Studies Towards the Synthesis of Tagetitoxin

By

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A Doctoral Thesis

Submitted for the award of

Doctor of Philosophy

At the University of East Anglia

December 2018

Abstract

The natural product tagetitoxin is a phytotoxin which was first isolated from the bacterium *Pseudomonas syringae* pv. *tagetis* in 1981. Tagetitoxin is an inhibitor of chloroplast and bacteria RNAP and also selectively inhibits RNAP III in eukaryotes. Multiple biological mechanisms of inhibition and several structures have been proposed for tagetitoxin. The structural ambiguity and potential useful biological activity have driven the desire for a total synthesis of tagetitoxin's proposed structures; none of which of yet have been successful.

This body of research describes the recent developments our group has contributed towards the synthesis of tagetitoxin. The main objective was to synthesize targets **323a** and **323b** which both contain the oxathiobicyclo[3.3.1]nonane ring system found in two of the proposed structures of tagetitoxin.

Our initial strategy focused on four synthetic routes derived from diacetone mannose (DAM). In this strategy, the route nearest to obtaining the bicyclic core of **323a** and **323b** was the dithiane-reduction route. In this route, the target precursors **389** and **415** (and analogues) were made, but attempted thioacetate deprotection and concomitant cyclization of the thiol/thiolate onto a ketone or sulfonate ester to yield the oxathiobicyclo[3.3.1]nonane ring system led to either decomposition or complex mixtures. This failure was attributed to the presence of isopropylidene groups hampering the cyclization by imposing steric constraints on ring closure.

We then conducted synthetic routes starting from D-galactose in the D-galactose and *exo*-glycal routes (avoiding the use of any isopropylidene groups). Failure to insert a hydroxyl-methylene group on the C_{-1} position by anomeric nitrile anion chemistry or ring-opening an anomeric *spiro*-epoxyacetal with TMSCN led us to attempt a hydroboration-oxidation on an *exo*-galactal derivative which was partially successful. Optimization of the hydroboration-oxidation pathway in the *exo*-glycal route is promising for future research.

Acknowledgements

I am extremely grateful to Professor Phil Page for not only handing me the opportunity to work in his research group but also giving me plenty of great advice and support throughout my PhD.

I would like to thank Charnwood Molecular Limited and the University of East Anglia for the funding of the project.

I am also very thankful to Dr. Yohan Chan who always gave me great help with regards to my project and various lab techniques throughout my research. I also admire his patience for actually listening to many of my (often silly/crazy) ideas.

I would also like to thank Dr. Richard Stephenson, Dr. Alan Haines and Dr. Tom Storr for their great advice during my PhD.

Additionally, I would like to acknowledge all previous and current members of the Page group who have helped me and also provided an enjoyable working environment: Alexandra Horton, Jamie Martin, Francesca Kinsey, Saud Almutairi, Cristina Macarov and especially Ross Goodyear, Nawaf Alsenani and Gregory Hughes.

I also appreciate the help and support given to me by Sarah Delf.

I am also grateful to Dr Colin Macdonald for his help with my NOESY spectra analysis.

I would like to thank my brother Rouvick and my in-laws Girish, Kusum and Dipun Patel for their continued support and patience.

I am also very grateful to my wife Trisha for her devotion and support.

Finally, I would also like to express my gratitude to my parents, Rousseau and Rinette Gama, who have always given me unconditional support and guidance, not only during my PhD but throughout my whole life.

List of Abbreviations

1D	One Dimensional
2D	Two Dimensional
9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetyl
aq	Aqueous
ASAP	Atmospheric Solids Analysis Probe
Bn	Benzyl
BOC	*tert*-Butyloxycarbonyl
Bz	Benzoyl
CI	Chemical Ionization
COLOC	Correlation Through Long Range Spectroscopy
COSY	Correlation Spectroscopy
DAM	Diacetone Mannose
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DIBAL	Diisobutylaluminum Hydride
DIPEA	*N,N'*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	*N,N'*-Dimethylpropyleneurea
DMS	Dimethyl Sulfide
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
DTT	Dithiothreitol
EI	Electron Ionization
Equiv.	Equivalent(s)
ESI	Electrospray Ionization
Et	Ethyl
FAB	Fast Atom Bombardment
FDMS	Field Desorption Mass Spectrometry
FTMS	Fourier Transform Mass Spectrometry
g	Gram(s)
h	Hour(s)
LiHMDS	Lithium bis(trimethylsilyl)amide
NaHMDS	Sodium bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence

HWE	Horner Wadsworth Emmons
IPDMS	Isopropyldimethylsilyl
*i*Pr	Isopropyl
IR	Infrared
J	Coupling Constant
KDO	3-Deoxy-D-manno-oct-2-ulosonic acid
LAH	Lithium Aluminium Hydride
LDA	Lithium diisopropylamide
LTEA	Lithium Tris(ethoxy)aluminium Hydride
M	Molar
*m*CPBA	*meta*-Chloroperbenzoic Acid
MCW	Methanol:Chloroform:Water
Me	Methyl
ml	Milliliter(s)
mmol	Millimole(s)
MOM	Methoxymethyl
mp	Melting Point
MS	Mass Spectrometry
Ms	Mesyl
NBS	*N*-Bromosuccinimide
n-BuLi	*n*-Butyl Lithium
t-BuLi	*tert*-Butyl Lithium
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
NTP	Nucleoside Triphosphate
Ph	Phenyl
PMB	*para*-Methoxybenzyl
p-TsOH	*para*-Toluenesulfonic Acid
PY	Pyridine
quant.	Quantitative
Ra-Ni	Raney Nickel
Red-Al®	Sodium Bis(2-methoxyethoxy)aluminium Hydride
Rf	Retention Factor
RNA	Ribonucleic Acid
RNAP	Ribonucleic Acid Polymerase
rt	Room Temperature
TBAB	Tetra-*n*-butylammonium Bromide
TBAF	Tetra-*n*-butylammonium Fluoride
TBAI	Tetra-*n*-butylammonium Iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
*t*Bu	*tert*-Butyl

TES	Triethylsilyl
Tf	Triflyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TOCSY	Total Correlation Spectroscopy
TOF	Time of Flight
Trt	Trityl
Ts	Tosyl
UTP	Uridine Triphosphate
UV	Ultraviolet

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Introduction

Background

The natural product tagetitoxin was first isolated in 1981,[1] and since then research has mostly focused on its interesting inhibitory activity of RNA Polymerase (RNAP), whilst comparatively little research has been carried out on its biosynthesis and chemical synthesis. Despite great developments in its biological research, tagetitoxin has yet to be isolated in a pure crystalline form and therefore no crystal structure of the natural product in its free form has been published. As a result, there has been debate about its structure in the literature. From a synthetic perspective, a total synthesis of tagetitoxin would provide the best means to confirm its structure.

Discovery and Isolation

In 1981, Mitchell and Durbin isolated and purified tagetitoxin from liquid cultures of the plant pathogenic bacterium *Pseudomonas syringae* pv. *Tagetis*.[1] The steps involved in the isolation, included multiple methanol precipitations and methanol:chloroform:water (MCW) extractions. These steps decreased the amount of unwanted mineral salts and carbohydrates present with the toxin, so that the resultant crude mixture could undergo chromatographic purification. Subsequent chromatographic steps involving gel filtration, ion-exchange and partition chromatography led to the isolation of tagetitoxin as a colourless glassy residue. Mitchell and Durbin, also concluded that the natural product contained a phosphate functional group (by formation of blue-grey colour upon spraying molybdate reagent on TLC plate spotted with the tagetitoxin sample), amino functional group (by ninhydrin staining TLC plate spotted with the tagetitoxin sample) and a sulfur atom (by ^{35}S-radioactive labelling).

Structure

A difficulty in the structural characterization of tagetitoxin has been the inability to obtain an X-ray crystal structure due to the natural product's non-crystalline glassy form. Furthermore, while its absolute stereochemical configuration has yet to be determined, several structures of tagetitoxin have been proposed.

Structure 1

The first structure was proposed by Mitchell and Hart in 1983.[2] IR spectroscopic analysis indicated the presence of hydroxyl group(s), carbonyl group(s) and phosphate functional

group(s) in the molecule. Field Desorption Mass Spectrometry (FDMS) suggested the molecular weight of the natural product to be 435 $gmol^{-1}$.

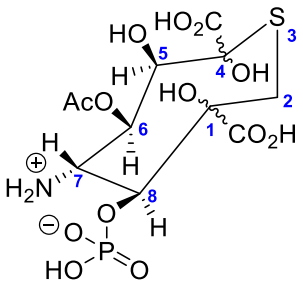
In the ^{31}P NMR, the presence of a doublet (J = 11.5 Hz) at 1.0 ppm downfield from a phosphate indicated the presence of a phosphate ester of a secondary alcohol function.

The sulfur atom was deduced to be part of a thiohemiketal functionality. This conclusion was reached firstly on the observation that adding strong acid to tagetitoxin did not liberate a sulfate, indicating the absence of a sulfate ester. Secondly, there was no red-colour observed when reacting tagetitioxin with sodium nitroprusside, suggesting the absence of a thiol in the molecule. Pre-treating the natural product with dilute hydrochloric acid, however, then gave a positive colour test for thiols; this was rationalized as there being a thiohemiketal which ring-opened in dilute acid. Thirdly, there was only one sulfur atom in the molecule because growing *P.s tagetis* in the presence of radioactively labelled phosphate ($^{32}PO_4^{3-}$) and sulfate ($^{35}SO_4^{2-}$) produced radiochemically pure tagetitoxin with phosphorous-sulfur ratio of 1:1.

Key conclusions made from the ^{13}C NMR data indicated eleven carbon environments including three carboxyl carbons and five carbons monosubstituted with oxygen. The functionalities on those five carbons were deduced to be an acetate, phosphate and either one hydroxyl and one ether group or three hydroxyl groups based from ^{1}H and ^{13}C NMR chemical shift data.

Further data from the ^{1}H NMR (more specifically the well-defined multiplets) gave much structural information about the framework of the natural product.

Using the MS and NMR data, the molecular formula for tagetitoxin was proposed to be $C_{11}H_{18}O_{13}SNP$. Finally, based on the molecular formula and the absence of any carbon-carbon multiple bond signals in the ^{13}C NMR spectrum, tagetitoxin was hypothesized to be a single ring structure. Combining all these analyses, structure **1** was proposed (**Figure 1**).

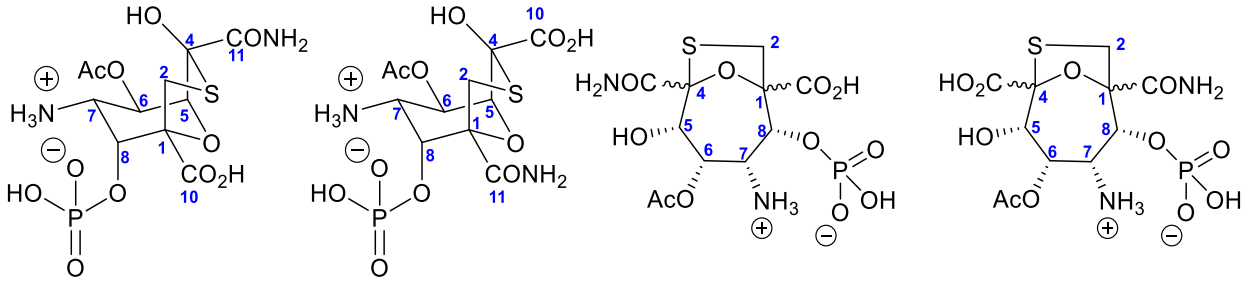


1

Figure 1: First proposed structure for tagetitoxin.[2]

Structures 2 and 3

In 1989, based on more refined NMR experiments and higher resolution MS measurements, four new structures (**Figure 2**) were proposed by Mitchell *et al.*[3]



2a **2b** **3a** **3a**

Figure 2: Revised structures for tagetitoxin.[3]

Fast atom bombardment (FAB) mass spectrograms showed the molecular weight to be 416 leading to the proposition of a new molecular formula, $C_{11}H_{18}O_{11}N_2SP$. The extra nitrogen in the molecular formula was concluded to be of an amide moiety from NMR data. The structure of tagetitoxin was proposed to be bicyclic based on the number of hydrogens in the molecular formula and the absence of any carbon-carbon multiple bond(s) from NMR data. Furthermore, from the data, the authors concluded that the oxygen-containing functional groups were a carboxylic acid and amide, acetate, phosphate and either two hydroxyl or two ether groups.

All four structures were strongly supported by nuclear Overhauser effect (nOe) experiments (for example the significant nOe experienced between H-C_{-5} and H-C_{-6}). In addition, nOe experiments were critical in disproving structure **1**, as the nOe observed between H-C_7 and H-C_{-2}

would not be expected for structure **1**, since these protons have a too distant spatial proximity from each other.

The authors utilized the Karplus relationship from the coupling constants of the protons in the four-carbon series (C_{-5} to C_{-8}), to deduce the dihedral angles between them. They found, while this data was in good agreement with structures **2** and **3**, it had better supported structures **2**. It, for example, showed that H-C_{-6} and H-C_{-7} should be in a true diaxial relationship, which is evident for structures **2** but not for structures **3** because of the constraints the five-membered oxathiane ring places on the seven-membered ring. There, however, was not enough evidence to completely discredit structures **3**.

COLOC pulse sequences gave further information on the oxathiane ring. For example, a strong correlation between the C_{-4} and the methylene protons on the oxathiane ring further supported the presence of a thiohemiketal or thioketal.

Finally, the authors preferred structures **2a** and **3a** where the amide moiety is bonded to C_{-4}, due to the lower ^{13}C NMR chemical shift of the carboxyl carbon bonded to C_{-4} than C_{-1}. However, since the chemical shift difference between the carboxyl carbons are low, structures **2b** and **3b** were not discounted.

In 2005, Gronwald *et al.* isolated tagetitoxin using a slightly different method.[4] They used the same procedure as Mitchell *et al.*,[1] except that they used partition chromatography instead off the initial methanol precipitation and MCW partitioning steps.

From electrospray ionization (ESI) mass spectrometry, Gronwald *et al.* concluded that the molecular weight of tagetitoxin was 678 rather than 416 as previously reported by Mitchell *et al.* This difference was explained by the presence of an ion at *m/z* = 679.5216, which they assigned as the protonated molecular ion. While they found an ion with *m/z* = 417.3316, they identified it as a fragment of their protonated molecular ion. The ion at *m/z* = 417.0361 previously identified as the protonated molecular ion by Mitchell *et al.*, was suggested by Gronwald *et al.* to be a fragment of minor contaminants.

The ^{1}H and ^{13}C NMR spectra reported by Mitchell *et al.* were mostly in agreement with the spectra from Gronwald *et al.*, with the only difference seen in the latter being the extra peaks in the ^{1}H NMR (1.75ppm and 2.53ppm) and the ^{13}C NMR (23.2ppm and 181.5ppm) spectra.

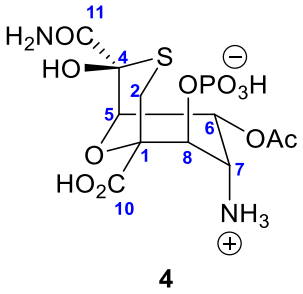
To account for the differences in the MS data despite good agreements with the NMR data, Gronwald *et al*. suggested that the higher molecular weight of 678 may be rationalized by the presence of atoms (such as oxygen, nitrogen and sulfur) and exchangeable protons not detected by 1D NMR experiments.

Furthermore, Structure **2** was supported by many 2D NMR experiments carried out by Gronwald *et al*. such as COSY, TOCSY and HMQC spectra, but there were some discrepancies with regards to the HMBC spectra.

Despite these conclusions, Gronwald *et al*. did not propose a new molecular formula nor a revised structure.

Structure 4

Later in 2005, Vassylyev *et al.* published an X-ray crystal structure of the bacterial *Thermus thermophilus* RNAP-tagetitoxin complex, showing tagetitoxin bound to the enzyme's active site.[5] Even though the structure of tagetitioxin was not being investigated in this paper, structure **4** was indirectly proposed (**Figure 3**).



4

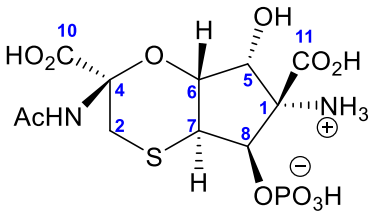
Figure 3: Structure of tagetitoxin indirectly proposed by Vassylyev *et al*.[5]

Whilst structure **4** has the same framework as structure **2**, the relative stereochemistry is different, where more specifically the chiral carbon centres bearing the phosphate group and the acetate group (C_{-8} and C_{-6}) have inverted.

Despite there being good agreement between the theoretical and experimental electron density maps of structure **4**, it is inconsistent with the previously reported NMR data.[2,3] Furthermore, whilst a resolution of 2.4 Å is good for studying a protein structure,[6] it is not deemed sufficient to fully clarify the structure of a small molecule like tagititoxin.[7]

Structure 5

Finally, in 2016, Aliev *et al.* further analysed a tagetitoxin sample originally isolated and purified by Mitchell.[1,2] They published more NMR and MS data which led them to propose a new structure (**Figure 4**) and refute previous structures.[8]



5

Figure 4: Structure proposed by Aliev *et al.*[8]

Aliev *et al.* concluded that the sample isolated by Gronwald *et al.*,[4] was less pure than that from Mitchell *et al.*[1,2] This was rationalized by the absence of the extra peaks Gronwald *et al.* observed in the ^{1}H NMR (1.75ppm and 2.53ppm) and ^{13}C NMR (181.5ppm).

Moreover, on analysing MS data, no species with a molecular weight of 678 was seen, which disagreed with Gronwald and co-workers' proposed molecular weight of tagetitioxin.

Key disagreements with the previous structures (**1**, **2**, **3** and **4**) were found from the HMBC spectrum and the long range J_{CH} values. These disagreements were:

1. A correlation between C_{-11} and H-C_{-8} is seen which is inconsistent with structures **2a**, **3a** and **4** because of the presence of six bonds between these atoms.
2. The J_{CH} value of 5.0 Hz, between C_{-10} and H'-C_{-2} is too large to be a $^{4}J_{CH}$ correlation. This is not consistent with structures **2b** and **3b**, since the size of the J_{CH} suggests that this pair of atoms should be closer together.
3. The cross peaks observed for C_{-7} with H-C_{-2} (J_{CH} = 5 Hz) and with H'-C_{-2} (J_{CH} = 3 Hz) are inconsistent with all structures **1** to **4**. This is due to the four-bond separation between these aforementioned atoms.
4. The J_{CH} value of 1.4 Hz for C_{-4} and H-C_{-6} is too small to be a J_{CH} correlation for atoms that have a ~180° dihedral angle, which is inconsistent structures **2a** and **2b**.

The key disagreements for previously reported structures were verified with the authors' proposed structure **5:**

1. C_{-11} and H-C_{-8} in structure **5** are 3 bonds apart, and therefore correlate.
2. C_{-10} and H'-C_{-2} in structure **5** are 3 bonds apart accounting for the $^3J_{CH}$ value of 5.0 Hz between them.
3. In structure **5**, C_{-7} is 3 bonds apart with H-C_{-2} and H'C_{-2} explaining the $^3J_{CH}$ coupling observed.
4. If the 6-membered ring of structure **5** is in a chair confirmation H-C_{-6} and C_{-4} will have a dihedral angle of ~60°, which accounts for the low $^3J_{CH}$ value between these.

The authors also concluded that there was *trans* stereochemistry at the ring junction due to the high coupling constant ($^3J_{HH}$ = 12.4Hz) between H-C_{-6} and H-C_{-7}. Further data from NOESY, vicinal $^3J_{HH}$ coupling constants, HMBC and DFT calculations (the latter was used to explain unexpected missing HMBC correlations), provided further support for structure **5**.

Biological Activity

Application of tagetitoxin to the stems of plants in the *Asteraceae* family such as zinnia (*Zinnia elegans* Jacq) and sunflower (*Helianthus annuus*) leads to apical chlorosis (bleaching of apical green plant tissue due to decreased amount of chlorophyll in that tissue).[2] This effect is due to the translocation of the toxin to apical regions of the plant where it inhibits chloroplast RNAP, suppressing differentiation of proplastids into chloroplasts, preventing new chlorophyll accumulation in these regions.[9] Two radiolabelling experiments supported this hypothesis.[10] Initially, Matthews and Durbin performed *in organello* incorporation reactions where tagetitoxin was added to isolated, intact chloroplasts and the rate of incorporation of radiolabelled uridine into RNA was measured.[10] It was observed that tagetitoxin application led to a decrease in the rate of incorporation of [^{3}H] uridine into RNA; indeed at tagetitoxin concentrations of 1mM, there was negligible [^{3}H] uridine incorporation. Furthermore, the addition of tagetitoxin to *in vitro* transcriptionally active chloroplast protein extracts reduced [^{32}P] UTP incorporation into RNA. Both experiments suggest that RNA synthesis in chloroplasts is suppressed due to tagetitoxin inhibition of chloroplast RNAP.

Moreover, tagetitoxin inhibits RNAP III *in vitro* in many eukaryotes such as yeast, insects and vertebrates.[11] This is in contrast to the other eukaryotic nuclear RNAPs, RNAP I and RNAP II which appear to be more resistant to inhibition from the toxin.[12] For example tagetitoxin at low concentrations (0.3-3.0 μm) inhibit RNAP III directed transcription in various organisms but has little effect on RNAP II directed transcription.[13]

Finally, inhibition of *in vitro* RNA synthesis directed by RNAP from *Escherichia Coli* by tagetitoxin at concentrations less than 1μM has also been reported.[10,13]

In summary, tagetitoxin inhibits chloroplast and bacterial RNAP. Tagetitoxin is also a selective inhibitor of RNAP III compared to the other nuclear RNAPs in a variety of eukaryotes.

Biological Mechanism of Inhibition

In 1994, Matthews and Durbin conducted abortive initiation assays to primarily investigate the inhibition kinetics of tagetitoxin on *E. Coli* RNAP.[12] They concluded that tagetitoxin acts an uncompetitive inhibitor of *E. Coli* RNAP which indicates that the toxin does not prevent the nucleotide triphosphate (NTP) substrate from binding with the enzyme. It was also inferred from these studies that tagetitoxin does not affect phosphodiester bond formation between an NTP substrate and the nascent RNA chain. The authors suggested that the inhibition may be due to tagetitoxin affecting the stability of the binding between the nascent RNA chain and the enzyme-DNA template complex. Despite advances in the understanding of the inhibitory effect of tagetitoxin on a RNAP, it was widely acknowledged that the exact mechanism of the toxin and its target site on RNAP were unclear.[5]

A breakthrough in the inhibition mechanism by tagetitoxin on RNAP was achieved by Vassylyev *et al*. in 2005, where an X-ray crystal structure of the complex between a bacterial RNAP (from *Thermus thermophilus*) and tagetitoxin was published.[5] Analysis of this structure led to a greater insight of the binding between tagetitoxin and RNAP. This structural analysis along with homology modelling and biochemical analyses allowed the authors to propose a more detailed inhibition mechanism.

The X-ray structure has shown that the RNAP binding site for tagetitoxin is located at the base of the RNAP secondary channel, adjacent to its active site. This suggests that tagetitoxin does not prevent NTP substrate binding, which is in agreement with the conclusions drawn by Matthews

and Durbin.[12] Moreover, the binding between tagetitoxin and the RNAP was primarily made up of 18 hydrogen bonds between 9 of the 11 oxygen atoms of the toxin with side chains of adjacent amino acid residues of the RNAP (**Figure 5**). In addition to the expected catalytic magnesium ions (cMg1and cMg2) found in a RNAP, a third magnesium ion (tMg) was observed in the RNAP/Tagetitoxin complex. The authors suggested that this well-fixed tMg coordinates to the phosphate group of tagetitoxin stabilizing the toxin further. The tMg is well-fixed because of its coordination to the side chains of two active site amino acid residues of RNAP.

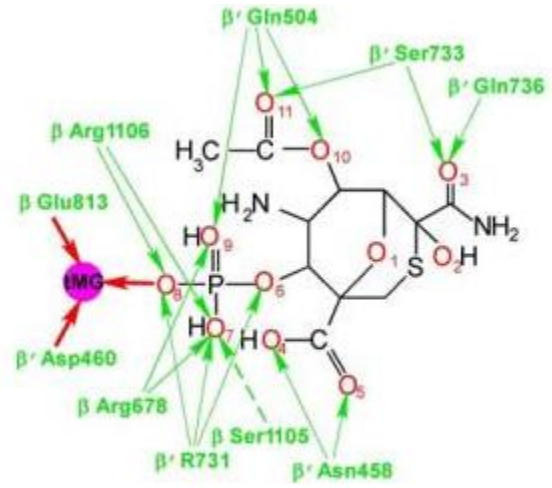


Figure : A schematic diagram of the tagetitoxin binding site on RNAP. [5]

Vassylyev and co-workers postulated a two-step mechanism for tagetitoxin inhibition RNAP (**Figure 6**). They proposed that the mechanism involves the stabilization of an inactive transcription intermediate whilst the NTP substrate is loading into the active site. In this mechanism, whilst tagetitoxin is being bound to its binding site in the enzyme, the NTP substrate enters the pre-insertion site. Due to the coordination of tagetitoxin to tMg, the NTP binds to the tMg rather than cMg2; binding to cMg2 would otherwise occur without tagetitoxin. The NTP substrate is then loaded into the insertion site by a simple rotation forming the insertion complex. In the resulting intermediate, the active site has a more compact conformation leading to tighter binding of the tMg-bound substrate and greater stabilization, locking the intermediate in an inactive state preventing the dissociation of the NTP substrate and the catalytic reaction. The authors also proposed that since the NTP coordinates to the tMg rather the cMg2, the positioning of cMg1 and cMg2 change. This change in orientation would decrease the stability of the pentavalent transition state formed during phosphodiester formation between the terminal 3'OH

of the nascent RNA chain and the α-phosphate functionality of the NTP substrate, further lowering the catalytic activity.

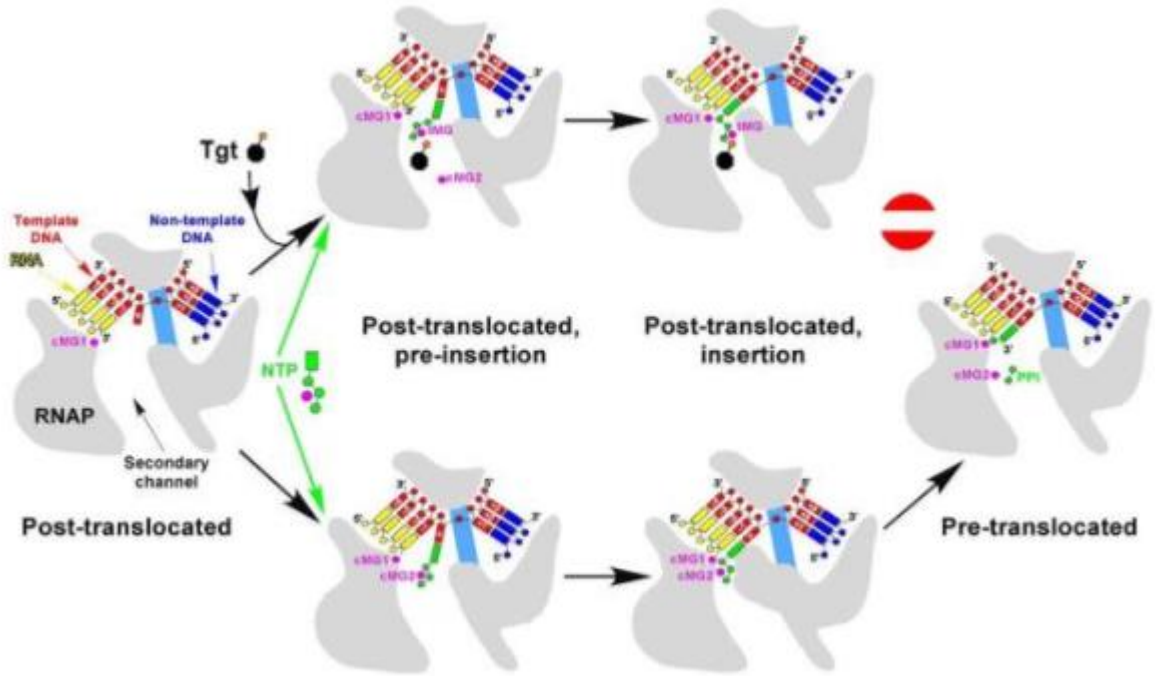


Figure 6: Proposed inhibitory mechanism of tagetitoxin on RNAP.[5]

This mechanism was contested by Artsimovitch *et al*. in 2011.[14] Based on theoretical modelling using molecular dynamics simulations, they suggested that the inhibitory effect of tagetitoxin on RNAP arises from the interaction between tagetitoxin and the side chains of two amino acid residues of the RNAP trigger loop (a flexible protein domain). During typical transcription, the trigger loop folds into a trigger helix; this leads to the catalytic amino acid residues being in an active configuration. These amino acid residues, then interact with the NTP substrate facilitating phosphodiester bond formation between the NTP and the nascent RNA chain.[15] However, due to the interaction of tagetitoxin with the trigger loop, instead of folding to a trigger helix, it is stabilized and trapped in an inactive state, which lowers catalytic activity. Klyuyev and Vassylyev later argued that this mechanism was in poor agreement with practical results in favour for theoretical models.[16]

Finally, in 2013, based on multiple transcription assays, the trigger loop mechanism was revised by Yuzenkova *et al*.[17] The nucleotide addition cycle consists of phosphodiester bond formation

(between the NTP substrate and the nascent RNA chain), a translocation of RNAP on the DNA template strand and then the binding of the next NTP substrate.[17] In between phosphodiester bond formation and translocation, the transcription elongation complex (the RNAP containing complex that additionally includes the DNA template strand and the nascent RNA chain) is in its pre-translocated state.[18,19] During the subsequent translocation, the trigger loop unfolds.[14] Yuzenkova and co-workers proposed that tagetitoxin stabilizes the folded conformation of the trigger loop when the transcription elongation complex is in its pre-translocated state.[17] As a result the subsequent translocation is slowed down due to the greater difficulty in unfolding the trigger loop; this leads to the overall rate of the RNA chain elongation to decrease.

Importance of Tagetitoxin

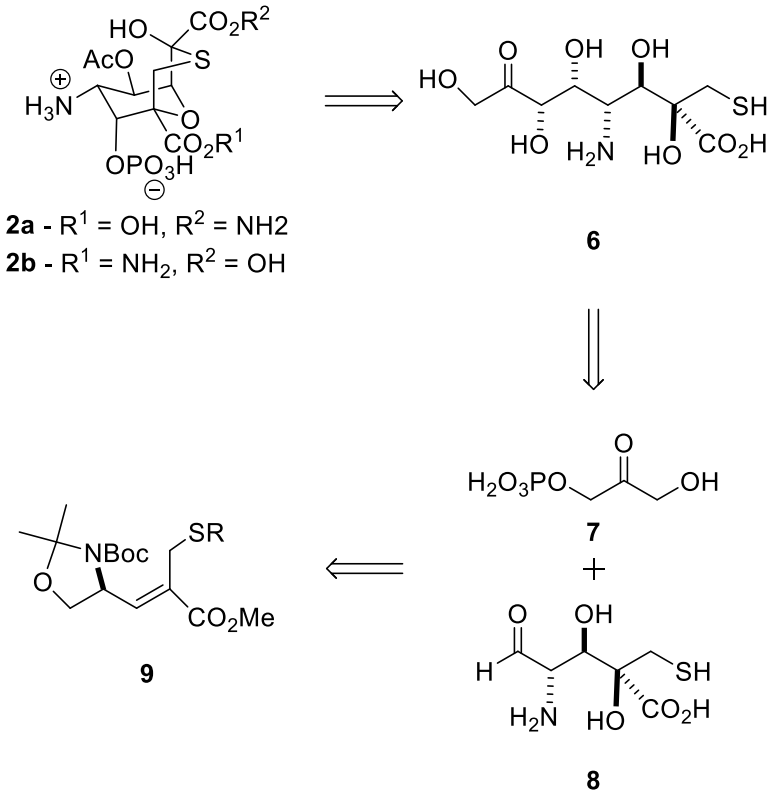
The importance of tagetitoxin originates from its biological activity. For example, due to the toxin's inhibition on chloroplast RNAP, its use as a plant growth regulator has been patented.[20] Furthermore, since tagetitoxin inhibits a variety of RNAPs, it can be a useful tool for molecular biologists investigating transcription. Finally, a total synthesis of the natural product would provide opportunities to synthesize a library of analogues; these analogues could be then assessed for herbicidal[21] and antibacterial activity.[22]

Previous Synthetic Studies of Tagetitoxin

Since all synthetic studies towards tagetitoxin were conducted prior to 2016, the targets were generally **2a** and **2b** as these were the accepted structures at the time.

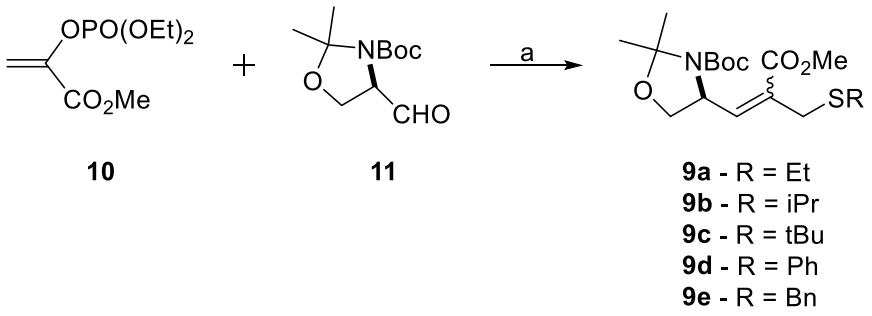
Sammakia *et al.*

In 1996, Sammakia *et al.* published their attempt to synthesize tagetitoxin.[23] Their retrosynthetic analysis of tagetitoxin involved a precursor **6** that can cyclize to give structures **2a** or **2b** (**Scheme 1**). Synthesis of precursor **6** was planned to be an enzymatic aldol-catalysed coupling of dihydroxy acetone phosphate **7** with aldehyde **8**. Aldehyde **8** could be made from oxazolidine olefin **9** in three steps: dihydroxylation of the olefin moiety; hydrolysis of the oxazolidine; and selective oxidation of the primary alcohol to an aldehyde.



Scheme 1: Retrosynthetic analysis of proposed tagetitoxin structures **2a** and **2b** by Sammakia *et al.*

A range of oxazolidine olefins **9** (**Scheme 2** and **Table 1**) were prepared in a one-pot synthesis. This involved a range of thiolate anions attacking a substituted methyl acrylate phosphonate **10** in a conjugate addition forming an ylide. The ylide, in turn, condensed with the oxazolidine aldehyde **11** to produce the olefins **9a** to **9e** with varying stereoselectivity.



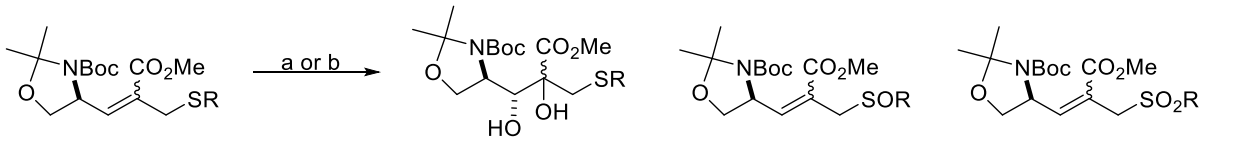
Reagents and conditions: a) RSH, NaH, THF, 0 ^{o}C. See **Table 1.**

Scheme 2: One-pot synthesis of oxazolidine olefins **9**.

R	Ethyl **9a**	*i*-Propyl **9b**	*t*-Butyl **9c**	Phenyl **9d**	Benzyl **9e**
Z:E	60:40	70:30	100:0	20:80	30:70

Table 1: Effect of the sulfur protecting group on the Z:E ratio of olefins **9a-e**

The authors then attempted a range of dihydroxylation methods on olefins **9** (**Scheme 3** and **Table 2**).



9 **12** **13** **14**

Reagents and conditions: a) AD-mix-b (1.5g/mmol of alkene **9**), 1:1 *t*BuOH, rt: H_2O; b) OsO_4 (10 equiv.), K_2CO_3 (3 equiv.), $K_3Fe(CN)_6$ (3 equiv.), 1:1 *t*BuOH: H_2O. See **Table 2**.

Scheme 3: Dihydroxylation attempts of olefins **9**.

Olefin	Conditions	Recovered **9** (%)	Yield of **12** (%)	Yield of **13** (%)	Yield of **14** (%)
9a	a	54	-	48	-
	b	30	-	70	-
9b	a	56	6	28	-
	b	39	15	44	-
9c	a	86	14	-	-
	b	32	55	11	-
9d	a	99	-	<1	-
	b	34	27	-	39
9e	a	82	-	10	-
	b	22	6	72	-

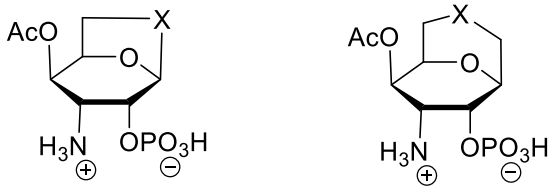
Table 2: Yields reported for compounds **12**, **13** and **14** from the dihydroxylations of olefins **9**

When using conventional methods of stoichiometric or catalytic amounts of osmium tetroxide, only sulfur oxidized products were isolated. This then led them to use AD-mix-β or

stoichiometric amounts of osmium tetroxide and potassium ferricyanide. However, for most of the olefins **9**, starting material and sulfur oxidized products (mainly sulfoxides) were the major compounds isolated. The most promising result was the dihydroxylation of the bulky t-butyl thioether substrate **9c** using stoichiometric osmium tetroxide and potassium ferricyanide. Despite this promising result, the synthesis to structures **1** and **2a** were not pursued and no research related to this synthetic strategy has yet to be reported.

Dent *et al.*

Due to tagetitoxin's reported biological activity, Dent *et al.* aimed to synthesize related analogues of the natural product for evaluation as herbicides and plant growth regulators.[21] Based on structures **2a** and **2b,** the authors thought that the acetate, amine and phosphate groups were key for the biological activity. They also suggested that the sulfur bridge was important to impose the desired stereochemistry on the pyranoid ring. As a result, structures **15** and **16** were their synthetic targets (**Figure 7**). To achieve their main goal of gaining greater knowledge on structure-activity relationships of tagetitioxin, Dent *et al.* would have to make carbohydrate-based vicinal *cis*-amino phosphates (where the latter in itself is useful synthetic methodology).

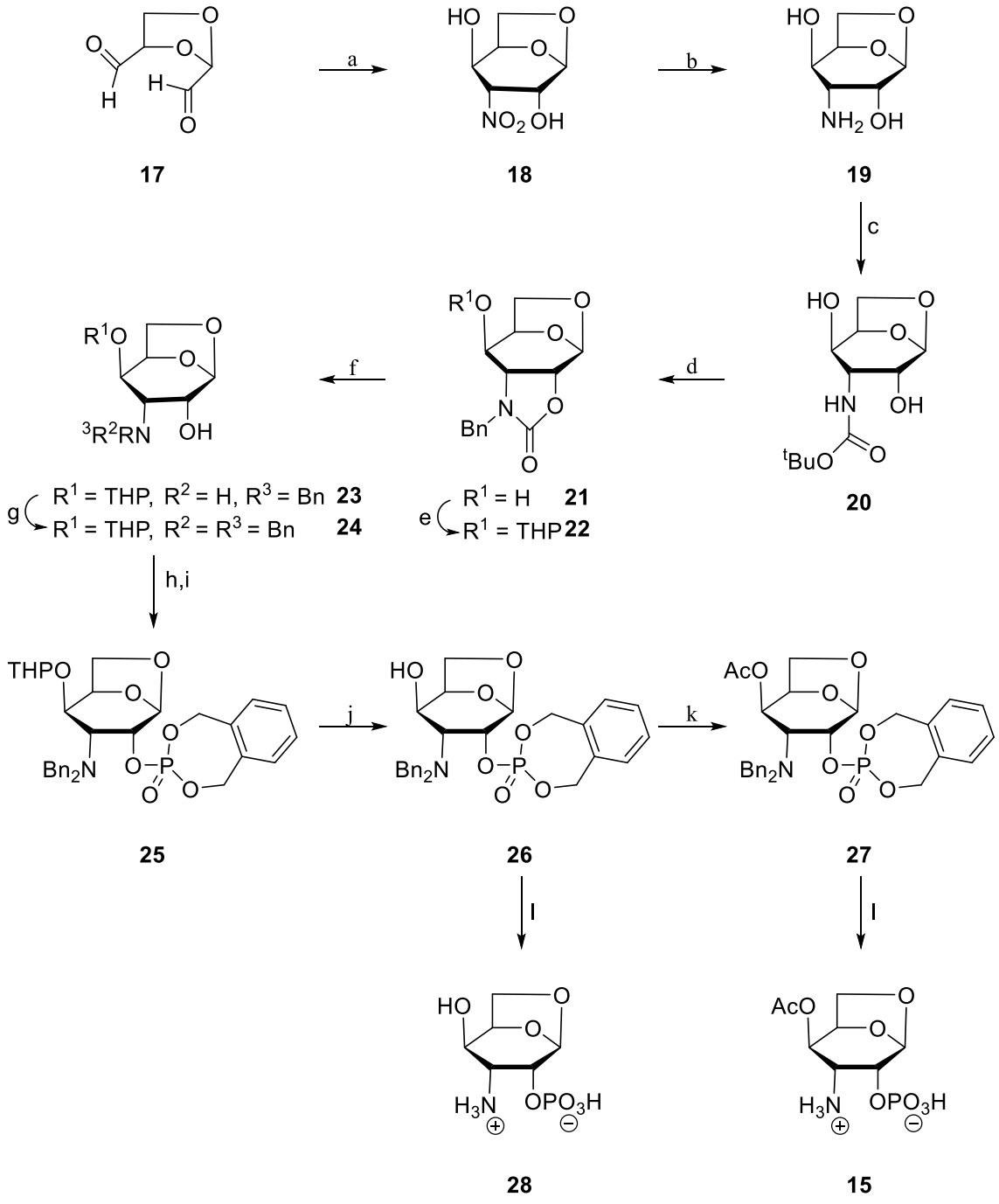


15 X = O, S **16**

Figure 7: Synthetic targets for Dent *et al.*

The authors were able to synthesize structure **15** (X=O) in a twelve-step route starting from dialdehyde **17** (**Scheme 4**), which is readily available from periodate oxidation of levoglucosan. The cyclic framework of their synthetic target was achieved by the cyclization of dialdehyde **17** with nitromethane furnishing **18**. After hydrogenolytic reduction of the nitro group to produce **19**, the formed amine was then *N*-Boc protected to give **20**. The authors then exploited the *syn*-stereochemistry of the C_{-2} and C_{-3} substituents; this would eventually allow them to esterify the C_{-2} and C_{-4} hydroxyl groups selectively. The *N*-Boc derivative **20** was then treated with bis(tributyltin) oxide in toluene under reflux, followed by addition of tetra-*n*-butylammonium

bromide and benzyl bromide to form the *N*-benzyloxazolidinone derivative **21**. The authors then carried out a three-step sequence of protections and deprotections of various groups to afford **24**. Compound **24** then underwent a phosphitylation using *o*-xylene-*N*,*N*-diethylphosphoramidite and 1*H*-tetrazole, which was followed by an oxidation using *m*-CPBA yielding phosphate ester **25**. The authors subsequently deprotected the tetrahydropyranly acetal (THP) and then acetylated the C_{-4} hydroxyl group, which formed compound **27**. Hydrogenolysis of the phosphate ester and benzyl amine moieties in **27** were performed leading to synthetic target **15**. Hydrogenolysis of intermediate **26** led to an additional analogue **28** which along with **15** were tested for herbicidal activity.



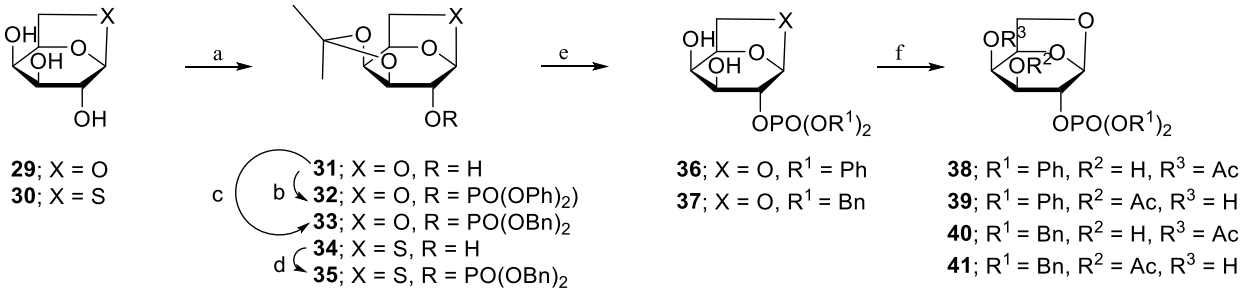
Scheme 4: Dent and co-workers' synthesis of analogues **15** and **28**.

Biological testing showed compound **15** and its deacylated analogue **28** to have no herbicidal activity against a variety of agriculturally important weeds:

Avena Fatua (wild oat), *Setaria viridis* (green foxtail), *Amaranthus retroflexus* (redroot pigweed) and *Chenopodium album* (fat hen).

A second set of analogues based on structure **15**, were then targeted by the authors using different synthetic methodology, whereby the insertion of the amino functionality at C_{-3} would be different. This would be achieved by forming a good leaving group at the C_{-3} position followed by a S_N2 reaction using a nitrogen-based nucleophile which could later be transformed to an amino functional group (e.g. azide nucleophile).

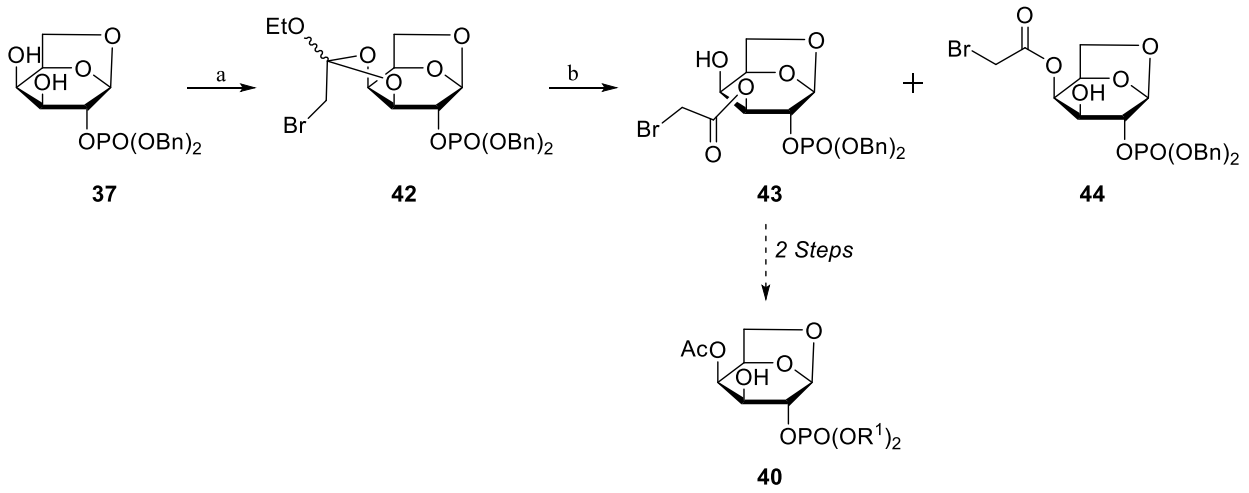
Their first attempted synthesis following the above methodology started from 1,6-anhydro-D-galactose **29** and it sulfur analogue **30** (**Scheme 5**). Acetonide formation of the hydroxyl groups on C_{-3} and C_{-4} in **29** and **30**, allowed subsequent selective phosphate ester formation on the C_{-2} position forming **32**, **33** and **35**. Phosphate ester formation was achieved using either a dialkyl chlorophosphate in pyridine or a pyrophosphate with a strong base (only the latter strategy was used on the sulfur analogue **34**). Subsequent steps (d, e and f) involved successive protections and deprotections of various groups in order to reach **38** or **40**. The authors began this sequence with an acetonide deprotection affording **36** and **37**. They, however, could not isolate the required diol from acetonide hydrolysis of sulfur species **35** (presumed to be because of the sulfur atom participating in reactions involving carbocations generated in these acidic conditions). Under a variety of conditions, Dent and co-workers, then unsuccessfully attempted to selectively acetylate the C_{-4} hydroxyl group over the C_{-3} hydroxyl group in **36** and **37**, since they only isolated inseparable mixtures of the monoacetates **38** and **39** or **40** and **41** respectively. The origin of this poor selectivity was attributed to either an inherent unselective reaction or ester migration occurring during the reaction.



Reagents and condtions a) $Me_2C(OMe)_2$, Me_2CO, TsOH; b) $ClPO(OPh)_2$, pyridine; c) BuLi, $[(BnO)_2PO]_2O$; d) NaH, $[(BnO)_2PO]_2O$; e) 2M HCl; f) Ac_2O and (PY or Bu_2SnO or $(Bu_3Sn)_2O$).

Scheme 5: Dent and co-workers' second route to analogues based on structure **15**.

As a result, the authors changed their approach in an attempt to isolate **40** (**Scheme 6**). This involved forming a cyclic brominated orthoacetate **42** (from **37**) and then subjecting this to mild acidic hydrolysis. This methodology was hypothesized to lead to bromoacetate **43**. Compound **43** could then be acetylated on the C_{-4} position, then deprotection of the C_{-3} bromoacetate in the presence of the C_{-4} acetate would lead to the desired **40**. Although brominated orthoacetate **42** was successfully synthesized, when subjected to mild hydrolysis an inseparable mixture of bromoacetates **43** and **44** were formed causing the authors to abandon this methodology.

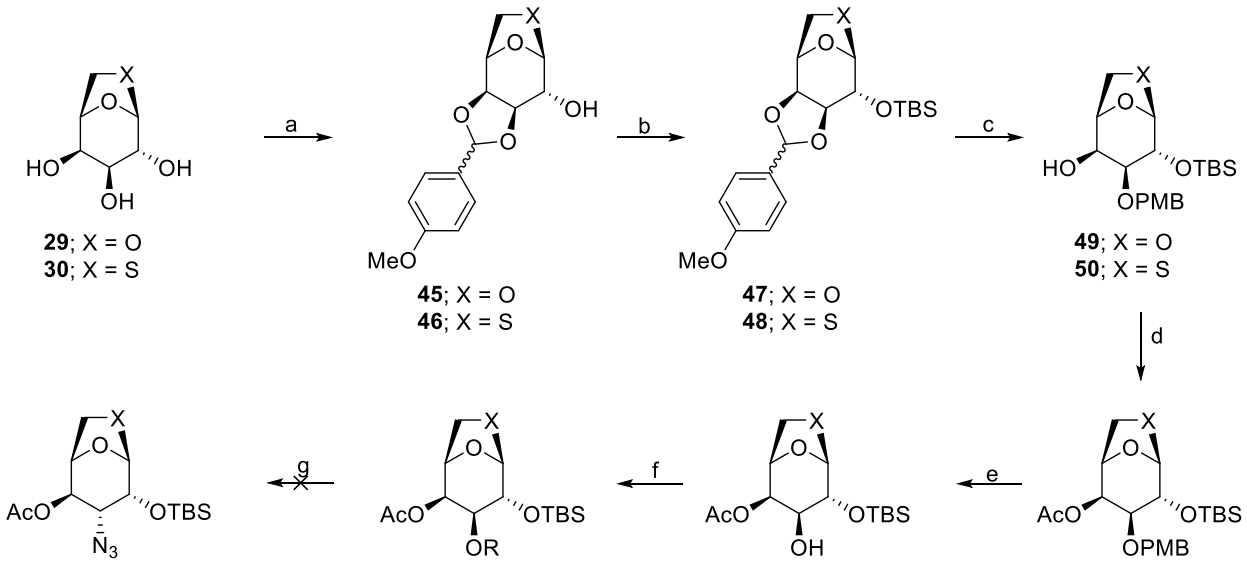


Reagents and condtions a) $BrCH_2C(OEt)_3$, TsOH; b) AcOH, H_2O.

Scheme 6: Dent and co-workers' alternative route to structure **40**.

Dent and co-workers' second attempted route in selectively functionalizing **29** and **30** exploited the regioselective reductive cleavage of a methoxybenzylidene acetal (S**cheme 7**). After forming a methoxybenzylidene acetal on the C_{-3} and C_{-4} position and successively silyl protecting the C_{-2}

hydroxyl group to form **47** and **48** respectively, treatment with $LiAlH_4$-$AlCl_3$ produced only the 3-O-*p*-methoxybenzyl ethers **49** and **50**. Subsequently via a series of protections and deprotections, compounds **53** and **54** were made where the hydroxyl group on C_{-3} was unprotected. This therefore allowed introduction of a good leaving group on the C_{-3} position (triflate, tosylate and mesylate) and displacement of that leaving group with an azide nucleophile. However, despite successfully synthesizing sulfonate esters **55 – 60**, treatment with sodium azide in DMF, HMPA or DMSO failed to yield compounds **61** and **62** as only starting material or decomposition was seen. The rationale for these observations was steric hindrance from the adjacent bulky silyl ether.

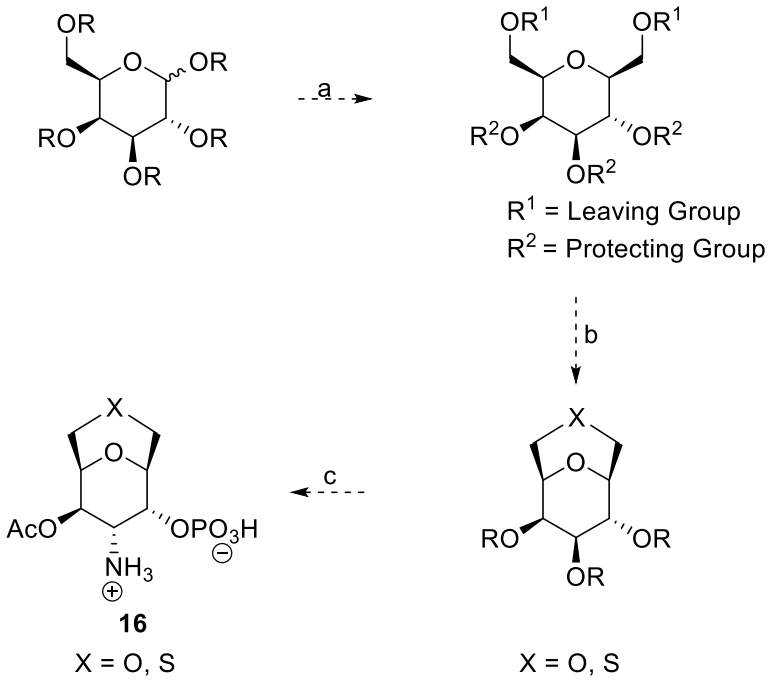


Reagents and conditions a) $MeOC_6H_4CH(OMe)_2$, TsOH; b) Bu^tMe_2SiCl, imidazole, DMF; c) $LiAlH_4$, $AlCl_3$, THF; d) Ac_2O pyridine; e) DDQ, DCM, H_2O; f) Tf_2O, MsCl or TsCl, pyridine; g) DMF, HMPA, or DMSO, NaN_3.

Scheme 7: Attempted synthesis of compounds **61** and **62** by Dent *et al.*

Dent *et al*. then focused on synthesizing compounds based on structure **16** starting from pentaprotected carbohydrates. Their strategy involved a one carbon chain extension at the C_{-1} position of a D-galactopyranose derivative, followed by ring closure linking this new carbon atom with the C_{-6} by a sulfur or oxygen atom. Following this, phosphorylation, acetylation and

introduction of the amino functionality (latter by S_N2 chemistry) would then yield **16** (**Scheme 8**).

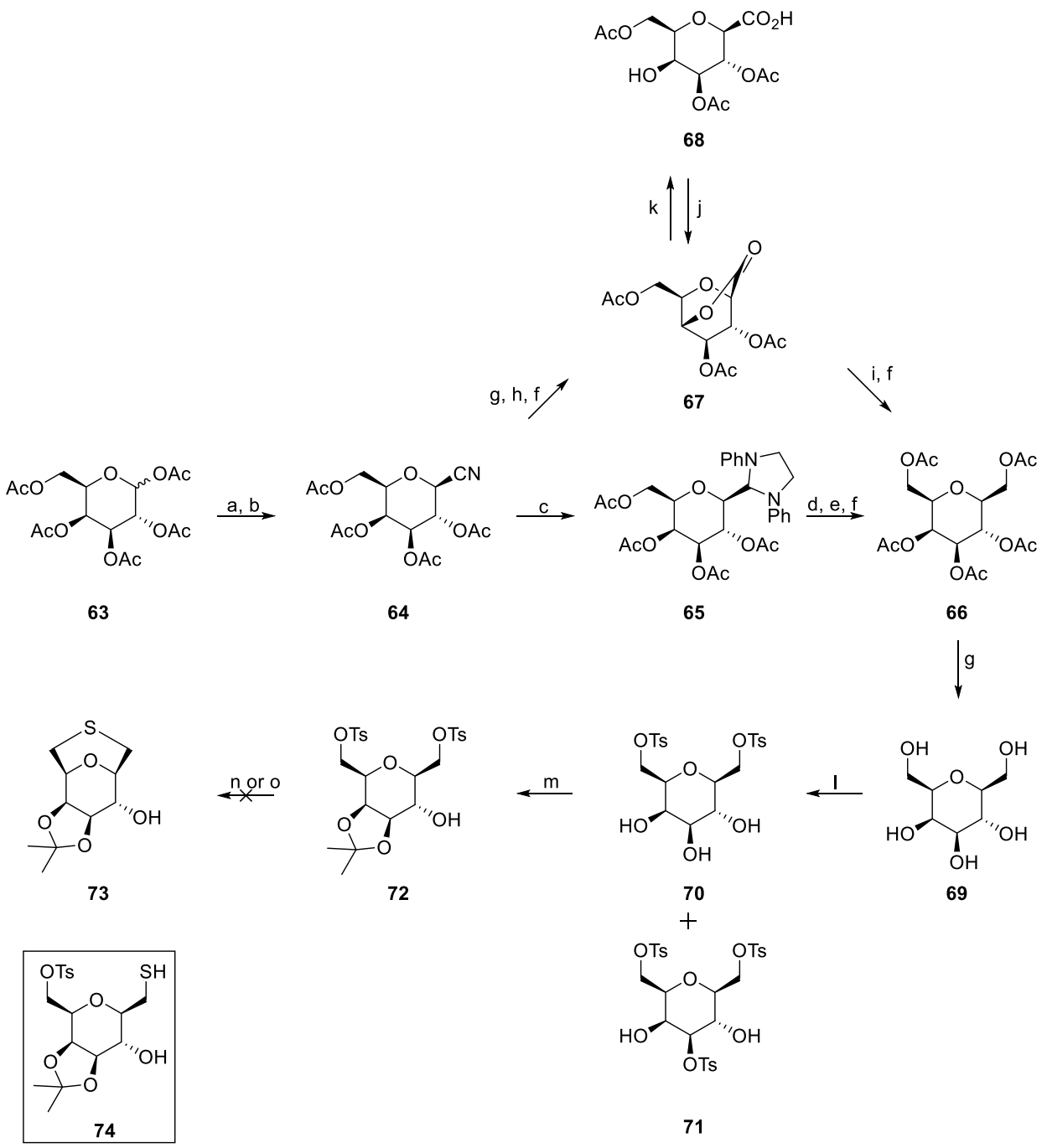


Methodologies: a) one carbon chain extension; b) ring closure; c) introduce functionalities.

Scheme 8: Dent and co-workers' methodology to synthesize analogue **16**.

In this strategy, the authors started with the bromination of D-galactose pentaacetate **63** to give the α-glycosyl bromide, which was then treated with mercuric cyanide in nitromethane to furnish the β-nitrile **64** (**Scheme 9**). Two approaches to synthesize **66** from **64** were successfully achieved. The first approach involved a reductive hydrolysis of a nitrile to an aldehyde using Raney nickel with the hydrogen source sodium hypophosphite in aqueous acetic acid and pyridine, followed by the *in-situ* trapping of that aldehyde with a diamine to form imidazolidine **65**. The success of this reaction was variable due to the occurrence of undesired side-reactions. The aldehyde was then regenerated by hydrolysis of the imidazolidine and then reduced using sodium borohydride. The resultant crude product was then acetylated to form **66**. The second approach involved deacylation of **64**, basic nitrile hydrolysis and then acetylation of the crude hydrolysis product which gave a mixture of γ-lactone **67** and hydroxy carboxylic acid **68**. However, under strong acetylation conditions, **68** was cleanly reconverted into γ-lactone **67**. Lithium aluminium hydride (LAH) reduction of the lactone and subsequent peracetylation gave

66. After compound **69** was formed from deacetylation of **66**, selective tosylation on the methylene alcohols produced compounds **70** and the undesired tri-tosylate **71**. Acetonide formation on ditosylate **70**, led to the bicyclic precursor **72**. Attempts at ring closure in **72** using sulfide nucleophiles (lithium or sodium sulfide) in DMF failed to produce the bicyclic structure **73**. However, thiol **74** was isolated where only one of the tosylates was displaced by the sulfide nucleophile. The authors attributed this result to the isopropylidene groups placing steric constraints on the ring closure.



Reagents and conditions a) HBr, HOAc; b) $Hg(CN)_2$, $MeNO_2$; c) Raney Ni, NaH_2PO_2, $PhHN(CH_2)_2NHPh$; d) TsOH, Me_2CO, DCM; e) $NaBH_4$ f) Ac_2O, PY; g) NaOMe, MeOH; h) 25% w/v NaOH; i) $LiAlH_4$; j) H_2O; k) Ac_2O, NaOAc; l) TsCl, pyridine; m) $Me_2C(OMe)_2$, TsOH; n) Na_2S, DMF; o) Li_2S, DMF.

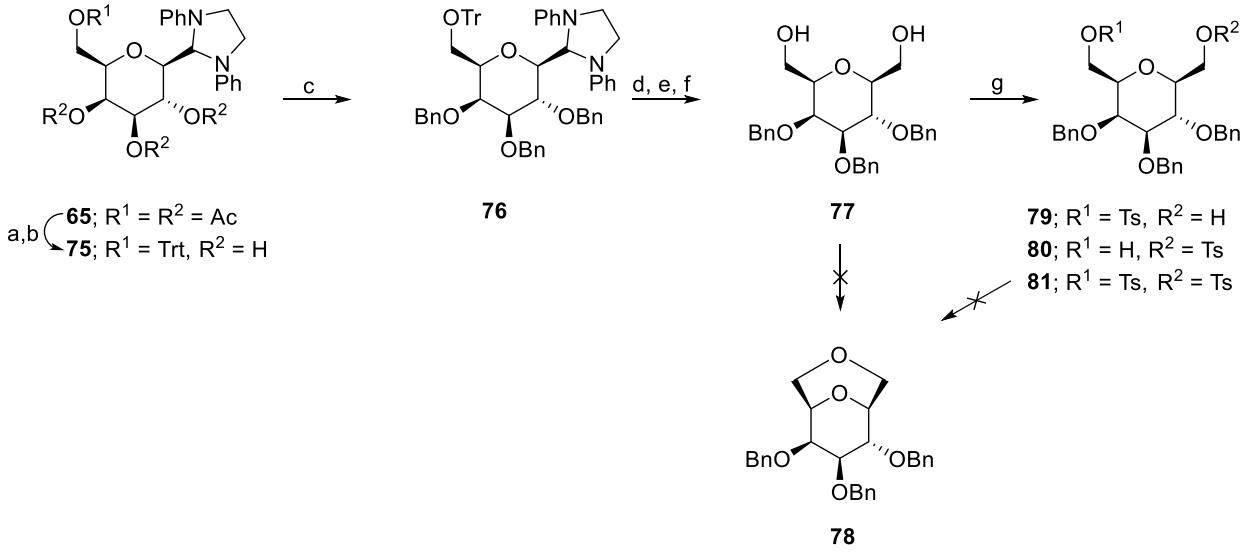
Scheme 9: Dent and co-workers' attempted synthesis of bicyclic structure **73**.

As the synthesis of **73** was unsuccessful, Dent *et al*. decided to replace the isopropylidene group with benzyl groups when forming further precursors for target **16** (X=O). Hence, starting from

compound **65**, they performed a sequence of deprotections and protections of various groups to reach the tri-benzylated compound **76** (**Scheme 10**). After unmasking the aldehyde in **76**, sodium borohydride reduction and trityl deprotection, diol **77** was isolated. Two different methods on **77** were undertaken in an attempt to isolate the desired cyclic ether **78**:

1. An acidic cyclodehydration in toluene under reflux.
2. Treatment with triphenylphosphine and diethyl azodicarboxylate (DEAD).

In both methods, however, starting material was only recovered. The authors then tried a mono-tosylation on diol **77** but this led to a mixture of the regiomeric mono-tosylates **79** and **80** in addition to di-tosylate **81**. Nevertheless, since they were able to isolate **79**, they attempted the cyclization using sodium hydride, but this gave a complex mixture.

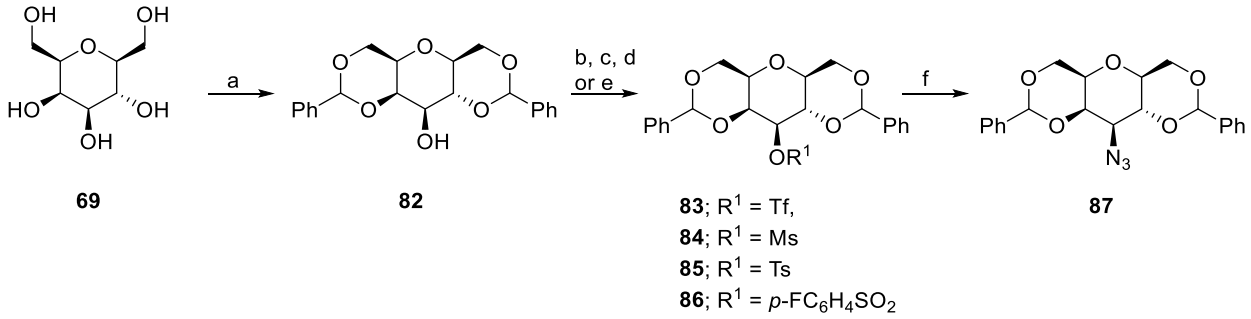


Reagents and conditions: a) NaOMe, MeOH; b) TrtCl, Et_3N; c) NaH, BnBr; d) TsOH, Me_2CO, DCM; e) $NaBH_4$; f) TsOH, MeH; g) TsCl, PY.

Scheme 10: Dent and co-workers' attempted synthesis of bicyclic structure **78**.

Finally, Dent *et al.* wanted to introduce a nitrogen functional group attached to the C_{-3} position prior to the ring closure to assess whether the substituent on this position in the previous routes sterically hindered the cyclization. They, therefore synthesized the di-benzylidene acetal **82** from **69** (**Scheme 11**). This allowed subsequent transformation of the C_{-3} hydroxyl group in **82** to a variety of sulfonate esters (compounds **83-86**). However, nucleophilic displacement of these sulfonate esters with an azide nucleophile under a range of conditions led to either no reaction or

decomposition of the starting material, except for tosylate **85** which furnished azide **87** but at only 10% yield. Due to the low yield, the synthesis was abandoned at this stage.



Reagents and conditions: a) $PhCH(OMe)_2$, TsOH; b) Tf_2O, PY; c) MsCl, PY; d) TsCl, DMAP, PY; e) *p*-$FC_6H_4SO_2Cl$, DMAP, PY; f) for **85**: NaN_3, DMSO, 180 ^oC.

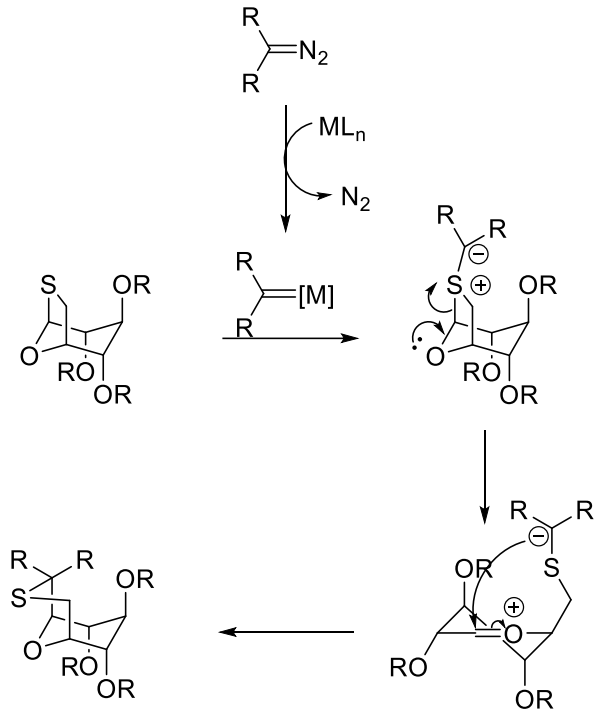
Scheme 11: Synthesis of azide **87** by Dent *et al*.

In summary, Dent *et al.* were successful in making the analogue **15** (**Scheme 4**) but only with an oxygen bridge rather than a sulfur bridge. They were also unsuccessful in the synthesis of analogue **17**, which is more closely related to tagetitoxin structures **2a** and **2b**.

Porter and Plet 2006

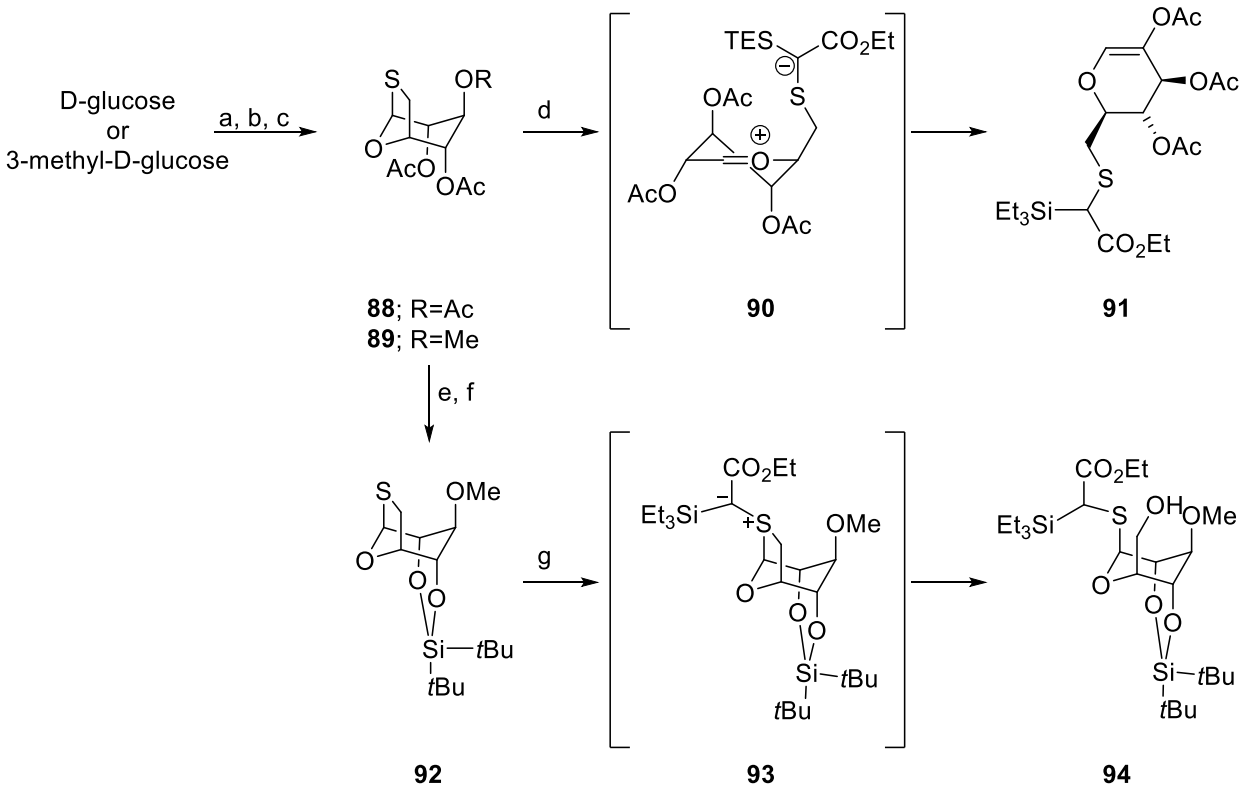
In 2006, Porter and Plet published the first synthesis of the bicyclic core of tagetitoxin from a carbohydrate precursor.[24]

Their first strategy, was based on a carbene-mediated ring expansion of a 1,3-oxathiolane moiety (**Scheme 12**). In this approach a metallocarbene would be generated from a transition metal catalysed decomposition of a diazo derivative. The nucleophilic sulfur atom would then attack the electrophilic carbon of the metallocarbene forming a sulfur ylide. This would cause the 1,3-oxathiolane moiety to ring open followed by a ring closure to form a 1,4-oxathiane moiety in a Stevens rearrangement.



Scheme 12: Carbene mediated ring expansion strategy of 1,3-oxathiolones to form the tagetitoxin bicyclic structure envisaged by Porter and Plet.

In order to test their ring expansion strategy towards the synthesis of the bicyclic core of tagetitoxin, the investigators firstly synthesized compound **88** (**Scheme 13**). Compound **88** was synthesized from D-glucose by selective tosylation on the C_{-6} hydroxyl group, peracetylation, bromination on the anomeric position and substitution of the two leaving groups using a xanthate species. They then attempted the ring expansion of **88** using ethyl diazo(triethylsilyl)acetate and catalytic rhodium(II)acetate, but only glycal **91** was formed rather than the intended sulfur bridged bicyclic structure. The authors explained this result from the behaviour of the zwitterion intermediate **90**; instead of **90** undergoing the desired C-C bond formation, it ring-flipped to the more stable conformer which was followed by a proton transfer affording **91**. Thus, Porter *et al.* synthesized the more constrained precursor **92**, in five steps from 3-methyl-D-glucose for the ring expansion, because the consequent zwitterion (analogous to **90**) would have a locked conformation preventing any ring flipping. Yet, when subjecting **92** to ethyl diazo(triethylsilyl)acetate and rhodium(II) heptafluorobutyrate, only alcohol **94** at low yield was isolated. This probably occurred because of nucleophilic ring opening of ylide **93** with a water molecule followed by a proton transfer.



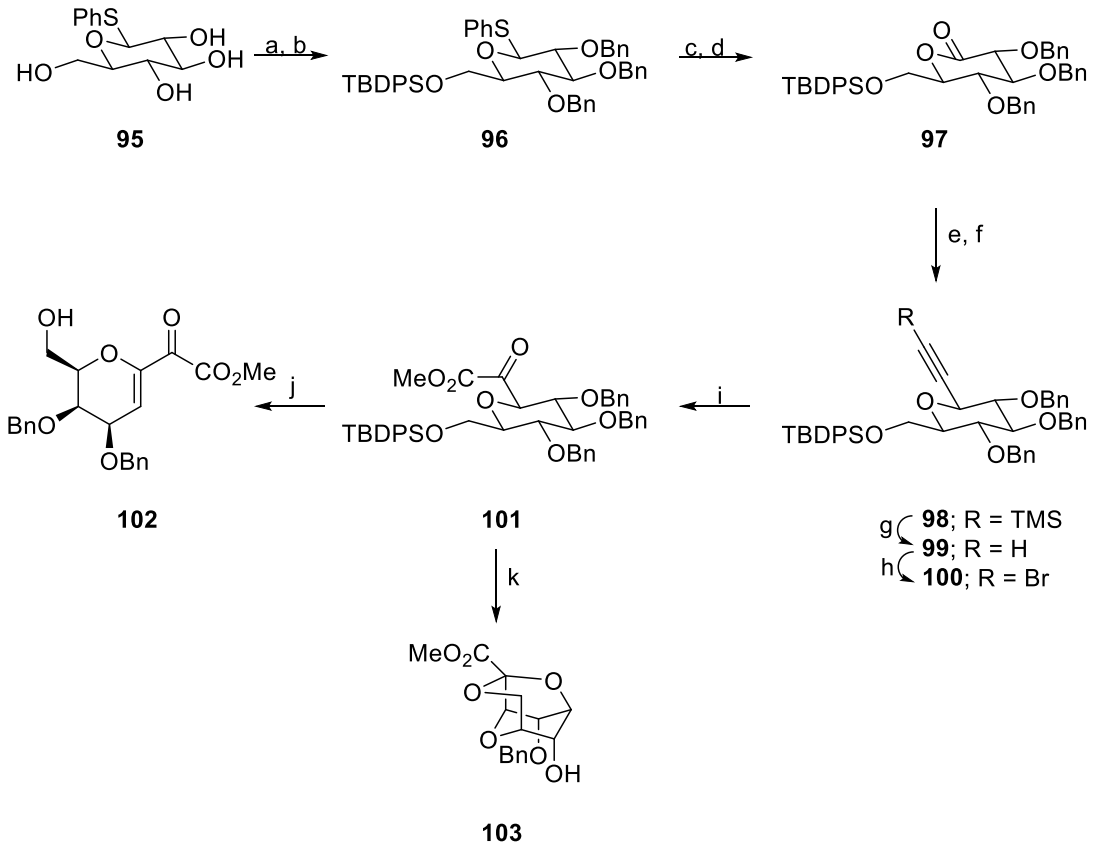
Reagets and conditions a) TsCl, pyridine, Ac_2O; b) HBr, AcOH; c) KSCSOEt, DMF, 50 °C (46% over 3 steps) or KSCSOEt, acetone, reflux (47% over 3 steps); d) $Et_3SiC(N_2)CO_2Et$, $Rh_2(OAc)_4$, benzene, reflux 34%; e) NH_3, MeOH, H_2O, 50%; f) tBu$_2$SiCl$_2$, Et_3N, DCM, 86%; g) $Et_3SiC(N_2)CO_2Et$, $Rh_2(O_2CC_3F_7)_4$, benzene, reflux, 21%.

Scheme 13: Porter and Plet's attempt to synthesize the bicyclic core of tagetitoxin using their ring expansion strategy.

As a result, to synthesize the 1,4-oxathiane ring of tagetitoxin, the investigators altered their approach from a ring expansion strategy to cyclization of a thiol onto an electrophilic ketone. The key methodology for this approach, involved the insertion of a bromoalkyne (masks an α-ketoester) and a thioacetate moiety (masks a thiol) onto a carbohydrate derivative, followed by the unmasking of these groups leading to cyclization.

Starting from the β-thioglycoside **95**, selective silyl protection of the primary alcohol and subsequent perbenzylation furnished **96** (**Scheme 14**). Compound **96** was then transformed into δ-lactone **97** by hydrolysis of the thioglycosidic linkage using *N*-bromosuccinimide (NBS), followed by oxidation when treated with Dess-Martin periodinane (DMP). Silyl alkyne **98** was then formed after cerium-mediated addition of trimethylsilylacetylene onto the lactone and sequent hydrosilane reduction on the C_{-1} position. The silyl alkyne moiety was then transformed

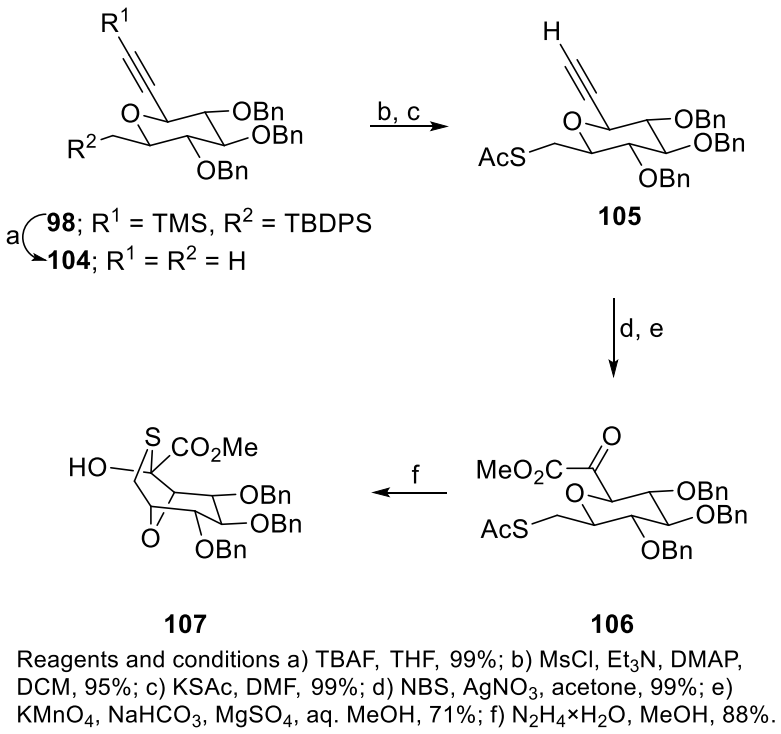
into a bromoalkyne by protodesilylation and bromination of the terminal alkyne. Oxidation of the bromoalkyne to an α-ketoester was achieved using potassium permanganate in aqueous methanol yielding **101**. Deprotection of the primary silyl ether in **101**, would then allow activation of the primary alcohol into a good leaving group and its displacement with a thioacetate nucleophile. However, when attempting to cleave the silyl ether with tetra-*n*-butylammonium fluoride (TBAF), elimination of the 2-benzyloxy group occurred forming glycal **102** in most likely an $E1_{cb}$ reaction. The authors therefore changed the conditions and used hydrogen fluoride – pyridine complex, but instead tricyclic ketal **103** was formed. To reach **103**, the silyl ether and the benzyl ethers on the C_{-3} and the C_{-4} in **101** must have been cleaved, which was followed by a ketal formation between the ketone and the liberated hydroxyl groups on the C_{-3} and C_{-6} centres.



Reagents and conditions a) TBDPSCl, imidazole, DMF, 99%; b) BnBr, NaH, DMF, 87%; c) NBS, acetone, 95%; d) Dess-martin periodinane, pyridine, DCM, 69%; e) TMS acetylene, n-BuLi, $CeCl_{3.7}H_2O$, THF, -78°C to rt, 96%; f) Et_3SiH, TMSOTf, DCM,74%; g) NaOH, MeOH, DCM, 100%; h) NBS, $AgNO_3$, acetone, 98%; i) $KMNO_4$, $NaHCO_3$, $MgSO_4$, aq. MeOH, 84%; j) 1M TBAF in THF, THF, -78°C to rt, 43% k) HF.pyridine, THF, -78°C to rt, 77%.

Scheme 14: Synthesis of intermediate **101** by Porter and Plet.

To overcome the difficulty in deprotecting the silyl ether on the C_{-6} position in the presence of the α-ketoester, the authors altered the sequence of the route; specifically, they planned to incorporate the sulfur functionality before the α-ketoester synthesis. Starting from **98**, double desilylation of the silyl alkyne and silyl ether occurred forming **104** (**Scheme 15**). The hydroxyl group on the C_{-6} centre transformed into a mesylate and was subsequently displaced with a potassium thioacetate nucleophile in DMF. Using the same previous methods, bromination of the alkyne and subsequent oxidation with potassium permanganate gave the α-ketoester bicyclic precursor **106**. Thioacetate deprotection and *in-situ* cyclization of the thiolate onto the ketone led to bicyclic thiohemiketal **107**.



Reagents and conditions a) TBAF, THF, 99%; b) MsCl, Et_3N, DMAP, DCM, 95%; c) KSAc, DMF, 99%; d) NBS, $AgNO_3$, acetone, 99%; e) $KMnO_4$, $NaHCO_3$, $MgSO_4$, aq. MeOH, 71%; f) $N_2H_4 \times H_2O$, MeOH, 88%.

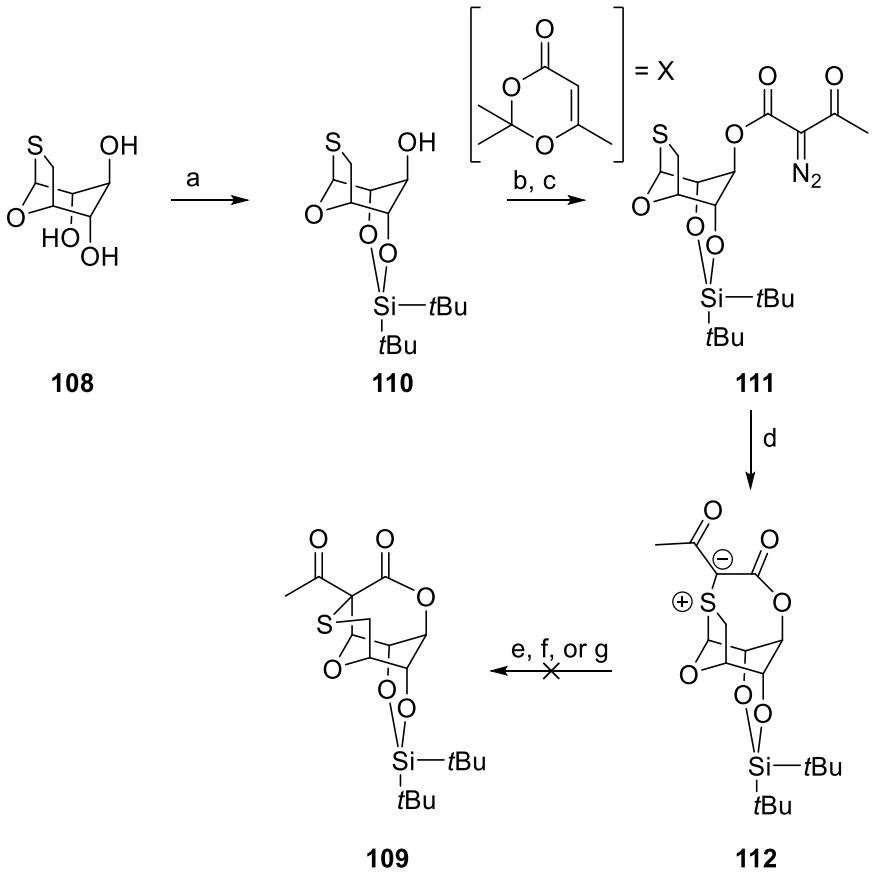
Scheme 15: Porter and Plet's synthesis of the bicyclic core of tagetitoxin (**107**).

In summary Porter and Plet attempted two strategies to synthesize the bicyclic core of tagetitioxin. Although the carbene-mediated ring expansion approach failed, they were successful in their methodology involving a thiolate cyclizing onto an electrophilic ketone. This was only achieved with inserting the thioacetate moiety before forming the α-ketoester, illustrating the importance in the order of the steps in the route. However, a carboxylic acid derivative on the anomeric position on the bicyclic core was still missing.

Porter *et al*. 2008

In 2008, Porter and co-workers again synthesized the core structure of tagetitoxin.[25] This was achieved by building on their previous work regarding the carbene-mediated ring expansion of a 1,3-oxathiolane moiety to a 1,4-oxathiane moiety.[24] The authors concluded, that their previous ring expansion attempts did not work because of the conformational flexibility of the zwitterion **90** leading to the undesired glycal **91**.[24] However, even when they incorporated a di-*tert*-butylsilane bridge on the C_{-2} and C_{-4} hydroxyl groups to form the more constrained precursor **92**, no ring expansion products were still observed (**Scheme 13**).[24] Nevertheless, Porter *et al*. still postulated that the conformational flexibility rationale was the cause for the ring expansion failure. They therefore aimed to synthesize the ylide in an intramolecular reaction (rather than intermolecular fashion as previously).[24] This would lead to a more constrained ylide and subsequent zwitterion intermediate, which would favour the desired C-C bond formation.

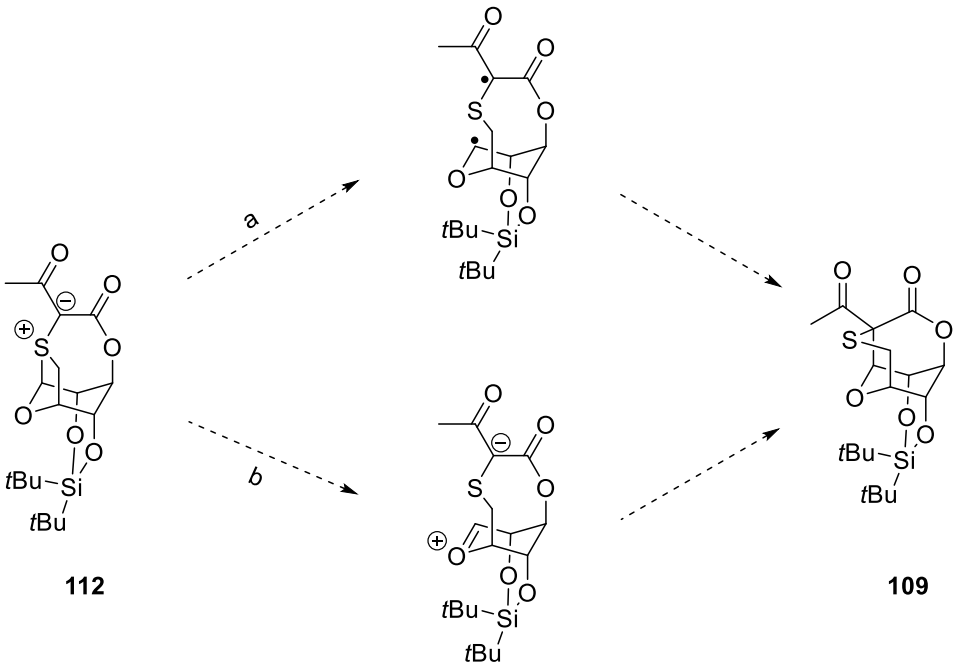
To test their postulate, the authors made thioanhydroglucose **108** in a four-step route according to the literature.[26,27] They then devised a synthetic route to tetracyclic structure **109** from thioanhydroglucose **108** (**Scheme 16**). Selective protection of the C_{-2} and C_{-4} hydroxyl groups with a di-*tert*-butylsilane bridge furnished **110**. This was followed by acetoacetylation and subsequent diazo transfer yielding **111**. Treatment of **111** with rhodium(II) acetate dimer formed isolable tetracyclic ylide **112** (further confirmed with X-ray crystallography). However, despite heating **112** in an array of solvents of different polarities such as xylene, methanol and DMSO, only starting material or decomposition (latter only observed at extended reaction times) were seen.



Reagents and conditions: a) *tert*-Bu_2SiCl_2, $AgNO_3$, Et_3N, DMF, 65%; b) **X**, xylene, reflux, 88%; c) *p*-$AcNHC_6H_4SO_2N_3$, Et_3N, MeCN, 100%; d) $Rh_2(OAc)_4$ (1 mol %), benzene, reflux, 88%; e) xylene, reflux; f) DMSO, reflux; g) MeOH, reflux.

Scheme 16: Attempted synthesis of tetracyclic **109** by a thermal promoted Stevens rearrangement by Porter *et al.*

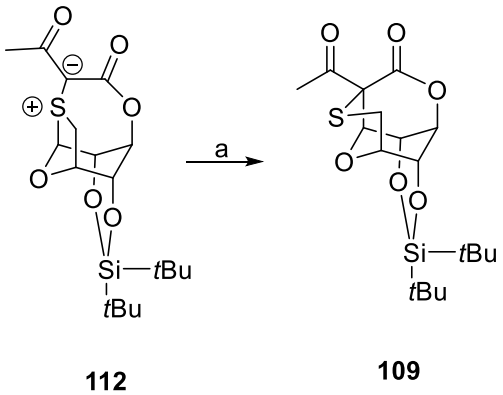
Porter *et al*. proposed two mechanisms for the thermally promoted Stevens rearrangement (**Scheme 17**). The homolysis mechanism **a**, is the general favoured mechanism for the Stevens rearrangement.[28,29] However, to account for the isolation of glycal **91** from their previous attempted ring expansion on **88**,[24] they suggested that heterolytic mechanism **b** would be favoured for these substrates under thermal conditions. Thus, they found it surprising when the ylide was generally stable under these conditions (dependent on reaction times). They also thought pathway **b** would be more favoured with acidic conditions (due to increased polarization of the C-S bond). Therefore, protic acids (such as trifluoroacetic acid and triflic acid) and Lewis acids (such as $[Cu(acac)_2]$) were then added to ylide **112** but these failed to induce the desired Stevens rearrangement.



Mechanisms: a) homolysis pathway; b) heterolytic pathway.

Scheme 17: Porter and co-workers' proposed mechanisms for the thermally promoted Stevens rearrangement.

Since, a Stevens rearrangement did not occur on ylide **112** under acidic or thermal conditions, Porter *et al*. attempted a photochemical variant of the Stevens rearrangement. They subjected ylide **112** to photolysis in acetonitrile, affording the tetracycle target **109** (**Scheme 18**).

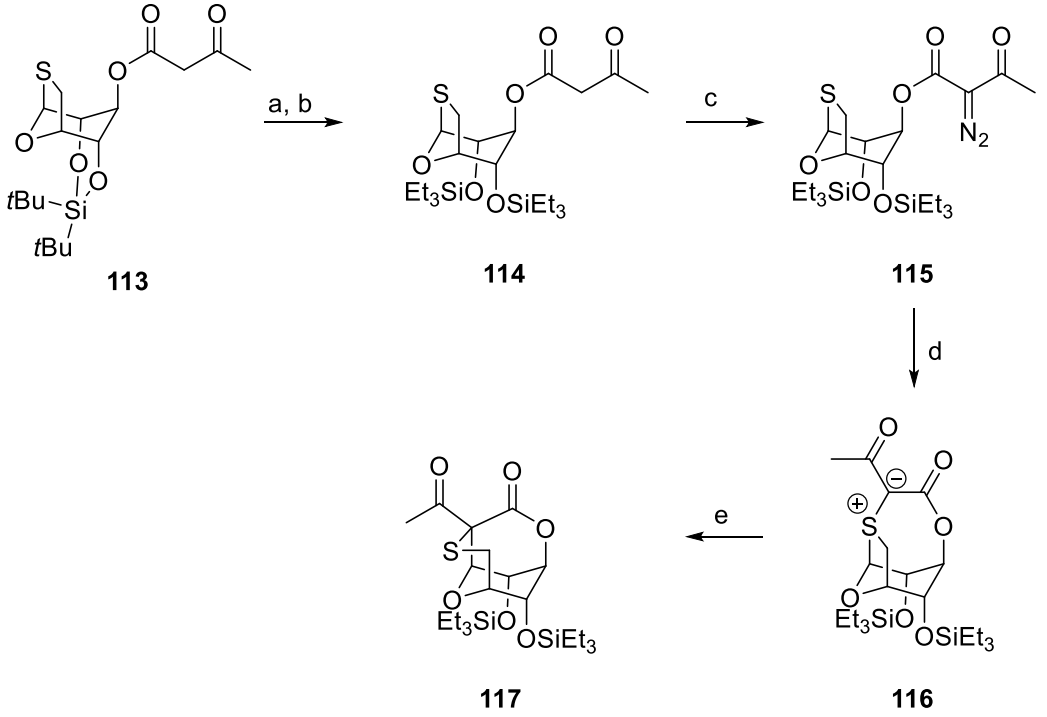


Reagents and conditions: a) hν (> 290 nm), MeCN, 69%.

Scheme 18: Porter and co-workers' synthesis of target **109** by a photo-Stevens reaction of **112**

Having made the tetracyclic structure **109**, the authors explored the scope of their methodology. More specifically, they synthesized further substrates to assess which structural features were important for ylide formation and the photo-Stevens rearrangement.

The first structural feature investigated was the effect the di-*tert*-butylsilylene protecting group (on the C_{-2} and C_{-4} hydroxyl groups) had on ylide formation or the photo-Stevens rearrangement. Hence, via a sequential deprotection-protection, the authors formed **114** from **113** where the bridged silyl ether on the C_{-2} and C_{-4} was replaced with two triethylsilyl (TES) ethers (**Scheme 19**). A Diazo transfer and subsequent rhodium-catalysed diazodecomposition led to ylide **116** (analogous to ylide **112** except with the non-bridged silyl ether protecting group). Photolysis of **116** yielded the tricyclic product **117** (with similar rates and yields to the previous example **109**).

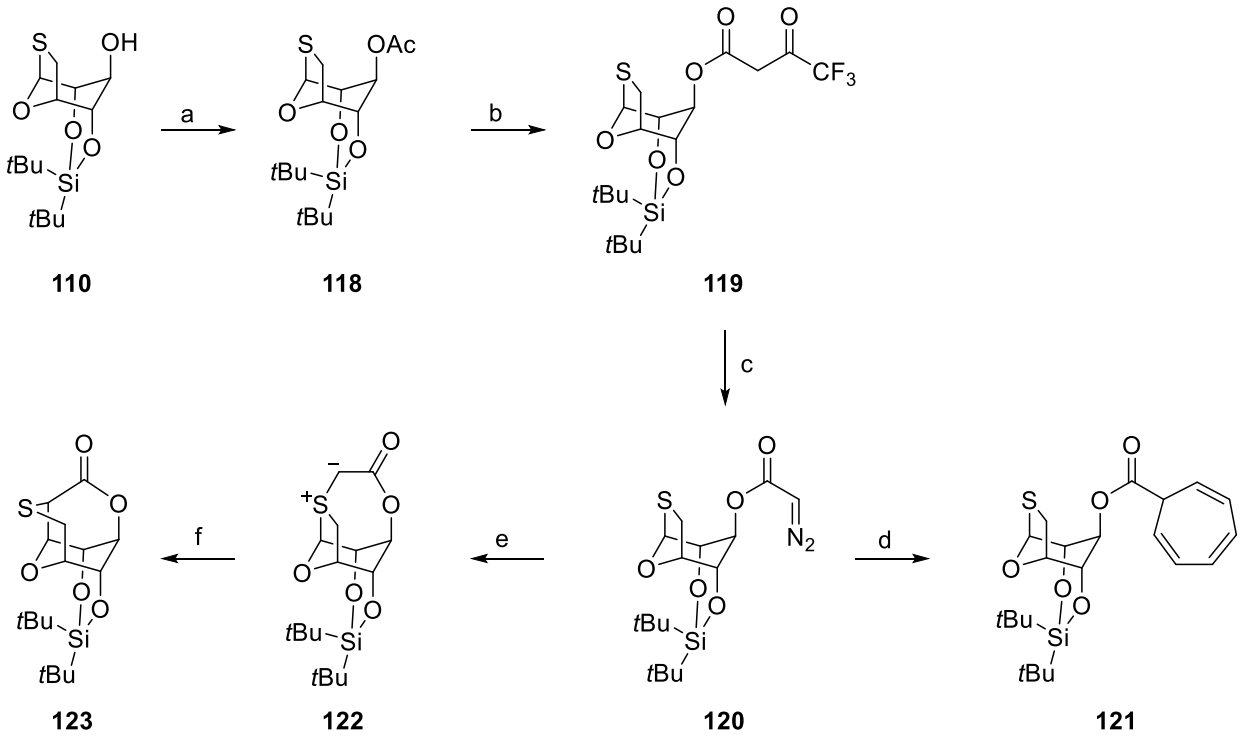


Reagents and conditions: a) TBAF, THF, 76%; b) Et_3SiCl, DMAP, Et_3N, DCM, 72%; c) *p*-$HOOCC_6H_4SO_2N_3$, Et_3N, MeCN, 75%; d) $Rh_2(OAc)_4$ 1 mol %, benzene, reflux, 53%; e) hv, MeCN, 65%.

Scheme 19: Porter and co-workers' synthesis of tricyclic structure **117**.

Finally, the authors wanted to examine whether the acetyl group alpha to the carbon centre of the ylide was important in this methodology. Diazoacetate **120** was therefore made in three steps from alcohol **110**, via acetylation, acetoacetylation and a diazo transfer (**Scheme 20**). Attempted

ylide formation using rhodium(II)acetate dimer in benzene failed and instead furnished **121**; this compound must have been produced from the formed rhodium carbenoid reacting with the benzene solvent.[30] As a result, the authors changed the solvent to dichloromethane which gave the desired ylide **122**. Since, **122** was unstable to column chromatography, the crude reaction mixture was directly subjected to photolysis yielding target compound **123**.



Reagents and conditions: a) Ac_2O, DMAP, Et_3N, DCM, 84%; b) LiHMDS, THF. -78 °C, $CF_3CO_2CH_2CF_3$; c) *p*-$HOOCC_6H_4SO_2N_3$, Et_3N, MeCN, 65%; d) $Rh_2(OAc)_4$ 1 mol %, benzene, reflux, 39%; e) $Rh_2(OAc)_4$ 1 mol %, DCM, reflux; f) hν, MeCN, 65%.

Scheme 20: Porter and co-workers' synthesis of tetracyclic **123**.

To summarize, Porter *et al.* developed another route to make the core structure of tagetitoxin. The key steps in this route were the intramolecular ylide formation, between the sulfur atom and an *in-situ* formed metallocarbenoid, followed by a photo-Stevens rearrangement. They additionally inferred that the silyl bridge tether between the oxygens on the C_{-2} and C_{-4} position as well as the acetyl group alpha to the nucleophilic carbon on the ylide were not important factors for this methodology to be successful. This strategy, however, would need to be explored further and adapted to achieve a total synthesis of tagetitoxin.

Porter *et al*. 2009

In 2009, Porter *et al.* adapted their previous strategy of forming the tagetitoxin bicyclic core (from a thiol/thiolate cyclizing onto an electrophilic ketone),[24] to attempt a total synthesis of tagetitoxin **124** and decarboxytagetitoxin 1**25** (**Figure 8**).[31]

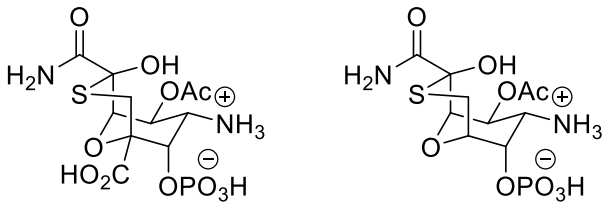
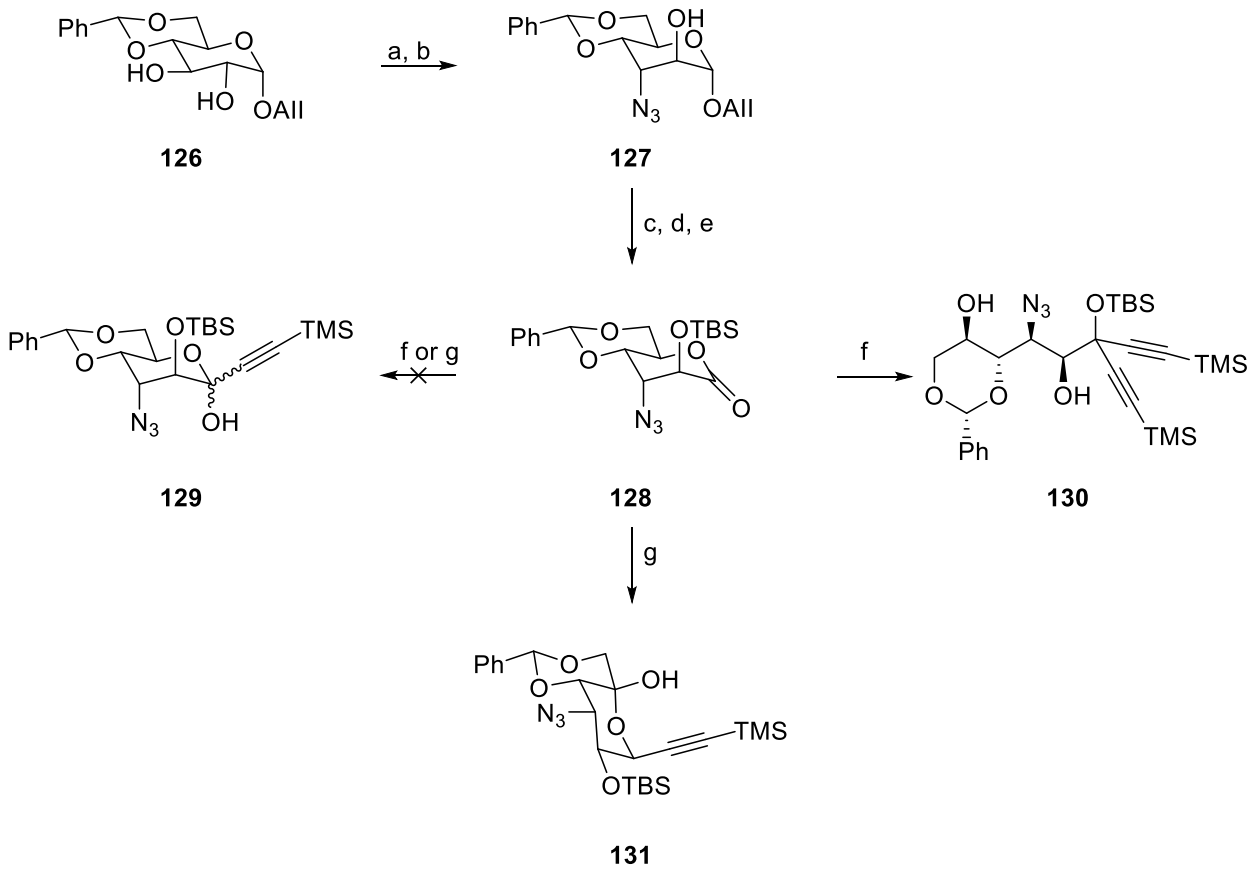


Figure 8: Synthetic targets for Porter *et al*.

Their initial target was decarboxytagetitoxin 1**25**, starting from D-glucose. The key methodology of this route was to invert the stereogenic centres at the C_{-2} and the C_{-3} positions with the incorporation of a nitrogen functionality at the C_{-3}, via the formation and subsequent *trans*-diaxial ring opening of a 2,3-β-epoxide with an azide nucleophile.

The diol **126** was prepared from D-glucose in two steps according to the literature (**Scheme 21**).[32] Diol **126** was doubly deprotonated using sodium hydride and then underwent selective tosylation at the O-2 position, which triggered the O-3 alkoxide to intramolecularly displace the tosylate to form the 2,3-β-epoxide. The epoxide was then ring-opened with sodium azide to form **127**. After silyl protection of the hydroxyl group on the C_{-2}, the anomeric allyl ether was deprotected to form a lactol, which in turn underwent a DMP oxidation yielding lactone **128**.

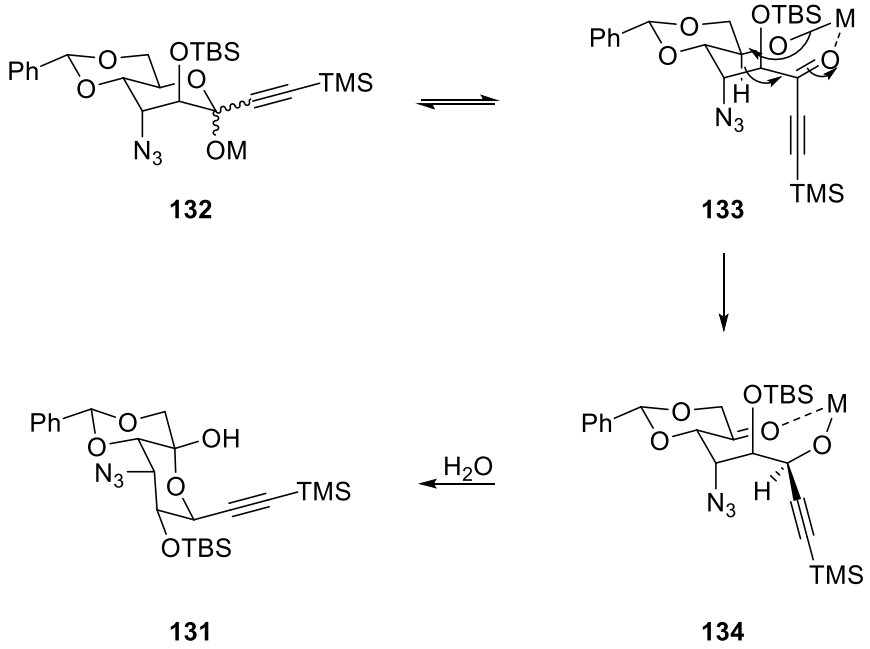


Reagents and conditions: a) NaH, DMF, rt then Ts-imidazole, 50°C b) NaN_3, NH_4Cl, H_2O, 2-methoxyethanol, reflux, 92%; c) TBSCl, imidazole, DMF, 80°C, 98%; d) Bu_3SnH, $ZnCl_2$, $Pd(PPh_3)_4$, THF, rt, 90%; e) DMP, pyridine, DCM, rt, 88%; f) TMS-Acetylene, BuLi, $CeCl_3.7H_2O$, THF, -78°C to rt, 32%; g) TMS-Acetylene, BuLi, $Yb(OTf)_3$,THF, -78°C to rt, 48%.

Scheme 21: Attempted synthesis of compound **129** by Porter *et al*.

Treatment of lactone **128** with an *in-situ* generated cerium-acetylide did not lead to the desired addition product; this was surprising, given the success when subjecting the related lactone **97** to these conditions in their previous work.[24] Instead the only compound isolated was the double addition product **130**. The authors hypothesized that after the desired nucleophilic attack of the cerium-acetylide onto the lactone, a ring opening to a ketone occurred, which then underwent a second organometallic addition. This was followed by a silyl migration from the O-2 position to the formed tertiary alkoxide producing **130**. As a result, Porter and co-workers carried out the reaction with ytterbium triflate instead of cerium chloride, so that an organoytterbium instead of an organocerium species would react with lactone **128**. Compound **131**, however, was formed instead of **129**. Porter and co-workers proposed a mechanism for this transformation (**Scheme 22**). Initially the ytterbium acetylide attacks the lactone to form **132** which ring opens to **133**.

Subsequently a transannular hydride shift occurs forming **134** which then cyclized to **131** upon workup.

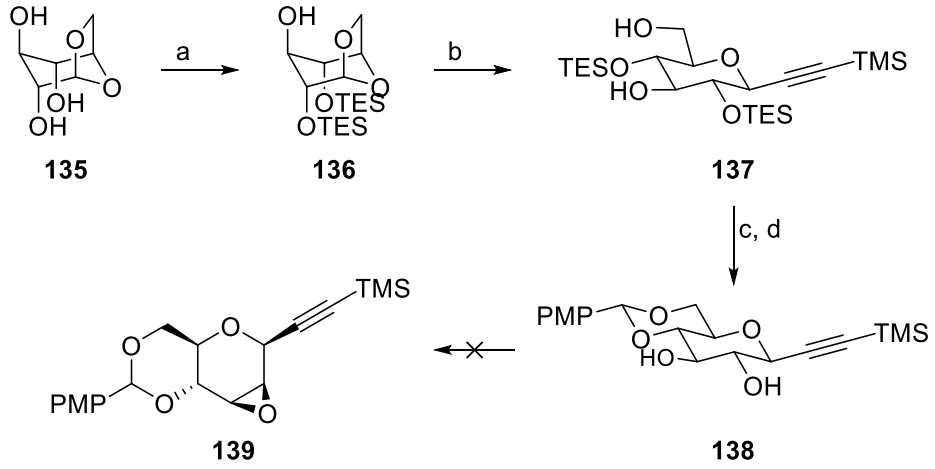


Scheme 22: Porter and co-workers' proposed mechanism for the formation of **131**.

To overcome problems arising from the introduction of the acetylene moiety at the anomeric position on **128**, the authors decided changed the order of the route. Specifically, they planned to incorporate the alkyne moiety prior to the inversion of the C_{-2} and C_{-3} chiral centres (i.e. to insert the alkyne moiety before they form the 2,3-β-epoxide). They rationalized that by carrying out the synthesis in this order, the acetylide would add to a glucose configured substrate (rather than an altrose configured substrate) which is more similar to the lactone **97** used for this analogous reaction in their previous successful strategy (**Scheme 14**).[24]

Porter *et al*. synthesized 1,6-anhydroglucose **135** from D-glucose in four steps from the literature.[33] Following selective silyl protection of the O-2 and O-4 to form **136**, the authors introduced an alkyne moiety on the anomeric position using Vasella's method (**Scheme 23**).[34] This method involved the reaction between a lithium acetylide and aluminium trichloride to form a $Al(C{\equiv}CTMS)_3$ species which upon treatment with **136**, led to **137**. Formation of **138** was then achieved by deprotection of the silyl ethers and sequent protection of the O-5 and O-6 in the form of a *p*-methoxybenzylidene acetal. Synthesis of epoxide **139** was, however, not achieved

using their previous strategy. This is because despite trying a range of conditions (TsCl, Ts-imidazole, Ts_2O and MsCl with either pyridine or sodium hydride as base) no regioselectivity was accomplished for the sulfonylation of one of the hydroxyl groups on C_{-2} or C_{-3} centres over the other (since only inseparable 1:1 mixtures of the respective mono-sulfonates were obtained).

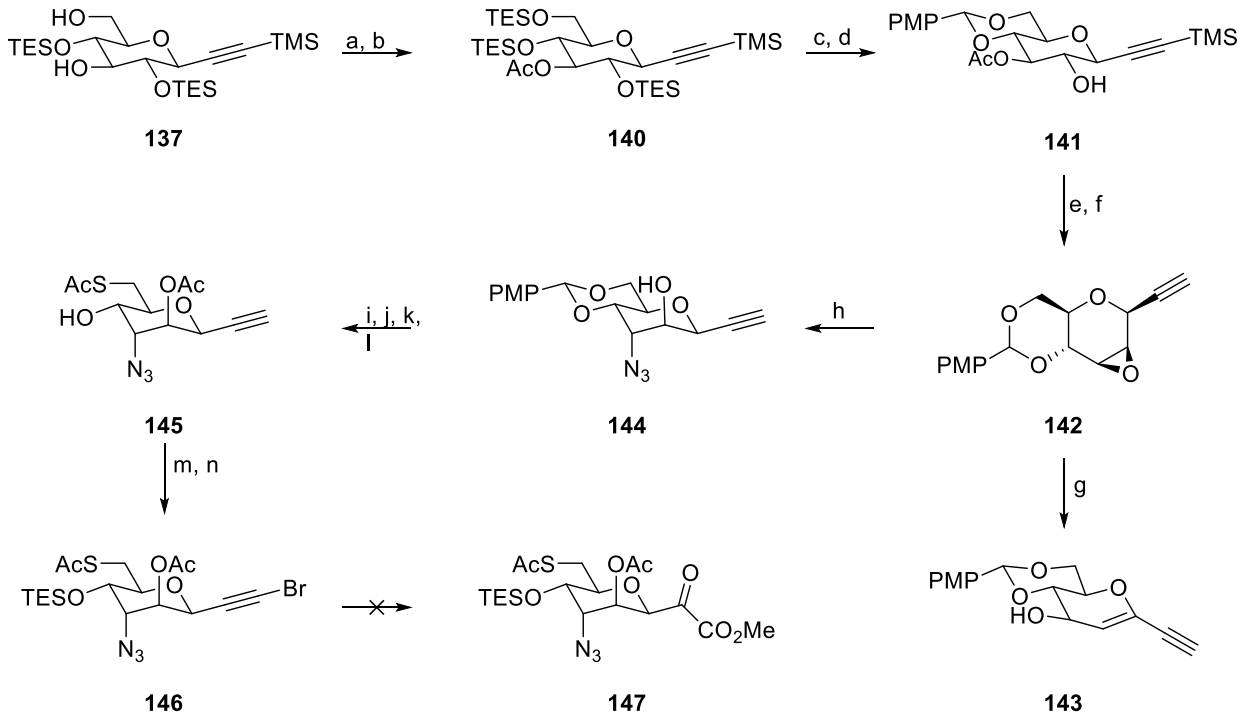


Reagents and conditons: a) TESCl, pyridine, 0°C, 79%; b) TMS-Acetylene, BuLi, $AlCl_3$, 2,4,6-collidine, toluene-THF, Sonnication, -15°C to 50°C, then add substrate, 130°C, 81%; c) AcOH, MeOH, H_2O, rt, 92%; d) 4-$MeOC_6H_4CH(OMe)_2$, TsOH, 4Å MS, MeCN, reflux, 95%.

Scheme 23: Attempted synthesis of epoxide **139** by Porter *et al.*

To solve this regioselective problem, the route was altered to make a substrate analogous to **138** with the exception of O-3 being protected (**Scheme 24**). Acetate **140** was therefore synthesized from **137** by a selective silyl protection on O-6 and sequent acetyl protection on O-3. Silyl ether cleavage and acetal formation then followed yielding **141**. Tosylation of the free hydroxyl group on C_{-2} was accomplished and then epoxide formation was attempted. Under basic conditions, deacetylation of O-3 and concomitant displacement of the tosylate as well as removal of the silyl group on the alkyne led to the epoxide **142** being formed. Yet, when attempting to ring open the epoxide with an azide nucleophile in acidic conditions, only partial hydrolysis of the acetal was seen. Thus, the authors tried non-acidic conditions such as heating the epoxide with sodium azide in DMF, but only elimination product **143** was observed. Trans-diaxial ring opening of epoxide **142** to azide **144** was eventually achieved using Yamamoto's procedure.[35] In this procedure, ytterbium triisopropoxide (formed *in-situ* from ytterbium triflate and lithium isopropoxide) activates the epoxide for nucleophilic attack from the azide.

The next target was to install the thioacetate on the C_{-6} position. To achieve this, they protected the 2-O with an acetyl group, hydrolysed the acetal and then performed a selective tosylation on the primary alcohol. This was followed by a displacement of the tosylate with a thioacetate nucleophile furnishing **145**. After silylation of the O-4, bromination of the terminal alkyne was achieved using NBS and catalytic $AgNO_3$. However, oxidation of the bromoalkyne moiety in **146** to an α-ketoester using potassium permanganate in methanol (as similarly carried out in the synthesis of **106** in their earlier work)[24] failed for this substrate as only decomposition was observed; this prevented the synthesis of decarboxytagetitoxin **2** being achieved.



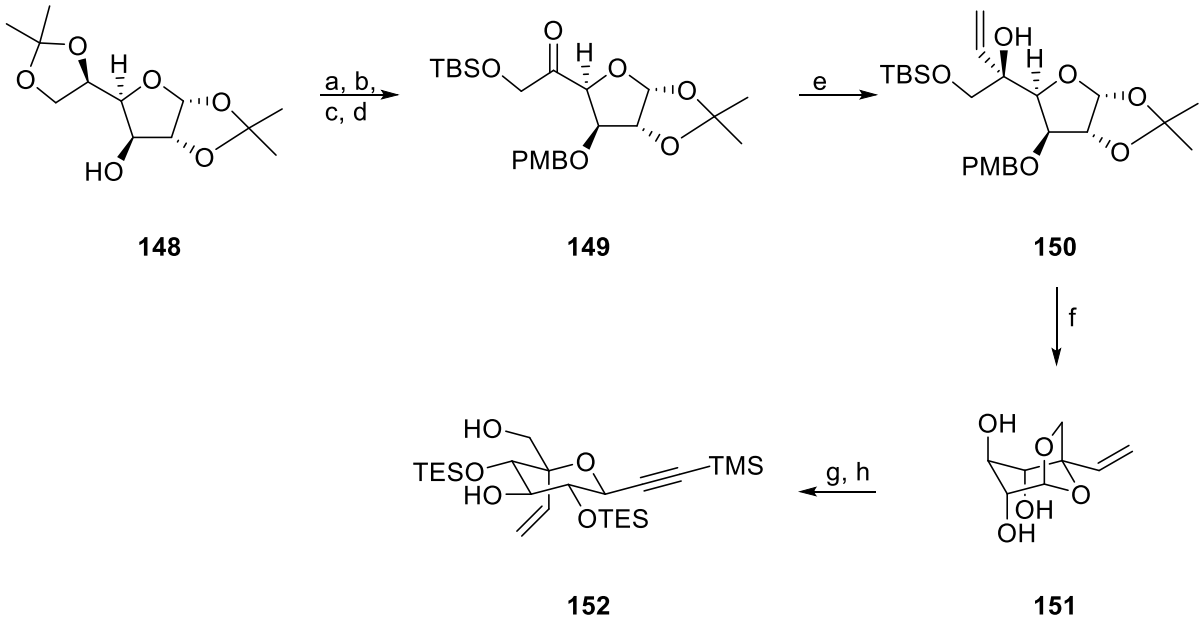
Reagents and conditions: a) TESCl, pyridine, 0°C, 92%; b) Ac_2O, 4-(1-pyrrolidino)pyridine, Et_3N, rt, 70%; c) AcOH, THF, H_2O, 45°C, 86%; d) 4-$MeOC_6H_4CH(OMe)_2$, TsOH, 4Å MS, MeCN, 80°C, 80%; e) TsCl, pyridine, 120°C, 72%. f) NaOMe, MeOH, DCM, rt, 64%; g) NaN_3, DMF, 90°C, 49%; h) $TMSN_3$, $Yb(OTf)_3$, Li*O*-*i*-Pr, THF, 60°C, 79%; i) Ac_2O, DMAP, pyridine , r.t., 99%; j) AcOH, THF, H_2O, 45°C, 81%; k) TsCl, pyridine, rt, 67%; l) KSAc, DMF, rt, 76%; m) TESCl, pyridine, 0-40°C, 82%; n) NBS, $AgNO_3$, acetone, rt, 73%.

Scheme 24: Attempted synthesis of bicyclic precursor **147** by Porter *et al*.

Porter *et al*. also focused on the total synthesis of tagetitoxin 1**24.** They adapted their previous strategy (shown in **Scheme 23**) to include the installation of a vinyl group on the C_{-5} of the glucose configured backbone, envisaging later oxidation of this group to a carboxylic acid derivative. Incorporation of the vinyl group, was based on an strategy described by Rao *et al*.,[36]

with the key step being stereoselective addition of a vinyl Grignard reagent to a 5-keto derivative of glucose.

Porter and co-workers synthesized a similar 5-keto derivative of glucose **149** to Rao *et al.* (the only difference being the protecting group on the O-3).[36] This was accomplished in four steps from compound **148 (Scheme 25)**: protection of the 3-O with a PMB group; hydrolysis of the 5,6-acetonide; selective silyl protection of the O-6; and finally a Swern oxidation of the remaining free hydroxyl group on the C_{-5} position. Subsequent stereoselective Grignard addition afforded **150**. Upon heating **150** in a mixture of acetic and trifluoracetic acid, global deprotection and concomitant cyclization occurred to give the desired 1,6-anhydroglucose derivative; it was also vital to have a thioanisole cation scavenger in the reaction mixture as it prevented unwanted side reactions. Due to the nature of the conditions (heat and acid), Fischer esterification side products were formed in addition. Thus, the investigators subjected the crude mixture to sodium methoxide in methanol to deacetylate the mixture of acetates producing **151** in high yield. Via the same methodology in their previous synthetic studies towards decarboxytagetitoxin (synthesis of **137** from **135** shown in **Scheme 23**), the authors performed two further steps to yield **152**. No further work on this route, however, has been published.



Reagents and conditions: a) NaH, PMBCl, THF, rt, 86%; b) 60% aq ACOH, rt, 80%; c) TBSCl, imidazole, DMF, rt, 81%; d) $(COCl)_2$, DMSO, Et_3N, DCM, -78°C, 79%; e) vinylmagnesium bromide, THF, rt, 76%; f) 80% aq AcOH, TFA, PhSMe, reflux then NaOMe, MeOH, rt, 73%; g) TESCl, pyridine, rt, 68%; h) TMS-Acetylene, BuLi, $AlCl_3$, 2,4,6-collidine, toluene-THF, sonicate, -15°C to 50°C, then added substrate, 130°C, 70%.

Scheme 25: Synthesis of compound **152** by Porter *et al*.

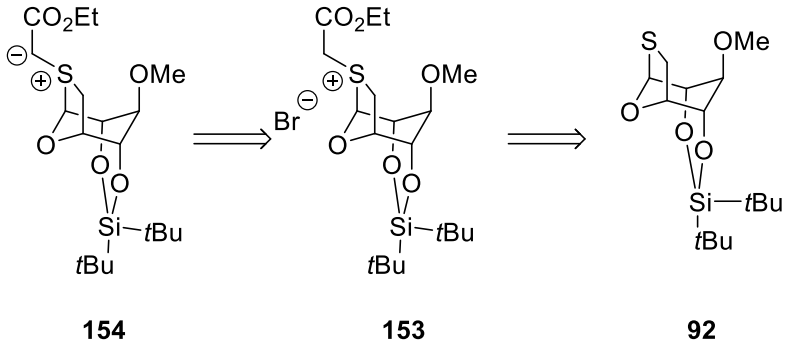
In summary, whilst Porter *et al*. have previously developed a successful synthetic route to the bicyclic core of tagetitoxin from thiol/thiolate cyclizing onto a ketone,[24] applying and adapting this methodology towards a total synthesis of the natural product and its non-natural decarboxy analogue have proved difficult despite isolating promising intermediates **146** and **152**.[31] In fact, since this paper, no further research related to this synthetic approach has yet to be reported.

Porter *et al*. 2012

In 2012, Porter and co-workers published another paper building on their earlier research concerning ring expansions of a 1,3-oxathiolane moiety in thioanhydrosugars to a 1,4-oxathiane moiety and its application towards tagetitoxin synthesis.[24,25,37] Although Porter and co-workers were previously successful in forming a sulfonium ylide from the reaction of a sulfur atom of a thioanhydrosugar with a metallaocarbenoid (generated in situ from a transition metal complex and α-diazoester),[24,25] they explored methods of forming the ylide without the use of a transition metal complex.[37] Furthermore, the authors aimed to adapt their previous successful ring

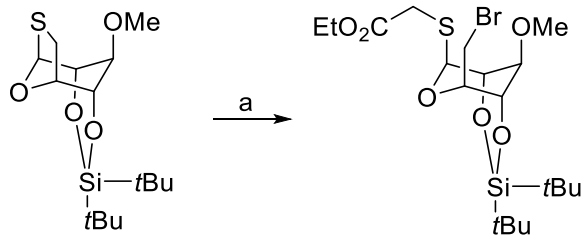
expansion methodology in synthesizing the tagetitioxin bicyclic core (based on a carbene-mediated intramolecular sulfonium ylide formation followed by a photochemical 1,2-Stevens rearrangement) to a closer related analogue of decarboxytagetitoxin.

Using compound **92** (made in their earlier studies),[24] Porter *et al*. planned to carry out an S-alkylation to form a sulfonium bromide salt **153** followed by a deprotonation to form the ylide **154** (**Scheme 26**).



Scheme 26: Porter and co-workers' retrosynthetic analysis of ylide **154**.

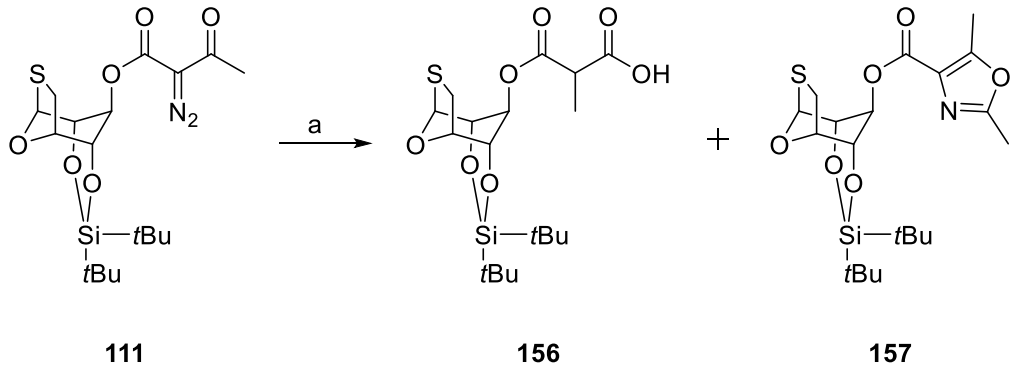
Reaction of **92** with ethyl bromoacetate produced no trace of sulfonium salt **153**, instead only compound **155** was isolated (**Scheme 27**); this was formed from nucleophilic attack of the bromide ion on the formed sulfonium ion. To prevent this undesired reaction, the authors added either silver salts (to form insoluble silver bromide removing the bromide nucleophile) or replaced the bromide leaving group on the alkylating agent with a non-nucleophilic group (such as a triflate). However, neither of these attempts yielded **153**.



Reagents and conditions: a) EtO_2CCH_2Br, MeCN, 72%.

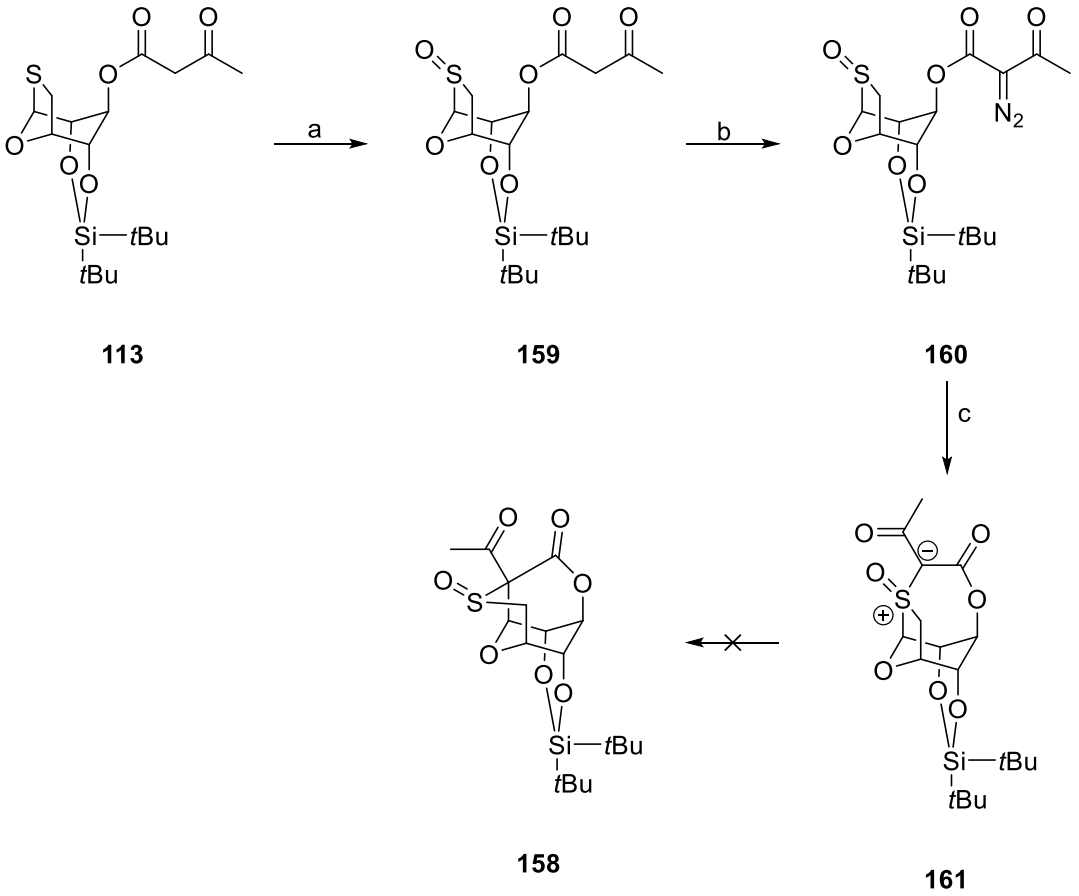
Scheme 27: Synthesis of compound **155** by Porter *et al*.

The authors considered another method of generating an ylide considered by forming a free carbene (rather than a metallocarbene) from diazo compound **111** under photolytic conditions **(Scheme 28)**. If successful, ylide formation and the subsequent photochemical 1,2-Stevens rearrangement could be done in one-pot. However, irradiation of **111** with UV light in acetonitrile only formed compounds **156** and **157**. Compound **156** was most likely formed by a Wolf rearrangement of the generated free carbene, followed by hydrolysis on the formed ketene intermediate. Whilst oxazole **157** was most likely produced by the reaction between the free carbene and acetonitrile. On changing the solvent to dichloromethane or chloroform, the major product malonate **156**.



Scheme 28: Synthesis of compounds **156** and **157** from **111** by Porter *et al*.

To further expand the scope of their methodology, the authors wanted to make **158** (**Scheme 29**); this is an analogue of compound **109** which they had successfully synthesized in their previous study.[25] The key difference between these congeners is the presence sulfoxide functionality in **158** rather than a thioether. The oxosulfonium ylide **161** was synthesized from compound **113** (made in their previous studies)[25] in three steps: controlled thioether oxidation; diazo transfer; and diazodecomposition using rhodium acetate. Only decomposition, however, was observed when irradiating tetracyclic ylide **161** with UV light.



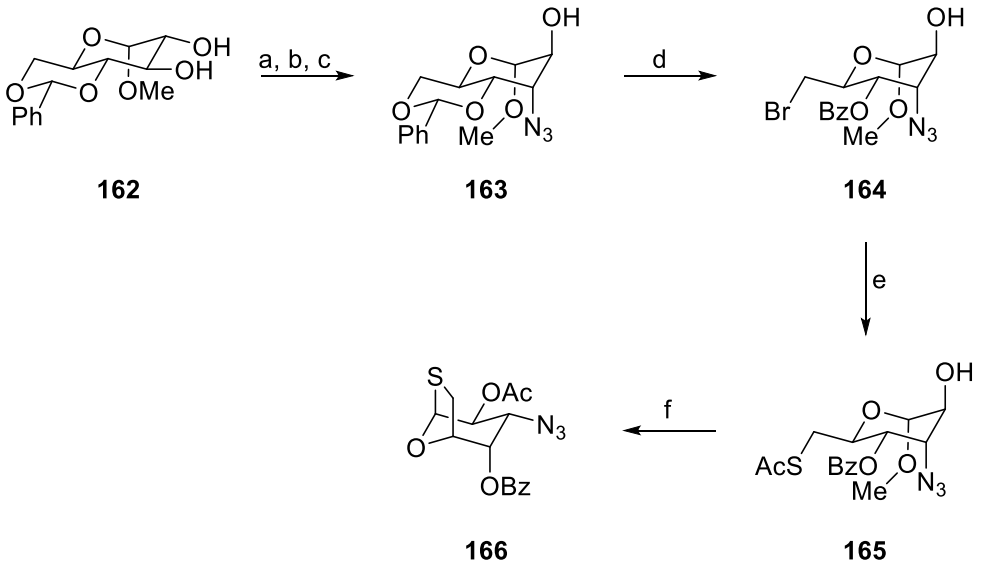
Reagents and conditions: a) *m*-CPBA, $NaHCO_3$, DCM, 80%; b) *p*-$HOOCC_6H_4SO_2N_3$, Et_3N, MeCN, 88%; c) $Rh_2(OAc)_4$, C_6H_6, reflux, 63%.

Scheme 29: Attempted synthesis of tetracyclic sulfoxide **158** by Porter *et al.*

Finally, Porter *et al.* tried to make a closely related analogue of decarboxytagetitoxin using their methodology on a photochemical 1,2-Stevens rearrangement of a sulfonium ylide. To achieve this, Porter and co-workers made key changes to their previously successful routes in synthesizing the tagetitoxin bicyclic core (**Schemes 18**, **19** and **20**).[25] One modification was to tether the diazo functionality through an equatorial oxygen at the C_{-2} position rather than the axial position at C_{-3}. This would affect the intramolecular ylide formation which would now occur between the sulfur atom of the 1,3-oxathiolane with the diazo functionality on the C_{-2} position instead of the C_{-3} position. This modification would allow the installation of a nitrogen functionality at the C_{-3} position as is the case with decarboxytagetitoxin.

The authors started the synthesis by making a 2,3-β-epoxy derivative in two steps from compound **162**, which was then ring opened with sodium azide to yield **163** (**Scheme 30**).

Subsequently, a Hanessian-Hullar oxidative ring opening of the benzylidene acetal moiety led to **164**.[38,39] A S_N2 displacement of the bromide with a thioacetate nucleophile followed to afford thioester **165**. Under strong acidic acetylation conditions, acetylation of the 2-OH, thioacetate cleavage and concomitant cyclization (where the formed thiol displaced the 1-OMe in a 5-*exo*-tet reaction) were all accomplished in one step, yielding **166**.



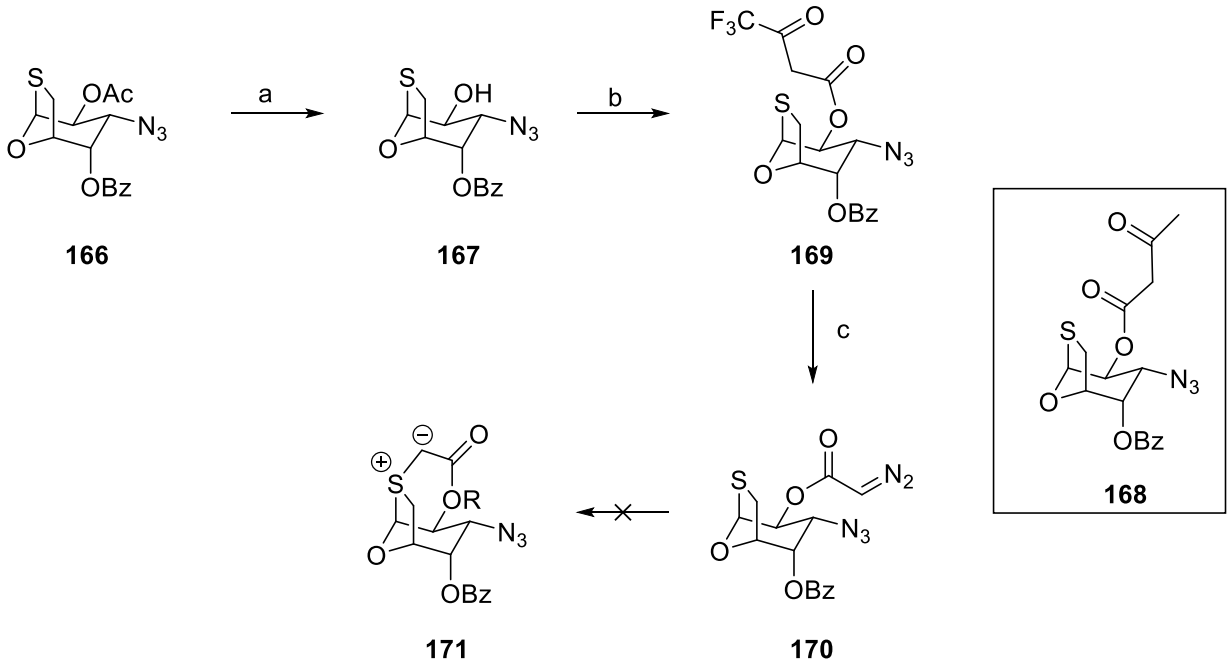
162 **163** **164** **165** **166**

Reagents and conditions: a) NaOMe, Ts-imidazole, DCM, reflux b) NaOMe, MeOH, Reflux, 81% (2steps); c) NaN_3, NH_4Cl, $MeOCH_2CH_2OH$, H_2O, reflux, 83%; d) NBS, $BaCO_3$, $CHCl_3$, reflux, 79%; e) KSAc, DMF, 95%; f) Ac_2O, AcOH, H_2SO_4, 60%.

Scheme 30: Synthesis of **166** by Porter *et al*.

The next goal for the authors, was to trifluoraceteylate the 2-OAc in **166** and to subsequently perform a detrifluoroacetylating diazo transfer to form **170** (**Scheme 31**). The trifluoroacetylation of **166** using LDA and trifluoroethyl trifluoroacetate, however, proved troublesome, because the only products observed were alcohol **167** and acetoacetate **168**. Since, only these products were seen without even adding the electrophile, the authors postulated that after the deprotonation of **166** by LDA, a Claisen condensation followed by an elimination took place to form a ketene and **167** (in its alkoxide form). The ketene then reacted with the ester enolate species forming **168**. Despite varying the base and temperature, compound **169** was not seen. The authors therefore attempted an alternative route whereby they deacetylated **166** to form **167**, which was then subjected to the 2-fluoroacetylderiative of Meldrum's acid under reflux furnishing **169**. Compound **169** then underwent a detrifluoroacetylating diazo transfer to form **170**.

Diazodecomposition and consequent intramolecular ylide formation from **170** was unsuccessful despite performing a range of conditions with various catalysts [$Rh_2(OAc)_4$, $CuPF_6(MeCN)_4$, AgOTf, $Cu(acac)_2$].

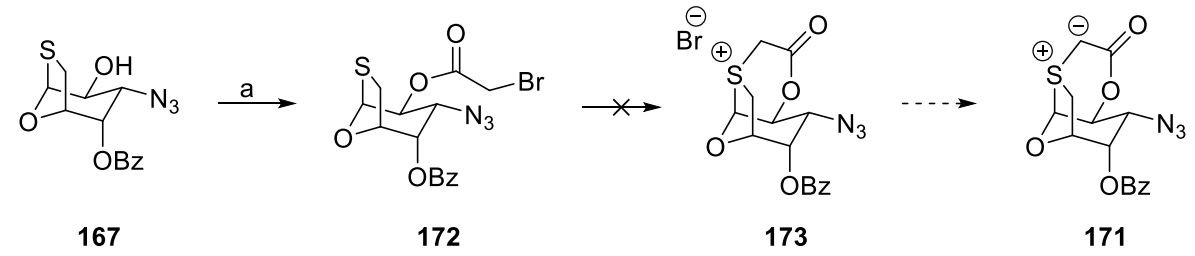


166 **167** **169** **168** **171** **170**

Reagents and conditions: a) guanidine, EtOH/DCM, 83%; b) 2,2-dimethyl-5-trifluoroacetyl-1,3-dioxan-4,6-dione, toluene, reflux; c) 4-$HO_2CC_6H_4SO_2N_3$, K_2CO_3, MeCN, 73%;

Scheme 31: Attempted synthesis of ylide **171** by Porter *et al*.

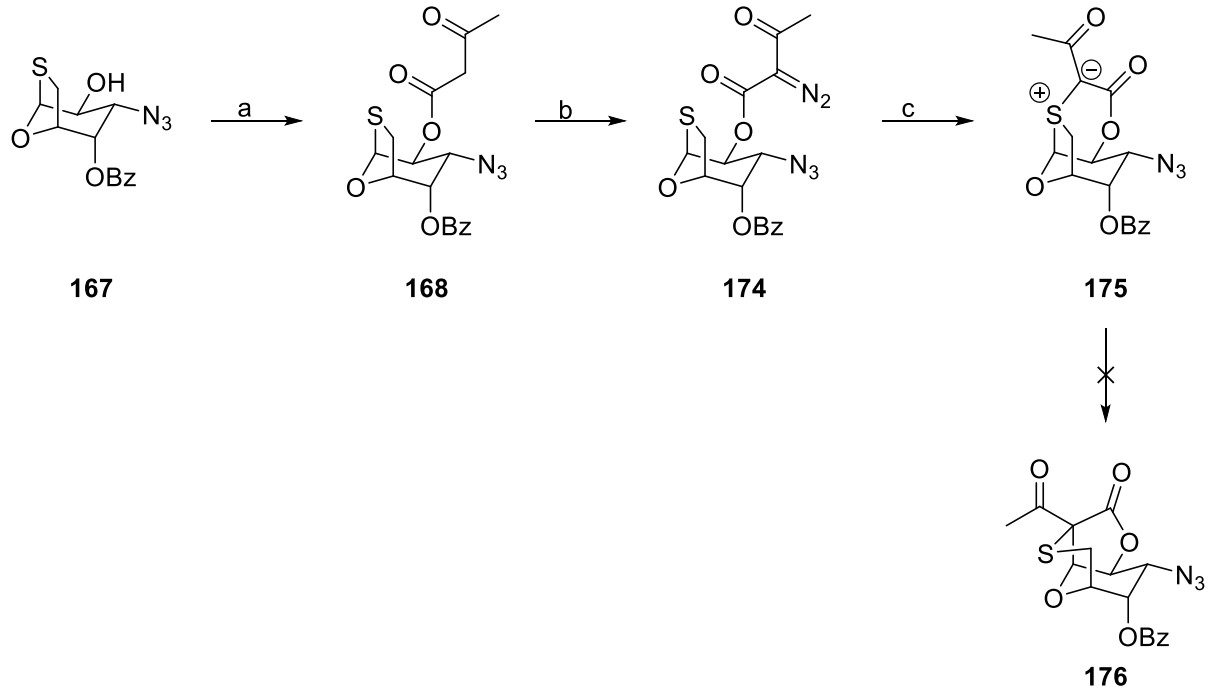
As a result, the authors changed their strategy for the synthesis of ylide **171** from a transition metal catalysed diazodecomposition to an intramolecular S-alkylation followed by deprotonation. Hence, **172** was made by acylation of the 2-OH in **167** with bromoacetyl bromide (**Scheme 32**). However, intramolecular displacement of the bromide by the sulfur atom to form sulfonium salt **173** was not observed with or without the presence of silver salts.



Reagents and conditions: a) $BrCH_2COBr$, DMAP, DCM, 57%.

Scheme 32: Attempted synthesis of sulfonium salt **173** by Porter *et al*.

As the authors previously made the thermally stable acetyl-substituted ylides **112** and **116**,[25] they aimed to synthesize ylide **175** (**Scheme 33**). To achieve this, acetoacetylation of **167** was performed to give **168**, which then underwent a diazo transfer to form **174**. Although ylide **175** was formed from **174** by diazodecomposition, it was impure and in low yield. Furthermore, irradiation of impure ylide **174** did not furnish the desired ring expansion product **176**.



Reagents and conditions: a) 2,2,6-trimethyl-4H-1,3-dioxin-4-one, xylene, reflux, 97%; b) $4\text{-}HO_2CC_6H_4SO_2N_3$, K_2CO_3, MeCN, 85%; c) $Rh_2(OAc)_4$, $CHCl_3$, reflux, 18%.

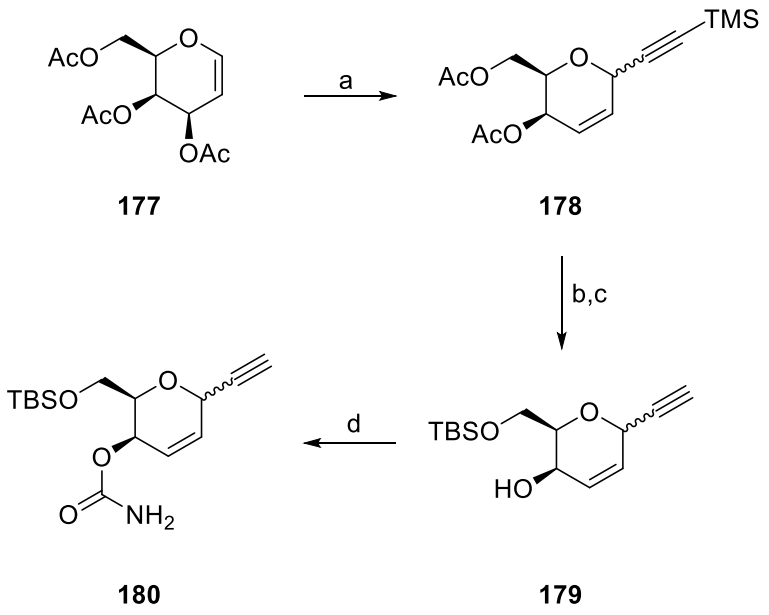
Scheme 33: Attempted synthesis of tricyclic **176** by Porter *et al.*

In summary, alternative methods to transition metal catalysed diazodecomposition for ylide formation such as photolytic conditions or S-alkylation followed by deprotonation failed due to undesired side reactions. Moreover, modifying their earlier successful methodology in making the tagetitoxin bicyclic core,[25] to closer related analogues of tagetitoxin by either sulfoxide incorporation instead of a thioether or to tether the diazo functionality through an equatorial linkage at the C_{-2} proved unsuccessful; the latter of which was explained by increased strain in the ylide. These results highlight the difficulty in expanding the scope of the ring expansion strategy and its applicability to a total synthesis of tagetitoxin. Thus, since this paper, no further related work to this strategy has been published.

Nishikawa *et al*.

In 2013, Nishikawa and co-workers synthesized a fully functionalized tagetitoxin core structure.[7]

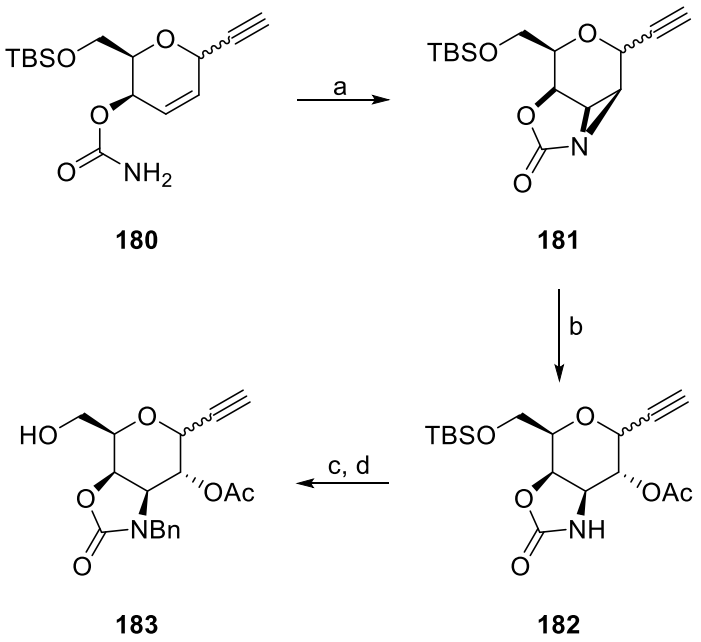
The first step in their synthesis of a tagetitoxin core structure was a Ferrier-type α-selective C-glycosylation of galactal **177** with tin acetylene and TMSOTf, producing **178** (**Scheme 34**). The yield and the selectivity in these conditions were much higher than using conventional methods, such as with bis(trimethylsilyl)acetylene and Lewis acids like $SnCl_4$.[40,41] After cleavage of the two acetates and TMS group using methanolic sodium methoxide, the primary alcohol was selectively silyl protected forming **179**. This allowed selective carbamoylation to then take place on the remaining free hydroxyl group via trichlorocetyl carbamoylation and subsequent hydrolysis to form **180**.



Reagents and conditions: a) tributylstannyl(trimethylsilyl)ethyne, TMSOTf, DCM, 0°C; b) NaOMe, MeOH, 0°C ; then Dowex®, 95% in 2 steps; c) TBSCl, Et_3N, DMAP, DCM, rt, 85%; d) trichloroacetyl isocyanate, DCM, 0°C ; then K_2CO_3, MeOH, H_2O, 0°C, 73%.

Scheme 34: Synthesis of compound **180** by Nishikawa *et al*.

The next target in the synthesis was the stereocontrolled installation of a nitrogen functionality at the C_{-3} position and an oxygen functionality at the C_{-2} position in a stereocontrolled manner. The authors envisaged that this could be accomplished by the synthesis of an 2,3-β-aziridine derivative and subsequent regioselective opening with an oxygen nucleophile (**Scheme 35**). Treatment of **180** under typical aziridination conditions of catalytic amounts of $Rh_2(OAc)_4$ and $PhI(OAc)_2$ with magnesium oxide,[42] afforded aziridine **181**, albeit in low yield (17%). However, upon modification of the conditions, namely using $Rh_2(OAc)_4$, PhIO and 4Å molecular sieves, the reaction was optimized to 70% yield. Aziridine **181** was then ring-opened regioselectively with an acetate nucleophile to furnish **182**. The carbamate was then benzylated under typical conditions, which was then followed by a silyl ether deprotection to afford **183**.

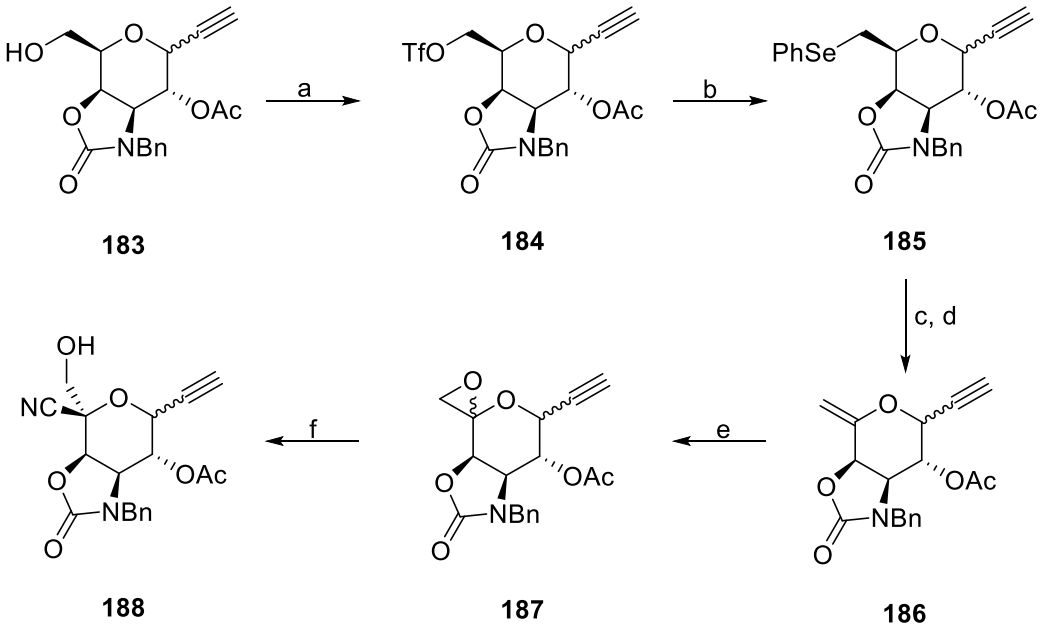


180 **181** **183** **182**

Reagents and conditions: e) $Rh_2(OAc)_4$, PhIO, MS-4Å, DCM, rt, 70%; b) AcOH, 80°C, 73%; c) NaH, BnBr, TBAI, DMF, 0°C, 90%; d) TBAF, AcOH, THF, rt, 78%.

Scheme 35: Synthesis of compound **183** by Nishikawa *et al*.

The investigators then aimed to incorporate a carboxylic acid derivative on the C_{-5} position. To achieve this, the authors planned to make an *exo*-glycal, carry out an epoxidation on it and finally ring open the *spiro*-epoxyacetal with a cyanide-based nucleophile in a regioselective and stereoselective fashion. The authors firstly activated the primary hydroxyl group as a triflate and displaced it with lithium phenylselenide (generated from diphenyldiselenide and *n*-BuLi) to produce selenide **185** (**Scheme 36**). Using mCPBA, **185** was then oxidized to give the selenoxide which then underwent a selenoxide elimination to give *exo*-glycal **186**. Electrophilic epoxidation was then successfully carried out on **186** to yield *spiro*-epoxyacetal **187**. When attempting to ring open the epoxide using TMSCN and a range of Lewis acids, the desired nitrile **188** was not observed. Treatment, however, with Et_2AlCN did produce **188** as a single diastereomer but only in an 8% yield. Eventually the authors found optimal conditions for this reaction using TMSCN and molecular iodine in toluene and hexane at 0 ^oC; this led to the isolation of **188** in sufficient yield (44%) after acidic hydrolysis of the TMS ether.

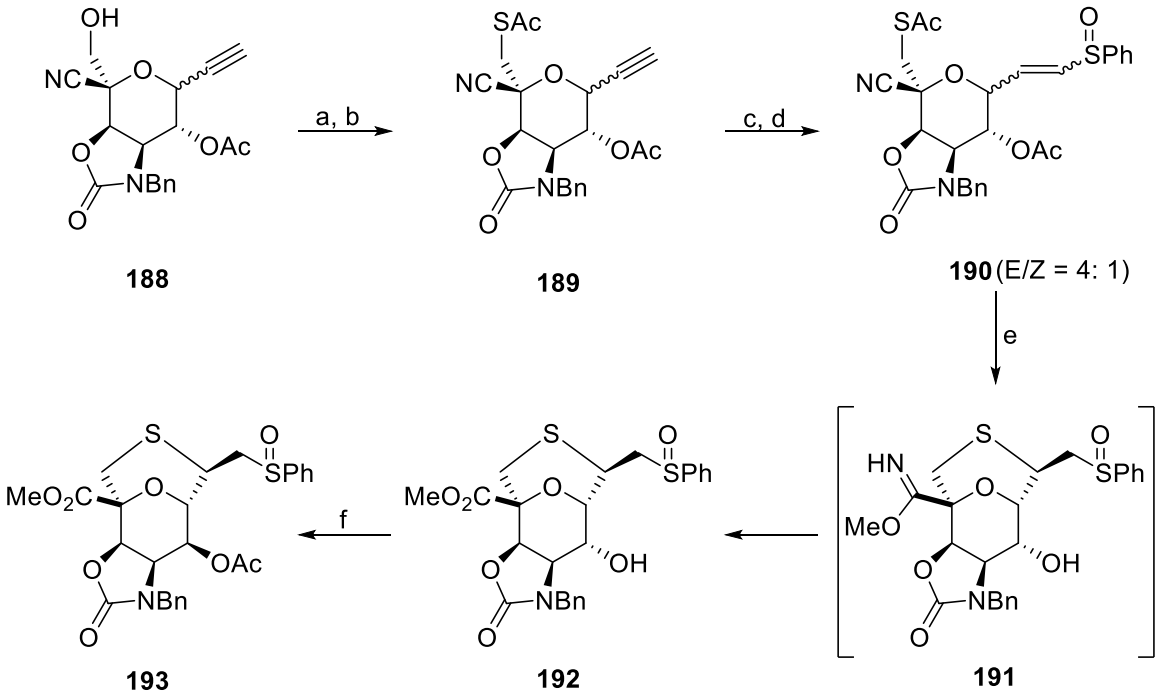


Reagents and conditions: a)Tf_2O, 2-6-lutidine, CH_3CN, -20°C, 93%; b) $(PhSe)_2$, *n*-BuLi, THF, -20°C, 86%; c) *m*-CPBA, DCM, -40°C; d) $NaHCO_3$, THF, 65°C, 88% in 2 steps; e) m-CPBA, $NaHCO_3$, DCM, rt, 98%; f) TMSCN, I_2, toluene, hexane, 0°C, then 1 M HCl aq. rt, 44%.

Scheme 36: Synthesis of nitrile **188** by Nishikawa *et al*.

Having succeeded in making a fully functionalized pyranoid framework of tagetitoxin (**188**), the authors then aimed to construct the 1,4-oxathiane moiety of the natural product. In order to achieve this, they firstly incorporated a sulfur functionality into the structure in the form of a thioacetyl group, using similar methodology to Porter *et al*.,[24] whereby the primary alcohol of **188** was transformed into a triflate and then displaced with a thioacetate nucleophile to afford **189** (**Scheme 37**). The authors then planned to deprotect the thioacetate group to release the thiolate which would then undergo a concomitant 6-*exo*-dig cyclization. Although treatment of **189** with LiSMe did cause the intended thioacetyl deprotection, only the undesired 7-endo-dig cyclization from the generated thiolate occurred. Therefore, Nishikawa and co-workers planned to modify their cyclization strategy; instead of an *in-situ* generated thiolate undergoing a 6-*exo*-dig cyclization, they envisaged that it would undergo a conjugate addition on an α,β-unsaturated sulfoxide in a 6-*exo*-trig cyclization. Thus, the authors synthesized the α,β-unsaturated sulfoxide **190** in two steps from **189** by a radical addition of thiophenol to the alkyne moiety and subsequent oxidation of the vinyl thioether with mCPBA. Treatment of **190** with lithium hydride in methanol led to initial thioester cleavage and an *in-situ* conjugate addition of the formed

thiolate on the vinyl sulfoxide, but deacetylation and nitrile transformation into an imidate were additionally observed leading to **191** forming. Subsequent acidic hydrolysis on the imidate was then carried out to give methyl ester **192**, which in turn was acetylated to form **193**.

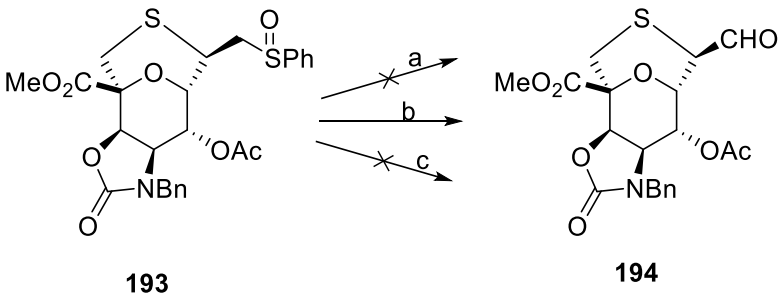


Reagents and conditions: a) Tf_2O, 2-6-lutidine, CH_3CN, -20°C; b) AcSH, NaH, DMF, rt, 89% in 2 steps; c) PhSH, AIBN, *t*-BuOH, 100°C; d) m-CPBA, DCM, -40°C, 62% in 2 steps; e) LiH, MeOH, 0°C to rt, then 1 M HCl aq., 0°C f) Ac_2O, pyridine, DCM, rt, 77% in 2 steps.

Scheme 37: Synthesis of compound **193** by Nishikawa *et al*.

Transformation of the sulfoxide moiety of **193** into an aldehyde via the Pummerer rearrangement to form **194** was attempted (**Scheme 38**). However, the use of conventional conditions such as acetic anhydride and sodium acetate only led to unreacted starting material. This prompted the authors to use the more electrophilic trifluoracetic anhydride instead. This led to starting material being recovered, although, epimerization of the chiral sulfoxide was observed (diastereomeric ratio changed from 1:7 to 2:1); this indicates that the sulfoxide must have been trifluoroacetylated initially but then underwent an intermolecular displacement with a trifluoroacetate nucleophile. In order to solve the aforementioned difficulties encountered in this transformation, a strong electrophilic activating agent with a poor nucleophilic leaving group (TMSOTf) and a non-nucleophilic base (Et_3N) were used; the former led to successful sulfoxide

activation and the latter led to successful elimination of the generated silylated sulfoxide to the thonium ion, which in turn underwent hydrolysis to form aldehyde **194**.

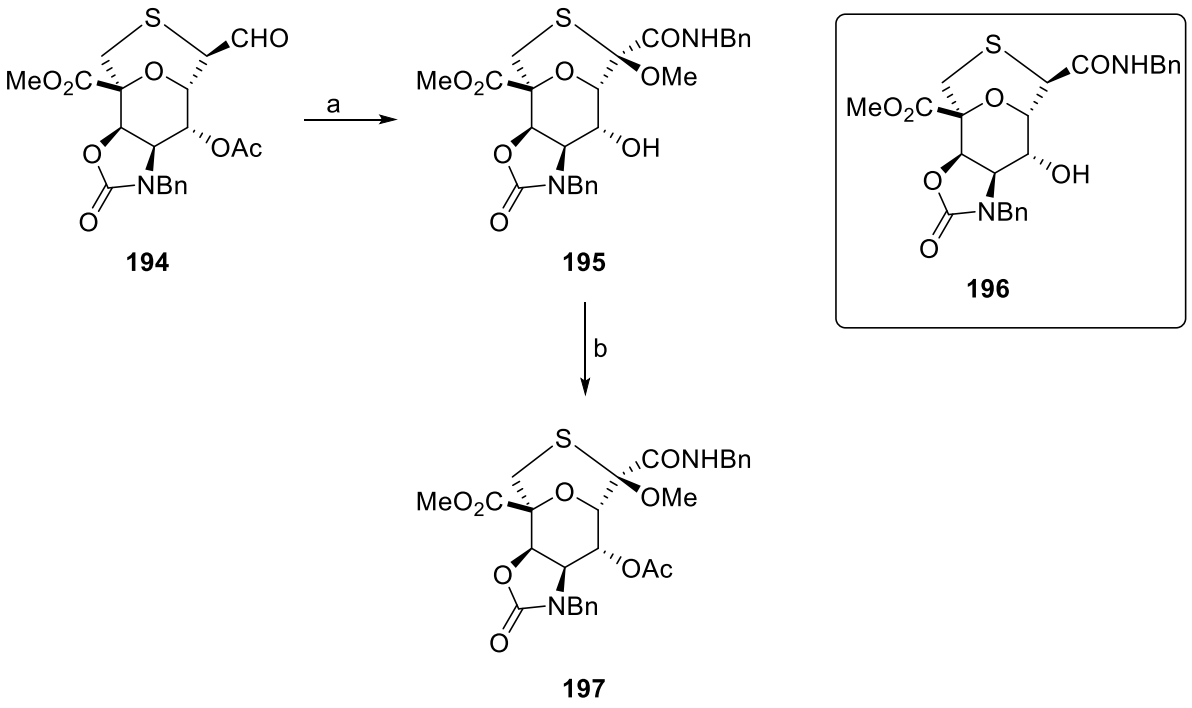


193 **194**

Reagents and conditions: a) NaOAc, Ac_2O; b) TMSOTf, Et_3N, DCM, 0 ^oC, 63%; c) $(CF_3CO)_2O$.

Scheme 38: Synthesis of compound **194** by Nishikawa *et al*.

The final objectives to synthesize the core structure of tagetitoxin was the conversion of the aldehyde into an amide and formation of a thioketal functionality. Surprisingly, the authors accomplished both these goals in one step (**Scheme 39**). Oxidative amidation of aldehyde **194** with benzylamine and iodine in methanol produced thioketal **195** rather than the expected compound **196**. It was postulated, that during the reaction, **196** was produced but then underwent acetate cleavage. Additionally, under these conditions, the sulfide was activated with iodine to form a sulfonium ion which was then trapped by a methanol molecule furnishing **195**. Acetylation of **195** gave the tagetitoxin core structure **197**.



Reagents and conditions: a) $BnNH_2$, I_2, MeOH, rt; b) Ac_2O, pyridine, rt, 30% in 2 steps.

Scheme 39: Synthesis of the core structure of tagetitoxin (**197**) by Nishikawa *et al*.

In summary, Nishikawa *et al*. synthesized the first fully functionalized tagetitoxin core. Their key methodology in constructing the bicyclic ring system involved the deprotection of a thioacetate and concomitant intramolecular conjugate addition of the free thiolate on a vinyl sulfoxide. Moreover, compared to previously synthesized tagetitoxin core structures,[24,31] compound **197** is the only one which has a carboxylic derivative on the pyranoid core of the natural product (which was accomplished by the synthesis and subsequent ring opening of a *spiro*-epoxyacetal).

Previous Work in The Page Group

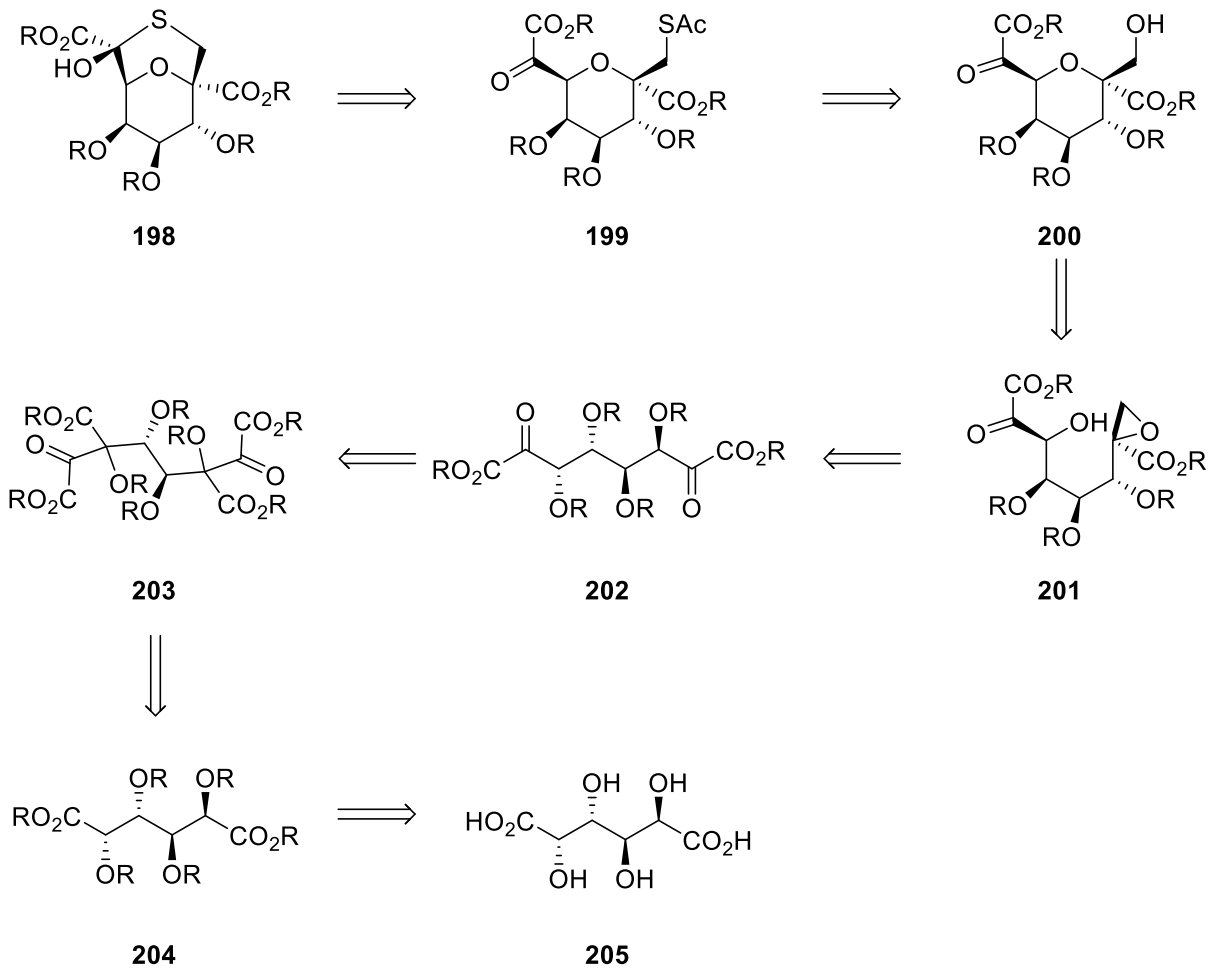
The targets in all previous studies in the Page group towards the synthesis of tagetitoxin have been structures **2a** and **2b**.[43–45] There have been several routes attempted by the Page group to make the bicyclic core of structures **2a** and **2b**. In all routes, the planned synthesis of the 1,4-oxathiane moiety in the bicyclic core has been based upon Porter and co-workers' methodology where a thioacetyl functionality is deprotected leading to an *in-situ* cyclization of a free thiol or thiolate onto a ketone.[24]

Roy

Early studies in the Page group towards the synthesis of tagetitoxin were carried out by Claud-Éric Roy.[43] Their synthetic pathways generally started from non-cyclic materials (such as mucic acid or *meso*-tartaric acid) before moving on to cyclic starting materials such as D-mannose.

Mucic Acid Route

The first strategy of the group began from a non-cyclic starting materiel mucic acid (**Scheme 40**).

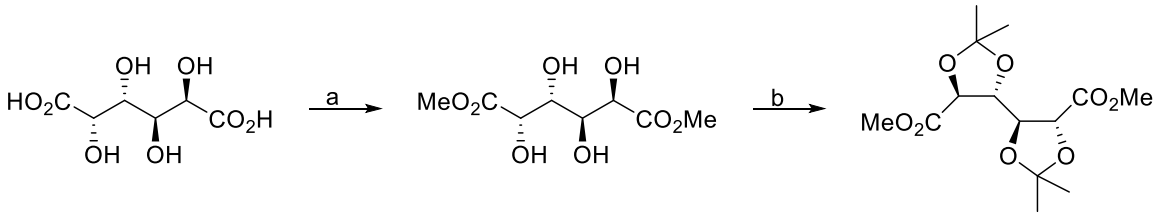


Scheme 40: Retrosynthesis of the target bicyclic structure **198** from mucic acid.

In this strategy, bicyclic precursor **199** could be derived from **200** by activating the hydroxyl into a good leaving group and then displacing it with a thioacetate nucleophile. The fully functionalized pyranoid core **200**, could be made from cyclization in terminal epoxide **201**. This

epoxide intermediate **201** could be synthesized from di-ketoester **202** via a Wittig or Tebbe olefination-epoxidation sequence or a Corey-Chaykovsky reaction on one of the ketones.[46–48] Compound **202** could be formed by a Krapcho decarboxylation of the two esters, other than the two α-ketoesters in **203**. Enolization of both esters in **204**, which then undergo nucleophilic attack on an esterified derivative of oxalic acid could then lead to the installation of the two α-ketoester moieties seen in **203**. Finally, **204** could be synthesized from readily available mucic acid **205** by esterification of the two carboxylic acid moieties followed by relevant hydroxyl group protection.

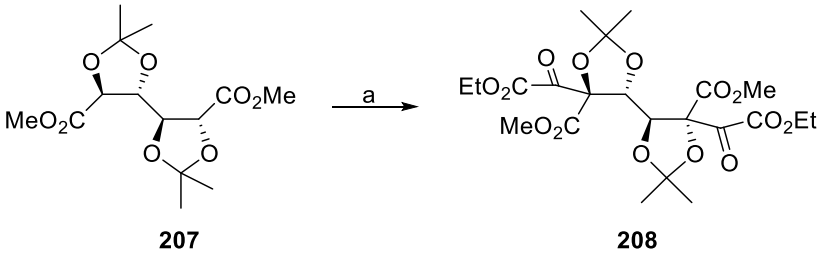
Roy began the route by synthesizing compound **207** in two steps from mucic acid **205** (**Scheme 41**) as described by Hirsch *et al*.[49] These steps were a Fischer esterification to form bis-methyl ester **206** which was then treated with acid in acetone to furnish bis-acetonide **207**. However, only low yields (17-25%) of **207** were obtained; changing the acid catalyst led to either lower yields or decomposition.



Reagents and conditions: a) MeOH, H_2SO_4, 90%; b) H_2SO_4, acetone, 17-25%.

Scheme 41: Two-step synthesis of **207** from mucic acid **205**.

The next planned step in the synthesis was the insertion of the two α-ketoester moieties to give **208** (**Scheme 42** and **Table 3**).



Reagents and conditions: a) Base, diethyl oxalate, solvent, temperature. See **Table 3.**

Scheme 42: Acylation attempts of **207**.

Entry	Base	Solvent	Temperature/ºC	Result
1[50]	EtONa	EtOH	rt	SM
2	NaH	THF	0	SM
3	LDA	THF	-78	SM
4	LDA	THF	-78	SM

Table 3: Conditions reported for the acylation attempts of compound **166**

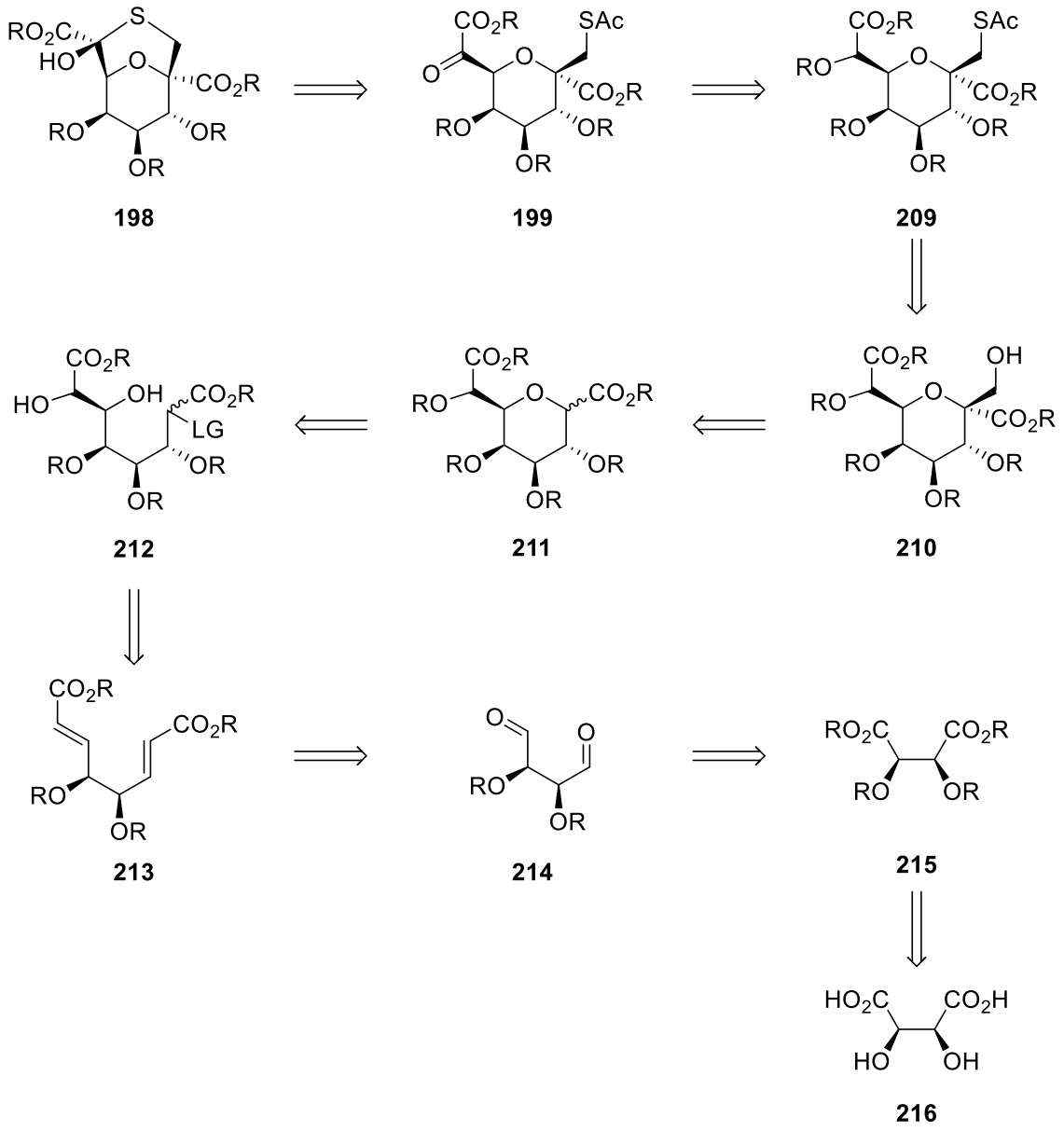
This was initially attempted using Kagan's conditions,[50] where sodium ethoxide was used as a base (to form the ester enolates), and diethyl oxalate used as the electrophile. Under these conditions, however, only starting material was recovered (entry 1). Consequently, the group used stronger bases such as sodium hydride and lithium diisopropylamide (LDA) but this similarly led to full starting material recovery (entries 2 to 4).

To investigate the failure of this reaction, the group attempted to alkylate **207** to assess the reactivity of the carbon being deprotonated. Only starting material, however, was observed when using ethyl iodide as the alkylating agent with the same bases used in the attempted acylation (LDA and sodium hydride). This unexpectedly suggests that under these conditions, the ester enolate of **207** is not generated or not reactive enough to attack the diethyl oxalate in a nucleophilic manner.

This route was therefore abandoned due to the low yields obtained with bis-acetonide **207** as well as the failure in producing bis-ketoester **208**.

Tartaric Acid Route

The group then moved onto a different strategy starting from *meso*-tartaric acid (**Scheme 43**).



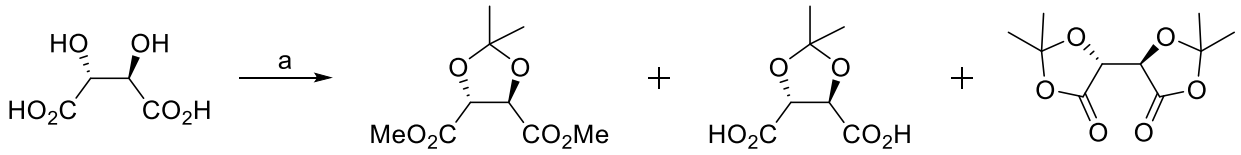
Scheme 43: Retrosynthesis of the target bicyclic structure **198** from *meso*-tartaric acid.

In this route, bicyclic precursor **199** could be formed from **209** by deprotection of the *exo*-cyclic secondary hydroxyl group and then subsequent oxidation of the α-hydroxyester to an α-ketoester. Similarly to the retrosynthetic analysis in the mucic acid route, the thioacetate moiety could be incorporated into the structure **210** by displacement chemistry. Intermediate **210** could be derived by reaction between the anomeric ester enolate of **211** with formaldehyde. The functionalized pyranoid core **211** could be made by a 6-*exo*-tet cyclization from attack of a nucleophilic hydroxyl onto an activated hydroxyl group (e.g. sulfonate ester) in the cyclic

precursor **212**, which in turn could be made by the bis-dihydroxylation of **213**. The bis-alkenylcarboxylic ester **213** could be synthesized by a Wittig olefination on both aldehydes of **214**. Finally, esterification and relevant hydroxyl group protection on *meso*-tartaric acid followed by ester reduction would furnish dialdehyde intermediate **214**.

It was planned that the synthesis would be first attempted with racemic tartaric acid and then the optimized conditions would be applied to *meso*-tartaric acid (due to the high cost of the latter).

Using Carmack's procedure,[51,52] Roy synthesized intermediate (±)-**218** from racemic tartaric acid **217** (**Scheme 44**). In this one-pot reaction, under acidic conditions (*p*-toluenesulfonic acid) in methanol and 2,2-dimethoxypropane under reflux, both carboxylic acids underwent a Fischer esterification in addition to the ketalization of the diol functionality. Although it was advantageous to have both the esterification and ketalization in one pot, the reaction was capricious, since results varied from quantitative yields of (±)-**218** to complex mixtures with undesired side products such as acid (±)-**219** and (±)-**220**.



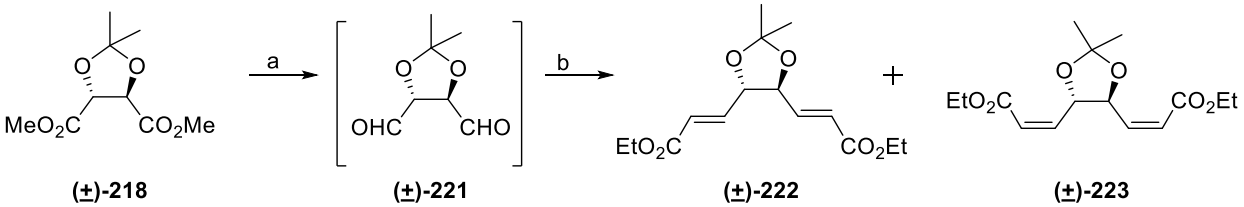
(±)-217 **(±)-218** **(±)-219** **(±)-220**

Reagents and conditions: a) MeOH, 2,2-DMP, *p*-TsOH, reflux, overnight, up to 100% of **(±)-218**.

Scheme 44: Synthesis of (±)-**218** from racemic tartaric acid (±)-**217**.

The next target in this strategy, was the synthesis of dialkene (±)-**222** from (±)-**218** by a one-pot bis-[ester reduction/Wittig olefination] (**Scheme 45**). In this step, the diester was reduced to the dialdehyde (±)-**221** using diisobutylaluminium hydride (DIBAL) which was followed by a Wittig olefination of the formed aldehydes. It was observed that for the reduction, the addition rate of the hydride and reaction time were significant variables that required optimization to avoid starting material decomposition or full reduction of the esters to alcohol moieties. After 3 hours at -78 ^{o}C, the Wittig ylide was then added to the reaction mixture, which led to an inseparable mixture of the (*E*,*E*)-dialkene (±)-**222** and its geometric isomer (*Z*,*Z*)-dialkene (±)-**223**. Since, however, it was important to perform the next steps with only one isomer (to help

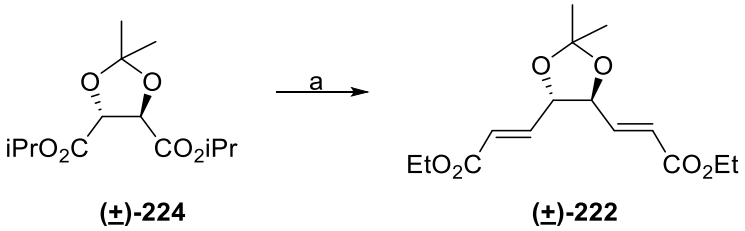
with the potential isolation of cyclized compound **211** later on in the synthesis), this mixture was not used further in the synthesis.



Reagents and conditions: a) DIBAL (1M in PhMe) over 30 min, PhMe, -78 °C, 3 h; b) Ph_3PCHCO_2Et, -78 °C to rt, 16 h.

Scheme 45: One-pot bis-[ester reduction/Wittig olefination] of intermediate **(±)-218**

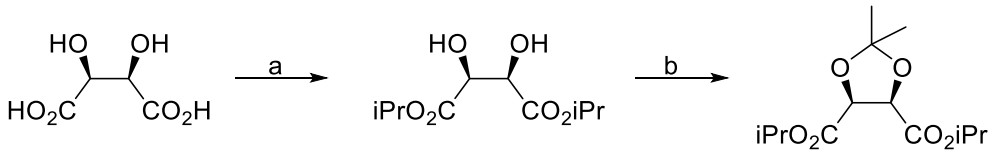
With the goal being to isolate only one geometric isomer of the dialkene, Roy planned to adapt a synthesis carried out by Saito *et al.*,[53] since they succeeded in making the (*E*,*E*)-dialkene (±)-**222** from a one-pot bis-[ester reduction/Horner Wadsworth-Emmons olefination] on (±)-**224** (**Scheme 46**). Saito *et al*. conclude that this type of diester starting material (with acetonide protecting group and isopropylic esters) in a toluene-hexane solvent system with diisopropylphosphonate as the Horner Wadsworth-Emmons (HWE) olefination reagent were key features for the success of the reaction.[53]



Reagents and conditions: a) DIBAL (1M in PhMe) over 30 min, PhMe/hexane, -78 °C, 3 h; then $(iPrO)_2P(O)CHCO_2Et$, - 78 °C to rt, 78%.

Scheme 46: Saito and co-workers' synthesis of dialkene **222** from compound **224**.[53]

However, Roy intended to perform this bis-[ester reduction/HWE] on isopropylic diester **225** rather than (±)-**224**. The synthesis would, therefore, be started from *meso*- rather than *rac*-tartaric acid (despite the high cost of the former). Thus, isopropylic diester **226** was synthesized in two steps from *meso*-tartaric acid **216** by a Fischer esterification and subsequent ketalization. (**Scheme 47**).

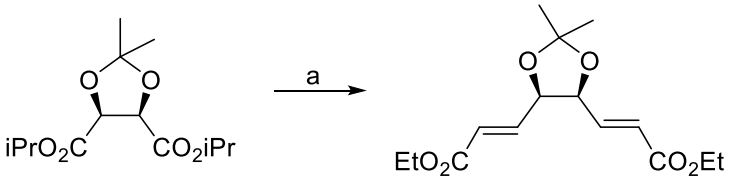


216 **225** **226**

Reagents and conditions: a) AcCl, *i*PrOH, relux, 16 h, 90-100%; b) 2,2-DMP, *p*-TsOH, PhMe, reflux 1h, then azeotropic distillation, 80-100%.

Scheme 47: Two-step synthesis of **226** from *meso*-tartaric acid **216**.

Roy then attempted the bis-[ester reduction/HWE] on **225** using conditions reported from Saito *et al*. (**Scheme 48**).[53] However, only low yields (13-15%) of dialkene **227** were obtained. Changing reaction times, rate of addition of reagents as well as the base that deprotonates the phosphonate from *n*-BuLi to non-nucleophilic LDA led to no improvement in yield.

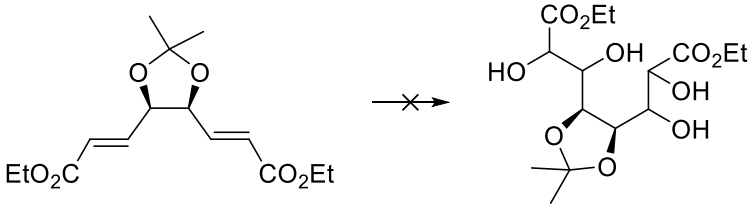


226 **227**

Reagents and conditions: a) DIBAL (1M in PhMe) over 30 min, PhMe, 2h, -78 ^{o}C; then 3 h; then $(iPrO)_2P(O)CHCO_2Et$, - 78 ^{o}C to rt, 13%.

Scheme 48: One-pot bis-[ester reduction/HWE olefination] of **226**.

Despite the poor yields for dialkene **227**, the bis-dihydroxylation using AD mix-β was attempted (**Scheme 49**). The crude ^{1}H NMR spectrum, however, showed a resultant complex mixture. Purification attempts by chromatography on silica gel or alumina proved futile because the mixture was lost with no recovery possibly due to its polarity.



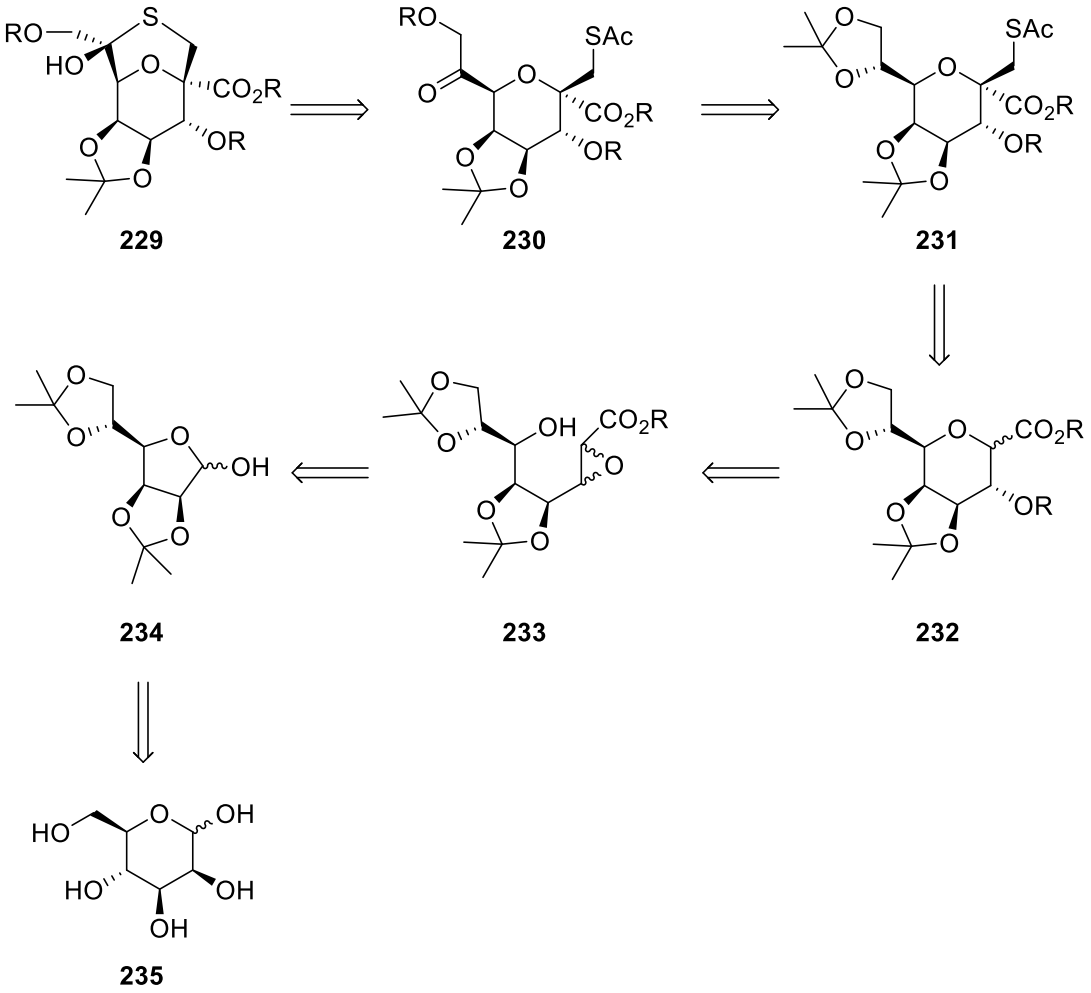
227 **228**

Scheme 49: Failed synthesis of **228** by bis-dihydroxylation of **227**.

The low yields of the dialkene **227** in addition to no single isolable product from the bis-dihydroxylation, led the group to focus on a different strategy.

Darzens Route

Roy then moved onto a strategy with the cyclic starting material D-mannose (**Scheme 50**).

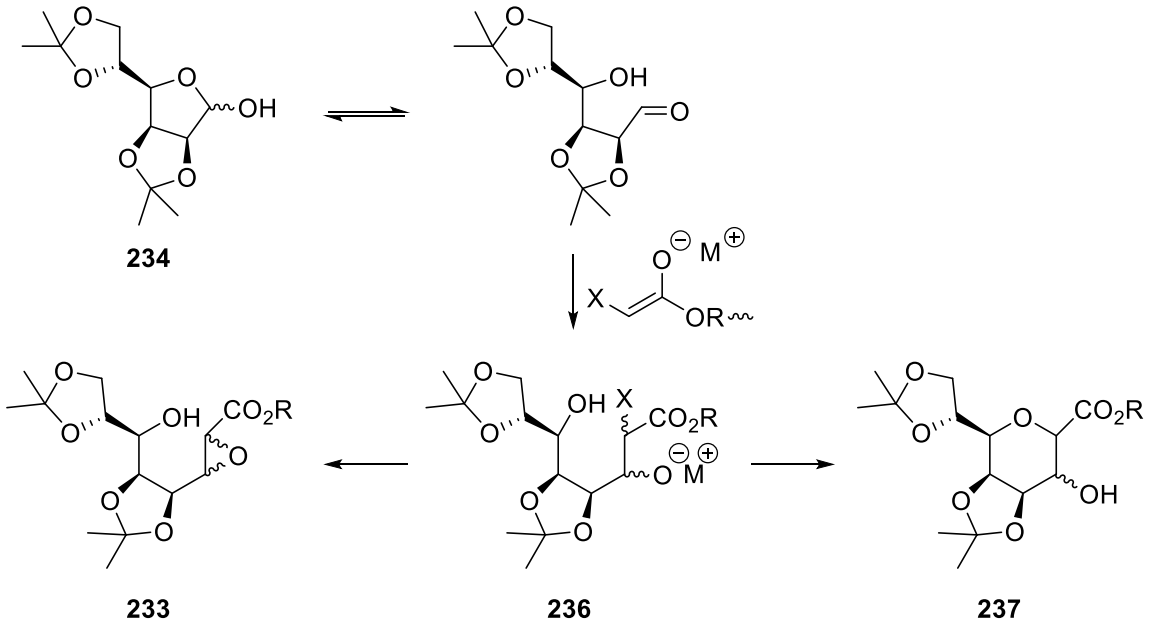


Scheme 50: Retrosynthesis of target structure **229** from D-mannose **235** in the Darzens route.

In this strategy, structure **229** is the synthetic target. If **229** were successfully made, the strategy would then be modified to install an ester on the thiohemiketal centre. The target precursor **230** could be synthesized from **231** in three-steps: selective acetonide hydrolysis; primary hydroxyl protection; and oxidation of the secondary alcohol. The insertion of the thioacetyl-methylene moiety on **232** to afford **231** is identical to the aforementioned methodology in the *meso*-tartaric acid route. The synthesis of the pyranoid core in **232** could be achieved by a 6-*endo*-tet

cyclization in glycidic ester **233** followed by a protection of the OH on C_{-2}. This glycidic ester **233** could form from a Darzens reaction between an α-haloester and diacetone mannose (DAM) **234**. Finally, DAM **234** could be synthesized from D-mannose **235** using acid catalysis in an acetone solvent.

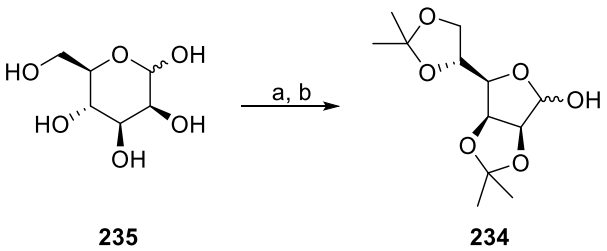
The key feature in this route is the proposed Darzens condensation reaction involving a nucleophilic addition of an α-haloester (using enolate chemistry) on the acyclic hydroxy-aldehyde form of DAM **234** followed by a 3-*exo*-tet cyclization to give epoxide **233** (**Scheme 51**). This reaction exploits the aldehyde chemical properties that most cyclic carbohydrate derivatives have, arising from the equilibrium between the 'closed' lactol form and the 'open' hydroxy-aldehyde form. Furthermore, in intermediate **236**, competing with the 3-*exo*-tet cyclization for epoxide formation, a 6-*exo*-tet cyclization could occur to give the desired glycoside **237**. Alternatively, even if epoxide formation occurs in the reaction, the formed epoxide intermediate could undergo a concomitant 6-*endo*-tet cyclization (although in competition with the more favourable undesired 5-*exo*-tet cyclization) to give the C-glycosyl ester **237**.



Scheme 51: Proposed mechanism for the Darzens reaction on DAM **234**.

For the first step of the route, Roy synthesized DAM from D-mannose using a literature procedure from Schmidt *et al.* (**Scheme 52**).[54] The reaction occurred by the protection of the *cis*-

hydroxyl groups in the furanose form of D-Mannose with isopropylidene groups. It was observed that neutralization of the crude reaction mixture prior to second stage of the reaction was critical, since without doing this only decomposition was observed.

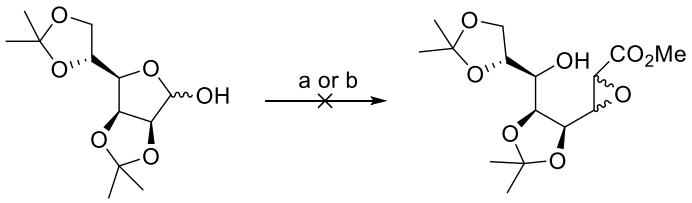


235 **234**

Reagents and condtions: a) H_2SO_4, acetone, rt, 3 h; b) Na_2CO_3, charcoal, acetone, reflux, 1 h, 75-90%.

Scheme 52: Synthesis of DAM **234** from D-mannose **235**.

Subsequently the Darzens reaction on DAM was attempted (**Scheme 53**). However, only starting material was observed in the reaction, despite trying different deprotonation conditions for the addition of the α-haloester.

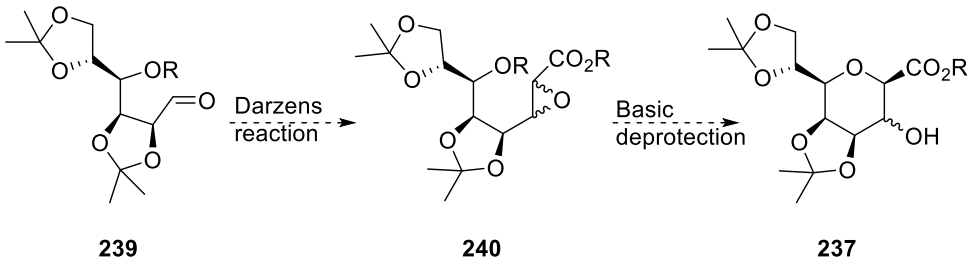


234 **238**

Reagents and condtions: a) Methyl bromoacetate, Et_3N, toluene, 0 ^oC to rt, overnight; b) Methyl bromoacetate, LDA, THF, -78 ^oC to RT, overnight.

Scheme 53: Attempted Darzens reaction on DAM **234.**

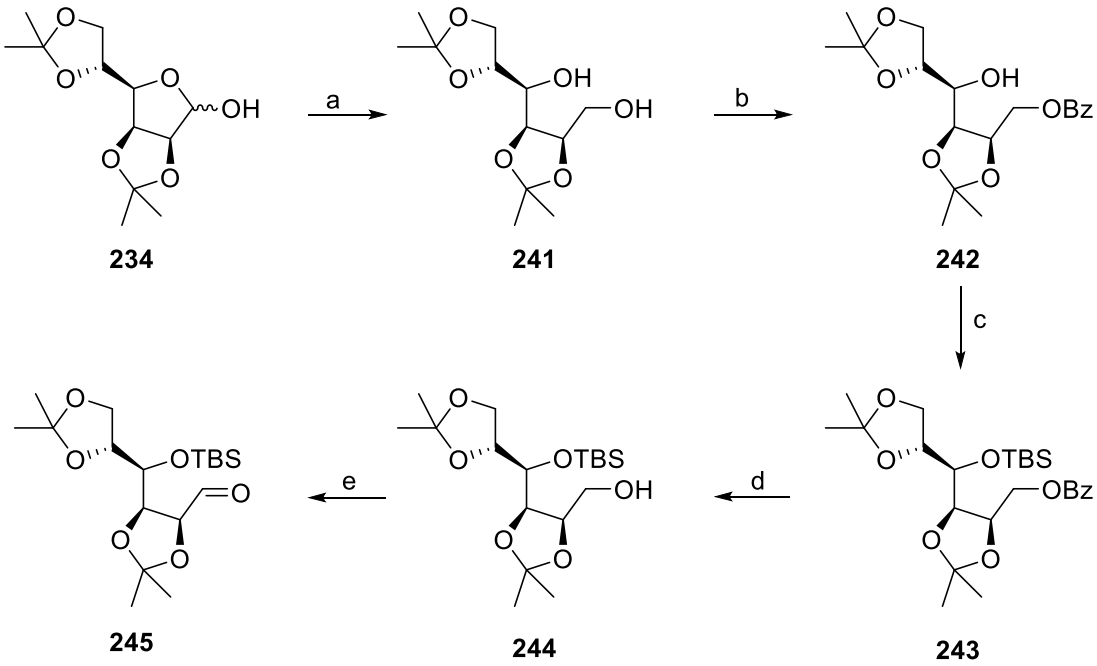
As a result, the group modified their strategy (**Scheme 54**). In this approach, the Darzens reaction would occur on a protected derivative of the 'open' form of DAM. Then basic deprotection and concomitant 6-*endo*-tet cyclization would then eventually lead to glycoside **237**.



239 **240** **237**

Scheme 54: Proposed synthetic approach to pyranoid **237**.

To make this protected derivative, Roy followed a synthesis performed by Hashimoto *et al.* (**Scheme 55**).[55] In this synthesis diol **241**, was synthesized by the total reduction of the lactol functionality in DAM **234** using LAH. A selective benzoylation on the primary hydroxyl group and subsequent silylation on the secondary alcohol then afforded **243**. Deprotection of the benzoyl group and subsequent oxidation of the resulting primary alcohol furnished aldehyde **245**.



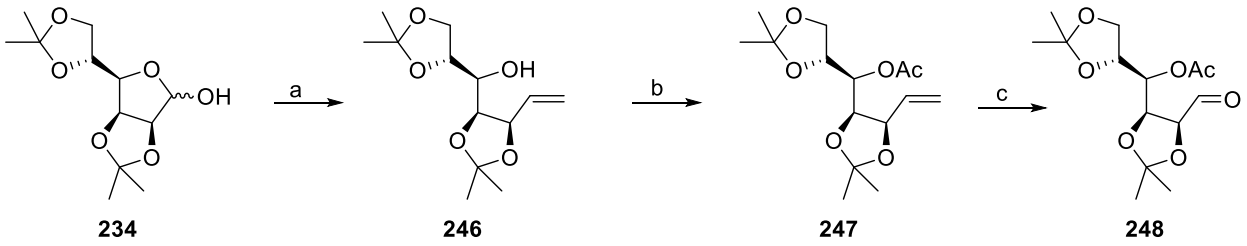
Reagents and condtions: a) LAH, THF, 0 ^{o}C to rt; b) BzCl, PY, rt; c) TBSCl, imidazole, DMF, 80 ^{o}C; d) 1N NaOH/MeOH rt; e) DCC, DMSO, TFA, PY, benzene.

Scheme 55: Hashimoto and co-workers' five-step synthesis of aldehyde **245** from DAM **234**. [55]

Although benzoyl **242** was reached easily by Roy using Hashimoto and co-workers' conditions, difficulties were encountered in the ensuing silylation of the secondary alcohol. The use of TBSCl was concluded to be ineffective under the conditions reported by Hashimoto *et al.*,[55] as

only decomposition was observed. The use of the more electrophilic silylating agent TBSOTf, with N,N-Diisopropylethylamine (DIPEA) in Et_2O, however, did furnish compound **243** but in low yield (37%). After Roy successfully isolated alcohol **244** in quantitative yield from the saponification of the benzoyl functionality in **243**, the oxidation to the target aldehyde **245** was then attempted. Surprisingly when using Moffatt-Pfitzner methodology as reported in Hashimoto and co-workers' synthesis,[55] only a mixture of starting material and decomposition was seen. Even applying range of other oxidations (Parikh-Doering, Swern and hypervalent iodine mediated oxidations) were similarly unsuccessful.

As a result, Roy planned to follow a synthesis towards an alternate protected aldehyde species with an acetyl protected secondary hydroxyl group published by Lopéz-Herrera *et al*. (**Scheme 56**).[56] The route consisted of a Wittig olefination of DAM forming terminal alkene **246**, then acetyl protection followed by ozonolysis yielding aldehyde **248**. An advantage of this synthesis was fewer steps compared to the synthesis of aldehyde **245** reported by Hashimoto and co-workers.[55]



234 **246** **247** **248**

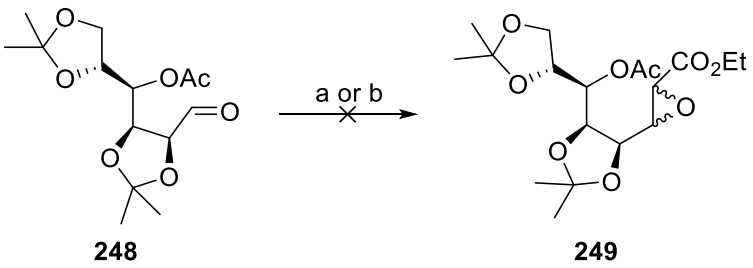
Reagents and condtions: a) Ph_3PCH_3Br, n-BuLi, HMPA, THF; b) Ac_2O, PY; c) , rt; c) O_3, $CHCl_3$, then SMe_2.

Scheme 56: Lopéz-Herrera and co-workers' three-step synthesis of aldehyde **248** from DAM **234**.[56]

The Wittig olefination on DAM **234** carried out by Roy, appeared capricious as terminal alkene **246** was formed in yields varying from 47% to 76%. Acetylation (84-97% yield) and sequent ozonolysis (up to 100% yield), however, proceeded smoothly to afford the desired aldehyde **248**.

The next step in the synthesis was the Darzens condensation on aldehyde **248** (**Scheme 57**). In both conditions attempted, glycidic ester **249** was not isolated. When the reaction was performed with LDA, only DAM was recovered. When using the milder base *t*-BuOK, mainly starting material and a small amount of DAM was isolated. The formation of DAM in both conditions

could be explained by an *in-situ* deprotection of the acetate by the deprotonated bromoacetate nucleophile liberating an anionic oxygen which could attack the aldehyde yielding DAM.



248 **249**

Reagents and condtions: a) LDA, THF, ethyl bromoacetate, -78 ^{o}C to rt;
b) *t*BuOK, Et_2O, ethyl bromoacetate, 0 ^{o}C to rt.

Scheme 57: Failed Darzens reactions of aldehyde **248**.

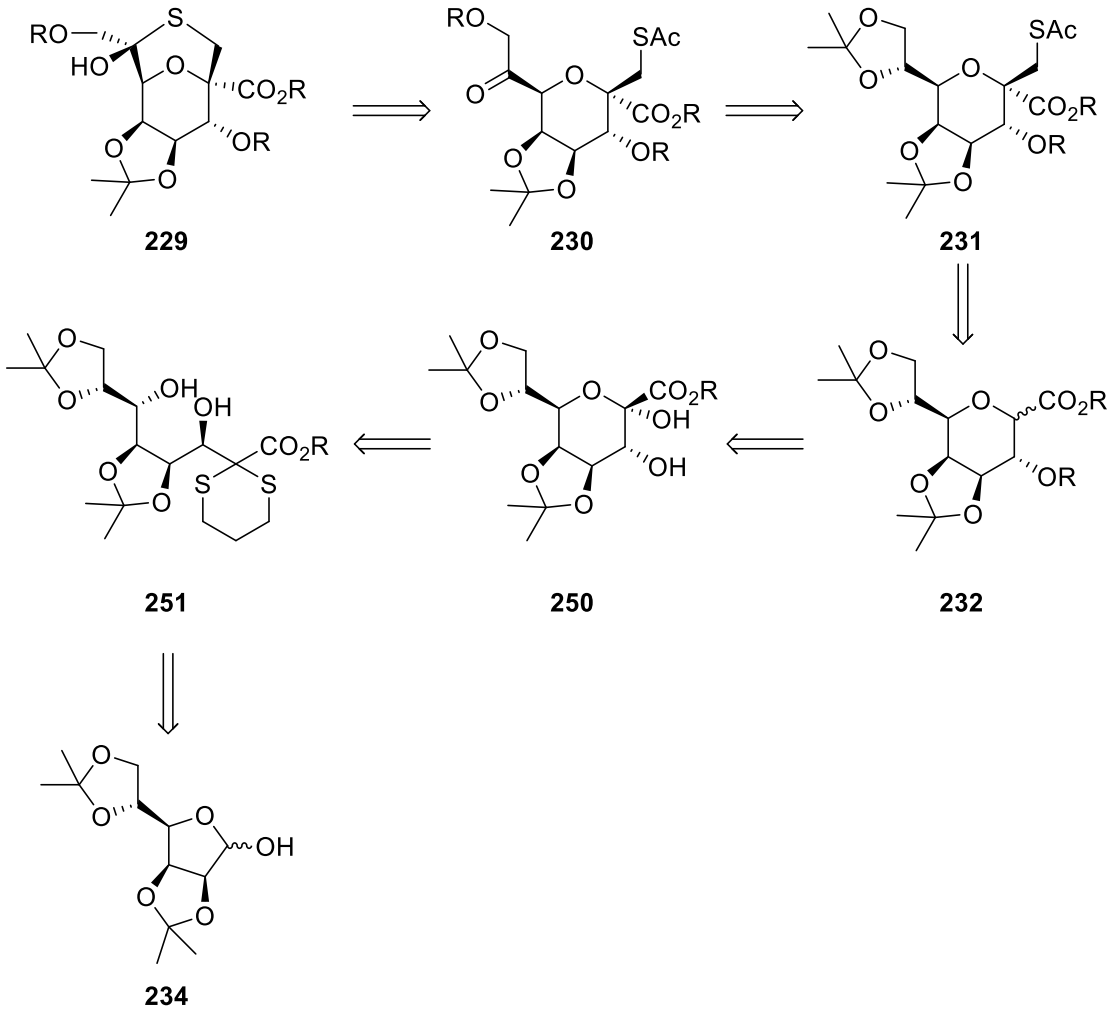
This route was abandoned due to the inability to isolate glycidic ester **249**.

Pearce

Continuing the work of Claude-Eric Roy, Pearce undertook a variety of routes starting from DAM **234**.[44]

Dithioacetal Route

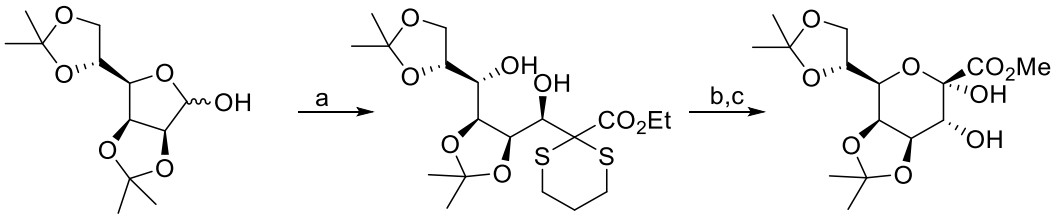
The first route attempted by Pearce involved the nucleophilic addition of a masked α-ketoester onto DAM **234** (**Scheme 58**).



Scheme 58: Retrosynthesis of target structure **229** from DAM **234** in the dithioacetal route.

The synthetic target **229** could be derived from intermediate **232** by the same methodology mentioned in the Darzens route.[43] Pearce proposed that pyranose **250** could lead to **232** in a three-step sequence involving selective protection of the C_{-2} hydroxyl group, activation of the anomeric alcohol into a good leaving group and displacement of the latter with a hydride source. Pyranose **250** could be obtained by dethioketalization of **251**, which in turn, would trigger a 6-*exo*-trig cyclization. The nucleophilic addition of a deprotonated 1,3-dithiane-2-carboxylate ester derivative on DAM **234** would yield intermediate **251**. Finally DAM **234** would be made from D-mannose **235** in identical fashion to previous work in the group.[43]

This route was largely inspired by the synthesis of intermediate **253** from DAM **234** reported by Reiner and Schmidt (**Scheme 59**).[57] Pearce planned to reproduce this synthesis except but without performing the transesterification after the dethioketalization.



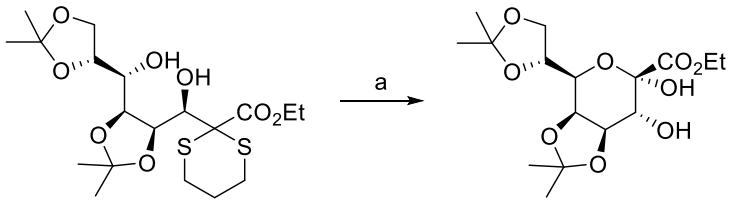
235 **252** **253**

Reagents and condtions: a) ethyl 1,3-dithiane-2-carboxylate, LDA, $MgBr_2$, THF, 76%; b) NBS, acetone; c) NaOMe, MeOH, 30% over 2 steps

Scheme 59: Reiner and Schmidt's two-step synthesis of pyranose **253** from DAM **234**.

After synthesizing DAM **234** from D-mannose **235**, Pearce then attempted the nucleophilic addition of ethyl 1,3-dithiane-2-carboxylate onto DAM with the goal of making **252**. The group decided to modify Reiner and Schmidt's procedure by not using $MgBr_2$ (for practicality reasons); therefore DAM **234** was added to a lithiated 1,3-dithiane derivative rather than a Grignard reagent 1,3-dithiane derivative, but only DAM was recovered. The group rationalized this observation by suggesting that the lithiated dithiane acted as a base rather than a nucleophile on the open hydroxy-aldehyde form of DAM to reform the closed lactol form. When repeating the conditions from the literature,[57] high yields of up to 98% of **252** were obtained, though the yields did decrease on a scale less than 10g of DAM.

The next step in this strategy involved the dethioketalization and *in-situ* cyclization of the hydroxyl group onto the formed ketone (**Scheme 60** and **Table 4**).



252 **254**

Reagents and conditions: a) see **Table 4.**

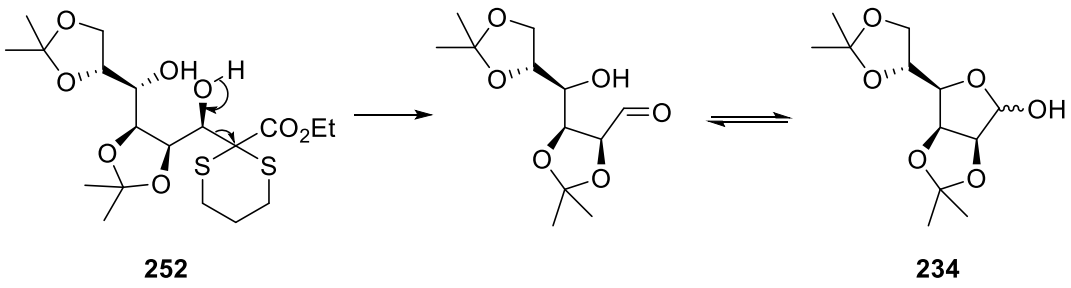
Scheme 60: Dethioketalization attempts of **252**.

Entry	Reagents and Conditions	Result
1[57]	NBS, 97% aqueous acetone, 0 °C, 3 min	40% **254**
2	NIS, Acetone, 0 °C, 3 min	40% **254**
3	NCS, Acetone, 0 °C, 3 min	10% **254**
4	DBDMH, Acetone, 0 °C, 3 min	40% **254**
5[58]	$HgCl_2$, (MeOH/H2O 9:1) reflux, 18 h	DAM **234**
6[59]	HgO, (MeOH/H2O 9:1) reflux, 18 h	DAM **234**
8[60]	H_2O_2 (MeOH/H2O 5:1) 6 h	DAM **234**
9[61]	mCPBA, DCM, RT, 4 h	DAM **234**
10[62]	Oxone® DCM, RT, 4 h	DAM **234**
11	MeI, DCM, reflux, 2 h	SM

Table 4: Conditions and results reported for dethioketalization attempts of compound **252**.

When using NBS in aqueous acetone (entry 1) as reported by Reiner and Schmidt,[57] pyranose **254** was isolated albeit in low yields (up to 40%). In addition to poor yields, there were scalability issues, where masses greater than ~200 mg of **252** led to little or no product and purification issues, due to the production of vast impurities in comparison to small yields of **254**. The stereochemistry of the resulting pyranose was confirmed by X-ray crystallography. To improve the yields, a variety of other dethioketalization procedures were attempted, such as the use of different halide donors (entries 2-4), mercury reagents (entries 5-6),[58,59] oxidants (entries 8-10)[60–62] and the use of methyl iodide (entry 11). None of these methods, however, led to any improvements; the only one with comparable success to NBS (entry 1) were the use of NIS (entry 2) and DBDMH (entry 4), presumably because of the dithiane deprotection mechanism of all three reagents being identical.

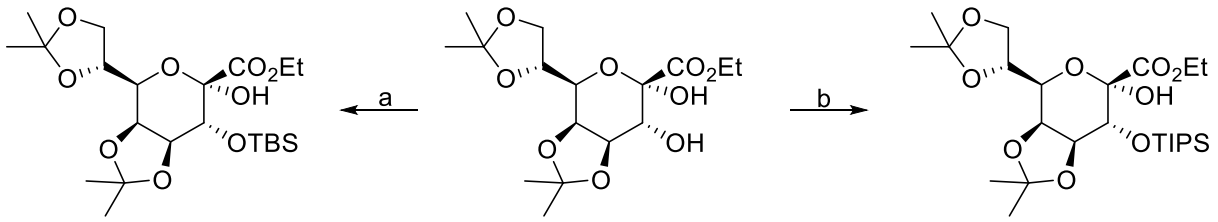
It was noticeable that in many dethioketalization conditions, DAM **234** was isolated which led the group to propose a mechanism for this (**Scheme 61**).



252 **234**

Scheme 61: Proposed mechanism for DAM **234** production in the dethioketalization attempts of **252**.

Despite the low yields of the dethioketalization, Pearce decided to continue the route with the next step being the selective protection of the hydroxyl group on the C_{-2} position in **254**. Attempts to protect the hydroxyl group as a TBDPS ether failed even after refluxing for several days; this failure was attributed to a steric rationale. Nevertheless, TBS and TIPS protection of the C_{-2} hydroxyl were achieved (**Scheme 62**), though only at low yields for the former.

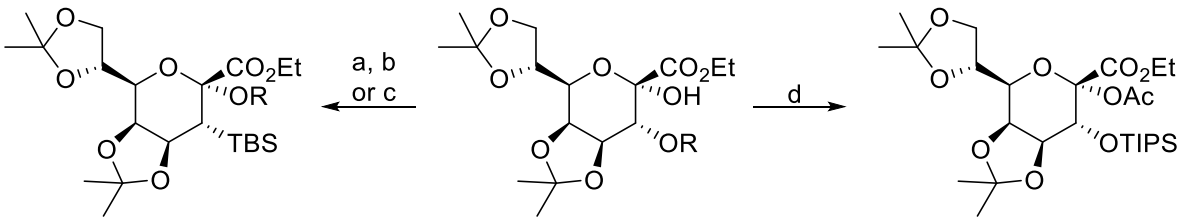


255 **254** **256**

Reagents and conditions: a) imidazole, TBSCl, DMF, 24 h, 32%; b) 2,6-Lutidene, TIPSOTf, DCM, - 78 ^{o}C, 1 h, 68%.

Scheme 62: Synthesis of silyl ethers **255** and **256**.

Pearce then attempted to activate the anomeric hydroxyl group. Initially, the hydroxyl group was methylated (**Scheme 63**), since there was literature precedent for the reductive cleavage of anomeric methoxy groups using triethylsilane and TMSOTf from Gray *et al*.[63] The group also mesylated and acetylated the anomeric alcohol as they thought the reduction of the mesylated compound would be easier to achieve due to better leaving group ability of the mesylate and acyl groups compared to the methoxy group.



257; R = Me
258; R = Ac
259; R = Ms

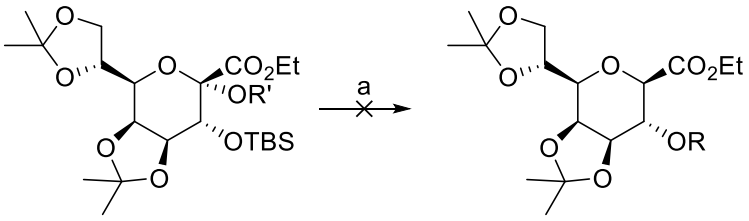
255; R = TBS
256; R = TIPS

260

Reagents and condtions: a) NaH, MeI, DMF, 88% **257**; b) Et_3N, Ac_2O, DMAP, DCM, 0 ^oC to rt, 19% **258**; c) Et_3N, MsCl, DMAP, DCM, 15-30% **259**; d) Et_3N, Ac_2O, DMAP, DCM, 0 ^oC to rt, 67%.

Scheme 63: Activation of anomeric hydroxyl group in **255** and **256**.

The reduction of the methylated, acetylated and mesylated products (**257**-**260**) using Et_3SiH and TMSOTf according to the literature[63] was unsuccessful (**Scheme 64**). Consequently, the group tried a range of combinations of Lewis acids ($BF_3.Et_2O$, $AlCl_3$ and $TiCl_4$) and hydride reductants (Et_3SiH and $NaBH_3CN$) but only starting material was recovered.



257; R = TBS, R' = Me
258; R = TBS, R' = Ac
259; R = TBS, R' = Ms
260; R = TIPS, R' = Ac

Reagents and condtions: a) Lewis acid, Et_3SiH or $NaBH_3CN$.

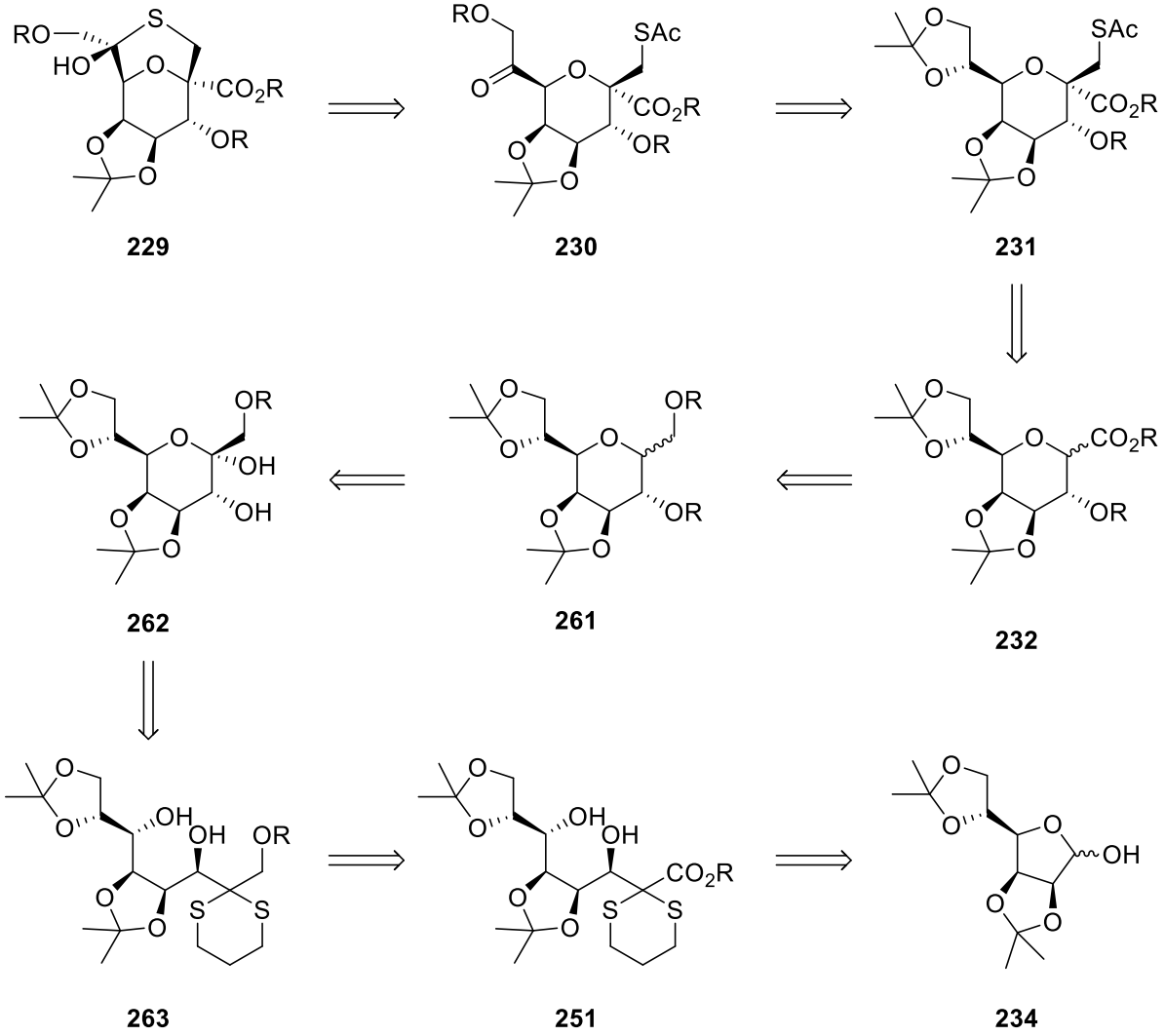
Scheme 64: Failed reductions of anomeric centre in compounds **257** – **260**.

Due to the low yields obtained in the dethioketalization and the failure of the reductions, the group decided to develop a new route.

Reduction Route

In order to synthesize target **229**, Pearce persevered with the dethioketalization strategy but aimed to reduce and thereby effectively remove the ester moiety. This would lead to the

dethioketalization and removal of the anomeric hydroxyl group being attempted on different substrates, as compared to the dithioacetal route (**Scheme 65**).

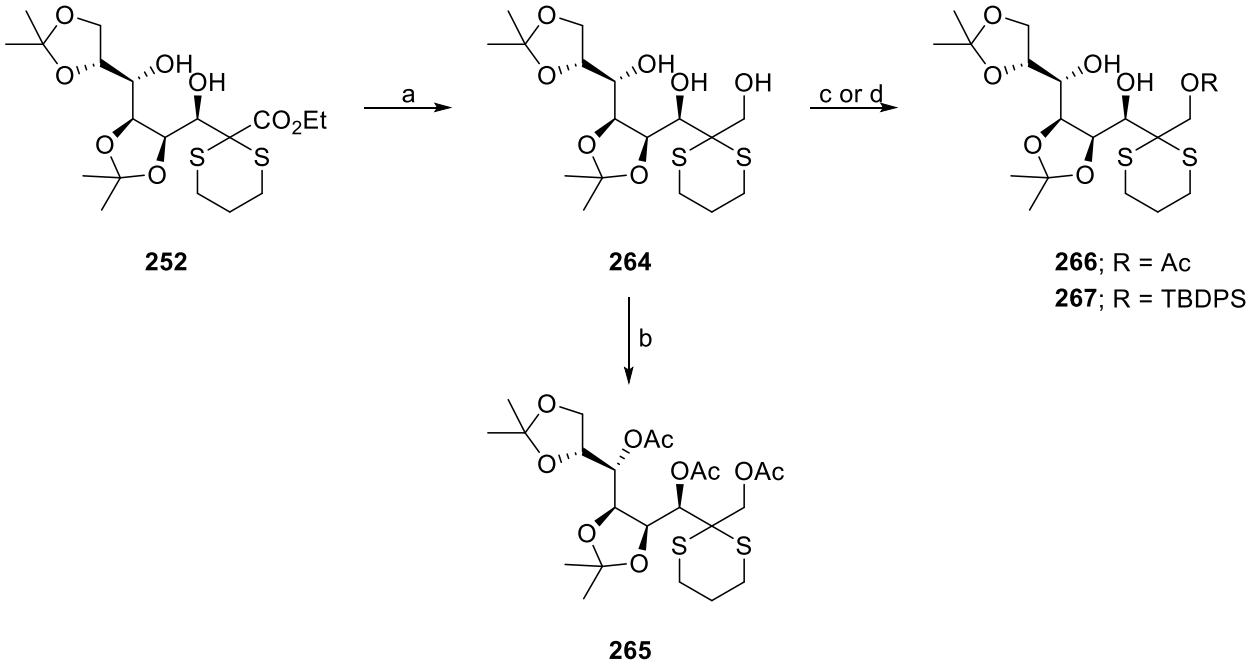


Scheme 65: Retrosynthesis of target structure **229** from DAM **234** in the Reduction route.

The retrosynthetic analysis for target **229** from intermediate **232** is identical to previous routes (i.e. the dithioacetal and Darzens routes). Structure **232** could derive from **261** in three steps: a selective deprotection of the methylene alcohol; primary alcohol oxidation to the carboxylic acid; followed by esterification. Activation and subsequent removal of the anomeric hydroxyl group in pyranose **262** could form intermediate **261**. Pyranose **262** could be formed from dethioketalization of intermediate **263**, which in turn could be made by the reduction of the ester moiety in **251** and then protection of the primary alcohol. Structure **251** could be synthesized

from D-mannose in 2 steps as previously achieved by Pearce in the dithioacetal route (where ester **252** was made).

Starting from compound **252**, the group successfully reduced the ethyl ester moiety using LAH to afford triol **264** (**Scheme 66).** Selective protection of the primary alcohol in **264** with an acetyl group proved challenging in any conditions using DMAP, since only the tri-acetylated compound **265** and starting material were recovered. Standard acetylation conditions without DMAP, however, afforded compound **266** in good yield. Pearce also formed the *tert*-butyldiphenylsilyl (TBDPS) ether of primary hydroxyl group albeit in low yield (18%).

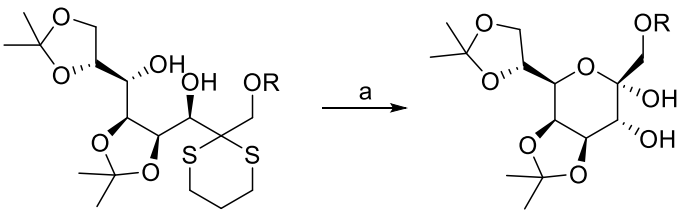


252 **264** **266**; R = Ac **267**; R = TBDPS **265**

Reagents and conditions: a) $LiAlH_4$, THF, 0 ^oC to rt, 3 h, 76%; b) Ac_2O, Et_3N, DMAP, DCM, 4 h, rt; c) Ac_2O, Et_3N, DCM, overnight, 67%; d) TBDPSCl, Et_3N, DMAP, DCM, rt, overnight, 18%.

Scheme 66: Synthesis of compounds **266** and **267**.

Compounds **266** and **267** were then subjected to the dethioketalization reaction (**Scheme 67**). Treatment with NBS in aqueous acetone led to no desired product, although replacing NBS with DBDMH gave pyranoses **268** and **269** in good yield.



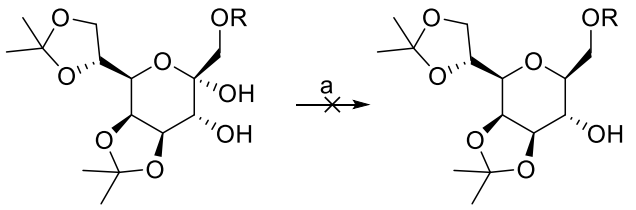
266; R = Ac
267; R = TBDPS

268; R = Ac
269; R = TBDPS

Reagents and conditions: a) DBDMH, 0 ^{o}C, 30 min (66 - 100%, R = Ac), (67%, R =TBDPS).

Scheme 67: Dethioketalization of compounds **266** and **267**.

The next step of the route was the reduction of the anomeric position in **268** and **269** using Gray's conditions (**Scheme 68**).[63] Unfortunately, under these conditions only decomposition of **268** and **269** observed.



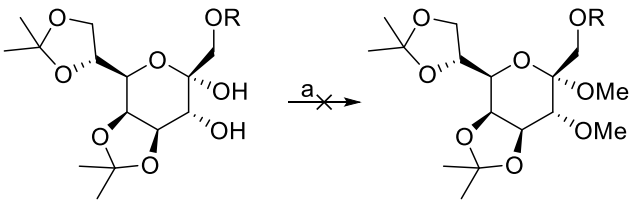
268; R = Ac
269; R = TBDPS

270; R = Ac
271; R = TBDPS

Reagents and condtions: a) TMSOTf, Et_3SiH, MeCN.

Scheme 68: Failed reductions of anomeric centre using Gray's conditions.[63]

As a result, the group opted to methylate the anomeric and C_{-2} hydroxyl groups in **268** and **269** in anticipation that this would aid removal of the anomeric hydroxyl group in the later reduction. However attempted methylations on **268** and **269** only led to decomposition (**Scheme 69**).



268; R = Ac
269; R = TBDPS

272; R = Ac
273; R = TBDPS

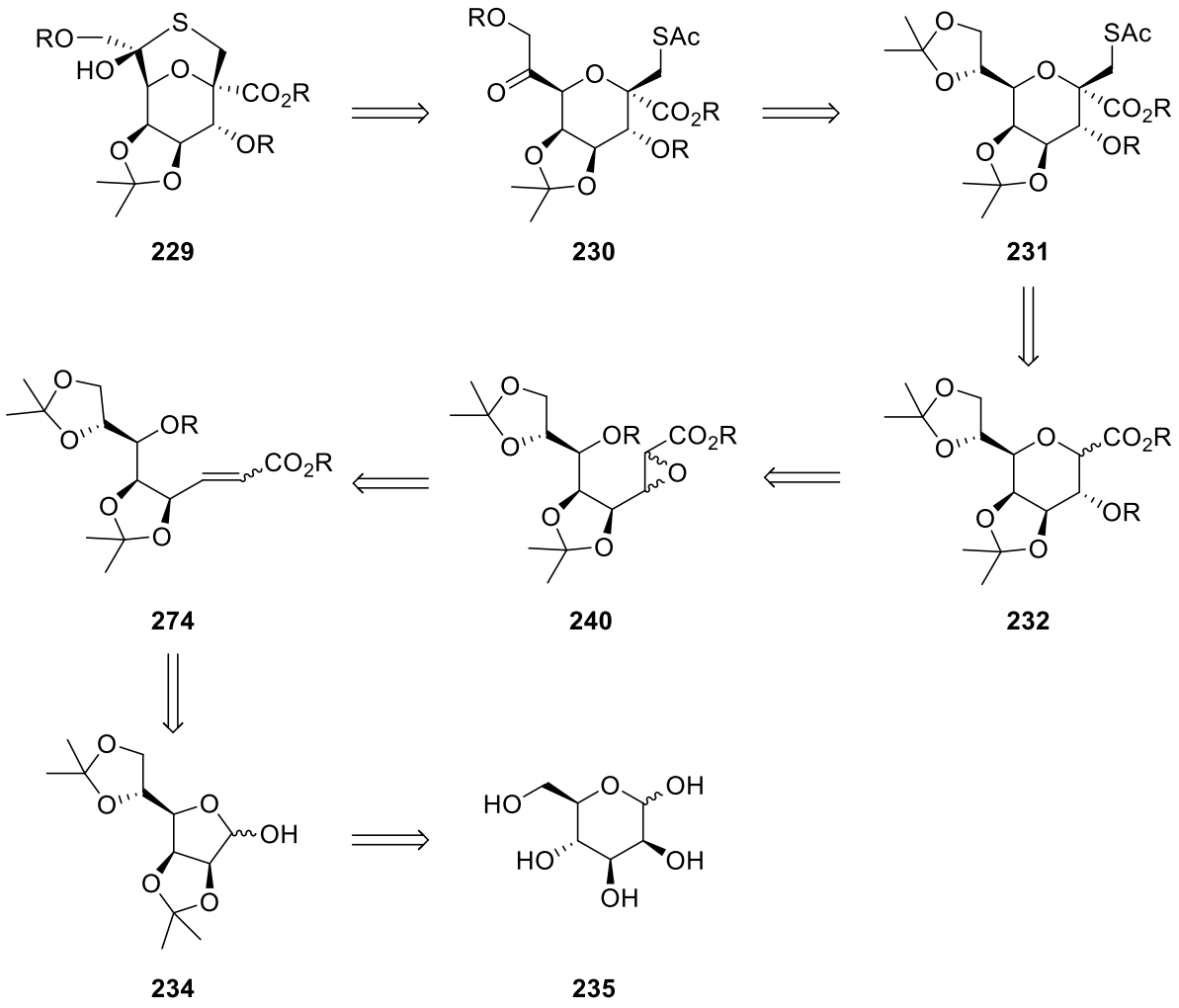
Reagents and condtions: a) NaH, MeI, DMF.

Scheme 69: Failed methylation of compounds **268** and **269**.

The unsuccessful attempted reductions of the anomeric centre and dimethylations steered the group away from the dethioketalization strategy in developing a new route.

Wittig Route

Pearce then opted for a different approach to reach target **229**; this involved a Wittig reaction on DAM to introduce the ester moiety instead of the nucleophilic addition of a deprotonated functionalized dithiane in his previous routes (**Scheme 70**).

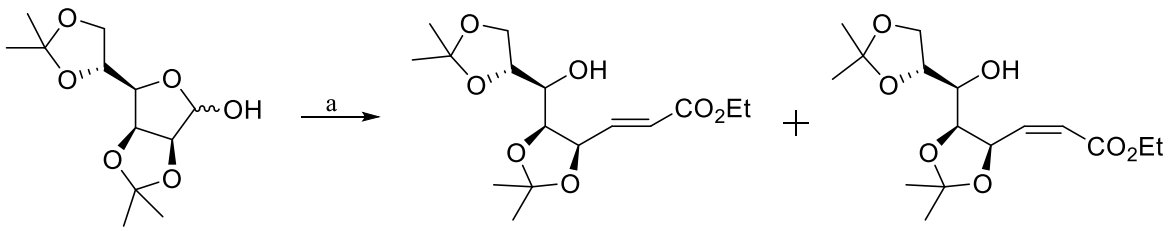


Scheme 70: Retrosynthesis of target structure **229** from DAM **234** in the Wittig route.

As explained in previous routes, target **229** could be derived from **232**. Similarly to the Darzens route performed by Roy,[43] the pyranoid core of **232** could be made by the deprotection of the secondary alcohol in glycidic ester **240** and concomitant 6-*endo*-tet cyclization. Glycidic ester **240** could originate from epoxidation of alkene **274**, which in turn could be made from a Wittig olefination of DAM **234** using an ester-stabilized ylide.

After synthesizing, the ethyl ester-stabilized ylide (from refluxing ethyl bromoacetate and triphenylphosphine in toluene followed by a NaOH wash), the Wittig olefination on DAM was attempted using previously published conditions (**Scheme 71**).[64] Under these conditions, the major *E*-alkene **275** and minor *Z*-alkene **276** products were isolated. The minor *Z*-alkene **276** was

discarded, presumably due to the low yields of the latter (10–20%). Hence, Pearce proceeded to the next step only with *E*-alkene **275**.

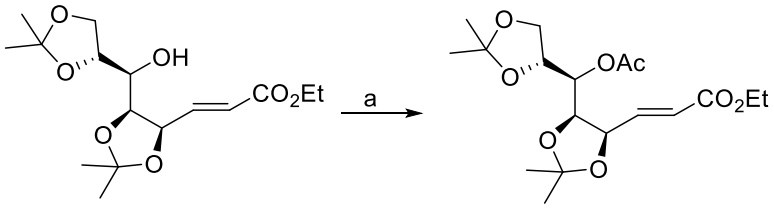


234 **275** **276**

Reagents and conditions: a) Ph_3PCHCO_2Et, toluene, reflux, 1 h, 50-70% **275**, 10-20% **276**.

Scheme 71: Wittig olefination of DAM **234**.

Acetylation of the secondary alcohol in *E*-alkene **275** was then achieved to afford compound **277** (**Scheme 72**).

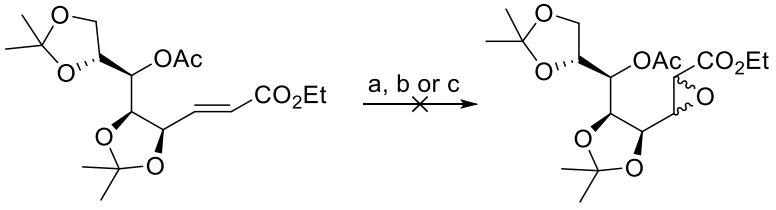


275 **277**

Reagents and conditions: a) Ac_2O, DMAP, Et_3N, DCM, 75%.

Scheme 72: Acetylation of compound **275**.

The group then aimed to synthesize glycidic ester **278** (**Scheme 73**). However, despite trying a range of epoxidation conditions, the glycidic ester was not isolated nor even observed.

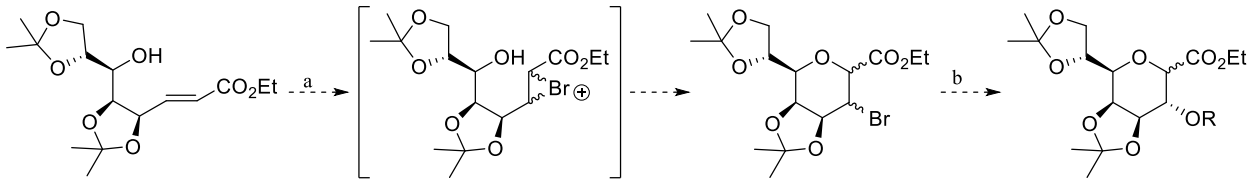


277 **249**

Reagents and conditions: a) Oxone®, MeCN/H_2O 10:1, rt; b) H_2O_2, MeCN/H_2O 1:1, NaOH, rt; c) *t*BuOOH, MeCN/H_2O 1:1, NaOH, rt.

Scheme 73: Failed epoxidations of alkene **277**.

The disappointing epoxidation results, led the group to slightly modify their methodology by devising other cyclization methods (**Scheme 74**). In this new strategy, a bromination on the unprotected *E*-alkene **275** would be performed; this could cause a 6-*endo*-tet cyclization (albeit in competition with the more favourable 5-*exo*-tet cyclization) of the secondary alcohol onto the bromonium ion to afford **279**. Subsequent displacement of the bromine on the C_{-2} with an oxygen nucleophile could afford pyranoid **280**.

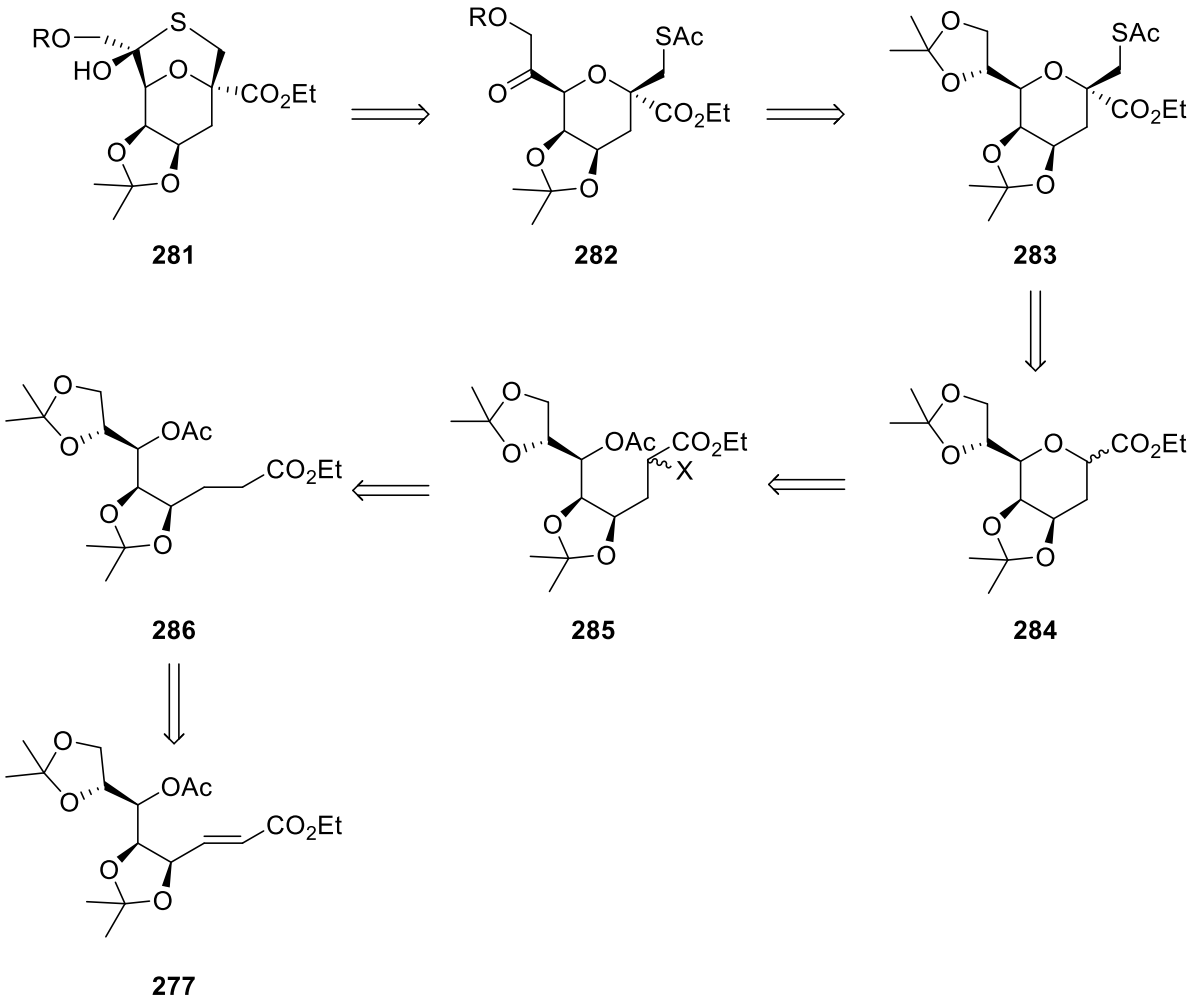


Methodologies: a) Bromination; b) Displacement chemistry.

Scheme 74: Proposed synthetic approach to pyranoid **280**.

Regrettably, the attempted bromination involving the addition of neat bromine to a solution of **275** in DCM at 0 ^{o}C led to a complex mixture, from which neither pyranoid **279** nor the 1,2-dibrominated compound were isolated.

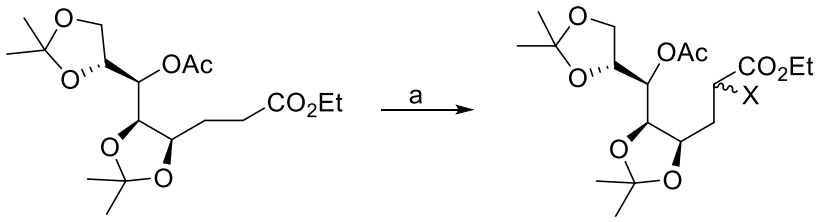
Finally, Pearce planned one last strategy starting from the acetyl-protected alkene **277**, whereby instead of functionalizing the alkene, a reduction would be attempted (**Scheme 75**).



Scheme 75: Retrosynthesis of target structure **281** from alkene **277**.

The only disadvantage of this strategy was the absence of a functionality on the C_{-2} position. If, however, synthetic target **281** was successfully made, however, methods to functionalize the C_{-2} position would be revisited. The retrosynthetic analysis for target **281** from **284** is identical in methodology to the previous target **229** from compound **232** (as mentioned in earlier routes). Compound **284** could be made from alkene **277** in three steps. Alkene **277** could firstly be reduced by a hydrogenation to give compound **286**. Then the ester in **286** could undergo an α-halogenation to form **285**, offering a good leaving group alpha to the ester and thus subsequent cleavage of the acetate group could trigger a 6-*exo*-tet cyclization to afford C-glycoside **284**.

Pearce successfully reduced alkene **277** with hydrogen gas over palladium on carbon to yield **286**. The following α-halogenation of the ester, however, proved difficult (**Scheme 76** and **Table 5**).



286 **285**

Reagents and conditions: a) see **Table 5**.

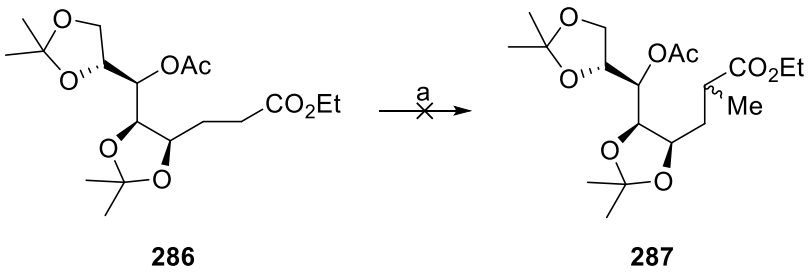
Scheme 76: α-Halogenations of ester **286.**

Entry	Reagents and Conditions	Result
1[65]	I_2, LDA, THF, -78 °C to rt	SM
2	Br_2, LDA, THF, -20 °C to rt	SM
3	Br_2, *t*-BuLi, HMPA, THF, -78 °C to rt	SM
4	I_2, DBU, DCM, rt	SM
5	NBS, NEt_3, DCM, rt	SM
6	NCS, LDA, THF, -78 °C to rt	SM

Table 5: Conditions and results reported for ester α-halogenation attempts of **286**.

Initially the group used Rathke's conditions which involved the use of LDA and iodine as the halogen donor but only starting material was isolated from the reaction (entry 1).[65] The group then tested a variety of other bases and halogen donors (entries 2 to 6), though again only starting material was recovered.

To identify the failure of these ester α-halogenation reactions, the group tried to alkylate **286** with methyl iodide using LDA as the base (**Scheme 77**). This would establish whether the lithium ester enolate of **286** is generated prior to the addition of the halogen donor. Surprisingly, no trace of compound **287** was observed suggesting the lithium ester enolate was not formed.



286 **287**

Reagents and conditions: a) LDA, MeI, THF, -78 ^{o}C to rt.

Scheme 77: Attempted alkylation of ester **286**.

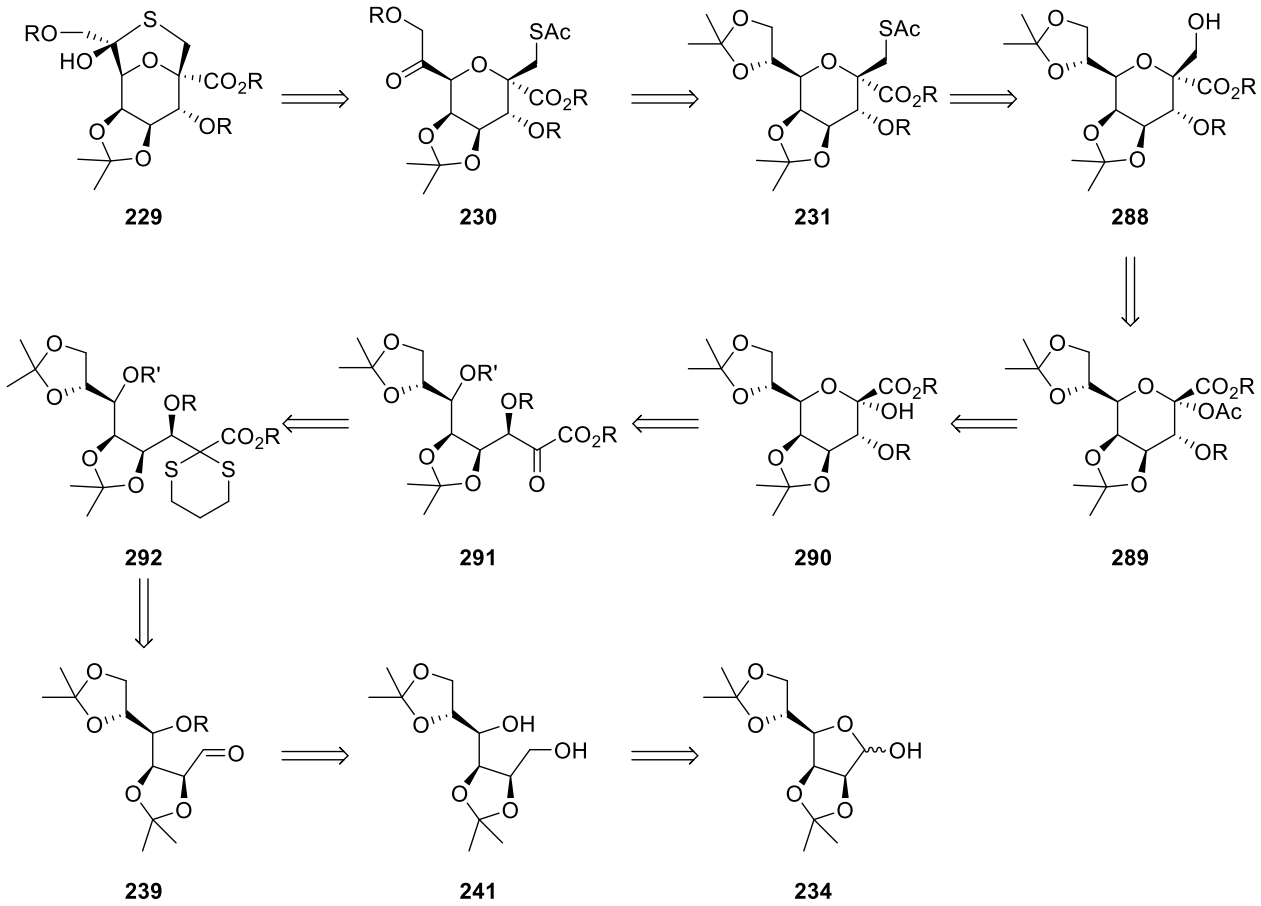
The lack of success in functionalizing alkenes **275** and **277** and incorporating a halide leaving group alpha to the ester in **286**, led to the abandonment of this route.

Mahoney

Following Pearce, Mahoney generally attempted a range of strategies to optimise the dithioacetal route (previously established by Pearce), to improve the route's feasibility and to progress further in the synthesis of the target **229**.[45]

Samarium Diiodide Route

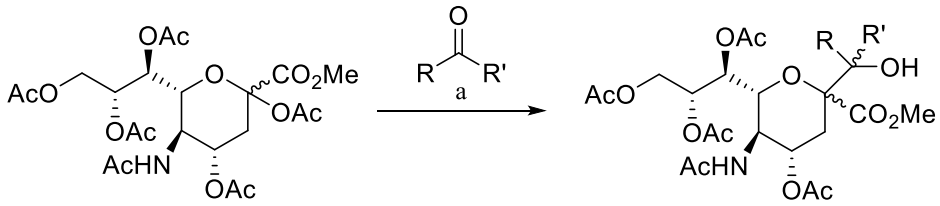
This first route carried out by Mahoney, specifically targeted the main problems encountered by Pearce in the dithioacetal route. These were poor yields, scalability and purification issues in the dethioketalization of compound **252** and the inability to remove the anomeric hydroxyl group from **255** and **256**.[44] It was hoped that in the samarium diiodide route would overcome these problems (**Scheme 78**). This is because the dethioketalization would be attempted on a different compound as compared to the dithioacetal route. Additionally, instead of the reductive cleavage of a methoxy or mesylate group on the anomeric position using a hydride or hydrosilane reductant endeavoured in the dithioacetal route, a samarium diiodide promoted coupling between the anomeric acetate **289** and formaldehyde would be attempted. If this coupling reaction were successful, then the removal of the anomeric oxygen functionality and the introduction of a methylene alcohol group could be achieved in one step.



Scheme 78: Retrosynthesis of target **229** from DAM **234** in the samarium diiodide route.

The retrosynthesis for target **229** from intermediate **231** is identical to previous routes undertaken in the group, for example the Darzens and dithioacetal routes. Intermediate **231** could form by activation of the primary alcohol in **288** followed by a displacement with a thioacetate nucleophile. Using samarium diiodide and a formaldehyde electrophile, alcohol **288** could be made from anomeric acetate **289**, which could be obtained from acetylation of pyranose **290**. The selective deprotection of OR' in the α-ketoester **291** should trigger a 6-*exo*-trig cyclization affording pyranose **290**. The dethioketalization in this route would be attempted on dithioketal **292** to yield compound **291**. Moreover, compound **292** could be formed from the nucleophilic addition of a deprotonated derivative of ethyl 1,3-dithiane-2-carboxylate onto aldehyde **239** followed by the protection of the formed secondary alcohol. The synthesis of aldehyde **239** could be achieved by a sequence of protections and deprotections on diol **241** followed by an oxidation of the primary alcohol. The LAH reduction of DAM using previous conditions in the group,[43] would furnish diol **241**.

The key feature of this route is the samarium diiodide mediated coupling reaction between formaldehyde and compound **289**. This was inspired by Malapelle *et al.* who succeeded in the transformation of the anomeric acetate in their *N*-acetylneuraminic acid derivative to the corresponding alcohol using samarium diiodide and a range of aldehydes and ketones (**Scheme 79**).[66] Malapelle and co-workers proposed that a samarium ester enolate was formed on the anomeric position which then reacted with an aldehyde or ketone electrophile to eventually furnish the resultant alcohols **294**.[66] Mahoney planned to apply this methodology to anomeric acetate **289** with a formaldehyde electrophile.

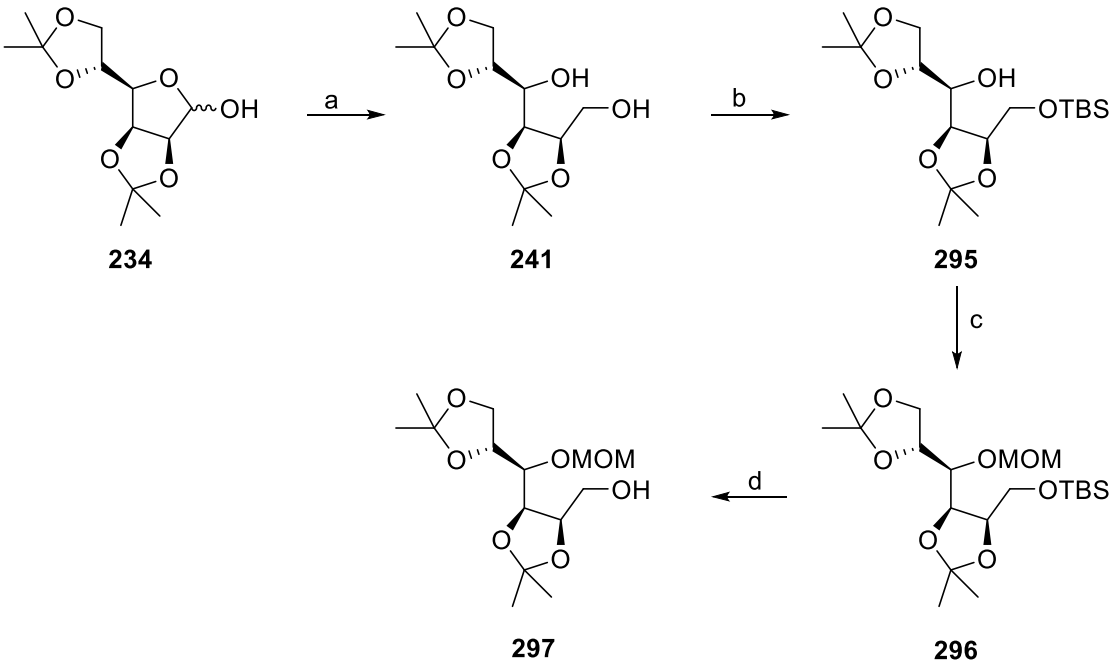


293 **294**

Reagents and condtions: a) SmI_2 (3 equiv.), THF, rt.

Scheme 79: Malapelle and co-workers' synthesis of compounds **294** from **293** using samarium diiodide and a range of aldehydes and ketones.[66]

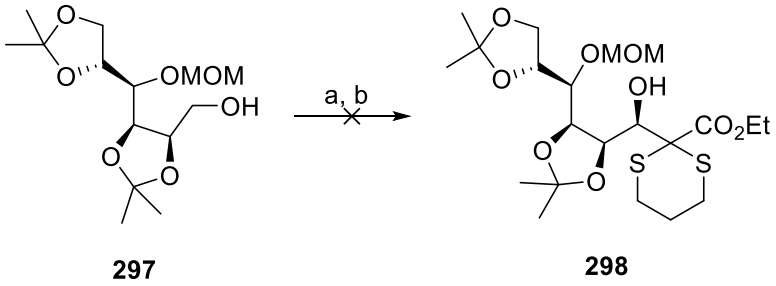
The synthesis began, with the LAH reduction of DAM using previous conditions employed by the group (**Scheme 80**).[43] The following steps comprised of successive selective protections and deprotections of both alcohols to ultimately reach alcohol **297**.



Reagents and condtions: a) LAH, THF, 0 °C to rt, 83%; b) TBSCl, imidazole, DMF, 96%; c) MOMCl, *i*Pr_2Et, DCM, 0 °C, 63%; d) TBAF, THF, 0 °C, 79%.

Scheme 80: Four-step synthesis of compound **297** from DAM **234**.

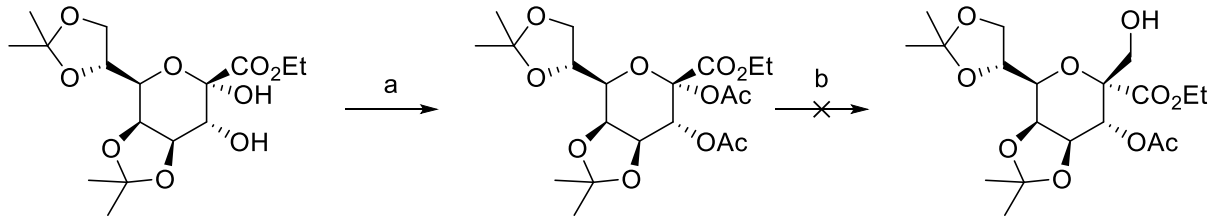
Mahoney, then attempted a Swern oxidation on **297** followed by a nucleophilic addition of the functionalized dithiane derivative (**Scheme 81**), but in the latter step only DAM **234** was isolated. To explain this result, Mahoney proposed that the MOM ether was surprisingly deprotected in these conditions, producing the alkoxide form of the hydroxy aldehyde, which is in equilibrium with DAM **234**.



Reagents and condtions: a) DMSO, $(COCl)_2$, DCM, -78 °C for 2 h, Et_3N, -78 °C to rt; b) LDA, $MgBr_2$, ethyl 1,3-dithiane-2-carboxylate, THF.

Scheme 81: Failed synthesis of **298** from **297**.

Due to this setback, Mahoney decided to form pyranose **254** from DAM **234** in two steps using the same synthesis previously completed by Pearce in the dithioacetal route (**Scheme 59**). Then after acetylating both hydroxyl groups in **254** (**Scheme 82**), Mahoney planned to apply the samarium diiodide methodology on the anomeric acetate **299**. Despite numerous attempts, the group failed to isolate **300** in the presence of samarium diiodide and paraformaldehyde. They attributed this failure to possible poor quality of the commercially available samarium diiodide solution in THF (since they noticed significant degradation over time). Attempts to synthesize their own samarium diiodide solution, however, were unsuccessful.



254 **299** **300**

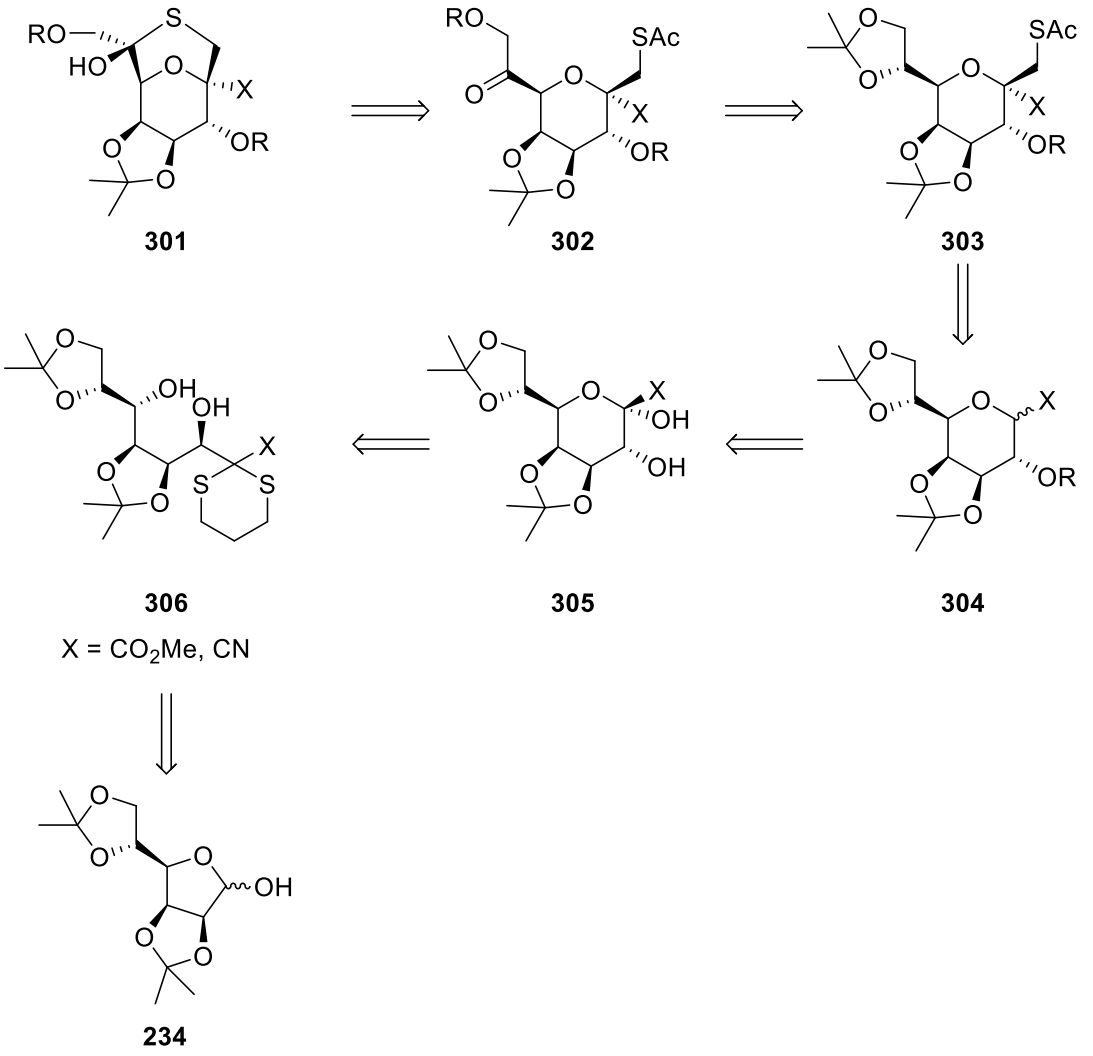
Reagents and condtions: a) Ac_2O, DMAP, Et_3N, DCM, 84%; b) SmI_2, CH_2O, THF.

Scheme 82: Attempted synthesis of **300**.

The failure to couple formaldehyde with **299** using samarium diiodide led Mahoney to investigate alternate strategies to synthesize the tagetitoxin bicyclic core **229**.

Nitrile-Dithiane and Methyl Ester-Dithiane Route

Mahoney's next route was identical to the dithioacetal route performed by Pearce with the exception of having a nitrile or methyl ester instead of an ethyl ester moiety (**Scheme 83**). It was hoped, that this change could improve the yields of the dethioketalization and aid in the removal of the anomeric hydroxyl group in **305**.

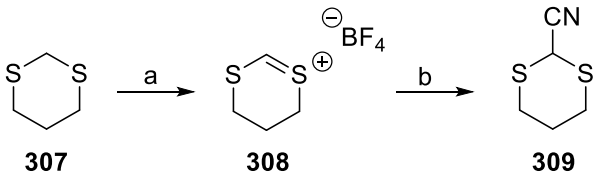


Scheme 83: Retrosynthesis of target **301** from DAM **234** in the nitrile-dithiane and methyl ester-dithiane route.

The retrosynthetic analysis for **301** from DAM **234** is identical in methodology to the retrosynthesis of **229** in the dithioacetal route (the only difference being the nature of the carboxylic acid derivative on the C_{-1} position).

In order to incorporate the nitrile or methyl ester functionality in the target **301**, the functionalized dithiane derivative undergoing nucleophilic addition on DAM would have a nitrile or methyl ester moiety instead of an ethyl ester moiety. Since these particular dithiane derivatives are not commercially available (unlike ethyl 1,3-dithiane-2-carboxylate), the first goal of the route was to synthesize these derivatives.

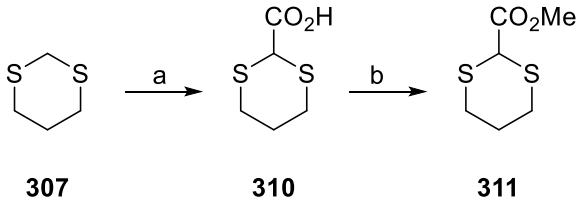
Using conditions previously published by the Page group in the literature,[67] the synthesis of 2-cyano-1,3-dithiane **309** was accomplished in two steps from 1,3-dithiane **307** (**Scheme 84**). The first step involved a hydride abstraction of 1,3-dithiane **307** when treated with triphenylcarbenium tetrafluoroborate in DCM under reflux to furnish salt **308**. Addition of TMSCN to the salt **308** afforded the desired functionalized dithiane **309**.



Reagents and conditions: a) Ph_3CBF_4, DCM, reflux, 45 min;
b) TMSCN, DCM, -20 °C, 1 h, 58% over two steps.

Scheme 84: Two-step synthesis of 2-cyano-1,3-dithiane **309** from 1,3-dithiane **307**

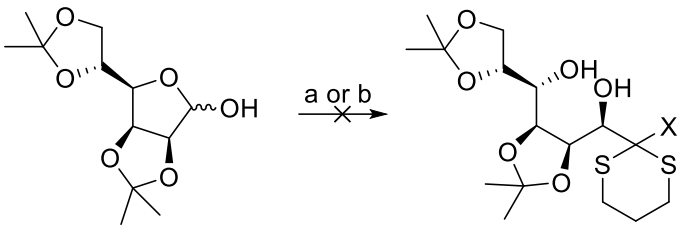
The synthesis of methyl 1,3-dithiane-2-carboxylate **311** was also achieved in two steps from 1,3-dithiane **307** (**Scheme 85)**. This synthesis involved the lithiation of the 1,3-dithiane and ensuing nucleophilic addition onto solid carbon dioxide to furnish carboxylic acid **310** after acidic work-up. This was followed by a Fischer esterification to yield **311**.



Reagents and conditions: a) *n*-BuLi, $CO_{2(s)}$, THF, -78 °C to rt, 68%; b) $HCl_{(g)}$, MeOH, 10 min, 85%.

Scheme 85: Two-step synthesis of ethyl 1,3-dithiane-2-carboxylate **311** from 1,3-dithiane **307**

The next aim of the group was to perform the nucleophilic addition of these functionalized dithiane derivatives **309** and **311** on DAM **234** (**Scheme 86**). Regrettably, under the same conditions used previously to synthesize **252** in the dithioacetal route, compounds **306** were not formed.



234 **306**

X = CO_2Me, CN

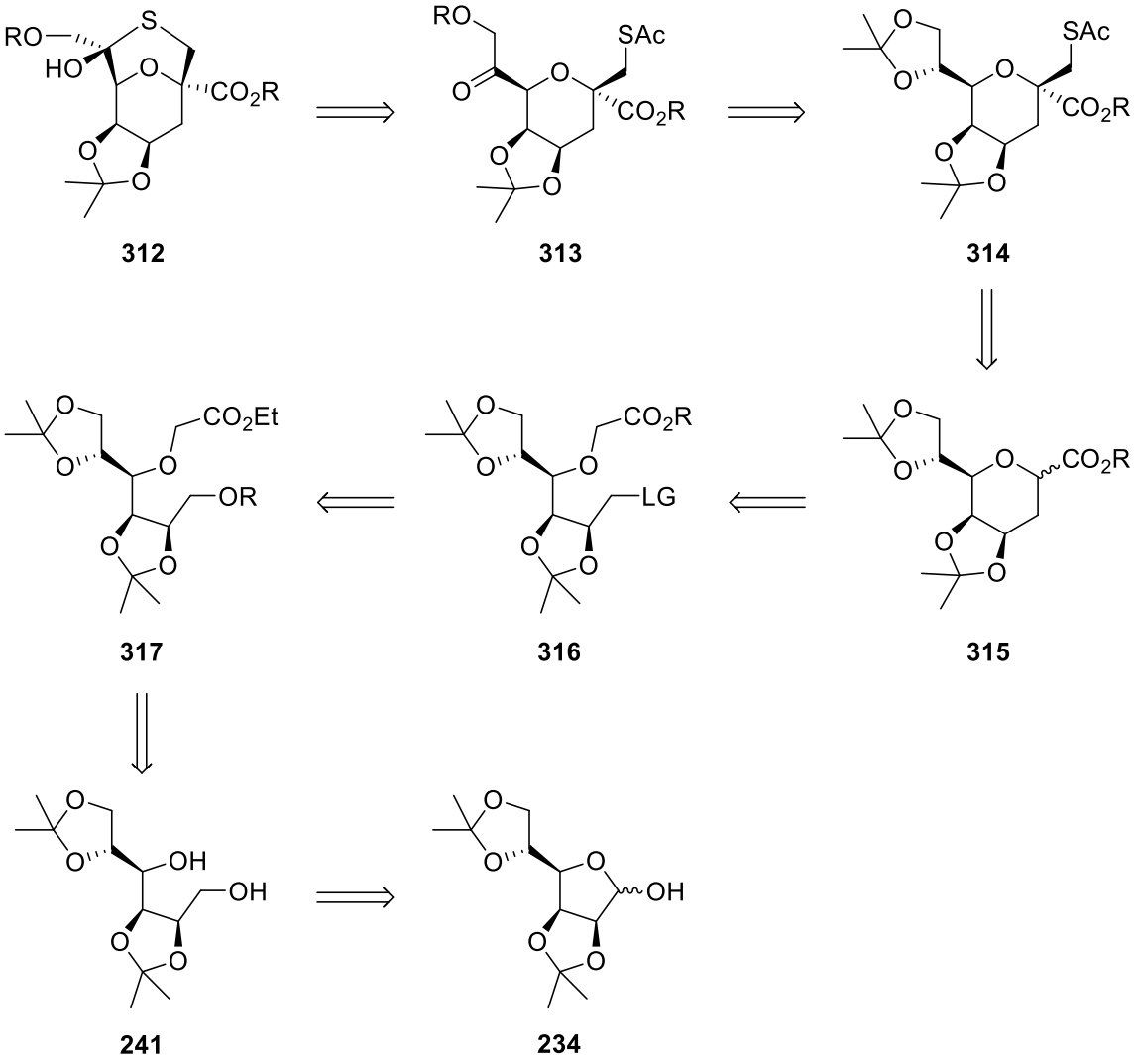
Reagents and conditions: a) 2-cyano-1,3-dithiane **309**, LDA, $MgBr_2$,THF; b) methyl 1,3-dithiane-2-carboxylate **311**, LDA, $MgBr_2$, THF.

Scheme 86: Attempted synthesis of compounds **306**.

These unsuccessful results led Mahoney to devise a new synthetic route away from the dithiane strategy.

KDO Route

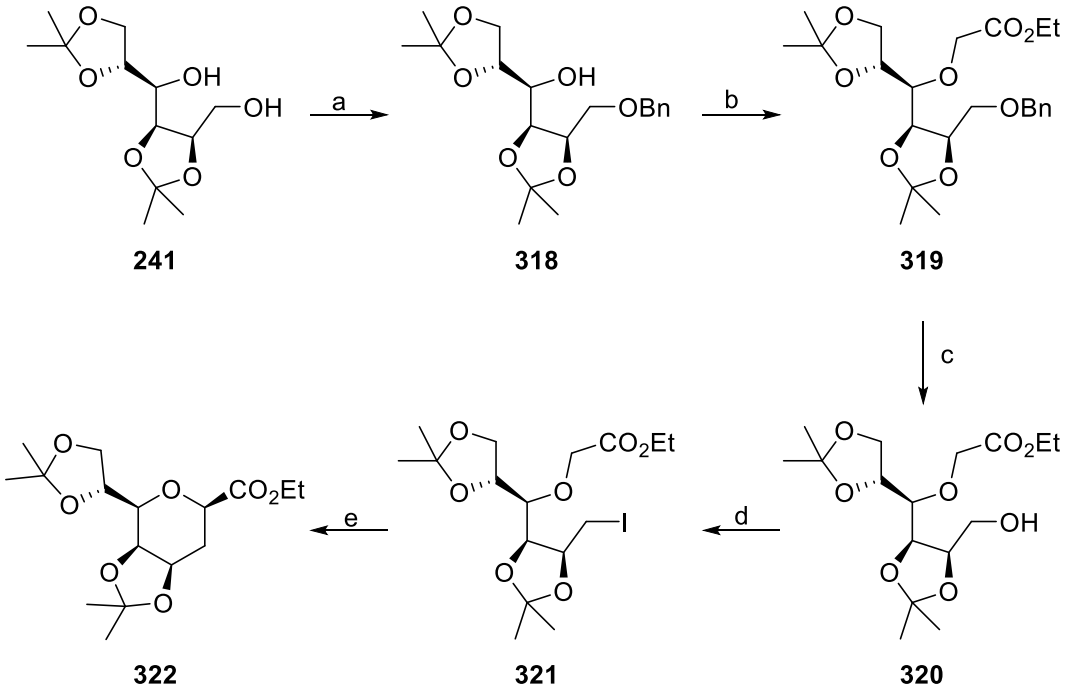
The group devised a new synthesis to target **312** from DAM **234**; although, there would be and absent functionality on the C_{-2} position (**Scheme 87**). If successful, however, this methodology would be revised to install an oxygen functionality on this position.



Scheme 87: Retrosynthesis of target **312** from DAM **234** in the KDO route.

The target bicyclic core **312** could be derived from **315** by the same methodology mentioned in aforementioned earlier routes for **229** from **232**. The pyranoid core **315** could be constructed by the formation of an ester enolate of **316**, which could consequently displace a leaving group in a cyclization reaction. Deprotection of the primary alcohol in **317** and subsequent transformation into a good leaving group (e.g. halide or sulfonate ester) would furnish **316**. The ester moiety would be introduced into the structure by selective protection of the primary alcohol in diol **241** followed by alkylation of the secondary alcohol with an α-halo ester. As already synthesized in the samarium diiodide route and Darzens route, diol **241** would be formed by the LAH reduction of DAM **234** (e.g. **Scheme 80**).

This route was largely inspired by the production of intermediate **322** part of Ohrui and co-workers' synthetic route towards 3-deoxy-D-manno-oct-2-ulosonic acid (KDO).[68] In this route, Ohrui *et al*. made pyranoid **322** from diol **241** in 5 steps using the methodology outlined in the above retrosynthetic analysis (**Scheme 88**).



Reagents and condtions a) NaH, BnBr, DMF, 0 °C to rt, 85%; b) NaH, ethyl bromoacetate, oxolane 0 °C to rt, 78%; c) $Pd(OH)_2$, MeOH, H_2, 97%; d) PPh_3, imidazole, I_2, 0 °C, 77%; e) LDA, oxolane, -75 °C, 84%.

Scheme 88: Ohrui and co-workers' five step synthesis of pyranoid **322** from diol **241**.[68]

Mahoney intended, therefore, to replicate this synthesis to reach pyranoid **322**. Initially, Mahoney was successful in benzylating the primary alcohol in **241** to afford **318** in 90% yield. However, after numerous efforts, the ensuing alkylation with ethyl bromoacetate under Ohrui and co-workers' conditions failed to furnish compound **319**. Attempts to modify the conditions such as varying the amounts of sodium hydride or ethyl bromoacetate proved unsuccessful.

The failure to synthesize ester **319** led Mahoney to discard this route.

Overall, work by the Page Group on the synthesis towards tagetitoxin led to a number of noteworthy intermediates via a range of strategies, and some of these routes will be explored further (described later within this thesis).

Project

Synthetic Target

Despite Aliev *et al*. contesting the proposed tagetitoxin structures **1** – **4** due to inconsistencies with NMR and MS data,[8] the aim of this project was to complete a total synthesis of structures **2a** and **2b** (**Figure 9**).

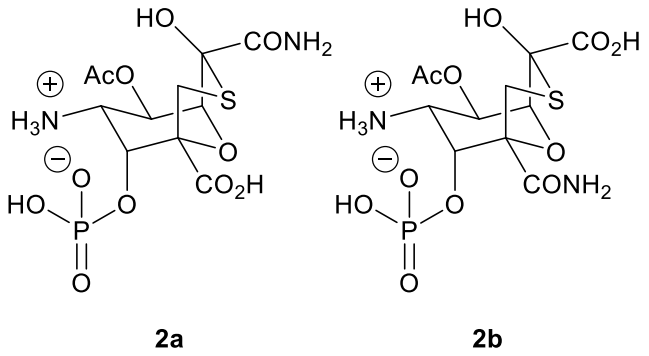


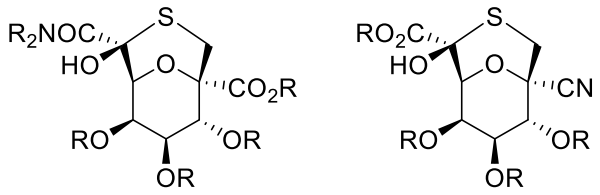
Figure 9: Proposed tagetitoxin structures **2a** and **2b**.

The two significant reasons for synthesizing structures **2a** and **2b** are:

1) Contributing to the debate surrounding the structure of the natural product. There are no published total syntheses of any of the proposed tagetitoxin structures **1** – **5**, and if we were to chemically synthesize structures **2a** and **2b**, their characterization data would be compared with the data collated from Aliev *et al*. This would provide evidence to support or refute the conclusions made in the literature regarding the structure of tagetitoxin.[8]
2) From a synthetic perspective, the large number of complex functionalities in **2a** and **2b**, make these structures interesting and challenging targets.

Complex Functionalities

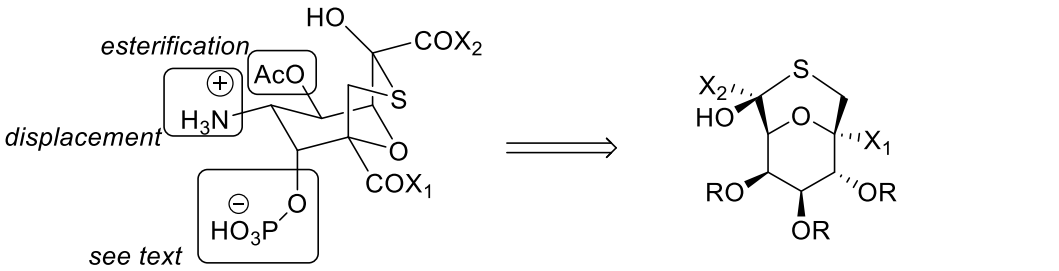
The primary aim of this project was to firstly synthesize intermediates **323a** and/or **323b** (**Figure 10**).



323a **323b**

Figure 10: Ultimate bicyclic targets **323a** and **323b** in project.

Intermediates **323a** and **323b** each contain the bicyclic core of structures **2a** and **2b** as well as key functionalities such as the thiohemiketal and carboxylic acid derivatives. We then envisaged phosphate, amino and acetate functionalities could be incorporated into the bicyclic structures **323a** and **323b** to achieve a total synthesis (**Scheme 89**).



2a; X_1 = OH, X_2 = NH_2
2b; X_1 **=** NH_2, X_2 = OH

323a; X_1 **=** CO_2R, X_2 = $CONR_2$
323b; X_1 = CN, X_2 = CO_2R

Scheme 89: Retrosynthetic analysis of the functional groups on pyranoid core in structures **2a** and **2b**.

The easiest functionality to install in the structure would be the acetate group by simple esterification of a free hydroxyl group on the C_{-4} centre with a range of acetylating agents (e.g. AcCl and Ac_2O) under various conditions.

Incorporation of the amino group would be more challenging since, in addition, the stereochemical configuration of the C_{-3} position has to be inverted. This could be achieved using displacement chemistry; the C_{-3} hydroxyl group could be activated into a good leaving group which could be substituted by an azide nucleophile in S_N2 fashion. The azide moiety could then be reduced into an amino group by a Staudinger reaction or hydrogenation.

The phosphorylation of the C_{-2} hydroxyl group could be achieved by numerous methods with the most common being:

1) Esterification using activated phosphonates (e.g. phosphoric acid chlorides or anhydrides).
2) Esterification using phosphoric acid or a derivative with activating agents such as DCC, trichloroacetonitrile or arylsulfonyl chlorides.
3) Phosphitylation using a phosphoramidite followed by oxidation with a peracid or a peroxide (e.g. mCPBA or H_2O_2).

The order and the methods in which these three functionalities would be selectively installed onto the structure would depend on the type of the protecting groups present on bicyclic structures **323a** and **323b**, in addition to the exact nature of the synthetic route from these compounds to structures **2a** or **2b**. The exact synthetic route would be determined once bicyclic **323a** and/or **323b** was synthesized.

Bicyclic Skeleton

To reach our ultimate bicyclic targets **323a** and **323b** (**Figure 10**), we attempted a variety of routes starting from readily available cyclic sugars such as D-mannose and D-galactose.

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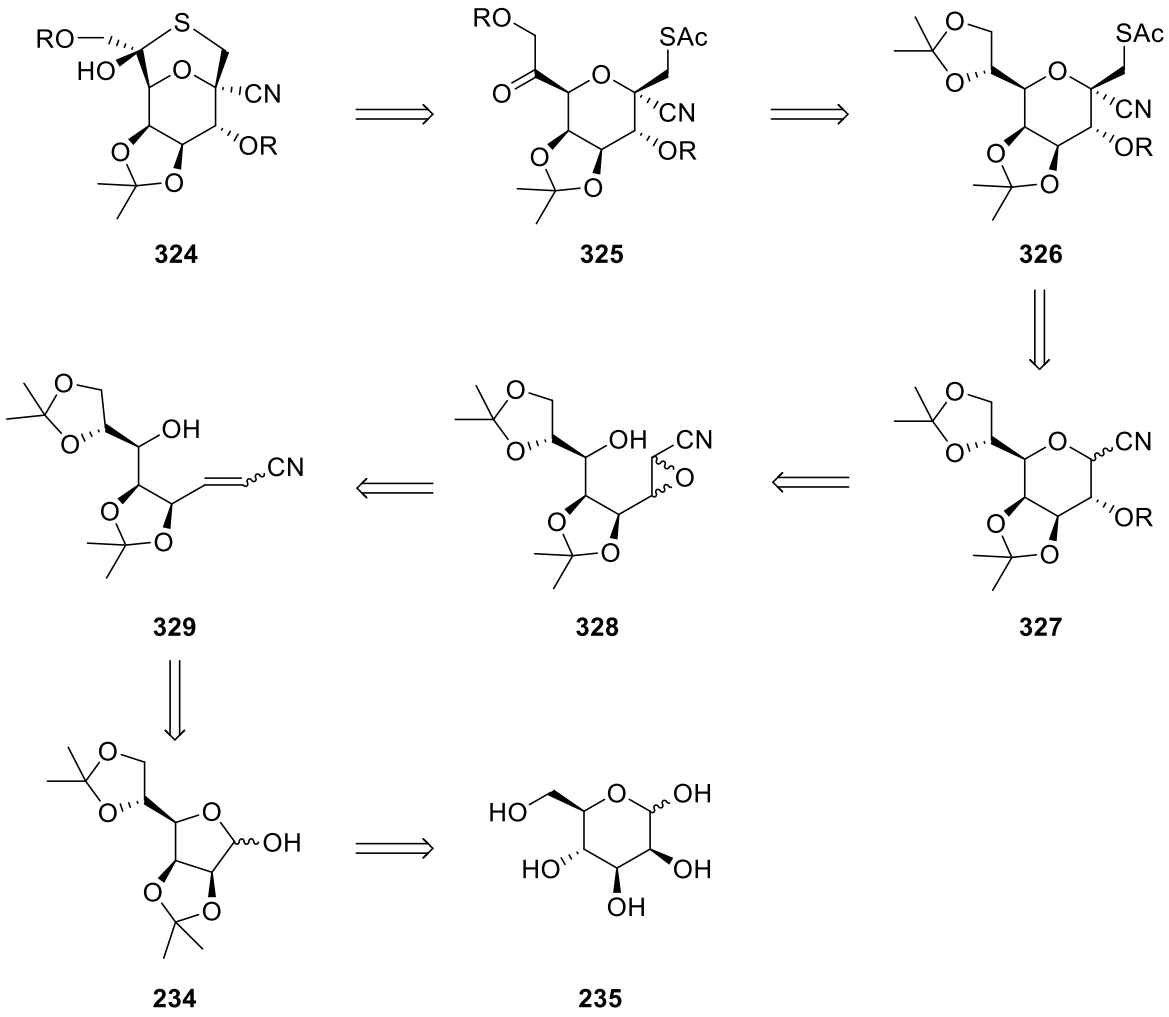
Results and Discussion

Nitrile-Wittig Route

Our first synthetic route was similar to the Wittig route previously performed by Pearce,[1] with the main difference being the presence of a nitrile instead of an ethyl ester functionality (**Scheme 90**).



Scheme 90: Retrosynthesis of target structure **324** from D-mannose in the nitrile-Wittig route.

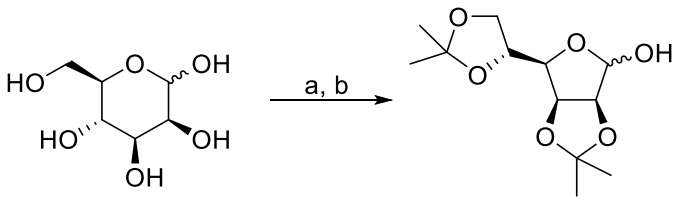
If this route to target **324** were successful, then this strategy would be adapted to incorporate a carboxylic acid derivative alpha to the thiohemiketal centre in order to reach our ultimate bicyclic targets **323a** and **323b**.

As planned in all previous routes from the Page group,[1–3] the synthesis of the 1,4-oxathiane moiety in target **324** is based on the strategy established by Porter and co-workers,[4] involving the

deprotection of the thioacetate moiety in **325** followed by an *in-situ* cyclization of the free thiol/thiolate onto the ketone. Intermediate **325** could be made from the selective hydrolysis of the *exo*-cyclic isopropylidene group in **326**, followed by protection of the primary alcohol and oxidation of the secondary alcohol. The installation of the thioacetyl-methylene moiety in **326** could be achieved in three steps: condensation between the anomeric nitrile anion of **327** with a formaldehyde electrophile would introduce the hydroxyl methylene functional group; activation of the aforementioned hydroxyl into a good leaving group (e.g. halide or sulfonate ester); and displacement of the leaving group with a thioacetate nucleophile. A 6-*endo*-tet cyclization of the hydroxyl group on the epoxide in glycidic nitrile **328** would construct the pyranoid core in **327**. Glycidic nitrile **328** could be formed by an epoxidation of alkene **329**, which in turn could be derived from a Wittig olefination on DAM **234** with a nitrile stabilized ylide. As previously achieved in the Page group, DAM **234** could be synthesized from D-mannose **235** in acetone under acidic catalysis.[1–3]

The key feature of this route is the epoxidation of alkene **327**. Since the alcohol in alkene **327** is not protected, we were hopeful that during the epoxidation step, the intramolecular 6-*endo*-tet cyclization (although in competition with the faster 5-*exo*-tet cyclization) in glycidic nitrile **328** would occur to form pyranoid **329**. If successful, pyranoid **329** could be reached potentially in at least two steps less than if we protected the hydroxyl group prior to the epoxidation, as carried out previously by Pearce in the Wittig route.[1]

The project began with the synthesis of DAM **234** from D-mannose **235** in 92% yield using conditions established from earlier work in the Page group (**Scheme 91**).[1–3] As discovered previously, this procedure did not afford 100% of a single anomer; though this was not important since the subsequent Wittig reaction only involves the ‘open’ hydroxy-aldehyde form of DAM **234** (thus negating the stereochemistry on the anomeric position).

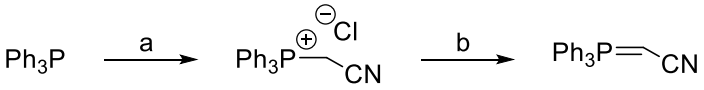


235 **234**

Reagents and conditions: a) H_2SO_4, Acetone, overnight; b) Na_2CO_3, activated charcoal, reflux, 2h, 92%.

Scheme 91: Synthesis of DAM **234** from D-mannose **235**.

Before the Wittig reaction could be attempted, the nitrile stabilized ylide **332** had to be synthesized in two steps from triphenylphosphine **330**; this was achieved using conditions from Aitken *et al*.[5] Firstly, the phosphonium chloride salt **331** was synthesized in 91% yield via displacement chemistry using triphenylphosphine and chloroacetonitrile in ethyl acetate under reflux (**Scheme 92**). The ylide **332** was then isolated in 74% yield by deprotonation of the phosphonium ion with a triethylamine base.

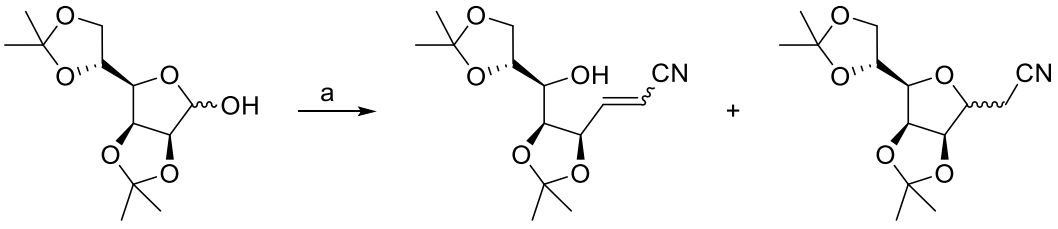


330 **331** **332**

Reagents and conditions: a) chloroacetonitrile, EtOAc, reflux, 3h, 91%; b) Et_3N, DCM, 30 mins, 74%.

Scheme 92: Two-step synthesis of ylide **332** from triphenylphosphine.

The Wittig reaction between stabilized ylide **332** and DAM **234** was then carried out (**Scheme 93** and **Table 6**).



234 **329** **333**

Reagents and conditions: a) Ph_3P=CHCN (1.1 equiv.), solvent, reflux, 24 h. See **Table 6**.

Scheme 93: Wittig olefination attempts on DAM **234**.

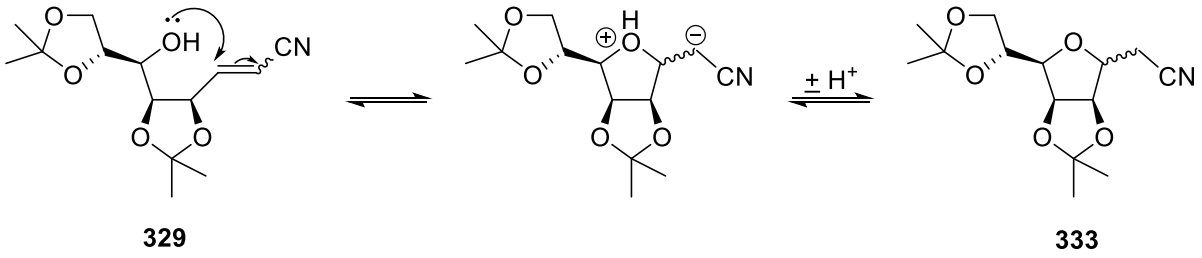
Entry	Solvent	Result [a]
1	THF	77% SM, 18% **333** (**β**:**α**, 63:37)
2	MeCN	46% SM, 45% **333** (**β**:**α**, 2:1)
3	Toluene	26% SM, 66% **333** (**β**:**α**, 2:1)

[a] The number of moles of recovered DAM **234** and C-glycosides **333** in the inseparable mixture were calculated from molar ratios observed in the ^{1}H NMR spectrum.

Table 6: Conditions and results reported for the attempted Wittig olefinations of DAM **234**.

We initially tried standard conditions, whereby DAM **234** and the ylide **332** were heated under reflux in THF, MeCN or toluene for 24 h (entries 1 to 3). In each case, TLC appeared to indicate no change during the reaction. After work-up and purification by column chromatography, an inseparable mixture of starting material DAM **234** and C-glycosides **α**- and **β**-**333** was isolated (explaining why no change appeared on TLC).

The formation of C-glycosides **333** does at least indicate that the Wittig reaction was successful in synthesizing alkenes **329**. This is because compounds **333** were probably formed from a 5-*exo*-trig conjugate addition in alkenes **329** (**Scheme 94**).



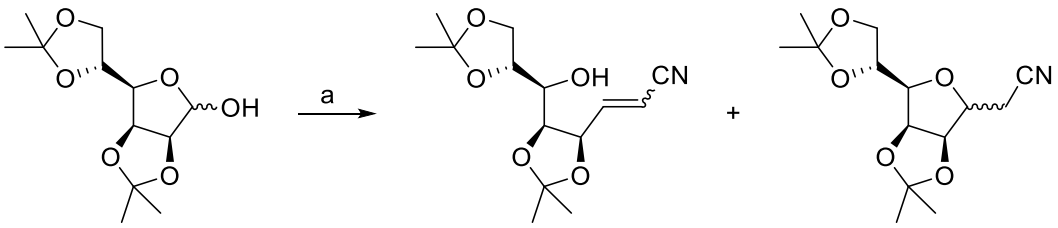
329 **333**

Scheme 94: Proposed mechanism for the synthesis of C-glycosides **333**.

The conversion of DAM **234** was fairly poor in all the Wittig attempts, but it did increase upon changing solvent from THF to MeCN to toluene (possibly due to the higher temperatures at which these solvents reflux at). Longer reaction times, though, made no significant difference in conversion.

As a result, alternative methods were sought to synthesize alkenes **329**. We envisaged the use of the Horner-Wadsworth-Emmons olefination (HWE) on DAM **234**, though the more basic

conditions in this reaction would even more likely promote the conjugate addition. Nevertheless, an HWE reaction with diethyl cyanomethylphosphonate was attempted (**Scheme 95** and **Table 7**).



234 **329** **333**

Reagents and conditions: a) see **Table 7**.

Scheme 95: HWE olefination attempts on DAM **234**.

Entry	Reagents and Conditions	Result
1	Diethyl cyanomethylphosphonate, *t*-BuOK (1.5 equiv.), THF, 0 °C, 30 mins, then DAM **234**, 0 °C to rt, overnight	98% **333** (**β**:**α**, 3:1)
2[a]	Diethyl cyanomethylphosphonate, K_2CO_3 (1 equiv.), THF, rt 30 mins, then DAM **234**, overnight	81% SM, 11% **333** (**β**:**α**, 66:34)

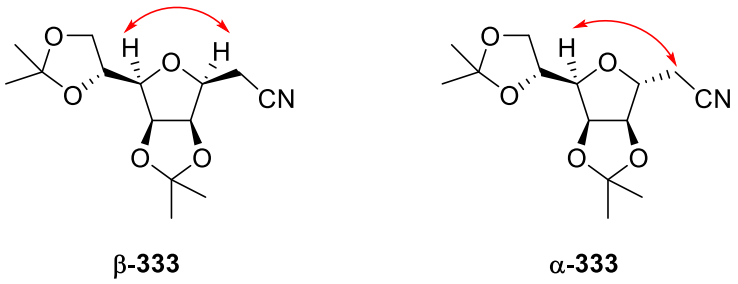
[a] The number of moles of recovered DAM **234** and C-glycosides **333** in the inseparable mixture were calculated from molar ratios observed in the ^{1}H NMR spectrum.

Table 7: Conditions and results reported for the attempted HWE olefinations of DAM **234**.

Unsurprisingly, when using common conditions (entry 1) only C-glycosides **333** were observed. With the goal of making the conditions less basic to suppress any conjugate additions, we replaced potassium *tert*-butoxide with the weaker base potassium carbonate (entry 2). These milder conditions, however, only caused a decrease in yield of the C-glycosides **333 (**because of a lower conversion of DAM **234**).

The C_{-1} stereochemistry in C-glycosides **α-333** and **β-333** were assigned from NMR analysis. For example, the lower ^{13}C chemical shift of C_{-1} in **β-333** (76.9 ppm) compared to **α-333** (80.3 ppm) signifies a *cis* relationship between the substituents on the C_{-1} and C_{-2} positions.[6,7]

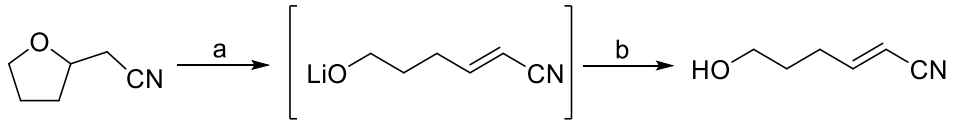
Furthermore, the small vicinal coupling constant between the H-C_{-1} and H-C_{-2} ($^3J_{1,2}$) in **α-333** (1.3 Hz) suggests that these protons have a *trans* relationship.[8] Finally from the NOESY spectra, there was a significant nOe between H-C_{-1} and H-C_{-4} in **β-333**, suggesting a *cis* relationship. This was unlike **α-333** where such a nOe was not observed (**Figure 11**). Additionally, in contrast to **β-333**, a nOe was observed between the methylene protons of the CH_2CN moiety and H-C_{-4} in **α-333**, which suggests a *cis* relationship.



β-333 **α-333**

Figure 11: NOESY analysis to assign stereochemistry at the C_{-1} position in β-**333** and α-**333**.

The failure of the Wittig and HWE olefinations, led us to investigate alternative strategies to synthesize alkene **329**. This led us to attempt a retro-Michael reaction of the C-glycosides **333**, which was inspired by the research conducted by Fleming *et al.*[9] In this work, Fleming and co-workers performed a retro-Michael reaction (i.e. a β-elimination of the ring oxygen) on a variety of compounds including **334** (**Scheme 96**).



334 **335**

Reagents and conditions: a) LDA (2 equiv.), THF, -78 °C, 5 min; b) AcOH, - 78 °C to rt, 67%.

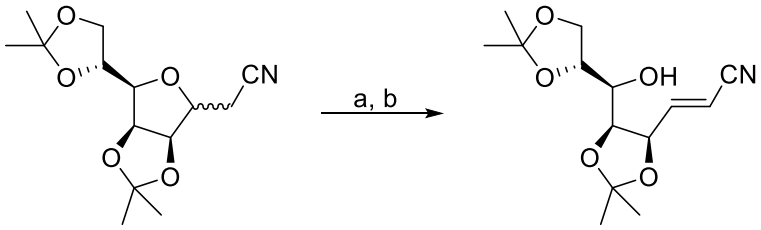
Scheme 96: Retro-Michael reaction on **334** by Fleming *et al.*[9]

The authors attributed the success of the reaction to three specific features of the conditions:

1. Use of a strong lithium base (i.e. LDA).
2. Low concentrations of **334** in THF (0.0018 M).
3. Shortest possible reaction time.

Using a lithium base will lead to the formation of a lithium alkoxide intermediate. The authors stated that the interaction between the lithium and the oxygen in this intermediate is strong enough to suppress unwanted intramolecular and intermolecular conjugate additions to the nitrile functionality, which could otherwise trigger an unwanted polymerization.[9] The low concentration and short reaction time would additionally help to suppress conjugate additions and thus polymerizations.

We therefore applied this retro-Michael methodology to C-glycosides **333** (**Scheme 97**).



333 ***E*-329**

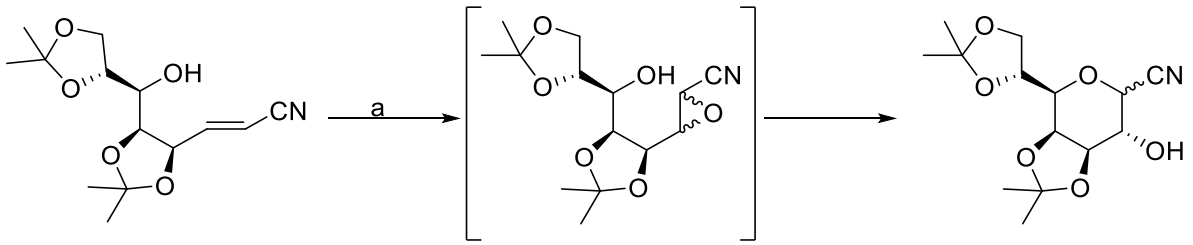
Reagents and conditions: a) LDA (3 equiv.), THF, -78 °C; b) HOAc, -78 °C to rt, 56%.

Scheme 97: Synthesis of alkene ***E*-329** by a retro-Michael reaction on **333**.

To our delight, the reaction did afford alkene ***E*-329** in yields of up to 56% after optimization. The high vicinal coupling constant between the alkene protons (16.2 Hz) indicated the *E*-stereochemistry of the formed double bond. The *Z*-alkene was also formed in the reaction but could not be isolated pure from column chromatography as it co-eluted with a number of other compounds and was thus discarded. The reaction was stereoselective towards the *E*-alkene, since analysis from the ^{1}H NMR spectrum of the crude material showed that the *E*:*Z* ratio always varied from 68:32 to 76:24.

The required low concentrations of **333** in THF provided practical and scalability issues. Increasing the concentration to 0.02 M had no effect on yield, though any further increase led to a 0% yield of ***E*-329** possibly due to decomposition or polymerization.

With alkene ***E*-329** in hand, we proceeded with the epoxidations using a range of conditions from the literature (**Scheme 98** and **Table 8**).



329 **328** **336**

Reagents and conditions: a) see **Table 8**.

Scheme 98: Epoxidation attempts on alkene **329**.

Entry	Reagents and Conditions	Product(s)
1[10]	H_2O_2 (35% wt. in H_2O), NaOH (6M/H_2O, 0.83 equiv.), 0 ^oC to rt, MeOH, 3 h	**333**
2	H_2O_2 (35% wt. in H_2O), NaOH (2M/H_2O, 0.83 equiv.), 0 ^oC to rt, MeOH, 3 h	**333**
3[11]	NaOCl (from bleach), MeCN, rt, 2 h	**333**
4[12]	mCPBA, K_2CO_3, DCM, rt, 48 h	SM
5[13]	H_2O_2 (35% wt. in H_2O), MeCN, 0 ^oC to rt, overnight	SM
6[14]	Oxone, $NaHCO_3$, 10:1 MeCN:H_2O, 0 ^oC, 48 h	SM
7	Oxone, $NaHCO_3$, 10:1 MeCN:H_2O, 0 ^oC to rt, 48 h	SM, **333**

Table 8: Conditions and results reported for the attempted epoxidations of alkene **329**.

We initially tried a standard nucleophilic epoxidation with hydrogen peroxide and sodium hydroxide in methanol, but only C-glycosides **333** were observed (entry 1). This suggests that, under these oxidizing conditions, deprotonation and intramolecular conjugate addition of the hydroxyl group in **329** were favoured compared to the desired nucleophilic attack of the perhydroxyl anion onto the alkene. Consequently, our next epoxidation attempt was carried out under less basic conditions, by repeating our initial entry with the exception of using the more dilute 2 M aqueous NaOH instead of 6 M (entry 2); we hoped that under these less basic conditions, the epoxidation would be preferred to the intramolecular conjugate addition. Once again, however, only compounds **333** were recovered. The same result occurring in an alternative

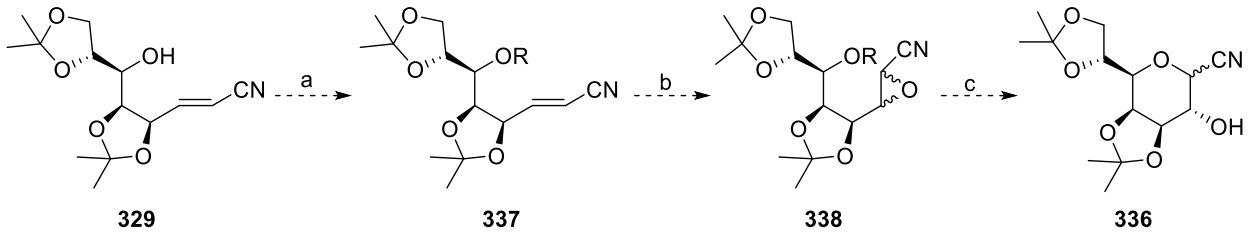
nucleophilic epoxidation using sodium hypochlorite (entry 3), prompted us to try electrophilic epoxidations.

Epoxidation using *m*CPBA only led to recovery of starting material (entry 4), possibly because of the alkene not being reactive enough as it too electron-deficient. We therefore next tested a more powerful electrophilic oxygen *trans*fer reagent by using hydrogen peroxide in acetonitrile (entry 5), which should trigger the formation of the more reactive peroxyimidic species,[15] but again only starting material was observed.

Finally, using a slightly modified procedure from the literature,[14] we tried epoxidations using oxone. Although this initially led to only starting material being recovered (entry 6). Upon increasing the temperature from 0 ^{o}C to rt, however, starting material and compound **333** were isolated (entry 7). This suggests that the electron-deficient nature of the alkene in **329** makes it too unreactive with the peroxymonosulfate anion of oxone, leading to the base promoted conjugate addition being more favoured over the epoxidation.

We concluded that no nucleophilic epoxidations under basic conditions could occur without triggering the intramolecular conjugate addition, while all electrophilic epoxidations failed, presumably to do with the poor nucleophilicity of the electron-deficient alkene.

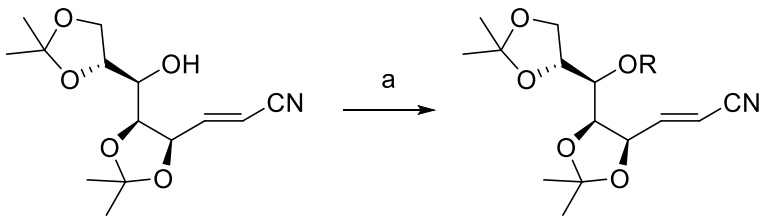
As a result, we planned to protect the hydroxyl group in **329** and only then perform the nucleophilic epoxidation, since this would prevent the intramolecular conjugate addition happening under basic oxidizing conditions. This strategy would differ from that first envisaged, since the epoxidation step would now lead to the O-protected epoxide **338** (**Scheme 99**). The removal of the protecting group under basic conditions would hopefully cause a concomitant 6-*endo*-tet cyclization to give pyranoid **336**.



Methodologies: a) protection; b) epoxidation; b) basic deprotection.

Scheme 99: Proposed synthetic approach to pyranoid **336** from alkene **329**.

We opted to protect the free hydroxyl group in **329** with a silyl and benzoyl group. Surprisingly, this protection step proved much more challenging than initially anticipated (**Scheme 100** and **Table 9**).



329 **339**; R = IPDMS
340; R = Bz

Reagents and conditions: a) see **Table 9**.

Scheme 100: Protection of alkene **329**.

Entry	R	Reagents and Conditions[a]	Products
1[16]	TIPS	Alkene **329**, DCM, Imidazole (2 equiv.), TIPSCl (2 equiv.), DMAP (0.2 equiv.), 72 h	SM
2	TBS	Alkene **329**, DCM, Imidazole (2 equiv.), TBSCl (2 equiv.), DMAP (0.2 equiv.), 72 h	SM
3	TBS	Alkene **329**, DCM, 2,6 – lutidine (3 equiv.), TBSOTf (2.5 equiv.), 72 h	SM
4	IPDMS	Alkene **329**, DCM, Imidazole (2 equiv.), IPDMSCl (2 equiv.), DCM, 24 h	82% **339**
5[17]	Bz	Alkene **329**, DCM, Et_3N (2 equiv.), BzCl (2 equiv.), DMAP (0.2 equiv.), 24 h	81% **333**
6	Bz	DCM, BzCl (2 equiv.), Et_3N (2 equiv.), DMAP (0.2 equiv.), Alkene **329**, 24 h	52% **340**, 21% SM, 17% **333**
7	Bz	DCM, BzCl (3.3 equiv.), Et_3N (4.4 equiv.), DMAP (0.2 equiv.), Alkene **329**, 24 h	quant. **340**

[a]Addition order as reported, temperature: 0 ^oC to rt.

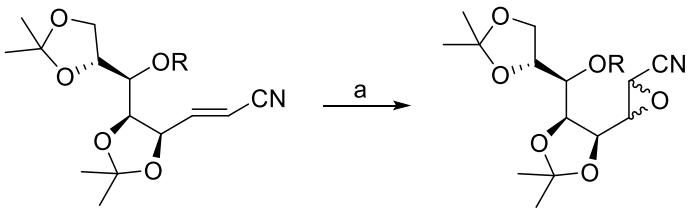
Table 9: Conditions and results reported for the attempted silyl ether- and benzoyl- protections of alkene **329**.

Using a slightly modified procedure from Trost,[16] we failed to protect the alcohol with a TIPS group, only starting material was recovered despite the long reaction time and the presence of the nucleophilic catalyst DMAP (entry 1). Given that the alcohol in **329** is secondary and surrounded by fairly bulky substituents, we attributed this failure to steric factors. We therefore tried to protect the alcohol with the smaller TBS group (entries 2 and 3). Yet, using TBSCl (entry 2) or even the more electrophilic TBSOTf (entry 3) did not make any difference. We were, however, successful in protecting the alcohol with the less bulky IPDMS group affording alkene **340** in 81% yield (entry 4). The success of the IPDMS protection provides further support to steric factors accounting for the failure of the TBS and TIPS protections.

Furthermore, we found that the order of addition of reagents was vital for the benzoylations. For example, under typical conditions from the literature,[17] when the triethylamine base was added to alkene **329** before benzoyl chloride and DMAP, only the cyclization products **333** were isolated (entry 5). However, when modifying the addition order (by adding alkene **329** to a solution of triethylamine, benzoyl chloride and DMAP), the desired benzoyl-protected alkene **340** was produced in various yields (entries 6 and 7) and the conjugate addition side-reaction reduced. In entry 5, the alkene was in a basic solution prior to the addition of the electrophile and nucleophilic catalyst. This meant that the conjugate addition was probably already triggered before the electrophile and nucleophile catalyst were even added. This was not the case in entries 6 and 7 because the alkene was never in a basic solution in the absence of the electrophile and DMAP catalyst. Once finding optimal conditions (e.g. addition order as well as equivalents of triethylamine and benzoyl chloride) this reaction did proceed smoothly in high yields of up to 85% of **340** with no sign of the unwanted intramolecular conjugate addition (entry 7).

Interestingly, in contrast to the benzoylations, the order of addition of reagents was not significant in the silyl ether protections. A possible reason for this could be due to imidazole and 2,6-lutidine being weaker bases than triethylamine; alkene **329** would thus be more likely to undergo a base-promoted intramolecular conjugate addition in the presence of triethylamine rather than 2,6-lutidine or imidazole.

Having successfully obtained protected derivatives **339** and **340**, our next goal was to form epoxides **341** and/or **342** (**Scheme 101** and **Table 10**).



339; R = IPDMS
340; R = Bz

341; R = IPDMS
342; R = Bz

Reagents and conditions: a) see **Table 10.**

Scheme 101: Epoxidation attempts on alkenes **339** and **340**.

Method	R	Reagents and Conditions [a]	Product
1[10]	IPDMS, Bz	H_2O_2 (35% wt. in H_2O), 6M NaOH (0.83eq), MeOH, 48 h	SM
2	IPDMS, Bz	*t*-BuOOH (70% wt. in H_2O), 6M NaOH (0.83eq), MeOH, 48 h	SM
3	IPDMS	H_2O_2 (35% wt. in H_2O), 6M NaOH (1eq), MeOH, 72 h	SM
4	IPDMS	*t*-BuOOH (70% wt. in H_2O), 6M NaOH (1eq), MeOH, 72 h	SM
5	Bz	H_2O_2 (35% wt. in H_2O), 6M NaOH (1eq), MeOH, 72 h	**329**
6	Bz	*t*-BuOOH (70% wt. in H_2O), 6M NaOH (1eq), MeOH, 72 h	**329**
7[11]	IPDMS, Bz	NaOCl (from bleach), MeCN, 72 h [b]	SM

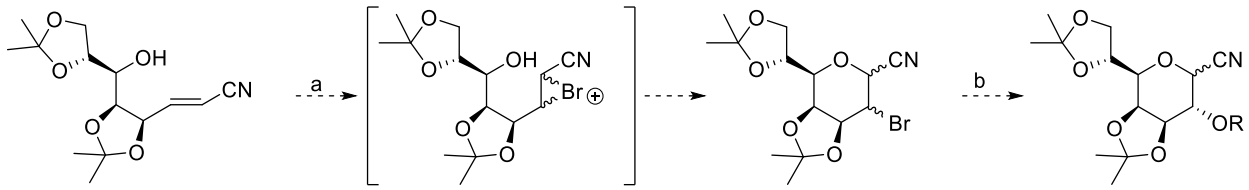
[a] temperature: 0 °C to rt; [b] room temperature.

Table 10: Conditions and results reported for the attempted epoxidations of alkene **339** and **340**.

We first attempted standard nucleophilic epoxidation conditions on the benzoyl- and IPDMS-protected alkenes with hydrogen peroxide and *tert*-butylperoxide (methods 1 and 2). Regrettably, neither set of conditions with each alkene furnished the desired epoxides, as only starting material was recovered. This influenced us to use more basic conditions by increasing the number of equivalents of sodium hydroxide (methods 3 – 6). While only starting material was recovered for the IPDMS-protected alkene **339** (methods 3 and 4), these stronger basic conditions did lead to the benzoyl ester being cleaved, yielding the unprotected alkene **329**

(methods 5 and 6). Further attempts were made using sodium hypochlorite (entry 7), though for each alkene **339** and **340** only starting material was recovered.

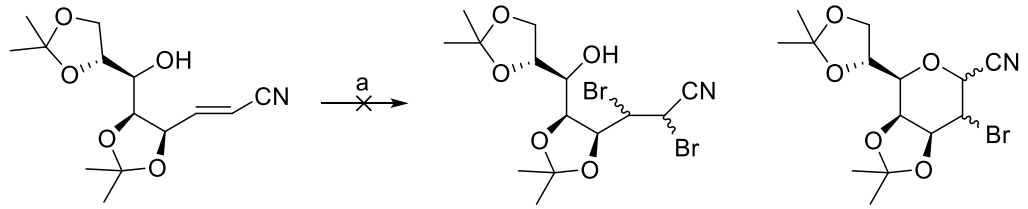
Confronted with these disappointing epoxidation results, we devised an alternative strategy to pyranoid **327**. In this strategy, we would directly brominate alkene **329** to form a bromonium ion intermediate **343** which could then undergo an intramolecular 6-*endo*-tet cyclization (but competing with an undesired faster 5-*exo*-tet cyclization) to afford compound **344** (**Scheme 102**). Displacement of the bromine with a nucleophilic oxygen species would then form pyranoid **327**. This methodology was identical to the approach followed by Pearce in the Wittig route (**Scheme 72**) with the only difference being the presence of a nitrile rather than an ethyl ester.[1]



Methodologies: a) Brominaton b) Displacement chemistry

Scheme 102: Proposed bromination strategy to pyranoid **327**.

Unfortunately, when subjected to standard bromination conditions, neither pyranoid **344** nor even the 1,2-dibrominated compound **345** were detected; only decomposition of the starting materials was observed (**Scheme 103**).

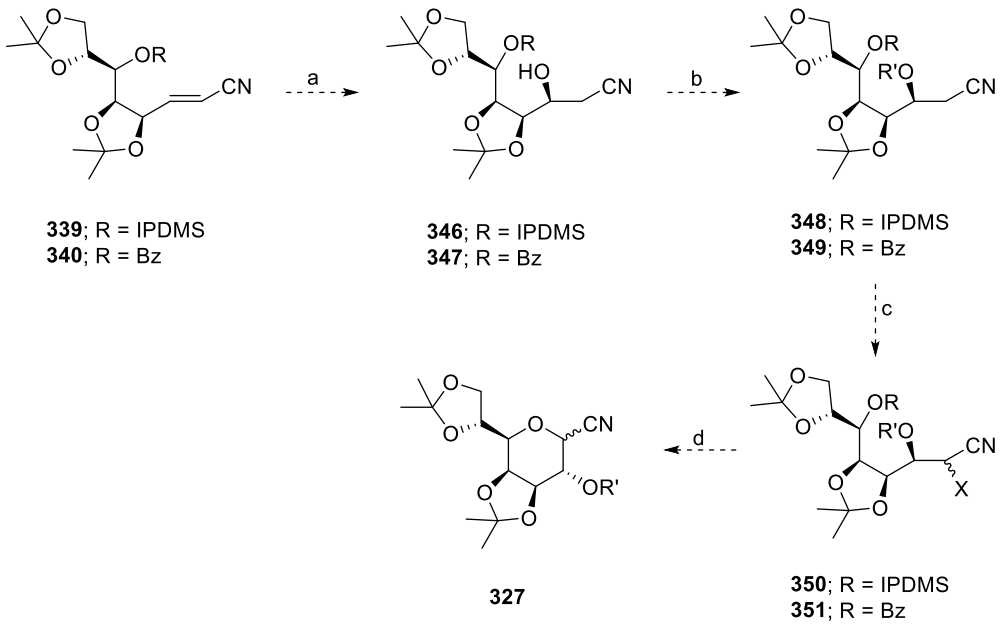


Reagents and conditions: a) Br_2, DCM, -78 ^{o}C to rt.

Scheme 103: Attempted bromination on alkene **327**.

After having no success in our bromination strategy, we decided to try another alternative synthetic approach to pyranoid **307** (**Scheme 104**). In this approach, an oxymercuration-

demercuration would be attempted on the IPDMS- and benzoyl-protected alkene derivatives **339** and **340**. Then, following a protection of the product alcohol (e.g. benzyl or trityl protection), halogenation alpha to the nitrile would be performed; this would install a good leaving group alpha to the nitrile. Finally, selective deprotection of the IPDMS or benzoyl protecting group in **350** or **351** would liberate the nucleophilic oxygen (in the form of an alcohol or alkoxide depending on the deprotection conditions), which in turn could displace the halide in a 6-*exo*-tet cyclization to afford pyranoid **327**.

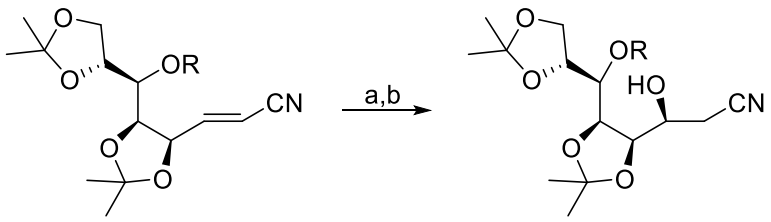


Methodologies: a) oxymercuration-demercration; b) Protection; c) α-halogenation to nitrile ; d) Deprotection and cyclization.

Scheme 104: Proposed synthetic approach to pyranoid **327** from alkenes **339** and **340**.

In this oxymercuration-demercuration strategy, there are more steps required to synthesize pyranoid **327** as compared to the epoxidation or bromination pathways. However, in contrast to the previous pathways, there would be no regioselective issues in the cyclization. This is because in this pathway, the 5-*exo*-tet cyclization would be much slower and unfavourable compared to the 6-*exo*-tet cyclization since the former process requires an alkoxide leaving group instead of a good halide leaving group as in the latter.

Consequently, the protected derivatives **339** and **340** were subjected to a range of oxymercuration-demercuration conditions (**Scheme 105** and **Table 11**).



339; R = IPDMS
340; R = Bz

346; R = IPDMS
347; R = Bz

Reagents and conditions: a) mercuric reagent (1 equiv.), catalyst, solvent; b) 3M $NaOH_{(aq)}$, $NaBH_4$ (0.5 M in 3 M $NaOH_{(aq)}$. See **Table 11**.

Scheme 105: Oxymercuration-demercuration attempts on compounds **339** and **340**.

Entry	Mercuric Reagent	Catalyst	Solvent	Product
1[18]	$Hg(OAc)_2$	None	1:1, THF:Water	SM
2	$Hg(OAc)_2$	70 % $HClO_{4\,(aq)}$ (0.2 equiv.)	1:1, THF:Water	SM
3	$Hg(TFA)_2$	None	1:1, THF:Water	SM
4	$Hg(TFA)_2$	70 % $HClO_{4\,(aq)}$ (0.2 equiv.)	1:1, THF:Water	SM
5	$Hg(OAc)_2$	None	1:1, Acetone:Water	SM

Table 11: Conditions and results reported for oxymercuration-demercuration attempts of compounds **339** and **340**.

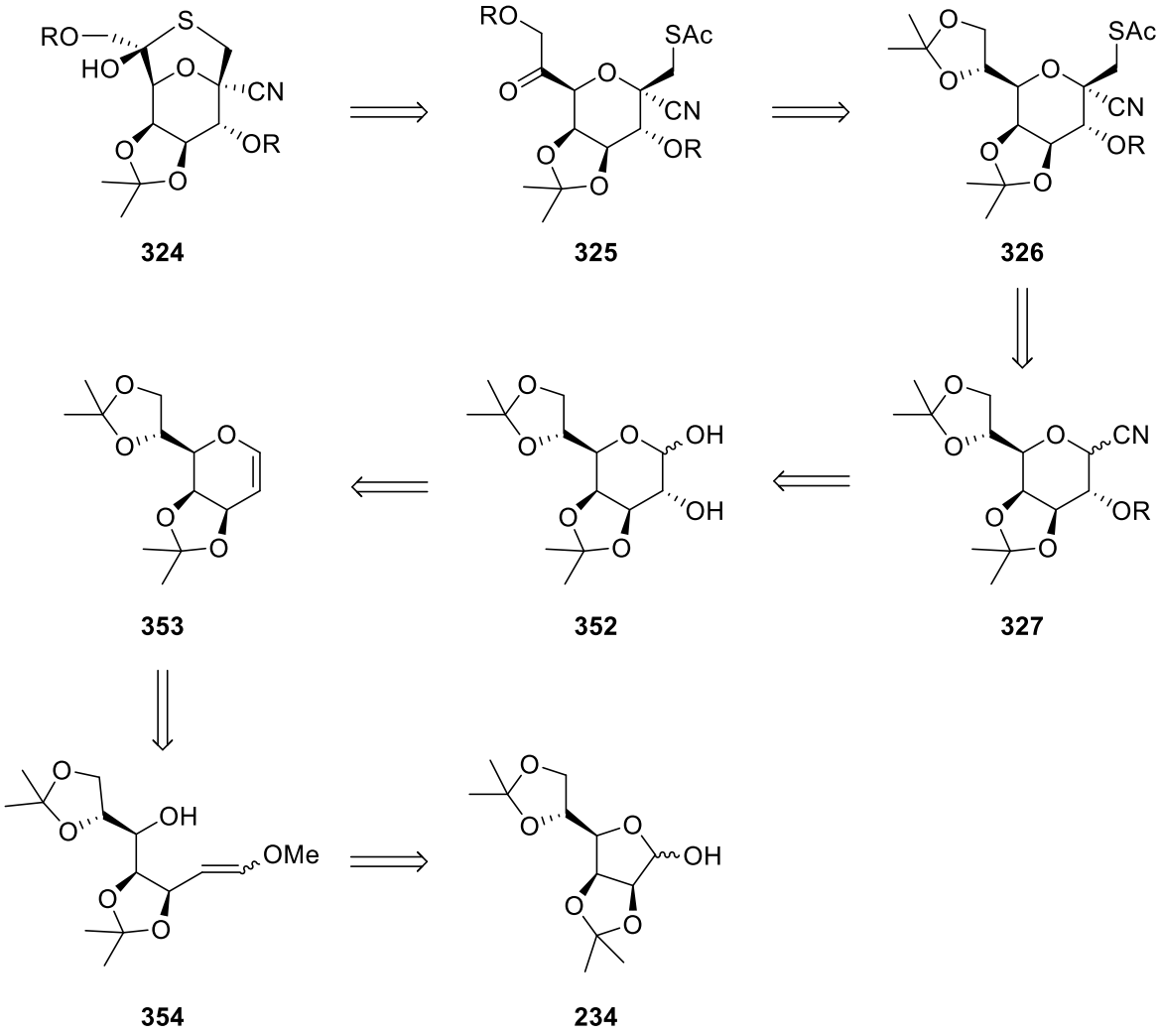
When applying standard literature conditions on **339** and **340** (entry 1),[18] only starting material was isolated. This prompted us to use more powerful conditions by also adding 70% perchloric acid (entry 2); the presence of perchloric acid should trigger the formation of the more electrophilic acetoxymercuric cation (part of the acetoxymercury perchlorate ion pair).[19,20] Unfortunately these powerful conditions still made no difference to the result. Attempts using the more electrophilic mercuric trifluoroacetate with or without perchloric acid were also unsuccessful (entries 3 and 4). Finally, in one last attempt the solvent system was modified whereby THF was replaced with acetone, but as expected this again made no difference (entry 5).

As with the attempted bromination and electrophilic epoxidations on alkene **327**, the probable reason for the failure of these oxymercuration-demercurations on **339** and **340** is the poor nucleophilicity of the electron-deficient alkene.

Considering the failures of the epoxidations, bromination and oxymercuration-demercurations we abandoned this route.

Vinyl-Transetherification Route

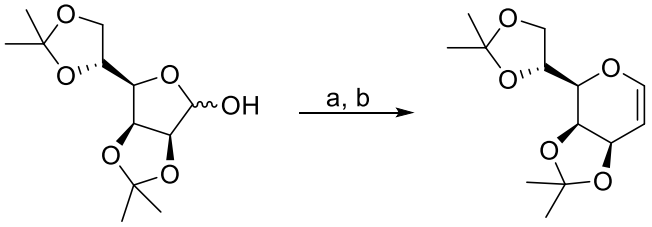
Following on from the disappointments of the nitrile-Wittig Route, in order to reach target **324**, we proposed an alternative strategy to synthesize intermediate pyranoid **327** (**Scheme 106**).



Scheme 106: Retrosynthesis of target structure **324** from DAM **234** in the vinyl-transetherification route.

The retrosynthesis of target **324** from **327** is identical to the nitrile-Wittig Route. In this route, pyranoid **327** could be made from diol **352** in a two-step sequence involving esterification of both hydroxyl groups (e.g. acetylation or benzoylation) followed by a C-glycosylation reaction with TMSCN. The esterification of the anomeric hydroxyl group will incorporate a good leaving group on the anomeric centre which would help to activate the molecule for the subsequent C-glycosylation reaction. Furthermore, esterification of the neighbouring C_{-2} hydroxyl group should additionally activate the molecule for the C-glycosylation due to its role in anchimeric assistance.[21] Diol **352** could derive from the dihydroxylation of glycal **353**. A mercuric acetate catalysed intramolecular vinyl-transetherification of enol ether **354** would construct the pyranoid framework in glycal **353**. Finally, enol ether **354** could be made by a Wittig olefination of DAM **234** with an ylide derived from (methoxylmethyl)triphenylphosphonium chloride.

The pivotal steps of this route were the Wittig olefination of DAM **234** and subsequent intramolecular vinyl-transetherifcation to afford glycal **353**. This exact synthesis has already been achieved by Wardrop *et al*. in 58% yield (over both steps) during their synthesis of KDO (**Scheme 107**); though characterization data for enol ether **354** and glycal **353** were not reported.[22]

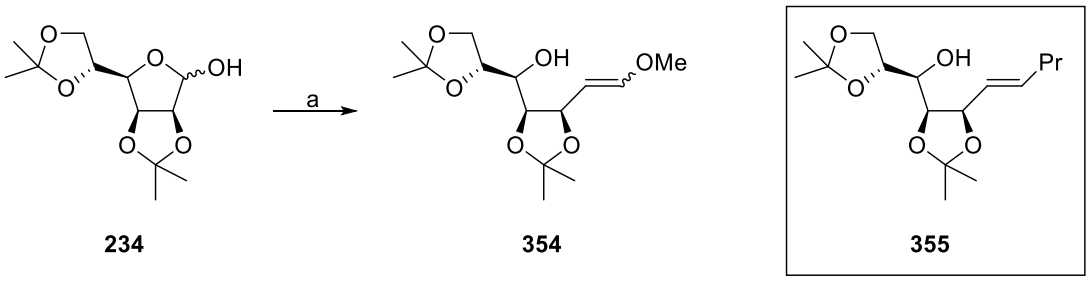


234 **353**

Reagents and conditions: a) $Ph_3PCH_2(OMe)Cl$, *t*-BuOK, THF, reflux, 4 h, 96%; b) $Hg(OAc)_2$ (0.3 equiv.), 110 ^oC, 20 mmHg, 3 h, 60%.

Scheme 107: Two-step synthesis of glycal **353** from DAM **234** by Wardrop *et al*.[22]

The route started with the attempted Wittig olefination of DAM **234** (**Scheme 108** and **Table 12**).



234 354 355

Reagents and conditions a) $(Ph_3PCH_2OMe)Cl$ (3 equiv.), base (3 equiv.), THF, -78 °C, 1 h, DAM **234**, reaction temperature, overnight. See **Table 12.**

Scheme 108: Wittig olefination attempts on DAM **234.**

Entry	Base	Reaction Temperature	Product(s)
1[22]	*t*-BuOK	Reflux	SM
2	*n*-BuLi	rt	9-36% **354** (*E*:*Z*, 7:3), 0-17% **355**
3	NaHMDS	rt	11% **354** (*E*:*Z*, varied from 1:0 to 4:1), 30% SM
4	LDA	rt	19% **354** (*E*:*Z*, 9:1), 61% SM
5	LDA	reflux	57% (*E*:*Z*, varied from 5:1 to 3:2)

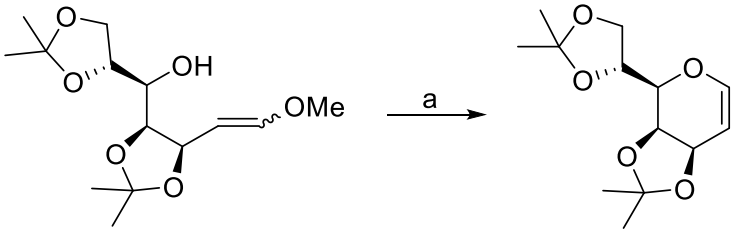
Table 12: Conditions and results reported for the Wittig olefination attempts on DAM **234**.

Surprisingly, when using conditions from Wardrop *et al.*,[22] no reaction seemingly occurred as only starting material was recovered (entry 1). This happened despite the mixture even being heated under reflux for very long reaction times (~72 h).

We therefore aimed to apply more powerful conditions and replaced the potassium *tert*-butoxide base with *n*-BuLi (entry 2). This change did considerably improve the conversion (no trace of starting material observed in the crude mixture) but a complex mixture was formed (hinting at many undesired side reactions) with the only products isolated after purification being the desired enol ether **354** (38% yield) and the side product **355** (17%). Compound **355** was probably formed from the nucleophilic addition of *n*-BuLi to the 'open' hydroxy aldehyde form of DAM **234**, followed by a dehydration of the formed alcohol. We also found, that when using *n*-BuLi, the reaction had scalability issues; for example, scaling up the reaction beyond 1 g of DAM **234** led to yields of **354** as low as 9%. The capricious nature of this reaction influenced us to change

the base to strong non-nucleophilic bases like NaHMDS (entry 3) or LDA (entry 4), but in these cases only low yields of enol ether **354** were obtained due to the occurrence of many side reactions (inferred from the presence of crude complex mixtures) and poor conversion of DAM **234**. When using LDA as the base, however, satisfactory yields of enol ether **354** (up to 57%) were obtained when increasing the reaction temperature (entry 5) due to a greater conversion of DAM **234** (inferred from no trace of DAM **234** being seen in crude mixture).

The next step involved the intramolecular vinyl-transetherification of **354** (**Scheme 109**). This was accomplished by subjecting enol ether **354** to catalytic mercuric acetate at 110 ºC under reduced pressure using Kugelrohr distillation apparatus, which furnished glycal **353** in yields up to 57%.[22,23]

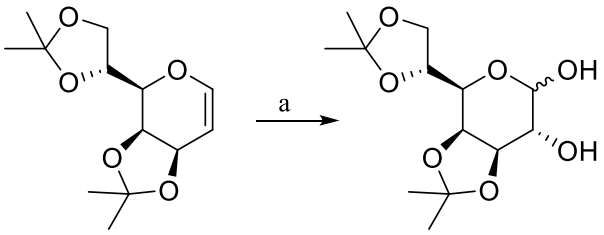


354 **353**

Reagents and conditions: a) $Hg(OAc)_2$, 110 ^oC, 20 mmHg, 3 h, 57%.

Scheme 109: Synthesis of glycal **353** from enol ether **354**.

The dihydroxylation of glycal **353** was then attempted (**Scheme 110** and **Table 13**).



353 **352**

Reagents and condtions a) see **Table 13**.

Scheme 110: Dihydroxylation attempts on glycal **353**.

Entry	Reagents and Conditions	Product
1[24]	AD-Mix-α, 1:1 *t*-BuOH:H_2O	SM
2[24]	AD-Mix-β, 1:1 *t*-BuOH:H_2O	SM
3	$OsCl_3$, NMO, 1:1 THF:H_2O, overnight	64% **352** (**α**:**β**, 14:1)

Table 13: Conditions and results reported for the dihydroxylation attempts on glycal **353**.

Our first attempts were Sharpless asymmetric dihydroxylations using AD-mix-α (entry 1) and AD-mix-β (entry 2) since these had the easiest osmium reagent (potassium osmate) to handle (i.e. least volatile).[24,25] We initially tried both AD-mixes, because it was difficult to predict which face of the alkene in **353** would preferentially be dihydroxylated by each AD-mix. This was due to the similar steric environment on both sides of the alkene moiety in **353** as well as the presence of four stereogenic centres in **353** that could also influence the stereoselectivity. Despite long reaction times (7 days) only starting material was observed for each AD-mix reaction. A possible reason for these results could arise from the bulky osmium-ligand complex formed in these conditions being sterically demanding in addition to glycal **353** being fairly bulky; this would cause the 1,3-dipolar cycloaddition between these species to be too slow because of the sterically congested transition state for this step.[26]

We then performed the dihydroxylation using osmium trichloride (entry 3). Under these conditions, we successfully isolated diols **352 (**14:1, **α**:**β)**. These anomers were inseparable in flash column chromatography. Consequently, several recrystallizations were attempted to separate the anomers, without success.

Theoretically from the dihydroxylation of glycal **353**, there are four possible stereoisomers that could be formed (**Figure 12**).

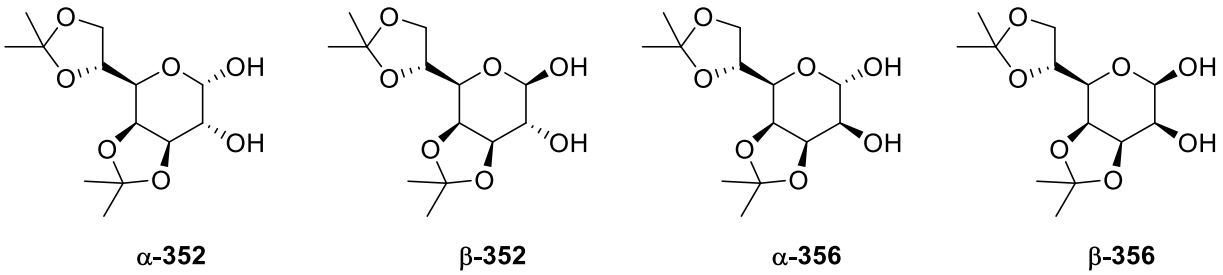


Figure 12: Every possible product from the dihydroxylation of glycal **353**.

From NMR analysis (see below), we assigned the stereochemical configuration on the C_{-1} and C_{-2} and deduced that the major stereoisomer isolated was diol **α-352**. We also suggest that the minor product, which co-eluted with diol **α-352** from column chromatography, was its anomer **β-352**.

From a range of similar compounds in the literature whose conformations have been determined from NMR and/or X-ray analysis, the most likely conformation(s) adopted by diols **352** and **356** is a hybrid between a twist-boat ($^{o}S_2$) and boat conformation ($B_{2,5}$),[27–30] ideal $^{o}S_2$ or $B_{2,5}$ conformations,[31–34] or a slightly flattened chair conformation (**Figure 13**).[34] The reason that the usual chair conformer is generally not the preferred conformation of the galactose ring originates from constraints imposed by the 3,4-O-isopropylidene group.[32]

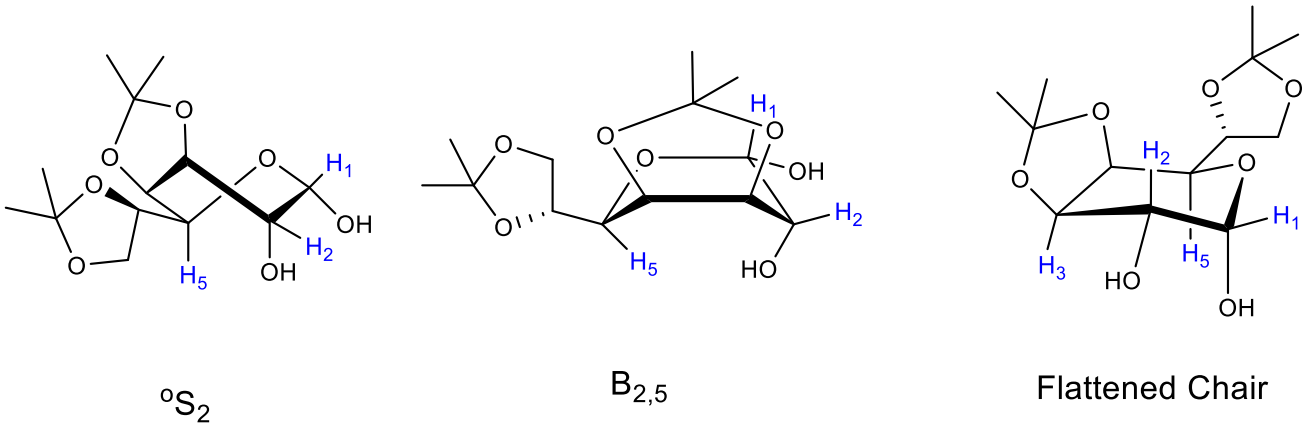


Figure 13: Proposed conformations of diol **α-352**.

From the NOESY spectrum, for the major product, a strong nOe was observed between one of the methyl groups on the 3,4-O-isopropylidene group with both H-C_{-1} and H-C_{-2} of the major product, implying that these are close in space. No matter what conformation is adopted, it is

very unlikely for these atoms to be close in space in diastereomers **β-352**, **α-356** or **β-356**, supporting the suggestion that the major product is diol **α-352**.

Furthermore, for the major product there were no nOes observed that would be expected for the diastereomers **β-352**, **α-356** or **β-356**. For example, if either diol **α-356** or **β-356** were the major products, a nOe between H-C_{-2} and H-C_{-5} should be observed if the $^{o}S_2$, $B_{2,5}$, or a hybrid between these conformations, were adopted. Moreover, if diol **β-352** or **β-356** were the major products, a nOe should be observed between H-C_{-1} and H-C_{-5} if a chair, flattened chair, $B_{2,5}$, $^{o}S_2$, or hybrid between these conformations, were adopted. Likewise, for **β-352** or **β-356**, a nOe should be observed between H-C_{-1} and H-C_{-3} if a chair or flattened chair conformation were adopted. As a result, since all these aforementioned nOes were absent, there is greater support that diol **α-352** is the major product.

With regards to the minor product, from the NOESY spectrum, there was an observed nOe between H-C_{-1} and H-C_{-5}. Also, there was no nOe observed between H-C_{-1} and the methyl group on the 3,4-O-isopropylidene. These nOe results suggest that H-C_{-1} is *cis* to H-C_{-5} and *trans* to the 3,4-O-isopropylidene group, which means that there is a β stereochemical configuration on the anomeric C_{-1} position. Hence, these observations from the NOESY spectrum indicate the minor product is **β-352** or **β-356**.

Additionally, in both the minor and the major product (to a lesser extent in the major product) the stereochemical configuration on C_{-2} can be assigned from the magnitude of the vicinal coupling constant between H-C_{-2} and H-C_{-3} ($^3J_{2,3}$) using the Karplus relationship.[35] The $^3J_{2,3}$ values for the minor (7.9 Hz) and the major (6.4 Hz) products seem too high for the H-C_{-2} being *cis* with H-C_{-3} (no matter which of the previously mentioned conformations are adopted). This indicates that H-C_{-2} is *trans* to H-C_{-3} and gives further evidence that the major product is **α-352** and minor product is **β-352**.

Finally, the vicinal coupling constant between H-C_{-1} and H-C_{-2} ($^3J_{1,2}$) in the major product is only 3.4 Hz whereas in the minor product it is 7.8 Hz. The larger $^3J_{1,2}$ for the latter suggests a *trans* relationship between H-C_{-1} and H-C_{-2} (providing further evidence that the minor product is **356**) while the former indicates a *cis* relationship between H-C_{-1} and H-C_{-2} (giving further indication that the major product is **α-352**).

From observing the stereochemistry of the major product **α-352**, it appears that the 1,3-dipolar cycloaddition with the osmium tetroxide occurs preferentially on the bottom face of glycal **353**. To rationalize the stereoselectivity of the dihydroxylation, the conformation of glycal **353** must be considered. The most likely conformations adopted are the half chair conformations $^{5}H_{4}$ and $^{4}H_{5}$ (with the former being less stable due to the significant destabilizing 1,3-pseudo axial – axial interaction between the axial substituent on C_{-5} and the pseudo-axial substituent on C_{-3}).[36,37] Attack on the bottom face by the osmium species in both conformations are each less sterically hindered compared to top face attack (**Figure 14**). Hence, the 1,3-dipolar cycloaddition on the bottom face is faster as it leads to a less sterically congested and thus more stable transition state.

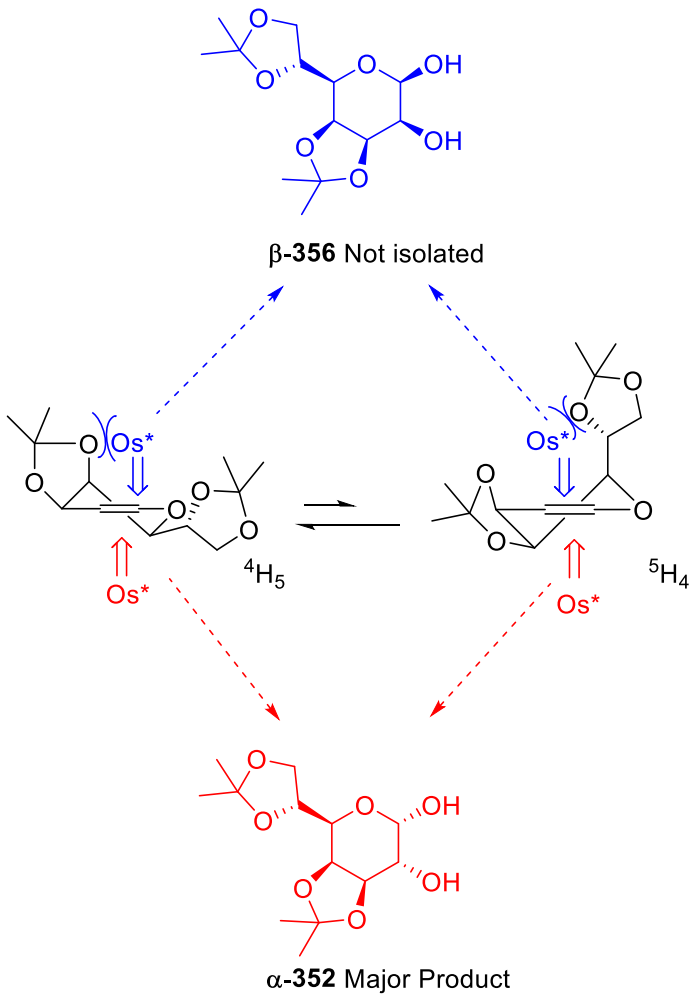
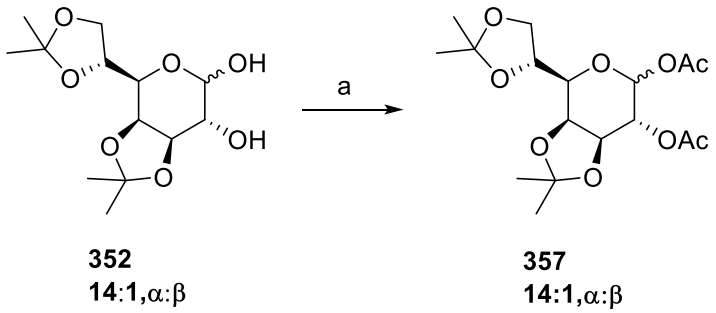


Figure 14: Rationale for stereoselectivity of dihydroxylation on glycal **353**. The osmium tetroxide species is denoted as Os*.

The minor product **β-352** was probably formed by the major product **α-352** undergoing mutarotation during the reaction.

Using a slightly modified procedure from the literature,[38] the diol was then diacetylated to afford **357** (**Scheme 111**).



352
14:1,α:β

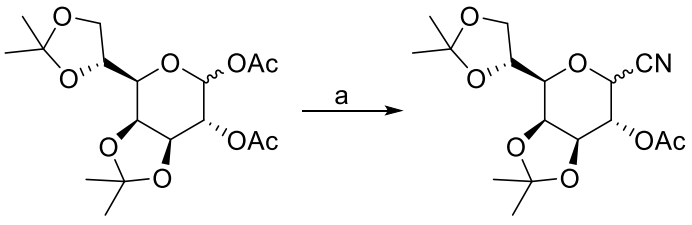
357
14:1,α:β

Reagents and conditions: a) PY, Ac_2O, 0 °C to rt, overnight, 68%.

Scheme 111: Synthesis of compounds **357**.

The diacetate **357** was isolated as an anomeric mixture because of the isomers being inseparable after column chromatography. The stereochemical configuration of the major product **α-357** was deduced to be identical to diol **α-352** because of the great similarities of the NOESY spectra and vicinal coupling constants (around the pyranoid ring) between these compounds.

We then aimed to perform the C-glycosylation of diacetate **357** with TMSCN to introduce the nitrile functionality onto the anomeric position (**Scheme 112** and **Table 14**).



357

358

Reagents and conditions: a) see **Table 14**.

Scheme 112: Attempted C-glycosylation of **357** with TMSCN.

Entry	Conditions	Result
1[39]	TMSCN, $BF_3.OEt_2$, NO_2Me	Decomposition
2[40]	TMSCN, $BF_3.OEt_2$, MeCN	Decomposition
3[41,42]	TMSCN, $SnCl_4$, MeCN	Decomposition
4	TMSCN, $SnCl_4$, NO_2Me	Decomposition
5[43]	TMSCN, $SnCl_4$, DCM [a]	Decomposition
6[44]	TMSCN, $HgBr_2$, NO_2Me	Complex mixture
7[39]	TMSCN, TMSOTf, NO_2Me	Complex mixture
8	TMSCN, MeCN	SM
9	TMSCN, MeCN, Reflux	SM

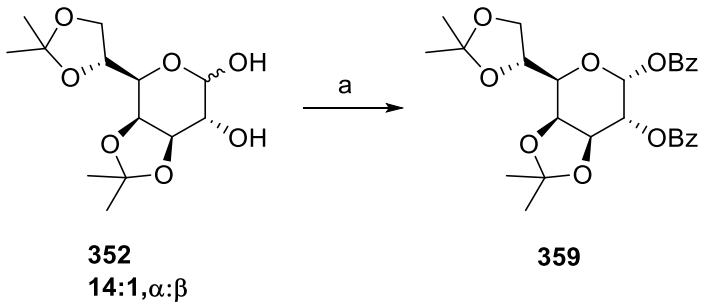
[a] The reaction was performed at rt rather than at reflux as reported in the literature.[43]

Table 14: Conditions and results reported for the attempted C-glycosylation of **357** with TMSCN.

Unfortunately, under common literature conditions involving TMSCN with a Lewis acid in a polar aprotic solvent (entries 1 to 7), no trace of the desired glycosyl nitrile **358** was detected. Instead only decomposition or the formation of complex mixtures were observed.

These poor results led us to try milder conditions by performing the reaction in the absence of any Lewis acid (entry 8); while this did not lead to any decomposition or complex mixtures, the conditions were unsurprisingly too mild for any reaction to occur, as only starting material was recovered. Repeating the reaction under these neutral conditions at higher temperatures (entry 9) for longer reaction times (72 h) was also not sufficient to trigger the reaction.

Since glycosyl nitrile **358** was not obtained, we decided to try the C-glycosylation with benzoyl ester groups on C_{-1} and C_{-2} instead of acetates, to see if this could influence the reaction. Therefore, from a modified procedure in the literature,[45] the diol was esterified using an excess of benzoyl chloride in a pyridine solvent (**Scheme 113**).



352
14:1,α:β

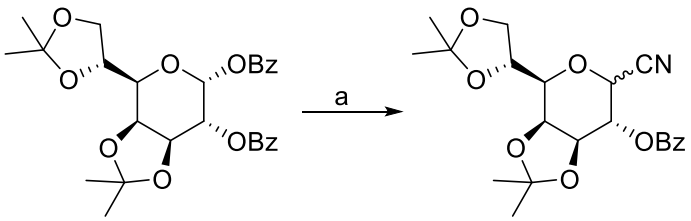
359

Reagents and conditions: a) PY, BzCl, 0 °C to rt, 24 h, 65%.

Scheme 113: Synthesis of compound **359**.

Attempts to grow a crystal of **359** for X-ray analysis failed. However, since the NMR data (i.e. vicinal coupling constants and NOESY spectra) were very similar to those of **α-357** and the diol **α-352**, the stereochemistry of the dibenzoylated compound **359** was inferred to be identical with these respective compounds.

We then moved onto the C-glycosylation reactions of the dibenzoylated compound **359** with TMSCN (**Scheme 114** and **Table 15**). Unfortunately, when subjecting dibenzoyl **359** to the same conditions as diacetyl **359**, the results were effectively identical, with no trace of desired nitrile **360** being observed.



359

360

Reagents and conditions: a) see **Table 15**.

Scheme 114: Attempted C-glycosylation of **359** with TMSCN.

Entry	Conditions	Result
1[39]	TMSCN, $BF_3.OEt_2$, NO_2Me	Decomposition
2[40]	TMSCN, $BF_3.OEt_2$, MeCN	Decomposition
3[41,42]	TMSCN, $SnCl_4$, MeCN	Decomposition
4	TMSCN, $SnCl_4$, NO_2Me	Decomposition
5[43]	TMSCN, $SnCl_4$, DCM [a]	Decomposition
6[44]	TMSCN, $HgBr_2$, NO_2Me	Complex mixture
7[39]	TMSCN, TMSOTf, NO_2Me	Complex mixture
8	TMSCN, MeCN	SM
9	TMSCN, MeCN, Reflux	SM

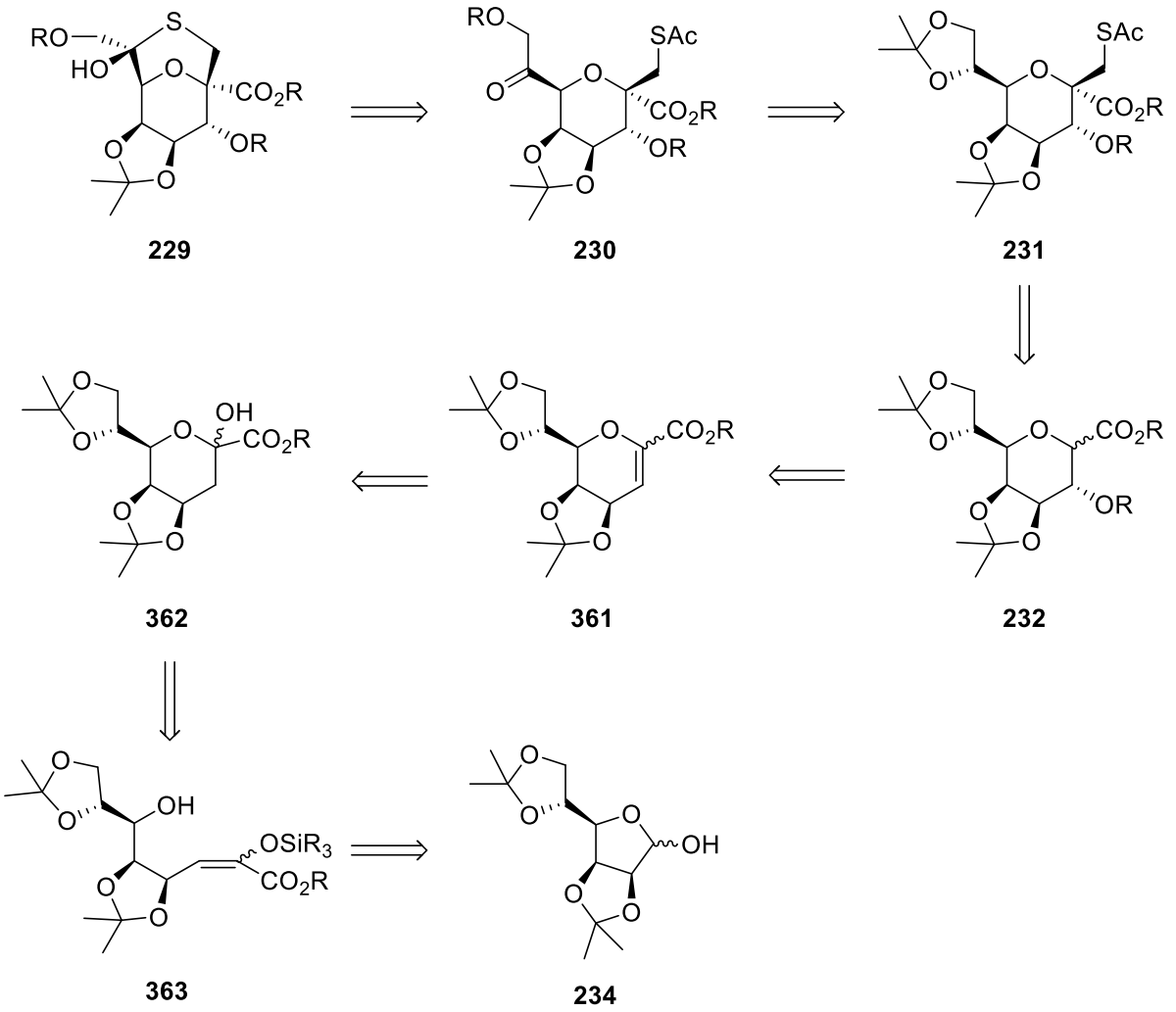
[a] The reaction was performed at rt rather than at reflux as reported in the literature.[43]

Table 15: Conditions and results reported for the C-glycosylation attempts of **359** with TMSCN.

Due to the inability to synthesize glycosyl nitriles **358** and **360**, we abandoned this route.

Silyl Enol Ether Route

In our next approach, we planned to synthesize a silyl enol ether from DAM **234** (**Scheme 115**).



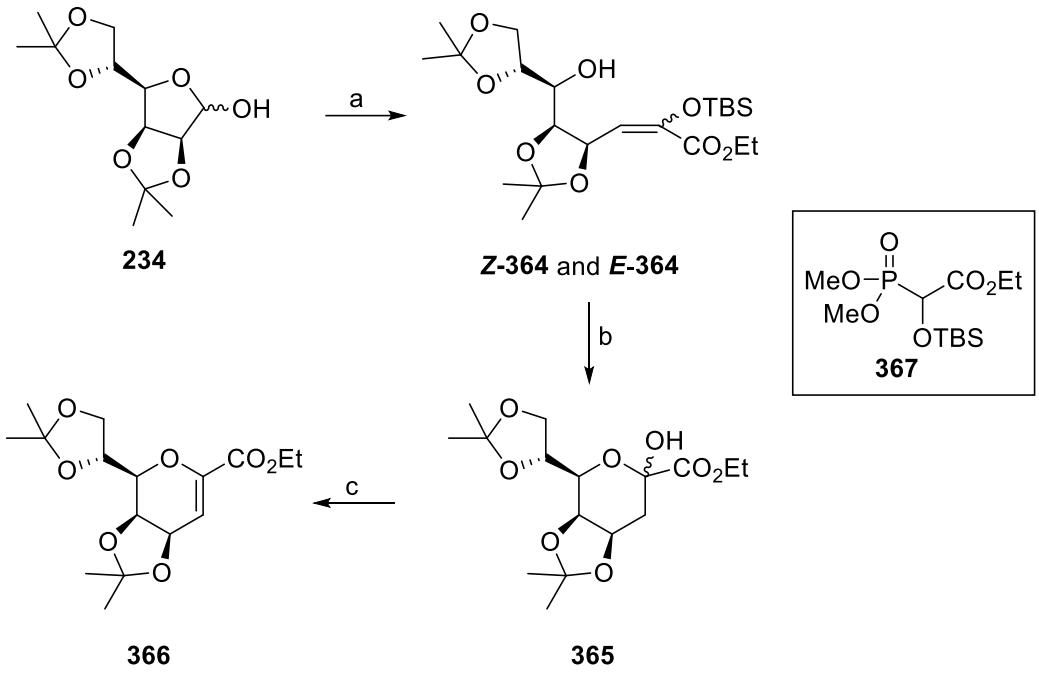
Scheme 115: Retrosynthesis of target **229** from DAM **234** in the Silyl Enol Ether Route.

If target **229** were successfully prepared, this strategy would be tailored to synthesize our ultimate bicyclic targets **323a** and **323b**.

Target **229** could derive from compound **232**, using the same retrosynthetic analysis described above for the previous target **324** from **327 (**in the nitrile-Wittig and vinyl-transetherification routes) with the only difference being the presence of an ester instead of a nitrile functionality on the C_{-1} position. Pyranoid **232** could be synthesized by the regioselective hydration of glycal **361** and subsequent protection of the formed alcohol. Glycal **361** could be synthesized by the dehydration of pyranose **362**. The deprotection of the silyl enol ether in **363** should trigger an intramolecular 6-*exo*-trig cyclization of the hydroxyl group on the formed α-ketoester to furnish

pyranose **362**. Silyl enol ether **363** could be synthesized from DAM **234** by a Wittig or HWE olefination with an appropriate ylide or phosphonate anion.

This route was inspired by the successful three-step synthesis of glycal **366** from DAM **234** executed by Chai *et al*. (**Scheme 116**).[46]

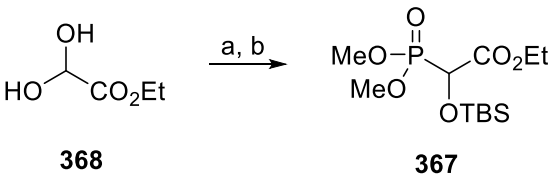


Reagents and conditions: a) **367**, *t*-BuOLi, THF, rt, 15 min, **234**, 50 °C, 1 h, 88%; b) TBAF (1M in THF), 20% AcOH $_{(aq)}$, 0 °C to rt, 3 h, quant.; c) MsCl, Et_3N, DCM, 0 °C, 1.5 h, 80%.

Scheme 116: Three-step synthesis of glycal **366** from DAM **234** by Chai *et al*.[46]

In this synthesis, the authors performed an HWE reaction between phosphonate **367** and DAM **234** to afford a mixture of *E* and *Z* silyl enol ethers ***E*-364** and ***Z*-364**. Subsequent treatment of the silyl enol ethers with TBAF and 20% AcOH led to desilylation and an *in-situ* 6-*exo*-trig cyclization to form an anomeric mixture of pyranoses **365**. Finally, glycal **366** was formed by dehydration of anomers **365**; this was achieved by mesylation of the anomeric hydroxyl group in **365** and subsequent elimination using MsCl and Et_3N.

Phosphonate **367**, however, had to be synthesized as it is not commercially available. Chai and co-workers synthesized **367** in two steps from ethyl glyoxylate hydrate **368** and dimethyl phosphite (**Scheme 117**).[46]



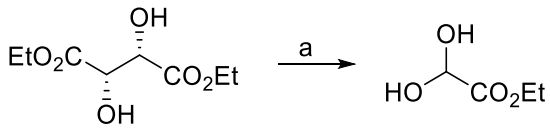
368 **367**

Reagents and conditions: a) dimethyl phosphite, Et_3N, toluene, 0 °C to rt, 3 h; b) TBSCl, imidazole, DMF, rt, 12 h, 76% (over 2 steps).

Scheme 117: Synthesis of phosphonate **367** by Chai *et al.*[46]

We therefore decided to replicate their synthesis to obtain glycal **366**.

Our first task in this route was to synthesize the TBS-protected phosphonate **367**. In order to achieve this feat, we had to first synthesize ethyl glyoxylate hydrate **368**. We aimed to do this by using Bailey and co-workers' conditions, where a periodate oxidative cleavage of the 1,2-diol in L-diethyl tartrate **369** was carried out (**Scheme 118**).[47]



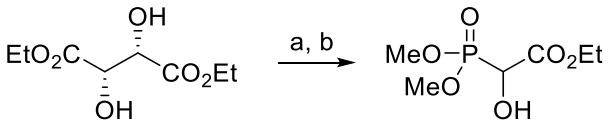
369 **368**

Reagents and conditions: a) $NaIO_4$, 5:1 DCM:water, reflux, 1 h, 94%.

Scheme 118: Synthesis of ethyl glyoxylate hydrate **368** by Bailey *et al.*[47]

However, our attempts at applying these conditions, were of limited success. The ^{1}H NMR spectrum of the crude material, showed a mixture of multiple compounds. Due to the complexity of the ^{1}H NMR spectrum, we were unable to confirm the presence of the hydrate **368**, although the presence of the ethyl glyoxylate as a free aldehyde was observed. Attempts to isolate the aldehyde or the hydrate (if latter was even formed) using column chromatography proved futile. Hence, the crude mixture was used directly for the next step.

We carried out the nucleophilic addition of dimethyl phosphite to our impure sample of the ethyl glyoxylate aldehyde using Chai and co-workers' conditions (**Scheme 119**).[46]

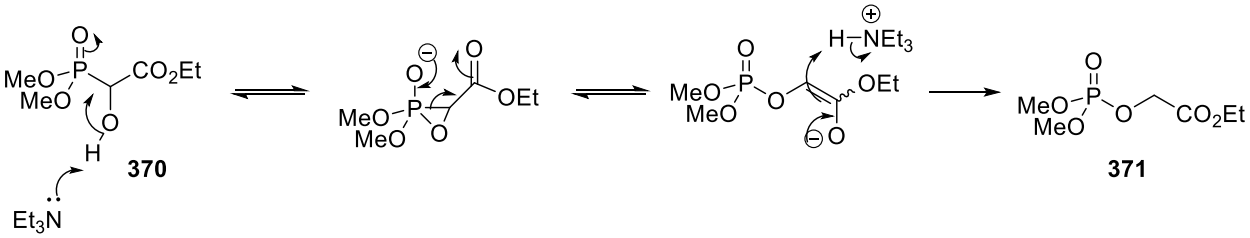


369 **370**

Reagents and conditions: a) $NaIO_4$, 5:1 DCM:water, reflux, 3 h; b) diemethyl phosphite, Et_3N, toluene, 0 °C to rt, overnight 41% (over two steps).

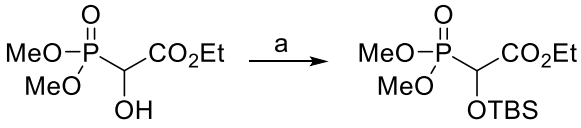
Scheme 119: Two-step synthesis of α-hydroxyphosphonate **370** from L-diethyl tartrate **369**.

We were able to isolate the α-hydroxyphosphonate **370**, albeit in poor yield (41% over two steps). The mediocre yield is probably the result of the use of an impure sample of the ethyl glyoxylate aldehyde as well as the production of the undesired organophosphate side-product **371** (31% yield over 2 steps). This compound was probably formed by a base-catalysed phospha-Brook rearrangement of α-hydroxyphosphonate **370** occurring during the reaction (**Scheme 120**).



Scheme 120: Proposed mechanism to account for the production of organophosphate **371**.

Finally, protection of the hydroxyl group in **370** with a TBS group under standard conditions gave phosphonate **367** in 91% yield (**Scheme 121**).

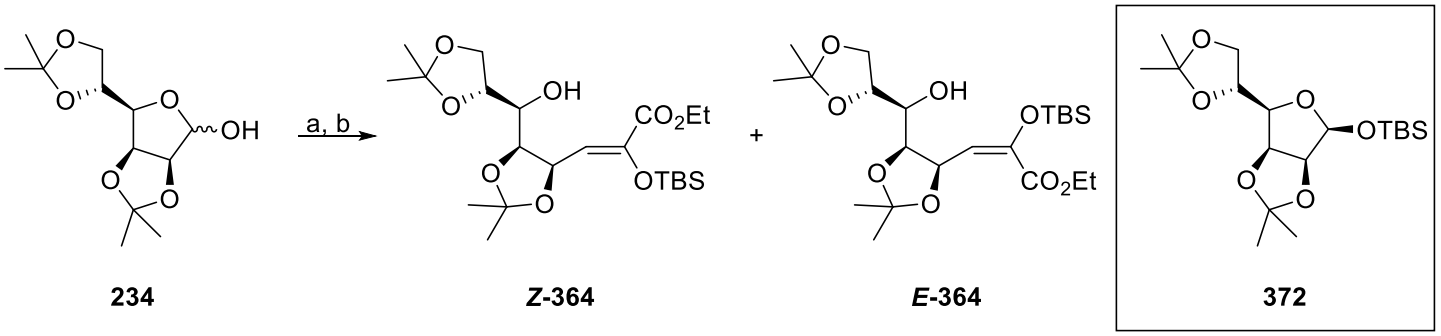


370 **367**

Reagents and conditions: a) TBSCl, imidazole, DCM, 0 °C to rt, overnight, 91%.

Scheme 121: Silyl protection of α-hydroxyphosphonate **367**.

The following step in the route involved the HWE condensation of DAM **234** with phosphonate **367** (**Scheme 122** and **Table 16**). Despite this reaction being carried out by Chai *et al.*,[46] this HWE olefination proved troublesome.



234 ***Z*-364** ***E*-364** **372**

Reagents and conditions: a) Base (1.2 equiv.), phosphonate **367** (1.2 equiv.), THF, deprotonation temperature, 1 h; b) DAM **234**, reaction temperature, 24 h. See **Table 16.**

Scheme 122: HWE olefination attempts between DAM **234** and phosphonate **367**.

Entry	Base	Deprotonation Temperature/ ^{O}C	Reaction Temperature/ ^{O}C	Products [a]
1	*t*-BuOK	rt	50	SM
2[46]	*t*-BuOLi	rt	50	SM
3 [b]	*t*-BuOLi	rt	Reflux	SM
4	*t*-BuOLi	50	50	2% ***Z*-364**, 8% ***E*-364**, 2% **372**, 60% SM
5	*t*-BuOLi	50	Reflux	3% ***Z*-364**, 15% ***E*-364**, 7% **372**, 51% SM
6	*n*-BuLi	0	50	Complex mixture
7	LDA	0	50	15% ***Z*-364**, 7% ***E*-364**, 24% **372**
8	LDA	0	rt	3% ***Z*-364**, 12% ***E*-364**, 3% **372**, 40% SM
9	NaH	0	50	17% ***Z*-364**, 28% ***E*-364**, 1% **372**, 11% SM
10 [c]	NaH	0	50	18% ***Z*-364**, 36% ***E*-364**, trace **372**

[a] Compounds ***E*-364** and **372** were inseparable in column chromatography. The number of moles of ***E*-364** and **372** in the inseparable mixture were calculated from molar ratios observed in the ^{1}H NMR spectrum. Since the yield of the ***E*-364** is based on the number of moles of ***E*-364** in the inseparable mixture, the yield of ***E*-364** derives from the aforementioned molar ratios seen in the ^{1}H NMR spectrum (same applies to **372**); [b] Reaction time: 72 h; [c] 1.5 equiv. of base and **367** were added.

Table 16: Conditions and results reported for HWE olefination attempts between DAM **234** and phosphonate **367**.

Unexpectedly, when using the conditions from Chai *et al.*,[46] with the exception of using *t*-BuOK instead of *t*-BuOLi (entry 1), only starting material was observed. Though we did not expect any difference, we decided to copy fully the conditions in the literature,[46] and hence changed the base to *t*-BuOLi (entry 2), but again only starting material was seen. Therefore, the HWE

condensation was carried out under more forceful conditions by firstly refluxing the reaction mixture and allowing longer reaction times (entry 3), but this made no difference.

Since we have already tried using more forceful reaction conditions, we attempted to use more powerful deprotonation conditions. Therefore prior to DAM **234** addition, the *t*-BuOLi base and the phosphonate **364** were heated at 50 ºC for 1 h (entry 4). After work-up, this led to a messy crude mixture with the only isolable products after column chromatography being starting material **234** (60%), ***Z*-364** (2%) and an inseparable mixture of the ***E*-364** (8%) and an unknown side product which we later identified as **372** (2%). The yields of the silyl enol ethers ***Z*-364** and ***E*-364** were still very low (10%) due to the large amount of unreacted starting material. We therefore repeated this more vigorous deprotonation in addition to subsequently heating the HWE reaction mixture at a higher temperature (entry 5). While this slightly improved the conversion and the yields of silyl enol ethers ***Z*-364** and ***E*-364**, this also caused the yield of the unwanted side product **372** to increase as well; there was also still a great amount of unreacted starting material (51%).

At this time, we attributed the low yields of the silyl enol ethers ***Z*-364** and ***E*-364** to the presence of large amounts of unreacted starting material. We postulated that there could be three possible reasons to explain the high amounts of unreacted starting material:

1. Issues regarding the deprotonation step of the phosphonate **367** by the *tert*-butoxide base.
2. Issues regarding the betaine-forming step involving the hydroxy-aldehyde form of DAM and the phosphonate ion of **367**;
3. Occurrence of unwanted side reactions of the phosphonate **367** and/or DAM **234** under the applied conditions (such as the one that leads to the undesired side product **372**).

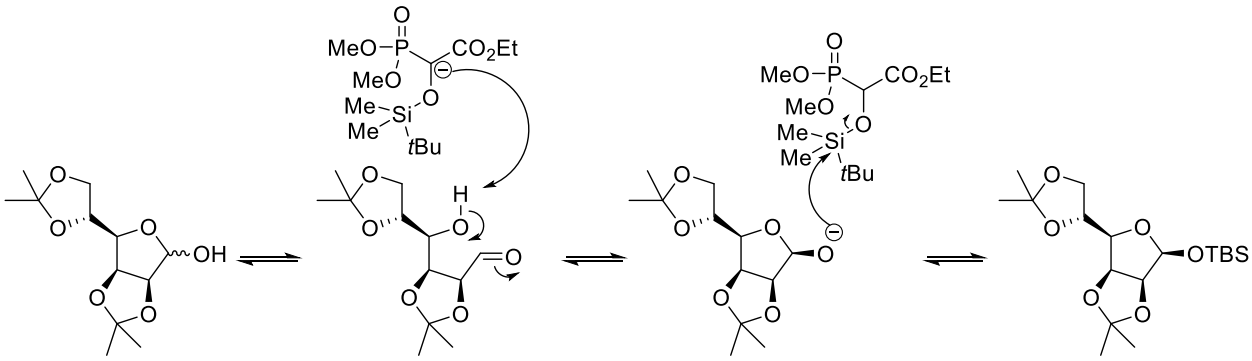
However, considering the success of this HWE reaction by Chai *et al.*,[46] each of these rationales appear surprising and unlikely. Nevertheless, since there was an improvement in conversion when using more powerful deprotonating conditions (entries 3 to 5) we therefore decided to use stronger bases than the *tert*-butoxide anion.

The first strong base that we used was *n*-BuLi (entry 6), but only a complex mixture was observed with no isolable products, suggesting many unwanted side reactions occurred which most likely have arisen from the nucleophilic character of *n*-BuLi.

This led us to use the strong non-nucleophilic base LDA (entry 7). This gave a complex crude mixture, with the only isolable products after purification being the silyl enol ethers ***Z*-364** and ***E*-364** as well as the side product **372**. While there was no trace of starting material seen in the ^{1}H NMR spectrum of the crude mixture (indicating an improved conversion), the yield of the silyl enol ethers **364** (22%) was still low (albeit higher than previous entries), and the yield of the undesired side product **372** increased to 24%. In order to reduce the number of unwanted side reactions, we repeated the HWE olefination with LDA, except under milder conditions, by lowering the reaction temperature from 50 ^{o}C to rt (entry 8). However, the only significant effect this had was a decrease in the conversion of the starting material and yields of the silyl enol ethers ***Z*-364** and ***E*-364**.

When using NaH as the base (entry 9), much higher yields of the silyl enol ethers ***Z*-364** and ***E*-364** (46%) were obtained and there were only trace amounts of the unwanted side-product **372**. Additionally, increasing the equivalents of NaH and the phosphonate **367** to 1.5 equiv. (entry 10) gave greater yields of the silyl enol ethers ***Z*-364** and ***E*-364** (probably due to a greater conversion of starting material). We generally found that, as in entries 9 and 10, the ^{1}H NMR spectra for the crude material were cleaner, hinting that there were fewer unwanted side reactions (including the side reaction that produces **372**).

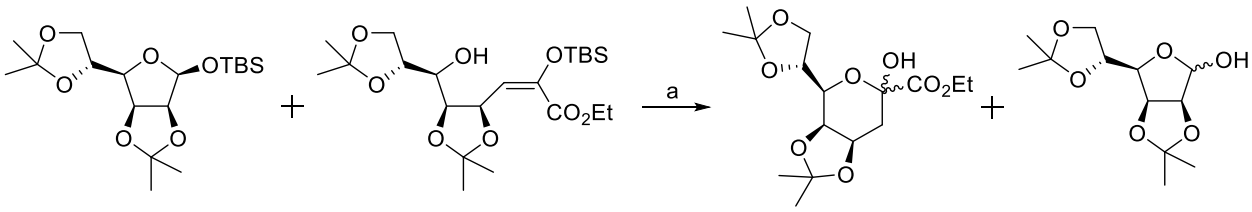
The most likely mechanism to account for the formation of the **372** would involve a silyl migration between the phosphonate **367** and DAM **234** (**Scheme 123**). A possible reason for this undesired reaction could arise from phosphonate **367** being bulky, and rather than attacking the hydroxy-aldehyde form of DAM in nucleophilic fashion to make the betaine intermediate, it acts as a base, deprotonating DAM, as there is greater steric hindrance in the former process. However, considering the success of this HWE reaction reported by Chai *et al.*,[46] this explanation seems unlikely. Furthermore, it is unclear why the yield of **372** varies considerably when different bases are used.



234 **372**

Scheme 123: Proposed mechanism to account for the formation of by-product **372**.

As mentioned above, when performing these HWE reactions, we did not know that the side-product inseparable from ***E*-364** was compound **372**. We were only able to identify compound **372** when performing the subsequent TBAF-based silyl ether and silyl enol ether deprotection step on the inseparable mixture containing ***E*-364** and **372** (**Scheme 124**).



372 ***E*-364** **365** **234**

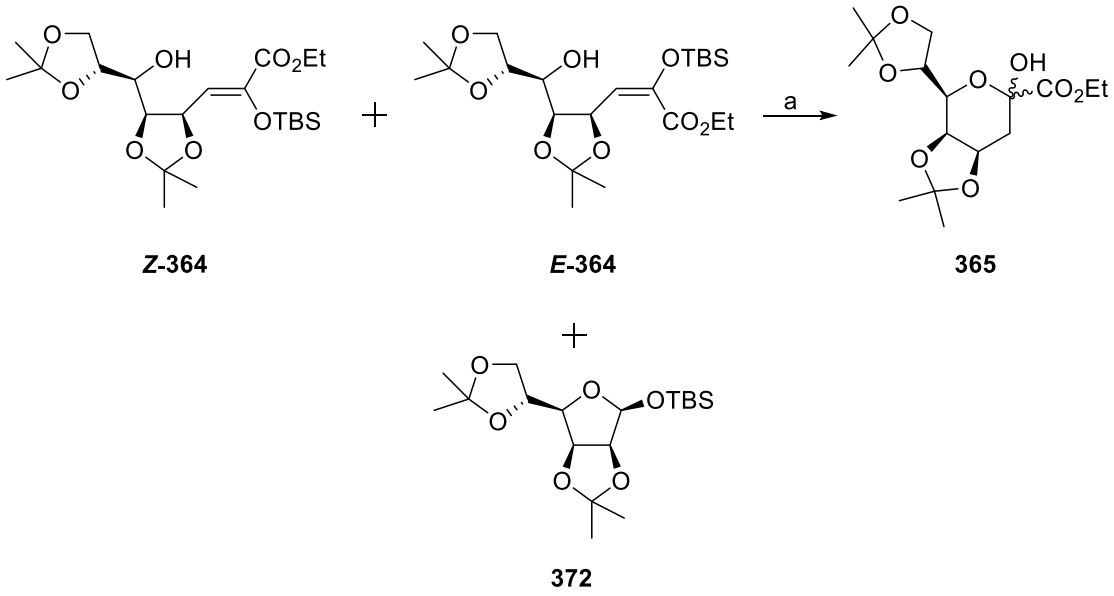
Reagents and conditions: a) TBAF (1 M in THF), 20% AcOH, THF, 0 ^{o}C to rt, 57% **365**, 31% DAM **234**, 51% recovered **372.**

Scheme 124: Treatment of the inseparable mixture of ***E*-364** and **372** with TBAF.

We found that the silyl enol ether ***E*-364** was UV active whereas **372** was not. We also discovered that ***E*-364** was desilylated faster than **372**. Hence, we ceased/quenched the reaction once ***E*-364** was consumed as shown by TLC (by UV visualization). As a result, after purification, compound **372**, DAM **234**, and the desired pyranoses **365** were isolated. This allowed us to fully characterize compound **372**. Furthermore, the production of DAM **234** from this silyl ether deprotection step provided further evidence of the presence of **372** in the starting inseparable mixture.

The next task in the route was deprotection of the silyl enol ethers to trigger the concomitant 6-*exo*-trig intramolecular cyclization to produce pyranoses **362**. Using Chai and co-workers'

conditions,[46] the silyl enol ethers ***Z*-364** and ***E*-364** were successfully transformed into pyranoses **362** (**α**:**β** varying from, 5:1 to 4:1) in yields of up to 79% (**Scheme 125**). As indicated above, due to ***E*-364** being inseparable from **372**, this additionally led to the production of DAM **234** in the reaction.

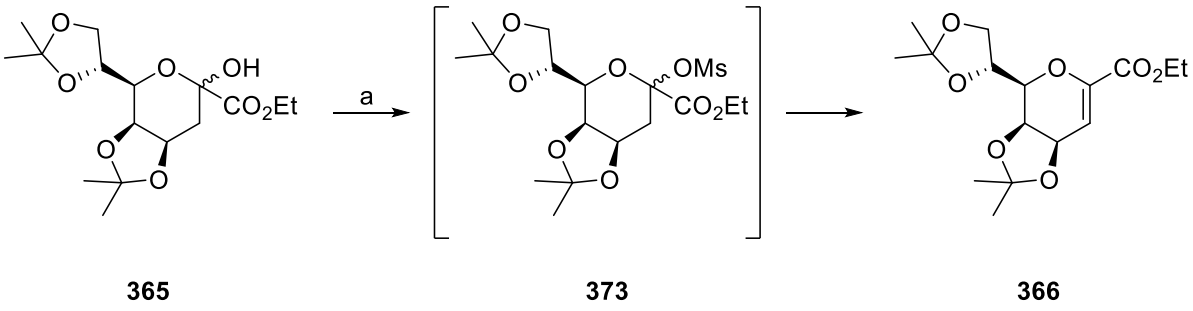


***Z*-364** ***E*-364** **365** **372**

Reagents and conditions: a) TBAF (1 M in THF), 20% AcOH, THF, 0 °C to rt, 79%.

Scheme 125: Synthesis of pyranoses **365** from the deprotection of silyl enol ethers ***Z*-364** and ***E*-364**.

In order to synthesize glycal **366**, we next attempted the dehydration of pyranoses **365** (**Scheme 126** and **Table 17**).



365 **373** **366**

Reagents and conditions: a) see **Table 17**.

Scheme 126: Attempted dehydration of pyranoses **366**.

Entry	Reagents and Conditions [a]	Yield of Glycal 366/%
1[46]	Et_3N (3 equiv.), MsCl (1.5 equiv.), DCM, 0 ^oC, overnight	8
2	Et_3N (5 equiv.), MsCl (1.5 equiv.), DCM, 0 ^oC, overnight	26
3[48]	Et_3N (3.4 equiv.), MsCl (3 equiv.), DCM, 0 ^oC to rt, 3 h, then DBU (3 equiv.), overnight	64 - 71

Table 17: Conditions and results reported for the dehydration attempts of pyranoses **365**.

We initially used Chai and co-workers' conditions, where an excess of base (3 equiv.) was used to trigger mesylation of the anomeric hydroxyl group in pyranoses **365** in addition to the consequent *in-situ* elimination of the anomeric mesylates **373** (entry 1).[46] However, despite numerous efforts, we were unable to replicate the yields (80%) reported by Chai *et al.*,[46] as we only could isolate glycal **366** in low yields of up to 8%. From the ^1H NMR spectrum of the crude material, there was a mixture of unknown compounds present alongside glycal **366**. Interestingly, these unknown compounds appeared to be very polar because they could only be isolated from flash column chromatography on silica gel using a very polar solvent system (9:1, DCM:methanol). We speculated that the intermediate anomeric mesylates **373** could be in the undesired mixture, though considering the high polarity of this mixture it seemed unlikely (the complexity of the NMR spectrum for this mixture made it difficult to interpret). As a result, we concluded that the production of this polar mixture arises from undesired side-reactions, reducing the yield of glycal **366**.

Applying more basic conditions by increasing the equivalents of triethylamine slightly decreased production of these polar products (as seen in the ^1H NMR spectrum of the crude material), which may explain the higher yield of glycal **366** (entry 2); though since the yield was still low, further improvement was required.

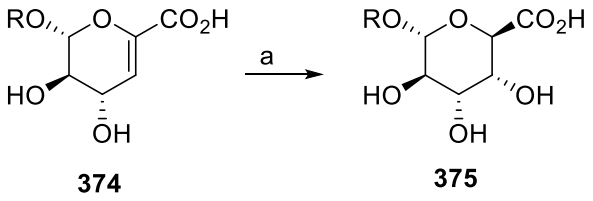
To our delight, from an alternative procedure in the literature involving even stronger basic conditions using DBU (entry 3),[48] there was no trace of the polar unknown mixture in the ^1H NMR spectrum of the crude material, and provided us higher yields of glycal **366** (up to 71%).

Our next goal was the hydration of the alkene in glycal **366**. There are three common methods for this transformation: an oxymercuration-demercuration; an aqueous acid catalysed hydration; and a hydroboration-oxidation reaction.

In an aqueous acid-catalysed hydration, we anticipated numerous issues such as possible unwelcome hydrolysis of the isopropylidene groups and the ethyl ester, and hence we discarded this method.

The choice between an oxymercuration-demercuration or hydroboration-oxidation of glycal **366** was based upon their predicted regioselectivity. From an electronics rationale, predicting the regiochemistry would depend on the 'victor' in the competition between the electron-withdrawing ability (by mesomeric and inductive effect) of the ethyl ester and ring oxygen (by inductive effect) against the electron-donating ability of the ring oxygen (by mesomeric effect) in glycal **366**.

Yamaguchi *et al*. performed an oxymercuration-demercuration on a range of compounds with a generic structure **374** (**Scheme 127**).[49] These compounds **374** have similar features to glycal **366** in that they both have an electron-withdrawing group on the C_{-1} position.



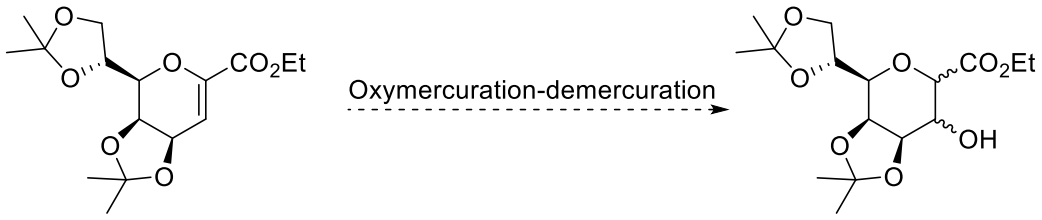
374 **375**

Reagents and conditions: a) $Hg(OAc)_2$, THF, H_2O, then $NaBH_4$.

Scheme 127: Yamaguchi and co-workers' syntheses of compounds **375** by an oxymercuration-demercuration process.[49]

In oxymercurations, the regioselectivity is generally governed by electronic factors, that is by nucleophilic attack of a water molecule onto the carbon of the mercurinium ion that can best accommodate a partial positive charge;[50,51] the regioselectivity observed in Yamaguchi and co-workers' example indicates that this carbon in question is C_{-2}. Hence, this observed regiochemistry suggests that the electron-withdrawing ability of the ester and ring oxygen is more powerful than the electron-donating ability of the ring oxygen. This literature example

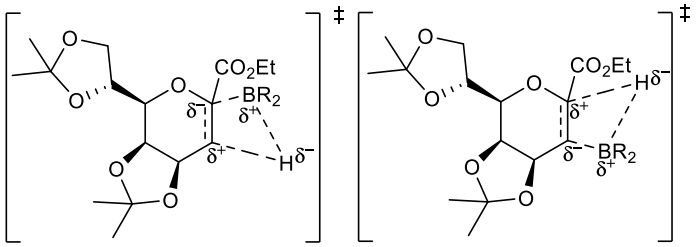
therefore indicates that performing an oxymercuration-demercuration on glycal **366** would lead to the desired compound **376** as the major regioisomer (**Scheme 128**).



366 **376**

Scheme 128: Predicted major regioisomer for an oxymercuration-demercuration of glycal **366**.

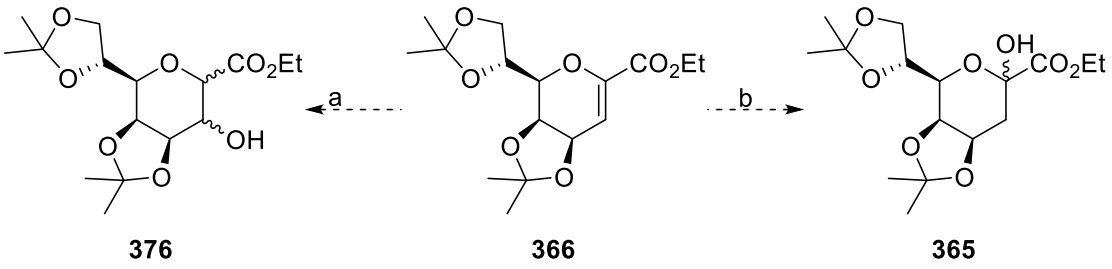
In contrast, the regioselectivity for hydroborations is based on steric and electronic factors. When based on electronic factors, presuming the electron-withdrawing ability of the ester and ring oxygen is more powerful than the electron-donating ability of the ring oxygen (as inferred from the regiochemistry seen in **Scheme 127**), the major expected product would be the unwanted **365**. This is because the regioselectivity would be dependent upon the relative stabilities of the four-centred transition states in the hydroboration (**Figure 15**) - since C_{-2} can stabilize a partial positive charge to a greater extent than C_{-1}, transition state **377** (which after oxidation would eventually lead to **365**) would be more stable than the transition state **378** (which after oxidation would eventually lead to the desired **376**).[52–54]



377 **378**

Figure 15: Transition states for the hydroboration of glycal **366**.

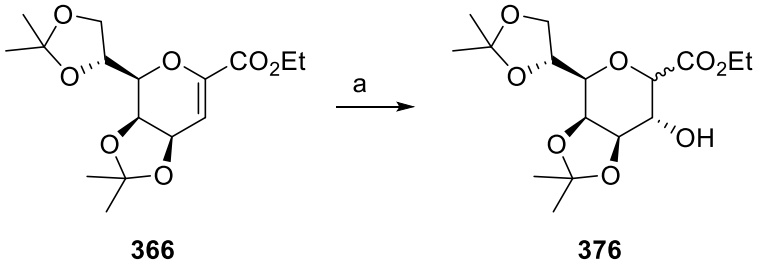
However, from a steric rationale, the desired compound **376** would be the major expected product since the trisubstituted C_{-1} position is more sterically hindered than the C_{-2} position; this effect would become more pronounced with bulkier boranes (**Scheme 129**).[55]



a) Hydroboration-oxidation using steric factors; b) Hydroboration-oxidation using electronic factors

Scheme 129: Predicted major regioisomer for a hydroboration-oxidation (with steric factors or electronic factors controlling regioselectivity) on glycal **366**.

As a result, due to a greater predicted regioselectivity for the desired product **376**, we chose to perform an oxymercuration-demercuration sequence on glycal **366** (**Scheme 130** and **Table 18**).



Reagents and conditions: a) see **Table 18.**

Scheme 130: Oxymercuration-demercuration attempts on glycal **366**.

Entry	Reagents and Conditions	Product
1[18]	$Hg(OAc)_2$ (1 equiv.), 1:1, THF:Water, 72 h, then 3M $NaOH_{(aq)}$ and $NaBH_4$ (0.5 M in 3M NaOH)	SM
2	$Hg(OAc)_2$ (1 equiv.), 70% $HClO_{4\,(aq)}$ (0.2 equiv.), 1:1 THF:Water, 72 h, then 3M $NaOH_{(aq)}$ and $NaBH_4$ (0.5 M in 3M NaOH)	SM
3	$Hg(TFA)_2$ (1 equiv.), 1:1, THF:Water, 72 h, then 3M $NaOH_{(aq)}$ and $NaBH_4$ (0.5 M in 3M NaOH)	SM
4	$Hg(TFA)_2$ (1 equiv.), 70% $HClO_{4\,(aq)}$ (0.2 equiv.), 1:1, THF:Water, 72 h, then 3M $NaOH_{(aq)}$ and $NaBH_4$ (0.5 M in 3M NaOH)	SM
5	$Hg(OAc)_2$ (1 equiv.), 70% $HClO_{4\,(aq)}$ (0.2 equiv.), 1:1, acetone:Water, 72 h, then 3M $NaOH_{(aq)}$ and $NaBH_4$ (0.5 M in 3M NaOH)	SM

Table 18: Conditions and results reported for the oxymercuration-demercuration attempts of glycal **366**.

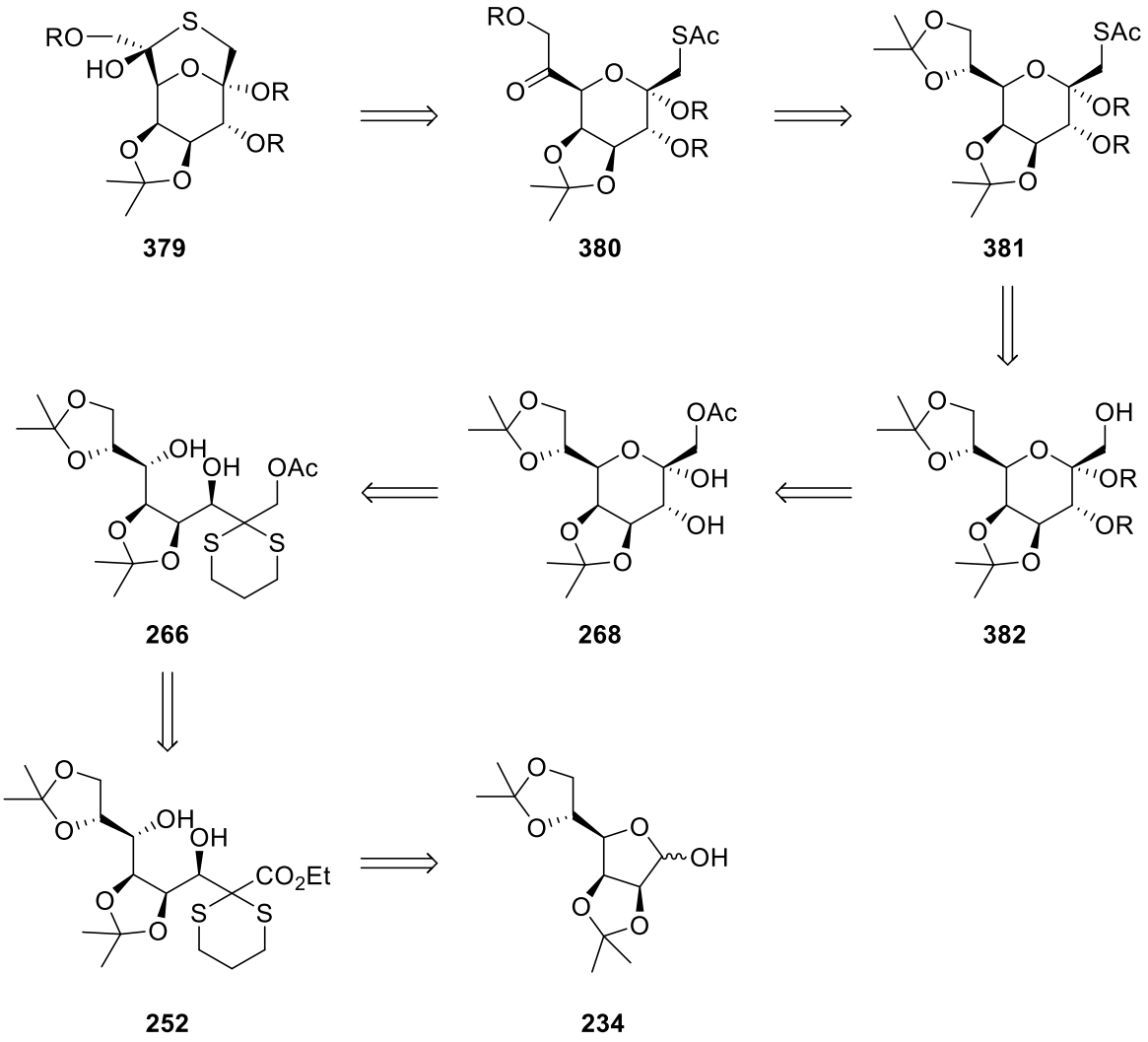
Similarly to the oxymercurations-demercurations processes previously attempted in the nitrile-Wittig route, we initially applied standard literature conditions to glycal **366** (entry 1).[18] However, even after very large reaction times (72 h), no change was observed by TLC. Although it would be unlikely for the organomercury compound and starting material to have the same retention factor (Rf) on silica gel, we still attempted the demercuration step, but after work-up, ^{1}H NMR analysis of the crude material indeed confirmed only starting material **366** was present. Even under greater activating conditions, such as the use of catalytic 70% perchloric acid and/or use of mercuric trifluoroacetate (entries 2- 4), no change in result occurred. An alternative solvent system also made no difference (entry 5).

These negative results suggest that despite the electron-donating ability of the ring oxygen, the alkene of **366** still seems to be too electron-deficient (due to the effects from the electron-withdrawing ester and ring oxygen) to react with the electrophilic mercuric reagents. However, this is perhaps surprising given of Yamaguchi and co-workers' successful oxymercuration-demercuration of their glycal **374** (**Scheme 127**).

We ceased further work on this route as our oxymercuration-demercuration reactions were unsuccessful, but future work regarding hydroboration-oxidations on glycal **366** was not excluded.

Dithiane-Reduction Route

The lack of success in the nitrile-Wittig, vinyl-transetherification and silyl enol ether routes prompted us to revisit the dithiane strategy established previously by the group (**Scheme 131**).[1,3]



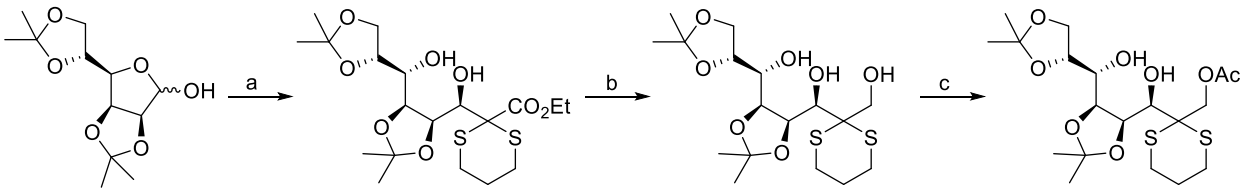
Scheme 131: The retrosynthesis of target **379** from DAM **234** in the Dithiane-Reduction route.

If target **379** were successfully synthesized, this route would be modified to install carboxylic acid derivatives on the C_{-1} and thiohemiketal centres.

As planned in previous routes, thioacetate cleavage of **380** should trigger the thiol/thiolate to cyclize onto the ketone to afford target **379**. The cyclization precursor **380** could be made by selective acetonide hydrolysis of **381** followed by selective protection of the primary alcohol and subsequent oxidation of the secondary alcohol. Similar to all previous routes, the thioacetyl functionality can be incorporated into the structure from **382** through a sequence involving displacement chemistry (i.e. activation of the primary hydroxyl group into a good leaving group and substitution of that leaving group with a thioacetate nucleophile in S_N2 fashion). Protection of the diol in pyranose **268** followed by deacetylation would afford intermediate **382**.

As already accomplished previously in the Page group, pyranose **268** could be synthesized from DAM **234** in four steps (**Schemes 64** and **65**).[1] We therefore planned to copy this four-step synthesis to **268**.

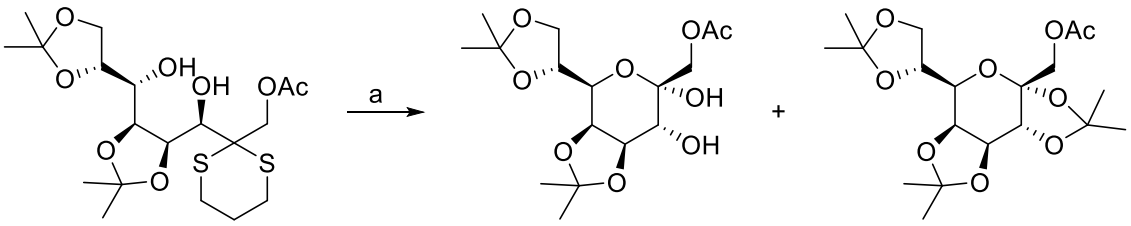
The route started with the nucleophilic addition of ethyl 1,3-dithiane-2-carboxylate (in the form of a functionalized Grignard reagent) to DAM **234** affording ester **252** in 97% yield (**Scheme 132**). Using LAH, the ester was then reduced to a primary alcohol, which in turn was selectively acetylated using acetic anhydride and triethylamine in DCM to form compound **266** in yields up to 75%.



Reagents and conditions: a) LDA, ethyl 1,3-dithiane-2-carboxylate, $MgBr_2$, THF, -20 °C, 2 h, then DAM **234**, -20 °C to rt, overnight, reflux, 5 h, 97%; b) $LiAlH_4$, THF, 0 °C to rt, 3 h, 96%; c) Ac_2O, Et_3N, DCM, overnight, 75%.

Scheme 132: Three step synthesis of **266** from DAM **234**.

We then intended to cleave the dithioketal in **266** and trigger the cyclization to form pyranose **268** using commercially available DBDMH in reagent grade acetone (**Scheme 133** and **Table 19**).



266 **268** **383**

Reagents and conditions: a) DBDMH, Acetone, 0 °C, 30 min, see **Table 19**.

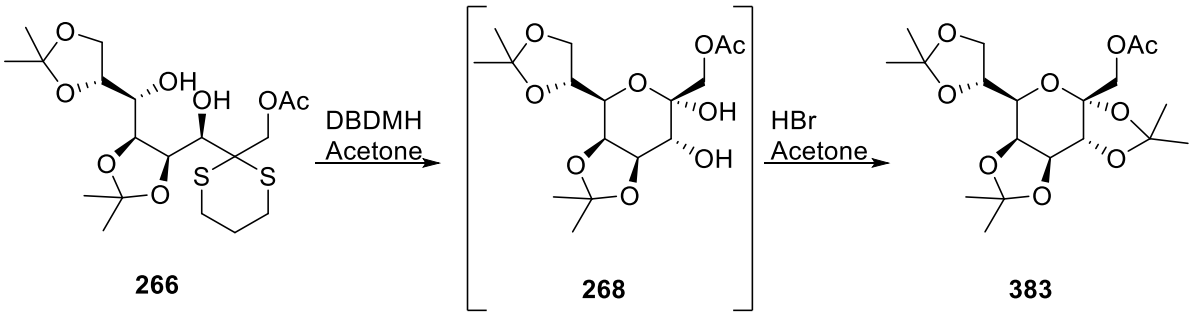
Scheme 133: Dethioketalization attempts on **266** using DBDMH.

Entry	DBDMH equiv.	Products
1	2.83	10% **383**
2 [a]	2.83	**268**
3 [a]	1	43% **383**
4 [a]	2	80-89% **383**

[a] Sample of DBDMH was recrystallized prior to use.

Table 19: Conditions and results obtained for the dethioketalization of **266**.

We initially performed the reaction in identical conditions to Pearce's successful dethioketalization of **266** (**Scheme 67**),[1] except for the solvent, where we used reagent grade acetone instead of 95% aqueous acetone (entry 1). The ^{1}H NMR spectrum of the crude material showed a complex mixture of compounds (indicating many side reactions and/or decomposition occurred). After purification, however, the triacetonide **383** was isolated in 7% yield. The formation of **383** could be explained by acetonide formation between the C_{-1} and C_{-2} hydroxyl groups in the intended product **268** (**Scheme 134**). This was possibly caused by the presence of catalytic quantities of HBr (possibly due to impure sample of DBDMH containing trace amounts of HBr and/or generated from reaction between DBDMH and water as the reaction was not under anhydrous conditions) accompanied by a large excess of acetone.

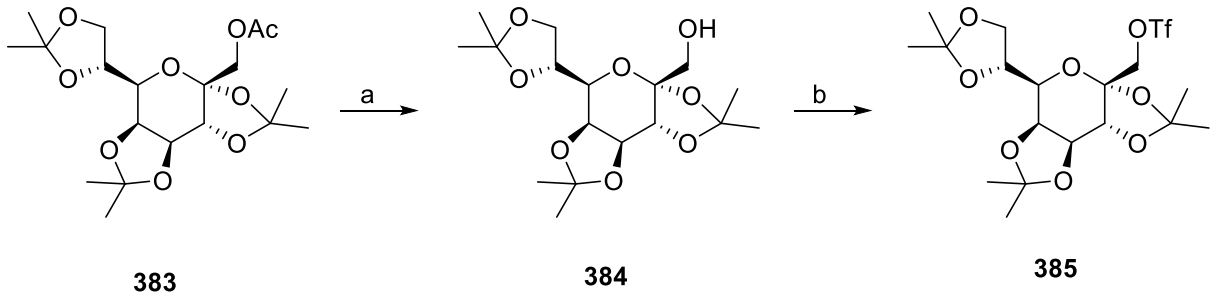


Scheme 134: Possible pathway for the production of triacetonide **383**.

In the retrosynthetic analysis for this route, pyranose **268** was initially planned to be synthesized from **266** by a dethioketalization and concomitant cyclization, then in a subsequent step, the C_{-1} and C_{-2} hydroxyl groups were to be protected with suitable groups. Hence, the formation of triacetonide **383** is very beneficial because it means the dethioketalization, cyclization and the protection of the C_{-1} and C_{-2} hydroxyl groups were achieved in one step rather than two. We therefore tried to optimize the conditions in order to achieve a high yield of triacetonide **383**.

With the aim of reducing the number of side reactions and/or decomposition, we repeated the reaction with purified DBDMH (recrystallized from water prior to use), but only **268** was observed in the ^{1}H NMR spectrum of the crude material (entry 2). However, by tailoring the equivalents of DBDMH (entries 3 and 4) we eventually produced **383** in yields as high as 89%.

Our next aim was to deprotect the acetyl group in **383**; this would allow us to activate the formed primary alcohol into a good leaving group, which would be needed subsequently to install the thioacetyl moiety into the structure by displacement chemistry. Deacetylation of **383** was achieved in 97% yield using K_2CO_3 in methanol according to a modified procedure from the literature (**Scheme 135**).[56] We planned to activate the primary alcohol as a triflate as these are known to be excellent leaving groups. Hence, a triflation of the primary alcohol was carried out to furnish **385** in 99% yield.

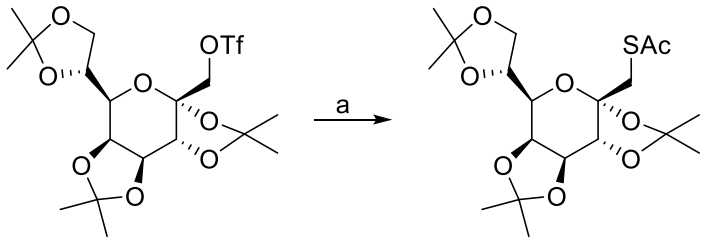


383 **384** **385**

Reagents and conditons: a) K_2CO_3, MeOH, rt, overnight, 97%; b) PY, Tf_2O, 0 ^oC to rt, 99%.

Scheme 135: Two-step synthesis of triflate **385** from **383**.

We proceed to the displacement of the triflate in **385** with a thioacetate nucleophile. Using slightly altered conditions to those of Repetto *et al.* we initially attempted the reaction using potassium thioacetate in acetonitrile for 16 h at rt (**Scheme 136**).[57] However, the conversion of triflate **385** to **386** was quite low. When repeating the reaction under refluxing conditions for 16 h, however, **386** was isolated in quantitative yield after work-up and purification.

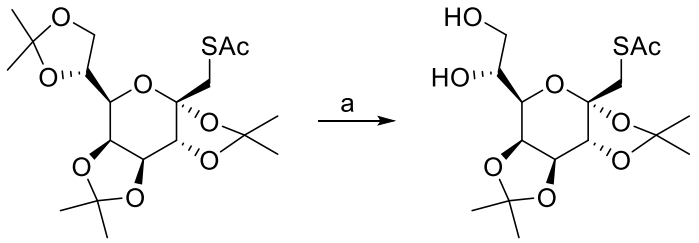


385 **386**

Reagents and condtions: a) KSAc, MeCN, reflux, 16 h, quant.

Scheme 136: Synthesis of **386** from **385**.

The next step involved the regioselective deprotection of the *exo*-cyclic acetonide. The conditions used were reported by Ma *et al.*, who successfully carried out a selective deprotection of a primary acetonide on a different substrate using 90% aqueous acetic acid at 40 ^oC.[58] Subjecting **386** to these conditions led us to obtain diol **387** in 80% yield (**Scheme 137**).

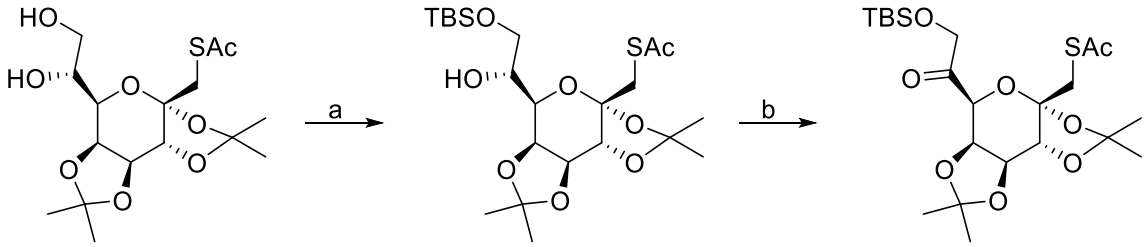


386 **387**

Reagents and conditions: a) 90% AcOH $_{(aq)}$, 40 ^{o}C, 24 h, 80%.

Scheme 137: Selective acetonide hydrolysis of **386**.

After successfully obtaining **387**, the next objective was to synthesize the precursor to target **379**/**391**. In order to do this, we then moved onto the selective protection of the primary alcohol in **387**; this would allow us subsequently to selectively oxidize the secondary alcohol into a ketone. Thus, the primary alcohol was selectively protected with the TBS group using standard conditions (**Scheme 138**). This was followed by a Swern oxidation, which provided the target precursor **389** in 86% yield.

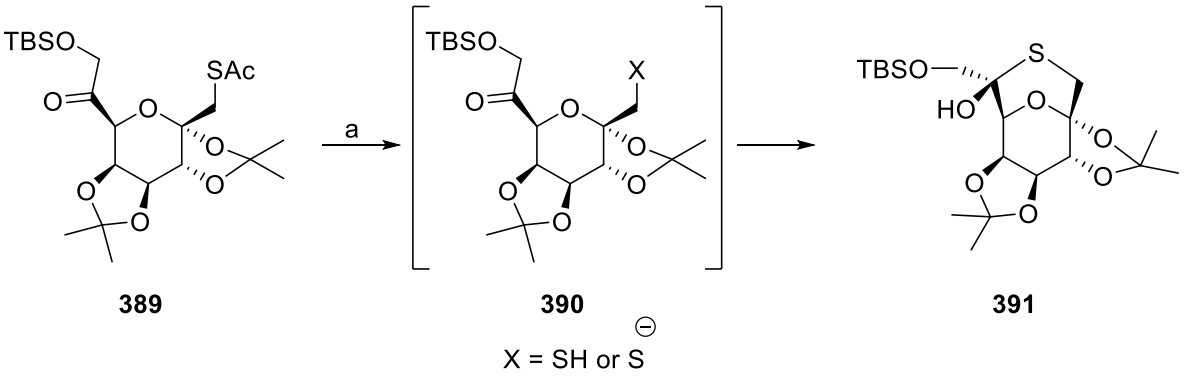


387 **388** **389**

Reagents and conditions: a) imidazole, TBSCl, DCM, 0 ^{o}C to rt, overnight, 63%; b) DMSO, $(CO)_2Cl_2$, - 78 ^{o}C, 30 mins, **388**, 1 h, Et_3N, -78 ^{o}C to rt, 86%.

Scheme 138: Synthesis of ketone **389**.

We were next tasked with the deprotection of the thioacetate in **389** to provide the thiol/thiolate intermediate **390**, which was expected to cyclize *in-situ* to furnish the synthetic target **391** (**Scheme 139** and **Table 20**).



Reagents and conditions: a) see **Table 20**.

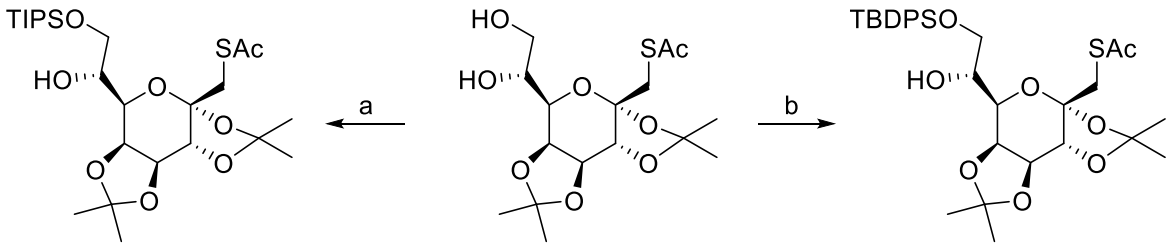
Scheme 139: Thioacetate deprotection attempts of compound **389**.

Entry	Reagents and Conditions	Result
1[59]	NaOMe, MeOH	Decomposition
2[60]	$NaHCO_3$, MeOH, reflux	Decomposition
3[60]	$NaHCO_3$, MeOH, rt	Decomposition
4[61]	K_2CO_3, MeOH	Decomposition
5[62]	NaSMe, MeOH	Decomposition
6[4,63]	$N_2H_4.H_2O$, MeOH	Complex mixture
7[64]	N_2H_4, THF	Complex mixture
8[65]	$N_2H_4.H_2O$, AcOH, DMF	Decomposition
9[66]	N_2H_5.OAc, THF	Decomposition

Table 20: Conditions and results obtained for the thioacetate deprotections of **389**.

Unfortunately, despite testing a large variety of deprotection procedures from the literature,[4,59–65] including common basic (entries 1 to 4), transthioesterification (entry 5) and hydrazinolysis (entries 6 to 9) conditions, only decomposition or complex mixtures were observed.

Since we were unable to obtain target **390** or even thiol **391**, we also used silyl protecting groups other than TBS, such as the TIPS and TBDPS groups. Hence, we selectively protected the primary alcohol in **387** with TIPS and TBDPS groups under standard conditions (**Scheme 140**).

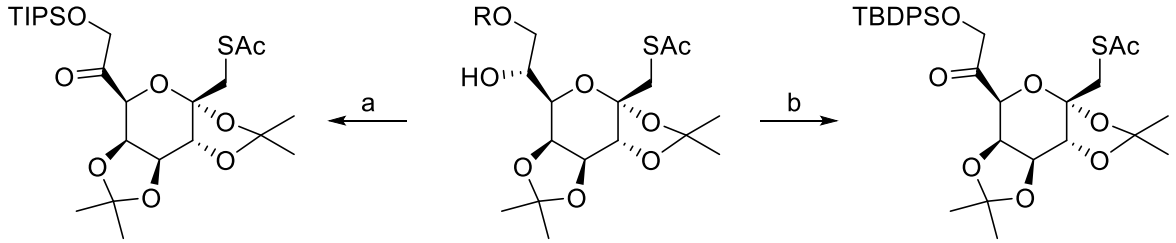


392 **387** **393**

Reagents and conditions: a) imidazole, DMAP, TIPSCl, DCM, 0 ^{o}C to rt, overnight, 90%; b) imidazole, DMAP, TBDPSCl, DCM, 0 ^{o}C to rt, 24 h, 74%.

Scheme 140: TIPS and TBDPS protection of the primary hydroxyl group in **387**.

Swern oxidations of the protected derivatives **392** and **393** were then carried out, allowing us to obtain ketones **394** and **395** (**Scheme 141**).

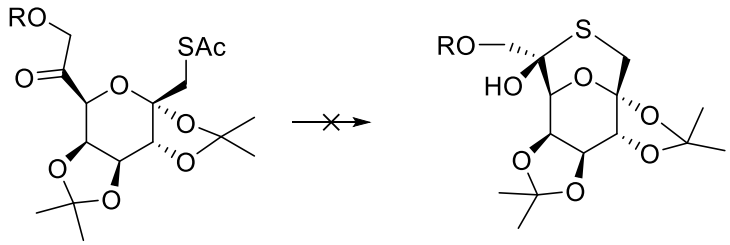


394 **392**; R = TIPS
393; R = TBDPS **395**

Reagents and conditions: a) DMSO, $(CO)_2Cl_2$, **-** 78 ^{o}C, 30 mins, **392**, 1 h, Et_3N, -78 ^{o}C to rt, 91% **394**.
b) DMSO, $(CO)_2Cl_2$, -78 ^{o}C, 30 mins, **393**, 1 h, Et_3N, -78 ^{o}C to rt, 83% **395.**

Scheme 141: Synthesis of ketones **394** and **395**.

Thioacetate deprotections of the TIPS and TBDPS-protected ketones **394** and **395** were then attempted. Regrettably, despite trying all the same procedures as previously carried out with the TBS ketone **381**, only decomposition or complex mixtures were seen (**Scheme 142**).

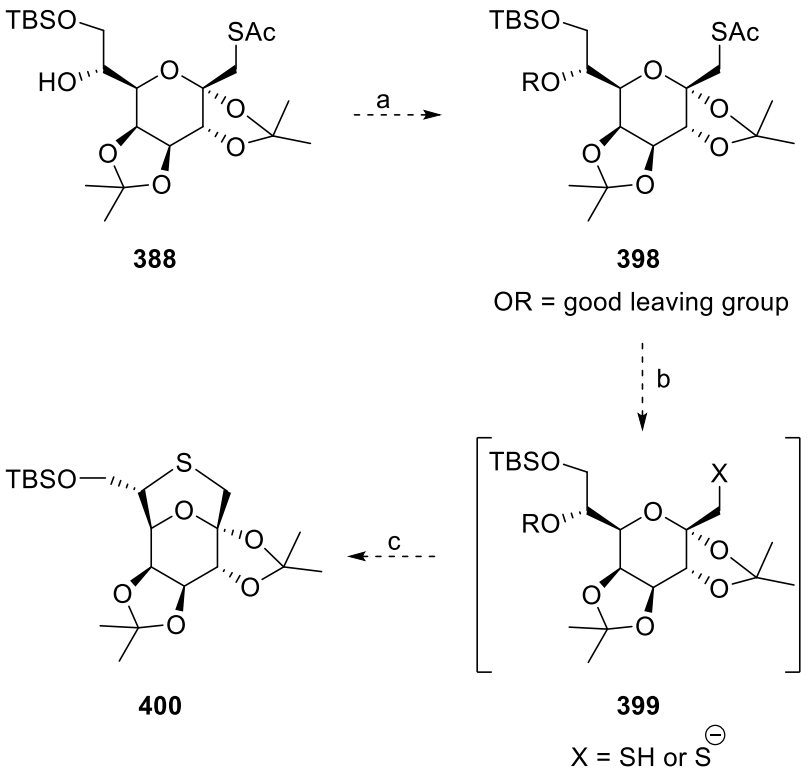


394; R = TIPS
395; R = TBDPS

396; R = TIPS
397; R = TBDPS

Scheme 142: Attempted syntheses of targets **396** and **397**.

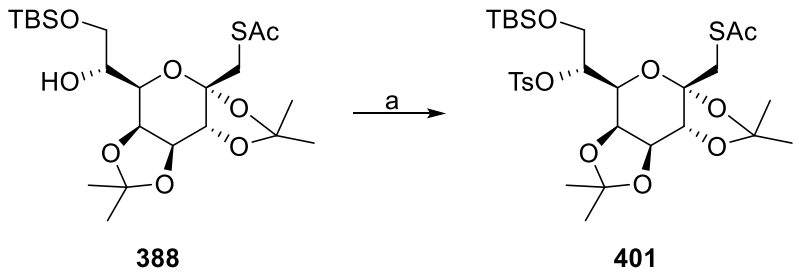
Confronted with these disappointing results, we decided to modify our cyclization strategy. In this strategy, instead of oxidizing the secondary alcohol in **388** to a ketone, we planned to activate it as a good leaving group such as a sulfonate ester (**Scheme 143**). The presence of a good leaving group in this position should aid the *in-situ* cyclization during the thioacetate deprotection. The major drawback to this strategy is the absence of a thiohemiketal functionality in target **400**. If **400** were successfully synthesized, however, the route would be revised to install a thiohemiketal functionality (for example using Pummerer reaction methodology).



Methodologies: a) activation of 2^{o} alcohol; b) thioacetate deprotection; c) *in-situ* cyclization.

Scheme 143: Proposed synthetic approach to target **400**.

We initially aimed to activate the hydroxyl group in **388** as a tosylate (**Scheme 144** and **Table 21**).



388 **401**

Reagents and conditions: a) see **Table 21**.

Scheme 144: Attempted tosylation of alcohol **388**.

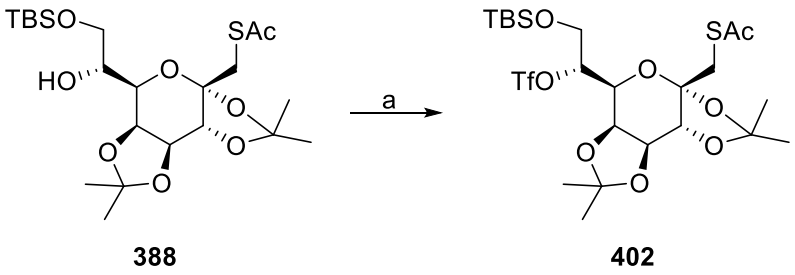
Entry	Reagents and Conditions [a]	Result
1[67]	Et_3N (1.5 equiv.), TsCl (1.1 equiv.), DCM	SM
2[68]	DMAP (1.9 equiv.), TsCl (1.46 equiv.), DCM	SM
3[69]	Et_3N (7 equiv.), DMAP (1 equiv.), TsCl (2 equiv.), DCM	SM
4[70]	DMAP (0.1 equiv.), TsCl (2 equiv.), pyridine [b]	SM

[a] reaction time: 72 h, temperature: 0 °C to rt; [b] 60 °C

Table 21: Conditions and results obtained for the attempted tosylation of alcohol **388**.

Using methods outlined in the literature (conditions increasing in severity from entries 1 to 4),[67–70] we did not obtain tosylate **401**, as only starting material was recovered. A possible reason for this failure could be steric hindrance in compound **401**. This is because the tosylation requires a secondary alcohol (adjacent to a large TBS group and pyranoid ring) to react with a bulky tosyl chloride electrophile, leading to a sterically congested transition state.

The lack of success in the tosylations prompted us to transform the secondary alcohol into a triflate (**Scheme 145**); this was accomplished in 96% yield under the same conditions used previously in the route (for the synthesis of **385** – **Scheme 135**).

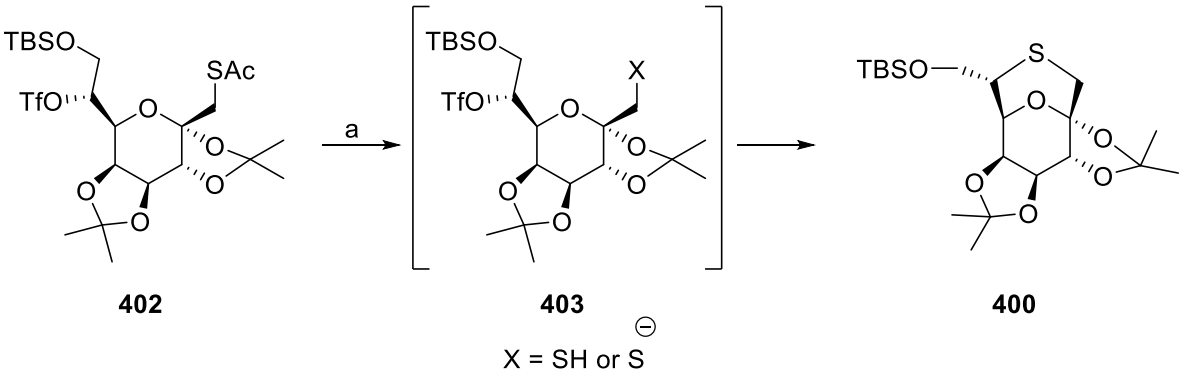


388 **402**

Reagents and conditions: a) PY, Tf_2O, 0 ^oC to rt, 96%.

Scheme 145: Synthesis of the secondary triflate **402**.

We proceeded to the thioacetate deprotection of triflate **402** (**Scheme 146** and **Table 22**). Similarly, to the previously attempted thioacetate deprotections of the ketone substrates **389**, **394** and **395**, however, the reaction was a failure as neither the thiol **403** or target **400** were isolated, only decomposition or complex mixtures were observed.



402 **403** **400**

X = SH or S ⊖

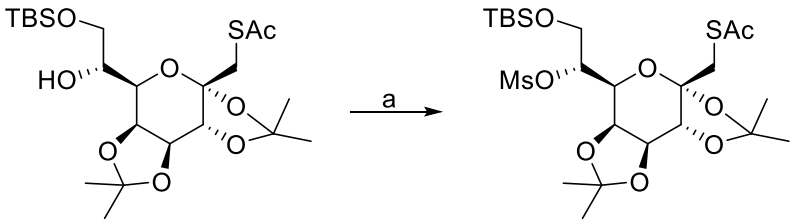
Reagents and conditions: a) see **Table 22**.

Scheme 146: Thioacetate deprotection attempts of compound **402**.

Entry	Reagents and Conditions	Result
1[59]	NaOMe, MeOH	Complex mixture
2[60]	$NaHCO_3$, MeOH, rt	Complex mixture
3[61]	K_2CO_3, MeOH	Complex mixture
4[62]	NaSMe, MeOH	Decomposition
5[4,63]	$N_2H_4.H_2O$, MeOH	Decomposition
6[64]	N_2H_4, THF	Decomposition
7[65]	$N_2H_4.H_2O$, AcOH, DMF	Complex mixture
8[66]	$N_2H_5.OAc$, THF	Decomposition

Table 22: Conditions and results obtained for the thioacetate deprotections of **402**.

We next decided to use a mesylate leaving group instead of a triflate to see if this could make any difference to the result of the thioacetate deprotections. We successfully synthesized mesylate **404** from compound **388** in 66% yield according to the conditions of Hoveyda *et al*. (**Scheme 147**).[71]

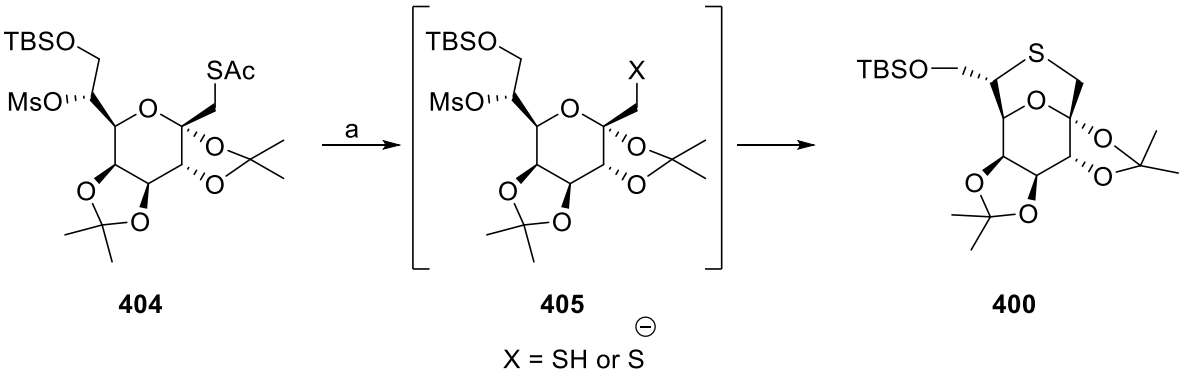


388 **404**

Reagents and conditions: a) Et_3N, MsCl, 0 ^oC to rt, 66%.

Scheme 147: Mesylation of **388**.

We attempted the thioacetate deprotection of **404**, but once again only decomposition and complex mixtures were observed (**Scheme 148** and **Table 23**).



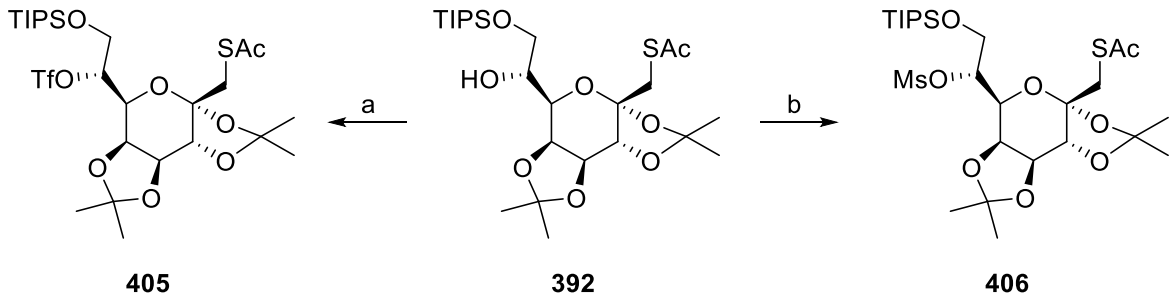
Reagents and conditions: a) see **Table 23**.

Scheme 148: Thioacetate deprotection attempts of compound **404**.

Entry	Reagents and Conditions	Result
1[59]	NaOMe, MeOH	Decomposition
2[60]	$NaHCO_3$, MeOH, rt	Complex mixture
3[61]	K_2CO_3, MeOH	Complex mixture
4[62]	NaSMe, MeOH	Decomposition
5[4,63]	$N_2H_4.H_2O$, MeOH	Decomposition
6[64]	N_2H_4, THF	Decomposition
7[65]	$N_2H_4.H_2O$, AcOH, DMF	Decomposition
8[66]	N_2H_5.OAc, THF	Decomposition

Table 23: Conditions and results obtained for the thioacetate deprotection of **404**.

With the lack of success using the TBS group in the attempted thioacetate deprotections of triflate **402** and mesylate **404**, we planned to use the TIPS group instead. As a result, under the same conditions used previously (for the synthesis of **402** and **404**) we synthesized the TIPS triflate **405** and mesylate **406** from **392** in yields of 98% and 64% respectively (**Scheme 149**).

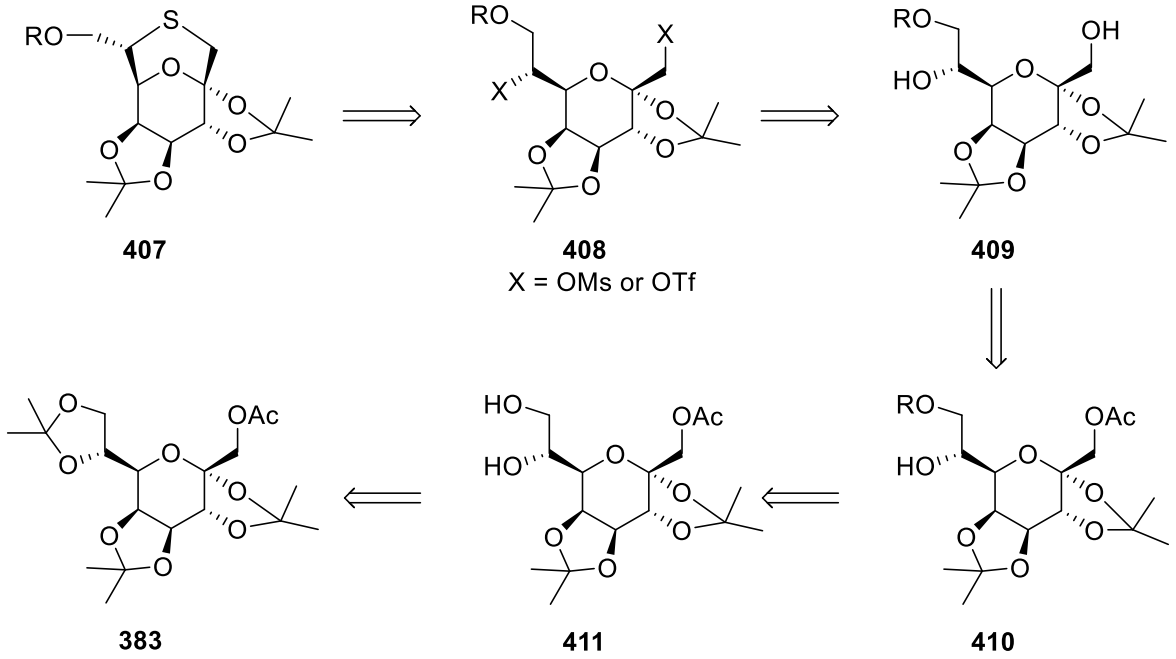


Reagents and conditions: a) PY, Tf_2O, 0 °C to rt, 98%; b) Et_3N, MsCl, 0 °C to rt, 64%.

Scheme 149: Triflation and mesylation of 392.

We then attempted the thioacetate deprotections (under all the same conditions previously tried for the TBS triflate **402** and mesylate **404**) of **405** and **406**. To our disappointment, only decomposition occurred.

The failure of the thioacetate deprotections in all the ketone, triflate and mesylate substrates, led us to consider a new route with a different cyclization strategy (**Scheme 150**).

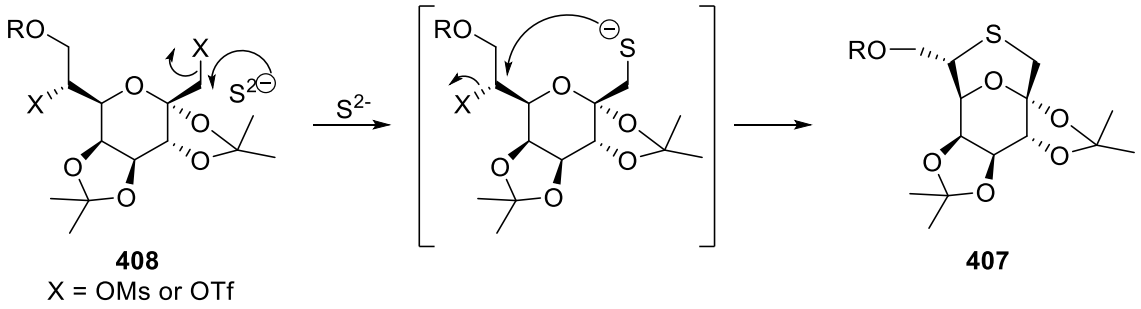


Scheme 150: Retrosynthetic analysis for target **407** compound **383**.

The 1,4-oxathiane moiety in target **407** could be made from the reaction between the disulfonate ester **408** and a sulfide anion (deriving from Li_2S or Na_2S). Sulfonylation of both hydroxyl

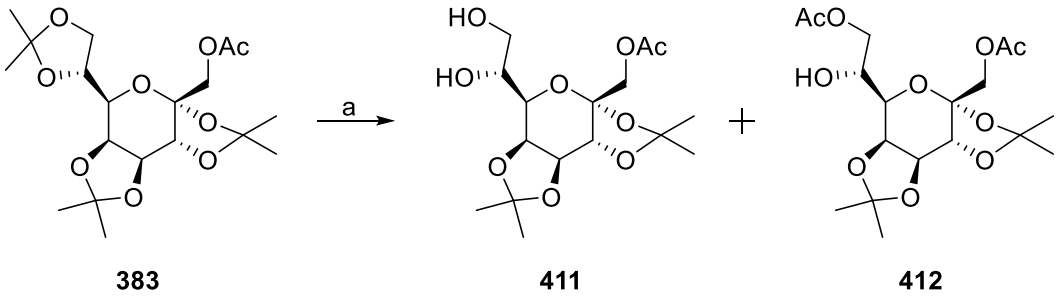
groups in **409** would lead to the target precursor **408**. Diol **409** could be made from deacetylation of compound **410**, which in turn could be synthesized from selective protection of the primary hydroxyl group in **411**. Regioselective isopropylidene hydrolysis of **383** could afford compound **411**. Compound **383** has already been made earlier in the route (in four synthetic steps from DAM **234**).

The key step in this strategy is the cyclization to target **407**. This step would involve two consecutive S_N2 reactions: the first being the substitution of the primary sulfonate ester with the sulfide ion, forming a thiolate, which in turn would intramolecularly displace the secondary sulfonate ester *in-situ* (**Scheme 151**).



Scheme 151: Proposed mechanism for the synthesis of target **407** from disulfonate ester **408**.

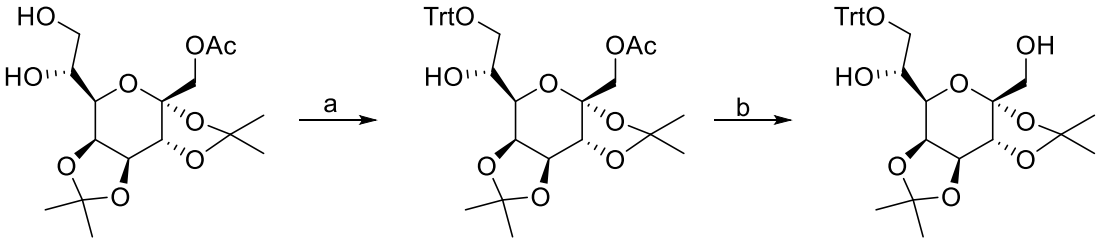
This route started with a selective acetonide hydrolysis of **383** using aqueous acetic acid (**Scheme 152**). The reaction afforded diol **411** in 90% yield, though a diacetylated side product **412** was also isolated in low yields (the extra acetylation was probably formed by Fischer esterification of the primary alcohol).



Reagents and conditions: a) 80% $AcOH_{(aq)}$, 50 ^{o}C, 90% **411** and 3% **412**.

Scheme 152: Regioselective isopropylidene hydrolysis of **383**.

The next step involved the selective protection of the primary alcohol; we chose to use the trityl protecting group. Regioselective tritylation of **411** was achieved in 89% yield using conditions from Peyrat *et al.*[72] Treatment of the trityl-protected compound **413** with sodium methoxide in methanol led to deacetylation, which furnished **414** in 94% yield (**Scheme 153**).

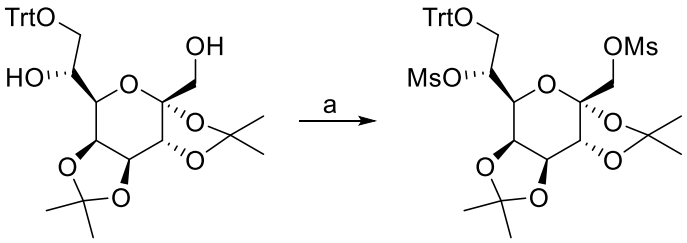


411 **413** **414**

Reagents and conditions: a) Et_3N, trityl chloride, 0 °C to rt, overnight, 89%; b) NaOMe, MeOH, 94%.

Scheme 153: Two-step synthesis of **414** from **411**.

We then aimed to activate both hydroxyl groups in **414** as mesylates. The dimesylation was carried out under conditions according to the literature,[73] which afforded **415** in 70% yield (**Scheme 154**).

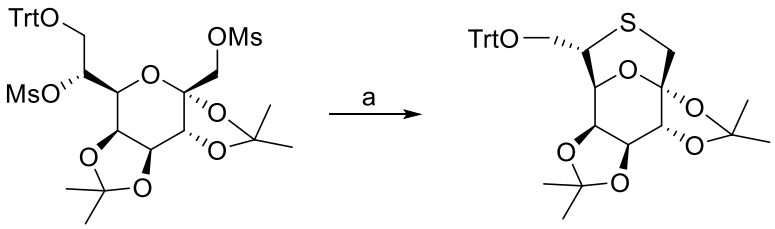


414 **415**

Reagents and conditions: a) Et_3N, MsCl, 0 °C to rt, 2 h, 70%.

Scheme 154: Dimesylation of **414**.

With dimesylate **415** in hand, we then attempted the cyclization to target **416** using an array of conditions from the literature (**Scheme 155** and **Table 24**).



415 **416**

Reagents and conditions: a) see **Table 24**.

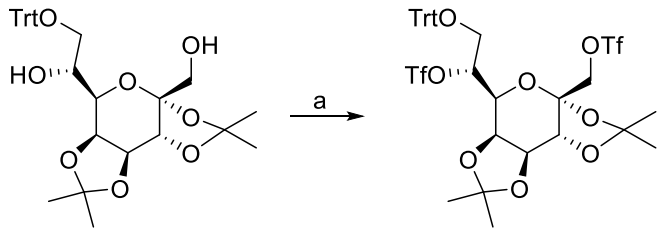
Scheme 155: Attempted synthesis of target **416** from dimesylate **415**.

Entry	Reagents and conditions	Result
1[74]	Li_2S, DMF, rt	SM
2[74]	Li_2S, DMSO, rt	SM
3[75]	Na_2S, DMSO, rt	SM
4[76]	Na_2S, DMF, 80 ºC	SM
5[77]	Na_2S, DMF, 100 ºC	SM
6[75]	Na_2S, DMSO:MeOH (2:1), 60 ºC	SM
7[78]	Na_2S, MeOH, reflux	SM
8[79]	Na_2S, EtOH, reflux	SM

Table 24: Conditions and results obtained for the attempted cyclization of **415**.

When **415** was subjected to conventional conditions such as lithium or sodium sulfide in a polar aprotic solvent (entries 1 to 5), only starting material was observed despite long reaction times. Repeating entries 1 to 3 at higher temperatures made no difference. Attempting other literature conditions (entries 4 to 8) led to the same unwanted outcome. Given the previous success of the thioacetate displacement of the triflate in **385**, these results were perhaps surprising, since we expected that at least the relatively unhindered primary mesylate of **415** would be displaced fairly easily by the sulfide anion.

Due to the lack of reactivity of dimesylate **415** with sulfide anions, we decided to transform both hydroxyl groups in **414** to triflates (as these are better leaving groups than mesylates). Hence, using a modified procedure from the literature,[80] **414** was treated with pyridine and triflic anhydride, giving ditriflate **417** (**Scheme 156**).

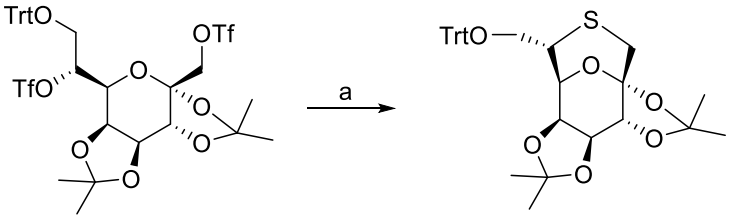


414 **417**

Reagents and conditions: a) PY, Tf_2O, 0 ^oC, 87%.

Scheme 156: Ditriflation of **414**.

The cyclization of **417** into target **416** was then attempted under a range of conditions (**Scheme 157** and **Table 25**). Unfortunately, in each attempt only decomposition or complex mixtures were observed. We also attempted the cyclization under milder conditions (entry 8) whereby the reaction was carried out at 0 ^oC, but a complex mixture still resulted.



417 **416**

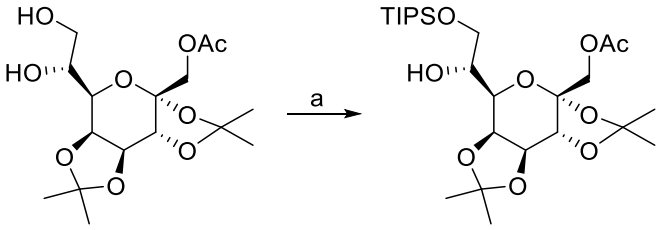
Reagents and conditions: a) see **Table 25.**

Scheme 157: Attempted synthesis of target **416** from ditriflate **417**.

Entry	Reagents and conditions	Result
1[74]	Li_2S, DMF, rt	Decomposition
2[74]	Li_2S, DMSO, rt	Decomposition
3[75]	Na_2S, DMSO, rt	Decomposition
4[76]	Na_2S, DMF, 80 ^oC	Complex mixture
5[75]	Na_2S, DMSO:MeOH (2:1), 60 ^oC	Decomposition
6[78]	Na_2S, MeOH, reflux	Complex mixture
7[79]	Na_2S, EtOH, reflux	Decomposition
8	Na_2S, DMF, 0 ^oC	Complex mixture

Table 25: Conditions and results obtained for the attempted cyclization of **417**.

We considered that one possible reason for the failures of the cyclizations to target **416** from dimesylate **415** and ditriflate **417** could be due to the large trityl group sterically hindering the secondary sulfonate ester. As a result, we decided to use a slightly less bulky TIPS group to protect the primary alcohol in **411** instead; this was accomplished in 89% yield (**Scheme 158**) under the same conditions previously used for the TIPS-protection of **387**.

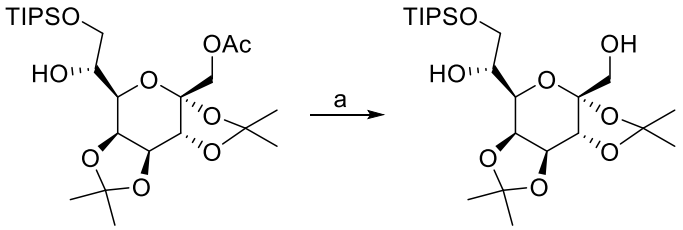


411 **418**

Reagents and conditions: a) imidazole, DMAP, TIPSCl, DCM, 0 °C to rt, 24 h, 89%.

Scheme 158: Regioselective TIPS protection of the primary hydroxyl group in **411**.

The next step involved the deacetylation of **418** (**Scheme 159** and **Table 26**). Surprisingly, this deacetylation step appeared more problematic than initially envisaged.



418 **419**

Reagents and conditions: a) see **Table 26.**

Scheme 159: Deacetylation attempts of **418**.

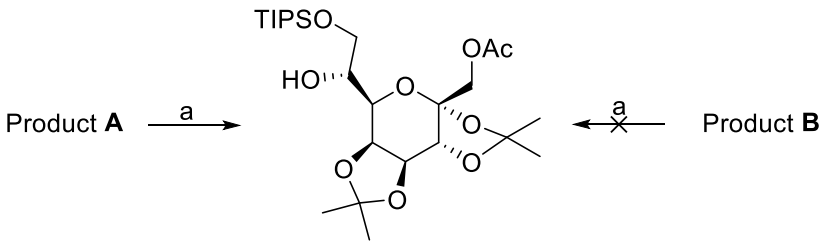
Entry	Reagents and conditions [a]	Results
1	NaOMe, MeOH, 3 h	77% **A**, 18% **B**
2	K_2CO_3, MeOH, 4 h	77% **A**, 13% **B**
3	DIBAL, THF	69% **A**

[a] room temperature

Table 26: Conditions and results reported for the attempted deacetylations of **418**

We initially attempted the deacetylation using sodium methoxide in methanol (entry 1). However, we isolated two isomeric products; a major product **A** and a minor product **B**. From NMR, IR and MS analysis we concluded that either of these products could be the desired compound **419**. When performing another base-promoted deacetylation using K_2CO_3 in methanol (entry 2), the same two isomeric products were isolated in similar yields to entry 1.

In order to diagnose whether product **A** or **B** is the desired compound **419**, we planned to mono-acetylate **A** and **B** respectively; If **A** is **419**, then mono-acetylation of **A** should lead to **418** (**418** has previously been made earlier in the route) and mono-acetylation of **B** will not lead to **418** (or vice versa). We found that in contrast to **B**, mono-acetylation of **A** produced **418** (**Scheme 160**); thus, we concluded that **A** is the desired product **419**.

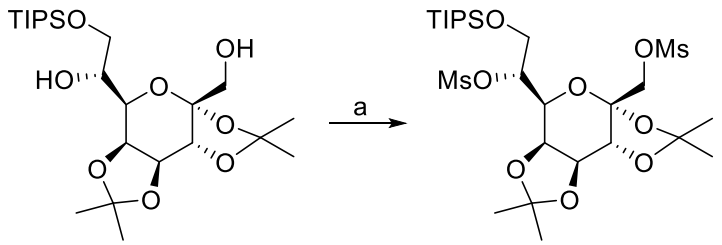


Reagents and conditions: a) Et_3N, Ac_2O, DCM, 0 ^oC to rt.

Scheme 160: Mono-acetylation of products **A** and **B**.

When performing the deacetylation under reductive rather than basic conditions (entry 3), only **419** (i.e. product **A**) was isolated. This indicates that the side reaction leading to the production of **B** requires basic conditions. Therefore, we speculate that **B** is formed from a base-promoted 1,4-intramolecular migration of the TIPS group in **419** (though more experiments would be required to confirm this).

Using the same conditions previously carried out (for **415**), both hydroxyl groups in **419** were then transformed into mesylates (**Scheme 161**).

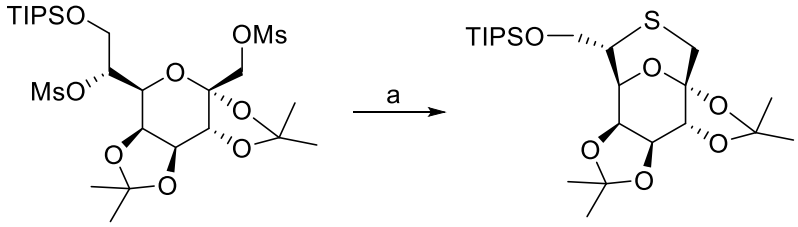


419 **420**

Reagents and conditions: a) Et_3N, MsCl, 0 ^oC to rt, 2 h, 85%.

Scheme 161: Dimesylation of **419**.

We then attempted the cyclization of **420** to give target **421** under a range of conditions (**Scheme 162** and **Table 27**). Yet, as with the attempted cyclizations with the trityl protected dimesylate **415**, only starting material was recovered with no trace of target **421** seen.



420 **421**

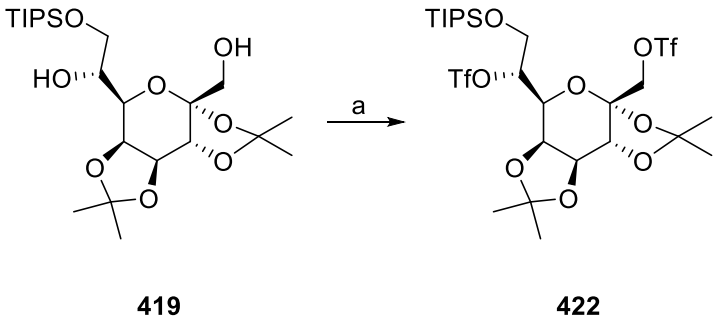
Reagents and conditions: a) see **Table 27**.

Scheme 162: Attempted synthesis of target **421** from dimesylate **420**.

Entry	Reagents and conditions	Result
1[74]	Li_2S, DMF, rt	SM
2[74]	Li_2S, DMSO, rt	SM
3[75]	Na_2S, DMSO, rt	SM
4[76]	Na_2S, DMF, 80 ^oC	SM
5[77]	Na_2S, DMF, 100 ^oC	SM
6[75]	Na_2S, DMSO:MeOH (2:1), 60 ^oC	SM
7[78]	Na_2S, MeOH, reflux	SM
8[79]	Na_2S, EtOH, reflux	SM

Table 27: Conditions and results obtained for the attempted cyclization of **420**.

Due to the failure of the cyclizations with the TIPS-protected dimesylate **420**, we planned to attempt the cyclizations with a ditriflate instead. Consequently, a ditriflation on **419** was completed, affording **422** in near quantitative yield (**Scheme 163**).

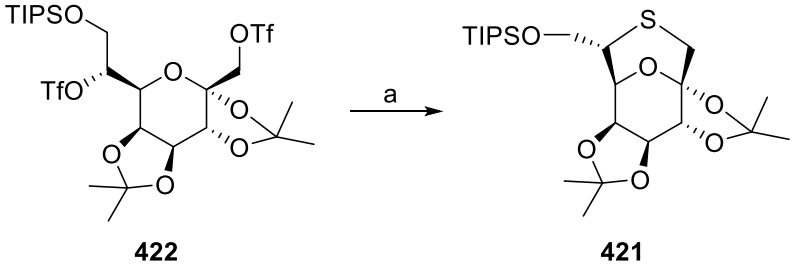


419 **422**

Reagents and conditions: a) PY, Tf_2O, 0 ^oC, 99%.

Scheme 163: Ditriflation of **419**.

With ditriflate **422** in hand we attempted the cyclizations with the sulfide anion, again under a range of conditions (**Scheme 164** and **Table 28**).



422 **421**

Reagents and conditions: a) see **Table 28**.

Scheme 164: Attempted synthesis of target **421** from ditriflate **422**.

Entry	Reagents and conditions	Result
1[74]	Li_2S, DMF, rt	Trace unknown product
2[74]	Li_2S, DMSO, rt	Unknown product
3[75]	Na_2S, DMSO, rt	Trace unknown product
4[76]	Na_2S, DMF, 80 ^oC	Decomposition
5[75]	Na_2S, DMSO:MeOH (2:1), 60 ^oC	Decomposition
6[78]	Na_2S, MeOH, reflux	Decomposition
7[79]	Na_2S, EtOH, reflux	Complex mixture
8	Na_2S, DMF, 0 ^oC	Decomposition

Table 28: Conditions and results obtained for the attempted cyclization of **422**.

Interestingly, in three sets of conditions (entries 1 to 3), the same unknown product was isolated in variable yields; thorough NMR and MS analysis ruled out this product from being target **421** or an intermediate thiol. Decomposition and complex mixtures were observed in the rest of the attempts (entries 4 to 8).

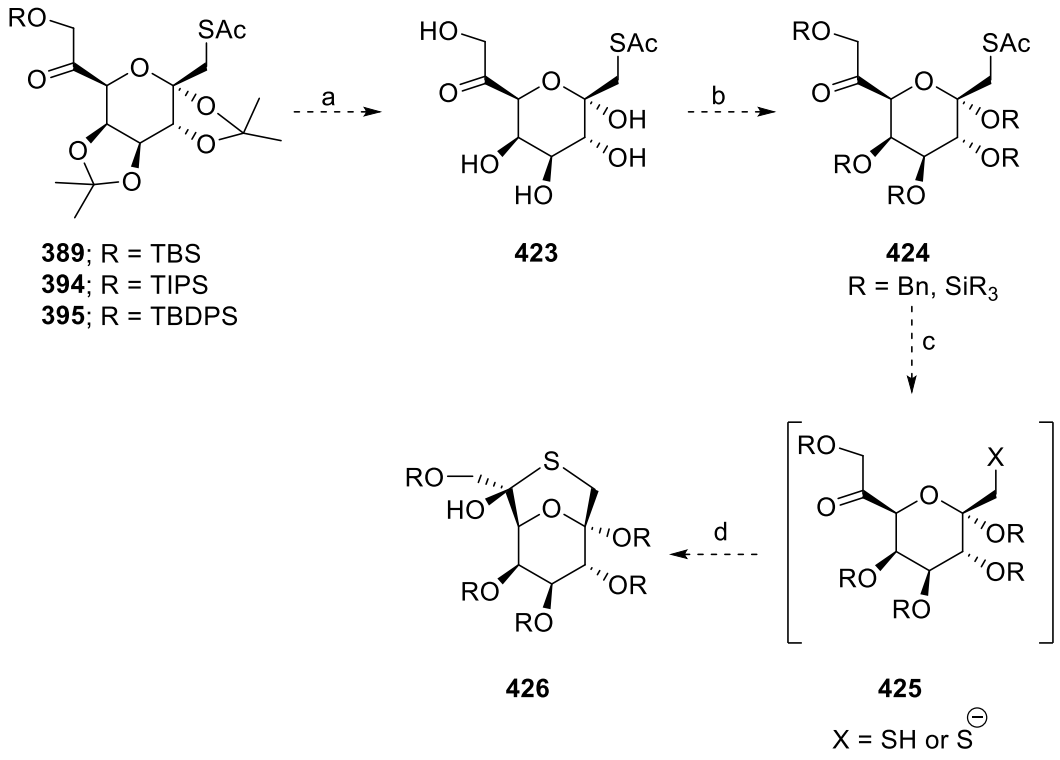
We concluded any future work with this cyclization strategy due to the failure of the cyclizations with the trityl-protected and TIPS-protected sulfonate esters **415**, **417**, **420** and **422**.

In the dithiane-reduction route, three cyclization strategies were attempted on numerous substrates:

1. Thioacetate deprotection and *in-situ* cyclization of the liberated thiol/thiolate onto a ketone.
2. Thioacetate deprotection and *in-situ* cyclization of the liberated thiol/thiolate onto a sulfonate ester.
3. Displacement of two sulfonate esters using a sulfide anion.

A common trait that all the substrates for these cyclization strategies have, are the two cyclic isopropylidene groups. Given that all three strategies failed, we postulated that maybe the presence of isopropylidene groups hinder the cyclization as they lead to steric constraints being

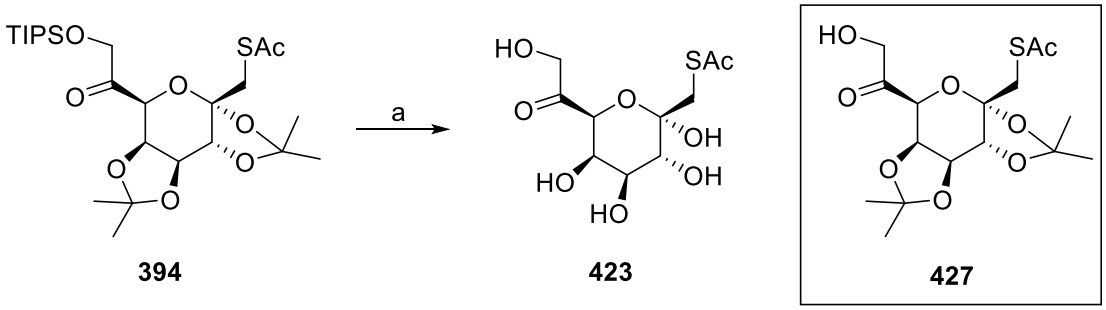
placed on ring closure. A consequence for the failure of the cyclization could lead to a whole host of side reactions occurring instead (leading to decomposition or complex mixtures being observed). We therefore aimed to attempt our initial cyclization approach with a substrate without any acetonide groups; we postulated that this could be achieved in three steps from either of the ketone substrates **389**, **394** or **395** (**Scheme 165**).



Methodologies: a) isopropylidene hydrolysis; b) protection with benzyl or silyl groups; c) thioacetate deprotection; d) *in-situ* cyclization.

Scheme 165: Proposed synthetic approach to target **426** from ketones **389**, **394** or **395.**

We chose to attempt this synthesis starting from the TIPS-protected ketone substrate **394.** Hence, our initial objective was to hydrolyse both acetonide groups in **394** (**Scheme 166** and **Table 29**).



394 **423** **427**

Reagents and conditions: a) see **Table 29**.

Scheme 166: Acetonide hydrolysis attempts on **394**.

Entry	Reagents and conditions	Results
1[81]	80% $AcOH_{(aq)}$, 70 °C	66% **427**
2	80% $AcOH_{(aq)}$, 90 °C	Decomposition
3[82]	90% $TFA_{(aq)}$, rt,	Decomposition
4[83]	H_2O:AcOH:TFA (2:3:5), rt	Decomposition
5[84]	DCM:TFA (2:1), rt	Decomposition
6[85]	$BF_3.OEt_2$, DCM:MeOH (1:1), rt	Decomposition
7[85]	$BF_3.OEt_2$, DCE:MeOH (1:1), rt	Decomposition
8[86]	1M $HCl_{(aq)}$:THF (1:1), rt	Decomposition

Table 29: Conditions and results reported for the attempted acetonide hydrolyses of **427**.

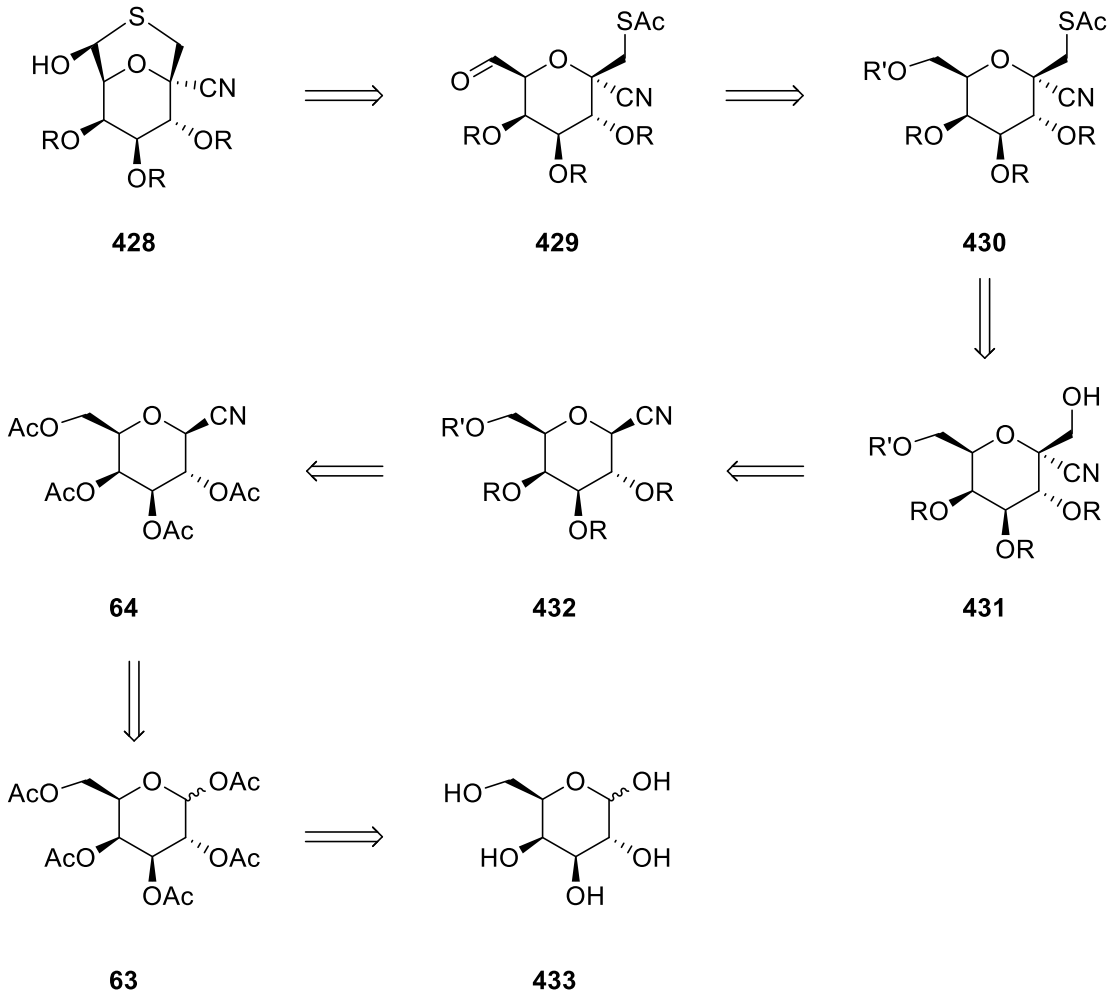
In our first attempt (entry 1), we attempted hydrolysis of both acetonide groups using 80% aqueous acetic acid at 70 °C according to a procedure by Komizo *et al.*[81] However, these conditions were not strong enough to hydrolyse the acetonides because only TIPS deprotection occurred, affording compound **427** in 66% yield. Heating at longer reaction times (~72 h) made no difference. We therefore heated the reaction mixture at higher temperatures (entry 2), but only decomposition was observed. Following this, we tested a range of conditions from the literature,[82–86] such as TFA, Lewis acid and aqueous HCl based procedures (entries 3 to 8), but only decomposition was found.

The lack of success in the three cyclization strategies and in the subsequent acetonide deprotections led us to abandon this route. However, in any future route we decided to not

incorporate any isopropylidene groups in the synthesis, as they could be hindering the cyclization to the bicyclic core by imposing steric constraints on ring closure.

D-Galactose Route

In this route, we planned to synthesize target **428** from D-galactose **433**, without any use of isopropylidene protecting groups (**Scheme 167**).

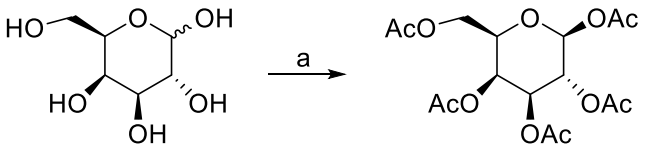


Scheme 167: Retrosynthesis of target structure **428** from D-galactose **433** in the D-galactose route.

If successful, this route would be revised and altered to install a carboxylic acid derivative on the thiohemiacetal centre in target **428**.

The bicyclic target structure **428** could be made from thioacetate deprotection of **429** and consequent *in-situ* cyclization of the thiol/thiolate onto the aldehyde. The target precursor **429** could be made from selective deprotection of the primary hydroxyl group in **430**, followed by oxidation into an aldehyde. Activation of the primary alcohol in **431** and subsequent substitution with a thioacetate nucleophile could form thioacetate **430**. Reaction between the anomeric nitrile anion of **432** with a formaldehyde electrophile would introduce the hydroxy methylene functional group. Intermediate **432** could be made from compound **64** in three steps: deacetylation of **64**; selective protection of the primary hydroxyl group (e.g. silyl protection); and protection of the three secondary hydroxyl groups (e.g. perbenzylation). Compound **64** could be made from D-galactose **433** in two steps. The first step would be a peracetylation of D-galactose to form D-galactose pentaacetate **63**, which in turn can then undergo a C-glycosylation reaction with TMSCN to form **64**; both these steps have already been accomplished in the literature.[87–89]

The route started with the peracetylation of D-galactose **433** (**Scheme 168**). Subjecting D-galactose **433** to typical literature conditions of NaOAc in Ac_2O at 120 ^oC,[87] led to the isolation of **β-63** in 64% yield.



433 **β-63**

Reagents and conditions: a) NaOAc, Ac_2O, 120 ^oC, 3 h, 64%.

Scheme 168: Synthesis of **β-63**.

The production of three other isomeric pentaacetate compounds (**Figure 16**) in this reaction contributed to the lower than expected yield of **β-63**. Nevertheless, **β-63** was still isolated from the mixture using a recrystallization procedure reported by Liu *et al.*[90]

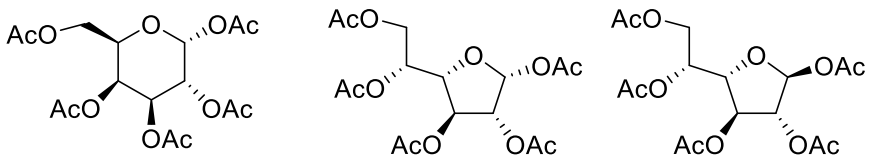
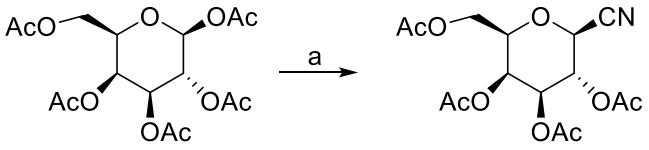


Figure 16: Other pentaacetate derivatives formed in peracetylation of D-galactose **433**.

It was also inferred that the reaction time was critical in achieving sufficient yields for **β-63**. For example, a reaction time too long (e.g. greater than 5 hours) generated increased amounts of the undesired pentaacetate furanoses at the expense of **β-63**, leading to yields being as low as 5%. Conversely, too short reaction times additionally led to low yields because of poor conversion to the penta-acetylated derivatives. It was found that the optimum reaction time was 3 hours.

Compound **α-63** was not isolated even though it could be used in the subsequent C-glycosylation step. This is because purification and isolation of **α-63** from the pentaacetate furanosides **α-434** and **β-434** by recrystallization and column chromatography proved difficult. Furthermore, from the molar ratios between **α-63**, **β-63**, **α-434** and **β-434** in the ^{1}H NMR spectrum of the crude material, if isolated, maximum yields of **α-63** would only be ~10-15%.

The C-glycosylation of **β-63** was then performed. According to conditions outlined in the literature,[88,89] **β-63** was treated with TMSCN and a Lewis acid ($BF_3.OEt_2$) in a polar aprotic solvent, furnishing glycosyl nitrile **64** in 67% yield (**Scheme 169**).

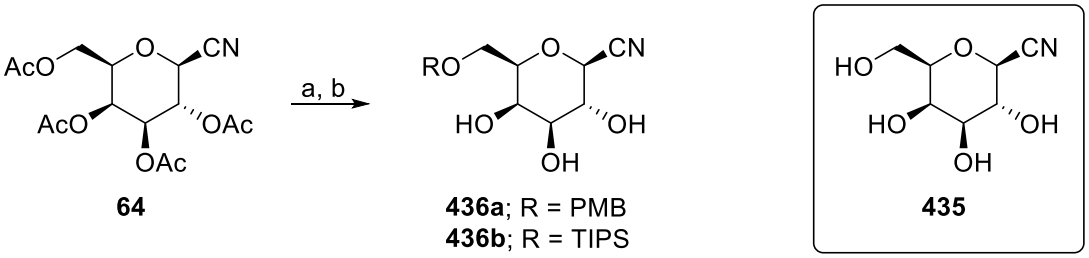


β-63 64

Reagents and conditions: a) TMSCN, $BF_3.OEt_2$, NO_2Me, 35-37 ^{o}C, 2 h, 67%.

Scheme 169: C-glycosylation of **β-63** with TMSCN.

The next goal in the route was the deprotection of the acetate groups in **64** followed by the selective protection of the primary alcohol (**Scheme 170** and **Table 30**).



64 **436a**; R = PMB **436b**; R = TIPS **435**

Reagents and Conditions: a) NaOMe (0.18 equiv.), MeOH, rt, 2 h; b) see **Table 30**.

Scheme 170: Deacetylation of **64** and selective protection of the primary alcohol.

Entry	R	Reagents and conditions [a]	Result
1[91]	PMB	NaH (1 equiv.), PMBCl (1 equiv.), DMF, 24 h	Complex mixture
2[92]	TIPS	Imidazole (2.5 equiv.), TIPSCl (1.5 equiv.), DMF, 72 h	26% **436b** (over 2 steps)
3	TIPS	Imidazole (4 equiv.), TIPSCl (2 equiv.), DMF, 72 h	42% **436b** (over 2 steps)

[a] Temperature: 0 °C to rt.

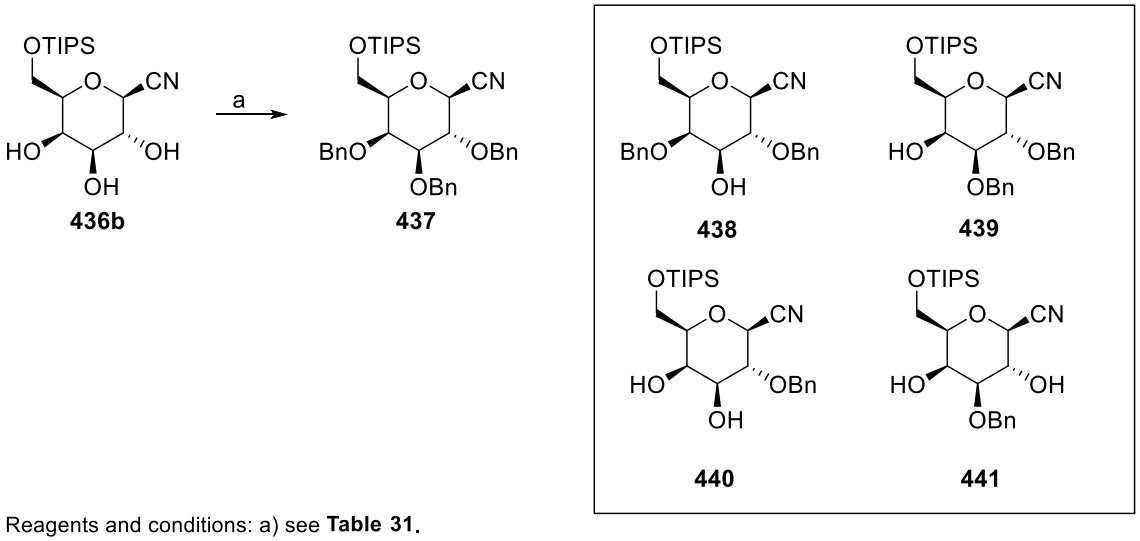
Table 30: Conditions and results reported for the regioselective protection.

From the literature,[92] we used sub-stoichiometric quantities of sodium methoxide in methanol for the deacetylation. The ^{1}H and ^{13}C NMR spectra of the crude material confirmed that all the acetates have been cleaved successfully and that the major product in the mixture was **435**. There were, however, a number of signals in the spectra belonging to impurities. Purification attempts by column chromatography on silica gel or alumina failed because the mixture was 'lost' with no recovery (perhaps due to its high polarity). We also tried to purify the mixture by recrystallization using numerous solvents, but this failed as well. Consequently, the crude mixture was used directly for the next step.

We initially tried to protect the primary alcohol selectively with a PMB group using modified conditions from the literature,[91] but only a complex mixture was observed (entry 1). We therefore tried a protection with the larger TIPS group (entries 2 and 3). Using conditions from Balmond *et al.*[92] we successfully isolated compound **436b**, albeit only in 26% yield (entry 2). This low yield occurred due to the poor conversion of **435** (since unreacted **435** was isolated

from the aqueous layer in the work-up). By increasing the equivalents of TIPSCl and imidazole, however, higher yields (42%) were reached (entry 3). Regrettably, increasing the equivalents further or adding DMAP in catalytic quantities (0.2 equiv.) made no significant improvement to the yield.

We then moved onto the perbenzylation of the TIPS silyl ether **436b** (**Scheme 171 and Table 31**).



Reagents and conditions: a) see **Table 31**.

Scheme 171: Perbenzylation attempts of **436b**.

Entry	Reagents and Conditions [a]	Result
1[93]	NaH (3.7 equiv.), BnBr (4.5 equiv.), DMF	44% **437**, 15% mono- and di- benzylated products (6% **438**, 3% **439**, 2% **440**, 4% **441**)
2	NaH (8 equiv.), BnBr (10 equiv.), DMF	41% **437**, 20% mono- and di- benzylated products (8% **438**, 7% **439**, 2% **440**, 3% **441**,)
3	NaH (8 equiv.), BnBr (10 equiv.), THF	57% **437**, 20% mono- and di- benzylated products (7% **438**, 3% **439**, 2% **440**, 8% **441**)
4	NaH (8equiv.), BnBr (10 equiv.), THF [b]	Decomposition
5[94]	NaH (4.95 equiv.), BnBr (4.5 equiv.), THF, TBAI (0.08 equiv.)	71% **437**
6	NaH (4.95 equiv.), BnBr (4.5 equiv.), THF	39% **437**, 36% mono- and di- benzylated products (23% **438**, 3% **439**, 3% **440**, 7% **441**)

[a] Reaction time: 72 h, temperature: 0 °C to rt; [b] 0 °C to heat under reflux for 4 h.

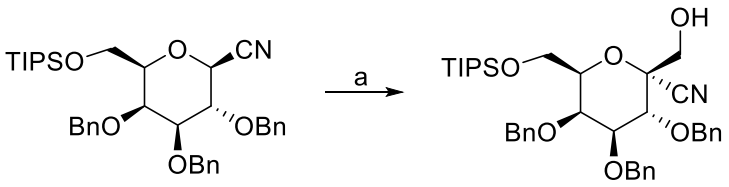
Table 31: Conditions and results reported for the attempted perbenzylations of **436b**.

We initially tried standard conditions using sodium hydride and benzyl bromide in DMF,[93] but got poor yields of the tribenzylated derivative **437** (entry 1). The isolation of mono- and di-benzylated intermediates accounted for the poor yield, and also indicates that these conditions were not powerful enough to induce complete perbenzylation.

To increase the conversion of these intermediates to the desired tribenzylated compound **437**, we tried more vigorous conditions by increasing the equivalents of the base and benzyl bromide electrophile, but no significant difference was observed (entry 2). Surprisingly, changing the solvent from DMF to THF slightly improved the yield for the tribenzylated derivative **437** (entry 3), though the presence of the mono and di-benzylated intermediates still suggested that more forcing conditions were needed. Consequently, we repeated the reaction using THF again but instead heated the reaction mixture under reflux (entry 4). These conditions seemed too strong, as only decomposition was observed after only a relatively short reaction time (4 h rather than 72 h).

In order to further improve the yield of **437**, from a modified procedure in the literature,[94] we decided to use TBAI as a catalyst in a THF solvent (entry 5). Gratifyingly, under these conditions, **437** was isolated in 71% yield. Since the equivalents of sodium hydride and benzyl bromide in this reaction (entry 5) were different from all previous attempts (entries 1 to 4), we wanted to prove whether the change in equivalents or the use of TBAI were pivotal in optimizing the reaction. We therefore repeated the reaction again without the use of TBAI (entry 6) and obtained a much lower yield of **437**; this result showed that using catalytic TBAI was critical to the success of the perbenzylation. The success of the reaction when using TBAI is most likely due to the displacement of the bromide in benzyl bromide with an iodide, generating a much more reactive benzyl iodide electrophile *in-situ*.[95]

The next step was the attempted formation and reaction of the nitrile anion of **437** with formaldehyde (**Scheme 172** and **Table 32**).



437 **442**

Reagents and conditions: a) Base (1.1 equiv.), THF, -78 °C, **437**, 1 h, CH_2O (0.6 M in THF, 1.1 equiv.), - 78 °C to rt, 24 h. See **Table 32**

Scheme 172: Attempted synthesis of **442** from **437**.

Entry	Base	Result
1	LiHMDS	SM
2	NaH	SM
3	LDA	SM
4	*t*-BuLi	SM
5	*t*-BuLi [a]	SM

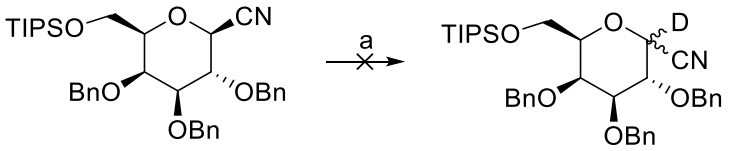
[a] DMPU (3 equiv.) additive was used in addition.

Table 32: Conditions and results reported for the attempted synthesis of **442** from **437**.

Unfortunately, despite using an array of strong bases (increasing in strength from entries 1 to 4), only starting material **437** was recovered in each attempt. Even when using a DMPU additive to

further increase the reactivity of (the already very strong base) *t*-BuLi,[96] the same result occurred.

In order to identify the failure of this reaction, we decided to repeat all the above attempts (entries 1 to 5) but replace the formaldehyde electrophile with D_2O (**Scheme 173**). This would establish whether a nitrile anion is formed prior to the addition of formaldehyde. Surprisingly in all cases, only starting material (with no diminishment of the anomeric proton signal) was recovered. These results suggest, that under each attempted set of conditions (entries 1 to 5 in **Table 32**), the nitrile anion was not formed. While this explains why the reaction with formaldehyde failed, it is unclear as to why the nitrile anion not formed.



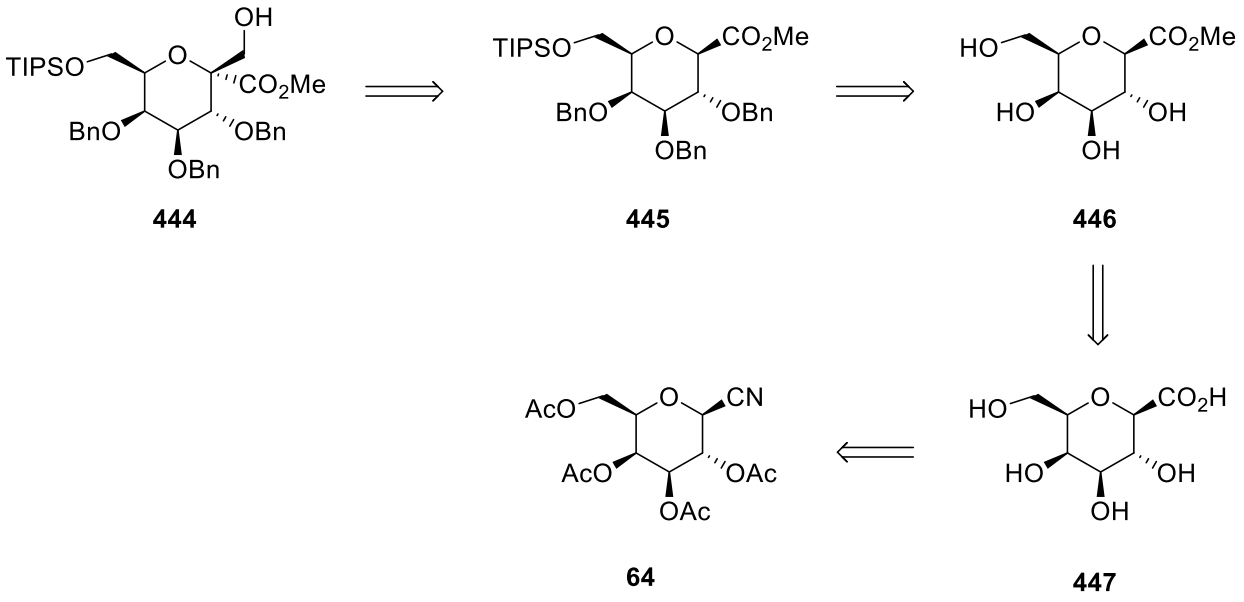
437 **443**

Reagents and conditions: a) Base (1.1 equiv.), THF, -78 °C, **437**, 1 h, D_2O (10 equiv.), - 78 °C to rt, 1 h.

Scheme 173: Deuteration attempts of **437**.

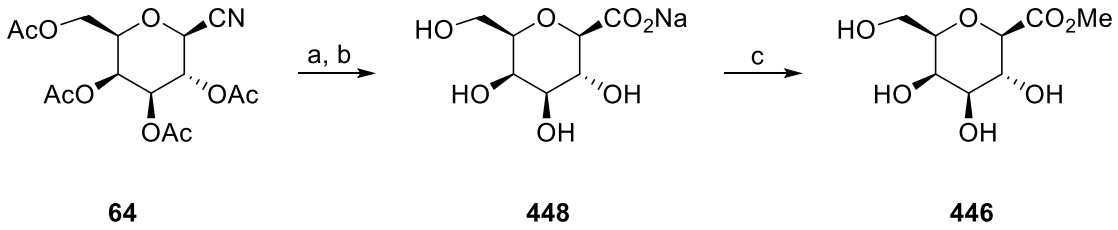
We also repeated all the previous attempts with D_2O at a higher deprotonation temperature (- 20 °C), but the same results were seen.

Confronted with these failures, we decided to replace the nitrile in **437** with an ester (**Scheme 174**). If successful, this would allow us to attempt a reaction with formaldehyde using an anomeric ester enolate of **445 (**instead of an anomeric nitrile anion of **437**). Compound **445** could derive from **446** by selective TIPS protection of the primary hydroxyl group followed by perbenzylation. Esterification of carboxylic acid **447** would form compound **446**. Finally, carboxylic acid **447** could be made by deacetylation and nitrile hydrolysis of **64**.



Scheme 174: Retrosynthesis for compound **444** from **64**.

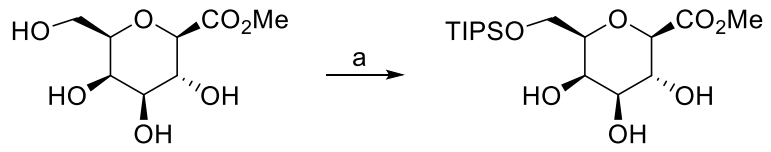
By the methodology mentioned in the above retrosynthetic analysis, we successfully synthesized the C-glycosyl ester derivative **446** in three steps from **64** (**Scheme 175**). These involved acetyl cleavage of **64**, followed by basic nitrile hydrolysis to afford carboxylate **448** in 60% yield (over two steps).[88] Subsequent treatment of the carboxylate with hydrogen chloride-methanol solution (prepared from addition of acetyl chloride to methanol) under reflux then led to Fischer esterification yielding **446**.[88]



Reagents and conditions: a) NaOMe, MeOH, rt, 2h; b) 12.5% NaOH $_{(aq)}$, reflux, 3 h, then rt, Amberlite IR-120 (H+-form), 60% over two steps; c) AcCl, MeOH, 0 ^{o}C, 5 min, **448**, reflux, 72 h, quant.

Scheme 175: Three-step synthesis of **446** from **64**.

Under the optimized conditions previously applied to C-glycosyl nitrile **435**, the primary alcohol in **446** was successfully protected with a TIPS group, albeit in low yield (**Scheme 176**).

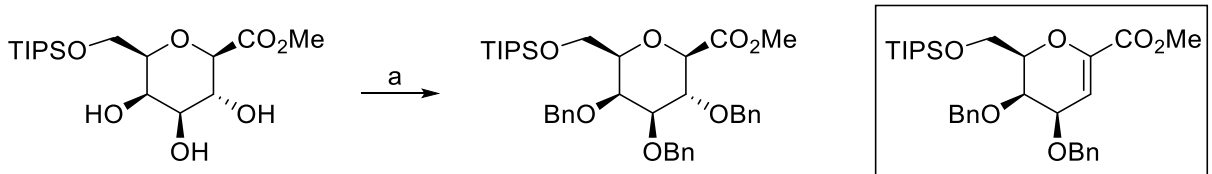


446 **449**

Reagents and conditions: a) imidazole, TIPSCl, DMF, 0 °C to rt, 72 h 24%.

Scheme 176: Selective TIPS protection of **446**.

We then moved onto the perbenzylation of compound **449** (**Scheme 177** and **Table 33**).



449 **450** **451**

Reagents and conditions: a) see **Table 33**.

Scheme 177: Perbenzylation attempts of compound **449**.

Entry	Reagents and Conditions [a]	Result
1[94]	NaH (4.95 equiv.), BnBr (4.5 equiv.), THF, TBAI (0.08 equiv.), 0 °C to rt	59% **451**
2	NaH (3 equiv.), BnBr (4.5 equiv.), THF, TBAI (0.08 equiv.), 0 °C to rt	51% **451**
3	K_2CO_3 (4.5 equiv.), BnBr (4.5 equiv.), MeCN, reflux	SM
4	K_2CO_3 (4.5 equiv.), BnBr (4.5 equiv.), DMF, 90 °C	SM
5[97]	Ag_2O (6 equiv.), BnBr (9 equiv.), DMF, 0 °C to rt	Complex mixture

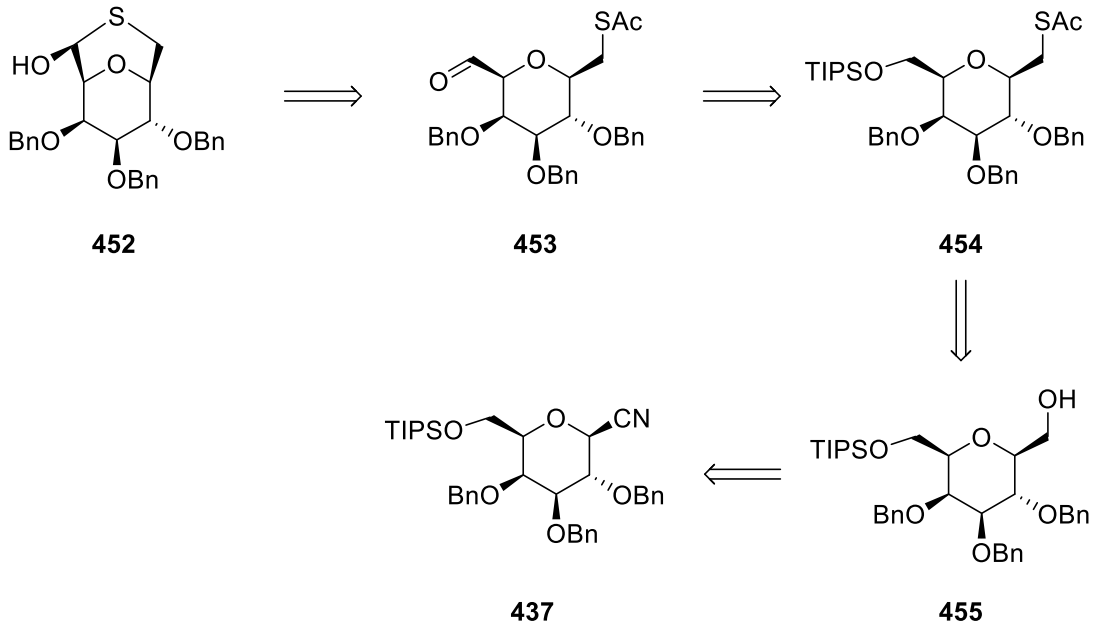
[a] Reaction time: 72 h.

Table 33: Conditions and results reported for the attempted perbenzylation of **449**.

We initially tried the same optimized conditions previously used for the perbenzylation of the C-glycosyl nitrile **436** (entry 1), but no trace of the desired tribenzylated compound **450** was observed. In fact, the only compound isolated after work-up and purification was the dibenzylated glycal **451**. Glycal **451** was probably formed by an E1cB elimination of the desired

tribenzylated compound **450**. In order to suppress the undesired β-elimination, we made the conditions less basic by decreasing the equivalents of the sodium hydride base, but again only glycal **451** was isolated (entry 2). These disappointing results indicated that milder conditions were required to suppress the elimination. We therefore replaced sodium hydride with the weaker base, potassium carbonate (entries 3 and 4), but despite heating for prolong times, these conditions were too mild for any benzylation to take place. Finally, when the benzylation was carried out in near neutral conditions,[95] using silver(I)oxide with benzyl bromide in DMF (entry 6),[97] only a complex mixture was observed.

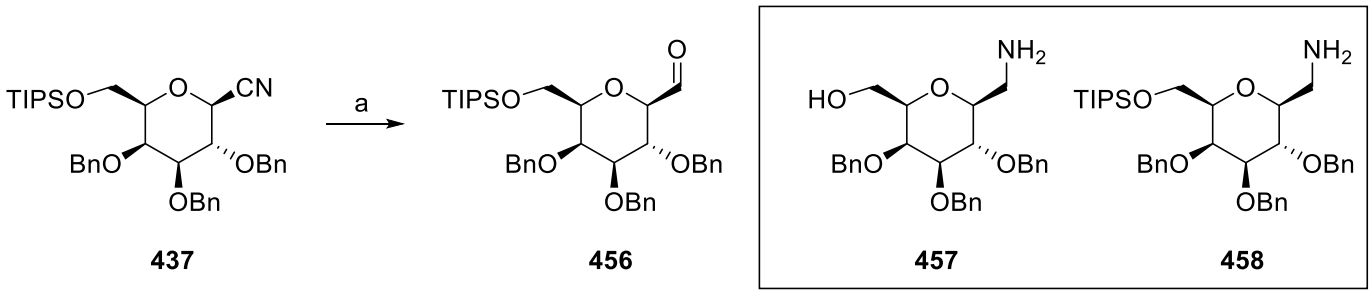
The lack of success in the perbenzylation of methyl ester **449** and reaction between formaldehyde and the tribenzylated nitrile **437**, led us to modify the strategy (**Scheme 178**).



Scheme 178: Retrosynthetic analysis for target **452** from **437**.

The retrosynthesis for target **452** from compound **455** is identical in methodology for the previous target **428** from **431**, with the only difference being the absence of a nitrile on the C_{-1} position (**Scheme 167**). Compound **455** can be synthesized from **437** by two consecutive reduction steps (reductive hydrolysis of the nitrile to an aldehyde and subsequent aldehyde reduction to an alcohol). A key disadvantage to this approach is that target **452** has carboxylic acid derivatives missing on the C_{-1} and thiohemiacetal centre, but if this strategy were successful, it would be revised to include both carboxylic acid derivatives.

We started this sequence with the attempted reduction of the nitrile moiety in **437** to an aldehyde using a range of metal hydride reagents (**Scheme 179** and **Table 34**).



437 **456** **457** **458**

Reagents and conditions: a) see **Table 34.**

Scheme 179: Attempted nitrile reductions of **437**.

Entry	Reagents and Conditions	Result
1[98]	DIBAL (1M in DCM, 1 equiv.), DCM, - 78 °C, 3 h, then 1M $NH_4Cl_{(aq)}$	Complex mixture
2[99]	$LiAlH_4$ (1 equiv.), EtOH (3 equiv.), Et_2O, 0 °C, **437**, 0 °C to rt, 16 h, then 1M $NH_4Cl_{(aq)}$	SM
3[100]	Red-Al® (3.5 M in toluene, 1 equiv.), toluene, - 78 °C to 0 °C, 2 h, then 1M tartaric $acid_{(aq)}$	78% **457**, 4% **458**

Table 34: Conditions and results tested for the attempted nitrile reductions of **437**.

Initially, from a modified procedure in the literature,[98] a diisobutylaluminium hydride (DIBAL) based reduction was attempted (entry 1). Unfortunately, despite the relatively mild conditions (low temperature and limited equivalents of DIBAL), a complex mixture resulted. Though there were distinctive aldehyde proton signals (**H**-COR) in the ^{1}H NMR spectrum of the crude complex mixture, there were no pure isolated products after purification by column chromatography.

We then tried an alkoxyaluminate hydride-based reduction (entry 2).[99] In this reaction, we had to first synthesize lithium tris(ethoxy)aluminium hydride (LTEA) *in-situ* (from reaction between

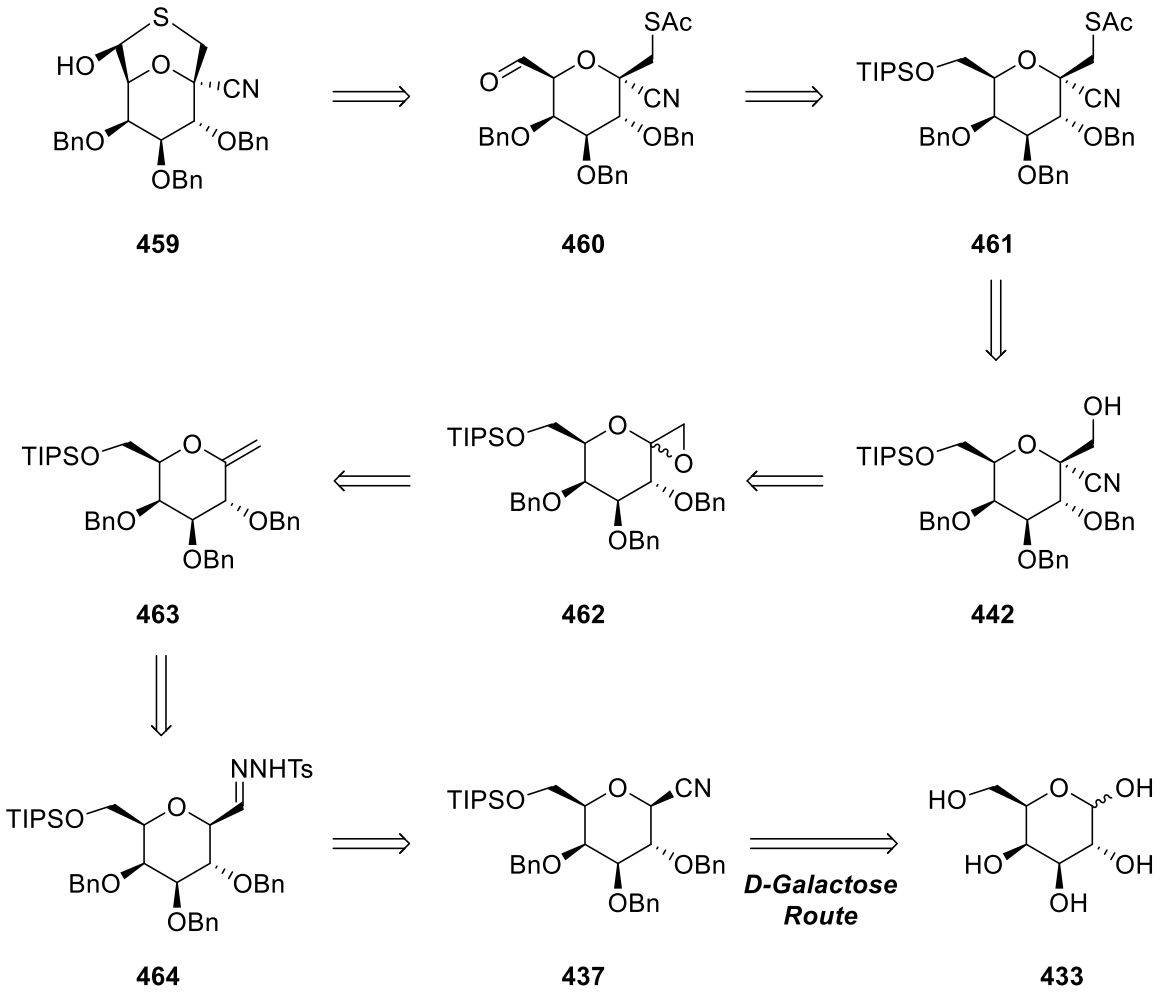
absolute ethanol and LAH) prior to the addition of nitrile **437**. However, these conditions were too mild for any reduction to take place as only starting material was observed.

Finally, we used Red-Al® for the nitrile reduction according to a modified procedure from Balskus and Jacobsen.[100] Unfortunately, the production of amines **457** and **458** showed that under these conditions over-reduction readily occurred (i.e. reduction did not cease at the imine stage). The formation of amine **457** can be explained by silyl ether cleavage of **458** occurring during the acidic work-up.

These disappointing reductive hydrolysis results led us to abandon this route.

Exo-Glycal Route

The failure to synthesize compound **442** by the reaction between formaldehyde and the tribenzylated nitrile **437** using nitrile-anion chemistry steered us to an alternative synthetic strategy. In this strategy, we aimed to synthesize **442** by the functionalization of an *exo*-glycal (**Scheme 180**).

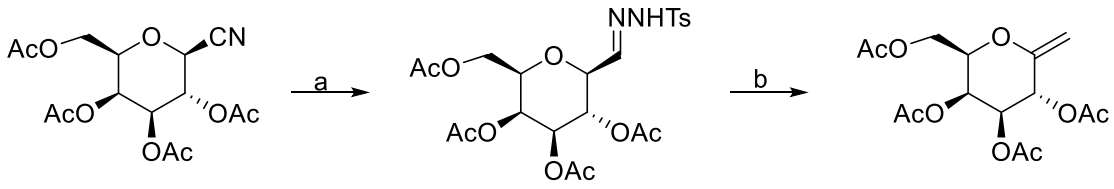


Scheme 180: Retrosynthesis for target **459** from D-galactose **433** in the *Exo*-Glycal route.

The retrosynthetic analysis for target **459** from compound **442** is identical to **428** from **431** in the D-galactose route (**Scheme 167**). Compound **442** could be made by ring opening of the anomeric epoxy acetal in **462** using a cyanide nucleophilic source (e.g. TMSCN) and a Lewis acid. Compound **462** could derive from an electrophilic epoxidation of the *exo*-glycal **463**, which in turn could be made by a Bamford-Stevens reaction of tosylhydrazone **464**. Reductive hydrolysis of the nitrile in **437** to an aldehyde, followed by trapping with tosylhydrazide, could form hydrazone **464**. Finally compound **437** has already been synthesized from D-galactose in five steps in the D-galactose route.

This synthetic approach was largely inspired by the research carried out by Tóth *et al*.[101,102] In their work, they successfully synthesized *exo*-glycal **466** from compound **64** in two steps (**Scheme 181**). In the first step, the authors subjected **64** to Raney-nickel and sodium

hypophosphite in aqueous acetic acid and pyridine alongside tosylhydrazide. These conditions caused the reduction of the nitrile moiety to an imine, which was then hydrolysed *in-situ* to an aldehyde. Due to the presence of tosylhydrazide, the aldehyde was then trapped with this reagent to form tosylhydrazone **465**. In the second step, tosylhydrazone **465** was treated with an excess of sodium hydride (10 equiv.) in 1,4-dioxane under reflux, which triggered an *in-situ* generation of a C-glycosylmethylene carbene, which eventually yielded *exo*-glycal **466** in an aprotic Bamford-Stevens reaction.

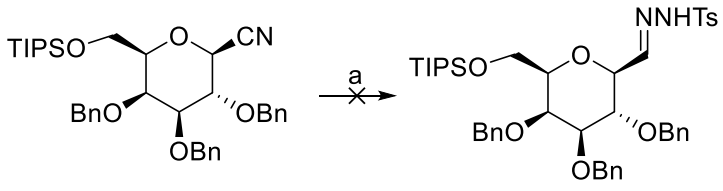


64 **465** **466**

Reagents and conditions: a) Ra-Ni, NaH_2PO_2, $TsNHNH_2$, PY, AcOH, H_2O, rt, 4 h, 90%; b) NaH, 1,4-dioxane, reflux, 82%.

Scheme 181: Tóth and co-workers' two-step synthesis of *exo*-glycal **466** from **64**.[101,102]

We therefore aimed to apply Tóth *et al.*'s methodology to compound **437**. Unfortunately, when subjecting **437** to Tóth and co-workers' reductive hydrolysis conditions, the desired tosylhydrazone **464** was not isolated due to the production of a complex mixture (**Scheme 182**).



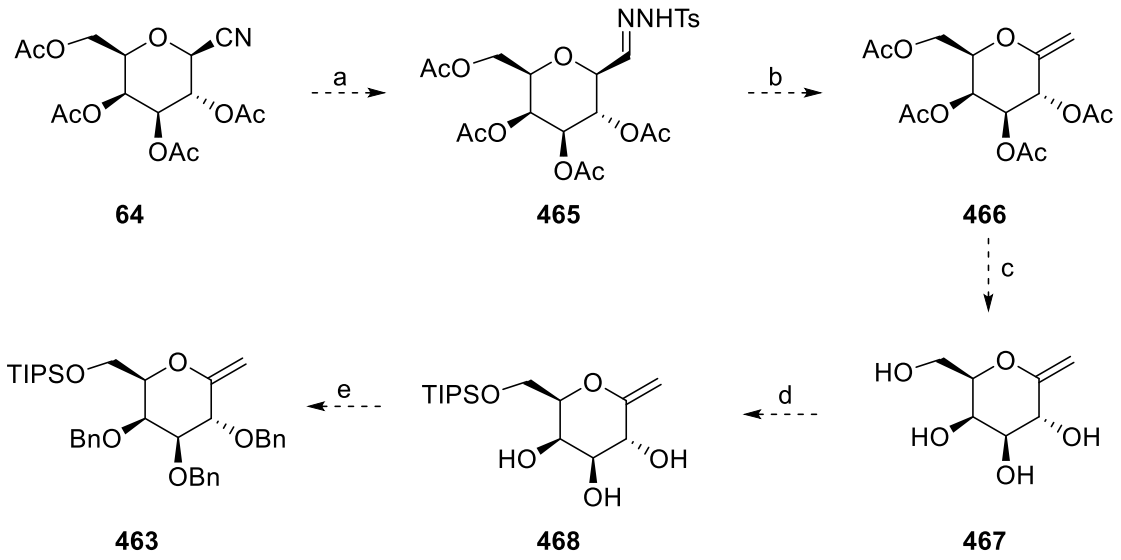
437 **464**

Reagents and conditions: a) Ra-Ni, NaH_2PO_2, $TsNHNH_2$, PY, AcOH, H_2O, rt, 24 h.

Scheme 182: Attempted synthesis of tosylhydrazone **464** from **437**.

Confronted with these failures, we devised an alternative route (simply by changing the order of steps) to the tribenzylated *exo*-glycal **463** (**Scheme 183**). In this route, we planned to copy Tóth and co-workers' two-step synthesis of **466** from glycosyl cyanide **64** (**64** has already been

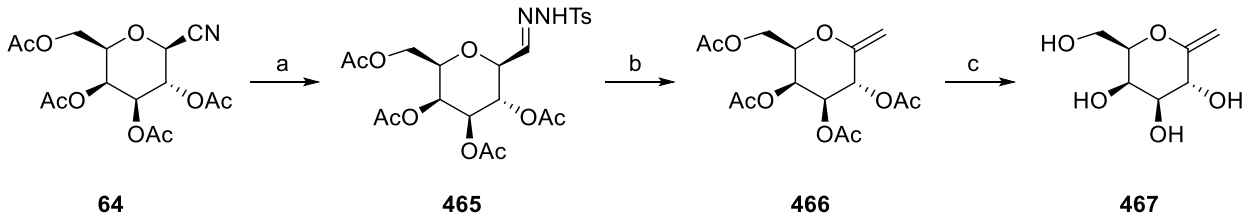
successfully synthesized in the D-galactose route).[101,102] Then compound **466** would be deacetylated to form **467**. Selective silyl protection of the primary hydroxyl group in **467** followed by perbenzylation would furnish the tribenzylated *exo*-glycal **463**.



Methodologies: a) nitrile transformation to hydrazone; b) Bamford-Stevens reaction; c) deacetylation; d) selective TIPS protection; e) perbenzylation.

Scheme 183: Proposed five-step synthesis of the tribenzylated *exo*-glycal **463** from **64**.

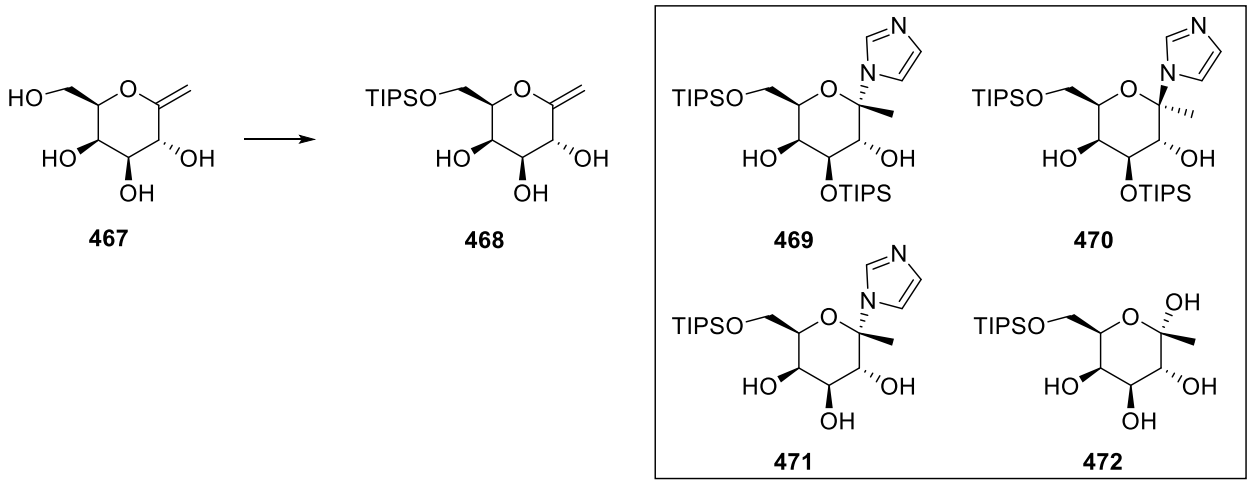
Using Tóth and co-workers' conditions, we firstly synthesized tosylhydrazone **465** in 83% yield (**Scheme 184**). We then performed a Bamford-Stevens reaction on **465** to form *exo*-glycal **466** in yields up to 72%. The reaction time was concluded to be pivotal for the yield (of both the final product after purification and the crude). For example, reaction times longer than 30 minutes led to a decrease in yield, hinting at possible product decomposition under the reaction conditions, whereas reaction times that were too short led to poor conversion. Treatment of compound **466** with sodium methoxide in methanol afforded the deacetylated product **467** in quantitative yield.



Reagents and conditions: a) Ra-Ni, NaH_2PO_2, $TsNHNH_2$, PY, AcOH, H_2O, 24 h, 83%; b) NaH, 1,4-dioxane, reflux, 30 min, 72%; c) NaOMe (0.18 equiv.), MeOH, rt, quant.

Scheme 184: Three-step synthesis of **467** from **64**.

With compound **467** in hand, we proceeded to the regioselective TIPS protection (**Scheme 185** and **Table 35**).



Reagents and conditions: a) see **Table 35.**

Scheme 185: Selective silyl protection attempts of **467**.

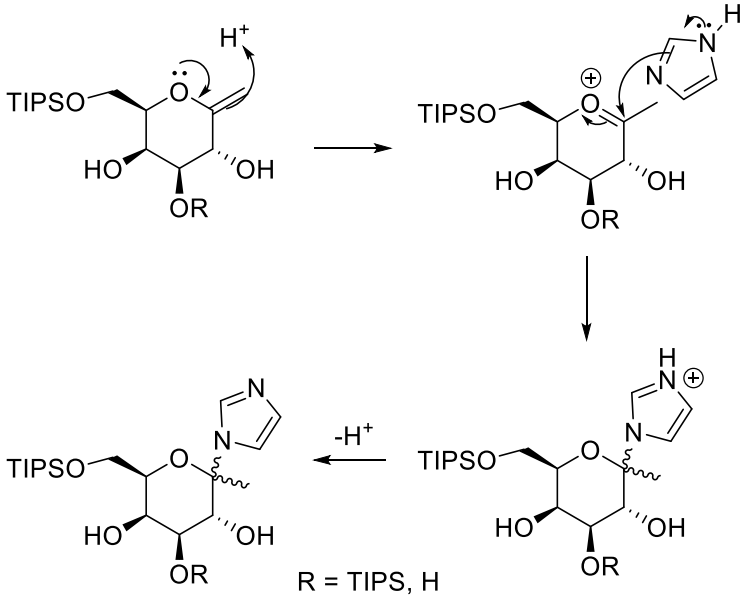
Entry	Reagents and Conditions [a]	Result
1	Imidazole (4 equiv.), TIPSCl (2 equiv.), DMF	43% **469**, 19% **470**, 11% **471**
2	Imidazole (3 equiv.), TIPSCl (1.5 equiv.), DMF	67% **471**, 13% **468**
3	Imidazole (2.2 equiv.), TIPSCl (1.1 equiv.), DMF	64% **471**, 11% **468**
4	K_2CO_3 (2.2 equiv.), TIPSCl (1.1 equiv.), DMF	Complex mixture
5	TIPSCl (1.1 equiv.), Pyridine	Complex mixture
6	2,6-lutidine (2 equiv.), TIPSOTf (1.1 equiv.), DMF	3% **472**

[a] reaction time: 24 h, temperature: 0 ºC to rt.

Table 35: Conditions and results reported for the attempted TIPS protection of **467**.

We initially applied the same optimized conditions used previously for the synthesis of **436** in the D-galactose route (entry 1). Under these conditions, however, no trace of the desired **468** was

observed; instead compounds **469**, **470** and **471** were isolated. The disilylated compounds **469** and **471** were formed due to the large number of equivalents of TIPSCl used (2 equiv.). The probable mechanism to account for these side products arise from the basicity of the *exo*-glycal (**Scheme 186**).



Scheme 186: Proposed mechanism for the formation of side-products **469**, **470** and **471**.

The silylation of alcohol leads to the formation of acid (effectively HCl), although it would be expected that the imidazole would neutralize these acidic conditions. Nevertheless, under these conditions, the *exo*-glycal was protonated to form an oxocarbenium ion. The imidazole then attacked the oxocarbenium ion in nucleophilic fashion to form the undesired side-products **469**, **470** and **471** after proton transfer.

The number of equivalents of imidazole and TIPSCl were then reduced (entries 2 and 3). The use of lower equivalents of TIPSCl (1.5 equiv. and 1.1 equiv.) led to no disilylated products being produced. While we isolated the desired product **468** in these entries, the yields were still very low (13% and 11% respectively) because of the large production of compound **471**.

In order to suppress this side reaction, we replaced the imidazole base with potassium carbonate (entry 4). This is because potassium carbonate is a stronger base (will more likely neutralize any acid and reduce the risk of the *exo*-glycal being protonated), and also the carbonate or

bicarbonate ion is a poor nucleophile (to prevent any nucleophilic addition on the oxocarbenium ion if it forms). However, under these conditions, only a complex mixture was formed.

The TIPS protection was then attempted in a pyridine solvent (entry 5). We anticipated that the large excess of pyridine would 'mop-up' any protons in solution decreasing the likelihood of the *exo*-glycal being protonated (entry 5). Unfortunately, since a complex mixture resulted, the desired product **468** was not isolated.

Finally, a standard TIPS protection using the more electrophilic TIPSOTf and non-nucleophilic base 2,6-lutidine was attempted (entry 6). These conditions led to a complex mixture with the only product isolated being compound **472** in 3% yield. The production of a complex mixture in these conditions suggests that many undesired side-reactions occurred. We speculate that the formation of **472** was due to the *exo*-glycal being protonated under the TIPS protection conditions to form the oxocarbenium ion, which in turn during the work-up underwent nucleophilic attack by water.

The assignment of the stereochemical configuration on the C_{-1} position in by-products **469**, **470**, **471** and **472** was inferred from NOESY spectra analysis (see below).

In compounds **469**, **471** and **472**, a nOe was observed between the methyl group of C_{-1} and H-C_{-2} (**Figure 17**), which suggests a *cis* relationship between the methyl group and H-C_{-2}. Furthermore, with respect to **469** and **471**, a nOe was seen between protons of the imidazole moiety and H-C_{-5}, which suggests that these also have a *cis* relationship. This was unlike compound **470**, where the observed nOes (between H-C_{-2} and protons of the imidazole moiety as well as between the methyl group and H-C_{-5}) suggested a *trans* relationship between the methyl group and H-C_{-2}.

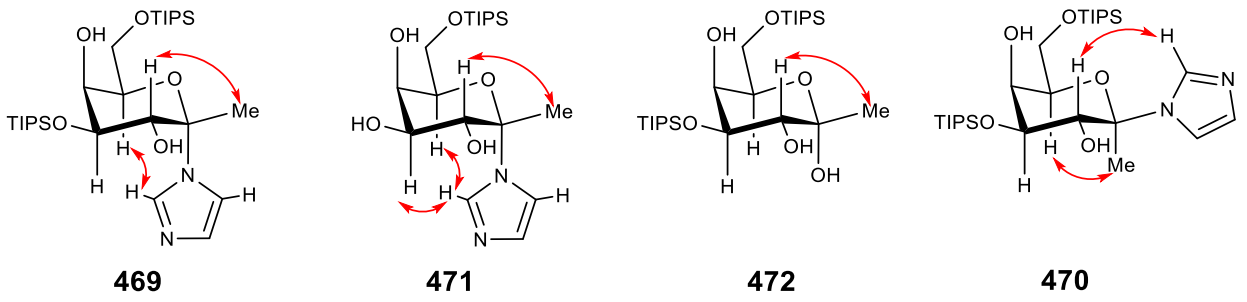


Figure 17: NOESY spectra analysis to assign stereochemistry on the C_{-1} position in **469**, **470**, **471** and **472**.

The yield for **469** was higher than its epimer **470**. Likewise, the epimers (defined in this context as opposite stereochemistry on the C_{-1} position) for **471** and **472** were not even isolated. These results imply that the nucleophile (e.g. imidazole or a water molecule) attacks the bottom face of the oxocarbenium ion more favourably than the top face.

The stereoselectivity can be explained by considering the conformations of the oxocarbenium ion (**Figure 18**). The most stable conformations of the oxocarbenium ion would be the $^{3}H_{4}$ and $^{4}H_{3}$ half chairs (with the former being less stable due to the 1,3-pseudo axial – axial interactions between the OR and CH_2OTIPS groups). The selectively is under kinetic control. There is less steric hindrance to the nucleophile when it attacks the bottom face of the more stable $^{4}H_{3}$ conformation (leading to a less sterically-congested chair-like transition state); hence bottom face attack is faster than top face attack. Under these conditions, bottom face attack on the $^{3}H_{4}$ conformation and top face attack on the $^{4}H_{3}$ conformation contribute little to the product distribution. This is because these non-axial nucleophilic attacks lead to high energy unstable twist-boat like transition states.[92]

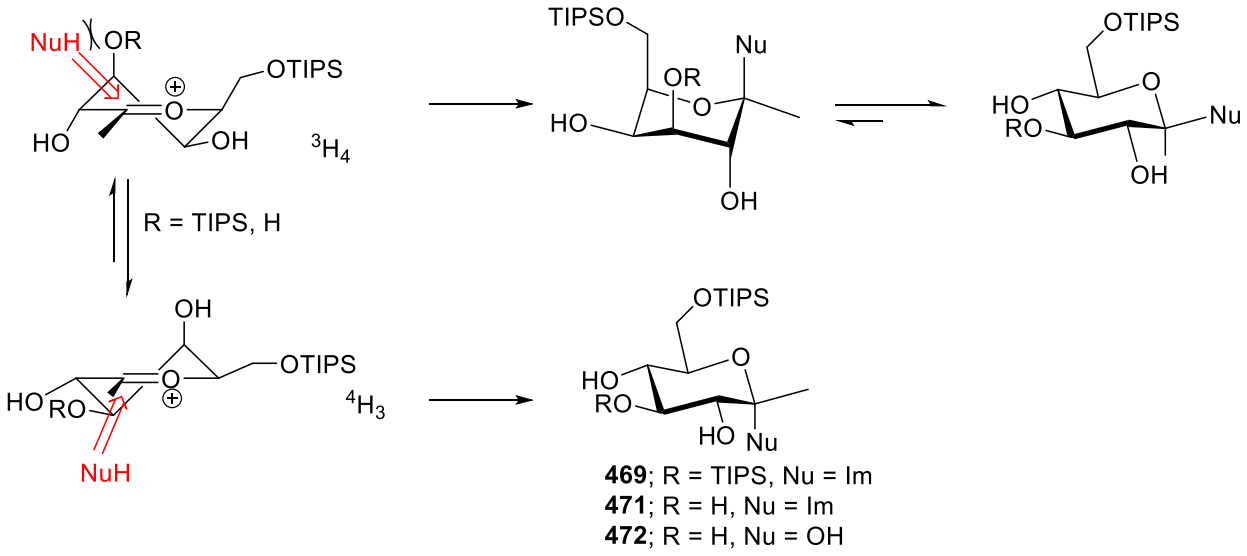
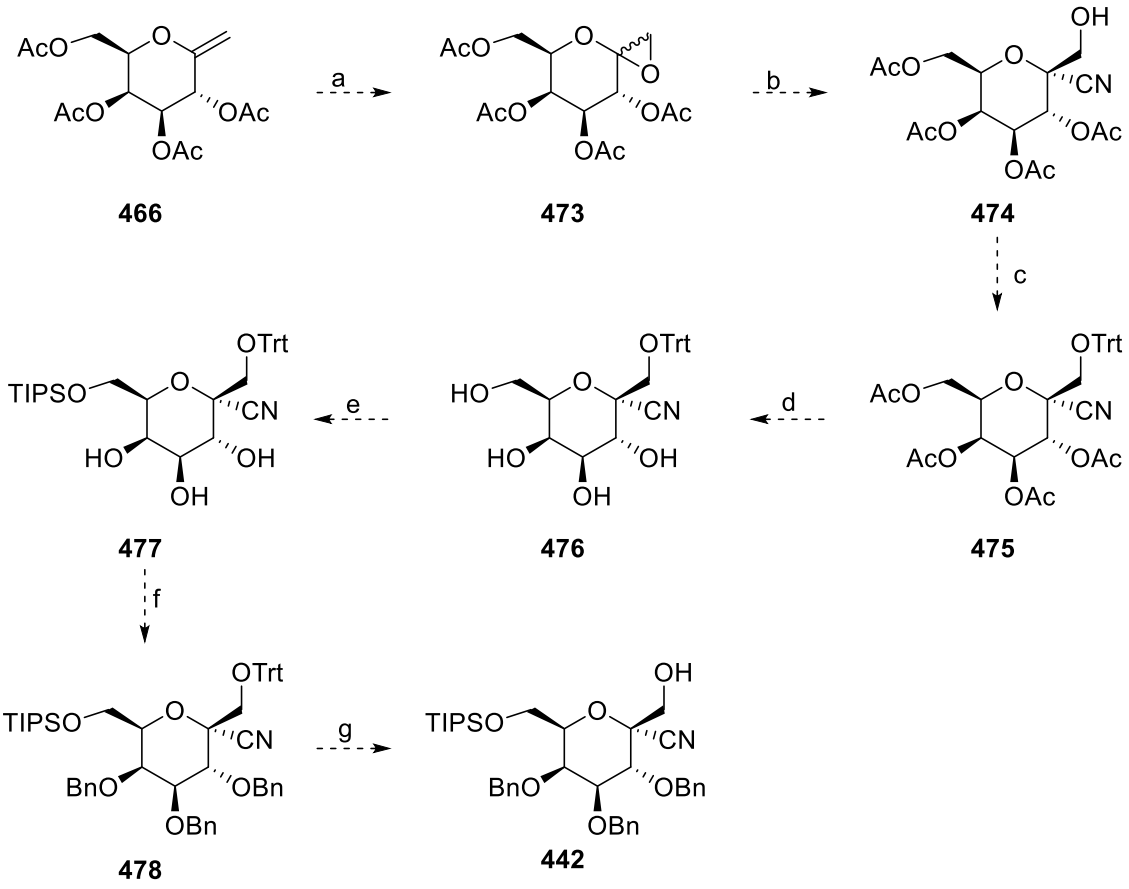


Figure 18: Proposed rationale for the stereoselectivity of nucleophilic attack on the oxocarbenium ion formed in the TIPS protections.

We pondered whether to try protecting groups other than TIPS (e.g. Trt, Bn, PMB etc.), but we anticipated the same problems regarding the basicity/reactivity of the *exo*-glycal in the protection conditions.

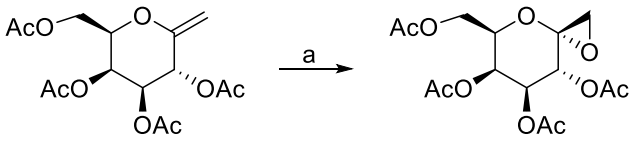
We concluded that due to the reactivity of the *exo*-glycal in these TIPS protection conditions, the *exo*-glycal **466** should be functionalized (i.e. epoxidation on the *exo*-glycal followed by ring opening the epoxide) prior to any of the protections; hence the route to compound **442** was modified (**Scheme 187**).



Methodologies: a) epoxidation; b) epoxide ring-opening; c) tritylation; d) deacetylation; e) selective TIPS protection; f) perbenzylation; g) detritylation.

Scheme 187: Proposed alternative synthetic route to compound **442**.

We subjected **466** to standard electrophilic epoxidation conditions using mCPBA in dichloromethane and aqueous sodium bicarbonate,[103] which furnished epoxide **α-473** in 98% yield (**Scheme 188**).

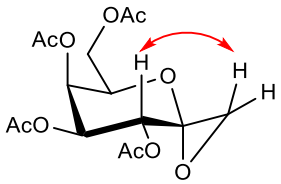


466 **α-473**

Reagents and conditions: a) mCPBA, 0.6 M $NaHCO_{3\ (aq)}$, DCM, 0 °C to rt, overnight, 98%.

Scheme 188: Epoxidation of **466**.

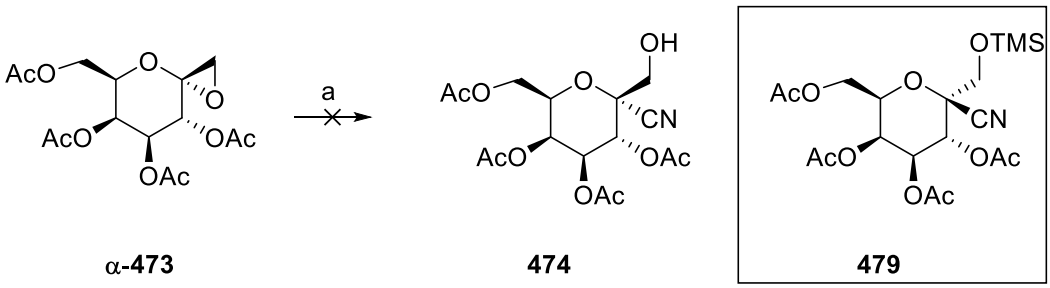
The stereochemistry on the anomeric centre of epoxide **α-473** was determined from the NOESY spectrum (**Figure 19**). The significant nOe between one of the methylene protons of the epoxide and H-C_{-2} indicated a *cis* relationship between these.



α-473

Figure 19: NOESY spectrum analysis to assign stereochemistry on the anomeric centre of epoxide **α-473**.

The epoxide ring-opening reaction with TMSCN was then attempted using the same conditions that Nishikawa *et al*. applied for their anomeric epoxy acetal **187** (**Scheme 36**).[104] When subjecting **α-473** to these conditions, however, only a complex mixture formed, with **479** being the only product isolated in 4% yield after purification (**Scheme 189**).

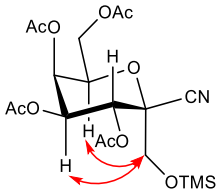


α-473 **474** **479**

Reagents and conditions: a) I_2 (2 equiv.), TMSCN (5 equiv.), 2:1 toluene:hexane, 0 °C.

Scheme 189: Attempted synthesis of **474**.

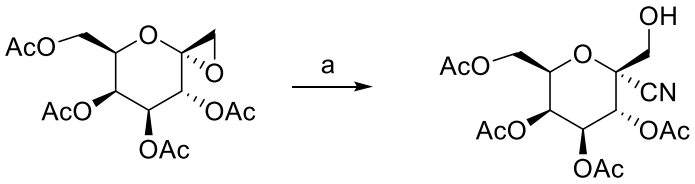
Unfortunately, due to the stereochemistry at the C_{-1} position, we could not continue the route with **479**. The stereochemistry on the C_{-1} position in **479** was deduced by analysis from its NOESY spectrum. The strong nOe observed between the methylene protons of the CH_2OTMS moiety with H-C_{-3} and H-C_{-5} suggested that these have a *cis* relationship (**Figure 20**).



479

Figure 20: NOESY spectrum analysis to assign stereochemistry on the C_{-1} position in **479**.

We then tried conventional epoxide ring-opening reactions of **α-473** with TMSCN using a range of Lewis acids (**Scheme 190** and **Table 36**).



α-473 **474**

Reagents and conditions: a) Lewis acid (2 equiv.), TMSCN (2 equiv.), DCM, -30 °C to rt, overnight. see **Table 36**.

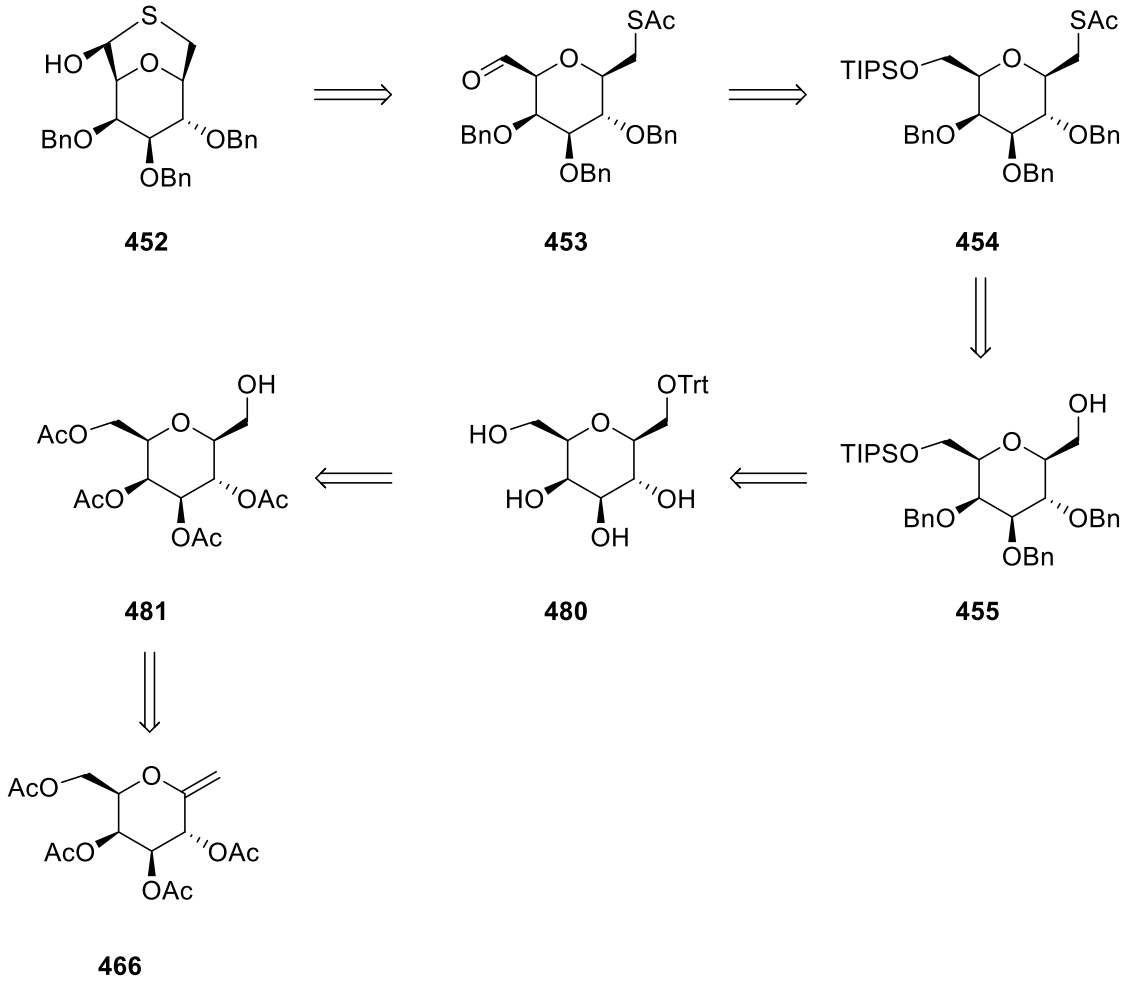
Scheme 190: Epoxide ring opening attempts of **α-473**.

Entry	Lewis Acid	Result
1[105]	$SnCl_4$	Complex mixture
2	$AlCl_3$	Complex mixture
3	$ZnCl_2$	Complex mixture
4	$BF_3.Et_2O$	Complex mixture
5	None	SM

Table 36: Conditions and results reported for the epoxide ring-opening attempts of **α-473**.

Regrettably, with each Lewis acid (entries 1 to 4), only complex mixtures were observed, which implied that many side-reactions occurred. In an attempt to reduce the number of side reactions, we performed the reaction without any Lewis acid (entry 5), though these conditions seemed too mild to trigger any reaction, since only starting material was recovered.

The lack of success in the ring-opening epoxide reaction forced us to once again re-evaluate the methodology. A new synthetic strategy towards target **452** was postulated, which involved a hydroboration-oxidation reaction on *exo*-glycal **466** instead of an epoxidation (**Scheme 191**).

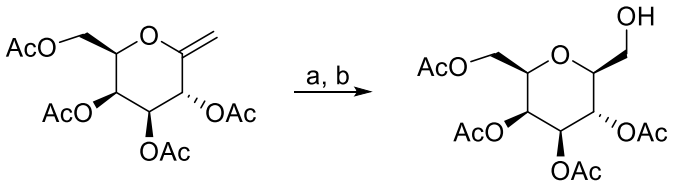


Scheme 191: Retrosynthesis for target **452** from **466**.

The retrosynthesis for target **452** from **455** has already been analysed in a previous route (**Scheme 178**). Compound **455** could be made from **480** in three steps: selective TIPS protection;

perbenzylation; and detritylation. Deacetylation and tritylation of compound **481** could yield **480**. Finally, a hydroboration-oxidation reaction on **466** could afford **481**.

Thus, we attempted the hydroboration-oxidation reaction on **466** (**Scheme 192** and **Table 37**).



466 **481**

Reagents and conditions: a) hydroboration reagent (2 equiv.), THF, 0 °C to rt, overnight; b) oxidative work-up. See **Table 37**.

Scheme 192: Hydroboration-oxidation attempts of **466**.

Entry	**Hydroboration Reagent**	**Oxidative Work-Up** [a]	**Result**
1[106]	BH_3.THF	30% $H_2O_{2\,(aq)}$	Decomposition
2	BH_3.DMS	30% $H_2O_{2\,(aq)}$	Decomposition
3	9-BBN	30% $H_2O_{2\,(aq)}$	Complex mixture
4	BH_3.THF	1:1 EtOH:THF, phosphate buffer (0.1 M, pH 7), 30% $H_2O_{2\,(aq)}$	Decomposition
5	BH_3.DMS	1:1 EtOH:THF, phosphate buffer (0.1 M, pH 7), 30% $H_2O_{2\,(aq)}$	Decomposition
6	9-BBN	1:1 EtOH:THF, phosphate buffer (0.1 M, pH 7), 30% $H_2O_{2\,(aq}$	10% **481** [b]

[a] Reaction time: 3 h; temperature: 0 °C to rt. [b] **481** was part of an inseparable mixture with an unknown compound (**481**:unknown compound, 7:1). Assuming the unknown compound is an isomer of **481**, the number of moles of **481** in the inseparable mixture (used for the yield calculation) were calculated from molar ratios seen in the ^{1}H NMR spectrum of the inseparable mixture.

Table 37: Conditions and results reported for the hydroboration-oxidation attempts of **481**.

We firstly tried the hydroboration using BH_3.THF (entry 1) according to a procedure from the literature.[106] Once full consumption of the starting material was observed by TLC visualization

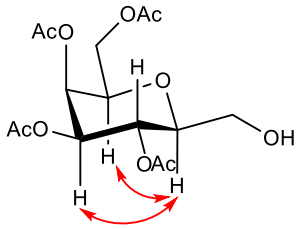
(hinting that the organoborane intermediate was synthesized), we then performed the oxidative work-up. Surprisingly, after work-up, a complex mixture was observed with a very low crude yield (7%). Replacing the hydroboration agent with BH_3.DMS made no difference to the result (entry 2). We pondered whether acetate hydrolysis occurred during the oxidative work-up in both entries 1 and 2; this would lead to the hydrolysed product dissolving in the aqueous layer rather than the organic layer in the work-up, which would account for the very low crude yields. Hence, we evaporated the aqueous layer (after quenching any remaining H_2O_2 with sodium sulfite) under reduced pressure, but no acetyl-hydrolysed products were observed.

9-BBN was then used as the hydroboration agent (entry 3). In this entry, while the crude yield increased dramatically (82%), there was no trace of the desired product **481** observed in the crude complex mixture. A possible reason for the apparent increase in crude yield could be due to the production of *cis*-1,5-cyclooctanediol (a by-product from 9-BBN hydrolysis).

The absence of any hydrolysed products upon evaporation of the aqueous layer of the work-up under reduced pressure for entries 1 and 2, and the higher crude yield when using 9-BBN in entry 3, each suggest that acetate hydrolysis may not have occurred in the work-up. Nevertheless, we aimed to repeat all the hydroboration-oxidations using milder oxidative work-up conditions involving a phosphate buffer according to the literature (entries 4 to 6),[107] in order to see if that could make a positive difference to the result.

The milder oxidative work-up for the hydroboration-oxidations using BH_3.THF and BH_3.DMS unfortunately made no difference (entries 4 and 5). For the 9-BBN hydroboration-oxidation, a complex mixture still resulted (entry 6), but the desired product was isolated after column chromatography in the form of an inseparable mixture with an unknown compound (**481**:unknown compound, **7**:1), albeit in very low yields (10%). We speculate that the unknown compound is a stereoisomer of **481**.

NMR analysis was used to assign the stereochemistry at the C_{-1} position in **481**. For example, the high $^3J_{1,2}$ (10 Hz) suggested a diaxial and thus *trans* relationship between H-C_{-1} and H-C_{-2}. Furthermore, the observed nOes between H-C_{-1} with H-C_{-3} and H-C_{-5} from the NOESY spectrum suggested that these protons are *cis* (**Figure 21**).

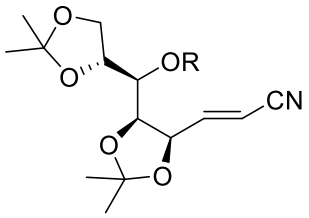


481

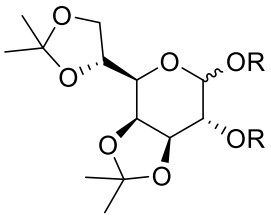
Figure 21: NOESY spectrum analysis to assign stereochemistry at the C_{-1} position in **481**.

Conclusion

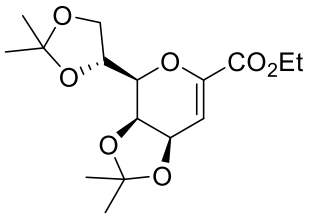
At the end of our studies towards the synthesis of tagetitoxin, numerous synthetic routes were investigated, leading to several interesting intermediates (**Figure 22**).



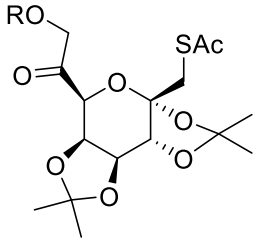
329; R = H
339; R = IPDMS
340; R = Bz



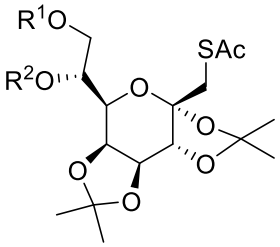
357; R = Ac
α-**359**; R = Bz



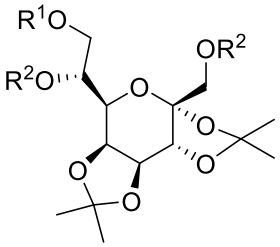
366



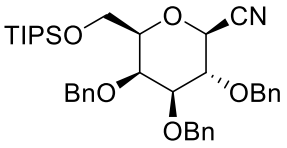
389; R = TBS
394; R = TIPS
395; R = TBDPS



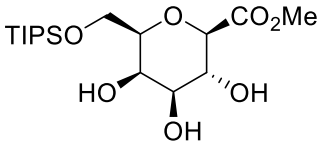
402; R^1 = TBS, R^2 = Tf
404; R^1 = TBS, R^2 = Ms
405; R^1 = TIPS, R^2 = Tf
406; R^1 = TIPS, R^2 = Ms



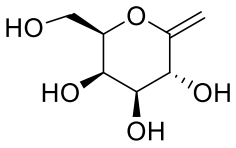
415; R^1 = Trt, R^2 = Ms
417; R^1 = Trt, R^2 = Tf
420; R^1 = TIPS, R^2 = Ms
422; R^1 = TIPS, R^2 = Tf



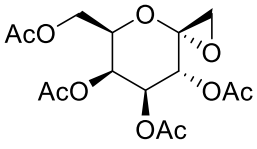
437



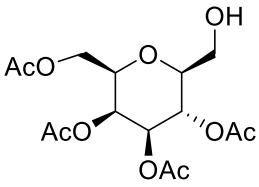
449



467



α-**473**



481

Figure 22: The key intermediates formed during the project.

In the nitrile-Wittig route, we eventually formed alkene **329** from retro-Michael methodology after difficulties in directly synthesizing it from Wittig and HWE olefinations of DAM **234**. Reactivity issues, though, arose with **329** and the protected derivatives **339** and **340** in

electrophilic epoxidations, halogenations and/or oxymercuration-demercuration reactions presumably due to the alkene being too electron-deficient. The lack of reactivity of these electron-deficient alkenes in the nucleophilic epoxidations, however, was surprising and not clearly understood.

In the vinyl-transetherifcation route, the diacetyl **357** and dibenzoyl α-**359** were each obtained after four steps from DAM **234**. Regrettably, the C-glycosylation reactions of these intermediates with TMSCN failed (with or without the use of Lewis acids), prompting us to reject this strategy.

In the silyl enol ether route, we replicated Chai and co-workers' three-step synthesis of glycal **366** from DAM **234** (though with modification of the conditions in the HWE olefination and anomeric dehydration steps).[46] Similarly to the nitrile-Wittig route, however, the failure in hydrating glycal **366** in an oxymercuration-demercuration reaction, led us to conclude that the alkene in glycal **366** was too unreactive with electrophilic mercuric reagents. This was surprising considering Yamaguchi and co-workers' success in their oxymercuration-demercuration of glycals **374**.[49]

The dithiane-reduction route was the strategy that was closest in obtaining the synthetic targets **379**, **400** and **407**. The lack of success in the thioacetate deprotections and concomitant cyclizations of the liberated thiol/thiolate onto a ketone or sulfonate ester in substrates **389** (and analogues) and **402** (and analogues) was a major setback. Changing the cyclization strategy to the nucleophilic displacement of two sulfonate esters in substrate **415** (and analogues) with a sulfide anion also failed. The failure of these three cyclization strategies was attributed to the presence of the isopropylidene groups hindering the cyclization by placing steric constraints on ring closure. We therefore aimed to deprotect the thioacetate functionality on a substrate without the isopropylidene groups. However, since efforts to hydrolyse both isopropylidene groups in ketone **394** were unsuccessful, we ceased work on this route and focused our efforts on a new strategy not involving isopropylidene groups.

In the D-galactose route, the tribenzylated nitrile **437** was isolated after five synthetic steps from D-galactose **433**. To our disappointment, we were unable to form the nitrile anion of **437** under a variety of conditions, which prevented any reaction with formaldehyde. These poor results, prompted us to synthesize the tribenzylated methyl ester **449**, but after trying numerous conditions, benzylations of **449** failed because of either undesired side-reactions or no reactions

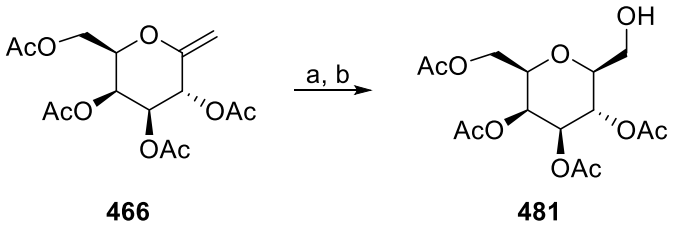
taking place at all. Endeavours to reductively hydrolyse the nitrile of **437** using a variety of metal hydride reagents did not afford the desired aldehyde, which forced us to abandon this route.

Finally, in the *exo*-glycal route, compound **467** was successfully synthesized in five steps from D-galactose. Attempts to protect *exo*-glycal **467** proved difficult, however, due to the basic nature of the *exo*-glycal under these conditions leading to many undesired side-reactions. We therefore aimed to functionalize the *exo*-glycal prior to any protections. This allowed us to isolate epoxide **α-473**, but we were unsuccessful in ring opening the epoxide with TMSCN and a Lewis acid. We thus performed a hydroboration on *exo*-glycal **466**, which furnished **481**, though in low yield and inseparable with an unknown compound.

Future Work

The main objective of this project was the synthesize targets **323a** and **323b** (**Figure 10**) which both contain the bicyclic core of the proposed structure of tagetitoxin. While we did not achieve this feat, the hydroboration-oxidation pathway in the *exo*-glycal route is promising for future research.

Due to the poor yield (and purity) of **381** (10%), the initial goal in any future work should be the optimization of the hydroboration-oxidation of **466** using 9-BBN (**Scheme 193**). This might involve changing the equivalents of 9-BBN and/or temperature of the reaction.

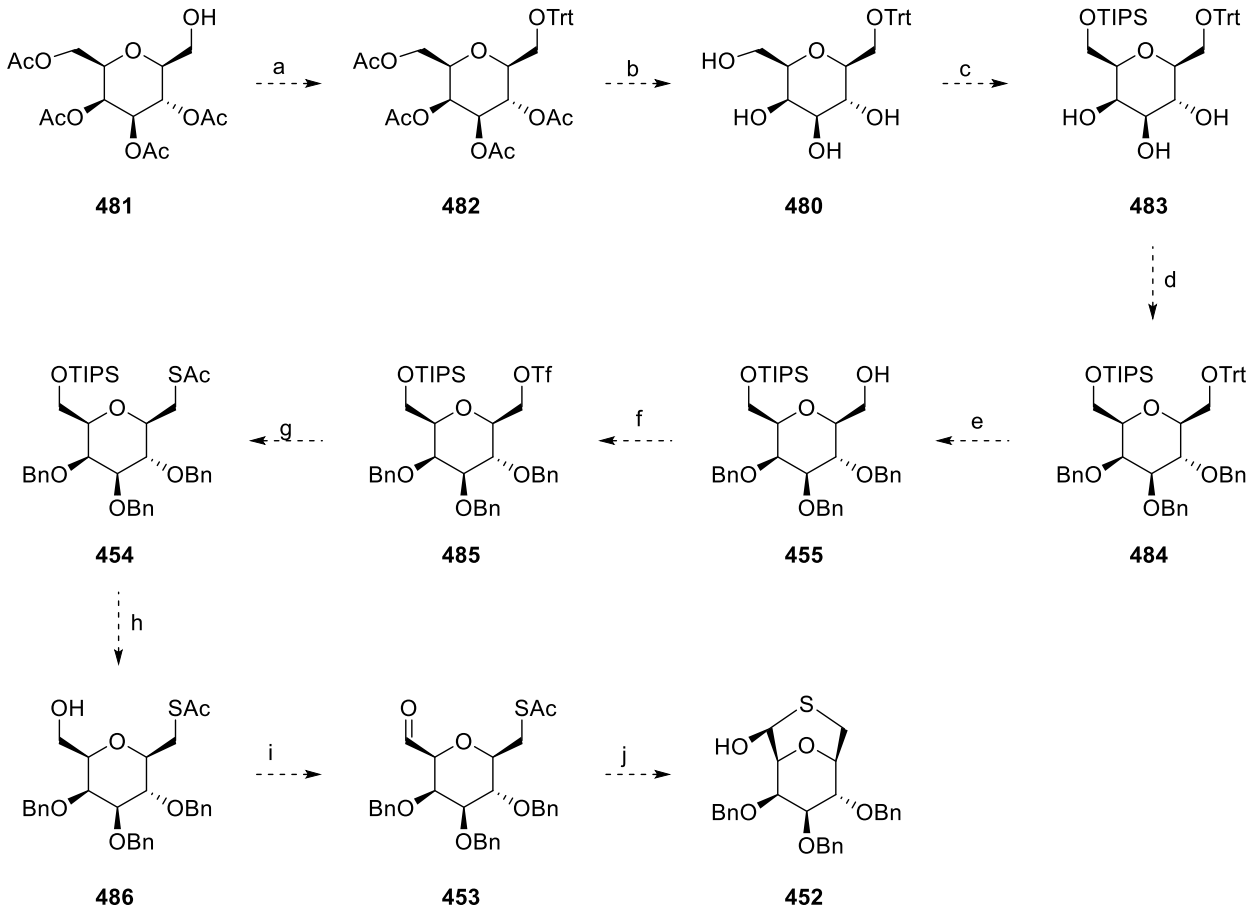


466 **481**

Reagents and conditions: a) 9-BBN (2 equiv.), THF, 0 °C to rt, overnight; b) 1:1 EtOH:THF, phosphate buffer (0.1 M, pH 7), 30% $H_2O_{2\ (aq)}$, 0 °C to rt, 3 h, 10%.

Scheme 193: Synthesis of **481** by the hydroboration-oxidation of **466** using 9-BBN.

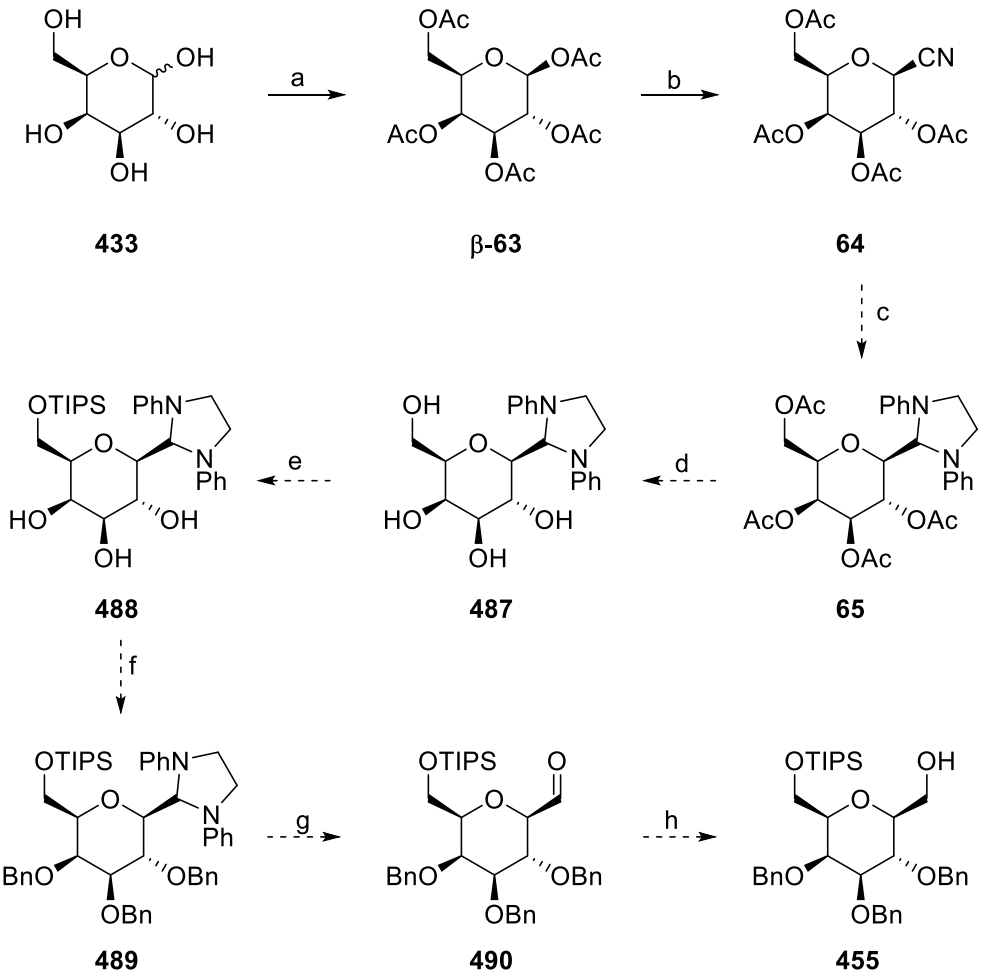
If this reaction can be optimized, the route to target **452** should be continued (**Schemes 191** and **194**). If target **452** were to be synthesized, the route should be revised and altered to install carboxylic acid derivatives on the C_{-1} position and thiohemiacetal centre.



Methodologies: a) tritylation; b) deacetylation; c) TIPS protection; d) perbenzylation; e) detritylation; f) triflation; g) thioacetate displacement; h) TIPS deprotection; i) 1^{o} OH oxidation; j) thioacetate deprotection and *in-situ* ring closure.

Scheme 194: Synthetic route to target **452** from **481**.

If, however, the hydroboration-oxidation reaction cannot be optimized, then an alternative route towards intermediate **455** should be investigated (**Scheme 195**).



Methodologies: a) peracetylation; b) C-glycosylation; c) reductive hydrolysis and *in-situ* Imidazolidine formation; d) deacetylation; e) TIPS protection; f) perbenzylation; g) imidazolidine hydrolysis; h) aldehyde reduction.

Scheme 195: Alternative synthetic route towards intermediate **455**.

We have already made compound **64** from **433** in the D-galactose route. Furthermore, Dent *et al.* have previously synthesized the imidazolidine derivative **65** from **64** by a Raney-nickel and sodium hypophosphite-based reductive hydrolysis alongside N,N′-Diphenylethylenediamine (**Scheme 9**).[108] A subsequent three-step sequence of deprotections and protections would lead to compound **489**. Unmasking of the aldehyde in **489** could then be achieved by imidazolidine hydrolysis; typical conditions would involve using *p*-TsOH (2-3 equiv.) in DCM at 0 ^{o}C to rt. Finally, reduction of the aldehyde **490** to alcohol **455** could be achieved using a metal hydride reductant such as $NaBH_4$.

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Experimental

General Experimental Details

Reagents and Solvents

All reagents obtained commercially were used without any further purification, unless otherwise stated. Triethylamine was stored over sodium hydroxide pellets.

For reactions performed under anhydrous conditions, solvents were obtained commercially dry except for: dichloromethane which was distilled over calcium hydride, tetrahydrofuran which was distilled under an argon atmosphere from the sodium/benzophenone ketyl radical, toluene which was dried over sodium and then distilled, acetonitrile which was stored under an argon atmosphere over activated MS 3Å for 24 hours, methanol which was stored under an argon atmosphere over activated MS 3Å for 24 hours, and N,N-dimethylformamide which was dried over activated MS 4Å overnight, vacuum distilled and then stored over activated MS 4Å under an argon atmosphere. Petroleum ether 40/60 was distilled before use to remove higher boiling point impurities. Petroleum ether 40/60 has been denoted as petrol.

Extractions were carried out using the reported organic solvent equivolumetric, unless stated otherwise.

Apparatus

For reactions requiring anhydrous conditions, glassware was flame-dried and allowed to cool to room temperature under a stream of argon or nitrogen. The reaction was then performed under an atmosphere of argon or nitrogen.

All reactions were carried out at room temperature unless otherwise stated.

Chromatography

Flash column chromatography on silica gel was carried out using Material Harvest Silica Gel 60 with 40-63 μm particle size. Individual solvent systems are reported in the experimental procedures.

Thin layer chromatography (TLC) was carried out on Merck aluminium backed plates coated with Kieselgel 60 F254 silica gel. The plates were visualized by irradiation of UV light (254nm)

and/or staining by aqueous potassium permanganate solution, ethanolic solution of phosphomolybdic acid or ethanolic solution of vanillin.

Compound Characterization Analysis

Infrared spectra were obtained using a Perkin Elmer Spectrum 100 Fourier Transformation-Infrared Spectrometer. Samples were dissolved in dichloromethane and applied onto sodium chloride plates as thin films.

High resolution mass spectra were acquired from the EPSRC UK National Mass Spectrometry Facility at the University of Swansea.

Melting points were carried out on a Büchi B-545 instrument.

Optical rotation measurements were obtained with a Bellingham and Stanley ADP-440 polarimeter operating at the sodium (D) line emission (λ=589 nm) at the reported temperature. The cell path length was 0.25 dm. The solutions for these measurements were prepared in volumetric flasks using solvents of spectrophotometric grade.

Proton, carbon and fluorine NMR experiments were carried out at 500, 126 and 471 MHz respectively using a Bruker Advance III 500 MHz NMR spectrometer or at 400, 101 and 376 MHz using a Bruker Ultrashield 400 MHz NMR spectrometer. Chemical shifts were reported in parts per million (ppm) relative to the residual solvent peak. Abbreviations for signals in proton NMR are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (J values) are reported in Hertz (Hz).

Numbering System

The assignments of the NMR spectroscopy measurements for any compound with a pyranose or furanose core, follow the standard numbering system (**Figure 23)**.

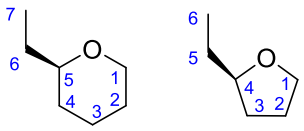
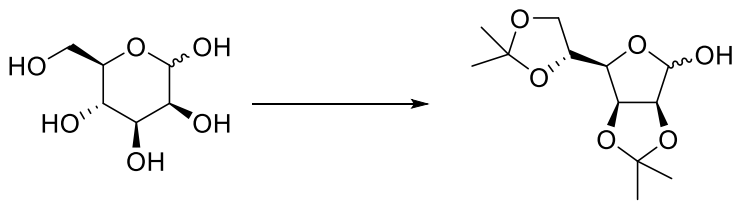


Figure 23: Numbering system used in experimental detail.

For all other compounds, the numbering system is designed by the author.

2,3;5,6-di-O-isopropylidene-α-D-mannofuranose (234)[1]

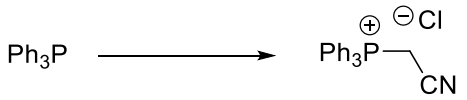


235 **234**

Concentrated sulfuric acid (14 ml) was added to a stirred suspension of D-mannose **235** (20 g, 110 mmol) in anhydrous acetone (600 ml). After stirring the reaction mixture overnight, the red coloured solution was neutralized with anhydrous sodium carbonate and filtered. The filtrate was heated under reflux for 1 hour with activated charcoal and sodium carbonate (2-3 g). After filtration through a pad of celite, the filtrate was evaporated under reduced pressure to give a crude colourless solid. Recrystallization from diethyl ether and petrol furnished the title compound as a colourless solid (26.652 g, 92%); IR ν_{max} (film)/cm^{-1}: 3432, 2978, 2947, 2900, 1458, 1438, 1373, 1227, 1203, 1070; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.32 (s, 3H, CH_3 Isopropylidene), 1.37 (s, 3H, CH_3 Isopropylidene), 1.45 (s, 3H, CH_3 Isopropylidene), 1.46 (s, 3H, CH_3 Isopropylidene), 3.04 – 3.13 (m, 1H, OH), 4.04 (dd, *J* = 8.7, 4.8 Hz, 1H, H'-C_6), 4.08 (dd, *J* = 8.7, 6.2 Hz, 1H, H'-C_6), 4.18 (dd, *J* = 7.2, 3.6 Hz, 1H, H-C_4), 4.40 (ddd, *J* = 7.2, 6.2, 4.8 Hz, 1H, H-C_5), 4.61 (d, *J* = 5.9 Hz, 1H, H-C_2), 4.80 (dd, *J* = 5.9, 3.6 Hz, 1H, H-C_3), 5.37 (d, *J* = 2.5 Hz, 1H, H-C_1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.6 (1C, CH_3 Isopropylidene), 25.2 (1C, CH_3 Isopropylidene), 26.0 (1C, CH_3 Isopropylidene), 27.0 (1C, CH_3 Isopropylidene), 66.7 (1C, C_6), 73.4 (1C, C_5), 79.8 (1C, C_4), 80.4 (1C, C_3), 85.6 (1C, C_2), 101.4 (1C, C_1), 109.2 (1C, C_q Isopropylidene), 112.8 (1C, C_q Isopropylidene).

The data is in agreement with literature reference.[1]

(Cyanomethyl)triphenylphosphonium Chloride (331)[2]

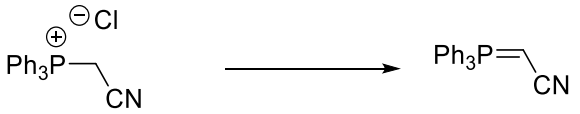


330 **331**

Chloroacetonitrile (2.4 ml, 38.2 mmol, 1 equiv.) was added dropwise to a stirred mixture of triphenylphosphine **330** (10 g, 38.2 mmol) in EtOAc (30 ml) at rt. The reaction mixture was then heated under reflux for 3 hours. After cooling to rt, the mixture was filtered and the precipitate was washed with Et_2O to afford a pure colourless solid (11.73 g, 91%); mp 260 – 264 ^oC decomposition [lit. 268 – 270 ^oC],[2] [lit. 263 ^oC decomposition][3]; IR ν_{max} (film)/cm^{-1}: 3056, 3010, 2972, 2715, 2251, 1586, 1439, 1113, 723; ^1H NMR (500 MHz, DMSO) δ 6.07 (d, *J* = 15.9 Hz, 2H, CH_2), 7.81 – 7.93 (m, 12H, 12 X H-C_{AR}), 7.96 – 8.02 (m, 3H, 3 X H-C_{AR}). ^{13}C NMR (126 MHz, DMSO) δ 14.3 (d, *J* = 55.1 Hz, 1C, CH_2), 112.9 (d, *J* = 9.2 Hz, 1C, $C_{q\ Nitrile}$), 116.3 (d, *J* = 88.7 Hz, 3C, 3 X C_{AR}), 130.6 (d, *J* = 13.2 Hz, 6C, 6 X C_{AR}), 133.8 (d, *J* = 10.9 Hz, 6C, 6 X C_{AR}), 136.0 (d, *J* = 3.0 Hz, 3C, 3 X C_{AR}).

The data is in agreement with literature reference.[2]

2-(Triphenylphosphoranylidene)acetonitrile (332)[2]

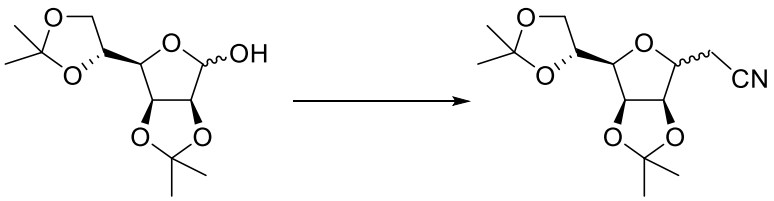


331 **332**

Et_3N (12.3 ml, 87.9 mmol, 2.53 equiv.) was added to a stirred suspension of **331** (11.73 g, 34.8 mmol) in dry DCM (160 ml). After stirring the suspension for 30 minutes, water (20 ml) was then added. The layers were then separated. and the organic phase was washed with water (2 x 20 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvents were removed under reduced pressure. Recrystallization from toluene gave the title compound as a colourless solid (8.70 g, 74%); mp 188 – 190 ºC [lit. 195 – 197 ºC],[2] [190 – 192 ºC][4]; IR ν_{max} (film)/cm^{-1}: 3052, 2138, 2972, 1435, 1105, 714; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.58 (s, 1H), 7.44 – 7.71 (m, 15H);; ^{13}C NMR (126 MHz, Chloroform-*d*) δ -2.0 (d, *J* = 136.2 Hz, 1C, CH), 127.5 (d, *J* = 91.8 Hz, 3C, 3 X C_{AR}), 129.2 (d, *J* = 12.3 Hz, 6C, 6 X C_{AR}), 132.7 (3C, 3 X C_{AR}), 132.9 (d, *J* = 10.1 Hz, 6C, 6 X C_{AR}).

The data is in agreement with the literature reference.[2]

2-((3aR,6R,6aS)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)acetonitrile (333)

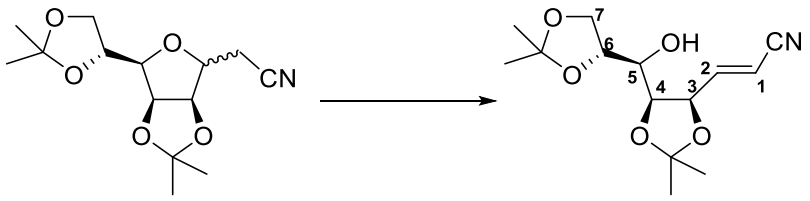


234 **333**

t-BuOK (3.88 g, 34.6 mmol, 1.5 equiv.) was added to a stirred solution of diethyl cyanomethylphosphonate (5.6 ml, 34.6 mmol, 1.5 equiv.) in dry THF (115 ml) at 0 °C. The mixture was stirred for 30 minutes at 0 °C. To this solution was added a solution of **234** (6.0 g, 23.1 mmol) in dry THF (156 ml) slowly. The reaction mixture was then warmed to rt and stirred overnight. The mixture was then treated with water (ca. 120ml) and DCM (ca. 120ml). The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure furnished a crude colourless solid. Purification by flash column chromatography on silica gel (petrol:EtOAc, 3:1) afforded an inseparable mixture (**α**:**β**, 1:3) of diastereomers **333** (6.429 g, 98%); IR ν_{max} (film)/cm^{-1}: 2987, 2938, 2878, 2253, 1373, 1068; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.33 (s, 3H, CH_3 Isopropylidene, β isomer), 1.35 (s, 3H, CH_3 Isopropylidene, α isomer), 1.37 (s, 6H, CH_3 Isopropylidene, both isomers), 1.44 (s, 6H, CH_3 Isopropylidene, both isomers), 1.48 (s, 3H, CH_3 Isopropylidene, β isomer), 1.50 (s, 3H,CH_3 Isopropylidene, α isomer), 2.54 (d, *J* = 6.4 Hz, 2H, CH_2, α isomer), 2.72 (d, *J* = 6.7 Hz, 2H, CH_2, β isomer), 3.58 (dd, *J* = 7.4, 3.6 Hz, 1H, H-C_4, β isomer), 3.83 (td, *J* = 6.7, 3.7 Hz, 1H, H-C_1, β isomer), 3.98 (dd, *J* = 7.4, 3.7 Hz, 1H, H-C_4, α isomer), 4.01 – 4.11 (m, 4H, H-C_6, H'-C_6, both isomers), 4.34 (td, *J* = 6.4, 1.3 Hz, H-C_1 α isomer), 4.36 - 4.41 (m, 2H, H-C_5 both isomers), 4.66 – 4.72 (m, 2H, H-C_2, both isomers), 4.80 (dd, *J* = 6.0, 3.6 Hz, 1H, H-C_3, β isomer), 4.87 (dd, *J* = 6.0, 3.7 Hz, 1H, H-C_3, α isomer). ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.7 (1C, CH_2, α isomer), 20.8 (1C, CH_2, β isomer), 24.6 (1C, CH_3 Isopropylidene, β isomer), 24.8 (1C, CH_3 Isopropylidene, α isomer), 25.2 (1C, CH_3 Isopropylidene, α isomer), 25.3 (1C, CH_3 Isopropylidene, β isomer), 25.7 (1C, CH_3 Isopropylidene, β isomer), 26.9 (1C, CH_3 Isopropylidene, α isomer), 27.0 (1C, CH_3 Isopropylidene, both isomers), 66.8 (1C, C_6, β isomer), 66.9 (1C, C_6, α isomer), 73.0 (1C, C_5, β isomer), 73.3 (1C, C_5, α isomer), 76.9 (1C, C_1, β isomer), 80.3 (1C, C_1, α isomer), 80.6 (1C, C_2, β isomer), 80.8 (1C, C_3, β isomer), 80.9 (1C, C_3,

α isomer), 81.6 (1C, C_{-4}, α isomer), 82.2 (1C, C_{-4}, β isomer), 84.6 (1C, C_{-2}, α isomer), 109.3 (1C, C_q Isopropylidene, β isomer), 109.5 (1C, C_q Isopropylidene, α isomer), 113.4 (1C, C_q Isopropylidene, β isomer), 113.7 (1C, C_q Isopropylidene, α isomer), 116.9 (1C, C_q Nitrile, α isomer), 117.2(1C, C_q Nitrile, β isomer); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 301.1757; $[C_{14}H_{21}NO_5+NH_4]^+$ requires 301.1758.

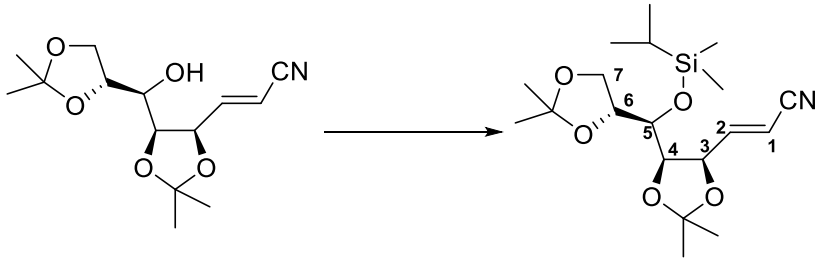
(*E*)-3-((4R,5S)-5-((R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylonitrile (*E*-329)



333 ***E*-329**

n-Butyl lithium (4.3 ml, 2.5 M in hexanes, 10.6 mmol, 3 equiv.) was added dropwise to a stirred solution of diisopropylamine (1.9 ml, 10.6 mmol, 3 equiv.) in dry THF (64 ml) at -78 ^{o}C. The solution was stirred for 1 hour at this temperature. A solution of **333** (1.008 g, 3.56 mmol) in dry THF (108 ml) at -78 ^{o}C was cannulated into the LDA solution. The dark orange solution was then stirred at -78 ^{o}C until TLC showed complete consumption of the starting material (~ 45 minutes). Glacial acetic acid (0.8 ml) and ethyl acetate (240 ml) were then added. The mixture was then warmed to rt slowly and then concentrated *in vacuo*. Purification by flash column chromatography on silica gel (petrol:EtOAc, 5:1) afforded the title compound as a colourless oil (0.564 g, 56%); $[\alpha]_D^{25}$ = + 31.1 (c 1.31 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3486, 2988, 2937, 2265, 1638, 1376, 1215, 1070; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.35 (s, 3H, $CH_{3\ Isopropylidene}$), 1.41 (s, 6H, 2 X $CH_{3\ Isopropylidene}$), 1.53 (s, 3H, $CH_{3\ Isopropylidene}$), 2.15 (d, *J* = 8.3 Hz, 1H, OH), 3.40 (td, *J* = 8.3, 2.3 Hz, 1H, H-C_{-5}), 3.92 – 4.01 (m, 2H, H-C_{-7}, H-C_{-6}), 4.06 – 4.16 (m, 1H, H'-C_{-7}), 4.47 (dd, *J* = 7.4, 2.4 Hz, 1H, H-C_{-4}), 4.76 (ddd, *J* = 7.4, 5.4, 1.7 Hz, 1H, H-C_{-3}), 5.66 (dd, *J* = 16.2, 1.7 Hz, 1H, H-C_{-1}), 6.88 (dd, *J* = 16.2, 5.4 Hz, 1H, H-C_{-2}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9 (1C, $CH_{3\ Isopropylidene}$), 25.3 (1C, $CH_{3\ Isopropylidene}$), 26.9 (1C, $CH_{3\ Isopropylidene}$), 27.0 (1C, $CH_{3\ Isopropylidene}$), 67.5 (1C, C_{-7}), 70.5 (1C, C_{-5}), 76.2 (1C, C_{-6}), 76.6 (1C, C_{-3}), 77.5 (1C, C_{-4}), 101.7 (1C, C_{-1}), 109.8 (1C, $C_{q\ Isopropylidene}$), 109.8 (1C, $C_{q\ Isopropylidene}$), 116.9 (1C, $C_{q\ Nitrile}$), 150.8 (1C, C_{-2}); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 301.1758; $[C_{14}H_{21}NO_5+NH_4]^+$ requires 301.1758.

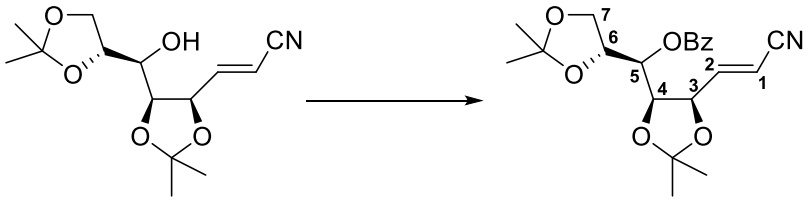
(*E*)-3-((4R,5R)-5-((R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((isopropyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylonitrile (339)



***E*-329** **339**

IPDMSCl (0.67 ml, 3.97 mmol, 2.0 equiv.) was added dropwise to a mixture of alkene ***E*-329** (0.562 g, 1.99 mmol) and imidazole (0.270 g, 3.97 mmol, 2.0 equiv.) in dry DCM at 0 ^{o}C. The reaction mixture was stirred for 24 hours at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 6:1) to furnish **339** as a pure colourless oil (0.622 g, 82%);$[\alpha]_D^{25}$ = + 64.2 (c 0.9 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2988, 2940, 2866, 2226, 1635, 1372, 1079; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 0.06 (s, 3H, $CH_{3\ IPDMS}$), 0.07 (s, 3H, $CH_{3\ IPDMS}$), 0.75 – 0.84 (m, 1H, H-$CMe_{2\ IPDMS}$), 0.95 – 0.90 (m, 6H, 2 X $CH_{3\ ipr(IPDMS)}$), 1.33 (s, 3H, $CH_{3\ Isopropylidene}$), 1.37 (s, 3H, $CH_{3\ Isopropylidene}$), 1.42 (s, 3H, $CH_{3\ Isopropylidene}$), 1.50 (s, 3H, $CH_{3\ Isopropylidene}$), 3.63 (dd, *J* = 8.9, 7.9 Hz, 1H, H-C_{-5}), 3.77 (dd, *J* = 8.3, 7.4 Hz, 1H, H-C_{-7}), 3.92 – 3.99 (m, 1H, H-C_{-6}), 4.10 – 4.18 (m, 2H, H'-C_{-7}, H-C_{-4}), 4.69 (ddd, *J* = 6.2, 4.4, 1.9 Hz, 1H, H-C_{-3}), 5.67 (dd, *J* = 16.3, 1.9 Hz, 1H, H-C_{-1}), 6.95 (dd, *J* = 16.3, 4.4 Hz, 1H, H-C_{-2}); ^{13}C NMR (126 MHz, $CDCl_3$) δ -3.6 (1C, $CH_{3\ Me\ (IPDMS)}$), -3.0 (1C, $CH_{3\ Me\ (IPDMS)}$), 15.4 (1C, $CHMe_{2\ ipr\ (IPDMS)}$), 17.0 (1C, $CH_{3\ ipr\ (IPDMS)}$), 17.1 (1C, $CH_{3\ ipr\ (IPDMS)}$), 25.3 (1C, $CH_{3\ Isopropylidene}$), 25.4 (1C, $CH_{3\ Isopropylidene}$), 26.4 (1C, $CH_{3\ Isopropylidene}$), 27.8 (1C, $CH_{3\ Isopropylidene}$), 68.6 (1C, C_{-7}), 72.9 (1C, C_{-5}), 76.5 (1C, C_{-3}), 77.4 (1C, C_{-6}), 81.4 (1C, C_{-4}), 101.5 (1C, C_{-1}), 109.0 (1C, $C_{q\ Isopropylidene}$), 110.2 (1C, $C_{q\ Isopropylidene}$), 117.4 (1C, $C_{q\ Nitrile}$), 152.6 (1C, C_{-2}); HRMS (NSI-FTMS) *m/z* found for $[M+H]^+$: 384.2203; $[C_{19}H_{33}NO_5Si+H]^+$ requires 384.2201.

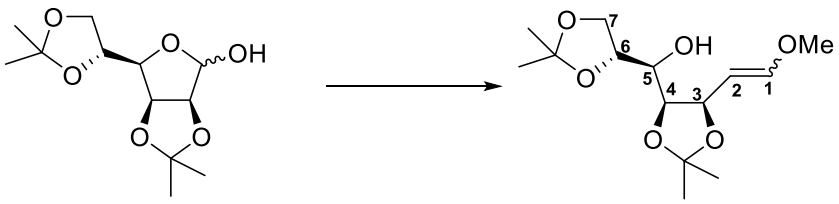
(R)-((4R,5R)-5-((*E*)-2-cyanovinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate (340)



***E*-329** **340**

DMAP (0.039 g, 0.32 mmol, 0.2 equiv.) was added to a stirred solution of Et_3N (0.99 ml, 7.07 mmol, 4.42 equiv.) in dry DCM (12 ml) at 0 ^oC. Benzoyl chloride (0.62 ml, 5.30 mmol, 3.31 equiv.) was then added dropwise. To this solution at 0 ^oC, was then added a solution of ***E*-329** (0.454 g, 1.60 mmol) in dry DCM (4 ml) dropwise. The reaction mixture was stirred at rt overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with DCM three times. The combined organic extracts were washed with water, then brine, and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent under reduced pressure afforded a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:1) to furnish the title compound as a pure yellow oil (0.620 g, quant.); $[\alpha]_D^{25}$ = - 29.7 (c 0.9 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3072, 2988, 2229, 1724, 1372, 1268; ^1H NMR (500 MHz, Chloroform-*d*) δ 1.36 (s, 6H, 2 X $CH_{3\ Isopropylidene}$), 1.42 (s, 3H, $CH_{3\ Isopropylidene}$), 1.61 (s, 3H, $CH_{3\ Isopropylidene}$), 3.98 (dd, *J* = 8.8, 6.2 Hz, 1H, H-C_{-7}), 4.03 (dd, *J* = 8.8, 6.2 Hz, 1H, H'-C_{-7}), 4.34 (dt, *J* = 7.2, 6.2 Hz, 1H, H-C_{-6}), 4.67 (dd, *J* = 7.6, 2.3 Hz, 1H, H-C_{-4}), 4.85 (ddd, *J* = 7.6, 4.1, 2.1 Hz, 1H, H-C_{-3}), 5.27 (dd, *J* = 7.2, 2.3 Hz, 1H, H-C_{-5}), 5.47 (dd, *J* = 16.1, 2.1 Hz, 1H, H-C_{-1}), 6.64 (dd, *J* = 16.1, 4.1 Hz, 1H, H-C_{-2}), 7.43 – 7.50 (m, 2H, 2 X H-C_{AR}), 7.56 – 7.64 (m, 1H, H-C_{AR}), 8.01 – 8.06 (m, 2H, 2 X H-C_{AR}).;^{13}C NMR (126 MHz, $CDCl_3$) δ 25.0 (1C, $CH_{3\ Isopropylidene}$), 25.5 (1C, $CH_{3\ Isopropylidene}$), 26.6 (1C, $CH_{3\ Isopropylidene}$), 26.9 (1C, $CH_{3\ Isopropylidene}$), 66.5 (1C, C_{-7}), 71.0 (1C, C_{-5}), 75.2 (1C, C_{-6}), 75.6 (1C, C_{-3}), 76.8 (1C, C_{-4}), 101.0 (1C, C_{-1}), 109.7 (1C, $C_{q\ Isopropylidene}$), 109.8 (1C, $C_{q\ Isopropylidene}$), 116.2 (1C, $C_{q\ Nitrile}$), 128.6 (2 X C_{AR}), 129.5 (1C, C_{AR}), 129.9 (2C, 2 X C_{AR}), 133.6 (1C, $C_{q\ AR}$), 148.2 (1C, C_{-2}), 165.7 (1C, $C_{q\ Benzoate}$); HRMS (NSI-FTMS) *m/z* found for $[M+H]^+$: 388.1756; $[C_{21}H_{25}NO_6+H]^+$ requires 388.1755.

(R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((4S,5R)-5-(2-methoxyvinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (354)

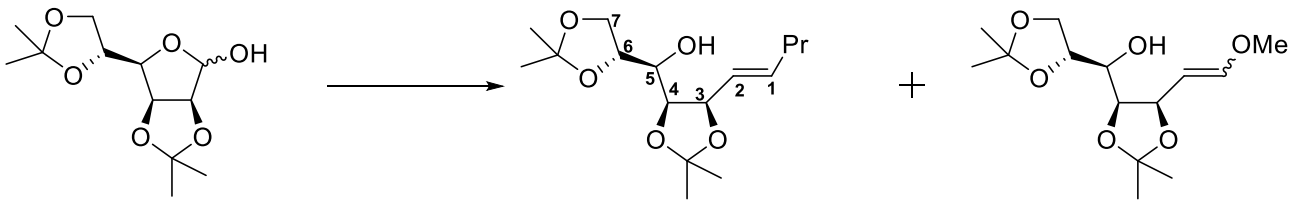


234 **354**

n-Butyl lithium (36.0 ml, 1.6M in hexanes, 57.6 mmol, 3 equiv.) was added dropwise to a stirred solution of diisopropylamine (8.1 ml, 57.6 mmol, 3 equiv.) in dry THF (140 ml) at -78 ^{o}C. After stirring for 1 hour at this temperature methoxymethyltriphenylphosphonium chloride (19.76 g, 57.6 mmol, 3 equiv.) was then added cautiously portion wise. The red-coloured solution was then stirred for 1 hour at -78 ^{o}C. A solution of **234** (5.0 g, 19.2 mmol) in dry THF (40 ml) at -78 ^{o}C was added to the ylide-solution slowly via a cannula transfer. The resultant mixture was then warmed to rt gradually before being refluxed overnight. The reaction mixture was then cooled to rt and quenched with brine (ca. 60 ml), and the layers were then separated. The aqueous layer was extracted with Et_2O three times. The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* furnished a crude dark brown oil. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 6:1) furnishing an inseparable mixture (**E**:**Z**, 5:1) of geometric isomers of vinyl ether **354** as a yellow oil (3.125 g, 57%); IR ν_{max} (film)/cm^{-1}: 3530, 2987, 2937, 1655, 1372, 1212, 1070; ^{1}H NMR (500 MHz, Chloroform-*d*) δ1.35 (s, 6H, CH_3 Isopropylidene, Both Isomers,), 1.38 – 1.41 (m, 12H, 2 X CH_3 Isopropylidene, Both Isomers), 1.50 (s, 3H, CH_3 Isopropylidene, Z Isomer), 1.51 (s, 3H, CH_3, Isopropylidene, Z Isomer), 2.17 (d, *J* = 8.1 Hz, 1H, OH, Z Isomer), 2.20 (d, *J* = 8.7 Hz, 1H, OH, E Isomer), 3.45 – 3.51 (m, 2H, H-C$_{-6}$, Both Isomers), 3.61 (s, 3H, CH_3 Methoxy, E Isomer), 3.63 (s, 3H, CH_3 Methoxy, Z Isomer), 3.98 – 4.13 (m, 6H, H-C$_{-7}$, H'-C$_{-7}$, H-C$_{-5}$, Both Isomers), 4.30 (dd, *J* = 7.4, 1.1 Hz, 1H, H-C$_{-4}$, E Isomer), 4.34 (dd, *J* = 7.4, 1.4 Hz, 1H, H-C$_{-4}$, Z Isomer), 4.66 (dd, *J* = 9.6, 7.4 Hz, 1H, H-C$_{-3}$, E Isomer), 4.74 (dd, *J* = 8.7, 6.3 Hz, 1H, H-C$_{-2}$, Z Isomer), 5.05 (dd, *J* = 12.7, 9.6 Hz, 1H, H-C$_{-2}$, E Isomer), 5.27 (ddd, *J* = 8.7, 7.4, 1.2 Hz, 1H, H-C$_{-3}$, Z Isomer), 6.13 (dd, *J* = 6.3, 1.2 Hz, 1H, H-C$_{-1}$, Z Isomer), 6.64 (d, *J* = 12.7 Hz, 1H, H-C$_{-1}$, E Isomer); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4 (1C, CH_3 Isopropylidene, E isomer), 24.5 (1C, CH_3 Isopropylidene, Z isomer), 25.4 (1C, CH_3 Isopropylidene, E isomer), 25.5 (1C, CH_3 Isopropylidene, Z isomer), 26.8 (2C,

$CH_{3\ Isopropylidene,\ Both\ isomers}$), 26.9 (1C, $CH_{3\ Isopropylidene,\ Z\ isomer}$), 27.0 (1C, $CH_{3\ Isopropylidene,\ E\ isomer}$), 56.3 (1C, $CH_{3,\ Methoxy,\ E\ Isomer}$), 60.2 (1C, $CH_{3,\ Methoxy,\ Z\ Isomer}$), 67.0 (1C, $C_{-7,\ Z\ Isomer}$), 67.2 (1C, $C_{-7,\ E\ Isomer}$), 70.9 (1C, $C_{-6,\ Z\ isomer}$), 71.0 (1C, $C_{-6,\ E\ Isomer}$), 71.4 (1C, $C_{-3,\ Z\ Isomer}$), 76.1 (1C, $C_{-4,\ Z\ Isomer}$), 76.3 (1C, $C_{-5,\ Z\ Isomer}$), 76.3 (1C, C_{-5} or $C_{-4,\ E\ Isomer}$), 76.4 (1C, C_{-5} or $C_{-4,\ E\ Isomer}$), 76.9 (1C, $C_{-3,\ E\ Isomer}$), 98.1 (1C, $C_{-2,\ E\ Isomer}$), 102.1 (1C, $C_{-2,\ Z\ Isomer}$), 107.9 (1C, $C_{q\ Isopropylidene,\ E\ Isomer}$), 108.0 (1C, $C_{q\ Isopropylidene,\ Z\ Isomer}$), 109.3 (1C, $C_{q\ Isopropylidene,\ Z\ Isomer}$), 109.4 (1C, $C_{q\ Isopropylidene,\ E\ Isomer}$), 150.3 (1C, $C_{-1,\ Z\ Isomer}$), 153.2 (1C, $C_{-1,\ E\ Isomer}$); HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 311.1465; $[C_{14}H_{24}O_6Na]^+$ requires 311.1465.

(2*R*,3*R*,4*R*,5*R*)-3-Hydroxy-1,2;4,5-di-*O*-isopropylidene-6-decene (355)[5]



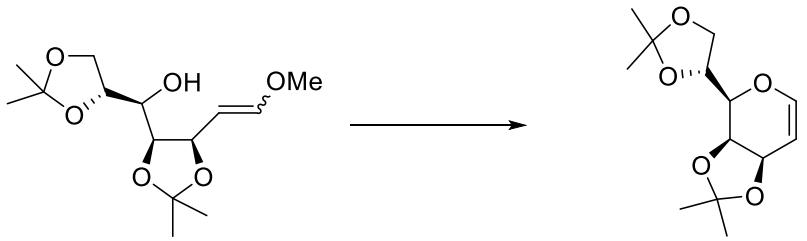
234 **355** **354**

n-Butyl lithium (2.08 ml, 2.5M in hexanes, 5.21 mmol, 3 equiv.) was added dropwise to a stirred mixture of methoxymethyltriphenylphosphonium chloride (1. 786 g, 5.21 mmol, 3 equiv.) in dry THF (15.6 ml) at -78 ºC. The red-coloured solution was then stirred for 1 hour at -78 ºC. A solution of **234** (0.5 g, 1.96 mmol) in dry THF (3.1 ml) at -78 ºC was added to the ylide-solution slowly via a cannula transfer. The resultant mixture was then warmed to rt gradually and left to stir overnight. The reaction mixture was then cooled to rt and quenched with brine, and the layers were then separated. The aqueous layer was extracted with Et_2O three times. The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* furnished a crude dark brown oil. The crude mixture was purified by flash column chromatography on silica gel (petrol:EtOAc, 8:1) furnishing compound **355** as a colourless oil (0.099 g, 17%);^{1}H NMR (500 MHz, Chloroform-*d*) δ 0.91 (t, *J* = 7.4 Hz, 3H, $CH_{3\ Propyl}$), 1.35 (s, 3H, $CH_{3\ Isopropylidene}$), 1.39 (s, 3H, $CH_{3\ Isopropylidene}$), 1.40 (s, 3H, $CH_{3\ Isopropylidene}$), 1.41 – 1.46 (m, 2H, $CH_{2\ Propyl}$), 1.52 (s, 3H, $CH_{3\ Isopropylidene}$), 2.12 – 2.13 (m, 2H, $CH_{2\ Propyl}$), 3.43 – 3.49 (m, 1H, H-C_{-5}), 3.97 – 4.05 (m, 2H, H-C_{-6}, H-C_{-7}), 4.06 – 4.12 (m, 1H, H'-C_{-7}), 4.33 (dd, *J* = 7.4, 1.3 Hz, 1H, H-C_{-4}), 4.69 (t, *J* = 7.8 Hz, 1H, H-C_{-3}), 5.73 (ddt, *J* = 15.4, 8.4, 1.3 Hz, 1H, H-C_{-2}), 5.84 (dt, *J* = 15.5, 6.7 Hz, 1H, H-C_{-1}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7 (1C, $CH_{3\ Propyl}$), 22.2 (1C, $CH_{2\ Propyl}$), 24.5 (1C, $CH_{3\ Isopropylidene}$), 25.3 (1C, $CH_{3\ Isopropylidene}$), 26.7 (1C, $CH_{3\ Isopropylidene}$), 26.8 (1C, $CH_{3\ Isopropylidene}$), 34.4 (1C, $CH_{2\ Propyl}$), 67.0 (1C, C_{-7}), 70.7 (1C, C_{-5}), 76.1 (1C, C_{-6}), 76.6 (1C, C_{-4}), 79.1 (1C, C_{-3}), 108.3 (1C, $C_{q\ Isopropylidene}$), 109.3 (1C, $C_{q\ Isopropylidene}$), 125.5 (1C, C_{-2}), 137.8 (1C, C_{-1}).

The data is in agreement with the literature reference.[5]

Further elution (petrol:EtOAc, 5:1) gave vinyl ether **354** as an inseparable mixture of geometric isomers (**E**:**Z**, 7:3) as a yellow oil (0.2 g, 36%).

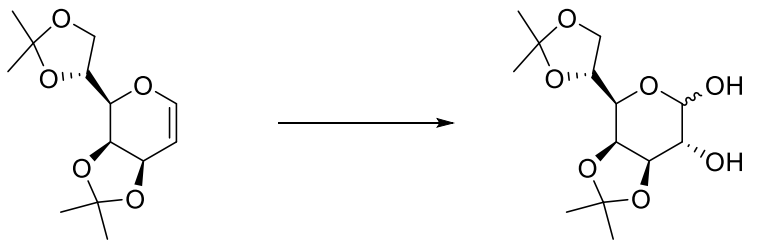
(3aR,4R,7aR)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-4,7a-dihydro-3aH-[1,3]dioxolo[4,5-c]pyran (353)



354 **353**

Mercuric acetate (0.135 g, 0.42 mmol, 0.2 equiv.) was added to a solution of **354** (0.610 g, 2.12 mmol) in a minimal volume of dry DCM in a Kugelrohr flask. The solution was evaporated to give a crude viscous oil (in a Buchi Kugelrohr apparatus) when heated at 110 ^{o}C and 20 mm Hg for 2 hours. The crude product was purified by flash column chromatography (petrol:EtOAc, 2:1) to yield the title compound as a pure colourless solid (0.312 g, 57%); mp 38 – 39 ^{o}C; $[\alpha]_D^{21}$ = -6.8 (c 1.18 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2986, 2935, 1648, 1371, 1084; ^{1}H NMR (400 MHz, Chloroform-*d*) δ1.38 (s, 6H, $CH_{3\ Isopropylidene}$), 1.43 (s, 3H, $CH_{3\ Isopropylidene}$), 1.45 (s, 3H, $CH_{3\ Isopropylidene}$), 3.77 (dd, *J* = 8.0, 1.2 Hz, 1H, H-C_{-5}), 4.03 – 4.15 (m, 2H, H-C_{-7}, H'-C_{-7}), 4.37 (ddd, *J* = 8.0, 6.1, 5.0 Hz, 1H, H-C_{-6}), 4.41 – 4.45 (dt, *J* = 6.2, 1.2 Hz, 1H, H-C_{-4}), 4.66 (dd, *J* = 6.2, 2.8 Hz, 1H, H-C_{-3}), 4.76 – 4.82 (ddd, *J* = 6.3, 2.8, 1.2 Hz, 1H, H-C_{-2}), 6.35 (d, *J* = 6.3 Hz, 1H, H-C_{-1}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.4 (1C, $CH_{3\ Isopropylidene}$), 27.0 (1C, $CH_{3\ Isopropylidene}$), 27.2 (1C, $CH_{3\ Isopropylidene}$), 28.3 (1C, $CH_{3\ Isopropylidene}$), 66.8 (1C, C_{-7}), 68.6 (1C, C_{-3}), 72.2 (1C, C_{-4}), 74.3 (1C, C_{-6}), 75.2 (1C, C_{-5}), 103.2 (1C, C_{-2}), 109.6 (1C, $C_{q\ Isopropylidene}$), 110.7 (1C, $C_{q\ Isopropylidene}$), 144.6 (1C, C_{-1}); HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 279.1203; $[C_{13}H_{20}O_5+Na]^+$ requires 279.1203.

(3aS,4R,6S,7R,7aR)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6,7-diol (352)

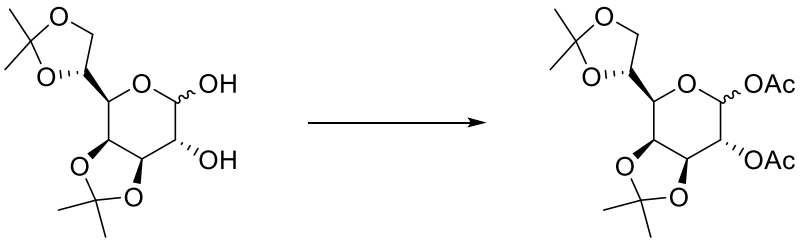


353 **352**

$OsCl_3$ (0.012 g, 0.04 mmol, 0.0167 equiv.) and NMO (0.832 g, 7.10 mmol, 2.9 equiv.) were added to a stirred solution of glycal **353** (0.628 g, 2.45 mmol) in 1:1 THF:H_2O (32.6 ml). The mixture was stirred overnight. Excess anhydrous Na_2SO_3 was then added to the mixture. After 1 hour, water and $CHCl_3$ were added to the mixture. The layers were separated and the aqueous layer was extracted with $CHCl_3$ twice. The combined organic extracts were washed with saturated aqueous Na_2SO_3, water, brine, and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave a crude residue. Purification by flash column chromatography on silica gel (petrol:EtOAc, 1:2) furnished an inseparable anomeric mixture **352** (**α**:**β**, 14:1) as a colourless solid (0.453 g, 64%); mp 133 - 135 ^oC; $[\alpha]_D^{21}$ = + 65.1 (c 0.99 in MeOH); IR ν_{max} (film)/cm^{-1}: 3363, 2988, 1378, 1220, 1065; ^1H NMR (500 MHz, DMSO-d_6) δ 1.26 (s, 3H, CH_3 Isopropylidene **α-352**), 1.27 (s, 6H, CH_3 Isopropylidene **α-352**, CH_3 Isopropylidene **β-352**), 1.32 (s, 3H, CH_3 Isopropylidene **α-352**), 1.34 (s, 3H, CH_3 Isopropylidene **β-352**), 1.38 (s, 3H, CH_3 Isopropylidene **α-352**), 1.39 (s, 6H, 2 X CH_3 Isopropylidene **β-352**), 3.15 (td, *J* = 7.9, 4.8 Hz, 1H, H-C_2 **β-352**), 3.44 (td, *J* = 6.4, 3.4 Hz, 1H, H-C_2 **α-352**), 3.65 (dd, *J* = 7.7, 2.1 Hz, 1H, H-C_5 **β-352**), 3.82 (dd, *J* = 8.4, 5.2 Hz, 1H, H-C_7 **α-352**), 3.86 (dd, *J* = 8.4, 5.3 Hz, 1H, H-C_7 **β-352**), 3.90 – 3.93 (m, 1H, H-C_3 **β-352**), 3.94 – 4.01 (m, 3H, H-C_5 **α-352**, H'-C_7 **α-352**, H'-C_7 **β-352**), 4.06 – 4.12 (m, 2H, H-C_3 **α-352**, H-C_4 **β-352**), 4.12 – 4.16 (m, 2H, H-C_6 **α-352**, H-C_6 **β-352**), 4.17 (dd, *J* = 6.0, 2.2 Hz, 1H H-C_4 **α-352**), 4.29 (dd, *J* = 7.9, 6.8 Hz, 1H, H-C_1 **β-352**), 4.88 (dd, *J* = 5.5, 3.4 Hz, 1H, H-C_1 **α-352**), 4.97 (d, *J* = 6.4 Hz, 1H, C_2-OH **α-352**), 5.10 (d, *J* = 4.8 Hz, 1H, C_2-OH **β-352**), 6.39 (d, *J* = 5.5 Hz, 1H, C_1-OH **α-352**), 6.70 (d, *J* = 6.8 Hz, 1H, C_1-OH **β-352**); ^{13}C NMR (126 MHz, DMSO) δ 25.2 (1C, CH_3 Isopropylidene **α-352**), 26.1 (1C, CH_3 Isopropylidene **α-352**), 26.6 (2C, 2 X CH_3 Isopropylidene **β-352**), 26.7 (1C, CH_3 Isopropylidene **α-352**), 27.8 (1C, CH_3 Isopropylidene **α-352**), 28.1 (1C, CH_3 Isopropylidene **β-352**), 28.5 (1C, CH_3 Isopropylidene **β-**

352), 66.3 (1C, C_{-7} **β-352**) 66.4 (1C, C_{-7} **α-352**), 67.9 (1C, C_{-5} **α-352**), 69.2 (1C, C_{-2} **α-352**), 72.4 (1C, C_{-4} **α-352**), 72.4 (1C, C_{-5} **β-352**), 73.1 (1C, C_{-4} **β-352**), 73.7 (1C, C_{-2} **β-352**) 73.8 (2C, C_{-6} **α-352**, C_{-6} **β-352**), 75.7 (1C, C_{-3} **α-352**), 79.3 (1C, C_{-3} **β-352**) 91.6 (1C, C_{-1} **α-352**), 96.7 (1C, C_{-1} **β-352**) 107.8 (1C, $C_{q\ Isopropylidene}$ **α-352**), 108.3 (1C, $C_{q\ Isopropylidene}$ **α-352**), 108.5 (1C, $C_{q\ Isopropylidene}$ **β-352**), 108.5 (1C, $C_{q\ Isopropylidene}$ **β-352**); HRMS (NSI-FTMS) *m/z* found for $[M+Na]^+$: 313.1257; $[C_{13}H_{27}O_7+Na]^+$ requires 313.1258.

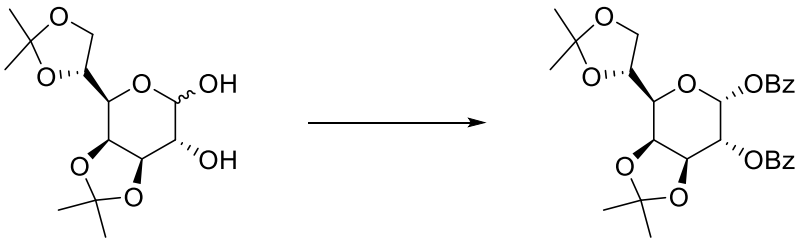
(3aS,4R,6R,7R,7aS)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6,7-diyl diacetate (357)



352 **357**

Ac_2O (0.49 ml, 5.17 mmol, 7.5 equiv.) was added dropwise to a stirred solution of **352** (0.200 g, 0.69 mmol) in pyridine (2.5 ml) at 0 ^oC. The reaction mixture was stirred at rt overnight. The mixture was then concentrated *in vacuo*. The residue was dissolved in DCM and treated with water. The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic layers were washed with saturated aqueous copper (II) sulfate, saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude colourless oil. Purification by flash column chromatography on silica gel (petrol:EtOAc, 9:2), furnished **357** (**α**:**β,** 14:1) as a colourless oil (0.176 g, 68%); $[\alpha]_D^{21}$ = + 72.4 (c 1.15 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2988, 2937, 1758, 1216, 1150, 1069; ^1H NMR (500 MHz, Chloroform-*d*) δ 1.37 (s, 3H, CH_3 Isopropylidene), 1.38 (s, 3H, CH_3 Isopropylidene), 1.43 (s, 3H, CH_3 Isopropylidene), 1.52 (s, 3H, CH_3 Isopropylidene), 2.08 (s, 3H, CH_3 Acetate), 2.10 (s, 3H, CH_3 Acetate), 3.92 – 4.00 (m, 2H, H-C_5, H-C_7), 4.07 (dd, *J* = 8.9, 6.2 Hz, 1H, H'-C_7), 4.29 – 4.41 (m, 3H, H-C_3, H-C_4, H-C_6), 5.13 (dd, *J* = 6.7, 3.8 Hz, 1H, H-C_2), 6.20 (d, *J* = 3.8 Hz, 1H, H-C_1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.9 (1C, CH_3 Acetate), 21.0 (1C, CH_3 Acetate), 25.3 (1C, CH_3 Isopropylidene), 26.6 (1C, CH_3 Isopropylidene), 27.1 (1C, CH_3 Isopropylidene), 27.6 (1C, CH_3 Isopropylidene), 66.9 (1C, C_7), 69.3 (1C, C_2), 70.8 (1C, C_5), 72.7 (1C, C_3 or C_4 or C_6), 72.8 (1C, C_3 or C_4 or C_6), 74.0 (1C, C_3 or C_4 or C_6), 89.4 (1C, C_1), 109.6 (1C, C_q Isopropylidene), 110.4 (1C, C_q Isopropylidene), 169.1 (1C, C_q Acetate), 170.1 (1C, C_q Acetate); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 392.1915; $[C_{17}H_{26}O_9+NH_4]^+$ requires 392.1915.

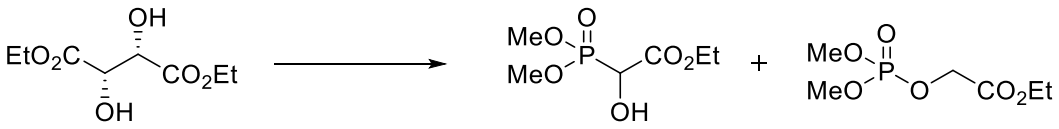
(3aS,4R,6R,7R,7aS)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6,7-diyl dibenzoate (359)



352 **359**

BzCl (0.24 ml, 2.087 mmol, 3 equiv.) was added dropwise to a stirred solution of **352** (0.201 g, 0.69 mmol) in pyridine (1 ml) at 0 ^{o}C. After 24 hours stirring at rt, the reaction mixture was diluted with DCM and quenched with water. The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic extracts were washed with saturated aqueous copper (II) sulfate, saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 8:1), yielding **359** as a pure colourless solid (0.223 g, 65%); mp 114 – 116 ^{o}C; $[\alpha]_D^{21}$ = + 104.3 (c 0.97 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3063, 2988, 2937, 1732, 1602, 1452, 1248, 1068; H NMR (500 MHz Chloroform-*d*) δ 1.37 (s, 3H, $CH_{3\ Isopropylidene}$), 1.43 (s, 6H, 2 X $CH_{3\ Isopropylidene}$), 1.61 (s, 3H, $CH_{3\ Isopropylidene}$), 4.00 (dd, *J* = 9.0, 4.4 Hz, 1H, H-C_{-7}), 4.06 – 4.16 (m, 2H, H'-C_{-7}, H-C_{-5}), 4.41 (ddd, *J* = 7.9, 6.2, 4.4 Hz, 1H, H-C_{-6}), 4.54 (dd, *J* = 6.3, 2.3 Hz, 1H, H-C_{-4}), 4.67 (t, *J* = 6.3 Hz, 1H, H-C_{-3}), 5.57 (dd, *J* = 6.3, 3.8 Hz, 1H, H-C_{-2}), 6.56 (d, *J* = 3.8 Hz, 1H, H-C_{-1}), 7.38 – 7.43 (m, 4H, 4 X H-C_{AR}), 7.53 – 7.60 (m, 2H, 2 X H-C_{AR}), 7.93 – 8.00 (m, 4H, 4 X H-C_{AR}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.4 (1C, $CH_{3\ Isopropylidene}$), 26.1 (1C, $CH_{3\ Isopropylidene}$), 27.1 (1C, $CH_{3\ Isopropylidene}$), 27.5 (1C, $CH_{3\ Isopropylidene}$), 67.1 (1C, C_{-7}), 69.5 (1C, C_{-2}), 71.5 (1C, C_{-5}), 72.8 (1C, C_{-4}), 73.1 (1C, C_{-3}), 74.0 (1C, C_{-6}), 90.2 (1C, C_{-1}), 109.6 (1C, $C_{q\ Isopropylidene}$), 110.7 (1C, $C_{q\ Isopropylidene}$), 128.6 (2C, 2 X C_{AR}), 128.7 (2C 2 X C_{AR}), 129.4 (1C, C_{AR}), 129. 4 (1C, C_{AR}), 130.0 (2C, 2 X C_{AR}), 130.0 (2C, 2 X C_{AR}), 133.6 (1C, $C_{q\ AR}$), 133.7 (1C, $C_{q\ AR}$), 164.6 (1C, $C_{q\ Benzoyl}$), 165.6 (1C, $C_{q\ Benzoyl}$); HRMS (ASAP-TOF) *m/z* found for $[M+NH_4]^+$: 516.2231; $[C_{27}H_{30}O_{69}+NH_4]^+$ requires 516.2233.

Ethyl 2-(dimethoxyphosphoryl)-2-hydroxyacetate (371)



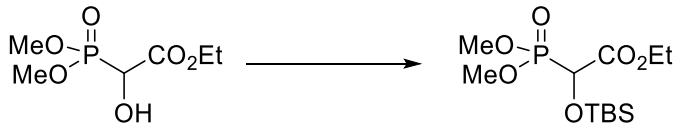
369 **370** **371**

Sodium periodate (10.37 g, 48.5 mmol, 2 equiv.) and water (10 ml) were added to a stirred solution of diethyl-L-tartrate (4.15 ml, 24.3 mmol) in DCM (50 ml). The biphasic mixture was then heated under reflux for 3 hours. The solution was then cooled to 0 ^{o}C before anhydrous $MgSO_4$ was added portion wise. Filtration and removal of the solvent under reduced pressure afforded ethyl glyoxylate in an unpurified state (4.433 g) and was used directly in the next step without any purification.

Et_3N (15.9 ml, 114.1 mmol, 3.09 equiv.) was added dropwise to a solution of dimethyl phosphite (3.99 ml, 43.6 mmol, 1.18 equiv.) in dry toluene (40 ml) at 0 ^{o}C. After leaving the solution to stir for 15 minutes at 0 ^{o}C, a solution of crude ethyl glyoxylate (4.433 g) in dry toluene (20 ml) was added. The reaction mixture was then warmed to rt and stirred overnight. The mixture was concentrated *in vacuo* forming a pale-yellow crude residue. Purification by flash column chromatography on silica gel (petrol:EtOAc, 1:3) afforded phosphonate **370** as a colourless solid (4.262 g, 41% over two steps); IR ν_{max} (film)/cm^{-1}: 3269, 2963, 2858, 1745, 1250, 1103, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H, $CH_{3\ Ester}$), 3.83 (d, *J* = 6.7 Hz, 3H, OCH_3), 3.86 (d, *J* = 6.6 Hz, 3H, OCH_3), 4.29 – 4.37 (m, 2H, $CH_{2\ Ester}$), 4.57 (d, J = 16.1 Hz, 1H, H-COH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1 (1C, $CH_{3\ Ester}$), 54.0 (d, *J* = 6.9 Hz, 1C, OCH_3), 54.4 (d, *J* = 6.8 Hz, 1C, OCH_3), 63.1 (1C, $CH_{2\ Ester}$), 68.6 (d, *J* = 156.1 Hz, 1C, CHOH), 169.3 (d, *J* = 1.2 Hz, 1C, $C_{q\ Ester}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 213.0527; $[C_6H_{13}O_6P+H]^+$ requires 213.0528.

Organophosphate **371** was also isolated as a pure colourless oil (3.233g, 31% over two steps); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.27 (t, *J* = 7.1 Hz, 3H, $CH_{3\ Ester}$), 3.80 (d, *J* = 11.3 Hz, 6H, 2 X OCH_3), 4.23 (q, *J* = 7.1 Hz, 1H, $CH_{2\ Ester}$), 4.55 (d, *J* = 11.4 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2 (1C, $CH_{3\ Ester}$), 54.8 (d, *J* = 6.1 Hz, 2C, 2 X OCH_3), 61.7 (1C, $CH_{2\ Ester}$), 63.6 (d, *J* = 5.0 Hz, 1C, OCH_2), 167.9 (d, *J* = 5.6 Hz, 1C, $C_{q\ Ester}$); HRMS (CI) *m/z* found for $[M+H]^+$: 213.0525; $[C_6H_{13}O_6P+H]^+$ requires 213.0528.

Ethyl 2-((*tert*-butyldimethylsilyl)oxy)-2-(dimethoxyphosphoryl)acetate (367)[6]

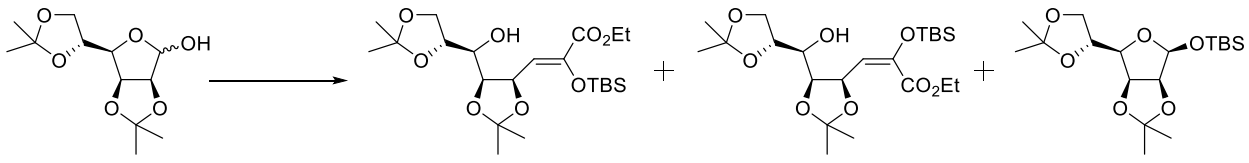


370 **367**

Imidazole (0.949 g, 13.9 mmol, 1.6 equiv.) and then TBSCl (1.580 g, 10.46 mmol, 1.2 equiv.) were added to a stirred solution of **370** (1.848 g, 8.71 mmol) in dry DCM (15.8 ml) at 0 ^{o}C. The resultant heterogenous mixture was stirred overnight at rt. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude yellow oil. The crude oil was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:2) to furnish the title compound as a pure colourless oil (2.60 g, 91%); IR ν_{max} (film)/cm^{-1}: 2958, 2931, 2897, 2858, 1754, 1262, 1139, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3H, $CH_{3\ Me\ (TBS)}$), 0.12 (s, 3H, $CH_{3\ Me\ (TBS)}$), 0.92 (s, 9H, 3 X $CH_{3\ tBu\ (TBS)}$), 1.30 (t, *J* = 7.1 Hz, 3H, $CH_{3\ Ester}$), 3.83 (d, *J* = 8.5 Hz, 3H, OCH_3), 3.85 (d, *J* = 8.5 Hz, 3H, OCH_3), 4.21 – 4.33 (m, 2H, $CH_{2\ Ester}$), 4.61 (d, *J* = 18.1 Hz, 1H, H-COTBDMS). ^{13}C NMR (126 MHz, $CDCl_3$) δ -5.2 (1C, $CH_{3\ Me\ (TBS)}$), -5.4 (1C, $CH_{3\ Me\ (TBS)}$), 14.2 (1C, $CH_{3\ Ester}$), 18.5 (1C, $C_{q\ tBu\ (TBS)}$), 25.7 (3C, 3 X $CH_{3\ tBu\ (TBS)}$), 54.2 (d, *J* = 6.9 Hz, 1C, OCH_3), 54.3 (d, *J* = 6.7 Hz, 1C, OCH_3), 62.0 (1C, $CH_{2\ Ester}$), 70.8 (d, J = 162.1 Hz, 1C, CHOTBS), 168.6 (d, *J* = 2.8 Hz, $C_{q\ Ester}$).

The data is in agreement with the literature reference.[6]

(*Z*)- and (*E*)-ethyl 2-((*tert*-butyldimethylsilyl)oxy)-3-((4R,5S)-5-((R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (*E*-364) and (*Z*-364)



234 ***Z*-254** ***E*-254** **372**

A solution of phosphonate **367** (1.158 g, 7.78 mmol, 1.5 equiv.) in dry THF (12.5 ml) was added dropwise to a stirred suspension of NaH (0.187 g, 7.78 mmol, 1.5 equiv.) in dry THF (12.5 ml) at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 1 hour. A solution of **234** (1.35 g, 5.19 mmol) in dry THF (12.5 ml) was then added dropwise to the suspension. The mixture was then warmed to rt and heated at 50 ^{o}C for 24 hours. The reaction was then cooled to rt and quenched with saturated aqueous NH_4Cl. Most of the THF was removed under reduced pressure. The aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* gave the crude product. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 15:2) to give an inseparable mixture (0.878 g, ***E*-364**:**372**, 50:1) of ***E*-364** (0.864 g, 36%) and by-product **372** (0.014 g, 1%) as a colourless oil.**

Characterization data for *E* silyl enol ether ***E*-364**; IR ν_{max} (film)/cm^{-1}: 3510, 2986, 2934, 2887, 2860, 1714, 1639, 1473, 1212, 1179, 1033; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 0.17 (s, 6H, 2 X $CH_{3\ Me\ (TBS)}$), 0.95 (s, 9H, 3 X $CH_{3\ tBu\ (TBS)}$), 1.34 (s, 3H, $CH_{3\ Isopropylidene}$), 1.37 (s, 3H, $CH_{3\ Isopropylidene}$), 1.40 (s, 3H, $CH_{3\ Isopropylidene}$), 1.52 (s, 3H, $CH_{3\ Isopropylidene}$), 3.35 (t, *J* = 7.5 Hz, 1H, H-C_{-7}), 3.96 – 4.01 (m, 2H, H-C_{-5}, H'-C_{-7}), 4.03 – 4.08 (m, 1H, H-C_{-6}), 4.16 – 4.24 (m, 2H, $CH_{2\ Ester}$), 4.64 (dd, *J* = 7.4, 1.1 Hz, 1H, H-C_{-4}), 5.48 (t, *J* = 7.4 Hz, 1H, H-C_{-3}), 5.73 (d, *J* = 7.4 Hz, 1H, H-C_{-2}); ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.8 (1C, $CH_{3\ Me\ (TBS)}$), -4.7 (1C, $CH_{3\ Me\ (TBS)}$), 14.3 (1C, $CH_{3\ Ester}$), 18.3 (1C, $C_{q\ tBu\ (TBS)}$), 24.2 (1C, $CH_{3\ Isopropylidene}$), 25.5 (1C, $CH_{3\ Isopropylidene}$), 25.7 (3C, 3 X $CH_{3\ tBu\ (TBS)}$), 26.8 (1C, $CH_{3\ Isopropylidene}$), 27.0 (1C, $CH_{3\ Isopropylidene}$), 61.3 (1C, $CH_{2\ Ester}$), 67.1 (1C, C_{-7}), 70.3 (1C, C_{-5}), 74.3 (1C, C_{-3}), 76.4 (1C, C_{-6}), 77.2 (1C, C_{-4}), 108.4 (1C, $C_{q\ Isopropylidene}$), 109.4(1 C, $C_{q\ Isopropylidene}$), 122.9 (1C, C_{-2}), 141.8 (1C, C_{-1}), 164.4 (1C, $C_{q\ Ester}$).

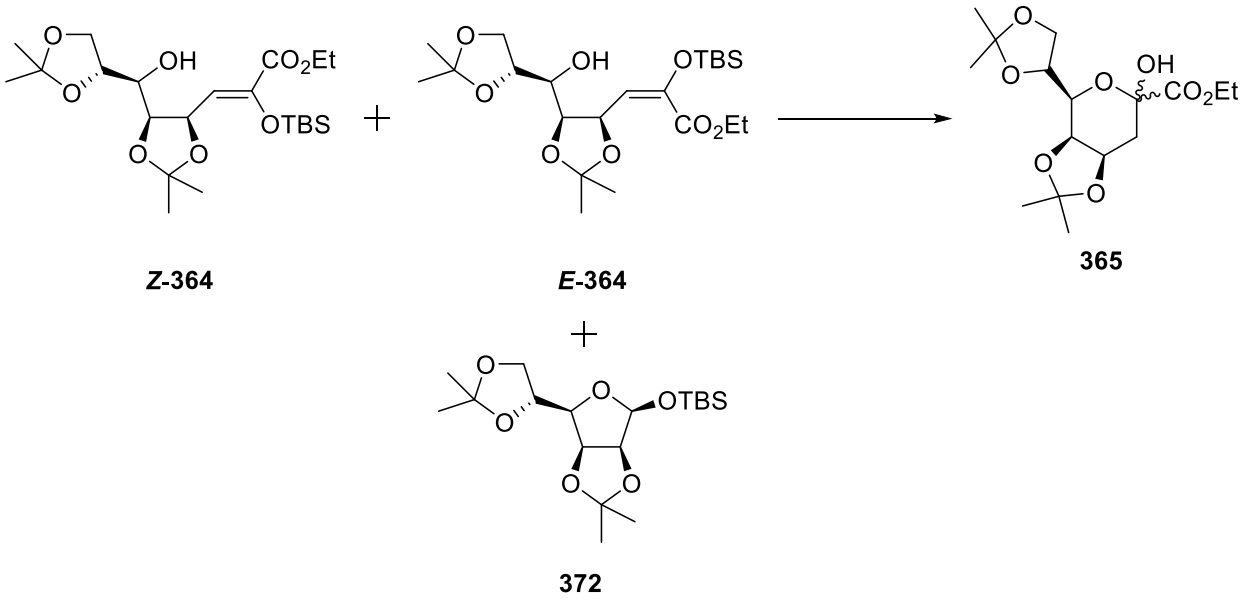
Characterization data for by-product **372**; $[\alpha]_D^{22}$ = -13.8 (c 1.45 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2985, 2931, 2858, 1372, 1252, 1212, 1048; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.13 (s, 6H, 2 X $CH_{3\ Me\ (TBS)}$), 0.92 (s, 9H, 3 X $CH_{3\ tBu\ (TBS)}$), 1.36 (s, 3H, $CH_{3\ Isopropylidene}$), 1.38 (s, 3H, $CH_{3\ Isopropylidene}$), 1.44 (s, 3H, $CH_{3\ Isopropylidene}$), 1.51 (s, 3H, $CH_{3\ Isopropylidene}$), 3.55 (dd, *J* = 7.7, 3.8 Hz, 1H, H-C_{-4}), 4.03 – 4.11 (m, 2H, H-C_6, H'-C_{-6}), 4.44 (ddd, *J* = 7.7, 5.9, 4.9 Hz, 1H, H-C_{-5}), 4.49 (dd, *J* = 6.1, 3.6 Hz, 1H, H-C_{-2}), 4.69 (dd, *J* = 6.1, 3.8 Hz, 1H, H-C_{-3}), 5.01 (d, *J* = 3.6 Hz, 1H, H-C_{-1}). ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.5 (1C, $CH_{3\ Me\ (TBS)}$), -4.3 (1C, $CH_{3\ Me\ (TBS)}$), 18.4 (1C, $C_{q\ tBu\ (TBS)}$), 25.5 (1C, $CH_{3\ Isopropylidene}$), 25.7 (1C, $CH_{3\ Isopropylidene}$), 25.9 (3C, 3 X $CH_{3\ tBu\ (TBS)}$), 26.0 (1C, $CH_{3\ Isopropylidene}$), 27.2 (1C, $CH_{3\ Isopropylidene}$), 67.1 (1C, C_{-6}), 73.5 (1C, C_{-5}), 76.9 (1C, C_{-4}), 79.6 (1C, C_{-3}), 80.7 (1C, C_{-2}), 98.1 (1C, C_{-1}), 109.3 (1C, $C_{q\ Isopropylidene}$), 113.7 (1C, $C_{q\ Isopropylidene}$); HRMS (ASAP-TOF) *m/z* found for $[M-H]^-$: 373.2047; $[C_{18}H_{34}O_6Si-H]^-$ requires 373.2040.

Further elution (petrol:EtOAc, 5:1) gave the *Z* silyl enol ether ***Z*-364** as a pure colourless oil (0.440 g, 18%); $[\alpha]_D^{22}$ = +40.8 (c 0.93 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3513, 2995, 2933, 2859, 1726, 1650, 1251, 1130, 1071; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 0.19 (s, 3H, $CH_{3\ Me\ (TBS)}$), 0.21 (s, 3H, $CH_{3\ Me\ (TBS)}$), 0.95 (s, 9H, 3 X $CH_{3\ tBu\ (TBS)}$), 1.31 (t, *J* = 7.1 Hz, 3H, $CH_{3\ Ester}$), 1.34 (s, 3H, $CH_{3\ Isopropylidene}$), 1.38 (s, 3H, $CH_{3\ Isopropylidene}$), 1.40 (s, 3H, $CH_{3\ Isopropylidene}$), 1.53 (s, 3H, $CH_{3\ Isopropylidene}$), 2.10 (d, *J* = 8.4 Hz, 1H, OH), 3.37 – 3.42 (m, 1H, H-C_{-5}), 3.97 – 4.03 (m, 2H, H-C_{-7}, H'-C_{-7}), 4.08 (td, *J* = 8.0, 2.6 Hz, 1H, H-C_{-6}), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H, 1H of $CH_{2\ Ester}$), 4.27 (dq, *J* = 10.8, 7.1 Hz, 1H, 1H of $CH_{2\ Ester}$), 4.45 (dd, *J* = 7.5, 1.3 Hz, 1H, H-C_{-4}), 5.30 (dd, *J* = 8.6, 7.5 Hz, 1H, H-C_{-3}), 6.21 (d, *J* = 8.6 Hz, 1H, H-C_{-2}). ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.2 (1C, $CH_{3\ Me\ (TBS)}$), -4.0 (1C, $CH_{3\ Me\ (TBS)}$), 14.3 (1C, $CH_{3\ Ester}$), 18.7 (1C, $C_{q\ tBu\ (TBS)}$), 24.4 (1C, $CH_{3\ Isopropylidene}$), 25.4 (1C, $CH_{3\ Isopropylidene}$), 26.0 (3C, 3 X $CH_{3\ tBu\ (TBS)}$), 26.7 (1C, $CH_{3\ Isopropylidene}$), 26.9 (1C, $CH_{3\ Isopropylidene}$), 61.6 (1C, $CH_{2\ Ester}$), 67.0 (1C, C_{-7}), 70.9 (1C, C_{-5}), 72.3 (1C, C_{-3}), 76.2 (1C, C_{-6}), 76.6 (1C, C_{-4}), 108.8 (1C, $C_{q\ Isopropylidene}$), 109.4 (1C, $C_{q\ Isopropylidene}$), 116.3 (1C, C_{-2}), 143.7 (1C, C_{-1}), 164.1 (1C, $C_{q\ Ester}$); HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 483.2377; $[C_{22}H_{40}O_8Si+Na]^+$ requires 483.2390.

*In the subsequent silyl enol ether deprotection step using TBAF, the by-product **372** was isolated and therefore fully characterized. The ^{1}H and ^{13}C NMR spectral interpretations of ***E*-364** were determined by comparison between the NMR spectra of the inseparable mixture of *E* silyl ***E*-364** and **372** with the NMR spectra for pure **372**.

* The number of moles of ***E*-364** and **372** in the inseparable mixture were calculated from molar ratios observed in the ^{1}H NMR spectrum. Since the yield of the ***E*-364** is based on the number of moles of ***E*-364** in the inseparable mixture, the yield of ***E*-364** derives from the aforementioned molar ratios seen in the ^{1}H NMR spectrum (same applies to **372**); [b] Reaction time: 72 h; [c] 1.5 equiv. of base and **367** were added.

(3aR,4R,7aR)-ethyl 4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-hydroxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (365)[6]



***Z*-364** ***E*-364** **365**

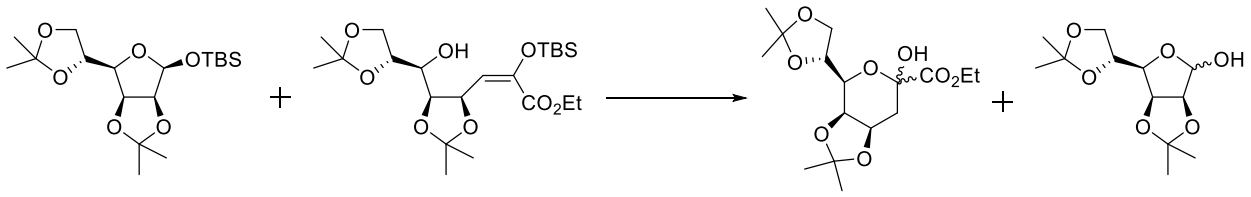
372

Compound ***Z*-364** (0.339 g, 0.76 mmol) and an inseparable mixture (0.601 g, ***E*-364**:**372**, 50:1) of ***E*-364** (0.591 g, 1.28 mmol) and **372** (0.01 g, 0.026 mmol) were dissolved in THF (2.1 ml). After cooling the stirred solution to 0 °C, 20% acetic acid (2.7 ml, 9.38 mmol, 4.6 equiv.) was added, followed by the dropwise addition of TBAF (2.04 ml, 1M in THF, 2.04 mmol, 1 equiv.). The reaction mixture was stirred at rt until the starting material was fully consumed (monitored by TLC). The reaction mixture was then neutralized with $NaHCO_3$, filtered and concentrated *in vacuo*. The residue was then treated with saturated aqueous $NaHCO_3$ and EtOAc. After separating the layers, the aqueous layer was extracted with EtOAc twice. The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. Purification by flash column chromatography on silica gel (petrol:EtOAc, 3:1) furnished an inseparable mixture (α:β, 5:1) of anomers **365** as a colourless oil (0.558 g, 79%)*; IR ν_{max} (film)/cm^{-1}: 3401, 2986, 2937, 1745, 1457, 1371, 1218, 1070; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.30 (t, *J* = 7.1 Hz, 3H, $CH_{3\ Ester,\ \alpha\ anomer}$), 1.33 (t, *J* = 7.2 Hz, 3H, $CH_{3\ Ester,\ \beta\ anomer}$), 1.35 (s, 3H, $CH_{3\ Isopropylidene,\ both\ anomers}$), 1.36 (s, 3H, $CH_{3\ Isopropylidene,\ \alpha\ anomer}$), 1.38 (s, 3H, $CH_{3\ Isopropylidene,\ \beta\ anomer}$), 1.41 (s, 3H, $CH_{3\ Isopropylidene,\ \beta\ anomer}$), 1.42 (s, 3H, $CH_{3\ Isopropylidene,\ \alpha\ anomer}$), 1.46 (s, 3H, $CH_{3\ Isopropylidene,\ \alpha\ anomer}$), 1.56 (s, 3H, $CH_{3\ Isopropylidene,\ \beta\ anomer}$), 1.88 (dd, *J* = 14.4, 4.9 Hz, 1H, $H\text{-}C_{2,\ \alpha\ anomer}$), 2.33 (d, *J* = 2.9 Hz, 2H, $H\text{-}C_{2}$, $H'C_{2,\ \beta\ anomer}$), 2.49 (dd,

J = 14.4, 6.7 Hz, 1H, H'-$C_{-2, \alpha \text{ anomer}}$), 3.44 (dd, *J* = 8.7, 1.8 Hz, 1H, H-$C_{-5, \beta \text{ anomer}}$), 3.61 (br, 1H, OH, $_{\alpha \text{ anomer}}$), 3.90 (dd, *J* = 8.0, 2.2 Hz, 1H, H-$C_{-5, \alpha \text{ anomer}}$), 3.97 – 4.02 (m, 1H, H-$C_{-7, \text{ both anomers}}$), 4.05 – 4.11 (m, 1H, H'-$C_{-7, \text{ both anomers}}$), 4.21 – 4.31 (m, 3H, $CH_{2\ \text{Ester}}$, H-$C_{-4, \text{ both anomers}}$), 4.32 – 4.37 (m, 1H, H-$C_{-6, \alpha \text{ anomer}}$), 4.43 (dd, *J* = 8.0, 1.8 Hz, 1H, H-$C_{-6, \beta \text{ anomer}}$), 4.48 – 4.53 (m, 1H, H-$C_{-3, \alpha \text{ anomer}}$), 4.72 – 4.75 (m, 2H, H-C_{-3}, OH, $_{\beta \text{ anomer}}$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2 (1C, $CH_{3\ \text{ester}, \alpha \text{ anomer}}$), 14.3 (1C, $CH_{3\ \text{ester}, \beta \text{ anomer}}$), 24.4 (1C, $CH_{3\ \text{Isopropylidene}, \beta \text{ anomer}}$), 25.2 (1C, $CH_{3\ \text{Isopropylidene}, \beta \text{ anomer}}$), 25.5 (1C, $CH_{3\ \text{Isopropylidene}, \alpha \text{ anomer}}$), 25.9 (1C, $CH_{3\ \text{Isopropylidene}, \alpha \text{ anomer}}$), 26.2 (1C, $CH_{3\ \text{Isopropylidene}, \beta \text{ anomer}}$), 27.1 (1C, $CH_{3\ \text{Isopropylidene}, \alpha \text{ anomer}}$), 27.2 (1C, $CH_{3\ \text{Isopropylidene}, \beta \text{ anomer}}$), 27.3 (1C, $CH_{3\ \text{Isopropylidene}, \alpha \text{ anomer}}$), 31.1 (1C, $C_{-2, \beta \text{ anomer}}$), 32.4 (1C, $C_{-2, \alpha \text{ anomer}}$), 62.1 (1C, $CH_{2\ \text{Ester}, \beta \text{ anomer}}$), 62.5 (1C, $CH_{2\ \text{Ester}, \alpha \text{ anomer}}$), 67.0 (1C, $C_{-7, \alpha \text{ anomer}}$), 67.3 (1C, $C_{-7, \beta \text{ anomer}}$), 70.0 (1C, $C_{-3, \alpha \text{ anomer}}$), 70.8 (1C, $C_{-5, \alpha \text{ anomer}}$), 70.8 (1C, $C_{-3, \beta \text{ anomer}}$), 71.4 (1C, $C_{-4, \alpha \text{ anomer}}$), 72.5 (1C, $C_{-6, \beta \text{ anomer}}$), 73.5 (1C, $C_{-4, \beta \text{ anomer}}$), 74.0 (1C, $C_{-5, \beta \text{ anomer}}$), 74.1 (1C, $C_{-6, \alpha \text{ anomer}}$), 94.5 (1C, $C_{-1, \alpha \text{ anomer}}$), 95.7 (1C, $C_{-1, \beta \text{ anomer}}$), 109.3 (1C, $C_{q\ \text{Isopropylidene}, \alpha \text{ anomer}}$), 109.5 (1C, $C_{q\ \text{Isopropylidene}, \alpha \text{ anomer}}$), 109.7 (1C, $C_{q\ \text{Isopropylidene}, \beta \text{ anomer}}$), 109.7 (1C, $C_{q\ \text{Isopropylidene}, \beta \text{ anomer}}$), 169.0 (1C, $C_{q\ \text{Ester}, \beta \text{ anomer}}$), 169.75 (1C, $C_{q\ \text{Ester}, \alpha \text{ anomer}}$).

*The number of moles of ***E*-364** and **372** in the starting material inseparable mixture were calculated from molar ratios seen in the ^{1}H NMR spectrum. Yield of **365** is based on the total number of moles of ***E*-364** in the inseparable mixture and ***Z*-364**.

(3aR,4R,7aR)-ethyl 4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-hydroxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (365)

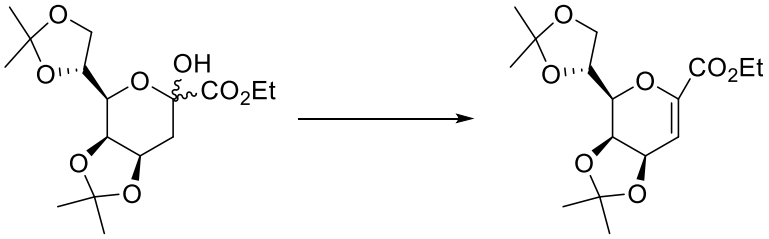


***E*-364** **372** **365** **234**

An inseparable mixture (0.4964 g, ***E*-364**:**372**, 4:1) of ***E*-364** (0.390 g, 0.85 mmol) and **372** (0.106 g, 0.21 mmol) were dissolved in THF (1.1 ml). After cooling the stirred solution to 0 ^{o}C, 20% acetic acid (1.12 ml, 3.90 mmol, 4.6 equiv.) was added, followed by the dropwise addition of TBAF (0.85 ml, 1M in THF, 0.85 mmol, 1 equiv.). The reaction mixture was stirred at rt until ***E*-364** was fully consumed (monitored by TLC with UV visualization). The reaction mixture was then neutralized with $NaHCO_3$, filtered and concentrated *in vacuo*. The residue was then treated with saturated aqueous $NaHCO_3$ and EtOAc. After separating the layers, the aqueous layer was extracted with EtOAc twice. The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. Purification by flash column chromatography on silica gel (petrol:EtOAc, 7:2) furnished the unreacted **372** (0.054 g), **234** (0.017 g, 31%) and an inseparable mixture (α:β, 4:1) of anomers **365** as a colourless oil (0.166 g, 57%). *

*The number of moles of ***E*-364** and **372** in the starting material inseparable mixture were calculated from molar ratios seen in the ^{1}H NMR spectrum. Yield of **365** is based on the total number of moles of ***E*-364** in the inseparable mixture. Yield of DAM **234** is based on the moles of **372** in inseparable mixture.

(3aR,4R,7aR)-ethyl 4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-4,7a-dihydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (366)[6]

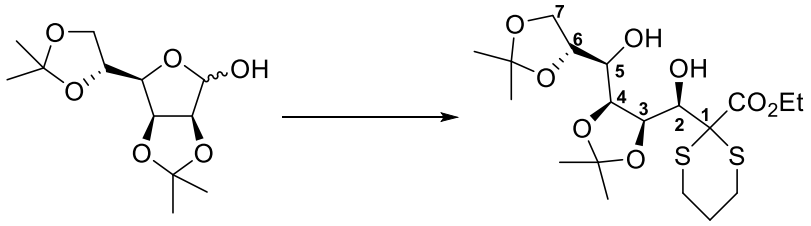


365 **366**

MsCl (0.12 ml, 1.55 mmol, 3 equiv.) was added dropwise over 5 minutes to a stirred solution of **365** (0.179 g, 0.52 mmol) and Et_3N (0.24 ml, 1.76 mmol, 3.4 equiv.) in dry DCM (5 ml) at 0 °C. After 3 hours stirring at rt (i.e. monitored by TLC until full consumption of starting material was observed), DBU (0.23 ml, 1.55 mmol, 3 equiv.) was added dropwise and the mixture was stirred at rt overnight. The mixture was then concentrated *in vacuo* furnishing a crude residue. Purification by flash column chromatography on silica gel (petrol:EtOAc, 4:1) gave glycal **366** as a colourless solid (0.120 g, 71%); mp 68-70 °C [lit. 69-71 °C][2]; $[\alpha]_D^{22}$ = +38.4 (c 1.24 in $CHCl_3$) [lit. $[\alpha]_D^{20}$ = +40.4 (c 0.47 in $CHCl_3$)][2]; IR ν_{max} (film)/cm^{-1}: 2986, 2918, 2854, 1733, 1652, 1221, 846; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.2 Hz, 3H, $CH_{3\ Ester}$), 1.39 (s, 9H, 3 X $CH_{3\ Isopropylidene}$), 1.45 (s, 3H, $CH_{3\ Isopropylidene}$), 3.83 (dd, *J* = 8.1, 1.0 Hz, 1H, H-C_{-5}), 4.14 – 4.27 (m, 4H, $CH_{2\ Ester}$, H-C_{-7}, H'-C_{-7}), 4.42 – 4.47 (m, 2H, H-C_{-4}, H-C_{-6}), 4.78 (dd, *J* = 6.1, 3.3 Hz, 1H, H-C_{-3}), 5.97 – 6.01 (m, 1H, H-C_{-2}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2 (1C, $CH_{3\ Ester}$), 25.5 (1C, $CH_{3\ Isopropylidene}$), 26.8 (1C, $CH_{3\ Isopropylidene}$), 27.1 (1C, $CH_{3\ Isopropylidene}$), 28.2 (1C, $CH_{3\ Isopropylidene}$), 61.6 (1C, $CH_{2\ Ester}$), 66.8 (1C, C_{-7}), 68.9 (1C, C_{-3}), 71.4 (1C, C_{-6}), 74.1 (1C, C_4), 76.5 (1C, C_{-5}), 109.8 (1C, $C_{q\ Isopropylidene}$), 110.2 (1C, C_{-2}), 111.2 (1C, $C_{q\ Isopropylidene}$), 144.3 (1C, C_{-1}), 162.2 (1C, $C_{q\ Ester}$).

The data is in agreement with the literature reference.[6]

Ethyl 2-((R)-((4R,5S)-5-((R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-1,3-dithiane-2-carboxylate (252)[1,7]



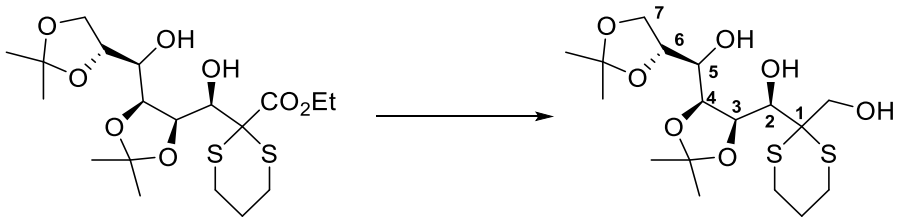
234 **252**

n-Butyl lithium (50.7 ml, 2.5M in hexanes, 126.8 mmol, 3.3 equiv.) was added dropwise to a stirred solution of diisopropylamine (17.8 ml, 126.8 mmol, 3.3 equiv.) in dry THF (200 ml) at -20 ^{o}C. After 30 minutes, ethyl 1,3-dithiane-2-carboxylate (18.2 ml, 115.3 mmol, 3.0 equiv.), was added dropwise to the solution at - 20 ^{o}C. The solution was stirred for 2 hours at -20 ^{o}C. This dark-red solution was then cannulated slowly into a suspension of $MgBr_2$ in dry THF (250 ml) at -20 ^{o}C, prepared from magnesium (4.2 g, 173.0 mmol, 4.5 equiv.) and 1,2-dibromoethane (13.3 ml, 153.7 mmol, 4.0 equiv.). Compound **234** (10 g, 38.4 mmol) was then added to the solution in one portion. The stirred reaction mixture was warmed to rt gradually overnight and then heated for 5 hours at 50 ^{o}C. After cooling to rt, the reaction mixture was poured into ice-cold saturated aqueous NH_4Cl (450 ml). After adding EtOAc (300 ml), the layers were then separated. The aqueous layer was then extracted with EtOAc (2 x 300 ml). The combined organic extracts were washed with water and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* gave a crude yellow oil. The crude product was purified by flash column chromatography on silica gel (toluene:EtOAc, 3:1) to yield the title compound as a pure yellow oil (16.932 g, 97%); $[\alpha]_D^{25}$ = -1.4 (c 1.12 in $CHCl_3$) [lit. $[\alpha]_D$ = -1.8 (c 1.0 in $CHCl_3$)][7]; IR ν_{max} (film)/cm^{-1}: 3454, 3054, 29885, 2935, 1728, 1424, 1381, 1215, 1064; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.33 (t, *J* = 7.1 Hz, 3H, $CH_{3\ Ester}$), 1.35 (s, 3H, $CH_{3\ Isopropylidene}$), 1.37 (s, 3H, $CH_{3\ Isopropylidene}$), 1.41 (s, 3H, $CH_{3\ Isopropylidene}$), 1.50 (s, 3H, $CH_{3\ Isopropylidene}$), 1.84 – 1.94 (m, 1H of $CH_{2\ Dithiane}$), 2.05 – 2.14 (m, 1H, 1H of $CH_{2\ Dithiane}$), 2.72 – 2.81 (m, 2H, $CH_{2\ Dithiane}$), 3.02 (ddd, *J* = 14.4, 11.5, 2.8 Hz, 1H of $CH_{2\ Dithiane}$), 3.22 (ddd, *J* = 14.4, 11.3, 3.0 Hz, 1H, 1H of $CH_{2\ Dithiane}$), 3.64 (ddd, *J* = 8.1, 3.1, 1.1 Hz, 1H, H-C_{-6}), 4.01 – 4.07 (m, 1H, H-C_{-7}), 4.09 – 4.15 (m, 2H, H'-C_{-7}, H-C_{-5}), 4.23 – 4.33 (m, 3H, $CH_{2\ Ester}$, H-C_{-4}), 4.43 (dd, *J* = 7.5, 1.1 Hz, 1H, H-C_{-3}), 4.58 (d, *J* = 7.5 Hz, 1H, H-C_{-2}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2 (1C, $CH_{3\ Ester}$), 24.3 (1C, $CH_{2\ Dithiane}$), 25.2 (1C, CH_3

$_{\text{Isopropylidene}}$), 25.5 (1C, $CH_{3\ \text{Isopropylidene}}$), 26.2 (1C, $CH_{3\ \text{Isopropylidene}}$), 27.0 (1C, $CH_{3\ \text{Isopropylidene}}$), 27.4 (1C, $CH_{2\ \text{Dithiane}}$), 27.7 (1C, $CH_{2\ \text{Dithiane}}$), 58.8 (1C, C_{-1}), 62.8 (1C, $CH_{2\ \text{Ester}}$), 67.7 (1C, C_{-7}), 70.7 (1C, C_{-6}), 72.6 (1C, C_{-4}), 77.1 (1C, C_{-2}), 74.3 (1C, C_{-5}), 75.8 (1C, C_{-3}), 109.3 (1C, $C_{q\ \text{Isopropylidene}}$), 109.4 (1C, $C_{q\ \text{Isopropylidene}}$), 170.0 (1C, $C_{q\ \text{Ester}}$).

The data is in agreement with the literature references.[1,7]

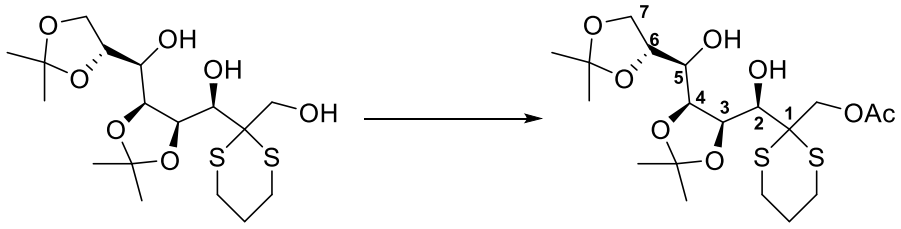
(R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((4S,5R)-5-((R)-hydroxy(2-(hydroxymethyl)-1,3-dithian-2-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (264)[1]



$LiAlH_4$ (1.104g, 29.10 mmol, 2 equiv.) was added cautiously portion wise to a solution of **252** (6.584 g, 14.55 mmol) in dry THF (100 ml) at 0 °C. The grey suspension was stirred at rt overnight. Then the excess $LiAlH_4$ was carefully quenched by the addition of anhydrous Na_2SO_4 (ca. 2 g), followed carefully by the dropwise addition of water until no effervescence was observed. The solution was then filtered through a pad of celite and the solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (petrol:EtOAc, 1:1) to afford **264** as a colourless gum (5.714 g, 96%); $[\alpha]_D^{25}$ = -2.7 (c 1.10 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3410, 2984, 2934, 1371, 1245, 1214, 1138, 1064, 853; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.36 (s, 3H, $CH_{3\ Isopropylidene}$), 1.42 (s, 3H, $CH_{3\ Isopropylidene}$), 1.43 (s, 3H, $CH_{3\ Isopropylidene}$), 1.57 (s, 3H, $CH_{3\ Isopropylidene}$), 1.98 – 2.06 (m, 2H, $CH_{2\ Dithiane}$), 2.72 – 2.84 (m, 4H, 2 X $CH_{2\ Dithiane}$), 3.35 (t, *J* = 7.4 Hz, 1H, OH), 3.61 – 3.65 (m, 1H, H-C_{-4}), 3.87 – 3.94 (m, 2H, 2 X OH), 3.94 – 3.98 (m, 2H, CH_2OH), 4.02 – 4.07 (m, 1H, H-C_{-7}), 4.08 – 4.11 (m, 1H, H-C_{-6}), 4.11 – 4.18 (m, 2H, H'-C_{-7}, H-C_{-5}), 4.46 (dd, *J* = 7.4, 0.9 Hz, 1H, H-C_{-3}), 4.83 (d, *J* = 7.4 Hz, 1H, H-C_{-2}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.6 (1C, $CH_{2\ Dithiane}$), 25.1 (1C, $CH_{2\ Dithiane}$), 25.4 (1C, $CH_{2\ Dithiane}$), 25.6 (1C, $CH_{3\ Isopropylidene}$), 25.6 (1C, $CH_{3\ Isopropylidene}$), 26.1 (1C, $CH_{3\ Isopropylidene}$), 27.1 (1C, $CH_{3\ Isopropylidene}$), 58.5 (1C, C_{-1}), 65.1 (1C, CH_2OH), 67.5 (1C, C_{-7}), 70.7 (1C, C_{-4}), 71.2 (1C, C_{-6}), 73.5 (1C, C_{-2}), 75.9 (1C, C_{-5}), 77.0 (1C, C_{-3}), 109.4 (1C, $C_{q\ Isopropylidene}$), 109.5 (1C, $C_{q\ Isopropylidene}$).

The data is in agreement with the literature reference.[1]

(2-((R)-((4R,5S)-5-((R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-1,3-dithian-2-yl)methyl acetate (266)[1]

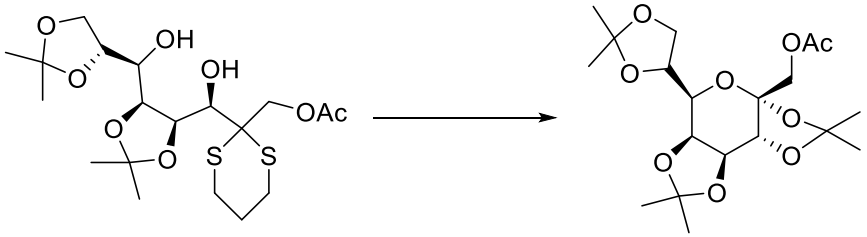


264 **266**

Acetic anhydride (0.32 ml, 3.36 mmol, 1.12 equiv.) was added to a stirred solution of **264** (1.230 g, 3.00 mmol) and Et_3N (0.47 ml, 3.36 mmol, 1.12 equiv.) in DCM (12 ml) at 0 °C. The reaction mixture was stirred overnight at rt. Saturated aqueous $NaHCO_3$ solution was then added, and the layers were separated. The aqueous layer was then extracted with DCM two times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:1) to yield the title compound as a pure colourless oil (1.022 g, 75%); $[\alpha]_D^{25}$ = -6.1 (c 1.05 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3456, 2985, 2941, 1743, 1379, 1218, 1066; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.36 (s, 3H, $CH_{3\ Isopropylidene}$), 1.42 (s, 6H, 2 X $CH_{3\ Isopropylidene}$), 1.54 (s, 3H, $CH_{3\ Isopropylidene}$), 1.84 – 1.93 (m, 1H, 1H of $CH_{2\ Dithiane}$), 2.03 – 2.10 (m, 1H of $CH_{2\ Dithiane}$), 2.12 (s, 3H, $CH_{3\ Acetate}$), 2.65 – 2.79 (m, 2H, $CH_{2\ Dithiane}$), 2.88 – 3.01 (m, 2H, $CH_{2\ Dithiane}$), 3.51 (d, *J* = 8.8 Hz, 1H, OH), 3.59 – 3.64 (m, 2H, OH, H-C_{-4}), 3.98 – 4.02 (m, 1H, H-C_{-6}), 4.06 (dd, *J* = 7.2, 4.2 Hz, 1H, H-C_{-7}), 4.10 – 4.16 (m, 2H, H'-C_{-7}, H-C_{-5}), 4.41 – 4.49 (m, 2H, 1H of CH_2OAc, H-C_{-3}), 4.69 – 4.74 (m, 1H, H-C_{-2}), 4.80 (d, *J* = 11.9 Hz, 1H, 1H of CH_2OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2 (1C, $CH_{3\ Acetate}$), 24.5 (1C, $CH_{2\ Dithiane}$), 25.2 (1C, $CH_{3\ Isopropylidene}$), 25.4 (1C, $CH_{3\ Isopropylidene}$), 25.9 (1C, $CH_{2\ Dithiane}$), 26.0 (1C, $CH_{2\ Dithiane}$), 26.2 (1C, $CH_{3\ Isopropylidene}$), 27.1 (1C, $CH_{3\ Isopropylidene}$), 56.7 (1C, $C_{q\ Dithiane}$), 63.8 (1C, CH_2OAc), 67.5 (1C, C_{-7}), 70.7 (1C, C_{-4}), 72.3 (1C, C_{-6}), 73.7 (1C, C_{-2}), 75.9 (1C, C_{-5}), 77.1 (1C, C_{-3}), 109.2 (1C, $C_{q\ Isopropylidene}$), 109.4 (1C, $C_{q\ Isopropylidene}$), 170.4 (1C, $C_{q\ Acetate}$).

The data is in agreement with the literature reference.[1]

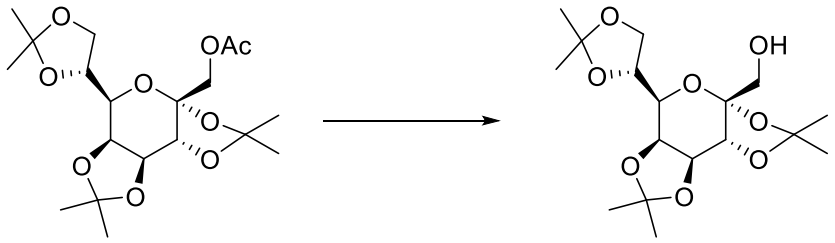
((3aR,5R,5aS,8aS,8bR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl acetate (383)



266 **383**

Freshly recrystallized DBDMH (1.166 g, 4.08 mmol, 2 equiv.) was added to a stirred solution of **266** (0.923 g, 2.04 mmol) in reagent grade acetone (34 ml) at 0 ^{o}C which formed a yellow coloured solution. After stirring at 0 ^{o}C for 30 mins, saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$ were added. The mixture was then extracted four times with EtOAc. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to furnish **383** as a pure colourless oil (0.678 g, 83%);$[\alpha]_D^{25}$ = -8.7 (c 1.01 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2989, 2937, 1752, 1259, 1224, 1073; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.35 (s, 6H, 2 X CH_3 Isopropylidene), 1.39 (s, 3H, CH_3 Isopropylidene), 1.41 (s, 3H, CH_3 Isopropylidene), 1.43 (s, 3H, CH_3 Isopropylidene), 1.52 (s, 3H, CH_3 Isopropylidene), 2.08 (s, 3H, CH_3 Acetate), 3.71 (dd, *J* = 8.8, 1.9 Hz, 1H, H-C_5), 3.94 (d, *J* = 11.7 Hz, 1H, 1H of CH_2OAc), 3.99 (dd, *J* = 8.8, 3.8 Hz, 1H, H-C_7), 4.05 (dd, *J* = 8.8, 6.0 Hz, 1H, H'-C_7), 4.20 – 4.26 (m, 1H, H-C_6), 4.34 (d, *J* = 2.7 Hz, 1H, H-C_2), 4.38 (dd, *J* = 7.9, 1.9 Hz, 1H, H-C_4), 4.43 (d, *J* = 11.7 Hz, 1H, 1H of CH_2OAc), 4.65 (dd, *J* = 7.9, 2.7 Hz, 1H, H-C_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.0 (1C, CH_3 Acetate), 24.4 (1C, CH_3 Isopropylidene), 25.3 (1C, CH_3 Isopropylidene), 25.4 (1C, CH_3 Isopropylidene), 25.9 (1C, CH_3 Isopropylidene), 26.7 (1C, CH_3 Isopropylidene), 27.3 (1C, CH_3 Isopropylidene), 64.8 (1C, CH_2OAc), 67.2 (1C, C_7), 69.6 (1C, C_5), 70.7 (1C, C_4), 70.8 (1C, C_2), 70.9 (1C, C_3), 73.4 (1C, C_6), 102.3 (1C, C_1), 109.1 (1C, C_q Isopropylidene), 109.6 (1C, C_q Isopropylidene), 109.7 (1C, C_q Isopropylidene), 170.2 (1C, C_q Acetate); HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 425.1786; $[C_{19}H_{30}O_9+Na]^+$ requires 425.1782.

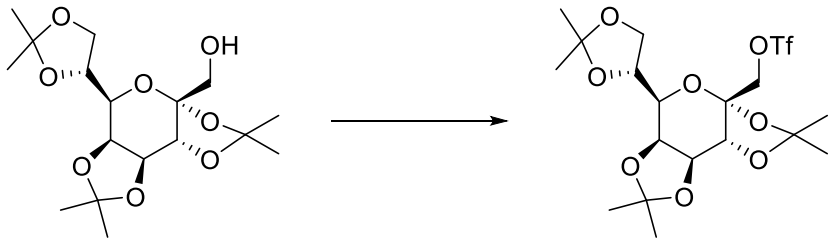
((3aR,5R,5aS,8aS,8bR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methanol (384)



383 **384**

Anhydrous K_2CO_3 (0.38 g, 2.74 mmol, 1.21 Equiv.) was added to a stirred solution of **383** (0.912 g, 2.27 mmol) in dry methanol (23 ml). The mixture was stirred at rt overnight. The solvent was then removed under reduced pressure. The residue was treated with water (ca. 25 ml) and Et_2O (ca. 25 ml), and the layers were separated. The aqueous layer was then extracted with Et_2O two times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 2:1) to yield the title compound as a pure colourless oil (0.792 g, 97%); $[\alpha]_D^{25}$ = -25.6 (c 0.78 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3501, 2989, 2941, 1372, 1211, 1072; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.36 (s, 3H, CH_3 Isopropylidene), 1.37 (s, 3H, CH_3 Isopropylidene), 1.39 (s, 3H, CH_3 Isopropylidene), 1.42 (s, 3H, CH_3 Isopropylidene), 1.45 (s, 3H, CH_3 Isopropylidene), 1.54 (s, 3H, CH_3 Isopropylidene), 3.59 – 3.69 (m, 2H, 2H of CH_2OAc), 3.68 – 3.75 (m, 1H, H-C_5), 3.99 (dd, *J* = 8.8, 3.7 Hz, 1H, H-C_7), 4.06 (dd, *J* = 8.8, 6.0 Hz, 1H, H'-C_7), 4.25 (ddd, *J* = 9.2, 6.0, 3.7 Hz, 1H, H-C_6), 4.36 (d, *J* = 2.7 Hz, 1H, H-C_2), 4.40 (dd, *J* = 7.9, 1.9 Hz, 1H, H-C_4), 4.66 (dd, *J* = 7.9, 2.7 Hz, 1H, H-C_3);^{13}C NMR (101 MHz, $CDCl_3$) δ 24.3 (1C, CH_3 Isopropylidene), 25.4 (1C, CH_3 Isopropylidene), 25.5 (1C, CH_3 Isopropylidene), 25.8 (1C, CH_3 Isopropylidene), 26.7 (1C, CH_3 Isopropylidene), 27.4 (1C, CH_3 Isopropylidene), 65.4 (1C, CH_2OH), 67.3 (1C, C_7), 69.7 (1C, C_5), 70.8 (1C, C_2), 70.9 (1C, C_3), 71.5 (1C, C_4), 73.4 (1C, C_6), 103.9 (1C, C_1), 109.0 (1C, C_q Isopropylidene), 109.6 (1C, C_q Isopropylidene), 109.7 (1C, C_q Isopropylidene); HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 383.1677; $[C_{17}H_{28}O_8+Na]^+$ requires 383.1676.

((3aR,5R,5aS,8aS,8bR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl trifluoromethanesulfonate (385)

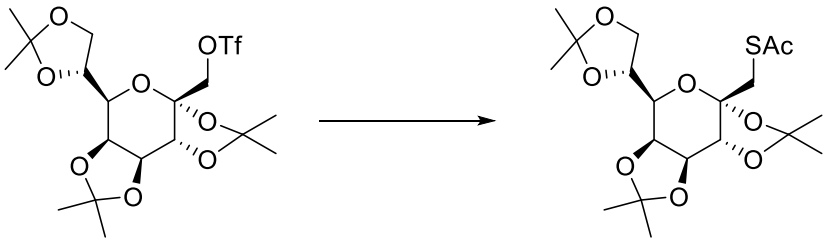


384 **385**

Pyridine (0.34 ml, 4.21 mmol, 1.5 equiv.) was added to a stirred solution of **384** (1.011 g, 2.81 mmol) in dry DCM (28 ml). After cooling the solution to 0 ^{o}C, trifluoromethanesulfonic anhydride (0.47 ml, 2.81 mmol, 1.0 Equiv.) was added dropwise over 15 minutes. The reaction mixture was stirred at 0 ^{o}C for 30 minutes then allowed to warm up to rt and monitored by TLC until full consumption of the starting material was observed. The mixture was diluted with DCM and was treated with ice-cold water (ca. 30 ml), and the layers were separated. The aqueous layer was then extracted with DCM twice. The combined organic extracts were then washed with water and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave the title compound as a pure yellow oil (1.374 g, 99%);$[\alpha]_D^{25}$ = -6.0 (c 1.68 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2991, 2939, 1383, 1210, 1146, 1074, 983; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.36 (s, 3H, $CH_{3\ Isopropylidene}$), 1.37 (s, 3H, $CH_{3\ Isopropylidene}$), 1.40 (s, 3H, $CH_{3\ Isopropylidene}$), 1.42 (s, 3H, $CH_{3\ Isopropylidene}$), 1.44 (s, 3H, $CH_{3\ Isopropylidene}$), 1.55 (s, 3H, $CH_{3\ Isopropylidene}$), 3.74 (dd, *J* = 8.8, 1.9 Hz, 1H, H-C_{-5}), 3.98 (dd, *J* = 8.9, 3.7 Hz, 1H, H-C_{-7}), 4.05 (dd, *J* = 8.9, 5.9 Hz, 1H, H'-C_{-7}), 4.22 (ddd, *J* = 8.8, 5.9, 3.7 Hz, 1H, H-C_{-6}), 4.32 (d, *J* = 2.7 Hz, 1H, H-C_{-2}), 4.38 (d, *J* = 10.5 Hz, 1H, 1H of CH_2OTf), 4.40 (dd, *J* = 7.9, 1.9 Hz, 1H, H-C_{-4}), 4.52 (d, *J* = 10.5 Hz, 1H, 1H of CH_2OTf), 4.69 (dd, *J* = 7.9, 2.7 Hz, 1H, H-C_{-3}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.3 (1C, $CH_{3\ Isopropylidene}$), 25.3 (1C, $CH_{3\ Isopropylidene}$), 25.4 (1C, $CH_{3\ Isopropylidene}$), 25.8 (1C, $CH_{3\ Isopropylidene}$), 26.7 (1C, $CH_{3\ Isopropylidene}$), 27.3 (1C, $CH_{3\ Isopropylidene}$), 67.1 (1C, C_{-7}), 70.1 (1C, C_{-5}), 70.5 (1C, C_{-4}), 70.6 (2C, C_{-2}, C_{-3}), 73.3 (1C, C_{-6}), 74.1 (1C, CH_2OTf), 100.6 (1C, C_{-1}), 109.7 (1C, $C_{q\ Isopropylidene}$), 109.8 (1C, $C_{q\ Isopropylidene}$), 110.3 (1C, $C_{q\ Isopropylidene}$); ^{19}F NMR (376

MHz, $CDCl_3$) δ -74.41; HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 515.1175; $[C_{18}H_{27}O_{10}F_3S+Na]^+$ requires 515.1174.

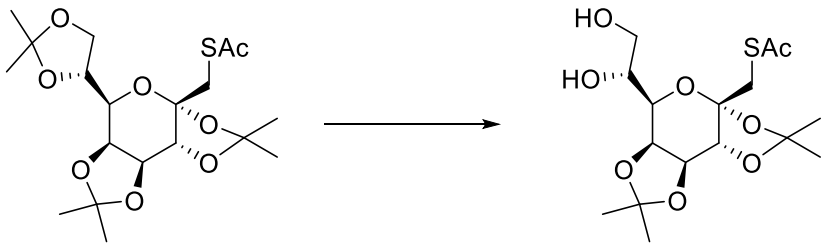
S-(((3aS,5R,5aS,8aS,8bR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (386)



385 **386**

Potassium thioacetate (0.658 g, 5.76 mmol, 4.4 equiv.) was added to a stirred solution of **385** (0.645 g, 1.31 mmol) in dry MeCN (87 ml), which formed a brown coloured solution. The mixture was heated under reflux for 16 h, then cooled to rt after which the solvent was removed *in vacuo*. The residue was treated with water (ca. 30 ml) and EtOAc (ca. 30 ml), and the layers were separated. The aqueous layer was then extracted with EtOAc two times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude brown oil. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 6:1) to furnish **386** as a pure yellow oil (0.548 g, quant.); $[\alpha]_D^{25}$ = -24.4 (c 0.87 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2994, 2937, 1697, 1210, 1070; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.36 (s, 6H, 2 X CH_3 Isopropylidene), 1.40 (s, 3H, CH_3 Isopropylidene), 1.41 (s, 3H, CH_3 Isopropylidene), 1.49 (s, 3H, CH_3 Isopropylidene), 1.50 (s, 3H, CH_3 Isopropylidene), 2.35 (s, 3H, CH_3 Thioacetate), 3.33 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.39 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.68 (dd, *J* = 8.5, 1.9 Hz, 1H, H-C_{-5}), 3.98 (dd, *J* = 8.8, 4.0 Hz, 1H, H-C_{-7}), 4.06 (dd, *J* = 8.8, 6.1 Hz, 1H, H'-C_{-7}), 4.21 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.24 (ddd, *J* = 8.5, 6.1, 4.0 Hz, 1H, H-C_{-6}), 4.36 (dd, *J* = 7.9, 1.9 Hz, 1H H-C_{-4}), 4.62 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.5 (1C, CH_3 Isopropylidene), 25.3 (1C, CH_3 Isopropylidene), 25.5 (1C, CH_3 Isopropylidene), 25.9 (1C, CH_3 Isopropylidene), 26.6 (1C, CH_3 Isopropylidene), 27.3 (1C, CH_3 Isopropylidene), 30.6 (1C, CH_3 Thioacetate), 37.3 (1C, CH_2SAc), 67.2 (1C, C_{-7}), 69.9 (1C, C_{-5}), 70.6 (1C, C_{-4}), 71.2 (1C, C_{-3}), 73.2 (1C, C_{-2}), 73.5 (1C, C_{-6}), 103.1 (1C, C_{-1}), 108.9 (1C, C_q Isopropylidene), 109.5 (1C, C_q Isopropylidene), 109.7 (1C, C_q Isopropylidene), 194.8 (1C, C_q Thioacetate); HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 441.1571; $[C_{19}H_{30}O_8S+Na]^+$ requires 441.1559.

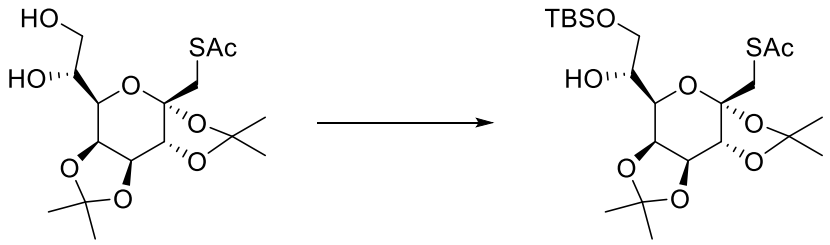
S-(((3aS,5R,5aS,8aS,8bR)-5-((R)-1,2-dihydroxyethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (387)



386 **387**

Compound **386** (0.532 g, 1.27 mmol), was dissolved in 90% Acetic acid (54 ml). The stirred reaction mixture was left at 40 ^{o}C for 24 hours. The mixture was then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:2) to afford the title compound as a pure colourless solid (0.387 g, 80%); mp 82-85 ^{o}C; $[\alpha]_D^{25}$ = -27.1 (c 1.05 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3434, 2989, 2937, 1697, 1210, 1071; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.35 (s, 3H, CH_3 Isopropylidene), 1.39 (s, 3H, CH_3 Isopropylidene), 1.49 (s, 6H, 2 X CH_3 Isopropylidene), 2.35 (s, 3H), 3.34 (d, *J* = 13.7 Hz, 1H, 1H of CH_2SAc), 3.38 (d, *J* = 13.7 Hz, 1H, 1H of CH_2SAc), 3.73 – 3.83 (m, 3H, H-C$_{-7}$, H'-C$_{-7}$, H-C$_{-5}$), 3.88 (ddd, *J* = 8.2, 4.7, 3.4 Hz, 1H, H-C$_{-6}$), 4.21 (d, *J* = 2.6 Hz, 1H, H-C$_{-2}$), 4.42 (dd, *J* = 7.9, 1.9 Hz, 1H, H-C$_{-4}$), 4.64 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C$_{-3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.4 (1C, CH_3 Isopropylidene), 25.0 (1C, CH_3 Isopropylidene), 25.8 (1C, CH_3 Isopropylidene), 26.3 (1C, CH_3 Isopropylidene), 30.4 (1C, CH_3 Thioacetate), 37.4 (1C, CH_2SAc), 64.1 (1C, C$_{-7}$), 69.1 (1C, C$_{-5}$), 70.0 (1C, C$_{-6}$), 70.6 (1C, C$_{-4}$), 71.2 (1C, C$_{-3}$), 73.0 (1C, C$_{-2}$), 102.9 (1C, C$_{-1}$), 108.8 (1C, C_q Isopropylidene), 109.6 (1C, C_q Isopropylidene), 194.6 (1C, C_q Thioacetate); HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 401.1237; $[C_{16}H_{26}O_8S+Na]^+$ requires 401.1246.

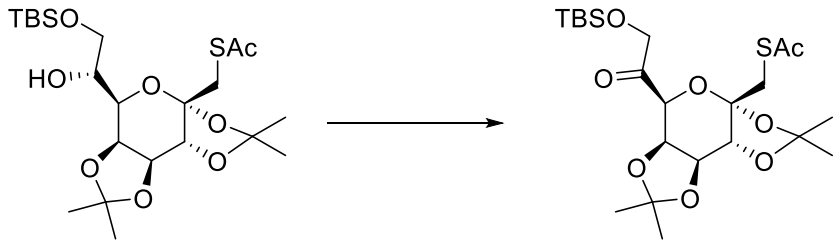
S-(((3aS,5R,5aS,8aS,8bR)-5-((R)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (388)



387 **388**

TBSCl (0.065 g, 0.43 mmol) was added to a stirred solution of **387** (0.136 g, 0.36 mmol) and imidazole (0.060 g, 0.90 mmol, 2.5 equiv.) in dry DCM (3.6 mL) at 0 ^{o}C. The resultant mixture was stirred overnight at rt. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude yellow oil. The crude oil was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to furnish the title compound as a pure colourless oil (0.112 g, 63%); $[\alpha]_D^{25}$ = -14.3 (c 1.15 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3530, 2934, 2857, 1698, 1382, 1210, 1073; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 0.08 (s, 3H, $CH_{3\ Me\ (TBS)}$), 0.09 (s, 3H, $CH_{3\ Me\ (TBS)}$), 0.90 (s, 9H, 3 X $CH_{3\ tBu\ (TBS)}$), 1.36 (s, 3H, $CH_{3\ Isopropylidene}$), 1.39 (s, 3H, $CH_{3\ Isopropylidene}$), 1.48 (s, 3H, $CH_{3\ Isopropylidene}$), 1.50 (s, 3H, $CH_{3\ Isopropylidene}$), 2.35 (s, 3H, $CH_{3\ Thioacetate}$), 3.34 (d, *J* = 13.7 Hz, 1H, 1H of CH_2SAc), 3.38 (d, *J* = 13.7 Hz, 1H, 1H of CH_2SAc), 3.61 – 3.67 (m, 1H, H-C_{-7}), 3.68 – 3.73 (m, 1H, H-C_{-5}), 3.79 – 3.87 (m, 2H, H-C_{-6}, H'-C_{-7}), 4.19 (d, *J* = 2.5 Hz, 1H, H-C_{-2}), 4.45 (dd, *J* = 8.9, 1.9 Hz, 1H, H-C_{-4}), 4.62 (dd, *J* = 8.0, 2.5 Hz, 1H, H-C_{-3}); ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.3 (1C, $CH_{3\ Me\ (TBS)}$), -5.2 (1C, $CH_{3\ Me\ (TBS)}$), 18.4 (1C, $C_{q\ tBu\ (TBS)}$), 24.5 (1C, $CH_{3\ Isopropylidene}$), 25.2 (1C, $CH_{3\ Isopropylidene}$), 25.9 (3C, 3 X $CH_{3\ tBu\ (TBS)}$), 26.1 (1C, $CH_{3\ Isopropylidene}$), 26.7 (1C, $CH_{3\ Isopropylidene}$), 30.5 (1C, $CH_{3\ Thioacetate}$), 37.6 (1C, CH_2SAc), 64.1 (1C, C_{-7}), 68.5 (1C, C_{-5}), 69.7 (1C, C_{-6}), 70.7 (1C, C_{-4}), 71.3 (1C, C_{-3}), 73.1 (1C, C_{-2}), 103.0 (1C, C_{-1}), 108.7 (1C, $C_{q\ Isopropylidene}$), 109.5 (1C, $C_{q\ Isopropylidene}$), 194.9 (1C, $C_{q\ Thioacetate}$); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 510.2536; $[C_{22}H_{40}O_8SSi+NH_4]^+$ requires 510.2551.

S-(((3aS,5S,5aR,8aS,8bR)-5-(2-((*tert*-butyldimethylsilyl)oxy)acetyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (389)

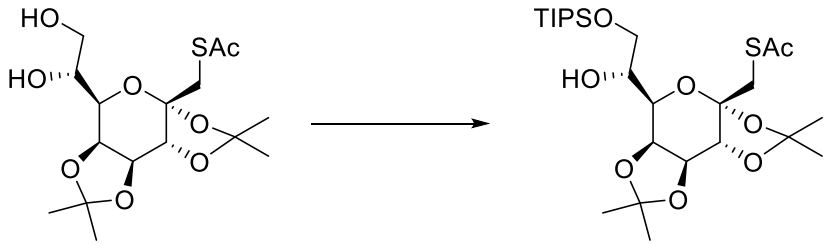


388 **389**

DMSO (0.13 ml, 1.92 mmol, 3.5 equiv.) was added dropwise to a stirred solution of oxalyl chloride (0.07 ml, 0.82 mmol, 1.5 equiv.) in DCM (4 ml) at -78 ^{o}C. The resultant stirred mixture was left for 30 minutes at this temperature. Then a solution of compound **388** (0.271 g, 0.55 mmol) dissolved in DCM was added dropwise to the reaction mixture at -78 ^{o}C. The reaction mixture was stirred for a 1 hour at this temperature. To this mixture was then added Et_3N (0.37 ml, 2.74 mmol, 5.0 equiv.) and was stirred at -78 ^{o}C for 10 minutes before being warmed slowly to rt. The mixture was then stirred at rt until the reaction was complete (monitored by TLC). Once complete, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under vacuo furnished **389** as a pure colourless oil (0.232 g, 86%); $[\alpha]_D^{25}$ = -64.7 (c 1.10 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2990, 2932, 2857, 1742, 1699, 1384, 1211, 1071; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 0.07 (s, 3H, $CH_{3\ Me\ (TBS)}$), 0.10 (s, 3H, $CH_{3\ Me\ (TBS)}$), 0.92 (s, 9H, 3 X $CH_{3\ tBu\ (TBS)}$), 1.29 (s, 3H, $CH_{3\ Isopropylidene}$), 1.40 (s, 3H, $CH_{3\ Isopropylidene}$), 1.47 (s, 3H, $CH_{3\ Isopropylidene}$), 1.50 (s, 3H, $CH_{3\ Isopropylidene}$), 2.38 (s, 3H, $CH_{3\ Thioacetate}$), 3.31 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.53 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 4.23 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.37 (d, *J* = 2.2 Hz, 1H, H-C_{-5}), 4.49 (d, *J* = 19.6 Hz, 1H, H-C_{-7}), 4.56 (dd, *J* = 7.8, 2.2 Hz, 1H, H-C_{-4}), 4.60 (d, *J* = 19.6 Hz, 1H, H'-C_{-7}), 4.61 – 4.64 (m, 1H, H-C_{-3}); ^{13}C NMR (126 MHz, $CDCl_3$) δ -5.4 (1C, $CH_{3\ Me\ (TBS)}$), -5.1 (1C, $CH_{3\ Me\ (TBS)}$), 18.6 (1C, $C_{q\ tBu\ (TBS)}$), 24.1 (1C, $CH_{3\ Isopropylidene}$), 25.0 (1C, $CH_{3\ Isopropylidene}$), 25.7 (1C, $CH_{3\ Isopropylidene}$), 26.0 (3C, 3 X $CH_{3\ tBu\ (TBS)}$), 26.5 (1C, $CH_{3\ Isopropylidene}$), 30.5 (1C, $CH_{3\ Thioacetate}$), 37.6 (1C, CH_2SAc), 68.9 (1C, C_{-7}), 71.1 (1C, C_{-3}), 72.0 (1C, C_{-4}), 73.1 (1C, C_{-2}), 74.8

(1C, C_{-5}), 102.9 (1C, C_{-1}), 109.2 (1C, $C_{q\ Isopropylidene}$), 109.9 (1C, $C_{q\ Isopropylidene}$), 194.4 (1C, $C_{q\ Thioacetate}$), 205.8 (1C, $C_{-6\ Ketone}$); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 508.2382; $[C_{22}H_{38}O_8SSi+NH_4]^+$ requires 508.2395.

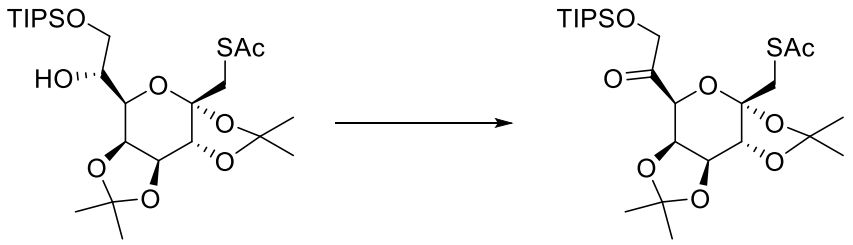
S-(((3aS,5R,5aS,8aS,8bR)-5-((R)-1-hydroxy-2-((triisopropylsilyl)oxy)ethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (392)



387 **392**

To a stirred solution of **387** (0.425 g, 1.12 mmol) in dry DCM (11 mL) at 0 ^{o}C, was added imidazole (0.191 g, 2.808 mmol, 2.5 equiv.) and DMAP (0.027 g, 0.225 mmol, 0.2 equiv.). TIPSCl (0.29 mL, 1.348 mmol, 1.2 equiv.), was then added dropwise to this suspension. The resultant mixture was stirred overnight at rt. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 6:1) to furnish the title compound as a pure colourless oil (0.538 g, 90%); $[\alpha]_D^{25}$ = -25.7 (c 0.56 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3548, 2941, 2867, 1698, 1382, 1210, 1072; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.04 – 1.08 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.09 – 1.17 (m, 3H, 3 X H-$CMe_{2\ TIPS}$), 1.37 (s, 3H, $CH_{3\ Isopropylidene}$), 1.39 (s, 3H, $CH_{3\ Isopropylidene}$), 1.48 (s, 3H, $CH_{3\ Isopropylidene}$), 1.50 (s, 3H, $CH_{3\ Isopropylidene}$), 2.34 (s, 3H, $CH_{3\ Thioacetate}$), 3.33 (d, *J* = 13.6 Hz, 1H, 1H of CH_2SAc), 3.38 (d, *J* = 13.6 Hz, 1H, 1H of CH_2SAc), 3.68 – 3.74 (m, 2H, H-C_{-7}, H-C_{-5}), 3.88 (ddd, *J* = 8.4, 5.9, 3.8 Hz, 1H, H-C_{-6}), 3.92 (dd, *J* = 9.6, 3.8 Hz, 1H, H'-C_{-7}), 4.19 (d, *J* = 2.5 Hz, 1H, H-C_{-2}), 4.46 (dd, *J* = 7.9, 1.9 Hz, 1H, H-C_{-4}), 4.62 (dd, *J* = 7.9, 2.5 Hz, 1H, H-C_{-3}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.1 (6C, 6 X $CH_{3\ TIPS}$), 18.1 (3C, 3 X $CHMe_{2\ TIPS}$), 24.5 (1C, $CH_{3\ Isopropylidene}$), 25.2 (1C, $CH_{3\ Isopropylidene}$), 25.9 (1C, $CH_{3\ Isopropylidene}$), 26.7 (1C, $CH_{3\ Isopropylidene}$), 30.5 (1C, $CH_{3\ Thioacetate}$), 37.7 (1C, CH_2SAc), 64.6 (1C, C_{-7}), 68.6 (1C, C_{-5}), 69.8 (1C, C_{-6}), 70.8 (1C, C_{-4}), 71.3 (1C, C_{-3}), 73.2 (1C, C_{-2}), 102.9 (1C, C_{-1}), 108.7 (1C, $C_{q\ Isopropylidene}$), 109.5 (1C, $C_{q\ Isopropylidene}$), 194.9 (1C, $C_{q\ Thioacetate}$); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 552.3015; $[C_{25}H_{46}O_8SSi+NH_4]^+$ requires 552.3021.

S-(((3aS,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-(2-((triisopropylsilyl)oxy)acetyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (394)

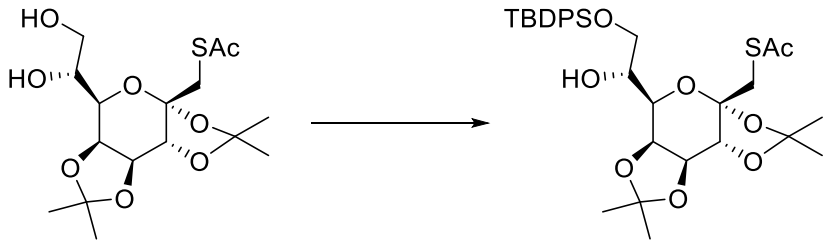


392 **394**

To a stirred solution of oxalyl chloride (0.08 ml, 1.01 mmol, 1.5 equiv.) in DCM (4 ml) at -78 ^{o}C, was added dropwise DMSO (0.16 ml, 2.34 mmol, 3.5 equiv.). The reaction mixture was stirred for 30 minutes at this temperature. Then a solution of compound **392** (0.359 g, 0.67 mmol) dissolved in DCM was added dropwise to the reaction mixture. The reaction mixture was stirred for a further hour at this temperature. To this mixture was then added Et_3N (0.45 ml, 3.36 mmol, 5.0 equiv.) and was stirred at -78 ^{o}C for 10 minutes before being warmed slowly to rt. The mixture was stirred at rt until the reaction was complete (monitored by TLC). Once complete, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as a pure colourless oil (0.322 g, 91%);$[\alpha]_D^{25}$ = -68.2 (c 0.98 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2942, 2894, 2867, 1743, 1699, 1256, 1130, 1071; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.04 – 1.08 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.09 – 1.17 (m, 3H, 3 X $HCMe_{2\ TIPS}$), 1.28 (s, 3H, $CH_{3\ Isopropylidene}$), 1.39 (s, 3H, $CH_{3\ Isopropylidene}$), 1.46 (s, 3H, $CH_{3\ Isopropylidene}$), 1.47 (s, 3H, $CH_{3\ Isopropylidene}$), 2.37 (s, 3H, $CH_{3\ Thioacetate}$), 3.32 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.52 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 4.22 (d, *J* = 2.2 Hz, 1H, H-C_{-2}), 4.41 (d, *J* = 1.7 Hz, 1H, H-C_{-5}), 4.55 (d, *J* = 19.3 Hz, 1H, H-C_{-7}), 4.59 – 4.63 (m, 2H, H-C_{-4}, H-C_{-3}), 4.65 (d, *J* = 19.3 Hz, 1H, H'-C_{-7}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.1 (3C, 3 X $CHMe_{2\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 24.2 (1C, $CH_{3\ Isopropylidene}$), 25.0 (1C, $CH_{3\ Isopropylidene}$), 25.7 (1C, $CH_{3\ Isopropylidene}$), 26.5 (1C, $CH_{3\ Isopropylidene}$), 30.5 (1C, $CH_{3\ Thioacetate}$), 37.6 (1C, CH_2SAc), 68.9 (1C, C-$_7$), 71.1 (1C, C-$_3$), 72.0 (1C, C-$_4$), 73.2 (1C, C-$_2$), 74.7 (1C, C-$_5$), 102.9 (1C, C-$_1$), 109.2 (1C, C_q

$_{\text{Isopropylidene}}$), 109.9 (1C, $C_{q\ \text{Isopropylidene}}$), 194.4 (1C, $C_{q\ \text{Thioacetate}}$), 205.2 (1C, $C_{\text{-6 Ketone}}$); HRMS (ASAP-OTF) *m/z* found for $[M+H]^+$: 533.2606; $[C_{25}H_{44}O_8SSi+H]^+$ requires 533.2604.

S-(((3aS,5R,5aS,8aS,8bR)-5-((R)-2-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (393)

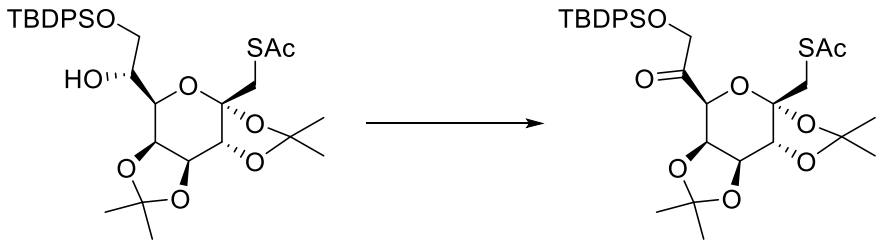


387 **393**

To a stirred solution of **387** (0.173 g, 0.46 mmol) in dry DCM (5 ml) at 0 ^{o}C, was added imidazole (0.094 g, 1.38 mmol, 3.0 equiv.l) and DMAP (11 mg, 0.0916 mmol, 0.2 equiv.). TBDPSCl (0.14 mL, 0.55 mmol, 1.2 equiv.), was then added dropwise to this suspension. The resultant mixture was stirred at rt for 24 hours. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to furnish the title compound as a pure colourless oil (0.209 g, 74%); $[\alpha]_D^{25}$ = -20.2 (c 0.98 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3072, 3049, 2890, 2934, 2858, 1742, 1699, 1428,1211, 1113, 1071; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.06 (s, 9H, 3 X $CH_{3\ tBu\ (TBDPS)}$), 1.35 (s, 3H, $CH_{3\ Isopropylidene}$), 1.38 (s, 3H, $CH_{3\ Isopropylidene}$), 1.41 (s, 3H, $CH_{3\ Isopropylidene}$), 1.47 (s, 3H, $CH_{3\ Isopropylidene}$), 2.30 (s, 3H, $CH_{3\ Thioacetate}$), 3.34 (s, 2H, CH_2SAc), 3.78 – 3.87 (m, 3H, H-C_{-5}, H-C_{-7}, H'-C_{-7}), 3.92 (ddd, *J* = 8.7, 5.2, 3.9 Hz, 1H, H-C_{-6}), 4.19 (d, *J* = 2.5 Hz, 1H, H-C_{-2}), 4.45 (dd, *J* = 7.9, 2.0 Hz, 1H, H-C_{-4}), 4.62 (dd, *J* = 7.9, 2.5 Hz, 1H, H-C_{-3}), 7.34 – 7.46 (m, 6H, 6 X H-C_{AR}), 7.66 – 7.72 (m, 4H, 4 X H-C_{AR}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.4 (1C, $C_{q\ tBu\ (TBDPS)}$), 24.5 (1C, $CH_{3\ Isopropylidene}$), 25.1 (1C, $CH_{3\ Isopropylidene}$), 25.9 (1C, $CH_{3\ Isopropylidene}$), 26.7 (1C, $CH_{3\ Isopropylidene}$), 27.1 (3C, 3 X $CH_{3\ tBu\ (TBDPS)}$), 30.5 (1C, $CH_{3\ Thioacetate}$), 37.7 (1C, CH_2SAc), 64.7 (1C, C_{-7}), 68.3 (1C, C_{-5}), 70.0 (1C, C_{-6}), 70.8 (1C, C_{-4}), 71.3 (1C, C_{-3}), 73.1 (1C, C_{-2}), 103.0 (1C, C_{-1}), 108.7 (1C, $C_{q\ Isopropylidene}$), 109.5 (1C, $C_{q\ Isopropylidene}$), 127.87 (2C, 2 X C_{AR}), 127.93 (2C, 2 X C_{AR}), 129.82 (1C, C_{AR}), 129.95 (1C, C_{AR}), 133.07 (1C, $C_{q\ AR}$), 133.24 (1C, $C_{q\ AR}$), 135.81 (2C, 2 X C_{AR}), 135.83 (2C, 2 X C_{AR}), 195.0 (1C,

$C_{q\ Thioacetate}$); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 634.2855; $[C_{32}H_{44}O_8SSi+NH_4]^+$ requires 634.2864.

S-(((3aS,5S,5aR,8aS,8bR)-5-(2-((*tert*-butyldiphenylsilyl)oxy)acetyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (395)



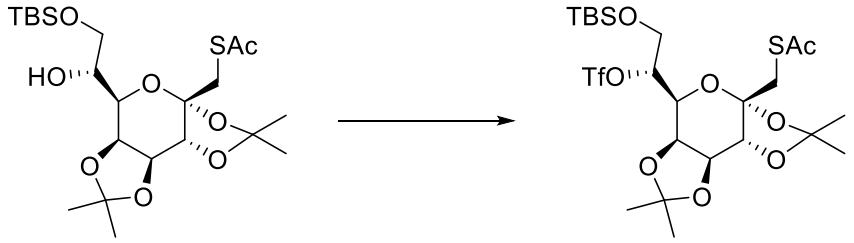
393 **395**

DMSO (0.08 ml, 1.10 mmol, 3.5 equiv.) was added dropwise to a stirred solution of oxalyl chloride (0.04 ml, 0.47 mmol, 1.5 equiv.) in DCM (4 ml) at -78 ºC and was left stirring for 30 minutes. Then a solution of alcohol **393** (0.193 g, 0.31 mmol) dissolved in DCM was added dropwise to the reaction mixture at -78 ºC. The reaction mixture was stirred for a further hour at this temperature. To this mixture was then added dropwise Et_3N (0.21 ml, 1.56 mmol, 5.0 equiv.) and was stirred at -78 ºC for 10 minutes before being warmed slowly to rt. The mixture was stirred at rt until the reaction was complete (monitored by TLC). Once complete, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as a pure colourless oil (0.160 g, 83%); $[\alpha]_D^{24}$ = -59.3 (c 1.09 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3552, 2989, 2934, 2858, 1695, 1473, 1428, 1210, 1105, 1072; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.09 (s, 9H, 3 X $CH_{3\ tBu\ (TBDPS)}$), 1.25 (s, 3H, $CH_{3\ Isopropylidene}$), 1.25 (s, 3H, $CH_{3\ Isopropylidene}$), 1.37 (s, 3H, $CH_{3\ Isopropylidene}$), 1.44 (s, 3H, $CH_{3\ Isopropylidene}$), 2.22 (s, 3H, $CH_{3\ Thioacetate}$), 3.23 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.40 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 4.18 (d, *J* = 2.2 Hz, 1H, H-C_{-2}), 4.36 (d, *J* = 1.8 Hz, 1H, H-C_{-5}), 4.49 (d, *J* = 19.3 Hz, 1H, H-C_{-7}), 4.55 – 4.61 (m, 2H, H-C_{-3}, H-C_{-4}), 4.67 (d, *J* = 19.3 Hz, 1H, H'-C_{-7}), 7.34 – 7.42 (m, 6H, 6 X H-C_{AR}), 7.65 – 7.70 (m, 4H, 4 X H-C_{AR}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.5 (1C, $C_{q\ tBu\ (TBDPS)}$), 24.2 (1C, $CH_{3\ Isopropylidene}$), 25.0 (1C, $CH_{3\ Isopropylidene}$), 25.5 (1C, $CH_{3\ Isopropylidene}$), 26.4 (1C, $CH_{3\ Isopropylidene}$), 26.9 (3C, 3 X $CH_{3\ tBu\ (TBDPS)}$), 30.3 (1C, $CH_{3\ Thioacetate}$), 37.4 (1C, CH_2SAc), 69.1 (1C, C_{-7}), 71.0 (1C, C_{-3}), 72.0 (1C, C_{-4}), 73.1 (1C, C_{-2}), 74.8 (1C, C_{-5}), 102.9 (1C, C_{-1}), 109.1 (1C, $C_{q\ Isopropylidene}$), 110.0 (1C, $C_{q\ Isopropylidene}$), 127.8 (2C, 2 X C_{AR}), 127.9 (2C, 2 X C_{AR}), 129.8 (1C, C_{AR}), 129.8 (1C, C_{AR}), 133.1

(1C, $C_{q\ AR}$), 133.4 (1C, $C_{q\ AR}$), 135.7 (2C, 2 X C_{AR}), 135.8 (2C, 2 X C_{AR}), 194.3 (1C, $C_{q\ Thioacetate}$), 204.8 (1C, $C_{\text{-6 Ketone}}$); HRMS (ASAP-OTF) *m/z* found for $[M+NH_4]^+$: 632.2711; $[C_{32}H_{42}O_8SSi+NH_4]^+$ requires 632.2714.

S-(((3aS,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((R)-1-(((trifluoromethyl)sulfonyl)oxy)-2-(*tert*-butyldimethylsilyloxy)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate

(402)



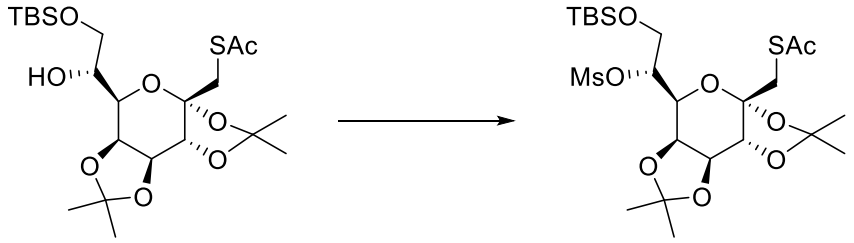
388 **402**

Trifluoromethanesulfonic anhydride (0.035 ml, 0.21 mmol, 1.0 Equiv.) was added dropwise over 15 minutes to a stirred solution of **388** (0.102 g, 0.21 mmol) and pyridine (0.025 ml, 0.31 mmol, 1.5 equiv.) in dry DCM (2 ml) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 30 minutes then allowed to warm up to rt and monitored by TLC until full consumption of the starting material was observed. The mixture was diluted with DCM and was treated with ice-cold water (ca. 15 ml), and the layers were separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were then washed with water and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave the title compound as a pure yellow oil (0.124 g, 96%); $[\alpha]_D^{24}$ = -15.0 (c 0.99 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2992, 2935, 2859, 1699, 1385, 1211, 1146, 1072, 837; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 0.08 (s, 6H, 2 X $CH_{3\ Me\ (TBS)}$), 0.90 (s, 9H, 3 X $CH_{3\ tBu\ (TBS)}$), 1.32 (s, 3H, $CH_{3\ Isopropylidene}$), 1.38 (s, 3H, $CH_{3\ Isopropylidene}$), 1.48 (s, 3H, $CH_{3\ Isopropylidene}$), 1.49 (s, 3H, $CH_{3\ Isopropylidene}$), 2.34 (s, 3H, $CH_{3\ Thioacetate}$), 3.29 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.40 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.88 (dd, *J* = 12.3, 5.3 Hz, 1H, H-C_{-7}), 4.07 (dd, *J* = 12.3, 2.4 Hz, 1H, H'-C_{-7}), 4.15 (dd, *J* = 7.2, 1.9 Hz, 1H, H-C_{-5}), 4.20 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.28 (dd, *J* = 7.9, 1.9 Hz, 1H, H-C_{-4}), 4.63 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}), 5.04 (ddd, *J* = 7.2, 5.3, 2.4 Hz, 1H, H-C_{-6}); ^{13}C NMR (126 MHz, $CDCl_3$) δ -5.5 (1C, $CH_{3\ Me\ (TBS)}$), -5.4 (1C, $CH_{3\ Me\ (TBS)}$), 18.5 (1C, $C_{q\ tBu\ (TBS)}$), 24.0 (1C, $CH_{3\ Isopropylidene}$), 25.1 (1C, $CH_{3\ Isopropylidene}$), 25.7 (1C, $CH_{3\ Isopropylidene}$), 26.0 (3C, 3 X $CH_{3\ tBu\ (TBS)}$), 26.7 (1C, $CH_{3\ Isopropylidene}$), 30.5 (1C, $CH_{3\ Thioacetate}$), 37.3 (1C, CH_2SAc), 61.5 (1C, C_{-7}), 67.1 (1C, C_{-5}), 69.8 (1C, C_{-4}), 71.3 (1C, C_{-3}), 73.0 (1C, C_{-2}), 87.3 (1C, C_{-6}), 103.0 (1C, C_{-1}), 109.1 (1C, $C_{q\ Isopropylidene}$),

110.0 (1C, $C_{q\ Isopropylidene}$), 119.9 (1C, $C_{q\ CF3\ (OTf)}$), 194.6 (1C, $C_{q\ Thioacetate}$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.09; HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 625.1786; $[C_{23}H_{39}F_3O_{10}S_2Si+H]^+$ requires 625.1784.

S-(((3aS,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((R)-1-((methylsulfonyl)oxy)-2-(*tert*-butyldimethylsilyloxy)ethyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate

(404)



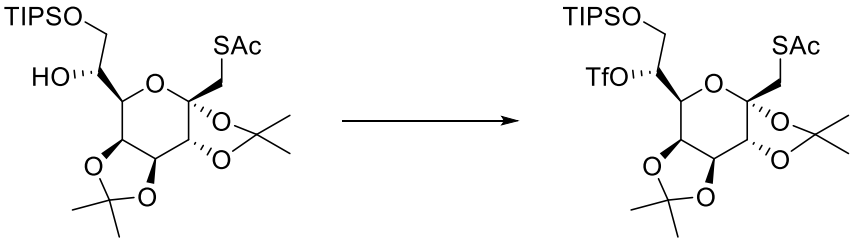
388 **404**

MsCl (0.058 ml, 0.75 mmol, 2 equiv.), was added dropwise to a stirred solution of **388** (0.185 g, 0.38 mmol) and Et_3N (0.26 ml, 1.87 mmol, 5 equiv.) in dry DCM (3.8 ml) at 0 ^oC. The orange mixture was stirred at rt for 3 hours. The reaction mixture was then quenched with brine and extracted with DCM three times. The combined organic extracts were washed with saturated aqueous NH_4Cl solution, water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure furnished a crude yellow oil. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to afford **404** as a pure colourless oil (0.142 g, 66%); $[\alpha]_D^{25}$ = -21.6 (c 0.96 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2989, 2935, 2857, 1698, 1360, 1176, 1072, 835; ^1H NMR (500 MHz, Chloroform-*d*) δ 0.09 (s, 6H, 2 X $CH_{3\ Me\ (TBS)}$), 0.91 (s, 9H, 3 X $CH_{3\ tBu\ (TBS)}$), 1.33 (s, 3H, $CH_{3\ Isopropylidene}$), 1.38 (s, 3H, $CH_{3\ Isopropylidene}$), 1.49 (s, 3H, $CH_{3\ Isopropylidene}$), 1.50 (s, 3H, $CH_{3\ Isopropylidene}$), 2.35 (s, 3H, $CH_{3\ Thioacetate}$), 3.09 (s, 3H, $CH_{3\ OMs}$), 3.31 (d, *J* = 13.7 Hz, 1H, 1H Of CH_2SAc), 3.40 (d, *J* = 13.7 Hz, 1H, 1H of CH_2SAc), 3.87 (dd, *J* = 11.9, 4.8 Hz, 1H, H-C_{-7}), 4.05 – 4.09 (m, 1H, H'-C_{-7}), 4.13 (dd, *J* = 7.5, 1.9 Hz, 1H, H-C_{-5}), 4.19 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.33 (dd, *J* = 7.9, 1.9 Hz, 1H, H-C_{-4}), 4.63 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}), 4.71 (ddd, *J* = 7.5, 4.8, 2.4 Hz, 1H, H-C_{-6}); ^{13}C NMR (126 MHz, $CDCl_3$) δ -5.3 (1C, $CH_{3\ Me\ (TBS)}$), -5.2 (1C, $CH_{3\ Me\ (TBS)}$), 18.6 (3C, 3 X $CH_{3\ tBu\ (TBS)}$), 24.4 (1C, $CH_{3\ Isopropylidene}$), 25.2 (1C, $CH_{3\ Isopropylidene}$), 25.9 (1C, $CH_{3\ Isopropylidene}$), 26.2 (3C, 3 X $CH_{3\ tBu\ (TBS)}$), 26.7 (1C, $CH_{3\ Isopropylidene}$), 30.5 (1C, $CH_{3\ Thioacetate}$), 37.4 (1C, CH_2SAc), 38.6 (1C, $CH_{3\ OMs}$), 62.3 (1C, C_{-7}), 67.0 (1C, C_{-5}), 70.2 (1C, C_{-4}), 71.4 (1C, C_{-3}), 73.0 (1C, C_{-2}), 81.6 (1C, C_{-6}), 103.0 (1C, C_{-1}), 109.1 (1C, $C_{q\ Isopropylidene}$), 109.7 (1C, $C_{q\ Isopropylidene}$), 194.7 (1C, $C_{q\ Thioacetate}$);

HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 588.2319; $[C_{23}H_{42}O_{10}S_2Si+NH_4]^+$ requires 588.2327.

(S-(((3aS,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((R)-1-(((trifluoromethyl)sulfonyl)oxy)-2-(triisopropylsilyloxy)ethyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate

(405)



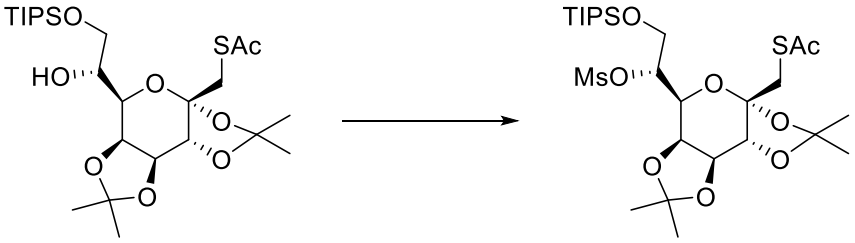
392 **405**

Trifluoromethanesulfonic anhydride (0.035 ml, 0.21 mmol, 1.0 Equiv.) was added dropwise over 15 minutes to a stirred solution of **392** (0.111 g, 0.21 mmol) and pyridine (0.025 ml, 0.31 mmol, 1.5 equiv.) in dry DCM (2 ml) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 30 minutes then allowed to warm up to rt and monitored by TLC until full consumption of the starting material was observed. The mixture was diluted with DCM and was treated with ice-cold water (ca. 15 ml), and the layers were separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were then washed with water and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* gave **405** as a pure yellow oil (0.135 g, 98%); $[\alpha]_D{}^{24}$ = -14.6 (c 0.85 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2943, 2896, 2869, 1699, 1385, 1211, 1146, 1071, 908; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.03 – 1.14 (m, 21H, 6 X $CH_{3\ TIPS}$, 3 X H-$CMe_{2\ TIPS}$), 1.31 (s, 3H, $CH_{3\ Isopropylidene}$), 1.38 (s, 3H, $CH_{3\ Isopropylidene}$), 1.47 (s, 3H, $CH_{3\ Isopropylidene}$), 1.48 (s, 3H, $CH_{3\ Isopropylidene}$), 2.34 (s, 3H, $CH_{3\ Thioacetate}$), 3.28 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.40 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.96 (dd, *J* = 12.4, 6.2 Hz, 1H, H-C_{-7}), 4.13 (dd, *J* = 6.2, 2.0 Hz, 1H, H-C_{-5}), 4.19 (d, *J* = 2.6 Hz, 1H, H-C_{-2}) 4.20 (dd, *J* = 12.4, 2.4 Hz, 1H, H'-C_{-7}), 4.28 (dd, *J* = 7.9, 2.0 Hz, 1H, H-C_{-4}), 4.62 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}), 5.09 (td, *J* = 6.2, 2.4 Hz, 1H, H-C_{-6}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.1 (3C, 3 X $CHMe_{2\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 24.0 (1C, $CH_{3\ Isopropylidene}$), 25.0 (1C, $CH_{3\ Isopropylidene}$), 25.7 (1C, $CH_{3\ Isopropylidene}$), 26.5 (1C, $CH_{3\ Isopropylidene}$), 30.5 (1C, $CH_{3\ Thioacetate}$), 37.4 (1C, CH_2SAc), 62.1 (1C, C_{-7}), 67.9 (1C, C_{-5}), 70.1 (1C, C_{-4}), 71.3 (1C, C_{-3}), 73.0 (1C, C_{-2}), 88.4 (1C, C_{-6}), 103.0 (1C, C_{-1}), 109.1 (1C, $C_{q\ Isopropylidene}$), 110.0 (1C, $C_{q\ Isopropylidene}$), 194.6 (1C, $C_{q\ Thioacetate}$); ^{19}F NMR

(376 MHz, $CDCl_3$) δ -75.02; HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 667.2260; $[C_{26}H_{45}F_3O_{10}S_2Si+H]^+$ requires 667.2254.

S-(((3aS,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((R)-1-((methylsulfonyl)oxy)-2-(triisopropylsilyloxy)ethyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate

(406)

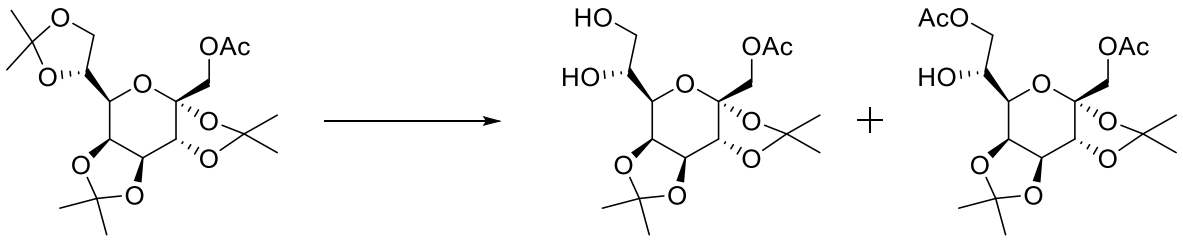


392 **406**

MsCl (0.039 ml, 0.51 mmol, 2 equiv.), was added dropwise to a stirred solution of **392** (0.136 g, 0.25 mmol) and Et_3N (0.18 ml, 1.27 mmol, 5 equiv.) in dry DCM (2.6 ml) at 0 ^oC. The mixture was stirred at rt until TLC showed complete consumption of starting material. The reaction mixture was then quenched with brine and extracted with DCM three times. The combined organic extracts were washed with saturated aqueous NH_4Cl solution, water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* furnished a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to afford the title compound as a pure colourless oil (0.099 g, 64%); $[\alpha]_D^{24}$ = -17.0 (c 0.99 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2942, 2894, 2867, 1698, 1360, 1175, 1071, 907; ^1H NMR (500 MHz, Chloroform-*d*) δ 1.05 – 1.16 (m, 21H, 6 X $CH_{3\ TIPS}$, 3 X H-$CMe_{2\ TIPS}$), 1.33 (s, 3H, $CH_{3\ Isopropylidene}$), 1.38 (s, 3H, $CH_{3\ Isopropylidene}$), 1.49 (s, 6H, 2 X $CH_{3\ Isopropylidene}$), 2.34 (s, 3H, $CH_{3\ Thioacetate}$), 3.09 (s, 3H, $CH_{3\ OMs}$), 3.30 (d, *J* = 13.7 Hz, 1H, 1H of CH_2SAc), 3.39 (d, *J* = 13.7 Hz, 1H, 1H of CH_2SAc), 3.92 (dd, *J* = 11.8, 5.8 Hz, 1H, H-C_{-7}), 4.12 (dd, *J* = 6.7, 1.9 Hz, 1H, H-C_{-5}), 4.16 (dd, *J* = 11.8, 2.4 Hz, 1H, H'-C_{-7}), 4.18 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.35 (dd, *J* = 7.9, 1.9 Hz, 1H, H-C_{-4}), 4.63 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}), 4.78 (ddd, *J* = 6.7, 5.8, 2.4 Hz, 1H, H-C_{-6}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.1 (3C, 3 X $CHMe_{2\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 24.3 (1C, $CH_{3\ Isopropylidene}$), 25.1 (1C, $CH_{3\ Isopropylidene}$), 25.8 (1C, $CH_{3\ Isopropylidene}$), 26.6 (1C, $CH_{3\ Isopropylidene}$), 30.5 (1C, $CH_{3\ Thioacetate}$), 37.5 (1C, CH_2SAc), 38.5 (1C, $CH_{3\ OMs}$), 62.6 (1C, C_{-7}), 67.7 (1C, C_{-5}), 70.4 (1C, C_{-4}), 71.4 (1C, C_{-3}), 73.1 (1C, C_{-2}), 82.3 (1C, C_{-6}), 103.0 (1C, C_{-1}),

109.1 (1C, $C_{q\ Isopropylidene}$), 109.7 (1C, $C_{q\ Isopropylidene}$), 194.7 (1C, $C_{q\ Thioacetate}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 613.2537; $[C_{26}H_{48}O_{10}S_2Si+H]^+$ requires 613.2537.

((3aR,5R,5aS,8aS,8bR)-5-((R)-1,2-dihydroxyethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl acetate (411)



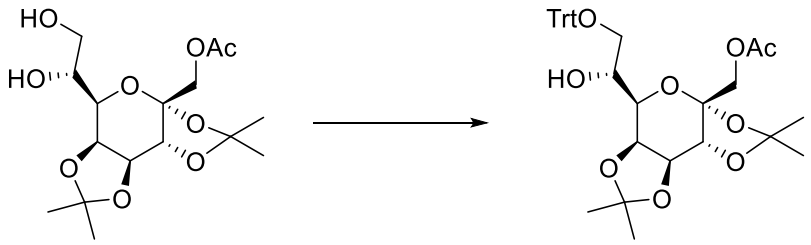
383 **411** **412**

Compound **383** (2.705 g, 6.72 mmol), was dissolved in 80% Acetic acid (67 ml). The stirred reaction mixture was heated at 50 ^{o}C until TLC showed complete consumption of starting material was observed, after which the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 1:1) to afford **411** as a pure colourless white solid (2.202 g, 90%); mp 118-119 ^{o}C; $[\alpha]_D^{22}$ = -2.1 (c 0.95 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3449, 2991, 2939, 1750, 1208, 1071; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.35 (s, 3H, $CH_{3\ Isopropylidene}$), 1.38 (s, 3H, $CH_{3\ Isopropylidene}$), 1.44 (s, 3H, $CH_{3\ Isopropylidene}$), 1.53 (s, 3H, $CH_{3\ Isopropylidene}$), 2.09 (s, 3H, $CH_{3\ Acetate}$), 3.71 – 3.84 (m, 2H, H-C$_{-7}$, H'-C$_{-7}$), 3.84 – 3.90 (m, 2H, H-C$_{-5}$, H-C$_{-6}$), 3.96 (d, *J* = 11.7 Hz, 1H, 1H of CH_2OAc), 4.33 (d, *J* = 2.7 Hz, 1H, H-C$_{-2}$), 4.43 (d, *J* = 11.7 Hz, 1H, 1H of CH_2OAc), 4.43 – 4.47 (m, 1H, H-C$_{-4}$), 4.67 (dd, *J* = 7.9, 2.7 Hz, 1H, H-C$_{-3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.0 (1C, $CH_{3\ Acetate}$), 24.5 (1C, $CH_{3\ Isopropylidene}$), 25.3 (1C, $CH_{3\ Isopropylidene}$), 26.0 (1C, $CH_{3\ Isopropylidene}$), 26.6 (1C, $CH_{3\ Isopropylidene}$), 63.9 (1C, C$_{-7}$), 64.9 (1C, CH_2OAc), 68.5 (1C, C$_{-5}$), 70.2 (1C, C$_{-6}$), 70.7 (1C, C$_{-2}$), 70.9 (1C, C$_{-4}$), 71.1 (1C, C$_{-3}$), 102.3 (1C, C$_{-1}$), 109.3 (1C, $C_{q\ Isopropylidene}$), 109.7 (1C, $C_{q\ Isopropylidene}$), 170.2 (1C, $C_{q\ Acetate}$); HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 385.1467; $[C_{16}H_{26}O_9+Na]^+$ requires 385.1469;

Compound **412** was also isolated as a colourless oil (0.095 g, 3%); $[\alpha]_D^{26}$ = +5.7 (c 0.84 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3448, 2990, 2940, 1745, 1250, 1072; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.36 (s, 3H, $CH_{3\ Isopropylidene}$), 1.39 (s, 3H, $CH_{3\ Isopropylidene}$), 1.45 (s, 3H, $CH_{3\ Isopropylidene}$), 1.53 (s, 3H, $CH_{3\ Isopropylidene}$), 2.09 (s, 3H, $CH_{3\ Acetate}$), 2.09 (s, 3H, $CH_{3\ Acetate}$), 3.86 (dd, *J* = 8.9, 2.0 Hz, 1H, H-C$_{-5}$), 3.96 (d, *J* = 11.7 Hz, 1H, 1H of CH_2OAc), 4.04 (ddd, *J* = 8.9, 5.4, 2.6 Hz, 1H, H-C$_{-6}$), 4.19 (dd, *J* = 11.8, 5.4 Hz, 1H, H-C$_{-7}$), 4.35 (d, *J* = 2.7 Hz, 1H, H-C$_{-2}$),

4.41 (dd, *J* = 11.8, 2.6, H'-C_{-7}), 4.43 (d, *J* = 11.7 Hz, 1H, 1H of CH_2OAc), 4.47 (dd, *J* = 7.9, 2.0 Hz, 1H, H-C_{-4}), 4.68 (dd, *J* = 7.9, 2.7 Hz, 1H, H-C_{-3}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0 (2C, 2 X $CH_{3\ Acetate}$), 24.5 (1C, $CH_{3\ Isopropylidene}$), 25.3 (1C, $CH_{3\ Isopropylidene}$), 26.0 (1C, $CH_{3\ Isopropylidene}$), 26.6 (1C, $CH_{3\ Isopropylidene}$), 64.9 (1C, CH_2OAc), 66.1 (1C, C_{-7}), 67.9 (1C, C_{-5}), 68.8 (1C, C_{-6}), 70.7 (2C, C_{-4}, C_{-2}), 71.1 (1C, C_{-3}), 102.3 (1C, C_{-1}), 109.1 (1C, $C_{q\ Isopropylidene}$), 109.8 (1C, $C_{q\ Isopropylidene}$), 170.2 (1C, $C_{q\ Acetate}$), 171.6 (1C, $C_{q\ Acetate}$); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 422.2014; $[C_{18}H_{28}O_{10}+NH_4]^+$ requires 422.2021;

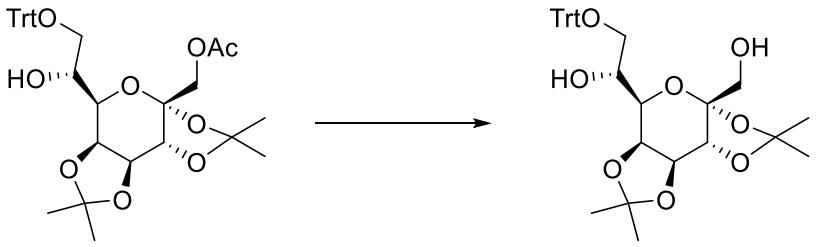
((3aR,5R,5aS,8aS,8bR)-5-((R)-1-hydroxy-2-(trityloxy)ethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl acetate (413)



411 **413**

Et_3N (0.10 ml, 0.74 mmol, 2 equiv.) was added to a stirred solution of **411** (0.134 g, 0.37 mmol) in dry DCM (2.2 ml). After cooling the resultant solution to 0 ^oC, trityl chloride (0.124 g, 0.44 mmol, 1.2 equiv.) was added in one portion. The mixture was stirred at rt overnight. The solvent was then removed under reduced pressure. The residue was treated with water and EtOAc. The layers were separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 4:1) to yield the title compound as a pure colourless solid (0.199 g, 89%); mp 64-67 ^oC; $[\alpha]_D^{26}$ = +4.9 (c 0.97 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3473, 3059, 3025, 2890, 2936, 1750, 1491, 1448, 1208, 1072; ^1H NMR (500 MHz, Chloroform-*d*) δ 1.33 (s, 3H, $CH_{3\ Isopropylidene}$), 1.37 (s, 3H, $CH_{3\ Isopropylidene}$), 1.40 (s, 3H, $CH_{3\ Isopropylidene}$), 1.41 (s, 3H, $CH_{3\ Isopropylidene}$), 2.08 (s, 3H, $CH_{3\ Acetate}$), 2.65 (d, *J* = 6.6 Hz, 1H, OH), 3.32 (dd, *J* = 9.6, 4.0 Hz, 1H, H-C_{-7},), 3.39 (dd, *J* = 9.6, 4.3 Hz, 1H, H'-C_{-7}), 3.88 – 3.97 (m, 2H, 1H of CH_2OAc, H-C_{-6}), 3.98 (dd, *J* = 8.2, 1.9 Hz, 1H, H-C_{-5}), 4.32 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.39 – 4.44 (m, 2H, H-C_{-4}, 1H of CH_2OAc), 4.63 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}), 7.20 – 7.25 (m, 3H, 3 X H-C_{AR}), 7.27 – 7.32 m, 6H, 6 X H-C_{AR}), 7.43 – 7.47 (m, 6H, 6 X H-C_{AR}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1 (1C, $CH_{3\ Acetate}$), 24.4 (1C, $CH_{3\ Isopropylidene}$), 25.3 (1C, $CH_{3\ Isopropylidene}$), 26.0 (1C, $CH_{3\ Isopropylidene}$), 26.6 (1C, $CH_{3\ Isopropylidene}$), 65.0 (1C, C_{-7}), 68.0 (1C, CH_2OAc), 69.6 (1C, C_{-5}), 70.7 (1C, C_{-6}), 71.1 (1C, C_{-2}), 71.1 (2C, C_{-3}, C_{-4}), 86.9 (1C, $C_{q\ Trityl}$), 102.3 (1C, C_{-1}), 109.0 (1C, $C_{q\ Isopropylidene}$), 109.5 (1C, $C_{q\ Isopropylidene}$), 127.2 (3C, 3 X C_{AR}), 128.0 (6C, 6 X C_{AR}), 128.9 (6C, 6 X C_{AR}), 143.9 (3C, 3 X $C_{q\ AR}$), 170.2 (1C, $C_{q\ Acetate}$); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 622.3007; $[C_{35}H_{40}O_9+NH_4]^+$ requires 622.3011.

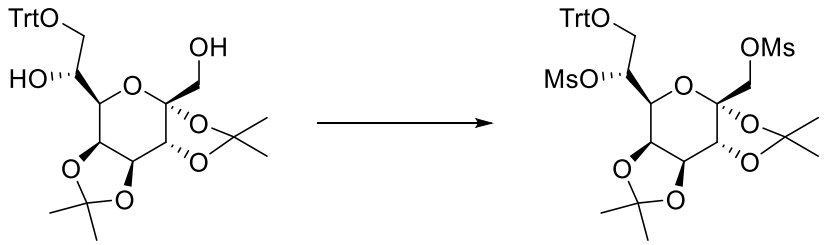
(R)-1-((3aR,5R,5aS,8aS,8bR)-3a-(hydroxymethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-(trityloxy)ethanol (414)



413 **414**

A methanolic solution of sodium methoxide (1.68 ml, 3.37 mmol, 2M in methanol, 3 equiv.) was added slowly to a stirred solution of **413** (0.678 g, 1.12 mmol) in dry methanol (11.2 ml). The mixture was stirred at rt until TLC showed complete consumption of starting material. The solvent was then removed *in vacuo*. The residue was treated with water (ca. 10 ml) and Et_2O (ca. 10 ml), and the layers were separated. The aqueous layer was extracted with Et_2O two times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:1) to yield the title compound as a pure colourless solid (0.591 g, 94%); mp 70-72 ^oC; $[\alpha]_D^{26}$ = +3.8 (c 1.36 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3476, 3059, 3033, 2989, 2936, 1491, 1449, 1213, 1072; ^1H NMR (400 MHz, Chloroform-*d*) δ 1.32 (s, 3H, $CH_{3\ Isopropylidene}$), 1.35 (s, 3H, $CH_{3\ Isopropylidene}$), 1.40 (s, 3H, $CH_{3\ Isopropylidene}$), 1.42 (s, 3H, $CH_{3\ Isopropylidene}$), 1.98 – 2.00 (m, 1H, OH), 2.69 (d, *J* = 6.5 Hz, 1H, OH), 3.32 (dd, *J* = 9.6, 4.1 Hz, 1H, H-C_{-7}), 3.39 (dd, *J* = 9.6, 4.2 Hz, 1H, H'-C_{-7}), 3.54 – 3.70 (m, 2H, 2H of CH_2OH), 3.87 – 4.00 (m, 2H, H-C_{-6}, H-C_{-5}), 4.32 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.39 (dd, *J* = 7.9, 1.8 Hz, 1H, H-C_{-4}), 4.62 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}), 7.19 – 7.31 (m, 9H, 9 X H-C_{AR}), 7.42 – 7.47 (m, 6H, 6 X H-C_{AR}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.3 (1C, $CH_{3\ Isopropylidene}$), 25.5 (1C, $CH_{3\ Isopropylidene}$), 25.8 (1C, $CH_{3\ Isopropylidene}$), 26.6 (1C, $CH_{3\ Isopropylidene}$), 64.0 (1C, C_{-7}), 65.7 (1C, CH_2OH), 68.0 (1C, C_{-6}), 69.7 (1C, C_{-5}), 71.0 (1C, C_{-3}), 71.1 (1C, C_{-4}), 71.4 (1C, C_{-2}), 86.9 (1C, $C_{q\ Trityl}$), 103.8 (1C, C_{-1}), 108.8 (1C, $C_{q\ Isopropylidene}$), 109.4 (1C, $C_{q\ Isopropylidene}$), 127.2 (3C, 3 X C_{AR}), 128.0 (6C, 6 X C_{AR}), 129.0 (6C, 6 X C_{AR}), 143.9 (3C, 3 X $C_{q\ AR}$); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 580.2901; $[C_{33}H_{38}O_8+NH_4]^+$ requires 580.2905.

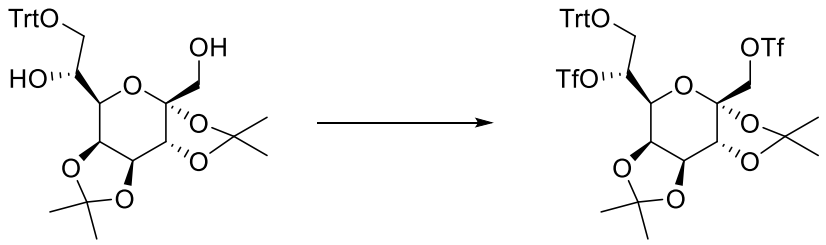
(R)-1-((3aR,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-3a-(((methylsulfonyl)oxy)methyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-(trityloxy)ethyl methanesulfonate (415)



414 **415**

MsCl (0.036 ml, 0.47 mmol, 2.5 equiv.) was added dropwise to a stirred solution of **414** (0.106 g, 0.19 mmol) and Et_3N (0.09 ml, 0.66 mmol, 3.5 equiv.) in dry DCM (1.9 ml) at 0 ^oC. The mixture was stirred at rt for 2 hours. Saturated aqueous $NaHCO_3$ was then added and the mixture was extracted three times with DCM. The combined organic extracts were washed with water twice, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude yellow oil. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:1) to yield the title compound as a pure colourless solid (0.133g, 70%); mp 75-79 ^oC; $[\alpha]_D^{22}$ = +7.2 (c 0.67 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3026, 2925, 2854, 1491, 1450, 1360 1176, 1073, 969; ^1H NMR (500 MHz, Chloroform-*d*) δ 1.31 (s, 6H, 2 X $CH_{3\ Isopropylidene}$), 1.32 (s, 3H, $CH_{3\ Isopropylidene}$), 1.34 (s, 3H, $CH_{3\ Isopropylidene}$), 2.96 (s, 3H, $CH_{3\ OMs}$), 3.00 (s, 3H, $CH_{3\ OMs}$), 3.25 (dd, *J* = 11.2, 3.8 Hz, 1H, H-C_{-7}), 3.68 (dd, *J* = 11.2, 2.3 Hz, 1H, H'-C_{-7}), 4.05 (d, *J* = 10.9 Hz, 1H, 1H of CH_2OMs), 4.17 (d, *J* = 10.9 Hz, 1H, 1H of CH_2OMs), 4.30 (d, *J* = 2.7 Hz, 1H, H-C_{-2}), 4.37 – 4.40 (m, 2H, H-C_{-4}, H-C_{-5}), 4.66 – 4.70 (m, 1H, H-C_{-3}), 4.85 (ddd, *J* = 7.3, 3.8, 2.3 Hz, 1H, H-C_{-6}), 7.20 – 7.25 (m, 3H, 3 x H-C_{AR}), 7.27 – 7.32 (m, 6H, 6 x H-C_{AR}), 7.45 – 7.49 (m, 6H, 6 x H-C_{AR}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.2 (1C, $CH_{3\ Isopropylidene}$), 25.3 (1C, $CH_{3\ Isopropylidene}$), 25.9 (1C, $CH_{3\ Isopropylidene}$), 26.5 (1C, $CH_{3\ Isopropylidene}$), 37.8 (1C, $CH_{3\ OMs}$), 38.8 (1C, $CH_{3\ OMs}$), 61.9 (1C, C_{-7}), 67.0 (1C, C_{-4}), 69.1 (1C, CH_2OMs), 70.1 (1C, C_{-5}), 70.4 (1C, C_{-2}), 80.0 (1C, C_{-3}), 79.9 (1C, C_{-6}), 87.1 (1C, $C_{q\ Trityl}$), 101.4 (1C, C_{-1}), 109.8 (1C, $C_{q\ Isopropylidene}$), 110.0 (1C, $C_{q\ Isopropylidene}$), 127.2 (3C, 3 X C_{AR}), 127.9 (6C, 6 X C_{AR}), 129.0 (6C, 6 X C_{AR}), 143.6 (3C, 3 X $C_{q\ AR}$); HRMS (ASAP-TOF) *m/z* found for $[M+NH_4]^+$: 736.2462; $[C_{35}H_{42}O_{12}S_2+NH_4]^+$ requires 736.2465.

(R)-1-((3aR,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-3a-((((trifluoromethyl)sulfonyl)oxy)methyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-(trityloxy)ethyl trifluoromethanesulfonate (417)

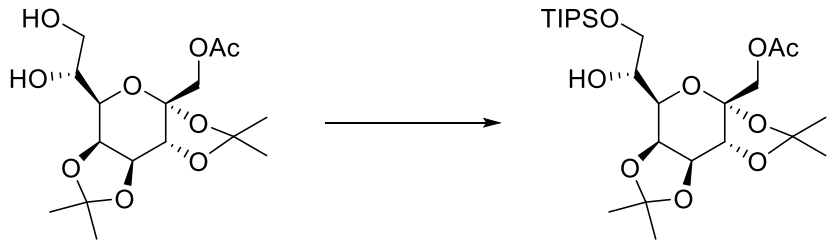


414 **417**

Trifluoromethanesulfonic anhydride (0.071 ml, 0.43 mmol, 2.4 equiv.) was added dropwise over 15 minutes to a stirred solution of pyridine (0.057 ml, 0.71 mmol, 4 equiv.) and **417** (0.100 g, 0.18 mmol) in dry DCM (1.8 ml) at 0 ºC. The reaction mixture was stirred at 0 ºC and monitored by TLC until full consumption of the starting material was observed. The mixture was diluted with DCM and was treated with ice-cold water (ca. 10 ml), and the layers were separated. The aqueous layer was then extracted with DCM twice. The combined organic extracts were washed with water, saturated aqueous copper sulfate solution and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* afforded a pure yellow oil (0.128 g, 87%); $[\alpha]_D^{22}$ = +4.9 (c 0.89 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3000, 2925, 2853, 1491, 1450, 1417, 1385, 1210, 1074, 983; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.29 (s, 3H, $CH_{3\ Isopropylidene}$), 1.31 (s, 3H, $CH_{3\ Isopropylidene}$), 1.33 (s, 3H, $CH_{3\ Isopropylidene}$), 1.35 (s, 3H, $CH_{3\ Isopropylidene}$), 3.43 (dd, *J* = 11.8, 3.5 Hz, 1H, H-C_{-7}), 3.62 (dd, *J* = 11.8, 2.3 Hz, 1H, H'-C_{-7}), 4.25 (d, *J* = 10.5 Hz, 1H, 1H of CH_2OTf), 4.31 (d, *J* = 2.7 Hz, 1H, H-C_{-2}), 4.37 (dd, *J* = 7.8, 2.1 Hz, 1H, H-C_{-4}), 4.39 (d, *J* = 10.5 Hz, 1H, 1H of CH_2OTf), 4.50 (dd, *J* = 7.7, 2.1 Hz, 1H, H-C_{-5}), 4.71 (dd, *J* = 7.8, 2.7 Hz, 1H, H-C_{-3}), 5.11 (ddd, *J* = 7.7, 3.5, 2.3 Hz, 1H, H-C_{-6}), 7.22 – 7.27 (m, 3H, 3 X H-C_{AR}), 7.27 – 7.33 (m, 6H, 6 X H-C_{AR}), 7.44 – 7.48 (m, 6H, 6 X H-C_{AR}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.7 (1C, $CH_{3\ Isopropylidene}$), 25.0 (1C, $CH_{3\ Isopropylidene}$), 25.6 (1C, $CH_{3\ Isopropylidene}$), 26.5 (1C, $CH_{3\ Isopropylidene}$), 61.2 (1C, C_{-7}), 66.8 (1C, C_{-5}), 69.5 (1C, C_{-4}), 70.3 (1C, C_{-2}), 70.6 (1C, C_{-3}), 73.5 (1C, CH_2OTf), 85.3 (1C, C_{-6}), 87.3 (1C, $C_{q\ Trityl}$), 100.6 (1C, C_{-1}), 110.0 (1C, $C_{q\ Isopropylidene}$), 110.7 (1C, $C_{q\ Isopropylidene}$), 127.4 (3C, 3 X C_{AR}), 128.0 (6C, 6 X C_{AR}), 129.0 (6C, 6 X C_{AR}), 143.2 (3C, 3 X $C_{q\ AR}$); ^{19}F NMR

(471 MHz, $CDCl_3$) δ -74.40, -75.08; HRMS (ASAP-TOF) *m/z* found for $[M]^+$: 826.1537; $[C_{35}H_{36}F_6O_{12}S_2]^+$ requires 826.1552.

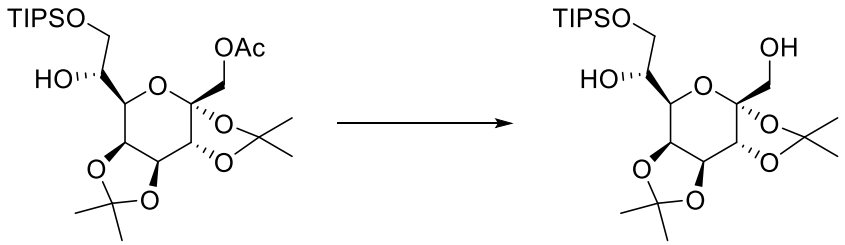
((3aR,5R,5aS,8aS,8bR)-5-((R)-1-hydroxy-2-((triisopropylsilyl)oxy)ethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl acetate (418)



411 **418**

To a stirred solution of **411** (0.753 g, 2.08 mmol) in dry DCM at 0 ºC, was added imidazole (0.353 g, 5.19 mmol, 2.5 equiv.) and DMAP (0.051 g, 0.42 mmol, 0.2 equiv.). TIPSCl (0.53 ml, 2.49 mmol, 1.2 equiv.), was then added dropwise to this suspension. The resultant mixture was stirred at rt for 24hr. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 11:2) to furnish the title compound as a pure colourless oil (0.961 g, 89%); $[\alpha]_D^{22}$ = +2.6 (c 0.91 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3543, 2990, 2943, 2895, 2867, 1753, 1230, 1073; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.04 – 1.08 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.08 – 1.16 (m, 3H, 3 X H-$CMe_{2\ TIPS}$), 1.36 (s, 3H, $CH_{3\ Isopropylidene}$), 1.39 (s, 3H, $CH_{3\ Isopropylidene}$), 1.45 (s, 3H, $CH_{3\ Isopropylidene}$), 1.51 (s, 3H, $CH_{3\ Isopropylidene}$), 2.09 (s, 3H, $CH_{3\ Acetate}$), 2.80 (d, *J* = 5.3 Hz, 1H, OH), 3.72 (dd, *J* = 9.6, 5.4 Hz, 1H, H-C_{-7}), 3.80 (dd, *J* = 8.4, 1.9 Hz, 1H, H-C_{-5}), 3.84 – 3.89 (m, 1H, H-C_{-6}), 3.91 (dd, *J* = 9.6, 3.8 Hz, 1H, H'-C_{-7}), 3.96 (d, *J* = 11.6 Hz, 1H, 1H of CH_2OAc), 4.33 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.42 (d, *J* = 11.6 Hz, 1H, 1H of CH_2OAc), 4.49 (dd, *J* = 7.9, 1.9 Hz, 1H, H-C_{-4}), 4.66 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.0 (3C, 3 X $CHMe_{2\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 21.0 (1C, $CH_{3\ Isopropylidene}$), 24.4 (1C, $CH_{3\ Isopropylidene}$), 25.3 (1C, $CH_{3\ Isopropylidene}$), 26.0 (1C, $CH_{3\ Isopropylidene}$), 26.8 (1C, $CH_{3\ Acetate}$), 64.4 (1C, C_{-7}), 65.0 (1C, CH_2OAc), 68.3 (1C, C_{-5}), 69.6 (1C, C_{-6}), 70.7 (1C, C_{-2}), 71.0 (1C, C_{-4}), 71.0 (1C, C_{-2}), 102.2 (1C, C_{-1}), 109.0 (1C, $C_{q\ Isopropylidene}$), 109.5 (1C, $C_{q\ Isopropylidene}$), 170.2 (1C, $C_{q\ Acetate}$); HRMS (ESI-TOF) *m/z* found for $[M+Na]^+$: 541.2821; $[C_{25}H_{46}O_9Si+Na]^+$ requires 541.2809.

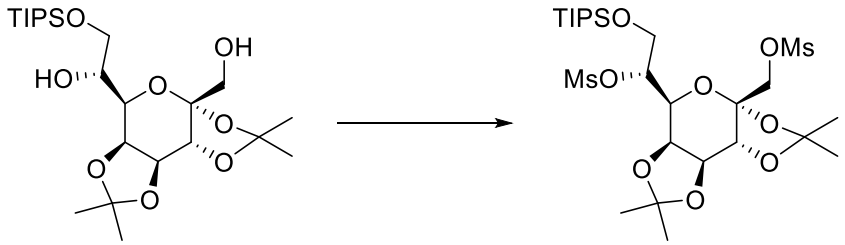
(R)-1-((3aR,5R,5aS,8aS,8bR)-3a-(hydroxymethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((triisopropylsilyl)oxy)ethanol (419)



418 **419**

Anhydrous K_2CO_3 (0.156 g, 1.13 mmol, 1.21 equiv.) was added to a stirred solution of **418** (0.485 g, 0.93 mmol) in dry methanol (9.4 ml). The mixture was stirred at rt until TLC showed complete consumption of starting material. The solvent was then removed under reduced pressure. The residue was treated with water and Et_2O, and the layers were separated. The aqueous layer was then extracted with Et_2O two times. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude oil. The crude product was purified by flash column chromatography (petrol:EtOAc, 4:1) to yield the title compound as a pure colourless oil (0.344 g, 77%); $[\alpha]_D^{22}$ = -14.2 (c 0.73 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3503, 2942, 2894, 2867, 1101, 1072; ^{1}H NMR (400 MHz, Chloroform-*d*) δ1.02 – 1.17 (m, 21H, 6X $CH_{3\ TIPS}$, 3 X H-$CMe_{2\ TIPS}$), 1.38 (s, 6H, 2 X $CH_{3\ Isopropylidene}$), 1.46 (s, 3H, $CH_{3\ Isopropylidene}$), 1.52 (s, 3H, $CH_{3\ Isopropylidene}$), 2.81 (br, 1H, OH), 3.63 (d, *J* = 11.6 Hz, 1H, 1H of CH_2OH), 3.69 (d, *J* = 11.6 Hz, 1H, 1H of CH_2OH), 3.73 – 3.79 (m, 1H, H-C_{-7}), 3.83 (dd, *J* = 8.4, 1.8 Hz, 1H, H-C_{-5}), 3.85 – 3.94 (m, 2H, H-C_{-6}, H'-C_{-7}), 4.35 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.51 (dd, *J* = 7.9, 1.8 Hz, 1H, H-C_{-4}), 4.67 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.0 (3C, 3 X $CHMe_{2\ TIPS}$), 18.1 (6C, 6 X $CH_{3\ TIPS}$), 24.3 (1C, $CH_{3\ Isopropylidene}$), 25.5 (1C, $CH_{3\ Isopropylidene}$), 25.8 (1C, $CH_{3\ Isopropylidene}$), 26.7 (1C, $CH_{3\ Isopropylidene}$), 64.3 (1C, C_{-7}), 65.6 (1C, CH_2OH), 68.3 (1C, C_{-5}), 69.9 (1C, C_{-6}), 70.9 (1C, C_{-4}), 71.0 (1C, C_{-3}), 71.5 (1C, C_{-2}), 103.8 (1C, C_{-1}), 108.8 (1C, $C_{q\ Isopropylidene}$), 109.4 (1C, $C_{q\ Isopropylidene}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 472.2888; $[C_{23}H_{44}O_8Si+H]^+$ requires 477.2884.

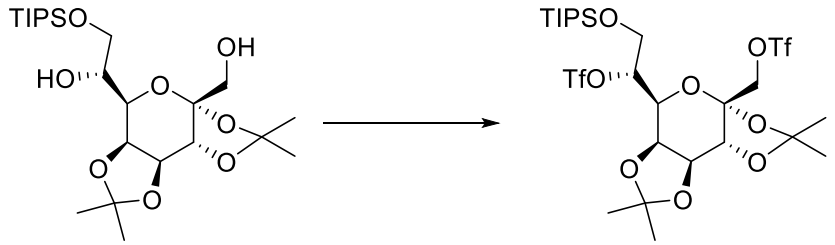
(R)-1-((3aR,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-3a-(((methylsulfonyl)oxy)methyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((triisopropylsilyl)oxy)ethyl methanesulfonate (420)



419 **420**

MsCl (0.039 ml, 0.50 mmol, 2.5 equiv.) was added dropwise to a stirred solution of **419** (0.095 g, 0.20 mmol) and Et_3N (0.084 ml, 0.60 mmol, 3 equiv.) in dry DCM (2 ml) at 0 ^oC. The mixture was stirred at rt for 2 hours. Saturated aqueous $NaHCO_3$ was then added and the mixture was extracted three times with DCM. The combined organic extracts were washed with water twice, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude yellow oil. The crude product was purified by flash column chromatography (petrol:EtOAc, 5:2) to yield **420** as a pure colourless oil (0.107 g, 85%); $[\alpha]_D^{26}$ = -12.4 (c 0.97 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2942, 2867, 1359, 1210, 1177, 1070, 969; ^1H NMR (500 MHz, Chloroform-*d*) δ 1.05 – 1.09 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.09 – 1.16 (m, 3H, 3 X H-$CMe_{2\ TIPS}$), 1.33 (s, 3H, $CH_{3\ Isopropylidene}$), 1.40 (s, 3H, $CH_{3\ Isopropylidene}$), 1.44 (s, 3H, $CH_{3\ Isopropylidene}$), 1.55 (s, 3H, $CH_{3\ Isopropylidene}$), 3.05 (s, 3H, $CH_{3\ OMs}$), 3.09 (s, 3H, $CH_{3\ OMs}$), 3.92 (dd, *J* = 11.8, 5.5 Hz, 1H, H-C_{-7}), 4.16 – 4.22 (m, 2H, H'-C_{-7}, 1H of CH_2OMs), 4.25 (dd, *J* = 6.5, 1.8 Hz, 1H, H-C_{-5}), 4.27 (d, *J* = 10.9 Hz, 1H of CH_2OMs), 4.33 (d, *J* = 2.6 Hz, 1H, H-C_{-2}), 4.38 (dd, *J* = 7.9, 1.8 Hz, 1H, H-C_{-4}), 4.68 (dd, *J* = 7.9, 2.6 Hz, 1H, H-C_{-3}), 4.75 (ddd, *J* = 6.4, 5.5, 2.3 Hz, 1H, H-C_{-6}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.1 (3C, 3 X $CHMe_{2\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 24.1 (1C, $CH_{3\ Isopropylidene}$), 25.4 (1C, $CH_{3\ Isopropylidene}$), 25.9 (1C, $CH_{3\ Isopropylidene}$), 26.8 (1C, $CH_{3\ Isopropylidene}$), 37.7 (1C, $CH_{3\ OMs}$), 38.5 (1C, $CH_{3\ OMs}$), 62.4 (1C, C_{-7}), 67.9 (1C, C_{-5}), 69.1 (1C, CH_2OMs), 70.4 (2C, C_{-2}, C_{-4}), 71.0 (1C, C_{-3}), 82.2 (1C, C_{-6}), 101.4 (1C, C_{-1}), 109.8 (1C, $C_{q\ Isopropylidene}$), 110.0 (1C, $C_{q\ Isopropylidene}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 633.2449; $[C_{25}H_{48}O_{12}S_2Si+H]^+$ requires 633.2435.

(R)-1-((3aR,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-3a-((((trifluoromethyl)sulfonyl)oxy)methyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-(triisopropylsilyl)oxy)ethyl trifluoromethanesulfonate (422)

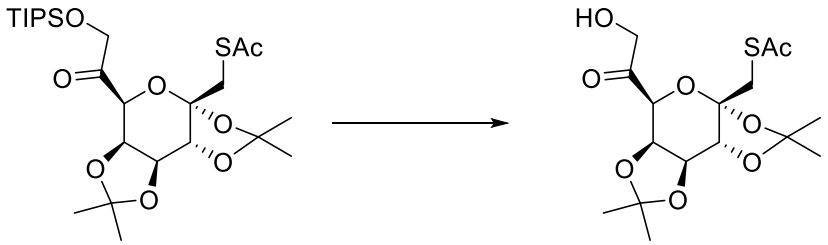


419 **422**

Trifluoromethanesulfonic anhydride (0.075 ml, 0.45 mmol, 2.4 equiv.) was added dropwise over 15 minutes to a stirred solution of **419** (0.089 g, 0.19 mmol) and pyridine (0.06 ml, 0.75 mmol, 4 equiv.) in dry DCM (1.9 ml) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C and monitored by TLC until full consumption of the starting material was observed. The mixture was diluted with DCM and was treated with ice-cold water (ca. 10 ml), and the layers were separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were washed with water, saturated aqueous copper sulfate solution, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* afforded the title compound as a pure yellow oil (0.131 g, 99%); $[\alpha]_D^{26}$ = -6.5 (c 0.93 in CHCl3); IR νmax (film)/cm-1: 2945, 2869, 1416, 1385, 1210, 1145, 1071, 920; 1H NMR (500 MHz, Chloroform-d) δ 1.05 – 1.09 (m, 18H, 6 X CH3 TIPS), 1.09 – 1.16 (m, 3H, 3 X H-CMe2 TIPS), 1.34 (s, 3H, $CH_{3\ Isopropylidene}$), 1.39 (s, 3H, $CH_{3\ Isopropylidene}$), 1.43 (s, 3H, $CH_{3\ Isopropylidene}$), 1.54 (s, 3H, $CH_{3\ Isopropylidene}$), 4.00 (dd, J = 12.2, 5.7 Hz, 1H, H-C-7), 4.20 (dd, J = 12.2, 2.5 Hz, 1H, H'-C-7), 4.28 (dd, J = 5.7, 1.9 Hz, 1H, H-C-5), 4.31 (d, J = 2.7 Hz, 1H, H-C-2), 4.34 (dd, J = 7.9, 1.9 Hz, 1H, H-C-4), 4.37 (d, J = 10.6 Hz, 1H, 1H of CH2OTf), 4.50 (d, J = 10.6 Hz, 1H, 1H of CH2OTf), 4.70 (dd, J = 7.9, 2.7 Hz, 1H, H-C-3), 5.07 (td, J = 5.7, 2.5 Hz, 1H, H-C-6); 13C NMR (101 MHz, CDCl3) δ 12.1(3C, 3 X CHMe2 TIPS), 18.0 (3C, 3 X CH3 TIPS), 18.0 (3C, 3 X CH3 TIPS), 23.7 (1C, CH3 Isopropylidene), 25.0 (1C, CH3 Isopropylidene), 25.6 (1C, CH3 Isopropylidene), 26.7 (1C, CH3 Isopropylidene), 61.8 (1C, C-7), 67.8 (1C, C-5), 69.9 (1C, C-4), 70.5 (1C, C-2), 70.6 (1C, C-3), 74.1 (1C, CH2OTf), 87.6 (1C, C-6), 100.6 (1C, C-1), 110.1 (1C, Cq Isopropylidene), 110.5 (1C, Cq Isopropylidene); 19F

NMR (471 MHz, CDCl3) δ -74.38, -74.93; HRMS (ASAP-TOF) m/z found for [M+H]+: 741.1870; [C25H42O12F6S2Si+H]+ requires 741.1870.

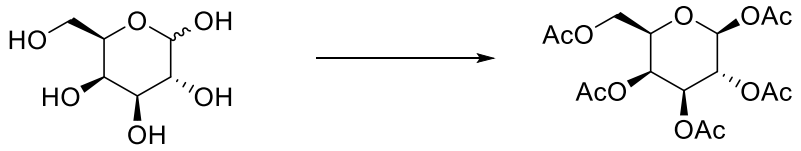
S-(((3aS,5S,5aR,8aS,8bR)-5-(2-hydroxyacetyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (427)



394 **427**

Compound **394** (0.084 g, 0.16 mmol), was dissolved in 80% Acetic acid (0.20 ml). The stirred reaction mixture was heated at 70 ^{o}C for 72 hours, after which the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 1:1) to afford the title compound as a colourless oil (0.039 g, 66%); $[\alpha]_D^{25}$ = -80.3 (c 1.17 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3496, 2890, 2937, 1731, 1698, 1211, 1070; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.30 (s, 3H, CH_3 Isopropylidene), 1.40 (s, 3H, CH_3 Isopropylidene), 1.47 (s, 3H, CH_3 Isopropylidene), 1.50 (s, 3H, CH_3 Isopropylidene), 2.39 (s, 3H, CH_3 Thioacetate), 3.31 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 3.52 (d, *J* = 13.8 Hz, 1H, 1H of CH_2SAc), 4.25 (d, *J* = 2.7 Hz, 1H, H-C$_2$), 4.36 (d, *J* = 20.5 Hz, 1H, H-C$_7$), 4.41 (d, *J* = 2.2 Hz, 1H, H-C$_5$), 4.55 (dd, *J* = 7.8, 2.2 Hz, 1H, H'-C$_4$), 4.56 (d, *J* = 20.5 Hz, 1H, H'-C$_7$), 4.65 (dd, *J* = 7.8, 2.7 Hz, 1H, H-C$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.1 (1C, CH_3 Isopropylidene), 24.9 (1C, CH_3 Isopropylidene), 25.7 (1C, CH_3 Isopropylidene), 26.5 (1C, CH_3 Isopropylidene), 30.5 (1C, CH_3 Thioacetate), 37.5 (1C, CH_2SAc), 68.0 (1C, C$_7$), 71.1 (1C, C$_3$), 72.1 (1C, C$_4$), 73.2 (1C, C$_2$), 74.6 (1C, C$_5$), 103.0 (1C, C$_1$), 109.3 (1C, C_q Isopropylidene), 110.2 (1C, C_q Isopropylidene), 194.3 (1C, C_q Thioacetate), 208.7 (1C, C$_6$ Ketone); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 394.1528; $[C_{16}H_{26}O_8S+NH_4]^+$ requires 394.1530.

(2S,3R,4S,5S,6R)-6-(acetoxymethyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (β-63)[8–11]

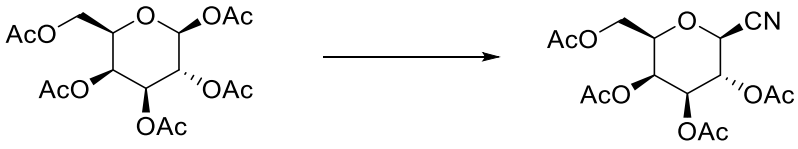


433 **β-63**

Sodium acetate (2.0 g, 24.4 mmol, 1.09 equiv.) was added to acetic anhydride (40 ml) at rt. The mixture was then heated to 120 °C and stirred for 30 minutes. Then D-galactose **433** (4.0 g, 22.2 mmol) was added portion wise to the stirred solution. The reaction mixture was stirred at 120 °C for 3 hours. The mixture was then cooled and poured into ice-cold water (ca. 40 ml), then neutralized with saturated aqueous $NaHCO_3$. The mixture was then extracted with DCM (ca. 200 X 3). The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude colourless residue. Recrystallization from hexane/ethyl acetate (2:1) afforded the title compound as a colourless solid (5.563 g, 64%); mp 140 – 143 °C [lit. 143-144 °C],[8] [lit. 139-142 °C][9]; $[\alpha]_D^{22}$ = +22.7 (c 1.04 in $CHCl_3$) [lit. $[\alpha]_D^{20}$ = +22 (c 1 in $CHCl_3$)],[10] [lit. $[\alpha]_D^{23.5}$ = +27.1 (c 1.03 in $CHCl_3$)][11]; IR ν_{max} (film)/cm^{-1}: 2984, 2941, 1752, 1223, 1067; ^{1}H NMR (400 MHz, Chloroform-d) δ 1.99 (s, 3H, $CH_{3\ Acetate}$), 2.04 (s, 6H, 2 X $CH_{3\ Acetate}$), 2.12 (s, 3H, $CH_{3\ Acetate}$), 2.16 (s, 3H, $CH_{3\ Acetate}$), 4.05 (ddd, J = 7.1, 6.1, 1.2 Hz, 1H, H-C_{-5}), 4.09-4.18 (m, 2H, H-C_{-7}, H'-C_{-7}), 5.07 (dd, J = 10.4, 3.4 Hz, 1H, H-C_{-3}), 5.33 (dd, J = 10.4, 8.3 Hz, 1H, H-C_{-2}), 5.42 (dd, J = 3.4, 1.2 Hz, 1H, H-C_{-4}), 5.70 (d, J = 8.3 Hz, 1H, H-C_{-1}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6 (1C, $CH_{3\ Acetate}$), 20.7 (1C, $CH_{3\ Acetate}$), 20.7 (2C, 2 X $CH_{3\ Acetate}$), 20.9 (1C, $CH_{3\ Acetate}$), 61.1 (1C, C_{-6}), 66.9 (1C, C_{-4}), 67.9 (1C, C_{-2}), 70.9 (1C, C_{-3}), 71.8 (1C, C_{-5}), 92.2 (1C, C_{-1}), 169.1 (1C, $C_{q\ Acetate}$), 169.5 (1C, $C_{q\ Acetate}$), 170.0 (1C, $C_{q\ Acetate}$), 170.2 (1C, $C_{q\ Acetate}$), 170.4 (1C, $C_{q\ Acetate}$).

Data is in agreement with the literature references.[8–11]

((2R,3S,4R,5S,6S)-2-(acetoxymethyl)-6-cyanotetrahydro-2H-pyran-3,4,5-triyl triacetate (64)[12,13]

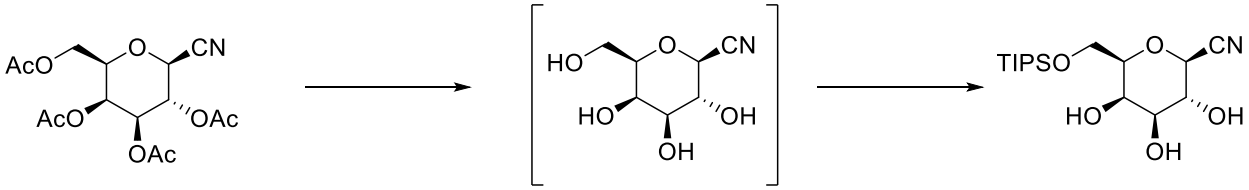


β-**63** **64**

TMSCN (9.6 ml, 76. 7 mmol, 3 equiv.) was added dropwise to a stirred solution of compound **β-63** (10.0 g, 25.6 mmol) in anhydrous nitromethane (42 ml), which formed a brown solution. After heating the solution to 35-37 ^{o}C, $BF_3.OEt_2$ (3.5 ml, 28.4 mmol, 1.1 equiv.) was added dropwise. The dark brown solution was stirred at 35-37 ^{o}C for 2 hours. The mixture was then concentrated *in vacuo*. The brown residue was dissolved in DCM and washed with water, then saturated aqueous $NaHCO_3$ three times, water, brine, and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* gave a crude brown residue. Recrystallization from methanol furnished **64** as yellow crystals (6.166 g, 67%); mp 166 -168 ^{o}C [lit. 169-170 ^{o}C][12,13]; $[\alpha]_D^{22}$ = +36.0 (c 1.10 in $CHCl_3$) [lit. $[\alpha]_D^{18}$ = +34.1 (c 1.33 in $CHCl_3$)],[12] [lit. $[\alpha]_D^{25}$ = +35.7 (c 3.74 in $CHCl_3$)][13]; IR ν_{max} (film)/cm^{-1}: 2984, 2941, 1752, 1223, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H, $CH_{3\ Acetate}$), 2.06 (s, 3H, $CH_{3\ Acetate}$), 2.12 (s, 3H, $CH_{3\ Acetate}$), 2.18 (s, 3H, $CH_{3\ Acetate}$), 3.91 – 3.97 (m, H-C_{-5}), 4.12 (d, *J* = 6.4 Hz, 2H, H-C_{-6}, H'-C_{-6}), 4.28 (d, *J* = 10.2 Hz, 1H, H-C_{-1}), 5.00 (dd, *J* = 10.2, 3.2 Hz, 1H, H-C_{-3}), 5.40-5.45 (m, 1H, H-C_{-4}), 5.53 (t, *J* = 10.2 Hz, 1H, H-C_{-2}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6 (2C, 2 X $CH_{3\ Acetate}$), 20.7 (1C, $CH_{3\ Acetate}$), 20.8 (1C, $CH_{3\ Acetate}$), 61.4 (1C, C_{-6}), 66.2 (1C, C_{-2}), 66.9 (1C, C_{-4}), 67.0 (1C, C_{-1}), 71.0 (1C, C_{-3}), 75.6 (1C, C_{-5}), 114.5 (1C, $C_{q\ Nitrile}$), 168.9 (1C, $C_{q\ Acetate}$), 170.0 (1C, $C_{q\ Acetate}$), 170.1 (1C, $C_{q\ Acetate}$), 170.5 (1C, $C_{q\ Acetate}$); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 375.1398; $[C_{15}H_{19}NO_9+NH_4]^+$ requires 375.1398.

Data is in agreement with the literature references.[12,13]

(2S,3R,4R,5R,6R)-3,4,5-trihydroxy-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-carbonitrile (436b)

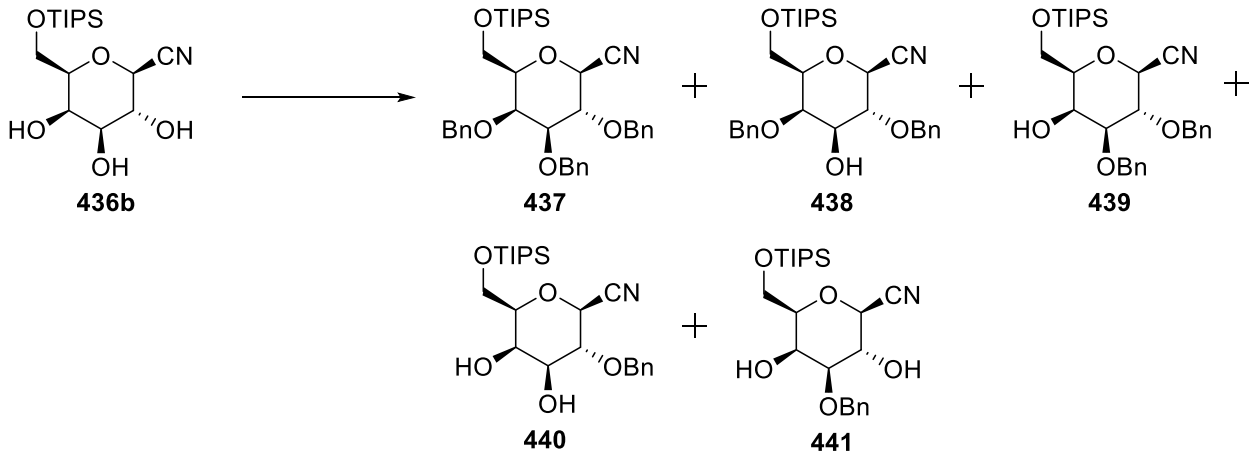


64 **435** **436b**

A solution of methanolic sodium methoxide (69 ml, 0.1M in MeOH, 6.9 mmol) was added dropwise to a stirred solution of **64** (13.970 g, 39.1 mmol) in dry methanol (30 ml). The mixture was stirred at rt for 2 h. The mixture was then concentrated *in vacuo* affording **435** (7.394 g) in an unpurified state, which was then used directly in the next step without any purification.

Crude **435** (7.394 g) was then dissolved in dry DMF (143 ml) and cooled to 0 ºC. To this stirred solution was added imidazole (2.66 g, 156.4 mmol, 4 equiv.) and TIPSCl (16.7 ml, 78.2 mmol, 2 equiv.). The mixture was stirred for 72 hours at rt and was then concentrated *in vacuo*. The residue was then treated with water and DCM, and the layers were then separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure furnished a colourless crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 1:1) to yield **436b** as a pure colourless oil (5.677 g, 42%); $[\alpha]_D^{24}$ = +28.1 (c 1.01 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3391, 2942, 2892, 2867, 1463, 1142, 1073; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 – 1.03 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.17 – 1.09 (m, 3H, H-$CMe_{2\ TIPS}$), 2.93 (br, 3H, 3 X OH), 3.44 – 3.49 (m, 1H, H-C_{-5}), 3.52 (dd, *J* = 8.6, 3.1 Hz, 1H, H-C_{-3}), 4.11 – 3.96 (m, 4H, H-C_{-6}, H'-C_{-6}, H-C_{-1}, H-C_{-2}), 4.19 (m, 4.16 – 4.21, 1H, H-C_{-4}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.9 (3C, 3 X $CHMe_{2\ TIPS}$), 17.9 (3C, 3 X $CH_{3\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 63.9 (1C, C_{-6}), 69.0 (C_{-2}), 69.5 (C_{-1}), 69.7 (C_{-4}), 74.6 (C_{-3}), 78.3 (C_{-5}), 116.6 (1C, $C_{Q\ Nitrile}$); HRMS (NSI-FTMS) *m/z* found for $[M+H]^+$: 346.2045; $[C_{16}H_{31}NO_5Si+H]^+$ requires 346.2044.

2S,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-carbonitrile (437)



Sodium hydride (0.045 g, 1.86 mmol, 3.7 equiv.) was added in one portion to a stirred solution of **436b** (0.174 g, 0.50 mmol) in dry DMF (2 ml) at 0 ºC. The mixture was then stirred at 0 ºC for a further 30 minutes. Then benzyl bromide (0.27 ml, 2.27 mmol, 4.5 equiv.), was added dropwise to the mixture. The mixture was then stirred for 72 hours at rt, then quenched cautiously with methanol. The mixture was then concentrated under reduced pressure. The residue was treated with water (ca. 10 ml) and EtOAc (ca. 10 ml), and the layers were separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. After Filtration, the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (petrol:EtOAc, 12:1) afforded the title compound **437** as a pure colourless oil (0.140 g, 45%);$[\alpha]_D^{23}$ = +21.0 (c 0.99 in $CHCl_3$);IR ν_{max} (film)/cm^{-1}: 3066, 3032, 2942, 2866, 1497, 1455, 1110; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.01 – 1.06 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.07 – 1.18 (m, 3H, H-$CMe_{2\ TIPS}$), 3.39 (td, *J* = 6.7 1.1 Hz, 1H, H-C_{-5}), 3.51 (dd, *J* = 9.6, 2.8 Hz, 1H, H-C_{-3}), 3.74- 3.83 (m, 2H, H_2-C_{-6}), 3.98 (dd, *J* = 2.8, 1.1 Hz, 1H, H-C_{-4}), 4.03 (d, *J* = 9.6 Hz, 1H, H-C_{-1}), 4.19 (t, *J* = 9.6 Hz, 1H, H-C_{-2}), 4.66 (d, *J* = 11.3 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.73 (d, *J* = 11.9 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.77 (d, *J* = 11.9 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.98 – 5.00 (m, 3H, 3H of $CH_2Ph_{\ Bn}$), 7.27 – 7.41 (m, 15H, 15 X H-C_{Ar}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.0 (3C, 3 X CH-$Me_{2\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 61.5 (1C, C_{-6}), 68.1 (1C, C_{-1}), 72.9 (1C, $CH_{2\ Bn}$), 73.4 (1C, C_{-4}), 75.1 (1C, $CH_{2\ Bn}$), 76.1 (1C, $CH_{2\ Bn}$), 76.5 (1C, C_{-2}), 80.1 (1C, C_{-5}), 83.2 (1C, C_{-3}), 117.0 (1C, $C_{q\ Nitrile}$), 127.8 (2C, 2 X C_{AR}), 127.8 (1C, C_{AR}), 128.0 (1C, C_{AR}),

128.1 (1C, C_{AR}), 128.3 (1C, C_{AR}), 128.5 (2C, 2 X C_{AR}), 128.6 (2C, 2 X C_{AR}), 128.7 (2C, 2 X C_{AR}), 128.7 (2C, 2 X C_{AR}), 137.4 (1C, $C_{q\ AR}$), 138.0 (1C, $C_{q\ AR}$), 138.5 (1C, $C_{q\ AR}$); HRMS (NSI-FTMS) *m/z* found for $[M+H]^+$: 616.3446; $[C_{37}H_{49}NO_5Si+H]^+$ requires 616.3453.

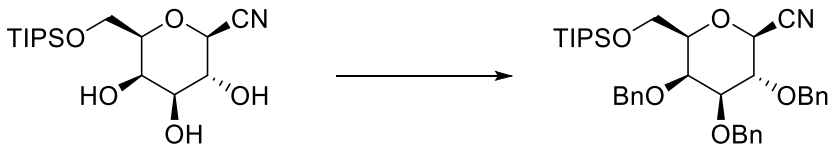
Further elution (petrol:EtOAc, 7:1) gave compound **438** as a pure colourless oil (0.017 g, 6%); $[\alpha]_D^{23}$ = +29.5 (c 0.84 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3501, 3096, 3073, 3033, 2943, 2866, 1497, 1456, 1210, 1108; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 – 1.08 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.09 – 1.17 (m, 3H, H-$CMe_{2\ TIPS}$), 3.45 – 3.51 (m, 1H, H-C_{-5}), 3.60 (dd, *J* = 9.1, 3.0 Hz, 1H), 3.81 – 3.90 (m, 3H, H_2-C_{-6}, H-C_{-2}), 3.96 – 4.01 (m, 2H, H-C_{-1}, H-C_{-4}), 4.73 (d, *J* = 11.5 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.81 (d, *J* = 11.5 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.84 (d, *J* = 10.8 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.92 (d, *J* = 10.8 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 7.43 – 7.29 (m, 10H, 10 X H-C_{AR}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.0 (3C, 3 X $CHMe_{2\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 61.2 (1C, C_{-6}), 67.7 (1C, C_{-1} or C_{-4}), 74.9 (1C, C_{-3}), 75.6 (1C, $CH_{2\ Bn}$), 75.6 (1C, $CH_{2\ Bn}$), 75.79 (1C, C_{-4} or C_{-1}), 77.5 (1C, C_{-2}) 79.9 (1C, C_{-5}), 117.0 (1C, $C_{q\ Nitrile}$), 128.1 (2C, 2 X C_{AR}), 128.3 (1C, C_{AR}), 128.5 (1C, C_{AR}), 128.7 (2C, 2 X C_{AR}), 128.8, 128.8 (2C, 2 X C_{AR}), 137.3 (1C, $C_{q\ AR}$), 138.2 (1C, $C_{q\ AR}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 526.2990; $[C_{30}H_{43}NO_5Si+H]^+$ requires 526.2989.

439 was also isolated as a pure colourless oil (0.009 g, 3%); $[\alpha]_D^{23}$ = +7.5 (c 1.01 in $CHCl_3$);IR ν_{max} (film)/cm^{-1}: 3480, 3090, 3065, 3032, 2943, 2866, 1463, 1455, 1211, 1105; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.02 – 1.08 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.09 – 1.16 (m, 3H, H-$CMe_{2\ TIPS}$), 2.97 (br, 1H, OH), 3.37 (ddd, *J* = 6.0, 4.7, 1.1 Hz, 1H, H-C_{-5}), 3.47 (dd, *J* = 8.9, 3.0 Hz, 1H, H-C_{-3}), 3.91 (dd, *J* = 10.3, 4.7 Hz, 1H, H-C_{-6}), 3.99 (dd, *J* = 10.4, 6.0, 1H, H'-C_{-6}), 4.02 (d, *J* = 10.1 Hz, 1H, H-C_{-1}), 4.10 (dd, *J* = 10.1, 8.9 Hz, 1H, H-C_{-2}), 4.13 – 4.15 (m, 1H, H-C_{-4}), 4.75 (s, 2H, $CH_2Ph_{\ Bn}$), 4.90 (s, 2H, $CH_2Ph_{\ Bn}$), 7.29 – 7.41 (m, 10H, 10 X H-C_{-AR}).^{13}C NMR (126 MHz, $CDCl_3$) δ 12.0 (3C, 3 X $CHMe_{2\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 62.9 (1C, C_{-6}), 66.8 (1C, C_{-4}), 68.0 (1C, C_{-1}) , 72.3 (1C, $CH_{2\ Bn}$), 75.9 (1C, C_{-2}), 76.2 (1C, $CH_{2\ Bn}$), 78.8 (1C, C_{-5}), 81.6 (1C, C_{-3}), 116.9 (1C, $C_{q\ Nitrile}$), 128.0 (2C, 2 X C_{AR}), 128.3 (1C, C_{AR}), 128.3 (1C, C_{AR}), 128.7 (4C, 4 X C_{AR}), 128.8 (2C, 2 X C_{AR}), 137.3 (1C, $C_{q\ AR}$), 137.6 (1C, $C_{q\ AR}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 526.2991; $[C_{30}H_{43}NO_5Si+H]^+$ requires 526.2989.

Further elution (petrol:EtOAc, 3:1) gave compound **440** as a pure colourless solid (0.005 g, 2%); $[\alpha]_D^{23}$ = +18.6 (c 0.99 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3432, 3065, 3033, 2943, 2890, 2867, 1498, 1463, 1367, 1212, 1108; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.04 – 1.09 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.09 – 1.17 (m, 3H, H-$CMe_{2\ TIPS}$), 3.40 – 3.43 (m, 1H, H-C_{-5}), 3.53 (br, 1H, OH), 3.57 (dd, *J* = 8.8, 3.2 Hz, 1H, H-C_{-3}), 3.91 – 3.95 (m, 1H, H-C_{-2}), 3.99 (dd, *J* = 10.8, 4.3 Hz, 1H, H-C_{-6}), 4.01 (d, *J* = 10.0 Hz, 1H, H-C_{-1}), 4.05 (dd, *J* = 10.8, 5.1 Hz, 1H, H'-C_{-6}), 4.15 (dd, *J* = 3.2, 1.0 Hz, 1H, H-C_{-4}), 4.88 (d, *J* = 10.9 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.95 (d, *J* = 10.9 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 7.31 – 7.35 (m, 1H, H-C_{AR}), 7.36 – 7.40 (m, 2H, 2 X H-C_{AR}), 7.41 – 7.44 (m, 2H, 2 X H-C_{-AR}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.9 (3C, 3 X $CHMe_{2\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 63.9 (1C, C_{-6}), 67.6 (1C, C_{-1}), 69.8 (1C, C_{-4}), 74.7 (1C, C_{-3}), 75.7 (1C, $CH_{2\ Bn}$), 77.1 (1C, C_{-2}), 78.1 (1C, C_{-5}), 117.0 (1C, $C_{q\ Nitrile}$), 128.5 (1C, C_{AR}) 128.6 (2C, 2 X C_{AR}), 128.8 (2C, 2 X C_{AR}), 137.4 (1C, $C_{q\ AR}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 436.2518; $[C_{23}H_{37}NO_5Si+H]^+$ requires 436.2519.

441 was also isolated as a pure colourless solid (0.009 g, 4%); $[\alpha]_D^{23}$ = +13.9 (c 0.66 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3450, 3070, 3032, 2943, 2895, 2866, 1497, 1463, 1367, 1100; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 – 1.08 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.09 – 1.15 (m, 3H, H-$CMe_{2\ TIPS}$) 2.65 (br, 1H, OH), 2.90 (br, 1H, OH), 3.34 (dd, *J* = 9.0, 3.0 Hz, 1H, H-C_{-3}), 3.39 – 3.43 (m, 1H, H-C_{-5}), 3.91 (dd, *J* = 10.3, 4.7 Hz, 1H, H-C_{-6}), 3.96 – 4.04 (m, 2H, H'-C_{-6}, H-C_{-1}), 4.14 – 4.21 (m, 2H, H-C_{-4}, H-C_{-2}), 4.69 (d, *J* = 11.9 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.78 (d, *J* = 11.9 Hz, 1H, , 1H of $CH_2Ph_{\ Bn}$), 7.30 – 7.41(m, 5H, 5 X H-C_{-AR}). ^{13}C NMR (101 MHz, $CDCl_3$) δ12.0 (3C, 3 X CH-$Me_{2\ TIPS}$). 18.0 (3C, 3 X $CH_{3\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 62.9 (1C, C_{-6}), 66.3 (1C, C_{-4}), 68.3 (1C, C_{-2}), 69.1 (1C, C_{-1}), 72.2 (1C, $CH_{2\ Bn}$), 79.0 (1C, C_{-5}), 81.4 (1C, C_{-3}), 116.4 (1C, $C_{q\ Nitrile}$), 128.1 (2C, 2 X C_{AR}), 128.5 (1C, C_{AR}), 128.9 (2C, 2 X C_{AR}), 137.5 (1C, $C_{q\ AR}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 436.2521; $[C_{23}H_{37}NO_5Si+H]^+$ requires 436.2519.

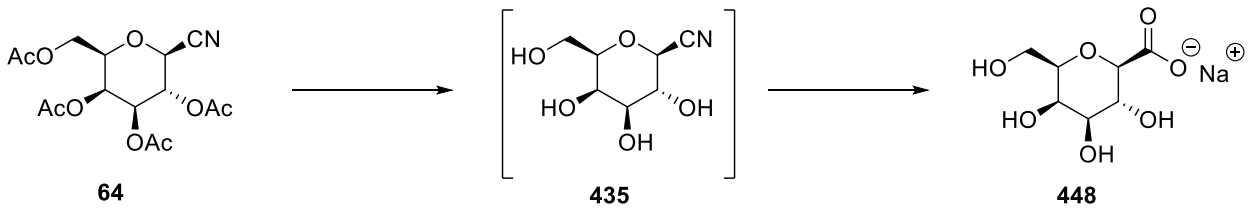
(2S,3R,4R,5R,6R)-3,4,5-trihydroxy-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-carbonitrile (437)



436b **437**

Sodium hydride (0.377 g, 15.69 mmol, 4.95 equiv.) in one portion was added to a stirred solution of **436b** (1.096 g, 3.17 mmol) in dry THF (12.7 ml) at 0 ^{o}C. The mixture was then stirred at 0 ^{o}C for a further 30 minutes. Then, after the dropwise addition of benzyl bromide (1.7 ml,14.30 mmol, 4.5 equiv.), TBAI (0.094 g, 0.25 mmol, 0.08 equiv.) was added. The mixture was then stirred for 72 hours at rt, then quenched cautiously with methanol. The mixture was then concentrated *in vacuo*. The residue was treated with water (ca. 50 ml) and EtOAc (ca. 50 ml). The layers were separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. After Filtration, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 12:1) to furnish **437** as a pure colourless oil (1.358 g, 70%).

Sodium (2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-carboxylate (448)[14]

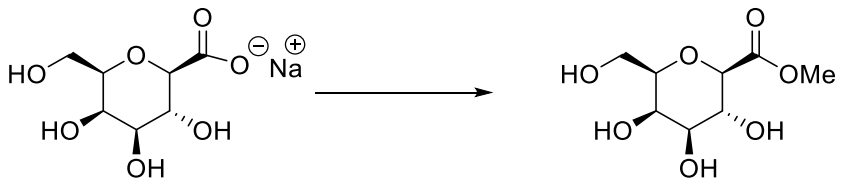


A solution of methanolic sodium methoxide (7.3 ml, 0.73 mmol, 0.1 M in methanol, 0.18 equiv.) was added dropwise to a stirred solution of **64** (1.449 g, 4.06 mmol) in dry methanol (3.1 ml). The mixture was stirred at rt for 2 h. The mixture was then concentrated *in vacuo* affording crude **435** (0.764 g), which was then used directly in the next step without any purification.

Crude **435** (0.764 g) was then dissolved in 12.5% aqueous NaOH (18 ml). The stirred solution was refluxed for 3 hours. After the brown reaction mixture was cooled to rt, water (60 ml) was added. The solution was then acidified with Amberlite IR-120 (H^+-form) and filtered. The filtrate was evaporated under reduced pressure to furnish **448** as a colourless solid (0.969 g, 60% over two steps); $[\alpha]_D^{22}$ = +75.8 (c 0.95 in H_2O) [lit. $[\alpha]_D^{25}$ = +51.8 (c 1.03 in H_2O)][14]; IR ν_{max} (film)/cm^{-1}: 3391, 2918, 1725, 1091; ^{1}H NMR (500 MHz, D_2O) δ 3.64 – 3.84 (m, 6H, H-C_{-1}, H-C_{-2}, H-C_3, H-C_5, H-C_{-6}, H'-C_{-6}), 3.95 (bd, *J* = 3.3 Hz, H-C_{-4}). ^{13}C NMR (126 MHz, D_2O; internal standard, methanol) δ 61.9 (1C, C_{-6}), 69.7 (1C, C_{-2}), 69.7 (1C, C_{-4}), 74.5 (1C, C_{-3}), 79.0 (1C, C_{-5}), 80.1 (1C, C_{-1}), 177.0 (1C, $C_{q\ carboxylate}$); HRMS (NSI-FTMS) *m/z* found for $[M-Na]^-$: 207.0510; $[C_7H_{12}O_7\text{-}Na]^-$ requires 207.0510.

Data is in agreement with the literature reference.[14]

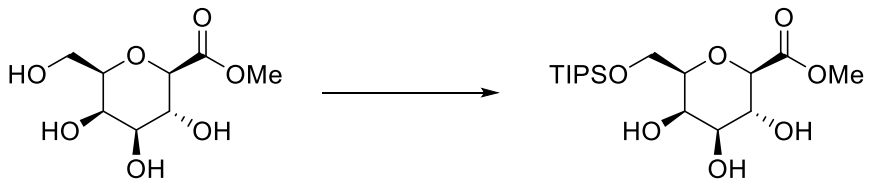
(2R,3R,4S,5R,6R)-methyl 3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-carboxylate (446)[15,16]



Acetyl chloride (1.24 ml, 17.4 mmol, 7.15 equiv.) was added dropwise over 10 minutes to dry methanol (7.5 ml) in a 3-neck round bottom flask fitted with a condenser at 0 °C and was stirred for 5 minutes. Compound **448** (0.969 g, 2.43 mmol) was added in one portion to the stirred solution. The solution was then heated under reflux for 72 hours. The mixture was then concentrated *in vacuo* furnishing a crude brown solid. The crude residue was purified by trituration with EtOAc affording the title compound as a pure brown solid (0.537 g, quant.); mp 121 – 122 °C [lit. 121 – 123 °C][15]; $[\alpha]_D^{22}$ = -33.8 (c 1.30 in H_2O) [lit. $[\alpha]_D^{20}$ = -32 (c 0.12 in H_2O)][15]; IR ν_{max} (film)/cm^{-1}: 3347, 2924, 2854, 1722, 1251, 1089; ^1H NMR (400 MHz, Deuterium Oxide) δ 3.70 – 3.86 (m, 5H, H-C_{-3}, H-C_{-4}, H-C_{-5}, H-C_{-6}, H'-C_{-6}), 3.87 (s, 3H, $CH_{3\ Ester}$), 3.97 – 4.05 (m, 2H, H-C_{-2}, H-C_{-1}); ^{13}C NMR (101 MHz, D_2O; internal standard, methanol) δ 53.6 (1C, $CH_{3\ Ester}$), 61.7 (1C, C_{-6}), 69.0 (1C, C_{-2}), 69.3 (1C, C_{-4}), 74.1 (1C, C_{-3}), 79.1 (1C, C_{-1}), 79.6 (1C, C_{-5}), 172.1 (1C, $C_{q\ Ester}$); HRMS (NSI-FTMS) *m/z* found for $[M+H]^+$: 223.0814; $[C_8H_{14}O_7+H]^+$ requires 223.0812.

Data is in agreement with the literature references.[15,16]

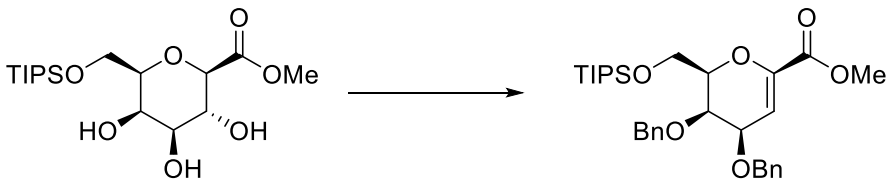
2R,3R,4S,5R,6R)-methyl 3,4,5-trihydroxy-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-carboxylate (449)



446 **449**

To a solution of **446** (0.338 g, 1.52 mmol) in dry DMF (5.6 ml) at 0 ^{o}C, was added imidazole (0.414 g, 6.08 mmol, 4 equiv.), then TIPSCl (0.65 ml, 3.04 mmol, 2 equiv.) dropwise. The mixture was stirred for 72 hours at rt and then concentrated *in vacuo*. The residue was then treated with water and DCM, and the layers were then separated. The aqueous layer was then extracted with DCM twice. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* furnished a colourless crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 1:2) to yield **449** as a pure colourless oil (0.141 g, 24%); $[\alpha]_D^{23}$ = +16.3 (c 0.81 in $CHCl_3$);IR ν_{max} (film)/cm^{-1}: 3390, 2944, 2891, 2867, 1739, 1244, 1105, 1071; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 – 1.03 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.16 – 1.08 (m, 3H, H-$CMe_{2\ TIPS}$), 3.16 (br, 2H, 2 X OH), 3.41 (br, 1H, OH), 3.54 (ddd, *J* = 6.6, 4.8, 1.2 Hz, 1H, H-C_{-5}), 3.61 (dd, *J* = 9.2, 3.3 Hz, 1H, H-C_{-3}), 3.78 – 3.82 (m, 4H, $CH_{3\ Ester}$, H-C_{-1}), 3.95 (dd, *J* = 10.2, 4.8 Hz, 1H, H-C_{-6}), 4.05 – 3.98 (m, 2H, H-C_{-6}, H-C_{-2}), 4.16 (dd, *J* = 3.3, 1.2 Hz, 1H, H-C_{-4}). ^{13}C NMR (101 MHz, $CDCl_3$) δ12.0 (3C, 3 X $CHMe_{2\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 18.0 (3C, 3 X $CH_{3\ TIPS}$), 52.8 (1C, $CH_{3\ Ester}$), 62.9 (1C, C_{-6}), 68.8 (1C, C_{-4}), 69.6 (1C, C_{-2}), 74.8 (1C, C_{-3}), 78.1 (1C, C_{-1}), 78.4 (1C, C_{-5}), 170.7 (1C, $C_{q\ Ester}$); HRMS (NSI-FTMS) *m/z* found for $[M+H]^+$: 379.2150; $[C_{17}H_{34}O_7Si+H]^+$ requires 371.2147.

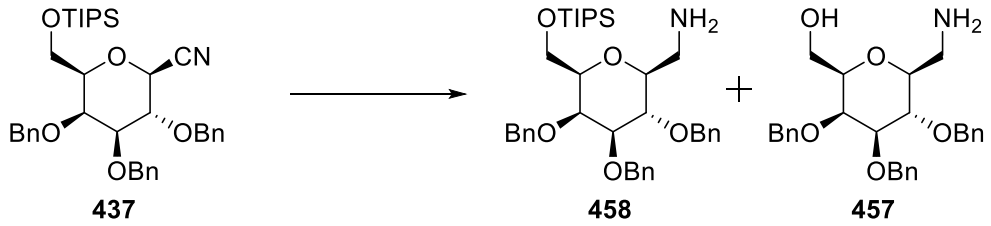
((2R,3R,4R)-methyl 3,4-bis(benzyloxy)-2-(((triisopropylsilyl)oxy)methyl)-3,4-dihydro-2H-pyran-6-carboxylate) (451)



449 **451**

Methyl ester **449** (0.190 g, 0.50 mmol) was dissolved in dry DMF (2 ml). After cooling the stirred solution to 0 ºC, sodium hydride (0.060 g, 2.48 mmol, 4.95 equiv.) was added in one portion. The mixture was stirred at 0 ºC for a further 30 minutes. Then, after the dropwise addition of benzyl bromide (1.7 ml,14.30 mmol, 4.5 equiv.), TBAI (0.094 g, 0.25 mmol, 0.08 equiv.) was added. The mixture was then stirred for 72 hours at rt, then quenched cautiously with methanol. The mixture was then concentrated under reduced pressure. The residue was treated with water (ca. 20 ml) and EtOAc (ca. 20 ml), and the layers were separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. After Filtration, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 10:1) to furnish glycal **451** as a pure colourless oil (0.160 g, 59%); $[\alpha]_D^{23}$ = +46.8 (c 0.88 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3089, 3064, 3031, 2943, 2890, 2866, 1737, 1651, 1497, 1455, 1285, 1103, 1063; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.04 – 1.10 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.11 – 1.19 (m, 3H, H-$CMe_{2\ TIPS}$), 3.81 (s, 3H, $CH_{3\ Ester}$), 4.00 – 4.12 (m, 3H, H-C_{-6}, H'-C_{-6}, H-C_{-5}), 4.13 – 4.18 (m, 1H, H-C_{-3}), 4.38 – 4.42 (m, 1H, H-C_{-4}), 4.67 (d, *J* = 12.1 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.74 (d, *J* = 12.1 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 4.76 (d, *J* = 11.6 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 5.01 (d, *J* = 11.6 Hz, 1H, 1H of $CH_2Ph_{\ Bn}$), 6.15 (t, *J* = 2.1 Hz, 1H, H-C_{-2}), 7.25 – 7.43 (m, 10H, 10 X H-C_{AR}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.0 (3C, 3 X $CHMe_{2\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 52.4 (1C, $CH_{3\ Ester}$), 61.1 (1C, C_{-6}), 69.3 (1C, C_{-3}), 71.1 (1C, $CH_{2\ Bn}$), 72.9 (1C, C_{-4}), 74.6 (1C, $CH_{2\ Bn}$), 78.5 (1C, C_{-5}), 109.7 (1C, C_{-2}), 127.6 (2C, 2 X C_{AR}), 127.6(1C, C_{AR}), 127.9 (1C C_{AR}), 128.0 (2C, 2 X C_{AR}), 128.3 (2C, 2 X C_{AR}), 128.6 (2C, 2 X C_{AR}), 138.1 (1C, $C_{q\ AR}$), 138.7 (1C, $C_{q\ AR}$), 143.9 (1C, C_{-1}), 162.8 (1C, $C_{q\ Ester}$); HRMS (NSI-FTMS) *m/z* found for $[M+NH_4]^+$: 558.3242; $[C_{31}H_{44}O_6Si+NH_4]^+$ requires 558.3245.

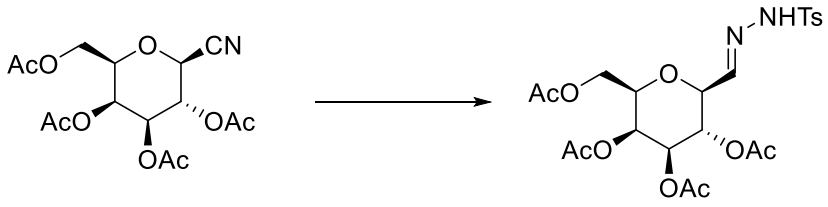
(((2S,3S,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)methanamine) (458) and (((2R,3S,4R,5S,6S)-6-(aminomethyl)-3,4,5-tris(benzyloxy)tetrahydro-2H-pyran-2-yl)methanol) (457)



Red-Al® (52 µl, 3.5 M in toluene, 0.18 mmol, 1 equiv.) was added dropwise to a stirred solution of **437** (0.111 g, 0.18 mmol) in dry toluene (1.8 ml) at -78 ^{o}C. The stirred reaction mixture was then warmed slowly to 0 ^{o}C over 30 minutes. After 90 minutes at 0 ^{o}C, 1M aqueous tartaric acid (ca. 1 ml) was added. After warming to rt, the suspension was poured into Et_2O (ca. 10 ml) and the layers were then separated. The aqueous layer was extracted with Et_2O (2 X 10 ml). The combined organic layers were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and the removal of the solvent under reduced pressure furnished a crude residue. The crude residue was purified by flash column chromatography on silica gel (DCM:methanol, 20:1) to afford **458** as a pure colourless oil (0.005 g, 4%); $[\alpha]_D^{23}$ = +34.5 (c 0.73 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3088, 3064, 3031, 2942, 2865, 1497, 1454, 1364, 1108, 1069; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.05 – 1.11 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.11 – 1.20 (m, 3H, H-$CMe_{2\ TIPS}$), 1.95 – 2.19 (br, 2H, 2 X OH), 2.81 (br, 1H, 1H of CH_2NH_2), 3.07 (s, 1H br, 1H, 1H of CH_2NH_2), 3.20 – 3.31 (m, 1H, H-C_{-1}), 3.42 – 3.48 (m, 1H, H-C_{-5}), 3.67 (dd, *J* = 9.4, 2.8 Hz, 1H, H-C-$_{-3}$), 3.73 – 3.87 (m, 3H, H-C_{-6}, H'-C_{-6}, H-C_{-2}), 4.04 – 4.09 (m, 1H, H-C_{-4}), 4.63 – 4.83 (m, 5H, 5 X CH_2Ph $_{Bn}$), 4.98 (d, *J* = 11.6 Hz, 1H , 1H of CH_2Ph $_{Bn}$), 5.01 (d, *J* = 11.6 Hz, 1H , 1H of CH_2Ph $_{Bn}$), 7.45 – 7.27 (m, 15H, 15 X H-C_{AR}). ^{13}C NMR (101 MHz, $CDCl_3$) δ12.0 (3C, 3 X $CHMe_{2\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 18.2 (3C, 3 X $CH_{3\ TIPS}$), 43.1 (1C, CH_2NH_2), 62.1 (1C, C_{-6}), 72.4 (1C, $CH_{2\ Bn}$), 73.9 (1C, C_{-4}), 74.8 (1C, $CH_{2\ Bn}$), 75.3 (1C, $CH_{2\ Bn}$), 76.5 (1C, C_{-2}), 78.9 (1C, C_{-5}), 80.9 (1C, C_{-1}), 85.1 (1C, C_{-3}), 127.6 (1C, C_{AR}), 127.7 (2C, 2 X C_{AR}), 127.8 (1C, C_{AR}), 127.9 (1C, C_{AR}), 128.1 (2C, 2 X C_{AR}), 128.3 (2C, 2 X C_{AR}), 128.4 (2C, 2 X C_{AR}), 128.6 (4C, 4 X C_{AR}), 138.4 (1C, $C_{q\ AR}$), 138.5 (1C, $C_{q\ AR}$), 139.1 (1C, $C_{q\ AR}$); HRMS (ESI-TOF) *m/z* found for $[M+H]^+$: 620.3776; $[C_{37}H_{53}NO_5Si+H]^+$ requires 620.3771.

Further elution (DCM:methanol, 10:1) gave compound **457** as a pure colourless solid (0.065 g, 78%); mp 122 – 144 ºC; $[\alpha]_D^{23}$ = +60.3 (c 0.69 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3367, 3309, 3088, 3063, 3030, 2917, 2863, 1469, 1454, 1102, 1027; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.44 (br, 2H, 2 X OH), 2.78 (d, *J* = 12.7 Hz, 1H, 1H of CH_2NH_2), 3.06 (d, *J* = 13.7 Hz, 1H, 1H of CH_2NH_2), 3.20 – 3.29 (m, 1H, H-C_{-1}), 3.38 – 3.49 (m, 2H, H-C_{-5}, H-C_{-6}), 3.64 (dd, *J* = 9.4, 2.7 Hz, 1H, H-C_{-3}), 3.68 – 3.81 (m, 2H, H-C_{-2}, H'-C_{-6}), 3.85 – 3.90 (m, 1H, H-C_{-4}), 4.64 (d, *J* = 10.6 Hz, 1H, 1H of CH_2Ph_{Bn}), 4.67 (d, *J* = 11.3 Hz, 1H, 1H of CH_2Ph_{Bn}), 4.73 (d, *J* = 11.7 Hz, 1H, 1H of CH_2Ph_{Bn}), 4.79 (d, *J* = 11.7 Hz, 1H, 1H of CH_2Ph_{Bn}), 4.82 (d, *J* = 10.6 Hz, 1H, 1H of CH_2Ph_{Bn}), 4.83 (d, *J* = 11.3 Hz, 1H, 1H of CH_2Ph_{Bn}), 7.24 – 7.43 (m, 15H, 15 X H-C_{AR}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 43.1 (1C, CH_2NH_2), 62.5 (1C, C_{-6}), 72.6 (1C, $CH_{2\ Bn}$), 73.8 (1C, C_{-4}), 74.4 (1C, $CH_{2\ Bn}$), 75.4 (1C, $CH_{2\ Bn}$), 76.4 (1C, C_{-2}), 79.1 (1C, C_{-5}), 80.6 (1C, C_{-1}), 85.1 (1C, C_{-3}), 127.7 (2C, 2 X C_{AR}), 127.9 (1C, C_{AR}), 128.0 (1C, C_{AR}), 128.0 (1C, C_{AR}), 128.3 (2C, 2 X C_{AR}), 128.5 (2C, 2 X C_{AR}), 128.6 (2C, 2 X C_{AR}), 128.6 (2C, 2 X C_{AR}), 128.7 (2C, 2 X C_{AR}), 138.28 (1C, $C_{q\ AR}$), 138.29 (1C, $C_{q\ AR}$), 138.42 (1C, $C_{q\ AR}$); HRMS (ESI-TOF) *m/z* found for $[M+H]^+$: 464.2438; $[C_{28}H_{33}NO_5Si+H]^+$ requires 464.2438.

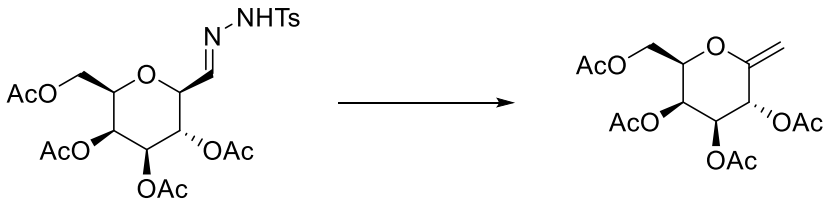
(2R,3S,4R,5S,6S)-2-(acetoxymethyl)-6-((E)-(2-tosylhydrazono)methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (465)[17]



Raney nickel grade 2800 (ca. 12.6 g from an aqueous suspension) was added to a stirred solution of pyridine (47.8 ml), acetic acid (28.6 ml) and water (28.6 ml). To the heterogenous mixture was then added sodium hypophosphite monohydrate (7.48 g, 70.5 mmol, 8.4 equiv.), tosylhydrazide (2.64 g, 14.3 mmol, 1.7 equiv.) and compound **64** (3.0 g, 8.40 mmol). After leaving the reaction for 24 hours, the mixture was filtered through a pad of celite and washed with DCM. The layers of the filtrate were then separated. The aqueous layer was extracted with DCM twice. The combined organic layers were washed with 10% aqueous HCl (ca. 2 X 30 ml), saturated aqueous $NaHCO_3$ solution (ca. 2 X 30 ml), water (ca. 30 ml), brine (ca. 30 ml), and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 3:2) to furnish **465** as a pure colourless solid (3.682 g, 83%); mp 68-70 ^oC; $[\alpha]_D^{26}$ = +10.1 (c 1.27 in $CHCl_3$) [lit. $[\alpha]_D$ = +6 (c 0.97 in $CHCl_3$)][17]; IR ν_{max} (film)/cm^{-1}: 3620, 3198, 2970, 1751, 1371, 1225, 1166, 1056; ^1H NMR (500 MHz, DMSO-d_6) δ 1.66 (s, 3H, $CH_{3\ Acetate}$), 1.90 (s, 3H, $CH_{3\ Acetate}$), 1.98 (s, 3H, $CH_{3\ Acetate}$), 2.10 (s, 3H, $CH_{3\ Acetate}$), 2.37 (s, 3H, $CH_{3\ Tosylate}$), 3.94 (dd, *J* = 11.5, 7.2 Hz, 1H, H-C_{-6}), 3.98 – 4.01 (m, 1H, H'-C_{-6}), 4.14 (dd, *J* = 10.0, 6.7 Hz, 1H, H-C_{-1}), 4.22 (ddd, *J* = 7.2, 5.2, 1.3 Hz, 1H, H-C_{-5}), 4.95 (t, *J* = 10.0 Hz, 1H, H-C_{-2}), 5.22 (dd, *J* = 10.0, 3.5 Hz, 1H, H-C_{-3}), 5.29 (dd, *J* = 3.5, 1.3 Hz, 1H, H-C_{-4}), 7.00 (d, *J* = 6.7 Hz, 1H, $HC{=}N_{\ hydrazone}$), 7.39 – 7.43 (m, 2H, 2 X $H\text{-}C_{AR\ Tosylate}$), 7.65 – 7.69 (m, 2H, 2 X $H\text{-}C_{AR\ Tosylate}$), 11.61 (s, 1H, NH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.4 (1C, $CH_{3\ Acetate}$), 20.7 (1C, $CH_{3\ Acetate}$), 20.8 (1C, $CH_{3\ Acetate}$), 20.8 (1C, $CH_{3\ Acetate}$), 21.7 (1C, $CH_{3\ Tosylate}$), 61.8 (1C, C_{-6}), 67.0 (1C, C_{-2}), 67.6 (1C, C_{-4}), 71.0 (1C, C_{-3}), 74.6 (1C, C_{-5}), 78.4 (1C, C_{-1}), 128.3 (2C, 2 X C_{AR}), 129.9 (2C, 2 X C_{AR}), 135.4 (1C, $C_{q\ AR}$), 144.3 (1C, $C_{q\ AR}$), 144.5 (1C, C_{-1}), 170.1 (1C, $C_{q\ Acetate}$), 170.2 (1C, $C_{q\ Acetate}$), 170.6 (1C, $C_{q\ Acetate}$), 170.7 (1C, $C_{q\ Acetate}$).

Data is in agreement with the literature references.[17]

(2R,3S,4S,5R)-2-(acetoxymethyl)-6-methylenetetrahydro-2H-pyran-3,4,5-triyl triacetate (466)[17]

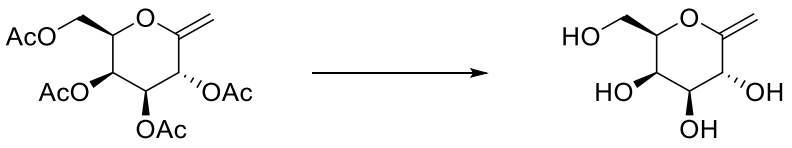


465 **466**

A stirred suspension of sodium hydride (0.582 g, 24.3 mmol, 10 equiv.) in dry 1,4-dioxane (61 ml) was heated under reflux. A solution of compound **465** (1.282 g, 2.43 mmol) in dry 1,4-dioxane (61 ml) was added to this mixture. The suspension was then refluxed for 30 minutes and then cooled to rt. The mixture was then filtered through a pad of celite and washed with DCM. The filtrate was evaporated under reduce pressure to give a crude residue. The crude residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 3:1) to furnish **466** as a pure colourless solid (0.605 g, 72%); $[\alpha]_D^{26}$ = +67.6 (c 0.84 in $CHCl_3$) [lit. $[\alpha]_D$ = +74 (c 1.45 in $CHCl_3$)][1]; IR ν_{max} (film)/cm^{-1}: 2942, 1751, 1666, 1374, 1219, 1085; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.00 (s, 3H, $CH_{3\ Acetate}$), 2.06 (s, 3H, $CH_{3\ Acetate}$), 2.13 (s, 3H, $CH_{3\ Acetate}$), 2.16 (s, 3H, $CH_{3\ Acetate}$), 4.01 (td, *J* = 6.5, 1.5 Hz, 1H, H-C_5), 4.11 – 4.23 (m, 2H, H-C_6, H'-C_6), 4.50 (t, *J* = 1.9 Hz, 1H, H-C=C_{Alkene}), 4.81 (t, *J* = 1.9 Hz, 1H, H'-C=C_{Alkene}), 5.05 (dd, *J* = 10.4, 3.1 Hz, 1H, H-C_3), 5.51 (dd, *J* = 3.1, 1.5 Hz, 1H, H-C_4), 5.68 (dt, *J* = 10.4, 1.9 Hz, 1H H-C_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8 (2C, 2 X $CH_{3\ Acetate}$), 20.8 (1C, $CH_{3\ Acetate}$), 20.9 (1C, $CH_{3\ Acetate}$), 61.7 (1C, C_6), 67.0 (1C, C_2), 67.7 (1C, C_4), 71.4 (1C, C_3), 75.7 (1C, C_5), 96.1 (1C, H_2C=C_{Alkene}), 154.1 (1C, C_1), 169.6 (1C, $C_{q\ Acetate}$), 170.1 (1C, $C_{q\ Acetate}$), 170.2 (1C, $C_{q\ Acetate}$), 170.5 (1C, $C_{q\ Acetate}$).

Data is in agreement with the literature references.[17]

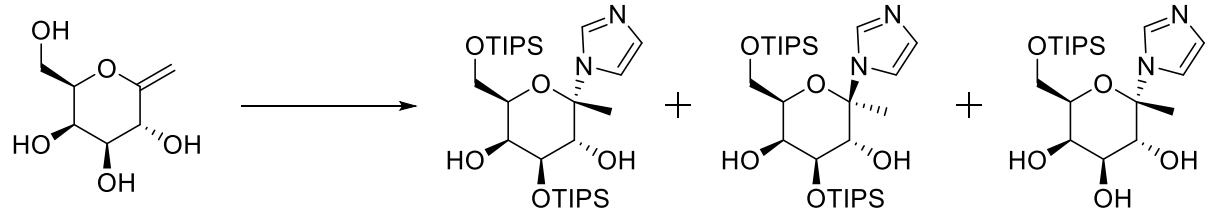
(2R,3R,4S,5R)-2-(hydroxymethyl)-6-methylenetetrahydro-2H-pyran-3,4,5-triol (467)



466 **467**

A solution of methanolic sodium methoxide (9.7 ml, 0.1 M in methanol, 0.97 mmol, 0.18 equiv.) was added dropwise to a stirred solution of **466** (1.850 g, 5.37 mmol) in dry methanol (4 ml). The mixture was stirred at rt and monitored by TLC until full consumption of **466** was observed. The mixture was then concentrated *in vacuo* affording **467** as a colourless solid (0.945 g, quant.); $[\alpha]_D^{25}$ = +86.4 (c 1.06 in H_2O); IR ν_{max} (film)/cm^{-1}: 3480, 3291, 3185, 2910, 1653, 1069; ^1H NMR (500 MHz, DMSO-d_6) δ 3.27 (dd, *J* = 9.6, 3.3 Hz, 1H, H-C_{-3}), 3.42 (td, *J* = 6.0, 1.3 Hz, 1H, H-C_{-5}), 3.54 (d, *J* = 6.0 Hz, 2H, H-C_{-6}, H'-C_{-6}), 3.78 (dd, *J* = 3.3, 1.3 Hz, 1H, H-C_{-4}), 3.97 (dt, *J* = 9.6, 2.0 Hz, 1H, H-C_{-2}), 4.38 (d, *J* = 2.0 Hz, 1H, H-C=C_{Alkene}), 4.49 (d, *J* = 2.0 Hz, 1H, H'-C=C_{Alkene}), 4.69 (br, 1H, OH). ^{13}C NMR (126 MHz, DMSO) δ 60.9 (1C, C_{-6}), 68.3 (1C, C_{-2}), 68.8 (1C, C_{-4}), 74.1 (1C, C_{-3}), 80.4 (1C, C_{-5}), 90.9 (1C, H_2C=C_{Alkene}), 162.4 (1C, C_{-1}); HRMS (NSI-FTMS) *m/z* found for $[M+H]^+$: 177.0756; $[C_7H_{12}O_5+H]^+$ requires 177.0757.

(2S,3R,4S,5S,6R)-2-(1H-imidazol-1-yl)-2-methyl-4-((triisopropylsilyl)oxy)-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-3,5-diol (469) and (2R,3R,4S,5S,6R)-2-(1H-imidazol-1-yl)-2-methyl-4-((triisopropylsilyl)oxy)-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-3,5-diol (470) and (2S,3R,4S,5R,6R)-2-(1H-imidazol-1-yl)-2-methyl-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triol (471)



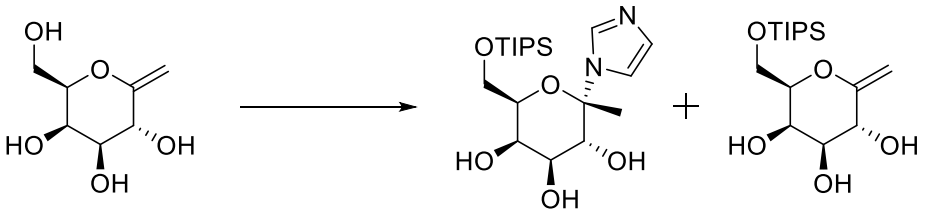
467 **469** **470** **471**

Compound **467** (0.424 g, 2.41 mmol) was dissolved in dry DMF (8.8 ml) and the solution was then cooled to 0 ^{o}C. To this stirred solution was added imidazole (0.656 g, 9.63 mmol, 4 equiv.), then TIPSCl (1.03 ml, 4.82 mmol, 2 equiv.) dropwise. The reaction mixture was stirred at rt for 48 hours. The mixture was then concentrated *in vacuo*. The residue was treated with water (ca. 20 ml) and EtOAc (ca. 20 ml), and the layers were then separated. The aqueous layer was extracted with EtOAc (2 X 20 ml). The combined organic extracts were then washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography (petrol:EtOAc, 1:2) to afford **469** as a pure colourless oil (0.571 g, 43%); mp 118-119 ^{o}C; $[\alpha]_D^{26}$ = +40.0 (c 0.96 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3155, 2943, 2867, 1464, 1101, 1073; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.03 – 1.17 (m, 42H, 6 X H-C$Me_{2\ TIPS}$, 12 X $CH_{3\ TIPS}$,), 1.73 (s, 3H, CH_3), 2.64 (br, 1H, OH), 3.23 (br, 1H, OH), 3.45 (td, *J* = 5.9, 1.3 Hz, 1H, H-C$_{-5}$), 3.88 – 4.00 (m, 4H, H-C$_{-6}$, H'-C$_{-6}$, H-C$_{-3}$, H-C$_{-4}$), 4.18 (d, *J* = 9.8 Hz, 1H, H-C$_{-2}$), 7.06 (br, 1H, H-C$_{AR}$), 7.35 (br, 1H, H-C$_{AR}$), 8.12 (br, 1H, H-C$_{AR}$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.0 (3C, 3 X C$HMe_{2\ TIPS}$), 12.5 (3C, 3 X C$HMe_{2\ TIPS}$), 18.0 (6C, 6 X $CH_{3\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 18.1 (3C, 3 X $CH_{3\ TIPS}$), 29.4 (1C, CH_3), 62.9 (1C, C$_{-6}$), 69.7 (1C, C$_{-4}$), 72.1 (1C, C$_{-3}$), 73.1 (1C, C$_{-5}$), 74.4 (1C, C$_{-2}$), 89.8 (1C, C$_{-1}$), 117.4 (1C, C$_{AR}$), 128.4 (1C, C$_{AR}$), 136.2 (1C, C$_{AR}$); HRMS (NSI-FTMS) *m/z* found for $[M+H]^+$: 557.3795; $[C_{28}H_{56}N_2O_5Si_2+H]^+$ requires 557.3811.

Further elution (petrol:EtOAc, 1:3) gave compound **470** as a pure colourless solid (0.249 g, 19%); $[\alpha]_D^{26}$ = +4.2 (c 1.04 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3569, 3141, 2943, 2892, 2867, 1464, 1383, 1235, 1103, 1071; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.03 – 1.07 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.07 – 1.22 (m, 24H, 6 X $CH_{3\ TIPS}$, 6 X H-$CMe_{2\ TIPS}$), 1.72 (s, 3H, CH_3), 3.78 (d, *J* = 9.4 Hz, H-C_{-2}), 3.80 – 3.83 (m, 1H, H-C_{-5}), 3.87 – 3.92 (m, 2H, H-C_{-6}, H-C_{-3}), 4.04 – 4.09 (m, 2H, H'-C_{-6}, H-C_{-4}), 6.77 (br, 1H, H-C_{AR}), 7.15 (br, 1H, H-C_{AR}), 7.57 (br, 1H, H-C_{AR}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.1 (3C, 3 X $CHMe_{2\ TIPS}$), 12.6 (3C, 3 X $CHMe_{2\ TIPS}$), 18.0 (6C, 3 X $CH_{3\ TIPS}$), 18.1 (6C, 3 X $CH_{3\ TIPS}$), 18.2 (6C, 6 X $CH_{3\ TIPS}$), 62.5 (1C, C_{-6}), 69.2 (C_{-4}), 73.6 (C_{-5}), 73.6 (C_{-3}), 74.2 (C_{-2}), 90.6 (1C, C_{-1}), 116.3 (1C, C_{AR}), 127.8 (1C, C_{AR}), 134.5 (1C, C_{AR}); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 557.3806; $[C_{28}H_{56}N_2O_5Si_2+H]^+$ requires 557.3811.

Further elution (DCM:Methanol, 10:1) gave compound **471** as a pure colourless solid (0.110 g, 11%); mp 144-145 ºC; $[\alpha]_D^{26}$ = +42.4 (c 1.00 in MeOH); IR ν_{max} (film)/cm^{-1}: 3376, 2942, 2866, 1464, 1376, 1219, 10921235, 1103, 1071; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.99 – 1.11 (m, 21H, 6 X $CH_{3\ TIPS}$, 3 X H-$CMe_{2\ TIPS}$), 1.56 (s, 3H, CH_3), 3.18 – 3.22 (m, 1H, H-C_{-5}), 3.44 – 3.51 (m, 1H, H-C_{-3}), 3.68 (ddd, *J* = 4.4, 3.2, 1.2 Hz, 1H, H-C_{-4}), 3.71 – 3.79 (m, 2H, H-C_{-6}, H'-C_{-6}), 3.87 (dd, *J* = 10.4, 5.5 Hz, 1H, H-C_{-2}), 4.69 (d, *J* = 4.4 Hz, 1H, OH), 5.03 (d, *J* = 5.1 Hz, 1H, OH, OH), 6.02 (d, *J* = 5.5 Hz, 1H, OH), 6.87 (t, *J* = 1.1 Hz, 1H, H-C_{AR}), 7.34 (t, *J* = 1.1 Hz, 1H, H-C_{AR}), 7.98 (t, *J* = 1.1 Hz, 1H, H-C_{AR}). ^{13}C NMR (126 MHz, DMSO) δ 11.4 (3C, 3 X $CHMe_{2\ TIPS}$), 17.8 (3C, 3 X $CH_{3\ TIPS}$), 17.8 (3C, 3 X $CH_{3\ TIPS}$), 29.2 (1C, CH_3), 63.1 (1C, C_{-6}), 68.5 (1C, C_{-4}), 69.4 (1C, C_{-3}), 72.6 (1C, C_{-2}), 74.1 (1C, C_{-5}), 89.6 (1C, C_{-1}), 117.3 (1C, C_{AR}), 127.4 (1C, C_{AR}), 135.9 (1C, $_{AR}$); HRMS (NSI-FTMS) *m/z* found for $[M+H]^+$: 401.2465; $[C_{19}H_{36}N_2O_5Si+H]^+$ requires 401.2472.

(3R,4S,5R,6R)-2-methylene-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triol (468)

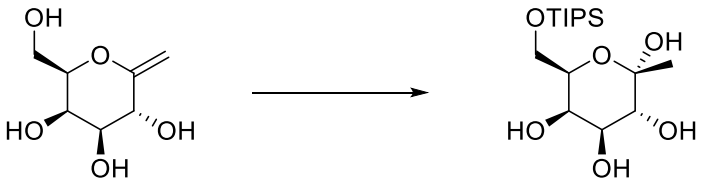


467 **471** **468**

To a solution of compound **467** (0.304 g, 1.73 mmol) in dry DMF (6.3 ml) at 0 ^{o}C was added imidazole (0.258 g, 3.80 mmol, 2.2 equiv.) then TIPSCl (0.41 ml, 1.90 mmol, 1.1 equiv.) dropwise. After 48 hours at rt, the mixture was then concentrated *in vacuo*. The residue was treated with water (ca. 15 ml) and EtOAc (ca. 15 ml), and the layers were then separated. The aqueous layer was extracted with EtOAc (2 X 15 ml). The combined organic extracts were then washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography (DCM:Methanol, 12:1) to furnish **471** as a pure colourless solid (0.439 g, 64%).

The title compound **468** was also isolated as pure colourless gum (0.114 g, 11%); $[\alpha]_D^{26}$ = +49.9 (c 0.77 in MeOH); IR ν_{max} (film)/cm^{-1}: 3369, 2942, 2866, 1660, 1463, 1092, 681; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.00 – 1.05 (m, 18H, 6 X $CH_{3\ TIPS}$), 1.06 – 1.12 (m, 3H, 3 X H-$CMe_{2\ TIPS}$), 3.28– 3.33 (m, 1H, H-C_{-3}), 3.47 – 3.51 (m, 1H, H-C_{-5}), 3.74 – 3.86 (m, 3H, H-C_{-6}, H'-C_{-6}, H-C_{-4}), 4.00 (ddt, *J* = 9.7, 5.7, 2.2 Hz, 1H, H-C_{-2}), 4.39 (d, *J* = 2.2 Hz, 1H, H-C=$C_{\ Alkene}$), 4.52 (d, *J* = 2.2 Hz, 1H, H'-C=$C_{\ Alkene}$), 4.67 (d, *J* = 4.6, 1H, OH), 4.95 (d, *J* = 5.2 Hz, 1H, OH), 5.15 (d, *J* = 5.7 Hz, 1H, OH). ^{13}C NMR (126 MHz, DMSO) δ 11.4 (3C, 3 X $CHMe_{2\ TIPS}$), 17.8 (6C, 6 X $CH_{3\ TIPS}$), 62.9 (1C, C_{-6}), 68.1 (1C, C_{-2}), 68.6 (1C, C_{-4}), 73.9 (1C, C_{-3}), 80.4 (1C, C_{-5}), 91.3 (1C, H_2C=$C_{\ Alkene}$), 162.2 (1C, C_{-1}); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 333.2090; $[C_{16}H_{32}O_5\,Si+H]^+$ requires 333.2097.

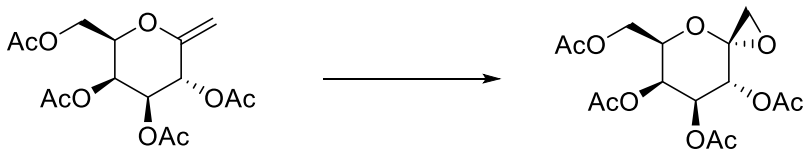
(2S,3R,4S,5R,6R)-2-methyl-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-2,3,4,5-tetraol (472)



467 **472**

To a stirred solution of compound **467** (0.349 g, 1.98 mmol) in dry DMF (26 ml) at 0 ^{o}C was added 2,6-lutidine (0.46 ml, 3.96 mmol, 2 equiv.) followed by the dropwise addition of TIPSOTf (0.59 ml, 2.18 mmol, 1.1 equiv.). The reaction mixture was stirred at 0 ^{o}C for 15 minutes then at rt for 24 hours. The reaction mixture was then quenched with water (10 ml) and saturated aqueous $NaHCO_3$ solution (10 ml). The solvents were evaporated under reduced pressure. The residue was treated with EtOAc and water, and the layers were then separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 2:1) to yield **472** as a pure colourless oil (0.021 g, 3%); $[\alpha]_D^{22}$ = +14.4 (c 0.73 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 3385, 2942, 2867, 2973, 1749, 1382, 1247, 1089; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.99 – 1.11 (m, 21H, 6 X $CH_{3\ TIPS}$, 3 X H-$CMe_{2\ TIPS}$), 1.37 (s, 3H, CH_3), 3.40 – 3.41 (m, 1H, H-C_{-6}), 3.42 – 3.43 (m, 1H, H-C_{-2}), 3.46 – 3.51 (m, 2H, H'-C_{-6}, H-C_{-4}), 3.60 – 3.64 (m, 1H, H-C_{-3}), 4.16 (m, 1H, H-C_{-5}), 4.97 (d, *J* = 7.8 Hz, 1H, OH), 5.26 (d, *J* = 4.4 Hz, 1H, OH); ^{13}C NMR (126 MHz, DMSO) δ 11.3 (3C, 3 X $CHMe_{2\ TIPS}$), 15.9 (1C, CH_3), 17.8 (6C, 6 X $CH_{3\ TIPS}$), 63.5 (1C, C_{-6}), 76.1 (1C, C_{-3}), 78.0 (1C, C_{-4}), 83.2 (1C, C_{-5}), 85.2 (1C, C_{-2}), 107.1 (1C, C_{-1}); HRMS (NSI-FTMS) *m/z* found for $[M+Na]^+$: 373.2018; $[C_{16}H_{34}O_6Si+Na]^+$ requires 373.2017.

(3S,5R,6S,7S,8R)-5-(acetoxymethyl)-1,4-dioxaspiro[2.5]octane-6,7,8-triyl triacetate (α-473)

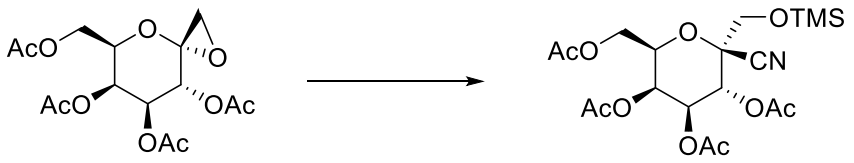


466 **α-473**

An aqueous solution of $NaHCO_3$ (0.62 ml, 0.6 M, 1.03 mmol, 3.62 equiv.) was added to a solution of **466** (0.099g, 0.29 mmol) in DCM (4.3 ml). mCPBA (0.059 g, 0.34 mmol, 1.3 equiv.) was added to the mixture at 0 ^oC. The reaction mixture was stirred at rt overnight. A saturated aqueous solution of $NaHCO_3$ was added and the layers were separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$, water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure at ambient temperature gave a pure colourless solid (0.103 g, 98%); mp 93-95 ^oC; $[\alpha]_D^{22}$ = +53.3 (c 0.96 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2973, 1749, 1373, 1215, 1079; ^1H NMR (500 MHz, Chloroform-*d*) δ 2.00 (s, 3H, $CH_{3\ Acetate}$), 2.04 (s, 3H, $CH_{3\ Acetate}$), 2.05 (s, 3H, $CH_{3\ Acetate}$), 2.18 (s, 3H, $CH_{3\ Acetate}$), 2.74 (d, *J* = 4.0 Hz, 1H of $CH_{2\ Epoxide}$), 3.07 (d, *J* = 4.0 Hz, 1H of $CH_{2\ Epoxide}$), 4.07 (dd, *J* = 11.4, 6.6 Hz, 1H, H-C_{-6}), 4.13 (dd, *J* = 11.4, 6.6 Hz, 1H, H'-C_{-6}), 4.29 (td, *J* = 6.6, 1.3 Hz, 1H, H-C_{-5}), 5.31 (dd, *J* = 10.8, 3.3 Hz, 1H, H-C_{-3}), 5.57 (dd, *J* = 3.3, 1.3 Hz, 1H, H-C_{-4}), 5.76 (d, *J* = 10.8 Hz, 1H, H-C_{-2}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.7 (2C, 2 X $CH_{3\ Acetate}$), 20.8 (1C, $CH_{3\ Acetate}$), 20.8 (1C, $CH_{3\ Acetate}$), 50.4 (1C, $CH_{2\ Epoxide}$), 61.3 (1C, C_{-6}), 64.0 (1C, C_{-2}), 68.0 (1C, C_{-4}), 70.0 (1C, C_{-3}), 72.0 (1C, C_{-5}), 82.0 (1C, C_{-1}), 170.0 (1C, $C_{q\ Acetate}$), 170.1 (1C, $C_{q\ Acetate}$), 170.2 (1C, $C_{q\ Acetate}$), 170.5 (1C, $C_{q\ Acetate}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 361.1133; $[C_{15}H_{20}O_{10}+H]^+$ requires 361.1135.

(2R,3R,4S,5S,6R)-6-(acetoxymethyl)-2-cyano-2-(((trimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate

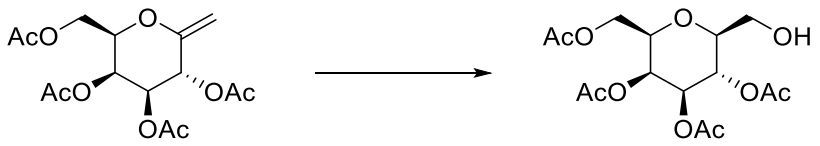
(479)



α-**473** **479**

To a stirred solution of epoxide **α-473** (0.201 g, 0.56 mmol) in toluene (6 ml) and hexane (3 ml) at 0 °C, was added iodine (0.283 g, 1.12 mmol, 2 equiv.) then TMSCN (0.35 ml, 2.79 mmol, 5 equiv.) dropwise. The mixture was stirred at 0 °C until TLC showed complete consumption of starting material. Once complete, a saturated aqueous solution of Na_2SO_3 (ca. 10 ml) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 X 10 ml). The combined organic extracts were washed with water (ca. 30 ml), brine (ca. 30 ml), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane:EtOAc, 3:1) to furnish **479** as a pure colourless oil (0.0094 g, 4%); $[\alpha]_D^{22}$ = -71.0 (c 0.49 in $CHCl_3$); IR ν_{max} (film)/cm^{-1}: 2960, 1755, 1371, 1215, 1060; ^{1}H NMR (500 MHz, Chloroform-*d*) δ0.21 (s, 9H, 3 X $CH_{3\ TMS}$), 1.99 (s, 3H, $CH_{3\ Acetate}$), 2.06 (s, 3H, $CH_{3\ Acetate}$), 2.12 (s, 3H, $CH_{3\ Acetate}$), 2.19 (s, 3H, $CH_{3\ Acetate}$), 4.08 (d, *J* = 11.5 Hz, 1H of CH_2OTMS), 4.12 (d, *J* = 6.5 Hz, 2H, H-C_{-6}, H'-C_{-6}), 4.19 (d, *J* = 11.5 Hz, 1H, 1H of CH_2OTMS), 4.59 (td, *J* = 6.5, 1.7 Hz, 1H, H-C_{-5}), 5.41 (dd, *J* = 3.5, 1.7 Hz, 1H, H-C_{-4}), 5.58 (dd, *J* = 10.3, 3.5 Hz, 1H, H-C_{-3}), 5.79 (d, *J* = 10.3 Hz, 1H, H-C_{-2}). ^{13}C NMR (126 MHz, $CDCl_3$) δ -0.7 (3C, 3 X $CH_{3\ TMS}$), 20.7 (1C, $CH_{3\ Acetate}$), 20.7 (1C, $CH_{3\ Acetate}$), 20.8 (1C, $CH_{3\ Acetate}$), 20.8 (1C, $CH_{3\ Acetate}$), 61.9 (1C, CH_2 of CH_2OTMS), 64.5 (1C, C_{-6}), 67.4 (1C, C_{-4}), 67.6 (1C, C_{-2}), 68.4 (1C, C_{-3}), 71.8 (1C, C_{-5}), 75.7 (1C, C_{-1}), 116.8 (1C, $C_{q\ Nitrile}$), 168.8 (1C, $C_{q\ Acetate}$), 170.0 (1C, $C_{q\ Acetate}$), 170.3 (1C, $C_{q\ Acetate}$), 170.5 (1C, $C_{q\ Acetate}$); HRMS (ASAP-TOF) *m/z* found for $[M+H]^+$: 460.1639; $[C_{19}H_{29}NO_{10}\,Si+H]^+$ requires 460.1639.

(2R,3S,4R,5S,6S)-2-(acetoxymethyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (481)



466 **481**

A solution of 9-BBN in THF (0.63 ml, 0.5 M in THF, 0.32 mmol, 1 equiv.) was added dropwise to a stirred solution of compound **466** (0.109 g, 0.32 mmol) in dry THF (2.5 ml) at 0 ^{o}C. The mixture was gradually warmed to rt and stirred until the starting material was fully consumed (monitored by TLC). Once complete, the reaction mixture was cooled to 0 ^{o}C and treated with 1:1 EtOH-THF (0.6 ml), pH 7 0.1 M potassium phosphate buffer (0.6 ml) and 30% aqueous H_2O_2 (0.97 ml). After being left for 5 hours stirring at rt, the reaction mixture was poured into a mixture of EtOAc (10 ml) and 30% aqueous $NaHSO_3$ (10 ml), and the layers were then separated. The aqueous layer was extracted with EtOAc twice. The combined organic extracts were washed with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, water, brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* gave a crude oil. Purification by flash column chromatography on silica gel (hexane:EtOAc 2:1 → 1:1) furnished an inseparable mixture (**481**:unknown compound, **7**:1) of **481** and an unknown compound (0.013 g, 11%)*; IR ν_{max} (film)/cm^{-1}: 3482, 2926, 2857, 1745, 1228, 1050; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.99 (s, 3H, $CH_{3\ Acetate}$), 2.05 s, 3H, $CH_{3\ Acetate}$), 2.07 (s, 3H, $CH_{3\ Acetate}$), 2.15 (s, 3H, $CH_{3\ Acetate}$), 3.48 (ddd, *J* = 10.0, 4.8, 2.3 Hz, 1H, H-C_{-1}), 3.61 (dd, *J* = 12.6, 4.8 Hz, 1H, 1H of CH_2OH), 3.73 (dd, *J* = 12.6, 2.3 Hz, 1H, 1H of CH_2OH), 3.90 – 3.95 (m, 1H, H-C_{-5}), 4.07-4.17 (m, 2H, H-C_{-6}, H'-C_{-6}), 5.10 (dd, *J* = 10.0, 3.5 Hz, 1H, H-C_{-3}), 5.21 (t, *J* = 10.0 Hz, 1H, H-C_{-2}), 5.44 (dd, *J* = 3.5, 1.1 Hz, 1H, H-C_{-4}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.8 (1C, $CH_{3\ Acetate}$), 20.8 (1C, $CH_{3\ Acetate}$), 20.9 (1C, $CH_{3\ Acetate}$), 20.9 (1C, $CH_{3\ Acetate}$), 61.7 (1C, CH_2OH), 61.9 (1C, C_{-6}), 66.4 (1C, C_{-2}), 67.8 (1C, C_{-4}), 72.0 (1C, C_{-3}), 74.5 (1C, C_{-5}), 78.7(1C, C_{-1}), 170.3 (1C, $C_{q\ Acetate}$), 170.4 (1C, $C_{q\ Acetate}$), 170.6 (1C, $C_{q\ Acetate}$), 170.7 (1C, $C_{q\ Acetate}$); HRMS (NSI-FTMS) *m/z* found for $[M+Na]^+$: 385.1099; $[C_{15}H_{22}O_{10}+Na]^+$ requires 385.1105.

*Assuming the unknown compound is an isomer of the title compound **481**, the number of moles of the title compound **481** in the inseparable mixture were calculated from molar ratios seen in

the ^{1}H NMR spectrum. Since the yield of **481** is based on the number of moles of **481** in the inseparable mixture, the yield of the **481** derives from the aforementioned molar ratios seen in the ^{1}H NMR spectrum of the inseparable mixture.

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