SYNTHETIC STUDIES OF THE BRYOSTATINS

JOHN A.A. LENNON

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CHRISTOPHER INGOLD LABORATORIES
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...... etc etc etc.').

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Well I don't believe it. Could this be a sexist comment?; Steve Corker and Don
('Three NMR's! How did he get that job? When I'm Head of The Department ......)
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Department' and/or 'Nobel Lauriate' are rated at zero. In fact, better odds can be
obtained on the National Lottery. Unfortunately, no-one has yet informed him that
his ingrained ability of being a complete and utter dickhead is not within the criteria.

Being an absolute twat is of no importance, honestly. Also unhappily, I predict
doom and gloom for his most burning and passionate project i.e. marrying the
Gold. No chance. Matrimonial thoughts of Gold making coffee and delivering the
latest copy of Tetrahedron Letters at the breakfast table is a definite pipedream.
for my parents
ABSTRACT

The bryostatins constitute a family of macrocyclic lactones, with potent antineoplastic properties, that have recently been isolated from the marine organism *Bugula neritina*.

This thesis discusses an asymmetric synthesis of an advanced intermediate corresponding to the C(17)-C(27) sector of bryostatin 1, starting from *trans-*1,4-hexadiene. A combination of a Sharpless asymmetric epoxidation and asymmetric dihydroxylation tactics were used to introduce the stereocentres at C(23) and C(26), C(25) and C(20) respectively, whilst substrate control introduced the fifth stereocentre at C(19).

Attempted syntheses of fragments of Bryostatin 1 and 11 are also discussed.
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GLOSSARY

PROTECTING GROUPS

Ac - Acetyl
Ali - Allyl
An - Anisyl
Bn - Benzyl
Bz - Benzoyl
DMPM - 3,4-Dimethoxybenzyl
MEM - Methoxyethoxymethyl
MOM - Methoxymethyl
MPM, PMB - p-Methoxybenzyl
Ms - Methanesulfonate (mesyl)
PMP - p-Methoxyphenyl
Pv - tert-Butylacetetyl (pivaloyl)
TBDPS - tert-Butyldiphenylsilyl
TBS - tert-Butyldimethylsilyl
TES - Triethylsilyl
THP - Tetrahydropyranyl
TMS - Trimethylsilyl
Ts - p-Toluenesulfonate (tosyl)

REAGENTS

AcCl - Acetyl chloride
Ac₂O - Acetic anhydride
AIBN - 2,2'-Azobisisobutyronitrile
BnBr - Benzyl bromide
BnCl - Benzyl chloride
CSA - Camphorsulfonic acid
DCC - Dicyclohexylcarbodiimide
DDQ - 2,3-Dichloro-5,6-dicyanobenzoquinone
DET - Diethyl tartrate
DHP - Dihydropyran
DIAD - Diisopropyl diazodicarboxylate
DIBAL - Diisobutylaluminium hydride
DIPT - Diisopropyl tartrate
DMAP - Dimethylaminopyridine
DMPMCl - 3,4-Dimethoxybenzyl chloride
DMPU - 1,3-Dimethyl-3,4,5,6-tetrahydro-2(H)-pyrimidinone
HMPA - Hexamethylphosphoric triamide
LDA - Lithium diisopropylamide
MCPBA - m-Chloroperbenzoic acid
MEMCl - Methoxyethoxymethyl chloride
MOMBr - Methoxymethyl bromide
MPMCl - p-Methoxybenzyl chloride
MsCl - Methanesulfonyl chloride
NMO - N-Methylmorpholine N-oxide
PCC - Pyridinium chlorochromate
PDC - Pyridinium dichromate
PPTS - Pyridinium p-toluenesulfonate
PTSA, TsOH - p-Toluenesulfonic acid
REDAL - Sodium bis(2-methoxyethoxy)aluminium hydride
TBAF - Tetrabutylammonium fluoride
TBDSiCl - tert-Butyldiphenylsilyl chloride
TBSCI - tert-Butyldimethylsilyl chloride
TESOTf - Triethylsilyl trifluoromethanesulfate
TMEDA - N,N,N,N - Tetramethylethylenediamine
TMSOMe - Trimethylsilylmethoxide
TMSOTf - Trimethylsilyl trifluoromethanesulfate
TPAP - \textit{tetra-}N-Propylammonium perruthenate
TsCl - \textit{p-}Toluenesulfonyl chloride
1.0 INTRODUCTION

1.1 ISOLATION, CHARACTERISATION AND BIOLOGICAL PROPERTIES OF THE BRYOSTATIN FAMILY OF ANTINEOPLASTIC AGENTS

From fossils it has been determined that marine organisms such as algae have been on this planet for between 3 and 4 billion years. Biosynthetic evolutionary processes over such incredibly long periods should favour the development of some very sophisticated chemical agents in marine organisms to protect them against predators. Some of these agents have been found to be useful in treating a variety of refractory human medical problems; the bryostatins fall into this category.

The bryostatins constitute a family of sixteen related macrocyclic lactones with a polyacetate derived backbone, that have recently been isolated, along with the structurally novel neristatin 1 (Schemes 1 and 2), from the marine organism Bugula neritina of the phylum Bryozoa.1-2 Bryozoa are commonly known as sea-mats and false corals due to their superficial appearance, and Bugula neritina is well known for its ability to attach and grow on ship hulls.

The bryostatins were first discovered in 1968 by a group from the Cancer Research Institute and the Department of Chemistry at the Arizona State University led by Pettit.1 From a collection of Bugula neritina taken from the Gulf of Mexico, bryostatin 1, the most abundant member, was isolated as a crystalline solid. However, it was not until the 1980’s that its structure, and that of the later discovered bryostatins, were fully elucidated by a combination of single-crystal X-ray analysis and spectroscopic techniques.1,3,4 Further geographically distant collections of Bugula neritina from the Gulfs of California and Sagami (Japan) suggested that the bryostatins may be true biosynthetic products of the animal and not a dietary source.
### Scheme 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryostatin 1</td>
<td>(R = O_2C-CH=CH-CH=CH-(CH_2)2CH_3)</td>
<td>(R' = O_2CCH_3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 2</td>
<td>(R = O_2C-CH=CH-CH=CH-(CH_2)2CH_3)</td>
<td>(R' = OH)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 4</td>
<td>(R = O_2C(CH_2)2CH_3)</td>
<td>(R' = O_2CC(CH_3)3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 5</td>
<td>(R = O_2CCH_3)</td>
<td>(R' = O_2CC(CH_3)3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 6</td>
<td>(R = O_2CCH_3)</td>
<td>(R' = O_2C(CH_2)2CH_3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 7</td>
<td>(R = O_2CCH_3)</td>
<td>(R' = O_2CCH_3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 8</td>
<td>(R = O_2C(CH_2)2CH_3)</td>
<td>(R' = O_2C(CH_2)2CH_3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 9</td>
<td>(R = O_2C(CH_2)2CH_3)</td>
<td>(R' = O_2CCH_3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 10</td>
<td>(R = H)</td>
<td>(R' = O_2CC(CH_3)3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 11</td>
<td>(R = H)</td>
<td>(R' = O_2CCH_3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 12</td>
<td>(R = O_2C-CH=CH-CH=CH-(CH_2)2CH_3)</td>
<td>(R' = O_2C(CH_2)2CH_3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 13</td>
<td>(R = H)</td>
<td>(R' = O_2C(CH_2)2CH_3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 14</td>
<td>(R = OH)</td>
<td>(R' = O_2CC(CH_3)3)</td>
<td>(R'' = H)</td>
</tr>
<tr>
<td>Bryostatin 14a</td>
<td>(R = O_2CCH_3)</td>
<td>(R' = O_2CC(CH_3)3)</td>
<td>(R'' = O_2CC(CH_3)3)</td>
</tr>
<tr>
<td>Bryostatin 15</td>
<td>(R = O_2C-CH=CH-CH=CH-(CH_2)2CH_3)</td>
<td>(R' = O_2CCH_3)</td>
<td>(R'' = H)</td>
</tr>
</tbody>
</table>
The bryostatins have aroused considerable medical interest mainly because of their diverse and substantial biological properties that include pronounced antileukaemic activity and the ability to act as immunostimulatory agents.\textsuperscript{1,3} Bryostatin 1 displays potent antitumour activity against a range of liquid and solid animal tumours that include the murine P388 lymphocytic leukaemia, where it leads to 52-96\% life extension at 10-70 \( \mu \)g/kg injection dose levels.\textsuperscript{1} Furthermore, it was found to afford 31-68\% life extension at 5-40 \( \mu \)g/kg in the murine M531 ovarian sarcoma.\textsuperscript{3} In other murine experiments, bryostatin 1 has proved to be dramatically (1 \( \mu \)g/mouse) effective against lethal whole body irradiation producing a 70\% survival rate.\textsuperscript{5} Bryostatin 1 has been found to cause differentiation of B-lymphocytes in an unprecedented fashion,\textsuperscript{5} and is capable of converting chronic leukaemia cells \textit{in vitro} into those typical of hairy cell leukaemia which is curable.\textsuperscript{5} Successful extensions of these experiments to Phase 2 may result in the first really curative technique for human chronic lymphocytic leukaemia.

Bryostatin 1 has now completed a very successful series of Phase human 1 clinical trials at hospitals in Oxford and Manchester where it was found to bring about a partial remission in two patients with metastatic malignant melanoma (a partial remission is defined as a 50\% or greater reduction in tumour size in the subject).\textsuperscript{6} Significantly, one of the patients remained in remission ten months from
the start of the treatment, and had never previously responded to other forms of cancer chemotherapy.

The biological mechanism by which bryostatin 1 induces tumour regression is still unknown, but its considerable therapeutic potential is based in part on its ability to influence protein kinase C which mediates one arm of a major signal transduction pathway involving lipophilic secondary messengers. Pettit et al hypothesise that bryostatin 1 synergises with interleukin-2 (IL-2) and interleukin-4 (IL-4) to activate protein kinase C, and that this stimulates resting T-cells to proliferate and to differentiate into cytotoxic T-lymphocytes. Bryostatin 1 then cooperatively activates the newly primed cytotoxic T-cells, along with IL-2 and IL-4, to promote the non-specific lysis of tumor cells. This mechanism was proposed on the basis of studies carried out in vitro on the stimulatory effects of bryostatin 1 on the development and effector functions of murine cytotoxic T-lymphocytes. However, further biological studies are going to be required before it is conclusively proven in vivo.

Typically the amounts of bryostatins isolated from nature are extremely small; 1 ton wet weight of *Bugula Neritina* yields only 630 mg of bryostatin 1 and much smaller amounts of the other rarer members. The exceptional biological activity of bryostatins coupled with their scarcity has made them important targets for total synthesis. However, such molecules present a considerable synthetic challenge due to their multiplicity of functionality and their numerous chiral centres. In the case of bryostatin 1 these include 11 chiral centres and 2 exocyclic $\alpha,\beta$-unsaturated esters.

Except for the three C(20) deoxy analogues, bryostatins 10, 11 and 13, the remaining members of this family differ in the nature of the ester functions at C(7) and C(20). In bryostatin 1 the ester functionality is acetyl and octa-2,4-dienoyl respectively. All the bryostatins may be considered as 26-membered macrolides in which there is embedded a 20-membered ring defined by taking the shorter path through the pyran oxygens rather than along the carbon chain. The longest chain
of carbon atoms is 27 and this has been used in the numbering system. The stereochemical designations of the eleven chiral centres in bryostatin 1 are 3(\(R\)), 5(\(R\)), 7(S), 9(S), 11(S), 15(R), 19(S), 20(S), 23(S), 25(R), 26(R).\(^1\) The oxygen substitution pattern, augmented by the gem-dimethyl substituents at C(8) and C(18), suggests a polyketide biosynthesis. The three pyran rings are approximately in the chair conformation and each has a 4-position substituent that projects outward. All of the macrocycle substituents are equatorial with reference to the pyran rings.

The crystal conformation of bryostatin 1 defines a roughly scoop-shaped molecule of dimensions 13 Å length, 8 Å width and an approximate height of 6 Å. An intramolecular hydrogen bond appears to exist between O(3) and OH(19), and two possible hydrogen bonds may also be present between OH(3) and O(5), and between OH(3) and O(11).\(^1\) In the crystalline conformation oxygens O(1), O(3), O(5), O(11), O(19A) and O(19B) are all on the inside of the large, oxygen-rich cavity. The arrangement of oxygens atoms in this cavity together with its size and shape suggests that the molecule may have cation-binding capabilities, similar to the polyether antibiotics. The axial (\(E,E\))-octa-2,4-dienoic acid acid substituent at C(20) would be expected to enhance lipid solubility and facilitate intracellular transport across cell membranes. It could be envisaged that this substituent could swing over the internal cavity of the macrolide by rotation about the C(20)-C(20) bond and "seal" one side.

According to Masamune,\(^9\) since the bryostatins are now in Phase 2 of clinical trials and the entire process of isolation apparently requires one good year of "hard labour", the synthetic approach to the bryostatins appears well justified in terms of their supply even for screening.
1.2 SYNTHETIC APPROACHES TO THE BRYOSTATINS

A number of synthetic approaches have been described to various bryostatins by a number of research groups. Each of these will be discussed in the following sections.

1.2.1 THE MASAMUNE TOTAL SYNTHESIS OF BRYOSTATIN 7

Masamune and coworkers initially concentrated their efforts on the synthesis of bryostatin 1 but ran into difficulties in the late stages of their synthesis. This led them to modify their original strategy so that they could successfully accomplish the total synthesis of bryostatin 7.

Masamune and coworkers began their retrosynthetic dissection of bryostatin 1 by cleavage of the lactone and the C(16)-C(17) double bond to produce two major fragments, aldehyde 2 and sulfone 3 (Scheme 3). They envisaged the application of a Julia-Lythgoe-Kocienski olefination to couple 2 and 3 and thus install the desired E-olefin geometry. After a series of functional group manipulations, eventual O-desilylation of the C(1) hydroxyl would allow oxidation to the corresponding acid and removal of the acetonide would set the stage for macrolactonisation.

Scheme 3
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Opening of the pyran rings in aldehyde 2 gave the open chain β-hydroxy ketone 4, which was further disconnected at the C(10)-C(11) bond to give the smaller fragments aldehyde 5 and ketone 6 (Scheme 4).

Scheme 4

To construct the 1,3-diol arrays of fragment 6, Masamune favoured a strategy that was founded on repetitive Wittig homologation, Sharpless asymmetric epoxidation\(^\text{13}\) and regioselective REDAL reduction.\(^\text{14}\) This had the advantage that the stereochemistry of all the newly installed stereocentres could be controlled (Scheme 5).

Scheme 5
The original 25 step synthesis of ketone 6 was considered to be far too lengthy for the creation of only three stereocentres, so a shorter route was devised (Scheme 6). To install the hydroxy stereocentres at C(3) and C(7) in compound 6 a series of stereoselective borolane-mediated aldol reactions were employed, and the C(5) stereocentre was set by a hydroxyl-directed anti-reduction with tetra-
butylammonium triacetoxyborohydride. The resulting 1,3-diol was protected as an isopropylidene acetal to give 19 which was then converted to ketone 6.
The stereochemical outcome of the si-directed aldol reactions can be rationalised in terms of a chair-like six-membered transition state in which the ligated boron atom is bonded to the oxygen atoms of the boron enolate and the aldehyde as shown in scheme 7. The very short B-C and B-O bond lengths lead to a compact transition state which magnify the steric interactions which control stereoselectivity. The approach of the aldehyde to the boron enolate occurs on the less sterically hindered face and depending on whether attack occurs on either its re- or si- faces would lead to transition states 20 and 21 respectively. However, the latter is disfavoured by a 1,3-diaxial interaction between the R substituent and the aldehyde. This leads to the reaction taking place via transition state 20.

Scheme 7

The aldol reaction between aldehyde 13 and boron enolate 14 proceeded with 20:1 selectivity whilst that between aldehyde 8 and 17 with a lower selectivity of 4:1. The difference in the degree of selectivity is related to the extent of the 1,3-diaxial interactions and therefore on the steric bulk of the R substituent of the boron enolate in each reaction. In the first instance the R substituent was the bulky SCEt3 group whilst in the latter case the less sterically demanding alkyl chain of 17.
The stereochemical course of the hydroxy-directed \textit{anti}-reduction with tetra-
\textit{n}-butylammonium triacetoxyborohydride has been suggested by Evans\textsuperscript{17} to
proceed via the favoured transition state illustrated in scheme 8. Ligand exchange

\textbf{Scheme 8}

\[
\begin{align*}
\text{OH} \quad \text{O} & \quad + \quad \text{Me}_4\text{NBH(OAc)}_3 \quad + \quad \text{AcOH} \\
\text{FAVOURED} & \quad \text{DISFAVOURED} \\
\text{anti} & \quad \text{syn}
\end{align*}
\]

between the substrate hydroxyl and one of the labile borohydride acetoxy ligands
is believed to afford an intermediate substrate-bound alkoxydiacetoxy borohydride
which is capable of intramolecular hydride delivery to an activated carbonyl.
Activation is normally achieved by protonation and for this reason these reactions
are normally conducted in the presence of acetic acid. After ligand exchange the
diastereoselectivity can be easily rationalised if one considers the energy of the
chair-like transition states 22 and 23. It is presumed that the 1,3-diaxial
interactions present in chair-like transition state 23 destabilise it relative to the
analogous nonbonding interactions in transition state 22.
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The synthesis of fragment 5 is outlined in scheme 9. Protection of the hydroxyl group in 24 as its tetrahydropyranyl ether\(^{19}\) was followed by treatment with \(n\)-BuLi, and reaction of the resulting alkynyl anion with gaseous formaldehyde. The resulting propargyl alcohol was then subjected to Corey's trisubstituted olefin synthesis.\(^{20,21}\) Acid hydrolysis followed by Collins oxidation\(^{22}\) delivered 5.

**Scheme 9**

\[
\begin{align*}
1. \text{DHP, PPTS} & & 1. \text{Allyl-MgBr, Cul} \\
2. n-\text{BuLi; HCHO (g)} & & 2. \text{TBDPSCI, imid} \\
3. \text{LiAlH}_4, \text{MeONa; I}_2 & & 3. \text{MeOH, PPTS} \\
(58\%) & & 4. \text{Collins (51\%)} \\
\end{align*}
\]

The next stage of the synthesis was assembly of 4 (Scheme 10). This was accomplished by a sequence involving an aldol reaction between 5 and 6, mediated by \((R, R)-2,5\text{-dimethylborolanyl triflate;}^{15}\) this proceeded with 6:1 stereoselectivity in favour of 4.

**Scheme 10**

\[
\begin{align*}
\text{CHO} & + \text{OTBDPS} \\
\text{OTBDPS} & \text{OMOM} \\
\text{OTBDPS} & \text{BOTf} \\
\text{OTBDPS} & \text{OMOM} \\
\text{OTBDPS} & \text{OMOM} \\
\end{align*}
\]

The conversion of \(\beta\)-hydroxy ketone 4 to aldehyde 2 (Scheme 11) initially involved transketalisation\(^{23}\) and a stereorandom cyclisation induced by Hg(OAc)_2.\(^{24}\) Acetylation\(^{25}\) of the resulting C(7)-hydroxyl resulted in 27 as a mixture of epimers at C(15). To complete the synthesis of aldehyde 2, epimers 27 were converted to their respective primary alcohols by oxidative demercuration.\(^{26}\)
and Swern oxidation followed by equilibration of the 1:1 aldehydic epimeric mixture delivered the equatorial diastereoisomer 2.

**Scheme 11**

With the C(1)-C(16) segment 2 in hand, attention was focused on southern hemisphere 3. Its retrosynthetic analysis began with cleavage of the glycoside linkage and ring opening to give open chain ketone 28 (Scheme 12). Ketone 28 was further dissected across the C(20)-C(21) bond to give vinyl iodide 29 and optically active aldehyde 30. Although the C(19) stereocentre in 30 was eventually going to be destroyed, its chirality was to have an important bearing on determining the stereochemical outcome of the C(20) stereocentre during C(20)-C(21) bond formation, since it offered the possibility of performing a chelation controlled addition between 30 and the vinyllithium reagent generated from halogen-metal exchange of 29 with n-BuLi. The choice of a vinyllithium addition would also enable the trisubstituted alkene in 28 to be set stereospecifically since vinyllithium
intermediates show little tendency to isomerise at low temperature, the conditions under which such a reaction would be carried out. The starting material for the synthesis of aldehyde 30 was 2,3-epoxy alcohol 31 available in 6 steps from 2,2-dimethylpropanediol 7.

**Scheme 12**

Formation of the primary urethane from 31 by treatment with phenylisocyanate followed by acid-catalysed intramolecular epoxide ring opening delivered carbonate 36, which was converted to an acetonide, and protected as a 3,4-dimethoxybenzyl ether 37. Hydrogenation of 37 with Raney-Ni resulted in de-O-benzylation and after O-mesylation of the primary alcohol nucleophilic displacement with sodium thiophenoxide furnished the thioester. Removal of the
acetonide and oxidative cleavage of the resulting diol with sodium periodate gave aldehyde 30, without oxidation of the thioether (Scheme 13).

Scheme 13

```
1. K₂CO₃ (s), MeOH
2. Me₂C(OOMe)₂
3. NaH, DMPMCl

1. PhNCO, Et₃N
2. BF₃·Et₂O, 10% H₂SO₄ (aq)
3. NaH, DMPMCl

1. Raney Ni, H₂
2. MsCl, PhSNa
3. HCl, MeOH
4. NaIO₄, pH7

17
BnO

1. Me₂C(OMe)₂

OH

20

17
BnO

OH

17
BnO

CH₂

ODMPM

17
BnO

OH

17
BnO

CHO

ODMPM

31
36
32
33
30
37
```

Scheme 14 shows the synthetic route to vinyl iodide 29. Using a known procedure, L-threonine 35 was converted into ester 38 in a yield of 64%. This was then homologated to provide aldehyde 33 (52%). Aldehyde 33 coupled with allenyl-ZnBr 34, to give compound 32 as the major product of an 8:1 mixture of epimeric alcohols (53%). The stereoselectivity could again be rationalised if one invokes a chair-like transition state in which the zinc atom is coordinated to the C(25)-O and the aldehyde carbonyl. After protection of the C(23)-hydroxyl in 34 as a p-methoxybenzyl ether, the resulting acetylene was converted into the alkynyl ester. Stannylcupration utilising Piers methodology gave 39. Reduction of the allylic ester in 39 with DIBAL led to the corresponding allylic alcohol and after protection as a t-butyldiphenylsilyl ether, halogen-metal exchange delivered iodide 29.

Scheme 14

```
1. NaN₂, H₂SO₄ (aq) MeOPC
2. MeOH, AcCl
3. Me₂C(OOMe)₂, TsOH
4. PCC

1. DIBAL-H
2. Ph₃PC₂H₂
3. Si₆BH₆, H₂O₂
4. PCC

35
38
39
```

23
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Scheme 14 (contd)

Coupling of iodide 29 and aldehyde 30 again took advantage of metal chelation to the C(19)-O functionality in 30. Hence, treatment of 29 with n-butyllithium resulted in halogen-metal exchange\(^\text{28}\) to give the corresponding vinyl lithium derivative which when reacted with 30 gave a 6:1 stereoselectivity in favour of 40 (Scheme 15). Protection of the newly installed C(20)-hydroxyl group as a tri-

Scheme 15

ethylsilyl ether\(^\text{34}\) was followed by the selective removal of the 3,4-dimethoxyphenylmethyl (MPM) ether (1 equiv of 2,3-dichloro-5,6-dicyanobenzoquinone)\(^\text{29}\) and Moffatt oxidation\(^\text{35}\) of the corresponding alcohol provided ketone 28 in 60-70\% yield. Oxidation of the thiophenyl ether to the corresponding sulfone was followed by the removal of the p-methoxybenzyl ether.\(^\text{29}\) Treatment of the resulting lactol with triethylsilyl triflate and
trimethylsilylmethoxlde resulted in formation of the methyl glycoside 3 in 40% overall yield for the three steps (Scheme 16).

**Scheme 16**

Fragments 2 and 3 were coupled via the Julia-Lithgoe-Kocienski olefination to give the desired (E)-olefin 41 (Scheme 17).

**Scheme 17**

Unfortunately when olefin 41 was converted into compound 42 this intermediate could not be transformed into bryostatin 1. The problem resided in Masamune's inability to define satisfactory reaction conditions for the successful removal of the C(3)-OMOM group, which had been introduced at a very early
stage in the synthesis. Invariably all the deprotections attempted under mild acidic conditions resulted in 42 undergoing extensive side reactions (Scheme 18).

\[ \text{Scheme 18} \]

Masamune and coworkers were therefore forced to revise their strategy. They now elected to leave introduction of the C(3) stereocentre to the end of the seco-acid synthesis. This simple modification proved very successful since it eventually led to a synthetic route being developed to bryostatin 7 (43).\(^1\) In their revised retrosynthetic analysis shown in scheme 19, macrolactonisation was again selected for closure of the 20-membered ring system in bryostatin 7. However, this time it was going to be executed on β-hydroxy acid 44. It was anticipated that the C(25)-hydroxyl group would preferentially lactonise after inspection of molecular models of 44. Disconnection of the C(2)-C(3) bond suggested aldehyde 45 and chiral enolate 14 as possible intermediates. A stereocontrolled aldol reaction between 45 and 14 was envisaged for establishing the C(3) stereocentre.

A further disconnection of 45 across the C(17)-C(16) double bond again led to the possibility of a Julia-Lithgoe-Kocienski olefination\(^2\) between 46 and the previously synthesised sulfone 3. Retrosynthetic cleavage of the C(11)-C(10) bond
in aldehyde 46 gave the previously synthesised 5 and ketone 47 which itself could be synthesised by utilising methodology used to construct the C(1)-C(10) section 6 of bryostatin 1 (1).
The synthetic tactics used to construct aldehyde 2 were again successfully employed in the synthesis of the new C(3)-C(16) fragment 46 (Scheme 20).

Scheme 20

Julia-Lythgoe-Kocienski olefination\(^\text{12}\) between 46 and 3 gave 51 in 60\% yield. During the reductive elimination step, the inclusion of Na\(_2\)HPO\(_4\) buffer proved essential for retention of the C(7) acetate in 51.\(^\text{37}\) A series of protecting group interchanges and a selective bis-allylic alcohol oxidation sequence finally led to 52 (Scheme 21). Swern oxidation\(^\text{27}\) of 52 followed by aldol reaction with chiral enolate 14 led to 53 with modest stereocontrol. Treatment of 53 with camphorsulfonic acid in MeOH resulted in selective removal of the acetonide with retention of the methyl acetal functionalities. Compound 54, however, failed to macrolactonise under thiophilic metal catalysis.\(^\text{38}\)
Masamune therefore elected to convert compound 54 into β-hydroxy acid 44 after temporary protection of the free hydroxyl groups as triethylsilyl ethers. Activation of the acid in 44 (Scheme 22) with dicyclohexylcarbodiimide and pyridinium p-tosylate in pyridine and dichloroethane at reflux resulted in selective macrolactonisaton to give 55 in 51% yield. However, the reaction
conditions also caused the loss of C(7)-acetate and hydrolysis of the C(9)-methyl acetal.

Scheme 22

The C(19)-methyl acetal in 55 resisted acid hydrolysis, probably due to a combination of excessive steric hindrance around the C(19) centre and the presence of the electron withdrawing C(20)-acetate group (Scheme 23).\(^4\) However, after removal of the C(20)-acetate, glycoside hydrolysis proceeded smoothly to give 56. The C(26)-hydroxyl group in 56 was selectively O-silylated,\(^4\) the C(7)- and C(20)-hydroxyl groups O-acetylated,\(^2\) and the resulting molecule treated with hydrogen fluoride-acetonitrile complex to effect O-desilylation\(^4\) to deliver bryostatin 7 (43).
1.2.2 The Evans’ Synthetic Approach To Bryostatin 1\textsuperscript{43,44}

A group led by D.A. Evans is continuing to work towards the total synthesis of bryostatin 1 (1). They recognised the recurring oxygenation pattern of the polyactate derived backbone in the bryostatins and proceeded with disconnections across the lactone linkage and the C(5), C(11), and C(19) ether linkages in 1 to give seco-acid 57, having carbonyl groups at C(13) and C(21) for the possible introduction of the unsaturated esters (Scheme 24).\textsuperscript{44} The recurring structural nature of 57 was further enhanced by retrosynthetic reduction of the C(13) carbonyl to give 58. Inspection of 58 revealed that both the C(1)-C(6) and C(11)-C(16) sections of 1 could potentially be obtained from the same triol 59, whilst the C(21)-C(27) section could be obtained from the one-carbon homologue 60 containing an additional stereocentre.
The synthesis of fragments 59 and 60 was based upon the use of meta-substituted anisyl rings as masked β-keto esters\(^\text{45}\) and the enantioselective asymmetric epoxidation/kinetic resolution of cinnamyl alcohols.\(^\text{13}\) Compound 59 was synthesised in a six step reaction sequence starting from trans-cinnamate 61. Thus, DIBAL reduction\(^\text{33}\) of the ester in 61 followed by Sharpless asymmetric epoxidation\(^\text{13}\) delivered epoxide 62 with an enantiomeric excess of 94% (Scheme 25). A sequence of \(O\)-silylation,\(^\text{46}\) Birch reduction\(^\text{47}\) and ozonolysis\(^\text{48}\) gave β-keto ester 64. Finally, hydroxyl-directed \(anti\)-reduction with the Saksena-Evans
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reagent\textsuperscript{16,17} afforded \textit{anti} 1,3-diol 59 which was suitable for the C(1)-C(6) and C(11)-C(16) sections of the bryostatins.

\begin{center}
\textbf{Scheme 25}
\end{center}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_25}
\end{figure}

Fragment 60 was synthesised in an eleven step sequence (Scheme 26). The aldol reaction between acetone and \textit{m}-anisaldehyde (65) was followed by sodium borohydride reduction\textsuperscript{49} and gave racemate 66. Sharpless kinetic resolution\textsuperscript{13} on 66 delivered \textit{anti} epoxy alcohol 67 (ee > 90\%). Mitsunobu inversion\textsuperscript{50} of the C(26) stereocentre in 67 was followed by saponification of the resulting benzoate ester. The C(26) hydroxyl was then protected as a tris(isopropyl)silyl ether\textsuperscript{46} to give \textit{syn} epoxy alcohol 68. Birch reduction\textsuperscript{47} of 68 resulted in silyl group migration but this setback was overcome by a sequence of selective epoxide ring opening of 68 via hydrogenolysis and a subsequent Birch reduction\textsuperscript{47} of the dialkylaluminium 70 to give dihydroanisole 71. Ozonolysis of 71 gave \textit{\(\beta\)}-keto ester 72 and hydroxyl-directed \textit{anti}-reduction with the Saksena-Evans reagent\textsuperscript{16,17} afforded \textit{anti} 1,3-diol 60.

\begin{center}
\textbf{Scheme 26}
\end{center}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_26}
\end{figure}
Further work conducted by the group on the total synthesis of bryostatin 1 (1) has led to the development of a route to synthon 73 corresponding to the C(17)-C(27) fragment.\(^\text{43}\) Retrosynthetic disconnection of the lactone linkage and the C(16)-C(17) double bond in 1 gave the fragments 73 and 74 as shown in scheme 27.

To control the olefin geometry at C(13) and C(21), the use of a tethered Horner-Wadsworth-Emmons reagent was envisaged.\(^\text{51}\) A primary alcohol at C(16) in 73 was planned to have a dual role. It would serve both as the aldehyde precursor for the subsequent coupling with sulfone synthon 74, and also as the anchor for a
tethered β-ketophosphonate reagent (Scheme 28). By a similar strategy the primary alcohol at C(26) could be utilised to control the C(21) olefin geometry.

**Scheme 28**

Thus far the details of their synthesis of fragment 75 have not been reported but it does apparently cyclise when treated with LiCl and Et₃N to give 73 in 60% yield (Scheme 29).⁴³

**Scheme 29**

1.2.3 Roy's Synthetic Approach To Bryostatin 1⁵²,⁵³

Rene Roy and his group at the University of Ottawa have also been working towards a total synthesis of bryostatin 1 (1). To date, they have reported the
synthesis of three key fragments, namely 76, 77 and 78, corresponding to the C(1)-C(9), C(17)-C(20) and C(21)-C(27) sections respectively. Their retrosynthetic analysis is based on dissections of the C(17)-C(16) double bond, the C(10)-C(9) bond and the C(1)-O acyl linkage to give fragments 76 and 79 (Scheme 30). Cleavage of the C(20)-C(21) bond in 79 suggested 78 and 80. They envisaged that 80 and the corresponding dithianyl anion of 78 would react together diastereoselectively due to the steric bulk of the chiral centre at C(19) in 80, thus installing the C(20)-hydroxyl with the desired stereochemistry.

Scheme 30

The retrosynthetic analysis of δ-lactone 76 is shown in scheme 31. It was envisaged that regioselective lactonisation could be achieved on compound 65 after treatment with a thiophilic metal. Compound 81 could potentially be obtained via a diastereoselective aldol condensation between aldehyde 83 and silyl enol ether 82 which would create the C(5) stereocentre. An Evans-Saksena stereoselective reduction on the resulting β-hydroxy ketone could then be used to install the C(7)-hydroxy stereocentre. In principle, aldehyde 83 could be
obtained from dimethyl 3-ketoglutaratate 84, whilst silyl enol ether 82 could be derived from diketene (85).

Scheme 31

Aldehyde 83 was synthesised in six steps from dimethyl 3-ketoglutaratate 84 as shown in scheme 32. Sodium borohydride reduction of 84 followed by protection of the hydroxyl group as a MOM ether delivered 86 in 87% yield. Enzyme catalysed enantioselective hydrolysis of 86 with α-chymotrypsin gave monoacid 87 in 91% yield and an enantiomeric excess greater than 94%. Reduction of a mixed anhydride derivative of 87 with sodium borohydride followed by pyridinium chlorochromate oxidation led to the desired aldehyde 83.

Scheme 32
Silyl enol ether 82 was obtained in an overall yield of 57% from diketene (85) (Scheme 33). Treatment of 85 with t-BuSNa followed by geminal dimethylation gave 89. Subsequent O-silylation of the enolate obtained from treatment of 89 with trimethylsilyl triflate and triethylamine delivered 82.

Scheme 33

The next stage of their synthesis was an aldol reaction to couple 82 and 83. They anticipated that a Mukaiyama aldol condensation would proceed with high selectivity in favour of the anti-diastereoisomer 90 due to 1,3-chelation control operating under TiIV or SnIV tetrachloride-catalysed conditions. However, under SnCl4 conditions the undesired syn-adduct 91 was obtained as the major product of a 1.5:1 mixture of diastereoisomers. TiCl4 conditions resulted in the loss of the C(3)-MOM group and also a 1.5:1 mixture of the corresponding syn:anti-adducts. The unusual stereochemical outcome was rationalised on the basis of a long range chelation effect played by the C(1)-carbomethoxy group which favoured attack on the si face of the aldehyde and hence transition state 92 (Scheme 34).

BF3·Et2O, which does not produce this 'cage-like' chelation, was also evaluated and delivered a 1.9:1 inseparable mixture of diastereoisomers in favour of 90 in 81% yield. Since BF3·Et2O cannot engage in multiple coordination, it forms an open complex such as 94, in which rigidity is imposed to minimise electrostatic repulsions. Nucleophilic attack on the less hindered side of complex 94 simulates chelation control and hence rationalises the stereoselectivity (Scheme 35).
The inseparable mixture of syn- and anti-β-hydroxy ketones 90 and 91 were then subjected to stereoselective reduction with Me₄NBH(OAc)₃,¹⁶ and for
the purpose of separation, these were converted to the acetones 95 and 96 respectively (Scheme 36). The purified acetone 95 was then reconverted to diol 91.

**Scheme 36**

![Chemical diagram](image)

81 by acidic methanolysis (Scheme 37). Treatment of 81 with Hg(CF₃CO₂)₂ resulted in selective lactonisation to give δ-lactone 97. To complete the synthesis of 76 the C(7)-hydroxyl group in 97 was acetylated and the C(3)-MOM ether removed under Lewis acid conditions.

**Scheme 37**

![Chemical diagram](image)

The retrosynthetic analysis of fragment 78 is shown in scheme 38. Dithiane 78 was selected since it contains a latent C(21)-carbonyl group that could...
potentially be employed for chain-extension at a later stage in the synthesis of the southern hemisphere. In principle, 78 could be obtained from the chiral template D-galactono-1,4-lactone (99), since comparison of the chirality in 78 with that in 99 indicates congruence.

**Scheme 38**

Treatment of 99 with hydrogen bromide in acetic acid followed by O-acetylation furnished 100 in 87% yield (Scheme 39). Simultaneous deoxygenation at C-3 and C-6 gave 102 in 82% yield. The C-3 deoxygenation proceeds via a β-acetoxy elimination to give an endocyclic alkene 101 that undergoes hydrogenation from the side opposite to the C-4 side-chain. Ring opening was effected by reduction with lithium borohydride and gave tetrol 98 in 96% yield. Sequential bis-isopropylidenation and kinetic de-O-isopropylidenation gave acetonide 103. Selective tosylation of the primary hydroxyl followed by its base-mediated intramolecular $S_N2$ displacement delivered epoxide 104. Epoxide ring opening with 2-lithiodithiane, and protection of the resulting C(23)-hydroxyl group as a benzoate ester furnished fragment 78.

**Scheme 39**
1. Me₂C(OEt)₂, TsOH, C₆H₆ (87%) →
2. MeOH, TsOH, 12 h, 25 °C (77%)

1. TsCl, py, -10 to 25 °C (84%)
2. K₂CO₃, MeOH (83%)

Lactol 77 was synthesised in 2 steps from the chiral template D-pantolactone 105 as shown in scheme 40. The coupling of fragments 77 and 78 has not been reported but model studies carried out involving lactol 77 and 2-lithiodithiane show high diastereoselectivity in favour of the anticipated anti-adduct in accordance with non chelation controlled addition.

1.2.4 The Nishiyama/Yamamura Synthetic Approach To The Bryostatins

A group led by Nishiyama and Yamamura reported the synthesis of two synthons corresponding to the C(1)-C(16) fragment of the bryostatins and a C(17)-C(27) fragment corresponding to the C(20) deoxybryostatins i.e. bryostatins 10, 11 and 13. Retrosynthetic cleavage of the C(16)-C(17) double bond and the lactone linkage gave northern hemisphere 106 whose retrosynthetic analysis is
outlined in scheme 41. Under Fischer glycosidation conditions, it was envisaged that 107 would cyclise and introduce the axial methyl glycoside at C(9) in 108. Stereoselective coupling of 109 with the chiral enolate derived from 108 was planned for establishing the C(4)-C(5) bond and stereoselectively installing the C(5) stereocentre.

Scheme 41

It was felt that fragments 111 and 112 could be unified by an $S_N2$-type iodide displacement of 110 with the 1,3-dithianyl anion obtained from 111 (Scheme 42). Both molecules could themselves potentially be obtained from 9 and 112 respectively. Compound 112 contains a O(13) carbonyl group that would allow the O(13) exocyclic $\alpha,\beta$-unsaturated ester to be introduced at a later stage of the synthesis.

Scheme 42
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The synthesis of the C(5)-C(9) fragment 111 is shown in scheme 43. Epoxy alcohol 9 underwent regioselective reduction with REDAL to give 1,3-diol 113 in 96% yield. Protection of the hydroxyl groups as t-butyldimethylsilyl ethers was followed by O-debenzylation. The resulting alcohol was oxidised under Swern conditions to furnish aldehyde 114. Treatment of 114 with 1,3-dithiol - MgBr2-OEt2 resulted in thioacetal formation and delivered 111.

Scheme 43

The synthesis of fragment 110 commenced with a stereospecific 1,4-copper(I)-catalysed addition of vinyl magnesium bromide to chiral enone 112 to give 115 (Scheme 44). The trans stereochemical outcome of the reaction was attributable to steric hindrance on the top-side of the vinylogous ester by the dialkoxy side chain. The carbonyl group was then protected as a dimethyl acetal, the double bond homologated to a benzyl ether and the C(15) stereocentre inverted in a five step reaction sequence that gave 116 in an overall yield of 56% for the 5 steps. Treatment of 116 with Amberlite IR - 120 B (H+) resin in MeOH selectively cleaved the acetonide. Glycol cleavage of the resulting diol with sodium periodate followed by borohydride reduction then furnished alcohol 117 which was converted to iodide 110 via the corresponding tosylate.
Base-induced coupling of fragments 110 and 111 produced adduct 118 in 89% yield (Scheme 45). Selective O-desilylation of the C(5) hydroxyl followed by Swern oxidation\(^ {27}\) provided aldehyde 109. In the presence of lithium iodide,\(^ {72}\) aldehyde 109 underwent a stereoselective aldol reaction with the enolate of 108\(^ {73}\) to give 24:1 selectivity in favour of the desired enantiomer 119.

**Scheme 45**
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β-Keto ester 120 was obtained in 90% yield by treatment of 119 with toluene and ethanol at reflux temperature (Scheme 46). The reaction is believed to proceed via a ketene type intermediate 121.66

Scheme 46

Anti-selective β-hydroxy ketone reduction on 120 with Me₄NBH(OAc)₃¹⁶ set the C(3) configuration (Scheme 47). Acetal hydrolysis of the latter and protection of the 1,3-diol unit as an isopropylidene acetal¹⁸ gave 122. The stereocontrolled introduction of the methoxycarbonylmethylene unit at C(13) proved problematic; the Horner - Emmons reaction⁵¹ delivered a mixture of the corresponding α,β-unsaturated esters in a 94% yield. The unseparated mixture was then subjected to thioacetal hydrolysis⁷⁴ followed by O-deacetalation under acidic methanolic conditions. These conditions also induced ring-closure of the pyran hemiketal ring system and methyl glycosidation²³ to deliver 106 as the major product, and its undesired geometrical isomer 123 in a ratio of 62:38.

Scheme 47
The retrosynthetic analysis of the C(17)-C(27) synthon 124 of the deoxygenated series of bryostatins is shown in scheme 48. Retrosynthetic cleavage of the C(19)-C(20) bond in 124 led to the key fragments 126 and 127.

Fragment 126 was synthesised in three steps from 2,2-dimethyl-1,3-propanediol (7) as shown in scheme 49.\textsuperscript{68}
The starting material for the synthesis of compound 127 was the chiral furanose derivative 129 (Scheme 50). Compound 129 was converted into 130 by a stepwise functional group protection. Treatment of dithiane 130 with Mel-NaHCO₃ (aq), followed by NaBH₄ reduction delivered the corresponding diol, which was transformed into epoxide 131 by a one-pot procedure employing p-TsCl and NaH. A three step homologation sequence involving a Grignard reaction in the presence of catalytic Cul, followed by alcohol protection as a p-methoxybenzyl ether, and m-chloroperbenzoic acid epoxidation led to diastereomeric 127.

The next step in the synthesis was the coupling of fragments 126 and 127. This was achieved by nucleophilic epoxide ring opening of 127 with the anion generated from the treatment of dithiane 126 with tert-Butyllithium and delivered mixture 132 in 97% yield (Scheme 51). Moffatt oxidation followed by oxidative removal of the C(23) p-methoxybenzyl group with DDQ delivered ketone 133 and set the stage for introduction of the α,β-unsaturated lactone moiety. However, the intramolecular Horner-Emmons reaction to construct the E-trisubstituted olefin at C(21) was unsuccessful, a possibility being the basic conditions that caused β-elimination of the hydroxy function at the C(20) position to give 135.
Eventually it was found that the \( \alpha,\beta \)-unsaturated lactone moiety could be successfully installed via Molander's Sml\(_2\) - mediated intramolecular Reformatsky reaction\(^\text{77}\) as shown in scheme 52. Hence, after bromoacetylation of compound 133, treatment with Sml\(_2\) at low temperature resulted carbon-carbon bond formation and afforded 137 as a 3:1 diastereomeric mixture. Lactone 137 provided two possibilities of derivatization with the coupling to the northern hemisphere in mind. Thus, treatment of 137 with Ac\(_2\)O, DMAP and pyridine effected a \( \beta \)-elimination to provide 125 possessing a siloxy ether at C(17).
On the other hand, a sequence of desilylation followed by oxidation on 137 afforded the spirobislactone 138 which on treatment with NEt₃ underwent β-elimination and ring opening to deliver C(17)-methyl ester 139 after esterification with diazomethane (Scheme 53).

1.2.5 The Vandewalle Approach To Bryostatin 1

Vandewalle and coworkers at the State University of Gent, Belgium, have synthesised three synthons, namely 140, 141 and 142, whose structures correspond to the C(1)-C(9), C(11)-C(16) and C(17)-C(27) sections of bryostatin 1 (1) respectively. Their retrosynthetic analysis began with the familiar disconnections of the lactone linkage and the C(16)-C(17) double bond. Cleavage
of the C(10)-C(11) bond led to the key fragments 141, 142 and 143 (Scheme 54).

**Scheme 54**

Fragment 140 was further dissected across the C(4)-C(5) bond as shown in scheme 55. The key steps in their plan were a stereoselective aldol condensation between 144 and 145, and an anti-selective β-hydroxy reduction to introduce the C(5) and C(3) stereogenic centres in 140 respectively. Ketone 144 could be obtained in two steps, in principle, from 1,3-butanediol 146. Retrosynthetic reduction of D-pantolactone 105 to triol 147 and homologation of the C(6)-hydroxyl group was envisaged to lead to aldehyde 145.
The synthesis of 145 is outlined in scheme 56. Reduction of D-pantolactone 105 with lithium aluminium hydride\textsuperscript{33,81} followed by acetal protection of the glycol unit gave primary alcohol 148. After protection of the C(9)-hydroxyl as a p-methoxybenzyl ether,\textsuperscript{29} the glycol unit was unmasked and converted to the epoxide 149 with sodium hydride and tosylimidazole. Epoxide ring opening with (CH$_2$=CH)$_2$CuCNLi$_2$ and protection of the resulting C(7)-hydroxyl group as a benzyl ether\textsuperscript{29} then gave alkene 150. Oxidative cleavage of the double bond in 150 resulted in aldehyde 145.
Selective protection of the primary hydroxyl of 1,3-butanediol 146 as a t-butyldiphenylsilyl ether\(^1\) followed by Collins oxidation\(^2\) afforded ketone 144. Aldol condensation between 144 and 145 led exclusively to the single diastereoisomer 151. The best conditions for diastereoselective reduction of β-hydroxy ketone 151 involved the use of lithium tri-t-butoxyaluminium hydride in the presence of lithium iodide\(^3\) at -78 °C which resulted in a selectivity of 17.6:1 in favour of the desired anti-diol. Finally, protection of the diol unit as an acetonide produced 140 (Scheme 57).

![Scheme 57](image)

The high syn-selectivity of the aforementioned LiAlH(t-BuO)\(_3\)-lithium iodide reduction can be rationalised if one invokes bidentate chelation between the lithium cation and the carbonyl and the C(1)-alkoxy groups. The C(5) hydroxyl then coordinates to the aluminium which directs hydride attack from the less hindered side to give the anti-product (Scheme 58).\(^8\)

![Scheme 58](image)
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The starting material for the synthesis of 141 was the known chiral tosylate\(^{45}\) 154 possessing the the desired C(15) stereocentre (Scheme 59). Iodination followed by nucleophilic displacement with lithium 2-trimethylsilyl-1,3-dithiane gave 155,\(^{83}\) and thus served to introduce a latent carbonyl group at C(13), to subsequently allow the exocyclic olefin unit to be introduced at that site at a later stage via an asymmetric Horner-Emmons reaction.\(^{51,84}\) Cleavage of the trimethylsilyl group in 155 gave 156, which was subsequently deprotonated and the resulting anion treated with BrCH\(_2\)CH(OMe)\(_2\) to furnish 157. Acetal hydrolysis under acidic conditions also induced ring-closure of the pyran hemiacetal ring system to provide hemiacetal 141.

Model studies were performed to determine the degree of stereocontrol that could be expected in setting the C(11) stereocentre. Keto-phosphonate 158 was deprotonated and reacted with 141 to give 159 as the sole product in 75% yield, thus establishing that the configuration at C(11) could be controlled by the C(15) stereogenic alcohol (Scheme 60). The mechanistic course of the reaction is depicted in scheme 61. With this model study, Vandewalle et al. were able to envisage a possible future route to a C(1)-C(16) fragment.
The key steps in their plan towards a southern hemisphere of bryostatin 1 were similar to those employed by Masamune and coworkers. The retrosynthetic analysis of their C(17)-C(27) section is shown in scheme 62. Disconnection of the C(20)-C(21) in bond led to aldehyde and vinyl iodide. Construction of this bond would not only control the E-geometry of the double bond it would also allow the stereochemistry of the newly formed hydroxyl to be controlled through diastereofacial selectivity induced by the C(19)-OTBS functionality in 166. It was envisaged that vinyl iodide would be available from acetylenic ester via the Masamune strategy.

Compound
166 could be synthesised from D-isobutyl lactate (167) via chelation-controlled allylation.

**Scheme 62**

The synthesis of vinyl iodide 165 was based on repeated chelation-controlled allylstannylations\(^\text{85}\) to set the C(23) and C(25) stereocentres in a predictable manner (Scheme 63).

**Scheme 63**
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Scheme 63 (contd)

The stereoselectivity observed can be rationalised if one invokes a stereoelectronically controlled addition of the allylstannane to chelate 174 as opposed to one on 175 (Scheme 64).79

Scheme 64

Aldehyde 164 was obtained from D-pantolactone (105) in 9 steps as shown in scheme 65.

Scheme 65
The final step of the synthesis of the Vandewalle southern hemisphere was the coupling between vinyl lithium derived from iodide 165 and aldehyde 166. This delivered a 2:1 separable mixture of the C(20) epimers, in favour of the desired product 142, in 50% yield (Scheme 66).

The use of vinyl iodide 165 to construct of the C(20)-C(21) bond also led the group to devise an entry into the C(20) deoxy series of bryostatins. Epoxide 171 was available from previously synthesised diol 179 via base-mediated intramolecular $S_N$2 displacement of the corresponding tosylate (Scheme 67).

Treatment of epoxide 181 with the vinyl anion derived from 165 in the presence of...
2-thienylCuCNLi and BF$_3$.Et$_2$O, gave alcohol 182 in 29% yield (Scheme 68).

\textbf{Scheme 68}

\begin{center}
\begin{tikzpicture}
    \node (181) at (0,0) {\includegraphics[width=0.5\textwidth]{181}};
    \node (165) at (2,0) {\includegraphics[width=0.5\textwidth]{165}};
    \node (182) at (4,0) {\includegraphics[width=0.5\textwidth]{182}};
    \node (scheme) at (1,0) {\textbf{Scheme 68}};
    \node (181) at (-1,0) {\includegraphics[width=0.5\textwidth]{181}};
    \node (165) at (2,0) {\includegraphics[width=0.5\textwidth]{165}};
    \node (182) at (4,0) {\includegraphics[width=0.5\textwidth]{182}};
    \node (scheme) at (1,0) {\textbf{Scheme 68}};
\end{tikzpicture}
\end{center}

\subsection{1.2.6 The Hoffmann Approach To The C(1)-C(9) Section Of The Bryostatins$^{86}$}

Hoffmann and Stiasny have reported a synthesis of the C(1)-C(9) section 183 of the bryostatins. Their route was predicated on the diastereoselective bromine/lithium-exchange outlined in their retrosynthetic analysis (Scheme 69).

\textbf{Scheme 69}

\begin{center}
\begin{tikzpicture}
    \node (183) at (0,0) {\includegraphics[width=0.5\textwidth]{183}};
    \node (184) at (2,0) {\includegraphics[width=0.5\textwidth]{184}};
    \node (185) at (4,0) {\includegraphics[width=0.5\textwidth]{185}};
    \node (186) at (6,0) {\includegraphics[width=0.5\textwidth]{186}};
    \node (187) at (8,0) {\includegraphics[width=0.5\textwidth]{187}};
    \node (188) at (10,0) {\includegraphics[width=0.5\textwidth]{188}};
    \node (scheme) at (1,0) {\textbf{Scheme 69}};
    \node (183) at (-1,0) {\includegraphics[width=0.5\textwidth]{183}};
    \node (184) at (2,0) {\includegraphics[width=0.5\textwidth]{184}};
    \node (185) at (4,0) {\includegraphics[width=0.5\textwidth]{185}};
    \node (186) at (6,0) {\includegraphics[width=0.5\textwidth]{186}};
    \node (187) at (8,0) {\includegraphics[width=0.5\textwidth]{187}};
    \node (188) at (10,0) {\includegraphics[width=0.5\textwidth]{188}};
    \node (scheme) at (1,0) {\textbf{Scheme 69}};
\end{tikzpicture}
\end{center}

The starting point for their synthesis was dibromide 188 prepared according
to scheme 70. Treatment of allylic chloride 191 with 192 in the presence of SnCl₂ followed by KOH work-up delivered racemic diol 193. This was converted to the corresponding sulfate 190 which was then reacted with LiCHBr₂ 189 and silylated to provide dibromide 188.

**Scheme 70**

Reaction of dibromide 188 with n-butyllithium at -110 °C gave the carbenoids 187 and 194 in a 3:1 ratio. The minor product 194 cyclized selectively at -110 °C to the bicyclo[3.1.0]hexane 195, leaving diastereomerically pure 187 in solution (Scheme 71).

**Scheme 71**

To complete the synthesis of 183 compound 187 was acetylated with the mixed borate ester 196 (Scheme 72). The boronate intermediate was quenched at low temperature with aqueous ammonium chloride to prevent the isopropoxy group migrating from the boron to carbon and displacing the bromide, a reaction
that was problematic when quenching was performed at higher temperatures.\textsuperscript{87} The crude \(\alpha\)-bromo-boronate 186 was then reacted with the dianion of \(t\)-butyl acetoacetate 185 to deliver boronate ester 184.\textsuperscript{88,89} A sequence of oxidation, hydroxy-directed \textit{anti}-reduction with tetra-\(n\)-butylammonium triacetoxyborohydride,\textsuperscript{16,17} and isopropylidination finally delivered compound 183.

**Scheme 72**

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {187};
\node (2) at (2,0) {186};
\node (3) at (4,0) {185};
\node (4) at (0,-2) {184};
\node (5) at (2,-2) {183};
\node (6) at (0,-4) {187};
\node (7) at (2,-4) {186};
\node (8) at (4,-4) {185};
\node (9) at (0,-6) {184};
\node (10) at (2,-6) {183};

\draw[->] (1) -- (2) node[midway, above] {1. \(\text{Pr-O-B(O)}\)} node[midway, below] {-110 °C};
\draw[->] (2) -- (3) node[midway, below] {2. \(\text{NH}_4\text{Cl aq. -110 °C}\)};
\draw[->] (4) -- (5) node[midway, above] {1. \(\text{Me}_4\text{N}^+\text{AcO}_3\text{BH}^-\) (93\%)} node[midway, below] {diastereoselectivity 9:1};
\draw[->] (4) -- (9) node[midway, below] {2. \((\text{CH}_3)_2\text{C(OCH}_3\text{)}_2\), \(\text{H}^+\)} (88\%);
\end{tikzpicture}
\end{center}

1.2.7 The Thomas C(10)-C(16) Fragment Synthesis\textsuperscript{90}

Thomas and Munt have reported the synthesis of a fragment corresponding to the C(10)-C(16) segment of the bryostatins. In their synthesis, the C(13) double bond geometry was to be set via the cyclisation of vinyl radical 199 (Scheme 73).

Their synthesis began with a Yamaguchi coupling\textsuperscript{91} of epoxide 202 with methyl lithiopropynoate 203 to give alcohol 201 (Scheme 74). The reaction between 201 and dimethyl diazomalonate 200 in the presence of \(\text{Rh}_2(\text{OAc})_4\)
delivered alkoxymalonate 204 which was then alkylated with Me₂N=CH₂⁺I⁻ to afford 205. N-Methylation of 205 with Mel resulted in decarboxylative elimination to afford enol ester 206.⁹² Conjugate addition of n-Bu₃SnCuLiBrMe₂S³² to 206 gave compound 207 which was then iodinated to deliver (E)-iodopyruvate 208. Subsequent treatment of 208 with tri-n-butyltin hydride resulted in radical mediated cyclisation via radical 199 to give a 4:1 mixture of olefins 209 and 210 respectively. A possible explanation of the preference for 209 lies with the observation that vinyl radical 199 equilibrates prior to cyclisation and due to the fact that the (Z)-radical cyclises quickest, the product with the methoxycarbonyl group trans to the newly formed carbon-carbon single bond is favoured. Also noteworthy is the observation that both products of the radical mediated cyclisation are 2,6-cis-disubstituted which implies stereoselective H⁻ transfer from the axial direction. Finally, after purification of 209, selective reduction of the C(10) ester with sodium borohydride delivered 198.
Scheme 74

[Chemical reactions and structures are depicted here.]

Chapter 1: Introduction

Page 63
1.2.8 The Hale Approach To The C(17)-C(27) Fragment of Bryostatin 1\textsuperscript{93}

Initial synthetic studies on the C(17)-C(27) section of bryostatin 1 (1) by the Hale group revolved around establishing the C(21) exocyclic olefin geometry via a radical mediated cyclisation-elimination of the phenylseleno-vinylstannane 212 (Scheme 75). Disconnection across the C(19)-O ether linkage in 212 gave compounds 213 and 214. Further disconnection of 214 led to epoxide 215 which could be prepared from D-glucose (216).

**Scheme 75**

Epoxide 215 was successfully synthesised in sixteen steps as shown in scheme 76.
Epoxide 215 was taken through to alcohol 216 but in poor yield, and as a result a more efficient synthetic route to the southern hemisphere of bryostatin 1 was sought.
2.1 DISCUSSION 1

The mechanism by which bryostatin 1 (1) induces tumour regression is unknown, but a hypothesis suggested by Pettit et al.\textsuperscript{7,8} has received some support from experiments \textit{in vitro}. However, further studies are going to be necessary before it is proven \textit{in vivo}. Such studies might be helped by the availability of different analogues of bryostatin 1 (1), and with this in mind, we elected to initiate a total synthesis programme on bryostatin 1 (1).

Bryostatin 1 (1) offers a unique and quite considerable synthetic challenge since it contains nine configurationally stable asymmetric centres, most of which are remote, and two stereodefined exocyclic $\alpha,\beta$-unsaturated esters. In addition, there is numerous free and masked hydroxyl functionality present within its structure, and differentiating between these groups will require the use of a quite elaborate protecting group strategy. Since bryostatin 1 (1) is susceptible to attack by strong acids and bases, protecting groups will have to be introduced that can be removed under neutral or mildly acidic conditions. Under strongly or acidic or basic conditions, the macrolactone would be susceptible to ring opening, and the C(13) and C(21) $\alpha,\beta$-unsaturated esters would be liable to isomerise. Under strongly nucleophilic conditions, (for example, in the presence of thiolate anions) these exocyclic alkenes might also act as possible nucleophile acceptors. In addition, the presence of double bonds clearly precludes the use of protecting groups that can be removed by catalytic hydrogenation.

Our latest retrosynthetic analysis of bryostatin 1 (1) has commenced with a protection of the respective anomeric hemiketals as methyl glycosides and a cleavage of the macrolactone to give $\beta$-hydroxy acid 230 (Scheme 77). Due to the susceptibility of lactones to ring opening reactions, we felt that lactonisation should be performed as late as possible in the synthesis. Macrolactonisation could potentially be achieved by treating \textit{seco}-acid 230 with DCC and PPTS to form an activated ester which could then cyclise under conditions of high dilution.\textsuperscript{94} Such a
cyclisation was performed successfully in Masamune's synthesis of bryostatin 7 (43), when many other cyclisation protocols failed.

**Scheme 77**

It was hoped that the mildly basic nitrogen of the acylimidate generated under the reaction conditions would participate in intramolecular hydrogen bonding with the C(25) hydroxy group and that this would potentially bring this hydroxyl into close proximity to the activated carbonyl. Clearly, as the hydrogen bond develops, the acyl imidate will become a better leaving group since its negative charge will be decreased. At the same time the anionic character of the hydroxy group will be increased, until eventually nucleophilic addition to the carbonyl site will be favoured, followed by expulsion of the dicyclohexyl urea leaving group. Mild acid hydrolysis of the methyl glycosides in the resulting lactone was then envisaged to deliver bryostatin 1 (1). This was expected to be a facile reaction due to the known acid lability of ketose (eg sucrose) and aldose 2,3-dideoxy glycosides.40

Retrosynthetic dissection of the C(2)-C(3) bond in acid 230 suggested aldehyde 231 and an asymmetric "thioacetate" aldol coupling reaction with 232. Subsequent retrosynthetic reduction of the carbonyl groups in 231 and protection of the resulting alcohols cleared its reactive functionality and actuated the C(15)-C(16) C-glycosidic linkage for retrosynthetic disconnection into glycosyl fluoride 234 and alkyne 233 (Scheme 78). Coupling of these fragments, utilising methodology developed by Kende in the synthesis of ambruticin,95 was expected
to proceed with inversion of configuration at the anomeric centre and retention of alkene geometry. Due to the fact that vinyl alanes are themselves not very nucleophilic, 234 might have to be converted to an "ate" complex with MeLi, in order to instigate coupling with electrophile 233.

**Scheme 78**

Thioglycosidation at C(15) in fluoride 233 and retro-cleavage of the glycosidic bond at C(9) allowed opening of the pyran ring and revealed ketone 235 after partial protection (Scheme 79). Recognition that a phenylsulfonyl unit could serve as a masked equivalent of the C(9) ketone in 235 (via a sulfone anion/oxidation transform) led to an incision being made across the C(9)-C(10) bond to give sulfone 236 and iodide 237. Use of the tactical combination of a catalytic asymmetric ene reaction between methyl glyoxylate 238 and the 1,1-disubstituted alkene 239, followed by alkene cleavage and hydroxyl-directed
reduction, was then envisaged for setting the C(7) and C(5) stereocentres in 236. An asymmetric ene reaction between methyl glyoxylate 238 and 240 was also considered an efficient way of stereoselectively installing the C(11) asymmetric centre and the exocyclic trisubstituted olefin in 237.

Scheme 79

In order to set the C(5) and C(11) stereocentres in sulfone 236 and iodide 237 respectively, a catalytic asymmetric glyoxylate-ene reaction using (S)-BINOL-\((i-\text{PrO})_2\text{TiCl}_2\),\(^{96}\) would be relied upon. The mechanistic outcome of the reaction can be predicted from the transition states shown for the reaction between methyl glyoxylate 238 and alkene 240 (Scheme 80).

Scheme 80
Although there are two sets of methylene hydrogens flanking the double bond in 240, the allylic hydrogens adjacent to the \( \text{CH}_2\text{OBn} \) group are sterically more accessible than those adjacent to the \((\text{EtS})_2\text{CH}\) group. Since steric accessibility is the major factor governing the regiochemical outcome of the ene-reaction, it follows that the newly created double bond in our ene-product will emerge adjacent to the \( \text{CH}_2\text{OBn} \) group. Molecular models of the chair-like transition state 242 that would appear most likely to lead to 241 reveal that it is remarkably free of steric repulsions (Scheme 81).

![Scheme 81](image)

On the other hand, the chair-like transition state that would probably lead to the undesired \((E)\)-alkene 243 geometry in the ene product appears to be plagued by serious steric repulsions between the catalyst ligands and the \( \text{CH}_2\text{OBn} \) group (Scheme 82). Models also indicate that the desired \((S)\)-alcohol stereochemistry at C(11) should prevail if \((S)\)-BINOL-\((i-\text{PrO})_2\text{TiCl}_2\) is used as the catalyst, since transition state 246 would have to prevail to obtain the \((R)\)-alcohol 245 stereochemistry at C(11); this suffers from serious 1,3-diaxial interaction between the \((\text{EtS})_2\text{CH}\) and \(\text{CO}_2\text{Me}\) groups.
Our new retrosynthetic analysis of the southern hemisphere 244 is shown in schemes 83 and 84.

It was felt that vinyl alane 244 could potentially be derived from alkyne 247, by a $[\sigma^2_s + \sigma^2_a + \sigma^0_o]$ cis-addition of diisobutylaluminium hydride, catalysed possibly, with zirconocene dichloride ($\text{Cp}_2\text{ZrCl}_2$). The regiochemistry of the
addition would be determined by a desire to minimise steric repulsions between the \( i\text{-Bu}_2\text{Al} \) moiety and the newly established vinylic group. A Wittig reaction on hemiacetal 249 with \( \text{PPh}_3/\text{CBr}_4 \) would in principle deliver dibromolefin 248 after silylation, and this could be converted to alkyne 247 via halogen-metal exchange and elimination with \( n\)-butyllithium.

A retrosynthetic oxidation/reduction sequence would allow interconversion of 249 into 250 and vice versa (Scheme 84).

Scheme 84

![Scheme 84](image)

Our tactic for installing the exocyclic trisubstituted alkene in 250 was based on a stereoselective Wittig reaction between ketone 251 and the stabilised ylide 252 (Scheme 85).

Scheme 85

![Scheme 85](image)

The key steps in our plan towards glycoside 253 were a Claisen condensation\(^98\) between anion 254 and ester 255 to establish the C(18)-C(19) bond, a subsequent unveiling of the C(20), C(21) and C(23) hydroxyl protecting
groups, a Fischer glycosidation to introduce the axial methyl glycoside at C(19), and a butyrolactonisation between the C(17)-ester and the C(20)-hydroxyl group (Scheme 86). Ester 255 would be obtainable from aldehyde 256 via a Wittig olefination/Sharpless asymmetric dihydroxylation (AD)\(^{99}\) strategy. Wittig homologation of aldehyde 258 followed by Sharpless asymmetric epoxidation\(^{13}\) and regioselective REDAL reduction\(^{14}\) was envisaged to allow the C(23) stereocentre to be introduced in 256 in a controlled manner. The two stereocentres in diol 259 would be set by a sequence involving a chemoselective AD reaction on diene 260.\(^{100}\) O-Silylation of 259 followed by oxidative cleavage and two carbon homologation would then be expected to give 258.

![Scheme 86](image)

Our synthetic approach to 250 commenced with the synthesis of diol 259. According to Sharpless,\(^{100}\) 259 could be prepared in one step via the osmium-catalysed asymmetric dihydroxylation of trans-1,4-hexadiene 260 with AD-mix-\(\beta\). Compound 259 was obtained in 46-58% yield after extractive work-up and isolation by flash SiO\(_2\) chromatography (Scheme 87); due to the volatility of 259, care must be taken when removing the solvents during purification, in order to avoid material losses. It was immediately apparent from the IR spectrum of 259 that dihydroxylation had been successful since a strong, broad O-H absorption
band was present at 3350 cm\(^{-1}\). Moreover, its 100 MHz \(^{13}\text{C}\) NMR spectrum in CDCl\(_3\) contained a signal at \(\delta 134.3\) in the region characteristic of terminal olefinic carbons. There was also a signal resonating at \(\delta 118.2\) which was attributable to the C(23) olefinic carbon. The 400 MHz \(^1\text{H}\) NMR spectrum of 259 in CDCl\(_3\) indicated the presence of 3 vinylic protons; the C(23) proton appeared as a multiplet at \(\delta 5.83\) while the terminal alkene protons resonated as multiplets at \(\delta 5.15\) and 5.12 respectively. The C(25) and C(26) methine protons appeared as single-proton multiplets at \(\delta 3.62\) and 3.39 respectively; their low-field positions were indicative of the presence of electron-withdrawing hydroxyl groups. The hydroxyl protons themselves resonated as broad singlets at \(\delta 2.65\) and \(\delta 2.54\) respectively. Multiplets at \(\delta 2.32\) and \(\delta 2.14\) were attributable to the C(24) methylene hydrogens whilst the C(27) methyl group resonated as a doublet at \(\delta 1.16\) (\(J = 6.3\) Hz). Further evidence for the structure of 259 came from its high resolution mass spectrum which contained an (M+NH\(_4\))^+ peak at \(m/e\) 134.1186. The low resolution mass spectrum contained a fragmentation peak at \(m/e\) 99 due to (M-OH)^+.

The absolute stereochemistry of compound 259 was proven by its conversion into known \((2R, 3R)-2,3\text{-hexanediol}\) 261. The spectral data of 261 correlated well with that reported in the literature and our optical rotation value was +18.4° (c 1, CHCl\(_3\)) which compared well with the literature value of +22.3° (c 1.22, CHCl\(_3\)). Sharpless had not previously performed a stereochemical correlation for diol 259 with a known compound. Our work confirmed the stereochemistry he had assigned using his mnemonic device.99
Silylation of the hydroxyl groups in 259 was accomplished in 84% yield by treatment with t-butyldimethylsilyl chloride and imidazole in dry DMF\textsuperscript{41} at 85 °C (Scheme 88). From the 400 MHz \textsuperscript{1}H NMR spectrum of 262 in CDCl\textsubscript{3} the presence of t-butyldimethylsilyl groups was immediately apparent; the t-butyl groups gave rise to two singlets at $\delta$ 0.86 and 0.85 each of which integrated to nine protons due to the methyl silyl groups. In addition, there were four singlets at very high field at $\delta$ 0.03, 0.02, 0.01 and 0.00; their chemical shifts were indicative of strong shielding of the methyl hydrogens by the electropositive silicon atom. The lack of a strong O-H absorption band in the IR spectrum further confirmed that the hydroxyl groups had been blocked. Our assignment was further validated by the observation of a (M+H)$^+$ ion at $m/e$ 345.2640 in its high resolution mass spectrum along with fragmentation peaks for (M-C\textsubscript{4}H\textsubscript{9})$^+$ and (M-t-BuMe\textsubscript{2}SiO)$^+$ at 287 and 213 respectively.

Oxidative cleavage of the double bond in 262 was successfully achieved with catalytic osmium tetraoxide (1.8 mol %) and sodium periodate (6.5 equiv) in aqueous THF\textsuperscript{102} to give aldehyde 258 in 70% yield. Its structure was proven by a combination of \textsuperscript{1}H, \textsuperscript{13}C and IR spectroscopy. The 400 MHz \textsuperscript{1}H NMR spectrum of 258 in CDCl\textsubscript{3} was particularly diagnostic, since it no longer contained vinylic proton resonances between $\delta$ 5.80 and 5.00. Moreover, there was a narrow triplet at $\delta$ 9.75 ($J = 2.7$ Hz) in the region where aldehyde resonances are typically found. Its multiplicity was due to vicinal coupling with the two non-equivalent C(24) methylene hydrogens, which themselves resonated as doublets of double-doublets.
at δ 2.63 \( (J = 2.7, 4.5, 15.7\) Hz) and δ 2.42 \( (J = 2.8, 7.9, 15.7\) Hz) respectively. Single proton multiplets at δ 4.14 and δ 3.81 were attributable to H(26) and H(25). The C(27) methyl group appeared as a doublet at δ 1.06 with a coupling of \( J = 6.2\) Hz with the C(26) hydrogen. The presence of a carbonyl group in the molecule was further corroborated by the 100 MHz \(^{13}\)C NMR spectrum of 258 in CDCl\(_3\) which exhibited a signal at δ 201.9, and its IR spectrum which displayed a C=O absorption band of medium intensity at 1732 cm\(^{-1}\) which was characteristic of an aldehyde group.

The action of sodium periodate in oxidative cleavage is twofold: (a) it serves as a co-oxidant to regenerate Os\(^{\text{VIII}}\) and (b) it also cleaves the glycol unit. Osmylation is believed to proceed via a cyclic osmate ester, and in the process Os\(^{\text{VIII}}\) is reduced to Os\(^{\text{VI}}\). Eyring plot data suggests that osmylation is a stepwise process, and this has been interpreted in terms of a 4-membered oxa-metallacycle 263 being formed. This intermediate then reacts with a ligand, in this case water, and this triggers rearrangement to the five membered osmium chelate 264 (Scheme 89).

**Scheme 89**

Periodate oxidation is believed to proceed via the cyclic intermediate 266 shown in scheme 90.
Our next objective was to convert aldehyde 258 into diol 270. This was achieved by the sequence of reactions shown in scheme 91. The C(21) and C(22) carbons were installed via a Wittig reaction between aldehyde 258 and stabilised ylide Ph₃P=CHCO₂Et in dry CH₂Cl₂. This proceeded smoothly to give the (E)-α,β-unsaturated ester 267 in 95% yield as essentially one geometrical isomer. As anticipated, the 400 MHz ¹H NMR spectrum of 267 in CDCl₃ no longer contained an aldehydic proton resonance at δ 9.75, but instead showed two signals in the olefinic region: H(23) resonated as a multiplet at δ 6.95, while H(22) resonated as a doublet of triplets at δ 5.80 (J = 1.4, 15.7 Hz). There appeared to be long range coupling (J = 1.4 Hz) between H(22) and the methylene hydrogens of the ethyl
group in addition to the expected $^{3}J_{H22-H23}$ coupling. The large coupling constant between H(22) and H(23) was indicative of a large dihedral angle and hence trans-olefin geometry. Also, the methylene protons of the ethyl group appeared as a two-proton quartet of doublets at $\delta$ 4.16 ($J = 1.1, 7.1 \text{ Hz}$) while the methyl group resonated as a triplet at $\delta$ 1.26 ($J = 7.1 \text{ Hz}$). The C(24) hydrogens were located in an upfield position as multiplets at $\delta$ 2.48 and 2.17 respectively, and each integrated to one proton. The presence of an (M+H)$^{+}$ ion at $m/e$ 417.2850 in the high resolution mass spectrum of 267 further reinforced our structural assignment.

Reduction of compound 267 with DIBAL$_3$ proceeded smoothly to deliver allylic alcohol 268 in 93% yield. Analysis of its 400 MHz $^1$H NMR spectrum in CDCl$_3$ indicated that the ethyl group had been lost since the signals at $\delta$ 4.16 and $\delta$ 1.26 had disappeared. They were now replaced by a broad signal at $\delta$ 1.26 which integrated to one proton and suggested the presence of an hydroxyl group in the molecule. In addition, there was a doublet at $\delta$ 4.07 ($J = 5.1 \text{ Hz}$) which integrated to 2 protons and was attributable to the C(21) methylene hydrogens of the newly installed CH$_2$OH group. Both vinylic protons now resonated as a complex multiplet at $\delta$ 5.65. The IR spectrum of 268 also suggested that reduction had been successful since there was no absorbance in the carbonyl region and a broad O-H absorption band was present at 3500 cm$^{-1}$.

Sharpless asymmetric epoxidation$^{13}$ was executed on (E)-allylic alcohol 268, with (-)-DET as the chiral additive. It proceeded smoothly over 48 h delivering epoxy alcohol 269 in 89% yield and 96% ee. The disappearance of the two proton olefinic multiplet at $\delta$ 5.65 in the 400 MHz $^1$H NMR spectrum of 269 in CDCl$_3$ and its replacement with multiplets at $\delta$ 2.93 and 3.05, each of which integrated to one proton, confirmed that epoxidation had been successful. The C(21) methylene protons were now diastereotopic and appeared as multiplets at $\delta$ 3.92 and $\delta$ 3.59 respectively. In addition, the lack of resonances in the olefinic region in the $^{13}$C NMR spectrum and a correct (M+H)$^{+}$ ion at $m/e$ 391.2694 in the high resolution mass spectrum of 269 further substantiated our assignment. The absolute
stereochemistry of 269 was assigned by the Sharpless face-selection rule for the asymmetric epoxidation, for which no violations have ever been found. The extent of asymmetric induction was evaluated by converting 269 into its (R)-MTPA ester 271 and analysing its 376 MHz $^{19}$F NMR spectrum in CDCl$_3$ (Spectrum 1). The combination of carboxyl activation by dicyclohexylcarbodiimide (DCC) and catalysis by 4-dimethylaminopyridine (DMAP) provided a useful method for the \textit{in situ} activation of $\alpha$-methoxy-$\alpha$-(trifluoromethyl)phenyl acetic acid [(R)-MTPA] for its reaction with 269 at room temperature$^{103,104}$ to yield Mosher ester 271 (Scheme 92). By integrating the trifluoromethyl signals in the $^{19}$F NMR spectrum of 271 we were able to determine that it was of 96% ee.

\textbf{Scheme 92}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {269};
\node (b) at (4,0) {271};
\path[->] (a) edge node[midway, above] {OTBS} node[midway, below] {OTBS} node[midway, above] {OTBS} (b);
\end{tikzpicture}
\end{center}

Regioselective reduction of epoxy alcohol 269 with REDAL$^{13}$ at -20 °C gave the 1,3-diol 270 in 82% yield. The origin of the regioselectivity of this epoxide ring-opening reaction is illustrated in scheme 93. The hydroxyl group of 269 is believed to be converted to an aluminium alkoxide by reaction with a molecule of REDAL and the epoxy oxygen coordinates to an aluminium which results in the weakening of the epoxide C-O bonds. Due to the bulk of the aluminium alkoxide species the hydride is delivered to the site of least steric hindrance.

\textbf{Scheme 93}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {272};
\node (b) at (4,0) {270};
\path[->] (a) edge node[midway, above] {OTBS} node[midway, below] {OTBS} node[midway, above] {OTBS} (b);
\end{tikzpicture}
\end{center}
SPECTRUM 1: $^{19}$F NMR DETERMINATION OF ENANTIOMERIC EXCESS OF EPQXY ALCOHOL 269 VIA ITS MOSHER ESTER 271

The presence of two broad, single-proton singlets at $\delta$ 4.28 and 3.17 respectively in the 400 MHz $^1$H NMR spectrum of 270, suggested the presence of two hydroxyl groups in the molecule.

The next stage in the synthesis was the selective protection of the secondary C(23)-hydroxyl. This was achieved by a two step procedure involving the protection
of the diol unit as its p-methoxybenzylidene acetal\textsuperscript{105} and a regioselective acetal reduction with DIBAL as described by Takano\textsuperscript{106} (Scheme 94).

**Scheme 94**

Protection of the 1,3-diol unit in 270 as a p-methoxybenzylidene acetal was achieved by treatment with anisaldehyde dimethyl acetal and a catalytic quantity of pyridinium p-toluenesulfonate (PPTS) in dry DMF at 22 mm Hg and 55 °C. These conditions delivered the thermodynamically more stable isomer 273 (with p-MeOC\textsubscript{6}H\textsubscript{4} group equatorial) in 78% yield. The 400 MHz \textsuperscript{1}H NMR spectrum of 273 in CDCl\textsubscript{3} revealed the four aromatic hydrogens of the p-methoxyphenyl group resonating as doublets at \( \delta 7.39 \) and \( \delta 6.84 \) (\( J = 8.8 \) Hz). The methoxy group gave rise to a singlet at \( \delta 3.79 \). The benzylidene proton resonated as singlet at \( \delta 5.40 \). The IR spectrum of 273 further confirmed its structure since no absorption band could be detected. Additionally the high resolution mass spectrum of 273 exhibited a peak at \( m/e 510.3206 \) which clearly corresponded to an \((M)^{+}\) ion.

Regioselective cleavage of acetal 273 with DIBAL in dry CH\textsubscript{2}Cl\textsubscript{2} at -40 °C delivered exclusively the primary alcohol 274 in 73% yield. The preferential formation of 274 over 275 is brought about by the steric effect of the bulky alkyl chain at C(24) which shields the oxygen at C(23) (Scheme 95).
Inspection of the 400 MHz $^1$H NMR spectrum of 274 in CDCl$_3$ confirmed the presence of the $p$-methoxybenzyl group since there was a two proton singlet at $\delta$ 4.49, which was attributable to the newly formed benzylic hydrogens, and the benzylidene acetal hydrogen at $\delta$ 5.40 had disappeared. The hydroxyl proton resonated as a broad singlet at $\delta$ 2.54, and gave rise to a broad absorption band at 3400 cm$^{-1}$ in its IR spectrum. The high resolution mass spectrum of 274 contained a peak at $m/e$ 512.3365 corresponding to the (M)$^+$ ion. There was also a peak at $m/e$ 377 due to the daughter ion (M - $p$-MeO-C$_6$H$_4$-CH$_2$O)$^+$. A two step sequence involving Swern oxidation$^{27}$ and Wittig olefination was used to introduce carbons C(19) and C(20) in 278 (Scheme 96).

A two step sequence involving Swern oxidation$^{27}$ and Wittig olefination was used to introduce carbons C(19) and C(20) in 278 (Scheme 96).
The Swern oxidation of alcohol \(274\) delivered aldehyde \(256\). Its structure was elucidated by \(^1\)H, \(^{13}\)C, IR and mass spectroscopy. The 400 MHz \(^1\)H NMR spectrum of \(256\) in CDCl\(_3\) revealed an aldehydic resonance at \(\delta 9.77\) (triplet, \(J = 2.3\) Hz). The installation of the carbonyl group at C(21) resulted in the C(22) methylene hydrogens now resonating further downfield as a two-proton double-doublet at \(\delta 2.65\) (\(J = 2.3, 5.7\) Hz), their splitting pattern arising from coupling with the aldehyde and the C(23) methine protons. Geminal coupling between the benzylic hydrogens resulted in the appearance of an AB quartet (\(J = 11.0\) Hz) at \(\delta 4.44\). Importantly, the IR spectrum of \(256\) no longer contained an hydroxyl absorption but did a show strong C=O absorption at 1727 cm\(^{-1}\). The 100 MHz \(^{13}\)C NMR spectrum of \(256\) in CDCl\(_3\) also displayed the expected aldehyde resonance at \(\delta 201.7\). A peak at \(m/e\) 533.3095 in the high resolution mass spectrum of \(256\) corresponded to \((\text{M+Na})^+\).

Treatment of crude aldehyde \(256\) with stabilised ylide Ph\(_3\)P=CHCO\(_2\)Et in dry CH\(_2\)Cl\(_2\) gave the (E)-\(\alpha,\beta\)-unsaturated ester \(278\) as essentially one geometrical isomer in an overall yield of 76% for the two steps. Examination of the 400 MHz \(^1\)H NMR spectrum of \(278\) in CDCl\(_3\) revealed that the aldehyde signal at \(\delta 9.77\) was no longer present. Instead there were now two resonances in the region characteristic of \(\alpha,\beta\)-unsaturated olefinic hydrogens. The vinylic protons H(21) and H(20) resonated as a doublet of triplets at \(\delta 6.97\) (\(J = 7.2, 15.7\) Hz) and a multiplet at \(\delta 5.86\) respectively. The large value for \(J_{H20-H21} = 15.7\) Hz was suggestive of trans-olefin geometry. The protons of the newly introduced ethyl ester were observed as an apparent two-proton quartet at \(\delta 4.17\) (\(J = 7.1\) Hz) and a three-proton triplet at \(\delta 1.27\) (\(J = 7.1\) Hz). The C(22) methylene hydrogens resonated as a two-proton multiplet now slightly further upfield at \(\delta 2.48\). The three proton complex multiplet between \(\delta 3.82\) and \(\delta 3.66\) was attributable to the C(26), C(25), and C(23) hydrogens respectively. The C(24) hydrogens each resonated as multiplets at \(\delta 1.92\) and \(\delta 1.36\) respectively whilst the C(27) methyl group appeared as the expected doublet at \(\delta 1.02\) (\(J = 6.2\) Hz). In addition, a strong absorption band at 1723 cm\(^{-1}\) in the IR spectrum of \(278\) was indicative of a carbonyl moiety in the
molecule. Our overall structural assignment was finally corroborated by the observation of a signal at \( m/e \) 603.3514 in the high resolution mass spectrum of 278 which clearly corresponded to the \((M+Na)^+\) ion.

The next stage of the synthesis was introduction of the C(20) stereocentre via Sharpless asymmetric dihydroxylation\(^99\). This was accomplished by treatment of 278 with AD-mix-\(\beta\) in \( t\)-BuOH: \( H_2\text{O} \) (1:1) at 0 °C in the presence of methanesulfonamide (Scheme 97). The best conditions utilised 5.6 g of AD-mix \(\beta\) for each mmol of 278 and four equivalents of methanesulfonamide. The inclusion of methanesulfonamide has been reported by Sharpless to increase the rate of reaction for non-terminal olefins yet it slows the reaction for terminal olefins. The AD reaction of 278 was totally stereoselective, furnishing diol 279 in 86% yield.

The structure of 279 was apparent after inspection of its 400 MHz \(^1\)H NMR spectrum in CDCl\(_3\). This indicated that the alkene found in 278 was no longer present there being no observable signals in the vinylic region of the spectrum. The C(21) hydrogen, which had previously resonated at \( \delta \) 6.97 in 278 was now shifted much further upfield, it appearing as a multiplet at \( \delta \) 4.11. The C(20) hydrogen also resonated much further upfield as a narrow doublet at \( \delta \) 3.99 (\( J = 1.8 \) Hz). Its splitting pattern was the result of coupling with the C(21) methine proton; the small \( J \) value was indicative of a dihedral angle of approximating 65° and suggestive of a syn relationship between the two OH groups. The appearance of a very broad singlet at \( \delta \) 2.85 that integrated to two protons confirmed that two hydroxyl groups were present in the molecule and this was further substantiated by the IR spectrum of 279 which contained a strong, broad O-H absorption band around 3450 cm\(^{-1}\). A
signal at \( m/e \) 637.3581 in the high resolution mass spectrum of 279, which corresponded to \((M+Na)^+\), reinforced these structural findings.

Completion of the C(17)-C(27) framework was accomplished in a further two steps as shown in scheme 98.

![Scheme 98](image)

The diol functionality in 279 was first protected as an isopropylidene acetal by treatment with 2,2-dimethoxypropane and catalytic pyridinium \( p \)-toluenesulfonate in acetone\(^{17}\) at 40 °C for 12 h; compound 255 was obtained in 91% yield after flash chromatography. Running the reaction at room temperature resulted in similar yields but the reaction times were in the order of five days. Two three-proton singlets at \( \delta \) 1.45 and 1.40 respectively in the 400 MHz \(^1\)H NMR spectrum of 255 in CDCl\(_3\) confirmed the presence of the geminal methyl groups in the newly installed isopropylidene acetal. The loss of the broad two proton singlet at \( \delta \) 2.85 and the absence of an OH absorption band in its IR spectrum further indicated that hydroxyl protection had been successful.

A Claisen condensation was then executed on 255 with approximately seven equivalents of the lithium enolate obtained from methyl isobutyrate and LDA in THF at -78 °C.\(^{98}\) After the ester had been added to the enolate anion, warming of the reaction mixture to -20 °C, delivered \( \beta \)-keto ester 280 in 84% yield. The structure of 280 was deduced by 400 MHz \(^1\)H NMR spectroscopy. More specifically, in CDCl\(_3\) there were now singlets at \( \delta \) 3.68, 1.36 and 1.35, which were attributable to the newly introduced methoxy and geminal dimethyl groups.
respectively. Moreover, none of the resonances associated with the ethyl ester were present. A signal at $\delta$ 206.0 in the 100 MHz $^{13}$C NMR spectrum of 280 in CDCl$_3$ and a medium intensity absorption band at 1758 cm$^{-1}$ in the IR spectrum further confirmed the presence of a ketone.

It was envisaged that removal of the acetonide unit from 280 under acid conditions would instigate cyclisation to a butyrolactone and also result in ring closure of the pyran hemiketal ring system. However, in view of the acid labile nature of t-butyldimethylsilyl ethers it was deemed necessary to make a change in protecting groups for the C(25) and C(26) hydroxyl groups with acid stable pivaloyl esters$^{107}$ as shown in scheme 99.

**Scheme 99**

O-Desilylation of 280 was accomplished with HF-pyridine complex$^{42}$ in THF at -5 °C and furnished diol 281 in 98% yield. The best conditions for obtaining 281 in high yield employed 2.6 ml of the HF/pyridine complex for every mmol of 280. From the 400 $^1$H NMR spectrum of 281 in CDCl$_3$ it was evident that the t-butyldimethylsilyl groups had been lost. The signals corresponding to the hydrogens of the two t-butyl groups at $\delta$ 0.88 and 0.86, and those of the four methyl groups in the region of $\delta$ 0.02 respectively could no longer be observed. Furthermore, the appearance of two broad resonances at $\delta$ 3.06 and 2.54 suggested the presence of two hydroxyl groups in the molecule. Our structural
assignment was further validated by the IR spectrum of 281 which contained a broad O-H absorbance in the region of 3425 cm\(^{-1}\), and the presence of an (M + Na\(^{+}\)) ion at \(m/e\) 505.2424 in its high resolution mass spectrum.

The hydroxyl groups in 281 were then acylated by treatment with pivaloyl chloride and excess pyridine in dry CH\(_2\)Cl\(_2\) to give 282 in 92\% yield. Two t-butyl singlets at \(\delta\) 1.20 and 1.16 respectively in the 400 \(^1\)H NMR spectrum in CDCl\(_3\) demonstrated that the pivaloyl esters had been introduced. The deshielding effects of the pivaloyl groups resulted in the C(25) and C(26) methines resonating much further downfield as multiplets at \(\delta\) 5.30 and \(\delta\) 4.91.

With 282 in hand the next stage of the synthesis required the unmasking of the C(20), C(21) and C(23) hydroxyl functionalities. The first step was the deprotection of the C(23)-hydroxyl group. Treatment of 282 with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) in CH\(_2\)Cl\(_2\)-H\(_2\)O (17:1\(^2\)) proceeded smoothly and resulted in the removal of the \(p\)-methoxybenzyl ether. Alcohol 283 was isolated as the sole product in 94\% yield after flash chromatography (Scheme 100).

**Scheme 100**

Analysis of the 400 \(^1\)H NMR spectrum of 283 in CDCl\(_3\) indicated that the signals for the \(p\)-methoxybenzyl moiety were no longer present. A broad singlet at \(\delta\) 3.24, and a broad O-H absorption at 3531 cm\(^{-1}\) in the IR spectrum, were both suggestive of successful hydroxyl deprotection. Our structural assignment was further reinforced by the high resolution mass spectrum of 283 which contained a signal at \(m/e\) 548.3431 which clearly corresponded to the (M+NH\(_4\))\(^{+}\) ion. As expected,
ring closure did not occur during this step due to the instability of the trans-fused 6,5-ring system.

Treatment of alcohol 283 with Amberlyst-15 (H+) resin in anhydrous methanol at 60 °C proceeded slowly over 30 h and resulted in the loss of acetonide group. As planned, these conditions induced butyrolactonisation and ring closure of the pyran hemiketal ring system to give a mixture of α and β-hemiacetals 284. The resin was removed from the reaction mixture by filtration, the filtrate concentrated in vacuo and the crude material, containing 284, was then subjected to Fischer glycosidation conditions using acetyl chloride in dry methanol at a concentration of 0.17 M and a temperature of 40 °C. After 28 h, the reaction mixture was worked-up and the desired α-methyl glycoside 253 was isolated by flash chromatography in 63% yield (Scheme 101).

![Scheme 101](image)

Evidence that the hydroxyl group and the γ-butyrolactone ring system had been formed was provided by the IR spectrum of 253 since it contained two intense bands in the region characteristic of O-H stretching frequencies, and two strong C=O stretching absorptions at 1793 and 1784 cm\(^{-1}\) respectively. The high frequency positions of both the C=O absorption bands were suggestive of significant angular strain within the bicyclic ring system. Inspection of the 400 \(^1\)H NMR spectrum of 253 in CDCl\(_3\) clearly indicated that the acetonide group had
been cleaved. The singlets due to the geminal dimethyl unit appeared at δ 1.33 and 1.25 respectively, while the methoxy group gave rise to a singlet at δ 3.31. The C(20) proton appeared as a doublet at δ 4.11 (J$_{20\text{eq}-21\text{ax}}$ = 2.8 Hz) whilst the C(21) and C(23) protons resonated as multiplets at δ 4.22 and 3.88 respectively. A complex multiplet integrating to four hydrogens was present between δ 1.80 and δ 1.64, which was attributable to the C(22) and C(24) methylene groups. The low field positions of the single proton multiplets at δ 5.23 and δ 4.93 respectively were attributable to the H(25) and H(26) atoms in the molecule. The remaining hydroxyl proton resonated as a broad doublet at δ 2.34 (J = 7.6 Hz). A 1,3-diaxial relationship between the axial C(23) hydrogen and the C(19) methyl glycoside was apparent from the 400 MHz $^1$H NMR NOESY spectrum in CDCl$_3$ since there was a significant NOE between them, which indicated they could mutually relax each others spin via through-space interactions due to their syn relationship with each other. Further verification for these assignments for 253 came from its $^1$H NMR COSY spectrum in CDCl$_3$ (Spectrum 2). The molecular mass of 253 was corroborated by the presence of a signal at m/z 473.2755 (Calcd. m/z 473.2751) in its high resolution mass spectrum; this indicated that 253 had an empirical formula of C$_{24}$H$_{41}$O$_9$.

To finalise the synthesis of 250 all that now remained was to install the exocyclic α,β-unsaturated ester (scheme 102).

**Scheme 102**
SPECTRUM 2: COSY $^1$H NMR 400 MHz Spectrum of 253 in CDC$_3$
Oxidation of glycoside 253 with catalytic ruthenium trichloride (8 mol%) and sodium periodate (2.0 equivalents) as a co-oxidant in MeCN:CCl₄:H₂O (2:2:3) resulted in ketone 251 in 92% yield after isolation by flash chromatography. The appearance of a signal at δ 199.2 in the 100 MHz ¹³C NMR spectrum of 251 in CDCl₃ corroborated the introduction of a ketone moiety in the molecule. Its 400 MHz ¹H NMR spectrum in CDCl₃ revealed its C(20) proton as the expected singlet at δ 4.16, and that the hydroxyl proton at δ 2.34 in 253 was now absent.

The synthesis of 250 was completed by the execution of a Wittig reaction on ketone 251 with stabilized ylide MeO₂CCH=PPh₃ in dry CH₂Cl₂. Isolation of the product and analysis of its 400 MHz ¹H NMR spectrum in C₆D₆ indicated that the olefination had been non-stereoselective, it delivering a 1:1 mixture of (E)- and (Z)-geometrical isomers 250 and 285 respectively (Scheme 103). However, the latter were successfully separated by multiple elution preparative TLC.

Scheme 103

\[ \begin{align*}
  &\text{MeO₂CCH=PPh₃} \quad (80\%) \\
  &\text{1:1 stereoselectivity}
\end{align*} \]

The olefin geometry of 250 and 285 was immediately apparent after comparison of their respective ¹H NMR spectra. The very low field chemical shift position of the C(20) equatorial hydrogen in 285 which resonated as a singlet at δ 6.49, was indicative of it residing in the deshielding cone of the α,β-unsaturated ester carbonyl group and therefore suggestive of (Z)-olefin geometry. The
corresponding C(22) equatorial hydrogen in 250 also appeared much further downfield than one would normally expect for an allylic methylene, resonating at δ 3.91 (double-doublet, \( J = 1.7, 14.0 \) Hz). Its position again reflected its occupancy of the C=O deshielding cone. The axial hydrogen at C(22) in 250 resonated as a doublet of double-doublets at δ 2.09 (\( J = 1.8, 11.8, 14.0 \) Hz). In the case of 250 this geometrical assignment was further confirmed by its 400 MHz \( ^1\)H NMR NOESY spectrum. This revealed a strong NOE between H(20) (δ 4.07) and the vinyl hydrogen at δ 5.85 which resonated as a narrow doublet (\( J = 1.7 \) Hz) (Spectrum 3).

The C(23) hydrogen resonated as a multiplet at δ 3.70 and gave rise to a significant NOE with the C(19) methyl glycoside signal at δ 3.11. The low-field signals at δ 5.37 (doublet of triplets, \( J = 4.6, 7.4 \) Hz) and δ 4.99 (doublet of quartets, \( J = 4.6, 6.5 \) Hz) in 250 were attributable to the hydrogens of C(25) and C(26) respectively. As one would expect, the methoxy group of the α,β-unsaturated ester appeared as a three proton singlet at δ 3.25 whilst the geminal dimethyl groups on the lactone portion resonated much further upfield at δ 1.38 and 0.92 respectively. A doublet at δ 1.00 (\( J = 6.5 \) Hz) was attributable of the C(27) methyl group and two singlets at δ 1.13 and 1.06 were clearly due to the pivaloyl ester groups. The C(24) hydrogens resonated as a two-proton double-doublet at δ 1.56 (\( J = 5.3, 7.3 \) Hz). Further verification for the proposed structure of 250 was obtained from its \( ^1\)H NMR COSY spectrum, (Spectrum 4). In addition, the peak at \( m/e \) 549.2672 in its high resolution mass spectrum corresponded to (M+Na)+, and the satisfactory microanalysis obtained for C\(_{27}\)H\(_{42}\)O\(_{10}\) (Calcd.: C, 61.58; H, 8.04%. Found: C, 61.42; H, 8.40%) further reinforced our structural assignment.

Molecular model studies of ketone indicated that the level of selectivity in favour of \textit{trans}-olefin geometry could possibly be improved if the steric factor of the five-membered ring system was utilised. The reaction between ketone 251 and the bulkier \( t\)-BuO\(_2\)CCH=PH\(_3\) in CH\(_2\)Cl\(_2\) showed this to be the case, delivering an improved 3:1 selectivity in favour of the desired geometrical isomer 286 (Scheme 104).
In conclusion, we have prepared an advanced intermediate whose structure incorporates carbons 17 to 27 of the bryostatin 1 skeleton.\textsuperscript{110}

During the synthesis it became apparent that the acidity of the conditions required for simultaneous Fischer glycosidation and lactonisation of a specie such as 280 would invariably lead to C(25) and C(26) O-desilylation. Hence, this resulted in the temporary introduction into the synthesis of the acid stable pivaloyl esters at C(25) and C(26). However, their presence, in conjunction with that of the lactone moiety in the molecule, was envisaged as creating problems in a successful synthesis of alkyne 247 and therefore this study would inevitably have to be modified. It is hoped that replacing the acid labile C(25) and C(26) \textit{tert}-butyldimethylsilyl ethers with acid stable benzyl ethers early in the synthesis will allow us to perform the aforementioned chemistry and deliver 289 (Scheme 105).

Also, if the selectivity of the final olefination cannot be improved from the present 3:1 level, we will attempt to isomerise the exocyclic alkene mixture with phenyldisulfide and \textit{u.v.} light to obtain a single (\textit{E})-olefin isomer 289. Lichtenhaler and coworkers have recently used this tactic with some success in their synthesis of (+)-anamarine.\textsuperscript{111} If this fails, a Peterson olefination approach will be investigated.
A sequence of reactions beginning with the reduction of 289 with diisobutylaluminium hydride followed by $O$-silylation of the allylic hydroxyl moiety should deliver hemiacetal 290. Debenzylation followed by reprotection of the corresponding 1,2 diol as an acetonide should in principle deliver 249. A Colvin-Gilbert alkynation reaction on lactol 249 followed by $O$-silylation will complete the synthesis of alkyne 247, and set the stage for hydrometallation and subsequent unification with the northern sector 233 (Scheme 106).
Chapter 2: Discussion 1

SPECTRUM 3: 400 MHz NOESY $^1$H NMR Spectrum of 250 in C$_6$D$_6$
SPECTRUM 4: 400 MHz COSY $^1$H NMR Spectrum of 250 in $C_6D_6$
2.2 DISCUSSION

ALTERNATIVE ROUTES TO THE BRYOSTATINS

Initial investigations into the development of a total synthesis of the bryostatins led to work on the C(20) deoxy member, namely bryostatin 11 291. Our retrosynthetic analysis began with a familiar cleavage of the macrolactone to give \(\omega\)-hydroxythiopyridyl ester 292, followed by dissection of the C(15)-C(16) bond to give 293 and 294 respectively (Scheme 107). Cleavage of the C(9)-C(10) bond in 294 led to target molecule 295, the C(10)-C(15) fragment.

Retrosynthetic comparison of glycoside fluoride 295 with methyl-\(\alpha\)-D-mannopyranoside 298 suggested the possibility of the early introduction of the
exocyclic double bond at C(13). The cis allylic methyl ester 297 could be obtained in principle from the olefination of the corresponding 3-keto sugar\textsuperscript{113,114} which could be obtained as a product of acetal elimination resulting in the deoxygenation of C(14). This early introduction of the double bond would therefore entail (in the synthesis) the deoxygenation of an allylic hydroxyl functionality positioned at C(12) to give 296 from which 295 could in principle be obtained from the corresponding phenyl sulphide (Scheme 108). This led to the proposed route shown in scheme 109.
The first step of our approach required the preparation of the di-\(O\)-benzylidene acetal 299. Benzaldehyde dimethyl acetal, and a catalytic amount of \(p\)-TsOH in DMF were reacted under vacuum on a rotary evaporator at a temperature of 70 °C. After aqueous work up this delivered the known compound 299 as a white solid in 81% yield. Treatment of 299 with \(n\)-BuLi in dry THF at a temperature of -30 °C gave, after recrystallisation, the known ketone 300 as a white solid in 58% yield. Ketone 300 reacted with the anion generated from trimethyl phosphonoacetate in dry DMF to deliver the \(\alpha,\beta\)-unsaturated ester 297 as a white solid in 81% yield. The 400 MHz \(^1\)H NMR spectrum of 297 in CDCl\(_3\) revealed the C(15) proton as an apparent doublet at \(\delta\) 4.91 (\(J_{H1^-H2_{equatorial}} = 3.4\) Hz). The C(14) protons appeared as multiplets at \(\delta\) 2.42 and \(\delta\) 3.92 respectively. In addition, there was a complex multiplet at \(\delta\) 4.1 - 4.3 which was attributable to the C(12), C(11) and equatorial C(10) protons. The axial C(10) proton resonated as a double doublet at \(\delta\) 3.82 (\(J_{H6a^-H5} = 4.8\) Hz and \(J_{H6a^-H6b} = 10.1\) Hz). There were also singlets at \(\delta\) 3.35 and \(\delta\)
3.70 due to the protons of the methoxy group at C(15) and the carboxymethoxymethylene group at C(13) respectively. The vinylic proton appeared as a triplet at δ 6.12 (J = 3.1 Hz). The benzylidene methine was observed at δ 5.65, while the aromatic protons resonated as a complex multiplet at δ 7.45.

The ester functionality in 297 was then reduced with DIBAL in dry CH₂Cl₂ and the resulting allylic alcohol isolated in 93% yield. Treatment of the allylic alcohol with t-butyldiphenylsilyl chloride and imidazole in dry DMF resulted in the formation of 301 which was isolated in 95% yield after flash chromatography. Analysis of its 400 MHz ¹H NMR spectrum in CDCl₃ indicated that the carboxymethylene protons at δ 3.72 had been lost. The appearance of a 9 proton singlet resonating at δ 1.02 was indicative of the presence of the t-butyldiphenylsilyl group. In addition, there were several overlapping resonances between δ 7.2 -7.6 that integrated to 15 protons which were due to the aromatic protons of the t-butyldiphenylsilyl and benzyl groups respectively. Furthermore, there was a 2 proton multiplet which resonated at δ 2.63 and was attributable to the allylic methylene hydrogens. The vinylic proton now resonated further upfield at δ 5.87 as an apparent doublet (J = 4.1 Hz).

The next step entailed debenzylidenation of 301 to the corresponding diol 302, with aqueous acetic acid. However, under all the reaction conditions studied this reaction was not selective. Furthermore, when 301 was treated with DDQ in CH₂Cl₂, analysis by 400 MHz ¹H NMR spectroscopy of the product indicated that desilylation had occurred in addition to oxidation of the resulting hydroxyl group to give rise to the α,β - unsaturated aldehyde 303 (Scheme 110).

The aldehydic proton resonated at δ 9.8 as a doublet (J = 7.8 Hz).
In view of these complications we decided to protect the C(13) allylic hydroxyl group as a benzyl ether (Scheme 111).29

**Scheme 111**

![Scheme 111](image)

Deprotonation of alcohol 304 with NaH in dry DMF followed by addition of benzyl bromide furnished benzyl ether 305 as a white solid in 75% yield. Its structure was confirmed by 400 MHz ¹H NMR spectroscopy. More specifically, the complex multiplet resonating in the aromatic region between δ 7.20 - 7.55, now integrated to 10 protons. Furthermore, the methylene protons of the benzyl group appeared as a singlet at δ 4.51. This modification of the substrate allowed us to successfully perform the desired debenzylidenation as shown in scheme 112.

**Scheme 112**

![Scheme 112](image)

This was achieved in 87% yield by treating a methanolic solution of 305 with a catalytic amount of p-toluenesulphonic acid for 3 hours and gave diol 306 as an oil. The 400 MHz ¹H NMR spectrum of 306 in CDCl₃ now revealed the complex multiplet centred around δ 7.28 integrated to 5 protons, and since the benzylidene methine proton at δ 5.65 was no longer present, this confirmed that we had achieved our objective. Furthermore, there was a signal between δ 1.5 - 1.7 integrating to 2 protons which corresponds to the two newly formed hydroxyl
protons. The IR spectrum of 306 also suggested that deprotection had been successful since there was a broad O-H absorption band present at 3500 cm⁻¹.

The primary hydroxyl group was protected as a pivaloyl ester by the treatment of 306 with pivaloyl chloride in a 1:1 solution of dry CH₂Cl₂ and pyridine at -20 °C (Scheme 113).

![Scheme 113](image)

Compound 307 was obtained as an oil in 72% yield after flash chromatography. The 400 MHz ¹H NMR spectrum confirmed the identity of 307. Thus, there was a singlet at δ 1.22 that integrated to 9 protons which corresponded to the t-butyl protons of the pivaloate ester.

The next step in our sequence involved reductive deoxygenation of the allylic ring hydroxyl in 307. We hoped that this could be achieved by nucleophilic substitution of the corresponding sulphonate ester or inverted halide. However, chlorination (SO₂Cl₂, pyridine and CH₂Cl₂)¹¹⁷, iodination (PPh₃, imidazole, I₂ in toluene)¹¹⁸ and tosylation (py, p-TsCl)¹¹⁹ all resulted in decomposition. Bromination was also attempted, with CBr₄, PPh₃ in dry THF.¹²⁰ This formed a product that was isolated by flash chromatography and then treated with n-Bu₃SnH. However, the resulting product has not yet been characterised.

In view of these failures, we next decided to examine free-radical reduction of the corresponding methyl xanthate. Deprotonation of 307 with NaH in dry THF followed by treatment with CS₂ and then Mel resulted in a clean conversion to the corresponding methyl xanthate.¹²¹ Reaction of the xanthate with n-Bu₃SnH and AIBN in toluene at reflux led to the formation of two major products that were
separated by preparative TLC. However, the isolated products have not yet been characterised.

In light of this we opted to protect the primary hydroxyl of 306 as a silyl ether, and then attempt the chemistry aforementioned (Scheme 114).

**Scheme 114**

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{HO} & \quad \text{O} \\
306 & \quad \text{OBn} \\
& \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{OBn}
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{HO} & \quad \text{O} \\
\text{TBDPSO} & \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{OBn}
\end{align*}
\]

Treatment of 306 with imidazole and \( t \)-butyldiphenylsilyl chloride in anhydrous DMF\(^{41} \) afforded 308 as a colourless oil in 52% yield after flash chromatography.

Attempted chlorination of 308 (\( SO_2Cl_2 \), pyridine and \( CH_2Cl_2 \))\(^{117} \) also resulted in decomposition, as did treatment with \( CCl_4 \) and \( PPh_3 \).\(^{122} \) Exposure of 308 to \( PPh_3 \), imidazole and \( I_2 \) in dry toluene\(^{118} \) resulted in the identification by tlc of a single, faster moving product. However, the 400 MHz \(^1H \) NMR spectrum of the product in CDCl\(_3 \) indicated that we had not formed the desired iodide.

Tosylation of 308 (pyridine, \( CH_2Cl_2 \) and \( p \)-toluenesulphonyl chloride)\(^{119} \) gave an oily product whose structure also resisted identification. Reductions via a triflate\(^{123} \) and a mesylate\(^{124} \) were also attempted but in each case the initial transformation of the hydroxyl group into the corresponding leaving group resulted in decomposition.

At this point it was decided to undertake the synthesis of the southern hemisphere of Bryostatin 11. Vinyl alane 293 could be obtained in principle from alcohol 309 which could, in turn, be obtained from the decarboxylation of \( \beta \)-lactone 310, thus installing the olefin with the desired geometry at C(21). A possible precursor for 310 would be compound 311 which itself could be
obtained in principle from the coupling of vinyl bromide 312 and lactone 313. Disconnection of the C(21)-C(22) bond led to iodide 315 and target molecule β-lactone 314 (Scheme 115).

Scheme 115

Retrosynthetic comparison of β-lactone 314 with (S)-malic acid 316 suggested that lactonisation of β-hydroxy acid 318 would give 314 (Scheme 116). This led to the proposed synthetic route shown in scheme 117.
Diol 320 had previously been prepared by another member of the group and hence the first step undertaken was the selective protection of the primary hydroxyl group as a pivaloyl ester. Treatment of diol with t-BuCOCl in a 1:1 solution of pyridine and CH$_2$Cl$_2$ gave the desired secondary alcohol as an oil in 85% yield. Treatment of this compound with imidazole and t-BuMe$_2$SiCl gave 321 as an oil in 82% yield. Inspection of the 400 MHz $^1$H NMR spectrum of 321 in CDCl$_3$ revealed the tert-butyl protons of the pivaloyl and silyl moieties as the expected
singlets resonating at $\delta$ 1.21 and 1.18 respectively. The aromatic protons of the $p$-methoxybenzyl group appeared as multiplets at $\delta$ 7.25 and 6.91 whilst the benzylic and $p$-methoxy protons resonated as a singlets at $\delta$ 4.49 and 3.81 respectively. The 3 proton multiplet resonating at $\delta$ 4.03 was attributable to the C(2) methine and the C(1) methylenes. The C(4) methylene protons resonated as a multiplet at $\delta$ 3.75 whilst the C(3) methylenes also resonated as a multiplet but further upfield at $\delta$ 1.75. The methyl protons of the tert-butylidemethylsilyl ether resonated as a six proton singlet at $\delta$ 0.09. The IR spectrum corroborated the presence of the pivaloyl fuctionality as a strong absorption was observed at 3440 cm$^{-1}$.

With the three hydroxyl groups in 321 protected as different functionality the first task was to selectively release primary hydroxyl C(4), thus making it available for oxidation to the corresponding acid. Deprotection of the secondary site would then give the desired $\beta$ hydroxy acid from which lactonisation could be attempted. Hence 321 was subjected to DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) in CH$_2$Cl$_2$-H$_2$O (17:1)$^{29}$ and gave the desired alcohol in 98% yield. Oxidation of this alcohol with RuCl$_3$.xH$_2$O in the presence of NaIO$_4$ as cooxidant gave acid 322 in 83% yield.$^{109}$ The 400 MHz $^1$H NMR spectrum of 322 in CDCl$_3$ was indicative of the loss of the $p$-methoxybenzyl group. No signals were present in the aromatic region and the signals due to the methylene and methoxy protons in the region of $\delta$ 3.8 and 4.4 were also absent. Also, from the 100 MHz $^{13}$C NMR spectrum of 322 in CDCl$_3$ signals at $\delta$ 178.2 and 176.8 indicated the presence of a second carbonyl group in the molecule. This was corroborated by its IR spectrum since two strong absorption bands were present in the carbonyl region at 1715 and 1735 cm$^{-1}$ respectively. Our structural assignment was further reinforced by the high resolution mass spectrum of 322 which contained a signal at 319 which corresponded to [M+H]$^+$ ion.

The next step involved the preparation of the (L)-$\beta$-hydroxy acid 318. Deprotection of the secondary site was achieved by treating 322 with HF-pyridine complex (1 ml per mmol substrate) followed by immediate isolation by flash
chromatography to give 318 in 89% yield.\textsuperscript{42} The singlets due to the protons of the $t$-BuMe$_2$Si group were absent from the 400 MHz $^1$H NMR spectrum of 318. A very broad signal resonating between $\delta$ 4.7 - 6.0 was now present and integrated to 2 protons. This was presumed to be due to the resonances of the acidic and hydroxyl protons respectively. The IR spectrum now contained one broad absorption band in the carbonyl region at 1720 cm$^{-1}$ and this was considered to be due to the overlap of the two carbonyl absorption bands. It was also observed that decomposition of the (L)-{$\beta$}-hydroxy acid 318 occurred if the crude product, obtained after aqueous work-up, was left to stand, and the decomposition was accelerated if it was heated. The product of this decomposition was isolated by flash chromatography as a white crystalline solid, the structure of which has eluded identification.

Lactonisation was attempted by treating acid 318 with benzene sulphonyl chloride in the presence of pyridine,\textsuperscript{125} but this only resulted in decomposition.

The failure of the lactonisation step led us to modify the route and this resulted in a more linear approach. The new retrosynthetic analysis had us disconnecting the lactonic linkage in 313 to give the corresponding {$\beta$}-hydroxy acid 323. This could be obtained in principle from the hydrolysis of the resulting product of a stereochemically controlled Evans aldol condensation\textsuperscript{126,127} between oxazolidinone 324 and aldehyde 325. Compound 324 could conceptually be obtained from the reduction of the enone obtained from the coupling of phosphonate 328 and aldehyde 327. This more linear approach could, in theory, start from D-glucose 216 (Scheme 118) and this led to the proposed route from diacetone-D-glucose 217 (Scheme 119).
Hemiacetal 223 had previously been prepared by another member of the group and so the first step of the route undertaken was the ring opening to give diol 224. Reduction of 223 with NaBH₄ gave diol 224 in 89% yield. From the 400 MHz ¹H NMR spectrum of 224 the aromatic protons of the benzyl group at C(26) appeared as a multiplet at δ 7.29 whilst the methylene protons resonated as doublets at δ 4.61 and 4.49 (J = 11.7 Hz). The vinylic protons of the allyl group appeared as multiplets at δ 5.89, 5.22 and 5.17, whilst its methylene protons resonated as a two proton multiplet at δ 4.05. The C(27) methyl group gave rise to a characteristic doublet at δ 1.17 (J = 6.2 Hz) whilst the C(26) proton resonated as a multiplet at δ 3.86. The two C(24) protons resonated as a 2 proton multiplet at δ 1.73. Multiplets were also observed at δ 3.75, 3.67, 3.57 and 3.45 and were attributable to the C(22), C(23) and C(25) protons, respectively. The two hydroxyl protons resonated as broad singlets at δ 3.0 and 2.4 respectively.
The next step was the selective protection of the primary hydroxyl group as pivaloyl ester. Treatment of diol 224 with t-BuCOCl in the presence of pyridine in dry CH₂Cl₂ gave alcohol 225 in 81% yield. Analysis of the 400 MHz ¹H NMR spectrum showed the presence of the t-butyl protons of the pivaloyl group as a 9 proton singlet that resonated at δ 1.21. The appearance of a strong absorption band at 1725 cm⁻¹ in the IR spectrum indicated that a carbonyl group was now present in the molecule.

Alcohol 225 was subjected to a Mitsunobu reaction with 4-methoxyphenol⁵⁰ to give the desired product 226 as an oil in 70% yield. The appearance of an additional multiplet in the aromatic region at δ 6.82 and a 3 proton singlet at δ 3.77 in the 400 MHz ¹H NMR spectrum of 226 was indicative of the presence of the anisyl group. The loss of the hydroxyl group was apparent from the IR spectrum as no absorption band was present in the region of 3500 cm⁻¹.

The pivaloyl group, having served its function as a temporary protecting group for the C(10) position, was successfully removed with methanolic sodium methoxide to give alcohol 227 in 79% yield. The absence of a 9 proton singlet in the region of δ 1.2 in the 400 MHz ¹H NMR spectrum and the appearance of a broad absorption band at 3440 cm⁻¹ in the IR spectrum indicated successful saponification.

Aldehyde 327 was obtained in only 43% yield by oxidation of 227 with tetra-n-propylammonium perruthenate (TPAP) in the presence of N-methylmorpholine N-oxide (NMO).¹²⁸ Swern oxidation²⁷ of 227 resulted in a 33% yield 327 whilst treatment with pyridinium dichromate¹²⁹ resulted in decomposition. 400 MHz ¹H NMR and IR spectroscopy indicated the successful oxidation to an aldehyde. The aldehydic proton resonated as a doublet at δ 9.2 (J = 2.0 Hz) in the 400 MHz ¹H NMR spectrum and a strong absorption band was present in the carbonyl region at 1730 cm⁻¹. A peak at m/z 407 in the mass spectrum corresponded to [M+Na]⁺. Due to the unacceptably low yield from this
oxidation step it was decided to consider different synthetic alternatives to achieving our desired goal.
3.0 EXPERIMENTAL

Materials and methods.

Reactions were carried out under a dry nitrogen atmosphere with freshly distilled dry solvents unless otherwise noted. THF, CH$_2$Cl$_2$, toluene and benzene were purified and dried by distillation from calcium hydride under nitrogen. Methanol was dried by treatment with sodium metal and distilled under nitrogen prior to use. Dry DMF was purchased from Aldrich and used directly. Flash column chromatography was carried out according to the method of Still et al. with Sorbsil C60 40/60A (230-400 mesh) silica gel. Precoated silica gel plates (250 µm) with a fluorescent indicator (E. Merck) were used for analytical thin layer chromatography. $^1$H and $^{13}$C NMR spectra were recorded in deuterochloroform solutions with a Varian AX-400 (400 MHz) spectrometer. Chemical shifts are reported in δ-values relative to the residual CHCl$_3$ peak at 7.24 ppm. All infrared spectra were recorded on a Nicolet model 205 FT-IR spectrophotometer. Optical rotations were measured on either an Optical Activity AA10 automatic polarimeter or a Perkin Elmer 141 polarimeter. Melting points were measured on a Reichert micro hot stage apparatus and are uncorrected. Microanalyses were performed on a Perkin Elmer 2400 CHN Elemental Analyser by the Microanalytical Laboratory at University College London. High-resolution mass spectra were measured at the London School of Pharmacy on a V.G. 7070H or VG-ZAB instrument with a Finnigan Incos II data system. High pressure liquid chromatography (HPLC) was performed on a Gilson analytical chromatograph equipped with Gilson 303 and 305 pump systems, a Gilson 811b dynamic mixer, a Gilson 805s manometric module, and a Gilson 115 u.v. absorbance detector set at 254 nm. 2D NMR were recorded at Roche Products, Welwyn Garden City, or at Kings' College London, on a Bruker AMX-400 (400 MHz) spectrometer.
A 5 L conical flask equipped with an overhead mechanical stirrer was charged with water (1.2 L), tert-butyl alcohol (1.2 L) and AD-mix β (200 g, 0.6 equivalents). After 10 min of vigorous stirring at room temperature the mixture was cooled to 0 °C and trans-1,4-hexadiene 260 (20.0 g, 243.9 mmol) added in one portion. After 24 h at 0 °C the reaction was quenched with solid Na₂SO₃ (217 g) and vigorously stirred at room temperature for 1 h. The mixture was then transferred to a separatory funnel, the organic layer collected and the aqueous layer extracted with EtOAc (5 x 200 ml). The combined organic extracts were washed with brine and dried over MgSO₄. After filtration and removal of the solvent in vacuo, the crude material was subjected to flash chromatography (2:1 hexane/Et₂O) to give 7.78 g (46%) of diol 259 as a liquid: \([\alpha]_D -2.9^\circ (c 1.0, \text{CH}_2\text{Cl}_2)\); IR (neat film) 3350 (br, s), 3078 (w), 2977 (m), 2933(m), 2903 (m), 1642 (m), 1457 (m), 1433 (m), 1405 (m), 1375 (m), 1144 (m), 1127 (m), 1055 (s), 990 (m), 914 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.83 (multiplet, 1H), 5.15 (multiplet, 1H), 5.12 (multiplet, 1H), 3.62 (multiplet, 1H), 3.39 (multiplet, 1H), 2.65 (broad s, 1H), 2.54 (broad s, 1H), 2.32 (multiplet, 1H), 2.14 (multiplet, 1H), 1.16 (d, J = 6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 134.3, 118.2, 74.9, 70.3, 38.0, 19.3 ppm; HRMS (El) for C₆H₁₂O₂N, [(M + NH₄)⁺], Calcd: 134.1181, Found: 134.1186.
**Experimental**

*(2R, 3R)-2,3-Hexanediol 261*

To a solution of 259 (125 mg, 1.08 mmol) in ethanol (1 ml) at room temperature was added Pd/C (50 mg) very cautiously. The reaction mixture was stirred vigorously under a hydrogen atmosphere for 3 h. The Pd/C catalyst was then removed by suction filtration and the filtrate concentrated *in vacuo* to give the crude product. Purification by flash chromatography (2:1 hexane/Et₂O) delivered 63 mg (50%) of pure 261 as a liquid; \([\alpha]_D^{20} -18.4^\circ\) (c 1.0, CHCl₃); IR (neat film) 3380 (br, s), 2966 (s), 2875 (s), 1462 (m), 1402 (m), 1376 (m), 1282 (m), 1152 (m), 1122 (m), 1066 (s), 1027 (m), 976 (m), 918(w); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 3.54 (multiplet, 1H), 3.29 (multiplet, 1H), 3.13 (broad s, 2H), 1.43 (complex multiplet, 4H), 1.15 (d, \(J = 6.3\) Hz, 3H), 0.91 (t, \(J = 6.9\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl₃) \(\delta\) 75.9, 70.9, 35.4, 19.4, 18.7, 14.0 ppm;

*Disilyl ether 262*

To a stirred solution of diol 259 (1.00 g, 8.61 mmol) and imidazole (1.81 g, 26.59 mmol) in dry DMF (8.6 ml) was added tert-butylidemethylsilyl chloride (3.20 g, 21.23 mmol) and the reaction mixture heated to 85 °C. After 4 h the reaction mixture was cooled to 0 °C and quenched with saturated NaHCO₃ (aq). The resulting mixture was extracted with Et₂O (3 x 20 ml), the combined organic extracts washed sequentially with H₂O and brine, and finally dried over MgSO₄. After filtration and
concentration in vacuo the crude product was purified by flash chromatography (neat hexane) to give 2.50 g (84%) of pure disilyl ether 252 as an oil: \([\alpha]_D +21.0^\circ\) (c 1.0, CH₂Cl₂); IR (neat film) 2957 (s), 2930 (s), 2894 (s), 2887 (s), 2859 (s), 1473 (m), 1463 (m), 1382 (w), 1361 (w), 1258 (s), 1105 (s), 1071 (m), 1014 (w), 1006 (w), 997 (w), 983 (w), 939 (w), 911 (m), 836 (s), 809 (m), 774 (s) cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) δ 5.81 (complex multiplet, 1H), 5.04 - 4.95 (complex multiplet, 2H), 3.74 (multiplet, 1H), 3.52 (multiplet 1H), 2.36 (multiplet, 1H), 2.01 (multiplet, 1H), 1.04 (d, \(J = 6.3\) Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 137.1, 116.1, 75.7, 70.7, 35.0, 25.9, 25.8, 18.0, 16.6, -4.3, -4.4, -4.5, -4.7 ppm; HRMS (El) for C₁₈H₄₁O₂Si₂, (M + H)+, Calcd: 345.2645, Found: 345.2640.

Aldehyde 258

To a stirred solution of disilyl ether 262 (1.26 g, 3.65 mmol) in THF (4.5 ml) at 0 °C was added aqueous OsO₄ (0.04 M, 1.50 ml, 0.06 mmol). After 10 min NaIO₄ (4.69 g, 21.93 mmol) was added and after a further 30 min at 0 °C the reaction mixture was allowed to warm to room temperature. After 8.5 h the reaction mixture was diluted with H₂O (5.0 ml) and multiply extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄ and filtered. Removal of the solvent in vacuo and purification of the residue by flash chromatography (150:1 hexane/EtOAc) gave 0.89 g (70%) of aldehyde 258 as an oil: IR (neat film) 2956 (s), 2931 (s), 2894 (m), 2859 (s), 1732 (m), 1715 (m), 1256 (m), 1004 (s), 836 (s), 776 (s) cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) δ 9.75 (t, \(J = 2.7\) Hz, 1H), 4.14 (multiplet, 1H), 3.81 (multiplet, 1H), 2.63 (ddd, \(J = 2.7, 4.5, 15.7\) Hz, 1H), 2.42 (ddd, \(J = 2.8, 4.5, 15.7\) Hz, 1H).
7.9, 15.7 Hz, 1H), 1.06 (d, \( J = 6.2 \text{ Hz}, 3\text{H} \)), 0.85 (s, 9H), 0.84 (s, 9H), 0.05 (s, 3H), 0.03 (s, 6H), 0.02 (s, 3H); \(^{13}\text{C} \text{NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 201.9, 70.7, 70.2, 45.3, 25.8, 25.7, 17.9, 16.4, -4.6, -4.7, -4.8 \text{ ppm}. \\

**Allylic ester 267**

![Chemical structure](image)

To a stirred solution of aldehyde 258 (16.7 g, 48.24 mmol) in dry CH$_2$Cl$_2$ (48 ml) was added (carbethoxymethylene)triphenylphosphorane (24.4 g, 70.0 mmol) in one portion. After 12 h at room temperature the reaction mixture was concentrated \textit{in vacuo}. Et$_2$O was then added to precipitate the Ph$_3$P=O solid by-product, which was then removed by filtration. The filtrate was then concentrated \textit{in vacuo} and the crude product subjected to flash chromatography (75:1 hexane/EtOAc) to give 19.1 g (95%) of allylic ester 267 as an oil: [\( \alpha \)]$_{D}^{\circ}$ +23.0° (c 0.3, CH$_2$Cl$_2$); IR (neat film) 2957 (s), 2931 (s), 2887 (m), 2859 (s), 1726 (s), 1657 (w), 1654 (w), 1473 (m), 1464 (m), 1367 (m), 1315 (m), 1259 (s), 1221 (w), 1174 (m), 1152 (m), 1103 (s), 1074 (m), 1049 (m), 1006 (m), 836 (s), 809 (m), 775 (s) cm$^{-1}$; \(^{1}\text{H} \text{NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta 6.95 \text{ (multiplet, 1H)}, 5.80 \text{ (dt, } J = 1.4, 15.7 \text{ Hz, 1H)}, 4.16 \text{ (qd, } J = 1.1, 7.1 \text{ Hz, 2H)}, 3.76 \text{ (multiplet, 1H)}, 3.60 \text{ (multiplet, 1H)}, 2.48 \text{ (multiplet, 1H)}, 2.17 \text{ (multiplet, 1H)}, 1.26 \text{ (t, } J = 7.1 \text{ Hz, 3H)}, 1.05 \text{ (d, } J = 6.3 \text{ Hz, 3H)}, 0.85 \text{ (s, 9H)}, 0.84 \text{ (s, 9H)}, 0.02 \text{ (s, 3H)}, 0.01 \text{ (s, 3H)}, 0.00 \text{ (s, 3H)}, -0.01 \text{ (s, 3H)}; \(^{13}\text{C} \text{NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 166.5, 147.9, 122.8, 74.8, 70.6, 60.0, 33.5, 25.8, 25.7, 18.0, 16.4, 14.3, -4.5, -4.6, -4.7, -4.8 \text{ ppm}; \text{HRMS (EI) for C}_{21}\text{H}_{45}\text{O}_{2}\text{Si}_{2}, (M + H)^{+}, \text{Calcd: 417.2856, Found: 417.2850}; \text{Anal. Calcd for C}_{21}\text{H}_{44}\text{O}_{4}\text{Si}_{2}: C, 60.52; H, 10.64. \text{Found: C, 60.66; H, 10.57.}
Allylic alcohol 268

To a stirred solution of allylic ester 267 (6.72 g, 16.1 mmol) in dry CH₂Cl₂ (30 ml) at -75 °C was added DIBAL (1.5 M in toluene, 24.0 ml, 36.0 mmol) dropwise over 3 min. The reaction mixture was then allowed to warm gradually to -60 °C and after 15 min at this temperature, quenched by the careful dropwise addition of MeOH. The mixture was then diluted with CH₂Cl₂ (40 ml) and allowed to warm to 0 °C. Saturated sodium potassium tartrate (aq) was added and after 10 min of vigorous stirring the mixture was transferred to a separatory funnel and the organic layer separated. The aqueous layer was multiply extracted with CH₂Cl₂, the combined organic extracts washed with brine and dried over MgSO₄. After filtration and removal of the solvent in vacuo, the crude product was purified by flash chromatography (40:1 hexane/EtOAc) to yield 5.63 g (93%) of 268 as a colourless syrup: [α]D +21.2° (c 0.6, CH₂Cl₂); IR (neat film) 3500 (br, w), 2957 (s), 2930 (s), 2895 (m), 2887 (s), 1473 (m), 1463 (w), 1257 (s), 1105 (s), 1074 (m), 1006 (m), 973 (w), 969 (w), 837 (s), 809 (m), 775 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.65 (complex multiplet, 2H), 4.07 (d, J = 5.1 Hz, 2H), 3.74 (multiplet, 1H), 3.51 (multiplet, 1H), 2.36 (multiplet, 1H), 2.01 (multiplet, 1H), 1.26 (broad s, 1H), 1.04 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 131.5, 130.6, 75.6, 70.7, 63.9, 33.3, 25.8, 18.0, 16.5, -4.4, -4.6, -4.8 ppm; HRMS (El) for C₁₉H₄₂O₃Si₂, (M + H)⁺, Calcd: 375.2751, Found: 375.2758. Anal Calcd. for C₁₉H₄₂O₃Si₂: C, 60.90; H, 11.30. Found: C, 60.79; H, 11.38.
Chapter 3. Experimental

Epoxy alcohol 269

To a stirred suspension of powdered 3 Å molecular sieves (100 mg) in dry CH$_2$Cl$_2$ (56 ml) at -20 °C, was added sequentially D-(-)-diethyltartrate (0.66 ml, 3.86 mmol), Ti(O-i-Pr)$_4$ (0.92 ml, 3.09 mmol) and tert-butyl hydroperoxide (7.1 M solution in CH$_2$Cl$_2$, 16.2 ml, 0.12 mol). After 30 min a solution of allylic alcohol 268 (7.15 g, 19.10 mmol) in dry CH$_2$Cl$_2$ (11 ml) was added dropwise over a period of 3 min. After the addition the mixture was stored at -25 °C for 48 h before being allowed to warm to 0 °C. It was then quenched by pouring into a 250 ml Erlenmeyer flask containing a solution of FeSO$_4$.2H$_2$O (21.5 g, 0.11 mol) and citric acid (7.2 g, 33.93 mmol) in water (70 ml) at 0 °C. After the mixture had been stirred vigorously for 30 min, it was transferred to a separatory funnel, and the organic phase separated. The aqueous phase was then extracted with Et$_2$O (1 x 70 ml), and the combined organic extracts vigorously stirred with 15% NaOH in brine (70 ml) at 0 °C for 1 h. The organic phase was then separated, and the aqueous layer extracted with Et$_2$O (1 x 70 ml). After drying (MgSO$_4$) the combined organic extracts were filtered and concentrated in vacuo to give the crude product. Purification by flash SiO$_2$ chromatography (40:1 hexane/EtOAc) delivered 6.66 g (89%) of epoxy alcohol 269 as a colourless syrup: [α]$_D$ +48.4° (c 0.5, CH$_2$Cl$_2$); IR (neat film) 3500 (br, w), 2957 (s), 2930 (s), 2895 (w), 2887 (w), 2859 (s), 1470 (w), 1460 (w), 1258 (m), 1106 (s), 1077 (m), 1005 (w), 836 (s), 775 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.92 (multiplet, 1H), 3.77 (complex multiplet, 2H), 3.59 (multiplet, 1H), 3.05 (multiplet, 1H), 2.93 (multiplet, 1H), 1.77 - 1.54 (complex multiplet, 3H), 1.03 (d, J = 5.6 Hz, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 72.5, 70.2, 61.6, 59.4, 54.0, 32.3, 25.8, 18.0,
16.2, -4.4, -4.6, -4.8 ppm; HRMS (EI) for C_{19}H_{43}O_3Si_2, (M + H)^+, Calcd: 391.2700, Found: 391.2694. Anal Calcd. for C_{19}H_{42}O_4Si_2: C, 58.41; H, 10.84. Found: C, 58.25; H, 10.96.

**Mosher ester 271**

![Mosher ester 271](image)

To a stirred solution of epoxy alcohol 269 (85 mg, 0.22 mmol), 4-dimethylamino pyridine (3 mg, 0.02 mmol) and dicyclohexylcarbodiimide (44 mg, 0.21 mmol) in dry CH_2Cl_2 (1.5 ml) was added R-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (50 mg, 0.21 mmol). After 4 h at room temperature the reaction mixture was diluted with CH_2Cl_2 (10 ml), washed sequentially with 5% aqueous acetic acid (5 ml), water (5 ml) and finally brine (5 ml). The organic extract was then dried over MgSO_4, filtered and the filtrate concentrated *in vacuo* to give the crude product. Purification by flash SiO_2 chromatography (60:1 hexane/EtOAc) delivered 30 mg (23%) of Mosher ester 271 as a colourless syrup: IR (neat film) 2956 (s), 2931 (s), 2891 (m), 2859 (s), 1756 (s), 1469 (w), 1259 (s), 1188 (s), 1171 (s), 1121 (s), 1107 (s), 1081 (m), 1018 (m), 1006 (m), 837 (s), 776 (s); \(^1\)H NMR (400 MHz, CDCl_3) \(\delta\) 7.51 (multiplet, \(2H\)), 7.38 (multiplet, \(3H\)), 4.64 (dd, \(J = 2.9, 12.2 \text{ Hz} \)), 4.13 (dd, \(J = 5.9, 12.2 \text{ Hz} \)), 3.75 (complex multiplet, \(2H\)), 3.55 (s, \(3H\)), 3.02 (multiplet, \(1H\)), 2.98 (multiplet, \(1H\)), 1.63 (multiplet, \(2H\)), 1.01 (d, \(J = 6.2 \text{ Hz} \)), 0.86 (s, \(9H\)), 0.84 (s, \(9H\)), 0.04 (s, \(3H\)), 0.02 (s, \(6H\)), 0.01 (s, \(3H\)); \(^{13}\)C NMR (100 MHz, CDCl_3) \(\delta\) 166.4, 132.0, 129.7, 128.5, 127.3, 124.6, 72.4, 70.2, 66.1, 55.6, 55.5, 54.4, 32.3, 25.8, 25.7, 18.0, 17.9, 16.2, -4.4, -4.6, -4.8, -4.9 ppm; \(^{19}\)F (376 MHz, CDCl_3) \(\delta\) 4.92; HRMS (FAB, MNOBA matrix) for C_{29}H_{49}O_6Si_2F_3Na, (M + Na)^+, Calcd: 629.2918, Found: 629.2914.
To a stirred solution of epoxy alcohol 269 (1.09 g, 2.79 mmol) in dry THF (0.7 ml) at -20 °C was added REDAL (1.7 M in THF, 8.20 ml, 13.94 mmol) dropwise over approximately 2 min. After the addition was complete the reaction mixture was stored at -20 °C for 12 h. It was then cooled to -78 °C, diluted with dry CH$_2$Cl$_2$ (10 ml) and then quenched by the careful dropwise addition of MeOH until effervescence ceased. The resulting mixture was allowed to warm to 0 °C and saturated sodium potassium tartrate (aq) added. After 20 min of vigorous stirring the mixture was transferred to a separatory funnel and the organic layer separated. The aqueous layer was diluted with H$_2$O and multiply extracted with CH$_2$Cl$_2$. The combined organic extract was washed with brine and dried over MgSO$_4$. After filtration and removal of the solvent in vacuo, the crude product was purified by flash chromatography (40:1 hexane/EtOAc) to give 0.90 g (82%) of 1,3-diol 270 as a white solid: mp 57 - 58 °C; [α]$_D$ +18.4° (c 0.5, CH$_2$Cl$_2$); IR (KBr) 3355 (br, m) 2956 (s), 2930 (s), 2888 (m), 2858 (s), 1474 (m), 1462 (m), 1388 (w), 1258 (s), 1252 (s), 1115 (s), 1092 (s), 1075 (s), 1050 (s), 1005 (w), 997(m), 940(w), 930 (w), 881 (m), 836 (s), 808 (m), 775 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.28 (broad s, 1H), 3.91 (broad multiplet, 1H), 3.85 - 3.69 (complex multiplet, 4H), 3.17 (s, 1H), 1.85 (multiplet, 1H), 1.68 (complex multiplet, 2H), 1.48 (multiplet, 1H), 1.12 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.84 (s, 9H), 0.07 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 73.9, 71.7, 69.7, 61.9, 40.3, 39.0, 25.7, 18.0, 17.9, 16.2, -4.7, -4.8, -4.9 ppm; HRMS (FAB, TGT matrix) for C$_{19}$H$_{45}$O$_4$Si$_2$, (M + H)$^+$, Calcd: 393.2856, Found: 393.2861. Anal Calcd. for C$_{19}$H$_{44}$O$_4$Si$_2$: C, 58.11; H, 11.29; Found: C, 57.91; H, 11.03.
Chapter 3. Experimental

*p*-Methoxybenzylidene acetal 273

![Chemical Structure](image)

A mixture of diol 270 (89 mg, 0.23 mmol), *p*-anisaldehyde dimethylacetal (0.10 ml, 0.59 mmol) and pyridinium *p*-toluene sulfonate (10 mg, 0.04 mmol) in dry DMF (1.5 ml) were rotated on a rotary evaporator under vacuum at a temperature of 55 °C for 1.5 h. The reaction mixture was then cooled to room temperature, quenched with saturated NaHCO₃ (aq) and multiply extracted with Et₂O. The combined organic extracts were sequentially washed with H₂O and brine and dried over MgSO₄. After filtration and removal of the solvent *in vacuo*, the crude product was subjected to flash chromatography (125:1 hexane/EtOAc) to yield 90 mg (78%) of pure acetal 273 as a colourless syrup:

IR (neat film) 2956 (s), 2931 (s), 2858 (s), 1617 (w), 1518 (w), 1468 (w), 1251 (s), 1107 (s), 1087 (s), 831 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.40 (s, 1H), 4.23 (multiplet, 1H), 3.94 (complex multiplet, 3H), 3.79 (s, 3H overlapping multiplet, 1H), 1.96 - 1.76 (complex multiplet, 2H), 1.84 (multiplet, 1H), 1.51 - 1.39 (complex multiplet, 2H), 1.04 (d, J = 6.3 Hz, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.01 (s, 6H), 0.00 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 159.6, 131.6, 127.3, 113.3, 100.7, 73.0, 70.3, 70.1, 67.1, 55.3, 36.2, 32.1, 25.8, 18.0, 16.2, -4.3, -4.6, -4.7, -4.8 ppm; HRMS (EI) for C₂₇H₅₀O₅Si₂, (M)⁺, Calcd: 510.3197, Found: 510.3206.
p-Methoxybenzyl Ether 274

To a stirred solution of acetal 273 (0.18 g, 0.35 mmol) in dry CH₂Cl₂ (0.35 ml) at -70 °C was added DIBAL (1.5 M in toluene, 0.56 ml, 0.84 mmol) dropwise over a minute and after the addition the reaction mixture was warmed to 0° C. After 2 h it was recooled to -70 °C, diluted with dry CH₂Cl₂ (2 ml) and quenched by the careful dropwise addition of MeOH. The resulting mixture was warmed to 0 °C and saturated sodium potassium tartrate (aq) added. After 20 min of vigorous stirring the mixture was transferred to a separatory funnel and the organic layer separated. The aqueous layer was multiply extracted with CH₂Cl₂, the combined organic extracts washed with brine and dried over MgSO₄. After filtration and removal of the solvent in vacuo, the resulting crude mixture was subjected to flash chromatography (40:1 hexane/EtOAc) to deliver 132 mg (73%) of pure alcohol 274 as a colourless syrup: [α]D +10.2° (c 0.5, CH₂Cl₂); IR (neat film) 3400 (br, w), 2956 (s), 2930 (s), 2894 (s), 2886 (s), 2858 (s), 1515 (s), 1473 (m), 1463 (w), 1250 (s), 1102 (s), 1041 (s), 836 (s), 808 (m), 775 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.49 (s, 2H), 3.83 (complex multiplet, 2H), 3.81 (s, 3H superimposed upon multiplet 2H that extended from 3.85 - 3.70), 2.54 (broad s, 1H), 2.12, (multiplet,1H), 1.97 (multiplet, 1H), 1.78 (multiplet, 1H), 1.44 (multiplet, 1H), 1.08 (d, J = 5.6 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s,3H), 0.05 (s, 3H), 0.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 130.6, 129.1, 113.8, 76.3, 72.7, 70.7, 69.6, 60.9, 55.3, 36.2, 34.6, 25.8, 18.0, 16.2, -4.1, -4.6, -4.8 ppm; HRMS (El) for C₂₇H₅₂O₅Si₂, (M)+, Calcd: 512.3353, Found:512.3365. Anal Calcd. for C₂₇H₅₂O₅Si₂: C, 63.23; H, 10.22. Found: C, 63.24; H, 10.26.
To a solution of oxalyl chloride (3.80 ml, 43.56 mmol) in dry CH₂Cl₂ (28 ml) at -78 °C was added DMSO (6.10 ml, 85.96 mmol) dropwise over 2 min. After 40 min a solution of alcohol 274 (4.43 g, 8.65 mmol) in dry CH₂Cl₂ (20 ml) was added dropwise over 3 min and the temperature allowed to warm to -55 °C. After a further 45 min at this temperature, Et₃N (18.0 ml, 0.13 mol) was added dropwise over 5 min and the reaction mixture stirred vigorously for 10 min. It was then diluted with CH₂Cl₂, allowed to warm gradually to 0 °C and the pH adjusted to 7 with dilute HCl (2 M). The mixture was then transferred to a separatory funnel and the organic layer collected. The aqueous layer was extracted with CH₂Cl₂ (3 x 40 ml), the organic extracts combined, washed with brine and dried over MgSO₄. After filtration and removal of the solvent in vacuo, the resulting crude aldehyde 256, which hydrated readily, was azeotropically dried by coevaporation with benzene (1 x 10 ml) and the residue subjected to olefination without any further purification. A small amount was taken for characterisation purposes and purified by flash chromatography with hexane/EtOAc (80:1): IR (neat film) 2956 (s), 2930 (s), 2894 (m), 2886 (m), 2858 (s), 1727 (s), 1515 (s), 1473 (m), 1464 (m), 1389 (w), 1378 (w), 1250 (s), 1102 (s), 1068 (s), 1039 (m), 1006 (m), 836 (s), 808 (m), 776 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.77 (t, J = 2.3 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.44 (ABq, J = 11.0 Hz, 2H), 4.10 (multiplet, 1H), 3.83 - 3.74 (complex multiplet, 2H), 3.77 (s, 3H), 2.65 (dd, J = 2.3, 5.7 Hz, 2H), 2.08 (multiplet, 1H), 1.42 (multiplet, 1H), 1.04 (d, J = 6.0 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.02 (s, 6H), 0.01 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 201.7, 159.1, 130.5, 128.9, 113.7, 72.2, 71.7, 70.5, 69.9, 55.3, 48.9, 35.3, 25.8, 18.0, 16.1, -4.1, -4.6, -4.8 ppm; HRMS (FAB,
MNOBA matrix) for C$_{27}$H$_{50}$O$_5$Si$_2$Na, (M + Na)$^+$, Calcd: 533.3094, Found: 533.3095.

$\alpha,\beta$-Unsaturated ester 278

To a stirred solution of crude aldehyde 256 (8.65 mmol, assuming 100% mass) in dry CH$_2$Cl$_2$ (8.0 ml) was added Ph$_3$P=CHCO$_2$Et (6.02 g, 17.28 mmol) in one portion. After 15 h at room temperature the solvent was removed in vacuo and the resulting crude mixture subjected to flash chromatography (30:1 hexane/EtOAc) to provide 3.79 g (76%, 2 steps) of allylic ester 278 as a colourless syrup: $[\alpha]_D^{+32.0^\circ}$ (c 0.1, CH$_2$Cl$_2$); IR (neat film) 2856 (s), 2931 (s), 2890 (m), 2858 (s), 1723 (s), 1515 (s), 1450 (w), 1251 (s), 1172 (s), 1098 (s), 1040 (s), 836 (s), 808 (m), 775 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.22 (d, $J = 8.7$ Hz, 2H), 6.97 (dt, $J = 7.2$, 15.7 Hz, 1H), 6.82 (d, $J = 8.7$ Hz, 2H), 5.86 (multiplet, 1H), 4.43 (ABq, $J = 11.2$ Hz, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 3.82 - 3.66 (complex multiplet, 3H), 2.48 (multiplet, 2H), 1.92 (multiplet, 1H), 1.36 (multiplet, 1H), 1.27 (t, $J = 7.1$ Hz, 3 H), 1.02 (d, $J = 6.2$ Hz, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 6H), -0.01 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.4, 158.9, 145.5, 130.9, 128.9, 123.3, 113.6, 74.8, 72.1, 70.5, 69.7, 60.1, 55.3, 37.3, 35.1, 25.8, 18.0, 16.2, 14.3, -4.1, -4.6, -4.7 ppm; HRMS (FAB, MNOBA matrix) for C$_{31}$H$_{56}$O$_6$Si$_2$Na, (M + Na)$^+$, Calcd: 603.3513, Found: 603.3514. Anal Calcd. for C$_{31}$H$_{56}$O$_6$Si$_2$: C, 64.09; H, 9.72. Found: C, 63.98; H, 9.91.
To a stirred suspension of H$_2$O (10 ml) and tert-butyl alcohol (12 ml) were added AD-mix-β (11.2 g, 4 equivalents) and MeSO$_2$NH$_2$ (0.76 g, 7.99 mmol) sequentially. After 10 min of vigorous stirring at room temperature the mixture was cooled to 0 °C, a solution of allylic ester 279 (1.16 g, 2.00 mmol) in tert-butyl alcohol (2 ml) added and the reaction mixture stored at 0 °C for 72 h. The reaction mixture was then diluted with water (12 ml) and quenched by the addition of solid Na$_2$SO$_3$ (12 g) and vigorously stirred for 1 h at room temperature. It was then transferred to a separatory funnel, the organic phase collected and the aqueous phase multiply extracted with EtOAc. The combined organics were then washed with saturated NaCl (aq), dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was subjected to flash chromatography (15:1 hexane/EtOAc) to deliver 1.06 g (86%) of diol 279 as a colourless syrup: [α]$_D$ +3.7° (c 0.6, CH$_2$Cl$_2$); IR (neat film) 3450 (br, m), 2956 (s), 2930 (s), 2887 (s), 2858 (s), 1739 (s), 1515 (m), 1465 (m), 1250 (s), 1104 (s), 1040 (s), 836 (s), 808 (s), 775 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.22 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.45 (ABq, J = 10.7 Hz, 2H), 4.25 (q, J = 7.0 Hz, 2H), 4.11 (multiplet, 1H), 3.99 (d, J = 1.8 Hz, 1H), 3.86 (multiplet, 1H), 3.77 (s, 3H), 3.76 (multiplet, 2H), 2.85 (very broad s, 2H), 2.12 (multiplet, 1H), 1.98 (multiplet, 1H), 1.83 (multiplet, 1H), 1.46 (multiplet, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.06 (d, J = 6.2 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 6H), 0.02 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.2, 159.2, 130.1, 129.2, 113.8, 76.5, 73.7, 72.8, 71.9, 70.8, 69.1, 61.7, 55.2, 37.9, 34.8, 25.8, 18.0, 16.2, 14.2, -4.2, -4.6, -4.7 ppm; HRMS (FAB, MNOBA matrix) for C$_{31}$H$_{58}$O$_8$Si$_2$Na, (M + Na)$^+$, Calcd: 637.3568,
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Found: 637.3581. Anal Calcd. for C$_3$H$_{38}$O$_8$Si$_2$: C, 60.55; H, 9.51. Found: C, 60.60; H, 9.41.

**Isopropylidene acetal 255**

To a stirred solution of diol 279 (1.26 g, 2.05 mmol) in acetone (4.4 ml) and 2,2-dimethoxypropane (4.4 ml) was added pyridinium p-toluenesulfonate (0.13 g, 0.52 mmol) and the reaction mixture warmed to 40 °C. After 12 h the solvent was removed *in vacuo* and the residue purified by flash chromatography (20:1 hexane/EtOAc) to yield 1.22 g (91%) of acetonide 255 as a colourless syrup: [α]$_D$ +33.5° (c 1.0, CH$_2$Cl$_2$); IR (neat film) 2956 (s), 2931 (s), 2895 (m), 2888 (m), 2858 (s), 1761 (m), 1735 (w), 1515 (s), 1473 (m), 1460 (m), 1455 (w), 1381 (m), 1250 (s), 1208 (w), 1186 (m), 1172 (m), 1103 (s), 1039 (m), 836 (s), 808 (m), 775 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.23 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 4.41 (ABq, $J = 11.0$ Hz, 1H), 4.18 (complex multiplet, 4H), 3.85 - 3.75 (complex multiplet, 3H), 3.78 (s, 3H), 2.02 (multiplet, 2H), 1.91 (multiplet, 1H), 1.45 (s, 3H), 1.43 (multiplet, 1H), 1.40 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.03 (d, $J = 6.2$ Hz, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.6, 158.8, 131.1, 128.7, 113.5, 110.7, 79.1, 75.9, 73.1, 72.0, 70.5, 69.2, 61.2, 55.2, 37.2, 35.1, 27.2, 25.6, 18.0, 17.9, 16.3, 14.1, -4.0, -4.7, -4.8 ppm; HRMS (FAB, MNOBA matrix) for C$_{34}$H$_{62}$O$_8$Si$_2$Na, (M + Na)$^+$, Calcd: 677.3881, Found: 677.3893. Anal Calcd. for C$_{34}$H$_{62}$O$_8$Si$_2$: C, 62.34; H, 9.54. Found: C, 62.29; H, 9.59.
β-Keto ester 280

To a stirred solution of i-Pr₂NH (0.89 ml, 6.32 mmol) in dry THF (0.90 ml) at -78 °C was added n-BuLi (1.6 M in hexanes, 3.90 ml, 6.24 mmol) dropwise over 1 min. After 40 min methyl isobutyrate (0.76 ml, 6.63 mmol) was added in one portion. After an additional 35 min a solution of ester 255 (0.59 g, 0.90 mmol) in dry THF (2 ml) was added dropwise over approximately 1 minute. The reactants were then stirred at -78 °C for 15 min and at -20 °C for 40 min. The reaction mixture was diluted with Et₂O (10 ml), quenched with saturated NH₄Cl (aq) and stirred at room temperature for 10 min. It was then transferred to a separatory funnel, the organic phase collected and the aqueous layer extracted with EtOAc (2 x 20 ml). The combined organic extract was washed with brine, dried over MgSO₄, filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (30:1 hexane/EtOAc) delivered 0.54 g (84%) of pure β-keto ester 280 as a colourless syrup: [α]D +38.4° (c 0.5, CH₂Cl₂); 2955 (s), 2931 (s), 2896 (m), 2886 (m), 2858 (s), 1758 (m), 1725 (m), 1715 (s), 1473 (m), 1464 (m), 1382 (m) 1250 (s), 1172 (m), 1152 (m), 1101 (s), 1039 (m), 836 (s), 809 (m), 775 (m) cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.25 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 1H), 4.23 (d, J = 8.5 Hz, 1H), 4.07 (td, J = 2.2, 8.5 Hz, 1H), 3.89 - 3.75 (complex multiplet, 3H), 3.80 (s, 3H), 3.68 (s, 3H), 2.13 (ddd, J = 2.2, 7.3, 14.2 Hz, 1H), 1.95 (complex multiplet, 2H), 1.47 (complex multiplet, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.06 (d, J = 6.2 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 6H); 13C NMR (100 MHz, CDCl₃) δ 206.0, 173.4, 158.8, 131.4, 128.8, 113.5, 109.5, 83.3, 75.7, 73.0, 71.9,
70.5, 68.8, 55.3, 53.7, 52.1, 37.0, 35.2, 27.3, 26.3, 25.9, 25.8, 22.0, 21.5, 18.0, 16.4, -4.0, -4.7, -4.8 ppm; HRMS (FAB, MNOBA matrix) for C_{37}H_{66}O_{9}Si{\text{II}}Na, (M + Na)^{+},

Diol 281

To a stirred solution of β-keto ester 280 (3.50 g, 4.93 mmol) in dry THF (40 ml) in a polyethylene bottle at -40 °C was added hydrogen fluoride-pyridine complex (13.0 ml) dropwise via a plastic syringe over 2 min and the reaction mixture allowed to warm to -5 °C. After 5 h it was diluted with EtOAc (40 ml) and quenched by the careful addition of super saturated NaHCO_{3} (aq). The mixture was then transferred to a separatory funnel, the organic layer separated and the aqueous layer multiply extracted with EtOAc. The combined organics were washed with saturated NaCl (aq) and dried over MgSO_{4}. After filtration and removal of the solvent in vacuo, the residue was subjected to flash chromatography (3:2 hexane/EtOAc) and gave 2.34 g (98%) of diol 281 as a colourless syrup: [α]_{D} +69.3^{\circ} (c 0.15, CH_{2}Cl_{2}); IR (neat film) 3425 (br, m), 2986 (m), 2952 (m), 2937 (m), 1755 (m), 1713 (s), 1515 (s), 1457 (m), 1383 (m), 1374 (m), 1303 (w), 1249 (s), 1173 (m), 1153 (m), 1088 (s), 1036 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl_{3}) δ 7.23 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.46 (ABq, J = 11 Hz, 2H), 4.17 (d, J = 8.4 Hz, 1H), 4.03 (multiplet, 1H), 3.91 (multiplet, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.55 (complex multiplet, 2H), 3.06 (broad s, 1H), 2.54 (broad s, 1H), 2.20 (ddd, J = 2.3, 7.1, 14.4 Hz, 1H), 1.94 (multiplet, 1H), 1.74 (complex multiplet, 2H), 1.40 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H),
1.13 (d, J = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 206.1, 173.3, 159.3, 130.1, 129.7, 113.9, 109.9, 83.5, 75.6, 73.7, 73.1, 70.8, 70.5, 55.3, 53.7, 52.2, 37.1, 36.5, 27.1, 26.4, 22.1, 21.4, 19.0 ppm; HRMS (FAB, MNOBA matrix) for C$_{25}$H$_{38}$O$_9$Na, (M + Na)$^+$, Calcd: 505.2414, Found: 505.2424. Anal Calcd. for C$_{25}$H$_{38}$O$_9$: C, 62.22; H, 7.94. Found: C, 62.09; H, 8.07.

Dipivaloate 282

To a stirred solution of diol 281 (0.87 g, 1.80 mmol) in dry pyridine (3.0 ml) and dry CH$_2$Cl$_2$ (2.6 ml) at 0 °C was added Me$_3$CCOCl (2.40 ml, 19.49 mmol) dropwise over 1 min, and the reaction mixture then allowed to warm to rt. After 4 days the reaction mixture was quenched by the addition of saturated NaHCO$_3$ (aq) and multiply extracted with EtOAc. The combined organic extracts were washed with saturated NaCl (aq) and dried over MgSO$_4$. After filtration and concentration in vacuo, the remaining pyridine was azeotropically removed by coevaporation with toluene (2 x 5 ml). The crude product was purified by flash chromatography (12:1 hexane/EtOAc) and gave 1.08 g (92%) of pure pivaloyl ester 282 as a colourless syrup: [$\alpha$]$_D$ +46.3° (c 0.7, CH$_2$Cl$_2$); IR (neat film) 2981 (s), 2959 (s), 2937 (s), 2910 (m), 2874 (s), 1757 (s), 1715 (s), 1516 (s), 1481 (m), 1460 (m), 1397 (m), 1382 (m), 1372 (m), 1281 (s), 1250 (s), 1157 (s), 1092 (s), 1040 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.30 (multiplet, 1H), 4.91 (multiplet, 1H), 4.33 (ABq, J = 10.1 Hz, 2H), 4.12 (d, J = 8.6 Hz, 1H), 4.00 (multiplet, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.48 (multiplet, 1H), 2.15 (multiplet, 1H), 1.84 - 1.71 (complex multiplet, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.20 (s,
9H), 1.16 (s, 9H), 1.12 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.0, 177.6, 177.5, 173.3, 159.3, 130.4, 130.0, 113.7, 109.8, 83.5, 75.3, 72.5, 71.2, 70.9, 55.3, 53.7, 52.2, 38.9, 38.8, 37.2, 36.5, 27.3, 27.2, 27.1, 26.3, 22.0, 21.4, 16.3 ppm; HRMS (FAB, NMOBA matrix) for C$_{35}$H$_{54}$O$_{11}$Na, (M + Na)$^+$, Calcd: 673.3564, Found: 673.3560. Anal Calcd. for C$_{35}$H$_{54}$O$_{11}$: C, 64.59; H, 8.36. Found: C, 64.51; H, 8.46.

Alcohol 283

To a stirred mixture of 282 (648 mg, 1.00 mmol), CH$_2$Cl$_2$ (7.7 ml) and water (0.45 ml) was added DDQ (452 mg, 1.99 mmol). After 3 h at room temperature the reaction mixture was quenched with saturated NaHCO$_3$ (aq), stirred vigorously for 10 min, filtered and the residue washed with CH$_2$Cl$_2$. The biphasic filtrate was transferred to a separatory funnel, the organic phase collected and the aqueous phase multiply extracted with CH$_2$Cl$_2$. The combined organic extract was then washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The resulting crude mixture was subjected to flash chromatography (4:1 hexane/EtOAc) and delivered 509 mg (96%) of alcohol 283 as a colourless syrup: $[\alpha]_D$ +26.0° (c 0.25, CH$_2$Cl$_2$); IR (neat film) 3531 (br, m), 2981 (s), 2961 (s), 2938 (m), 2875 (m), 1756 (m), 1729 (s), 1715 (s), 1481 (m), 1460 (m), 1435 (w), 1397 (w), 1383 (m), 1372 (m), 1282 (s), 1240 (m), 1213 (m), 1157 (s), 1090 (m), 1041 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.19 (dt, J = 3.8, 9.5 Hz, 1H), 4.96 (dq, J = 3.9, 6.4 Hz, 1H), 4.26 (d, J = 8.5 Hz, 1H), 4.05 (td, J = 3.8, 8.5 Hz, 1H), 3.75 - 3.64 (multiplet, 1H), 3.67 (s, 3H), 3.24 (broad s, 1H), 1.93 (dt, J = 3.5, 14.1 Hz, 1H), 1.77 (dt, J = 8.5, 14.3 Hz, 1H).
Hz, 1H), 1.63 (multiplet, 2H), 1.39 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.21 (s, 9H), 1.17 (s, 9H), 1.15 (d, J = 6.5 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 206.2, 178.7, 177.6, 173.3, 110.0, 83.6, 77.8, 71.5, 71.0, 65.4, 53.7, 52.2, 41.0, 39.0, 38.9, 27.2, 27.1, 27.0, 26.4, 22.1, 16.4 ppm; HRMS (El) for C\(_{27}\)H\(_{50}\)O\(_{10}\)N, (M + NH\(_4^+\)), Calcd: 548.3435, Found: 548.3431. Anal Calcd. for C\(_{27}\)H\(_{46}\)O\(_{10}\): C, 61.11; H, 8.74. Found: C, 60.73; H, 9.09.

**Methyl glycoside 253**

To a stirred solution of alcohol 283 (1.60 g, 3.02 mmol) in dry MeOH (27 ml) was added Amberlyst-15 resin (H\(^+\)) (2.5 g) and the reaction mixture heated to 60 °C for 30 h. The resin was then removed by filtration and the filtrate concentrated *in vacuo* to give the crude mixture of hemiacetals 284. These were then redissolved in dry MeOH (18 ml), cooled to 0 °C and acetyl chloride (2.5 ml, 21.7 mmol) added dropwise over 2 min. After the addition the reaction mixture was heated to 40 °C for a further 28 h. It was then cooled to 0 °C and quenched by the addition of solid NaHCO\(_3\). Water (40 ml) was then added and the mixture multiply extracted with EtOAc (3 x 20 ml). The combined organic extracts were washed with brine and dried over MgSO\(_4\). After filtration and concentration *in vacuo* the crude product was purified by flash chromatography (6:1 hexane/EtOAc) and gave 0.90 g (63%) of glycoside 253 as a colourless foam: [α]\(_D\) +28.5° (c 0.2, CH\(_2\)Cl\(_2\)); IR (neat film) 3537 (m), 3468 (m), 2977 (s), 2941 (m), 1793 (s), 1784 (s), 1728 (s), 1711 (s), 1482 (m), 1466 (m), 1462 (w), 1389 (m), 1370 (w), 1284 (s), 1229 (m), 1215 (m), 1186 (s), 1158 (s), 1130 (s), 1125 (s), 1100 (s), 1057 (s), 1043 (s) cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 5.23 (multiplet, 1H), 4.93 (multiplet, 1H), 4.22 (multiplet, 1H), 4.11
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(d, J = 2.8 Hz, 1H), 3.88 (multiplet, 1H), 3.31 (s, 3H), 2.34 (broad d, J = 7.6 Hz, 1H), 1.80 - 1.64 (multiplet, 4H), 1.33 (s, 3H), 1.25 (s, 3H), 1.20 (s, 9H), 1.17 (s, 9H), 1.14 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.5, 177.7, 177.4, 102.3, 73.5, 73.4, 70.3, 70.2, 63.8, 63.7, 61.0, 50.4, 50.3, 48.6, 38.9, 38.8, 36.7, 33.0, 27.2, 27.1, 19.6, 18.2, 15.7 ppm; HRMS (FAB, MNOBA matrix) for C$_{24}$H$_{41}$O$_9$, (M + H)$^+$, Calcd: 473.2751, Found: 473.2755. Anal Calcd. for C$_{24}$H$_{40}$O$_9$: C, 61.00; H, 8.53. Found: C, 60.64; H, 8.83.

Ketone 251

![Image of ketone 251]

To a stirred solution of glycoside 253 (86 mg, 0.18 mmol) in CCl$_4$ (0.4 ml) and MeCN (0.4 ml) at room temperature was added H$_2$O (0.6 ml) followed by RuCl$_3$.H$_2$O (3 mg, 0.01 mmol). After 5 min NaI$_4$ (77 mg, 0.36 mmol) was added in one portion and the reaction mixture stirred for a further 3 h. H$_2$O (2 ml) was then added and the biphasic mixture extracted with EtOAc (3 x 5 ml). The organics were combined, washed with saturated NaCl (aq) and dried over MgSO$_4$. After filtration and removal of the solvent in vacuo, the crude product was purified by flash chromatography (12:1 hexane/EtOAc) to give 79 mg (92%) of ketone 251 as a colourless foam: [$\alpha$]$_D$ -11.6$^\circ$ (c 0.5, CH$_2$Cl$_2$); IR (neat film) 2976 (s), 2937 (m), 2361 (s), 2340 (m), 1799 (s), 1735 (s), 1721 (s), 1701 (w), 1477 (m), 1460 (m), 1395 (m), 1369 (w), 1281 (s), 1229 (m), 1206 (w), 1144 (s), 1112 (s), 1092 (m), 1056 (m), 1039 (s), 989 (w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.22 (multiplet, 1H), 4.94 (multiplet, 1H), 4.16 (s, 1H), 3.91 (multiplet, 1H), 3.28 (s, 3H), 2.68 (dd, $J = 11.8$, 14.1 Hz, 1H), 2.35 (multiplet, 1H), 1.94 (ddd, $J = 2.2$, 9.8, 14.8 Hz, 1H), 1.78 (ddd, $J = 2.4$, 10.1, 14.6 Hz, 1H), 1.41 (s, 3H), 1.24 (s, 3H), 1.18 (s, 9H), 1.17 (s, 9H), 1.14
(d, J = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 199.2, 178.2, 177.6 177.3, 106.5, 77.7, 69.9, 68.3, 50.4, 47.6, 43.7, 38.9, 38.8, 37.0, 27.1, 19.3, 18.6, 15.5 ppm; HRMS (FAB, MNOBA matrix) for C$_{24}$H$_{38}$O$_{9}$Na, (M + Na)$^+$, Calcd: 493.2414, Found: 493.2418.

**Olefins 250 and 285**

![Chemical Structures]

To a stirred solution of ketone 251 (139 mg, 0.30 mmol) in dry CH$_2$Cl$_2$ (0.3 ml) was added Ph$_3$P=CHCO$_2$Me (148 mg, 0.44 mmol) in one portion. After 12 h at room temperature the solvent was removed *in vacuo* and the residue subjected to flash chromatography (12:1 hexane/EtOAc) to deliver 125 mg (80%) of a 1:1 mixture of geometrical isomers 250 and 285 which were separated by multiple elution preparative TLC (9:1 hexane: EtOAc).

**250**

IR (neat film) 2980 (m), 1793 (s), 1729 (s), 1481 (w), 1464 (w), 1439 (w), 1398 (w), 1371 (w), 1283 (m), 1266 (w), 1238 (m), 1193 (m), 1166 (s), 1148 (s), 1125 (s), 1044 (m), 1029 (m), 988 (m), 886 (w) cm$^{-1}$; $^1$H NMR (400 MHz, C$_6$D$_6$) δ 5.85 (d, J = 1.7 Hz, 1H), 5.37 (dt, J = 4.6, 7.4 Hz, 1H), 4.99 (dq, J = 4.6, 6.5 Hz, 1H), 4.07 (s, 1H), 3.91 (dd, J = 1.7, 14.0 Hz, 1H), 3.70 (multiplet, 1H), 3.25 (s, 3H), 3.11 (s, 3H), 2.09 (ddd, J = 1.8, 11.8, 14.0 Hz, 1H), 1.56 (dd, J = 5.3, 7.3 Hz, 2H), 1.38 (s, 3H), 1.13 (s, 9H), 1.06 (s, 9H), 1.00 (d, J = 6.5 Hz, 3H), 0.92 (s, 3H); $^{13}$C NMR (100 MHz, C$_6$D$_6$) 177.9, 177.2, 176.8, 165.4, 148.0, 122.9, 104.4, 78.3, 70.6, 68.1, 51.0, 50.1, 48.1, 38.8, 37.2, 30.7, 27.2, 19.4, 18.8, 15.8 ppm; HRMS (FAB, MNOBA matrix)
C\textsubscript{27}H\textsubscript{42}O\textsubscript{10}Na, (M + Na)	extsuperscript{+}, Calcd: 549.2676, Found: 549.2672. Anal Calcd. for C\textsubscript{27}H\textsubscript{42}O\textsubscript{10}: C, 61.58; H, 8.04. Found: C, 61.42; H, 8.40.

\textbf{285}

\textsuperscript{1}H NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\) 6.49 (s, 1H), 5.76 (d, \(J = 2.0\) Hz, 1H), 5.34 (multiplet, 1H), 5.01 (dq, \(J = 4.2, 6.4\) Hz, 1H), 3.62 (multiplet, 1H), 3.24 (s, 3H), 3.09 (s, 3H), 2.12 (multiplet, 1H), 1.50 (multiplet, 3H), 1.37 (s, 3H), 1.17 (s, 9H), 1.08 (s, 9H), 1.04 (d, \(J = 6.5\) Hz, 3H), 1.01 (s, 3H); \textsuperscript{13}C NMR (100 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\) 178.2, 177.1, 176.7, 165.1, 147.8, 123.2, 104.6, 70.7, 70.6, 70.1, 68.1, 51.0, 49.9, 48.2, 38.8, 37.2, 36.8, 27.2, 19.4, 18.8, 16.0 ppm.

\textbf{Olefins 286 and 287}

To a stirred solution of ketone 251 (70 mg, 0.15 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (0.2 ml) was added Ph\textsubscript{3}P=CHCO\textsubscript{2}Bu\textsuperscript{t} (170 mg, 0.30 mmol) in one portion. After 12 h at room temperature the solvent was removed \textit{in vacuo} and the residue subjected to flash chromatography (12:1 hexane/EtOAc) to deliver 51 mg (60%) of a 3:1 mixture of geometrical isomers 286 and 287. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 5.98 (s, 1H, H(20) minor isomer), 5.93 (d, \(J = 1.9\) Hz, 1H, vinyl proton), 5.92 (multiplet), 5.22 (multiplet, 1H), 4.91 (multiplet, 1H), 4.26 (s, H(20) major isomer), 3.67 (dd, \(J = 2.0, 12.4\) Hz), 3.67 - 3.50 (complex multiplet), 3.26 (s, OMe major isomer), 2.55 - 2.02 (complex multiplet), 1.88 - 1.70 (complex multiplet), 1.45 (s, t-Bu), 1.36 (s), 1.182 (s, OPv minor isomer), 1.177 (s, OPv major), 1.168 (s, OPv major isomer), 1.12 (d, \(J = 6.4\) Hz, H(27) major isomer).
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Di-O-benzylidine acetal 299\textsuperscript{13}

A mixture of a-methyl-D-mannopyranoside 298 (25 g, 0.13 mol), benzaldehydediacetal (50 ml, 0.33 mol) and p-TsOH (1.22 g, 6.41 mmol) in DMF (170 ml) was rotated under a vacuum on a rotary evaporator at a temperature of 70 °C. After 5 h the reaction was quenched with saturated NaHCO\textsubscript{3} solution and the resulting white precipitate collected by filtration and washed with petroleum ether. Recrystallisation from propan-1-ol resulted in 38.4 g of 299 (81% yield) as white crystals which was used directly for the next step: Mp 179-183 °C (Lit. value\textsuperscript{13} 181 °C); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.5 (complex m, 4 H), 7.4 (complex m, 6 H), 5.81 (s, 1 H), 5.77 (s, 1 H), 4.90 (d, \(J = 3.5\) Hz, 1 H), 4.2 (complex m, 4 H), 3.85 (complex m, 2 H) 3.73 (s, 3 H).

Hexopyranoside-3-ulose 300\textsuperscript{14}

To a solution of 299 (11.98 g, 32.38 mmol) in THF (240 ml) at -45 °C was added \(n\)-BuLi (1.6 M in hexanes, 45.0 ml, 71.2 mmol) gradually over 5 min. The reaction mixture was then allowed to warm to -30 °C and after 1 h added to an ice cold solution of saturated NH\textsubscript{4}Cl (250 ml). After 5 min of vigorous stirring the THF was removed \textit{in vacuo} and the crude product collected by filtration, recrystallised from
ethanol to give 4.99 g of 300 (58% yield) as a white solid that was used without any further purification for the next step: Mp 172-177 °C (Lit. value$^{114}$ 176-177 °C); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.48 (complex m, 2 H), 7.35 (complex m, 3 H), 5.79 (s, 1 H), 4.85 (m, 1 H), 4.18 (complex m, 3 H), 3.85 (complex m, 2 H) 3.73 (s, 3 H), 2.39 (m, 1 H).

3-(Carbomethoxymethylene)-2,3-dideoxy hexopyranoside 297$^{114}$

A stirred solution of 300 (3.20 g, 12.10 mmol) in DMF (28 ml) at 0 °C was treated with a cooled solution of KOBu-t (3.84 g, 32.02 mmol) and dimethyl phosphonoacetate (12.8 ml, 32.0 mmol) in DMF (40 ml) and after 5 min of vigorous stirring at this temperature the mixture was allowed to warm to rt. After 15 h the reaction mixture was poured into ice water (500 ml) and the resulting suspension filtered. The residue was dissolved in CHCl$_3$, dried over MgSO$_4$, filtered and the filtrate concentrated in vacuo to afford 3.13 g of crude 3-(carbomethoxymethylene)-2,3-dideoxy hexopyranoside 297 (81% yield) as a white solid which was used directly for the next step. Mp 122-127 °C (Lit. value$^{114}$ 124-126 °C); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.52 (complex m, 2 H), 7.38 (complex m, 3 H), 6.12 (t, J = 3.1 Hz, 1 H), 5.65 (s, 1 H), 4.91 (dd, J$_{H1-H2}$ axial = 0 Hz and J$_{H1-H2}$ equi = 3.4 Hz, 1 H), 4.2 (complex m, 3 H), 3.85 (complex m, 2 H), 3.70 (s, 3 H), 3.35 (s, 3 H), 2.41 (m, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) 167.1, 150.0, 137.4, 129.2, 128.3, 112.6, 101.7, 99.4, 79.6, 69.6, 65.7, 55.2, 51.2, 33.8 ppm.
3-(Hydroxymethylene)-2,3-dideoxy hexopyranoside 304

To a solution of 3-(carbomethoxymethylene)-2,3-dideoxy hexopyranoside 297 (2.63 g, 8.19 mmol) in CH₂Cl₂ (20 ml) at -78 °C was added DIBAL (25% in ether, 12 ml, 18.0 mmol) dropwise over 3 min. After a further 30 min the reaction mixture was allowed to warm to -40 °C and over a further 2 h allowed to warm gradually to -10 °C. The reaction was then quenched with saturated sodium potassium tartrate (aq). The resulting mixture was multiply extracted with CH₂Cl₂, the combined extracts dried over MgSO₄, filtered and concentrated in vacuo to give 2.24 g of crude allylic alcohol 304 (93% yield) as white solid. Mp 153-154 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (complex m, 3 H), 7.34 (complex m, 2 H), 5.98 (t, J = 7.3 Hz, 1 H), 5.52 (s, 1 H), 4.45 (d, J = 4.1 Hz, 1 H), 4.22 (m, 3 H), 3.95 (m, 1 H), 3.28 (s, 3 H), 2.90 (d, J = 7.1 Hz, 2 H), 2.64 (m, 1 H), 2.15 (m, 1 H), 1.65 (broad, 1 H); ¹³C NMR (100 MHz, CDCl₃) 139.0, 137.4, 129.2, 128.3, 112.6, 101.7, 99.4, 79.6, 69.6, 65.7, 55.2, 51.2, 33.8 ppm.

Allylic silyl ether 301

To a solution of allylic alcohol (1.36 g, 4.65 mmol) and imidazole (0.35 g, 9.30 mmol) in DMF (23 ml) at 0 °C was added t-BuPh₂SiCl (1.3 ml, 5.2 mmol) and after 10 min the mixture was allowed to warm to rt. After a further 90 min the reaction
mixture was quenched with saturated NaHCO₃, washed with water followed by brine, dried over MgSO₄, filtered and concentrated in vacuo. The resulting concentrate was subjected to flash chromatography using petrol/EtOAc as eluant (20:1) and gave 2.36 g of 297 as an oil (95% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.68 (complex m, 3 H), 7.54 (complex m, 2 H), 7.37 (complex m, 10 H), 5.87 (d, J = 4.1 Hz, 1 H), 5.64 (s, 1 H), 4.71 (d, J = 4.1 Hz, 1 H), 4.28 (m, 3 H), 3.95 (m, 1 H), 3.75 (m, 1 H), 3.28 (m, 3 H), 2.64 (m, 2 H), 2.15 (m, 1 H), 1.02 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) 137.6, 135.6, 130.3, 129.5, 128.9, 128.2, 127.6, 127.5, 126.2, 121.0, 101.5, 98.8, 98.7, 79.3, 69.5, 59.9, 54.6, 33.0, 26.7 ppm.

**Attempted debenzylidination of allylic silyl ether 301 with AcOH**

A stirred solution of 301 (60 mg, 0.11 mmol) in AcOH, THF and H₂O (6:3:1 volumetric ratio, 3 ml) was heated to 70 °C. After 12 h tlc analysis of the reaction mixture (petrol/EtOAc 2:1) indicated decomposition.

**Attempted debenzylidination of allylic silyl ether 301 with DDQ**

To a stirred solution of 301 (60 mg, 0.11 mmol) in CH₂Cl₂ (6 ml) was added DDQ (120 mg, 0.54 mmol), the reaction vessel sealed and heated to 50 °C. After 2 h the reaction mixture was quenched with saturated NaHCO₃ solution, multiply extracted with chloroform, the combined extracts dried over MgSO₄, filtered and concentrated in vacuo. The residue was subjected to flash chromatography using petrol/EtOAc (8:1) followed by chloroform/MeOH (200:1) as eluants afforded 0.02 g (41%) aldehyde 303: ¹H NMR (400 MHz, CDCl₃) δ 9.88 (d, J = 7.8 Hz, 1 H), 7.48
(complex m, 2 H), 7.35 (complex m, 3 H), 5.88 (t, $J = 7.8$ Hz, 1 H), 5.79 (s, 1 H), 4.85 (m, 1 H), 4.29 (complex m, 3 H), 3.89 (complex m, 2 H) 3.75 (s, 3 H), 2.89 (m, 1 H).

**Allylic benzyl ether 305**

![Image of the molecule](image_url)

To a stirred solution of 304 (2.24 g, 7.66 mmol) in DMF (30 ml) was added NaH (60%, 610 mg, 15.33 mmol). After 20 min benzyl bromide (1.20 ml, 10.12 mmol) was added, and after a further 2 h the reaction mixture was quenched with aqueous MeOH. The resulting mixture was multiply extracted with ether, the combined extracts dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was then washed with petrol to remove the excess BnBr and this gave 2.19 g of crude product 305 (75% yield) as a white solid which was used directly for the next step: Mp 96-99 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.54 (complex m, 2 H), 7.54 (complex m, 8 H), 5.88 (t, $J = 3.3$ Hz, 1 H), 5.63 (s, 1 H), 4.78 (d, $J = 3.6$ Hz, 1 H), 4.51 (s, 2 H), 4.13 (complex m, 4 H), 3.78 (complex m, 2 H), 3.32 (s, 3 H), 2.82 (d, $J = 14.4$ Hz, 1 H), 2.34 (m, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) 138.4, 137.5, 133.1, 128.9, 128.3, 128.3, 127.7, 127.5, 126.2, 118.3, 101.5, 98.8, 98.6, 71.9, 69.5, 65.7, 65.2, 54.6, 33.3 ppm.
To a stirred solution of 305 (2.18 g, 5.73 mmol) in MeOH (340 ml) at rt was added p-TsOH (0.15 g, 0.79 mmol). After 5 h the mixture was reduced in volume by approximately 75% and quenched with saturated NaHCO₃. The resulting mixture was extracted with EtOAc, dried over MgSO₄, filtered and concentrated in vacuo. Flash chromatography of the resulting residue using petrol/EtOAc as eluant (2:1) gave 1.36 g of diol 306 as an oil (87% yield): $^1$H NMR (400 MHz, CDCl₃) δ 7.31 complex m, 5 H), 5.88 (t, $J = 6.6$ Hz, 1 H), 4.77 (d, $J = 3.7$ Hz, 1 H), 4.51 (s, 2 H), 4.08 (complex m, 3 H), 3.85 (d, $J = 3.9$ Hz, 2 H), 3.52 (complex m, 1 H), 3.29 (s, 3 H), 2.74 (m, 1 H), 2.2 (broad m, 2 H), 1.65 (broad s, 1 H); $^{13}$C NMR (100 MHz, CDCl₃) 138.3, 137.6, 128.3, 127.8, 127.5, 118.6, 98.2, 73.7, 72.1, 69.1, 65.4, 63.2, 54.6, 33.1 ppm.

Pivaloyl ester 307

To a stirred solution of 306 (0.30 g, 1.03 mmol) in CH₂Cl₂ (1 ml) and pyridine (1 ml) at -70 °C was added t-BuCOCl (0.13 ml, 1.03 mmol) dropwise over a minute. After 15 min the mixture was allowed to warm to -20 °C and after a further hour at this temperature the reaction mixture was diluted with chloroform (10 ml). The reaction mixture was then washed sequentially with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The concentrate was then subjected to
flash chromatography (petrol/EtOAc 9:1) and delivered 0.28 g of 307 (72% yield) as a colourless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (complex m, 5 H), 5.95 (t, $J = 5.0$ Hz, 1 H), 4.78 (d, $J = 3.5$ Hz, 1 H), 4.52 (m, 3 H), 4.25 (m, 1 H), 4.09 (m, 2 H), 3.85 (t, $J = 3.7$ Hz, 1 H), 3.65 (complex m, 1 H), 3.31 (s, 3 H), 2.82 (m, 1 H), 2.74 (d, $J = 14.3$ Hz, 1 H), 2.20 (m, 1 H), 1.8 (broad, 1 H), 1.23 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$) 179.4, 138.3, 136.7, 128.3, 127.7, 127.5, 119.0, 98.1, 72.8, 71.9, 68.4, 65.4, 64.0, 54.5, 38.9, 33.0, 27.2, 27.1 ppm.

**Attempted chlorination of pivaloyl ester 307**

To a stirred solution of 307 (20 mg, 0.05 mmol) in pyridine (0.15 ml) and CH$_2$Cl$_2$ (0.20 ml) at -65 °C was added SO$_2$Cl$_2$ (0.05 M in CH$_2$Cl$_2$, 1.0 ml, 0.05 mmol) dropwise over a minute. The mixture was then allowed to warm to -35 °C over 90 min. Tlc analysis (petrol/EtOAc 5:1) of the reaction mixture at this time indicated decomposition.

**Attempted bromination of pivaloyl ester 307**

To a stirred solution of 307 (10 mg, 0.03 mmol), imidazole (4 mg, 0.06 mmol) and PPh$_3$ (33 mg, 0.13 mmol) in toluene (1 ml) was added iodine (32 mg, 0.13 mmol). Tlc analysis (petrol/EtOAc 5:1) of the reaction mixture after 12 h indicated decomposition.

**Attempted tosylation of pivaloyl ester 307**

To a solution of 307 (120 mg, 0.32 mmol) in pyridine (1.6 ml) at rt was added p-TsOH (180 mg, 0.97 mmol). After 6 h at rt the mixture was gradually heated to 70 °C. Tlc analysis (petrol/EtOAc 5:1) of the reaction mixture after 48 h indicated decomposition.
Attempted xanthate reduction of pivaloyl ester 307

A solution of 307 (40 mg, 0.10 mmol) and imidazole (10 mg, 0.20 mmol) in THF (2 ml) was treated with NaH (60%, 10 mg, 0.30 mmol). After 10 min CS$_2$ (0.02 ml, 0.31 mmol) was added and after a further 20 min Mel (0.02 ml, 0.33 mmol) added. After an additional 30 min the reaction mixture was quenched with water, multiply extracted with EtOAc, the combined extracts dried over MgSO$_4$, filtered and concentrated in vacuo. The resulting residue was dissolved in toluene (3.0 ml), a catalytic amount of AIBN added (3 mg) followed by n-Bu$_3$SnH (0.03 ml, 0.25 mmol) and the reaction mixture heated to reflux. After 3 h the toluene was removed in vacuo and the residue subjected to preparative tlc using petrol/EtOAc (6:1) as eluant. The resulting product was obtained as an oil which has yet to be characterised.

Attempted reduction via bromination of pivaloyl ester 307

To a solution of 307 (0.19 g, 0.50 mmol) in THF (2 ml) was sequentially added PPh$_3$ (0.52 g, 1.99 mmol) and CBr$_4$ (0.66 g, 1.99 mmol). After 25 h the reaction mixture was diluted with ether (10 ml), the resulting mixture filtered and the filtrate concentrated in vacuo. The residue was dissolved in dry THF (0.1 ml) treated with n-Bu$_3$SnH (0.05 ml, 0.42 mmol) and left overnight. Water was added to the reaction mixture and the biphasic mixture extracted with chloroform, dried over MgSO$_4$, filtered and concentrated in vacuo. Flash chromatography of the residue with petrol/EtOAc (6:1) as eluant afforded an oil which has yet to be characterised.
Silyl ether 308

To a solution of 306 (0.14 g, 0.48 mmol) and imidazole (70 mg, 0.96 mmol) in DMF (2 ml) at -10 °C was added TBDPSiCl (0.13 ml, 0.50 mmol) dropwise over a minute and the temperature maintained below 0 °C. After 75 min the reaction mixture was diluted with ether (10 ml) and quenched with saturated NaHCO₃ solution. The resulting biphasic mixture was then multiply extracted with ether, the combined extracts washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Flash chromatography of the residue using petrol/EtOAc as eluant (20:1) gave 130 mg of alcohol 308 as a colourless oil (52% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.68 (complex m, 5 H), 7.37 (complex m, 10 H), 5.95 (t, J = 7.0 Hz, 1 H), 4.72 (d, J = 2.9 Hz, 1 H), 4.51 (s, 2 H), 4.11 (complex m, 3 H), 3.88 (d, J = 5.2 Hz, 2 H), 3.57 (m, 1 H), 3.24 (s, 3 H), 2.71 (dd, J = 1.1 and 14.3 Hz, 1 H), 2.21 (m, 1 H), 1.8 (broad, 1 H), 1.05 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) 137.0, 135.6, 135.5, 130.0, 129.9, 129.8, 128.3, 127.8, 127.7, 127.4, 118.8, 98.1, 72.9, 71.8, 71.2, 65.9, 65.4, 54.5, 32.8, 26.8, 26.7 ppm.

Attempted tosylation of silyl ether 308

To a solution of 308 (0.11 g, 0.20 mmol) in dry pyridine (1.0 ml) was added p-TsOH (50 mg, 0.24 mmol) and the mixture heated to 40 °C. After 48 h EtOAc was added, the mixture washed sequentially with water and brine, dried over MgSO₄ and filtered. The filtrate was coevaporated with toluene to deliver an oil, which after purification by flash chromatography has yet to be characterised.
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**Attempted chlorination of silyl ether 308**

A solution of 308 (71 mg, 0.14 mmol) in CCl₄ (0.22 ml) was treated with PPh₃ (0.04 g, 0.14 mmol) and the mixture heated to 60 °C. After an hour tlc analysis (petrol/EtOAc 5:1) of the reaction mixture indicated decomposition.

**Attempted reduction of silyl ether 308 via an iodide**

A solution of 308 (0.34 g, 0.64 mmol), imidazole (0.32 g, 1.26 mmol) and PPh₃ (0.33 g, 1.26 mmol) in toluene at rt was treated with iodine (0.32 g, 1.26 mmol) and the reaction mixture heated to 65 °C. After 4 h the reaction mixture was diluted with MeOH and quenched with saturated NaHS₂O₇. The biphasic mixture was multiply extracted with chloroform, the combined extracts dried over MgSO₄, filtered and concentrated *in vacuo*. The concentrate was subjected to flash chromatography using petrol/EtOAc as eluant (30:1) and the resulting product dissolved in THF (0.10 ml), treated with n-Bu₃SnH (0.02 ml, 0.07 mmol) and heated to 65 °C. The reaction mixture was concentrated after 2 h to deliver a crude oil, which when purified by flash chromatography gave a product which has yet to be characterised.

**Attempted mesylation of silyl ether 308**

To a solution of silyl ether 308 (85 mg, 0.16 mmol) in pyridine (0.01 ml, 0.18 mmol) and DMF (0.2 ml) a solution of LiCl (7 mg, 0.16 mmol, in 0.1 ml DMF) was added. After 30 min the temperature was reduced to -5 °C and CH₃SO₂Cl (0.02 ml, 0.21 mmol) added. The temperature was maintained between -10 and 0 °C for a further 2 h after which time tlc analysis (3:1 petrol/EtOAc) of the reaction mixture indicated decomposition.
Attempted reduction of silyl ether 308 via a triflate

To a solution of triflic anhydride (0.02 ml, 0.13 mmol) in CH$_2$Cl$_2$ (0.14 ml) at 0 °C was added dropwise a solution of silyl ether 308 (69 mg, 0.13 mmol) in CH$_2$Cl$_2$ (0.1 ml) and pyridine (0.01 ml, 0.13 mmol). Tlc analysis (3:1 petrol/EtOAc) of the reaction mixture after 45 min indicated decomposition.

**(S)** - 1-O-Pivaloyl-4-O-p-methoxybenzylbutan-2-ol 331

To a stirred solution of diol 320 (1.79 g, 7.91 mmol) in pyridine (6.0 ml) and CH$_2$Cl$_2$ (6 ml) at -65 °C was added pivaloyl chloride (1.25 ml, 10.15 mmol) dropwise over 5 min and after a further 15 min the reaction mixture stored at -35 °C. After 16 h the reaction was quenched with water and the biphasic mixture extracted with CH$_2$Cl$_2$, dried over MgSO$_4$, filtered and concentrated in vacuo. Flash chromatography of the residue using petrol/EtOAc as eluant (15:1) delivered 2.00 g of 331 (85% yield) as a colourless oil. IR (neat film) 3400 (broad, s), 2910 (complex, s), 1728 (s), 1613 (m), 1515 (s), 1481 (w), 1460 (w), 1301 (m), 1286 (m), 1249 (s), 1172 (s), 1095 (m), 1035 (m), 666 cm$^{-1}$ (w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.25 (complex m, 2 H), 6.87 (complex m, 2 H), 4.44 (s, 2 H), 4.05 (m, 3 H), 3.79 (s, 3 H), 3.65 (m, 2 H), 2.9 (broad, 1 H), 1.78 (dd, J = 5.6 and 11.2 Hz, 2 H), 1.21 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$) 178.5, 159.2, 129.8, 129.3, 129.2, 113.8, 72.9, 69.0, 68.0, 67.7, 55.3, 38.7, 32.9, 27.1, 27.0 ppm; Mass spectrum (FAB, MNHOBA matrix) m/z 312 [M+Na]$^+$. 
Silyl ether 321

To a stirred solution of pivaloyl ester 331 (296 mg, 0.99 mmol) and imidazole (135 mg, 1.98 mmol) in DMF (1.5 ml) was added TBSCI (179 mg, 1.19 mmol). After 12 h the reaction mixture was quenched with saturated NaHCO₃ and the biphasic mixture multiply extracted with ether. The ethereal layers were combined, washed sequentially with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. Flash chromatography of the residue using petrol/ethyl acetate as eluant (10:1) delivered 358 mg of 321 (87% yield) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (complex m, 2 H), 6.91 (complex m, 2 H), 4.49 (s, 2H), 4.03 (complex m, 3 H), 3.81 (s, 3 H), 3.75 (m, 2 H), 1.76 (complex m, 2 H), 1.21 (s, 9 H), 1.18 (s, 9 H), 0.09 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) 178.2, 159.6, 129.8, 129.3, 129.2, 113.8, 72.9, 68.8, 67.5, 59.6, 38.8, 36.3, 27.2, 25.7, 17.9 ppm.

¹° Alcohol 332

To a stirred mixture of 321 (135 mg, 0.33 mmol), CH₂Cl₂ (2.0 ml) and water (0.1 ml) at rt was added DDQ (267 mg, 1.18 mmol) in one portion. After 2 h the reaction was quenched with saturated NaHCO₃, diluted with CH₂Cl₂, the resulting suspension filtered. The filtrate was multiply extracted with CH₂Cl₂, the combined extracts dried over MgSO₄, filtered and concentrated in vacuo. The resulting concentrate was subjected to flash chromatography using petrol:ether (20:1) followed by petrol/ethyl acetate (7:1) to give 94 mg of alcohol 332 (98% yield) as an oil. IR (neat film) 3450 (broad, s), 2900 (complex, s), 1733 (s), 1470 (m), 1286 (m), 1257 (m), 1162 (s), 1126 (m), 1033 (m), 838 (s), 777 (m), 666 cm⁻¹(w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.03 (complex m, 3 H), 3.75 (m, 2 H), 2.10 (broad, 1 H),
1.75 (complex m, 2 H), 1.18 (s, 9 H), 0.09 (s, 6 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 178.4, 68.8, 67.5, 59.6, 38.8, 36.3, 27.2, 25.7, 17.9 ppm; Mass spectrum (FAB, MNOBA matrix) m/z 305 [M+H]⁺.

**Acid 322**

![Diagram of acid 322]

To a stirred mixture of alcohol 332 (639 mg, 2.19 mmol), CCl\(_4\) (2.8 ml), MeCN (2.8 ml) and water (4.2 ml) was added NaIO\(_4\) (2.34 g, 10.9 mmol) gradually followed immediately by a catalytic amount of RuCl\(_3\).xH\(_2\)O (20 mg, 0.09 mmol). After 4 h water was added, the biphasic mixture extracted with CH\(_2\)Cl\(_2\), dried over MgSO\(_4\), filtered and concentrated in vacuo. Flash chromatography of the residue using petrol:ethyl acetate (30:1) as eluant afforded 0.56 g of acid 322 (84% yield) as an oil: IR (neat film) 2910 (multiplet, s), 1735 (s), 1716 (s), 1284 (w), 1255 (w), 1157 (m), 1125 (m), 838 (m), 779 (w), 666 cm\(^{-1}\) (w); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 4.30 (m, 1 H), 4.02 (m, 2 H), 2.55 (m, 2 H), 1.18 (s, 9 H), 0.84 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 178.2, 177.8, 67.2, 67.1, 38.8, 37.9, 27.2, 25.6, 17.9 ppm. Mass spectrum (FAB, MNBOA matrix) m/z 319 [M+H]⁺.

**β-Hydroxy acid 318**

![Diagram of β-hydroxy acid 318]

To a stirred solution of acid 322 (54 mg, 0.18 mmol) in THF (0.8 ml) at 0 °C was added HF-pyridine complex (0.2 ml) dropwise over 5 min and after the addition was completed the reaction mixture was allowed to warm to rt. After 4 h the reaction mixture was quenched by being emptied into water, extracted with EtOAc, dried over MgSO\(_4\), filtered and concentrated in vacuo with the water bath held at a temperature below 20 °C. Immediate flash chromatography using petrol/ethyl
acetate (3:1) as eluant afforded 31 mg of β-hydroxy acid 318 (89% yield) as an oil.

IR (neat film) 3450 (broad, s), 2910 (multiplet, s), 1722 (s), 1480 (w), 1450 (m), 1280 (s), 1160 (s), 1120 (s), 1040 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.0 - 4.7 (broad, 2 H), 4.30 (m, 1 H), 4.14 (m, 2 H), 2.60 (m, 2 H), 1.23 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) 178.7, 176.4, 66.9, 66.4, 38.8, 37.7, 27.1 ppm; Mass spectrum (FAB, MNBOA matrix) m/z 205 [M+H]^⁺.

**Attempted lactonisation of β-hydroxy acid 318**

To a solution of β-hydroxy acid 318 (11 mg, 0.05 mmol) in pyridine (0.7 ml) at 0 °C was added a solution of benzene sulfonyl chloride (1.09 M in pyridine, 0.10 ml, 0.11 mmol) dropwise. The temperature of the reaction mixture was then reduced to -35 °C and after an hour returned to 0 °C. After a further 2 h a further amount of benzene sulfonyl chloride solution was added (0.10 ml, 0.11 mmol) and the reaction mixture stored at 0 °C for 12 hr. TLC analysis (10:1 Petrol/EtOAc) of the reaction mixture indicated decomposition.

**3,6-Dideoxy-5-O-benzyl-2-O-allyl-D-glucitol 224**

To a solution of hemiacetal 223 (6.32 g, 22.7 mmol) in ethanol (80 ml) at rt was gradually added sodium borohydride (1.72 g, 45.5 mmol). After 2 h the reaction mixture was concentrated in vacuo and the residue coevaporated with MeOH. Water was then added and the mixture multiply extracted with ethyl acetate, the combined extracts dried over MgSO₄, filtered and concentrated in vacuo to give 6.20 g of the crude 224 (89% yield) as an oil which was used directly for the next step: IR (neat film) 3416 (m, br), 2925 (m), 2871 (m), 1641 (v.w), 1493 (w), 1450
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(m), 1372 (m), 1337 (m), 1205 (w), 1076 (s, br), 924 (m), 737 (m), 699 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.29 (complex m, 5 H), 5.89 (ddd, J = 5.1, 10.4 and 17.2 Hz, 1 H), 5.22 (ddd, J = 1.5, 3.0 and 17.2, 1 H), 5.17 (dd, J = 1.2 and 10.4, 1 H), 4.61 (d, Jₐβ = 11.8, 1 H), 4.49 (d, Jₐβ = 11.6, 1 H), 4.05 (complex m, 2 H), 3.86 (complex m, 1 H), 3.75 (dd, J = 3.7 and 11.4, 1 H), 3.67 (complex m, 1 H), 3.57 (d, J = 11.5, 1 H), 3.45 (complex m, 1 H), 2.95 - 3.05 (br s, 1 H), 2.40 - 2.49 (br s, 1 H), 1.73 (complex m, 2 H), 1.17 (d, J = 6.2, 3 H); ¹³C NMR (100 MHz, CDCl₃) 138.4, 134.6, 128.4, 128.2, 127.7, 117.4, 78.0, 77.9, 77.7, 71.0, 70.9, 70.7, 70.3, 63.5, 33.3, 14.2 ppm. Mass spectrum (FAB, MNOBA matrix) m/z 281 (M + H)⁺.

1-O-Pivaloyl-5-O-benzyl-2-O-allyl-3,6-dideoxy-D-glucitol 225

To a solution of diol 224 (0.70 g, 2.5 mmol) in dichloromethane (1.9 ml) and pyridine (1.9 ml) at -65 °C was added trimethylacetyl chloride (0.41 ml, 3.0 mmol) dropwise over 5 min and and then stored at -35 °C for 16 h. The reaction mixture was then quenched with water and multiply extracted with CH₂Cl₂. The combined extracts were washed sequentially with water and brine, dried over MgSO₄, concentrated in vacuo and coevaporated with toluene. Flash chromatography of the residue with hexane-ethyl acetate (15:1) as eluant, gave 0.74 g (81% yield) of mono pivaloate 225 as an oil: IR (neat film) 3498 (m, br), 2972 (m), 2870 (m), 1725 (s), 1642 (v.w), 1478 (m), 1447 (m), 1396 (m), 1365 (m), 1282 (m), 1161 (s), 1094 (s), 1035 (m), 996 (m), 921 (m), 737 (m), 698 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.23 (complex m, 5 H), 5.82 (complex m, 1 H), 5.15 (complex m, 2 H), 4.55 (d, Jₐβ = 11.7 Hz, 1 H), 4.42 (d, Jₐβ = 11.8 Hz, 1 H), 4.12 (complex m, 2 H), 3.96 (complex m, 2 H), 3.71 (complex m, 2 H), 3.36 (dd, J = 5.0 and 6.3; 6.2 Hz, 1 H), 3.10 (d, J = 2.4 Hz, 1 H), 1.77 (complex m, 1 H), 1.59 (complex m, 1 H), 1.12 (d, J = 4.3 Hz, 12
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H); $^{13}$C NMR (100 MHz, CDCl$_3$) 178.2, 138.4, 134.3, 128.3, 127.6, 127.5, 117.5, 77.6, 76.7, 72.8, 70.8, 65.4, 38.7, 34.3, 27.1, 14.7 ppm. Mass spectrum (FAB, MNOBA matrix) $m/z$ 387 (M + Na)$^+$. 

1-O-Pivaloyl-5-O-benzyl-4-O-anisyl-2-O-allyl-3-deoxy-D-galactitol 226

![Chemical structure](image)

To a solution of pivaloate 225 (5.49 g, 15.1 mmol), Ph$_3$P (5.14 g, 19.6 mmol) and $p$-methoxyphenol (4.30 g, 34.6 mmol) in dry THF (58 ml) was added diisopropylazodicarboxylate (3.9 ml, 19.8 mmol) dropwise and the reaction mixture heated to gentle reflux. After 3 h the reaction mixture was concentrated *in vacuo* and the residue subjected to flash chromatography with hexane-ethyl acetate (40:1) as eluant to give 3.70 g of the anisyl ether 226 (70% yield) as a yellow oil; IR (neat film) 2972 (s), 2863 (m), 1725 (s), 1643 (w), 1588 (w), 1502 (s), 1478 (m), 1455 (m), 1396 (m), 1376 (m), 1282 (s), 1227 (s), 1157 (s), 1110 (s), 1039 (s), 925 (m), 827 (m), 737 (m), 698 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 (complex m, 5 H), 6.71 (complex m, 4 H), 5.75 (complex m, 1 H), 5.17 (ddd, $J = 1.7, 3.4$ and 4.9 Hz, 1 H), 5.07 (ddd, $J = 1.2, 2.9$ and 4.1 Hz, 1 H), 4.61 (d, $J_{AB} = 11.9$ Hz, 1 H), 4.55 (complex m, 1 H), 4.49 (d, $J_{AB} = 11.9$ Hz, 1 H), 4.21 (dd, $J = 4.1$ and 11.6 Hz, 1 H), 4.6 (complex m, 2 H), 3.73 (complex m, 6 H), 1.84 (complex m, 2 H), 1.21 (complex m, 12 H); $^{13}$C NMR (100 MHz, CDCl$_3$) 178.3, 153.8, 153.0, 138.5, 134.8, 128.3, 127.8, 127.7, 127.5, 116.8, 114.5, 76.2, 74.5, 73.5, 71.2, 66.3, 55.7, 38.8, 32.8, 29.7, 27.2, 14.8 ppm. Mass spectrum (FAB, MNOBA matrix) $m/z$ 570 (M$^+$) and $m/z$ 493 (M + Na)$^+$. 

150
To a solution of anisyl ether 226 (394 mg, 0.84 mmol) in methanol (2.4 ml) at rt was added 10% NaOMe solution (2.4 ml). After 4 h the mixture was neutralized with Amberlyst-15 H⁺ ion exchange resin and filtered. The filtrate was concentrated in vacuo and the residue subjected to flash chromatography with hexane-ethyl acetate (12:1) as eluant. This provided 227 mg of alcohol 227 (70%) as an oil: IR (neat film) 3443 (m, br), 2933 (m), 2863 (m), 1643 (w), 1588 (w), 1498 (s), 1451 (m), 1376 (m), 1337 (w), 1290 (w), 1227 (s), 1180 (m), 1106 (s), 1039 (s), 921 (m), 827 (m), 788 (w), 737 (m), 698 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (complex m, 5 H), 6.82 (complex m, 4 H), 5.82 (complex m, 1 H), 5.21 (ddd, J = 1.7, 3.3 and 4.9 Hz, 1 H), 5.11 (ddd, J = 1.6, 2.9 and 10.4 Hz, 1 H), 4.63 (d, J = 11.9 Hz, 1 H), 4.51 (complex m, 2 H), 4.05 (complex m, 1 H), 3.78 (complex m, 6 H), 3.62 (complex m, 1 H), 3.55 (complex m, 1 H), 2.28 (dd, J = 5.4 and 5.5 Hz, 1 H), 2.05 (complex m, 1 H), 1.78 (complex m, 1 H), 1.25 (d, J = 6.4 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) 154.0, 152.9, 138.8, 135.1, 128.5, 128.0, 127.8, 117.0, 114.8, 77.0, 76.6, 74.7, 71.5, 70.9, 64.4, 55.9, 32.2, 14.8 ppm. Mass spectrum (FAB, MNOBA matrix) m/z 386 (M)⁺ and m/z 409 (M + Na)⁺.

**Aldehyde 327: Swern oxidation of 227**

To a solution of (COCl)₂ (0.17 ml, 1.9 mmol) in CH₂Cl₂ (0.14 ml) at -70 °C was added dimethylsulfoxide (0.14 ml, 1.9 mmol) dropwise over a minute. After 40 min a solution of alcohol 227 (92 mg, 0.24 mmol) in CH₂Cl₂ (0.78 ml) was added.
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dropwise over 2 min and after a further hour the reaction was quenched with dry Et₃N (0.83 ml). After 10 min the mixture was allowed to warm to rt, water added and the biphasic mixture multiply extracted with chloroform, the combined extracts washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The concentrate was subjected to flash chromatography using petrol/EtOAc as eluant (20:1) and delivered 32 mg of aldehyde 327 (33%) as an oil: IR (neat film) 2900 (multiplet, m), 1733 (s), 1505 (s), 1455 (w), 1227 (s), 1106 (m), 1086 (m), 1038 (m), 828 (w), 763 (m), 748 (s), 699 (m), 666 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.66 (d, J = 2.0 Hz, 1 H), 7.28 (complex m, 5 H), 6.76 (complex m, 4 H), 5.75 (complex m, 1 H), 5.13 (m, 2 H), 4.51 (complex m, 3 H), 4.02 (m, 1 H), 3.93 (m, 1 H), 3.74 (s, 3 H), 3.72 (m, 1 H), 2.02 (m, 1 H), 1.87 (m, 1 H), 1.19 (d, J = 6.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) 154.0, 152.6, 138.3, 133.7, 128.3, 127.7, 127.6, 118.1, 114.5, 80.3, 76.6, 75.7, 74.3, 71.8, 71.2, 55.6, 30.5, 14.6 ppm; Mass spectrum (FAB, MNOBA matrix) m/z 407 (M + Na)⁺.

Aldehyde 327: Oxidation of 227 with Tetra-n-propylammonium perruthenate

To a solution of alcohol 227 (1.55 g, 4.01 mmol) in CH₂Cl₂ (14 ml) containing molecular sieves was added N-methylmorpholine N-oxide (1.06 g, 8.00 mmol) and after 30 min tetra-n-propylammonium perruthenate (72 mg, 0.12 mmol) was added. After 2 hr the reaction mixture was emptied into CH₂Cl₂, washed sequentially with Na₂SO₃ solution, brine and finally CuSO₄ solution, dried over MgSO₄ and concentrated in vacuo. Flash chromatography of the concentrate (petrol/EtOAc 5:1) gave 0.65 g (43%) of aldehyde 327.
4.0 REFERENCES


References


42. For hydrogen fluoride-acetonitrile O-desilylation:-
For hydrogen fluoride-pyridine O-desilylation:-
References


OTBS

HO

OTBS

[Chemical structure diagram]

V-JL-40

[Graph showing peaks at various PPM values]

180 160 140 120 100 80 60 40 20 0 PPM
IV-JL-105

[Chemical structure diagram with labels: EtO, PMB, OTBS, HO, OH]

[Graph with peaks at various PPM values]
Actual 549.2676

Measured 549.2672

549