Synthesis of Bradyrhizose and its Disaccharides

by

Claude Larrivée Aboussafy

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Department of Chemistry
University of Alberta

Abstract

Bradyrhizose, a bicyclic monosaccharide, was reported in 2011 by Molinaro and coworkers at the University of Naples in Italy. This unusual carbohydrate was isolated from the lipopolysaccharide (LPS) of *Bradyrhizobium* sp. BTAi1 and sp. ORS278 as the only component of the O-antigen. These nitrogen-fixing bacteria live in symbiosis with legumes *Aeschynomene sensitiva* and *indica*. It was found that neither the LPS or the pure O-antigen from *Bradyrhizobium* sp. BTAi1 are recognized by plants as a microbe-associated molecular pattern (MAMP). This is the first example of an LPS not activating a defense response and indicates that the LPS and the O-antigen from these bacteria are non-immunogenic. Synthesizing this molecule, and disaccharides containing it, will provide compounds that can be used to probe the role of this monosaccharide in bacterial symbiosis with the legume.

Two different approaches for the synthesis of bradyrhizose are discussed in this thesis. For the first route, the monosaccharide was envisioned to be obtained from a furan derivative *via* the Achmatowicz reaction. For the second route, two different strategies were investigated starting with *myo*-inositol as the basis of the cyclohexanol moeity of bradyrhizose. The racemic synthesis of bradyrhizose was achieved using the second route. The enantiomers were separated at a late stage of the synthesis to afford D- and L-bradyrhizose.

The synthesis of bradyrhizose donors and acceptors (D- and L-) was accomplished starting with an intermediate used in the synthesis of the monosaccharide. The reactivity of this unusual monosaccharide in glycosylations was studied using a trichloroacetimidate donor and various types of acceptors. Disaccharides containing different enantiomeric forms of the monosaccharide

(D,D; L,L; D,L; L,D) were synthesized and will be tested for their ability to induce reactive oxygen species (ROS) in different plants and legumes.

Preface

This thesis is an original work by Claude Larrivée Aboussafy. No part of this thesis has been previously published.

Dédiée à
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qui nous a quittés le
16 avril 2016

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Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	2,2'-azobis(2-methylpropionitrile)
All	allyl
app	apparent
Ar	aryl
ATP	adenosine triphosphate
BC	before Christ
Bn	benzyl
br	broad
n-Bu	normal butyl
t-Bu	*tert*-butyl
calcd	calculated
CAN	ammonium cerium(IV) nitrate
CM	complex mixture
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
CSIR	Council of Scientific and Industrial Research
d	doublet
DCC	*N,N'*-dicyclohexylcarbodiimide
dd	doublet of doublets

ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DHQ-CLB	*O*-(4-chlorobenzoyl)hydroquinine
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
DIBAL-H	diisobutylaluminium hydride
DIC	*N,N'*-diisopropylcarbodiimide
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMP	Dess–Martin Periodinane
DMSO	dimethyl sulfoxide
DP	desired product
dppp	1,3-bis(diphenylphosphino)propane
dt	doublet of triplets
dq	doublet of quadruplets
EI	electron impact ionization
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
h	hour
HMBC	heteronuclear multiple-bond correlation spectroscopy
HPLC	high performance liquid chromatography
HR	hypersensitive response

HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
*i*Pr	isopropyl
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LPS	lipopolysaccharide
m	multiplet
MAMP	microbe-associated molecular pattern
Me	methyl
MeOH	methanol
mol	mole
MOM	methoxy methyl
mp	melting point
Ms	methanesulfonyl
MTP	methoxy(trifluoromethyl)phenylacetyl
MTPA	methoxy(trifluoromethyl)phenylacetic acid
MVK	methyl vinyl ketone
NaHMDS	sodium bis(trimethylsilyl)amide
NAP	2-methylnaphtyl
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance spectroscopy
Nod	nodulation

NOE	nuclear Overhauser effect spectroscopy
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	phenyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridium *p*-toluenesulfonate
pyr	pyridine
q	quartet
rt	room temperature
RaNi	Raney Nickel
RCM	ring-closing metathesis
Red-Al®	sodium bis(2-methoxyethoxy)aluminumhydride
ROESY	rotating-frame nuclear Overhauser effect correlation spectroscopy
ROS	reactive oxygen species
SM	starting material
S_N	nucleophilic substitution
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCIA	trichloroisocyanuric acid
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy

Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
Ts	*p*-toluenesulfonyl
UV	ultraviolet
2D	two-dimension

Chapter 1: Introduction

Legumes have been used in agriculture to improve the fertility of the soil since the ancient civilisations. As early as the 5th century BC, Egyptians, Greeks and eventually Romans practiced methods of fertilizing the soil using legumes through green manuring, crop rotation and intercropping.[1,2,3] Green manuring improves the soil by growing legumes that would later be used to mulch the soil.[2,3] The soil would also be enriched with nutrients through a process known as crop rotation, where the legume and non-legume crops are interchanged.[2,3] Lastly, intercropping is a method of planting legumes in the space between rows of other plants, which is another way of providing various nutrients to the soil and thereby improving the health of the crop.[2,3] These people successfully improved their harvest using these techniques unaware that bacteria were mainly involved in these processes.

In 1647, the Italian biologist and physicist Marcello Malpighi made a drawing of the bumps found on the roots of a legume plant, thinking they were abnormal plant growths where insects lay their eggs.[4] By the 19th century, legume crops were being used all over Europe to improve soil fertility. Meanwhile, in Germany, leguminous plants were observed to be nitrogen accumulators and non-leguminous plants nitrogen consumers. In 1888, the German agricultural chemists Hermann Hellriegel and Hermann Wilfarth discovered that atmospheric nitrogen was transformed into ammonia in legume root nodules by bacteria.[1] These bacteria were isolated in the same year by the Dutch microbiologist Martinus Beijerinck and they were placed in the genus Rhizobium: “rhiza” for roots and “bios” for life.

1.1 Rhizobia and nitrogen fixation

Atmospheric nitrogen, which is the most abundant gas on Earth, is inert for most organisms.[5] Nitrogen is an essential element for life on this planet, especially for the biosynthesis of nucleotides and amino acids, the building blocks of nucleic acids and proteins. The incorporation of this inert gas into biological systems is credited to the symbiotic relationship between bacteria and plants. This is achieved through a process called nitrogen fixation and only anaerobic prokaryotes named diazotrophs are able to perform this transformation. This conversion requires sixteen molecules of ATP for each molecule of N_2, so this is a energy intensive process for the bacteria (Scheme 1-1).[5]

$$N_2 + 8\ H^+ + 16\ ATP + 8e^- \longrightarrow 2\ NH_3 + H_2 + 16\ ADP + 16\ P_i$$

Scheme 1-1: Conversion of nitrogen in ammonia by diazotrophs.[5]

1.1.1 Symbiosis between rhizobia and legumes and advantages in agriculture

Rhizobia are Gram-negative bacteria that live symbiotically with legumes. They need the host plant to be able to fix nitrogen because they cannot do this process independently.[5] The relationship between the legume and the bacteria is mutualistic. Rhizobia can be found in nodules on the roots or the stems of the legume where they fix the nitrogen for the plant in exchange for carbohydrates. The nodules are specialized organs of the plant that resemble bumps. Their principal functions are to facilitate exchanges between the legume and the bacteria and also to serve as the site for the nitrogen fixation process. The mechanism of recognition between the bacteria and the plant is very specific. Each species of bacteria will usually infect one or two legume species.

Rhizobia have been widely used in agriculture to decrease the extensive use of chemical fertilizers and to improve fertility using a legume-based cropping system.[6] This process starts with atmospheric nitrogen being transformed to compounds like ammonia inside the nodules on the roots of the plant to help the legumes grow. After the legumes die, the fixed nitrogen will be released into the soil and will be available for other plants. This technique has been used by humans for a long time and is still practiced extensively today.

1.1.2 Formation of nodules

Before the formation of nodules takes place on the roots of the legume, the bacteria and the plant must recognize each other. Most rhizobial species will induce the formation of nodules using a Nod factor dependent pathway (Figure 1-1 (a)).[7] First, flavonoid signals from the legume will be detected by the bacterial NodD proteins.[8] Upon detection, the bacteria will initiate the biosynthesis of lipochitooligosaccharides (Nod factors) followed by the secretion of these molecules, which will be recognized by receptor kinases on the surface of the root.[7] The Nod factors are signaling molecules composed of four or five β-(1→4)-linked *N*-acetyl-glucosamine residues carrying an N-linked acyl group; their substitution patterns will determine the bacteria–legume specificity.[8] The N-linked acyl group can vary and the *N*-acetyl-glucosamine can be substituted with acetyl, carbamoyl, methyl or sulphuryl groups and also sugars such as fucose or arabinose. The receptor kinases will then trigger nodule formation through a symbiotic response in the plant root.[7] After the recognition between the legume and the bacteria, the roots will curl, trapping the bacteria inside a pocket. The trapped bacteria will continue to produce Nod factors and will accumulate forming an intracellular infection.

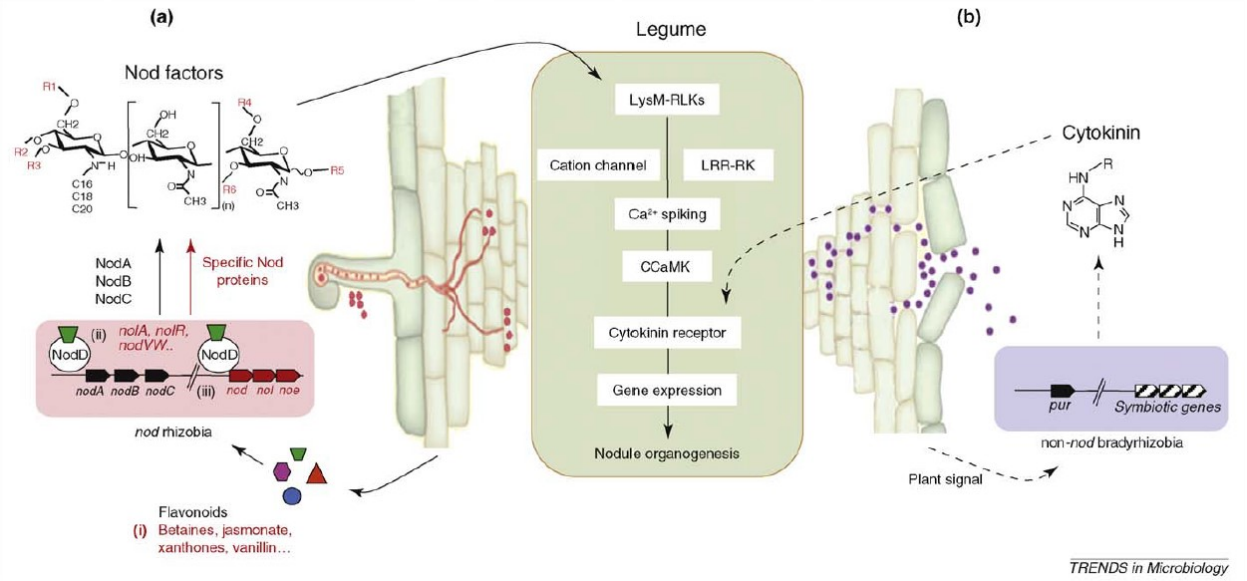


Figure 1-1: Nodulation strategies in rhizobia (a) Nod factor dependent pathway (b) Hypothesis for the Nod factor independent pathway. Reprinted with permission from Elsevier.[7]

1.2 Photosynthetic strains of *Bradyrhizobium* sp. BTAi1 and sp. ORS278

Bradyrhizobium sp. BTAi1 and sp. ORS278 are nitrogen-fixing bacteria living in symbiosis with the aquatic legumes *Aeschynomene sensitiva* and *indica*.[9] These rhizobia are unusual as they can induce nodule formation not only on the roots of legumes, but also on the stems.[10] These two species are also photosynthetic, which is uncommon for the rhizobia. This feature allows them to reside above ground.

In 2007, Giraud and coworkers sequenced the complete genome of *Bradyrhizobium* sp. BTAi1 and sp. ORS278.[9] They discovered that these two species lack the canonical *nodABC* genes, meaning that they cannot produce Nod factors. Thus, these symbioses are the only ones between rhizobia and legumes that do not use Nod factors for the recognition step. This discovery was intriguing because all other species of rhizobia use the Nod factor dependent pathway for nodule formation. Girard and co-workers also found several other genes from the two *Bradyrhizobium*

strains involved in symbiosis, like the modification of O-antigen of lipopolysaccharide (LPS) and the biosynthesis of exopolysaccharides.

1.2.1 Nod-factor independent signaling pathway

The Nod factor independent nitrogen fixation process is not well understood (Figure 1-1 (b))[7]. The hypothesis is that the bacteria will enter the plant via cracks in the roots. Then accumulation of cytokinin-like compounds produced by the bacteria may by-pass the Nod factor signaling pathway and induce the formation of the nodules.[7] More investigation has to be done to understand the nature of the interaction between these two *Bradyrhizobium* species and legumes.

In 2005, Parrilli and co-workers demonstrated that chemically-synthesized LPS O-antigen [α-L-Rha-(1→3)-α-L-Rha-(1→3)-α-L-Rha-(1→2)]$_n$ fragments of glycans present in numerous phytopathogenic bacteria induced *PR-1* gene expression, an immune response, and also supressed the hypersensitive response (HR) in the plant *Arabidopsis thaliana*.[11] In 2010, Molinaro, Parrilli and co-workers from University of Naples in Italy showed that the O-antigen of *Burkholderia rhizoxinica*, an intracellular bacteria, is indispensable for the symbiosis with the fungus *Rhizopus microspores*.[12] After making these discoveries, they decided to investigate if the lipopolysaccharides (LPS) of *Bradyrhizobium* sp. BTAi1 and sp. ORS278 could be a key factor for the recognition between the plant and the bacteria.[13]

1.2.2 Lipopolysaccharide (LPS)

The LPS is a vital component of Gram-negative bacteria and plays a key role in plant–microbe interactions.[14] LPS consists of an O-antigen polysaccharide linked to a core oligosaccharide composed of an outer and inner core (Figure 1-2).[15] The O-antigen consists of

reapeating monosaccharides (homopolymer) or oligosaccharide units (heteropolymer). The outer core is composed mainly of hexoses and the inner core contains 3-deoxy-D-*manno*-octulosonic acid (Kdo) and D-glycero-D-*manno*-heptose (Hep). The core oligosaccharide is covalently linked to lipid A, which is part of the outer membrane of Gram-negative bacteria. The lipid A is a glucosamine based phospholipid and is attached to a Kdo residue from the inner core. Bacterial LPS is a strong elicitator of the immune system in all eukaryotes.[15]

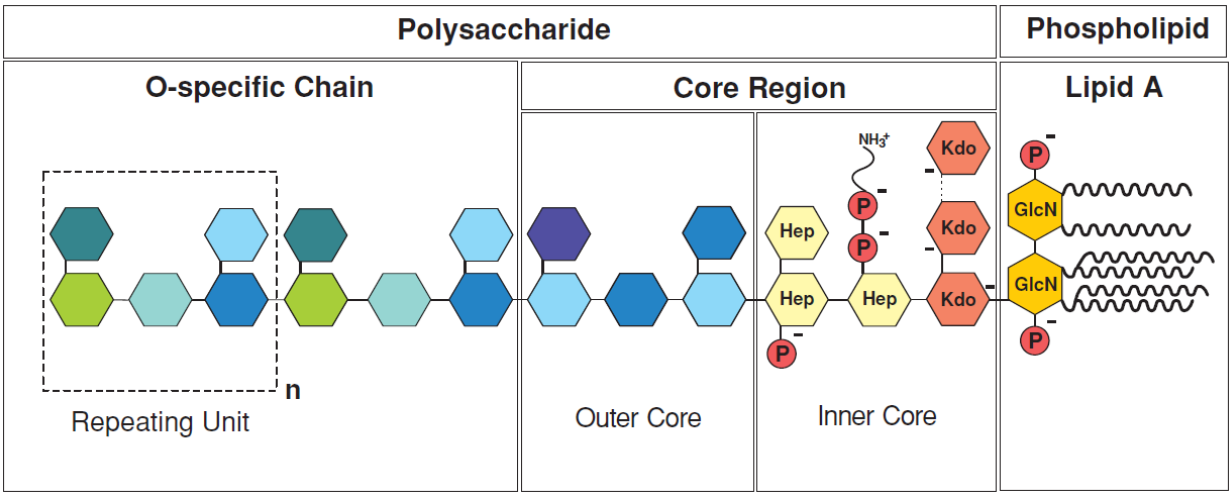


Figure 1-2: General chemical structure of LPS from Gram-negative bacteria. Abbreviations of monosaccharide residues: GlcN, glucosamine; Kdo, 3-deoxy-D-*manno*-octulosonic acid; Hep, D-glycero-D-*manno*-heptose. Reprinted with permission from Sage Publishing.[15]

While studying the LPSs of *Bradyrhizobium* sp. BTAi1 and sp. ORS278, Molinaro and co-workers discovered a new unique bicyclic monosaccharide as the only component of the O-antigen of these two species.[13,17] They decided to name the new carbohydrate bradyrhizose (**1.1**) (Figure 1-3 (a) and (b)). This unusual monosaccharide features an inositol moiety having a *trans*-decalin junction to a galactopyranose derivative. It contains an axial methyl group on the inositol backbone and two tertiary hydroxyl groups. Bradyrhizose is also deoxygenated at C-6 on the inositol ring.

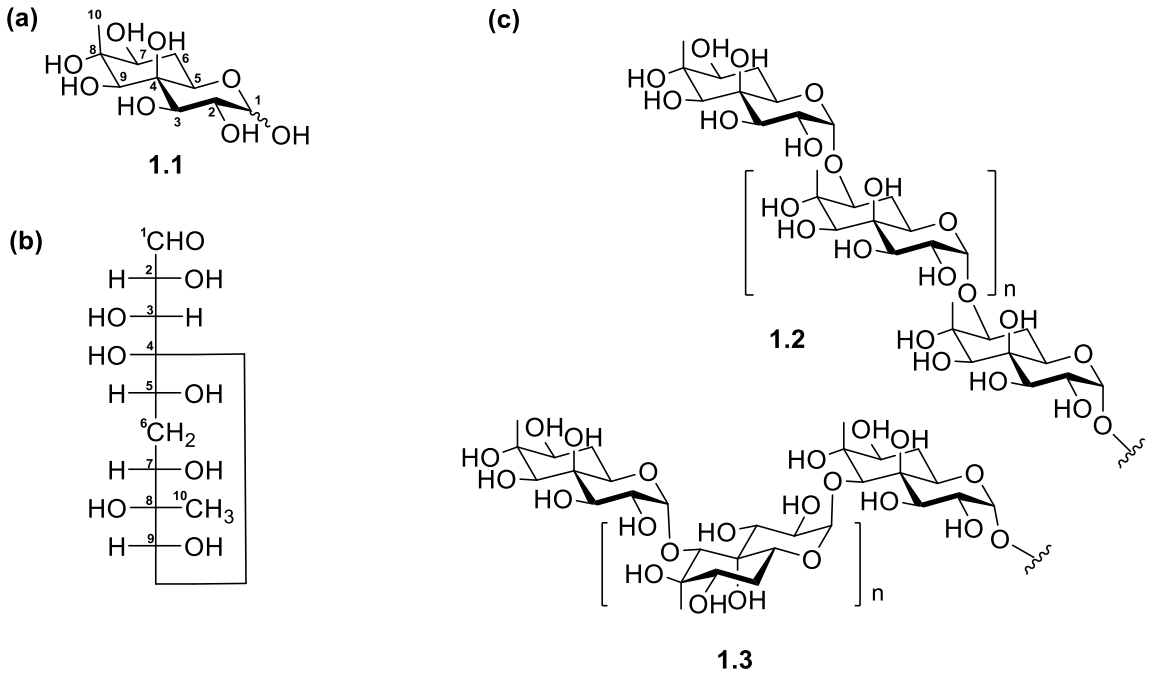


Figure 1-3: (a) Structure of bradyrhizose (b) Fischer projection of bradyrhizose (c) O-antigens from *Bradyrhizobium* sp. BTAi1 and sp. ORS278.[13,17]

The O-chain polysaccharide from sp. BTAi1 is an α-(1→7)-linked homopolymer (**1.2**) (Figure 1-3 (c)). Conformational analysis of an octasaccharide fragment of this polymer has been performed using molecular modelling.[13] The data indicates that the homopolymer forms a compact two-fold right-handed helix where the methylene groups of the bicyclic structure point to the inside, forming a hydrophobic tunnel (Figure 1-4). The methyl and hydroxyl groups point to the outside of the helix. The polysaccharide in sp. ORS278 is either an α-(1→7) (**1.2**) or α-(1→9) (**1.3**) linked homopolymer (Figure 1-3 (c)).[17]

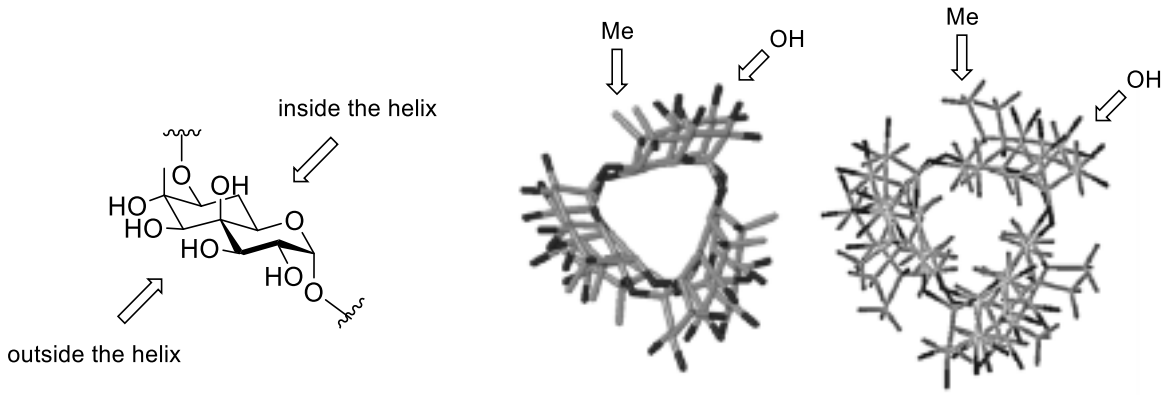


Figure 1-4: Two different sketches of the hydrophobic tunnel indside the helix of the α-(1→7)-linked bradyrhizose octasaccharide. Reprinted with permission from John Wiley and Sons.[13]

1.2.3 Role of the O-antigen

In 2011, Molinaro and co-workers evaluated the LPS and the O-antigen of *Bradyrhizobium* sp. BTAi1 for their interactions with plants.[13] They tested the polymers for their ability to activate the innate immune system in *Lotus japonicas*, *Arabidopsis thaliana* and *Aeschynomene indica* by elicitation of respiratory burst, or rapid release of reactive oxygen species (ROS). This phenomenon happens when the immune cells come in contact with the bacteria. They found that neither the LPS or the pure O-antigen from *Bradyrhizobium* sp. BTAi1 are recognized by plants as a microbe-associated molecular pattern (MAMP). This is the first example of an LPS not activating a defense response. This discovery indicates that the LPS and the O-antigen from *Bradyrhizobium* sp. BTAi1 are non-immunogenic.

In 2016, Giraud and co-workers made different mutants lacking the O-antigen and they discovered that there was no effect on the symbiosis between the mutants and the *Aeschynomene afraspera* and *indica* legumes.[16] They also found eleven genes responsible for the biosynthesis of the O-antigen precursor bradyrhizose and identified two of them: *rfaL*, encoding for an O-antigen

ligase and *gdh*, encoding for dTDP-glucose 4,6-dehydratase. With these results, Giraud and co-workers advanced three hypotheses: 1) the core oligosaccharide is non-immunogenic like the O-antigen (based on the mutant experiments); 2) bradyrhizobia are coated with other non-immunogenic surface polysaccharides that could be blocking the antigenic epitope and 3) bacteria could produce unknown signals that could suppress the innate immunity of the legume. More work still needs to be done to understand the biosynthesis of bradyrhizose, the role of the O-antigen and the Nod factor independent pathway of nodulation.

1.3 Bradyrhizose and Caryose

1.3.1 Structure

Bradyrhizose (**1.1**), 4,9-*cyclo*-6-deoxy-8-*C*-methyl-D-*xylo*-D-*galacto*-nonose, is the second bicyclic monosaccharide to be found in nature; both are present in bacterial polysaccharides.[13] This new carbohydrate is composed of a polyhydroxycyclohexane ring *trans*-fused to a six-membered ring monosaccharide. To elucidate the structure of this new molecule, the LPS was first chemically degraded by mild acid hydrolysis to cleave the lipid A.[17] The core oligosaccharide was still linked to the O-antigen, but this did not complicate the analysis because the O-antigen is a lot larger in number of monosaccharides than the core region. The structure of the O-antigen polysaccharide was characterized by extensive 2D NMR spectroscopic experiments.[13,17] First, the ^{1}H NMR spectrum revealed the homopolymeric structure because of a single peak in the anomeric region (Figure 1-5 (a)). The COSY and TOCSY spectra showed two different spins systems. The HMBC spectrum was useful to locate the quaternary carbons, identify the (1→7)-linkage and the structure (Figure 1-5 (a)). Finally, the NOE correlations helped to find the relative configuration of the

monosaccharide (Figure 1-5 (b)). The absolute configuration of the new carbohydrate was established using circular dichroic spectra of a derivatized methyl glycoside.[17]

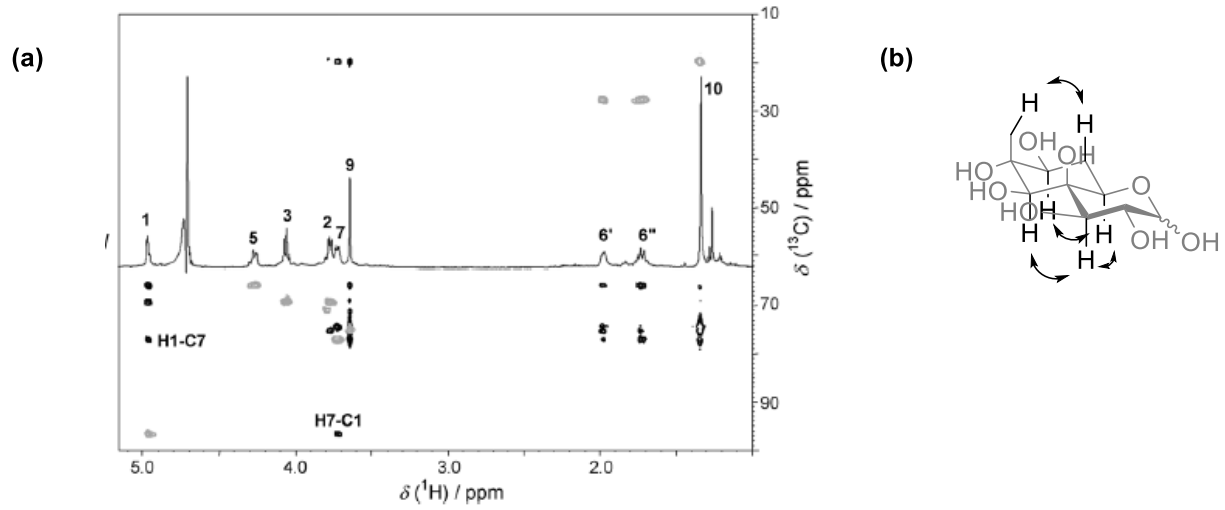


Figure 1-5: (a) ^{1}H NMR of the polysaccharide from *Bradyrhizobium* sp. BTAi1 LPS, HSQC in grey, HMBC in black. Reprinted with permission from John Wiley and Sons.[13] (b) NOE correlations in bradyrhizose.

The first and only other bicyclic monosaccharide was discovered in 1996 and was named caryose (**1.4**), or 4,8-*cyclo*-3,9-dideoxy-L-*erythro*-D-*ido*-nonose (Figure 1-6).[18] It was isolated from the LPS fraction of *Pseudomonas caryophylli*, a phytopatogenic bacterium causing the decay of *Dianthus caryophyllus*, flowers known as carnations. Only one synthesis of this monosaccharide has been done and it was reported in 1997.[19]

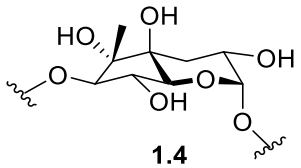


Figure 1-6: Structure of caryose (**1.4**) as found in *P. caryophylli* LPS.[20]

1.3.2 Isomeric equilibrium

Because of their structure, both bradyrhizose and caryose can exist in several cyclic forms as a free reducing sugar in solution. In D_2O, caryose exists as an isomeric mixture of three bicyclic compounds: a six-membered ring *cis*-fused to a five-membered ring (**1.5**) and also two spiro compounds made of two five-membered rings (α and β anomers (**1.7**)) (Figure 1-7).[18,19] By integration of the resonances in the ^1H NMR spectrum, the α-pyranose form (**1.5**) is slightly more abundant than the (1*R)*-furanose isomer (**1.7)** and the (1*S)*-furanose isomer is the least abundant (**1.7**). Presumably these structures interconvert through the open-chain aldehyde **1.6**, although that form is not seen in D_2O solution.

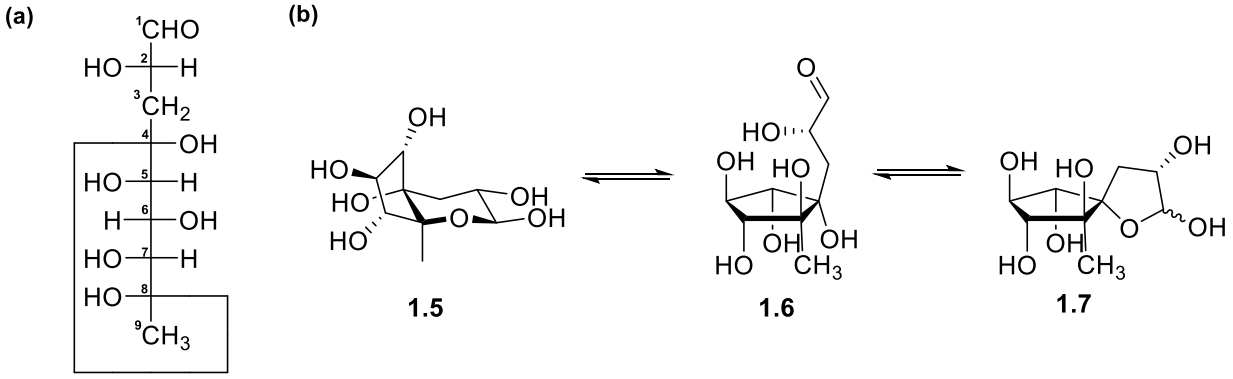


Figure 1-7: (a) Fischer projection of caryose (b) Isomeric mixture of caryose in D_2O.[19]

After completing the first synthesis of bradyrhizose in 2015 (see below), Yu and co-workers discovered that bradyrhizose is also an isomeric mixture like caryose.[21] The isomeric equilibrium in D_2O is composed of three different pyranose forms and two furanose forms (Figure 1-8).[21]

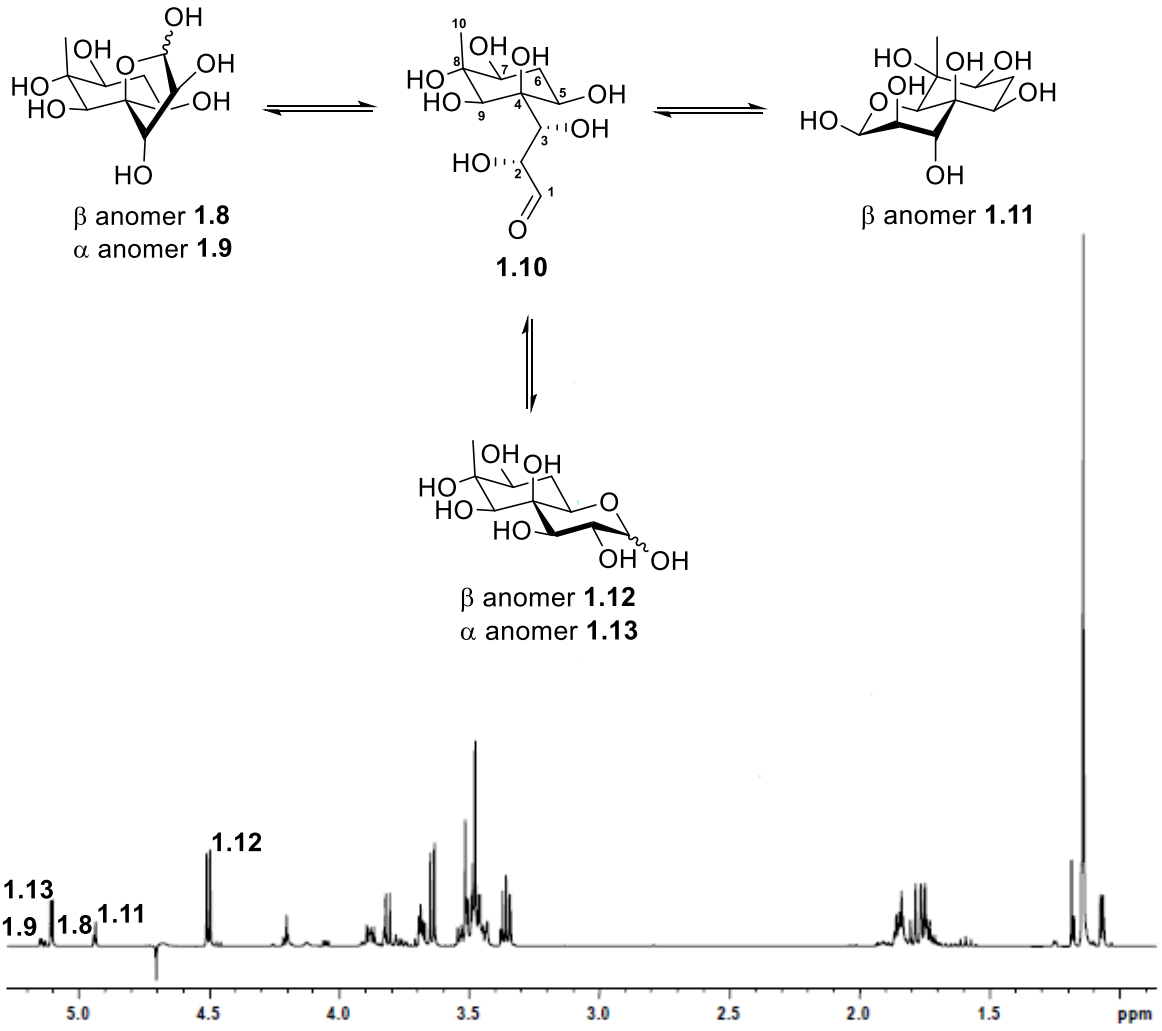
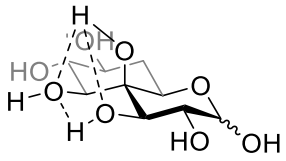


Figure 1-8: Isomeric mixture of bradyrhizose as determined from the ^{1}H NMR spectrum in D_2O. Reprinted with permission from Royal Society of Chemistry.[21]

The 1,5-bradyrhizose (pyranose) isomers are the most abundant (**1.12** and **1.13**), followed by the β-1,9-isomer (**1.11**), which is also a pyranose. The least abundant are the 1,4-bradyrhizose (furanose) isomers (**1.8** and **1.9**). The β anomers are the predominant isomers in both the pyranose and furanose forms. The 1,5-pyranose forms **1.12** and **1.13** are present in 55.7% and 27.8% respectively. It is possible that these are the most abundant isomers because of the hydrogen bonds forming a stable tricyclic structure (**1.14**) composed of three chair conformations (Figure 1-9). It

is also possible that the β-1,9-bradyrhizose (**1.11**) is not in a chair conformation due to negative steric interactions between all of the axial hydroxyl groups present in the molecule. The other conformations of cyclohexane and the pyranose ring have more torsional strain, which could explain the lower abundance of this form (7.7%). The α-1,9-bradyrhizose isomer (anomer of **1.11**) might not be observed because it would have an extra 1,3-diaxial interaction with the C-3 hydroxyl group. The furanose forms (**1.8** and **1.9**) also have more torsional strain than the pyranose forms, leading to a lower abundance (4.4% each for a total of 8.8%).



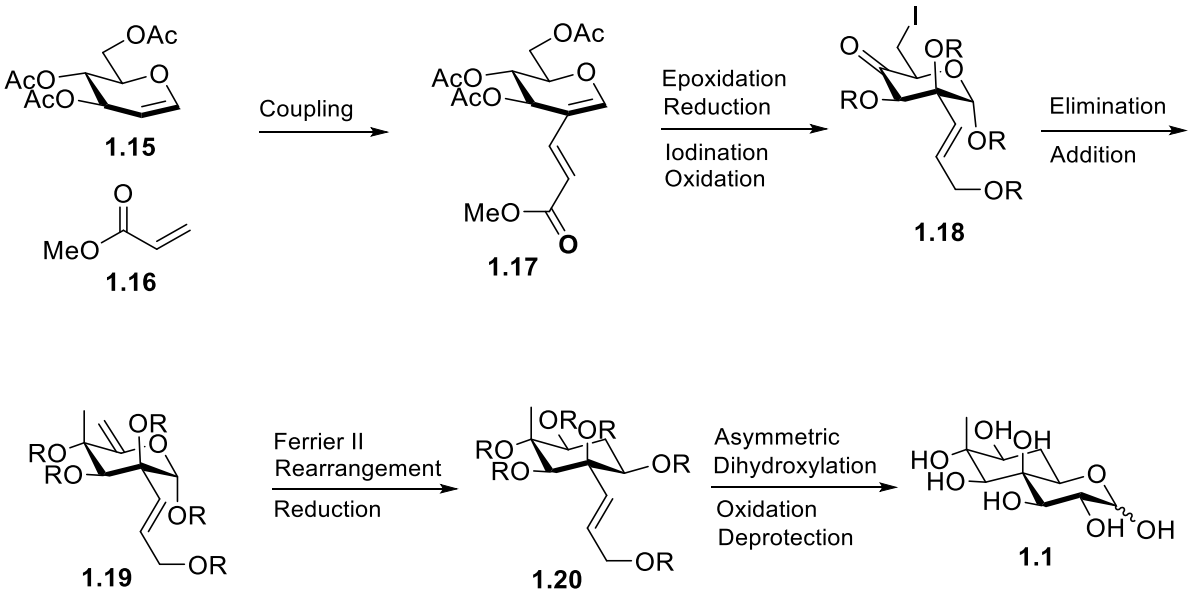
1.14

Figure 1-9: Possible hydrogen bonds stabilizing the 1,5-pyranose form of bradyrhizose.

1.3.3 Reported synthesis

While the biosynthesis of bradyrhizose still remains unknown, a synthesis has already been reported by the Yu group in 2015 (Scheme 1-2)[21], just a few months before I completed my own synthesis. The Yu synthesis was done in 26 steps with an overall yield of 9% starting with tri-*O*-acetyl-D-glucal (**1.15**) and methyl acrylate (**1.16**). The general approach is shown in Scheme 1-2. First, a coupling between glycal **1.15** and methyl acrylate (**1.26**) gave the conjugated glycal **1.17**. Epoxidation of the alkene, followed by reduction of the ester, iodination at the C-6 and oxidation at C-4 were performed to give the intermediate **1.18**. Elimination and addition of a methyl group on the ketone were achieved to give compound **1.19**. A Ferrier II rearrangement was done on intermediate **1.19** to make the inositol moiety in compound **1.20**. From there, an asymmetric

dihydroxylation was performed followed by oxidation of the primary alcohol to the aldehyde; subsequent deprotection gave bradyrhizose (**1.1**).

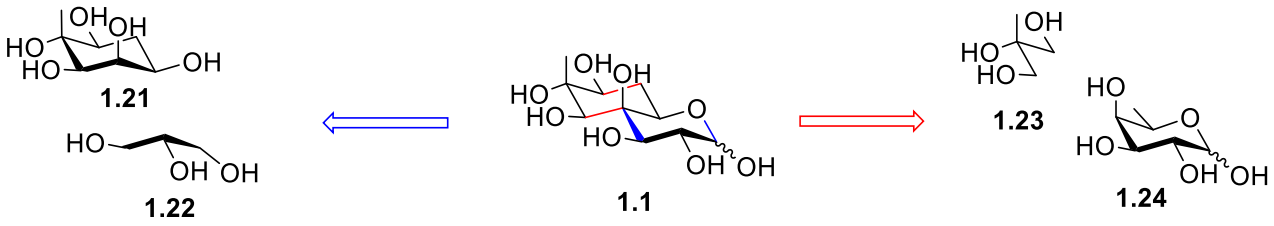


Scheme 1-2: Synthesis of bradyrhizose by Yu and co-workers.[21]

1.4 Objectives

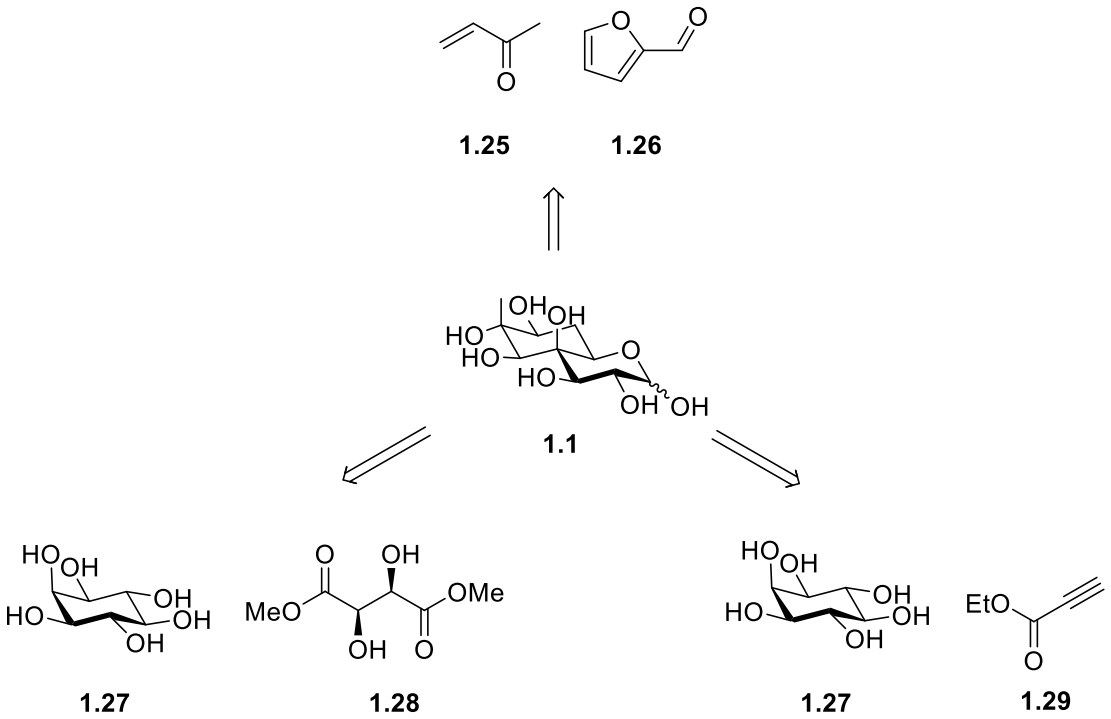
1.4.1 Synthesis of bradyrhizose

After the discovery of this unique bicyclic monosaccharide, we decided to carry out its chemical synthesis. In developing a route to bradyrhizose, two principal synthetic disconnections were considered (Scheme 1-3). The disconnection indicated with the red arrow shows that bradyrhizose (**1.1**) could come from a monosaccharide derived from galactose (**1.24**) and a four carbons unit produced from glycerol (**1.23**). In the disconnection indicated by the blue arrow, bradyrhizose (**1.1**) could originate from an inositol moiety (**1.21**) and also a three carbons unit like glycerol (**1.22**).



Scheme 1-3: Possible synthetic disconnections of bradyrhizose.

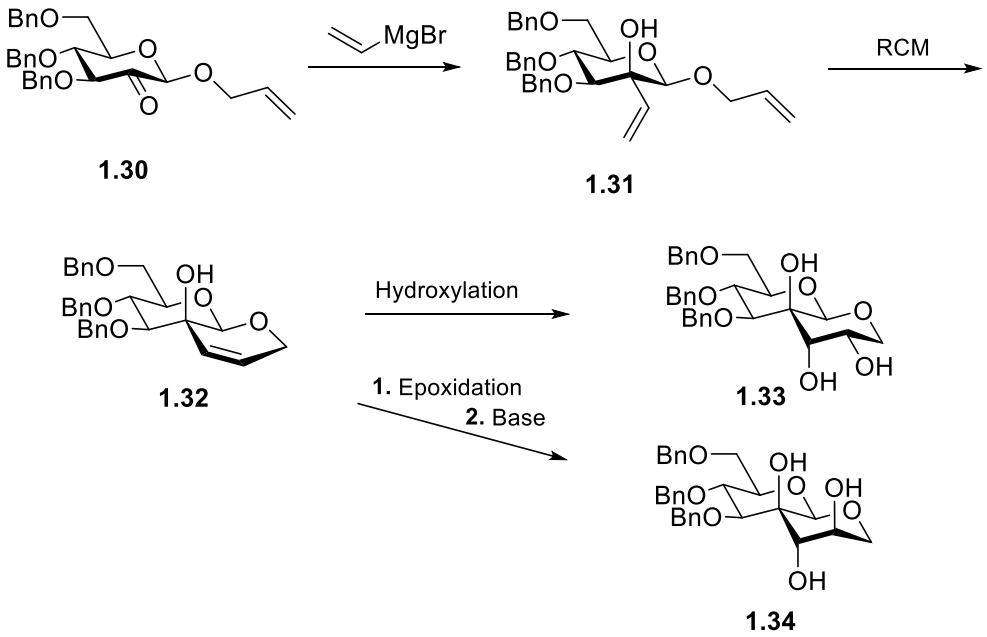
This thesis will present two approaches based on the general synthetic disconnections shown above (Scheme 1-3). For the first route, the monosaccharide was envisioned to be obtained from a furan derivative *via* the Achmatowicz reaction. The furan intermediate could be made from furfural (**1.26**) and methyl vinyl ketone (**1.25**) (Scheme 1-4). This route will be discussed in the second chapter of this thesis.



Scheme 1-4: Retrosyntheses of bradyrhizose.

The third chapter will focus on the second route starting with *myo*-inositol (**1.27**) as the basis of the cyclohexanol part of bradyrhizose (**1.1**). Two different strategies will be explored using this idea. The first is a convergent route using a ring closing metathesis (RCM) and a carboxylic acid derived from (+)-dimethyl L-tartrate (**1.28**). The second is a linear synthesis, which has as a key step the addition of ethyl propiolate (**1.29**) to the inositol moiety (Scheme 1-4). With regard to this route, starting with a meso compound will lead to a racemic product and therefore, the separation of the enantiomers will also be discussed.

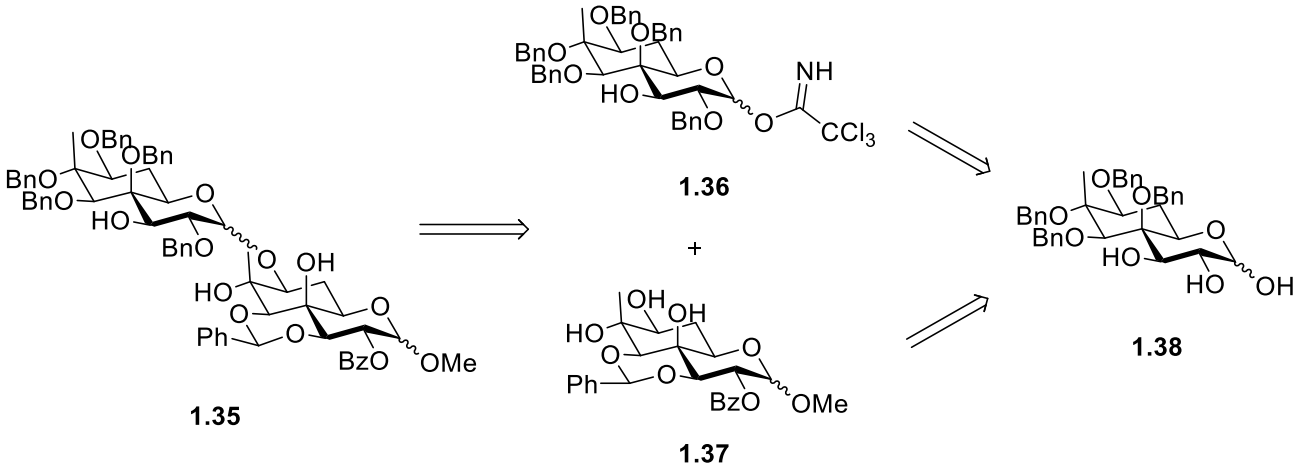
The feasibility of using RCM to access structures of this type was recently reported by Ziegler and coworkers.[22] They added vinylmagnesium bromide to ketone **1.30** to get the tertiary hydroxyl **1.31,** which was then submitted to RCM conditions to afford dioxadecalin **1.32** in good yield. Compound **1.32** can be further transformed by dihydroxylation or epoxidation followed by nucleophilic opening to obtain bicyclic hexol **1.33** or a.**1.34**.



Scheme 1-5: RCM to obtain the dioxadecalin **1.32**.[22]

1.4.2 Glycosylations

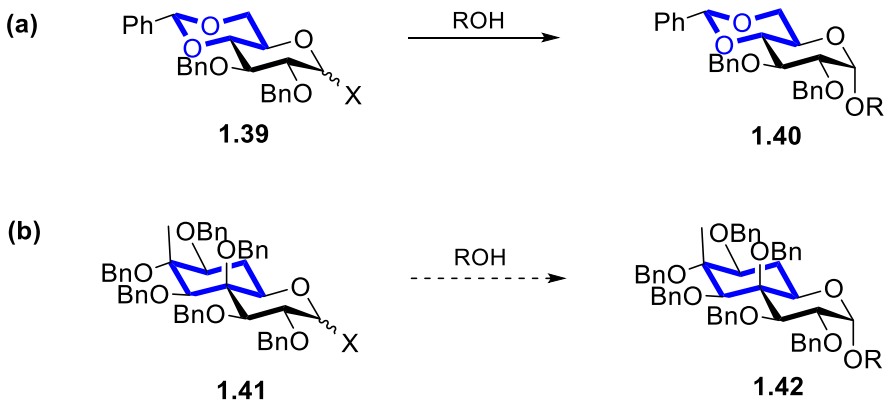
We also set out to explore the glycosylation chemistry of bradyrhizose, through the synthesis of disaccharides **1.35**. The goal is to make an α-(1→7) linkage, which will mimic the naturally occurring bradyrhizose homopolymer. It was envisioned that the synthesis of **1.35** could be achieved by first synthesizing an acceptor (**1.37**) and a donor (**1.36**) starting from **1.38**, a late stage intermediate from the synthesis of bradyrhizose (Scheme 1-6). The donor (**1.36**) has a free secondary hydroxyl group but its position is very hindered, which we anticipated would prevent side reactions. Also, the acceptor (**1.37**) has three free hydroxyl groups, two tertiary and one secondary. The predicted low reactivity of the tertiary hydroxyl groups, due to steric congestion, should make the glycosylation at the secondary alcohol preferred.



Scheme 1-6: Retrosynthesis of the acceptor (**1.37**), the donor (**1.36**) and the disaccharide (**1.35**).

The synthesis of 1,2-*cis*-glycosidic linkages is usually more difficult than the preparation of their 1,2-*trans* counterparts because there is no possibility of neighbouring group participation. In nature, the bradyrhizose glycosidic linkage is 1,2-*cis*, which could be anticipated to lead to challenges in making oligosaccharides containing this residue. However, the structure of the

monosaccharide may provide advantages. Professor Crich from Wayne State University discovered that the 4,6-*O*-benzylidene acetal group is strongly α-directing in the glucopyranose series (Scheme 1-7 (a)).[23,24] Because the shape (the trans-decalin framework) of bradyrhizose resembles the 4,6-*O*-benzylidene protected glucopyranose **1.39**, we hypothesized that the inositol ring of bradyrhizose could also act as an α-directing group (Scheme 1-7 (b)). The reactivity of the bradyrhizose donor with different alcohols will also be discussed in the fourth chapter of this thesis.



Scheme 1-7: (a) α-Selectivity in glycosylation of 4,6-*O*-benzylidene protected glucopyranose.[23] (b) Hypothesis of α-selectivity in glycosylation with bradyrhizose donor.

1.5 References

(1) Hirsch, A. M.; Lum, M. R.; Downie, J. A. What Makes the Rhizobia-Legume Symbiosis So Special? *Plant Physiol.* **2001**, *127*, 1484–1492.

(2) Blackshaw, R. E.; Molnar, L. J.; Moyer, J. R. Suitability of Legume Cover Crop-Winter Wheat Intercrops on the Semi-Arid Canadian Prairies. *Can. J. Plant Sci.* **2010**, *90*, 479–488.

(3) Thiessen Martens, J. R.; Entz, M. H. Integrating green manure and grazing systems: A review. *Can. J. Plant Sci.* **2011**, *91*, 811–824.

(4) Hirsch, A. M. *Brief History of the Discovery of Nitrogen-Fixing Organisms*, 2009, https://www.mcdb.ucla.edu/Research/Hirsch/famousfixers.php (accessed March 16, 2016).

(5) Campbell, N. A.; Reece, J. B.; Urry, L. A.; Cain, M. L.; Wasserman, S. A.; Minorsky, P. V.; Jackson, R. B. *Biology*; *Eight Edition*; Wilbur, B., Ed.; Pearson Benjamin Cummings: San Franscisco, 2008; pp 793-795.

(6) Grossman, D. J. *Legume Inoculation for Organic Farming Systems*, 2015 http://articles.extension.org/pages/64401/legume-inoculation-for-organic-farming-systems (accessed Jan 19, 2016).

(7) Masson-Boivin, C.; Giraud, E.; Perret, X.; Batut, J. Establishing Nitrogen-Fixing Symbiosis with Legumes: How Many Rhizobium Recipes? *Trends Microbiol.* **2009**, *17*, 458–466.

(8) Downie, J. A. The Roles of Extracellular Proteins, Polysaccharides and Signals in the Interactions of Rhizobia with Legume Roots. *FEMS Microbiol. Rev.* **2010**, *34*, 150–170.

(9) Giraud, E.; Moulin, L.; Vallenet, D.; Barbe, V.; Cytryn, E.; Avarre, J.-C.; Jaubert, M.; Simon, D.; Cartieaux, F.; Prin, Y.; Bena, G.; Hannibal, L.; Fardoux, J.; Kojadinovic, M.; Vuillet, L.; Lajus, A.; Cruveiller, S.; Rouy, Z.; Mangenot, S.; Segurens, B.; Dossat, C.; Franck, W. L.; Chang, W.-S.; Saunders, E.; Bruce, D.; Richardson, P.; Normand, P.; Dreyfus, B.; Pignol, D.; Stacey, G.; Emerich, D.; Verméglio, A.; Médigue, C.; Sadowsky, M. Legumes Symbioses: Absence of *Nod* Genes in Photosynthetic Bradyrhizobia. *Science* **2007**, *316*, 1307–1312.

(10) Fleischman, D.; Kramer, D. Photosynthetic Rhizobia. *Biochim. Biophys. Acta* **1998**, *1364*, 17–36.

(11) Bedini, E.; De Castro, C.; Erbs, G.; Mangoni, L.; Dow, J. M.; Newman, M. A.; Parrilli, M.; Unverzagt, C. Structure-Dependent Modulation of a Pathogen Response in Plants by Synthetic O-Antigen Polysaccharides. *J. Am. Chem. Soc.* **2005**, *127*, 2414–2416.

(12) Leone, M. R.; Lackner, G.; Silipo, A.; Lanzetta, R.; Molinaro, A.; Hertweck, C. An Unusual Galactofuranose Lipopolysaccharide That Ensures the Intracellular Survival of Toxin-Producing Bacteria in Their Fungal Host. *Angew. Chemie - Int. Ed.* **2010**, *49*, 7476–7480.

(13) Silipo, A.; Leone, M. R.; Erbs, G.; Lanzetta, R.; Parrilli, M.; Chang, W. S.; Newman, M. A.; Molinaro, A. A Unique Bicyclic Monosaccharide from the Bradyrhizobium Lipopolysaccharide and Its Role in the Molecular Interaction with Plants. *Angew. Chemie - Int. Ed.* **2011**, *50*, 12610–12612.

(14) Gnauck, A.; Lentle, R. G.; Kruger, M. C. The Characteristics and Function of Bacterial Lipopolysaccharides and Their Endotoxic Potential in Humans. *Int. Rev. Immunol.* **2015**, *185*, 1–31.

(15) Alexander, C.; Rietschel, E. T. Bacterial Lipopolysaccharides and Innate Immunity. *J. Endotoxin Res.* **2001**, *7*, 167–202.

(16) Busset, N.; De Felice, A.; Chaintreuil, C.; Gully, D.; Fardoux, J.; Romdhane, S.; Molinaro, A.; Silipo, A.; Giraud, E. The LPS *O*-Antigen in Photosynthetic *Bradyrhizobium* Strains Is Dispensable for the Establishment of a Successful Symbiosis with *Aeschynomene* Legumes. *PLOS ONE* [Online] **2016**, http://dx.doi.org/10.1371/journal.pone.0148884 (accessed Apr 17, 2016).

(17) Leone, M. R. Structure of Macromolecules from Gram-Negative Bacteria Involved in Elicitation of Plant Immune System. Ph.D. thesis, Univeristy of Naples Federico II, 2010.

(18) Adinolfi, M.; Corsaro, M. M.; De Castro, C.; Evidente, A.; Lanzetta, R.; Molinaro, A.; Parilli, M. Caryose : A Carbocyclic Monosaccharide from *Pseudomonas caryophylli*. *Carbohydr. Res.* **1996**, *284*, 111–118.

(19) Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Manna R. Synthesis of Caryose, the Carbocyclic Monosaccharide Component of the Lipopolysaccharide from *Pseudomonas caryophylli*. *Tetrahedron* **1997**, *53*, 11767–11780.

(20) De Castro, C.; Molinaro, A.; Lanzetta, R.; Holst, O.; Parrilli, M. The Linkage between O-Specific Caryan and Core Region in the Lipopolysaccharide of *Burkholderia caryophylli* Is Furnished by a Primer Monosaccharide. *Carbohydr. Res.* **2005**, *340*, 1802–1807.

(21) Li, W.; Silipo, A.; Molinaro, A.; Yu, B. Synthesis of Bradyrhizose, a Unique Inositol-Fused Monosaccharide Relevant to a Nod-Factor Independent Nitrogen Fixation. *Chem. Commun.* **2015**, *51*, 6964–6967.

(22) Borowski, D.; Zweibohmer, T.; Ziegler, T. 1,2-Annulated Sugars: Synthesis of Polyhydroxylated 2,10-Dioxadecalins with β-Manno Configuration. *European J. Org. Chem.* **2016**, *Early view*.

(23) Crich, D. Methodology Development and Physical Organic Chemistry: A Powerful Combination for the Advancement of Glycochemistry. *J. Org. Chem.* **2011**, *76*, 9193–9209.

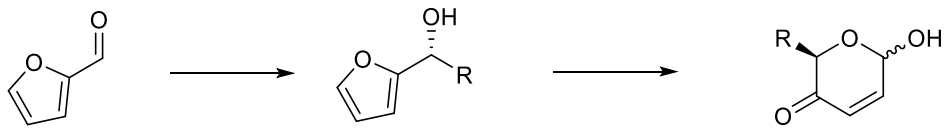
(24) Crich, D. Mechanism of a Chemical Glycosylation Reaction. *Acc. Chem. Res.* **2010**, *43*, 1144–1153.

Chapter 2: Towards the synthesis of bradyrhizose: Route starting with furfural

The first route designed for the synthesis of bradyrhizose was inspired by the work of Professor George A. O'Doherty from Northeastern University. His research has focused on the synthesis of enantiopure natural products such as monosaccharides from inexpensive achiral starting materials. In this method, different monosaccharides are obtained by asymmetric synthesis from furfural. A route to bradyrhizose using this strategy will be discussed in this chapter.

2.1 Introduction

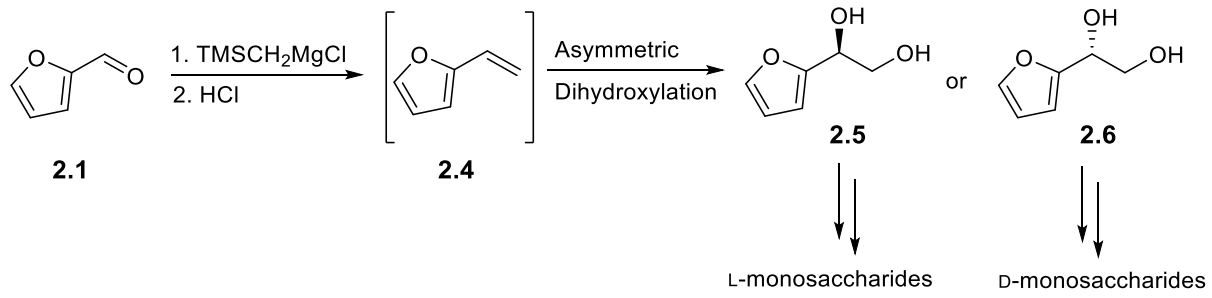
The synthesis of monosaccharides is usually done by modification of readily available carbohydrates.[1] This is a valid method for the preparation of monosaccharides with different functional groups, but the syntheses can be long and involve extensive protection and deprotection steps. An alternative method for the synthesis of monosaccharides is the use of non-carbohydrates as starting materials. This strategy can be attractive for the synthesis of unusual carbohydrates because it can reduce the number of steps in the synthesis. One common starting material is furfural (**2.1**), which is cheap and readily available. Furfural can be transformed to the chiral furfuryl alcohols **2.2** that can undergo an Achmatowicz reaction to produce dihydropyrans (**2.3)**, which have a monsaccharide backbone (Scheme 2-1).[2,3]



2.1 **2.2** **2.3**

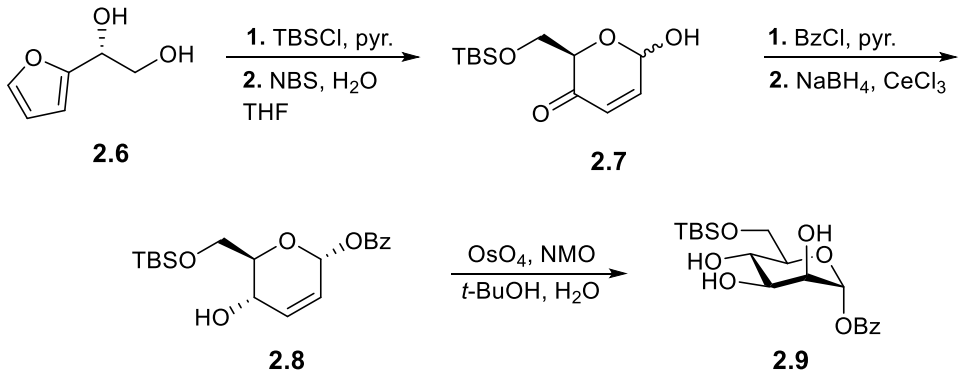
Scheme 2-1: Achmatowicz reaction.

The Achmatowicz reaction, an oxidative ring expansion reaction, was first adapted by Cavill, Laing and Williams in 1969 for the synthesis of 6-hydroxy-*2H*-pyran-3(*6H*)-ones.[2] A few years later, Achmatowicz and co-workers refined this reaction to synthesize various monosaccharides.[3] In the late 1990s and early 2000s, Professor Ogasawara and Professor O'Doherty used furfural (**2.1**) to synthesize vinyl furan **2.4** followed by an asymmetric dihydroxylation of the alkene to afford either of the possible chiral furfuryl alcohols **2.5** or **2.6** (Scheme 2-2).[4,5] These intermediates could then undergo the Achmatowicz reaction leading, after subsequent transformations, to D-or L-monosaccharides.



Scheme 2-2: Synthesis of chiral furfuryl alcohol.

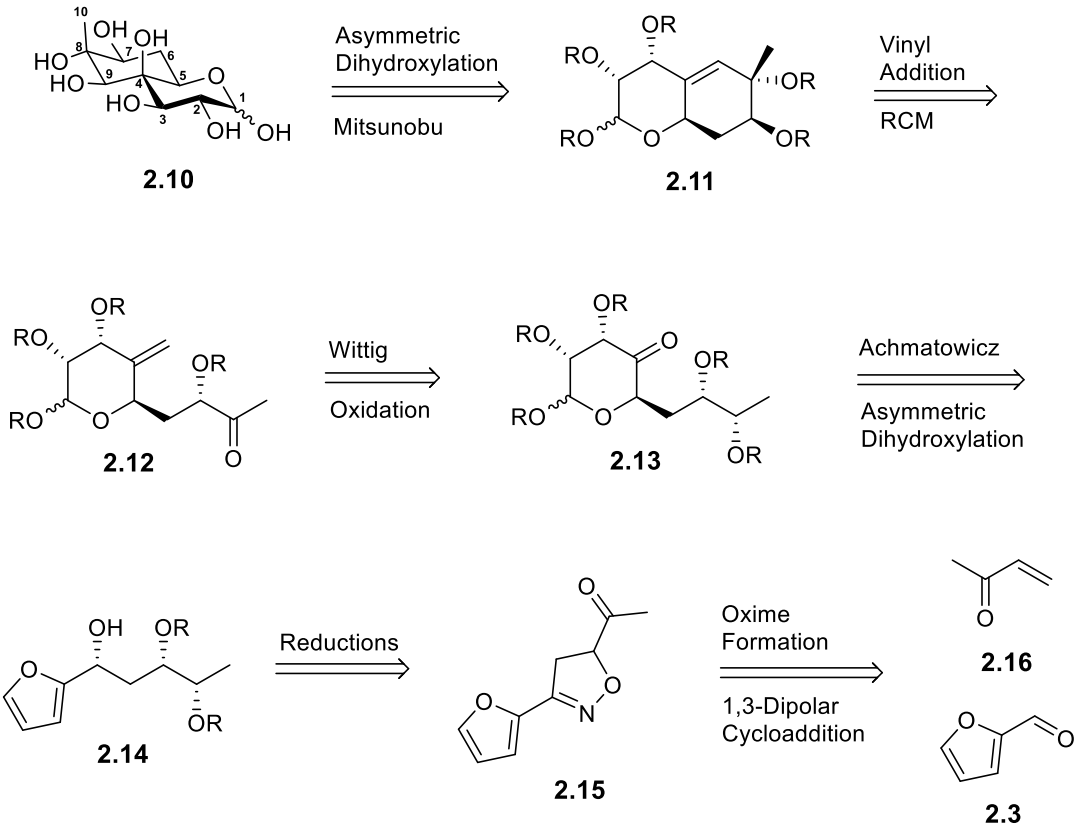
The utility of the oxidative ring expansion reaction can be exemplified by the synthesis of the D-mannose derivative shown in Scheme 2-3.[5] After protection of the primary hydroxyl group, the furfuryl alcohol can undergo an Achmatowicz rearrangement to give the dihydropyran **2.7**. The anomeric hydroxyl group is then protected with a benzoyl group to afford the α-anomer as the major isomer. The ketone is reduced using Luche conditions to give compound **2.8**. Asymmetric dihydroxylation is then performed on the alkene to give the D-mannose derivative **2.9** in 38% overall yield from furfural (**2.3**). This is an economical and useful method for making different monosaccharides. We believed this approach would be a suitable way to synthesize bradyrhizose, by making the R group in the chiral furfuryl alcohol **2.1** in Scheme 2-1 a polyhydroxylated chain.



Scheme 2-3: Synthesis of a D-mannose derivative.[5]

2.2 Retrosynthesis

The retrosynthesis of bradyrhizose using the Achmatowicz reaction as a key step is shown in Scheme 2-4. We envisioned that bradyrhizose (**2.10**) could be obtained by asymmetric dihydroxylation of the alkene present in the bicyclic intermediate **2.11** followed by a Mitsunobu reaction at the C-3 of the monosaccharide. Compound **2.11** could be constructed by the addition of a vinyl group to ketone **2.12** followed by a ring closing metathesis (RCM) between the two alkenes. Intermediate **2.12** could be prepared by a Wittig reaction on the ketone, then an oxidation of the hydroxyl group at the C-8 position of monosaccharide derivative **2.13**. The synthesis of tetrahydropyranone **2.13** could be achieved by an asymmetric dihydroxylation of the corresponding dihydropyran, which would be made by Achmatowicz reaction of the chiral furfuryl alcohol **2.14**. The 1,2,4-triol **2.14** could be obtained by reduction of the ketone and the isoxazoline ring of compound **2.15**. Finally, 5-acetyl-3-furyl-2-isoxazoline (**2.15**) could be prepared by a 1,3-dipolar cycloaddition of methyl vinyl ketone (MVK, **2.16**) and an oxime derived from furfural (**2.3**).

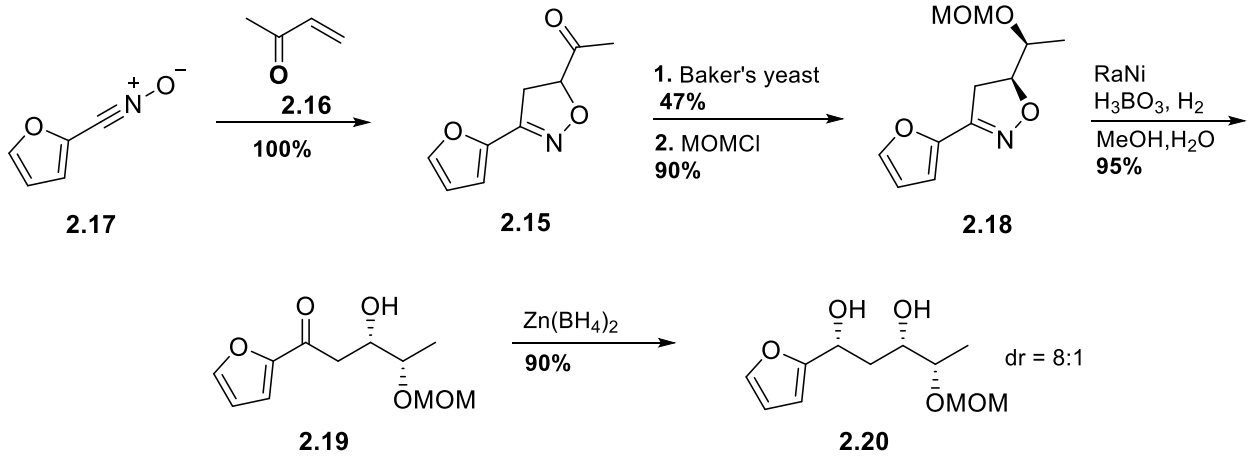


Scheme 2-4: Retrosynthesis of bradyrhizose from furfural and methyl vinyl ketone.

2.3 Results and Discussion

We envisioned that the synthesis of the 1,2,4-triol could be done based upon the work of Ticozzi and Zanarotti (Scheme 2-5).[6] They first performed a 1,3-dipolar cycloadditon of a nitrile oxide (**2.17**) with MVK (**2.16**) to give the isoxazoline **2.15** in a quantitative yield. The ketone was then reduced using Baker's yeast to give two diastereomers that were separable by silica gel column chromatography. The free hydroxyl group of the desired diastereomer was protected using the methoxy methyl ether (MOM) group followed by a reduction of the isoxazoline ring using Raney Nickel (RaNi) and boric acid to give the 2,3-dihydroxyketone **2.19**. The last step was the

diastereoselective reduction of the ketone using zinc borohydride to give the 1,2,4-triol **2.20** in a good yield and diastereomeric ratio (8:1).



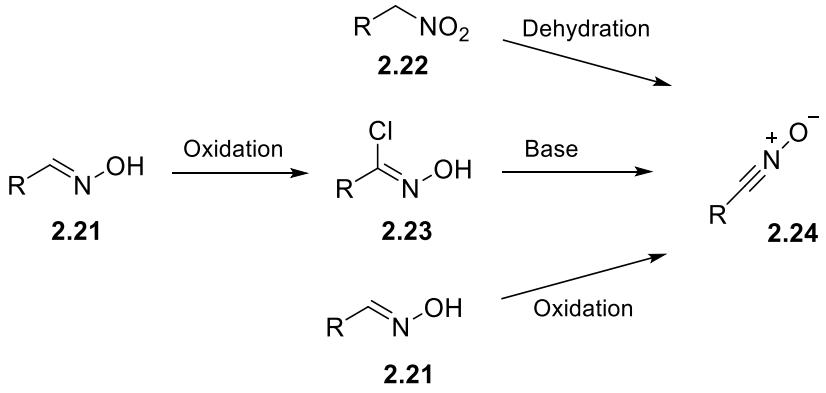
Scheme 2-5: Synthesis of enantiomerically pure 1,2,4-triol **2.20** from nitrile oxide and MVK.[6]

This route appeared to be feasible for the synthesis of the early intermediate **2.14** (Scheme 2-4). The only problem was that the publication did not include procedures, but each step was known in the literature for different substrates. Therefore, we decided to try this method to build the protected 1,2,4-triol **2.14**.

2.3.1 Synthesis of 5-acetyl-3-furyl-2-isoxazoline and Baker's yeast reduction

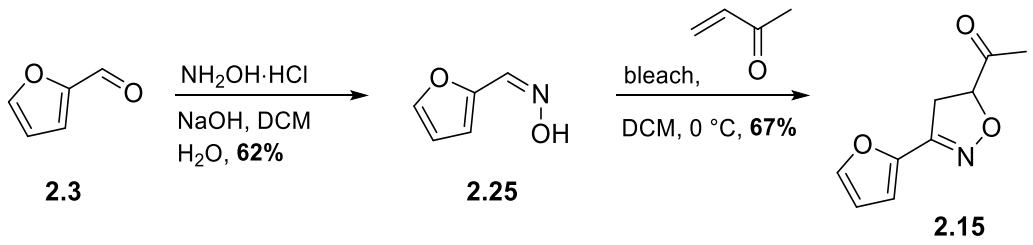
The first step toward the synthesis of bradyrhizose was the 1,3-dipolar cycloaddition of a nitrile oxide with an alkene. This reaction has been well documented and different reagents have been used to make nitrile oxides (Scheme 2-6).[7] These reactive intermediates (**2.24)** can be prepared by the dehydration of nitro compounds (**2.22**) or by the oxidation of oximes (**2.21**) in either a one or two step process. The two step process involves first the formation of the

hydroximoyl chloride (**2.23**) and then further oxidation to the nitrile oxide (**2.24**). I chose to use the oxime approach because of the commercial avaibility of the precursors.



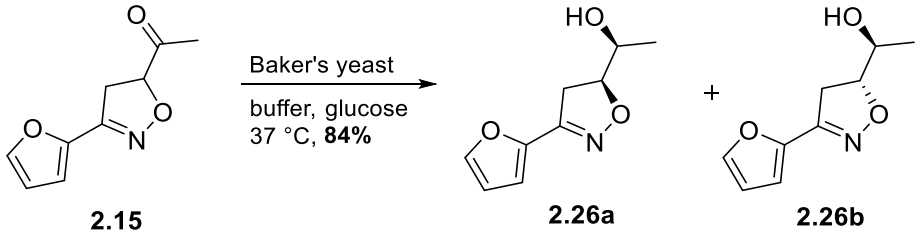
Scheme 2-6: Formation of nitrile oxides. [7]

The synthesis started with the reaction of furfural (**2.3**) and hydroxylamine hydrochloride to give oxime **2.25** in 62% yield after recrystallization (Sheme 2-7).[8] The formation of the corresponding hydroximoyl chloride using NCS[9] was unsuccessful. An alternative method of forming the nitrile oxide is direct oxidation of the oxime using (diacetoxyiodo)benzene.[10] However, when attempted, this reaction did not lead to the formation of the desired intermediate. The last option was to make the hydroximoyl chloride *in situ* and adding MVK to make the isoxazoline in one step. By adding bleach[11] to a mixture of the oxime and MVK in CH_2Cl_2 at 0 °C, the isoxazoline (**2.15**) was finally obtained in 67% yield (Sheme 2-7).



Scheme 2-7: Synthesis of isoxazoline **2.15**.

With isoxazoline **2.15** in hand, the reduction of the ketone moiety was successfully achieved using Baker's yeast.[12] The desired product was obtained in 84% yield as an inseparable mixture of diastereomers (**2.26a** and **b**) (Scheme 2-8).

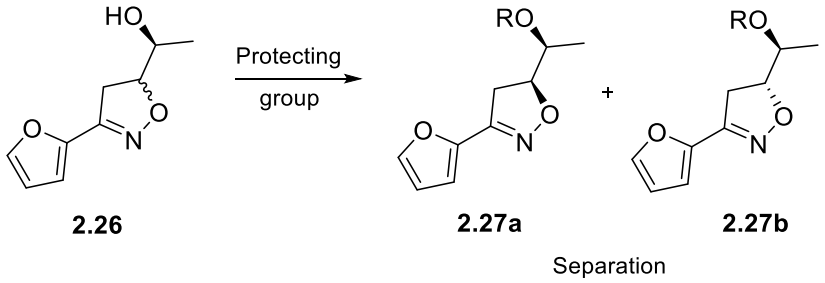


Scheme 2-8: Reduction of ketone **2.15** with Baker's yeast.

2.3.2 Separation of the diastereomers

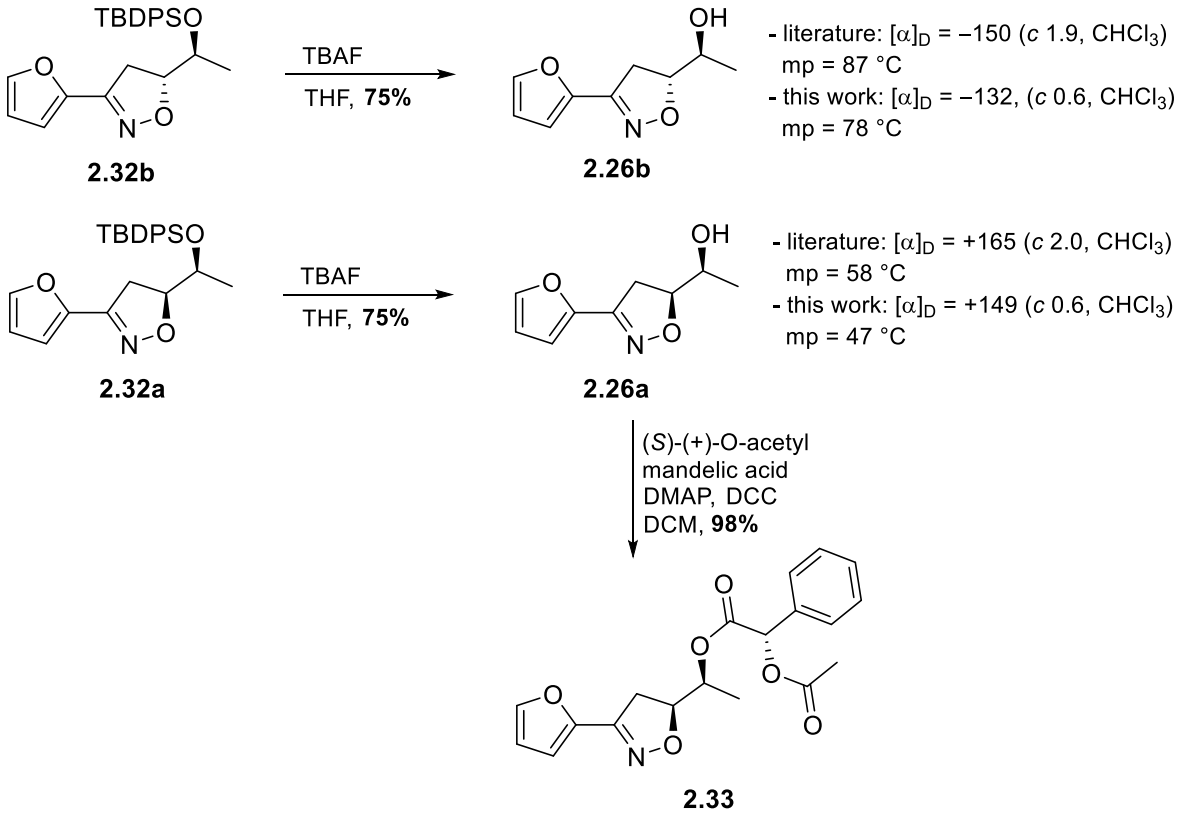
As mentioned earlier, Ticozzi and Zanarotti were able to separate the diastereomers **2.26** by flash chromatography.[6] However, after trying many different solvent systems, it was not possible to do so. Therefore, different protecting groups were installed on the hydroxyl group to ease the separation of the diastereomers. The bulky TBDPS group was found to be the most efficient in allowing the separation of the isomers, although obtaining them in pure form was still difficult (Table 2-1).

Table 2-1: Separation of the mixture of diastereomers **2.26**.



Compounds	R	Yield (%)	Separation
2.28	Ac	81	no
2.29	Bz	82	no
2.30	(*S*)-(+)-*O*-acetylmandelic ester	97	no
2.31	TBS	91	no
2.32	TBDPS	89	yes

After the separation, the desired diastereomer (**2.32a** or **2.32b**) needed to be identified before continuing the synthesis. The stereochemistry of compounds **2.32a** and **2.32b** could not be determined directly as they were both new compounds obtained as oils. It was anticipated that obtaining X-ray crystallographic data on one or both of these compounds would be difficult. Instead, I chose to compare the specific rotations and melting points of deprotected isomers **2.26a** and **2.26b** (obtained by desilylation with tetra-*n*-butyl ammonium fluoride (TBAF)) to the known compounds reported by Ticozzi and Zanarotti[6] (Scheme 2-9). The melting points of the compounds were both lower than the reported values, which did not verify the identity of each isomer. However, the specific rotations of compounds **2.26a** and **2.26b** were both of the right sign and the rotations were similar to those reported earlier.



Scheme 2-9: Deprotection of **2.32a** and **2.32b** and comparison of the specific rotation and melting point of the product **2.26a** and **2.26b** with the literature data.[6] Derivatization of **2.26a** for crystal structure determination.

To obtain more definitive information about the structure of the molecules, the desired diastereomer **2.26a** based on the melting point and rotation was then reacted with (*S*)-(+)-*O*-acetylmandelic acid to give a derivative (**2.33**) that could be crystallized (Scheme 2-9). A crystal structure (Figure 2-1) was obtained and the stereochemistry of the molecule could be unequivocally determined. As shown in Figure 2-1, C-13 and C-11 in **2.33** have the desired absolute stereochemistry, when compared to the known stereocenter at C-2.

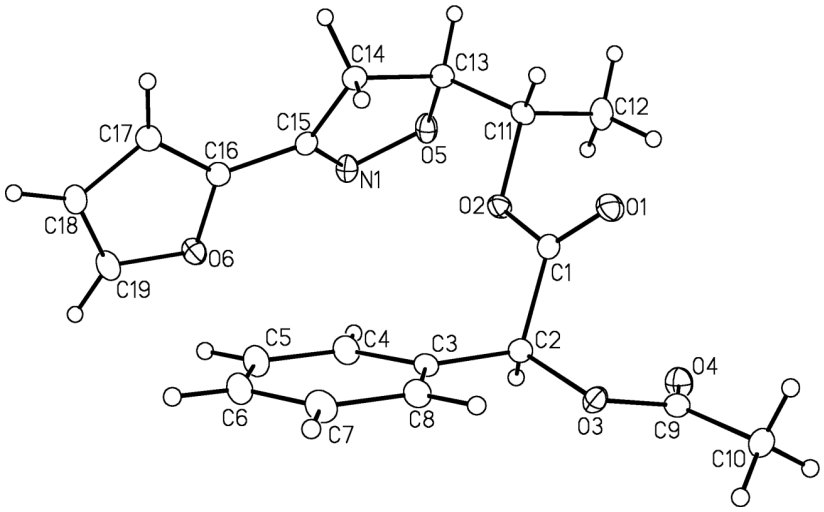


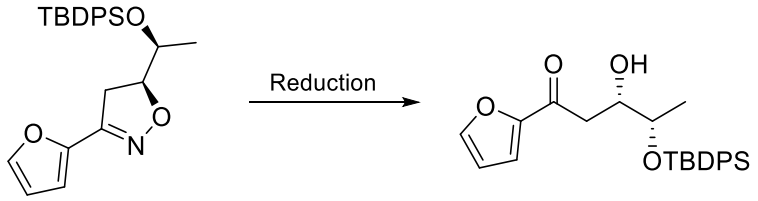
Figure 2-1: X-ray crystal structure (ORTEP) of compound **2.33**. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

2.3.3 Synthesis of the 2,3-dihydroxyketone

Having established the stereochemistry of **2.26**, the next step was the reduction of the isoxazoline ring of **2.32a** to the β-hydroxyketone **2.34**. Different methods and conditions were tried for this step as shown in Table 2-2. First, RaNi, boric acid and hydrogen in methanol and water (Table 2-2, Entry 1) was chosen, as the same reaction was reported by Ticozzi and Zanarotti with a yield of 95–100%; however, this yield could not be reproduced.[6] The solvent ratio and composition were varied (Table 2-2, Entries 2 and 3) but this did not improve the yield above 50%. Freshly RaNi was prepared[13] and its use did not change the yield for the desired product (Table 2-2, Entry 4). Different equivalents of iron with ammonium chloride were also tested, which did not form the product unless excess amounts of iron was used and in these cases only a low (20%) (Table 2-2, Entries 5,6 and 7) yields were obtained.[14,15] Cu(0) nanoparticules made from copper sulfate, sodium dodecyl sulfate and ascorbic acid have been reported to reduce the isoxazoline ring but this method did not work with substrate **2.32a** (Table 2-2, Entry 8).[16] The use of palladium on

carbon with hydrogen in acetic acid[17] (Table 2-2, Entry 9) and molybdenum hexacarbonyl[18] (Table 2-2, Entry 10) resulted in no consumption of the starting material. Commercial samarium iodide[19] as well as freshly prepared samarium iodide[20] gave a yield of 39%, less than the RaNi reaction (Table 2-2, Entry 11). Finally, we tried the reaction with zinc in acetic acid, THF and water, without good results (Table 2-2, Entry 12). After all these efforts to get the 2,3-dihydroxyketone, the use of RaNi, boric acid and hydrogen was chosen as the optimal conditions to produce a small amount of the desired compound **2.34** to try the next step.

Table 2-2: Reduction of isoxazoline **2.32a** to 2,3-dihydroxyketone **2.34**.

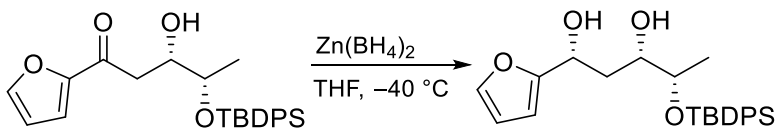


2.32a **2.34**

Entry	Reagents	Equivalent(s) of metal	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	RaNi, $B(OH)_3$, H_2	catalytic	MeOH/H_2O	23	4	42-49
2	RaNi, $B(OH)_3$, H_2	catalytic	THF/H_2O	23	24	41
3	RaNi, $B(OH)_3$, H_2	catalytic	THF/MeOH/H_2O	23	4	40
4	RaNi*, $B(OH)_3$, H_2	catalytic	MeOH/H_2O	23	16	43
5	Fe, NH_4Cl	10	EtOH/H_2O	80	16	SM
6	Fe, NH_4Cl	30	EtOH/H_2O	80	48	SM
7	Fe, NH_4Cl	50	EtOH/H_2O	80	48	20
8	$CuSO_4 \cdot 5H_2O$, SDS, ascorbic acid	1	H_2O	60	24	SM
9	Pd/C, AcOH, H_2	0.25	MeOH/H_2O	23	24	SM
10	$Mo(CO)_6$	0.5	MeCN	80	48	SM
11	SmI_2 or SmI_2*	4.5	THF	23	0.08	39
12	Zn	100	THF/H_2O/AcOH	50	2	CM

*Freshly prepared SM = starting material CM = complex mixture

The diastereoselective reduction of the ketone in **2.34** to give the diol **2.35** was attempted using freshly prepared zinc borohydride[21] without success (Sheme 2-10). The ketone was reduced in 87% yield, however, with poor diastereoselectivity (2:1). Given the difficulties in this reduction, as well as problems in the reduction of the isoxazoline ring in **2.32a**, and the difficulites in separating the diasteromers resulting from the Baker's yeast reduction of **2.15**, I decided to abandon this approach to bradyrhizose.



2.34 **2.35**

Scheme 2-10: Attempted diastereoselective reduction of ketone **2.34**.

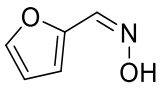
2.3.4 Summary and conclusion

In summary, a 1,3-dipolar cycloaddition of MVK (**2.16**) and furaldehyde oxime (**2.25**) was done using commercial bleach to give the isoxazoline **2.15** in 41% after two steps (Scheme 2-7). Baker's yeast reduction of **2.15** gave a mixture of diastereomeric alcohols **2.26**, which could only be separated after their conversion to the corresponding TBDPS ethers. The desired compound, **2.32a**, was obtained in 35% yield over the two steps (Scheme 2-8 and Table 2-1). The stereochemistry of the compound was verified by X-ray crystallographic analysis (Figure 2-1) of an *O*-acteylmandelic acid derivative **2.33**, which was obtained by cleavage of the silyl ether in **2.32a** and then treatment with (*S*)-(+)-*O*-acetylmandelic acid and DCC. The isoxaline ring in **2.32a** was reduced using RaNi and boric acid to give the ring opened product **2.34** in 42–49% yield. With an overall yield of 6–7% after five steps, and not being able to reproduce the results from

Ticozzi and Zanarotti,[6] I chose to stop pursuing this route to bradyrhizose and explored an alternate strategy. The next approach is based on the other synthetic disconnection mentioned in Chapter 1 (Scheme 1-2), where the target is made from an inositol derivative. The route starting from *myo*-inositol will be discussed in Chapter 3.

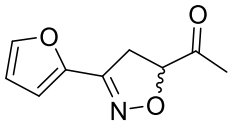
2.4 Experimental

General Methods: Reactions were carried out in oven-dried glassware. All reagents used were purchased from commercial sources and were used without further purification unless noted. Solvents used in reactions were purified by successive passage through columns of alumina and copper under argon. Unless stated otherwise, all reactions were carried out at room temperature under a positive pressure of argon and were monitored by TLC on silica gel 60 F254 (0.25 mm, E. Merck). Spots were detected under UV light or by charring with a solution of ammonium molybdate (12 g) and ceric ammonium nitrate (0.42 g) in H_2O (235 mL) and concentrated sulfuric acid (15 mL). Unless otherwise indicated, all column chromatography was performed on silica gel 60 (40–60 μM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 21 ± 2 °C at the sodium D line (589 nm) and are in units of deg·mL(dm·g)$^{-1}$. ^{1}H NMR spectra were recorded at 500 MHz, and chemical shifts are referenced to TMS (0.0 ppm, $CDCl_3$). ^{13}C NMR spectra were recorded at 125 MHz, and ^{13}C chemical shifts are referenced to internal $CDCl_3$ (77.2 ppm, $CDCl_3$. In the processing of reaction mixtures, solutions of organic solvents were washed with equal amounts of aqueous solutions. Organic solutions were concentrated under vacuum at < 40°C (bath). Electrospray mass spectra were recorded on samples suspended in mixtures of THF with CH_3OH and added NaCl.



2.25

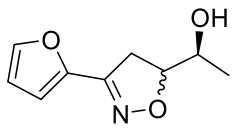
(*Z*)-2-Furaldehyde oxime (2.25).[8] An aqueous solution of NaOH (4.84 g in 18 mL of H_2O) was added dropwise to a cooled (0 °C) mixture of furfural (10 mL, 121 mmol) and hydroxylamine hydrochloride (8.41 g, 121 mmol) in H_2O (30 mL) and CH_3OH (5 mL). The reaction mixture was stirred at 0 °C for 2 h, then allowed to warm to rt for 1 h. The precipitate was filtered, washed with cold water and dried (P_2O_5) under vacuum. The crude solid product was collected and purified by recrystallization using benzene and petroleum ether to yield **2.25** (8.37 g, 62%) as white needles. R_f 0.42 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.77 (br, 1 H, OH), 7.52 (s, 1 H, N=CH), 7.49 (dd, 1 H, $J_{3,5}$ = 0.7 Hz, $J_{4,5}$ = 1.7 Hz, H-5), 7.14 (d, 1 H, $J_{3,4}$= 3.5 Hz, H-3), 6.55 (ddd, 1 H, J = 0.6 Hz, $J_{4,5}$ = 1.7 Hz, $J_{3,4}$ = 3.5 Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 145.0 (C-2), 143.4 (C-5), 137.4 (C-1), 118.2 (C-3), 112.3 (C-4). HRMS (EI) Calcd for [$M^{+\bullet}$] $C_5H_5NO_2$: 111.0320. Found 111.0321.



2.15

5-Acetyl-3-furyl-2-isoxazoline (2.15). Commercial bleach (Chlorox®, 5.4 mL) was added to a cooled (0 °C) solution of **2.25** (200 mg, 1.80 mmol) and methyl vinyl ketone (300 µL, 3.60 mmol) in CH_2Cl_2 (7.2 mL). The reaction mixture was stirred for 30 min at 0 °C and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 to 7:3 hexanes–EtOAc) to yield

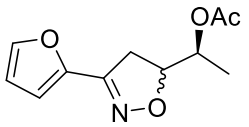
2.15 (216 mg, 67%) as an orange oil. R_f 0.24 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.55 (dd, 1 H, $J_{2fur,4fur}$ = 0.7 Hz, $J_{3fur,4fur}$ = 1.8 Hz, H-4 furyl), 6.78 (dd, 1 H, $J_{2fur,4fur}$ = 0.7 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-2 furyl), 6.52 (dd, 1 H, $J_{3fur,4fur}$ = 1.8 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-3 furyl), 5.01 (dd, 1 H, $J_{4a,5}$ = 6.1 Hz, $J_{4b,5}$ = 11.8 Hz, H-5), 3.62 (dd, 1 H, $J_{4a,5}$ = 6.1 Hz, $J_{4a,4b}$ = 17.1 Hz, H-4a), 3.48 (dd, 1 H, $J_{4b,5}$ = 11.8 Hz, $J_{4a,4b}$ = 17.1 Hz, H-4b), 2.37 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 207.2 (C=O), 148.8 (C=N), 144.8 (C-4 furyl), 143.9 (C-1 furyl), 112.7 (C-2 furyl), 111.8 (C-3 furyl), 84.0 (C-5), 37.1 (C-4), 26.4 (CH_3). HRMS (ESI) Calcd for $[M + H]^+$ $C_9H_{10}NO_3$: 180.0655. Found 180.0655.



XX

3-Furyl-5-((1′*S*)-hydroxyethyl)-4,5-dihydroisoxazole (2.26). A solution of **2.15** (200 mg, 1.12 mmol) in EtOH (3 mL) was added to a warmed (35 °C) mixture of Baker's yeast (5.6 g) in water (33 mL) containing KH_2PO_4 (66 mg), Na_2HPO_4 (33 mg), $MgSO_4$ (33 mg) and glucose (10 g). After stirring for 2 h at 35 °C, the reaction mixture was filtered through Celite® 545 and the precipitate was washed thoroughly with EtOAc. The filtrate was separated and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (4:1 to 3:2 hexanes–EtOAc) to yield **2.26** (170 mg, 84%) as a colorless oil (diastereomeric mixture, 1:1). R_f 0.30 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.52–7.51 (m, 1 H, H-4 furyl), 6.73–6.71 (m, 1 H, H-2 furyl), 6.50–6.48 (m, 1 H, H-3 furyl), 4.63 (ddd, 0.5 H, $J_{1',5}$ = 3.3 Hz, $J_{4a,5}$ = 8.6 Hz, $J_{4b,5}$ = 10.8 Hz, H-5), 4.56 (ddd, 0.5 H, $J_{1',5}$ = 5.5 Hz, $J_{4a,5}$ = 7.7 Hz, $J_{4b,5}$ = 10.6 Hz, H-5), 4.13 (dq, 0.5 H, $J_{1',5}$ = 3.3 Hz, $J_{1',2'}$ = 6.6 Hz, H-1'), 3.82–3.76

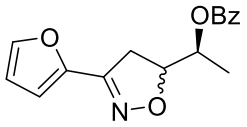
(m, 0.5 H, H-1'), 3.40–3.33 (m, 0.5 H, H-4), 3.24–3.13 (m, 0.5 H, H-4), 2.30–1.96 (br, 1 H, OH), 1.28 (d, 1.5 H, $J_{1',2'}$ = 6.6 Hz, H-2'), 1.21 (d, 1.5 H, $J_{1',2'}$ = 6.4 Hz, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 149.3 (C=N), 149.2 (C=N), 144.7 (C-1 furyl), 144.6 (C-1 furyl), 144.4(3) (C-4 furyl), 144.3(8) (C-4 furyl), 111.9(8) (C-2 furyl), 111.9(7) (C-2 furyl), 111.7(4) (C-3 furyl), 111.6(9) (C-3 furyl), 84.9 (C-5), 84.5 (C-5), 69.1 (C-1′), 67.0 (C-1′), 36.9 (C-4), 34.1 (C-4), 19.0 (C-2′), 18.0 (C-2′). HRMS (ESI) Calcd for $[M + H]^+$ $C_9H_{12}NO_3$: 182.0812. Found 182.0812.



2.28

3-Furyl-5-(((1′*S*)-*O*-acetyl)-hydroxyethyl)-4,5-dihydroisoxazole (2.28). Acetic anhydride (200 µL, 2.09 mmol) was added to a solution of **2.26** (126 mg, 0.695 mmol) in pyridine (2 mL). After stirring overnight at rt, the solvent was evaporated and the resulting crude product was purified by silica gel column chromatography (9:1 to 7:3 hexanes–EtOAc) to yield **2.28** (126 mg, 81%) as a colorless oil (diastereomeric mixture, 1:1). R_f 0.46 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.52–7.51 (m, 1 H, H-4 furyl), 6.73–6.72 (m, 1 H, H-2 furyl), 6.50–6.48 (m, 1 H, H-3 furyl), 5.09–5.02 (m, 1 H, H-1'), 4.77–4.68 (m, 1 H, H-5), 3.82–3.76 (m, 0.5 H, H-4), 3.40–3.31 (m, 1 H, H-4), 3.20–3.07 (m, 0.5 H, H-4), 2.04 (s, 1.5 H, C=OCH_3), 2.03 (s, 1.5 H, C=OCH_3), 1.30 (d, 1.5 H, $J_{1',2'}$ = 6.4 Hz, H-2') 1.28 (d, 1.5 H, $J_{1',2'}$ = 6.4 Hz, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.5 (C=O), 170.3 (C=O), 148.6 (C=N), 148.4 (C=N), 144.6 (C-1 furyl), 144.6 (C-1 furyl), 144.4(0) (C-4 furyl), 144.3(9) (C-4 furyl), 111.8(3) (C-2 furyl), 111.7(8) (C-2 furyl), 111.7 (C-3 furyl), 82.1 (C-5), 81.4 (C-5), 70.6 (C-1′), 70.4 (C-1′), 36.5(4) (C-4), 36.4(5) (C-4), 21.2

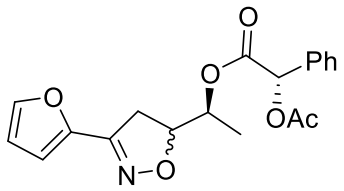
(C=O<u>C</u>H$_3$), 21.1 (C=O<u>C</u>H$_3$), 15.6 (C-2′). HRMS (ESI) Calcd for [M + Na]$^+$ $C_{11}H_{13}NNaO_4$: 246.0737. Found 246.0732.



2.29

3-Furyl-5-(((1′*S*)-*O*-benzoate)-hydroxyethyl)-4,5-dihydroisoxazole (2.29). Benzoyl chloride (153 µL, 1.32 mmol) was added to a cooled (0 °C) solution of **2.26** (160 mg, 0.883 mmol) in pyridine (4 mL). After stirring overnight at rt, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous solution of $NaHCO_3$. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 to 4:1 hexanes–EtOAc) to yield **2.29** (206 mg, 82%) as a colorless oil (diastereomeric mixture, 1:1). R_f 0.49 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.01–7.97 (m, 2 H, Ar), 7.57–7.49 (m, 2 H, H-4 furyl, Ar) 7.43–7.37 (m, 2 H, Ar), 6.75 (d, 0.5 H, $J_{2fur,3fur}$ = 3.5 Hz, H-2 furyl), 6.71 (d, 0.5 H, $J_{2fur,3fur}$ = 3.5 Hz, H-2 furyl), 6.51 (dd, 0.5 H, $J_{3fur,4fur}$ = 1.8 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-3 furyl), 6.46 (dd, 0.5 H, $J_{3fur,4fur}$ = 1.8 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-3 furyl), 5.31–5.25 (m, 1 H, H-1'), 4.92–4.83 (m, 1 H, H-5), 3.45 (dd, 0.5 H, $J_{4a,5}$ = 11.0 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4a), 3.32 (dd, 0.5 H, $J_{4a,5}$ = 11.1 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4b), 3.30 (dd, 0.5 H, $J_{4b,5}$ = 7.2 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4b), 3.19 (dd, 0.5 H, $J_{4b,5}$ = 7.2 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4b), 1.46 (d, 1.5 H, $J_{1',2'}$ = 6.6 Hz, H-2'), 1.42 (d, 1.5 H, $J_{1',2'}$ = 6.4 Hz, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 165.8 (C=O), 148.7 (C=N), 148.4 (C=N), 144.7 (C-1 furyl), 144.6 (C-1 furyl), 144.5 (C-4 furyl), 144.4 (C-4 furyl), 133.1 (Ar), 130.0 (Ar), 129.9 (Ar), 129.7(2) (Ar), 129.6(9) (Ar), 128.3(8) (Ar), 128.3(6) (Ar), 111.9 (C-2 furyl), 111.8(3) (C-2 furyl), 111.7(7) (C-3 furyl), 111.7 (C-3 furyl),

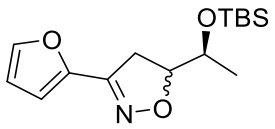
82.2 (C-5), 81.5 (C-5), 71.5 (C-1′), 71.4 (C-1′), 36.8 (C-4), 36.2 (C-4), 15.9 (C-2′), 15.8 (C-2′). HRMS (ESI) Calcd for $[M + H]^+$ $C_{16}H_{16}NO_4$: 286.1074. Found 286.1076.



2.30

3-Furyl-5-((1′*S*)-(*O*-((*S*)-*O*-acetylphenylacetate)hydroxyethyl)-4,5-dihydroisoxazole (2.30). A solution of DCC (109 mg, 0.531 mmol) in CH_2Cl_2 (2 mL) was added to a cooled (0 °C) solution of **2.26** (77 mg, 0.425 mmol), DMAP (26 mg, 0.220 mmol) and (*S*)-(+)-*O*-acetylmandelic acid (103 mg, 0.531 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 3 h, then filtered through a short pad of silica. The silica was rinsed with EtOAc and the filtrate was evaporatedconcentrated. The resulting crude product was purified by silica gel column chromatography (4:1 hexanes–EtOAc) to yield **2.30** (147 mg, 97%) as a colourless oil (diastereomeric mixture, 1:1). R_f 0.39 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.51 (d, 1 H, $J_{3fur,4fur}$ = 1.7 Hz, H-4 furyl), 7.44–7.38 (m, 2 H, Ar), 7.36–7.32 (m, 1.5 H, Ar), 7.25–7.20 (m, 1.5 H, Ar), 6.57 (d, 1 H, $J_{2fur,3fur}$ = 3.5 Hz, H-2 furyl), 6.49 (dd, 0.5 H, $J_{3fur,4fur}$ = 1.8 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-3 furyl), 6.48 (dd, 0.5 H, $J_{3fur,4fur}$ = 1.8 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-3 furyl), 5.88 (s, 0.5 H, C<u>H</u>Ph), 5.85 (s, 0.5 H, C<u>H</u>Ph), 5.08-5.03 (m, 1 H, H-1'), 4.65 (ddd, 0.5 H, $J_{1',5}$ = 3.1 Hz, $J_{4a,5}$ = 7.9 Hz, $J_{4b,5}$ = 11.4 Hz, H-5), 4.55 (ddd, 0.5 H, $J_{1',5}$ = 5.3 Hz, $J_{4a,5}$ = 7.5 Hz, $J_{4b,5}$ = 11.0 Hz, H-5), 3.12 (dd, 0.5 H, $J_{4b,5}$ = 11.4 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4b), 3.07 (dd, 0.5 H, $J_{4b,5}$ = 11.0 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4b), 2.84 (dd, 0.5 H, $J_{4a,5}$ = 7.5 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4a), 2.68 (dd, 0.5 H, $J_{4a,5}$ = 7.9 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4a), 2.18 (s, 1.5 H, C(=O)CH_3), 2.11 (s, 1.5 H, C(=O)CH_3), 1.40 (d, 1.5 H, $J_{1',2'}$ = 6.4 Hz, H-2'), 1.34 (d, 3 H, $J_{1',2'}$ = 6.4 Hz, H-2'). ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.4 (C=O),

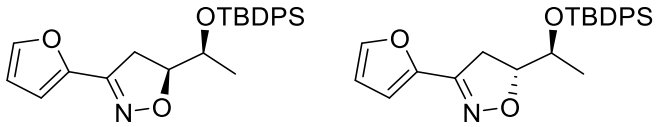
168.5 (C=O), 168.1 (C=O), 148.2 (C=N), 148.1 (C=N), 144.5 (C-1 furyl), 144.3 (C-4 furyl), 144.1 (C-4 furyl), 133.6 (Ar), 133.5 (Ar), 129.2 (Ar), 129.1 (Ar), 128.8 (Ar), 128.7 (Ar), 127.5 (Ar), 127.3 (Ar), 111.9 (C-2 furyl), 111.8 (C-2 furyl), 111.7(2) (C-3 furyl), 111.6(8) (C-3 furyl), 81.9 (C-5), 81.0 (C-5), 74.6(3) (CHOAc), 74.6(0) (CHOAc), 71.8(1) (C-1′), 71.7(8) (C-1′), 36.2 (C-4), 36.1 (C-4), 20.7 ($C{=}OCH_3$), 20.5 ($C{=}OCH_3$), 16.2 (C-2′), 15.9 (C-2′). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{19}H_{19}NNaO_6$: 380.1105. Found 380.1102.



2.31

3-Furyl-5-(((1′*S*)-*O*-*tert*-butyldimethylsilyl)-hydroxyethyl)-4,5-dihydroisoxazole (2.31). Imidazole (128 mg, 1.89 mmol) and TBSCl (142 mg, 0.944 mmol) were added to a cooled (0 °C) solution of **2.26** (114 mg, 0.629 mmol) in DMF (1.5 mL). The ice bath was removed and the reaction mixture was stirred for 3 h at rt. EtOAc and water were added to the mixture and the layers were separated. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to yield **2.31** (116 mg, 62%) as colorless oil (diastereomeric mixture, 1:1). R_f 0.54 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.51–7.50 (m, 1 H, H-4 furyl), 6.71–6.69 (m, 1 H, H-2 furyl), 6.49–6.47 (m, 1 H, H-3 furyl), 4.64 (ddd, 0.5 H, $J_{1',5}$ = 5.1 Hz, $J_{4a,5}$ = 7.7 Hz, $J_{4b,5}$ = 10.8 Hz, H-5), 4.52 (ddd, 0.5 H, $J_{1',5}$ = 3.9 Hz, $J_{4a,5}$ = 7.7 Hz, $J_{4b,5}$ = 10.8 Hz, H-5), 4.04–3.96 (m, 1 H, CH-OTBS), 3.35 (dd, 0.5 H, $J_{4a,5}$ = 7.7 Hz, $J_{4a,4b}$ = 16.7 Hz, H-4a), 3.27–3.15 (m, 1.5 H, H-4), 1.17 (d, 1.5 H, $J_{1',2'}$ = 6.4 Hz, H-2') 1.15 (d, 1.5 H, $J_{1',2'}$ = 6.2 Hz, H-2'), 0.87 (s, 4.5 H, *t*-Bu), 0.83 (s, 4.5 H, *t*-Bu), 0.08 (s, 1.5 H, Si-CH_3), 0.08 (s, 1.5 H, Si-CH_3), 0.07 (s, 1.5 H, Si-CH_3), 0.04 (s, 1.5 H,

Si-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 148.6 (C=N), 145.3 (C-1 furyl), 145.1 (C-1 furyl), 144.1(4) (C-4 furyl), 144.0(8) (C-4 furyl), 111.6 (C-2 furyl), 111.5 (C-2 furyl), 111.4 (C-3 furyl), 111.2 (C-3 furyl), 85.2 (C-5), 83.9 (C-5), 68.8 (C-1′), 68.5 (C-1′), 35.5 (C-4), 34.7 (C-4), 25.7(4) (SiC($\underline{C}H_3)_3$), 25.7(0) (SiC($\underline{C}H_3)_3$), 20.5 (C-2′), 18.1 (Si$\underline{C}(CH_3)_3$), 18.0(2) (C-2′), 17.9(6)(Si$\underline{C}(CH_3)_3$), –4.5(5) (Si$\underline{C}H_3$), –4.5(7) (Si$\underline{C}H_3$), –4.8 (Si$\underline{C}H_3$). HRMS (ESI) Calcd for [M + Na]$^+$ $C_{15}H_{25}NNaO_4Si$: 318.1496. Found 318.1491.

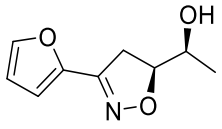


2.32a **2.32b**

(5*S*)-((1′*S*)-(*O*-(*tert*-Butyldiphenylsilyl)hydroxyethyl)-3-furyl-4,5-dihydroisoxazole (2.32a) and (5*R*)-((1′*S*)-(*O*-(*tert*-Butyldiphenylsilyl)hydroxyethyl)-3-furyl-4,5-dihydroisoxazole (2.32b). *tert*-Butyl(chloro)diphenylsilane (487 μL, 1.87 mmol) and imidazole (294 mg, 4.32 mmol) were added to a solution of **2.26** (261 mg, 1.44 mmol) in DMF (4 mL). The reaction mixture was stirred at rt overnight. Water was added and the aqueous solution was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to yield **2.32a** (253 mg, 42%) and **2.32b** (247 mg, 41%) as colorless oils. (**2.32a**): R_f 0.36 (9:1 hexanes–EtOAc); $[\alpha]_D$ +37.4 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.70–7.67 (m, 4 H, Ar), 7.52 (dd, 1 H, $J_{2fur,4fur}$ = 0.7 Hz, $J_{3fur,4fur}$ = 1.8 Hz, H-4 furyl), 7.44–7.35 (m, 6 H, Ar), 6.72 (d, 1 H, $J_{2fur,3fur}$ = 3.5 Hz, H-2 furyl), 6.50 (dd, 1 H, $J_{3fur,4fur}$ = 1.8 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-3 furyl), 4.66 (ddd, 1 H, $J_{1',5}$ = 4.6 Hz, $J_{4a,5}$ = 7.7 Hz, $J_{4b,5}$ = 11.0 Hz, H-5), 4.05 (dq, 1 H, $J_{1',5}$ = 4.6 Hz, $J_{1',2'}$ = 6.4 Hz, H-1′), 3.32 (dd, 1 H, $J_{4a,5}$ = 7.7 Hz, $J_{4a,4b}$ = 17.0 Hz, H-4a), 3.25 (dd, 1 H, $J_{4b,5}$ = 11.0 Hz, $J_{4a,4b}$ = 17.0 Hz, H-4b),

1.08 (d, 3 H, $J_{1',2'}$ = 6.4 Hz, H-2'), 1.05 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 148.6 (C=N), 145.0(7) (C-1 furyl), 145.0(6) (C-4 furyl), 135.9 (Ar), 135.8 (Ar), 134.8 (Ar), 134.0 (Ar), 133.6 (Ar), 129.8 (Ar), 129.7(3) (Ar), 129.6(6) (Ar), 127.7(3) (Ar), 127.7(1) (Ar), 111.6 (C-2 furyl), 111.5 (C-3 furyl), 83.3 (C-5), 69.5 (C-1′), 35.4 (C-4), 25.9 (SiC($\underline{C}H_3$)$_3$), 19.3 (Si$\underline{C}$(CH_3), 17.5 (C-2′). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{25}H_{29}NNaO_3Si$: 442.1809. Found 442.1806.

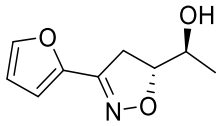
(**2.32b**): R_f 0.39 (2:1 hexanes–EtOAc); $[\alpha]_D$ −76.2 (*c* 1.6, $CHCl_3$); 7.74–7.71 (m, 2 H, Ar), 7.69–7.67 (m, 2 H, Ar), 7.52 (dd, 1 H, $J_{2fur,4fur}$ = 0.7 Hz, $J_{3fur,4\ fur}$ = 1.8 Hz, H-4 furyl), 7.44–7.35 (m, 6 H, Ar), 6.68 (d, 1 H, $J_{2fur,3fur}$ = 3.5 Hz, H-2 furyl), 6.50 (dd, 1 H, $J_{3fur,4fur}$ = 1.8 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-3 furyl), 4.56 (ddd, 1 H, $J_{1',5}$ = 3.9 Hz, $J_{4a,5}$ = 7.7 Hz, $J_{4b,5}$ = 10.8 Hz, H-5), 4.10 (dq, 1 H, $J_{1',5}$ = 3.9 Hz, $J_{1',2'}$ = 6.4 Hz, H-1′), 3.41 (dd, 1 H, $J_{4a,5}$ = 7.7 Hz, $J_{4a,4b}$ = 16.5 Hz, H-4a), 3.24 (dd, 1 H, $J_{4b,5}$ = 10.8 Hz, $J_{4a,4b}$ = 16.5 Hz, H-4b), 1.03 (d, 3 H, $J_{1',2'}$ = 6.4 Hz, H-2'), 1.02 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 148.6 (C=N), 145.3 (C-1 furyl), 144.1 (C-4 furyl), 136.8 (Ar), 135.9 (Ar), 134.8 (Ar), 134.5 (Ar), 133.2 (Ar), 129.7 (Ar), 129.6 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 111.6 (C-2 furyl), 111.3 (C-3 furyl), 85.3 (C-5), 69.7 (C-1′), 35.2 (C-4), 26.9 (SiC($\underline{C}H_3$)$_3$), 20.0 (C-2′), 19.3 (Si$\underline{C}$(CH_3)$_3$). HRMS (ESI) Calcd for $[M + H]^+$ $C_{25}H_{30}NO_3Si$: 420.1989. Found 420.1986.



2.26a

(5*S*)-3-Furyl-((1′*S*)-hydroxymethyl)-4,5-dihydroisoxazole (2.26a). A solution of TBAF (1.0 M in THF, 1.16 mL, 1.16 mmol) was added to a solution of **2.32a** (324 mg, 0.772 mmol) in THF (3 mL). The reaction mixture was stirred at rt for 30 min and an saturated aqueous solution of NH_4Cl

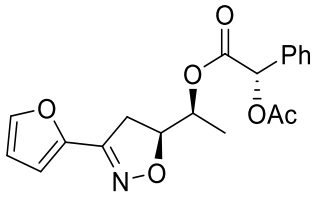
was added. The aqueous solution was extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (7:3 hexanes–EtOAc) to yield **2.26a** (105 mg, 75%) as a white solid. mp = 47−49 °C; R_f 0.30 (3:2 hexanes–EtOAc); $[\alpha]_D$ +149.4 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.53 (dd, 1 H, $J_{2fur,4fur}$ = 0.6 Hz, $J_{3fur,4fur}$ = 1.7 Hz, H-4 furyl), 6.74 (d, 1 H, $J_{2fur,3fur}$ = 3.3 Hz, H-2 furyl), 6.50 (dd, 1 H, $J_{3fur,4fur}$ = 1.7 Hz, $J_{2fur,3fur}$ = 3.3 Hz, H-3 furyl), 4.57 (ddd, 1 H, $J_{1',5}$ = 5.5 Hz, $J_{4a,5}$ = 7.5 Hz, $J_{4b,5}$ = 10.9 Hz, H-5), 3.80 (ddd, 1 H, $J_{1',5}$ = 5.5 Hz, $J_{1',OH}$ = 5.9 Hz, $J_{1',2'}$ = 6.4 Hz, H-1′), 3.37 (dd, 1 H, $J_{4b,5}$ = 10.8 Hz, $J_{4a,4b}$ = 16.7 Hz, H-4b), 3.17 (dd, 1 H, $J_{4a,5}$ = 7.5 Hz, $J_{4a,4b}$ = 16.7 Hz, H-4a), 2.27 (d, 1H, $J_{1',OH}$ = 5.9 Hz, OH), 1.30 (d, 3 H, $J_{1',2'}$ = 6.4 Hz, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 149.3 (C=N), 144.7 (C-1 furyl), 144.4 (C-4 furyl), 112.0 (C-2 furyl), 111.8 (C-3 furyl), 84.5 (C-5), 69.1 (C-1′), 37.0 (C-4), 19.0 (C-2′). HRMS (EI) Calcd for [$M^{+\bullet}$] $C_9H_{11}NO_3$: 181.0739. Found 181.0740.



2.26b

(5*R*)-3-Furyl-((1′*S*)-hydroxymethyl)-4,5-dihydroisoxazole (2.26b). A solution of TBAF (1.0 M in THF, 218 µL, 0.218 mmol) was added to a solution of **2.32b** (61 mg, 0.145 mmol) in THF (1 mL). The reaction mixture was stirred at rt for 30 min and an saturated aqueous solution of NH_4Cl was added. The aqueous solution was extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (7:3 hexanes–EtOAc) to yield **2.26b** (20 mg, 77%) as a white solid. mp = 77−78 °C; R_f 0.30 (3:2 hexanes–EtOAc); $[\alpha]_D$ −132.0 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.52–7.50 (m, 1 H, H-4 furyl), 6.71 (d, 1 H, $J_{2fur,3fur}$ = 3.3 Hz, H-2 furyl), 6.49–6.47 (m, 1 H, H-3

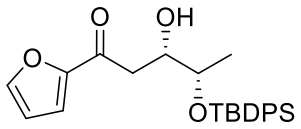
furyl), 4.64–4.59 (m, 1 H, H-5), 4.15–4.09 (m, 1 H, H-1′), 3.37 (dd, 1 H, $J_{4a,5}$ = 8.1 Hz, $J_{4a,4b}$ = 16.7 Hz, H-4a), 3.21 (dd, 1 H, $J_{4b,5}$ = 10.8 Hz, $J_{4a,4b}$ = 16.7 Hz, H-4b), 2.12 (br, 1H, OH), 1.21 (d, 3 H, $J_{1',2'}$ = 6.6 Hz, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 149.4 (C=N), 144.8 (C-1 furyl), 144.4 (C-4 furyl), 112.0 (C-2 furyl), 111.7 (C-3 furyl), 84.9 (C-5), 67.0 (C-1′), 34.1 (C-4), 18.0 (C-2′). HRMS (EI) Calcd for [$M^{+\bullet}$] $C_9H_{11}NO_3$: 181.0739. Found 181.0740.



2.33

(5*S*)-3-Furyl-((1′*S*)-((*O*)-(*S*)-acetylphenylacetate))-hydroxymethyl)-4,5-dihydroisoxazole (2.33). A solution of DCC (113 mg, 0.550 mmol) in CH_2Cl_2 (2 mL) was added to a cooled (0 °C) solution of **2.26a** (80 mg, 0.440 mmol), DMAP (27 mg, 0.220 mmol) and (*S*)-(+)-*O*-acetylmandelic acid (107 mg, 0.550 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at rt for 3 h and filtered through a silica plug. The silica plug was rinsed with EtOAc and the filtrate was evaporated. The resulting crude product was purified by silica gel column chromatography (4:1 hexanes–EtOAc) to yield **2.33** (155 mg, 98%) as a white solid. mp = 75−76 °C; R_f 0.39 (3:2 hexanes–EtOAc); $[\alpha]_D$ +172.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.51 (d, 1 H, $J_{2fur,4fur}$ = 0.7 Hz, $J_{3fur,4fur}$ = 1.8 Hz, H-4 furyl), 7.42–7.40 (m, 2 H, Ar), 7.25–7.20 (m, 3 H, Ar), 6.58 (d, 1 H, $J_{2fur,4fur}$ = 0.7 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-2 furyl), 6.51 (dd, 1 H, $J_{3fur,4fur}$ = 1.8 Hz, $J_{2fur,3fur}$ = 3.5 Hz, H-3 furyl), 5.87 (s, 1 H, C<u>H</u>Ph), 5.09 (dq, 1 H, $J_{1',5}$ = 3.1 Hz, $J_{1',2'}$ = 6.4 Hz, H-1′), 4.67 (ddd, 1 H, $J_{1',5}$ = 3.1 Hz, $J_{4a,5}$ = 7.9 Hz, $J_{4b,5}$ = 11.6 Hz, H-5), 3.14 (dd, 1 H, $J_{4b,5}$ = 11.6 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4b), 2.70 (dd, 1 H, $J_{4a,5}$ = 7.9 Hz, $J_{4a,4b}$ = 16.9 Hz, H-4a), 2.13 (s, 3 H, C(=O)CH_3), 1.42 (d, 3 H, $J_{1',2'}$ = 6.4 Hz, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.4 (C=O), 168.6 (C=O),

148.2 (C=N), 144.5 (C-1 furyl), 144.3 (C-4 furyl), 133.5 (Ar), 129.1 (Ar), 128.7 (Ar), 127.3 (Ar), 111.8 (C-2 furyl), 111.7 (C-3 furyl), 81.0 (C-5), 74.6 (CHOAc), 71.8 (C-1′), 36.2 (C-4), 20.5 (C(=O)$\underline{C}H_3$), 15.9 (C-2′). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{19}H_{23}N_2O_6$: 375.1551. Found 375.1551.



2.34

(3*S*,4*S*)-4-*O*-(*tert*-Butyldiphenylsilyl)-1-(2-furyl)-3,4-dihydroxypentan-1-one (2.34). Freshly prepared Raney nickel (an amount that fits on the tip of a spatula) was added to a solution of **2.32a** (65 mg, 0.155 mmol) and boric acid (11 mg, 0.170 mmol) in CH_3OH (3.5 mL) and H_2O (0.5 mL). After stirring under H_2 atmosphere for 20 h, the reaction mixture was filtered and the filtrate was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to yield **2.34** (31 mg, 47%) as a colorless oil. R_f 0.37 (4:1 hexanes–EtOAc); $[\alpha]_D$ –48.9 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.70–7.67 (m, 4 H, Ar), 7.60 (dd, 1 H, $J_{2fur,4fur}$ = 0.7 Hz, $J_{3fur,4fur}$ = 1.7 Hz, H-4 furyl), 7.46–7.35 (m, 6 H, Ar), 7.18 (dd, 1 H, $J_{2fur,4fur}$ = 0.7 Hz, $J_{2fur,3fur}$ = 3.7 Hz, H-2 furyl), 6.55 (dd, 1 H, $J_{3fur,4fur}$ = 1.7 Hz, $J_{2fur,3fur}$ = 3.7 Hz, H-3 furyl), 4.15–4.11 (m, 1 H, H-3), 3.94 (app dq, 1 H, $J_{3,4}$ = 4.4 Hz, $J_{4,5}$ = 6.4 Hz, H-4), 3.04 (dd, 1 H, $J_{2,3}$ = 3.9 Hz, $J_{2,2'}$ = 16.3 Hz, H-2), 2.98 (dd, 1 H, $J_{2,3}$ = 8.6 Hz, $J_{2,2}$ = 16.3 Hz, H-2′), 2.82 (d, 1H, J = 4.9 Hz, OH), 1.12 (d, 3 H, $J_{4,5}$ = 6.3 Hz, H-5), 1.09 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 188.7 (C=O), 152.8 (C-1 furyl), 146.6 (C-4 furyl), 135.9 (Ar), 135.8 (Ar), 134.0 (Ar), 133.5 (Ar), 129.9 (Ar), 129.8 (Ar), 127.8 (Ar), 127.6 (Ar), 117.6 (C-2 furyl), 112.3 (C-3 furyl), 71.6(3) (C-3), 71.6(1) (C-4),

40.8 (C-2), 27.1 (SiC($\underline{C}H_3)_3$), 19.4 (Si$\underline{C}(CH_3)_3$), 18.7 (C-5). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{25}H_{30}NaO_4Si$: 445.1806. Found 445.1802.

2.5 References

(1) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. Modern Methods of Monosaccharide Synthesis from Non-Carbohydrate Sources, *Chem. Rev.* **1996**, *96*, 1195.

(2) Deska, J.; Thiel, D.; Gianolio, E. The Achmatowicz Rearrangement - Oxidative Ring Expansion of Furfuryl Alcohols. *Synth.* **2015**, *47*, 3435–3450.

(3) Achmatowicz Jr., O.; Bielski, R. Stereoselective Total Synthesis of Methyl α-D- and α-L-Glucopyranosides. *Carbohydr. Res.* **1977**, *55*, 165–176.

(4) Taniguchi, T.; Nakamura, K.; Ogasawara, K. Non-Carbohydrate Route to Levoglucosenine and Its Enantiomer Employing Asymmetric Dihydroxylation. *Synlett* **1996**, 971–972.

(5) Harris, J. M.; Keränen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. Syntheses of Four D- and L-Hexoses via Diastereoselective and Enantioselective Dihydroxylation Reactions. *Carbohydr. Res.* **2000**, *328*, 17–36.

(6) Ticozzi, C.; Zanarotti, A. Baker's Yeast Reduction of 5-Acetyl-2-Isoxazolines Synthesis of Enantiomerically Pure 2,3-Dihydroxy Ketones and 1,2,4-Triols. *Tetrahedron Lett.* **1988**, *29*, 6167–6170.

(7) Belen'kii, L. I. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*; *Second Edition*; Henry Feuer, Ed. John Wiley & Sons, Inc.: 2008; pp 1-107.

(8) Goto, G.; Kawakita, K.; Okutani, T.; Miki, T. An Improved Synthesis of *N*-Hydroxyamino Acids and Their Esters Using (*Z*)-2-Furaldehyde Oxime. *Chem. Pharm. Bull.* **1986**, *34*, 3202–3207.

(9) Ghabrial, S. S.; Thomsen, I.; Torssell, K. B. G.; Synthesis of Biheteroaromatic Compounds via the Isoxazoline Route. *Acta Chemica Scandinavica*. **1987**, 426–434.

(10) Das, B.; Holla, H.; Mahender, G.; Banerjee, J.; Ravinder Reddy, M. Hypervalent Iodine-Mediated Interaction of Aldoximes with Activated Alkenes Including Baylis-Hillman Adducts: A New and Efficient Method for the Preparation of Nitrile Oxides from Aldoximes. *Tetrahedron Lett.* **2004**, *45*, 7347–7350.

(11) Diaz-Velandia, J.; Durán-Díaz, N.; Robles-Camargo, J.; Loaiza, A. E. Síntesis y Evaluación "*in vitro*" de la Actividad Antifúngica de Oximas, éteres de oxima e Isoxazoles.*Universitas Scientiarum* **2011**, *16*, 294–302.

(12) Cremonesi, G.; Dalla Croce, P.; Forni, A.; Gallanti, M.; La Rosa, C. Stereoselective Synthesis of β-Substituted-L-Threonines from Enantiopure 5-Acetyl-2-Isoxazolines. *Tetrahedron* **2011**, *67*, 2925–2933.

(13) Adkins, H.; Billica, H. R. The Preparation of Raney Nickel Catalysts and Their Use Under Conditions Comparable with Those for Platinum and Palladium Catalysts. *J. Am. Chem. Soc.* **1948**, *70*, 695–698.

(14) Han, B.; Yang, X. L.; Fang, R.; Yu, W.; Wang, C.; Duan, X. Y.; Liu, S. Oxime Radical Promoted Dioxygenation, Oxyamination, and Diamination of Alkenes: Synthesis of Isoxazolines and Cyclic Nitrones. *Angew. Chemie - Int. Ed.* **2012**, *51*, 8816–8820.

(15) Jiang, D.; Chen, Y. Reduction of Δ^2-Isoxazolines to β-Hydroxy Ketones with Iron and Ammonium Chloride as Reducing Agent. *J. Org. Chem.* **2008**, *73*, 9181–9183.

(16) Gayen, K. S.; Sengupta, T.; Saima, Y.; Das, A.; Maiti, D. K.; Mitra, A. Cu(0) Nanoparticle Catalyzed Efficient Reductive Cleavage of Isoxazoline, Carbonyl Azide and Domino Cyclization in Water Medium. *Green Chem.* **2012**, *14*, 1589–1592.

(17) Gefflaut, T.; Martin, C.; Delor, S.; Besse, P.; Veschambre, H.; Bolte, J. Deoxysugars via Microbial Reduction of 5-Acyl-Isoxazolines : Application to the Synthesis of 3-Deoxy-D-Fructose and Derivatives. *J. Org. Chem.* **2001**, *66*, 2296–2301.

(18) Baraldi, P. G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. Ring Cleavage of 3,5-Disubstituted 2-Isoxazolines by Molybdenum Hexacarbonyl and Water to β-Hydroxy Ketones. *Synthesis* **1987**, 276–278.

(19) Bode, J. W.; Carreira, E. M. Stereoselective Syntheses of Epothilones A and B via Nitrile Oxide Cycloadditions and Related Studies. *J. Org. Chem.* **2001**, *66*, 6410–6424.

(20) Procter, D. J; Flowers II, R. A.; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide*; RSC Publishing: Cambridge, UK: 2009, pp 1–204.

(21) Narasimhan, S.; Balakumar, R. Synthetic Applications of Zinc Borohydride. *Aldrichimica Acta* **1998**, *31*, 19–26.

Chapter 3: Synthesis of bradyrhizose: Route starting with *myo*-inositol

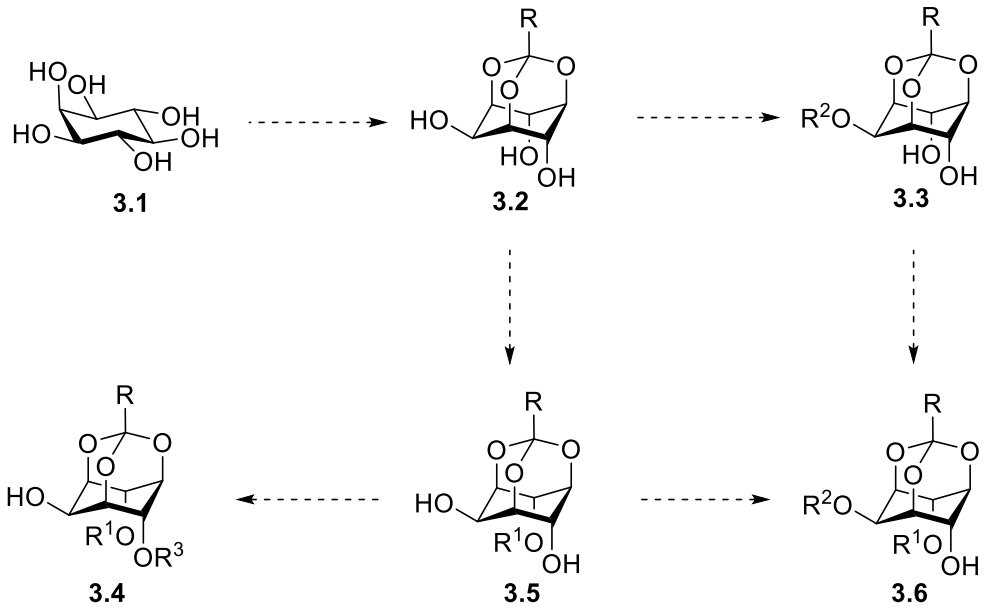
The second route I designed for the synthesis of bradyrhizose was inspired by the work of Dr. M. S. Shashidhar from CSIR-National Chemical Laboratory in India. The focus of his research is the synthesis and structure of inositol derivatives and the mechanisms of reactions involving them. This chapter will discuss a route to bradyrhizose starting with *myo*-inositol, an inexpensive meso compound.

3.1 Introduction

myo-Inositol is the most abundant inositol in nature.[1] This cyclohexanehexol was first isolated by Scherer in 1850 from muscle tissue and its chemical formula was correctly reported based on elemental analysis.[1,2] The structure of *myo*-inositol was later elucidated by Posternak, and by Dangschat and Fischer, in 1942.[1,3,4] Inositol derivatives are important in biology and are mainly found in the phosphorylated form.[5] They play key roles in various biological events such as cellular signaling and anchoring of membrane proteins. Synthesizing derivatives of inositol may provide further insight to the biological functions of inositol molecules.

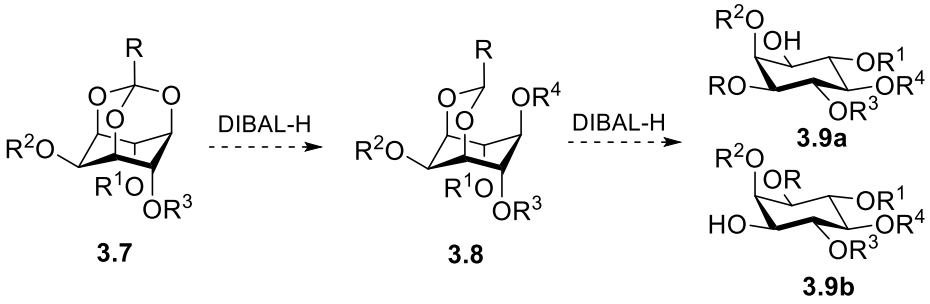
Different methods are known for synthesizing these compounds and the approach that will be discussed in this work is the derivatization of *myo*-inositol (**3.1**) (Scheme 3-1). Three of the hydroxyl groups can be protected with an orthoester to form a rigid adamantane-like structure (**3.2**).[5,6] The other hydroxyl groups can be differentiated depending on the reagent used to form the desired intermediates e.g., **3.3**, **3.4**, **3.5** or **3.6**.[5,6,7,8,9] The use of sodium and lithium bases encourage the reaction of the axial hydroxyl groups by chelation between the two hydroxyl groups

with the metal.[9,10] Reaction of the equatorial group, being more nucleophilic and less hindered, is favored by the use of a weaker base without a chelating metal. Using this approach, it is therefore possible to distinguish between the two axial and the equatorial hydroxyl groups of the *myo*-inositol orthoester **3.2**.



Scheme 3-1: Formation of di-*O*-subtituted *myo*-inositol ortho esters.[5]

In addition, the regioselective opening of the orthoester **3.7** to provide the corresponding benzylidene acetal **3.8** can be achieved using DIBAL-H (Scheme 3-2).[6,8,11] After protection of the resulting free hydroxyl group, the benzylidene acetal functionalilty in derivative **3.8** can also be opened to give orthogonally protected *myo*-inositol derivatives such as **3.9**. The synthesis of bradyrhizose I developed uses this approach for the differentiation of the hydroxyl groups in *myo*-inositol.



Scheme 3-2: Regioselective opening of orthoester **3.7** followed by reductive opening of the benzylidene acetal **3.8**.[6,8,11]

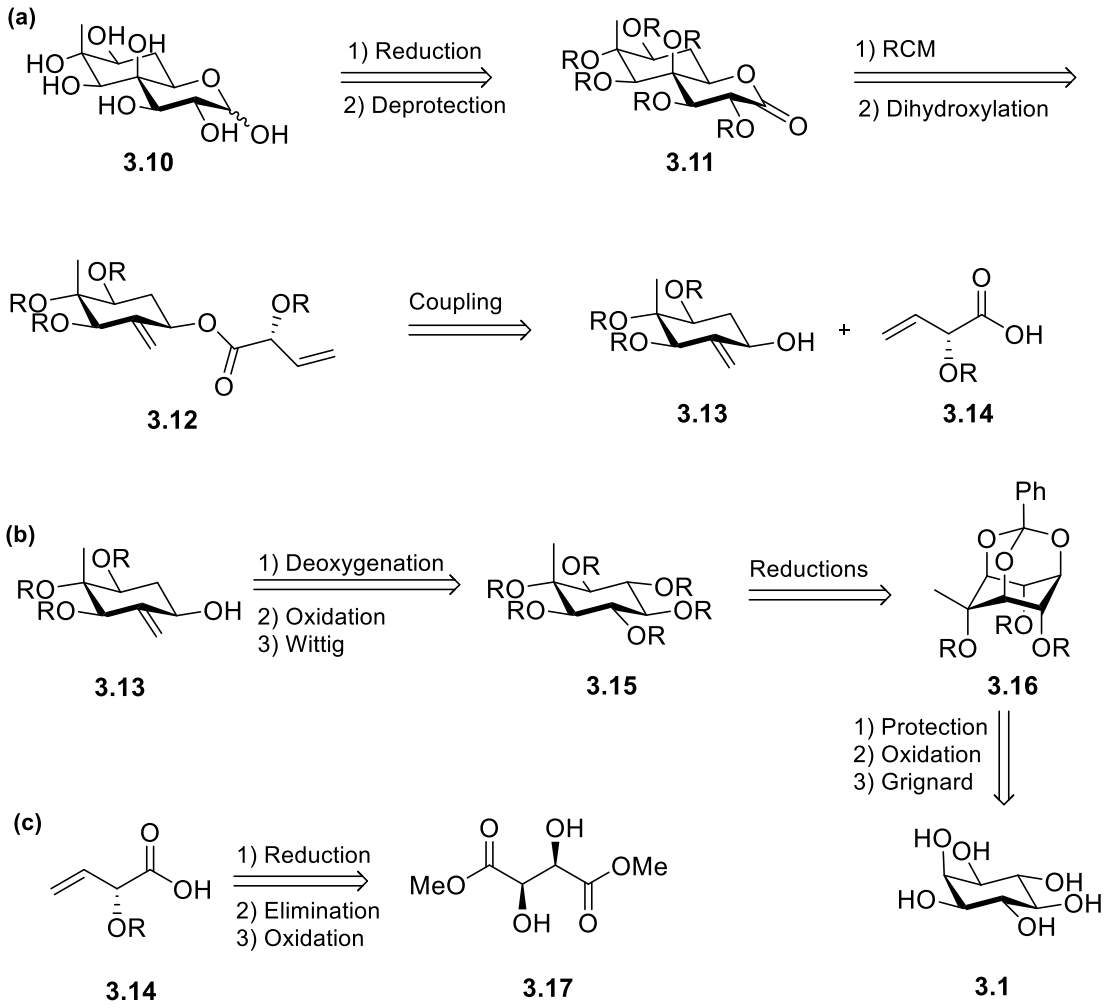
3.2 Convergent route using ring closing metathesis (RCM) and a carboxylic acid from (+)-dimethyl L-tartrate

3.2.1 Retrosynthesis

The first retrosynthesis of bradyrhizose using *myo*-inositol as the starting material (Scheme 3-3) was based on the synthetic disconnections mentioned in Chapter 1 (Scheme 1-3). As shown earlier, the monosaccharide could be made in a convergent way from *myo*-inositol and (+)-dimethyl L-tartrate. A more detailed retrosynthetic analysis is provided in Scheme 3-3.

Bradyrhizose (**3.10**) could be obtained by a reduction of lactone **3.11** to the lactol followed by a deprotection (Scheme 3-3 (a)). The lactone **3.11** could be prepared by a RCM between the two alkenes in compound **3.12** followed by an asymmetric dihydroxylation on the newly formed olefin. Intermediate **3.12** can be made by coupling of inositol derivative **3.13** and carboxylic acid **3.14**. Derivative **3.13** can be formed by several modifications of **3.15** involving a deoxygenation and an oxidation step, followed by a Wittig reaction. Intermediate **3.15** could be obtained by reductions of the orthobenzoate **3.16**. The *scyllo*-inositol compound **3.16** could be made by protection, oxidation and Grignard addition on *myo*-inositol (**3.1**). The carboxylic acid **3.14** can be

prepared by reduction of the ester, substitution and elimination followed by oxidation of (+)-dimethyl L-tartrate (**3.17**).

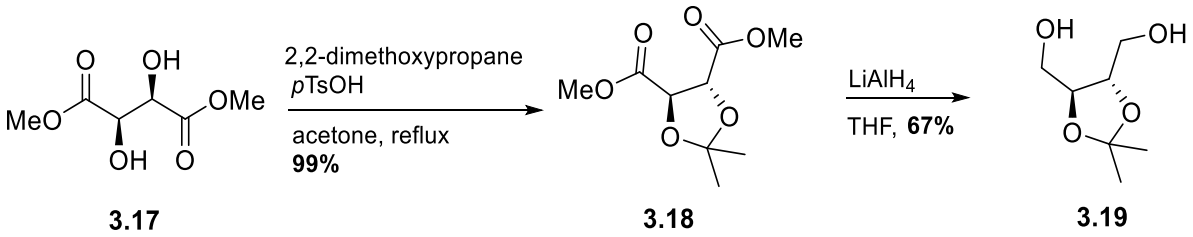


Scheme 3-3: (a) Retrosynthesis of bradyrhizose (**3.10**) from **3.13** and **3.14**. (b) Retrosynthesis of inositol moiety **3.13**. (c) Retrosynthesis of carboxylic acid **3.14**.

3.2.2 Synthesis of the carboxylic acid moiety

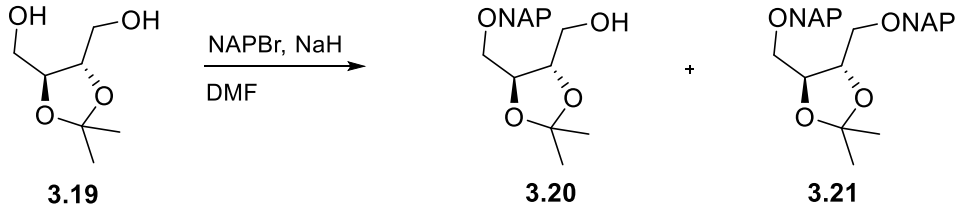
The carboxylic acid moiety was synthesized from (+)-dimethyl L-tartrate (**3.17**). The first two steps, which are known in the literature, involved the protection of the 1,2-diol using 2,2-dimethoxypropane and *p*-toluenesulfonic acid to give the desired isopropylidene acetal **3.18** in

quantitative yield (Scheme 3-4).[12] The esters were then reduced using $LiAlH_4$ to give diol **3.19** in 67% yield.



Scheme 3-4: Synthesis of diol **3.19**.[12]

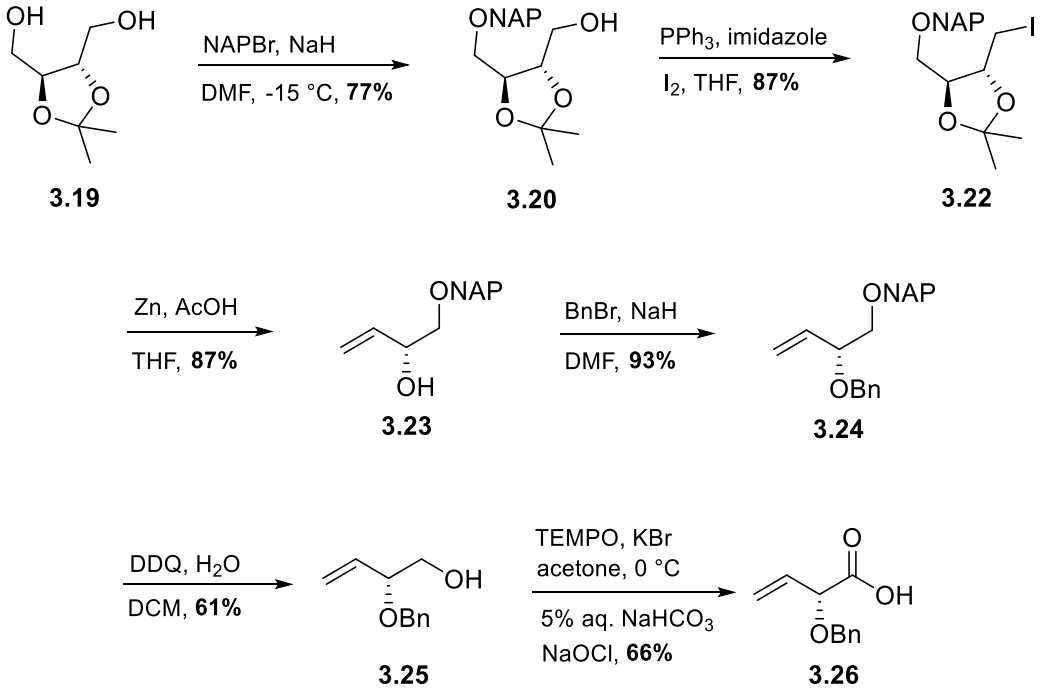
The following step towards the carboxylic acid moiety involved the protection of one of the primary hydroxyl groups with a 2-methylnaphthyl group (Scheme 3-5). At first, the reaction was attempted at 0 °C with 1.1 equivalents of the alkyl bromide, which resulted in an approximately 1:1 ratio between the mono- and di-alkyated compounds (**3.20** and **3.21**, respectively). By cooling the reaction to –15 °C (Scheme 3-6), compound **3.20** was obtained in 77% yield with only 15% of **3.21**.



Scheme 3-5: Mono- and di-alkylation of diol **3.19** using 2-(bromomethyl)naphthelene.

With compound **3.20** in hand, substitution of the free hydroxyl group with iodide to afford **3.22** proceeded under standard conditions in 87% yield (Scheme 3-6).[13] Intermediate **3.22** was then treated with zinc dust and acetic acid to produce allylic alcohol **3.23** in 87% yield. The free

hydroxyl group was protected using benzyl bromide in 93% yield (**3.24**) and the 2-methylnaphthyl group was removed using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give **3.25** in 61% yield. Finally, the primary hydroxyl group was oxidized to the carboxylic acid using TEMPO, potassium bromide and sodium hypochlorite to afford the desired compound **3.26** in 66% yield.[14] In summary, the carboxylic acid **3.26** was synthesized in eight steps from (+)-dimethyl L-tartrate (**3.17**) with an overall yield of 15%.

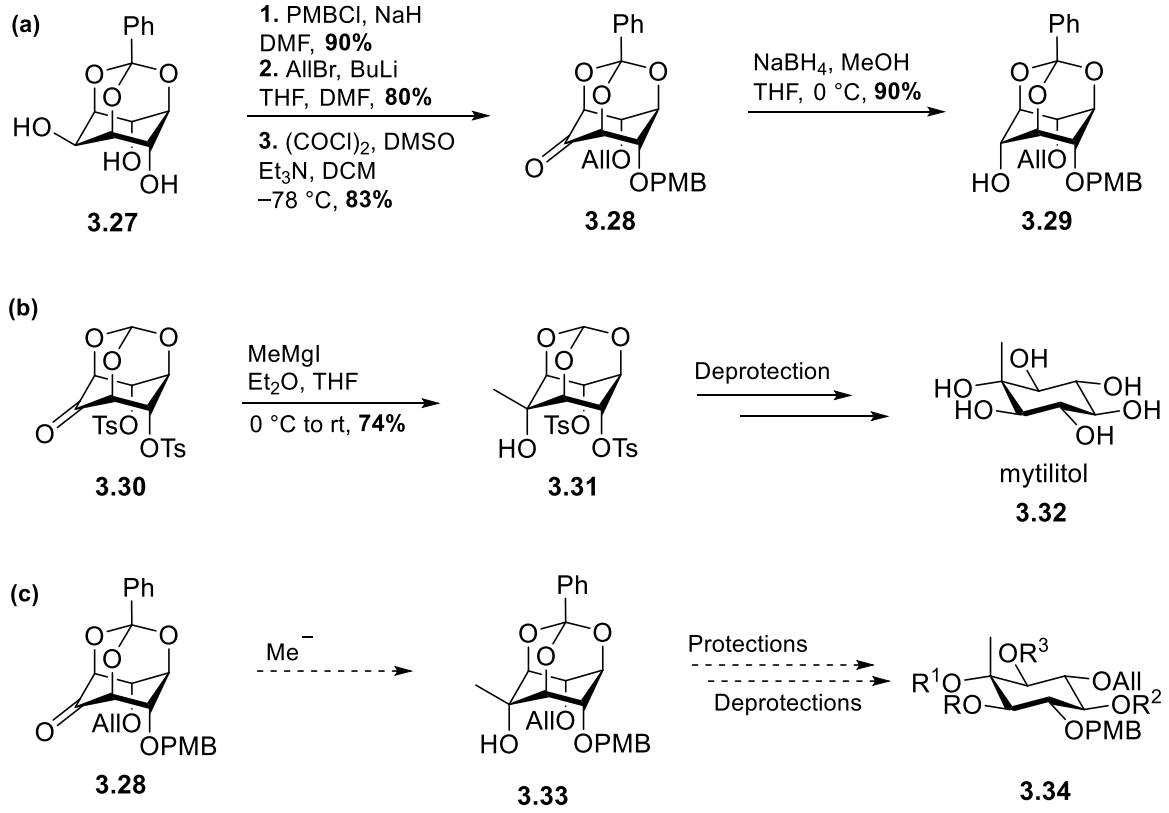


Scheme 3-6: Synthesis of the carboxylic acid **3.26**.

3.2.3 Synthesis of the inositol derivative

The design of this route to bradyrhizose was adapted by the work of Shashidhar and co-workers (Scheme 3-7 (a) and (b)), starting from *myo*-inositol orthoesters (**3.27** and **3.30**).[6] In the first example (Scheme 3-7 (a)), they protected the two axial hydroxyl groups in **3.27** with p-methoxybenzyl (PMB) and allyl groups then oxidized the remaining equatorial hydroxyl group to

afford the ketone **3.28** in good yield (60% over three steps). Afterwards, the reduction of the ketone **3.28** using sodium borohydride gave the *scyllo*-inositol derivative **3.29** (equatorial attack from the hydride). In the second example, shown in Scheme 3-7 (b), they used methylmagnesium iodide to add a methyl group to the ketone **3.30** and they obtained the methyl in the equatorial position.[15,16] After deprotection, they obtained mytilitol (**3.32**), a natural inositol derivative occurring in marine algae, which has an axial methyl group and a *scyllo* configuration (Scheme 3-7 (b)).

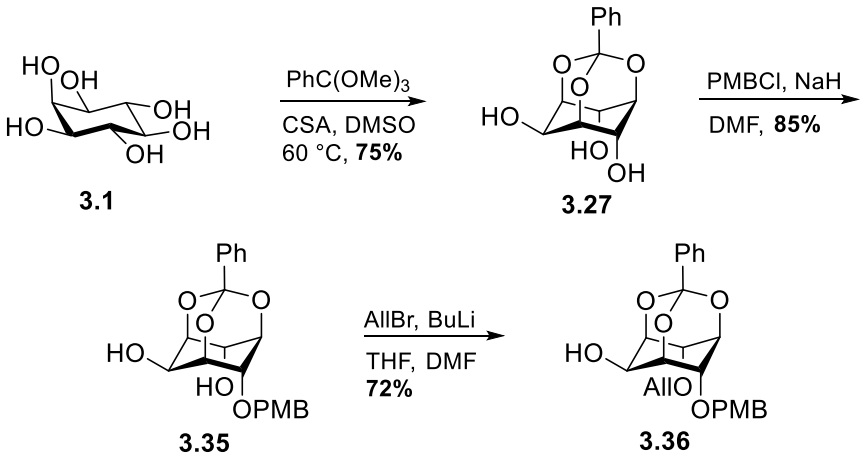


Scheme 3-7: (a) Synthesis of *scyllo*-inositol derivative **3.29** by Shashidhar and co-workers.[6] (b) Synthesis of mytilitol (**3.32**) by Shashidhar and co-workers.[15,16] (c) Hypothesis for introduction of the methyl group, required to access bradyrhizose.

By adding a methyl group to the ketone **3.28**, the *scyllo*-inositol derivative **3.33**, with the methyl group in the equatorial position (Scheme 3-7 (c)) should be obtained. Further protection

and deprotection steps should give an orthogonally protected *scyllo*-inositol derivative (**3.34**) where the methyl group would be in the axial position, like in mytilitol (**3.32**).

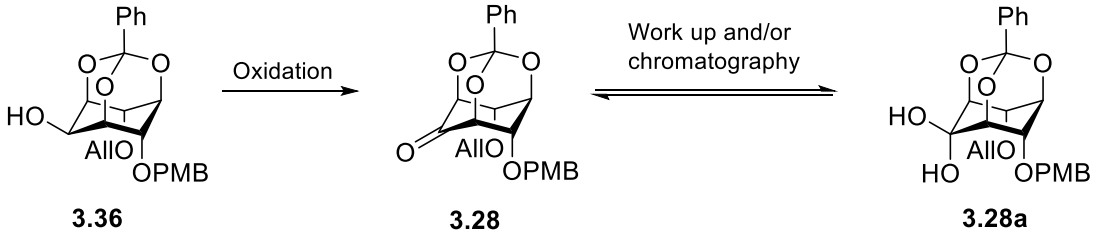
The four first steps in this sequence were known in the literature. The synthesis started by reacting *myo*-inositol (**3.1**) with trimethylorthobenzoate to get the desired product orthobenzoate derivative **3.27** in 75% yield after recrystallization (Scheme 3-8).[17] One of the axial hydroxyl groups was protected as a PMB ether to give compound **3.35** in 85% yield, and then the other axial hydroxyl group was protected as an allyl ether to give the known compound **3.36** in 72% yield.[6] Using one equivalent of alkylating reagent with a sodium or lithium base on compound **3.27** should give axial selectivity only, because of the first axial proton is more acidic and the metal (Na or Li) chelates the two axial hydroxyl groups.[9,10] For the second alkylation, a lithium base must be used because it showed a better regioselectivity for the axial position in *myo*-inositol derivatives than the sodium base (suggested by picrate extraction experiments).[9]



Scheme 3-8: Synthesis of the known compound **3.36**.[6,17]

The next step was the oxidation of the equatorial hydroxyl group in compound **3.36** to the ketone **3.28** (Scheme 3-9). Different conditions were tested to oxidize the hydroxyl group and, unfortunately, a mixture of the ketone and the hydrate **3.28a** was obtained in all cases. These two compounds were inseparable, so the mixture was dried under vacuum with P_2O_5 in attempt to

convert the hydrate back to the ketone, which was unsuccessful. Using a Dean–Stark apparatus and heating the substrates at reflux in toluene was also attempted, but the hydrate could not be converted back to the ketone. The rigid tricylic structure of **3.28** presumably is strained by the introduction of an sp^2-hybridized carbon during the oxidation. This strain can be alleviated by formation of the hydrate, in which this carbon is sp^3 hybridized.

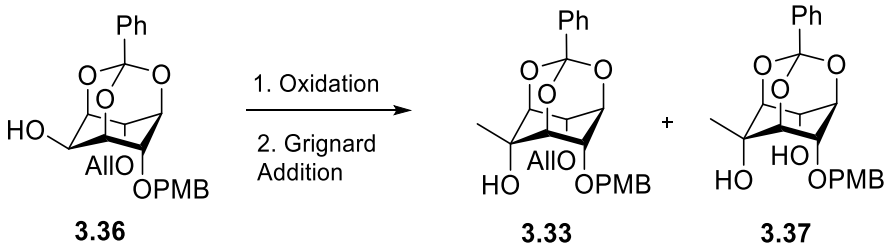


3.36 **3.28** **3.28a**

Scheme 3-9: Attempts to synthesize ketone **3.28** from **3.36**.

The next strategy was to make the ketone **3.28** and, without purification, to add the Grignard reagent to get the desired product **3.33** (Table 3-1). A number of different oxidation and Grignard reaction conditions were tested, which ultimately resulted in the successful synthesis of **3.36** in very good yield (95%). First, Dess–Martin Periodinane (DMP) oxidation was performed to form the crude intermediate, followed by addition of MeMgBr in Et_2O at –78 °C to afford 44% of **3.33** and 5% of side product **3.37** (Table 3-1, Entry 1), in which the allyl group was cleaved. Swern oxidation conditions was then tested, which improved the yield of **3.33** to 66% (Table 3-1, Entry 2). At this point, it was noticed that the crude ketone was partially insoluble in Et_2O, and therefore the solvent was changed to THF, which resulted in a 75% yield of **3.33** (Table 3-1, Entry 3). Finally, sonication of the crude ketone before cooling the solution for the Grignard reaction improved the solubility of the material and the yield of **3.33** to 95% (Table 3-1, Entry 4).

Table 3-1: Synthesis of compound **3.33**.

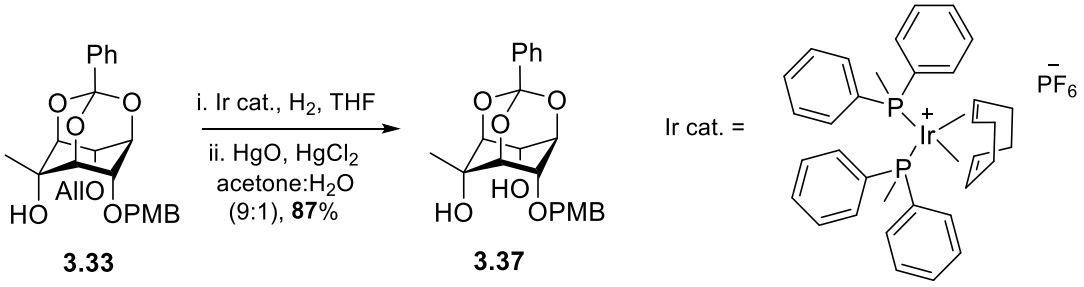


3.36 **3.33** **3.37**

Entry	Oxidation	Grignard Addition	Yield of 3.33
1	DMP	MeMgBr, Et_2O, –78 °C	44
2	Swern	MeMgBr, Et_2O, –78 °C	66
3	Swern	MeMgBr, THF, –78 °C	75
4	Swern	MeMgBr, THF, –78 °C*	95

*Sonication was performed for dissolution of the crude.

After obtaining **3.33**, it was important to make sure that the stereochemistry at the tertiary alcohol was correct. Alcohol **3.33** was not a solid and therefore getting a crystal structure of this compound was not possible. On the other hand, the minor compound **3.37** (Table 3-1 and Scheme 3-10) was a solid. So the question became: do **3.37** and **3.33** share the same stereochemistry? If so, a crystal structure of **3.37** would also tell the stereochemistry of the methyl group in **3.33**.



3.33 **3.37**

Scheme 3-10: Synthesis of minor compound **3.37** from major compound **3.33**.

To determine this, the allyl group was then removed from compound **3.33** and the ^{1}H NMR spectra of the two compounds were compared. They were shown to be the same. Diol **3.37** was then recrystallized and a crystal structure was obtained (Figure 3-1). The methyl group (C-14) in **3.37**, and by inference **3.33**, was attached to C-2 in the equatorial orientation, as predicted.

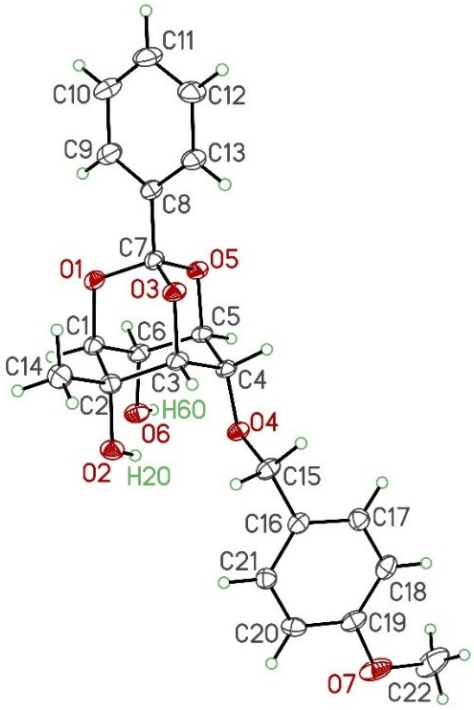
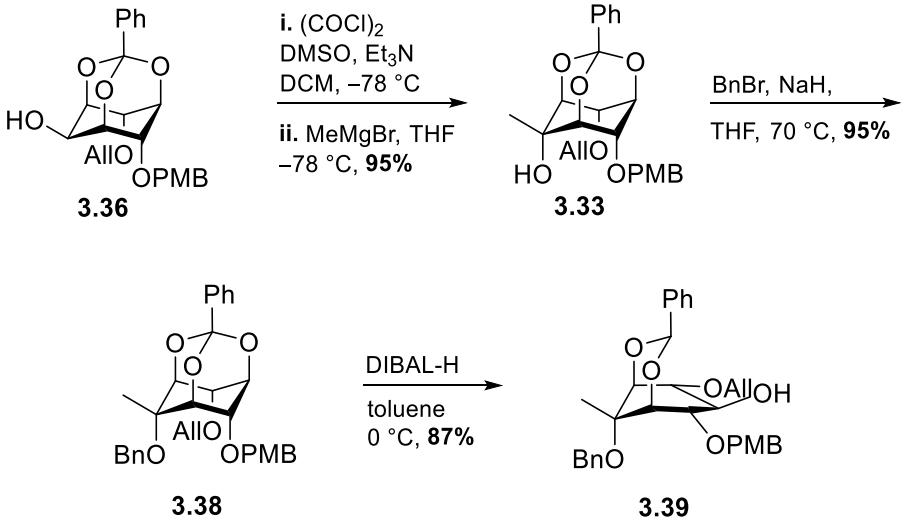


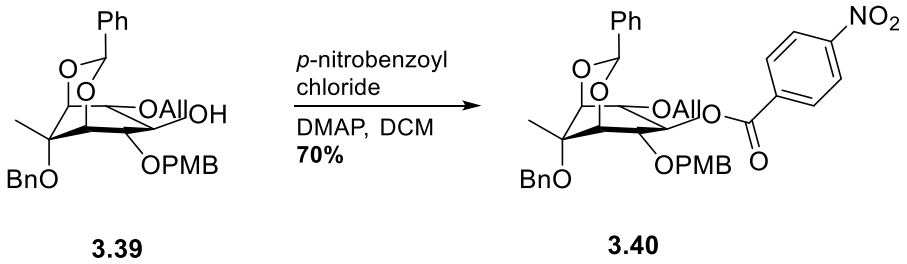
Figure 3-1: X-ray crystal structure (ORTEP) of compound **3.37**. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Based on the ^{1}H NMR spectroscopic and the X-ray crystallographic analysis of **3.37**, the oxidation/Grignard addition steps gave the desired compound **3.33** with the correct stereochemistry in 95% yield (Scheme 3-11). The free hydroxyl was then protected as a benzyl ether to give compound **3.38** also in 95% yield. The next step was the opening of the orthoester using DIBAL-H to give only the bicyclic compound **3.39** in 87% yield.[6]



Scheme 3-11: Synthesis of the bicyclic compound **3.39**.[6]

To verify the regioselectivity of this reaction, the *p*-nitrobenzoyl derivative **3.40** was synthesized from compound **3.39** (Scheme 3-12). The ^{1}H NMR spectrum showed proton in bold as a deshielded doublet of doublets. This proton was deshielded because the proton is situated in the desheilding cone of the ester carbonyl group and was a doublet of doublets because of the two adjacent non-equivalent protons. If the opening was happening at one of the other two positions possible, a doublet would be observed because the adjacent carbon has no protons attached to it. The regioselectivity of bicyclic intermediate **3.39** was then confirmed using derivative **3.40**.



Scheme 3-12: Synthesis of *p*-nitrobenzoyl derivative **3.40**.

The conformation of structure **3.40** was determined using NMR spectroscopy as shown in Figure 3-2 (a). First, the ^{1}H NMR spectrum showed that H-2 and H-6 are doublets with a coupling constant of 2.0 Hz. H-3 and H-5 are also doublets, but the coupling constant is 8.0 Hz. H-4 is an apparent triplet (or doublet of doublets) meaning that it is coupled to both H-3 and H-5. The lack of coupling between H-2/H-3 and H-5/H-6 suggests an angle close to 90 ° between them (based on the Karplus equation). Also, H-2 and H-6 appear to be coupled in a long range W coupling. Using the data from the ^{1}H NMR spectrum, it is possible to assume that the cyclohexane ring is similar to a half chair conformation. Compound **3.39** shared the same features. Finally, the ROESY spectrum of compound **3.40** supported this conformation; there is an NOE correlation between the two protons in bold (Figure 3-2 (b)).

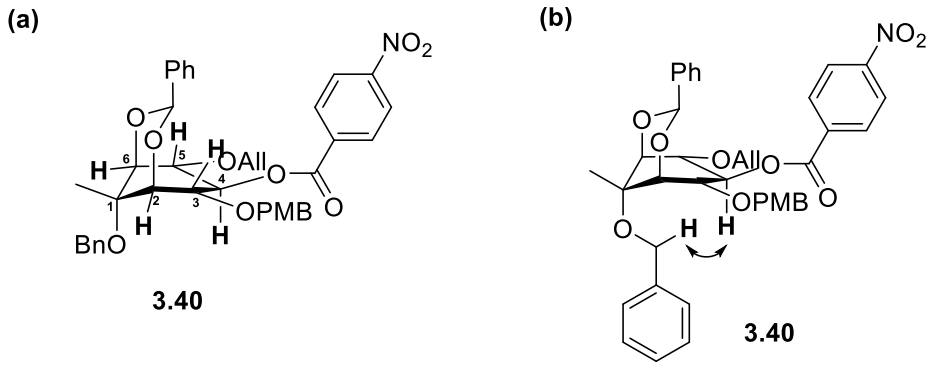
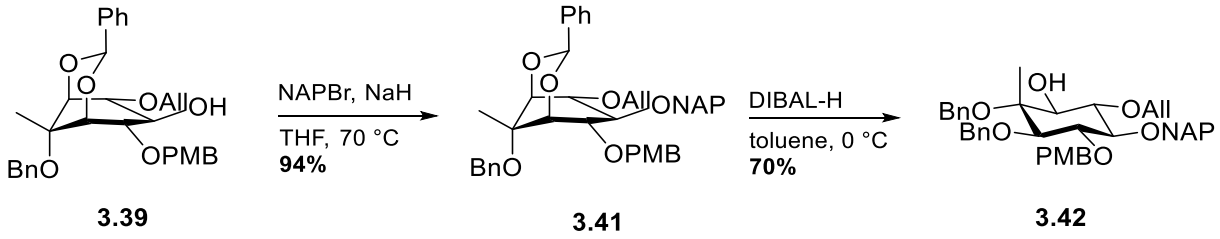


Figure 3-2: (a) NMR spectroscopic data supporting the conformation of compound **3.40**. (b) NOE correlation in compound **3.40**.

The following step of the synthesis involved the protection of the free hydroxyl group in compound **3.39** (Scheme 3-13). The 2-methylnaphthyl group was chosen for this purpose, and the reaction gave the desired compound **3.41** in 94% yield. The opening of the benzylidene acetal was then performed using DIBAL-H to give the cyclohexanol intermediate **3.42** in 70% yield.



Scheme 3-13: Synthesis of compound **3.42**.

The regioselectivity of the reductive opening of the benzylidene acetal was determined using the X-ray crystal structure obtained from **3.42**. As shown in Figure 3-3, the free hydroxyl group at C-1 is between the tertiary protected alcohol at C-2 and the allyl ether at C-6 and also on the opposite side of the ring from the PMB ether at C-4.

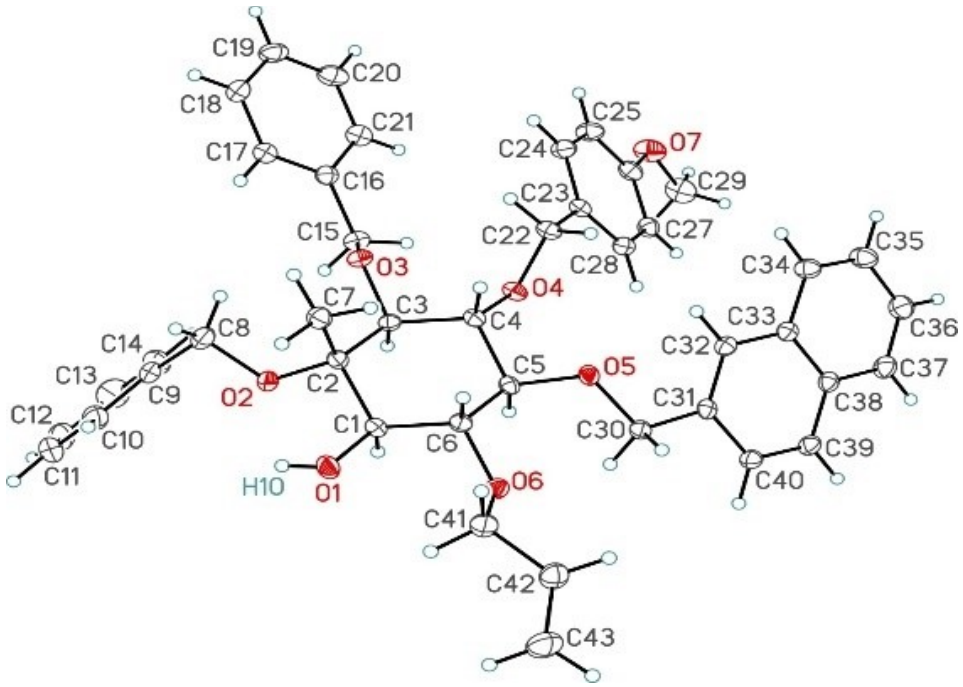
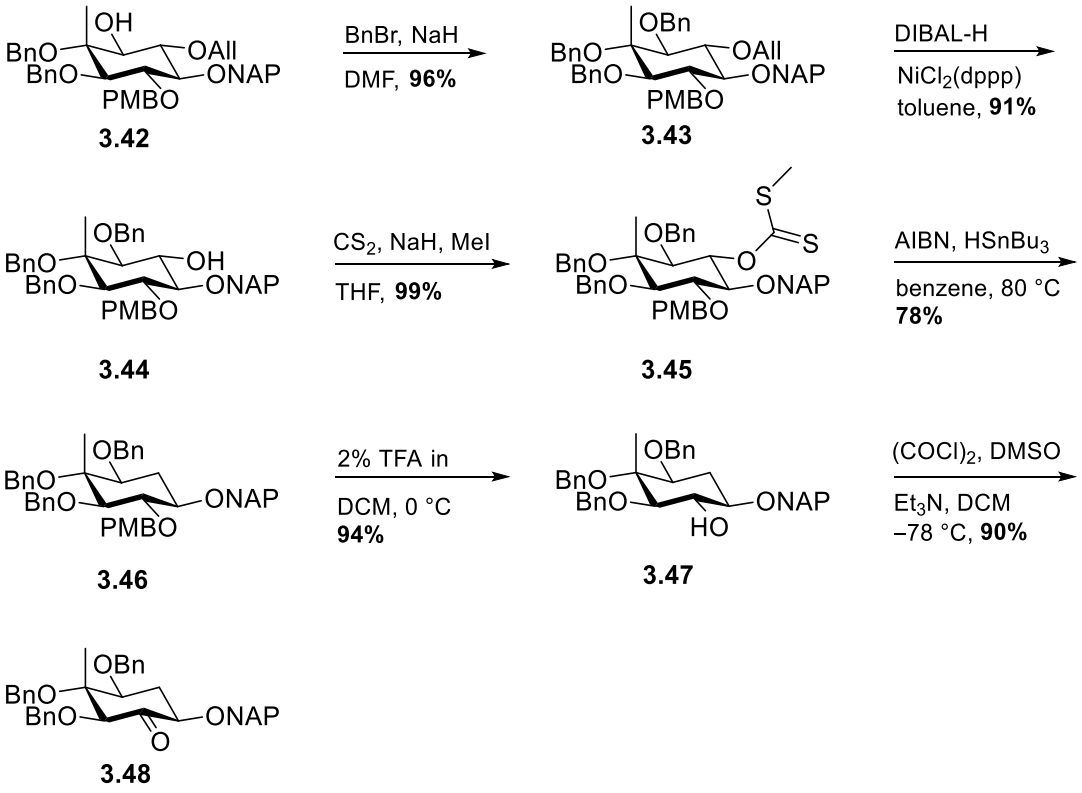


Figure 3-3: X-ray crystal structure (ORTEP) of compound **3.42**. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

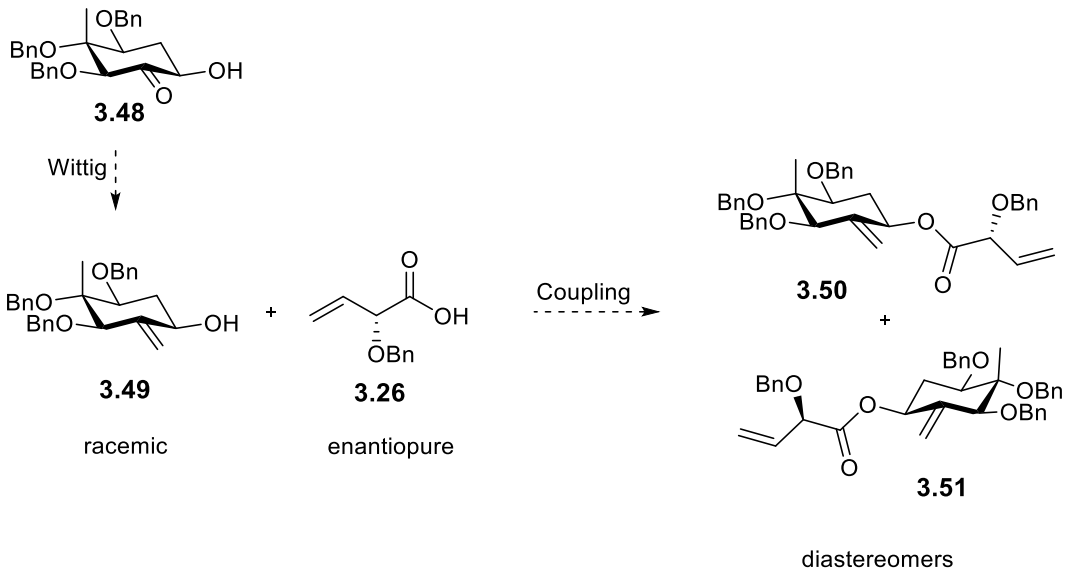
With **3.42** in hand, the free hydroxyl group was then converted to a benzyl ether to give the fully protected intermediate **3.43** in 96% yield (Scheme 3-14). The allyl group was then deprotected using DIBAL-H and $NiCl_2$(dppp) affording the corresponding free hydroxyl group (**3.44**) in 91% yield.[6,18] Xanthate **3.45** was then synthesized in 99% yield, followed by a Barton–McCombie deoxygenation to give the deoxygenated compound **3.46** in 78% yield. The next step was the deprotection of the PMB group. At first, oxidative cleavage using ammonium cerium(IV) nitrate (CAN) or DDQ were tested, but both reactions resulted in a low yield of the product. Finally, acidic cleavage using 2% TFA in CH_2Cl_2 at 0 °C was found to favour the deprotection of the PMB group, providing the desired product **3.47** in 94%. The oxidation of this hydroxyl group using Swern oxidation conditions gave the ketone **3.48** in 90% yield.



Scheme 3-14: Synthesis of ketone **3.48**.

3.2.4 Summary

The carboxylic acid **3.26** was synthesized in eight steps in an overall yield of 15% starting from (+)-dimethyl L-tartrate (**3.17**). The synthesis of the inositol derivative required for the proposed approach to bradyrhizose was stopped at ketone **3.48**. The coupling of the racemic inositol derivative **3.49** with the enantiopure carboxylic acid **3.26** would result in two diastereomers being formed, and only one of them (**3.50**) could be used to continue the synthesis (Scheme 3-15). The other diastereomer (**3.51**) would have to be further transformed to give the enantiomer of the desired compound **3.50**. At this time I had reached this stage in the project, I had a conversation with Professor George A. O'Doherty (Northeastern University) during a conference, who suggested an alternative route to avoid the loss of half of the material. This route also involved ketone **3.48** and so did not require the design of a new intermediate. In this approach, **3.48** was coupled with an alkyl propiolate, an achiral reagent.



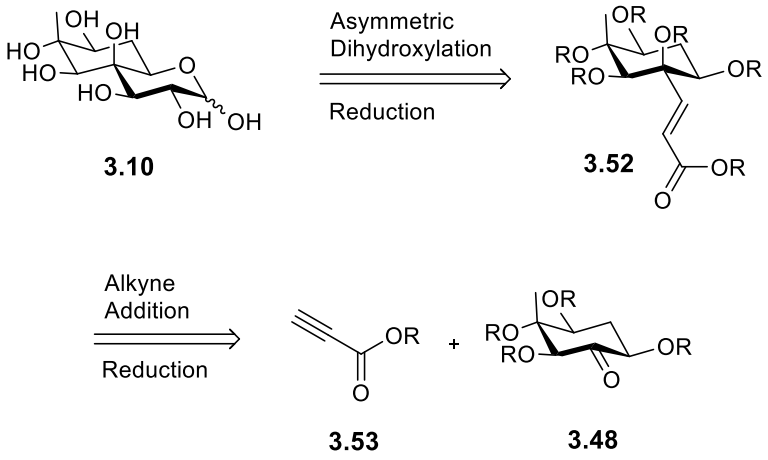
Scheme 3-15: Synthesis of alkene **3.49** from the ketone **3.48** and coupling of racemic inositol derivative **3.49** with enantiopure carboxylic acid **3.26**.

3.3 Linear route using an alkyl propiolate

As mentioned above, the linear route using an alkyl propiolate was an idea from Professor George A. O'Doherty. This synthesis uses the inositol intermediate **3.48** described in the previous section.

3.3.1 Retrosynthesis

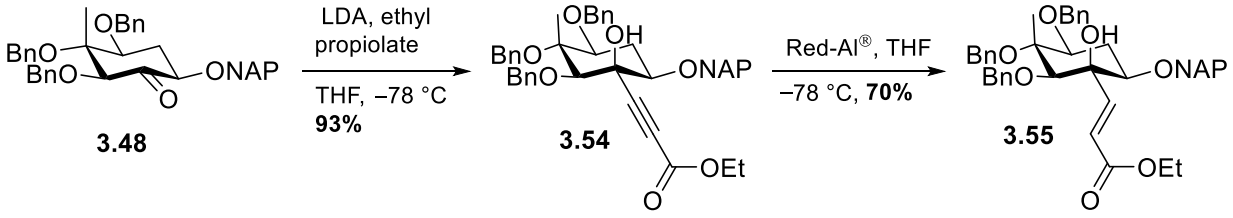
The retrosynthesis for this section is shorter because one of the intermediates had already been synthesized. Bradyrhizose (**3.10**) could be obtained by an asymmetric dihydroxylation on the alkene **3.52** followed by a reduction of the ester to the corresponding aldehyde. Intermediate **3.52** could be assembled by adding an alkyl propiolate (**3.53**) to the ketone **3.48** to form a propargylic alcohol, then by reduction of the alkyne to the *E*-alkene.



Scheme 3-16: Retrosynthesis for the linear route using an alkyl propiolate (**3.53**).

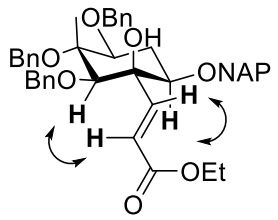
3.3.2 Synthesis using the NAP protecting group

The coupling between ketone **3.48** and ethyl propiolate processed smoothly to give the desired propargylic alcohol **3.54** in 93% yield (Scheme 3-17). The stereochemistry of the new stereogenic center formed could not be determined at this stage. The verification was made after the next step, the reduction of alkyne **3.54** to *E*-alkene **3.55**. The first trials were alkyne hydrosilylation using $[Cp^*Ru(MeCN)_3]PF_6$ as a catalyst and triethylsilane or triethoxysilane[19] but no desired product was observed. After a literature search, it was found that the alkyne of a propargylic alcohol can be reduced to the *E*-alkene using Red-Al® at –78 °C.[20,21] Thus, this reaction was performed, and 70% of the desired compound **3.55** was obtained; unreacted starting material was also recovered. The stereochemistry at the alkene was verified with the coupling constant (15.5 Hz) between the two alkene protons in compound **3.55**.



Scheme 3-17: Synthesis of compound **3.55**.

After the reduction step, a ROESY experiment was done on compound **3.55** to verify the stereochemistry of the stereocenter made in the previous step (addition of ethyl propiolate). As expected, the alkene protons had strong NOE correlations with the ring protons, suggesting that the hydroxyl group was in the axial position, as shown in Figure 3-4.

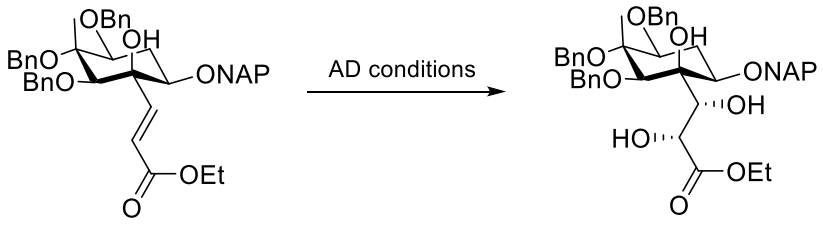


3.55

Figure 3-4: NOE correlations in compound **3.55**.

The next step to continue the synthesis was the asymmetric dihydroxylation (AD) of the alkene. Several different conditions were explored without success (Table 3-2). First, the Sharpless asymmetric dihydroxylation[22] using AD-mix-α was performed, but no reaction occurred after three days (Table 3-2, Entry 1). Then, more reagents were added one by one, but no changes were observed (Table 3-2, Entry 2). The starting material was partially insoluble in the usual solvent system (*t*-BuOH and H_2O) and so therefore the *t*-BuOH was replaced with *t*-BuOMe, yet no desired product was detected (Table 3-2, Entry 3). Finally, by adding $NaHCO_3$, a new spot was detectable by TLC after three days (Table 3-2, Entry 4), but the reaction was very slow and only starting material was recovered.

Table 3-2: Attempted asymmetric dihydroxylation of **3.55**.

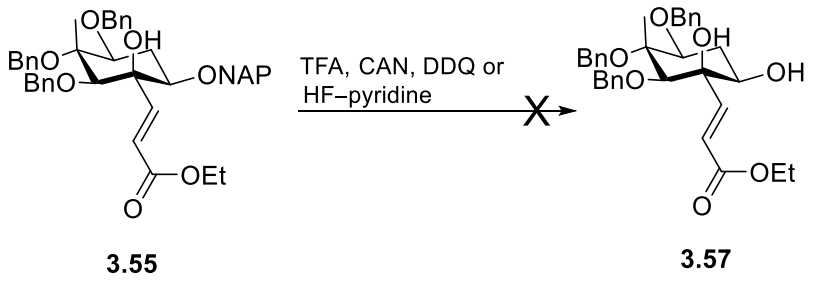


3.55 **3.56**

Entry	Reaction conditions for AD	Equiv. of $K_2OsO_4.H_2O$	Isolated yield of 3.56
1	AD-mix-α, $MeSO_2NH_2$ *t*-BuOH:H_2O (1:1), 6 days	0.004	-
2	$K_2OsO_4.H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 3 days	0.02	-
3	$K_2OsO_4.H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOMe:H_2O (1:1), 3 days	0.02	-
4	$K_2OsO_4.H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, *t*-BuOMe:H_2O (1:1), 3 days	0.02	-

$(DHQ)_2PHAL$: Hydroquinine 1,4-phthalazinediyl diether

After the poor results from the asymmetric dihydroxylation, I thought that perhaps the size of the NAP group was hindering the reaction. The next option investigated was to deprotect the NAP group on **3.55** before the asymmetric dihydroxylation. Different conditions were tried to remove the NAP group (TFA, DDQ, CAN and HF–pyridine) but all these reactions gave multiple products. If the NAP protecting group could not be removed cleanly, the synthesis could not be completed (at some point it would be necessary to remove this group). Therefore, a different protecting group for this position needed to be found.

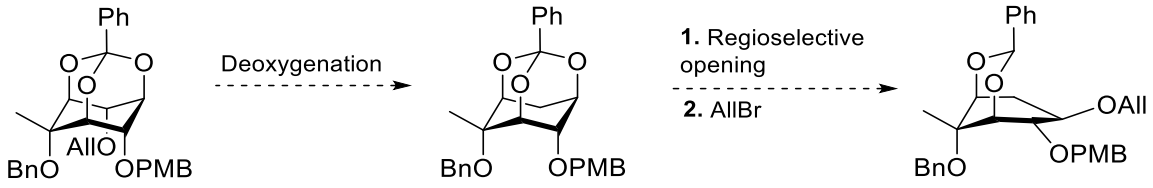


3.55 **3.57**

Scheme 3-18: Attempts to deprotect the NAP group on compound **3.55**.

3.3.3 Alternative approaches

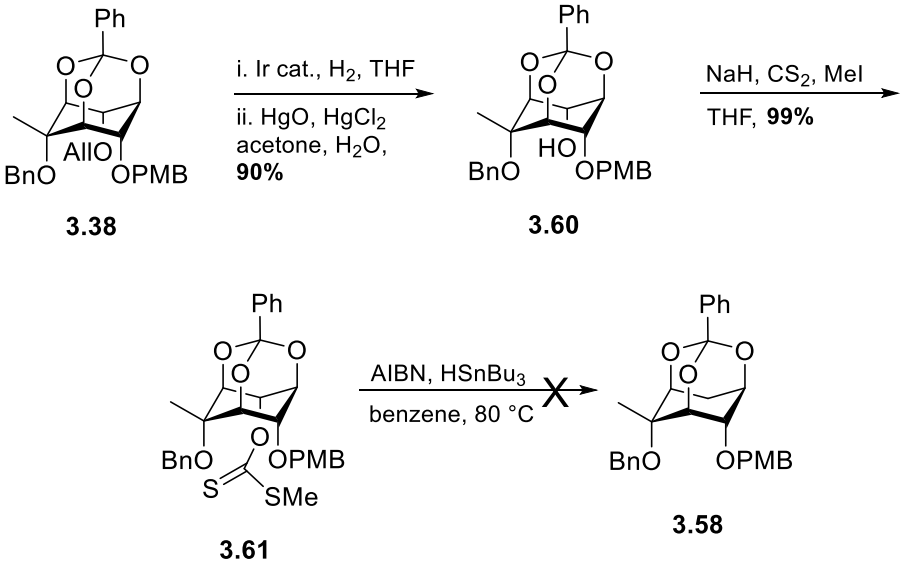
The initial idea I explored was to change the order of the reactions to reuse a protecting group later in the synthesis and be able to do the deprotection at the end of the synthesis. For example, if the deoxygenation could be done on the orthobenzoate substrate **3.38**, the allyl group could be reused after the regioselective opening reaction on compound **3.58** (Scheme 3-19).



3.38 **3.58** **3.59**

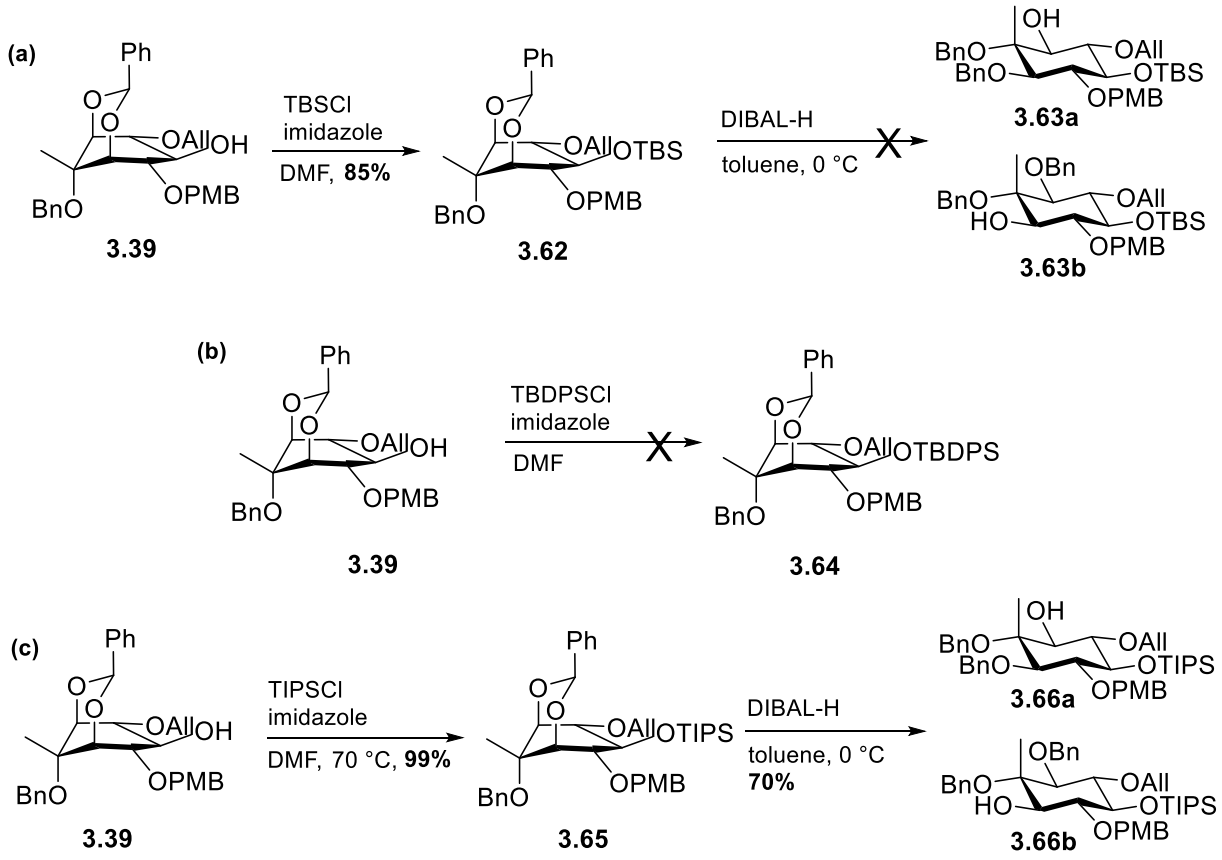
Scheme 3-19: Altenative approach: early deoxygenation.

To explore this possibility, the allyl group in **3.38** was removed by treatment with (1,5-cyclooctadiene)bis-(methyldiphenylphosphine)iridium (I) hexafluorophosphate catalyst, which isomerised the double bond, followed by the cleavage of the resulting vinyl ether with aqueous mercuric salts to give alcohol **3.60** in 90% yield (Scheme 3-20). The xanthate **3.61** was then formed in 99% yield and the Barton–McCombie deoxygenation was performed. Unfortunately, the deoxygenation gave a complex mixture and this approach was abandoned.



Scheme 3-20: Attempted synthesis of intermediate **3.58**.

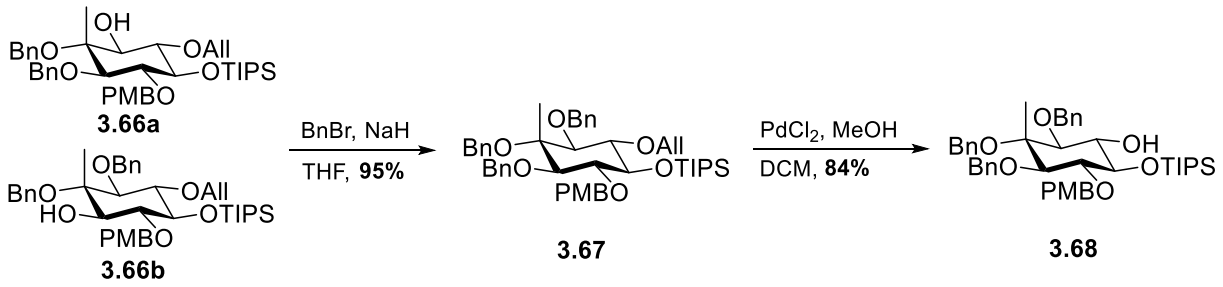
The next idea was to take intermediate **3.39** and protect it with a silyl group. Different silyl groups were explored as shown in Scheme 3-21. The *t*-butyl-dimethylsilyl (TBS) group was first installed in 85% yield (**3.62**) (Scheme 3-21 (a)). The reductive opening of the benzylidene acetal was then tried using DIBAL-H, but the silyl group did not survive these conditions. I then attempted to prepare a derivative containing a TBDPS group (**3.64**), but it could not be obtained, presumably because it is too sterically demanding (Scheme 3-21 (b)). Finally, success was found with the triisopropylsilyl (TIPS) group. This group was installed in 99% yield to give the desired compound **3.65**. Subsequent DIBAL-H reduction[6] of the benzylidene acetal gave the desired product **3.66** in 70% yield (Scheme 3-21 (c)). The continuation of the synthesis using the TIPS protecting group will be discussed in the next section.



Scheme 3-21: (a) Synthesis using TBS group. (b) Synthesis using TBDPS group. (c) Synthesis using TIPS group.

3.3.4 Synthesis using TIPS protecting group

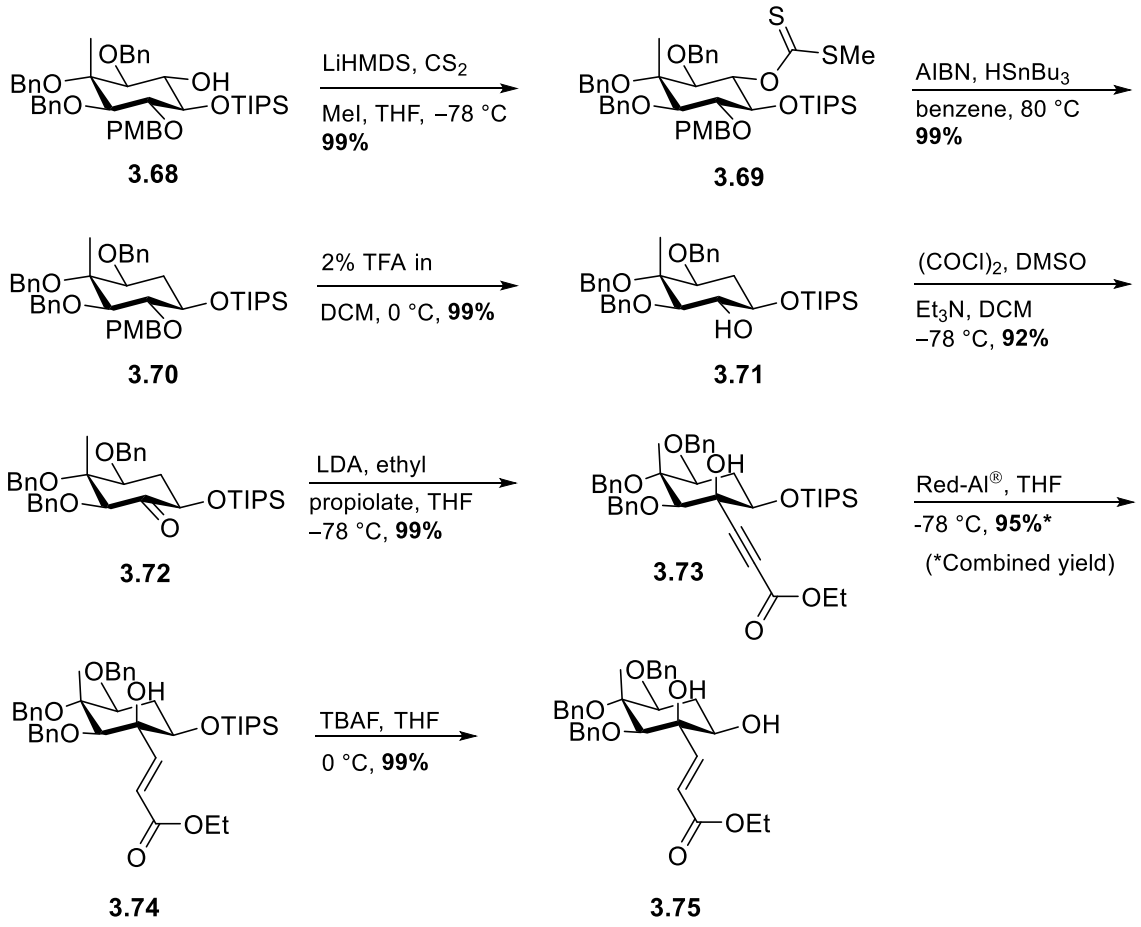
As mentioned in the previous section, the benzylidene acetal opening was performed on the TIPS protected bicyclic intermediate **3.65** to give the desired product **3.66** in 70% yield (Scheme 3-21 (c)). The next step was the protection of the free hydroxyl groups using benzyl bromide to give the desired fully protected inositol compound **3.67**, which was obtained in 95% yield (Scheme 3-22). The allyl group was then deprotected using palladium(II) chloride to give compound **3.68** in an 84% yield.



Scheme 3-22: Synthesis of intermediate **3.68**.

The xanthate formation from **3.68** was more complicated than expected. The previous conditions used on the compound **3.44** containing the NAP protecting group (see Scheme 3-14) were tried first, but no desired product was observed. The ^{1}H NMR spectrum showed a mixture of two compounds: the starting material and the product resulting from migration of the silyl group to the adjacent free hydroxyl group. The next idea was to convert **3.68** into the corresponding iodide or a mesylate followed by a reduction. However, neither the desired mesylate or iodide could be formed under the conditions studied (MsCl, Et_3N, DCM and I_2, PPh_3, imidazole, THF, 70 °C, respectively). A Wolff–Kishner type reduction on the ketone derived from **3.68** was also attempted, but this failed as well. Finally, after a literature search, it was found that Ley and co-workers made a xanthate on a highly functionalized molecule using NaHMDS at –78 °C.[23] Notably, this substrate had a silyl group, although not adjacent to the alcohol and thus silyl migration was less of a concern. The reaction was performed on **3.68** and the desired product, **3.69**, was obtained in 99% yield (Scheme 3-23). The next steps followed the route used for the substrate with the NAP protecting group. Barton–McCombie deoxygation of the xanthate gave **3.70** in 99% yield. Then, deprotection of the PMB group was done using 2% TFA in CH_2Cl_2 to give **3.71** in 99% yield. The free hydroxyl group was oxidized using the Swern procedure, giving a 92% yield of ketone **3.72**. Ethyl propiolate was then deprotonated using LDA and the ketone was

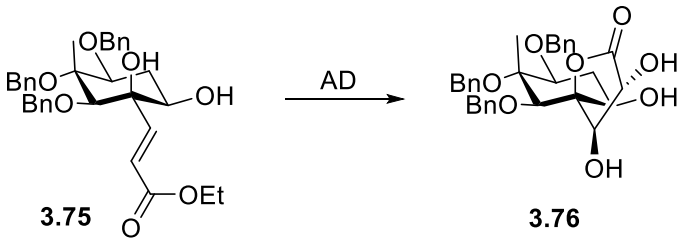
added to the mixture to provide propargylic alcohol **3.73** in 99% yield. The alkyne in **3.73** was reduced to the *E*-alkene using Red-Al® to give the desired compound **3.74**. This reaction never went to completion; however, re-isolation of the starting material was possible and this was subjected to the reaction again. After three cycles, the compound was obtained in 95% combined yield. Finally, the TIPS protecting group was removed using TBAF to give diol **3.75** in 99% yield.



Scheme 3-23: Synthesis of the diol **3.75**.

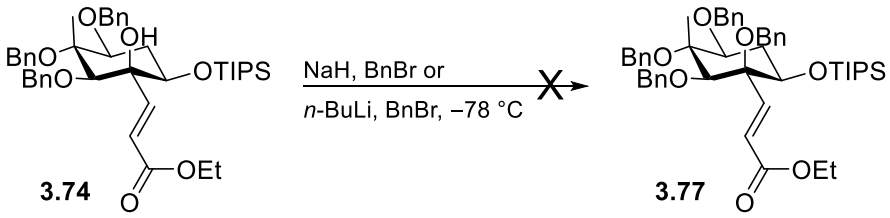
The asymmetric dihydroxylation was then attempted on the diol. However, the reaction was very slow and many spots were present on the TLC. One major compound was formed and it

was isolated. After characterization, the product was identified by NMR analysis to be the five-membered ring lactone **3.76** (Scheme 3-24).



Scheme 3-24: Asymmetric dihydroxylation (AD) of diol **3.75**.

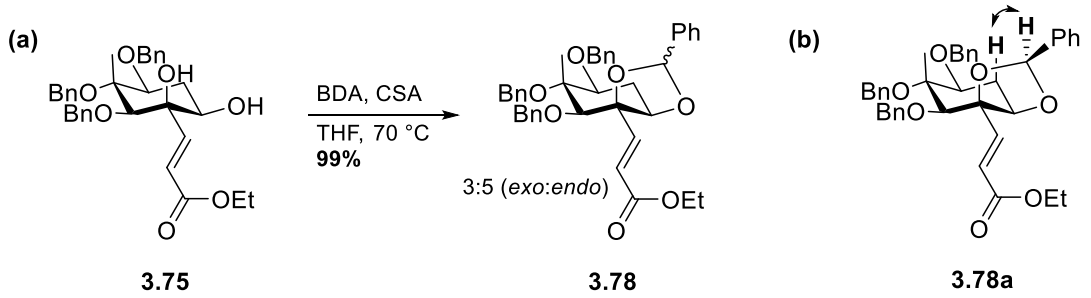
After this result, it was decided that the tertiary hydroxyl group should be protected to prevent cyclization. First, using intermediate **3.74**, we tried different conditions to protect the free hydroxyl group as a benzyl ether; however, no desired compound was observed (Scheme 3-25).



Scheme 3-25: Attempts to benzylate the tertiary hydroxyl group in compound **3.74**.

The next approach was to install a benzylidene acetal on diol **3.75**. The idea was that it would be possible to differentiate the two different hydroxyl groups (secondary and tertiary) by a regioselective opening, which was necessary to form the hemiacetal ring of bradyrhizose. The benzylidene acetal was installed in 99% using benzadehyde dimethylacetal and CSA (Scheme 3-26 (a)) to give compounds **3.78** as a 3:5 *exo*:*endo* mixture. The ratio of the regioisomers was

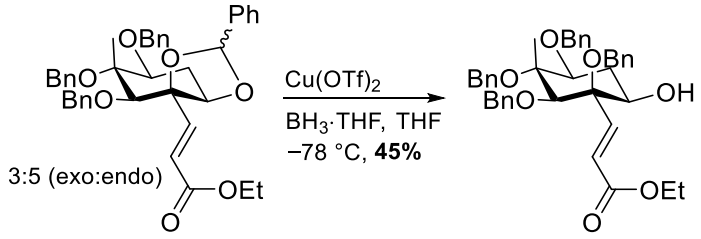
determined by a ROESY experiment. As shown in Scheme 3-26 (b), there was an NOE correlation between the axial methylene proton form the inositol ring with the benzylidene acetal proton.



3.75 **3.78** **3.78a**

Scheme 3-26: (a) Synthesis of compound **3.78**. (b) NOE correlation in minor (*exo*) compound **3.78a.**

With **3.78** in hand, the regioselective opening of the benzylidene acetal was performed using borane and copper(II) triflate at –78 °C[24], but only 45% of desired compound **3.79** was obtained (Scheme 3-27).

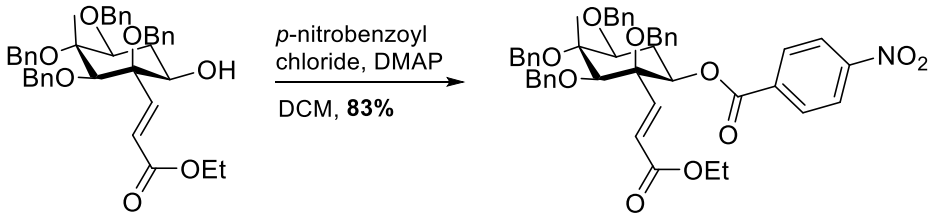


3.78 **3.79**

Scheme 3-27: Regioselective opening of benzylidene acetal **3.78**.

The signals in the ^{1}H NMR spectrum of the newly formed intermediate were very broad so it was not possible to determine if it was the right regioisomer. The regioselectivity of the reation was then verified by reacting compound **3.79** with *p*-nitrobenzoyl chloride to give product **3.80** (Scheme 3-28). The signals in the ^{1}H NMR spectrum were now sharp and, after analysis, it was

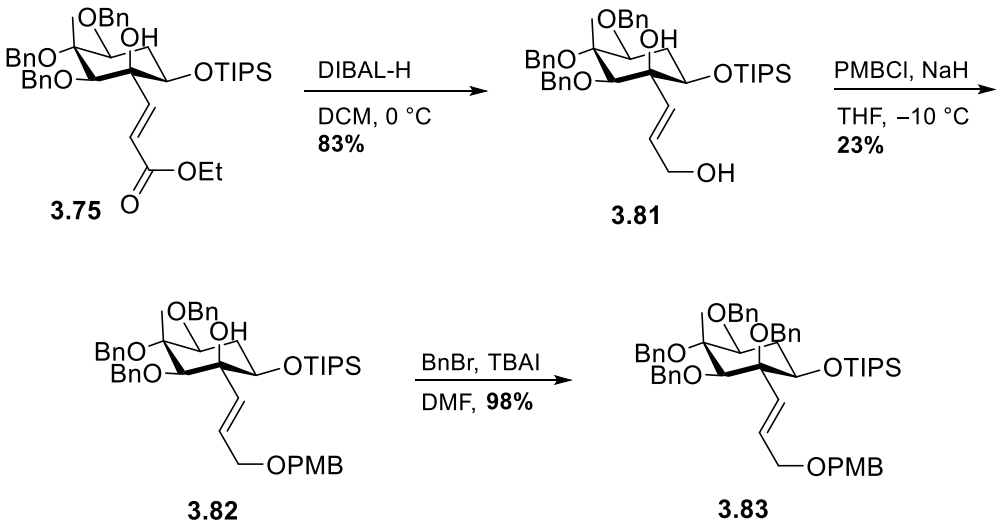
found that the proton bearing the nitrobenzoyl group was a deshielded doublet of doublet, so the compound was the correct regioisomer.



3.79 **3.80**

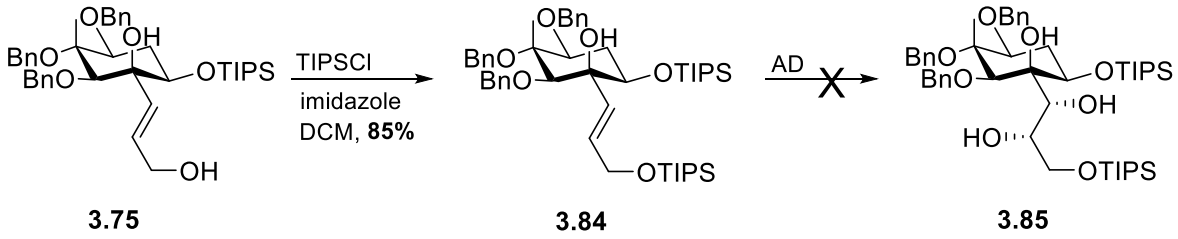
Scheme 3-28: Determination of the regioselectivity of the reductive opening of the benzylidene acetal **3.78** by derivatization.

While trying to improve the regioselective opening step on intermediate **3.78**, it was suspected that conversion of the ester to a primary alcohol might improve the outcome. The primary hydroxyl could be reoxidized after to the aldehyde to form the hemiacetal. To explore this possibility, the ester moeity of compound **3.75** was then reduced using DIBAL-H to give the diol **3.81** in 83% (Scheme 3-29). The next step was to protect the primary hydroxyl with a PMB group, but this reaction was not very selective and the desired compound **3.82** was obtained only in 23% yield (one diprotected and two monoprotected compounds were formed). Finally, protection of the tertiary hydroxyl worked well with benzyl bromide, but only a small amount of product **3.83** was made. Because the PMB protection step was low yielding, this idea was abandoned.



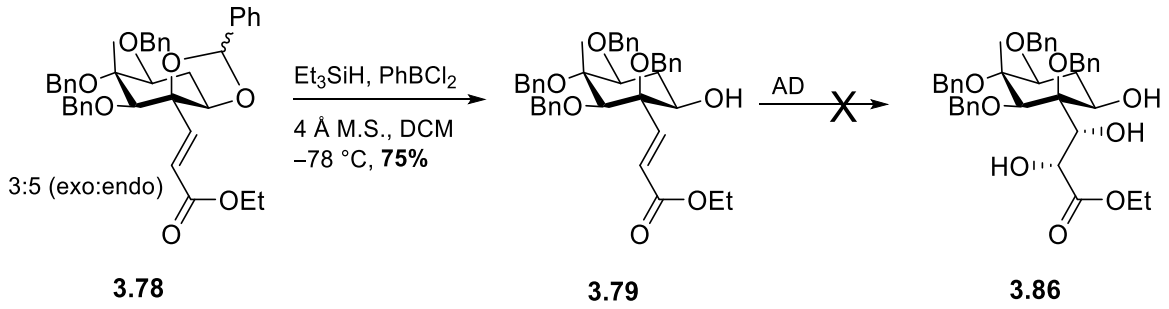
Scheme 3-29: Synthesis of compound **3.83**.

Instead, the sterically bulky TIPS was chosen for the protection of the primary hydroxyl group, to form compound **3.84** in 85% yield (Scheme 3-30). The asymmetric dihydroxylation was attempted but after three days no product was formed.



Scheme 3-30: Synthesis of compound **3.84** and attempted AD.

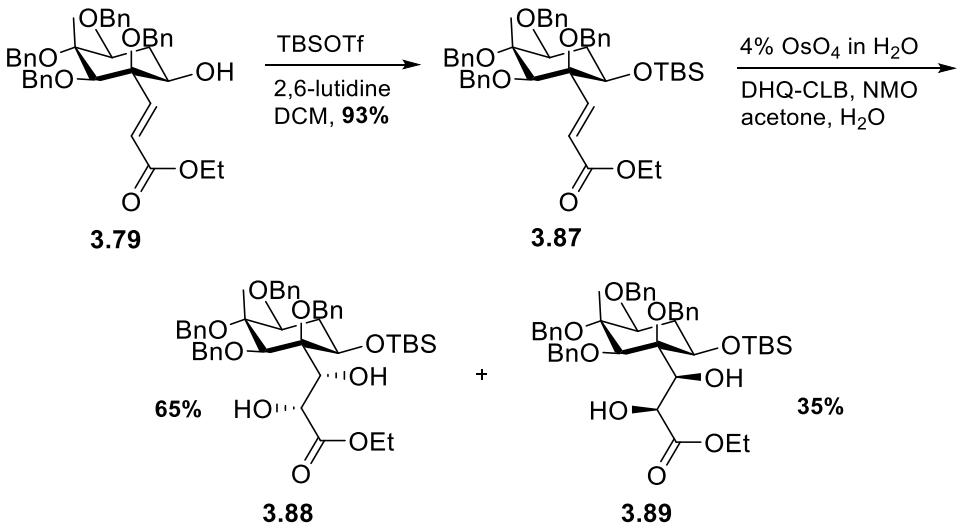
Given these failures, I returned to the regioselective opening of the benzylidene acetal. A new combination of reagents – triethylsilane and dichlorophenylborane[25] – was tested and this gave the desired compound **3.79** in 75% yield (Scheme 3-31). The asymmetric dihydroxylation was then attempted but only starting material was recovered after three days.



3.78 **3.79** **3.86**

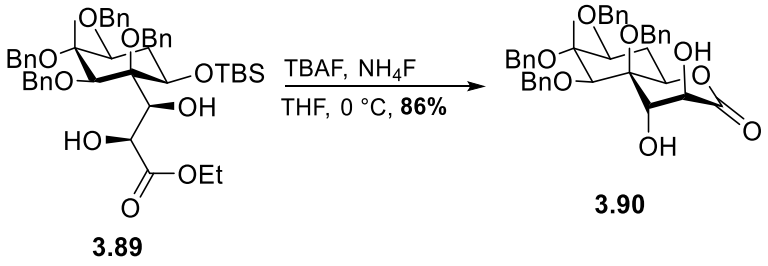
Scheme 3-31: Synthesis of compound **3.79** and attempted AD.

To determine if the free hydroxyl group in **3.79** was hindering the reaction, this functionality was protected with a TBS group to give **3.87** in 93% yield (Scheme 3-32). The asymmetric dihydroxylation was performed on this intermediate. At first, potassium osmate and $(DHQ)_2PHAL$ were used, but the reaction did not complete and the yield of the desired compound was low. An aqueous solution of osmium tetroxide was prepared and the *O*-(4-chlorobenzoyl)hydroquinine (DHQ-CLB) ligand was synthesized,[22] which gave good results with similar compounds.[26] Under these conditions, the desired diol **3.88** was finally obtained in 65% yield after purification. Also formed was the diasteromeric product **3.89**.



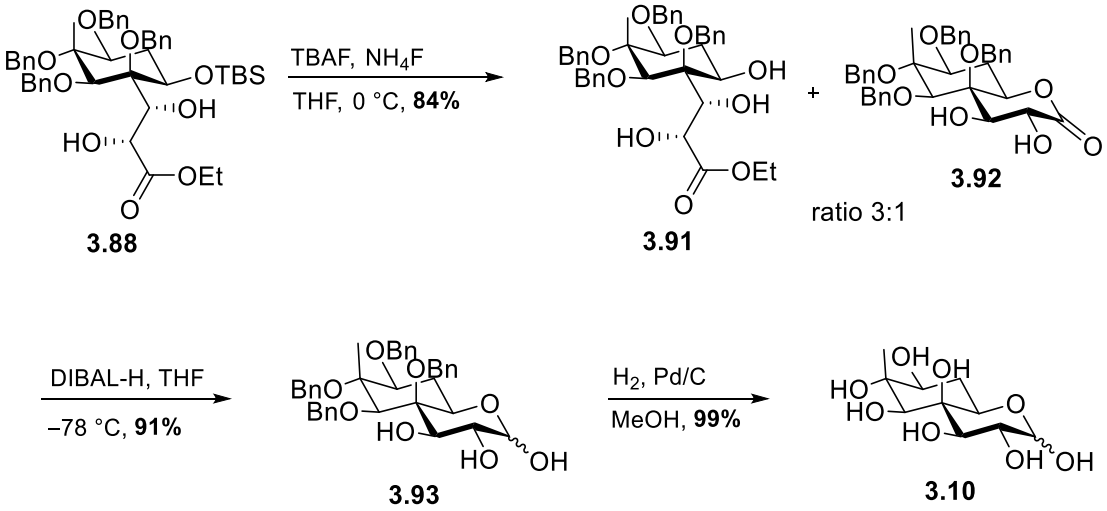
Scheme 3-32: Synthesis of diol **3.88**.

The deprotection of the TBS group in **3.88** proved not straightforward. Therefore, at this point, it was decided to do the optimization of this step with the undesired diastereomer from the asymmetric dihydroxylation to conserve the precious compound **3.88**. TBAF was tried at first but the yield was not reproducible and the use of TFA in CH_2Cl_2 also gave a low yield of the product. After doing some research, we decided to buffer the TBAF reaction with ammonium fluoride. Under these conditions, lactone **3.90** was obtained in 86% yield from diol **3.89** (Scheme 3-33).



Scheme 3-33: TBS deprotection of undesired diastereomer **3.89**.

This optimized reaction was applied to the correct diastereomer **3.88** and the triol **3.91** and lactone **3.92** were obtained in a ratio 3:1 in 84% yield (Scheme 3-34). This mixture was then reduced using DIBAL-H at –78 °C to give the lactol **3.93** in 91% yield. Finally, deprotection of the benzyl groups using palladium on carbon in methanol gave racemic bradyrhizose (**3.10**) in 99% yield.



Scheme 3-34: Synthesis of bradyrhizose (**3.10**).

3.3.5 Summary

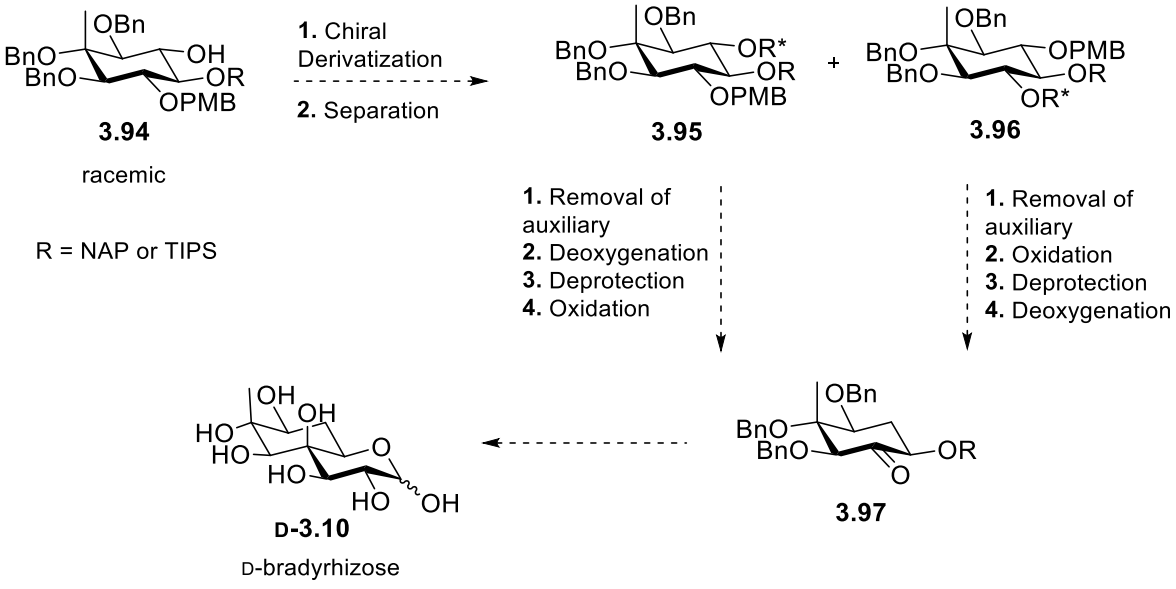
The synthesis of bradyrhizose (**3.10**) was accomplished using a linear route with ethyl propiolate. The initial route involving a NAP protecting group could not be used as this group could not be selectively removed in the presence of benzyl groups. Therefore, a route employing a TIPS protecting group was used. Using this approach, a racemic synthesis of bradyrhizose was achieved in 25 steps with a 6% overall yield. The NMR spectra looked identical to those described by Yu and coworkers.[27] The next section will talk of the separation of the enantiomers.

3.4 Separation of the bradyrhizose enantiomers

The synthesis described in the last section was racemic and therefore chiral auxiliaries were explored to separate the enantiomers. Two approaches will be presented in this section, which ultimately led to the isolation of D- and L-bradyrhizose.

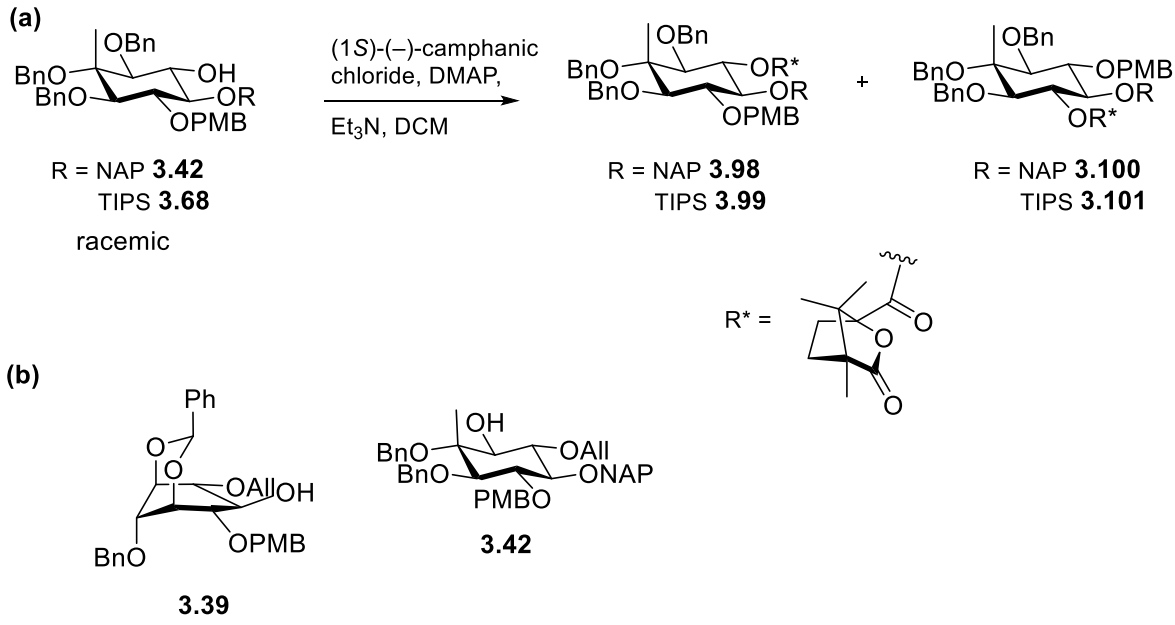
3.4.1 Early stage separation: Conversion of the wrong enantiomer to the right one

The first idea for the separation of the enantiomers is presented in Scheme 3-35. By taking compound **3.94** and doing a chiral derivatization and then separation of the resulting diastereoisomers (**3.95** and **3.96**), it could be possible to convert both diastereomers to a single enantiomer (**3.97**). This would involve doing the same reactions, but in a different order. D-Bradyrhizose (**3.10a**) could then be obtained using this approach without losing half of the material to make the naturally occurring enantiomer.



Scheme 3-35: Early stage separation: Conversion of the incorrect enantiomer to the correct one.

To explore this possibility, the reaction was first tried on the NAP derivative **3.42** using camphanic chloride as the reagent to introduce the chrial auxiliary (Scheme 3-36 (a)). This derivatizing agent was chosen because it has been reported to separate *myo*-inositol orthoester derivatives[15,28] However, separation was not observed for compound **3.42**. The same reaction was performed for the TIPS derivative **3.68** without success.

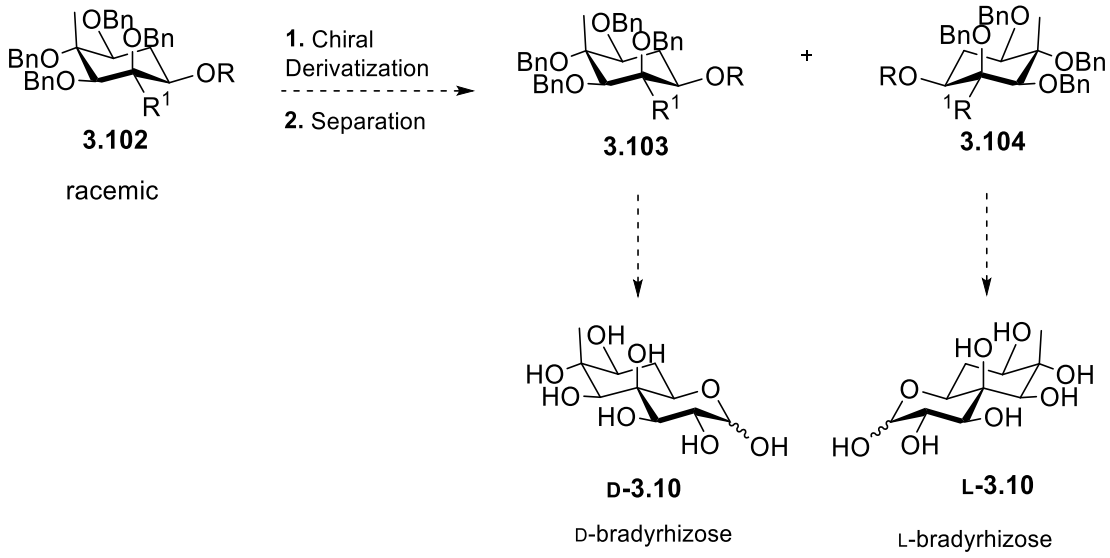


Scheme 3-36: (a) Derivatization of **3.42** and **3.68** using (1*S*)-(–)-camphanic chloride. (b) The derivatization was also tried on compound **3.39** and **3.42**.

This method was also attempted on two earlier intermediates (Scheme 3-36 (b)) but no separation was observed after derivatization of either compound. After this idea failed for the separation of the enantiomers, a different approach was taken.

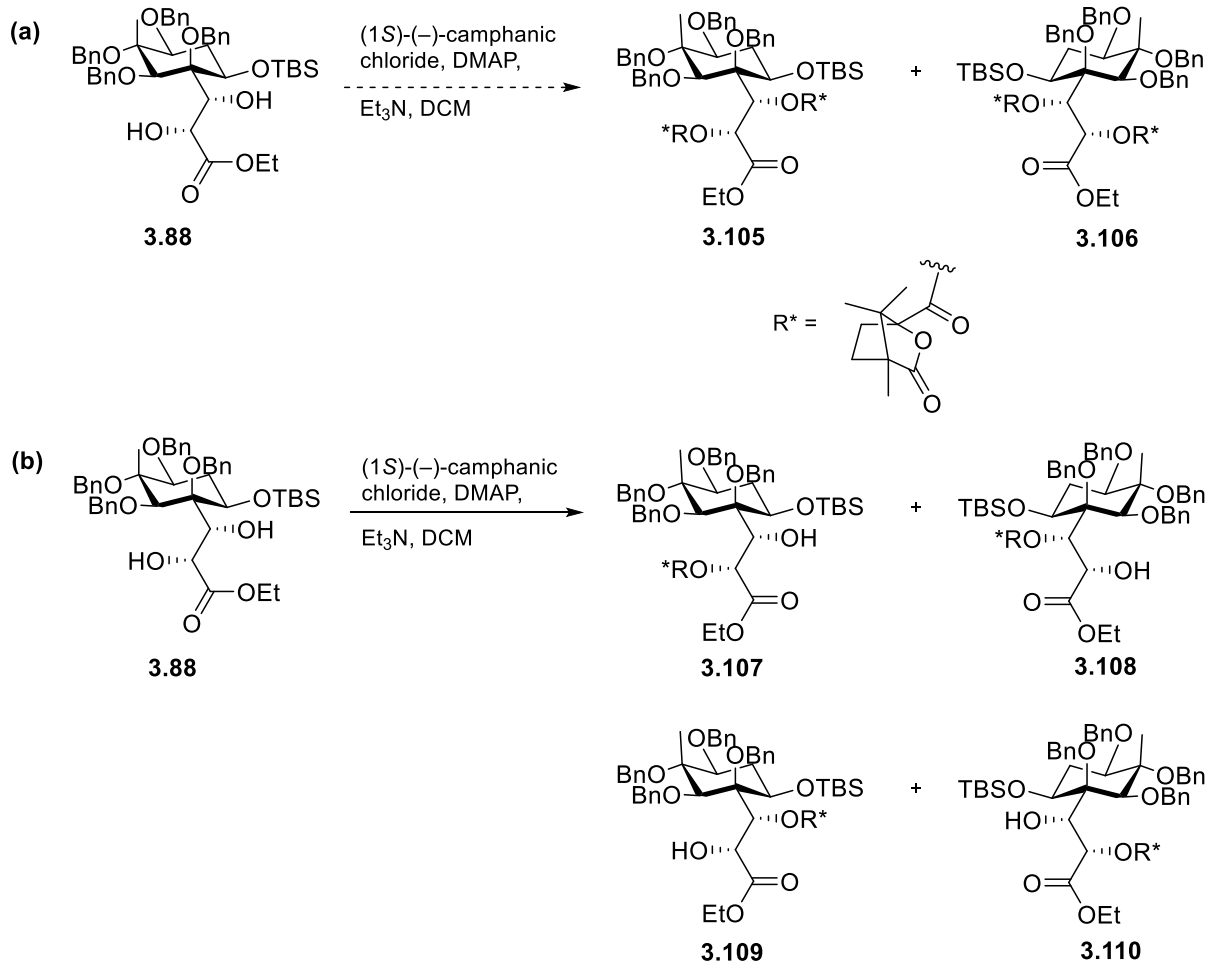
3.4.2 Late stage separation: Synthesis of D-bradyrhizose and L-bradyrhizose

A late stage separation was perhaps a better approach for resolving the enantiomers. First, this process will be more economical, because the derivatization would be done later in the synthesis and therefore less of the expensive chiral derivatizing agent would be used. Second, this method would enable us to get D-bradyrhizose (**D-3.10**), the natural occurring monosaccharide, and also L-bradyrhizose (**L-3.10**), a new carbohydrate never synthesized before (Scheme 3-37). Access to both stereoisomers would be useful for subsequent biological investigations. Therefore, I investigated a number of different late stage intermediates in derivatization reactions.



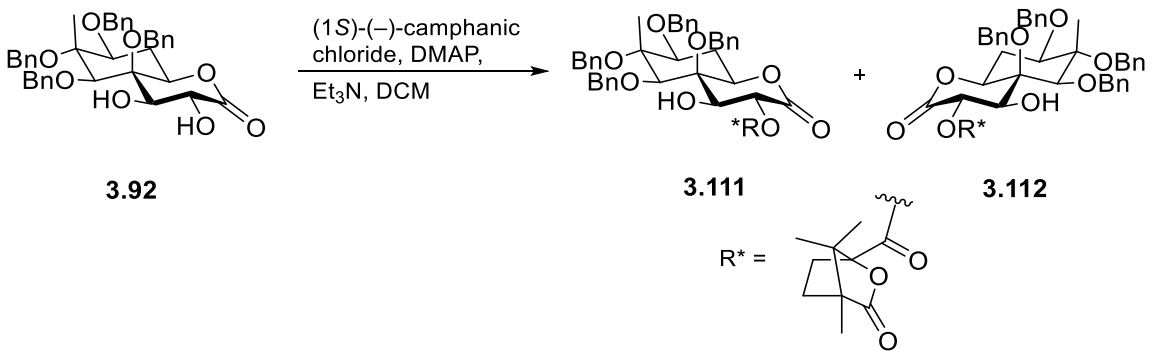
Scheme 3-37: Late stage separation approach: Synthesis of D-bradyrhizose (**D-3.10**) and L-bradyrhizose (**L-3.10**).

The first intermediate to be derivatized was the racemic diol **3.88**; however, the reaction did not proceed as expected. Instead of making two separable compounds with two auxiliaries each, four inseparable mono-substituted compounds were obtained (Scheme 3-38).



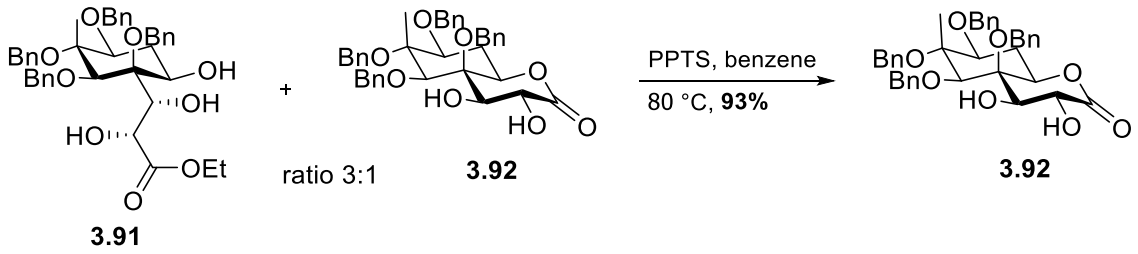
Scheme 3-38: (a) Expected derivatization of compound **3.88** with (1*S*)-(–)-camphanic chloride. (b) Reaction of compound **3.88** with (1*S*)-(–)-camphanic chloride.

The next reaction performed was the derivatization of the lactone **3.92** on a very small scale (3 mg) to see if the diastereomers would be separable (Scheme 3-39). In this case, only one of the two hydroxyl groups was derivatized, producing two compounds. Fortunately, a separation was observed by TLC. With that success in hand, I moved to produce more of lactone **3.92**.



Scheme 3-39: Reaction of lactone **3.92** with (1*S*)-(–)-camphanic chloride.

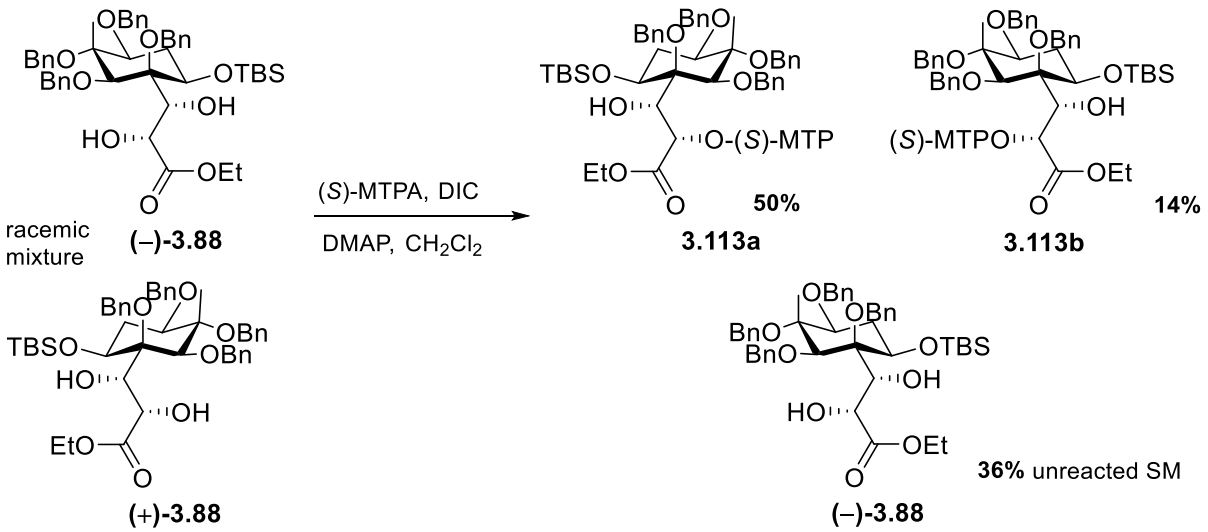
As mentioned earlier (Scheme 3-33), the deprotection of the open chain ester **3.88** with TBAF yielded the triol **3.91** and the lactone **3.92** in a ratio 3:1; therefore, the lactone is not the major product. Also, during the purification, it is very difficult to separate the two compounds, making it almost impossible to access the pure lactone **3.92**. However, by taking the mixture of triol **3.91** and lactone **3.92** and heating with pyridium *p*-toluenesulfonate (PPTS) in benzene at reflux,[29] lactone **3.92** was obtained in 93% yield (Scheme 3-40).



Scheme 3-40: Conversion of the mixture of triol **3.91** and lactone **3.92** to lactone **3.92**.

Having the lactone **3.92** in hand, a larger scale of the derivatization reaction was carried out (Scheme 3-39) but the two diastereomers could not be isolated. Both compounds decomposed on silica. I then tried the chiral derivatizing agents ((*S*)-(+)-*O*-acetylmandelic acid, (*R*)-(–)-α-methoxyphenylacetic acid and (*S*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetic acid) with different substrates: **3.79** (Scheme 3-31) and **3.88** (Scheme 3-41). The use of (*S*)-(–)-α-methoxy-

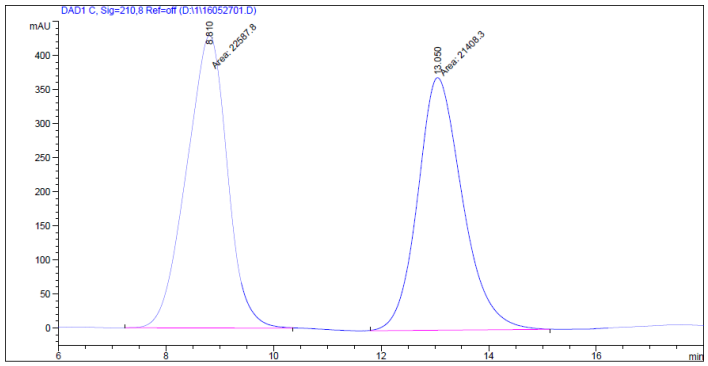
α-(trifluoromethyl)phenylacetic acid ((*S*)-MTPA) provided derivatives of racemate **3.88** that could be separated (Scheme 3-41). (*S*)-MTPA reacted preferentially with the **(+)-3.88** enantiomer to give diastereomer **3.113a** in 50% yield. The other enantiomer **(–)-3.88** reacted with (*S*)-MTPA to give diastereomer **3.113b** in 14% yield. In addition, unreacted starting material was recovered.



Scheme 3-41: Separation of enantiomers **(–)-3.88** and **(+)-3.88** using (*S*)-MTPA.

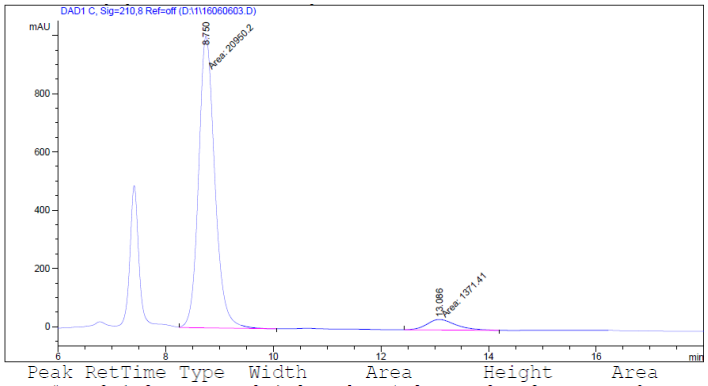
The unreacted enantiomer, **(–)-3.88**, determined to be only one enantiomer (Figure 3-5) by chiral HPLC. The starting material was separated as shown in Figure 3-5 (a). The derivatization reaction was first performed using 1.5 equivalents of (*S*)-MTPA, but the enantiomeric excess of the remaining starting material **3.88** was only 88% (Figure 3-5 (b)). By adding 2 equivalents of (*S*)-MTPA, the remaining **3.88** was only one enantiomer (Figure 3-5 (c)).

(a)



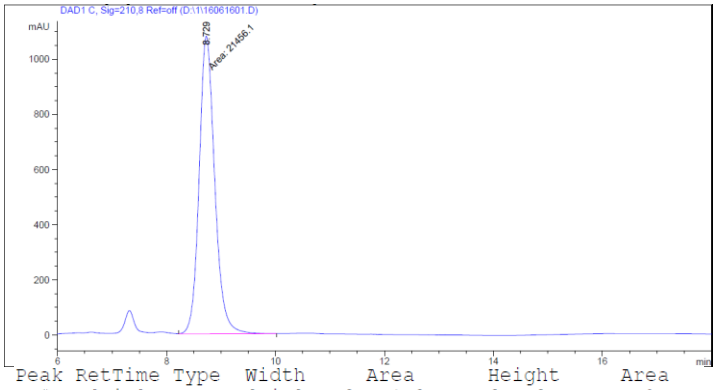
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.810	MM	0.8780	2.25878e4	428.79379	51.3406
2	13.050	MM	0.9634	2.14083e4	370.37372	48.6594

(b)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.750	MM	0.3484	2.09502e4	1002.11981	93.8561
2	13.086	MM	0.6290	1371.41296	36.33802	6.1439

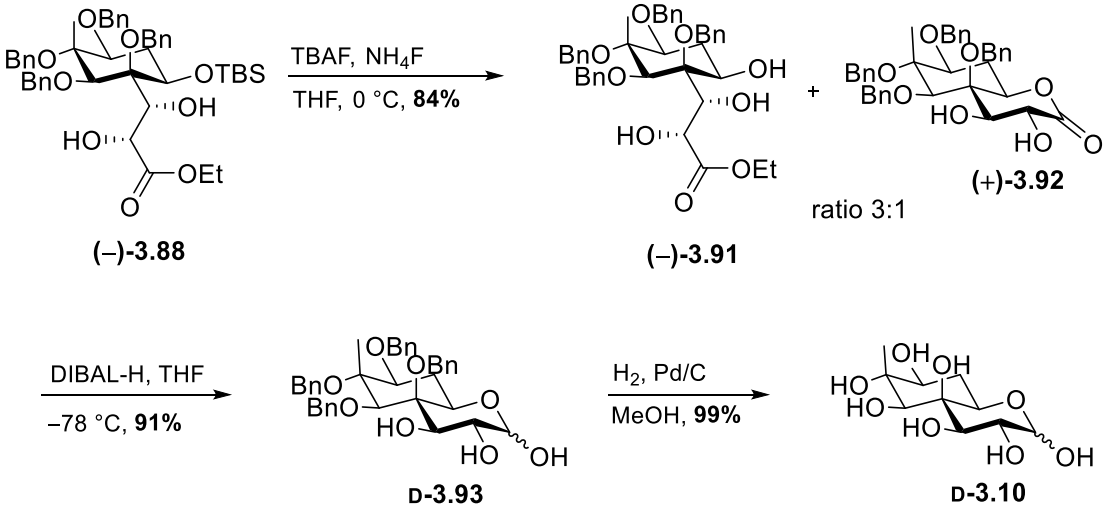
(c)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.729	MM	0.3310	2.14561e4	1080.34241	100.0000

Figure 3-5: (–)-3.88 tR : 8.8 min. **(+)-3.88** tR : 13.1 min. Chiralpak-IA column (1:99 *i*-PrOH–hexanes) at 5 °C **(a)** HPLC data for racemic compound **3.88**. (b) HPLC data for recovered SM (**3.88**) using 1.5 equiv of (*S*)-MTPA. (c) HPLC data for recovered SM (**3.88**) using 2 equiv of (*S*)-MTPA.

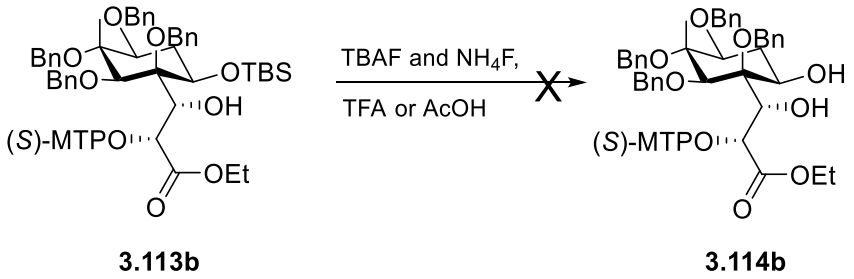
After the separation, the unreacted enantiomer **(–)-3.88** was reacted with TBAF and ammonium fluoride to give the triol **(–)-3.91** and lactone **(+)-3.92** in 84% yield (Scheme 3-42). The mixture was then treated with DIBAL-H to give lactol **D-3.93** in 91%. The benzyl groups were removed to give D-bradyrhizose **D-3.10** in 99% yield. The NMR spectra of **D-3.10** were the same as those published by Yu and coworkers.[27] The optical rotation found for D-bradyrhizose was +20.4 (*c* 0.2, H_2O), which differed in magnitude but not in sign from the one reported by the same group (+6.5 (*c* 0.2, H_2O)).



Scheme 3-42: Synthesis of D-bradyrhizose (**D-3.10**).

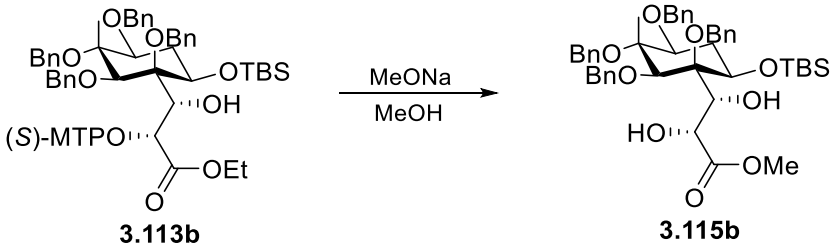
I then turned my attention to the conversion of the (*S*)-MTPA derivatized compounds **3.113a** and **3.113b** into L-bradyrhizose and **D-3.93**, respectively. The same steps should work for both compounds: deprotection of the TBS group with TBAF followed by reduction and removal of the auxiliary using DIBAL-H to form the lactol and finally hydrogenation. The TBS deprotection was first tried with compound **3.113b** using TBAF and NH_4F, but the yield of the

desired compound **3.114b** was low and side products were formed (Scheme 3-43). Cleavage of the silyl group with TFA and AcOH were also tried with poor results.



Scheme 3-43: Attempted deprotection of the TBS group of compound **3.113b**.

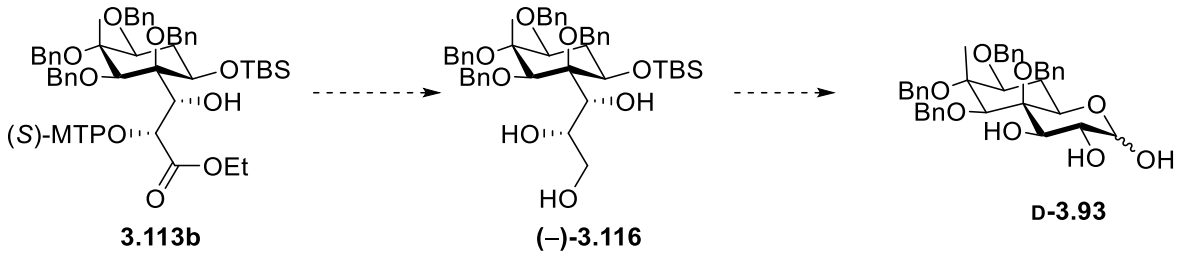
Faced with this challenge, the removal of the auxiliary first was the next approach I investigated. First, cleavage with sodium methoxide in methanol was performed on diastereomer **3.113b**, but the reaction was not completed and other structurally-uncharacterized side products were formed (Scheme 3-44).



Scheme 3-44: Removal of the chiral auxiliary in **3.113b** using sodium methoxide in methanol.

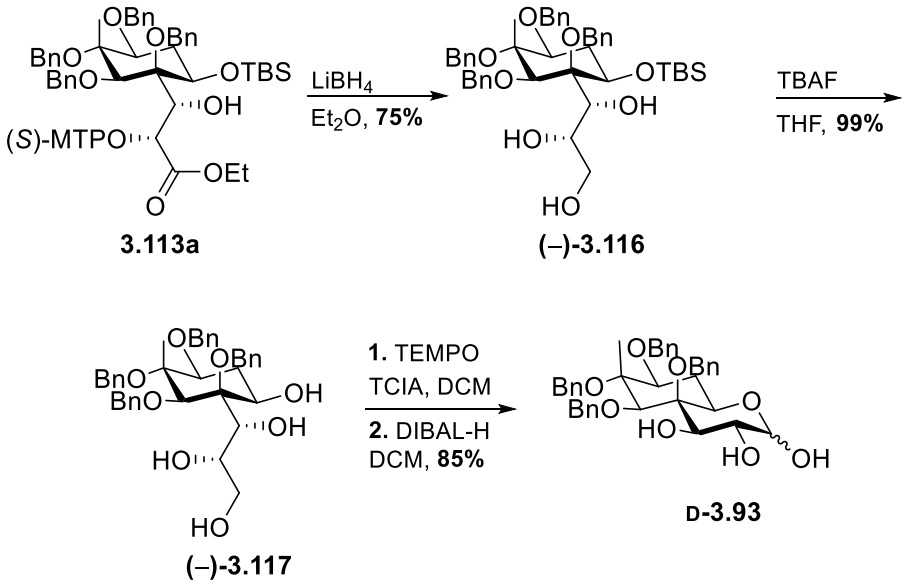
The last attempt explored was the removal of the auxiliary using a reducing agent, mindful that this approach would also reduce the ethyl ester present in compound **3.113b** (Scheme 3-45). This is not a serious problem, however, as the primary hydroxyl group in the product (**(–)-3.116**) could then be oxidized to the aldehyde to form the lactol **D-3.93** after deprotection of the TBS

group. The first reducing agent tried was $LiAlH_4$, but the yield of the desired compound **(–)-3.116** was only 50–60%. DIBAL-H was then used, but the chiral auxiliary was not cleaved using this reducing agent.



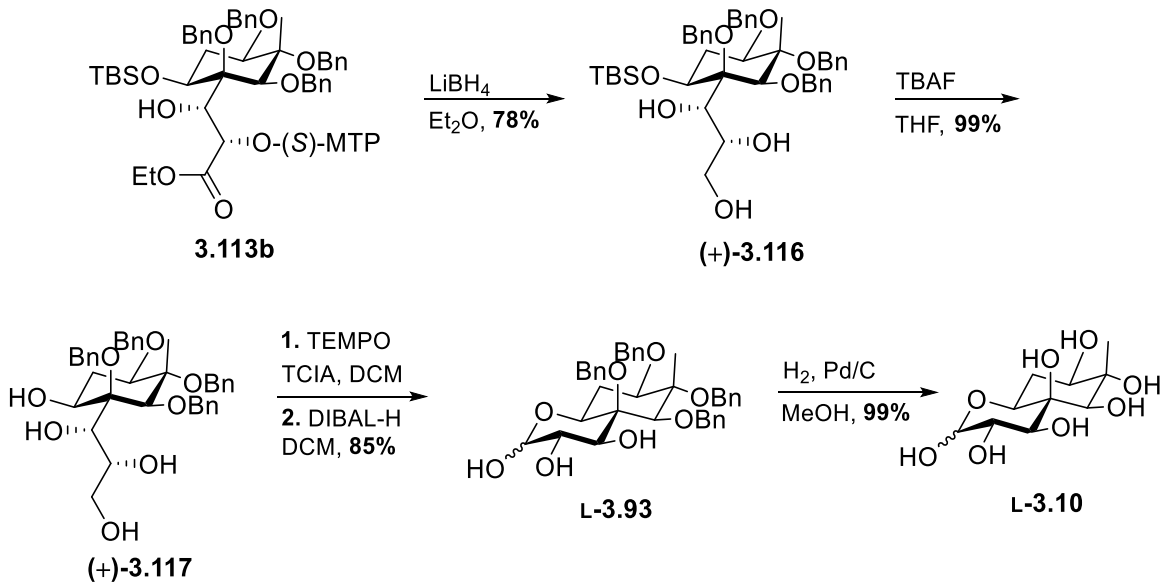
Scheme 3-45: Removal of the (*S*)-MTP ester in compound **3.113b** by reduction.

$LiBH_4$ is known to be a good reducing agent for esters and it is milder than $LiAlH_4$. This reagent was used to reduce compound **3.113b** and 75% of the desired compound **(–)-3.116** was obtained (Scheme 3-46). The TBS group was then deprotected using TBAF in 99% yield. The primary hydroxyl group of tetraol **(–)-3.117** was oxidized to form a mixture of lactol **D-3.93** and lactone **(+)-3.92** (overoxidation), and the mixture was reduced back to the lactol **D-3.93** using DIBAL-H in 85% yield for the two steps.[27] The product of this sequence is identical to the lactol converted previously to D-bradyrhizose (Scheme 3-42) by hydrogenation.



Scheme 3-46: Synthesis of D-lactol **D-3.93**.

The same procedure was done on diastereomer **3.113a** (Scheme 3-47) to provide L-bradyrhizose. First, reduction of **3.113a** with $LiBH_4$ gave triol **(+)-3.116** in 78% yield. The TBS protecting group was then deprotected using TBAF in 99%. The oxidation and reduction reactions were performed on intermediate **(+)-3.117** to give lactol **L-3.93** in 85% yield.[27] Finally, deprotection of the benzyl groups afforded L-bradyrhizose (**L-3.10**) in 99% yield. All enantiomers made in this sequence had the same specific rotation magnitudes as those in the D-series, with opposite signs.



Scheme 3-47: Synthesis of L-bradyrhizose (**L-3.10**).

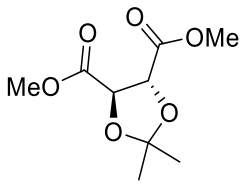
3.5 Summary

The racemic synthesis of bradyrhizose (**3.10**) was done starting from *myo*-inositol (**3.1**) in 25 steps with a 6% overall yield. Through derivitatization of intermediate **3.88** with (*S*)-MTPA, it was possible to resolve the racemic mixture. The resulting diastereomeric products **3.113a** and **3.113b** were converted to L-bradyrhizose (**L-3.10**), a new carbohydrate, and D-bradyrhizose (**D-3.10**), the natural monosaccharide. The next chapter will describe the synthesis of a donor and an acceptor from the lactol intermediates (**D-3.93** and **L-3.93**) to synthesize bradyrhizose-continaing disaccharides.

3.6 Experimental

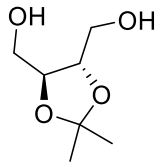
General Methods:

Reactions were carried out in oven-dried glassware. All reagents used were purchased from commercial sources and were used without further purification unless noted. Solvents used in reactions were purified by successive passage through columns of alumina and copper under argon. Unless stated otherwise, all reactions were carried out at room temperature under a positive pressure of argon and were monitored by TLC on silica gel 60 F254 (0.25 mm, E. Merck). Spots were detected under UV light or by charring with a solution of ammonium molybdate (12 g) and ceric ammonium nitrate (0.42 g) in H_2O (235 mL) and concentrated sulfuric acid (15 mL). Unless otherwise indicated, all column chromatography was performed on silica gel 60 (40–60 μM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 21 ± 2 °C at the sodium D line (589 nm) and are in units of deg·mL(dm·g)-1. ^{1}H NMR spectra were recorded at 500 MHz, and chemical shifts are referenced to either TMS (0.0 ppm, $CDCl_3$), HOD (4.78 ppm, D_2O) or DMSO-d_5 (2.50 ppm, quint, J_{HD} = 1.9 Hz, DMSO-d_6). ^{13}C NMR spectra were recorded at 125 MHz, and ^{13}C chemical shifts were referenced to internal $CDCl_3$ (77.2 ppm, $CDCl_3$), external dioxane (67.4 ppm, D_2O) or DMSO-d_6 (39.5 ppm, DMSO-d_6). In the processing of reaction mixtures, solutions of organic solvents were washed with equal amounts of aqueous solutions. Organic solutions were concentrated under vacuum at < 40°C (bath). Electrospray mass spectra were recorded on samples suspended in mixtures of THF with CH_3OH and added NaCl. The separation of the racemic mixture **3.88** and the determination of the enantiomeric excess for chiral compound **(–)-3.88** were done using an Agilent HPLC instrument with Chiralpak-IA (4.6 x 150 mm, inner diameter x length; particle size 5 μm) column (1:99 *i*-PrOH–hexanes) at 5 °C.



3.18

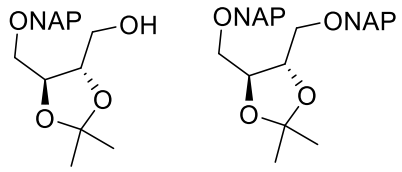
Dimethyl (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (3.18).[10] A solution of (+)-dimethyl L-tartrate (2.0 g, 11.2 mmol), 2,2-dimethoxypropane (4.2 mL), and *p*-TsOH·H_2O (10 mg 0.053 mmol) in acetone (2 mL) were heated at reflux for 24 h. The mixture was cooled to rt and the solvent was evaporated. The resulting crude product was purified by silica gel column chromatography (9:1 → 3:2 hexanes–EtOAc) to yield **3.18** (2.43 g, 99%) as yellow oil. R_f 0.60 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 4.79 (s, 2 H, H-4, H-5), 3.81 (s, 6 H, 2 x OCH_3), 1.48 (s, 6 H, 2 x CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.1 (C=O), 113.9 (C-2), 76.8 (C-4, C-5), 52.8 (OCH_3), 26.3 (CH_3).



3.19

(4*S*,5*S*)-2,2-Dimethyl-4,5-di(hydroxymethyl)-1,3-dioxolane (3.19).[10] A solution **3.18** (2.44 g, 11.2 mmol) in THF (24 mL) was added slowly (30 min) to a solution of $LiAlH_4$ (22.4 mL, 22.4 mmol, 1.0M in THF) at 0 °C. The mixture was heated at reflux for 30 min and then cooled to rt. Water (1.7 mL) was added slowly at 0 °C, followed by an aqueous solution of NaOH (0.85 mL, 15% w/v). The mixture was stirred for 3 h, and then filtered through a short column of silica (EtOAc). The resulting crude product was purified by silica gel column chromatography (2:3 → 0:1 hexanes–EtOAc) to yield **3.19** (1.22 g, 67%) as yellow oil. R_f 0.32 (2:3 hexanes–EtOAc); ^{1}H

NMR (500 MHz, $CDCl_3$, δ_H) 4.01–3.98 (m, 2 H, H-4 and H-5), 3.82–3.76 (m, 2 H, CH_2), 3.74–3.68 (m, 2 H, CH_2), 2.52 (br, 2 H, OH) 1.43 (s, 6 H, 2 x CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 109.3 (C-2), 78.1 (C-4 and C-5), 62.1 (CH_2), 27.0 (CH_3).

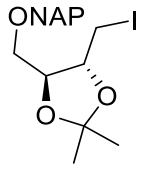


3.20 **3.21**

(4*S*,5*S*)-2,2-Dimethyl-5-hydroxymethyl-4-(2-naphthylmethyl)oxymethyl-1,3-dioxolane (3.20) and **(4*S*,5*S*)-2,2-Dimethyl-4,5-di-(2-naphthylmethyl)oxymethyl-1,3-dioxolane (3.21)**. Sodium hydride (36 mg, 0.901 mmol, 60% dispersion in mineral oil) was added to a cooled (−15 °C) solution of **3.19** (132 mg, 0.819 mmol) in DMF (3 mL). After stirring for 30 min, 2-(bromomethyl)naphthalene (199 mg, 0.901 mmol) was added to the reaction mixture and the stirring was continued overnight at −15 °C. Water was added, then the mixture was warmed to rt. The aqueous solution was extracted with EtOA and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to yield **3.20** (191 mg, 77%) and **3.21** (54 mg, 15%) as colorless oils. (**3.20**): R_f 0.27 (7:3 hexanes–EtOAc); $[\alpha]_D$ +6.8 (*c* 0.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.86–7.83 (m, 3 H, Ar), 7.78 (s, 1 H, Ar), 7.52–7.46 (m, 3 H, Ar), 4.78 (d, 1 H, *J* = 12.8 Hz, C$\underline{H}_2$Ar), 4.75 (d, 1 H, *J* = 12.8 Hz, C$\underline{H}_2$Ar), 4.10 (ddd, 1 H, *J* = 5.3 Hz, *J* = 8.3 Hz, *J* = 8.3 Hz, H-4), 3.97 (ddd, 1 H, *J* = 4.4 Hz, *J* = 8.3 Hz, *J* = 8.4 Hz, H-5), 3.80 (ddd, 1 H, *J* = 4.2 Hz, *J* = 8.4 Hz, *J* = 11.7 Hz, C$\underline{H}_2$OH), 3.74 (dd, 1 H, *J* = 5.1 Hz, *J* = 9.9 Hz, C$\underline{H}_2$ONAP), 3.73–3.68 (m, 1H, C$\underline{H}_2$OH), 3.61 (dd, 1 H, *J* = 5.7 Hz, *J* = 9.9 Hz, C$\underline{H}_2$ONAP), 2.24 (dd, 1 H, *J* = 4.6 Hz, *J* = 8.1 Hz, OH), 1.44 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 135.0 (Ar), 133.2 (Ar), 133.1 (Ar),

128.3 (Ar), 127.9 (Ar), 127.7 (Ar), 126.7 (Ar), 126.2 (Ar), 126.0 (Ar), 125.7 (Ar), 109.4 (C-2), 79.6 (C-4), 76.6 (C-5), 73.8 ($\underline{C}H_2Ar$), 70.4 ($\underline{C}H_2ONAP$), 62.4 (CH_2OH), 27.0(2) (CH_3), 27.0(0) (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{18}H_{22}NaO_4$: 325.1410. Found 325.1407.

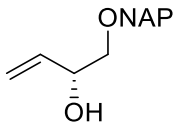
(**3.21**): R_f 0.24 (9:1 hexanes–EtOAc); $[\alpha]_D$ –20.9 (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.87–7.81 (m, 6 H, Ar), 7.79 (s, 2 H, Ar), 7.53−7.49 (m, 4 H, Ar), 7.48 (d, 1 H, J = 1.8 Hz, Ar), 7.46 (d, 1 H, J = 1.7 Hz, Ar), 4.79 (d, 2 H, J = 12.3 Hz, $C\underline{H}_2Ar$), 4.76 (d, 2 H, J = 12.3 Hz, $C\underline{H}_2Ar$), 4.17–4.12 (m, 2 H, H-4, H-5), 3.73–3.68 (m, 4 H, 4 x $C\underline{H}_2ONAP$), 1.51 (s, 6 H, 2 x CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 135.5 (Ar), 133.3 (Ar), 133.0 (Ar), 128.2 (Ar), 127.9 (Ar), 127.7 (Ar), 126.5 (Ar), 126.1 (Ar), 125.9 (Ar), 125.7 (Ar), 109.8 (C-2), 77.6 (C-4, C-5), 73.7 ($\underline{C}H_2Ar$), 70.8 ($\underline{C}H_2ONAP$), 27.1 (CH_3). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{29}H_{34}NO_4$: 460.2482. Found 460.2484.



3.22

(4*R*,5*S*)-2,2-Dimethyl-4-iodomethyl-5-(2-naphthylmethyl)oxymethyl-1,3-dioxolane (3.22). Imidazole (214 mg, 2.10 mmol), triphenylphosphine (826 mg, 3.15 mmol) and iodine (800 mg, 3.15 mmol) were added to a solution of **3.20** (635 mg, 2.10 mmol) in THF (6 mL). After stirring for 2 h, water was added and the aqueous solution was extracted with Et_2O. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.22** (753 mg, 87%) as a colorless oil. R_f 0.42 (9:1 hexanes–EtOAc); $[\alpha]_D$ –10.9 (*c* 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.87–

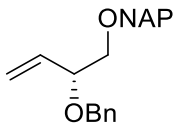
7.83 (m, 3 H, Ar), 7.80 (s, 1 H, Ar), 7.52–7.46 (m, 3 H, Ar), 4.79 (d, 1 H, J = 12.7 Hz, C$\underline{H}_2$Ar), 4.76 (d, 1 H, J = 12.7 Hz, C$\underline{H}_2$Ar), 4.02 (ddd, 1 H, J = 5.0 Hz, J = 5.1 Hz, J = 7.5 Hz, H-5), 3.90 (ddd, 1 H, J = 5.1 Hz, J = 5.3 Hz, J = 7.5 Hz, H-4), 3.73 (dd, 1 H, J = 5.1 Hz, J = 10.3 Hz, C$\underline{H}_2$ONAP), 3.69 (dd, 1 H, J = 5.0 Hz, J = 10.3 Hz, C$\underline{H}_2$ONAP), 3.38 (dd, 1 H, J = 5.1 Hz, J = 10.5 Hz, C$\underline{H}_2$I), 3.31 (dd, 1 H, J = 5.3 Hz, J = 10.5 Hz, C$\underline{H}_2$I), 1.50 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 135.3 (Ar), 133.3 (Ar), 133.1 (Ar), 128.3 (Ar), 127.9 (Ar), 127.7 (Ar), 126.5 (Ar), 126.2 (Ar), 126.0 (Ar), 125.6 (Ar), 109.9 (C-2), 80.1 (C-5), 77.7 (C-4), 73.7 (C$\underline{H}_2$Ar), 70.6 (C$\underline{H}_2$ONAP), 27.4 (CH_3), 27.3 (CH_3), 6.4 (C$\underline{H}_2$I). HRMS (ESI) Calcd for [M + K]$^+$ $C_{18}H_{21}IKO_3$: 451.0167. Found 451.0168.



3.23

(*R*)-1-(2-Naphthylmethyloxy)but-3-en-2-ol (3.23). Zinc metal (1.89 g, 28.9 mmol) and acetic acid (2.07 mL, 36.2 mmol) were added to a solution of **3.22** (750 mg, 1.82 mmol) in THF (6 mL). After stirring for 6 h, the reaction mixture was filtered through Celite® 545 and the precipitate was washed with Et_2O. The filtrate was diluted with Et_2O and washed with water. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (4:1 hexanes–EtOAc) to give **3.23** (361 mg, 87%) as a colorless oil. R_f 0.42 (7:3 hexanes–EtOAc); $[\alpha]_D$ +2.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.87–7.83 (m, 3 H, Ar), 7.80 (s, 1 H, Ar), 7.53–7.47 (m, 3 H, Ar), 5.87 (ddd, 1 H, $J_{2,3}$ = 5.5 Hz, $J_{3,4cis}$ = 10.6 Hz, $J_{3,4trans}$ = 17.2 Hz, H-3), 5.39 (ddd, 1 H, $J_{2,4trans}$ = 1.5 Hz, $J_{4cis,4trans}$ = 1.5 Hz, $J_{3,4trans}$ = 17.2 Hz, H-4 *trans*), 5.22 (ddd, 1 H, $J_{2,4cis}$ = 1.5 Hz, $J_{4cis,4trans}$ = 1.5 Hz, $J_{3,4cis}$ = 10.6 Hz, H-4 *cis*), 4.77 (d, 1 H, J = 12.7 Hz, C$\underline{H}_2$Ar), 4.74 (d, 1 H, J = 12.7 Hz, C$\underline{H}_2$Ar), 4.43–4.37 (m, 1 H, H-2), 3.60

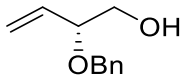
(dd, 1 H, J = 3.5 Hz, J = 9.7 Hz, H-1), 3.44 (dd, 1 H, J = 8.1 Hz, J = 9.7 Hz, H-1), 2.55 (d, 1 H, J = 3.5 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 136.6 (C-3), 135.3 (Ar), 133.3 (Ar), 133.1 (Ar), 128.3 (Ar), 127.9 (Ar), 127.8 (Ar), 126.6 (Ar), 126.2 (Ar), 126.0 (Ar), 125.7 (Ar), 116.5 (C-4), 74.1 ($\underline{C}H_2Ar$), 73.5 (C-1), 71.6 (C-2). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{15}H_{16}NaO_2$: 251.1043. Found 251.1039.



3.24

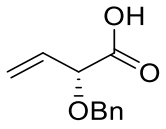
(*R*)-2-(Benzyloxy)-1-(2-naphthylmethyloxy)but-3-ene (3.24). Sodium hydride (76 mg, 1.90 mmol, 60% dispersion in mineral oil) was added to a solution of **3.23** (360 mg, 1.58 mmol) in DMF (4 mL). After stirring for 30 min, benzyl bromide (206 μL, 1.73 mmol) was added and the reaction mixture was stirred for 3 h. Water was added and the aqueous solution was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.24** (468 mg, 93%) as a yellow oil. R_f 0.41 (9:1 hexanes–EtOAc); $[\alpha]_D$ +14.5 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.86–7.78 (m, 4 H, Ar), 7.51–7.46 (m, 3 H, Ar), 7.41–7.27 (m, 5 H, Ar), 5.85 (ddd, 1 H, $J_{2,3}$ = 7.2 Hz, $J_{3,4cis}$ = 10.4 Hz, $J_{3,4trans}$ = 17.3 Hz, H-3), 5.70 (ddd, 1 H, $J_{2,4trans}$ = 1.3 Hz, $J_{4cis,4trans}$ = 1.7 Hz, $J_{3,4trans}$ = 17.3 Hz, H-4 *trans*), 5.33 (ddd, 1 H, $J_{2,4cis}$ = 1.1 Hz, $J_{4cis,4trans}$ = 1.7 Hz, $J_{3,4cis}$ = 10.4 Hz, H-4 *cis*), 4.78 (d, 1 H, J = 12.5 Hz, $C\underline{H}_2Ar$), 4.74 (d, 1 H, J = 12.5 Hz, $C\underline{H}_2Ar$), 4.70 (d, 1 H, J = 12.1 Hz, $C\underline{H}_2Ar$), 4.52 (d, 1 H, J = 12.1 Hz, $C\underline{H}_2Ar$), 4.13–4.08 (m, 1 H, H-2), 3.67 (dd, 1 H, J = 6.6 Hz, J = 10.3 Hz, H-1), 3.61 (dd, 1 H, J = 4.4 Hz, J = 10.3 Hz, H-1); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.6 (Ar), 135.9 (Ar), 135.8 (C-3), 133.3 (Ar), 133.0 (Ar), 128.3 (Ar), 128.1 (Ar), 127.9 (Ar), 127.7(4) (Ar), 127.7(1) (Ar), 127.5 (Ar), 126.3 (Ar), 126.1 (Ar), 125.8

(Ar), 125.7 (Ar), 118.4 (C-4), 79.5 (C-2), 73.4 (<u>C</u>H_2Ar), 73.1 (C-1), 71.6 (<u>C</u>H_2Ar). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{22}H_{26}NO_2$: 336.1958. Found 336.1960.



3.25

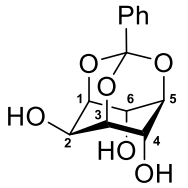
(*R*)-2-(Benzyloxy)but-3-en-1-ol (3.25). DDQ (105 mg, 0.462 mmol) was added to a solution of **3.24** (98 mg, 0.308 mmol) in CH_2Cl_2 (9 mL) and H_2O (1 mL). After stirring for 4 h, the reaction mixture was diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$ and water. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.25** (34 mg, 61%) as a colourless oil. R_f 0.39 (7:3 hexanes–EtOAc); $[\alpha]_D$ –49.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.39–7.29 (m, 5 H, Ar), 5.78 (ddd, 1 H, $J_{2,3}$ = 7.3 Hz, $J_{3,4cis}$ = 10.5 Hz, $J_{3,4trans}$ = 17.4 Hz, H-3), 5.38 (ddd, 1 H, $J_{2,4trans}$ = 1.1 Hz, $J_{4cis,4trans}$ = 1.7 Hz, $J_{3,4trans}$ = 17.4 Hz, H-4 *trans*), 5.36 (ddd, 1 H, $J_{2,4cis}$ = 0.9 Hz, $J_{4cis,4trans}$ = 1.7 Hz, $J_{3,4cis}$ = 10.5 Hz, H-4 *cis*), 4.68 (d, 1 H, *J* = 11.7 Hz, C<u>H</u>$_2$Ar), 4.42 (d, 1 H, *J* = 11.6 Hz, C<u>H</u>$_2$Ar), 4.00–3.95 (m, 1 H, H-2), 3.65–3.58 (m, 2 H, 2 x H-1), 2.06 (dd, 1 H, *J* = 5.7 Hz, *J* = 7.3 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.1 (Ar), 135.1 (C-3), 128.5 (Ar), 127.9 (Ar), 127.8 (Ar), 119.4 (C-4), 81.1 (C-2), 70.6 (<u>C</u>H_2Ar), 65.3 (C-1). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{11}H_{14}NaO_2$: 201.0886. Found 201.0886.



3.26

(*R*)-2-(Benzyloxy)but-3-enoic acid (3.26). A 5% aqueous solution of $NaHCO_3$ (1.45 mL) was added to a solution of **3.25** (99 mg, 0.555 mmol) in acetone (4 mL). The reaction mixture was

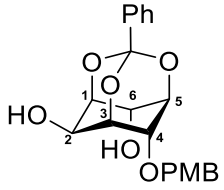
cooled to 0 °C and potassium bromide (7 mg, 0.055 mmol) and TEMPO (87 mg, 0.555 mmol) were added. A 5% aqueous solution of NaOCl (1.25 mL) was then added dropwise over 20 min. The reaction mixture was vigorously stirred and kept at 0 °C for 1 h. A 5% aqueous solution of NaOCl (1.25 mL) and a 5% aqueous solution of $NaHCO_3$ (1.45 mL) were then added and the reaction mixture was stirred at 0 °C for an additional 2 h. The acetone was removed by evaporation and the aqueous solution was washed with Et_2O. The aqueous solution was acidified to pH 3.5 with a 10% aqueous solution of citric acid and extracted with EtOAc. The EtOAc solution was washed with water and brine, then dried (Na_2SO_4), filtered and concentrated. The resulting product was not further purified and yielded **3.26** (69 mg, 65%) as a colorless oil. R_f 0.30 (3:2 hexanes–EtOAc); $[\alpha]_D$ –10.7 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.40–7.32 (m, 5 H, Ar), 5.93 (ddd, 1 H, $J_{2,3}$ = 6.2 Hz, $J_{3,4cis}$ = 10.3 Hz, $J_{3,4trans}$ = 17.2 Hz, H-3), 5.56 (ddd, 1 H, $J_{2,4\ trans}$ = 1.3 Hz, $J_{4cis,4\ trans}$ = 1.3 Hz, $J_{3,4trans}$ = 17.2 Hz, H-4 *trans*), 5.44 (ddd, 1 H, $J_{2,4\ cis}$ = 1.3 Hz, $J_{4\ cis,4\ trans}$ = 1.3 Hz, $J_{3,4\ cis}$ = 10.3 Hz, H-4 *cis*), 4.68 (d, 1 H, *J* = 11.7 Hz, C$\underline{H}_2$Ar), 4.64 (d, 1 H, *J* = 11.7 Hz, C$\underline{H}_2$Ar), 4.49 (ddd, 1 H, $J_{2,4}$ = 1.3 Hz, $J_{2,4}$ = 1.3 Hz, $J_{2,3}$ = 6.2 Hz, H-2); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 174.0 (C=O), 136.6 (Ar), 131.7 (C-3), 128.6 (Ar), 128.3 (Ar), 128.1 (Ar), 120.3 (C-4), 78.2 (C-2), 71.6 (C$\underline{H}_2$Ar). HRMS (ESI) Calcd for $[M - H]^+$ $C_{11}H_{11}O_3$: 192.0786. Found 192.0784.



3.27

***myo*-Inositol 1,3,5-orthobenzoate (3.27)**.[13] Oven dried *myo*-inositol (2.0 g, 11.1 mmol), CSA (52 mg, 0.222 mmol), and trimethylorthobenzoate (2.0 mL, 11.7 mmol) in dry DMSO (3.6 mL) were heated to 70 °C on a rotary evaporator for 4 h. The mixture was cooled to rt and neutralized using

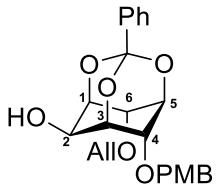
Et_3N (31 μL, 0.222 mmol). The DMSO was evaporated and water was added. The precipitate was filtered. The solid was dried, then recrystallized from EtOAc to give **3.27** (2.21 g, 75%) as a white solid. R_f 0.22 (2:3 hexanes–EtOAc); ^{1}H NMR (500 MHz, DMSO-d_6, δ_H) 7.57–7.54 (m, 2 H, Ar), 7.38–7.32 (m, 3 H, Ar), 5.50 (br, 2 H, C-4-OH, C-6-OH), 5.32 (br, 1 H, C-2-OH), 4.41–4.39 (m, 2 H, H-4, H-6), 4.22–4.19 (m, 1 H, H-5), 4.17–4.14 (m, 2 H, H-1, H-3), 4.09–4.06 (m, 1 H, H-2); ^{13}C NMR (125 MHz, DMSO-d_6, δ_C) 137.8 (Ar), 129.0 (Ar), 127.5 (Ar), 125.4 (Ar), 106.4 (C-Ar), 75.8 (C-1, C-3), 70.1 (C-5), 67.2 (C-4, C-6), 57.7 (C-2).



3.35

***Racemic* 4-*O*-(4-methoxybenzyl)-*myo*-inositol 1,3,5-orthobenzoate (3.35)**.[6] Sodium hydride (981 mg, 24.5 mmol, 60% dispersion in mineral oil) was added to a cooled (0 °C) solution of **3.27** (5.94 g, 22.3 mmol) in DMF (47 mL). The reaction mixture was stirred for 30 min at 0 °C, then a solution of *p*-methoxybenzyl chloride (3.03 mL, 22.3 mmol) in DMF (11 mL) was added. The reaction mixture warmed to rt overnight. Water was then added and the reaction mixture was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (4:1 → 3:2 hexanes–EtOAc) to give **3.35** (7.31 g, 85%) as a colourless oil. R_f 0.21 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.64–7.60 (m, 2 H, Ar), 7.39–7.35 (m, 3 H, Ar), 7.30–7.26 (m, 2 H, Ar), 6.95–6.91 (m, 2 H, Ar), 4.68 (d, 1 H, J = 11.4 Hz, CH_2Ar), 4.64 (d, 1 H, J = 11.4 Hz, CH_2Ar), 4.61–4.56 (m, 1 H, H-6), 4.55–4.52 (m, 1 H, H_{inos}), 4.43–4.40 (m, 2 H, 2 x H_{inos}), 4.39–4.36 (m, 1 H, H_{inos}), 4.15 (ddd, 1 H, J = 2.0 Hz, J = 2.2 Hz, $J_{2,OH}$ = 12.1 Hz, H-2), 3.84 (s, 3 H, CH_3), 3.79 (d, 1 H, $J_{6,OH}$

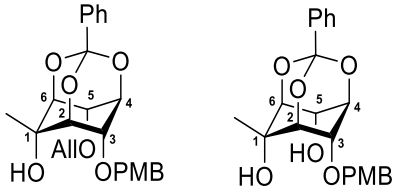
= 10.5 Hz, C-6-OH), 3.11 (d, 1 H, $J_{2,OH}$ = 11.9 Hz, C-2-OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 160.1 (Ar), 136.6 (Ar), 129.9 (Ar), 129.7 (Ar), 128.1 (Ar), 127.9 (Ar), 125.2 (Ar), 114.3 (Ar), 107.4 (<u>C</u>Ar), 76.1 (C_{inos}), 73.7 (C_{inos}), 73.7 (<u>C</u>H_2Ar), 72.9 (C_{inos}), 68.2 (C_{inos}), 67.8 (C-6), 60.1 (C-2), 55.4 (CH_3).



3.36

***Racemic* 6-*O*-allyl-4-*O*-(4-methoxybenzyl)-*myo*-inositol 1,3,5-orthobenzoate (3.36)**.[6] *n*-Butyllithium (2.7 mL, 6.73 mmol, 2.5M in hexanes) was added to a cooled (0 °C) solution of **3.35** (2.16 g, 5.61 mmol) in THF (22 mL). The reaction mixture was stirred for 5 min at 0 °C, then a solution of AllBr (0.51 mL, 5.89 mmol) in DMF (10.7 mL) was added. The reaction mixture was stirred for 48 h while warming to rt. Ice was added and the reaction mixture was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 → 3:2 hexanes–EtOAc) to give **3.36** (1.72 g, 72%) as a colourless oil. R_f 0.49 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.65–7.62 (m, 2 H, Ar), 7.40–7.35 (m, 3 H, Ar), 7.30–7.27 (m, 2 H, Ar), 6.91–6.88 (m, 2 H, Ar), 5.93 (app ddt, 1 H, J = 17.1 Hz, J = 10.3 Hz, J = 5.7 Hz, C<u>H</u>=CH_2), 5.32 (app dq, 1 H, J = 17.3 Hz, J = 1.7 Hz, *trans*), 5.23 (app dq, 1 H, J = 10.5 Hz, J = 1.3 Hz, CH=C<u>H</u>$_2$ *cis*), 4.65 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.56 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.54–4.51 (m, 1 H, H_{inos}), 4.47–4.42 (m, 3H, H_{inos}), 4.39–4.36 (m, 1H, H_{inos}), 4.24–4.10 (m, 3H, H-2, C<u>H</u>$_2$CH=CH_2), 3.82 (s, 3 H, CH_3), 3.06 (d, 1 H, J = 11.9 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.4 (Ar), 137.0 (Ar), 134.1 (<u>C</u>H=CH_2), 129.7 (Ar), 129.6 (Ar), 129.3 (Ar), 128.1 (Ar), 125.2 (Ar), 117.7 (CH=<u>C</u>H_2), 113.9

(Ar), 108.0 (CAr), 74.4(4) (C_{inos}), 74.4(0) (C_{inos}), 73.6 (C_{inos}), 73.2 (C_{inos}), 71.3 (CH_2Ar), 70.9 ($CH_2CH=CH_2$), 68.7 (C_{inos}), 60.7 (C-2), 55.3 (CH_3).

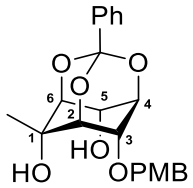


3.33 **3.37**

***Racemic* 5-*O*-allyl-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-*scyllo*-inositol 2,4,6-orthobenzoate (3.33) and *racemic* 3-*O*-(4-methoxybenzyl)-1-*C*-methyl-*scyllo*-inositol 2,4,6-orthobenzoate (3.37)**. A solution of DMSO (16.2 mL, 227 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a cooled (–78 °C) solution of oxalyl chloride (14.0 mL, 165 mmol) in CH_2Cl_2 (50 mL). After 30 min, a solution of **3.36** (29.4 g, 68.9 mmol) in CH_2Cl_2 (250 mL) was added slowly to the reaction mixture. After 1 h, Et_3N (0.51 mL, 5.89 mmol) was added slowly and the reaction mixture was stirred for an additional hour at –78 °C and then warmed to rt. The solution was concentrated and the crude compound was used without purification for the next step. THF (600 mL) was added to the crude compound and the mixture was sonicated for 15 min. The reaction mixture was then cooled (–78 °C) and methylmagnesium bromide solution (115 mL, 344 mmol) was added dropwise. After 1 h, a saturated aqueous solutiom of NH_4Cl was added slowly to the reaction mixture at –78 °C. The mixture was warmed to rt, then water and CH_2Cl_2 were added. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 → 4:1 hexanes–EtOAc) to give **3.33** (28.7 g, 95%) as a colorless oil and **3.37** (715 mg, 3%) as a white solid. (**3.33**): R_f 0.40 (4:1 hexanes–EtOAc); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.63–7.57 (m, 2 H, Ar), 7.38–7.34 (m, 3 H, Ar), 7.30–7.27 (m, 2 H, Ar), 6.91–6.87 (m, 2 H, Ar), 5.90 (app ddt, 1 H, J = 17.2 Hz, J = 10.4 Hz, J = 5.7 Hz, CH=CH_2),

5.27 (app dq, 1 H, J = 17.2 Hz, J = 1.5 Hz, CH=C$\underline{H}_2$ *trans*), 5.20 (app dq, 1 H, J = 10.4 Hz, J = 1.5 Hz, CH=C$\underline{H}_2$ *cis*), 4.69–4.3 (m, 4 H, C$\underline{H}_2$Ar, OH, 2 x H_{inos}), 4.54–4.50 (m, 2 H, 2 x H_{inos}), 4.23–4.14 (m, 4 H, 2 x C$\underline{H}_2$CH=CH$_2$, 2 x H_{inos}), 3.82 (s, 3 H, OCH_3), 1.63 (d, 3 H, $J_{CH3,OH}$ = 1.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.4 (Ar), 136.7 (Ar), 133.6 (C$\underline{H}$=CH$_2$), 129.6 (Ar), 129.1 (Ar), 128.1 (Ar), 125.3 (Ar), 117.9 (CH=C$\underline{H}_2$), 113.9 (Ar), 107.5 (C$\underline{C}$Ar), 74.2(3) (C_{inos}), 74.2(0) (C_{inos}), 74.0 (C_{inos}), 73.6 (C_{inos}), 71.4 (C-1), 70.6 (C$\underline{H}_2$Ar), 68.5 (C_{inos}), 67.7 (C$\underline{H}_2$CH=CH$_2$), 55.3 (OCH_3), 25.0 (CH_3). HRMS (ESI) Calcd for $[M + H]^+$ $C_{25}H_{29}O_7$: 441.1908. Found 441.1900.

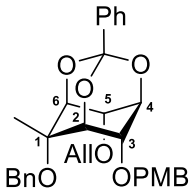
(**3.37**): mp = 117−119 °C; R_f 0.28 (7:3 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.62–7.58 (m, 2 H, Ar), 7.38–7.34 (m, 3 H, Ar), 7.32–7.28 (m, 2 H, Ar), 6.93–6.89 (m, 2 H, Ar), 4.72 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.72–4.68 (m, 1 H, H-5), 4.67 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.59–4.55 (m, 2 H, H-2, H-3), 4.19–4.15 (m, 2 H, H-4, H-6), 3.94 (d, 1 H, J = 0.6 Hz, OH), 3.82 (s, 3 H, OCH_3), 3.30 (d, 1 H, J = 7.9 Hz, OH), 1.66 (d, 3 H, $J_{CH3,OH}$ = 1.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.4 (Ar), 136.4 (Ar), 129.9 (Ar), 129.6 (Ar), 128.6 (Ar), 128.1 (Ar), 125.4 (Ar), 114.1 (Ar), 107.2 (C$\underline{C}$Ar), 75.5 (C_{inos}), 74.0(1) (C_{inos}), 74.0(0) (C_{inos}), 72.1 (C$\underline{H}_2$Ar), 69.8 (C_{inos}), 68.8 (C-1), 68.4 (C-2), 55.3 (OCH_3), 26.1 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{22}H_{24}NaO_7$: 423.1414. Found 423.1415.



3.37

***Racemic* 3-*O*-(4-methoxybenzyl)-1-*C*-methyl-*scyllo*-inositol 2,4,6-orthobenzoate (3.37)**. To a solution of **3.36** (51 mg, 0.116 mmol) in THF (0.6 mL), degassed under vacuum and stirring under an Ar atmosphere, (1,5-cyclooctadiene)bis-(methyldiphenylphosphine)iridium I

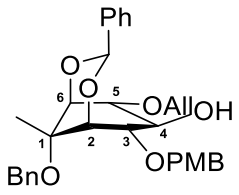
hexafluorophosphate catalyst (5 mg, 0.00637 mmol) was added followed by further degassing of the mixture under vacuum. The suspension was stirred for 15 min at 0 °C, and the catalyst was then activated with H_2 (2 min under a H_2 atmosphere). At this point, the solution became nearly colorless. The excess H_2 was removed by three cycles of placing the flask under vacuum and then flushing the flask with Ar. The reaction mixture was then stirred for 3 h at rt under an Ar atmosphere. The solvent was then evaporated, and the residue was dissolved in acetone–water (10:1, 4.45 mL) before HgO (35 mg, 0.162 mmol) and $HgCl_2$ (38 mg, 0.139 mmol) were added. After 1 h, the solvent was evaporated and the residue was diluted with Et_2O and washed with a 10% aqueous solution of KI, a saturated aqueous solution of $Na_2S_2O_3$, and water. The aqueous layers were extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (7:3 hexanes–EtOAc) to give **3.37** (40 mg, 87%) as a white solid. The mp, R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained on the same compound (**3.37**) previously described.



3.38

***Racemic* 5-*O*-allyl-1-*O*-benzyl-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-*scyllo*-inositol 2,4,6-orthobenzoate (3.38)**. Sodium hydride (5.22 g, 130 mmol, 60% wt in mineral oil), benzyl bromide (23.2 mL, 196 mmol) and TBAI (2.41 g, 6.52 mmol) were added to a solution of **3.36** (28.7 g, 65.2 mmol) in THF (600 mL). The reaction mixture was heated at reflux for 2 h. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography

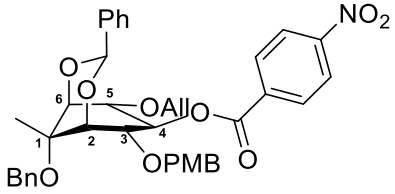
(19:1 to 17:3 hexanes–EtOAc) to give **3.38** (32.9 g, 95%) as a yellow oil. R_f 0.60 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.66–7.62 (m, 2 H, Ar), 7.40–7.36 (m, 5 H, Ar), 7.21–7.15 (m, 5 H, Ar), 6.80–6.76 (m, 2 H, Ar), 5.87 (app ddt, 1 H, J = 17.2 Hz, J = 10.5 Hz, J = 5.9 Hz, C<u>H</u>=CH_2), 5.22 (app dq, 1 H, J = 17.2 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *trans*), 5.13 (app dq, 1 H, J = 10.5 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *cis*), 4.66–4.63 (m, 3 H, 2 x C<u>H</u>$_2$Ar, H_{inos}), 4.59 (s, 2 H, 2 x C<u>H</u>$_2$Ar), 4.52 (ddd, 1 H, J = 6.6 Hz, J = 3.3 Hz, J = 1.3 Hz, H_{inos}), 4.49 (ddd, 1 H, J = 6.6 Hz, J = 3.3 Hz, J = 1.3 Hz, H_{inos}), 4.45–4.41 (m, 2 H, 2 x H_{inos}), 4.17–4.10 (m, 2 H, 2 x C<u>H</u>$_2$CH=CH_2), 3.80 (s, 3 H, OCH_3), 1.80 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.1 (Ar), 138.9 (Ar), 136.9 (Ar), 134.7 (<u>C</u>H=CH_2), 130.2 (Ar), 129.5 (Ar), 128.1 (Ar), 127.8 (Ar), 127.5 (Ar), 126.8 (Ar), 125.3 (Ar), 117.3 (CH=<u>C</u>H_2), 113.6 (Ar), 108.1 (<u>C</u>Ar), 74.1 (C_{inos}), 73.9 (C_{inos}), 73.8 (C_{inos}), 73.7 (C_{inos}), 71.4 (<u>C</u>H_2Ar), 71.1 (<u>C</u>H_2CH=CH_2), 70.9 (C-1), 69.2 (C_{inos}), 63.8 (<u>C</u>H_2Ar), 55.3 (OCH_3), 21.7 (CH_3). HRMS (ESI) Calcd for $[M + K]^+$ $C_{32}H_{34}KO_7$: 569.1936. Found 569.1932.



3.39

***Racemic* 5-*O*-allyl-1-*O*-benzyl-2,6-*O*-benzylidene-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-*scyllo*-inositol (3.39)**. DIBAL-H (109 mL, 109 mmol, 1.0M in toluene) was added to a cooled (0 °C) solution of **3.38** (10.5 g, 19.8 mmol) in toluene (140 mL). The reaction mixture was stirred at 0 °C for 30 min. A saturated aqueous solution of potassium sodium tartrate and CH_2Cl_2 were added at 0 °C and the mixture was stirred overnight while warming to rt. The aqueous solution was extracted with CH_2Cl_2 and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give

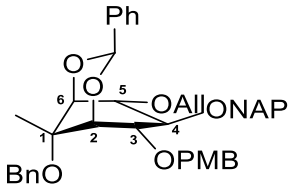
3.39 (9.17 g, 87%) as a colourless oil. R_f 0.23 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.50–7.47 (m, 2 H, Ar), 7.43–7.35 (m, 5 H, Ar), 7.33–7.29 (m, 2 H, Ar), 7.28–7.23 (m, 3 H, Ar), 6.88–6.84 (m, 2 H, Ar), 5.93 (app ddt, 1 H, J = 17.2 Hz, J = 10.4 Hz, J = 5.7 Hz, C<u>H</u>=CH_2), 5.59 (s, 1 H, C<u>H</u>Ar), 5.30 (app dq, 1 H, J = 17.2 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *trans*), 5.18 (app dq, 1 H, J = 10.4 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *cis*), 4.76 (d, 1 H, J = 11.7 Hz, C<u>H</u>$_2$Ar), 4.63 (s, 2 H, 2 x C<u>H</u>$_2$Ar), 4.59 (d, 1 H, J = 1.7 Hz, C<u>H</u>$_2$Ar), 4.54 (ddd, 1 H, J = 7.7 Hz, J = 7.7 Hz, J = 2.8 Hz, H-4), 4.29–4.24 (m, 1 H, C<u>H</u>$_2$CH=CH_2), 4.26 (d, 1 H, J = 2.6 Hz, H-2/H-6), 4.19 (d, 1 H, J = 2.4 Hz, H-2/H-6), 4.15 (app ddt, 1 H, J = 13.2 Hz, J = 5.7 Hz, J = 1.5 Hz, C<u>H</u>$_2$CH=CH_2), 3.94 (d, 1 H, J = 7.5 Hz, H-3/H-5), 3.89 (d, 1 H, J = 7.5 Hz, H-3/H-5), 3.80 (s, 3 H, OCH_3), 2.43 (d, 1 H, J = 3.3 Hz, OH), 1.78 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.3 (Ar), 138.4 (Ar), 137.5 (Ar), 134.6 (<u>C</u>H=CH_2), 130.2 (Ar), 129.4(0) (Ar), 129.3(8) (Ar), 128.5 (Ar), 128.3 (Ar), 127.5 (Ar), 127.3 (Ar), 126.4 (Ar), 117.2 (CH=<u>C</u>H$_2$), 113.9 (Ar), 92.7 (<u>C</u>HAr), 82.9 (C-3/C-5), 82.7 (C-3/C-5), 78.4 (C-2/C-6), 78.3 (C-2/C-6), 74.8 (C-4), 73.4 (<u>C</u>H$_2$CH=CH_2), 71.3 (<u>C</u>H$_2$Ar), 70.8 (C-1), 63.7 (<u>C</u>H$_2$Ar), 55.3 (OCH_3), 19.3 (CH_3). HRMS (ESI) Calcd for $[M + H]^+$ $C_{32}H_{37}O_7$: 533.2534. Found 533.2534.



3.40

Racemic **5-*O*-allyl-1-*O*-benzyl-2,6-*O*-benzylidene-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-(4-nitrobenzoate)-*scyllo*-inositol (3.40)**. *p*-Nitrobenzoyl chloride (10 mg, 0.0518 mmol) was added to a solution of **3.39** (23 mg, 0.0432 mmol) and DMAP (8 mg, 0.0648 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 2 h at rt. Water was added and the mixture was

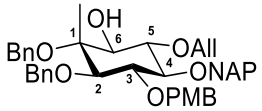
extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.40** (29 mg, 99%) as a yellow oil. R_f 0.44 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.27 (d, 2 H, J = 8.4 Hz, Ar), 8.09 (d, 2 H, J = 8.4 Hz, Ar), 7.56–7.37 (m, 10 H, Ar), 7.08 (d, 2 H, J = 8.1 Hz, Ar), 6.56 (d, 2 H, J = 8.1 Hz, Ar), 6.21 (dd, 1 H, $J_{3,4}$ = 8.1 Hz, $J_{4,5}$ = 8.1 Hz, H-4), 5.74 (s, 1 H, C<u>H</u>Ar), 5.74–5.64 (m, 1 H, C<u>H</u>=CH$_2$), 5.16 (d, 1 H, J = 17.2 Hz, CH=C<u>H$_2$</u> *trans*), 5.04 (d, 1 H, J = 10.6 Hz, CH=C<u>H$_2$</u> *cis*), 4.72 (s, 2 H, 2 x C<u>H$_2$</u>Ar), 4.66 (d, 1 H, J = 12.2 Hz, C<u>H$_2$</u>Ar), 4.38 (d, 1 H, J = 12.2 Hz, C<u>H$_2$</u>Ar), 4.34 (d, 1 H, J = 2.0 Hz, H-2/H-6), 4.27 (d, 1 H, J = 2.0 Hz, H-2/H-6), 4.18–4.10 (m, 3 H, H-3, H-5, C<u>H$_2$</u>CH=CH$_2$), 3.96 (dd, 1 H, J = 12.5 Hz, J = 5.6 Hz, C<u>H$_2$</u>CH=CH$_2$), 3.66 (s, 3 H, OCH_3), 1.82 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 163.8 (C=O), 159.2 (Ar), 150.5 (Ar), 138.0 (Ar), 137.3 (Ar), 135.9 (Ar), 134.0 (<u>C</u>H=CH$_2$), 130.8 (Ar), 130.0 (Ar), 129.5 (Ar), 129.3 (Ar), 128.6 (Ar), 128.5 (Ar), 127.9 (Ar), 127.6 (Ar), 126.3 (Ar), 123.4 (Ar), 117.8 (CH=<u>C</u>H$_2$), 113.6 (Ar), 92.6 (<u>C</u>HAr), 79.7 (C_{inos}), 78.8 (C_{inos}), 78.6 (C_{inos}), 78.1 (C_{inos}), 77.7 (C_{inos}), 73.3 (<u>C</u>H$_2$CH=CH$_2$), 70.4 (<u>C</u>H$_2$Ar/C-1), 70.3 (<u>C</u>H$_2$Ar/C-1), 64.3 (<u>C</u>H$_2$Ar), 55.1 (OCH_3), 19.2 (CH_3). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{39}H_{43}N_2O_{10}$: 699.2912. Found 699.2906.



3.41

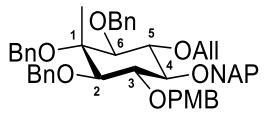
Racemic **5-*O*-allyl-1-*O*-benzyl-2,6-*O*-benzylidene-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-(2-naphthylmethyl)-*scyllo*-inositol (3.41)**. Sodium hydride (302 mg, 7.55 mmol, 60% wt in mineral oil), was added to a solution of **3.39** (2.68 g, 5.03 mmol) in THF (120 mL). The reaction mixture was stirred for 30 min and 2-naphthylmethyl bromide (1.67 g, 7.55 mmol) was added. The

reaction mixture was then heated at reflux overnight. After cooling to rt, water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.41** (3.18 g, 94%) as a yellow oil. R_f 0.51 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.85–7.83 (m, 1 H, Ar), 7.80–7.75 (m, 3 H, Ar), 7.52–7.45 (m, 5 H, Ar), 7.42–7.33 (m, 5 H, Ar), 7.24–7.20 (m, 5 H, Ar), 6.81–6.77 (m, 2 H, Ar), 5.96 (app ddt, 1 H, J = 17.2 Hz, J = 10.4 Hz, J = 5.3 Hz, C<u>H</u>=CH_2), 5.63 (s, 1 H, C<u>H</u>Ar), 5.30 (app dq, 1 H, J = 17.2 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *trans*), 5.16 (app dq, 1 H, J = 10.4 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *cis*), 4.95 (d, 1 H, J = 11.9 Hz, C<u>H</u>$_2$Ar), 4.92 (d, 1 H, J = 11.9 Hz, C<u>H</u>$_2$Ar), 4.75 (d, 1 H, J = 11.5 Hz, C<u>H</u>$_2$Ar), 4.66 (s, 2 H, 2 x C<u>H</u>$_2$Ar), 4.61 (d, 1 H, J = 11.5 Hz, C<u>H</u>$_2$Ar), 4.47 (dd, 1 H, $J_{3,4}$ = 7.0 Hz, $J_{4,5}$ = 7.0 Hz, H-4), 4.29 (app ddt, 1 H, J = 13.1 Hz, J = 5.1 Hz, J = 1.7 Hz, C<u>H</u>$_2$CH=CH_2), 4.27 (d, 1 H, J = 2.4 Hz, H-2/H-6), 4.19 (d, 1 H, J = 2.4 Hz, H-2/H-6), 4.16 (app ddt, 1 H, J = 13.1 Hz, J = 5.5 Hz, J = 1.5 Hz, C<u>H</u>$_2$CH=CH_2), 4.12 (d, 1 H, J = 7.0 Hz, H-3/H-5), 4.05 (d, 1 H, J = 7.1 Hz, H-3/H-5), 3.77 (s, 3 H, OCH_3), 1.80 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.1 (Ar), 138.6 (Ar), 137.5 (Ar), 136.3 (Ar), 134.6 (Ar), 133.0 (<u>C</u>H=CH_2), 130.3 (Ar), 129.3 (Ar), 129.2 (Ar), 128.5 (Ar), 128.1 (Ar), 128.0 (Ar),127.9(7) (Ar), 127.6 (Ar), 127.3 (Ar), 127.1 (Ar), 126.7 (Ar), 126.4 (Ar), 126.3 (Ar), 125.9 (Ar), 125.7 (Ar), 116.8 (CH=<u>C</u>H$_2$), 113.7 (Ar), 92.8 (<u>CH</u>Ar), 83.6 (C-3/C-5), 83.1 (C-3/C-5), 82.8 (C-4), 78.5 (C-2/C-6), 78.1 (C-2/C-6), 74.0 (<u>C</u>H$_2$Ar), 72.9 (<u>C</u>H$_2$Ar), 70.9 (<u>C</u>H$_2$CH=CH_2/C-1), 70.6 (C-1/<u>C</u>H$_2$CH=CH_2), 63.7 (<u>C</u>H$_2$Ar), 55.2 (OCH_3), 19.2 (CH_3). HRMS (ESI) Calcd for $[M + K]^+$ $C_{43}H_{44}KO_7$: 711.2719. Found 711.2717.



3.42

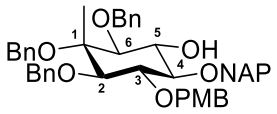
Racemic **5-*O*-allyl-1,2-di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-(2-naphthylmethyl)-*scyllo*-inositol (3.42)**. DIBAL-H (12.0 mL, 12.0 mmol, 1.0M in toluene) was added to a cooled (0 °C) solution of **3.41** (539 mg, 0.801 mmol) in toluene (8 mL). The reaction mixture was stirred at 0 °C for 3 h. A saturated aqueous solution of potassium sodium tartrate and CH_2Cl_2 were added at 0 °C and the mixture was stirred at overnight while warming to rt. The aqueous solution was extracted with CH_2Cl_2 and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.41** (378 mg, 70%) as colourless oil. R_f 0.33 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.85–7.77 (m, 4 H, Ar), 7.50–7.45 (m, 3 H, Ar), 7.34–7.23 (m, 10 H, Ar), 7.16–7.12 (m, 2 H, Ar), 6.78–6.74 (m, 2 H, Ar), 5.98 (app ddt, 1 H, J = 17.2 Hz, J = 10.5 Hz, J = 5.9 Hz, C<u>H</u>=CH$_2$), 5.30 (app dq, 1 H, J = 17.2 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *trans*), 5.19 (app dq, 1 H, J = 10.5 Hz, J = 1.6 Hz, CH=C<u>H</u>$_2$ *cis*), 5.05 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 5.01 (d, 1 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 4.89 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.85 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.82–4.70 (m, 4 H, 4 x C<u>H</u>$_2$Ar), 4.43 (app ddt, 1 H, J = 12.5 Hz, J = 5.5 Hz, J = 1.3 Hz, C<u>H</u>$_2$CH=CH$_2$), 4.32 (app ddt, 1 H, J = 12.5 Hz, J = 5.7 Hz, J = 1.3 Hz, C<u>H</u>$_2$CH=CH$_2$), 3.76 (s, 3 H, OCH_3), 3.72 (d, 1 H, J = 9.9 Hz, H-2/H-6), 3.67–3.55 (m, 3 H, 3 x H_{inos}), 3.37–3.33 (m, 1 H, H_{inos}), 2.41 (br s, 1 H, OH), 1.42 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.2 (Ar), 139.5 (Ar), 139.0 (Ar), 136.0 (Ar), 134.9 (Ar), 133.4 (<u>C</u>H=CH$_2$), 133.0 (Ar), 130.7 (Ar), 129.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 127.3 (Ar), 126.5 (Ar), 126.1 (Ar), 126.0(7) (Ar), 125.9(6) (Ar), 125.9 (Ar), 117.2 (CH=<u>C</u>H$_2$), 113.8 (Ar), 84.1 (C_{inos}), 83.4 (C_{inos}), 83.0 (C_{inos}), 81.7 (C_{inos} 79.8 (C-1), 75.8 (CH_2Ar), 75.7 (CH_2Ar), 75.5 (C_{inos}), 75.4 (CH_2Ar), 74.3 (<u>C</u>H$_2$CH=CH$_2$), 65.5 (CH_2Ar), 55.3 (OCH_3), 13.2 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{43}H_{46}NaO_7$: 697.3136. Found 697.3139.



3.43

Racemic **5-*O*-allyl-1,2,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-(2-naphthylmethyl)-*scyllo*-inositol (3.43)**. Sodium hydride (188 mg, 4.70 mmol, 60% wt in mineral oil) was added to a solution of **3.42** (2.64 g, 3.92 mmol) in DMF (64 mL). After 30 min, benzyl bromide (700 μL, 5.88 mmol) was added and the reaction mixture was stirred at rt overnight. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 → 9:1 hexanes–EtOAc) to give **3.43** (2.88 g, 96%) as a yellow oil. R_f 0.27 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.89–7.81 (m, 4 H, Ar), 7.54–7.48 (m, 3 H, Ar), 7.39–7.24 (m, 15 H, Ar), 7.19–7.15 (m, 2 H, Ar), 6.81–6.77 (m, 2 H, Ar), 6.00 (app ddt, 1 H, J = 17.2 Hz, J = 10.5 Hz, J = 5.7 Hz, C$\underline{H}$=CH_2), 5.29 (app dq, 1 H, J = 17.2 Hz, J = 1.7 Hz, CH=C$\underline{H}_2$ *trans*), 5.17 (app dq, 1 H, J = 10.5 Hz, J = 1.7 Hz, CH=C$\underline{H}_2$ *cis*), 5.09 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 5.06 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.97 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.96 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.88 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.84 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.82–4.78 (m, 4 H, 4 x C$\underline{H}_2$Ar), 4.43 (d, 2 H, J = 5.7 Hz, 2 x C$\underline{H}_2$CH=CH_2), 3.79 (s, 3 H, OCH_3), 3.66–3.55 (m, 4 H, 4 x H_{inos}), 3.50 (dd, 1 H, J = 9.4 Hz, J = 9.4 Hz, H_{inos}), 1.53 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.2 (Ar), 139.6 (Ar), 139.1 (Ar), 139.0 (Ar), 136.2 (Ar), 135.2 (C$\underline{H}$=CH_2), 133.4 (Ar), 133.0 (Ar), 130.8 (Ar), 129.5 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4(4) (Ar), 127.3(6) (Ar), 127.3 (Ar), 127.2 (Ar), 126.6 (Ar), 126.1 (Ar), 126.0 (Ar), 125.8 (Ar), 116.8 (CH=C$\underline{H}_2$), 113.8 (Ar), 85.3 (C_{inos}), 83.4 (C_{inos}), 82.6(2) (C_{inos}), 82.5(6) (C_{inos}), 80.4 (C-1), 76.1 (C$\underline{H}_2$Ar), 75.6 (2 x C$\underline{H}_2$Ar), 75.5 (C$\underline{H}_2$Ar), 74.6 (C$\underline{H}_2$CH=CH_2),

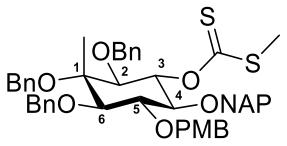
66.1 (CH_2Ar), 55.3 (OCH_3), 13.1 (CH_3). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{50}H_{56}NO_7$: 782.4051. Found 782.4042.



3.44

Racemic **1,2,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-(2-naphthylmethyl)-*scyllo*-inositol (3.44)**. DIBAL-H (1.10 mL, 1.10 mmol, 1.0M in toluene) was added to a cooled (0 °C) solution of **3.43** (280 mg, 0.366 mmol) and [1,3-bis(diphenylphosphino)propane]dichloronickel(II) in toluene (3 mL). The reaction mixture was stirred at rt for 3 h. A saturated aqueous solution of potassium sodium tartrate and CH_2Cl_2 were then added and the mixture was stirred at rt overnight. The aqueous solution was extracted with CH_2Cl_2 and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.44** (241 mg, 91%) as a colourless oil. R_f 0.44 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.89–7.81 (m, 4 H, Ar), 7.54–7.47 (m, 3 H, Ar), 7.38–7.25 (m, 15 H, Ar), 7.20–7.16 (m, 2 H, Ar), 6.81–6.78 (m, 2 H, Ar), 5.10 (d, 1 H, J = 11.7 Hz, CH_2Ar), 5.07 (d, 1 H, J = 11.9 Hz, CH_2Ar), 5.01 (d, 1 H, J = 11.3 Hz, CH_2Ar), 4.94 (d, 1 H, J = 11.2 Hz, CH_2Ar), 4.88–4.79 (m, 6 H, 6 x CH_2Ar), 3.79 (s, 3 H, OCH_3), 3.73 (dd, 1 H, J = 9.0 Hz, J = 9.0 Hz, H_{inos}), 3.69 (d, 1 H, J = 9.3, H-2/H-6), 3.62 (dd, 1 H, J = 9.3 Hz, J = 9.2 Hz, H_{inos}), 3.57 (dd, 1 H, J = 9.1 Hz, J = 9.0 Hz, H_{inos}), 3.52 (d, 1 H, J = 9.9, H-2/H-6), 2.55 (d, 1 H, J = 1.8, OH), 1.54 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.2 (Ar), 139.4 (Ar), 139.0 (Ar), 138.8 (Ar), 136.2 (Ar), 133.4 (Ar), 129.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.0 (Ar), 127.7(3) (Ar), 127.6(7) (Ar), 127.4(1) (Ar), 127.3(9) (Ar), 127.3 (Ar), 127.2 (Ar), 126.6 (Ar), 126.1 (Ar), 126.0 (Ar), 125.9 (Ar), 113.8 (Ar), 85.6 (C_{inos}),

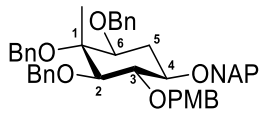
85.0 (C_{inos}), 83.0 (C_{inos}), 82.5 (C_{inos}), 80.7 (C-1), 75.5(9) (2C x $\underline{C}H_2Ar$), 75.5(4) ($\underline{C}H_2Ar$), 75.4(8) ($\underline{C}H_2Ar$), 74.3 (C_{inos}), 66.1 ($\underline{C}H_2Ar$), 55.3 (OCH_3), 13.2 (CH_3). HRMS (ESI) Calcd for $[M + K]^+$ $C_{47}H_{48}KO_7$: 763.3032. Found 763.3027.



3.45

Racemic **1,2,6-tri-*O*-benzyl-5-*O*-(4-methoxybenzyl)-1-*C*-methyl-3-*O*-(*S*-methylxanthate)-4-*O*-(2-naphthylmethyl)-*scyllo*-inositol (3.45)**. Sodium hydride (175 mg, 4.39 mmol, 60% wt in mineral oil) was added to a cooled (0 °C) solution of **3.44** (636 mg, 0.877 mmol) in THF (20 mL). After 30 min, CS_2 (791 μL, 13.2 mmol) was added and the reaction mixture was stirred for 1 h while warming to rt. Methyl iodide (273 μL, 4.39 mmol) was then added and the mixture was stirred at rt for an additional 2 h. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 → 9:1 hexanes–EtOAc) to give **3.45** (708 mg, 99%) as a yellow oil. R_f 0.24 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.87–7.79 (m, 3 H, Ar), 7.75 (s, 1 H, Ar), 7.51–7.47 (m, 2 H, Ar), 7.42 (dd, 1 H, J = 8.4 Hz, J = 1.7 Hz, Ar), 7.38–7.24 (m, 15 H, Ar), 7.19–7.15 (m, 2 H, Ar), 6.83–6.79 (m, 2 H, Ar), 6.33 (dd, 1 H, J = 9.9 Hz, J = 9.7 Hz, H-3), 5.00–4.94 (m, 2 H, 2 x $C\underline{H}_2Ar$), 4.91–4.87 (m, 2 H, 2 x $C\underline{H}_2Ar$), 4.82–4.69 (m, 6 H, 6 x $C\underline{H}_2Ar$), 3.84–3.66 (m, 4 H, H-2, H-4, H-5, H-6), 3.80 (s, 3 H, OCH_3), 2.53 (s, 3H, SCH_3), 1.58 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 215.9 (C=S), 159.2 (Ar), 139.4 (Ar), 138.8 (Ar), 138.3 (Ar), 135.5 (Ar), 133.3 (Ar), 133.0 (Ar), 130.6 (Ar), 129.6 (Ar), 128.3(4) (Ar), 128.3(1) (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.8 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4

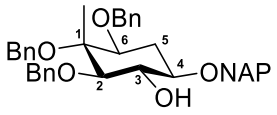
(Ar), 127.3 (Ar), 126.9 (Ar), 126.2 (Ar), 126.0 (Ar), 125.9 (Ar), 113.8 (Ar), 85.3 (C_{inos}), 83.5 (C-3), 83.3 (C_{inos}), 82.4 (C_{inos}), 81.3 (C_{inos}), 80.6 (C-1), 75.8 (2C x $\underline{C}H_2Ar$), 75.6(5) ($\underline{C}H_2Ar$), 75.5(9) ($\underline{C}H_2Ar$), 66.3 ($\underline{C}H_2Ar$), 55.3 (OCH_3), 19.3 (SCH_3), 13.0 (CH_3). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{49}H_{54}NO_7S_2$: 832.3336. Found 832.3338.



3.46

***Racemic* 1,2,6-tri-*O*-benzyl-5-deoxy-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-(2-naphthylmethyl)-*scyllo*-inositol (3.46)**. A solution of *n*-Bu_3SnH (1.40 mL, 5.20 mmol) and AIBN (107 mg, 0.650 mmol) in degassed benzene (21 mL) was added to a solution of **3.45** (1.06 g, 1.30 mmol) in degassed benzene (23 mL) at 80 °C over a period of 60 min. The reaction mixture was heated at reflux for 2 h, cooled and the solvent evaporated. The resulting crude product was purified by silica gel column chromatography (19:1 to 9:1 hexanes–EtOAc) to give **3.46** (719 mg, 78%) as a colourless oil. R_f 0.39 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.91–7.82 (m, 4 H, Ar), 7.55–7.50 (m, 3 H, Ar), 7.40–7.23 (m, 17 H, Ar), 6.85–6.81 (m, 2 H, Ar), 4.96–4.78 (m, 8 H, 8 x $C\underline{H}_2Ar$), 4.67 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 4.63 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 3.81 (s, 3 H, OCH_3), 3.65–3.52 (m, 4 H, H-2, H-3, H-4, H-6), 2.42 (ddd, 1 H, $J_{5eq,5ax}$ = 13.0 Hz, $J_{4,5ax}$ = 4.4 Hz, $J_{5ax,6}$ = 4.4 Hz, H-5_{eq}), 1.65–1.55 (m, 1 H, H-5_{ax}), 1.56 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.2 (Ar), 139.9 (Ar), 139.3 (Ar), 138.6 (Ar), 136.0 (Ar), 133.4 (Ar), 133.1 (Ar), 131.1 (Ar), 129.7 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2(5) (Ar), 128.2(2) (Ar), 128.0 (Ar), 127.7 (Ar), 127.5(9) (Ar), 127.5(7) (Ar), 127.5(0) (Ar), 127.4(6) (Ar), 127.4 (Ar), 127.3(4) (Ar), 127.3(2) (Ar), 127.2(5) (Ar), 127.1 (Ar), 126.5 (Ar), 126.1 (Ar), 125.9(4) (Ar), 125.9(3) (Ar), 113.7 (Ar), 85.5 (C_{inos}), 84.6 (C_{inos}), 82.1 (C-1), 79.7 (C_{inos}), 77.4 (C_{inos}), 75.7 ($\underline{C}H_2Ar$), 75.5 ($\underline{C}H_2Ar$), 72.8

($\underline{C}H_2Ar$), 72.3 ($\underline{C}H_2Ar$), 66.2 ($\underline{C}H_2Ar$), 55.3 (OCH_3), 32.1 (C-5), 11.8 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{47}H_{48}NaO_6$: 731.3343. Found 731.3329.



3.47

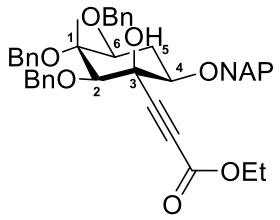
Racemic **1,2,6-tri-*O*-benzyl-5-deoxy-1-*C*-methyl-4-*O*-(2-naphthylmethyl)-*scyllo*-inositol (3.47)**. TFA (1.70 mL) was added to a cooled (0 °C) solution of **3.46** (2.20 g, 3.12 mmol) in CH_2Cl_2 (170 mL). The reaction mixture was stirred at 0 °C for 2 h. Saturated aqueous solution of $NaHCO_3$ was added at 0 °C The reaction mixture was warmed to rt then extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 to 9:1 hexanes–EtOAc) to give **3.47** (1.84 g, 94%) as as a colorless oil. R_f 0.62 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.88–7.85 (m, 3 H, Ar), 7.82 (s, 1 H, Ar), 7.54–7.48 (m, 3 H, Ar), 7.36–7.25 (m, 15 H, Ar), 4.95 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.88 (s, 2 H, 2 x $C\underline{H}_2Ar$), 4.85 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.78 (d, 1 H, J = 11.2 Hz, $C\underline{H}_2Ar$), 4.77 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.64 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 4.57 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 3.71 (dd, 1 H, $J_{2,3}$ = 9.4 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 3.59 (dd, 1 H, $J_{5ax,6}$ = 12.3 Hz, $J_{5eq,6}$ = 4.6 Hz, H-6), 3.46–3.40 (m, 1 H, H-4), 3.39 (d, 1 H, $J_{2,3}$ = 9.7 Hz, H-2), 2.64 (s, 1 H, OH), 2.39 (ddd, 1 H, $J_{5ax,5eq}$ = 12.8 Hz, $J_{4,5eq}$ = 4.6 Hz, $J_{5eq,6}$ = 4.6 Hz, H-5$_{eq}$), 1.57–1.48 (m, 1 H, H-5$_{ax}$), 1.50 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.8 (Ar), 138.9 (Ar), 138.4 (Ar), 135.9 (Ar), 133.3 (Ar), 133.1 (Ar), 128.4(3) (Ar), 128.3(8) (Ar), 128.2(9) (Ar), 128.2(6) (Ar), 127.9 (Ar), 127.7(5) (Ar), 127.7(3) (Ar), 127.6 (Ar), 127.3 (Ar), 127.1 (Ar), 126.5 (Ar), 126.1 (Ar), 125.9 (Ar), 125.8 (Ar), 85.3 (C-2), 81.9 (C-1), 80.1 (C-6), 76.3 (C-4), 76.0 (C-3), 75.6 ($\underline{C}H_2Ar$), 72.3

($\underline{C}H_2Ar$), 72.0 ($\underline{C}H_2Ar$), 66.1 ($\underline{C}H_2Ar$), 31.6 (C-5), 11.8 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{39}H_{40}NaO_5$: 611.2768. Found 611.2771.

3.48

Racemic **2,3,4-tri-*O*-benzyl-5-deoxy-3-*C*-methyl-6-*O*-(2-naphthylmethyl)-*scyllo*-inososse (3.48)**. A solution of DMSO (382 μL, 5.38 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise to a cooled (–78 °C) solution of oxalyl chloride (331 μL, 3.91 mmol) in CH_2Cl_2 (2.5 mL). After 30 min, a solution of **3.47** (960 mg, 1.63 mmol) in CH_2Cl_2 (30 mL) was added slowly to the reaction mixture. After 1 h, Et_3N (1.25 mL, 8.97 mmol) was added slowly and the reaction mixture was stirred for 4 h at –78 °C. Water was added and the reaction mixture was warmed to rt then extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 to 9:1 hexanes–EtOAc) to give **3.48** (861 mg, 90%) as a colorless oil. R_f 0.69 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.88–7.84 (m, 3 H, Ar), 7.80 (s, 1 H, Ar), 7.56–7.49 (m, 3 H, Ar), 7.38–7.26 (m, 15 H, Ar), 5.02 (d, 1 H, J = 11.9 Hz, $C\underline{H}_2Ar$), 4.86 (d, 1 H, J = 11.7 Hz, $C\underline{H}_2Ar$), 4.78 (d, 1 H, J = 11.2 Hz, $C\underline{H}_2Ar$), 4.74–4.66 (m, 4 H, 4 x $C\underline{H}_2Ar$), 4.49 (d, 1 H, J = 11.7 Hz, $C\underline{H}_2Ar$), 4.06 (d, 1 H, $J_{2,4}$ = 1.1 Hz, H-2), 4.00 (ddd, 1 H, $J_{4,5ax}$ = 12.6 Hz, $J_{4,5eq}$ = 6.8 Hz, $J_{2,4}$ = 1.3 Hz, H-4), 3.88 (dd, 1 H, $J_{5ax,6}$ = 12.1 Hz, $J_{5eq,6}$ = 5.0 Hz, H-6), 2.49 (ddd, 1 H, $J_{5eq,5ax}$ = 12.8 Hz, $J_{4,5eq}$ = 6.8 Hz, $J_{5eq,6}$ = 5.0 Hz, H-5_{eq}), 1.77 (ddd, 1 H, $J_{4,5ax}$= 12.1 Hz, $J_{5eq,5ax}$ = 12.1 Hz, $J_{5ax,6}$ = 12.1 Hz, H-5_{ax}), 1.38 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 204.4 (C-1), 139.3 (Ar)), 138.3 (Ar), 137.5 (Ar), 134.8 (Ar), 133.2(4) (Ar), 132.2(8) (Ar), 128.4(2) (Ar), 128.3(8) (Ar), 128.2 (Ar), 128.1 (Ar), 127.9(3) (Ar), 127.8(5) (Ar), 127.7(5) (Ar), 127.6(7) (Ar), 127.6(6) (Ar), 127.3 (Ar), 127.2 (Ar), 126.9 (Ar),

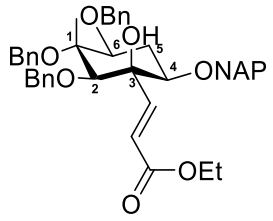
126.2 (Ar), 126.1 (Ar), 126.0 (Ar), 85.6 (C-2), 83.8 (C-3), 78.1 (C-6), 76.3 (C-4), 73.0 (CH_2Ar), 72.9 (CH_2Ar), 72.1 (CH_2Ar), 66.6 (CH_2Ar), 33.4 (C-5), 11.4 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{39}H_{38}NaO_5$: 609.2611. Found 609.2614.



3.54

***Racemic* 1,2,6-tri-*O*-benzyl-5-deoxy-3-(ethoxycarbonylethynyl)-1-*C*-methyl-4-*O*-(2-naphthylmethyl)-3-*myo*-inositol (3.54)**. *n*-BuLi (1.43 mL, 2.29 mmol, 1.6M in hexanes) was added dropwise to a cooled (–78 °C) solution of $(i\text{-Pr})_2NH$ (331 μL, 3.91 mmol) in THF (9 mL). After 30 min, ethyl propiolate (232 μL, 2.29 mmol) was added to the mixture. After another 30 min, a solution of **3.48** (745 mg, 1.27 mmol) in THF (13 mL) was added slowly to the reaction mixture. After 3 h, saturated aqueous solution of NH_4Cl was added and the reaction mixture was warmed to rt then extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 → 9:1 hexanes–EtOAc) to give **3.54** (808 mg, 93%) as a colorless oil. R_f 0.64 (4:1 hexanes–EtOAc); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.91–7.85 (m, 4 H, Ar), 7.60 (dd, 1 H, J = 8.4 Hz, J = 1.7 Hz, Ar), 7.56–7.50 (m, 2 H, Ar), 7.41–7.37 (m, 2 H, Ar), 7.35–7.23 (m, 13 H, Ar), 4.98 (d, 1 H, J = 12.1 Hz, C$\underline{H}_2$-Ar), 4.94 (d, 1 H, J = 10.5 Hz, C$\underline{H}_2$Ar), 4.91 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.88 (d, 1 H, J = 10.3 Hz, C$\underline{H}_2$Ar), 4.79 (d, 1 H, J = 11.3 Hz, C$\underline{H}_2$Ar), 4.74 (d, 1 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 4.60 (d, 1 H, J = 11.7 Hz, C$\underline{H}_2$Ar), 4.53 (d, 1 H, J = 11.7 Hz, C$\underline{H}_2$Ar), 4.28 (app qd, 2 H, J = 7.2 Hz, J = 0.9 Hz, C$\underline{H}_2$CH$_3$), 3.60 (dd, 1 H, $J_{4,5ax}$ = 12.1 Hz, $J_{4,5eq}$ = 4.4 Hz, H-4), 3.60 (s, 1 H, H-2), 3.44 (dd, 1 H, $J_{5ax,6}$ = 12.3 Hz, $J_{5eq,6}$ = 4.0 Hz, H-6), 3.06 (s, 1 H, OH), 2.15 (ddd, 1 H, $J_{5eq,5ax}$

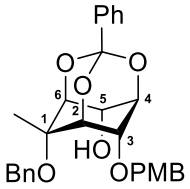
= 12.8 Hz, $J_{4,5eq}$ = 4.4 Hz, $J_{5eq,6}$ = 4.4 Hz, H-5_{eq}), 1.88 (ddd, $J_{4,5ax}$= 12.5 Hz, $J_{5eq,5ax}$= 12.5 Hz, $J_{5ax,6}$= 12.5 Hz, H-5_{ax}), 1.60 (s, 3 H, CH_3), 1.35 (t, 3 H, J= 7.2 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 153.2 (C=O), 139.7 (Ar), 138.2 (Ar), 138.0 (Ar), 134.9 (Ar), 133.2(4) (Ar), 133.2(2) (Ar), 128.5 (Ar), 128.4 (Ar), 128.3(4) (Ar), 128.2(7) (Ar), 128.2(5) (Ar), 128.0 (Ar), 127.8 (Ar), 127.7(5) (Ar), 127.6(8) (Ar), 127.6 (Ar), 127.2(1) (Ar), 127.1(6) (Ar), 127.1 (Ar), 126.3 (Ar), 126.2 (Ar), 126.1 (Ar), 88.5 ($\underline{C}$≡C–C=O), 84.8 (C-2), 82.4 (C-3), 79.9 (C-6), 76.8 (C-1), 76.2 (C-4), 75.4 (CH_2Ar), 73.5 (CH_2Ar), 72.7 (CH_2Ar), 71.8 (C≡$\underline{C}$–C=O), 66.0 (CH_2Ar), 62.1 ($\underline{C}H_2CH_3$), 28.7 (C-5), 14.1 ($CH_2\underline{C}H_3$), 12.0 (CH_3). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{44}H_{48}NO_7$: 702.3425. Found 702.3419.



3.55

***Racemic* 1,2,6-tri-*O*-benzyl-5-deoxy-3-((*E*)-ethoxycarbonylethenyl)-1-*C*-methyl-4-*O*-(2-naphthylmethyl)-3-*myo*-inositol (3.55)**. Red-Al® (88 μL, 109 mmol, 60% wt in toluene) was added to a cooled (–78 °C) solution of **3.54** (800 mg, 1.17 mmol) in THF (11 mL). The reaction mixture was stirred at –78 °C for 30 min. A saturated aqueous solution of potassium sodium tartrate and CH_2Cl_2 were added at –78 °C and the mixture was stirred overnight while warming to rt. The aqueous solution was extracted with CH_2Cl_2 and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.55** (618 mg, 77%) as a colourless oil. Alkyne **3.54** could be recovered and the reaction done again. R_f 0.62 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.88–7.82 (m, 3 H, Ar), 7.71 (s, 1 H, Ar), 7.55–7.49 (m, 2 H, Ar), 7.39 (dd, 1 H, J= 8.4 Hz, J

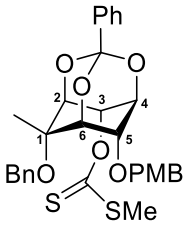
= 1.7 Hz, Ar), 7.35–7.24 (m, 13 H, Ar), 7.20–7.17 (m, 2 H, Ar), 6.81 (d, 1 H, J = 15.4 Hz, C<u>H</u>=CH–C=O), 6.27 (d, 1 H, J = 15.6 Hz, CH=C<u>H</u>–C=O), 4.81 (d, 1 H, J = 15.4 Hz, C<u>H</u>$_2$Ar), 4.78–4.72 (m, 3 H, 3 x C<u>H</u>$_2$Ar), 4.65–4.61 (m, 2 H, 2 x C<u>H</u>$_2$Ar), 4.56 (d, 1 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 4.52 (d, 1 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 4.25 (q, 2 H, J = 7.2 Hz, C<u>H</u>$_2$CH$_3$), 3.47 (dd, 1 H, $J_{5ax,6}$ = 12.5 Hz, $J_{5eq,6}$ = 4.2 Hz, H-6), 3.40 (dd, 1 H, $J_{4,5ax}$ = 11.9 Hz, $J_{4,5eq}$ = 4.2 Hz, H-4), 3.38 (s, 1 H, H-2), 2.22 (ddd, 1 H, $J_{5eq,5ax}$ = 12.7 Hz, $J_{4,5eq}$ = 4.2 Hz, $J_{5eq,6}$ = 4.2 Hz, H-5$_{eq}$), 1.94 (ddd, 1 H, $J_{4,5ax}$ = 12.3 Hz, $J_{5eq,5ax}$ = 12.3 Hz, $J_{5ax,6}$ = 12.3 Hz, H-5$_{ax}$), 1.67 (s, 3 H, CH$_3$), 1.32 (t, 3 H, J = 7.2 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.2 (C=O), 151.3 (<u>C</u>=C–C=O), 139.8 (Ar), 138.3 (Ar), 137.8 (Ar), 134.9 (Ar), 133.2 (Ar), 133.1 (Ar), 128.4 (Ar), 128.3(1) (Ar), 128.2(5) (Ar), 128.2 (Ar), 127.9 (Ar), 127.7(3) (Ar), 127.6(6) (Ar), 127.6 (Ar), 127.3 (Ar), 127.1 (Ar), 126.9 (Ar), 126.2 (Ar), 126.1 (Ar), 125.0 (Ar), 123.2 (Ar), 83.7 (C-2), 82.7 (C-3), 80.5 (C-6), 78.6 (C-1), 75.8 (CH$_2$Ar), 75.2 (C-4), 71.9 (CH$_2$Ar), 71.8 (CH$_2$Ar), 66.1 (CH$_2$Ar), 60.4 (<u>C</u>H$_2$CH$_3$), 28.8 (<u>C</u>-5), 14.3 (CH$_2$<u>C</u>H$_3$), 11.9 (CH$_3$). HRMS (ESI) Calcd for $[M + K]^+$ $C_{44}H_{46}KO_7$: 725.2875. Found 725.2874.



3.60

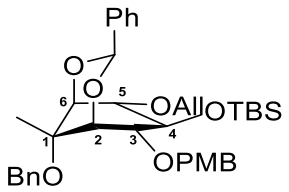
***Racemic* 1-*O*-benzyl-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-*scyllo*-inositol 2,4,6-orthobenzoate (3.60)**. To a solution of **3.38** (268 mg, 0.505 mmol) in THF (2.6 mL), degassed under vacuum and stirring under an Ar atmosphere, (1,5-cyclooctadiene)bis-(methyldiphenylphosphine)iridium I hexafluorophosphate catalyst (23 mg, 0.0278 mmol) was added followed by further degassing of the mixture under vacuum. The suspension was stirred for 15 min at 0 °C, and the catalyst was then activated with H_2 (2 min under a H_2 atmosphere). At this point, the solution became nearly

colorless. The excess of H_2 was removed by three cycles of placing the flask under vacuum and then flushing the flask with Ar. The reaction mixture was then stirred for 3 h at rt under an Ar atmosphere. The solvent was then evaporated, and the residue was dissolved in acetone–water (10:1, 16.7 mL) before HgO (164 mg, 0.0.606 mmol) and $HgCl_2$ (153 mg, 0.707 mmol) were added. After 1 h, the solvent was evaporated and the residue was diluted with Et_2O and washed with a 10% aqueous solution of KI, a saturated aqueous solution of $Na_2S_2O_3$, and water. The aqueous layers were extracted with EtOAc and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.60** (40 mg, 87%) as a colorless oil. R_f 0.37 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.66–7.61 (m, 2 H, Ar), 7.40–7.36 (m, 3 H, Ar), 7.26–7.21 (m, 3 H, Ar), 7.19–7.15 (m, 2 H, Ar), 7.15–7.12 (m, 2 H, Ar), 6.84–6.80 (m, 2 H, Ar), 4.69 (d, 1 H, J = 10.8 Hz, C$\underline{H}_2$Ar), 4.75–4.52 (m, 7 H, 4 x H_{inos}, 3 x C$\underline{H}_2$Ar), 4.40 (d, 1 H, $J_{6,OH}$ = 12.3 Hz, OH), 4.34–4.32 (m, 1 H, H_{inos}), 3.82 (s, 3 H, OCH_3), 1.84 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.5 (Ar), 137.5 (Ar), 136.7 (Ar), 129.9 (Ar), 129.6 (Ar), 129.1 (Ar), 128.4 (Ar), 128.1 (Ar), 127.7 (Ar), 127.6 (Ar), 125.4 (Ar), 114.0 (Ar), 107.5 ($\underline{C}$Ar), 74.3(5) (C_{inos}), 74.3(1) (C_{inos}), 73.6 (C_{inos}) 73.5 (C-1), 71.9 ($\underline{C}H_2$Ar), 69.6 (C_{inos}), 68.0 (C_{inos}), 64.5 ($\underline{C}H_2$Ar), 55.3 (OCH_3), 21.4 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{29}H_{30}NaO_7$: 513.1884. Found 513.1886.



3.61

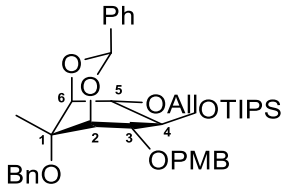
Racemic **1-*O*-benzyl-5-*O*-(4-methoxybenzyl)-1-*C*-methyl-3-*(S*-methylxanthate)-*scyllo*-inositol 2,4,6-orthobenzoate (3.61)**. Sodium hydride (265 mg, 6.63 mmol, 60% wt in mineral oil) was added to a cooled (0 °C) solution of **3.60** (650 mg, 1.33 mmol) in THF (30 mL). After 30 min, CS_2 (1.20 mL, 20.0 mmol) was added and the reaction mixture was stirred at rt for 1 h. MeI (413 μL, 6.63 mmol) was then added and the mixture was stirred at rt for an additional 2 h. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 to 9:1 hexanes–EtOAc) to give **3.61** (771 mg, 99%) as yellow oil. R_f 0.38 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.69–7.64 (m, 2 H, Ar), 7.42–7.37 (m, 3 H, Ar), 7.34–7.30 (m, 2 H, Ar), 7.26–7.20 (m, 5 H, Ar), 6.84–6.80 (m, 2 H, Ar), 6.43 (app td, 1 H, J = 3.5 Hz, J = 1.3 Hz, H-3) 4.78–4.76 (m, 1 H, H_{inos}), 4.67 (d, 1 H, J = 10.6 Hz, C$\underline{H}_2$-Ar), 4.63–4.60 (m, 1 H, H_{inos}), 4.59 (s, 2 H, 2 x C$\underline{H}_2$Ar), 4.58–4.52 (m, 3 H, 2 x H_{inos}, 1 x C$\underline{H}_2$Ar), 3.81 (s, 3 H, OCH_3), 2.20 (s, 3 H, SCH_3), 1.82 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 215.4 (C=S), 159.4 (Ar), 138.6 (Ar), 136.4 (Ar), 129.7(1) (Ar), 129.6(7) (Ar), 129.6(6) (Ar), 128.1 (Ar), 128.0 (Ar), 127.5 (Ar), 127.1 (Ar), 125.4 (Ar), 113.8 (Ar), 108.2 (C$\underline{C}$Ar), 75.1 (C-3), 73.7 (C_{inos}), 73.5 (C_{inos}), 72.6 (C_{inos}), 72.1 (C$\underline{H}_2$Ar), 71.1 (C-1), 67.8 (C_{inos}), 63.9 (C$\underline{H}_2$Ar), 55.3 (OCH_3), 21.5 (CH_3), 18.7 (SCH_3). HRMS (ESI) Calcd for $[M + H]^+$ $C_{31}H_{33}O_7S$: 581.1662. Found 581.1671.



3.62

Racemic **5-*O*-allyl-1-*O*-benzyl-2,6-*O*-benzylidene-4-*O*-(*t*-butyldimethylsilyl)-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-*scyllo*-inositol (3.62)**. Imidazole (77 mg, 1.13 mmol) and TBSCl (74 mg, 0.488 mmol) were added to a solution of **3.39** (200 mg, 0.376 mmol) in DMF (1 mL). The reaction mixture was stirred overnight. Water was added and the aqueous solution was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.62** (198 mg, 81%) as a yellow oil. R_f 0.53 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.60–7.56 (m, 2 H, Ar), 7.48–7.39 (m, 5 H, Ar), 7.36–7.32 (m, 2 H, Ar), 7.30–7.23 (m, 3 H, Ar), 6.88–6.84 (m, 2 H, Ar), 5.96 (app ddt, 1 H, J = 17.2 Hz, J = 10.5 Hz, J = 5.3 Hz, C<u>H</u>=CH_2), 5.68 (s, 1 H, C<u>H</u>PhC<u>H</u>Ar), 5.29 (app dq, 1 H, J = 17.2 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *trans*), 5.17 (app dq, 1 H, J = 10.5 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *cis*), 4.72 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.65 (s, 2 H, 2 x C<u>H</u>$_2$Ar), 4.57 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.54 (app t, 1 H, J = 7.3 Hz, C-4), 4.27 (d, 1 H, J = 2.2 Hz, H-2/H-6), 4.26 (app ddt, 1 H, J = 12.7 Hz, J = 5.1 Hz, J = 1.7 Hz, C<u>H</u>$_2$CH=CH_2), 4.19 (d, 1 H, J = 2.2 Hz, H-2/H-6), 4.06 (app ddt, 1 H, J = 12.7 Hz, J = 5.3 Hz, J = 1.7 Hz, C<u>H</u>$_2$CH=CH_2), 3.91 (d, 1 H, J = 7.2 Hz, H-3/H-5), 3.84–3.80 (m, 4 H, H-3/H-5, OCH_3), 1.80 (s, 3 H, CH_3), 0.93 (s, 9 H, SiC(CH_3)$_3$), 0.06 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 158.9 (Ar), 138.5 (Ar), 137.7 (Ar), 134.6 (Ar), 130.5 (<u>C</u>H=CH_2), 129.3 (Ar), 128.8 (Ar), 128.5 (Ar), 128.1 (Ar), 127.3 (Ar), 127.1 (Ar), 126.4 (Ar), 116.4 (CH=<u>C</u>H_2), 113.6 (Ar), 92.8 (<u>CH</u>Ar), 84.9 (C-3/C-5), 84.7 (C-3/C-5), 77.9 (C-2/C-6), 77.8 (C-2/C-6), 75.3 (C-4), 73.1 (C-1), 71.0

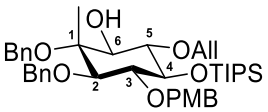
($\underline{C}H_2Ar$), 70.5 ($\underline{C}H_2CH=CH_2$), 63.6 ($\underline{C}H_2Ar$), 55.3 (OCH_3), 26.0 ($SiC(\underline{C}H_3)_3$), 19.3 (CH_3), 18.2 ($Si\underline{C}(CH_3)_3$), –4.4 (2 x $SiCH_3$). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{38}H_{50}NaO_7Si$: 669.3218. Found 669.3222.



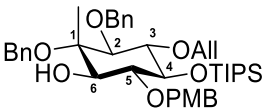
3.65

Racemic **5-*O*-allyl-1-*O*-benzyl-2,6-*O*-benzylidene-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-*scyllo*-inositol (3.65)**. Imidazole (1.05 g, 15.5 mmol) and TIPSCl (6.61 mL, 30.9 mmol) were added to a solution of **3.39** (5.50 g, 10.3 mmol) in DMF (90 mL). The reaction mixture was heated at 70 °C overnight. Water was added and the aqueous solution was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.65** (7.03 g, 99%) as a yellow oil. R_f 0.68 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.59–7.56 (m, 2 H, Ar), 7.46–7.40 (m, 3 H, Ar), 7.37–7.34 (m, 2 H, Ar), 7.32–7.22 (m, 5 H, Ar), 6.87–6.84 (m, 2 H, Ar), 5.95 (app ddt, 1 H, J = 17.2 Hz, J = 10.5 Hz, J = 5.1 Hz, $C\underline{H}=CH_2$), 5.67 (s, 1 H, $C\underline{H}Ar$), 5.28 (app dq, 1 H, J = 17.2 Hz, J = 1.8 Hz, $CH=C\underline{H}_2$ *trans*), 5.15 (app dq, 1 H, J = 10.5 Hz, J = 1.8 Hz, $CH=C\underline{H}_2$ *cis*), 4.73 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.65–4.61 (m, 3 H, 2 x $C\underline{H}_2Ar$, H-4), 4.54 (d, 1 H, J = 11.2 Hz, $C\underline{H}_2Ar$), 4.29–4.24 (m, 2 H, $C\underline{H}_2CH=CH_2$, H-2/H-6), 4.19 (d, 1 H, J = 2.2 Hz, H-2/H-6), 4.05 (app ddt, 1 H, J = 12.8 Hz, J = 5.3 Hz, J = 1.7 Hz, $C\underline{H}_2CH=CH_2$), 3.94 (d, 1 H, J = 6.8 Hz, H-3/H-5), 3.85–3.82 (m, 4 H, H-3/H-5, OCH_3), 1.80 (s, 3 H, CH_3), 1.17–1.08 (m, 3 H, 3 x SiCH), 1.17–1.08 (m, 18 H, 3 x $SiCH(C\underline{H}_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 158.8 (Ar), 138.5 (Ar), 137.7 (Ar), 134.7 ($\underline{C}H=CH_2$), 130.7 (Ar), 129.4 (Ar), 128.6 (Ar), 128.5 (Ar),

128.0 (Ar), 127.1 (Ar), 127.0 (Ar), 126.4 (Ar), 116.0 (CH=$\underline{C}H_2$), 113.5 (Ar), 92.8 ($\underline{CH}$Ar), 85.7 (C-3/C-5), 85.5 (C-3/C-5), 77.5 (C-2/C-6), 77.4 (C-2/C-6), 75.7 (C-4), 72.9 (C-1), 70.7 ($\underline{C}H_2$Ar), 70.2 ($\underline{C}H_2$CH=CH_2), 63.4 ($\underline{C}H_2$Ar), 55.3 (OCH_3), 19.3 (CH_3), 18.2 (3 x SiCH($\underline{C}H_3$)$_2$), 12.6 (3 x Si$\underline{C}$H(CH_3)$_2$). HRMS (ESI) Calcd for $[M + H]^+$ $C_{41}H_{57}O_7Si$: 689.3868. Found 689.3872.



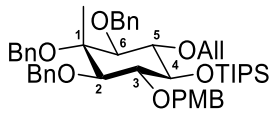
3.66a



3.66b

***Racemic* 5-*O*-Allyl-1,2-di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-*scyllo*-inositol (3.66a)** and ***racemic* 3-*O*-Allyl-1,2-di-*O*-benzyl-5-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-*scyllo*-inositol (3.66b)**. DIBAL-H (72 mL, 72.0 mmol, 1.0M in toluene), was added to a cooled (0 °C) solution of **3.65** (3.21 g, 4.66 mmol) in toluene (86 mL). The reaction mixture was stirred overnight at 0 °C. A saturated aqueous solution of potassium sodium tartrate and CH_2Cl_2 were added and the mixture was stirred at rt overnight. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 to 17:3 hexanes–EtOAc) to give **3.66a** and **3.66b** (2.25 g, 70%) as a colorless oil (isomeric mixture 4:1). R_f 0.58 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.34–7.18 (m, 12 H, Ar), 6.92–6.89 (m, 0.4 H, Ar), 6.85–6.82 (m, 1.6 H, Ar), 5.99 (app ddt, 0.8 H, J = 17.2 Hz, J = 10.6 Hz, J = 5.3 Hz, C$\underline{H}$=CH_2), 5.92 (app ddt, 0.2 H, J = 17.2 Hz, J = 10.6 Hz, J = 5.1 Hz, C$\underline{H}$=CH_2), 5.31 (app dq, 0.8 H, J = 17.2 Hz, J = 1.8 Hz, CH=C$\underline{H}_2$ *trans*), 5.23 (app dq, 0.2 H, J = 17.2 Hz, J = 1.8 Hz, CH=C$\underline{H}_2$ *trans*), 5.18 (app dq, 0.8 H, J = 10.5 Hz, J = 1.7 Hz, CH=C$\underline{H}_2$ *cis*), 5.12 (app dq, 0.20 H, J = 10.5 Hz, J = 1.7 Hz, CH=C$\underline{H}_2$ *cis*), 4.94 (d, 0.8 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.86–4.67 (m, 5.8 H, C$\underline{H}_2$Ar), 4.47–4.27 (m, 1.8 H, C$\underline{H}_2$CH=CH_2), 4.22 (app ddt, 0.2 H, J = 12.5 Hz, J = 5.1 Hz, J = 1.5 Hz, C$\underline{H}_2$CH=CH_2),

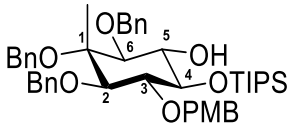
3.85–3.81 (m, 4 H, H_{inos}, OCH_3), 3.74–3.57 (m, 2 H, 2 x H_{inos}), 3.40 (dd, 0.8 H, J = 9.2 Hz, J = 9.2 Hz, H_{inos}), 3.27 (dd, 0.4 H, J = 9.4 Hz, J = 9.4 Hz, H_{inos}), 3.19 (dd, 0.8 H, J = 9.4 Hz, J = 9.4 Hz, H_{inos}), 2.40 (d, 0.8 H, J = 2.2 Hz, OH), 2.26 (d, 0.2 H, J = 1.8 Hz, OH), 1.45 (s, 2.4 H, CH_3), 1.41 (s, 0.6 H, CH_3), 1.24–1.06 (m, 21 H, $SiCH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.1 (Ar), 158.6 (Ar), 139.5 (Ar), 139.4 (Ar), 138.9 (Ar), 138.8 (Ar), 135.3 ($\underline{C}H=CH_2$), 131.3 (Ar), 131.2 (Ar), 129.0 (Ar), 128.4 (Ar), 128.3(3) (Ar), 128.2(5) (Ar), 128.2 (Ar), 128.0 (Ar), 127.5 (Ar), 127.4(3) (Ar), 127.4(0) (Ar), 127.3(4) (Ar), 127.2(7) (Ar), 127.2 (Ar), 116.3 ($CH=\underline{C}H_2$), 115.4 (Ar), 113.8 (Ar), 113.4 (Ar), 84.7(1) (C_{inos}), 84.6(7) (C_{inos}), 83.7 (C_{inos}), 83.2 (C_{inos}), 83.0 (C_{inos}), 82.6 (C_{inos}), 79.8 (C-1), 79.7 (C-1), 76.1(3) (C_{inos}), 76.1(0) (C_{inos}), 75.6 ($\underline{C}H_2Ar$), 75.1 ($\underline{C}H_2Ar$), 75.0 ($\underline{C}H_2Ar$), 74.5 ($\underline{C}H_2Ar$), 73.9 (2 x $\underline{C}H_2CH=CH_2$), 65.4 ($\underline{C}H_2Ar$), 65.3 ($\underline{C}H_2Ar$), 55.3 (OCH_3), 18.4 ($SiCH(CH_3)_2$), 18.3(5) ($SiCH(CH_3)_2$), 18.3(3) ($SiCH(CH_3)_2$), 13.6 ($SiCH(CH_3)_2$), 13.4 (CH_3), 13.3 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{41}H_{58}NaO_7Si$: 713.3844. Found 713.3838.



3.67

***Racemic* 5-*O*-Allyl-1,2,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-*scyllo*-inositol (3.67)**. Sodium hydride (484 mg, 12.1 mmol, 60% wt in mineral oil) was added to a solution of **3.66** (4.18 g, 6.05 mmol) in THF (65 mL). After 30 min, benzyl bromide (3.60 mL, 30.2 mmol) was added and the reaction mixture was stirred at rt overnight. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.67** (4.48 g, 95%) as a yellow oil. R_f 0.49 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.39–7.19 (m, 17 H, Ar), 6.87–6.84 (m, 2

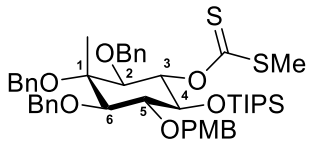
H, Ar), 5.95 (app ddt, 1 H, J = 17.2 Hz, J = 10.6 Hz, J = 5.1 Hz, C<u>H</u>=CH$_2$), 5.25 (app dq, 1 H, J = 17.2 Hz, J = 1.8 Hz, CH=C<u>H</u>$_2$ *trans*), 5.13 (app dq, 1 H, J = 10.6 Hz, J = 1.8 Hz, CH=C<u>H</u>$_2$ *cis*), 4.97 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.93 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.88–4.80 (m, 5 H, 5 x C<u>H</u>$_2$Ar), 4.47 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.47 (app ddt, 1 H, J = 12.5 Hz, J = 5.3 Hz, J = 1.7 Hz, C<u>H</u>$_2$CH=CH$_2$), 4.24 (app ddt, 1 H, J = 12.5 Hz, J = 5.0 Hz, J = 1.7 Hz, C<u>H</u>$_2$CH=CH$_2$), 3.86–3.82 (m, 1 H, H$_{inos}$), 3.84 (s, 3 H, OCH$_3$), 3.64 (d, 1 H, J = 9.7 Hz, H-2/H-6), 3.60 (d, 1 H, J = 9.9 Hz, H-2/H-6), 3.39 (dd, 1 H, J = 9.4 Hz, J = 9.4 Hz, H$_{inos}$), 3.28 (dd, 1 H, J = 9.5 Hz, J = 9.4 Hz, H$_{inos}$), 1.57 (s, 3 H, CH$_3$), 1.22–1.09 (m, 21 H, 3 x SiC<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (125 MHz, CDCl$_3$, δ_C) 158.6 (Ar), 139.6 (Ar), 139.0 (Ar), 138.9 (Ar), 135.4 (<u>C</u>H=CH$_2$), 131.5 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.3(8) (Ar), 127.3(5) (Ar), 127.3 (Ar), 127.1 (Ar), 115.4 (CH=<u>C</u>H$_2$), 113.4 (Ar), 86.1(3) (C-2/C-6), 86.0(7) (C2/C6), 83.2 (C$_{inos}$), 82.8 (C$_{inos}$), 80.5 (C-1), 75.3(9) (C$_{inos}$), 75.3(8) (<u>C</u>H$_2$Ar), 75.3 (<u>C</u>H$_2$Ar), 74.5 (<u>C</u>H$_2$Ar), 73.9 (<u>C</u>H$_2$CH=CH$_2$), 66.1 (<u>C</u>H$_2$Ar), 55.3 (OCH$_3$), 18.4(1) (SiCH(<u>C</u>H$_3$)$_2$), 18.4(0) (SiCH(<u>C</u>H$_3$)$_2$), 13.6 (3 x Si<u>C</u>H(CH$_3$)$_2$), 13.2 (CH$_3$). HRMS (ESI) Calcd for [M + NH$_4$]$^+$ $C_{48}H_{68}NO_7Si$: 798.4760. Found 798.4750.



3.68

***Racemic* 1,2,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-*scyllo*-inositol (3.68)**. Palladium(II) chloride (477 mg, 2.69 mmol) was added to a solution of **3.67** (21.0 g, 26.9 mmol) in CH_2Cl_2 (300 mL) and MeOH (300 mL). The reaction mixture was stirred at rt overnight. The solution was filtered through silica and the silica was rinsed with EtOAc. The solvent was then evaporated and the crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.68** (17.1 g, 86%) as a colourless oil. R_f 0.37 (9:1

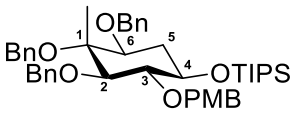
hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.41–7.19 (m, 17 H, Ar), 6.85–6.81 (m, 2 H, Ar), 4.97 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.91(d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.86 (d, 1 H, J = 10.6 Hz, C$\underline{H}_2$Ar), 4.83–4.77 (m, 5 H, 5 x C$\underline{H}_2$Ar), 3.82 (s, 3 H, OCH_3), 3.81 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 8.8 Hz, H-4), 3.65 (d, 1 H, $J_{2,3}$ = 9.7, H-2), 3.53 (ddd, 1 H, $J_{5,6}$ = 9.9 Hz, $J_{4,5}$ = 8.8 Hz, $J_{5,OH}$ = 2.0 Hz, H-5), 3.47 (d, 1 H, $J_{5,6}$ = 9.9, H-6), 3.42 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 2.44 (d, 1 H, $J_{5,OH}$ = 2.0, OH), 1.55 (s, 3 H, CH_3) 1.26–1.17 (m, 3 H, 3 x SiC$\underline{H}$(CH_3)$_2$), 1.14–1.09 (m, 18 H, 3 x SiCH(C$\underline{H}_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 158.7 (Ar), 139.4 (Ar), 138.9 (Ar), 138.8 (Ar), 131.3 (Ar), 128.4(8) (Ar), 128.4(6) (Ar), 128.3 (Ar), 128.2 (Ar), 127.6(8) (Ar), 127.6(6) (Ar), 127.3(0) (Ar), 127.2(6) (Ar), 127.2(0) (Ar), 127.1(6) (Ar), 113.5 (Ar), 86.0 (C-2), 85.0 (C-6), 83.4 (C-3), 80.7 (C-1), 76.1(C-4), 75.6 (C$\underline{H}_2$Ar), 75.3 (C$\underline{H}_2$Ar), 74.9 (C$\underline{H}_2$Ar), 74.9 (C-5), 66.0 (C$\underline{H}_2$Ar), 55.3 (OCH_3), 18.4 (2C x SiCH(C$\underline{H}_3$)$_2$), 13.4 (SiC$\underline{H}$(CH_3)$_2$/CH_3), 13.3 (CH_3/SiC$\underline{H}$(CH_3)$_2$). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{45}H_{64}NO_7Si$: 758.4447. Found 758.4437.



3.69

Racemic **1,2,6-tri-*O*-benzyl-5-*O*-(4-methoxybenzyl)-1-*C*-methyl-3-*O*-(*S*-methylxanthate)-4-*O*-triisopropylsilyl-*scyllo*-inositol (3.69)**. LiHMDS (5.66 mL, 5.66 mmol, 1.0M in THF) was added to a cooled (–78 °C) solution of **3.68** (3.75 g, 5.06 mmol) and CS_2 (3.04 mL, 50.6 mmol) in THF (300 mL). After 30 min, methyl iodide (1.58 mL, 25.3 mmol) was added and the reaction mixture was stirred at –78 °C for 1 h. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 → 9:1 hexanes–EtOAc) to give **3.69** (4.19 g, 99%) as a yellow oil. R_f 0.47 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$,

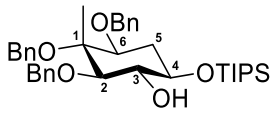
δ_H) 7.33–7.19 (m, 17 H, Ar), 6.88–6.84 (m, 2 H, Ar), 6.18 (dd, 1 H, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 9.7 Hz, H-3), 5.00 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.91 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.84 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.80–4.74 (m, 3 H, 3 x C$\underline{H}_2$Ar), 4.71 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.67 (d, 1 H, J = 10.6 Hz, C$\underline{H}_2$Ar), 4.15 (dd, 1 H, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.84 (s, 3 H, OCH_3), 3.71 (d, 1 H, $J_{5,6}$ = 9.5, H-6), 3.69 (d, 1 H, J = 9.7, H-2), 3.52 (dd, 1 H, $J_{5,6}$ = 9.4 Hz, $J_{4,5}$ = 9.2 Hz, H-5), 2.57 (s, 3H, SCH_3), 1.61 (s, 3 H, CH_3), 1.15–1.02 (m, 21 H, 3 x SiC$\underline{H}$(C$\underline{H}_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 215.7 (C=S), 158.7 (Ar), 139.4 (Ar), 138.7 (Ar), 138.4 (Ar), 131.2 (Ar), 128.3(0) (Ar), 128.2(5) (Ar), 128.1(3) (Ar), 128.0(6) (Ar), 127.7 (Ar), 127.4 (Ar), 127.3 (Ar), 127.2(4) (Ar), 127.2(0) (Ar), 113.5 (Ar), 86.3 (C-6), 84.3 (C-2), 83.8 (C-3), 82.9 (C-5), 80.2 (C-1), 75.7 (C$\underline{H}_2$Ar), 75.5 (C$\underline{H}_2$Ar), 74.7 (C$\underline{H}_2$Ar), 73.8 (C-4), 66.2 (C$\underline{H}_2$Ar), 55.3 (OCH_3), 19.5 (SCH_3), 18.4(0) (SiCH(C$\underline{H}_3$)$_2$), 18.3(9) (SiCH(C$\underline{H}_3$)$_2$), 13.7 (3 x SiC$\underline{H}$(CH$_3$)$_2$), 13.0 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{47}H_{62}NaO_7S_2Si$: 853.3598. Found 853.3597.



3.70

Racemic **1,2,6-tri-*O*-benzyl-5-deoxy-3-*O*-(4-methoxybenzyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-*scyllo*-inositol (3.70)**. A solution of *n*-Bu_3SnH (4.95 mL, 18.4 mmol) and AIBN (377 mg, 2.30 mmol) in degassed benzene (75 mL) was added to a solution of **3.69** (3.82 g, 4.60 mmol) in degassed benzene (155 mL) at 80 °C over a period of 60 min. The reaction mixture was heated at reflux for 2 h, then cooled, and the solvent evaporated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.70** (3.32 g, 99%) as a colourless oil. R_f 0.40 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.39–7.21 (m, 17 H, Ar), 6.84–6.80 (m, 2 H, Ar), 488–4.82 (m, 4 H, 4 x C$\underline{H}_2$Ar), 4.79 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.76 (d, 1 H, J = 10.6 Hz, C$\underline{H}_2$Ar), 4.70 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.64 (d, 1 H, J =

11.9 Hz, C<u>H</u>$_2$Ar), 3.85–3.79 (m, 1 H, H-4), 3.82 (s, 3 H, OCH$_3$), 3.55 (dd, 1 H, $J_{5ax,6}$ = 12.3 Hz, $J_{5eq,6}$ = 4.4 Hz, H-6), 3.49 (d, 1 H, $J_{2,3}$ = 9.9 Hz, H-2), 3.39 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 2.17 (ddd, 1 H, $J_{5eq,5ax}$ = 13.0 Hz, $J_{4,5eq}$ = 4.8 Hz, $J_{5eq,6}$ = 4.8 Hz, H-5$_{eq}$), 1.62–1.54 (m, 1 H, H-5$_{ax}$), 1.56 (s, 3 H, CH$_3$), 1.14–1.06 (m, 21 H, 3 x SiC<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (125 MHz, CDCl$_3$, δ_C) 158.8 (Ar), 140.0 (Ar), 139.4 (Ar), 138.7 (Ar), 131.4 (Ar), 129.1 (Ar), 128.4 (Ar), 128.2(3) (Ar), 128.1(6) (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 127.3 (Ar), 127.2 (Ar), 127.0 (Ar), 113.5 (Ar), 85.8 (C-3), 85.5 (C-2), 82.1 (C-1), 79.6 (C-6), 75.6 (<u>C</u>H$_2$Ar), 75.2 (<u>C</u>H$_2$Ar), 72.5 (<u>C</u>H$_2$Ar), 71.1 (C-4), 66.1 (<u>C</u>H$_2$Ar), 55.3 (OCH$_3$), 36.1 (C-5), 18.2(5) (SiCH(<u>C</u>H$_3$)$_2$), 18.2(0) (SiCH(<u>C</u>H$_3$)$_2$), 12.7 (3 x Si<u>C</u>H(CH$_3$)$_2$), 11.9 (CH$_3$). HRMS (ESI) Calcd for [M + Na]$^+$ $C_{45}H_{60}NaO_6Si$: 747.4051. Found 747.4047.



3.71

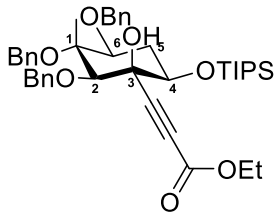
***Racemic* 1,2,6-tri-*O*-benzyl-5-deoxy-1-*C*-methyl-4-*O*-triisopropylsilyl-*scyllo*-inositol (3.71)**. TFA (8 mL) was added to a cooled (0 °C) solution of **3.70** (2.85 g, 3.94 mmol) in CH_2Cl_2 (400 mL). The reaction mixture was stirred at 0 °C for 2 h. A saturated aqueous solution of $NaHCO_3$ was added and the reaction mixture was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 to 9:1 hexanes–EtOAc) to give **3.71** (2.36 g, 99%) as as a colorless oil. R_f 0.45 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$, δ_H) 7.40–7.26 (m, 15 H, Ar), 4.92 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.86 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.85 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.79 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.68 (d, 1 H, J = 11.7 Hz, C<u>H</u>$_2$Ar), 4.65 (d, 1 H, J = 11.7 Hz, C<u>H</u>$_2$Ar), 3.69–3.63 (m, 1 H, H-4), 3.59 (dd, 1 H, $J_{5ax,6}$ = 12.3 Hz, $J_{5eq,6}$ = 4.4 Hz, H-6), 3.55–3.49 (m, 1 H, H-3), 3.40 (d, 1 H, $J_{2,3}$ = 9.7 Hz, H-2), 2.55 (d, 1 H, $J_{3,OH}$ = 1.3 Hz, OH), 2.17 (ddd, 1 H, $J_{5ax,5eq}$ =

13.0 Hz, $J_{4,5eq}$ = 4.8 Hz, $J_{5eq,6}$ = 4.8 Hz, H-5$_{eq}$), 1.59–1.50 (m, 1 H, H-5$_{ax}$), 1.52 (s, 3 H, CH_3), 1.12–1.09 (m, 21 H, SiCH(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.9 (Ar), 139.1 (Ar), 138.6 (Ar), 128.4 (Ar), 128.3(2) (Ar), 128.2(6) (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 127.3 (Ar), 127.1 (Ar), 85.3 (C-2), 82.1 (C-1), 80.0 (C-6), 77.4 (C-3), 75.5 ($\underline{C}H_2Ar$), 72.4 ($\underline{C}H_2Ar$), 70.8 (C-4), 66.1 ($\underline{C}H_2Ar$), 35.5 (C-5), 18.1 (SiCH($\underline{C}H_3$)$_2$), 12.6 (Si$\underline{C}$H(CH_3)$_2$), 11.9 (CH_3). HRMS (ESI) Calcd for $[M + H]^+$ $C_{37}H_{53}O_5Si$: 605.3657. Found 605.3658.

3.72

***Racemic* 2,3,4-tri-*O*-benzyl-5-deoxy-3-*C*-methyl-6-*O*-triisopropylsilyl-*scyllo*-inososе (3.72)**. A solution of DMSO (877 μL, 12.3 mmol) in CH_2Cl_2 (12 mL) was added dropwise to a cooled (–78 °C) solution of oxalyl chloride (760 μL, 8.98 mmol) in CH_2Cl_2 (24 mL). After 30 min, a solution of **3.71** (2.26 g, 1.63 mmol) in CH_2Cl_2 (60 mL) was added slowly to the reaction mixture. After 1 h, Et_3N (2.87 mL, 20.6 mmol) was added slowly and the reaction mixture was stirred for 4 h at –78 °C. Water was added and the reaction mixture was warmed to rt and then extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 → 9:1 hexanes–EtOAc) to give **3.72** (2.07 g, 92%) as as a colorless oil. R_f 0.43 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.38–7.28 (m, 15 H, Ar), 4.86 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.82 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.79 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.72 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.71 (d, 1 H, J = 11.7 Hz, C$\underline{H}_2$Ar), 4.46 (d, 1 H, J = 11.7 Hz, C$\underline{H}_2$Ar), 4.30 (ddd, 1 H, $J_{5ax,6}$ = 12.5 Hz, $J_{5eq,6}$ = 6.8 Hz, $J_{2,6}$ = 1.1 Hz, H-6), 4.07 (d, 1 H, $J_{2,6}$ = 0.9 Hz, H-2), 3.90 (dd, 1 H, $J_{4,5ax}$ = 12.1 Hz, $J_{4,5eq}$ = 4.8 Hz, H-4), 2.39 (ddd, 1 H, $J_{5ax,5eq}$ = 13.0 Hz, $J_{5eq,6}$ = 6.8 Hz, $J_{4,5eq}$ = 4.8 Hz, H-5$_{eq}$), 1.73 (ddd, 1 H, $J_{4,5ax}$= 12.5 Hz, $J_{5eq,5ax}$= 12.5 Hz, $J_{5ax,6}$= 12.5 Hz, H-5$_{ax}$), 1.38 (s, 3 H, CH_3), 1.17–1.05 (m, 21 H, 3 x SiC$\underline{H}$(C$\underline{H}_3$)$_2$); ^{13}C

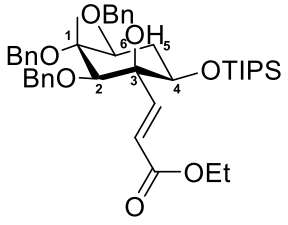
NMR (125 MHz, $CDCl_3$, δ_C) 204.2 (C-1), 139.5 (Ar), 138.4 (Ar), 137.6 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 127.8 (Ar), 127.7(3) (Ar), 127.6(8) (Ar), 127.3 (Ar), 127.2 (Ar), 85.3 (C-6), 83.8 (C-3), 78.0 (C-4), 73.0 ($\underline{C}H_2Ar$), 72.7 ($\underline{C}H_2Ar$), 72.1 (C-2), 66.5 ($\underline{C}H_2Ar$), 36.7 (C-5), 18.0 ($SiCH(\underline{C}H_3)_2$), 17.9 ($SiCH(\underline{C}H_3)_2$), 12.3 (3 x $Si\underline{C}H(CH_3)_2$), 11.4 (CH_3). HRMS (ESI) Calcd for $[M + H]^+$ $C_{37}H_{51}O_5Si$: 603.3500. Found 603.3498.



3.73

***Racemic* 1,2,6-tri-*O*-benzyl-5-deoxy-3-(ethoxycarbonylethynyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-3-*myo*-inositol (3.73)**. *n*-BuLi (23.3 mL, 37.3 mmol, 1.6M in hexanes) was added dropwise to a cooled (–78 °C) solution of $(i\text{-Pr})_2NH$ (5.51 mL, 39.3 mmol) in THF (146 mL). After 30 min, ethyl propiolate (3.88 mL, 38.3 mmol) was added to the mixture. After another 30 min, a solution of **3.72** (12.47 g, 20.7 mmol) in THF (181 mL) was added slowly to the reaction mixture. After 3 h, a saturated aqueous solution of NH_4Cl was added and the reaction mixture was warmed to rt then extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (49:1 → 19:1 hexanes–EtOAc) to give **3.73** (14.5 g, 99%) as a colorless oil. R_f 0.27 (9:1 hexanes–EtOAc); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.43–7.40 (m, 2 H, Ar), 7.35–7.26 (m, 13 H, Ar), 4.99 (d, 1 H, J = 10.6 Hz, $C\underline{H}_2Ar$), 4.90 (d, 1 H, J = 10.6 Hz, $C\underline{H}_2Ar$), 4.84 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.79 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.68 (d, 1 H, J = 11.7 Hz, $C\underline{H}_2Ar$), 4.62 (d, 1 H, J = 11.7 Hz, $C\underline{H}_2Ar$), 4.23 (q, 2 H, J = 7.2 Hz, $C\underline{H}_2CH_3$), 3.97 (dd, 1 H, $J_{4,5ax}$ = 11.7 Hz, $J_{4,5eq}$ = 4.6 Hz, H-4), 3.62 (s, 1 H, H-2), 3.52 (dd, 1 H, $J_{5ax,6}$ = 12.3 Hz, $J_{5eq,6}$ = 4.2 Hz, H-6), 2.99 (br, 1 H, OH), 1.97

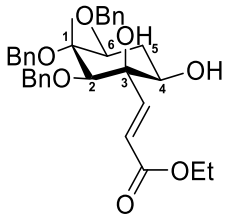
(ddd, 1 H, $J_{5eq,5ax}$ = 12.8 Hz, $J_{4,5eq}$ = 4.4 Hz, $J_{5eq,6}$ = 4.4 Hz, H-5_{eq}), 1.86 (ddd, 1 H, $J_{4,5ax}$ = 12.1 Hz, $J_{5eq,5ax}$ = 12.1 Hz, $J_{5ax,6}$ = 12.1 Hz, H-5_{ax}), 1.63 (s, 3 H, CH_3), 1.29 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.16–1.06 (m, 21 H, 3 x Si$C\underline{H}(C\underline{H}_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 153.1 (C=O), 139.8 (Ar), 138.4 (Ar), 138.2 (Ar), 128.4 (Ar), 128.3 (2 x Ar), 128.2 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.3 (Ar), 127.1 (Ar), 88.9 ($\underline{C}$≡C–C=O), 85.1 (C-2), 82.3 (C-1), 80.2 (C-4), 76.7 (C-3), 75.2 ($\underline{C}H_2Ar$), 74.5 (C≡$\underline{C}$–C=O), 72.5 ($\underline{C}H_2Ar$), 71.7 (C-6), 66.2 ($\underline{C}H_2Ar$), 61.8 ($\underline{C}H_2CH_3$), 33.0 (C-5), 18.2 (SiCH($\underline{C}H_3)_2$), 18.1 (SiCH($\underline{C}H_3)_2$), 14.0 ($CH_2\underline{C}H_3$), 12.6 (3 x Si$\underline{C}$H($CH_3)_2$), 11.9 (CH_3). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{42}H_{60}NO_7Si$: 718.4134. Found 718.4130.



3.74

Racemic **1,2,6-tri-*O*-benzyl-5-deoxy-3-((*E*)-ethoxycarbonylethenyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-3-*myo*-inositol (3.74)**. Red-Al® (13.5 mL, 40.0 mmol, 60% wt in toluene) was added to a cooled (–78 °C) solution of **3.73** (14.0 g, 20.0 mmol) in THF (300 mL). The reaction mixture was stirred at –78 °C for 30 min. A saturated aqueous solution of potassium sodium tartrate and CH_2Cl_2 were added at –78 °C and the mixture was stirred at rt overnight. The aqueous solution was extracted with CH_2Cl_2 and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.74** (9.10 g, 65%) as a colourless oil. Alkyne **3.73** was recovered and the reaction was done again twice to give **3.74** in 95% yield (combined). R_f 0.26 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.37–7.18 (m, 15 H, Ar), 6.81 (d, 1 H, J = 15.2 Hz, C$\underline{H}$=CH–C=O), 6.22 (d, 1 H, J = 15.4 Hz, CH=C$\underline{H}$–C=O), 4.86 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.79 (d, 1 H, J = 11.6

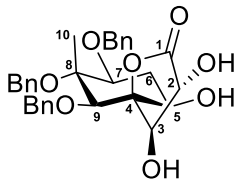
Hz, C<u>H</u>$_2$Ar), 4.76 (d, 1 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 4.69 (d, 1 H, J = 11.7 Hz, C<u>H</u>$_2$Ar), 4.63 (d, 1 H, J = 11.9 Hz, C<u>H</u>$_2$Ar), 4.57 (d, 1 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 4.26–4.16 (m, 2 H, C<u>H</u>$_2$CH$_3$), 3.81 (dd, 1 H, $J_{4,5ax}$ = 11.4 Hz, $J_{4,5eq}$ = 4.4 Hz, H-4), 3.53 (dd, 1 H, $J_{5ax,6}$ = 12.3 Hz, $J_{5eq,6}$ = 4.2 Hz, H-6), 3.40 (s, 1 H, H-2), 2.53 (s, 1 H, OH), 1.99 (ddd, 1 H, $J_{5ax,5eq}$ = 12.7 Hz, $J_{4,5eq}$ = 4.4 Hz, $J_{5eq,6}$ = 4.4 Hz, H-5$_{eq}$), 1.91 (ddd, 1 H, $J_{4,5ax}$ = 11.9 Hz, $J_{5ax,5eq}$ = 11.9 Hz, $J_{5ax,6}$ = 11.9 Hz, H-5$_{ax}$), 1.70 (s, 3 H, CH$_3$), 1.28 (t, 3 H, J = 7.0 Hz, CH$_2$C<u>H</u>$_3$), 1.11–0.93 (m, 21 H, 3 x SiC<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 151.6 (<u>C</u>=C–C=O), 139.9 (Ar), 138.5 (Ar), 138.0 (Ar), 128.4 (Ar), 128.3(5) (Ar), 128.2(8) (Ar), 128.1 (Ar), 127.7 (Ar), 127.6(5) (Ar), 127.5(6) (Ar), 127.4 (Ar), 127.1 (Ar), 123.5 (C=<u>C</u>–C=O), 83.5 (C-2), 82.6 (C-1), 80.8 (C-6), 79.2 (C-3), 75.8 (<u>C</u>H$_2$Ar), 72.3 (<u>C</u>H$_2$Ar), 71.0 (C-4), 66.2 (<u>C</u>H$_2$Ar), 60.2 (<u>C</u>H$_2$CH$_3$), 33.5 (C-5), 18.0(9) (SiCH(<u>C</u>H$_3$)$_2$), 18.0(7) (SiCH(<u>C</u>H$_3$)$_2$), 14.3 (CH$_2$<u>C</u>H$_3$), 12.6 (3 x Si<u>C</u>H(CH$_3$)$_2$), 11.7 (CH$_3$). HRMS (ESI) Calcd for [M + Na]$^+$ $C_{42}H_{58}NaO_7Si$: 725.3844. Found 725.3852.



3.75

***Racemic* 1,2,6-tri-*O*-benzyl-5-deoxy-3-((*E*)-ethoxycarbonylethenyl)-1-*C*-methyl-3-*myo*-inositol (3.75)**. TBAF (2.10 mL, 2.10 mmol, 1.0M in THF) was added to a cooled (0 °C) solution of **3.74** (985 mg, 1.40 mmol) in THF (35 mL). The reaction mixture was stirred for 15 min at 0 °C, then a saturated aqueous solution of $NaHCO_3$ was added and the reaction mixture was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (4:1 → 1:1 hexanes–EtOAc) to give **3.75** (760 mg, 99%) as a white solid. mp = 107–108 °C; R_f 0.17 (7:3 hexanes–

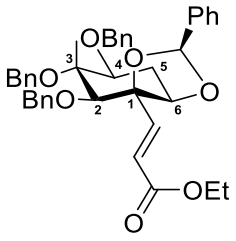
EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.37–7.27 (m, 13 H, Ar), 7.24–7.19 (m, 2 H, Ar), 6.95 (d, 1 H, J = 15.6 Hz, C<u>H</u>=CH–C=O), 6.21 (d, 1 H, J = 15.4 Hz, CH=C<u>H</u>–C=O), 4.81 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.80 (d, 1 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 4.74 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.73 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.63 (d, 1 H, J = 10.6 Hz, C<u>H</u>$_2$Ar), 4.56 (d, 1 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 4.26–4.18 (m, 2 H, C<u>H</u>$_2$CH$_3$), 3.65–3.59 (m, 2 H, H-4, H-6), 3.53 (s, 1 H, H-2), 2.89 (br, 1 H, OH), 2.27 (ddd, 1 H, $J_{5ax,5eq}$ = 13.0 Hz, $J_{4,5eq}$ = 4.0 Hz, $J_{5eq,6}$ = 4.0 Hz, H-5$_{eq}$), 1.96 (br s, 1 H, H-5$_{ax}$), 1.63 (s, 3 H, CH$_3$), 1.31 (t, 3 H, J = 7.2 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 150.4 (<u>C</u>=C–C=O), 139.5 (Ar), 138.2 (Ar), 137.8 (Ar), 128.4 (Ar), 128.3(4) (Ar), 128.3(2) (Ar), 128.1 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 127.3 (Ar), 123.0 (C=<u>C</u>–C=O), 84.2 (C-2), 81.9 (C-1), 80.3 (2C, C-4, C-6), 76.3 (C-3), 76.0 (<u>C</u>H$_2$Ar), 71.8 (<u>C</u>H$_2$Ar), 65.9 (<u>C</u>H$_2$Ar), 60.5 (<u>C</u>H$_2$CH$_3$), 29.7 (C-5), 14.3 (2C, CH$_2$<u>C</u>H$_3$, <u>C</u>H$_3$). HRMS (ESI) Calcd for [M + Na]$^+$ $C_{33}H_{38}NaO_7$: 569.2510. Found 569.2506.



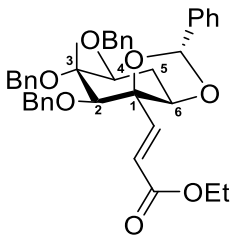
3.76

***Racemic* 7,8,9-tri-*O*-benzyl-bradyrhizose-1,4-lactone (3.76)**. Potassium osmate(VI) dihydrate (2 mg, 0.00410 mmol) was added to a cooled (0 °C) solution of **3.75** (112 mg, 0.205 mmol), $(DHQ)_2PHAL$ (7 mg, 0.00820 mmol), $K_3Fe(CN)_6$ (202 mg, 0.615 mmol), potassium carbonate (85 mg, 0.615 mmol), sodium bicarbonate (52 mg, 0.615 mmol) and $MeSO_2NH_2$ (20 mg, 0.205 mmol) in *t*-BuOH (0.5 mL) and water (0.5 mL). The reaction mixture was stirred for 2 h at 0 °C, then overnight at rt. A saturated aqueous solution of sodium thiosulfate was added and the reaction mixture was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and

concentrated. The resulting crude product was purified by silica gel column chromatography (49:1 CH_2Cl_2–MeOH) to give **3.76** (11 mg, 10%) as a colorless oil. The starting material could be recovered. R_f 0.31 (24:1 CH_2Cl_2–MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.35–7.15 (m, 15 H, Ar), 4.99 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.85 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.83 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.72–4.51 (m, 7 H, 3 x C$\underline{H}_2$Ar, H-2, H-3, 2 x OH), 4.08 (d, 1 H, J = 9.2 Hz, OH), 3.87 (s, 1 H, H-9), 3.63–3.55 (m, 2 H, H-5, H-7), 2.30 (ddd, 1 H, $J_{5ax,5eq}$ = 12.7 Hz, $J_{4,5eq}$ = 4.4 Hz, $J_{5eq,6}$ = 4.4 Hz, H-6$_{eq}$), 1.96 (ddd, 1 H, $J_{4,5ax}$ = 12.5 Hz, $J_{5eq,5ax}$ = 12.5 Hz, $J_{5ax,6}$ = 12.5 Hz, H-6$_{ax}$), 1.58 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 175.1 (C-1), 139.5 (Ar), 138.6 (Ar), 138.2 (Ar), 128.4 (Ar), 128.3 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4(4) (Ar), 127.3(8) (Ar), 127.3 (Ar), 127.2 (Ar), 88.6 (C-4), 83.2 (C-8), 80.2 (C-5/C-7), 78.7 (C-9), 74.5 (C-3/C-2), 74.4 (C$\underline{H}_2$Ar), 74.0 (C-3/C-2), 71.6 (C$\underline{H}_2$Ar), 66.3 (C$\underline{H}_2$Ar), 65.2 (C-5/C-7), 32.6 (C-6), 11.7 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{31}H_{34}NaO_8$: 557.2146. Found 557.2136.



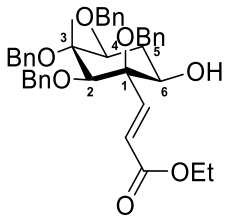
3.78a



3.78b

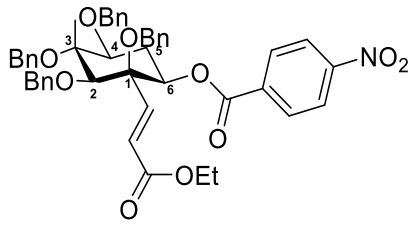
***Racemic exo*-2,3,4-tri-*O*-benzyl-1,6-benzylidene-5-deoxy-1-((*E*)-ethoxycarbonylethenyl)-3-*C*-methyl-1-*myo*-inositol (3.78a)** and ***racemic endo*-2,3,4-tri-*O*-benzyl-1,6-benzylidene-5-deoxy-1-((*E*)-ethoxycarbonylethenyl)-3-*C*-methyl-1-*myo*-inositol (3.78b)**. Benzaldehyde dimethyl acetal (1.18 mL, 8.11 mmol) and CSA (75 mg, 0.324 mmol) were added to a solution of **3.75** (887 mg, 1.62 mmol) in THF (10 mL). The reaction mixture was heated at reflux overnight. After cooling, a saturated aqueous solution of $NaHCO_3$ was added and the reaction mixture was

extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.78a** and **3.78b** (1.01 g, 99%) as as a colorless oil (inseparable diastereomeric mixture, 3:7). R_f 0.42 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.53–7.50 (m, 2 H, Ar), 7.45–7.25 (m, 18 H, Ar), 7.12 (d, 0.3 H, J = 15.4 Hz, C<u>H</u>=CH–C=O), 7.05 (d, 0.7 H, J = 15.6 Hz, C<u>H</u>=CH–C=O), 6.30 (d, 0.7 H, J = 15.8 Hz, CH=C<u>H</u>–C=O), 6.21 (s, 0.3 H, C<u>H</u>Ar), 6.08 (d, 0.3 H, J = 15.8 Hz, CH=C<u>H</u>–C=O), 5.89 (s, 0.7 H, C<u>H</u>Ar), 4.85–4.58 (m, 5.7 H, C<u>H</u>$_2$Ar), 4.41 (dd, 0.3 H, $J_{5ax,6}$ = 9.9 Hz, $J_{5eq,6}$ = 6.4 Hz, H-6), 4.29–4.10 (m, 3 H, H_{inos}, C<u>H</u>$_2$CH$_3$), 3.70–3.61 (m, 2 H, H-2, H_{inos}), 2.36–2.19 (m, 1.3 H, H-5$_{eq}$, H-5$_{ax}$), 2.04 (app q, 0.7 H, J = 12.7 Hz, H-5$_{ax}$), 1.62 (s, 0.9 H, CH_3), 1.60 (s, 2.1 H, CH_3), 1.29 (t, 2.1 H, J = 7.2 Hz, CH$_2$C<u>H</u>$_3$), 1.23 (t, 0.9 H, J = 7.2 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.3 (C=O), 166.1 (C=O), 149.2 (<u>C</u>=C–C=O), 147.9 (<u>C</u>=C–C=O), 139.0 (Ar), 138.9 (Ar), 138.4 (Ar), 138.3 (Ar), 138.1 (Ar), 138.0 (Ar), 137.6 (Ar), 137.3 (Ar), 129.3 (Ar), 129.1 (Ar), 128.4 (Ar), 128.3(5) (Ar), 128.3(1) (Ar), 128.2(4) (Ar), 128.1(9) (Ar), 128.1(3) (Ar), 128.0(9) (Ar), 127.6 (Ar), 127.5(1) (Ar), 127.4(7) (Ar), 127.3(3) (Ar), 127.2(8) (Ar), 127.0 (Ar), 126.8 (Ar), 121.6 (C=<u>C</u>–C=O), 104.3 (<u>C</u>HPh<u>C</u>HAr), 103.0 (<u>C</u>HAr), 84.9 (C-1/C-3), 84.8 (C-1/C-3), 84.3 (C-2), 83.2 (C-2), 82.1 (C-1/C-3), 81.7 (C-1/C-3), 79.5 (C-6), 78.7 (C_{inos}), 78.3 (C_{inos}), 77.5 (C_{inos}), 76.6 (<u>C</u>H$_2$Ar), 76.3 (<u>C</u>H$_2$Ar), 71.9(3) (<u>C</u>H$_2$Ar), 71.8(9) (<u>C</u>H$_2$Ar), 65.3 (<u>C</u>H$_2$Ar), 60.6 (<u>C</u>H$_2$CH$_3$), 60.3 (<u>C</u>H$_2$CH$_3$), 31.2 (C-5), 29.7 (C-5), 14.8 (CH_3), 14.5 (CH_3), 14.2 (CH$_2$<u>C</u>H$_3$). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{40}H_{46}NO_7$: 652.3269. Found 652.3269.



3.79

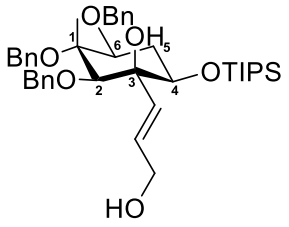
Racemic **1,2,3,4-tetra-*O*-benzyl-5-deoxy-1-((*E*)-ethoxycarbonylethenyl)-3-*C*-methyl-1-*myo*-inositol (3.79).** Copper(II) triflate (6 mg, 0.0161 mmol) was added to a cooled (– 15 °C) solution of **3.78** (102 mg, 0.161 mmol) and borane–tetrahydrofuran complex solution (805 µL, 0.805 mmol, 1.0M in THF) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at – 15 °C for 2 h, and Et_3N and MeOH were added. The mixture was then concentrated and the resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.79** (43 mg, 43%) as a colorless oil. R_f 0.44 (7:3 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.41–7.27 (m, 20 H, Ar), 7.14 (d, 1 H, J = 16.1 Hz, C<u>H</u>=CH–C=O), 6.17 (d, 1 H, J = 16.3 Hz, CH=C<u>H</u>–C=O), 5.04–4.91 (m, 2 H, 2 x C<u>H</u>$_2$Ar), 4.87–4.70 (m, 5 H, 5 x C<u>H</u>$_2$Ar), 4.58 (d, 1 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 4.28–4.18 (m, 2 H, C<u>H</u>$_2$CH$_3$), 3.71–3.62 (m, 3 H, H-2, H-4, H-6), 2.27 (ddd, 1 H, $J_{5ax,5eq}$ = 13.0 Hz, $J_{4,5eq}$ = 4.2 Hz, $J_{5eq,6}$ = 4.2 Hz, H-5$_{eq}$), 2.03 (br s, 1 H, H-5$_{ax}$), 1.73 (s, 3 H, CH$_3$), 1.31 (t, 3 H, J = 7.2 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 146.9 (<u>C</u>=C–C=O), 139.6 (Ar), 139.0 (Ar), 138.7 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 127.6 (Ar), 127.4(3) (Ar), 127.4(1) (Ar), 127.3(9) (Ar), 127.2 (Ar), 123.6 (C=<u>C</u>–C=O), 87.5 (C-2), 82.0 (C-1/C-3), 81.9 (C-1/C-3), 80.7 (C-4/C-6), 76.7 (<u>C</u>H$_2$Ar), 76.6 (<u>C</u>H$_2$Ar), 71.7 (<u>C</u>H$_2$Ar), 70.2 (C-4/C-6), 66.0 (<u>C</u>H$_2$Ar), 60.6 (<u>C</u>H$_2$CH$_3$), 29.7 (C-5), 14.3 (2C, CH$_2$<u>C</u>H$_3$, <u>C</u>H$_3$). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{40}H_{44}NaO_7$: 659.2979. Found 659.2978.



3.80

Racemic **1,2,3,4-tetra-*O*-benzyl-5-deoxy-1-((*E*)-ethoxycarbonylethenyl)-3-*C*-methyl-6-*O*-(4-nitrobenzoate)-1-*myo*-inositol (3.80).** *p*-Nitrobenzoyl chloride (23 mg, 0.125 mmol) was added to a solution of **3.79** (53 mg, 0.0832 mmol) and DMAP (12 mg, 0.0998 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 2 h at rt. Water was added and the mixture was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 → 17:3 hexanes–EtOAc) to give **3.80** (54 mg, 83%) as a yellow oil. R_f 0.35 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.28 (d, 2 H, J = 8.4 Hz, Ar), 8.16 (d, 2 H, J = 9.0 Hz, Ar), 7.47–7.28 (m, 20 H, Ar), 7.04 (d, 1 H, J = 16.1 Hz, C<u>H</u>=CH–C=O), 6.03 (d, 1 H, J = 16.3 Hz, CH=C<u>H</u>–C=O), 5.19 (dd, 1 H, $J_{5ax,6}$ = 11.4 Hz, $J_{5eq,6}$ = 4.4 Hz, H-6), 5.02–4.97 (m, 2 H, 2 x C<u>H</u>$_2$Ar), 4.90 (d, 1 H, J = 12.8 Hz, C<u>H</u>$_2$Ar), 4.87 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.80 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.73 (d, 1 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 4.70 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.62 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.12 (q, 2 H, J = 7.0 Hz, C<u>H</u>$_2$CH$_3$), 3.84 (dd, 1 H, $J_{4,5ax}$ = 11.2 Hz, $J_{4,5eq}$ = 4.8 Hz, H-4), 3.71 (s, 1 H, H-2), 2.43–2.30 (m, 2 H, H-5$_{eq}$, H-5$_{ax}$), 1.79 (s, 3 H, CH_3), 1.20 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.4 (C=O), 164.0 (Ar), 150.7 (Ar), 145.8 (<u>C</u>=C–C=O), 139.7 (Ar), 139.5 (Ar), 138.4 (Ar), 138.2 (Ar), 135.1 (Ar), 130.8 (Ar), 128.4(2) (Ar), 128.4(0) (Ar), 128.3(3) (Ar), 128.3(2) (Ar), 127.6(4) (Ar), 127.5(8) (Ar), 127.5 (Ar), 127.4(2) (Ar), 127.3(6) (Ar), 127.2 (Ar), 126.6 (Ar), 124.3 (C=<u>C</u>–C=O), 123.7 (Ar), 87.2 (C-2), 83.1 (C-1/C-3), 81.9 (C-1/C-3), 80.9 (C-4), 76.6 (<u>C</u>H$_2$Ar), 72.9 (C-6), 71.9 (<u>C</u>H$_2$Ar), 68.0 (<u>C</u>H$_2$Ar), 66.2 (<u>C</u>H$_2$Ar), 60.7 (<u>C</u>H$_2$CH$_3$), 29.2 (C-5), 14.2

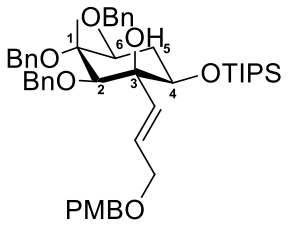
($CH_2\underline{C}H_3$), 11.9 ($\underline{C}H_3$). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{47}H_{47}NNaO_{10}$: 808.3092. Found 808.3091.



3.81

Racemic **1,2,6-tri-*O*-benzyl-5-deoxy-3-((*E*)-3'-hydroxy-1'-propenyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-3-*myo*-inositol (3.81)**. DIBAL-H (2.18 mL, 2.18 mmol, 1.0M in toluene) was added to a cooled (0 °C) solution of **3.75** (495 mg, 0.704 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 0 °C for 2 h. A saturated aqueous solution of potassium sodium tartrate and CH_2Cl_2 were added at 0 °C and the mixture was stirred overnight while warming to rt. The aqueous solution was extracted with CH_2Cl_2 and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.81** (386 mg, 83%) as a colourless oil. R_f 0.50 (7:3 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.39–7.26 (m, 15 H, Ar), 5.97 (app dt, 1 H, $J_{1',2'}$ = 15.4 Hz, $J_{2',3'}$ = 5.1 Hz, H-2'), 5.44 (dt, 1 H, $J_{1',2'}$ = 15.4 Hz, $J_{1',3'}$ = 1.7 Hz, H-1'), 4.88 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.83 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.81 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.70 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.67–4.63 (m, 2 H, 2 x C$\underline{H}_2$Ar), 4.12–4.04 (m, 2 H, 2 x H-3'), 3.71 (dd, 1 H, $J_{4,5ax}$ = 11.6 Hz, $J_{4,5eq}$ = 4.6 Hz, H-4), 3.54 (dd, 1 H, $J_{5ax,6}$ = 12.3 Hz, $J_{5eq,6}$ = 4.2 Hz, H-6), 3.33 (s, 1 H, H-2), 2.43 (s, 1 H, OH), 1.99 (ddd, 1 H, $J_{5ax,5eq}$ = 12.7 Hz, $J_{4,5eq}$ = 4.4 Hz, , $J_{5eq,6}$ = 4.4 Hz, H-5_{eq}), 1.92 (ddd, 1 H, $J_{4,5ax}$ = 11.9 Hz, $J_{5eq,5ax}$ = 11.9 Hz, $J_{5ax,6}$ = 11.9 Hz, H-5_{ax}), 1.73 (s, 3 H, CH_3), 1.07–0.97 (m, 21 H, 3 x SiC$\underline{H}$($C\underline{H}_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 140.0 (Ar), 138.7(4) (Ar), 138.6(8) (Ar), 134.8 (C-1'), 130.8 (C-2'), 128.4 (Ar), 128.3 (Ar), 128.1 (Ar), 127.7 (Ar), 127.6 (Ar),

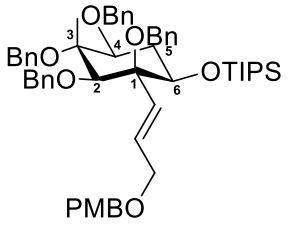
127.5(2) (Ar), 127.4(6) (Ar), 127.1 (Ar), 84.3 (C-2), 82.9 (C-1), 81.0 (C-6), 78.5 (C-3), 75.9 ($\underline{C}H_2Ar$), 72.3 ($\underline{C}H_2Ar$), 71.4 (C-4), 66.2 ($\underline{C}H_2Ar$), 63.1 (C-3'), 33.6 (C-5), 18.1(3) (SiCH($\underline{C}H_3)_2$), 18.1(2) (SiCH($\underline{C}H_3)_2$), 12.6 (3 x Si$\underline{C}$H$(CH_3)_2$), 11.7 (CH_3). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{40}H_{60}NO_6Si$: 678.4184. Found 678.4188.



3.82

Racemic **1,2,6-tri-*O*-benzyl-5-deoxy-3-((*E*)-3'-*O*-(4-methoxybenzyl)-1'-propenyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-3-*myo*-inositol (3.82)**. Sodium hydride (12 mg, 0.311 mmol, 60% dispersion in mineral oil) was added to a cooled (–10 °C) solution of **3.81** (98 mg, 0.148 mmol) in DMF (4 mL). The reaction mixture was stirred for 30 min at –10 °C, then *p*-methoxybenzyl chloride (20 µL, 0.148 mmol) was added. The reaction mixture was stirred for 2 h at –10 °C, and water was added. The reaction mixture was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.82** (27 mg, 23%) as a colourless oil. R_f 0.25 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.37–7.17 (m, 17 H, Ar), 6.86–6.83 (m, 2 H, Ar), 6.00 (app dt, 1 H, $J_{1',2'}$ = 15.4 Hz, $J_{2',3'}$ = 5.1 Hz, H-2'), 5.63 (dt, 1 H, $J_{1',2'}$ = 15.4 Hz, $J_{1',3'}$ = 1.5 Hz, H-1'), 4.84 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.78 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.75 (d, 1 H, J = 10.6 Hz, C$\underline{H}_2$Ar), 4.68 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.64 (d, 1 H, J = 10.8 Hz, C$\underline{H}_2$Ar), 4.63 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.42 (s, 2 H, 2 x C$\underline{H}_2$Ar), 4.01–3.99 (m, 2 H, 2 x H-3'), 3.81 (s, 3 H, OCH_3), 3.70 (dd, 1 H, $J_{4,5ax}$ = 11.4 Hz, $J_{4,5eq}$ = 4.8 Hz, H-4), 3.50 (dd, 1 H, $J_{5ax,6}$ = 12.1 Hz, $J_{5eq,6}$ = 4.4 Hz, H-6), 3.31 (s, 1 H, H-2), 2.41 (s, 1 H, OH), 1.97 (ddd, 1 H, $J_{5eq,5ax}$ = 12.7 Hz, $J_{4,5eq}$ = 4.6

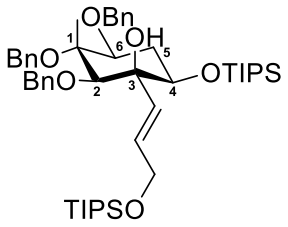
Hz, $J_{5eq,6}$ = 4.6 Hz, H-5_{eq}), 1.91 (ddd, 1 H, $J_{4,5ax}$ = 11.7 Hz, $J_{5eq,5ax}$ = 11.7 Hz, $J_{5ax,6}$ = 11.7 Hz, H-5_{ax}), 1.69 (s, 3 H, CH_3), 1.04–0.96 (m, 21 H, 3 x SiC<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.0 (Ar), 140.1 (Ar), 138.7 (Ar), 138.6 (Ar), 135.6 (C-1'), 130.7 (Ar), 129.0 (C-2'), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 127.3 (Ar), 127.0 (Ar), 113.7 (Ar), 84.6 (C-2), 82.8 (C-1), 80.9 (C-6), 78.6 (C-3), 76.1 (CH_2Ar), 72.3 (CH_2Ar), 72.0 (CH_2Ar), 71.5 (C-4), 69.9 (CH_2OPMB), 66.1 (CH_2Ar), 55.3 (OCH_3) 33.6 (C-3'), 29.7 (C-5), 18.2 (SiCH(<u>C</u>H$_3$)$_2$), 18.1 (SiCH(<u>C</u>H$_3$)$_2$), 12.7 (3 x Si<u>C</u>H(CH$_3$)$_2$), 11.7 (CH_3). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{48}H_{68}NO_7Si$: 798.4760. Found 798.4760.



3.83

Racemic **1,2,3,4-tetra-*O*-benzyl-5-deoxy-1-((*E*)-3'-*O*-(4-methoxybenzyl)-1'-propenyl)-3-*C*-methyl-6-*O*-triisopropylsilyl-1-*myo*-inositol (3.83)**. Sodium hydride (2 mg, 0.0338 mmol, 60% dispersion in mineral oil) was added to a solution of **3.82** (22 mg, 0.0282 mmol), TBAI (11 mg, 0.0282 mmol) and benzyl bromide (10 μL, 0.0845 mmol) in DMF (0.5 mL). The reaction mixture was stirred for 2 h and water was added. The reaction mixture was extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.83** (24 mg, 98%) as a colourless oil. R_f 0.37 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.45 (d, 2 H, J = 7.0 Hz, Ar), 7.39–7.22 (m, 18 H, Ar), 7.13–7.09 (m, 2 H, Ar), 6.82–6.78 (m, 2 H, Ar), 5.94 (dt, 1 H, J = 16.3 Hz, J = 5.1 Hz, H-2'), 5.88 (d, 1 H, J = 16.3 Hz, H-1'), 4.95–4.85 (m, 3 H, 3 x C<u>H</u>$_2$Ar), 4.82 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.76 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.72–4.64 (m, 3 H, 3 x

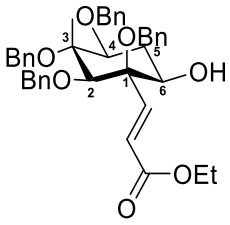
C<u>H</u>$_2$Ar), 4.35 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.32 (d, 1 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 4.00 (dd, 1 H, J = 12.5 Hz, J = 5.5 Hz, H-3'), 3.96–3.89 (m, 2 H, H-6, H-3',), 3.80 (s, 3 H, OCH_3), 3.57 (dd, 1 H, $J_{4,5ax}$ = 12.1 Hz, $J_{4,5eq}$ = 4.2 Hz, H-4), 3.43 (s, 1 H, H-2), 2.18 (ddd, 1 H, $J_{4,5ax}$ = 11.1 Hz, $J_{5eq,5ax}$ = 11.1 Hz, $J_{5ax,6}$ = 11.1 Hz, H-5_{ax}), 2.02 (ddd, 1 H, $J_{5ax,5eq}$ = 12.3 Hz, $J_{4,5eq}$ = 4.0 Hz, $J_{5eq,6}$ = 4.0 Hz, H-5_{eq}), 1.73 (s, 3 H, CH_3), 1.13–1.02 (m, 21 H, 3 x SiC<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.0 (Ar), 141.4 (Ar), 140.2 (Ar), 139.5 (Ar), 138.8 (Ar), 132.3 (C-1'/C-2'), 130.4 (C-1'/C-2'), 129.6 (Ar), 129.0 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 127.0 (Ar), 126.9 (Ar), 126.4 (Ar), 126.2 (Ar), 113.7 (Ar), 87.0 (C-2), 83.7 (C-3/C-1), 83.2 (C-1/C-3), 81.7 (C-4), 76.1 (<u>C</u>H$_2$Ar), 73.7 (C-6), 72.2 (<u>C</u>H$_2$Ar), 71.6 (<u>C</u>H$_2$Ar), 70.3 (<u>C</u>H$_2$OPMB), 67.3 (<u>C</u>H$_2$Ar), 66.1 (<u>C</u>H$_2$Ar), 55.3 (OCH_3), 33.8 (C-5), 18.3 (3 x SiCH(<u>C</u>H$_3$)$_2$), 12.9 (3 x Si<u>C</u>H(CH$_3$)$_2$), 12.1 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{55}H_{70}NaO_7Si$: 893.4783. Found 893.4779.



3.84

Racemic **1,2,6-tri-*O*-benzyl-5-deoxy-3-((*E*)-3'-*O*-triisopropylsilyl-1'-propenyl)-1-*C*-methyl-4-*O*-triisopropylsilyl-3-*myo*-inositol (3.84)**. Imidazole (60 mg, 0.885 mmol) and TIPSCl (158 μL, 0.737 mmol) were added to a solution of **3.81** (389 mg, 0.590 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 4 h and then water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.84** (400 mg, 83%) as a yellow oil. R_f 0.41 (9:1 hexanes–EtOAc); ^{1}H NMR (500 MHz,

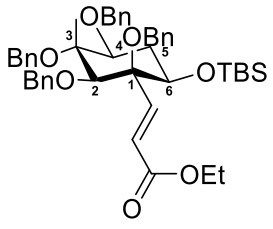
$CDCl_3$, δ_H) 7.40–7.23 (m, 15 H, Ar), 5.98 (dt, 1 H, $J_{1',2'}$ = 15.2 Hz, $J_{2',3'}$ = 3.7 Hz, H-2'), 5.74 (dt, 1 H, $J_{1',2'}$ = 15.2 Hz, $J_{1',3'}$ = 2.0 Hz, H-1'), 4.87 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.81 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.78–4.72 (m, 2 H, 2 x C$\underline{H}_2$Ar), 4.68 (d, 1 H, J = 10.6 Hz, C$\underline{H}_2$Ar), 4.67 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.30 (dd, 2 H, $J_{2',3'}$ = 3.7 Hz, $J_{1',3'}$ = 2.0 Hz, H-3'), 3.77 (dd, 1 H, $J_{4,5ax}$ = 11.2 Hz, $J_{4,5eq}$ = 5.0 Hz, H-4), 3.56 (dd, 1 H, $J_{5ax,6}$ = 11.9 Hz, $J_{5eq,6}$ = 5.0 Hz, H-6), 3.36 (s, 1 H, H-2), 2.43 (s, 1 H, OH), 2.03–1.91 (m, 2 H, H-5_{eq}, H-5_{ax}), 1.73 (s, 3 H, CH_3), 1.18–0.89 (m, 42 H, 6 SiC$\underline{H}$(C$\underline{H}_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 140.1 (Ar), 138.8 (2 x Ar), 132.2 (C-1'), 131.0 (C-2'), 128.4 (Ar), 128.3 (Ar), 128.0 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.3 (Ar), 127.1 (Ar), 85.4 (C-2), 82.8 (C-1), 81.0 (C-6), 78.7 (C-3), 76.4 (C$\underline{H}_2$Ar), 72.4 (C$\underline{H}_2$Ar), 71.5 (C-4), 66.4 (C$\underline{H}_2$Ar), 63.0 (CH_2OTIPS), 33.7 (C-5), 18.2 (SiCH(C$\underline{H}_3$)$_2$), 18.1 (SiCH(C$\underline{H}_3$)$_2$), 12.7 (3 x SiC$\underline{H}$(CH$_3$)$_2$), 12.0 (3 x SiC$\underline{H}$(CH$_3$)$_2$), 11.7 (CH_3). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{49}H_{80}NO_6Si_2$: 834.5519. Found 834.5533.



3.79

Racemic **1,2,3,4-tetra-*O*-benzyl-5-deoxy-1-((*E*)-ethoxycarbonylethenyl)-3-*C*-methyl-1-*myo*-inositol (3.79).** Molecular sieves (1.0 g, activated powder 4 Å) were added to a solution of **3.78** (568 mg, 0.895 mmol) in CH_2Cl_2 (16 mL). The reaction mixture was stirred at rt for 2 h, then cooled to –78 °C. $PhBCl_2$ (396 µL, 2.69 mmol) and Et_3SiH (429 µL, 3.04 mmol) were added to the reaction mixture. After 5 min, Et_3N (2 mL) and MeOH (2 Ml) were added and the mixture was allowed to warmed to rt. The mixture was then filtered through Celite® 545 and rinsed with CH_2Cl_2. The filtrate was washed with saturated aqueous solution of $NaHCO_3$ and the organic

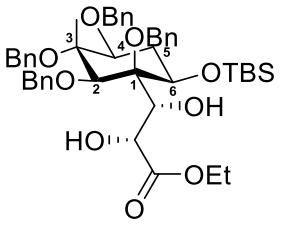
extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.79** (427 mg, 75%) as a colorless oil. The R_f, ^1H NMR, ^{13}C NMR and MS data correspond to that obtained on compound **3.79** previously described.



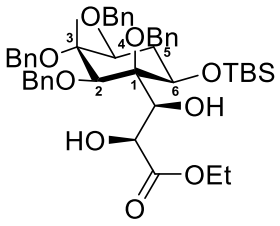
3.87

***Racemic* 1,2,3,4-tetra-*O*-benzyl-6-*O*-(*t*-butyldimethyl)silyl-5-deoxy-1-((*E*)-ethoxycarbonylethenyl)-3-*C*-methyl-1-*myo*-inositol (3.87).** 2,6-Lutidine (183 μL, 1.58 mmol) followed by TBSOTf (181 μL, 0.787 mmol) were added to a cooled (0 °C) solution of **3.79** (334 mg, 0.525 mmol) in CH_2Cl_2 (4 mL). The ice bath was removed and the mixture was stirred for 30 min. Methanol was added, then water, and the mixture was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.87** (366 mg, 93%) as a colorless oil. R_f 0.68 (4:1 hexanes–EtOAc); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.47–7.44 (m, 2 H, Ar), 7.41–7.26 (m, 18 H, Ar), 7.02 (d, 1 H, J = 16.1 Hz, C<u>H</u>=CH–C=O), 6.10 (d, 1 H, J = 16.1 Hz, CH=C<u>H</u>–C=O), 4.94–4.88 (m, 5 H, 5 x C<u>H</u>$_2$Ar), 4.70 (s, 2 H, 2 x C<u>H</u>$_2$Ar), 4.61 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.25–4.15 (m, 2 H, C<u>H</u>$_2$CH$_3$), 3.78 (dd, 1 H, $J_{5ax,6}$ = 11.9 Hz, $J_{5eq,6}$ = 3.7 Hz, H-6), 3.65 (dd, 1 H, $J_{4,5ax}$ = 12.1 Hz, $J_{4,5eq}$ = 4.4 Hz, H-4), 3.49 (s, 1 H, H-2), 2.15 (ddd, 1 H, $J_{4,5ax}$ = 12.0 Hz, $J_{5eq,5ax}$ = 12.0 Hz, $J_{5ax,6}$ = 12.0 Hz, H-5$_{ax}$), 2.00 (ddd, 1 H, $J_{5eq,5ax}$ = 12.0 Hz, = 12.5 Hz, $J_{4,5eq}$ = 4.2 Hz, $J_{5eq,6}$ = 4.2 Hz, H-5$_{eq}$), 1.74 (s, 3 H, CH_3), 1.27 (t, 3 H, J = 7.2 Hz, CH$_2$C<u>H</u>$_3$), 0.94 (s, 9 H, 3 x SiC(CH$_3$)$_3$), 0.10 (s, 3 H, SiCH$_3$), 0.09 (s, 3 H, SiCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.9

(C=O), 147.8 (C=C–C=O), 140.5 (Ar), 140.1 (Ar), 138.8 (Ar), 138.6 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 127.3 (Ar), 127.1 (Ar), 126.7 (Ar), 126.3 (Ar), 124.0 (C=C–C=O), 86.3 (C-2), 83.6 (C-1/C-3), 83.4 (C-1/C-3), 81.4 (C-4), 76.2 (CH_2Ar), 72.9 (C-6), 72.1 (CH_2Ar), 67.7 (CH_2Ar), 66.1 (CH_2Ar), 60.3 (CH_2CH_3), 33.6 (C-5), 25.8 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), 14.3 (CH_2CH_3), 12.1(CH_3), –4.1 ($SiCH_3$), –4.9 ($SiCH_3$). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{46}H_{62}NO_7Si$: 768.4290. Found 768.4285.



3.88



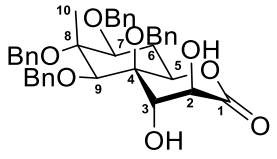
3.89

***Racemic* 1,2,3,4-tetra-*O*-benzyl-6-*O*-(*t*-butyldimethyl)silyl-5-deoxy-1-(ethoxycarbonyl-(1'*R*,2'*R*)-ethanediol)-3-*C*-methyl-1-*myo*-inositol (3.88)** and ***racemic* 1,2,3,4-tetra-*O*-benzyl-6-*O*-(*t*-butyldimethyl)silyl-5-deoxy-1-(ethoxycarbonyl-(1'*S*,2'*S*)-ethanediol)-3-*C*-methyl-1-*myo*-inositol (3.89).** 4-Methylmorpholine *N*-oxide (535 mg, 4.57 mmol) and DHQ-CLB (2.20 g, 4.74 mmol) were added to a solution of **3.87** (2.64 g, 3.51 mmol) in acetone (30 mL). Water (5 mL) was added, followed by osmium tetroxide (1.12 mL, 0.176 mmol, 4% solution in H_2O). The reaction mixture was stirred in the dark at rt overnight and then EtOAc and a saturated aqueous solution of $Na_2O_3S_2$ were added and the mixture was stirred for 2 h. The aqueous and organic layer were separated and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude products were purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.88** (1.78 g, 65%) and **3.89** (962 mg, 35%) as colorless oils. (**3.88**): R_f 0.50 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.44–7.41 (m, 2 H, Ar), 7.39–7.24 (m, 18 H, Ar), 5.12 (d, 1 H, J = 11.4 Hz, CH_2Ar), 5.06 (d, 1 H, J = 11.0 Hz, CH_2Ar), 5.01 (d, 1 H, J = 11.0 Hz, CH_2Ar), 4.98 (d,

1 H, $J_{1',2'}$ = 8.6 Hz, H-1'), 4.86 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.81 (d, 1 H, $J_{1',2'}$ = 8.4 Hz, H-2'), 4.74 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.65 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.62 (s, 2 H, 2 x C$\underline{H}_2$Ar), 4.50 (dd, 1 H, $J_{5ax,6}$ = 12.1 Hz, $J_{5eq,6}$ = 4.0 Hz, H-6), 4.37 (d, 1 H, J = 7.2 Hz, OH), 4.30–4.17 (m, 2 H, C$\underline{H}_2$CH$_3$), 3.60 (dd, 1 H, $J_{4,5ax}$ = 12.3 Hz, $J_{4,5eq}$ = 4.6 Hz, H-4), 3.60 (s, 1 H, H-2), 3.32 (d, 1 H, J = 7.2 Hz, OH), 2.16 (ddd, 1 H, $J_{4,5ax}$ = 12.0 Hz, $J_{5eq,5ax}$ = 12.0 Hz, $J_{5ax,6}$ = 12.0 Hz, H-5$_{ax}$), 1.89 (ddd, 1 H, $J_{5eq,5ax}$ = 12.1 Hz, $J_{4,5eq}$ = 4.2 Hz, $J_{5eq,6}$ = 4.2 Hz, H-5$_{eq}$), 1.71 (s, 3 H, CH$_3$), 1.18 (t, 3 H, J = 7.2 Hz, CH$_2$C$\underline{H}_3$), 0.93 (s, 9 H, 3 x SiC(CH$_3$)$_3$), 0.15 (s, 3 H, SiCH$_3$), 0.10 (s, 3 H, SiCH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$, δ_C) 173.7 (C=O), 140.0 (Ar), 139.8 (Ar), 139.0 (Ar), 138.5 (Ar), 128.5 (Ar), 128.3(2) (Ar), 128.2(5) (Ar), 127.9 (Ar), 127.7 (Ar), 127.5 (Ar), 127.3(5) (Ar), 127.3(1) (Ar), 127.2 (Ar), 127.0 (Ar), 126.8 (Ar), 84.1 (C-2), 83.9 (C-1/C-3), 81.7 (C-4), 80.2 (C-3/C-1), 75.7 (C$\underline{H}_2$Ar), 72.4 (C-6), 71.9 (C$\underline{H}_2$Ar), 71.3 (C-1'/C-2'), 71.0 (C-1'/C-2'), 67.4 (C$\underline{H}_2$Ar), 66.1 (C$\underline{H}_2$Ar), 62.3 (C$\underline{H}_2$CH$_3$), 33.2 (C-5), 25.8 (3 x SiC(C$\underline{H}_3$)$_3$), 18.1 (SiC(CH$_3$)$_3$), 14.0 (CH$_2$C$\underline{H}_3$), 11.4 (CH$_3$), –3.6 (SiCH$_3$), –4.3 (SiCH$_3$). HRMS (ESI) Calcd for [M + Na]$^+$ $C_{46}H_{60}NaO_9Si$: 807.3899. Found 807.3894.

(**3.89**): R_f 0.46 (7:3 hexanes–EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$, δ_H) 7.44–7.41 (m, 2 H, Ar), 7.37–7.25 (m, 18 H, Ar), 5.12 (d, 1 H, $J_{1',2'}$ = 8.3 Hz, H-1'), 5.12 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 5.04 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.97 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.88 (d, 1 H, $J_{1',2'}$ = 8.1 Hz, H-2'), 4.83 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.79 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.69 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.63 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.60 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.40–4.24 (m, 4 H, C$\underline{H}_2$CH$_3$, H-2, OH), 3.88 (dd, 1 H, $J_{5ax,6}$ = 11.6 Hz, $J_{5eq,6}$ = 3.9 Hz, H-6), 3.62 (dd, 1 H, $J_{4,5ax}$ = 11.7 Hz, $J_{4,5eq}$ = 4.6 Hz, H-4), 3.51 (d, 1 H, J = 6.1 Hz, OH), 2.16–2.04 (m, 2 H, H-5$_{ax}$, H-5$_{eq}$), 1.66 (s, 3 H, CH$_3$), 1.32 (t, 3 H, J = 7.2 Hz, CH$_2$C$\underline{H}_3$), 0.96 (s, 9 H, SiC(CH$_3$)$_3$), 0.12 (s, 3 H, SiCH$_3$), 0.10 (s, 3 H, SiCH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$, δ_C) 173.6 (C=O), 139.8 (2 x Ar), 138.9

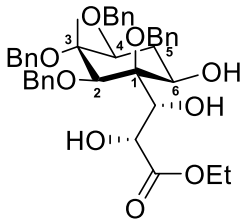
(Ar), 138.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 127.6(9) (Ar), 127.6(6) (Ar), 127.5(0) (Ar), 127.4(5) (Ar), 127.4 (Ar), 127.0(3) (Ar), 126.9(5) (Ar), 84.5 (C-2), 84.2 (C-1/C-3), 81.5 (C-4), 81.2 (C-1/C-3), 74.2 ($\underline{C}H_2Ar$), 71.8 ($\underline{C}H_2Ar$), 71.2 (C-6), 71.0 (C-1'/C-2'), 70.8 (C-1'/C-2'), 66.6 ($\underline{C}H_2Ar$), 65.6 ($\underline{C}H_2Ar$), 62.4 ($\underline{C}H_2CH_3$), 33.2 (C-5), 26.0 ($SiC(\underline{C}H_3)_3$), 18.1 ($Si\underline{C}(CH_3)_3$), 14.2 ($CH_2\underline{C}H_3$), 12.7 (CH_3), –3.1 ($SiCH_3$), –4.6 ($SiCH_3$). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{46}H_{60}NaO_9Si$: 807.3899. Found 807.3902.



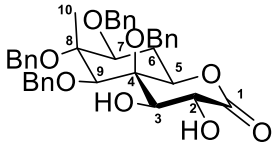
3.90

***Racemic* 4,7,8,9-tetra-*O*-benzyl-2,3-epi-bradyrhizose-1,5-lactone (3.90**). Ammonium fluoride (6 mg, 0.170 mmol) followed by TBAF (170 μL, 0.170 mmol, 1.0M in THF) were added to a cooled (0 °C) solution of **3.89** (89 mg, 0.113 mmol) in THF (5 mL). After 30 min, brine and EtOAc were added and the mixture was separated. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude products were purified by silica gel column chromatography (3:2 to 2:3 hexanes–EtOAc) to give **3.90** (60 mg, 86%) as a colorless oil. R_f 0.29 (24:1 CH_2Cl_2–MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.43–7.23 (m, 20 H, Ar), 5.11 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 5.04 (d, 1 H, J = 11.9 Hz, $C\underline{H}_2Ar$), 4.89 (d, 1 H, J = 11.2 Hz, $C\underline{H}_2Ar$), 4.88 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.81–4.77 (m, 2 H, 2 x $C\underline{H}_2Ar$), 4.69 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 4.57 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 4.53–4.48 (m, 2 H, H-3, H-7), 4.13 (br, 1 H, H-2), 3.93 (s, 1 H, H-9), 3.63 (dd, 1 H, $J_{5,6ax}$ = 12.5 Hz, $J_{5,6eq}$ = 4.4 Hz, H-5), 3.31 (s, 1 H, OH), 2.39 (dd, 1 H, J = 15.4 Hz, J = 4.6 Hz, OH), 2.30 (ddd, 1 H, $J_{6ax,6eq}$ = 12.5 Hz, $J_{5,6eq}$ = 4.6 Hz, $J_{6eq,7}$ = 4.6 Hz, H-6_{eq}), 2.13 (ddd, 1 H, $J_{5,6ax}$ = 12.5 Hz, $J_{6eq,6ax}$ = 12.5 Hz, $J_{6ax,7}$ = 12.5 Hz, H-6_{ax}), 1.71 (s, 3 H, H-10); ^{13}C NMR (125

MHz, $CDCl_3$, δ_C) 173.4 (C=O), 139.6 (Ar), 138.9 (Ar), 138.2 (Ar), 138.1 (Ar), 128.8 (Ar), 128.5 (Ar), 128.3(5) (Ar), 128.3(1) (Ar), 128.0 (Ar), 127.7(5) (Ar), 127.6(5) (Ar), 127.6 (Ar), 127.5(1) (Ar), 127.4(9) (Ar), 127.4 (Ar), 127.3 (Ar), 83.2 (C-8), 80.9 (C-9), 80.6 (C-7), 77.9 (C-4), 75.5 ($\underline{C}H_2Ar$), 74.3 (C-2), 73.6 (C-3/C-7), 71.8 ($\underline{C}H_2Ar$), 70.8 (C-3/C-7), 67.5 ($\underline{C}H_2Ar$), 66.3 ($\underline{C}H_2Ar$), 28.3 (C-6), 11.4 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{38}H_{40}NaO_8$: 647.2615. Found 647.2620.



3.91

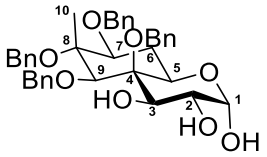


3.92

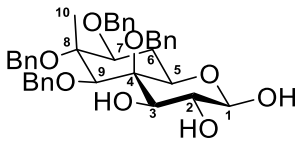
***Racemic* 1,2,3,4-tetra-*O*-benzyl-5-deoxy-1-(ethoxycarbonyl-(1'*R*,2'*R*)-ethanediol)-3-*C*-methyl-1-*myo*-inositol (3.91)** and ***racemic* 4,7,8,9-tetra-*O*-benzyl-bradyrhizose-1,5-lactone (3.92)**. Ammonium fluoride (77 mg, 2.07 mmol) followed by TBAF (2.07 mL, 2.07 mmol, 1.0M in THF) were added to a cooled (0 °C) solution of **3.88** (1.25 g, 1.59 mmol) in THF (80 mL). After 5 min, brine and EtOAc were added and the mixture was separated. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude products were purified by silica gel column chromatography (7:3 → 2:3 hexanes–EtOAc) to give **3.91** and **3.92** (1.78 g, 84%) as a colorless oil (ratio 3:1). (**3.91**): R_f 0.33 (24:1 CH_2Cl_2–MeOH); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.42–7.40 (m, 2 H, Ar), 7.39–7.26 (m, 18 H, Ar), 5.12 (d, 1 H, J = 11.2 Hz, $C\underline{H}_2Ar$), 5.08 (d, 1 H, J = 10.3 Hz, $C\underline{H}_2Ar$), 5.03–4.98 (m, 2 H, $C\underline{H}_2Ar$, H-1'), 4.86 (d, 1 H, J = 11.0 Hz, $C\underline{H}_2Ar$), 4.76 (d, 1 H, J = 11.0 Hz, $C\underline{H}_2Ar$), 4.69 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 4.65 (d, 1 H, J = 11.2 Hz, $C\underline{H}_2Ar$), 4.54 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.46–4.39 (m, 2 H, H-2', H-6), 4.35–4.18 (m, 3 H, OH, $C\underline{H}_2CH_3$), 3.64 (dd, 1 H, $J_{4,5ax}$ = 12.3 Hz, $J_{4,5eq}$ = 4.6 Hz, H-4), 3.62 (s, 1 H, H-2), 3.52 (d, 1 H, J =

6.4 Hz, OH), 2.55 (d, 1 H, J = 10.5 Hz, OH), 2.12 (ddd, 1 H, $J_{5ax,5eq}$ = 12.1 Hz, $J_{4,5eq}$ = 4.4 Hz, $J_{5eq,6}$ = 4.4 Hz, H-5_{eq}), 1.93 (ddd, Hz, $J_{4,5ax}$ = 12.0 Hz, $J_{5eq,5ax}$ = 12.0 Hz, $J_{5ax,6}$ = 12.0 Hz, H-5_{ax}), 1.76 (s, 3 H, CH_3), 1.18 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 173.5 (C=O), 139.7 (Ar), 139.1 (Ar), 138.9 (Ar), 138.3 (Ar), 128.4(2) (Ar), 128.3(5) (Ar), 128.3(3) (Ar), 128.2(8) (Ar), 128.2(5) (Ar), 127.6(3) (Ar), 127.6(0) (Ar), 127.5 (Ar), 127.4 (Ar), 127.2 (Ar), 126.9 (Ar), 84.4 (C-2), 83.5 (C-1/C-3), 81.2 (C-4), 80.5 (C-1/C-3), 76.1 ($\underline{C}H_2Ar$), 71.4 ($\underline{C}H_2Ar$), 71.1 (C-2'/C-6), 71.0 (C-2'/C-6), 69.9 (C-1'), 67.2 ($\underline{C}H_2Ar$), 66.2 ($\underline{C}H_2Ar$), 62.6 ($\underline{C}H_2CH_3$), 33.8 (C-5), 14.0 ($CH_2\underline{C}H_3$), 11.3 (CH_3). HRMS (ESI) Calcd for $[M + H]^+$ $C_{40}H_{47}O_9$: 671.3215. Found 671.3215.

(**3.92**): R_f 0.30 (24:1 CH_2Cl_2–MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.41–7.26 (m, 20 H, Ar), 5.53 (d, 1 H, J = 12.1 Hz, $C\underline{H}_2Ar$), 5.30 (d, 1 H, J = 12.1 Hz, $C\underline{H}_2Ar$), 5.17 (d, 1 H, J = 11.0 Hz, $C\underline{H}_2Ar$), 4.88 (d, 1 H, J = 11.0 Hz, $C\underline{H}_2Ar$), 4.78 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 4.76 (d, 1 H, J = 11.2 Hz, $C\underline{H}_2Ar$), 4.71 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.56 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 4.46 (d, 1 H, $J_{2,3}$ = 9.7 Hz, H-2), 4.44 (s, 1 H, OH), 4.29 (d, 1 H, $J_{2,3}$ = 9.7 Hz, H-3), 4.05 (dd, 1 H, $J_{5,6ax}$ = 12.3 Hz, $J_{5,6eq}$ = 4.2 Hz, H-5), 3.85 (s, 1 H, H-9), 3.68 (dd, 1 H, $J_{6eq,7}$ = 11.9 Hz, $J_{6eq,7}$ = 4.8 Hz, H-7), 3.16 (s, 1 H, OH), 2.31 (ddd, 1 H, $J_{6eq,6ax}$ = 12.3 Hz, $J_{5,6eq}$ = 4.6 Hz, $J_{6eq,7}$ = 4.6 Hz, H-6_{eq}), 2.23 (ddd, 1 H, $J_{5,6ax}$ = 12.0 Hz, $J_{6ax,6eq}$ = 12.0 Hz, $J_{6ax,7}$ = 12.0 Hz, H-6_{ax}), 1.74 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 171.8 (C=O), 139.1 (Ar), 137.7 (Ar), 128.9 (Ar), 128.5(4) (Ar), 128.4(5) (Ar), 128.4(2) (Ar), 128.3(8) (Ar), 128.1 (Ar), 127.9 (Ar), 127.7(4) (Ar), 127.6(6) (Ar), 127.5 (Ar), 127.4 (Ar), 126.7 (Ar), 88.3 (C-9), 83.2 (C-8), 81.0 (C-7), 79.1 (C-3), 76.6 (C-4), 76.6 (C-5), 75.4 ($\underline{C}H_2Ar$), 71.6 ($\underline{C}H_2Ar$), 70.8 (C-2), 69.4 ($\underline{C}H_2Ar$), 66.4 ($\underline{C}H_2Ar$), 28.9 (C-6), 11.3 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{38}H_{40}NaO_8$: 647.2615. Found 647.2621.



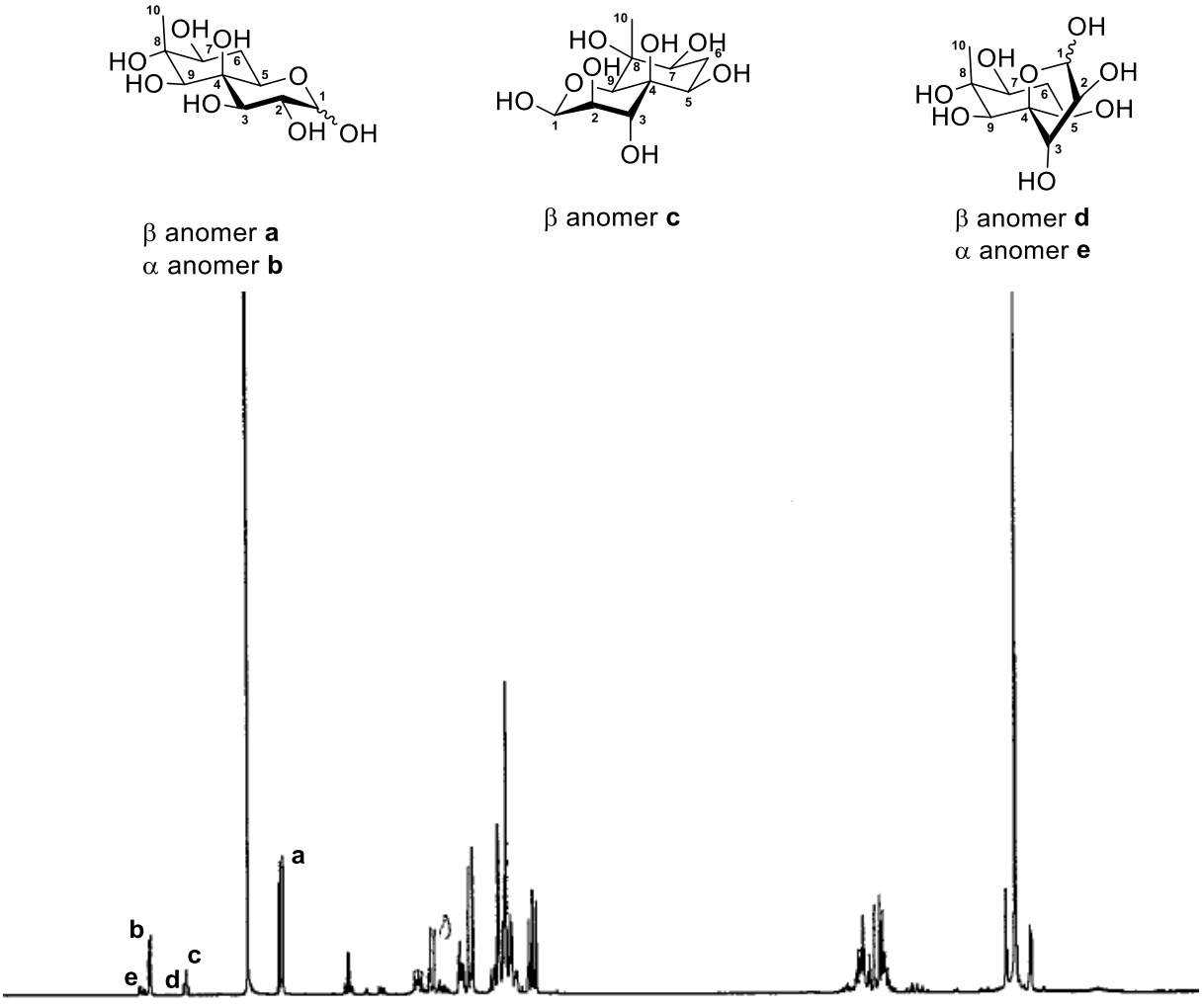
3.93α



3.93β

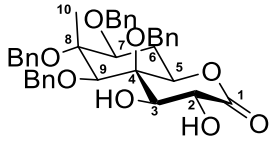
***Racemic* 4,7,8,9-tetra-*O*-benzyl-1,5-α-bradyrhizose (3.93α)** and ***racemic* 4,7,8,9-tetra-*O*-benzyl-1,5-β-bradyrhizose (3.93β)**. DIBAL-H (10 mL, 10.0 mmol, 1.0M in THF) was added to a cooled (–78 °C) solution of a mixture of **3.91** and **3.92** (667 g, 0.994 mmol) in THF (60 mL). The reaction mixture was stirred for 90 min then MeOH (3 mL) and a 10% aqueous solution of HCl and CH_2Cl_2 were added at –78 °C. The mixture was warmed to rt and extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (49:1 CH_2Cl_2–MeOH) to give **3.93α** and **3.93β** (567 mg, 91%) as a colorless oil (diastereomeric ratio 0.55:0.45). R_f 0.23 (24:1 CH_2Cl_2–MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.41–7.23 (m, 20 H, Ar), 5.50 (d, 0.55 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 5.45 (d, 0.45 H, J = 11.7 Hz, C$\underline{H}_2$Ar), 5.33 (app t, 0.55 H, J = 2.8 Hz, H-1α), 5.23–5.12 (m, 2 H, C$\underline{H}_2$Ar), 4.86–4.83 (m, 1 H, C$\underline{H}_2$Ar), 4.75 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.72–4.67 (m, 2 H, 2 x C$\underline{H}_2$Ar), 4.60 (app t, 0.45 H, J = 6.2 Hz, H-1β), 4.51 (d, 0.55 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 4.50 (d, 0.45 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 4.30 (s, 0.45 H, OH), 4.27 (s, 0.55 H, OH), 4.13 (d, 0.55 H, $J_{2,3}$ = 9.9 Hz, H-3α), 4.07–4.01 (m, 0.55 H, H-2α), 3.93 (br, 0.45, C-1-OHβ), 3.89–3.75 (m, 2 H, H-2β, H-9α, H-3β, H-5/H-7α), 3.71–3.62 (m, 1.45 H, H-9β, H-5, H-7), 3.37 (br, 0.55 H, C-1-OHα), 3.25 (dd, 0.45 H, J = 11.4 Hz, J = 4.4 Hz, H-5/H-7β), 3.01 (br, 0.45 H, C-2-OHβ), 2.69 (d, 0.55 H, $J_{2,OH}$ = 5.0 Hz, C-2-OHα), 2.20–2.05 (m, 2 H, 2 x H-6), 1.67 (s, 1.65 H, H-10), 1.66 (s, 1.35 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.5(4) (Ar), 139.4(8) (Ar), 139.4 (Ar), 138.2 (Ar), 138.0 (Ar), 137.8 (Ar), 137.7 (Ar), 128.8 (Ar), 128.5 (Ar), 128.4(2) (Ar), 128.3(7) (Ar), 128.3 (Ar), 128.2(3) (Ar), 128.2(0) (Ar), 128.1(5) (Ar), 128.1 (Ar), 128.0 (Ar), 127.7 (Ar), 127.6(5) (Ar), 127.6(1) (Ar),

127.5(7) (Ar), 127.3(1) (Ar), 127.2(6) (Ar), 127.1 (Ar), 127.0(1) (Ar), 127.9(6) (Ar), 126.8 (Ar), 97.6 (C-1β), 92.6 (C-1α), 89.6 (C-9α), 89.4 (C-9β), 83.5 (C-8), 83.4 (C-8), 82.0(7) (C_{brady}), 81.9(6) (C_{brady}), 80.0 (C_{brady}), 76.4 (C-4), 76.3 ($\underline{C}H_2Ar$), 76.2 ($\underline{C}H_2Ar$), 75.9 (C-4), 73.4 (C_{brady}), 72.7 (C_{brady}), 71.4 ($\underline{C}H_2Ar$), 71.3 ($\underline{C}H_2Ar$), 69.7 (C_{brady}), 68.9(2) ($\underline{C}H_2Ar$), 68.8(8) ($\underline{C}H_2Ar$), 67.7 (C_{brady}), 66.1 ($\underline{C}H_2Ar$), 66.0 ($\underline{C}H_2Ar$), 28.9 (C-6), 28.7 (C-6), 11.5 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{38}H_{42}NaO_8$: 626.2772. Found 647.2779.



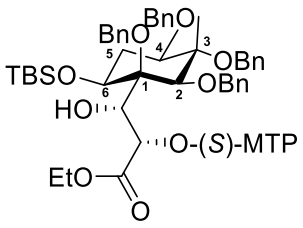
***Racemic* bradyrhizose (3.10)**. Palladium on carbon (70 mg, 0.0654 mmol, 10 wt. % loading) was added to a solution of **3.93** (82 mg, 0.131 mmol) in MeOH (5 mL) under Ar. The reaction mixture

was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium on carbon was filtered through Celite® 545 and the filtrate was concentrated. The resulting crude product was purified by reverse phase column chromatography (C-18 silica gel, H_2O) to give **3.10** (34 mg, 99%) as a colorless oil (isomeric mixture). ^{1}H NMR (500 MHz, D_2O, δ_H) 5.27 (d, 0.05 H, J = 5.3 Hz, H-1**e**), 5.25 (br, 0.03 H), 5.23 (d, 0.24 H, J = 4.0 Hz, H-1**b**), 5.07–5.05 (m, 0.13 H, H-1**c** and H-1**d**), 4.62 (d, 0.56 H, J = 8.07 Hz, H-1**a),** 4.34–4.29 (m, 0.18 H), 4.23 (br, 0.03 H), 4.18–4.15 (m, 0.05 H), 4.04–3.86 (m, 0.81 H), 3.82–3.73 (m, 0.96 H), 3.68–3.45 (m, 3.47 H), 2.03–1.82 (m, 2.22 H), 1.76–1.67 (m, 0.14 H), 1.31–1.18 (m, 3.48 H); ^{13}C NMR (125 MHz, D_2O, δ_C) 97.6 (C-1**a**), 93.3 (C-1**b**), 79.4, 79.3, 78.7, 78.4(9), 78.4(6), 75.4, 74.4, 73.9, 73.6, 73.2, 73.0, 71.5, 70.1, 66.4, 32.0 (C-6), 31.9 (C-6), 15.1 (C-10), 15.0 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{10}H_{18}NaO_8$: 289.0894. Found 289.0896.

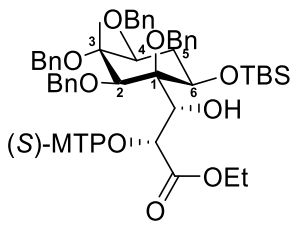


3.92

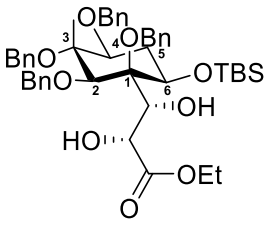
Racemic **4,7,8,9-tetra-*O*-benzyl-bradyrhizose-1,5-lactone (3.92)**. Pyridinium *p*-toulenesulfonate (15 mg, 0.0597 mmol) was added to a solution of **3.91** and **3.92** (106 mg, 0.158 mmol) in benzene (27 mL). The mixture was heated at reflux for 3 h before being cooled and concentrated. The resulting crude product was purified by silica gel column chromatography (49:1 CH_2Cl_2–MeOH) to give **3.92** (91 mg, 93%) as a colorless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained for compound **3.92** previously described.



3.113a



3.113b



(–)-3.88

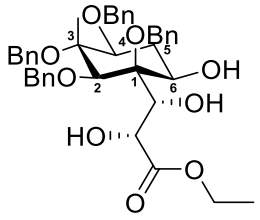
(–)-1,2,3,4-tetra-*O*-benzyl-6-*O*-(*t*-butyldimethyl)silyl-5-deoxy-1-(ethoxycarbonyl-2'-*O*-((2'*S*)-2-phenyl-2-methoxy-3,3,3-trifluoropropionoyl)-(1'*S*,2'*S*)-ethanediol)-3-*C*-methyl-1-*myo*-inositol (3.113a), (–)-1,2,3,4-tetra-*O*-benzyl-6-*O*-(*t*-butyldimethyl)silyl-5-deoxy-1-(ethoxycarbonyl-2'-*O*-((2'*S*)-2-phenyl-2-methoxy-3,3,3-trifluoropropionoyl)-(1'*R*,2'*R*)-ethanediol)-3-*C*-methyl-1-*myo*-inositol (3.113b) and **(–)-1,2,3,4-tetra-*O*-benzyl-6-*O*-(*t*-butyldimethyl)silyl-5-deoxy-1-(ethoxycarbonyl-(1'*S*,2'*S*)-ethanediol)-3-*C*-methyl-1-*myo*-inositol ((–)-3.88).** *N,N*-Diisopropylcarbodiimide (362 μL, 2.34 mmol) was added to a solution of **3.88** (914 mg, 1.16 mmol), (*S*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (547 mg, 2.34 mmol) and DMAP (72 mg, 0.592 mmol) in CH_2Cl_2 (12 mL). The reaction mixture was stirred for 2 h and then water was added. The aqueous and organic layer were separated and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude products were purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **3.113a** (583 mg, 50%), **3.113b** (170 mg, 14%) as colorless oils and unreacted **(–)-3.88** (329 mg, 36%). (**3.113a**): R_f 0.45 (9:1 hexanes–EtOAc); $[\alpha]_D$ –9.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.67 (d, 2 H, *J* = 7.5 Hz, Ar), 7.44–7.22 (m, 23 H, Ar), 5.62 (d, 1 H, *J* = 8.3 Hz, OH), 5.26–5.20 (m, 3 H, C$\underline{H}_2$Ar, H-1', H-2'), 4.94 (d, 1 H, *J* = 10.5 Hz, C$\underline{H}_2$Ar), 4.91 (d, 1 H, *J* = 10.5 Hz, C$\underline{H}_2$Ar), 4.73 (d, 1 H, *J* = 11.0 Hz, C$\underline{H}_2$Ar), 4.69 (d, 1 H, *J* = 11.2 Hz, C$\underline{H}_2$Ar), 4.48 (d, 1 H, *J* = 11.9 Hz, C$\underline{H}_2$Ar), 4.39 (d, 1 H, *J* = 11.6 Hz, C$\underline{H}_2$Ar), 4.34–4.19 (m, 3 H, C$\underline{H}_2$Ar, C$\underline{H}_2$CH$_3$), 3.98 (s, 3 H, OCH_3), 3.70 (dd, 1 H, $J_{5ax,6}$ = 12.1 Hz, $J_{5eq,6}$ = 3.9 Hz, H-6), 2.84 (s, 1 H, H-2), 2.48 (dd, 1 H, $J_{4,5ax}$ = 12.3 Hz, $J_{4,5eq}$ =

4.6 Hz, H-4), 1.88 (ddd, 1 H, $J_{4,5ax}$ = 12.1 Hz, $J_{5eq,5ax}$ = 12.1 Hz, $J_{5ax,6}$ = 12.1 Hz, H-5_{ax}), 1.54 (s, 3 H, CH_3), 1.47 (ddd, 1 H, $J_{5eq,5ax}$ 11.7 Hz, $J_{4,5eq}$ = 4.2 Hz, $J_{5eq,6}$ = 4.2 Hz, H-5_{eq}), 1.24 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.10 (s, 3 H, $SiCH_3$), –0.03 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 167.0 (2 x C=O), 139.7 (Ar), 139.2 (Ar), 138.6 (Ar), 132.9 (Ar), 129.9 (Ar), 128.8 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 127.9(5) (Ar), 127.9(0) (Ar), 127.6 (Ar), 127.5 (Ar), 127.3(5) (Ar), 127.3(0) (Ar), 127.1(3) (Ar), 127.0(6) (Ar), 126.8 (Ar), 123.1 (q, 1 C, J = 294.5, CF_3), 84.8 (C-2), 84.2 (q, 1 C, J = 27.7, $\underline{C}CF_3$), 83.2 (C-3), 81.5 (C-4), 79.5 (C-1), 76.5 (C-2'), 76.1 ($\underline{C}H_2Ar$), 73.0 (C-1') 71.2 ($\underline{C}H_2Ar$), 70.2 (C-6), 66.9 ($\underline{C}H_2Ar$), 65.8 ($\underline{C}H_2Ar$), 62.0 ($\underline{C}H_2CH_3$), 56.7 (OCH_3) 33.7 (C-5), 25.8 ($SiC(\underline{C}H_3)_3$), 18.0 ($Si\underline{C}(CH_3)_3$), 14.0 ($CH_2\underline{C}H_3$), 11.2 (CH_3), –3.0 ($SiCH_3$), –3.9 ($SiCH_3$). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{56}H_{67}F_3NaO_{11}Si$: 1023.4297. Found 1023.4294.

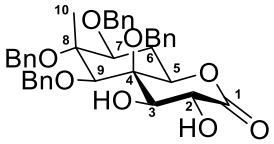
(**3.113b**): R_f 0.43 (9:1 hexanes–EtOAc); $[\alpha]_D$ –31.1 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.74–7.69 (m, 2 H, Ar), 7.47–7.43 (m, 3 H, Ar), 7.41–7.38 (m, 2 H, Ar), 7.36–7.24 (m, 18 H, Ar), 5.46–5.42 (m, 2 H, OH, H-2'), 5.28 (dd, 1 H, J = 7.7 Hz, J = 2.9 Hz, H-1'), 5.15 (d, 1 H, J = 11.7 Hz, $C\underline{H}_2Ar$), 5.03 (d, 1 H, J = 10.5 Hz, $C\underline{H}_2Ar$), 4.97 (d, 1 H, J = 10.5 Hz, $C\underline{H}_2Ar$), 4.83 (d, 1 H, J = 11.6 Hz, $C\underline{H}_2Ar$), 4.69 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.54 (s, 2 H, 2 x $C\underline{H}_2Ar$), 4.50 (d, 1 H, J = 11.9 Hz, $C\underline{H}_2Ar$), 4.47 (dd, 1 H, $J_{5ax,6}$ = 12.1 Hz, $J_{5eq,6}$ = 4.0 Hz, H-6), 4.28–4.13 (m, 2 H, $C\underline{H}_2CH_3$), 3.48 (s, 3 H, OCH_3), 3.42 (dd, 1 H, $J_{4,5ax}$ = 12.3 Hz, $J_{4,5eq}$ = 4.4 Hz, H-4), 3.28 (s, 1 H, H-2), 2.11 (ddd, 1 H, $J_{4,5ax}$ = 12.1 Hz, $J_{5eq,5ax}$ = 12.1 Hz, $J_{5ax,6}$ = 12.1 Hz, H-5_{ax}), 1.84 (ddd, 1 H, $J_{5eq,5ax}$ = 11.9 Hz, $J_{4,5eq}$ = 4.2 Hz, $J_{5eq,6}$ = 4.2 Hz, H-5_{eq}), 1.66 (s, 3 H, CH_3), 1.20 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.05 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 167.1 (2 x C=O), 139.7 (Ar), 139.4 (Ar), 138.8 (Ar), 138.2 (Ar), 131.1 (Ar), 129.9 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2(7) (Ar), 128.2(5) (Ar), 128.0 (Ar), 127.9

(Ar), 127.8 (Ar), 127.4 (Ar), 127.2 (Ar), 127.1(3) (Ar), 127.0(5) (Ar), 124.5 (q, 1 C, J = 289.1, CF_3), 84.2 (C-2), 85.4 (q, 1 C, J = 27.6, $\underline{C}CF_3$), 83.3 (C-3), 80.7 (C-4), 79.9 (C-1), 76.7 (C-2'), 75.8 ($\underline{C}H_2Ar$), 72.7 (C-1'), 71.8 ($\underline{C}H_2Ar$), 70.4 (C-6), 67.1 ($\underline{C}H_2Ar$), 65.4 ($\underline{C}H_2Ar$), 62.0 ($\underline{C}H_2CH_3$), 55.5 (OCH_3), 33.0 (C-5), 25.8 ($SiC(\underline{C}H_3)_3$), 18.0 ($Si\underline{C}(CH_3)_3$), 14.0 ($CH_2\underline{C}H_3$), 11.8 (CH_3), –3.0 ($SiCH_3$), –4.1 ($SiCH_3$). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{56}H_{67}F_3NaO_{11}Si$: 1023.4297. Found 1023.4312.

(**(–)-3.88**): The R_f, ^1H NMR, ^{13}C NMR and MS data correspond to that obtained for the racemic compound **3.88** previously described. $[\alpha]_D$ –57.2 (*c* 0.3, $CHCl_3$).

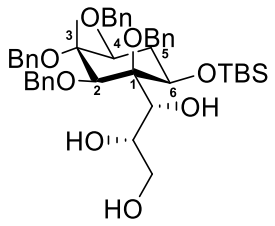


(–)-3.91



(+)-3.92

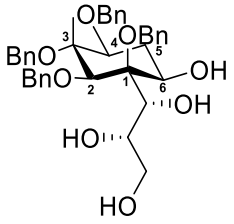
(–)-1,2,3,4-tetra-*O*-benzyl-5-deoxy-1-(ethoxycarbonyl-(1'*R*,2'*R*)-ethanediol)-3-*C*-methyl-1-*myo*-inositol (–)-3.91) and **D-4,7,8,9-tetra-*O*-benzyl-bradyrhizose-1,5-lactone ((+)-3.92)**. Ammonium fluoride (23 mg, 0.627 mmol) followed by TBAF (627 µL, 0.627 mmol, 1.0M in THF) were added to a cooled (0 °C) solution of **(–)-3.88** (3.78 mg, 0.482 mmol) in THF (80 mL). After 5 min, brine and EtOAc were added and the mixture was separated. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude products were purified by silica gel column chromatography (7:3 to 2:3 hexanes–EtOAc) to give **(–)-3.91** and **(+)-3.92** (270 mg, 84%) as a colorless oil (mixture). The mp, R_f, ^1H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **3.91** and **3.92** previously described. (**(–)-3.91**): $[\alpha]_D$ –40.7 (*c* 0.1, $CHCl_3$). (**(+)-3.92**): $[\alpha]_D$ +5.3 (*c* 0.3, $CHCl_3$).



(–)-3.116

(–)-1,2,3,4-tetra-*O*-benzyl-6-*O*-(*t*-butyldimethyl)silyl-5-deoxy-1-((1'*R*,2'*S*)-propane-1,2,3-triol)-3-*C*-methyl-1-*myo*-inositol ((–)-3.116). Lithium borohydride solution (237 μL, 0.474 mmol, 2.0M in THF) was added to a solution of **3.113a** (95 mg, 0.0948 mmol) in Et_2O (5 mL). After 1 h, additioinal lithium borohydride solution (118 μL, 0.237 mmol, 2.0M in THF) was added. The mixture was stirred for 2 h and a saturated aqueous solution of ammonium chloride was added. The aqueous layer was extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **(–)-3.116** (52 mg, 75%) as a yellow oil. R_f 0.27 (7:3 hexanes–EtOAc); $[\alpha]_D$ –30.4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.45–7.25 (m, 20 H, Ar), 5.11 (d, 1 H, *J* = 11.9 Hz, C$\underline{H}_2$Ar), 5.03 (d, 1 H, *J* = 11.6 Hz, C$\underline{H}_2$Ar), 4.97 (d, 1 H, *J* = 11.4 Hz, C$\underline{H}_2$Ar), 4.88 (d, 1 H, *J* = 11.2 Hz, C$\underline{H}_2$Ar), 4.74 (d, 1 H, *J* = 11.2 Hz, C$\underline{H}_2$Ar), 4.64 (d, 1 H, *J* = 7.0 Hz, C1'-OH), 4.63 (s, 2 H, 2 x C$\underline{H}_2$Ar), 4.56 (d, 1 H, *J* = 7.0 Hz, H-1'), 4.52 (d, 1 H, *J* = 11.9 Hz, C$\underline{H}_2$Ar), 4.46 (dd, 1 H, $J_{5ax,6}$ = 12.1 Hz, $J_{5eq,6}$ = 3.9 Hz, H-6), 3.74–3.57 (m, 4 H, H-2, H-4, H-2',H-3'), 3.56–3.47 (m, 1 H, H-3'), 2.92 (d, 1 H, *J* = 8.4 Hz, C-2'-OH), 2.64 (br s, 1 H, C3'-OH), 2.15 (ddd, 1 H, $J_{4,5ax}$ = 12.3 Hz, $J_{5ax,5eq}$ = 12.3 Hz, $J_{5ax,6}$ = 12.3 Hz, H-5$_{ax}$), 1.92 (ddd, 1 H, $J_{5ax,5eq}$ = 11.9 Hz, $J_{4,5eq}$ = 4.2 Hz, $J_{5eq,6}$ = 4.2 Hz, H-5$_{eq}$), 1.72 (s, 3 H, CH_3), 0.93 (s, 9 H, $SiC(CH_3)_3$), 0.14 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.9 (Ar), 139.7 (Ar), 138.8 (Ar), 138.4 (Ar), 128.5(0) (Ar), 128.4(9) (Ar), 128.3 (Ar), 128.1 (Ar), 127.8 (Ar), 127.6 (Ar), 127.4

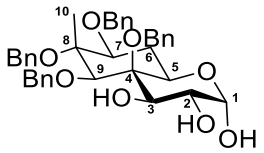
(Ar), 127.2 (Ar), 127.1 (Ar), 127.0 (Ar), 126.9 (Ar), 83.8 (C-2), 83.8 (C-3), 81.6 (C-4), 80.3 (C-1), 75.7 ($\underline{C}H_2Ar$), 72.3 (C-6), 72.0 ($\underline{C}H_2Ar$), 71.5 (C-1'), 69.5 (C-2'), 66.6 ($\underline{C}H_2Ar$), 66.2 ($\underline{C}H_2Ar$), 66.0 (C-3'), 33.2 (C-5), 25.9 ($SiC(\underline{C}H_3)_3$), 18.0 ($Si\underline{C}(CH_3)_3$), 11.5 (CH_3), –3.5 ($SiCH_3$), –4.3 ($SiCH_3$). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{44}H_{58}NaO_8Si$: 765.3793. Found 765.3799.



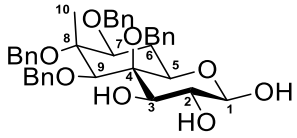
(–)-3.117

(–)-1,2,3,4-tetra-*O*-benzyl-5-deoxy-1-((1'*R*,2'*S*)-propane-1,2,3-triol)-3-*C*-methyl-1-*myo*-inositol ((–)-3.117). A solution of TBAF (100 μL, 0.100 mmol, 1.0M in THF) was added to a solution of **(–)-3.116** (57 mg, 0.0767 mmol) in THF (3 mL). The reaction mixture was stirred for 30 min and brine was added. The aqueous layer was extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (1:1 hexanes–EtOAc then 19:1 CH_2Cl_2–MeOH) to give **(–)-3.117** (47 mg, 98%) as a colorless oil. R_f 0.28 (24:1 CH_2Cl_2:MeOH); $[\alpha]_D$ –11.2 (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.41–7.21 (m, 20 H, Ar), 5.05 (d, 1 H, J = 10.5 Hz, $C\underline{H}_2Ar$), 5.04 (d, 1 H, J = 11.8 Hz, $C\underline{H}_2Ar$), 4.93 (d, 1 H, J = 10.6 Hz, $C\underline{H}_2Ar$), 4.83 (d, 1 H, J = 11.2 Hz, $C\underline{H}_2Ar$), 4.72 (d, 1 H, J = 11.0 Hz, $C\underline{H}_2Ar$), 4.65 (d, 1 H, J = 11.5 Hz, $C\underline{H}_2Ar$), 4.54 (d, 1 H, $J_{1',2'}$ = 7.4 Hz, H-1'), 4.50 (d, 1 H, J = 11.4 Hz, $C\underline{H}_2Ar$), 4.46 (d, 1 H, J = 11.8 Hz, $C\underline{H}_2Ar$), 4.40–4.33 (m, 2 H, OH, H-6), 3.73–3.68 (m, 1 H, H-2'), 3.64 (dd, 1 H, J = 11.1 Hz, J = 5.1 Hz, H-3'), 3.60 (dd, 1 H, $J_{4,5ax}$ = 12.0 Hz, $J_{4,5eq}$ = 4.5 Hz, H-4), 3.56 (s, 1 H, H-2), 3.53–3.47 (m, 1 H, H-3'), 3.19 (br, 1 H, OH), 2.81–2.69 (m, 2 H, C-6-OH, OH), 2.07 (ddd, 1 H, $J_{5ax,5eq}$ = 12.2 Hz, $J_{4,5eq}$ = 4.4 Hz, $J_{5eq,6}$ = 4.4 Hz,

H-5$_{eq}$), 1.92 (ddd, 1 H, $J_{4,5ax}$ = 12.2 Hz, $J_{5ax,5eq}$ = 12.2 Hz, $J_{5ax,6}$ = 12.2 Hz, H-5$_{ax}$), 1.73 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.6 (Ar), 139.1 (Ar), 138.8 (Ar), 138.3 (Ar), 128.5 (Ar), 128.4(0) (Ar), 128.3(8) (Ar), 128.3 (Ar), 128.0 (Ar), 127.6(1) (Ar), 127.5(6) (Ar), 127.5(3) (Ar), 127.5(0) (Ar), 127.2 (Ar), 127.1 (Ar), 84.3 (C-2), 83.5 (C-3), 81.1 (C-4), 80.2 (C-1), 76.1 (CH_2Ar), 71.4 (CH_2Ar), 71.3 (C-1'), 70.0 (C-6), 69.7 (C-2'), 67.0 (CH_2Ar), 66.5 (CH_2Ar), 66.2 (C-3'), 33.7 (C-5), 11.4 (CH_3). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{38}H_{44}NaO_8$: 651.2928. Found 651.2936.

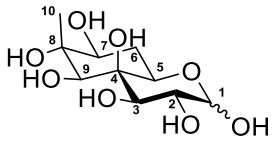


D-3.93α



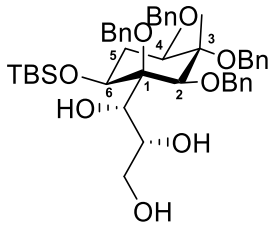
D-3.93β

4,7,8,9-tetra-*O*-benzyl-1,5-α-D-bradyrhizose (D-3.93α) and **4,7,8,9-tetra-*O*-benzyl-1,5-β-D-bradyrhizose (D-3.93β)**. Trichloroisocyanuric acid (45 mg, 0.191 mmol), followed by TEMPO (0.5 mg, 0.00355 mmol) were added to a cooled (0 °C) solution of **(–)-3.117** (45 mg, 0.0709 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at 0 °C for 30 min and a saturated aqueous solution of $Na_2S_2O_3$ was added, followed by an extraction with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The resulting crude product was used without further purification. DIBAL-H (354 μL, 0.354 mmol, 1.0M in cyclohexane) was added to a cooled (–78 °C) solution of the crude product in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred for 90 min before MeOH (1 mL) and a 10% aqueous solution of HCl (1 mL) were added at –78 °C. The mixture was warmed to rt and extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product were purified by silica gel column chromatography (49:1 CH_2Cl_2–MeOH) to give **D-3.93α** and **D-3.93β** (41 mg, 91%) as a colorless oil (diastereomeric mixture, 0.45:0.55). The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to the that of the racemic compounds **3.93α** and **3.93β** previously described. $[\alpha]_D$ +9.1 (*c* 0.2, $CHCl_3$).



D-3.10

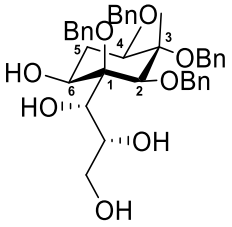
D-Bradyrhizose (D-3.10). Palladium on carbon (15 mg, 0.0143 mmol, 10 wt. % loading) was added to a solution of **D-3.93** (18 mg, 0.0286 mmol) in MeOH (1.5 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium on carbon was filtered through Celite® 545 and the solvent evaporated. The resulting crude product was purified by reverse phase column chromatography (C-18 silica gel, H_2O) to give **D-3.10** (8 mg, 99%) as colorless oil (isomeric mixture). The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compound **3.10** previously described. $[\alpha]_D$ +20.4 (*c* 0.2, H_2O).



(+)-3.116

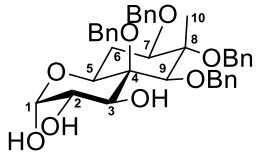
(+)-1,2,3,4-tetra-*O*-benzyl-6-*O*-(*t*-butyldimethyl)silyl-5-deoxy-1-((1'*S*,2'*R*)-propane-1,2,3-triol)-3-*C*-methyl-1-*myo*-inositol ((+)-3.116). Lithium borohydride solution (1.32 mL, 2.65 mmol, 2.0M in THF) was added to a solution of **3.113b** (530 mg, 0.529 mmol) in Et_2O (28 mL). After 1 h, additional lithium borohydride solution (660 µL, 1.32 mmol, 2.0M in THF) was added. The mixture was stirred for 2 h and a saturated aqueous solution of ammonium chloride was added. The aqueous layer was extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered

and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **(+)-3.116** (307 mg, 78%) as a yellow oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the **(–)-3.116** enantiomer previously described. $[\alpha]_D$ +29.2 (*c* 0.1, $CHCl_3$).

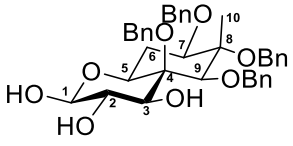


(+)-3.117

(+)-1,2,3,4-tetra-*O*-benzyl-5-deoxy-1-((1'*S*,2'*R*)-propane-1,2,3-triol)-3-*C*-methyl-1-*myo*-inositol ((+)-3.117). A solution of TBAF (569 μL, 0.100 mmol, 1.0M in THF) was added to a solution of **(+)-3.116** (313 mg, 0.422 mmol) in THF (16.5 mL). The reaction mixture was stirred for 30 min and brine was added. The aqueous layer was extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (1:1 hexanes–EtOAc, then 19:1 CH_2Cl_2–MeOH) to give **(+)-3.117** (264 mg, 99%) as a colorless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the **(–)-3.117** enantiomer previously described. $[\alpha]_D$ +11.8 (*c* 0.1, $CHCl_3$).



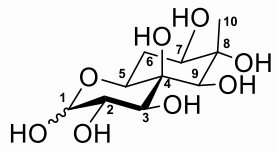
L-3.93α



L-3.93β

4,7,8,9-tetra-*O*-benzyl-1,5-α-L-bradyrhizose (L-3.93α) and **4,7,8,9-tetra-*O*-benzyl-1,5-β-L-bradyrhizose (L-3.93β)**. Trichloroisocyanuric acid (255 mg, 1.10 mmol), followed by TEMPO (2 mg, 0.0122 mmol) were added to a cooled (0 °C) solution of **(+)-3.117** (256 mg, 0.407 mmol) in

CH_2Cl_2 (11.5 mL). The mixture was stirred at 0 °C for 30 min and a saturated aqueous solution of $Na_2S_2O_3$ was added, followed by an extraction with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The resulting crude product was used without further purification. DIBAL-H (1.77 mL, 1.77 mmol, 1.0M in cyclohexane) was added to a cooled (–78 °C) solution of the crude in CH_2Cl_2 (12.5 mL). The reaction mixture was stirred for 90 min then MeOH (3 mL) and a 10% aqueous solution of HCl were added at –78 °C. The mixture was warmed to rt and extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude products were purified by silica gel column chromatography (49:1 CH_2Cl_2–MeOH) to give **L-3.93α** and **L-3.93β** (216 mg, 85%) as a colorless oil (diastereomeric mixture, 0.45:0.55). The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained on the racemic compounds **3.93α** and **3.93β** previously described. $[\alpha]_D$ –9.6 (*c* 0.2, $CHCl_3$).



L-3.10

L-Bradyrhizose (L-3.10). Palladium on carbon (10.4 mg, 0.00980 mmol, 10 wt. % loading) was added to a solution of **L-3.93** (12.3 mg, 0.0.0196 mmol) in MeOH (1 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium on carbon was filtered through Celite® 545 and the solvent evaporated. The resulting crude product did not need further purification to give **L-3.10** (5.2 mg, 99%) as a colorless oil (isomeric mixture). The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compound **3.10** previously described. $[\alpha]_D$ –21.8 (*c* 0.2, H_2O).

3.7 References

(1) Duchek, J.; Adams, D. R.; Hudlicky, T. Chemoenzymatic Synthesis of Inositols, Conduritols, and Cyclitol Analogues. *Chem. Rev.* **2011**, *111*, 4223–4258.

(2) Scherer, J. Über Eine Neue, Aus Dem Muskelfleisch Gewonnene Zuckerart. *Justus Liebigs Ann. Chem.* **1850**, *73*, 322–328.

(3) Posternak, T. Recherches Dans La Série Des Cyclites VI. Sur La Configuration de La Méso-Inosite, de La Scyllite et D'un Inosose Obtenu Par Voie Biochimique (Scyllo-Ms-Inosose). *Helv. Chim. Acta* **1942**, *25*, 746–752.

(4) Dangschat, G. Acetonierung Und Konfiguration Des Meso-Inosits. *Naturwissenschaften* **1942**, *30*, 146–147.

(5) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. Regioselective Protection and Deprotection of Inositol Hydroxyl Groups. *Chem. Rev.* **2003**, *103*, 4477–4503.

(6) Jagdhane, R. C.; Shashidhar, M. S. Orthogonally Protected Cyclohexanehexols by A "one Reaction - One Product" approach: Efficient Access to Cyclitols and Their Analogs. *Eur. J. Org. Chem.* **2010**, 2945–2953.

(7) Shashidhar, M. S. Regioselective Protection of *Myo*-Inositol Orthoesters – Recent Developments. *ARKIVOC* **2002**, 63–75.

(8) Godage, H. Y.; Riley, A. M.; Woodman, T. J.; Thomas, M. P.; Mahon, M. F.; Potter, B. V. L. Regioselective Opening of *Myo*-Inositol Orthoesters: Mechanism and Synthetic Utility. *J. Org. Chem.* **2013**, *78*, 2275–2288.

(9) Devaraj, S.; Shashidhar, M. S.; Dixit, S. S. Chelation Controlled Regiospecific O-Substitution of *Myo*-Inositol Orthoesters: Convenient Access to Orthogonally Protected *Myo*-Inositol Derivatives. *Tetrahedron* **2005**, *61*, 529–536.

(10) Devaraj, S.; Jagdhane, R. C.; Shashidhar, M. S. Relative Reactivity of Hydroxyl Groups in Inositol Derivatives: Role of Metal Ion Chelation. *Carbohydr. Res.* **2009**, *344*, 1159–1166.

(11) Gilbert, I. H.; Holmes, A. B.; Pestchanker, M. J.; Young, R. C. Lewis Acid-Catalysed Rearrangements of *Myo*-Inositol Orthoformate Derivatives. *Carbohydr. Res.* **1992**, *234*, 117–130.

(12) Fürstner, A.; Wuchrer, M. Concise Approach to The "Higher Sugar" core of the Nucleoside Antibiotic Hikizimycin. *Chem. Eur. J.* **2006**, *12*, 76–89.

(13) Prasad, K. R.; Swain, B. Enantioselective Synthesis of Possible Diastereomers of Heptadeca-1-Ene-4,6-Diyne-3,8,9,10-Tetrol; Putative Structure of a Conjugated Diyne Natural Product Isolated from Hydrocotyle Leucocephala. *J. Org. Chem.* **2011**, *76*, 2029–2039.

(14) Boger, D. L.; Borzilleri, R. M.; Nukui, S. Synthesis of (*R*)-(4-Methoxy-3,5-Dihydroxyphenyl)Glycine Derivatives: The Central Amino Acid of Vancomycin and Related Agents. *J. Org. Chem.* **1996**, *61*, 3561–3565.

(15) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Gonnade, R. G.; Bhadbhade, M. M. Sulfonate Protecting Groups. Regioselective Sulfonylation of *Myo*-Inositol Orthoesters - Improved Synthesis of Precursors of D- and L-*Myo*-Inositol 1,3,4,5-Tetrakisphosphate, *Myo*-Inositol 1,3,4,5,6-Pentakisphosphate and Related Derivatives. *Carbohydr. Res.* **2002**, *337*, 2399–2410.

(16) Sarmah, M. P.; Shashidhar, M. S.; Sureshan, K. M.; Gonnade, R. G.; Bhadbhade, M. M. Sulfonate Protecting Groups. Synthesis of O- and C-Methylated Inositols: D- and L-Ononitol, D- and L-Laminitol, Mytilitol and *Scyllo*-Inositol Methyl Ether. *Tetrahedron* **2005**, *61*, 4437–4446.

(17) Bhosekar, G.; Murali, C.; Gonnade, R. G.; Shashidhar, M. S.; Bhadbhade, M. M. Identical Molecular Strings Woven Differently by Intermolecular Interactions in Dimorphs of *Myo*-Inositol 1,3,5-Orthobenzoate. *Cryst. Growth Des.* **2005**, *5*, 1977–1982.

(18) Taniguchi, T.; Ogasawara, K. Extremely Facile and Selective Nickel-Catalyzed Allyl Ether Cleavage. *Angew. Chemie - Int. Ed.* **1998**, *37*, 1136–1137.

(19) Trost, B. M.; Ball, Z. T. Alkyne Hydrosilylation Catalyzed by a Cationic Ruthenium Complex: Efficient and General Trans Addition. *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655.

(20) Spino, C.; Beaulieu, C. A Practical and Highly Stereoselective Umpolung Alternative to the Alkylation of Chiral Enolates. *J. Am. Chem. Soc.* **1998**, *120*, 11832–11833.

(21) Meta, C. T.; Koide, K. Trans-Selective Conversions of γ-Hydroxy-α,*β*-Alkynoic Esters to γ -Hydroxy- α,*β* -Alkenoic Esters. *Org. Lett.* **2004**, *6*, 1785–1787.

(22) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483–2547.

(23) Ley, S. V. The Changing Face of Organic Synthesis. *Tetrahedron* **2010**, *66*, 6270–6292.

(24) Shie, C.-R.; Tzeng, Z.-H.; Wang, C.-C.; Hung, S.-C. Metal Trifluoromethanesulfonate Catalyzed Regioselective Reductive Ring Opening of Benzylidene Acetals. *J. Chin. Chem. Soc.* **2009**, *56*, 510–523.

(25) Sakagami, M.; Hamana, H. A Selective Ring Opening Reaction of 4,6-*O*-Benzylidene Acetals in Carbohydrates Using Trialkylsilane Derivatives. *Tetrahedron Lett.* **2000**, *41*, 5547–5551.

(26) Brimacombe, J. S.; Mcdonald, G.; Rahman, M. A. Double Asymmetric Induction in the Catalytic Osmylation of Some α,β-Unsaturated Octuronic Acid-Derivatives. *Carbohydr. Res.* **1989**, *205*, 422–427.

(27) Li, W.; Silipo, A.; Molinaro, A.; Yu, B. Synthesis of Bradyrhizose, a Unique Inositol-Fused Monosaccharide Relevant to a Nod-Factor Independent Nitrogen Fixation. *Chem. Commun.* **2015**, *51*, 6964–6967.

(28) Riley, A. M.; Godage, H. Y.; Mahon, M. F.; Potter, B. V. L. Chiral Desymmetrisation of *Myo*-Inositol 1,3,5-Orthobenzoate Gives Rapid Access to Precursors for Second Messenger Analogues. *Tetrahedron Asymmetry* **2006**, *17* , 171–174.

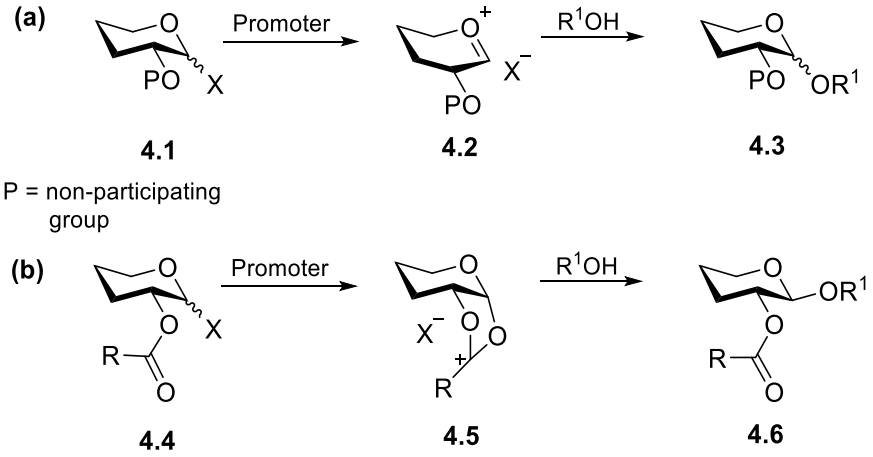
(29) Ahmed, M. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. De Novo Enantioselective Syntheses of *Galacto*-Sugars and Deoxy Sugars via the Iterative Dihydroxylation of Dienoate. *Org. Lett.* **2005**, *7*, 745–748.

Chapter 4: Glycosylations of Bradyrhizose

After completing the synthesis of bradyrhizose, the next objective was to carry out glycosylations using this unusual bicyclic monosaccharide. To do so, the syntheses of a bradyrhizose donor and acceptor were first accomplished. The synthesis of different bradyrhizose disaccharides using a trichloroacetimidate donor in glycosylation reactions will be discussed in this chapter.

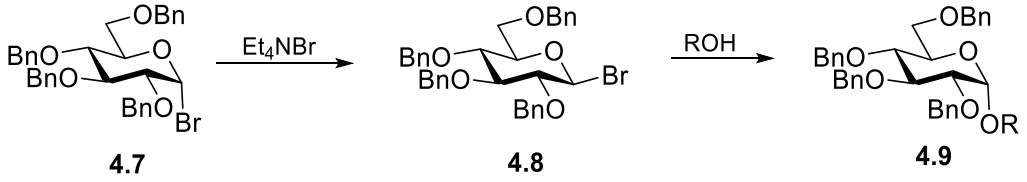
4.1 Introduction

In Chapter 1, it was mentioned that the stereoselective preparation of 1,2-*cis*-glycosidic linkages is more difficult than the synthesis of the 1,2-*trans* linkages. As shown in Scheme 4-1 (a), glycosylations using donors without a participating group on O-2 (**4.1**) will often give a mixture of *cis* and *trans*-glycosidic linkages (**4.3**). Glycosylation reactions using donors with a participating group on O-2 (**4.4**) will lead generally to the 1,2-*trans* linkage (**4.6**), explained by an S_N2-type reaction on intermediate **4.5** (Scheme 4-1 (b)). For many years and still today, research has been done to improve the stereoselectivity of the 1,2-*cis*-glycosidic bond formation.[1] This linkage is present in numerous biologically-relevant carbohydrates.[1,2] For instance, the bradyrhizose homopolymer has 1,2-*cis*-α-glycosidic linkages. Synthesizing oligosaccharides containing α-bradyrhizose residues is likely to be challenging.



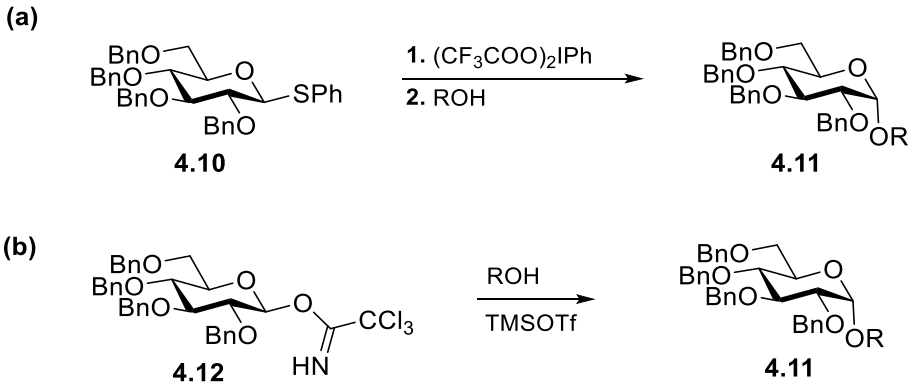
Scheme 4-1: (a) Glycosylation with a donor containing a non-participating group on O-2. (b) Glycosylation with a donor containing a participating group on O-2.[1]

The halide ion method first described in 1974 by Professor Lemieux from University of Alberta allowed the synthesis of α-linked disaccharides using glucose, galactose and fucose derivatives (1,2-*cis*-glycosidic linkages); the reaction for glucose is shown in Scheme 4-2.[3,4,5] The more reactive intermediate **4.8** can be made by treating donor **4.7** with tetraethylammonium bromide. Bromide **4.8** can undergo an S_N2-type reaction with the alcohol to give the desired compound **4.9**.



Scheme 4-2: Halide ion method.[3,4,5]

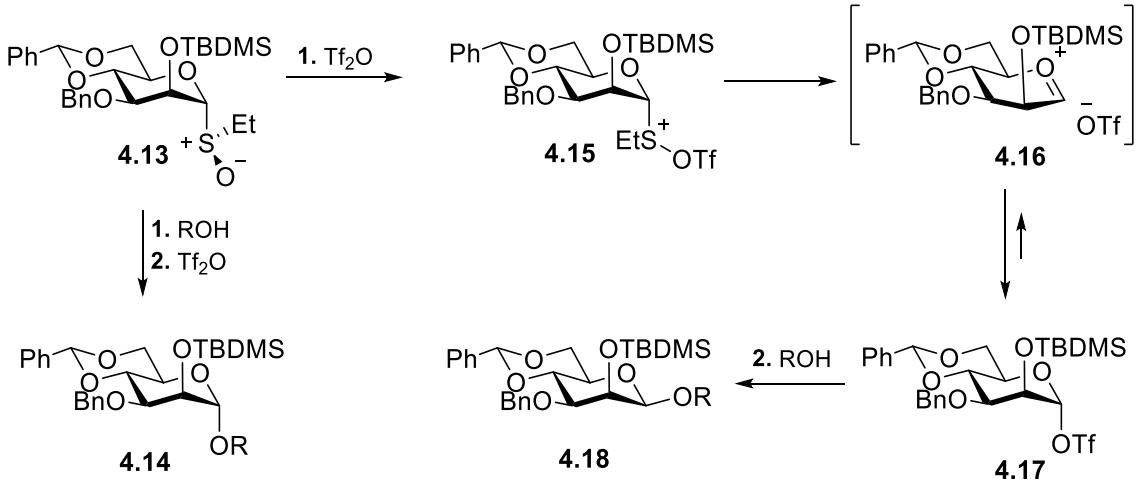
Newer methods have been developed since and mostly involving the use of 2-*O*-alkylated thioglycoside or trichloacetimidate donors in nonpolar solvents like CH_2Cl_2 and Et_2O.[1] These two methods can give good α-selectivity (**4.9**) depending on the donor, the reagents and how the reaction is carried out. For example, thioglycoside donor **4.10** can be activated using bis(trifluoroacetoxy)iodobenzene to give the predominantly α-glycoside **4.11** (Scheme 4-3 (b)).[1,6] Also by using a β-trichloroacetimidate donor **4.12** with TMSOTf, the α-anomer **4.11** can be obtained.[1,7] Both of these reactions proceed via S_N2-type reactions.



Scheme 4-3: (a) Glycosylation using thioglycoside donor **4.10**.[1,6] (b) Glycosylation using trichloroacetimidate donor **4.12**. [1,7]

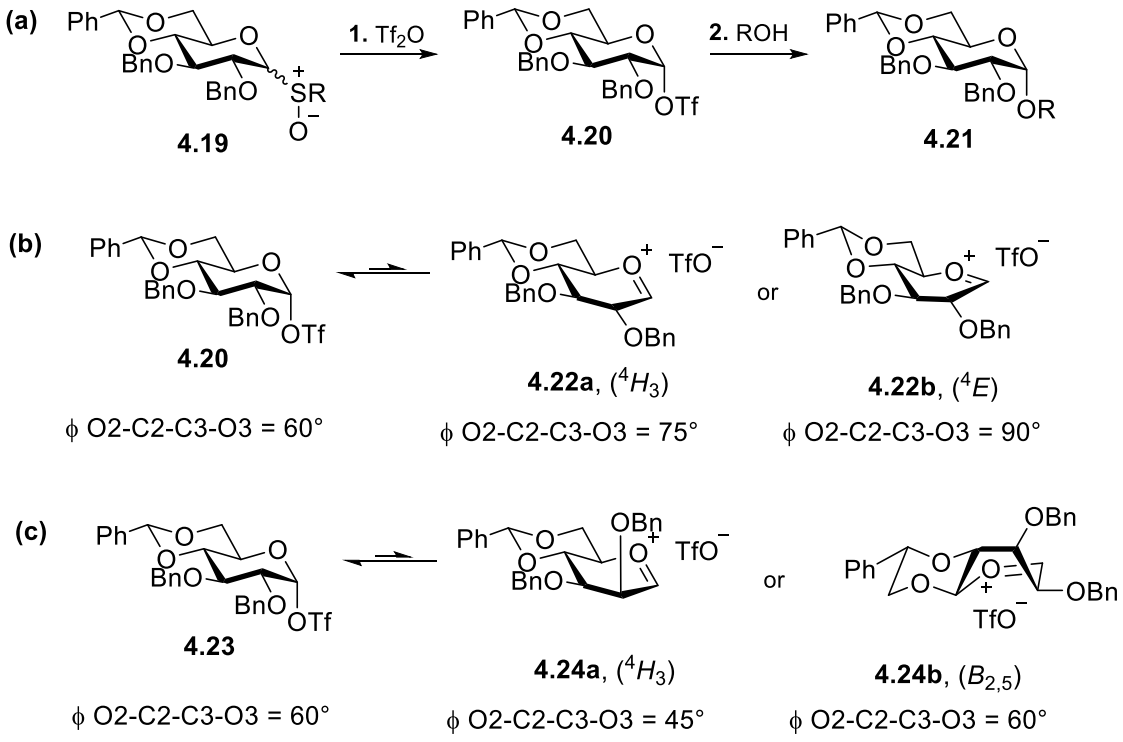
In 1996, Professor Crich from Wayne State University discovered that the 4,6-*O*-benzylidene acetal group is strongly β-directing in the mannopyranose series (Scheme 4-4).[8,9,10] The correct order of addition of reagents is required for the formation of the 1,2-*cis* linkage. If triflic anhydride is added first to the donor **4.13**, the oxocarbenium ion **4.16** will be formed, followed by the α-triflate **4.17**, which is more stable. The alcohol is then added to form the β-mannoside **4.18** in a S_N2-like displacement. If the triflic anhydride is added after the alcohol, the

oxocarbenium ion **4.16** will also be formed, but now the alcohol and the triflate compete giving the α-mannoside **4.14** as the major product.



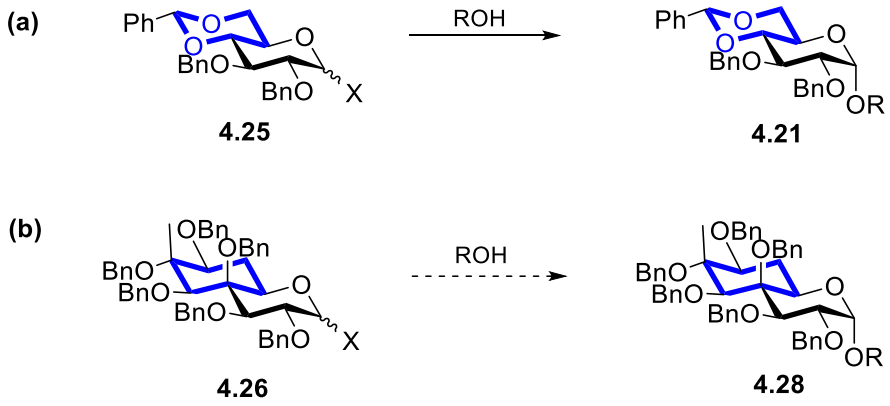
Scheme 4-4: β-Selectivity in glycosylation of 4,6-*O*-benzylidene protected mannopyranose derivatives.[10]

The 4,6-*O*-benzylidene acetal group is also strongly directing in the glucopyranose series but in this case the major product is the α-glucoside (Scheme 4-5 (a)).[10,11] This reaction is believed to proceed through a reactive oxocarbenium ion-pair intermediate (**4.22**) favoring the α-selectivity (Scheme 4-5 (b)). The O-2–C-2–C-3–O-3 torsion angle is expanded in the oxocarbenium ion making it more stable, in contrary to the torsion angle in the mannopyranose series, where the O-2–C-2–C-3–O-3 torsion angle is contracted (Scheme 4-5 (c)). This make the α-triflate more reactive in the mannopyranose series.



Scheme 4-5: (a) α-Selectivity in glycosylation of 4,6-*O*-benzylidene protected glucopyranose.[11] (b) Explanation of the α-selectivity in the glucopyranose series.[10] (c) Explanation of the β-selectivity in the mannopyranose series.[10]

Because the shape (the trans-decalin framework) of bradyrhizose resembles the 4,6-*O*-benzylidene protected glucopyranose **4.25** (Scheme 4-6), we hypothesized that the inositol ring of bradyrhizose donor **4.26** could also act as an α-directing group. This hypothesis will be explored in this chapter.



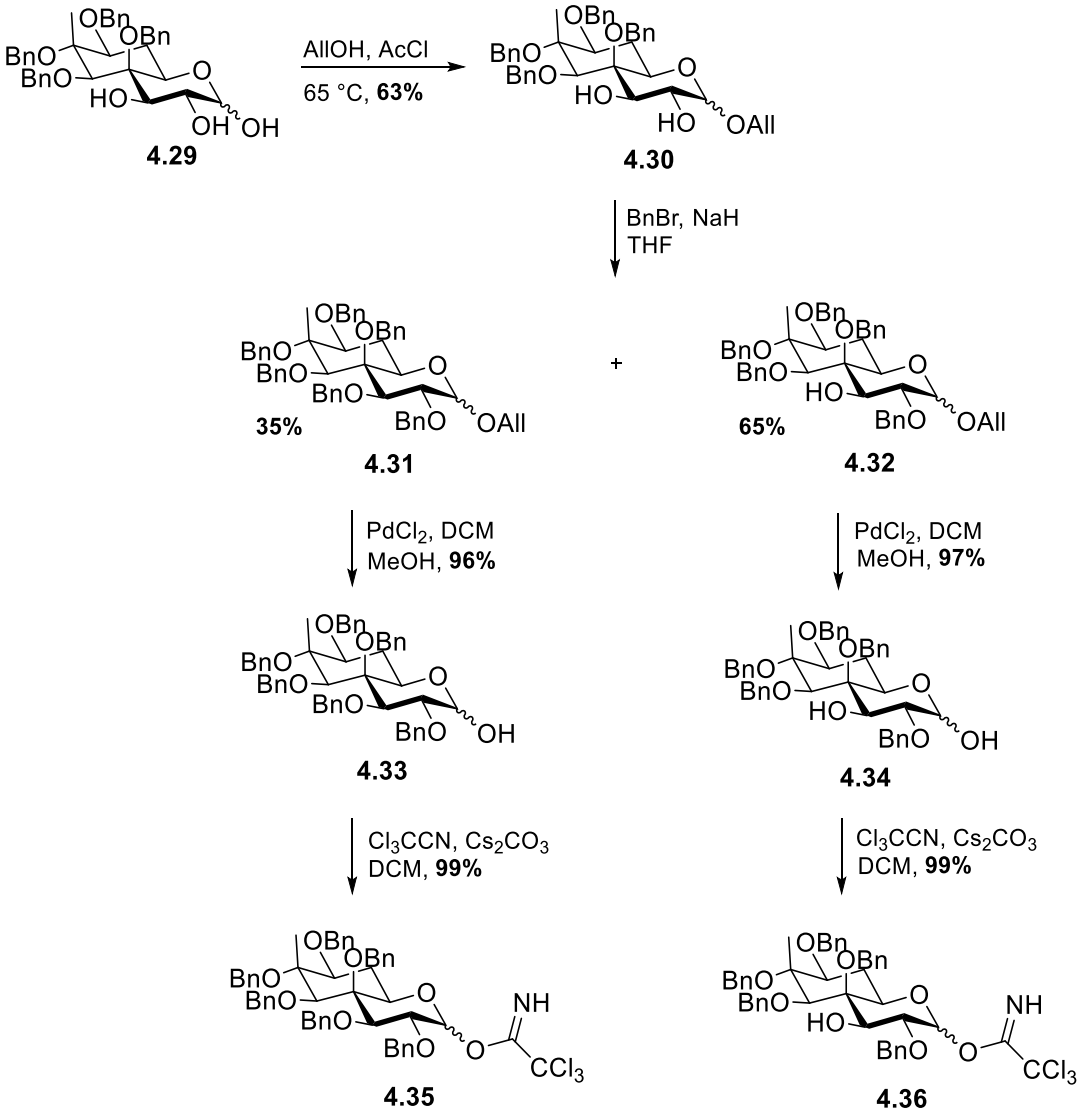
Scheme 4-6: Hypothesis that the inositol ring of bradyrhizose donor **4.26** could act as an α-directing group like the 4,6-*O*-benzylidene protected glucopyranose **4.25**.

4.2 Synthesis of the donors

As mentioned in the introduction, most recent syntheses of 1,2-cis glycosides employ thioglycoside or a trichloroacetimidate donor with an alkyl protecting group on O-2. Therefore, I chose to make donors in which a benzyl group was installed on O-2. In choosing between a thioglycoside or trichloroacetimidate donor, I chose the latter as we believed that it could be accessed in fewer steps than the thioglycoside. Thus, I selected **4.35** as an initial target (Scheme 4-7).

The synthesis of the donor started with racemic lactol **4.29** (Scheme 4-7), a protected bradyrhizose derivative that had been prepared in the course of making the unprotected monosaccharide. The first step was a Fischer glycosylation using allyl alcohol. The addition of acetyl chloride in allyl alcohol generated HCl in situ and when this was added to a solution of **4.29** in allyl alcohol, the allyl glycoside **4.30** was produced in 63% yield. Following this reaction, most of the starting material can be recovered and the reaction can be done again to yield more **4.30**. The second step was the protection of the free hydroxyl groups using benzyl bromide. Benzyl bromide was added at room temperature but only 35% of the fully protected compound **4.31** could

be obtained. The major product was **4.32**, in which the C-3 hydroxyl group remained unprotected. Because the O-3 in **4.30** appeared to be hindered and less reactive, we hypothesized that the free hydroxyl group at this position would not be a problem during the glycosylations. It was then decided to use both **4.31** and **4.32** to prepare donors. To do this, the allyl group in **4.31** and **4.32** was removed using palladium(II) chloride to provide, respectively, **4.33** in 96% yield and **4.34** in 97% yield. The trichloacetimidate donors **4.35** and **4.36** were both made, in 99% yield, from the corresponding reducing sugars **4.33** and **4.34** and were used in the glycosylation reactions without purification.

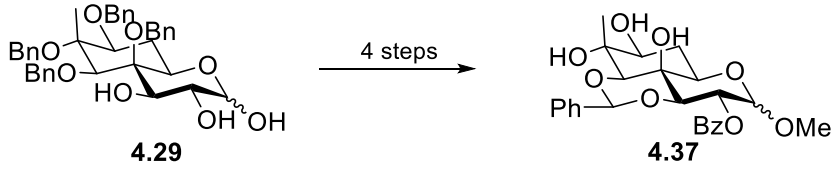


Scheme 4-7: Synthesis of donors **4.35** and **4.36**.

The synthesis of the D-donors (**D-4.35** and **D-4.36**) and L-donors (**L-4.35** and **L-4.36**) were performed using the same strategy starting with pure D-lactol (**D-4.29**) and L-lactol (**L-4.29**). All the enantiomers made in this section had similar specific rotation values with opposite signs.

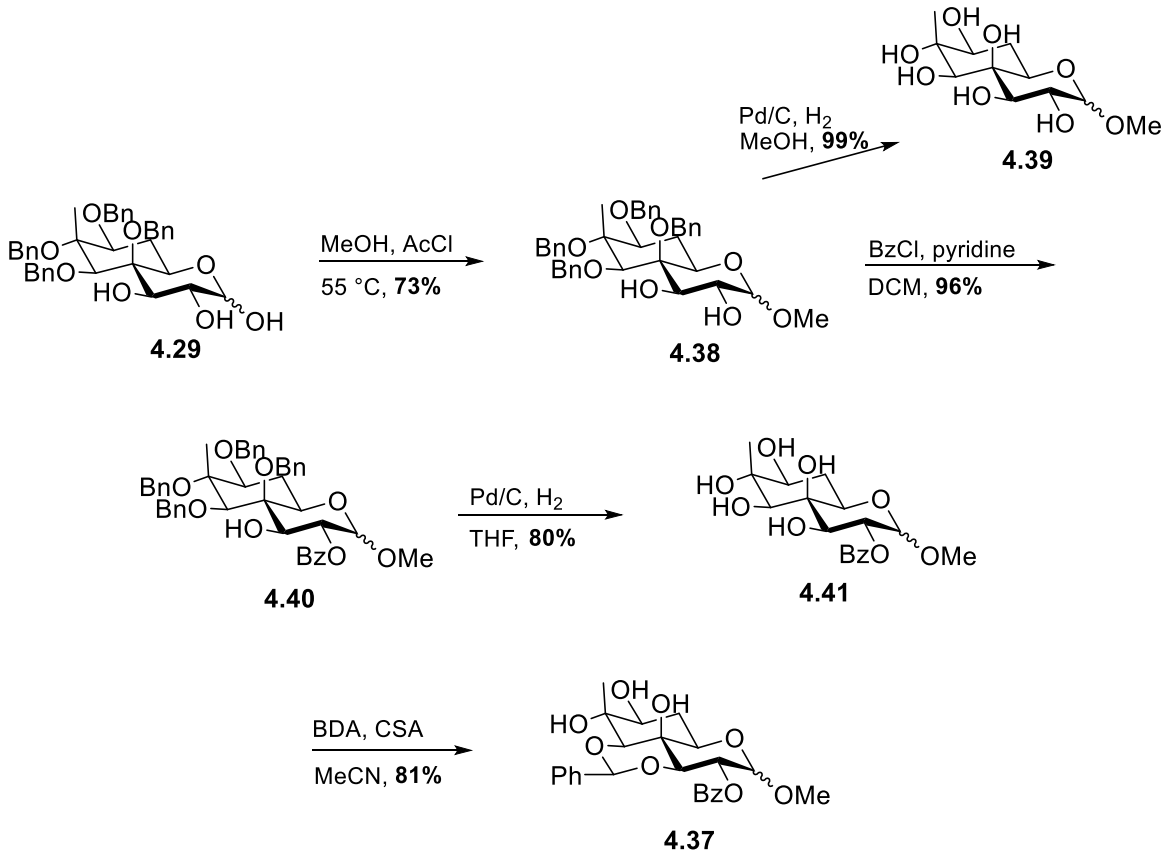
4.3 Synthesis of the acceptor

The synthesis of the acceptor **4.37** also started with the racemic lactol **4.29** (Scheme 4-8). The acceptor **4.37** was designed with three free hydroxyl groups, two tertiary and one secondary. We predicted that the tertiary hydroxyl groups should have a lower reactivity due to steric hindrance, which should make the glycosylation at the secondary alcohol favored.



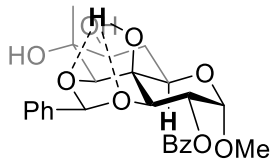
Scheme 4-8: Acceptor (**4.37**) containing three free hydroxyl groups.

The first step was a Fischer glycosylation this time using methanol containing HCl, which was generated using acetyl chloride in methanol. The methyl glycoside **4.38** was obtained in 73% yield from **4.29** (Scheme 4-7). As it was observed for the reaction of **4.29** with allyl alcohol, the starting material could be recovered and the reaction can be done again to yield more of the desired product **4.38**. To provide a small amount of material for biological evaluation, the tetra-*O*-benzylated methyl glycoside **4.38** was converted into the deprotected methyl glycoside **4.39**. This was achieved by hydrogenolysis of the benzyl ethers using Pd/C in methanol, which afforded **4.39** in quantitative yield. The second step of the synthesis of the acceptor was the protection of O-2 using benzoyl chloride. The desired product **4.40** was obtained in 96% yield, pointing again to the very low nucleophilicity of the C-3 hydroxyl in this intermediate. The benzyl groups were removed using palladium on carbon to give **4.41** in 80% yield. Two of the secondary hydroxyl groups were then protected as a benzylidene acetal to yield triol **4.37** in 81% yield.



Scheme 4-9: Synthesis of acceptor **4.37** and methyl glycoside **4.39**.

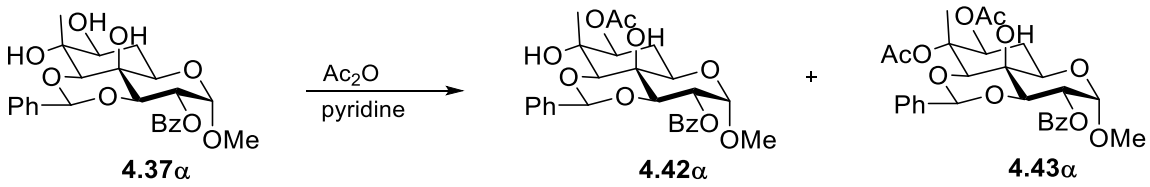
The last step for the synthesis of acceptor **4.37** was regioselective. To confirm the regioselectivity of this reaction, we first analyzed the ^{1}H NMR spectrum. The coupling constants for the pyranose ring protons correlated to it being in a chair conformation, as would be expected for the molecule. After analysis of the ^{1}H NMR and COSY spectra, we could see a correlation between the proton of the hydroxyl group at C-4 with H-5 as shown in Figure 4-1 (bold **H**). The magnitude of the coupling is 1.6 Hz, corresponding to an average value of a W coupling (0–2 Hz). This long range (^{4}J) coupling would be possible if the C-4 hydroxyl group was conformationally-fixed via a hydrogen bond to the two oxygens in the benzylidene acetal ring.



4.37α

Figure 4-1: COSY correlation in compound **4.37α.**

To further confirm the structure of the acceptor (**4.37)**, we acetylated the remaining free hydroxyl groups (Scheme 4-9). Two new compounds (**4.42α** and **4.43α**) were isolated and this allowed us to confirm the structure of **4.37.** By comparing the ^{1}H NMR spectra of the starting material **4.37α** and the two products, **4.42α** and **4.43α** (Table 4-1), it was possible to assign the resonances of the ring hydrogens adjacent to the free hydroxyl groups in **4.37α.** As shown in Table 4-1, H-7 became more deshielded in compound **4.42α** and H-9 stayed about the same, indicating that there was only an acetyl group on O-7. When moving to compound **4.43α**, H-7 is even more deshielded, as well as H-9, indicating that both protons are in the deshielding cone of the ester carbonyl group of C-8. A difference can also be seen on the methyl group (H-10). The other protons were omitted from the table because no changes were observed. The W-coupling between the C-4-OH and H-5 was also observed in these two compounds, also showing that this position was not acetylated.



4.37α **4.42α** **4.43α**

Scheme 4-10: Derivatization of compound **4.37α** to verify the position of the benzylidene acetal.

Table 4-1: Chemical shifts of selected proton for compounds **4.37α**, **4.42α** and **4.43α**.

Compounds	H-7 (ppm)	H-9 (ppm)	H-10 (ppm)
4.37α	3.75	3.75	1.46
4.42α	4.94	3.78	1.53
4.43α	6.02	5.21	1.59

Compound **4.37α** was a solid and recrystallization was performed to obtain material for a crystal structure (Figure 4-2). The structure clearly showed the position of the benzylidene acetal (spanning C-2 and C-9) making a tricyclic structure. The 'W' relationship between the C-4-OH (H9O) and H-5 (H5C) can clearly be seen in Figure 4-2. It should also be noted that this structure also confirmed the overall structure of my synthetic bradyrhizose.

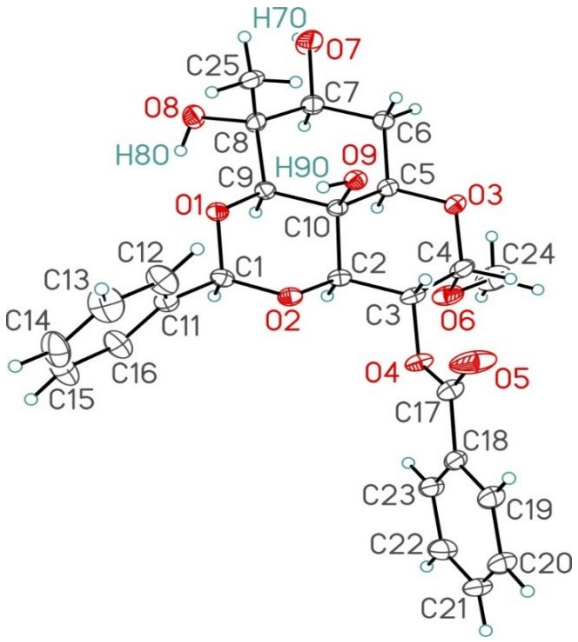


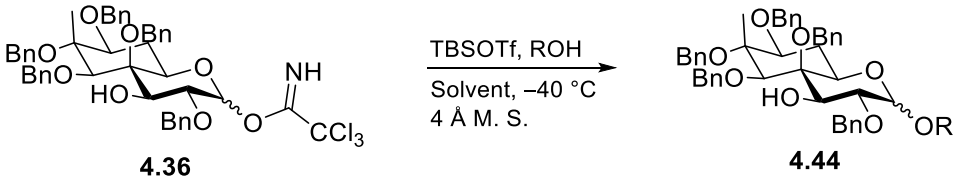
Figure 4-2: X-ray crystal structure (ORTEP) of acceptor **4.37α**. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

The synthesis of the D-acceptor (**D-4.37**) and L-acceptor (**L-4.37**) was done using the same strategy starting with pure D-lactol (**D-4.29**) and L-lactol (**L-4.29**). All enantiomers made in this section also had similar specific rotation values with opposite signs.

4.4 Glycosylations of bradyrhizose donor 4.36 with achiral acceptors

To test our hypothesis that the inositol moiety of bradyrhizose is α-directing like the benzylidene acetal in the glucose counterparts, we reacted the racemic bradyrhizose donor **4.36** with different achiral alcohols. As shown in Table 4-3, three different alcohols (10 equivalents) and donor **4.36** were subjected to glycosylation conditions (TBSOTf, 4Å molecular sieves, 1:1 CH_2Cl_2–Et_2O or Et_2O, –40 °C). First, *p*-methoxyphenol was used and the reaction gave a 75% yield of the α-glycoside (**3.45α)** as the only product (Table 4-3, Entry 1). The next glycosylation, with octanol as the acceptor, was also performed in CH_2Cl_2–Et_2O (1:1) and a 78% yield of compound **3.46** was obtained in a ratio of 2:11 for α:β ratio (Table 4-3, Entry 2). The same reaction was done using Et_2O as the solvent, and a 91% yield of **3.46** in a 2:5 α:β ratio (Table 4-3, Entry 3) was produced. Cyclohexanol was then used with Et_2O as solvent to give a 93% yield of **3.47** in a α:β ratio of 4:9 (Table 4-3, Entry 4). These results showed that there is no significant difference in reactivity between the secondary and primary alcohol. Also, using Et_2O as the solvent seemed to increase the α-selectivity of the glycosylation reaction. Because of the insufficient amount of donor, it was not possible to do more experiments to better understand the selectivity of these glycosylations.

Table 4-2: Glycosylations of achiral alcohols with racemic donor **4.36**.



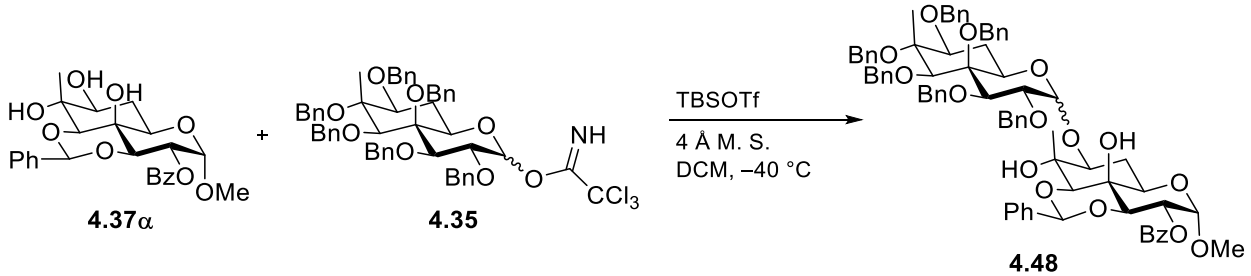
4.36 **4.44**

Entry	Products	Alcohols	Solvents	Ratio α:β	Isolated yield (%)
1	**3.45α**	PMPOH	CH_2Cl_2:Et_2O (1:1)	1:0	75
2	**3.46**	Octanol	CH_2Cl_2:Et_2O (1:1)	2:11	78
3	**3.46**	Octanol	Et_2O	2:5	91
4	**3.47**	Cyclohexanol	Et_2O	4:9	93

4.5 Synthesis of the disaccharides

4.5.1 Racemic glycosylations

The first glycosylation to prepare the disaccharides was tried using racemic acceptor **4.37α** and racemic donor **4.35** (Scheme 4-11). This reaction led to a number of inseparable products as determined by TLC.

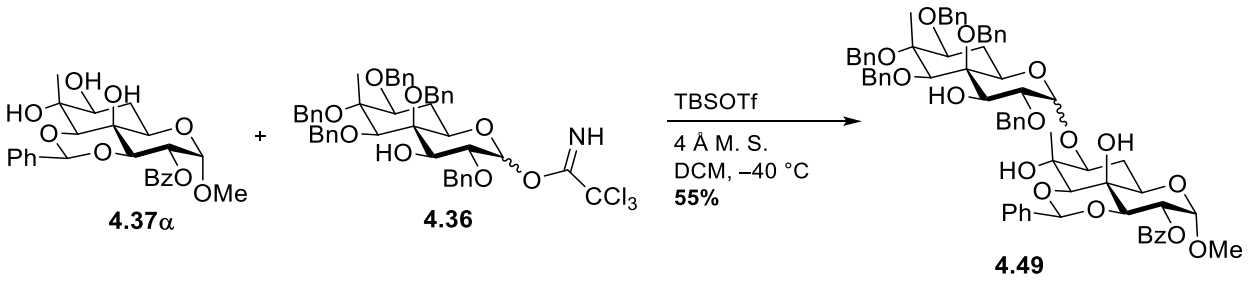


4.37α **4.35** **4.48**

Scheme 4-11: Glycosylation using racemic donor **4.35** and racemic acceptor **4.37α**.

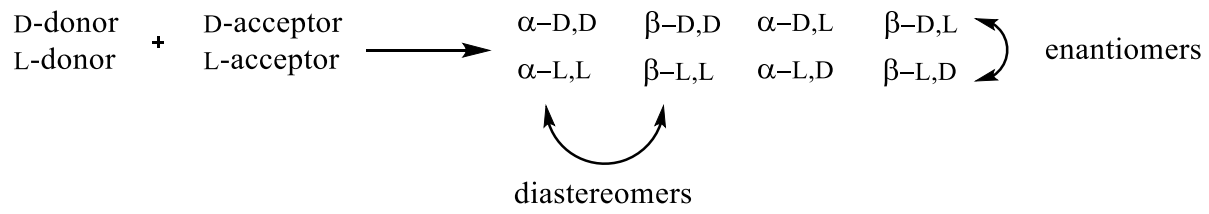
The second glycosylation was tried using the racemic donor having a free C-3 hydroxyl group (**4.36**) (Scheme 4-12). In this case, three different spots on TLC were isolated, but they were

all mixtures of compounds when analyzed by NMR spectroscopy and it was not possible to isolate or identify the different disaccharides.



Scheme 4-12: Glycosylation using racemic donor **4.36** and racemic acceptor **4.37α**.

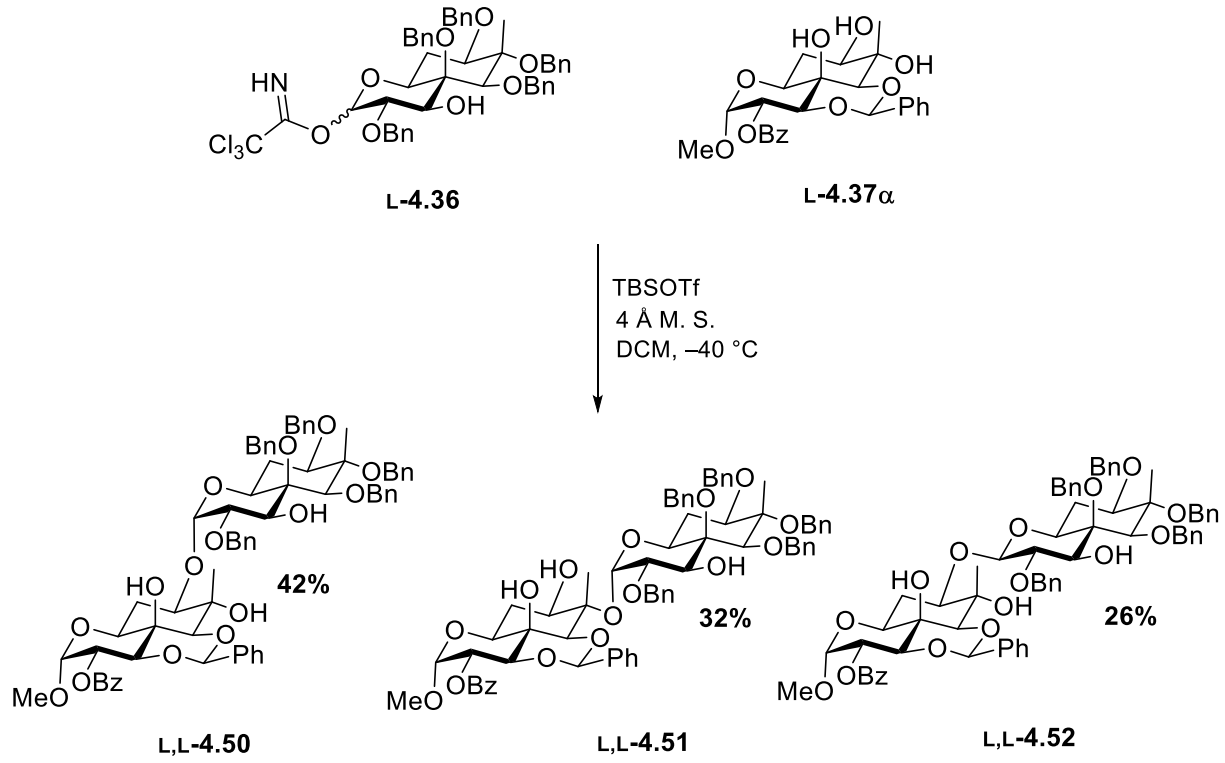
After performing these glycosylations, I concluded that the disaccharides could not be isolated in acceptable yield by reacting racemic donors and acceptors. The reaction of the racemic donor **4.36** with the racemic acceptor **4.37α** could give eight different disaccharides (four pairs of enantiomers) as shown in Scheme 4-13 (assuming that the reaction only occurs at the secondary hydroxyl group of the acceptor). The large number of isomers, made their separation essentially impossible. Moreover, if I did succeed in separating the compounds, determining the stereochemistry of each monosaccharide in the products (e.g., D,D/L,L or D,L/L,D) would be very difficult if not impossible. Therefore, I moved to the use of enantiopure donors and acceptors to facilitate the separation and identification of the different disaccharides.



Scheme 4-13: Possible products arising from glycosylation between racemic donor **4.36** and racemic acceptor **4.37α**.

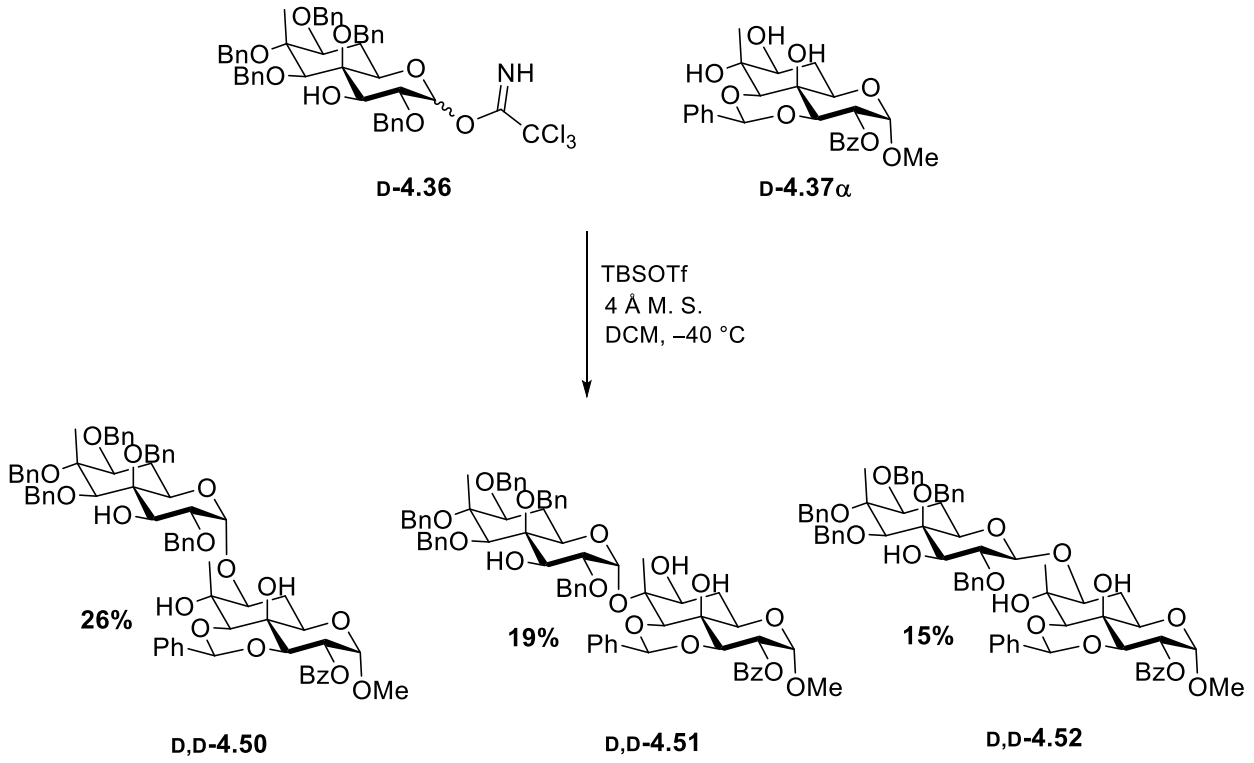
4.5.2 Glycosylations using enantiopure donors and acceptors

The first glycosylation was done using the L-donor (**L-4.36**) and the L-acceptor (**L-4.37α**) (Scheme 4-14). The normal glycosylation conditions (adding the promotor to a mixture of both donor and acceptor) were tried, but only a 20% yield of the disaccharide could be obtained using two equivalents of the donor after 3 h and the acceptor was also recovered. The inverse glycosylation procedure,[12,13] which is done by adding the donor to a mixture of acceptor and promoter, was then performed also using two equivalents of donor and all the acceptor was consumed after 30 min. By using this technique, it was possible to get quantitative yield of the disaccharides. This glycosylation gave three products: the α-(1→7)-linked disaccharide (**L,L-4.50)**, the α-(1→8)-linked disaccharide (**L,L-4.51)** and the β-(1→7)-linked disaccharide (**L,L-4.52)** in a ratio of 42:32:26. The major compound, **L,L-4.50**, was the desired one, having an α-(1→7)-glycosidic linkage, which is that present in the bradyrhizose homopolymer. The structures of the products could be determined using NMR spectroscopy, in particular HMBC to assign the glycosidic linkages.



Scheme 4-14: Glycosylation between L-donor **L-4.36** and L-acceptor **L-4.37α.**

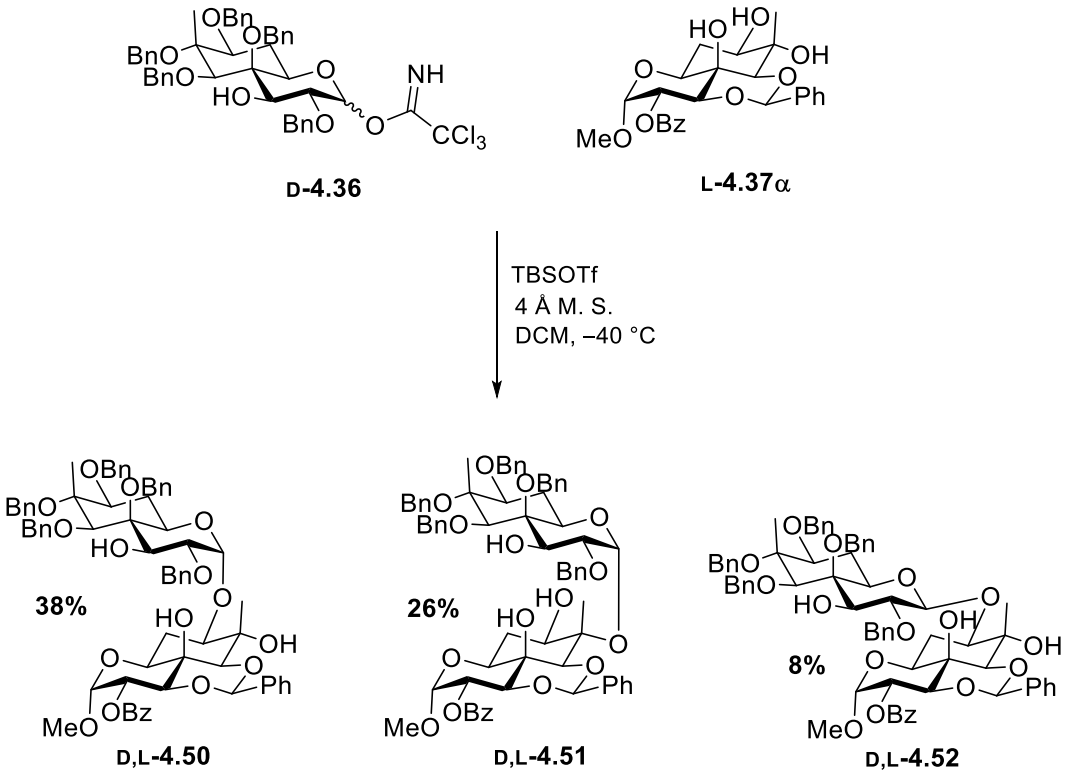
The glycosylation using D-donor (**D-4.36**) and D-acceptor (**D-4.37α**) is shown in Scheme 4-15. The inverse glycosylation procedure was performed using 1.4 equivalent of donor (insufficient material) to provide a 60% yield of the disaccharides. The remaining acceptor was recovered. This glycosylation also gave three products; α-(1→7)-linked (**D,D-4.50)**, α-(1→8)-linked (**D,D-4.51)** and β-(1→7)-linked (**D,D-4.52)** in a ratio of 43:32:25, similar to the L,L-glycosylation. The major compound **D,D-4.50** was also the desired one, like for the previous glycosylation. Based on this result it appears that using two equivalents of donor is necessary to obtain a quantitative yield of the disaccharides.



D-4.36 **D-4.37α** **D,D-4.50** **D,D-4.51** **D,D-4.52**

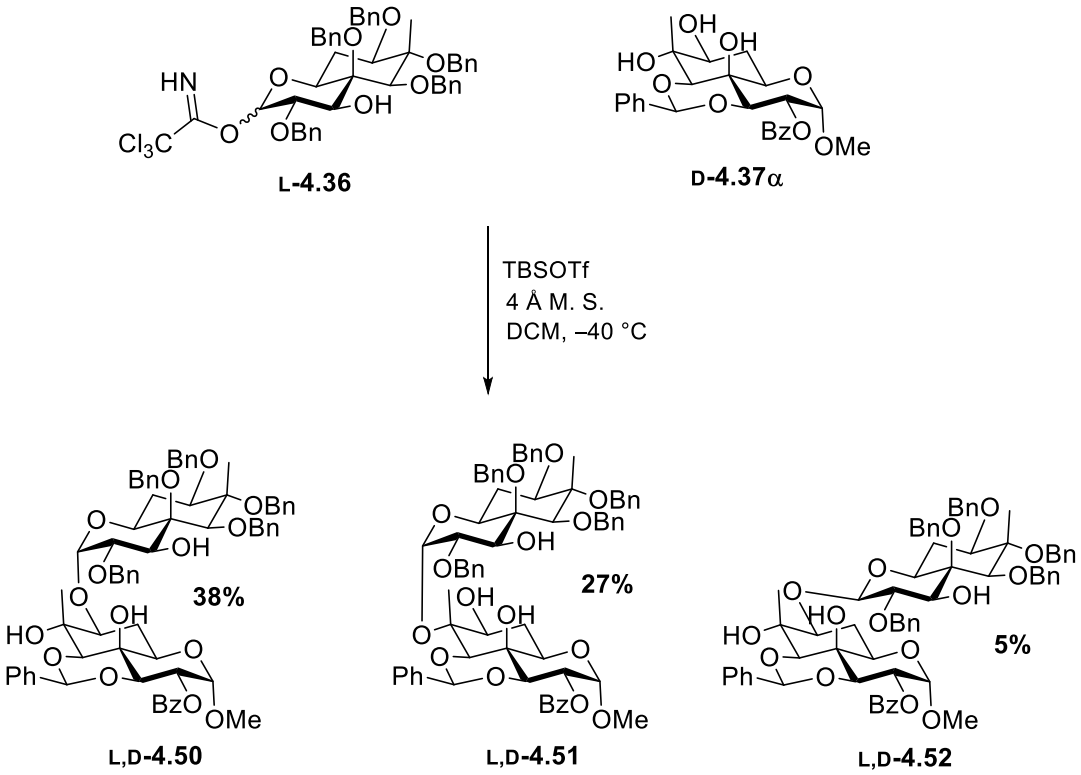
Scheme 4-15: Glycosylation between D-donor **D-4.36** and D-acceptor **D-4.37α.**

The next glycosylation was done using D-donor (**D-4.36**) and L-acceptor (**L-4.37α**) (Scheme 4-16). The normal glycosylation conditions were first tried but only a 10% yield could be obtained using two equivalents of donor after 3 h. The inverse glycosylation procedure was also performed using two equivalents and a 72% yield of the disaccharides was obtained. Allowing the reaction mixture to proceed for a longer time did not improve the yield. This glycosylation gave three disaccharides: α-(1→7)-linked, α-(1→8)-linked and β-(1→7)-linked (**D,L-4.50**:**D,L-4.51**:**D,L-4.52**, respectively**)** in a ratio of 53:36:11. The major compound **D,L-4.50** was the α-(1→7)-linked product found in the natural polysaccharide.



Scheme 4-16: Glycosylation between D-donor **D-4.36** and L-acceptor **L-4.37α.**

The last glycosylation was done using L-donor (**L-4.36**) and D-acceptor (**D-4.37α**) (Scheme 4-17). The inverse glycosylation procedure was also performed using 2.2 equivalents of donor and 70% yield of the disaccharides was obtained. This glycosylation also gave the same three products; α-(1→7)-linked, α-(1→8)-linked and β-(1→7)-linked, this time in a ratio of 54:39:7 (**L,D-4.50**:**L,D-4.51**:**L,D-4.52**), similar to the D,L-glycosylation. The major compound **L,D-4.50** was also the desired one.



Scheme 4-17: Glycosylation between L-donor **L-4.36** and D-acceptor **D-4.37α.**

Table 4-3 provides a summary of the results for the glycosylation using enantiopure donors **4.36** and acceptors **4.37α**. All the glycosylations gave the α-(1→7)-linked product as the major product.

Table 4-3: Glycosylations of entantiopure donors **4.36** and acceptors **4.37α**.

Donors	Acceptors	Equiv. of donor	Yield (%)	Ratio of products α-(1→7) : α-(1→8) : β-(1→7)
D-4.36	**D-4.37α**	1.4	60	43 : 32 : 25
L-4.36	**L-4.37α**	2.0	100	42 : 32 : 26
D-4.36	**L-4.37α**	2.0	72	53 : 36 : 11
L-4.36	**D-4.37α**	2.2	70	54 : 39 : 7

4.5.3 Discussion

As mentioned in the last section, the desired α-(1→7)-linkage was the major product in all glycosylations between the D- and L-donors and acceptors. The diastereomeric excess (de) for the α-(1→7)-glycosidic linkage for the D,D-, L,L-, D,L- and L,D-glycosylations were respectively 27%, 24%, 65% and 77% (% calculated by using this equation: $\frac{(\alpha-(1\rightarrow7))-(\beta-(1\rightarrow7))}{((\alpha-(1\rightarrow7))+(\beta-(1\rightarrow7))} * 100\%$). The D,L (or L,D) pair thus seem to be matched for the α-(1→7)-linked products.[14]

Regioselectivity was another issue to be considered as the acceptor had three different free hydroxyl groups. The (1→7)-linked products were the major ones in all glycosylations, and only α-(1→8)-linked disaccharides were isolated. None of the β-(1→8)-linked disaccharide was formed, nor were any products with a (1→4) linkage produced. The regioselectivity observed in the products for the D,D-, L,L-, D,L- and L,D-glycosylations were, respectively, 68:32, 68:32, 64:36 and 61:39 ((1→7):(1→8)), indicating an inherent ~2:1 preference for reaction at OH-7. This result is not surprising as one would expect the secondary hydroxyl group (leading to the (1→7)-glycosidic linkage) would be the favored site of reactivity, compared to the reaction of the tertiary hydroxyl group leading to the (1→8)-glycosidic linkage. A steric argument can also be used to explain the lack of reactivity of the C-4 hydroxyl group. This alcohol would be expected to be the least nucleophilic of the three given that it is significantly sterically hindered by virtue of its axial orientation, its 1,3-diaxial relationship with regard to the C-8 methyl group and it being embedded in the centre of the fused tricyclic ring system.

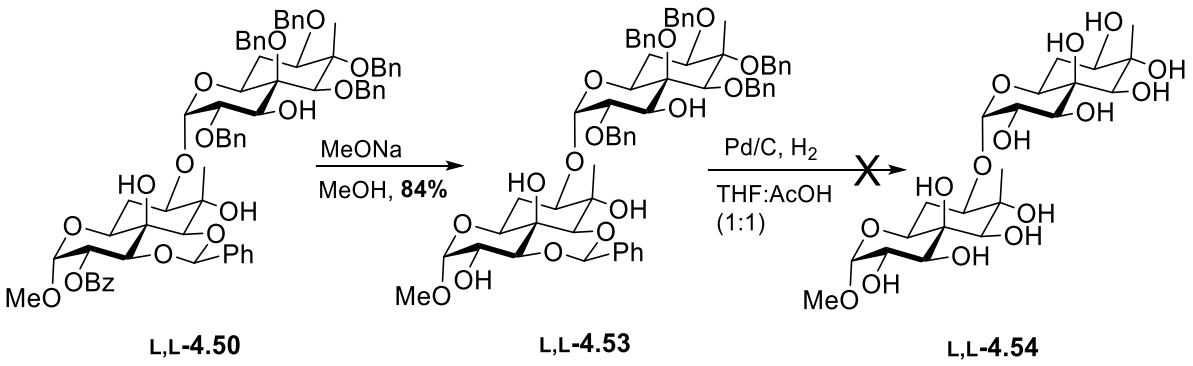
After the NMR spectrum of all different disaccharides were available, it was possible to go back to the racemic glycosylation (Scheme 4-11) and look at the distribution of the different products in this reaction using the ^{1}H NMR spectrum. The reaction with the racemic donors and

acceptors gave a similar result as the glycosylation using the enantiopure donors and acceptors. The products having the desired α-(1→7)-glycosidic linkage were obtained in 28% (ratio D,D/LL:D,L/L,D 1:1). The α-(1→8)-linked and β-(1→7)-linked compounds from the D,D- or L,L-glycosylations were obtained in 26% in a ratio of about 1:1; however, spectral overlap made this difficult to determine. Finally, 12% of the α-(1→8)-linked products from the D,L- and L,D-glycosylation were obtained, containing a very small amount (5%) of β-(1→7)-linked compounds.

In summary, although all glycosylation favored the α-(1→7)-linked products, which correspond to that present in the natural product, poor regioselectivity was observed (2:1) with regard to reaction at the C-7 or C-8 hydroxyl group.

4.5.4 Deprotection of the disaccharides

With the disaccharides in hand, the final step was removal of the protecting groups. As an example, the deprotection of disaccharide **L,L-4.50** is shown in Scheme 4-18. First, the benzoyl group was removed using sodium methoxide in methanol to give **L,L-4.53** in 84% yield. To remove the benzyl groups, hydrogenolysis using Pd/C in THF–AcOH (1:1) under a H_2 atmosphere was attempted, but this reaction did not work. An impurity was isolated and the starting material seemed to have decomposed. No trace of the starting material **L,L-4.50**, intermediates (those lacking one or more benzyl groups) or desired product **L,L-4.54** could be detected by MS or ^{1}H NMR spectroscopy. Thus, deprotected disaccharide (**L,L-4.54**) could not be obtained.



Scheme 4-18: Tentative of deprotection of **L,L-4.50**.

The hydrogenolysis was then done using $Pd(OH)_2$ in MeOH under H_2 atmosphere to give the other disaccharides in quantitative yield. Table 4-4 summarizes the deprotection reactions for the disaccharides. Some disaccharides (indicated by a "-") were not deprotected because there was insufficient material (< 1 mg) to carry out the reactions.

Table 4-4: Deprotection of the disaccharides.

Disaccharides (SM)	MeOH/MeONa (DP)	MeOH/MeONa Yield (%)	Hydrogenolysis (DP)	Hydrogenolysis Yield (%)
D,D-4.50	**D,D-4.53**	78	**D,D-4.54**	99
D,D-4.51	**D,D-4.55**	-	**D,D-4.56**	-
D,D-4.52	**D,D-4.57**	99	**D,D-4.58**	99
L,L-4.50	**L,L-4.53**	84	**L,L-4.54**	-
L,L-4.51	**L,L-4.55**	81	**L,L-4.56**	99
L,L-4.52	**L,L-4.57**	88	**L,L-4.58**	99
D,L-4.50	**D,L-4.53**	93	**D,L-4.54**	99
D,L-4.51	**D,L-4.55**	99	**D,L-4.56**	99
D,L-4.52	**D,L-4.57**	-	**D,L-4.58**	-
L,D-4.50	**L,D-4.53**	58	**L,D-4.54**	99
L,D-4.51	**L,D-4.55**	99	**L,D-4.56**	99
L,D-4.52	**L,D-4.57**	-	**L,D-4.58**	-

Eight deprotected disaccharides were obtained; two from each glycosylation. These new compounds will be tested (as well racemic, D- and L-bradyrhizose) for their ability to induce ROS in Arabidopsis and other plants/legumes by Associate Professor Newman at the University of Copenhagen.

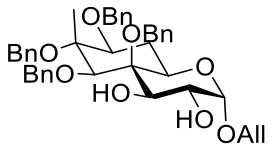
4.6 Summary

Racemic and enantiopure bradyrhizose donors and acceptors have been synthesized in four steps and good yield from the lactol **4.29** (a precursor in the synthesis of bradyrhizose). With a route to these compounds in place, a few glycosylations were performed using the racemic donor **4.36** and achiral alcohols. The inositol moiety of bradyrhizose seemed to be not as α-directing as a 4,6-*O*-benzylidene acetal in a glucopyranose ring. This could be because of the use of the trichloroacetimidate donor instead of a thioglycoside donor, or because of the possible non-chair conformation of bradyrhizose donor. Further investigation is necessary to obtain a better understanding of the glycosylation of this unusual monosaccharide. The glycosylations using racemic or enantiopure donors and acceptors gave three different linked disaccharides; α-(1→7), α-(1→8) and β-(1→7). Disaccharides having α-(1→7)-glycosidic linkages, like the natural bradyrhizose homopolymer, were the major compounds in all glycosylations. Different deprotected disaccharides will be sent to be tested for their immunogenicity with plants by Associate Professor Newman at the University of Copenhagen.

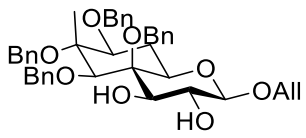
4.7 Experimental

General Methods:

Reactions were carried out in oven-dried glassware. All reagents used were purchased from commercial sources and were used without further purification unless noted. Solvents used in reactions were purified by successive passage through columns of alumina and copper under argon. Unless stated otherwise, all reactions were carried out at room temperature under a positive pressure of argon and were monitored by TLC on silica gel 60 F254 (0.25 mm, E. Merck). Spots were detected under UV light or by charring with a solution of ammonium molybdate (12 g) and ceric ammonium nitrate (0.42 g) in H_2O (235 mL) and concentrated sulfuric acid (15 mL). Unless otherwise indicated, all column chromatography was performed on silica gel 60 (40–60 μM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 21 ± 2 °C at the sodium D line (589 nm) and are in units of deg·mL(dm·g)-1. ^{1}H NMR spectra were recorded at 500 MHz, and chemical shifts are referenced to either TMS (0.0 ppm, $CDCl_3$), HOD (4.78 ppm, D_2O and CD_3OD). ^{13}C NMR spectra were recorded at 125 MHz, and ^{13}C chemical shifts were referenced to internal $CDCl_3$ (77.2 ppm, $CDCl_3$), external dioxane (67.4 ppm, D_2O) or CD_3OD (48.9 ppm, CD_3OD). In the processing of reaction mixtures, solutions of organic solvents were washed with equal amounts of aqueous solutions. Organic solutions were concentrated under vacuum at < 40°C (bath). Electrospray mass spectra were recorded on samples suspended in mixtures of THF with CH_3OH and added NaCl.



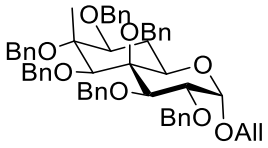
4.30α



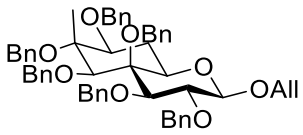
4.30β

***Racemic* allyl 4,7,8,9-tetra-*O*-benzyl-1,5-α-bradyrhizopyranoside (4.30α)** and ***racemic* allyl 4,7,8,9-tetra-*O*-benzyl-1,5-β-bradyrhizopyranoside (4.30β)**. To a stirred solution of **4.29** (131 mg, 0.209 mmol) in AllOH (5 mL), HCl (250 μL of a solution of AcCl (0.1 mL) in AllOH (2.5 mL)) was added and the mixture was stirred at 65 °C for 2 days. After cooling to rt, water was added and the aqueous layer was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude products were purified by silica gel column chromatography (7:3 hexanes–EtOAc) to give **4.30α** and **4.30β** (88 mg, 63%) as a colorless oil (inseparable diastereomeric mixture 1:1). The starting material **4.29** can be recovered by silica gel column chromatography (97:3 CH_2Cl_2–MeOH) and the reaction can be done again to yield more product **4.30α** and **4.30β**. R_f 0.34 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.41–7.24 (m, 20 H, Ar), 6.04–5.91 (m, 1 H, C<u>H</u>=CH_2), 5.56 (d, 0.5 H, J = 12.1 Hz, C<u>H</u>$_2$Ar), 5.43 (d, 0.5 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 5.37 (app dq, 0.5 H, J = 17.2 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *trans*), 5.35 (app dq, 0.5 H, J = 17.2 Hz, J = 1.7 Hz, CH=C<u>H</u>$_2$ *trans*), 5.29–5.24 (m, 1 H, CH=C<u>H</u>$_2$ *cis*), 5.22 (d, 0.5 H, J = 12.1 Hz, C<u>H</u>$_2$Ar), 5.17–5.11 (m, 1.5 H, C<u>H</u>$_2$Ar), 5.01 (d, 0.5 H, J = 4.0 Hz, H-1α), 4.86 (d, 0.5 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.84 (d, 0.5 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.79–4.67 (m, 3 H, C<u>H</u>$_2$Ar), 4.56 (d, 0.5 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.53 (d, 0.5 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.45 (app ddt, 0.5 H, J = 12.5 Hz, J = 5.1 Hz, J = 1.5 Hz, C<u>H</u>$_2$CH=CH_2), 4.38 (d, 0.5 H, $J_{1,2}$ = 7.3 Hz, H-1β), 4.28–4.22 (m, 1 H, C<u>H</u>$_2$CH=CH_2 and OH), 4.17 (app ddt, 0.5 H, J = 12.7 Hz, J = 6.2 Hz, J = 1.3 Hz, C<u>H</u>$_2$CH=CH_2), 4.15–4.02 (m, 2 H, H-2α, H-3α, OH, C<u>H</u>$_2$CH=CH_2), 3.93 (dd, 0.5 H, $J_{1,2}$ = 7.3 Hz, $J_{2,3}$ = 9.5 Hz, H-2β), 3.88 (d, 0.5 H, $J_{2,3}$ = 9.5 Hz, H-3β), 3.77 (s, 0.5 H, H-9), 3.72–3.63 (m, 2 H, H-9, H-7, H-

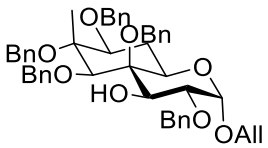
5), 3.27 (dd, 0.5 H, $J_{5,6ax}$ = 11.2 Hz, $J_{5,6eq}$ = 4.6 Hz, H-5), 2.51 (br, 0.5 H, C-2-OHβ), 2.22–2.01 (m, 2.5 H, H-6, OH), 1.68 (s, 1.5 H, H-10), 1.66 (s, 1.5 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.5 (Ar), 139.5 (Ar), 139.4 (Ar), 138.2(1) (Ar), 138.1(7) (Ar), 137.9 (Ar), 137.7 (Ar), 133.9 (CH=CH_2), 133.7 (CH=CH_2), 128.7 (Ar), 128.4(4) (Ar), 128.3(6) (Ar), 128.2 (Ar), 128.1(3) (Ar), 128.0(5) (Ar), 127.9 (Ar), 127.6(4) (Ar), 127.5(7) (Ar), 127.3(0) (Ar), 127.2(7) (Ar), 127.2 (Ar), 127.0 (Ar), 126.9 (Ar), 126.8 (Ar), 117.9 (CH=CH_2), 102.7 (C-1β), 97.8 (C-1α), 89.7 (C-9), 89.6 (C-9), 83.7 (C-8), 83.5 (C-8), 82.3 (C-7), 82.2 (C-7), 80.0 (C-3β), 77.6 (C-3α), 77.0 (C-4), 76.5 (CH_2Ar), 76.3 (CH_2Ar), 76.2 (CH_2Ar), 76.0 (CH_2Ar), 72.5 (C-5), 72.0 (C-2β), 71.5 (CH_2Ar), 71.4 (CH_2Ar), 70.3 (CH_2CH=CH_2), 70.3 (CH_2CH=CH_2), 69.6 (C-2α), 69.0(0) (CH_2Ar), 68.9(6) (CH_2Ar), 68.9 (CH_2Ar), 67.8 (C-5), 66.1 (CH_2Ar), 28.9 (C-6), 28.8 (C-6), 11.6 (C-10), 11.4 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{41}H_{46}NaO_8$: 689.3085. Found 689.3086.



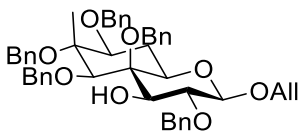
4.31α



4.31β



4.32α



4.32β

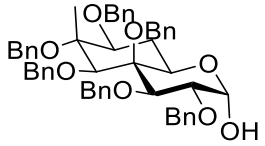
***Racemic* allyl 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-α-bradyrhizopyranoside (4.31α)**, ***racemic* allyl 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-β-bradyrhizopyranoside (4.31β)**, ***racemic* allyl 2,4,7,8,9-penta-*O*-benzyl-1,5-α-bradyrhizopyranoside (4.32α)** and ***racemic* allyl 2,4,7,8,9-penta-*O*-benzyl-1,5-β-bradyrhizopyranoside (4.32β)**. Sodium hydride (18 mg, 0.453 mmol, 60% wt in mineral oil) was added to a solution of **4.30** (100 mg, 0.151 mmol) in THF (3.5 mL). After 30 min, benzyl bromide (90 μL, 0.755 mmol) was added and the reaction mixture was stirred at rt overnight. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 → 9:1 hexanes–EtOAc) to give **4.31α** and **4.31β** (40 mg, 31%, inseparable

diastereomeric mixture 36:64) and **4.32α** and **4.32β** (76 mg, 67%, diastereomeric mixture 65:35) as yellow oils. **(4.31α)** and **(4.31β)**: R_f 0.58 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.46–7.41 (m, 1 H, Ar), 7.39–7.04 (m, 29 H, Ar), 6.06–5.92 (m, 1 H, C<u>H</u>=CH_2), 5.70 (d, 0.36 H, J = 12.7 Hz, C<u>H</u>$_2$Ar), 5.65 (d, 0.64 H, J = 12.5 Hz, C<u>H</u>$_2$Ar), 5.51 (d, 0.64 H, J = 12.5 Hz, C<u>H</u>$_2$Ar), 5.45 (d, 0.36 H, J = 12.7 Hz, C<u>H</u>$_2$Ar), 5.42–5.30 (m, 1 H, CH=C<u>H</u>$_2$ *trans*), 5.29–5.21 (m, 1.36 H, CH=C<u>H</u>$_2$ *cis*, C<u>H</u>$_2$Ar), 5.18 (d, 0.64 H, J = 11.7 Hz, C<u>H</u>$_2$Ar), 5.06 (d, 0.64 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 5.01 (d, 0.36 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.88–4.41 (m, 9.72 H, C<u>H</u>$_2$Ar, C<u>H</u>$_2$CH=CH_2, H-1α and H-1β), 4.23–4.07 (m, 1.64 H, H-3α, C<u>H</u>$_2$Ar and C<u>H</u>$_2$CH=CH_2), 4.03 (dd, 0.36 H, J = 9.9 Hz, J = 3.5 Hz, H-2α), 3.86 (dd, 0.64 H, J = 9.5 Hz, J = 7.5 Hz, H-2β), 3.76–3.62 (m, 3 H, H-3β, H-9, H-7 and H-5α), 3.23 (dd, 0.64 H, $J_{5,6ax}$ = 11.4 Hz, $J_{5,6eq}$ = 4.0 Hz, H-5β), 2.22–2.09 (m, 1.28 H, H-6β_{ax}), 2.06 (ddd, 0.36 H, $J_{5,6ax}$ = 12.3 Hz, $J_{6eq,6ax}$ = 12.3 Hz, $J_{6ax,7}$ = 12.3 Hz, H-6α_{ax}), 1.95 (ddd, 0.36 H, $J_{6eq,6ax}$ = 12.1 Hz, $J_{5,6eq}$ = 3.5 Hz, $J_{6eq,7}$ = 3.5 Hz, H-6α_{eq}), 1.72 (s, 1.08 H, H-10), 1.70 (s, 1.92 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 140.4 (Ar), 139.7 (Ar), 139.3 (Ar), 139.2 (Ar), 138.9 (Ar), 138.7 (Ar), 138.5 (Ar), 138.1 (Ar), 137.8 (Ar), 134.3 (<u>C</u>H=CH_2), 134.1 (<u>C</u>H=CH_2), 128.5 (Ar), 128.3 (Ar), 128.1 (Ar), 127.8 (Ar), 127.5 (Ar), 127.3 (Ar), 127.1 (Ar), 126.8 (Ar), 126.6(5) (Ar), 126.5(5) (Ar), 126.3 (Ar), 126.2 (Ar), 118.4 (CH=<u>C</u>H$_2$), 117.3 (CH=<u>C</u>H$_2$), 103.3 (C-1β), 96.1 (C-1α), 88.8 (C-9), 88.7 (C-9), 87.7 (C-3β), 84.3 (C-8), 84.2 (C-8), 84.0 (C-3α), 82.0 (C-7), 81.9 (C-2β), 81.3 (C-7), 78.8 (C-4), 77.9 (C-2α), 77.7 (<u>C</u>H$_2$Ar), 76.1(3) (<u>C</u>H$_2$Ar), 76.0(6) (<u>C</u>H$_2$Ar), 75.6 (<u>C</u>H$_2$Ar), 75.4 (<u>C</u>H$_2$Ar), 73.6 (<u>C</u>H$_2$Ar), 72.9 (C-5β), 71.6 (<u>C</u>H$_2$Ar), 71.5 (<u>C</u>H$_2$CH=CH_2), 70.3 (<u>C</u>H$_2$CH=CH_2), 69.3 (<u>C</u>H$_2$Ar), 69.2 (<u>C</u>H$_2$Ar), 68.5(3) (<u>C</u>H$_2$Ar), 68.5(1) (C-5α), 66.3(4) (<u>C</u>H$_2$Ar), 66.2(9) (<u>C</u>H$_2$Ar), 29.1 (C-6β), 28.8 (C-6α), 11.7(4) (C-10), 11.6(8) (C-10). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{55}H_{62}NO_8$: 864.4470. Found 864.4471.

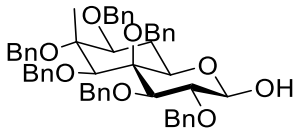
(4.32α): R_f 0.45 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δH) 7.39−7.22 (m, 25 H, Ar), 5.93 (dddd, 1 H, J = 16.7 Hz, J = 10.5 Hz, J = 6.2 Hz, J = 5.3 Hz, C<u>H</u>=CH$_2$), 5.56 (d, 1 H, J = 12.3 Hz, C<u>H</u>$_2$Ar), 5.34 (app dq, 1 H, J = 6.2 Hz, J = 5.3 Hz, CH=C<u>H</u>$_2$ *trans*), 5.25–5.19 (m, 2 H, CH=C<u>H</u>$_2$ *cis*, C<u>H</u>$_2$Ar), 5.01 (d, 1 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 4.84–4.79 (m, 3 H, 2 x C<u>H</u>$_2$Ar, H-1), 4.76–4.67 (m, 3 H, 3 x C<u>H</u>$_2$Ar), 4.60 (d, 1 H, J = 12.1 Hz, C<u>H</u>$_2$Ar), 4.56 (d, 1 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 4.34 (d, 1 H, $J_{2,3}$ = 9.9 Hz, H-3), 4.14 (app ddt, 1 H, J = 13.2 Hz, J = 5.3 Hz, J = 1.5 Hz, C<u>H</u>$_2$CH=CH$_2$), 3.99 (app ddt, 1 H, J = 13.0 Hz, J = 6.4 Hz, J = 1.1 Hz, C<u>H</u>$_2$CH=CH$_2$), 3.87 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 3.7 Hz, H-2), 3.76 (s, 1 H, OH), 3.71 (s, 1 H, H-9), 3.68–3.61 (m, 2 H, H-5, H-7), 2.05 (ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{6eq,6ax}$ = 12.1 Hz, $J_{6ax,7}$ = 12.1 Hz, H-6$_{ax}$), 1.95 (ddd, 1 H, $J_{6eq,6ax}$ = 12.1 Hz, $J_{5,6eq}$ = 4.0 Hz, $J_{6eq,7}$ = 4.0 Hz, H-6$_{eq}$), 1.65 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 140.0 (Ar), 139.7 (Ar), 138.4 (Ar), 138.3 (Ar), 138.1 (Ar), 134.0 (C<u>H</u>=CH$_2$), 128.5 (Ar), 128.4(0) (Ar), 128.3(8) (Ar), 128.3 (Ar), 128.1(9) (Ar), 128.1(5) (Ar), 127.8 (Ar), 127.7(2) (Ar), 127.7(0) (Ar), 127.5(8) (Ar), 127.5(6) (Ar), 127.5 (Ar), 127.2 (Ar), 127.0 (Ar), 126.8 (Ar), 117.8 (CH=C<u>H</u>$_2$), 96.3 (C-1), 89.7 (C-9), 83.5 (C-8), 82.0 (C-5), 76.9 (C-4), 76.2 (C-2/C-3), 76.1 (C-2/C-3), 76.0 (C<u>H</u>$_2$Ar), 73.2 (C<u>H</u>$_2$Ar), 71.7 (C<u>H</u>$_2$Ar), 68.9 (C<u>H</u>$_2$Ar), 68.7 (C<u>H</u>$_2$CH=CH$_2$), 67.4 (C-7), 66.2 (C<u>H</u>$_2$Ar), 29.4 (C-6), 11.5 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{48}H_{52}NaO_8$: 779.3554. Found 779.3563.

(4.32β): R_f 0.52 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δH) 7.41−7.22 (m, 25 H, Ar), 5.97 (app ddt, 1 H, J = 16.9 Hz, J = 10.8 Hz, J = 5.7 Hz, C<u>H</u>=CH$_2$), 5.41–5.32 (m, 2 H, CH=C<u>H</u>$_2$ *trans*, C<u>H</u>$_2$Ar), 5.22 (d, 1 H, J = 10.3 Hz, CH=C<u>H</u>$_2$ *cis*), 5.15 (d, 1 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 5.04 (d, 1 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 4.90 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.81–4.68 (m, 5 H, 5 x C<u>H</u>$_2$Ar), 4.53 (d, 1 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 4.47 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1), 4.44 (app dd, 1 H, J = 13.0 Hz, J = 5.5 Hz, C<u>H</u>$_2$CH=CH$_2$), 4.15 (app dd, 1 H, J = 12.7 Hz, J = 6.1 Hz, C<u>H</u>$_2$CH=CH$_2$),

3.93 (d, 1 H, $J_{2,3}$ = 9.4 Hz, H-3), 3.89 (s, 1 H, OH), 3.74 (app t, 1 H, J = 8.8 Hz, H-2), 3.64 (dd, 1 H, $J_{6ax,7}$ = 11.0 Hz, $J_{6eq,7}$ = 5.7 Hz, H-7), 3.58 (s, 1 H, H-9), 3.22 (dd, 1 H, $J_{5,6ax}$ = 13.0 Hz, $J_{5,6eq}$ = 5.5 Hz, H-5), 2.20–2.09 (m, 2 H, 2 x H-6), 1.63 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.7 (Ar), 139.6 (Ar), 138.2(1) (Ar), 138.5 (Ar), 138.3 (Ar), 138.2 (Ar), 134.1 (CH=CH_2), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.1(2) (Ar), 128.1(1) (Ar), 127.7 (Ar), 127.6(2) (Ar), 127.5(9) (Ar), 127.5 (Ar), 127.2 (Ar), 126.9 (Ar), 126.8 (Ar), 117.3 (CH=CH_2), 103.4 (C-1), 89.4 (C-9), 83.7 (C-8), 82.2 (C-7), 80.0 (C-2), 79.8 (C-3), 76.4 (C-4), 75.8 (CH_2Ar), 75.0 (CH_2Ar), 72.3 (C-5), 71.5 (CH_2Ar), 70.4 (CH_2CH=CH_2), 68.9 (CH_2Ar), 66.2 (CH_2Ar), 29.0 (C-6), 11.6 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{48}H_{52}NaO_8$: 779.3554. Found 779.3560.



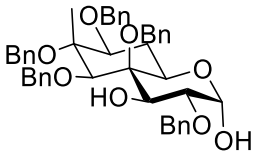
4.33α



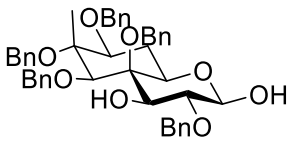
4.33β

***Racemic* 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-α-bradyrhizopyranose (4.33α)** and ***racemic* 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-β-bradyrhizopyranose (4.33β)**. Palladium(II) chloride (1 mg, 0.00543 mmol) was added to a solution of **4.31** (46 mg, 0.0543 mmol) in CH_2Cl_2 (0.6 mL) and MeOH (0.6 mL). The reaction mixture was stirred at rt overnight. The solution was filtered through Celite® 545 and the Celite was rinsed with EtOAc. The filtrate was then concentrated and the crude product was purified by silica gel column chromatography (17:3 hexanes–EtOAc) to give **4.33α** and **4.33β** (41 mg, 96%, inseparable diastereomeric mixture 7:3) as a colourless oil. R_f 0.55 and 0.42 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.43–7.04 (m, 30 H, Ar), 5.70 (d, 0.3 H, J = 12.5 Hz, CH_2Ar), 5.68 (d, 0.7 H, J = 12.8 Hz, CH_2Ar), 5.49 (d, 0.3 H, J = 12.5 Hz, CH_2Ar), 5.46 (d, 0.7 H, J = 12.8 Hz, CH_2Ar), 5.20–5.11 (m, 1.7 H, CH_2Ar), 5.09–5.02 (m, 1 H, CH_2Ar), 4.84–4.45 (m, 8.3 H, CH_2Ar, H-1α, H-1β), 4.08 (d, 0.7 H, J = 9.9 Hz, H-3α), 4.01 (dd, 0.7 H, J = 9.9 Hz,

J = 3.5 Hz, H-2α), 3.90 (dd, 0.7 H, *J* = 11.4 Hz, *J* = 4.8 Hz, H-5α), 3.75–3.63 (m, 2.6 H, H-2β, H-3β, H-9, H-7), 3.30 (dd, 0.3 H, *J* = 11.0 Hz, *J* = 5.1 Hz, H-5β), 3.00–2.91 (m, 1 H, OH), 2.17–2.10 (m, 2 H, H-6), 1.71 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 140.4 (Ar), 139.7 (Ar), 139.6 (Ar), 139.3 (Ar), 139.2 (Ar), 138.7 (Ar), 138.5 (Ar), 137.9 (Ar), 137.3 (Ar), 128.5 (Ar), 128.3 (Ar), 128.1 (Ar), 128.0 (Ar), 127.8 (Ar), 127.5 (Ar), 127.3 (Ar), 127.1 (Ar), 126.9 (Ar), 126.8 (Ar), 126.6 (Ar), 126.4 (Ar), 126.3 (Ar), 98.0 (C-1β), 91.6 (C-1α), 88.6 (C-9β), 88.5 (C-9α), 87.7 (C-3β), 84.2(2) (C-8β), 84.1(9) (C-8α), 83.9 (C-3α), 82.4 (C-7/ C-2β), 81.7(3) (C-7/C-2β), 81.6(9) (C-7/C-2β), 78.8 (C-4), 78.4 (C-2α), 77.7 (C-4), 76.2 (CH_2Ar), 76.1 (CH_2Ar), 75.6(3) (CH_2Ar), 75.5(8) (CH_2Ar), 75.2 (CH_2Ar), 73.7 (CH_2Ar), 73.1 (C-5β), 71.5 (CH_2Ar), 71.4 (CH_2Ar), 69.2(1) (CH_2Ar), 69.1(6) (CH_2Ar), 69.0 (C-5α), 66.3 (CH_2Ar), 66.2 (CH_2Ar), 29.1 (C-6β), 28.9 (C-6α), 11.7 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{52}H_{54}NaO_8$: 829.3711. Found 829.3712.



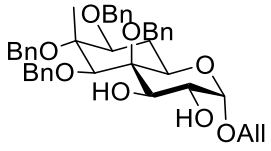
4.34α



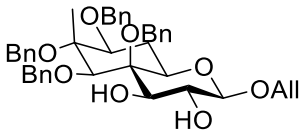
4.34β

***Racemic* 2,4,7,8,9-penta-*O*-benzyl-1,5-α-bradyrhizopyranose (4.34α)** and ***racemic* 2,4,7,8,9-penta-*O*-benzyl-1,5-β-bradyrhizopyranose (4.34β)**. Palladium(II) chloride (2.2 mg, 0.0126 mmol) was added to a solution of **4.32** (95 mg, 0.126 mmol) in CH_2Cl_2 (1.2 mL) and MeOH (1.2 mL). The reaction mixture was stirred at rt overnight. The solution was filtered through Celite® 545 and the Celite was rinsed with EtOAc. The filtrate was then concentrated and the crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **4.34α** and **4.34β** (87 mg, 97%, inseparable diastereomeric mixture 60:40) as a colourless oil. R_f 0.48 and 0.30 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.43–7.26 (m, 25 H, Ar), 5.53 (d, 0.6 H, *J* = 11.9 Hz, CH_2Ar), 5.47 (d, 0.4 H, *J* = 11.7 Hz, CH_2Ar), 5.28–5.19 (m, 1.6 H, CH_2Ar, H-1α), 5.16

(d, 0.6 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 5.10 (d, 0.4 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.91 (d, 0.4 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.88–4.67 (m, 6 H, C<u>H</u>$_2$Ar, H-2α, H-1β), 4.55 (d, 0.4 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 4.52 (d, 0.6H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.32 (d, 0.6, J = 9.7 Hz, H-3α), 4.13 (s, 0.6 H, OHα), 4.03 (s, 0.4 H, OHβ), 3.98 (d, 0.4 H, J = 9.4 Hz, H-3β), 3.92–3.86 (m, 1.2 H, H-2α, H-5α), 3.78 (s, 0.6 H, H-9α), 3.72–3.62 (m, 1.8 H, H-2β, H-9β, H-7), 3.31–3.24 (m, 0.8 H, H-5β, C-1OHβ), 3.17 (br, 0.6 H, OH), 2.20–2.04 (m, 2 H, H-6), 1.70 (s, 1.8 H, H-10), 1.68 (s, 1.2 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.7 (Ar), 139.6 (Ar), 138.3(3) (Ar), 138.2(5) (Ar), 138.2 (Ar), 138.1 (Ar), 137.7 (Ar), 128.6(3) (Ar), 128.5(8) (Ar), 128.4 (Ar), 128.3(4) (Ar), 128.2(8) (Ar), 128.2 (Ar), 128.1 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6(2) (Ar), 127.5(8) (Ar), 127.2 (Ar), 127.1 (Ar), 127.0 (Ar), 97.9 (C-1β), 91.7 (C-1α), 89.6 (C-9α), 89.4 (C-9β), 83.7 (C-8β), 83.5 (C-8α), 82.0(0) (C-2β/C-7), 81.9(7) (C-2β/C-7), 81.1 (C-2β/C-7), 80.1 (C-3β), 76.8 (C-4), 76.7 (C-2α/C-3α), 76.6 (C-2α/C-3α), 76.3 (C-4), 76.1 (<u>C</u>H$_2$Ar), 75.9 (<u>C</u>H$_2$Ar), 74.9 (<u>C</u>H$_2$Ar), 73.7 (<u>C</u>H$_2$Ar), 72.6 (C-5β), 71.5 (<u>C</u>H$_2$Ar), 71.4 (<u>C</u>H$_2$Ar), 69.0(2) (<u>C</u>H$_2$Ar), 68.9(5) (<u>C</u>H$_2$Ar), 67.5 (C-5α), 66.2 (<u>C</u>H$_2$Ar), 66.1 (<u>C</u>H$_2$Ar), 29.1 (C-6), 28.7 (C-6), 11.6 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{45}H_{48}NaO_8$: 739.3241. Found 739.3239.



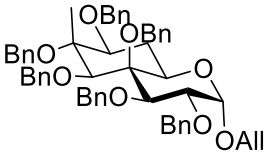
D-4.30α



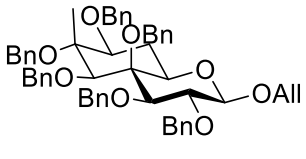
D-4.30β

Allyl 4,7,8,9-tetra-*O*-benzyl-1,5-α-D-bradyrhizopyranoside (D-4.30α) and **allyl 4,7,8,9-tetra-*O*-benzyl-1,5-β-D-bradyrhizopyranoside (D-4.30β)**. To a stirred solution of **D-4.29** (115 mg, 0.183 mmol) in AllOH (5 mL), HCl (213 µL of a solution of AcCl (0.1 mL) in AllOH (2.5 mL)) was added and the mixture was stirred at 65 °C for 2 days. After cooling to rt, water was added and the aqueous layer was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered

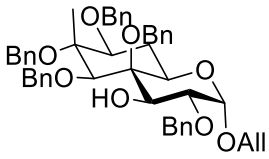
and concentrated. The resulting crude products were purified by silica gel column chromatography (7:3 hexanes–EtOAc) to give **D-4.30α** and **D-4.30β** (77 mg, 63%, inseparable diastereomeric mixture 11:9) as a colorless oil . The starting material **D-4.29** can be recovered by silica gel column chromatography (97:3 CH_2Cl_2–MeOH) and the reaction can be done again to yield more product **D-4.30α** and **D-4.30β**. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.30α** and **D-4.30** previously described. $[\alpha]_D$ +20.8 (*c* 0.1, $CHCl_3$).



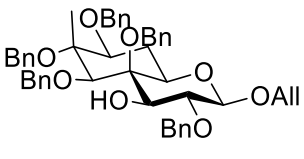
D-4.31α



D-4.31β



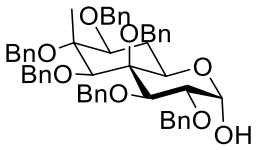
D-4.32α



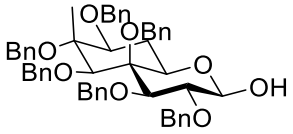
D-4.32β

Allyl 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-α-D-bradyrhizopyranoside (D-4.31α), **allyl 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-β-D-bradyrhizopyranoside (D-4.31β)**, **allyl 2,4,7,8,9-penta-*O*-benzyl-1,5-α-D-bradyrhizopyranoside (D-4.32α)** and **allyl 2,4,7,8,9-penta-*O*-benzyl-1,5-β-D-bradyrhizopyranoside (D-4.32β)**. Sodium hydride (16 mg, 0.390 mmol, 60% wt in mineral oil) was added to a solution of **D-4.20** (87 mg, 0.130 mmol) in THF (2 mL). After 30 min, benzyl bromide (77 μL, 0.652 mmol) was added and the reaction mixture was stirred at rt overnight. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 → 9:1 hexanes–EtOAc) to give **D-4.31α** and **D-4.31β** (34 mg, 31%, inseparable diastereomeric mixture 1:3) and **D-4.32α** and **D-4.32β** (66 mg, 67%, diastereomeric mixture 65:35) as a yellow oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.31α, 4.31β, 4.32α** and **4.32β** previously described. (**D-4.31α**) and

(**D-4.31β**): $[\alpha]_D$ +5.2 (*c* 0.1, $CHCl_3$). (**D-4.32α**): $[\alpha]_D$ +13.8 (*c* 0.1, $CHCl_3$). (**D-4.32β**): $[\alpha]_D$ –3.8 (*c* 0.1, $CHCl_3$).

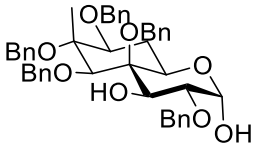


D-4.33α

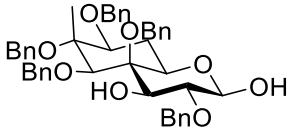


D-4.33β

2,3,4,7,8,9-Hexa-*O*-benzyl-1,5-α-D-bradyrhizopyranose (D-4.33α) and 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-β-D-bradyrhizopyranose (D-4.33β), Palladium(II) chloride (0.7 mg, 0.00398 mmol) was added to a solution of **D-4.31** (34 mg, 0.0398 mmol) in CH_2Cl_2 (0.4 mL) and MeOH (0.4 mL). The reaction mixture was stirred at rt overnight. The solution was filtered through Celite® 545 and the Celite was rinsed with EtOAc. The filtrate was then concentrated and the crude product was purified by silica gel column chromatography (17:3 hexanes–EtOAc) to give **D-4.33α** and **D-4.33β** (31 mg, 96%, inseparable diastereomeric mixture 7:3) as a colourless oil. The R_f, ^1H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.33α** and **4.33β** previously described. $[\alpha]_D$ –4.4 (*c* 0.1, $CHCl_3$).



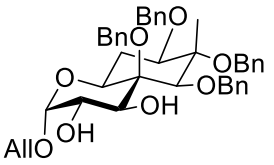
D-4.34α



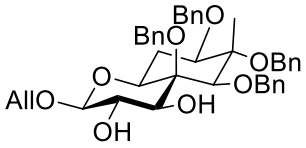
D-4.34β

2,4,7,8,9-Penta-*O*-benzyl-1,5-α-D-bradyrhizopyranose (D-4.34α) and **2,4,7,8,9-penta-*O*-benzyl-1,5-β-D-bradyrhizopyranose (D-4.34β)**. Palladium(II) chloride (1.5 mg, 0.00871 mmol) was added to a solution of **D-4.32** (66 mg, 0.0871 mmol) in CH_2Cl_2 (0.9 mL) and MeOH (0.9 mL). The reaction mixture was stirred at rt overnight. The **D-4.34β** solution was filtered through Celite® 545 and the Celite was rinsed with EtOAc. The filtrate was then concentrated and the crude product

was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **D-4.34α** and **D-4.34β** (61 mg, 97%, inseparable diastereomeric mixture 6:4) as a colourless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.34α** and **4.34β** previously described. $[\alpha]_D$ –6.2 (*c* 0.1, $CHCl_3$).

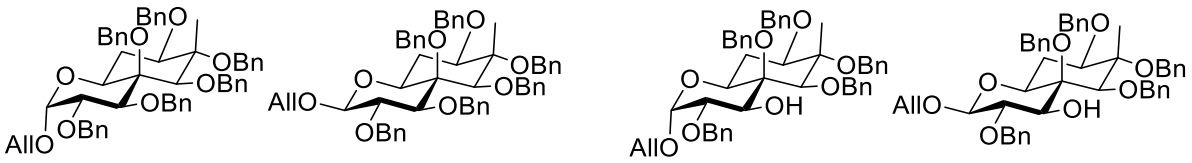


L-4.30α



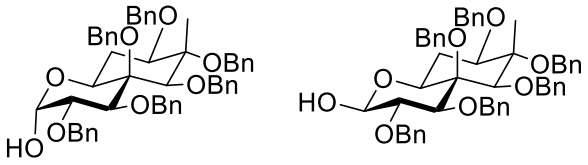
L-4.30β

Allyl 4,7,8,9-tetra-*O*-benzyl-1,5-α-L-bradyrhizopyranoside (L-4.30α) and **allyl 4,7,8,9-tetra-*O*-benzyl-1,5-β-L-bradyrhizopyranoside (L-4.30β)**. To a stirred solution of **L-4.29** (90 mg, 0.145 mmol) in AllOH (4 mL), HCl (160 μL of a solution of AcCl (0.1 mL) in AllOH (2.5 mL)) was added and the mixture was stirred at 65 °C for 2 days. After cooling to rt, water was added and the aqueous layer was extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude products were purified by silica gel column chromatography (7:3 hexanes–EtOAc) to give **L-4.30α** and **L-4.30β** (61 mg, 63%, inseparable diastereomeric mixture 1:1) as a colorless oil. The starting material **L-4.29** can be recovered by silica gel column chromatography (97:3 CH_2Cl_2–MeOH) and the reaction can be done again to yield more product **L-4.30α** and **L-4.30β**. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.30α** and **4.30β** previously described. $[\alpha]_D$ –11.8 (*c* 0.1, $CHCl_3$).



L-4.31α **L-4.31β** **L-4.32α** **L-4.32β**

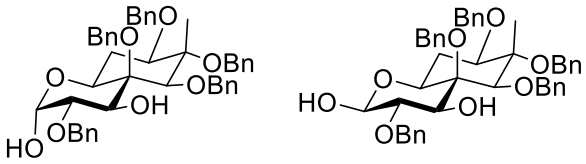
Allyl 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-α-L-bradyrhizopyranoside (L-4.31α), **allyl 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-β-L-bradyrhizopyranoside (L-4.31β)**, **allyl 2,4,7,8,9-penta-*O*-benzyl-1,5-α-L-bradyrhizopyranoside (L-4.32α)** and **allyl 2,4,7,8,9-penta-*O*-benzyl-1,5-β-L-bradyrhizopyranoside (L-4.32β)**. Sodium hydride (14 mg, 0.0.353 mmol, 60% wt in mineral oil) was added to a solution of **L-4.30** (78 mg, 0.118 mmol) in THF (2 mL). After 30 min, benzyl bromide (70 μL, 0.590 mmol) was added and the reaction mixture was stirred at rt overnight. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 → 9:1 hexanes–EtOAc) to give **L-4.31α** and **L-4.31β** (31 mg, 31%, inseparable diastereomeric mixture 1:3) and **L-4.32α** and **L-4.32β** (60 mg, 67%, inseparable diastereomeric mixture 65:35) as yellow oils. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.31α, 4.31β, 4.32α** and **4.32β** previously described. (**L-4.31α**) and (**L-4.31β**): $[\alpha]_D$ –3.4 (*c* 0.1, $CHCl_3$). (**4.32α**): $[\alpha]_D$ –11.6 (*c* 0.1, $CHCl_3$). (**L-4.32β**): $[\alpha]_D$ +2.0 (*c* 0.1, $CHCl_3$).



L-4.33α **L-4.33β**

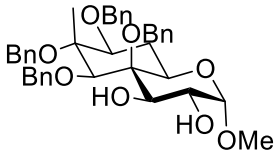
2,3,4,7,8,9-Hexa-*O*-benzyl-1,5-α-L-bradyrhizopyranose (L-4.33α) and 2,3,4,7,8,9-hexa-*O*-benzyl-1,5-β-L-bradyrhizopyranose (L-4.33β), Palladium(II) chloride (0.5 mg, 0.00297 mmol)

was added to a solution of **L-4.31** (25 mg, 0.0297 mmol) in CH_2Cl_2 (0.3 mL) and MeOH (0.3 mL). The reaction mixture was stirred at rt overnight. The solution was filtered through Celite® 545 and the Celite was rinsed with EtOAc. The filtrate was then concentrated and the crude product was purified by silica gel column chromatography (17:3 hexanes–EtOAc) to give **L-4.33α** and **L-4.33β** (23 mg, 96%, inseparable diastereomeric mixture 65:35) as a colourless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic **4.33α** and **4.33β** previously described. $[\alpha]_D$ +3.0 (*c* 0.1, $CHCl_3$).

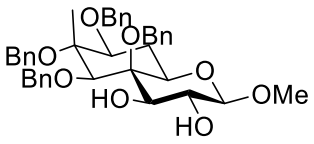


L-4.34α **L-4.34β**

2,4,7,8,9-Penta-*O*-benzyl-1,5-α-L-bradyrhizopyranose (L-4.34α) and **2,4,7,8,9-penta-*O*-benzyl-1,5-β-L-bradyrhizopyranose (L-4.34β)**. Palladium(II) chloride (1.3 mg, 0.00727 mmol) was added to a solution of **L-4.32** (55 mg, 0.727 mmol) in CH_2Cl_2 (1 mL) and MeOH (1 mL). The reaction mixture was stirred at rt overnight. The solution was filtered through Celite® 545 and the Celite was rinsed with EtOAc. The filtrate was then and the crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **L-4.34α** and **L-4.34β** (47 mg, 91%, inseparable diastereomeric mixture 6:4) as a colourless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.34α** and **4.34β** previously described. $[\alpha]_D$ +2.4 (*c* 0.1, $CHCl_3$).



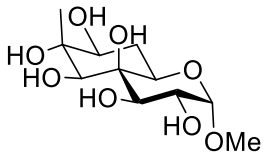
4.38α



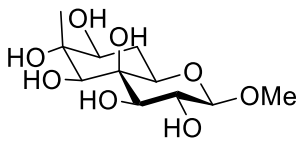
4.38β

***Racemic* methyl 4,7,8,9-tetra-*O*-benzyl-1,5-α-bradyrhizopyranoside (4.38α)** and ***racemic* methyl 4,7,8,9-tetra-*O*-benzyl-1,5-β-bradyrhizopyranoside (4.38β)**. To a stirred solution of **4.29** (76 mg, 0.121 mmol) in MeOH (5 mL), HCl (45 μL of a solution of AcCl (0.5 mL) in MeOH (3 mL)) was added and the mixture was stirred at 60 °C for 2 days. After cooling to rt, the solvent was evaporated and the resulting crude product was purified by silica gel column chromatography (7:3 hexanes–EtOAc) to give **4.38α** and **4.38β** (56 mg, 73%, inseparable diastereomeric mixture 6:4) as a colorless oil. The starting material **4.29** can be recovered by silica gel column chromatography (97:3 CH_2Cl_2–MeOH) and the reaction can be done again to yield more product **4.38α** and **4.38β**. R_f 0.54 (1:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.41–7.24 (m, 20 H, Ar), 5.55 (d, 0.6 H, J = 12.1 Hz, C$\underline{H}_2$Ar), 5.43 (d, 0.4 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 5.22 (d, 0.6 H, J = 12.1 Hz, C$\underline{H}_2$Ar), 5.18–5.11 (m, 1.4 H, C$\underline{H}_2$Ar), 4.89–4.83 (m, 1.6 H, C$\underline{H}_2$Ar, H-1α), 4.80–4.67 (m, 3 H, C$\underline{H}_2$Ar), 4.58–4.52 (m, 1 H, C$\underline{H}_2$Ar), 4.29–4.25 (m, 0.8 H, OH, H-1β), 4.15 (s, 0.6 H, OH), 4.11–4.02 (m, 1.2 H, H-3α, H-2α), 3.92–3.86 (m, 0.8 H, H-2β, H-3β), 3.77 (s, 0.6 H, H-9α), 3.74–3.66 (m, 1.4 H, H-9β, H-7), 3.65–3.60 (m, 1.8 H, OCH_3β, H-5α), 3.48 (s, 1.8 H, OCH_3α), 3.28 (dd, 0.4 H, J = 11.7 Hz, J = 4.0 Hz, H-5β), 2.60 (br, 0.4 H, OHβ), 2.27–2.04 (m, 2.6 H, H-6, OH), 1.68 (s, 1.8 H, H-10), 1.67 (s, 1.2 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.6 (Ar), 139.5 (Ar), 139.4 (Ar), 138.2(2) (Ar), 138.1(6) (Ar), 137.9 (Ar), 137.7 (Ar), 128.7 (Ar), 128.4(3) (Ar), 128.3(8) (Ar), 128.3 (Ar), 128.2 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.7 (Ar), 127.5 (Ar), 127.3 (Ar), 127.1 (Ar), 127.0 (Ar), 126.9 (Ar), 126.8 (Ar), 104.7 (C-1β), 99.6 (C-1α), 89.6(1) (C-9α), 89.5(8) (C-9β), 83.7 (C-8β), 83.5 (C-8α), 82.3 (C-7), 82.2 (C-7), 80.0 (C-2/C-3β), 77.5 (C-

2/C-3α), 76.5 (C-4), 76.3 (C-4), 76.2 (CH$_2$Ar), 76.0 (CH$_2$Ar), 72.5 (C-5β), 72.0 (C-2/C-3β), 71.5 (CH$_2$Ar), 71.4 (CH$_2$Ar), 69.6 (C-2/C-3α), 69.0 (CH$_2$Ar), 68.9 (CH$_2$Ar), 67.5 (C-5α), 66.2 (CH$_2$Ar), 66.1 (CH$_2$Ar), 57.3 (OCH$_3$β), 55.7 (OCH$_3$α), 28.9 (C-6), 28.8 (C-6), 11.6 (C-10), 11.5 (C-10). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{39}H_{48}NO_8$: 658.3374. Found 658.3365.

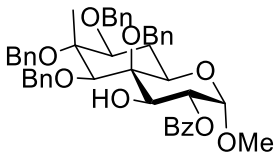


4.39α

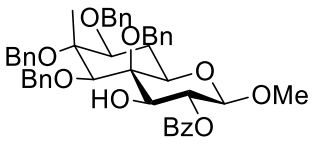


4.39β

***Racemic* methyl 1,5-α-bradyrhizopyranoside (4.39α)** and ***racemic* methyl 1,5-β-bradyrhizopyranoside (4.39β)**. Palladium on carbon (15 mg, 0.0140 mmol, 10 wt. % loading) was added to a solution of **4.38** (18 mg, 0.0279 mmol) in MeOH (2 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium on carbon was filtered and the filtrate was solvent concentrated. The resulting crude product was purified by reverse phase column chromatography (C-18 silica gel, H_2O) to give **4.39α** and **4.39β** (8 mg, 99%, inseparable diastereomeric mixture 3:2) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD, δ_H) 4.65 (d, 0.6 H, J = 3.9 Hz, H-1α), 4.17 (d, 0.4 H, J = 7.9 Hz, H-1β), 3.78 (d, 0.6 H, J = 9.5 Hz, H-2α), 3.74 (dd, 0.6 H, J = 9.5 Hz, J = 3.5 Hz, H-3α), 3.64 (dd, 0.6 H, J = 12.5 Hz, J = 4.0 Hz, H-5α**),** 3.59 (d, 0.4 H, J = 9.0 Hz, H-3β**),** 3.54–3.43 (m, 3.6 H, H-2β, H-7, H-9, OCH$_3$β), 3.40–3.32 (m, 2.2 H, OCH$_3$α, H-5β), 1.99–1.81 (m, 1.4 H, C-6 ax, C-6β$_{eq}$), 1.75 (ddd, 0.6 H, $J_{6eq,6ax}$ = 11.5 Hz, $J_{5,6eq}$ = 4.0 Hz, $J_{6eq,7}$ = 4.0 Hz, C-6α$_{eq}$), 1.27 (s, 3 H, H-10); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 106.1 (C-1β), 101.6 (C-1α), 80.8 (C-9), 80.6 (C-9), 80.1 (C-3β), 78.5(4) (C-8), 78.5(2) (C-8), 77.0 (C-3α), 74.3 (C-4), 74.2 (C-2β/C-7), 74.0 (C-2β/-7), 73.7 (C-4), 73.2 (C-2β/C-7), 72.2 (C-5β), 70.9 (C-2α), 67.2 (C-5α), 57.3 (OCH$_3$β), 55.8(OCH$_3$α), 32.9 (C-6), 32.8 (C-6), 15.5(0) (C-10), 15.4(5) (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{11}H_{20}NaO_8$: 303.1050. Found 303.1049.



4.40α

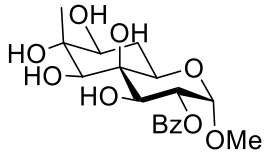


4.40β

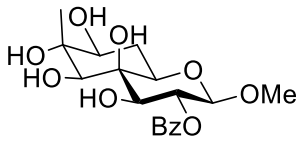
***Racemic* methyl 2-*O*-benzoyl-4,7,8,9-tetra-*O*-benzyl-1,5-α-bradyrhizopyranoside (4.40α)** and ***racemic* methyl 2-*O*-benzoyl-4,7,8,9-tetra-*O*-benzyl-1,5-β-bradyrhizopyranoside (4.40β)**. To a stirred solution of **4.38** (37 mg, 0.0577 mmol) in CH_2Cl_2 (0.5 mL) and pyridine (0.5 mL), benzoyl chloride (20 μL, 0.173 mmol) was added at 0 °C. The mixture was stirred at rt for 2 h. A saturated aqueous solution of $CuSO_4$ was added and the aqueous layer was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **4.40α** and **4.40β** as separable compounds (total: 41 mg, 96%, diastereomeric mixture 3:2) as colourless oils. (**4.40α**): R_f 0.33 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.15–8.11 (m, 2 H, Ar), 7.61–7.56 (m, 1 H, Ar), 7.50–7.43 (m, 4 H, Ar), 7.40–7.26 (m, 18 H, Ar), 5.60 (d, 1 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 5.53 (dd, 1 H, $J_{2,3}$ = 10.3 Hz, $J_{1,2}$ = 4.0 Hz, H-2), 5.28 (d, 1 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 5.22 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 5.12 (d, 1 H, J = 4.0 Hz, H-1), 4.88 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.77 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.75 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.72 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.57 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.52 (d, 1 H, J = 10.3 Hz, H-3), 4.23 (s, 1 H, OH), 3.85 (s, 1 H, H-9), 3.78–3.72 (m, 2 H, H-5, H-7), 3.44 (s, 3 H, OCH_3), 2.23–2.09 (m, 2 H, 2 x H-6), 1.71 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.4 (C=O), 139.5 (Ar), 139.4 (Ar), 138.2 (Ar), 137.7 (Ar), 133.1 (Ar), 130.0 (Ar), 128.7 (Ar), 128.4(5) (Ar), 128.3(6) (Ar), 128.3(4) (Ar), 128.2(6) (Ar), 128.0 (Ar), 127.7(2) (Ar), 127.6(8) (Ar), 127.6 (Ar), 127.3 (Ar), 127.2 (Ar), 127.1 (Ar), 97.8 (C-1), 89.6 (C-9), 83.6 (C-8), 82.4 (C-5/C-7), 77.0 (C-4), 76.1 (C$\underline{H}_2$Ar), 74.8 (C-3), 71.7 (C-2), 71.5

(<u>C</u>H$_2$Ar), 69.3 (<u>C</u>H$_2$Ar), 67.1 (C-5/C-7), 66.1 (<u>C</u>H$_2$Ar), 55.8 (OCH$_3$), 28.7 (C-6), 11.6 (C-10). HRMS (ESI) Calcd for [M + Na]$^+$ $C_{46}H_{48}NaO_9$: 767.3191. Found 767.3190.

(**4.40β**): R_f 0.25 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.13–8.18 (m, 2 H, Ar), 7.61–7.56 (m, 1 H, Ar), 7.49–7.44 (m, 4 H, Ar), 7.39–7.26 (m, 18 H, Ar), 5.63 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 7.9 Hz, H-2), 5.52 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 5.24 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 5.18 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.85 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.75 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.74 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 4.67 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.56 (d, 1 H, J = 7.9 Hz, H-1), 4.54 (d, 1 H, J = 11.2 Hz, C<u>H</u>$_2$Ar), 4.25 (s, 1 H, OH), 4.12 (d, 1 H, J = 4.0 Hz, H-3), 3.73–3.68 (m, 2 H, H-7, H-9), 3.36 (s, 3 H, OCH$_3$), 3.36 (dd, 1 H, J = 11.5 Hz, J = 4.0 Hz, H-5), 2.28–2.15 (m, 2 H, 2 x H-6), 1.69 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.8 (C=O), 139.5 (Ar), 139.1 (Ar), 138.1 (Ar), 137.5 (Ar), 133.0 (Ar), 130.1 (Ar), 129.9 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6(4) (Ar), 127.6(0) (Ar), 127.5(7) (Ar), 127.3 (Ar), 127.1 (Ar), 102.5 (C-1), 89.1 (C-9), 83.8 (C-8), 82.3 (C-7), 78.5 (C-3), 76.3 (C-4), 75.8 (<u>C</u>H$_2$Ar), 72.6 (C-5), 72.4 (C-2), 71.4 (<u>C</u>H$_2$Ar), 69.4 (<u>C</u>H$_2$Ar), 66.2 (<u>C</u>H$_2$Ar), 56.5 (OCH$_3$), 28.8 (C-6), 11.6 (C-10). HRMS (ESI) Calcd for [M + Na]$^+$ $C_{46}H_{48}NaO_9$: 767.3191. Found 767.3188.



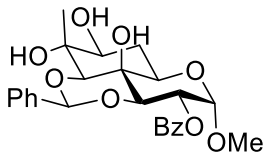
4.41α



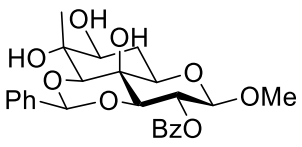
4.41β

***Racemic* methyl 2-*O*-benzoyl-1,5-α-bradyrhizopyranoside (4.41α)** and ***racemic* methyl 2-*O*-benzoyl-1,5-β-bradyrhizopyranoside (4.41β)**. Palladium on carbon (90 mg, 0.0876 mmol, 10 wt. % loading) was added to a solution of **4.40** (130 mg, 0.175 mmol) in MeOH (10 mL) under Ar.

The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium on carbon was filtered and the solvent concentrated. The resulting crude product was purified by column chromatography (19:1 → 9:1 CH_2Cl_2–MeOH) to give **4.41α** and **4.41β** (54 mg, 80%, inseparable diastereomeric mixture 7:3) as a colorless oil. R_f 0.38 (9:1 CH_2Cl_2–MeOH); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 8.06–7.99 (m, 2 H, Ar), 7.61–7.56 (m, 1 H, Ar), 7.48–7.43 (m, 2 H, Ar), 5.23 (dd, 0.3 H, $J_{2,3}$ = 9.2 Hz, $J_{1,2}$ = 8.3 Hz, H-2β), 5.18 (dd, 0.7 H, $J_{2,3}$ = 9.7 Hz, $J_{1,2}$ = 3.9 Hz, H-2α), 4.98 (d, 0.7 H, J = 4.0 Hz, H-1α), 4.51 (d, 0.3 H, J = 8.1 Hz, H-1β), 4.19 (d, 0.7 H, J = 9.9 Hz, H-3α), 3.96 (d, 0.3 H, J = 9.4 Hz, H-3β), 3.75 (dd, 0.7 H, $J_{5,6ax}$ = 12.5 Hz, $J_{5,6eq}$ = 4.0 Hz, H-5α), 3.58–3.51 (m, 2 H, H-5β, H-7α, H-9), 3.49 (dd, 0.3 H, $J_{6ax,7}$ = 12.1 Hz, $J_{6eq,7}$ = 4.2 Hz, H-7β), 3.43 (s, 0.9 H, OCH_3β), 3.33 (s, 2.1 H, OCH_3α), 2.04–1.86 (m, 1.3 H, H-6), 1.79 (ddd, 0.7 H, $J_{6ax,6eq}$ = 11.9 Hz, $J_{5,6eq}$ = 4.0 Hz, $J_{6eq,7}$ = 4.0 Hz, H-6_{eq}), 1.29 (s, 3 H, H-10); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 167.9 (C=Oα), 167.5 (C=Oβ), 134.4 (Ar), 134.3 (Ar), 131.6 (Ar), 131.3 (Ar), 130.8 (Ar), 130.7 (Ar), 129.5 (Ar), 103.7 (C-1β), 98.8 (C-1α), 80.7 (C-9α), 80.5 (C-9β), 78.5(5) (C-8), 78.5(2) (C-8), 78.3 (C-3β), 74.9 (C-3α), 74.6(1) (C-4), 74.5(6) (C-2β), 74.1(5) (C-2α), 74.1(2) (C-4), 74.0 (C-5β/C-7), 73.9 (C-5β/C-7), 72.4 (C-5β/C-7), 67.2 (C-5α), 57.1 (OCH_3β), 55.8 (OCH_3α), 32.8 (C-6β), 32.7 (C-6α), 15.5(0) (C-10α), 15.4(5) (C-10β). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{18}H_{24}NaO_9$: 407.1313. Found 407.1316.



4.37α



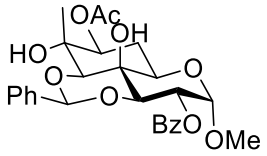
4.37β

Racemic **methyl 2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-bradyrhizopyranoside (4.37α)** and ***racemic*** **methyl 2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-β-bradyrhizopyranoside (4.37β)**.

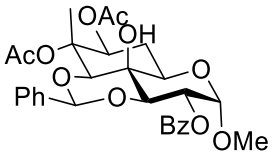
Benzaldehyde dimethyl acetal (120 μL, 0.798 mmol) and CSA (6 mg, 0.0266 mmol) were added to a solution of **4.41** (51 mg, 0.133 mmol) in MeCN (5 mL). The reaction mixture was placed on the rotary evaporator to remove the MeOH formed. Et_3N was added and the mixture was concentrated. The resulting crude product was purified by silica gel column chromatography (1:0 → 19:1 CH_2Cl_2–MeOH) to give **4.37α** and **4.37β** as separable products (51 mg, 81%, diastereomeric mixture 7:3) as a white solid. (**4.37α**): mp = 194–196 ˚C; R_f 0.34 (19:1 CH_2Cl_2–MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.09–8.04 (m, 2 H, Ar), 7.60–7.55 (m, 1 H, Ar), 7.54–7.48 (m, 2 H, Ar), 7.48–7.42 (m, 2 H, Ar), 7.40–7.34 (m, 3 H, Ar), 5.80 (s, 1 H, C<u>H</u>Ar), 5.54 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 3.7 Hz, H-2), 5.19 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 4.36 (d, 1 H, $J_{2,3}$ = 9.9 Hz, H-3), 3.86 (ddd, 1 H, $J_{5,6ax}$ = 11.9 Hz, $J_{5,6eq}$ = 4.0 Hz, $J_{4OH,5}$ = 1.5 Hz, H-5), 3.75 (dd, 1 H, $J_{6ax,7}$ = 11.9 Hz, $J_{6eq,7}$ = 4.2 Hz, H-7), 3.69 (s, 1 H, H-9), 3.44 (s, 3 H, OCH_3), 2.95 (d, 1 H, $J_{4OH,5}$ = 1.5 Hz, 4-OH), 2.27 (br s, 1H, OH), 2.20 (br, 1H, OH), 2.16 (ddd, 1 H, $J_{5,6ax}$ = 11.9 Hz, $J_{6ax,6eq}$ = 11.9 Hz, $J_{6ax,7}$ = 11.9 Hz, H-6_{ax}), 2.09 (ddd, 1 H, $J_{6ax,6eq}$ = 11.9 Hz, $J_{5,6eq}$ = 4.4 Hz, $J_{6eq,7}$ = 4.4 Hz, H-6_{eq}), 1.46 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 136.6 (Ar), 133.2 (Ar), 129.9 (Ar), 129.8 (Ar), 129.3(8) (Ar), 128.3(7) (Ar), 128.3 (Ar), 126.1 (Ar), 102.7 (<u>C</u>HAr), 98.5 (C-1), 83.2 (C-9), 78.0 (C-3), 76.1 (C-8), 73.4 (C-7), 69.9 (C-2), 67.7 (C-4), 64.8 (C-5), 55.9 (OCH_3), 30.6 (C-6), 16.8 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{25}H_{28}NaO_9$: 495.1626. Found 495.1624.

(**4.37β**): mp = 261–264 ˚C; R_f 0.29 (19:1 CH_2Cl_2–MeOH);); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 8.02–7.97 (m, 2 H, Ar), 7.61–7.50 (m, 3 H, Ar), 7.48–7.42 (m, 2 H, Ar), 7.30–7.25 (m, 3 H, Ar), 5.73 (s, 1 H, C<u>H</u>Ar), 5.51 (dd, 1 H, $J_{2,3}$ = 9.7 Hz, $J_{1,2}$ = 7.9 Hz, H-2), 4.67 (d, 1 H, $J_{1,2}$ = 7.7 Hz, H-1), 4.10 (d, 1 H, $J_{2,3}$ = 9.7 Hz, H-3), 3.67 (dd, 1 H, $J_{5,6ax}$ = 11.7 Hz, $J_{5,6eq}$ = 4.4 Hz, H-5), 3.62 (s, 1 H, H-9), 3.61 (dd, 1 H, $J_{6ax,7}$ = 12.1 Hz, $J_{6eq,7}$ = 4.4 Hz, H-7), 3.47 (s, 3 H, OCH_3), 2.09

(ddd, 1 H, $J_{5,6ax}$ = 11.9 Hz, $J_{6eq,6ax}$ = 11.9 Hz, $J_{6ax,7}$ = 11.9 Hz, H-6$_{ax}$), 1.98 (ddd, 1 H, $J_{6ax,6eq}$ = 11.9 Hz, $J_{5,6eq}$ = 4.2 Hz, $J_{6eq,7}$ = 4.2 Hz, H-6$_{eq}$), 1.36 (s, 3 H, H-10); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 167.1 (C=O), 138.9 (Ar), 134.4 (Ar), 131.2 (Ar), 130.6 (Ar), 129.9 (Ar), 129.6 (Ar), 128.9 (Ar), 127.6 (Ar), 104.3 (C-1), 104.2 (CHAr), 84.6 (C-9), 82.6 (C-3), 76.7 (C-8), 74.7 (C-7), 72.2 (C-2), 71.1 (C-5), 68.3 (C-4), 57.3 (OCH_3), 32.7 (C-6), 16.4 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{25}H_{28}NaO_9$: 495.1626. Found 495.1626.



4.42α

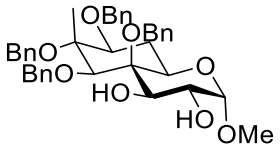


4.43α

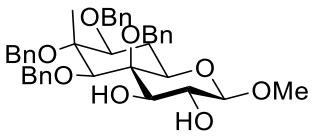
Racemic **methyl α-7-*O*-acetyl-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-bradyrhizopyranoside (4.42α)** and ***racemic*** **methyl α-2-7,8-di-*O*-acetyl-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-bradyrhizopyranoside (4.43α)**. To a stirred solution of **4.37α** (5 mg, 0.0.0106 mmol) in pyridine (0.5 mL), acetic anhydride (10 μL, 0.105 mmol) and DMAP (1 mg) were added at rt and the mixture was stirred overnight. A saturated aqueous solution of $CuSO_4$ was added and the aqueous layer was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **4.42α** (3.5 mg, 63%) and **4.43α** (2 mg, 33%) as colourless oils. (**4.42α**): R_f 0.12 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.10–8.06 (m, 2 H, Ar), 7.61–7.57 (m, 1 H, Ar), 7.55–7.50 (m, 2 H, Ar), 7.49–7.44 (m, 2 H, Ar), 7.42–7.36 (m, 3 H, Ar), 5.84 (s, 1 H, CHAr), 5.54 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 3.7 Hz, H-2), 5.19 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 4.94 (dd, 1 H, $J_{6ax,7}$ = 11.9 Hz, $J_{6eq,7}$ = 4.8 Hz, H-7), 4.40 (d, 1 H, $J_{2,3}$ = 9.9 Hz, H-3), 3.93 (ddd, 1 H, $J_{5,6ax}$ = 11.9 Hz, $J_{5,6eq}$ = 4.8 Hz, $J_{4OH,5}$ = 1.5 Hz, H-5), 3.78 (s, 1 H, H-9), 3.45 (s, 3 H, OCH_3), 2.47 (d, 1 H, J = 1.7 Hz, 4-OH), 2.24–2.09 (m, 5 H, 2 x H-6, (C=O)CH_3), 1.53 (s, 3 H, H-10); ^{13}C NMR

(125 MHz, $CDCl_3$, δ_C) 170.7 (C=O), 166.0 (C=O), 136.6 (Ar), 133.2 (Ar), 129.9 (Ar), 129.7 (Ar), 129.4 (Ar), 128.4(0) (Ar), 128.3(9) (Ar), 128.3 (Ar), 126.1 (Ar), 102.8 (CHAr), 98.6 (C-1), 83.0 (C-9), 77.9 (C-3), 74.6(8) (C-7), 74.6(5) (C-8), 69.8 (C-2), 67.4 (C-4), 66.4 (C-5), 56.0 (OCH_3), 28.7 (C-6), 21.2 ((C=O)CH_3), 11.6 (C-10). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{27}H_{34}NO_{10}$: 532.2177. Found 532.2172.

(**4.43α**): R_f 0.43 (3:2 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.10–8.07 (m, 2 H, Ar), 7.62–7.57 (m, 1 H, Ar), 7.53–7.45 (m, 4 H, Ar), 7.41–7.35 (m, 3 H, Ar), 6.02 (dd, 1 H, $J_{6ax,7}$ = 11.9 Hz, $J_{6eq,7}$ = 5.0 Hz, H-7), 5.83 (s, 1 H, CHAr), 5.52 (dd, 1 H, $J_{2,3}$ = 10.1 Hz, $J_{1,2}$ = 3.9 Hz, H-2), 5.21 (s, 1 H, H-9), 5.18 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 4.45 (d, 1 H, $J_{2,3}$ = 9.9 Hz, H-3), 4.01 (ddd, 1 H, $J_{5,6ax}$ = 12.5 Hz, $J_{5,6eq}$ = 4.4 Hz, $J_{4OH,5}$ = 1.5 Hz, H-5), 3.45 (s, 3 H, OCH_3), 3.03 (d, 1 H, J = 1.8 Hz, 4-OH), 2.29 (ddd, 1H, $J_{5,6ax}$ = 11.9, $J_{6eq,6ax}$ = 11.9, $J_{6ax,7}$ = 11.9, H-6_{ax}), 2.15 (s, 3H, (C=O)CH_3), 2.10–2.04 (m, 1 H, H-6_{eq}), 2.01 (s, 3H, (C=O)CH_3), 1.59 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 171.3 (C=O), 170.0 (C=O), 166.1 (C=O), 136.6 (Ar), 133.2 (Ar), 129.9 (Ar), 129.8 (Ar), 129.3 (Ar), 128.4 (Ar), 128.3 (Ar), 126.1 (Ar), 102.4 (CHAr), 98.5 (C-1), 85.5 (C-8), 78.7 (C-3), 78.0 (C-9), 69.7 (C-2), 69.0 (C-7), 67.9 (C-4), 63.9 (C-5), 55.9 (OCH_3), 29.2 (C-6), 22.8 ((C=O)CH_3), 20.9 ((C=O)CH_3), 16.4 (C-10). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{29}H_{36}NO_{11}$: 574.2283. Found 574.2274.



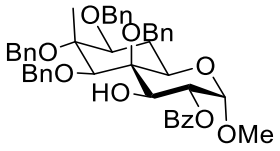
D-4.38α



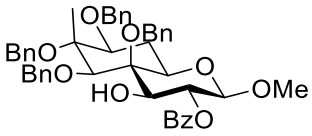
D-4.38β

Methyl 4,7,8,9-tetra-*O*-benzyl-1,5-α-D-bradyrhizopyranoside (D-4.38α) and **methyl 4,7,8,9-tetra-*O*-benzyl-1,5-β-D-bradyrhizopyranoside (D-4.38β)**. To a stirred solution of **D-4.29** (76 mg, 0.121 mmol) in MeOH (5 mL), HCl (45 μL of a solution f AcCl (0.5 mL) in MeOH (3 mL)) was

added and the mixture was stirred at 60 °C for 2 days. After cooling to rt, the solvent was evaporated and the resulting crude product was purified by silica gel column chromatography (7:3 hexanes–EtOAc) to give **D-4.38α** and **D-4.38β** (56 mg, 73%, inseparable diastereomeric mixture 53:47) as a colorless oil. The starting material **D-4.19** can be recovered by silica gel column chromatography (97:3 CH_2Cl_2–MeOH) and the reaction can be done again to yield more product **D-4.38α** and **D-4.38β**. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.38α** and **4.38β** previously described. $[\alpha]_D$ +13.2 (*c* 0.1, $CHCl_3$).

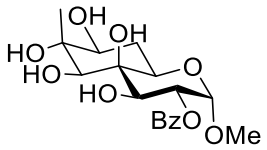


D-4.40α

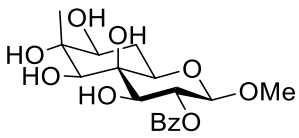


D-4.40β

Methyl 2-*O*-benzoyl-4,7,8,9-tetra-*O*-benzyl-1,5-α-D-bradyrhizopyranoside (D-4.40α) and **methyl 2-*O*-benzoyl-4,7,8,9-tetra-*O*-benzyl-1,5-β-D-bradyrhizopyranoside (D-4.40β)**. To a stirred solution of **D-4.38** (77 mg, 0.120 mmol) in CH_2Cl_2 (1.5 mL) and pyridine (1.5 mL), benzoyl chloride (70 μL, 0.600 mmol) was added at 0 °C. The mixture was stirred at rt for 2 h. A saturated aqueous solution of $CuSO_4$ was added and the aqueous layer was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (3 x) (19:1 hexanes–EtOAc) to give **D-4.40α** and **D-4.40β** (86 mg, 96%, diastereomeric mixture 3:1) as colourless oils . The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.40α** and **4.40β** previously described. (**D-4.40α**): $[\alpha]_D$ +65.2 (*c* 0.1, $CHCl_3$). (**D-4.40β**): $[\alpha]_D$ +18.0 (*c* 0.1, $CHCl_3$).

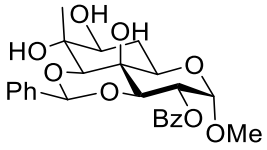


D-4.41α

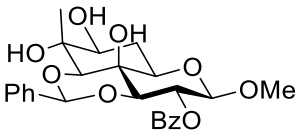


D-4.41β

Methyl 2-*O*-benzoyl-1,5-α-D-bradyrhizopyranoside (D-4.41α) and **methyl 2-*O*-benzoyl-1,5-β-D-bradyrhizopyranoside (D-4.41β)**. Palladium on carbon (36.5 mg, 0.344 mmol, 10 wt. % loading) was added to a solution of **D-4.40** (51 mg, 0.0687 mmol) in MeOH (10 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred for 3 days. The palladium on carbon was filtered and the filtrate was concentrated. The resulting crude product was purified by column chromatography (19:1 → 9:1 CH_2Cl_2–MeOH) to give **D-4.41α** and **D-4.41β** (21 mg, 80%, inseparable diastereomeric mixture 22:3) as a colorless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.41α** and **4.41β** previously described. $[\alpha]_D$ +120.0 (*c* 0.1, CH_3OH).



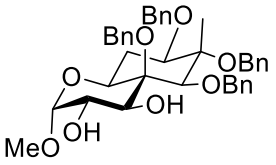
D-4.37α



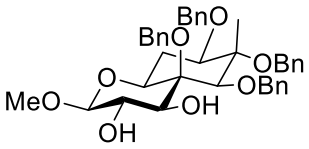
D-4.37β

Methyl 2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (D-4.37α) and **methyl 2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-β-D-bradyrhizopyranoside (D-4.37β)**. Benzaldehyde dimethyl acetal (17 μL, 0.115 mmol) and CSA (1.7 mg, 0.00764 mmol) were added to a solution of **D-4.41** (15 mg, 0.0382 mmol) in MeCN (5 mL). The reaction mixture was placed on the rotary evaporator to remove the MeOH formed. Et_3N was added and the mixture was concentrated. The resulting crude product was purified by silica gel column chromatography (1:0 to 19:1 CH_2Cl_2–MeOH) to give **D-4.37α** and **D-4.37β** (14.4 mg, 80%, inseparable diastereomeric mixture 22:3) as

a white solid. The mp, R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.37α** and **4.37β** previously described. (**D-4.37α**): $[\alpha]_D$ +129.2 (*c* 0.1, $CHCl_3$). (**D-4.37β**): $[\alpha]_D$ +20.0 (*c* 0.1, $CHCl_3$).

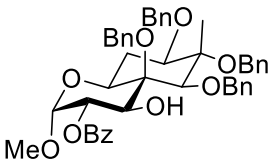


L-4.38α

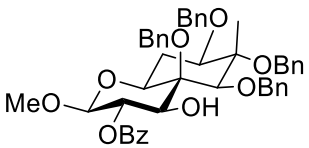


L-4.38β

Methyl 4,7,8,9-tetra-*O*-benzyl-1,5-α-L-bradyrhizopyranoside (L-4.38α) and **methyl 4,7,8,9-tetra-*O*-benzyl-1,5-β- L-bradyrhizopyranoside (L-4.38β)**. To a stirred solution of **L-4.29** (76 mg, 0.121 mmol) in MeOH (5 mL), HCl (45 µL of a solution of AcCl (0.5 mL) in MeOH (3 mL)) was added and the mixture was stirred at 60 °C for 2 days. After cooling to rt, the solvent was evaporated and the resulting crude product was purified by silica gel column chromatography (7:3 hexanes–EtOAc) to give **L-4.38α** and **L-4.38β** (56 mg, 73%, inseparable diastereomeric mixture 57:43) as a colorless oil. The starting material **L-4.29** can be recovered by silica gel column chromatography (97:3 CH_2Cl_2–MeOH) and the reaction can be done again to yield more product **L-4.38α** and **L-4.38β**. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.38α** and **4.38β** previously described. $[\alpha]_D$ –18.0 (*c* 0.1, $CHCl_3$).



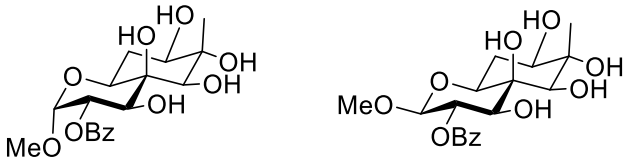
L-4.40α



L-4.40β

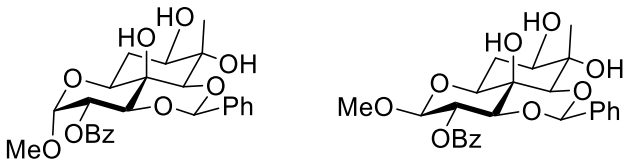
Methyl 2-*O*-benzoyl-4,7,8,9-tetra-*O*-benzyl-1,5-α-L-bradyrhizopyranoside (L-4.40α) and **methyl 2-*O*-benzoyl-4,7,8,9-tetra-*O*-benzyl-1,5-β-L-bradyrhizopyranoside (L-4.40β)**. To a

stirred solution of **L-4.38** (67 mg, 0.104 mmol) in CH_2Cl_2 (1.3 mL) and pyridine (1.3 mL), benzoyl chloride (61 μL, 0.522 mmol) was added at 0 °C. The mixture was stirred at rt for 2 h. A saturated aqueous solution of $CuSO_4$ was added and the aqueous layer was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (19:1 hexanes–EtOAc) to give **L-4.40α** and **L-4.40β** (74 mg, 96%, diastereomeric mixture 57:43) as colourless oils diastereomeric mixture 57:43. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.40α** and **4.40β** previously described. (**L-4.40α**): $[\alpha]_D$ –69.6 (*c* 0.1, $CHCl_3$). (**L-4.40β**): $[\alpha]_D$ –11.8 (*c* 0.2, $CHCl_3$).



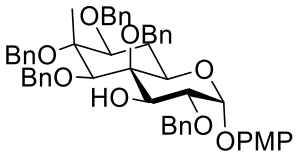
L-4.41α **L-4.41β**

Methyl 2-*O*-benzoyl-1,5-α-L-bradyrhizopyranoside (L-4.41α) and **methyl 2-*O*-benzoyl-1,5-β-L-bradyrhizopyranoside (L-4.41β)**. Palladium on carbon (36.5 mg, 0.344 mmol, 10 wt. % loading) was added to a solution of **L-4.40** (51 mg, 0.0687 mmol) in MeOH (10 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred for 3 days. The palladium on carbon was filtered and the filtrate was concentrated. The resulting crude product was purified by column chromatography (19:1 → 9:1 CH_2Cl_2–MeOH) to give **L-4.41α** and **L-4.41β** (21 mg, 80%, inseparable diastereomeric mixture 7:3) as a colorless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.41α** and **4.41β** previously described. $[\alpha]_D$ –64.8 (*c* 0.1, CH_3OH).



L-4.37α **L-4.37β**

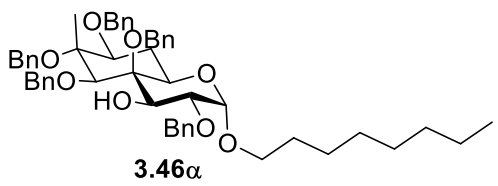
Methyl 2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-L-bradyrhizopyranoside (L-4.37α) and **methyl 2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-β-L-bradyrhizopyranoside (L-4.37β)**. Benzaldehyde dimethyl acetal (26 μL, 0.176 mmol) and CSA (2.7 mg, 0.0118 mmol) were added to a solution of **L-4.41** (23 mg, 0.0588 mmol) in MeCN (5 mL). The reaction mixture was placed on the rotary evaporator to remove the MeOH formed. Et_3N was added and the mixture was concentrated. The resulting crude product was purified by silica gel column chromatography (1:0 → 19:1 CH_2Cl_2–MeOH) to give **L-4.37α** and **L-4.37β** (23 mg, 83%, diastereomeric mixture 7:3) as a white solid . The R_f, ^1H NMR, ^{13}C NMR and MS data correspond to that obtained from the racemic compounds **4.37α** and **4.37β** previously described. (**L-4.37α**): $[\alpha]_D$ –154.0 (*c* 0.1, $CHCl_3$). (**L-4.37β**): $[\alpha]_D$ –23.4 (*c* 0.1, $CHCl_3$).



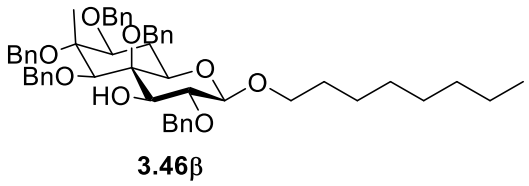
3.45α

***Racemic p*-methoxyphenyl 2,4,7,8,9-penta-*O*-benzyl-1,5-α-bradyrhizopyranoside (3.45α)**. Cesium carbonate (1 mg, 0.00311 mmol) was added to a cooled (0 °C) solution of **3.34** (22 mg, 0.0311 mmol) and trichloroacetonitrile (16 μL, 0.156 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt overnight then filtered through Celite® 545. The filtrate was concentrated and the crude product was used for the next step without further purification.

p-Methoxylphenol (37 mg, 0.302 mmol) and molecular sieves (~30 mg, activated powder 4 Å) were added to the crude trichloroacetimidate in CH_2Cl_2 (0.5 mL) and Et_2O (0.5 mL). The mixture was stirred for 1 h at rt then cooled to –40 °C and stirred for 15 min. TBSOTf (66 μL of a solution of TBSOTf (10 μL) in CH_2Cl_2 (1 mL)) was added and the mixture was stirred at –40 °C for 30 min. Et_3N (50 μL) was added and the reaction mixture was warmed to rt. The solvent was evaporated and the resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.4α** (18 mg, 75%) as a colorless oil. R_f 0.37 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.41–7.23 (m, 25 H, Ar), 7.06–7.01 (m, 2 H, Ar), 6.89–6.85 (m, 2 H, Ar), 5.62 (d, 1 H, J = 12.3 Hz, C$\underline{H}_2$Ar), 5.37 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 5.27 (d, 1 H, J = 12.1 Hz, C$\underline{H}_2$Ar), 5.08 (d, 1 H, J = 10.6 Hz, C$\underline{H}_2$Ar), 4.83 (d, 1 H, J = 10.8 Hz, C$\underline{H}_2$Ar), 4.82 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.78–4.73 (m, 2 H, 2 x C$\underline{H}_2$Ar), 4.64 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.62 (d, 1 H, J = 11.5 Hz, C$\underline{H}_2$Ar), 4.54 (d, 1 H, $J_{2,3}$ = 10.1 Hz, H-3), 4.50 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 4.01 (dd, 1 H, $J_{2,3}$ = 10.1 Hz, $J_{1,2}$ = 3.9 Hz, H-2), 3.94 (s, 1 H, OH), 3.83 (s, 3 H, OCH_3), 3.82–3.77 (m, 2 H, H-9, H-5), 3.64 (dd, 1 H, $J_{6ax,7}$ = 11.9 Hz, $J_{6eq,7}$ = 4.8 Hz, H-7), 2.09 (app q, 1 H, J = 12.1 Hz, H-6 ax), 1.97 (app dt, 1 H, J = 11.9 Hz, J = 4.2 Hz, H-6 eq), 1.69 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 155.0 (Ar), 151.3 (Ar), 139.9 (Ar), 139.6 (Ar), 138.2(9) (Ar), 138.2(8) (Ar), 137.9 (Ar), 128.6 (Ar), 128.4(5) (Ar), 128.3(8) (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 127.9 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 127.2 (Ar), 127.0(3) (Ar), 126.9(5) (Ar), 117.9 (Ar), 114.6 (Ar), 96.8 (C-1), 89.7 (C-9), 83.5 (C-8), 82.0 (C-7), 76.4 (C-3), 76.2 (C$\underline{H}_2$Ar, C-4), 75.9 (C-2), 73.2 (C$\underline{H}_2$Ar), 71.6 (C$\underline{H}_2$Ar), 69.1 (C$\underline{H}_2$Ar), 68.1 (C-5), 66.2 (C$\underline{H}_2$Ar), 55.7 (OCH_3), 28.8 (C-6), 11.6 (C-10). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{52}H_{54}NaO_9$: 845.3660. Found 845.3663.



3.46α

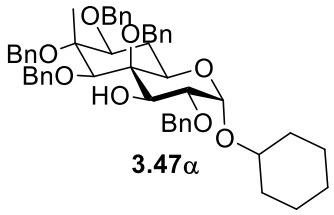


3.46β

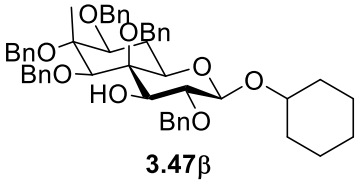
***Racemic* octyl 2,4,7,8,9-penta-*O*-benzyl-1,5-α-bradyrhizopyranoside (3.46α) and *racemic* octanyl 2,4,7,8,9-penta-*O*-benzyl-1,5-β-bradyrhizopyranoside (3.46β)**. Cesium carbonate (3 mg, 0.00908 mmol) was added to a cooled (0 °C) solution of **3.34** (22 mg, 0.0303 mmol) and trichloroacetonitrile (15 μL, 0.152 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt overnight then filtered through Celite® 545. The filtrate was concentrated and the crude product was used for the next step without further purification.

Octanol (50 μL, 0.313 mmol) and molecular sieves (~30 mg, activated powder 4 Å) were added to the crude trichloroacetimidate in Et_2O (1 mL). The mixture was stirred for an hour at rt then cooled to –40 °C and stirred for 15 min. TBSOTf (53 μL of a solution of TBSOTf (10 μL) in CH_2Cl_2 (1 mL)) was added and the mixture was stirred at –40 °C for 30 min. Et_3N (50 μL) was added and the reaction mixture was warmed to rt. The solvent was evaporated and the resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.46α** and **3.46β** (22 mg, 85%, inseparable diastereomeric mixture 2:5) as a colorless oil. R_f 0.47 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.42–7.22 (m, 25 H, Ar), 5.58 (d, 0.3 H, J = 12.3 Hz, C$\underline{H}_2$Ar), 5.39 (d, 0.7 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 5.23 (d, 0.3 H, J = 12.1 Hz, C$\underline{H}_2$Ar), 5.16 (d, 0.7 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 5.05 (d, 0.7 H, J = 10.8 Hz, C$\underline{H}_2$Ar), 5.02 (d, 0.3 H, J = 10.8 Hz, C$\underline{H}_2$Ar), 4.91 (d, 0.7 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.86–4.69 (m, 5.4 H, C$\underline{H}_2$Ar, H-1α), 4.60–4.50 (m, 1.3 H, C$\underline{H}_2$Ar), 4.42 (d, 0.7 H, J = 7.7 Hz, H-1β), 4.33 (d, 0.3 H, J = 10.1 Hz, H-3α), 4.00–3.88 (m, 2 H, H-3β, H_{octyl}, OHβ), 3.86 (dd, 0.3 H, $J_{2,3}$ = 10.1 Hz, $J_{1,2}$ = 3.9 Hz, H-2α), 3.76–3.51 (m, 4.3 H, H-2β, OHα, H_{octyl}, H-5α, H-7, H-9), 3.44–3.36 (m, 0.3 H, H_{octyl}α), 3.23 (dd, 0.7 H, $J_{5,6ax}$= 11.2 Hz,

$J_{5,6eq}$= 4.2 Hz, H-5β), 2.21–2.03 (m, 1.7 H, H-6), 2.00–1.94 (m, 0.3 H, H-6eqα), 1.74–1.59 (m, 5 H, H-10, H_{octyl}), 1.48–1.21 (m, 10 H, H_{octyl}), 0.95–0.86 (m, 3 H, H_{octyl}); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 140.1 (Ar), 139.7(1) (Ar), 139.6(8) (Ar), 139.6(4) (Ar), 139.6 (Ar), 138.4 (Ar), 138.3 (Ar), 138.2 (Ar), 128.5 (Ar), 128.4(1) (Ar), 128.3(9) (Ar), 128.3 (Ar), 128.2 (Ar), 128.1(4) (Ar), 128.1(0) (Ar), 128.0(7) (Ar), 127.8 (Ar), 127.7(4) (Ar), 127.7(1) (Ar), 127.6(2) (Ar), 127.6(0) (Ar), 127.5(9) (Ar), 127.5(6) (Ar), 127.2(4) (Ar), 127.2(3) (Ar), 126.9 (Ar), 126.8 (Ar), 104.3 (C-1β), 97.3 (C-1α), 89.8 (C-9α), 89.5 (C-9β), 83.8 (C-8β), 83.5 (C-8α), 82.3 (C-7β), 82.2 (C-7α), 80.0 (C-2β), 79.8 (C-3β), 76.9 (C-4), 76.4(3) (C-4), 76.3(6) (C-2α), 76.2 (C-3α), 76.1 ($\underline{C}H_2Ar$), 75.8 ($\underline{C}H_2Ar$), 74.9 ($\underline{C}H_2Ar$), 73.1 ($\underline{C}H_2Ar$), 72.3 (C-5β), 71.7 ($\underline{C}H_2Ar$), 71.5 ($\underline{C}H_2Ar$), 70.2 (C_{octyl}), 68.9(4) (C_{octyl}), 68.9(0) ($\underline{C}H_2Ar$), 68.5 ($\underline{C}H_2Ar$), 67.3 (C-5α), 66.2(4) ($\underline{C}H_2Ar$), 66.2(2) ($\underline{C}H_2Ar$), 31.9(3) (C_{octyl}), 31.8(6) (C_{octyl}), 29.8 (C_{octyl}), 29.7 (C_{octyl}), 29.6 (C_{octyl}), 29.5 (C_{octyl}), 29.4 (C_{octyl}), 29.3 (C_{octyl}), 29.1 (C-6), 28.9 (C-6), 26.3 (C_{octyl}), 26.2 (C_{octyl}), 22.7(2) (C_{octyl}), 22.6(9) (C_{octyl}), 14.2 (C_{octyl}), 14.1 (C_{octyl}), 11.7 (C-10β), 11.5 (C-10α). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{53}H_{64}NaO_8$: 851.4493. Found 851.4501.



3.47α

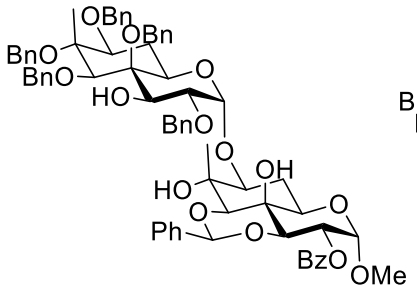


3.47β

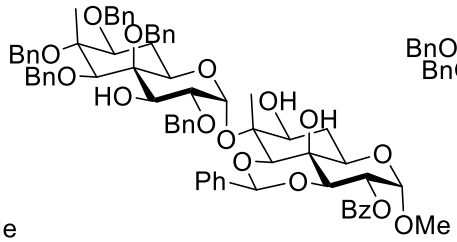
Racemic **cyclohexyl 2,4,7,8,9-penta-*O*-benzyl-1,5-α-bradyrhizopyranoside (3.47α)** and ***racemic*** **cyclohexyl 2,4,7,8,9-penta-*O*-benzyl-1,5-β-bradyrhizopyranoside (3.47β)**. Cesium carbonate (3.3 mg, 0.0.0101 mmol) was added to a cooled (0 °C) solution of **3.24** (24 mg, 0.0336 mmol) and trichloroacetonitrile (16 μL, 0.168 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt overnight then filtered through Celite® 545. The filtrate was concentrated and the crude product was used for the next step without further purification.

Cyclohexanol (37 μL, 0.349 mmol) and molecular sieves (~30 mg, activated powder 4 Å) were added to the crude trichloroacetimidate in Et_2O (1 mL). The mixture was stirred for an hour at rt then cooled to –40 °C and stirred for 15 min. TBSOTf (60 μL of a solution of TBSOTf (10 μL) in CH_2Cl_2 (1 mL)) was added and the mixture was stirred at –40 °C for 30 min. Et_3N (50 μL) was added and the reaction mixture was warmed to rt. The solvent was evaporated and the resulting crude product was purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **3.47α** and **3.47β** (26 mg, 93%, inseparable diastereomeric mixture 4:9) as a colorless oil. R_f 0.45 (4:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.45–7.23 (m, 25 H, Ar), 5.60 (d, 0.3 H, J = 12.3 Hz, C$\underline{H}_2$Ar), 5.40 (d, 0.7 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 5.24 (d, 0.3 H, J = 12.3 Hz, C$\underline{H}_2$Ar), 5.18 (d, 0.7 H, J = 11.6 Hz, C$\underline{H}_2$Ar), 5.06 (d, 0.7 H, J = 10.8 Hz, C$\underline{H}_2$Ar), 5.02 (d, 0.3 H, J = 10.6 Hz, C$\underline{H}_2$Ar), 4.99–4.94 (m, 1 H, C$\underline{H}_2$Ar and H-1α), 4.88–4.67 (m, 5 H, C$\underline{H}_2$Ar), 4.62 (d, 0.7 H, J = 11.7 Hz, C$\underline{H}_2$Ar), 4.59–4.52 (m, 1.3 H, C$\underline{H}_2$Ar, H-1β), 4.34 (d, 0.3 H, $J_{2,3}$ = 10.1 Hz, H-3α), 3.94 (d, 0.7 H, J = 9.4 Hz, H-3β), 3.89 (s, 0.7 H, OHβ), 3.86 (dd, 0.3 H, $J_{2,3}$ = 10.1 Hz, $J_{1,2}$ = 3.9 Hz, H-2α), 3.79–3.61 (m, 3.7 H, H-2β, H-5α, H-7, H-9α, H_{cyclo}), 3.59 (s, 0.7 H, H-9β), 3.55–3.47 (m, 0.3 H, H_{cyclo}α), 3.24 (dd, 0.7 H, $J_{5,6ax}$ = 10.8 Hz, $J_{5,6eq}$ = 5.0 Hz, H-5β), 2.23–1.74 (m, 8.7 H, H-6, H_{cyclo}), 1.70–1.63 (m, 3.3 H, H-10, H_{cyclo}), 1.62–1.17 (m, 6 H, H_{cyclo}); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.8 (Ar), 139.7 (Ar), 138.7 (Ar), 138.6 (Ar), 138.4 (Ar), 138.3 (Ar), 138.2 (Ar), 128.4(9) (Ar), 128.4(8) (Ar), 128.4 (Ar), 128.3(4) (Ar), 128.3(3) (Ar), 128.1(7) (Ar), 128.1(4) (Ar), 128.1 (Ar), 127.8 (Ar), 127.7(5) (Ar), 127.7(3) (Ar), 127.7(1) (Ar), 127.6(9) (Ar), 127.6(4) (Ar), 127.6(1) (Ar), 127.5(9) (Ar), 127.5(7) (Ar), 127.5 (Ar), 127.3 (Ar), 127.2 (Ar), 127.0 (Ar), 126.9 (Ar), 126.8 (Ar), 102.2 (C-1β), 95.7 (C-1α), 89.9 (C-9α), 89.5 (C-9β), 83.8 (C-8β), 83.6 (C-8α), 82.4 (C_{brady}β), 82.1 (C_{brady}α), 80.3 (C_{brady}), 79.8 (C-3β), 77.0 (C-4), 76.5 (C_{cyclo}α), 76.3 (C-2α), 76.1(4) (C-3α), 76.0(6) (C$\underline{H}_2$Ar), 75.8 (C$\underline{H}_2$Ar), 74.9 (C$\underline{H}_2$Ar), 72.9 (C$\underline{H}_2$Ar), 72.2 (C-5β), 71.8 (C$\underline{H}_2$Ar), 71.5

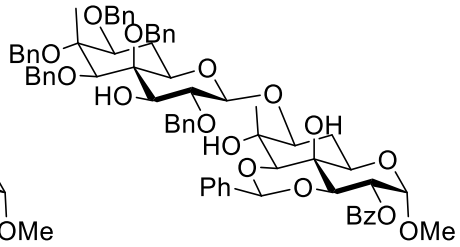
(<u>C</u>H$_2$Ar), 70.4 (C-), 68.9(3) (<u>C</u>H$_2$Ar), 68.8(8) (<u>C</u>H$_2$Ar), 67.4 (C$_{brady}$), 66.3 (<u>C</u>H$_2$Ar), 66.2 (<u>C</u>H$_2$Ar), 35.6 (C$_{cyclo}$), 33.8 (C$_{cyclo}$), 33.5 (C$_{cyclo}$), 32.0 (C$_{cyclo}$), 29.4 (C$_{cyclo}$), 29.2 (C-6), 29.0 (C-6), 25.7 (C$_{cyclo}$), 24.2 (C$_{cyclo}$), 24.1 (C$_{cyclo}$), 22.7 (C$_{cyclo}$), 11.7 (C-10β), 11.5 (C-10α). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{51}H_{58}NaO_8$: 821.4024. Found 821.4023.



D,D-4.50



D,D-4.51



D,D-4.52

Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-D-bradyrhizopyranosyl-(1→7)-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (D,D-4.50), methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-D-bradyrhizopyranosyl-(1→8)-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-D-L-bradyrhizopyranoside (D,D-4.51) and **methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-β-D-bradyrhizopyranosyl-(1→7)-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (D,D-4.52)**. Cesium carbonate (2 mg, 0.00675 mmol) was added to a cooled (0 °C) solution of **D-4.34** (18 mg, 0.0247 mmol) and trichloroacetonitrile (13 µL, 0.124 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt overnight then filtered through Celite® 545. The filtrate was concentrated and the crude trichloroacetimidate was used for the next step without further purification.

Molecular sieves (~20 mg, activated powder 4 Å) were added to a solution of **D-4.37α** (8.5 mg, 0.0180 mmol) in CH_2Cl_2 (0.5 mL) at rt. The mixture was stirred for 1 h then cooled to –40 °C and stirred for 15 min. TBSOTf (42 µL of a solution of TBSOTf (20 µL) in CH_2Cl_2 (2 mL)) was added followed by a solution of the crude trichloroacetimidate in CH_2Cl_2 (0.4 mL). The mixture was stirred at –40 °C for 30 min and Et_3N (50 µL) was added. The reaction mixture was warmed

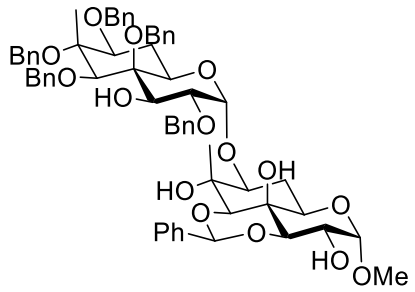
to rt and the solvent was evaporated. The resulting crude products were purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **D,D-4.50** (5.5 mg, 26%) and **D,D-4.51** and **D,D-4.52** (7.1 mg, 34%) as colorless oils. Another silica gel column chromatography (9:1 hexanes–acetone) was necessary to purify **D,D-4.50**. Compounds **D,D-4.51** and **D,D-4.52** were separated by preparative TLC (9:1 toluene–EtOAc) to give **D,D-4.51** (1.6 mg, 8%) and **D,D-4.52** (3.4 mg, 16%). (**D,D-4.50**): R_f 0.37 (3:2 hexanes–EtOAc); $[\alpha]_D$ +82.6 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.10–8.05 (m, 2 H, Ar), 7.61–7.52 (m, 3 H, Ar), 7.48–7.43 (m, 2 H, Ar), 7.41–7.23 (m, 28 H, Ar), 5.84 (s, 1 H, C<u>H</u>Ar), 5.58 (d, 1 H, *J* = 12.3 Hz, C<u>H</u>$_2$Ar), 5.54 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 3.7 Hz, H-2), 5.23 (d, 1 H, *J* = 12.3 Hz, C<u>H</u>$_2$Ar), 5.21 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 5.06 (d, 1 H, *J* = 10.6 Hz, C<u>H</u>$_2$Ar), 4.91 (d, 1 H, $J_{1',2'}$ = 3.9 Hz, H-1'), 4.81 (d, 1 H, *J* = 11.0 Hz, C<u>H</u>$_2$Ar), 4.80 (d, 1 H, *J* = 10.6 Hz, C<u>H</u>$_2$Ar), 4.75 (d, 1 H, *J* = 11.9 Hz, C<u>H</u>$_2$Ar), 4.73 (d, 1 H, *J* = 11.0 Hz, C<u>H</u>$_2$Ar), 4.68 (d, 1 H, *J* = 11.6 Hz, C<u>H</u>$_2$Ar), 4.56 (d, 1 H, *J* = 11.7 Hz, C<u>H</u>$_2$Ar), 4.54 (d, 1 H, *J* = 11.4 Hz, C<u>H</u>$_2$Ar), 4.36 (d, 1 H, $J_{2,3}$ = 9.9 Hz, H-3), 4.33 (d, 1 H, $J_{2',3'}$ = 10.1 Hz, H-3'), 3.94 (dd, 1 H, $J_{5',6'ax}$ = 12.1 Hz, $J_{5',6'eq}$ = 3.9 Hz, H-5'), 3.90 (dd, 1 H, $J_{2',3'}$ = 10.1 Hz, $J_{1',2'}$ = 3.9 Hz, H-2'), 3.86 (s, 1 H, C-3'-OH), 3.76 (dd, 1 H, $J_{5,6ax}$ = 11.4 Hz, $J_{5,6eq}$ = 4.6 Hz, H-5), 3.74 (s, 1 H, H-9'), 3.67 (s, 1 H, H-9), 3.61 (dd, 1 H, $J_{6'ax,7'}$ = 11.9 Hz, $J_{6'eq,7'}$ = 4.8 Hz, H-7'), 3.48–3.43 (m, 4 H, H-7, CH_3O), 2.95 (d, 1 H, $J_{4OH,5}$ = 1.7 Hz, C-4-OH), 2.72 (br s, 1H, C-8-OH), 2.17 (ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{6eq,6ax}$ = 12.1 Hz, $J_{6ax,7}$ = 12.1 Hz, H-6$_{ax}$), 2.08–2.00 (m, 2 H, H-6$_{eq}$, H-6'$_{ax}$), 1.97 (ddd, 1 H, $J_{6ax,6eq}$ = 11.9 Hz, $J_{5,6eq}$ = 4.4 Hz, $J_{6eq,7}$ = 4.4 Hz, H-6'$_{eq}$), 1.68 (s, 3 H, H-10'), 1.45 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 140.0 (Ar), 139.5 (Ar), 138.3 (Ar), 138.1 (Ar), 136.7 (Ar), 133.2 (Ar), 129.9 (Ar), 129.8 (Ar), 129.4 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.3 (Ar), 126.9 (Ar), 126.2 (Ar), 102.8 (<u>C</u>HAr), 98.6 (C-1), 97.5 (C-1'), 89.8 (C-9), 83.4 (C-8'), 82.9 (C-9'), 81.7 (C-7'), 81.2 (C-

7), 78.0 (C-3), 76.4 (C-2'), 76.2(3) (C-3'), 76.2(2) ($\underline{C}H_2Ar$), 75.2 (C-8), 73.4 ($\underline{C}H_2Ar$), 71.6 ($\underline{C}H_2Ar$), 69.9 (C-2), 69.5 (C-4), 69.0 ($\underline{C}H_2Ar$), 68.1 (C-5'), 67.4 (C-4'), 66.3 ($\underline{C}H_2Ar$), 64.3 (C-5), 56.0 (OCH_3), 28.9 (C-6/C-6'), 28.7 (C-6/C-6'), 18.0 (C-10), 11.6 (C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{70}H_{74}NaO_{16}$: 1193.4869. Found 1193.4887.

(**D,D-4.51**): R_f 0.35 (1:1 hexanes–EtOAc); $[\alpha]_D$ +47.6 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.08–8.04 (m, 2 H, Ar), 7.61–7.56 (m, 1 H, Ar), 7.55–7.51 (m, 2 H, Ar), 7.49–7.44 (m, 2 H, Ar), 7.42–7.22 (m, 26 H, Ar), 7.10–7.05 (m, 2 H, Ar), 5.79 (s, 1 H, C$\underline{H}$Ar), 5.56 (d, 1 H, J = 12.1 Hz, C$\underline{H}_2$Ar), 5.42 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 3.9 Hz, H-2), 5.21 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 5.18 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 5.15 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 5.10 (d, 1 H, $J_{1',2'}$ = 4.0 Hz, H-1'), 4.86 (d, 1 H, J = 11.7 Hz, C$\underline{H}_2$Ar), 4.71–4.64 (m, 4 H, 4 x C$\underline{H}_2$Ar), 4.52 (d, 1 H, $J_{2,3}$ = 9.9 Hz, H-3'), 4.34 (d, 2 H, J = 9.9 Hz, H-3), 4.33 (s, 1H, OH), 3.93 (dd, 1 H, $J_{2',3'}$ = 10.1 Hz, $J_{1',2'}$ = 4.0 Hz, H-2'), 3.85 (dd, 1 H, $J_{5',6'ax}$ = 12.5 Hz, $J_{5',6'eq}$ = 3.7 Hz, H-5'), 3.83 (s, 1 H, H-9'), 3.81 (s, 1 H, H-9), 3.75–3.69 (m, 3 H, H-5, H-7, C$\underline{H}_2$Ar), 3.64 (d, 1 H, J = 11.4 Hz, C$\underline{H}_2$Ar), 3.52 (br d, J = 1.1 Hz, OH), 3.43 (s, 3H, OCH_3), 3.41 (dd, 1 H, $J_{6'ax,7'}$ = 11.9 Hz, $J_{6'eq,7'}$ = 5.1 Hz, H-7'), 2.96 (d, 1 H, $J_{4OH,5}$ = 1.7 Hz, C-4-OH), 2.23 (ddd, 1 H, $J_{5,6ax}$ = 11.9 Hz, $J_{6eq,6ax}$ = 11.9 Hz, $J_{6ax,7}$ = 11.9 Hz, H-6_{ax}), 2.09 (ddd, 1 H, $J_{6eq,6ax}$ = 11.9 Hz, $J_{5,6eq}$ = 4.0 Hz, $J_{6eq,7}$ = 4.0 Hz, H-6_{eq}), 1.83 (ddd, 1 H, $J_{5',6'ax}$ = 12.3 Hz, $J_{6'eq,6'ax}$ = 12.3 Hz, $J_{6'ax,7'}$ = 12.3 Hz, H-$6'_{ax}$), 1.60 (s, 3 H, H-10'), 1.55–1.51 (m, 1 H, H-$6'_{eq}$), 1.51 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 139.6 (Ar), 139.7 (Ar), 138.3 (Ar), 137.8 (Ar), 137.4 (Ar), 137.1 (Ar), 133.1 (Ar), 129.8 (Ar), 129.4 (Ar), 128.9 (Ar), 128.7 (Ar), 128.6 (Ar), 128.4 (Ar), 128.2(4) (Ar), 128.1(9) (Ar), 128.1 (Ar), 127.9 (Ar), 127.8 (Ar), 127.3 (Ar), 127.1 (Ar), 127.0 (Ar), 126.9 (Ar), 125.8 (Ar), 101.6 ($\underline{C}$HAr), 98.5 (C-1), 90.5 (C-1'), 89.9 (C-9'), 83.5 (C-8'), 82.2 (C-7'), 81.9 (C-8), 78.9 (C-9), 78.0 (C-3), 77.6 (C-3')76.9 ($\underline{C}H_2$Ar), 74.9 (C-2'), 74.7 ($\underline{C}H_2$Ar), 70.4 ($\underline{C}H_2$Ar), 70.0 (C-2, C-5/C-7),

69.0 (CH_2Ar), 68.2 (C-4/C-4'), 68.1 (C-4/C-4'), 67.9 (C-5'), 66.1 (CH_2Ar), 64.9 (C-5/C-7), 55.9 (OCH_3), 29.9 (C-6), 28.6 (C-6'), 15.4 (C-10), 11.4 (C-10'). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{70}H_{78}NO_{16}$: 1188.5315. Found 1188.5343.

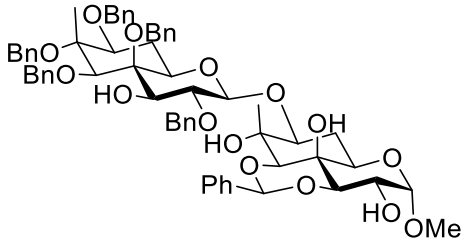
(**D,D-4.52**): R_f 0.36 (1:1 hexanes–EtOAc); $[\alpha]_D$ +46.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.09–8.05 (m, 2 H, Ar), 7.60–7.55 (m, 1 H, Ar), 7.52–7.22 (m, 32 H, Ar), 5.79 (s, 1 H, CHAr), 5.52 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 3.9 Hz, H-2), 5.38 (d, 1 H, *J* = 11.4 Hz, CH_2Ar), 5.20 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 5.13 (d, 1 H, *J* = 11.6 Hz, CH_2Ar), 5.08 (d, 1 H, *J* = 11.0 Hz, CH_2Ar), 4.93 (d, 1 H, *J* = 11.0 Hz, CH_2Ar), 4.83 (d, 1 H, *J* = 11.0 Hz, CH_2Ar), 4.79 (d, 1 H, *J* = 11.0 Hz, CH_2Ar), 4.75–4.70 (m, 4 H, 3 x CH_2Ar, H-1'), 4.52 (d, 1 H, *J* = 11.4 Hz, CH_2Ar), 4.33 (d, 1 H, $J_{2,3}$ = 9.9 Hz, H-3), 4.08 (s, 1 H, OH), 3.97 (d, 1 H, $J_{2',3'}$ = 9.2 Hz, H-3'), 3.86–3.79 (m, 2 H, H-2', H-5), 3.71 (dd, 1 H, $J_{6ax,7}$ = 11.9 Hz, $J_{6eq,7}$ = 4.8 Hz, H-7), 3.67 (s, 1 H, H-9), 3.64 (dd, 1 H, $J_{6'ax,7'}$ = 11.6 Hz, $J_{6'eq7'}$ = 5.1 Hz, H-7'), 3.60 (s, 1 H, H-9'), 3.46 (s, 3H, OCH_3), 3.26 (dd, 1 H, $J_{5',6'ax}$ = 11.6 Hz, $J_{5',6'eq}$ = 4.0 Hz, H-5'), 2.92 (d, 1 H, $J_{4OH,5}$ = 1.5 Hz, C-4-OH), 2.75 (br s, 1H, OH), 2.30–2.12 (m, 4 H, 2 x H-6, 2 x H-6'), 1.63 (s, 3 H, H-10'), 1.42 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 139.5(4) (Ar), 139.5(0) (Ar), 138.2 (Ar), 138.0 (Ar), 137.8 (Ar), 136.7 (Ar), 133.2 (Ar), 129.9 (Ar), 129.8 (Ar), 129.3 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4(1) (Ar), 128.3(6) (Ar), 128.3 (Ar), 128.2(4) (Ar), 128.1(6) (Ar), 128.0 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 127.3 (Ar), 127.1 (Ar), 127.0 (Ar), 126.2 (Ar), 105.4 (C-1'), 102.7 (CHAr), 98.6 (C-1), 89.2 (C-9'), 83.8 (C-8'), 82.6 (C-9/C-7/C-7'), 82.4(4) (C-9/C-7/C-7'), 82.4(0) (C-9/C-7/C-7'), 80.6 (C-3'), 80.3 (C-2'), 78.0 (C-3), 76.5 (C-4/C-4'), 76.1 (C-8), 75.8 (CH_2Ar), 74.9 (CH_2Ar), 72.4 (C-5'), 71.5 (CH_2Ar), 70.0 (C-2), 68.9 (CH_2Ar), 67.4 (C-4/C-4'), 66.2 (CH_2Ar), 64.9 (C-5), 56.1 (OCH_3), 30.9 (C-6/C-6'), 29.1 (C-6/C-6'), 17.6 (C-10), 11.7 (C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{70}H_{74}NaO_{16}$: 1193.4869. Found 1193.4897.



D,D-4.53

Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-D-bradyrhizopyranosyl-(1→7)-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (D,D-4.53). A solution of MeONa in MeOH (0.15 mL, 0.5 M in MeOH) was added to **D,D-4.50** (5.5 mg, 0.00470 mmol) in MeOH (3 mL). The mixture was stirred for 3 h at rt. Amberlite® IR120 H^+ form resin was added until neutral pH and the mixture was filtered. The filtrate was evaporated and the resulting crude product was purified by silica gel column chromatography (3:2 hexanes–EtOAc) to give **D,D-4.53** (3.9 mg, 78%) as a colorless oil. R_f 0.27 (2:3 hexanes–EtOAc); $[\alpha]_D$ +46.7 (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.61–7.56 (m, 2 H, Ar), 7.45–7.22 (m, 28 H, Ar), 5.79 (s, 1 H, C<u>H</u>Ar), 5.57 (d, 1 H, *J* = 12.3 Hz, C<u>H</u>$_2$Ar), 5.23 (d, 1 H, *J* = 12.1 Hz, C<u>H</u>$_2$Ar), 5.05 (d, 1 H, *J* = 10.8 Hz, C<u>H</u>$_2$Ar), 4.91 (d, 1 H, $J_{1',2'}$ = 3.9 Hz, H-1'), 4.90 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 4.80 (d, 1 H, *J* = 10.5 Hz, C<u>H</u>$_2$Ar), 4.78 (d, 1 H, *J* = 10.1 Hz, C<u>H</u>$_2$Ar), 4.73 (d, 1 H, *J* = 11.7 Hz, C<u>H</u>$_2$Ar), 4.73 (d, 1 H, *J* = 10.8 Hz, C<u>H</u>$_2$Ar), 4.67 (d, 1 H, *J* = 11.4 Hz, C<u>H</u>$_2$Ar), 4.56 (d, 1 H, *J* = 11.9 Hz, C<u>H</u>$_2$Ar), 4.53 (d, 1 H, *J* = 11.4 Hz, C<u>H</u>$_2$Ar), 4.32 (d, 1 H, $J_{2',3'}$ = 10.1 Hz, H-3'), 4.18 (ddd, 1 H, $J_{2,3}$ = 9.7 Hz, $J_{2,OH}$ = 9.7 Hz, $J_{1,2}$ = 3.9 Hz, H-2), 3.93 (dd, 1 H, $J_{5',6'ax}$ = 12.3 Hz, $J_{5',6'eq}$ = 3.9 Hz, H-5'), 3.93 (d, 1 H, $J_{2,3}$ = 9.5 Hz, H-3), 3.89 (dd, 1 H, $J_{2',3'}$ = 10.1 Hz, $J_{1',2'}$ = 3.9 Hz, H-2'), 3.86 (s, 1 H, C-3'-OH), 3.73 (s, 1 H, H-9'), 3.68 (dd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{5,6eq}$ = 4.4 Hz, H-5), 3.60 (s, 1 H, H-9), 3.59 (dd, 1 H, $J_{6'ax,7'}$ = 11.9 Hz, $J_{6'eq,7'}$ = 4.8 Hz, H-7'), 3.52 (s, 3 H, CH_3O), 3.44 (dd, 1 H, $J_{6ax,7}$ = 11.9 Hz, $J_{6eq,7}$ = 4.8 Hz, H-7), 2.83 (d, 1 H, $J_{4OH,5}$ = 1.5 Hz, C-4-OH), 2.68 (br s, 1H, C-8-OH), 2.15–1.92 (m, 5 H, 2 x H-6, 2 x H-6', C-2-

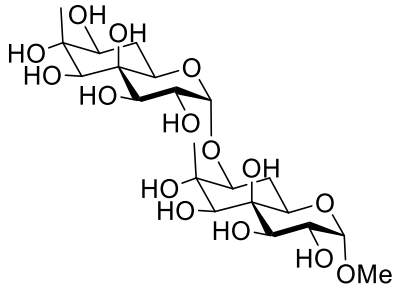
OH), 1.67 (s, 3 H, H-10'), 1.43 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 140.0 (Ar), 139.5 (Ar), 138.3 (Ar), 138.1 (Ar), 136.7 (Ar), 129.5 (Ar), 128.5(4) (Ar), 128.5(0) (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 127.3 (Ar), 126.9 (Ar), 126.3 (Ar), 103.2 (CHAr), 100.7 (C-1), 97.4 (C-1'), 89.8 (C-9'), 83.4 (C-8'), 82.9 (C-9), 81.8 (C-7'), 81.3 (C-3), 81.1 (C-7), 76.8 (C-4'), 76.3(4) (C-3'/C-2'), 76.2(5) (C-2'/C-3'), 76.2 (CH_2Ar), 75.1 (C-8), 73.4 (CH_2Ar), 71.6 (CH_2Ar), 68.9 (CH_2Ar), 68.1 (C-5'), 67.6 (C-2), 67.2 (C-4), 66.3 (CH_2Ar), 65.0 (C-5), 56.0 (OCH_3), 28.9 (C-6/C-6'), 28.7 (C-6/C-6'), 17.9 (C-10), 11.4 (C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{63}H_{70}NaO_{15}$: 1089.4607. Found 1089.4617.



D,D-4.57

Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-β-D-bradyrhizopyranosyl-(1→7)-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (D,D-4.57). A solution of MeONa in MeOH (0.15 mL, 0.5 M in MeOH) was added to **D,D-4.52** (3.0 mg, 0.00256 mmol) in MeOH (3 mL). The mixture was stirred for 3 h at rt. Amberlite® IR120 H^+ form resin was added until the pH of the solution was neutral and then the mixture was filtered. The filtrate was concentrated and the resulting crude product was purified by silica gel column chromatography (3:2 hexanes–EtOAc) to give **D,D-4.57** (2.7 mg, 99%) as a colorless oil. R_f 0.23 (2:3 hexanes–EtOAc); $[\alpha]_D$ +24.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.57–7.53 (m, 2 H, Ar), 7.43–7.23 (m, 28 H, Ar), 5.75 (s, 1 H, CHAr), 5.37 (d, 1 H, J = 11.6 Hz, CH_2Ar), 5.13 (d, 1 H, J = 11.6 Hz, CH_2Ar), 5.08 (d, 1 H, J = 11.0 Hz, CH_2Ar), 4.92 (d, 1 H, J = 11.2 Hz, CH_2Ar), 4.89 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 4.82 (d, 1 H, J = 11.0 Hz, CH_2Ar), 4.79 (d, 1 H, J = 11.0 Hz, CH_2Ar), 7.43–7.23 (m, 4 H, 3 x CH_2Ar, H-1'), 4.52 (d, 1 H, J

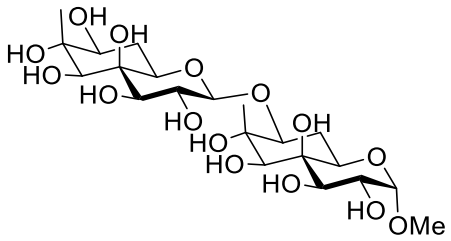
= 11.6 Hz, C<u>H</u>$_2$Ar), 4.17 (ddd, 1 H, $J_{2,3}$ = 9.4 Hz, $J_{2,OH}$ = 9.4 Hz, $J_{1,2}$ = 3.9 Hz, H-2), 4.07 (s, 1 H, OH), 3.96 (d, 1 H, $J_{2',3'}$ = 9.0 Hz, H-3'), 3.90 (d, 1 H, $J_{2,3}$ = 9.4 Hz, H-3), 3.80 (dd, 1 H, $J_{2',3'}$ = 9.0 Hz, $J_{1',2'}$ = 7.7 Hz, H-2'), 3.74 (br dd, 1 H, $J_{5',6'ax}$ = 10.8 Hz, $J_{5',6'eq}$ = 5.9 Hz, H-5), 3.68 (dd, 1 H, $J_{5,6ax}$ = 10.8 Hz, $J_{5,6eq}$ = 5.7 Hz, H-7), 3.64 (dd, 1 H, $J_{6'ax,7'}$ = 11.4 Hz, $J_{6'eq,7'}$ = 5.3 Hz, H-7'), 3.60–3.57 (m, 2 H, H-9, H-9'), 3.52 (s, 3 H, CH_3O), 3.25 (dd, 1 H, $J_{6ax,7}$ = 11.6 Hz, $J_{6eq,7}$ = 4.2 Hz, H-5'), 2.80 (d, 1 H, $J_{4OH,5}$ = 1.7 Hz, C-4-OH), 2.25–2.11 (m, 4 H, 2 x H-6, 2 x H-6'), 2.72 (br s, 1H, C-2-OH), 1.63 (s, 3 H, H-10'), 1.39 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.5(2) (Ar), 139.5(1) (Ar), 138.2 (Ar), 138.0 (Ar), 137.8 (Ar), 136.7 (Ar), 129.4 (Ar), 128.6 (Ar), 128.4(4) (Ar), 128.4(2) (Ar), 128.3(4) (Ar), 128.2(8) (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 127.3 (Ar), 127.1 (Ar), 127.0 (Ar), 126.3 (Ar), 105.3 (C-1'), 103.1 (<u>C</u>HAr), 100.8 (C-1), 89.1 (C-9'), 83.8 (C-8'), 82.5 (C-9), 82.4(3) (C-7/C-7'), 82.3(9) (C-7/C-7'), 81.3 (C-3), 80.5 (C-3'), 80.2 (C-2'), 76.5 (C-4/C-4'), 76.0 (C-8), 75.8 (<u>C</u>H$_2$Ar), 74.9 (<u>C</u>H$_2$Ar), 72.4 (C-5'), 71.5 (<u>C</u>H$_2$Ar), 68.9 (<u>C</u>H$_2$Ar), 67.6 (C-2), 67.2 (C-4/C-4'), 66.2 (<u>C</u>H$_2$Ar), 65.2 (C-5), 56.1 (OCH_3), 31.0 (C-6/C-6'), 29.1 (C-6/C-6'), 17.5 (C-10), 11.6 (C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{63}H_{70}NaO_{15}$: 1089.4607. Found 1089.4628.



D,D-4.54

Methyl 1,5-α-D-bradyrhizopyranosyl-(1→7)-1,5-α-D-bradyrhizopyranoside (D,D-4.54). Palladium hydroxide on carbon (7.0 mg, 0.00997 mmol, 20 wt. % loading) was added to a solution of **D,D-4.53** (3.9 mg, 0.00365 mmol) in MeOH (4 mL) under Ar. The reaction mixture was then

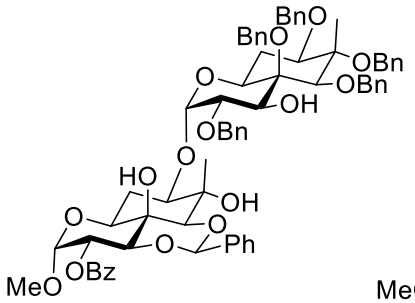
placed under a positive pressure of H_2(g) and stirred overnight. The palladium hydroxide on carbon was filtered through Celite® and the filtrate was concentrated. The resulting crude product was purified by reverse phase column chromatography (C-18 silica gel, H_2O) to give **D,D-4.54** in quantitative yield and as a colorless oil. $[\alpha]_D$ +103.6 (*c* 0.1, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 4.89 (d, 1 H, $J_{1',2'}$ = 4.1 Hz, H-1'), 4.66 (d, 1 H, $J_{1,2}$ = 4.1 Hz, H-1), 4.10 (dd, 1 H, $J_{5,6ax}$ = 12.0 Hz, $J_{5,6eq}$ = 4.4 Hz, H-5/H-5'), 3.87 (d, 1 H, $J_{2,3}$ = 9.7 Hz, H-3), 3.80 (d, 1 H, $J_{2',3'}$ = 9.5 Hz, H-3'), 3.77 (dd, 1 H, $J_{2,3}$ = 9.7 Hz, $J_{1,2}$ = 4.1 Hz, H-2), 3.76 (dd, 1 H, $J_{2',3'}$ = 9.5 Hz, $J_{1',2'}$ = 3.8 Hz, H-2'), 3.64–3.59 (m, 1 H, H-5/H-5'), 3.55–3.49 (m, 4 H, H-7, H-7', H-9, H-9'), 3.39 (s, 3 H, OCH_3), 1.94–1.79 (m, 4 H, H-6, H-6'), 1.35 (s, 3 H, H-10'/H-10), 1.28 (s, 3 H, H-10'/H-10); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 101.6 (C-1), 98.2 (C-1'), 80.8 (C-9/C-9'), 79.5 (C-7/C-7'), 79.4 (C-9/C-9'), 78.6 (C-4/C-8), 77.7 (C-8/C-8'/C-4/C-4'), 77.0 (C-3/C-3'), 76.9 (C-3/C-3'), 74.4 (C-8/C-8'/C-4/C-4'), 74.2 (C-8/C-8'/C-4/C-4'), 74.1 (C-8/C-8'/C-4/C-4'), 70.9 (C-2, C-2'), 67.4 (C-5/C-5'), 67.1 (C-5/C-5'), 55.8 (OCH_3), 32.5 (C-6/C-6'), 29.3 (C-6/C-6'), 16.2 (C-10/C-10'), 15.5 (C-10/C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{21}H_{36}NaO_{15}$: 551.1946. Found 551.1941.



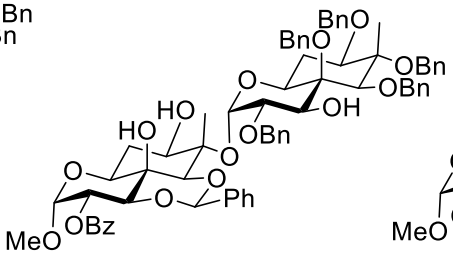
D,D-4.58

Methyl 1,5-β-D-bradyrhizopyranosyl-(1→7)-1,5-α-D-bradyrhizopyranoside (D,D-4.58). Palladium hydroxide on carbon (5.3 mg, 0.00752 mmol, 20 wt. % loading) was added to a solution of **D,D-4.57** (2.8 mg, 0.00262 mmol) in MeOH (3 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium hydroxide on carbon was filtered through Celite® and the filtrate concentrated. The resulting crude product was purified

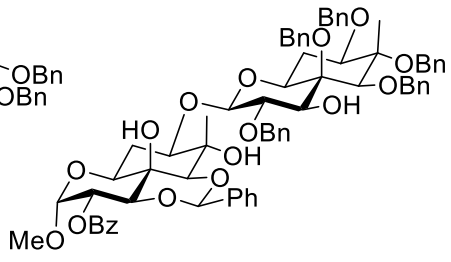
by reverse phase column chromatography (C-18 silica gel, H_2O) to give **D,D-4.58** in quantitative yield and as a colorless oil. $[\alpha]_D$ +24.0 (*c* 0.1, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 4.66 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H-1), 4.53 (d, 1 H, $J_{1',2'}$ = 7.9 Hz, H-1'), 3.79 (d, 1 H, $J_{2,3}$ = 9.5 Hz, H-3), 3.75 (dd, 1 H, $J_{2,3}$ = 9.7 Hz, $J_{1,2}$ = 4.1 Hz, H-2), 3.66 (dd, 1 H, $J_{5,6ax}$ = 12.3 Hz, $J_{5,6ax}$ = 4.4 Hz, H-5/H-5'), 3.62–3.58 (m, 2 H, H-3', H-7/H-7'), 3.54 (dd, 1 H, $J_{2',3'}$ = 9.2 Hz, $J_{1',2'}$ = 7.9 Hz, H-2'), 3.52 (s, 1 H, H-9/H-9'), 3.51 (dd, 1 H, $J_{6ax,7}$ = 12.3 Hz, $J_{6eq,7}$ = 4.1 Hz, H-7/H-7'), 3.47 (s, 1 H, H-9/H-9'), 3.40 (s, 3 H, OCH_3), 3.38 (dd, 1 H, $J_{5,6ax}$ = 11.6 Hz, $J_{5,6ax}$ = 4.0 Hz, H-5/H-5'), 2.03 (ddd, 1 H, $J_{6eq,6ax}$ = 12.3 Hz, $J_{5,6eq}$ = 4.6 Hz, $J_{6eq,7}$ = 4.6 Hz, H-6_{eq}/H-6'$_{eq}$), 1.97 (ddd, 1 H, $J_{5,6ax}$ = 12.3 Hz, $J_{6eq,6ax}$ = 12.3 Hz, $J_{6ax,7}$ = 12.3 Hz, H-6_{ax}/H-6'$_{ax}$), 1.96 (ddd, 1 H, $J_{5,6ax}$ = 12.0 Hz, $J_{6eq,6ax}$ = 12.0 Hz, $J_{6ax,7}$ = 12.0 Hz, H-6_{ax}/H-6'$_{ax}$), 1.85 (ddd, 1 H, $J_{6eq,6ax}$ = 12.0 Hz, $J_{5,6eq}$ = 4.4 Hz, $J_{6eq,7}$ = 4.4 Hz, H-6_{eq}/H-6'$_{eq}$), 1.36 (s, 3 H, H-10/H-10'), 1.28 (s, 3 H, H-10/H-10'); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 106.7 (C-1'), 101.6 (C-1), 84.3 (C-3'/C-7/C-7'), 80.7 (C-9'/C-9), 80.2 (C-9'/C-9), 80.1 (C-3'/C-7/C-7'), 78.6 (C-8/C-8'/C-4/C-4'), 78.5 (C-8/C-8'/C-4/C-4'), 77.0 (C-3), 74.0(3) (C-3'/C-7/C-7'), 73.9(8) (C-8/C-8'/C-4/C-4'), 73.8 (C-2'), 73.6 (C-8/C-8'/C-4/C-4'), 72.2 (C-2), 70.9 (C-5/C-5'), 67.1 (C-5/C-5'), 55.9 (OCH_3), 33.1 (C-6/C-6'), 32.3 (C-6/C-6'), 16.4 (C-10/C-10'), 15.4 (C-10/C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{21}H_{36}NaO_{15}$: 551.1946. Found 551.1942.



L,L-4.50



L,L-4.51

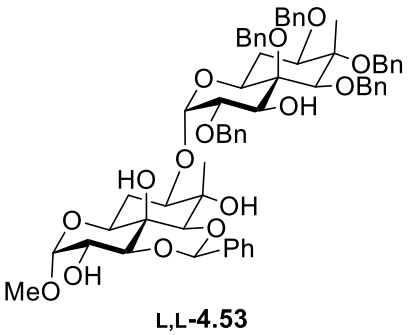


L,L-4.52

2,4,7,8,9-Penta-*O*-benzyl-1,5-α-L-bradyrhizopyranosyl-(1→7)-2-*O*-benzoyl-3,9-*O*-benzylidene-1-*O*-methyl-1,5-α-L-bradyrhizopyranoside (L,L-4.50), 2,4,7,8,9-Penta-*O*-benzyl-

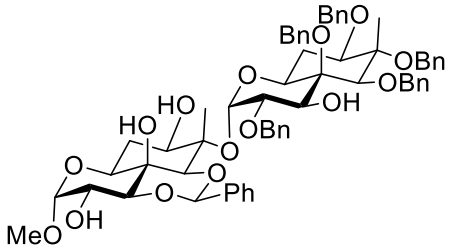
1,5-α-L-bradyrhizopyranosyl-(1→8)-2-*O*-benzoyl-3,9-*O*-benzylidene-1-*O*-methyl-1,5-α-L-bradyrhizopyranoside (L,L-4.51) and **2,4,7,8,9-Penta-*O*-benzyl-1,5-β-L-bradyrhizopyranosyl-(1→7)-2-*O*-benzoyl-3,9-*O*-benzylidene-1-*O*-methyl-1,5-α-L-bradyrhizopyranoside (L,L-4.52)**. Cesium carbonate (3 mg, 0.00921 mmol) was added to a cooled (0 °C) solution of **L-4.34** (16.3 mg, 0.0190 mmol) and trichloroacetonitrile (10 μL, 0.0949 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt overnight then filtered through Celite® 545. The filtrate was concentrated and the crude trichloroacetimidate was used in the next step without further purification.

Molecular sieves (~20 mg, activated powder 4 Å) were added to a solution of **L-4.37α** (5.4 mg, 0.0114 mmol) in CH_2Cl_2 (0.5 mL) at rt. The mixture was stirred for 1 h then cooled to –40 °C and stirred for 15 min. TBSOTf (52 μL of a solution of TBSOTf (20 μL) in CH_2Cl_2 (2 mL)) was added followed by a solution of the crude trichloroacetimidate in CH_2Cl_2 (0.4 mL). The mixture was stirred at –40 °C for 30 min and Et_3N (50 μL) was added. The reaction mixture was warmed to rt and the solvent was evaporated. The resulting crude products were purified by silica gel column chromatography (9:1 hexanes–EtOAc and 9:1 hexanes–acetone) to give **L,L-4.50** (5.5 mg, 42%) and **L,L-4.51** and **L,L-4.52** (7.5 mg, 58%) as colorless oils. Another silica gel column (9:1 hexanes–acetone) was necessary to purify **L,L-4.50**. Disaccharides **L,L-4.51** and **L,L-4.52** were separated by preparative TLC (9:1 toluene–EtOAc) to give **L,L-4.51** (2.3 mg, 18%) and **L,L-4.52** (1.8 mg, 14%). The R_f, ^1H NMR, ^{13}C NMR and MS correspond to that obtained for compounds **D,D-4.50**, **D,D-4.51** and **D,D-4.52** previously described. (**L,L-4.50**): $[\alpha]_D$ –91.0 (*c* 0.1, $CHCl_3$). (**L,L-4.51**): $[\alpha]_D$ –58.8 (*c* 0.1, $CHCl_3$). (**L,L-4.52**): $[\alpha]_D$ –61.6 (*c* 0.1, $CHCl_3$).



L,L-4.53

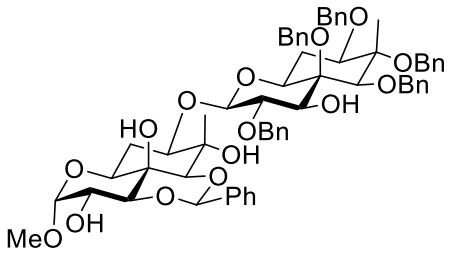
Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-L-bradyrhizopyranosyl-(1→7)-3,9-*O*-benzylidene-1,5-α-L-bradyrhizopyranoside (L,L-4.53). A solution of MeONa in MeOH (0.15 mL, 0.5 M in MeOH) was added to **L,L-4.50** (5.5 mg, 0.00470 mmol) in MeOH (3 mL). The mixture was stirred for 3 h at rt. Amberlite® IR120 H^+ form resin was added until the pH of the solution was neutral. The resin was filtered off, and the filtrate was concentrated. The filtrate was concentrated and the resulting crude product was purified by silica gel column chromatography (3:2 hexanes–EtOAc) to give **L,L-4.53** (4.2 mg, 84%) as a colorless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS correspond to that obtained for compound **D,D-4.53** previously described. $[\alpha]_D$ –70.0 (*c* 0.1, $CHCl_3$).



L,L-4.55

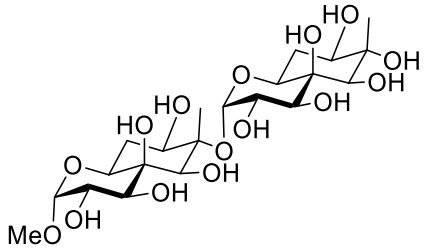
Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-L-bradyrhizopyranosyl-(1→8)-3,9-*O*-benzylidene-1,5-α-L-bradyrhizopyranoside (L,L-4.55). A solution of MeONa in MeOH (0.15 mL, 0.5 M in MeOH) was added to **L,L-4.51** (2.3 mg, 0.00196 mmol) in MeOH (3 mL). The mixture was stirred for 3 h at rt. Amberlite® IR120 H^+ form resin was added until the pH of the solution was neutral and then the mixture was filtered. The filtrate was concentrated and the resulting crude product was purified by silica gel column chromatography (3:2 hexanes–EtOAc) to give **L,L-4.55** (1.7 mg,

81%) as a colorless oil. R_f 0.21 (2:3 hexanes–EtOAc); $[\alpha]_D$ –26.4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.57–7.55 (m, 2 H, Ar), 7.38–7.31 (m, 7 H, Ar), 7.30–7.19 (m, 19 H, Ar), 7.08–7.05 (m, 2 H, Ar), 5.71 (s, 1 H, C<u>H</u>Ar), 5.51 (d, 1 H, *J* = 12.0 Hz, C<u>H</u>$_2$Ar), 5.17 (d, 1 H, *J* = 11.0 Hz, C<u>H</u>$_2$Ar), 5.11 (d, 1 H, *J* = 11.9 Hz, C<u>H</u>$_2$Ar), 5.04 (d, 1 H, $J_{1',2'}$ = 4.0 Hz, H-1'), 4.84 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H-1), 4.83 (d, 1 H, *J* = 11.9 Hz, C<u>H</u>$_2$Ar), 4.67–4.61 (m, 4 H, 4 x C<u>H</u>$_2$Ar), 4.48 (d, 1 H, $J_{2',3'}$ = 10.0 Hz, H-3'), 4.30 (s, 1 H, OH), 4.06 (ddd, 1 H, $J_{2,3}$ = 9.4 Hz, $J_{2,OH}$ = 9.4 Hz, $J_{1,2}$ = 3.8 Hz, H-2), 3.89 (dd, 1 H, $J_{2',3'}$ = 10.0 Hz, $J_{1',2'}$ = 3.8 Hz, H-2'), 3.87 (d, 1 H, $J_{2,3}$ = 9.5 Hz, H-3), 3.80 (dd, 1 H, $J_{5',6'ax}$ = 12.4 Hz, $J_{5',6'eq}$ = 3.6 Hz, H-5'), 3.79 (s, 1 H, H-9'), 3.69 (s, 1 H, H-9), 3.66 (d, 1 H, $J_{2,3}$ = 11.4 Hz, C<u>H</u>$_2$Ar), 3.65 (br dd, 1 H, $J_{5,6ax}$ = 11.4 Hz, $J_{5,6eq}$ = 3.7 Hz, H-7), 3.61 (d, 1 H, $J_{2,3}$ = 11.4 Hz, C<u>H</u>$_2$Ar), 3.61–3.57 (m, 1 H, H-5), 3.51 (br d, 1 H, *J* = 1.2 Hz, OH), 3.48 (s, 3 H, CH_3O), 3.36 (dd, 1 H, $J_{6'ax,7'}$ = 11.9 Hz, $J_{6'eq,7'}$ = 4.7 Hz, H-7'), 2.82 (d, 1 H, $J_{4OH,5}$ = 1.7 Hz, C-4-OH), 2.16 (ddd, 1 H, $J_{5,6ax}$ = 11.9 Hz, $J_{6eq,6ax}$ = 11.9 Hz, $J_{6ax,7}$ = 11.9 Hz, H-6$_{ax}$), 2.04 (ddd, 1 H, $J_{6eq,6ax}$ = 11.9 Hz, $J_{5,6eq}$ = 4.1 Hz, $J_{6eq,7}$ = 4.1 Hz, H-6$_{eq}$), 2.00 (br d, 1 H, $J_{2,OH}$ = 9.7 Hz, C-2-OH), 1.78 (ddd, 1 H, $J_{5',6'ax}$ = 12.0 Hz, $J_{6'eq,6'ax}$ = 12.0 Hz, $J_{6'ax,7'}$ = 12.0 Hz, H-6'$_{ax}$), 1.56 (s, 3 H, H-10'), 1.50–1.46 (m, 1 H, H-6'$_{eq}$), 1.46 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.6 (Ar), 139.4 (Ar), 138.3 (Ar), 137.8 (Ar), 137.4 (Ar), 137.2 (Ar), 129.4 (Ar), 128.9 (Ar), 128.7 (Ar), 128.6(4) (Ar), 128.5(9) (Ar), 128.4 (Ar), 128.2(3) (Ar), 128.2(0) (Ar), 128.1 (Ar), 127.9 (Ar), 127.7 (Ar), 127.3 (Ar), 127.2 (Ar), 127.0 (Ar), 126.9 (Ar), 126.0 (Ar), 101.9 (<u>C</u>HAr), 100.7 (C-1), 90.4 (C-1'), 89.8 (C-9'), 83.5 (C-8'), 82.3 (C-7'), 81.8 (C-8), 81.4 (C-3), 78.8 (C-9), 77.4 (C-3'), 76.9 (<u>C</u>H$_2$Ar), 76.4 (C-4/C-4'), 74.9 (C-2'), 74.7 (<u>C</u>H$_2$Ar), 70.4 (<u>C</u>H$_2$Ar), 68.9 (<u>C</u>H$_2$Ar), 68.0(4) (C-5'), 68.0(0) (C-4/C-4'), 67.8 (C-2), 67.6 (C-7), 66.1 (<u>C</u>H$_2$Ar), 65.2 (C-5), 55.9 (OCH_3), 29.4 (C-6), 28.6 (C-6'), 15.4 (C-10), 11.4 (C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{63}H_{70}NaO_{15}$: 1089.4607. Found 1089.4606.



L,L-4.57

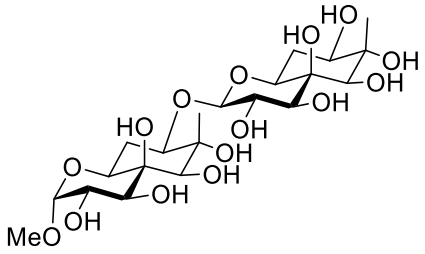
Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-β-L-bradyrhizopyranosyl-(1→7)-3,9-*O*-benzylidene-1,5-α-L-bradyrhizopyranoside (L,L-4.57). A solution of MeONa in MeOH (0.15 mL, 0.5 M in MeOH) was added to **L,L-4.52** (1.8 mg, 0.00154 mmol) in MeOH (3 mL). The mixture was stirred for 3 h at rt. Amberlite® IR120 H^+ form resin was added until the pH of the solution was neutral and the mixture was filtered. The filtrate was concentrated and the resulting crude product was purified by silica gel column chromatography (3:2 hexanes–EtOAc) to give **L,L-4.57** (1.4 mg, 88%) as a colorless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained for compound **D,D-4.57** previously described. $[\alpha]_D$ –23.6 (*c* 0.1, $CHCl_3$).



L,L-4.56

Methyl 1,5-α-L-bradyrhizopyranosyl-(1→8)-1,5-α-L-bradyrhizopyranoside (L,L-4.56). Palladium on carbon (3.4 mg, 0.00327 mmol, 10 wt. % loading) was added to a solution of **L,L-4.55** (1.7 mg, 0.00159 mmol) in MeOH (2 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium on carbon was filtered and the filtrate was concentrated. The resulting crude product was purified by reverse phase column chromatography (C-18 silica gel, H_2O) to give **L,L-4.56** in quantitative yield and as a colorless oil.

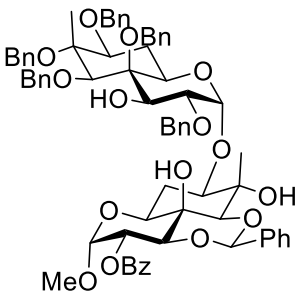
$[\alpha]_D$ –97.1 (*c* 0.07, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 5.35 (d, 1 H, $J_{1',2'}$ = 4.1 Hz, H-1'), 4.66 (d, 1 H, $J_{1,2}$ = 4.1 Hz, H-1), 3.99 (dd, 1 H, $J_{5,6ax}$ = 12.3 Hz, $J_{5,6eq}$ = 4.1 Hz, H-5/H-5'), 3.84 (d, 1 H, $J_{2,3}$ = 9.7 Hz, H-3/H-3'), 3.82 (d, 1 H, $J_{2,3}$ = 9.5 Hz, H-3/H-3'), 3.79–3.73 (m, 3 H, H-2, H-2', H-9/H-9'), 3.73–3.69 (m, 2 H, H-7/H-7', H-5/H-5'), 3.55 (dd, 1 H, $J_{5,6ax}$ = 12.0 Hz, $J_{5,6eq}$ = 4.4 Hz, H-7/H-7'), 3.52 (s, 1 H, H-9/H-9'), 3.39 (s, 3 H, OCH_3), 1.95 (ddd, 1 H, $J_{5,6ax}$ = 12.0 Hz, $J_{6eq,6ax}$ = 12.0 Hz, $J_{6ax,7}$ = 12.0 Hz, H-6_{ax}/H-$6'_{ax}$), 1.87 (ddd, 1 H, $J_{5,6ax}$ = 12.3 Hz, $J_{6eq,6ax}$ = 12.3 Hz, $J_{6ax,7}$ = 12.3 Hz, H-6_{ax}/H-$6'_{ax}$), 1.78 (ddd, 1 H, $J_{6eq,6ax}$ = 12.0 Hz, $J_{5,6eq}$ = 4.1 Hz, $J_{6eq,7}$ = 4.1 Hz, H-6_{eq}/H-$6'_{eq}$), 1.75 (ddd, 1 H, $J_{6eq,6ax}$ = 11.8 Hz, $J_{5,6eq}$ = 4.1 Hz, $J_{6eq,7}$ = 4.1 Hz, H-6_{eq}/H-$6'_{eq}$), 1.39 (s, 3 H, H-10'/H-10), 1.29 (s, 3 H, H-10'/H-10); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 101.6 (C-1), 94.2 (C-1'), 85.7 (C-8/C-4/C-4'/C-8'), 80.8 (C-9/C-9'), 79.8 (C-9/C-9'), 78.5 (C-8/C-4/C-4'/C-8'), 77.0 (C-3/C-3'), 76.9 (C-3/C-3'), 74.4 (C-8/C-4/C-4'/C-8'), 74.3 (C-8/C-4/C-4'/C-8'), 74.2 (C-7/C-7'), 72.1 (C-7/C-7'), 71.1 (C-2/C-2'), 70.9 (C-2/C-2'), 67.7 (C-5/C-5'), 66.7 (C-5/C-5'), 55.8 (OCH_3), 32.7 (C-6/C-6'), 32.4 (C-6/C-6'), 15.5 (C-10/C-10'), 12.4 (C-10/C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{21}H_{36}NaO_{15}$: 551.1946. Found 551.1944.



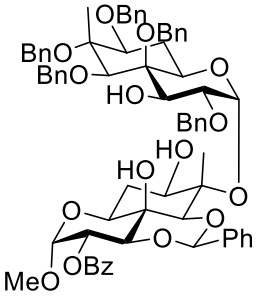
L,L-4.58

Methyl 1,5-β-L-bradyrhizopyranosyl-(1→7)-1,5-α-L-bradyrhizopyranoside (L,L-4.58). Palladium on carbon (2.6 mg, 0.00245 mmol, 10 wt. % loading) was added to a solution of **L,L-4.57** (1.4 mg, 0.00131 mmol) in MeOH (1.5 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium on carbon was filtered and the filtrate was concentrated. The resulting crude product was purified by reverse phase column

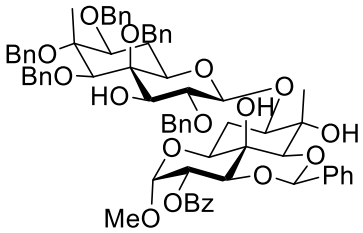
chromatography (C-18 silica gel, H_2O) to give **L,L-4.58** in quantitative yield and as a colorless oil. The R_f, ^1H NMR, ^{13}C NMR and MS data correspond to that obtained for compound **D,D-4.58** previously described. $[\alpha]_D$ –17.1 (*c* 0.07, CH_3OH).



D,L-4.50



D,L-4.51



D,L-4.52

Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-D-bradyrhizopyranosyl-(1→7)-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-L-bradyrhizopyranoside (D,L-4.50), methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-D-bradyrhizopyranosyl-(1→8)-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-L-bradyrhizopyranoside (D,L-4.51) methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-β-D-bradyrhizopyranosyl-(1→7)-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-L-bradyrhizopyranoside (D,L-4.52). Cesium carbonate (3 mg, 0.00921 mmol) was added to a cooled (0 °C) solution of **D-4.34** (23.9 mg, 0.0333 mmol) and trichloroacetonitrile (17 µL, 0.167 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt overnight then filtered through Celite® 545. The filtrate was concentrated and the crude trichloroacetimidate was used in the next step without further purification.

Molecular sieves (~20 mg, activated powder 4 Å) were added to a solution of **L-4.37α** (8.1 mg, 0.0171 mmol) in CH_2Cl_2 (0.5 mL) at rt. The mixture was stirred for 1 h and then cooled to –40 °C and stirred for 15 min. TBSOTf (67 µL of a solution of TBSOTf (10 µL) in CH_2Cl_2 (1 mL)) was added followed by a solution of the crude trichloroacetimidate in CH_2Cl_2 (0.4 mL). The mixture was stirred at –40 °C for 30 min and Et_3N (50 µL) was added. The reaction mixture was warmed

to rt and the solvent was evaporated. The resulting crude products were purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **D,L-4.50** (7.6 mg, 38%) and **D,L-4.51** and **D,L-4.52** (6.8 mg, 34%) as colorless oils. Another silica gel column (9:1 hexanes–acetone) was necessary to purify **D,L-4.50**. Disaccharides **D,L-4.51** and **D,L-4.52** were separated by preparative TLC (1:1 hexanes–EtOAc) to give **D,L-4.51** (5.2 mg, 26%) and **D,L-4.52** (1.1 mg, 6%). (**D,L-4.50**): R_f 0.36 (3:2 hexanes–EtOAc); $[\alpha]_D$ –25.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.10–8.06 (m, 2 H, Ar), 7.61–7.52 (m, 3 H, Ar), 7.48–7.44 (m, 2 H, Ar), 7.41–7.22 (m, 28 H, Ar), 5.86 (s, 1 H, C<u>H</u>Ar), 5.53 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 3.9 Hz, H-2), 5.51 (d, 1 H, *J* = 10.6 Hz, C<u>H</u>$_2$Ar), 5.22 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 5.20 (d, 1 H, *J* = 11.0 Hz, C<u>H</u>$_2$Ar), 5.17 (d, 1 H, *J* = 11.9 Hz, C<u>H</u>$_2$Ar), 4.85 (d, 1 H, $J_{1',2'}$ = 3.9 Hz, H-1'), 4.83 (d, 1 H, *J* = 11.0 Hz, C<u>H</u>$_2$Ar), 4.82 (d, 1 H, *J* = 11.9 Hz, C<u>H</u>$_2$Ar), 4.75–4.68 (m, 4 H, 4 x C<u>H</u>$_2$Ar), 4.54 (d, 1 H, *J* = 11.4 Hz, C<u>H</u>$_2$Ar), 4.42 (d, 1 H, $J_{2',3'}$ = 10.1 Hz, H-3'), 4.38 (d, 1 H, $J_{2,3}$ = 10.1 Hz, H-3), 4.27 (s, 1 H, OH), 3.88 (dd, 1 H, $J_{2',3'}$ = 9.9 Hz, $J_{1',2'}$ = 3.9 Hz, H-2'), 3.86–3.81 (m, 2 H, H-5, H-9'), 3.78 (s, 1 H, H-9), 3.76 (dd, 1 H, $J_{5',6'ax}$ = 11.9 Hz, $J_{5',6'eq}$ = 3.9 Hz, H-5'), 3.68 (dd, 1 H, $J_{6'ax,7'}$ = 11.9 Hz, $J_{6'eq,7'}$ = 4.8 Hz, H-7'), 3.56 (br, 1 H, OH), 3.47 (dd, 1 H, $J_{6ax,7}$ = 12.3 Hz, $J_{6eq,7}$ = 4.2 Hz, H-7), 3.45 (s, 3 H, CH_3O), 3.01 (d, 1 H, $J_{4OH,5}$ = 1.7 Hz, C-4-OH), 2.24 (ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{6eq,6ax}$ = 12.1 Hz, $J_{6ax,7}$ = 12.1 Hz, H-6$_{ax}$), 2.11 (ddd, 1 H, $J_{6eq,6ax}$ = 11.7 Hz, $J_{5,6ax}$ = 4.4 Hz, $J_{6ax,7}$ = 4.4 Hz, H-6$_{eq}$), 2.02 (ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{6eq,6ax}$ = 12.1 Hz, $J_{6ax,7}$ = 12.1 Hz, H-6'$_{ax}$), 1.99–1.92 (m, 1 H, H-6'$_{eq}$), 1.67 (s, 3 H, H-10'), 1.50 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.1 (C=O), 139.6 (Ar), 139.4 (Ar), 138.1 (Ar), 137.9 (Ar), 137.5 (Ar), 136.7 (Ar), 133.2 (Ar), 129.9 (Ar), 129.8 (Ar), 129.2 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 128.0 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.3 (Ar), 127.0 (Ar), 126.9 (Ar), 126.2 (Ar), 102.6 (<u>C</u>HAr), 102.2 (C-1'), 98.6 (C-1), 89.7 (C-9'), 85.8 (C-7), 83.4 (C-8'), 82.1 (C-7'), 82.0 (C-9), 77.9 (C-3), 77.5 (C-3'), 76.9 (C-

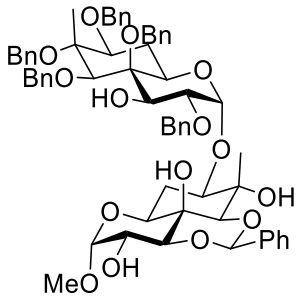
4/C-4'), 76.3 (CH$_2$Ar), 75.7 (C-8), 75.4 (C-2'), 74.1 (CH$_2$Ar), 71.7 (CH$_2$Ar), 70.0 (C-2), 69.0 (CH$_2$Ar), 68.1 (C-5'), 67.6 (C-4/C-4'), 66.2 (CH$_2$Ar), 64.9 (C-5), 56.0 (OCH_3), 29.4 (C-6), 28.7 (C-6'), 17.6 (C-10), 11.5 (C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{70}H_{74}NaO_{16}$: 1193.4869. Found 1193.4888.

(**D,L-4.51**): R_f 0.23 (1:1 hexanes–EtOAc); $[\alpha]_D$ –32.2 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.12–8.09 (m, 2 H, Ar), 7.62–7.57 (m, 1 H, Ar), 7.56–7.52 (m, 2 H, Ar), 7.50–7.45 (m, 2 H, Ar), 7.42–7.24 (m, 26 H, Ar), 7.17–7.12 (m, 2 H, Ar), 5.70 (s, 1 H, CHAr), 5.53 (d, 1 H, *J* = 11.9 Hz, CH$_2$Ar), 5.53 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 3.9 Hz, H-2), 5.22 (d, 1 H, $J_{1',2'}$ = 4.0 Hz, H-1'), 5.21 (d, 1 H, $J_{1',2'}$ = 3.9 Hz, H-1), 5.19–5.14 (m, 2 H, 2 x CH$_2$Ar), 4.79 (d, 1 H, *J* = 11.7 Hz, CH$_2$Ar), 4.78 (d, 1 H, *J* = 11.0 Hz, CH$_2$Ar), 4.72 (d, 1 H, *J* = 10.8 Hz, CH$_2$Ar), 4.70 (d, 1 H, *J* = 11.0 Hz, CH$_2$Ar), 4.67 (d, 1 H, *J* = 11.6 Hz, CH$_2$Ar), 4.40 (d, 1 H, $J_{2',3'}$ = 10.1 Hz, H-3'), 4.37 (d, 1 H, $J_{2,3}$ = 10.1 Hz, H-3), 4.17 (s, 1 H, OH), 4.13 (d, 1 H, *J* = 11.7 Hz, CH$_2$Ar), 4.10 (d, 1 H, *J* = 11.4 Hz, CH$_2$Ar), 3.92 (dd, 1 H, $J_{2',3'}$ = 9.9 Hz, $J_{1',2'}$ = 3.9 Hz, H-2'), 3.87 (br ddd, 1 H, $J_{5,6ax}$ = 11.9 Hz, $J_{5,6eq}$ = 4.0 Hz, $J_{5,OH}$ = 1.3 Hz, H-5), 3.78–3.70 (m, 3 H, H-7, H-5', H-9'), 3.62 (s, 1 H, H-9), 3.46 (s, 3 H, CH_3O), 3.45 (dd, 1 H, $J_{6'ax,7'}$ = 11.7 Hz, $J_{6'eq,7'}$ = 4.8 Hz, H-7'), 3.40 (br, 1 H, OH), 2.96 (d, 1 H, $J_{4OH,5}$ = 1.7 Hz, C-4-OH), 2.18 (ddd, 1 H, $J_{5,6ax}$ = 12.3 Hz, $J_{6eq,6ax}$ = 12.3 Hz, $J_{6ax,7}$ = 12.3 Hz, H-6$_{ax}$), 2.06 (ddd, 1 H, $J_{6eq,6ax}$ = 12.1 Hz, $J_{5,6ax}$ = 4.0 Hz, $J_{6ax,7}$ = 4.0 Hz, H-6$_{eq}$), 1.94 (ddd, 1 H, $J_{5',6'ax}$ = 12.1 Hz, $J_{6'eq,6'ax}$ = 12.1 Hz, $J_{6'ax,7'}$ = 12.1 Hz, H-6'$_{ax}$), 1.74 (ddd, 1 H, $J_{6'eq,6'ax}$ = 12.5 Hz, $J_{5',6'eq}$ = 4.4 Hz, $J_{6'eq,7}$ = 4.4 Hz, H-6'$_{eq}$), 1.63 (s, 3 H, H-10'), 1.51 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 139.7 (Ar), 139.5 (Ar), 138.2 (Ar), 137.9 (Ar), 137.4 (Ar), 136.8 (Ar), 133.2 (Ar), 129.9 (Ar), 129.2 (Ar), 128.7 (Ar), 128.6 (Ar), 128.4 (Ar), 128.3(2) (Ar), 128.2(8) (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 127.3 (Ar), 127.0 (Ar), 126.9 (Ar), 125.9 (Ar), 102.0 (CHAr), 98.5 (C-1), 92.0 (C-1'), 90.0

(C-9'), 83.6 (C-8'), 83.3 (C-9), 82.6 (C-7'), 82.2 (C-8), 78.1 (C-3), 77.2 (C-3'), 76.8 (C-4/C-4'), 76.3 ($\underline{C}H_2Ar$), 75.8 (C-2'), 74.4 ($\underline{C}H_2Ar$), 74.2 (C-7), 71.3 ($\underline{C}H_2Ar$), 70.0 (C-2), 69.0 ($\underline{C}H_2Ar$), 68.1 (C-4/C-4'), 67.6 (C-5'), 66.2 ($\underline{C}H_2Ar$), 65.0 (C-5), 55.9 (OCH_3), 29.7 (C-6), 29.0 (C-6'), 11.6 (C-10), 11.4 (C-10'). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{70}H_{78}NO_{16}$: 1188.5315. Found 1188.5341.

(**D,L-4.52**): R_f 0.33 (1:1 hexanes–EtOAc); $[\alpha]_D$ –44.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.10–8.05 (m, 2 H, Ar), 7.60–7.52 (m, 3 H, Ar), 7.48–7.44 (m, 2 H, Ar), 7.40–7.23 (m, 28 H, Ar), 5.86 (s, 1 H, C$\underline{H}$Ar), 5.53 (dd, 1 H, $J_{2,3}$ = 10.1 Hz, $J_{1,2}$ = 3.7 Hz, H-2), 5.43 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 5.21 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 5.14 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 5.07 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.85 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.80–4.73 (m, 3 H, C$\underline{H}_2$Ar), 4.70 (d, 1 H, J = 11.0 Hz, C$\underline{H}_2$Ar), 4.66 (d, 1 H, J = 11.2 Hz, C$\underline{H}_2$Ar), 4.52 (d, 1 H, $J_{1',2'}$ = 7.5 Hz, H-1'), 4.43 (d, 1 H, J = 11.9 Hz, C$\underline{H}_2$Ar), 4.41 (s, 1 H, OH), 4.37 (d, 1 H, $J_{2,3}$ = 10.1 Hz, H-3), 3.98 (s, 1 H, OH), 4.94 (d, 1 H, $J_{2',3'}$ = 9.5 Hz, H-3'), 3.81 (br ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{5,6eq}$ = 3.9 Hz, $J_{5,OH}$ = 1.3 Hz, H-5), 3.75 (s, 1 H, H-9), 3.75 (dd, 1 H, $J_{2',3'}$ = 9.4 Hz, $J_{1',2'}$ = 7.5 Hz, H-2'), 3.66 (dd, 1 H, $J_{6ax,7}$ = 12.3 Hz, $J_{6eq,7}$ = 4.4 Hz, H-7), 3.61 (dd, 1 H, $J_{6'ax,7'}$ = 11.6 Hz, $J_{6'eq,7'}$ = 5.1 Hz, H-7'), 3.61 (s, 1 H, H-9'), 3.43 (s, 3 H, CH_3O), 3.32 (dd, 1 H, $J_{5',6'ax}$ = 11.6 Hz, $J_{5',6'eq}$ = 4.2 Hz, H-5'), 3.00 (d, 1 H, $J_{4OH,5}$ = 1.7 Hz, C-4-OH), 2.34 (ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{6eq,6ax}$ = 12.1 Hz, $J_{6ax,7}$ = 12.1 Hz, H-6_{ax}), 2.21–2.09 (m, 3 H, H-6_{eq}, 2 x H-6'), 1.61 (s, 3 H, H-10'), 1.49 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 139.6 (Ar), 139.4 (Ar), 137.9(9) (Ar), 137.9(5) (Ar), 136.7 (Ar), 133.2 (Ar), 129.9 (Ar), 129.8 (Ar), 129.2 (Ar), 128.6 (Ar), 128.4(1) (Ar), 128.3(8) (Ar), 128.3 (Ar), 128.2(5) (Ar), 128.2(0) (Ar), 127.9 (Ar), 127.8 (Ar), 127.6(5) (Ar), 127.5(7) (Ar), 127.3 (Ar), 127.0 (Ar), 126.8 (Ar), 126.2 (Ar), 104.6 (C-1'), 102.6 ($\underline{C}$HAr), 98.5 (C-1), 89.0 (C-9'), 86.0 (C-7), 83.5 (C-8'), 82.6 (C-9), 81.8 (C-7'), 80.0 (C-3'), 79.5 (C-2'), 77.9 (C-3), 75.9(4) ($\underline{C}H_2Ar$),

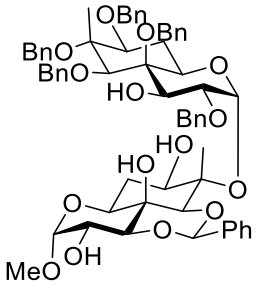
75.8(7) (CH_2Ar), 75.3 (C-4/C-4'), 74.5 (C-8), 72.6 (C-5'), 71.3 (CH_2Ar), 69.9(2) (C-2), 68.8(6) (CH_2Ar), 67.3 (C-4/C-4'), 66.3 (CH_2Ar), 64.7 (C-5), 55.9 (OCH_3), 30.3 (C-6), 28.8 (C-6'), 14.1 (C-10), 11.4 (C-10'). HRMS (ESI) Calcd for $[M + NH_4]^+$ $C_{70}H_{78}NO_{16}$: 1188.5315. Found 1188.5337.



D,L-4.53

Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-D-bradyrhizopyranosyl-(1→7)-3,9-*O*-benzylidene-1,5-α-L-bradyrhizopyranoside (D,L-4.53). A solution of MeONa in MeOH (0.15 mL, 0.5 M in MeOH) was added to **D,L-4.50** (8.0 mg, 0.00683 mmol) in MeOH (3 mL) The mixture was stirred for 3 h at rt. Amberlite® IR120 H^+ form resin was added until neutral pH and the mixture was filtered. The filtrate was concentrated and the resulting crude product was purified by silica gel column chromatography (3:2 hexanes–EtOAc) to give **D,L-4.53** (7.3 mg, 93%) as a colorless oil. R_f 0.36 (2:3 hexanes–EtOAc); $[\alpha]_D$ –21.2 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.61–7.57 (m, 2 H, Ar), 7.43–7.22 (m, 28 H, Ar), 5.81 (s, 1 H, CHAr), 5.51 (d, 1 H, *J* = 12.1 Hz, CH_2Ar), 5.19 (d, 1 H, *J* = 11.2 Hz, CH_2Ar), 5.16 (d, 1 H, *J* = 11.5 Hz, CH_2Ar), 4.90 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 4.86–4.78 (m, 3 H, 2 x CH_2Ar, H-1'), 4.75–4.67 (m, 4 H, CH_2Ar), 4.54 (d, 1 H, *J* = 11.4 Hz, CH_2Ar), 4.40 (d, 1 H, $J_{2,3}$ = 10.1 Hz, H-3'), 4.25 (s, 1 H, OH), 4.18 (br ddd, 1 H, $J_{2,3}$ = 9.0 Hz, $J_{2,OH}$ = 9.0 Hz, $J_{1,2}$ = 3.5 Hz, H-2), 3.95 (d, 1 H, $J_{2',3'}$ = 9.4 Hz, H-3), 3.87 (dd, 1 H, $J_{2',3'}$ = 10.1 Hz, $J_{1',2'}$ = 3.9 Hz, H-2'), 3.82 (s, 1 H, H-9'), 3.77–3.71 (m, 2 H, H-5, H-5'), 3.70 (s, 1 H, H-9), 3.67 (dd, 1 H, $J_{5,6ax}$ = 11.7 Hz, $J_{5,6eq}$ = 5.0 Hz, H-7'), 3.53 (br, 1 H, OH), 3.51 (s, 3 H, CH_3O), 3.44

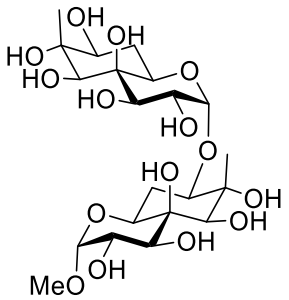
(dd, 1 H, $J_{6'ax,7'}$ = 12.3 Hz, $J_{6'eq,7'}$ = 4.4 Hz, H-7), 2.90 (d, 1 H, $J_{4OH,5}$ = 1.1 Hz, C-4-OH), 2.19 (ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{6eq,6ax}$ = 12.1 Hz, $J_{6ax,7}$ = 12.1 Hz, H-6_{ax}), 2.12–2.05 (m, 1 H, H-6_{eq}), 2.01 (ddd, 1 H, $J_{5',6'ax}$ = 11.9 Hz, $J_{6'eq,6'ax}$ = 11.9 Hz, $J_{6'ax,7'}$ = 11.9 Hz, H-6'$_{ax}$), 1.98–1.91 (m, 1 H, H-6'$_{eq}$), 1.67 (s, 3 H, H-10'), 1.48 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.5 (Ar), 138.1 (Ar), 137.9 (Ar), 137.5 (Ar), 136.7 (Ar), 129.3 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2(4) (Ar), 128.2(0) (Ar), 128.0 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.3 (Ar), 127.0 (Ar), 126.9 (Ar), 126.4 (Ar), 103.0 (CHAr), 102.2 (C-1'), 100.8 (C-1), 89.7 (C-9'), 85.8 (C-7), 83.4 (C-8'), 82.2 (C-7'), 82.0 (C-9), 81.2 (C-3), 77.5 (C-3'), 76.9 (C-4/C-4'), 76.3 (CH_2Ar), 75.6 (C-8), 75.3 (C-2'), 74.0 (CH_2Ar), 71.7 (CH_2Ar), 69.0 (CH_2Ar), 68.0 (C-5'), 67.6 (C-2), 67.4 (C-4/C-4'), 66.2 (CH_2Ar), 65.2 (C-5), 56.0 (OCH_3), 30.7 (C-6), 28.7 (C-6'), 17.6 (C-10), 11.4 (C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{63}H_{70}NaO_{15}$: 1089.4607. Found 1089.4630.



D,L-4.55

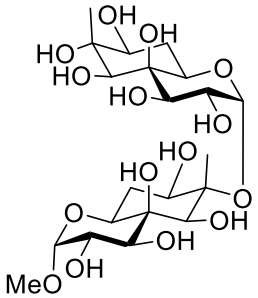
Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-D-bradyrhizopyranosyl-(1→8)-3,9-*O*-benzylidene-1,5-α-L-bradyrhizopyranoside (D,L-4.55). A solution of MeONa in MeOH (0.15 mL, 0.5 M in MeOH) was added to **D,L-4.51** (5.2 mg, 0.00444 mmol) in MeOH (3 mL) The mixture was stirred for 3 h at rt. Amberlite® IR120 H^+ form resin was added until neutral pH and the mixture was filtered. The filtrate was concentrated and the resulting crude product was purified by silica gel column chromatography (3:2 hexanes–EtOAc) to give **D,L-4.55** (4.7 mg, 99%) as a colorless oil. R_f 0.22 (3:7 hexanes–EtOAc); $[\alpha]_D$ –16.2 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.64–

7.60 (m, 2 H, Ar), 7.42–7.20 (m, 26 H, Ar), 7.13–7.08 (m, 2 H, Ar), 5.72 (s, 1 H, C<u>H</u>Ar), 5.52 (d, 1 H, J = 11.9 Hz, C<u>H</u>$_2$Ar), 5.19 (d, 1 H, $J_{1',2'}$ = 4.0 Hz, H-1'), 5.17 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 5.16 (d, 1 H, J = 11.9 Hz, C<u>H</u>$_2$Ar), 4.89 (d, 1 H, $J_{1',2'}$ = 4.0 Hz, H-1), 4.81 (d, 1 H, J = 11.6 Hz, C<u>H</u>$_2$Ar), 4.75 (d, 1 H, J = 11.0 Hz, C<u>H</u>$_2$Ar), 4.69 (d, 1 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 4.68 (d, 1 H, J = 10.8 Hz, C<u>H</u>$_2$Ar), 4.66 (d, 1 H, J = 11.7 Hz, C<u>H</u>$_2$Ar), 4.40 (d, 1 H, $J_{2,3}$ = 9.9 Hz, H-3'), 4.19 (s, 1 H, OH), 4.19–4.12 (m, 1 H, H-2), 4.03 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 3.98 (d, 1 H, J = 11.4 Hz, C<u>H</u>$_2$Ar), 3.94 (d, 1 H, $J_{2,3}$ = 9.4 Hz, H-3), 3.92 (dd, 1 H, $J_{2,3}$ = 10.1 Hz, $J_{1,2}$ = 4.0 Hz, H-2'), 3.78 (br ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{5,6eq}$ = 4.4 Hz, $J_{5,OH}$ = 1.3 Hz, H-5), 3.74 (s, 1 H, H-9'), 3.71 (dd, 1 H, $J_{6ax,7}$ = 11.9 Hz, $J_{6eq,7}$ = 4.2 Hz, H-7), 3.70 (dd, 1 H, $J_{5',6'ax}$ = 12.5 Hz, $J_{5',6'eq}$ = 3.9 Hz, H-5'), 3.56 (s, 1 H, H-9), 3.52 (s, 3 H, CH_3O), 3.49 (br, 1 H, OH), 3.39 (dd, 1 H, $J_{5,6ax}$ = 11.9 Hz, $J_{5,6eq}$ = 4.8 Hz, H-7'), 2.84 (d, 1 H, $J_{4OH,5}$ = 1.7 Hz, C-4-OH), 2.12 (ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{6eq,6ax}$ = 12.1 Hz, $J_{6ax,7}$ = 12.1 Hz, H-6$_{ax}$), 2.03 (ddd, 1 H, $J_{6eq,6ax}$ = 12.1 Hz, $J_{5,6ax}$ = 4.4 Hz, $J_{6ax,7}$ = 4.4 Hz, H-6$_{eq}$), 1.90 (ddd, 1 H, $J_{5',6'ax}$ = 12.1 Hz, $J_{6'eq,6'ax}$ = 12.1 Hz, $J_{6'ax,7'}$ = 12.1 Hz, H-6'$_{ax}$), 1.76–1.70 (m, 1 H, H-6'$_{eq}$), 1.61 (s, 3 H, H-10'), 1.50 (s, 3 H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.4 (Ar), 138.1 (Ar), 137.9 (Ar), 137.4 (Ar), 136.9 (Ar), 129.3 (Ar), 128.7 (Ar), 128.6 (Ar), 128.3(7) (Ar), 128.3(6) (Ar), 128.3 (Ar), 128.2(2) (Ar), 128.1(7) (Ar), 128.0 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 127.3 (Ar), 127.0 (Ar), 126.0 (Ar), 102.2 (<u>C</u>HAr), 100.6 (C-1), 91.9 (C-1'), 90.0 (C-9'), 83.5 (C-8'), 83.2 (C-9), 82.6 (C-7'), 82.2 (C-8), 81.5 (C-3), 77.4 (C-3'), 77.0 (C-4/C-4'), 76.3 (<u>C</u>H$_2$Ar), 75.8 (C-2'), 74.5 (<u>C</u>H$_2$Ar), 74.3 (C-7), 71.0 (<u>C</u>H$_2$Ar), 69.0 (<u>C</u>H$_2$Ar), 67.9 (C-4/C-4'), 67.7 (C-5'), 67.6 (C-2), 66.2 (<u>C</u>H$_2$Ar), 65.3 (C-5), 56.0 (OCH_3), 30.2 (C-6), 28.7 (C-6'), 11.4 (C-10), 11.3 (C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{63}H_{70}NaO_{15}$: 1089.4607. Found 1089.4635.



D,L-4.54

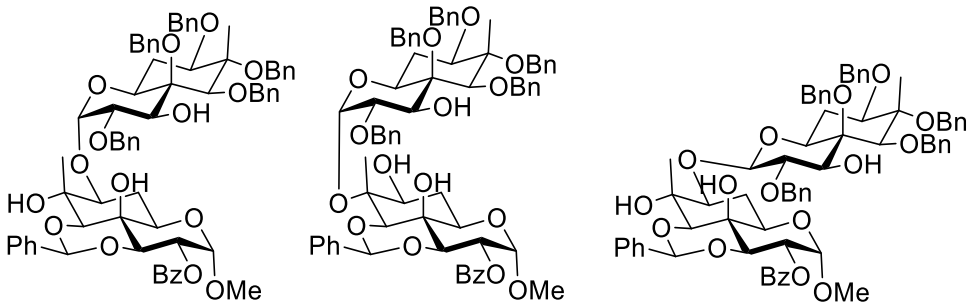
Methyl 1,5-α-D-bradyrhizopyranosyl-(1→7)-1,5-α-L-bradyrhizopyranoside (D,L-4.54). Palladium hydroxide on carbon (6.8 mg, 0.00637 mmol, 20 wt. % loading) was added to a solution of **D,L-4.53** (12.4 mg, 0.0116 mmol) in MeOH (7 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium hydroxide on carbon was filtered through Celite® and the filtrate was concentrated. The resulting crude product was purified by reverse phase column chromatography (C-18 silica gel, H_2O) to give **D,L-4.54** (in quantitative yield and as a colorless oil. $[\alpha]_D$ +10.0 (*c* 0.1, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 4.99 (d, 1 H, $J_{1',2'}$ = 4.0 Hz, H-1'), 4.64 (d, 1 H, $J_{1',2'}$ = 3.9 Hz, H-1), 3.83–3.71 (m, 5 H, H-2, H-2', H-3, H-3', H-5/H-5'), 3.67–3.62 (m, 1 H, H-5/H-5'), 3.52–3.46 (m, 4 H, 2 x H-7,H-7', H-9, H-9'), 3.37 (s, 3 H, OCH_3), 2.00–1.93 (m, 2 H, 2 x H-6/H-6'), 1.89 (ddd, 1 H, $J_{5,6ax}$ = 12.3 Hz, $J_{6eq,6ax}$ = 12.3 Hz, $J_{6ax,7}$ = 12.3 Hz, H-6ax/H-6'$_{ax}$), 1.71 (ddd, 1 H, $J_{6eq,6ax}$ = 11.9 Hz, $J_{5,6ax}$ = 4.2 Hz, $J_{6ax,7}$ = 4.2 Hz, H-6$_{eq}$/H-6'$_{eq}$), 1.34 (s, 3 H, H-10/H-10'), 1.26 (s, 3 H, H-10/H-10); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 102.8 (C-1'), 101.6 (C-1'), 84.4 (C-7/C-7'), 80.8 (C-9/C-9'), 80.1 (C-9/C-9'), 78.5 (C-8/C-4/C-8'/C-4'), 78.4 (C-8/C-4/C-8'/C-4'), 77.2 (C-3/C-3'), 76.9 (C-3/C-3'), 74.3(1) (C-8/C-4/C-8'/C-4'), 74.2(6) (C-7/C-7''), 74.0 (C-8/C-4/C-8'/C-4'), 71.5 (C-2/C-2'), 70.9 (C-2/C-2'), 68.0 (C-5/C-5'), 67.0 (C-5/C-5'/), 55.9 (OCH_3), 32.7 (C-6/C-6'), 31.9 (C-6/C-6'), 16.4 (C-10/C-10'), 15.4 (C-10/C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{21}H_{36}NaO_{15}$: 551.1946. Found 551.1938.



D,L-4.56

Methyl 1,5-α-D-bradyrhizopyranosyl-(1→8)-1,5-α-L-bradyrhizopyranoside (D,L-4.56). Palladium hydroxide on carbon (4.9 mg, 0.00459 mmol, 20 wt. % loading) was added to a solution of **D,L-4.55** (8.8 mg, 0.0116 mmol) in MeOH (5 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium hydroxide on carbon was filtered through Celite® and the filtrate was concentrated. The resulting crude product was purified by reverse phase column chromatography (C-18 silica gel, H_2O) to give **D,L-4.56** in quantitative yield and as a colorless oil. $[\alpha]_D$ +4.0 (*c* 0.1, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 5.27 (d, 1 H, $J_{1',2'}$ = 4.0 Hz, H-1'), 4.63 (d, 1 H, $J_{1',2'}$ = 4.0 Hz, H-1), 3.96 (dd, 1 H, $J_{5,6ax}$ = 12.3 Hz, $J_{5,6eq}$ = 4.2 Hz, H-5/H-5'), 3.83–3.66 (m, 7 H, 2 x H-2, 2 x H-3, H-5/H-5', H-7/H-7', H-9/H-9'), 3.53 (dd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{5,6eq}$ = 4.4 Hz, H-7/H-7'), 3.50 (s, 1 H, H-9/H-9'), 3.37 (s, 3 H, OCH_3), 1.95 (ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{6eq,6ax}$ = 12.1 Hz, $J_{6ax,7}$ = 12.1 Hz, H-6_{ax}/H-$6'_{ax}$), 1.87 (ddd, 1 H, $J_{5,6ax}$ = 12.1 Hz, $J_{6eq,6ax}$ = 12.1 Hz, $J_{6ax,7}$ = 12.1 Hz, H-6_{ax}/H-$6'_{ax}$), 1.77 (ddd, 1 H, $J_{6eq,6ax}$ = 11.9 Hz, $J_{5,6ax}$ = 4.4 Hz, $J_{6ax,7}$ = 4.4 Hz, H-6_{eq}/H-$6'_{eq}$), 1.74 (ddd, 1 H, $J_{6eq,6ax}$ = 11.9 Hz, $J_{5,6ax}$ = 4.4 Hz, $J_{6ax,7}$ = 4.4 Hz, H-6_{eq}/H-$6'_{ax}$), 1.35 (s, 3 H, H-10/H-10'), 1.26 (s, 3 H, H-10 /H-10'); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 101.5 (C-1), 94.4 (C-1'), 85.9 (C-8/C-8'/C-4/C-4'), 80.7 (C-9/C-9'), 78.7 (C-9/C-9'), 78.5 (C-8/C-8'/C-4/C-4'), 76.8(2) (C-3/C-3'), 76.8(1) (C-3/C-3'), 74.3(4) (C-8/C-8'/C-4/C-4'), 74.3(2) (C-8/C-8'/C-4/C-4'), 74.1 (C-7/C-7'), 72.5 (C-2'), 71.0 (C-7/C-7'), 70.9 (C-2), 68.0 (C-5/C-5'), 66.7 (C-5/C-5'), 55.8 (OCH_3), 32.8 (C-6/C-6'), 32.6 (C-6/C-6'), 15.5 (C-

10/C-10'), 13.3 (C-10/C-10'). HRMS (ESI) Calcd for $[M + Na]^+$ $C_{21}H_{36}NaO_{15}$: 551.1946. Found 551.1938.

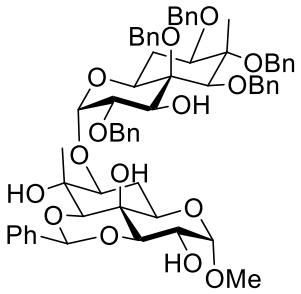


L,D-4.50 L,D-4.51 L,D-4.52

Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-L-bradyrhizopyranosyl-(1→7)-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (L,D-4.50), methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-L-bradyrhizopyranosyl-(1→8)-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (L,D-4.51) and **methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-β-L-bradyrhizopyranosyl-(1→7)-2-*O*-benzoyl-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (L,D-4.52)**. Cesium carbonate (3 mg, 0.00921 mmol) was added to a cooled (0 °C) solution of **L-4.34** (19 mg, 0.0275 mmol) and trichloroacetonitrile (14 µL, 0.138 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt overnight then filtered through Celite® 545. The filtrate was concentrated and the crude trichloroacetimidate was used for the next step without further purification.

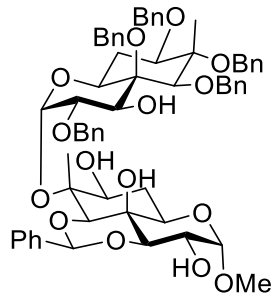
Molecular sieves (~20 mg, activated powder 4 Å) were added to a solution of **D-4.37α** (5.8 mg, 0.0123 mmol) in CH_2Cl_2 (0.5 mL) at rt. The mixture was stirred for 1 h then cooled to –40 °C and stirred for 15 min. TBSOTf (56 µL of a solution of TBSOTf (10 µL) in CH_2Cl_2 (1 mL)) was added followed by a solution of the crude trichloroacetimidate in CH_2Cl_2 (0.4 mL). The mixture was stirred at –40 °C for 30 min and Et_3N (50 µL) was added. The reaction mixture was warmed to rt and the solvent was evaporated. The resulting crude products were purified by silica gel column chromatography (9:1 hexanes–EtOAc) to give **L,D-4.50** (5.5 mg, 38%) and **L,D-4.51** and **L,D-4.52**

(4.6 mg, 32%) as colorless oils. Another silica gel column (9:1 hexanes–acetone) was necessary to purify **L,D-4.50**. Disaccharides **L,D-4.51** and **L,D-4.52** were separated by preparative TLC (1:1 hexanes–EtOAc) to give **L,D-4.51** (3.8 mg, 26%) and **L,D-4.52** (0.8 mg, 5%). The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained for compounds **D,L-4.50**, **D,L-4.51** and **D,L-4.52** previously described. (**L,D-4.50**): $[\alpha]_D$ +22.0 (*c* 0.1, $CHCl_3$). (**L,D-4.51**): $[\alpha]_D$ +40.4 (*c* 0.1, $CHCl_3$). (**L,D-4.52**): $[\alpha]_D$ +34.6 (*c* 0.1, $CHCl_3$).



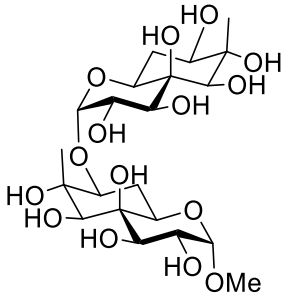
L,D-4.53

Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-L-bradyrhizopyranosyl-(1→7)-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (L,D-4.53). A solution of MeONa in MeOH (0.15 mL, 0.5 M in MeOH) was added to **L,D-4.50** (5.5 mg, 0.00470 mmol) in MeOH (3 mL). The mixture was stirred for 3 h at rt. Amberlite® IR120 H^+ form resin was added until the pH of the solution was neutral and the mixture was filtered. The filtrate was concentrated and the resulting crude product was purified by silica gel column chromatography (3:2 hexanes–EtOAc) to give **L,D-4.53** (2.9 mg, 58%) as a colorless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained for compound **D,L-4.53** previously described. $[\alpha]_D$ +8.0 (*c* 0.1, $CHCl_3$).



L,D-4.55

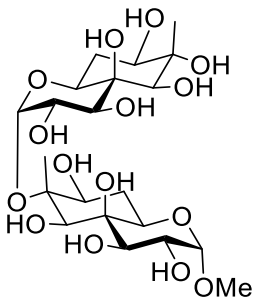
Methyl 2,4,7,8,9-Penta-*O*-benzyl-1,5-α-L-bradyrhizopyranosyl-(1→8)-3,9-*O*-benzylidene-1,5-α-D-bradyrhizopyranoside (L,D-4.55). A solution of MeONa in MeOH (0.15 mL, 0.5 M in MeOH) was added to **L,D-4.51** (3.8 mg, 0.00470 mmol) in MeOH (3 mL). The mixture was stirred for 3 h at rt. Amberlite® IR120 H^+ form resin was added until the pH of the solution was neutral and the mixture was filtered. The filtrate was concentrated and the resulting crude product was purified by silica gel column chromatography (3:2 hexanes–EtOAc) to give **L,D-4.55** (3.5 mg, 99%) as a colorless oil. The R_f, ^{1}H NMR, ^{13}C NMR and MS data correspond to that obtained for compound **D,L-4.55** previously described. $[\alpha]_D$ +4.4 (*c* 0.1, $CHCl_3$).



L,D-4.54

Methyl 1,5-α-L-bradyrhizopyranosyl-(1→7)-1,5-α-D-bradyrhizopyranoside (L,D-4.54). Palladium hydroxide on carbon (5.3 mg, 0.00499 mmol, 20 wt. % loading) was added to a solution of **L,D-4.53** (2.9 mg, 0.0.0272 mmol) in MeOH (3 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium hydroxide on carbon

was filtered and the filtrate was concentrated. The resulting crude product was purified by reverse phase column chromatography (C-18 silica gel, H_2O) to give **L,D-4.54** in quantitative yield and as a colorless oil. The R_f, ^1H NMR, ^{13}C NMR and MS data correspond to that obtained for compound **D,L-4.54** previously described. $[\alpha]_D$ –14.2 (*c* 0.1, $CHCl_3$).



L,D-4.56

Methyl 1,5-α-L-bradyrhizopyranosyl-(1→8)-1,5-α-D-bradyrhizopyranoside (L,D-4.56). Palladium hydroxide on carbon (7.0 mg, 0.00660 mmol, 20 wt. % loading) was added to a solution of **L,D-4.55** (3.7 mg, 0.0.0347 mmol) in MeOH (4 mL) under Ar. The reaction mixture was then placed under a positive pressure of H_2(g) and stirred overnight. The palladium hydroxide on carbon was filtered and the filtrate was concentrated. The resulting crude product was purified by reverse phase column chromatography (C-18 silica gel, H_2O) to give **L,D-4.56** in quantitative yield and as a colorless oil. The R_f, ^1H NMR, ^{13}C NMR and MS data correspond to that obtained for compound **D,L-4.56** previously described. $[\alpha]_D$ –5.0 (*c* 0.1, $CHCl_3$).

4.8 References

(1) Demchenko, A. V. 1,2-Cis *O*-Glycosylation: Methods, Strategies, Principles. *Curr. Org. Chem.* **2003**, *7*, 35–79.

(2) Nigudkar, S. S.; Demchenko, A. V. Stereocontrolled 1,2-*cis* Glycosylation as the Driving Force of Progress in Synthetic Carbohydrate Chemistry. *Chem. Sci.* **2015**, *6*, 2687–2704.

(3) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V; James, K. Halide Ion Catalyzed Glycosidation Reactions. Syntheses of α-Linked Disaccharides. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.

(4) Lemieux, R. U.; James, K.; Nagabhushan, T. L. Chemical Syntheses of α-linked Disaccharides *Can. J. Chem.* **1973**, 51, 42–47.

(5) Lemieux, R. U.; Sakakibara, S. Chemical Synthesis of. α-Linked 2'-Amino-2'deoxydisaccharides. *Can. J. Chem.* **1973**, *51*, 48–52.

(6) Sun, L.; Li, P.; Zhao, K. Stabilization of Glycosyl Sulfonium Ions for Stereoselective *O*-Glycosylation. *Tetrahedron Lett.* **1994**, *35*, 7147–7150.

(7) Wegmann, B.; Schmidt, R. R. The Application of the Trichloroacetimidate Method to the Synthesis of α-D-Gluco- and α-D-Galactopyranosides. *J. Carbohydr. Chem.* **1987**, *6*, 357–375.

(8) Crich, D.; Sun, S. Formation of *β*-Mannopyranosides of Primary Alcohols Using the Sulfoxide Method. *J. Org. Chem.* **1996**, *61*, 4506–4507.

(9) Crich, D.; Sun, S. Direct Synthesis of β-Mannopyranosides by the Sulfoxide Method. *J. Org. Chem.* **1997**, *62*, 1198–1199.

(10) Crich, D. Mechanism of a Chemical Glycosylation Reaction. *Acc. Chem. Res.* **2010**, *43*, 1144–1153.

(11) Crich, D. Methodology Development and Physical Organic Chemistry: A Powerful Combination for the Advancement of Glycochemistry. *J. Org. Chem.* **2011**, *76*, 9193–9209.

(12) Schmidt, R. R.; Toepfer, A. Glycosylation with Highly Reactive Glycosyl Donors: Efficiency of the Inverse Procedure. *Tetrahedron Lett.* **1991**, *32*, 3353–3356.

(13) Gao, P. C.; Zhu, S. Y.; Cao, H.; Yang, J. S. Total Synthesis of Marine Glycosphingolipid Vesparioside B. *J. Am. Chem. Soc.* **2016**, *138*, 1684–1688.

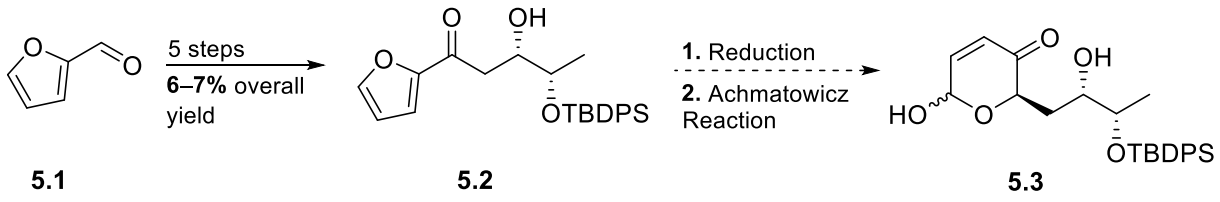
(14) Bohé, L.; Crich, D. Double Diastereoselection, Regioselectivity, and the Importance of Donor-Acceptor Complementarity in the Stereoselectivity of Glycosylation Reactions. *Trends Glycosci. Glycotechnol.* **2010**, *22*, 1–15.

Chapter 5: Conclusion

In this thesis, I have described two different approaches for the synthesis of bradyrhizose (Chapter 2 and 3). The racemic synthesis was accomplished, as well as the synthesis of D- and L-bradyrhizose (Chapter 3). Bradyrhizose donors and acceptors were synthesized to study the reactivity of the donor and to produce disaccharides containing this monosaccharide (Chapter 4).

5.1 Synthesis

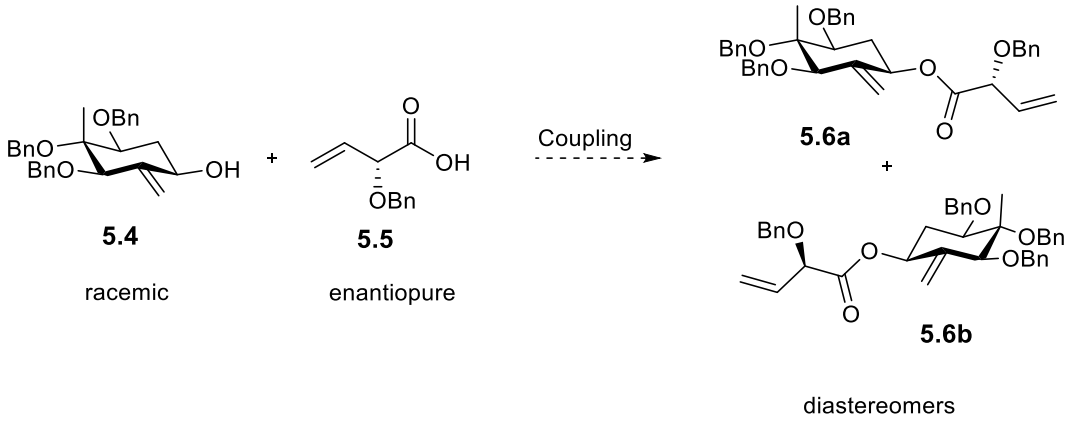
Two different approaches for the synthesis of bradyrhizose were discussed in this thesis. The monosaccharide in the first route was envisioned to be obtained from a furan derivative *via* the Achmatowicz reaction (Scheme 5-1). This route was abandoned after five steps (6–7% overall yield), because the results of key steps, based upon earlier work from Ticozzi and Zanarotti,[1] were not reproducible.



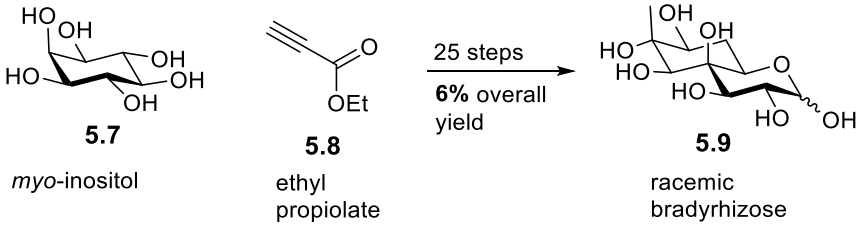
Scheme 5-1: First route starting with furfural (**5.1**).

In the second route, two strategies were investigated starting with *myo*-inositol. The first approach involved the coupling of a racemic compound (**5.4**) and an enantiopure carboxylic acid (**5.5**) (Scheme 5-2). This coupling would give diastereomers, so we decided to replace the enantiopure compound with an achiral reagent. The racemic synthesis of bradyrhizose (**5.9**) was

then achieved using *myo*-inositol (**5.7**) and ethyl propiolate (**5.8**) in 25 steps and 6% overall yield (Scheme 5-3).

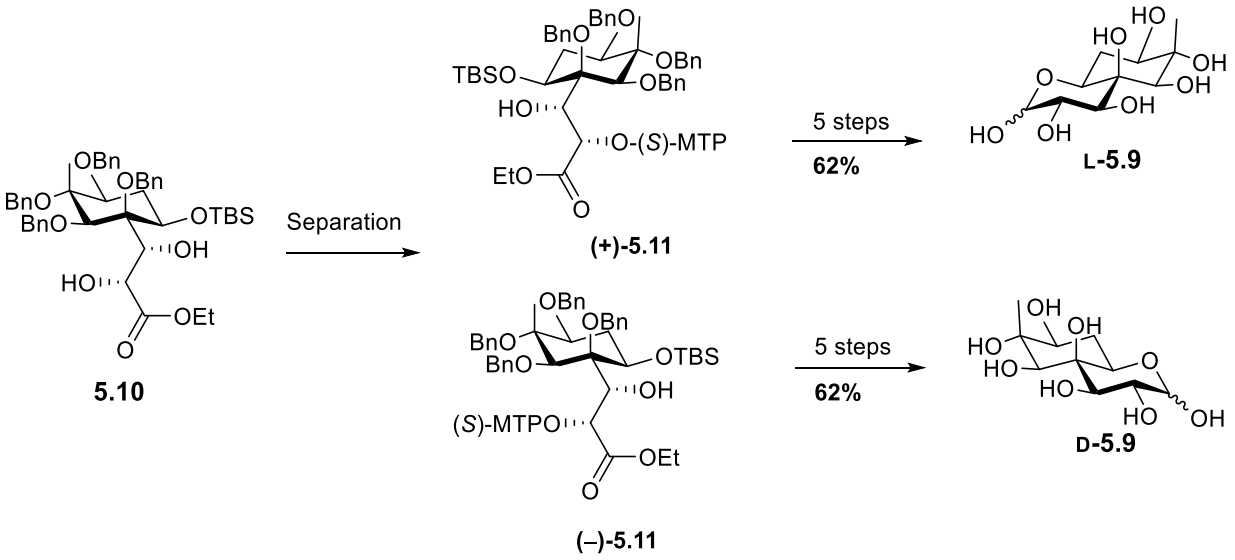


Scheme 5-2: Synthesis using a racemic and an enantiopure compound.



Scheme 5-3: Racemic synthesis of bradyrhizose (**5.9**).

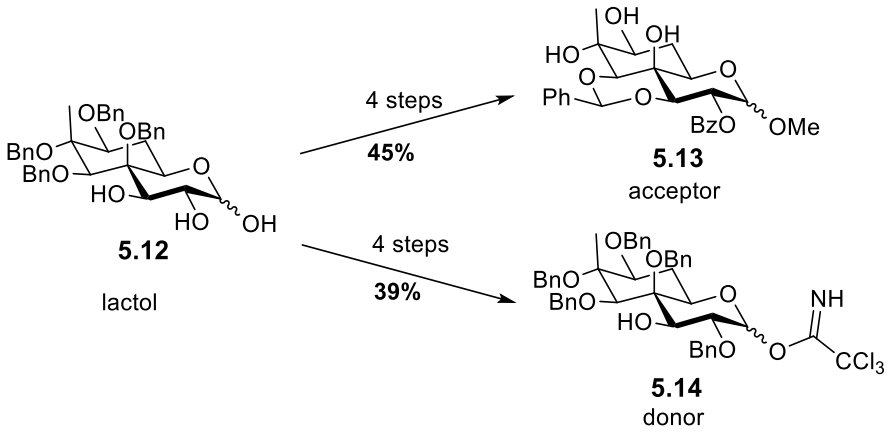
The enantiomers were separated at a late stage of the synthesis using (*S*)-MTPA and diol **5.10** to afford D- and L-bradyrhizose (**D-5.9** and **L-5.9**) in five steps and 62% yield after the separation (Scheme 5-4).



Scheme 5-4: Synthesis of D- and L-bradyrhizose (**D-5.9** and **L-5.9**).

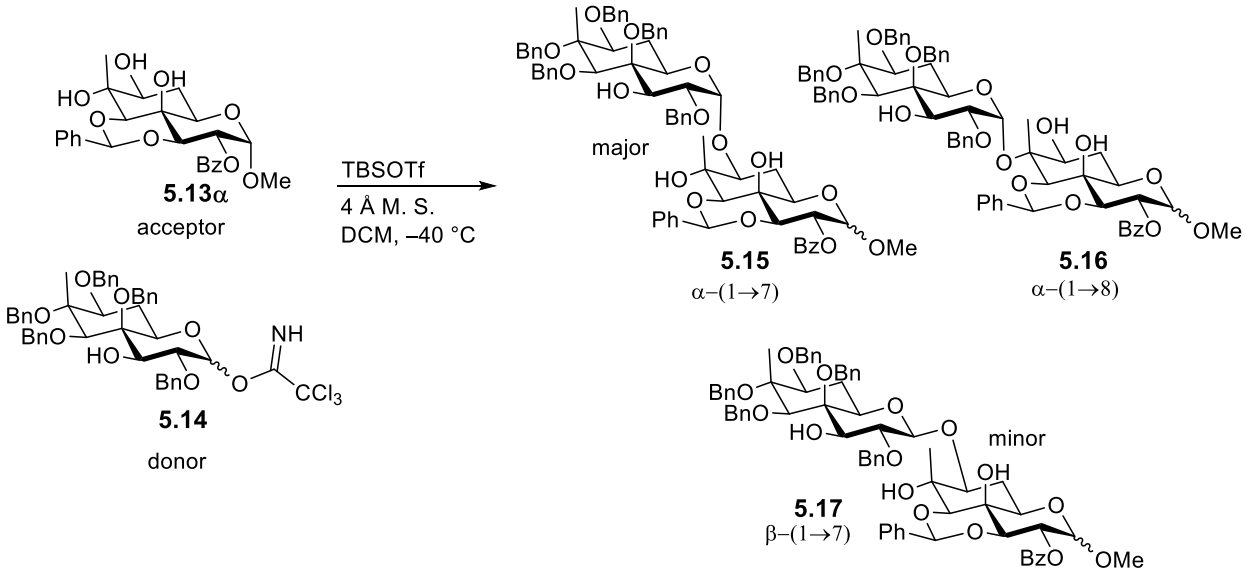
5.2 Glycosylations

Racemic and enantiopure donors (**5.14**) and acceptors (**5.13**) were synthesized in four steps from the lactol **5.12** (Scheme 5-5). A few glycosylations were performed using the racemic donor and achiral alcohols. The inositol part of bradyrhizose seemed to be not as α-directing as the benzylidene acetal in the glucopyranose series,[2] despite sharing a number of structural similarities.



Scheme 5-5: Synthesis of donor **5.14** and acceptor **5.13**.

The glycosylations using racemic or enantiopure donors and acceptors gave three different disaccharides; α-(1→7), α-(1→8) and β-(1→7) (Scheme 5-6). The desired disaccharides, having the α-(1→7)-glycosidic linkage present in the O-Chain of the LPS in which it is a constituent,[3] were the major compounds in all the glycosylations.



Scheme 5-6: Example of glycosylation with donor **5.14** and acceptor **5.13**.

Most of the disaccharides were deprotected in good yield and were sent for testing with plants and legumes by Associate Professor Newman at the University of Copenhagen (Figure 5-1).

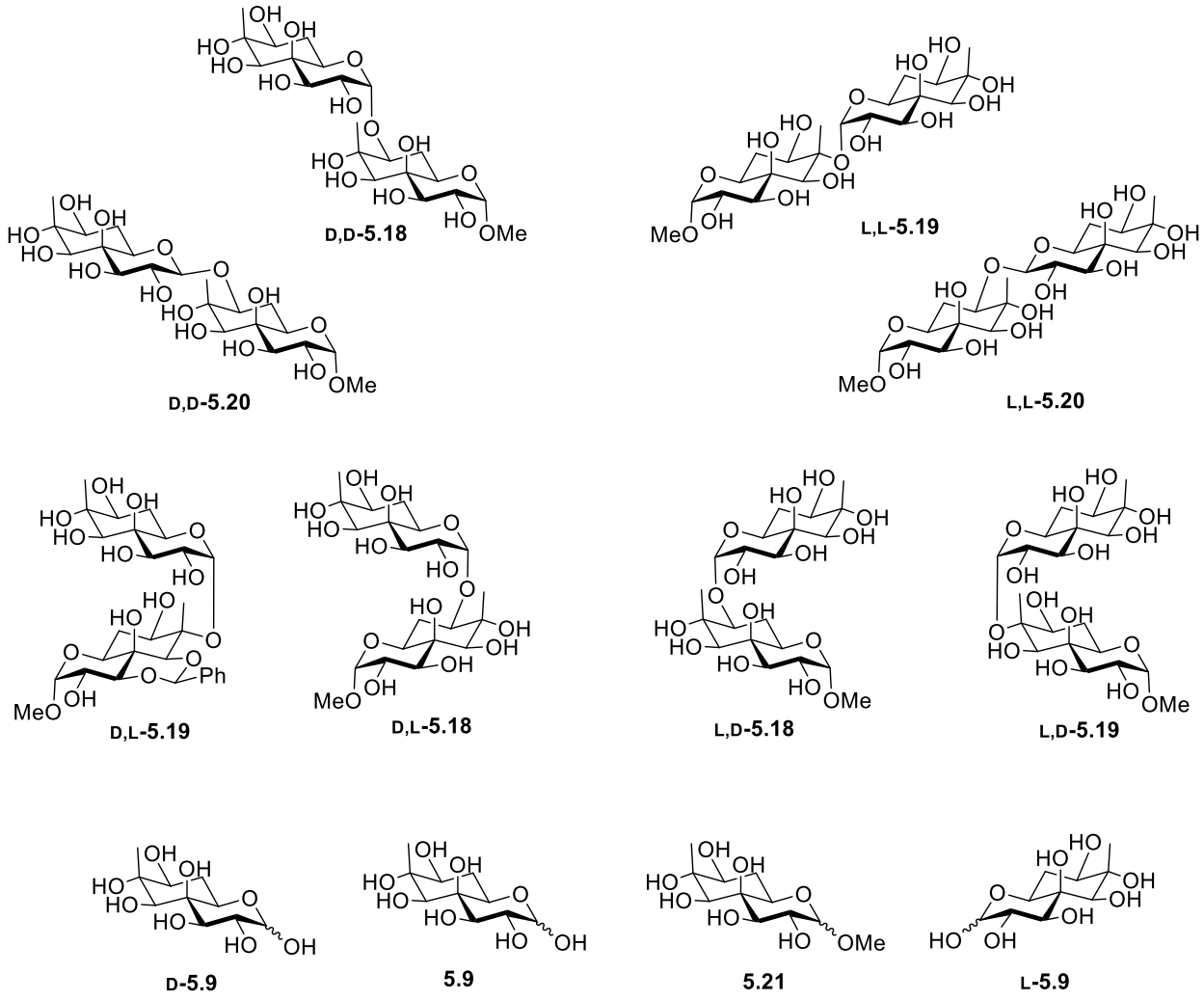
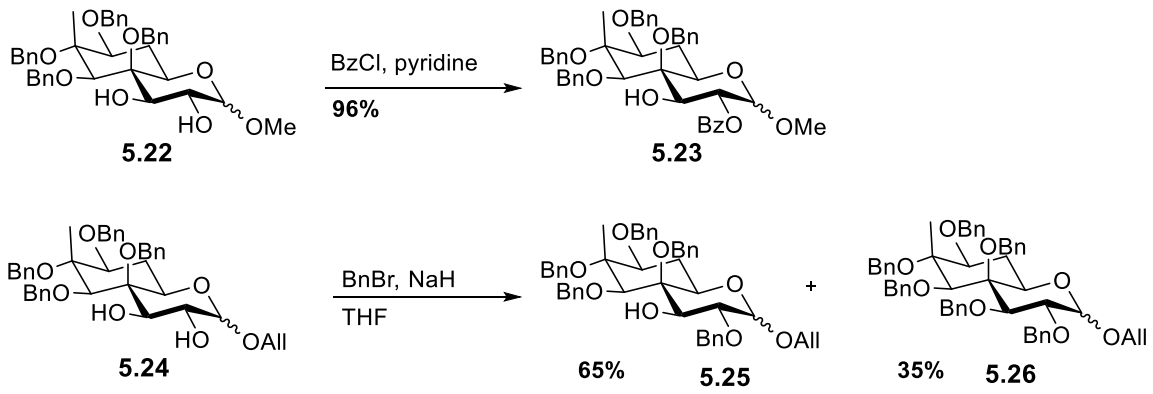


Figure 5-1: Compounds sent for testing with plants and legumes.

5.3 Future work

There is far more to discover in the reactivity of the different hydroxyl groups in bradyrhizose as well as in glycosylation reactions involving this unusual monosaccharide. In this work, the relative reactivity of the hydroxyl groups at C-2 and C-3 in structure **5.22** and **5.24** has been investigated (Scheme 5-7). In this compound, the C-3 hydroxyl group seems to be more hindered then the C-2 hydroxyl group. Also, the acceptor **5.13α** designed for the glycosylation

reactions had three free hydroxyl groups (Scheme 5-6). As mentioned in Chapter 4, the C-4 hydroxyl group did not react in the glycosylation or acetylation reactions and the regioselectivity ratio between C-7:C-8 hydroxyl groups was about 2:1. It would be interesting to determine if protection of the C-8 hydroxyl group of the acceptor **5.13α** would affect the selectivity of the glycosylation at O-7. Different donors and acceptors could be made to study the influence of protecting groups on the reactivity and selectivity of the donors and the acceptors in the glycosylation reactions of O-7. The glycosylation conditions could also be varied to find the best one to favor the α-selectivity.



Scheme 5-7: Reactivity of the hydroxyl at the second position in **5.22** and **5.24**.

Derivatives of bradyrhizose could also be made by modifying the synthesis in Chapter 3 (Figure 5-2). For example, compound **5.27** could be made by omitting the Barton–McCombie deoxygenation at C-6. Compound **5.28** could come from the diastereomer in the asymmetric dihydroxylation reaction. Compound **5.29** could be obtained by adding a hydride instead of a methyl group on the *myo*-inositol orthobenzoate ketone. Compounds **5.30**, **5.31** and others can be assembled by a mix of these startegies.

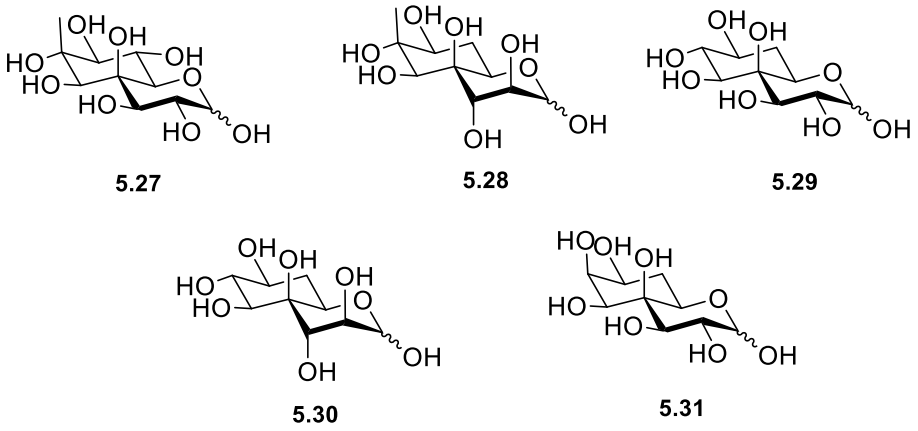
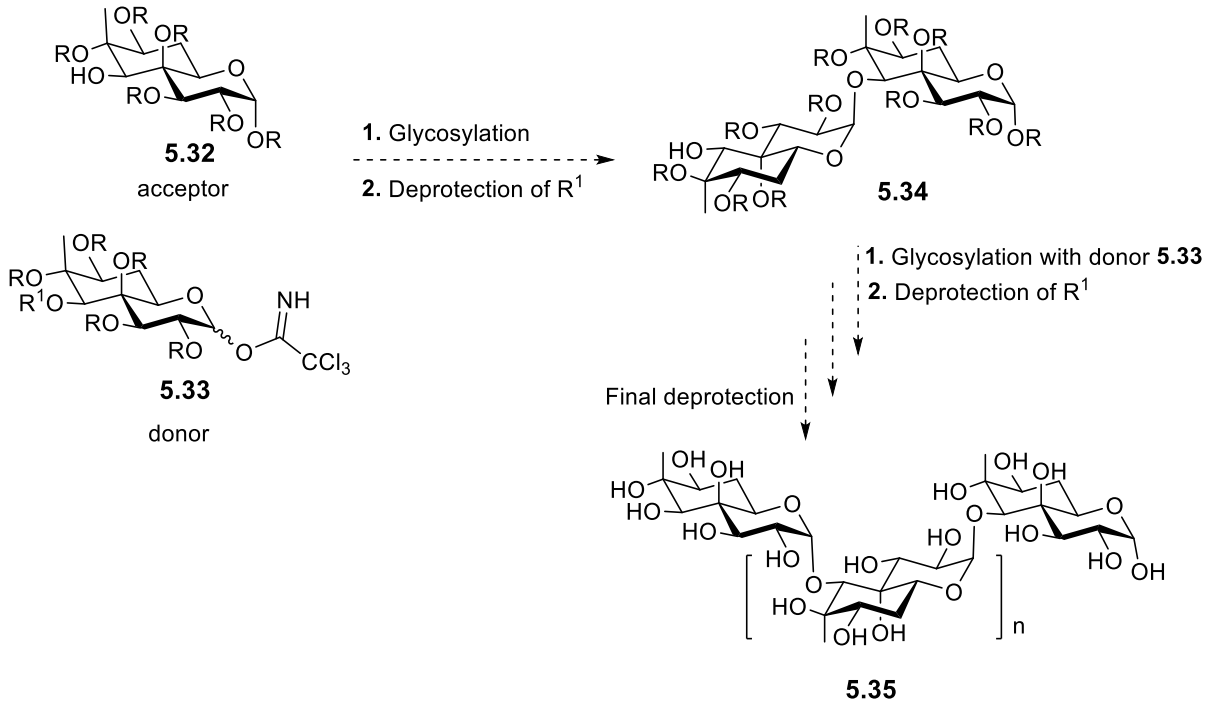


Figure 5-8: Possible derivatives of bradyrhizose.

By modifying the protecting groups on the donor, it would be possible to make oligosaccharides connected O-7 or O-9 position (Scheme 5-8), like the one found in *Bradyrhizobium* sp. BTAi1 and sp. ORS278. A different protecting group (R^1) must be used at the O-7 or O-9 and the elongation of the oligosaccharide would be possible by adding the same donor (**5.33**) after deprotection of R^1. The oligosaccharides and the bradyrhizose derivatives (Figure 5-2) could all be tested for their immunogenicity in plants and legumes.



Scheme 5-9: Synthesis of oligosaccharide **5.35** with α-(1→9)-glycosidic linkages.

5.4 References

(1) Ticozzi, C.; Zanarotti, A. Baker's Yeast Reduction of 5-Acetyl-2-Isoxazolines Synthesis of Enantiomerically Pure 2,3-Dihydroxy Ketones and 1,2,4-Triols. *Tetrahedron Lett.* **1988**, *29*, 6167–6170.

(2) Crich, D. Methodology Development and Physical Organic Chemistry: A Powerful Combination for the Advancement of Glycochemistry. *J. Org. Chem.* **2011**, *76*, 9193–9209.

(3) Silipo, A.; Leone, M. R.; Erbs, G.; Lanzetta, R.; Parrilli, M.; Chang, W. S.; Newman, M. A.; Molinaro, A. A Unique Bicyclic Monosaccharide from the Bradyrhizobium Lipopolysaccharide and Its Role in the Molecular Interaction with Plants. *Angew. Chemie - Int. Ed.* **2011**, *50*, 12610–12612.

Bibliography

Achmatowicz Jr., O.; Bielski, R. Stereoselective Total Synthesis of Methyl α-D- and α-L-Glucopyranosides. *Carbohydr. Res.* **1977**, *55*, 165–176.

Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Manna R. Synthesis of Caryose, the Carbocyclic Monosaccharide Component of the Lipopolysaccharide from *Pseudomonas caryophylli*. *Tetrahedron* **1997**, *53*, 11767–11780.

Adinolfi, M.; Corsaro, M. M.; De Castro, C.; Evidente, A.; Lanzetta, R.; Molinaro, A.; Parilli, M. Caryose : A Carbocyclic Monosaccharide from *Pseudomonas caryophylli*. *Carbohydr. Res.* **1996**, *284*, 111–118.

Adkins, H.; Billica, H. R. The Preparation of Raney Nickel Catalysts and Their Use Under Conditions Comparable with Those for Platinum and Palladium Catalysts. *J. Am. Chem. Soc.* **1948**, *70*, 695–698.

Ahmed, M. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. De Novo Enantioselective Syntheses of *Galacto*-Sugars and Deoxy Sugars via the Iterative Dihydroxylation of Dienoate. *Org. Lett.* **2005**, *7*, 745–748.

Alexander, C.; Rietschel, E. T. Invited Review: Bacterial Lipopolysaccharides and Innate Immunity. *J. Endotoxin Res.* **2001**, *7*, 167–202.

Baraldi, P. G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. Ring Cleavage of 3,5-Disubstituted 2-Isoxazolines by Molybdenum Hexacarbonyl and Water to β-Hydroxy Ketones. *Synthesis* **1987**, 276–278.

Bedini, E.; De Castro, C.; Erbs, G.; Mangoni, L.; Dow, J. M.; Newman, M. A.; Parrilli, M.; Unverzagt, C. Structure-Dependent Modulation of a Pathogen Response in Plants by Synthetic O-Antigen Polysaccharides. *J. Am. Chem. Soc.* **2005**, *127*, 2414–2416.

Belen'kii, L. I. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*; *Second Edition*; Henry Feuer, Ed. John Wiley & Sons, Inc.: 2008; pp 1-107.

Bhosekar, G.; Murali, C.; Gonnade, R. G.; Shashidhar, M. S.; Bhadbhade, M. M. Identical Molecular Strings Woven Differently by Intermolecular Interactions in Dimorphs of *Myo*-Inositol 1,3,5-Orthobenzoate. *Cryst. Growth Des.* **2005**, *5*, 1977–1982.

Blackshaw, R. E.; Molnar, L. J.; Moyer, J. R. Suitability of Legume Cover Crop-Winter Wheat Intercrops on the Semi-Arid Canadian Prairies. *Can. J. Plant Sci.* **2010**, *90*, 479–488.

Bode, J. W.; Carreira, E. M. Stereoselective Syntheses of Epothilones A and B via Nitrile Oxide Cycloadditions and Related Studies. *J. Org. Chem.* **2001**, *66*, 6410–6424.

Boger, D. L.; Borzilleri, R. M.; Nukui, S. Synthesis of (*R*)-(4-Methoxy-3,5-Dihydroxyphenyl)Glycine Derivatives: The Central Amino Acid of Vancomycin and Related Agents. *J. Org. Chem.* **1996**, *61*, 3561–3565.

Bohé, L.; Crich, D. Double Diastereoselection, Regioselectivity, and the Importance of Donor-Acceptor Complementarity in the Stereoselectivity of Glycosylation Reactions. *Trends Glycosci. Glycotechnol.* **2010**, *22*, 1–15.

Borowski, D.; Zweibohmer, T.; Ziegler, T. 1,2-Annulated Sugars: Synthesis of Polyhydroxylated 2,10-Dioxadecalins with β-Manno Configuration. *European J. Org. Chem.* **2016**, *Early view*.

Brimacombe, J. S.; Mcdonald, G.; Rahman, M. A. Double Asymmetric Induction in the Catalytic Osmylation of Some α,β-Unsaturated Octuronic Acid-Derivatives. *Carbohydr. Res.* **1989**, *205*, 422–427.

Busset, N.; De Felice, A.; Chaintreuil, C.; Gully, D.; Fardoux, J.; Romdhane, S.; Molinaro, A.; Silipo, A.; Giraud, E. The LPS *O*-Antigen in Photosynthetic *Bradyrhizobium* Strains Is Dispensable for the Establishment of a Successful Symbiosis with *Aeschynomene* Legumes. *PLOS ONE* [Online] **2016**, http://dx.doi.org/10.1371/journal.pone.0148884 (accessed Apr 17, 2016).

Campbell, N. A.; Reece, J. B.; Urry, L. A.; Cain, M. L.; Wasserman, S. A.; Minorsky, P. V.; Jackson, R. B. *Biology*; *Eight Edition*; Wilbur, B., Ed.; Pearson Benjamin Cummings: San Franscisco, 2008; pp 793-795.

Cremonesi, G.; Dalla Croce, P.; Forni, A.; Gallanti, M.; La Rosa, C. Stereoselective Synthesis of β-Substituted-L-Threonines from Enantiopure 5-Acetyl-2-Isoxazolines. *Tetrahedron* **2011**, *67*, 2925–2933.

Crich, D. Methodology Development and Physical Organic Chemistry: A Powerful Combination for the Advancement of Glycochemistry. *J. Org. Chem.* **2011**, *76*, 9193–9209.

Crich, D. Mechanism of a Chemical Glycosylation Reaction. *Acc. Chem. Res.* **2010**, *43*, 1144–1153.

Crich, D.; Sun, S. Direct Synthesis of β-Mannopyranosides by the Sulfoxide Method. *J. Org. Chem.* **1997**, *62*, 1198–1199.

Crich, D.; Sun, S. Formation of *β*-Mannopyranosides of Primary Alcohols Using the Sulfoxide Method. *J. Org. Chem.* **1996**, *61*, 4506–4507.

Dangschat, G. Acetonierung Und Konfiguration Des Meso-Inosits. *Naturwissenschaften* **1942**, *30*, 146–147.

Das, B.; Holla, H.; Mahender, G.; Banerjee, J.; Ravinder Reddy, M. Hypervalent Iodine-Mediated Interaction of Aldoximes with Activated Alkenes Including Baylis-Hillman Adducts: A New and Efficient Method for the Preparation of Nitrile Oxides from Aldoximes. *Tetrahedron Lett.* **2004**, *45*, 7347–7350.

De Castro, C.; Molinaro, A.; Lanzetta, R.; Holst, O.; Parrilli, M. The Linkage between O-Specific Caryan and Core Region in the Lipopolysaccharide of *Burkholderia caryophylli* Is Furnished by a Primer Monosaccharide. *Carbohydr. Res.* **2005**, *340*, 1802–1807.

Demchenko, A. V. 1,2-Cis *O*-Glycosylation: Methods, Strategies, Principles. *Curr. Org. Chem.* **2003**, *7*, 35–79.

Devaraj, S.; Jagdhane, R. C.; Shashidhar, M. S. Relative Reactivity of Hydroxyl Groups in Inositol Derivatives: Role of Metal Ion Chelation. *Carbohydr. Res.* **2009**, *344*, 1159–1166.

Devaraj, S.; Shashidhar, M. S.; Dixit, S. S. Chelation Controlled Regiospecific O-Substitution of *Myo*-Inositol Orthoesters: Convenient Access to Orthogonally Protected *Myo*-Inositol Derivatives. *Tetrahedron* **2005**, *61*, 529–536.

Deska, J.; Thiel, D.; Gianolio, E. The Achmatowicz Rearrangement - Oxidative Ring Expansion of Furfuryl Alcohols. *Synth.* **2015**, *47*, 3435–3450.

Diaz-Velandia, J.; Durán-Díaz, N.; Robles-Camargo, J.; Loaiza, A. E. Síntesis y Evaluación "*in vitro*" de la Actividad Antifúngica de Oximas, éteres de oxima e Isoxazoles.*Universitas Scientiarum* **2011**, *16*, 294–302.

Downie, J. A. The Roles of Extracellular Proteins, Polysaccharides and Signals in the Interactions of Rhizobia with Legume Roots. *FEMS Microbiol. Rev.* **2010**, *34*, 150–170.

Duchek, J.; Adams, D. R.; Hudlicky, T. Chemoenzymatic Synthesis of Inositols, Conduritols, and Cyclitol Analogues. *Chem. Rev.* **2011**, *111*, 4223–4258.

Fleischman, D.; Kramer, D. Photosynthetic Rhizobia. *Biochim. Biophys. Acta - Bioenerg.* **1998**, *1364*, 17–36.

Fürstner, A.; Wuchrer, M. Concise Approach to The "Higher Sugar" core of the Nucleoside Antibiotic Hikizimycin. *Chem. Eur. J.* **2006**, *12*, 76–89

Gao, P. C.; Zhu, S. Y.; Cao, H.; Yang, J. S. Total Synthesis of Marine Glycosphingolipid Vesparioside B. *J. Am. Chem. Soc.* **2016**, *138*, 1684–1688.

Gayen, K. S.; Sengupta, T.; Saima, Y.; Das, A.; Maiti, D. K.; Mitra, A. Cu(0) Nanoparticle Catalyzed Efficient Reductive Cleavage of Isoxazoline, Carbonyl Azide and Domino Cyclization in Water Medium. *Green Chem.* **2012**, *14*, 1589–1592.

Gefflaut, T.; Martin, C.; Delor, S.; Besse, P.; Veschambre, H.; Bolte, J. Deoxysugars via Microbial Reduction of 5-Acyl-Isoxazolines : Application to the Synthesis of 3-Deoxy-D-Fructose and Derivatives. *J. Org. Chem.* **2001**, *66*, 2296–2301.

Ghabrial, S. S.; Thomsen, I.; Torssell, K. B. G.; Synthesis of Biheteroaromatic Compounds via the Isoxazoline Route. *Acta Chemica Scandinavica*. **1987**, 426–434.

Gilbert, I. H.; Holmes, A. B.; Pestchanker, M. J.; Young, R. C. Lewis Acid-Catalysed Rearrangements of *Myo*-Inositol Orthoformate Derivatives. *Carbohydr. Res.* **1992**, *234*, 117–130

Giraud, E.; Moulin, L.; Vallenet, D.; Barbe, V.; Cytryn, E.; Avarre, J.-C.; Jaubert, M.; Simon, D.; Cartieaux, F.; Prin, Y.; Bena, G.; Hannibal, L.; Fardoux, J.; Kojadinovic, M.; Vuillet, L.; Lajus, A.; Cruveiller, S.; Rouy, Z.; Mangenot, S.; Segurens, B.; Dossat, C.; Franck, W. L.; Chang, W.-S.; Saunders, E.; Bruce, D.; Richardson, P.; Normand, P.; Dreyfus, B.; Pignol, D.; Stacey, G.; Emerich, D.; Verméglio, A.; Médigue, C.; Sadowsky, M. Legumes Symbioses: Absence of Nod Genes in Photosynthetic Bradyrhizobia. *Science* **2007**, *316*, 1307–1312.

Gnauck, A.; Lentle, R. G.; Kruger, M. C. The Characteristics and Function of Bacterial Lipopolysaccharides and Their Endotoxic Potential in Humans. *Int. Rev. Immunol.* **2015**, *185*, 1–31.

Godage, H. Y.; Riley, A. M.; Woodman, T. J.; Thomas, M. P.; Mahon, M. F.; Potter, B. V. L. Regioselective Opening of *Myo*-Inositol Orthoesters: Mechanism and Synthetic Utility. *J. Org. Chem.* **2013**, *78*, 2275–2288.

Goto, G.; Kawakita, K.; Okutani, T.; Miki, T. An Improved Synthesis of *N*-Hydroxyamino Acids and Their Esters Using (*Z*)-2-Furaldehyde Oxime. *Chem. Pharm. Bull.* **1986**, *34*, 3202–3207.

Grossman, D. J. *Legume Inoculation for Organic Farming Systems*, 2015 http://articles.extension.org/pages/64401/legume-inoculation-for-organic-farming-systems (accessed Jan 19, 2016).

Han, B.; Yang, X. L.; Fang, R.; Yu, W.; Wang, C.; Duan, X. Y.; Liu, S. Oxime Radical Promoted Dioxygenation, Oxyamination, and Diamination of Alkenes: Synthesis of Isoxazolines and Cyclic Nitrones. *Angew. Chemie - Int. Ed.* **2012**, *51*, 8816–8820.

Harris, J. M.; Keränen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. Syntheses of Four D- and L-Hexoses via Diastereoselective and Enantioselective Dihydroxylation Reactions. *Carbohydr. Res.* **2000**, *328*, 17–36.

Hirsch, A. M. *Brief History of the Discovery of Nitrogen-Fixing Organisms*, 2009, https://www.mcdb.ucla.edu/Research/Hirsch/famousfixers.php (accessed March 16, 2016).

Hirsch, A. M.; Lum, M. R.; Downie, J. A. What Makes the Rhizobia-Legume Symbiosis So Special? *Plant Physiol.* **2001**, *127*, 1484–1492.

Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. Modern Methods of Monosaccharide Synthesis from Non-Carbohydrate Sources, *Chem. Rev.* **1996**, *96*, 1195.

Jagdhane, R. C.; Shashidhar, M. S. Orthogonally Protected Cyclohexanehexols by A "one Reaction - One Product" approach: Efficient Access to Cyclitols and Their Analogs. *Eur. J. Org. Chem.* **2010**, 2945–2953.

Jiang, D.; Chen, Y. Reduction of Δ^2-Isoxazolines to β-Hydroxy Ketones with Iron and Ammonium Chloride as Reducing Agent. *J. Org. Chem.* **2008**, *73*, 9181–9183.

Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483–2547.

Lemieux, R. U.; Hendriks, K. B.; Stick, R. V; James, K. Halide Ion Catalyzed Glycosidation Reactions. Syntheses of α-Linked Disaccharides. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.

Lemieux, R. U.; James, K.; Nagabhushan, T. L. Chemical Syntheses of α-linked Disaccharides *Can. J. Chem.* **1973**, 51, 42–47.

Lemieux, R. U.; Sakakibara, S. Chemical Synthesis of. α-Linked 2'-Amino-2'deoxydisaccharides. *Can. J. Chem.* **1973**, *51*, 48–52.

Leone, M. R. Structure of Macromolecules from Gram-Negative Bacteria Involved in Elicitation of Plant Immune System, Univeristy of Naples Federico II, 2010.

Leone, M. R.; Lackner, G.; Silipo, A.; Lanzetta, R.; Molinaro, A.; Hertweck, C. An Unusual Galactofuranose Lipopolysaccharide That Ensures the Intracellular Survival of Toxin-Producing Bacteria in Their Fungal Host. *Angew. Chemie - Int. Ed.* **2010**, *49*, 7476–7480.

Ley, S. V. The Changing Face of Organic Synthesis. *Tetrahedron* **2010**, *66*, 6270–6292.

Li, W.; Silipo, A.; Molinaro, A.; Yu, B. Synthesis of Bradyrhizose, a Unique Inositol-Fused Monosaccharide Relevant to a Nod-Factor Independent Nitrogen Fixation. *Chem. Commun.* **2015**, *51*, 6964–6967.

Masson-Boivin, C.; Giraud, E.; Perret, X.; Batut, J. Establishing Nitrogen-Fixing Symbiosis with Legumes: How Many Rhizobium Recipes? *Trends Microbiol.* **2009**, *17*, 458–466.

Meta, C. T.; Koide, K. Trans-Selective Conversions of γ-Hydroxy-α,*β*-Alkynoic Esters to γ -Hydroxy- α,*β* -Alkenoic Esters. *Org. Lett.* **2004**, *6*, 1785–1787.

Narasimhan, S.; Balakumar, R. Synthetic Applications of Zinc Borohydride. *Aldrichimica Acta* **1998**, *31*, 19–26.

Nigudkar, S. S.; Demchenko, A. V. Stereocontrolled 1,2-*cis* Glycosylation as the Driving Force of Progress in Synthetic Carbohydrate Chemistry. *Chem. Sci.* **2015**, *6*, 2687–2704.

Posternak, T. Recherches Dans La Série Des Cyclites VI. Sur La Configuration de La Méso-Inosite, de La Scyllite et D'un Inososе Obtenu Par Voie Biochimique (*Scyllo*-Ms-Inososе). *Helv. Chim. Acta* **1942**, *25*, 746–752.

Prasad, K. R.; Swain, B. Enantioselective Synthesis of Possible Diastereomers of Heptadeca-1-Ene-4,6-Diyne-3,8,9,10-Tetrol; Putative Structure of a Conjugated Diyne Natural Product Isolated from Hydrocotyle Leucocephala. *J. Org. Chem.* **2011**, *76*, 2029–2039.

Procter, D. J; Flowers II, R. A.; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide*; RSC Publishing: Cambridge, UK: 2009, pp 1–204.

Riley, A. M.; Godage, H. Y.; Mahon, M. F.; Potter, B. V. L. Chiral Desymmetrisation of *Myo*-Inositol 1,3,5-Orthobenzoate Gives Rapid Access to Precursors for Second Messenger Analogues. *Tetrahedron Asymmetry* **2006**, *17* , 171–174.

Sakagami, M.; Hamana, H. A Selective Ring Opening Reaction of 4,6-*O*-Benzylidene Acetals in Carbohydrates Using Trialkylsilane Derivatives. *Tetrahedron Lett.* **2000**, *41*, 5547–5551.

Sarmah, M. P.; Shashidhar, M. S.; Sureshan, K. M.; Gonnade, R. G.; Bhadbhade, M. M. Sulfonate Protecting Groups. Synthesis of O- and C-Methylated Inositols: D- and L-Ononitol, D- and L-Laminitol, Mytilitol and *Scyllo*-Inositol Methyl Ether. *Tetrahedron* **2005**, *61*, 4437–4446.

Scherer, J. Über Eine Neue, Aus Dem Muskelfleisch Gewonnene Zuckerart. *Justus Liebigs Ann. Chem.* **1850**, *73*, 322–328.

Schmidt, R. R.; Toepfer, A. Glycosylation with Highly Reactive Glycosyl Donors: Efficiency of the Inverse Procedure. *Tetrahedron Lett.* **1991**, *32*, 3353–3356.

Shashidhar, M. S. Regioselective Protection of *Myo*-Inositol Orthoesters – Recent Developments. *ARKIVOC* **2002**, 63–75.

Shie, C.-R.; Tzeng, Z.-H.; Wang, C.-C.; Hung, S.-C. Metal Trifluoromethanesulfonate Catalyzed Regioselective Reductive Ring Opening of Benzylidene Acetals. *J. Chin. Chem. Soc.* **2009**, *56*, 510–523.

Silipo, A.; Leone, M. R.; Erbs, G.; Lanzetta, R.; Parrilli, M.; Chang, W. S.; Newman, M. A.; Molinaro, A. A Unique Bicyclic Monosaccharide from the Bradyrhizobium Lipopolysaccharide and Its Role in the Molecular Interaction with Plants. *Angew. Chemie - Int. Ed.* **2011**, *50*, 12610–12612.

Spino, C.; Beaulieu, C. A Practical and Highly Stereoselective Umpolung Alternative to the Alkylation of Chiral Enolates. *J. Am. Chem. Soc.* **1998**, *120*, 11832–11833.

Sun, L.; Li, P.; Zhao, K. Stabilization of Glycosyl Sulfonium Ions for Stereoselective *O*-Glycosylation. *Tetrahedron Lett.* **1994**, *35*, 7147–7150.

Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. Regioselective Protection and Deprotection of Inositol Hydroxyl Groups. *Chem. Rev.* **2003**, *103*, 4477–4503.

Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Gonnade, R. G.; Bhadbhade, M. M. Sulfonate Protecting Groups. Regioselective Sulfonylation of *Myo*-Inositol Orthoesters - Improved Synthesis of Precursors of D- and L-*Myo*-Inositol 1,3,4,5-Tetrakisphosphate, *Myo*-Inositol 1,3,4,5,6-Pentakisphosphate and Related Derivatives. *Carbohydr. Res.* **2002**, *337*, 2399–2410.

Taniguchi, T.; Nakamura, K.; Ogasawara, K. Non-Carbohydrate Route to Levoglucosenine and Its Enantiomer Employing Asymmetric Dihydroxylation. *Synlett* **1996**, 971–972.

Taniguchi, T.; Ogasawara, K. Extremely Facile and Selective Nickel-Catalyzed Allyl Ether Cleavage. *Angew. Chemie - Int. Ed.* **1998**, *37*, 1136–1137.

Ticozzi, C.; Zanarotti, A. Baker's Yeast Reduction of 5-Acetyl-2-Isoxazolines Synthesis of Enantiomerically Pure 2,3-Dihydroxy Ketones and 1,2,4-Triols. *Tetrahedron Lett.* **1988**, *29*, 6167–6170.

Thiessen Martens, J.; Entz, M. Integrating Green Manure and Grazing Systems: A Review. *Can. J. Plant Sci.* **2011**, *91*, 811–824.

Trost, B. M.; Ball, Z. T. Alkyne Hydrosilylation Catalyzed by a Cationic Ruthenium Complex: Efficient and General Trans Addition. *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655.

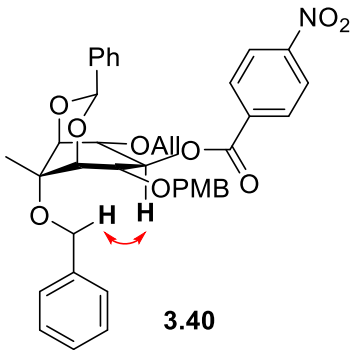
Unverzagt, C. Structure-Dependent Modulation of a Pathogen Response in Plants by Synthetic O-Antigen Polysaccharides. *J. Am. Chem. Soc.* **2005**, *127*, 2414–2416.

Wegmann, B.; Schmidt, R. R. The Application of the Trichloroacetimidate Method to the Synthesis of α-D-Gluco- and α-D-Galactopyranosides. *J. Carbohydr. Chem.* **1987**, *6*, 357–375

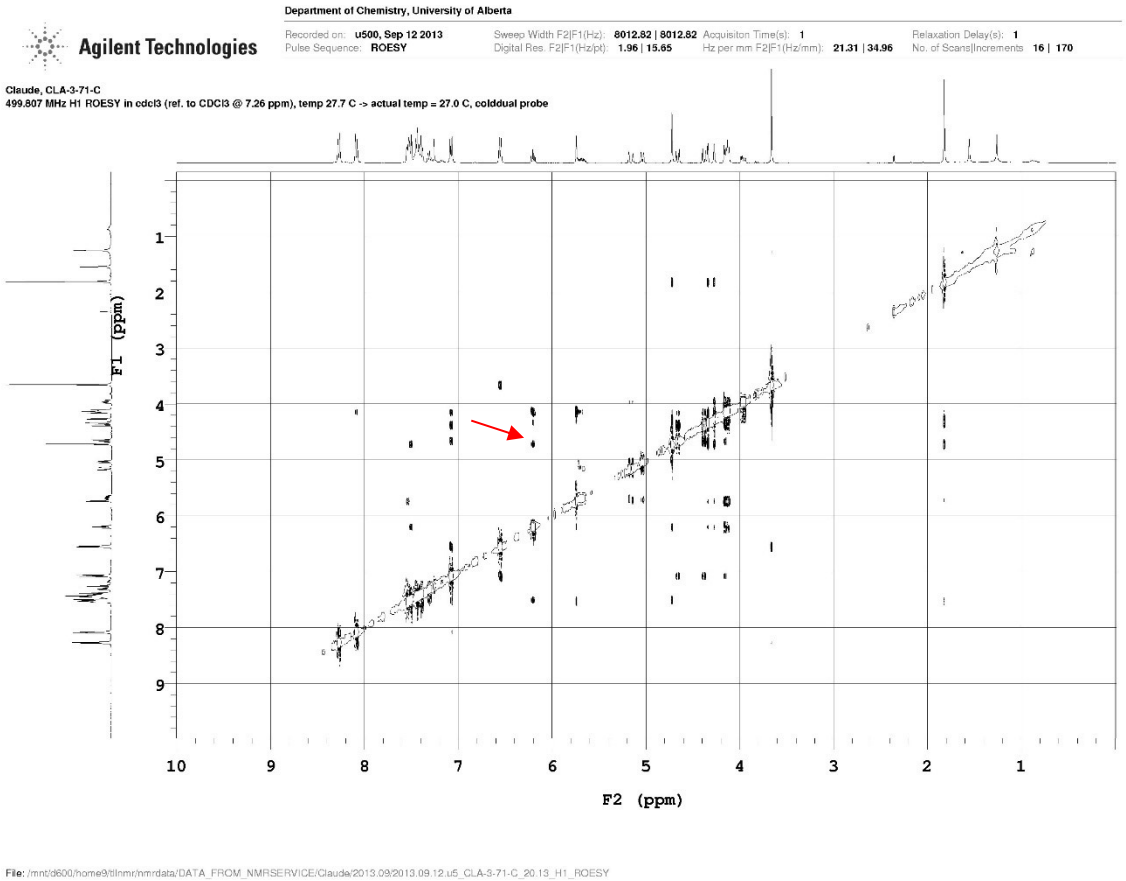
Appendices

Appendix 1: Selected copies of NMR spectra

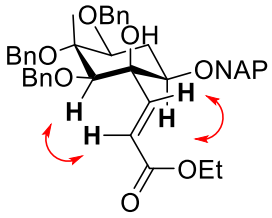
ROESY spectrum of 3.40



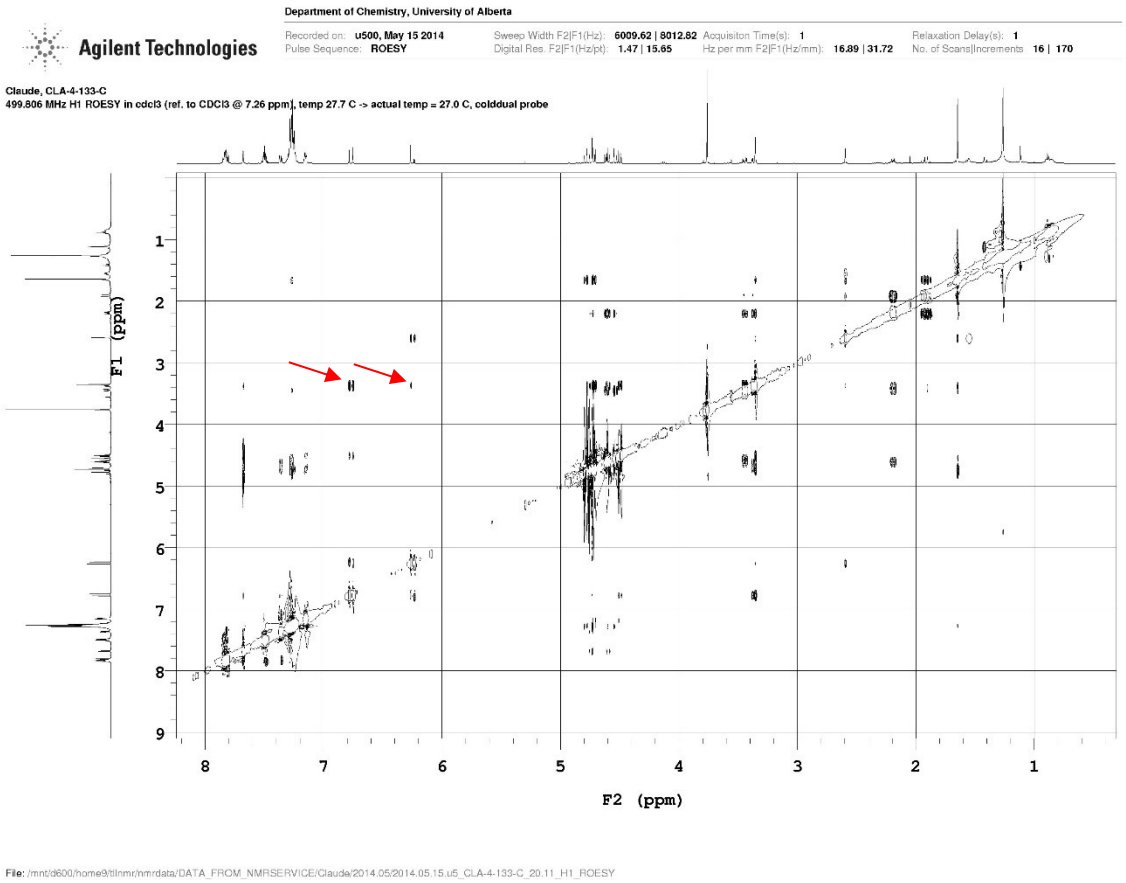
3.40



ROESY spectrum of 3.55

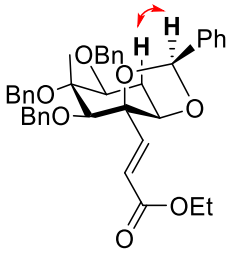


3.55

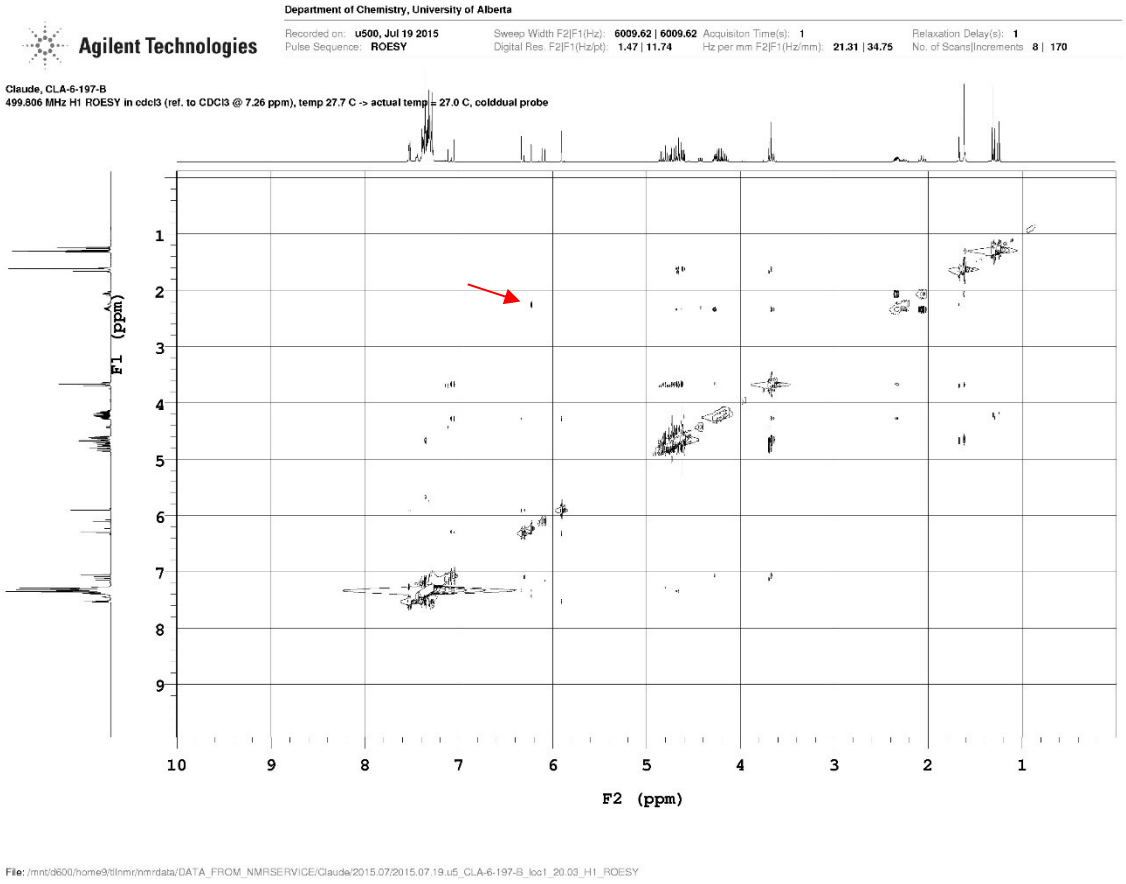


File: /mnt/d600/home9/tlnmr/nmrdata/DATA_FROM_NMRSERVICE/Claude/2014.05/2014.05.15.u5_CLA-4-133-C_20.11_H1_ROESY

ROESY spectrum of 3.78



3.78a



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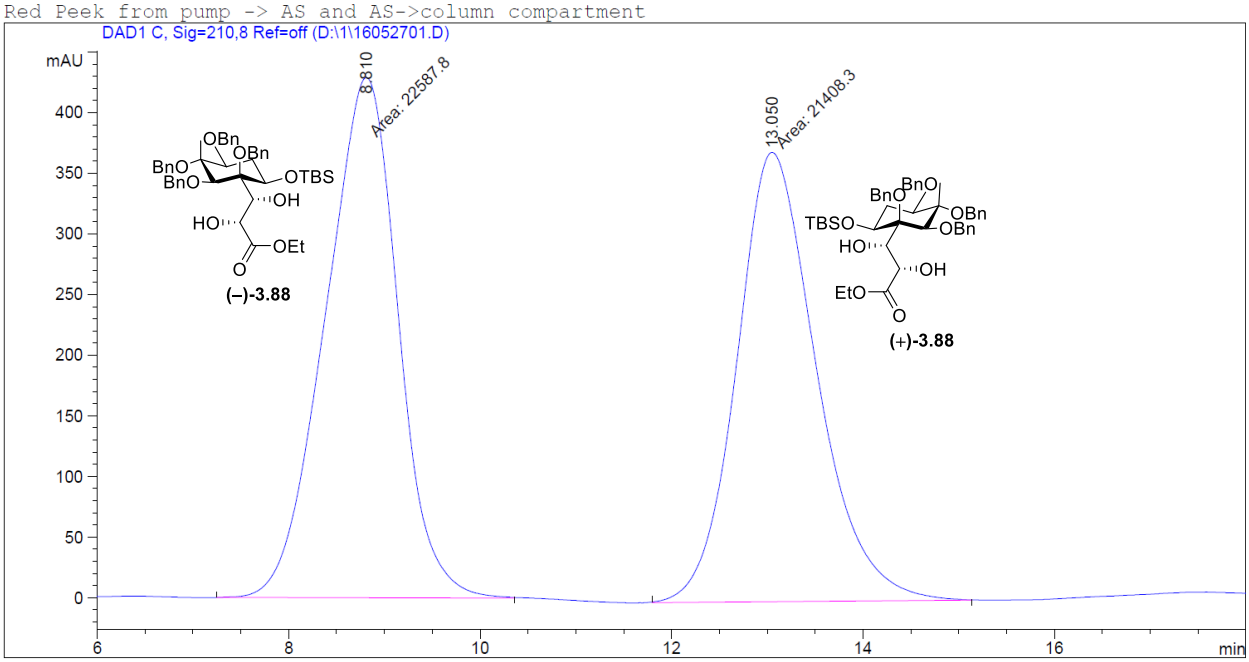
Appendix 2: Chromatographs for enantiomeric excess measurements

HPLC data for racemic compound 3.88

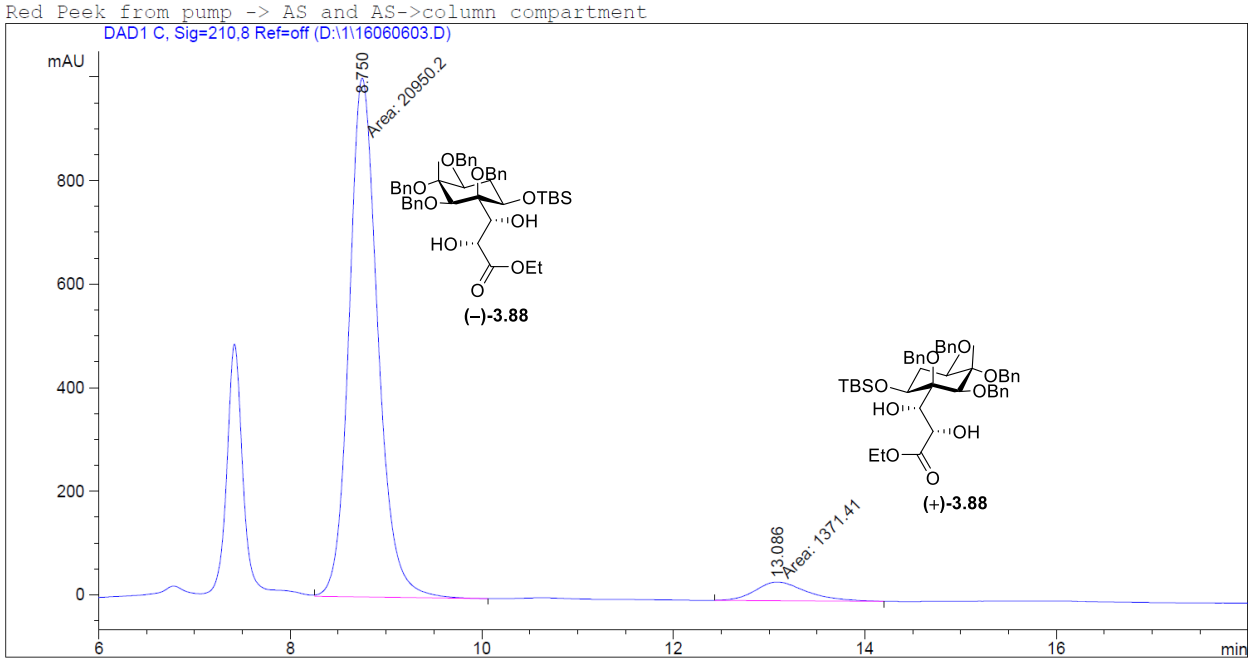
```
==================================================================
Injection Date  : 5/27/2016 12:45:49 PM          Seq. Line :   1
Sample Name     : ClA-0-8161c                     Location : Vial 1
Acq. Operator   : Ed                                 Inj :   1
Acq. Instrument : Instrument 1                  Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\1\METHODS\EDH99 5.M
Last changed    : 3/30/2015 4:21:12 PM by Ho-Yan
Analysis Method : C:\HPCHEM\1\METHODS\GEN_ANRR.M
Last changed    : 10/3/2016 12:59:56 PM by Ed
                  (modified after loading)
Agilent SB-C18 4.6*250mm, 5um; 1mL/min, 40'C
M.P.A:0.1% AA/FA in H2O M.P.B:0.1% AA/FA in ACN
Red Peek from pump -> AS and AS->column compartment
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.810 MM    0.8780 2.25878e4   428.79379  51.3406
   2  13.050 MM    0.9634 2.14083e4   370.37372  48.6594

Totals :                  4.39961e4   799.16751

==================================================================
                        *** End of Report ***
```

HPLC data for recovered SM (3.88) after reaction with 1.5 equivalent of (*S*)-MTPA

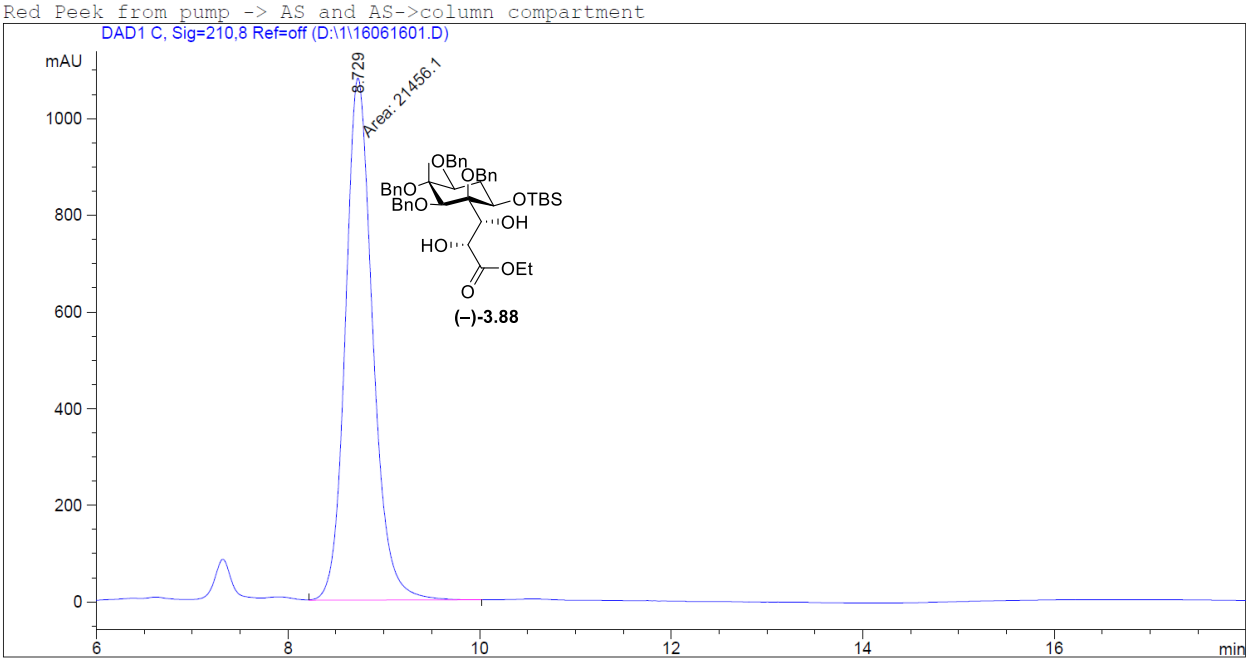
```
======================================================================
Injection Date  : 6/6/2016 4:10:46 PM           Seq. Line :   3
Sample Name     : ClA-8-193D                     Location : Vial 2
Acq. Operator   : Samantha                          Inj :   1
Acq. Instrument : Instrument 1                 Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 0.5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\EDH99 5.M
Last changed    : 6/6/2016 3:02:41 PM by Samantha
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\GEN_ANRR.M
Last changed    : 10/3/2016 12:59:56 PM by Ed
                  (modified after loading)
Agilent SB-C18 4.6*250mm, 5um; 1mL/min, 40'C
M.P.A:0.1% AA/FA in H2O M.P.B:0.1% AA/FA in ACN
Red Peek from pump -> AS and AS->column compartment
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.750 MM    0.3484 2.09502e4  1002.11981  93.8561
   2  13.086 MM    0.6290 1371.41296   36.33802   6.1439

Totals :                  2.23216e4  1038.45783

======================================================================
                        *** End of Report ***
```

HPLC data for recovered SM (3.88) after reaction with 2.0 equivalent of (*S*)-MTPA

```
======================================================================
Injection Date  : 6/16/2016 11:01:52 AM          Seq. Line :   1
Sample Name     : ClA-8-207D                      Location : Vial 3
Acq. Operator   : Ed                                  Inj :   1
Acq. Instrument : Instrument 1                  Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\1\METHODS\EDH99 5.M
Last changed    : 6/16/2016 11:29:32 AM by Ed
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\GEN_ANRR.M
Last changed    : 10/6/2016 2:54:08 PM by Ed
                  (modified after loading)
Agilent SB-C18 4.6*250mm, 5um; 1mL/min, 40'C
M.P.A:0.1% AA/FA in H2O M.P.B:0.1% AA/FA in ACN
Red Peek from pump -> AS and AS->column compartment
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.729 MM    0.3310 2.14561e4  1080.34241 100.0000

Totals :                  2.14561e4  1080.34241

======================================================================
                        *** End of Report ***
```

Appendix 3: Crystal structure reports

X-ray crystallographic data for 2.33

XCL Code: TLL1301 **Date:** 14 January 2013

Compound: 1-{3-(furan-2-yl)-4,5-dihydroisoxazol-5-yl}ethyl (acetyloxy)(phenyl)acetate

Formula: $C_{19}H_{19}NO_6$

Supervisor: T. L. Lowary **Crystallographer:** M. J. Ferguson

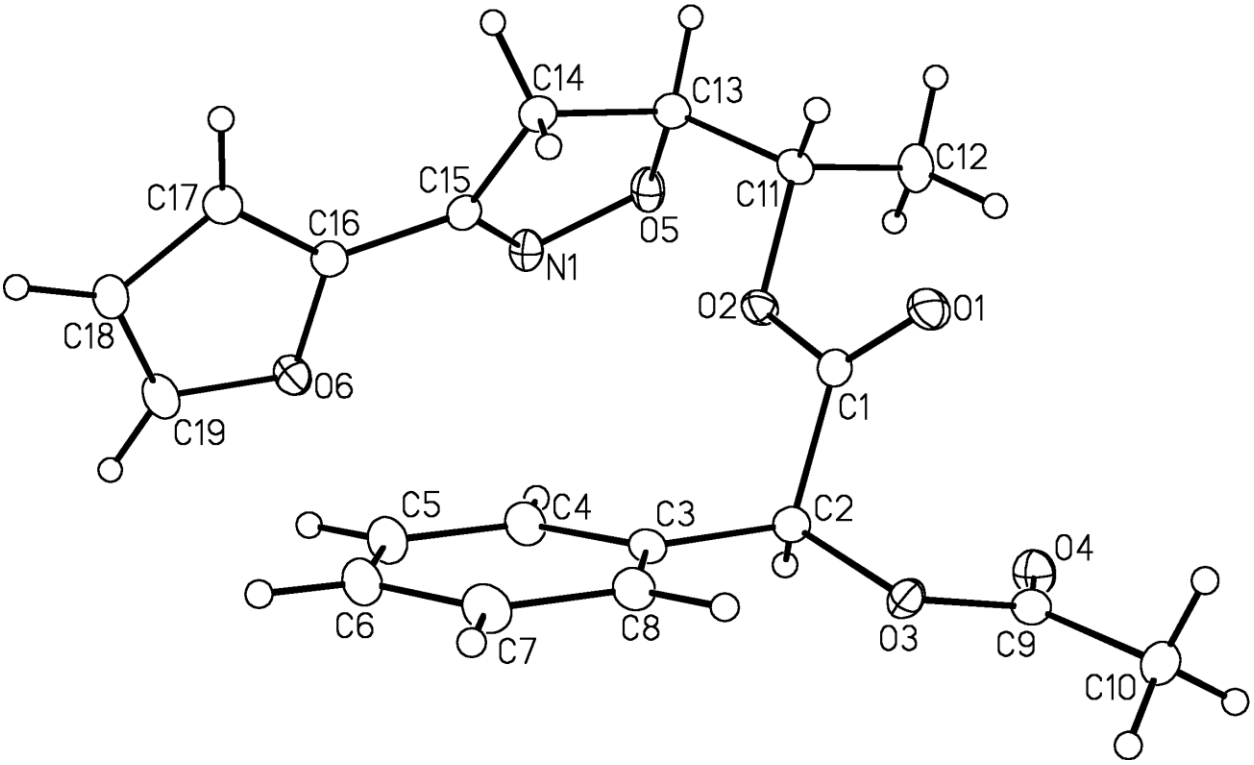


Figure Legend: Perspective view of the 1-{3-(furan-2-yl)-4,5-dihydroisoxazol-5-yl}ethyl (acetyloxy)(phenyl)acetate molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Table 1. Crystallographic Experimental Details

A. Crystal Data

formula	$C_{19}H_{19}NO_6$
formula weight	357.35
crystal dimensions (mm)	0.52 × 0.30 × 0.08
crystal system	monoclinic
space group	$P2_1$ (No. 4)
unit cell parameters[a]	
a (Å)	9.7367 (6)
b (Å)	8.6594 (6)
c (Å)	11.3723 (7)
β (deg)	110.3450 (10)
V (Å^3)	899.03 (10)
Z	2
ρ_{calcd} (g cm^{-3})	1.320
μ (mm^{-1})	0.099

B. Data Collection and Refinement Conditions

diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–100
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	54.94
total data collected	8180 (-12 ≤ h ≤ 12, -11 ≤ k ≤ 11, -14 ≤ l ≤ 14)
independent reflections	2203 (R_{int} = 0.0195)

number of observed reflections (*NO*)	2013 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–97*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[c])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9917–0.9503
data/restraints/parameters	2203 / 0 / 236
Flack absolute structure parameter[d]	0.1(8)
goodness-of-fit (*S*)[e] [all data]	1.044
final *R* indices[f]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0268
wR_2 [all data]	0.0670
largest difference peak and hole	0.151 and –0.159 e Å^{-3}

[a]Obtained from least-squares refinement of 7537 reflections with $4.46° < 2\theta < 48.40$

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

[d]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. The low anomalous scattering power of the atoms in this structure (none heavier than oxygen) implies that the data cannot be used for absolute structure assignment. Friedel pairs were merged prior to final refinement and thus the calculated Flack parameter is meaningless.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0336P)^2 + 0.1084P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.61394(14)	0.42028(16)	0.83726(12)	0.0395(3)*
O2	0.74452(12)	0.29414(15)	0.73902(10)	0.0310(3)*
O3	0.39810(12)	0.21507(15)	0.76265(10)	0.0310(3)*
O4	0.55869(14)	0.08954(17)	0.92448(11)	0.0408(3)*
O5	1.01148(13)	0.23018(17)	0.71087(11)	0.0383(3)*
O6	0.77760(15)	0.13216(15)	0.33456(11)	0.0363(3)*
N1	0.95329(15)	0.18020(19)	0.58509(13)	0.0342(3)*
C1	0.62508(18)	0.3209(2)	0.76768(14)	0.0281(3)*
C2	0.50365(17)	0.2069(2)	0.70090(15)	0.0282(3)*
C3	0.42897(17)	0.2441(2)	0.56353(15)	0.0275(3)*
C4	0.4965(2)	0.1989(2)	0.47943(17)	0.0372(4)*
C5	0.4329(2)	0.2326(3)	0.35353(17)	0.0442(5)*
C6	0.3011(2)	0.3117(3)	0.30996(16)	0.0422(4)*
C7	0.2334(2)	0.3557(2)	0.39285(17)	0.0401(4)*
C8	0.29687(19)	0.3226(2)	0.51956(16)	0.0328(4)*
C9	0.44571(19)	0.1585(2)	0.88122(15)	0.0317(4)*
C10	0.34148(19)	0.1968(2)	0.94651(16)	0.0372(4)*
C11	0.87146(18)	0.3902(2)	0.80256(15)	0.0343(4)*
C12	0.9508(2)	0.3282(3)	0.93265(16)	0.0495(6)*
C13	0.96435(19)	0.3882(2)	0.72016(16)	0.0347(4)*
C14	0.8872(2)	0.4401(2)	0.58471(16)	0.0336(4)*
C15	0.88628(17)	0.2929(2)	0.51655(14)	0.0285(3)*
C16	0.81689(17)	0.2771(2)	0.38253(15)	0.0297(3)*
C17	0.7821(2)	0.3822(2)	0.28934(16)	0.0364(4)*
C18	0.7173(2)	0.2988(2)	0.17572(16)	0.0383(4)*
C19	0.7160(2)	0.1505(3)	0.20773(17)	0.0384(4)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C1	1.199(2)	C3	C8	1.385(2)
O2	C1	1.3327(19)	C4	C5	1.379(3)
O2	C11	1.456(2)	C5	C6	1.385(3)
O3	C2	1.4339(18)	C6	C7	1.379(3)
O3	C9	1.356(2)	C7	C8	1.386(2)
O4	C9	1.197(2)	C9	C10	1.488(2)
O5	N1	1.4110(18)	C11	C12	1.510(3)
O5	C13	1.459(2)	C11	C13	1.512(2)
O6	C16	1.369(2)	C13	C14	1.528(2)
O6	C19	1.365(2)	C14	C15	1.490(3)
N1	C15	1.277(2)	C15	C16	1.443(2)
C1	C2	1.525(2)	C16	C17	1.348(2)
C2	C3	1.511(2)	C17	C18	1.422(3)
C3	C4	1.392(2)	C18	C19	1.336(3)

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O2	C11	116.20(13)	O3	C9	O4	122.45(16)
C2	O3	C9	114.44(12)	O3	C9	C10	111.03(15)
N1	O5	C13	109.61(13)	O4	C9	C10	126.51(16)
C16	O6	C19	105.86(14)	O2	C11	C12	109.87(16)
O5	N1	C15	108.92(14)	O2	C11	C13	105.85(13)
O1	C1	O2	124.97(16)	C12	C11	C13	112.99(15)
O1	C1	C2	124.12(15)	O5	C13	C11	109.08(15)
O2	C1	C2	110.91(14)	O5	C13	C14	105.05(14)
O3	C2	C1	106.71(13)	C11	C13	C14	115.53(15)
O3	C2	C3	109.06(12)	C13	C14	C15	100.65(15)
C1	C2	C3	112.80(14)	N1	C15	C14	115.25(14)
C2	C3	C4	118.55(15)	N1	C15	C16	121.65(16)
C2	C3	C8	122.04(14)	C14	C15	C16	123.10(16)
C4	C3	C8	119.41(16)	O6	C16	C15	118.08(15)
C3	C4	C5	120.34(18)	O6	C16	C17	110.29(14)
C4	C5	C6	120.10(17)	C15	C16	C17	131.62(17)
C5	C6	C7	119.74(17)	C16	C17	C18	106.39(17)
C6	C7	C8	120.46(17)	C17	C18	C19	106.50(16)
C3	C8	C7	119.95(16)	O6	C19	C18	110.95(17)

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C11	O2	C1	O1	2.8(2)	C2	C3	C4	C5	-179.09(17)
C11	O2	C1	C2	-176.69(14)	C8	C3	C4	C5	0.4(3)
C1	O2	C11	C12	80.79(19)	C2	C3	C8	C7	179.28(17)
C1	O2	C11	C13	-156.90(15)	C4	C3	C8	C7	-0.2(3)
C9	O3	C2	C1	-68.61(17)	C3	C4	C5	C6	-0.1(3)
C9	O3	C2	C3	169.25(15)	C4	C5	C6	C7	-0.4(3)
C2	O3	C9	O4	-9.2(2)	C5	C6	C7	C8	0.6(3)
C2	O3	C9	C10	169.66(15)	C6	C7	C8	C3	-0.3(3)
C13	O5	N1	C15	4.84(17)	O2	C11	C13	O5	-61.98(18)
N1	O5	C13	C11	117.16(14)	O2	C11	C13	C14	56.0(2)
N1	O5	C13	C14	-7.26(16)	C12	C11	C13	O5	58.3(2)
C19	O6	C16	C15	-179.76(14)	C12	C11	C13	C14	176.32(17)
C19	O6	C16	C17	-0.40(19)	O5	C13	C14	C15	6.55(16)
C16	O6	C19	C18	0.8(2)	C11	C13	C14	C15	-113.68(17)
O5	N1	C15	C14	-0.13(19)	C13	C14	C15	N1	-4.23(19)
O5	N1	C15	C16	179.10(13)	C13	C14	C15	C16	176.55(14)
O1	C1	C2	O3	-15.3(2)	N1	C15	C16	O6	23.0(2)
O1	C1	C2	C3	104.43(19)	N1	C15	C16	C17	-156.25(19)
O2	C1	C2	O3	164.16(13)	C14	C15	C16	O6	-157.87(16)
O2	C1	C2	C3	-76.10(17)	C14	C15	C16	C17	22.9(3)
O3	C2	C3	C4	-160.87(16)	O6	C16	C17	C18	-0.1(2)
O3	C2	C3	C8	19.7(2)	C15	C16	C17	C18	179.12(17)
C1	C2	C3	C4	80.8(2)	C16	C17	C18	C19	0.6(2)
C1	C2	C3	C8	-98.69(18)	C17	C18	C19	O6	-0.9(2)

Table 6. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0415(7)	0.0382(7)	0.0436(7)	-0.0130(6)	0.0208(6)	-0.0051(6)
O2	0.0245(5)	0.0371(7)	0.0318(6)	-0.0078(5)	0.0105(4)	-0.0041(5)
O3	0.0266(5)	0.0383(7)	0.0294(6)	0.0061(5)	0.0113(5)	0.0002(5)
O4	0.0372(7)	0.0453(8)	0.0356(7)	0.0045(6)	0.0073(6)	0.0062(6)
O5	0.0308(6)	0.0542(8)	0.0279(6)	0.0036(6)	0.0079(5)	0.0079(6)
O6	0.0411(7)	0.0302(7)	0.0323(6)	0.0002(5)	0.0059(5)	0.0040(5)
N1	0.0299(7)	0.0435(9)	0.0291(7)	0.0028(7)	0.0102(6)	0.0070(7)
C1	0.0287(8)	0.0301(8)	0.0267(7)	0.0001(7)	0.0111(6)	0.0010(7)
C2	0.0261(7)	0.0281(8)	0.0317(8)	-0.0018(7)	0.0115(7)	0.0002(7)
C3	0.0276(7)	0.0255(8)	0.0287(8)	-0.0039(6)	0.0087(6)	-0.0031(6)
C4	0.0308(8)	0.0456(11)	0.0363(10)	-0.0067(8)	0.0132(7)	0.0024(8)
C5	0.0430(10)	0.0588(13)	0.0344(9)	-0.0109(9)	0.0182(8)	-0.0054(10)
C6	0.0468(10)	0.0474(12)	0.0284(8)	-0.0009(9)	0.0082(8)	-0.0053(9)
C7	0.0384(10)	0.0369(10)	0.0389(10)	0.0003(8)	0.0057(8)	0.0050(8)
C8	0.0330(8)	0.0318(9)	0.0345(8)	-0.0042(7)	0.0127(7)	0.0014(7)
C9	0.0315(9)	0.0315(9)	0.0294(8)	0.0017(7)	0.0071(7)	-0.0053(7)
C10	0.0383(9)	0.0438(11)	0.0301(9)	0.0054(8)	0.0128(7)	-0.0029(8)
C11	0.0279(8)	0.0431(11)	0.0306(8)	-0.0094(8)	0.0086(7)	-0.0095(8)
C12	0.0375(10)	0.0807(17)	0.0292(9)	-0.0026(10)	0.0101(8)	-0.0066(10)
C13	0.0283(8)	0.0426(11)	0.0320(9)	-0.0018(8)	0.0089(7)	-0.0071(8)
C14	0.0355(9)	0.0319(9)	0.0337(9)	0.0005(7)	0.0122(7)	-0.0034(8)
C15	0.0240(7)	0.0325(9)	0.0299(8)	0.0032(7)	0.0107(6)	0.0011(7)
C16	0.0265(7)	0.0306(9)	0.0318(8)	0.0000(7)	0.0098(6)	0.0022(7)
C17	0.0381(10)	0.0328(10)	0.0343(9)	0.0032(8)	0.0073(8)	-0.0010(8)
C18	0.0368(9)	0.0459(12)	0.0286(8)	0.0040(9)	0.0070(7)	0.0025(9)
C19	0.0376(10)	0.0421(10)	0.0309(9)	-0.0044(8)	0.0060(8)	0.0076(8)

The form of the anisotropic displacement parameter is:

$$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$$

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H2	0.5452	0.1001	0.7096	0.034
H4	0.5868	0.1445	0.5089	0.045
H5	0.4795	0.2015	0.2966	0.053
H6	0.2576	0.3356	0.2233	0.051
H7	0.1425	0.4091	0.3629	0.048
H8	0.2499	0.3538	0.5762	0.039
H10A	0.3565	0.1257	1.0169	0.045
H10B	0.2408	0.1870	0.8876	0.045
H10C	0.3585	0.3030	0.9780	0.045
H11	0.8384	0.4983	0.8088	0.041
H12A	0.8856	0.3318	0.9816	0.059
H12B	1.0378	0.3914	0.9739	0.059
H12C	0.9806	0.2212	0.9269	0.059
H13	1.0527	0.4543	0.7593	0.042
H14A	0.7866	0.4773	0.5708	0.040
H14B	0.9430	0.5218	0.5601	0.040
H17	0.7978	0.4905	0.2979	0.044
H18	0.6819	0.3403	0.0933	0.046
H19	0.6772	0.0688	0.1500	0.046

X-ray crystallographic data for 3.37

XCL Code: TLL1303 **Date:** 25 September 2013

Compound: 2-*C*-Methyl-4-*O*-(4-methoxybenzyl)-*scyllo*-inositol 1,3,5-orthobenzoate

Formula: $C_{22}H_{24}O_7$

Supervisor: T. L. Lowary **Crystallographer:** R. McDonald

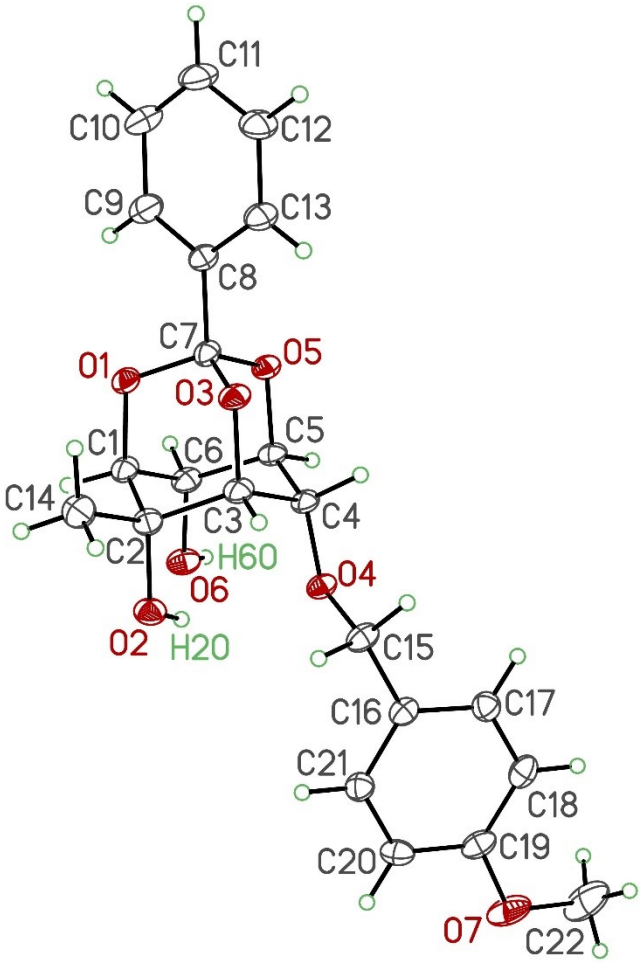


Figure Legend: Perspective view of the 2-*C*-methyl-4-*O*-(4-methoxybenzyl)-*scyllo*-inositol 1,3,5-orthobenzoate molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

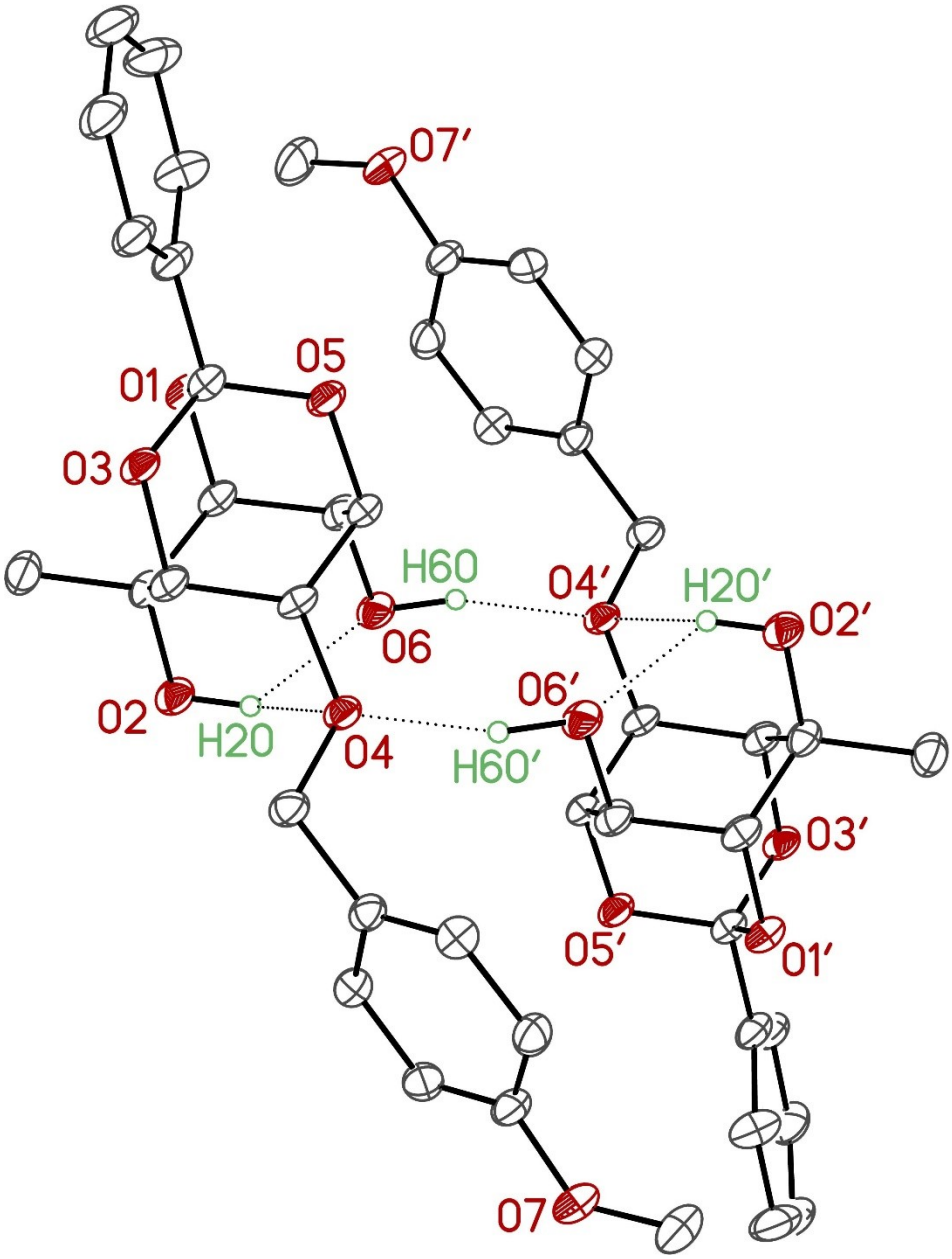


Figure Legend: Illustration of hydrogen-bonded interactions (dotted lines) within and between adjacent molecules in the crystal lattice. Primed atoms are related to unprimed ones via the crystallographic inversion center (0, 0, 0).

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{22}H_{24}O_7$
formula weight	400.41
crystal dimensions (mm)	0.29 × 0.07 × 0.02
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	6.0738 (5)
b (Å)	31.982 (2)
c (Å)	10.2483 (8)
β (deg)	102.879 (5)
V (Å^3)	1940.7 (3)
Z	4
ρ_{calcd} (g cm^{-3})	1.370
μ (mm^{-1})	0.850
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100
scan type	ω and ϕ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	142.76
total data collected	12688 ($-7 \le h \le 7$, $-39 \le k \le 39$, $-12 \le l \le 12$)
independent reflections	3770 (R_{int} = 0.0664)
number of observed reflections (*NO*)	2489 [$F_o^2 \ge 2\sigma(F_o^2)$]

structure solution method	direct methods/dual space (*SHELXD*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	1.0000–0.7800
data/restraints/parameters	3770 / 0 / 271
extinction coefficient (x)[e]	0.0027(6)
goodness-of-fit (S)[f] [all data]	0.987
final R indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0682
wR_2 [all data]	0.2117
largest difference peak and hole	0.279 and –0.545 e Å^{-3}

[a]Obtained from least-squares refinement of 3898 reflections with $5.52° < 2\theta < 141.94°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr.* **2002**, *D58*, 1772-1779.

[d]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

[e]$F_c^* = kF_c[1 + x\{0.001F_c^2\lambda^3/\sin(2\theta)\}]^{-1/4}$ where k is the overall scale factor.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.1343P)^2]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	-0.1145(3)	0.14763(5)	-0.0280(2)	0.0341(5)*
O2	-0.1410(3)	0.07417(6)	0.2459(2)	0.0378(5)*
O3	0.2355(3)	0.14658(5)	0.1182(2)	0.0331(5)*
O4	0.2253(3)	0.03244(5)	0.17412(18)	0.0308(5)*
O5	0.1844(3)	0.11182(5)	-0.0847(2)	0.0338(5)*
O6	-0.2184(3)	0.03613(5)	0.0018(2)	0.0378(5)*
O7	0.4350(5)	-0.14385(6)	0.4399(2)	0.0620(7)*
C1	-0.1917(5)	0.11089(7)	0.0310(3)	0.0325(6)*
C2	-0.0774(5)	0.11034(7)	0.1804(3)	0.0323(6)*
C3	0.1784(5)	0.10996(7)	0.1880(3)	0.0325(6)*
C4	0.2562(4)	0.07230(7)	0.1176(3)	0.0308(6)*
C5	0.1256(4)	0.07295(7)	-0.0279(3)	0.0302(6)*
C6	-0.1318(5)	0.07320(7)	-0.0456(3)	0.0339(6)*
C7	0.1196(4)	0.14700(7)	-0.0174(3)	0.0303(6)*
C8	0.1848(5)	0.18590(8)	-0.0836(3)	0.0370(7)*
C9	0.0321(6)	0.20360(10)	-0.1906(4)	0.0520(9)*
C10	0.0941(7)	0.23875(10)	-0.2533(4)	0.0607(10)*
C11	0.3052(6)	0.25627(9)	-0.2116(4)	0.0575(10)*
C12	0.4571(6)	0.23824(9)	-0.1073(4)	0.0496(8)*
C13	0.3981(5)	0.20310(8)	-0.0429(3)	0.0410(7)*
C14	-0.1463(5)	0.14779(8)	0.2533(3)	0.0431(7)*
C15	0.3627(5)	0.02804(8)	0.3095(3)	0.0356(7)*
C16	0.3842(4)	-0.01765(8)	0.3419(3)	0.0319(6)*
C17	0.5613(5)	-0.04093(8)	0.3159(3)	0.0373(7)*
C18	0.5845(5)	-0.08324(9)	0.3446(3)	0.0410(7)*
C19	0.4275(6)	-0.10246(8)	0.4050(3)	0.0410(7)*
C20	0.2484(5)	-0.07986(8)	0.4325(3)	0.0395(7)*
C21	0.2278(5)	-0.03777(8)	0.4014(3)	0.0348(6)*
C22	0.6049(8)	-0.16905(11)	0.4018(4)	0.0785(14)*
H2O	-0.127(8)	0.0504(16)	0.197(5)	0.107(18)
H6O	-0.226(6)	0.0154(12)	-0.073(4)	0.079(13)

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C1	1.447(3)	C4	C5	1.525(4)
O1	C7	1.402(3)	C5	C6	1.533(4)
O2	C2	1.433(3)	C7	C8	1.511(3)
O3	C3	1.454(3)	C8	C9	1.390(4)
O3	C7	1.411(3)	C8	C13	1.384(4)
O4	C4	1.430(3)	C9	C10	1.388(4)
O4	C15	1.458(3)	C10	C11	1.377(5)
O5	C5	1.450(3)	C11	C12	1.374(5)
O5	C7	1.420(3)	C12	C13	1.390(4)
O6	C6	1.426(3)	C15	C16	1.498(3)
O7	C19	1.369(3)	C16	C17	1.382(4)
O7	C22	1.430(5)	C16	C21	1.395(4)
C1	C2	1.534(4)	C17	C18	1.385(4)
C1	C6	1.526(4)	C18	C19	1.391(4)
C2	C3	1.538(4)	C19	C20	1.386(4)
C2	C14	1.519(3)	C20	C21	1.383(4)
C3	C4	1.532(4)			

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O1	C7	111.93(18)	O1	C7	O3	110.6(2)
C3	O3	C7	111.79(18)	O1	C7	O5	111.1(2)
C4	O4	C15	111.87(19)	O1	C7	C8	108.4(2)
C5	O5	C7	111.4(2)	O3	C7	O5	109.83(19)
C19	O7	C22	117.2(3)	O3	C7	C8	109.1(2)
O1	C1	C2	108.0(2)	O5	C7	C8	107.8(2)
O1	C1	C6	106.9(2)	C7	C8	C9	119.6(3)
C2	C1	C6	113.4(2)	C7	C8	C13	120.9(3)
O2	C2	C1	111.6(2)	C9	C8	C13	119.4(3)
O2	C2	C3	110.2(2)	C8	C9	C10	119.6(3)
O2	C2	C14	105.9(2)	C9	C10	C11	121.0(3)
C1	C2	C3	106.1(2)	C10	C11	C12	119.2(3)
C1	C2	C14	111.6(2)	C11	C12	C13	120.6(3)
C3	C2	C14	111.5(2)	C8	C13	C12	120.1(3)
O3	C3	C2	108.5(2)	O4	C15	C16	108.0(2)
O3	C3	C4	105.6(2)	C15	C16	C17	121.0(3)
C2	C3	C4	113.4(2)	C15	C16	C21	120.9(3)
O4	C4	C3	115.4(2)	C17	C16	C21	118.1(2)
O4	C4	C5	108.76(19)	C16	C17	C18	122.1(3)
C3	C4	C5	107.6(2)	C17	C18	C19	118.6(3)
O5	C5	C4	106.45(19)	O7	C19	C18	123.9(3)
O5	C5	C6	106.47(19)	O7	C19	C20	115.7(3)
C4	C5	C6	114.2(2)	C18	C19	C20	120.5(3)
O6	C6	C1	109.5(2)	C19	C20	C21	119.7(3)
O6	C6	C5	113.5(2)	C16	C21	C20	121.0(3)
C1	C6	C5	107.3(2)				

Table 5. Hydrogen-Bonded Interactions

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	∠D–H···A (deg)	Note
O2–H2O···O4	0.92(5)	2.28(5)	2.829(3)	118(3)	
O2–H2O···O6	0.92(5)	2.01(5)	2.727(3)	133(4)	
O6–H6O···O4[a]	1.01(4)	1.85(4)	2.833(3)	165(3)	[a]At $\bar{x}$, $\bar{y}$, $\bar{z}$.

Table 6. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C7	O1	C1	C2	61.7(3)	O3	C3	C4	C5	-61.1(2)
C7	O1	C1	C6	-60.7(3)	C2	C3	C4	O4	-63.9(3)
C1	O1	C7	O3	-61.6(2)	C2	C3	C4	C5	57.6(3)
C1	O1	C7	O5	60.6(3)	O4	C4	C5	O5	-173.26(19)
C1	O1	C7	C8	178.9(2)	O4	C4	C5	C6	69.5(3)
C7	O3	C3	C2	-59.7(3)	C3	C4	C5	O5	61.1(3)
C7	O3	C3	C4	62.2(3)	C3	C4	C5	C6	-56.0(3)
C3	O3	C7	O1	60.4(2)	O5	C5	C6	O6	178.1(2)
C3	O3	C7	O5	-62.5(3)	O5	C5	C6	C1	-60.8(3)
C3	O3	C7	C8	179.5(2)	C4	C5	C6	O6	-64.7(3)
C15	O4	C4	C3	-64.5(3)	C4	C5	C6	C1	56.4(3)
C15	O4	C4	C5	174.6(2)	O1	C7	C8	C9	-30.6(4)
C4	O4	C15	C16	-160.5(2)	O1	C7	C8	C13	152.3(3)
C7	O5	C5	C4	-61.4(3)	O3	C7	C8	C9	-151.0(3)
C7	O5	C5	C6	60.8(3)	O3	C7	C8	C13	31.8(4)
C5	O5	C7	O1	-60.8(3)	O5	C7	C8	C9	89.8(3)
C5	O5	C7	O3	61.8(3)	O5	C7	C8	C13	-87.4(3)
C5	O5	C7	C8	-179.4(2)	C7	C8	C9	C10	-178.5(3)
C22	O7	C19	C18	-5.0(5)	C13	C8	C9	C10	-1.3(5)
C22	O7	C19	C20	174.3(3)	C7	C8	C13	C12	178.3(3)
O1	C1	C2	O2	-178.6(2)	C9	C8	C13	C12	1.1(5)
O1	C1	C2	C3	-58.6(2)	C8	C9	C10	C11	0.4(6)
O1	C1	C2	C14	63.2(3)	C9	C10	C11	C12	0.8(6)
C6	C1	C2	O2	-60.3(3)	C10	C11	C12	C13	-1.0(5)
C6	C1	C2	C3	59.7(3)	C11	C12	C13	C8	0.0(5)
C6	C1	C2	C14	-178.6(2)	O4	C15	C16	C17	91.0(3)
O1	C1	C6	O6	-175.88(19)	O4	C15	C16	C21	-90.1(3)
O1	C1	C6	C5	60.5(3)	C15	C16	C17	C18	-179.8(3)
C2	C1	C6	O6	65.2(3)	C21	C16	C17	C18	1.2(4)
C2	C1	C6	C5	-58.4(3)	C15	C16	C21	C20	-179.4(3)
O2	C2	C3	O3	178.8(2)	C17	C16	C21	C20	-0.5(4)
O2	C2	C3	C4	61.8(3)	C16	C17	C18	C19	-1.8(4)
C1	C2	C3	O3	57.9(2)	C17	C18	C19	O7	-179.0(3)
C1	C2	C3	C4	-59.1(3)	C17	C18	C19	C20	1.7(5)
C14	C2	C3	O3	-63.9(3)	O7	C19	C20	C21	179.6(3)
C14	C2	C3	C4	179.1(2)	C18	C19	C20	C21	-1.0(5)
O3	C3	C4	O4	177.38(19)	C19	C20	C21	C16	0.4(4)

Table 7. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0335(10)	0.0221(8)	0.0462(12)	0.0051(8)	0.0077(9)	0.0002(7)
O2	0.0441(12)	0.0267(9)	0.0450(13)	0.0018(8)	0.0149(9)	-0.0060(8)
O3	0.0376(11)	0.0205(8)	0.0394(12)	0.0021(7)	0.0051(8)	-0.0058(7)
O4	0.0361(10)	0.0214(8)	0.0322(11)	0.0023(7)	0.0021(8)	-0.0030(7)
O5	0.0405(11)	0.0206(8)	0.0420(12)	0.0044(8)	0.0129(9)	0.0011(7)
O6	0.0470(12)	0.0247(9)	0.0400(12)	-0.0008(8)	0.0057(9)	-0.0101(8)
O7	0.104(2)	0.0245(10)	0.0582(16)	0.0099(10)	0.0194(14)	0.0093(11)
C1	0.0302(14)	0.0215(11)	0.0439(18)	0.0029(11)	0.0042(12)	-0.0035(9)
C2	0.0363(15)	0.0210(11)	0.0397(17)	-0.0017(11)	0.0090(12)	-0.0035(9)
C3	0.0356(15)	0.0203(11)	0.0405(17)	0.0024(11)	0.0065(12)	-0.0055(9)
C4	0.0325(14)	0.0189(11)	0.0400(16)	0.0057(10)	0.0062(11)	-0.0028(9)
C5	0.0393(15)	0.0185(11)	0.0332(15)	0.0015(10)	0.0092(12)	-0.0023(10)
C6	0.0375(15)	0.0222(12)	0.0396(17)	0.0004(11)	0.0039(12)	-0.0062(10)
C7	0.0297(14)	0.0224(11)	0.0372(16)	0.0018(10)	0.0040(11)	-0.0006(9)
C8	0.0412(16)	0.0217(11)	0.0503(19)	0.0037(11)	0.0148(13)	0.0017(10)
C9	0.0487(19)	0.0398(16)	0.066(2)	0.0177(15)	0.0092(16)	0.0031(14)
C10	0.072(2)	0.0415(17)	0.070(3)	0.0261(17)	0.019(2)	0.0122(16)
C11	0.077(3)	0.0279(14)	0.075(3)	0.0141(15)	0.033(2)	0.0015(15)
C12	0.058(2)	0.0288(14)	0.066(2)	0.0001(14)	0.0221(17)	-0.0100(13)
C13	0.0490(18)	0.0245(12)	0.0512(19)	0.0032(12)	0.0145(14)	-0.0013(11)
C14	0.0514(18)	0.0295(14)	0.051(2)	-0.0063(12)	0.0171(15)	-0.0008(12)
C15	0.0416(15)	0.0264(12)	0.0333(16)	0.0012(11)	-0.0036(12)	-0.0024(11)
C16	0.0345(14)	0.0241(12)	0.0336(16)	-0.0012(10)	0.0005(12)	-0.0026(10)
C17	0.0339(15)	0.0364(14)	0.0409(18)	0.0005(12)	0.0070(12)	-0.0006(11)
C18	0.0452(17)	0.0354(14)	0.0402(18)	-0.0024(12)	0.0048(13)	0.0116(12)
C19	0.0576(19)	0.0227(12)	0.0395(18)	0.0022(11)	0.0041(14)	0.0014(12)
C20	0.0500(18)	0.0318(13)	0.0391(17)	0.0028(12)	0.0151(13)	-0.0069(12)
C21	0.0357(14)	0.0306(13)	0.0378(17)	-0.0004(11)	0.0078(12)	-0.0005(10)
C22	0.124(4)	0.0382(17)	0.069(3)	0.0026(18)	0.012(2)	0.031(2)

The form of the anisotropic displacement parameter is:

$$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$$

Table 8. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H1	-0.3593	0.1123	0.0202	0.039
H3	0.2623	0.1107	0.2837	0.039
H4	0.4204	0.0758	0.1193	0.037
H5	0.1721	0.0487	-0.0772	0.036
H6	-0.2031	0.0767	-0.1428	0.041
H9	-0.1138	0.1917	-0.2207	0.062
H10	-0.0108	0.2509	-0.3262	0.073
H11	0.3453	0.2805	-0.2545	0.069
H12	0.6039	0.2499	-0.0789	0.060
H13	0.5043	0.1909	0.0292	0.049
H14A	-0.0696	0.1465	0.3481	0.052
H14B	-0.3101	0.1474	0.2451	0.052
H14C	-0.1036	0.1736	0.2137	0.052
H15A	0.2902	0.0427	0.3739	0.043
H15B	0.5139	0.0404	0.3151	0.043
H17	0.6706	-0.0275	0.2770	0.045
H18	0.7051	-0.0988	0.3234	0.049
H20	0.1403	-0.0932	0.4725	0.047
H21	0.1054	-0.0223	0.4208	0.042
H22A	0.5924	-0.1979	0.4318	0.094
H22B	0.7545	-0.1580	0.4434	0.094
H22C	0.5843	-0.1686	0.3043	0.094

X-ray crystallographic data for 3.42

XCL Code: TLL1401 **Date:** 11 June 2014

Compound: 2,3-Bis(benzyloxy)-4-{(4-methoxybenzyl)oxy}-2-methyl-5-(naphthalen-2-ylmethoxy)-6-(prop-2-en-1-yloxy)cyclohexanol

Formula: $C_{43}H_{46}O_7$

Supervisor: T. L. Lowary **Crystallographer:** R. McDonald

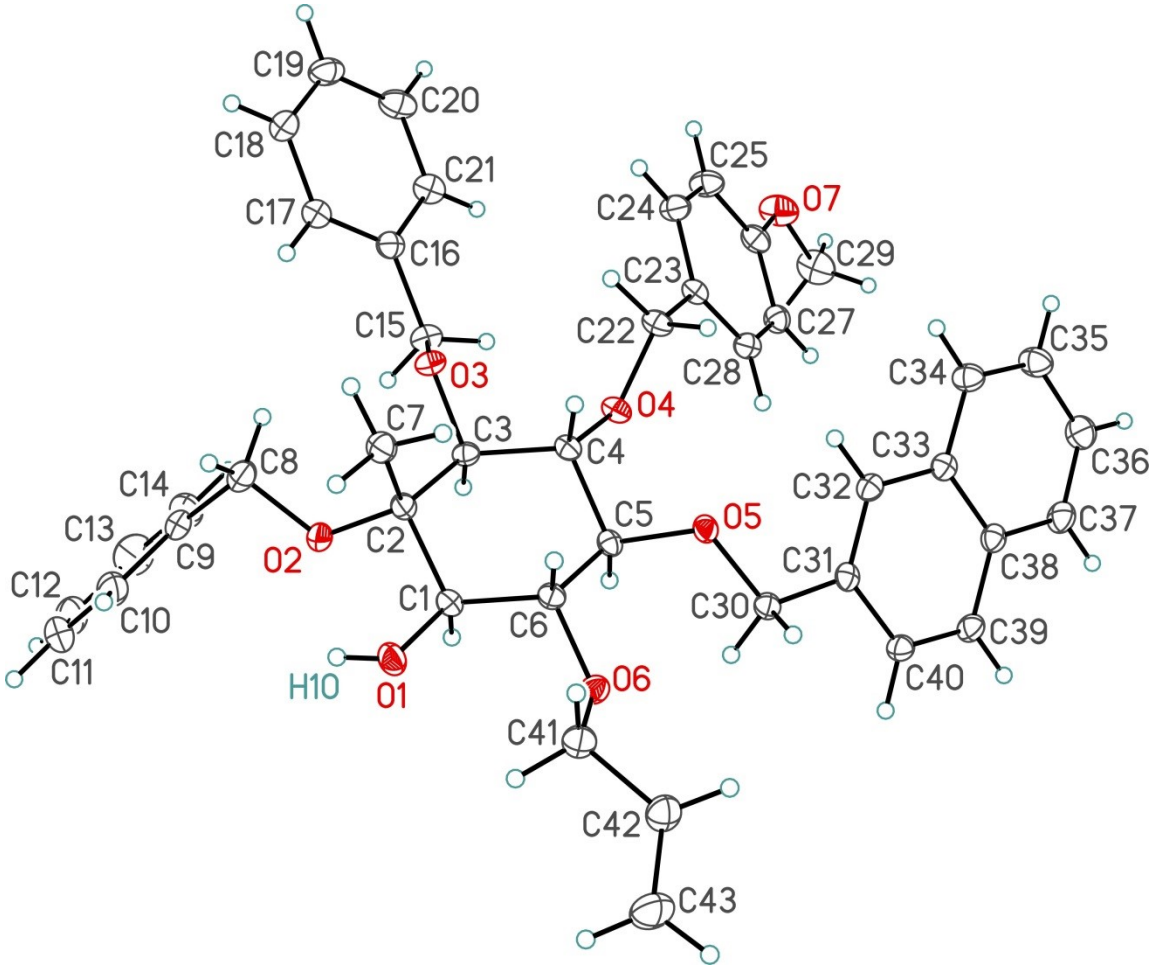


Figure Legend: Perspective view of the 2,3-bis(benzyloxy)-4-{(4-methoxybenzyl)oxy}-2-methyl-5-(naphthalen-2-ylmethoxy)-6-(prop-2-en-1-yloxy)cyclohexanol molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

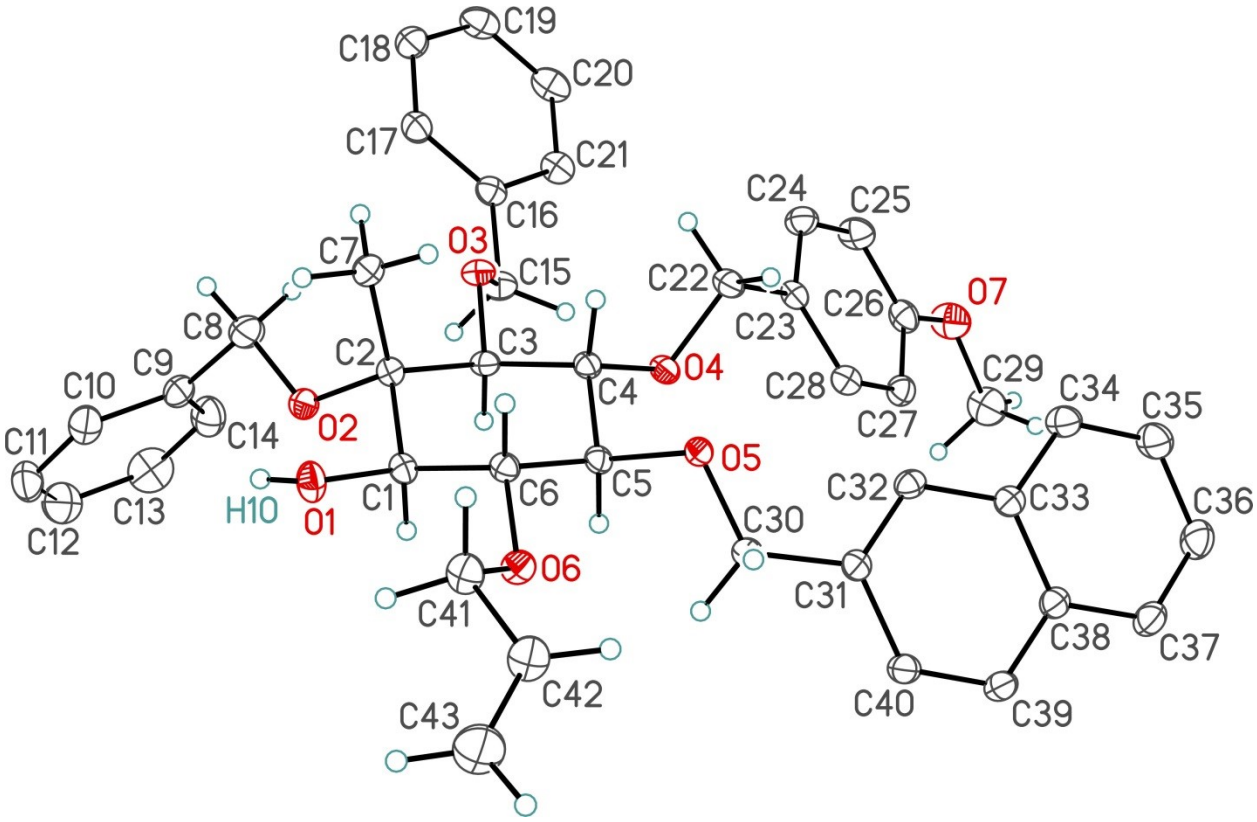


Figure Legend: Alternate view of the molecule. Aromatic-group hydrogens have been omitted.

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{43}H_{46}O_7$
formula weight	674.80
crystal dimensions (mm)	0.75 × 0.13 × 0.10
crystal system	orthorhombic
space group	*Pbcn* (No. 60)
unit cell parameters[a]	
a (Å)	15.8086 (2)
b (Å)	8.50710 (10)
c (Å)	52.6797 (7)
V (Å^3)	7084.65 (15)
Z	8
ρ_{calcd} (g cm^{-3})	1.265
μ (mm^{-1})	0.680
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100
scan type	ω and ϕ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	146.19
total data collected	45813 (-19 ≤ *h* ≤ 19, -10 ≤ *k* ≤ 9, -65 ≤ *l* ≤ 65)
independent reflections	6990 (R_{int} = 0.0399)
number of observed reflections (*NO*)	6469 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods/dual space (*SHELXD*[c])

refinement method	full-matrix least-squares on F^2 (*SHELXL–2013*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	1.0000–0.6161
data/restraints/parameters	6990 / 0 / 455
goodness-of-fit (S)[e] [all data]	1.144
final R indices[f]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0470
wR_2 [all data]	0.1198
largest difference peak and hole	0.306 and –0.295 e Å^{-3}

[a]Obtained from least-squares refinement of 9959 reflections with $6.52° < 2\theta < 144.66°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr.* **2002**, *D58*, 1772-1779.

[d]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0476P)^2 + 3.5278P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.13474(8)	0.16678(15)	0.46789(2)	0.0334(3)*
O2	0.00634(6)	0.09052(13)	0.43542(2)	0.0304(2)*
O3	0.00282(6)	0.27991(12)	0.38685(2)	0.0268(2)*
O4	0.16661(7)	0.27778(12)	0.36417(2)	0.0262(2)*
O5	0.30209(6)	0.35063(12)	0.39678(2)	0.0257(2)*
O6	0.29610(7)	0.20273(13)	0.44509(2)	0.0285(2)*
O7	0.17006(9)	0.23214(17)	0.24555(2)	0.0479(3)*
C1	0.14426(9)	0.16441(18)	0.44090(3)	0.0248(3)*
C2	0.06214(9)	0.21760(17)	0.42795(3)	0.0249(3)*
C3	0.07567(9)	0.21392(17)	0.39909(3)	0.0235(3)*
C4	0.15475(9)	0.30502(17)	0.39073(3)	0.0226(3)*
C5	0.23392(9)	0.25263(17)	0.40490(3)	0.0224(3)*
C6	0.22078(9)	0.26267(18)	0.43369(3)	0.0240(3)*
C7	0.03119(10)	0.37701(19)	0.43733(3)	0.0311(3)*
C8	-0.08343(10)	0.1094(2)	0.43430(4)	0.0425(4)*
C9	-0.12015(10)	-0.0497(2)	0.43979(3)	0.0339(4)*
C10	-0.13297(11)	-0.0998(2)	0.46462(3)	0.0402(4)*
C11	-0.16342(12)	-0.2485(3)	0.46967(4)	0.0484(5)*
C12	-0.18214(13)	-0.3499(3)	0.44998(5)	0.0543(5)*
C13	-0.17002(14)	-0.3011(3)	0.42534(5)	0.0585(6)*
C14	-0.13904(12)	-0.1531(3)	0.42030(4)	0.0466(5)*
C15	-0.02691(10)	0.19157(19)	0.36554(3)	0.0309(3)*
C16	-0.10249(10)	0.27367(18)	0.35434(3)	0.0288(3)*
C17	-0.16558(11)	0.3375(2)	0.36953(3)	0.0353(4)*
C18	-0.23463(11)	0.4131(2)	0.35874(4)	0.0416(4)*
C19	-0.24142(11)	0.4254(2)	0.33261(4)	0.0424(4)*
C20	-0.17934(12)	0.3614(2)	0.31734(3)	0.0419(4)*
C21	-0.11004(11)	0.2860(2)	0.32812(3)	0.0354(4)*
C22	0.15884(10)	0.41604(18)	0.34892(3)	0.0286(3)*
C23	0.16463(9)	0.36903(17)	0.32147(3)	0.0256(3)*
C24	0.10373(10)	0.4190(2)	0.30407(3)	0.0334(4)*
C25	0.10801(12)	0.3728(2)	0.27887(3)	0.0387(4)*
C26	0.17246(11)	0.2755(2)	0.27071(3)	0.0333(4)*
C27	0.23441(10)	0.22536(19)	0.28756(3)	0.0305(3)*
C28	0.22963(10)	0.27363(18)	0.31280(3)	0.0280(3)*
C29	0.22827(15)	0.1156(3)	0.23750(3)	0.0515(5)*
C30	0.38429(9)	0.28051(18)	0.39837(3)	0.0257(3)*
C31	0.43067(9)	0.28203(17)	0.37333(3)	0.0237(3)*

C32	0.40526(9)	0.36795(18)	0.35280(3)	0.0254(3)*
C33	0.45279(9)	0.36668(17)	0.32981(3)	0.0254(3)*
C34	0.42845(11)	0.4553(2)	0.30828(3)	0.0339(4)*
C35	0.47464(12)	0.4498(2)	0.28632(3)	0.0403(4)*
C36	0.54704(12)	0.3543(2)	0.28471(3)	0.0409(4)*
C37	0.57304(10)	0.2691(2)	0.30524(3)	0.0358(4)*
C38	0.52728(9)	0.27399(18)	0.32836(3)	0.0273(3)*
C39	0.55280(10)	0.18799(19)	0.35002(3)	0.0314(3)*
C40	0.50607(9)	0.19174(18)	0.37172(3)	0.0286(3)*
C41	0.31366(11)	0.2591(2)	0.47022(3)	0.0340(4)*
C42	0.40649(11)	0.2527(2)	0.47461(3)	0.0397(4)*
C43	0.44140(14)	0.1828(3)	0.49411(4)	0.0575(6)*
H1O	0.0903(15)	0.113(3)	0.4703(4)	0.051(6)

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	O2	2.7325(16)[a]	C13	C14	1.377(3)
O1	C1	1.4301(17)	C15	C16	1.504(2)
O1	H1O	0.85(2)	C16	C17	1.389(2)
O2	C2	1.4497(18)	C16	C21	1.391(2)
O2	C8	1.4295(19)	C17	C18	1.389(2)
O2	H1O	2.27(2)[a]	C18	C19	1.384(3)
O3	C3	1.4343(17)	C19	C20	1.381(3)
O3	C15	1.4305(18)	C20	C21	1.391(3)
O4	C4	1.4307(16)	C22	C23	1.503(2)
O4	C22	1.4297(17)	C23	C24	1.396(2)
O5	C5	1.4281(17)	C23	C28	1.387(2)
O5	C30	1.4323(17)	C24	C25	1.386(2)
O6	C6	1.4275(17)	C25	C26	1.381(2)
O6	C41	1.4353(18)	C26	C27	1.389(2)
O7	C26	1.3760(19)	C27	C28	1.394(2)
O7	C29	1.417(2)	C30	C31	1.509(2)
C1	C2	1.535(2)	C31	C32	1.366(2)
C1	C6	1.519(2)	C31	C40	1.421(2)
C2	C3	1.5355(19)	C32	C33	1.425(2)
C2	C7	1.524(2)	C33	C34	1.415(2)
C3	C4	1.535(2)	C33	C38	1.419(2)
C4	C5	1.5240(19)	C34	C35	1.369(2)
C5	C6	1.5332(18)	C35	C36	1.406(3)
C8	C9	1.501(3)	C36	C37	1.365(3)
C9	C10	1.391(2)	C37	C38	1.418(2)
C9	C14	1.384(3)	C38	C39	1.414(2)
C10	C11	1.380(3)	C39	C40	1.361(2)
C11	C12	1.381(3)	C41	C42	1.487(2)
C12	C13	1.377(3)	C42	C43	1.309(3)

[a]Nonbonded distance.

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O1	H1O	103.1(15)	C15	C16	C17	121.74(14)
C2	O2	C8	120.59(12)	C15	C16	C21	119.51(15)
C3	O3	C15	114.27(11)	C17	C16	C21	118.75(15)
C4	O4	C22	113.90(11)	C16	C17	C18	120.64(16)
C5	O5	C30	115.08(11)	C17	C18	C19	120.18(17)
C6	O6	C41	115.46(12)	C18	C19	C20	119.65(16)
C26	O7	C29	117.23(14)	C19	C20	C21	120.23(17)
O1	C1	C2	110.41(12)	C16	C21	C20	120.54(17)
O1	C1	C6	108.94(12)	O4	C22	C23	108.46(12)
C2	C1	C6	113.61(12)	C22	C23	C24	120.59(14)
O2	C2	C1	100.02(11)	C22	C23	C28	121.18(13)
O2	C2	C3	109.78(12)	C24	C23	C28	118.22(14)
O2	C2	C7	112.34(12)	C23	C24	C25	120.60(15)
C1	C2	C3	108.43(11)	C24	C25	C26	120.29(15)
C1	C2	C7	112.93(13)	O7	C26	C25	116.11(15)
C3	C2	C7	112.59(12)	O7	C26	C27	123.57(16)
O3	C3	C2	108.97(11)	C25	C26	C27	120.32(15)
O3	C3	C4	109.11(11)	C26	C27	C28	118.77(15)
C2	C3	C4	112.77(12)	C23	C28	C27	121.80(14)
O4	C4	C3	107.78(11)	O5	C30	C31	112.71(12)
O4	C4	C5	108.91(11)	C30	C31	C32	123.63(13)
C3	C4	C5	112.37(11)	C30	C31	C40	117.08(13)
O5	C5	C4	107.59(11)	C32	C31	C40	119.26(14)
O5	C5	C6	111.48(11)	C31	C32	C33	120.92(14)
C4	C5	C6	110.91(11)	C32	C33	C34	122.26(14)
O6	C6	C1	111.27(12)	C32	C33	C38	119.15(14)
O6	C6	C5	106.45(11)	C34	C33	C38	118.59(14)
C1	C6	C5	108.93(11)	C33	C34	C35	120.95(15)
O2	C8	C9	105.94(14)	C34	C35	C36	120.33(16)
C8	C9	C10	120.90(17)	C35	C36	C37	120.25(16)
C8	C9	C14	120.91(17)	C36	C37	C38	120.79(16)
C10	C9	C14	118.14(17)	C33	C38	C37	119.06(14)
C9	C10	C11	120.86(18)	C33	C38	C39	118.75(14)
C10	C11	C12	120.19(19)	C37	C38	C39	122.19(14)
C11	C12	C13	119.3(2)	C38	C39	C40	120.70(14)
C12	C13	C14	120.5(2)	C31	C40	C39	121.21(14)
C9	C14	C13	120.99(18)	O6	C41	C42	108.78(13)
O3	C15	C16	108.95(12)	C41	C42	C43	123.69(19)

O1	H1O	O2	114.3(18)[a]

[a]Angle includes nonbonded O–H···O interaction.

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C8	O2	C2	C1	161.26(14)	O4	C4	C5	O5	64.00(14)
C8	O2	C2	C3	-84.86(17)	O4	C4	C5	C6	-173.84(11)
C8	O2	C2	C7	41.24(19)	C3	C4	C5	O5	-176.66(11)
C2	O2	C8	C9	172.36(13)	C3	C4	C5	C6	-54.50(16)
C15	O3	C3	C2	-134.89(13)	O5	C5	C6	O6	-63.49(14)
C15	O3	C3	C4	101.59(14)	O5	C5	C6	C1	176.44(11)
C3	O3	C15	C16	-179.45(12)	C4	C5	C6	O6	176.65(11)
C22	O4	C4	C3	116.08(13)	C4	C5	C6	C1	56.58(15)
C22	O4	C4	C5	-121.75(13)	O2	C8	C9	C10	85.15(19)
C4	O4	C22	C23	-174.86(12)	O2	C8	C9	C14	-92.2(2)
C30	O5	C5	C4	-152.74(12)	C8	C9	C10	C11	-177.27(17)
C30	O5	C5	C6	85.44(14)	C14	C9	C10	C11	0.2(3)
C5	O5	C30	C31	124.22(12)	C8	C9	C14	C13	177.76(18)
C41	O6	C6	C1	-86.69(15)	C10	C9	C14	C13	0.3(3)
C41	O6	C6	C5	154.76(12)	C9	C10	C11	C12	-0.4(3)
C6	O6	C41	C42	-153.25(14)	C10	C11	C12	C13	0.1(3)
C29	O7	C26	C25	-171.48(17)	C11	C12	C13	C14	0.4(3)
C29	O7	C26	C27	7.8(3)	C12	C13	C14	C9	-0.6(3)
O1	C1	C2	O2	-65.39(14)	O3	C15	C16	C17	-42.6(2)
O1	C1	C2	C3	179.70(12)	O3	C15	C16	C21	137.65(15)
O1	C1	C2	C7	54.21(16)	C15	C16	C17	C18	179.83(16)
C6	C1	C2	O2	171.88(11)	C21	C16	C17	C18	-0.4(3)
C6	C1	C2	C3	56.97(16)	C15	C16	C21	C20	179.99(16)
C6	C1	C2	C7	-68.52(16)	C17	C16	C21	C20	0.2(3)
O1	C1	C6	O6	59.83(15)	C16	C17	C18	C19	0.1(3)
O1	C1	C6	C5	176.87(12)	C17	C18	C19	C20	0.3(3)
C2	C1	C6	O6	-176.64(11)	C18	C19	C20	C21	-0.5(3)
C2	C1	C6	C5	-59.60(16)	C19	C20	C21	C16	0.2(3)
O2	C2	C3	O3	78.03(14)	O4	C22	C23	C24	129.36(15)
O2	C2	C3	C4	-160.66(11)	O4	C22	C23	C28	-49.80(19)
C1	C2	C3	O3	-173.62(12)	C22	C23	C24	C25	-178.55(16)
C1	C2	C3	C4	-52.31(16)	C28	C23	C24	C25	0.6(2)
C7	C2	C3	O3	-47.93(16)	C22	C23	C28	C27	178.09(15)
C7	C2	C3	C4	73.39(15)	C24	C23	C28	C27	-1.1(2)
O3	C3	C4	O4	-65.65(14)	C23	C24	C25	C26	0.5(3)
O3	C3	C4	C5	174.35(11)	C24	C25	C26	O7	178.14(17)
C2	C3	C4	O4	173.11(11)	C24	C25	C26	C27	-1.2(3)
C2	C3	C4	C5	53.11(16)	O7	C26	C27	C28	-178.53(16)

C25	C26	C27	C28	0.7(3)	C34	C33	C38	C39	178.65(15)
C26	C27	C28	C23	0.4(2)	C33	C34	C35	C36	0.6(3)
O5	C30	C31	C32	12.5(2)	C34	C35	C36	C37	-1.6(3)
O5	C30	C31	C40	-169.36(12)	C35	C36	C37	C38	0.7(3)
C30	C31	C32	C33	178.79(13)	C36	C37	C38	C33	1.2(3)
C40	C31	C32	C33	0.7(2)	C36	C37	C38	C39	-179.61(17)
C30	C31	C40	C39	-178.98(14)	C33	C38	C39	C40	1.1(2)
C32	C31	C40	C39	-0.8(2)	C37	C38	C39	C40	-178.11(16)
C31	C32	C33	C34	-179.54(15)	C38	C39	C40	C31	-0.2(2)
C31	C32	C33	C38	0.3(2)	O6	C41	C42	C43	-127.1(2)
C32	C33	C34	C35	-178.96(16)					
C38	C33	C34	C35	1.2(2)					
C32	C33	C38	C37	178.10(14)					
C32	C33	C38	C39	-1.2(2)					
C34	C33	C38	C37	-2.1(2)					

Table 6. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0327(6)	0.0452(7)	0.0224(5)	0.0045(5)	0.0021(4)	-0.0057(5)
O2	0.0227(5)	0.0306(6)	0.0379(6)	0.0069(5)	0.0030(4)	-0.0007(4)
O3	0.0273(5)	0.0244(5)	0.0288(5)	-0.0019(4)	-0.0046(4)	0.0055(4)
O4	0.0376(6)	0.0207(5)	0.0202(5)	0.0001(4)	0.0026(4)	0.0033(4)
O5	0.0251(5)	0.0197(5)	0.0324(5)	0.0030(4)	0.0057(4)	0.0004(4)
O6	0.0267(5)	0.0333(6)	0.0255(5)	-0.0021(4)	-0.0033(4)	0.0011(4)
O7	0.0683(9)	0.0517(8)	0.0237(6)	-0.0045(5)	-0.0034(6)	0.0111(7)
C1	0.0277(7)	0.0252(7)	0.0215(7)	0.0020(5)	0.0011(5)	-0.0013(6)
C2	0.0254(7)	0.0237(7)	0.0257(7)	0.0025(6)	0.0025(5)	0.0003(6)
C3	0.0247(7)	0.0208(7)	0.0252(7)	-0.0003(5)	-0.0008(5)	0.0037(5)
C4	0.0286(7)	0.0186(7)	0.0206(6)	-0.0007(5)	0.0023(5)	0.0018(5)
C5	0.0262(7)	0.0170(7)	0.0241(7)	-0.0001(5)	0.0030(5)	-0.0014(5)
C6	0.0261(7)	0.0225(7)	0.0234(7)	0.0000(5)	-0.0005(5)	0.0003(6)
C7	0.0342(8)	0.0298(8)	0.0292(7)	-0.0010(6)	0.0056(6)	0.0041(6)
C8	0.0254(8)	0.0427(10)	0.0593(11)	0.0118(9)	0.0042(7)	0.0035(7)
C9	0.0211(7)	0.0413(10)	0.0393(9)	0.0046(7)	0.0019(6)	0.0009(6)
C10	0.0361(9)	0.0492(11)	0.0351(9)	0.0002(8)	0.0012(7)	-0.0020(8)
C11	0.0424(10)	0.0573(13)	0.0455(10)	0.0137(9)	0.0091(8)	-0.0032(9)
C12	0.0383(10)	0.0481(12)	0.0764(15)	0.0081(10)	0.0023(10)	-0.0139(9)
C13	0.0558(13)	0.0582(14)	0.0616(13)	-0.0162(11)	-0.0104(10)	-0.0097(10)
C14	0.0469(10)	0.0585(13)	0.0343(9)	0.0013(8)	-0.0008(8)	-0.0021(9)
C15	0.0327(8)	0.0267(8)	0.0334(8)	-0.0044(6)	-0.0062(6)	0.0021(6)
C16	0.0284(7)	0.0249(8)	0.0330(8)	0.0010(6)	-0.0041(6)	-0.0040(6)
C17	0.0339(8)	0.0374(9)	0.0344(8)	0.0073(7)	0.0013(7)	0.0019(7)
C18	0.0289(8)	0.0432(11)	0.0527(10)	0.0093(8)	0.0033(7)	0.0034(7)
C19	0.0345(9)	0.0386(10)	0.0541(10)	0.0076(8)	-0.0166(8)	-0.0015(7)
C20	0.0523(11)	0.0377(10)	0.0359(9)	0.0019(7)	-0.0159(8)	-0.0032(8)
C21	0.0409(9)	0.0326(9)	0.0326(8)	-0.0019(7)	-0.0040(7)	-0.0018(7)
C22	0.0389(8)	0.0219(8)	0.0250(7)	0.0014(6)	0.0003(6)	0.0025(6)
C23	0.0305(7)	0.0223(7)	0.0239(7)	0.0029(5)	0.0001(6)	-0.0018(6)
C24	0.0340(8)	0.0355(9)	0.0308(8)	0.0015(6)	-0.0012(6)	0.0081(7)
C25	0.0436(9)	0.0438(10)	0.0288(8)	0.0021(7)	-0.0088(7)	0.0068(8)
C26	0.0433(9)	0.0337(9)	0.0228(7)	0.0012(6)	0.0008(6)	-0.0021(7)
C27	0.0321(8)	0.0306(9)	0.0288(7)	-0.0008(6)	0.0039(6)	0.0000(6)
C28	0.0299(8)	0.0261(8)	0.0279(7)	0.0006(6)	-0.0029(6)	-0.0010(6)
C29	0.0739(14)	0.0500(12)	0.0306(9)	-0.0096(8)	0.0042(9)	0.0064(10)
C30	0.0255(7)	0.0218(7)	0.0298(7)	0.0016(6)	0.0015(6)	0.0007(6)
C31	0.0241(7)	0.0170(7)	0.0299(7)	-0.0031(5)	0.0011(5)	-0.0048(5)

C32	0.0239(7)	0.0227(7)	0.0297(7)	-0.0035(6)	0.0000(6)	0.0014(5)
C33	0.0257(7)	0.0221(7)	0.0284(7)	-0.0036(6)	-0.0005(6)	-0.0020(6)
C34	0.0369(8)	0.0334(9)	0.0313(8)	-0.0008(7)	-0.0004(6)	0.0068(7)
C35	0.0470(10)	0.0439(10)	0.0300(8)	0.0040(7)	0.0010(7)	0.0055(8)
C36	0.0413(9)	0.0502(11)	0.0313(8)	0.0001(7)	0.0085(7)	0.0019(8)
C37	0.0295(8)	0.0390(10)	0.0389(9)	-0.0028(7)	0.0068(7)	0.0043(7)
C38	0.0249(7)	0.0239(8)	0.0333(8)	-0.0024(6)	0.0015(6)	-0.0019(6)
C39	0.0247(7)	0.0296(8)	0.0401(9)	0.0013(7)	0.0018(6)	0.0044(6)
C40	0.0262(7)	0.0246(8)	0.0349(8)	0.0028(6)	-0.0018(6)	0.0013(6)
C41	0.0350(8)	0.0418(10)	0.0251(7)	-0.0030(6)	-0.0043(6)	-0.0020(7)
C42	0.0363(9)	0.0480(11)	0.0349(9)	-0.0034(8)	-0.0045(7)	-0.0042(8)
C43	0.0464(11)	0.0800(16)	0.0461(11)	0.0045(11)	-0.0144(9)	0.0041(11)

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H1	0.1556	0.0534	0.4356	0.030
H3	0.0817	0.1020	0.3936	0.028
H4	0.1455	0.4199	0.3937	0.027
H5	0.2469	0.1413	0.4002	0.027
H6	0.2118	0.3745	0.4389	0.029
H7A	0.0214	0.3722	0.4557	0.037
H7B	-0.0217	0.4042	0.4287	0.037
H7C	0.0740	0.4572	0.4337	0.037
H8A	-0.1010	0.1461	0.4173	0.051
H8B	-0.1026	0.1869	0.4471	0.051
H10	-0.1206	-0.0306	0.4783	0.048
H11	-0.1715	-0.2813	0.4867	0.058
H12	-0.2032	-0.4524	0.4534	0.065
H13	-0.1831	-0.3700	0.4117	0.070
H14	-0.1305	-0.1214	0.4032	0.056
H15A	-0.0428	0.0842	0.3710	0.037
H15B	0.0184	0.1829	0.3526	0.037
H17	-0.1614	0.3294	0.3875	0.042
H18	-0.2773	0.4566	0.3693	0.050
H19	-0.2885	0.4775	0.3252	0.051
H20	-0.1840	0.3689	0.2994	0.050
H21	-0.0675	0.2426	0.3175	0.042
H22A	0.2046	0.4911	0.3531	0.034
H22B	0.1039	0.4678	0.3522	0.034
H24	0.0589	0.4853	0.3095	0.040
H25	0.0664	0.4081	0.2672	0.046
H27	0.2792	0.1594	0.2820	0.037
H28	0.2721	0.2403	0.3244	0.034
H29A	0.2180	0.0905	0.2196	0.062
H29B	0.2209	0.0207	0.2478	0.062
H29C	0.2861	0.1551	0.2395	0.062
H30A	0.3784	0.1705	0.4042	0.031
H30B	0.4183	0.3379	0.4111	0.031
H32	0.3552	0.4294	0.3539	0.030
H34	0.3794	0.5195	0.3091	0.041
H35	0.4577	0.5108	0.2721	0.048
H36	0.5780	0.3490	0.2693	0.049
H37	0.6224	0.2059	0.3040	0.043

H39	0.6031	0.1269	0.3494	0.038
H40	0.5242	0.1329	0.3860	0.034
H41A	0.2841	0.1930	0.4829	0.041
H41B	0.2933	0.3685	0.4721	0.041
H42	0.4425	0.3021	0.4626	0.048
H43A	0.4070	0.1324	0.5064	0.069
H43B	0.5012	0.1825	0.4959	0.069

X-ray crystallographic data for 4.37α

XCL Code: TLL1503 **Date:** 7 January 2016

Compound: 8,9,9b-Trihydroxy-5-methoxy-9-methyl-2-phenyloctahydro-3a*H*-[1,3]-dioxino[4,5,6-*de*]chromen-4-yl benzoate

Formula: $C_{26}H_{30}Cl_2O_9$ ($C_{25}H_{28}O_9$•CH_2Cl_2)

Supervisor: T. L. Lowary **Crystallographer:** R. McDonald

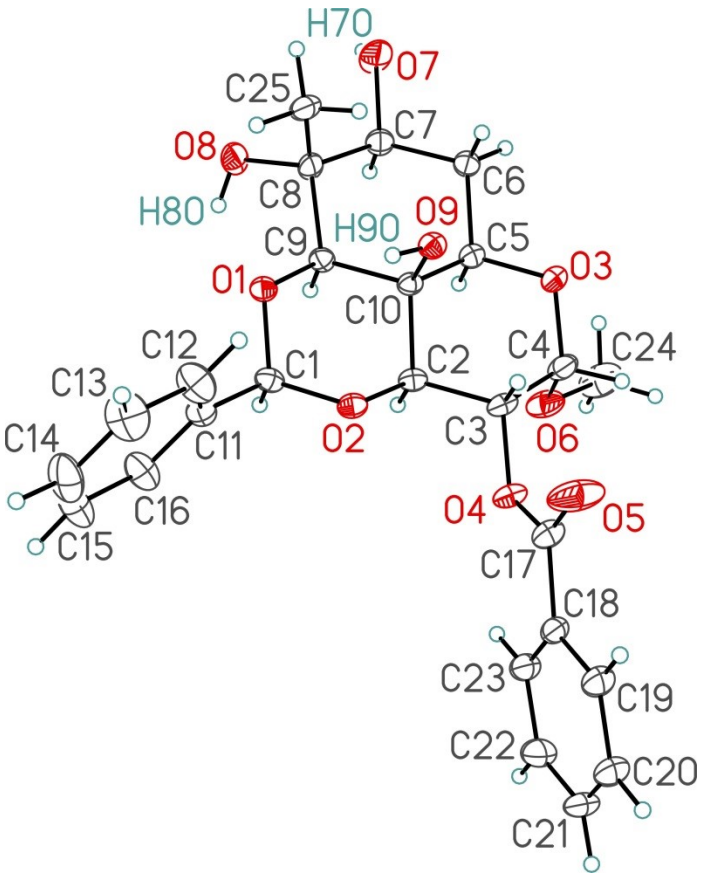


Figure Legend: Perspective view of the 8,9,9b-Trihydroxy-5-methoxy-9-methyl-2-phenyloctahydro-3a*H*-[1,3]dioxino[4,5,6-*de*]chromen-4-yl benzoate molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

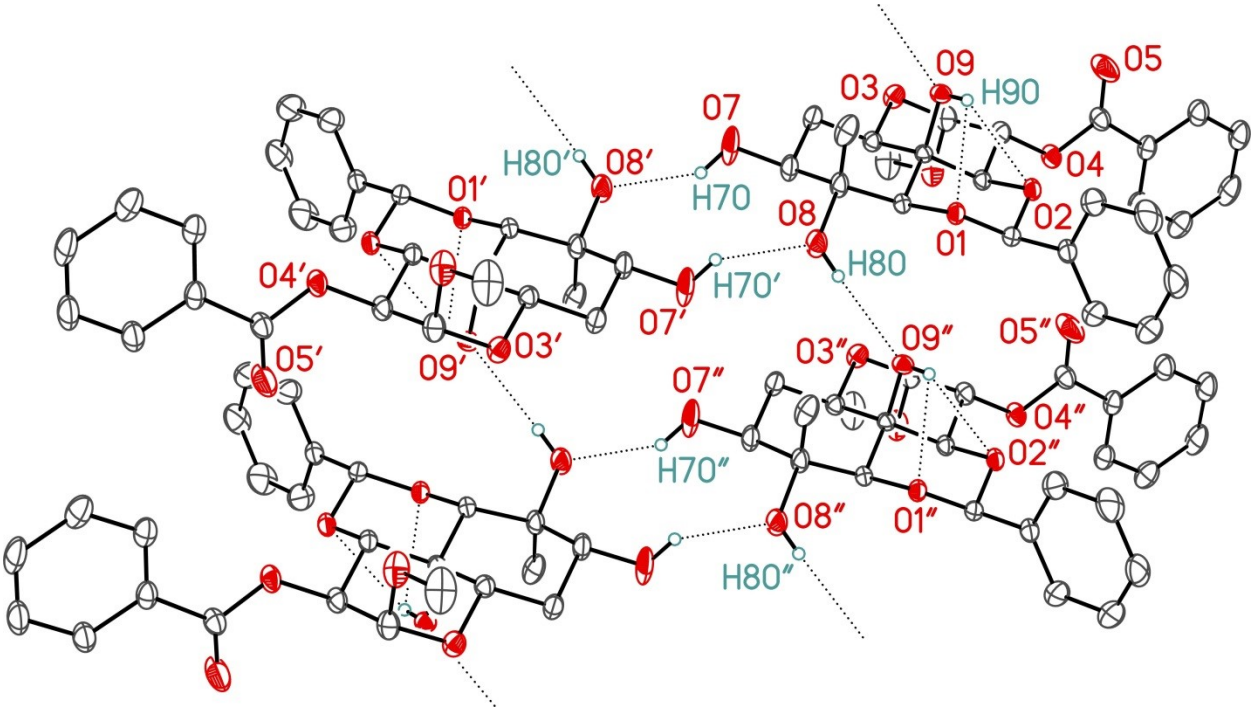


Figure Legend: Illustration of hydrogen-bonded interactions (dotted lines) within and between adjacent molecules in the crystal lattice. Primed atoms are related to unprimed ones via the crystallographic inversion center ($^1/_2$, 0, $^1/_2$). Double-primed atoms are related to unprimed ones via the crystallographic translational operation (1+*x*, *y*, *z*), i.e. translation by 5.68560 (10) Å (the length of the unit cell's *a* axis) in a direction parallel to the crystal unit cell's *a* axis.

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{26}H_{30}Cl_2O_9$
formula weight	557.40
crystal dimensions (mm)	0.38 × 0.15 × 0.10
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	5.68560 (10)
b (Å)	15.7385 (3)
c (Å)	29.0307 (5)
β (deg)	94.9272 (9)
V (Å^3)	2588.15 (8)
Z	4
ρ_{calcd} (g cm^{-3})	1.430
μ (mm^{-1})	2.716
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100
scan type	ω and ϕ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	148.14
total data collected	18121 ($-7 \le h \le 7$, $-16 \le k \le 18$, $-36 \le l \le 36$)
independent reflections	5190 (R_{int} = 0.0197)
number of observed reflections (*NO*)	4891 [$F_o^2 \ge 2\sigma(F_o^2)$]

structure solution method	direct methods/dual space (*SHELXD*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–2014*[d,e])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	1.0000–0.8379
data/restraints/parameters	5190 / 0 / 311
goodness-of-fit (*S*)[f] [all data]	1.101
final *R* indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0521
wR_2 [all data]	0.1283
largest difference peak and hole	0.283 and –0.299 e Å^{-3}

[a]Obtained from least-squares refinement of 9927 reflections with $6.12° < 2\theta < 147.70°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr.* **2002**, *D58*, 1772-1779.

[d]Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3–8.

[e]Attempts to refine peaks of residual electron density as disordered or partial-occupancy solvent dichloromethane chlorine or carbon atoms were unsuccessful. The data were corrected for disordered electron density through use of the SQUEEZE procedure as implemented in *PLATON* (Spek, A. L. *Acta Crystallogr.* **2015**, *C71*, 9–18. *PLATON* - a multipurpose crystallographic tool. Utrecht University, Utrecht, The Netherlands). A total solvent-accessible void volume of 408.2 Å^3 with a total electron count of 136 (consistent with 4 molecules of solvent dichloromethane, or one molecule per formula unit of the molecule of interest) was found in the unit cell.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0381P)^2 + 1.9968P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.3247(2)	0.25095(8)	0.39427(4)	0.0299(3)*
O2	0.1272(2)	0.26732(8)	0.32008(4)	0.0308(3)*
O3	-0.2026(2)	0.03365(9)	0.33336(4)	0.0365(3)*
O4	-0.1166(2)	0.18539(9)	0.23940(4)	0.0366(3)*
O5	-0.4588(3)	0.25480(16)	0.23941(6)	0.0791(7)*
O6	-0.0141(3)	0.02062(9)	0.26523(5)	0.0486(4)*
O7	0.2185(4)	-0.00575(11)	0.48381(6)	0.0655(5)*
O8	0.5391(3)	0.13032(10)	0.46250(5)	0.0502(4)*
O9	-0.1322(2)	0.18280(8)	0.38247(4)	0.0297(3)*
C1	0.3413(3)	0.28203(11)	0.34826(6)	0.0300(4)*
C2	0.0888(3)	0.17765(11)	0.31562(6)	0.0283(4)*
C3	-0.1367(3)	0.15800(12)	0.28624(6)	0.0329(4)*
C4	-0.1898(4)	0.06254(13)	0.28696(6)	0.0384(4)*
C5	0.0143(3)	0.04803(12)	0.36128(6)	0.0300(4)*
C6	-0.0008(3)	0.01202(13)	0.40937(6)	0.0363(4)*
C7	0.2321(4)	0.02967(13)	0.43865(7)	0.0398(5)*
C8	0.2981(3)	0.12490(12)	0.44306(6)	0.0359(4)*
C9	0.2925(3)	0.16040(11)	0.39362(6)	0.0279(4)*
C10	0.0633(3)	0.14212(11)	0.36403(5)	0.0256(3)*
C11	0.3905(3)	0.37524(12)	0.35063(6)	0.0348(4)*
C12	0.2393(4)	0.43010(14)	0.37041(9)	0.0534(6)*
C13	0.2885(5)	0.51618(16)	0.37194(11)	0.0682(8)*
C14	0.4867(5)	0.54722(15)	0.35390(11)	0.0651(7)*
C15	0.6359(5)	0.49342(17)	0.33369(11)	0.0657(7)*
C16	0.5880(4)	0.40708(15)	0.33247(9)	0.0522(6)*
C17	-0.2926(4)	0.23327(13)	0.22006(6)	0.0382(4)*
C18	-0.2561(4)	0.25612(12)	0.17119(6)	0.0360(4)*
C19	-0.4319(4)	0.30350(15)	0.14692(7)	0.0471(5)*
C20	-0.4151(5)	0.32129(17)	0.10051(8)	0.0566(6)*
C21	-0.2253(5)	0.29173(17)	0.07891(8)	0.0593(7)*
C22	-0.0488(5)	0.24601(16)	0.10316(8)	0.0537(6)*
C23	-0.0630(4)	0.22788(13)	0.14967(7)	0.0410(5)*
C24	-0.0611(6)	-0.06874(16)	0.25990(9)	0.0702(8)*
C25	0.1479(4)	0.17262(14)	0.47514(6)	0.0465(5)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C1	1.433(2)	C5	C10	1.508(2)
O1	C9	1.437(2)	C6	C7	1.536(3)
O2	C1	1.426(2)	C7	C8	1.548(3)
O2	C2	1.432(2)	C8	C9	1.538(2)
O3	C4	1.430(2)	C8	C25	1.516(3)
O3	C5	1.434(2)	C9	C10	1.525(2)
O4	C3	1.440(2)	C11	C12	1.378(3)
O4	C17	1.337(2)	C11	C16	1.375(3)
O5	C17	1.189(3)	C12	C13	1.383(3)
O6	C4	1.393(3)	C13	C14	1.373(4)
O6	C24	1.437(3)	C14	C15	1.366(4)
O7	C7	1.433(2)	C15	C16	1.386(3)
O8	C8	1.439(2)	C17	C18	1.495(3)
O9	C10	1.4262(19)	C18	C19	1.389(3)
C1	C11	1.494(3)	C18	C23	1.382(3)
C2	C3	1.510(2)	C19	C20	1.387(3)
C2	C10	1.531(2)	C20	C21	1.375(4)
C3	C4	1.533(3)	C21	C22	1.378(4)
C5	C6	1.516(2)	C22	C23	1.389(3)

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O1	C9	110.17(13)	C9	C8	C25	115.21(16)
C1	O2	C2	109.14(12)	O1	C9	C8	110.84(14)
C4	O3	C5	111.80(14)	O1	C9	C10	107.24(13)
C3	O4	C17	116.61(14)	C8	C9	C10	113.90(14)
C4	O6	C24	112.2(2)	O9	C10	C2	108.60(13)
O1	C1	O2	110.96(13)	O9	C10	C5	108.31(14)
O1	C1	C11	108.62(15)	O9	C10	C9	111.07(13)
O2	C1	C11	109.46(14)	C2	C10	C5	110.00(14)
O2	C2	C3	111.61(14)	C2	C10	C9	107.72(14)
O2	C2	C10	107.61(13)	C5	C10	C9	111.12(14)
C3	C2	C10	107.51(14)	C1	C11	C12	120.89(18)
O4	C3	C2	109.85(15)	C1	C11	C16	119.73(18)
O4	C3	C4	109.76(14)	C12	C11	C16	119.4(2)
C2	C3	C4	110.59(15)	C11	C12	C13	119.7(2)
O3	C4	O6	111.87(16)	C12	C13	C14	120.4(3)
O3	C4	C3	110.54(15)	C13	C14	C15	120.3(2)
O6	C4	C3	107.96(17)	C14	C15	C16	119.4(2)
O3	C5	C6	110.34(14)	C11	C16	C15	120.8(2)
O3	C5	C10	109.33(14)	O4	C17	O5	123.96(18)
C6	C5	C10	110.08(15)	O4	C17	C18	111.98(17)
C5	C6	C7	109.13(15)	O5	C17	C18	124.06(18)
O7	C7	C6	108.94(16)	C17	C18	C19	117.25(19)
O7	C7	C8	109.43(17)	C17	C18	C23	122.12(17)
C6	C7	C8	114.34(16)	C19	C18	C23	120.54(19)
O8	C8	C7	107.81(16)	C18	C19	C20	119.6(2)
O8	C8	C9	106.69(15)	C19	C20	C21	119.8(2)
O8	C8	C25	107.30(16)	C20	C21	C22	120.6(2)
C7	C8	C9	106.81(15)	C21	C22	C23	120.2(2)
C7	C8	C25	112.66(17)	C18	C23	C22	119.2(2)

Table 5. Hydrogen-Bonded Interactions

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	∠D–H···A (deg)
O7–H7O···O8[a]	0.84	2.08	2.793(2)	142.7
O8–H8O···O9[b]	0.84	2.37	3.213(2)	177.1
O9–H9O···O1	0.84	2.42	2.8041(17)	108.8
O9–H9O···O2	0.84	2.49	2.7719(17)	100.4

[a]At 1–*x*, $\bar{y}$, 1–*z*. [b]At 1+*x*, *y*, *z*.

Table 6. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C9	O1	C1	O2	63.32(17)	O3	C5	C10	O9	57.53(17)
C9	O1	C1	C11	-176.31(13)	O3	C5	C10	C2	-61.02(17)
C1	O1	C9	C8	174.59(14)	O3	C5	C10	C9	179.79(13)
C1	O1	C9	C10	-60.53(16)	C6	C5	C10	O9	-63.83(17)
C2	O2	C1	O1	-63.69(17)	C6	C5	C10	C2	177.62(14)
C2	O2	C1	C11	176.44(14)	C6	C5	C10	C9	58.43(19)
C1	O2	C2	C3	179.72(13)	C5	C6	C7	O7	-179.01(17)
C1	O2	C2	C10	61.99(16)	C5	C6	C7	C8	58.2(2)
C5	O3	C4	O6	60.6(2)	O7	C7	C8	O8	69.6(2)
C5	O3	C4	C3	-59.8(2)	O7	C7	C8	C9	-176.10(16)
C4	O3	C5	C6	-176.69(16)	O7	C7	C8	C25	-48.6(2)
C4	O3	C5	C10	62.11(18)	C6	C7	C8	O8	-167.94(16)
C17	O4	C3	C2	-129.80(17)	C6	C7	C8	C9	-53.6(2)
C17	O4	C3	C4	108.40(19)	C6	C7	C8	C25	73.9(2)
C3	O4	C17	O5	1.1(3)	O8	C8	C9	O1	-71.63(19)
C3	O4	C17	C18	-178.58(16)	O8	C8	C9	C10	167.34(15)
C24	O6	C4	O3	64.1(2)	C7	C8	C9	O1	173.27(15)
C24	O6	C4	C3	-174.02(17)	C7	C8	C9	C10	52.2(2)
O1	C1	C11	C12	-57.9(2)	C25	C8	C9	O1	47.3(2)
O1	C1	C11	C16	122.7(2)	C25	C8	C9	C10	-73.7(2)
O2	C1	C11	C12	63.4(2)	O1	C9	C10	O9	-59.36(17)
O2	C1	C11	C16	-116.0(2)	O1	C9	C10	C2	59.45(17)
O2	C2	C3	O4	65.80(18)	O1	C9	C10	C5	179.99(13)
O2	C2	C3	C4	-172.89(14)	C8	C9	C10	O9	63.65(19)
C10	C2	C3	O4	-176.41(14)	C8	C9	C10	C2	-177.54(15)
C10	C2	C3	C4	-55.11(18)	C8	C9	C10	C5	-57.0(2)
O2	C2	C10	O9	59.73(17)	C1	C11	C12	C13	-179.7(2)
O2	C2	C10	C5	178.11(13)	C16	C11	C12	C13	-0.3(4)
O2	C2	C10	C9	-60.65(17)	C1	C11	C16	C15	179.1(2)
C3	C2	C10	O9	-60.62(17)	C12	C11	C16	C15	-0.2(4)
C3	C2	C10	C5	57.75(18)	C11	C12	C13	C14	0.0(4)
C3	C2	C10	C9	179.00(14)	C12	C13	C14	C15	0.8(5)
O4	C3	C4	O3	178.09(14)	C13	C14	C15	C16	-1.4(4)
O4	C3	C4	O6	55.42(19)	C14	C15	C16	C11	1.1(4)
C2	C3	C4	O3	56.7(2)	O4	C17	C18	C19	177.88(18)
C2	C3	C4	O6	-65.94(18)	O4	C17	C18	C23	1.4(3)
O3	C5	C6	C7	-179.07(16)	O5	C17	C18	C19	-1.8(3)
C10	C5	C6	C7	-58.3(2)	O5	C17	C18	C23	-178.3(2)

C17	C18	C19	C20	-175.4(2)	C20	C21	C22	C23	1.2(4)
C23	C18	C19	C20	1.1(3)	C21	C22	C23	C18	0.1(3)
C17	C18	C23	C22	175.1(2)					
C19	C18	C23	C22	-1.2(3)					
C18	C19	C20	C21	0.2(4)					
C19	C20	C21	C22	-1.4(4)					

Table 7. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0323(6)	0.0283(6)	0.0284(6)	0.0065(5)	-0.0005(5)	-0.0002(5)
O2	0.0349(6)	0.0297(6)	0.0273(6)	0.0064(5)	0.0007(5)	0.0050(5)
O3	0.0408(7)	0.0416(8)	0.0260(6)	0.0016(5)	-0.0038(5)	-0.0079(6)
O4	0.0438(7)	0.0447(8)	0.0211(6)	0.0048(5)	0.0011(5)	0.0103(6)
O5	0.0671(12)	0.1258(18)	0.0460(9)	0.0332(10)	0.0142(8)	0.0516(12)
O6	0.0777(11)	0.0391(8)	0.0294(7)	-0.0045(6)	0.0075(7)	0.0092(7)
O7	0.0927(14)	0.0530(10)	0.0448(9)	0.0303(8)	-0.0279(9)	-0.0235(9)
O8	0.0422(8)	0.0553(9)	0.0490(8)	0.0227(7)	-0.0192(7)	-0.0138(7)
O9	0.0269(6)	0.0349(7)	0.0277(6)	-0.0016(5)	0.0044(5)	0.0034(5)
C1	0.0287(8)	0.0310(9)	0.0310(9)	0.0071(7)	0.0059(7)	0.0037(7)
C2	0.0322(9)	0.0287(9)	0.0241(8)	0.0035(6)	0.0041(6)	0.0055(7)
C3	0.0385(10)	0.0404(10)	0.0194(8)	0.0019(7)	0.0008(7)	0.0057(8)
C4	0.0496(11)	0.0407(11)	0.0236(8)	-0.0007(7)	-0.0042(8)	-0.0007(9)
C5	0.0314(9)	0.0317(9)	0.0264(8)	0.0019(7)	0.0002(7)	0.0000(7)
C6	0.0419(10)	0.0340(10)	0.0318(9)	0.0083(7)	-0.0029(8)	-0.0086(8)
C7	0.0460(11)	0.0372(11)	0.0345(10)	0.0146(8)	-0.0072(8)	-0.0056(8)
C8	0.0374(10)	0.0376(10)	0.0303(9)	0.0116(8)	-0.0113(7)	-0.0075(8)
C9	0.0274(8)	0.0271(9)	0.0287(8)	0.0060(7)	0.0000(6)	0.0015(6)
C10	0.0239(8)	0.0303(9)	0.0226(8)	0.0026(6)	0.0022(6)	0.0037(6)
C11	0.0356(9)	0.0316(10)	0.0362(9)	0.0089(7)	-0.0018(7)	0.0029(7)
C12	0.0541(13)	0.0336(11)	0.0739(16)	0.0040(10)	0.0135(12)	0.0050(10)
C13	0.0736(18)	0.0350(13)	0.096(2)	-0.0020(13)	0.0073(15)	0.0143(12)
C14	0.0613(15)	0.0291(12)	0.101(2)	0.0120(12)	-0.0128(14)	-0.0035(10)
C15	0.0509(14)	0.0447(14)	0.102(2)	0.0169(14)	0.0084(14)	-0.0101(11)
C16	0.0453(12)	0.0395(12)	0.0727(16)	0.0081(11)	0.0107(11)	-0.0026(9)
C17	0.0409(10)	0.0430(11)	0.0299(9)	0.0024(8)	-0.0025(8)	0.0071(8)
C18	0.0455(11)	0.0328(10)	0.0281(9)	0.0030(7)	-0.0060(8)	-0.0065(8)
C19	0.0503(12)	0.0484(12)	0.0403(11)	0.0111(9)	-0.0086(9)	-0.0027(10)
C20	0.0639(15)	0.0600(15)	0.0423(12)	0.0204(11)	-0.0156(11)	-0.0084(12)
C21	0.0798(17)	0.0660(16)	0.0299(10)	0.0172(10)	-0.0068(11)	-0.0203(13)
C22	0.0674(15)	0.0589(15)	0.0354(11)	0.0046(10)	0.0086(10)	-0.0112(12)
C23	0.0504(12)	0.0400(11)	0.0318(10)	0.0042(8)	-0.0006(8)	-0.0043(9)
C24	0.122(3)	0.0410(14)	0.0463(13)	-0.0123(10)	0.0014(14)	0.0086(14)
C25	0.0684(14)	0.0472(12)	0.0231(9)	0.0019(8)	-0.0002(9)	-0.0160(11)

The form of the anisotropic displacement parameter is:

$$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$$

Table 8. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H7O	0.3282	-0.0410	0.4893	0.098
H8O	0.6268	0.1422	0.4415	0.075
H9O	-0.0997	0.2342	0.3877	0.045
H1	0.4741	0.2525	0.3344	0.036
H2	0.2259	0.1503	0.3021	0.034
H3	-0.2698	0.1894	0.2989	0.039
H4	-0.3453	0.0520	0.2691	0.046
H5	0.1457	0.0192	0.3466	0.036
H6A	-0.0297	-0.0500	0.4075	0.044
H6B	-0.1336	0.0388	0.4239	0.044
H7	0.3614	-0.0002	0.4239	0.048
H9	0.4256	0.1343	0.3782	0.033
H12	0.1020	0.4089	0.3829	0.064
H13	0.1844	0.5541	0.3856	0.082
H14	0.5202	0.6063	0.3555	0.078
H15	0.7713	0.5150	0.3206	0.079
H16	0.6929	0.3694	0.3189	0.063
H19	-0.5629	0.3236	0.1620	0.056
H20	-0.5343	0.3538	0.0837	0.068
H21	-0.2158	0.3029	0.0470	0.071
H22	0.0830	0.2268	0.0880	0.064
H23	0.0585	0.1964	0.1665	0.049
H24A	0.0665	-0.0956	0.2445	0.084
H24B	-0.0708	-0.0946	0.2904	0.084
H24C	-0.2111	-0.0769	0.2412	0.084
H25A	-0.0181	0.1702	0.4629	0.056
H25B	0.1653	0.1465	0.5059	0.056
H25C	0.1992	0.2320	0.4774	0.056