Studies Towards a Total a Synthesis of Tagetitoxin

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Abstract

Tagetitoxin is a phytotoxin produced by the bacterium *Pseudomonas syringae* pv. *tagetis*. It is a selective inhibitor of RNA polymerase III in eukaryotic cells and RNA polymerase in bacteria. Since its initial isolation and partial characterization, more than thirty years have passed without a fully characterized structure for tagetitoxin. While much research has been carried out on the biological aspects of tagetitoxin, particularly with interests towards its activity as an inhibitor of RNA polymerase, very few published works are available from a synthetic perspective.

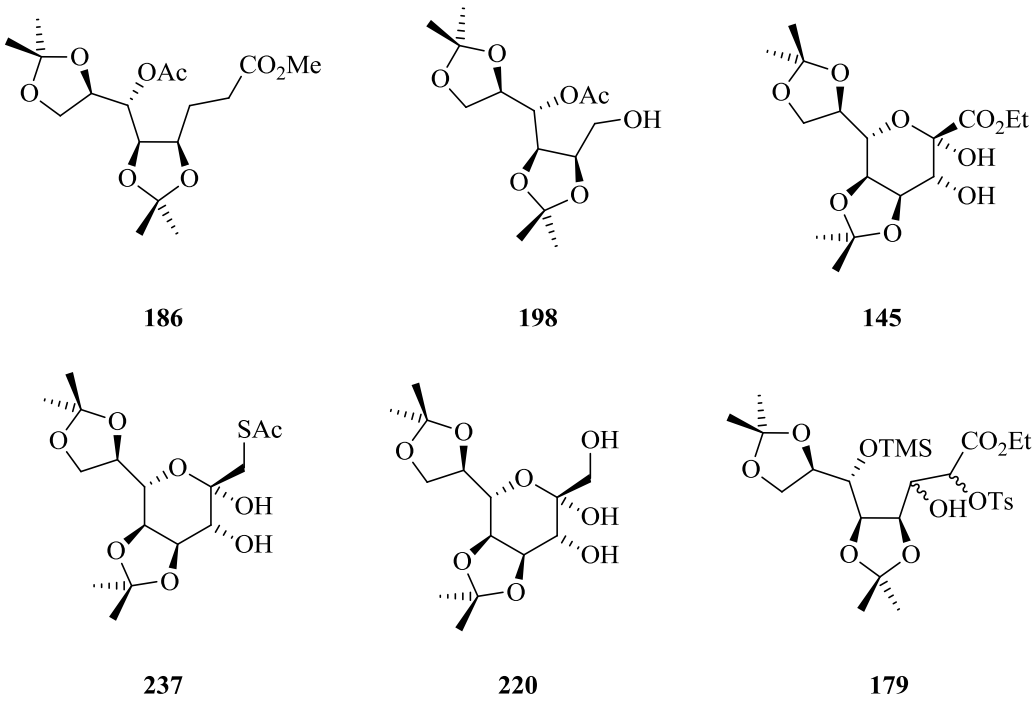

Figure 1: Synthetic intermediates towards tagetitoxin

In this thesis several promising synthetic intermediates towards the goal of tagetitoxin were synthesized (**Figure 1**). Herein the previous work related to the biology and synthetic studies of tagetitoxin and the recent studies conducted in the group towards a total synthesis of the molecule is described.

Acknowledgments

First and foremost I would like to thank Professor Phil Page for the opportunity to work on this project within the group, for his encouragement and advice throughout the course of my PhD and his unwavering resolve during the difficult and sometimes unfathomable chemistry moments, and perhaps most importantly his ability to always be available for a pint at the end of the day.

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Finally I would like thank my family and especially Katie for her support, patience and understanding throughout my PhD.

Abbreviations

Å	Ångström
aq.	aqueous (solution)
Ar	aromatic (proton)
$[\alpha]_D$	specific optical rotation at the sodium D line
cat.	catalytic
cm^{-1}	wave number
°C	degrees Celsius
c	concentration
δ	chemical shift
DAM	Diacetone mannose
DBDMH	1,3-dibromo-5,5dimethylhydantoin
DCM	dichloromethane
DIPA	diisopropylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethylsulfoxide
eq.	equivalent
FAB	fast atom bombardment
h	hour(s)
Hz	Hertz
IBX	2-iodoxybenzoic acid
IR	Infrared
Kdo	3-deoxy-D-*manno*-2-octulosonic acid
$LAlH_4$	lithium aluminium hydride
LDA	lithium diisopropylamine
M	molarity
m-CPBA	*meta*-chloroperbenzoic acid
min	minute(s)
mp	melting point
m/z	mass to charge ratio

Ms	Mesyl
MS	mass spectrometry
NBS	*N*-bromo succinimide
NIS	*N*-iodo succinimide
NCS	*N*-chloro succinimide
NMR	nuclear magnetic resonance
NTP	nucleotidyl triphosphate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
ppm	parts per million
*p*TSA	*para*-toluenesulfonyl acid
pyr	pyridine
RNA	ribonucleic acid
rt	room temperature
sat.	saturated
SM	starting material(s)
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
Tgt	tagetitoxin
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TLE	thin layer electrophoresis
Troc	2,2,2-Trichlorethoxycarbonyl
Ts	Tosyl
TMS	trimethylsilyl

All other abbreviations are used according to the IUPAC nomenclature or SI units.

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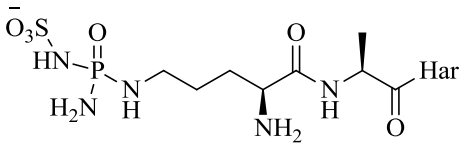
Introduction

Background

Since its initial isolation and partial characterization,[1] more than thirty years have passed without a fully characterized structure for tagetitoxin. While much research has been carried out on the biological aspects of tagetitoxin, particularly with interests towards its activity as an inhibitor of RNA polymerase, very few published works are available from a synthetic perspective. In fact at the time of writing this thesis there are no publications of a total synthesis of tagetitoxin and also there have been no crystal structures of the toxin in its free form.

Discovery

In 1981 a new toxin of the *Pseudomonas syringae pv. Tagetis* family was produced in culture and isolated for the first time by Mitchell *et al.* [1] It was found to cause apical chlorosis in marigolds and zinnia. The toxin was partially characterized and found to contain a phosphorus, sulfur and also an amino function. These three features are only present in one other *Pseudomonas* toxin, phaseolotoxin (**Figure 2**). However tagetitoxin was found to be distinct from phaseolotoxin in t.l.c and t.l.e experiments.



Phaseolotoxin

Figure 2: Phaseolotoxin structure

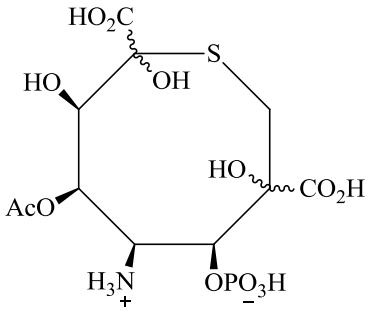
Structure

In 1983 Mitchell and Hart published the first proposed structure of tagetitoxin.[2] After purification of an extract from the culture medium by ion exchange chromatography and partition chromatography a noncrystalline glassy residue was obtained in *ca* 40% recovery. IR analysis of the residue gave only limited information, indicating the presence of an –OH, a carbonyl probably due to carboxylate group(s) and a phosphate group. Using field desorption mass spectrometry, tagetitoxin was found to have a MW of 435. In addition to an oxygen, other heteroatomic components of tagetitoxin were nitrogen in an amine moiety (confirmed

with ninhydrin staining), a phosphorus in a phosphate ester (blue colour with molybdate reagent and ^{31}P NMR) and sulfur (incorporation of ^{35}S). ^{31}P NMR showed a doublet (J = 11.5 Hz) at δ 1.0 downfield from the phosphate consistent with the presence of a phosphate ester of a secondary alcohol function. The ^{13}C NMR spectrum indicated 11 carbon atoms in total, three present in carbonyl groups and five adjacent to oxygen. The functionalities in the five carbons adjacent to oxygen were determined from ^{1}H and ^{13}C NMR chemical shifts to be an acetyl, phosphate and either three hydroxyl functions or one hydroxyl and an ether function.

Combining the mass spec and NMR data, Mitchell and Hart deduced the molecular formula of tagetitoxin to be $C_{11}H_{18}O_{13}SNP$ and suggested the presence of three hydroxyl functions as opposed to one hydroxyl function and an ether moiety. Using the data from the molecular formula and functional groups outlined, an acyclic compound would have to contain 20 hydrogens. As the ^{13}C NMR spectrum showed no signs of a carbon-carbon double bond it was deduced that tagetitoxin was a single ring structure. These assumptions were made based on the sulfur atom of tagetitoxin being present in a thiol or thioether. These assumptions were supported by the fact that the sulfur was not in a sulphate ester since strong acid hydrolysis of tagetitoxin did not liberate sulphate. Also the treatment of tagetitoxin with sodium nitroprusside gave no colour reaction indicating no sulfur was present, but when the toxin was pretreated with dilute hydrochloric acid a positive colour test for thiols was observed. A double labelling experiment was performed by growing *P.s Tagetis* in the presence of $^{32}PO_4^{3-}$ and $^{35}SO_4^{2-}$ which confirmed a sulfur-phosphorus ratio of 1:1 indicating the presence of only one sulfur atom in tagetitoxin.

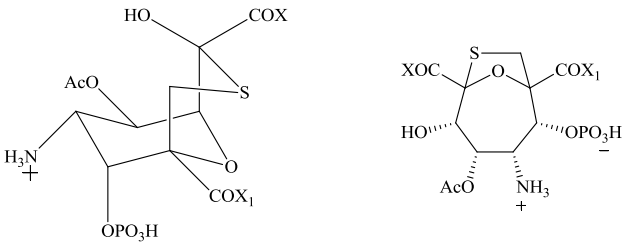
The ^{1}H NMR spectrum of tagetitoxin showed only a single methyl group (present in the acetyl function) and well defined multiplets leading to useful information about the carbon skeleton. Using the NMR data in combination with the mass spectrometric and functional group knowledge the group proposed the following structure for tagetitoxin **1** (**Figure 3**).



1

Figure 3: First proposed structure for tagetitoxin by Mitchell and Hart

This first proposed structure was not disputed until six years later, when Mitchell *et al* suggested a revised structure for tagetitoxin based on new higher resolution MS and NMR data.[3] FAB mass spectrometry gave a (M+H) of 417.0361, indicating that tagetitoxin had a molecular formula of $C_{11}H_{17}N_2O_{11}PS$ in contrast to the previously reported $C_{11}H_{18}O_{13}SNP$. [2] The additional nitrogen present was deduced to be an amide from the NMR data, since the ^{13}C NMR data confirmed only one C-N bond and there was no phosphoramide nitrogen as shown by the ^{31}P chemical shift. This new data led to the following functional groups containing oxygen; one acetyl, one phosphate, one carboxylic acid, one carboxamide, and two oxygens present in either hydroxyl or ether groups. A fully saturated non-cyclic compound with these substituents would have 21 hydrogens; as the revised molecular formula only contained 17 hydrogens and the ^{13}C NMR data confirmed no carbon-carbon double bonds, it was deduced tagetitoxin must contain two rings. Using these data two possible ring structures were proposed, **2** and **3** (**Figure 4**).



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

a $X_1 = OH, X_2 = NH_2$
b $X = NH_2, X_2 = OH$

Figure 4: Revised structures for tagetitoxin.

These structures were both supported by nOe experiments. The coupling constants of the protons in 4-carbon series allowed the dihedral angles to be determined. These angles were more suited to the proposed structure **2** over **3** as the protons on C-6 and C-7 are in a true diaxial interrelationship. The 5-membered ring in structure **3** places constraint on the 7-membered ring that does not allow a true diaxial relationship between the C-6 and C-7 protons. Using this result, the authors' favoured structure **2,** but structure **3** could not be totally discounted.

Gronwald *et al* later published an article indicating that the previous structural assumptions made by Mitchell [3] and Hart [2] for tagetitoxin were incorrect due to errors in mass spec analysis.[4] Gronwald found that even using the same purification techniques used by previous authors that the MW of tagetitoxin was 678. This was significantly higher than the 416 previously reported by Mitchell.[3] Although the MS data was clearly different from previous reports, the NMR data obtained was similar to the data reported by Mitchell. This led Gronwald to conclude that the extra mass might be accounted for by the presence of oxygen, nitrogen and sulfur atoms and exchangeable protons that are not detected by 1D NMR. Using the data obtained the group concluded that previous proposed structures for tagetitoxin were incorrect; however they did not to propose a structure themselves.

In 2005 an article published by Vassylyev [5] confirmed the structure proposed by Mitchell [3] from a crystal structure of the *Thermus thermophilus* RNA polymerase (RNAP)-tagetitoxin complex.

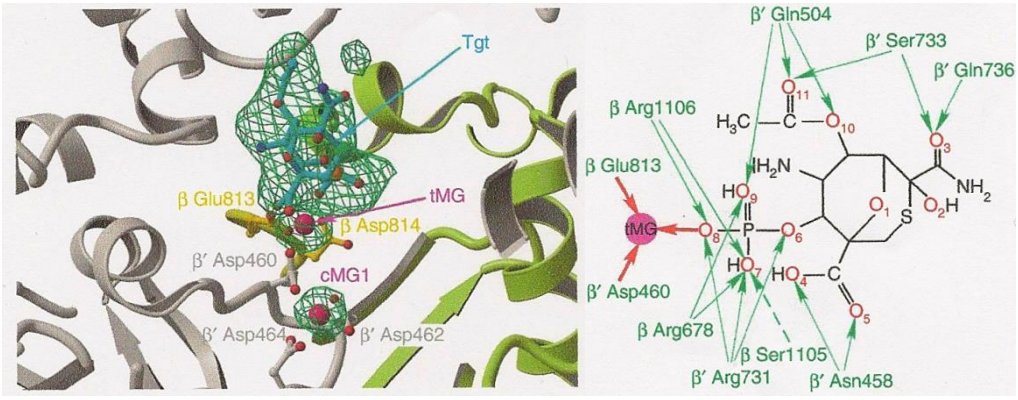


Figure 5: Left Structure of RNAP-tagetitoxin binding complex. Right tagetitoxin binding site. [5]

As well as confirming the bicyclic structure of tagetitoxin, this also removes the ambiguity of where the carboxamide and carboxylic acid groups are located. This bicyclic structure is the target molecule our group is working towards which is described in this thesis.

Biological activity

Tagetitoxin is a bacterial phytotoxin that induces chlorosis and leaf spot in the *Asteraceae* family of plants such as zinnia (*Zinnia elegans* Jacq) and sunflower (*Helianthus annuus*).[6,7] This chlorosis happens through the translocation of the toxin to the apical regions where it inhibits RNA Polymerase (RNAP) in chloroplasts; this subsequently suppresses the chloroplast biogenesis.[8,6] Tagetitoxin has also been shown to inhibit *in vitro* RNAPs of bacteria, insects and vertebrates at micromolar concentrations. In eukaryotic cells, RNAP III has been shown to be inhibited by tagetitoxin while RNAPs I and II were resistant.[5]

In 1990 Mathews *et al*. found that concentrations of just 0.3-3.0 μM of tagetitoxin were needed to inhibit RNAP III in *Xenopus leavis* oocytes, however RNAP II from wheat germ required concentrations of more than 100 μM to produce the same effect.[8] It was also established that tagetitoxin affects the incorporation of uridine into RNA in chloroplasts; this was found when [^{32}P] UTP was inhibited from incorporation to RNA upon addition of tagetitoxin to a transcriptionally active chloroplast protein.[9]

The simplest mechanism which can be envisaged for the inhibition of RNAP by tagetitoxin is a direct competition with the nucleotidyl triphosphate (NTP) substrate. However, this can be ruled out for two reasons: Firstly, kinetic data obtained shows tagetitoxin acting as an uncompetitive inhibitor, [8,9] which suggest that tagetitoxin does not prevent substrate binding. Secondly, it was shown that tagetitoxin inhibits catalytic reactions that use different substrates such as pyrophosphorolysis and exonucleic cleavages.

In 2005, Vassylyev and co-workers inspected the crystal structure of tagetitoxin-RNAP complex of bacterium *T. Thermophilus*, which argued against the competition between tagetitoxin and NTP substrate.[5] They suggested that the mechanism by which tagetitoxin acted was by stabilising some inactive intermediate during the substrate loading into the active site.

Structural analysis also indicated that the intermediate could either be formed during the preinsertion or insertion stage. The authors suggested that the intermediate was more likely to be formed in the pre-insertion stage, and then stabilised in the insertion step, suggesting a concerted two-step model (**Figure 6**).

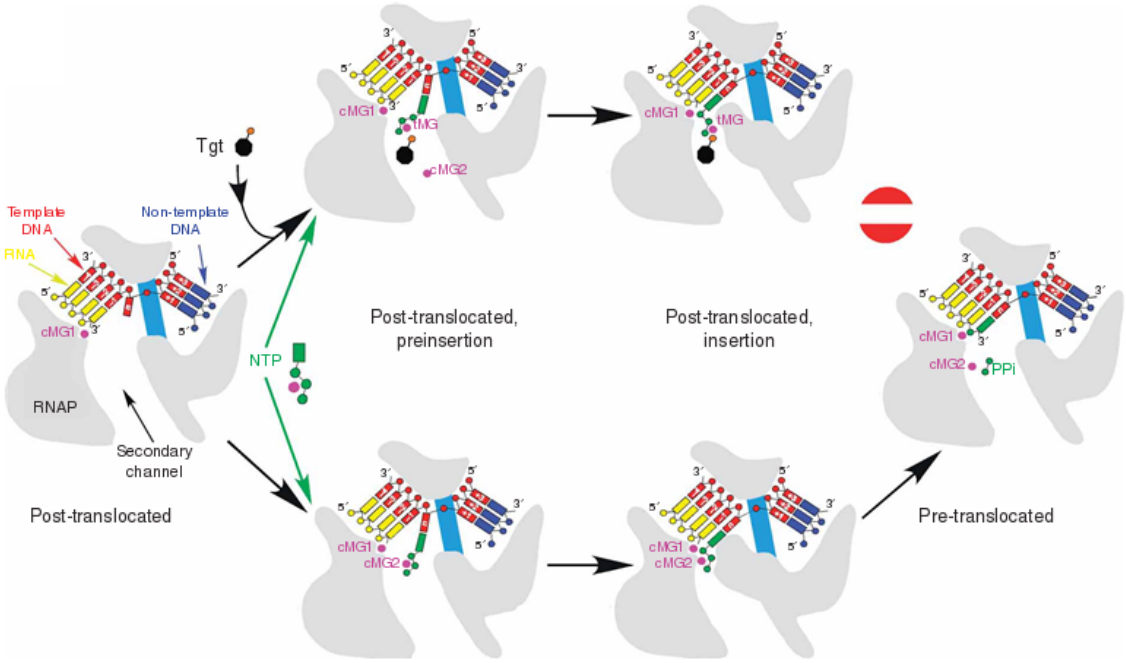


Figure 6: Proposed mode of action for tagetitoxin. [5]

The authors reasoned that during the binding in the pre-insertion step and in the presence of tagetitoxin, the phosphate of the NTP substrate, which coordinates the Mg^{2+} in the cMG2 ion site, would probably switch interactions to a well-fixed Mg^{2+} in the tMG ion site. Thus, a subsequent loss of interaction with cMG2 occurs. This theory suggests that the resulting interaction of NTP with the Mg^{2+} binding site tMG would not be disturbed during the isomerisation; the more compact conformation of the active site in the insertion stage would result in a tighter binding of tMG-bound substrate to prevent both the dissociation of the substrate and the catalytic reaction, therefore irreversibly locking RNAP in a non-productive state (**Figure 6**).

Before 2005 it was known that tagetitoxin inhibits RNAP, however the mechanism was still not proven. Vassylyev *et al*. published a crystal structure of (RNAP)-tagetitoxin complex at a resolution of 2.4 Å. [5 The bacterial *T. thermophilus* RNAP (ttRNAP)-tagetitoxin complex showed that the binding site of tagetitoxin is situated at the base of the RNAP secondary channel and not the enzyme's active site. This binding was mediated exclusively by polar

interactions, whereby 9 of the 11 tagetitoxin oxygen atoms form 18 hydrogen bonding interactions with the adjacent protein side chain (**Figure 7**).

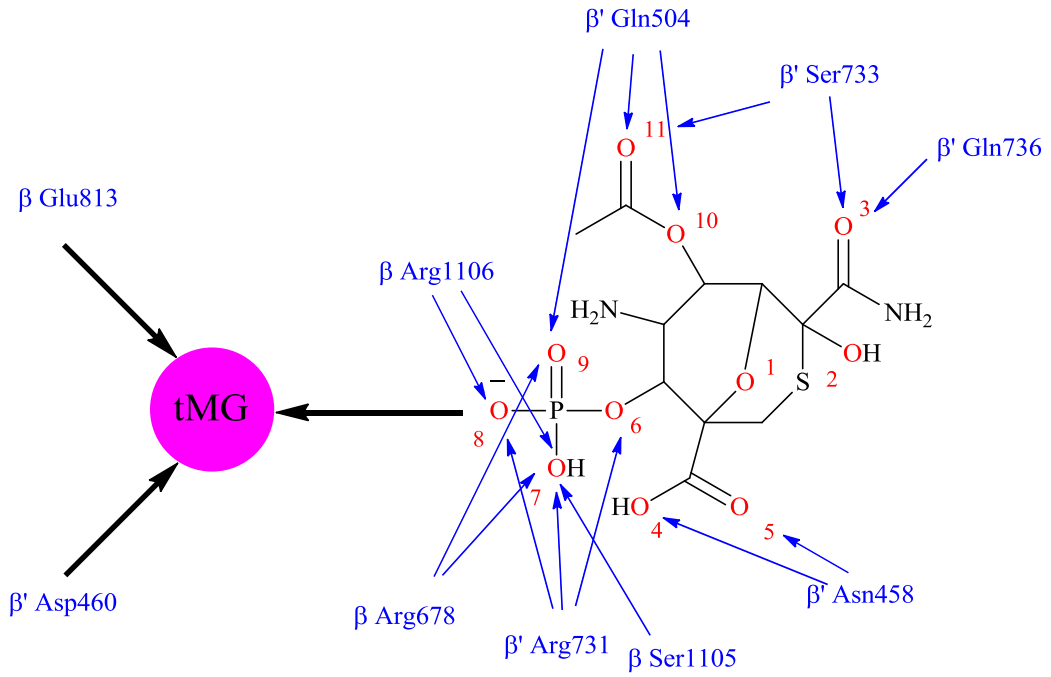


Figure 7: Tagetitoxin's binding locations to RNAP

This extensive network, which consisted of a set of basic and acidic side chains, forms a concerted mode of recognition that could be essential for the binding of tagetitoxin. The network is also highly unstable to small alterations in conformation or position of even one single residue.

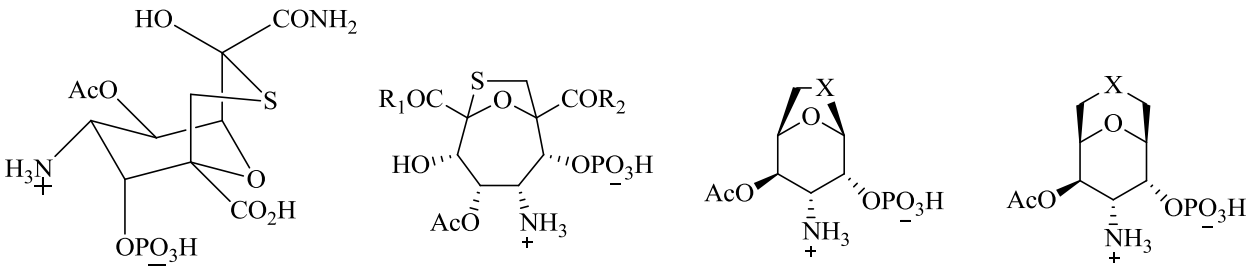
Tagetitoxin also showed very strong interactions with three highly conserved RNAP basic residues (β Arg678, β Arg1106 and β′Arg731). The authors also suggested that β′Asn458 was probably involved in substrate recognition. It was further noted that the binding sites of tagetitoxin and nucleotidyl triphosphate do not overlap, which suggests that competition with the substrate is not a major factor in tagetitoxin's mode of action.

The authors suggested that the RNAP-tagetitoxin complex was strengthened by the well-fixed Mg^{2+} ion binding site that mediates RNAP interactions with tagetitoxin. It was shown that the phosphate group in tagetitoxin was also coordinated to the Mg^{2+} ion and two other active site residues, β´Asp460 and β Glu813. Since RNAP contains more than one Mg^{2+} binding site (e.g. cMG1, cMG2 and tMG), Vassylyev anticipated that the side chain of β´Asp460 was better fixed in the complex by bridging the two Mg^{2+} ions (cMG1 and tMG). Consequently, this would favour coordination and strengthen the binding of the catalytic cMG1. As a result tagetitoxin increases the RNAP affinity for the major catalytic Mg^{2+} ion, cMG1.

Previous synthetic approaches to tagetitoxin

Furneaux *et al.*

Due to the biological activity of tagetitoxin and the lack of synthetic work on the molecule at the time, Furneaux and co-workers were interested in preparing substructures and analogues of tagetitoxin for evaluation as potential herbicides and plant growth regulators.[2] Working from one of the revised structures for tagetitoxin 4 proposed by Mitchell *et al.*[3] they suggested that the acetate, amine and phosphate groups were important for the activity of the toxin, and the sulfur bridge was required to insure the geometry of the pyranoid ring.



2

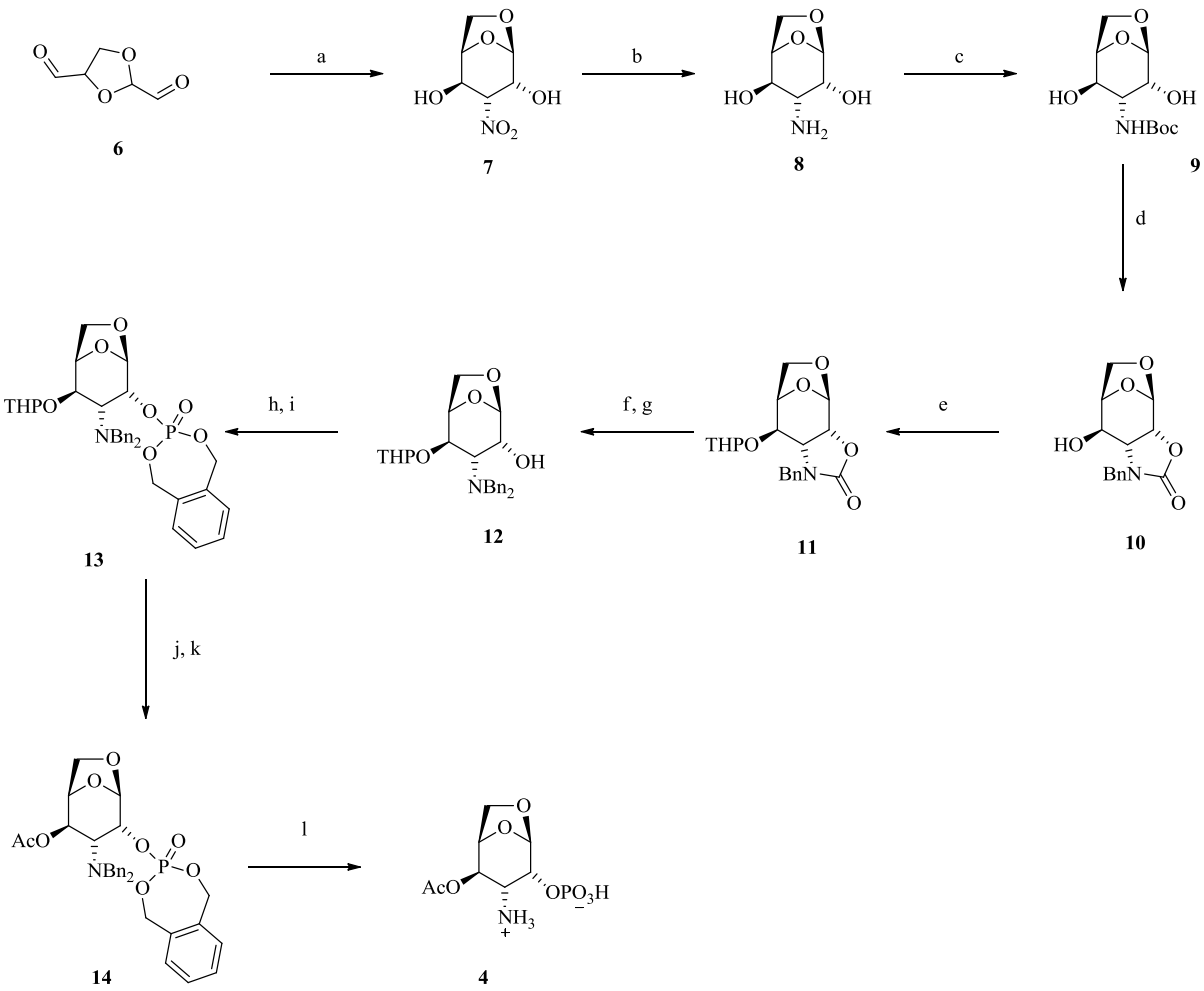
3a R^1=OH, R^2=NH_2
3b R^1=NH_2, R^2=OH

4

5

Figure 8: Initial Structures of tagetitoxin and the proposed analogues

The authors decided to start from D-hexoses as these can be easily transformed into 1,6-anhydro-D-hexoses, which show herbicidal activity and also have structural similarities to **2**.



Reagents and conditions: a) $MeNO_2$, NaOMe, MeOH; b) H_2, Pd/C, 2M HCl, 50 p.s.i; c) $(Boc)_2O$, $NaCO_3$, H_2O, THF; d) $(Bu_3Sn)_2O$, Bu_4NBr, BnBr, toluene; e) dihydropyran, TsOH; f) NaOH, EtOH; g) Bu_2SnO, Bu_4NBr, BNBr, toluene; h) *O*-xylene-*N,N*-diethylphosphoramidite, 1*H*-tetrazole; i) *m*CPBA; j) 2M HCl; k) AC_2O, py; l) H_2, Pd/C, 50 p.s.i, EtOH, AcOH.

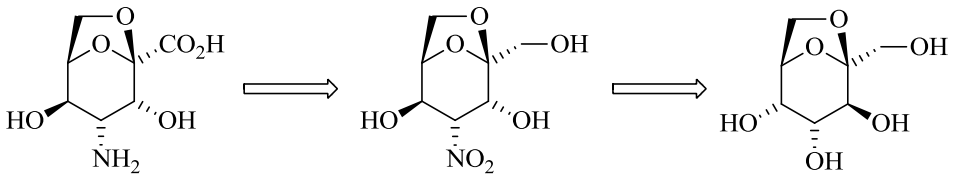
Scheme 1: Furneaux's synthetic work towards the [3.2.1] bicyclic analogue 4

Their first route towards the analogue **4** proceeded from the cyclization of the dialdehyde **6** with nitromethane to give 1,6-anhydro-3-deoxy-3-nitro-D-gulose **7**. The compound was subjected to a hydrogenation to give the amine **8**. The configuration of the amine was confirmed by the large H^1NMR coupling constant between C-3 and C-4 ($J_{3,4}$ = 9.9 Hz) and by the crystal structure of the amine in its hydrochloride salt form. Using the *syn* configuration of the C-2 and C-3 substituents to their advantage, the group were able to esterify the C-2 and

C-4 hydroxyl groups selectively. Amine **8** was *N*-Boc protected to give compound **9**, which was treated with bis(tributyltin) oxide, followed by tetrabutylammonium bromide and benzyl bromide in toluene under reflux to give the *N*-benzyl protected cyclic carbamate **10**. The free hydroxyl group at C-4 was then protected as the THP ether using dihydropyran under acidic conditions; the product was then subjected to a ring opening of the carbamate and a second *N*-benzyl protection to give compound **11**. Introduction of the phosphate group was preceded by a phosphitylation of the C-2 hydroxyl group with *o*-xylene *N*,*N*-diethylphosphoramidite and 1*H*-tetrazole, followed by an oxidation with *m*CPBA; removal of the THP group followed by an acetate protection and another hydrogenation and acidic work up gave the tagetitoxin analogue **4** (**Scheme 1**).

The tagetitoxin analogue **4** showed no activity when tested against agriculturally important weeds such as *Avena fatua* (wild oat), *Setaria viridis* (green foxtail), *Amaranthus retroflexus* (redroot pigweed) or *Chenopodium album* (fat hen).

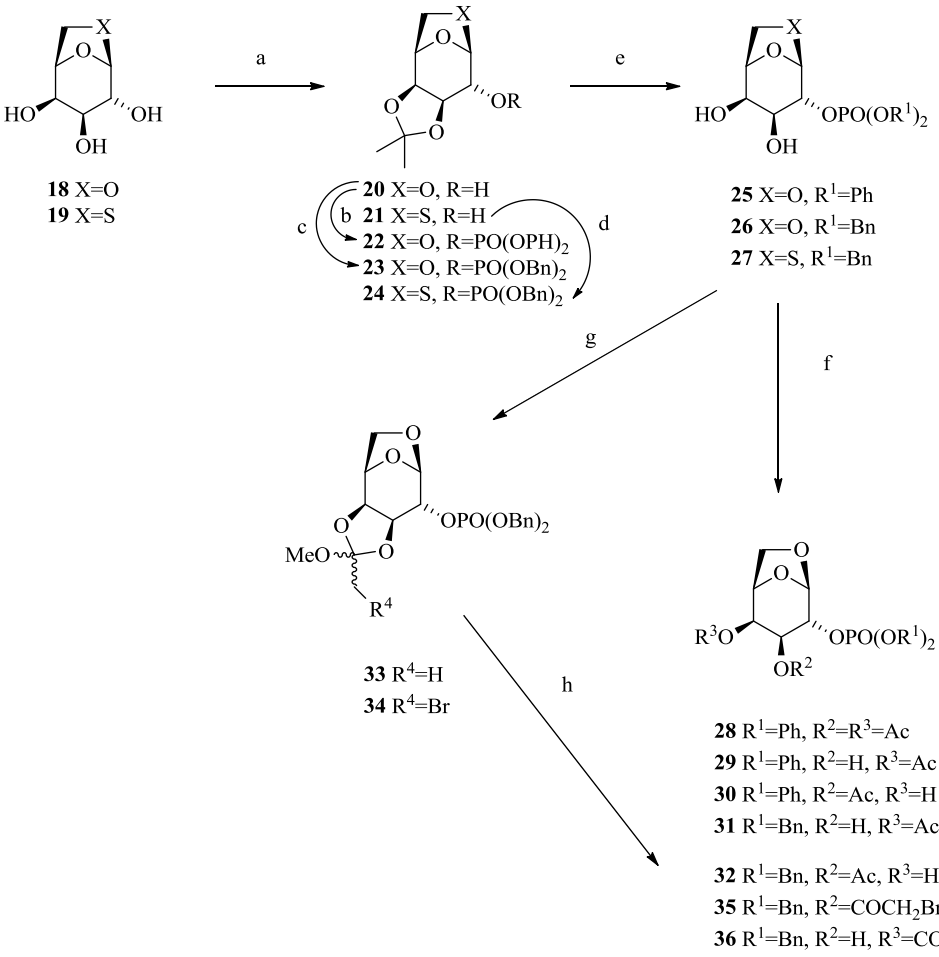
Furneaux also suggested that his route could be modified to form analogues containing a carboxylic acid group at the C-1 position. Thus periodate oxidation of 2,7-anhydrosedoheptulose **15** gave a dialdehyde which was converted to 4-deoxy-4-nitro-D-gulo-anhydride **16** using the procedure previously described by Furneaux (**Scheme 2**).



17 **16** **15**

Scheme 2: Proposed retrosynthetic route for carboxylic acid analogue 17

In an alternative method used by Furneaux to reach analogues based on compound **4** it was necessary to functionalize the O-2 and O-4 positions of 1,6-anhydro-D-galactose **18** differently; a good leaving group at the C-3 position was also needed to introduce the amino function with an inverted configuration. Phosphate **25** was prepared by the route indicated in **scheme 3** and then treated with acetic anhydride (1.3 equiv) in pyridine to give the diacetate **28** (18%) and an inseparable mixture of monoacetates **29** and **30** (64%). The mixture contained over 90% of the 4-ester **29**, which was derived by the selective reaction of the more accessible equatorial hydroxyl group. After developing an acceptable procedure for the selective acetylation of compound **25**, the group attempted to reproduce the same results with the anhydrides **26** and **27**. Unfortunately attempts to produce compound **27** were unsuccessful due to the sensitivity of compound **24** to acidic conditions. The group presumed the sensitivity to be due to the participation of the sulfur atom in reactions of carbocations generated under the conditions used. Acetylation of diol **26** using acetic anhydride and bases, pyridine, dibutyltin oxide or bis(tributyltin)oxide resulted in a 1:1 inseparable mixture of the monoacetates **31** and **32**, very different from the selectivity observed for compound **25**. Using the bulkier pivaloyl chloride and dibutyltin oxide also gave inseparable mixtures of the monoesters. A selective acetylation on diol **26** was finally achieved when it was first converted to the cyclic orthoacetate **33** and subjected to a mild hydrolysis. This method gave the acetate **32** exclusively, but the authors were unable to make use of this result. The brominated orthoester **34** was expected to give an O-3 ester, which could be removed in the presence of an acetate group at C-4. The ester, however did not undergo hydrolysis selectively, and gave an inseparable mixture of bromoacetates **35** and **36**.

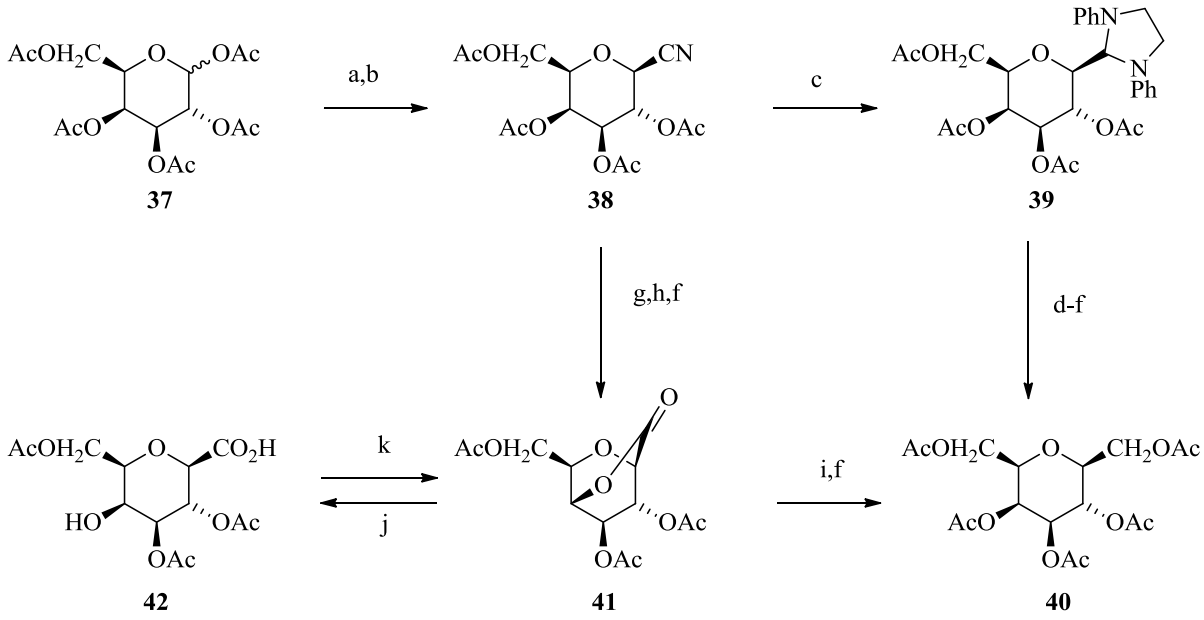


Reagents and conditions: a) $Me_2C(OMe)_2$, Acetone, TsOH; b) $ClPO(OPH)_2$, py; c) BuLi, $[(BnO)_2PO]_2O$; d) NaH, $[(BnO)_2PO]_2O$; e) 2M HCl; f) Ac_2O and (py or Bu_2SnO or $(Bu_3Sn)_2O$); g) for **33**: $MeC(OEt)_3$, TsOH; for **34**: $BrCH_2C(OEt)_3$, TsOH; h) AcOH, H_2O

Scheme 3: Furneaux's second route to analogues based on structure 4

Having successfully developed a route to the tagetitoxin analogue **4** (X=O), the group focused their attention on the production of the closely related analogue **5**. D-Galactose pentaacetate **37** was converted into the α-glycosyl bromide and then treated with mercury(II) cyanide in nitromethane to give the β-nitrile **38 (Scheme 4)**. Reductive hydrolysis with Raney nickel and then trapping the unstable aldehyde with dianilinoethane gave the imidazolidine **39**. The aldehyde was regenerated as its *p*-toluenesulfonic acid salt, reduced with sodium borohydride, and acetylated to give the pentaacetate **40**. A second approach to this product was also achieved by the deacetylation of nitrile **38** with sodium methoxide and subsequent treatment with refluxing aqueous sodium hydroxide (6 M). Acetylation of the crude hydrolysis product gave a syrupy lactone. A sample of the lactone crystallized on

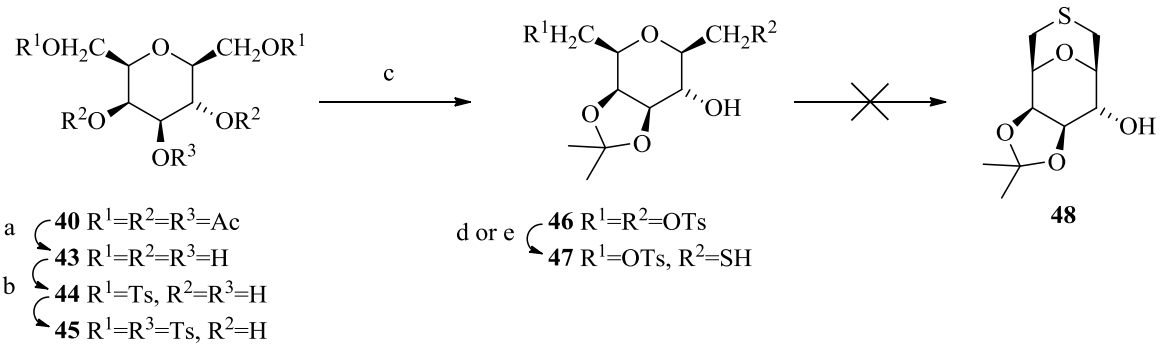
standing, and X-ray structural analysis and NMR analysis showed this to be the 5,1-hydroxy acid **42.**



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) MeONa, MeOH; h) 25% w/v NaOH; i) $LiAlH_4$; j) H_2O k) Ac_2O, NaOAc.

Scheme 4: Furneaux's approach to the tagetitoxin analogue 5

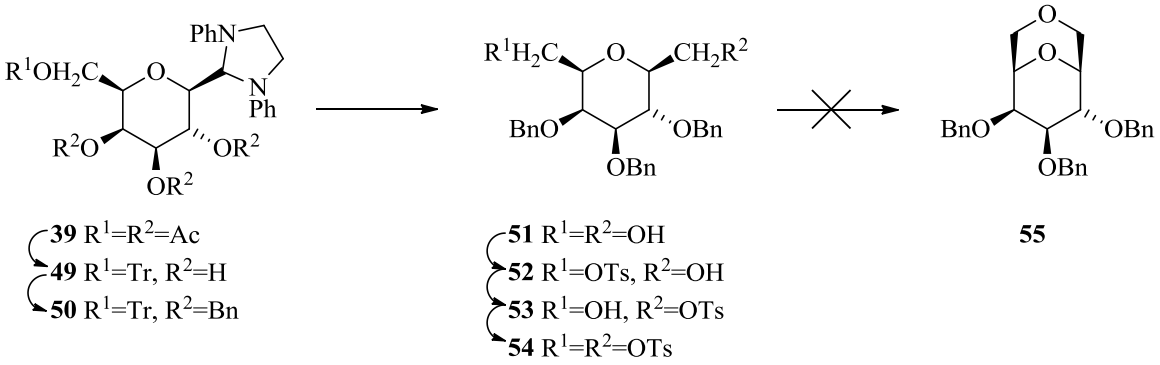
The lactone was thought to be the 2,6-anhydroheptono-1,5-lactone ester **41**; this was confirmed when the hydroxyl acid **42** was converted into the lactone when heated in acetic anhydride in the presence of sodium acetate. Lithium aluminium hydride reduction of the lactone and peracetylation gave the desired pentaacetate **40**. Deacetylation of the anhydride **40** gave the pentaol **43**, followed by a selective tosylation of the primary alcohols to give the tosylate **44**. Four equivalents of tosyl chloride were required to obtain the ditosylate **44** in 33% yield, but this also resulted in the tritosylate **45** being isolated in 25% yield. The ditosylate was converted into the acetonide **46**. Subsequent attempts to form the cyclic sulphide **48** by treatment in DMF with either lithium sulfide or sodium sulfide, were unsuccessful, the only product isolated being thiol **47**; no traces of the cyclic sulphide were found even under extreme conditions (**Scheme 5**).



Reagents and conditions: a) MeONa, MeOH; b) TsCl, py; c) $Me_2C(OMe)_2$, TsOH; d) Na_2S, DMF; e) Li_2S, DMF.

Scheme 5: Furneaux's approach to the tagetitoxin analogue 5

After the unsuccessful attempts to form the analogue **5** (X=S), the group turned their attention towards the oxygen analogue. Starting from tetraacetate **39,** a selective deacetylation followed by tritylation of the primary alcohol gave compound **49** (**Scheme 6**). Benzylation of the remaining alcohols gave compound **50**, and deprotection of the aldehyde function followed by a borohydride reduction and the detritylation gave the diol **51**. While successful tosylation of **51** to give the monotosylates **52** and **53** and the ditosylate **54** was achieved, treatment with sodium hydride failed to give the desired compound **55**.



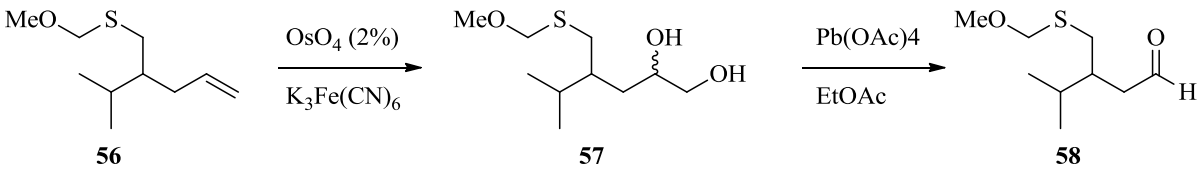
Reagents and conditions: a) MeONa, MeOH; b)TrCl, Et_3N; c) NaH, BnBr; d) TsOH, Me_2CO, DCM; e) $NaBH_4$; f) TsOH, MeOH; g) TsCl, py.

Scheme 6: Furneax's approach to the oxygen analogue 5

In conclusion, Furneaux was able to produce the tagetitoxin analogue **4** (X=O) as indicated in **scheme 1,** but he was unable to produce an analogue of the more closely related compound **5**, and in both cases was unable to incorporate the sulfur present in tagetitoxin.

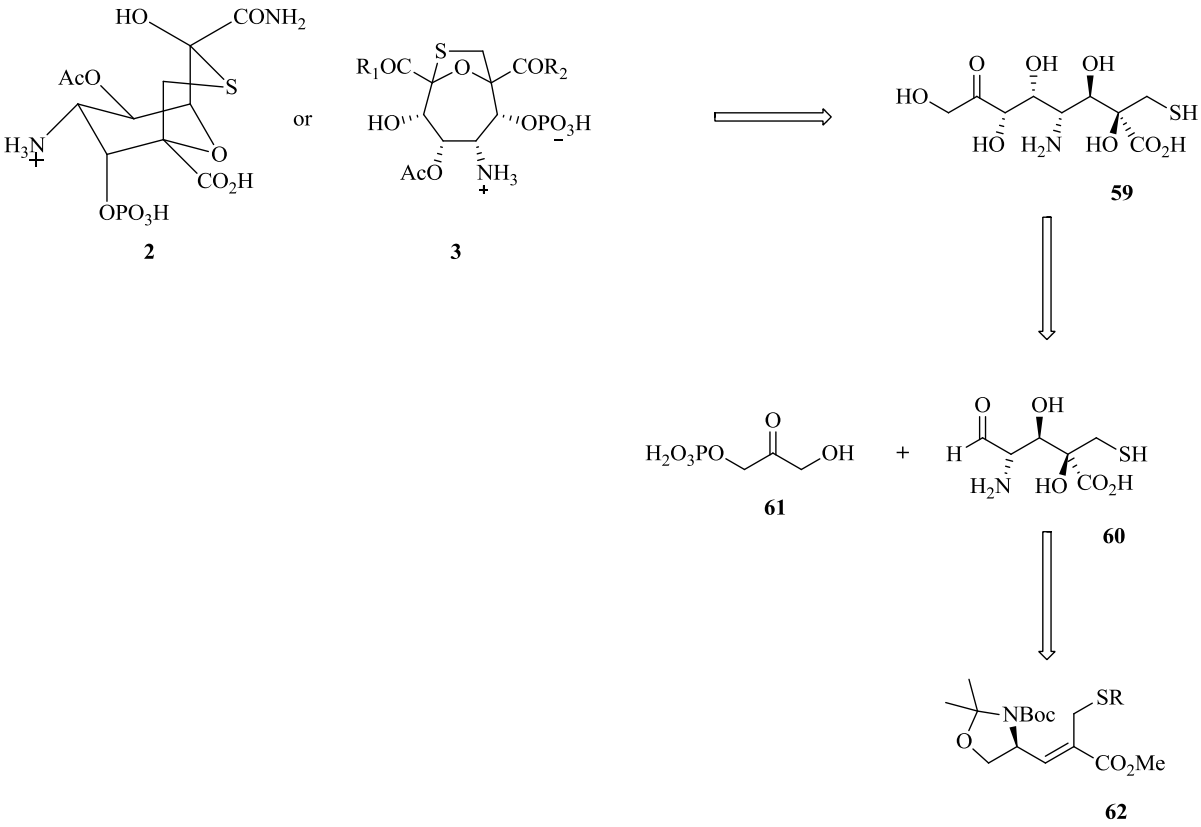
Sammakia *et al.*

Sammakia's work describes their studies of the dihydroxylation of olefins in the presence of sulfur functionalities, which they go on to use in their retrosynthetic analysis of tagetitoxin.[12] Their initial work was conducted on compound **56**. The Yamamoto procedure (OsO_4, 0.02 equiv; $K_3Fe(CN)_6$, 3 equiv; *t*-BuOH / water, 1:1) gave diols **57** in a 1:1 mixture of diastereoisomers, which was subjected to an oxidative cleavage with $Pb(OAc)_4$ in ethyl acetate to give the desired aldehyde **58** in 53% yield after purification (**Scheme 7**).



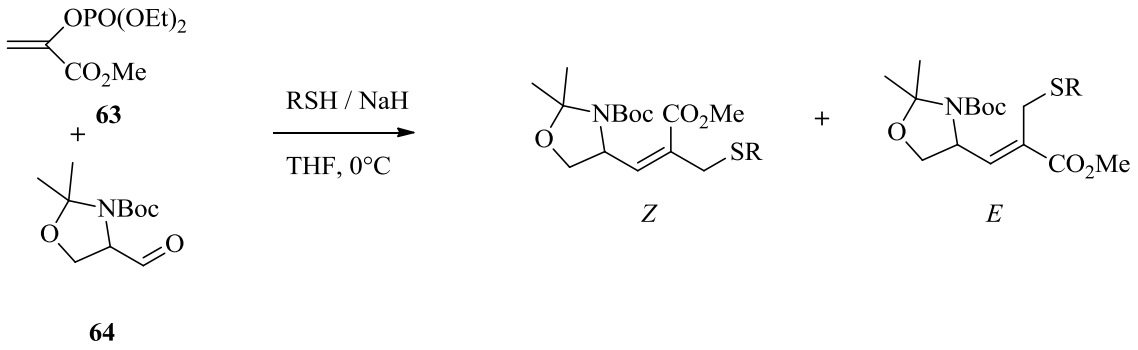
Scheme 7: Sammakia's initial studies on the dihydroxylation and oxidative cleavage in the presence of sulfur functionalities

Sammakia's retrosynthetic approach to tagetitoxin involved an enzymatic coupling of dihydroxy acetone phosphate **61** with aldehyde **60** to form the fully functionalised tagetitoxin precursor **59**. This precursor could then be cyclized to form either of the two proposed structures for tagetitoxin **2** and **3**. Aldehyde **60** could be prepared from the oxazolidine **62** by a dihydroxylation of the olefin, then a hydrolysis of the oxazolidine and oxidation of the primary alcohol to an aldehyde (**Scheme 8**).



Scheme 8: Sammakia's Retrosynthetic analysis of Tagetitoxin

Sammakia's synthesis began with the preparation of alkenes **62a-e** in a one pot synthesis by the generation of a phosphonate from alkene **63** *in situ*, followed by a condensation with the oxazolidine **64**. The authors were able to produce a range of oxazolidine alkenes with variously protected thiols with different steric and electronic properties (**Scheme 9**).



Scheme 9: One pot procedure for generation of oxazolidine alkenes with varying sulfur protecting groups

The ratio of *Z* to *E* alkenes was influenced by the protecting group present on the thiol as shown in **table 1.**

R	Ethyl	*i*-Propyl	*t*-Butyl	Phenyl	Benzyl
Z:E	60:40	70:30	100:0	20:80	30:70

Table 1: Effect of protecting group R of *Z*:*E* alkene ratio

Using conventional methods of dihydroxylation with catalytic or stoichiometric amounts of OsO_4 gave only the sulfur-oxidized products, which led the group to examine the use of ferricyanide co-oxidants. AD-mix-β gave poor results on substrates **62a-e**, probably due to the bulky nature of the osmium ligand complex and the electron deficient and sterically hindered alkenes. Attempted dihydroxylations of **62a**, **62b** and **62e** gave little if any of the desired product using both methods (**Table 2**). Over-oxidation was observed in most cases generally producing the sulfoxide product; substrate **62d** was the only compound to form the expected sulfone due to over-oxidation using $K_3Fe(CN)_6$. The bulky *t*-butyl thiol substrate **62c** was the only substrate to produce a reasonable amount of the dihydroxylation product using AD-mix-β; this was also the most successful substrate with $K_3Fe(CN)_6$, which produced isolated yields between 50% and 63%. The dihydroxylation gave a diastereoisomeric ratio of 25:1, the major isomer being the desired result for the author's proposed tagetitoxin synthesis. However, no further publications on the synthesis of tagetitoxin have been reported by this group.

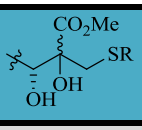
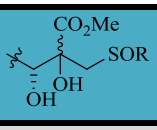
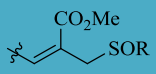
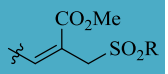
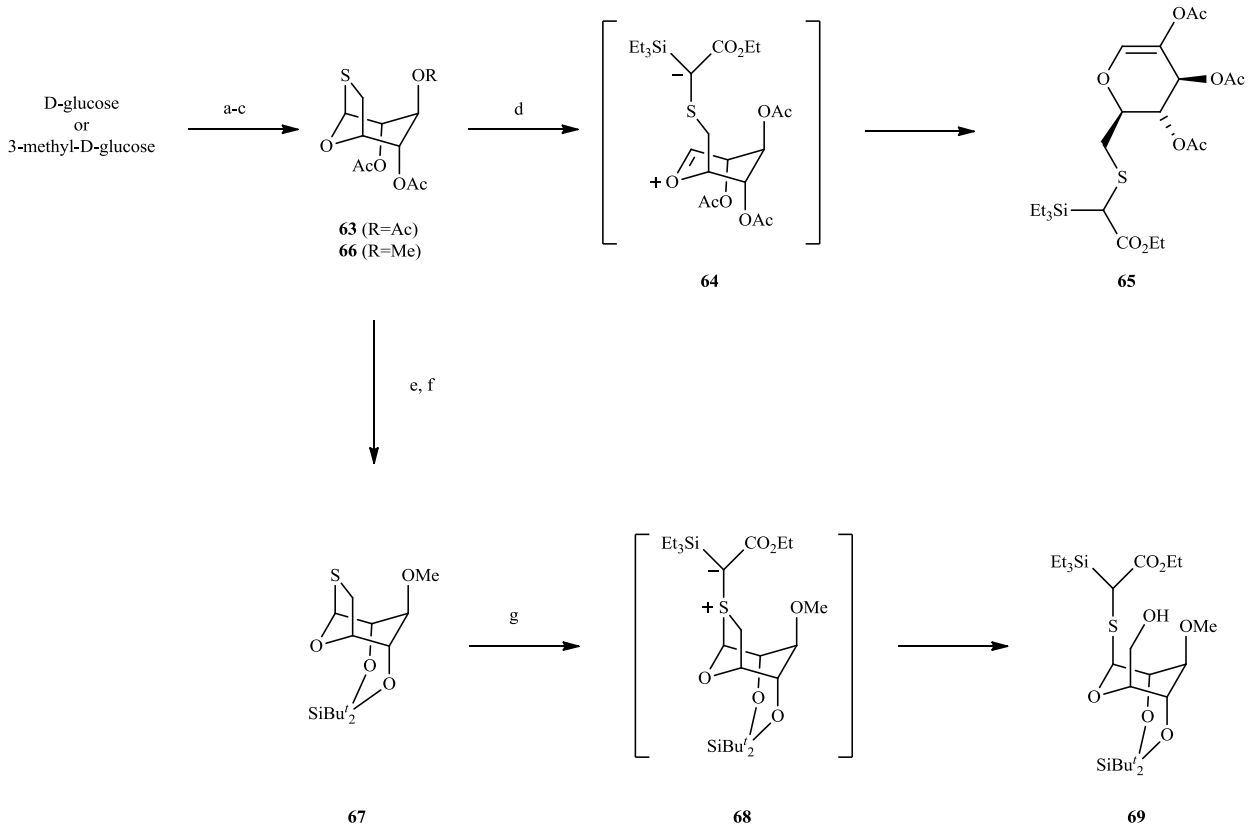
R	Oxidant	Recovered SM				
Et (62a)	AD-Mix-β	54	-	-	46	-
	$K_3Fe(CN)_6$	30	-	-	70	-
***i*-Pr (62b)**	AD-Mix-β	56	6	-	28	-
	$K_3Fe(CN)_6$	39	15	-	44	-
***t*-Bu (62c)**	AD-Mix-β	86	14	-	-	-
	$K_3Fe(CN)_6$	32	55	-	11	-
Ph (62d)	AD-Mix-β	99	-	-	<1	-
	$K_3Fe(CN)_6$	34	27	-	-	39
Bn (62e)	AD-Mix-β	82	-	-	10	-
	$K_3Fe(CN)_6$	22	6	-	72	-

Table 2: Attempted dihydroxylations of *Z* alkenes using ferricyanide co-oxidants.
Conditions: AD mix-β: 1.5 g/mmol alkene in 30 ml of 1:1 *t*-butanol-water, RT 72h; $K_3Fe(CN)_6$: 3 eq. $K_3Fe(CN)_6$ and K_2CO_3, 10 eq. OsO_4 in 30 ml of 1:1 *t*- butanol –water, RT 72h.

Porter *et al.*

In 2006 Michael J. Porter and Julien R. H. Plet submitted a paper on the first synthesis of the tagetitoxin bicyclic core, achieved by a cyclization of a thiol onto an electrophilic ketone [13]. Their first strategy was to attempt a carbene ring expansion of a 1,3-oxathiolane, starting from a carbohydrate precursor. D-Glucose was converted to a bicyclic monothioacetal **63** through the displacement of an anomeric bromide and a 6-tosylate with potassium *O*-ethylxanthate. They then attempted a ring expansion using ethyl diazo(triethylsilyl)acetate and a catalytic amount of rhodium(II) acetate; this, however, did not lead to the predicted bicycle but instead gave the glycal **65**. This outcome was suggested by Porter to occur through a sulfur ylid formation and heterolytic C-S bond cleavage to give zwitterion **64**, instead of the desired C-C bond formation; the intermediate was presumed to undergo a ring-flip to the more stable conformer, followed by a proton transfer to give the observed product **65**.

To try to prevent this from occurring the authors designed a conformationally constrained substrate whose derived zwitterion would be unable to ring-flip. 3-Methyl-D-glucose was converted to bicycle **66** under the same conditions used to produce compound **63**. The acetate groups were removed and a di-*tert*-butylsilylene was added to bridge the hydroxyl groups to give **67**. This compound was treated with ethyl diazo(triethylsilyl)acetate as before and with catalytic rhodium(II) heptafluorobutyrate to give the primary alcohol **69** in a low yield as the only isolable product. It appears in that while the sulfur ylid **68** formed it did not undergo C-S bond heterolysis and ring expansion. Instead water seems to have reacted with the ylid to form bicycle **69** (**Scheme 10**).

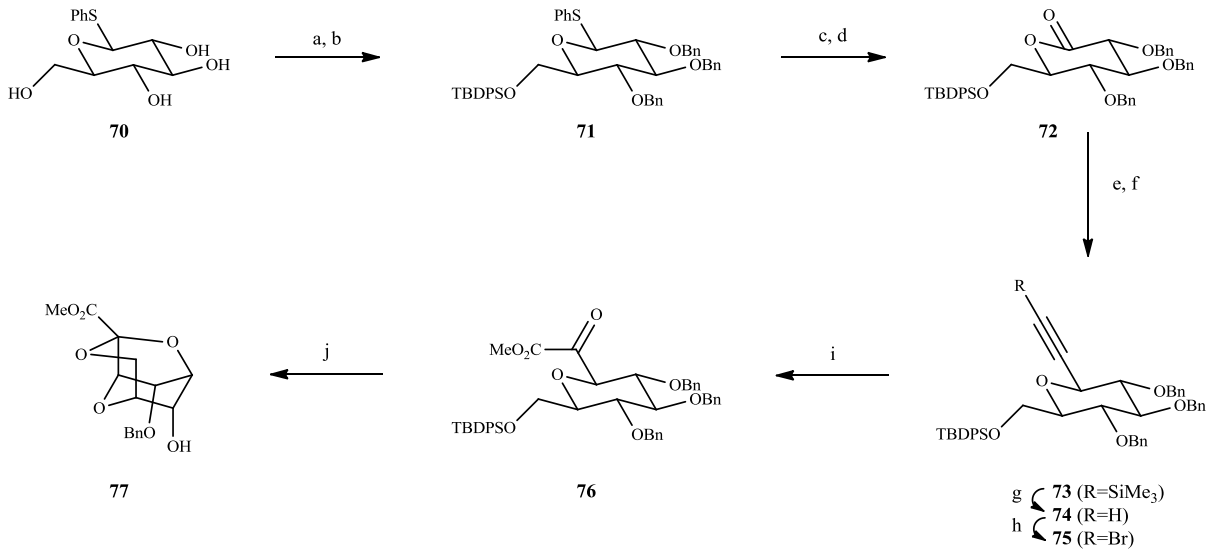


Reagents and conditions: a) TsCl, pyridine; Ac_2O; b) HBr AcOH; c) KSCSOEt, DMF, 50 °C (46% **63** over 3 steps) or KSCSOEt, acetone, reflux (47% **66** over 3 steps); d) $Et_3SiC(N_2)CO_2Et$, $Rh_2(OAc)_4$, benzene, reflux 34%; e) NH_3, MeOH, H_2O, 50%; f) $^tBu_2SiCl_2$, Et_3N, DCM, 86%; g) $Et_3SiC(N_2)CO_2Et$, $Rh_2(O_2CC_3F_7)_4$, benzene, reflux, 21%.

Scheme 10: Porter's synthetic work using carbene mediated ring expansion of 1,3-oxathiolanes

After the lack of success using the ring expansion method, Porter moved on to forming the 1,4-oxathiane ring of tagetitoxin by the cyclization of a thiol onto an electron deficient ketone.

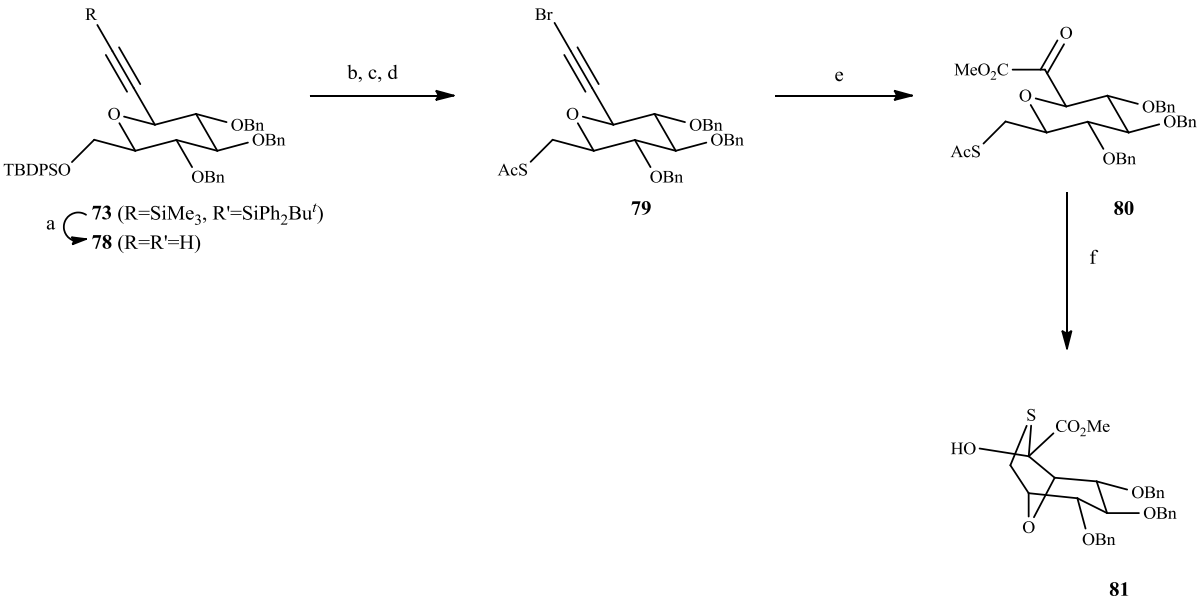
The authors began with phenyl 1-thio-β-D-glucopyranoside **70** and selectively protected the primary alcohol with TBDPS and the remaining hydroxyl groups with benzyl groups to give the fully protected compound **71**. The thioglycoside linkage was hydrolysed using NBS and aqueous acetone and then oxidized to the δ-lactone **72** using DMP. Cerium-mediated addition of trimethylsilylacetylene followed by deoxygenation and desilylation gave the terminal alkyne **74**. Bromination with NBS and silver nitrate gave **75,** which was oxidized by permanganate in aqueous methanol to give the α-ketoester **76**. When the silyl ether was treated with TBAF, a simultaneous elimination of the 2-benzyloxy group was observed to form an enol ether. When **76** was treated with HF-pyridine only the single product, tricyclic acetal **77,** was observed. In this case the silyl ether and the 3 and 4-benzyl ethers had been cleaved and an acetal had formed between the ketone and the 6-hydroxy group (**Scheme 11**).



Reagents and conditions: a) TBDPSCl, imidazole, DMF, 99%; b) BnBr, NaH, DMF 87%; c) NBS, aq. acetone, 95%; d) DMP, pyridine, DCM, 69% e) TMSC≡CH, *n*-BuLi, $CeCl_3 \cdot 7H_2O$, 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)HF·py, THF, -78 °C to rt, 77%.

Scheme 11: Porter's synthetic work on the formation of a 1,4-oxathane ring

The formation of this acetal prevented the introduction of the sulfur group at C-6 however; using the same steps in a different order enabled the Porter group to produce the bicyclic core of the tagetitoxin skeleton successfully (**Scheme 12**).



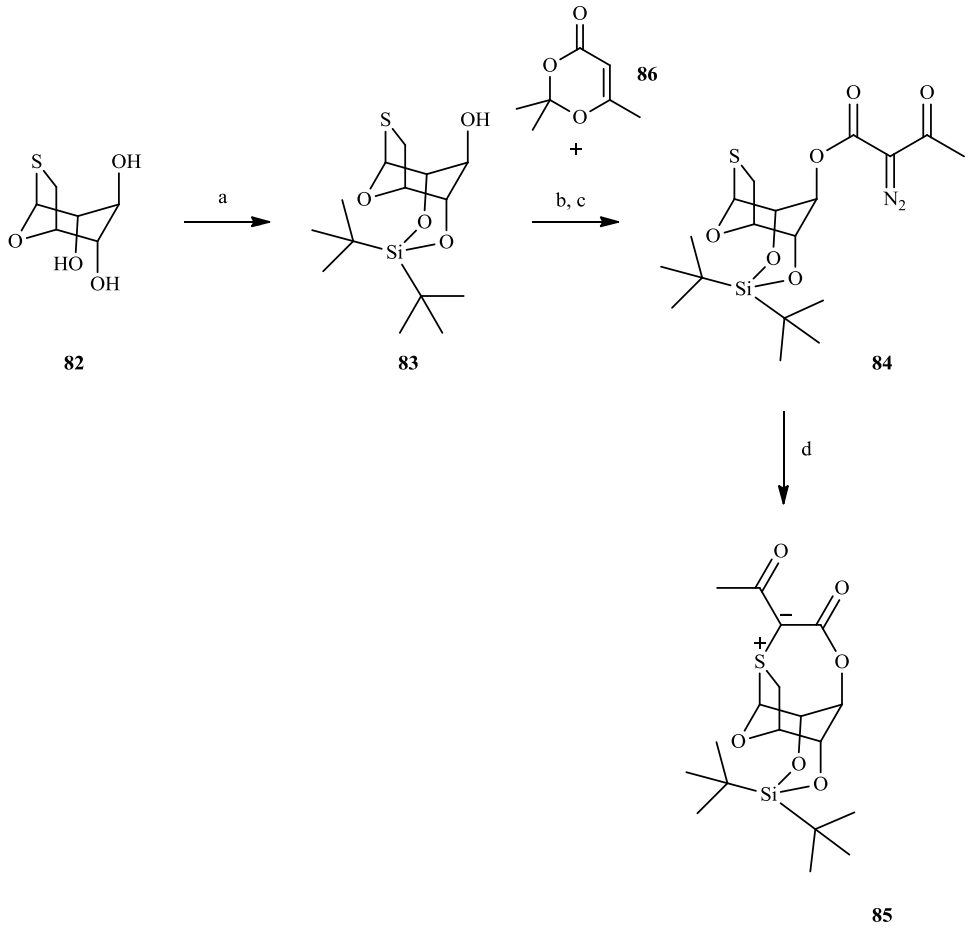
Reagents and conditions: a) TBAF, THF, 99%; b) MsCl, Et_3N, DMAP, DCM, 95%; c) KSAc, DMF, 99%; d) NBS, $AgNO_3$, acetone, 99%; e) $KMnO_4$, $NaHCO_3$, $MgSO_4$, aq. MeOH, 71%; f)$N_2H_4{\cdot}H_2O$, MeOH, 88%

Scheme 12: Porter's synthesis of the bicyclic core of tagetitoxin

Starting from compound **73** as described in **scheme 11**, Porter's group decided to remove both silyl groups simultaneously using TBAF to give the primary alcohol **78**. The alcohol was mesylated and subsequently displaced with potassium thioacetate, and the alkyne was brominated as before to give compound **79**. Oxidation with $KMnO_4$ gave the ketoester **80,** and removal of the *S*-acetyl protecting group led to the bicyclic compound **81**. Using this route, Porter *et al.* successfully synthesized the bicyclic core structure of tagetitoxin.

Two years later Porter *et al*. reported an alternative method for synthesizing the tagetitoxin bicyclic core utilizing a photo-Stevens rearrangement.[14] Building on their previous work which aimed to produce the tagetitoxin core by a ring expansion using a sulfur ylid rearrangement, [13] they concluded that the failure of the expected ring expansion was due to the conformational flexibility of the monocyclic intermediate **64**. They decided that carrying

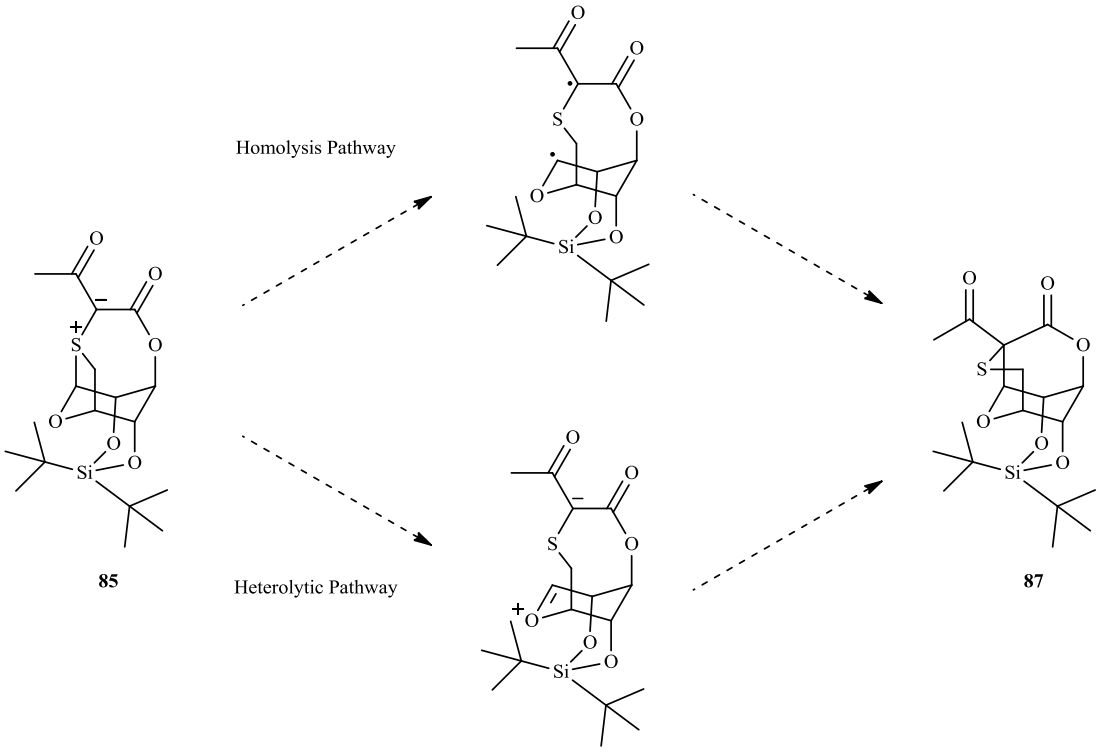
out the ylid formation intramolecularly would lead to a more constrained intermediate, from which the desired C-C bond formation would be favoured.



Reagents and conditions: a) *t*-Bu_2SiCl_2, $AgNO_3$, Et_2N, DMF, 65%; b) **86**, xylene, reflux, 88%; c) *p*-$AcNHC_6H_4SO_2N_3$, Et_3N, MeCN, 100%; d) $Rh_2(OAc)_4$ 1 mol %, benzene, reflux, 88%.

Scheme 13: Porter's Synthesis of ylid 85

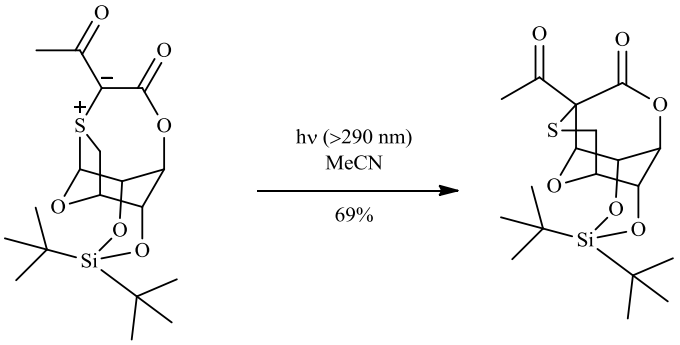
D-glucose was converted to 1,6-thioanhydroglucose **82** in four steps using the procedure reported by Akagi.[15] The C-2 and C-4 hydroxyl were protected using a di-*tert*-butylsilene bridge to give **83** (**Scheme 13**). Acetoacetylation was followed by a diazo transfer to give **84**, which, when treated with 1 mol % rhodium(II) acetate, was converted to isolable tetracyclic ylid **85**. After successfully producing the desired ylid **85,** the group attempted a [1,2]-rearrangement of the sulfonium ylid under elevated temperatures using a variety of solvents to form compound **87**. This, however, proved unsuccessful, even when microwave irradiation was used, in most cases only starting material was recovered, and decomposition was observed after prolonged heating periods.



Scheme 14: Porter's proposed pathways for 1,2 thermal rearrangement

Porter's group proposed two possible mechanisms for the thermal rearrangement of the ylid to give the desired compound **87** (**Scheme 14**). The homolysis pathway is the usual mechanism of the Stevens rearrangement, but, they believed that the heterolytic pathway would be favoured in this case due to their experience with compound **63** to give compound **65** (**Scheme 10**).[13] In an attempt to promote the heterolysis pathway, protic (TFA, TfOH) and Lewis [$Cu(acac)_2$] acids were added to the ylid **85** with the expectation that this would increase the polarization of the C-S bond. This was unsuccessful and no evidence of the ring expansion product was observed.

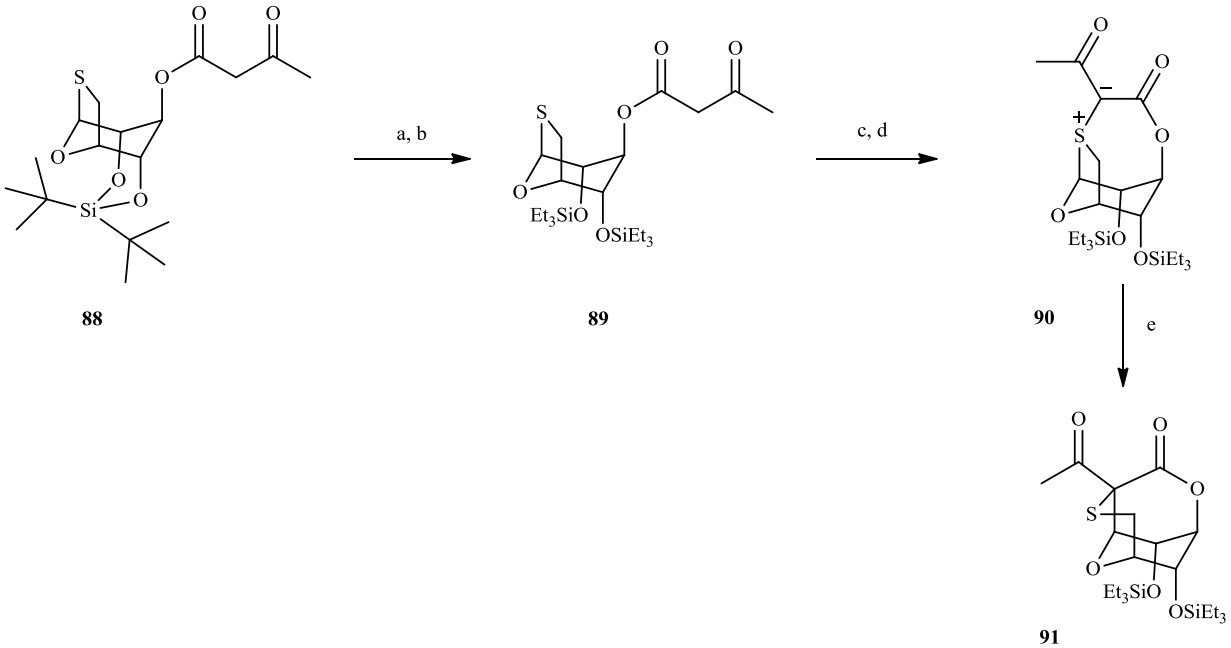
After the failure of the thermal- and acid-catalysed promotion of the Stevens rearrangement, Porter decided to use the photochemical variant (**Scheme 15**).



85 **87**

Scheme 15: Photo-Stevens rearrangement

Ylid **85** was subjected to photolysis in acetonitrile, which successfully converted **85** to the desired compound **87**. With the success of the photo-Stevens strategy the group turned their attention towards determining the structural elements necessary for the ylid formation and subsequent photo-Stevens reaction. They began by altering the bis-*tert*-butylsilene protecting group present on the C-2 and C-4 hydroxyls to bis-triethylsilyl groups (**Scheme 16**).

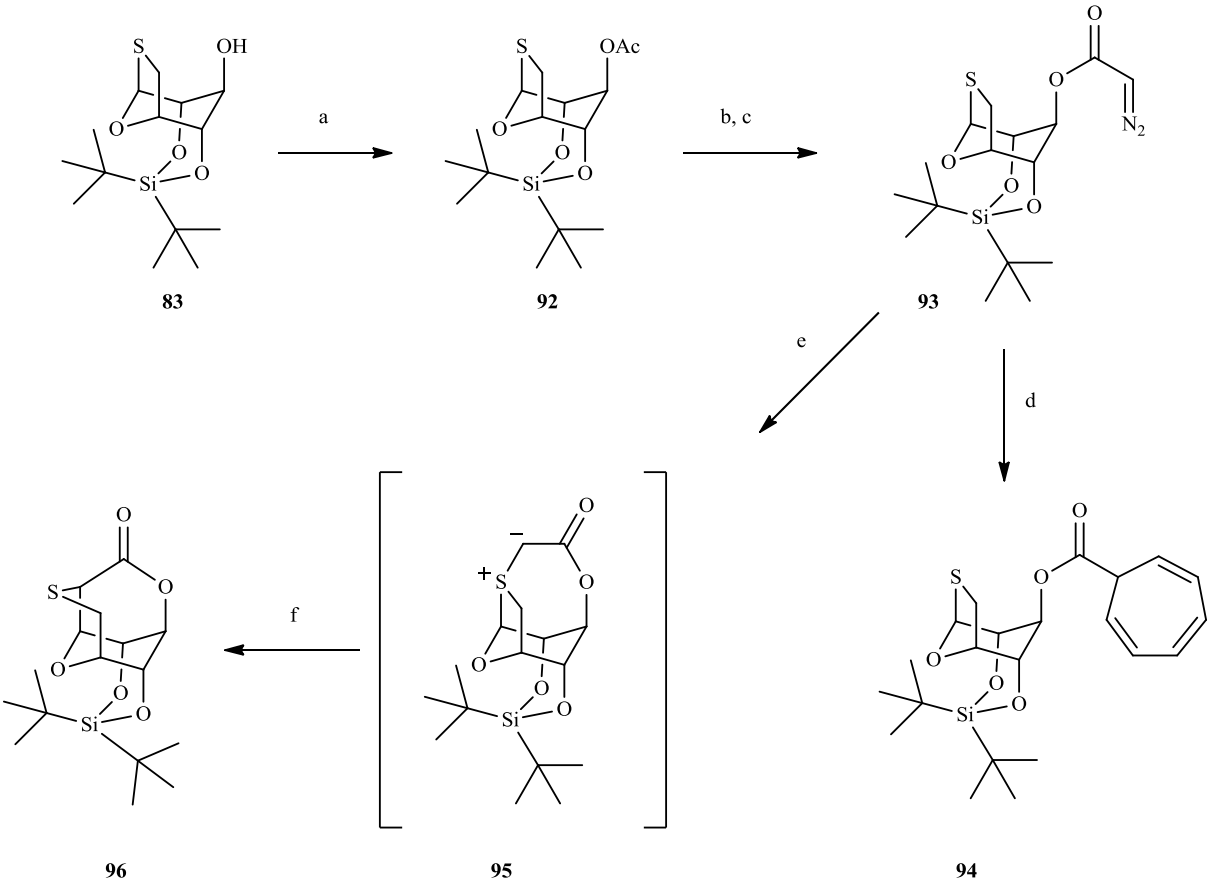


88 **89** **90** **91**

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) hν, MeCN, 65%

Scheme 16: Bis-triethylsilyl protected substrate

Converting to the bis-triethylsilyl groups had no effect on the rate or yield of the ylid formation or photo-Stevens reaction.



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 17: Diazoacetate substrate

Diazoacetate **93** was also synthesized by Porter (**Scheme 17**), following treatment with rhodium(II) acetate in refluxing benzene the undesired cycloheptatriene **94** was obtained. Changing the solvent to dichloromethane gave the ylid **95,** which, when subjected to photolysis, gave the desired tetracycle **96** in 65% yield.

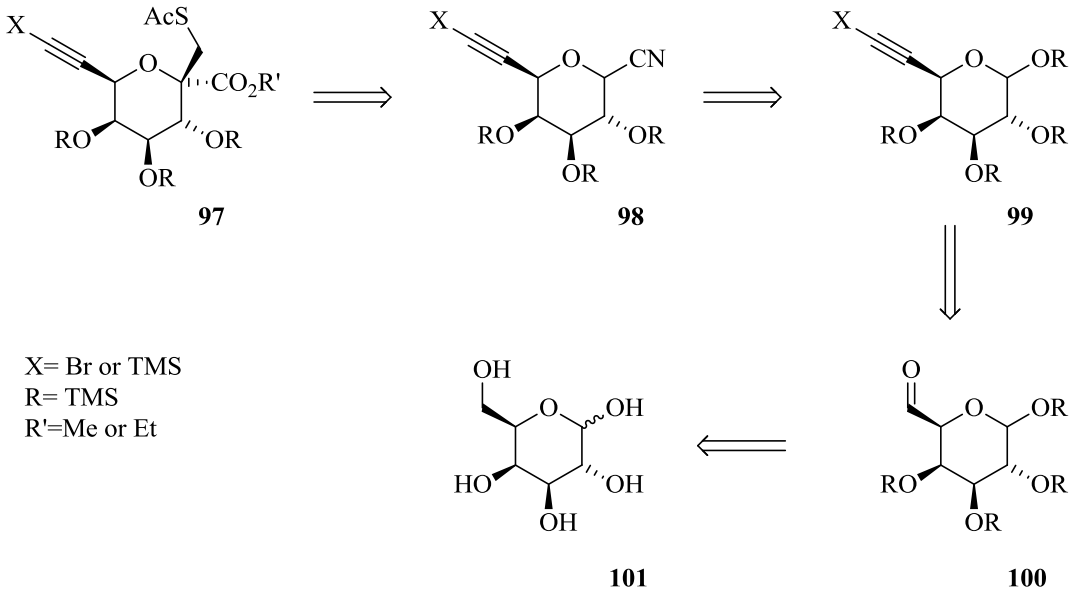
In conclusion Porter *et al* has successfully synthesized the tagetitoxin bicyclic core using two methods, the cyclisation of a thiol onto an electrophilic ketone, and a photo-Stevens rearrangement. At the time of writing these are the only successful attempts to synthesize the

tagetitoxin core structure that have been published however, a total synthesis has yet to be achieved.

Previous work in the Page group

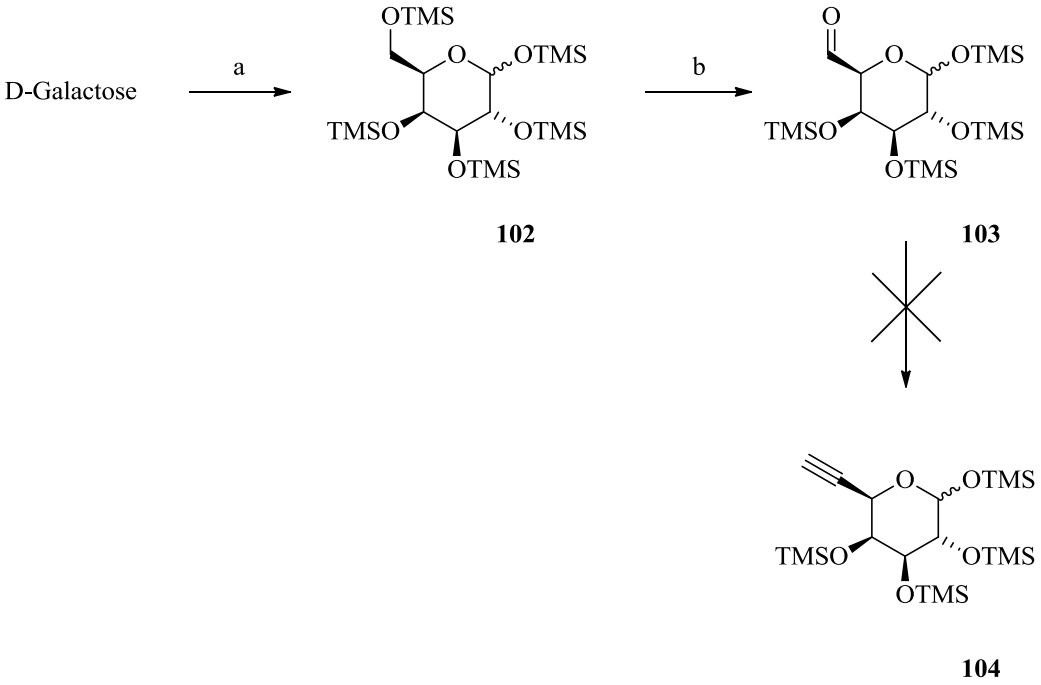
D-galactose route

Initial studies towards the synthesis of tagetitoxin in the Page group were conducted by Claud-Éric Roy.[16] The first route undertaken by our group began with the functionalization of a pyranose ring with the goal of maintaining the configurations of the O-2, O-3 and O-4 hydroxyls until their conversion to the desired moieties later in the synthesis.



Scheme 18: Initial retrosynthesis proposed by the page group from D-galactose

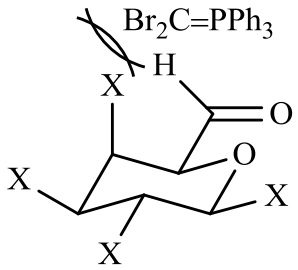
Starting from D-galactose, a short sequence of steps was reported in the literature [17] to obtain compound **100**, which could be converted to the alkyne **99** using known methodology. The cyano moiety would be introduced by a glycosidation reaction. The thioacetate functionality could be achieved by the condensation of formaldehyde on the anomeric carbon followed by a displacement of the protected hydroxyl with a thioacetate anion. The cyano group would be converted to an ester using well known literature procedures.[18]



Reagents and conditions: a) TMSCl, pyridine, 3 h, 100%; b) $(COCl_2)_2$, DMSO, DCM, −78 °C, then Et_3N, −50 °C.

Scheme 19: Attempted synthesis alkyne 104 from D-galactose

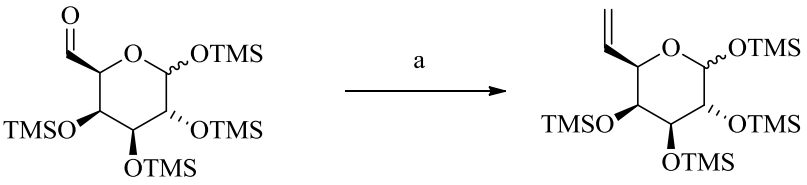
Silylation of D-galactose proceeded smoothly to give compound **102,** but initial attempts to oxidize the primary alcohol to the aldehyde using chromium trioxide led to no desired product being isolated. Several other oxidation procedures were attempted, including PCC, PDC, and sulfur trioxide-pyridine complex without any success. Lastly a Swern procedure was used to achieve the aldehyde in good yields (80-98%). A Corey-Fuchs procedure [19] was used to convert the aldehyde into the desired alkyne; this, however, proved unsuccessful and resulted in recovery of starting material in every attempt and variation of the procedure. This led to the deduction that a possible explanation for the lack of reactivity could be steric hindrance by the -OTMS group on the C-4 position preventing the ylid from reacting with the aldehyde (**Figure 9**).



X=OTMS

Figure 9: Steric hindrance generated from the C-4 OTMS group.

Several further attempts were made to produce the desired alkyne **104** using a Seyferth-Gilbert reaction with the Ohira-Bestmann protocol.[20] Unfortunately, these all proved unsuccessful. To deduce the reactivity and accessibility of the aldehyde, a standard Wittig reaction was performed using a methylene-phosphorus ylid to form the terminal alkene.



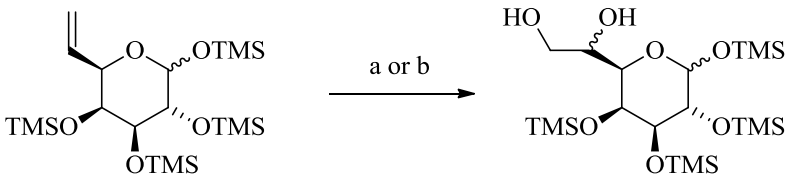
103 **105**

Reagents and conditions: a) Ph_3PMeBr, *t*BuOK, 49%

Scheme 20: Wittig reaction on aldehyde 103

Several procedures were used to synthesize alkene **105** including phosphonium species generated *in situ* or pre-synthesized; also two different bases were used to form the ylid, *t*BuOK and *n*BuLi. The best yield was obtained when the phosphonium bromide was formed before the olefination step and *t*BuOK was used a base (**Scheme 20**). The relatively low yields overall were presumed to be due to steric hindrance around the pyranose cycle of the aldehyde **103**.

With the alkene in hand an alternative strategy was devised to reach the final α-ketoester by a dihydroxylation and sequential oxidation. Common methods for the dihydroxylation reaction were attempted including $OsCl_3$ and AD-mix (**Scheme 21**).



105 **106**

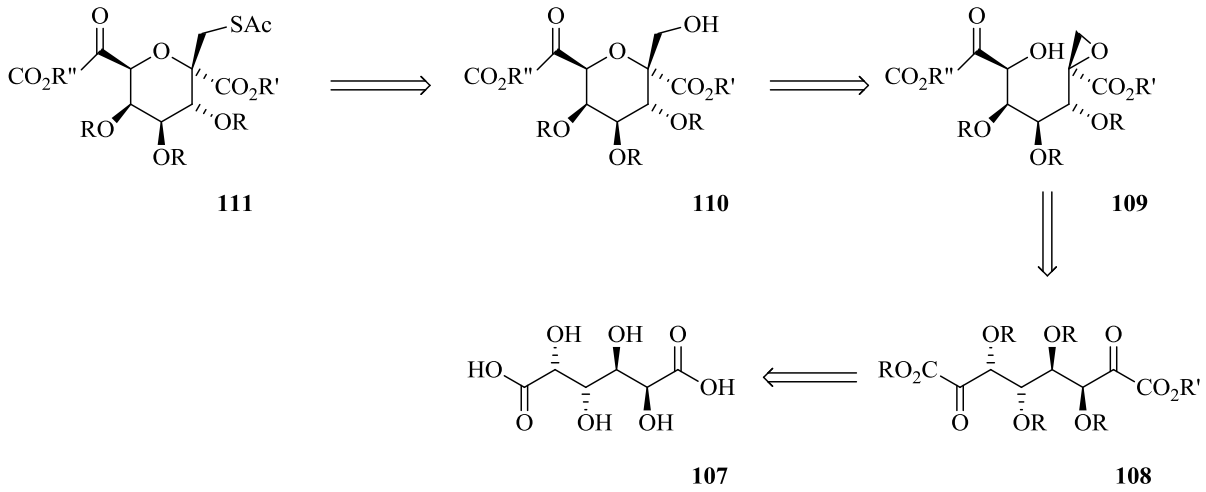
Reagents and conditions: a) AD-mix β, *t*BuOH, H_2O; b) $OsCl_3$, NMO, THF, rt, 18 h

Scheme 21: Attempted dihydroxylation of alkene 105

The first attempts to produce the diol using AD-mix were unsuccessful and only starting material was recovered from the reaction mixture. Under the $OsCl_3$ NMO conditions, the disappearance of the alkene signals observed by ^1H NMR spectroscopy indicated that the reaction had proceeded to give the diol, but after purification more complex mixtures were isolated, indicating that the product was unstable during flash chromatography. Later in this strategy it was planned to use anomeric chemistry to substitute the silyl ether with a cyanide moiety which would later be converted to the desired ester functionality. With this strategy in mind it was decided to protect the diol functionality in order to purify the crude mixture and reduce the likelihood of participation of the hydroxyl groups; ketal and acetate protecting groups were chosen for this purpose. Standard conditions for forming the acetal were used (2,2-DMP with catalytic amounts of acid), but instead of obtaining the desired ketal protected compound an unexpected loss of mass was observed. The introduction of acetate groups was also attempted but did not yield the desired compounds, instead giving a more complex mixture of products. Due to the instability of the silyl ether protecting groups under these conditions this strategy was abandoned, and other potential routes were examined before any further work on this step was conducted.

Mucic acid route

In an alternative approach to starting with a cyclic precursor, a new route was devised that would begin with the meso compound galactaric acid (mucic acid).

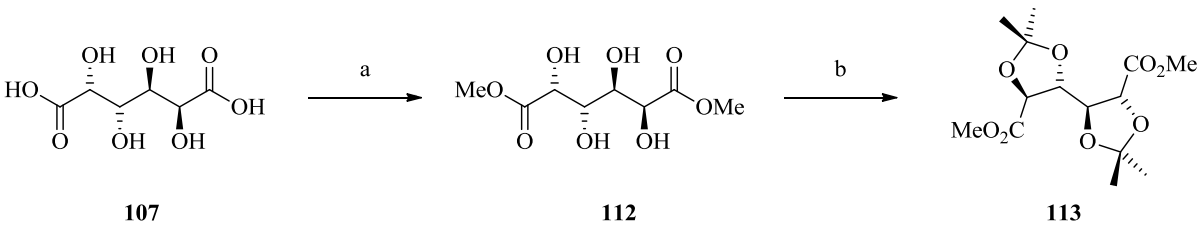


Scheme 22: Retrosynthesis from galactaric acid

Using this strategy, the pyranose ring would be formed through a ring closure by attack of a nucleophilic oxygen onto an epoxide to give an advanced intermediate towards the tagetitoxin synthesis **110** (**Scheme 22**). The precursor **111** would derive from a displacement of an activated hydroxyl by a thioacetate anion. Intermediate **110**, fully functionalized at this stage, could be derived from the terminal epoxide **109**. This intermediate could be achieved through a Tebbe olefination-epoxidation sequence, [21] or a Corey-Chaykovsky reaction [22] on one of the two ketone carbonyls from di-ketoester **108,** which could be synthesized in a few short steps from galactaric acid.

To obtain the di-ketoester **113**, a procedure by Hirsch *et al.*[23] was followed (**Scheme 23**). The initial step was a methyl ester formation using MeOH and THF to give diester **112** in nearly quantitative yields (90-99%). The next step was the bis-ketal formation using acetone and a Lewis acid. The fully protected compound **113** was obtained in very low yields despite

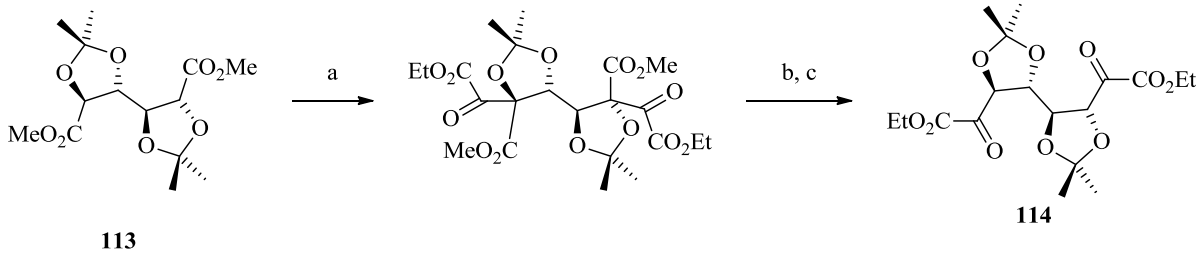
several attempts (17-25%, lit. 27%). Changing the Lewis acid catalyst for Brønsted acids (H_2SO_4, *p*TSA, HCl) led to reduced yields, and in some cases, decomposition.



Reagents and conditions: a) MeOH, THF, 90% b) Lewis acid, acetone, 17-25%

Scheme 23: Formation of dimethyl bis-acetonide galactarate 113

X-ray crystal structure analysis confirmed the structure of compound **113** and matched the result documented in the literature.[23] The second stage in this strategy was to obtain the di-ketoester moieties; the simplest route seemed to be the formation of the enolates of the ester functions on **113** and allow the enolate to attack a derivative of oxalic acid, diethyl oxalate. Following this would be a decarboxylation under acidic conditions and subsequent esterification to give the diketoester **114** (**Scheme 24**).

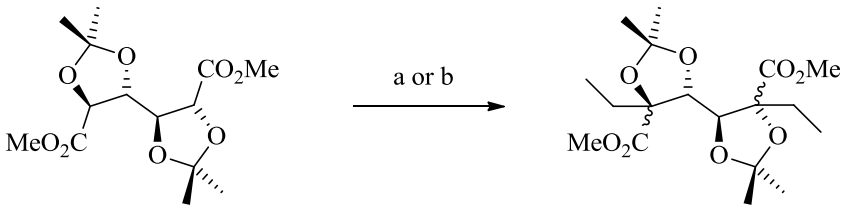


Reagents and conditions: a) EtONa, diethyl oxalate, EtOH, RT; b) HCl *aq*, reflux, 6 h; c) *p*-TsOH, EtOH, toluene, reflux 6 h

Scheme 24: Formation of α-ketoester moiety

Unfortunately, several attempts to achieve the di-ketoester **114,** including the use of several bases and conditions, were unsuccessful and resulted in only starting material being

recovered. This led the group to try several alkylation reactions on compound **113** to assess the reactivity of the carbon to be deprotonated (**Scheme 25**). Both conditions failed to alkylate the esters and only starting material was recovered from the reactions. In one final attempt to investigate whether the enolate of ester **113** was being generated, following a similar procedure, LDA was used to form the enolate of ester **113** and D_2O was added to quench the reaction. While the di-deuteriated compound was observed by ^1H NMR spectroscopy, further work on this route was abandoned due to the very poor yields for the bis-ketal formation and the lack of success producing the ketoester moieties.



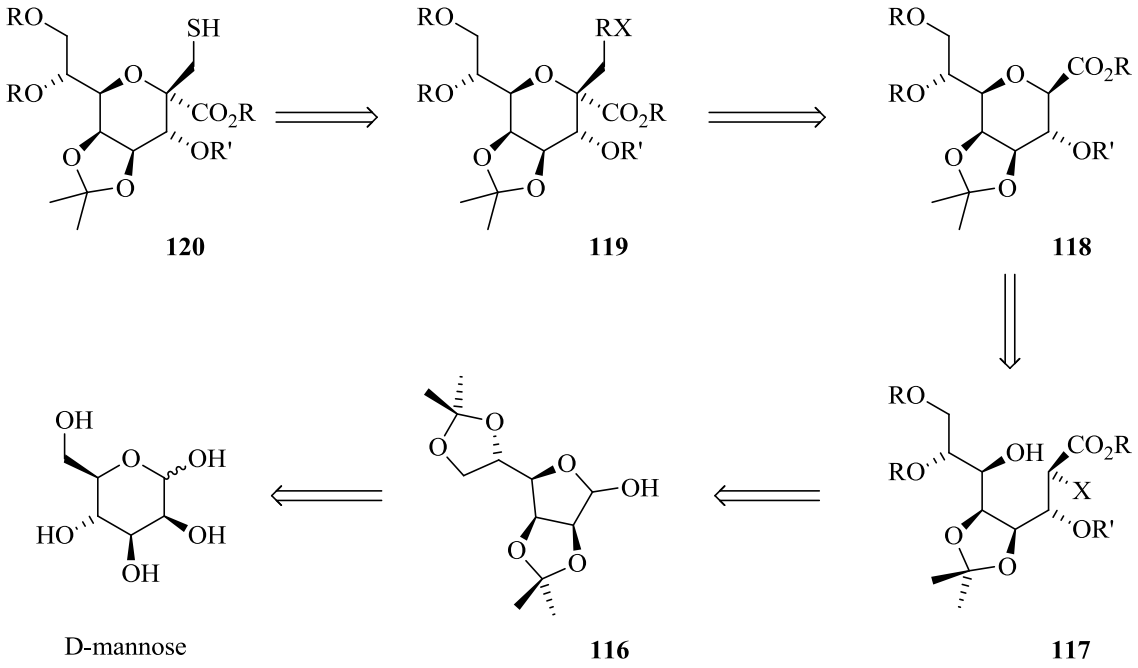
113 **115**

Reagents and conditions: a) NaH, EtI, THF, 0 °C; b) LDA, EtI, THF, –78 °C

Scheme 25: Alkylation attempts on compound 113

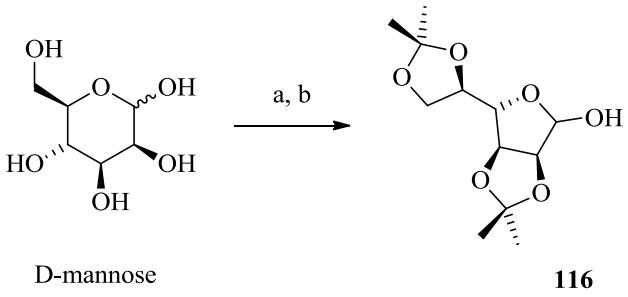
D-mannose route

A new strategy was devised beginning with the compound diacetone mannose **116**, which can be easily prepared from D-Mannose in acetone with H_2SO_4 (**Scheme 26**). Diacetone mannose could be converted to alcohol **117**, which in turn could be cyclized to form pyranose **118**. This could be converted to the intermediate **119** using enolate chemistry already reported in the literature.[24]



Scheme 26: Retrosynthesis from diacetone mannose

The first step in this strategy was the protection of mannose to form diacetone mannose **116**; this is a well-established reaction in carbohydrate chemistry first reported by Schmidt in 1963.[25]



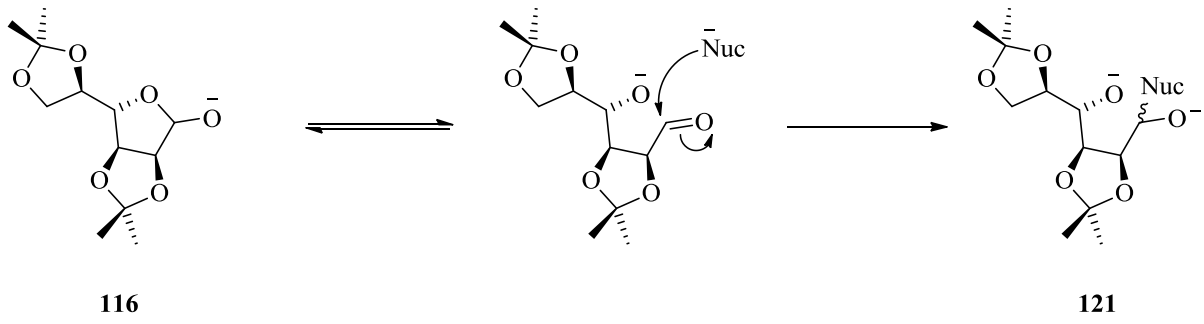
Reagents and conditions: a) H_2SO_4, acetone, rt, 3 h; b) Na_2CO_3, charcoal, acetone, reflux, 1 h.

Scheme 27: Schmidt's synthesis of diacetone mannose

This procedure led to a variety of problems initially; the order of addition of sulfuric acid and mannose in acetone was critical, leading to decomposition of the starting material if not performed correctly. The problem was aggravated with smaller scale reactions, prompting the use of dilute sulfuric acid to prevent the decomposition of starting material, which led to the

production of an unidentifiable compound that had the same *m/z* as the desired product but did not match the NMR data expected. Neutralizing the reaction mixture before the second stage of the reaction was also found to be crucial as refluxing a slightly acidic solution also led to decomposition. Finally, an optimum reaction procedure was found and diacetone mannose was produced in good yields (75-90%) giving a mixture of the α- and β-form; the crystallization procedure in the literature was not always sufficient to yield only the α-anomer, this, however, was not required for the next step in the synthesis.

The next step in the synthesis was the addition of a masked α-ketoester onto the aldehyde moiety of diacetone mannose. The lactol function of diacetone mannose can exist in its closed form and the open hydroxy-aldehyde form shown in **scheme 28**, and therefore a nucleophilic species was chosen to add to the aldehyde function. Several methods were attempted to condense ethyl diazoacetate and ethyl and methyl bromoacetate onto diacetone mannose without success (**Table 3**).



116 **121**

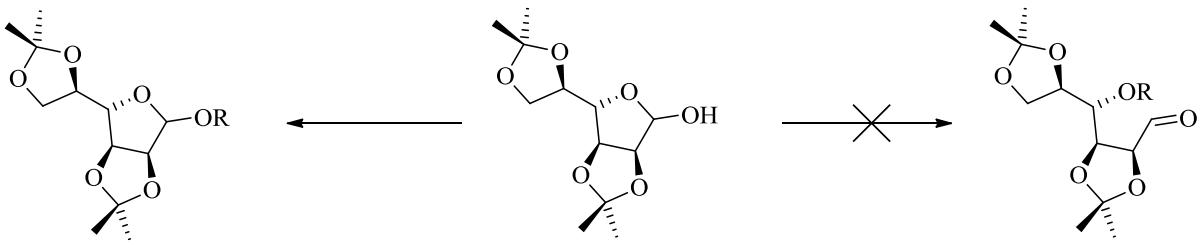
Scheme 28: Proposed reactivity of lactol-hydroxy aldehyde equilibrium

Method	Conditions	Result
1	Ethyl diazoacetate, Et_2Zn, DCM, −78 °C to rt, overnight	SM
2	Ethyl diazoacetate, Et_2Zn, DCM, 0 °C to rt, 48 h	SM
3	Ethyl diazoacetate, $Ti(OiPr)_4$, DME, H_2O, rt, 120 h	SM
4	Ethyl diazoacetate, neat, 24 h	SM
5	Methyl bromoacetate, LiBr, TEA, Toluene, 0 °C to rt, overnight	SM
6	Ethyl bromoacetate, LDA, THF, −78 °C to rt, overnight	SM

Table 3: Reagents and conditions for addition of ketoester onto diacetone mannose

With the lack of successful results to produce ketoester intermediates **121**, another route was explored. While still focusing on the aldehyde moiety of diacetone mannose, the hydroxyl

group in the open form would be protected before any reaction involving the aldehyde was performed. Initially the protection of the open form hydroxyl was attempted directly from diacetone mannose.

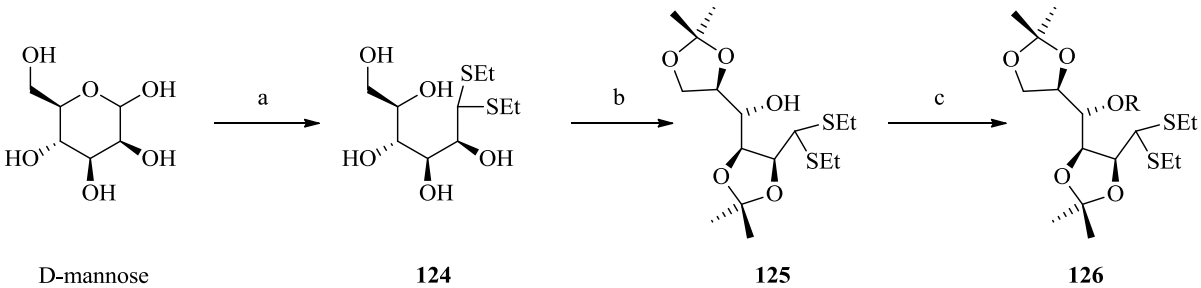


R= TBDPS, TBDMS, TIPS

Scheme 29: Protection of 4-hydroxyl

Despite several procedures to protect the 4-O hydroxyl of diacetone mannose with a variety of silyl ethers, the end result was always either a protection of the 1-O hydroxyl **123** or recovery of starting material, the desired compound **122** never being observed (**Scheme 29**).

A new route to synthesize the target aldehyde was formulated involving the protection of the aldehyde function first as a thioacetal; subsequent protections of the different hydroxyl groups, and hydrolysis of the thioacetal would lead to the desired intermediate (**Scheme 30**).



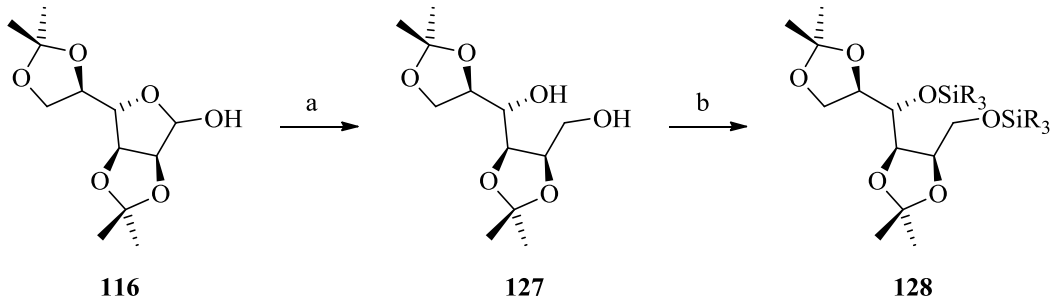
Reagents and conditions: a) EtSH, HCl, 89%; b) acetone, H_2SO_4; c) protection, cleavage

Scheme 30: Synthesis of protected aldehyde

The initial thioacetal formation proceeded smoothly, D-mannose was dissolved in ethanethiol and HCl was used as a catalyst to give the protected compound **124** in 89% yield. The second

step was the selective 2,3-5,6-diisopropylidene formation. Acetone and sulfuric acid were used as previously described for the formation of diacetone mannose, but this procedure was not successful on this compound. Every attempt led to an inseparable mixture of compounds or decomposition of the starting material.

The lack of success of the thioacetal procedure prompted the group to try a sequential silylation protection method on diacetone mannose. The synthesis began with the reduction of diacetone mannose **116** with lithium aluminium hydride to give the diol **127** in high to quantitative yields. Several silylation procedures were tried using TESCl and TMSCl, leading to the diprotected species of both silyl ethers in good yields (**Scheme 31**).

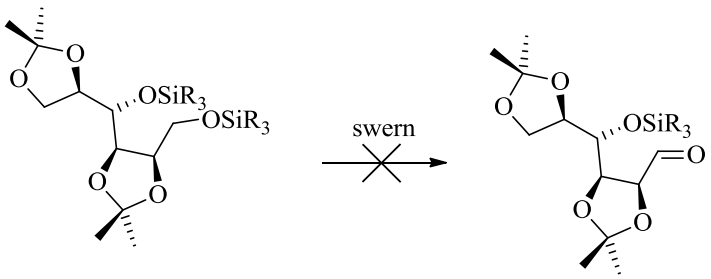


116 **127** **128**

Reagents and conditions: a) $LiAlH_4$, Et_2O, 4 h, 0 °C to rt; b) base, R_3SiCl, solvent

Scheme 31: Reduction and disilylation procedure

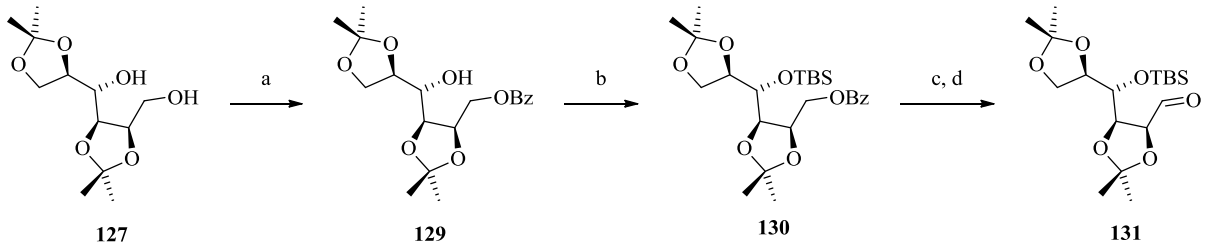
The next step was the selective oxidation of the primary silyl ether. Following literature procedures on silyl ether oxidations, [26] Swern reactions were performed on the disilylated compounds (**Scheme 32**).



128 **122**

Scheme 32: Selective oxidation on the primary silyl ether

Several attempts were made to oxidize the primary ether to form the desired aldehyde **122**, but none of the reactions led to the product and the route was therefore abandoned.



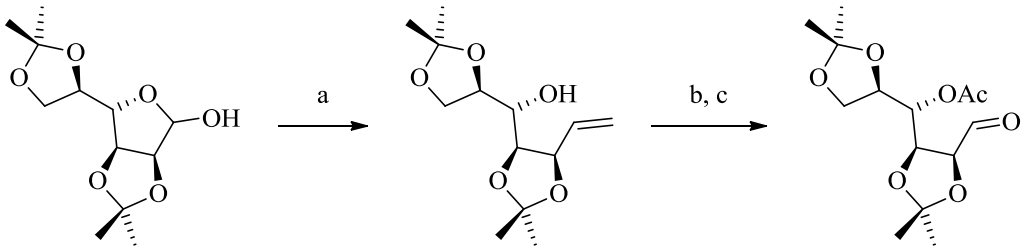
127 **129** **130** **131**

Reagents and conditions: a) BzCl, pyridine, 0 °C, rt; b) TBSCl, base, solvent; c) saponification; d) oxidation.

Scheme 33: Proposed synthesis for the aldehyde intermediate 131

A revised strategy for the synthesis of the desired silylated aldehyde was devised involving the sequential protection of diacetone mannose using a benzoylation, following a procedure by Hasimoto, [27] where diacetone mannose was converted to the TBS protected aldehyde **131** in five steps. Using this procedure, the benzoyl protected compound **129** was successfully prepared in 55% to 80% yield depending on the conditions used (**Scheme 33**). In some cases a by-product of this reaction was the di-benzoylated compound. The next step in this synthesis was the protection of the remaining secondary alcohol with the TBS ether. Two methods were reported in the literature, TBSOTf in TBME or pyridine, or TBSCl in DMF. TBSCl was unsuccessful in producing the target compound, the desired intermediate was never isolated and the reaction gave a complex mixture of unknown compounds. Using

TBSOTf gave better results, yielding the target compound **130** in 37% yield. The following step in this route was the saponification of the ester to deprotect the hydroxyl function and the subsequent oxidation to the aldehyde moiety. Saponification of the ester proceeded in almost quantitative yields without the need for purification, but none of the oxidation procedures led to the desired aldehyde **131**.



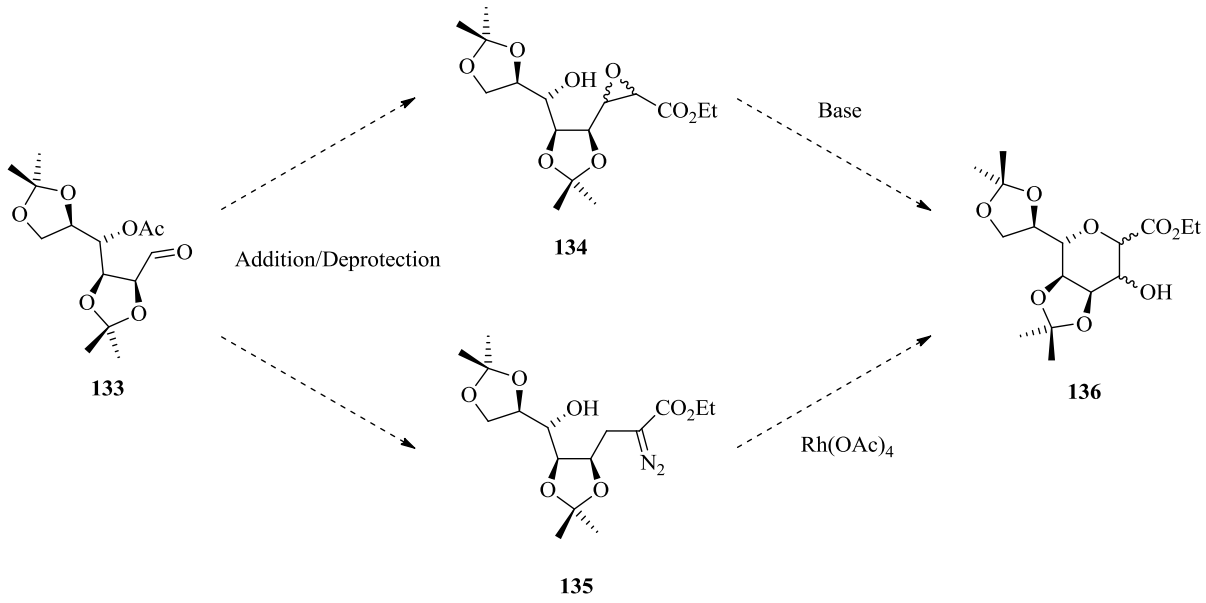
116 **132** **133**

Reagents and conditions: a) Ph_3PCH_3Br, BuLi, THF, –20 °C, overnight; b) acetylation; c) ozonolysis

Scheme 34: Synthesis of aldehyde intermediate via Wittig procedure

An alternate route to the protected aldehyde compound **133** using a Wittig olefination step was reported by López-Herrera. [28] The first step is the Wittig reaction to form the terminal olefin **132**, an acetylation followed by ozonolysis would then lead to the desired compound **133** (**Scheme 133**).

The olefination was performed with methyltriphenylphosphonium bromide and butyl lithium in THF at -20 °C. The reaction was successful and produced the desired alkene **132** in 47% to 76% yield. The next step was the protection of the secondary hydroxyl group; using acetic anhydride and pyridine the acetylation proceeded very smoothly to give between 84% and 97% yield. Several attempts at a silyl protection of this intermediate were made, to produce a shorter method of reaching the silyl ether mentioned earlier, but the desired product was never observed. The last step in this route was the ozonolysis; the reaction was performed at -78 °C to prevent any decomposition of the aldehyde. Both triphenylphosphine and dimethylsulfide were used as reducing agents and both led to the aldehyde in good yields Chromatography was necessary to remove triphenylphosphine oxide, whereas when using DMS, evaporation under reduced pressure was sufficient to obtain the pure compound.

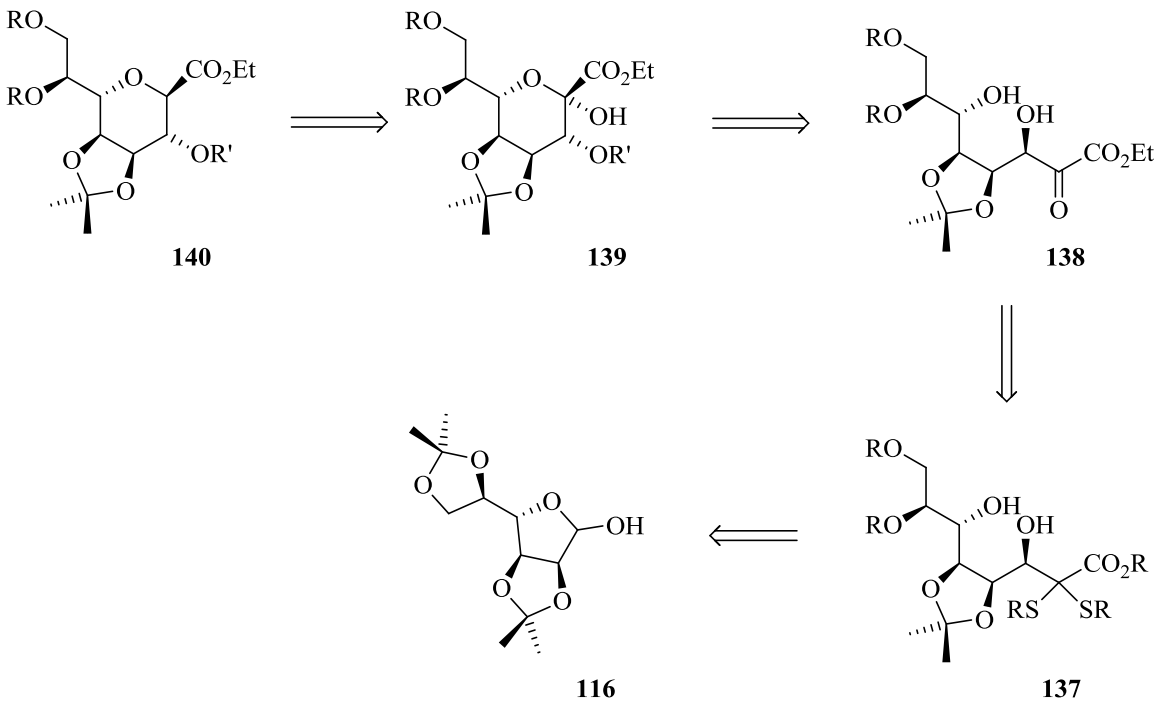


Scheme 35: Proposed routes for pyranoside 136

With aldehyde **133** in hand, the next step for the group was to add functionalities to the C-1 position. Two possible pathways were devised (**Scheme 35**). The first route was based on a Darzens reaction; an alkyl-haloacetate would be condensed onto the carbonyl group, followed by elimination of the halogen by attack from the anionic oxygen. The second route would consist of an alkyl-diazoacetate condensing onto the carbonyl group, the acetate ester would then be cleaved and the resulting diol treated with $Rh(OAc)_4$ in order to trigger the formation of the epoxide or the direct 6-endo-tet cyclization to form pyranoside **136**. Both routes were attempted but neither gave the desired pyranoside of the α-epoxyester, which led to the route being abandoned.

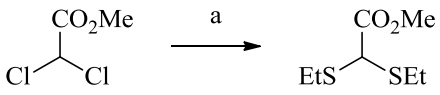
Dithioacetal route

The final strategy previously attempted by the group consisted of a nucleophilic addition of a synthetically equivalent α-ketoester onto diacetone mannose (**Scheme 36**).



Scheme 36: retrosynthesis of pyranoside ester 140

This route was developed from the synthesis of 3-deoxy-D-manno-2-octulusonic acid (KDO) which utilized thioacetal species to achieve the intermediate **139**.[29] The first step in this route was to synthesize one of the nucleophilic addition species as it was not commercially available and was relatively simple to produce on a large scale.

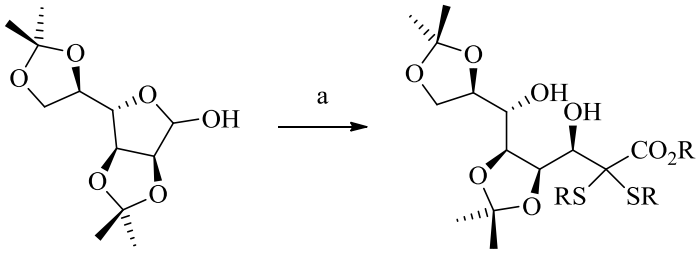


141 **142**

Reagents and conditions: a) MeONa, then EtSH, 82%.

Scheme 37: Formation of dithioacetal 142

Diethyldithioacetal **142** was formed from methyl dichloroacetate and ethane thiol using the literature procedure.[30] The next step was the nucleophilic addition onto diacetone mannose, performed as repoted in the literature.[29]



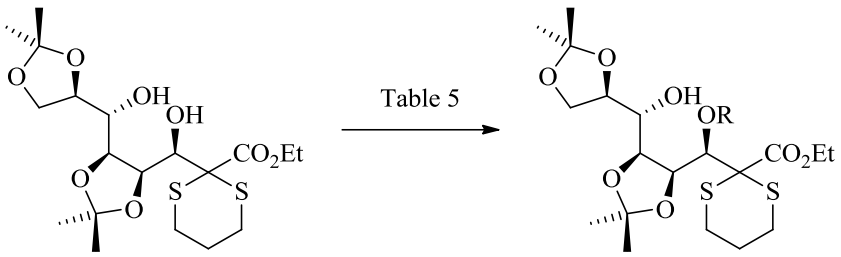
116 **137**

Reagents and conditions: a) LDA, dithioacetal species, **116**

Method	Thioacetal	Conditions	Yield
1	Diethyl dithioacetal	DIPA, BuLi then dithioacetal, then $MgBr_2$, then **116**	SM
2	Ethyl dithiolane carboxylate	DIPA, BuLi then dithiolane, then $MgBr_2$, then **116**	SM
3	Ethyl dithiane carboxylate	DIPA, BuLi then dithiane, then **116**	SM
4	Ethyl dithiane carboxylate	DIPA, BuLi then dithiane, then $MgBr_2$, then **116**	65%

Table 4: reagents and conditions for nucleophilic addition reaction

The next step in this synthesis was the selective protection of the C-3 hydroxyl group before the dethioketalization to trigger the cyclization to form the desired intermediate **139**. Several protecting groups were chosen, including a stable silyl group TBDMS, a benzyl group and a benzoyl group (**Table 5**).

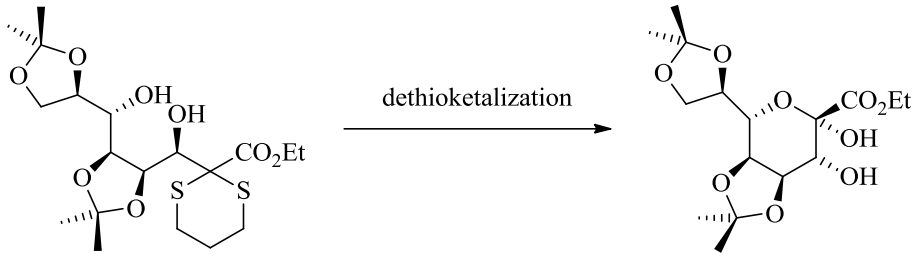


Scheme 38: Protection of C-3 hydroxyl on intermediate 143

Method	R group	Conditions	Yield
1	TBS	TBDMSCl, imidazole, DMAP, Et_2O, overnight, rt	SM
2	TBS	TBSCL, imidazole, DMAP, Et_2O, 3 d, rt	SM, diacetone mannose
3	Bn	DIAD, Ph_3P, BnOH, THF, reflux, overnight	Decomposition
4	Bn	MeMgBr, BnBr, THF	SM, Diacetone mannose
5	Bz	BzCl, pyridine, THF, then dithiane **143**	SM

Table 5: Reagents and conditions for protection of C-3 hydroxyl on compound 143

Unfortunately all the attempts to protect the C-3 hydroxyl were unsuccessful, in some cases even leading to the decomposition of the starting material, which reverted back to diacetone mannose **116**. This lack of reactivity was blamed on the steric hindrance in the compound **143**. The formation of diacetone mannose was thought to occur due to a fragmentation process initiated by deprotonation of the hydroxyl group α- to the dithiane group, which would revert to an aldehyde and reform the lactol ring of diacetone mannose. Following the poor results from the protection reactions, the sequence was altered to begin with the dethioketalization step and then proceeded to protect the hydroxyl afterwards (**Scheme 39**).



143 **145**

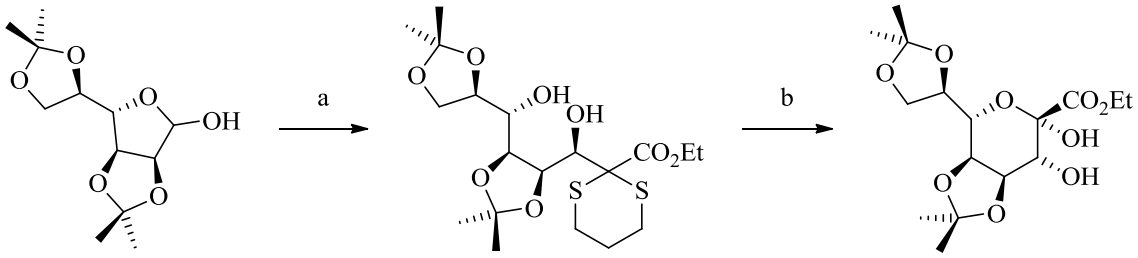
Scheme 39: Dethioketalization and cyclization of compound 143

Initial attempts for the dethioketalization were performed as stated in the literature, [29] but the yields of the pyranose **145** obtained were significantly lower (18%), than that reported in the previous work (76%). This low yield was exacerbated when the reaction was scaled up, often leading to little if any product. Several methods were attempted to remove the dithiane group, NBS, I_2 and NIS all giving disappointing results. Even after using the purest components possible for the reaction, (recrystallized NBS, HPLC grade acetone and distilled water) the yields were not improved. Only a small quantity of pyranose **145** was obtained, which after purification led to either decomposition or total loss of the compound.

The initial studies on the synthesis of tagetitoxin in the Page group led to a number of possible routes that would be investigated further as described in this thesis. It also ruled out several routes that were deemed too problematic or simply not possible to undertake.

Project

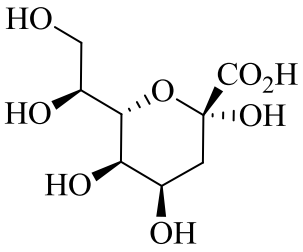
Following on from previous work in the group our aim was to build on several of the intermediates produced, particularly with the work on dithioacetal protected ketoesters, as we believed this was the most promising route developed at that point (**Scheme 40**).



116 **143** **145**

Reagents and conditions: a) LDA, $MgBr_2$, dithiane, **116**; b) NBS, acetone/water

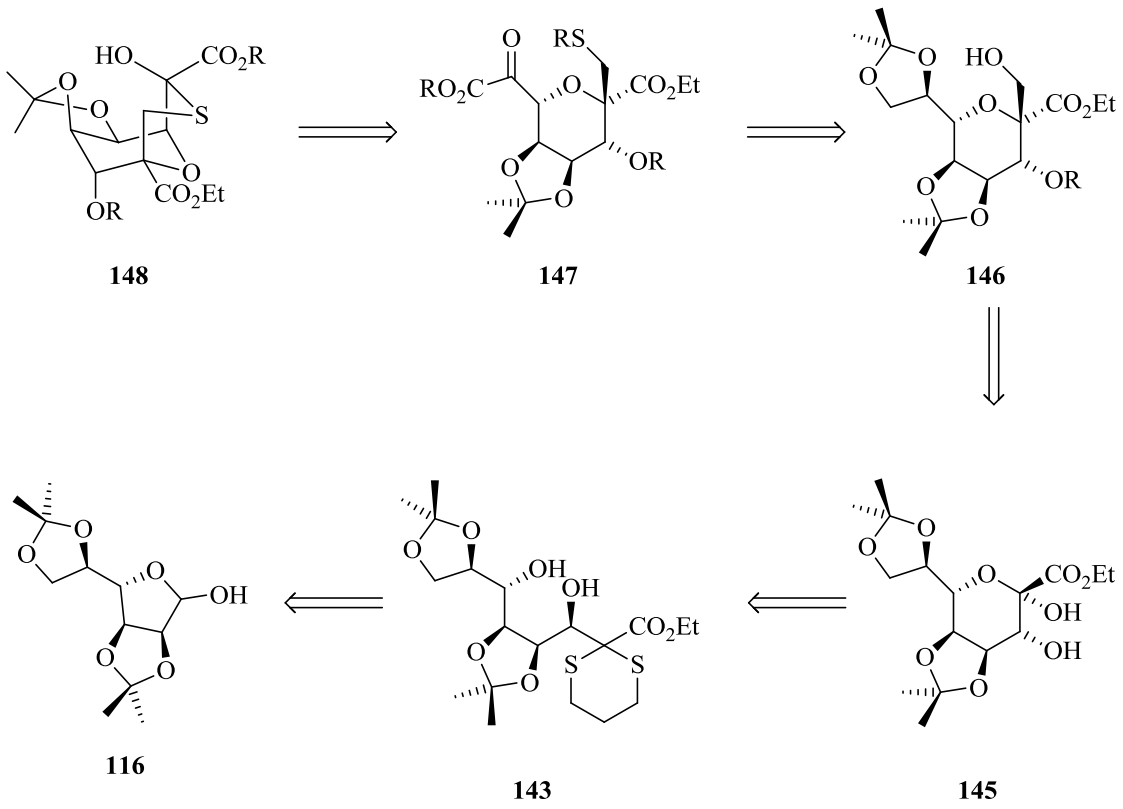
Scheme 40: Preparation of pyranose intermediate 145



KDO

Figure 10: Structure of 3-Deoxy-D-gluco-oct-2-ulosonic Acid (KDO)

We also noted that one of our advanced intermediates was an almost identical structure to 3-deoxy-D-gluco-oct-2-ulosonic acid (**KDO) (Figure 9)**. There are many publications on KDO synthesis and syntheses of analogues using several different methods.[31,32,33,29] Therefore several of our synthetic routes began with modified versions of these syntheses. It must also be noted that from here onwards we abandoned any attempts to synthesize our target with smaller linear molecules and concentrated solely on working from a sugar starting material, in most cases this was D-mannose or the protected diacetone mannose **116**. We believed this was a far simpler method of obtaining the desired intermediate as most of the stereochemistry would be known and correct at the beginning of the synthesis.



Scheme 41: Retrosynthesis for target bicyclic compound 148

Our initial goal was always to reproduce the bicyclic structure of tagetitoxin **148** while ensuring that each of the functional groups were chemically different enough to convert each one individually to the correct moieties of the natural product. Working from pyranose **145**, we believed that the secondary hydroxyl could be protected without any reactions involving the tertiary hydroxyl α- to the ester moiety. This alcohol would then be converted to a suitable leaving group and displaced with either a hydride source. Simple enolate chemistry with formaldehyde would follow to form **146**. This primary alcohol could then be converted to another leaving group, *e.g.* mesylate or tosylate and displaced with a thioacetate anion to form the protected thiol. The primary acetonide group could then be selectively deprotected to the diol followed by oxidation to the α-ketoester or ketoacid to give **147**. Removal of the acetate on the thiol function should lead to the cyclization to form the target bicyclic structure **148**. From this structure, theoretically each functional group could be introduced using known carbohydrate chemistry to give the natural product tagetitoxin **2a**.

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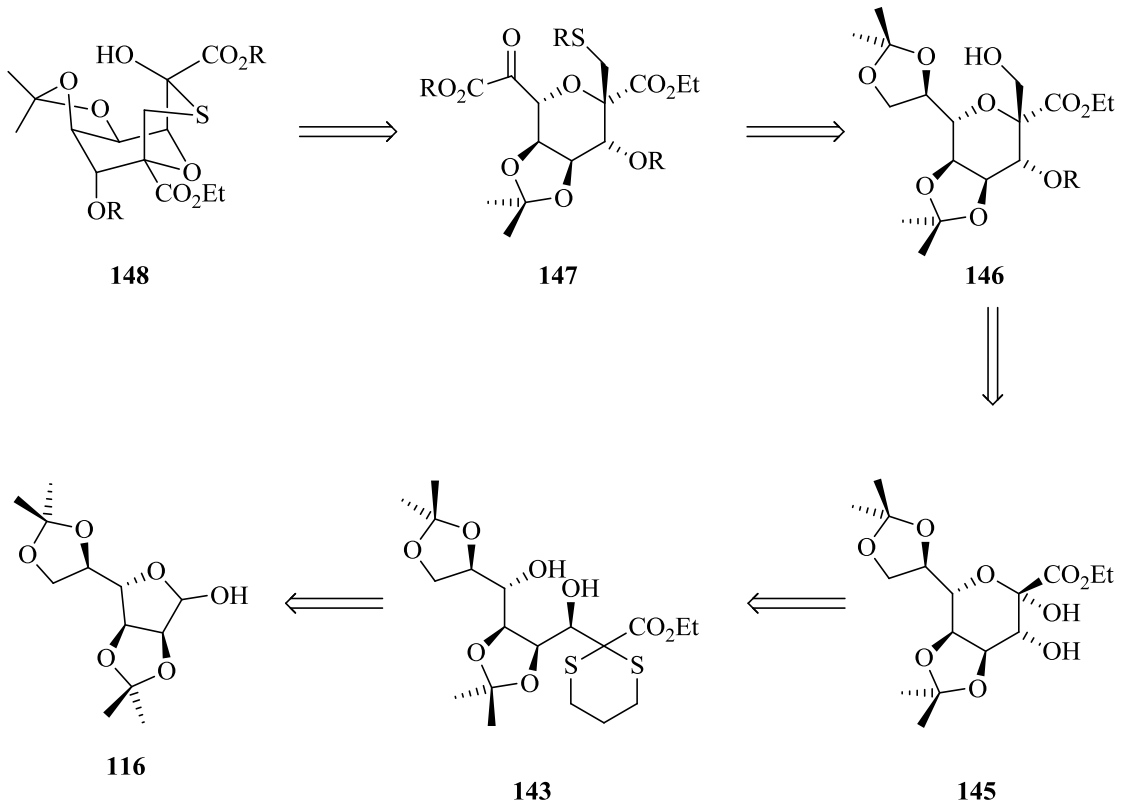
Results and Discussion

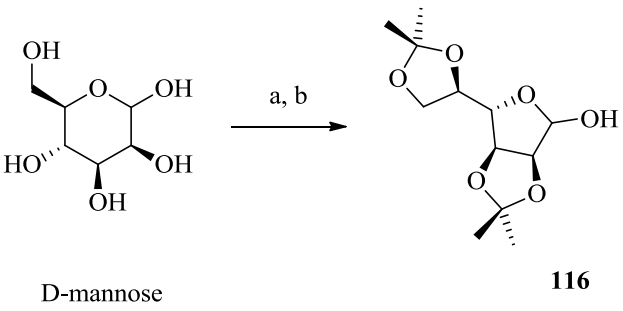
Dithioacetal protected ketoester route

In our initial route we decided to continue the work previously conducted in the group on the addition of a dithioacetal-protected ketoester onto diacetone mannose **116** (**Scheme 42**).



Scheme 42: Initial Retrosynthesis via the dithioacetal route

Following the procedure in the literature [1] D-mannose was successfully converted to diacetone mannose **116** in 60-80% yield (**Scheme 43**). The crystallization procedure used in the literature was not sufficient to give 100% of the single anomer; however this was not necessary as the next step in the procedure involves the open form of the protected furanose therefore negating the stereochemistry at the anomeric carbon atom.

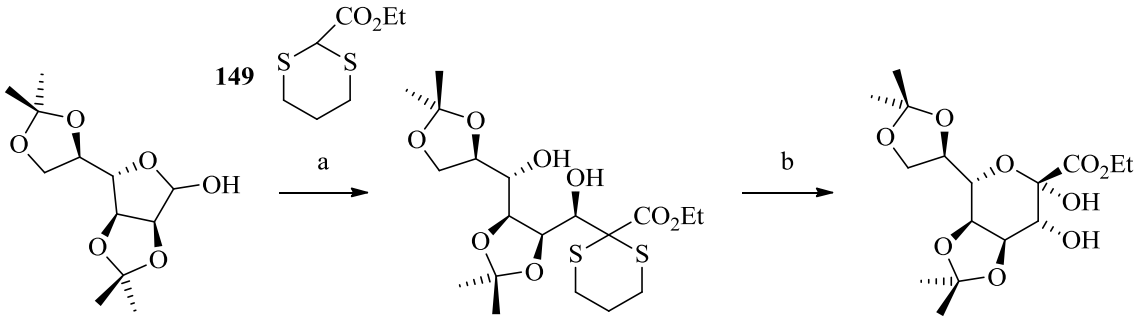


D-mannose **116**

Reagents and conditions: a) acetone, H_2SO_4 3-4 h; b) $NaCO_3$, activated carbon, reflux 2 h.

Scheme 43: Synthesis of diacetone mannose 116

The next step in the synthesis was the nucleophilic addition of the dithiane protected ketoester onto diacetone mannose (DAM). Following the previous work in the group we decided to use the procedure reported by Schmidt *et al.* [2]



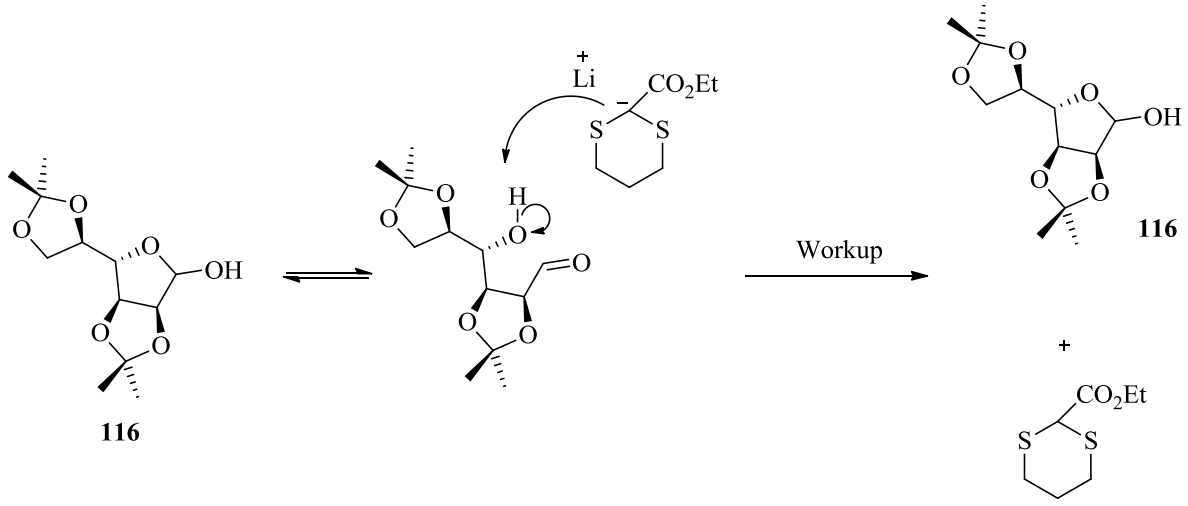
116 **143** **145**

Reagents and conditions: a) LDA, $MgBr_2$, dithiane **149**, **116**; b) NBS, acetone/water

Scheme 44: Addition of protected ketoester and subsequent deprotection and cyclization to form pyranose 145

The addition of dithiane **149** to diacetone mannose proceeded smoothly in very high yields of up to 98% after finding the optimal conditions and scale. We found working with less than 10 g of diacetone mannose reduced the yield; also more than three equivalents of dithiane **149** were needed to achieve a high yield. The presence of $MgBr_2$ was also crucial to the reaction; without it, only starting materials were recovered. We postulate that this may be due to the

potential of the lithiated dithiane to act as a base on the open form of diacetone mannose, as opposed to a nucleophile (**Scheme 45**).



Scheme 45: Possible mechanism for failed dithiane addition without the presence of magnesium dibromide

The addition of the $MgBr_2$ to reaction effectively converts the lithiated dithiane into a Grignard reagent by transmetalation leading to a nucleophilic attack instead of a deprotonation. With compound **143** in hand we moved on to the removal of the dithiane group and the cyclization to form the pyranose ring **145**. Using the literature procedure outlined by Schmidt, [2] the dithiane group was removed with NBS in acetone and water. The stereochemistry of **145** indicated that the cyclisation of the hydroxyl onto the ketone always occurred from a Re face approach. This was confirmed by X-Ray crystal structure determination for compound **145** (**Figure 11**).

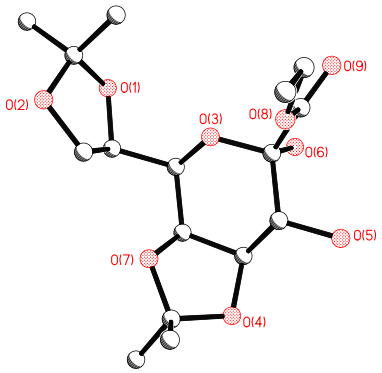
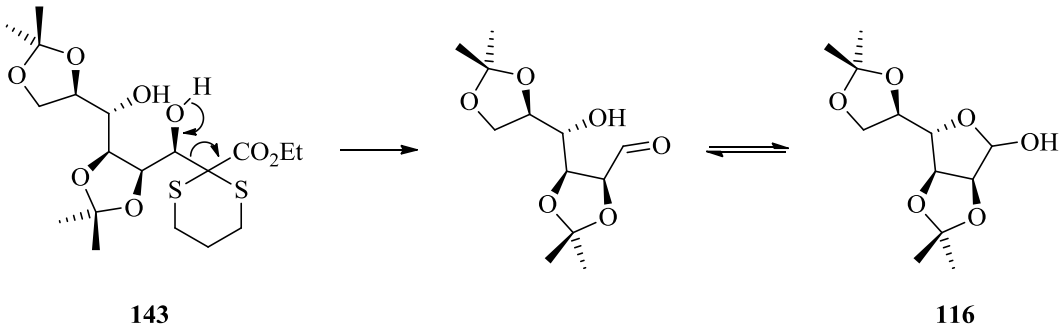


Figure 11: X-Ray crystal structure for 145

This reaction proved to be extremely troublesome, often giving little or no yield of product; the best yield obtained was 40%, and that only on very small scale reactions 100-200 mg. Purification of this compound was also hindered due to such small yields combined with a large amount of impurities obtained from the reaction. We found the best method to achieve a usable amount of pyranose **145** without lowering the percentage yield was to perform the reaction in twelve small scale carousel reaction vessels simultaneously. After workup the reaction mixtures were combined and extracted together and purified on a larger scale. This was the only method we devised that would yield gram quantities of the desired compound, and only after several repetitions of the procedure. We also found that diacetone mannose **116** made up a large proportion of the impurities in the reaction mixture, and this lead us to propose a mechanism for this possibility (**Scheme 46**). Although compound **143** was very stable in open bench conditions and even when heated to temperatures over 150 °C, we found that addition of a strong base led to complete conversion to diacetone mannose; we therefore concluded that this was the most likely competing reaction during the dithiane deprotection.



143 **116**

Scheme 46: Proposed mechanism for presence of diacetone mannose during dithiane removal

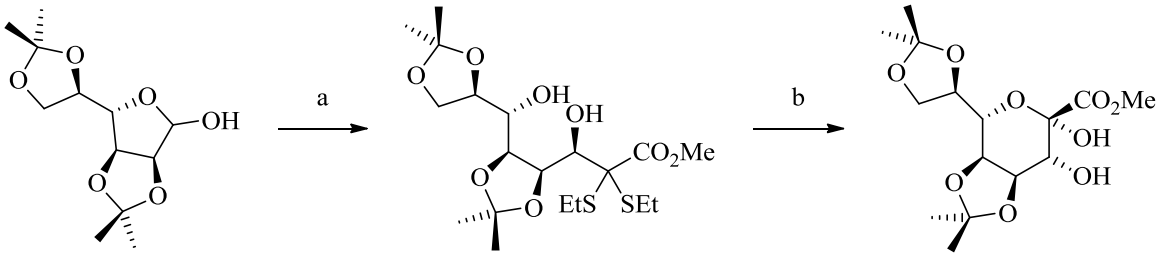
With the disappointing yields obtained from the NBS deprotection of the dithiane group, we decided to investigate alternatives for the removal of dithiane groups and conversion to ketones, including mercury reagents, [3,4,5] halogen donors and several oxidants [6,7,8] (**Table 6**). Disappointingly, none of these approaches improved the yield for the dethioketalization; in fact most of the alternatives to NBS gave far poorer results, usually yielding only diacetone mannose.

Only NIS and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) gave comparable results to NBS, presumably because the mechanism of dithiane removal is identical with all three reagents.

	Reagents and Conditions	Result/Yield
1	$HgCl_2$, (MeOH/H_2O 9:1) reflux, 18 h	DAM
2	HgO, (MeOH/H_2O 9:1) reflux, 18 h	DAM
3	IBX (DMSO/H_2O 9:1) 5% AcOH, RT, 6 h	DAM
4	H_2O_2 (MeOH/H_2O 5:1) 6 h	DAM
5	NIS, Acetone, 0 °C, 3 min	40%
6	NCS, Acetone, 0 °C, 3 min	10%
7	DBDMH, Acetone, 0 °C, 3 min	40%
8	DDQ, DCM, reflux 30 min	15%
9	MeI, DCM, reflux, 2 h	SM
10	mCPBA, DCM, RT, 4 h	DAM
11	Oxone® DCM, RT, 4 h	DAM

Table 6: Dethioketalization reagents and results

Schmidt *et al*.[2] also reported the use of a diethylmercaptal thioketal-protected ketoester where the dithioketal moiety had been utilized to form compound **150**, which was then treated with NIS to form the desired pyranose ring **151** in good yield (76% lit) (**Scheme 47**).

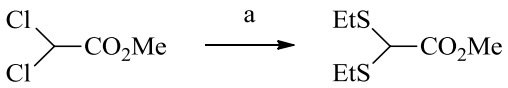


116 **150** **151**

Reagents and conditions: a) $(EtS)_2CHCOOMe$, LDA, $MgBr_2$, THF 76%; b) NIS, acetone 76%

Scheme 47: Diethyl mercaptal route

As the yields reported for this route were much higher than with the dithiane compound **143** and were also reported to work on a larger scale we decided to proceed with this method. Unlike dithiane **149**, methyl glyoxylate diethyl mercaptal **152** was not commercially available and was prepared following the procedure by Lerner (**Scheme 48**).[9]



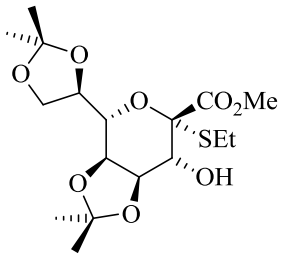
152

Reagents and conditions: a) Na, MeOH, EtSH, methyl dichloroacetate

Scheme 48: Preparation of diethylmercaptal 152

With sufficient quantities of compound **152** in hand, we proceeded with Schmidts' procedure, unfortunately we could not duplicate the high yields reported in the literature, and after several attempts only managed to produce compound **150** in 34% yield. This disappointing result led to only a few grams of the desired compound being obtained and was a lengthy procedure when compared to the dithiane route. When we treated compound **150** with NIS we were again confronted with very low yields 24% (lit 76%). During the attempts to improve the yield of this reaction we also noticed an unexpected product after purification, initially thought to be the desired compound plus an impurity. However, after several purifications we concluded that the unknown compound must be **153** (**Figure 9**). While this was not the desired compound we were trying to achieve, it did offer a potentially useful

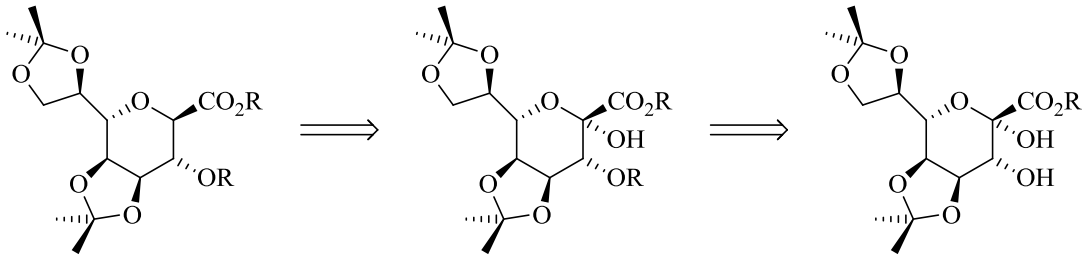
route towards compound **146**. If we could have produced compound **153** as the major product during the reaction of dithioketal **150** with NIS, we would have explored the possibility of cleaving the thioether bond to remove the ethane thiol function and proceed with an enolate addition to formaldehyde.



153

Figure 9: Unexpected product during NIS reaction

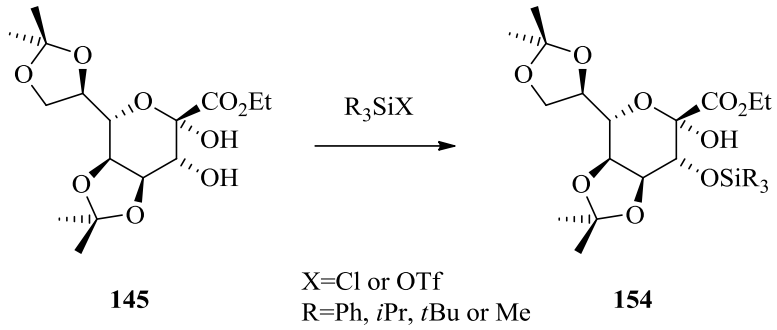
Despite the very low yields of compounds **145** and **150** we decided to continue with the route. Our next task was the selective protection of the secondary hydroxyl at **C-3** and then an activation and removal of the tertiary hydroxyl at C-2 (**Scheme 48**).



145 R=Et
150 R=Me

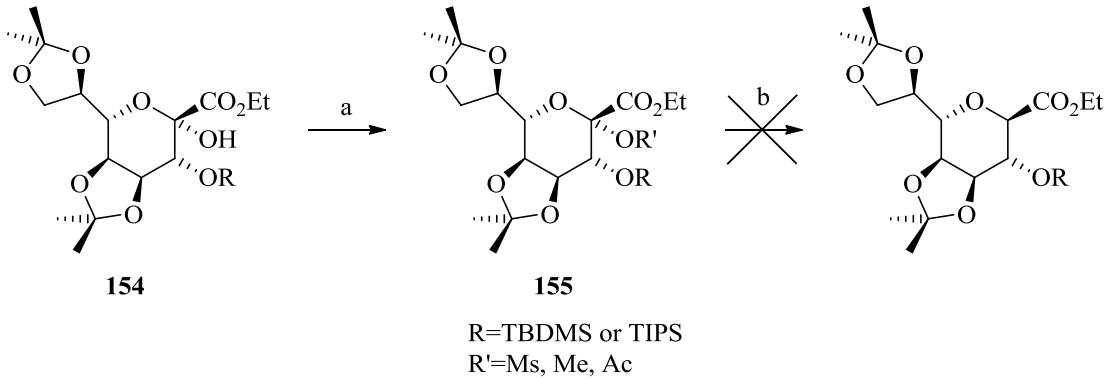
Scheme 48: Retrosynthesis from compounds 145 and 150

A range of bulky silyl protecting groups were chosen to protect the secondary hydroxyl, including TBDMSCl, TBDMSOTf, TIPSCl and TBDPSCl. This would enable us to activate and remove the tertiary alcohol at C-2 without affecting the hydroxyl at position C-3 (**Scheme 49**).



Scheme 49: Silyl protection of 3-OH on compound 145

All attempts to produce the *tert*-butyldiphenylsilyl ether of the C-3 hydroxyl were unsuccessful even after several days under reflux conditions; presumably the TBDPS group was simply too bulky for our substrate. TBDMS and TIPS ethers of the C-3 hydroxyl were successfully synthesized but with very low yields (20%-30%). This was again attributed to the bulky nature of both groups. Having obtained the TBDMS and TIPS silyl ethers **154** our next task was the activation and removal of the C-2 hydroxyl (**Scheme 50**).

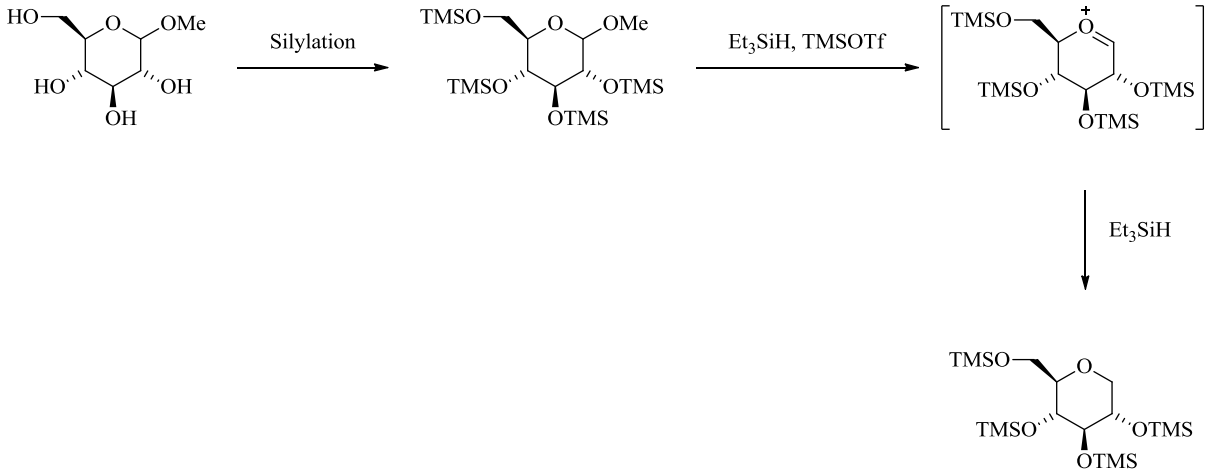


Reagents and conditions: a) NaH, MeI, DMF or Et_3N, MsCl, DMAP, DCM or Ac_2O, Et_3N, DMAP, DCM; b) Lewis acid, Et_3SiH

Scheme 50: Activation and removal of C-2 hydroxyl

Following work reported by Gray *et al.*[10] (**Scheme 51**) on the reductive cleavage of methoxy groups in the anomeric position of alkyl glycosides we began by methylation of the hydroxy group at position C-2 on compound **154**, this proceeded smoothly to give compound **155a** in

88% yield. We also mesylated the hydroxyl at position C-2 as we believed this would provide a better leaving group than the methoxy moiety, however the yields for this reaction were disappointingly low 15%-30%. A tosylation was also attempted without success, most likely due to the tertiary nature of the alcohol.

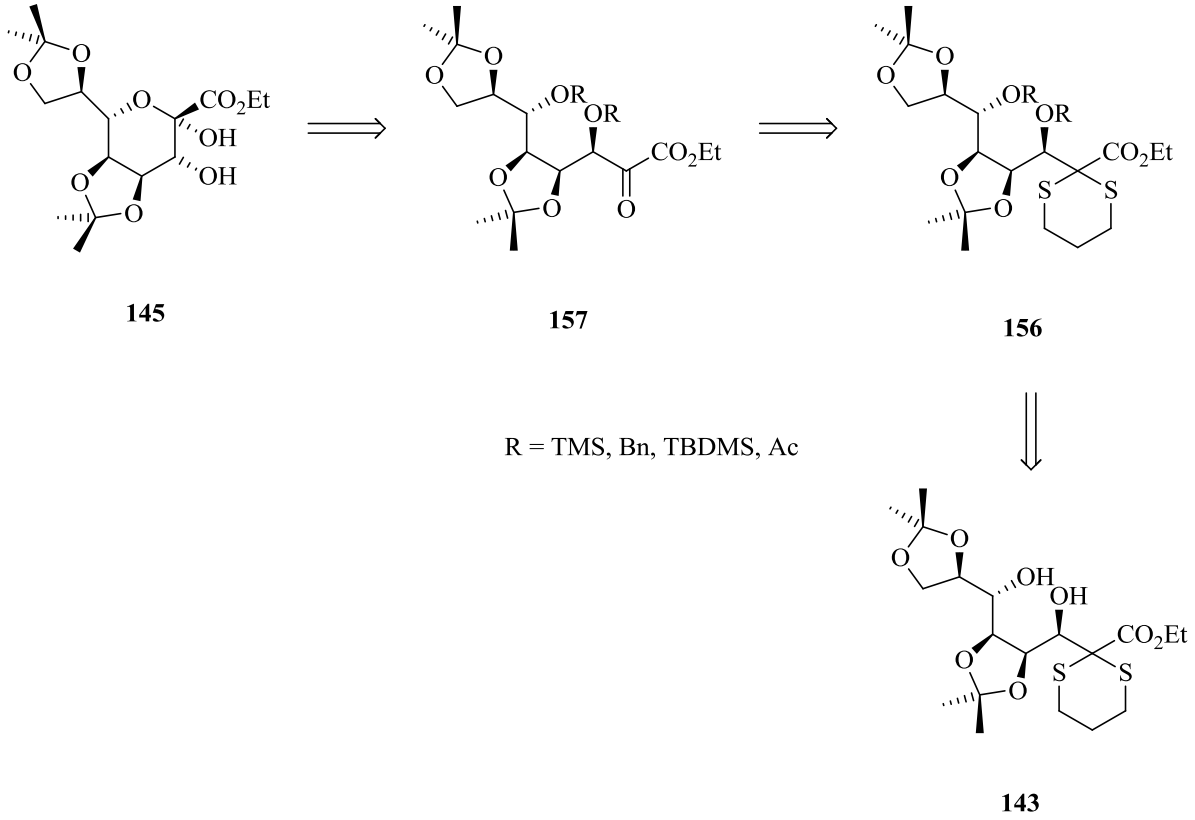


Scheme 51: Gray's synthesis of anhydroalditols from alkyl glycosides [10]

With the mesylated and methylated products in hand we attempted the removal of the anomeric hydroxyl using Gray's [10] conditions. This proved unsuccessful on both the mesylate and the methoxy groups. After several attempts using Gray's conditions, we tested a range of Lewis acids ($TiCl_4$, $AlCl_3$, $SnCl_3$ and BF_3•Et_2O) and hydride donors ($NaBH_3CN$ and Et_3SiH) under similar conditions in all cases starting material was the only compound recovered from the reaction (**Scheme 50**).

Following these disappointing results we decided to revisit the dethioketalization reaction (**Scheme 44**) as we believed the lack of success with the removal of the anomeric hydroxyl from compound **154** was partly due to the very small amount of pyranose **145** we had to work with. We believed the poor yields obtained previously by the dethioketalization reaction could be improved if the mechanism for reversion back to diacetone mannose could be prevented. A simple protection of the hydroxyl groups in compound **143** was proposed to prevent formation of the aldehyde moiety present in the open form of diacetone mannose, as

we presumed this would prevent any possible mechanism for diacetone mannose being produced and would also lead to a clean and efficient conversion of the dithiane moiety to a ketone. Subsequent removal of the hydroxyl protecting groups would lead to a cyclization to form the desired pyranose **145** (**Scheme 52**).



145 **157** **156** **143**

Scheme 52: Hydroxyl protection of dithiane 143 before dethioketalization and cyclization

We proceeded to protect both hydroxyls on dithiane **143** with several protecting groups. Forming the TMS and TBDMS ethers proved problematic giving poor or zero yields. The benzyl ether also proved difficult to form. Forming the acetate groups however, was highly successful, often being produced in 99% yield with Ac_2O, Et_3N and DMAP. The diacetylated compound was also a crystalline material, enabling an X-ray crystal structure determination to be made (**Figure 12**), giving us an absolute stereochemistry (due to the sulfur atoms) for compound **158** (**Scheme 53**).

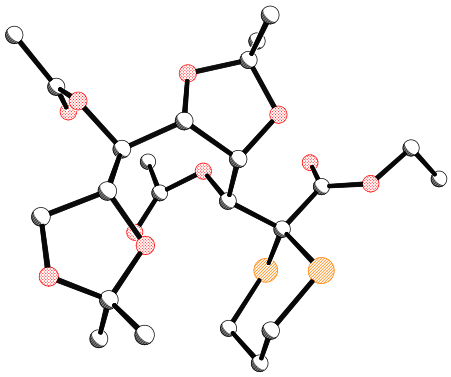
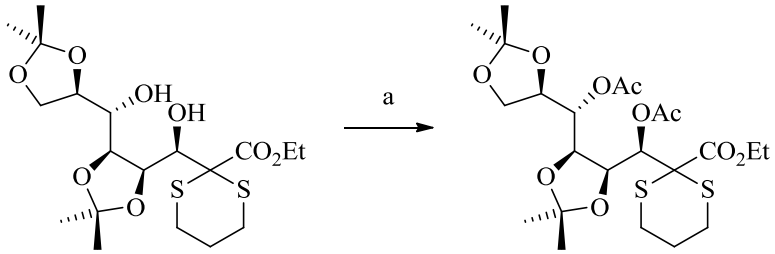


Figure 12: X-ray crystal structure of compound 158

This reaction proved to be effective when working on larger scales (5g-10g), and also no decomposition or formation of diacetone mannose was detected.

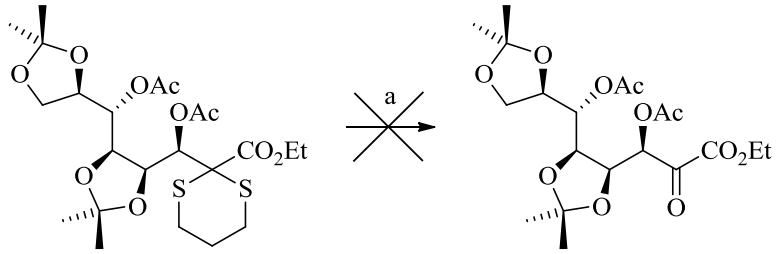


143 **158**

Reagents and conditions: a) Ac_2O, Et_3N, DMAP, DCM, 0 °C, 99%

Scheme 53: Acetylation of dithiane 143

With the protected compound **158** in hand we moved on to the removal of the dithiane group, believing the dethioketalization to be a mere formality at this stage, and we were therefore surprised and disappointed to find no reactivity when dithiane **158** was treated with NBS under the same conditions used previously on compound **143** (**Scheme 54**).

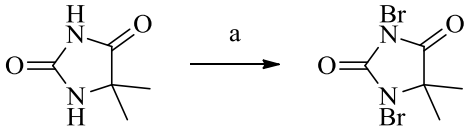


158 **159**

Reagents and conditions: a) NBS, acetone/H_2O

Scheme 54: No reaction when dithiane 158 was treated with NBS

While there appeared to be no reactivity with the acetate protected compound **158** and NBS, we were able to recover almost all of the starting material after each reaction. This result was not entirely without merit, as we had successfully prevented the unwanted production of diacetone mannose. After increasing the temperature and reaction time with NBS led to no improvement, we decided to repeat the reaction using the range of reagents listed in **Table 6**. Again we were surprised to see no reactivity with any of the reagents except 1,3-dibromo-5,5-dimethylhydantoin **160** (DBDMH), prepared with 5,5-dimethylhydantoin, sodium hydroxide and elemental bromine using the procedure outlined by in the literature [11] (**Scheme 55**).

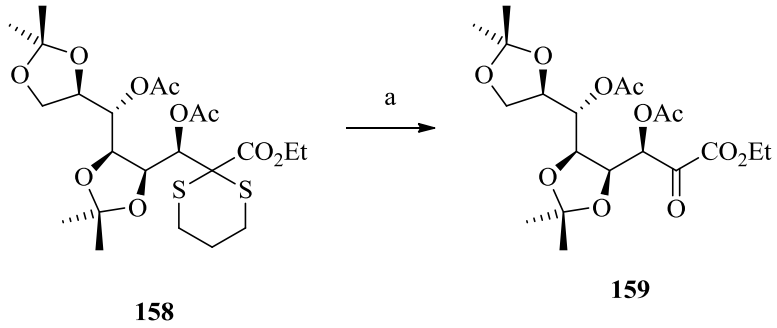


5,5-dimethylhydantoin **160**

Reagents and conditions: a) NaOH, Br_2, H_2O

Scheme 55: Preparation of 1,3-dibromo-5,5-dimethylhydantoin

This was an especially surprising result as the mechanism for the reaction of DBDMH with the dithiane was assumed to be identical as that for NBS, which had shown no reactivity at all with the dithiane. The reaction with DBDMH proceeded smoothly to give compound **159** in between 54% and 84% yield (**Scheme 56**).

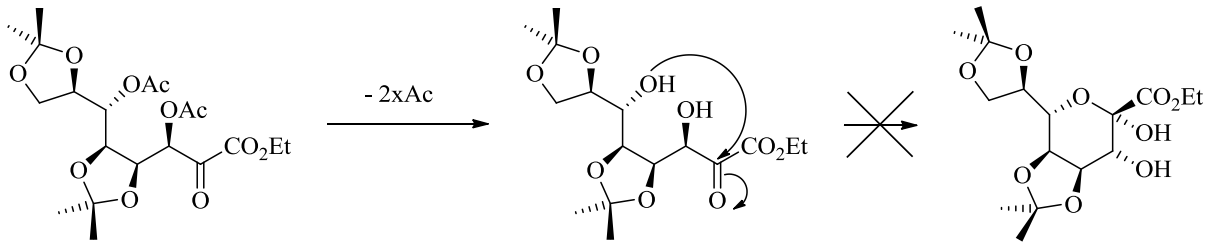


158 **159**

Reagents and conditions: a) DBDMH, acetone/H_2O

Scheme 56: Dethioketalization of compound 158 with DBDMH

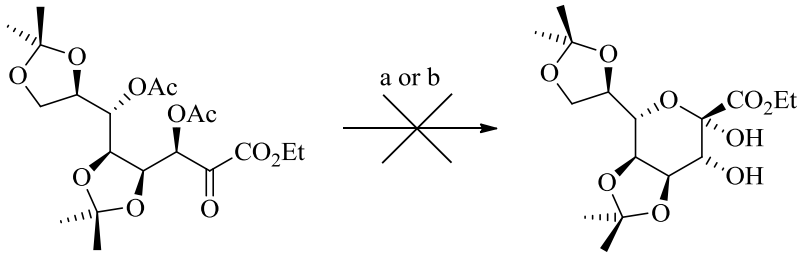
Having successfully produced the acetate-protected ketoester **159,** we believed that a simple removal of the acetate groups would promote the cyclization of the compound to form the desired pyranose **145** in a good yield (**Scheme 57**).



159 **145**

Scheme 57: Removal of acetates and cyclization to form pyranose 145

However this was not the case; when subjected to standard acetate deprotection conditions, (MeOH, K_2CO_3) the desired pyranose **145** was not detected. Complete decomposition of the starting material was observed. After this disappointing result we tried an alternate strategy for the removal of the acetate groups. An ion exchange resin, activated Amberlite® IRA-400, was used as a hydroxyl anion donor. This also led to a decomposition of the starting material and no product was observed (**Scheme 58**).

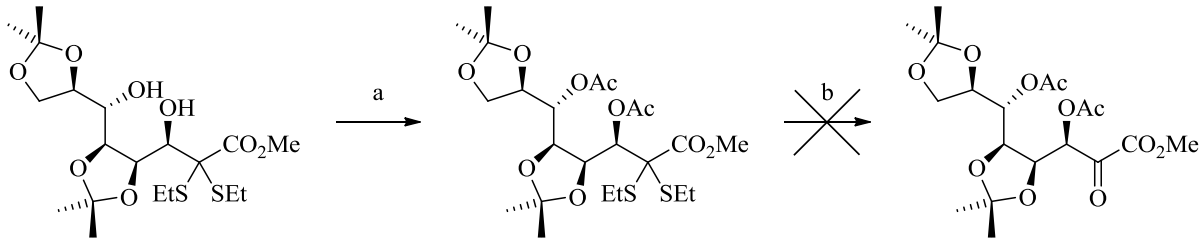


159 **145**

Reagents and conditions: a) K_2CO_3, MeOH; b) Activated Amberlite® IRA-400, MeOH

Scheme 58: Attempted acetate removal

We also used the acetate protection methodology on the diethylmercaptal protected ketoester **149**, despite the poor yields experienced with its production. Conversion to the diacetate **160** was achieved in the same high yields >95% achieved with the dithiane **158**. However all attempts to remove the diethylmercaptal moiety were unsuccessful (**Scheme 59**), even when using the DBDMH compound that worked previously with the dithiane **158**.



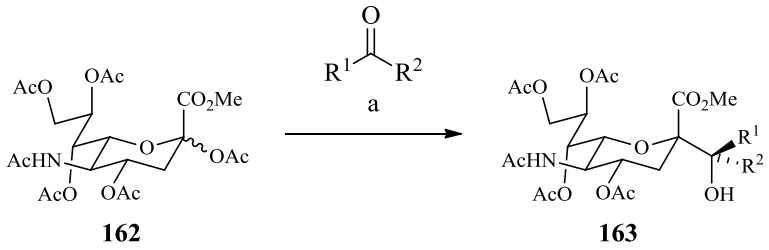
149 **160** **161**

Reagents and conditions: a) Ac_2O, Et_3N, DMAP, DCM; b) DBDMH, Acetone/H_2O

Scheme 59: Acetate protection and attempted removal of diethyl mercaptal moiety

Faced with the disappointing results from the protected compounds **159** and **160,** we decided to abandon this route and continue with the small yields of compound **145** we were able to obtain.

One of our investigations into the removal of the anomeric hydroxyl on pyranose **145** led us to a report of a samarium diiodide-promoted coupling of anomeric acetates with carbonyl compounds.[11] The authors described a procedure to convert the anomeric acetate in the *N*-acetylneuraminic acid derivative **162** to the corresponding alcohol **163** using samarium diodide and a range of ketones and aldehydes (**Scheme 60**).

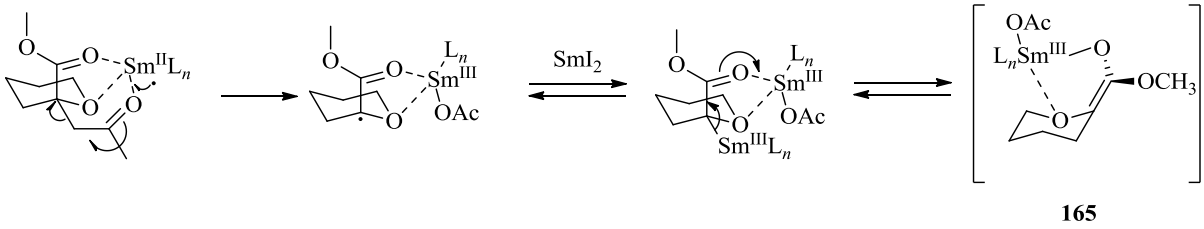


162 **163**

Reagents and Conditions: a) SmI_2 3 equiv, THF, r.t

Scheme 60: Samarium diodide promoted coupling between acetate and carbonyl compounds

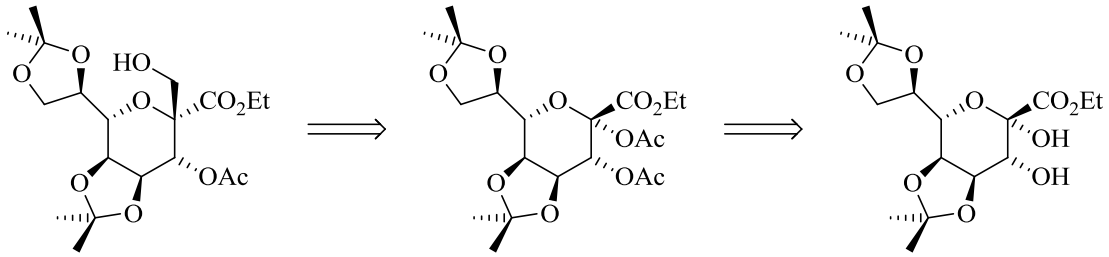
The group also proposed a mechanism for the formation of the reactive samarium enolate **165** that reacts with the carbonyl compounds reported (**Scheme 61**).



165

Scheme 61: Postulated mechanism for the formation of the samarium enolate 165 [11]

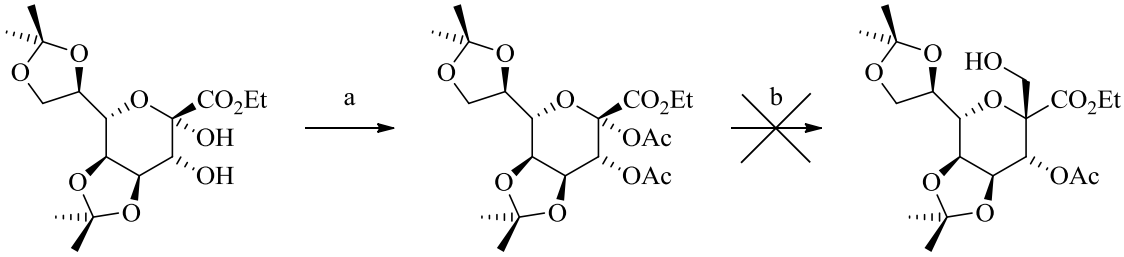
We believed we could apply this procedure to our compound **145** to remove the anomeric hydroxyl and introduce the methylene alcohol group in one step. Conversion of the diacetate **163** to the alcohol **164** would take place using a modified version of the samarium diiodide procedure the authors described using formaldehyde as the carbonyl source; theoretically this would give us the desired alcohol. Diacetate **163** could be prepared simply using Ac_2O, Et_3N and DMAP from pyranose **145** (**Scheme 62**).



164 **163** **145**

Scheme 62: Retrosynthesis of alcohol 164 from pyranose 145

We began with the diacetylation of pyranose **145** using Ac_2O, Et_3N and DMAP which resulted in the production of compound **163** in 88% yield. This was followed by the samarium diiodide mediated coupling reaction. Unfortunately we were unable to reproduce the results reported in the literature and no alcohol **164** was detected (**Scheme 63**).



145 **163** **164**

Reagents and conditions: a) Ac_2O, Et_3N, DMAP, DCM 88%; b) SmI_2, CH_2O, THF

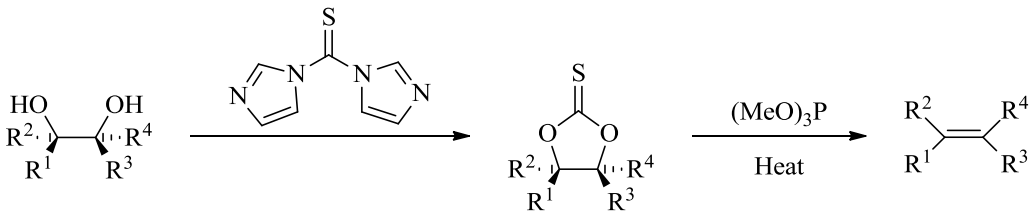
Scheme 63: Attempted samarium diiodide reaction

Initially we were using commercially available samarium diiodide solution in THF. After the lack of success with the reaction we attempted to prepare our own solution of samarium diiodide in THF. Following the procedure outlined in the literature, [11] samarium powder and 1,2-diiodoethane were stirred in THF overnight under argon. Again, disappointingly we were unable to reproduce the results reported in the literature and failed to detect any samarium diiodide in the solution, confirmed due to the lack of any dark blue colour. We attempted to produce a SmI_2 solution using several methods and reagents including CHI_3, I_2 and 1,2-diiodoethane. Unfortunately even after microwave irradiation we were unable to produce a

samarium diiodide solution. While the methods we chose to produce samarium diiodide had been reported to work in the literature, it must be noted that we found it to be an extremely difficult reagent to produce and also to work with. After our unsuccessful attempts at producing a samarium diiodide solution and with no sign of any improvement using the commercially available samarium diiodide, we chose to abandon this route.

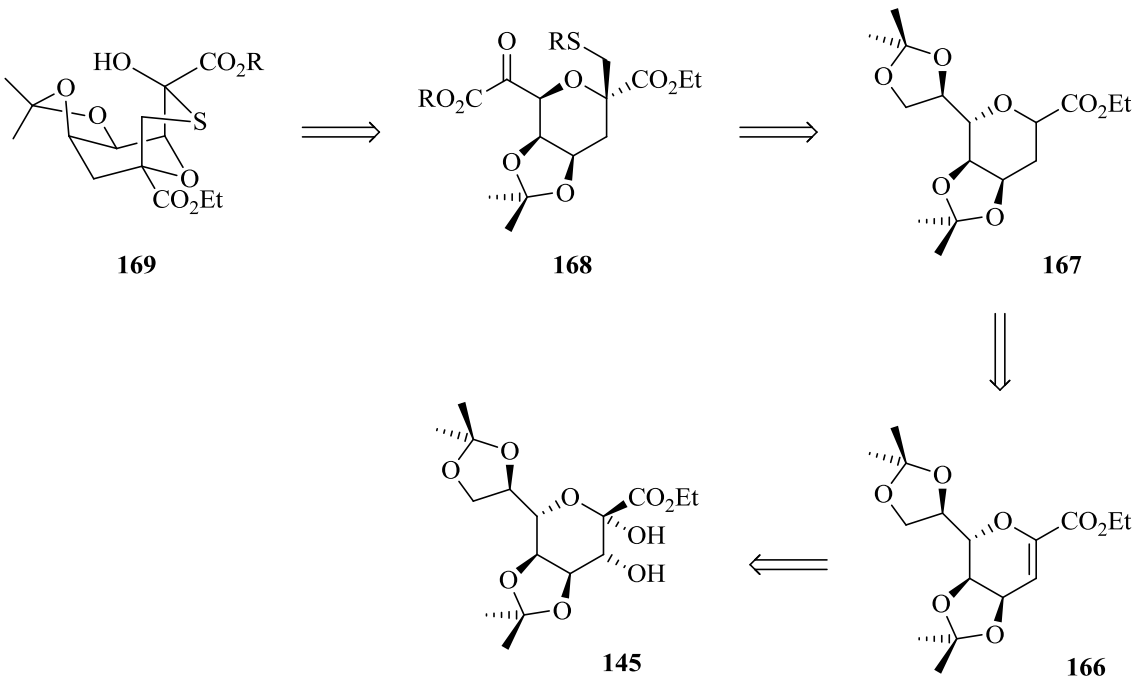
Corey-Winter olefination

Going back to pyranose **145** we envisaged a new route based on the conversion of the diol functionality in compound **145** to an alkene using a Corey-Winter olefination [12] (**Scheme 64**).



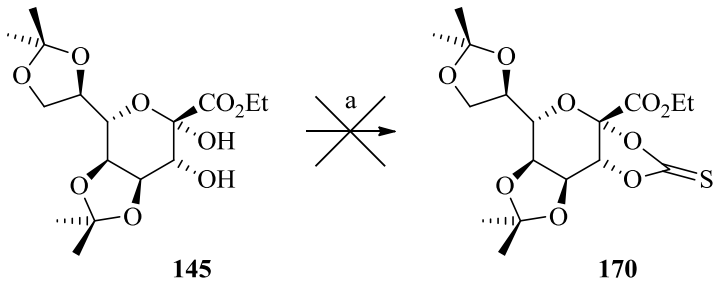
Scheme 64: Corey-Winter olefination

Alkene **166** would then be reduced to the alkane by hydrogenation giving compound **167**; simple enolate chemistry could then be used to introduce the methylene alcohol function followed by mesylation or tosylation of the primary alcohol and subsequent displacement with a thioacetate anion. Selective removal of the primary acetal followed by oxidation and esterification would lead to compound **168,** which would cyclize to bicycle **169** upon deprotection of the thiol (**Scheme 65**).



Scheme 65: Retrosynthesis from 145 using a Corey-Winter olefination

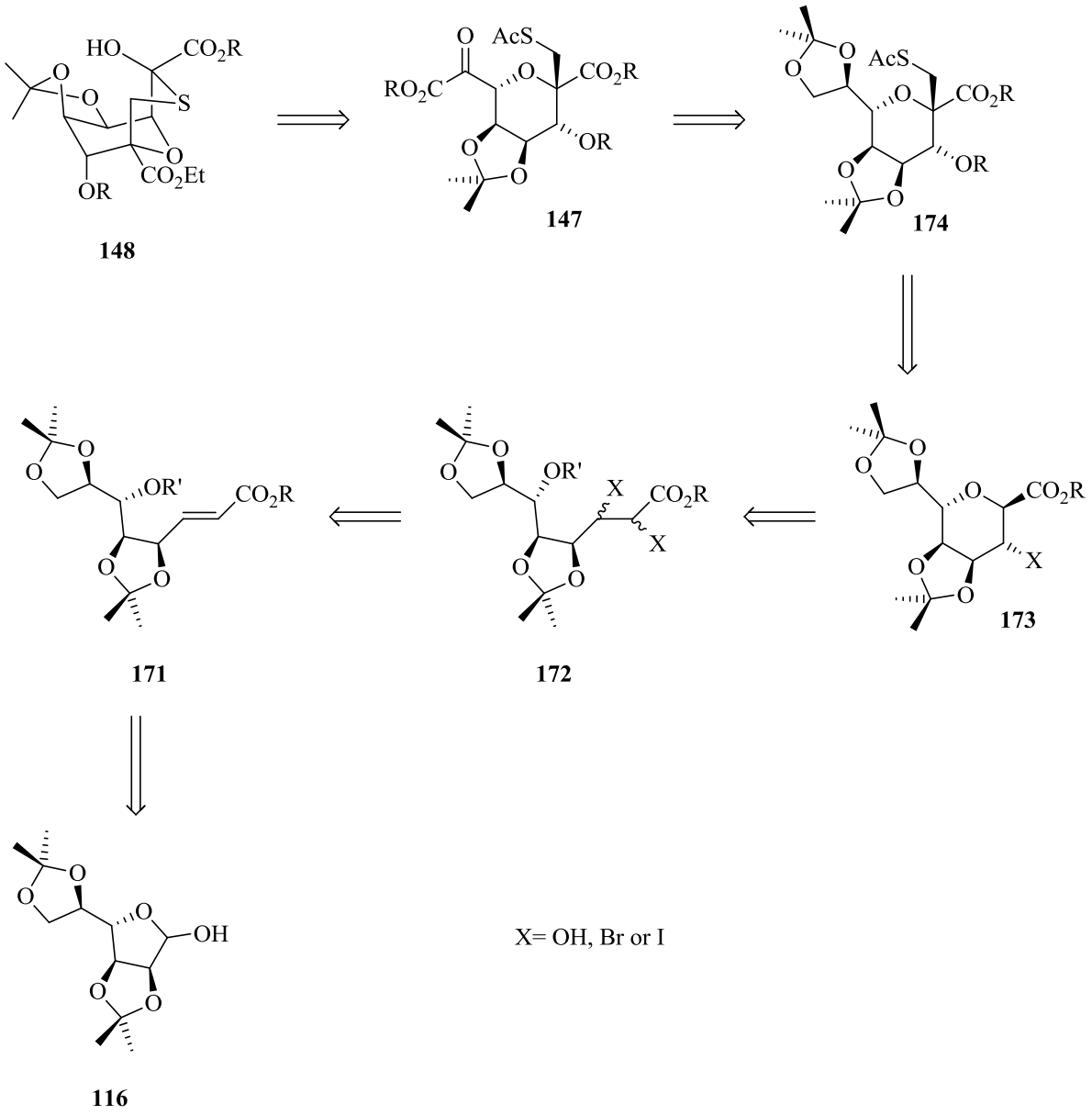
While this route would leave no functionality at C-3 we believed it was a worthy sacrifice to aid the synthesis of the bicyclic core. Alternate strategies for introducing functionality at this position would be revisited later if the route proved successful. Unfortunately when diol **145** was subjected to the Corey-Winter olefination conditions, the thionocarbonate **170** was not observed (**Scheme 66**). Due to this result we decided not to proceed any further with this strategy, and focused our efforts on an alternative to the dithiane route.



Reagents and conditions: a) thiocarbonyldiimidazole, toluene, reflux 30 min

Scheme 66: Corey winter olefination attempt on pyranose 145

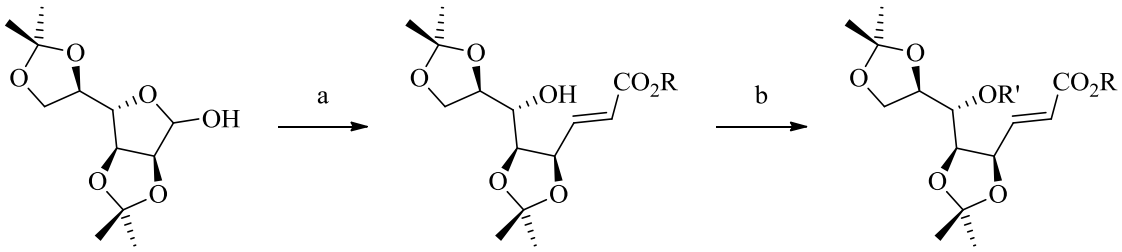
Wittig route



Scheme 67: Retrosynthesis from diacetone mannose using Wittig procedure

Following the unsuccessful attempts to remove or substitute the anomeric hydroxyl from pyranose **145,** a new route was postulated involving a Wittig reaction to introduce the ester moiety. We would begin from diacetone mannose **116** as we did with the dithiane route, a Wittig reaction on the aldehyde function of the open form furanose would lead to alkene **171** after a simple protection of the secondary hydroxyl. The alkene would then be subjected to either a bromination, iodination or a dihydroxylation to give the functionalized product **172**.

Removal of the protecting group on the secondary alcohol and subsequent displacement of either the halogen or manipulated hydroxyl group alpha to the ester function would lead to the cyclized pyranose **173**. The protected thiol function would be introduced as described above using enolate chemistry to introduce the primary alcohol, then a displacement with a thioacetate anion to give **174**. Following a selective acetal removal and then oxidation and protection, compound **147** would only require the removal of the acetate protection on the thiol to enable the cyclization to give the bicyclic structure **148** (**Scheme 67**).



116 **175a, 175b** **171a, 171b**

R=Me or Et
R'= TMS or Ac or TFAc

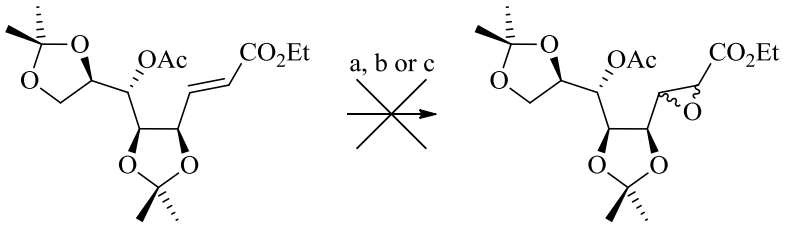
Reagents and conditions: a) Ph_3PCHCO_2Me or Ph_3PCHCO_2Et, toluene, reflux, 1 h;
b) Ac_2O, $TFAc_2O$ or TMSCl, Et_3N, DMAP, DCM rt

Scheme 68: Wittig reaction and hydroxyl protection from diacetone mannose

The first step was a Wittig reaction performed with the ethyl and methyl ester-stabilized ylids prepared from methyl bromoacetate and ethyl bromoacetate with triphenylphosphine heated under reflux in toluene, followed by a NaOH wash. The reaction was carried out using conditions outlined in the literature.[13] Diacetone mannose was refluxed with the corresponding ester ylid for 1 hour in toluene to give the alkenes **175a-b**. Under these conditions the *E*-alkene was the major product, easily separated from the *Z*-alkene using flash column chromatography. Yields varied between 50-70% for the *E*-isomer and between 10-20% for the *Z*-isomer. With the desired alkenes **175** in hand, we proceeded to protect the hydroxyl moiety with a trimethylsilyl group and acetate group. The acetate was formed in good yields following reaction of **175a-b** with acetic anhydride, triethylamine and DMAP in

DCM to give the protected alkene **171a-b**. The TMS protection gave poorer results, with yields between 20-50% (**Scheme 68**).

Initially, after we obtained the protected alkene **171** we attempted an epoxidation in the hope that this would lead to a cyclization to the pyranose **173** after removal of the protecting group, but after several epoxidation conditions were tried we were unable to form the epoxide **176** and also unable to salvage any starting material from each reaction (**Scheme 69**).

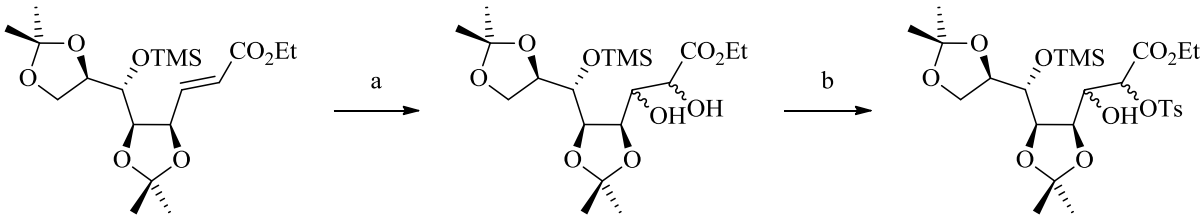


171a **176**

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 69: Epoxidation attempts on alkene 171

This led us to abandon any further epoxidation attempts and move on to a dihydroxylation reaction to give the diol **178,** to be followed by selectively tosylating the hydroxyl α to the ester moiety. We believed the bulkier nature of the tosyl group compared to the mesyl would enable only the hydroxyl α to the ester group reacting, as the second alcohol would be sterically hindered by the TMS group or acetal group in close proximity.

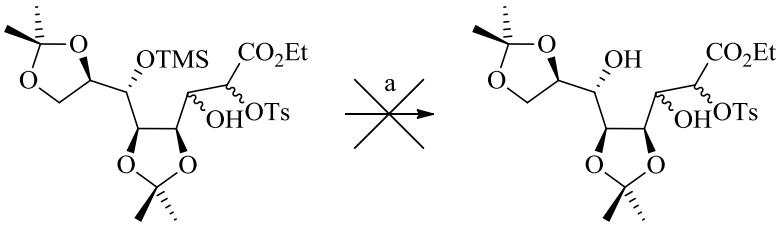


177 **178** **179**

Reagents and conditions: a) $OsCl_3$ 5%, NMO, THF/H_2O 1:1, rt, overnight; b) TsCl, Pyr, DCM, rt, overnight.

Scheme 70: Dihydroxylation of alkene 177 and tosylation of hydroxyl α to ester

Alkene **177** was successfully converted to the diol **178** using $OsCl_3$ and NMO in 67% yield. The tosylation was also successful and gave compound **179**, but in a low yield <20%. This was probably due to the fairly mild reaction conditions used that were necessary to prevent formation of the ditosylated compound (**Scheme 70**).



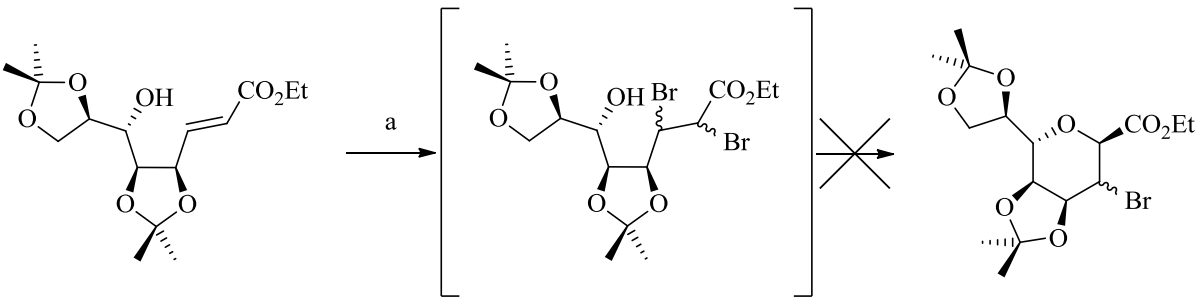
179 **180**

Reagents and conditions: a) TBAF, THF, rt, overnight.

Scheme 71: Attempted removal of TMS group

Unfortunately when we came to remove the TMS group from compound **179** expecting to obtain compound **180**, or possibly even direct cyclization to the pyranose **173**, we were disappointed to find complete decomposition of the starting material and did not observe either the cyclized product or the diol **179** (**Scheme 71**).

After the low yield from the tosylation reaction and the unexpected result from the TMS removal we decided to move on to a different method of functionalizing the alkene. We postulated that a direct bromination of the alkene could lead to a cyclization to form compound **173** in a single step. We attempted the reaction by adding neat molecular bromine to a solution of the alkene in DCM at 0 °C, but this did not lead to the desired result and gave a mixture of unidentified compounds, and pyranose **173** was not isolated from the reaction mixture (**Scheme 72**).

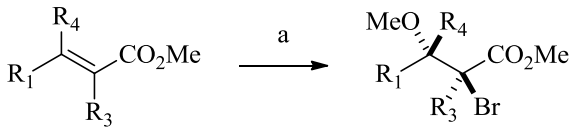


175 **173**

Reagents and conditions: a) Br_2, DCM, 0 °C

Scheme 72: Bromination of alkene 175

With the failure of the direct bromination on the unprotected alkene we moved on to a method of methoxy-bromination reported in the literature, [14] in which the authors successfully added a bromide and a methoxy group across a double bond with the bromide positioned α to the ester function. The authors produced a range of compounds by methoxy-bromination of an alkene to give the substituted compounds **182** (**Scheme 73**).

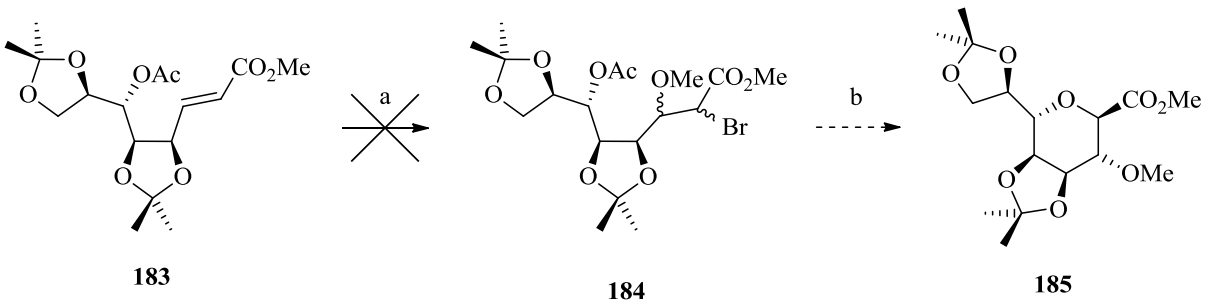


181 **182**

Reagents and conditions: Br_2, $AgNO_3$, MeOH, rt

Scheme 73: Methoxy-bromination of alkenes [14]

Following the procedure outlined in the literature we attempted to apply the method to our alkene **183**, which would put the bromide in the correct position to allow cyclization to the desired ring **185**, after removal of the acetate protecting group (**Scheme 74**).



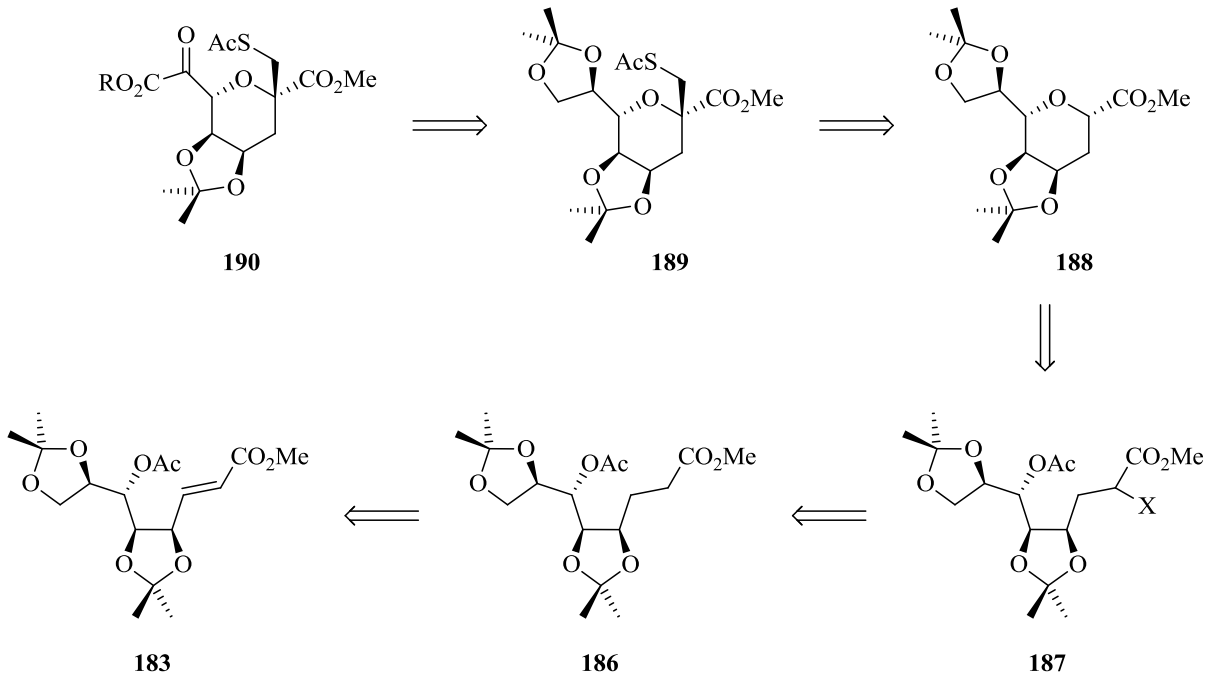
183 **184** **185**

Reagents and conditions: a) Br_2, $AgNO_3$, MeOH, 0°C to rt, 1 h; b) MeOH, KOH, rt.

Scheme 74: Attempted methoxy-bromination and cyclization from alkene 183

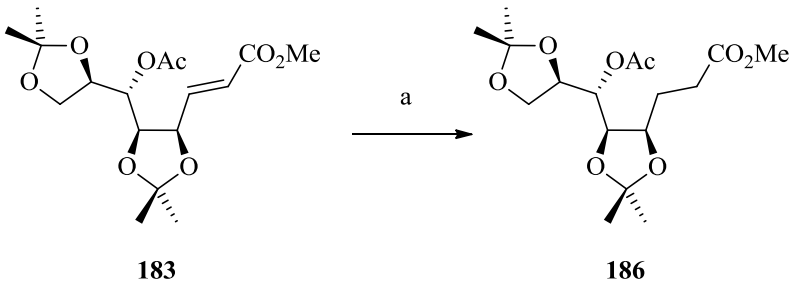
After following the procedure reported in the literature, [14] we were disappointed to find no trace of compound **184**; in every attempt at the reaction only starting material was recovered. We also tried the reaction at higher temperatures and longer reaction times to promote the methoxy-bromination but this did not lead to any improvement on the yield. Substituting molecular bromine for NBS did not improve the yield either; the reaction was also attempted in the absence of silver nitrate with no success.

After being confronted with the poor results from functionalizing the alkene, we considered a new route which would involve the reduction of alkene **183** to the alkane **186**. A suitable leaving group, most likely a halide could be introduced from the enolate of **186** to give compound **187**. Removal of the acetate group and cyclization by elimination of the halide would give compound **188**. The protected thiol could be introduced by an enolate addition of formaldehyde, tosylation of the resulting primary alcohol and then displacement of the tosylate with a thioacetate anion would give **189**. Selective removal of the primary acetal and oxidation to the ketoester would give **190**, which would cyclize to the bicyclic structure after removal of the acetate group protecting the thiol moiety (**Scheme 75**).



Scheme 75: Retrosynthesis from reduction of the alkene 183

We proceeded with a hydrogenation of alkene **183** with hydrogen gas over palladium on carbon. The reaction gave almost quantitative yields of alkane **186** and required no purification after filtering through celite to remove the Pd/C solids (**Scheme 76**).

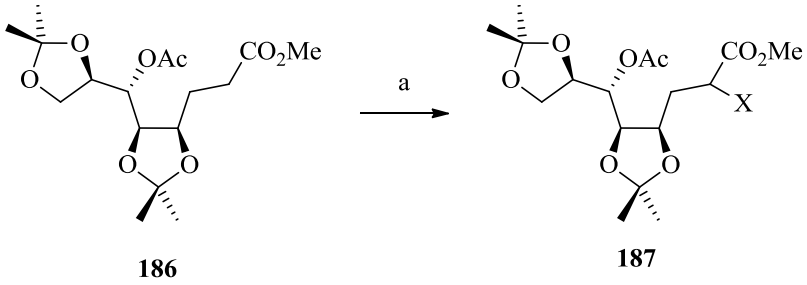


Reagents and conditions: a) H_2, Pd/C, MeOH, 4 h, rt

Scheme 76: Hydrogenation of alkene 18

Our next task was the α-halogenation of the ester to introduce a suitable leaving group, as in **187**. Following the method of α-halogenation of lithium ester enolates reported by Rathke, [15] LDA was added to alkane **186** at −78 °C in THF to form the lithium enolate. This was added to a solution of iodine in THF also at −78 °C and allowed to reach room temperature.

Unfortunately this did not lead to the alpha halogenated ester **187**; we isolated only starting material from the reaction (**Scheme 77**).



186 **187**

Reagents and conditions: a) see table 6

Scheme 77: Attempted alpha halogenations of ester 187

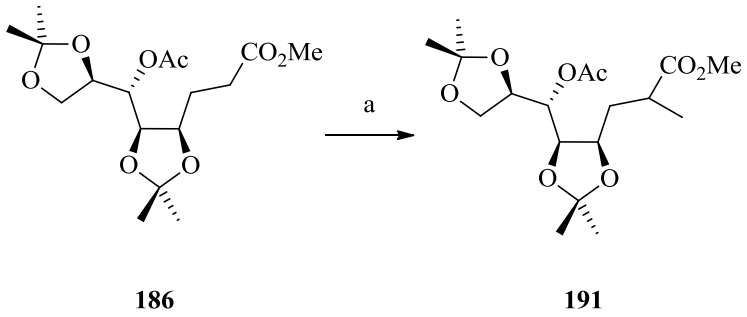
Following this result we decided to test a range of bases and halogen donors to attempt to halogenate α to the ester. Several methods for brominating and iodonating were tried all without any success; in all cases only starting material was recovered (**Table 7**). We also tried NCS to introduce a chloride α to the ester, which also resulted in only starting material being recovered from the reaction.

Method	Reagents and conditions	Result
1	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 7: Methods for attempted alpha ester halogenation

After having no success with halogenating alkane **186** we decided to test if we were generating the lithium enolate before adding the halogenating reagent. To test if the enolate was being formed we reacted the alkane with LDA (using the same procedure as the

halogenation attempts) then added MeI as an alkylating reagent. If the lithium enolate was formed and was sufficiently reactive, we would isolate compound **191** (**Scheme 78**).



186 **191**

Reagents and conditions: a) MeI, LDA, THF, –20 °C to rt

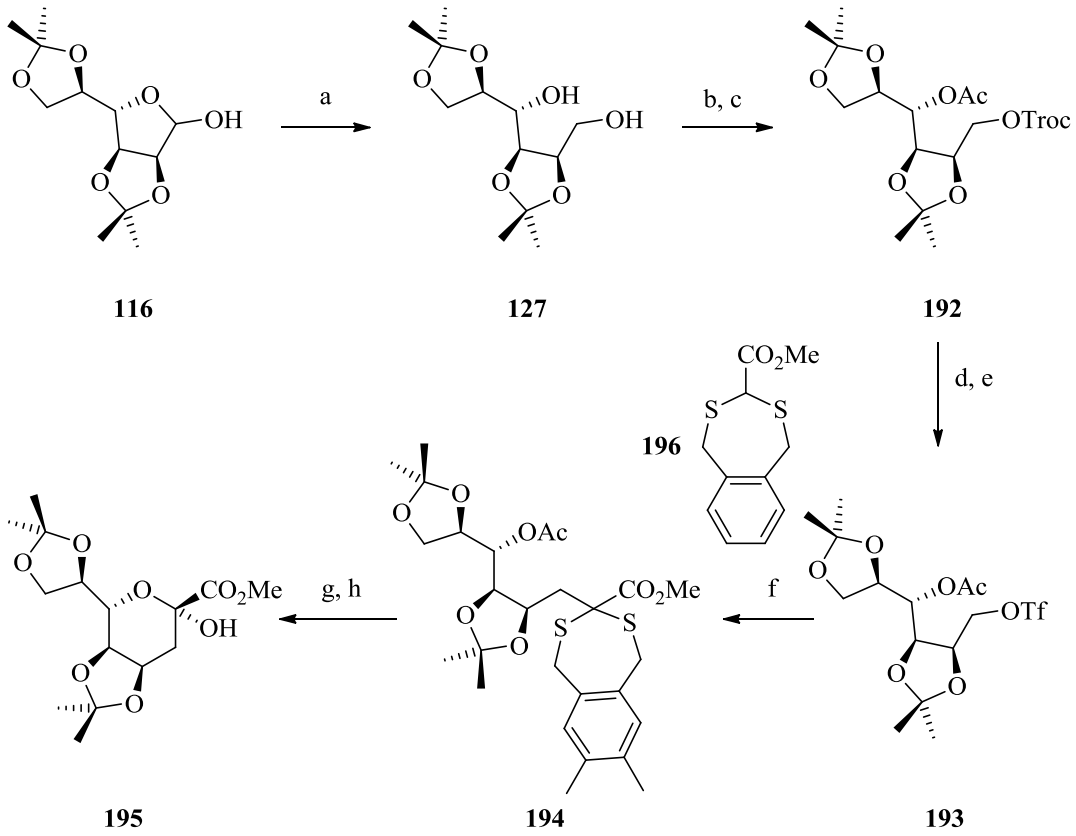
Scheme 78: Alkylation of alkane 186

Surprisingly we were unable to observe any trace of compound **191** from the reaction, leading us to believe that we were ether not generating the lithium enolate of the ester or that it is unreactive. While this explains why we were unsuccessful in halogenating alkane **186** it is unclear why we might not be able to produce the enolate. After this result we concluded any further work on this route, however further investigation of introducing a suitable leaving group alpha to the ester moiety in compound **186** was not ruled out.

Sequential protection-deprotection of DAM route

After consulting the literature on syntheses of KDO we discovered a report by Shiba *et al.*[16] that described a procedure for the synthesis of KDO starting from diacetone mannose. Their procedure involved the reduction of diacetone mannose to the diol **127**, the primary alcohol group was then selectively protected with 2,2,2-trichloroethoxycarbonyl chloride, followed by an acetylation of the secondary alcohol with acetic anhydride. With two distinctly different protecting groups in place, the authors were able to remove the Troc group and triflate the deprotected primary hydroxyl to give compound **193,** while leaving the acetate group untouched. The triflate was then displaced with lithiated methyl ester dithioketal **196**.

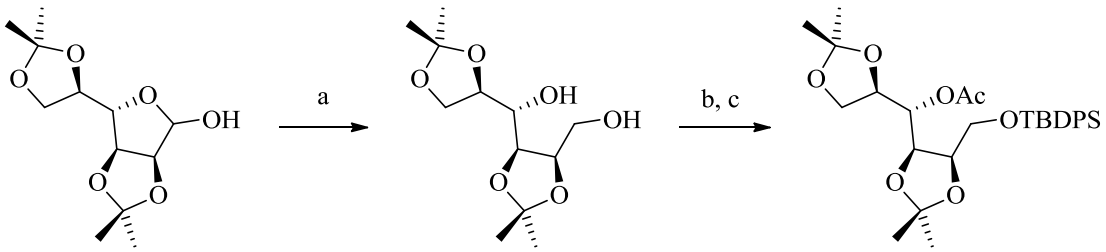
Removal of the acetate and dithioketal groups gave the diisopropylidene derivative of KDO methyl ester **195** (**Scheme 79**).



Reagents and conditions: a) $LiAlH_4$, Et_2O, 1 h, rt, 100%; b) TrocCl, py, DCM, 0 °C, 30 min; c) Ac_2O, py, DMAP, DCM, rt, 2 h; d) Zn, AcOH, EtOAc, 0 °C, 30 min 96% over 3 steps; e) Tf_2O, py, DCM, -45 °C 15 min; f) **196**, BuLi, HMPA, THF, -75 °C to 0 °C, 1 h, 73%; g) 0.1 M NaOMe, rt, 2 h; h) NBS, *aq* acetone 95%, 0 °C, 2 min, 57% over 2 steps.

Scheme 79: Shiba's synthesis of KDO from diacetone mannose following a reduction and sequential protection of primary and secondary hydroxyls [16]

Shibas' synthesis highlighted the fact that the removal of the secondary hydroxyl from **194** by the triflation and displacement with the dithioketal group, as opposed to the direct addition of the methyl ester dithioketal group to the aldehyde function of diacetone mannose, greatly improved the yield of the dethioketalization reaction using NBS.

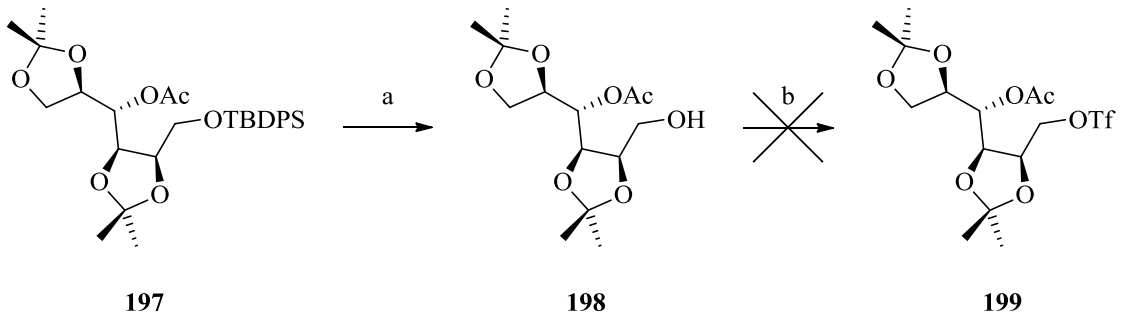


116 **127** **197**

Reagents and conditions: a) $LiAlH_4$, Et_2O, rt, 1 h, quantitative; b) TBDPSCl, Et_3N, DMAP, DCM, overnight, rt, 59%; c) Ac_2O, Et_3N, DMAP, DCM, rt, overnight, 92%

Scheme 80: Synthesis of independently protected compound 197

Following the procedure from the literature, [16] we reduced lactol diacetone mannose **116** to the diol **127** with $LiAlH_4$ in quantitative yield. We chose to use TBDPSCl to selectively protect the primary hydroxyl function due to its extremely bulky nature. Using 1.1 equiv of the silylating agent under mild reaction conditions we were confident that the secondary alcohol function would remain unchanged. We were successful in producing the singly protected silyl ether in 59% yield, and we were also able to recover the majority of unreacted starting material from this reaction. With the TBDPS protected primary alcohol in hand, we acetylated the secondary hydroxyl to give the protected species **197** in 92% yield (**Scheme 80**). The silyl ether group was removed with TBAF in THF overnight in 52% yield to give alcohol **198.** After initial reactions on a small scale we performed the reduction of diacetone mannose, sequential protections and removal of TBDPS on a large scale without purification until the final step with an overall yield of 55%. When we came to the triflation of alcohol **198** we were unable to produce compound **199** using the same conditions reported by Shiba *et al*. (**Scheme 81**). Even after increased reaction time, increased temperature and the addition of DMAP we were unable to produce the triflate **199**; in each case we recovered only starting material.

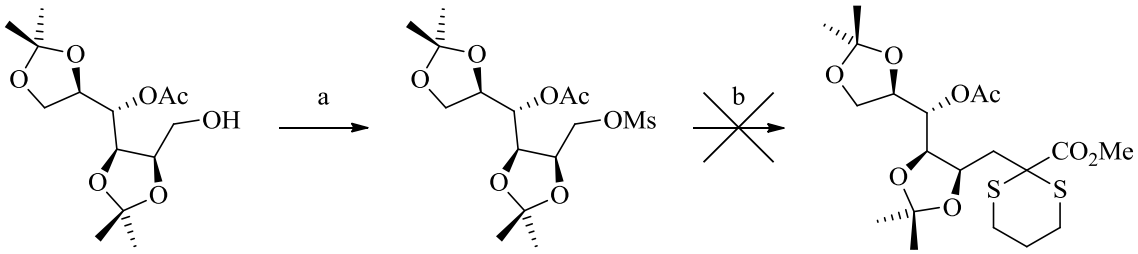


197 **198** **199**

Reagents and conditions: a) TBAF, THF, rt, overnight, 52%; b) Tf_2O, py, DCM, -45 °C.

Scheme 81: TBDPS removal and attempted triflation

Following the lack of success in triflating alcohol **198** we decided to substitute the triflate with a mesylate, hoping this would not adversely affect the next step in the route. Alcohol **198** was successfully converted to mesylate **200** in 83% yield. Unfortunately we were unable to displace the mesylate with the dithiane methyl ester and did not observe any of compound **201** after reaction workup; in all attempts of the reaction we recovered only starting material (**Scheme 82**).



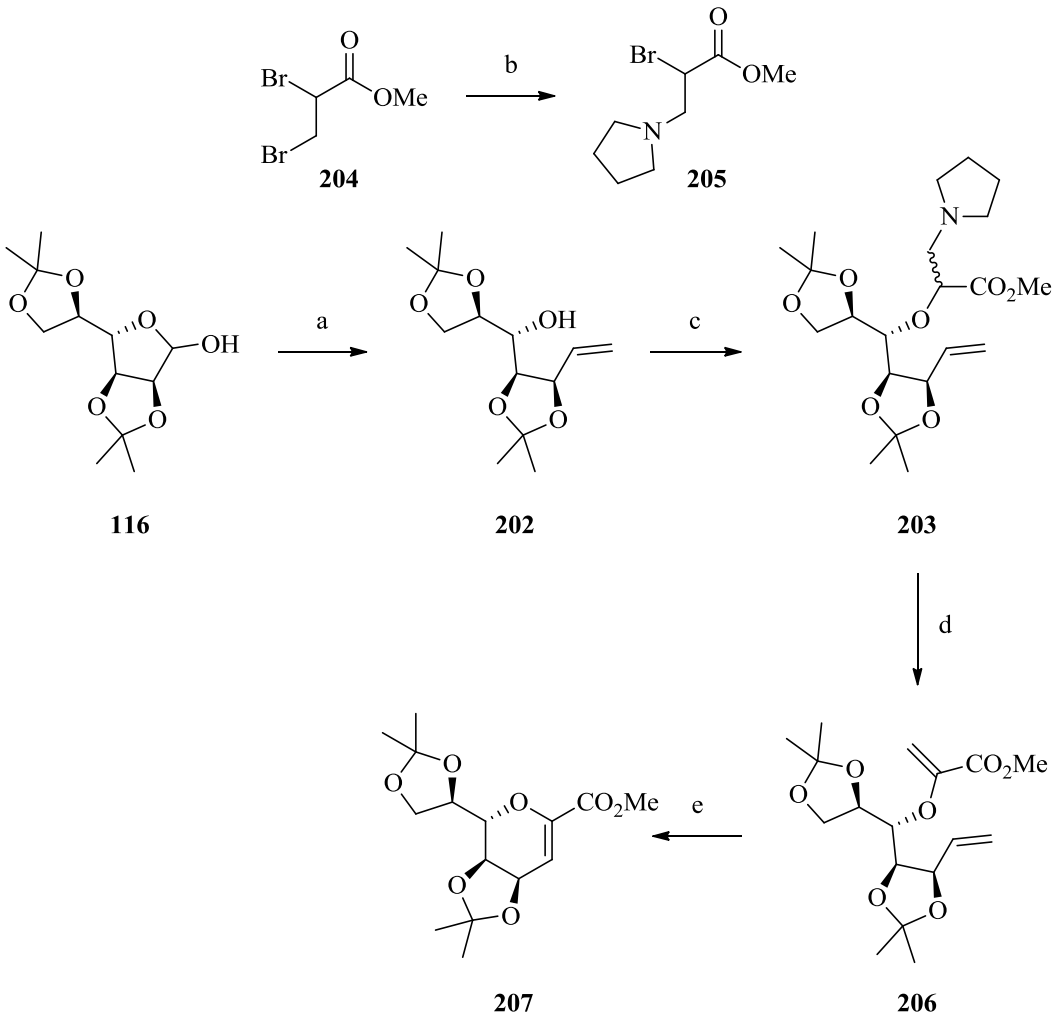
198 **200** **201**

Reagents and conditions: a) MsCl, DMAP, Et_3N, DCM, rt, overnight, 83%; b) Methyl 1,3-dithiane-2-carboxylate, LDA, THF, -20 °C to reflux

Scheme 82: Mesylation of alcohol 198 and attempted displacement with methyl ester dithiane

While we were unsuccessful in moving forward with this synthetic route towards the bicyclic structure **190**, it certainly warrants further investigation.

Ring-closing metathesis route



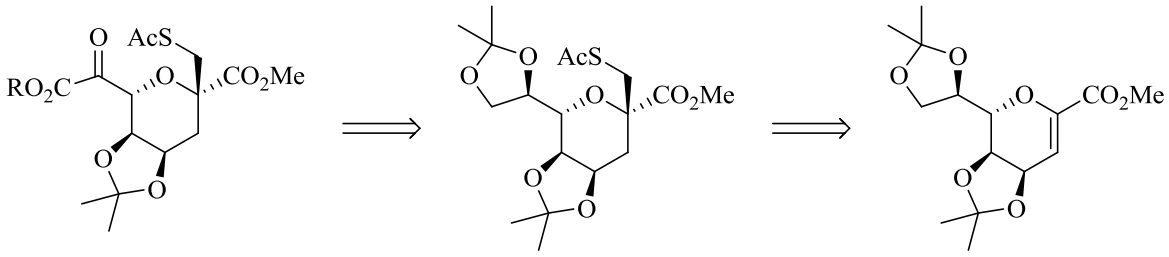
Reagents and conditions: a) Ph_3PCH_3Br, *n*BuLi, THF, rt, 98%; b) Pyrrolidine, Et_3N, toluene, 0 °C, 30 min, 91%; c) **205**, NaH, THF/DMF, 0 °C→rt, 18 h, 75%; d) MeI, Na_2CO_3, MeOH, reflux, 48 h, 78%; e) Grubbs 2nd generation, toluene, 70 °C, 1 h, 84%

Scheme 83: Hekking's synthesis of KDO precursor utilizing ring closing metathesis [17]

An interesting synthesis of KDO precursor **207** reported by Hekking *et al.*[17] involved the use of a ring-closing metathesis reaction to generate alkene **207**. This compound was very similar to compound **166**, which we had previously attempted to make using a Corey-Winter olefination on diol **145**. Hekking's route began with the conversion of diacetone mannose **116** into terminal alkene **202**. Addition of compound **205** in the presence of NaH gave ester **203**

in 75% yield. The second alkene function was generated by the methylation of the pyrrolidine-nitrogen with MeI and subsequent elimination to give diene **206**. Finally a ring closing metathesis reaction using Grubbs 2nd generation catalyst gave alkene **207** (**Scheme 83**).

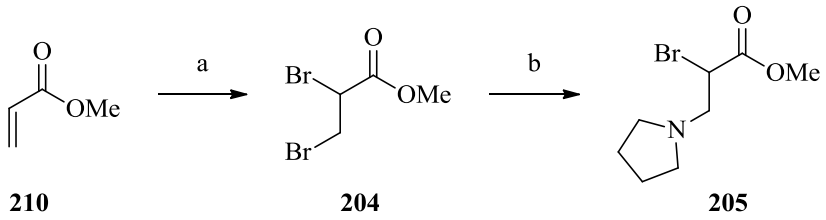
As compound **207** was identical to compound **166** except for the methyl ester function as opposed to the ethyl ester, we believed it was a valid route to follow. Our target bicyclic structure could be formed from the removal of the acetate function on compound **209**. A selective removal of the primary acetal in **208** followed by an oxidation and protection to the ketoester function would yield **209**. A hydrogenation of Hekking's KDO precursor, alkene **207**, followed by addition of the acetate protected thiol function would give compound **208** (**Scheme 84**).



Scheme 84: Retrosynthesis of bicyclic structure precursor 209 from Hekking's final compound

Following the route reported by Hekking, we began with a Wittig reaction to convert diacetone mannose to the terminal alkene **202.** While the reaction was successful we were only able to achieve a yield of 50%, far lower than the 93% reported in the literature [18]. We performed the reaction with commercially available Ph_3PCH_3Br, and also with Ph_3PCH_3I that we prepared by the addition of MeI to PPh_3 in refluxing toluene. Both reagents gave the same 50% yield consistently. With the alkene **202** in hand, our next step was the preparation of bromide **205**. Molecular bromine was added to methyl acrylate **210** in DCM at room temperature to give the dibromo compound **204**; this was in turn reacted with pyrrolidine and Et_3N to give **205.** We found this compound to be extremely unstable: while purification was unnecessary as initial H^1NMR spectroscopy of the crude product indicated high purity, if the

compound was left for more than a few hours, it decomposed from a clear oil to an unidentified brown solid, even if immediately stored under argon at −30 °C in darkness (**Scheme 85**).



210 **204** **205**

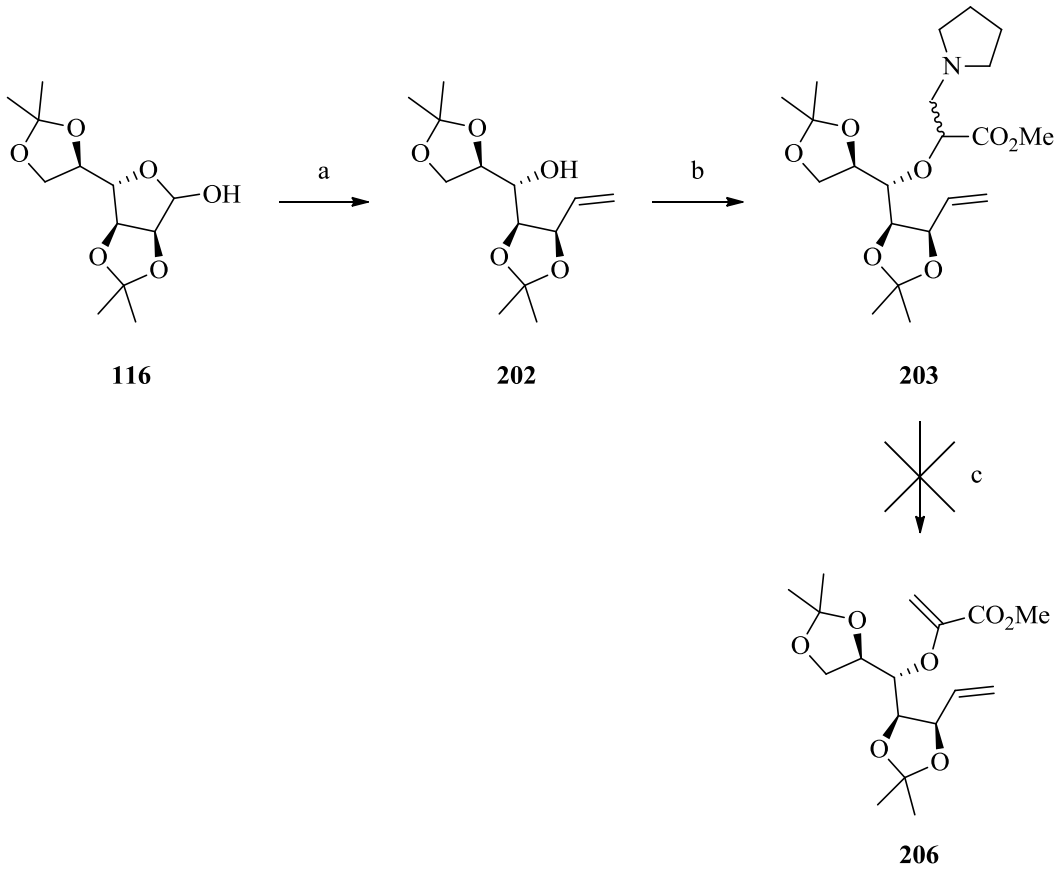
Reagents and conditions: a) Br_2, DCM, rt, 30 min, 88%; b) Pyrrolidine, Et_3N, toluene, 0 °C, 30 min

Scheme 85: Preparation of compounds 204 and 205

Due to the unstable nature of compound **205** it was used immediately after production for the reaction with alkene **202**, but we were unable to reproduce the yields reported by Hekking, in fact in most cases we were unable to produce any trace of compound **203** and at best managed a 10% yield. It is possible this was due to the unstable nature of bromide **205** leading to impurities in the reaction and lowering the yield. All our attempts to improve the yield of the reaction were unsuccessful. Using the small amounts of compound **203** we were able to obtain, we proceeded with the next step in the synthesis, unfortunately the reaction of compound **203** with MeI and Na_2CO_3 did not lead to the elimination to form diene **206 (Scheme 86)**.

This was a disappointing result as we were unable to attempt the ring closing metathesis reaction. Due to the very low yields we obtained for compound **203** and the failure to produce compound **206,** we abandoned any further study on this route.

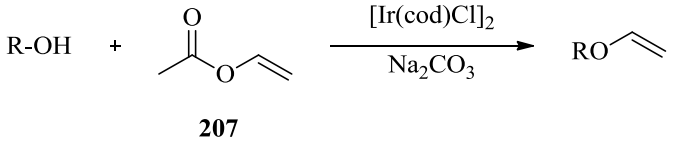
Olefin metathesis route



Reagents and conditions: a) Ph_3PCH_3I, *n*BuLi, THF, rt, 98%; b) **205**, NaH, THF/DMF, 0 °C→rt, 18 h, 10%; c) MeI, Na_2CO_3, MeOH, reflux, 48 h

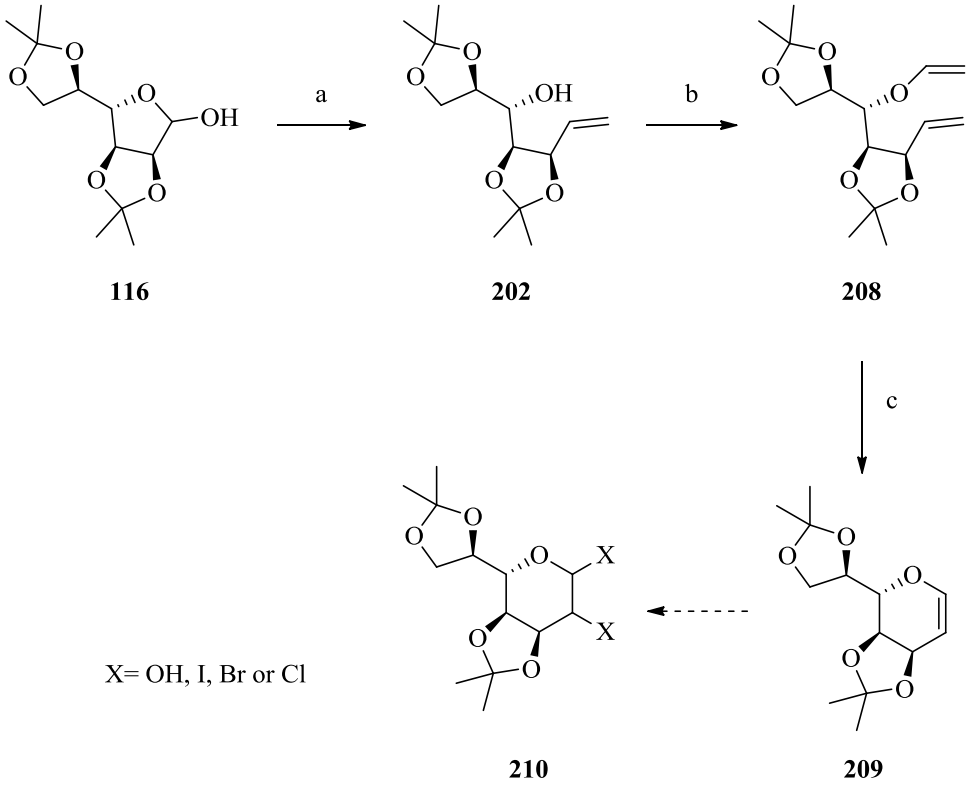
Scheme 86: Our synthesis towards ring closing metathesis reaction

As we were unsuccessful in generating the diene **206** and therefore unable to attempt the ring closing metathesis reaction we proposed a different route that would still utilize a ring closing metathesis step. A report published by Okimoto *et al.*[19] involved the use of an $[Ir(cod)Cl]_2$ catalyst and vinyl acetate **207** to generate vinyl ethers from alcohols under fairly mild conditions (**Scheme 87**).



Scheme 87: Okimoto's synthesis of vinyl ethers from alcohols [19]

We believed we could apply this reaction to our synthesis, reacting vinyl acetate directly to alcohol **202** using the conditions reported by Okimoto. This would give diene **208**, which would undergo a ring-closing metathesis reaction to generate alkene **209**. From alkene **209** we envisaged several methods for functionalizing the double bond, including asymmetric epoxidation, dihydroxylation or halogenation reactions (**Scheme 88**).



116 **202** **208** **209** **210**

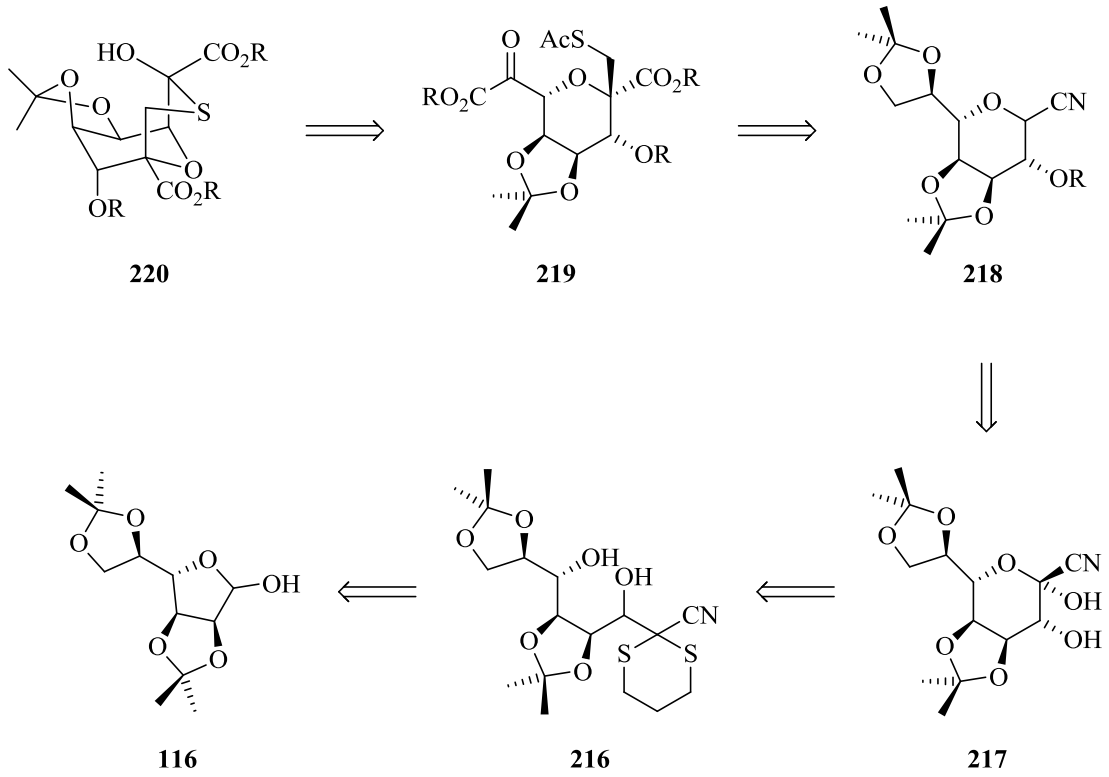
Reagents and conditions: a) Ph_3PCH_3Br, *n*BuLi, THF, rt; b) vinyl acetate, $[Ir(cod)Cl]_2$, Na_2CO_3, toluene; c) Grubbs 2nd generation, toluene, 70 °C, 1 h

Scheme 88: Our proposed synthesis of alkene 209

Unfortunately all our attempts to generate vinyl ether **208** failed. We therefore abandoned any further work towards a ring-closing metathesis reaction.

Nitrile dithiane route

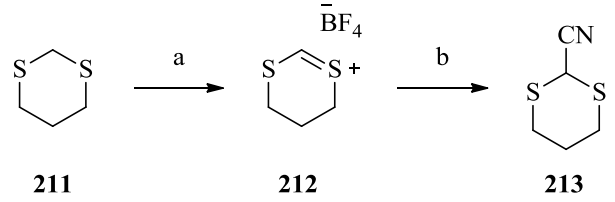
With a lack of success with both the Wittig reaction routes and the ring closing metathesis routes we decided to revisit the dithiane method. In this case we changed the ester moiety to a nitrile, in the hope this would aid in the removal of the anomeric hydroxyl group of compound **217** (**Scheme 89**).



Scheme 89: Retrosynthesis from diacetone mannose using nitrile dithiane

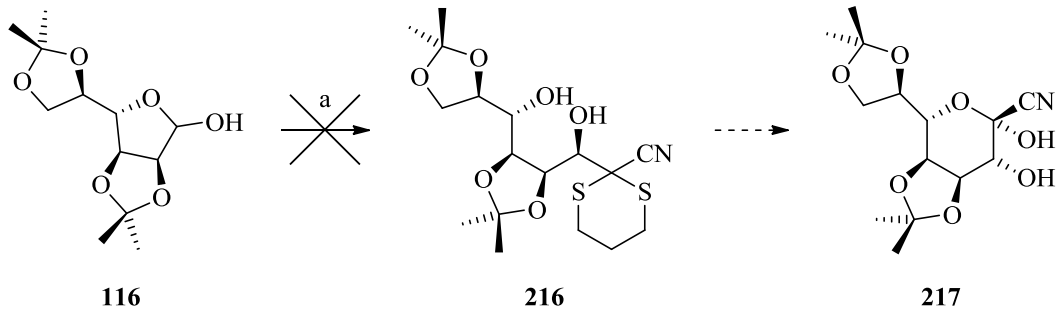
The nitrile moiety could be converted to an ester at a later stage in the synthesis and eventually converted to the carboxylic acid in the final target compound **2a**.

Our first step in this route was the generation of 2-cyano-1,3-dithiane **213** following the procedure reported in the literature by the Page group.[20] 1,3-Dithiane **211** was treated with triphenylcarbenium tetrafluoroborate in DCM under reflux to give tetrafluoroborate salt **212**. Addition of TMSCN to salt **212** in cold DCM (−20 °C) gave nitrile **213** in 50% yield over two steps.



Reagents and conditions: a) $PhC^{+}BF_4^{-}$, DCM, reflux, 45 min;
b) TMSCN, DCM, -20 °C, 1 h

Scheme 90: Synthesis of 2-cyano-1,3-dithiane 213



Reagents and conditons: a) LDA, **213**, $MgBr_2$, THF, –20 °C → rt

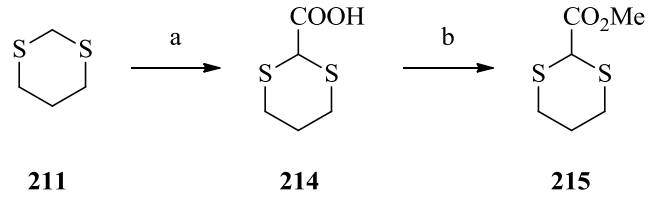
Scheme 91: Attempted synthesis of nitrile 217

Our next task was the nucleophilic attack of the anion of nitrile dithiane **213** on diacetone mannose **116**. Initially we repeated the reaction using identical conditions to those used to form dithiane **143**, this, however, proved unsuccessful (**Scheme 91**). Surprised by this result we attempted to confirm whether the lithiated cyano-dithiane was being generated. Therefore, dithiane **213** was reacted with several lithiating reagents (*n*BuLi, *t*BuLi, *s*BuLi) in THF followed by the addition of D_2O, with the aim of replacing the proton at the C-2 position with a deuterium atom. Unfortunately after repeated attempts we were unable to introduce the deuterium atom leading us to conclude we were not generating the lithiated species, or that the lithiated species was unreactive.

We also explored the possibility that a different ester group present at the C-2 position of the dithiane might have an effect on the yield of the dethioketalization. In the report by Schmidt *et al.*[2] they showed a far greater yield for the dethioketalization reaction on the methyl ester

compound **150**, compared to ethyl ester **143**. While we were unable to duplicate this yield with the diethylmercaptaldithioketal species **150**, we proposed that the methyl ester dithiane **215** might give more promising results.

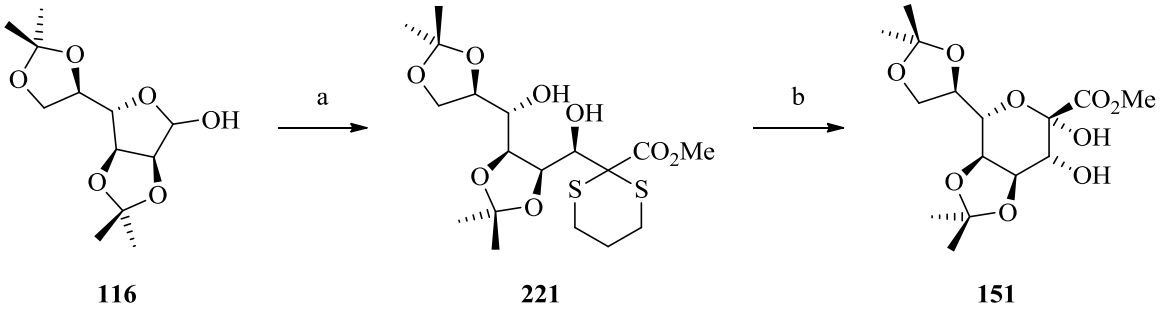
Dithiane **215** was prepared from commercially available 1,3-dithiane **211**, following the literature procedure, [21] lithiation with *n*BuLi in THF followed by the addition of solid carbon dioxide and an acidic workup led to dithiane carboxylic acid **214**. HCl gas was then bubbled through a solution of **214** in MeOH to give the methyl ester **215** (**Scheme 92**).



Reagents and conditions: a) *n*BuLi, CO_2(s), THF, –78 °→ rt b) HCl(g), MeOH, 10 min

Scheme 92: Preparation of methyl ester dithiane 215

With dithiane **215** in hand we began the next step in the synthesis. Following the same conditions used to form compound **143**, dithiane **215** was coupled with diacetone mannose successfully to give compound **221** in 83% yield. Dethioketalization of **221** by NBS in 95% aqueous acetone gave pyranose **151**; we were pleased to find the yield was slightly higher (40-60%) when compared with our previous attempts with the ethyl ester **143** (**Scheme 93**).

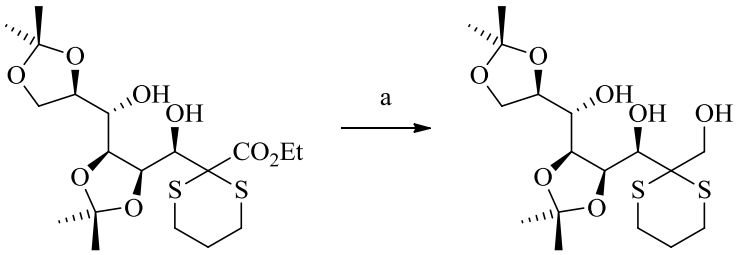


Reagents and conditions: a) **215**, LDA, $MgBr_2$, THF, -20 °C → reflux, 83%; b) NBS, 95% aqueous acetone, 0 °C, 3 min, 40-60%

Scheme 93: Preparation of methyl ester 151 through dithiane 221

Reduction route

While we were successful in producing dithiane methyl ester **221**, and subsequently increasing the yield of the dethioketalization by a modest amount, the difficulty in removing the anomeric hydroxyl still remained. With this in mind we decided to continue the dethioketalization strategy but remove the ester moiety completely. A simple reduction of ester **143** to the triol **222** was conducted with $LiAlH_4$ (**Scheme 94**)

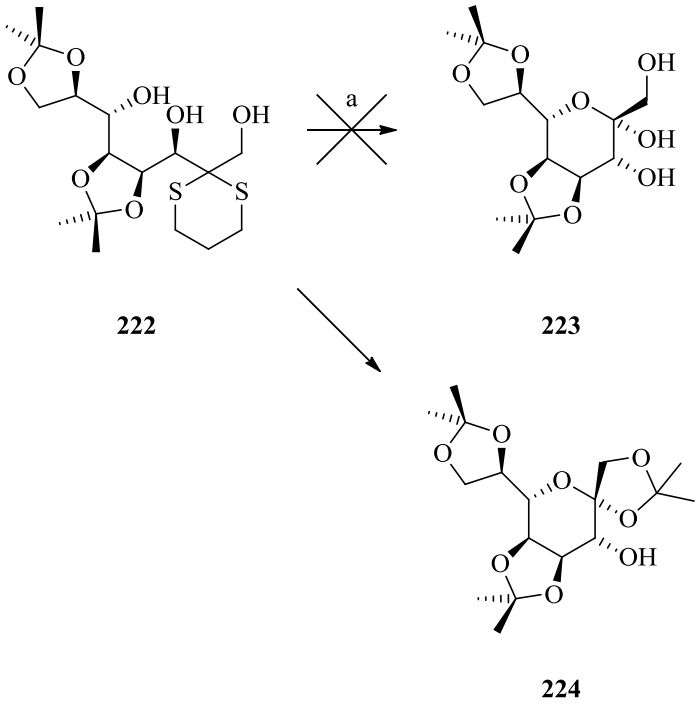


143 **222**

Reagents and conditions: a) $LiAlH_4$, Et_2O, rt, 3 h. 76%

Scheme 94: Reduction of ester 143 to triol 222

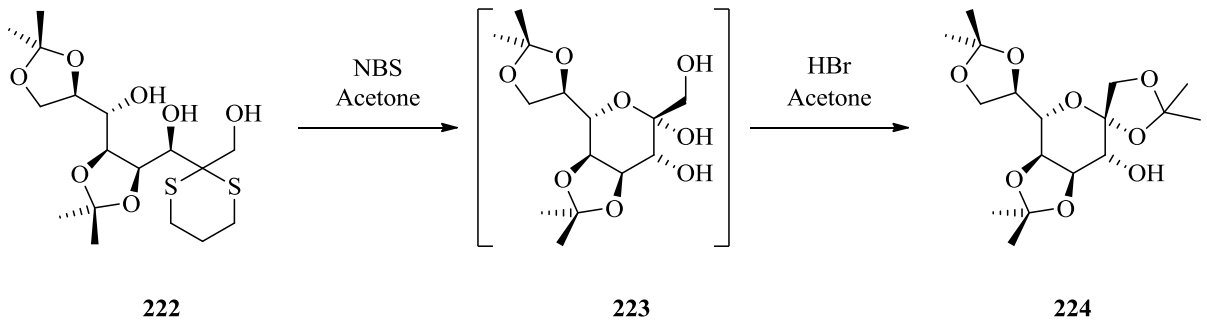
We believed removing the ester moiety in this way would reduce the likelihood of a reversion back to diacetone mannose **116** following reaction with NBS, without the ester moiety present the dithiane anion, likely generated during the production of diacetone mannose when reacting **145** with NBS would be far less stable. We therefore subjected compound **222** to the dethioketalization conditions using NBS in 95% aqueous acetone (**Scheme 95**).



Reagents and conditions: a) NBS, 95% acetone, 0 °C, 3 min

Scheme 95: Dethioketalization of dithiane 222

Fully expecting to generate pyranose **223**, we were surprised to find no trace of this compound after work up. Instead we found the major product of the reaction (55%) to be the tri-acetal protected species **224**. While this was not the intended target it was pleasing to note the lack of any diacetone mannose present after workup. We presumed the formation of the tri-acetal species was due to catalytic amounts of HBr present in the reaction generated by NBS and water, combined with the large excess of acetone this could lead to acetal formation between the primary and tertiary alcohols present in the intended product **223** (**Scheme 96**).



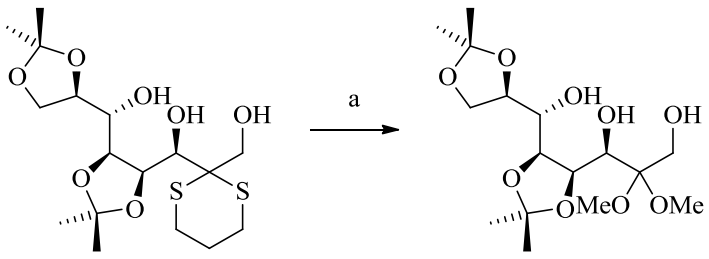
Scheme 96: Possible route for the formation of tri-acetal 224

This was not an entirely unhelpful result; it proved that removing the ester moiety from the dithiane prevented the formation of diacetone mannose during dethioketalization. Working from this result we deduced that changing the solvent from acetone and also the conditions used for the dethioketalization would prevent the formation of the third acetal (**Table 8**).

Method	Conditions	Result
1	NBS, 95% Acetone, 0 °C, 3 min	**224**
2	NBS, DCM, 0 °C, 3 min	SM
3	HgO, $HgCl_2$, MeOH:H_2O, reflux, 1 h	SM
4	NBS, MeOH:H_2O, 0 °C, 3 min	**225**
5	NBS, MeCN;H_2O, 0 °C, 3 min	87% **223**

Table 8: Conditions tried for dethioketalization of triol 222

NBS and DCM led to no reaction and complete recovery of starting material, as did the use of mercury reagents in MeOH under reflux conditions. We noted an interesting result when NBS was used in MeOH and water, it appeared that the dithiane had been successfully removed but before cyclization could occur the ketone moiety was converted to a ketal to give **225 (Scheme 97**).



222 **225**

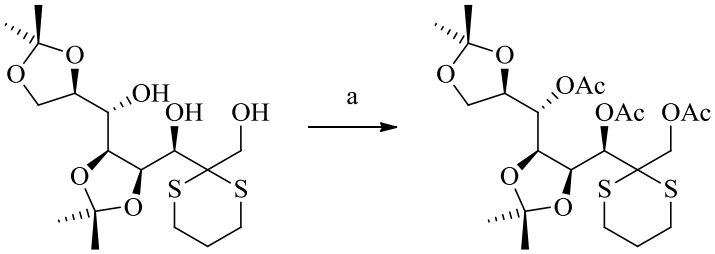
Reagents and conditons: a) NBS, MeOH:H_2O, 0 °C, 3 min

Scheme 97: Formation of ketal 225

This formation of ketal **225** could be explained in a similar fashion to the formation of tri-acetal **224**. Catalytic amounts of HBr and the great excess of MeOH in the reaction mixture presumably led to formation of the ketal **225**.

We were pleased to find the combination of NBS in acetonitrile and water gave the desired product **223** in 87% yield.

Protection of the primary hydroxyl on compound **222** before the dethioketalization reaction was also investigated. Acetylation of the primary hydroxyl proved problematic when using DMAP in the reaction mixture, leading to production of the tri-acetylated compound **226**, and a large proportion of starting material recovered (**Scheme 98**).

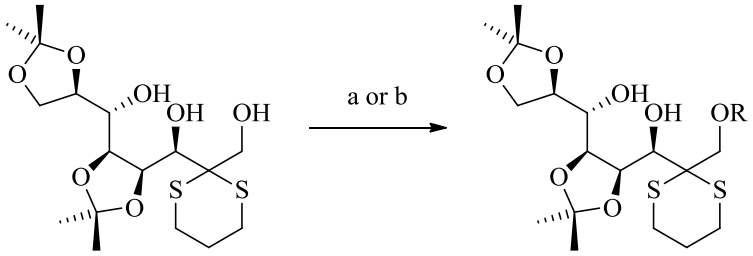


222 **226**

Reagents and conditions: a) Ac_2O, Et_3N, DMAP, DCM, rt, 4 h

Scheme 98: Production of undesired tri-acetyl compound 226

Repeating the procedure without the presence of DMAP, and over a longer reaction time led to acetylation of the primary hydroxyl only, to give **227**. We also attempted to form the tertiarybutyldiphenylsilyl ether of the primary alcohol; the reaction was successful but in a very low yield (18%) (**Scheme 99**).

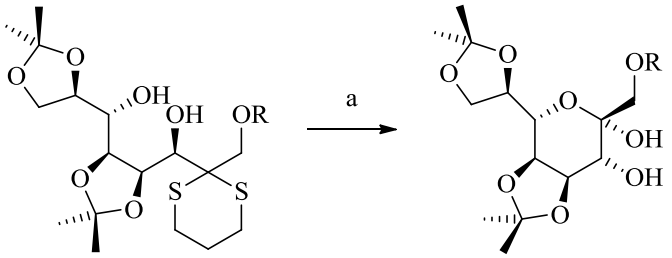


222 R=TBDPS or Ac **227**

Reagents and conditions: a) Ac_2O, Et_3N, DCM, rt, overnight, 67%; b) TBDPSCl, Et_3N, DMAP, DCM, rt, overnight, 18%

Scheme 99: Protection of primary hydroxyl on triol 222

Both compounds were subjected to the dethioketalization reaction initially using NBS in aqueous acetone. Unfortunately both compounds were unreactive to this method. When treated with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), however, both compounds reacted in good yield to give the corresponding protected pyranoses (**Scheme 100**).

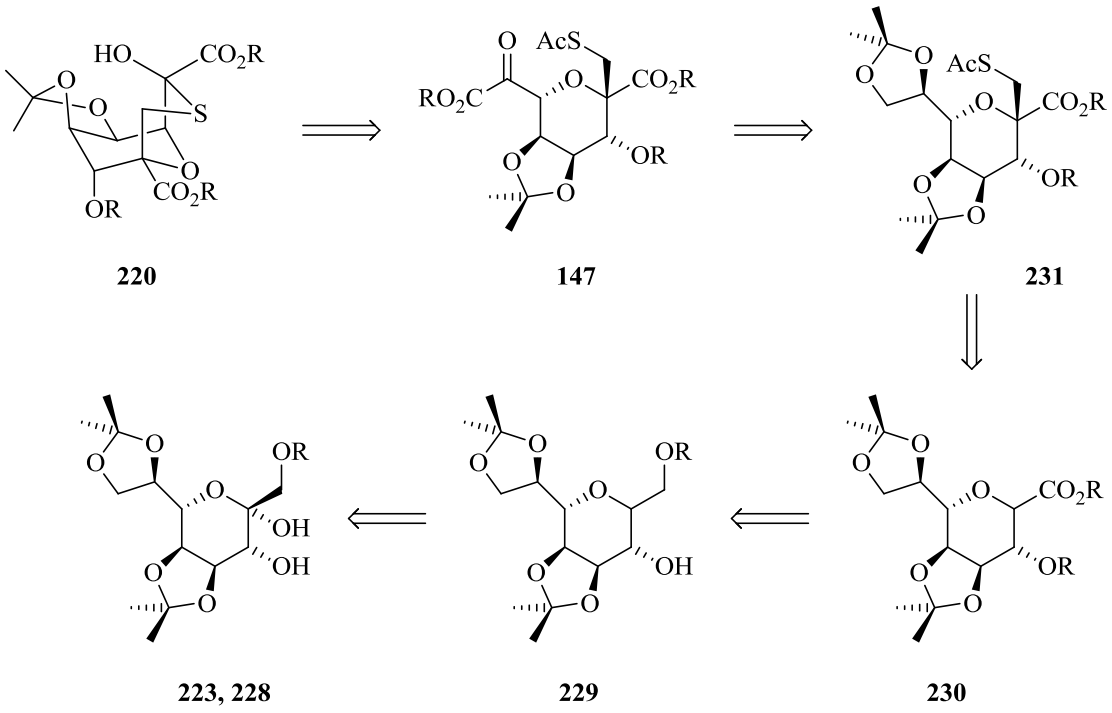


227 R=TBDPS or Ac **228**

Reagents and conditions: a) DBDMH, 95% acetone, 0 °C, 3 min, (66-100% R=Ac) (67% R=TBDPS)

Scheme 100: Dethioketalization of protected compounds 227

Our next step in this route was to remove the anomeric hydroxyl group on compounds **223** and **228**. Following the removal of the hydroxyl group the ester functionality would need to be restored giving compound **230**; this would enable the enolate addition of formaldehyde and subsequent displacement of the primary alcohol with the thioacetate anion to give **231**. The retrosynthesis from this compound was identical to our previous routes, generation of keto-ester **147**, followed by removal of the acetate function leading to the bicyclic structure **220** (**Scheme 101**)

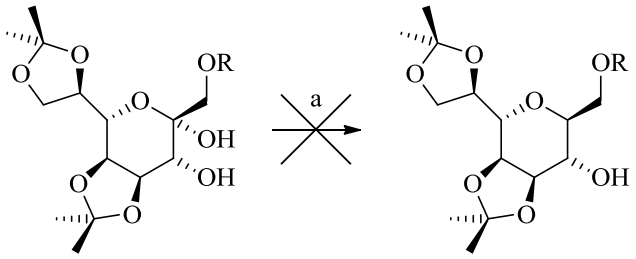


220 **147** **231**

223, 228 **229** **230**

Scheme 101: Retrosynthesis of bicyclic structure 220 from triol 223

Our initial attempt to remove the anomeric hydroxyl from compounds **223** and **228** followed the procedure outlined in the literature, [10] unfortunately this method was unsuccessful on both the triol **223** and the acetate protected compound **228**. As well as failing to remove the anomeric hydroxyl these conditions also led to decomposition of the compound preventing any recovery of starting material.

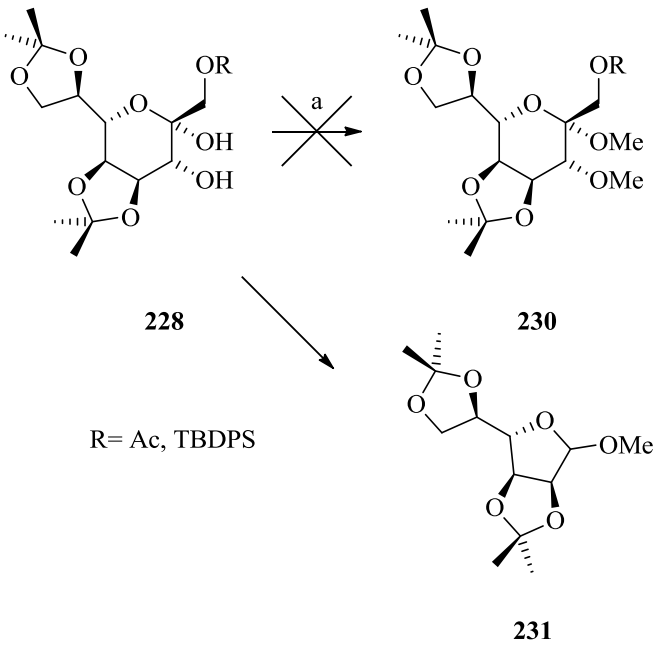


223, 228 R= Ac, H **229**

Reagents and conditions: a) TMSOTf, Et_3SiH, MeCN

Scheme 102: Attempted removal of anomeric hydroxyl using Gray's procedure [10]

Following the disappointing results from the attempted anomeric hydroxyl removal we considered converting the hydroxyl moiety to a methoxy group in the hope that this would aid the removal of the group in the anomeric position. We believed this would be a simple procedure and expected a clean conversion to compound **230** using the same conditions used to generate compound **154** in a previous route. Unfortunately we were surprised to find that when reacting the acetate protected compound **228** we observed complete decomposition of the starting material, and no trace of the intended product was detected. When applying the same conditions to TBDPS protected compound **228** we not only observed a decomposition of the starting material and none of the intended product, but we also identified one of the decomposition products as the methoxy diacetone mannose compound **231** (**Scheme 103**).



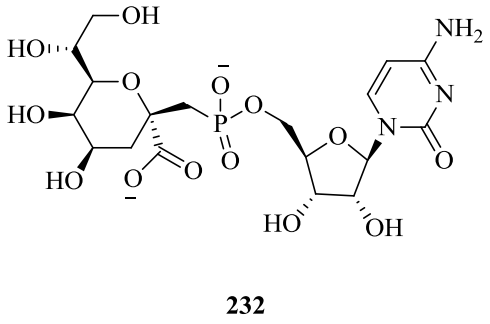
Reagents and conditions: a) NaH, MeI, DMF

Scheme 103: Attempted methylation of diols 228

Following these disappointing results we postponed any further work on this route and proceeded to move to our final strategy.

D-Arabinose route

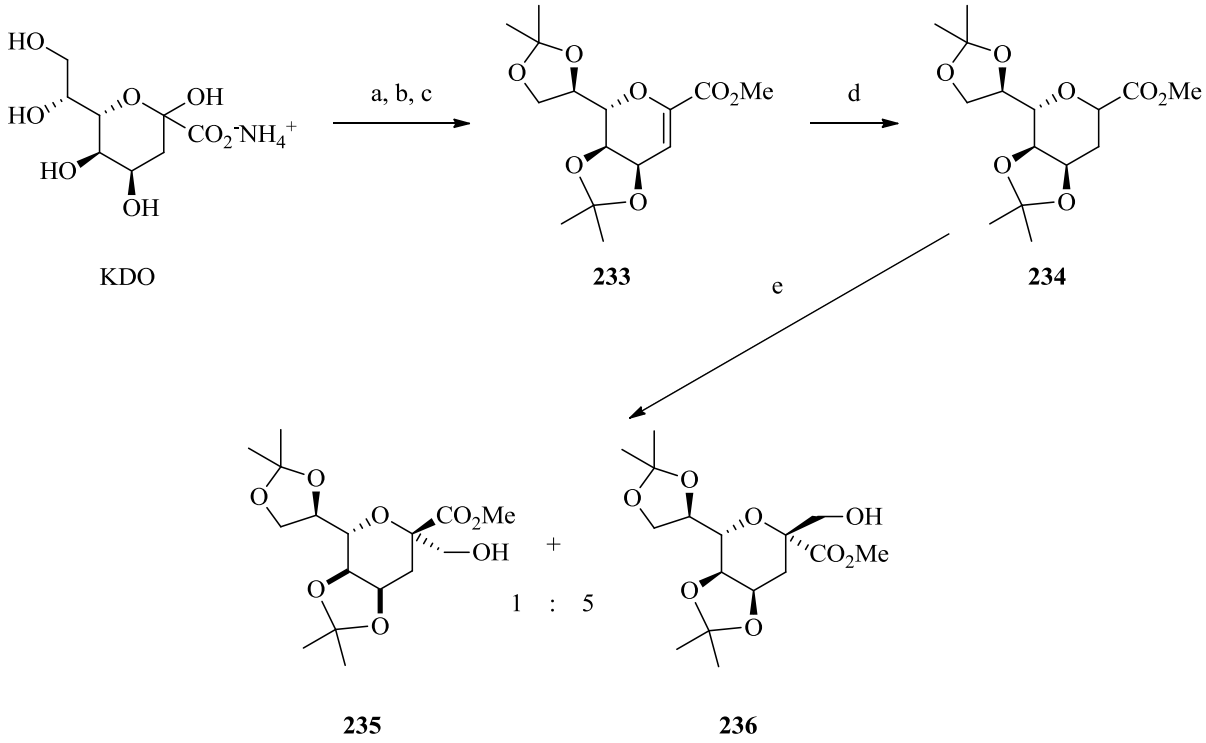
A report published in the literature by Norbeck *et al.*[22] described a synthesis of a phosphonate analogue of cytidine 5-monophospho-3-deoxy-D-*manno*-2-octulosonic acid **232** (**Figure 13**).



232

Figure 13: Cytidine 5-monophospho-3-deoxy-D-manno-2-octulosonic acid 232

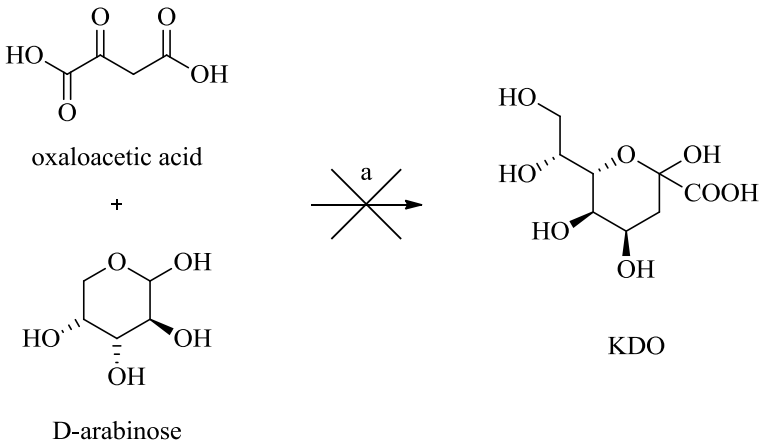
During their synthesis of **232**, Norbeck and colleagues proceeded through compound **236**, which was one of our target precursors for the bicyclic structure (**Scheme 104**).



Reagents and Conditons: a) Acetone, H_2SO_4; b) CH_2N_2, Et_2O; c) MsCl, Et_3N, DCM, 66% over 3 steps; d) W-2-Ra-Ni, H_2, EtOH, 88%; e) LDA, CH_2O, THF, 91%

Scheme 104: Norbeck's synthesis of 236 starting from KDO [22]

Perhaps the most intriguing part of Norbeck's synthesis was their production of KDO, which they reported was performed in a single step, following a Cornforth condensation [23] of D-arabinose and oxaloacetate. We attempted to replicate this very short synthesis of KDO, following the conditions in the literature. [23] We reacted oxalic acid and D-arabinose in water under basic conditions, unfortunately we were unable to reproduce the results reported and after several attempts we were unable to obtain any of the product KDO (**Scheme 105**).



Reagents and conditions: a) (i) H_2O, 10 M NaOH, (ii) AcOH, 0 °C

Scheme 105: Attempted condensation of oxaloacetic acid and D-arabinose

Due to time constraints and the lack of any promising results from this method no further work was attempted with this strategy.

Conclusion and Future work

Conclusion

During our synthetic studies towards tagetitoxin **2a** a range of strategies were investigated, leading to several key compounds of interest. Our first strategy involving the use of a dithiane protected ketoester followed by a dethioketalization led to compounds **145** and **151**. While we were unable to progress any further with this route it still presents as the most likely method to reaching the goal of the bicyclic structure, prompting us to revisit the use of a dithiane later in our work.

Compounds **179** and **186**, both produced involving the use of a Wittig reaction to introduce the ester moiety, which would eventually become the carboxylic acid function in the final compound, showed significant promise. While it was unfortunate that we were unable to displace the tosylate group with the hydroxyl moiety after removal of TMS on compound **179**, leading to a cyclization, this route did show an alternative way of introducing the ester moiety. Work on compound **186** to introduce a suitable leaving group α- to the ester was also

unsuccessful. We believed if a suitable group (I, Cl, Br) was in this position, deprotection of the hydroxyl would lead to a cyclization.

Compound **198** seemed to be a significant step forward in our work with diacetone mannose. Using this strategy of reduction and sequential protection we had hoped to eliminate a hydroxyl group from an intermediate further on in the synthesis, however, the inability to generate the triflate from the primary hydroxyl was a major setback. Mesylating the primary hydroxyl as an alternative to triflation was inadequate to promote the displacement with a lithiated dithiane protected ketoester, leading to the abandonment of this route.

One of our final synthetic routes led to intermediate **220**, and it was only due to time constraints that more extensive work was not carried out on this compound. Having removed the problem of low yields for dethioketalization we were confident that this route would lead to the bicyclic structure. Our lack of success in removing the anomeric hydroxyl was unfortunate, but further work on this route should not be discounted (**Figure 14**).

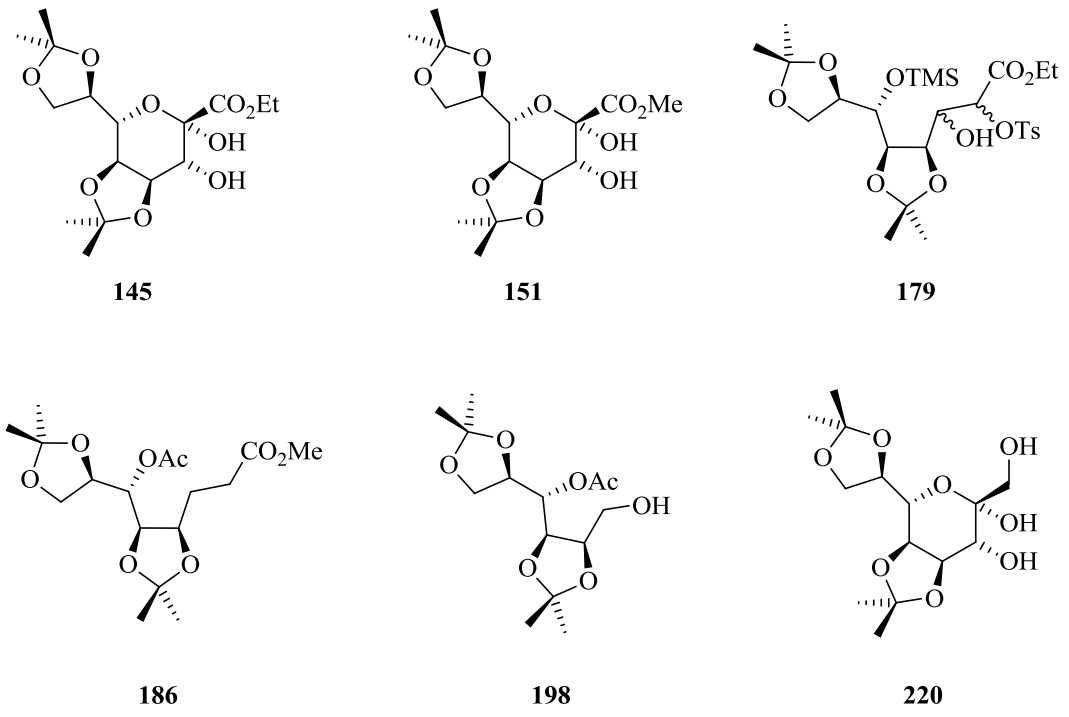


Figure 14: Synthetic intermediates formed during the project

Future Work

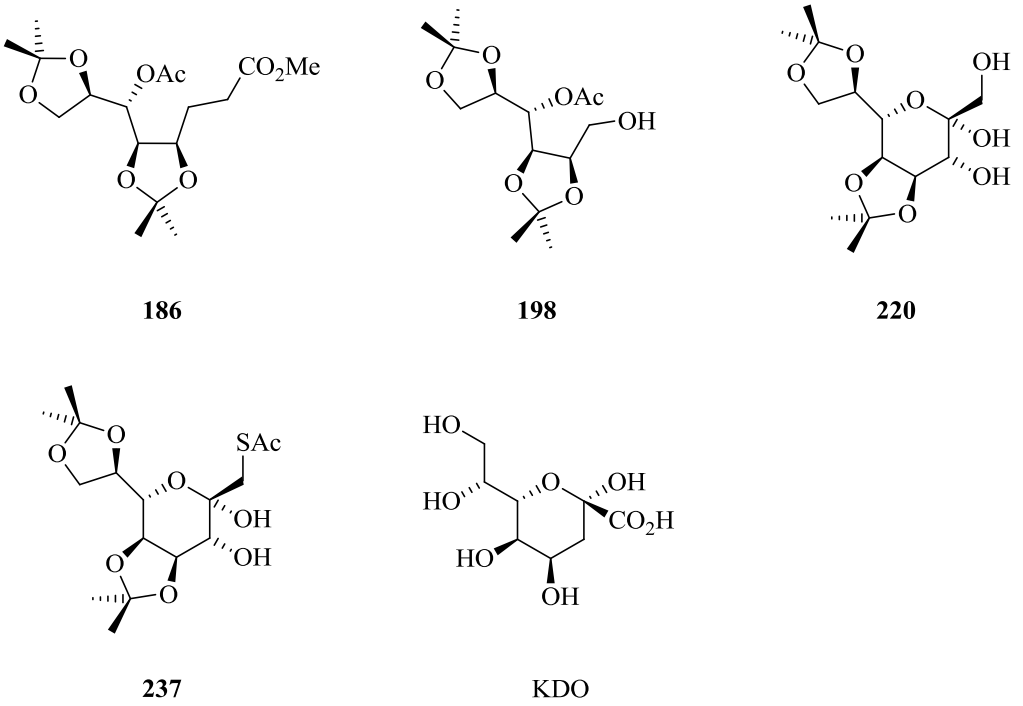


Figure 15: Compounds meriting further study

While we were unable to produce the core bicyclic structure of tagetitoxin, we did synthesize a number of intermediates which prompt further studies. Compound **186** certainly merits further studies; halogenation alpha to the ester still appears to be the most likely strategy to proceed further with this route, despite our lack of success with this methodology.

The reduction of diacetone mannose followed by the sequential protection and deprotection of the primary and secondary hydroxyl group to give compound **198** also requires further study. Triflation of the primary alcohol and subsequent displacement with the dithiane protected ketoester should work, despite our unsuccessful attempts at the triflation. Also, during our synthetic work, only the acetate protection was used on the secondary hydroxyl. A large range of alternate protecting groups could be screened for further study.

One of our most promising intermediates, compound **220**, leaves many options for further work. Continued attempts for the removal of the anomeric hydroxyl group would be prudent. A different strategy for this compound would also involve the tosylation of the primary

hydroxyl group, followed by displacement with a thioacetate anion. This would give an interesting intermediate **237**. The remaining hydroxyl groups could be protected and the previously proposed route for deprotection of the primary ketal, followed by oxidation to a ketoester, and finally removal of the acetate group protecting the primary thiol would lead to the bicyclic structure. This would leave the functionalization of the protected hydroxyl groups for a later stage in the synthesis.

Finally, the work conducted on the direct conversion of D-arabinose and oxaloacetic acid to KDO warrants further investigation. If successfully completed in reasonable yields this provides a fast and efficient route to more advanced intermediates (**Figure 15**)

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Experimental

Experimental Procedures

Air sensitive reactions were run using flame-dried glassware and under an argon atmosphere. Extractions were performed using the reported organic solvent and, if not indicated, were equivolumetric. Where petroleum ether fractions 40/60 has been used, it is referred to in the term "petrol".

Chromatography on silica gel was performed using a standard purification procedure using Fluka Kieselgel 60, 0.023-0.063 mm particle size with the reported solvent systems. Thin layer chromatography was performed using Merck aluminium-backed plates coated with Kieselgel 60 F254 silica coating. The plates were visualized by U.V. irradiation at a wavelength of 254 nm, or by dipping the plate in an ethanolic solution of phosphomolybdic acid, or potassium permanganate solution.

Fourier transformation Infrared spectroscopy was recorded using a Perkin Elmer Model spectrophotometer in the range of 4000-500 cm^{-1}. Samples were dissolved in the reported solvent and applied onto a sodium plate as thin films.

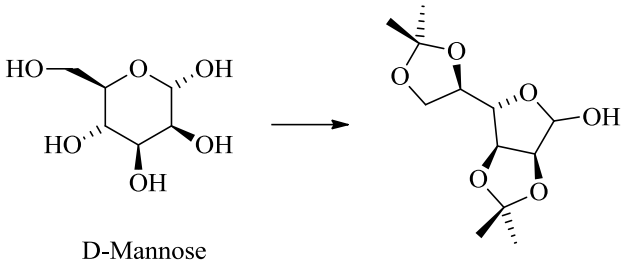
Nuclear magnetic resonance spectroscopy was acquired using a Varian Unity Plus instrument operating at a frequency of 399.96 MHz for 1H NMR analyses and 100.58 MHz for 13C NMR analyses. The spectra were calibrated where possible to the signals of tetramethylsilane, at d = 0.00 ppm, or else using the residual peak of $CHCl_3$ present in $CDCl_3$, at δ = 7.26 ppm. Chemical shifts (δ) are reported in ppm. When possible, coupling constants (J) are shown denoting the multiplicity as: singlet (s), doublet (d), triplet (t), quarter (q), multiplet (m) or any combination of those. The size of the coupling constant is given in Hertz. Carbons are shown as follows: CH_3, CH_2, CH and C_q (quaternary carbons).

Optical rotations values were measured with a Bellingham and Stanley ADP-440 polarimeter, operating at λ = 589 nm, corresponding to the sodium line (D), at the temperatures indicated. The solvent used for these measurements were of spectrophotometric grade and the solutions for these measurements were prepared in volumetric flasks for maximum accuracy.

High resolution mass spectroscopy was carried out by the EPSRC national mass spectrometry service at the University of Wales, Swansea, utilizing electrospray (ES), nanoelectrospray (NESP) and MALDI-TOF ionization techniques.

Melting points were obtained using an Electrothermal-IA 9100 melting point instrument.

2,3;5,6-di-O-isopropylidene-α-D-mannofuranose (116)[1]



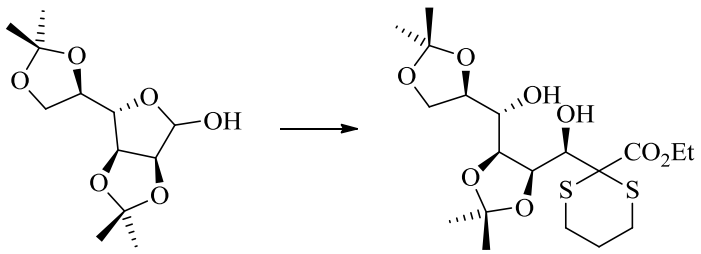
D-Mannose

116

D-Mannose (20 g) was stirred with anhydrous acetone (600 mL); concentrated sulfuric acid (14 mL) was added to the solution and stirred for 3-4 h at rt until all of the sugar had dissolved. The light yellow solution was neutralized with anhydrous sodium carbonate and filtered. The filtrate was refluxed for a further 1 h with activated charcoal and 2-3 g sodium carbonate. The solution was filtered through celite and evaporated under reduced pressure to give a colourless solid. Crystallization using diethyl ether and petrol gave the product **116** as colourless crystals, 20 g from the first crystallization and a further 6-7 g from recrystallization of the mother liquor (26.6 g, 92%).

Rf 0.42, (1:1), (toluene:EtOAc); M.p. 122-123 °C; IR ν_{max} (film)/cm^{-1}: 3427, 2985, 2945, 2898, 1457, 1437, 1373, 1226, 1203, 1069; δ_H (300 MHz, $CDCl_3$): 1.32, 1.37, 1.45, 1.46 (4s, 12H, $CH_{3\ isopropylidene}$), 4.06 (dd, 2H, J = 3.45, 5.44Hz, 6-H), 4.17 (dd, 1H, J = 3.62, 7.16 Hz, 5-H), 4.40 (dd, 1H, J = 6.5, 11.53 Hz, 4-H), 4.61 (d, 1H, J = 5.91Hz, 2-H), 4.80 (dd, 1H, J = 3.67, 5.91 Hz, 3-H), 5.37 (s, 1H, 1-H), δ_C (100 MHz, $CDCl_3$): 24.23, 25.16, 25.68, 26.55 (4 CH_3), 65.80 (C-6), 72.75 (C-5), 79.09 (C-4), 79.26 (C-3), 85.38 (C-2), 100.30 (C-1), 107.83, 111.26 ($2C_{q\ isopropylidene}$); *m/z* $[M+H]^+$: 261.1333; $[C_{12}H_{21}O_6+H]^+$ requires 261.1333.

Ethyl 2-deoxy-4,5:7,8-di-O-isopropylidene-D-glycero-D-galacto-octulosonate 1,3-propane dithio-acetal (143)[2]



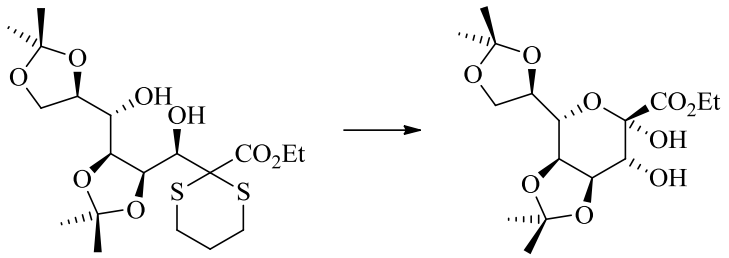
116 **143**

A solution of DIPA (16.8 mL, 126 mmol) in 145 mL of THF was cooled to −20 °C, *n*BuLi, 2.5M in hexanes, (50.56 mL, 126 mmol) was added dropwise, and this solution stirred for 15 minutes. Ethyl 1,3-dithiane-2-carboxylate (18.1 mL, 115.2 mmol) was then added slowly to the solution and stirred for 2 h at −20 °C. The mixture was cannulated slowly into a solution of $MgBr_2$ in 185 mL of THF, prepared from Mg (4.2 g, 172 mmol) and 1,2-dibromoethane (13.2 mL, 152.8 mmol) at −20 °C. Compound **116** (10 g, 38.4 mmol, was added to the solution without any solvent, the reaction mixture was left to reach rt over 3 h, heated to 50 °C for a further 3 h, then poured into ice-cold saturated aqueous NH_4Cl solution (400 mL). The solution was extracted with EtOAc 3x200 mL; the organic layer was washed with water and then brine and dried over $MgSO_4$. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (toluene:EtOAc) (4:1) to give **143** as a yellow glassy residue (16.62 g,95.6%).

Rf 0.5 (1:1), (toluene:EtOAc); IR ν_{max} (film)/cm^{-1}: 3452, 2983, 2933, 1727, 1424, 1380, 1370, 1245, 1215, 1063; δ_H (400 MHz, $CDCl_3$): 1.36 (t, 3H, J = 7.2 Hz, $CH_{3\ ester}$), 1.36, 1.38, 1.43, 1.52 (4s, 12H, $CH_{3\ isopropylidene}$), 1.91 (m, 1H, $CH_{2\ dithiane}$), 2.10 (m, 1H, $CH_{2\ dithiane}$), 2.78 (m, 2H, $CH_{2\ dithiane}$), 3.02 (dd, 1H, J = 2.8 Hz, J = 11.6 Hz, $CH_{2\ dithiane}$), 3.23 (dd, 1H, J = 2.8 Hz, J = 11.2 Hz, $CH_{2\ dithiane}$), 3.64 (d, 1H, J = 6 Hz, 5-H), 3.78 (d, 1H, J = 2.4 Hz, OH), 3.95 (d, 1H, J = 10 Hz, CH_{carbo}), 4.03-4.08 (m, 1H, CH_{carbo}), 4.11-4.16 (m, 2H, CH_{carbo}), 4.25-4.33 (m, 3H, $CH_{2\ ester}$, CH_{carbo}), 4.44 (dd, 1H, J = 1.2 Hz, J = 7.6 Hz, 4-H), 4.58 (d, 1H, J = 7.6 Hz, 3-H); δ_C (100 MHz, $CDCl_3$): 14.10 ($CH_{3\ ester}$), 24.16 ($CH_{2\ dithiane}$), 25.14, 25.14, 26.10, 26.93 (4 $CH_{3\ isopropylidene}$), 27.25, 27.56 (2 $CH_{2\ dithiane}$), 54.65 ($C_{q\ dithiane}$), 62.76 ($CH_{2\ ester}$), 67.60

($CH_{2\ carbo}$), 70.63, 72.50, 74.17, 75.71, 77.30 (5 $CH_{\ carbo}$), 109.20, 109.36 (2 $C_{q\ isopropylidene}$), 169.94 ($C_{q\ ester}$); *m/z* $[M+H]^+$: 453.1612; $[C_{19}H_{32}O_8S_2+H]^+$ requires 453.1611.

Ethyl 4,5:7,8-di-O-isopropylidene-α-D-glycero-D-galacto-2-octulopyranosanate (145)[2]



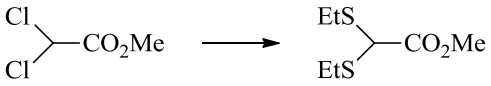
143 **145**

A solution of **143** (150 mg, 330 μmol) in 95% acetone (5 mL) was treated with NBS (210 mg, 1.18 mmol) dissolved in 95% acetone (10 mL) and the mixture stirred vigorously for 3 min at 0 °C. Saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ were added to the reaction mixture, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The crude residue was purified by column chromatography (toluene:acetone) (5:1) to give **145** (48 mg, 40%). Compound **145** was further purified by recrystallization from hot ethanol to give a crystal for X-ray crystal structure determination.

Rf 0.29 (1:1) (toluene:EtOAc); M.p. 123-124 °C; IR ν_{max} (film)/cm^{-1}: 3443, 2987, 2933, 2360, 2339, 1775, 1741, 1711, 1431, 1373; δ_H (600 MHz, DMSO-*d6*): 1.19 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.26 (s, 6H, $CH_{3\ isopropylidene}$), 1.32 (s, 3H, $CH_{3\ isopropylidene}$), 1.40 (s, 3H, $CH_{3\ isopropylidene}$), 3.75 (td, 1H, J = 7.7, 1.5 Hz, 7-H), 3.83 (dd, 1H, J = 8.5, 5.0 Hz, 7-H), 3.93 (dd, 1H, J = 8.4, 2.5 Hz, 5-H), 3.96 (dd, 1H, J = 8.4, 6.4 Hz, $CH_{\ carbo}$), 4.05 (dd, 1H, J = 7.5, 5.6 Hz, $CH_{\ carbo}$), 4.09-4.16 (m, 2H, $CH_{2\ ester}$), 4.16-4.22 (m, 2H, $CH_{\ carbo}$), 5.23 (d, 1H, J = 7.8 Hz, OH), 6.91 (d, 1H, J = 1.6 Hz, OH); δ_C (75 MHz, $CDCl_3$): 14.01 ($CH_{3\ ester}$), 25.54, 26.43, 26.94, 28.27 (4 $CH_{3\ isopropylidene}$), 63.43 ($CH_{2\ ester}$), 66.91 ($CH_{2\ carbo}$), 66.99 ($CH_{\ carbo}$), 71.01 ($CH_{\ carbo}$), 73.01 ($CH_{\ carbo}$), 74.13 ($CH_{\ carbo}$), 77.41 ($CH_{\ carbo}$), 95.25 (C_q C-1), 109.59, 109.99

(2 $C_{q\ isopropylidene}$), 169.47 ($C_{q\ ester}$); *m/z* $[M+NH_4]^+$: 380.1920; $[C_{16}H_{26}O_9+NH_4]^+$ requires 380.1915

Methyl bis(ethylthio)acetate (152)[3]

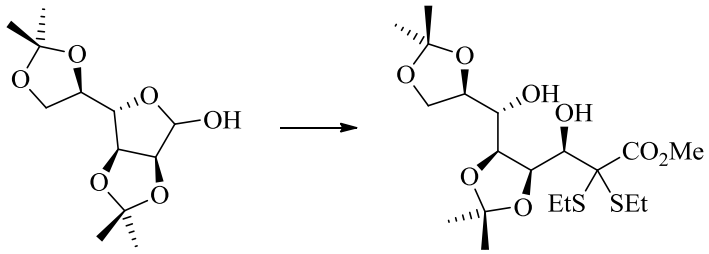


152

Sodium metal (0.322 g, 14 mmol) was placed in a 3-neck flask with a condenser under nitrogen atmosphere. The flask was cooled to 0 °C and methanol (20 mL) was added slowly. After all the sodium had reacted, ethanethiol (2.48 g, 14 mmol) was added dropwise to the solution. Methyl dichloroacetate (2.86 g, 7 mmol) was added dropwise and the solution was stirred for 48 h at rt. The mixture was treated with water (10 mL) then diethyl ether (50 mL). The ethereal layer was washed with water then brine and dried over $MgSO_4$. The liquid was evaporated to dryness to give a yellow oil. The oil was distilled to give the pure compound **152** as a clear and colourless oil (1.11g 76%)

bp 125-127 °C (5 Torr); δ_H (400 MHz, $CDCl_3$): 1.27 9t, 6H, J = 7.4 Hz, $2CH_3$), 2.72 (q, 4H, J = 7.4 Hz, $2CH_2$), 3.78 (s, 3H, $CH_{3\ ester}$), 4.38 (s, 1H, CH).

Methyl 2-deoxy4,5:7,8-di-O-isopropylidene-D-glycero-D-galacto-octulosonate diethylthioacetal (150)[2]

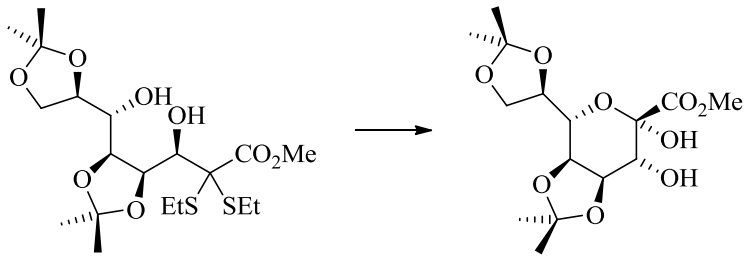


116 **150**

A solution of DIPA (17.8 mL, 127 mmol) in dry THF (127 mL) was treated with *n*BuLi, 2.5 M in hexanes (50.6 mL, 127 mmol) at −20 °C. After 15 min compound **152** (22.3 g, 115 mmol) was added slowly. The dark red solution was stirred at −20 °C for 2 h and then cannulated to a solution of $MgBr_2$ in THF (127 mL) at −20 °C prepared from magnesium (4.2 g , 165 mmol) and 1,2-dibromoethane (13.2 mL, 152 mmol). Compound **116** (10 g, 38 mmol) was added without solvent, the reaction mixture was warmed to rt and stirred for 3 h. the reaction was then heated to 50 °C and stirred for a further 3 h. The solution was poured into ice-cold saturated aqueous NH_4Cl (400 mL) and extracted with EtOAc 3 times. The organic layer was washed with water then brine, and dried over $MgSO_4$. The mixture was evaporated to dryness *in vacuo* and purified by column chromatography (toluene:EtOAc, 6:1) to give **150** as a yellow glassy residue (7.82 g, 45%)

Rf 0.54 (toluene:EtOAc, 1:1); δ_H (300 MHz, $CDCl_3$): 1.24 (td, 6H, J = 7.5, 5.0 Hz, CH_3 $_{mercaptal}$), 1.36 (s, 6H, CH_3 $_{isopropylidene}$), 1.41 (s, 3H, CH_3 $_{isopropylidene}$), 1.50 (s, 3H, CH_3 $_{isopropylidene}$), 2.55-2.79 (m, 4H, CH_2 $_{mercaptal}$), 3.61 (d, 1H, J = 6.9 Hz, CH $_{carbo}$), 3.79 (s, CH_3 $_{ester}$), 4.00-4.17 (m, 4H, CH $_{carbo}$), 4.43 (d, 1H, J = 7.6 Hz, 4-H), 4.77 (d, 1H, J = 7.6 Hz, 3-H); *m/z* $[M+H]^+$: 455.1768; $[C_{19}H_{34}O_8S_2+H]^+$ requires 455.1768.

Methyl 4,5:7,8-di-O-isopropylidene-α-D-glycero-D-galacto-2-octulopyranosonate (151)[2]

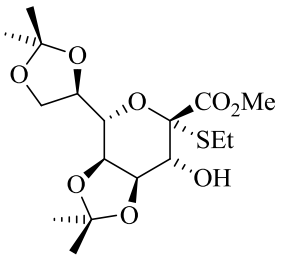


150 **151**

A solution of **150** (1 g, 2.1 mmol) in 95% acetone (45 mL) was treated with NIS (1.2 g, 5.34 mmol) at 0 °C and stirred for 30 min. Et_3N (2.2 ml) was added to the solution followed by saturated aqueous $Na_2S_2O_3$. The solution was extracted with EtOAc 3x50 mL and the organic layers combined and dried over $MgSO_4$. The crude product was purified by column chromatography (toluene:acetone, 5:1) to give the product **151** as a colourless solid (175 mg, 24%).

Rf 0.21 (toluene:EtOAc, 1:1); δ_H (400 MHz, $CDCl_3$): 1.33, 1.36, 1.38, 1.52 (4s, 12H, $CH_{3\ isopropylidene}$), 2.89 (s, 1H, OH), 3.83 (s, 3H, $CH_{3\ ester}$), 3.92-4.04 (m, 3H, CH_{carbo}), 4.14 (ddd, 2H, J = 10.2, 7.8, 1.9 Hz, H-7), 4.28 (dd, 1H, J = 5.3, 2.3 Hz, H-5), 4.34 (ddd, 1H, J = 8.4, 6.1, 3.1 Hz H-4), 4.68 (s, 1H, H-2).

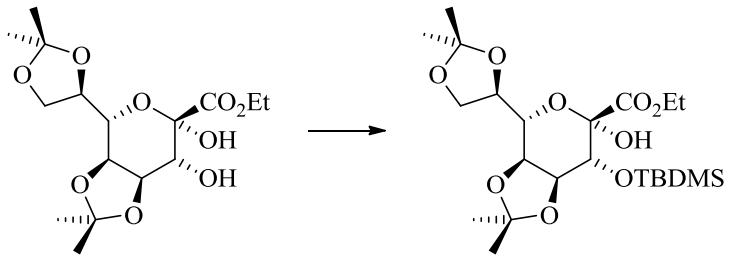
Side product from previous reaction (153)



153

IR ν_{max} (film)/cm^{-1}: 3436, 2985, 2934, 1726, 1436, 1373, 1261, 1215, 1165, 1115; δ_H (600 MHz, DMSO-*d6*): 1.11 (t, 3H, J = 7.5 Hz, $CH_{3\ mercaptal}$), 1.23, 1.26, 1.27, 1.32 (4s, 12H, $CH_{3\ isopropylidene}$) 2.35-2.48 (m, 2H, $CH_{2\ mercaptal}$) 3.65 (s, 3H, $CH_{3\ ester}$), 3.75 (dd, 1H, J = 8.3, 4.9 Hz, H-7), 3.91 (d, 1H, J = 7.9 Hz, 5-H), 4.01 (dd, 1H, J = 11.9, 5.4 Hz, 7-H), 4.10 (dd, 1H, J = 12.9, 6.3 Hz, 6-H), 4.27 (dd, 1H J = 7.6, 1.2 Hz, 4-H), 4.39 (dd, 1H, J = 7.5, 3.7 Hz, 3-H), 4.47 (dd, 1H, J = 6.7, 3.7 Hz, 2-H), 6.31 (d, 1H, J = 6.7 Hz, OH); δ_C (75 MHz, $CDCl_3$): 14.22 ($CH_{3\ mercaptal}$), 21.39 ($CH_{2\ mercaptal}$), 25.60, 25.97, 26.85, 27.30 ($4CH_{3\ isopropylidene}$), 52.95 ($CH_{3\ ester}$), 66.70 (CH, 2-C), 70.40, 71.50, 72.56, 74.32, 75.42, ($5CH_{carbo}$), 87.85 (C_q, 1-C), 109.59, 110.23 ($2C_{q\ isopropylidene}$), 170.69 ($C_{q\ ester}$); *m/z* $[M+NH_4]^+$: 410.1845; $[C_{17}H_{28}O_8S+NH_4]^+$ requires 410.1843.

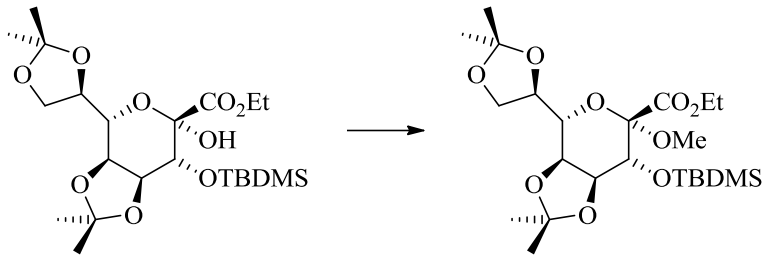
(3aS,4S,6R,7R,7aS)-ethyl 7-((tert-butyldimethylsilyl)oxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-hydroxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (154)



To a solution of **145** (150 mg, 414μm) in DMF (2 mL) imidazole (37.5 mg, 551μm) and TBDMSCl (124 mg, 822 μm) were added and left to stir at rt under a nitrogen atmosphere for 24 h. The solution was then diluted with $CHCl_3$ and washed with water then brine. The organic layer was dried over $MgSO_4$ and concentrated to dryness *in vacuo*. Purification by column chromatography gave **154** as a colourless oil (64 mg, 32.4%).

δ_H (400 MHz, $CDCl_3$): 0.05, 0.16 (2s, 6H, $Si(CH_3)_2$), 0.84 (s, 9H, $SiC(CH_3)_3$), 1.33 (t, 3H, J = 7.17 Hz, $CH_{3\ ester}$), 1.36, 1.37, 1.40 (3s, 12H, $CH_{3\ isopropylidene}$), 3.9-4.4 (m, 9H, $CH_{\ carbo}$, $CH_{2\ ester}$); *m/z* $[M+NH_4]^+$: 494.2772; $[C_{22}H_{40}O_9Si+NH_4]^+$ requires 494.2780.

(3aS,4S,6R,7R,7aS)-ethyl 7-((tert-butyldimethylsilyl)oxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-methoxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (155)

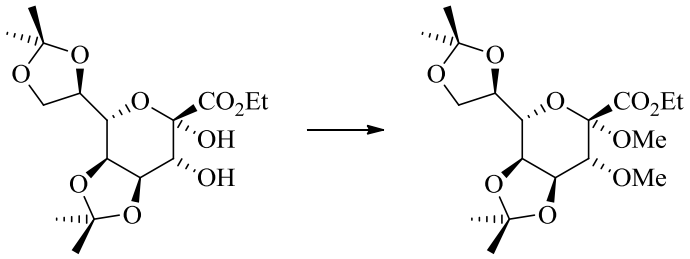


154 **155**

NaH (5.23 mg, 209 μmol) was added to a solution of **154** (100 mg, 209 μmol) in DMF (2 mL), followed by MeI (19 μL, 0.314 mmol) and stirred at rt for 2 h. The solution was diluted with $CHCl_3$ and washed with water then brine and dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude mixture was purified by column chromatography (petrol:EtOAc, 4:1) to give the pure compound **155** as a colourless oil (90 mg, 88%).

δ_H (300 MHz, $CDCl_3$): 0.06 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 1.29 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.32, 1.36, 1.39, 1.43 (4s, 12H, $CH_{3\ isopropylidene}$), 3.31-4.42 (m, 9H, $CH_{\ carbo}$, $CH_{2\ ester}$); δ_C (100 MHz, $CDCl_3$): -4.98, -4.74 (2C, $Si(CH_3)_2$), 14.26 ($CH_{3\ ester}$), 18.34 (C_q, $SiC(CH_3)_3$), 25.64, 25.73, 25.88, 26.43, 27.02, (7C, $4CH_{3\ isoproylidene}$, $SiC(CH_3)_3$), 50.48 (OCH_3), 61.59 ($CH_{2\ ester}$), 67.09, 70.40, 70.88, 72.82, 74.27, 75.48 (6C, 2C-7C $_{carbo}$), 98.17 (C_{q} 1-C), 109.26, 110.36 ($2C_{q\ isopropylidene}$), 167.19 ($C_{q\ ester}$); *m/z* $[M+NH_4]^+$: 508.2926; $[C_{23}H_{42}O_9SI+NH_4]^+$ requires 508.2936.

(3aS,4S,6R,7R,7aS)-ethyl 4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6,7-dimethoxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (238)

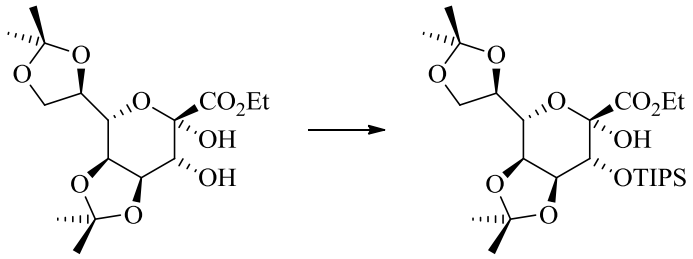


145 **238**

NaH (52.3 mg, 2.09 mmol) was added to a solution of **145** (0.5 g, 1.05 mmol) in DMF (10 mL), MeI was added (188 µL, 3.14 mmol) and the solution was left to stir for 2 h at rt. The mixture was diluted with $CHCl_3$ and washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude mixture was purified using column chromatography (petrol:EtOAc, 3:1) to give the pure compound **238** as a colourless solid (307 mg, 75%).

δ_H (400 MHz, DMSO-*d6*): 1.22 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.27, 1.28, 1.33, 1.41 (4s, 12H, $CH_{3\ isopropylidene}$), 3.26, 3.37 (2s, 6H, OCH_3), 3.61 (d, 1H, 3.7 Hz, 7-H), 3.72 (dd, 1H, J = 7.4, 1.0 Hz, 7-H), 3.90 (dd, 1H, J = 8.6, 5.1 Hz, CH_{carbo}), 3.98-4.07 (m, 1H, CH_{carbo}), 4.11-4.31 (m, 5H, CH_{carbo}, $CH_{2\ ester}$); *m/z* $[M+NH_4]^+$: 408.2228; $[C_{18}H_{30}O_9+NH_4]^+$ requires 408.2228.

(3aS,4S,6R,7R,7aS)-ethyl 4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-hydroxy-2,2-dimethyl-7-((triisopropylsilyl)oxy)tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (239)

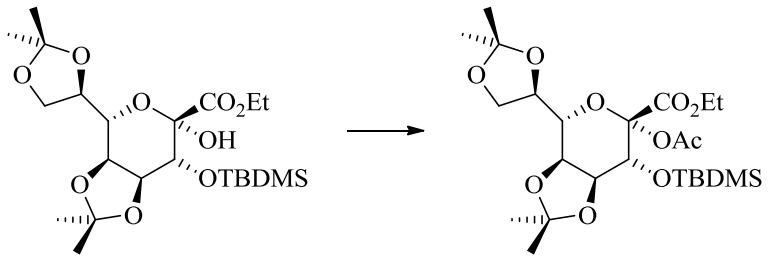


145 **239**

TIPSOTf (0.81 mL, 3 mmol) was added dropwise to a solution of **145** (0.9 g, 2.5 mmol) and 2,6-lutidene (0.35 mL, 3 mmol) in DCM (20 mL) at −78 °C and stirred for 1 h. Saturated aqueous $NaHCO_3$ was added to the solution followed by extracting with DCM. The organic layer was washed with water then brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the crude mixture was purified via column chromatography (petrol:EtOAc, 5:1) to give the pure product **239** (0.88 g, 68%).

IR ν_{max} (film)/cm^{-1}: 3463, 2943, 2868, 1748, 1464, 1371, 1247, 1219, 1148, 1073, 970, 920, 883, 815, 732; δ_H (300 MHz, $CDCl_3$): 0.96-1.12 (m, 21H, $Si(CH(CH_3)_2)_3$), 1.21 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.26, 1.28, 1.31, 1.40 (4s, 12H, $CH_{3\ isopropylidene}$), 3.84 (dd, 1H, J = 8.5, 4.9 Hz, 7-H), 3.98 (ddd, 2H, J = 9.9, 7.2, 4.4 Hz, CH_{carbo}), 4.03-4.24 (m, 5H, CH_{carbo}, $CH_{2\ ester}$), 4.27 (dd, J = 4.6, 2.5 Hz, 2-H), 6.90 (s, 1H, OH).

(3aS,4S,6S,7R,7aS)-ethyl 6-acetoxy-7-((tert-butyldimethylsilyl)oxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (240)

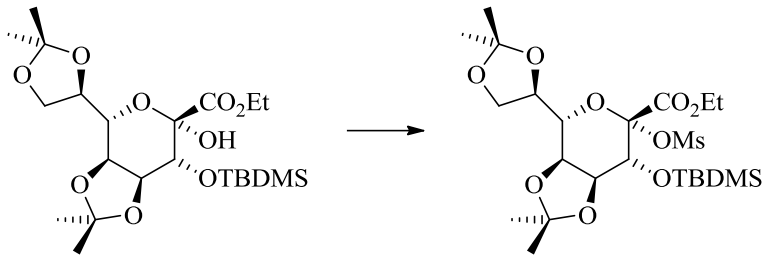


154 **240**

Ac_2O (198 µL, 2.1 mmol) was added to a solution of **154** (0.45 g, 0.94 mmol) and Et_3N (292 µL, 2.1 mmol) in DCM (25 mL) at 0 °C. DMAP was added (72 mg, 0.59 mmol) and the solution was stirred at rt overnight. Saturated $NaHCO_3$ solution was added and the mixture was extracted with DCM. The organic layer was washed with water then brine and dried over $MgSO_4$. Purification by column chromatography (petrol:EtOAc, 4:1) gave the pure compound **240** (91 mg, 18.6%).

IR ν_{max} (film)/cm^{-1}: 2932, 1756, 1473, 1371, 1308, 1249, 1216, 1142, 1077, 972, 949, 873, 829, 783; δ_H (400 MHz, $CDCl_3$): 0.14 (s, 3H, $SiCH_3$), 0.18 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.26 (t, 3H, $CH_{3\ ester}$), 1.36, 1.4, 1.54 (3s, 12H, $CH_{3\ isopropylidene}$), 2.06 (s, 3H, $CH_{3\ acetyl}$), 4.06 (d, 2H, J = 5.2 Hz, 7-H), 4.09-4.15 (m, 2H, $CH_{2\ ester}$), 4.15-4.24 (m, 1H, CH_{carbo}), 4.25-4.32 (m, 2H, CH_{carbo}), 4.39 (dt, 1H, J = 7.8, 5.2 Hz, 6-H), 5.36 (d, 1H, J = 6.3 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): -3.79, -3.50 (2C, $SiCH_3$), 13.90 ($CH_{3\ ester}$), 18.88 (C_q, $SiC(CH_3)_3$), 20.97 (CH_3, $OC(O)CH_3$), 25.59, 25.95, 26.30, 27.01, 27.23 ($7CH_3$, $SiC(CH_3)_3$, $CH_{3\ isopropylidene}$), 62.19 ($CH_{2\ ester}$), 66.68, 69.79, 71.43, 72.86, 74.34, 74.70 ($2\text{-}7C_{carbo}$), 95.63 (C_q, 1-C), 109.50, 110.26 ($2C_{q\ isopropylidene}$), 167.64, 169.74 ($2C_{q,}$ $C{=}O_{\ ester,\ acetate}$); *m/z* $[M+NH_4]^+$: 536.2885; $[C_{24}H_{42}O_{10}Si+NH_4]^+$ requires 536.2883.

(3aS,4S,6S,7R,7aS)-ethyl 7-((tert-butyldimethylsilyl)oxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-((methylsulfonyl)oxy)tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (241)

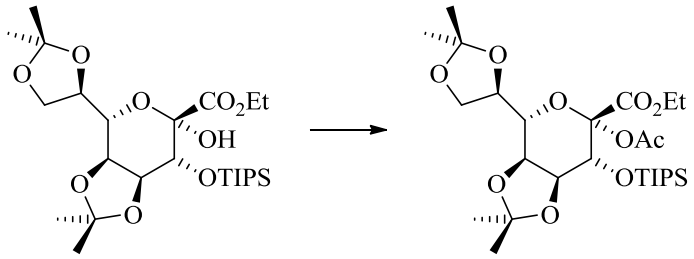


154 **241**

MsCl (71 μL, 0.92 mmol) was added to a solution of **154** (0.4 g, 0.84 mmol), Et_3N (128 μL, 0.92 mmol) and DMAP (65 mg, 0.53 mmol) in DCM (10 mL) at 0 °C. The solution was left to stir at rt for 3 h and then refluxed overnight. Saturated $NaHCO_3$ solution was added and the mixture was extracted with DCM. The organic layer was washed with water then brine and dried over $MgSO_4$. The crude mixture was purified by column chromatography (petrol:EtOAC, 9:1) to give the pure product **241** as a colourless oil (94 mg, 20%).

IR ν_{max} (film)/cm^{-1}: 2987, 2933, 2859, 1754, 1473, 1381, 1372, 1251, 1222, 1152, 1089, 1073, 1052, 1006, 950, 906, 842, 781; δ_H (300 MHz, $CDCl_3$): 0.07 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.82 (s, 9H, $SiC(CH_3)_3$), 1.33 (t, 3H, J = 7.2 Hz, $CH_{3\ ester}$), 1.35, 1.38 (2s, 12H, $CH_{3\ isopropylidene}$), 1.54 (s, 3H, $CH_{3\ mesyl}$) 4.01 (d, 1H J = 9.3 Hz, 7-H), 4.06-4.39 (m, 5H, CH_{carbo}), 4.45 (s, 2H, $CH_{2\ ester}$), 4.54 (t, 1H, J = 1.5 Hz, 2-H).

(3aS,4S,6S,7R,7aS)-ethyl 6-acetoxy-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-7-((triisopropylsilyl)oxy)tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (242)

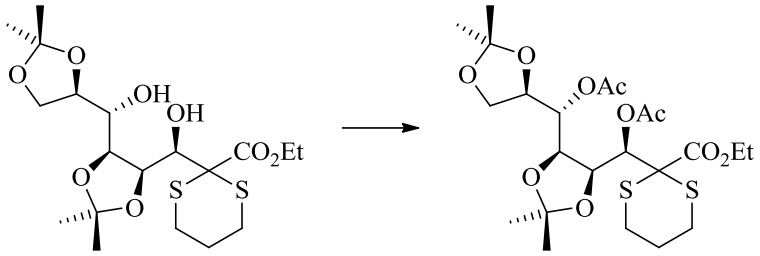


239 **242**

Ac_2O (132 µL, 1.4 mmol) was added to a solution of **239** (325 mg, 0.63 mmol), Et_3N (194 µL, 1.4 mmol) and DMAP (39 mg, 0.32 mmol) in DCM (25 mL) at 0°C. The reaction was allowed to reach rt and stirred for 4 h. Saturated $NaHCO_3$ solution was added and the mixture was extracted with DCM. The organic layer was washed with water then brine and dried over $MgSO_4$. The crude mixture was purified by column chromatography (petrol:EtOAC, 9:1) to give the pure product **242** as a colourless oil (0.234 g, 67%).

IR ν_{max} (film)/cm^{-1}: 2985, 2943, 2868, 1761, 1739, 1464, 1370, 1300, 1244, 1220, 1149, 1072, 1076, 1041, 1008, 971; δ_H (400 MHz, $CDCl_3$): 1.04-1.13 (m, 18H, $CH_{3\ TIPS}$), 1.13-1.19 (m, 3H, $Si(CH)_3$), 1.26 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.33, 1.34, 1.37, 1.50 (4s, 12H, $CH_{3\ isopropylidene}$), 2.07 (s, 3H, $CH_{3\ acetyl}$), 3.88 (dd, 1H, J = 9.0, 3.3 Hz, 7-H), 4.02-4.13 (m, 2H, CH_{carbo}), 4.12-4.28 (m, 2H, $CH_{2\ ester}$), 4.36 (ddd, 1H, J = 9.1, 6.0, 3.3 Hz, 6-H), 4.39-4.51 (m, 2H, 3-H, 4-H), 4.58 (d, 1H, J= 3.7 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): 12.44 ($CH_{3\ ester}$), 13.78 ($3C_{q,}$ $Si(C(CH_3)_2)_3$), 17.95, 17.98 ($6CH_{3\ TIPS}$), 21.11 ($CH_{3\ acetate}$), 24.92, 25.41, 25.46, 27.08 ($4CH_{3\ isopropylidene}$), 62.20 ($CH_{2\ ester}$), 67.28 ($CH_{2,}$ 7-C), 69.83, 71.75, 72.04, 73.46 (4CH, 3C-6C), 74.57 (CH, 2-C), 96.81 ($C_{q,}$ 1-C), 109.60, 111.15 ($2C_{q\ isopropylidene}$), 167.99, 169.03 ($2C_q$, 2C=O).

Ethyl 2-((R)-acetoxy((4S,5R)-5-((S)-acetoxy((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1,3-dithiane-2-carboxylate (158)

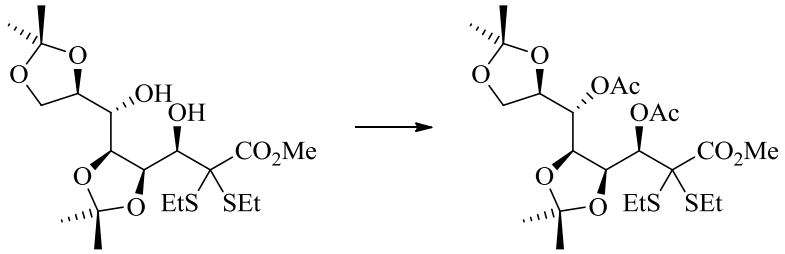


143 **158**

Ac_2O (4.6 mL, 48.4 mmol), Et_3N (6.7 mL, 48.4 mmol) and DMAP (0.92 g, 7.5 mmol) were added to a solution of **143** (5 g, 11 mmol) in DCM (100 mL) at 0 °C and stirred for 3 h at rt. The solution was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was washed with water then brine and dried over $MgSO_4$. The solution was evaporated to dryness and purified by column chromatography (petrol:EtOAc, 5:1) to give the pure compound **158** as a yellow solid (5.8 g, 98%). The compound was further purified by recrystallization from hot ethanol to give a crystal for X-ray crystal structure determination.

IR ν_{max} (film)/cm^{-1}: 2986, 2938, 2901, 1746, 1427, 1371, 1217, 1160, 1067, 1038, 982, 884, 845, 735, 702; δ_H (400 MHz, $CDCl_3$): 1.31 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.33, 1.37, 1.45, 1.47 (4s, $CH_{3\ isopropylidene}$), 1.86-2.07 (m, 2H, $CH_{2\ dithiane}$), 2.10, 2.11 (2s, 6H, $CH_{3\ acetyl}$), 2.80-2.93(m, 3H, $CH_{2\ dithiane}$), 3.16 (ddd, 1H, J = 13.3, 9.7, 3.4 Hz, $CH_{2\ dithiane}$), 3.85 (dd, 1H, J = 8.5, 7.4 Hz, 7-H), 4.05 (dd, 1H, J = 8.5, 6.1 Hz, 7-H), 4.15 (td, 1H, J = 7.2, 6.1 Hz, 6-H), 4.21 (q, 2H, J = 7.1 Hz, $CH_{2\ ester}$), 4.44 (dd, 1H, J = 6.1, 5.4 Hz, CH_{carbo}), 4.91 (dd, 1H, J = 6.1, 5.4 Hz, CH_{carbo}), 5.39 (dd, 1H, J = 7.0, 5.3 Hz, 5-H), 5.71 (d, 1H, J = 5.3 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): 13.84 ($CH_{3\ ester}$), 20.85, 21.16 ($2CH_{3\ acetate}$), 24.03, 25.72, 25.81 ($3CH_{2\ dithiane}$), 25.91, 26.30, 27.18, 27.57 ($4CH_{3\ isopropylidene}$), 58.12 (C_q, 1-C), 62.68 ($CH_{2\ ester}$), 70.29, (CH_2, 7-C), 71.73, 74.71, 75.95, 77.69 ($4CH_{carbo}$), 108.76, 110.09 ($2C_{q\ isopropylidene}$), 169.10, 169.61, 170.19 ($3C_q$, C=O); *m/z* $[M+NH_4]^+$: 554.2077; $[C_{23}H_{36}O_{10}S_2+NH_4]^+$ requires 554.2088.

(R)-methyl 3-acetoxy-3-((4S,5R)-5-((S)-acetoxy((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-bis(ethylthio)propanoate (160)

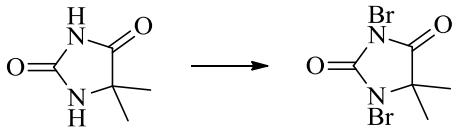


150 **160**

Ac_2O (0.92 mL, 9.68 mmol), Et_3N (1.35 mL, 9.68 mmol) and DMAP (183.5 mg, 1.5 mmol) were added to a solution of **150** (1 g, 2.2 mmol) in DCM (20 mL) at 0 °C and stirred for 3 h at rt. The solution was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was washed with water then brine and dried over $MgSO_4$. The solution was evaporated to dryness and purified by column chromatography (petrol:EtOAc, 5:1) to give the pure compound **160** as a yellow solid (1.05 g, 88%).

IR ν_{max} (film)/cm^{-1}: 2985, 2935, 2874, 1747, 1456, 1434, 1371, 1217, 1159, 1111, 1066, 1041, 980, 917, 847; δ_H (400 MHz, $CDCl_3$): 1.16 (t, 3H, J = 7.5 Hz, SEt), 1.21 (t, 3H, J = 7.5 Hz, SEt), 1.31, 1.34, 1.41, 1.44 (4s, 12H, $CH_{3\ isopropylidene}$), 2.08, 2.09 (2s, 6H, $CH_{3\ acetyl}$), 2.57, 2.80 (m, 4H, SEt), 3.75 (s, 3H, $CH_{3\ ester}$), 3.83 (dd, 1H, J = 8.5, 7.2 Hz, 7-H), 4.01 (dd, 1H, J = 8.5, 6.0 Hz, 7-H), 4.12 (dt, 1H, J = 13.1, 6.6 Hz, 6-H), 4.41 (dd, 1H, J = 6.0, 4.6 Hz, 4-H), 4.91 (t, 1H, J = 6.0 Hz, 3-H), 5.31 (dd, 1H, J = 6.9, 4.6 Hz, 5-H), 5.44 (d, 1H, J = 6.0 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): 12.85, 13.35 ($2CH_{3\ mercaptal}$), 20.82, 21.15 ($2CH_{3\ acetate}$), 24.73, 25.41 ($2CH_{3\ isopropylidene}$), 25.66, 25.72 ($2CH_{2\ mercaptal}$), 25.81, 26.37 ($2CH_{3\ isopropylidene}$), 53.25 ($CH_{3\ ester}$), 66.86, (CH_2, 7-C), 68.59 (C_q, $C(SEt)_2$), 70.18, 72.15, 74.98, 75.86, 77.18 ($5CH_{carbo}$), 108.49, 109.79 ($2C_{q\ isopropylidene}$), 169.21, 169.53, 170.25 ($3C_q$, C=O); *m/z* $[M+NH_4]^+$: 556.2235; $[C_{23}H_{38}O_{10}S_2+NH_4]^+$ requires 556.2245.

1,3-dibromo-5,5-dimethylhydantoin (160)[4]

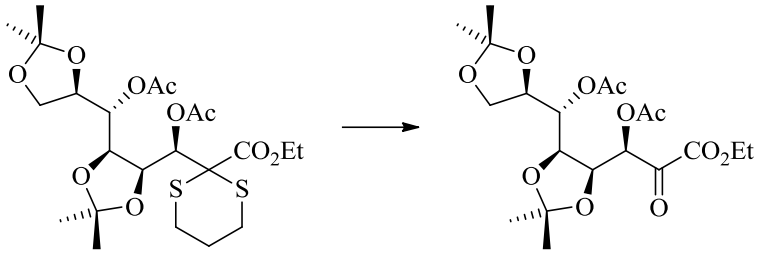


5,5-dimethylhydantoin **160**

5,5-dimethylhydantoin (5 g, 39 mmol) was dissolved in a 5% solution of NaOH at room temperature. Neat bromine (4 mL, 78 mmol) was added to the solution dropwise and left to stir for 1 h. After formation of a colourless precipitate, the solution was filtered and the solid was washed with ice-cold water until the filtrate ran clear. The solid was then dried in a vacuum oven at 50 °C to give the pure compound **160** (8.8 g, 72%).

IR ν_{max} (film)/cm^{-1}: 1777, 1725, 1456, 1383, 1336, 1202, 1118, 854, 734; δ_H (300 MHz, $CDCl_3$): 1.38 (s, 6H, $2CH_3$); δ_C (75 MHz, $CDCl_3$): 23.8 ($2CH_3$), 68.9 (C_q 5-C), quaternary carbonyls not observed.

(R)-ethyl 3-acetoxy-3-((4S,5R)-5-((S)-acetoxy((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxopropanoate (159)

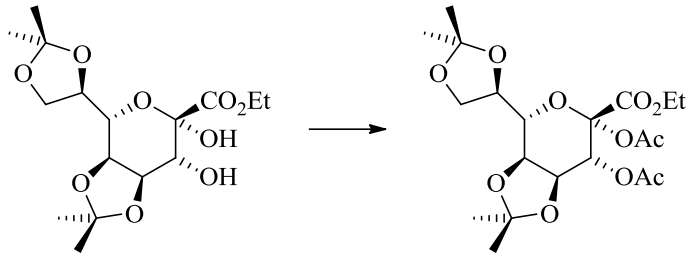


158 **159**

A solution of **158** (1 g, 1.9 mmol) in 95% acetone (50 mL) was treated with compound **160** (1.2 g, 4.1 mmol) dissolved in 95% acetone (20 mL) and stirred vigorously for 45 min at room temperature. Saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ were added to the reaction mixture, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The crude residue was purified by column chromatography (petrol:EtOAc, 5:1) to give **159** as a yellow oil (0.7 g, 84%). Compound **159** was further purified be recrystallization from hot ethanol to give a pale yellow solid.

IR ν_{max} (film)/cm^{-1}: 2987, 2940, 1747, 1457, 1372, 1218, 1160, 1077, 1038, 984, 941, 890, 849, 734; δ_H (400 MHz, $CDCl_3$): 1.30 (s, 3H, $CH_{3\ isopropylidene}$), 1.37 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.38 (s, 3H, $CH_{3\ isopropylidene}$), 1.45, 1.46 (2s, 6H, $CH_{3\ isopropylidene}$), 2.09, 2.23 (2s, 6H, $CH_{3\ acetyl}$) 3.68-3.76 (m, 1H, 7-H), 4.04-4.14 (m, 2H, 6-H, 7-H) 4.29-4.37 (m, 2H, $CH_{2\ ester}$), 4.40 (dd, 1H, J = 8.3, 6.1 Hz, 4-H), 4.88 (dd, 1H, J = 6.1, 3.1 Hz, 3-H), 5.09-5.17 (m, 1H, 5-H), 6.1 (d, 1H, J = 3.1 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): 14.0 ($CH_{3\ ester}$), 20.6, 20.9 ($2CH_{3\ acetyl}$), 25.5, 25.7, 26.1 ($4CH_{3\ isopropylidene}$), 62.8 ($CH_{2\ ester}$), 67.7 (CH_2, 7-C), 70.7 (CH, 5-C), 74.8 (CH, 3-C), 75.4 (CH, 6-C), 76.6 (CH, 2-C), 77.9 (CH, 4-C), 110.1, 110.9 ($2C_{q\ isopropylidene}$), 160.0, 169.9, 170.2, 187.3 ($4C_q$, C=O).

(3aS,4S,6S,7R,7aS)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(ethoxycarbonyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6,7-diyl diacetate (163)

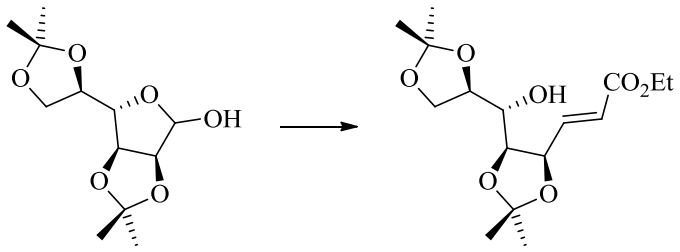


145 **163**

Ac_2O (0.29 mL, 3.0 mmol), Et_3N (0.42 mL, 3.0 mmol) and DMAP (0.24 g, 2.0 mmol) were added to a solution of **145** (250 mg, 0.69 mmol) in DCM (25 mL) at 0 °C and stirred for 3 h at rt. The solution was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was washed with water then brine and dried over $MgSO_4$. The solution was evaporated to dryness and purified by column chromatography (petrol:EtOAc, 5:1) to give a colourless solid **163** (0.27 g, 88%).

IR ν_{max} (film)/cm^{-1}: 2988, 1754, 1373, 1218, 1168, 1068, 969, 929, 874; δ_H (500 MHz, $CDCl_3$): 1.25 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.36, 1.38, 1.42, 1.53 (4s, 12H, $CH_{3\ isopropylidene}$), 2.11, 2.15 (2s, 6H, $CH_{3\ acetyl}$), 3.71 (dd, 1H, J = 8.2, 1.9 Hz, 5-H), 3.97 (dd, 1H, J = 9.1, 4.1 Hz, 7-H), 4.10 (dd, 1H, J = 9.1, 6.2 Hz, 7-H), 4.18 (qd, 2H, J = 7.1, 2.2 Hz, $CH_{2\ ester}$), 4.35-4.40 (m, 2H, 4-H, 3-H), 4.44 (ddd, 1H, J = 8.2, 6.2, 4.1 Hz, 6-H), 5.23 (d, 1H, J = 6.9 Hz, 2-H); δ_C (100 MHz, $CDCl_3$): 14.0 ($CH_{3\ ester}$), 20.9 ($2CH_{3\ acetyl}$), 25.4, 26.3, 27.1, 27.5 ($4CH_{3\ isoproylidene}$), 62.8 ($CH_{2\ ester}$), 67.1 (CH_2, 7-C), 69.7 (CH, 2-C), 71.7 (CH, 5-C), 72.3 (CH, 4-C), 73.6 (CH, 6-C), 73.8 (CH, 3-C), 95.9 (C_q, 1-C), 109.7, 110.7 ($2C_{q\ isopropylidene}$), 164.9, 168.1, 169.8 ($3C_q$, C=O).

(E)-ethyl 3-((4R,5S)-5-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (175)

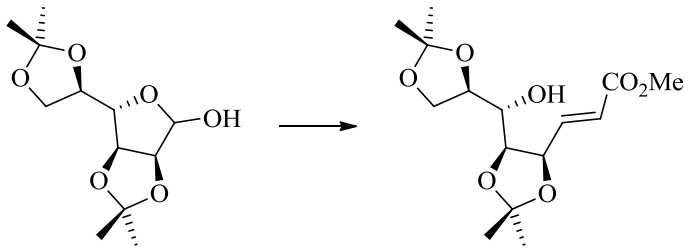


116 **175**

A solution of **116** (8.8 g 19.2 mmol) and ethyl 2-(triphenylphosphoranylidene)acetate (13 g 21.2 mmol) in toluene (250 mL) was heated under reflux for 1 h. The solvent was then removed under reduced pressure and the crude residue was triturated with cold diethyl ether to precipitate the triphenylphosphine oxide by-product. The solid was filtered off and the solution evaporated to dryness. The crude mixture was purified by column chromatography (petrol:Et_2O, 1:1) to give the pure compound **175** as a colourless oil (7.04 g, 63%).

IR ν_{max} (film)/cm^{-1}: 3497, 2986, 2937, 1719, 1660, 1459, 1372, 1303, 1256, 1213, 1162, 1069, 983, 850; δ_H (400 MHz, $CDCl_3$): 1.29 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.35, 1.40, 1.42, 1.55 (4s, 12H, $CH_{3\ isopropylidene}$), 3.44 (dd, 1H, J = 8.0, 2.1 Hz, 5-H), 3.96-4.03 (m, 2H, 6-H, 7-H), 4.07-4.14 (m, 1H, 7-H), 4.21 (q, 2H, J = 7.1 Hz, $CH_{2\ ester}$), 4.46 (dd, 1H, J = 7.5, 2.1 Hz, 4-H), 4.83 (dd, 1H, J = 7.6, 6.2 Hz, 3-H), 6.09 (dd, 1H, J = 15.7, 1.5 Hz, 1-H), 7.06 (dd, 1H, J = 15.7, 6.2 Hz, 2-H); δ_C (100 MHz, $CDCl_3$): 14.4 ($CH_{3\ ester}$), 24.7, 25.2, 26.7, 26.7 ($4CH_{3\ isopropylidene}$), 60.6 ($CH_{2\ ester}$), 67.2 (CH_2, 7-C), 70.5 (CH, 5-C), 76.2 (CH, 6-C) 76.6 (CH, 3-C), 77.4 (CH, 4-C), 109.4, 109.5 ($2C_{q\ isopropylidene}$), 123.7 (CH_{alkene}, 1-C), 143.7(CH_{alkene}, 2-C), 165.8 (C_q C=O); *m/z* $[M+NH_4]^+$: 348.2013; $[C_{16}H_{26}O_7+NH_4]^+$ requires 348.2017.

(E)-methyl 3-((4R,5S)-5-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (243)

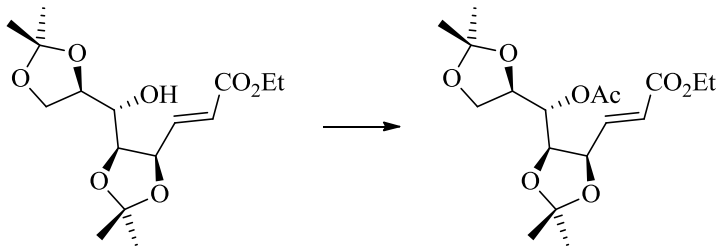


116 **244**

A solution of **116** (1 g 3.8 mmol) and methyl 2-(triphenylphosphoranylidene)acetate (1.6 g 4.8 mmol) in toluene (50 mL) was heated under reflux for 1 h. The solvent was then removed under reduced pressure and the crude residue was triturated with cold diethyl ether to precipitate the triphenylphosphine oxide by-product. The solid was filtered off and the solution evaporated to dryness. The crude mixture was purified by column chromatography (petrol:Et_2O, 1:1) to give the pure compound as a colourless oil (0.8 g, 66%).

IR ν_{max} (film)/cm^{-1}: 3505, 2988, 2938, 1726, 1438, 1372, 1307, 1258, 1213, 1163, 1118, 1069, 888, 851; δ_H (300 MHz, $CDCl_3$): 1.34, 1.40, 1.41, 1.54 (4s, 12H, $CH_{3\ isopropylidene}$), 3.42 (td, 1H, J = 7.8, 2.1 Hz, CH_{carbo}), 3.75 (s, 3H, $CH_{3\ ester}$), 3.38-3.47 (m, 2H, CH_{carbo}), 4.03-4.15 (m, 1H, CH_{carbo}), 4.47 (dd, 1H, J = 7.5, 2.0 Hz, CH_{carbo}), 4.82 (ddd, 1H, J = 7.7, 6.2, 1.5 Hz, 3-H), 6.10 (dd, 1H, J = 15.7, 1.5 Hz, 1-H_{alkene}), 7.07 (dd, 1H, J = 15.7, 6.2 Hz, 2-H_{alkene}); δ_C (75 MHz, $CDCl_3$): 25.1, 25.5, 26.7, 27.0 ($4CH_{3\ isopropylidene}$), 51.7 ($CH_{3\ ester}$), 67.4, 70.5, 70.8, 77.4, 81.2 ($5C_{carbo}$), 109.6, 109.7 ($2C_{q\ isopropylidene}$), 123.3 (CH_{alkene}, 1-C), 144.1 (CH_{alkene}, 2-C) 166.5 (C_q C=O).

(E)-ethyl 3-((4R,5R)-5-((S)-acetoxy((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (171)

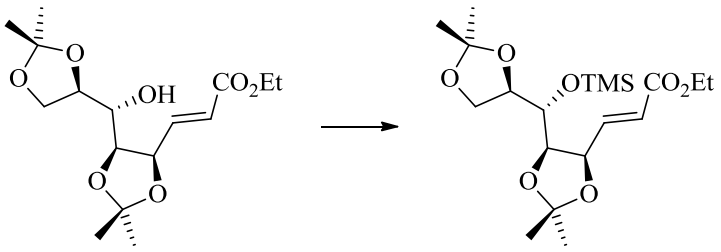


175 **171**

Ac_2O (252 μL, 2.67 mmol) and pyridine (216 μL, 2.67 mmol) were added to a solution of **175** (0.8 g, 2.43 mmol) in DCM and left to stir for 48 h at rt. Saturated aqueous $NaHCO_3$ solution was added to the mixture, the solution was extracted with DCM, washed with $CuSO_4$ solution, water and brine and dried over $MgSO_4$. The solent was removed *in vacuo* and the crude mixture was purified by column chromatography (petrol:EtOAc, 5:1) to give the pure compound **171** (0.66 g, 75%)

δ_H (400 MHz, $CDCl_3$): 1.29 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.35, 1.38, 1.40, 1.56 (4s, 12H, $CH_{3\ isopropylidene}$), 2.02 (s, 3H, $CH_{3\ acetyl}$), 3.86 (dd, 1H, J = 8.7, 6.5 Hz, 7-H), 3.98 (dd, 1H, J = 8.7, 6.1 Hz, 7-H), 4.15-4.23 (m, 3H, $CH_{2\ ester}$, 6-H), 4.52 (dd, 1H, J = 7.2, 2.1 Hz, 4-H), 4.83 (ddd, 1H, 7.1, 5.3, 1.8 Hz, 3-H), 4.97 (dd, 1H, J = 6.9, 2.1 Hz, 5-H), 6.05 (dd, 1H, J = 15.7, 1.8 Hz, 1-H), 6.82 (dd, 1H, 15.6, 5.3 Hz, 2-H); δ_C (100 MHz, $CDCl_3$): 14.7 ($CH_{3\ ester}$), 21.2 ($CH_{3\ acetyl}$), 25.2, 25.6, 26.8, 27.1 ($4CH_{3\ isopropylidene}$), 61.1 ($CH_{2\ ester}$), 66.7, 72.0, 74.9, 75.8, 78.7 ($5C_{carbo}$), 110.3, 110.5 ($C_{q\ isopropylidene}$), 123.9 (CH_{alkene}, 1-C), 143.2 (CH_{alkene}, 2-C), 167.8, 171.3 ($2C_q$ C=O).

(E)-ethyl 3-((4R,5R)-5-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((trimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (244)

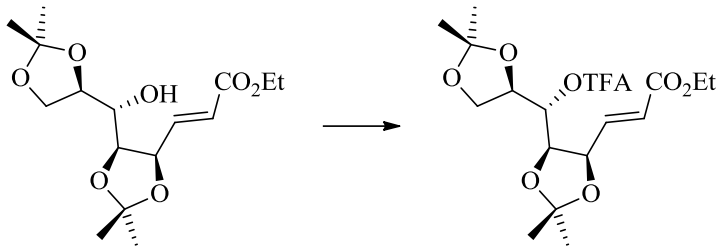


175 **244**

Alkene **175** (0.5 g, 1.52 mmol) was added to a solution of TMSCl (203 μL, 1.67 mmol) and Et_3N (232 μL, 1.67 mmol) in DCM (2 mL) and stirred at rt overnight. Saturated aqueous $NaHCO_3$ was added to the solution and the mixture was extracted with DCM. The organic layer was washed with water then brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude mixture was purified by column chromatography (petrol:EtOAc, 3:1) to give the pure compound **244** (0.23 g, 38%).

IR ν_{max} (film)/cm^{-1}: 2985, 1721, 1658, 1457, 1370, 1301, 1249, 1216, 1154, 1110, 1076, 1035, 983, 876, 839; δ_H (400 MHz, $CDCl_3$): 0.12 (s, 9H, $Si(CH_3)_3$), 1.28 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.33, 1.37, 1.42, 1.53 (4s, 12H, $CH_{3\ isopropylidene}$), 3.71 (t, 1H, J = 7.2 Hz, 7-H), 3.80 (t, 1H, J = 7.6 Hz, 7-H), 3.99 (dd, 1H, J = 6.7, 6.4 Hz, 5-H), 4.09 (dd, 1H, J = 8.1, 6.4, 6-H), 4.15 (dd, 1H, J = 7.5, 6.2 Hz 4-H), 4.20 (q, 2H, J = 7.1 Hz, $CH_{2\ ester}$), 4.72 (dd, 1H, J = 8.2, 3.7 Hz, 3-H), 6.06 (dd, 1H, J = 15.7, 1.5 Hz, 1-H), 7.07 (dd, 15.7, 5.8 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): 0.7 ($3CH_{3\ TMS}$), 14.3 ($CH_{3\ ester}$), 25.4, 25.7, 26.3, 27.6 ($4CH_{3\ isopropylidene}$), 60.6 ($CH_{2\ ester}$), 67.7, 72.5, 77.3, 80.9 ($4C_{\ carbo}$), 109.0, 110.0 ($2C_{q\ isopropylidene}$), 123.7 ($CH_{\ alkene}$, 1-C), 144.8 ($CH_{\ alkene}$, 2-C), 166.3 (C_q C=O); *m/z* $[M+NH_4]^+$: 420.2414; $[C_{19}H_{34}O_7Si+NH_4]^+$ requires 420.2412.

(E)-ethyl 3-((4R,5R)-5-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(2,2,2-trifluoroacetoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (245)

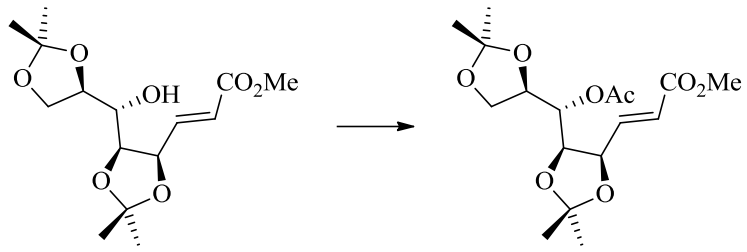


175 **245**

TFAA (1 mL, 6.8 mmol) pyridine (20 mL) and DMAP (0.18 g, 1.5 mmol) were added to a solution of **175** (1.5 g, 4.5 mmol) in DCM at 0 °C. The solution was allowed to reach rt and stirred for 4 h. Saturated $NaHCO_3$ solution was added and the mixture was extracted with DCM. The organic layers were combined, washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography (petrol:EtOAc, 5:1) to give compound **245** (0.71 g, 37%).

IR ν_{max} (film)/cm^{-1}: 2988, 2939, 1794, 1720, 1664, 1371, 1338, 1309, 1216, 1149, 1060, 1041, 986; δ_H (300 MHz, $CDCl_3$): 1.27 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.34, 1.39, 1.54 (3s, 12H, $CH_{3\ isopropylidene}$), 3.86 (dd, 1H, J = 8.9, 6.9 Hz, 7-H), 4.04 (dd, 1H, J = 8.9, 6.1 Hz), 4.10-4.30 (m, 3H, $CH_{2\ ester}$, 6-H), 4.51 (dd, 1H, J = 7.3, 1.9 Hz, 4-H), 4.92 (ddd, 1H, J = 7.4, 4.5, 2.0 Hz, 3-H), 5.17 (dd, 1H, J = 5.1, 1.9 Hz, 5-H), 6.11 (dd, 1H, J = 15.7, 1.9 Hz, 1-H), 6.81 (dd, 1H, J = 15.7, 4.5 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): 14.1 ($CH_{3\ ester}$), 25.3, 25.5, 26.1, 26.2 ($4CH_{3\ isopropylidene}$), 60.8 ($CH_{2\ ester}$), 65.5, 74.3, 75.3, 75.7, 76.2 ($5C_{\ carbo}$), 109.6, 110.6 ($2C_{q\ isopropylidene}$), 123.9 ($CH_{\ alkene}$, 1-C), 140.1 ($CH_{\ alkene}$, 2-C), 165.5 (C_q, C=O). TFA carbons not observed.

(E)-methyl 3-((4R,5R)-5-((S)-acetoxy((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (246)

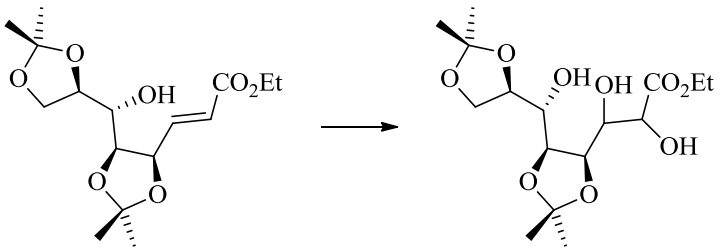


244 **246**

Ac_2O (1.5 mL, 16.1 mmol) Et_3N (3 mL, 21.9 mmol) and DMAP (0.45 g, 3.7 mmol) were added to a solution of **244** in DCM at 0 °C. The solution was allowed to reach rt and stirred for 1 h. Saturated $NaHCO_3$ solution was added and the mixture was extracted with DCM. The organic layers were combined, washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography (petrol:EtOAc, 5:1) to give **246** (2.1 g, 81%).

IR ν_{max} (film)/cm^{-1}: 2987, 2939, 1747, 1725, 1663, 1457, 1437, 1371, 1310, 1214, 1162, 1124, 1070, 1041, 983; δ_H (400 MHz, $CDCl_3$): 1.34, 1.38, 1.40, 1.56 (4s, 12H, $CH_{3\ isopropylidene}$), 2.02 (s, 3H, $CH_{3\ acetyl}$), 3.74 (3, 3H, $CH_{3\ ester}$), 3.85 (dd, 1H, J = 8.1, 6.5 Hz, 7-H), 3.98 (dd, 1H, J = 8.6, 6.2 Hz, 7-H) 4.19 (dd, 1H, J = 6.8, 6.6 Hz, 6-H), 4.52 (dd, 1H, J = 7.2, 1.5 Hz, 4-H), 4.79-4.85 (m, 1H, 3-H), 4.96 (dd, 1H, J = 7.0, 1.5 Hz, 5-H), 6.06 (dd, 1H, J = 15.7, 1.8 Hz, 1-H), 6.83 (dd, 1H, J = 15.7, 5.3 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): 18.5 ($CH_{3\ acetyl}$), 25.4, 25.6, 26.4, 26.7 ($4CH_{3\ isopropylidene}$), 52.0 ($CH_{3\ ester}$), 70.4, 70.8, 75.2, 75.9, 76.9 ($5C_{carbo}$), 109.6, 109.9 ($2C_{q\ isopropylidene}$), 122.5 (CH_{alkene}, 1-C), 142.5 (CH_{alkene}, 2-C), 166.3, 170.1 ($2C_q$, C=O).

Ethyl 3-((4R,5S)-5-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,3-dihydroxypropanoate (247)

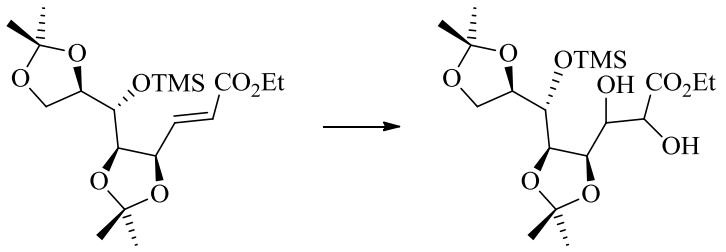


175 **247**

$OsCl_3$ (15.9 mg, 0.05 mmol) and NMO (1.02 g, 8.7 mmol) were added to a solution of **175** (1 g, 3 mmol) in THF:H_2O, 1:1 (40 mL) and stirred overnight at rt. Anhydrous Na_2SO_3 was added to the solution followed by water. The Mixture was then extracted with $CHCl_3$ and the organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude mixture purified by column chromatography (toluene:acetone, 4:1) to give the pure product **247** (0.6 g, 55%).

δ_H (300 MHz, $CDCl_3$): 1.31 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.35, 1.40, 1.49 (3s, 12H, $CH_{3\ isopropylidene}$), 3.94-4.17 (m, 4H, CH_{carbo}), 4.19-4.37 (m, 4H, $CH_{2\ ester}$, CH_{carbo}), 4.42 (dd, 1H, J = 6.1, 1.5 Hz, 1-H), 4.47 (dd, 1H, J = 5.2, 1.3 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): 14.7 ($CH_{3\ ester}$), 25.4, 25.6, 26.2, 26.4 ($4CH_{3\ isopropylidene}$), 61.8 ($CH_{2\ ester}$), 66.8, 69.6, 71.2, 74.1, 76.2, 76.8, 77.1 ($7CH_{carbo}$), 110.2, 112.9 ($C_{q\ isopropylidene}$), 175.3 ($C_{q,}$ C=O); *m/z* $[M+NH_4]^+$: 382.2067; $[C_{16}H_{28}O_9+NH_4]^+$ requires 382.2072.

Ethyl 3-((4R,5R)-5-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((trimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,3-dihydroxypropanoate (178)

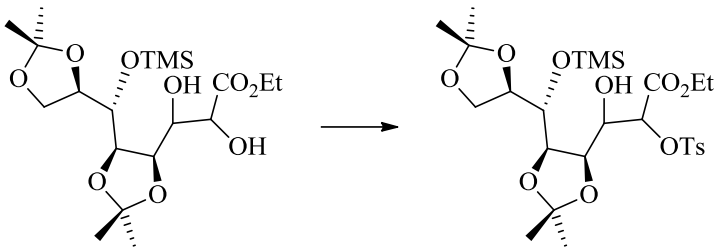


244 **178**

$OsCl_3$ (3.7 mg, 0.01 mmol) and NMO (0.23 g, 2.0 mmol) were added to a solution of **244** (0.23 g, 0.6 mmol) in THF:H_2O, 1:1 (10 mL) and stirred overnight at rt. Anhydrous Na_2SO_3 was added to the solution followed by water. The Mixture was then extracted with $CHCl_3$ and the organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude mixture purified by column chromatography (petrol:EtOAc, 4:1) to give the pure product **247** (0.16 g, 63%).

IR ν_{max} (film)/cm^{-1}: 3451, 2985, 1738, 1370, 1247, 1215, 1156, 1096, 1156, 1054, 972, 893, 840, 752; δ_H (400 MHz, $CDCl_3$): 0.14 (s, 9H, $Si(CH_3)_3$), 1.27 (t, 3H, J = 7.2 Hz, $CH_{3\ ester}$), 1.30, 1.32, 1.39, 1.44 (4s, $CH_{3\ isopropylidene}$), 3.28, (d, 1H, J = 6.3 Hz, 2-OH), 3.35 (d, 1H, J = 7.6 Hz, 1-OH), 3.80 (t, 1H, J = 7.5 Hz, 7-H), 4.01-4.16 (m, 5H, $5CH_{carbo}$), 4.19 (t, 1H, J = 5.7 Hz, CH_{carbo}), 4.25 (q, 2H, 7.0 Hz, $CH_{2\ ester}$), 4.5 (d, 1H, J = 5.6 Hz, 2-H); δ_C (75 MHz, $CDCl_3$): 0.8 ($Si(CH_3)_3$), 14.1 ($CH_{3\ ester}$), 25.1, 25.8, 26.2, 27.3 ($4CH_{3\ isopropylidene}$), 62.0 ($CH_{2\ ester}$), 67.2, 70.1, 70.8, 70.9, 75.8, 77.5, 79.2 ($7CH_{carbo}$), 108.6, 109.6 ($C_{q\ isopropylidene}$), 174.0 (C_q, C=O); *m/z* $[M+H]^+$: 437.2199; $[C_{19}H_{36}O_9Si+H]^+$ requires 437.2201.

Ethyl 3-((4R,5R)-5-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((trimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-(tosyloxy)propanoate (179)

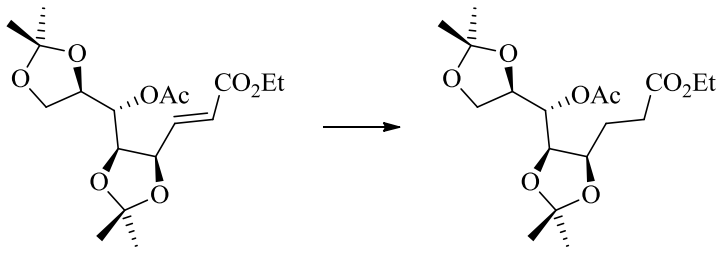


178 **179**

TsCl (240 mg, 1.26 mmol) was added to a solution of **178** (0.5 g, 1.15 mmol) and pyridine (102 µL, 1.26 mmol) in DCM (5 mL) at rt and stirred overnight. Saturated $NaHCO_3$ solution was added to the mixture followed by extraction with DCM, the organic layers were combined, washed $CuSO_4$ solution, water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue purified by column chromatography (petrol:EtOAc, 5:1) to give the pure compound **179** (128 mg, 19%).

IR ν_{max} (film)/cm^{-1}: 3450, 2985, 1766, 1599, 1370, 1249, 1177, 1190, 1037, 841, 755; δ_H (400 MHz, $CDCl_3$): 0.13 (s, 9H, $Si(CH_3)_3$), 1.20 (s, 3H, $CH_{3\ isopropylidene}$), 1.24 (t, 3H, J = 7.1 Hz, $CH_{3\ ester}$), 1.32, 1.38, 1.40 (3s, 9H, $CH_{3\ isopropylidene}$), 2.43 (s, 3H, $CH_{3\ tosyl}$), 3.27 (d, 1H, J = 7.6 Hz, OH), 3.71-3.81 (m, 1H, CH_{carbo}), 3.95 (dd, 1H, 9.8, 5.2 Hz, CH_{carbo}), 4.00-4.11 (m, 3H, CH_{carbo}), 4.14-4.25 (m, 4H, $CH_{2\ ester}$, CH_{carbo}), 5.24 (d, 1H, J = 1.5 Hz, 1-H), 7.32 (d, 2H, J = 8.0 Hz, CH_{aryl}), 7.86 (d, 2H, J = 8.3 Hz, CH_{aryl}); δ_C (75 MHz, $CDCl_3$): 0.0 ($Si(CH_3)_3$), 13.2 ($CH_{3\ ester}$), 20.9 ($CH_{3\ tosyl}$), 24.4, 24.8, 25.4, 26.6 ($4CH_{3\ isopropylidene}$), 61.4 ($CH_{2\ ester}$), 66.9, 69.4, 70.2, 74.3, 76.7, 77.2, 78.6 ($7CH_{carbo}$), 107.9, 109.2 ($C_{q\ isopropylidene}$), 127.7, 129.0, 133.2, 144.3 (C_{aryl}), 167.3 (C_q, C=O).

Ethyl 3-((4R,5R)-5-((S)-acetoxy((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (248)

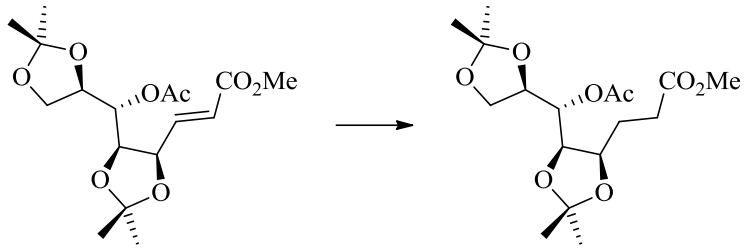


171 **248**

A solution of **171** (2 g, 5.4 mmol) in EtOAc (100 mL) was degassed with argon for 10 min. Pd/C (10%) was added to the solution and the reaction vessel was flushed with hydrogen gas and stirred under a hydrogen atmosphere for 2 h. The solution was filtered through a pad of celite and the solvent removed *in vacuo* to give the pure compound **248** (2 g, 99%).

IR ν_{max} (film)/cm^{-1}: 2985, 2938, 1733, 1457, 1370, 1212, 1158, 1064, 1037, 980, 845; δ_H (400 MHz, $CDCl_3$): 1.21 (t, 3H, J = 6.8 Hz, $CH_{3\ ester}$), 1.29, 1.30, 1.33, 1.44 (4s, 12H, $CH_{3\ isopropylidene}$), 1.60-1.87 (m, 2H, CH_2, 1-H), 2.06 (s, 3H, $CH_{3\ acetyl}$), 2.29-2.51 (m, 2H, CH_2, 2-H), 3.86 (t, 1H, J = 7.7 Hz, 7-H), 3.96 (dd, 1H, J = 13.8, 7.6 Hz, 7-H), 4.03-4.10 (m, 2H, CH_{carbo}), 4.10-4.17 (m, 2H, $CH_{2\ ester}$), 4.17-4.25 (m, 1H, CH_{carbo}), 5.07 (t, 1H, J = 6.7 Hz, 5-H); δ_C (75 MHz, $CDCl_3$): 14.3 ($CH_{3\ ester}$), 21.32 ($CH_{3\ acetyl}$), 24.7 (CH_2, 2-C), 25.5, 25.7, 26.5, 26.8 ($4CH_{3\ isopropylidene}$), 31.3 (CH_2, 1-C), 60.5 ($CH_{2\ ester}$), 66.1 (CH_2, 7-C), 70.4, 75.6, 76.2, 76.3 (CH_{carbo}), 108.7, 109.2 ($C_{q\ isopropylidene}$), 170.1, 172.9 ($2C_q$, C=O).

Methyl 3-((4R,5R)-5-((S)-acetoxy((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (186)

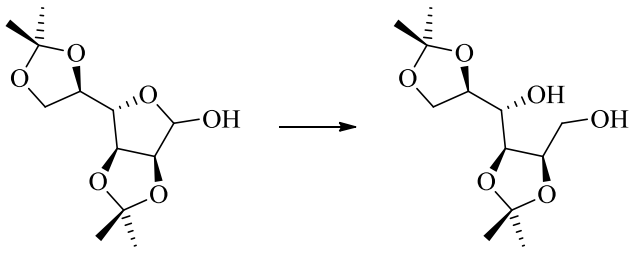


246 **186**

A solution of **246** (8 g, 22.3 mmol) in EtOAc (250 mL) was degassed with argon for 10 min. Pd/C (10%) was added to the solution and the reaction vessel was flushed with hydrogen gas and stirred under a hydrogen atmosphere for 3 h. The solution was filtered through a pad of celite and the solvent removed *in vacuo* to give the pure compound **186** (7.97 g, 99%).

δ_H (400 MHz, $CDCl_3$): 1.28, 1.30, 1.35, 1.44 (4S, 12H, $CH_{3\ isopropylidene}$), 1.64-1.73 (m, 1H, CH_2, 2-H), 1.76-1.84 (m, 1H, CH_2, 2-H), 2.08 (s, 3H, $CH_{3\ acetyl}$), 2.34-2.56 (m, 2H, CH_2, 1-H), 3.64 (s, $CH_{3\ ester}$), 3.88 (dd, 1H, J = 8.0, 4.0 Hz, 7-H), 3.97 (dd, 1H, J = 8.0, 4.0 Hz, 7-H), 4.11-4.20 (m, 2H, CH_{carbo}), 4.23 (dd, 1H, 9.6, 8.0 Hz, CH_{carbo}), 5.08 (t, 1H, 9.6 Hz, 5-H), δ_C (100 MHz, $CDCl_3$): 21.2 ($CH_{3\ acetyl}$), 25.4, 25.5, 26.3, 26.5 ($CH_{3\ isopropylidene}$), 27.5 (CH_2, 2-C), 29.7 (CH_2, 1-C), 51.8 ($CH_{3\ ester}$), 66.7 (CH_2, 7-C), 73.3, 75.8, 77.4, 77.8 (CH_{carbo}), 110.3, 111.9 ($C_{q\ isopropylidene}$), 171.3, 174.7 (C_q, C=O).

(S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (127)[5]

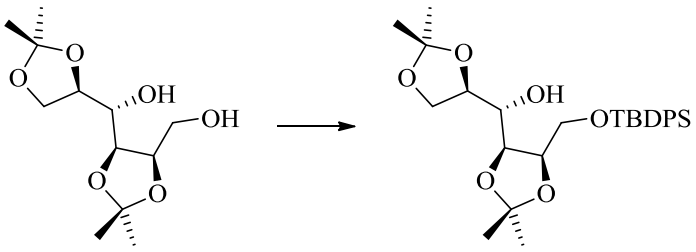


116 **127**

$LiAlH_4$ (2.2 g, 58 mmol) was added to a solution of **116** (10 g, 38 mmol) in diethyl ether (200 mL), at 0 °C the solution was allowed to reach rt and stirred for 1 h. Anhydrous Na_2SO_4 was added to the solution. Water was added drop wise until the reaction stopped fizzing. The solution was filtered through celite and the solvent removed *in vacuo* to yield the pure compound **127** (10.1 g, quantitative).

IR ν_{max} (film)/cm^{-1}: 3449, 2987, 1373, 1216, 1158, 1067, 850; δ_H (400 MHz, $CDCl_3$): 1.36, 1.40, 1.41, 1.52 (4s, 12H, $CH_{3\ isopropylidene}$), 2.54, (s, 1H, 1-OH), 3.08 (s, 1H, 4-OH), 3.58 (d, 1H, J = 6.8 Hz, 4-H), 3.78-3.95 (m, 2H, CH_2, 1-H), 4.00-4.15 (m, 3H, 5-H, 6-H), 4.32 (dt, 1H, J = 7.3, 4.4 Hz, 2-H), 4.40 (dd, 1H, J = 7.3, 1.5 Hz 3-H); δ_C (75 MHz, $CDCl_3$): 25.8, 25.2, 26.6, 26.7 ($4CH_{3\ isopropylidene}$), 60.7 (CH_2, 1-C), 67.3, 70.3, 75.8, 76.0, 77.1 ($4CH_{\ carbo}$), 108.4, 109.5 ($2C_{q\ isopropylidene}$).

(S)-((4S,5R)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (249)

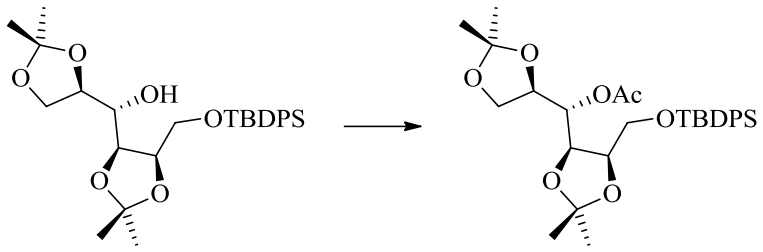


127 **249**

TBDPSCl, (1.48 mL, 5.7 mmol) Et_3N (0.8 mL, 5.7 mmol) and DMAP (0.23 g, 1.9 mmol) were added to a solution of **127** (1 g, 3.8 mmol) and left to stir overnight. Saturated $NaHCO_3$ solution was added to the mixture and the solution was extracted with DCM. The organic layer was washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography (petrol:EtOAc, 4:1) to give the pure compound **249** (1.13 g, 59%).

IR ν_{max} (film)/cm^{-1}: 3459, 2986, 2934, 2859, 1473, 1428, 1380, 1256, 1213, 1113, 1067, 702; δ_H (400 MHz, $CDCl_3$): 1.06 (s, 9H, $SiC(CH_3)_3$), 1.36, 1.36, 1.39, 1.48 (4s, $CH_{3\ isopropylidene}$), 2.88 (d, 1H, J = 6.9 Hz, OH), 3.77 (t, 1H, J = 7.6 Hz, CH_{carbo}), 3.84 (dd, 1H, J = 10.9, 4.3 Hz, CH_{carbo}), 4.00 (dd, 1H, J = 7.7, 4.6 Hz), 4.02-4.16 (m, 3H, CH_{carbo}), 4.28 (td, 1H, J = 7.0, 4.3 Hz, 2-H), 4.41 (d, 1H, J = 7.0 Hz, 3-H); δ_C (75 MHz, $CDCl_3$): 19.25 ($C_{q\ TBDPS}$), 24.8, 25.4, 26.8 ($3CH_{3\ isopropylidene}$), 26.9 ($CH_{3\ TBDPS}$), 26.9 ($CH_{3\ isopropylidene}$), 62.6 (CH_2, 1-C), 67.7, 70.5, 75.8, 76.0, 77.0 (CH_{carbo}), 108.5, 109.5 ($C_{q\ isopropylidene}$), 128.0, 130.1, 133.2, 135.86, 135.90 (C_{aryl}).

(S)-((4R,5R)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate (197)

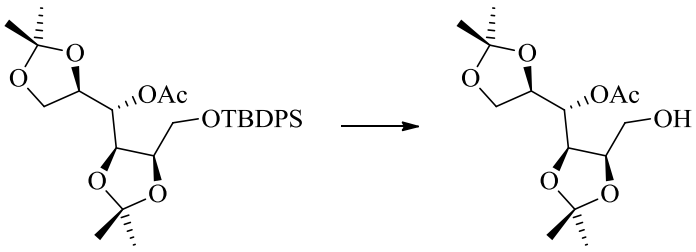


249 **197**

Ac_2O, (0.42 mL, 4.4 mmol) Et_3N (0.61 mL, 4.4 mmol) and DMAP (122 mg, 1 mmol) were added to a solution of **249** (1 g, 2 mmol) in DCM and stirred for 4 h at rt). Saturated $NaHCO_3$ was added to the solution and the mixture was extracted with DCM. The organic layers were combined and washed with water then brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (petrol:EtOAc, 5:1) to give the pure compound **197** (1g, 92%).

IR ν_{max} (film)/cm^{-1}: 2934, 1748, 1428, 1371, 1216, 1113, 1069, 851, 740, 703; δ_H (300 MHz, $CDCl_3$): 1.06 (s, 9H, $SiC(CH_3)_3$), 1.33, 1.34, 1.45, (3s, 12H, $CH_{3\ isopropylidene}$), 1.92 (s, 3H, $CH_{3\ acetyl}$), 3.71 (dd, 2H, 6.2, 1.5 Hz, 1-H), 3.90 (dd, 1H, J = 8.6, 6.8 Hz, 6-H), 3.98 (dd, 1H, J = 8.6, 6.2 Hz, 6-H), 4.22 (dd, 1H, J = 12.7, 6.4 Hz, CH_{carbo}), 4.27-4.39 (m, 2H, CH_{carbo}), 5.23 (dd, 1H, J = 6.2, 2.1 Hz, 4-H), 7.33-7.47 (m, 6H, CH_{aryl}), 7.33-7.47 (m, 4H, CH_{aryl}); δ_C (75 MHz, $CDCl_3$): 19.3 ($C_{q\ TBDPS}$), 21.1 ($CH_{3\ acetyl}$), 25.6, 25.7, 26.5, 26.6 ($4CH_{3\ isopropylidene}$), 26.9 ($CH_{3\ TBDPS}$), 62.5 (CH_2, 1-C), 66.2, 70.6, 75.5, 75.8, 77.4 ($5CH_{carbo}$), 109.3, 109.4 ($C_{q\ isopropylidene}$), 127.9, 128.0, 130.0, 133.3, 133.5, 135.92, 135.94 (C_{aryl}), 170.1 (C_q, C=O).

(R)-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)((4R,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate (198)

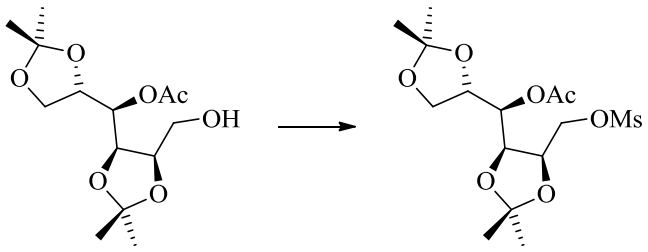


197 **198**

TBAF (1M in THF) (5.5 mL, 5.5 mmol) was added to a solution of **197** (1 g, 1.8 mmol) in THF (50 mL) and stirred at rt overnight. EtOAc (100 mL) was added to the solution and the organic layer was washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography to give the pure compound **198** (0.29 g, 52%).

IR ν_{max} (film)/cm^{-1}: 3490, 2987. 2937, 1737, 1457, 1371, 1211, 1157, 1066, 1038, 985, 916, 847, 730; δ_H (300 MHz, $CDCl_3$): 1.30, 135, 1.36, 1.47 (4s, 12H, $CH_{3\ isopropylidene}$), 2.05 (s, 3H, $CH_{3\ acetyl}$), 2.27 (d, 1H, J = 9.0 Hz, OH), 3.47 (t, 1H, J = 7.9 Hz, CH_{carbo}), 3.92-4.00 (m, 2H, CH_{carbo}), 4.05 (td, 1H, J = 8.4, 6.4 Hz, 2-H), 4.22-4.30 (m, 1H, CH_{carbo}), 4.35-4.43 (m, 3H, CH_{carbo}); δ_C (75 MHz, $CDCl_3$): 20.9 ($CH_{3\ acetyl}$), 24.6, 25.2, 26.76, 26.79 ($4CH_{3\ isopropylidene}$), 64.0 (CH_2, 1-C), 67.2, 70.2, 75.1, 75.3, 76.2 ($5CH_{carbo}$), 109.0, 109.6 ($C_{q\ isopropylidene}$), 170.9 (C_q, C=O).

(S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((4R,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate (200)

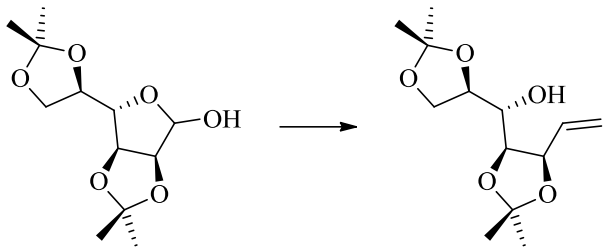


198 **200**

MsCl (0.1 mL, 1.2 mmol) was added to a solution of **198** (0.25 g, 0.82 mmol) and Et_3N (0.22 mL, 1.6 mmol) in DCM (25 mL) at rt. DMAP (50 mg, 0.41 mmol) was added and the solution was stirred overnight. Saturated $NaHCO_3$ was added to the solution and the mixture was extracted with DCM. The organic layers were combined, washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography (petrol:EtOAc, 5:1) to give the pure compound **200** (0.26 g, 83%).

IR ν_{max} (film)/cm^{-1}: 2987, 1742, 1356, 1215, 1173, 1046, 947, 860, 826, 793; δ_H (400 MHz, $CDCl_3$): 1.32, 1.35, 1.40, 1.47 (4s, 12H, $CH_{3\ isopropylidene}$), 2.08 (s, 3H, $CH_{3\ acetyl}$), 3.11 (s, 3H, $CH_{3\ mesyl}$), 3.95-4.03 (m, 1H, CH_{carbo}), 4.11-4.18 (m, 2H, CH_2, 1-H), 4.19-4.32 (m, 3H, CH_{carbo}), 4.32-4.38 (m, 1H, CH_{carbo}), 4.77 (dd, 1H, 4-H); δ_C (75 MHz, $CDCl_3$): 20.8 ($CH_{3\ acetyl}$), 25.1, 25.7, 26.0, 27.3 ($CH_{3\ isopropylidene}$), 39.3 ($CH_{3\ mesyl}$), 63.0 (CH_2, 1-C), 66.8 (CH_2, 6-C), 74.9, 75.0, 76.6, 79.0 ($4CH_{carbo}$), 109.4, 110.5 ($C_{q\ isopropylidene}$), 170.8 (C_q, C=O).

(S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)methanol (202)[6]

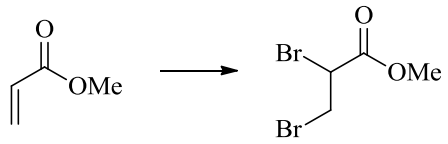


116 **202**

*n*BuLi (2.5M) (1.3 mL, 3.25 mmol), was added to a suspension of Ph_3PCH_3I (1.6 g, 4.0 mmol) in THF (14 mL) at −25 °C. The solution was cooled to −78 °C and a solution of **116** (0.35 g, 1.3 mmol) in THF (10 mL) was added. The solution was allowed to reach rt and stirred overnight. The solution was refluxed for 30 min, allowed to cool to rt and washed with water. The mixture was extracted with DCM and the organic layers were dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue purified by column chromatography (petrol:EtOAc, 5:1) to give the pure compound **202** (180 mg, 52%).

δ_H (300 MHz, $CDCl_3$): 1.34, 1.39, 1.41, 1.53 (4s, 12H, $CH_{3\ isopropylidene}$), 2.20 (d, 1H, J = 7.9 Hz, OH), 3.45 (t, 1H, J = 7.3 Hz, 5-H), 3.95-4.15 9m, 3H, 6-H, 7-H), 4.39 (dd, 1H, J = 7.5, 1.3 Hz, 4-H), 4.70 (t, 1H, J = 7.6 Hz, 3-H), 5.29-5.45 (m, 2H, $CH_{2\ alkene}$, 1-H), 6.02-6.18 (m, 1H, CH_{alkene}, 2-H); δ_C (75 MHz, $CDCl_3$): 24.6, 25.4, 26.7, 26.9 ($4CH_{3\ isopropylidene}$), 67.3, 70.7. 76.2. 76.8. 79.3 (CH_{carbo}), 108.9, 109.5 ($C_{q\ isopropylidene)}$, 120.0 (CH_2, 1-C), 134.4 (CH, 2-C).

Methyl 2, 3-dibromopropanoate (204)[6]

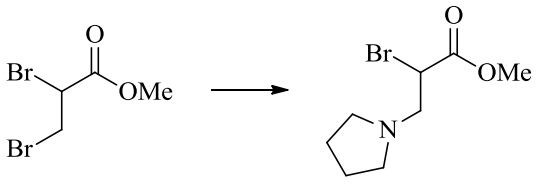


210 **204**

Neat bromine (1.3 mL, 25.3 mmol) was added to a solution of methyl acrylate **210** (2.1 mL, 23 mmol) in DCM (25 mL) at rt and stirred for 30 min. Saturated $Na_2S_2O_3$ was added to the solution followed by extraction with DCM. The organic layers were combined and washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the pure compound **204** (5 g, 88.3%).

δ_H (300 MHz, $CDCl_3$): 3.67 (dd, 1H, J = 9.9, 4.4 Hz, CH_2Br), 3.84 (s, 3H, $CH_{3\ ester}$), 3.92 (dd, 1H, J = 11.4, 9.9 Hz, CH_2Br), 4.45 (dd, 1H, J = 11.4, 4.4 Hz, CHBr); δ_C (75 MHz, $CDCl_3$): 29.5 (CH_2Br), 40.6 (CHBr), 53.3 ($CH_{3\ ester}$), 168.2 (C_q, C=O).

Methyl 2-bromo-3-(pyrrolidin-1-yl)propanoate (205)[6]

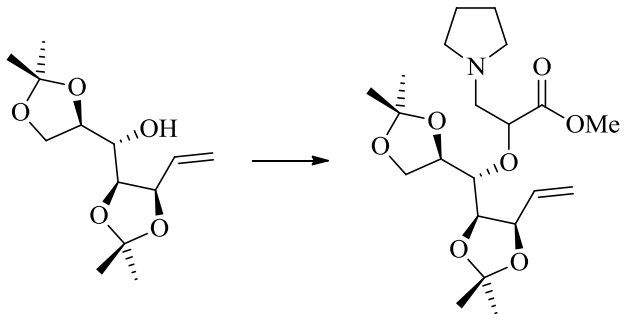


204 **205**

Pyrrolidine (1.7 mL, 20.5 mmol) and Et_3N (2.84 mL, 20.5 mmol) were added to a solution of **204** (5 g, 20.5 mmol) in toluene (60 mL), at 0 °C and stirred for 30 min. The solution was filtered through celite and washed with water. The solvent was removed *in vacuo* to give the pure product **205** (4.3 g, 90%).

δ_H (300 MHz, $CDCl_3$): 1.70-1.81 (m, 4H, $CH_{2\ pyrrolidine}$), 2.50-2.76 (m, 4H, $NCH_{2\ pyrrolidine}$), 2.89 (dd, 1H, J = 12.8, 5.9 Hz, CH_2Br), 3.23 (dd, 1H, J = 12.8, 9.3 Hz, CH_2Br), 3.78 (s, 3H, $CH_{3\ ester}$), 4.28 (dd, 1H, J = 9.1, 6.1 Hz, CHBr).

Methyl 2-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((4R,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)methoxy)-3-(pyrrolidin-1-yl)propanoate (203)[6]



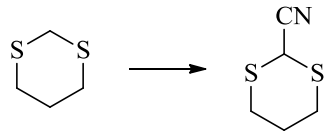
202 **203**

NaH (89 mg, 3.7 mmol), was added to a solution of **202** (0.45 g, 1.7 mmol) in THF (50 mL) and DMF (15 mL) at 0 °C and stirred for 1 h at rt. The solution was cooled to 0 °C and compound **205** (1.5 g, 6.3 mmol) was added and the solution was stirred at rt for 18 h. The solution was quenched with water and extracted with petrol. The organic layers were combined and dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography (EtOAc:petrol:Et_3N, 66:33:1) to give the pure compound **203** (72 mg, 10%).

IR ν_{max} (film)/cm^{-1}: 2984, 2935, 2787, 1750, 1663, 1457, 1435, 1370, 1211, 1146, 1057, 1034, 925, 852, 794; δ_H (300 MHz, $CDCl_3$): 1.30, 1.30, 1.39, 1.46 (4s, 12H, $CH_{3\ isopropylidene}$), 1.63-1.83 (m, 4H, $CH_{2\ pyrrolidene}$), 2.42-2.66 (m, 4H, $NCH_{2\ pyrrolidene}$), 2.75 (dd, 2H, J = 8.0, 6.2 Hz, CH_2N), 3.70 (s, 3H, $CH_{3\ ester}$), 3.72-3.83 (m, 1H, $CHCO_2Me$), 4.03-4.14 (m, 4H, 5-H, 6-H, 7-H), 4.35 (dd, 1H, J = 6.9, 5.5 Hz, 4-H), 4.47-4.55 (m, 1H, 3-H), 5.20-5.39 (m, 2H, $CH_{2\ alkene}$, 1-H), 5.95-6.11 (m, 1H, CH_{alkene}, 2-H); δ_C (75 MHz, $CDCl_3$): 14.1 ($CH_{2\ pyrrolidene}$), 25.3, 25.5, 26.1, 26.2 ($CH_{3\ isopropylidene}$), 60.8 ($CH_{3\ ester}$), 65.5 ($NCH_{2\ pyrrolidene}$), 74.3, 75.3, 75.7, 76.2

(CH_{carbo}), 109.6, 110.6 ($C_{q\ isopropylidene}$), 123.9 ($CH_{2\ alkene}$, 1-C), 140.1 (CH_{alkene}, 2-C), 165.5 (C_q, C=O).

2-cyano-1,3-dithiane (213)[7]

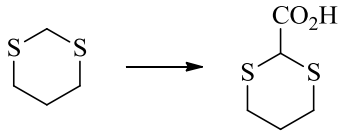


211 **213**

Triphenylcarbenium tetrafluoroborate (3.02 g, 9.1 mmol) was added to a solution of 1,3-dithiane **211** (1 g, 8.3 mmol) in DCM (60 mL) and the mixture was heated under reflux for 45 min. the solution was allowed to cool to rt and the solvent was removed *in vavuo*. The solid was triturated with cold diethyl ether to give 1,3-dithienium tetrafluoroborate as a yellow solid (1.55g). TMSCN (0.93 mL, 7.5 mmol) was added to a solution of 1,3-dithienium tetrafluoroborate (1.55 g, 7.5 mmol) in DCM (100 mL) under a nitrogen atmosphere at −20 °C. The solution was stirred for 1 h at −20 °C and quenched by the addition of HCl 1M (2 mL). The solution was washed the saturated NH_4Cl solution and the aqueous layer extracted with DCM. The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (petrol:EtOAc, 9:1), to give the pure compound **213** (0.72 g, 60%).

IR ν_{max} (film)/cm^{-1}: 2931, 2908, 2843, 2228, 1669, 1438, 1427, 1412, 1286, 1274, 1242, 1212, 942, 910, 766; δ_H (400 MHz, $CDCl_3$): 1.95-2.08 (m, 1H, $CH_{2\ dithi}$), 2.16-2.26 (m, 1H, $CH_{2\ dithi}$), 2.76-2.85 (m, 2H, $SCH_{2\ dithi}$), 3.28-3.38 (m, 2H, $SCH_{2\ dithi}$), 4.42 (s, 1H, SCHCN); δ_C (75 MHz, $CDCl_3$): 25.0 ($CH_{2\ dithi}$), 26.9 ($SCH_{2\ dithi}$), 28.6 (SCH_{dithi}), 116.0 (CN).

1,3-dithiane-2-carboxylic acid (214)[8]

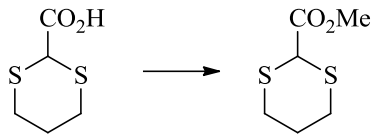


211 **214**

*n*BuLi (2.5 M) (35.6 mL, 91.3 mmol), was added to a solution of 1,3-dithiane **211** (10 g, 83 mmol) in THF (250 mL) at −20 °C. the solution was stirred at −20 °C for 1.5 h then cooled to −78 °C and added to CO_2(s). The solution was stirred at −78 °C for 30 min, then allowed to reach −40 °C and stirred for a further 2 h. Saturated NH_4Cl solution in MeOH was added slowly and the reaction was allowed to reach rt. Diethyl ether (250 mL) and water (100 mL) were added to the solution and the aqueous layer was extracted with diethyl ether. Conc HCl (5 mL) was added to the aqueous layer and extracted with petrol. The petrol fractions were combined and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the pure compound **214** (8 g, 59%).

IR ν_{max} (film)/cm^{-1}: 2971, 2942, 2927, 2908, 2826, 2681, 2570, 1692, 1422, 1212, 1301, 1242, 922; δ_H (300 MHz, $CDCl_3$): 1.91-2.24 (m, 2H, $CH_{2\ dithi}$), 2.50-2.69 (m, 2H, $SCH_{2\ dithi}$), 3.35-3.50 (m, 2H, SCH_2), 4.16 (s, 1H, SCH_{dithi}), 10.76 (s, 1H, COOH); δ_C (75 MHz, $CDCl_3$): 24.6 ($CH_{2\ dithi}$), 25.5 ($SCH_{2\ dithi}$), 39.0 (SCH_{dithi}), 176.3 (C_q, C=O).

Methyl 1,3-dithiane-2-carboxylate (215)[8]

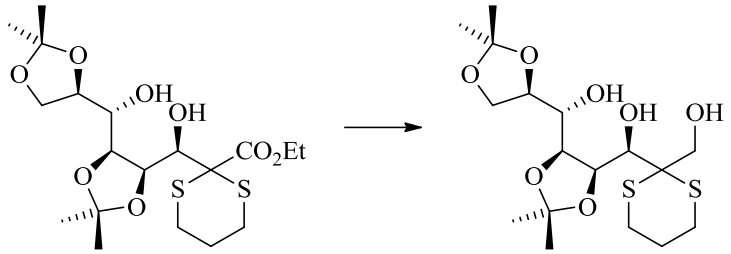


214 **215**

HCl gas was bubbled through a solution of **214** (8 g, 49 mmol) in MeOH (50 mL) over 5 min. The solvent was removed *in vacuo* and dissolved in diethyl ether; the ethereal solution was washed with water then brine and evaporated to dryness. The crude residue was purified by Kugerohl distillation to give the pure compound **215** (7.7 g, 89%).

IR ν_{max} (film)/cm^{-1}: 2928, 1726, 1426, 1285, 1138, 1000, 914, 815; δ_H (300 MHz, $CDCl_3$): 1.93-2.22 (m, 2H, $CH_{2\ dithi}$), 2.50-2.66 (m, 2H, $SCH_{2\ dithi}$), 3.31-3.46 (m, 2H, $SCH_{2\ dithi}$), 3.78 (s, 3H, $CH_{3\ ester}$), 4.19 (s, 1H, $SCH_{\ dithi}$); δ_C (75 MHz, $CDCl_3$): 25.0 ($CH_{2\ dithi}$), 26.1 ($SCH_{2\ dithi}$), 26.3 ($SCH_{\ dithi}$), 40.0 ($CH_{3\ ester}$), 170.6 (C_q, C=O).

(S)-((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 (222)

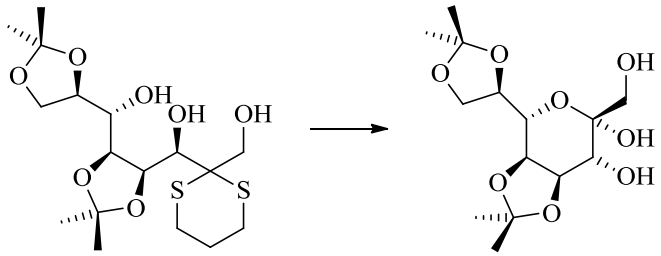


143 **222**

$LiAlH_4$ (0.17 g, 4.4 mmol) was added to a solution of **143** (1 g, 2.2 mmol) in diethyl ether (50 mL) at rt and stirred for 3 h. Anhydrous Na_2SO_4 was added to the solution followed by water. The solution was filtered through a pad of celite and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (petrol:EtOAc, 4:1) to give the pure compound **222** (0.69 g, 76%).

IR ν_{max} (film)/cm^{-1}: 3416, 2984, 2934, 1372, 1245, 1215, 1137, 1064, 911, 853; δ_H (400 MHz, $CDCl_3$): 1.35, 1.41, 1.41 1.56 (4s, 12H, $CH_{3\ isopropylidene}$), 1.94-2.06 (m, 2H, $CH_{2\ dithi}$), 2.71-2.85 (m, 4H, $CH_{2\ dithi}$), 3.41 (t, 1H, J = 7.1 Hz, 1-OH), 3.62 (dd, 1H, J = 7.5, 3.1 Hz, CH_{carbo}), 3.92-4.00 (m, 4H, CH_2OH, CH_{carbo}), 4.00-4.06 (m, 1H, CH_{carbo}), 4.06-4.17 (m, 3H, CH_{carbo}, OH), 4.44 (d, 1H, J = 7.4 Hz, 4-H), 4.81 (d, 1H, J = 7.4 Hz, 3-H); δ_C (101 MHz, $CDCl_3$): 24.6 ($CH_{2\ dithi}$), 25.1 ($SCH_{2\ dithi}$), 25.4 ($SCH_{2\ dithi}$), 25.49, 25.54, 26.1, 27.1 ($4CH_{3\ isopropylidene}$), 58.4 ($C_{q\ dithi}$), 65.0, 67.5, 70.7, 71.2, 73.5, 75.8, 76.9 (CH_{carbo}), 109.38, 109.43 ($C_{q\ isopropylidene}$); *m/z* $[M+Na]^+$: 433.1315; $[C_{17}H_{30}O_7S_2+Na]^+$ requires 433.1325.

(3aR,4S,6S,7R,7aR)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(hydroxymethyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6,7-diol (223)

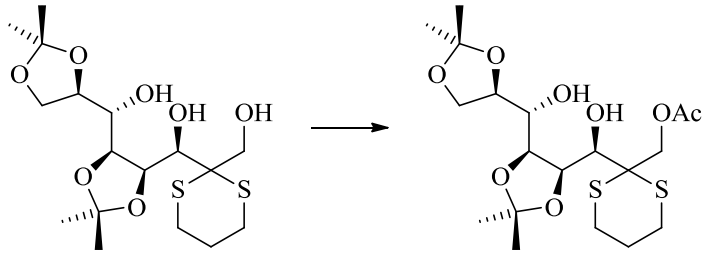


222 **223**

NBS (0.38 g, 2.1 mmol) was added to a solution of **222** (0.25 g, 0.61 mmol) in a 9:1 mixture of acetonitrile and water (20 mL) at 0 °C. The solution was stirred vigorously for 3 min at 0 °C, saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solutions were added and the mixture was extracted with EtOAc. The organic layers were washed with water then brine and dried over $MgSO_4$. The crude residue was purified by column chromatography (petrol:EtOAc, 1:1) to give the pure compound **223** (0.17 mg, 87%).

IR ν_{max} (film)/cm^{-1}: 3411. 2988. 2924. 1374, 1220, 1150, 1065, 840; δ_H (400 MHz, $CDCl_3$): 1.36, 1.37, 1.43, 1.48 (4s, $CH_{3\ isopropylidene}$), 2.69 (s, 1H, CH_2O**H**), 3.10 (s, 1H, 2-OH), 3.66 (s, 2H, C**H**$_2$OH), 3.73 (d, 1H, J = 4.5 Hz, 2-H), 3.98-4.08 (m, 3H, 6-H, 7-H), 4.23 (s, 1H, 1-OH), 4.25-4.37 (m, 3H, 3-H, 4-H, 5-H); δ_C (101 MHz, $CDCl_3$): 25.4, 25.9, 27.0, 27.5 ($4CH_{3\ isopropylidene}$), 66.6 (CH_2OH), 66.7 (CH_2, 7-C), 69.2 (CH, 6-C), 69.5 (CH, 2-C), 72.8, 74.3, 76.4 ($CH_{\ carbo}$, 3-C, 4-C, 5-C), 96.2 (C_q, 1-C), 109.5, 109.9 ($2C_{q\ isopropylidene}$); *m/z* $[M+Na]^+$: 343.1363; $[C_{14}H_{24}O_8+Na]^+$ requires 343.1363.

(2-((R)-((4R,5S)-5-((S)-((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 (227)

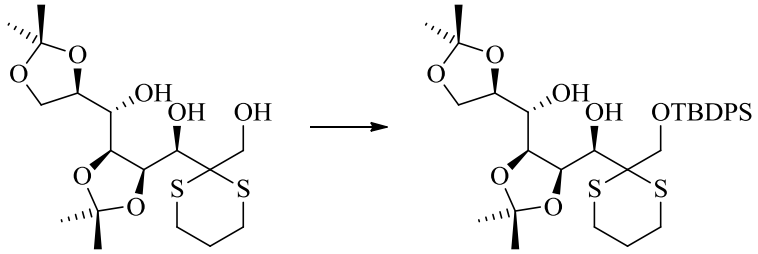


222 **227**

Ac_2O (0.25 mL, 2.7 mmol) was added to a solution of **222** (1 g, 2.4 mmol) and Et_3N (0.38 mL, 2.7 mmol) at 0 °C and left to stir overnight at rt. Saturated $NaHCO_3$ was added to the solution and the mixture was extracted with DCM. The organic layers were combined and washed with water then brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (petrol:EtOAc, 5:1) to give the pure compound **227** (0.72 g, 67%).

IR ν_{max} (film)/cm^{-1}: 3462, 2985, 1742, 1372, 1216, 1138, 1066; δ_H (400 MHz, $CDCl_3$): 1.36, 1.42, 1.54 (3s, 12H, $CH_{3\ isopropylidene}$), 1.82-1.97 (m, 1H, $CH_{2\ dithi}$), 2.02-2.12 (m, 1H, $CH_{2\ dithi}$), 2.12)s, 3H, $CH_{3\ acetyl}$), 2.64-2.80 (m, 2H, SCH_2), 2.86-3.03 (m, 2H, SCH_2), 3.52 (d, 1H, J 8.8 Hz, 4-H), 3.62 (d, 2H, J = 8.2 Hz, 7-H), 4.00 (d, 1H, J = 8.1 Hz, 3-H), 4.02-4.13 (m, 2H, CH_2OAc), 4.12-4.16 (m, 1H, 6-H), 4.41-4.50 (m, 2H, 5-H, 2-OH), 4.71 (d, 1H, J = 7.6 Hz, 2-H), 4.81 (d, 1H, J = 11.9 Hz, 5-OH); δ_C (75 MHz, $CDCl_3$): 21.0 ($CH_{3\ acetyl}$), 24.3 ($CH_{2\ dithi}$), 25.0, 25.2 ($2CH_{3\ isopropylidene}$), 25.70 (SCH_2), 25.74, 26.0 ($2CH_{3\ isopropylidene}$), 26.9 (SCH_2), 56.6 ($C_{q\ dithi}$), 63.8, 67.4, 70.6, 72.2, 73.6, 75.8, 77.0 ($7CH_{carbo}$), 109.1, 109.4 ($C_{q\ isopropylidene}$), 170.4 (C_q, C=O); *m/z* $[M+Na]^+$: 475.1420; $[C_{19}H_{32}O_8S_2+Na]^+$ requires 475.1431.

(R)-(2-(((tert-butyldiphenylsilyl)oxy)methyl)-1,3-dithian-2-yl)((4R,5S)-5-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (250)

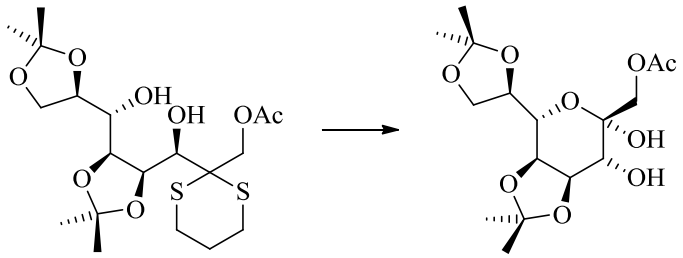


222 **250**

TBDPSCl, (0.95 mL, 3.6 mmol) Et_3N (0.5 mL, 3.6 mmol) and DMAP (0.15 g, 1.2 mmol) were added to a solution of **222** (1 g, 2.4 mmol) and left to stir overnight. Saturated $NaHCO_3$ solution was added to the mixture and the solution was extracted with DCM. The organic layer was washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography (petrol:EtOAc, 4:1) to give the pure compound **250** (0.28 g, 18%).

IR ν_{max} (film)/cm^{-1}: 3413, 2932, 1428, 1380, 1244, 1213, 1113, 1063, 823; δ_H (300 MHz, $CDCl_3$): 1.06 (s, 9H, $Si(CH_3)_3$), 1.36, 1.40, 1.42 ,1.58 (4s, 12H, $CH_{3\ isopropylidene}$), 1.74-1.95 (m, 2H, $CH_{2\ dithi}$), 2.24-2.40 (m, 1H, $CH_{2\ dithi}$), 2.46-2.74 (m, 3H, $CH_{2\ dithi}$), 3.57 (dd, 1H, J = 8.2, 2.3 Hz, 4-H), 3.92 (dd, 1H, J = 10.6, 1.3 Hz, 3-H), 3.98-4.07 (m, 1H, CH_2OSi), 4.11-4.23 (m, 3H, CH_2OSi, 7-H), 4.30-4.41 (m, 2H, 6H, 5-H, 4.46 (d, 1H, J = 2.3 Hz, 2-OH), 4.69 (d, 1H, J = 7.4 Hz, 5-OH), 4.87 (d, 1H, J = 9.9 Hz, 2-H) 7.36-7.51 (m, 6H, CH_{aryl}), 7.74-7.86 (m 4H, CH_{aryl}); δ_C (75 MHz, $CDCl_3$): 19.1 (C_q, SiC), 24.5 ($CH_{2\ dithi}$), 25.1, ($CH_{3\ isopropylidene}$), 25.4 (SCH_2), 25.7 ($CH_{3\ isopropylidene}$), 26.1 ($CH_{2\ dithi}$), 26.3 ($CH_{3\ isopropylidene}$), 26.8 ($SiC(\mathbf{C}H_3)_3$), 27.0 ($CH_{3\ isopropylidene}$), 56.6 ($C_{q\ dithi}$), 66.6, 68.0, 71.7, 73.8, 74.5, 75.4, 77.4 ($7C_{carbo}$), 109.35, 109.42 ($2C_{q\ isopropylidene}$), 128.0, 128.1, 130.3, 130.4, 132.3, 132.6, 136.1, 136.4 (C_{aryl}); *m/z* $[M+Na]^+$: 671.2492; $[C_{33}H_{48}O_7S_2Si+]^+$ requires 671.2503.

((3aR,4S,6S,7R,7aR)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6,7-dihydroxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methyl acetate (228)

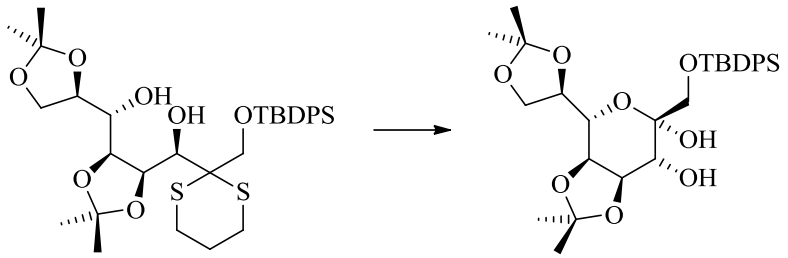


227 **228**

DBDMH (0.47 g, 1.7 mmol) was added to a solution of **227** (0.25 g, 0.6 mmol) in 95% acetone (10 mL) at 0 °C and stirred for 30 min. Saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solutions were added and the mixture was extracted with EtOAc. The organic layer was washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue purified by column chromatography (petrol:EtOAc, 4:1) to give the pure compound **228** (0.14 g, 66%)

IR ν_{max} (film)/cm^{-1}: 3415. 2987, 2937, 1745, 1374, 1243, 1220, 1152, 1064, 842; δ_H (300 MHz, $CDCl_3$): 1.35, 1.40, 1.46 (3s, 12H, $CH_{3\ isopropylidene}$), 2.09 ($CH_{3\ acetyl}$), 3.11 (d, 1H, J = 4.6 Hz, 2-OH), 3.81 (t, 1H, J = 4.8 Hz, 2-H), 3.94-4.07 (m, 3H, 7-H, 6-H), 4.11 (d, 1H, CH_2OAc), 4.15 (s, 1H, 1-OH), 4.26 (m, 1H, CH_{carbo}), 4.32 (d, 1H, CH_2OAc), 4.30-4.41 (m, 2H, CH_{carbo}); δ_C (75 MHz, $CDCl_3$): 20.8 ($CH_{3\ acetyl}$), 25.4, 25.5, 26.9, 27.1 ($4CH_{3\ isopropylidene}$), 66.7, 67.3, 69.4, 72.4, 74.1, 75.6 ($6C_{carbo}$), 95.2 (C_q, 1-C), 109.5, 110.0 ($2C_{q\ isopropylidene}$), 171.9 (C_q, C=O); *m/z* $[M+Na]^+$: 385.1474; $[C_{16}H_{26}O_9+Na]^+$ requires 385.1469.

(3aR,4S,6S,7R,7aR)-6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6,7-diol (251)



250 **251**

DBDMH (0.33 g, 1.2 mmol) was added to a solution of **250** (0.25 g, 0.4 mmol) in 95% acetone (10 mL) at 0 °C and stirred for 30 min. Saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solutions were added and the mixture was extracted with EtOAc. The organic layer was washed with water then brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude residue purified by column chromatography (petrol:EtOAc, 4:1) to give the pure compound **251** (0.15 g, 67%).

IR ν_{max} (film)/cm^{-1}: 3257, 2986, 2931, 2859, 1462, 1428, 1380, 1371, 1248, 1214, 1113, 1060, 1001, 907; δ_H (400 MHz, $CDCl_3$): 1.09 (s, 9H, $SiC(CH_3)_3$), 1.12, 1.32, 1.34, 1.41 (4s, 12H, $CH_{3\ isopropylidene}$), 1.74 (d, 1H, J = 15.1 Hz, 2-OH), 3.18 (m, 4H, CH_2OSi, CH_{carbo}), 3.48 (m, 3H, CH_{carbo}, 1-OH), 3.85-3.97 (m, 1H, CH_{carbo}), 4.58 (s, 1H, CH_{carbo}), 4.76 (s, 1H, 1-OH), 4.88 (d, 1H, J = 11.7 Hz, 2-H); δ_C (101 MHz, $CDCl_3$): 19.4 (C_q, SiC), 25.3, 25.2, 26.0, 26.8 ($4CH_{3\ isopropylidene}$), 27.0 ($SiC(\mathbf{C}H_3)_3$), 61.5, 66.9, 67.8, 70.2, 72.4, 74.6, 75.5, 75.8 ($8C_{carbo}$), 108.8, 109.6 ($C_{q\ isopropylidene}$), 128.0, 128.1, 130.1, 130.3, 131.7, 132.6, 135.7, 135.9 (C_{aryl}).

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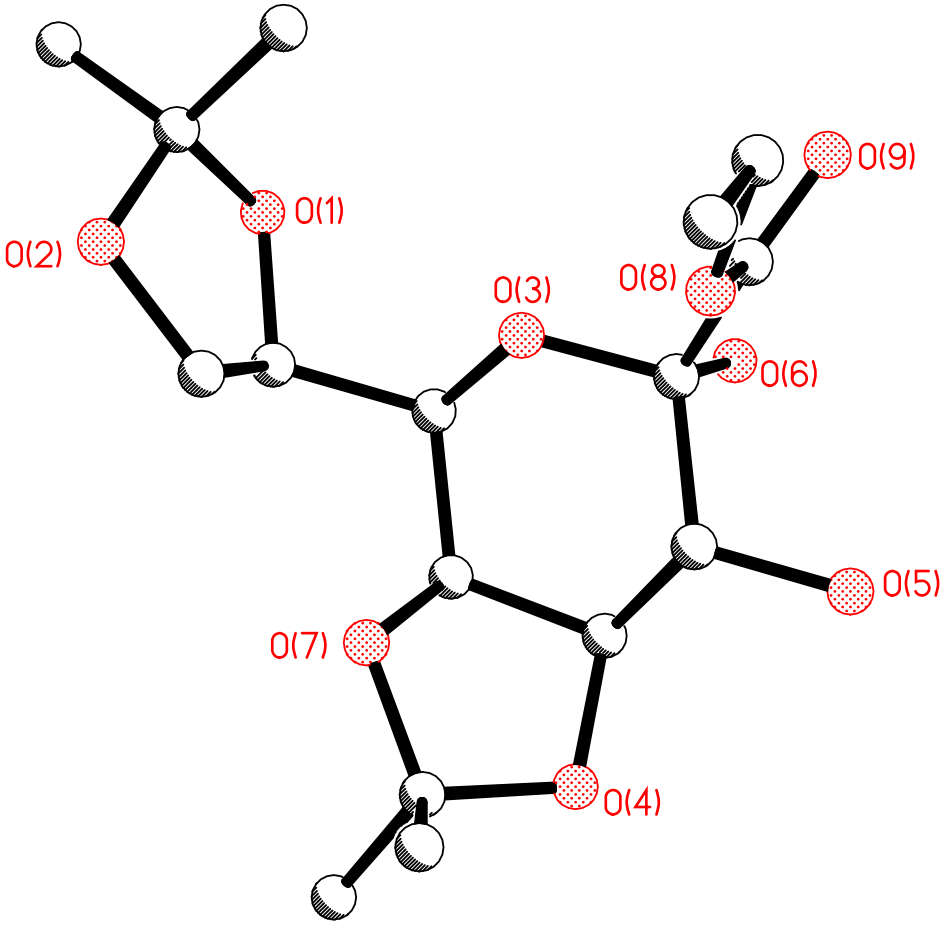
Appendix

X-ray Structure Report for compound 145



Experimental

Data Collection

A colorless prism crystal of $C_{16}H_{26}O_9$ having approximate dimensions of 0.150 x 0.150 x 0.150 mm was mounted in a loop. All measurements were made on a diffractometer using graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 3828 carefully centered reflections in the range $7.26 < 2\theta < 48.50^o$ corresponded to a primitive orthorhombic cell with dimensions:

a = 9.669(3) Å

b = 11.832(3) Å

c = 16.455(4) Å

V = 1882.6(9) $Å^3$

For Z = 4 and F.W. = 362.38, the calculated density is 1.278 g/cm^3. The reflection conditions of:

h00: h = 2n

0k0: k = 2n

00l: l = 2n

uniquely determine the space group to be:

$P2_12_12_1$ (#19)

The data were collected at a temperature of -180 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 56.1°.

Data Reduction

Of the 11235 reflections that were collected, 3805 were unique (R_{int} = 0.0814). No decay correction was applied.

The linear absorption coefficient, μ, for Mo-Kα radiation is 1.045 cm^{-1}. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically and the rest were refined using the riding model.The final cycle of full-matrix least-squares refinement[2] on F^2 was based on 3805 observed reflections and 234 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.0685$$

$$wR2 = [\Sigma (w (Fo^2 - Fc^2)^2) / \Sigma \, w(Fo^2)^2]^{1/2} = 0.1425$$

The standard deviation of an observation of unit weight[3] was 1.09. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.35 and -0.24 $e^-/Å^3$, respectively. The absolute structure was deduced based on Flack parameter, -1.8(16), using 1538 Friedel pairs.[4]

Neutral atom scattering factors were taken from Cromer and Waber[5]. Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf'' were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[8]. All calculations were performed using the CrystalStructure[9] crystallographic software package except for refinement, which was performed using SHELXL-97[10].

References

(1) SIR2004: M.C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G.L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna (2005)

(2) Least Squares function minimized: (SHELXL97)

$\Sigma w(F_O^2-F_C^2)^2$ where w = Least Squares weights.

(3) Standard deviation of an observation of unit weight:

$[\Sigma w(F_O^2-F_C^2)^2/(N_O-N_V)]^{1/2}$

where: N_O = number of observations

N_V = number of variables

(4) Flack, H. D. (1983), Acta Cryst. A39, 876-881.

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(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) CrystalStructure 4.0: Crystal Structure Analysis Package, Rigaku Corporation (2000-2010). Tokyo 196-8666, Japan.

(10) SHELX97: Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{16}H_{26}O_9$
Formula Weight	362.38
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.150 X 0.150 X 0.150 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	3828 (7.3 - 48.5^o)
Lattice Parameters	a = 9.669(3) Å b = 11.832(3) Å c = 16.455(4) Å

	V = 1882.6(9) $Å^3$
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.278 g/cm^3
F_{000}	776.00
μ(MoKα)	1.045 cm^{-1}

B. Intensity Measurements

Diffractometer	
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Detector Aperture	2.0 - 2.5 mm horizontal 2.0 mm vertical
Crystal to Detector Distance	21 mm
Temperature	-180.0°C
Scan Type	ω-2θ
$2\theta_{max}$	56.1°
No. of Reflections Measured	Total: 11235 Unique: 3805 (R_{int} = 0.0814) Friedel pairs: 1538

Corrections Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\ \sigma^2(Fo^2) + (0.0404 \cdot P)^2 + 1.5183 \cdot P\ ]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	56.1^o
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	3805
No. Variables	234
Reflection/Parameter Ratio	16.26
Residuals: R1 ($I>2.00\sigma(I)$)	0.0685

Residuals: R (All reflections)	0.0873
Residuals: wR2 (All reflections)	0.1425
Goodness of Fit Indicator	1.094
Flack Parameter	-1.8(16)
Max Shift/Error in Final Cycle	0.003
Maximum peak in Final Diff. Map	0.35 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.24 $e^-/Å^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O1	0.8619(3)	0.1995(2)	0.68811(13)	2.23(4)
O5	0.8083(3)	-0.0508(2)	0.8146(2)	2.97(5)
O6	0.9659(3)	0.1530(2)	0.8118(2)	2.51(5)
O8	0.9772(3)	0.3585(2)	0.5777(2)	2.83(5)
O10	0.8129(3)	0.3351(2)	0.4808(2)	2.76(5)
O14	0.9100(3)	0.0100(2)	0.56658(13)	2.49(5)
O16	0.9374(3)	-0.1330(2)	0.6583(2)	2.60(5)
O19	0.7245(4)	0.2558(3)	0.8559(2)	5.15(8)
O20	0.6090(3)	0.1645(3)	0.7584(2)	3.97(6)
C2	0.9829(4)	0.1751(3)	0.6413(2)	2.00(6)
C3	1.0026(4)	0.0492(3)	0.6280(2)	2.11(6)
C4	0.9649(4)	-0.0273(3)	0.6986(2)	2.13(6)
C5	0.8370(4)	0.0124(3)	0.7444(2)	2.22(6)
C6	0.8513(4)	0.1392(3)	0.7622(2)	2.32(6)
C7	0.9699(4)	0.2394(3)	0.5616(2)	2.17(6)
C9	0.8651(4)	0.4144(3)	0.5371(3)	2.92(7)
C11	0.8334(4)	0.2266(3)	0.5157(2)	2.52(6)
C12	0.7569(5)	0.4474(4)	0.5990(3)	4.59(10)
C13	0.9226(5)	0.5132(4)	0.4903(3)	4.42(10)
C15	0.9036(4)	-0.1101(3)	0.5742(2)	2.58(7)
C17	1.0105(4)	-0.1649(3)	0.5204(3)	3.19(7)
C18	0.7588(4)	-0.1489(4)	0.5561(3)	3.50(8)
C19	0.7215(4)	0.1923(3)	0.7992(2)	2.93(7)

C20	0.4815(5)	0.2223(6)	0.7802(3)	6.00(13)
C21	0.3701(6)	0.1793(8)	0.7332(4)	9.1(3)

$$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$$

Table 2. Atomic coordinates and B_{iso} involving hydrogen atoms

atom	x	y	z	B_{iso}
H6o	0.973(4)	0.2326(10)	0.827(3)	3.4(8)
H2	1.0653	0.2047	0.6712	2.40
H3	1.1001	0.0341	0.6110	2.53
H4	1.0450	-0.0353	0.7366	2.55
H5	0.7564	0.0032	0.7069	2.67
H5o	0.893(3)	-0.062(4)	0.846(3)	5.8(12)
H7	1.0480	0.2175	0.5249	2.60
H11A	0.8404	0.1677	0.4732	3.02
H11B	0.7571	0.2070	0.5532	3.02
H12A	0.7269	0.3801	0.6289	5.51
H12B	0.6774	0.4812	0.5711	5.51
H12C	0.7963	0.5024	0.6370	5.51
H13A	0.8493	0.5469	0.4571	5.31
H13B	0.9977	0.4872	0.4549	5.31
H13C	0.9584	0.5698	0.5283	5.31
H17A	1.1029	-0.1392	0.5364	3.83
H17B	0.9931	-0.1440	0.4637	3.83
H17C	1.0049	-0.2472	0.5261	3.83
H18A	0.7337	-0.1266	0.5007	4.20
H18B	0.6945	-0.1140	0.5947	4.20
H18C	0.7537	-0.2313	0.5611	4.20
H20A	0.4622	0.2109	0.8387	7.20
H20B	0.4916	0.3044	0.7703	7.20

H21A	0.3581	0.0986	0.7447	10.88
H21B	0.3903	0.1896	0.6753	10.88
H21C	0.2851	0.2200	0.7471	10.88

Table 3. Anisotropic displacement parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	0.0308(13)	0.0228(11)	0.0310(12)	0.0087(10)	0.0007(10)	0.0037(10)
O5	0.035(2)	0.0371(13)	0.041(2)	-0.0031(12)	-0.0016(12)	0.0110(12)
O6	0.037(2)	0.0222(10)	0.0358(12)	0.0025(10)	-0.0076(11)	-0.0009(10)
O8	0.036(2)	0.0200(11)	0.052(2)	-0.0031(10)	-0.0122(12)	0.0033(11)
O10	0.038(2)	0.0284(12)	0.0387(13)	-0.0018(11)	-0.0071(11)	0.0070(10)
O14	0.038(2)	0.0220(11)	0.0345(12)	0.0006(10)	-0.0052(11)	-0.0006(10)
O16	0.039(2)	0.0194(11)	0.0408(13)	-0.0022(10)	-0.0041(11)	0.0001(10)
O19	0.057(2)	0.090(3)	0.049(2)	0.025(2)	0.000(2)	-0.026(2)
O20	0.032(2)	0.075(2)	0.044(2)	0.017(2)	0.0012(12)	-0.007(2)
C2	0.018(2)	0.021(2)	0.036(2)	0.0010(12)	-0.002(2)	-0.0012(13)
C3	0.020(2)	0.024(2)	0.037(2)	0.0022(13)	-0.0029(13)	-0.0029(13)
C4	0.029(2)	0.0173(13)	0.035(2)	0.0006(13)	-0.007(2)	0.0002(13)
C5	0.025(2)	0.031(2)	0.029(2)	-0.001(2)	-0.005(2)	0.003(2)
C6	0.029(2)	0.029(2)	0.031(2)	0.004(2)	-0.004(2)	0.001(2)
C7	0.027(2)	0.021(2)	0.035(2)	-0.0014(13)	0.004(2)	0.0026(13)
C9	0.036(2)	0.026(2)	0.049(2)	0.003(2)	-0.012(2)	0.005(2)

C11	0.032(2)	0.028(2)	0.036(2)	-0.005(2)	-0.005(2)	0.006(2)
C12	0.062(3)	0.051(3)	0.061(3)	0.027(3)	-0.002(3)	-0.000(2)
C13	0.061(3)	0.038(2)	0.069(3)	-0.009(2)	-0.019(3)	0.017(2)
C15	0.033(2)	0.022(2)	0.043(2)	-0.001(2)	-0.003(2)	-0.003(2)
C17	0.046(3)	0.025(2)	0.050(3)	0.001(2)	0.005(2)	-0.006(2)
C18	0.043(3)	0.039(2)	0.051(3)	-0.009(2)	-0.003(2)	-0.009(2)
C19	0.040(3)	0.038(2)	0.034(2)	0.012(2)	-0.002(2)	0.000(2)
C20	0.038(3)	0.139(5)	0.052(3)	0.039(3)	0.000(3)	-0.015(3)
C21	0.061(4)	0.191(9)	0.092(5)	0.051(5)	-0.008(4)	-0.018(5)

The general temperature factor expression: $\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 4. Bond lengths (Å)

atom	atom	distance	atom	atom	distance
O1	C2	1.430(4)	O1	C6	1.416(4)
O5	C5	1.404(4)	O6	C6	1.386(4)
O8	C7	1.436(4)	O8	C9	1.435(5)
O10	C9	1.413(5)	O10	C11	1.420(4)
O14	C3	1.428(4)	O14	C15	1.428(4)
O16	C4	1.441(4)	O16	C15	1.446(5)
O19	C19	1.197(5)	O20	C19	1.320(5)
O20	C20	1.454(6)	C2	C3	1.517(5)
C2	C7	1.521(5)	C3	C4	1.517(5)
C4	C5	1.521(5)	C5	C6	1.535(5)
C6	C19	1.530(5)	C7	C11	1.528(5)
C9	C12	1.510(6)	C9	C13	1.507(6)
C15	C17	1.507(6)	C15	C18	1.504(6)
C20	C21	1.420(8)			

Table 5. Bond lengths involving hydrogens (Å)

atom	atom	distance	atom	atom	distance
O5	H5o	0.98(3)	O6	H6o	0.978(15)
C2	H2	1.000	C3	H3	1.000
C4	H4	1.000	C5	H5	1.000
C7	H7	1.000	C11	H11A	0.990
C11	H11B	0.990	C12	H12A	0.980
C12	H12B	0.980	C12	H12C	0.980
C13	H13A	0.980	C13	H13B	0.980
C13	H13C	0.980	C17	H17A	0.980
C17	H17B	0.980	C17	H17C	0.980
C18	H18A	0.980	C18	H18B	0.980
C18	H18C	0.980	C20	H20A	0.990
C20	H20B	0.990	C21	H21A	0.980
C21	H21B	0.980	C21	H21C	0.980

Table 6. Bond angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C2	O1	C6	115.0(3)	C7	O8	C9	109.3(3)
C9	O10	C11	106.6(3)	C3	O14	C15	106.8(3)
C4	O16	C15	108.7(3)	C19	O20	C20	117.1(4)
O1	C2	C3	112.2(3)	O1	C2	C7	107.2(3)
C3	C2	C7	112.2(3)	O14	C3	C2	110.0(3)
O14	C3	C4	101.4(3)	C2	C3	C4	116.5(3)
O16	C4	C3	102.1(3)	O16	C4	C5	110.3(3)
C3	C4	C5	112.9(3)	O5	C5	C4	113.8(3)
O5	C5	C6	112.4(3)	C4	C5	C6	108.9(3)
O1	C6	O6	112.9(3)	O1	C6	C5	109.5(3)
O1	C6	C19	101.3(3)	O6	C6	C5	107.4(3)
O6	C6	C19	111.9(3)	C5	C6	C19	113.8(3)
O8	C7	C2	109.1(3)	O8	C7	C11	103.3(3)
C2	C7	C11	116.6(3)	O8	C9	O10	105.5(3)
O8	C9	C12	109.2(4)	O8	C9	C13	108.5(3)
O10	C9	C12	111.5(4)	O10	C9	C13	108.2(3)
C12	C9	C13	113.6(4)	O10	C11	C7	103.4(3)
O14	C15	O16	105.1(3)	O14	C15	C17	110.3(3)
O14	C15	C18	109.0(3)	O16	C15	C17	109.0(3)
O16	C15	C18	110.1(3)	C17	C15	C18	113.0(3)
O19	C19	O20	124.9(4)	O19	C19	C6	123.3(4)
O20	C19	C6	111.7(3)	O20	C20	C21	109.9(5)

Table 7. Bond angles involving hydrogens (o)

atom	atom	atom	angle	atom	atom	atom	angle
C5	O5	H5o	110(3)	C6	O6	H6o	109(3)
O1	C2	H2	108.4	C3	C2	H2	108.4
C7	C2	H2	108.4	O14	C3	H3	109.5
C2	C3	H3	109.5	C4	C3	H3	109.5
O16	C4	H4	110.4	C3	C4	H4	110.4
C5	C4	H4	110.4	O5	C5	H5	107.1
C4	C5	H5	107.1	C6	C5	H5	107.1
O8	C7	H7	109.2	C2	C7	H7	109.2
C11	C7	H7	109.2	O10	C11	H11A	111.1
O10	C11	H11B	111.1	C7	C11	H11A	111.1
C7	C11	H11B	111.1	H11A	C11	H11B	109.1
C9	C12	H12A	109.5	C9	C12	H12B	109.5
C9	C12	H12C	109.5	H12A	C12	H12B	109.5
H12A	C12	H12C	109.5	H12B	C12	H12C	109.5
C9	C13	H13A	109.5	C9	C13	H13B	109.5
C9	C13	H13C	109.5	H13A	C13	H13B	109.5
H13A	C13	H13C	109.5	H13B	C13	H13C	109.5
C15	C17	H17A	109.5	C15	C17	H17B	109.5
C15	C17	H17C	109.5	H17A	C17	H17B	109.5
H17A	C17	H17C	109.5	H17B	C17	H17C	109.5
C15	C18	H18A	109.5	C15	C18	H18B	109.5
C15	C18	H18C	109.5	H18A	C18	H18B	109.5
H18A	C18	H18C	109.5	H18B	C18	H18C	109.5

O20	C20	H20A	109.7	O20	C20	H20B	109.7
C21	C20	H20A	109.7	C21	C20	H20B	109.7
H20A	C20	H20B	108.2	C20	C21	H21A	109.5
C20	C21	H21B	109.5	C20	C21	H21C	109.5
H21A	C21	H21B	109.5	H21A	C21	H21C	109.5
H21B	C21	H21C	109.5				

Table 8. Torsion Angles(°)

(Those having bond angles > 160 or < 20 degrees are excluded.)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
C2	O1	C6	O6	55.1(4)	C2	O1	C6	C5	-64.5(3)
C2	O1	C6	C19	174.9(2)	C6	O1	C2	C3	51.6(3)
C6	O1	C2	C7	175.2(2)	C7	O8	C9	O10	-14.6(4)
C7	O8	C9	C12	105.3(3)	C7	O8	C9	C13	-130.4(3)
C9	O8	C7	C2	-131.1(3)	C9	O8	C7	C11	-6.4(3)
C9	O10	C11	C7	-34.9(3)	C11	O10	C9	O8	31.5(4)
C11	O10	C9	C12	-87.0(3)	C11	O10	C9	C13	147.4(3)
C3	O14	C15	O16	25.7(3)	C3	O14	C15	C17	-91.7(3)
C3	O14	C15	C18	143.7(3)	C15	O14	C3	C2	-163.0(3)
C15	O14	C3	C4	-39.1(3)	C4	O16	C15	O14	-0.7(4)
C4	O16	C15	C17	117.5(3)	C4	O16	C15	C18	-118.0(3)
C15	O16	C4	C3	-22.4(3)	C15	O16	C4	C5	97.8(3)
C19	O20	C20	C21	-177.5(3)	C20	O20	C19	O19	4.9(6)
C20	O20	C19	C6	-171.4(4)	O1	C2	C3	O14	77.1(3)
O1	C2	C3	C4	-37.5(4)	O1	C2	C7	O8	66.9(3)
O1	C2	C7	C11	-49.6(3)	C3	C2	C7	O8	-169.5(3)
C3	C2	C7	C11	74.0(4)	C7	C2	C3	O14	-43.7(4)
C7	C2	C3	C4	-158.3(3)	O14	C3	C4	O16	37.0(3)
O14	C3	C4	C5	-81.4(3)	C2	C3	C4	O16	156.4(3)
C2	C3	C4	C5	38.0(4)	O16	C4	C5	O5	72.4(3)
O16	C4	C5	C6	-161.3(2)	C3	C4	C5	O5	-174.1(3)
C3	C4	C5	C6	-47.9(4)	O5	C5	C6	O1	-172.4(3)

O5	C5	C6	O6	64.7(4)	O5	C5	C6	C19	-59.8(4)
C4	C5	C6	O1	60.6(3)	C4	C5	C6	O6	-62.4(3)
C4	C5	C6	C19	173.2(3)	O1	C6	C19	O19	-107.4(4)
O1	C6	C19	O20	69.0(3)	O6	C6	C19	O19	13.2(5)
O6	C6	C19	O20	-170.4(3)	C5	C6	C19	O19	135.2(4)
C5	C6	C19	O20	-48.4(4)	O8	C7	C11	O10	24.9(3)
C2	C7	C11	O10	144.5(3)					

Table 9. Possible hydrogen bonds

Donor	H	Acceptor	D...A	D-H	H...A	D-H...A	
O5	H5o	O8[1]	2.932(4)	0.98	2.01(3)	156(4)	
O6	H6o	O16[2]	2.744(3)	0.98	1.824(15)	155(4)	
O6	H6o	O19	2.731(4)	0.98	2.469(15)	95(3)	intramol.

Symmetry Operators:

(1) -X+2,Y+1/2-1,-Z+1/2+1

(2) -X+2,Y+1/2,-Z+1/2+1

Table 10. Intramolecular contacts less than 3.60 Å

atom	atom	distance	atom	atom	distance
O1	O8	2.843(4)	O1	O14	3.040(3)
O1	O19	3.136(4)	O1	O20	2.736(4)
O1	C4	2.867(4)	O1	C9	3.556(5)
O1	C11	2.868(5)	O1	C12	3.434(6)
O5	O6	2.854(4)	O5	O16	3.020(4)
O5	O20	3.326(4)	O5	C19	3.008(5)
O6	O19	2.731(4)	O6	O20	3.563(4)
O6	C2	2.822(4)	O6	C3	3.282(4)
O6	C4	2.831(4)	O14	C5	3.009(4)
O14	C7	2.777(4)	O14	C11	2.797(4)
O19	C5	3.585(5)	O19	C20	2.688(6)
O20	C5	2.856(5)	C2	C5	2.928(5)
C2	C9	3.500(5)	C3	C6	2.854(5)
C3	C11	3.240(5)	C3	C17	3.092(5)

C3	C18	3.529(5)	C4	C17	3.383(5)
C4	C18	3.398(5)	C5	C15	3.218(5)
C7	C12	3.268(6)	C7	C13	3.476(5)
C11	C12	3.041(6)	C11	C13	3.524(6)
C19	C21	3.571(7)			

Table 11. Intramolecular contacts less than 3.60 Å involving hydrogens

atom	atom	distance	atom	atom	distance
O1	H6o	2.56(4)	O1	H3	3.277
O1	H4	3.389	O1	H5	2.556
O1	H7	3.239	O1	H11A	3.562
O1	H11B	2.442	O1	H12A	2.688
O5	H4	2.630	O6	H2	2.578
O6	H4	2.660	O6	H5	3.198
O6	H5o	2.70(5)	O8	H2	2.530
O8	H11A	3.131	O8	H11B	2.811
O8	H12A	2.575	O8	H12B	3.243
O8	H12C	2.629	O8	H13A	3.231
O8	H13B	2.538	O8	H13C	2.636
O10	H7	2.762	O10	H12A	2.629
O10	H12B	2.629	O10	H12C	3.249
O10	H13A	2.561	O10	H13B	2.572
O10	H13C	3.210	O14	H2	3.245
O14	H4	3.134	O14	H5	2.746
O14	H7	2.878	O14	H11A	2.510
O14	H11B	2.770	O14	H17A	2.615
O14	H17B	2.613	O14	H17C	3.247
O14	H18A	2.587	O14	H18B	2.589
O14	H18C	3.231	O16	H3	2.643
O16	H5	2.510	O16	H5o	3.23(4)

O16	H17A	2.566	O16	H17B	3.249
O16	H17C	2.642	O16	H18A	3.258
O16	H18B	2.581	O16	H18C	2.658
O19	H6o	2.47(4)	O19	H20A	2.607
O19	H20B	2.717	O20	H5	2.529
O20	H12A	3.514	O20	H21A	2.559
O20	H21B	2.536	O20	H21C	3.206
C2	H6o	3.13(4)	C2	H4	3.003
C2	H5	3.179	C2	H11A	3.091
C2	H11B	2.647	C2	H12A	3.472
C3	H5	2.765	C3	H7	2.653
C3	H11A	3.304	C3	H11B	3.261
C3	H17A	2.860	C3	H17B	3.542
C3	H18B	3.592	C4	H2	2.947
C4	H5o	2.56(4)	C4	H17A	3.264

Table 11. Intramolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
C4	H18B	3.288	C5	H6o	3.22(3)
C5	H2	3.391	C5	H3	3.369
C5	H18B	3.194	C6	H2	2.669
C6	H4	2.819	C6	H5o	2.78(5)
C7	H3	2.854	C7	H12A	3.086
C7	H13B	3.428	C9	H7	2.932
C9	H11A	3.112	C9	H11B	2.681
C11	H2	3.411	C11	H12A	2.797
C11	H12B	3.489	C12	H11B	2.943
C12	H13A	2.763	C12	H13B	3.355
C12	H13C	2.691	C13	H12A	3.356
C13	H12B	2.745	C13	H12C	2.709
C15	H3	2.624	C15	H4	3.130
C15	H5	2.931	C17	H3	2.918
C17	H18A	2.734	C17	H18B	3.345
C17	H18C	2.689	C18	H5	3.065
C18	H17A	3.345	C18	H17B	2.729
C18	H17C	2.695	C19	H6o	2.52(4)
C19	H5	2.726	C19	H5o	3.52(5)
C19	H12A	3.578	C19	H20A	2.600

C19	H20B	2.632	H6o	H2	2.735
H6o	H4	3.570	H6o	H5o	3.58(5)
H2	H3	2.274	H2	H4	3.044
H2	H7	2.418	H2	H11B	3.557
H3	H4	2.287	H3	H7	2.640
H3	H17A	2.389	H3	H17B	3.374
H4	H5	2.869	H4	H5o	2.346
H4	H17A	3.560	H5	H5o	2.754
H5	H11B	3.494	H5	H18B	2.384
H7	H11A	2.258	H7	H11B	2.854
H7	H13B	3.426	H11B	H12A	2.415
H11B	H12B	3.347	H12A	H13C	3.575
H12A	H20B	3.375	H12B	H13A	2.624
H12B	H13C	2.996	H12C	H13A	3.051
H12C	H13B	3.578	H12C	H13C	2.508
H17A	H18C	3.571	H17B	H18A	2.590
H17B	H18C	2.999	H17C	H18A	3.016

Table 11. Intramolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H17C	H18B	3.573	H17C	H18C	2.504
H20A	H21A	2.273	H20A	H21B	2.788
H20A	H21C	2.283	H20B	H21A	2.788
H20B	H21B	2.291	H20B	H21C	2.266

Table 12. Intermolecular contacts less than 3.60 Å

atom	atom	distance	atom	atom	distance
O5	$O8^{1}$	2.932(4)	O6	$O16^{2}$	2.744(3)
O6	$C17^{2}$	3.510(5)	O8	$O5^{2}$	2.932(4)
O10	$C7^{3}$	3.501(5)	O10	$C21^{4}$	3.569(7)
O16	$O6^{1}$	2.744(3)	O16	$O19^{1}$	3.532(5)
O19	$O16^{2}$	3.532(5)	O19	$C17^{2}$	3.405(5)
O19	$C18^{5}$	3.533(5)	C7	$O10^{4}$	3.501(5)
C17	$O6^{1}$	3.510(5)	C17	$O19^{1}$	3.405(5)
C17	$C18^{6}$	3.493(6)	C18	$O19^{7}$	3.533(5)
C18	$C17^{8}$	3.493(6)	C21	$O10^{3}$	3.569(7)

Symmetry Operators:

(1) -X+2,Y+1/2-1,-Z+1/2+1

(2) -X+2,Y+1/2,-Z+1/2+1

(3) X+1/2-1,-Y+1/2,-Z+1

(4) X+1/2,-Y+1/2,-Z+1

(5) -X+1/2+1,-Y,Z+1/2

(6) X+1/2,-Y+1/2-1,-Z+1

(7) -X+1/2+1,-Y,Z+1/2-1

(8) X+1/2-1,-Y+1/2-1,-Z+1

Table 13. Intermolecular contacts less than 3.60 Å involving hydrogens

atom	atom	distance	atom	atom	distance
O1	H4[1]	3.492	O5	H2[2]	3.148
O5	H11A[3]	3.285	O5	H21C[4]	3.033
O6	H12C[2]	3.029	O6	H13C[2]	2.903
O6	H17A[1]	3.568	O6	H17C[1]	2.930
O6	H21C[5]	3.359	O8	H4[1]	3.310
O8	H5o[1]	2.01(4)	O8	H11B[6]	3.545
O10	H2[7]	3.495	O10	H3[7]	2.986
O10	H7[7]	2.638	O10	H21B[6]	2.692
O14	H12B[6]	3.439	O16	H6o[2]	1.82(3)
O16	H2[2]	3.400	O16	H21C[4]	3.175
O19	H13A[8]	2.954	O19	H17A[1]	2.733
O19	H17B[3]	3.054	O19	H17C[1]	3.259
O19	H17C[3]	3.575	O19	H18A[3]	2.860
O19	H18C[3]	3.395	O20	H17B[3]	3.529
C2	H5o[1]	3.34(5)	C2	H21C[5]	3.443
C4	H6o[2]	2.933(15)	C4	H12C[2]	3.574
C7	H5o[1]	3.10(5)	C7	H11B[6]	3.418
C9	H3[7]	3.589	C9	H5o[1]	3.04(4)
C9	H7[7]	3.589	C11	H7[7]	2.916
C11	H21B[6]	3.342	C12	H4[1]	3.321
C12	H5o[1]	3.51(3)	C12	H7[7]	3.471
C12	H17A[7]	3.511	C12	H21A[9]	3.324

C13	H3[7]	3.580	C13	H5o[1]	3.35(4)
C13	H17A[7]	3.460	C13	H17C[10]	3.002
C13	H18A[6]	3.296	C13	H18B[6]	3.207
C15	H6o[2]	2.74(3)	C17	H6o[2]	2.79(4)
C17	H12B[6]	3.098	C17	H13A[6]	3.580
C17	H13C[11]	3.181	C17	H18A[12]	3.296
C17	H18C[12]	2.972	C17	H20A[13]	3.051
C18	H6o[2]	3.52(4)	C18	H13B[7]	3.172
C18	H13C[7]	3.353	C18	H17A[14]	3.299
C18	H17B[14]	3.565	C18	H17C[14]	3.060
C18	H20A[4]	3.212	C19	H17B[3]	3.458
C19	H18A[3]	3.432	C20	H17B[3]	3.168
C20	H18B[9]	3.300	C20	H18C[9]	3.507
C21	H2[15]	3.134	C21	H12C[4]	3.395
H6o	O16[1]	1.82(3)	H6o	C4[1]	2.933(15)

Table 13. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H6o	C15[1]	2.74(3)	H6o	C17[1]	2.79(4)
H6o	C18[1]	3.52(4)	H6o	H4[1]	2.945
H6o	H12C[2]	3.567	H6o	H13C[2]	3.131
H6o	H17A[1]	2.809	H6o	H17C[1]	2.435
H6o	H18C[1]	3.245	H6o	H21C[5]	3.291
H2	O5[1]	3.148	H2	O10[6]	3.495
H2	O16[1]	3.400	H2	C21[5]	3.134
H2	H4[1]	3.592	H2	H5o[1]	2.806
H2	H21A[5]	3.325	H2	H21B[5]	3.148
H2	H21C[5]	2.472	H3	O10[6]	2.986
H3	C9[6]	3.589	H3	C13[6]	3.580
H3	H12B[6]	3.094	H3	H13A[6]	2.825
H3	H21A[5]	3.413	H3	H21B[5]	3.518
H4	O1[2]	3.492	H4	O8[2]	3.310
H4	C12[2]	3.321	H4	H6o[2]	2.945
H4	H2[2]	3.592	H4	H12A[2]	3.281
H4	H12C[2]	2.622	H4	H21A[5]	3.419
H5	H20B[4]	3.380	H5	H21C[4]	3.459
H5o	O8[2]	2.01(4)	H5o	C2[2]	3.34(5)
H5o	C7[2]	3.10(5)	H5o	C9[2]	3.04(4)

H5o	C12[2]	3.51(3)	H5o	C13[2]	3.35(4)
H5o	H2[2]	2.806	H5o	H7[2]	3.413
H5o	H11A[3]	3.322	H5o	H12C[2]	3.111
H5o	H13B[2]	3.489	H5o	H13C[2]	2.959
H5o	H18A[3]	3.596	H5o	H21C[4]	3.462
H7	O10[6]	2.638	H7	C9[6]	3.589
H7	C11[6]	2.916	H7	C12[6]	3.471
H7	H5o[1]	3.413	H7	H11A[6]	3.137
H7	H11B[6]	2.557	H7	H12A[6]	3.276
H7	H12B[6]	3.097	H11A	O5[13]	3.285
H11A	H5o[13]	3.322	H11A	H7[7]	3.137
H11A	H21B[6]	3.009	H11B	O8[7]	3.545
H11B	C7[7]	3.418	H11B	H7[7]	2.557
H11B	H13B[7]	3.404	H12A	H4[1]	3.281
H12A	H7[7]	3.276	H12A	H21A[9]	3.418
H12B	O14[7]	3.439	H12B	C17[7]	3.098
H12B	H3[7]	3.094	H12B	H7[7]	3.097

Table 13. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H12B	H17A^{7}	2.673	H12B	H17B^{7}	2.686
H12B	H18C^{10}	3.485	H12B	H20A^{9}	3.378
H12B	H21A^{9}	3.352	H12C	O6^{1}	3.029
H12C	C4^{1}	3.574	H12C	C21^{9}	3.395
H12C	H6o^{1}	3.567	H12C	H4^{1}	2.622
H12C	H5o^{1}	3.111	H12C	H18C^{10}	3.415
H12C	H20A^{9}	3.534	H12C	H21A^{9}	2.703
H12C	H21C^{9}	3.298	H13A	O19^{16}	2.954
H13A	C17^{7}	3.580	H13A	H3^{7}	2.825
H13A	H17A^{7}	2.623	H13A	H17C^{10}	3.080
H13A	H18B^{6}	3.535	H13A	H18C^{10}	3.266
H13A	H21B^{6}	3.568	H13B	C18^{6}	3.172
H13B	H5o^{1}	3.489	H13B	H11B^{6}	3.404
H13B	H17C^{10}	3.355	H13B	H18A^{6}	2.909
H13B	H18B^{6}	2.557	H13B	H21B^{6}	3.169
H13C	O6^{1}	2.903	H13C	C17^{10}	3.181
H13C	C18^{6}	3.353	H13C	H6o^{1}	3.131
H13C	H5o^{1}	2.959	H13C	H17B^{10}	3.565
H13C	H17C^{10}	2.211	H13C	H18A^{6}	2.786
H13C	H18B^{6}	3.096	H13C	H18C^{10}	3.122
H17A	O6^{2}	3.568	H17A	O19^{2}	2.733
H17A	C12^{6}	3.511	H17A	C13^{6}	3.460
H17A	C18^{12}	3.299	H17A	H6o^{2}	2.809

H17A	H12B^{6}	2.673	H17A	H13A^{6}	2.623
H17A	H18A^{12}	3.108	H17A	H18C^{12}	2.655
H17A	H20A^{13}	3.421	H17B	O19^{13}	3.054
H17B	O20^{13}	3.529	H17B	C18^{12}	3.565
H17B	C19^{13}	3.458	H17B	C20^{13}	3.168
H17B	H12B^{6}	2.686	H17B	H13C^{11}	3.565
H17B	H18B^{12}	3.594	H17B	H18C^{12}	2.948
H17B	H20A^{13}	2.246	H17C	O6^{2}	2.930
H17C	O19^{2}	3.259	H17C	O19^{13}	3.575
H17C	C13^{11}	3.002	H17C	C18^{12}	3.060
H17C	H6o^{2}	2.435	H17C	H13A^{11}	3.080
H17C	H13B^{11}	3.355	H17C	H13C^{11}	2.211
H17C	H18A^{12}	2.705	H17C	H18B^{12}	3.164
H17C	H18C^{12}	2.812	H17C	H20A^{13}	3.131

Table 13. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H18A	O19[13]	2.860	H18A	C13[7]	3.296
H18A	C17[14]	3.296	H18A	C19[13]	3.432
H18A	H5o[13]	3.596	H18A	H13B[7]	2.909
H18A	H13C[7]	2.786	H18A	H17A[14]	3.108
H18A	H17C[14]	2.705	H18B	C13[7]	3.207
H18B	C20[4]	3.300	H18B	H13A[7]	3.535
H18B	H13B[7]	2.557	H18B	H13C[7]	3.096
H18B	H17B[14]	3.594	H18B	H17C[14]	3.164
H18B	H20A[4]	2.791	H18B	H20B[4]	3.018
H18B	H21C[4]	3.267	H18C	O19[13]	3.395
H18C	C17[14]	2.972	H18C	C20[4]	3.507
H18C	H6o[2]	3.245	H18C	H12B[11]	3.485
H18C	H12C[11]	3.415	H18C	H13A[11]	3.266
H18C	H13C[11]	3.122	H18C	H17A[14]	2.655
H18C	H17B[14]	2.948	H18C	H17C[14]	2.812
H18C	H20A[4]	2.747	H18C	H21C[4]	3.230
H20A	C17[3]	3.051	H20A	C18[9]	3.212
H20A	H12B[4]	3.378	H20A	H12C[4]	3.534
H20A	H17A[3]	3.421	H20A	H17B[3]	2.246
H20A	H17C[3]	3.131	H20A	H18B[9]	2.791
H20A	H18C[9]	2.747	H20B	H5[9]	3.380
H20B	H18B[9]	3.018	H21A	C12[4]	3.324
H21A	H2[15]	3.325	H21A	H3[15]	3.413

H21A	H4[15]	3.419	H21A	H12A[4]	3.418
H21A	H12B[4]	3.352	H21A	H12C[4]	2.703
H21B	O10[7]	2.692	H21B	C11[7]	3.342
H21B	H2[15]	3.148	H21B	H3[15]	3.518
H21B	H11A[7]	3.009	H21B	H13A[7]	3.568
H21B	H13B[7]	3.169	H21C	O5[9]	3.033
H21C	O6[15]	3.359	H21C	O16[9]	3.175
H21C	C2[15]	3.443	H21C	H6o[15]	3.291
H21C	H2[15]	2.472	H21C	H5[9]	3.459
H21C	H5o[9]	3.462	H21C	H12C[4]	3.298
H21C	H18B[9]	3.267	H21C	H18C[9]	3.230

Symmetry Operators:

(1) -X+2,Y+1/2,-Z+1/2+1

(2) -X+2,Y+1/2-1,-Z+1/2+1

(3) -X+1/2+1,-Y,Z+1/2

(4) -X+1,Y+1/2-1,-Z+1/2+1

(5) X+1,Y,Z

(6) X+1/2,-Y+1/2,-Z+1

(7) X+1/2-1,-Y+1/2,-Z+1

(8) -X+1/2+1,-Y+1,Z+1/2

(9) -X+1,Y+1/2,-Z+1/2+1

(10) X,Y+1,Z

(11) X,Y-1,Z

(12) X+1/2,-Y+1/2-1,-Z+1

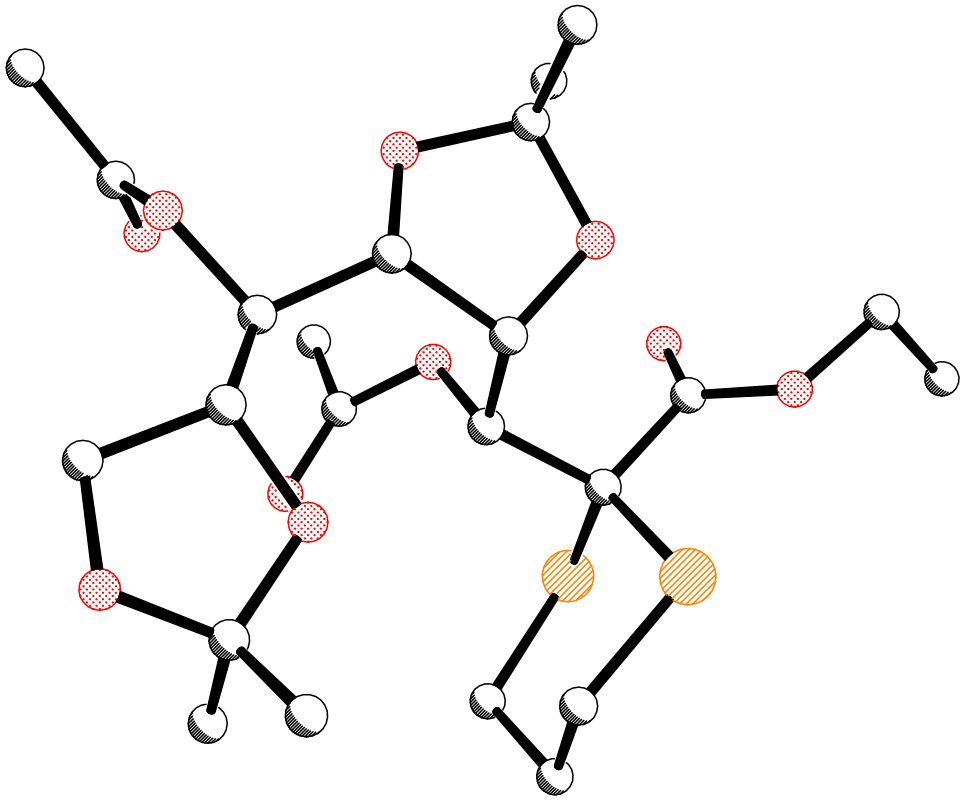
(13) -X+1/2+1,-Y,Z+1/2-1

(14) X+1/2-1,-Y+1/2-1,-Z+1

(15) X-1,Y,Z

(16) -X+1/2+1,-Y+1,Z+1/2-1

X-ray Structure Report for compound 158



Experimental

Data Collection

A colorless prism crystal of $C_{23}H_{36}O_{10}S_2$ having approximate dimensions of 0.200 x 0.200 x 0.180 mm was mounted in a loop. All measurements were made on a Rigaku Mercury70 diffractometer Mo-Kα radiation.

Cell constants and an orientation matrix for data collection corresponded to a primitive orthorhombic cell with dimensions:

a = 10.505(3) Å

b = 14.468(3) Å

c = 17.268(4) Å

V = 2624.6(9) $Å^3$

For Z = 4 and F.W. = 536.65, the calculated density is 1.358 g/cm^3. The reflection conditions of:

h00: h = 2n

0k0: k = 2n

00l: l = 2n

uniquely determine the space group to be:

$P2_12_12_1$ (#19)

The data were collected at a temperature of -180 ± 1°C to a maximum 2θ value of 50.7°.

Data Reduction

Of the 16354 reflections that were collected, 4769 were unique (R_{int} = 0.0734); equivalent reflections were merged. Data were collected and processed using CrystalClear (Rigaku).

The linear absorption coefficient, μ, for Mo-Kα radiation is 2.552 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.658 to 0.955. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[2] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement[3] on F^2 was based on 4769 observed reflections and 316 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.0435$$

$$wR2 = [\Sigma (w (Fo^2 - Fc^2)^2) / \Sigma \, w(Fo^2)^2]^{1/2} = 0.1340$$

The standard deviation of an observation of unit weight[4] was 1.11. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.42 and -0.63 $e^-/Å^3$, respectively. The absolute structure was deduced based on Flack parameter, 0.04(8), using 2064 Friedel pairs.[5]

Neutral atom scattering factors were taken from Cromer and Waber[6]. Anomalous dispersion effects were included in Fcalc[7]; the values for Δf' and Δf'' were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[9]. All calculations were performed using the CrystalStructure[10] crystallographic software package except for refinement, which was performed using SHELXL-97[11].

References

(1) CrystalClear: Rigaku Corporation, 1999. CrystalClear Software User's Guide, Molecular Structure Corporation, (c) 2000.J.W.Pflugrath (1999) Acta Cryst. D55, 1718-1725.

(2) SIR2004: M.C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G.L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna (2005)

(3) Least Squares function minimized: (SHELXL97)

$\Sigma w(F_o^2-F_c^2)^2$ where w = Least Squares weights.

(4) Standard deviation of an observation of unit weight:

$[\Sigma w(F_o^2-F_c^2)^2/(N_o-N_v)]^{1/2}$

where: N_O = number of observations

N_V = number of variables

(5) Flack, H. D. (1983), Acta Cryst. A39, 876-881.

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(9) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(10) CrystalStructure 4.0: Crystal Structure Analysis Package, Rigaku Corporation (2000-2010). Tokyo 196-8666, Japan.

(11) SHELX97: Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{23}H_{36}O_{10}S_2$
Formula Weight	536.65
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.200 X 0.200 X 0.180 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 10.505(3) Å b = 14.468(3) Å c = 17.268(4) Å V = 2624.6(9) $Å^3$
Space Group	$P2_12_12_1$ (#19)

Z value	4
D_{calc}	1.358 g/cm^3
F_{000}	1144.00
μ(MoKα)	2.552 cm^{-1}

B. Intensity Measurements

Diffractometer	Mercury70
Radiation	MoKα (λ = 0.71075 Å)
Voltage, Current	50kV, 16mA
Temperature	-180.0°C
Detector Aperture	70 x 70 mm
Pixel Size	0.068 mm
$2\theta_{max}$	50.7°
No. of Reflections Measured	Total: 16354 Unique: 4769 (R_{int} = 0.0734) Friedel pairs: 2064
Corrections	Lorentz-polarization Absorption (trans. factors: 0.658 - 0.955)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\ \sigma^2(Fo^2) + (0.0837 \cdot P)^2 + 0.2810 \cdot P\ ]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	50.7^o
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	4769
No. Variables	316
Reflection/Parameter Ratio	15.09
Residuals: R1 ($I>2.00\sigma(I)$)	0.0435

Residuals: R (All reflections)	0.0482
Residuals: wR2 (All reflections)	0.1340
Goodness of Fit Indicator	1.110
Flack Parameter (Friedel pairs = 2064)	0.04(8)
Max Shift/Error in Final Cycle	0.002
Maximum peak in Final Diff. Map	0.42 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.63 $e^-/Å^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
S20	0.49355(7)	0.98225(5)	0.79422(4)	1.43(2)
S24	0.57206(7)	0.80565(5)	0.87725(4)	1.46(2)
O1	-0.0725(2)	0.76218(13)	0.79921(10)	1.37(4)
O5	0.3253(2)	0.72887(13)	0.80835(9)	1.25(4)
O6	0.0188(3)	0.6328(2)	0.84776(12)	2.21(4)
O8	0.1064(2)	0.9539(2)	0.87881(11)	1.70(4)
O10	-0.0630(2)	0.9843(2)	0.95888(11)	1.80(4)
O14	0.1181(2)	0.74709(13)	0.69612(10)	1.31(4)
O16	0.2966(2)	0.8310(2)	0.66748(10)	1.45(4)
O25	0.5574(2)	0.73224(13)	0.71848(11)	1.71(4)
O26	0.5744(2)	0.87864(13)	0.67513(10)	1.51(4)
O29	0.2753(2)	0.7287(2)	0.93588(10)	1.54(4)
C2	0.0417(3)	0.8144(2)	0.8158(2)	1.18(5)
C3	0.1111(3)	0.8308(2)	0.7393(2)	1.08(5)
C4	0.2504(3)	0.8639(2)	0.7411(2)	1.24(5)
C5	0.3338(3)	0.8278(2)	0.8067(2)	1.15(5)
C6	-0.0693(3)	0.6701(2)	0.8168(2)	1.50(5)
C7	-0.0034(3)	0.9047(2)	0.8508(2)	1.49(5)
C9	0.0690(3)	1.0025(2)	0.9487(2)	1.55(5)
C11	-0.0867(3)	0.8972(2)	0.9220(2)	1.89(6)
C12	0.1444(3)	0.9656(3)	1.0167(2)	2.08(6)
C13	0.0874(3)	1.1048(2)	0.9352(2)	1.84(5)
C15	0.2087(3)	0.7647(2)	0.6359(2)	1.39(5)

C17	0.1439(3)	0.8087(3)	0.5658(2)	1.78(6)
C18	0.2769(3)	0.6757(2)	0.6177(2)	1.87(5)
C19	0.4768(3)	0.8561(2)	0.7990(2)	1.33(5)
C21	0.4472(3)	1.0157(2)	0.8912(2)	1.68(5)
C22	0.5312(4)	0.9748(3)	0.9546(2)	2.01(6)
C23	0.5173(3)	0.8699(2)	0.9615(2)	1.81(5)
C25	0.5390(3)	0.8138(2)	0.7259(2)	1.40(5)
C26	0.6426(3)	0.8457(2)	0.6075(2)	1.63(5)
C27	0.7832(3)	0.8377(3)	0.6233(2)	2.21(6)
C28	-0.1898(4)	0.6235(2)	0.7926(2)	2.14(6)
C29	0.3024(3)	0.6871(2)	0.8771(2)	1.41(5)
C30	0.3130(3)	0.5849(2)	0.8683(2)	1.89(5)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

Table 2. Atomic coordinates and B_{iso} involving hydrogen atoms

atom	x	y	z	B_{iso}
H2	0.0974	0.7802	0.8530	1.42
H3	0.0606	0.8764	0.7085	1.29
H4	0.2522	0.9330	0.7415	1.49
H5	0.3004	0.8525	0.8568	1.38
H7	-0.0476	0.9424	0.8103	1.79
H11A	-0.1776	0.8902	0.9079	2.27
H11B	-0.0606	0.8448	0.9553	2.27
H12A	0.1317	0.8987	1.0208	2.50
H12B	0.1154	0.9956	1.0644	2.50
H12C	0.2350	0.9787	1.0088	2.50
H13A	0.0553	1.1393	0.9799	2.21
H13B	0.0408	1.1235	0.8886	2.21
H13C	0.1782	1.1179	0.9283	2.21
H17A	0.1052	0.8676	0.5812	2.13
H17B	0.0778	0.7671	0.5463	2.13
H17C	0.2072	0.8197	0.5252	2.13
H18A	0.2150	0.6291	0.6010	2.24
H18B	0.3213	0.6538	0.6641	2.24
H18C	0.3388	0.6864	0.5762	2.24
H21A	0.4499	1.0839	0.8951	2.02
H21B	0.3582	0.9959	0.9002	2.02
H22A	0.5085	1.0036	1.0048	2.41
H22B	0.6212	0.9900	0.9435	2.41

H23A	0.4265	0.8551	0.9706	2.17
H23B	0.5657	0.8488	1.0074	2.17
H26A	0.6287	0.8889	0.5639	1.96
H26B	0.6088	0.7845	0.5922	1.96
H27A	0.7973	0.7941	0.6659	2.65
H27B	0.8171	0.8985	0.6377	2.65
H27C	0.8267	0.8155	0.5767	2.65
H28A	-0.2317	0.5970	0.8381	2.57
H28B	-0.1703	0.5743	0.7555	2.57
H28C	-0.2465	0.6688	0.7682	2.57
H30A	0.2311	0.5561	0.8809	2.27
H30B	0.3787	0.5615	0.9035	2.27
H30C	0.3362	0.5700	0.8148	2.27

Table 3. Anisotropic displacement parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S20	0.0181(4)	0.0147(4)	0.0214(4)	-0.0026(3)	0.0024(3)	-0.0019(3)
S24	0.0158(4)	0.0211(4)	0.0187(4)	0.0015(3)	-0.0028(3)	-0.0006(3)
O1	0.0140(10)	0.0167(10)	0.0213(9)	-0.0037(8)	-0.0005(9)	0.0007(8)
O5	0.0185(10)	0.0143(10)	0.0148(9)	0.0003(8)	0.0003(9)	-0.0002(7)
O6	0.0277(13)	0.0229(11)	0.0333(11)	-0.0010(10)	-0.0077(11)	0.0038(9)
O8	0.0176(11)	0.0208(10)	0.0262(10)	-0.0047(9)	0.0063(9)	-0.0107(8)
O10	0.0163(10)	0.0259(11)	0.0262(10)	-0.0025(10)	0.0049(9)	-0.0103(9)
O14	0.0176(10)	0.0186(11)	0.0134(8)	-0.0040(8)	0.0032(8)	-0.0017(8)
O16	0.0148(10)	0.0222(11)	0.0180(9)	-0.0039(9)	0.0010(8)	-0.0021(8)
O25	0.0231(11)	0.0163(11)	0.0256(10)	0.0027(9)	0.0047(9)	-0.0045(8)
O26	0.0204(11)	0.0184(10)	0.0187(9)	-0.0018(9)	0.0051(9)	0.0012(8)
O29	0.0214(11)	0.0226(11)	0.0145(9)	0.0012(9)	0.0009(9)	0.0006(8)
C2	0.0110(13)	0.020(2)	0.0136(12)	-0.0022(11)	-0.0025(10)	-0.0004(10)
C3	0.016(2)	0.0111(13)	0.0135(11)	0.0005(11)	-0.0008(11)	-0.0025(10)

C4	0.018(2)	0.0125(13)	0.0166(12)	-0.0008(12)	0.0015(12)	0.0004(10)
C5	0.0153(13)	0.0119(13)	0.0166(12)	-0.0031(11)	-0.0006(12)	0.0009(10)
C6	0.023(2)	0.021(2)	0.0128(12)	0.0000(13)	0.0003(13)	-0.0033(11)
C7	0.015(2)	0.0169(13)	0.025(2)	-0.0018(12)	0.0010(13)	-0.0028(11)
C9	0.017(2)	0.024(2)	0.0179(13)	-0.0014(13)	0.0064(12)	-0.0035(11)
C11	0.017(2)	0.028(2)	0.027(2)	-0.002(2)	0.0058(13)	-0.0080(13)
C12	0.024(2)	0.035(2)	0.0203(13)	0.002(2)	0.0031(13)	0.0040(13)
C13	0.021(2)	0.023(2)	0.025(2)	0.0006(13)	0.000(2)	-0.0053(12)
C15	0.015(2)	0.020(2)	0.0167(12)	-0.0042(12)	0.0021(12)	-0.0015(11)
C17	0.026(2)	0.028(2)	0.0129(12)	-0.004(2)	-0.0019(12)	0.0010(12)
C18	0.022(2)	0.025(2)	0.024(2)	0.0006(13)	0.0047(13)	-0.0069(12)
C19	0.0135(13)	0.017(2)	0.0202(12)	0.0005(12)	0.0026(12)	0.0009(11)
C21	0.021(2)	0.021(2)	0.0222(13)	-0.0008(13)	0.0018(12)	-0.0033(12)
C22	0.026(2)	0.026(2)	0.024(2)	-0.001(2)	0.0019(13)	-0.0059(12)
C23	0.021(2)	0.026(2)	0.0219(13)	-0.000(2)	-0.0029(13)	-0.0053(12)
C25	0.012(2)	0.022(2)	0.0193(13)	-0.0027(12)	0.0005(11)	-0.0000(12)
C26	0.022(2)	0.024(2)	0.0151(12)	-0.0000(13)	-0.0018(12)	-0.0007(12)

C27	0.026(2)	0.034(2)	0.024(2)	0.007(2)	0.009(2)	-0.0005(13)
C28	0.029(2)	0.022(2)	0.031(2)	-0.005(2)	-0.003(2)	-0.0017(12)
C29	0.0102(13)	0.024(2)	0.020(2)	-0.0009(12)	-0.0027(11)	0.0057(12)
C30	0.031(2)	0.017(2)	0.023(2)	-0.001(2)	0.002(2)	0.0071(12)

The general temperature factor expression: $\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 4. Bond lengths (Å)

atom	atom	distance	atom	atom	distance
S20	C19	1.835(3)	S20	C21	1.810(3)
S24	C19	1.834(3)	S24	C23	1.820(3)
O1	C2	1.447(4)	O1	C6	1.367(4)
O5	C5	1.434(4)	O5	C29	1.354(3)
O6	C6	1.198(4)	O8	C7	1.439(4)
O8	C9	1.451(4)	O10	C9	1.422(4)
O10	C11	1.433(4)	O14	C3	1.424(4)
O14	C15	1.433(4)	O16	C4	1.442(3)
O16	C15	1.439(4)	O25	C25	1.202(4)
O26	C25	1.337(4)	O26	C26	1.451(4)
O29	C29	1.214(4)	C2	C3	1.527(4)
C2	C7	1.516(4)	C3	C4	1.541(4)
C4	C5	1.524(4)	C5	C19	1.563(4)
C6	C28	1.493(5)	C7	C11	1.513(4)

C9	C12	1.513(4)	C9	C13	1.511(5)
C15	C17	1.526(4)	C15	C18	1.507(4)
C19	C25	1.547(4)	C21	C22	1.525(5)
C22	C23	1.529(5)	C26	C27	1.506(5)
C29	C30	1.490(5)			

Table 5. Bond lengths involving hydrogens (Å)

atom	atom	distance	atom	atom	distance
C2	H2	1.000	C3	H3	1.000
C4	H4	1.000	C5	H5	1.000
C7	H7	1.000	C11	H11A	0.990
C11	H11B	0.990	C12	H12A	0.980
C12	H12B	0.980	C12	H12C	0.980
C13	H13A	0.980	C13	H13B	0.980
C13	H13C	0.980	C17	H17A	0.980
C17	H17B	0.980	C17	H17C	0.980
C18	H18A	0.980	C18	H18B	0.980
C18	H18C	0.980	C21	H21A	0.990
C21	H21B	0.990	C22	H22A	0.990
C22	H22B	0.990	C23	H23A	0.990
C23	H23B	0.990	C26	H26A	0.990
C26	H26B	0.990	C27	H27A	0.980
C27	H27B	0.980	C27	H27C	0.980
C28	H28A	0.980	C28	H28B	0.980
C28	H28C	0.980	C30	H30A	0.980
C30	H30B	0.980	C30	H30C	0.980

Table 6. Bond angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C19	S20	C21	101.45(13)	C19	S24	C23	102.30(14)
C2	O1	C6	116.4(3)	C5	O5	C29	118.3(2)
C7	O8	C9	107.6(2)	C9	O10	C11	106.1(3)
C3	O14	C15	105.3(2)	C4	O16	C15	109.8(2)
C25	O26	C26	115.8(3)	O1	C2	C3	107.8(2)
O1	C2	C7	105.6(3)	C3	C2	C7	111.1(3)
O14	C3	C2	110.2(2)	O14	C3	C4	103.0(2)
C2	C3	C4	119.0(2)	O16	C4	C3	101.5(2)
O16	C4	C5	110.4(3)	C3	C4	C5	117.1(3)
O5	C5	C4	108.7(2)	O5	C5	C19	108.9(3)
C4	C5	C19	113.5(3)	O1	C6	O6	123.9(3)
O1	C6	C28	110.9(3)	O6	C6	C28	125.2(3)
O8	C7	C2	108.0(3)	O8	C7	C11	103.0(3)
C2	C7	C11	116.3(3)	O8	C9	O10	106.1(3)
O8	C9	C12	109.4(3)	O8	C9	C13	108.1(3)
O10	C9	C12	110.5(3)	O10	C9	C13	109.0(3)
C12	C9	C13	113.5(3)	O10	C11	C7	101.4(3)
O14	C15	O16	105.6(2)	O14	C15	C17	110.7(3)
O14	C15	C18	108.3(3)	O16	C15	C17	108.0(3)
O16	C15	C18	110.1(3)	C17	C15	C18	113.8(3)
S20	C19	S24	112.13(15)	S20	C19	C5	110.93(19)

S20	C19	C25	108.49(19)	S24	C19	C5	110.90(18)
S24	C19	C25	102.27(18)	C5	C19	C25	111.8(3)
S20	C21	C22	113.9(2)	C21	C22	C23	112.7(3)
S24	C23	C22	114.5(2)	O25	C25	O26	125.0(3)
O25	C25	C19	123.0(3)	O26	C25	C19	112.0(3)
O26	C26	C27	111.3(3)	O5	C29	O29	123.6(3)
O5	C29	C30	109.9(3)	O29	C29	C30	126.5(3)

Table 7. Bond angles involving hydrogens (°)

atom	atom	atom	angle	atom	atom	atom	angle
O1	C2	H2	110.7	C3	C2	H2	110.7
C7	C2	H2	110.7	O14	C3	H3	108.1
C2	C3	H3	108.0	C4	C3	H3	108.1
O16	C4	H4	109.2	C3	C4	H4	109.2
C5	C4	H4	109.1	O5	C5	H5	108.5
C4	C5	H5	108.5	C19	C5	H5	108.5
O8	C7	H7	109.7	C2	C7	H7	109.7
C11	C7	H7	109.7	O10	C11	H11A	111.5
O10	C11	H11B	111.5	C7	C11	H11A	111.5
C7	C11	H11B	111.5	H11A	C11	H11B	109.3
C9	C12	H12A	109.5	C9	C12	H12B	109.5
C9	C12	H12C	109.5	H12A	C12	H12B	109.5
H12A	C12	H12C	109.5	H12B	C12	H12C	109.5
C9	C13	H13A	109.5	C9	C13	H13B	109.5
C9	C13	H13C	109.5	H13A	C13	H13B	109.5
H13A	C13	H13C	109.5	H13B	C13	H13C	109.5
C15	C17	H17A	109.5	C15	C17	H17B	109.5
C15	C17	H17C	109.5	H17A	C17	H17B	109.5
H17A	C17	H17C	109.5	H17B	C17	H17C	109.5
C15	C18	H18A	109.5	C15	C18	H18B	109.5
C15	C18	H18C	109.5	H18A	C18	H18B	109.5
H18A	C18	H18C	109.5	H18B	C18	H18C	109.5
S20	C21	H21A	108.8	S20	C21	H21B	108.8

C22	C21	H21A	108.8	C22	C21	H21B	108.8
H21A	C21	H21B	107.7	C21	C22	H22A	109.1
C21	C22	H22B	109.1	C23	C22	H22A	109.1
C23	C22	H22B	109.1	H22A	C22	H22B	107.8
S24	C23	H23A	108.6	S24	C23	H23B	108.6
C22	C23	H23A	108.6	C22	C23	H23B	108.6
H23A	C23	H23B	107.6	O26	C26	H26A	109.4
O26	C26	H26B	109.4	C27	C26	H26A	109.4
C27	C26	H26B	109.4	H26A	C26	H26B	108.0
C26	C27	H27A	109.5	C26	C27	H27B	109.5
C26	C27	H27C	109.5	H27A	C27	H27B	109.5
H27A	C27	H27C	109.5	H27B	C27	H27C	109.5
C6	C28	H28A	109.5	C6	C28	H28B	109.5
C6	C28	H28C	109.5	H28A	C28	H28B	109.5

Table 7. Bond angles involving hydrogens (°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
H28A	C28	H28C	109.5	H28B	C28	H28C	109.5
C29	C30	H30A	109.5	C29	C30	H30B	109.5
C29	C30	H30C	109.5	H30A	C30	H30B	109.5
H30A	C30	H30C	109.5	H30B	C30	H30C	109.5

Table 8. Torsion Angles(°)

(Those having bond angles > 160 or < 20 degrees are excluded.)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
C19	S20	C21	C22	60.4(2)	C21	S20	C19	S24	-56.30(17)
C21	S20	C19	C5	68.31(18)	C21	S20	C19	C25	-168.51(16)
C19	S24	C23	C22	-56.6(3)	C23	S24	C19	S20	54.75(18)
C23	S24	C19	C5	-69.86(18)	C23	S24	C19	C25	170.78(15)
C2	O1	C6	O6	3.7(4)	C2	O1	C6	C28	-176.66(17)
C6	O1	C2	C3	103.3(3)	C6	O1	C2	C7	-137.91(19)
C5	O5	C29	O29	8.1(4)	C5	O5	C29	C30	-173.02(19)
C29	O5	C5	C4	-131.3(2)	C29	O5	C5	C19	104.6(3)
C7	O8	C9	O10	-2.3(3)	C7	O8	C9	C12	116.9(3)
C7	O8	C9	C13	-119.1(2)	C9	O8	C7	C2	-144.8(2)
C9	O8	C7	C11	-21.1(3)	C9	O10	C11	C7	-39.0(3)
C11	O10	C9	O8	26.6(3)	C11	O10	C9	C12	-91.9(3)
C11	O10	C9	C13	142.84(19)	C3	O14	C15	O16	30.2(3)
C3	O14	C15	C17	-86.4(3)	C3	O14	C15	C18	148.11(18)
C15	O14	C3	C2	-166.89(18)	C15	O14	C3	C4	-39.0(3)
C4	O16	C15	O14	-8.4(3)	C4	O16	C15	C17	110.1(2)
C4	O16	C15	C18	-125.2(2)	C15	O16	C4	C3	-14.6(3)
C15	O16	C4	C5	110.2(3)	C25	O26	C26	C27	-86.0(3)

C26	O26	C25	O25	-1.5(4)	C26	O26	C25	C19	175.37(19)
O1	C2	C3	O14	-46.9(3)	O1	C2	C3	C4	-165.51(19)
O1	C2	C7	O8	171.74(18)	O1	C2	C7	C11	56.6(3)
C3	C2	C7	O8	-71.6(3)	C3	C2	C7	C11	173.2(2)
C7	C2	C3	O14	-162.2(2)	C7	C2	C3	C4	79.2(3)
O14	C3	C4	O16	32.5(3)	O14	C3	C4	C5	-87.7(3)
C2	C3	C4	O16	154.8(2)	C2	C3	C4	C5	34.5(4)
O16	C4	C5	O5	-63.0(3)	O16	C4	C5	C19	58.3(3)
C3	C4	C5	O5	52.4(3)	C3	C4	C5	C19	173.72(19)
O5	C5	C19	S20	178.64(16)	O5	C5	C19	S24	-56.1(3)
O5	C5	C19	C25	57.4(3)	C4	C5	C19	S20	57.4(3)
C4	C5	C19	S24	-177.28(18)	C4	C5	C19	C25	-63.8(3)
O8	C7	C11	O10	36.5(3)	C2	C7	C11	O10	154.4(3)
S20	C19	C25	O25	169.7(2)	S20	C19	C25	O26	-7.3(3)
S24	C19	C25	O25	51.0(3)	S24	C19	C25	O26	-125.95(18)
C5	C19	C25	O25	-67.7(3)	C5	C19	C25	O26	115.3(3)
S20	C21	C22	C23	-67.4(3)	C21	C22	C23	S24	65.1(3)

Table 9. Intramolecular contacts less than 3.60 Å

atom	atom	distance	atom	atom	distance
S20	O26	2.683(2)	S20	C4	3.209(3)
S20	C23	3.324(3)	S24	O5	3.061(2)
S24	O25	2.944(2)	S24	O29	3.461(3)
S24	C21	3.318(4)	S24	C29	3.312(3)
O1	O14	2.689(3)	O1	C11	2.887(4)
O5	O6	3.573(3)	O5	O14	2.926(3)
O5	O16	2.862(3)	O5	O25	2.891(3)
O5	C2	3.228(4)	O5	C3	2.943(4)
O5	C15	3.262(4)	O5	C18	3.419(4)
O5	C25	2.928(4)	O6	O14	3.268(3)
O6	O29	3.392(3)	O6	C2	2.695(4)
O6	C3	3.557(4)	O6	C29	3.122(4)
O6	C30	3.187(4)	O8	C3	2.996(4)
O8	C4	3.104(4)	O8	C5	3.254(4)

O14	C5	3.185(4)	O14	C6	3.076(4)
O16	O25	3.213(3)	O16	O26	3.001(3)
O16	C19	2.978(4)	O16	C25	2.750(4)
O25	C5	3.122(4)	O25	C18	3.519(4)
O25	C26	2.678(4)	O25	C27	3.264(4)
O26	C4	3.595(4)	O26	C5	3.477(4)
O29	C2	3.444(4)	O29	C5	2.721(4)
O29	C23	3.291(4)	C2	C5	3.079(4)
C2	C9	3.572(4)	C2	C29	3.466(4)
C3	C6	3.284(4)	C3	C17	3.032(4)
C3	C18	3.533(4)	C4	C7	3.323(4)
C4	C17	3.324(4)	C4	C18	3.468(4)
C4	C25	3.128(4)	C4	C29	3.515(4)
C5	C15	3.357(4)	C5	C21	3.307(4)
C5	C23	3.351(4)	C6	C7	3.513(4)
C7	C12	3.376(4)	C7	C13	3.379(5)
C11	C12	3.090(5)	C11	C13	3.523(5)

C19	C22	3.240(4)	C19	C29	3.341(4)
C25	C27	3.137(4)			

Table 10. Intramolecular contacts less than 3.60 Å involving hydrogens

atom	atom	distance	atom	atom	distance
S20	H4	2.787	S20	H5	2.968
S20	H22B	2.907	S24	H5	2.955
S24	H21B	3.575	S24	H22B	2.947
O1	H3	2.672	O1	H7	2.627
O1	H11A	2.859	O1	H11B	2.951
O1	H28A	2.994	O1	H28B	3.003
O1	H28C	2.335	O5	H2	2.623
O5	H4	3.263	O5	H18B	2.718
O5	H23A	3.509	O5	H30A	2.966
O5	H30B	2.980	O5	H30C	2.305
O6	H2	2.288	O6	H28A	2.687
O6	H28B	2.683	O6	H28C	3.150
O6	H30A	2.556	O6	H30C	3.503
O8	H2	2.554	O8	H3	3.184
O8	H4	2.840	O8	H5	2.539
O8	H11A	3.162	O8	H11B	2.703
O8	H12A	2.592	O8	H12B	3.262
O8	H12C	2.644	O8	H13A	3.246
O8	H13B	2.555	O8	H13C	2.632
O8	H21B	2.740	O10	H7	2.641
O10	H12A	2.619	O10	H12B	2.619
O10	H12C	3.249	O10	H13A	2.589
O10	H13B	2.592	O10	H13C	3.231

O14	H2	2.760	O14	H4	3.135
O14	H17A	2.645	O14	H17B	2.638
O14	H17C	3.270	O14	H18A	2.578
O14	H18B	2.585	O14	H18C	3.230
O16	H3	2.661	O16	H5	3.284
O16	H17A	2.558	O16	H17B	3.244
O16	H17C	2.636	O16	H18A	3.253
O16	H18B	2.578	O16	H18C	2.657
O16	H26B	3.592	O25	H18B	2.885
O25	H18C	3.428	O25	H26A	3.582
O25	H26B	2.371	O25	H27A	2.824
O26	H27A	2.647	O26	H27B	2.646
O26	H27C	3.279	O29	H2	2.469
O29	H5	2.268	O29	H12A	3.237

Table 10. Intramolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
O29	H23A	2.494	O29	H30A	2.712
O29	H30B	2.710	O29	H30C	3.171
C2	H4	3.079	C2	H5	2.862
C2	H11A	3.008	C2	H11B	2.674
C3	H5	2.858	C3	H7	2.625
C3	H17A	2.783	C3	H17B	3.477
C4	H2	2.790	C4	H7	3.539
C4	H17A	3.156	C4	H18B	3.400
C4	H21B	3.532	C5	H2	2.699
C5	H3	3.408	C5	H18B	3.524
C5	H21B	2.930	C5	H23A	3.018
C6	H2	2.448	C6	H11B	3.481
C7	H3	2.579	C7	H4	3.308
C7	H5	3.281	C7	H12A	3.263
C7	H13B	3.266	C9	H7	2.823
C9	H11A	3.137	C9	H11B	2.659
C9	H21B	3.153	C11	H2	2.833
C11	H12A	2.860	C11	H12B	3.547
C11	H13B	3.583	C12	H11B	2.969
C12	H13A	2.756	C12	H13B	3.360
C12	H13C	2.703	C12	H21B	3.047
C12	H23A	3.460	C13	H7	3.490
C13	H12A	3.360	C13	H12B	2.749

C13	H12C	2.710	C13	H21B	3.307
C15	H3	2.570	C15	H4	3.076
C17	H3	2.792	C17	H18A	2.771
C17	H18B	3.373	C17	H18C	2.712
C18	H17A	3.370	C18	H17B	2.765
C18	H17C	2.726	C19	H4	2.791
C19	H21B	2.949	C19	H22B	3.504
C19	H23A	3.010	C21	H4	3.509
C21	H5	2.882	C21	H12C	3.062
C21	H13C	3.253	C21	H23A	2.706
C21	H23B	3.377	C22	H5	3.444
C22	H12C	3.249	C23	H5	2.920
C23	H12C	3.454	C23	H21A	3.376
C23	H21B	2.690	C25	H4	3.482

Table 10. Intramolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
C25	H5	3.421	C25	H18B	3.424
C25	H26A	3.147	C25	H26B	2.461
C25	H27A	2.919	C25	H27B	3.515
C29	H2	2.574	C29	H5	2.420
C29	H23A	3.196	H2	H3	2.884
H2	H4	3.353	H2	H5	2.377
H2	H7	2.893	H2	H11A	3.432
H2	H11B	2.598	H2	H12A	3.386
H2	H30A	3.565	H3	H4	2.246
H3	H7	2.301	H3	H17A	2.252
H3	H17B	3.223	H4	H5	2.362
H4	H7	3.369	H4	H17A	3.307
H4	H21B	3.096	H5	H12A	3.407
H5	H12C	3.270	H5	H21B	2.288
H5	H23A	2.369	H7	H11A	2.297
H7	H11B	2.876	H7	H13B	3.091
H11B	H12A	2.443	H11B	H12B	3.425
H12A	H13C	3.584	H12A	H21B	3.461
H12A	H23A	3.277	H12B	H13A	2.617
H12B	H13C	3.015	H12C	H13A	3.036
H12C	H13B	3.586	H12C	H13C	2.519
H12C	H21A	3.356	H12C	H21B	2.292
H12C	H22A	2.897	H12C	H23A	2.771

H13C	H21A	2.952	H13C	H21B	2.631
H17A	H18C	3.591	H17B	H18A	2.637
H17B	H18C	3.025	H17C	H18A	3.054
H17C	H18B	3.600	H17C	H18C	2.531
H18B	H30C	2.876	H18C	H26B	3.184
H21A	H22A	2.306	H21A	H22B	2.405
H21A	H23A	3.566	H21B	H22A	2.402
H21B	H22B	2.863	H21B	H23A	2.478
H21B	H23B	3.565	H22A	H23A	2.389
H22A	H23B	2.319	H22B	H23A	2.866
H22B	H23B	2.394	H26A	H27A	2.850
H26A	H27B	2.358	H26A	H27C	2.347
H26B	H27A	2.358	H26B	H27B	2.850
H26B	H27C	2.348			

Table 11. Intermolecular contacts less than 3.60 Å

atom	atom	distance	atom	atom	distance
O1	C27[1]	3.566(4)	O6	C23[2]	3.294(4)
O10	C30[2]	3.406(4)	O25	C28[3]	3.341(4)
O26	C30[4]	3.297(4)	O29	C11[5]	3.383(4)
O29	C23[2]	3.539(4)	C11	O29[2]	3.383(4)
C23	O6[5]	3.294(4)	C23	O29[5]	3.539(4)
C26	C30[4]	3.517(5)	C27	O1[3]	3.566(4)
C28	O25[1]	3.341(4)	C30	O10[5]	3.406(4)
C30	O26[6]	3.297(4)	C30	C26[6]	3.517(5)

Symmetry Operators:

(1) X-1,Y,Z

(2) X+1/2-1,-Y+1/2+1,-Z+2

(3) X+1,Y,Z

(4) -X+1,Y+1/2,-Z+1/2+1

(5) X+1/2,-Y+1/2+1,-Z+2

(6) -X+1,Y+1/2-1,-Z+1/2+1

Table 12. Intermolecular contacts less than 3.60 Å involving hydrogens

atom	atom	distance	atom	atom	distance
S20	H18B[1]	3.234	S20	H30C[1]	2.890
S24	H11A[2]	2.949	S24	H12A[3]	3.498
S24	H28C[2]	3.331	O1	H27A[4]	2.717
O6	H22A[5]	3.223	O6	H23A[5]	3.289
O6	H23B[5]	2.563	O8	H28B[6]	2.977
O10	H18A[6]	2.830	O10	H22B[4]	3.329
O10	H26A[7]	2.670	O10	H30A[5]	3.560
O10	H30B[5]	2.541	O14	H13B[8]	2.851
O14	H27A[4]	3.478	O16	H12B[9]	3.212
O25	H21A[10]	2.908	O25	H28C[2]	2.413
O26	H12B[9]	3.308	O26	H30A[1]	3.421
O26	H30B[1]	3.014	O26	H30C[1]	2.928
O29	H11A[3]	3.237	O29	H11B[3]	2.763
O29	H23B[5]	2.659	C3	H27A[4]	3.572
C3	H28B[6]	3.578	C4	H28B[6]	3.159
C6	H23B[5]	3.362	C6	H27A[4]	3.460
C7	H28B[6]	3.566	C9	H26A[7]	3.276
C9	H30B[5]	3.371	C11	H22B[4]	3.369
C11	H30B[5]	3.093	C12	H17C[7]	3.478
C12	H28A[3]	2.967	C12	H30B[5]	3.138
C13	H17B[6]	2.937	C13	H17C[7]	2.875
C13	H18A[6]	3.257	C13	H26A[7]	3.178
C13	H27A[1]	3.466	C13	H27C[1]	3.186

C13	H28B^{6}	3.434	C15	H13B^{8}	3.350
C17	H12C^{9}	3.471	C17	H13A^{8}	3.318
C17	H13A^{9}	3.572	C17	H13B^{8}	3.401
C17	H13C^{9}	3.204	C17	H21A^{9}	3.476
C17	H22A^{9}	3.324	C17	H26B^{11}	3.066
C17	H27C^{4}	3.339	C18	H13B^{8}	3.423
C18	H21A^{10}	3.171	C18	H22B^{10}	3.080
C18	H27C^{11}	3.401	C21	H18B^{1}	3.289
C21	H18C^{1}	3.387	C22	H11A^{2}	3.392
C22	H17A^{7}	3.468	C22	H18C^{1}	3.394
C22	H30A^{3}	3.561	C23	H11A^{2}	3.349
C23	H11B^{3}	3.520	C25	H28C^{2}	3.164
C26	H13A^{9}	3.036	C26	H17B^{12}	3.190
C26	H17C^{12}	3.382	C26	H30A^{1}	3.327

Table 12. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
C26	H30B[1]	3.135	C26	H30C[1]	3.518
C27	H3[2]	3.311	C27	H13C[10]	3.328
C27	H17A[2]	3.487	C27	H17B[2]	3.520
C27	H17C[12]	3.522	C27	H18C[12]	3.512
C27	H28C[2]	3.512	C27	H30A[1]	3.164
C28	H4[8]	2.894	C28	H13B[8]	3.499
C28	H27A[4]	3.301	C29	H11B[3]	3.266
C29	H23B[5]	3.229	C30	H11B[3]	3.475
C30	H12B[3]	3.577	C30	H23B[5]	3.503
C30	H26A[10]	3.128	C30	H27B[10]	3.026
H2	H23B[5]	3.066	H3	C27[4]	3.311
H3	H27A[4]	3.100	H3	H27B[4]	2.853
H3	H27C[4]	3.463	H3	H28B[6]	3.148
H4	C28[6]	2.894	H4	H12B[9]	3.515
H4	H28A[6]	2.750	H4	H28B[6]	2.218
H4	H28C[6]	3.417	H7	H18A[6]	3.569
H7	H27B[4]	3.363	H7	H28B[6]	3.189
H11A	S24[4]	2.949	H11A	O29[5]	3.237
H11A	C22[4]	3.392	H11A	C23[4]	3.349
H11A	H18A[6]	3.482	H11A	H22B[4]	2.632
H11A	H23B[4]	3.253	H11A	H30B[5]	3.382
H11B	O29[5]	2.763	H11B	C23[5]	3.520
H11B	C29[5]	3.266	H11B	C30[5]	3.475

H11B	H23A[5]	3.167	H11B	H23B[5]	3.167
H11B	H30B[5]	2.862	H12A	S24[5]	3.498
H12A	H28A[3]	2.828	H12A	H30B[5]	3.017
H12B	O16[7]	3.212	H12B	O26[7]	3.308
H12B	C30[5]	3.577	H12B	H4[7]	3.515
H12B	H17A[7]	3.552	H12B	H17C[7]	3.328
H12B	H26A[7]	3.060	H12B	H28A[3]	2.685
H12B	H30B[5]	2.678	H12C	C17[7]	3.471
H12C	H17A[7]	3.054	H12C	H17C[7]	2.993
H12C	H28A[3]	2.883	H13A	C17[6]	3.318
H13A	C17[7]	3.572	H13A	C26[7]	3.036
H13A	H17B[6]	2.361	H13A	H17C[7]	2.682
H13A	H18A[6]	3.168	H13A	H18C[7]	3.219
H13A	H26A[7]	2.450	H13A	H26B[7]	2.818

Table 12. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H13A	H27C[1]	2.998	H13B	O14[6]	2.851
H13B	C15[6]	3.350	H13B	C17[6]	3.401
H13B	C18[6]	3.423	H13B	C28[6]	3.499
H13B	H17B[6]	2.670	H13B	H18A[6]	2.694
H13B	H26A[7]	3.515	H13B	H27A[1]	3.142
H13B	H27C[1]	3.164	H13B	H28B[6]	2.924
H13B	H28C[6]	3.527	H13C	C17[7]	3.204
H13C	C27[1]	3.328	H13C	H17A[7]	3.492
H13C	H17B[6]	3.476	H13C	H17C[7]	2.251
H13C	H26B[1]	3.307	H13C	H27A[1]	3.035
H13C	H27C[1]	2.860	H13C	H28B[6]	3.236
H13C	H28C[6]	3.545	H17A	C22[9]	3.468
H17A	C27[4]	3.487	H17A	H12B[9]	3.552
H17A	H12C[9]	3.054	H17A	H13C[9]	3.492
H17A	H21A[9]	3.340	H17A	H22A[9]	2.577
H17A	H27B[4]	3.212	H17A	H27C[4]	3.022
H17B	C13[8]	2.937	H17B	C26[11]	3.190
H17B	C27[4]	3.520	H17B	H13A[8]	2.361
H17B	H13B[8]	2.670	H17B	H13C[8]	3.476
H17B	H18C[11]	3.351	H17B	H21A[9]	3.398
H17B	H22A[9]	3.513	H17B	H26A[11]	2.999
H17B	H26B[11]	2.525	H17B	H27C[4]	2.779
H17B	H27C[11]	3.574	H17C	C12[9]	3.478

H17C	C13[9]	2.875	H17C	C26[11]	3.382
H17C	C27[11]	3.522	H17C	H12B[9]	3.328
H17C	H12C[9]	2.993	H17C	H13A[9]	2.682
H17C	H13C[9]	2.251	H17C	H21A[9]	3.117
H17C	H21B[9]	3.500	H17C	H22A[9]	3.434
H17C	H26A[11]	3.487	H17C	H26B[11]	2.729
H17C	H27C[11]	2.915	H18A	O10[8]	2.830
H18A	C13[8]	3.257	H18A	H7[8]	3.569
H18A	H11A[8]	3.482	H18A	H13A[8]	3.168
H18A	H13B[8]	2.694	H18A	H21A[10]	3.582
H18A	H22B[10]	2.758	H18A	H26A[11]	3.000
H18A	H27C[11]	3.383	H18B	S20[10]	3.234
H18B	C21[10]	3.289	H18B	H21A[10]	2.801
H18B	H22B[10]	3.071	H18C	C21[10]	3.387

Table 12. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H18C	C22[10]	3.394	H18C	C27[11]	3.512
H18C	H13A[9]	3.219	H18C	H17B[12]	3.351
H18C	H21A[10]	2.716	H18C	H22A[10]	3.394
H18C	H22B[10]	2.893	H18C	H26A[11]	3.451
H18C	H27C[11]	2.644	H21A	O25[1]	2.908
H21A	C17[7]	3.476	H21A	C18[1]	3.171
H21A	H17A[7]	3.340	H21A	H17B[7]	3.398
H21A	H17C[7]	3.117	H21A	H18A[1]	3.582
H21A	H18B[1]	2.801	H21A	H18C[1]	2.716
H21A	H26B[1]	2.975	H21B	H17C[7]	3.500
H21B	H28B[6]	3.523	H22A	O6[3]	3.223
H22A	C17[7]	3.324	H22A	H17A[7]	2.577
H22A	H17B[7]	3.513	H22A	H17C[7]	3.434
H22A	H18C[1]	3.394	H22A	H27B[13]	3.261
H22A	H27C[13]	3.375	H22A	H30A[3]	3.180
H22B	O10[2]	3.329	H22B	C11[2]	3.369
H22B	C18[1]	3.080	H22B	H11A[2]	2.632
H22B	H18A[1]	2.758	H22B	H18B[1]	3.071
H22B	H18C[1]	2.893	H22B	H30A[3]	3.313
H23A	O6[3]	3.289	H23A	H11B[3]	3.167
H23B	O6[3]	2.563	H23B	O29[3]	2.659
H23B	C6[3]	3.362	H23B	C29[3]	3.229
H23B	C30[3]	3.503	H23B	H2[3]	3.066

H23B	H11A[2]	3.253	H23B	H11B[3]	3.167
H23B	H30A[3]	2.938	H26A	O10[9]	2.670
H26A	C9[9]	3.276	H26A	C13[9]	3.178
H26A	C30[1]	3.128	H26A	H12B[9]	3.060
H26A	H13A[9]	2.450	H26A	H13B[9]	3.515
H26A	H17B[12]	2.999	H26A	H17C[12]	3.487
H26A	H18A[12]	3.000	H26A	H18C[12]	3.451
H26A	H30A[1]	2.988	H26A	H30B[1]	2.560
H26A	H30C[1]	3.374	H26B	C17[12]	3.066
H26B	H13A[9]	2.818	H26B	H13C[10]	3.307
H26B	H17B[12]	2.525	H26B	H17C[12]	2.729
H26B	H21A[10]	2.975	H27A	O1[2]	2.717
H27A	O14[2]	3.478	H27A	C3[2]	3.572
H27A	C6[2]	3.460	H27A	C13[10]	3.466

Table 12. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H27A	C28[2]	3.301	H27A	H3[2]	3.100
H27A	H13B[10]	3.142	H27A	H13C[10]	3.035
H27A	H28B[2]	3.553	H27A	H28C[2]	2.573
H27B	C30[1]	3.026	H27B	H3[2]	2.853
H27B	H7[2]	3.363	H27B	H17A[2]	3.212
H27B	H22A[14]	3.261	H27B	H30A[1]	2.359
H27B	H30B[1]	3.209	H27B	H30C[1]	3.070
H27C	C13[10]	3.186	H27C	C17[2]	3.339
H27C	C18[12]	3.401	H27C	H3[2]	3.463
H27C	H13A[10]	2.998	H27C	H13B[10]	3.164
H27C	H13C[10]	2.860	H27C	H17A[2]	3.022
H27C	H17B[2]	2.779	H27C	H17B[12]	3.574
H27C	H17C[12]	2.915	H27C	H18A[12]	3.383
H27C	H18C[12]	2.644	H27C	H22A[14]	3.375
H28A	C12[5]	2.967	H28A	H4[8]	2.750
H28A	H12A[5]	2.828	H28A	H12B[5]	2.685
H28A	H12C[5]	2.883	H28B	O8[8]	2.977
H28B	C3[8]	3.578	H28B	C4[8]	3.159
H28B	C7[8]	3.566	H28B	C13[8]	3.434
H28B	H3[8]	3.148	H28B	H4[8]	2.218
H28B	H7[8]	3.189	H28B	H13B[8]	2.924
H28B	H13C[8]	3.236	H28B	H21B[8]	3.523
H28B	H27A[4]	3.553	H28C	S24[4]	3.331

H28C	O25[4]	2.413	H28C	C25[4]	3.164
H28C	C27[4]	3.512	H28C	H4[8]	3.417
H28C	H13B[8]	3.527	H28C	H13C[8]	3.545
H28C	H27A[4]	2.573	H30A	O10[3]	3.560
H30A	O26[10]	3.421	H30A	C22[5]	3.561
H30A	C26[10]	3.327	H30A	C27[10]	3.164
H30A	H22A[5]	3.180	H30A	H22B[5]	3.313
H30A	H23B[5]	2.938	H30A	H26A[10]	2.988
H30A	H27B[10]	2.359	H30B	O10[3]	2.541
H30B	O26[10]	3.014	H30B	C9[3]	3.371
H30B	C11[3]	3.093	H30B	C12[3]	3.138
H30B	C26[10]	3.135	H30B	H11A[3]	3.382
H30B	H11B[3]	2.862	H30B	H12A[3]	3.017
H30B	H12B[3]	2.678	H30B	H26A[10]	2.560

Table 12. Intermolecular contacts less than 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H30B	H27B[10]	3.209	H30C	S20[10]	2.890
H30C	O26[10]	2.928	H30C	C26[10]	3.518
H30C	H26A[10]	3.374	H30C	H27B[10]	3.070

Symmetry Operators:

(1) -X+1,Y+1/2,-Z+1/2+1 (2) X+1,Y,Z

(3) X+1/2,-Y+1/2+1,-Z+2 (4) X-1,Y,Z

(5) X+1/2-1,-Y+1/2+1,-Z+2 (6) -X,Y+1/2,-Z+1/2+1

(7) -X+1/2,-Y+2,Z+1/2 (8) -X,Y+1/2-1,-Z+1/2+1

(9) -X+1/2,-Y+2,Z+1/2-1 (10) -X+1,Y+1/2-1,-Z+1/2+1

(11) X+1/2-1,-Y+1/2+1,-Z+1 (12) X+1/2,-Y+1/2+1,-Z+1

(13) -X+1/2+1,-Y+2,Z+1/2 (14) -X+1/2+1,-Y+2,Z+1/2-1