trans*-out" rule.[21,22] This rule is exemplified in Scheme 1.5 below, where cyclopropane **16** can ring open through two possible disrotatory motions. Firstly, breaking the C-2–C-3 bond via rotation inwards is accompanied by the loss of X^2 (through orbital considerations), forming **17**, which when quenched by a nucleophile forms the *cis*-alkene product **18**. Alternatively, rotation outwards results in the loss of X^1, formation of transoid allylic cation **19**, which when quenched with a nucleophile forms the *trans*-alkene product **20**.

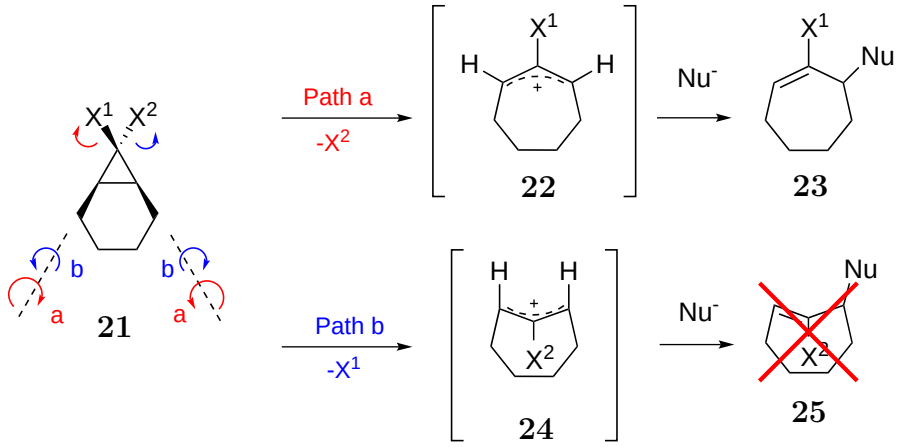


16 **17** **18** **19** **20**

Scheme 1.5 The "*cis*-in *trans*-out" Rule[21,22]

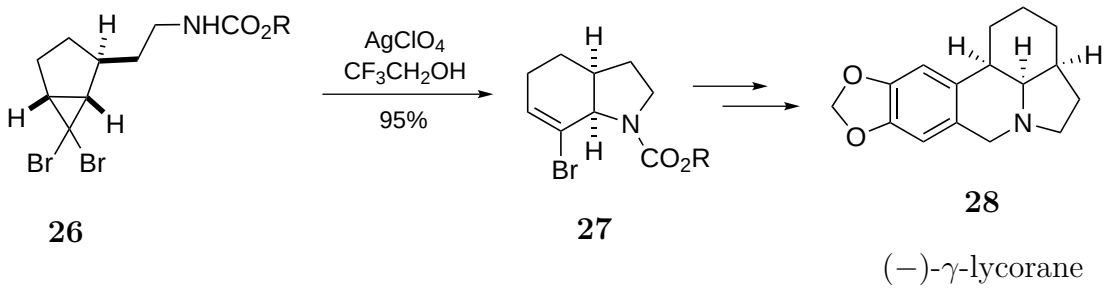
The example above shows the ring opening of a *cis*-disubstituted cyclopropane (**16**). Ring opening of *trans*-substituted cyclopropanes may result in *cis*- or *trans*-alkene products depending on the position of attack of the nucleophile on the halo-π-allyl intermediate (see Scheme 1.4). Cyclopropane ring opening reaction of *gem*-dihalocyclopropanes contained in fused bicyclic structures leads to the formation of expanded ring structures. However, only one of the two possible *cis*-in *trans*-out modes can operate with a fused medium sized ring. Scheme 1.6 shows the two possi-

ble ring expansion reactions of bicyclo[4.1.0]heptane (**21**) through either an inwards or outwards disrotary mechanism. However the cyclopropane ring opening is limited due to the geometric constraints of the second (cyclohexane) ring such that rotation occurs inwards (forming intermediate **22**), leading to loss of endocyclic halide X^1 and forming the *cis*-disubstituted cycloheptene **23**. This is favoured over rotation outwards (forming intermediate **24**, with loss of exocyclic halide X^2), as the *trans*-disubstitured cycloheptene **25** cannot form. The inwards rotation is favoured in systems containing three to six membered rings as it is not possible to form stable cyclic compounds of four to seven members with a *trans*-double bond.[23]



Scheme 1.6 The "*cis*-in *trans*-out" Rule for Bicyclic Compounds[20]

Ring expansion reactions of bicyclic substrates while in the presence of either silver or thermal conditions have been used in a number of natural product syntheses. A ring-expansion cyclisation sequence is observed when a tethered nucleophilic group such as an amine or alcohol is present. Banwell *et al.* utilised *gem*-dibromocyclopropanes **26** in the synthesis of (−)-, (+)- and (±)-γ-lycorane by reacting them with silver perchlorate to ring-open the cyclopropane. This was followed by intramolecular nucleophilic attack, forming an additional five membered ring and producing key intermediate **27** in 95% yield.[24,25]



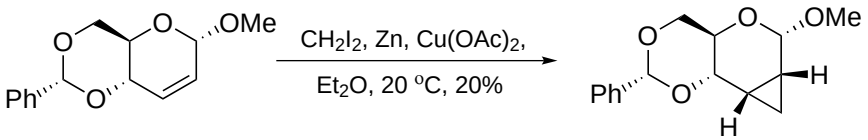
Scheme 1.7 Synthesis of (−)-γ-lycorane (**28**) via a Cyclopropane Ring Opening Reaction[24,25]

1.2 Cyclopropanated Carbohydrates

Carbohydrates are naturally occurring and inexpensive polyhydroxylated compounds which represent some of the most utilised chiral pool reagents due to their diversity, numerous chiral centres and high degree of oxygenation. Carbohydrate chemistry is a well-established field of organic chemistry. In recent years, it has seen renewed interest with numerous syntheses of mono-, oligo- and polysaccharides.[26] General manipulations of these structures are well precedented with a large range of protecting group strategies available, enabling high chemoselectivity, sensitivity and efficiency.

The shared area of research combining cyclopropane and carbohydrate chemistry is quite large, with a diverse range of structures reported,[27] equally divided between pyranoside- and furanoside-based carbohydrates. The majority of furanoside-based cyclopropanated carbohydrates have been synthesised from unsaturated carbohydrates using the Simmons-Smith method, in which the common goal is the generation of conformationally constrained nucleosides.[28] Pyranoside cyclopropanation has more variation with synthetic methods including the use of diazo reagents,[16] ylide reagents,[29] Simmons-Smith[11,16] and Mąkosza[7] methods and their modifications. What follows is a selection of preparations and reaction of cyclopropanated pyranoside carbohydrates.

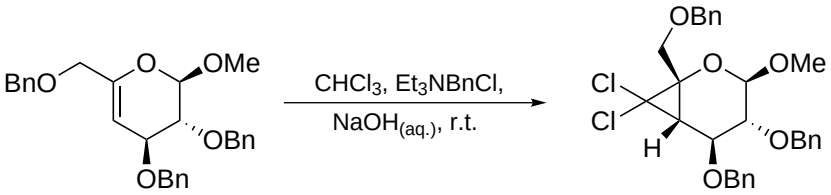
An early example of a Simmons-Smith cyclopropanated carbohydrate was published in 1969 by Albano *et al.* (Scheme 1.8).[30] A zinc-copper couple was prepared from zinc metal and copper diacetate, and reacted in the presence of diiodomethane and alkene **29** to generate cyclopropanated sugar **30** in 20% yield. The carbene is selectively added to the α-face due to coordination of the active zinc species to the neighbouring protected alcohol groups.[30]



29 **30**

Scheme 1.8 Stereoselective Simmons-Smith Cyclopropanation[30]

The Corsaro group showed that Mąkosza cyclopropanation of certain sugars can also be achieved stereoselectively. Cyclopropanation of **31** produced exclusively cyclopropane **32**.[31] The dichlorocarbene addition is directed by steric bulk such that addition occurs from below (α-face), due to the C-3 benzyl group blocking the top (β) face (Scheme 1.9).[31]

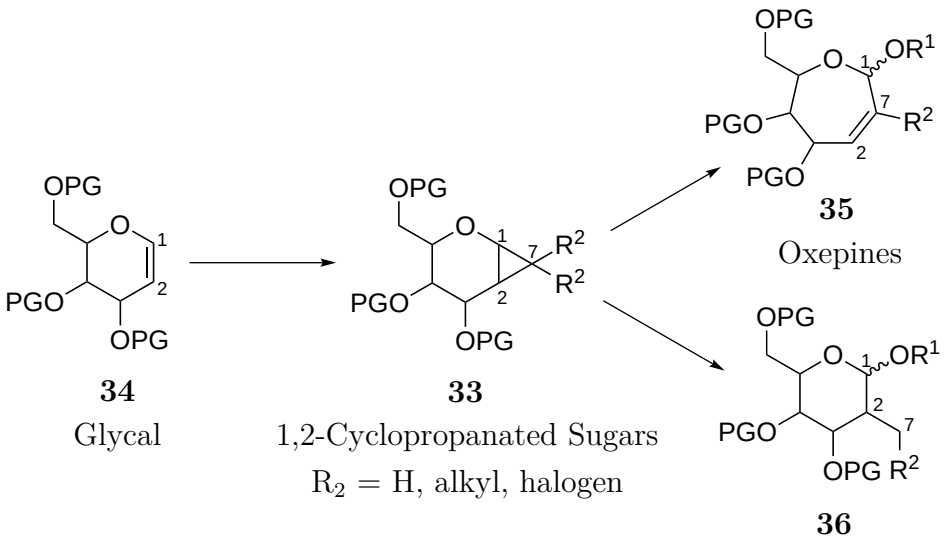


31 **32**

Scheme 1.9 Stereoselective Mąkosza Cyclopropanation[31]

1.2.1 Synthesis and Ring Expansion of 1,2-Cyclopropanated Carbohydrates

1,2-Cyclopropanated carbohydrates **33** can be synthesised by the addition of a carbene to a glycal **34**. Many (protected) glycals are commercially available, while others are readily accessible from the corresponding sugar. 1,2-Cyclopropanated carbohydrates are of great interest due to the range of ring opening reactions the cyclopropane can undergo, providing oxepines **35** and 2-*C*-branched pyranosides **36** (Scheme 1.10).[27] Oxepines such as **35** can be dihydroxylated to form seven–membered septanoside rings (as shown in Scheme 1.17 and Scheme 1.18) which are present in a range of natural products, and are often synthetically challenging as aldohexose sugars tend to form the thermodynamically more favorable furanoside and pyranoside rings. Oxepines **35** can be synthesised by the ring expansion of 1,2-cyclopropanated pyranosides (**33**). The selected examples that follow show a range of methods for synthesising 1,2-cyclopropanated pyranosides, followed by their ring expansion to form oxepines. Formation of 2-*C*-branched sugars will be discussed in subsection 1.2.2 (page 13).

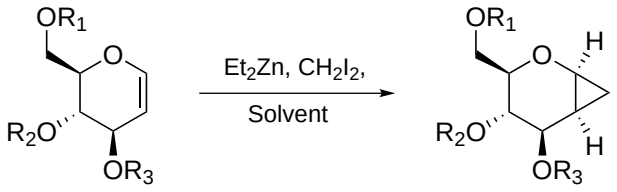


Scheme 1.10 Synthesis and Ring Expansion of 1,2-Cyclopropanated Carbohydrates

Hoberg and co-workers have published multiple papers on the synthesis and ring

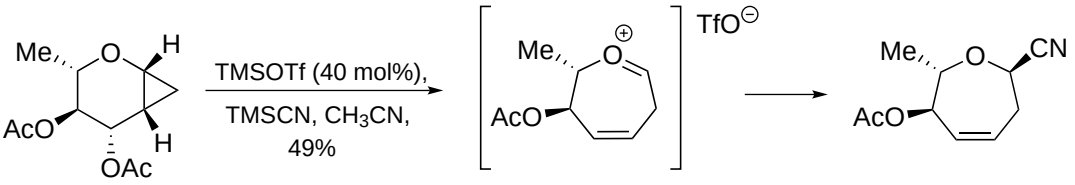
expansion of 1,2-cyclopropanated sugars.[32–35] A range of protected and unprotected glucals (**37**-**40**) were cyclopropanated using diethyl zinc and diiodomethane in several solvent systems, including toluene and diethyl ether/hexane mixtures (Table 1.1). The protecting groups included benzyl (**37**), methyl (**38**), *tert*-butyldimethylsilyl ethers (**39**), and isopropylidenyl acetals (**40**).[32]

Table 1.1 1,2-Cyclopropanated Sugar Synthesis[32]



Glucal	Protecting Groups	Product (% Yield)	Conditions
37	R_1, R_2, R_3 = Bn	**41** (92%)	Et_2O/hexane, 25 °C, 6 h
38	R_1, R_2, R_3 = Me	**42** (94%)	Et_2O/hexane, 0 °C, 1.5 h
39	R_1 = TBS, R_2, R_3 = H	**43** (88%)	Toluene, reflux, 14 h
40	R_1, R_2 = CMe_2, R_3 = H	**44** (33%)	Et_2O/hexane, 40 to 0 °C, 6 h

Ring expansion of the 1,2-cyclopropanated sugars were performed in the presence of a Lewis acid catalyst. This is shown by the example below (Scheme 1.11), where cyclopropane **45** in the presence of TMSOTf ring expands to form intermediate **46**, which can be attacked by CN^- to form oxepine **47**.[32]

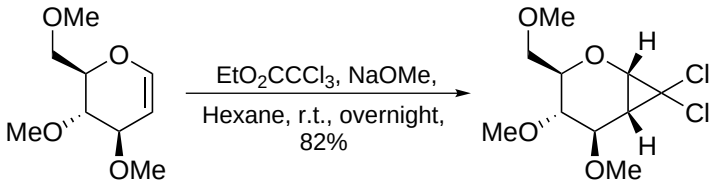


45 **46** **47**

Scheme 1.11 Ring Expansion of 1,2-Cyclopropanated Sugar **45**[32]

The first synthesis of a 1,2-*gem*-dihalocyclopropanated sugar was reported more than four decades ago by the Brimacombe group who synthesised cyclopropane **48** in 82% yield from glucal **49** (Scheme 1.12). The dichlorocarbene was generated by reaction of ethyl trichloroacetate and sodium methoxide in hexane at room temperature. As with other examples (e.g. that of Scheme 1.9), the cyclopropanation occured exclusively from the α-face due to steric bulk on the top face of the molecule.[36]

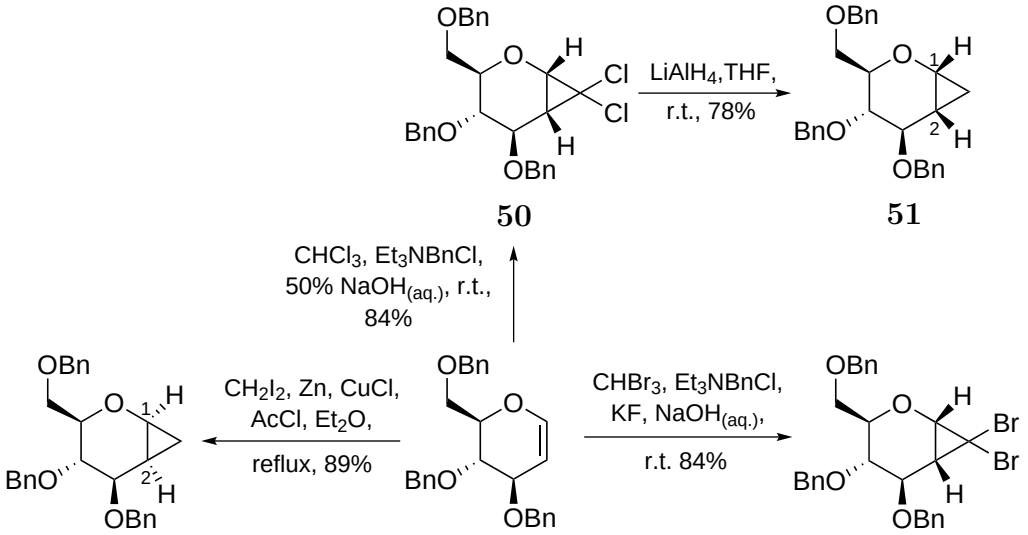
Recently, two reports from the Nagarajan group demonstrated the preparation of a range of 1,2-cyclopropanated sugars through the use of Simmons-Smith and Mąkosza methodologies on various glycals, as exemplified by the reaction of tri-*O*-benzyl-D-glucal (**37**) shown in Scheme 1.13. Firstly, **37** was cyclopropanated using a slightly modified Simmons-Smith cyclopropanation using a zinc-copper couple, CH_2I_2 and



49 **48**

Scheme 1.12 First Synthesis of a 1,2-Cyclopropanated Carbohydrate[36]

acetyl chloride in refluxing diethyl ether. This produced the β-cyclopropane **41** in 89% yield. Mąkosza cyclopropanation with chloroform provided the α-*gem*-dichlorocyclopropane **50** in 84% yield. The chloride functionality of **50** was then reduced at room temperature with lithium aluminium hydride ($LiAlH_4$), producing **51** in 78% yield, with the opposite stereochemistry at C-1 and C-2 compared to cyclopropane **41**. A modified Mąkosza cyclopropanation was used to generate α-*gem*-dibromocyclopropane **52**. The modification encompassed use of a more dilute solution of sodium hydroxide and the addition of potassium fluoride, which provided **52** in 84% yield. Tri-*O*-benzyl-D-galactal and di-*O*-benzyl-L-rhamnal were also explored and behaved similarly.[37,38]



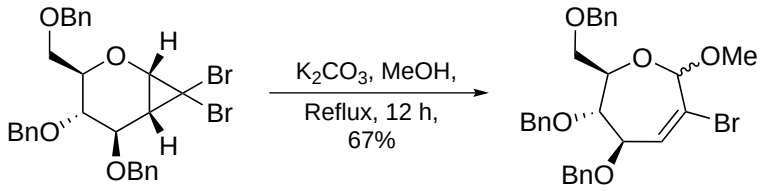
50 **51**

41 **37** **52**

Scheme 1.13 Synthesis of **41** and **51**[37,38]

Nagarajan then explored ring expansion of **52** in an attempt to form oxepines **53** and **54**.[38] Unfortunately, ring expansion failed in the presence of silver ions and other Lewis acid catalysts, and refluxing in acetic acid led to the destruction of the sugar. However, treatment of **52** with a solution of potassium carbonate in methanol was reported to yield ring-expanded oxepines **53** and **54** as a mixture of anomers (α:β, 1.3:1) in 67% yield (Scheme 1.14).[38]

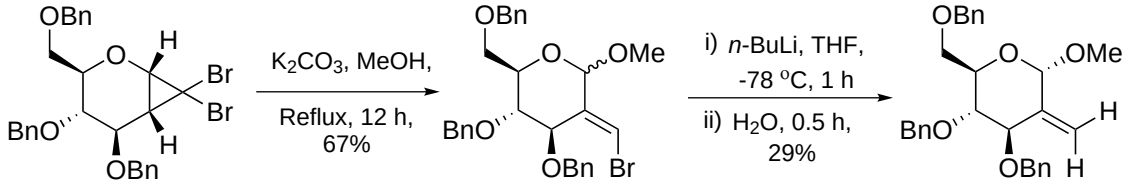
More recently, Harvey and Hewitt have proposed alternative structures for the above products **53** and **54**. Repetition of the reaction of **52** with potassium carbon-



52 **53**, **54**

Scheme 1.14 Nagarajan's Reported Base-Mediated Oxepine Synthesis[38]

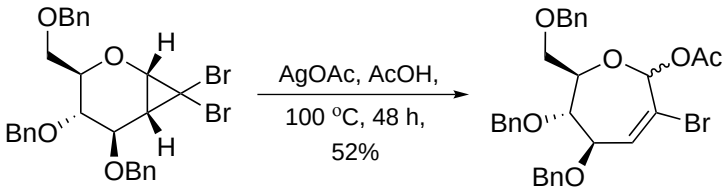
ate in methanol resulted in the isolation and structural elucidation of 2-*C*-*exo*-bromomethylene pyranosides **55** and **56**.[39] These revised structural determinations were confirmed by bromide-for-lithium exchange followed by an aqueous quench of the α-anomer **55**. This generated known compound **57**, which had spectral data consistent with a previous literature report.[40]



52 **55**, **56** **57**

Scheme 1.15 Synthesis of *C*-Branched Pyranosides **55** and **56**[39]

Harvey and Hewitt further explored cyclopropane ring-expansion reactions of **52** in an attempt to form oxepines **53** and **54**. By careful use of silver(I) acetate and heat (100 °C) in acetic acid, ring expansion of cyclopropane **52** led to oxepines **58** and **59**, isolated as an inseparable mixture in 52% yield (α:β 3.5:1, Scheme 1.16).[39] These reaction conditions were extended to non-nucleophilic silver(I) salts such as silver(I) triflate and silver(I) nitrate in the presence of a variety of alcohols such as allyl alcohol, phenol and benzyl alcohol. In the cases of phenol and benzyl alcohol, toluene was used as a solvent together with five equivalents of the desired alcohol. The yields of these reactions varied, with a maximum yield of 65% for the optimised conditions.[41]

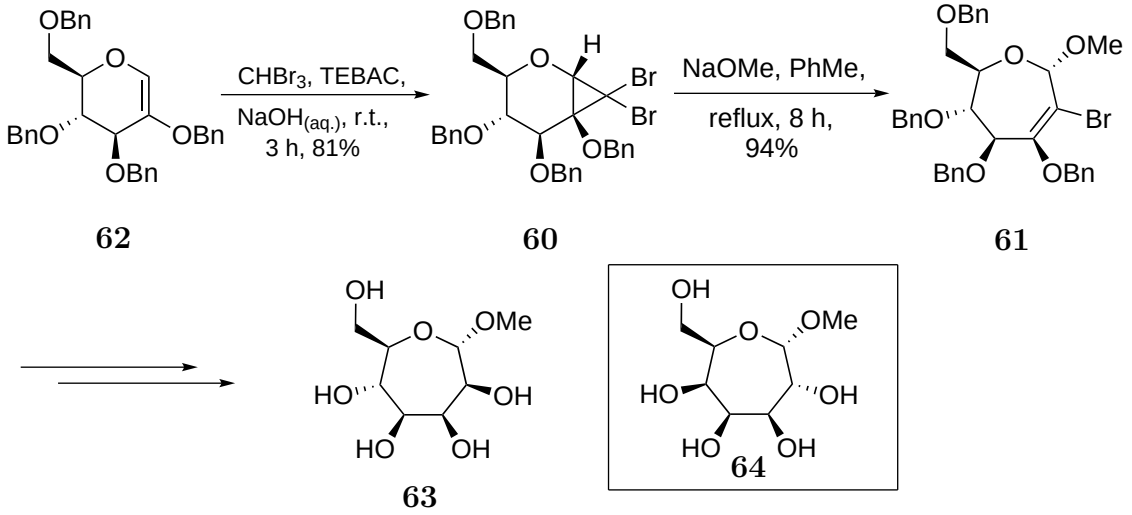


52 **58**, **59**

Scheme 1.16 Silver Mediated Oxepine Formation[39]

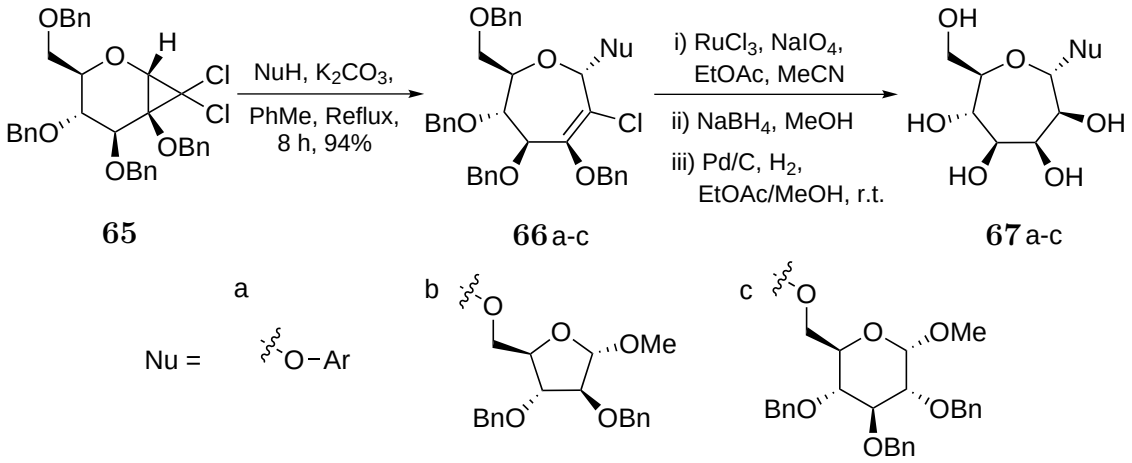
Recent work by Jayaraman *et al.* utilised basic conditions to ring expand cyclopropane **60**, forming oxepine **61** (Scheme 1.17).[42] They began by synthesising cyclopropane **60** from **62** using Mąkosza cyclopropanation. Treatment of **60** with sodium

methoxide in refluxing toluene gave high yields (up to 94%) of a single oxepine product **61**. The target methyl septanoside (**63**) could then be synthesised from oxepine **61** using an oxidation, reduction and hydrogenolysis sequence. The methodology was also extended to a galactose-based precursor providing methyl septanoside **64**.[42]



Scheme 1.17 Synthesis of Septanosides **63** and **64** through a Key Cyclopropane Ring Expansion Reaction[42]

The above methodology was extended to the formation and ring expansion of *gem*-dichlorocyclopropane **65**, and to the use of sugar and phenolic glycosyl acceptors.[43] *gem*-Dichlorocyclopropane **65** was ring expanded in refluxing toluene in the presence of a nucleophile under basic conditions to give a range of oxepines (Scheme 1.18). Yields of **66**a were excellent when using various phenols phenols (76-85%), while sugar-derived nucleophiles also provided good yields of **66**b,c (58% and 63%). Subsequent oxidation, reduction and hydrogenation provided a range of septanosides (**67**a-c).[43]

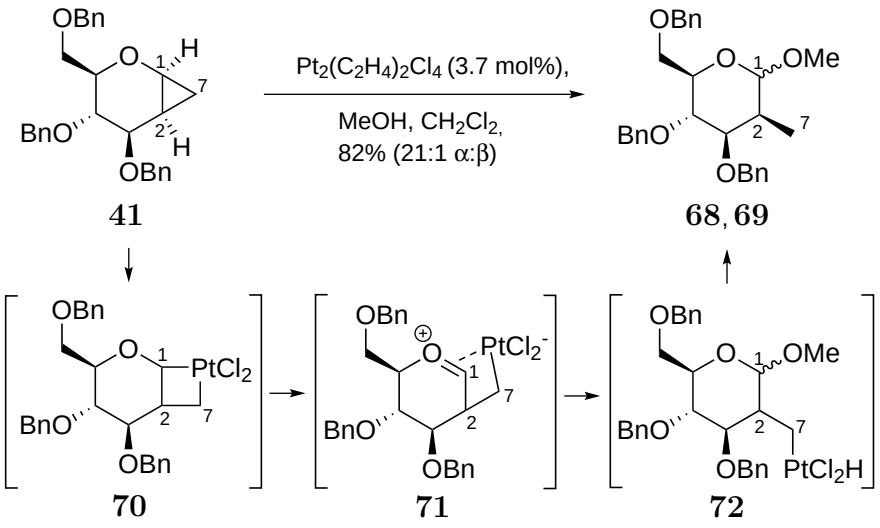


Scheme 1.18 Ring Expansions of 1,2-Cyclopropanated Sugar **62** using a Variety of Nucleophiles[43]

1.2.2 Synthesis of 2-*C*-Branched Sugars

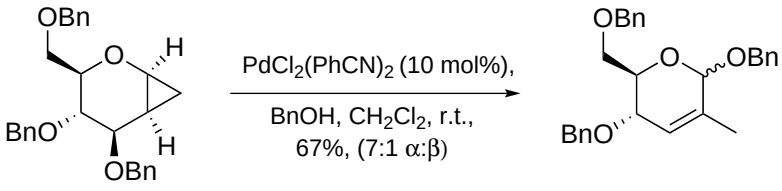
It is inherently difficult to synthesise branched carbohydrate structures on carbons 2–5 with stereo- and regiochemical control, due to the chemical similarities of these centres. The use of toxic tin or mercury reagents and long reaction sequences are often required to distinguish between these positions. Synthesis of 2-*C*-branched sugars has received some attention in the literature, with the majority coming from cyclopropane ring opening reactions of 1,2-cyclopropanated carbohydrates. The cyclopropane may or may not contain functionality as shown in the examples that follow.

Two reports from the Madsen group demonstrated the use of a novel platinum-catalysed cyclopropane ring opening reaction leading to 2-*C*-branched carbohydrates.[44,45] The example below (Scheme 1.19) shows that, when cyclopropane **41** is treated with Zeise's dimer with an equivalent of methanol, ring opening occurs forming methyl 2-*C*-methyl glycosides **68** and **69**.[44] The proposed mechanism for the formation of **68** and **69** first involves platinum insertion into the C-1–C-7 bond, forming a platinacyclobutane **70**. Formation of an oxonium ion, **71**, breaking the platinacyclobutane, results in attack at C-1 by methanol, forming **72**. Reductive elimination regenerates the platinum catalyst and produces methyl 2-*C*-methyl glycoside anomers **68** and **69** (Scheme 1.19).[44]



Scheme 1.19 Cyclopropane Ring Opening Reaction with Zeise's Dimer[44]

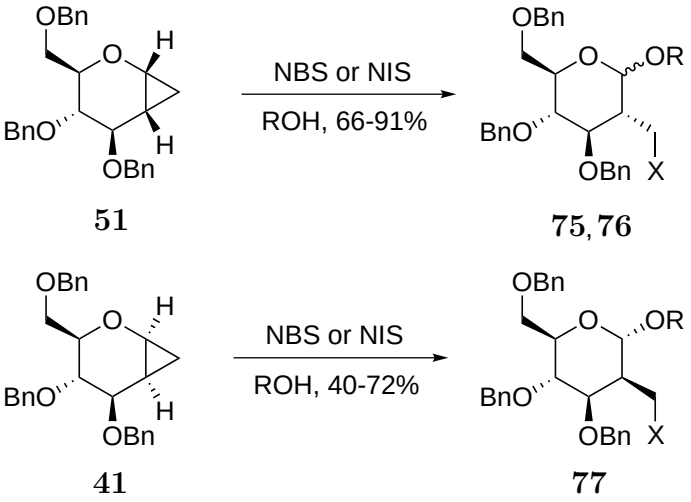
This methodology was extended to other nucleophiles including allyl and benzyl alcohols, phenols and some sugars, giving the desired 2-*C*-branched products in moderate-to-high yields (50-97%). The stereochemistry at C-2 comes from the cyclopropane starting material with the α-anomers predominating. Use of the electrophilic palladium catalyst $PdCl_2(PhCN)_2$ with benzyl alcohol led to ring opening and rearrangement to provide isomeric olefins **73** and **74** in 67% yield (Scheme 1.20).[45]



41 **73, 74**

Scheme 1.20 Cyclopropane Ring Opening Reaction with $PdCl_2(PhCN)_2$[45]

Several research groups have explored cyclopropane ring opening of unfunctionalised 1,2-cyclopropanated carbohydrates via haloetherification. Nagarajan and co-workers used haloetherification of diastereomeric cyclopropanes **41** and **51** to produce a range of halo-2-*C*-methyl glycosides.[38] Reaction of **51** with NBS (*N*-bromosuccinimide) or NIS (*N*-iodosuccinimide) as electrophilic sources of bromine or iodine, caused ring opening of the cyclopropane followed by nucleophilic attack; when the reactions were performed in simple alcohols, solvolysis resulted, giving the products **75** and **76** in 66-91% yield as mixtures of anomers. When cyclopropane **41** was subjected to the same conditions the reactions proceeded at a slower rate and gave lower yields (40-72%); however only the α-anomer, **77**, was isolated (Scheme 1.21). This methodology has been extended to sugar nucleophiles but required the use of an non-nucleophilic solvent (acetonitrile). Longer reaction times at room temperature were required, providing the desired disaccharides in 60-66% yield.[38]

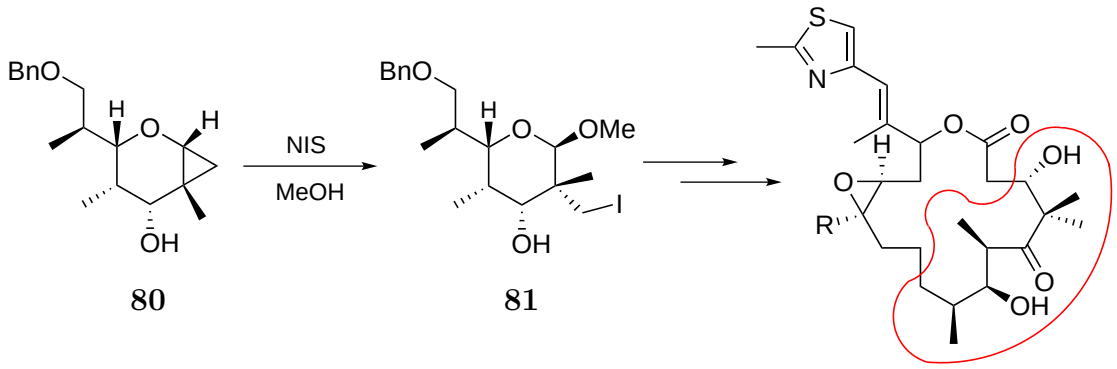


51 **75, 76**

41 **77**

Scheme 1.21 Cyclopropane Ring Opening by Haloetherification[38]

Danishefsky and co-workers used a related cyclopropane ring opening in their total synthesis of (−)-epothilones A (**78**) and B (**79**). This involved reaction of *pseudo*-sugar **80** in methanol with NIS, a source of electrophilic iodine. This provided **81**, which contains a quaternary centre and four of the seven stereocentres contained in (−)-epothilones A and B (Scheme 1.22).[46,47] Ley and co-workers utilised similar methodology in their work towards the total synthesis of altohyrtin A (spongistatin 1), demonstrating the application and flexibility of this methodology.[48]



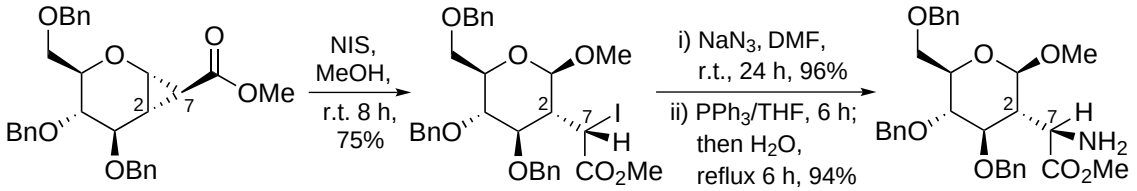
80 **81**

78 R = H, (−)-epothilone A

79 R = Me, (−)-epothilone B

Scheme 1.22 Synthesis of Epothilones A and B[46,47]

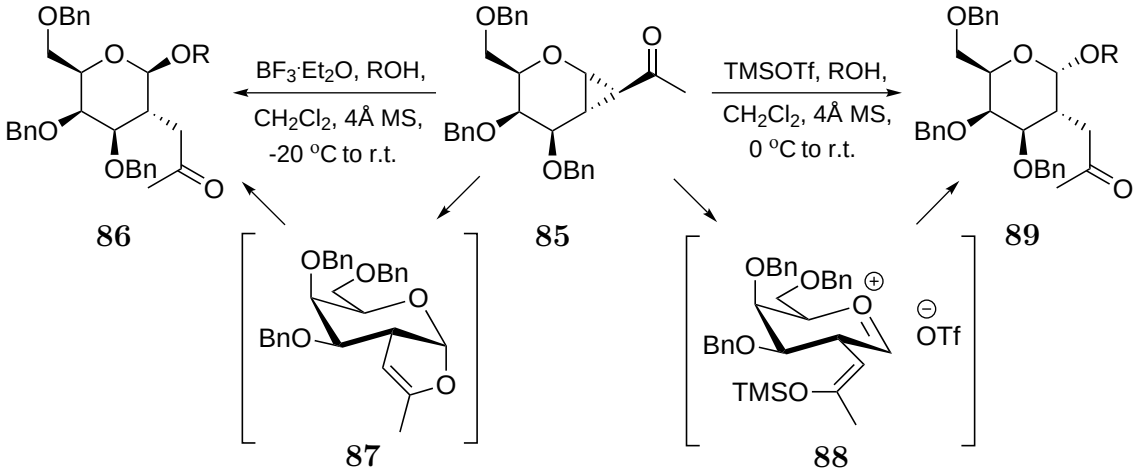
The Chandrasekaran group used iododetherifications in the ring opening of a range of cyclopropanecarboxylate sugars with NIS in good yields (65-85%).[49] These iodide compounds were treated with sodium azide, which were then reduced, producing glyco-amino acids. In the example below (Scheme 1.23), iodide **82** was synthesised in 75% yield from cyclopropane **83** as a single anomer (β), which was then transformed into **84** in very high yield (90%). The stereochemisty of the C-2 centre is determined by the starting material cyclopropane, and the C-7 centre is dependent on the stereospecific nature of the cyclopropane ring opening reaction.[49] This methodology was then extended to include several different glycal substrates, including tri-*O*-benzyl-D-galactal, di-*O*-benzyl-L-rhamnal,[49] and numerous glycosyl acceptors.[50]



83 **82** **84**

Scheme 1.23 Synthesis of Glyco-amino Acids via Cyclopropane **83**[49]

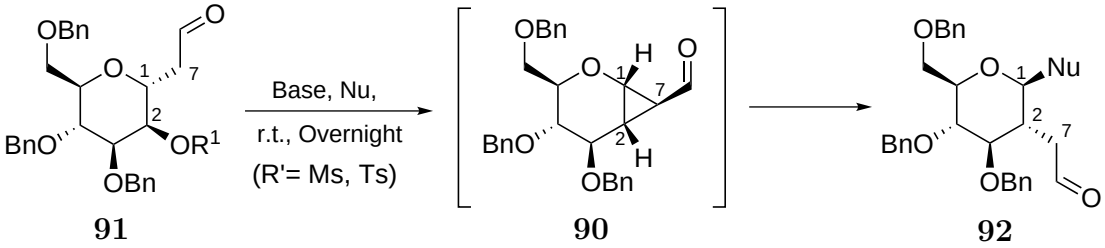
Shao *et al.* explored cyclopropane ring opening reactions of a similar cyclopropanated sugar **85** under Lewis acidic conditions ($BF_3 \cdot Et_2O$ or TMSOTf) in the presence of an alcohol (Scheme 1.24).[51] The alcohols utilised include several monosaccharides, amino acids and several other complex alcohols. Use of $BF_3 \cdot Et_2O$ gave primarily the β-pyranoside **86** (1:3-1:20 α:β). This is due to neighbouring group participation by the enolate, forming intermediate **87** blocking the α-face; thus the nucleophile, an alcohol, attacks from the β-face. Use of TMSOTf causes protection of the enolate as the TMS enol ether (**88**), which prevents neighbouring group participation, therefore the α-pyranoside **89** is favoured due to the anomeric effect (4:1-20:1 α:β).



Scheme 1.24 Synthesis of Pyranosides **86** and **89**[51]

Five years prior to the work above, Shao *et al.* published work proposing a similar cyclopropane, **90**, as an intermediate when aldehyde **91** was treated with base (Table 1.2).[52] This cyclopropane was formed by deprotonation at the carbonyl α-centre (C-7) and the resulting enolate acting as a nucleophile in an intramolecular S_N2-like attack at C-2. The cyclopropane **90** can then be attacked at the anomeric centre by a nucleophile, producing 2-*C*-branched-β-glycoside **92**. Shao *et al.* proposed that the nucleophile directly attacks the C-1 position, breaking the C-1–C-7 bond and producing only the β-anomer; in contrast, the formation of an oxonium intermediate would provide a mixture of anomers. Nucleophiles used included alcohols, thiols and azides, with a variety of solvent/base/nuclephile systems with yields for reactions with alcohol nucleophiles varying from 51–76% (Table 1.2). Reactions with sodium azide produced the corresponding glycosylamines in 50–52% yield while use of thiophenol or thiophenol-like nucleophiles generated the corresponding thioglycosides in high yields (67–86%).[52]

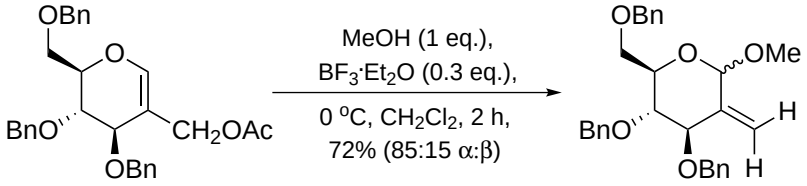
Table 1.2 Synthesis of 2-*C*-Branched Glycosides from *C*-Glycoside **91**[52]



R^1	Solvent/Base	Nucleophile	% Yield
Ms	MeOH/TEA	MeOH	72
Ms	EtOH/TEA	EtOH	71
Ts	$MeCN/K_2CO_3$	PhOH	62
Ts	MeOH/TEA	AllylOH	76
Ms and Ts	MeOH/TEA or $MeCN/K_2CO_3$	NaN_3	50-52
Ms and Ts	$MeOH/K_2CO_3$ or $MeCN/K_2CO_3$	PhSH	67-86

2-*C*-Methylene Sugars

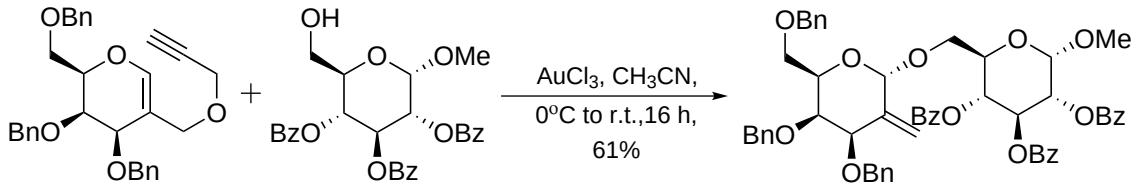
2-*C*-Methylene glycosides have received some attention in the literature, with the majority containing unfunctionalised methylene groups such as compounds **93** and **94**. Synthesis of these compounds is generally not through the use of cyclopropanated carbohydrates. Matsuda *et al.* identified that the 2-*C*-methylene group of these nucleosides is essential for inactivation of the ribonucleotide phosphate reductase enzyme, which is involved in tumour progression.[53] Booma and Balasubramanian used a BF_3-catalysed Ferrier-type rearrangement of 2-*C*-acetoxymethyl glycal **95** in dichloromethane with an equivalent of alcohol to form methyl 2-*C*-methylene glycosides **93** and **94** in 72% yield with an α:β ratio of 85:15 (Scheme 1.25).[40]



95 **93**, **94**

Scheme 1.25 Ferrier-type Rearrangement Forming 2-*C*-Methylene Glucals[40]

Synthesis of 2-*C*-methylene sugars has been explored in several studies, employing Nafion-H, Montmorillonite K-10 and $Pd(PPh_3)_4$ catalysts.[54] Recently, Ghosh *et al.*[55] reported an $InCl_3$-mediated synthesis using a similar transformation to Booma and Balasubramanian to obtain 2-*C*-methylene glycosides.[55] Hotha *et al.* reported a catalytic gold method, with mild reaction conditions that tolerate many different aglycones.[56] The example below shows the gold-catalysed reaction of the sugar nucleophile **96** with glycal **97**, giving disaccharide **98** in 61% yield, exclusively as the α-anomer (Scheme 1.26).[56]

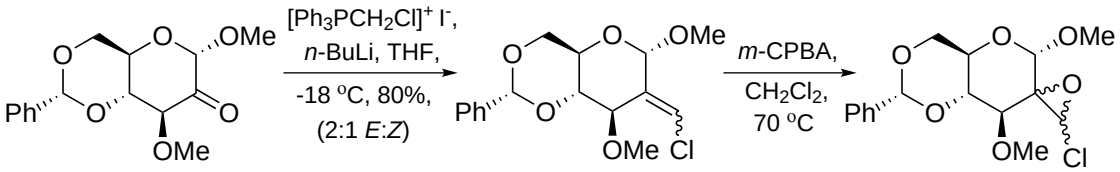


97 **96** **98**

Scheme 1.26 Synthesis of 2-*C*-Branched Disaccharide **98**[56]

2-*C*-Halomethylene glycosides have been reported twice in the literature. The most recent example was seen in Scheme 1.15, whereby Harvey and Hewitt ring opened 1,2-cyclopropanated sugar **52** under basic conditions, providing pyranosides **55** and **56**.[39] The second example is shown below, whereby Sato *et al.* treated ketone **99** with a premixed solution of chloromethyltriphenylphosphonium iodide and *n*-BuLi to synthesise 2-*C*-chloromethylene sugars **100** and **101** in 80% yield with an *E*:*Z* ratio of 2:1.[57] The products **100** and **101** were further functionalised by epoxida-

tion, which proceeded in high yield (75%) to give a mixture of four diastereomers, **102-105** (Scheme 1.27).[57]



99 **100, 101** **102 - 105**

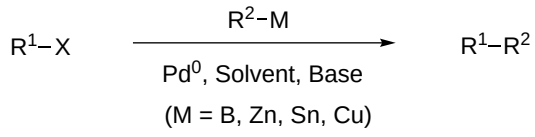
Scheme 1.27 Synthesis of Chloroalkenes **100** and **101** Followed by Epoxidation[57]

1.3 Palladium–Catalysed Cross–Coupling Reactions

1.3.1 General Palladium–Catalysed Cross–Coupling

Carbon–carbon bond formation reactions are one of the most important types of reactions. Their formation is generally thermodynamically favourable (depending on the starting materials) but kinetically unfavourable, as large activation energies make these reactions unfeasible without the aid of a catalyst. Palladium–catalysed cross–coupling reactions have been an excellent avenue of research for this chemistry, since their discovery in the late 1970's and early 1980's. These processes are used in small-scale research laboratory experiments through to the industrial scale. Five named reactions will be discussed: the Suzuki, Stille, Negishi, Sonogashira and Heck reactions. While the Heck reaction is not strictly a cross-coupling reaction, it is often classed with cross-coupling reactions. The importance of these carbon–carbon bond forming reactions was recognised in 2010 when Richard F. Heck, Ei-ichi Negishi and Akira Suzuki were jointly awarded the Nobel Prize in chemistry.

The general palladium-catalysed cross-coupling reaction involves carbon–carbon bond formation between aryl/alkenyl and occasionally alkyl halides or triflates and an organometallic reagent. The organometallic species can vary significantly in its organic functionality and in the metal (the various named reactions use different metals) which typically includes boron, zinc, tin or copper. The scheme below (Scheme 1.28) shows a generic cross-coupling reaction, while more detail on the five named reactions follow.

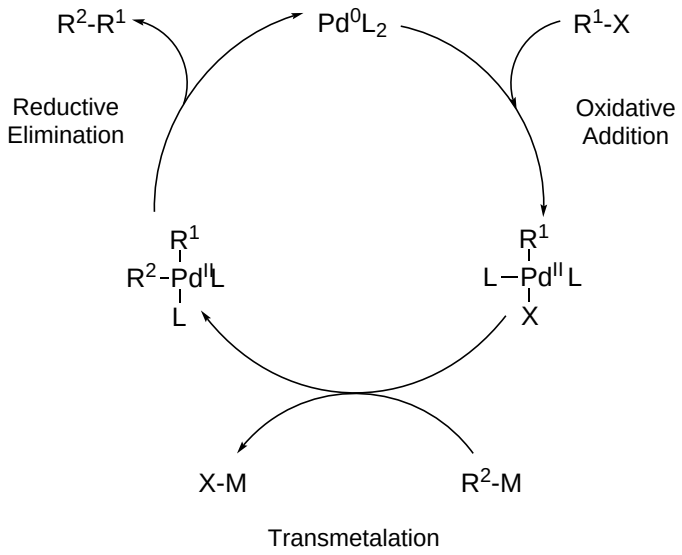


Scheme 1.28 Palladium-Catalysed Cross-Coupling Reactions

1.3.2 Suzuki, Negishi and Stille Cross–Coupling Reactions

Reaction Mechanisms and Other Considerations

The Suzuki, Negishi and Stille cross-coupling reactions all follow a similar catalytic cycle, though they differ in the organometallic reagent used. The Suzuki reaction uses boron reagents in the form of organoboronic acids, organoboronate esters or potassium organotrifluoroborate salts, where the transferred organic group is an alkyl, alkenyl or aryl group. The Negishi reaction uses alkyl or aryl zinc reagents which can be difficult to handle due to their high reactivity. The Stille reaction uses alkyl or alkenyl tin reagents, which have their drawbacks due to the toxicity of organotin compounds. A general catalytic cycle for these three reactions is shown below (Scheme 1.29).



Scheme 1.29 Catalytic Cycle for Suzuki, Negishi and Stille Cross-Coupling Reactions

The proposed catalytic cycle is based on an understanding of coordination chemistry, the reactivity of the catalyst and analysis of products formed. Firstly the organohalide (or organotriflate) oxidatively adds to the palladium(0) catalyst, increasing the oxidation state of palladium by two. Transmetalation follows, in which the organometallic compound transfers its alkyl/alkenyl/aryl group to the palladium while removing the halide group from the palladium. The transmetalation step is thought to be the slowest (rate limiting) mechanistic step and activation of boron reagents often facilitates the Suzuki reaction. The driving force of transmetalation is the metal halide byproduct produced, which is thermodynamically favoured compared to the organometallic reagent.[58] The final mechanistic step is reductive elimination which ejects the cross-coupled product and regenerates the Pd(0) catalyst; this elimination step requires a *cis* relationship between the organic groups (R^1 and R^2).

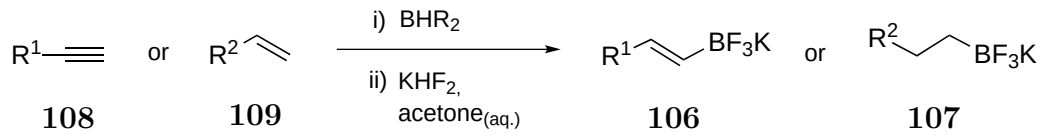
The Pd(0) catalyst can be added directly to the reaction as $Pd(dba)_2$, $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ or it can be generated *in situ* through reduction of a Pd(II) precatalyst such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ or $PdCl_2$.[58] The palladium catalyst is sterically and electronically complex, with its properties, specifically the catalytic activity, highly dependent on the steric and electronic properties of the ligands coordinated to the palladium. Phosphine ligands are the most common ligands in these catalysts, however in recent years *N*-heterocyclic carbenes and some nitrogen ligands have been successfully used.[59] These latter ligands can provide increased air- and water-stability compared to traditional phosphine ligands.[60] Cross-coupling reactions are usually performed under inert atmospheres using dry, degassed solvents to avoid destruction of the catalyst. There are, however, examples in the literature of palladium-catalysed cross-coupling reactions using aqueous alcohols or water as solvents.[58]

Suzuki Cross-Coupling Reaction

The Suzuki reaction is one of the most powerful carbon-carbon bond forming reactions. It utilises organoboron reagents which have low toxicity and their use provides a carbon-carbon bond formation reaction with high functional group tolerance. These reagents are readily available, both commercially and synthetically.[58] Three-coordinate boron compounds such as organoboronic acids and esters are highly electrophilic, with the organic group on the boron only weakly nucleophilic. This makes transmetalation slow; however if a nucleophilic base (or fluoride source) is added, a four-coordinate boronate anion forms, significantly increasing the nucleophilicity of the organic group. The bases most commonly used are K_3PO_4, CsF, NaOEt, KF, Cs_2CO_3 and K_2CO_3.[60] The palladium(0) catalyst can also be replaced by a nickel(0) or iron(I) catalyst.[58]

Classically, organoboron reagents are formed by addition of the relevant Grignard or alkyl/aryl lithium compound to a trialkylborate.[61] While for simple structures this is efficient, there is limited control of stereochemistry and multiple additions of the alkylating reagent can occur.[58] More recently, organotrifluoroborate potassium salts (e.g. **106**, **107**) have gained prominence as activated boron reagents. These compounds can be synthesised through the addition of dialkylborane to alkynes (**108**) or alkenes (**109**) in a hydroboration reaction, followed by treatment with KHF_2 in acetone. The hydroboration reaction proceeds through a *cis*-anti-Markovnikov addition as shown in Scheme 1.30.[62]

There are many examples of Suzuki cross-coupling reactions in organic synthesis.

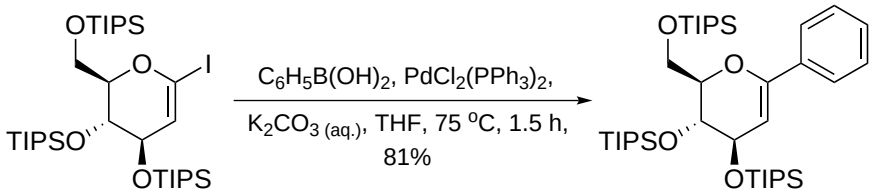


108 **109** **106** **107**

Scheme 1.30 Formation of Potassium Organotrifluoroborates[62]

What follows is a small range of examples that involve relevant carbohydrate-derived substrates, and showcase the flexibility of this methodology.

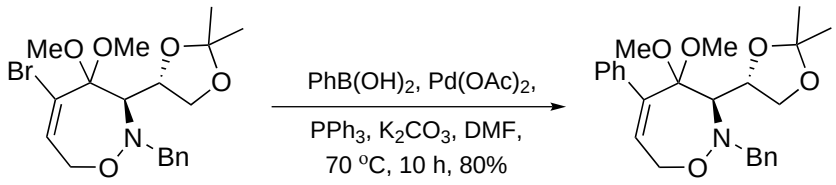
A Suzuki cross-coupling reaction of iodoglucal **110** was used by Friesen and Loo to give a range of *C*-glycosides.[63] The example below shows coupling of **110** with phenylboronic acid, using an aqueous THF solvent system heated to 75 °C for 1.5 hours, provided **111** in 81% yield (Scheme 1.31). Friesen and Loo also used iodoglycal **110** in Negishi and Stille cross-couplings. In all cases aromatic organometallic reagents were used giving optimised yields of 68–90%.[63]



110 **111**

Scheme 1.31 Suzuki Cross-Coupling of 1-Iodo-Glucal **110**[63]

Reissig and Al-Harrasi performed a Suzuki cross-coupling on an 1,2-oxazepine substrate **112** (Scheme 1.32).[64] Phenylboronic acid was used as the coupling reagent and a $Pd(OAc)_2/PPh_3$ catalyst system afforded **113** in 80% yield upon heating to 70 °C in DMF for 10 hours. Substrate **112** was also used in Stille, Sonogashira and Heck reactions to produce dienes and enynes.[64]

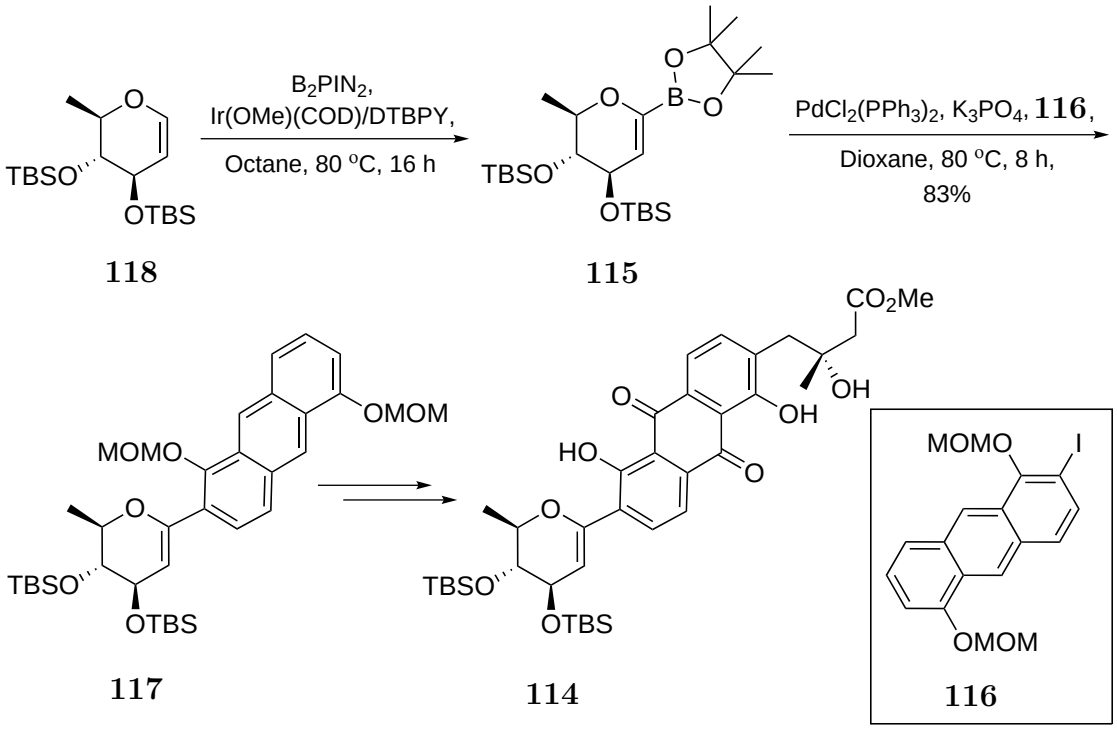


112 **113**

Scheme 1.32 Palladium-Catalysed Cross-Coupling of an Oxazepine[64]

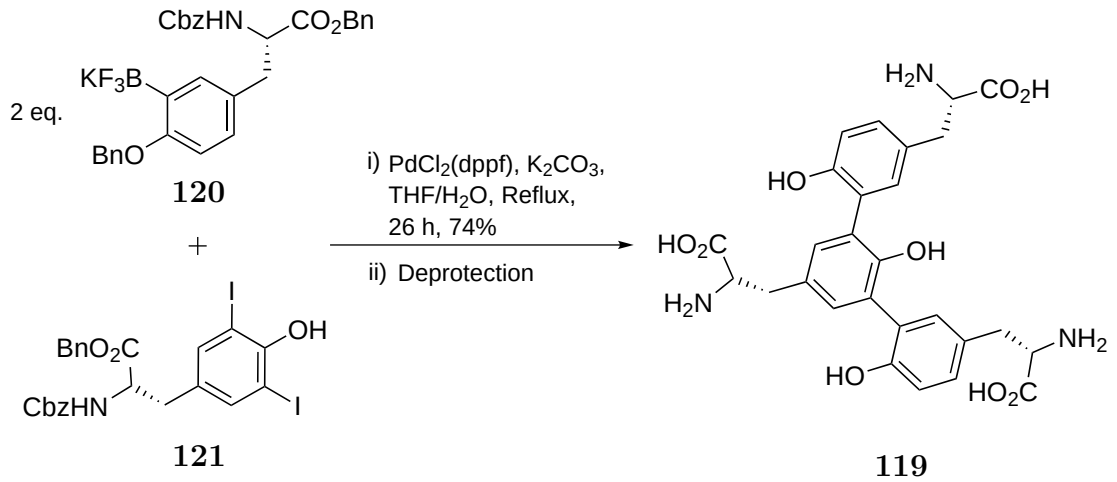
A key step in the synthesis of vineomycine B2 methyl ester (**114**) as reported by the Miyaura group is the Suzuki cross-coupling of the boronate ester **115** with iodoanthracene **116** producing **117** in 83% yield (Scheme 1.33). This reaction used a $PdCl_2(PPh_3)_2$ catalyst, K_3PO_4 as a base and 1,4-dioxane as a solvent with heating to 80 °C for eight hours. The boronate **115** was synthesised by an iridium-catalysed reaction of glycal **118** with B_2PIN_2. This is another example where a Suzuki reac-

tion has been used to form the often synthetically challenging C-glycosides.[61]



Scheme 1.33 Synthesis of Vineomycine B2 Methyl Ester via a Suzuki Cross-Coupling[61]

The synthesis of the natural product trityrosine (**119**) reported by Skaff *et al.* in 2005 used a Suzuki cross–coupling reaction as a key synthetic step (Scheme 1.34).[65] The use of organotrifluoroborate **120** was crucial, as the corresponding pinacol borate reagent gave only a singly cross-coupled product when reacted with **121**. The reaction used a $Pd(dppf)Cl_2$ catalyst, in conjunction with potassium carbonate in refluxing aqueous THF for 26 hours, yielding the desired doubly cross-coupled product in 74%. Global deprotection completed the synthesis of trityrosine (**119**).[65]

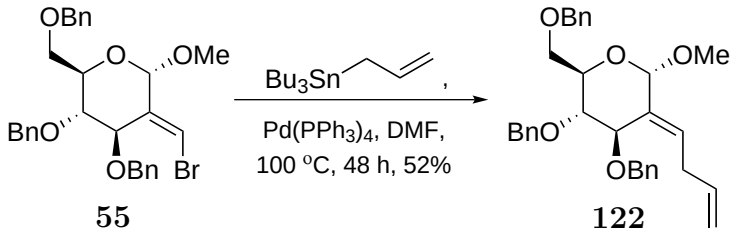


Scheme 1.34 Synthesis of Trityrosine[65]

Stille Cross–Coupling Reaction

The Stille cross-coupling reaction involves the coupling of a tin organometallic reagent to an sp^2-hybridised C-X group. This reaction has been widely used in organic chemistry, usually under inert atmospheres using dry degassed solvents. These reactions are still performed today but, due to the toxicity and difficulty in separation of tin reagents and byproducts, the use of Stille cross-coupling in industrial and pharmaceutical applications is becoming very limited.[60] Synthesis of stannane compounds is usually achieved via a tributyltin halide compound and the relevant Grignard reagent.[60,66]

There are many examples of Stille cross-coupling reactions being used in organic synthetic chemistry, often in the later stages of syntheses. A Stille cross-coupling has been performed on the alkenyl bromide **55** synthesied by Harvey and Hewitt (see Scheme 1.15) to provide the non-conjugated 2-*C*-branched diene **122** (Scheme 1.35).[41]



55 **122**

Scheme 1.35 Stille Cross-Coupling of **55**[41]

No Stille cross-coupling reactions were attempted in this study and they will not be discussed further as Suzuki cross-couplings were preformed in preference.

Negishi Cross-Coupling Reaction

The Negishi cross–coupling reaction uses organozinc compounds as the organometallic reagent in couplings to an sp^2-hybridised C-X bond. Negishi reagents can be synthesised by adding zinc metal to a halogenic species, enabling the zinc to insert into the C-X bond. The zinc metal is often activated by addition of I_2 to expose a fresh zinc surface, as formation can be slow if zinc oxide layers are present.[60] These reagents are usually highly air- and water-sensitive and so their use can be somewhat limited.[60] While there are many literature examples of the Negishi cross-coupling in organic synthesis none were attempted in this study and will therefore not be discussed further.

1.3.3 Sonogashira Cross-Coupling Reaction

The Sonogashira reaction couples terminal alkynes with haloalkene, haloaryl or haloalkyne groups. This reaction is important, as it provides a method for synthesising enyne and diyne functionalities which are present in many natural products.[67] Sonogashira found that addition of a copper(I) halide salt allows the previously reported alkene/alkyne palladium-catalysed cross-coupling reaction to proceed at room temperature, compared to the 100 °C temperature previously required.[67] The discovery of this reaction has led to a large number of applications, as it is useful in construction of synthetic targets and in forming useful intermediate structures due to the myriad of reactivities of alkynes.[67]

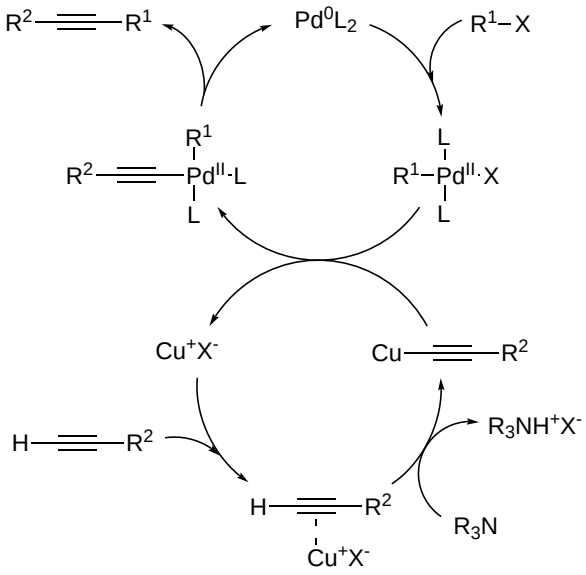
Reaction Mechanism

The reaction mechanism of the Sonogashira reaction has generated continual discussion. The original mechanism put forward by Sonogashira (Scheme 1.36) involves the use of two catalytic cycles and is generally considered to be the most likely mechanism. The first cycle uses catalytic palladium as with the Suzuki, Negishi and Stille reactions and involves oxidative addition, transmetalation and reductive elimination steps as described previously. The second catalytic cycle involves a copper(I) salt (usually a halide), a base and a terminal alkyne. It is proposed that the copper forms an η^2 complex with the alkyne, weakening the terminal C-H alkyne bond. The terminal alkyne can then be deprotonated by the base (usually a tertiary amine). The coordination is believed to be necessary as the amine bases used in these reactions are not strong enough to deprotonate a non-complexed terminal alkyne. The deprotonated alkyne then changes its coordination, forming a copper acetylide species, which can undergo transmetalation with palladium, regenerating the copper halide species. Reductive elimination within the palladium catalytic cycle produces the desired products, regenerating the palladium(0) catalyst. There are examples of copper-free Sonogashira reactions where it is suggested that the alkyne can coordinate to palladium and be deprotonated in a similar way to the copper(I) mechanism.[67]

Sonogashira Cross-Coupling Reactions in Organic Synthesis

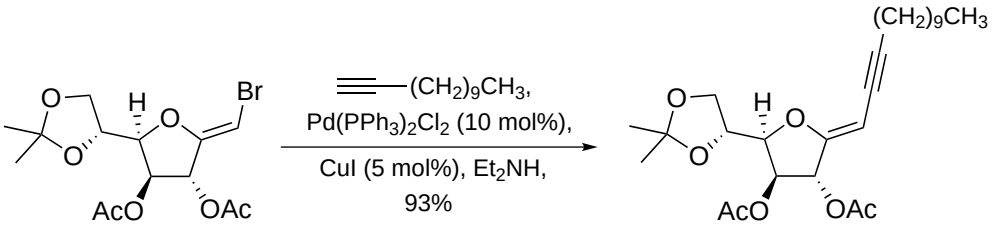
There are numerous examples of Sonogashira cross-coupling reactions in organic synthesis, many involved in natural product synthesis. What follows is a limited selection of examples involving sugar substrates or leading to natural products.

Gómaz *et al.* used Sonogashira cross-couplings of furanose and pyranose halo-*exo*-



Scheme 1.36 Mechanism of the Sonogashira Cross-Coupling Reaction[67]

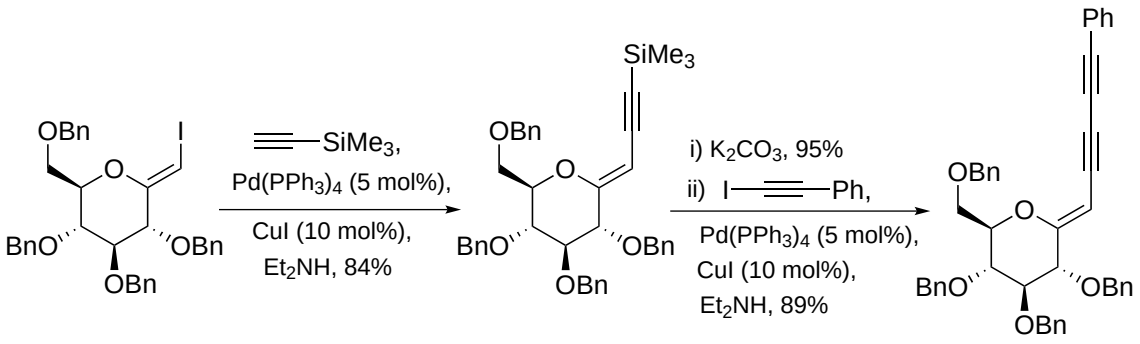
glycal substrates with a range of alkynes to form enediynes or enynes, which have potential applications in natural product synthesis, anticancer antibiotics and new materials.[68] In Scheme 1.37, furanose **123** is cross-coupled with dodec-1-yne using a $PdCl_2(PPh_3)_2$ catalyst, providing the product enyne **124** in 93% yield.[68]



123 **124**

Scheme 1.37 A Sonogashira Reaction with Sugar Substrate **123**[68]

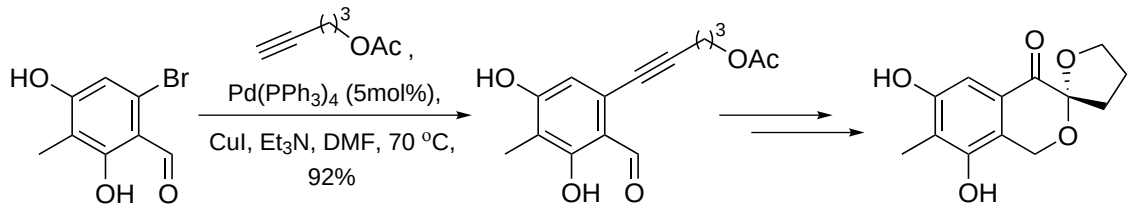
Scheme 1.38 shows a similar example to that above, except the substrate used was a pyranose sugar, **125**. This iodoalkene was cross-coupled with trimethylsilyl acetylene to give **126** in 84% yield. This compound was desilylated, then a second Sonogashira cross-coupling gave **127** which has unusual enediyne functionality.[68]



125 **126** **127**

Scheme 1.38 A Sonogashira Reaction Sequence with Sugar Substrate **125**[68]

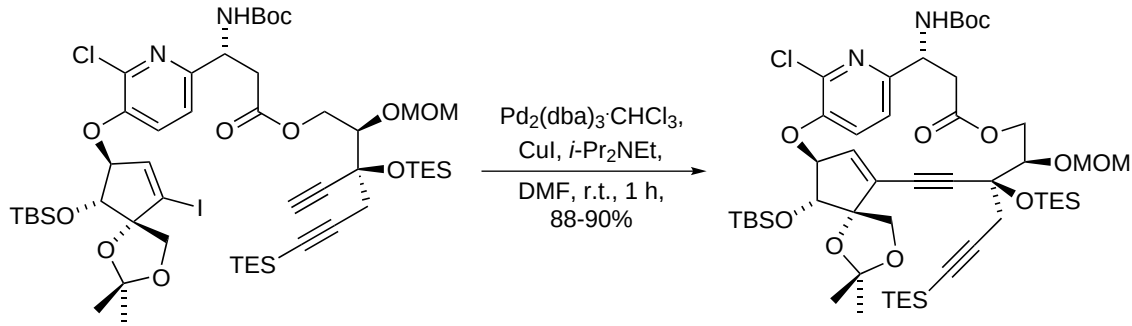
There are many examples of Sonogashira cross-coupling reactions in natural product synthesis. One such example is the synthesis of (±)-terreinol (**128**) by Wei *et al.* A key reaction step was the Sonogashira cross-coupling of arylbromide **129** with 5-acetylpent-1-yne, producing **130** in 92% yield. Of note is the functional group tolerance of the Sonagashira reaction, as **129** contains phenolic and aldehyde functionalities which remain unaffected and do not interfere with the Sonogashira reaction.[69]



129 **130** **128**

Scheme 1.39 A Sonogashira Cross-Coupling used in the Synthesis of Terreinol[69]

Intramolecular Sonogashira cross-couplings have been exploited in the synthesis of natural products. An example of this is a key step in the synthesis of the chromophore ansamacrolide by the Hirama group.[70] Terminal alkyne **131** was treated with a palladium(0) catalyst, CuI and Hünig's base (i-Pr_2NEt) in DMF, at room temperature for one hour, which closed the macrocycle ring, forming **132** in 88-90% yield.[70]



131 **132**

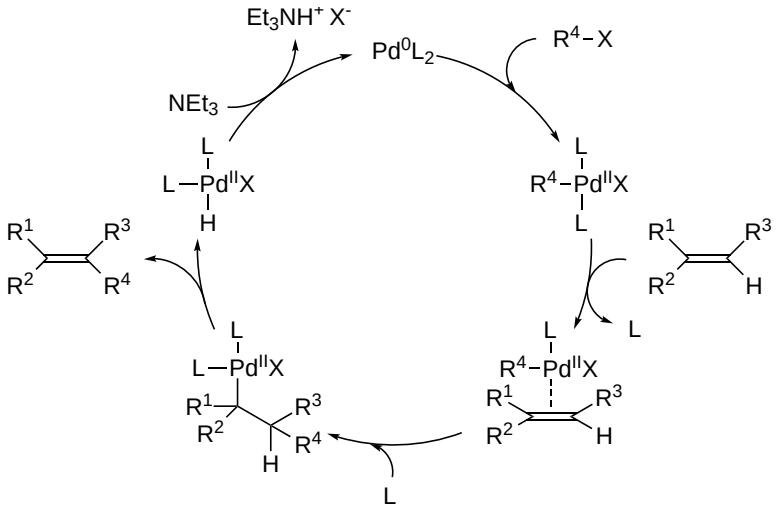
Scheme 1.40 Key Intramolecular Sonogashira Cross-Coupling in the Synthesis of Ansamacrolide[70]

1.3.4 Heck Reaction

The Heck reaction is not strictly a cross-coupling reaction, due to differences in its mechanism, however it is often referred to as one. This reaction is highly useful and versatile for creating carbon-carbon bonds between sp^2 centres. The Heck reaction occurs between an alkene and an alkenyl halide or triflate using a palladium(0) catalyst.

Reaction Mechanism

The mechanism for the Heck reaction is different from the four reactions discussed previously. The oxidative addition step occurs first as previously, however this is followed by ligand dissociation and coordination of the alkene substrate. A migratory insertion follows, with the final step involving β-hydride elimination to generate the product and a palladium(II) hydride species. The active palladium(0) catalyst is regenerated via reaction of the palladium hydride with a base such as triethylamine.[71] The alkene in this reaction must contain a hydrogen substituent (needed for reductive elimination), therefore tetrasubstituted alkenes cannot undergo Heck reactions. The Heck reaction can be inter- or intra-molecular and can compete with (other) cross-coupling reactions.[71,72]



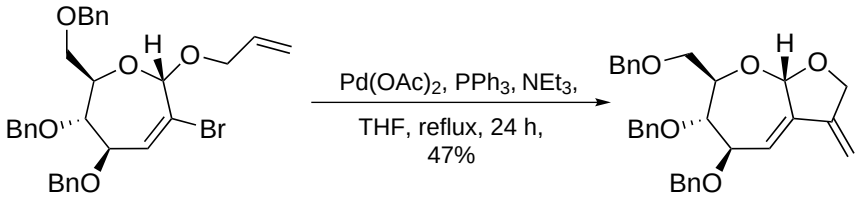
Scheme 1.41 Mechanism for the Heck Reaction

Heck Reactions in Organic Synthesis

There are many examples of Heck reactions in organic synthesis. They are often used as ring closing reactions. The examples that follow show Heck reactions of sugar-derived substrates and in the synthesis of natural products.

Hewitt reported the intramolecular Heck reaction of allyl oxepine **133** upon treatment with palladium acetate, triphenylphosphine and triethylamine in THF at reflux for 24 hours, to form the bicyclic compound **134** in 47% yield.[41] Compound **134** contains a furo[2,3-*b*]oxepine bicycle, which is present in several natural products including fabianane[73] and azadirachtin.[74]

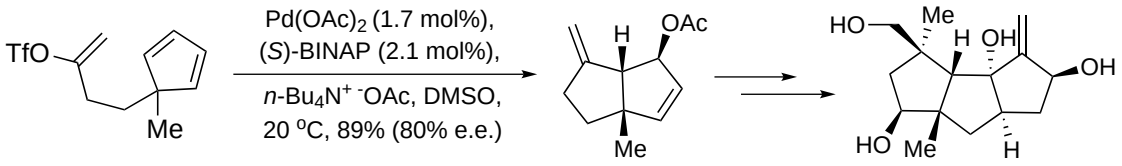
A Heck like reaction (β hydride elimination is replaced by a nucelophilic attack) is a key step in the synthesis of Δ9(12)-capnellene-3β,8β,10α,14-tetraol (**135**) by Shibasaki *et al.*[75] This ring closing reaction began with **136** and formed bicyclic



133 **134**

Scheme 1.42 Heck Reaction of **133** to give Bicyclic Compound **134**[41]

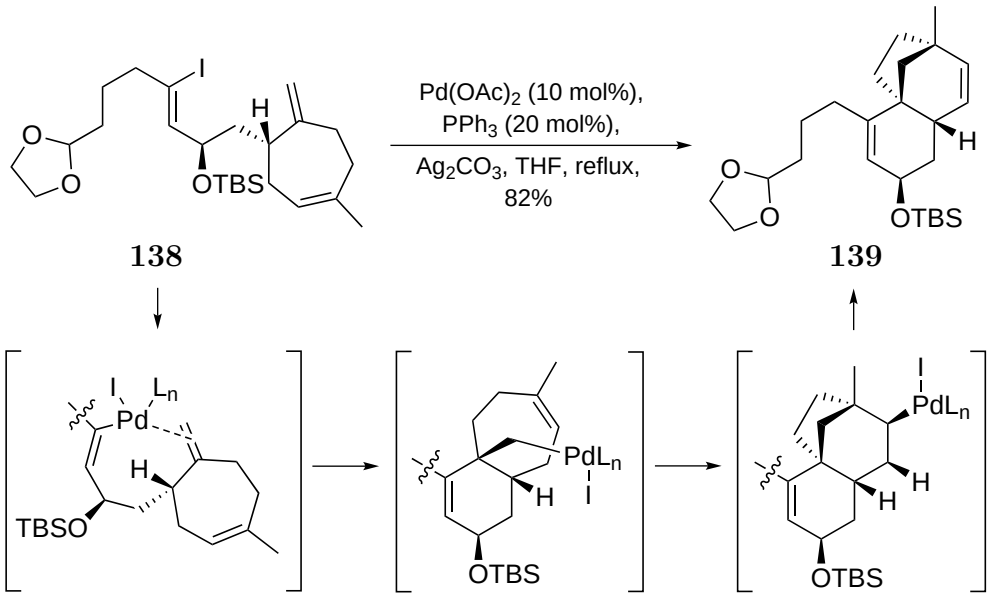
system **137** in 89% yield with 80% e.e. This reaction forms three new chiral centres, with the chirality generated through the use of the chiral (*S*)-BINAP ligands on the palladium catalyst.[75]



136 **137** **135**

Scheme 1.43 Synthesis of Tetraol **135** involving a Heck Reaction[75]

The Heck reaction has also been used in a cascade sequence forming multiple carbon-carbon bonds. Overman *et al.* synthesised three of the four rings of the scopadulcic acid family of diterpenes using two consecutive one pot Heck cyclisation reactions.[76,77] Triene **138** was treated with palladium acetate, triphenylphosphine and silver carbonate in refluxing THF, providing **139** in 82%. This synthesis impressively involves the formation of two quaternary chiral centres.[76,77]



138 **139**

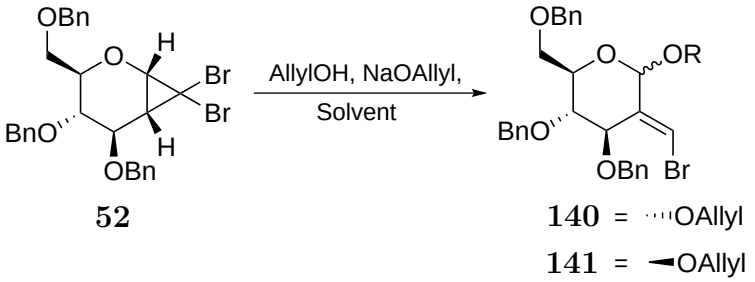
Scheme 1.44 Synthesis of Tricyclic Compound **139**[76,77]

1.4 Research Objectives

The research objectives for this thesis are three-fold: 1) The cyclopropane ring opening reaction that affords 2-*C*-branched pyranosides observed by Harvey and Hewitt[39] will be further explored with emphasis on further functionalisation of the anomeric centre (C-1 position) through the use of alternative nucleophiles and solvents. 2) The mechanism of the cyclopropane ring opening reaction will be investigated further in an attempt to gain evidence about the preferred pathway.[41] 3) Palladium-catalysed cross-coupling of the alkenylbromide products from these cyclopropane ring opening reactions will be utilised to variably functionalise the 2-*C* branch.

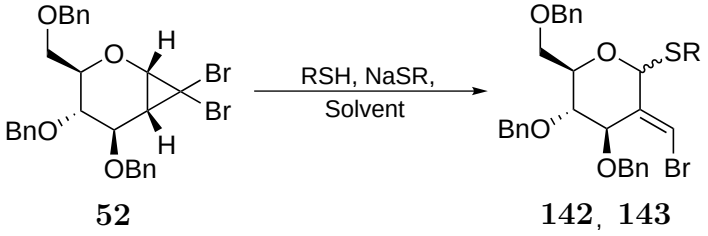
1.4.1 Cyclopropane Ring Opening Reactions

Hewitt has explored the use of several oxygen nucleophiles in the ring opening of cyclopropane **52**, including allyl alcohol (Scheme 1.45). Further optimisation of the cyclopropane ring opening under basic conditions will be attempted with allyl alcohol. Changes in temperature, solvent, additives and addition methods will be explored. Optimisation of the yield of allyl glycosides **140** and **141** is desirable as they will be the substrates for palladium-catalysed cross-coupling reactions.



Scheme 1.45 Cyclopropane Ring Opening of **52** with Allyl Alcohol

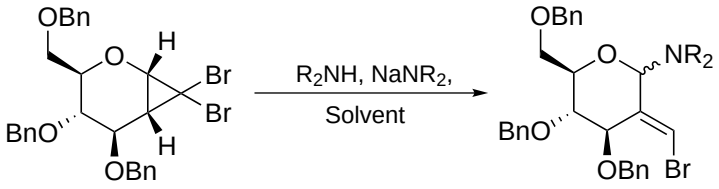
Sulfur nucleophiles will be explored with the aim of producing a range of thioglycosides (**142** and **143**). If successful, further funtionalisation at the anomeric centre through glycosidation reactions or at the 2-*C*-branch with palladium-catalysed cross-coupling reactions could be explored.



Scheme 1.46 Proposed Cyclopropane Ring Opening of **52** with Thiols

Initial exploration of amines was conducted by Hewitt using diethylamine but analy-

sis of these compounds was not completed due their instability.[41] We plan to expand the work on amine nucleophiles by first repeating the reaction with diethylamine with a view to possible extension into a range of secondary amine nucleophiles to obtain a variety of glycosylamines (**144** and **145**).



52 **144**, **145**

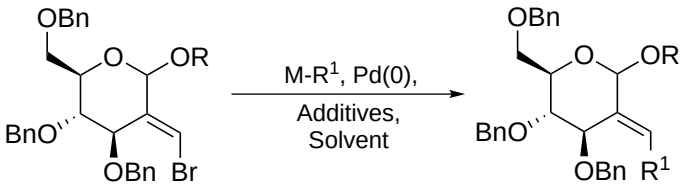
Scheme 1.47 Proposed Cyclopropane Ring Opening of **52** with Amines

1.4.2 Mechanistic Studies

The cyclopropane ring opening reaction of **52** in basic conditions may proceed by several possible mechanisms. We aim to further explore these mechanisms through the use of deuterium labelling reactions and attempted trapping of possible intermediates, such as the postulated cyclopropene.

1.4.3 Palladium-Catalysed Cross-Coupling Reactions

To functionalise the 2-*C*-branch, palladium-catalysed cross-coupling reactions will be explored with substrates **146**. These substrates contain a bromoalkene functionality ideal for cross-coupling reactions. Initially the allyl glycosides **140** and **141** will be explored as they contain the allyl aglycone as an orthogonal protecting group to the benzyl protecting groups. There is precedence for palladium-catalysed cross-coupling reactions as shown by Hewitt (Scheme 1.35).[41] The ultimate goal is production of a library of 2-*C*-branched pyranosides.



146 **147**

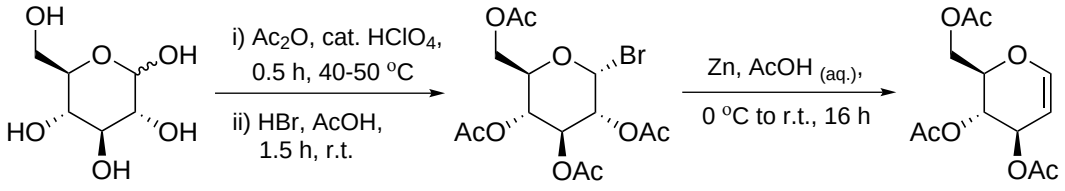
Scheme 1.48 Proposed Palladium-Catalysed Cross-Coupling Reactions

Chapter 2

Synthesis of 2-*C*-Branched Sugars

2.1 Synthesis of Cyclopropanes 52, 152, 50 and 153

1,2-Cyclopropanated carbohydrates can be synthesised through addition of carbenes to glycals as demonstrated by Hoberg, Nagarajan and others (see subsection 1.2.1, page 8). For the purpose of this project, tri-*O*-benzyl-D-glucal (**37**, see Scheme 2.2) was used as a substrate, as there is literature precedence for its cyclopropanation and it is easily accessible from D-glucose (**148**) in five steps. The synthetic methodology for preparing these compounds was pioneered by Emil Fischer and Karl Zach in 1913.[78] Synthesis of **37** began with the peracetylation of D-glucose (**148**) using acetic anhydride and catalytic perchloric acid (Scheme 2.1). Addition of HBr as a 33 wt% solution in acetic acid provided α-bromoglycoside **149** as a white solid. Compound **149** was then dissolved in diethyl ether and reacted with zinc dust in the presence of aqueous acetic acid to provide tri-*O*-acetyl-D-glucal (**150**) in 87% over three steps.

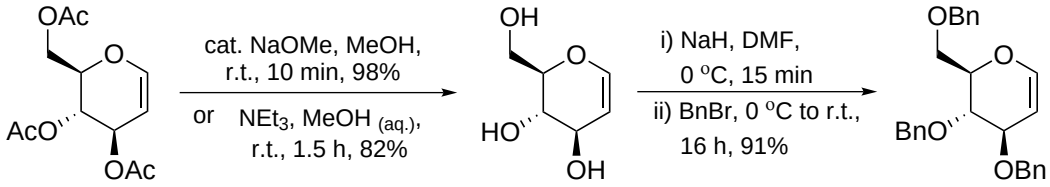


148 **149** **150**

Scheme 2.1 Synthesis of **150**

Deacetylation of **150** was attempted using two different methods. Firstly, use of Kozikowski's procedure,[79] involving treatment of **150** with triethylamine in aqueous methanol, stirring at room temperature for 90 minutes before concentration of the solution, produced **151** as a thick oil. This was isolated as a mixture with residual triethylamine which was removed via its azeotrope with methanol. Subsequent purification by dissolving in methanol and treating with portions of acetone, then

diethyl ether caused precipitation of impurities and provided **151** in 82% yield. The second method used catalytic sodium methoxide in methanol followed by the purification above. This proved to be the superior method, providing **151** in 98% yield with a reaction time of only ten minutes. Reprotection of **151** with benzyl groups provided the desired product, **37**, in excellent yields of up to 91% (Scheme 2.2).

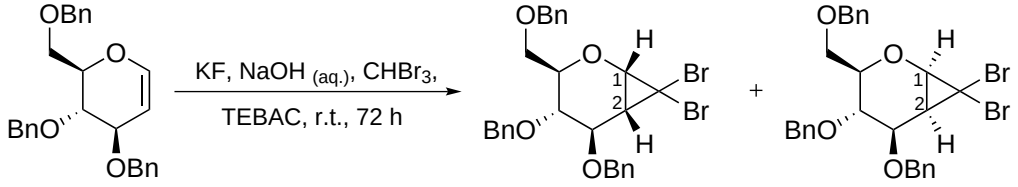


150 **151** **37**

Scheme 2.2 Synthesis of Tri-*O*-benzyl-D-glucal **37**

Nagarajan *et al.* showed that Mąkosza cyclopropanation of glucal **37** using bromoform, TEBAC and 50% aqueous sodium hydroxide failed to form the desired cyclopropane cleanly;[38] Hewitt confirmed this result.[41] However, application of a modification by Mąkosza[80] which used a suspension of potassium fluoride in a dilute solution of sodium hydroxide solution and longer reaction times resulted in formation of the desired cyclopropane **52**. Nagarajan isolated cyclopropane **52** in 84% yield. Hewitt produced cyclopropane **52** in 66% yield, together with a minor cyclopropane, **152**, in 10% yield.[41]

Repetition of this method involved magnetic stirring of the biphasic reaction at room temperature for two days. This resulted in the synthesis of **52** in isolated yields of between 40 and 60% as well as isolation of the minor isomer, **152**, in 8-11% yields. The reaction time was extended to three days which increased the isolated yields of both cyclopropanes, affording maximum yields of 75% for **52** and 11% for **152**.

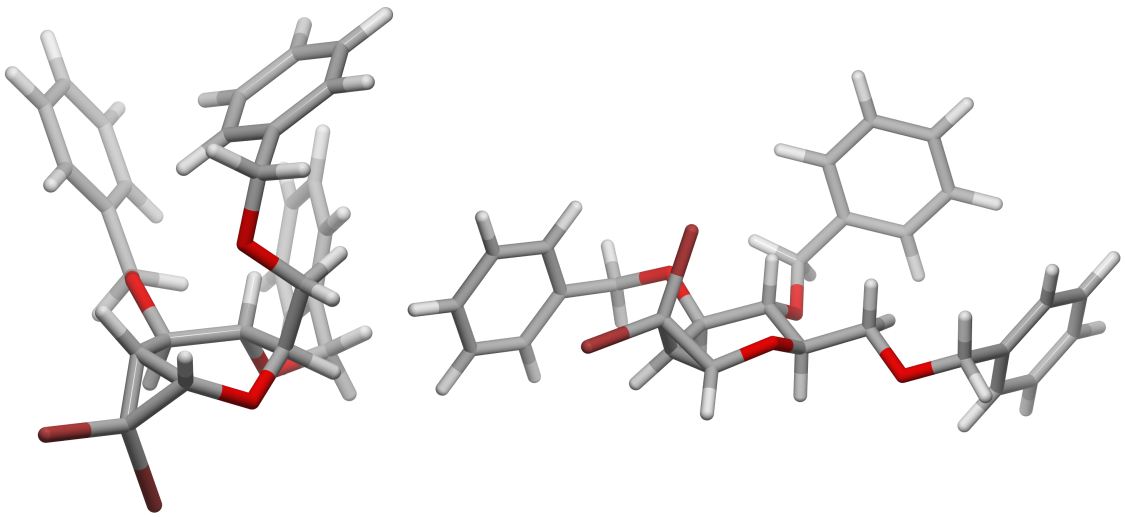


37 75% **52** 11% **152**

Scheme 2.3 Synthesis of Cyclopropanes **52** and **152**

The ^{1}H NMR spectra of the major product **52** matched the data of Nagarajan and Hewitt with characteristic cyclopropane proton peaks at 3.95 ppm (a doublet corresponding to H-1, $^3J_{H-H}$ = 7.8 Hz) and 1.87 ppm (a doublet of doublets corresponding to H-2, $^3J_{H-H}$ = 7.8, 4.9 Hz). Assignment of the minor product as **152** was consistent with the structure proposed by Hewitt with the C-2 proton appearing as a triplet ($^3J_{H-H}$ = 7.9 Hz) at 2.29 ppm. These coupling constants highlight

the fact that these cyclopropane-fused pyranose sugars are not in a chair conformation. Computational modeling of cyclopropanes **52** and **152** using MacroModel[a] confirmed this, with Figure 2.1 below showing the calculated lowest energy conformations of these two cyclopropanes. From these models the H-1–H-2 and H-2–H-3 dihedral angles were generated, with the H-1–H-2 angle for both cyclopropanes being 6° (± 4° for the four lowest energy conformations). The H-2–H-3 dihedral angle for the lowest energy conformer of **52** was 120° (up to 145° for the four lowest enegy conformations). For **152**, the H-2–H-3 dihedral angle was 8° (± 4° for the four lowest conformations). According to the Karplus equation[81] the dihedral angles generated are consistent with the $^{3}J_{H-H}$ = 7.8 Hz coupling in H-2 observed for **52** between protons H-1 and H-2, and the $^{3}J_{H-H}$ = 4.9 Hz coupling between protons H-2 and H-3. In contrast, the triplet for H-2 ($^{3}J_{H-H}$ = 7.9 Hz) in **152** is consistent with the similar dihedral angles between H-1–H-2 and H-2–H-3, providing strong evidence for the assigned structures. These assignments are also consistent with the majority of dibromocarbene addition occurring from the less sterically hindered face, in this case the α-face.



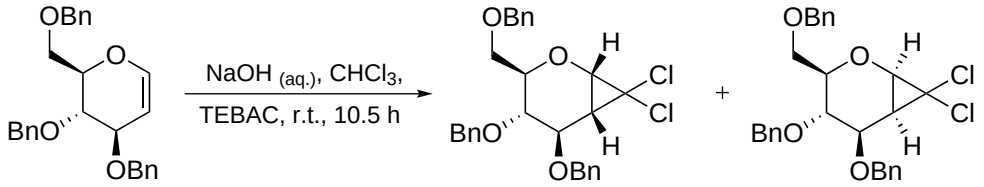
(a) **52** (b) **152**

Figure 2.1 Cyclopropanes **52** and **152**

To explore the rate dependence of the base-mediated cyclopropane ring opening reaction on leaving group identity, we aimed to synthesise similar *gem*-dichloro- and *gem*-diiodo-cyclopropanes. These would be tested in cyclopropane ring opening reactions using basic/nucleophilic conditions similar to those used to ring open cy-

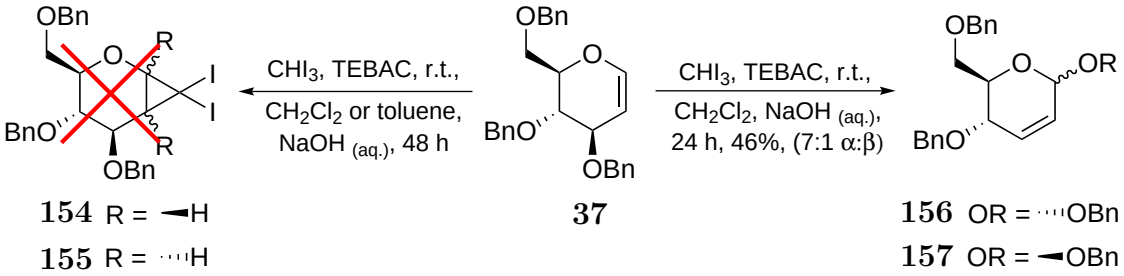
[a]Conformational searches were done with a mixed torsional/low mode sampling method as implemented in MacroModel (version 9.7, Schrödinger, LLC, New York, NY, 2009), running over 80000 steps, saving all structures in a 10 kJmol^{-1} window of the calculated global minimum using OPLS_2005 forcefield, a constant dielectric (1), in a vacuum. Minimisation was carried out through 5000 iterations or to a convergence threshold of 0.001 (kJmol^{-1}Å^{-1}) - all of the structures terminated on the convergence limit. Images were generated using: CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org).

clopropane **52**. This would give an indication as to whether the leaving halide had any effect on the rate of reaction. Along with the synthesis of **52** Nagarajan reported the synthesis of a series of *gem*-dichlorocyclopropanes,[38] including that of **50** from **37** in 84% yield using Mąkosza cyclopropanation at 35 °C for four hours. Synthesis of **50** was attempted at room temperature, with the expectation of a longer reaction time at the lower temperature, which was observed. The major product (**50**) was isolated in 60% yield, matching previously reported spectral data; while a minor isomer, **153**, was isolated in 15% yield (Scheme 2.4). ^{1}H NMR analysis of the minor cyclopropane **153** shows the C-2 proton resonates as a triplet ($^3J_{H-H}$ = 8.0 Hz) at 2.05 ppm. As with *gem*-dibromocyclopropane **152**, the coupling constant of 8.0 Hz between H-2 and H-3 suggests they are on the same face of the pyran ring. Mass spectral results provided [M+Na]$^+$ = 521.1271, with the characteristic Cl_2 isotope pattern and suitable for the molecular formula $C_{28}H_{28}O_4^{35}Cl_2$. These results are consistent with the proposed structure **153**.



Scheme 2.4 Synthesis of Cyclopropanes **50** and **153**

The synthesis of *gem*-diiodocyclopropane **154** (along with minor cyclopropane **155**) was then attempted. This would provide a series of three *gem*-dihalocyclopropanes on which to test the leaving group effect. There are very few reports of *gem*-diiodocyclopropanes in the literature, most likely due to their high reactivity.[7] Three different methods were attempted, with all three using iodoform and aqueous sodium hydroxide. Where the methods differed was in the organic solvent used (required as iodoform is a solid at room temperature where as bromoform and chloroform are liquids) and whether the Mąkosza modified method, using a suspension of potassium fluoride in a weaker solution of sodium hydroxide, was used. The first two methods used toluene and dichloromethane as solvents and the Mąkosza modified method. Both reactions were stirred for two days at room temperature; however no reaction was observed, with starting material recovered (Scheme 2.5). A third method was employed using dichloromethane and a 50% aqueous sodium hydroxide solution. After 24 hours, no reaction was observed by TLC analysis; however the ^{1}H NMR spectrum of the crude reaction mixture showed complete consumption of the starting material, with predominantly one compound formed. The material formed was not a *gem*-diiodocyclopropane but an inseparable anomeric mixture of 2,3-unsaturated benzyl glycosides **156** and **157** (7:1 α:β) in 46 % yield.



154 R = H

155 R = H

37

156 OR = OBn

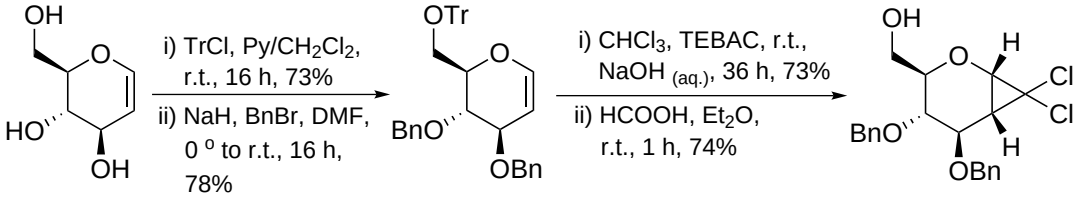
157 OR = OBn

Scheme 2.5 Attempted Synthesis of Cyclopropanes **154** and **155**

It is proposed that **156** and **157** formed through a Ferrier rearrangement that is promoted by either iodoform or iodine generated from iodoform. Iodine is known to act as a Lewis acid in the Ferrier rearrangement, with the benzyl alcohol thus released able to quench the oxonium intermediate formed. While iodine is not a commonly used Lewis acid, there are examples in the literature where it has been used.[82] At this stage, further attempts to obtain **154** were abandoned.

2.2 Synthesis of Cyclopropane 158

In an attempt to explore the base-mediated cyclopropane ring opening mechanism, cyclopropane **158** was synthesised. This compound has been previously prepared by Nagarajan through the cyclopropanation of glucal **159** followed by deprotection of the trityl ether under acidic conditions (Scheme 2.6).[38] Literature methods[83] were used to synthesise **159** through selective trityl protection of the 6-OH position in **151**, followed by benzylation of 3- and 4-OH positions.

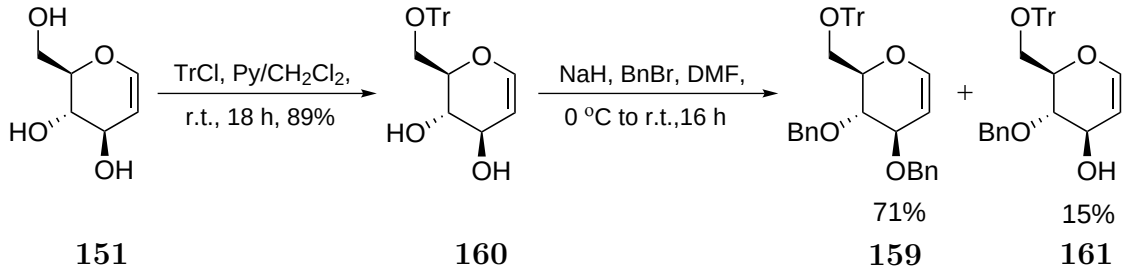


151 **159** **158**

Scheme 2.6 Nagarajan's Synthesis of Cyclopropane **158**[38]

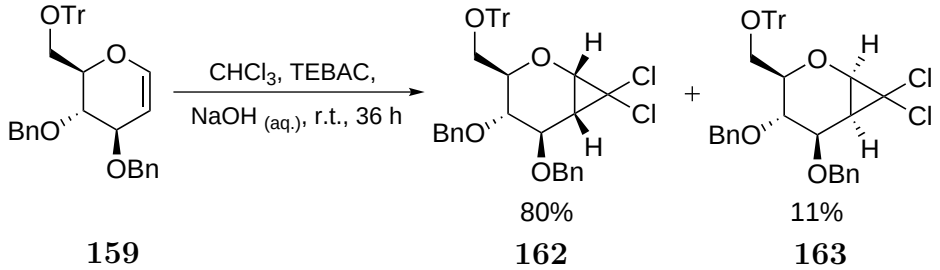
Firstly, repetition of Schmidt *et al.* trityl and benzyl protection sequence was performed, providing **159** in good yield. Selective protection of the primary hydroxyl (6-OH) of D-glucal (**151**) was performed by adding trityl chloride to **151** in a solution of pyridine/dichloromethane (1:1 mixture). The reaction proceeded in high yield (89%) to give the known trityl ether **160** (Scheme 2.7).[83] The remaining hydroxyl groups (3- and 4-OH) were benzylated using sodium hydride and benzyl bromide. The literature method reported used less than two equivalents of benzyl bromide, making benzyl bromide the limiting reagent. With no foreseeable rea-

son to use fewer than 2 equivalents, 2.6 equivalents were used, making the limiting reagent glucal **160**, rather than benzyl bromide. This resulted in a 71% yield of **159**, similar to that reported by Schmidt. A second product, a monobenzylated glucal **161** was also isolated in 15% yield. We expected benzylation to occur first at the sterically less-hindered 3-OH; however the mono-benzylated product was the 4-OBn compound **161** (according to HMBC NMR data).



Scheme 2.7 Synthesis of **159**

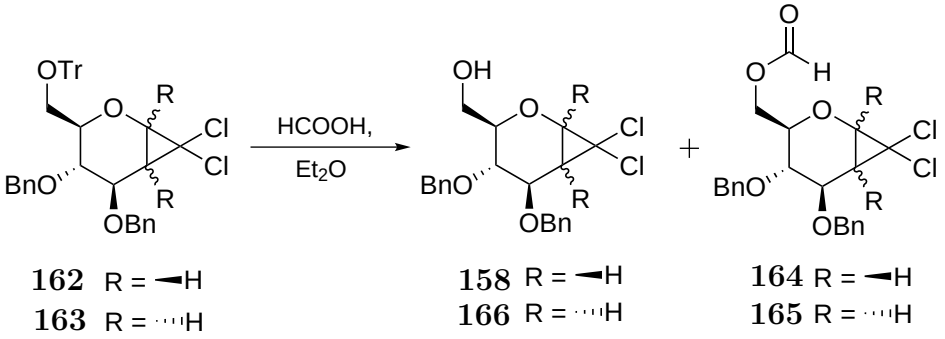
Cyclopropanation of **159** using Nagarajan's method[38] resulted in the synthesis of cyclopropanes **162** and **163** in 80% and 11% yields, respectively (Scheme 2.8). As with the cyclopropanes previously discussed in section 2.1 (page 31), the two isomeric cyclopropanes can be distinguished in the ^{1}H NMR spectrum with the H-2 proton of the major product appearing as a doublet of doublets ($^3J_{H-H}$ = 7.8, 4.9 Hz) at 1.87 ppm, and in the case of the minor product, as triplet ($^3J_{H-H}$ = 7.7 Hz) at 2.12 ppm. As with the above-mentioned compounds, the major product is assigned as **162** with the cyclopropane on the sterically less hindered bottom (α) face. The minor product contains a triplet ($^3J_{H-H}$ = 7.7 Hz) similar to **152** and **153** and is therefore assigned as **163**. The minor cyclopropane **163**, as with **153**, has not previously been reported. The relative amount of the minor cyclopropane has also decreased, likely resulting from the increased steric bulk on the top face of the glucal due to the trityl protecting group which hinders carbene attack from above.



Scheme 2.8 Synthesis of **162**

Nagarajan used formic acid in diethyl ether, a known literature method, to deprotect the trityl group.[38,84] Repeating this procedure with an 8:1 mixture of **162**:**163** was unsuccessful, as after several hours the reaction was incomplete, with significant amounts of cyclopropane **162** remaining. The reaction was therefore left for 16

hours, which produced three products: the previously reported **158** (22%) and two an unexpected products **164** (45%) and **165** (8%) (no **166** was isolated, Scheme 2.9).



Scheme 2.9 Deprotection of **162** and **163** and the Unexpected Formation of **164** and **165**

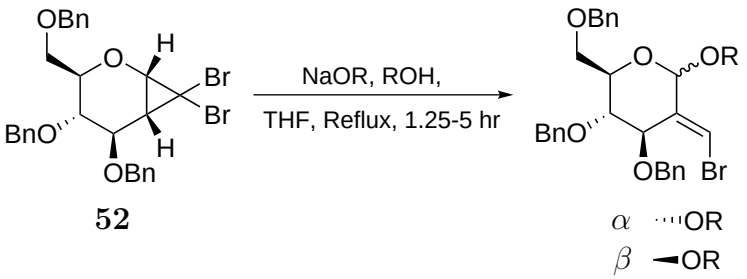
The cyclopropanes **164** and **165** arise from the reaction of alcohols **158** and **166** with formic acid under the acidic conditions. Analysis of the work-up process highlighted the problem, as the crude reaction mixture was concentrated to remove the diethyl ether before quenching the acid. This exposed alcohols **158** and **166** to concentrated formic acid, excellent conditions for ester formation. Altering this work-up to include a separation between dichloromethane and water resulted in an increased isolated yield (up to 61%) of alcohol **158**. Alcohol **158** was used in the cyclopropane ring opening reactions as described in subsection 2.8.3 (page 80).

2.3 Cyclopropane Ring Opening Reactions with NaOAllyl/AllylOH

Work by Harvey and Hewitt identified the products from the cyclopropane ring opening reactions of cyclopropanes **52** and **152** with K_2CO_3 in refluxing methanol as **55** and **56**.[39] Further exploration of basic/nucleophilic conditions allowed optimisation by the use of sodium methoxide and methanol in refluxing THF for 1.5 hours, producing 2-*C*-branched anomers **55** and **56** in a 2.3:1 ratio. This method was then expanded to include the use of sodium allyloxide/allyl alcohol, providing glycosides **140** and **141** in a 2.3:1 ratio, and sodium benzyloxide/benzyl alcohol, providing glycosides **167** and **168** in a 1:1.1 ratio (Table 2.1).[39]

Further optimisation of the synthesis of allyl glycosides **141** and **140** was attempted to obtain higher yields and facilitate their use in palladium cross coupling reactions (see section 2.9). Ring opening reactions using allyl and methyl alcohols were also performed to obtain information on the mechanism of the cyclopropane reaction in the hope of gaining evidence in favour of one reaction mechanism.

Table 2.1 Harvey and Hewitt Cyclopropane Ring Opening Reaction with **52**[39]



52

R	Glycosides (α, β)	% Yield (α, β)	Anomer Ratio (α:β)
Me	**55**, **56**	49, 22	2.3:1
Allyl	**140**, **141**	49, 22	2.3:1
Bn	**167**, **168**	30, 33	1:1.1

Repetition of Harvey and Hewitt's procedure for cyclopropane ring opening of **52** with sodium allyloxide and allyl alcohol provided **140** and **141** in similar yields (60-70%). To confirm the anomeric assignments of these glycosides, 1D NOESY experiments were performed. Use of deuterated chloroform as an NMR solvent failed to allow this confirmation due to lack of resolution between the H-5 and H-4 signals, and the H-6a and H-6b signals. Use of benzene-d_6 as the NMR solvent did not suffer this resolution problem (Figure 2.2), and irradiation of H-5 in **141** showing significant nOe enhancement of the H-1 and H-3 signals with very similar intensity (Figure 2.3). Irradiation of H-1 complimented this result showing enhancement of H-3 and H-5. This is strong evidence that all three protons (H-1, H-3 and H-5) are on the same face of the molecule, indicating that **141** is the β-anomer (Figure 2.4).

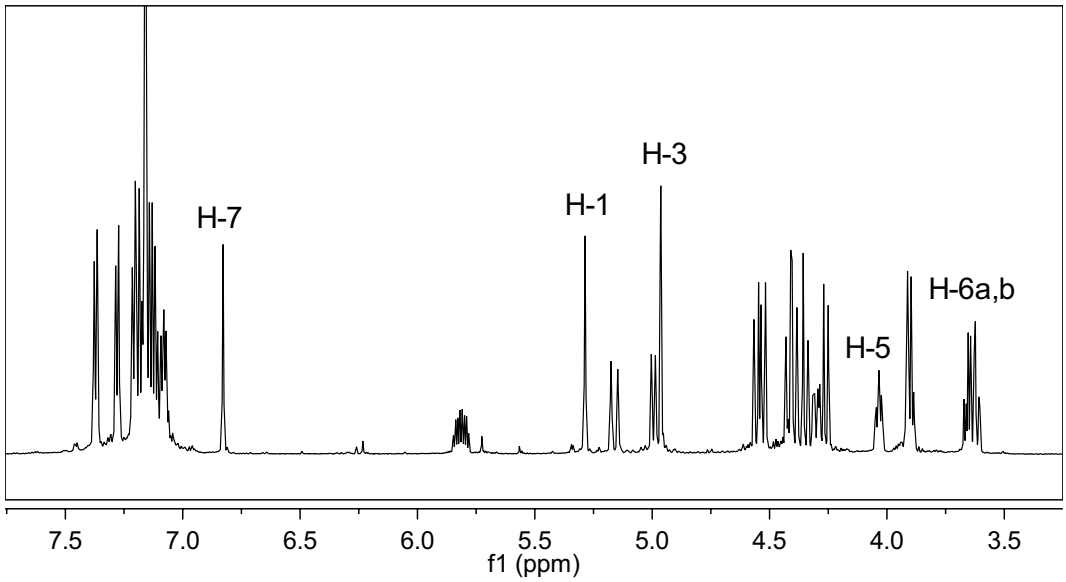


Figure 2.2 ^{1}H NMR spectrum of **141** in C_6D_6 (500 MHz)

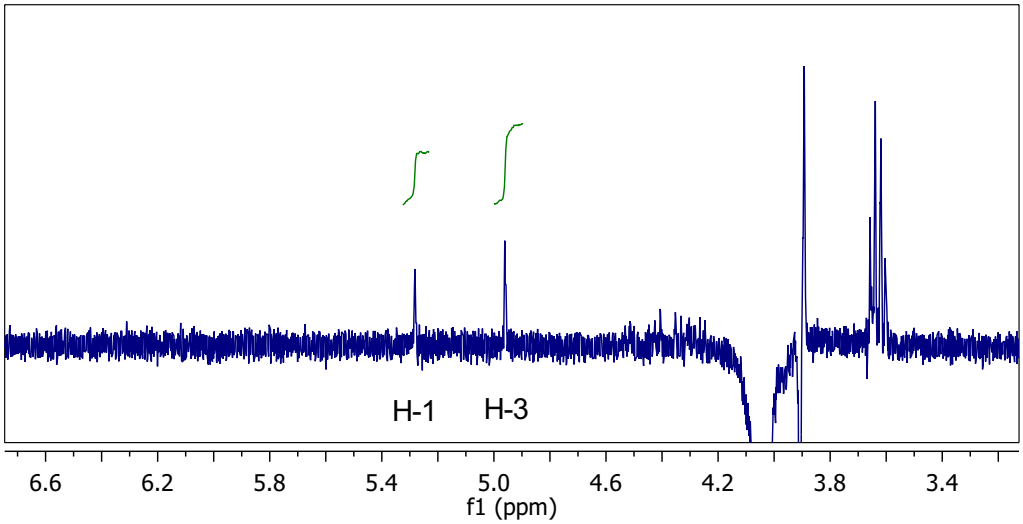
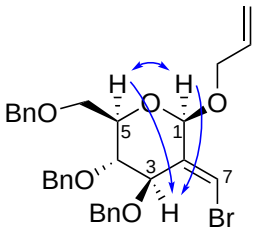


Figure 2.3 nOe Correlations Irradiating H-5

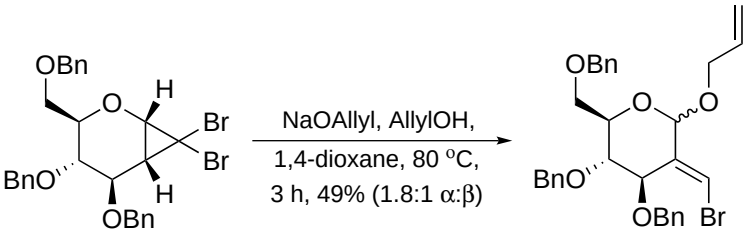


141

Figure 2.4 nOe Correlations in **141**

Optimisation of the formation of **140** and **141** was first explored through the use of increased reaction temperature and, secondly, by introducing a silver(I) salt. As shown in subsection 1.1.2 (page 3), we would expect cyclopropane ring expansions to occur under these conditions, however work by Hewitt showed that ring expansion of **52** required the use of both 100 °C and a silver(I) salt. To synthesise **140** and **141**, a reaction at 80 °C was explored using the alternative solvent 1,4-dioxane (THF boils at 66 °C), which has similar ether properties to THF but has a higher boiling point of 101 °C. The reaction procedure followed was that of Harvey and Hewitt,[39] with the addition of solid cyclopropane to a solution containing sodium allyloxide and allyl alcohol in 1,4-dioxane, followed by heating the reaction to 80 °C (Scheme 2.10). The reaction was complete in three hours, faster than when using THF reflux (five hours); however, the yield of reaction was lower at only 49% and with a similar anomeric ratio (1.8:1 α:β).

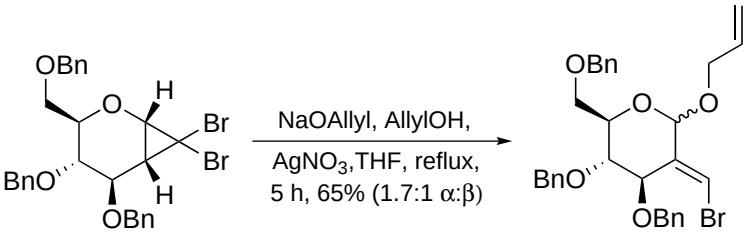
The use of a silver(I) nitrate was then explored employing dark conditions and using refluxing THF as solvent. This resulted in cyclopropane ring opening of **52**, providing a mixture of the desired products **141** and **140** in a combined yield of 65% (1.7:1 ratio). The reaction time of five hours was the same as reactions without the silver(I) additive, and with no trace of oxepine formation it suggests that the



52 **140, 141**

Scheme 2.10 Cyclopropane Ring Opening of **52** using Increased Temperature

silver(I) salt had no effect on the reaction mechanism.

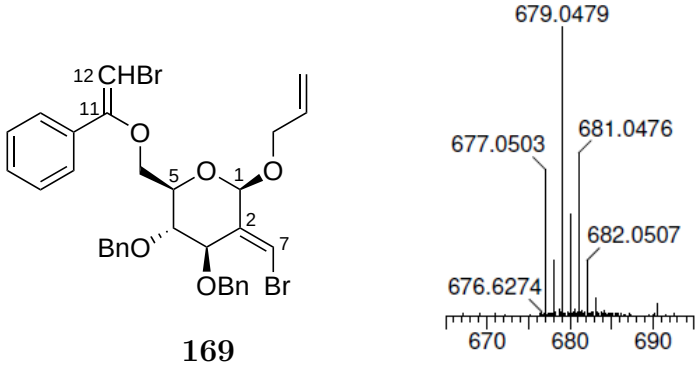


52 **140, 141**

Scheme 2.11 Cyclopropane Ring Opening of **52** using Silver Nitrate

With only modest results, in terms of yields of **140** and **141**, under the standard reaction conditions of THF reflux, a development was made when the crude reaction mixture, foregoing the aqueous work-up, was loaded onto a silica chromatography column after being concentrated under reduced pressure. While the yield of the reaction proved to be similar to that reported by Hewitt, a third product was isolated in 3-8% quantities. The structure of this product was eventually elucidated as the dibromide **169** (Figure 2.5) through use of mass spectrometry, 1D and 2D NMR experiments. Identification of this product was difficult, as it had an identical R_f value to that of the starting cyclopropane **52** ($R_f = 0.40$ (9:1 hexanes:ethyl acetate)) and it often decomposed before characterisation when exposed to air or water. Dibromide **169** had ^{1}H and ^{13}C NMR spectra very similar to allyl glycoside **141**, with the exceptions that it had two fewer benzyl protons and an additional singlet peak at 5.83 ppm. In the ^{13}C NMR spectrum, compound **169** differs from **141** in having two additional carbon signals at 89.7 and 157.3 ppm and the loss of one benzyl carbon (77-75 ppm). HSQC experiments showed that the peak at 5.83 ppm was attached to the carbon at 89.7 ppm and that the carbon at 157.3 ppm was not protonated. HMBC experiments showed the proton at 5.83 ppm coupled to the carbon peak at 157.3 ppm with no other couplings involving these peaks in the 2D NMR data (COSY, HMBC). 1D nOe experiments performed by irradiating the singlet at 5.83 ppm provided no further information. From analysis of the remaining data it was determined that the altered benzyl protecting group was at 6-OH. This was determined from the HMBC correlations between the benzyl protons of the two remaining benzyl groups and the C-3, C-4 signals. Mass spectrometry of

the compound gave m/z $[M+Na]^+ = 677.0503$, and a distictive Br_2 isotope patern suitable for the molecular formula $C_{32}H_{32}O_5^{79}Br_2Na^+$, consistent with structure **169**.

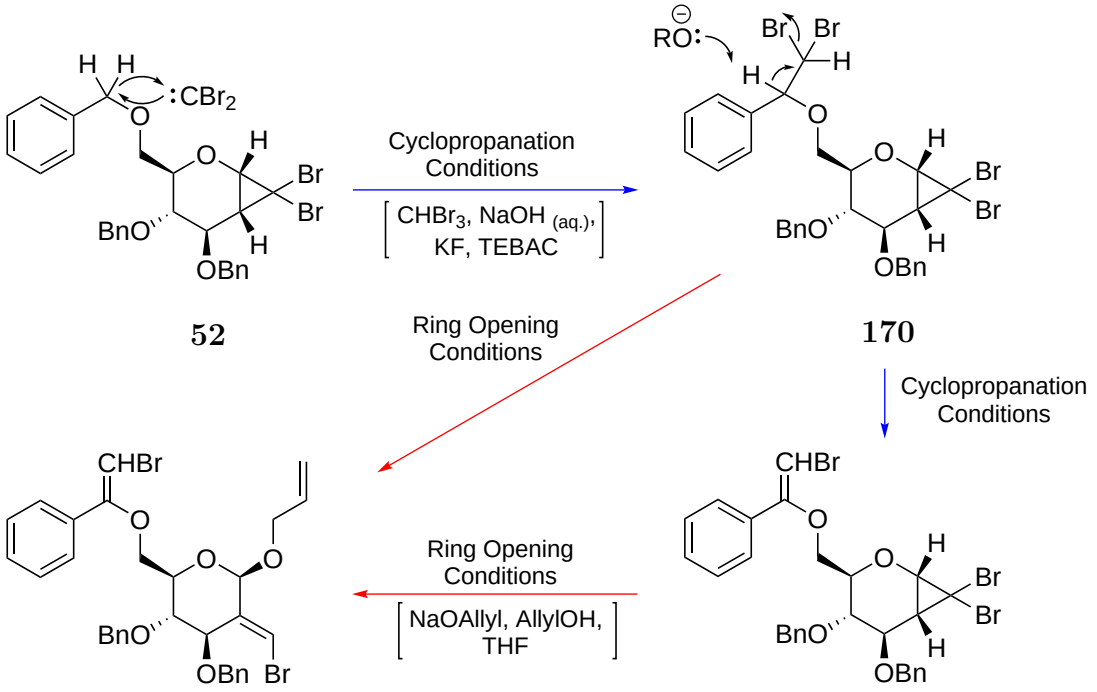


169

Figure 2.5 Structure and Partial Mass Spectrum of **169**

The anomeric configuration of **169** was assigned as β based on the spectral similarities to compound **141** and an nOe correlation between the H-1 and H-5 when irradiating H-1. The α-anomer was not obtained as it was either formed in too small an amount or it degraded. The *E*-configuration of the C-2–C-7 bromoalkene was assigned on the basis of 1D nOe correlations between H-1 and H-7, consistent with the geometry of the bromoalkenes **140** and **141**. The geometry of the C-11–C-12 bromoalkene is unknown as 1D nOe experiments irradiating H-12 resulted in no correlations. Scheme 2.12 demonstrates possible pathways for the formation of **169**. It has been shown in the literature that carbenes can insert into active carbon-hydrogen bonds.[85] Dibromocarbenes generated under Mąkosza cyclopropanation conditions could insert into C-H bonds of the benzyl protecting groups. Insertion into the C-6 benzyl group would produce tetrabromide **170** which could undergo elimination to **171** under the basic conditions of the Mąkosza reaction. Upon isolation of either **170** or **171** with cyclopropane **52**, **169** would arise from the basic conditions (sodium allyloxide) used to ring opening the cyclopropane. Di-adduct **170** may have formed due to the increased reaction time of the cyclopropanation (three days extended from two days); however **169** is a minor contaminant and is not likely to affect the mechanism of the cyclopropane ring opening reaction or be of synthetic interest.

To further optimise the synthesis of **140** and **141**, the solubility of both **52** and sodium allyloxide was enhanced by addition of the cyclopropane **52** to the sodium allyloxide/allyl alcohol as a solution in THF instead of addition in solid form. Initially, both solutions (cyclopropane in THF and allyl alcohol/sodium allyloxide in THF) were heated to 40 °C before the cyclopropane solution was injected into the basic solution. This method resulted in a significant decrease in reaction time, with the reaction complete according to TLC analysis as soon as a sample was taken (*ca.*



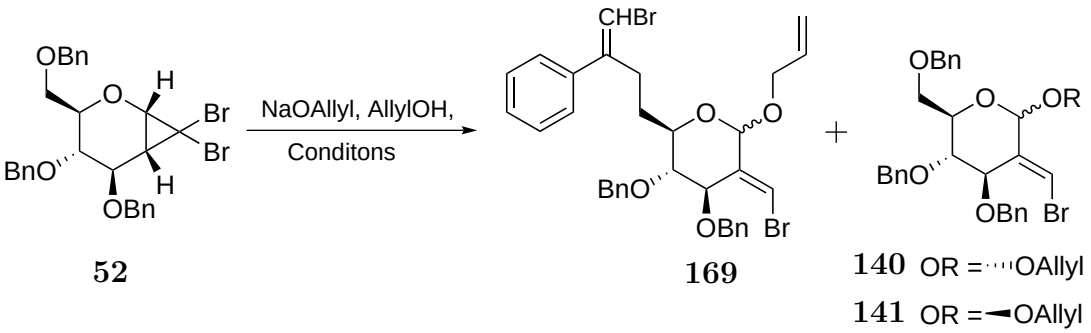
Scheme 2.12 Proposed Mechanism of Formation of **169**

10 minutes). Repeating this injection technique for solutions at room temperature and at 0 °C resulted in longer reaction times (40 hours); however small increases in yield occurred with decreasing temperature. The yields obtained were marginally greater than those obtained by Harvey and Hewitt and are summarised in Table 2.2.

Two alternative solvents were explored: DME (1,2-dimethoxyethane) and DMF (*N*,*N*-dimethylformamide). Firstly, a reaction was carried out at room temperature with DME as solvent, using the injection method as discussed previously. This resulted in complete consumption of starting material (**52**) in one hour providing a mixture of allyl glycosides **140** and **141** (1.2:1 α:β) in a combined yield of 74%. When DMF was used as a solvent at room temperature, using the injection method, rapid consumption of the starting material (*ca.* 30 minutes) resulted. However, isolation of the glycoside products was problematic as removal of the DMF (using an aqueous sat. copper sulfate wash) resulted in a significant loss of material, providing a complex mixture of products in 13% crude yield. The reaction was not purified nor the use of DMF as a solvent explored any further. All the results from the ring opening of cyclopropane **52** with allyl oxide and allyl alcohol are shown in the table below (Table 2.2).

While both anomeric cyclopropanes **52** and **152** undergo the cyclopropane ring opening reaction under nucleophilic/basic conditions, to give the same products, the reaction with **152** is considerably slower.[41] This was indicated by the work of Hewitt and reiterated in this work. A 1.05:1 mixture of cyclopropanes **52** and

Table 2.2 Cyclopropane Ring Opening with NaOAllyl/AllylOH

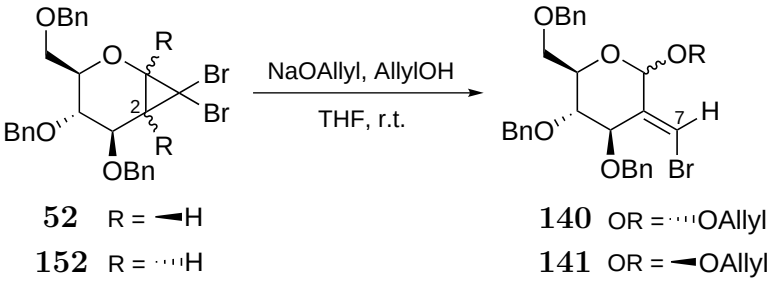


Solvent	Conditions	Time (h)	**169**	**140**	**141**	Total % (**140** + **141**)	α:β
1,4-Dioxane	80 °C	3	-	31	18	49	1.9:1
THF	$AgNO_3$, reflux	6	-	41	24	65	1.7:1
THF	Injection, 40 °C	0.17	2	41	21	62	1.9:1
THF	Injection, r.t.	40	3	32	38	70	1:1.2
THF	Injection, 0 °C to r.t.	40	5	34	39	73	1.2:1
DME	Injection, r.t.	1	8	39	33	74	1.2:1
DMF	Injection, r.t.	0.3	-	-	-	-	-

152 was dissolved in THF and injected into a solution of THF containing sodium allyloxide and allyl alcohol. The resulting mixture was stirred at room temperature for 60 hours, during which aliquots of 50 μL were removed at relevant time intervals for analysis and displayed the slower reaction of the minor cyclopropane. Table 2.3 below shows the integrals from relevent peaks relating to each species; cyclopropanes **52** and **152** were measured by integration of their H-2 signals, and allyl glycosides **140** and **141** by integration of their H-7 signals. The four spectra shown in Figure 2.6 are entries 1, 2, 3 and 7 from Table 2.3 showing firstly, the mixture of cyclopropanes before their addition to the reaction mixture (A). Secondly, the reaction after 30 minutes showing approximately 50% consumption of **52** with the majority of **152** remaining (B). Thirdly, the reaction after four hours showing the complete consumption of cyclopropane **52** with the majority of **152** remaining (C). Thirdly, the reaction after 60 hours showing incomplete consumption of **152** (D). For this reason, all other cyclopropane ring opening reactions explored utilised the major cyclopropanes such as **52**. The mechanistic consequences of this reaction will be discussed further in section 2.8 (page 66).

The leaving group dependence of chloride vs bromide was explored through reaction of *gem*-dichlorocyclopropane **50** with sodium allyloxide/allyl alcohol. A solution of **50** in THF was injected into a THF solution containing sodium allyloxide and allyl alcohol and the reaction stirred at room temperature for five days. This resulted in the formation of only trace amounts of the allyl glycosides **172** and **173**, with the majority of the material being unreacted cyclopropane starting material **52**. Repetition of a modified procedure in which, after the addition of cyclopropane **50** the

Table 2.3 Competitive Cyclopropane Ring Opening of **52** and **152** with NaOAllyl/AllylOH



52 R = H
152 R = H
140 OR = OAllyl
141 OR = OAllyl

Entry	Time (hr)	**52**	**152**	**141**	**140**
1	0	51.5	48.5	0	0
2	0.5	25	48	11	16
3	4	0	48	25	27
4	24	0	45	28	27
5	36	0	43	29	28
6	48	0	39	31	30
7	60	0	38	32	30

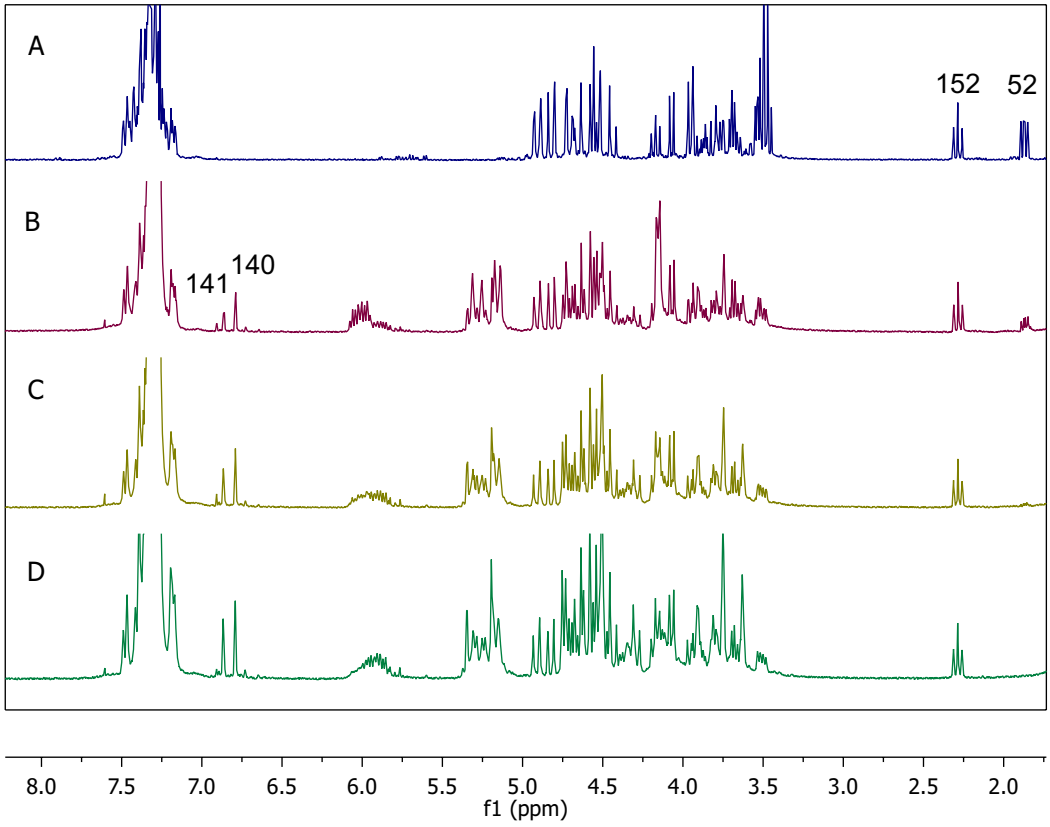
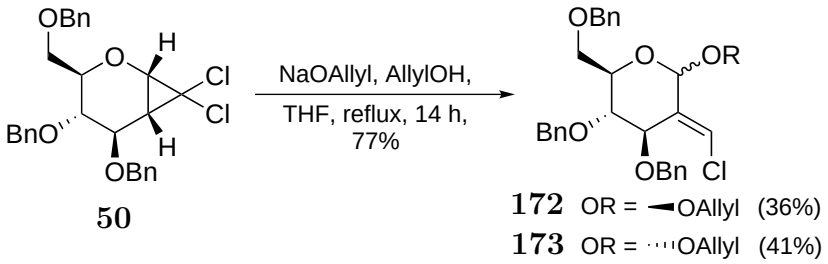


Figure 2.6 ^{1}H-NMR Spectra of a Mixed Cyclopropane Ring Opening Reaction at t = 0 (A), 0.5 (B), 4 (C) and 60 (D) hours

THF solution was heated to reflux, resulted in complete consumption of starting material after 14 hours, forming **172** in 36% and **173** in 41% yield (combined yield 77%, Scheme 2.13). Ring opening of *gem*-dichlorocyclopropane **50** was significantly slower than ring opening with gem-dibromocyclopropane **52** suggesting there is a leaving group dependence (Br^- vs Cl^-). This will be discussed in more detail in sec-

tion 2.8 (page 66). Due to the slow reaction of the major *gem*-dichlorocyclopropane isomer **50**, and the minor *gem*-dibromocyclopropane **152**, ring opening of the minor *gem*-dichlorocyclopropane **153** was not explored.



50

Scheme 2.13 Cyclpropane Ring Opening of **50**

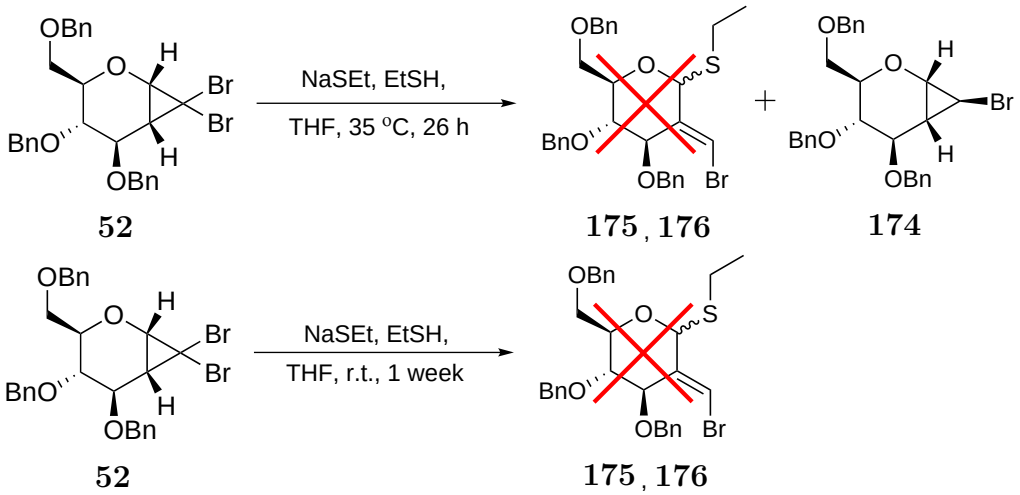
2.4 Cyclopropane Ring Opening Reaction with Thiols

Thioglycosides were first reported by Fischer in 1909[78] and are well known for their orthogonality under a variety of protecting group manipulation conditions. Their glycosidation reactions have been well researched and a variety of promoters/catalysts have been used, most notably *n*-iodosuccinimide (NIS) and silver triflate.[86] Thioglycosides are typically synthesised by reacting a peracetylated sugar with a thiol under Lewis acidic conditions, commonly with $BF_3 \cdot EtO_2$.

We envisaged the synthesis of thioglycosides could take place by reacting **52** with mixtures of thiols and their corresponding sodium thiolates. In DMSO, thiols such as thiophenol (pKa = 10.3),[87] benzylthiol (pKa = 15.4)[87] and butanethiol (pKa = 17.03)[87] are more acidic than alcohols such as methanol (pKa = 29.0),[88] isopropanol (pKa = 30.3)[88] and phenol (pKa = 18.0).[89] All of these compounds are more acidic than water (pKa = 31.4).[88] This suggests sodium thiolates are less basic that the corresponding sodium alkoxides, however, thiols are better nucleophiles, sulfur being a softer atom type than oxygen. Therefore it was not certain whether cyclopropane ring opening would occur and, if so, whether 2-*C*-branched thioglycosides or thiooxepines would be the predominant product.

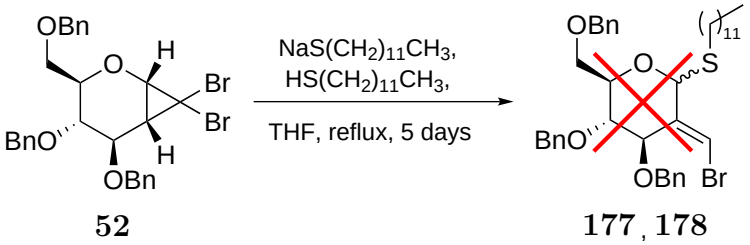
Exploration began with the use of ethanethiol and sodium ethanethiolate in THF at two different temperatures: 35 °C (ethanethiol reflux) and room temperature (Scheme 2.14). The sodium ethanethiolate was synthesised using the same method as sodium alkoxides, where the alcohol is treated with sodium hydride. Ethanethiol is a volatile compound with a boiling point of 35 °C; adding sodium hydride slowly to this compound generates heat, causing evaporation of the ethanethiol. While this was controlled (cooling in ice and fitting with a reflux condenser), the low boiling

point of ethanethiol is experimentally problematic for ring opening reactions, as previous work using alcohols showed that long reaction times and/or the use of heat were needed to ring open cyclopropane **52**. The reaction heated to 35 °C showed TLC evidence of products forming: two slower moving spots were observed after four hours. After 22 hours a third product was seen by TLC and after 26 hours complete consumption of **52** was observed. The ^{1}H NMR spectrum of the crude reaction mixture showed a complex mixture of compounds including some which appeared to contain alkene protons. The one compound that was identified was the monobromocyclopropane **174** (9%) which had previously been synthesised by Hewitt through other means.[41] The reaction at room temperature showed no reaction by ^{1}H NMR spectroscopy after one week.



Scheme 2.14 Cyclopropane Ring Opening of **52** with Ethanethiol

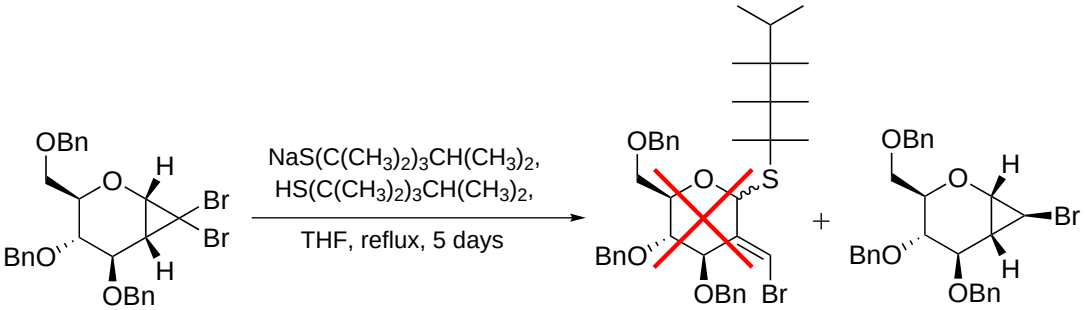
Exploration of higher boiling point thiols began with *n*-dodecanethiol. The experimental problems of ethanethiol were alleviated as *n*-dodecanethiol has a boiling point of 274-278 °C. The injection method was used whereby a portion of *n*-dodecanethiol was treated with sodium hydride, the resulting mixture diluted with THF and treated with a solution of cyclopropane **52** in THF. The solution was heated to reflux and stirred for five days (Scheme 2.15). ^{1}H NMR spectroscopy of the resulting residue showed starting material **52** and *n*-dodecanethiol as well as several other compounds which did not contain any alkene or sugar functionalities.



Scheme 2.15 Cyclopropane Ring Opening of **52** with *n*-Dodecanethiol

A third highly branched thiol, *t*-dodecanethiol (2,3,3,4,4,5-hexamethylhexane-2-thi-

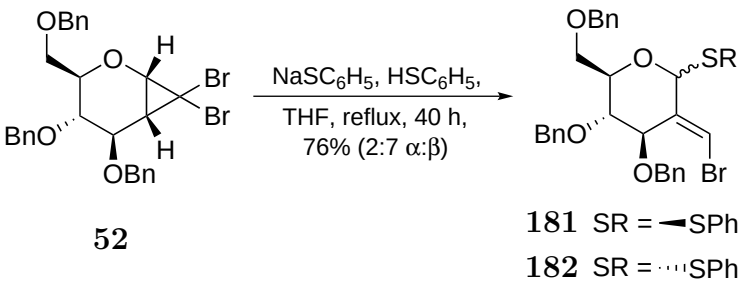
ol), was explored. It has similar desirable physical properties to *n*-dodecanethiol: it is liquid at room temperature and has a boiling point of over 200 °C. Using the injection method described above, *t*-dodecanethiol was treated with sodium hydride, diluted with THF, a solution of cyclopropane **52** was injected and the reaction heated to reflux. After five hours at reflux, several new products were observed by TLC, with the reaction determined to be complete after eight hours (Scheme 2.16). The ^{1}H NMR spectrum showed only traces of starting material cyclopropane **52** remaining, some monobromide **174** (10 mg, 12%), as well as a complex mixture that could not be identified. The steric bulk of the *t*-dodecanethiol may prevent the cyclopropane ring opening reaction from occurring. We observed an increased amount of the monobromocyclopropane **174** compared to reactions with ethanethiol and *n*-dodecanethiol.



52 **179 , 180** **174**

Scheme 2.16 Cyclopropane Ring Opening of **52** with *t*-Dodecanethiol

The fourth thiol to be explored was thiophenol. This avoids the problems of a low boiling point experienced with ethanethiol and it contains less bulk and no hydrophobic tail in comparison to *n*-dodecanethiol and *t*-dodecanethiol. The injection method was applied, and after heating in refluxing THF for 40 hours, complete consumption of starting material was observed (Scheme 2.17). The ^{1}H NMR spectrum showed major and minor products which both appeared to contain a bromoalkene functionality and a possible anomeric centre. Column chromatography of the crude reaction mixture provided compounds **181** and **182** in 76% yield, as an inseparable mixture in a 7:2 ratio.

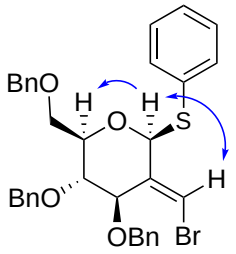


52

Scheme 2.17 Cyclopropane Ring Opening of **52** with Thiophenol

Identification of thioglycosides **181** and **182** was confirmed by mass spectrometry,

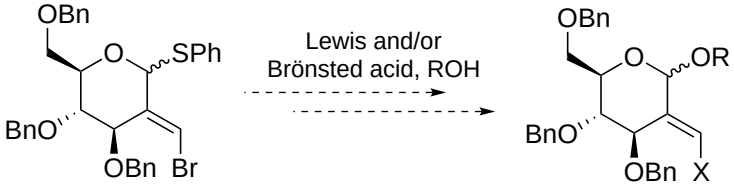
which displayed a Br isotope pattern and a quasimolecular ion peak of $[M+Na]^+$ = 677.0503, corresponding to the formula $C_{34}H_{33}O_4S^{79}BrNa^+$ consistent with **181** and **182**. 1D nOe experiments irradiating H-7 and H-1 of **181** showed enhancement of H-1 and H-7 respectively. This indicates these products are 2-*C*-branched thioglycosides, not thiol-oxepines, as we would not expect to see this nOe correlation in the oxepine structures. The major isomer **181** was assigned as the β-anomer, based on an nOe correlation between H-1 and H-5 when irradiating H-1 (Figure 2.7).



181

Figure 2.7 nOe Correlations in **181**

The synthesis of branched thioglycosides **181** and **182** has implications for the mechanistic studies, which will be discussed further in section 2.8 (page 66). These thioglycosides have potential application as glycosyl donors, which gives access to a range of glycosides containing aglycones that are not suitable as nucleophiles in the cyclopropane ring opening reaction, such as sugar nucleophiles. These glycosidation reactions use Lewis or Brönsted acids as catalysts and it will be shown in section 2.5 (page 48) and section 2.6 (page 52) that the branched bromoalkenes are generally unstable when exposed to acidic or aqueous conditions. For this reason, derivatisation of the bromoalkene functionality might be necessary prior to glycosidation. Unfortunately, due to time constraints, none of these reactions have been explored.



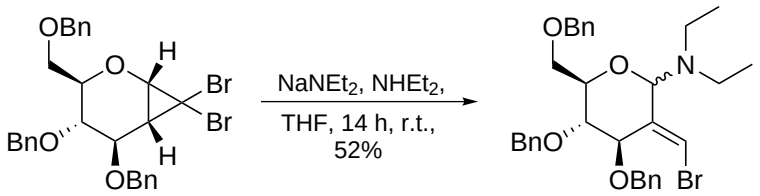
181 , **182**

Scheme 2.18 Proposed Glycosidation Reactions of Thioglycosides **181** and **182**

2.5 Cyclopropane Ring Opening Reaction with Amine Nucleophiles

Hewitt performed a ring opening of cyclopropane **52** with the amine nucleophile diethylamine. The reaction went to completion, providing a 1:1 mixture of two

compounds that were unable to be identified, as they degraded before full NMR characterisation could be obtained.[41] Use of deuterated chloroform, even when neutralised with potassium carbonate before use, resulted in degradation of the products. Cyclopropane ring opening of **52** with diethylamine was attempted using the injection method at room temperature. After 14 hours, the same two compounds seen by Hewitt were observed in a 1:1 mixture (Scheme 2.19). They are assumed to be glycosylamines **183** and **184**. Due to the degradation seen by Hewitt, the compounds were presumed to be acid sensitive, so extra precautions were taken. Column chromatography of the 1:1 mixture of glycosylamines was performed with an eluent of 5:1 petroleum:ethyl acetate containing 3% triethylamine. Alumina was used to dry and neutralise deuterated chloroform prior to its use as an NMR solvent. Full NMR characterisation was obtained on the mixture of anomers **183** and **184**. Mass spectrometry analysis of this mixture of compounds provided a quasimolecular ion peak $[M+H]^+ = 580.2062$, corresponding to the protonated form of glycosylamines **183** and **184**. A sodium quasimolecular ion peak was also observed which complemented this result. Based on the chemical shift of the H-7 and H-1 signals in **183** (6.83 and 4.90 ppm) and **184** (6.79 and 5.17 ppm), **183** and **184** are assumed to be 2-*C*-branched glycosyl amines not oxepines due to the similarity of these chemical shifts to the previously synthesised 2-*C*-branched sugars.

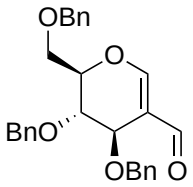


52 **183**, **184**

Scheme 2.19 Cyclopropane Ring Opening using Diethylamine providing Glycosylamines **183** and **184**

Further to the glycosylamines, four other products were collected from the column chromatography. Firstly, an aldehyde was obtained in a significant amount (10 mg, 13%). The structure of this compound was elucidated through the use of NMR spectroscopy and mass spectrometry as **185** (Figure 2.8). Aldehyde **185** has been previously synthesised from other precursors, and comparison of its spectral data matched those which had been previously reported.[90]

There are several possible mechanisms for the formation of **185** from the initially formed glycosylamines (Scheme 2.20). The first one begins with pyran ring opening of **183** and **184** forming iminium **186** (blue pathway). Rotation about the C-2–C-3 bond followed by conjugate addition (the 5-OH attacking C-7) results in the formation of **187**. Elimination of the bromide followed by hydrolysis of the iminium



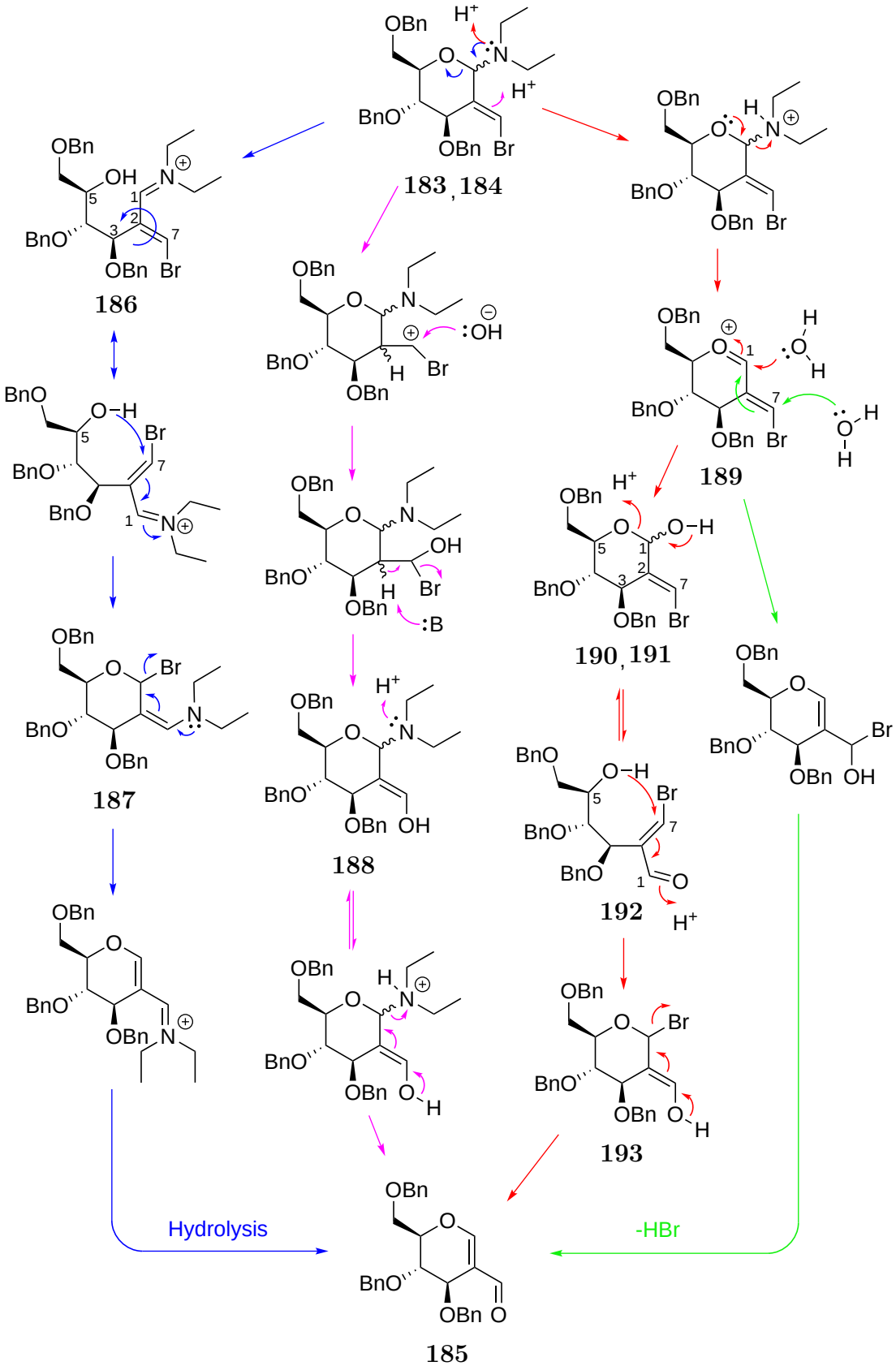
185

Figure 2.8 Aldehyde **185**

functionality results in the formation of aldehyde **185**. The second possible mechanism (pink pathway), involves hydration of the bromoalkene. Elimination of HBr would regenerate the alkene in the form of enol **188**. Protonation of the aminal nitrogen and elimination of the amine group would result in the formation of aldehyde **185**. The third mechanism begins with protonation of the aminal nitrogen (red pathway). This causes the amine group to leave, forming oxonium intermediate **189**. This compound could undergo addition of water at either C-1 (red pathway) or at C-7 (green pathway). The red pathway leads to free sugars **190** and **191** which are in equilibrium with aldehyde **192** (Shown after rotation about the C-2–C-3 bond). Conjugate addition of the 5-OH to the α,β-unsaturated aldehyde functionality in **192** results in the formation of glycobromide **193**. Elimination of the bromide forms aldehyde **185**. The second branch (green pathway) results in formation of an unstable geminal bromohydrin which, upon elimination of HBr, leads to aldehyde **185**.

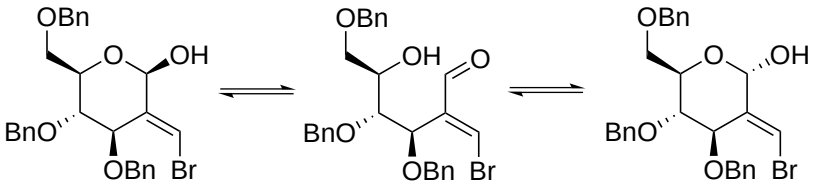
While all three mechanisms are valid, the second mechanism (pink pathway) appears unlikely as we would expect the aminal nitrogen to protonate before the bromoalkene functionality. The other two mechanisms are similar; however we believe the mechanism on the right, involving two possible branches (red and green pathways) is more likely. Our evidence for this is the isolation of the free sugars **190**, **191** and aldehyde **192** as the other three products isolated from the column chromatography of **183** and **184**. The red pathway is the only pathway which accounts for the formation of these three products.

These three products (**190**, **191** and **192**) were initially inseparable, showing functionalities of interest in the ^{1}H NMR spectrum with an aldehyde peak at 9.41 ppm and peaks between 5-7 ppm indicative of H-1 and H-7 signals present in other 2-*C*-glycosides throughout this project. Preparative TLC of this mixture of compounds using 2:1 petrolum:ethyl acetate containing 3% triethylamine separated these three fractions. ^{1}H NMR spectroscopy of each of these fractions provided three identical spectra all containing a mixture of three products and trace amounts of aldehyde **185**. Mass spectrometry data of one of these mixtures showed the three isomeric compounds contained one bromine atom (based on the isotope pattern) with a quasimolecular ion $[M+Na]^+ = 547.1096$ corresponding to the molecular formula



Scheme 2.20 Possible Mechanisms of Aldehyde **185** Formation

$C_{28}H_{29}O_5^{79}BrNa$ consistent with the ring opened aldehyde/hemiacetal isomers **190**, **191** and **192**. 1D nOe correlations confirmed their structures as 2-*C*-branched sugars as irradiation of H-1 showed a correlation with H-7 and a broad singlet at 1.58 ppm associated with the free sugar hydroxyl. This also explains why three products are seen in the NMR spectra, as the three compounds are in equilibrium in solution (Scheme 2.21).



190 **192** **191**

Scheme 2.21 Free Sugar Equilibrium

It is known that glycosylamines are acid labile. In the case of **183** and **184** this is amplified by the anomeric centre being an allylic position. The lack of stability of glycosylamines **183** and **184** provides uncertainty with respect to their use in further reactions or applications. Because of this no other amine nucleophiles were explored.

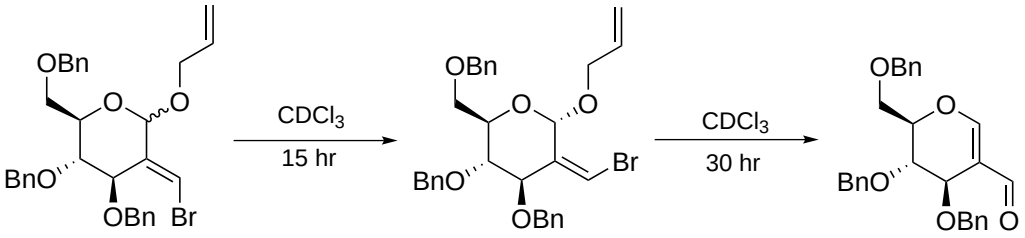
2.6 Identification and Synthesis of *Z*-bromoalkene 194

2.6.1 Isolation and Identification of 194

Ring opening of cyclopropane **52** under basic conditions resulted in formation of compounds containing exclusively *E*-bromoalkene, with no evidence of the formation of the corresponding *Z*-bromoalkenes. Synthesis of *Z*-isomer **194** and/or its anomer **195** would provide an alternative substrate for further functionalisation and confirm its absence in the cyclopropane ring opening of **52** with sodium allyloxide/allyl alcohol.

Z-Bromoalkene **194** was produced as a single anomer when an NMR sample of a crude mixture of **140**, **141** and **52** (1:1:1.5) in deutero-chloroform was re-examined after 15 hours. The sample showed complete conversion of **140** and **141** to **194**, with the only other product present being cyclopropane **52**. Upon re-examination after 30 hours the sample had mostly degraded into previously identified aldehyde **185** (Scheme 2.22).

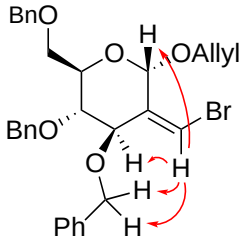
Z-Bromoalkene **194** was characterised through the use of NMR spectroscopy and mass spectrometry. An intramolecular Heck reaction with the allyl group (see sub-



140, **141** **194** **185**

Scheme 2.22 Conversion of **140** and **141** to **194**

section 2.9.1, page 83) confirmed the structure of the *Z*-bromoalkene functionality. It was apparent from the ^{13}C and ^{1}H NMR spectra that **194** was related to **140** and **141**. This was confirmed by mass spectrometry which showed the $[M+Na]^+$ ion was consistent with the molecular formula of $C_{31}H_{33}O_5BrNa^+$ corresponding to the structure **194** as well as **141** and **140**. nOe difference experiments, irradiating the H-7 proton, showed enhancement of H-3 (and a small enhancement of H-1 which is still within 5Å distance) and benzyl protons (the benzyl at O-3, Figure 2.9). These peaks would only be enhanced if the bromoalkene present was the *Z*-isomer. Comparisons with the nOe difference experiments performed with the *E*-bromoalkene products **140** and **141** (which showed enhancement of only H-1 when irradiating H-7) were consistent with the assignment of the bromoalkene moiety in **194**. The anomeric assignment could not be determined through nOe spectroscopy as no enhancements were observed between H-1 and H-5 or H-6a,b. The anomeric configuration is assigned as the α-anomer with more discussion of this to follow in section 2.7 (page 62).



194

Figure 2.9 nOe Correlations Used in Determining the Stereochemistry of the Bromoalkene in **194**

From the ^{1}H NMR spectra in Figure 2.10, it is obvious that **194** contains proton signals that have shifted significantly relative to **140** and **141**. Firstly, the H-7 resonance has shifted to 6.38 ppm from 6.82 or 6.79 ppm. This upfield shift may be due to shielding from the O-3 benzyl group. H-7 also exhibits an allylic coupling ($^{3}J_{H-H}$ = 2.2 Hz) to H-3. The H-1 resonance also shifts from 5.35 or 5.20 ppm to 5.77 ppm. This increase could be due to its proximity to the electronegative bromine in **194**. Of note are the coupling constants between H-3, H-4 and H-5 which are consistent with axial-axial proton interactions; $^{3}J_{H-H}$ = 9.4 Hz (H-3–H-4) and $^{3}J_{H-H}$ = 9.7 Hz (H-4–H-5). There is also no coupling observed between H-1 and

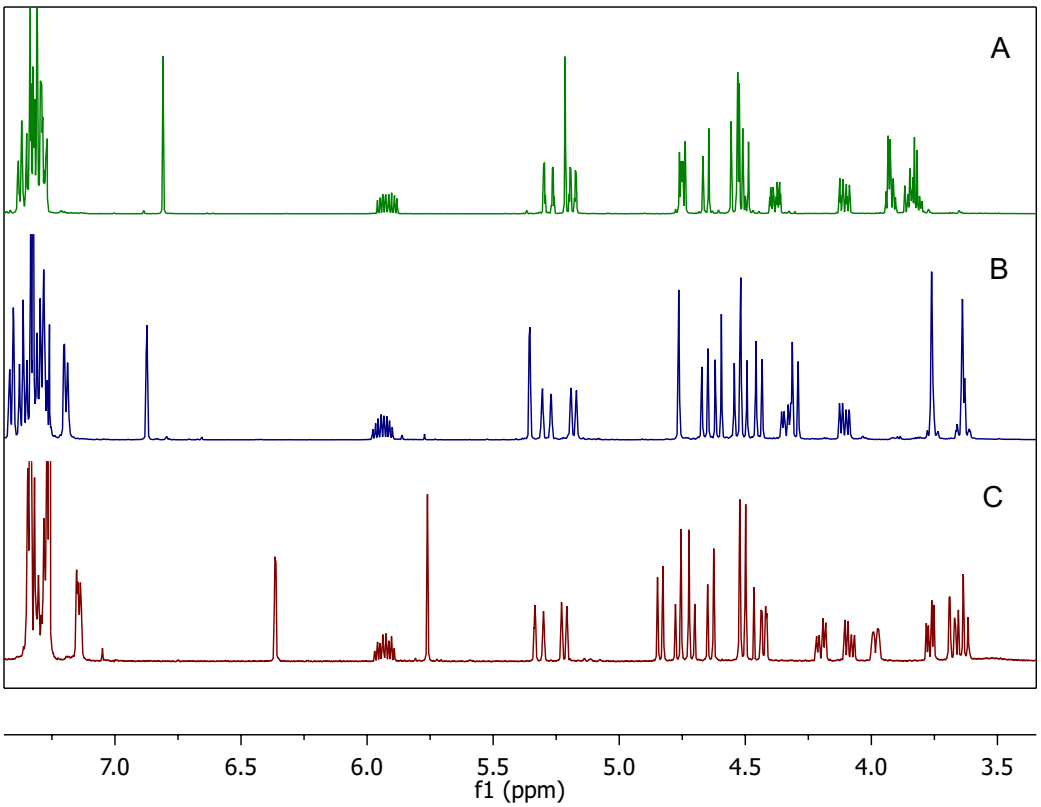


Figure 2.10 ^{1}H NMR Spectra of *E*-Bromoalkenes **140** (A) and **141** (B), and *Z*-Bromoalkene **194** (C)

H-7 in **194** compared to the coupling as seen in **141** ($^{3}J_{H-H}$ = 1.7 Hz) and COSY correlations present in **140** and **141**.

To explore the mechanism of formation of **194**, ^{1}H NMR studies with a range of samples were conducted (Table 2.4). A crude reaction mixture from the formation of **140** and **141** (entry 2), a purified mixture of **140** and **141** (entry 4) as well as separated samples of **141** (entry 5) and **140** (entry 6) were dissolved and stored in deuterated chloroform to test their stability. In all cases the solvent was pre-treated with K_2CO_3 to neutralise the weakly acidic deuterated chloroform. An additional two samples (the crude reaction mixture containing **140** and **141** (entry 1), and a purified mixture of **140** and **141** (entry 3)) in unneutralised deuterated chloroform were also analysed. ^{1}H NMR spectra of these samples, taken periodically over seven days, indicated that samples in unneutralised deuterated chloroform formed **194**, while the samples containing neutralised deuterated chloroform resulted in no change in composition.

Detailed analysis of the ^{1}H NMR spectra for entry 3 in Table 2.4 showed interesting transformations from a mixture of **140** and **141** to **194** (Figure 2.11). Initially, the amount of **141** increases and **194** begins to form, at the expense of **140** (B). This continues until complete conversion of **140** to **141** and **194** is observed (C-E). **141** then fully converts to **194** (F). As time increases aldehyde **185** also began to

Table 2.4 Stability of **140** and **141** in $CDCl_3$

Entry	Compound(s)	Solvent	Change in Composition (After 1 week)
1	Crude **141**, **140**	$CDCl_3$	Full
2	Crude **141**, **140**	$CDCl_3$ treated with K_2CO_3	None
3	**141**, **140**	$CDCl_3$	Full
4	**141**	$CDCl_3$ treated with K_2CO_3	None
5	**141**, **140**	$CDCl_3$ treated with K_2CO_3	None
6	**140**	$CDCl_3$ treated with K_2CO_3	None

form (not shown in Figure 2.11). This experiment was performed to qualitatively follow the formation of **194** from **141** and **140**, not to obtain quantitative kinetic data.

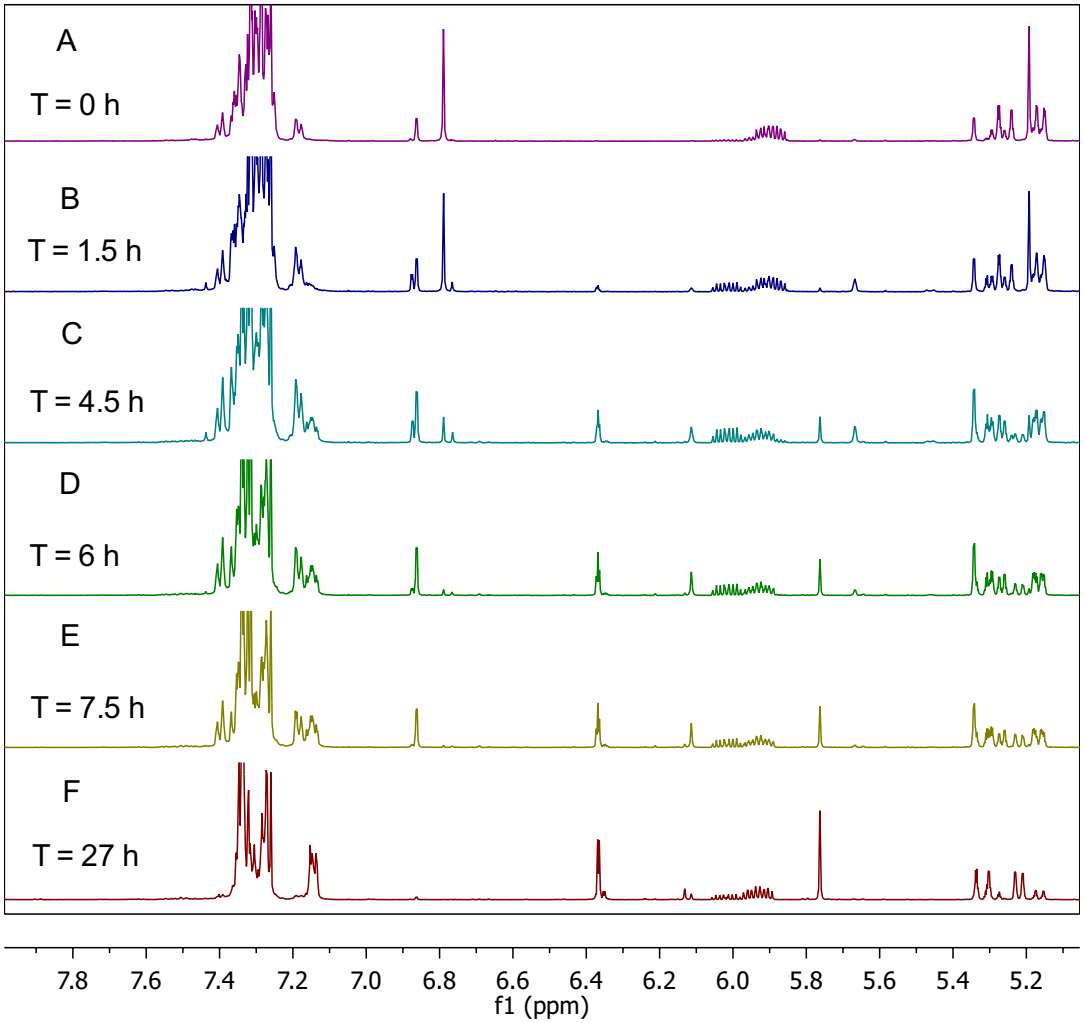


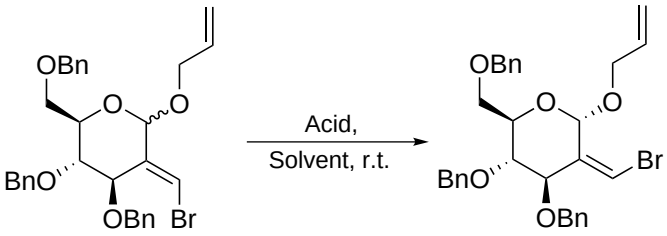
Figure 2.11 ^{1}H-NMR Spectra showing Conversion of **140** and **141** to **194** in $CDCl_3$ over 27 Hours

The results of these ^{1}H NMR experiments suggest several important characteristics of glycosides **140** and **141**. Firstly, these compounds are acid sensitive. Wet chloroform is weakly acidic and residual water was observed in the ^{1}H NMR spectra of the unneutralised samples. Secondly, the partial convergence of **140** and **141** to

141 may indicate appropriate conditions under which one glycoside anomer can be selectively obtained (briefly explored in subsection 2.6.2, page 56). Thirdly, only one *Z*-bromoalkene anomer **194**, is observed, with no evidence for formation of the second anomer **195**. If acidic conditions are responsible for these isomerisations then the reactions are likely to be under reversible conditions, with the predominant product formed being the thermodynamic product. Lastly, lengthy storage of these glycoside products in unneutralised deuterochloroform results in the formation of aldehyde **185**. Over time, an increase in the water present in the sample was observed in the ^{1}H NMR spectra, consistent with water being responsible for the formation of **185**. With respect to the proposed mechanism (Scheme 2.20, page 51), this suggests the hydrolysis of glycosyl amines **183** and **184** to free sugars **190** and **191** occurs before rearrangement to aldehyde **185**, consistent with the red pathway.

2.6.2 Synthesis-Scale Preparation of 194

According to the preceding ^{1}H NMR experiments, acidic conditions appeared to cause *E*- to *Z*-bromoalkene isomerisation of **140** and **141**. To further explore this reaction and test its synthetic utility, laboratory scale experiments were carried out with mixtures of **141** and **140** in the presence of an acid and a solvent at room temperature (Scheme 2.23).

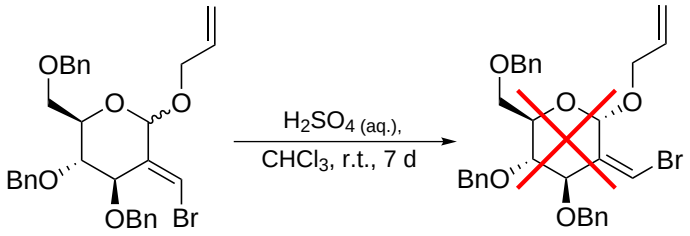


140, **141** **194**

Scheme 2.23 General Acid-Promoted *E*- to *Z*-Bromoalkene Isomerisation

Firstly, 10% aqueous sulfuric acid in chloroform was explored (Scheme 2.24). After a week stirring at room temperature the starting material was unchanged. It was surmised that aqueous sulfuric acid failed to promote the isomerism because it is not miscible with chloroform.

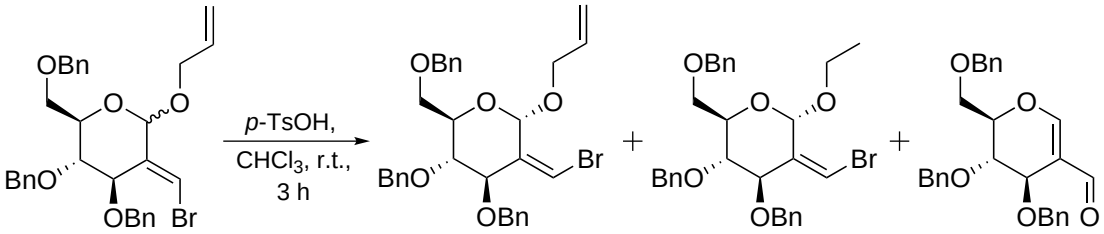
Use of the organic-soluble acid, *p*-toluenesulfonic acid (*p*-TsOH), was then explored. A mixture of **140** and **141** (1:3) was dissolved in chloroform before the addition of *p*-TsOH $\cdot$ H_2O (0.5 equivalents). After stirring at room temperature for three hours, TLC analysis showed complete consumption of the starting material and formation of two products. After purification, the faster moving fraction (R_f = 0.40 (9:1 hexanes:ethyl acetate)) contained a mixture of two glycosides: the previously



140, **141** **194**

Scheme 2.24 Attempted Alkene Isomerisation of **140** and **141**

identified *Z*-bromoalkene **194** and an ethyl glycoside, thought to be **196** in 24% yield (ratio 2:5). The higher polarity spot (R_f = 0.30 (5:1 hexanes:ethyl acetate)) contained the previously isolated aldehyde **185** (Scheme 2.25) in 42% yield. This experiment demonstrated that an acid facilitates the isomerisation of **140** and **141** to **194**, as summerised from the $CDCl_3$ results. The presence of water, introduced through the use of *p*-TsOH · H_2O, appears to result in significant formation of aldehyde **185**. While no further identification work was done on compound **196**, it was likely formed through attack of ethanol, present in 1-2% in chloroform as a stabiliser (the amount of **196** is consistent with 1-2% ethanol). The similar polarity of the two glycosides **194** and **196**, was consistent with the similarities in the structures.

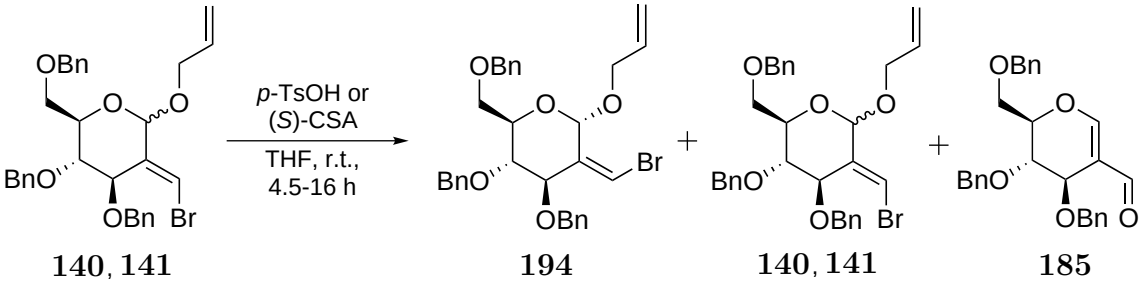


140, **141** **194** **196** **185**

Scheme 2.25 Bromoalkene Isomerisation Forming **194** and **196**

Chloroform is stabilised by ethanol to prevent possible photooxidation to phosgene, a highly toxic gas.[91] Rather than purifying chloroform to remove the ethanol (and trace water), and risk phosgene production, the use of an alternative solvent, THF, was explored. Again *p*-TsOH · H_2O was used as an acid, however prior to use it was dried by distillation of its azeotrope with toluene to remove the one equivalent of water present in the commercially available material. A reaction was carried out using a 3:1 mixture of **140**:**141**, in THF treated with 20 mol% *p*-TsOH. Stirring at room temperature for 16 hours resulted in the formation of a complex mixture, containing **141**, **140**, **194** and **185**. Use of a different organic acid, (*S*)-camphorsulfonic acid (*S*-CSA), gave a similar result: the reaction formed a complex mixture of **141**, **140**, **194** and **185** after 4.5 hours (Table 2.5).

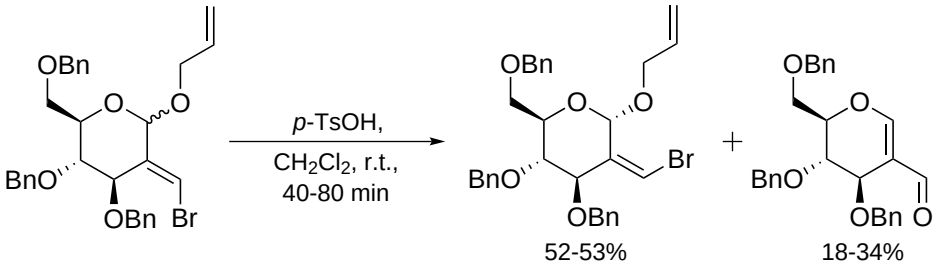
Exploration of reactions in dichloromethane catalysed with dried *p*-TsOH resulted



140, **141** **194** **140**, **141** **185**

Scheme 2.26 Bromoalkene Isomerisation using THF as a Solvent

in a significant increase in isolated yield of **194** (52%), along with aldehyde **185** (34% yield), and a reduction in reaction time to 40 minutes. Repetition of this reaction, with the addition of 3Å molecular sieves prior to the addition of dried *p*-TsOH, disappointingly provided little improvement, increased the reaction time to 80 minutes, providing **194** in 53% yield, despite the expected decrease in the formation of aldehyde **185** (18% yield).

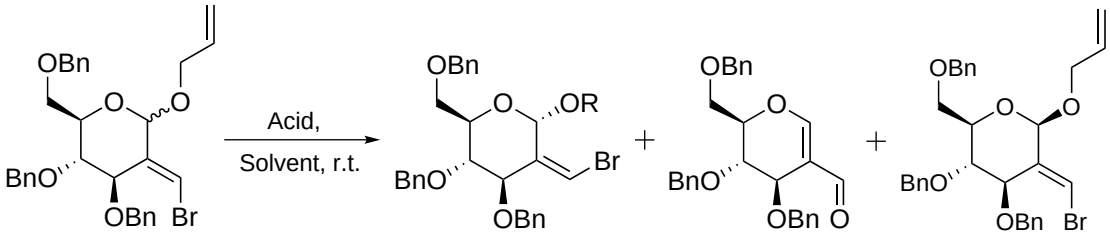


140, **141** **194** **185**

Scheme 2.27 Bromoalkene Isomerisation using Dichloromethane as a Solvent

A reaction using allyl alcohol as a solvent and a 1.7:1 mixture of **140**:**141** resulted in isolation, after four hours, of the β-anomer **141** in 63% yield. This is consistent with the NMR experiments in deuterated chloroform. This result was not explored further but suggests that **141** is more thermodynamically stable than **140**. This will be discussed in more detail in section 2.7 (page 62). The selectivity of the acid-promoted isomerisation in allyl alcohol suggested that the initially formed mixture of **140** and **141** from cyclopropane ring opening might be converted into the β-anomer **141**. The reaction mixture from ring opening of cyclopropane **52** under standard sodium allyloxide/allyl alcohol conditions, containing **140** and **141** (see section 2.3, page 37), was treated with excess *p*-TsOH to quench unreacted base and to create an acidic solution. The isomerisation of the anomeric centre occurred, as expected, under the acidic conditions, however *Z*-bromoalkene **194** was the major product, albeit in modest yield (28%) with a poor yield of **141** (9%). This result showed that efficient formation of **194** or **141** is best done over two steps: first isolation of the mixture of glycosides **141** and **140** from cyclopropane ring opening, followed by isomerisation using dichloromethane or allyl alcohol as solvent, respectively. The yield of the acid isomerisation reactions are summarised in Table 2.5.

Table 2.5 Synthesis of **194** in Acidic Conditions



140, **141** **194** R = Allyl **196** R = Et **185** **141**

Entry	Solvent	Acid	Time (h)	Product % Yield			
				194	**196**	**185**	**141**
1	$CHCl_3$	$H_2SO_{4\,(aq.)}$	216	Recovered Starting Material **140**, **141**			
2	$CHCl_3$	*p*-TsOH $\cdot$ H_2O	3	24[a]		42	-
3	THF	*p*-TsOH	16	Complex Mixture Including: **194**, **140**, **141**			
4	THF	*S*-CSA	4.5	Complex Mixture Including: **194**, **140**, **141**			
5	CH_2Cl_2	*p*-TsOH	0.67	52	-	34	-
6	CH_2Cl_2[b]	*p*-TsOH	1.33	53	-	18	-
7	AllyOH	*p*-TsOH	4	-	-	-	63

[a] A mixture of **194** and **196** (2:5 ratio) was obtained

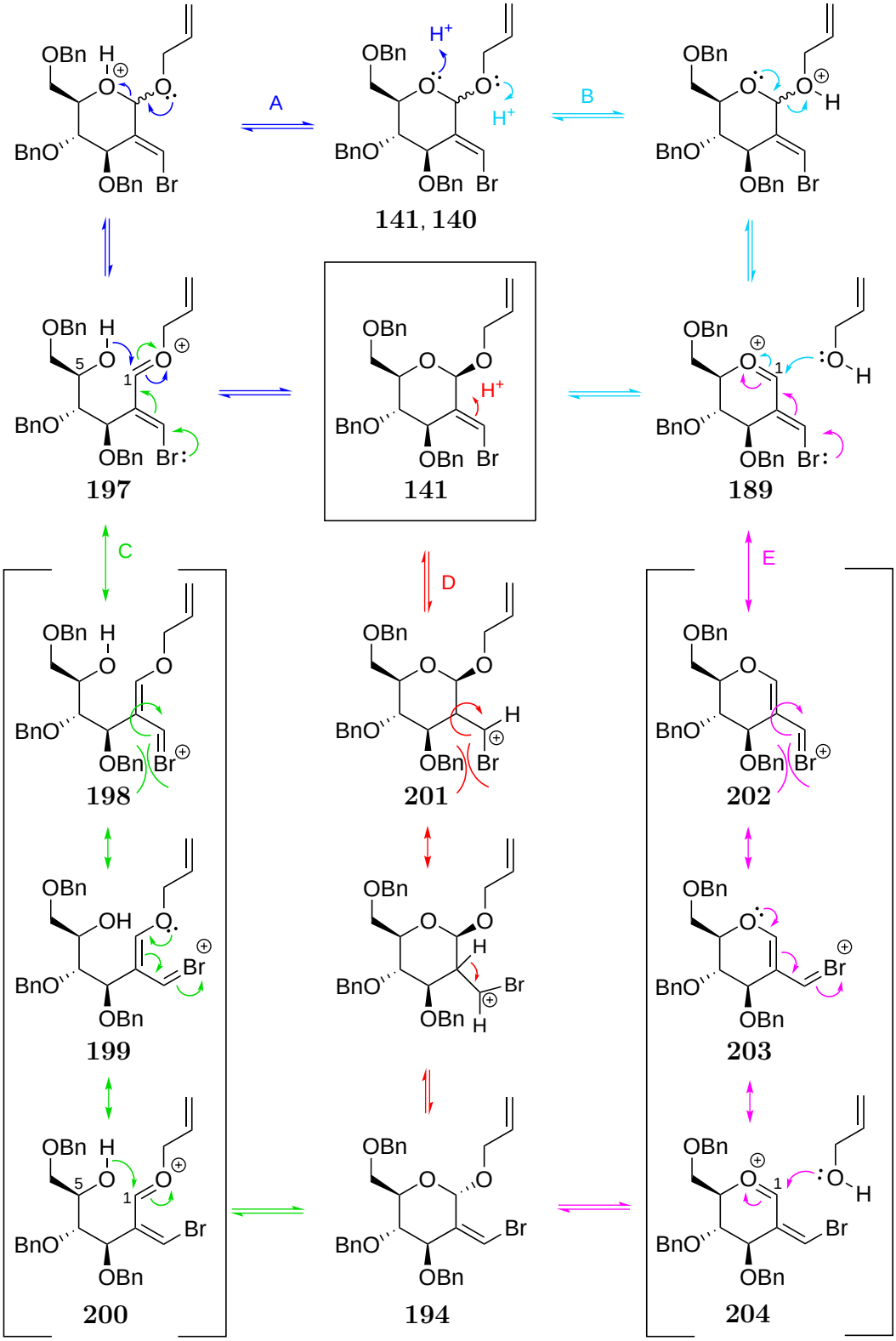
[b] 3Å molecular sieves were used to predry the solvent and during the reaction

2.6.3 Proposed Mechanisms for Anomeric and Bromoalkene Isomerisations

Formation of **194** involves the stereoisomerisation of two functional groups: the anomeric centre (C-1), and the bromoalkene functionality. Scheme 2.28 shows the proposed mechanisms for both of these isomerisations. Firstly, the isomerisation of the anomeric centre may occur through two possible mechanisms. Pathway A (dark blue) begins with protonation of the pyran oxygen of **140** and **141** followed by ring opening of the pyran to form the acyclic oxonium species **197**. The pyran can then be reformed by attack of the 5-OH on the oxonium cation (C-1), delivering a single isomer, **141**. Alternatively, the allyl aglycone could be protonated as shown in pathway B (light blue). The aglycone may then leave, forming oxonium species **189**. Allyl alcohol can then face-selectively attack the oxonium (C-1) of **189** forming **141**. As all steps are reversible, the more thermodynamically stable product would be expected to predominate. While the anomeric effect predicts the α-anomer to be the lowest energy configuration conformation in most *O*-glycosides, it is likely that **140** and **141** do not exist in the usual chair conformation. Experimentally, overall conversion of **140** to **141** occurs under the acidic conditions.

The isomerisation of the *E*-bromoalkene to the *Z*-bromoalkene has three possible mechanisms. The first pathway follows pathway A to **197**, then pathway C (green) branches off forming **198**, the resonance structure of **197**. Because of the steric bulk of the C-3 benzyl protecting group, rotation about the C-2–C-7 bond could occur, providing **199**. Formation of the resonance structure **200**, followed by attack on the oxonium cation (C-1) by the 5-OH produces **194**. The middle pathway, pathway D (red), occurs through protonation of the bromoalkene, forming resonance-stabilised cation **201**. Rotation about the C-2–C-7 bond can then occur to decrease the steric interaction between the bromine and the C-3 benzyl protecting group. The added proton can then be eliminated reforming the bromoalkene, now in the *Z* configuration of the product **194**. The third possible mechanism follows pathway B to **189**. Pathway E (pink) then branches off, whereby **202**, a resonance structure of **189**, can undergo rotation about the C-2–C-7 bond, providing **203**. Formation of the resonance structure **204**, followed by attack on the oxonium cation (C-1) by allyl alcohol forms **194**. Again, all the mechanistic steps involved are reversible, such that the thermodynamic product is expected to predominate. With pathway D (red), the last mechanistic step has to encompass isomerisation of the anomeric centre through pathways analogous to A and/or B.

While all the proposed mechanisms are valid we favour pathway B (light blue) followed by pathway E (pink). Pathway B accounts better for the formation of ethyl glycoside **196** (Scheme 2.25, page 57) and aldehyde **185** (which is believed to



Scheme 2.28 Possible Mechanisms of Bromoalkene Isomerisation of **140** and **141** to **194** in Acidic Conditions

form from hemi-acetals **190** and **191** (section 2.5, red mechanism in Scheme 2.20, page 51). These by-products would be accessible through pathway B as they could be formed through nucleophilic attack of ethanol or water at the C-1 position of oxonium ion **189**, in competition with allyl alcohol. Formation of these alternative glycosides via Path A while possible, is less likely. As this pathway is less likely then pathway C, which is reliant on pathway A is also less likely to be in operation. Pathway D also appears unlikely as the acetal functionality of **140** and **141** is expected to be more acid sensitive (higher likelihood of being protonated) than the bromoalkene functionality.

2.7 Conformational Analysis of *E*- and *Z*-Bromo -alkenes, α and β Anomers

Synthesis of **194** under acidic conditions as discussed in the previous section allowed confirmation that the cyclopropane ring-opening reaction of **52** under basic/nucleophilic conditions did not produce *Z*-bromoalkene **194** (based on the lack of its signals in the ^{1}H NMR spectrum of the crude reaction mixture). Under the acidic conditions of isomerisation, it is proposed that all of the mechanistic steps involved in forming **194** (Scheme 2.28) are reversible. The lowest energy (thermodynamic) product is, therefore, expected to predominate. This suggests that the *Z*-bromoalkene is thermodynamically more stable that the *E*-bromoalkene, indicating that the cyclopropane ring opening reaction of **52**, occurs through a kinetically controlled process (see section 2.8, page 66). Under the acidic reaction conditions, prior to the *E*/*Z* isomerisation of the bromoalkene, partial anomeric resolution was observed from the **141**/**140** mixture. The convergence to the **141** (β-anomer) suggests that it is thermodynamically more stable than **140** (α-anomer). This is unexpected as the anomeric effect predicts the α-anomer to be the lowest energy configuration in most *O*-glycosides existing in the usual $^4C_1$ chair conformation.

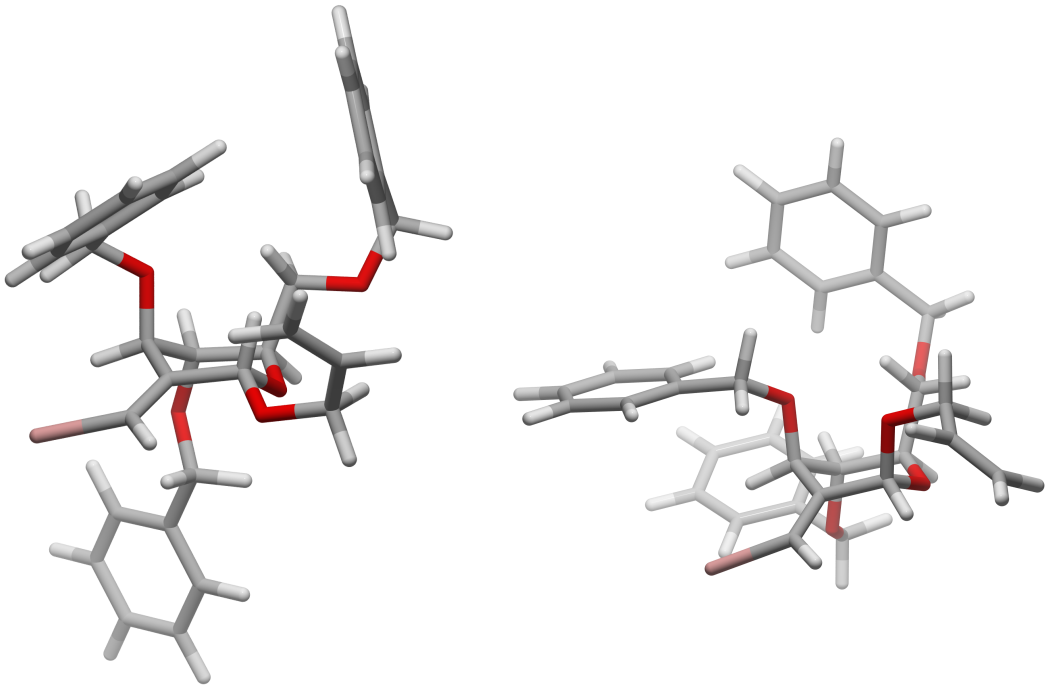
To explore the experimental observations above, computational modeling of the four possible isomers **141**, **140**, **194** and **195** (α and β-anomers of the *E*- and *Z*-bromoalkenes, respectively) was performed. The geometry and the relative energy was calculated for each isomer for comparison. Two programs were used to perform these calculations. Initial attempts to perform conformational searches using Spartan© failed after repeated iterations were unable to finish.[b] This was attributed to the three benzyl groups in each of these molecules acting as flexible 'arm' type

[b]Conformational searches were attempted using Spartan© '08, Version 1.2.0. using the Merck molecular force field (MMFF) to determine the equilibrium conformation of each structure at ground state.

structures, producing a large number of local minimum geometries with small variations in energy making it computationally expensive to find a global minimum. MacroModel[c] was then used to perform a conformational search providing geometries for each structure. Once the geometries were calculated, the Spartan program was used to calculate the energies of the finessed optimised geometries of each compound.[d] The relative energies of the four isomers (compared to the lowest energy compound **194**) are shown in Table 2.6 while the optimised geometries are shown in Figure 2.12 and Figure 2.13.

Table 2.6 Relative Energy of Four Isomers

Compound	Configuration	Relative Energy ($kJmol^{-1}$)
140	α, E	11.51
141	β, E	9.10
194	α, Z	0.00
195	β, Z	4.94



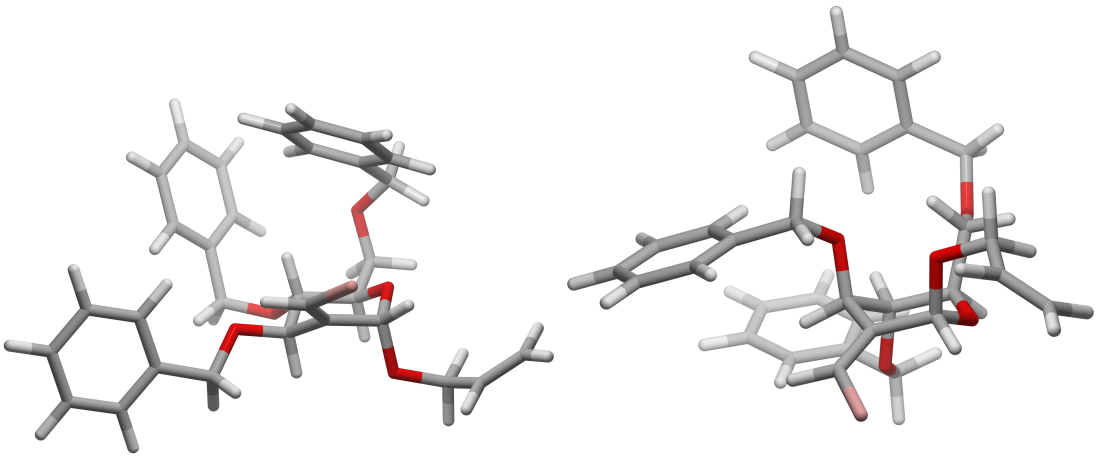
(a) **140** (b) **141**

Figure 2.12 α- and β-E-bromoalkenes **140** and **141**

The differences between the α- and β-anomers of the E-bromoalkene (**140**, **141**)

[c]Lowest energy conformers of these compounds were initially obtained using mixed torsional/low mode sampling conformational search as implemented in MacroModel (version 9.7, Schrödinger, LLC, New York, NY, 2009) using the OPLS-2005 forcefield.

[d]All geometry optimisations were performed using Spartan© '08, Version 1.2.0. Geometry optimizations were carried out with Density Functional Theory (DFT) calculations performed at the B3LYP level with the 6-31G* data set in dichloromethane. The Spartan© default values were used for grid size and other parameters. Images were generated using: CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org).

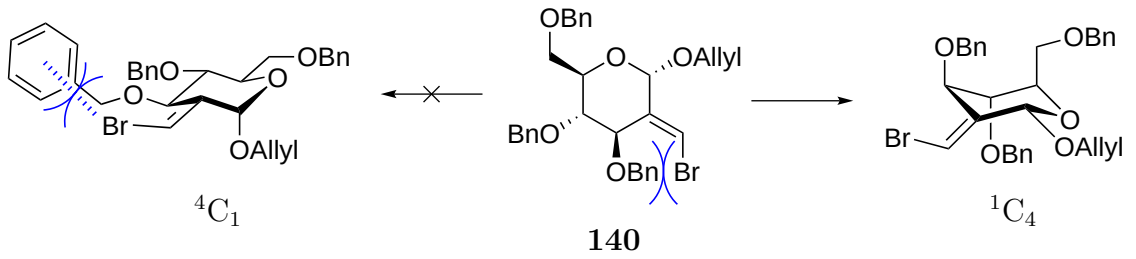


(a) **194** (b) **195**

Figure 2.13 α- and β-*Z*-bromoalkenes **194** and **195**

are of interest due to the observed isomerisation of the anomeric centre from **140** to **141** under acidic conditions as discussed in section 2.6 (Table 2.5, page 59). From Figure 2.12 we see that both of these anomers contain *pseudo*-axial benzyloxy groups at C-3 and C-4, with C-5 also containing a *pseudo*-axial *C*-branch. In both isomers the pyran ring is in a $^1C_4$ chair conformation.[92] Therefore the β-anomer **141** has a *pseudo*-axial allyloxy aglycone. The anomeric effect suggests that this would be lower energy than the α-anomer **140**, which reflects the computational results in Table 2.6. Rationalising why the benzyl substituents arrange themselves in a *pseudo*-axial conformation is difficult. It may be that the $^1C_4$ chair conformation minimises steric interactions between the C-3 benzyl group and the bromine (Scheme 2.29). The veracity of the computational results might be determined by inspection of the NMR spectra. Unfortunately, in the ^{1}H NMR spectra of **140** and **141** in $CDCl_3$, the $^3J_{H-H}$ coupling constants between H-3 and H-4, and H-4 and H-5 are not resolved, as they appear as overlaying multiplets. The ^{1}H NMR spectrum of **141** in C_6D_6 showed $^3J_{H-H} = 8.8$ Hz between H-4 and H-5, which corresponds to near axial-axial proton interactions while the H-3, H-4 $^3J_{H-H}$ is not resolved. The coupling constant between H-4 and H-5 ($^3J_{H-H} = 8.8$ Hz) in **141** suggests a significant conformational difference between the model of **141** and the ^{1}H NMR of **141** in C_6D_6. However, the computational models may not account for solvent interactions (calculations are based on molecules in dichloromethane)) which will occur to significant degree in C_6D_6 due to potential π-stacking interaction between the benzyl groups and the solvent. There is no conclusive evidence as to why **141** forms from a mixture of **140** and **141** under acidic conditions, although the calculated energies indicate a preference for **141** is possible.

The differences between the α- and β-anomers of the *Z*-bromoalkene (**194**, **195**) are of interest as only **194** was observed experimentally. The energy difference between



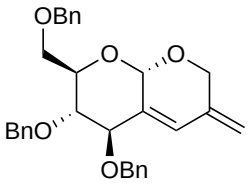
Scheme 2.29 Steric Interactions between C-3-OBn and Br in **140** in Two Chair Conformations

them (4.94 kJmol^{-1}) indicates **194** is favoured, however the biggest difference between the two structures is the conformation of the pyran ring as **194** occupies a $^4C_1$ chair conformation while **195** occupies the $^1C_4$ ring conformation. These conformations give *pseudo*-axial allyloxy groups such that the allyloxy oxygen has the least interaction with the bromine atom.

The biggest difference between the four structures is only **194** occupies a $^4C_1$ chair conformation. The other three compounds **140**, **141** and **195** occupy a $^1C_4$ chair conformation which contain *pseudo*-axial benzyloxy groups. Generally, axial benzyloxy groups around a six membered ring increase the energy due to 1,3-diaxial steric interactions, so we would expect **194** to have the lowest energy. From Table 2.6 this is what is observed with **194** being 4.94 kJmol^{-1} lower in energy compared to **195** and 9.10 and 11.51 kJmol^{-1} lower than the *E*-bromoalkenes **140** and **141** respectively. The conformation of **194**, containing equatorial benzyloxy groups, with minimal steric interaction between the C-3 benzyl group and the bromoalkene functionality is consistent with the $^3J_{H-H}$ coupling constants observed in the ^{1}H NMR of **194**. The coupling constants, $^3J_{H-H} = 9.4$ Hz between H-3 and H-4, and $^3J_{H-H} = 9.7$ Hz between H-4 and H-5 are consistent with axial-axial proton coupling. Computationally, **195** is also predicted to have axial benzyloxy functionalities similar to the *E*-bromoalkene isomers. If **195** occupies a $^4C_1$ confirmation, as shown in Figure 2.13 then the oxygen of the β-allyloxy aglycone, would have a strong steric interaction with the bromine atom. However, **195** has not been experimentally observed, and while the above reason justifies why **195** is not the thermodynamically favoured product the relative energies of these models must be analysed cautiously due to uncertainty about the conformation in dichloromethane compared to those in the NMR solvents, $CDCl_3$ and C_6D_6.

The stereochemistry of the anomeric (C-1) centre in the *Z*-bromoalkene has been tentatively assigned as α based on the computational modeling, as the α-anomer provides less steric interaction between the allyl oxygen and the bromine of the *Z*-bromoalkene; and the anomeric effect (for *O*-glycosides) which suggests that the α-anomer would predominate under reversible conditions. 1D nOe experiments failed

to confirm the stereochemistry at C-1. To determine the stereochemistry of the anomeric centre conclusively, further derivatisation or X-ray crystallography is required. No crystals were obtained so X-ray crystallography was not explored. A Heck reaction was successfully performed on **194** providing **205** (Figure 2.14) (see section subsection 2.9.1, page 83). Reduction of the alkenes in **205** or **194** would provide evidence for the stereochemistry of the anomeric centre either through the $^{3}J_{H-H}$ coupling between H-1 and H-2 or possible nOe correlations in the reduced form of **205**. This has not been explored due to time constraints.



205

Figure 2.14 Bicyclic Compound **205**

2.8 Studies Directed Towards Determination of the Ring Opening Reaction Mechanism

2.8.1 Proposed Mechanisms for the Ring Opening of 52

From his studies of the cyclopropane ring opening reactions with **52**, Hewitt proposed several mechanisms for the formation of 2-*C*-branched glycosides **55** and **56** (Scheme 2.30).[41] Of the five possible pathways shown in Scheme 2.30 the first three (pathways A, B and C) begin with cleavage of the C-1–C-7 bond of cyclopropane **52**, aided by the ring oxygen, (shown in red), forming zwitterion **206**. Pathway A (red) continues with protonation of the anion, followed by loss of the C-2 proton forming glycal **207**. Electron donation from the pyran oxygen ejects a bromide ion, forming oxonium ion **208**. Nucleophilic attack at C-1 by methanol results in the formation of the products **55** and **56**. Alternatively, zwitterion **206** could be attacked at C-1 by methanol (pathway B, black) and the anion at C-7 protonated forming an anomeric mixture of **209** and **210**. Subsequent elimination of HBr forms the products **55** and **56**. Thirdly, pathway C (pink) occurs when zwitterion **206** is deprotonated at C-2 forming the glucal anion **211**. Protonation at C-7 follows, leading to the formation of **207** which can then follow pathway A (red) to the products **55** and **56**. The fourth and fifth proposed mechanisms (pathways D and E) begin with the extraction of the C-2 proton in **52**, presumably through an acid/base reaction with sodium methoxide, forming **212** (Green pathway). Anion **212** can undergo cyclopropane ring opening, forming glucal anion **211** (pathway D, purple). **211** can then follow pathway C (pink) and then pathway A (red) to the products

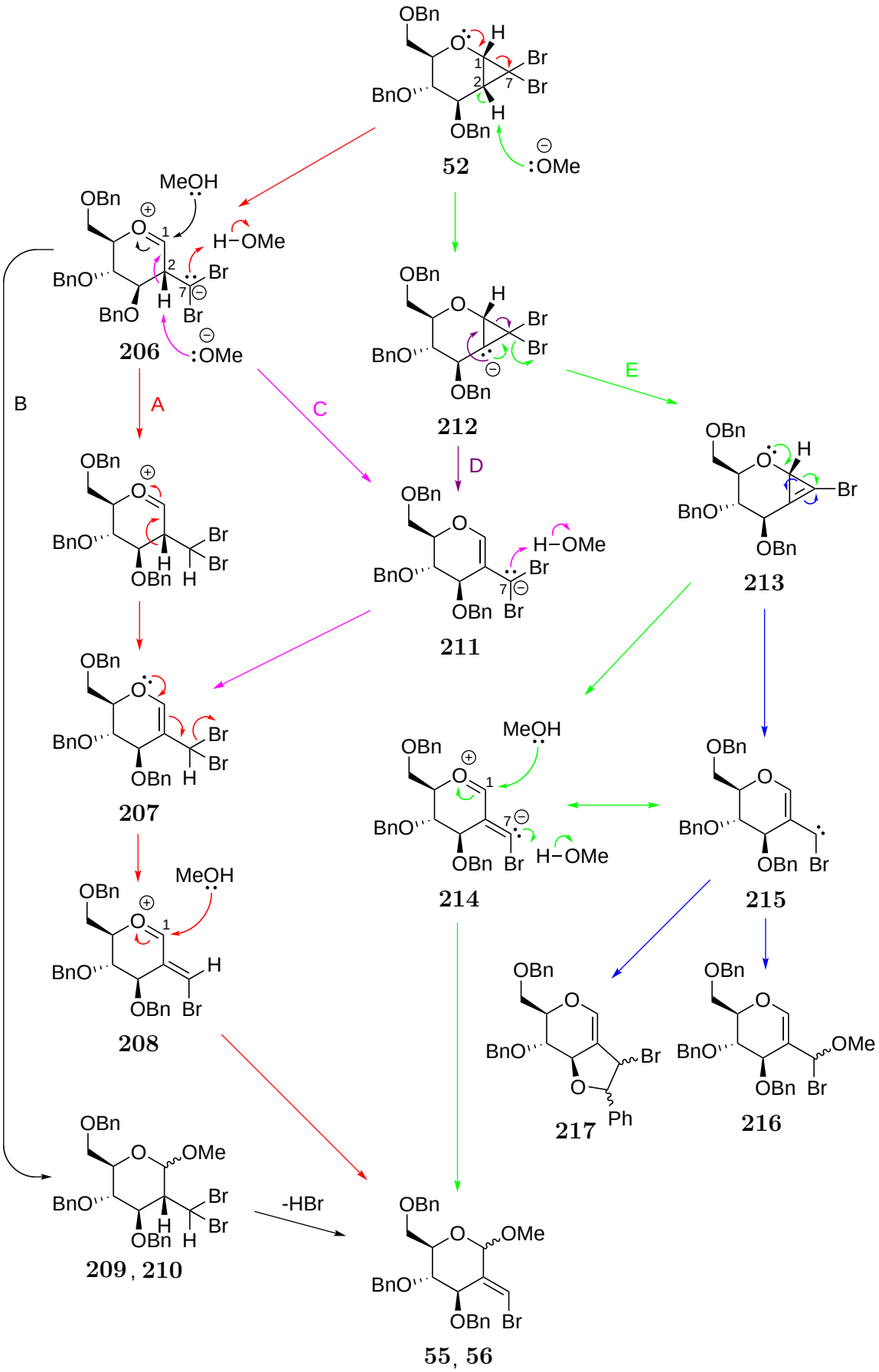
55 and **56**. Alternatively, **212** could form cyclopropene **213** (pathway E, green). Cyclopropene **213** can ring open, producing resonance structures **214** (green) and **215** (blue pathway), which are resonance structures. Protonation of C-7 and attack of methanol at C-1 in **214** results in the formation of the products **55** and **56**. The carbene resonance form **215** would be expected to insert into the methanol O-H or C-3 benzyloxy C-H bonds, leading to byproducts **216** and **217**. As these were not detected in the reactions, the carbene **215** is not likely to be a dominant resonance form.

Hewitt tentatively dismissed pathways A-D (red, black, pink and purple) based on the fact that neutral intermediate species **207** and **209**/**210** should be sufficiently long-lived that free rotation about the C-2–C-7 bond would occur and the subsequent elimination of HBr should result in a mixture of *E*- and *Z*-bromoalkene products. This is not the case as the *E*-bromoalkene products are the only products observed. Furthermore, the results in section 2.6 (page 52) suggest that formation of the *Z*-bromoalkene would be favoured, giving further weight to the pathway E (green).

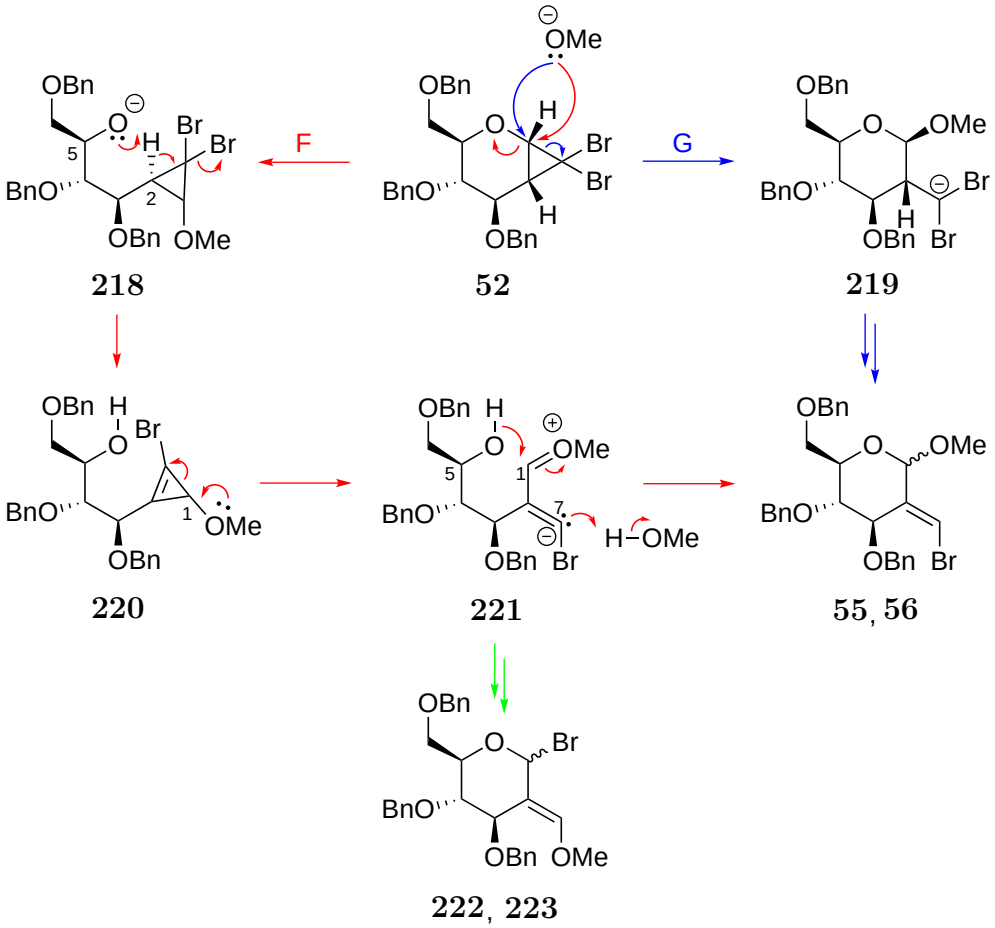
The evidence for the pathway E mechanism (green) in Scheme 2.30 is more compelling. This involves the formation of cyclopropene **213**, which is ring opened stereospecifically providing only the *E*-bromoalkene moiety. Of the five proposed pathways (A-E), pathway E is the only one involving stereospecificity towards the *E*-bromoalkene moiety.

Additional mechanisms have been considered and are shown in Scheme 2.31. They involve nucleophilic attack at the C-1 centre of **52** by sodium methoxide. Either ring opening of the pyran ring (pathway F, red), leading to **218**, could occur, or ring opening of the cyclopropane ring (pathway G, blue), forming **219**, could occur. If ring opening of the pyran occurs the alkoxide functionality at C-5 in **218** could then extract the C-2 proton, forming cyclopropene intermediate **220**. The cyclopropene ring then opens through the intramolecular formation of an oxonium ion at C-1, providing zwitterion **221**. The formation of zwitterion **221** would be rapid due to the ring strain of the cyclopropene ring. The 5-OH in **221** can then attack the C-1 position, reforming the pyran ring, protonation at C-7 leads to the desired products **55** and **56**. Formation of **219** (pathway G, blue) followed by protonation at C-7 and subsequent elimination of HBr, as shown in pathway B (black) in Scheme 2.30, also results in the desired products **55** and **56**.

Both of these mechanisms are plausible, however, we do not believe them to be in operation for two reasons. Firstly, the trajectory of nucleophilic attack of the C-1



Scheme 2.30 Mechanisms Proposed by Hewitt for the Ring Opening of **52**[41]



Scheme 2.31 Alternative Mechanisms for Ring Opening of **52**

centre in **52** appears unlikely. Assuming an S_N2 mechanism, the trajectory of the nucleophile would pass very close to either the pyran ring oxygen (cyclopropane ring opening) or a bromine atom on the cyclopropane (pyran ring opening), both of which contain considerable electron density and would hinder the reaction. Secondly, experimentally the crude reaction mixtures provide **55** and **56** very cleanly with no organic byproducts. If pathway F (red) was in operation then we would expect so see a range of byproducts, such as **222** and **223** which could form from zwitterion **221**.

On balance, the most plausible mechanism is pathway E shown in Scheme 2.30 (green pathway), involving the formation of cyclopropene intermediate **213**. However, the successful cyclopropane ring opening with sodium thiophenolate/thiophenol shows that this ring opening reaction proceeds with a much weaker base (section 2.4, page 45). There is a strong argument that the C-2 proton (pKa = 46 for unsubstituted cyclopropane[93]) would not be extracted under these reaction conditions, as thiophenol has a pKa = 10.3.[87]

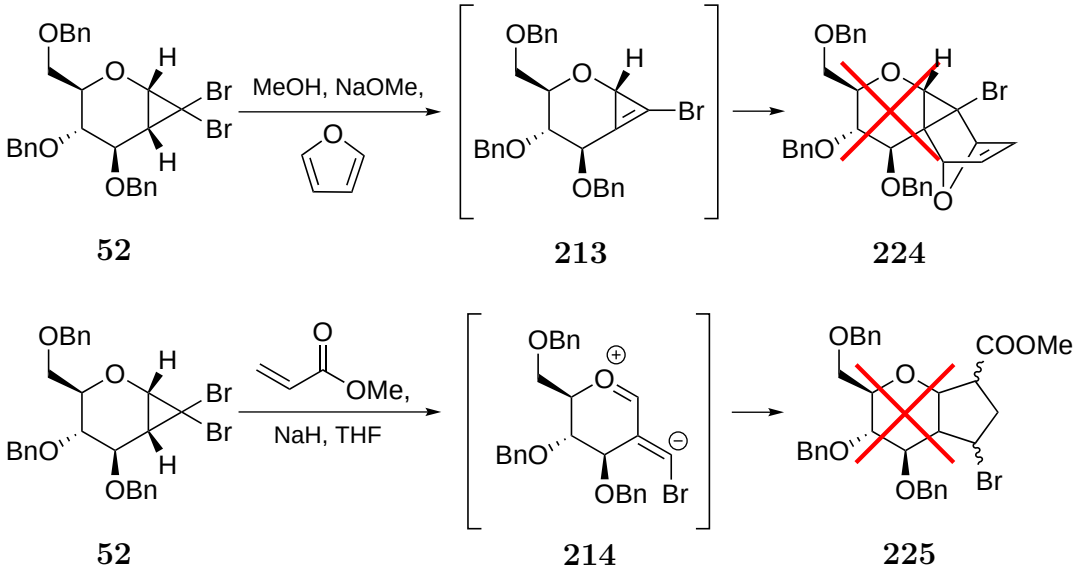
Several other reactions provide interesting information on the cyclopropane ring opening mechanism. Firstly, the preferential ring opening of **52** over **152** (Table 2.3,

Figure 2.6) is surprising given that the C-2 protons are both accessible, further computational work could be done to explore the acidity of these protons. Secondly, the cyclopropane ring opening of *gem*-dichlorocyclopropane **50** under sodium allyloxide/allyl alcohol conditions (Scheme 2.13, page 45) was also considerably slower than cyclopropane ring opening of **52** requiring heating at reflux overnight. There are several considerations as to why this reaction was considerable slower including bromide being a better leaving group then chloride, bromide having a larger ionic radius than chloride which may alter the geometry of the molecule and chloride being more electronegative than bromide. Further explorations with this cyclopropane (**50**) could be informative. Thirdly, cyclopropane ring opening reaction of **52** under sodium allyloxide/allyl alcohol conditions with a silver nitrate additive showed no change in reaction time, tentatively suggesting that the leaving of a bromide is not part of the rate determining step. Further cyclopropane ring opening reactions with **52** and other similar cyclopropanes have therefore been performed in order to explore the mechanistic possibilities. Attempts to synthesise stable forms of the various postulated intermediates and trapping of a cyclopropene species are described below.

2.8.2 Cyclopropene Trapping and Other Ring Opening Reactions

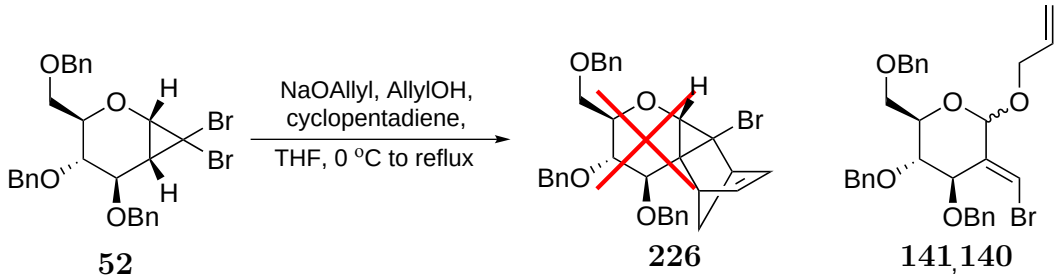
Attempts by Hewitt to trap a cyclopropene intermediate such as **213** through a Diels-Alder reaction were unsuccessful.[41] The attempted [4+2] cycloaddition reaction used furan as the solvent and resulted in minimal consumption of starting material, forming trace amounts of **55** and **56** with no evidence of trapped cyclopropene species **224** as shown in Scheme 2.32. Hewitt also explored a cycloaddition reaction with a dipolarophile, methyl acrylate, in an attempt to trap the expected zwitterion **214**. The synthesis of **214** was attempted with sodium hydride in the presence of methyl acrylate in THF as a solvent. Minimal consumption of starting material was observed, with none of the fused pyranocyclopentene **225** observed. Changing the solvent to DMF resulted in the formation of a complex mixture that appeared to contain none of the expected products.

Further attempts to trap cyclopropene **213** began with modification of the sodium allyloxide/allyl alcohol cyclopropane ring opening reaction through the addition of cyclopentadiene (Scheme 2.33). The reaction used THF as a solvent, initially at 0 °C, and after slowly warming to room temperature, the reaction was heated to THF reflux. This resulted in the formation of **140** and **141** only, with no other identifiable products recovered except cyclopentadiene and dicyclopentadiene (Scheme 2.33). The cyclopentadiene (35 eq.) was added to the basic solution before the addition of the cyclopropane **52**. When the cyclopentadiene was added it was observed that the



Scheme 2.32 Attempted Cyclopropene Trapping by Hewitt[41]

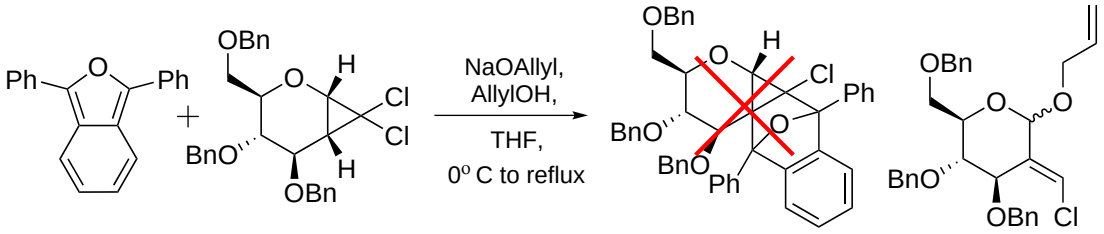
colourless solution containing sodium allyloxide/allyl alcohol and THF changed to a deep red colour. This colour is attributed to the aromatically stabilised cyclopentadiene anion, formed through deprotonation of cyclopentadiene, as cyclopentadiene has a lower pKa than allyl alcohol (in DMSO cyclopentadiene pKa = 18.0,[94] related alcohols have pKa 25-30, e.g. methanol pKa = 29.0[88]). In a modification of this method, by removing the use of sodium allyloxide and allyl alcohol instead using sodium hydride to partially deprotonate cyclopentadiene (which is also used as a solvent) before addition of the cyclopropane **52**, resulted in a complex mixture of products from which neither the desired ring opened products nor cyclopropene trapping products could be identified.



Scheme 2.33 Attempted Trapping of Cyclopropene **213** using Cyclopentadiene

A second attempt to trap the chloro analogue of cyclopropene **213** was made using 1,3-diphenylisobenzofuran (DPIBF, **227**). Following Halton's procedure,[95] DPIBF was dissolved in THF in the dark at 0 °C before the addition of *gem*-dichlorocyclopropane **50**. After three hours with no observed reaction (according to TLC) the reaction was allowed to warm to room temperature. After a further five hours and with no observed reaction by TLC, the reaction was heated to reflux for a further 24 hours. The reaction was stopped after complete consumption of the starting material was observed, yielding only the previously identified **172** and

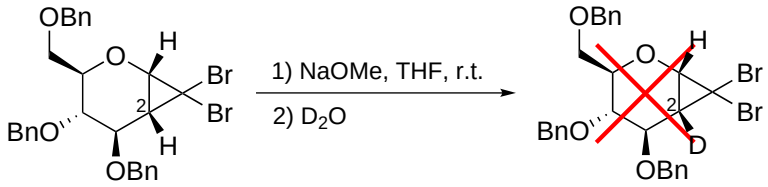
173, as well as recovered DPIBF (Scheme 2.34). A second attempt was made, with a slightly modified procedure, by performing the reaction at room temperature followed by heating to reflux. This also resulted in only the formation of **172**, **173** and unreacted DPIBF.



227 **50** **228** **172, 173**

Scheme 2.34 Attempted Trapping of Cyclopropene using **227**

An attempt was made to test whether deprotonation was occurring at C-2 as shown in Scheme 2.35. Cyclopropane **52** was treated with a solution of sodium methoxide in THF without the presence of a proton source. After 20 minutes stirring at room temperature the reaction was quenched with D_2O. If the C-2 proton had been removed, the resulting anion would have been deuterated. This was not observed nor any cyclopropane ring opened products, and only recovered starting material, **52**, was obtained.

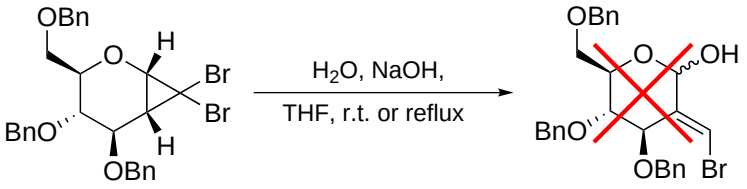


52 **229**

Scheme 2.35 Attempted H/D Exchange of H-2 in **52**

Several reactions were performed in an attempt to ring open cyclopropane **52** with sodium hydroxide and water as shown in Scheme 2.36. This would lead to the formation of hemi-acetals **190** and **191**, as well as aldehyde **192** as previously identified in section 2.4 (page 45). Initially, reactions were performed at room temperature, however, after stirring the reaction for one week no reaction was observed (TLC), with only starting material (**52**) recovered. A second attempt involved heating the reaction at reflux for one week. This also failed to ring open the cyclopropane, with unreacted **52** again being recovered.

This was a very interesting and slightly unexpected result suggesting that water may not be a suitable proton source, or sodium hydroxide may not be a suitable base/nucleophile for the cyclopropane ring opening reaction of **52**. The pKa of water in DMSO is 31.4,[88] higher than simple alcohols, which indicates the problem may

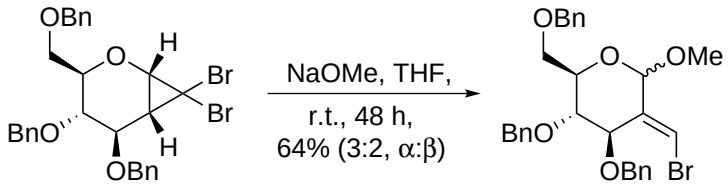


52 **190**, **191**

Scheme 2.36 Attempted Cyclopropane Ring Opening of **52** with H_2O and NaOH

be due to water not acting as a suitable proton source. Easy access to the free sugars **190** and **191** could be helpful in synthesising other glycoside products as these hemi-acetals would be good glycosyl donors once activated. However, section 2.4 (page 45) showed that these free sugars under acidic conditions rearrange to aldehyde **185**. This aldehyde is synthetically useful; however, there are more efficient literature routes to this aldehyde through Vilsmeier-Haack reactions of glucals.[96]

Hewitt explored cyclopropane ring opening reactions of **52** with sodium methoxide in the absence of methanol (sodium methoxide generated from methanol and sodium), in THF at reflux. These reactions failed to proceed, with only starting material cyclopropane recovered.[41] This was an odd result, as none of the proposed mechanisms specifically require the presence of an exogenous proton source. This reaction was further explored using the injection method discussed earlier in section 2.3 (page 37). The reaction was carried out at room temperature and resulted in the formation of the ring opened products **55** and **56** albeit much more slowly than that with methanol. Firstly, trace amounts were observed by TLC after one hour and after two days the reaction showed a reasonable extent of conversion (16% recovered starting material), yielding **55** (39%) and **56** (25%).



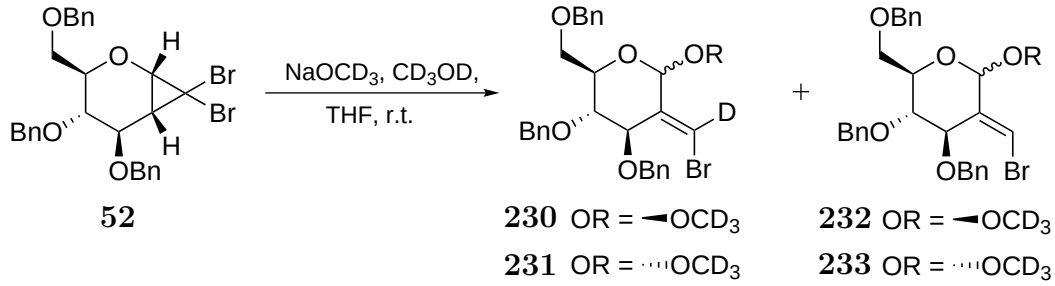
52 **55**, **56**

Scheme 2.37 Cyclopropane Ring Opening of **52** without MeOH

There are two possible explanations for this result. Over time, moisture may have slowly entered the flask and reacted with sodium methoxide to form methanol. Due to there being an excess of base (three equivalents relative to **52**) the reaction could then proceed. The second explanation is that an exogenous protic species is not necessary for the reaction to proceed due to liberation of a proton during the early steps of the reaction mechanism, however, this is not consistent with the fact that the rate of reaction was considerably slower than that in the presence of the protic species (alcohol). A control reaction with only methanol resulted in recovery of starting

material, with no other products being formed after heating the reaction to THF reflux for one week. This was consistent with the results of Nagarajan[38] and Hewitt.[41]

Hewitt performed a cyclopropane ring opening reaction using **52**, sodium d_3-methoxide and d_4-methanol. The reaction used d_4-methanol as a solvent which was heated to reflux for two hours. This resulted in the formation of **230** and **231** along with trace amounts of **232** and **233** in a combined yield of 49% (Scheme 2.38). This result suggests that the C-2 proton in **52** was not transferred to C-7 during the ring opening reaction and that the alkene proton/deuteron results from an intermolecular process.



52

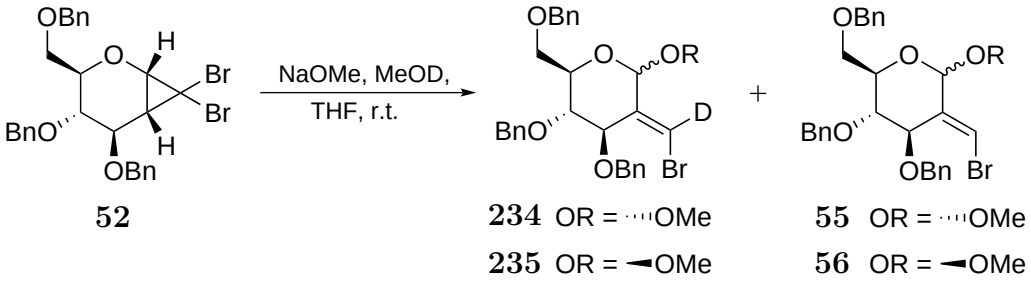
230 OR = ◄OCD$_3$ **231** OR = ····OCD$_3$

232 OR = ◄OCD$_3$ **233** OR = ····OCD$_3$

Scheme 2.38 Cyclopropane Ring Opening of **52** using $NaOCD_3/CD_3OD$ by Hewitt[41]

This chemistry was further explored with a cyclopropane ring opening of **52** using sodium methoxide/d_1-methanol. Firstly, the injection method was used at room temperature (with THF as a solvent) resulting in formation of a mixture of **234**, **235** and the protonated compounds **55** and **56**. The ratio of protonated to deuterated compounds (1:1.7, Table 2.7) was significantly higher (a greater amount of protonated product) than expected even when considering possible proton sources (H/D exchange in the d_1-methanol, addition of moisture, formation of methanol from extraction of the C-2 proton by sodium methoxide during the reaction). A second reaction, using the injection method, was performed using d_1-methanol as a solvent. This reaction was initially performed at room temperature; however, after 1.5 hours, TLC analysis showed minimal formation of glycoside products. The reaction was therefore heated to reflux and, after 16 hours, complete consumption of the starting material cyclopropane **52** was observed. The resulting products had a protonated to deuterated ratio of 1:6.5, which was higher than expected (Table 2.7) and warranted further exploration. A reasonable conclusion would be that the d_1-methanol contained a significant amount of methanol or water. An ^{1}H NMR spectrum of the d_1-methanol showed that only 3.6% methanol (or water) was present, consistent with the age of the bottle and the degree of deuteron labeling stated on the bottle of 98%.

The amount of protonated products (**55** and **56**) is of interest when using d_1-methanol (as an exogenous deuteron source), as the formation of significant amounts of **55** and **56** implies that the protonation/deuteration reactions may not be com-

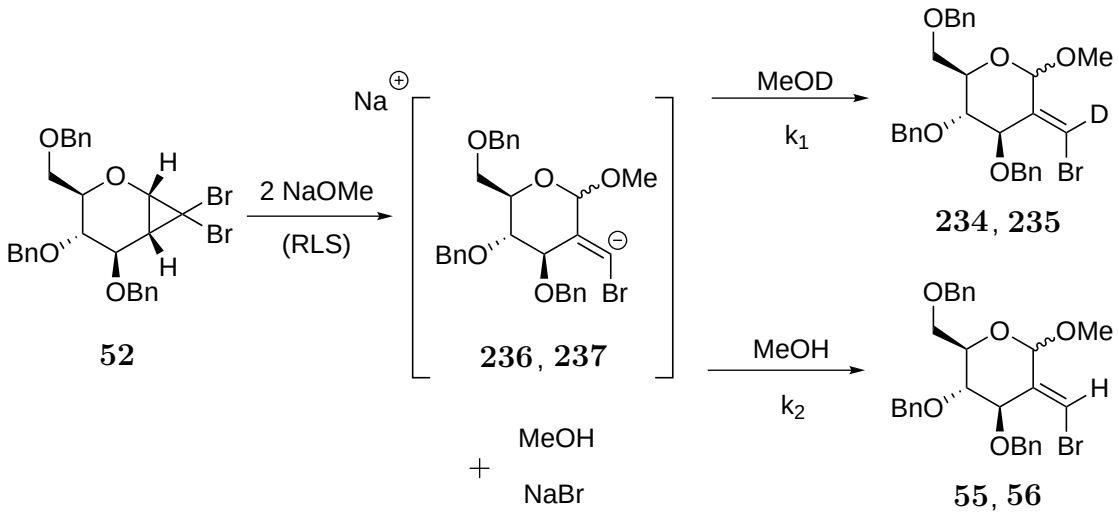


Scheme 2.39 Cyclopropane Ring Opening of **52** using NaOMe/MeOD

Table 2.7 Proton:Deuteron Ratios in Cyclopropane Opened Products

Entry	Conditions	Protonated (**55**, **56**)	Deuterated (**234**, **235**)	Ratio (H:D)
1	7 eq. of MeOD, r.t., 2 h	3.0, 1.0	5.0, 1.7	1:1.7
2	MeOD solvolysis, reflux, 16 h	1.9, 1.0	10.8, 7.9	1:6.5

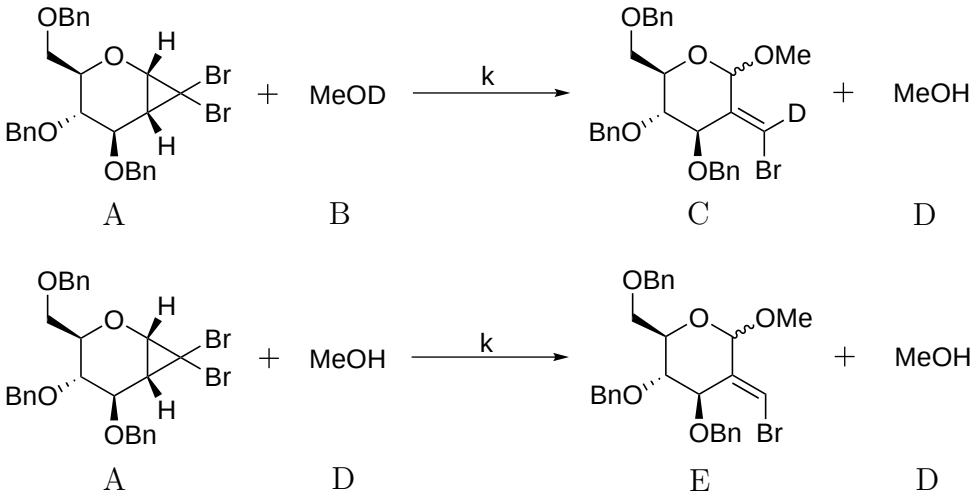
pletely intermolecular. Hewitt's proposed mechanisms (pathways A-E Scheme 2.30, page 68) all involve protonation on an anion at C-7 by an exogenous proton source. To quantify the expected amount of protonated products a simple mathematical model was developed. The model relies on the the rate limiting step (RLS) occurring in the formation of anions such as **236** and **237** through the use of sodium methoxide, with the subsequent protonation/deuteration at C-7 occurring as an acid/base reaction with the products reflecting the ratio of protons:deuterons in solution.



Scheme 2.40 Simplified Cyclopropane Ring Opening Reaction of **52** for Statistical Analysis

Two overall competitive reactions can then be used to model these reactions as shown in Scheme 2.41 (and Equations 2.1 and 2.2). Each species in the reaction is

denoted by a letter (A-E) and the concentration of that species is represented by the italicised letter. Several assumptions must be made in order to model these competitive reactions with differential equations. Firstly, we assume that anions such as **236** and **237** form as the rate limiting step. Secondly, it is assumed that the sum of the amounts of methanol and d_1-methanol is constant ($B + D = B_0 + D_0$). This is a reasonable assumption given that for every molecule of **52** that is reacted (forming either a molecule of C or E) one molecule of methanol or d_1-methanol is also reacted and one molecule of methanol is generated. Thirdly, the rate constants (k_1 and k_2) are equal such that formation of the products C and E is dependent only on the proton:deuteron ratio in solution. Fourthly, we assume that the proton source is purely methanol and that any protonation occurs at the same rate as deuteration. Lastly, the protonation/deuteration reaction can be modeled by a second order differential equation, first order in both the anion and the proton/deuteron. This is a reasonable assumption as zeroth order in either anion or proton source requires the protonation/deuteration to occur independently of the concentration of the anions or independently of the ratio.[e] The reaction could be second order, however, this is unlikely as the reaction being modelled is a simple acid/base reaction. The integrated form of the differential equations were generated (Equations 2.3-2.7) and then evaluation as $t \rightarrow \infty$ (complete consumption of cyclopropane **52**, A) was performed. The calculated ratio of C:E (deuterated:protonated products) can be compared with the experimental results as shown in Table 2.7.



Scheme 2.41 Simplistic Competitive Ring Opening of **52** using MeOD/MeOH

[e]Modeling first order differential equations in proton/deuteron and zeroth order in cyclopropane **52**, followed by evaluation of the integrated forms for complete consumption of cyclopropane, provides the same equations (Equations 2.8-2.12).

$$\mathrm{A} + \mathrm{B} \longrightarrow \mathrm{C} + \mathrm{D} \tag{2.1}$$

$$\mathrm{A} + \mathrm{D} \longrightarrow \mathrm{E} + \mathrm{D} \tag{2.2}$$

$$A = A_0 \exp\left[-k(B_0 + D_0)t\right] \tag{2.3}$$

$$B = B_0 \exp\left[\frac{A_0}{B_0 + D_0}\left(\exp\left[-k\left(B_0 + D_0\right)t\right] - 1\right)\right] \tag{2.4}$$

$$C = B_0\left[1 - \exp\left(\frac{A_0}{B_0 + D_0}\left[\exp\left(-k\left[B_0 + D_0\right]t\right) - 1\right]\right)\right] \tag{2.5}$$

$$D = D_0 + B_0\left[1 - \exp\left(\frac{A_0}{B_0 + D_0}\left[\exp\left(-k\left[B_0 + D_0\right]t\right) - 1\right]\right)\right] \tag{2.6}$$

$$E = A_0\left[1 - \exp\left(-k\left[B_0 + D_0\right]t\right)\right] - B_0\left[1 - \exp\left(\frac{A_0}{B_0 + D_0}\left[\exp\left(-k\left[B_0 + D_0\right]t\right) - 1\right]\right)\right] \tag{2.7}$$

The equations formed, Equations 2.8-2.12 (full derivation of these equations can be found in Appendix A) contain the values A_0, B_0 and D_0 as well as k which are the initial concentrations of the species A, B and D at $t = 0$ and k is the rate constant for the reactions. Evaluating these equations as $t \to \infty$ (as $\lim_{t\to\infty} \exp[-xt] = 0$, $x > 0$) we obtain $A = 0$, which is complete consumption of the cyclopropane starting material **52**. Evaluations of Equations 2.4–2.7 as $t \to \infty$ led to equations 2.8-2.12.

$$A = 0 \tag{2.8}$$

$$B = B_0 \exp\left[-\frac{A_0}{B_0 + D_0}\right] \tag{2.9}$$

$$C = B_0\left[1 - \exp\left(-\frac{A_0}{B_0 + D_0}\right)\right] \tag{2.10}$$

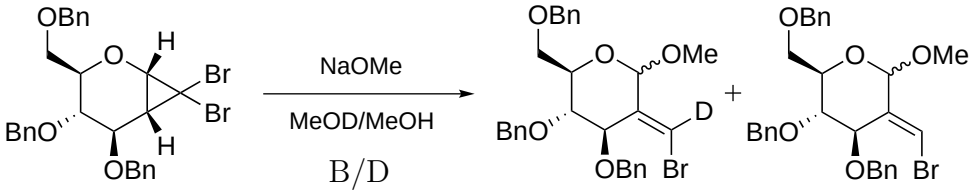
$$D = D_0 + B_0\left[1 - \exp\left(-\frac{A_0}{B_0 + D_0}\right)\right] \tag{2.11}$$

$$E = A_0 - B_0\left[1 - \exp\left(-\frac{A_0}{B_0 + D_0}\right)\right] \tag{2.12}$$

These equations can then be evaluated by introducing the experimental values for A_0, B_0 and D_0 from Table 2.7. Firstly, we can set the concentration of $A_0 = 1$, which is the initial concentration of cyclopropane **52**. This sets B_0 and D_0 as $B + D$ $= B_0 + D_0 =$ the equivalents of d_1-methanol used. In the first experiment where THF was used as a solvent, seven equivalents of d_1-methanol were used. For the second reaction d_1-methanol is used as a solvent such that approx 245 equivalents of d_1-methanol were used. The d_1-methanol is not 100% d_1-methanol as it contains minor amounts of methanol. The ^{1}H NMR spectrum of the d_1-methanol used

showed the ratio of d_1-methanol:methanol as 27.2:1 which is 96.4[5]% d_1-methanol. Using this ratio for B_0 and D_0, concentrations for each of C and E were calculated as $t \rightarrow \infty$ as well as the ratio of C:E (deuteron:proton ratio) as shown in Table 2.8 below (entries 1 and 3).

Table 2.8 Statistical Concentrations of C and E at $t = \infty$



52 **234**, **235** **55**, **56**

A C E

Entry	Initial Conditions A_0	D_0	C	E	Ratio of C:E (D:H)
1	6.75	0.25	0.90	0.10	8.9:1
2	6.75	2.25	0.71	0.29	2.4:1
3	236.30	8.70	0.96	0.04	25.7:1
4	236.30	10.70	0.95	0.05	21.1:1

Entries 2 and 4 in Table 2.8 assume that two equivalents of exogenous water are quenched by sodium methoxide (quenching of two of the three equivalents of sodium methoxide still allows the base/nucleophile ring opening to occur) providing two additional equivalents of methanol at the beginning of the reaction (D_0 and $B_0 + D_0$ increases by two equivalents).

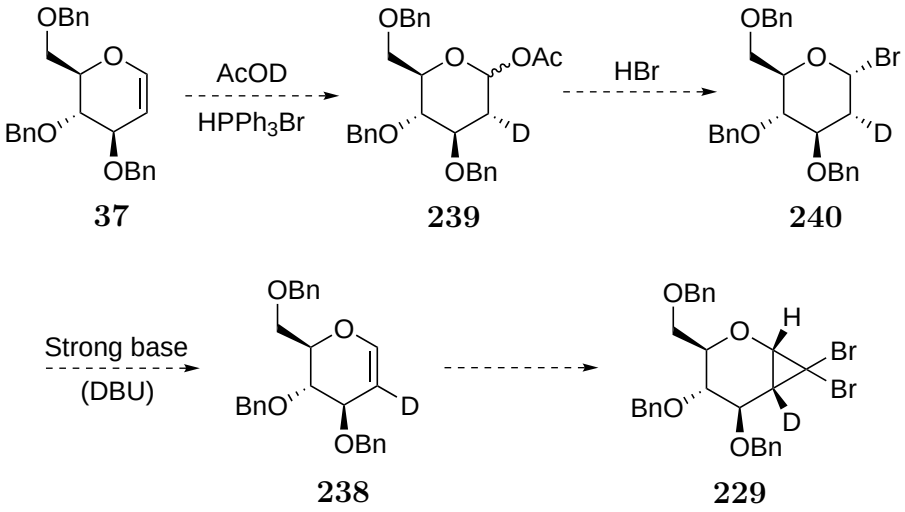
The mathematical model and experimental results are not consistent. The biggest difference between the experimental and statistical analysis is when solvolysis is used. The experimental ratio of C:E (D:H) is 6.5:1 while the statistical analysis predicts a ratio of 25.7:1. Accounting for possible quenching of sodium methoxide by water (two equivalents) the statistical analysis ratio is 21.1:1, more that three times that of the experimental result. Use of seven equivalents of d_1-methanol (96:4 d_1-methanol:methanol) gave an experimental ratio of 1.7:1, while the statistical analysis provides ratios of 8.9:1 and 2.4:1. While these experimental and statistical results are closer in magnitude, there is still a significant difference in the results.

There are several possible reasons for these inconsistent results, as the model has its limitations. It assumes the formation of anions **236** and **237** (or similar) which are proposed in the mechanisms by Hewitt.[41] It also assumes that protonation is completely dependent on the statistical ratio of d_1-methanol/methanol and not subject

to local increases (e.g. extraction of the H-2 proton). Finally, the model assumes that the rate constants for these two reactions (k_1, k_2) are equal and that any proton source in methanol is due to methanol not water. The generated ratios from the mathematical analysis suggests one or more of these assumptions may not be correct. It is likely that the rate constants are not equal or that water is affecting the statistical nature of the protonation. If water is affecting the rate of reaction, then the form (H_2O or NaOH) it exists in would effect the ratio. Using d_1-methanol solvolysis we would expect water to be quenched by sodium methoxide providing a higher concentration of methanol (along with NaOH). In THF, the pKa of water (31.4)[88] is higher than methanol (29.0)[88] such that we would expect sodium methoxide and water to exist in preference over sodium hydroxide and methanol. This may or may not affect the rate of protonation. Because of the complexity of competitive reaction equation using different rate constants (k_1, k_2) can not be formed.

There are several alternative explanations for the difference between the experimental and mathematical ratios including the possibility that the protonation step is intrinsically part of the mechanism, or, formation of anions **236** and **237** (or similar) do not form or their formation was not the rate limiting step. Overall the inconsistencies in these results suggest a complex mechanism is in operation.

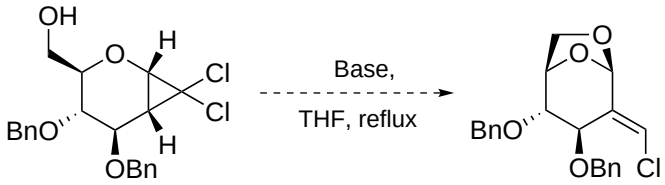
Experimentally, expansion on these reactions could be explored. Firstly, we envisage the synthesis and use of **229** in cyclopropane ring opening reactions with sodium methoxide/methanol. The C-7 H/D ratio could then be analysed in a similar method to above providing more information about possible transfer of the C-2 H/D in **52**/**229** to C-7 in the cyclopropane ring opening reaction. We envisage **229** could be synthesised through cyclopropanation of **238**. **238** has been reported once, synthesised using Kozikowski's procedure[97] (see section 2.1, page 31) from D-glucose-2-d_1. Alternatively (due to the high cost of D-glucose-2-d_1) we envisage the synthesis of **238** through an addition, exchange and elimination reaction sequence. Firstly AcOD could be added across the alkene bond in **37**. This addition could be catalysed through the use of $HPPh_3Br$ with literature precedents of the addition occurring with high stereoselectivity from the bottom face of the alkene.[98,99] The acetyl glycoside (**239**) could be transformed into an α-bromoglycoside (**240**) by reaction with HBr in acetic acid.[79] Subsequent treatment of **240** with a strong base such as DBU (as seen before in the formation of 2,3,4,6-tetra-*O*-benzyl-D-glucal[100]) should eliminate HBr/DBr, with this elimination occurring through an antiperiplanar conformation, resulting in elimination of the axial proton, not the added deuteron, thus forming the desired compound **238**. Unfortunately this synthesis was not initiated due to time constraints.



Scheme 2.42 Possible Synthesis of **229**

2.8.3 Attempted Ring Opening Reaction with 158

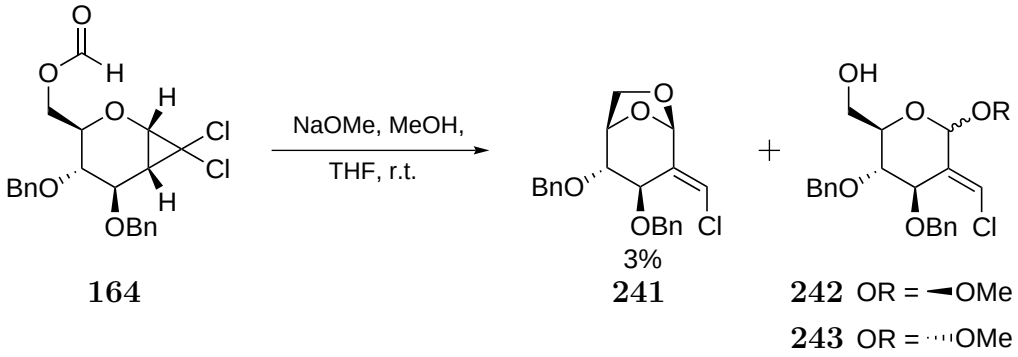
As described in section 2.2 (page 35), the hydroxylated cyclopropane **158** was synthesised using literature procedures.[38,83] The purpose of this synthesis was to explore the possibility of intramolecular nucleophilic attack accompanying the cyclopropane ring opening, which was expected to produce **241**. This would be a useful synthetic intermediate and formation of it through cyclopropane ring opening would be informative from a mechanistic point of view as nucleophilic attack by 6-OH is geometrically constrained.



Scheme 2.43 Possible Synthesis of **241**

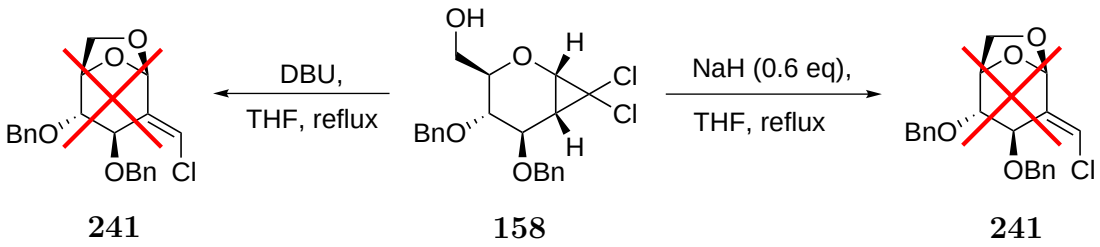
Firstly, to explore these ring opening reactions, formate ester **164**, which was isolated during the synthesis of **158**, was treated with methanol and sodium methoxide (Scheme 2.44). This precursor was initially used in preference to **158** as the deprotection of a formate ester, providing an alkoxide, is well known with sodium methoxide in methanol, the same conditions used for the ring opening reaction. The reaction was performed in refluxing THF for 48 hours, resulting in the formation of trace amounts of **241** (3%) with 12% recovered starting material and the remaining cyclopropane ring opened providing methyl glycosides **242** (23%) and **243** (21%).

While this was a good result, the yield of **241** required boosting. It was envisaged that reactions using **158** and a non-nucleophilic strong base might provide **241**. The reversibility of the acid/base reaction was important, as deprotonation of the



Scheme 2.44 Synthesis of **241**

hydroxyl functionality would produce a proton source propagating the formation of only **241**. To test this theory, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in THF was treated with a solution of **158** in THF. The reaction was heated to reflux for five days; however no reaction was observed, with only starting material cyclopropane **158** recovered. A non-reversible base was then explored (sodium hydride) as shown below in Scheme 2.45. As shown previously the cyclopropane ring opening reaction operates better in the presence of a protic species such that only 0.6 equivalents of NaH was used. This would irreversibly deprotonate 0.6 equivalents of **158** at the 6-OH providing the base and the remaining **158** would provide a proton source at 6-OH. However after heating at reflux for five days no reaction was observed, with only starting material recovered.

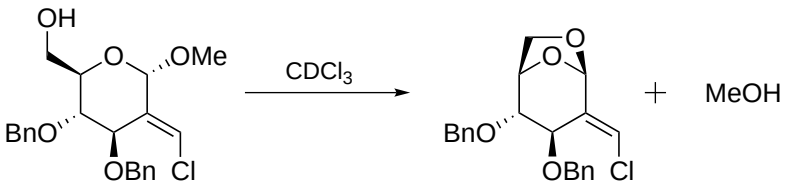


Scheme 2.45 Attempted Synthesis of **241** Using DBU or NaH

The failure of the reaction with DBU and **158** could be explained two ways. Firstly that DBU did not deprotonate the hydroxyl group, meaning no strong nucleophile was present and therefore the reaction could not proceed, or secondly that the reaction is not possible with the constrained conformational flexibility of the nucleophile. The failure of the second reaction, where **158** was deprotonated with sodium hydride, could be explained by the hydroxyl group not providing the proton source required for propagation of the reaction. Alternatively, the conformational constraint could prevent the formation of **241**. Due to time constraints, no further reactions were performed with **158**.

Interestingly, **241** (9:1 ratio with **242**) was produced from **243** that was stored for 17 days in unneutralised deutero-chloroform as observed by NMR spectroscopy (Scheme 2.46). The mechanism is likely to be related to reactions described in sec-

tion 2.6 (page 52) where isomerisation of the anomeric centre of **140** is observed. No isomerisation of the chloroalkene functionality was observed, with the nOe correlation between H-1 and H-7 still observed in **241**.

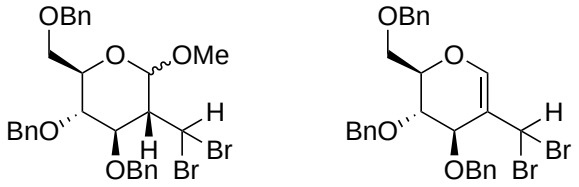


242 **241**

Scheme 2.46 Observed Formation of **241**

2.8.4 Attempted Synthesis of 209 and 210

While the above results failed to provide any conclusive evidence to discount any of the proposed mechanisms, further work has been done to synthesise the proposed intermediates **209** and **210**, pathway B (black) in Scheme 2.30 (page 68). While they are not the only stable intermediates (a third being **207**) three possible synthetic routes to these compounds were explored. Figure 2.15 below shows the structures of these three intermediates.



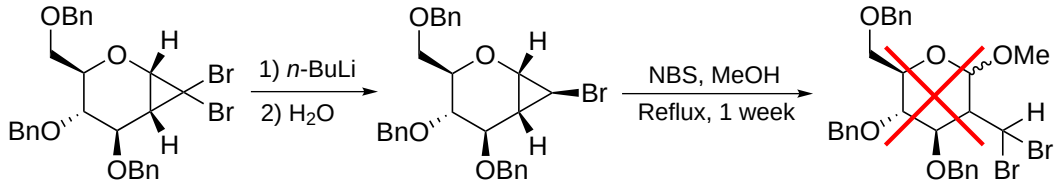
209, 210 **207**

Figure 2.15 Stable Intermediates **209**, **210** and **207**

These compounds will help determine the mechanism of the cyclopropane ring opening in several ways. Firstly, their stability in basic conditions could be tested and, if they are not stable, they may provide the products **55** and **56** thus strengthening the case for pathways A-D (red, black, pink, purple) in Scheme 2.30 (page 68). Alternatively if *Z*-bromoalkenes are produced from **209**/**210**, this would indicate that they are not intermediates in the ring opening mechanism which gave only *E*-bromoalkene products **55** and **56**.

Several different methods, to synthesise **209** and **210** were explored. The first use bromoetherification of the monobromocyclopropane **174**. The synthesis of **174** was previously achieved by Hewitt, who treated **52** with *n*-BuLi followed by quenching with water, giving modest yields (up to 26%).[41] Repetition of this method resulted in an increase in yield (up to 79%) with a shorter reaction time of 30 minutes. There are many examples of haloetherification shown in subsection 1.2.2 (page 13) which

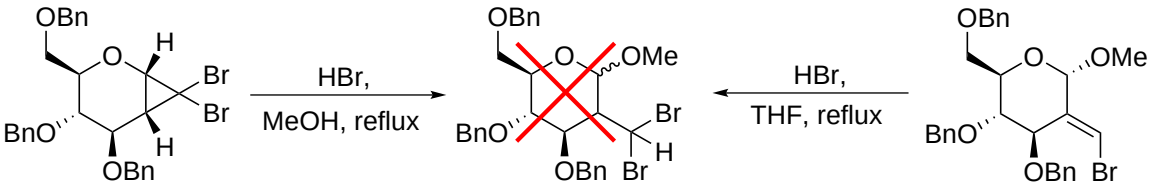
all use an electrophilic source of iodine or bromine with the most common reagents being NIS or NBS. However, bromoetherification of **174** with NBS in methanol proved unsuccessful (with no conversion of starting material) even when refluxing in methanol for one week (Scheme 2.47).



52 **174** **209, 210**

Scheme 2.47 Attempted Bromoetherification of **174**

The second synthetic route involved the treatment of **52** with strong acid. Nagarajan performed similar reactions with the parent methylene cyclopropane (**41**), from which the yields were modest and reaction times generally of several weeks.[38] Treatment of **52** with HBr in methanol was attempted, but the desired **209** and **210** were not observed after one week. The third route involved treatment of **55** with HBr in the hope that addition would occur affording the desired products, **209** and **210**. Reacting **52** with HBr in acetic acid and THF and heating to reflux for one week resulted in the formation of a complex mixture, from which none of the desired compounds could be identified (Scheme 2.48). Further attempts to synthesise **209** and **210** were considered; however, due to the time constraints, they were not pursued.



52 **209, 210** **55**

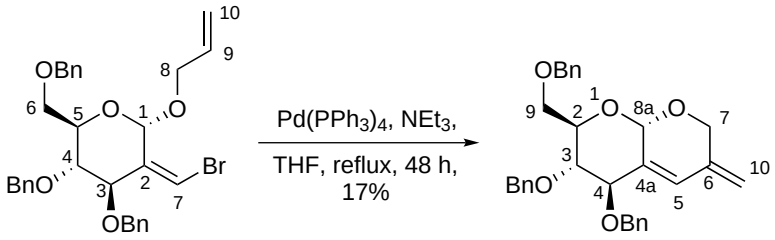
Scheme 2.48 Attempted Synthesis of **209** and **210**

2.9 Palladium-Catalysed Cross-Coupling Reactions

2.9.1 Heck Reactions of 141 and 194

The Heck reaction is widely used for coupling an alkyl/alkenyl/aryl halide or triflate with an alkene. Cyclopropane ring opened products **140**, **141** and **194** contain an alkenylbromide functionality ideal for cross-coupling reactions. The intramolecular Heck reaction of **194** was successful when heating in THF for two days in the presence of $Pd(PPh_3)_4$ and triethylamine (Scheme 2.49). This produced **205** in a low

yield (17%), coincidently very similar to the molar percentage of palladium catalyst. This could suggest that only one turnover of the catalyst occurs, indicating that the base used, in this case triethylamine, was not able to regenerate the catalyst. The reaction used THF as solvent, heated to reflux for two days.



194 **205**

Scheme 2.49 Intramolecular Heck Reaction of **194**, Forming **205**

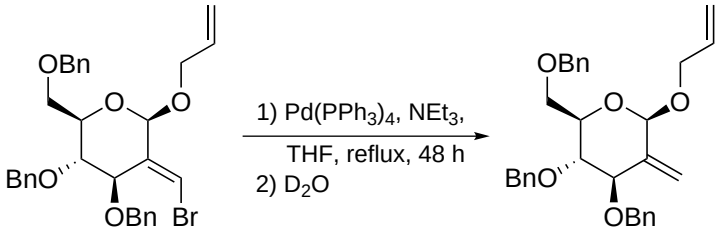
The ^{1}H NMR spectrum of **205** contains significant differences to that of **194**. The new product is missing the characteristic proton signals for H-7 and H-9 in **194**. Instead, the defining feature is four singlets at 6.23, 5.51, 5.01 and 4.97 ppm corresponding to H-5, H-8a and the two methylene protons H-10a and H-10b respectively. These four singlets, the remaining protons in the molecule (protons H-2–H-4 and H-9a,b in **205** are similar to H-3–H-5 and H-6a,b in **194**) and the mass spectrum quasimolecular ion peak of m/z $[M+Na]^+$ of 507.2144, is consistent with the molecular formula $C_{31}H_{32}O_5Na^+$ expected for **205**.

The configuration at the 8a carbon is assumed to arise from that present in the starting material. 2D NOESY experiments showed no correlation between H-8a and H-2 or H-8a and H-9a,b as expected for this structure. However, the absence of an nOe correlation does not provide conclusive evidence about stereochemistry. Nonetheless, it is presumed no isomerisation of H-1 (H-8a in the product) occurs during the reaction. The 8a centre of **205** is therefore tentatively assigned as *S*, based on the starting material stereochemistry.

The Heck reaction of *E*-bromoalkene **141** was also explored. This was done to explore a possible *E*- to a *Z*-bromalkene isomerisation under catalytic palladium conditions (and possible formation of **205**) and as a control reaction for Suzuki cross-coupling reactions described in subsection 2.9.3 (page 86). Thus a solution of **141** in THF was treated with $Pd(PPh_3)_4$ and triethylamine and heated to reflux for two days. This resulted in the formation of small amounts of the desbromo reduced product **244** with none of the *E*-alkenylbromide or Heck product **205** observed. The desbromo product **244** is easy to identify, as the H-7 peak of **141** at 6.82 ppm becomes two apparent triplets at 5.30 and 5.15 ppm, consistent with the methylidene present in **244**. The mass spectrum of this compound displayed a quasimolecular ion peak at m/z $[M+Na]^+ = 509.2311$, consistent with the molecular formula

$C_{31}H_{34}O_5Na^+$ for compound **244**.

The formation of this product is difficult to explain, with the most likely explanation being a reaction between the alkenylbromide of **141** and a palladium hydride species. How this species is formed is unexplained. Similar observations have been made by Schuster, another group member, when performing Sonogashira cross-coupling reactions of oxepines derived from cyclopropane **52**.[101] In an attempt to discount the water quench as the cause of the reduction a second reaction was performed with the reaction quenched with D_2O rather than water after two days at THF reflux (Scheme 2.50). Protic **244** was still produced (in 17% yield) with no deuterated analogue present.

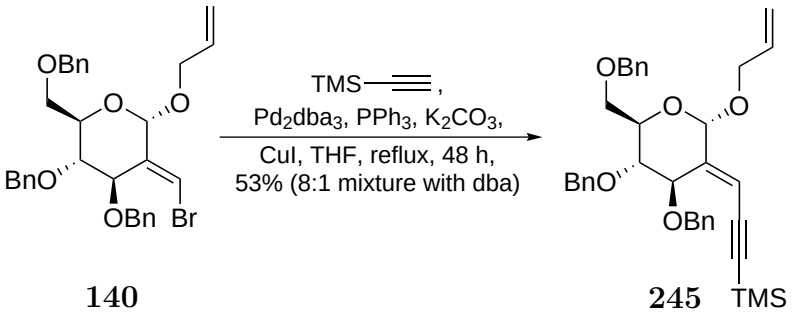


141 **244**

Scheme 2.50 Attempted Intramolecular Heck Reaction of **141**

2.9.2 Sonogashira Cross-Coupling of 140

The Sonogashira cross-coupling reaction is an efficient way to synthesise enynes, a motif seen in a number of natural products.[67] The mechanism of this reaction is generally regarded as comprising two catalytic cycles, one involving palladium and the other a copper catalyst (Further details on the mechanism are shown in subsection 1.3.3, page 24). The alkenylbromide functionalities in **140**, **141** and **194** are suitable for a Sonogashira reaction. One such reaction involved dissolving **140** in THF and then successively adding tris(dibenzylideneacetone)dipalladium, triphenylphosphine, potassium carbonate, copper iodide and finally trimethylsilylacetylene (Scheme 2.51). After stirring at reflux for two days the reaction was stopped and the ^{1}H NMR spectrum of the crude material recorded, this showed complete consumption of the starting material. The starting material **140**, product **245** and dibenzylideneacetone all have similar R_f values (R_f = 0.25 (9:1 hexanes:ethyl acetate)) on silica gel, making purification of the product, **245**, difficult. The product was therefore isolated as a mixture with dibenzylideneacetone (8:1 mixture) in 53% yield. Removal of dibenzylideneacetone was a significant problem throughout this work, making Pd_2dba_3 as undesirable pre-catalyst. An attempt to remove this ligand was made by stirring with powdered charcoal for 30 minutes. This resulted in a significant reduction in the amount of dibenzylideneacetone, however it also significantly decreased the yield of the desired product.



140 **245**

Scheme 2.51 Sonogashira Cross-Coupling of **140** and TMSA

Identification of the product was relatively straightforward. In the ^{1}H NMR spectrum, there was a significant decrease in the chemical shift of the C-7 proton, which moved from 6.82 ppm in **141** to 5.99 ppm in **245**. Observation in the ^{13}C NMR spectrum of the two alkyne peaks and methyls attached to the silicon atom was further confirmation. The most significant evidence of cross-coupling is present in the HMBC spectrum where correlation of H-7 to both of the alkyne carbon peaks confirm the attachment at the 7 position has taken place. The mass spectrum of **245** also confirms this structure with a $[M+Na]^{+}$ quasimolecular ion at m/z = 605.2704 (Formula $C_{36}H_{42}O_5SiNa^{+}$).

2D-NOESY spectroscopy were also explored to determine the geometry of the alkene. It showed a correlation between H-1 and H-7, confirming the retention of the *E*-alkene. The NOESY also indicated that **245** is the α-glycoside, with weak correlations observed between H-1 and H-6a (and no correlation observed between H-1 and H-5). This is consistant with the anomeric configuration of the starting material.

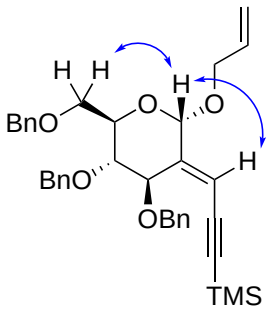


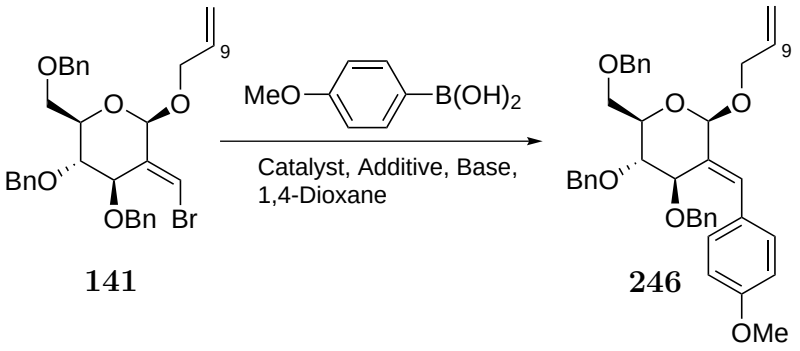
Figure 2.16 nOe Correlations in **245**

2.9.3 Suzuki Cross-Coupling

The Suzuki cross-coupling reaction is an extremely powerful carbon-carbon bond forming reaction. There are a variety of boron compounds that can be utilised for these reactions including boronic acids, boronate esters and potassium trifluoroboronates. We aimed to explore and optimise the cross-coupling of **140** and/or **141** with a variety of boron reagents to provide a variety of compounds.

The first organoboron reagent explored was *p*-methoxyphenyl boronic acid. The solvent 1,4-dioxane was used in all cases, heated to reflux to allow at least partial solubility of all reagents. The table below (Table 2.9) shows the resulting attempts to optimise the production of **246** using **141**, Pd_2dba_3, an additive and a base.

Table 2.9 Suzuki Cross-Coupling Reactions with *p*-Methoxyphenylboronic Acid



141 **246**

Entry	Precatalyst, Additive	Base	Conditions	Conversion	Yield (%)
1	Pd_2dba_3, PPh_3	K_2CO_3	Reflux 36 h	degradation[a]	-
2	Pd_2dba_3, PPh_3	$K_3PO_4 \cdot H_2O$	Reflux 48 h	degradation	-
3	Pd_2dba_3, PPh_3	KF	Reflux 20 h	30:70 **246**:**141**	32
4	Pd_2dba_3	KF	Reflux 20 h	**246**	44

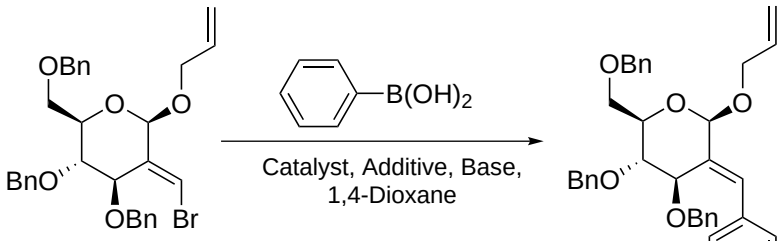
[a]Complete loss of allyl multiplet at 6.00–5.90 ppm

The general procedure involved dissolving the substrate **141** in 1,4-dioxane at room temperature. The palladium catalyst was then added along with any additives such as PPh_3 and the reaction stirred at room temperature for five minutes. The boron species was added followed by the base. The first two entries in Table 2.9 involved the use of either potassium carbonate or tripotassiumphosphate hydrate as a base and heating the reaction to reflux for 36 or 48 hours. TLC analysis of these reactions every 4–16 hours showed the remaining starting material spot (R_f = 0.35 (9:1 hexanes:ethyl acetate)) and increasing high polarity products (R_f = 0 – 0.1 (9:1 hexanes:ethyl acetate)). ^{1}H NMR spectroscopy of these reaction mixtures showed complete degradation of the starting material. Entry 1 showed complete loss of the allyl multiplet at 6.00–5.90 ppm (H-9). The deprotection of allyl ether protecting groups is known to occur through reaction with palladium(0).[102–104] It is likely this is occurring with complete loss of the allyl aglycone. Entries 3 and 4 used potassium fluoride as the activator of the boronic acid. Use of a PPh_3 additive (entry 3) resulted in partial conversion to **246** (30% conversion with remaining starting material) while reaction without the PPh_3 additive resulted in complete conversion to the desired product, **246** isolated in 44%.

Due to the lack of polarity difference between **141** or **246**, the unsubstituted phenyl-

boronic acid was explored as boron reagent with the aim to produce and separate **247**. The table below (Table 2.10) shows a range of reaction conditions explored in an attempt to optimise the Suzuki cross-coupling. All of the reactions used 1,4-dioxane as solvent and the same general method as described above in the synthesis of **246**. A range of palladium precatalysts were explored.

Table 2.10 Suzuki Cross-Coupling Reactions with Phenylboronic acid



141 **247**

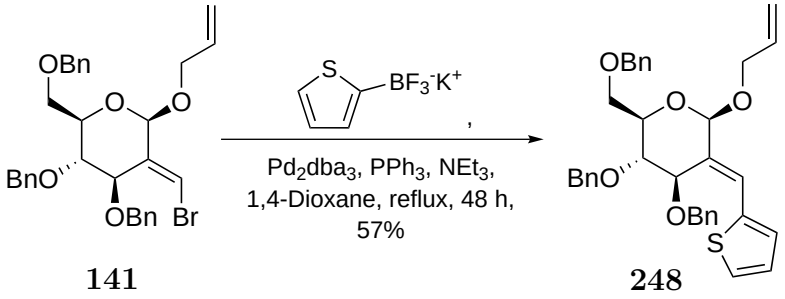
Entry	Precatalyst, Additive	Base	Conditions	Conversion	Yield (%)
1	Pd_2dba_3, PPh_3	K_2CO_3	Reflux 3 d	degradation	-
2	$Pd(PPh_3)_4$	K_2CO_3	Reflux 20 h	**247**+trace**244**	31
3	$Pd(PPh_3)_4$	K_2CO_3	r.t. 20 h	No reaction	-
4	$Pd(PPh_3)_4$	KF	Reflux 20 h	degradation	-
5	$Pd(PPh_3)_4$	NaOMe	Reflux 20 h	degradation[a]	-
6	$Pd(PPh_3)_4$	$K_3PO_4 \cdot H_2O$	Reflux 20 h	12:45 **247**:**141**	-
7	$Pd(PPh_3)_2Cl_2$	KF	Reflux 20 h	degradation[a]	-
8	$Pd(PPh_3)_2Cl_2$	K_2CO_3	Reflux 20 h	degradation[a]	-
9	$Pd(dppf)Cl_2$	KF	Reflux 20 h	degradation[a]	-
10	$Pd(dppf)Cl_2$	K_2CO_3	Reflux 20 h	degradation[a]	-
11	$Pd(OAc)_2$, XantPhos	NaOtBu	Reflux 20 h	3:2 **247**:**244**	66

[a]Complete loss of allyl multiplet at 6.00–5.90 ppm

Most of the reactions displayed in Table 2.10 showed degradation of the sugar compound. Entries 5,7,8,9 and 10 again showed loss of the allyl peak (H-9) from the allyl glycoside which would be present in the desired product. Entries 2, 6 and 11 showed varying ratios of conversion to the desired product **247** as a mixture with either the reduced product **244** (entry 2 and 11) or starting material (entry 6). An isolated yield of 31% was once achieved (entry 2) seperated from the trace amounts of **244**. Entry 11 using $Pd(OAc)_2$ and Xantphos formed **247** in 40% conversion which could not be separated from **244** in significant quantities (66% yield of a 3:2 mixture).

Reactions with the α-anomer were attempted using *p*-methoxyphenyl or phenylboronic acids however degradation occurred in all cases. Cross-coupling of the chloroalkene allyl glycoside **172** and phenylboronic acid in 1,4-dioxane was attempted (using $Pd(PPh_3)_4$ and K_2CO_3), however after two days heating at reflux no reaction was observed by ^{1}H NMR spectroscopy; instead starting material remained.

The above attempts failed to find optimal cross coupling conditions, however, two other boron reagents were investigated. Firstly, a reaction of **141** with methyl boronic acid was explored using the same conditions as entry 2 of Table 2.10. Degradation of the starting material was observed after two days heating at reflux. The second reagent explored was potassium thiophen-2-yl trifluoroboronate. With 1,4-dioxane as a solvent, a Pd_2dba_3, PPh_3 catalyst system, and triethylamine as a base, clean conversion to **248** (57%) was achieved (Scheme 2.52).



141 **248**

Scheme 2.52 Suzuki Coupling Forming **248**

Confirming the identity of **246**, **247** and **248** was done in three ways. First, 1D and 2D NMR spectroscopy with specific focus on the HMBC experiment which showed correlations between H-7 and the carbons formed in the carbon-carbon bond forming reaction. Secondly, mass spectrometry was used to confirm the molecular formulae of each of these products. Thirdly, 1D nOe difference experiments irradiating H-1 and H-7 confirmed the *E* configuration of the alkene as well as the anomeric configuration indicating no isomerisation during these reactions (H-1–H-5 correlations seen).

Several general conclusions can be made about the palladium-catalysed cross-couplings performed above. Generally the reactivity was low, forming products in low-medium yields. This could be due to two reasons; the catalyst system was ineffective or the bromoalkene was unreactive. High temperatures were used in these reactions which contributed to the degradation of the starting materials. Many of the Suzuki reactions, using nucleophilic bases, resulted in degradation with complete loss of the allyl multiplet peak at 6.00–5.90 ppm. This may be due to deprotection of the anomeric centre (by palladium(0)) followed by degradation of the free sugars. Activation of the *p*-methoxyphenyl boronic acid using potassium fluoride resulted in some conversion while use of the activated potassium thiophenyl-trifluoroboronate compound resulted in very clean conversion. This suggests that activation of the boron in the other reactions with boronic acids may be the source of the low reactivity.

There is room for significant improvement of the reaction conditions for the pallad-

ium-catalysed cross-couplings of alkenyl bromides **140**, **141** and **194**. Determining a method for monitoring reaction progress would be a top priority as the formation of most of the products above could not be determined by TLC. Decreasing reaction times and temperatures should be considered, as significant degradation was observed with the long reaction times and high temperatures, which would rely on more active boron compounds, less nucleophilic bases and more active catalysts. In this way, optimal conditions for the palladium-catalysed cross-coupling of alkenyl bromides **140**, **141** and **194** may be found.

2.10 Conclusions

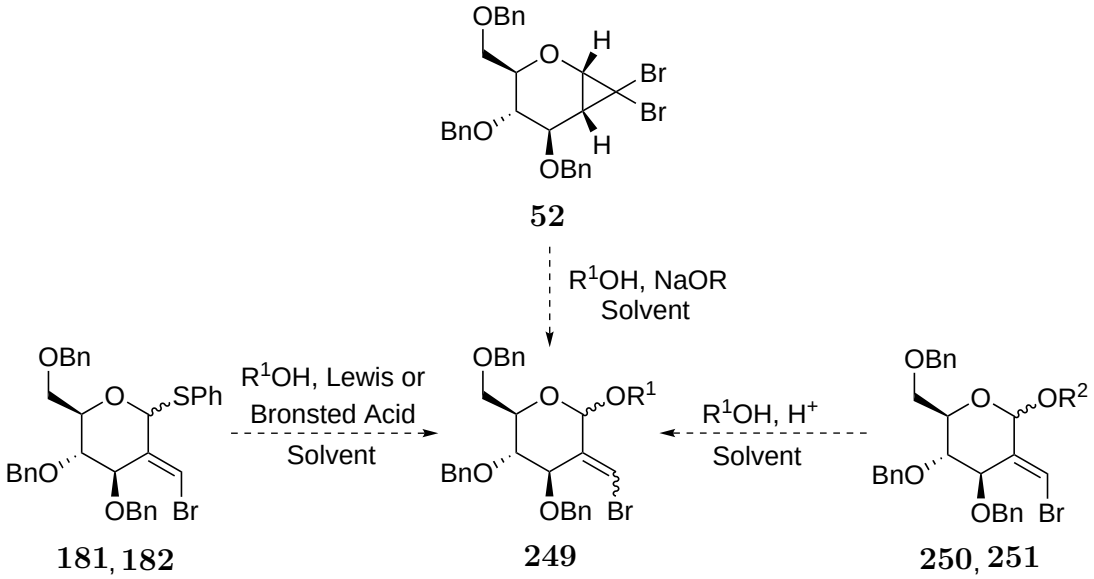
The three main research goals of this thesis were achieved. Firstly, the cyclopropane ring opening of **52** forming 2-*C*-branched pyranosides was further optimised through the used of sodium allyl oxide and allyl alcohol. A new method whereby the cyclopropane was added as a solution resulted in a significant reduction in reaction time and an increase in yield. Use of this method to explore the use of sulfur and nitrogen nucleophiles resulted in the formation of 2-*C*-branched thioglycosides (using thiophenol) and 2-*C*-branched glycosylamines. Rapid degradation of the glycosylamines was observed generating a 2-*exo*-aldehyde **185** as well as free sugars **190** and **191** in equilibrium with the corresponding aldehyde **192**.

It was found that treatment of **140** and **141** with acid in allyl alcohol caused convergence to the β-anomer **141**, while use of dichloromethane as a solvent resulted in the formation of the *Z*-bromoalkene **194**. Secondly, the mechanism for the formation of 2-*C*-branched pyranosides from **52** was explored through reactions that attempted to trap a possible cyclopropene. Use of d_1-methanol to explore the protonation/deuteration at C-7 led to exploration of the expected amount of protonated product through a mathematical analysis. This suggested that simple acid/base reaction involving an exogenous proton/deuteron source may not be in operation. Ring opening of cyclopropane **158**, which contained an internal nucleophile, was explored as were reactions to synthesise neutral intermediates **209** and **210**. These reactions provided some useful information, but, they did not help discount any of the proposed mechanisms. Thirdly, three named palladium-catalysed cross-coupling reaction were explored (Heck, Sonogashira and Suzuki) providing a small range of 2-*C*-branched pyranosides.

Chapter 3

Future Work

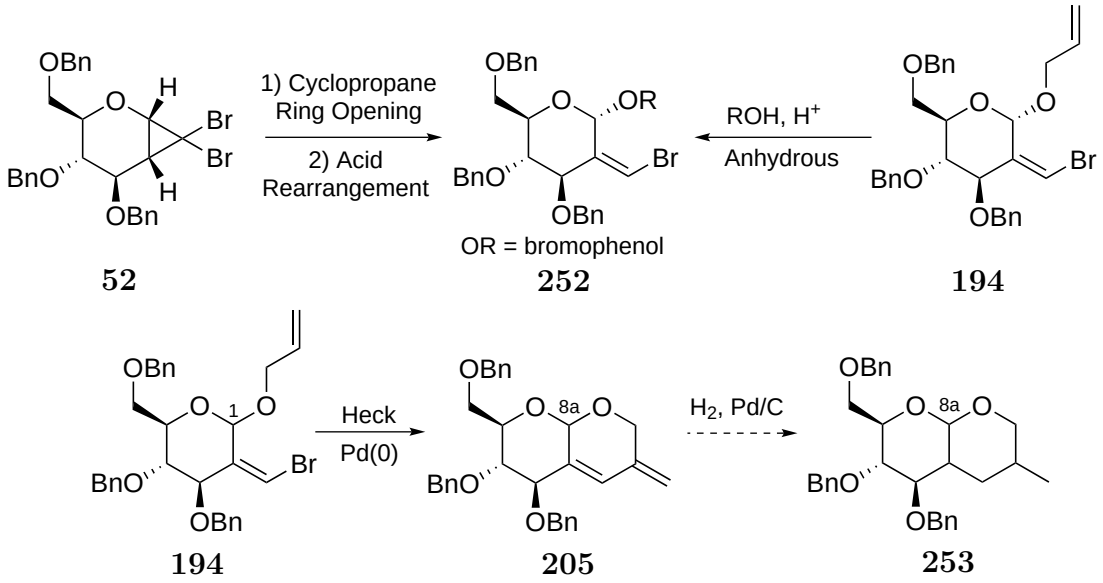
In several sections of this thesis, there have been indications where further work could be explored. Firstly, the expansion of the cyclopropane ring opening reaction using more complex nucleophiles would give the ability to expand into disaccharides, polysaccharides and glycoconjugates (**249**). If direct nucleophilic attack reactions do not provide the desired products, two other methods could be explored, the first being a glycosidation reaction with thioglycosides such as **181** and **182** as mentioned in section 2.4 (page 45). Alternatively, acid-promoted glycosidation could be explored, however the *E*- to *Z*-bromoalkene isomerisation observed in section 2.6 (page 52) may be difficult to control.



Scheme 3.1 Possible Expansion into Complex Alcohols

The isomerisation of the bromoalkene under acidic conditions could be explored further as discussed above. Further optimisation to improve the yield of **194** would be desirable and could be explored through the use of a range of non-aqueous acids and other solvents. Confirmation of the configuration at the anomeric centre (C-1) would be necessary in order to use this isomerisation method in further work. The best avenue to determine this stereochemistry would be crystallography, however,

crystal growth throughout this project proved to be difficult. Use of bromophenol as the aglycone (in the ring opening of cyclopropane **52**) could aid the crystal growth process. Alternatively, the bicyclic product **205** produced when **194** underwent an intramolecular Heck reaction could be hydrogenated, with the $^3J_{H-H}$ coupling constants within the ring system or nOe correlations providing conclusive evidence of the stereochemistry at the 8a centre in the starting material **194**.



Scheme 3.2 Expansion of Acid Rearrangement Reactions and Confirmation of the C-1 Stereochemistry

Determining the mechanism of the cyclopropane ring opening reaction proved elusive, however, it created several possible directions for future work. Firstly, computational modeling to determine the pKa of the C-2 proton of both cyclopropanes **52** and **152** could rule out (or provide evidence for) the cyclopropene reaction mechanism (pathway E (green), Scheme 2.30, page 68). Kinetic experiments in the ring opening reaction of cyclopropane **52** with sodium methoxide and methanol/d_1-methanol could be explored to provide more data for the mathematical modeling results. The deuterated cyclopropane **254** was proposed in section 2.8 (page 66) which could be used in similar cyclopropane ring opening reactions to further test whether the C-7 proton (deuteron) is transferred only from an exogenous source or if some internal transfer is possible. Use of catalytic methanol should be explored to test if the reaction can proceed under such conditions. Further attempts should be made to form neutral intermediates **209** and **210** through non-cyclopropanated carbohydrate methods, to test if the HBr elimination occurs stereospecifically as seen in the cyclopropane ring openings **52** and **152**. Alternatively, a mixture of *E*- and *Z*-bromoalkenes would indicate that these are not intermediates in the cyclopropane ring opening of **52** and **152**.

Lastly, further exploration of the palladium-catalysed cross-coupling reaction to pro-

vide a greater range of compounds would be desirable. Testing more active organometallic reagents, more active catalysts, varying solvent, temperature and shorter reaction times would be beneficial towards this goal.

Chapter 4

Experimental

4.1 General Experimental

Unless otherwise stated, the following conditions apply. All reactions were performed under argon (zero grade) in vacuum-dried glassware using dry solvents and standard syringe techniques. Tetrahydrofuran (THF) was freshly distilled in the presence of sodium benzophenone ketyl radical ion. Dichloromethane (CH_2Cl_2), and diethylamine (Et_2NH) were distilled in the presence of calcium hydride. Methanol (MeOH), allyl alcohol (AllylOH), 1,4-dioxane and toluene were distilled in the presence of sodium. Acetic anhydride was used as received. Anhydrous *N*,*N*-dimethylformamide (DMF) and methanol-d_1 were purchased from Aldrich Chemical Company and were used without further purification. Chloroform and bromoform were both used as received (with small amounts of ethanol as stabiliser). Sodium hydride (NaH) was obtained as a 60% (w/w) dispersion in paraffin oil and was used as obtained, unless otherwise stated. *n*-BuLi (*n*-butyllithium) was obtained as a 1.6 $molL^{-1}$ solution in hexanes, unless otherwise stated. Potassium fluoride dihydrate was crystallised from a super-saturated aqueous solution of potassium fluoride. All other reagents were of commercial quality and distilled prior to use if necessary.

Reaction progress was monitored using aluminium-backed thin layer chromatography (TLC) plates pre-coated with silica UV254 and visualised by either UV fluorescence quenching (254 nm) or anisaldehyde dip. Purification of products via flash chromatography was conducted using a column filled with Silica Zeoprep 60 (40-63 microns) as the matrix, obtained from Pure Science Ltd, with solvent systems as indicated. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 500 (operating at 500 MHz for ^1H and 125 MHz for ^{13}C) spectrometer, NOESY spectra were recorded on either a Varian Unity Inova 300 (300 MHz for ^1H) or on a Varian Direct Drive instrument equipped with an inverse-detected triple resonance HCN probe operating at 25 °C (600 MHz for ^1H). All chemical shifts (δ) were referenced to solvent peaks if possible ($CDCl_3$: ^1H - 7.26 ppm, ^{13}C - 77.16 ppm; C_6D_6: ^1H -

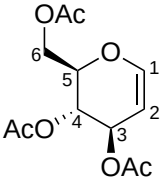
7.16 ppm, ^{13}C - 128.06 ppm). Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured on an Autopol II polarimeter from Rudolph Research Analytical. Infrared spectra were obtained on a Brucker Tensor 27 spectrometer. High-resolution mass spectrometry (HRMS) was performed on a Waters Q-TOF Premier^{TM} Tandem Mass Spectrometer operating in ESI mode. The structure of each compound is presented with the corresponding method of preparation and spectroscopic data.

4.2 Chapter 2 Experimental

Tri-*O*-acetyl-D-glucal (150)

Using a modification of Kozikowski's procedure,[79] a magnetically stirred solution of D-glucose (**148**) (132 mg, 0.7 mmol) in acetic anhydride (76 mL, 804.0 mmol) was treated dropwise with conc. perchloric acid (0.45 mL, 6.9 mmol). Additional D-glucose (**148**) (19.71 g, 109.3 mmol) was added slowly over 45 minutes, at a rate that maintained a temperature of 40–50 °C. Upon complete addition of D-glucose, the solution was allowed to cool to room temperature, then treated with a 33% (w/w) solution of hydrobromic acid in acetic acid (78 mL, 430 mmol). After 90 minutes, the solution was diluted with dichloromethane (180 mL) and washed with ice-cold water (2 x 50 mL), then cold sat. sodium bicarbonate solution (6 x 50 mL). The organic phase was dried, filtered and concentrated to afford crude tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**149**) as an off-white solid. This was used without further purification.

A mechanically stirred dispersion of zinc dust (47.92 g, 733.1 mmol) in water (150 mL) was cooled to 0 °C, diluted with acetic acid (150 mL), then treated dropwise with a solution of **149** in diethyl ether (150 mL) over one hour. The reaction was allowed to warm to room temperature and left to proceed overnight. The solution was filtered, then diluted with dichloromethane (200 mL). The solution was washed successively with water (3 x 60 mL), sat. sodium bicarbonate solution (4 x 50 mL), then brine (60 mL). The organic phase was dried, filtered and concentrated to provide **150** as a white solid (26.11 g, 87%). Spectral data matched those which have been previously reported.[105]

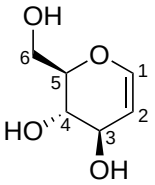


R_f = 0.3 (3:1 hexanes:ethyl acetate); m.p. 49.0–51.0 °C (lit.[106] m.p. 50–52 °C); $[\alpha]_D^{23.5}$ −8.26 (*c* 0.97, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 6.46 (dd, J = 6.1, 1.2 Hz, 1H, H-1), 5.33 (m, 1H, H-3), 5.22 (dd, J = 7.5, 5.6 Hz, 1H, H-4), 4.84 (dd, J = 6.1, 3.2 Hz, 1H, H-2), 4.39 (dd, J = 12.2, 5.9 Hz, 1H, H-6a), 4.25 (m, 1H, H-5), 4.19 (dd, J = 12.2, 3.2 Hz, 1H ,H-6b), 2.09 (s, 3H, C$\underline{H}_3$CO), 2.07 (s, 3H, C$\underline{H}_3$CO), 2.04 (s, 3H, C$\underline{H}_3$CO); ^{13}C NMR: ($CDCl_3$)

δ_C 170.8 (C, $CH_3\underline{C}O$), 170.6 (C, $CH_3\underline{C}O$), 169.8 (C, $CH_3\underline{C}O$), 145.8 (CH, C-1), 99.1 (CH, C-2), 74.1 (CH, C-5), 67.6 (CH, C-3), 67.3 (CH, C-4), 61.5 (CH_2, C-6), 21.1 (CH_3, $\underline{C}H_3CO$), 20.94 (CH_3, $\underline{C}H_3CO$), 20.88 (CH_3, $\underline{C}H_3CO$); IR (Film from CH_2Cl_2): ν_{max} 2961, 1738, 1650, 1369, 1215, 1032, 912, 730 cm^{-1}.

D-Glucal (151)

A) Sodium (626 mg, 27.2 mmol) was reacted with methanol (600 mL) and then treated with a solution of **150** (26.11 g, 95.9 mmol) in methanol (225 mL). The reaction was stirred at room temperature for 10 minutes and then the solution was concentrated to provide crude D-glucal (**151**). The crude product was treated successively with portions of methanol (15 mL), then successively diluted with acetone (100 mL) and diethyl ether (200 mL), which led to the precipitation of impurities. The solution was filtered and concentrated to afford **151** (13.68 g, 98%). Spectral data matched those which have been previously reported.[79]



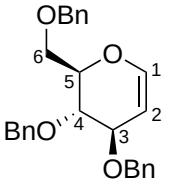
$[\alpha]_D^{26.6}$ −9.29 (*c* 1.08, H_2O) ^{1}H NMR: (D_2O) δ_H 6.41 (dd, J = 6.1, 1.5 Hz, 1H, H-1), 4.82–4.81 (complex m, 3H, 3 x OH), 4.80 (dd, J = 6.1, 2.4 Hz, 1H, H-2), 4.23 (ddd, J = 6.8, 2.2, 1.9 Hz, 1H, H-3), 3.92–3.85 (complex m, 3H, H-5,6a,b), 3.67 (dd, J = 9.0, 7.1 Hz, 1H, H-4); ^{13}C NMR: (D_2O) δ_C 143.6 (CH, C-1), 102.7 (CH, C-2), 78.1 (CH, C-5), 68.7 (CH, C-4), 68.2 (CH, C-3), 60.0 (CH_2, C-6); IR (KBr): ν_{max} 3372, 2887, 1653, 1416, 1385, 1232, 1137, 1098, 1073, 1045, 1017 cm^{-1}.

B) Using the method of Kozikowski,[79] a solution of triethylamine (110 mL, 780 mmol) in methanol (50% aqueous solution, 1100 mL) was treated with **150** (25.51 g, 93.7 mmol) and stirred for 90 minutes. The mixture was concentrated to liberate D-glucal (**151**) as a brown oil, contaminated with triethylamine. The crude mixture was treated successively with portions of methanol (15 mL), then successively diluted with acetone (100 mL) and diethyl ether (200 mL), which led to the precipitation of impurities. The solution was filtered and concentrated to afford **151** as a light brown solid (11.23 g, 82%), which was used without further purification.

Tri-*O*-benzyl-D-glucal (37)

A solution of **151** (4.458 g, 30.5 mmol) in DMF (200 mL) was cooled to 0 °C and then treated with sodium hydride (6.712 g, 167.8 mmol). The solution was stirred at 0 °C for 25 minutes, then treated with benzyl bromide (11.97 mL, 100.6 mmol) and allowed to warm to room temperature. After 17 hours, the solution was quenched with water (20 mL) and then extracted with diethyl ether (3 x 200 mL). The organic fractions were combined, dried, filtered and concentrated to give the crude product

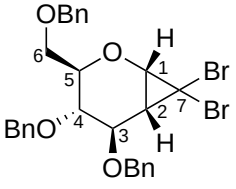
as a yellow oil. Chromatography of the oil (9:1 hexanes:ethyl acetate) afforded **37** (11.51 g, 91%) as a white crystaline solid. The spectral data matched those reported previously.[107]



$R_f = 0.35$ (9:1 hexanes:ethyl acetate); m.p. 53.5–55.0 °C (lit.[107] m.p. 53–55 °C); $[\alpha]_D^{23.4}$ −4.90 (*c* 1.02, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.33–7.23 (complex m, 15H, Bn) 6.43 (dd, J = 6.1, 1.3 Hz, 1H, H-1), 4.88 (dd, J = 6.4, 2.7 Hz, 1H, H-2), 4.83 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.640 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.637 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.60 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.564 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.562 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.21 (ddd, J = 6.4, 2.7, 1.3 Hz, 1H, H-3), 4.06 (ddd, J = 8.8, 5.1, 3.0 Hz, 1H, H-5), 3.86 (dd, J = 8.8, 6.1 Hz, 1H, H-4), 3.80 (dd, J = 10.5, 5.1 Hz, 1H, H-6a), 3.75 (dd, J = 10.5, 3.0 Hz, 1H, H-6b); ^{13}C NMR: ($CDCl_3$) δ_C 144.9 (CH, C-1), 138.5 (C, Bn), 138.3 (C, Bn), 138.1 (C, Bn), 128.6 (CH, Bn), 128.4 (CH, Bn), 128.1 (CH, Bn), 127.94 (CH, Bn), 127.89 (CH, Bn), 127.80 (CH, Bn), 127.79 (CH, Bn), 100.1 (CH, C-2), 76.8 (CH, C-5), 75.9 (CH, C-3), 74.5 (CH, C-4), 73.9 (CH_2, $PhCH_2$), 73.7 (CH_2, $PhCH_2$), 70.6 (CH_2, $PhCH_2$), 68.7 (CH_2, C-6); IR (Film from CH_2Cl_2): ν_{max} 3087, 3064, 3030, 2865, 1648, 1496, 1454, 1239, 1100, 1070, 1027, 735, 697 cm^{-1}.

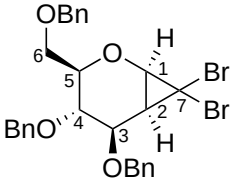
1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1,2-*C*-(dibromomethylene)-D-*glycero*-D-*gulo*-hexitol (52) and 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1,2-*C*-(dibromomethylene)-D-*glycero*-D-*talo*-hexitol (152)

A) As reported by Nagarajan,[38] a solution of **37** (2.505 g, 6.01 mmol) and TEBAC (22 mg, 0.1 mmol) in bromoform (10.0 mL, 114.3 mmol) was treated dropwise with a solution of sodium hydroxide (2.012 g, 52.0 mmol) and potassium fluoride (15.10 g, 258.4 mmol) in water (15.0 mL). The biphasic mixture was stirred at room temperature for three days. The solution was diluted with water (20 mL) and extracted with diethyl ether (3 x 80 mL), then the organic fractions were combined and washed with brine (30 mL). The ethereal solution was dried, filtered and concentrated to provide a crude mixture of cyclopropanes in bromoform. Purification by column chromatography (14:1 hexanes:ethyl acetate) liberated **52** as a white solid (2.644 g, 75%) and **152** as a yellow oil (390 mg, 11%) in a combined yield of 86%.



52: Spectral data matched those which have been previously reported.[38] $R_f = 0.40$ (9:1 hexanes:ethyl acetate); m.p. 60.5–62.0 °C (lit.[38] m.p. 58–60 °C); ^{1}H NMR: ($CDCl_3$) δ_H 7.47–7.22 (complex m, 15H, Bn), 4.90 (d, J = 11.2 Hz, 1H, $PhCH_2$), 4.81 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.70 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.534 (d, J = 11.2 Hz, 1H, $PhCH_2$), 5.527 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.44 (d, J = 12.2 Hz, 1H, $PhCH_2$), 3.95 (d, J = 7.8 Hz, 1H, H-1), 3.87 (ddd, J = 7.6, 3.7, 2.7 Hz, 1H, H-5), 3.79 (dd, J = 9.5, 7.6 Hz, 1H, H-4), 3.68 (dd, J = 9.5, 4.9 Hz, 1H, H-3), 3.55 (dd, J = 10.5,

2.7 Hz, 1H, H-6a), 3.51 (dd, J = 10.5, 3.7 Hz, 1H, H-6b), 1.87 (dd, J = 7.8, 4.9 Hz, 1H, H-2); ^{13}C NMR: ($CDCl_3$) δ_C 138.3 (C, Bn), 138.1 (C, Bn), 137.9 (C, Bn), 128.7 (CH, Bn), 128.6 (CH, Bn), 128.51 (CH, Bn), 128.3 (CH, Bn), 128.03 (CH, Bn), 128.01 (CH, Bn), 127.94 (CH, Bn), 127.88 (CH, Bn), 127.81 (CH, Bn), 80.4 (CH, C-5), 80.1 (CH, C-3), 75.2 (CH, C-4), 74.8 (CH_2, $PhCH_2$), 73.5 (CH_2, $PhCH_2$), 71.9 (CH_2, $PhCH_2$), 70.3 (CH_2, C-6), 59.4 (CH, C-1), 35.4 (CH, C-2), 34.1 (C, C-7); IR (Film from CH_2Cl_2): ν_{max} 3063, 3030, 2860, 1496, 1454, 1092, 1027, 734, 696 cm^{-1}.



152: Spectral data matched those which have been previously reported.[41] R_f = 0.25 (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.50–7.18 (complex m, 15H, Bn), 4.92 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.83 (d, J = 11.1 Hz, 1H, $PhCH_2$), 4.72 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.67 (d, J = 12.1 Hz, 1H, $PhCH_2$), 4.57 (d, J = 12.1 Hz, 1H, $PhCH_2$), 4.56 (d, J = 11.1 Hz, 1H, $PhCH_2$), 4.18 (apparent t, J = 7.8 Hz, 1H, H-3), 4.08 (d, J = 7.8 Hz, 1H, H-1), 3.96 (dd, J = 10.3, 7.4 Hz, 1H, H-4), 3.78 (dd, J = 11.0, 1.7 Hz, 1H, 1H, H-6a), 3.68 (dd, J = 11.0, 5.4 Hz, 1H, H-6b), 3.52 (ddd, J = 10.3, 5.4, 1.7 Hz, 1H, H-5), 2.29 (apparent t, J = 7.9 Hz, 1H, H-2); ^{13}C NMR: ($CDCl_3$) δ_C 138.3 (C, Bn), 138.2 (C, Bn), 137.9 (C, Bn), 128.7 (CH, Bn), 128.4 (CH, Bn), 128.2 (CH, Bn), 128.1 (CH, Bn), 128.0 (CH, Bn), 127.83 (CH, Bn), 127.79 (CH, Bn), 127.7 (CH, Bn), 78.6 (CH, C-3), 78.5 (CH, C-5), 76.6 (CH, C-4), 74.8 (CH_2, $PhCH_2$), 73.7 (CH_2, $PhCH_2$), 71.1 (CH_2, $PhCH_2$), 69.1 (CH_2, C-6), 62.8 (CH, C-1), 33.8 (CH, C-2), 30.9 (C, C-7); IR (Film from CH_2Cl_2): ν_{max} 3063, 3030, 2861, 1496, 1454, 1091, 1027, 734, 696 cm^{-1}; HRMS: m/z $C_{28}H_{28}O_4^{79}Br_2Na^+$ [M+Na]$^+$ calcd 609.0252, found 609.0247.

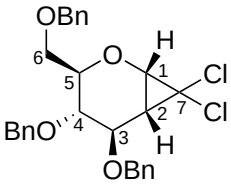
B) Using a modification of Nagarajan's procedure,[38] a solution of **37** (1.00 g, 2.40 mmol) and TEBAC (15 mg, 0.07 mmol) in bromoform (4.0 mL, 45.7 mmol) was treated dropwise with a solution of sodium hydroxide (818 mg, 20.5 mmol) and potassium fluoride (6.79 g, 116.9 mmol) in water (6.0 mL). The biphasic mixture was stirred at room temperature for three days. The solution was diluted with water (10 mL) and extracted with diethyl ether (3 x 30 mL), then the organic fractions were combined and washed with brine (30 mL). The etheral solution was dried, filtered and concentrated under reduced presure for three hours to remove all bromoform to provide a mixture of cyclopropanes as a brown solid. Purification by column chromatography (14:1 hexanes:ethyl acetate) liberated **52** as a white solid (904 mg, 64%) and **152** as a yellow oil (130 mg, 9%) in a combined yield of 73%.

C) Using a modification of Nagarajan's procedure,[38] a solution of tri-*O*-benzyl-D-glucal (**37**) (0.995 g, 2.39 mmol) and TEBAC (16 mg, 0.07 mmol) in bromoform (4.0 mL, 45.7 mmol) was treated dropwise with a solution of sodium hydroxide (791 mg, 19.8 mmol) and potassium fluoride (6.50 g, 111.9 mmol) in water (6.0 mL).

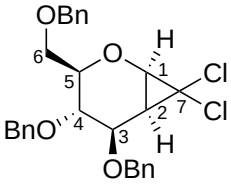
The biphasic mixture was heated to an average of 35 °C (±5 °C) and stirred for two days. The solution was diluted with water (10 mL) and then extracted with diethyl ether (3 x 30 mL), then the organic fractions were combined and washed with brine (30 mL). The etheral solution was dried, filtered and concentrated to provide a crude mixture of cyclopropanes. Purification by column chromatography (14:1 hexanes:ethyl acetate) liberated **52** as a white solid (728 mg, 52%) and **152** as a yellow oil (170 mg, 12%) in a combined yield of 64%.

1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1,2-*C*-(dichloromethylene)-D-*glycero*-D-*gulo*-hexitol (50) and 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1,2-*C*-(dichlormethylene)-D-*glycero*-D-*talo*-hexitol (153)

As reported by Nagarajan,[38] a solution of **37** (1.605 g, 3.85 mmol) and TEBAC (20 mg, 0.088 mmol) in chloroform (10 mL) was treated dropwise with a 33 wt% aqueous solution of sodium hydroxide (5.035 g in 10.0 g H_2O) with rapid stirring. The biphasic mixture was stirred at room temperature for 10.5 hours. The biphasic mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 30 mL). The organic fractions were combined and dried, filtered and concentrated to provide a crude mixture of cyclopropanes. Purification by column chromatography (14:1 hexanes:ethyl acetate) liberated major cyclopropane **50** as a white solid (1.161 g, 60%) and minor cyclopropane **153** as a yellow oil (290 mg, 15%) in a combined yield of 75%.

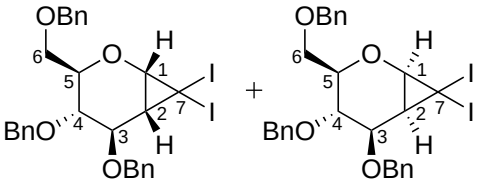


50: Spectral data matched those which have been previously reported.[38] m.p. 61.0–62.5 °C (lit.[38] m.p. 62–63 °C); $R_f = 0.40$ (9:1 hexanes:ethyl acetate); $[\alpha]_D^{25.3}$ +69.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.43–7.22 (complex m, 15H, Bn), 4.90 (d, J = 11.2 Hz, 1H, $PhCH_2$), 4.80 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.69 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.55 (d, J = 11.2 Hz, 1H, $PhCH_2$), 4.53 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.44 (d, J = 12.2 Hz, 1H, $PhCH_2$), 3.89 (d, J = 8.0 Hz, 1H, H-1), 3.84 (m, 1H, H-5), 3.78–3.76 (complex m, 2H, H-3,4), 3.56 (dd, J = 10.6, 2.8 Hz, 1H, H-6a), 3.52 (dd, J = 10.6, 3.7 Hz, 1H, H-6b), 1.79 (m, 1H, H-2); ^{13}C NMR: ($CDCl_3$) δ_C 138.3 (C, Bn), 138.1 (C, Bn), 137.8 (C, Bn), 128.65 (CH, Bn), 128.58 (CH, Bn), 128.5 (CH, Bn), 128.3 (CH, Bn), 128.04 (CH, Bn), 128.02 (CH, Bn), 127.93 (CH, Bn), 127.89 (CH, Bn), 127.8 (CH, Bn), 80.0 (CH, C-5), 77.6 and 75.3 (CH, C-3, and CH, C-4), 74.7 (CH_2, $PhCH_2$), 73.5 (CH_2, $PhCH_2$), 72.0 (CH_2, $PhCH_2$), 70.3 (CH_2, C-6), 61.6 (C, C-7), 59.1 (CH, C-1), 34.4 (CH, C-2); IR (Film from CH_2Cl_2): ν_{max} 3088, 3064, 3031, 2862, 1496, 1454, 1363, 1251, 1093, 1026, 733, 696 cm^{-1}; HRMS: *m/z* $C_{28}H_{28}O_4^{35}Cl_2Na^+$ $[M+Na]^+$ calcd 521.1262, found 521.1271.



153: $R_f = 0.25$ (9:1 hexanes:ethyl acetate); $[\alpha]_D^{22.3}$ −10.8 (c 1.15, CH_2Cl_2) ^{1}H NMR: ($CDCl_3$) δ_H 7.46–7.17 (complex m, 15H, Bn), 4.89 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.83 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.72 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.64 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.56 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.55 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.18 (apparent t, J = 7.8 Hz, 1H, H-3), 4.00 (d, J = 8.1 Hz, 1H, H-1), 3.86 (dd, J = 10.3, 7.6 Hz, 1H, H-4), 3.77 (dd, J = 11.0, 1.9 Hz, 1H, H-6a), 3.67 (dd, J = 11.0, 5.3 Hz, 1H, H-6b), 3.48 (ddd, J = 10.3, 5.3, 1.9 Hz, 1H, H-5), 2.13 (apparent t, J = 8.1 Hz, 1H, H-2); ^{13}C NMR: ($CDCl_3$) δ_C 138.3 (C, Bn), 138.2 (C, Bn), 137.9 (C, Bn), 128.7 (CH, Bn), 128.6 (CH, Bn), 128.53 (CH, Bn), 128.49 (CH, Bn), 128.2 (CH, Bn), 128.1 (CH, Bn), 128.0 (CH, Bn), 127.9 (CH, Bn), 127.7 (CH, Bn), 78.6 (CH, C-5), 78.0 (CH, C-3), 76.8 (CH, C-4), 74.9 (CH_2, $PhCH_2$), 73.7 (CH_2, $PhCH_2$), 71.4 (CH_2, $PhCH_2$), 69.1 (CH_2, C-6), 62.4 (CH, C-1), 61.8 (C, C-7), 32.9 (CH, C-2); IR (Film from CH_2Cl_2): ν_{max} 3088, 3064, 3031, 2917, 2862, 1496, 1454, 1364, 1091, 1026, 731, 696 cm^{-1}; HRMS: m/z $C_{28}H_{28}O_4^{35}Cl_2Na^+$ $[M+Na]^+$ calcd 521.1262, found 521.1261.

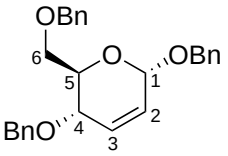
Attempted synthesis of 1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1,2-*C*-(diiodomethylene)-D-*glycero*-D-*gulo*-hexitol (154) and 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1,2-*C*-(diiodomethylene)-D-*glycero*-D-*talo*-hexitol (155)



154 **155**

A) Glucal **37** (210 mg, 0.50 mmol), iodoform (2.820 g, 7.16 mmol) and TEBAC (10 mg, 0.04 mmol) were dissolved in dichloromethane (10.0 mL). This was treated dropwise with a 33 wt% aqueous solution of sodium hydroxide (4.052 g in 8.36 g H_2O). The solution was rapidly stirred at room temperature for 16 hours before being diluted with water (20 mL) and extracted with dichloromethane (3 x 25 mL). The organic fractions were combined and dried, filtered and concentrated to provide a crude mixture of **156** as a solid with iodoform. Purification by column chromatography (9:1 hexanes:ethyl acetate) provided **156** (97 mg, 46%) as a clear oil.

Benzyl 4,6-di-*O*-benzyl-2,3-didehydro-α-D-*erythro*-hex-2-enopyranoside (156)



Spectral data matched those which have been previously reported.[108] $R_f = 0.35$ (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.32–7.20 (complex m, 15H, Bn), 6.05 (d, J = 10.3 Hz, 1H, H-3), 5.76 (ddd, J = 10.3, 2.6, 2.2 Hz, 1H, H-2), 5.10 (d, J = 2.2 Hz, 1H, H-1), 4.78 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.62 (d, J = 12.2 Hz, 1H, $PhCH_2$),

4.57 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.56 (d, J = 12.7 Hz, 1H, $PhCH_2$), 4.48 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.41 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.16 (ddd, J = 9.5, 3.1, 1.7 Hz, 1H, H-4), 3.97 (apparent dq, J = 9.5, 2.0 Hz, 1H, H-5), 3.69 (dd, J = 10.6, 4.1 Hz, 1H, H-6a), 3.60 (dd, J = 10.6, 2.0 Hz, 1H, H-6b); ^{13}C NMR: ($CDCl_3$) δ_C 138.3 (C, Bn), 138.19 (C, Bn), 138.17 (C, Bn), 130.9 (CH, C-3), 128.50 (CH, Bn), 128.49 (CH, Bn), 128.46 (CH, Bn), 128.45 (CH, Bn), 128.1 (CH, Bn), 128.0 (CH, Bn), 127.93 (CH, Bn), 127.86 (CH, Bn), 127.7 (CH, Bn), 126.6 (CH, C-2), 94.1 (CH, C-1), 73.5 (CH_2, $PhCH_2$), 71.2 (CH_2, $PhCH_2$), 70.5 (CH, C-4), 70.2 (CH_2, $PhCH_2$), 69.4 (CH, C-5), 68.9 (CH_2, C-6); IR (Film from CH_2Cl_2): ν_{max} 3063, 3030, 2865, 1496, 1454, 1094, 1071, 1039, 1025, 733, 696 cm^{-1}; HRMS: m/z $C_{27}H_{28}O_4Na^+$ $[M+Na]^+$ calcd 439.1885, found 439.1883.

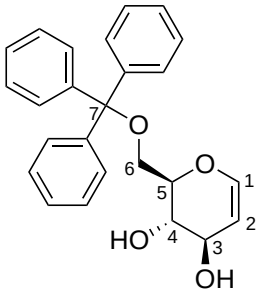
B) Glucal **37** (300 mg, 0.72 mmol), iodoform (2.886 g, 7.33 mmol), TEBAC (12 mg, 0.05 mmol) in dichloromethane (5.0 mL) was treated dropwise with a solution of sodium hydroxide (244 mg, 6.10 mmol) and potassium fluoride (1.800 g, 31.0 mmol) in water (2.0 mL). The solution was rapidly stirred at room temperature for 16 hours before being diluted with water (15 mL) and extracted with dichloromethane (3 x 20 mL). The organic fractions were combined and dried, filtered and concentrated to provide a solid that contained unreacted starting material **37** and iodoform. Purification by column chromatography (9:1 hexanes:ethyl acetate) provided **37** (208 mg, 69%) as a white solid.

C) Glucal **37** (98 mg, 0.24 mmol), iodoform (470 mg, 1.19 mmol), TEBAC (8 mg, 0.04 mmol) in toluene (1.0 mL) was treated dropwise with a solution of sodium hydroxide (161 mg, 4.03 mmol) and potassium fluoride (1.302 g, 22.4 mmol) in water (1.5 mL). The solution was rapidly stirred at room temperature for 48 hours before addition of further toluene (0.5 mL) and iodoform (200 mg, 0.51 mmol). This was treated with sodium hydroxide (180 mg, 4.5 mmol) in water (1.0 mL) and stirred for a further 48 hours. The reaction mixture was diluted with water (20 mL) and extracted with dichlormethane (3 x 25 mL). The organic fractions were combined and dried, filtered and concentrated to provide unreacted starting material **37** as a solid with iodoform. Purification by column chromatography (9:1 hexanes:ethyl acetate) provided **37** (71 mg, 69%) as a white solid.

1,5-Anhydro-2-deoxy-6-*O*-trityl-D-*arabino*-hex-1-enitol (160)

As reported by Schmidt *et al.*,[83] D-glucal (**151**) (5.047 g, 34.5 mmol) was dissolved in a 1:1 mixture of dichloromethane and pyridine (75 mL). Trityl chloride (12.92 g, 46.3 mmol) was added over three minutes at room temperature. The solution was stirred for 18 hours at room temperature before the solution was concentrated

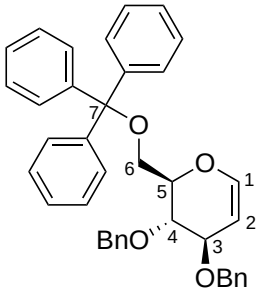
and then extracted with chloroform (3 x 60 mL). The organic fractions were combined, washed with sat. sodium bicarbonate solution (2 x 60 mL), dried, filtered and concentrated to provide a light yellow solid (**160**) contaminated with triphenylmethanol. Purification by column chromatography (1:1 hexanes:ethyl acetate) provided **160** (11.92 g, 89%) as a white solid. Spectral data matched those which have been previously reported.[83]



$R_f = 0.53$ (2:1 ethyl acetate:hexanes); m.p. 62.0–64.0 °C; $[\alpha]_D^{25.8}$ +27.1 (*c* 0.49, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.48–7.20 (complex m, 15H, Ph), 6.40 (dd, J = 6.1, 1.6 Hz, 1H, H-1), 4.76 (dd, J = 6.1, 2.2 Hz, 1H, H-2), 4.24 (m, 1H, H-3), 3.90 (ddd, J = 9.5, 7.1, 3.5 Hz, 1H, H-4), 3.84 (dt, J = 9.5, 3.4 Hz, 1H, H-5), 3.57 (dd, J = 10.4, 3.5 Hz, 1H, H-6a), 3.36 (dd, J = 10.4, 3.5 Hz, 1H, H-6b), 2.33 (d, J = 3.5 Hz, 1H, OH-4), 4.41 (d, J = 5.1 Hz, 1H, OH-3); ^{13}C NMR: ($CDCl_3$) δ_C 144.7 (CH, C-1), 143.6 (C, Ph), 128.7 (CH, Ph), 128.2 (CH, Ph), 127.4 (CH, Ph), 102.6 (CH, C-2), 87.1 (C, C-7), 76.7 (CH, C-5), 71.8 (CH, C-4), 69.6 (CH, C-3), 63.0 (CH_2, C-6); IR (Film from CH_2Cl_2): ν_{max} 3382, 3061, 3033, 2920, 2882, 1647, 1491, 1449, 1229, 1099, 1056, 1032, 1002, 735, 702 cm^{-1}; HRMS: *m/z* $C_{25}H_{24}O_4Na^+$ $[M+Na]^+$ calcd 411.1572, found 411.1573.

1,5-Anhydro-3,4-di-*O*-benzyl-2-deoxy-6-*O*-trityl-D-*arabino*-hex-1-enitol (159)

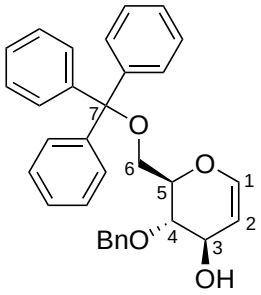
In a slight modification of Schmidt's procedure,[83] glycal **160** (11.210 g, 28.9 mmol) was dissolved in DMF (180 mL) and cooled in an ice/salt bath to −10 °C. Sodium hydride (2.794 g, 69.9 mmol) was added slowly, portionwise over one minute and the solution stirred at −10 °C for 15 minutes followed by addition of benzyl bromide (8.25 mL, 69.4 mmol). The solution was allowed to warm to room temperature and stirred for 16 hours, followed by quenching with water (80 mL) and extraction with chloroform (3 x 100 mL). The organic fractions were combined, dried, filtered and concentrated to give the crude product as a pale yellow solid. Chromatography of the solid (gradient elution 9:1 to 0:1 hexanes:ethyl acetate) afforded **159** (11.61 g, 71%) as a white solid and **161** (2.79 g, 15%) as a brown oil.



159: Spectral data matched those which have been previously reported.[83] R_f = 0.40 (9:1 hexanes:ethyl acetate); m.p. 115–116 °C (lit.[83] m.p. 116 °C); $[\alpha]_D^{26.9}$ −4.41 (*c* 1.10, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.51–7.04 (complex m, 25H, Ar), 6.52 (dd, J = 6.1, 1.5 Hz, 1H, H-1), 4.90 (dd, J = 6.1, 2.4 Hz, 1H, H-2), 4.76 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.65 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.58 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.53 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.20 (m, 1H, H-3), 4.04 (m, 1H, H-5), 4.01 (dd, J = 8.8, 5.9

Hz, 1H, H-4), 3.56 (dd, J = 10.2, 2.2 Hz, 1H, H-6a), 3.43 (dd, J = 10.2, 4.1 Hz, 1H, H-6b); ^{13}C NMR: ($CDCl_3$) δ_C 145.0 (CH, C-1), 144.0 (C, Ph), 138.5 (C, Bn), 138.2 (C, Bn), 128.9 (CH, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 127.96 (CH, Ar), 127.94 (CH, Ar), 127.8 (CH, Ar), 127.7 (CH, Ar), 127.1 (CH, Ar), 99.9 (CH, C-2), 86.6 (C, C-7), 77.1 (CH, C-5), 76.2 (CH, C-3), 74.8 (CH, C-4), 74.0 (CH_2, $PhCH_2$), 71.0 (CH_2, $PhCH_2$), 62.3 (CH_2, C-6); IR (Film from CH_2Cl_2): ν_{max} 3061, 3031, 2927, 2878, 1647, 1491, 1449, 1095, 1066, 1026, 908, 732, 695 cm^{-1}; HRMS: m/z $C_{39}H_{36}O_4Na^+$ $[M+Na]^+$ calcd 591.2511, found 591.2520.

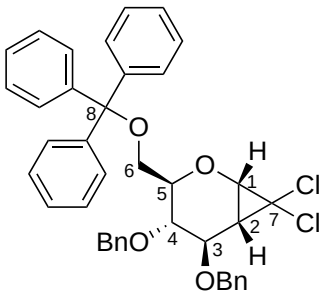
1,5-Anhydro-4-*O*-benzyl-2-deoxy-6-*O*-trityl-D-*arabino*-hex-1-enitol (161)



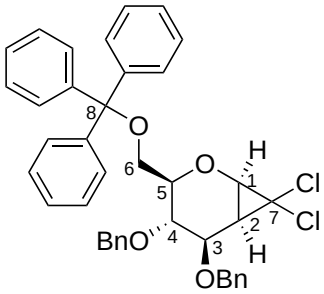
161: R_f = 0.37 (3:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.51–7.07 (complex m, 20H, Ar), 6.50 (dd, J = 6.1, 1.4 Hz, 1H, H-1), 4.76 (dd, J = 6.1, 2.4 Hz, 1H, H-2), 4.62 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.48 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.31 (m, 1H, H-3), 3.95 (apparent dt, J = 9.3, 2.9 Hz, 1H, H-5), 4.82 (dd, J = 9.3, 6.6 Hz, 1H, H-4), 3.65 (dd, J = 10.3, 2.4 Hz, 1H, H-6a), 3.29 (dd, J = 10.3, 3.4 Hz, 1H, H-6b), 1.96 (br s, 1H, OH-3); ^{13}C NMR: ($CDCl_3$) δ_C 144.9 (CH, C-1), 143.9 (C, Ph), 138.3 (C, Bn), 128.9 (CH, Ar), 128.6 (CH, Ar), 128.1 (CH, Ar), 127.99 (CH, Ar), 127.97 (CH, Ar), 127.2 (CH, Ar), 102.5 (CH, C-2), 86.6 (C, C-7), 77.5 (CH, C-4), 77.0 (CH, C-5), 74.0 (CH_2, $PhCH_2$), 69.4 (CH, C-3), 62.3 (CH_2, C-6); IR (Film from CH_2Cl_2): ν_{max} 3372, 3061, 3030, 2927, 2879, 1650, 1492, 1449, 1091, 1029, 1001, 901, 744, 696 cm^{-1}; HRMS: m/z $C_{32}H_{30}O_4Na^+$ $[M+Na]^+$ calcd 501.2042, found 501.2044.

1,5-Anhydro-3,4-di-*O*-benzyl-6-*O*-(triphenylcarbinyl)-2-deoxy-1,2-*C*-(dichloromethylene)-D-*glycero*-D-*gulo*-hexitol (162) and 1,5-anhydro-3,4-di-*O*-benzyl-6-*O*-(triphenylcarbinyl)-2-deoxy-1,2-*C*-(dichloromethylene)-D-*glycero*-D-*talo*-hexitol (163)

As reported by Nagarajan,[38] glycal **159** (2.742 g, 4.82 mmol) and TEBAC (24 mg, 0.11 mmol) in chloroform (12 mL) were treated dropwise with a 33 wt% aqueous solution of sodium hydroxide (6.009 g in 12.0 g of water). The biphasic mixture was stirred at room temperature for three days. The solution was then diluted with water (50 mL) and then extracted with dichloromethane (3 x 50 mL). The organic fractions were combined, dried, filtered and concentrated to provide a crude mixture of cyclopropanes. Purification by column chromatography (14:1 hexanes:ethyl acetate) liberated **162** as a white solid (2.527 g, 80%) and **163** as a white solid (354 mg, 11%) in a combined yield of 92%.



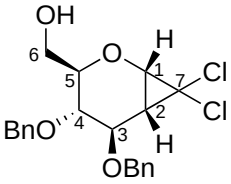
162: Spectral data matched those which have been previously reported.[38] $R_f = 0.40$ (9:1 hexanes:ethyl acetate); m.p. 51.0–53.0 °C; $[\alpha]_D^{22.7}$ +48.1 (*c* 1.02, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.47–7.22 (complex m, 25H, Ar), 4.81 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.80 (d, J = 10.7 Hz, 1H, $PhCH_2$), 4.70 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.25 (d, J = 10.7 Hz, 1H, $PhCH_2$), 4.06 (d, J = 8.0 Hz, 1H, H-1), 3.88–3.84 (complex m, 2H H-4,5), 3.78 (dd, J = 8.8, 4.9 Hz, 1H, H-3), 3.48 (dd, J = 10.2, 3.0 Hz, 1H, H-6a), 3.17 (dd, J = 10.2, 3.0 Hz, 1H, H-6b), 1.87 dd, J = 8.0, 4.9 Hz, 1H, H-2); ^{13}C NMR: ($CDCl_3$) δ_C 143.8 (C, Ph), 138.1 (C, Bn), 137.7 (C, Bn), 128.8 (CH, Ar), 128.7 (CH, Ar), 128.4 (CH, Ar), 128.11 (CH, Ar), 128.10 (CH, Ar), 128.08 (CH, Ar), 128.06 (CH, Ar), 127.8 (CH, Ar), 127.3 (CH, Ar), 86.9 (C, C-8), 80.5 (CH, C-5), 77.6 (CH, C-3), 75.9 (CH, C-4), 75.0 (CH_2, $PhCH_2$), 72.2 (CH_2, $PhCH_2$), 63.7 (CH_2, C-6), 61.8 (C, C-7), 59.3 (CH, C-1), 34.7 (CH, C-2); IR (Film from CH_2Cl_2): ν_{max} 3087, 3061, 3031, 2919, 2869, 1492, 1449, 1158, 1093, 1029, 736, 698 cm^{-1}; HRMS: *m/z* $C_{40}H_{36}O_4^{35}Cl_2Na^+$ $[M+Na]^+$ calcd 673.1888, found 673.1897.



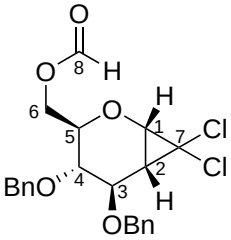
163: $R_f = 0.35$ (9:1 hexanes:ethyl acetate); m.p. 49.0–51.0 °C; $[\alpha]_D^{24.1}$ −40.4 (*c* 0.99, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.51–7.17 (complex m, 23H, Ar), 6.90–6.88 (complex m, 2H, Ar), 4.88 (d, J = 11.9 Hz, 1H, $PhCH_2$), 4.75 (d, J = 11.9 Hz, 1H, $PhCH_2$), 4.70 (d, J = 10.6 Hz, 1H, $PhCH_2$), 4.34 (d, J = 10.6 Hz, 1H, $PhCH_2$), 4.14–4.08 (complex m, 2H, H-3,4), 4.05 (d, J = 8.0 Hz, 1H, H-1), 3.56 (dd, J = 10.3, 2.0 Hz, 1H, H-6a), 3.41 (ddd, J = 9.7, 3.9, 2.0 Hz, 1H, H-5), 3.19 (dd, J = 10.3, 3.9 Hz, 1H, H-6b), 2.12 (apparent t, J = 7.7 Hz, 1H, H-2); ^{13}C NMR: ($CDCl_3$) δ_C 144.0 (C, Ph), 138.3 (C, Bn), 138.0 (C, Bn), 129.0 (CH, Ar), 128.7 (CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 128.09 (CH, Ar), 128.08 (CH, Ar), 128.0 (CH, Ar), 127.9 (CH, Ar), 127.0 (CH, Ar), 86.7 (C, C-8), 78.4 (CH, C-5), 78.2 (CH, C-4), 76.6 (CH, C-3), 74.9 (CH_2, $PhCH_2$), 71.6 (CH_2, $PhCH_2$), 62.33 (CH_2, C-6), 62.25 (CH, C-1), 62.1 (C, C-7), 33.1 (CH, C-2); IR (Film from CH_2Cl_2): ν_{max} 3061, 3031, 2930, 2875, 1492, 1449, 1182, 1090, 1023, 910, 736, 698 cm^{-1}; HRMS: *m/z* $C_{40}H_{36}O_4^{35}Cl_2Na^+$ $[M+Na]^+$ calcd 673.1888, found 673.1884.

1,5-Anhydro-3,4-di-*O*-benzyl-2-deoxy-1,2-*C*-(dichloromethylene)-D-*glycero*-D-*gulo*-hexitol (158), 1,5-anhydro-3,4-di-*O*-benzyl-6-*O*-(formyl)-2-deoxy-1,2-*C*-(dichloromethylene)-D-*glycero*-D-*gulo*-hexitol (164) and 1,5-anhydro-3,4-di-*O*-benzyl-6-*O*-(formyl)-2-deoxy-1,2-*C*-(dichloromethylene)-D-*glycero*-D-*talo*-hexitol (165)

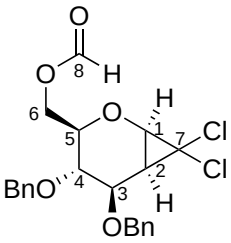
A) In a slight modification of Nagarajan's procedure,[38] a mixture of cyclopropanes **162** and **163** (1.208 g, 1.85 mmol, 8:1 ratio) was dissolved in diethyl ether (6 mL). This was treated with formic acid (5 mL) and stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and then diluted with dichloromethane (10 mL). The dichlormethane layer was then washed with sat. sodium bicarbonate solution (5 x 20 mL) dried and concentrated to provided a crude mixture of cyclopropanes as a pale yellow oil with white precipitate. Purification by column chromatography (gradient elution, 9:1 to 3:1 hexanes:ethyl acetate) liberated unreacted starting material **162** as a white solid (100 mg, 8%), triphenylmethanol byproduct (349 mg), **164** as a clear oil (366 mg, 45%), **165** as a clear oil (62 mg, 8%) and desired product **158** as a white solid (170 mg, 22%).



158: Spectral data matched those which have been previously reported.[38] $R_f = 0.45$ (3:1 hexanes:ethyl acetate); m.p. 80.0–81.5 °C (lit.[38] m.p. 83–84 °C); $[\alpha]_D^{26.6}$ +63.6 (*c* 1.05, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.43–7.29 (complex m, 10H, Bn), 4.93 (d, J = 11.2 Hz, 1H, $PhCH_2$), 4.81 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.72 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.67 (d, J = 11.2 Hz, 1H, $PhCH_2$), 3.87 (d, J = 8.3 Hz, 1H, H-1), 3.81 (dd, J = 9.5, 3.9 Hz, 1H, H-3), 3.87 (dt, J = 8.6, 3.9 Hz, 1H, H-5), 3.68 (d, J = 3.9, 2H, H-6a,b), 3.60 (dd, J = 9.5, 8.6 Hz, 1H, H-4), 1.84 (dd, J = 8.6, 3.9 Hz, 1H, H-2), 1.68 (br s, 1H, 6-OH); ^{13}C NMR: ($CDCl_3$) δ_C 138.1 (C, Bn), 137.6 (C, Bn), 128.7 (CH, Bn), 128.6 (CH, Bn), 128.3 (CH, Bn), 128.15 (CH, Bn), 128.12 (CH, Bn), 79.6 (CH, C-5), 77.2 (CH, C-3), 75.0 (CH_2, $PhCH_2$), 74.8 (CH, C-4), 72.2 (CH_2, $PhCH_2$), 62.8 (CH_2, C-6), 60.9 (C, C-7), 58.9 (CH, C-1), 33.9 (CH, C-2); IR (Film from CH_2Cl_2): ν_{max} 3375, 3032, 2976, 2864, 1496, 1454, 1365, 1095, 1026, 733, 696 cm^{-1}; HRMS: *m/z* $C_{21}H_{22}O_4^{35}Cl_2Na^+$ $[M+Na]^+$ calcd 431.0793, found 431.0793.



164: $R_f = 0.30$ (9:1 hexanes:ethyl acetate); $[\alpha]_D^{26.8}$ +53.8 (*c* 0.80, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 8.03 (apparent q, J = 0.7 Hz, 1H, CHO), 7.43–7.27 (complex m, 10H, Bn), 4.95 (d, J = 11.2 Hz, 1H, $PhCH_2$), 4.81 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.70 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.63 (d, J = 11.2 Hz, 1H, $PhCH_2$), 4.30 (ddd, J = 12.0, 5.1, 0.7, 1H, H-6a), 4.15 (ddd, J = 12.0, 2.7, 0.7, 1H, H-6b), 3.87 (dddd, J = 8.3, 5.1, 2.7, 0.7 Hz, 1H, H-5), 3.86 (d, J = 8.1 Hz, 1H, H-1), 3.80 (dd, J = 9.5, 4.4 Hz, 1H, H-3), 3.57 (dd, J = 9.5, 8.3 Hz, 1H, H-4), 1.82 (dd, J = 8.1, 4.4 Hz, 1H, H-2); ^{13}C NMR: ($CDCl_3$) δ_C 160.6 (C, CHO), 137.7 (C, Bn), 137.5 (C, Bn), 128.73 (CH, Bn), 128.66 (CH, Bn), 128.5 (CH, Bn), 128.2 (CH, Bn), 128.13 (CH, Bn), 128.08 (CH, Bn), 77.9 (CH, C-5), 77.2 (CH, C-3), 74.9 (CH_2, $PhCH_2$), 74.5 (CH, C-4), 72.1 (CH_2, $PhCH_2$), 63.3 (CH_2, C-6), 61.0 (C, C-7), 58.6 (CH, C-1), 34.1 (CH, C-2); IR (Film from CH_2Cl_2): ν_{max} 3062, 3031, 2919, 2869, 1726, 1496, 1453, 1152, 1128, 1089, 1027, 735, 697 cm^{-1}; HRMS: *m/z* $C_{22}H_{22}O_5^{35}Cl_2Na^+$ $[M+Na]^+$ calcd 459.0742, found 459.0733.



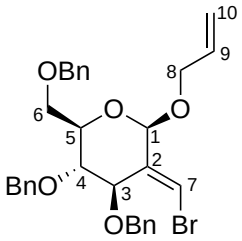
165: $R_f = 0.25$ (9:1 hexanes:ethyl acetate); $[\alpha]_D^{26.8}$ −36.8 (*c* 1.05, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 8.00 (s, 1H, CHO) 7.45–7.23 (complex m, 10H, Bn), 4.88 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.85 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.70 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.57 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.47 (dd, J = 12.0, 1.2 Hz, 1H, H-6a), 4.22 (dd, J = 12.0, 5.1 Hz, 1H, H-6b), 4.19 (apparent t, J = 7.8 Hz, 1H, H-3), 3.96 (d, J = 8.1 Hz, 1H, H-1), 3.80 (dd, J = 10.4, 7.6 Hz, 1H, H-4), 3.50 (ddd, J = 10.4, 5.1, 1.7 Hz, 1H, H-5), 2.12 (apparent t, J = 8.1 Hz, 1H, H-2); ^{13}C NMR: ($CDCl_3$) δ_C 160.7 (C, CHO), 137.8 (C, Bn), 137.7 (C, Bn), 128.8 (CH, Bn), 128.6 (CH, Bn), 128.24 (CH, Bn), 128.19 (CH, Bn), 128.18 (CH, Bn), 128.1 (CH, Bn), 77.9 (CH, C-3), 76.2 (CH, C-5), 75.9 (CH, C-4, 74.7 (CH_2, $PhCH_2$), 71.3 (CH_2, $PhCH_2$), 62.5 (CH_2, C-6), 62.2 (CH, C-1), 61.4 (C, C-7), 32.8 (C, C-2); IR (Film from CH_2Cl_2): ν_{max} 3065, 3031, 2918, 2870, 1724, 1497, 1454, 1170, 1088, 1027, 734, 698 cm^{-1}; HRMS: *m/z* $C_{22}H_{22}O_5^{35}Cl_2Na^+$ $[M+Na]^+$ calcd 459.0742, found 459.0743.

B) In a slight modification of Nagarajan's procedure,[38] cyclopropane **162** (1.320 g, 2.03 mmol) was dissolved in diethyl ether (5 mL). This was treated with formic acid (5 mL) and stirred at room temperature for four hours. The reaction mixture was concentrated *in vacuo* and then diluted with dichloromethane (10 mL). The dichlormethane layer was then washed with sat. sodium bicarbonate solution (5 x 20 mL) dried and concentrated to provided a crude mixture of cyclopropanes as an off-white solid. Purification by column chromatography (gradient elution, 9:1 to 5:1 hexanes:ethyl acetate) liberated unreacted starting material **162** as a white solid (485 mg, 37%), triphenylmethanol as a white solid (297 mg), **164** as a clear oil (144 mg, 45%) and the desired product **158** as a white solid (270 mg, 33%).

C) In a slight modification of Nagarajan's procedure,[38] cyclopropane **162** (467 mg, 0.72 mmol) was dissolved in diethyl ether (2 mL). This was treated with formic acid (2.5 mL) and stirred at room temperature for one hour. The reaction mixture was diluted with diethyl ether (20 mL) then washed with sat. sodium bicarbonate solution (3 x 50 mL). The ethereal layer was then dried and concentrated to provide a crude mixture of cyclopropanes as an off-white solid. Purification by column chromatography (gradient elution, 14:1 to 5:1 hexanes:ethyl acetate) liberated unreacted starting material **162** as a white solid (53 mg, 11%), triphenylmethanol as a white solid (132 mg), **164** as a clear oil (31 mg, 10%) and the desired product **158** as a white solid (178 mg, 61%).

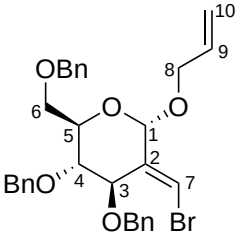
Allyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-β-D-*arabino*-hexopyranoside (141) and allyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-α-D-*arabino*-hexopyranoside (140)

A) Using a modification of Harvey and Hewitt's procedure, allyl alcohol (120 μL, 1.76 mmol) was treated with sodium hydride (21 mg, 0.53 mmol), then once evolution of hydrogen had ceased the solution was diluted with THF (1.0 mL) and cooled to 0 °C. This was treated with a solution of **52** (98 mg, 0.17 mmol) in THF (0.7 mL) cooled to 0 °C. The reaction was allowed to warm slowly to room temperature where it was stirred for 40 hours. The solution was then concentrated to provide crude products **140** and **141** as a yellow oil. Upon separation by column chromatography (14:1 hexanes:ethyl acetate) 2-*C*-branched sugars **169** (5 mg, 5%), **140** (32 mg, 34%) and **141** (37 mg, 39%). **140** and **141** were obtained in a combined yield of 73%. Spectral data matched that which has been previously reported.[39]



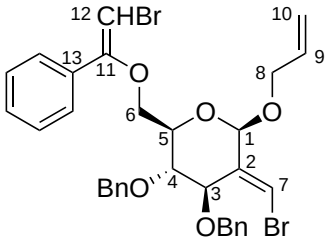
141: R_f = 0.35 (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.42–7.17 (complex m, 15H, Bn), 6.82 (d, J = 1.7 Hz, 1H, H-7), 5.94 (dddd, J = 17.3, 10.5, 6.1, 5.0 Hz, 1H, H-9), 5.35 (d, J = 1.7 Hz, 1H, H-1), 5.29 (apparent dq, J = 17.3, 1.5 Hz, 1H, H-10a), 5.18 (apparent dq, J = 10.5, 1.5 Hz, 1H, H-10b), 4.77 (s, 1H, H-3), 4.66 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.61 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.53 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.51 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.45 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.34 (ddt, J = 12.9, 5.0, 1.5 Hz, 1H, H-8a), 4.30 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.11 (ddt, J = 12.9, 6.1, 1.5 Hz, 1H, H-8b), 3.77–3.75 (complex m, 2H, H-4,5), 3.65–3.63 (complex m, 2H, H-6); (C_6D_6) δ_H 7.38–7.07 (complex m, 15H, Bn), 6.83 (d, J = 1.5 Hz, 1H, H-7), 5.81 (dddd, J = 17.1, 10.5, 6.1, 5.1 Hz, 1H, H-9), 5.30 (d, J = 1.5 Hz, 1H, H-1), 5.16 (dd, J = 17.1, 1.5 Hz, 1H, H-10a), 5.00 (d, J = 10.5 Hz, 1H, H-10b), 4.97 (s, 1H, H-3), 4.56 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.53 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.42 (d, J = 12.6 Hz, 1H, $PhCH_2$), 4.40 (d, J = 12.6 Hz, 1H, $PhCH_2$), 4.35 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.30 (dd, J = 13.0, 5.1 Hz, 1H, H-8a), 4.26 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.04 (ddd, J = 9.0, 6.1, 2.4 Hz, 1H, H-5), 3.92–3.88 (complex m, 2H, H-4,8b), 3.66 (dd, J = 11.0, 6.1 Hz, 1H, H-6a), 3.62 (dd, J = 11.0, 2.4 Hz, 1H, H-6b); ^{13}C NMR: ($CDCl_3$) δ_C 138.4 (C, Bn), 138.2 (C, Bn), 137.8 (C, Bn), 137.7 (CH, C-2), 134.3 (CH_2, C-9), 128.5 (CH, Bn), 128.4 (CH, Bn), 128.2 (CH, Bn), 128.0 (CH, Bn), 127.91 (CH, Bn), 127.88 (CH, Bn), 127.8 (CH, Bn), 127.6 (CH, Bn), 117.3 (CH_2, C-10), 112.7 (CH, C-7), 97.6 (CH, C-1), 79.4 (CH, C-4), 76.2 (CH, C-3), 73.3 (CH_2, $PhCH_2$), 71.7 (CH_2, $PhCH_2$), 71.6 (CH, C-5), 70.9 (CH_2, $PhCH_2$), 69.6 (CH_2, C-6), 68.4 (CH_2, C-8); (C_6D_6) δ_C 139.2 (C, Bn), 138.8 (C, Bn), 138.54 (CH, C-2), 138.46 (C, Bn), 134.8 (CH_2, C-9), 128.60 (CH, Bn), 128.57 (CH, Bn), 128.5 (CH, Bn), 128.4 (CH, Bn), 128.2 (CH, Bn), 128.0 (CH, Bn), 127.7 (CH, Bn), 127.6 (CH, Bn), 116.8 (CH_2, C-10), 112.8 (CH, C-7), 97.4 (CH, C-1), 80.2 (CH, C-4), 77.1 (CH, C-3), 73.1 (CH_2, $PhCH_2$), 72.2 (CH, C-5), 71.8 (CH_2, $PhCH_2$), 71.0 (CH_2, $PhCH_2$), 70.5 (CH_2, C-6), 68.3 (CH_2, C-8); IR (Film from CH_2Cl_2): ν_{max} 3064, 3030, 2916, 2864, 1496, 1454,

1095, 1043, 1028, 734, 697 cm^{-1}; HRMS: *m/z* $C_{31}H_{33}O_5^{79}BrNa^+$ $[M+Na]^+$ calcd 587.1409, found 587.1413.



140: R_f = 0.25 (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.40–7.26 (complex m, 15H, Bn), 6.79 (s, 1H, H-7), 5.91 (dddd, J = 17.1, 10.5, 5.9, 5.0 Hz, 1H, H-9), 5.27 (apparent dq, J = 17.1, 1.7 Hz, 1H, H-10a), 5.20 (s, 1H, H-1), 5.12 (apparent dq, J = 10.5, 1.5 Hz, 1H, H-10b), 4.737 (d, J = 3.4 Hz, 1H, H-3), 4.735 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.65 (d, J = 12.4 Hz, 1H, $PhCH_2$), 4.53 (d, J = 12.4 Hz, 1H, $PhCH_2$), 4.51 (s, 2H, $PhCH_2$), 4.48 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.37 (ddt, J = 13.0 5.0, 1.7 Hz, 1H, H-8a), 4.09 (ddt, J = 13.0 5.9, 1.5 Hz, 1H, H-8b), 3.93–3.89 (complex m, 2H, H-4,5), 3.84 (dd, J = 10.0, 5.8 Hz, 1H, H-6a), 3.80 (dd, J = 10.0, 5.1 Hz, 1H, H-6b); ^{13}C NMR: ($CDCl_3$) δ_C 138.5 (C, Bn), 138.4 (C, Bn), 137.9 (C, Bn), 136.9 (CH, C-2), 134.2 (CH, C-9), 128.52 (CH, Bn), 128.46 (CH, Bn), 128.4 (CH, Bn), 128.3 (CH, Bn), 128.0 (CH, Bn), 127.90 (CH, Bn), 127.86 (CH, Bn), 127.67 (CH, Bn), 127.63 (CH, Bn), 117.3 (CH_2, C-10), 114.8 (CH, C-7), 99.0 (CH, C-1), 76.0 (CH, C-4), 75.1 (CH, C-5), 74.4 (CH, C-3), 73.4 (CH_2, $PhCH_2$), 72.2 (CH_2, $PhCH_2$), 70.78 and 70.75 (CH_2, $PhCH_2$ and CH_2, C-6), 68.8 (CH_2, C-8); IR (Film from CH_2Cl_2): ν_{max} 3064, 3030, 2917, 2849, 1496, 1453, 1091, 1043, 1021, 731, 696 cm^{-1}.

Allyl 3,4-di-*O*-benzyl-6-*O*-(2-bromo-1-phenylethenyl)-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-β-D-arabino-hexopyranoside (169)



169: R_f = 0.40 (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.45–7.16 (complex m, 15H, Ar), 6.89 (d, J = 1.9 Hz, 1H, H-7), 5.95 (dddd, J = 17.3, 10.3, 6.2, 4.9 Hz, 1H, H-9), 5.83 (s, 1H, H-12), 5.37 (d, J = 1.9 Hz, 1H, H-1), 5.31 (apparent dq, J = 17.3, 1.7 Hz, 1H, H-10a), 5.20 (apparent dq, J = 10.3, 1.6 Hz, 1H, H-10b), 4.76 (s, 1H, H-3), 4.65 (d, J = 12.3 Hz, 1H, $PhCH_2$), 4.53 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.44 (d, J = 12.3 Hz, 1H, $PhCH_2$), 4.40 (ddt, J = 13.0, 4.9, 1.5 Hz, 1H, H-8a), 4.36 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.14 (ddt, J = 13.0, 6.2, 1.5 Hz, 1H, H-8b), 3.95 (dd, J = 10.2, 1.7 Hz, 1H, H-6a), 3.86 (dd, J = 10.2, 5.3 Hz, 1H, H-6b), 3.82 (ddd, J = 8.8, 5.3, 1.7 Hz, 1H, H-5), 3.79 (d, J = 8.8 Hz, 1H, H-4), ^{13}C NMR: ($CDCl_3$) δ_C 157.3 (C, C-11), 138.1 (C, Bn), 137.7 (C, Bn), 137.5 (C, C-2), 134.3 (CH, C-9), 134.0 (C, C-13), 130.5 (CH, Ar), 129.2 (CH, Ar), 128.7 (CH, Ar), 128.493 (CH, Ar), 128.485 (CH, Ar), 128.13 (CH, Ar), 128.09 (CH, Ar), 127.9 (CH, Ar), 127.0 (CH, Ar), 117.5 (CH_2, C-10), 112.9 (CH, C-7), 97.0 (CH, C-1), 89.7 (CH, C-12), 79.3 (CH, C-4), 76.1 (CH, C-3), 71.6 (CH, C-5, and CH_2, $PhCH_2$), 70.9 (CH_2, $PhCH_2$), 70.1 (CH_2, C-6), 68.5 (CH_2, C-8); IR (Film from CH_2Cl_2): ν_{max} 3064, 3031, 2918, 2868, 1495, 1454, 1066, 1027, 728, 696 cm^{-1}; HRMS: *m/z* $C_{32}H_{32}O_5^{79}Br_2Na^+$ $[M+Na]^+$ calcd 677.0514, found 677.0503.

B) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (120 μL, 1.76 mmol) was treated with sodium hydride (20 mg, 0.50 mmol), once evolution of hydrogen had ceased the solution was diluted with THF (1.0 mL) and heated to 40 °C. This was treated with a solution of **52** (98 mg, 0.17 mmol) in THF (0.7 mL), preheated to 40 °C. The reaction was stirred for 10 minutes before being concentrated to provide crude products **140** and **141** as a yellow oil. Upon separation by column chromatography (14:1 hexanes:ethyl acetate) 2-*C*-branched sugars **169** (2 mg, 2%), **140** (39 mg, 41%) and **141** (20 mg, 21%). **140** and **141** were obtained in a combined yield of 62%.

C) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (120 μL, 1.76 mmol) was treated with sodium hydride (20 mg, 0.50 mmol), once evolution of hydrogen had ceased the solution was diluted with THF (1.0 mL). This was treated with a solution of **52** (98 mg, 0.17 mmol) in THF (0.7 mL) and stirred at room temperature for 40 hours. The solution was then concentrated to provide crude products **140** and **141** as a yellow oil. Upon separation by column chromatography (14:1 hexanes:ethyl acetate), 2-*C*-branched sugars **169** (8 mg, 8%), **140** (30 mg, 32%) and **141** (35 mg, 38%). **140** and **141** were obtained in a combined yield of 70%.

D) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (120 μL, 1.76 mmol) was treated with sodium hydride (23 mg, 0.58 mmol), once evolution of hydrogen had ceased the solution was diluted with DME (1.0 mL). This was treated with a solution of **52** (101 mg, 0.17 mmol) in DME (0.7 mL) and stirred at room temperature for 1 hour. The solution was then concentrated to provide crude products **140** and **141** as a yellow oil. Upon separation by column chromatography (14:1 hexanes:ethyl acetate) 2-*C*-branched sugars **169** (8 mg, 8%), **140** (44 mg, 45%) and **141** (28 mg, 29%). **140** and **141** were obtained in a combined yield of 74%.

E) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (120 μL, 1.76 mmol) was treated with sodium hydride (22 mg, 0.55 mmol), once evolution of hydrogen had ceased the solution was diluted with DMF (1.0 mL). This was treated with a solution of **52** (103 mg, 0.18 mmol) in DMF (0.7 mL) and stirred at room temperature for 20 minutes. The solution was diluted with water (10 mL) and extracted with dichloromethane (3 x 30 mL) and then washed with sat. copper sulfate (2 x 5 mL). The ^{1}H NMR spectrum of the crude product (13 mg) showed a complex mixture of products including: an aldehyde, **140**, **141** and one other major unknown alkene product.

F) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (150 μL, 2.21 mmol) was treated with sodium hydride (35 mg, 0.88 mmol), once evolution of hydrogen had ceased the solution was diluted with 1,4-dioxane (2.2 mL). This was treated with **52** (130 mg, 0.22 mmol) and heated to 80 °C for three hours. The solution was diluted with water (10 mL) and extracted with dichloromethane (3 x 30 mL). The organic fractions were combined, dried and concentrated to provide crude products **140** and **141** as a yellow oil. Upon separation by column chromatography (14:1 hexanes:ethyl acetate) 2-*C*-branched sugars **140** (39 mg, 31%) and **141** (20 mg, 18%) were obtained in a combined yield of 49%.

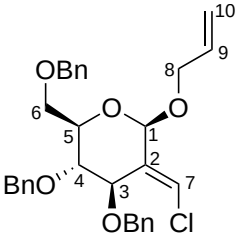
G) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (150 μL, 2.21 mmol) was treated with sodium hydride (36 mg, 0.88 mmol), once evolution of hydrogen had ceased the solution was diluted with THF (2.2 mL) and silver nitrate (49 mg, 0.29) was added. This was treated with **52** (130 mg, 0.22 mmol) and heated to reflux for six hours. The solution was filtered through Celite® washing with dichloromethane (10 mL). Water (10 mL) was added and the products extracted with dichloromethane (2 x 30 mL). The organic fractions were combined, dried and concentrated to provide crude products **140** and **141** as a yellow oil. Upon separation by column chromatography (14:1 hexanes:ethyl acetate), 2-*C*-branched sugars **140** (51 mg, 41%) and **141** (30 mg, 24%) were obtained in a combined yield of 65%.

H) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (1.75 mL, 25.7 mmol) was treated with sodium hydride (315 mg, 7.88 mmol), once evolution of hydrogen had ceased the solution was diluted with THF (15.5 mL). This treated with a solution of **52** (1.50 g, 2.55 mmol) in THF (10 mL) then heated to reflux for 18 hours. The reaction was cooled to room temperature then concentrated to provide crude products **140** and **141** as a yellow oil. Upon separation by column chromatography (14:1 hexanes:ethyl acetate) 2-*C*-branched sugars **140** (377 mg, 26%) and **141** (463 mg, 32%) were obtained in a combined yield of 58%.

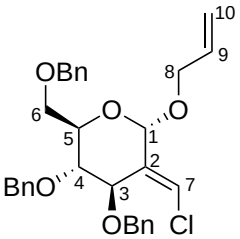
Allyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(chloromethylene)-2-deoxy-β-D-*arabino*-hexopyranoside (172) and allyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(chloromethylene)-2-deoxy-α-D-*arabino*-hexopyranoside (173)

A) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (140 μL, 2.06 mmol) was treated with sodium hydride (24 mg, 0.60 mmol), once evolution of hydrogen had ceased the solution was diluted with THF (1.3 mL). This was treated with a solution of **50** (100 mg, 0.20 mmol) in THF (0.7 mL) then heated to reflux for 14 hr. The reaction was cooled to room temperature and concentrated to provide crude products **172** and **173** as a yellow oil. Upon separation by column

chromatography (14:1 hexanes:ethyl acetate) 2-*C*-branched sugars **172** (37 mg, 36%) and **173** (43 mg, 41%) were obtained in a combined yield of 77%.



172: $R_f = 0.35$ (9:1 hexanes:ethyl acetate); $[\alpha]_D^{23.6}$ +54.7 (*c* 0.50, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.38–7.14 (complex m, 15H, Bn), 6.68 (d, J = 1.7 Hz, 1H, H-7), 5.94 (dddd, J = 17.2, 10.5, 6.1, 4.9 Hz, 1H, H-9), 5.35 (d, J = 1.7 Hz, 1H, H-1), 5.25 (apparent dq, J = 17.2, 1.5 Hz, 1H, H-10a), 5.18 (apparent dq, J = 10.5, 1.3 Hz, 1H, H-10b), 4.75 (s, 1H, H-3), 4.63 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.58 (d, J = 12.1 Hz, 1H, $PhCH_2$), 4.51 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.48 (d, J = 12.1 Hz, 1H, $PhCH_2$), 4.41 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.30 (ddt, J = 13.0, 4.9, 1.5 Hz, 1H, H-8a), 4.28 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.07 (ddt, J = 13.0, 6.1, 1.2 Hz, 1H, H-8b), 3.75–3.71 (complex m, 2H, H-4,5), 3.64–3.59 (complex m, 2H, H-6a,b); (C_6D_6) δ_H 7.37–7.08 (complex m, 15H, Bn), 6.64 (d, J = 1.0 Hz, 1H, H-7), 5.82 (dddd, J = 17.4, 10.5, 6.1, 4.9 Hz, 1H, H-9), 5.31 (s, 1H, H-1), 5.17 (dd, J = 17.4, 1.7 Hz, 1H, H-10a), 5.00 (dd, J = 10.5, 1.2 Hz, 1H, H-10b), 4.98 (s, 1H, H-3), 4.56 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.52 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.43 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.37 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.35 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.30 (dd, J = 13.2, 4.9 Hz, 1H, H-8a), 4.27 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.05 (ddd, J = 9.0, 5.9, 2.4 Hz, 1H, H-5), 3.91 (d, J = 9.0 Hz, 1H, H-4), 3.90 (dd, J = 13.2, 6.1 Hz, 1H, H-8b), 3.66 (dd, J = 11.0, 5.9 Hz, 1H, H-6a), 3.62 (dd, J = 11.0, 2.4 Hz, 1H, H-6b); ^{13}C NMR: ($CDCl_3$) δ_C 138.4 (C, Bn), 138.2 (C, Bn), 137.8 (C, Bn), 134.7 (CH, C-2), 134.3 (CH_2, C-9), 128.5 (CH, Bn), 128.4 (CH, Bn), 128.12 (CH, Bn), 128.07 (CH, Bn), 127.91 (CH, Bn), 127.88 (CH, Bn), 127.8 (CH, Bn), 127.6 (CH, Bn), 123.1 (CH, C-7), 117.3 (CH_2, C-10), 96.9 (CH, C-1), 79.3 (CH, C-4), 74.4 (CH, C-3), 73.2 (CH_2, $PhCH_2$), 71.8 (CH_2, $PhCH_2$), 71.5 (CH, C-5), 71.0 (CH_2, $PhCH_2$), 69.6 (CH_2, C-6), 68.3 (CH_2, C-8); (C_6D_6) δ_C 139.2 (C, Bn), 138.8 (C, Bn), 138.5 (C, Bn), 135.7 (CH, C-2), 134.8 (CH_2, C-9), 128.60 (CH, Bn), 128.56 (CH, Bn), 128.5 (CH, Bn), 128.4 (CH, Bn), 128.2 (CH, Bn), 128.0 (CH, Bn), 127.7 (CH, Bn), 127.6 (CH, Bn), 123.2 (CH, C-7), 116.8 (CH_2, C-10), 97.0 (CH, C-1), 80.0 (CH, C-4), 75.2 (CH, C-3), 73.1 (CH_2, $PhCH_2$), 72.1 (CH, C-5), 71.9 (CH_2, $PhCH_2$), 71.1 (CH_2, $PhCH_2$), 70.4 (CH_2, C-6), 68.3 (CH_2, C-8); IR (Film from CH_2Cl_2): ν_{max} 3064, 3031, 2916, 2865, 1496, 1454, 1093, 1043, 1028, 735, 697 cm^{-1}; HRMS: *m/z* $C_{31}H_{33}O_5^{35}ClNa^+$ $[M+Na]^+$ calcd 543.1914, found 543.1918.

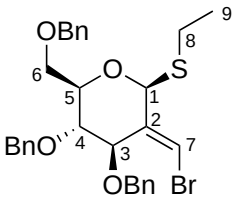


173: $R_f = 0.25$ (9:1 hexanes:ethyl acetate); $[\alpha]_D^{24.5}$ +4.40 (*c* 0.70, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.33–7.21 (complex m, 15H, Bn), 6.58 (s, 1H, H-7), 5.87 (dddd, J = 17.1, 10.5, 6.0, 4.9 Hz, 1H, H-9), 5.23 (apparent dq, J = 17.1, 1.7 Hz, 1H, H-10a), 5.14 (s, 1H, H-1), 5.13 (apparent dq, J = 10.5, 1.5 Hz, 1H, H-10b), 4.72 (d, J = 3.6 Hz, 1H, H-3), 4.69 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.60 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.50 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.48–4.47 (complex m, 2H,

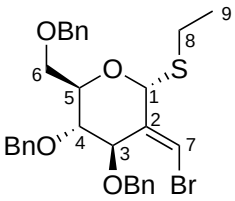
$PhCH_2$), 4.43 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.33 (ddt, J = 13.0, 4.9, 1.5 Hz, 1H, H-8a), 4.05 (ddt, J = 13.0, 6.0, 1.3 Hz, 1H, H-8b), 3.90–3.85 (complex m, 2H, H-4,5), 3.79 (dd, J = 10.0, 5.9 Hz, 1H, H-6a), 3.76 (dd, J = 10.0, 5.1 Hz, 1H, H-6b); (C_6D_6) δ_H 7.28–7.07 (complex m, 15H, Bn), 6.11 (s, 1H, H-7), 5.79 (dddd, J = 17.3, 10.5, 5.6, 4.9 Hz, 1H, H-9), 5.21 (apparent dq, J = 17.3, 1.7 Hz, 1H, H-10a), 5.00 (apparent dq, J = 10.5, 1.7 Hz, 1H, H-10b), 4.96 (s, 1H, H-1), 4.92 (m, 1H, H-3), 4.79 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.52 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.48 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.42 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.38–4.36 (complex m, 2H, $PhCH_2$), 4.33 (ddt, J = 13.2, 4.9, 1.7 Hz, 1H, H-8a), 4.12–4.10 (complex m, 2H, H-4,5), 3.95–3.89 (complex m, 2H, H-6a,b), 3.88 (ddt, J = 13.2, 5.6, 1.7 Hz, 1H, H-8b); ^{13}C NMR: ($CDCl_3$) δ_C 138.5 (C, Bn), 138.4 (C, Bn), 137.9 (C, Bn), 134.2 (CH, C-9), 134.0 (CH, C-2), 128.5 (CH, Bn), 128.4 (CH, Bn), 128.3 (CH, Bn), 128.02 (CH, Bn), 128.0 (CH, Bn), 127.9 (CH, Bn), 127.8 (CH, Bn), 127.66 (CH, Bn), 127.63 (CH, Bn), 124.8 (CH, C-7), 117.2 (CH_2, C-10), 98.2 (CH, C-1), 75.9 (CH, C-4), 75.0 (CH, C-5), 73.4 (CH_2, $PhCH_2$), 72.6 (CH, C-3), 72.3 (CH_2, $PhCH_2$), 70.77 and 70.74 (CH_2, $PhCH_2$, and CH_2, C-6), 68.7 (CH_2, C-8); (C_6D_6) δ_C 139.16 (C, Bn), 139.15 (C, Bn), 138.7 (C, Bn), 134.7 (CH, C-9), 134.6 (CH, C-2), 128.57 (CH, Bn), 128.56 (CH, Bn), 128.5 (CH, Bn), 128.4 (CH, Bn), 128.2 (CH, Bn), 128.0 (CH, Bn), 127.8 (CH, Bn), 127.70 (CH, Bn), 127.67 (CH, Bn), 124.6 (CH, C-7), 116.5 (CH_2, C-10), 98.6 (CH, C-1), 76.4 and 75.2 (CH, C-4, and CH, C-5), 73.4 (CH_2, $PhCH_2$), 73.2 (CH, C-3), 72.2 (CH_2, $PhCH_2$), 71.2 (CH_2, $PhCH_2$), 70.9 (CH_2, C-6), 68.7 (CH_2, C-8); IR (Film from CH_2Cl_2): ν_{max} 3064, 3031, 2864, 1496, 1454, 1091, 1072, 1026, 734, 696 cm^{-1}; HRMS: m/z $C_{31}H_{33}O_5^{35}ClNa^+$ $[M+Na]^+$ calcd 543.1914, found 543.1909.

B) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (140 μL, 2.06 mmol) was treated with sodium hydride (24 mg, 0.60 mmol), once evolution of hydrogen had ceased the solution was diluted with THF (1.3 mL). This was treated with a solution of **50** (102 mg, 0.20 mmol) in THF (0.7 mL) then stirred at room temperature for seven days. The reaction was then concentrated to provide recovery starting material cyclopropane **50** with traces of **172** and **173** as a light yellow oil.

Attempted Synthesis of Ethyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-1-thio-β-D-*arabino*-hexopyranoside (175) and ethyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*- (bromomethylene)-2-deoxy-1-thio-α- D-*arabino*-hexopyranoside (176)



175

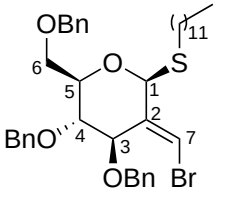


176

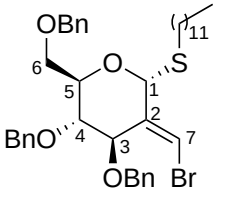
A) A portion of ethanethiol (120 μL, 1.66 mmol) was treated with sodium hydride (12 mg, 0.50 mmol), once the sodium hydride had reacted, the solution was diluted with THF (1.0 mL), then treated with a solution of cyclopropane **52** (105 mg, 0.18 mmol) in THF (0.70 mL) and heated to 35 °C. After 26 hours the reaction was cooled, quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide a complex mixture of products. Purification by column chromatography (14:1 hexanes:ethyl acetate) isolated monobromocyclopropane **174** (8 mg, 9%) as the only identifiable product.

B) A portion of ethanethiol (120 μL, 1.66 mmol) was treated with sodium hydride (12 mg, 0.50 mmol), once the sodium hydride had reacted, the solution was diluted with THF (1.0 mL), then treated with a solution of cyclopropane **52** (99 mg, 0.17 mmol) in THF (0.7 mL). The reaction was stirred at room temperature for one week, at which point the reaction was quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide starting material cyclopropane **52** (84 mg, 85%).

Attempted Synthesis of *n*-dodecyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-1-thio-β-D-*arabino*-hexopyranoside (177) and *n*-dodecyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-1-thio-α-D-*arabino*-hexopyranoside (178)



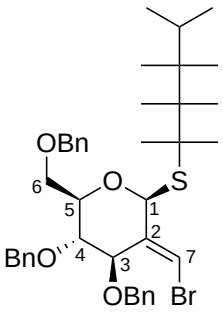
177



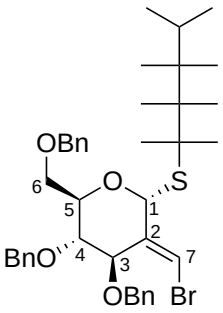
178

A portion of *n*-dodecanethiol (400 μL, 1.67 mmol) was treated with sodium hydride (13 mg, 0.53 mmol), once the sodium hydride had reacted, the solution was diluted with THF (1.0 mL), then treated with a solution of cyclopropane **52** (100 mg, 0.17 mmol) in THF (0.70 mL) and heated to reflux. After five days the reaction was cooled, quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide starting material cyclopropane **52** (82 mg, 80%).

Attempted Synthesis of *t*-dodecyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-1-thio-β-D-*arabino*-hexopyranoside (179) and *n*-dodecyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-1-thio-α-D-*arabino*-hexopyranoside (180)



179

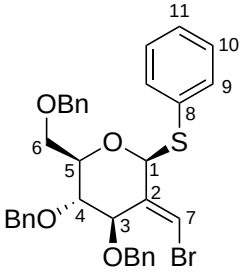


255

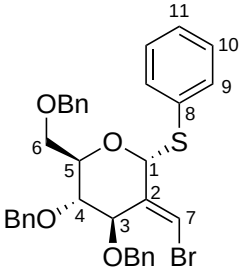
A portion of *t*-dodecanethiol (400 μL, 1.70 mmol) was treated with sodium hydride (13 mg, 0.53 mmol), once the sodium hydride had reacted, the solution was diluted with THF (1.0 mL), then treated with a solution of cyclopropane **52** (102 mg, 0.17 mmol) in THF (0.70 mL) and heated to reflux. After eight hours the reaction was cooled, quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide a complex mixture of products. Purification by column chromatography (14:1 hexanes:ethyl acetate) isolated monobromocyclopropane **174** (10 mg, 12%) as the only identifiable product.

Phenyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-1-thio-β-D-*arabino*-hexopyranoside (181) and phenyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-1-thio-α-D-*arabino*-hexopyranoside (182)

A portion of thiophenol (175 μL, 1.71 mmol) was treated with sodium hydride (12 mg, 0.50 mmol), once the sodium hydride had reacted, the solution was diluted with THF (1.0 mL), then treated with a solution of cyclopropane **52** (105 mg, 0.18 mmol) in THF (0.7 mL) and heated to reflux. After 40 hours the reaction was cooled, quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide a crude mixture of **181** and **182**. Purification by column chromatography (14:1 hexanes:ethyl acetate) provided **181** and **182** as an inseparable 7:2 mixture (81 mg, 76%).



181



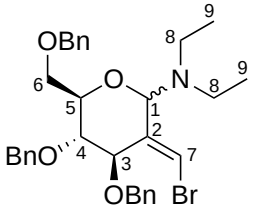
182

181 and **182**: R_f = 0.25 (5:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.67–7.16 (complex m, 20H, $Ar_{\mathbf{181}\text{ and }\mathbf{182}}$), 7.05 (d, J = 2.2 Hz, 0.22H, H-$7_{\mathbf{182}}$), 6.80 (d, J = 0.9 Hz, 0.78H, H-$7_{\mathbf{181}}$), 6.05 (d, J = 2.0 Hz, 0.22H, H-$1_{\mathbf{182}}$), 5.79 (d, J = 0.9 Hz, 0.78H, H-$1_{\mathbf{181}}$), 4.81 (d, J = 1.5 Hz, 0.22H, H-$3_{\mathbf{182}}$), 4.796 (d, J = 1.9 Hz, 0.78H, H-$3_{\mathbf{181}}$), 4.793 (d, J = 12.1 Hz, 0.78H, $PhCH_{2\ \mathbf{181}}$), 4.66 (d, J = 12.2 Hz, 0.22H, $PhCH_{2\ \mathbf{182}}$), 4.59 (d, J = 12.0 Hz, 0.22H, $PhCH_{2\ \mathbf{182}}$), 4.54 (d, J = 3.6 Hz, 1.56H, $PhCH_{2\ \mathbf{181}}$), 4.513 (d, J = 11.6 Hz, 0.78H, $PhCH_{2\ \mathbf{181}}$), 4.505 (d, J = 10.8 Hz, 0.22H, $PhCH_{2\ \mathbf{182}}$), 4.46 (d, J = 10.8 Hz, 0.22H, $PhCH_{2\ \mathbf{182}}$), 4.45 (d, J = 12.2 Hz, 0.22H, $PhCH_{2\ \mathbf{182}}$), 4.44 (d, J = 12.1 Hz, 0.78H, $PhCH_{2\ \mathbf{181}}$), 4.38 (d, J = 11.6 Hz, 0.78H, $PhCH_{2\ \mathbf{181}}$), 4.32 (d, J = 11.5 Hz, 0.22H, $PhCH_{2\ \mathbf{182}}$), 4.06 (ddd J = 8.5, 5.0, 3.6 Hz, 0.22H, H-$5_{\mathbf{182}}$),

3.94 (m, 0.22H, H-4$_{\mathbf{182}}$), 3.81 (dd, J = 6.3, 1.9 Hz, 0.78H, H-4$_{\mathbf{181}}$), 3.77 (d, J = 6.3 Hz, 0.78H, H-6a$_{\mathbf{181}}$), 3.76 (d, J = 4.6 Hz, 0.78H, H-6b$_{\mathbf{181}}$), 3.69 (apparent td, J = 6.3, 4.6 Hz, 0.78H, H-5$_{\mathbf{181}}$), 3.650 (d, J = 5.0 Hz, 0.22H, H-6a$_{\mathbf{182}}$), 3.648 (d, J = 3.6 Hz, 0.22H, H-6b$_{\mathbf{182}}$); ^{13}C NMR: ($CDCl_3$) δ_C 138.4 (C, Bn$_{\mathbf{181}}$), 138.3 (C, Bn$_{\mathbf{181}}$), 138.1 (C, Ar or C-2$_{\mathbf{182}}$), 138.0 (C, Ar or C-2 $_{\mathbf{182}}$), 137.8 (C, C-2$_{\mathbf{181}}$), 137.7 (C, Ar or C-2 $_{\mathbf{182}}$), 137.5 (C, Bn$_{\mathbf{181}}$), 137.2 (C, Ar or C-2 $_{\mathbf{182}}$), 135.5 (C, C-8$_{\mathbf{181}}$), 132.8 (CH, C-9/10$_{\mathbf{181}}$), 131.7 (CH, Ar$_{\mathbf{182}}$), 131.1 (CH, C-9/10$_{\mathbf{181}}$), 130.5 (CH, Ar$_{\mathbf{182}}$), 129.4 (CH, Ar$_{\mathbf{182}}$), 129.0 (CH, Ar), 128.6 (CH, Ar), 128.55 (CH, Ar), 128.49 (CH, Ar), 128.47 (CH, Ar), 128.46 (CH, Ar), 128.42 (CH, Ar), 128.23 (CH, Ar), 128.21 (CH, Ar), 128.19 (CH, Ar), 128.04 (CH, Ar), 127.99 (CH, Ar), 127.90 (CH, Ar), 127.88 (CH, Ar), 127.8 (CH, Ar), 127.7 (CH, Ar), 127.4 (CH, Ar), 112.9 (CH, C-7$_{\mathbf{181}}$), 112.5 (CH, C-7$_{\mathbf{182}}$), 87.5 (CH, C-1$_{\mathbf{182}}$), 86.2 (CH, C-1$_{\mathbf{181}}$), 79.0 (CH, C-4$_{\mathbf{182}}$), 77.8 (CH, C-5$_{\mathbf{181}}$), 77.6 (CH, C-4$_{\mathbf{181}}$), 75.8 (CH, C-3$_{\mathbf{182}}$), 74.6 (CH, C-3$_{\mathbf{181}}$), 73.4 (CH_2, PhCH$_2$ $_{\mathbf{181}}$), 73.2 (CH_2, PhCH$_2$ $_{\mathbf{182}}$), 72.0 (CH, C-5$_{\mathbf{182}}$), 71.8 (CH_2, PhCH$_2$ $_{\mathbf{182}}$), 71.6 (CH_2, PhCH$_2$ $_{\mathbf{181}}$), 71.0 (CH_2, PhCH$_2$ $_{\mathbf{182}}$), 70.9 (CH_2, PhCH$_2$ $_{\mathbf{181}}$), 70.7 (CH_2, C-6$_{\mathbf{181}}$), 70.1 (CH_2, C-6$_{\mathbf{182}}$), IR (Film from CH_2Cl_2): ν_{max} 3061, 3031, 2917, 2864, 2850, 1582, 1496, 1477, 1454, 1439, 1091, 1071, 1027, 738, 696 cm^{-1}; HRMS: m/z $C_{34}H_{33}O_4S^{79}BrNa^+$ $[M+Na]^+$ calcd 639.1181, found 639.1191.

***N,N*-Diethyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-β-D-*arabino*-hexopyranosyl amine (183) and *N,N*-diethyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-α-D-*arabino*-hexopyranosyl amine (184)**

A portion of diethylamine (170 μL, 1.64 mmol) was treated with sodium hydride (12 mg, 0.50 mmol), once the sodium hydride had reacted, the solution was diluted with THF (1.0 mL), then treated with a solution of cyclopropane **52** (101 mg, 0.17 mmol) in THF (0.7 mL). The reaction was stirred at room temperature for 14 hours at which point the reaction was cooled, quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide a crude mixture of **183** and **184**. Purification by column chromatography (5:1 hexanes:ethyl acetate with 3% NEt_3) provided **183** and **184** as an inseparable 1:1 mixture (50 mg, 50%), **185** (10 mg, 13%) and free sugars **190**, **191** and aldehyde **192** (16 mg, 18%).

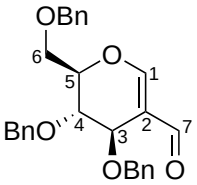


183, **184**

183 and **184**: R_f = 0.67 (5:1 hexanes:ethyl acetate + 5% NEt_3); ^{1}H NMR: ($CDCl_3$) δ_H 7.38–7.22 (complex m, 15H, Bn), 6.83 (d, J = 1.8 Hz, 0.5H, H-7$_{\mathbf{183}}$), 6.79 (d, J = 1.8 Hz, 0.5H, H-7$_{\mathbf{184}}$), 5.17 (d, J = 1.8 Hz, 0.5H, H-1$_{\mathbf{184}}$), 4.90 (d, J = 1.8 Hz, 0.5H, H-1$_{\mathbf{183}}$), 4.80 (d, J = 1.7 Hz, 0.5H, H-3$_{\mathbf{184}}$), 4.72 (d, J = 3.6 Hz, 0.5H, H-3$_{\mathbf{183}}$), 4.69–4.37 (complex m, 6H, PhCH$_2$), 3.89–3.50

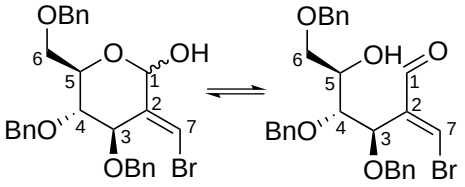
(complex m, 4H, H-4, H-5, H-6a,b), 2.86–2.69 (complex m, 4H, H-8), 1.06–1.02 (complex m, 6H, H-9); ^{13}C NMR: ($CDCl_3$) δ_C 140.0 (C, C-2$_{\mathbf{183}}$), 138.63 (2×C, 2×Bn), 138.62 (C, Bn), 138.3 (C, Bn), 137.99 (C, Bn), 137.95 (C, Bn), 137.4 (C, C-2$_{\mathbf{184}}$), 128.50 (CH, Bn), 128.47 (CH, Bn), 128.44 (CH, Bn), 128.43 (CH, Bn), 128.40 (CH, Bn), 128.37 (CH, Bn), 128.1 (CH, Bn), 127.97 (CH, Bn), 127.94 (CH, Bn), 127.91 (CH, Bn), 127.86 (CH, Bn), 127.83 (CH, Bn), 127.81 (CH, Bn), 127.80 (CH, Bn), 127.79 (CH, Bn), 127.63 (CH, Bn), 127.61 (CH, Bn), 127.58 (CH, Bn), 112.8 (CH, C-7$_{\mathbf{183}}$), 111.7 (CH, C-7$_{\mathbf{184}}$), 91.1 (CH, C-1$_{\mathbf{183}}$), 87.9 (CH, C-1$_{\mathbf{184}}$), 78.9 (CH, C-4/5$_{\mathbf{184}}$), 78.2 (CH, C-4/5$_{\mathbf{183}}$), 76.3 (CH, C-3$_{\mathbf{184}}$), 75.7 (CH, C-4/5$_{\mathbf{184}}$), 75.2 (CH, C-4/5$_{\mathbf{183}}$), 74.1 (CH, C-3$_{\mathbf{183}}$), 73.4 (CH_2, $PhCH_2$), 73.3 (CH_2, $PhCH_2$), 71.67 and 71.66 (CH_2, C-6, and CH_2, $PhCH_2$), 71.4 (CH_2, $PhCH_2$), 71.2 (CH_2, $PhCH_2$), 70.8 (CH_2, $PhCH_2$), 69.7 (CH_2, C-6), 43.2 (CH_2, C-8), 42.6 (CH_2, C-8), 14.5 (CH_2, C-9), 13.6 (CH_2, C-9); IR (Film from CH_2Cl_2): ν_{max} 3064, 3030, 2917, 2849, 1605, 1496, 1453, 1091, 1043, 1021, 731, 696 cm^{-1}; HRMS: *m/z* $C_{32}H_{38}NO_4^{79}BrNa^+$ $[M+Na]^+$ calcd 602.1882, found 602.1895; HRMS: *m/z* $C_{32}H_{39}NO_4^{79}Br^+$ $[M+H]^+$ calcd 580.2069, found 580.2062.

1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-*C*-2-formyl-D-*arabino*-hex-1-enitol (185)



185: Spectral data matched that which has been previously reported.[90] R_f = 0.30 (5:1 hexanes:ethyl acetate); $[\alpha]_D^{23.3}$ −3.87 (*c* 0.67, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 9.41 (s, 1H, CHO), 7.40 (s, 1H, H-1), 7.35–7.23 (complex m, 15H, Bn), 4.13 (apparent ddt, *J* = 8.0, 4.7, 2.0 Hz, 1H, H-5), 4.65 (d, *J* = 11.4 Hz, 1H, $PhCH_2$), 4.56 (d, *J* = 11.4 Hz, 1H, $PhCH_2$), 4.54 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.52 (d, *J* = 12.1 Hz, 1H, $PhCH_2$), 4.47 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.45 (d, *J* = 12.1 Hz, 1H, $PhCH_2$), 4.41 (apparent t, *J* = 2.2 Hz, 1H, H-3), 3.83 (apparent t, *J* = 2.2 Hz, 1H, H-4), 3.79 (dd, *J* = 10.9, 8.0 Hz, 1H, H-6a), 3.62 (dd, *J* = 10.9, 4.5 Hz, 1H, H-6b); ^{13}C NMR: ($CDCl_3$) δ_C 190.5 (CHO, C-7), 164.5 (CH, C-1), 138.3 (C, Bn), 137.7 (C, Bn), 137.3 (C, Bn), 128.7 (CH, Bn) 128.6 (CH, Bn), 128.5 (CH, Bn), 128.2 (CH, Bn), 128.05 (CH, Bn), 127.98 (CH, Bn), 127.91 (CH, Bn), 127.86 (CH, Bn), 117.9 (C, C-2), 79.5 (CH, C-5), 73.5 (CH_2, $PhCH_2$), 72.6 (CH_2, $PhCH_2$), 71.8 (CH_2, $PhCH_2$), 71.5 (CH, C-4), 68.6 (CH_2, C-6), 65.4 (CH, C-3); IR (Film from CH_2Cl_2): ν_{max} 3064, 3031, 2866, 1672, 1624, 1496, 1454, 1199, 1071, 1028, 910, 732, 698 cm^{-1}; HRMS: *m/z* $C_{28}H_{28}O_5Na^+$ $[M+Na]^+$ calcd 467.1834, found 467.1834.

3,4,6-Tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-β-D-*arabino*-hexopyranose (190), 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-D-*arabino*-hexose (192) and 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-α-D-*arabino*-hexopyranose (191)

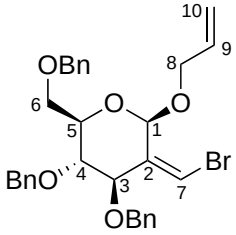


190, **191** **192**

190, **191** and **192**: $R_f = 0.4$ (2:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 9.48 (s, 0.19H, H-$1_{\mathbf{192}}$), 7.43 (d, J = 1.7 Hz, 0.19H, H-$7_{\mathbf{192}}$), 7.40–7.15 (complex m, 15H, Bn), 6.88 (d, J = 1.7 Hz, 0.62H, H-$7_{\mathbf{190}}$), 6.76 (s, 0.19H, H-$7_{\mathbf{191}}$), 5.67 (s, 0.62H, H-$1_{\mathbf{190}}$), 5.46 (d, J = 10.1 Hz, 0.19H, H-$1_{\mathbf{191}}$), 4.88 (d, J = 4.1 Hz, 0.19H, H-$3_{\mathbf{192}}$), 4.76 (d, J = 1.7 Hz, 0.62H, H-$3_{\mathbf{190}}$), 4.74 (s, 0.19H, H-$3_{\mathbf{191}}$), 4.68–4.30 (complex m, 6H, $PhCH_2$), 3.87–3.56 (complex m, 4H, H-4, H-5, H-6a,b), 1.58 (br s, 1-$OH_{\mathbf{190+191}}$); ^{13}C NMR: ($CDCl_3$) δ_C 189.9 (CH, $CHO_{\mathbf{192}}$), 141.1 (CH, C-$7_{\mathbf{192}}$). 138.6 (C, C-$2_{\mathbf{190}}$), 138.23 (C, Bn), 138.20 (C, $Bn_{\mathbf{190}}$), 138.1 (C, $Bn_{\mathbf{190}}$), 137.9 (C, Bn), 137.8 (C, Bn), 137.6 (C, $Bn_{\mathbf{190}}$), 137.5 (C, Bn), 137.4 (C, Bn), 137.3 (C, Bn), 137.2 (C, Bn), 128.75 (CH, Bn), 128.70 (CH, Bn), 128.64 (CH, Bn), 128.60 (CH, Bn), 128.58 (CH, Bn), 128.55 (CH, Bn), 128.51 (CH, Bn), 128.49 (CH, Bn), 128.33 (CH, Bn), 128.29 (CH, Bn), 128.23 (CH, Bn), 128.18 (CH, Bn), 128.16 (CH, Bn), 128.12 (CH, Bn), 128.08 (CH, Bn), 128.05 (CH, Bn), 127.99 (CH, Bn), 127.97 (CH, Bn), 127.95 (CH, Bn), 127.9 (CH, Bn), 127.8 (CH, Bn), 113.2 (CH, C-$7_{\mathbf{191}}$), 113.1 (CH, C-$7_{\mathbf{190}}$), 96.1 (CH, C-$1_{\mathbf{191}}$), 92.4 (CH, C-$1_{\mathbf{190}}$), 80.0 (CH, C-4/$5_{\mathbf{192}\text{ or }\mathbf{191}}$), 78.8 (CH, C-$4_{\mathbf{190}}$), 77.6 (CH, C-$3_{\mathbf{192}}$), 76.5 (CH, C-$3_{\mathbf{191}}$), 75.7 (CH, C-$3_{\mathbf{190}}$), 74.8 ($CH_2$, $PhCH_{2\ \mathbf{192}\text{ or }\mathbf{191}}$), 73.9 (CH, C-4/$5_{\mathbf{192}\text{ or }\mathbf{191}}$), 73.7 ($CH_2$, $PhCH_{2\ \mathbf{192}\text{ or }\mathbf{191}}$), 73.5 ($CH_2$, $PhCH_{2\ \mathbf{192}\text{ or }\mathbf{191}}$), 73.4 ($CH_2$, $PhCH_{2\ \mathbf{190}}$, and CH_2, $PhCH_{2\ \mathbf{192}\text{ or }\mathbf{191}}$), 72.3 ($CH_2$, $PhCH_{2\ \mathbf{192}\text{ or }\mathbf{191}}$), 72.0 (CH, C-$5_{\mathbf{190}}$), 71.8 (CH, C-4/$5_{\mathbf{192}\text{ or }\mathbf{191}}$), 71.6 ($CH_2$, $PhCH_{2\mathbf{190}}$), 71.3 (CH, C-4/$5_{\mathbf{192}\text{ or }\mathbf{191}}$), 70.9 ($CH_2$, $PhCH_{2\ \mathbf{190}}$), 70.8 (CH_2, $PhCH_{2\ \mathbf{192}\text{ or }\mathbf{191}}$), 70.10 ($CH_2$, C-$6_{\mathbf{192}\text{ or }\mathbf{191}}$), 70.05 ($CH_2$, C-$6_{\mathbf{192}\text{ or }\mathbf{191}}$), 69.8 ($CH_2$, C-$6_{\mathbf{190}}$); IR (Film from CH_2Cl_2): ν_{max} 3048, 3088, 3064, 3031, 2920, 2864, 1725, 1495, 1454, 1090, 1072, 1064, 1048, 1029, 732, 697 cm^{-1}; HRMS: *m/z* $C_{28}H_{29}O_5^{79}BrNa^+$ $[M+Na]^+$ calcd 547.1096, found 547.1105.

Allyl 3,4,6-tri-*O*-benzyl-(2*Z*)-2-*C*-(bromomethylene)-2-deoxy-β-D-*arabino*-hexopyranoside (194)

A) A mixture of **52**, **140** and **141** (1.5:1:1) was added to deuterated chloroform for ^{1}H NMR analysis. This solution was allowed to sit at room temperature for 15 hours before repetition of the ^{1}H NMR analysis, which showed an absence of **140** and **141**, with full conversion to **194**.



194: $R_f = 0.40$ (9:1 hexanes:ethyl acetate); $[\alpha]_D^{22.5}$ +20.3 (c 0.89, CH_2Cl_2); m.p. 49.5–51.0 °C; ^{1}H NMR: ($CDCl_3$) δ_H 7.37–7.14 (complex m, 15H, Bn), 6.38 (d, J = 2.2 Hz, 1H, H-7), 5.94 (dddd, J = 17.3, 10.5, 6.1, 5.4 Hz, 1H, H-9), 5.77 (s, 1H, H-1), 5.33 (apparent dq, J = 17.3, 1.5 Hz, 1H, H-10a), 5.23 (apparent dq, J = 10.5, 1.4 Hz, 1H, H-10b), 4.85 (d, J = 10.6 Hz, 1H, $PhCH_2$), 4.77 (d, J = 11.2 Hz,

1H, $PhCH_2$), 4.72 (d, J = 11.2 Hz, 1H, $PhCH_2$), 4.65 (d, J = 12.3 Hz, 1H, $PhCH_2$), 4.519 (d, J = 12.3 Hz, 1H, $PhCH_2$), 4.517 (d, J = 10.6 Hz, 1H, $PhCH_2$), 4.44 (d, J = 9.3, 2.2 Hz, 1H, H-3), 4.21 (ddt, J = 13.0, 5.4, 1.5 Hz, 1H, H-8a), 4.10 (ddt, J = 13.0, 6.1, 1.4 Hz, 1H, H-8b), 3.99 (ddd, J = 10.0, 3.9, 2.0 Hz, 1H, H-5), 3.78 (dd, J = 10.6, 3.9 Hz, 1H, H-6a), 3.69 (dd, J = 10.6, 2.0 Hz, 1H, H-6b), 3.65 (apparent t, J = 9.5 Hz, 1H, H-4); ^{13}C NMR: ($CDCl_3$) δ_C 138.2 (C, Bn), 138.1 (C, Bn and C, C-2), 137.9 (C, Bn), 133.8 (CH, C-9), 128.7 (CH, Bn), 128.52 (CH, Bn), 128.51 (CH, Bn), 128.034 (CH, Bn), 128.027 (CH, Bn), 128.0 (CH, Bn), 127.9 (CH, Bn), 127.82 (CH, Bn), 127.79 (CH, Bn), 118.0 (CH_2, C-10), 103.4 (CH, C-7), 97.2 (CH, C-1), 82.3 (CH, C-3), 79.7 (CH, C-4), 75.2 (CH_2, $PhCH_2$), 74.3 (CH_2, $PhCH_2$), 73.6 (CH_2, $PhCH_2$), 71.5 (CH, C-5), 68.7 (CH_2, C-6), 68.1 (CH_2, C-8); IR (Film from CH_2Cl_2): ν_{max} 3065, 3031, 2914, 2867, 1497, 1454, 1106, 1027, 909, 731, 697 cm^{-1}. HRMS: *m/z* $C_{31}H_{33}O_5^{79}BrNa^+$ $[M+Na]^+$ calcd 587.1409, found 587.1416.

B) Using a modification of Harvey and Hewitt's procedure,[39] allyl alcohol (160 μL, 2.35 mmol) was treated with sodium hydride (17 mg, 0.72 mmol), once evolution of hydrogen had ceased the solution was diluted with THF (2.4 mL) followed by treatment with cyclopropane **52** (144 mg, 0.24 mmol) and heated at reflux overnight (14 hours). The solution was allowed to cool to room temperature, followed by treatment with *p*-TsOH (84 mg, 0.488 mmol). This solution was stirred at room temperature for two hours, before being quenched with a solution of 10% aqueous NaOH (20 mL). The mixture was extracted with dichloromethane (3 x 15 mL), then the organic fractions were combined, dried, filtered and concentrated to provide a crude mixture of **194** and **141**. Purification by column chromatography (14:1 hexanes:ethyl acetate) liberated **194** (39 mg, 28%) as a clear oil and **141** (13 mg, 9%) as a clear oil.

C) Allyl glycoside **140** (40 mg, 0.071 mmol) was dissolved in chloroform (1.0 mL) and treated with 10% aqueous H_2SO_4 solution (0.1 mL). The reaction was stirred at room temperature for nine days with no reaction occuring during this time. The mixture was diluted with water (5 mL), extracted with dichloromethane (3 x 10 mL), then the organic fractions were combined, dried, filtered and concentrated. Purification by column chromatography (14:1 hexanes:ethyl acetate) liberated unreacted starting material **140** (35 mg, 88%) as a clear oil.

D) A mixture of allyl glycosides **140** and **141** (3:1 mixture, 30 mg, 0.053 mmol) were dissolved in chloroform (0.4 mL) and treated with *p*-TsOH $\cdot$ H_2O (5 mg, 0.026 mmol). The reaction was stirred at room temperature for three hours, then quenched with sat. sodium bicarbonate solution (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated

to provided a crude mixture of **185**, **194** and **196**. Purification by column chromatography (gradient 14:1 to 5:1 hexanes:ethyl acetate) liberated a clear oil of **194** and **196** as an inseparable mixture (2:5 ratio, 7 mg, 24%) and aldehyde **185** as a white solid (10 mg, 42%).

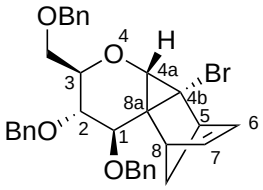
E) A mixture of allyl glycosides **140** and **141** (3:1 mixture, 103 mg, 0.182 mmol) were dissolved in THF (2.0 mL) and treated with CSA (9 mg, 0.039 mmol). The reaction was stirred at room temperature for 4.5 hours, then quenched with sat. sodium bicarbonate solution (15 mL) and extracted with dichloromethane (3 x 15 mL). The organic fractions were combined, dried, filtered and concentrated to provide a complex crude mixture containing: **140**, **141**, **185** and **194** as well as several unidentified products.

F) A mixture of allyl glycosides **140** and **141** (3:1 mixture, 101 mg, 0.179 mmol) were dissolved in THF (2.0 mL) and treated with *p*-TsOH (7 mg, 0.04 mmol). The reaction was stirred at room temperature for 16 hours, then quenched with sat. sodium bicarbonate solution (15 mL) and extracted with dichloromethane (3 x 15 mL). The organic fractions were combined, dried, filtered and concentrated to provide a complex crude mixture containing: **140**, **141**, **194** and **185** as well as several unidentified products.

G) A mixture of allyl glycosides **140** and **141** (1:1 mixture, 100 mg, 0.177 mmol) were dissolved in dichloromethane (1.8 mL) and treated with *p*-TsOH (3 mg, 0.017 mmol). The reaction was stirred at room temperature for 40 minutes, then quenched with K_2CO_3 (0.5 g), diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide a crude mixture of **185** and **194**. Purification by column chromatography (gradient 14:1 to 5:1 hexanes:ethyl acetate) liberated **194** (52 mg, 52%) as a clear oil and **185** as a white solid (27 mg, 34%).

H) A mixture of allyl glycosides **140** and **141** (1:1 mixture, 100 mg, 0.177 mmol) were dissolved in dichloromethane (1.8 mL). 4Å molecular sieves (0.2 g) were added and the solution stirred for 15 minutes. The solution was then treated with *p*-TsOH (3 mg, 0.017 mmol). The reaction was stirred at room temperature for 80 minutes, then quenched with K_2CO_3 (0.5 g), diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide a mixture of **185** and **194**. Purification by column chromatography (gradient 14:1 to 5:1 hexanes:ethyl acetate) liberated **194** (53 mg, 53%) as a clear oil and **185** as a white solid (14 mg, 18%).

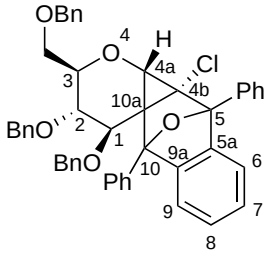
Attempted synthesis of (1*R*, 2*S*, 3*R*, 4a*S*, 4b*R*, 5*R*, 8*S*, 8a*R*)-1,2-Dibenzyloxy-3-(benzyloxymethyl)-4b-bromo-5,8-methano-cyclohex-1′-ena[4′,5′:2,3]-cyclopropa[1,2-*b*]pyran (226)



A) Using a modification of Harvey and Hewitt's procedure, allyl alcohol (110 μL, 1.62 mmol) was treated with sodium hydride (21 mg, 0.85 mmol), once evolution of hydrogen had ceased the solution was diluted with THF (1.0 mL) and cyclopentadiene (500 μL, 5.95 mmol). This was treated with a solution of **52** (100 mg, 0.17 mmol) in THF (0.7 mL) giving a red solution. The solution was heated to reflux where the solution turned to black after four hours at reflux. The reaction was cooled to room temperature and quenched with water (5 mL). The reaction was extracted with dichloromethane (3 x 10 mL), then the organic fractions combined, dried, filtered and concentrated to provide a crude mixture of and **140** and **141**. Upon separation by column chromatography (14:1 hexanes:ethyl acetate) 2-*C*-branched sugars **140** (32 mg, 34%) and **141** (37 mg, 39%) were obtained in a combined yield of 73%. Spectral data matched that which has been previously reported.

B) Using a modification of Harvey and Hewitt's procedure, cyclopentadiene (1.00 mL, 11.89 mmol) was treated with sodium hydride (22 mg, 0.55 mmol), once evolution of hydrogen had ceased the orange solution was treated with a solution of **52** (100 mg, 0.17 mmol) in cyclopentadiene (0.70 mL, 8.32 mmol). The solution was heated to 140 °C where where the solution turned to black after one hour. The reaction was cooled to room temperature and quenched with water (5 mL). The reaction was extracted with dichloromethane (3 x 10 mL), then the organic fractions combined, dried, filtered and concentrated to provide a crude mixture of complex mixture of products, none of which were identifiable.

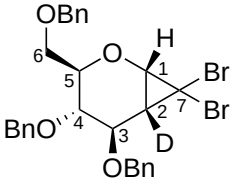
Attempted synthesis of (1*R*, 2*S*, 3*R*, 4a*S*, 4b*R*, 5*R*, 10*S*, 10a*R*)-1,2-Dibenzyloxy-3-(benzyloxymethyl)-4b-chloro-5,10-diphenyl-5,10-epoxy-4b,5,10,10a-tetrahydronaphthaleno[2′,3′:2,3]-cyclopropa[1,2-*b*]pyran (228)



Using a modification of Halton's method,[95] allyl alcohol (130 μL, 1.91 mmol) was treated with sodium hydride (13 mg, 0.55 mmol), then once evolution of hydrogen had ceased the solution was diluted with THF (1.3 mL). The flask was then kept from the light and cooled to 0 °C before addition of DPIBF (56 mg, 0.21 mmol). This solution was treated with a solution of **50** (99 mg, 0.20 mmol) in THF (0.7 mL) and stirred at 0 °C for one hour before being warmed to room temperature. After 24 hours stirring at room temper-

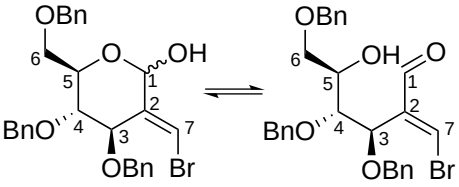
ature the solution was heated to reflux for 48 hours. The solution was then cooled and quenched with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide a crude mixture of **50**, **172**, **173** and DPIBF. Purification by column chromatography (gradient 14:1 to 0:1 hexanes:ethyl acetate) resulted in recovery of starting material **50** (28 mg, 28%) and 2-*C*-branched sugars **172** (27 mg, 26%) and **173** (25 mg, 24%).

Attempted Synthesis of 1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-d_1-2-deoxy-1,2-*C*-(dibromomethylene)-D-*glycero*-D-*gulo*-hexitol (254)



A portion of methanol (100 μL, 2.47 mmol) was treated with metalic sodium (20 mg, 0.87 mmol), once the sodium had reacted, the solution was condensed to dryness under reduced presure. The sodium methoxide produced was dissolved in THF (0.7 mL) and then added to a solution of **52** (101 mg, 0.17 mmol) in THF (1.0 mL). The solution was stirred at room temperature for 25 minutes before being quenched with D_2O (0.2 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide unreacted starting material **52** (81 mg, 80%).

Attempted Synthesis of 3,4,6-Tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-β-D-*arabino*-hexopyranose (190), 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-D-*arabino*-hexose (192) and 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-α-D-*arabino*-hexopyranose (191)



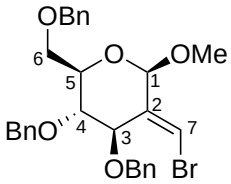
190, **191** **192**

Sodium hydroxide (20 mg, 0.5 mmol) was added to water (22 μL, 1.22 mmol) and dissolved in THF (1.0 mL). This was treated with a solution of **52** (100 mg, 0.17 mmol) in THF (0.7 mL) and heated to reflux. After five days, no reaction was observed. The solution was then diluted with water (5 mL) and extracted with diethyl ether (3 x 10 mL). The organic fractions were combined, dried, filtered and condensed to provide recovered starting material **52** (85 mg, 85%).

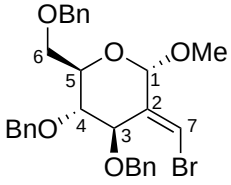
Methyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-β-D-*arabino*-hexopyranoside (56) and methyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene)-2-deoxy-α-D-*arabino*-hexopyranoside (55)

A) As reported by Harvey and Hewitt,[39] a portion of methanol (75 μL, 1.85 mmol) was treated with metallic sodium (6 mg, 0.26 mmol), once the sodium had reacted,

the solution was diluted with THF (1.7 mL), then treated with cyclopropane **52** (100 mg, 0.17 mmol) and heated at reflux for four hours. The solution was cooled, quenched with water (10 mL) and separated with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provide crude products **55** and **56** as a yellow oil. Upon separation by column chromatography (14:1 hexanes:ethyl acetate) 2-*C*-branched sugars **55** (28 mg, 30%) and **56** (18 mg, 20%) were obtained in a combined yield of 50%. Spectral data matched that which has been previously reported.[39]



56: $R_f = 0.35$ (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.41–7.18 (complex m, 15H, Bn), 6.82 (d, $J = 1.7$ Hz, 1H, H-7), 5.19 (d, $J = 1.7$ Hz, 1H, H-1), 4.74 (s, 1H, H-3), 4.65 (d, $J = 12.0$ Hz, 1H, $PhCH_2$), 4.61 (d, $J = 12.2$ Hz, 1H, $PhCH_2$), 4.53 (d, $J = 11.5$ Hz, 1H, $PhCH_2$), 4.51 (d, $J = 12.2$ Hz, 1H, $PhCH_2$), 4.44 (d, $J = 12.0$ Hz, 1H, $PhCH_2$), 4.30 (d, $J = 11.5$ Hz, 1H, $PhCH_2$), 3.75 (d, $J = 9.0$ Hz, 1H, H-4), 3.70 (ddd, $J = 9.0, 5.2, 2.7$ Hz, 1H, H-5), 3.65 (dd, $J = 11.0, 2.7$ Hz, 1H, H-6a), 3.29 (dd, $J = 11.0, 5.2$ Hz, 1H, H-6b), 3.47 (s, 3H, OMe); ^{13}C NMR: ($CDCl_3$) δ_C 138.5 (C, Bn), 138.2 (C, Bn), 137.8 (C, Bn), 137.6 (CH, C-2), 128.5 (CH, Bn), 128.4 (CH, Bn), 128.2 (CH, Bn), 128.0 (CH, Bn), 127.92 (CH, Bn), 127.88 (CH, Bn), 127.83 (CH, Bn), 127.6 (CH, Bn), 112.7 (CH, C-7), 99.1 (CH, C-1), 79.4 (CH, C-4), 76.2 (CH, C-3), 73.3 (CH_2, $PhCH_2$), 71.7 (CH_2, $PhCH_2$), 71.6 (CH, C-5), 70.9 (CH_2, $PhCH_2$), 69.6 (CH_2, C-6), 55.3 (CH_3, OMe).



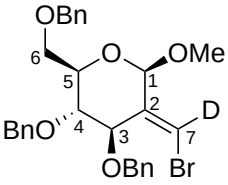
55: $R_f = 0.25$ (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.37–7.24 (complex m, 15H, Bn), 6.79 (s, 1H, H-7), 5.06 (s, 1H, H-1), 4.72 (d, $J = 11.5$ Hz, 1H, $PhCH_2$), 4.70 (d, $J = 3.6$ Hz, 1H, H-3), 4.63 (d, $J = 11.6$ Hz, 1H, $PhCH_2$), 4.53 (s, 2H, $PhCH_2$), 4.51 (d, $J = 11.6$ Hz, 1H, $PhCH_2$), 4.50 (d, $J = 11.5$ Hz, 1H, $PhCH_2$), 3.92 (dd, $J = 5.0, 3.8$ Hz, 1H, H-4), 4.70 (apparent q, $J = 5.3$ Hz, 1H, H-5), 3.82 (dd, $J = 10.0, 5.9$ Hz, 1H, H-6a), 3.78 (dd, $J = 10.0, 5.1$ Hz, 1H, H-6b), 3.48 (s, 3H, OMe); ^{13}C NMR: ($CDCl_3$) δ_C 138.5 (C, Bn), 138.4 (C, Bn), 137.9 (C, Bn), 137.1 (CH, C-2), 128.54 (CH, Bn), 128.47 (CH, Bn), 128.4 (CH, Bn), 128.0 (CH, Bn), 127.92 (CH, Bn), 127.85 (CH, Bn), 127.69 (CH, Bn), 127.68 (CH, Bn), 114.8 (CH, C-7), 101.3 (CH, C-1), 76.1 (CH, C-4), 75.0 (CH, C-5), 74.7 (CH, C-3), 73.4 (CH_2, $PhCH_2$), 72.3 (CH_2, $PhCH_2$), 71.0 (CH_2, $PhCH_2$), 70.7 (CH_2, C-6), 55.9 (CH_3, OMe).

B) Using a modification of Harvey and Hewitt's procedure,[39] methanol (0.2 mL, 4.94 mmol) was treated with sodium hydride (12 mg, 0.51 mmol). Once evolution of hydrogen had ceased, the solution was condensed to dryness under reduced presure. The solid produced was disolved in THF (1.0 mL) and treated with a solution of **52** (101 mg, 0.17 mmol) in THF (0.70 mL). The reaction was stirred at room temperature for 48 hours. The reaction was then condensed providing a

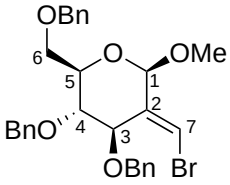
crude mixture of **55** and **56**. Upon separation by column chromatography (14:1 hexanes:ethyl acetate), 2-*C*-branched sugars **55** (36 mg, 39%) and **56** (22 mg, 25%) were obtained in a combined yield of 64% as well as starting material **52** (16 mg, 16%). Spectral data matched that which has been previously reported.

Methyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene-d_1)-2-deoxy-β-D-*arabino*-hexopyranoside (235) and methyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(bromomethylene-d_1)-2-deoxy-α-D-*arabino*-hexopyranoside (234)

A solution of cyclopropane **52** (99 mg, 0.17 mmol) suspended in d_1-methanol (1.0 mL) was treated with a solution of premixed d_1-methanol (1.0 mL) and sodium hydride (22 mg, 0.55 mmol) and heated to reflux for 16 hours. The solution was cooled to room temperature and condensed to provide crude products **234** and **235** as a yellow solid. Upon separation by column chromatography (14:1 hexanes:ethyl acetate), 2-*C*-branched sugars **55** and **234** were isolated in a 1:5 ratio as an inseparable mixture (40 mg, 44%) and **56** and **235** were isolated in a 1:7.4 ratio as an inseparable mixture (24 mg, 26%). The combined yield obtained was 70%.

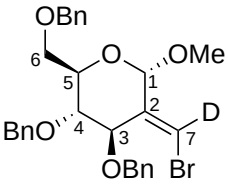


235

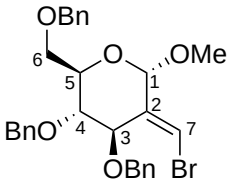


56

56 and **235**: R_f = 0.35 (9:1 hexanes:ethyl acetate); $[\alpha]_D^{22.4}$ +92.8 (*c* 0.83, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.41–7.18 (complex m, 15H, Bn), 6.82 (d, J = 1.2 Hz, 0.11H, H-7), 5.19 (s, 1H, H-1), 4.74 (s, 1H, H-3), 4.65 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.61 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.53 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.51 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.44 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.30 (d, J = 11.5 Hz, 1H, $PhCH_2$), 3.75 (dd, J = 9.0, 0.8 Hz, 1H, H-4), 4.70 (ddd, J = 9.0, 5.2, 2.7 Hz, 1H, H-5), 3.65 (dd, J = 11.0, 2.7 Hz, 1H, H-6a), 3.29 (dd, J = 11.0, 5.2 Hz, 1H, H-6b), 3.47 (s, 3H, OMe); ^{13}C NMR: ($CDCl_3$) δ_C 138.5 (C, Bn), 138.2 (C, Bn), 137.8 (C, Bn), 137.6 (CH, C-2), 128.6 (CH, Bn), 128.5 (CH, Bn), 128.43 (CH, Bn), 128.38 (CH, Bn), 128.2 (CH, Bn), 128.02 (CH, Bn), 127.96 (CH, Bn), 127.92 (CH, Bn), 127.88 (CH, Bn), 127.83 (CH, Bn), 127.6 (CH, Bn), 112.7 (CH, C-7), 112.5 (t, J = 30.2 Hz, CD, C-7), 99.1 (CH, C-1), 79.4 (CH, C-4), 76.2 (CH, C-3), 73.3 (CH_2, $PhCH_2$), 71.7 (CH_2, $PhCH_2$), 71.6 (CH, C-5), 70.9 (CH_2, $PhCH_2$), 69.6 (CH_2, C-6), 55.3 (CH_3, Me); IR (Film from CH_2Cl_2): ν_{max} 3088, 3063, 3030, 2865, 1496, 1454, 1070, 1045, 1028, 735, 697 cm^{-1}; HRMS: *m/z* $C_{29}H_{30}DO_5^{79}BrNa^+$ $[M+Na]^+$ calcd 562.1315, found 562.1309.



234



55

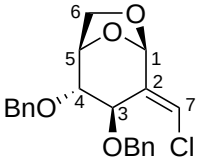
55 and **234**: R_f = 0.25 (9:1 hexanes:ethyl acetate); $[\alpha]_D^{22.7}$ +20.2 (*c* 0.95, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.37–7.24 (complex m, 15H, Bn), 6.79 (s, 0.14H, H-7), 5.06 (s, 1H, H-1), 4.72 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.70 (d, J = 3.6 Hz,

1H, H-3), 4.63 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.53 (s, 2H, $PhCH_2$), 4.51 (d, J = 11.6 Hz, 1H, $PhCH_2$), 4.50 (d, J = 11.5 Hz, 1H, $PhCH_2$), 3.92 (dd, J = 5.0, 3.8 Hz, 1H, H-4), 4.70 (apparent q, J = 5.4 Hz, 1H, H-5), 3.82 (dd, J = 10.0, 5.9 Hz, 1H, H-6a), 3.78 (dd, J = 10.0, 5.1 Hz, 1H, H-6b), 3.48 (s, 3H, OMe); ^{13}C NMR: ($CDCl_3$) δ_C 138.5 (C, Bn), 138.4 (C, Bn), 137.9 (C, Bn), 137.1 (CH, C-2), 128.54 (CH, Bn), 128.47 (CH, Bn), 128.4 (CH, Bn), 128.0 (CH, Bn), 127.92 (CH, Bn), 127.85 (CH, Bn), 127.69 (CH, Bn), 127.68 (CH, Bn), 114.8 (CH, C-7), 114.6 (t, J = 30.3 Hz, CD, C-7), 101.3 (CH, C-1), 76.1 (CH, C-4), 75.0 (CH, C-5), 74.7 (CH, C-3), 73.4 (CH_2, $PhCH_2$), 72.3 (CH_2, $PhCH_2$), 71.0 (CH_2, $PhCH_2$), 70.7 (CH_2, C-6), 55.9 (CH_3, OMe); IR (Film from CH_2Cl_2): ν_{max} 3088, 3063, 3030, 2917, 2864, 1496, 1454, 1090, 1072, 1027, 734, 696 cm^{-1}; HRMS: m/z $C_{29}H_{30}DO_5^{79}BrNa^+$ $[M+Na]^+$ calcd 562.1315, found 562.1313.

B) A portion of d_1-methanol (70 μL, 1.72 mmol) was treated with sodium hydride (20 mg, 0.50 mmol), then once the sodium hydride had reacted, the solution was diluted with THF (1.0 mL), then treated with a solution of cyclopropane **52** (100 mg, 0.17 mmol) in THF (0.7 mL) and the reaction stirred at room temperature for two hours. The solution was then concentrated to provide crude products **55**, **234**, **56** and **235** as a yellow oil in a ratio of 3:5:1:1.7.

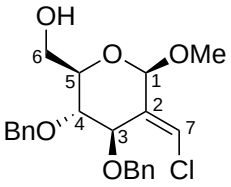
1,6-Anhydro-3,4-di-*O*-benzyl-(2*E*)-2-*C*-(chloromethylene)-2-deoxy-β-D-*arabino*-hexopyranoside (241), methyl 3,4-di-*O*-benzyl-(2*E*)-2-*C*-(chloromethylene)-2-deoxy-β-D-*arabino*-hexopyranoside (243) and methyl 3,4-di-*O*-benzyl-(2*E*)-2-*C*-(chloromethylene)-2-deoxy-α-D-*arabino*-hexopyranoside (242)

A) A portion of methanol (100 μL, 2.47 mmol) was treated with sodium hydride (28 mg, 0.70 mmol), then once evolution of hydrogen had ceased, the solution was diluted with THF (1.7 mL), then treated with a solution of formyl ester cyclopropane **164** (104 mg, 0.24 mmol) in THF (0.7 mL) and heated at reflux for 48 hours. The solution was cooled and concentrated to provide a crude mixture of products with the main components **242** and **243** as a yellow oil. Upon separation by column chromatography (14:1 hexanes:ethyl acetate) 2-*C*-branched sugars **242** (22 mg, 23%) and **243** (20 mg, 21%) as well as bycyclic compound **241** (2 mg, 3%) and hydroxylated cyclopropane **158** (12 mg, 12%). Compounds **242** and **243** were obtained in a combined yield of 44%.

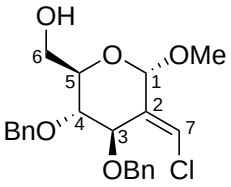


241: R_f = 0.63 (3:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.38–7.29 (complex m, 10H, Bn), 6.49 (s, 1H, H-7), 5.64 (d, J = 1.2 Hz, 1H, H-1), 4.68 (d, J = 12.5 Hz, 1H, $PhCH_2$), 4.62 (m, 1H, H-5), 4.62 (d, J = 11.1 Hz, 1H, $PhCH_2$), 4.60 (m, 1H, H-3), 4.58

(d, J = 12.5 Hz, 1H, $PhCH_2$), 4.43 (d, J = 11.1 Hz, 1H, $PhCH_2$), 4.25 (dd, J = 7.1, 1.0 Hz, 1H, H-6a), 3.75 (dd, J = 7.1, 6.1 Hz, 1H, H-6b), 3.59 (apparent t, J = 1.5 Hz, 1H, H-4); ^{13}C NMR: ($CDCl_3$) δ_C 138.3 (C, Bn), 137.7 (C, Bn), 134.3 (CH, C-2), 128.7 (CH, Bn), 128.5 (CH, Bn), 128.1 (CH, Bn), 128.03 (CH, Bn), 128.02 (CH, Bn), 127.9 (CH, Bn), 122.9 (CH, C-7), 101.8 (CH, C-1), 77.5 (CH, C-4), 75.1 (CH, C-5), 71.7 (CH_2, $PhCH_2$), 71.3 (CH, C-3), 71.2 (CH_2, $PhCH_2$), 64.7 (CH_2, C-6); IR (Film from CH_2Cl_2): ν_{max} 3064, 3031, 2898, 1496, 1454, 1105, 1070, 1025, 975, 735, 697 cm^{-1}; HRMS: *m/z* $C_{21}H_{21}O_4^{35}ClNa^+$ $[M+Na]^+$ calcd 395.1026, found 395.1024.



243: R_f = 0.20 (3:1 hexanes:ethyl acetate); $[\alpha]_D^{20.7}$ +46.8 (*c* 0.62, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.34–7.17 (complex m, 10H, Bn), 6.62 (d, J = 1.7 Hz, 1H, H-7), 5.15 (d, J = 1.7 Hz, 1H, H-1), 4.72 (s, 1H, H-3), 4.60 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.51 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.38 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.35 (d, J = 11.5 Hz, 1H, $PhCH_2$), 3.74 (dd, J = 12.0, 2.8 Hz, 1H, H-6a), 3.71 (dd, J = 8.8, 1.5 Hz, 1H, H-4), 3.62 (dd, J = 12.0, 4.9 Hz, 1H, H-6b), 3.53 (ddd, J = 8.8, 4.9, 2.9 Hz, 1H, H-5), 3.40 (s, 3H, OMe), 1.82 (br s, 1H, 6-OH); ^{13}C NMR: ($CDCl_3$) δ_C 138.0 (C, Bn), 137.9 (C, Bn), 134.4 (CH, C-2), 128.6 (CH, Bn), 128.5 (CH, Bn), 128.2 (CH, Bn), 128.08 (CH, Bn), 128.06 (CH, Bn), 128.0 (CH, Bn), 123.4 (CH, C-7), 98.6 (CH, C-1), 79.0 (CH, C-4), 74.1 (CH, C-3), 72.2 (CH, C-5), 71.8 (CH_2, $PhCH_2$), 71.1 (CH_2, $PhCH_2$), 62.9 (CH_2, C-6), 55.4 (CH_3, OMe); IR (Film from CH_2Cl_2): ν_{max} 3471, 3065, 3031, 2916, 1496, 1454, 1351, 1048, 1028, 735, 697 cm^{-1}; HRMS: *m/z* $C_{22}H_{25}O_5^{35}ClNa^+$ $[M+Na]^+$ calcd 427.1288, found 427.1288.



242: R_f = 0.10 (3:1 hexanes:ethyl acetate); $[\alpha]_D^{21.6}$ +7.89 (*c* 0.38, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.38–7.26 (complex m, 10H, Bn), 6.63 (s, 1H, H-7), 5.05 (s, 1H, H-1), 4.74 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.73 (d, J = 4.2 Hz, 1H, H-3), 4.67 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.55 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.52 (d, J = 11.5 Hz, 1H, $PhCH_2$), 3.93 (dd, J = 6.6, 4.2 Hz, 1H, H-4), 3.83–3.80 (complex m, 2H, H-6a,b), 3.64 (dt, J = 6.6, 4.4 Hz, 1H, H-5), 3.48 (s, 3H, OMe), 2.17 (br s, 1H, 6-OH); ^{13}C NMR: ($CDCl_3$) δ_C 138.2 (C, Bn), 137.5 (C, Bn), 134.3 (CH, C-2), 128.6 (CH, Bn), 128.5 (CH, Bn), 128.08 (CH, Bn), 128.07 (CH, Bn), 128.0 (CH, Bn), 127.8 (CH, Bn), 125.0 (CH, C-7), 100.8 (CH, C-1), 76.6 (CH, C-4), 76.1 (CH, C-5), 73.6 (CH, C-3), 72.7 (CH_2, $PhCH_2$), 71.3 (CH_2, $PhCH_2$), 63.3 (CH_2, C-6), 55.9 (CH_3, OMe); IR (Film from CH_2Cl_2): ν_{max} 3445, 3064, 3031, 2919, 1497, 1454, 1086, 1070, 1028, 735, 697 cm^{-1}; HRMS: *m/z* $C_{22}H_{25}O_5^{35}ClNa^+$ $[M+Na]^+$ calcd 427.1288, found 427.1292.

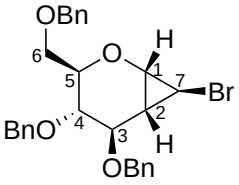
B) Hydroxylated cyclopropane **158** (171 mg, 0.42 mmol) was dissolved in THF, treated with DBU (190 μL, 1.27 mmol) and heated to reflux for five days. The reaction was then cooled to room temperature, diluted with water (5 mL) and ex-

tracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated providing only unreacted starting material **158** (138 mg, 81%).

B) Hydroxylated cyclopropane **158** (100 mg, 0.24 mmol) was dissolved in THF, treated with NaH (6 mg, 0.13 mmol) and heated to reflux for five days. The reaction was then cooled to room temperature and concentrated providing only unreacted starting material **158** (77 mg, 77%).

1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-1,2-*C*-((S)-bromomethylene)-D-*glycero*-D-*gulo*-hexitol (256)

A) In a modification of Hewitt's method,[41] *gem*-dibromocyclopropane **52** (124 mg, 0.21 mmol) was dissolved in THF (1.7 mL) and cooled to −78 °C. The reaction was treated with *n*-butyllithium (0.20 mL, 0.32 mmol) and stirred for an hour at −78 °C. The reaction was then treated with sat. ammonium chloride solution (2 mL) and warmed to room temperature. The mixture was then extracted with dichloromethane (20 x 3 mL), the organic fractions were combined, dried and concentrated to provide **256** as a light brown oil. This oil was purified by flash chromatography (14:1 hexanes:ethyl acetate), to provide monobromocyclopropane **256** as a colourless oil (40 mg, 37%).

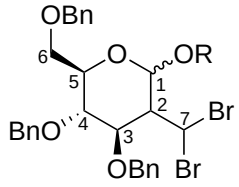


174: Spectral data matched that which has been previously reported.[41] R_f = 0.38 (9:1 hexanes:ethyl acetate); $[\alpha]_D^{26.8}$ +21.7 (*c* 0.87, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.37–7.23 (complex m, 15H, Bn), 4.74 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.70 (d, J = 11.4 Hz, 1H, $PhCH_2$), 4.60 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.55–4.49 (complex m, 3H, $PhCH_2$), 3.81 (dd, J = 7.8, 1.6 Hz, 1H, H-1), 3.77 (td, J = 5.9, 3.6 Hz, 1H, H-5), 3.74 (dd, J = 6.3, 3.0 Hz, 1H, H-3), 3.66 (dd, J = 10.2, 5.9 Hz, 1H, H-6a), 3.543 (dd, J = 10.2, 3.6 Hz, 1H, H-6b), 3.539 (apparent t, J = 5.7 Hz, 1H, H-4), 3.01 (dd, J = 4.6, 1.6 Hz, 1H, H-7), 1.53 (dd, J = 7.8, 4.6, 3.0 Hz, 1H, H-2); ^{13}C NMR: ($CDCl_3$) δ_C 138.2 (C, Bn), 138.1 (C, Bn), 137.8 (C, Bn), 128.7 (CH, Bn), 128.6 (CH, Bn), 128.1 (CH, Bn), 128.0 (CH, Bn), 127.93 (CH, Bn), 127.88 (CH, Bn), 127.85 (CH, Bn), 127.82 (CH, Bn), 76.1 (CH, C-3), 75.4 (CH, C-5), 74.9 (CH, C-4), 73.5 (CH_2, $PhCH_2$), 73.3 (CH_2, $PhCH_2$), 71.6 (CH_2, $PhCH_2$), 69.5 (CH_2, C-6), 56.8 (CH, C-1), 26.5 (CH, C-2), 20.6 (C, C-7); IR (Film from CH_2Cl_2): ν_{max} 3063, 3030, 2864, 1510, 1496, 1454, 1093, 1073, 1028, 735, 697 cm^{-1}; HRMS: *m/z* $C_{28}H_{29}O_4^{79}BrNa^+$ $[M+Na]^+$ calcd 531.1147, found 531.1154.

B) In a modification of Hewitt's method,[41] *gem*-dibromocyclopropane **52** (104 mg, 0.18 mmol) was dissolved in THF (1.7 mL) and cooled to −86 °C in an ethyl ac-

etate/liquid nitrogen cold bath. The reaction was treated with *n*-butyllithium (0.10 mL, 0.32 mmol) and stirred for 25 minutes at −86 °C. The reaction was then treated with sat. ammonium chloride solution (2 mL) and warmed to room temperature. The mixture was then extracted with dichloromethane (3 x 10 mL), then the organic fractions were combined, dried and concentrated to provide **256** as a light brown oil. This oil was purified by flash chromatography (14:1 hexanes:ethyl acetate), to provide monobromocyclopropane **256** as a colourless oil (61 mg, 79%).

Attempted synthesis of Methyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(dibromomethyl)-2-deoxy-α-D-*arabino*-hexopyranoside (257) and methyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(dibromomethyl)-2-deoxy-β-D-*arabino*-hexopyranoside (258)



257 OR = ····OMe

258 OR = ▬OMe

A) 52 (101 mg, 0.17 mmol) was dissolved in methanol (1.7 mL) and the solution heated to reflux. After five days no reaction had occurred as seen by TLC analysis. The reaction was cooled to room temperature and concentrated providing recovered starting material **52** (94 mg, 93%).

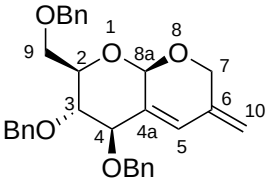
B) 52 (99 mg, 0.17 mmol) was dissolved in methanol (1.7 mL) and treated with 33 wt% HBr in acetic acid (200 μL, 1.10 mmol). The reaction was heated to reflux for 48 hours, at which time no reaction was observed by TLC analysis. The reaction was diluted with water (10 mL) and quenched with K_2CO_3, then extracted with diethyl ether (3 x 10 mL). The organic fractions were combined, dried, filtered and concentrated to provided recovered starting material **52** (84 mg, 85%).

B) 56 (28 mg, 0.05 mmol) was dissolved in methanol (1.0 mL) and treated with 33 wt% HBr in acetic acid (200 μL, 1.10 mmol). The reaction was heated to reflux for one week, at which time the reaction was cooled to room temperature and the reaction quenched causiously with portions of K_2CO_3. The reaction was diluted with water (3 mL) and extracted with dichloromethane (3 x 5 mL). The organic fractions were combined, dried, filtered and concentrated providing a complex mixture which none of the desired compounds could be identified.

(2*R*, 3*S*, 4*R*, 8a*R*)-3,4-Dibenzyloxy-2-(benzyloxymethyl)-6-methylidene-3,4,7,8a-tetrahydro-2*H*-pyrano[2,3-*b*]pyran (205)

194 (27 mg, 0.048 mmol) was dissolved in THF (1.0 mL). This was treated with triethylamine and the solution was then degassed for five minutes through sonocation. $Pd(PPh_3)_4$ (14 mg, 20 mol%) was added and the solution heated to reflux.

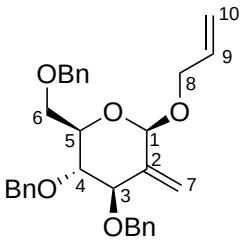
After 26 hours, extra $Pd(PPh_3)_4$ (3 mg, 5 mol%) was added and heated at reflux for a further 22 hours. The reaction was then cooled, quenched with water (3 mL) and extracted with dichloromethane (3 x 5 mL). The organic fractions were combined, dried, filtered through Celite® and concentrated to provide a crude mixture of **194** and **205**. Purification by column chromatography (5:1 hexanes:ethyl acetate) afforded starting material **194** (11 mg, 41%) and **205** (4 mg, 17%) as clear oils.



205: R_f = 0.25 (5:1 hexanes:ethyl acetate); $[\alpha]_D^{22.1}$ +33.0 (*c* 0.19, CH_2Cl_2); ^{1}H NMR: ($CDCl_3$) δ_H 7.38–7.15 (complex m, 15H, Bn), 6.32 (s 1H, H-5), 5.51 (s, 1H, H-8a), 5.01 (s, 1H, H-10a), 4.97 (s, 1H, H-10b), 4.62 (d, J = 12.1 Hz, 1H, $PhCH_2$), 4.60 (d, J = 12.3 Hz, 1H, $PhCH_2$), 4.54 (d, J = 12.3 Hz, 1H, $PhCH_2$), 4.47 (d, J = 11.4 Hz, 1H, $PhCH_2$), 4.46 (d, J = 14.1 Hz, 1H, H-7a), 4.36 (d, J = 12.1 Hz, 1H, $PhCH_2$), 4.35 (d, J = 11.4 Hz, 1H, $PhCH_2$), 4.34 (d, J = 14.1 Hz, 1H, H-7b), 3.98 (s, 1H, H-4), 3.83 (d, J = 9.3 Hz, 1H, H-3), 3.72 (ddd J = 9.3, 5.1, 2.2 Hz, 1H, H-2), 3.68 (dd J = 10.9, 2.2 Hz, 1H, H-9a), 3.62 (dd J = 10.9, 5.1 Hz, 1H, H-9b); ^{13}C NMR: ($CDCl_3$) δ_C 138.5 (C, Bn), 138.3 (C, C-6), 138.0 (C, Bn), 137.7 (C, Bn), 134.4 (C, C-4a), 131.1 (CH, C-5), 128.6 (CH, Bn), 128.5 (CH, Bn), 128.4 (CH, Bn), 128.11 (CH, Bn), 128.09 (CH, Bn), 128.00 (CH, Bn), 127.98 (CH, Bn), 127.96 (CH, Bn), 127.6 (CH, Bn), 112.5 (CH_2, C-10), 94.2 (CH, C-8a), 80.1 (CH, C-4), 79.9 (CH, C-3), 73.4 (CH_2, $PhCH_2$), 73.2 (CH, C-2), 71.6 (CH_2, $PhCH_2$), 70.1 (CH_2, $PhCH_2$), 69.1 (CH_2, C-9), 65.9 (CH_2, C-7); IR (Film from CH_2Cl_2): ν_{max} 3087, 3063, 3030, 2917, 2864, 1496, 1454, 1375, 1095, 1064, 1028, 735, 698 cm^{-1}; HRMS: *m/z* $C_{31}H_{32}O_5Na^+$ $[M+Na]^+$ calcd 507.2147, found 507.2144.

Allyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(methylene)-2-deoxy-β-D-*arabino*-hexopyranoside (244)

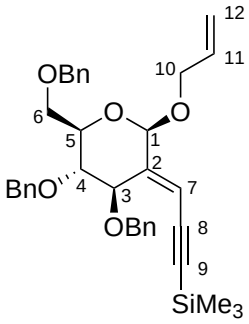
194 (27 mg, 0.048 mmol) was dissolved in THF (1.0 mL) and the solution degassed for five minutes through sonocation. The solution was then treated with K_2CO_3 (18 mg, 0.13) and $Pd(PPh_3)_4$ (10 mg, 20 mol%) was added and the solution heated to reflux. After 20 hours the reaction was cooled, quenched with water (4 mL) and extracted with dichloromethane (3 x 5 mL). The organic fractions were combined, dried, filtered through Celite® and concentrated providing crude **244**. Purification by column chromatography (5:1 hexanes:ethyl acetate) isolated **244** (4 mg, 19%).



244: R_f = 0.35 (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.39–7.14 (complex m, 15H, Bn), 5.92 (dddd, J = 17.1, 10.5, 6.1, 5.1 Hz, 1H, H-9), 5.30 (dd, J = 2.0, 1.5 Hz, 1H, H-7a), 5.29 (apparent dq, J = 17.1, 1.5 Hz, 1H, H-10a), 5.21 (s, 1H, H-1), 5.19 (apparent dq, J = 10.5, 1.7 Hz, 1H, H-10b), 5.15 (apparent t, J = 1.5 Hz, 1H, H-7b), 4.87 (d, J = 10.8 Hz, 1H, $PhCH_2$), 4.77 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.71 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.63 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.50 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.49 (d, J = 10.8 Hz, 1H, $PhCH_2$), 4.46 (dt J = 9.0, 2.0 Hz, 1H, H-3), 4.18 (ddt, J = 12.9, 5.1, 1.5 Hz, 1H, H-8a), 4.02 (ddt, J = 12.9, 6.1, 1.5 Hz, 1H, H-8b), 3.97 (ddd, J = 9.8, 3.9, 2.0 Hz, 1H, H-5), 3.76 (dd, J = 10.8, 3.9 Hz, 1H, H-6a), 3.67 (dd, J = 10.8, 2.0 Hz, 1H, H-6b), 3.62 (dd, J = 9.8, 9.0 Hz, 1H, H-4); ^{13}C NMR: ($CDCl_3$) δ_C 142.4 (C, C-2), 138.45 (C, Bn), 138.44 (C, Bn), 138.3 (C, Bn), 134.0 (CH, C-9), 128.6 (CH, Bn), 128.49 (CH, Bn), 128.48 (CH, Bn), 128.1 (CH, Bn), 128.0 (CH, Bn), 127.9 (CH, Bn), 127.83 (CH, Bn), 127.80 (CH, Bn), 127.75 (CH, Bn), 117.6 (CH, C-10), 110.8 (CH_2, C-7), 100.7 (CH, C-1), 81.3 (CH, C-3), 80.1 (CH, C-4), 75.2 (CH_2, $PhCH_2$), 73.63 (CH_2, $PhCH_2$), 73.57 (CH_2, $PhCH_2$), 70.9 (CH, C-5), 68.9 (CH_2, C-6), 67.8 (CH_2, C-8); IR (Film from CH_2Cl_2): ν_{max} 3032, 2922, 2855, 1496, 1453, 1099, 1065, 1025, 735, 697 cm^{-1}; HRMS: m/z $C_{31}H_{34}O_5Na^+$ $[M+Na]^+$ calcd 509.2304, found 509.2304.

Allyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(2′-trimethylsilylethynyl methylidene)-2-deoxy-α-D-*arabino*-hexopyranoside (245)

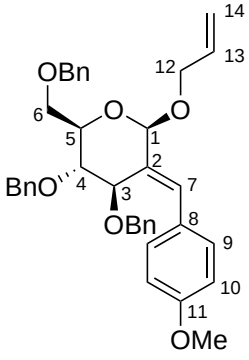
Pd_2dba_3 (3 mg, 4 mol%) was added to THF (2.0 mL), giving a dark red coloured solution. The solution turned a light yellow colour when treated with PPh_3 (3 mg, 0.011 mmol). This was followed by successive addition of triethylamine (0.10 mL, 0.72 mmol) and CuI (2 mg, 10 mol%). This solution was then treated with a solution of **140** (42 mg, 0.074 mmol) in THF (1.0 mL). TMSA (50 μL, 0.35 mmol) was added and the reaction heated to THF reflux for two days. The reaction was then diluted with water (4 mL) and then extracted with dichloromethane (3 x 5 mL). The organic fractions were combined, dried and concentrated to provided a mixture of **140** and **245**. Upon separation by column chromatography (14:1 hexanes:ethyl acetate), starting material **140** (11 mg, 26%) was isolated along with and **245** (23 mg, 53%) as a yellow oil.



245: $R_f = 0.35$ (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.37–7.22 (complex m, 15H, Bn), 5.99 (s, 1H, H-7), 5.74 (dddd, J = 17.2, 10.6, 5.9, 4.9 Hz, 1H, H-11), 5.26 (apparent dq, J = 17.2, 1.5 Hz, 1H, H-12a), 5.15 (apparent dq, J = 10.6, 1.5 Hz, 1H, H-12b), 5.10 (s, 1H, H-1), 4.80 (d, J = 12.1 Hz, 1H, $PhCH_2$), 4.76 (d, J = 3.8 Hz, 1H, H-3), 4.64 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.52 (d, J = 1.3 Hz, 2H, $PhCH_2$), 4.49 (d, J = 11.8 Hz, 1H, $PhCH_2$), 4.47 (d, J = 12.1 Hz, 1H, $PhCH_2$), 4.35 (ddt, J = 13.2 Hz, 4.9, 1.5 Hz, 1H, H-10a), 4.08 (ddt, J = 13.2 Hz, 5.9, 1.5 Hz, 1H, H-10b), 3.87 (dd, J = 5.1, 3.8 Hz, 1H, H-4), 3.65 (m, 1H, H-5), 3.634 (d, J = 4.4 Hz, 1H, H-6a), 3.632 (d, J = 6.2 Hz, 1H, H-6b), 0.16 (s, 9H, $SiMe_3$); ^{13}C NMR: ($CDCl_3$) δ_C 144.4 (C, C-2), 138.9 (C, Bn), 138.5 (C, Bn), 138.0 (C, Bn), 134.3 (CH, C-11), 128.5 (CH, Bn), 128.4 (CH, Bn), 128.3 (CH, Bn), 128.0 (CH, Bn), 127.9 (CH, Bn), 127.85 (CH, Bn), 127.80 (CH, Bn), 127.6 (CH, Bn), 127.5 (CH, Bn), 117.0 (CH_2, C-12), 114.4 (CH, C-7), 102.7 (C, C-9), 100.6 (C, C-8), 99.4 (CH, C-1), 77.1 (CH, C-4), 75.1 (CH, C-3), 74.9 (CH, C-5), 73.4 (CH_2, $PhCH_2$), 72.2 (CH_2, $PhCH_2$), 71.0 (CH_2, $PhCH_2$), 70.8 (CH_2, C-6), 68.9 (CH_2, C-10), −0.08 (CH_3, Me); IR (Film from CH_2Cl_2): ν_{max} 3064, 3031, 2957, 2917, 2866, 2140, 1496, 1454, 1336, 1250, 1092, 1071, 1028, 845, 735, 697 cm^{-1}; HRMS: m/z $C_{36}H_{42}O_5SiNa^+$ $[M+Na]^+$ calcd 605.2699, found 605.2704.

Allyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(4′-methoxyphenylmethylidene)-2-deoxy-α-D-*arabino*-hexopyranoside (246)

General Method: Palladium catalyst (20 mol%) was dissolved in 1,4-dioxane then sucessively treated with base (K_2CO_3, $K_3PO_4 \cdot H_2O$ or KF, 3.0 eq.), additive and 4-methoxyphenylboronic acid (2.0 eq.). The solution was then treated with a pre-mixed solution of **141** (1.0 eq.) in 1,4-dioxane and heated to reflux. After 20–48 hours the solution was cooled to room temperature, quenched with water (5 mL) and extracted with dichlormethane (3 x 10 mL). The organic fractions were combined, dried, filtered through Celite® and concentrated. The oil provided was purified where appropriate.

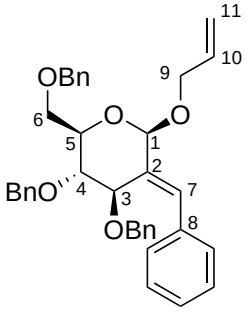


246: $R_f = 0.35$ (9:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.37–7.27 (complex m, 8H, Bn), 7.22–7.15 (complex m, 6H, 3×Bn, H-7, 2×H-9), 7.12–7.10 (complex m, 2H, Bn), 7.00–6.98 (complex m, 2H, Bn), 6.72 (m, 2H, H-10), 6.03 (dddd, J = 17.3, 10.5, 6.1, 5.1 Hz, 1H, H-13), 5.51 (d,J = 1.7 Hz, 1H, H-1), 5.35 (apparent dq, J = 17.3, 1.7 Hz, 1H, H-14a), 5.20 (apparent dq, J = 10.5, 1.5 Hz, 1H, H-14b), 4.65 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.63 (br s, 1H, H-3), 4.55 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.47 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.42 (ddt, J = 13.0, 5.1, 1.5 Hz, 1H, H-12a), 4.32 (d, J =

11.5 Hz, 1H, $PhCH_2$), 4.23 (d, J = 11.5 Hz, 1H, $PhCH_2$), 4.19 (ddt, J = 13.0, 6.1, 1.5 Hz, 1H, H-12b), 4.09 (d, J = 12.2 Hz, 1H, $PhCH_2$), 3.86 (ddd, J = 9.3, 5.4, 2.9 Hz, 1H, H-5), 3.81 (s, 3H, OMe), 3.74 (dd, J = 9.3, 1.2 Hz, 1H, H-4), 3.71 (dd, J = 11.0, 2.9 Hz, 1H, H-6a), 3.67 (dd, J = 11.0, 5.4 Hz, 1H, H-6b); ^{13}C NMR: ($CDCl_3$) δ_C 159.0 (C, C-11), 138.6 (C, Bn), 138.1 (C, Bn), 137.9 (C, Bn), 134.8 (CH, C-13), 133.2 (C, C-8), 132.8 (C, C-2), 130.4 (CH, C-9), 128.42 (CH, Bn), 128.41 (CH, Bn), 128.3 (CH, Bn), 128.2 (CH, Bn), 128.0 (CH, Bn), 127.87 (CH, Bn), 127.83 (CH, Bn), 127.60 (CH, Bn), 127.59 (CH, Bn), 117.1 (CH_2, C-14), 113.6 (CH, C-10), 98.0 (CH, C-1), 79.8 (CH, C-4), 73.2 (CH_2, $PhCH_2$), 72.7 (CH, C-3), 71.4 (CH_2, $PhCH_2$, and CH, C-5), 70.0 (CH_2, $PhCH_2$), 69.9 (CH_2, C-6), 68.4 (CH_2, C-12), 55.4 (CH_3, OMe); IR (Film from CH_2Cl_2): ν_{max} 3064, 3030, 2907, 2865, 1607, 1510, 1497, 1454, 1249, 1096, 1066, 1029, 735, 698 cm^{-1}; HRMS: m/z $C_{38}H_{40}O_6Na^+$ $[M+Na]^+$ calcd 615.2723, found 615.2725.

Allyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(phenylmethylidene)-2-deoxy-α-D-*arabino*-hexopyranoside (247)

General Method: Palladium catalyst (20 mol%) was dissolved in 1,4-dioxane then sucessively treated with base (K_2CO_3, KF, NaOMe, $K_3PO_4 \cdot H_2O$ or NaO*t*-Bu, 3.0 eq.), additive and phenylboronic acid (2.0 eq.). The solution was then treated with a pre-mixed solution of **141** (1.0 eq.) in 1,4-dioxane and heated to reflux. After 20–72 hours the solution was cooled to room temperature, quenched with water (5 mL) and extracted with dichlormethane (3 x 10 mL). The organic fractions were combined, dried, filtered through Celite® and concentrated. The crude oil provided was purified where appropriate.

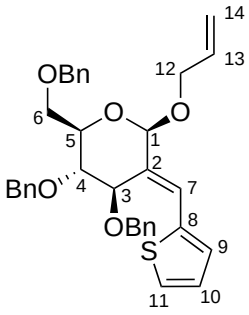


247: R_f = 0.35 (5:1 hexanes:ethyl acetate); ^{1}H NMR: ($CDCl_3$) δ_H 7.42–7.18 (complex m, 20H, Ar), 6.83 (d, J = 1.7 Hz, 1H, H-7), 6.00 (dddd, J = 17.1, 10.5, 6.4, 5.1 Hz, 1H, H-10), 5.56 (s, 1H, H-1), 5.34 (apparent dq, J = 17.1, 1.5 Hz 1H, H-11a), 5.19 (apparent dd, J = 10.5, 1.5 Hz 1H, H-11b), 4.93 (d, J = 10.7 Hz, 1H, $PhCH_2$), 4.83 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.79 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.613 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.609 (m, 1H, H-3), 4.55 (d, J = 10.7 Hz, 1H, $PhCH_2$), 4.49 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.20 (ddt, J = 12.6, 5.1, 1.3 Hz, 1H, H-9a), 4.05 (ddt, J = 12.6, 6.4, 1.5 Hz, 1H, H-9b), 4.01 (ddd, J = 9.5, 3.9, 2.0 Hz, 1H, H-5), 3.77 (dd, J = 10.5, 3.9 Hz, 1H, H-6a), 3.72 (m, 1H, H-4), 3.67 (dd, J = 10.5, 2.0 Hz, 1H, H-5b); ^{13}C NMR: ($CDCl_3$) δ_C 138.5 (C, Bn), 138.34 (C, Bn), 138.25 (C, Bn), 136.3 (C, C-8), 135.0 (C, C-2), 134.1 (CH, C-10), 129.0 (CH, Ar), 128.9 (CH, Ar), 128.6 (CH, Ar), 128.53 (CH, Ar), 128.47 (CH, Ar), 128.3 (CH, Ar), 128.08 (CH, Ar), 128.06 (CH, Ar), 128.0 (CH, Ar), 127.8 (CH, Ar), 127.7 (CH, Ar), 127.4 (CH, Ar), 124.7 (CH, C-7),

118.0 (CH_2, C-11), 96.2 (CH, C-1), 81.9 (CH, C-3), 80.2 (CH, C-4), 75.3 (CH_2, $PhCH_2$), 74.3 (CH_2, $PhCH_2$), 73.6 (CH_2, $PhCH_2$), 71.5 (CH, C-5), 68.9 (CH_2, C-6), 67.8 (CH_2, C-9); IR (Film from CH_2Cl_2): ν_{max} 3009, 2997, 2850, 2801, 1423, 1401, 1261, 1100, 1025, 1027, 802, 697 cm^{-1}; HRMS: *m/z* $C_{37}H_{38}O_5Na^+$ $[M+Na]^+$ calcd 585.2617, found 585.2623.

Allyl 3,4,6-tri-*O*-benzyl-(2*E*)-2-*C*-(2′-thiophenylmethylidene)-2-deoxy-α-D-*arabino*-hexopyranoside (248)

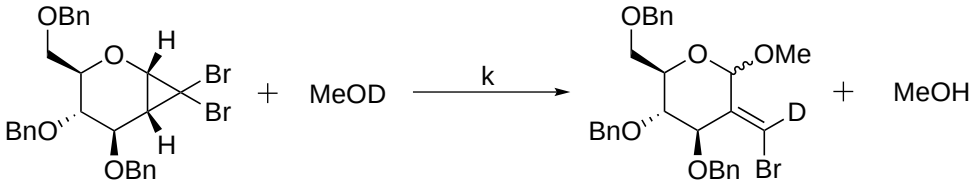
Pd_2dba_3 (3 mg, 11 mol%) was disolved in 1,4-dioxane (4.0 mL) giving a dark red coloured solution. The solution was then successively treated with PPh_3 (8 mg, 0.03 mmol), NEt_3 (30 μL, 0.22 mmol) and potassium thiophen-2-yl trifluoroboronate (26 mg, 0.14 mmol). The solution was then treated with a pre-mixed solution of **141** (35 mg, 0.062 mmol) in 1,4-dioxane (0.50 mL). The reaction was heated to reflux for two days, cooled to room temperature, quenched with water (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried, filtered through Celite® and concentrated providing a crude mixture of **141** and **248** as a yellow oil. Purification by column chromatography (14:1 hexanes:ethyl acetate) resulted in the isolation of **141** (11 mg, 31%) and **248** (20 mg, 57%) as clear oils.



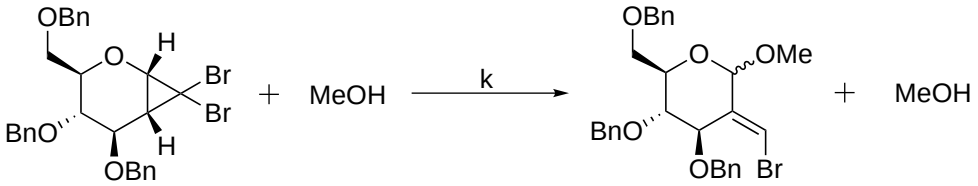
248: R_f = 0.35 (5:1 hexanes:ethyl acetate); ^1H NMR: ($CDCl_3$) δ_H 7.34–7.25 (complex m, 12H, 11×Bn and H-11), 7.23 (d, *J* = 1.7 Hz, 1H, H-7), 7.21–7.19 (complex m, 2H, Bn), 7.16–7.14 (complex m, 2H, Bn), 7.00 (dt, *J* = 3.4, 1.0 Hz, 1H, H-9), 6.94 (dd, *J* = 5.2, 3.4 Hz, 1H, H-10), 6.01 (dddd, *J* = 17.3, 10.4, 6.1, 5.1 Hz, 1H, H-13), 5.50 (d, *J* = 1.7 Hz, 1H, H-1), 5.34 (apparent dq, *J* = 17.3, 1.7 Hz 1H, H-14a), 5.19 (apparent dq, *J* = 10.4, 1.7 Hz 1H, H-14b), 5.03 (s, 1H, H-3), 4.612 (d, *J* = 12.2 Hz, 1H, $PhCH_2$), 4.611 (d, *J* = 12.2 Hz, 1H, $PhCH_2$), 4.54 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.52 (d, *J* = 12.2 Hz, 1H, $PhCH_2$), 4.40 (ddt, *J* = 13.1, 5.1, 1.7 Hz, 1H, H-12a), 4.35 (d, *J* = 12.2 Hz, 1H, $PhCH_2$), 4.30 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.34 (ddt, *J* = 13.1, 6.1, 1.5 Hz, 1H, H-12b), 3.81–3.80 (complex m, 2H, H-4,5), 3.67–3.61 (complex m, 2H, H-6); ^{13}C NMR: ($CDCl_3$) δ_C 138.6 (C, Bn), 138.3 (C, Bn), 138.1 (C, C-8), 137.8 (C, Bn), 134.7 (CH, C-13), 132.6 (C, C-2), 129.9 (CH, C-9), 128.43 (CH, Bn), 128.40 (CH, Bn), 128.35 (CH, Bn), 128.2 (CH, Bn), 128.0 (CH, Bn), 127.9 (CH, Bn), 127.7 (CH, Bn), 127.6 (CH, Bn), 127.1 (CH, C-10), 126.3 (CH, C-11), 126.2 (CH, C-7), 117.1 (CH_2, C-14), 97.6 (CH, C-1), 79.7 (CH, C-4), 73.8 (CH, C-3), 73.2 (CH_2, $PhCH_2$), 71.6 (CH_2, $PhCH_2$), 71.4 (CH, C-5), 70.3 (CH_2, $PhCH_2$), 69.9 (CH_2, C-6), 68.5 (CH_2, C-12); IR (Film from CH_2Cl_2): ν_{max} 3064, 3030, 2906, 2864, 1719, 1672, 1606, 1496, 1454, 1096, 1067, 1027, 735, 697 cm^{-1}; HRMS: *m/z* $C_{35}H_{36}O_5SNa^+$ $[M+Na]^+$ calcd 591.2181, found 591.2178.

Apendix A: Derivation of Kinetic Equations

What follows is a mathmatical analysis giving the statistical amounts of the protonated and deuterated products. Concentrations of each species are denoted in italics eg [A]=A.



A B C D



A D E D

$$A + B \longrightarrow C + D \tag{4.1}$$

$$A + D \longrightarrow E + D \tag{4.2}$$

Finding an Equation for A

$$-\frac{dA}{dt} = kAB + kAD \tag{4.3}$$

$$= kA(B + D) \tag{4.4}$$

As

$$B + D = B_0 + D_0 \tag{4.5}$$
$$\Rightarrow \frac{dA}{dt} = kA(B_0 + D_0) \tag{4.6}$$
$$\frac{dA}{A} = -k(B_0 + D_0)dt \tag{4.7}$$

As $-k(B_0 + D_0)$ is constant

$$\int \frac{dA}{A} = -k(B_0 + D_0) \int dt \tag{4.8}$$
$$\Rightarrow \ln A = -k(B_0 + D_0)t + G \tag{4.9}$$
$$A = \exp(G) \exp[-k(B_0 + D_0)t] \tag{4.10}$$

When $t = 0$

$$A_0 = \exp(G) \tag{4.11}$$
$$\Rightarrow A = A_0 \exp[-k(B_0 + D_0)t] \tag{4.12}$$

Equation for B

$$-\frac{dB}{dt} = kAB \tag{4.13}$$
$$= kBA_0 \exp[-k(B_0 + D_0)t] \tag{4.14}$$
$$\frac{dB}{B} = -kA_0 \exp[-k(B_0 + D_0)t]\ dt \tag{4.15}$$

As $-kA_0$ is constant

$$\int \frac{dB}{B} = -kA_0 \int \exp[-k(B_0 + D_0)t]dt \tag{4.16}$$
$$\Rightarrow \ln B = \frac{A_0}{B_0 + D_0} \exp[-k(B_0 + D_0)t] + H \tag{4.17}$$
$$B = \exp(H) \exp\left[\frac{A_0}{B_0 + D_0} \exp(-k[B_0 + D_0]t)\right] \tag{4.18}$$

When $t = 0$

$$B_0 = \exp(H) \exp\left[\frac{A_0}{B_0 + D_0}\right] \tag{4.19}$$

$$\exp(H) = B_0 \exp\left[-\frac{A_0}{B_0 + D_0}\right] \tag{4.20}$$

$$\Rightarrow \; B = B_0 \exp\left[\frac{A_0}{B_0 + D_0} \left(\exp\left[-k\left(B_0 + D_0\right) t\right] - 1\right)\right] \tag{4.21}$$

Equation for C

$$C = D - D_0 \tag{4.22}$$

Rearanging 4.5 provides

$$D = D_0 + B_0 - B \tag{4.23}$$

$$\Rightarrow \; C = B_0 - B \tag{4.24}$$

$$= B_0 \left[1 - \exp\left(\frac{A_0}{B_0 + D_0} \left[\exp\left(-k\left[B_0 + D_0\right] t\right) - 1\right]\right)\right] \tag{4.25}$$

Equation for D

$$D = D_0 + C \tag{4.26}$$

$$= D_0 + B_0 \left[1 - \exp\left(\frac{A_0}{B_0 + D_0} \left[\exp\left(-k\left[B_0 + D_0\right] t\right) - 1\right]\right)\right] \tag{4.27}$$

Equation for E

$$E = A_0 - A - C \tag{4.28}$$

$$= A_0 \left[1 - \exp\left(-k\left[D_0 + A_0\right] t\right)\right] - B_0 \left[1 - \exp\left(\frac{A_0}{B_0 + D_0} \left[\exp\left(-k\left[B_0 + D_0\right] t\right) - 1\right]\right)\right] \tag{4.29}$$

Evaluations as $t \to \infty$ then:

$$\lim_{t \to \infty} \exp[-xt] = 0 \tag{4.30}$$

$$\exp(-xt) \to \exp(-x\infty) = 0 \tag{4.31}$$

Where x is a positive constant.

The equations for A, B, C, D and E become:

$$A = 0 \tag{4.32}$$

$$B = B_0 \exp\left[-\frac{kA_0}{B_0 + D_0}\right] \tag{4.33}$$

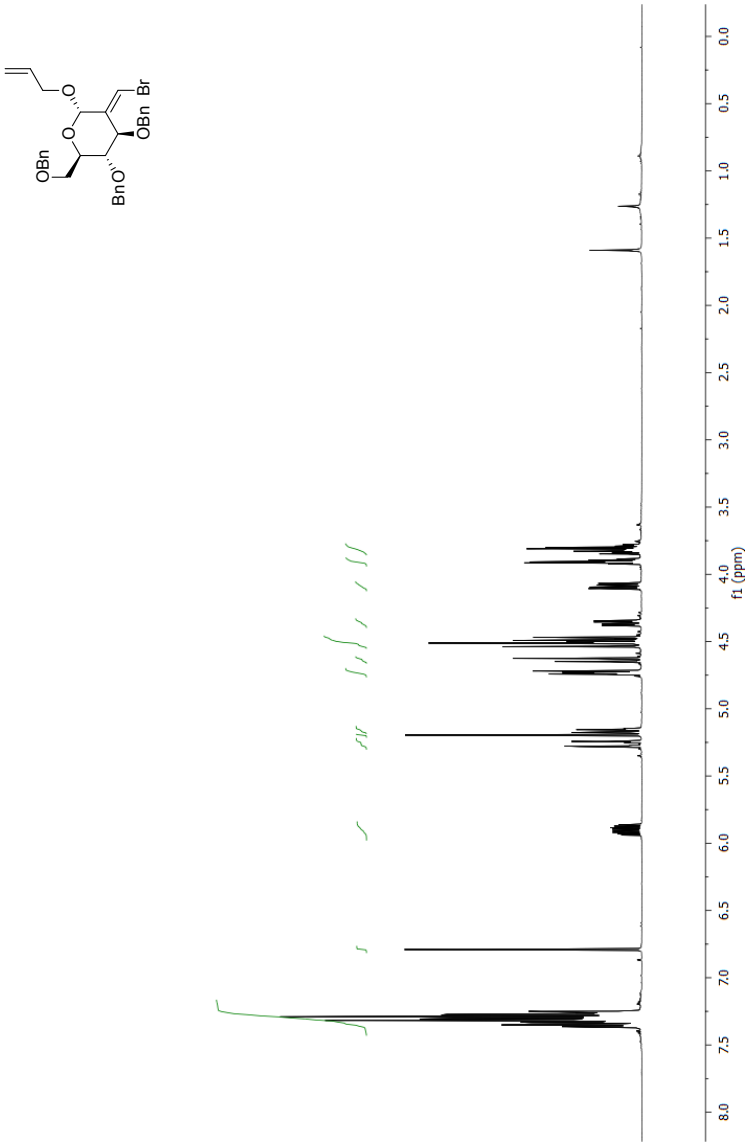
$$C = B_0 \left[1 - \exp\left(-\frac{kA_0}{B_0 + D_0}\right)\right] \tag{4.34}$$

$$D = D_0 + B_0 \left[1 - \exp\left(-\frac{kA_0}{B_0 + D_0}\right)\right] \tag{4.35}$$

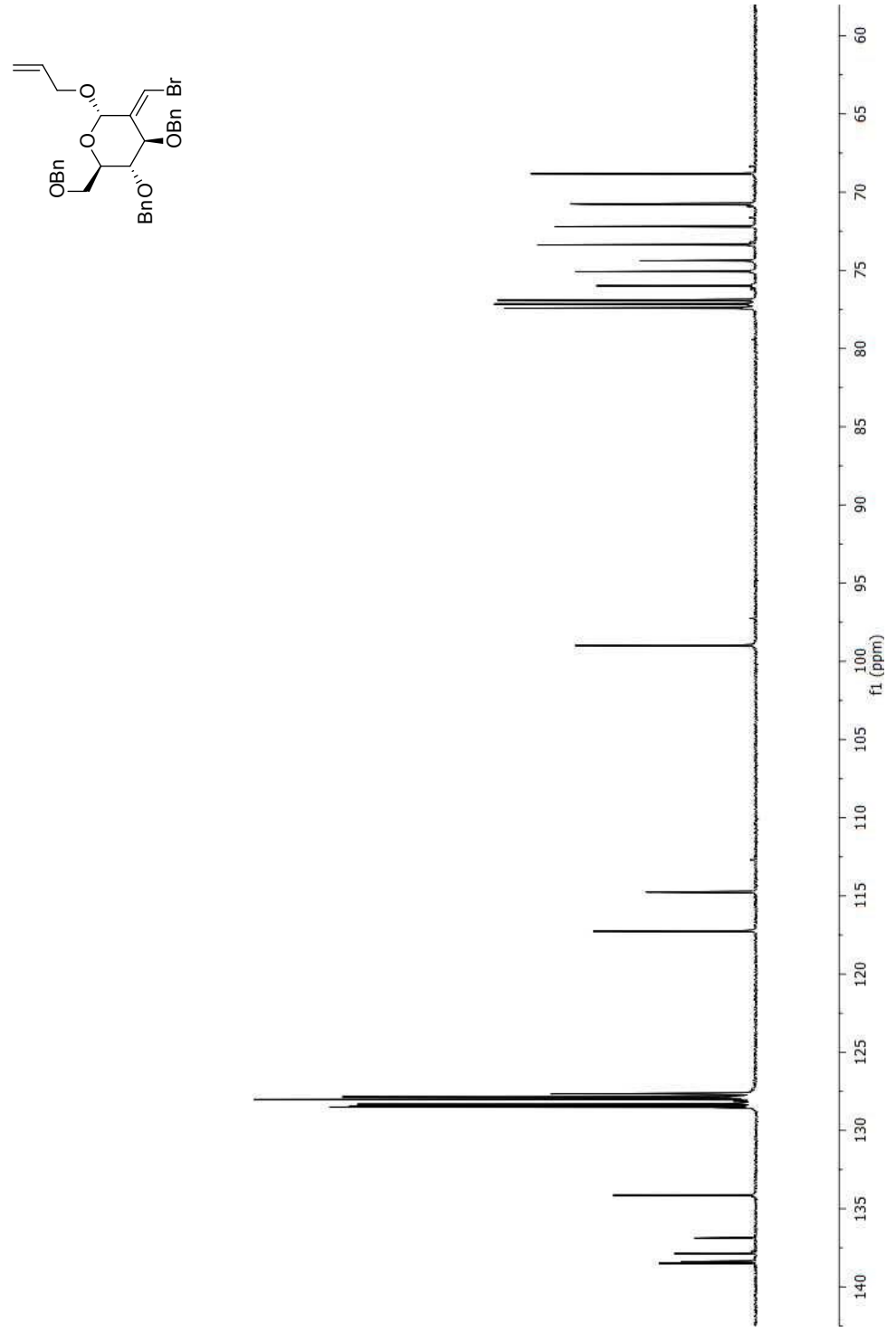
$$E = A_0 - B_0 \left[1 - \exp\left(-\frac{kA_0}{B_0 + D_0}\right)\right] \tag{4.36}$$

Apendix B: Spectra

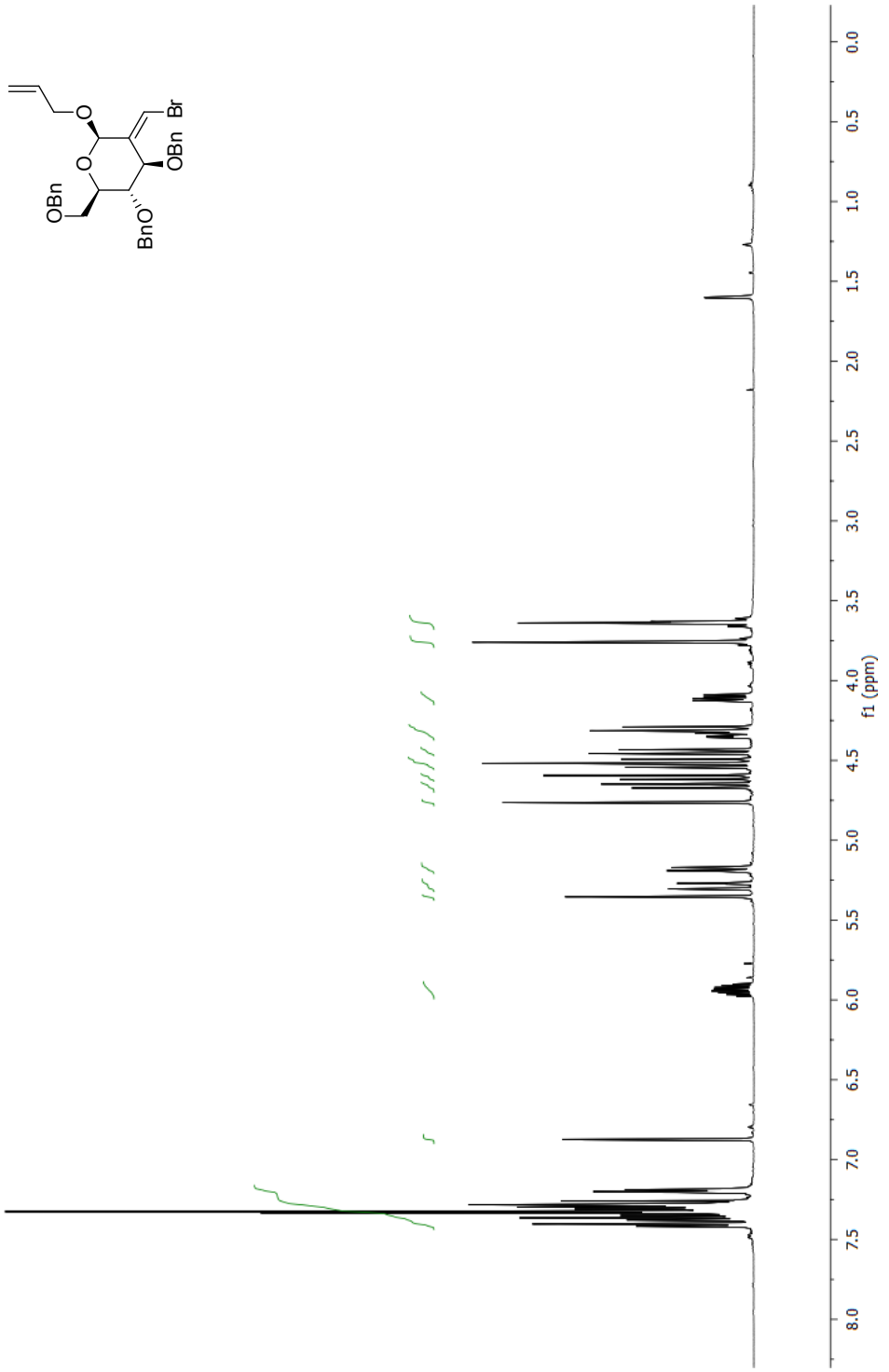
Selected spectra of key compounds



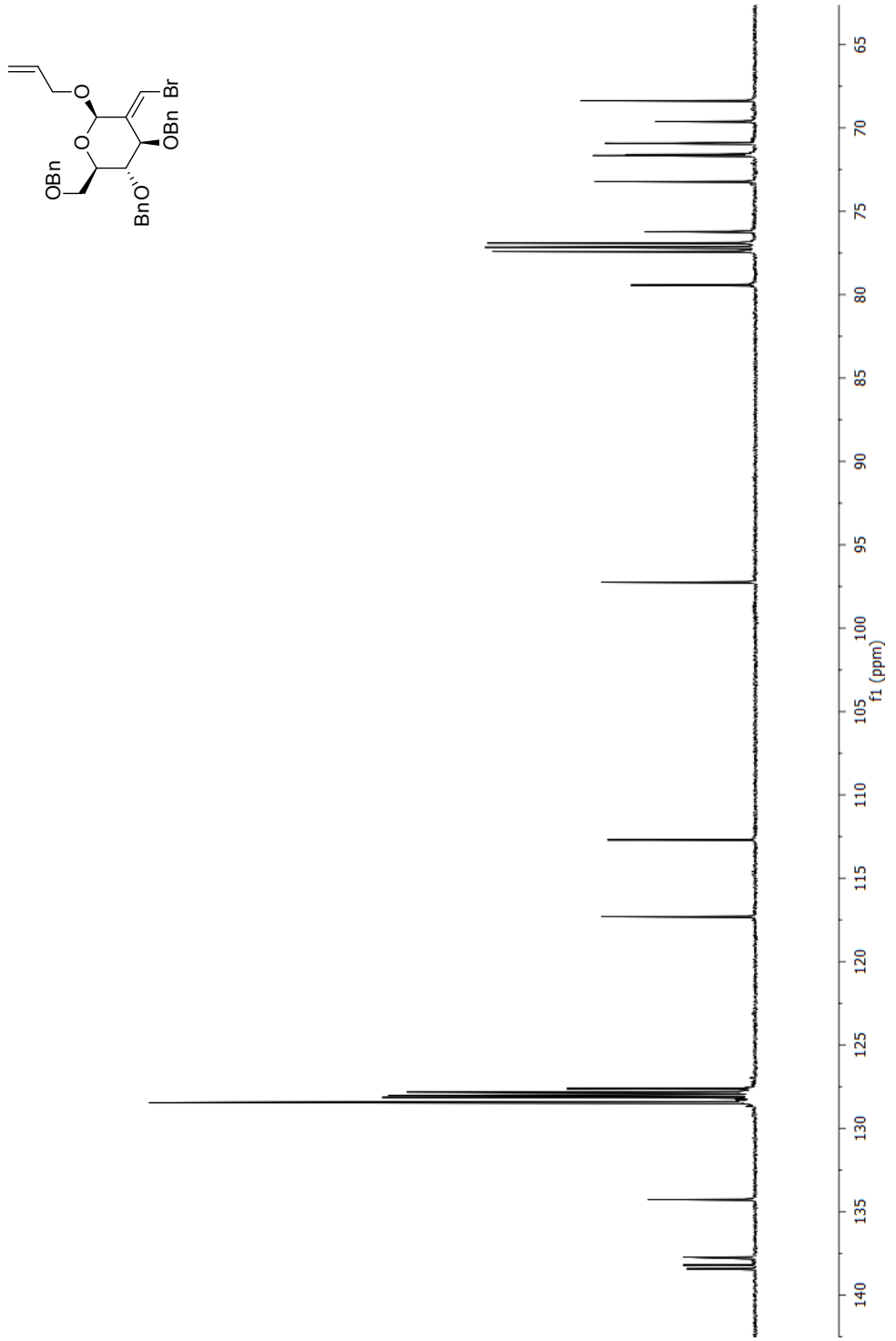
^{1}H-NMR Spectrum of 2-*C*-branched sugar **140** (500 MHz, $CDCl_3$)



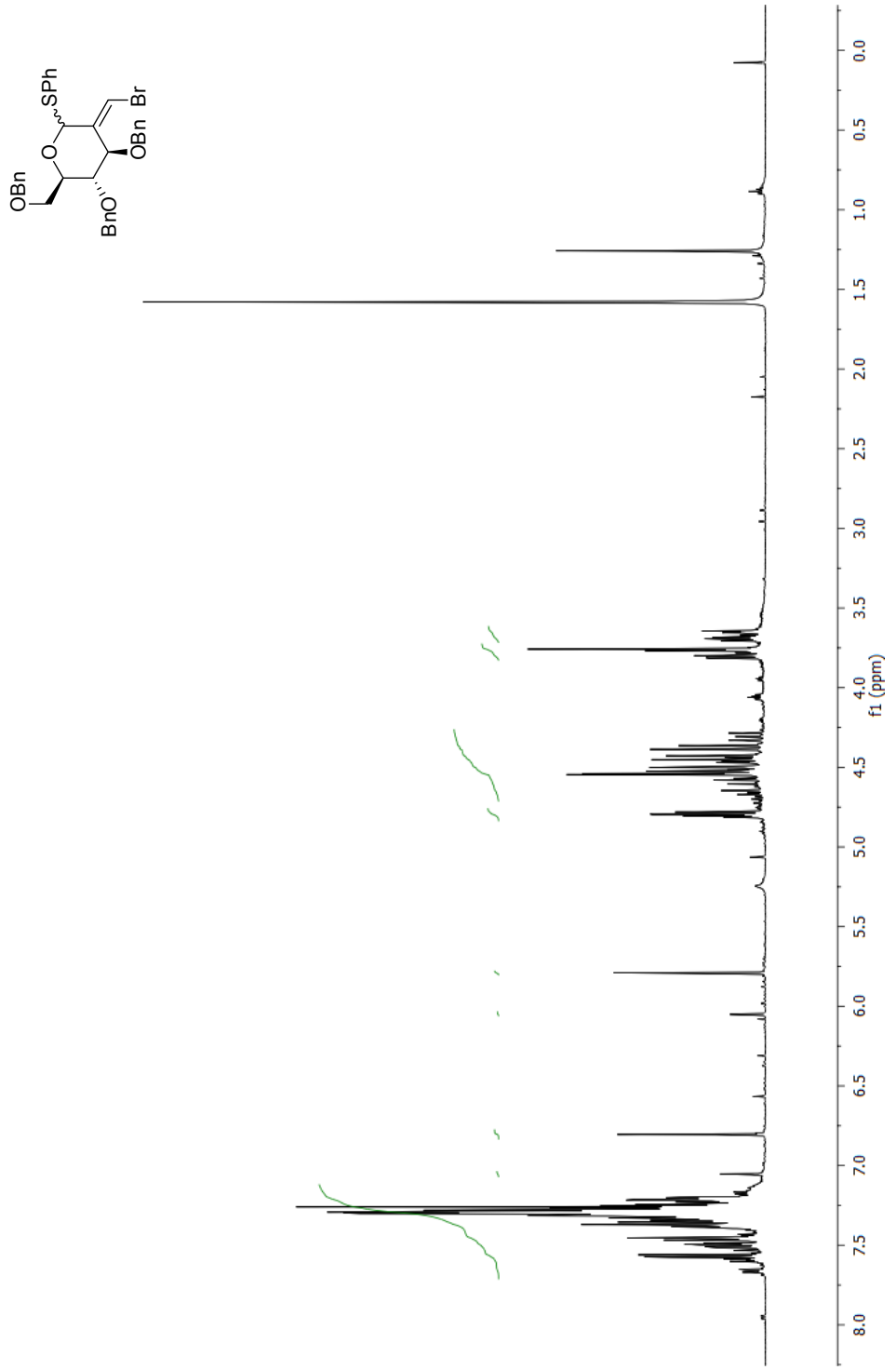
^{13}C-NMR Spectrum of 2-*C*-branched sugar **140** (125 MHz, $CDCl_3$)



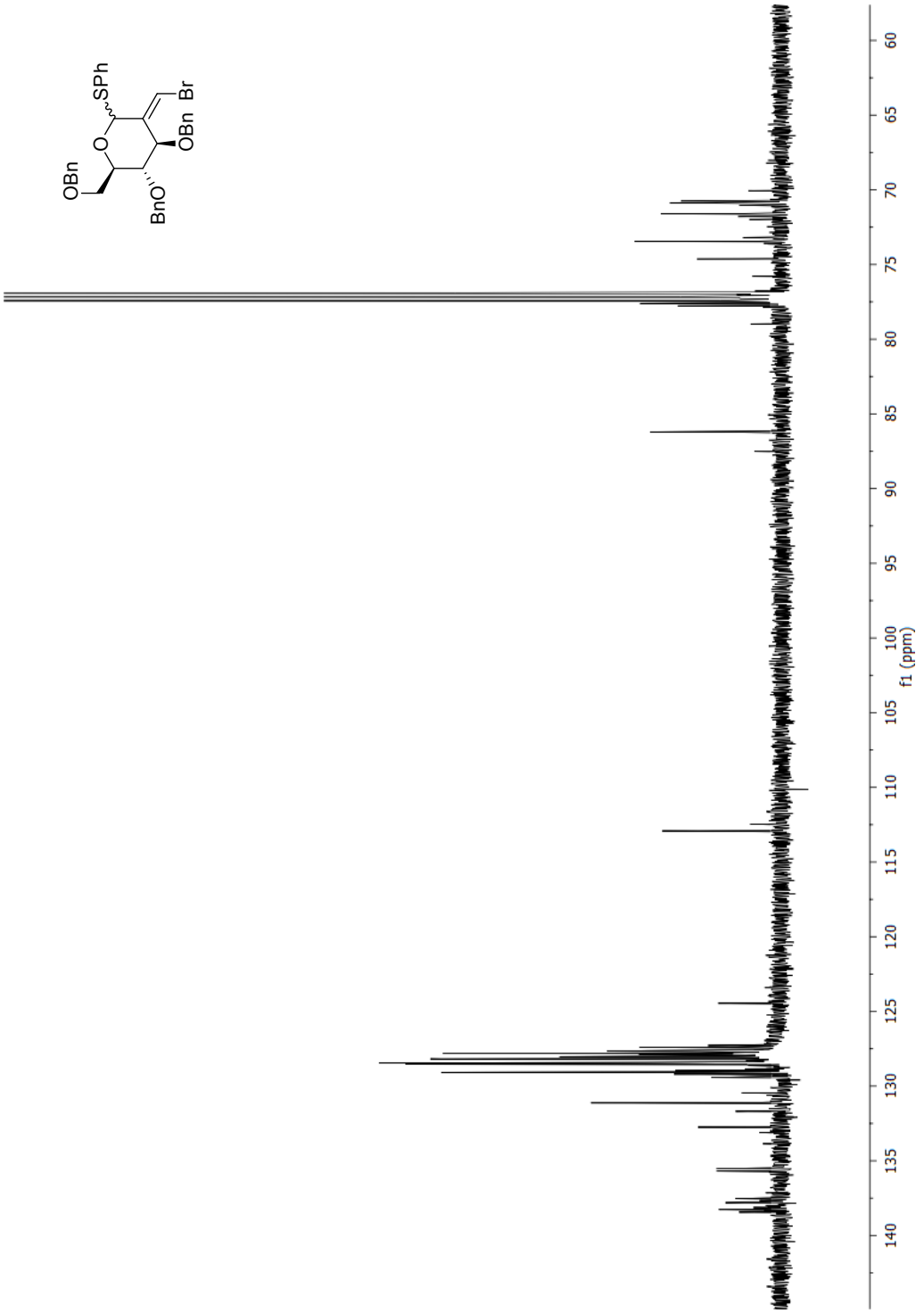
^{1}H-NMR Spectrum of 2-*C*-branched sugar **140** (500 MHz, $CDCl_3$)



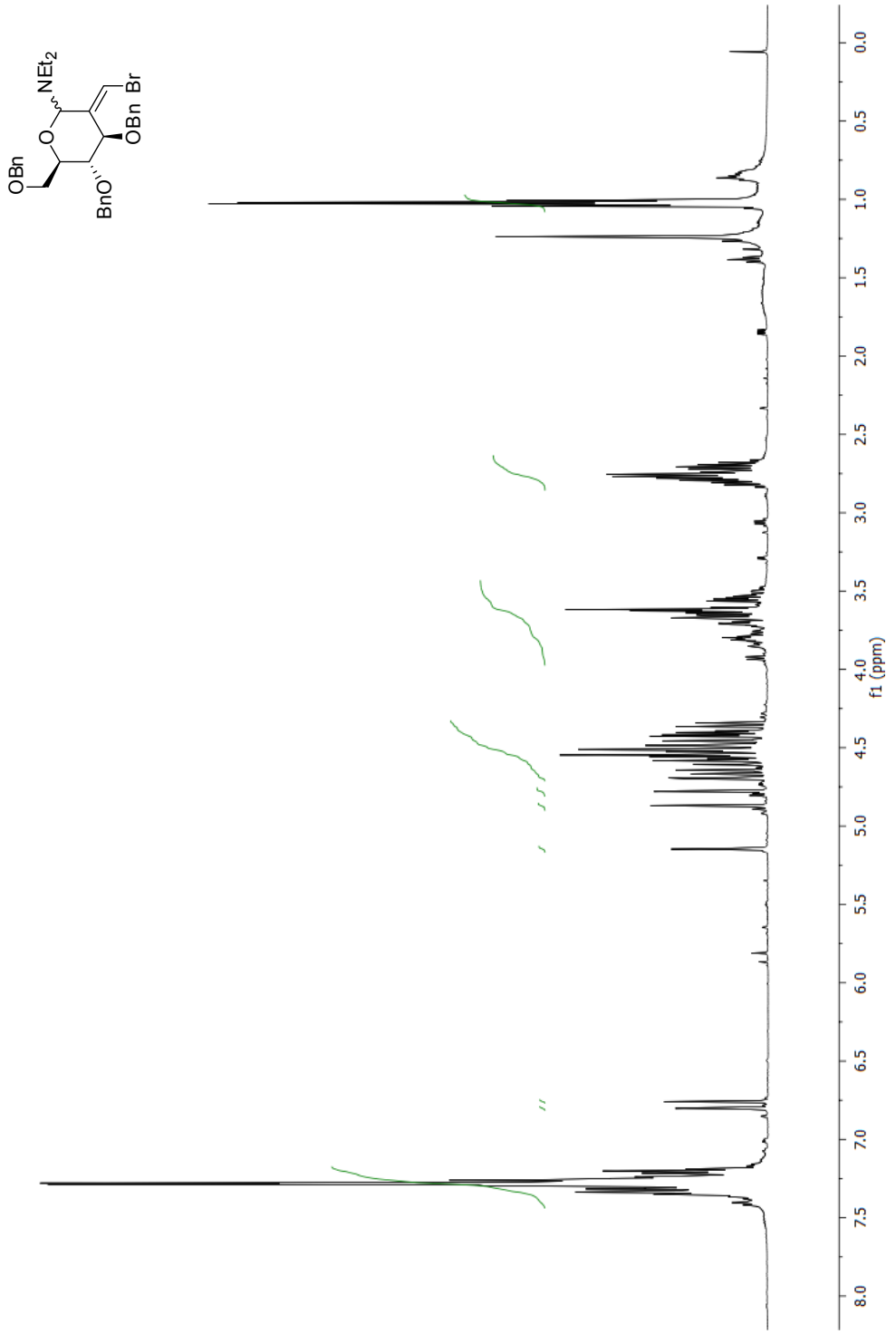
^{13}C-NMR Spectrum of 2-*C*-branched sugar **140** (125 MHz, $CDCl_3$)



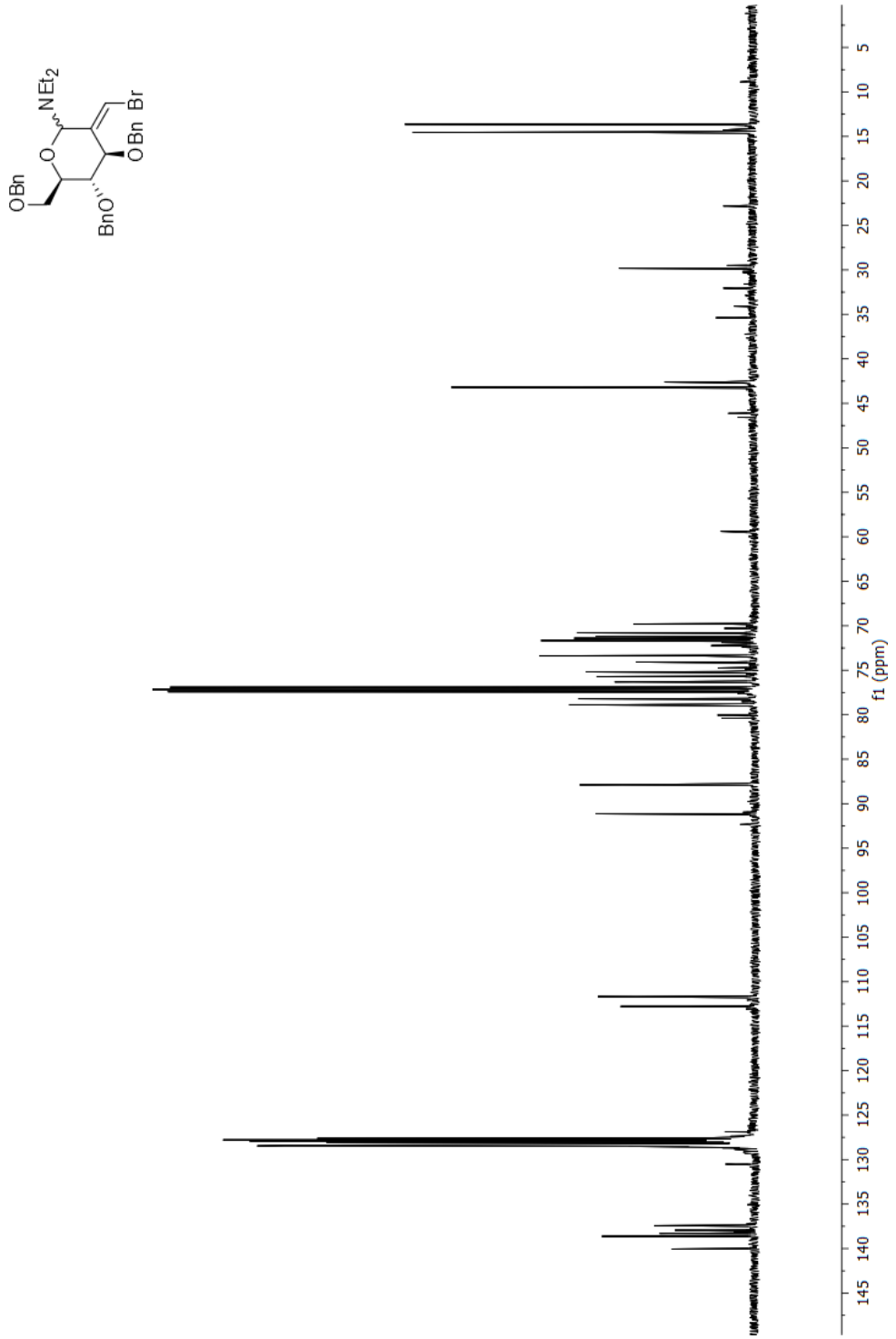
^{1}H-NMR Spectrum of 2-*C*-branched Thioglycosides **181** and **182** (500 MHz, $CDCl_3$)



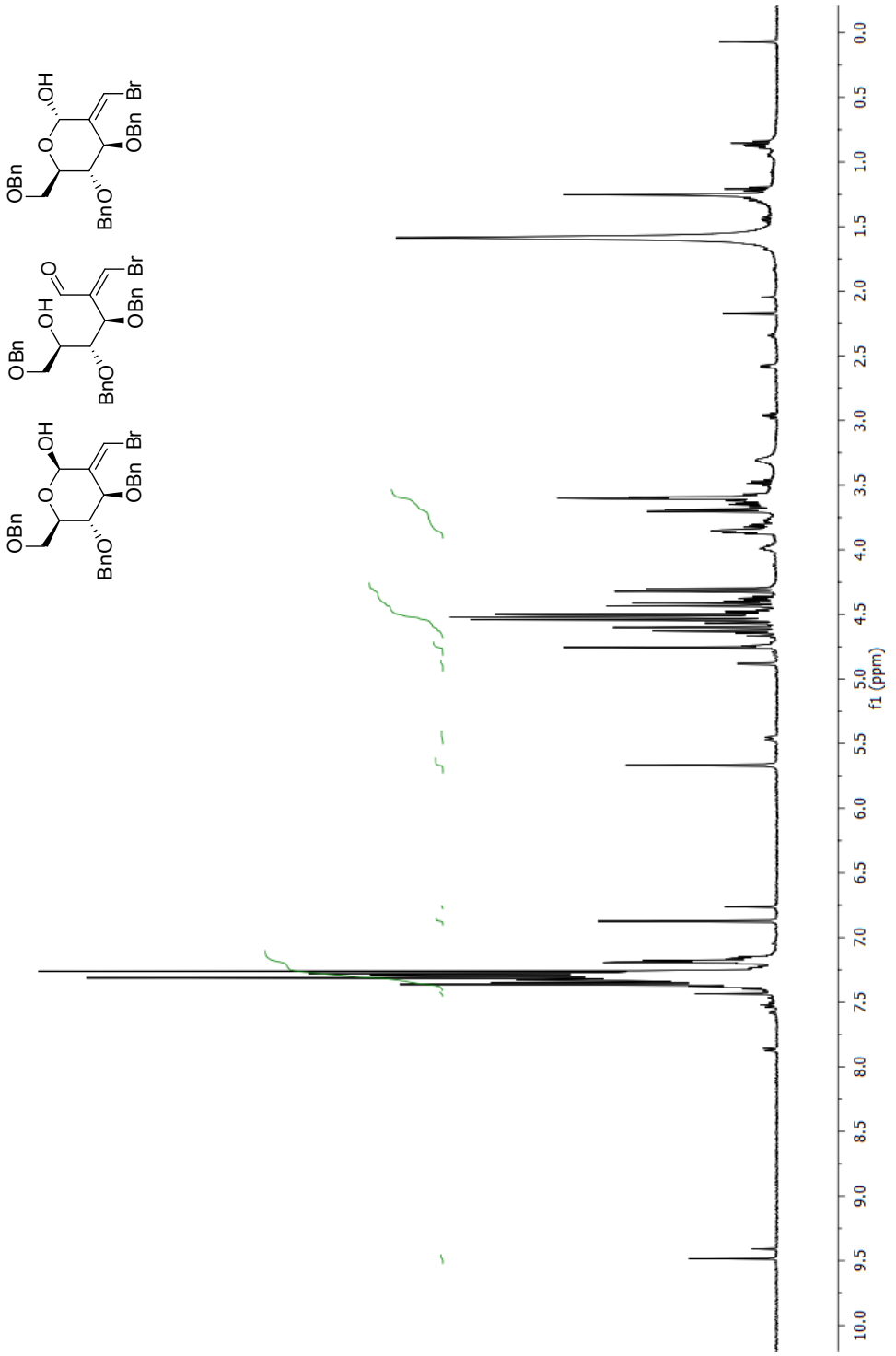
^{13}C-NMR Spectrum of 2-*C*-branched Thioglycosides **181** and **182** (125 MHz, $CDCl_3$)



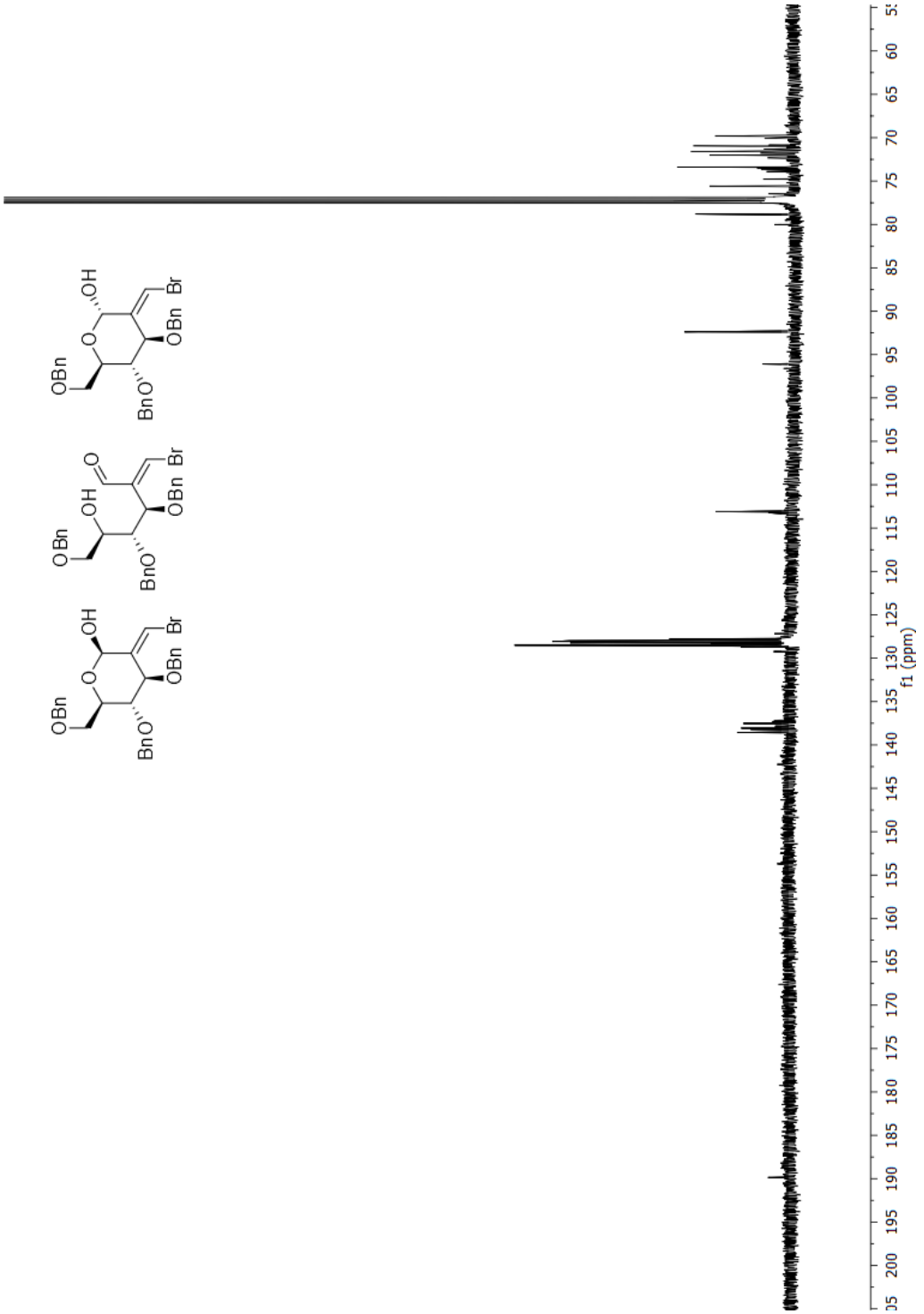
^{1}H-NMR Spectrum of 2-*C*-branched Glycosylamines **183** and **184** (500 MHz, $CDCl_3$)



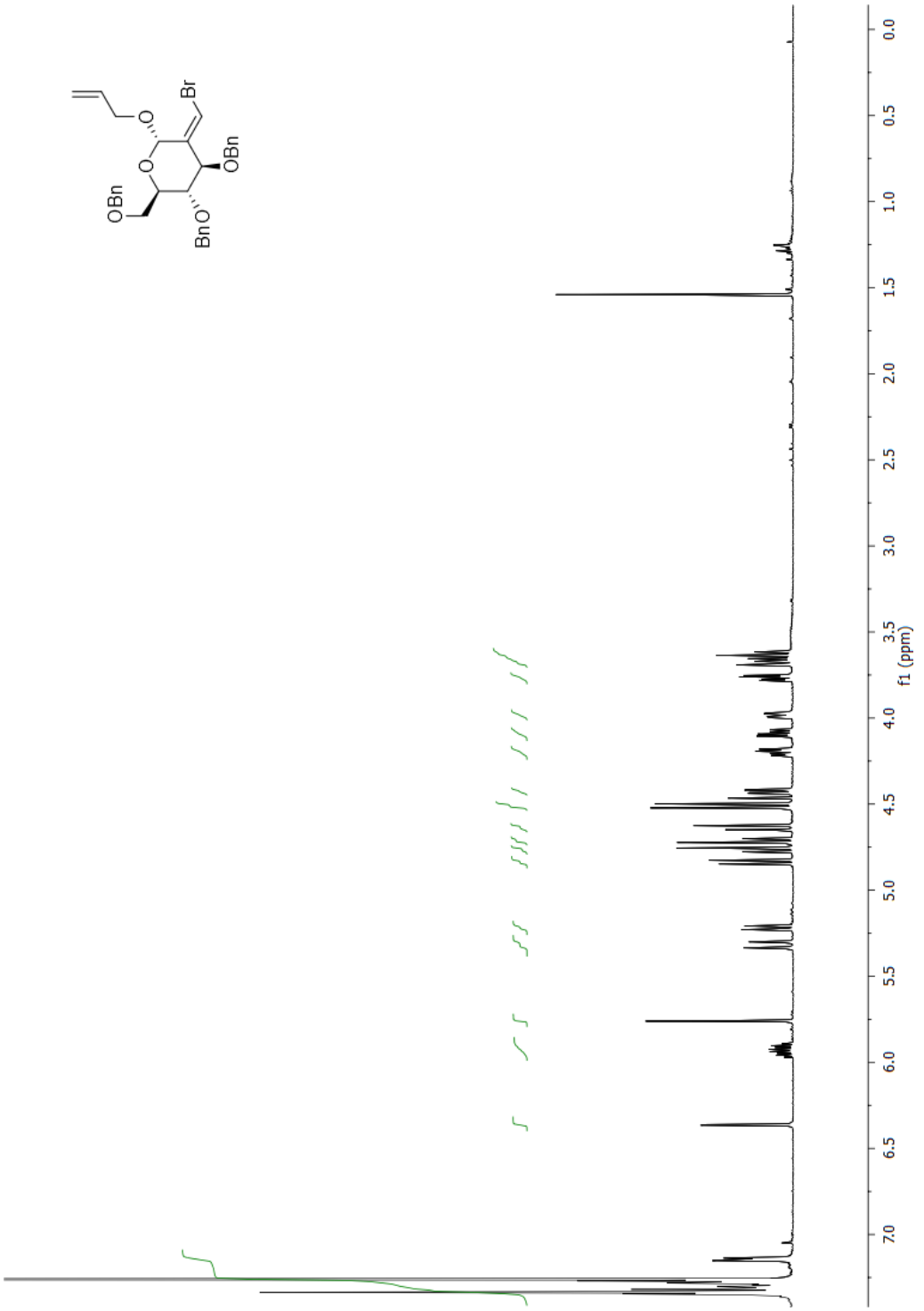
^{13}C-NMR Spectrum of 2-*C*-branched Glycosylamines **183** and **184** (125 MHz, $CDCl_3$)



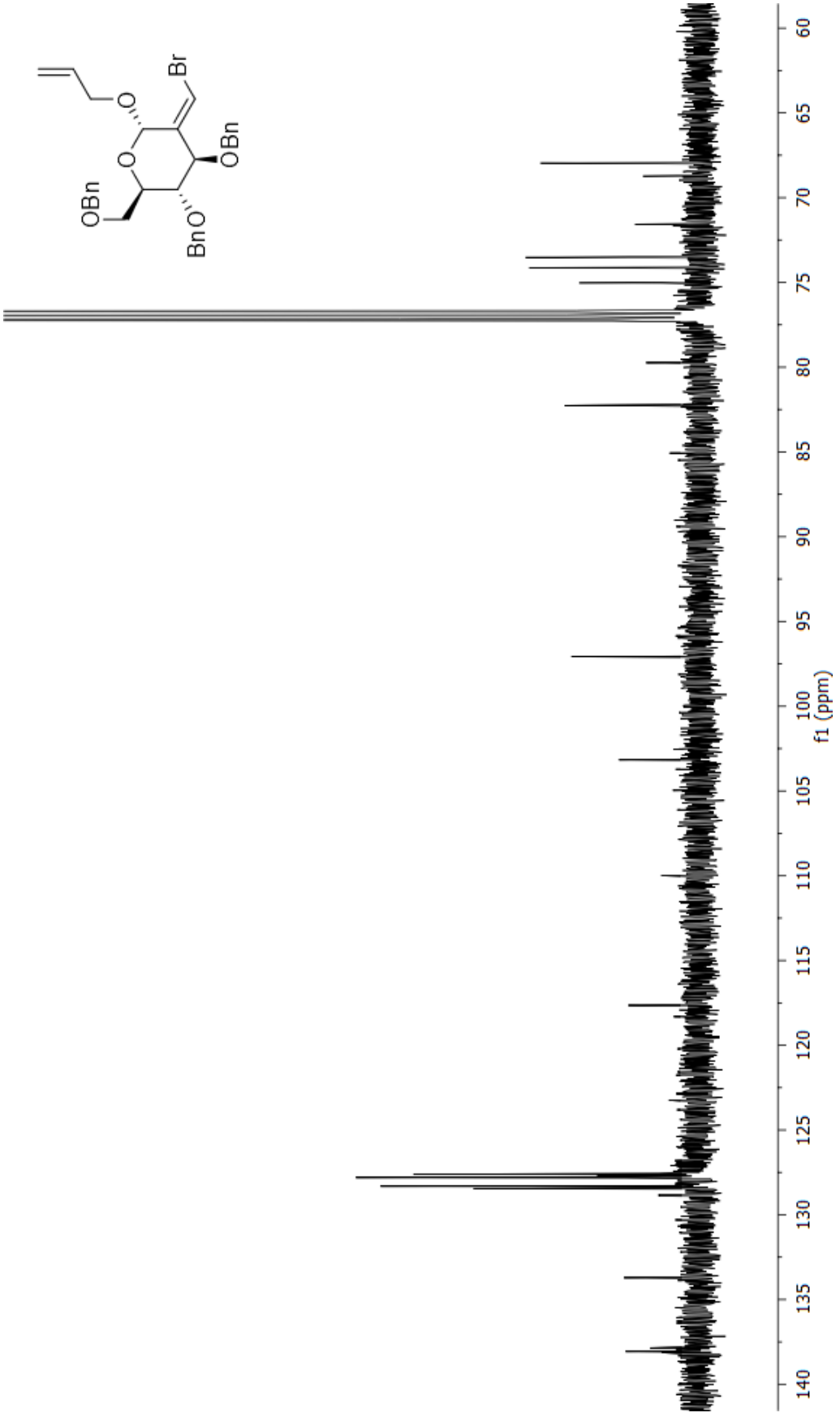
^{1}H-NMR Spectrum of Free Sugars **190**, aldehyde **192** and **191** (500 MHz, $CDCl_3$)



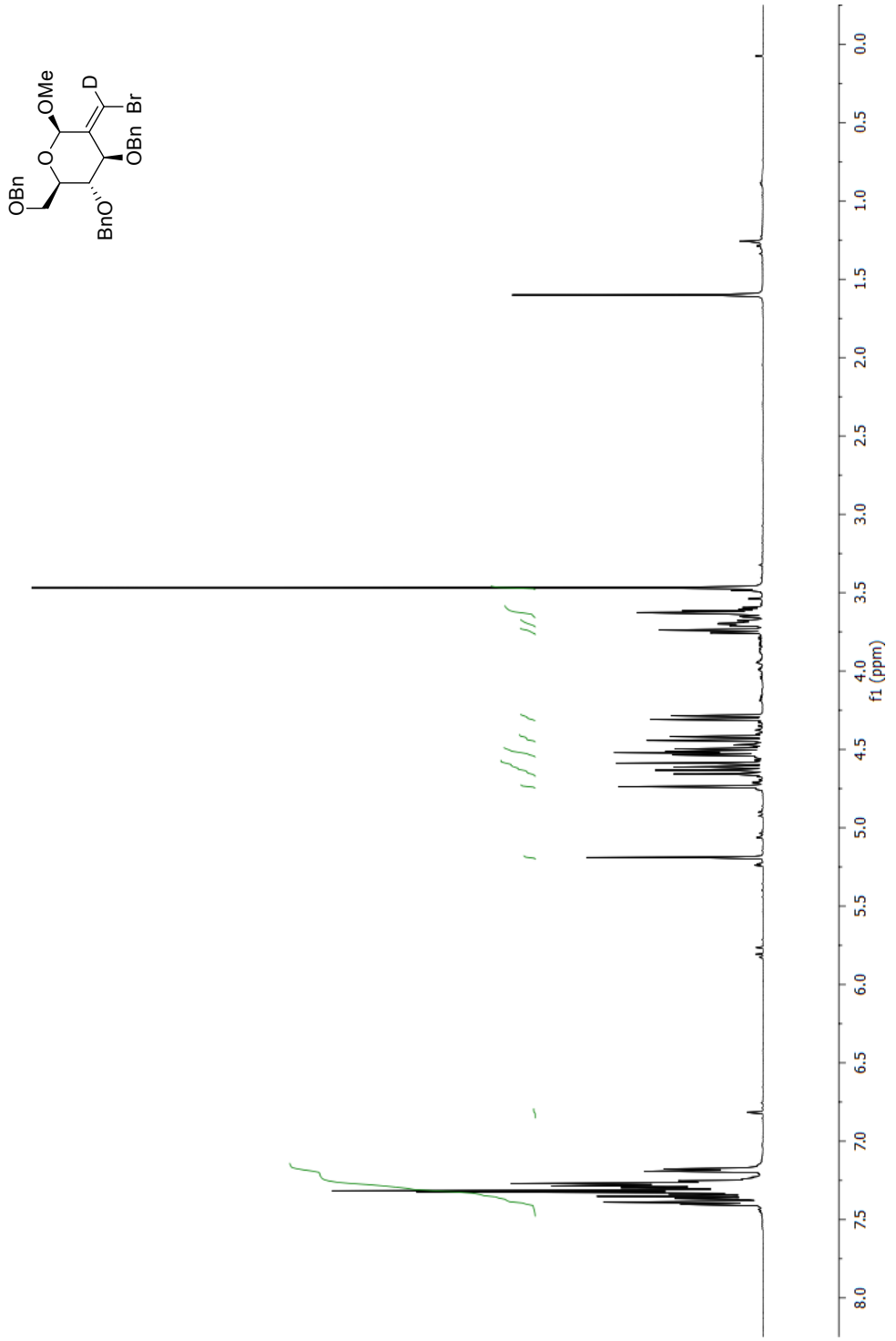
^{13}C-NMR Spectrum of Free Sugars **190**, aldehyde **192** and **191** (125 MHz, $CDCl_3$)



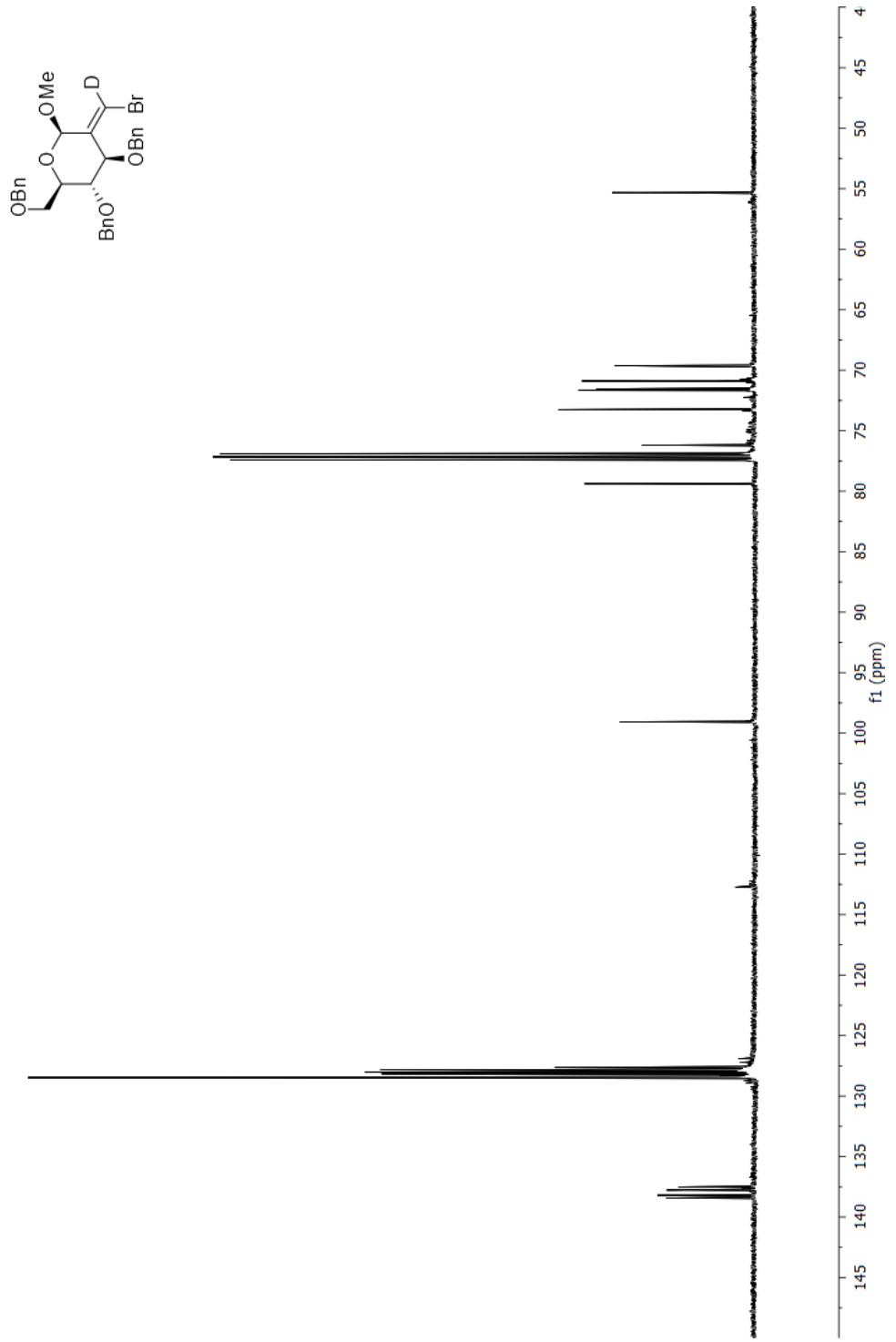
^{1}H-NMR Spectrum of 2-*C*-branched sugar **194** (500 MHz, $CDCl_3$)



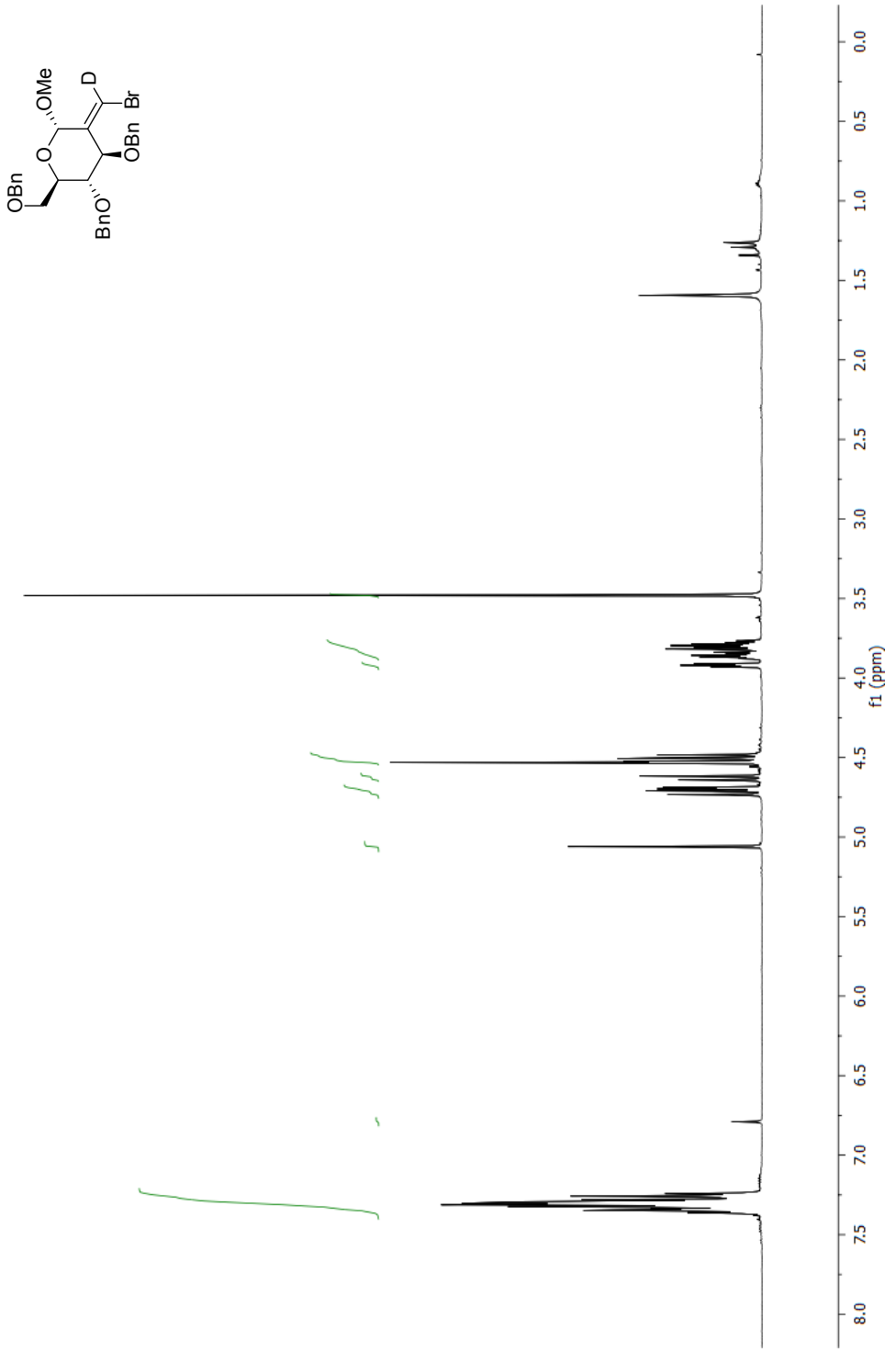
^{13}C-NMR Spectrum of 2-*C*-branched sugar **194** (125 MHz, $CDCl_3$)



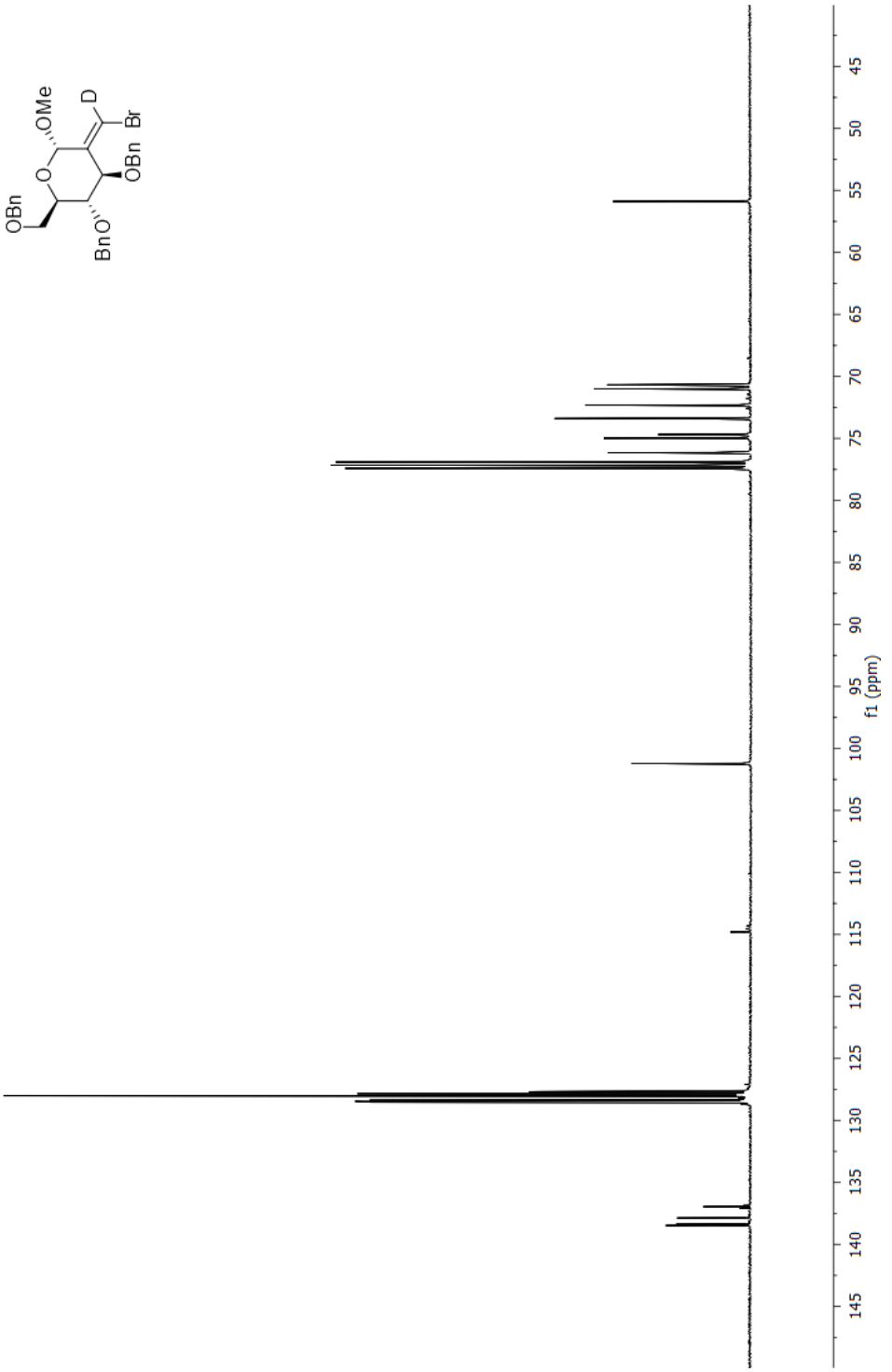
^{1}H-NMR Spectrum of 2-*C*-branched sugar **235** (500 MHz, $CDCl_3$)



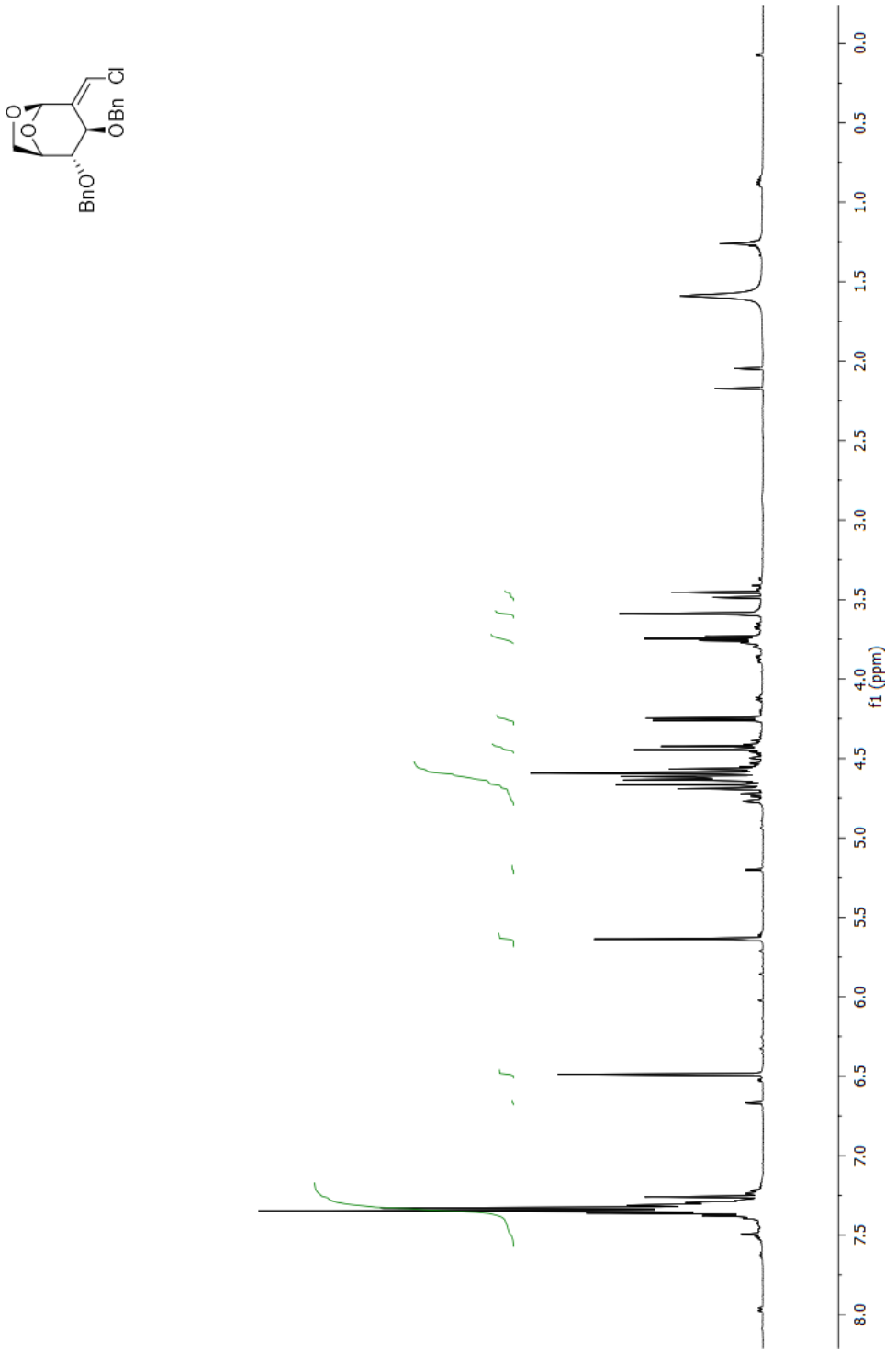
^{13}C-NMR Spectrum of 2-*C*-branched sugar **235** (125 MHz, $CDCl_3$)



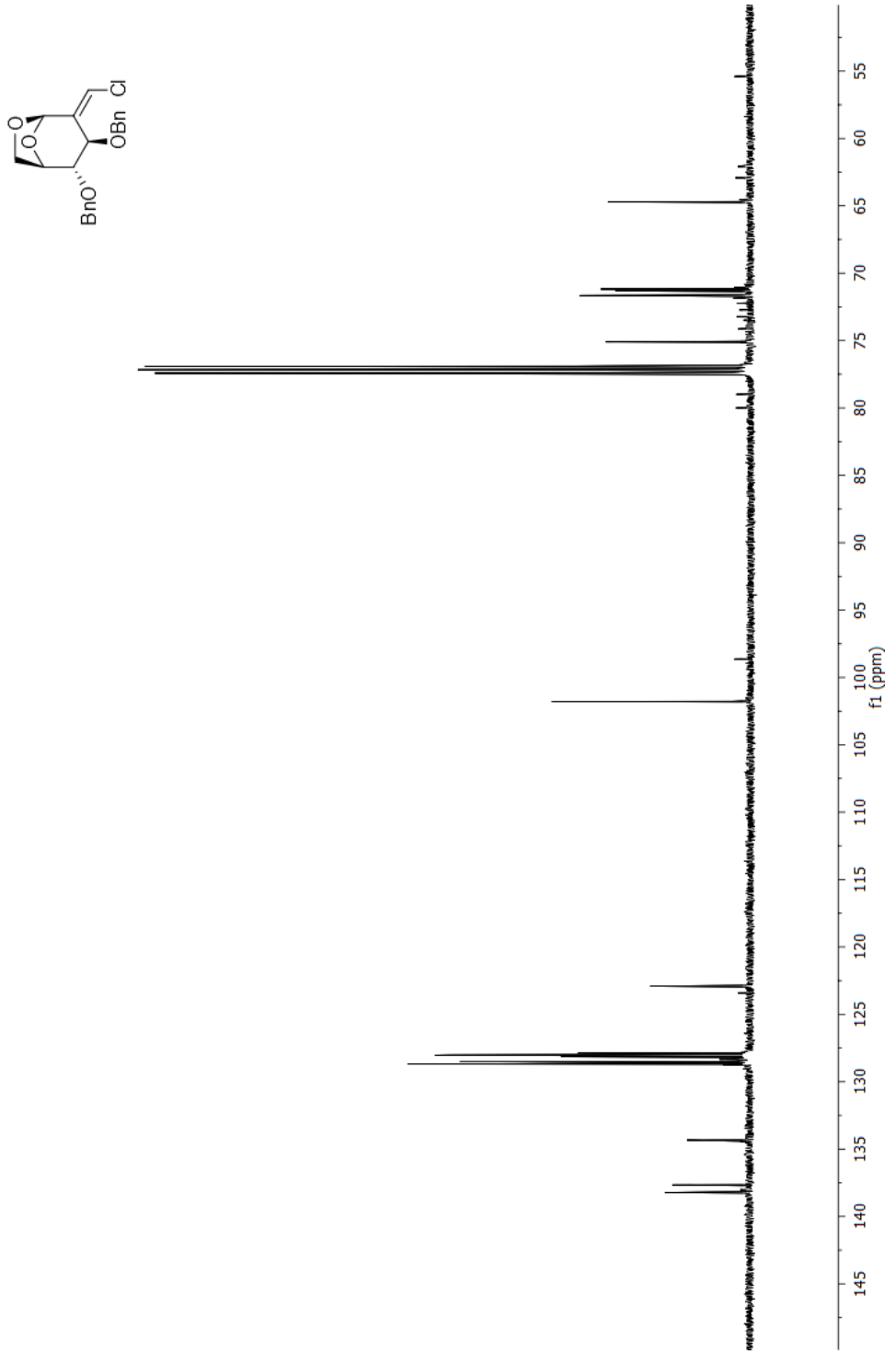
^{1}H-NMR Spectrum of 2-*C*-branched sugar **234** (500 MHz, $CDCl_3$)



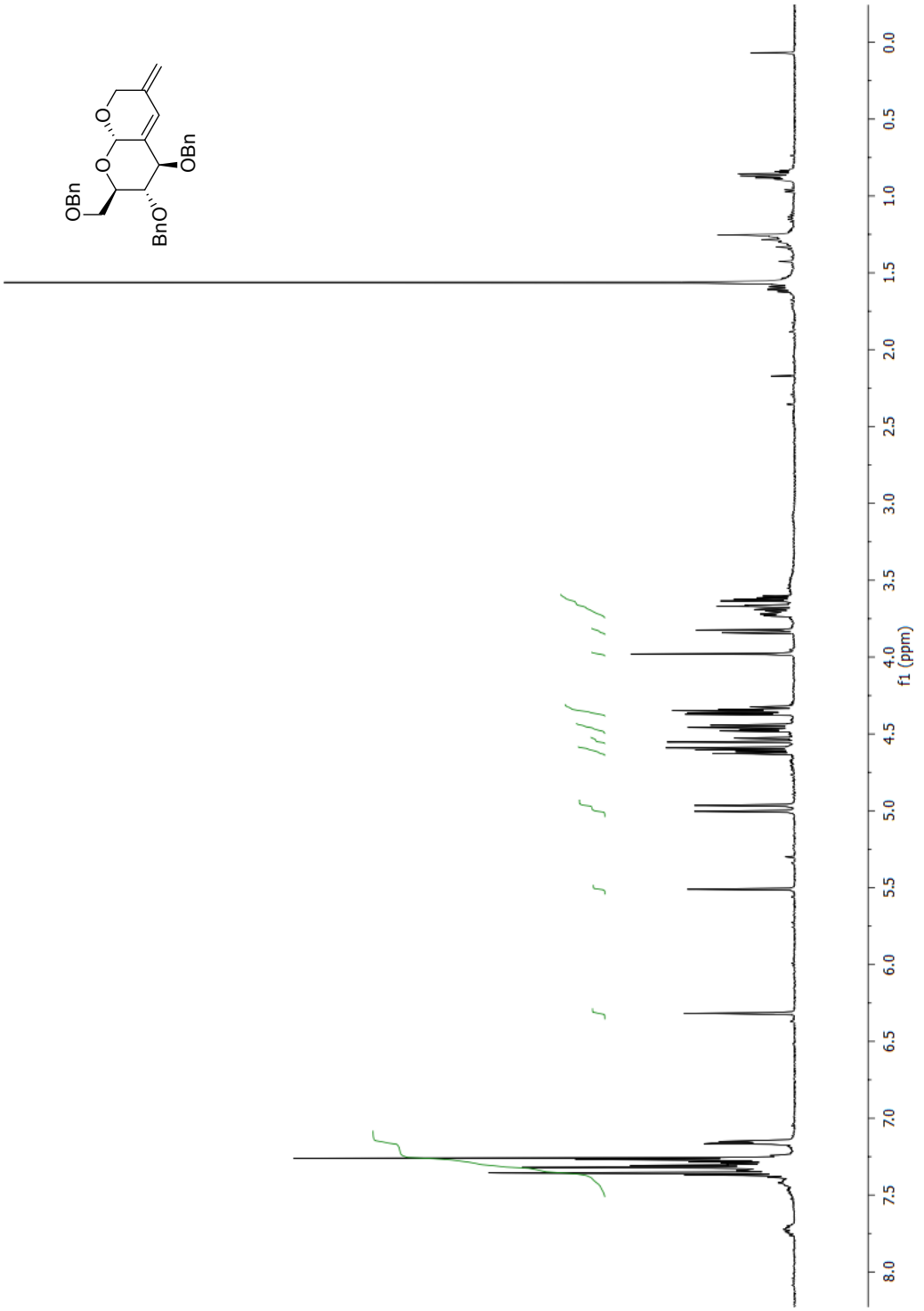
^{13}C-NMR Spectrum of 2-*C*-branched sugar **234** (125 MHz, $CDCl_3$)



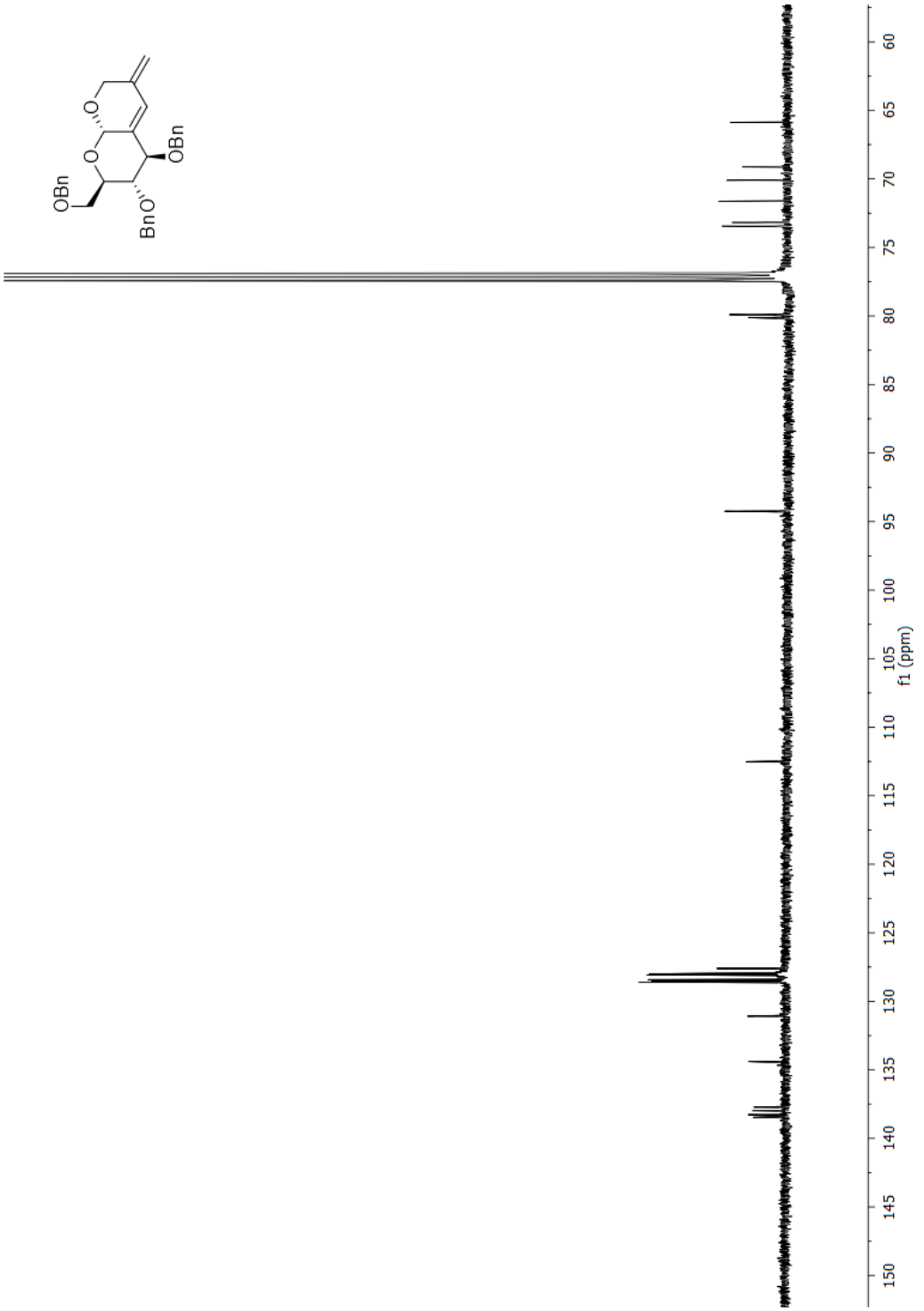
^{1}H-NMR Spectrum of bicyclic compound **241** (500 MHz, $CDCl_3$)



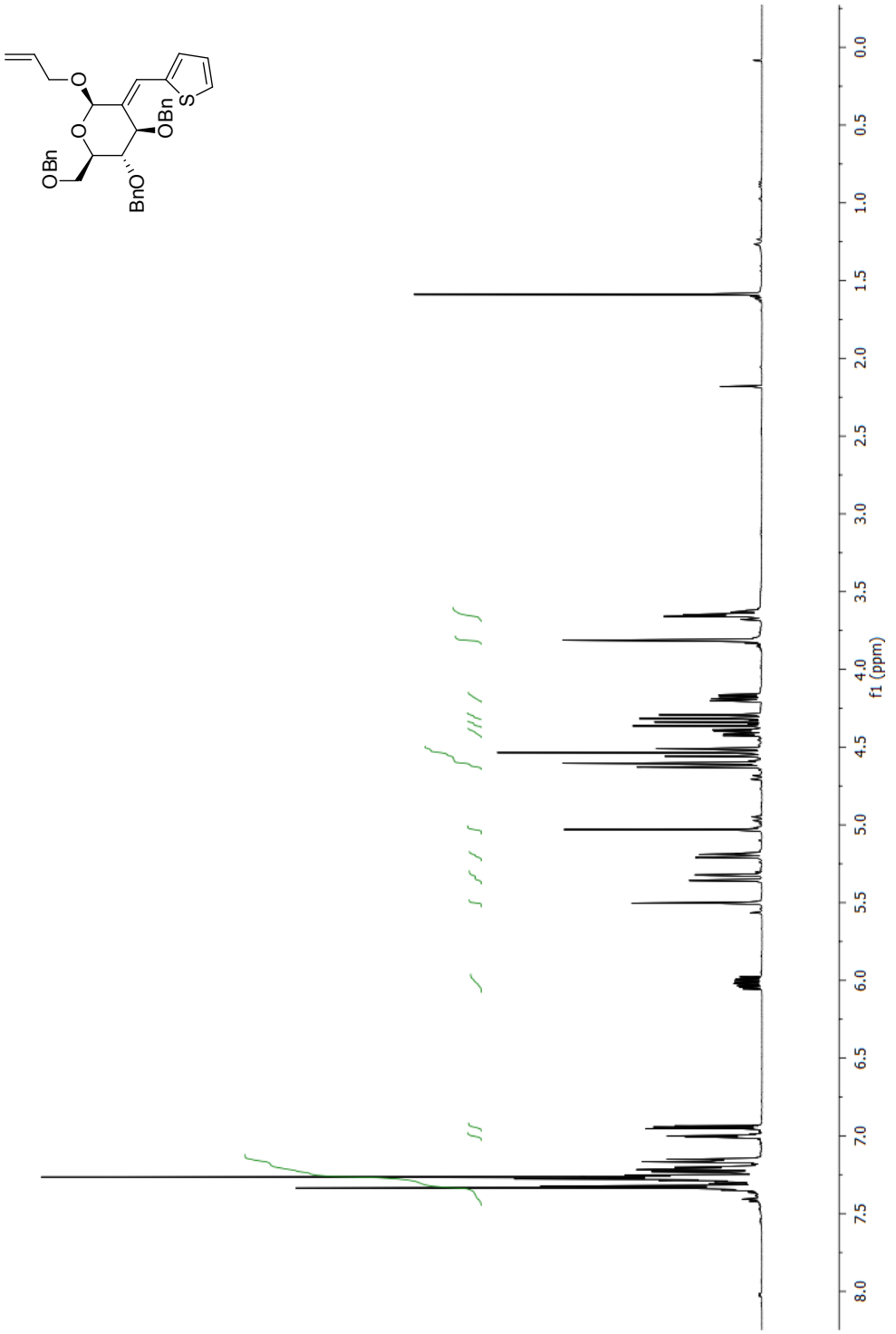
^{13}C-NMR Spectrum of bicyclic compound **241** (125 MHz, $CDCl_3$)



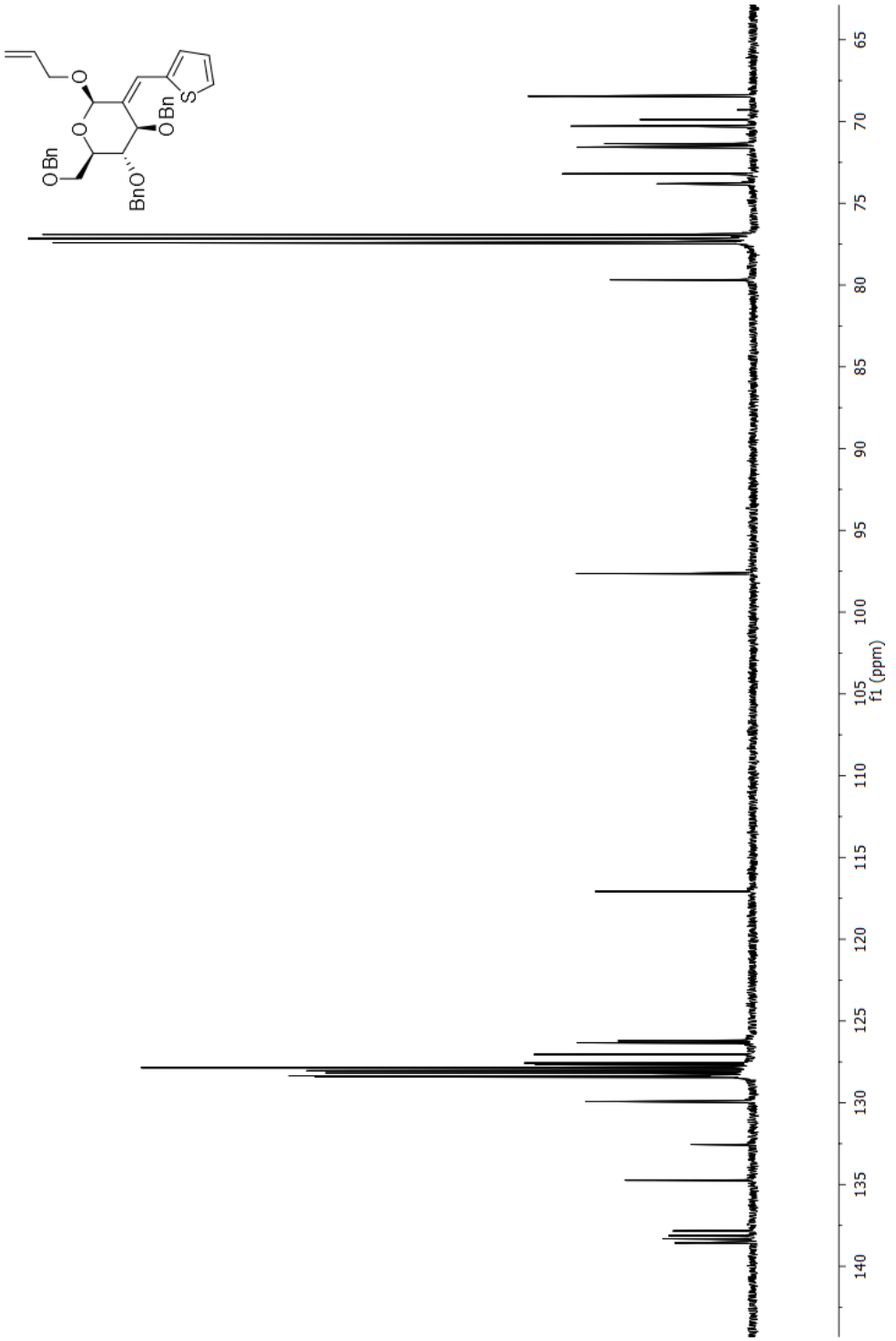
^{1}H-NMR Spectrum of Bicycle Compound **205** (500 MHz, $CDCl_3$)



^{13}C-NMR Spectrum of Bicycle Compound **205** (125 MHz, $CDCl_3$)



^{1}H-NMR Spectrum of **248** (500 MHz, $CDCl_3$)



^{13}C-NMR Spectrum of **248** (125 MHz, $CDCl_3$)

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