Carbohydrates as precursors to macrocyclic and iminosugar frameworks

By

Rekha Chadda

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Professor Paul V Murphy,

National University of Ireland Galway

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Abstract

Natural products have been perceived as privileged structures in drug discovery based on their evolutionary experience. **Chapter 1**, explores previous exploitation of this platform by medicinal chemists to identify some potent inhibitors of tumour cell migration, including migrastatin and isomigrastatin. Other analogues of these 14- and 12-ring frameworks have been prepared based on both, quinic and glucuronic acid. These derivatives have shown promise as potent inhibitors of tumour cell migration.

Chapter 2 describes the synthesis of novel macrocyclic frameworks structurally related to glucuronic acid. A Lewis-acid induced anomerisation of the β- to the corresponding α-anomer, was vital in the preparation of the α-macrocycles. The macrolactams prepared were biologically evaluated and a couple of key compounds found to be potent inhibitors of tumour cell migration.

Chapter 3 introduces iminosugars, a class of natural products known for their broad therapeutic potential. This work focuses on the allylic azide rearrangement and Huisgen cycloaddition, which together can provide access to nitrogen-containing frameworks from D-mannose.

Chapter 4 outlines difficulties in relation to stereochemical assignment, from the formation of two new stereocentres in this diastereoselective reaction resulting in piperidine *C*-glycosyl iminosugars. This work, based on previous studies, required an innate conformational restraint in the form of an isopropylidine group for a successful cycloaddition.

Chapter 5 explores enforcement of the tandem rearrangement-cycloaddition to prepare *C*-glycosyl pyrrolidines. Contradictory to previous reports, removal of the isopropylidine restraint enhanced the cyclisation resulting in improved selectivity, yield and reaction times. This work also showed regioselectivity was also an important factor in the tandem cycloaddition.

Chapter 6 explores employment of similar methodology for the preparation of α,α-disubstituted quaternary iminosugars, reiterating success of the cycloaddition (with improved selectivity, yield and reaction times) in absence of a conformational restraint. Studies of the alkene-azide vs. alkyne-azide reactivity were also explored, identifying two novel triazole-fused scaffolds.

The stereoselectivities of the nitrogen-containing products (Chapters **4**-**6**) were all assigned by Nuclear Overhauser Spectroscopy experiments. Further clarification by observation of ^{1}H NMR J values ($J_{1,2}$, $J_{4,5}$), X-ray crystallography and comparisons with available literature analytical data were also made where possible.

Abbreviations

2,2-DMP	2,2-Dimethoxypropane
*p*TsOH	*p*-Toluenesulfonic acid
2-HOPy	2-Hydroxypyridine
THF	Tetrahydrofuran
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
DMAP	4-Dimethylaminopyridine
DCM,CH_2Cl_2	Dichloromethane
TESCl	Triethylsilane chloride
DMF	Dimethylformamide
Grubbs II	Grubbs 2nd generation
TBAF	Tetrabutylammonium flouride
TFA	Trifluoroacetic acid
BnBr	Benzyl bromide
TBAI	Tetrabutylammonium iodide
AllylTMS	Allyltrimethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
MeCN	Acetonitrile
Ac_2O	Acetic anhydride
NaOMe	Sodium methoxide
MeOH	Methanol
BAIB	(Diacetoxyiodo)benzene
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
$MeSO_2Cl$	Methanesulfonyl chloride
NEt_3	Triethylamine
EtOH	Ethanol
HOBt	1-Hydroxybenzotriazole
DIPEA, DIEA	N,N-Diisopropylethylamine
EDCl	N-(3-Dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride
Et_2O	Diethyl ether
$TiBr_4$	Titanium(IV) tetrabromide
$MgBr_2$-OEt_2	Magnesium bromide ethyl etherate
AgOTf	Silver triflate
$TMSN_3$	Azidotrimethylsilane
AcOH	Acetic acid
D_2O	Deuterium oxide
BF_3Et_2O	Boron trifluoride diethyl etherate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

Chapter 1 Macrocyclic inhibitors of tumour cell migration and Lewis-acid induced anomerisation

1.1 Natural products – privileged structures in drug discovery

Natural products and their derivatives have played a huge role in drug discovery with an estimated 40 % of all medicines developed from these molecules.[1] Natural products, derived from plant, microorganisms and marine sources, can be categorised as primary and secondary metabolites. Primary metabolites are crucial for the survival of an organism. These components are involved in essential biological processes such as growth, development and reproduction. Secondary metabolites, while not essential for basic functioning, are involved in various other mechanisms, such as, defence. These "privileged structures" have gathered a lot of attention as an approach to access new bioactive molecules. It has been proposed that such compounds and their derivatives have a greater likelihood of specific biological activity (in comparison to the contending randomly assembled "man-made" synthetic scaffolds) due to their evolutionary experience. [2]

Traditional medicine practitioners were among the first to exploit natural products for their therapeutic benefits. Subsequent clinical, pharmacological and chemical studies of such compounds have provided access to an array of bioactive molecules, including some of the most effective drugs currently on the market. These medicines have been used for therapeutic purposes in a variety of illness, such as, malaria and cancer.

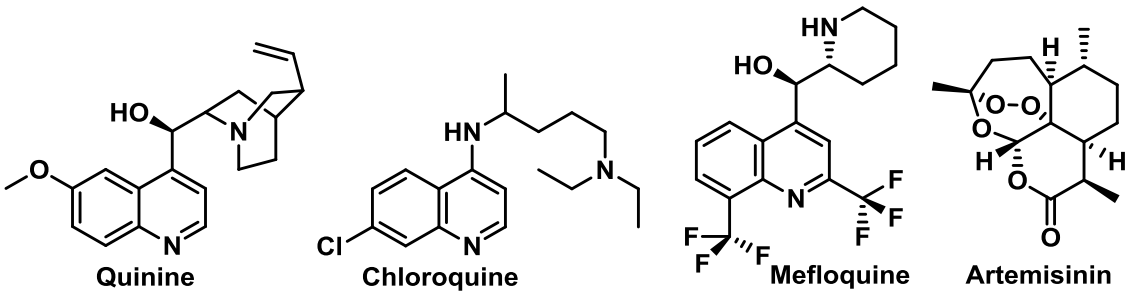


Figure 1.1 Some anti-malarial natural products

The anti-malarial small-molecule quinine (Novo-Quinine®), was isolated from the bark of Cinchona species by Caventou and Pelletier in the 1820s.[3] This potent compound provided the basis for synthetic analogues chloroquine (Aralen®) and mefloquine (Lariam®), which were employed as alternative anti-malaria treatments around the 1950s.[4] However, with the development of increased resistance to anti-malarial therapeutics, access to new drug candidates became vital. In 1972, Tu Youyou isolated Artemisinin from *Artemisia annua*. [5,6] This potent anti-malaria compound became a game-changer aiding treatment of multi-drug resistant *Plasmodium falciparum* malaria. Youyou was awarded the 2011 Lasker Award in Clinical Medicine and Nobel Prize in Medicine in 2015, for this significant breakthrough.

Vincristine and vincaleukoblastine, marketed as Oncovin® and Velban®, were isolated from periwinkle plant *Vinca rosea* by two independent research teams between 1950-1960.[7,8]

This breakthrough was one of many, as soon after, isolation of components from the bark of *Taxus brevifolia* led to the discovery one of the most widely-used breast cancer drugs, paclitaxel.[9] This therapeutic, marketed as Taxol®, was approved for administration in 1993. This naturally derived drug is involved in the inhibition of the uncontrolled cell division process of cancerous cells.[10]

Other key bioactive classes include camptothecins. The anti-cancer camptothecin, 20-(*S*)-camptothecin, was first discovered and isolated by Wall and Wani in 1966 from the bark of *Camptotheca acuminate*.[11] While this camptothecin showed promise, problems regarding toxicity and poor solubility, hindered progression of the drug candidate. As such, efforts turned to the preparation of more water-soluble synthetic analogues. This approach lead to the identification of topotecan and irinotecan, marketed as the anti-cancer therapeutics, Hycamtin® and Camptosar®.

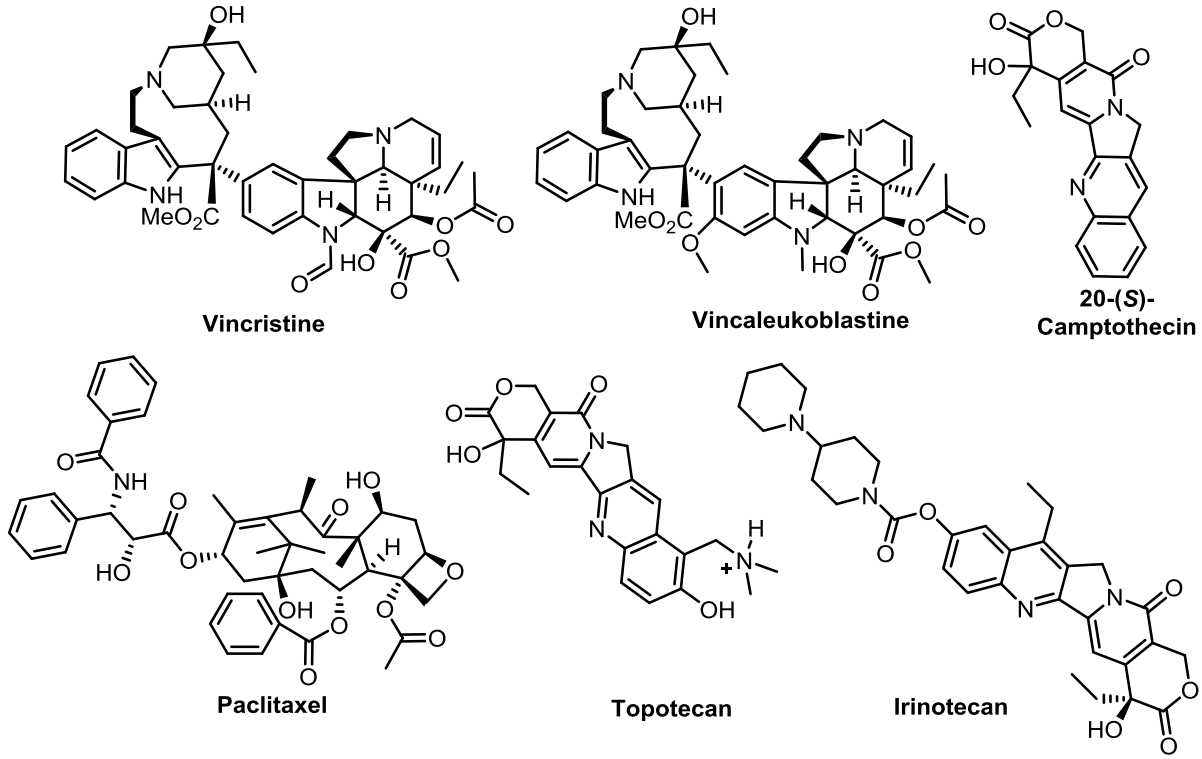


Figure 1.2 Privileged natural product structures in drug discovery

Glutarimide-containing macrocycles are another class of molecules that have received attention as anti-cancer agents (Figure 1.3).

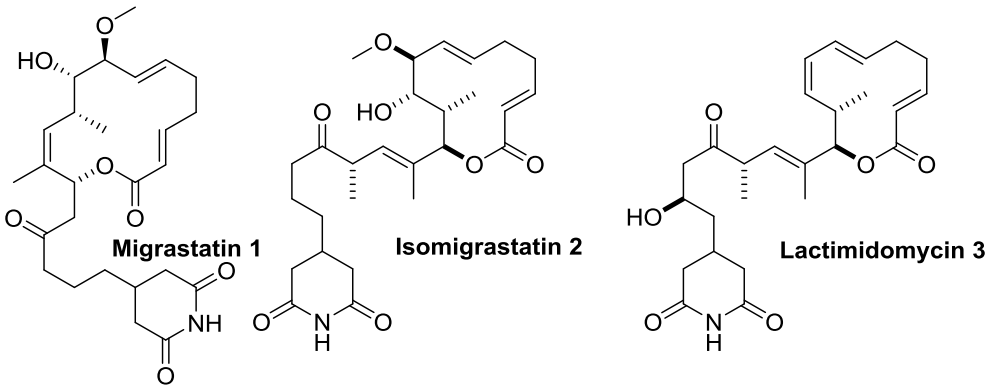
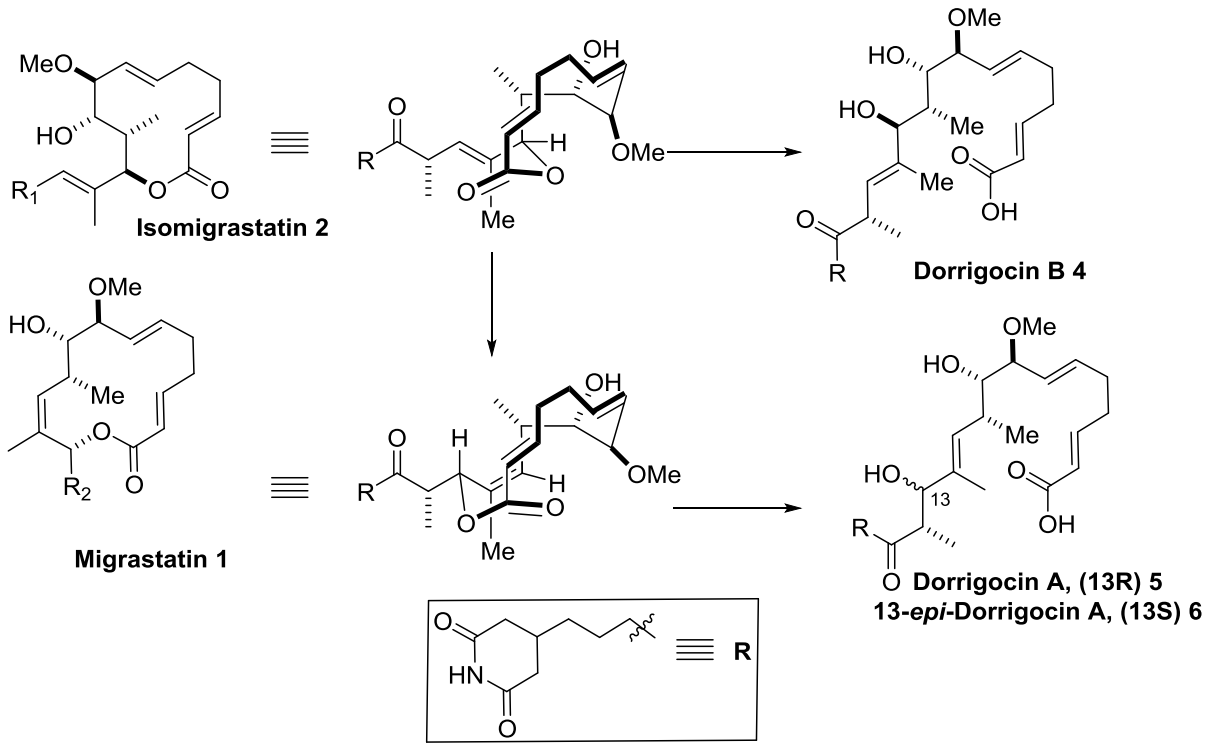


Figure 1.3 Glutarimide-containing macrocycles

Lactimidomycin **3** was first isolated from *Streptomyces amphibiosporus* strain ATCC 53964 in 1992.[12] This particular 12-membered glutarimide showed a range of bioactivities, especially in the treatment of leukaemia tumours.[12] In 2010, Fürstner and co-workers[13] reported the total synthesis of lactimidomycin. A 14-membered ring, resembling lactimidomycin, migrastatin **1** had been previously isolated from *Streptomyces* sp. strain MK-929-43F1 in 2000.[14] This 14-membered macrocyclic natural product has been reported to inhibit cell migration[14,15] and hinder multi-drug resistance[16]. Migrastatin was also isolated from *Streptomyces platensis* strain NRRL18993 in 2002, along with a 12-membered macrocyclic analogue, isomigrastatin.[17]

The stability of these macrocycles can be effected by the unsaturated lactone moiety. In 2005, Shen and co-workers[18] reported how isomigrastatin can be decomposed into its shunt metabolites, migrastatin **1** and the dorrigocins **4**-**6**. Furthermore, thermolysis of isomigrastatin was reported to form these same metabolites *via*. hydrolysis (Scheme 1.1).[19] Dorrigocin A and dorrigocin B are non-cyclic glutarimides resembling the non-cyclic forms of migrastatin and isomigrastatin, respectively. The dorrigocins are known for their inhibition of ras i.e. a GTPase protein involved in multiple biological processes.[20] While stability of these macrocycles may be problematic, the potent bioactivities have created wide interest and synthesis of their derivatives has been exploited as a means of drug discovery.[21,22]



Scheme 1.1 Thermolysis of isomigrastatin **2** to afford migrastatin **1** and dorrigocin derivatives **4**-**6** **(**Adapted with permission from reference 19. Copyright (2006) American Chemical Society)

1.2 Cancer and its capability to migrate and spread to other parts of the body

1.2.1 Background

The human body is a highly-ordered organism consisting of trillions of cells. When the division and apoptosis of these cells becomes uncontrollable, a tumour may form. Tumours can be categorised as benign or malignant. A benign tumour can be described as a localised neoplasm which does not invade neighbouring tissues or spread to other parts of the body (a process more commonly known as metastasis). Malignant tumours are more problematic, susceptible to invading nearby tissue and metastasis, thus forming a secondary tumour. These neoplasms are defined as cancerous growths. Cancer is a prominent problem within Ireland, with the number of cancer cases and mortalities increasing annually by 3 % and 1%, respectively.[23]

Treatment of both malignant and benign tumours is important in medicine. Current treatments of this disease include; surgery, radiation therapy, chemotherapy and biological therapy. Surgery involves removal of the tumour. This procedure may be used in combination with radiation therapy and/or chemotherapy to ensure complete removal of the neoplasm. However, both treatments can induce death of normal healthy cells, thus leading to severe side effects including; nausea, vomiting and hair loss. Biologic therapies involve aiding the immune system to recognise and attack cancer cells. One advantage of this type of therapy is the fewer side effects. However, biological drug therapies are among the most expensive therapeutics available and as such efforts using traditional therapies, such as small molecule-based chemotherapeutics are still at the forefront of cancer research. One approach

to cancer treatment using small molecules, involves inhibition of tumour metastasis. This type of chemotherapy could be used in combination with other drugs to potentially cure cancer.

1.2.2 Tumour metastasis – a complex biological process

Tumour metastasis is the primary cause of death in the majority of cancer patients. This complex biological process involves; (i) local infiltration of nearby organs/tissues by the cancer cells, (ii) entry of cancer to cells into vasculature, (iii) transport of the cancerous cells to a different area of the body (iv) exit of cancerous cells out of the vasculature to suitable growth sites (v) colonisation by the cancerous cells and (vi) subsequent blood vessel growth, a process more commonly known as angiogenesis, to support the secondary neoplasm with sufficient oxygen and nutrients.[24] Thus, tumour metastasis can be hindered by prevention of any of these steps. Ideally, targeting the primary cancer cell migratory step, would prohibit the cascade process.

1.2.3 Cancer cell migration

Cell migration is an essential feature of cells involved in many biological pathways, including, immune surveillance, tissue repair and regeneration. The mechanism of this biological pathway is highly complex.

Cell migration is initiated in response to chemoattractants. Upon interaction of these chemical signals with cell surface extracellular receptors, chemoattractants can trigger signalling pathways causing actin polymerisation. Actin-bundling subsequently occurs to organise the new actin filaments. These actions can lead to the formation of cell membrane protrusions (such as, lamellipodia and filopodia) on the leading edges of migratory cells. The lamellipodia (sheet-like) and filopodia (rod-like) protrusions serve as traction sites for migration as the cell moves forward.

1.3 Bioactivities of migrastatin, isomigrastatin and analogues

1.3.1 Danishefsky

As previously stated, upon isolation and structure elucidation of migrastatin in 2000 (and subsequent evaluation of biological activities), the 14-membered macrocycle was identified as a potent inhibitor of tumour cell migration, thus showing potential as a tumour metastasis suppressor. [14,15,25,26] Danishefsky and co-workers[27] were the first to make a breakthrough in the synthesis of these macrocycles reporting the preparation of the migrastatin core and analogues in 2002. A year later, they reported the first total synthesis of migrastatin.[28] Subsequently, Danishefsky and co-workers biologically evaluated migrastatin against the macrocyclic core and derivatives, associating the latter with tumour cell migration activity three orders higher than the contending glutarimide-containing natural product upon comparison of IC_{50} values in a chamber cell migration assay of 4T1 mouse breast tumour cells (Figure 1.4).[29] Stability studies of these compounds in mouse plasma were also performed. Results showed that analogues with ester functionality, migrastatin core **7** and 2,3-dihydromigrastatin **9**, were unstable in comparison to the contending migrastatin analogues

containing ketone **8** and amide **10** functionalities.[30] Other cell lines have been investigated against the migrastatin lactam and ketone, with promising inhibitory activity reported in numerous cell lines including; MDA-MB-231 (human breast tumour), Lovo-229 (human colon tumour) and PC-3 (human prostate tumour).[31]

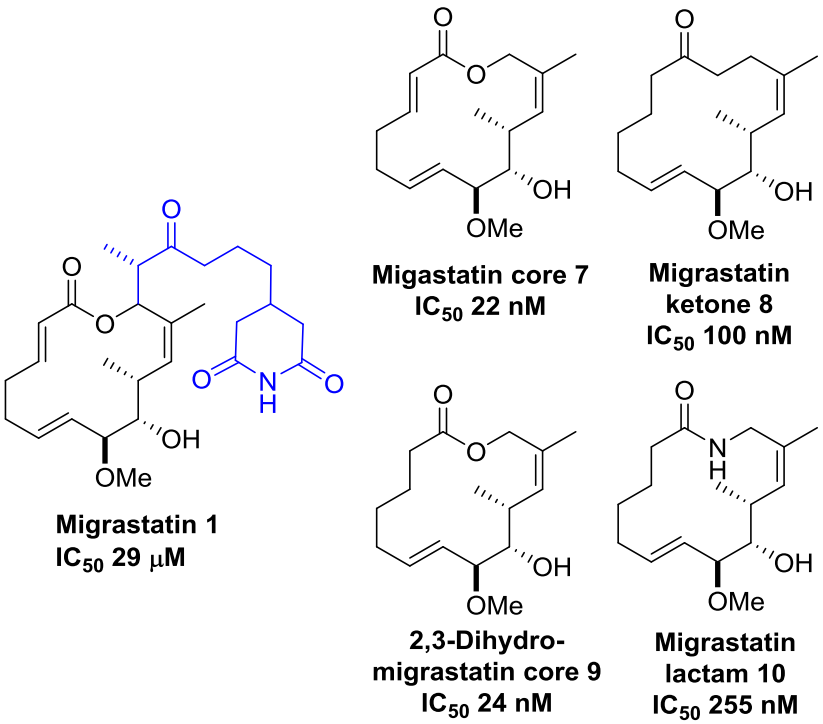
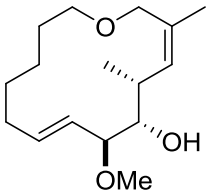


Figure 1.4 Bioactive macrocycles migrastatin 1, migrastatin core 7 and derivatives 8-10 prepared by Danishefsky

Based upon sufficient biological evidence for the anti-metastatic activity of the migrastatin macrolactone **9**, lactam **10** and ketone **8**, *in-vivo* studies were performed utilising the 4T1 mouse mammary model.[31] As expected based on previous stability studies, the inhibition of metastasised 4T1 cells in lungs was greater for the macrolactam **10** and macroketone **8** (91-99 %) in comparison to the macrolactone **9**.[31] Danishefsky and co-workers also investigated the mechanism of **8** and **10** in tumour cell migration.[31] They reported both 14-ring macrocycles could inhibit formation of lamellipodia protrusions, a process facilitated by GTPase Rac protein. Further exploration of the mechanism was undertaken by examining the effects of the macrocycles on Rac activation. These studies evidenced decreased Rac activity in cells treated with the macrocycles, thus concluding the mechanism of **8** and **10** is at (or upstream of) Rac activation.

Oskarsson and Danishefsky[32] succeeded in preparing another analogue of the migrastatin core, migrastatin ether **11** (Figure 1.5), with promising inhibitory activity of migration in breast cancer cell lines: MDA-MB-231 (human breast cancer), MDA-MB-435 (human breast cancer), LM2-4175 (human breast cancer) and 4T1 (mouse mammary cancer). *In vivo* studies of this migrastatin analogue were also performed and showed an 87 % reduction in metastasis when the mice were

administered with the macrocycle (40mg/kg, 3 times/week) from day 1. Administration of the macrocycle to the mice from day 15 resulted in a 47 % reduction of metastasis. Studies of dosage effects (40mg/kg and 200 mg/kg) were also performed. In the control sample (administered with saline solution instead of **11**), all mice had died after 50 days. The survival of the experimental group was dependent on dosage, with an increased survival rate (50 %) for the higher dosage group (200mg/kg) in comparison to the contending lower dosage (40mg/kg, survival rate of 30 %). The secondary tumour was undetectable in the higher dosage group after 9 weeks. [32]



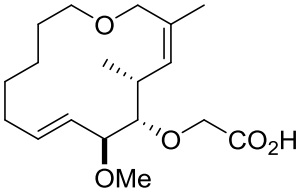
Migrastatin ether 11

IC_{50} (nM)

4T1	MDA-MB-231	MDA-MB-435
470	300	370

Figure 1.5 IC_{50} values for migrastatin ether in different breast cancer cell lines

Lecomte and Danishefsky[33] soon after prepared another migrastatin core analogue related to migrastatin ether **11**, migrastatin acid **12 (**Figure 1.6). Their reports showed acid **12** to be an inhibitor of lung cancer cell lines; A549, H1975 and H299. Further *in vivo* mouse models evidenced **12** to be 5 times more potent than migrastatin ether **11** at the same dosage. In addition, toxicity was neglible.[33] This carboxylic acid was expected to reduce permeability of the macrocycle through the cell membrane, indicating the main target for this analogue could be a cell surface receptor.



Migrastatin acid 12

IC_{50} (μM)

A549	H1975	H299
0.66	0.510	5.02

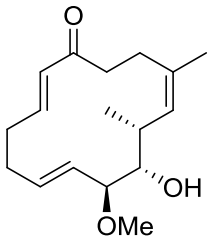
Figure 1.6 IC_{50} values for migrastatin acid **12** in cancer cell lines A549, H1975 and H299

1.3.2 Chen

In 2010, Chen and co-workers[34] reported the target of the macroketone **8** to be Fascin, a protein involved in actin-bundling critical in the formation of protrusions for cell migration. Chen[34] also published co-crystallisation of fascin with **8** and suggested the migrastatin analogue binds to Fascin at the same site as actin, thus hindering actin assembly. Since then, the crystallographic data have been retracted due to the incorrect structure of **8** in the X-ray crystal structure.[35]

1.3.3 Murphy

In 2003, Murphy and Krol[36] prepared and biologically evaluated a series of macrocycles based on migrastatin. Macroketone **8** and its unsaturated derivative **13** (Figure 1.7) were found to be strong inhibitors of tumour cell migration in canine adenocarcinoma cell lines: CMT-W1, CMT-W1M and CMT-W2. Further mechanistic investigations of **13** evidenced disruption of the formation of filopodia protrusions through the prevention of fascin-dependent cross-linking of actin filaments.[36]



unsaturated macroketone 13

IC_{50} (μM)

CMT-W1	CMT-W1M	CMT-W2
66	55	51

Figure 1.7 IC_{50} values for migrastatin acid **12** in canine cancer cell lines CMT-W1, CMT-W1M and CMT-W2

Since then, Lo Re and Murphy[36] have reported migrastatin and isomigrastatin analogues with high inhibition activity against breast cancer cell lines MCF7 and MDA-MB-361 (Figure 1.8). Murphy and co-workers[37] have also investigated other mechanisms of action including the effect of macroketone **8** on epithelial cadherin. Disregulation of this protein in cancer cells, can lead to detachment of cancer cells from the primary tumour.[38–40] As such, the specific target of the these macrocycles is still debated.[35,41]

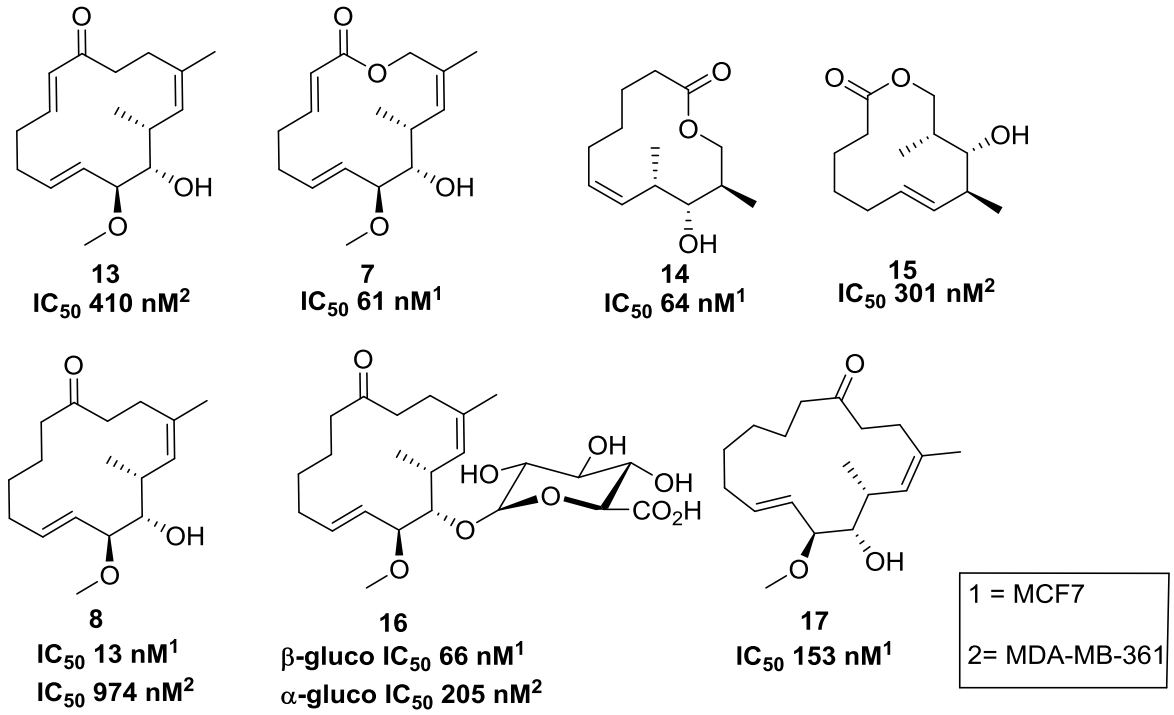
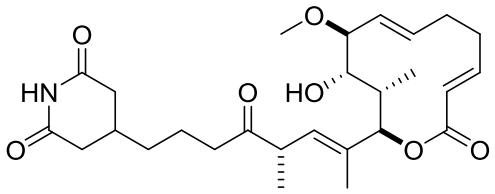


Figure 1.8 Bioactive migrastatin and isomigrastatin analogues prepared by Lo Re and Murphy

The biosynthetic precursor to migrastatin, isomigrastatin was another glutarimide-containing macrocycle found to have tumour cell migration activity. The first total synthesis of this macrocycle was completed by Danishefsky and co-workers[42] in 2007. Subsequent biological evaluation evidenced this 12-membered macrocycle as a potent inhibitor of tumour cell migration (Figure 1.9).[21]



Isomigrastatin 2

IC_{50} (nM)

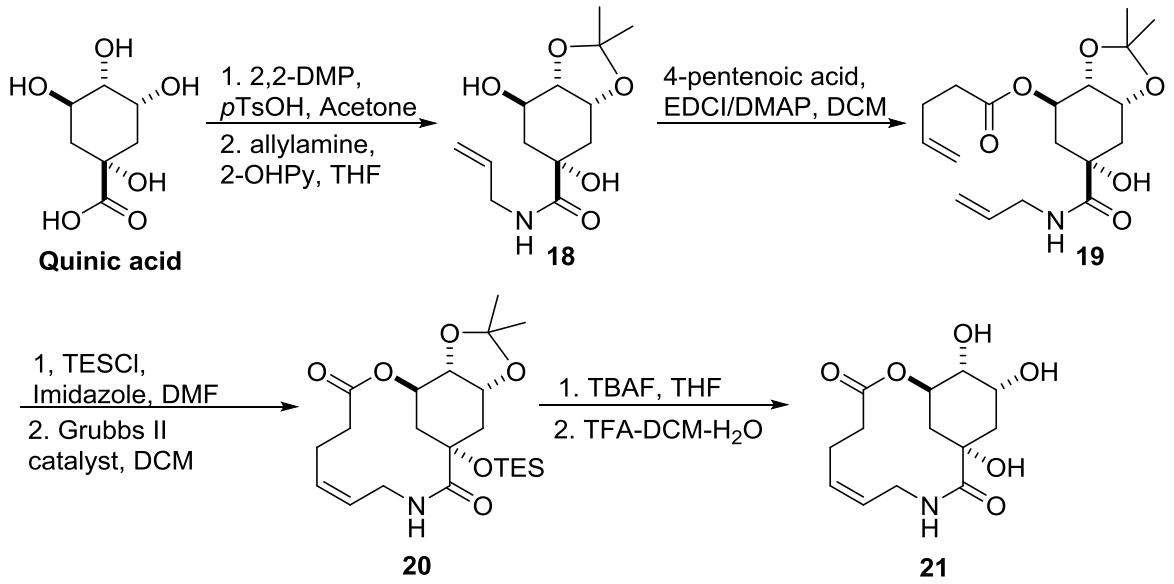
4T1	MDA-MB-231
23	32

Figure 1.9 IC_{50} values for isomigrastatin of adenocarcinoma mammary cells in both mice (4T1) and human (MDA-MB-231)

1.4 Macrolides- inhibitors of tumour metastasis

1.4.1 Preparation a of new class of macrolides by Bewley based on quinic acid

In 2007, Metafaria and Bewley[43] reported the synthesis of macrocycles with anti-cell migratory activity from quinic acid. The macrocycle **21** has a resemblance to both isomigrastatin **2** and migrastatin **1** with both inner 12-membered and outer 14-membered ring frameworks.



Scheme 1.2 Preparation of macrolide **21** by Bewley and co-workers (Adapted with permission from "synthetic macrolides that inhibit breast cancer cell migration in vitro", Org. Lett., Vol. 129, 2007, ACS publishing 2007)

Treatment of quinic acid with 2,2-dimethoxypropane and *p*-TsOH in acetone afforded the acetonide protected intermediate which was subsequently subjected to allylamine and 2-HOPy to afford the amide **18**. Chemoselective esterification of the amide with 4-pentenoic acid in the presence of EDCl/DMAP yielded lactone **19**. Silylation of the 3° alcohol using TES-Cl with imidazole afforded the silylated intermediate, which could be reacted with Grubbs-II catalyst *via* ring closing metathesis to yield amide 12-ring macrocycle **20**. Subsequent deprotection of the silyl-protecting group using TBAF and removal of the acetonide functionality yielded macrocycle **21**.

This macrocycle was shown to inhibit tumour cell migration of 4T1 breast cancer cells on a nanomolar level. The mechanism of action of this heterocyclic framework was also investigated and reports suggested the macrocycle inhibits formation of lamellipodia protrusions.[43]

1.4.2 Previous work within the Murphy group

In 2010, Yan[44] reported (in her PhD work) the synthesis of a new class of macrolides defined by a glucose sugar moiety embedded in the ring framework. In particular macrocycle **22** prepared by Yan had a structural resemblance to migrastatin **1** and isomigrastatin **2** and to Bewley's quinic acid derivative **21** due to the 12-inner and 14-outer ring frameworks, all previously shown to be potent inhibitors of tumour cell migration.

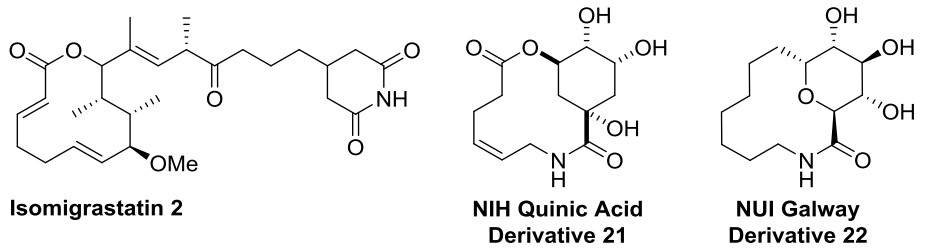
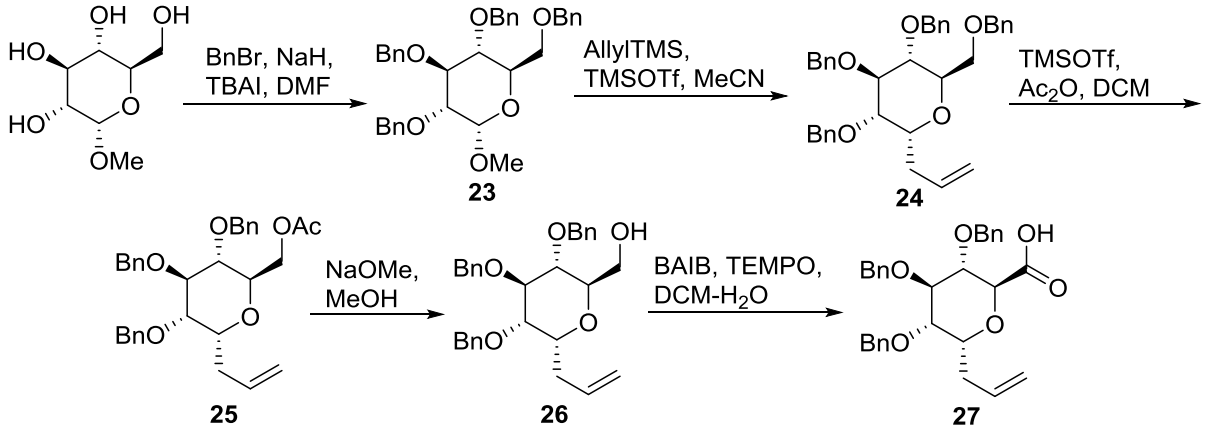


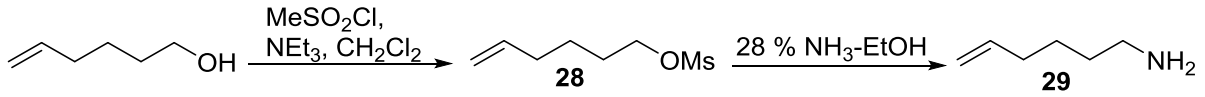
Figure 1.10 Isomigrastatin and analogues

This framework could be synthesised from methyl α-D-glucopyranoside, an inexpensive and easily accessible starting material. Benzylation of the simple sugar with sodium hydride and tetrabutylammonium iodide afforded the fully protected glucopyranoside **23**. Subsequent glycosylation yielded *C*-glycosyl intermediate **24**. A sequence of chemoselective transformations were then performed to prepare the key intermediate acid **27**.



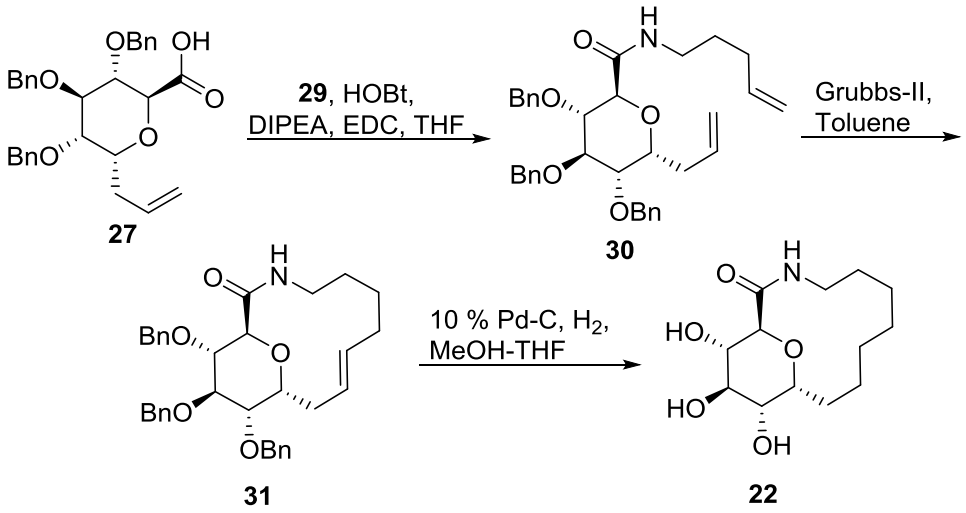
Scheme 1.3 Preparation of 2,3,4-tribenzyl glucuronic acid **27**

With acid **27** in hand, the required amine **29** was prepared from hex-5-enol *via*. an intermediate mesylate **28**.



Scheme 1.4 Preparation of amine **29**

Amide coupling of these intermediates using HOBt, DIPEA and EDC yielded amide **30**. Subsequent ring closing metathesis using Grubbs II generation catalyst afforded the lactam **31**. Reductive debenzylation of this framework provided access to deprotected macrolactam **22**.



Scheme 1.5 Preparation of Macrolactam **22**

Preliminary biological evaluation identified this macrolactam as an inhibitor of tumour cell migration in a scratch assay. As such, further investigations into the biological evaluation of this new class of macrolides by preparation of derivatives of **22** were of interest. It was envisaged thio- and oxy- analogues of **22** could be prepared with different configurations by utilising the Lewis-acid induced anomerisation of 1,2-*cis* macrolactams to 1,2-*trans* macrolactams.

1.5 Lewis-acid induced anomerisation

1.5.1 Participating and non-participating groups in glycosylation

Glycosylation involves the reaction of an electrophilic glycosyl or donor with a nucleophile to form a new glycosidic linkage. This transformation involves 3 key components; (i) activation of the glycosyl donor (e.g. trichloroacetimidate, thioglycoside, glycosyl halide) (ii) formation of oxo-carbenium cation intermediate and (iii) nucleophilic attack of the planar ring.

The side from which the nucleophile attacks is highly dependent on the presence of participating or non-participating protecting groups. As shown in Figure 1.11, when a participating protecting group, such as an acetyl group, is present at C-2, attack of this group on the oxocarbenium intermediate results in formation of the β-*O*-glycosyl product. In contrast, utilisation of a non-participating protecting group can give a mixture of products.

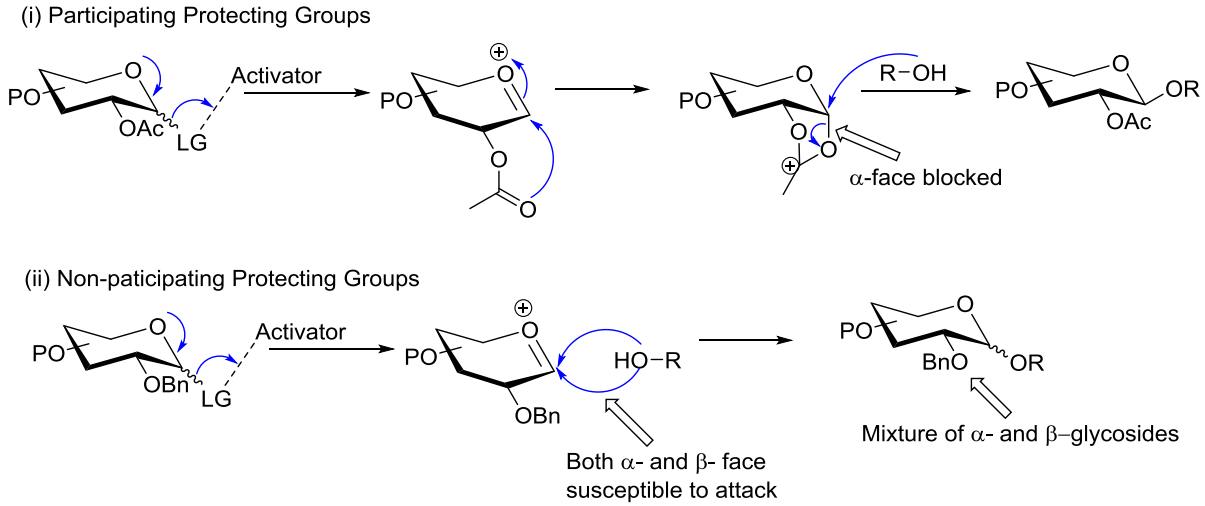


Figure 1.11 Influence of protecting groups on the stereochemical outcome of glycosylation

1.5.2 The anomeric effect

This phenomena was originally defined by the increased preference of an electronegative substituent at the anomeric carbon to have an axial orientation relative to cyclohexane.[45–47] Since then, various studies have suggested physical interpretations of this effect (Figure 1.12) including; (i) hyperconjugation of the lone pair of electrons on the endocyclic oxygen with the vacant σ* orbital of the C−X bond, thereby stabilizing the axial configuration and (ii) minimisation of dipole alignment of the endocyclic oxygen and the electronegative substituent at C-1.

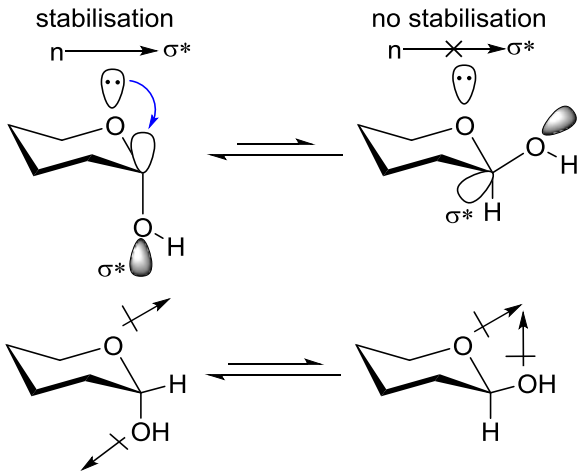


Figure 1.12 Rationalisation of the anomeric effect

1.5.3 Anomerisations catalysed by Lewis acids

The β-glycoside can be accessed in a stereoselective manner through protecting group manipulation. However, formation of α-glycosides from glycosylation reactions has proven difficult. One approach to access the α-glycoside in a stereoselective manner is anomerisation. Pacsu[48,49] first reported the epimerisation of the β- to the corresponding α-anomer in acetylated *C*-glycosides utilising the Lewis acids $SnCl_4$ and $TiCl_4$. His reports showed $TiCl_4$ could perform the transformation with greater

efficiency than $SnCl_4$. Lindberg and Limieux subsequently studied anomerisation. Lindberg[50] proposed that anomerisation involved an acid-promoted reversible cleavage of the anomeric C-O endocyclic bond, endocyclic cleavage. The acyclic structure allows rotation to occur, which in the presence of an equilibrium, will favour the α-orientation due to the anomeric effect.[51] Limieux[52] subsequently suggested exocyclic cleavage *via* anomeric C-O exocyclic bond, could also explain anomerisation. This mechanism involved S_N2 displacement of the substituent at the anomeric carbon to form an oxo-carbenium intermediate. Subsequent nucleophilic attack of the substituent on the anomeric carbon could yield the preferred α anomer if the reaction is under thermodynamic control.

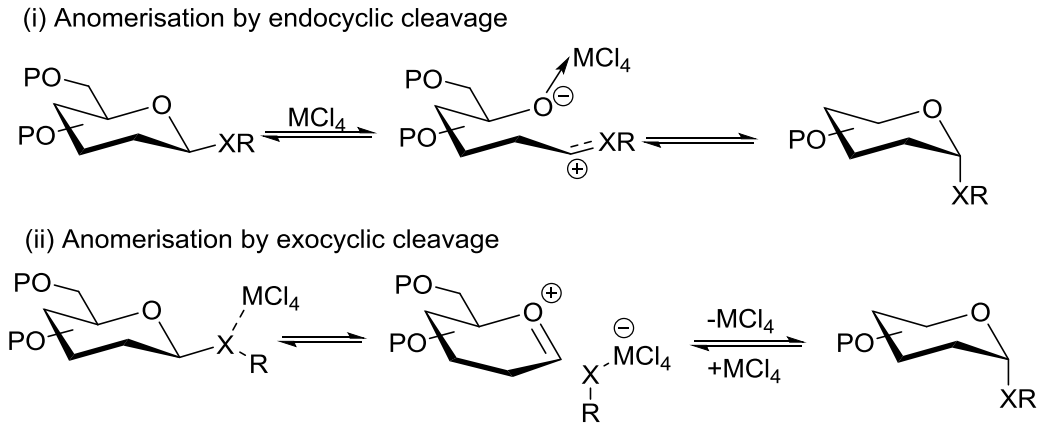
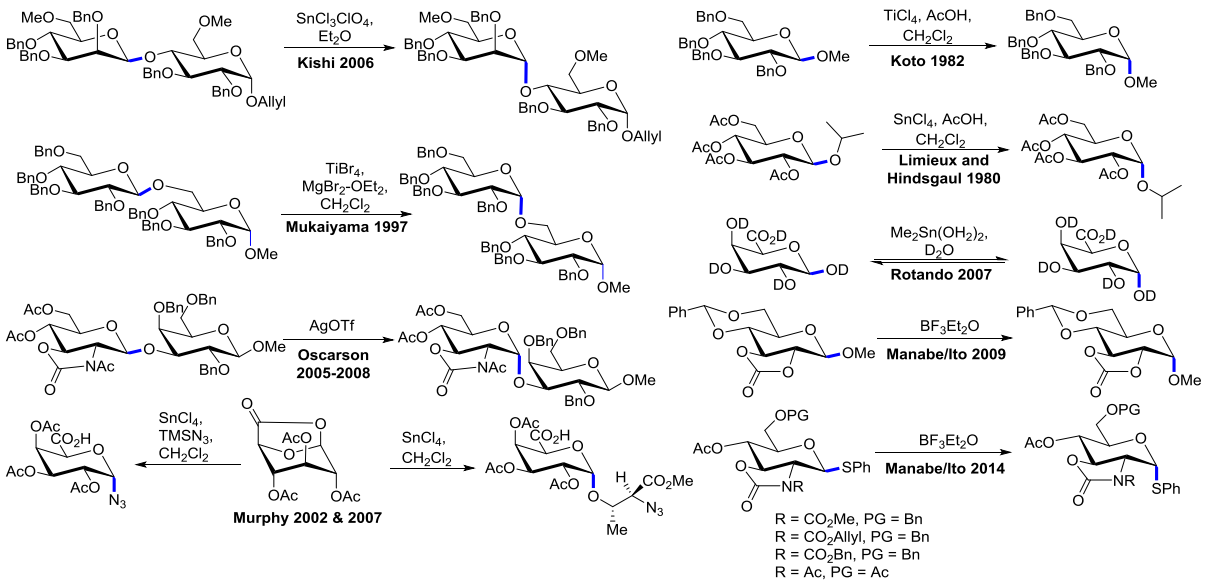


Figure 1.13 Mechanisms of anomerisation *via*. endocyclic and exocyclic cleavage

A summary of some investigations, of Lewis acid-promoted anomerisation to yield α-glycosides, is provided in Scheme 1.6.[53] Early investigations of this reaction within the Murphy group found $SnCl_4$-induced glycosylation of glucuronic acid lactone could yield the α-glycosides, in the presence of 2-*O*-acetyl groups known to give the β-glycoside due to protecting group participation.[54,55] Further research by Murphy and co-worker's evidenced a tandem glycosylation-anomerisation reaction and showed greater efficiency of the anomerisation reaction (catalysed by $TiCl_4$ and $SnCl_4$) for glucuronides in comparison to glucosides.[56] Murphy proposed that the presence of the carbonyl function at C-6 of glucuronides could promote the formation of a stable 5-membered chelate in comparison to the 7-membered chelate observed in glucosides, thus increasing anomerisation efficiency.[56]



Scheme 1.6 Some of the anomerisation studies reported since the 1980's (Adapted from, Lewis acid promoted anomerisation: recent developments and applications, Carbohydrate Chemistry, Vol 41, 2015, RSC publishing 2015)

Pilgrim and Murphy subsequently studied the impact of electronic and structural factors on the rate of anomerisation.[57] A series of β-glycosides with an exocyclic thio- or oxy- substituent at the anomeric carbon were prepared. The rate of anomerisation for these glycosides were determined and shown to follow 1st order equilibrium kinetics. The gluco- and galactouronic acid derivatives exhibited increased rates in comparison to gluco- and galactopyranosides, respectively. Furthermore, the β-*S*-glycosides proceeded to give the corresponding α-glycoside with greater efficiency than β-*O*-glycosides. However, a higher α:β ratio for the latter was observed. Murphy rationalised this result by considering the higher electronegativity value of oxygen, thus having an increased preference for α-configuration.[58] Other reasons could involve steric factors due to the bulky sulfur substituent favouring β-configuration.[57] The reaction could be promoted by installing electron-releasing substituents at C-6 such as, allyl ester fuctionality. It was suggested that the increased rate observed for the allyl ester substrate could be explained through the additional coordination of the olefin π-donor to the Lewis acid. While this result was promising, the free acid functionality prevailed leading to the highest anomerisation rates.[57]

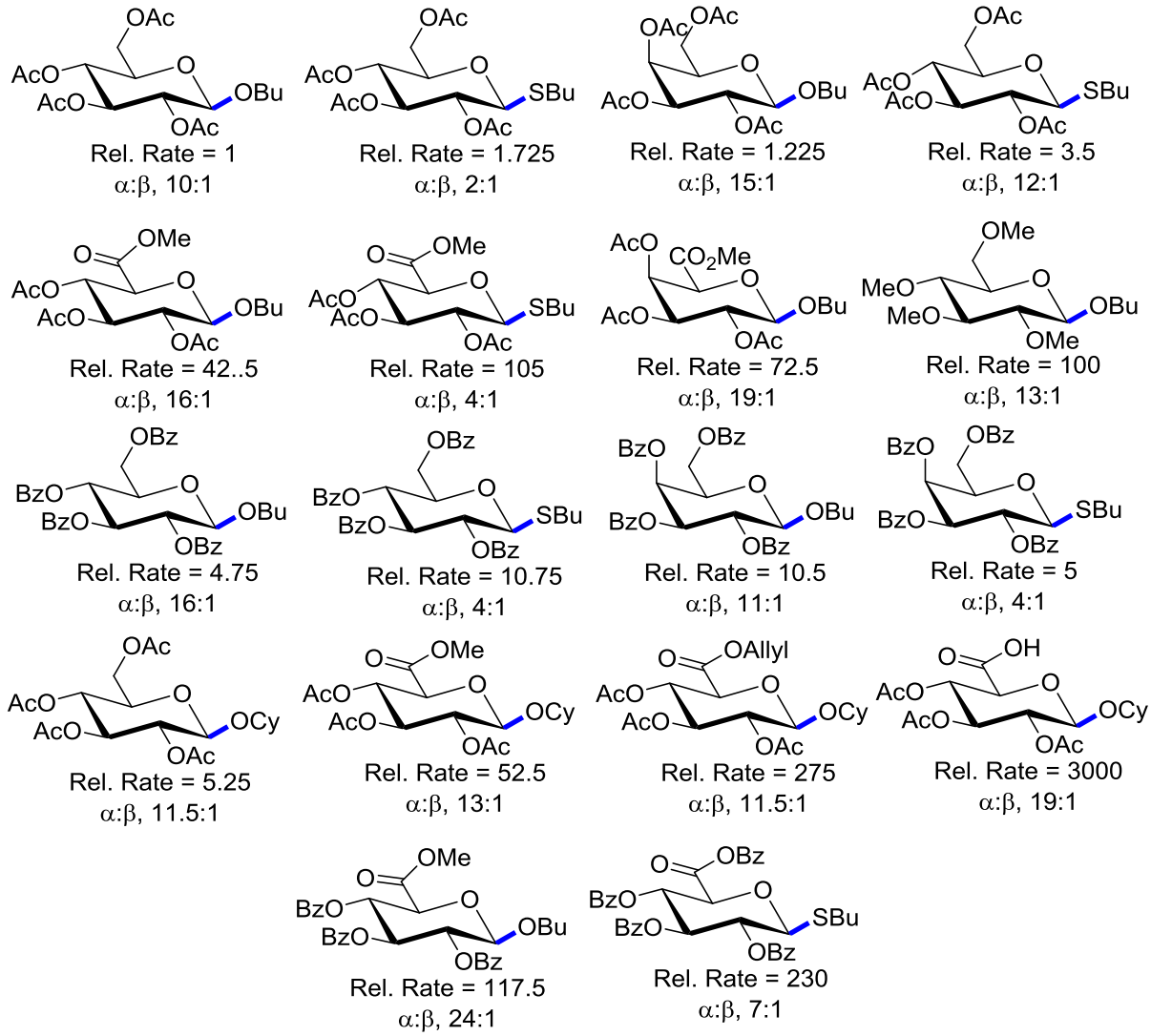
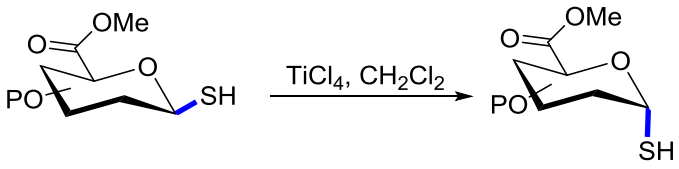


Figure 1.14 Relative reaction rates reported by Pilgrim and Murphy

Other factors such as pyranose configuration also had an impact on anomerisation rates with gluco-configured pyranoses shown to be generally less efficient than the corresponding galacto-configured pyranoses. Murphy rationalised this result based on C-4 configuration, with increased electron-donating properties of axial substituents, providing electron density for interaction of the endocyclic oxygen with the Lewis acid and also stabilising cation formation.[59] Rates of anomerisation were also affected by aglycon electronic properties with increased epimerisation evidenced with electron releasing substituents such as, -cyclohexyl. Protecting groups also proved important with higher rates observed for pyranosides with benzoyl- in comparison to the acetyl- functionality. Presence of benzoyl- protecting groups also leads to a higher α:β ratio. However, the reasons underlying this result require further investigations as benzoyl substituents were perceived as more electron-withdrawing than acetyl groups upon consideration of the pK_a values of benzoic acid (4.19) and acetic acid (4.78), thus the benzoyl protecting group should hinder formation of the α-anomer.

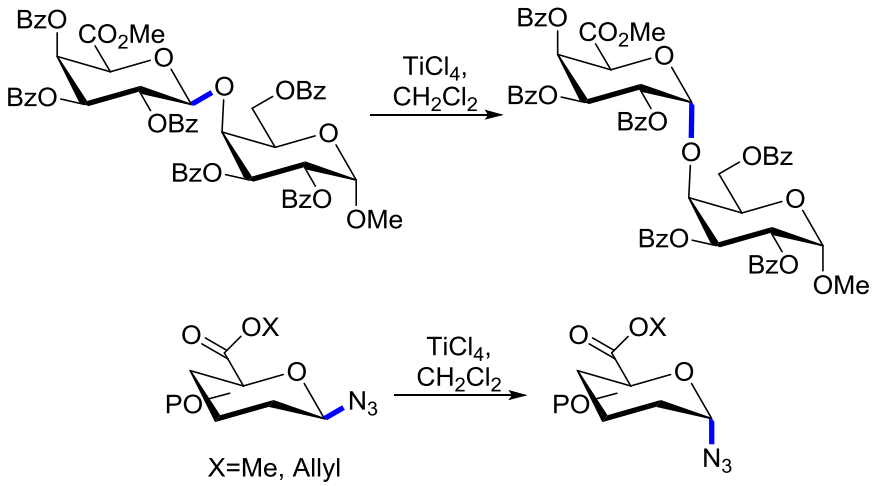
Murphy and co-workers also showed the α:β ratio was impacted by the nature of the Lewis acid, Lewis acid concentration and temperature.[57]

Based on this methodology, O'Reilly and Murphy[60], utilised this strategy to prepare α-*S*-glycosyl thiol (Scheme 1.7).



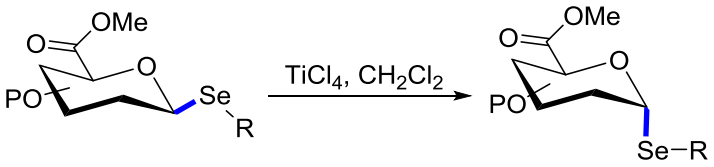
Scheme 1.7 Lewis acid induced anomerisation of free thiols

Farrell, Zhou and Murphy[61] subsequently utilised Lewis acids to anomerise β-disaccharides and *β*-glycosyl azides.



Scheme 1.8 Lewis-acid induced formation of α-disaccharides and α-azides

Furthermore, McDonagh and Murphy[62] extended the scope of this reaction to prepare α-Se glycosides.



Scheme 1.9 Lewis-acid induced anomerisation of β-Se-glycosides

1.6 Aim of research

As outlined in the introduction, the natural products isomigrastatin and its derivatives have proven to be potent inhibitors of tumour cell migration. With this mind, multiple analogues of such structures have been prepared and proven to have anti-cell migratory activity. Research by Metaferia and Bewley[43] identified a new class of molecules derived from quinic acid, exhibiting anti cell migratory

activity. Yan[44] subsequently prepared analogues of this framework based upon glucuronic acid. With promising preliminary results achieved from this framework, it was proposed to synthesise derivatives of this structure with the intention of identifying new macrolactams with high biological activity against tumour cell migration and thus, tumour metastasis. Access to the α-*S* and α-*O* macrolactams were hoped to be achieved utilising Lewis acid induced anomerisation of the corresponding β-macrolactams.

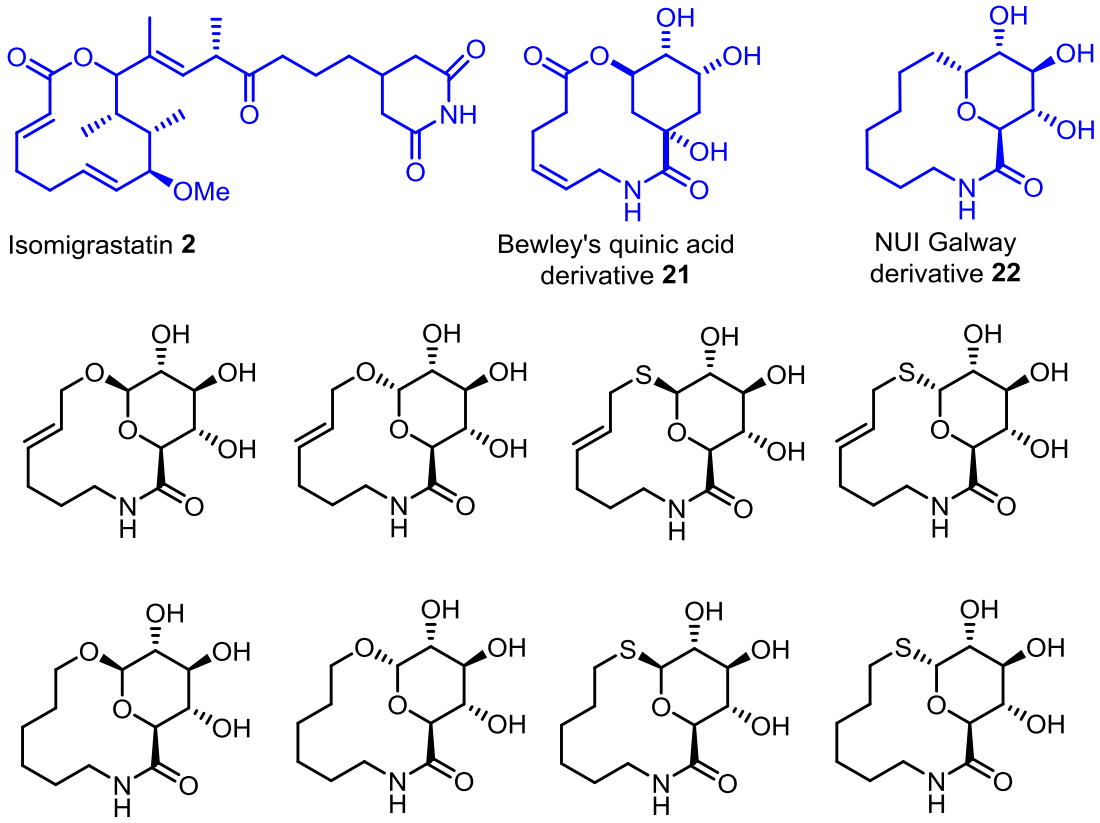
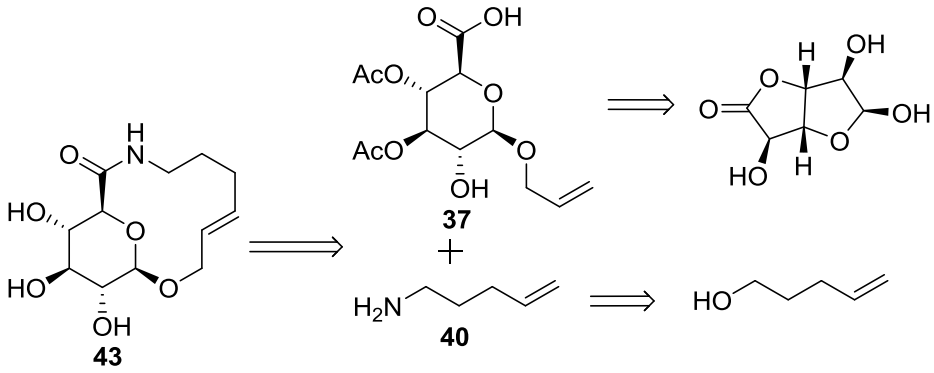


Figure 1.15 Target compounds which have structural resemblance to **2** and **21**

Chapter 2 Preparation of glucuronic acid derived macrocycles

2.1 Planning synthesis of macrolactams

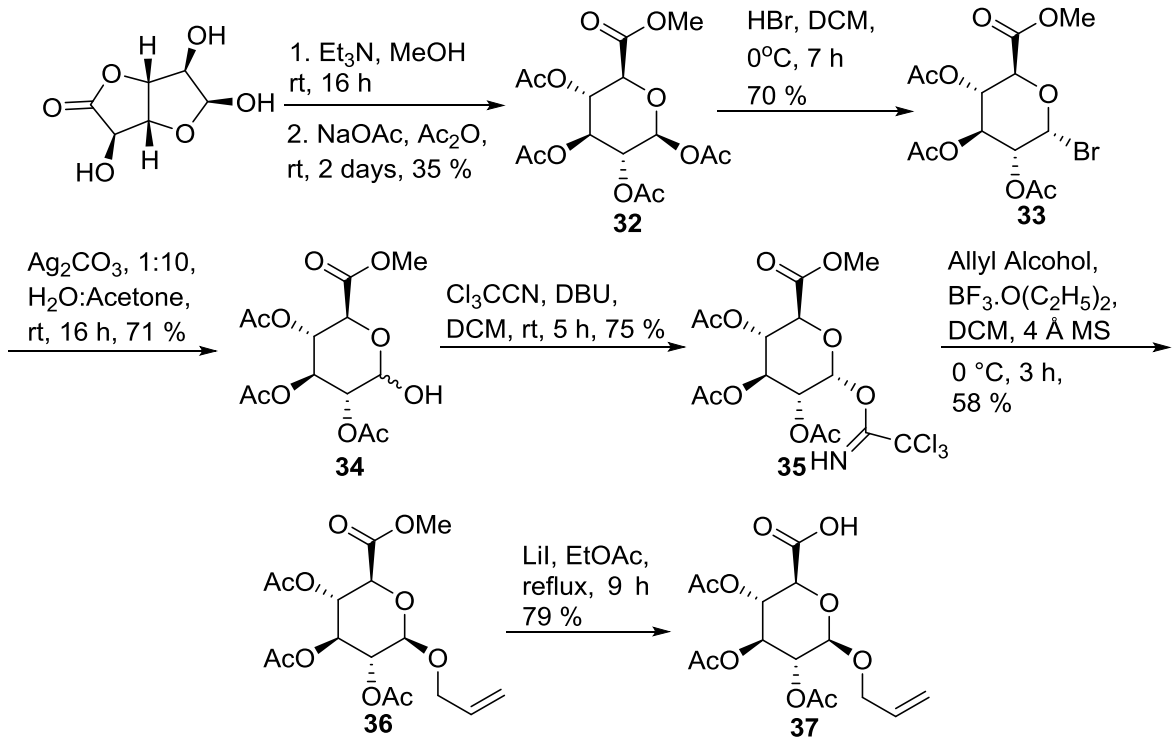
This chapter describes the manipulation of economical and commercially available D-glucurono-3,6-lactone to give novel 12-membered ring macrolactams. Taking macrocycle **43** as an example, it was envisaged the 12-membered ring could be prepared from acid **37** following an amide coupling with **40**, ring closing metathesis and deprotection. It was believed synthon **37** could be accessed from a bicyclic lactone following base-induced ring-opening acetylation, substitution of the anomeric acetyl functionality with a bromide, consecutive glycosylations and subsequent selective cleavage of ester functionality at C-6. Preparation of synthon **40** could be executed by conversion of 4-penten-1-ol to its mesylate intermediate and subsequent amination.



Scheme 2.1 Retrosynthesis from D-Glucurono-3,6-lactone

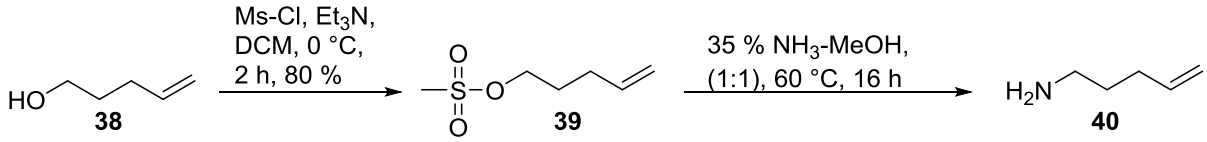
2.2 Preparation of *O*-glycosyl macrolactams

The synthesis of ester **36** was carried using a route previously reported. [63–65] Base-induced ring opening of D-glucurono-3,6-lactone and subsequent acetylation with sodium acetate and acetic anhydride yielded the protected glucuronic acid methyl ester **32**.[65] The α-bromide **33** could then be generated following treatment of **32** with hydrobromic acid in acetic acid. Conversion of the α-bromide **32** to hemiacetal **34** proceeded using Koenigs-Knorrs conditions[66], promoted by silver carbonate. The resulting hemiacetal was reacted with DBU and trichloroacetonitrile to form the glycosyl donor **35**.[65] Subsequent glycosylation with allyl alcohol afforded **36**.[63] Lithium iodide was then employed to selectively cleave the methyl ester at C-6 and yield precursor **37** with conditions, first utilised by Mayato and Vázquez[67] and more recently applied by McDonagh and Murphy[68].



Scheme 2.2 Preparation of acid **37**

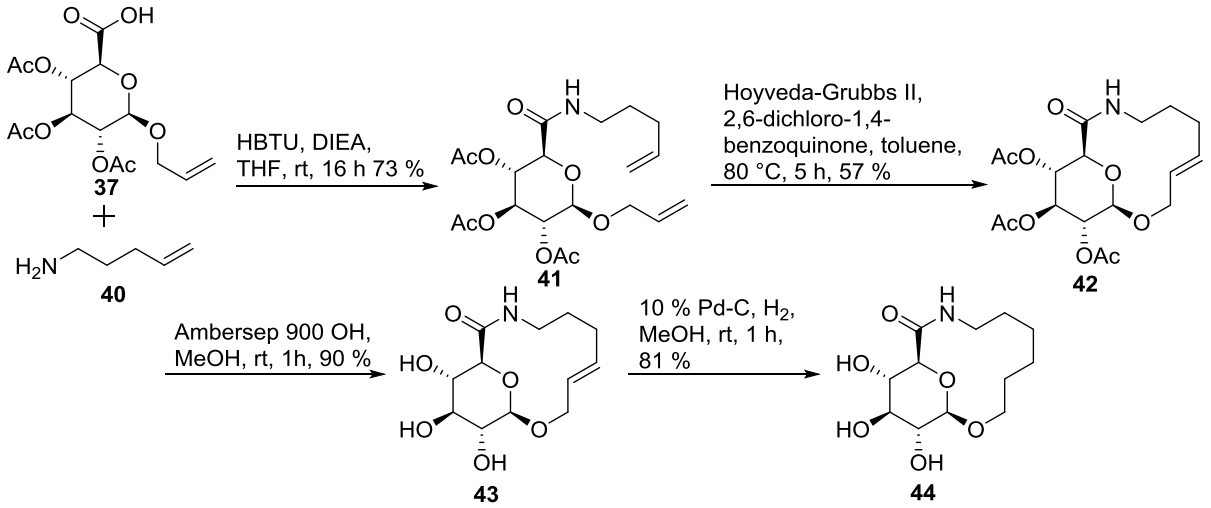
With **37** in hand, preparation of synthon **40** was investigated. Conversion of alcohol **38** to sulfonate **39** was performed using methanesulfonyl chloride and triethylamine. With an excellent leaving group in place it was possible to form **40** by treatment with 35 % aq NH_3 in MeOH. Due to the volatility and instability of **40**, it was brought on immediately to undergo an amide coupling with acid **37**.



Scheme 2.3 Preparation of amine **40**

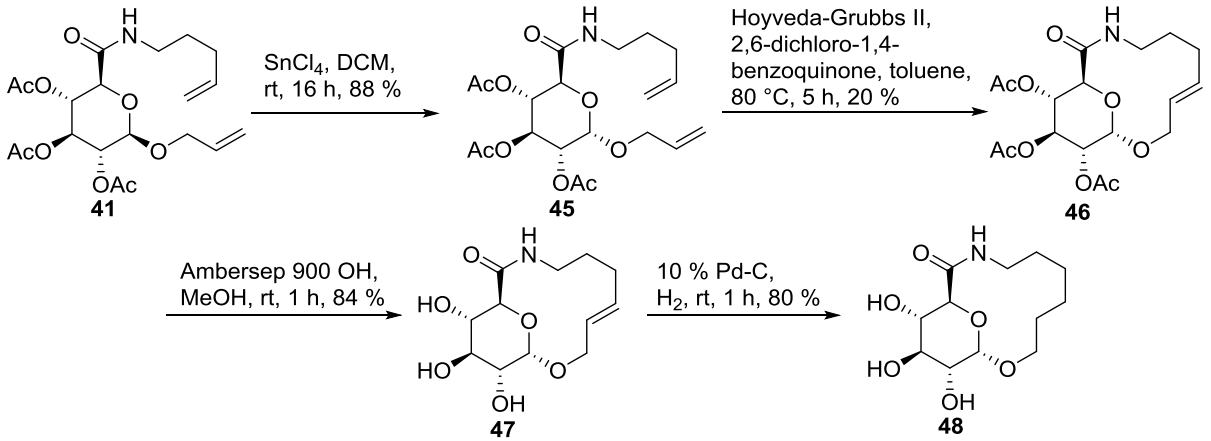
The amide **41** was subsequently subjected to numerous ring closing metathesis conditions in an attempt to yield **42**. Initially ring closing metathesis using Grubbs II and Hoyveya-Grubbs II catalysts were attempted with little success. Additives had been previously described by Grubbs and co-workers to promote ring closing metathesis.[69] As such, 2,6-dichloro-1,4-benzoquinone, in combination with Grubbs II did provide access to the ring-closed product **42** with modest yields (25 %) and a high level of impurities. Investigation of Hoyveda-Grubbs II in combination with the quinone additive yielded the *trans*-olefin **42** in a selective manner and with an improved yield (57 %).[70] In order to reproduce the yields recorded in this ring-closing metathesis, the use of degassed anhydrous solvent, and an inert atmosphere were vital. Treatment of the ring-closed product with Ambersep 900 OH resin in methanol provided **43**. The alkene geometry could be clearly identified by the *J* value of 15.1 Hz for the coupling

between the alkene protons in the ^{1}H NMR spectrum which is consistent with the *trans* alkene being present rather than the *cis*-alkene: δ 5.72 (dddd, *J* = 15.1, 9.2, 3.7, 1.9 Hz, 1H, alkene-H) and δ 5.62 (dddd, *J* = 15.2, 9.7, 4.0, 1.2 Hz, 1H, alkene-H). The conversion of **43** to **44** proceeded using catalytic amount of Pd-C and H_2.



Scheme 2.4 Synthetic route to macrolactams **43** & **44**

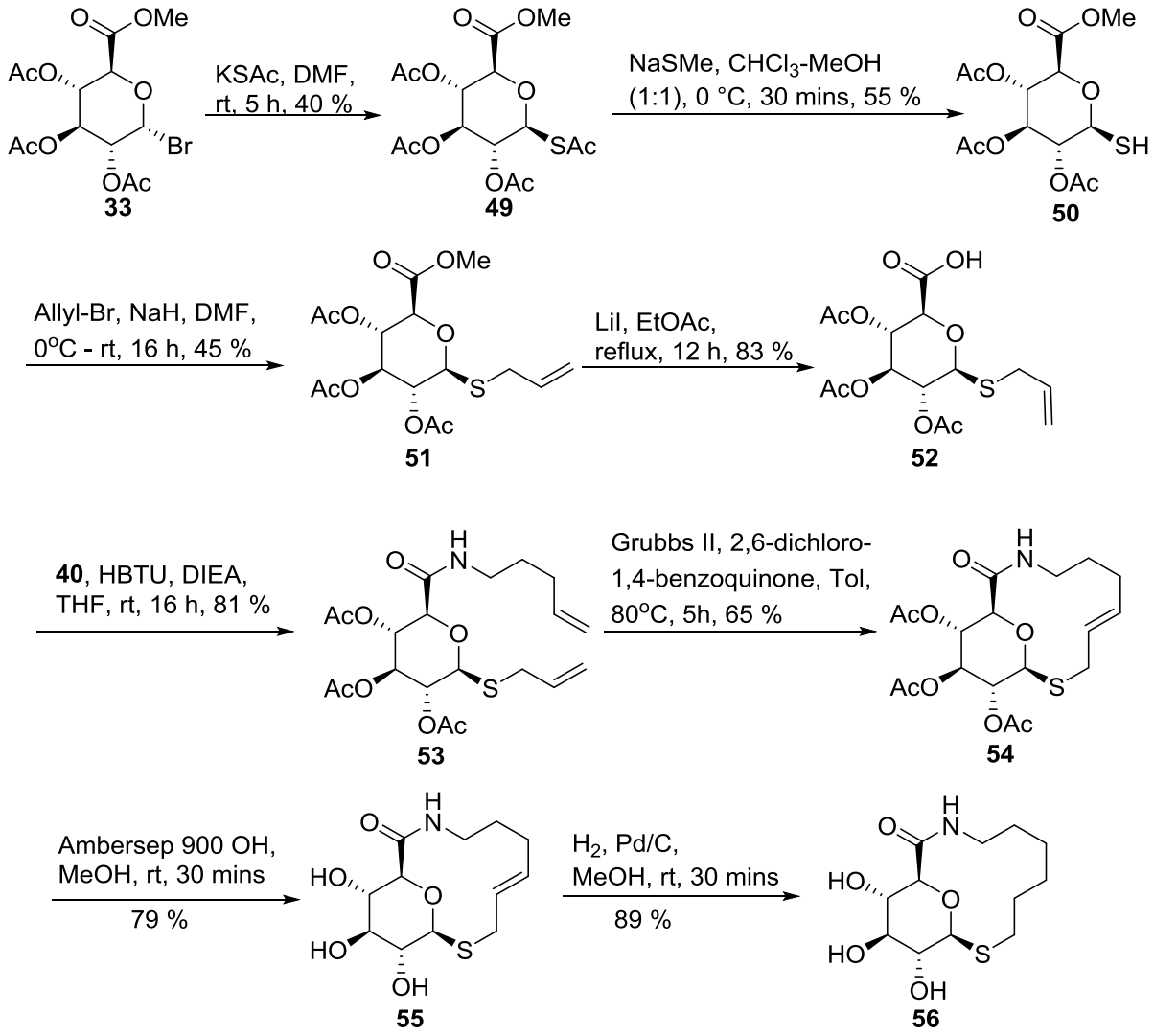
Anomerisation of β-macrolactam **42** to the α-macrolactam **46** using the Lewis acids, tin tetrachloride and titanium tetrachloride was attempted. However, these investigations led only to the decomposition of **42**. Hence, alternative routes were explored to prepare the α-*O*-macrolactams. The β-amide **41** was anomerised to the α-amide **45** using tin tetrachloride. The α-amide **45** then underwent similar transformations as **41** to achieve the synthesis of macrolactams **46, 47** and **48.** The alkene geometry could again be confirmed by a *J* value of 15.5 Hz for the coupling between the alkene protons in the ^{1}H NMR spectrum of **47**, which is consistent with the *trans* alkene.



Scheme 2.5 Synthetic route to macrolactams **47** & **48**

2.3 Preparation of *S*-glycosyl macrolactams

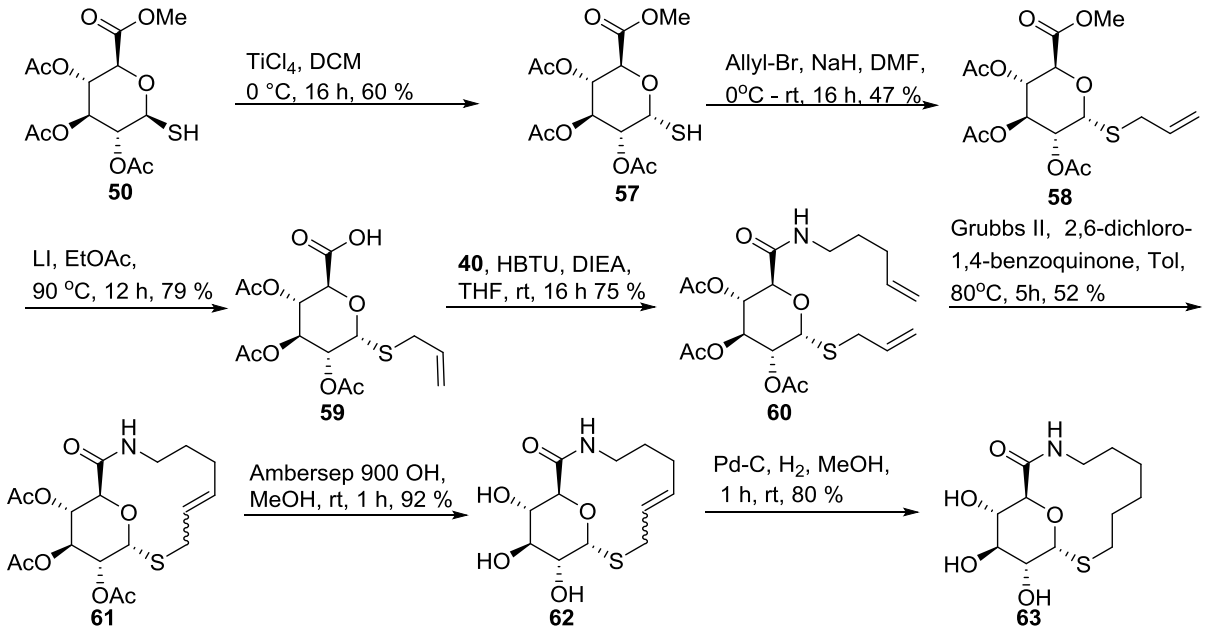
Attempts were subsequently made to synthesise the thio-macrolactam derivatives. The displacement of bromide from **33** with potassium thioacetate afforded the β-thioglycoside **49**.[71] Selective *S*-deacetylation with sodium thiomethoxide yielded the glycosyl thiol **50**.[72] Direct alkylation using sodium hydride and allyl bromide afforded modest yields of thioglycoside **51.** The thioglycoside underwent similar reactions as **36** *via* intermediates **52**-**54** to give macrolactams **55** and **56** with the *trans* geometry verified by the *J* value for the coupling constant between alkene protons in **55** (15.1 Hz).



Scheme 2.6 Synthetic route to macrolactams **55** and **56**

Anomerisation of acetylated β-macrolactam **54** was also attempted but proved unsuccessful. As such, it was necessary to use anomerisation of thiol **50** as previously employed by O'Reilly and Murphy[60] to access the required α-*S*-macrolactams. The β-glycosyl thiol **50** was anomerised to the α-anomer **57** using conditions previously developed by O' Reilly and Murphy.[60] This free thiol was converted to amide **60** through intermediates **58** and **59**. The α-anomer **60** was then converted to **61**, a mixture of stereoisomeric macrolactams, and subsequently deprotected to afford **62**. Olefin geometry of **61**/**62**

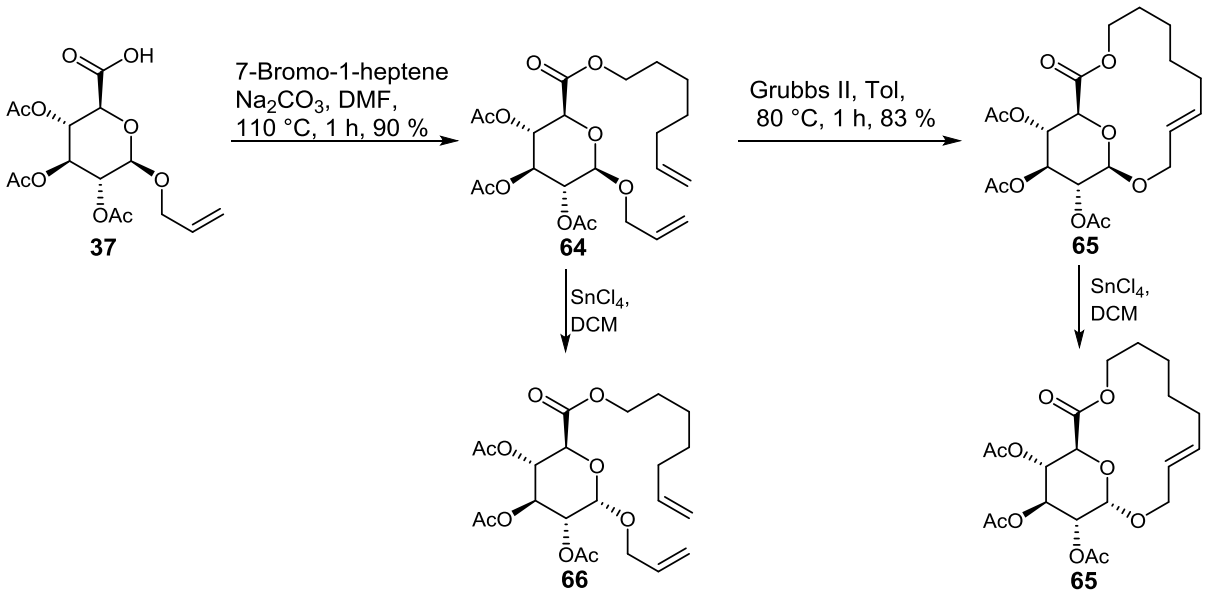
could not be confirmed due to overlapping alkene proton signals. Reduction of macrolactam **62** yielded **63**.



Scheme 2.7 Synthetic route to macrolactams **62** and **63**

2.4 Comparison of anomerisation reaction for 64 and 65

A larger 14-membered macrolactone was also prepared for investigation of the anomerisation reaction. Ester coupling conditions utilising DIAD and triphenylphosphine were first performed to access the desired lactone from **37**. However, DIAD by-products could not be separated from ester **64** and as a result an alternative route was explored. Deprotonation of acid **37** and subsequent reaction with 7-bromo-1-heptene afforded **64**. This ester was then treated with Grubbs II generation metathesis catalyst to yield ring-closed product **65** with *trans*-olefin geometry (15.5 Hz). A minor side product could also be detected by NMR which was in inseparable from the major product (major:minor, 9:1). 2D NOESY experiments clarified the minor side product was not a rotamer (see section 2.5). Both **64** and **65** could be anomerised using $SnCl_4$ to obtain the required α-anomers **66** and **67**.



Scheme 2.8 Preparation and anomerisation of **64** and **65**

2.5 Rotamers

Upon ^{1}H-NMR analysis of the deprotected macrocycles, a minor set of signals could be seen in the spectra of **43, 44, 47, 56** and **63** which indicated the presence of another substance, which was inseparable from the major substance by flash chromatography. One possible explanation for this is that there are interconverting rotamers present. Rotamers are a set of conformers arising from restricted rotation about a single bond. Rotamers could arise because of the presence of the amide in the macrocyclic ring, with both the *cis* and *trans* amides being present and in equilibrium. Murphy and co-workers[73] have previously demonstrated use of ROESY and NOESY experimentation to identify presence of different amide bond rotamers in solution. Sweeney[74] has also employed a similar protocol to recognise different rotamers of a 14-membered macrolactam. Other methods to identify such species have involved more complicated procedures including; variable-temperature NMR, solvent switching[75,76] and complexing agents[77]. The use of NOESY/ROESY technique detects chemical exchange occurring between two rotamers. In relation to NMR, chemical exchange can be described as the change a nucleus encounters (in more than one conformer) in which the NMR parameters differ.[78]

As such, 2D NOESY experiments were performed on the relevant macrocycles. As an example, the 2D NOESY spectrum for compound **44** is shown below (Figure 2.1). This experiment shows a ^{1}H-NMR spectrum on both the X- and Y- axes. The diagonal signal (red-coloured) represents the protons irradiated at a specific frequency (500MHz). The NOE experiment causes a change in phase of spacially proximate protons (blue-coloured crosspeaks) and correlations are observed off the diagonal. As shown in Figure 2.1, red-coloured crosspeaks are also observed off the diagonal. These red-coloured correlations (in the same phase as the signals on the diagonal) account for the protons which underwent significant chemical exchange with the corresponding proton irradiated in the conformer i.e. the

rotamers. Thus there is evidence that the two sets of signals observed in the NMR are due to presence of two rotamers.

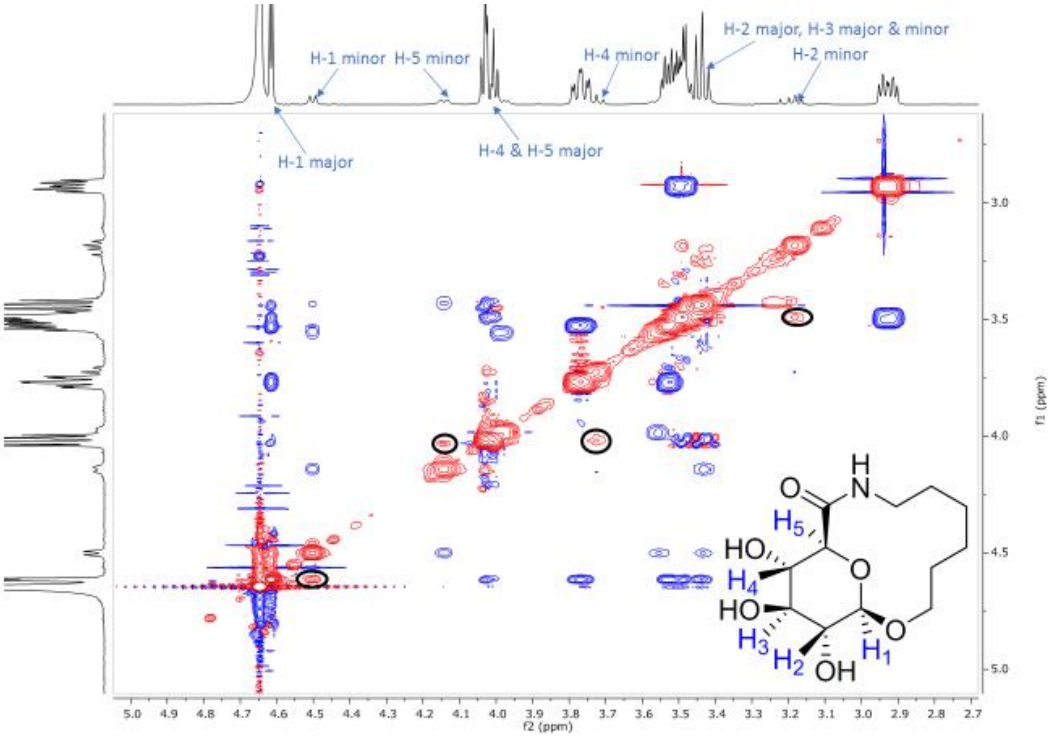


Figure 2.1 2D NOESY experiment of **44**

2.5.1 Rotamers with different ring conformations

In some cases, in particular for the β-glycosides of *O*-macrolactams, upon macrocycle formation a noticeable H-1 *J*-value change was observed. As shown in Table 2.2, upon ring closing metathesis of amide **41** to give **42**, the H-1 *J*-value decreases from 8.0→4.8 Hz, which can be due to a shift in the orientation of the anomeric proton from axial in **41**, to equatorial or pseudoequatorial in **42**. The presence of both the *trans* alkene and a *trans* – amide would add constraint to the 12-membered macrocycle **42**. In order to alleviate this strain it is possible the pyranose changes its conformation from $^4C_1$ to a twist boat, which would explain the change in *J* value. Other notably unusual *J*-values in **42** for a $^4C_1$ conformation included H-2 (5.1 Hz) and H-3 (5.4 Hz). The lowering in J values ($J_{1,2}$ and $J_{2,3}$) is suggestive of this. Subsequent removal of the acetyl- groups in **43** resulted in an increased H-1 J-value (6.0 Hz), which indicates that some distortion of the pyranose ring is still occurring after removal of the protecting groups. There was also presence of minor product in solution which had a larger H-1 J-value (7.8 Hz), identified by 2D NOESY experiments as a rotamer. It is possible that one of the rotamers adopts the $^4C_1$ chair conformation but the amide is in the less strained *cis* geometry in this case, contrasting with the other which prefers the twist boat conformation.

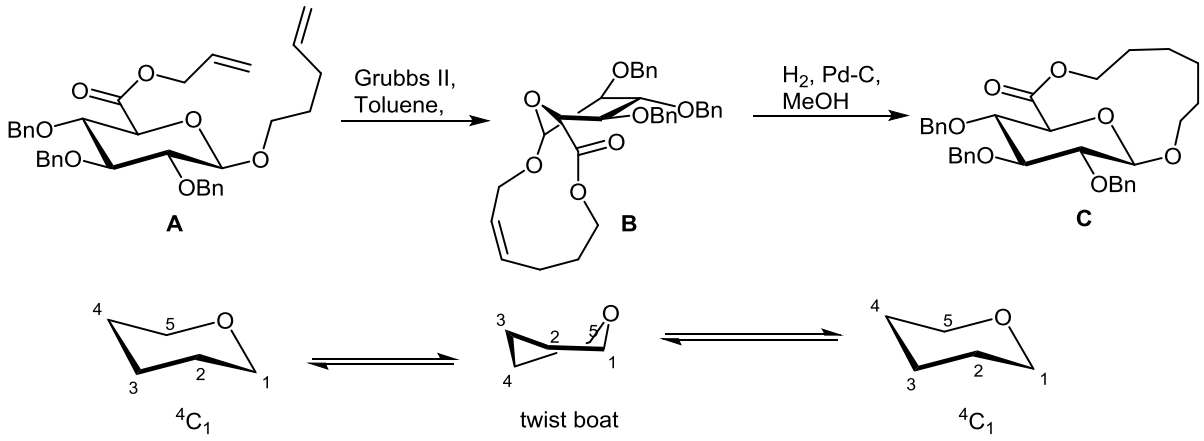
Reduction of the *trans* alkene, and the apparent removal of strain due to this feature afforded macrolactam **44** with a low $J_{1,2}$ value (3.5 Hz), indicating that the macrocyclic ring could still occupy a twist boat conformation. A minor product, identified as a rotamer by 2D NOESY experiments, was

also present with a higher H-1 J-value (7.9 Hz), thus indicating to adopt a chair conformation. Whether the presence of rotamers was indicative of amide bond isomerism in an attempt to alleviate strain formed by the macrocylic structure remained unknown.

Compound (ratio)	**H-1, H-1***	**H-2**	**H-3**	**H-4**	**H-5, H-5***
41	8.0	overlapping	overlapping	overlapping	9.8
42	4.8	5.1	9.0, 5.4	10.6, 9.0	10.6
43 (93:7)	6.0, 7.8	overlapping	overlapping	9.8, 8.3	9.7, 9.5
44 (13:87)	3.5, 7.9	overlapping	overlapping	overlapping	overlapping, 9.9

*Table 2.1 J values for carbohydrate ring of **41-44***

Previous work by Yan[44], has evidenced formation of a twist-boat type structure in the 12-membered macrolactone with a β−glycoside shown below (Scheme 2.9) upon analysis of ^{1}H NMR *J* values (Table 2.3). In this case, lactone functionality eliminated the amide isomerism variable. This example demonstrates distortion of the sugar ring to lead to removal of strain imposed in the system upon macrocycle formation.



Scheme 2.9 Formation of twist-boat type conformation upon ring closing metathesis by Yan

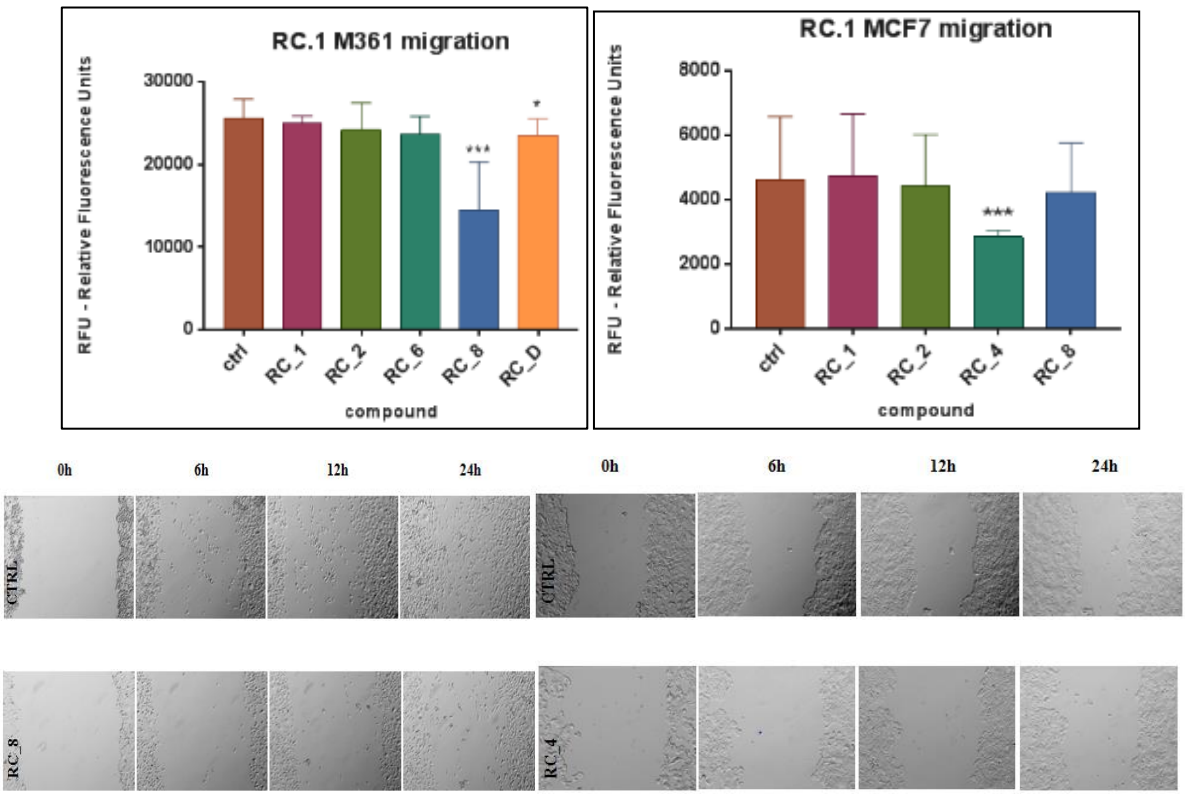
	H-1	H-2	H-3	H-4	H-5
A	7.5	9.0, 8.0	9.0	9.0	overlapping
B	4.0	10.0, 4.0	10.0, 9.0	9.0, 3.5	3.5
C	7.5	8.5	9.0	overlapping	overlapping

*Table 2.2 J values for carbohydrate ring of **A-C***

2.6 Biological evaluation

Biological testing of the macrocycles synthesised were carried on various cell lines in the research group of Professor Magdalena Krol at Warsaw University of Life Sciences, Poland. Cell viability tests were first performed to evaluate the toxicity of the macrolactams on cell lines; MDA-MB-231, MDA-MB-361, MCF-7 and MIAPaCa-2. This XTT assay was undertaken, utilising reduction of 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-*2H*-tetrazolium-5-carboxanilide salt by functioning cell mitochondrion. A subsequent Boyden chamber assay, a strategy often utilised to study tumour cell

migration, was then performed and results compared against known active macrolactone **10** (Chapter 1), a recognised inhibitor of tumour cell migration. These results in combination with XTT tests demonstrated the migration of the cancer cells was hindered in the presence of macrocycles with encouraging bioactivities observed from the treatment of MDA-MB-361 and MCF-7 with macrocycles **63** (RC_8) and **62** (RC_4), respectively.



2.7 Conclusions

In this chapter, a series of novel macrolactams were prepared for biological evaluation. While efforts to obtain the α-macrolactam from the corresponding β-macrolactam *via*. Lewis-acid induced anomerisation were unsuccessful, it was found that a larger 14-ring system could undergo the transformation. Determination of reaction rates identified slower transformation of macrocycle **65** to the corresponding α-anomer in comparison to contending ester **64**. NOESY experiments detected rotamers were present in solution, some indicated by ^{1}H *J* values to occupy a non-chair conformation. Biological evaluations were subsequently performed on the macrocycles, identifying **62** and **63** as inhibitors of tumour cell migration in cell lines MBA-MB-361 and MCF-7. The mechanism of action of these macrocycles has yet to be investigated.

Chapter 3 Introduction to iminosugars, allylic azides and Huisgen cycloaddition

3.1 Overview of Iminosugars

As previously discussed in Chapter 1, natural products have been proven to be a valuable source of bioactive compounds. Iminosugars are a class of natural products, which have received a lot of attention in relation to their biological activities and therapeutic potential. These polyhydroxylated alkaloids are mimics of sugars in that the endocyclic oxygen atom (embedded in the ring of the carbohydrate) has been substituted with a nitrogen atom. This alteration has led to identification of agents with potent bioactivity.[79]

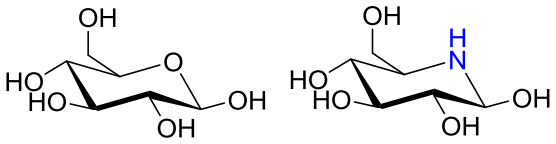


Figure 3.1 Glucose and its natural iminosugar analogue, Nojirimycin

These carbohydrate analogues were traditionally categorised under 5 structurally diverse classes; piperidines, pyrrolidines, pyrrolidizines, indolizidines and nortropanes. However, in recent years, progression in this field has resulted in extension of the initial categories to other structural motifs such as; azepanes, conidines and quinolizidines.

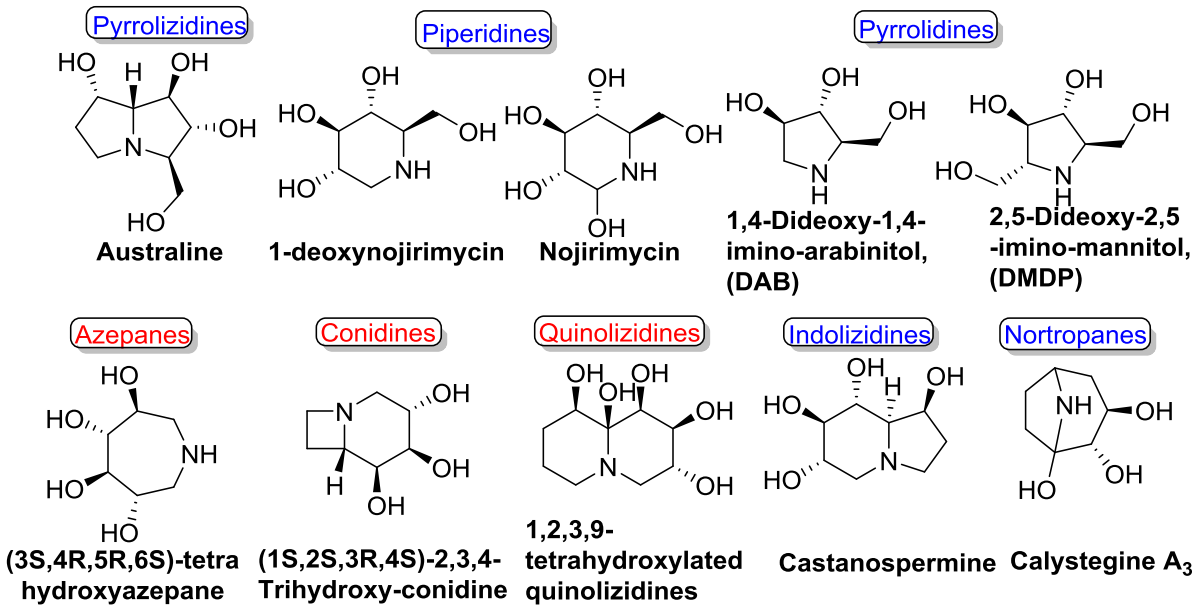


Figure 3.2 Naturally-occurring and synthetically-derived iminosugars

Iminosugars emerged within the scientific community in the 1960s when the first syntheses and isolation of these natural sugar mimics were reported by Paulsen[80,81], Jones[82,83] and Inouye[84], and these compounds were shown to be potent glycosidase inhibitors.[85]

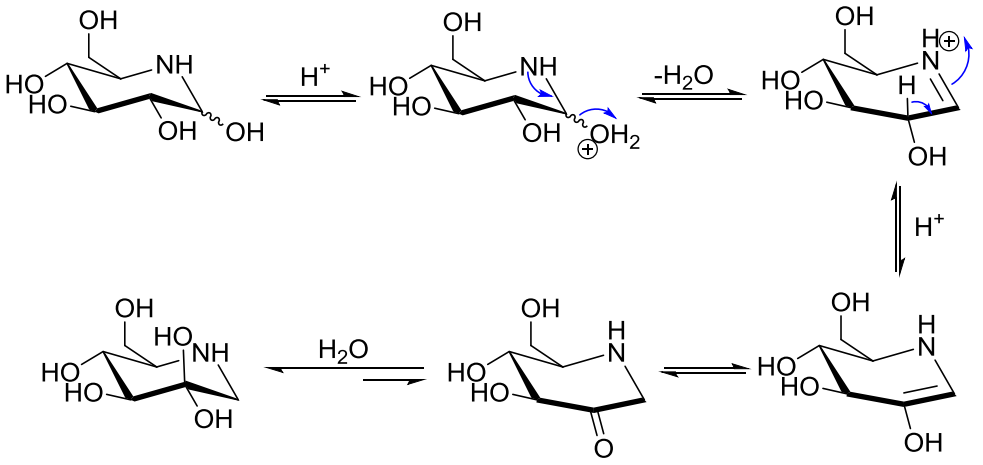


Figure 3.3 Amadori rearrangement of Nojirimycin

While biological activity of the carbohydrate analogues were promising, the Amadori rearrangement of the hemiaminal functionality decreases their stability, thus hindering their therapeutic applications.[86] This problem can be overcome by storage of the iminosugars with a hemiaminal function as their bisulfite adducts.[87] Alternative options include preparation of iminosugars lacking the hemiaminal function, such as deoxy-iminosugars (e.g. 1-deoxynojirimycin) and *C*-glycosyl iminosugars (e.g. β-homonojirimycin).

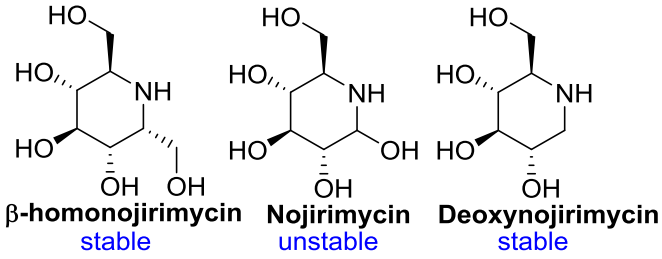


Figure 3.4 Naturally-occurring iminosugar analogues with glucose configuration

3.2 Natural occurring *C*-glycosyl Iminosugars

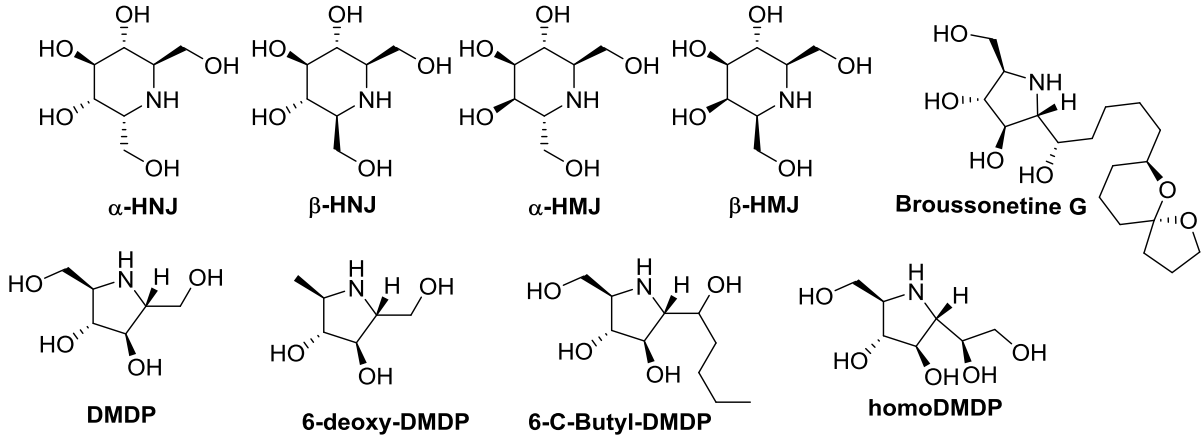


Figure 3.5 Selected examples of naturally occurring C-glycosyl iminosugars

Over the years, an extensive library of iminosugars from different categories has been isolated. Due to the topic of this thesis a brief overview of polyhydroxylated *C*-glycosyl piperidines, α,α-disubstituted piperidines and *C*-glycosyl pyrrolidines is provided below.

3.2.1 *C*-Glycosyl piperidine type iminosugars & their α,α-disubstituted counterparts

α-Homonojirimycin (α-HNJ), an inhibitor of both α- and β-glycosidases became the first *C*-glycosyl iminosugar to be isolated from *Omphalea diandra* in 1988.[88,89] Almost a decade later, β-homonojirimycin (β-HNJ,), α-homannojirimycin (α-HMJ, α-mannosidase inhibitor) and β-homonojirimycin (β-HMJ, β-mannosidase inhibitor) were isolated from *Aglaonema treubii*[90] and *Hyacinthus orientalis*[91]. As shown by β-HMJ and α-HMJ, when the iminosugar displays the same configuration as the target glycosidase it can be beneficial, however, iminosugars do not always require identical configuration to that of the glycosidase enzyme for successful inhibitory activity. Fleet and co-workers[92] have reported an example of the latter in relation to the bioactivity of β-HMJ, which they found to be a potent α-L-fucosidase inhibitor.[92]

While piperidine iminosugars with a quaternary centre α to the anomeric carbon have not yet been isolated, synthetic strategies to such structural motifs has been driven by attempts to fine-tune glycosidase inhibition specificity. In the past decade, the synthesis of such derivatives has been prepared by Dhavale[93] and Acena[94] (Figure 3.19).

3.2.2 *C*-Glycosyl pyrrolidine type iminosugars

In the 1970s, 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) became first C-glycosyl pyrrolidine to be isolated, from the leaves of *Derris elliptica*.[95] This polyhydroxylated pyrrolidine was found to be a potent inhibitor of both yeast and mammalian α- glucosidases.[96] In the same decade, isolation of the 6-deoxy analogue of DMDP (6-deoxy-DMDP) from *Angylocalyx pynaertii* was reported and was shown to be a β-mannosidase inhibitor.[97] Almost 25 years later, 2,5-dideoxy-2,5-imino-glycero-D-manno-heptitol (homo-DMDP) became the first naturally occurring alkyl-DMDP to be isolated[98]. This particular *C*-glycosyl pyrrolidine had been previously synthesised by Wong and co-workers[99]. Other, naturally occurring *C*-glycosyl pyrrolidines known for their efficiency as glycosidase inhibitors include broussonetine G[100–102] and 6-C-butyl-DMDP[103].

3.3 Biological activity and therapeutic applications

Many glycosidase enzymes are involved in an extensive number of crucial biological pathways. As such, interest has grown in the application of small-molecule sugar mimics, such as iminosugars, for therapeutic purposes. Replacement of the O-atom of the carbohydrate with a N-atom prevents enzymes from processing the sugar mimics.[104] However, these carbohydrate analogues can still interact with the active site, thus hindering enzymatic transformations of normal sugars. Some of the processing enzymes inhibited by iminosugars include: glycosidases[105,106], glycosyl transferases[107], glycogen phosphorylase[108,109], nucleoside-processing-enzymes[110], and metalloproteinases[111]. These selected

examples demonstrate the extensive potential applications of iminosugars in the inhibition of a wide variety of glycoprocesses.

It is the inhibition of these biological pathways which provide merit for the development of iminosugars to treat a variety of illnesses including; non-insulin dependent (type II) diabetes, viral diseases (e.g. hepatitis B, HIV), lysosomal disorders (e.g. Gaucher disease) and rare disorders (cystic fibrosis).[105]

3.3.1 Glycosidase Inhibition

Iminosugars are predominantly known for their glycosidase inhibition activities.[105,112] Glycosidases can be described as enzymes capable of hydrolysing glycosidic linkages. Cleavage of the glycosidic bond glycosidases can occur *via*. different mechanisms categorised under retaining and inverting glycosidases.

3.3.1.1 Retaining Glycosidase

Over half a century ago, the first mechanism for retaining glycosidases was proposed.[113] The mechanism involves a double displacement performed *via*. glycosylation and subsequent deglycosylation. The first step involves formation of covalent enzyme-glycosyl intermediate from the concerted action of two carboxylate moieties *via*. an oxo-carbenium type transition state (Figure 3.6).The aglycon then diffuses out of the active site of the enzyme allowing a water molecule to attack the enzyme-glycosyl intermediate under base catalysis by the carboxylate residue.[114–116]

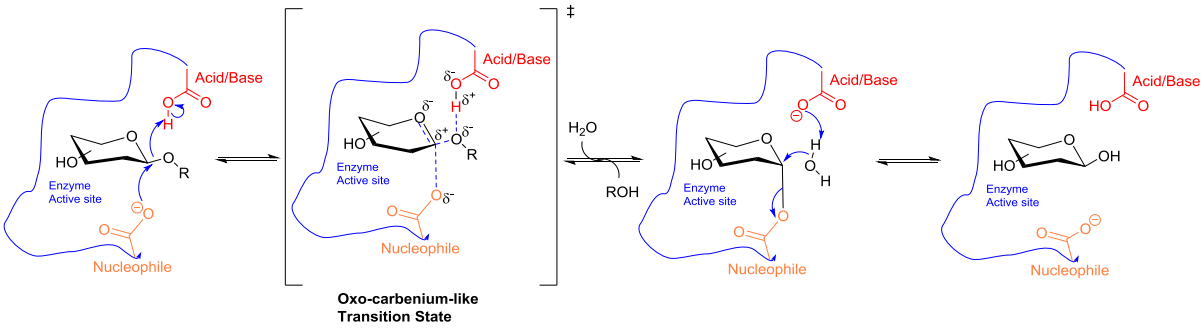


Figure 3.6 Mechanism of retaining glycosidase *via*. oxo-carbenium type transition state[112]

3.3.1.2 Inverting Glycosidase

The mechanism for inverting glycosidases involves formation of opposing stereochemistry to that of the initial carbohydrate at the carbon α to the endocyclic oxygen (Figure 3.7). This process takes place *via*. a single-displacement mechanism. The inverting glycosidases have a larger active site in comparison to retaining glycosidases.[117] Thus, the water molecule can join the carbohydrate in the active site of the enzyme from the beginning of the transformation. This active site possesses both carboxylate and carboxylic acid functionality enabling the water molecule to react with the carbohydrate under base catalysis of the carboxylate moiety. This transformation occurs in a concerted fashion through an oxo-carbenium type transition state, yielding the hemiacetal with opposing stereochemistry to that of the precursor carbohydrate.

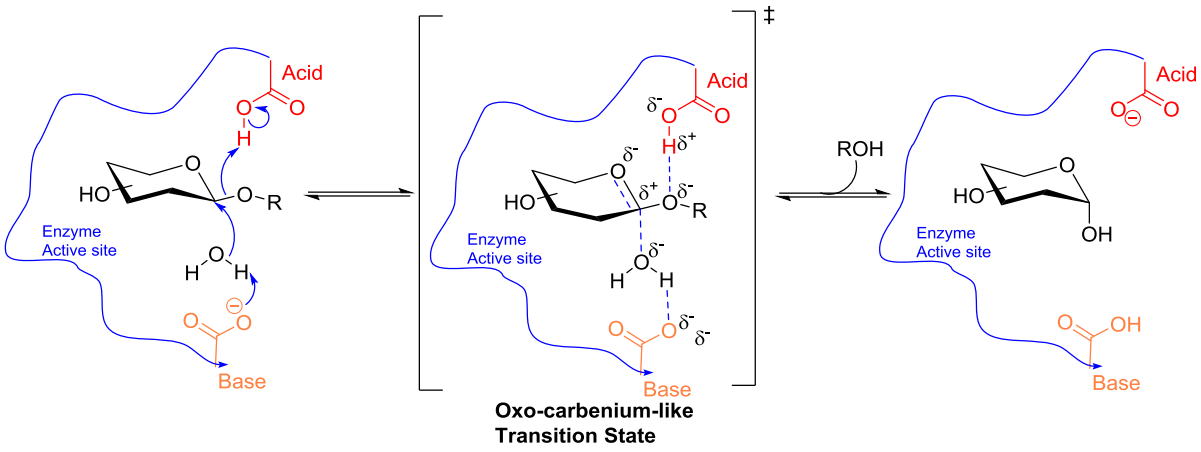


Figure 3.7 Mechanism of inverting glycosidase *via*. oxo-carbenium type transition state[112]

3.3.1.3 Iminosugars as Glycosidase Inhibitors

Fleet and co-workers[118] have introduced an extensive number of iminosugar-inhibiting glycosidases. The effectiveness of the sugar mimics has been credited to the structural and electronic mimicry of the carbohydrate cationic transition state.[119] At physiological pH, iminosugars exist as a protonated species (Figure 3.8). This allows the iminosugar to compete with carbohydrate substrates for the active site of glycosidases, thus hindering hydrolysis of the carbohydrate.[119]

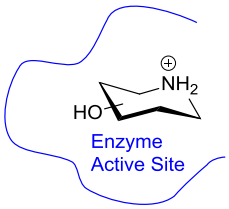


Figure 3.8 Enzyme-inhibitor complex

3.3.2 Cancer

As previously discussed in Chapter 1, the treatment of cancer is constantly met with new obstacles due to the development of resistance. There are multiple processes involved in cancer development, previously coined as the "hallmarks of cancer"[120] (Figure 3.9). Glycosylation has been accepted to play a significant role in some of these processes.[121] Thus, glycosidase and glycosyl transferase inhibitors (e.g. iminosugars) could provide a suitable route of treating this illness. Progression in the research of cancer treatments via. alteration of cell glycosylation has predominantly focused on the inhibition of mannosidases and glucosidases associated with glycoconjugate formation.[122] Inhibitors of glucosidases (e.g. 1-DNJ and castanospermine) and inhibitors of mannosidases (swainosine and DMDP) were investigated and reported to supress both, tumour progression and metastasis.[123–127] The indolizidine swainosine, became the first iminosugar to undergo clinical evaluation as a glycosylation suppressor in cancer treatment and reached Phase II clinical trials. However, subsequent progression was not approved due to lack of bioactivity even though previous reports had shown promise.[128]

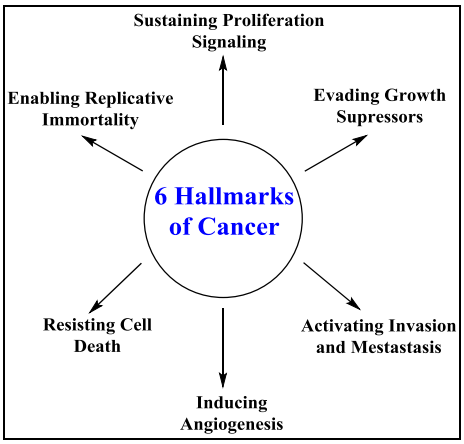


Figure 3.9 6 Hallmarks of cancer

Siastatin B[123] was also reported as a glycosidase inhibitor with anti-cancer activity. Based on these reports, Nishimura and co-workers[129] prepared a new family of *gem*-diamine 1-*N* iminosugars, with similar functionality to Siastatin B in an attempt to access new anti-cancer agents through the inhibition of glycosidases. A couple of the compounds prepared have been identified as heparanase inhibitors[130], which play an important role in tumour invasion, metastasis and angiogenesis.[131]

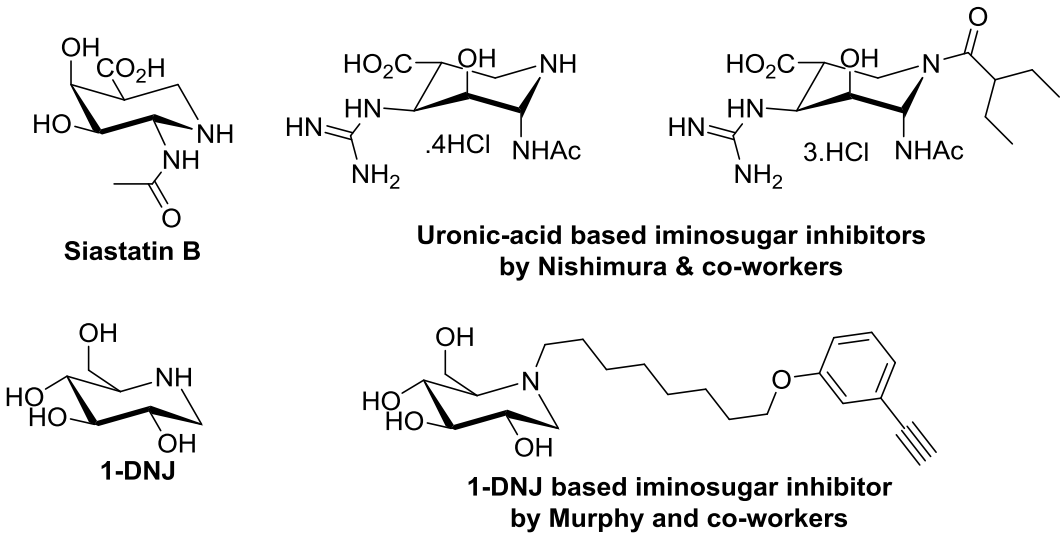


Figure 3.10 Polyhydroxylated piperidines with anti-cancer activity based on different natural product iminosugar frameworks

Inhibition of angiogenesis has been recognised as a potential cancer treatment due to the requirement of sufficient blood vessel network for tumour growth and metastasis. Frameworks known to inhibit angiogenesis include 1-DNJ[132] (inhibits biosynthesis of cell surface oligosaccharides required for angiogenesis) and aryl-1,2,3-triazoles[133] (hinders angiogenesis target enzyme, methionine aminopeptidase II[134]). Murphy and co-workers have used this basis to prepare bifunctional frameworks and in the process, have identified an inhibitor of angiogenesis which is more active than either

functionality alone (Figure 3.10).[135,136] This particular compound, *N*-(8-(3-ethynylphenoxy)octyl-1-deoxynojirimycin, was also found to supress cell migration and induce apoptosis (cell death) in a lung cancer cell line.[137] While iminosugars have yet to be marketed as anti-cancer therapeutics, efforts continue in this field as metabolic reprogramming continuously proves to play a key role in cancer development.[138]

3.3.3 HIV and peptidomimetics

The human immune deficiency virus (HIV), like many viruses, has a lipid envelope which is embedded with glycoproteins including; transmembrane glycoprotein gp41 and extracellular glycoprotein gp120. These protein receptors are involved in the HIV infection process. However, for infection to occur a CD4 receptor and relevant co-receptor are required on the surface of the host cell. In the case that both receptor and co-receptor co-exist in proximity on the host cell surface, gp120 of the virus can interact with CD4 receptors of the host cell. Subsequent binding to gp41 results in a conformational alteration of gp120 enabling fusion of the virus with the host cell. The proximity of gp41 and gp120 on the envelope surface makes them susceptible to interaction with molecules (including glycosidase inhibitors such as iminosugars) which can disrupt the viral-cell complex. Compounds with these properties have promise as anti-HIV agents.[139]

Other approaches to treat HIV include the targeting of HIV protease within the infected cell. The HIV protease enzyme is responsible for formation of infectious viral proteins, thus inhibiting this enzyme prevents further spread of the viral infection. While this approach can limit further infection of normal cells, the mutation rate of the protease as it replicates results in high-levels of enzyme resistance to inhibitors. As such, a need for new inhibitors which can supress the protease enzyme are in constant demand.[140]

Some α-glucosidase inhibitors such as, castanospermine, dihydroxypyrrolidine and 1-DNJ were first identified as HIV inhibitors in the 1980s.[141–143] Interestingly, α-mannosidases such as α-DMJ had no anti-viral activity.[141] In particular, castanospermine and 1-DNJ iminosugars, have been shown to hinder the infectious performance of HIV in-vitro without damaging lymphocytes.[143,144]

1n 1998, Fleet and co-workers tested a wide range of iminosugars against HIV and identified *N*-butyl 1-deoxynojirimycin (NB-DNJ) as an inhibitor of both replication and reinfection of the virus.[145] Further investigations of NB-DNJ were undertaken with the mechanism of action of high interest. As an example, one study proposed NB-DNJ had an effect on gp120 thus preventing the receptor from undergoing conformational changes post-CD4 binding.[146] This compound underwent clinical trials and progressed as far as phase II. However, side-effects such as weight-loss, diarrhoea and abdominal pain were observed in human clinical trials thus the potential drug candidate was not taken any further.[147] Efforts were subsequently undertaken to find a derivative of NB-DNJ with similar anti-viral activity but without undesired side effects. As such, perbutylated-*N*-butyl-1-DNJ was developed (Figure 3.11).

This drug candidate was shown to release the active drug NB-DNJ post-intestinal absorption thus preventing gastrointestinal side effects.[148]

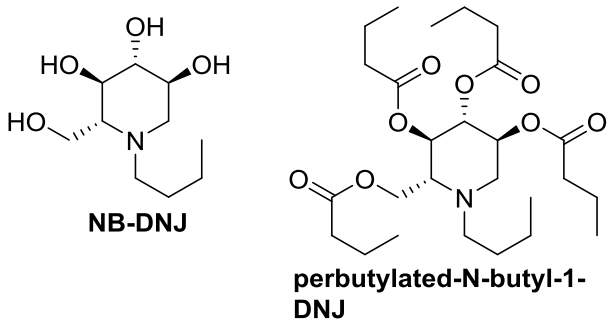


Figure 3.11 DNJ-based iminosugar inhibitors of HIV

Other approaches to synthesise anti-HIV agents include peptidomimetics. The main principle behind this synthetic tool revolves around the anchoring of pharmacophoric groups to non-peptide ligands as a means of guiding the peptide-mimic to the required binding site.[149] Peptidomimetics have an advantage over traditional non-peptide scaffolds due to their enhanced pharmacokinetic properties. Previous work within the Murphy group in this field has involved grafting peptide chains onto known glycosidase inhibitors, such as DMJ and DNJ.[150,151] Subsequently, Chery and Murphy[152] designed and prepared a DMJ derivative as a potential HIV protease inhibitor (Figure 3.12).

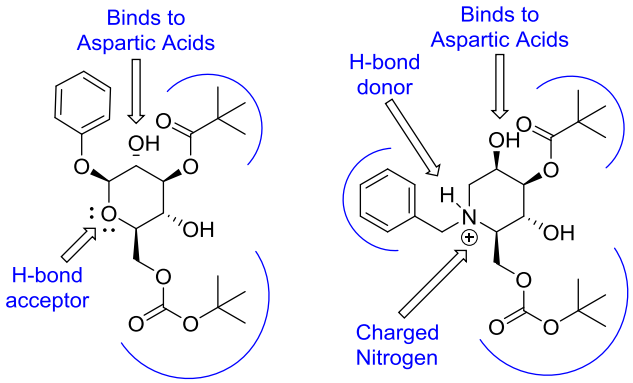


Figure 3.12 Design of peptidomimetics by Chery and Murphy. Reprinted with permission from reference **152**. Copyright (2004) Elsevier

The use of iminosugars for peptidomimetic design over contending carbohydrate molecules is perceived as advantageous, as a consequence of (i) the cationic character of the nitrogen atom at physiological pH[153], (ii) the H-bond donor characteristic of the endocyclic nitrogen and (iii) the ability to anchor covalently linked pharmacophoric side-chains to the nitrogen atom. In the specific case of HIV, Murphy and co-workers computationally predicted H-bonding existed between a carbonyl group of the HIV-protease amide backbone and the protonated nitrogen of the iminosugar ligand.[154,155] Pyrrolidines decorated with sidechains have also been proved useful in the targeting of HIV-protease (Figure 3.13).[156]

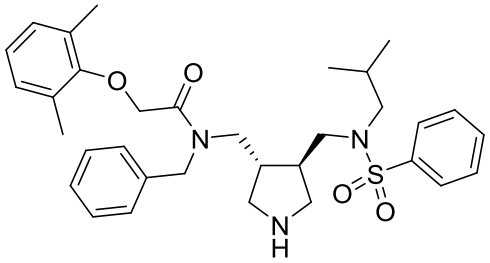


Figure 3.13 Computationally-designed pyrrolidine-based peptidomimetic

3.3.4 Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) on chromosome 7 which encodes CFTR protein. This protein is vital for the transportation of sodium and chloride in and out of various organs of the body including; lungs, pancreas and skin. Numerous mutations can occur on the CFTR gene leading to different mechanisms of action for the hindered expression and function of CFTR. While there are ~1,900 mutations of the CFTR gene worldwide the most common mutation (F508 deletion, present in approx. 70 % of all cystic fibrosis cases) suppresses transport of the CFTR protein to the cell surface causing degradation of the CFTR protein in the endoplasmic reticulum (ER). In this particular mutation, the CFTR sparse cell surface hinders the rate at which chloride can be transported out of cells.

While there is no cure for cystic fibrosis at present, medications based on small molecules have been developed to control symptoms associated with the disorder. More recently, efforts have turned towards stem cells as a means of gene therapy[157]. However, due to the cost associated with such therapies, efforts to prolong life expectancy and quality using small molecules continues to be of paramount importance.

Piperidine NB-DNJ was identified as a potential treatment for cystic fibrosis. The alkyl-DNJ iminosugar underwent clinical trials, however treatment of symptoms of CF with NB-DNJ proved neglible[158], even-though previous studies had outlined effective treatment of F508del-CFTR trafficking using low concentrations of the drug-candidate on a daily basis.[159] Pyrrolidine-based iminosugars have also shown promise in the treatment of cystic fibrosis. Interestingly, 1,4-dideoxy-2-hydroxymethyl-1,4-imino-L-threitol (isoLAB) has previously been shown by Fleet[160] to rescue the CFTR function in a similar fashion to NB-DNJ. IsoLAB does not exhibit glycosidase inhibition properties demonstrating iminosugars can act as ligands to target proteins independent of glycosylation.[160]

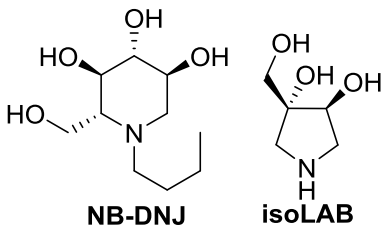


Figure 3.14 Iminosugar inhibitors of F508 deletion CFTR trafficking

3.3.5 Iminosugars - current drugs

To summarise, this section explored some of the applications for iminosugars isolated and prepared since the 1980s. While numerous biologically active compounds have been discovered only a small number have been approved for therapeutic use (Figure 3.15).

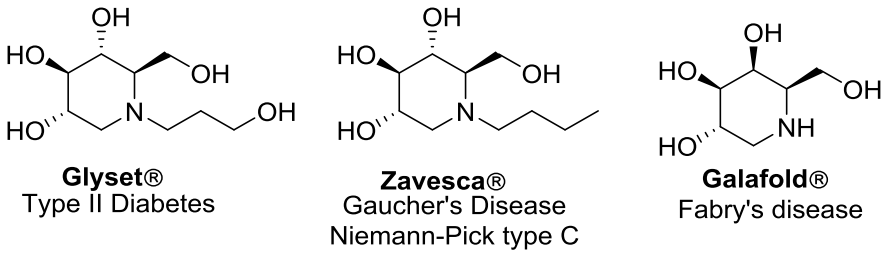


Figure 3.15 Some iminosugars currently on the market

Currently, there are some potential drug candidates in the pipeline (Figure 3.16). However, it seems this particular class of molecules are limited due to their lack of specificity for glycosidases leading to side effects or inactivity in clinical trials. Thus, manipulation of these highly bioactive structures as a means of increasing specificity has become an important component of further research within this area. Alternative approaches could involve further exploration of *C*-glycosyl piperidines (Chapter 4), pyrrolidines (Chapter 5) and extension to access the relatively unexplored quaternary-centred iminosugars (Chapter 6).

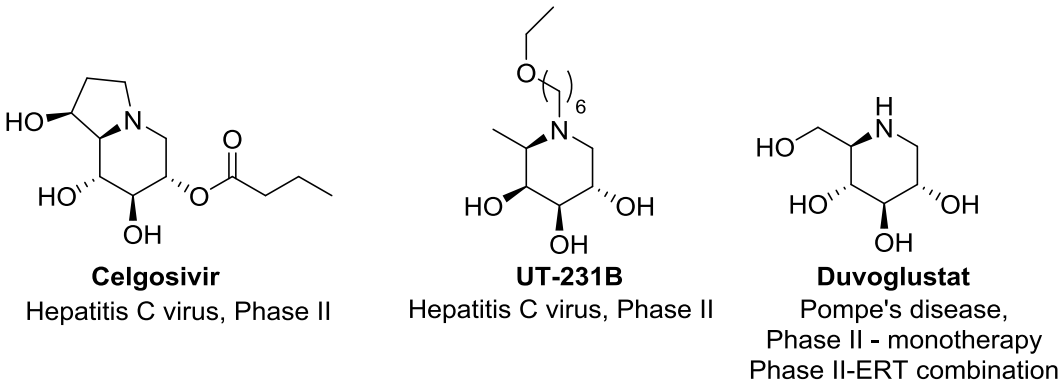


Figure 3.16 Some iminosugars in clinical trials

3.4 Synthetic strategies of *C*-glycosyl iminosugars

When considering synthetic routes to 5-ring and 6-ring iminosugars, numerous challenges arise including; (i) efficient ring formation, (ii) generation of ≥ 4 chiral centres with a high level of stereo control and (iii) protecting group considerations. Currently, two main synthetic approaches have been developed; (i) intramolecular cycloadditions and (ii) *C*-glycosylation of iminosugars with the iminosugar as an electrophilic donor. The approach chosen can be determined by the disconnections performed during the retrosynthesis. The disconnections, C5/C4-N and/or C1-N, are required for intramolecular cyclisation. The C1-CH_2R disconnection is required for the less explored intermolecular

C-glycosylation. Martin and co-workers[161] performed an extensive review on iminosugars in 2009 outlining the various synthetic approaches.

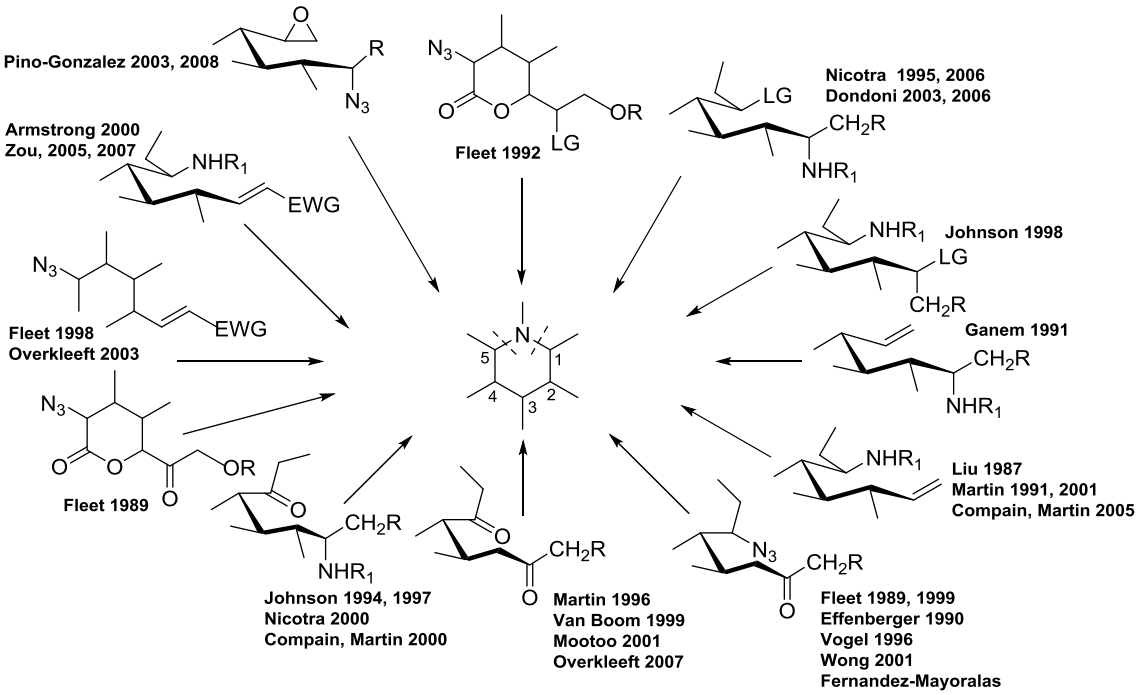


Figure 3.17 Some of the intramolecular cycloaddition performed to synthesise piperidines. Reprinted with permission from reference **161**. Copyright (2009) Elsevier

Preparation of these nitrogen-containing frameworks using the intramolecular cycloaddition involve careful determination of suitable starting materials. Such syntheses can involve preparation of the iminosugars from a chiral starting material with the required stereochemistry already in position. In the case of iminosugars, the comparable carbohydrates are an ideal choice due to the availability of these building blocks with various stereo-configurations embedded in the ring framework.

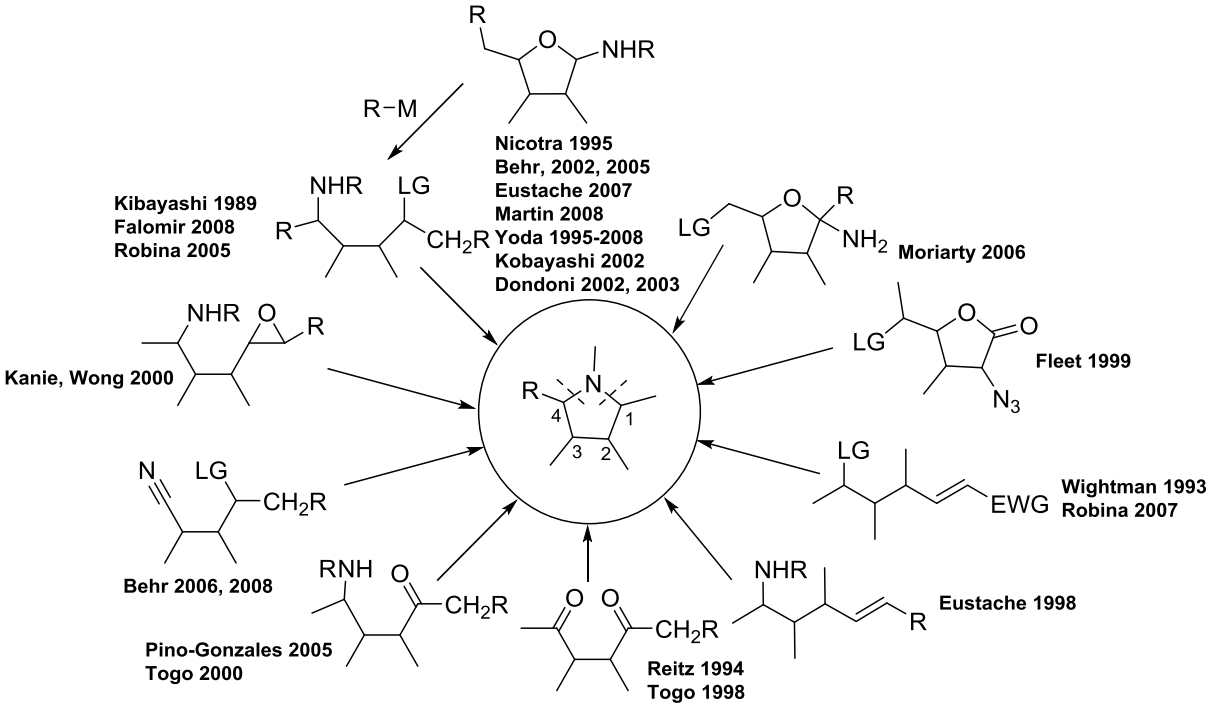


Figure 3.18 Some of the intramolecular cycloadditions performed to synthesise pyrrolidines. Reprinted with permission from reference **161**. Copyright (2009) Elsevier

Similar problems as outlined above are observed in the preparation of α-quaternary centered 6-ring iminosugars. These piperidine structural motifs have been prepared through intramolecular cycloadditions[93] and carbon trifluoride rearrangements[94].

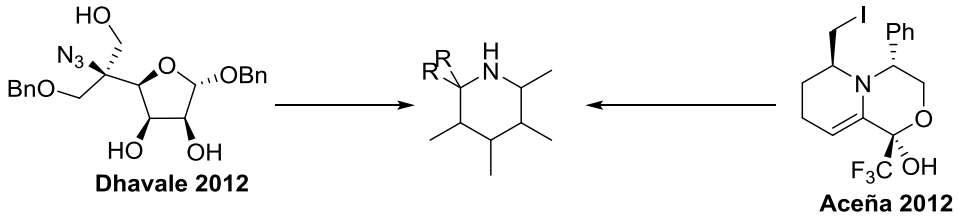


Figure 3.19 Access to α-quaternary-centered iminosugars

3.5 1,3-Dipolar Cycloaddition

3.5.1 Overview

The 1,3-dipolar cycloaddition, more commonly known as the Huisgen cycloaddition, involves cyclisation of a dipolaraphile (such as alkenes or alkynes) with a 1,3-dipole to generate five-ring heterocycles.

In 1938, Smith and co-workers were the first to recognise the 1,3-dipolar cycloaddition.[162] However, it was not until the 1950s, that Huisgen and co-workers solidified and utilised this concept of cyclisation upon mechanistic investigations of diazolkanes with angulary strained double bonds.[163] Since then, use of this transformation has been exploited as an ideal synthetic strategy within the chemistry community. In 2002, Sharpless[164] and Meldal[165] independently performed intermolecular regioselective formation

of 1,4-triazoles *via*. copper catalysis of alkynes and azides in the Huisgen cycloaddition. In 2008, Fokin and co-workers reported a ruthenium variant providing access to 1,2,3-triazoles in a regioselective manner.[166] These catalysts have enabled performance of the 1,3-Huisgen cyclisation with high yields under benign conditions, thus providing evidence for the suitability of this cycloaddition in click chemistry.[167]

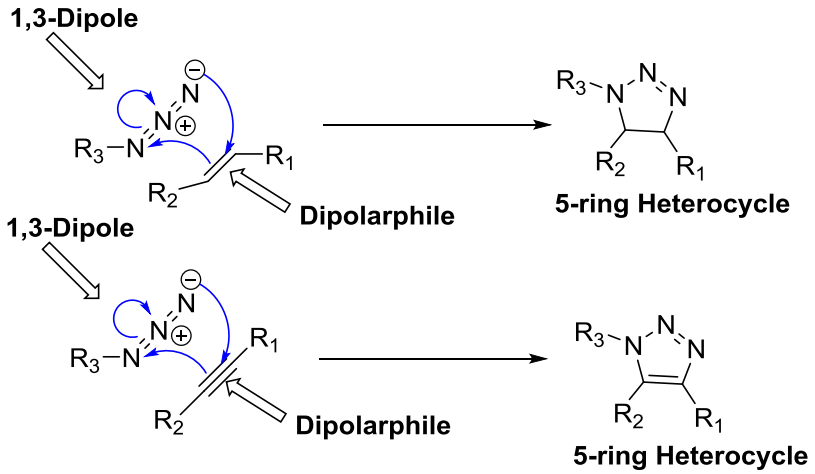


Figure 3.20 Intramolecular cycloaddition of 1,3-dipole with a dipolarphile to afford 5-ring heterocycle

A 1,3-dipole can be described as a zwitterionic system sharing 4 π electrons across 3 atoms, carbon, oxygen and hydrogen. The dipoles can be divided into 2 categories; propargyl-allenyl dipoles (e.g. ozone) and allyl dipoles (e.g. azides).

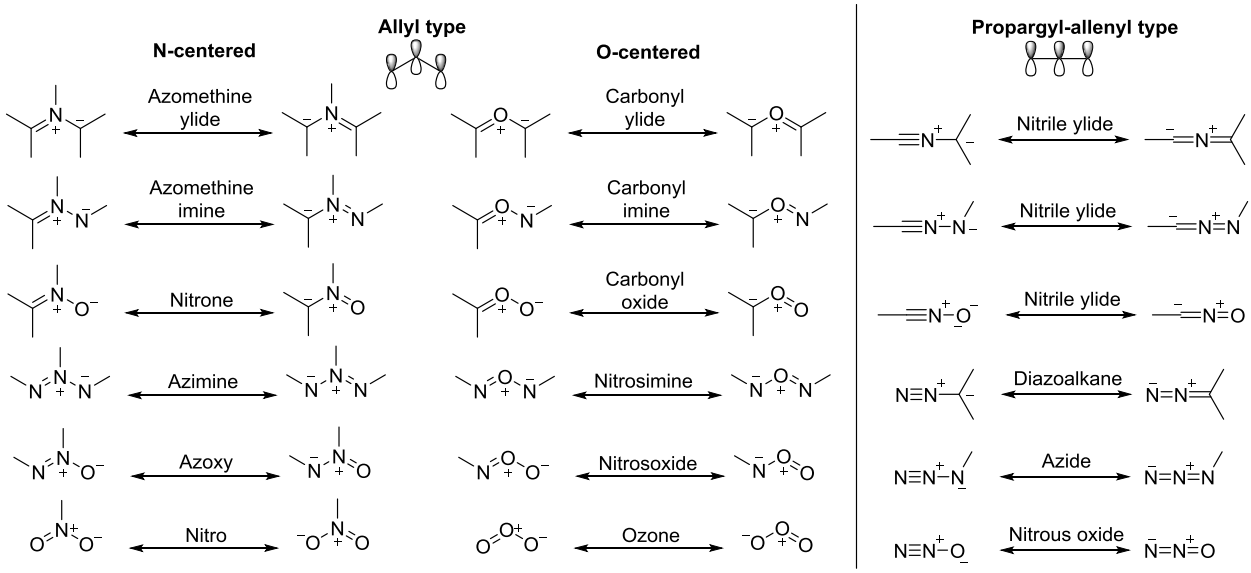


Figure 3.21 Examples of allyl and propargyl-allenyl dipolarphiles

Some of the chemical diversity exhibited by azides, including their 1,3-dipolar functionality and regioselective reactivity with electrophiles and nucleophiles, can be explained by examining their resonance structures[168] (Figure 3.22). Due to high energy and flexible functionality, azides have

become key players in synthetic chemistry and have been used in some pivotal transformations such as, Schmidt rearrangement[169], Staudinger rearrangement[170], Curtius rearrangement[170] and in particular, the 1,3-Huisgen Cycloaddition.

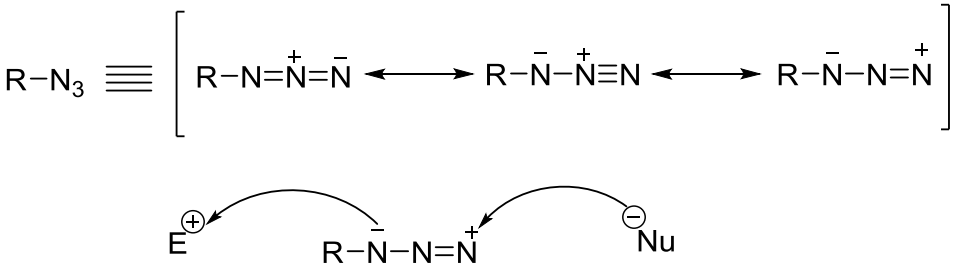
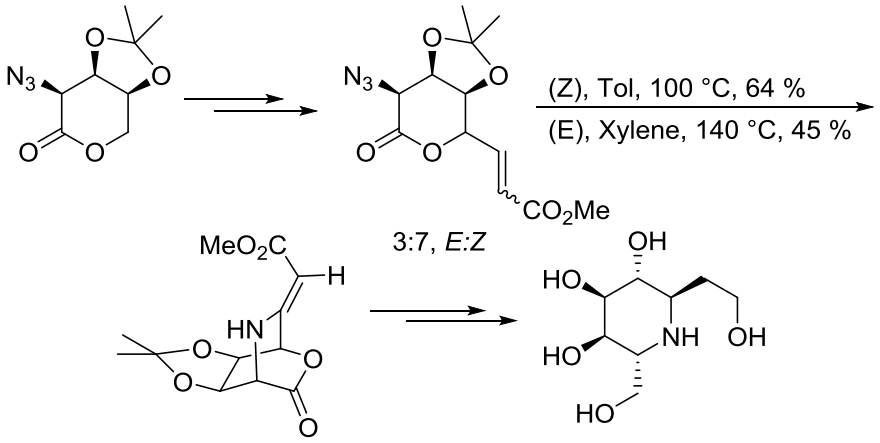


Figure 3.22 Mesomeric structures and reactivities of azides with electrophiles and nucleophiles

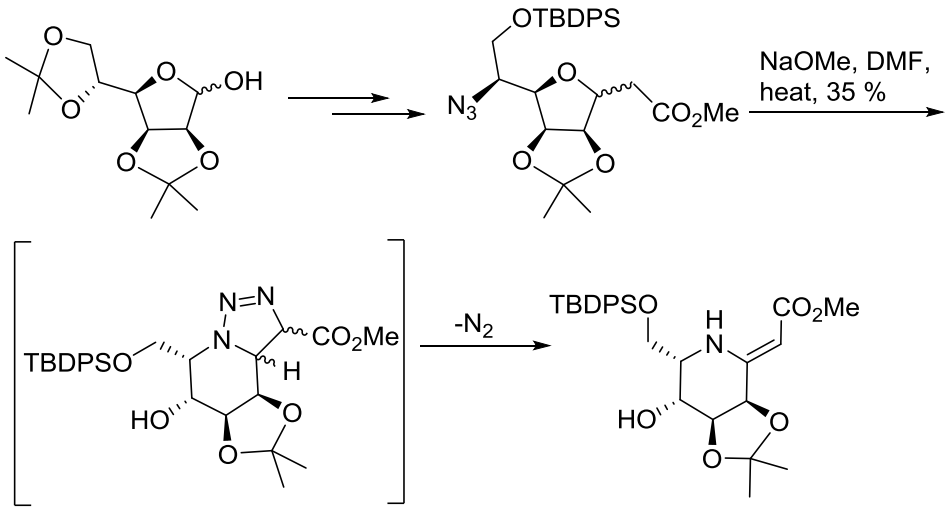
3.5.2 Intramolecular 1,3-Dipolar cycloaddition to access *C*-glycosyl iminosugars

Fleet and co-workers became the first to exploit the 1,3-dipolar cycloaddition in the synthesise of *C*-glycosyl piperidine iminosugars in 1998.[171] In this approach the α-HMJ analogue was prepared upon cyclisation of the azidoester and subsequent reductions of the resulting bicyclic vinylogous urethane.[171]



Scheme 3.1 Preparation of α-HMJ analogue using Huisgen cycloaddition by Fleet and co-workers

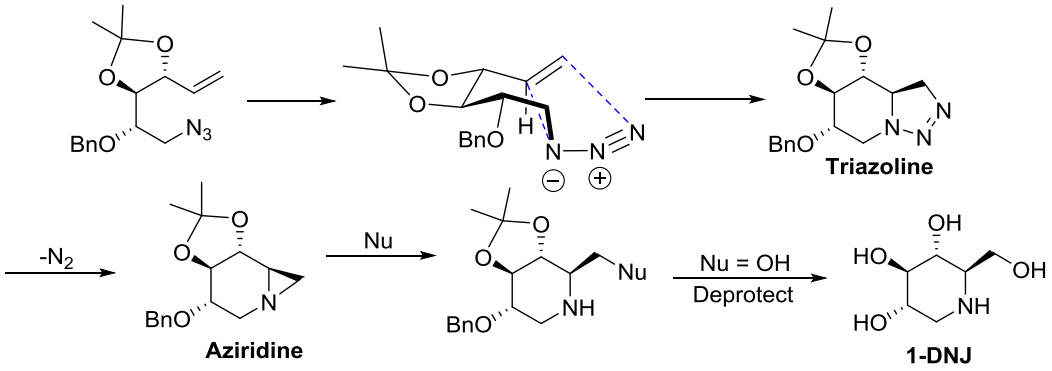
Further to this, Overkleeft and co-workers[172] reported the preparation of related piperidines using a tandem retro-Michael-[2+3]-cycloaddition (Scheme 3.2).



Scheme 3.2 Preparation of piperidine derivatives by Overkleeft and co-workers

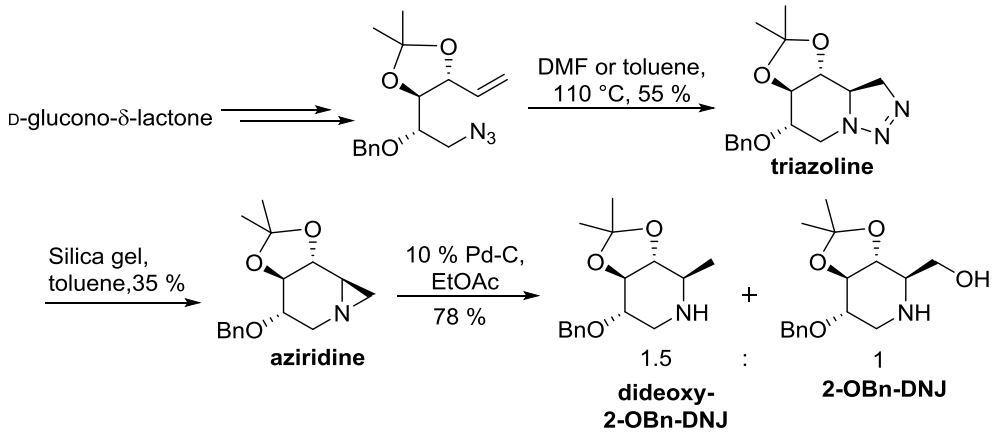
3.5.3 Previous research in the Murphy group using the 1,3-dipolar cycloaddition to prepare 1-DNJ

In 2007, Zhou and Murphy[173] reported the synthesis of 1-DNJ using the 1,3-Huisgen cycloaddition between alkenes and azides. This reaction involved the thermal promotion of an azide with an alkene in the presence of a restraint to form a triazoline intermediate which was subsequently decomposed in a productive manner *via*. an aziridine intermediate to form the iminosugar, 1-DNJ (Scheme 3.3).



Scheme 3.3 Preparation of 1-DNJ using Huisgen cycloaddition. Reprinted with permission from reference **173**. Copyright (2008) American Chemical Society

The azide precursor required for this transformation was synthesised starting from D-glucono-δ-lactone. As shown in Scheme 3.4, the cycloaddition occurred upon heating the azide, with yields of 55 % achieved for the triazoline intermediate after chromatographic purification, although full conversion of azide had been observed using TLC. The triazoline decomposed in the presence of silica gel to afford the aziridine intermediate suggesting the acidic gel can cause expulsion of nitrogen. This suggests the low yielding 1,2,3-triazoline in the previous step could have been due to decomposition of the triazoline during purification. Treatment of an isolated fraction of aziridine with 10% Pd-C afforded an inseparable mixture of piperidines, dideoxy-2-OBn-DNJ and 2-OBn-DNJ. The 2-OBn-DNJ derivative could be explained by aziridine hydrolysis in the presence of water.



Scheme 3.4 Formation and decomposition of Huisgen Cycloaddition. Reprinted with permission from reference **173**. Copyright (2008) American Chemical Society

With this mind, a one-pot cycloaddition was investigated as a means of avoiding loss of yield from triazoline isolation. In this study, different nucleophiles were investigated in an attempt to increase triazoline degradation efficiency.

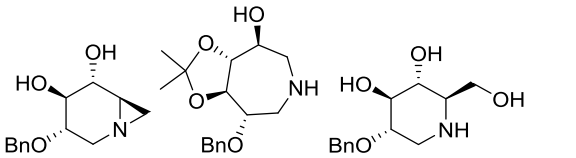
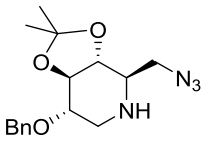
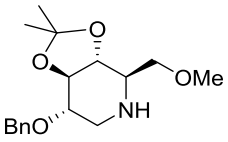
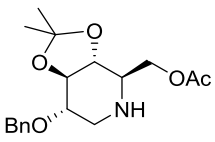
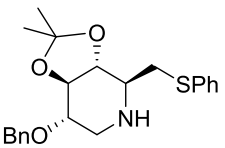
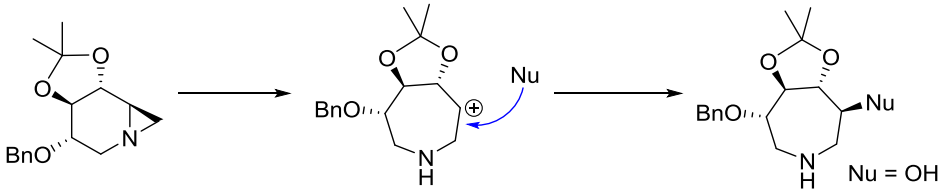
Entry	Reaction Conditions	Result
1	70 % AcOH, rt, 15 h	 Aziridine 15 % Azepane 33% 2-*O*-benzyl DNJ 14 %
2	Toluene, 110 °C, 1 h NaN_3 (5 Eq), AcOH (1.5 eq)	 35 %
3	Toluene, 110 °C, 1 h MeOH, 60 °C, 1 h	 20 %
4	Toluene, 110 °C, 1 h AcOH (5 Eq), 110 °C, 1 h	 45 %
5	Toluene, 110 °C, 1 h PhSH (5 Eq), rt, 15 h	 57 %

Table 3.1 One-pot investigations of Huisgen cycloaddition

When using non-polar solvents (e.g. toluene) the 6-membered piperidine ring was formed in good yields dependent on the nucleophile chosen (Table 3.1, entries 2-5). However, when using harsh acidic conditions, the azepane, aziridine and piperidine were observed (Table 3.1, entry 1).

Murphy and Zhou proposed azepane formation resulted from the formation of a cationic 7-membered ring (Scheme 3.5) followed by nucleophilic attack of water.

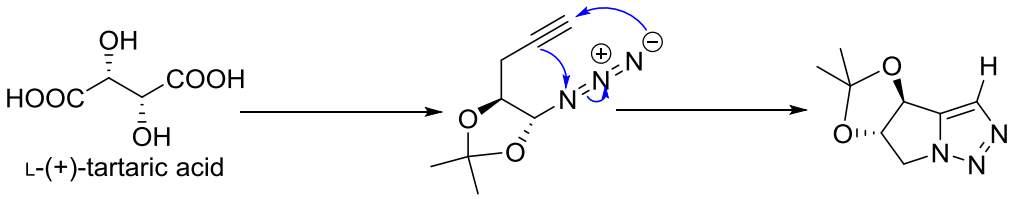


Scheme 3.5 Mechanism for azepane formation involving cationic transition state. Reprinted with permission from reference **173**. Copyright (2008) American Chemical Society

To summarise, Murphy and Zhou explored the 1,3-dipolar cycloaddition between azides and alkenes to afford a 1,2,3-triazoline which was decomposed under different conditions to optimise the preparation of natural product 1-DNJ, and its derivatives.

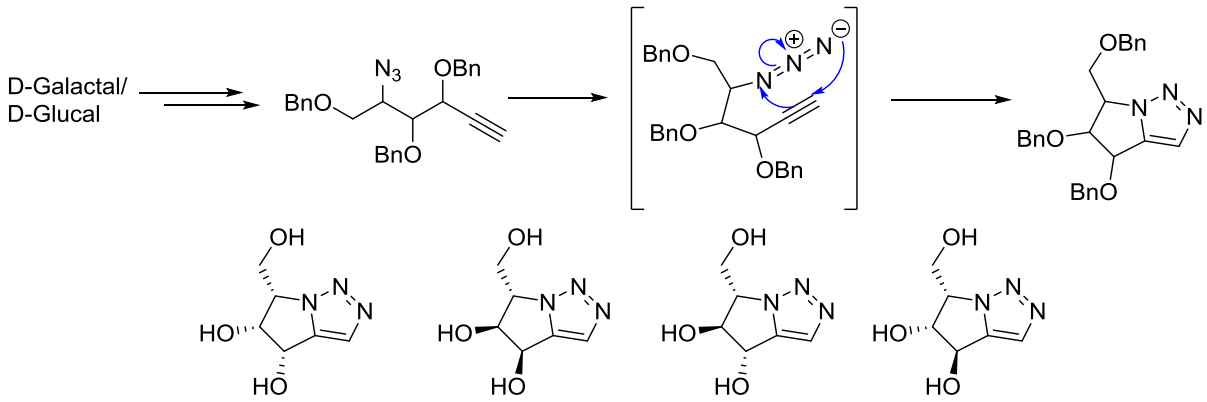
3.5.4 1,3-Dipolar cycloaddition to synthesise pyrrolidine-fused triazoles

In 2012, Wakhloo and co-workers[174] prepared polyhydroxylated pyrrolidine-fused triazoles in water using the Huisgen 1,3-dipolar cycloaddition (Scheme 3.6).



Scheme 3.6 Preparation of pyrrolidine-fused iminosugars derivatives by Wakhloo and co-workers

A couple of years later, Arora and Shaw[175] reported preparation of the *C*-glycosy triazole-fused pyrrolidines using the 1,3-dipolar cycloaddition (Scheme 3.).



Scheme 3.7 Preparation of C-glycosyl pyrrolidine-fused triazole iminosugars by Arora and Shaw

3.6 Allylic azide rearrangement

The allylic azide rearrangement (Figure 3.23) was first reported by Winstein and Young in 1960.[176] The interconversion can occur at room temperature resulting in a mixture of isomers, which has been primarily regarded as a synthetic disadvantage in the past. In 1995, Trost and Pulley[177] showed that having a hydroxyl group in proximity to the azide can provide stabilising intramolecular hydrogen bonding, thus shifting the equilibrium of the allylic azide rearrangement (Figure 3.23).

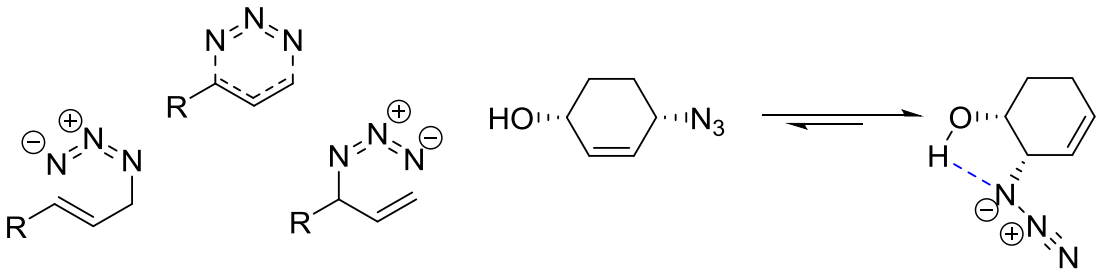
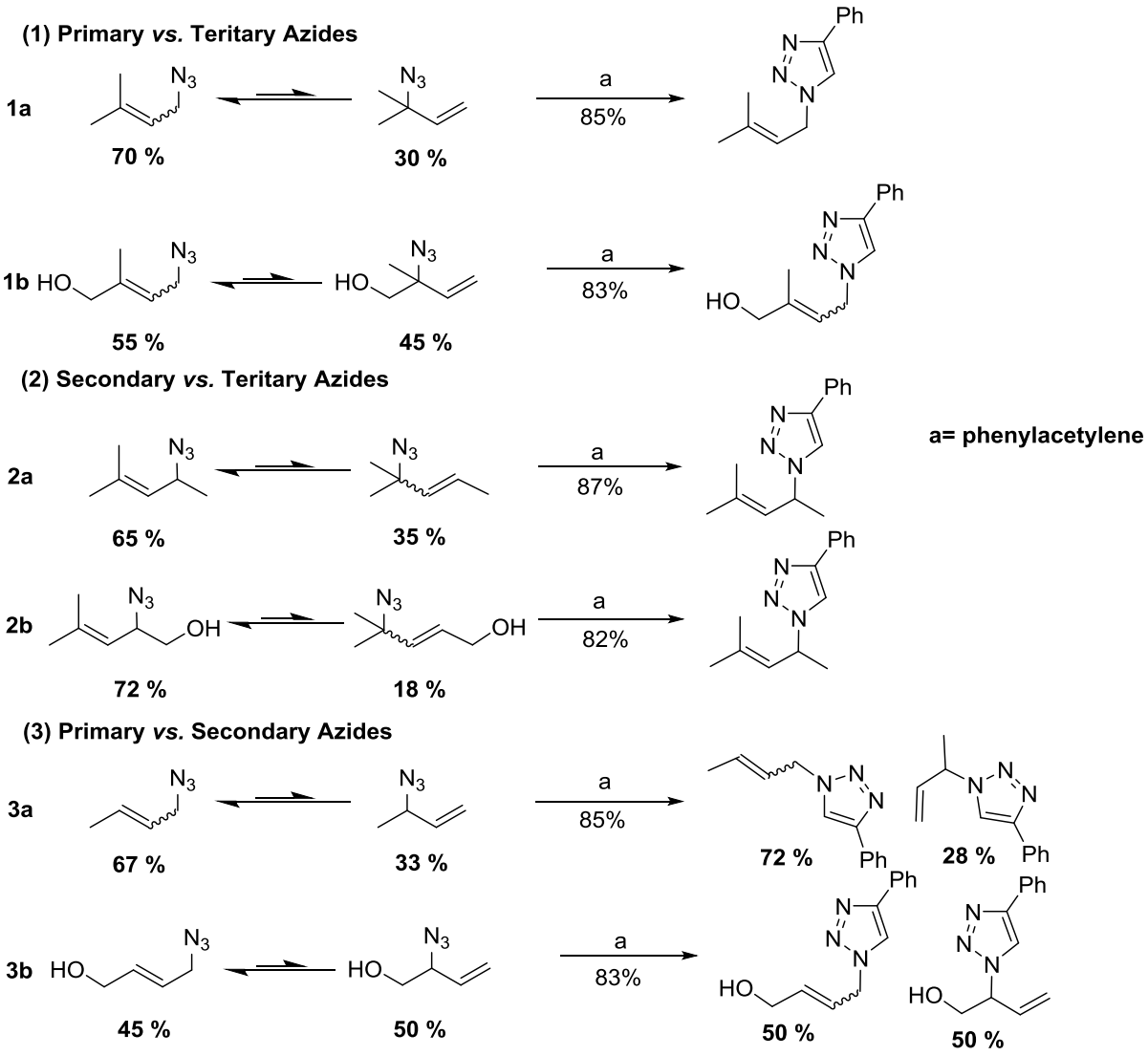


Figure 3.23 Mechanism for allylic azide rearrangement and equilibrium shift due to intramolecular H-bonding

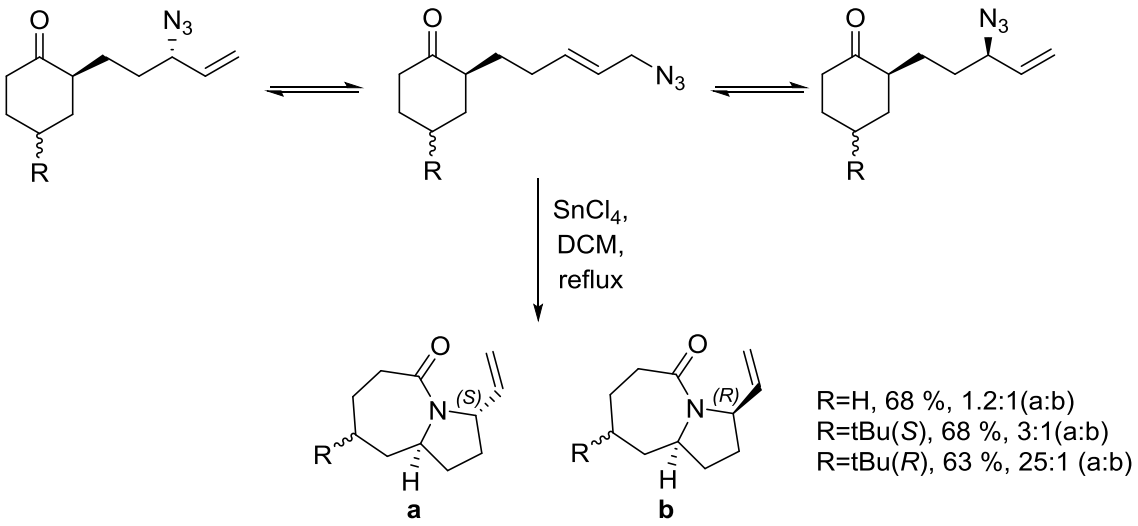
Sharpless and co-workers[178] performed a study in relation to the selectivity of this rearrangement. As shown in Scheme 3.8, in the primary vs. tertiary system (1a), while the teritary azide was evidenced, trapping experiments with phenylacetylene only provided access to the primary triazole. Introduction of the hydroxyl function (1b), while there was an increase in the amount of tertiary azide, the trapping experiments again only yielded the primary triazole.

Subsequent studies (2, 2c) of the secondary vs. tertiary azide system afforded the secondary triazoles, with no tertiary triazoles observed. The primary vs. secondary azide system (3a, 3b) had more success, with isolation of the secondary triazoles, particularly in the presence of the hydroxyl function. From this study, it could be deduced that while primary and secondary azides were capable of undergoing the 1,3-Huisgen cycloaddition in the presence of a suitable catalyst, tertiary azides were less susceptible to the transformation. Furthermore, as previously observed by Pulley[177], the presence of the hydroxyl function can provide intramolecular H-bonding, supporting an equilibrium shift of the interconverting allylic-azide system.



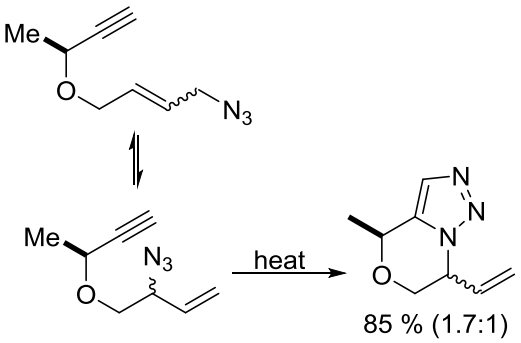
Scheme 3.8 Sharpless and co-workers investigations of the regioselectivity of the allylic-azide rearrangement. Adapted with the permission from reference **178**. Copyright (2005) American Chemical Society.

In 2012, Aubé and co-workers[179] demonstrated manipulation of the cycloaddition in combination with the Schmidt reaction to afford substituted lactams in a stereoselective manner (Scheme 3.9). They evidenced the substituents and their configurations had a direct effect on stereoselectivity of the products observed.



Scheme 3.9 Preparation of lactams through allylic azide in tandem with intramolecular Schmidt reaction by Aubé. Adapted with permission from reference **179**. Copyright (2012) American Chemical Society

Subsequently, Aubé and co-workers[180] reported a tandem allylic azide rearrangement and Huisgen 1,3-dipolar cycloaddition (with an alkyne as the dipolarphile) to afford triazoles in a stereoselective manner (Scheme 3.10).



Scheme 3.10 Huisgen cycloaddition in tandem with the allylic azide rearrangement by Aubé and co-workers

Moynihan *et al*[181] also reported a combination of the rearrangement and cycloaddition (using both alkynes and alkenes as dipolaraphiles) to yield *C*-glycosyl iminosugars (Figure 3.24).

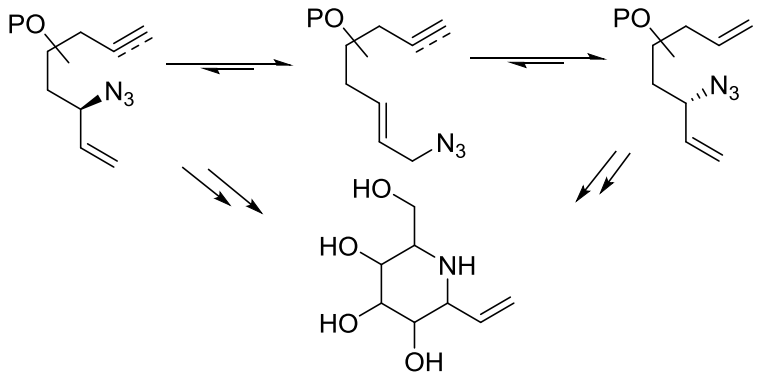
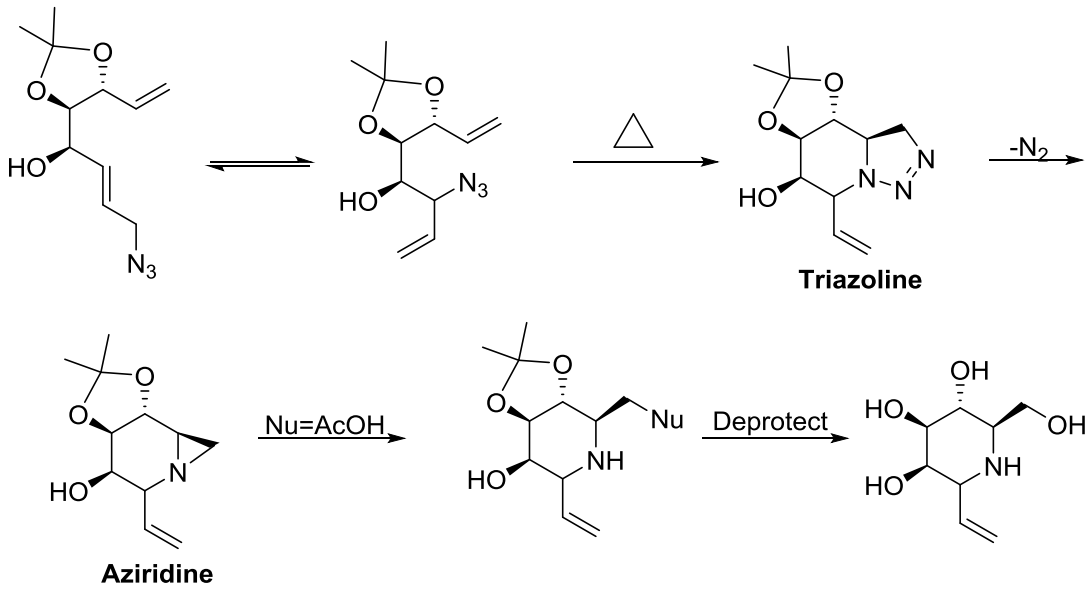


Figure 3.24 Allylic azide rearrangement in tandem with Huisgen cycloaddition to afford iminosugars. Adapted with the permission from reference **181**. Copyright (2015) American Chemical Society

As previously reported by Zhou & Murphy[173], Moynihan, Chadda and Murphy observed triazoline intermediates which could subsequently be broken down in the presence of a suitable nucleophile (acetic acid) to afford iminosugars in a diastereoselective manner (Scheme 3.11).



Scheme 3.11 Allylic azide rearrangement in tandem with the Huisgen Cycloaddition

Both publications[173,181], had reported the requirement of an isopropylidene constraint for successful cycloaddition. With this in mind, Moynihan attempted to optimised thr efficiency of triazoline formation *via*. alteration of the diol restraint (Figure 3.25). Various protecting groups were employed, however the highest yields of desired polyhydroxylated piperidines were obtained from the isopropylidine protecting group.

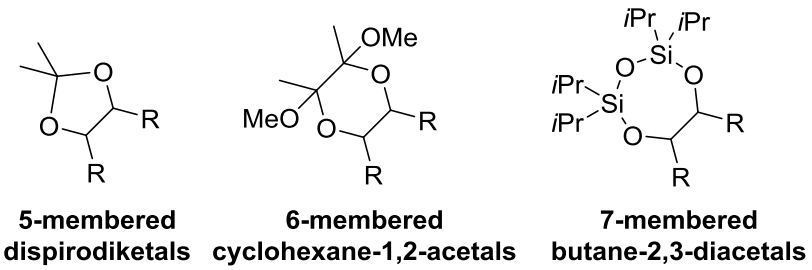


Figure 3.25 5-, 6- and 7-membered diol protecting groups

3.7 Aims and targets of thesis

As outlined in this chapter, iminosugars have been shown to have high potency, in particular as, glycosidase inhibitors. They have so far proved invaluable in medicine with multiple derivatives either in the pipe-line or available for the treatment of a wide-variety of diseases. As such, developing methods to access new iminosugar derivatives is necessary for further expansion of the library of nitrogen-containing polyhydroxyated frameworks available. The main synthetic route in this thesis, will utilise the allylic azide rearrangement in tandem with Huisgen cycloaddition to acquire iminosugar piperidines for structure determination (Chapter 4). Further exploitation of this rearrangement-cycloadditon will provide access to pyrrolidines (Chapter 5) and α,α-disubstituted piperidine iminosugars (Figure 3.26, Chapter 6). Increasing yields of the cycloaddition will also be at the forefront of this research by investigations of nucleophiles efficiency in triazoline decomposition and preferred solvents for the intramolecular cyclisation.

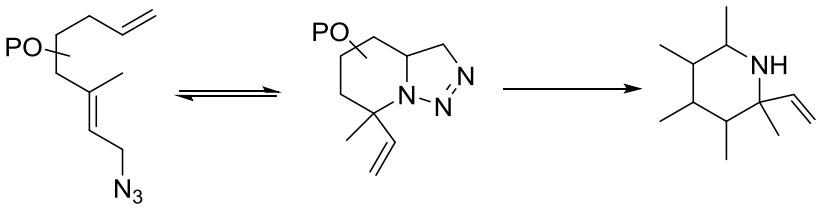


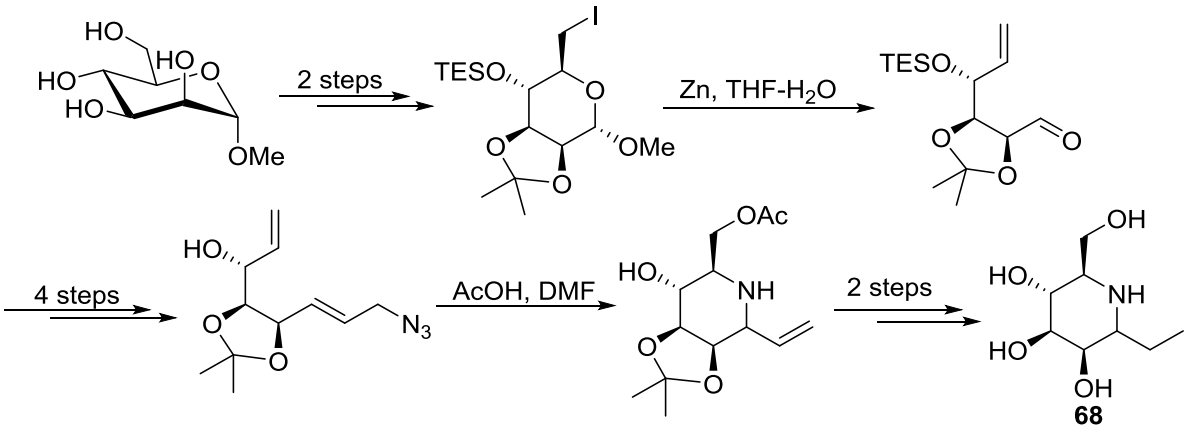
Figure 3.26 Preparation of α-quaternary piperidine iminosugars

4 Chapter 4 Preparation and identification of *C*-glycosyl iminosugar derivatives

4.1 Route designed by Moynihan to piperidine iminosugars

As previously discussed in Chapter 3, Moynihan developed a new route to piperidine *C*-glycosyl iminosugars from the corresponding methyl D-glycopyranosides. This work highlighted the importance of an innate conformational restraint in the form of an isopropylidene protecting group for the desired transformation to occur.

As shown in Scheme 4.1, Moynihan[181] prepared the natural product **68** using a synthetic line from methyl-α-D-mannopyranoside. This synthesis involved a key reductive fragmentation of the sugar to afford an aldehyde intermediate which could subsequently be manipulated to afford the precursor azide. Rearrangement-cycloaddition of the azide afforded the polyhydroxylated alkaloid which could be transformed to the natural product **68** following removal of protecting groups and reduction of the alkene functionality.



Scheme 4.1 Preparation of natural product homomannojirimycin alkyl derivative **68** by Moynihan

Upon preparation of **68**, Moynihan[181] had previously performed 1D NOE experiments to decipher the orientation at C-1 and C-5. Using the analysis obtained, Moynihan suggested the mannonorjirimycin derivative α anomer was formed from this synthetic route.

Newman projection models of the secondary allylic azide stereoisomers complimented the findings on the basis of minimisation of gauche interactions. As shown in Figure 4.1, cycloaddition of the secondary allylic azide with *R* configuration would place the vinyl group and the C-H bond in proximity. In the contending reaction where the carbon directly attached to the secondary azide has *S* configuration, the cyclisation would place the vinyl group in proximity to the C-O bond which is disfavoured due to gauche interactions. For this reason, reaction pathways from the *R*-configured isomer would proceed faster resulting in the 1,2-*trans* product.

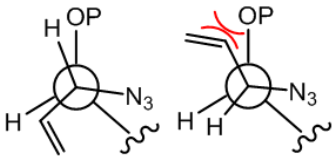
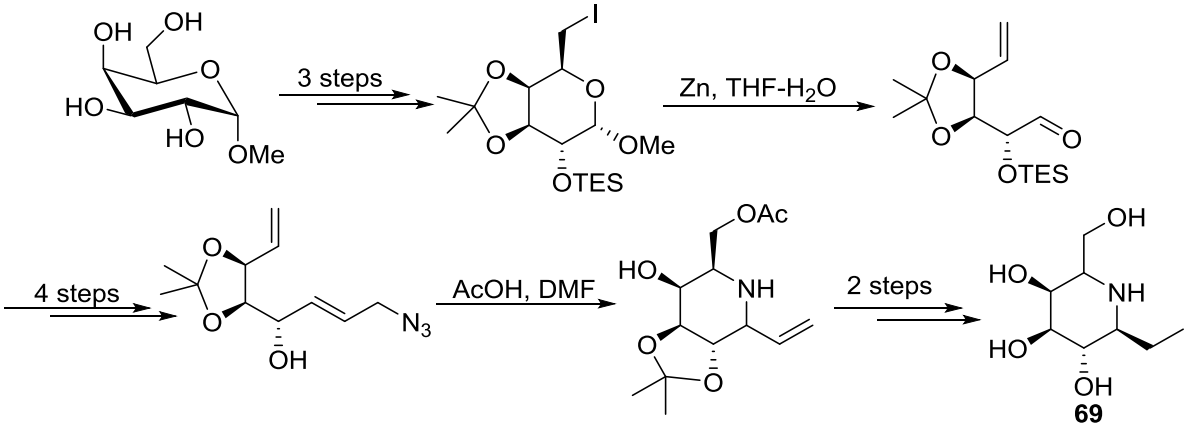


Figure 4.1 Newman projections of the secondary allylic azide stereoisomers viewing along C-1 and C-2

However, the data obtained for **68** were in excellent agreement with a natural product previously isolated and reported as the β anomer, with the authors stating they used NOE experiments to assign the stereochemistry.[182] In order to confirm the stereochemistry generated at C-1 and C-5 during the cycloaddition, ^{1}H and ^{13}C NMR spectroscopic data of **68** were compared to previous literature reports. Independently, Fleet and co-workers[183] had reported the synthesis of the β anomer. However, ^{13}C NMR data of the Fleet synthesised compound varied from both Moynihan's data and those of the natural product. From these results, Moynihan had concluded that the orientation at C-1 was downwards facing i.e. the α anomer. However, further clarification was required before publication of the results, ideally through acquisition of an X-ray crystal structure.

Moynihan also used a similar synthetic pattern to prepare the β-configured iminosugar **69** from methyl α-D-galactopyranoside (Scheme 4.2). Efforts were made to verify orientation at C-1 using ^{1}H NMR data ($J_{1,2}$ = 9.1 Hz). A *J*-value of this magnitude would only be possible if the ethyl group at C-1 was equatorially orientated. However, efforts to establish stereo-orientation at C-5 was difficult as the $J_{4,5}$ would be small (≤3 Hz) regardless of the orientation, axial or equatorial, at C-5. Moynihan also used Newman projections viewing along C-1 and C-2 to explain the stereochemical outcome at C-1 by comparison of the contending transition states. The stereochemical outcome expected from the Newman projections was the 1,2-*trans* product i.e the β anomer.



Scheme 4.2 Preparation of β-homopyranonojirimycin alkyl derivative **69** by Moynihan

Murphy[184] subsequently explained the configuration generated at C-5 to be a result of minimisation of allylic strain of the reacting conformer. This analysis showed C-5 should be downwards facing.

Murphy[184] also compared ^{13}C data of Moynihan's product to previously isolated isomers by Fleet and co-workers[185] (Scheme 4.7) in an attempt to understand the stereochemical outcome of the cycloaddition at C-5. These comparisons showed stereochemistry at C-5 for **69** was in agreement with literature reports for altrose configured iminosugars **91** and **92** (*vide infra*).[184] To further confirm this result, NOESY experiments were required for the iminosugar product.

This chapter will outline the steps undertaken to verify the stereochemistry of iminosugars **68** and **69** at C-1 and C-5, respectively, using the line of syntheses previously employed by Moynihan to access the required derivatives.[181]

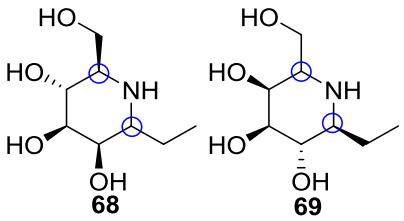
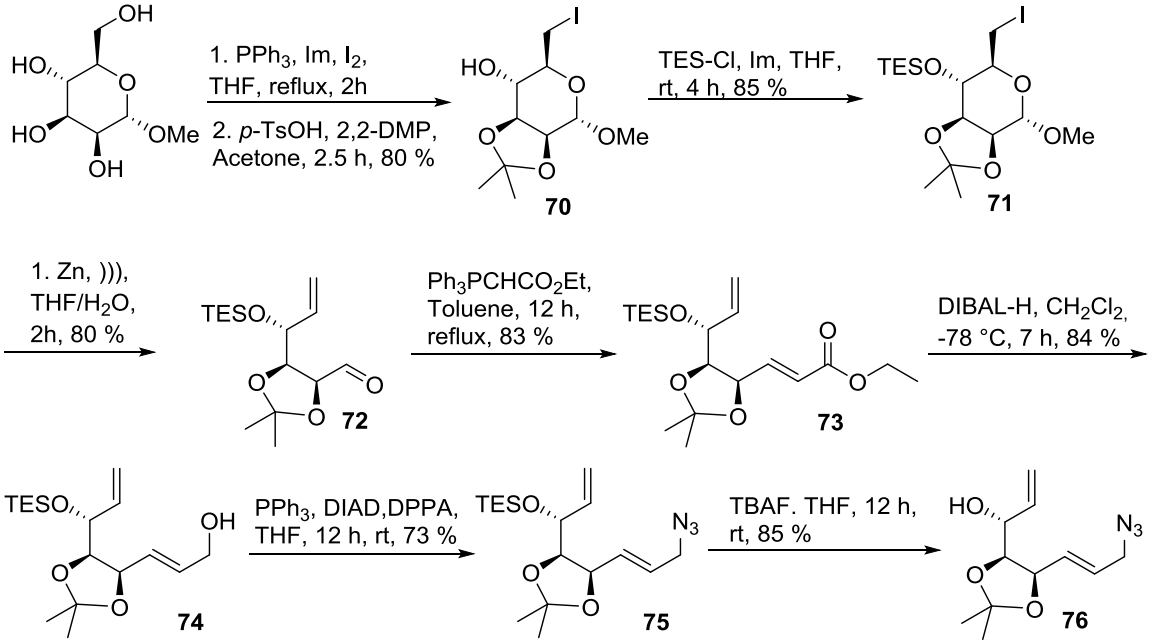


Figure 4.2 Preparation of C-glycosyl iminosugars synthesised by Moynihan

4.2 Manno-configured iminosugars

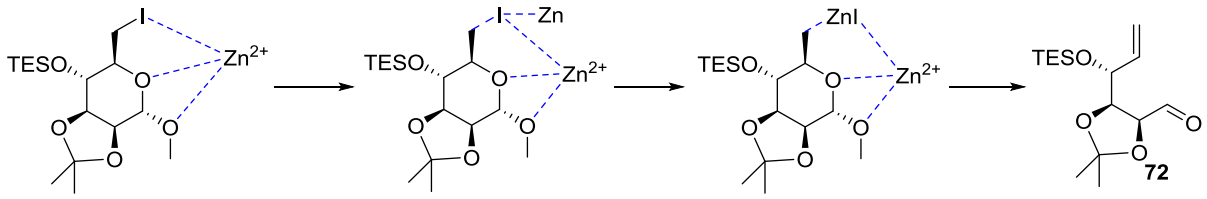
4.2.1 Preparation of precursor azide 76

As shown in Scheme 4.3, Appel reaction conditions developed by Garegg[186–188] and implemented by Moynihan[184] were used to convert methyl α-D-mannopyranoside to the 6-iodo sugar. Without purification, this iodide was treated with *p*-TsOH and 2,2-DMP in acetone to form the desired isopropylidene **70,**[184] where the acetonide is installed on the *cis* diol group.



Scheme 4.3 Preparation of precursor azide **76**

The isopropylidene derivative **70** was subsequently treated with a triethylsilyl chloride in the presence of imidazole to form **71**.[184] Zinc reductive fragmentation, using preactivated zinc in THF/H_2O (9:1) was employed to yield aldehyde **72**. The procedure to reduce and fragment methyl-6-deoxy-6-halo-pyranosides using zinc was first described by Bernet and Vasella[189], however reaction complications were observed with this methodology due to harsh conditions. Later, sonication was utilised by Madsen[190,191] to optimise experimental conditions for this reaction. As shown in Scheme 4.4, it is suggested that zinc undergoes an exchange with iodine followed by elimination to obtain the aldehyde **72**.

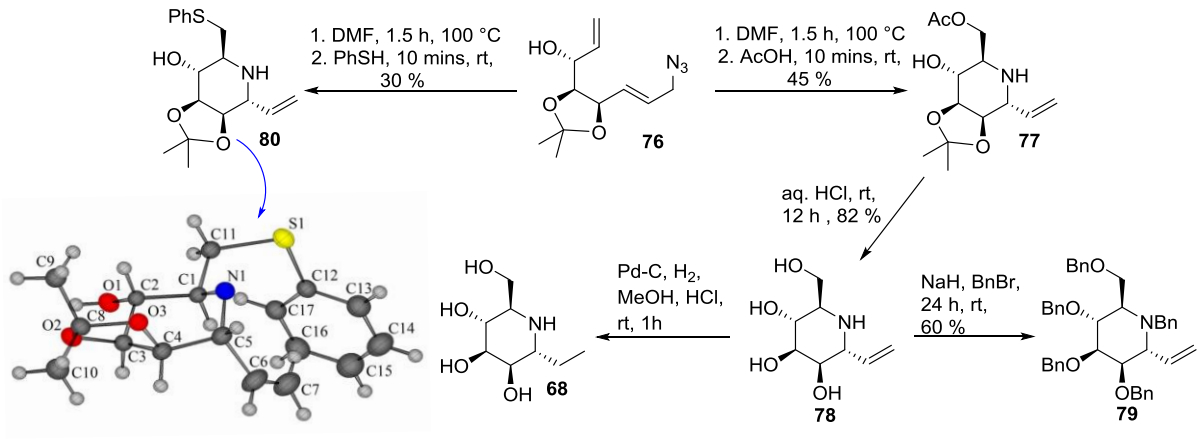


Scheme 4.4 Mechanism of zinc-reductive fragmentation

Wittig reaction conditions were performed on **72** to achieve full conversion to ester **73**. Reduction of the ester afforded the alcohol **74**. Mitsunobu type conditions[181] were utilised to displace -OH moiety and achieve the azide **75**. TBAF was then employed to remove the triethylsilane protecting group providing access to the precursor azide **76.**

With azide **76** in hand, the tandem cycloaddition was performed leading to **77** (Scheme 4.5). Efforts were made to achieve crystals of this compound using a variety of solvents and crystal growing techniques including; solvent evaporation, slow cooling, sublimation, co-crystallants (with triphenylphosphine) and solvent saturation. None proved successful. As a result, iminosugar derivatives **78** and **68** were prepared by deprotection of **77** using aqueous hydrochloric acid and subsequent hydrogenation. Crystal growing techniques were again attempted on these compounds, but with no success. Preparation of derivatives from **78** were then explored as a means of obtaining crystals. An example of this type of strategy included protection of **78** with benzyl protecting groups, however this afforded **79** a clear oil and subsequent crystal growing pursuits failed. Experimental attempts to anchor other protecting groups (e.g. OAc**,** OBz) onto the sugar were also unsuccessful.

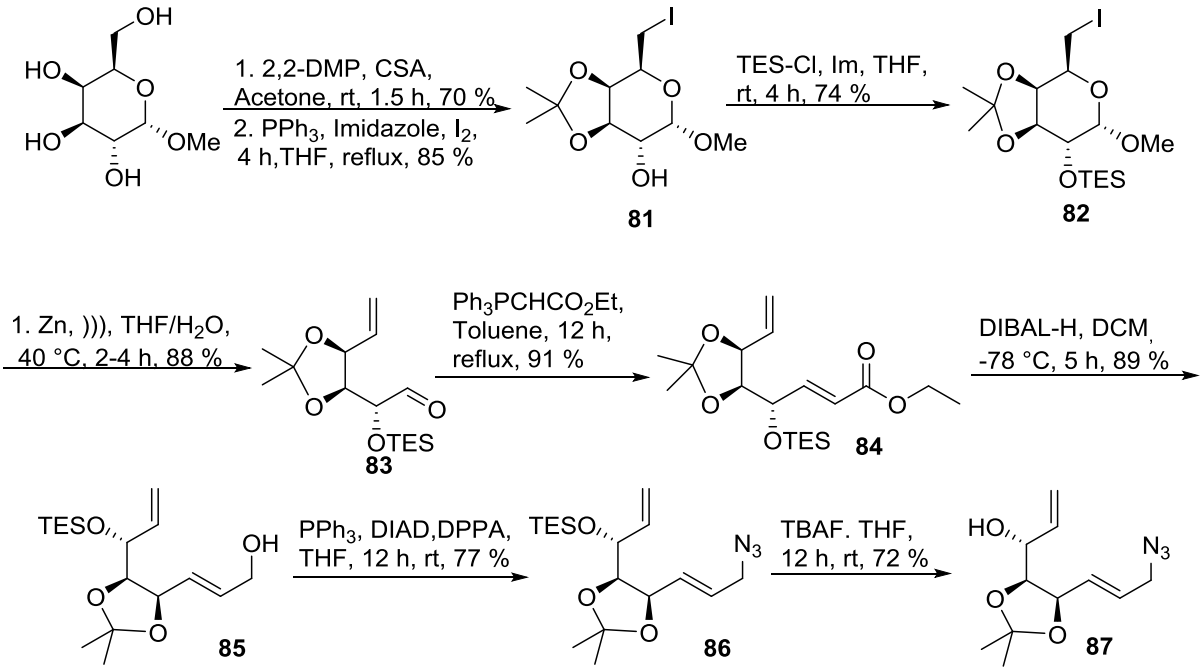
As a means of resolving this situation, it was hopec that treating **76** with other nucleophiles could yield other potentially crystalline molecules with the same stereo-orientation as **77**. Due to success with synthesis of pyrrolidines (Chapter 5), thiophenol was regarded as a suitable molecule for this transformation and provided access to **80**, as a waxy yellow solid. Zhou had previously successfully employed thiophenol to synthesise piperidines.[173] Efforts to crystallise **80**, were successful from hexane/ethyl acetate. The X-ray crystal structure confirmed Moynihan's original results, clarifying that the substituent at C-1 in **68** is axially oriented.



Scheme 4.5 Preparation of iminosugars *via*. rearrangement-cycloaddition and X-ray crystal structure of **80**

4.3 Galactose iminosugar 69

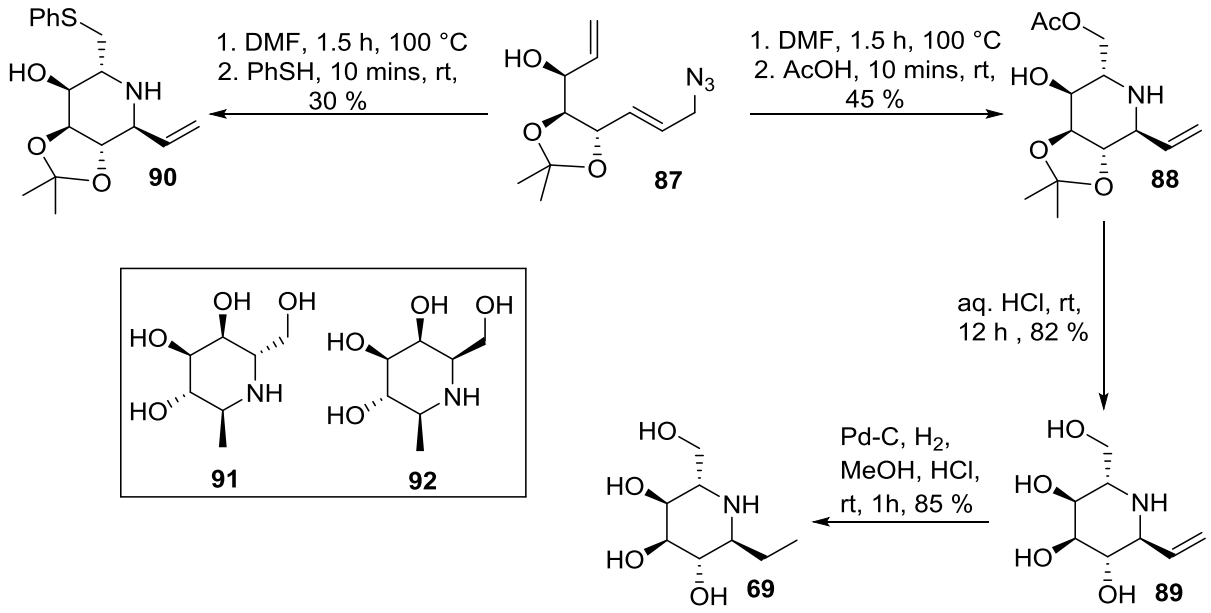
As shown in Scheme 4.6, precursor azide **87** could be prepared from methyl-α-D-galactopyrannoside using the route developed by Moynihan[181,184] and undertaking similar transformations as the corresponding mannose-configured pyranose through intermediates **81**-**86**.



Scheme 4.6 Preparation of galacto-configured azide precursor **87**

Cycloaddition of **87** using acetic acid as the nucleophile afforded **88**. Subsequent deprotection and reduction yielded **89** and **69**. Both 1D and 2D NOESY experiments were performed on these polyhydroxylated alkaloids, however the data obtained were inconclusive. In an attempt to resolve this problem thiophenol piperidine derivative **90** was prepared from azide **87**. It was hoped that crystal growth could further confirm the configuration at C-5 *via* X-ray crystallography. While crystal growing efforts were unsuccessful, 1D NOESY experiments of **90** provided the required correlation peaks for

stereochemistry determination. No crosspeak was observed between H-3 and H-5, which would be expected for the galacto-configured iminosugar. A weak cross peak was observed between H-3 and one of the H-6 protons, supporting the altrose configuration. Taken together with a comparison of the ^{13}C data for **69** and Fleet's data (for **91** and **92),** the altrose configuration was proposed for **69**, **88**, **89** and **90**.



Scheme 4.7 Preparation of iminosugars **69**, **88**-**90** and Fleet's altro- and galacto-configured iminosugars **91** and **92**

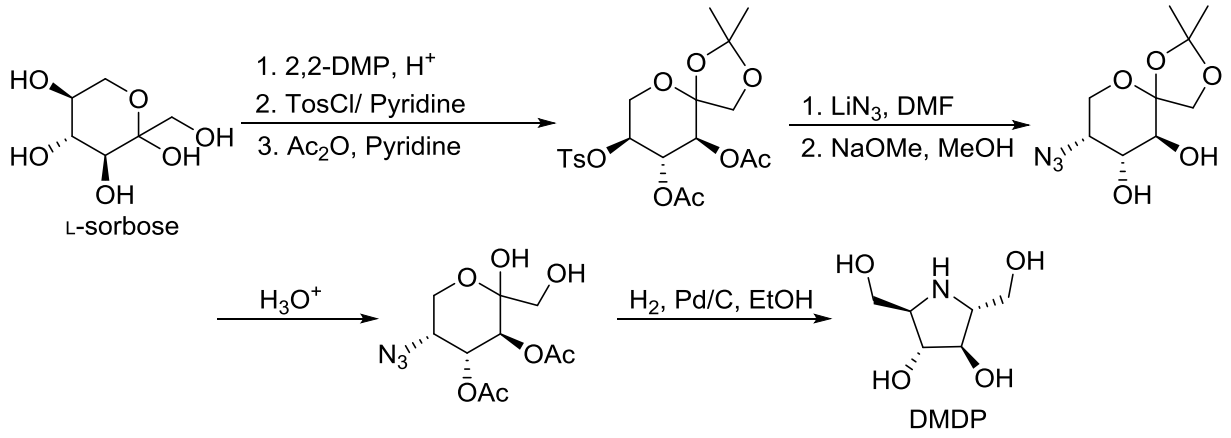
4.4 Conclusion

In this chapter, the stereochemistries of the manno- and altro- configure iminosugars **68** and **69**, were determined by X-ray crystallography and NOESY experiments. Thiophenol was also shown to be as a suitable nucleophile for the rearrangement-cycloaddition reaction resulting in *C*-glycosyl polyhydroxylated piperidines.

Chapter 5 Synthesis of Pyrrolidine Iminosugars Derivatives

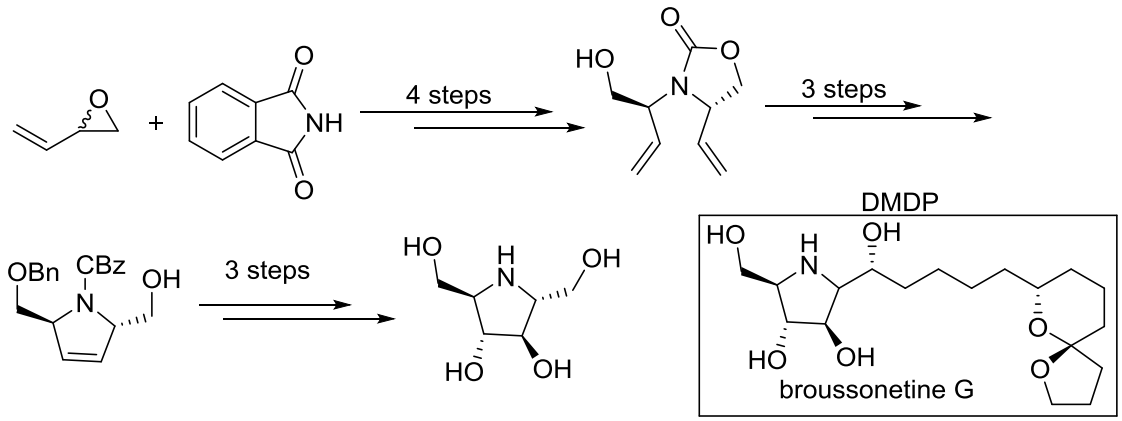
5.1 Previous syntheses of DMDP and analogues

One of the first preparations of 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP) was reported by Card and Hitz[192] in 1985. This total synthesis of the pyrrolidine alkaloid started from L-sorbose and involved 7 steps. The key transformation involves reduction of azide to the corresponding amine, intramolecular addition of the amine to the carbohydrate aldehyde functionality and subsequent stereoselective imine reduction.



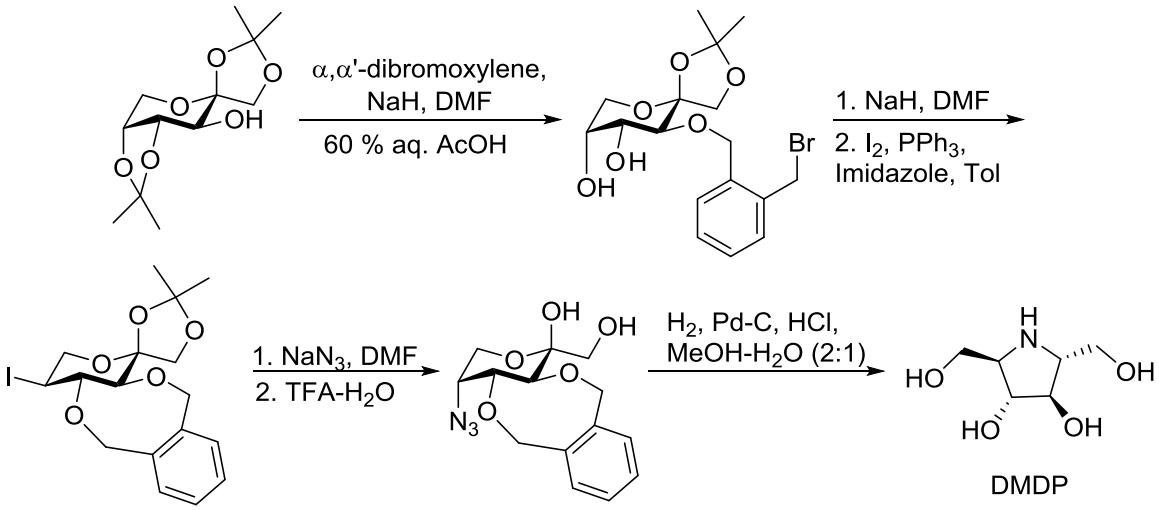
Scheme 5.1 Preparation of DMDP by Card and Hitz

Trost and Woltering[102] reported synthesis of DMDP from phthalimide and butadiene monoxide involving a palladium catalysed asymmetric allylic alkylation. They also investigated this transformation for the preparation of DMDP *C*-alkyl analogues, such as broussonetine G.



Scheme 5.2 Preparation of DMDP and broussonetine G from phthalimide and butadiene monoxide

More recently, Moreno and Fernández[193] reported preparation of DMDP from di-isopropylated-β-D-fructopyranose involving a similar azide intermediate to Card and Hitz[192].



Scheme 5.3 Preparation of DMDP from 1,2:4,5-di-O-isopropylidene-β-D-fructopyranose

Fleet and co-workers[194] reported preparation of DMDP and 9 stereoisomers from glucuronolactone (Figure 5.1).

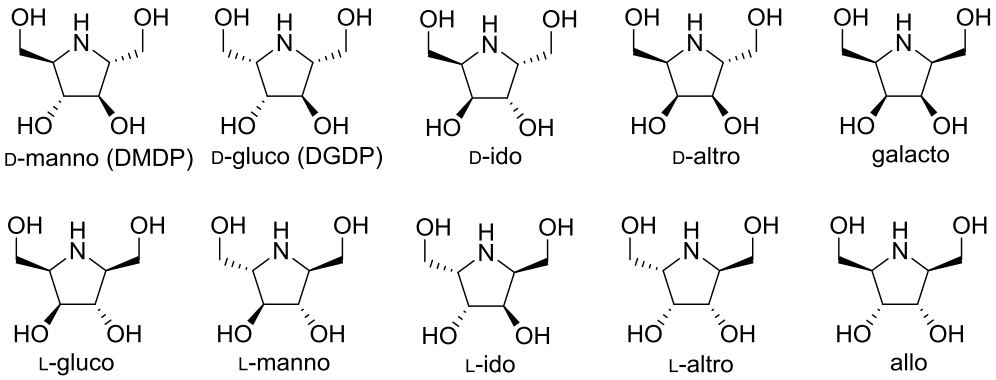
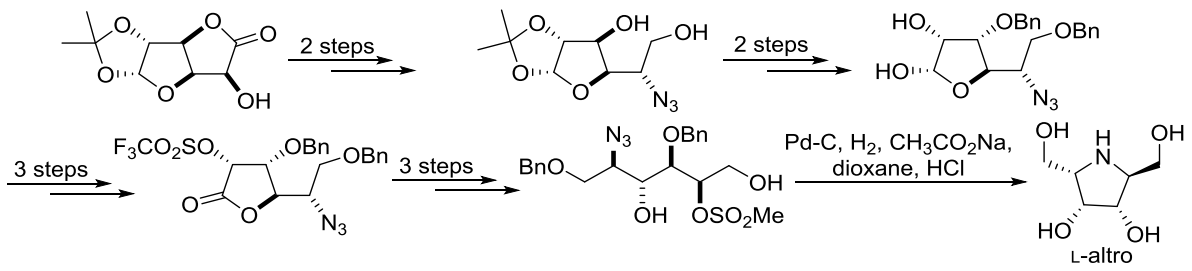


Figure 5.1 Preparation of DMDP and stereoisomers

As an example, the synthetic route to the L-altro pyrrolidine has been outlined below in Scheme 5.4. Starting from glucuronolactone, insertion of the azide moiety followed by fragmentation of the sugar ring afforded a chiral intermediate which could undergo catalytic hydrogenation to yield the protected pyrrolidine. Subsequent addition of HCl afforded the deprotected L-altro configured 2,5-dideoxy-2,5-iminohexitol.

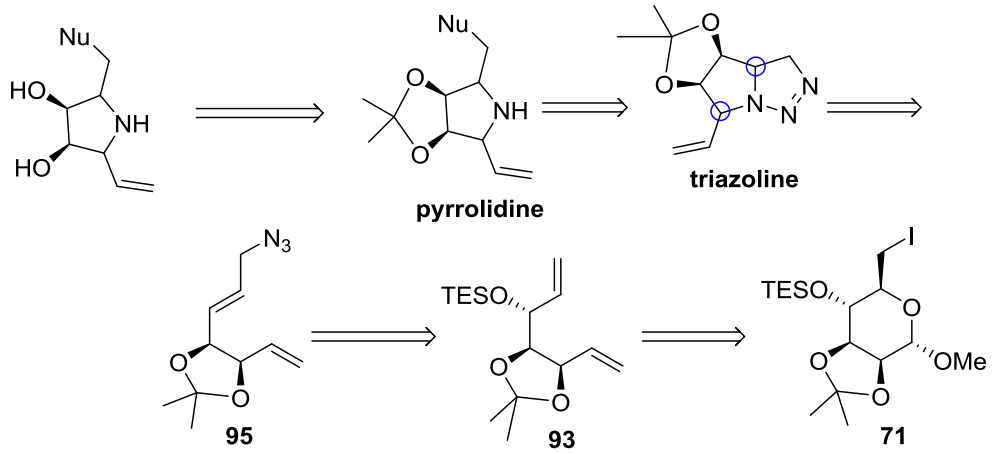


Scheme 5.4 Preparation of L-altro configured 2,5-dideoxy-2,5-iminohexitols from glucuronolactone

5.2 Results and Discussion

5.2.1 Planning synthesis of pyrrolidines

The main aim of this section of work was to develop a route to 5-membered iminosugar analogues from monosaccharide precursors. Methyl α-D-mannopyranoside was considered an ideal precursor for two reasons; i) it is an inexpensive, commercially available, starting material ii) Moynihan[181] has previously employed this sugar for the preparation of *C*-glycosyl piperidines. The synthetic route used herein to *C*-glycosyl pyrrolidines was based on Moynihan's route (Scheme 5.5). In the synthesis planning, it was expected reductive fragmentation of **71** followed by Wittig reaction would provide access to **93**. Removal of the silyl group and incorporation of the azide moiety would afford desired azide **95**. After introduction of the azide moiety, it was expected that the allylic azide would undergo rearrangement in tandem with the 1,3-dipolar cycloaddition generating the 1,2,3-triazoline with two new stereocentres. Expulsion of nitrogen resulting in aziridine formation and subsequent reaction of nucleophiles with this unstable heterocycle intermediate would yield the desired pyrrolidine derivatives.

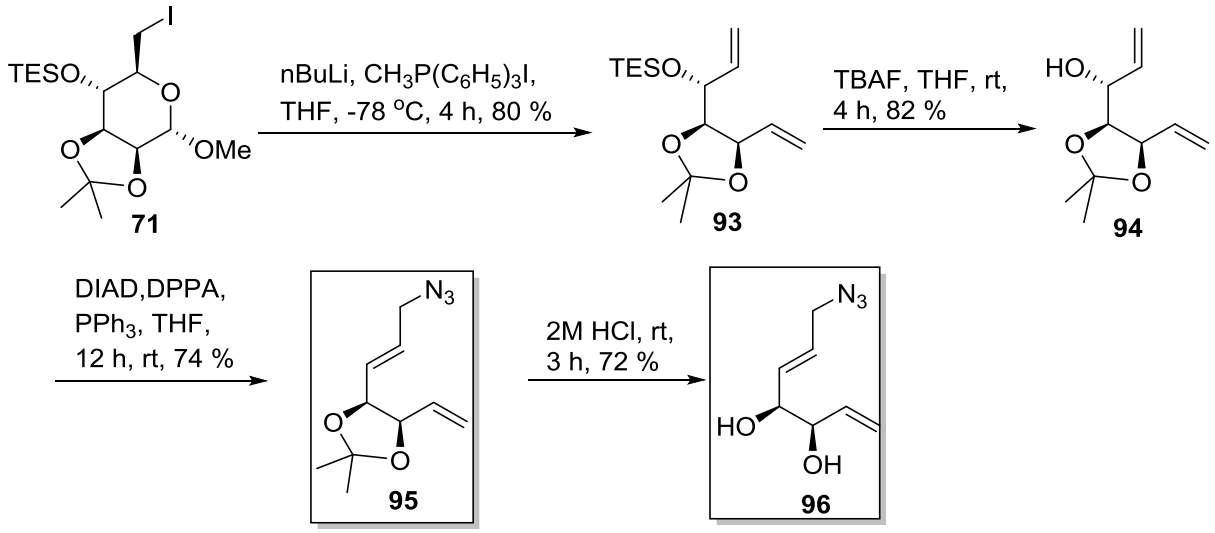


Scheme 5.5 Retrosynthesis from methyl α-D-mannopyranoside

5.2.2 Preparation of precursors for pyrrolidine formation

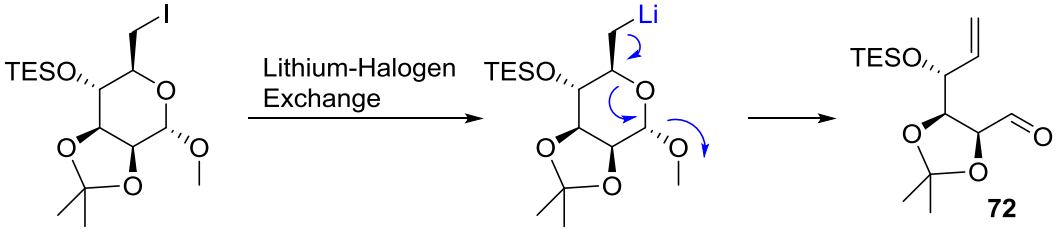
As shown in Scheme 5.6, the fully protected sugar was subjected to various conditions with a view to producing alkene **93**. Originally, zinc reductive fragmentation, using preactivated zinc in THF/H_2O (9:1),

followed by Wittig reaction was employed. The subsequent Wittig reaction gave access to **93**. However, this route provided the desired diene in low yields (~50 % over 2 steps).



Scheme 5.6 Synthesis of *cis*-acetonide diol

A one pot reductive fragmentation (Scheme 5.7) promoted by nBuLi followed by an *in-situ* Wittig reaction, developed by Brock and Thomson[195] was used instead and this provided access to **93** with improved yields (80 %). In this reaction lithium halogen exchange occurs, and the intermediate formed undergoes elimination to provide the aldehyde **72**. Careful reaction monitoring was crucial during this step as prolonged reaction times led to epimerisation at the carbon atom α to the aldehyde. The in-situ generated aldehyde was then subjected to Wittig reaction conditions to obtain the alkene **93**.



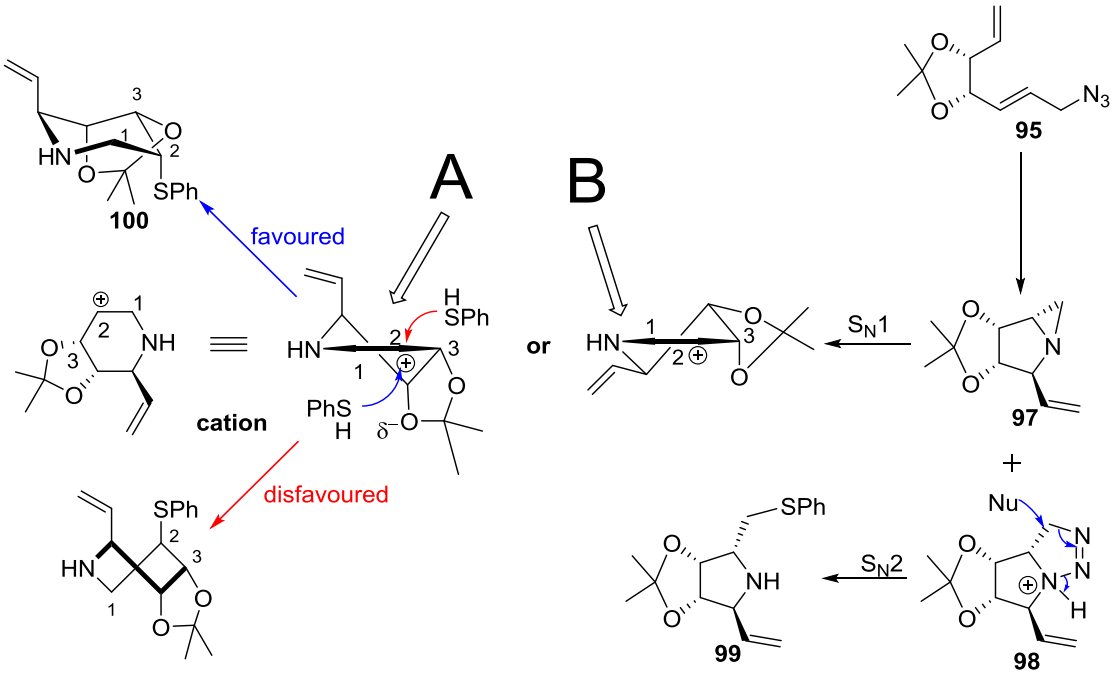
Scheme 5.7 nButylithium promoted reductive fragmentation

Removal of the triethylsilyl protecting group was achieved using TBAF to afford **94**. While the reaction progressed smoothly, removal of the fluorotriethylsilane formed provided some difficulties. Various work-up conditions (satd. $NaHCO_3$, $CaCO_3$, DOWEX 50WX8[196], 1M NaOH) were attempted to remove the undesired impurity. However, the use of 3M NaOH in the work-up led to complete removal of the impurity**.** The alcohol **94** was then subjected to Mitsunobu-type conditions[184] (DIAD, DPPA) to afford the desired azide **95**. While four isomers were potentially observable due to allylic azide rearrangement, the *trans*-

primary azide **95** was the isomer observed by NMR analysis. This result was expected as the less substituted azide is usually the preferred isomer.[178]

5.2.3 Allylic azide rearrangement and cycloaddition of acetonide protected azide 95, derived from *cis*-diol

With azide **95** in hand it was subjected to various conditions in an attempt to form pyrrolidine products. In a typical procedure azide **95** was heated at 100 °C for 1-3 h in DMF to promote formation of the triazoline intermediate **98**. The nucleophile was then added and reaction heated at the required temperature for a further 12 - 36 h. Efficient breakdown of the triazoline intermediate **98** produced proved difficult as evidenced by unproductive reactions with a range of nucleophiles (CsOAc, NaN_3, AcOH, NaOAc, TBAI, diethyl malonate). However, improvements were observed when S and Se based nucleophiles were investigated (Table 5.1). In one case (entry 1) both the pyrrolidine **99** (25%), piperidine **100** (11%) were formed.



Scheme 5.8 Mechanism for cycloaddition of **95** providing piperidines and pyrrolidines through S_{N1} and S_{N2} pathways

While other products were not isolated, it was suspected the prolonged heating could have resulted in decomposition of the iminosugars, thus reducing reaction yields. In this instance, while the reactions appear stereoselective, the lack of regioselectivity indicates that competition between S_{N1} and S_{N2} (Scheme 5.8) is occurring leading to the 6- and 5-ring systems, respectively.

Entry	Reaction Conditions	Results

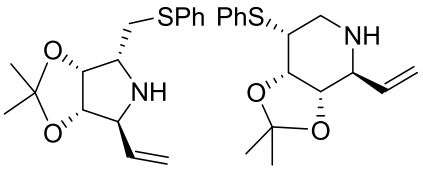
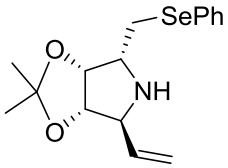
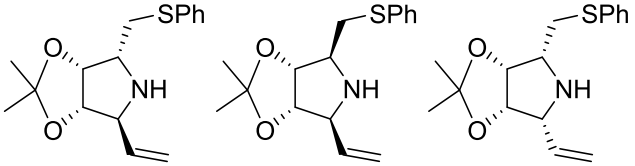
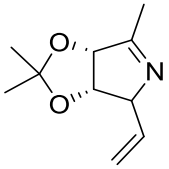
1	DMF, 100 ˚C, 1-3 h PhSH, DMF, 100 ˚C, 3 days	 **99** **100** **25 %** **11 %**
2	DMF, 100 ˚C, 1-3 h Ph_2Se_2, DMF, rt, 12 h	 **101** **50 %**
3	Tol, 100 ˚C, 1 h PhSH, Tol, 100 ˚C, 16 h	 **99** **102** **103** **30 %** **7 %** **10 %**
4	Tol, reflux, 12 h	 **104** **10 %**

Table 5.1 Pyrrolidine derivatives resulting from cycloaddition

In DMF, the presence of a stronger Se containing nucleophile resulted in the formation of the pyrrolidine **101** in 50% yield. When the triazoline generated *in-situ* in toluene was treated with thiophenol then only pyrrolidines were observed (entry 3), thus regioselectivity could be increased using a non-polar solvent. It is not understood why there is an apparent increased stereoselectivity in the case of toluene in comparison to DMF. It was noted that the S- and Se- substituted iminosugar derivatives were relatively unstable, and so, it is possible products were decomposed during the reaction/work-up/isolation process. However, solvents have been previously shown to effect stereoselectivities of reactions and this could account for the selectivities observed.[197] Excessive heating of azide **95** in the absence of a nucleophile led to isolation of the imine **104** (10 %). The low yield could be contributed to rapid decomposition of this unstable ketimine. A mechanism[198] for this transformation involves decomposition of the triazoline ring with expulsion of nitrogen (Figure 5.2).

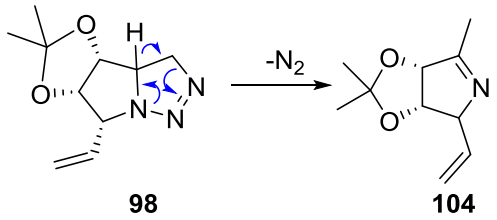


Figure 5.2 Mechanism for imine formation

The reaction of azide **95** in deuterated DMF was monitored by NMR with a view to gaining a greater understanding of reaction progression. A set of ^{1}H-NMR spectra obtained on heating of the reaction at different temperatures and reaction times are provided in Figure 5.3.

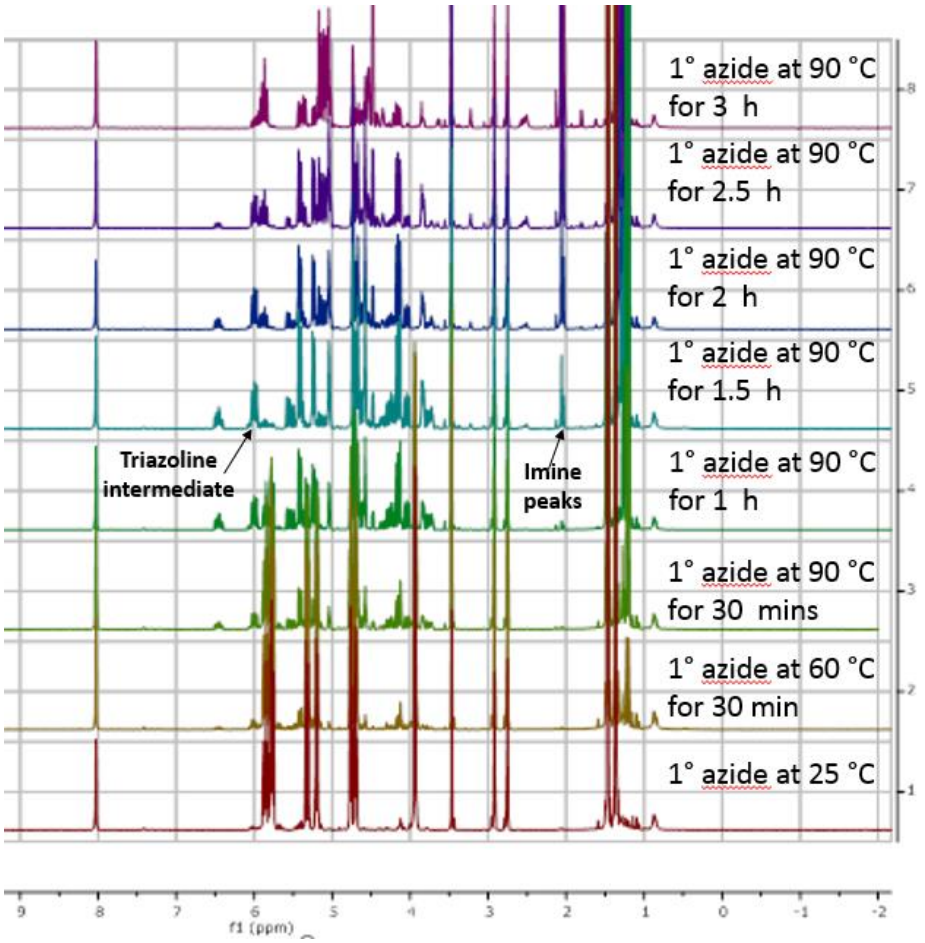


Figure 5.3 NMR reaction monitoring experiment for azide **95** in deuterated DMF from 20-90 °C

In the NMR experiment, after 1.5 h at 90 °C consumption of azide **95** was complete. Analysis of signals present at 1.5 h indicated the main component present in the mixture was the triazoline supported by the presence of signals for its ring; CH_2 at δ 4.04 ppm (1H, dd, J = 16.3 Hz and 10 Hz) and at δ 4.68 ppm (1H, dd, J = 16.3 Hz and 2.3 Hz). Evidence for the formation of two imines was also observed; two signals at δ

2.06 (br s) and 2.03 (d, J = 2.2 Hz). Prolonged heating of the mixture at 90 °C showed triazoline depletion after 3 h, with a coinciding increased intensity of the imine signals. Breakdown of triazoline intermediates to form imines (-CH_3 singlet at δ 2.06 and doublet at δ 2.03) had previously been observed by Moynihan[181] and Damani[198]. Isolation of imine **104** further confirmed triazoline decomposition to form ketimines.

From the results shown (Figure 5.3 and Table 5.1), it could be deduced that the poor yields for the cycloaddition were due to breakdown of the triazoline ring to the imine. It is speculated use of the highly nucleophilic Se enabled breakdown of the triazoline intermediates more efficiently, leading to higher yields of **101**. However, to our knowledge no reports describing the use of nucleophiles to breakdown the triazoline ring have been published and thus we could not provide further clarification on this matter. Efforts to maximize the yields were attempted by addition of nucleophiles before complete conversion of the azide **95** to the subsequent triazoline intermediates as a means of avoiding imine formation. However, these attempts lead to further complicated mixtures.

The stereochemical preference exhibited at C-1 of the main thio- and seleno- pyrrolidine products (Table 5.1, entries 1-3) could be rationalised by considering steric hindrance in the transition structures (see Newman projections in Figure 5.4). Here, cycloaddition of the secondary allylic azide with *S* configuration would place the vinyl group and the C-H bond in proximity. In the contending reaction where the secondary azide has the *R* configuration, the cyclisation would place the vinyl group in proximity to the C-O bond which is disfavored due to gauche interactions. For this reason, reaction pathways from the *S*-configured isomer would proceed faster resulting in the 1,2-*trans* isomer as the major product.

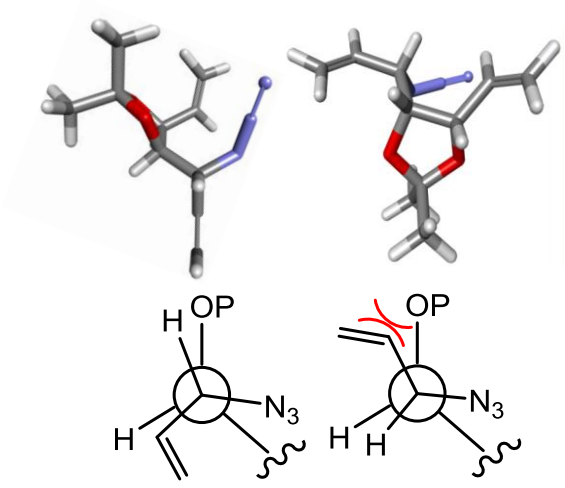


Figure 5.4 R and S computationally derived transition structures and Newman projections of 2° allylic azide intermediates

On the basis of previous reports of the cycloaddition[173,184], the stereochemical outcome for the main thio- and seleno- pyrrolidine products (Table 5.1, entries 1-3) at C-4 was expected to be the 3,4-*trans* product. However, on analysis of NOESY experiments of the iminosugar derivatives, it was concluded these substituents were facing downwards in the main iminosugar products (Table 5.1, entries 1-3). While these results were different to previously observed *cis*-products (Chapter 4), computational energy calculations by Murphy[199] did indicate the lowest energy conformer would result in formation of the 3,4-*cis* product. [200]

In the case of piperidine formation (Table 5.1, entry 1), it was speculated that a pathway involving **A** (Scheme 5.8) was preferred due to electrostatic interactions.[201] As such, attack from the bottom-face afforded the preferred chair conformation transition state structure which results in the 3,4-*cis* product. Nucleophilic attack from the contending up-face was hindered as this pathway involves the disfavoured twist-boat transition state structure, thus supressing formation of the 3,4-*trans* product.

5.2.4 Allylic azide rearrangement and cycloaddition of unprotected azide 96

The isopropylidene was removed from **95** using dilute acid to give diol **96**. Upon removal of the conformational restraint employed by the isopropylidene substituent, the reaction times were reduced and yields increased, respectively. This was not in accordance with results reported previously where conformational constraint was found to aid piperidine formation[184]. Isolation of triazoline **105** was observed from the treatment of **96** with DMF at 100 °C. NOESY experiments were not useful in determination of the stereochemistry at C-1 for **105**. However, based on the stereochemistry of the main products (Table 5.2, entries 2-4) it could be deduced that the C-1 of **105** has 1,2-*trans* configuration.

The addition of nucleophiles (after 30 mins) to the reaction containing the aziridine was investigated next and results are summarised in Table 5.2. The piperidine **106** was formed in very good yield (90 %) and selectivity when acetic acid was the chosen nucleophile (entry 2). The piperidine **107** (entry 3) was observed for the reaction of sodium azide but in lower yield (35%). While the yield of products from reaction with thiophenol was 80% (entry 4) two products resulted, piperidine **108** and pyrrolidine **109**, indicating contending S_{N1} and S_{N2} mechanism pathways were in operation. Isolation of pyrrolidine **109** was explained by an increased preference for the S_N^2 pathway (compared with acetic acid as nucleophile), due to use of the stronger thiophenol nucleophile. The stereochemical orientation at C-1 and C-4 were rationalised on the basis of steric hindrance (similar to Figure 5.4) and coulombic interactions (similar to Scheme 5.8), respectively.

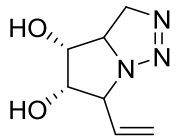
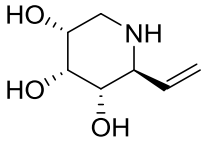
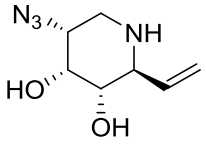
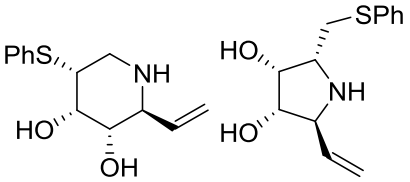
Entry	Reaction Conditions	Results
1	1. DMF, 100 ˚C, 30 min	 **105**
2	1. DMF, 100 ˚C, 30 min 2. AcOH (5 equiv), rt, 10 min 3. 2M HCl, 12 h	 90 % **106**
3	1. DMF, 100 ˚C, 30 min 2. NaN_3 (5 equiv), AcOH (1.5 equiv), rt, 10 min	 **107** 35 %
4	1. DMF, 100 ˚C, 30 min 2. PhSH (5 equiv), rt, 10 min	 **108** 48 % **109** 32 %

Table 5.2 Piperidine and pyrrolidine derivatives resulting from cycloaddition of **96**

Reaction monitoring was undertaken to comprehend the increased yields, the effect of increased nucleophile reactivity and decreased reaction times observed. Azide **96** was heated in deuterated DMF (Figure 5.5) and ^{1}H NMR analysis utilised to monitor reaction progression, similar to azide **95** (Figure 5.3). As can be seen in Figure 5.5, characteristic triazoline methylene signals were identified at δ 4.2 (dd) and 4.8 (dd)**.** Prolonged heating lead to decomposition of the triazoline to the aziridine as evidenced by δ 2.40 (td, *J* = 5.5, 3.3 Hz, 1H), 2.16 (d, *J* = 3.3 Hz, 1H) and 1.60 (d, *J* = 5.5 Hz, 1H). In addition, imine (not shown) may also be present with a signal for a methyl group observed at δ 2.02 (br s) and δ 1.99 (d, J = 2.5 Hz). Using the observations from NMR analysis, increased efficiency in the formation of the triazoline ring could be attributed to absence of the acetonide constraint with full conversion to the triazoline complete after 15 min at 90 °C. It is possible that the diol provided increased hydrogen bonding promoting formation of the secondary azide and thus favouring formation of triazoline intermediate **105**.

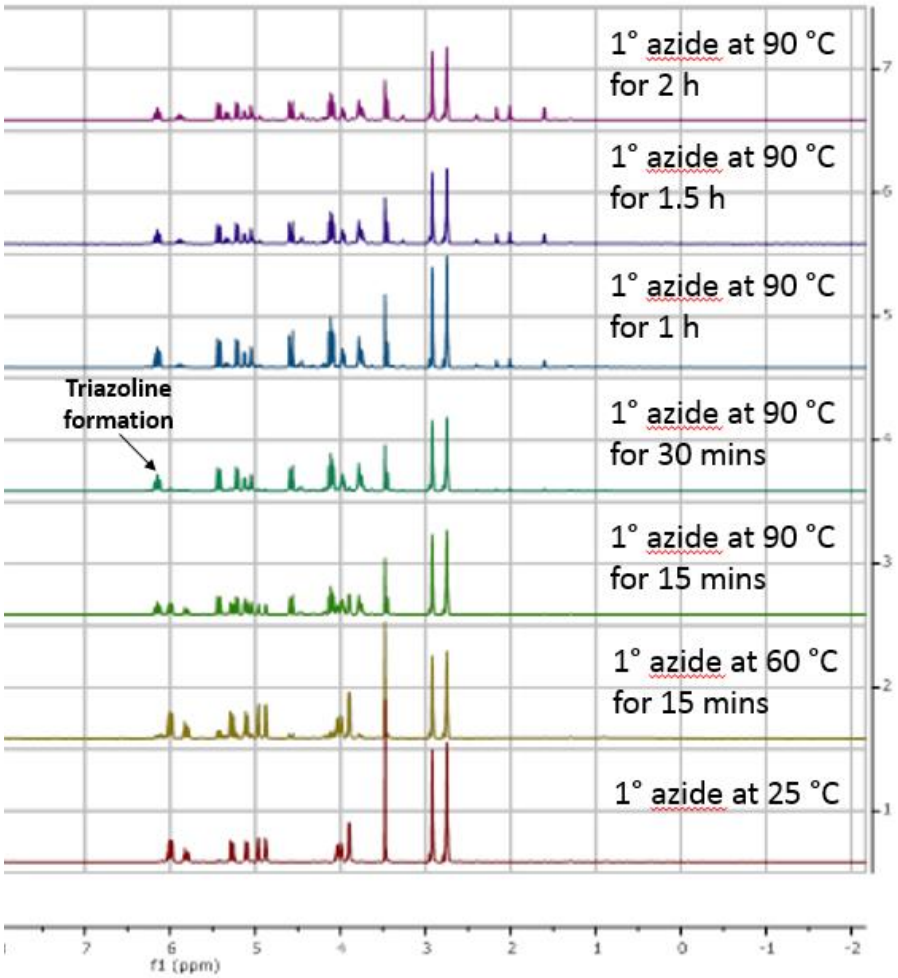
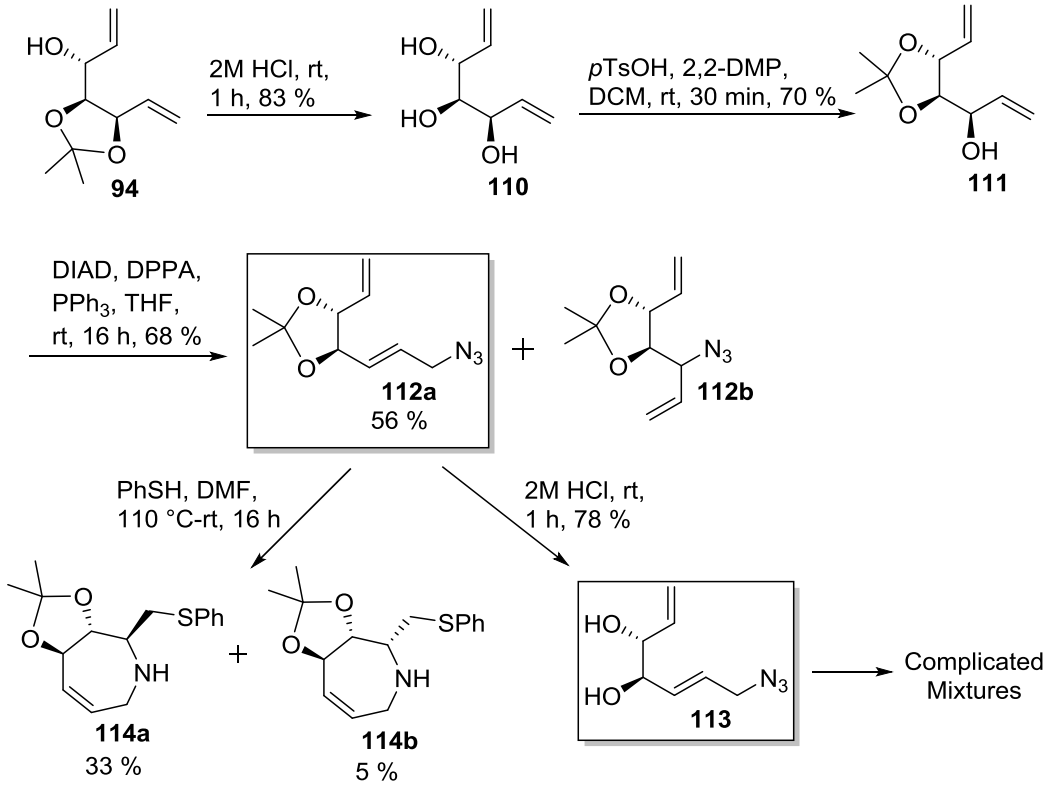


Figure 5.5 NMR reaction monitoring experiment for azide **96** in deuterated DMF from 20-90 °C

5.2.5 Preparation of acetonide 112 and diol 113

Efforts were also made to synthesise the pyrrolidine ring with an isopropylidene constraint, derived from a *trans* diol. To achieve synthesis of the required precursor azide **112a**, **94** was treated with dilute acid to afford **110**. Subsquent to introduction of the *trans*-acetonide moiety in **111**, the isopropylidene derivative was converted to **112** by exchange of the -OH group with azide functionality. The major isomer observed after purification was the *trans* primary azide **112a**. A minor impurity thought to be the secondary azide, **112b**, was visualized using TLC. This product was isolated upon purification *via* column chromatography. However, when NMR analysis of the relevant fractions were performed, a mixture of **112a** and **112b** were observed. **112a** was treated with dilute acid to afford the deprotected azide **113**.



Scheme 5.9 Cycloaddition of **112a** & **113**

5.2.6 Allylic azide rearrangement and cycloaddition of *trans* -acetonide and -diol azides

Attempts to obtain pyrrolidines from **112a** were compromised by formation of azepanes (Scheme 5.9). It is possible **112a** could not form the pyrrolidine intermediate due to a high level of constraint resulting from the presence of the *trans* acetonide in the transition state structure. For this reason, the cycloaddition may prefer to form the azepane triazoline intermediate leading to **114a** and **114b**. Formation of the *cis*-alkene was expected as it is known to be strongly favored compared to the *trans* alternative in small rings.[202] Attempts to form other azepane derivatives from azide **112a** were investigated by varying nucleophiles (AcOH, NaN_3), reaction times and solvents (toluene and DMF), however none were successful. The treatment of **113** with thiophenol led to the formation of numerous inseparable products and thus, unlike the reaction of azide **96** no useful product could be isolated from the reaction. This result suggests that orientation of the hydroxyl groups play a role regarding the feasibility of the rearrangement-cycloaddition.

5.2.7 Deprotection and conversion to salts

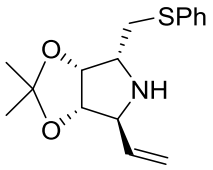
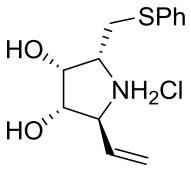
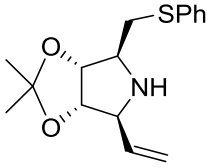
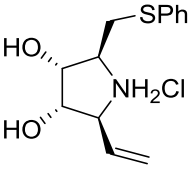
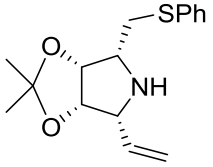
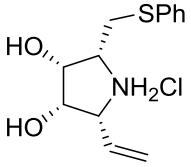
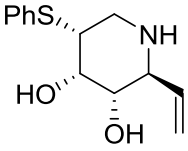
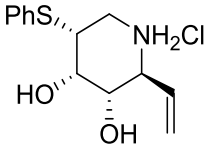
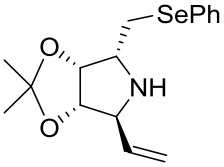
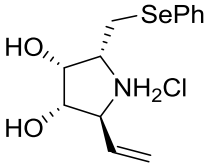
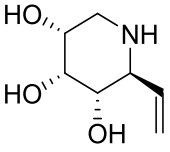
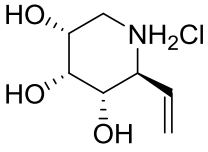
Entry	Precursor	Product
1	 **99**	 **115**
2	 **102**	 **116**
3	 **103**	 **117**
4	 **108**	 **118**
5	 **101**	 **119**
6	 **106**	 **120**

Table 5.3 Conversion of iminosugars to their HCl salts

Due to instability of the iminosugars synthesized, the major products were treated with 1M HCl to remove the acetonide protecting group (where required) and to form the more stable salt counterparts for storage purposes (Table 5.3). The conversion to the HCl salt enabled crystallization of **119** confirming the configuration at C-1 and C-4 (Figure 6.6).

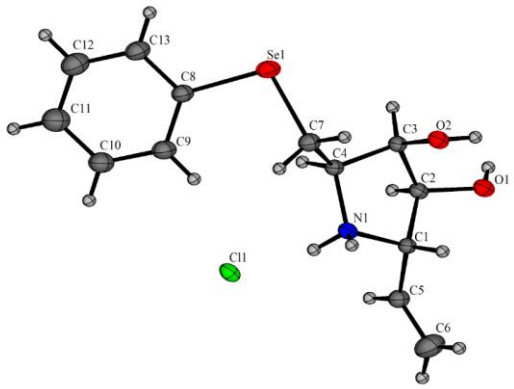
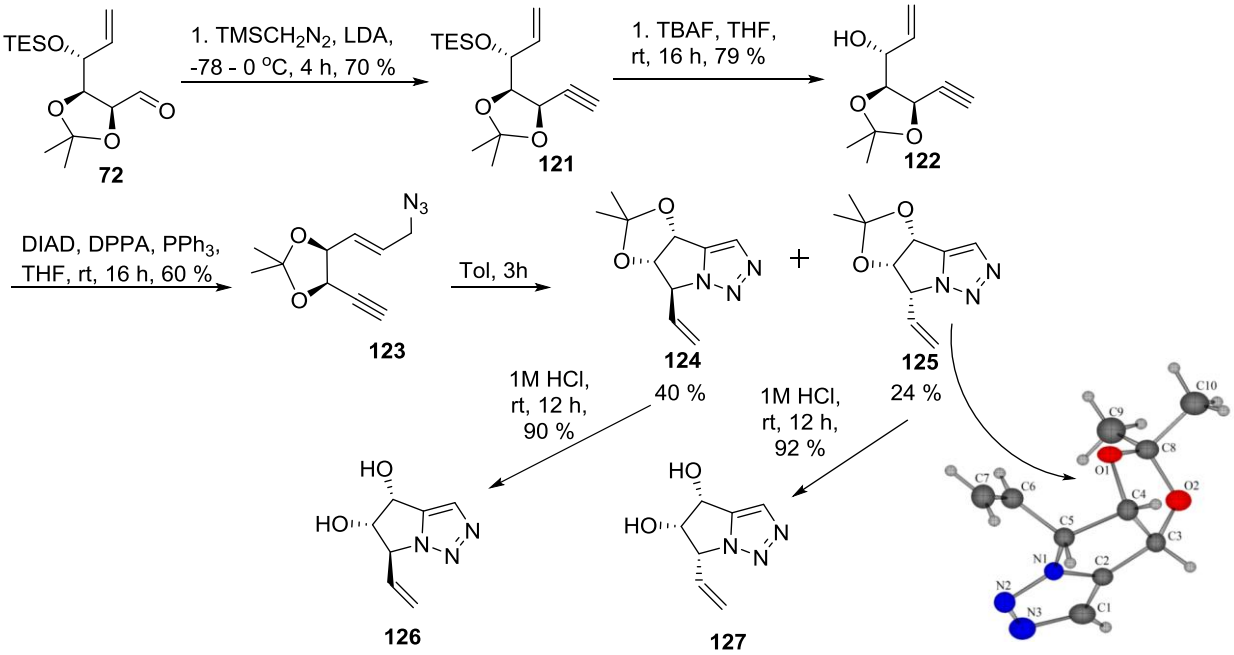


Figure 6.6 X-ray crystal structure of **119**

5.2.8 Allylic azide rearrangement followed by azide-alkyne cycloaddition. Route to dihydropyrrolotriazoles

With pyrrolidine-based iminosugars in hand, prepared by allylic azide rearrangement coupled to Huisgen alkene-azide cycloaddition, it was decided to study the synthesis of their fused-triazole analogues. It was envisaged the triazoles could be prepared as outlined in Scheme 5.10. The sequence commencing from the zinc reductive fragmentation (previously discussed) [189,191] of halogenated-mannopyrannoside **71** to give aldehyde **72**.



Scheme 5.10 Preparation of pyrrolotriazoles and X-ray crystal structure of **125**

Different conditions, such as, Ohira-Bestmann[203] and Corey Fuch[204] reactions were investigated for the conversion of **72** to alkyne **121** but these were unsuccessful. The Colvin procedure performed the conversion successfully yielding **121.**[205,206] The alkyne **121** was deprotected using TBAF to afford **122**. The alcohol **122** was converted to azide **123** by procedures similar to those previously described. The azide **123** was then subsequently heated in toluene to give the triazole **124** and **125** as the major and minor products, respectively.

The stereochemical assignment at C-1 was predicted to be upwards facing for the major product from the cycloaddition of **123**. This orientation was verified by X-ray crystal structure determination of **125**. **124** and **125** were deprotected to yield **126** and **127**, respectively.

5.2.9 Assignment of structures

Identification of ring size and stereochemical orientation were a very important component of the analysis of the products obtained. Analysis carried out for **109** and **118** are provided as typical examples of the use of NMR spectroscopy experiments undertaken to elucidate their structures.

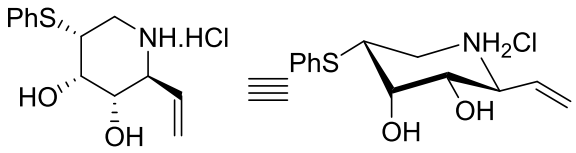


Figure 5.5 Chair conformation of **118**

The spectrum for **118** was recorded in D_2O. Assignments were made for all compounds using COSY, HSQC and HMBC. The observed *J*-values between ring protons indicated that the chair conformation shown in Figure 5.7 was preferred. A *J*-value of 10.6 Hz for $^1H_{1,2}$ (diaxial protons), for example, would only be possible in the conformation shown. The other J-values further supported the shown conformation.

In the case of **118**, HMBC experiments were used to establish its piperidine ring. As shown in Figure 5.6 there is a three-bond correlation between C-1 and H-5 & H-5', protons of a methylene group, but not between C-1 and H-4. A correlation between C-1 and H-4 would have been required for a pyrrolidine ring system.

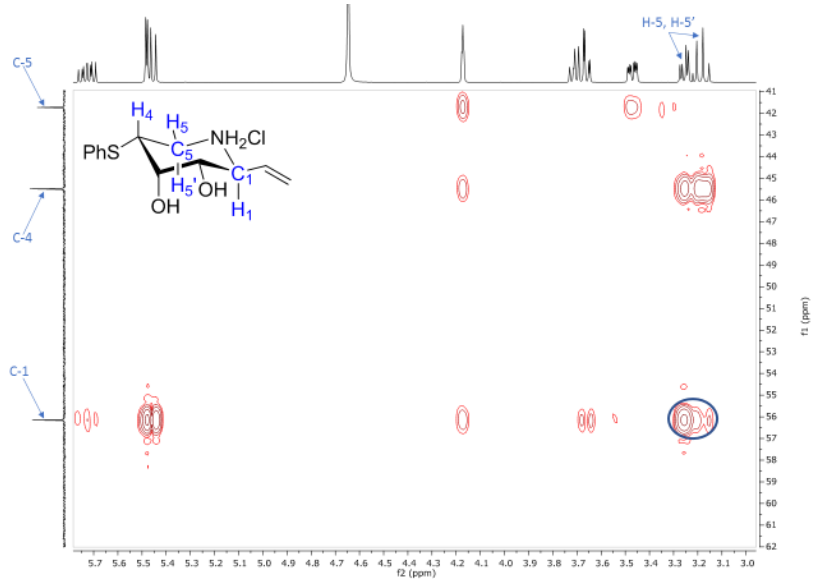


Figure 5.6 HMBC of **118**

From the NOESY experiments for **118** (Figure 5.7) it was possible to see a correlation or crosspeak between H-2 and H-4, implying the -S substituent is equatorially oriented at C-4. There is also a correlation between H-6 and H-2 indicating the vinyl group is equatorially oriented.

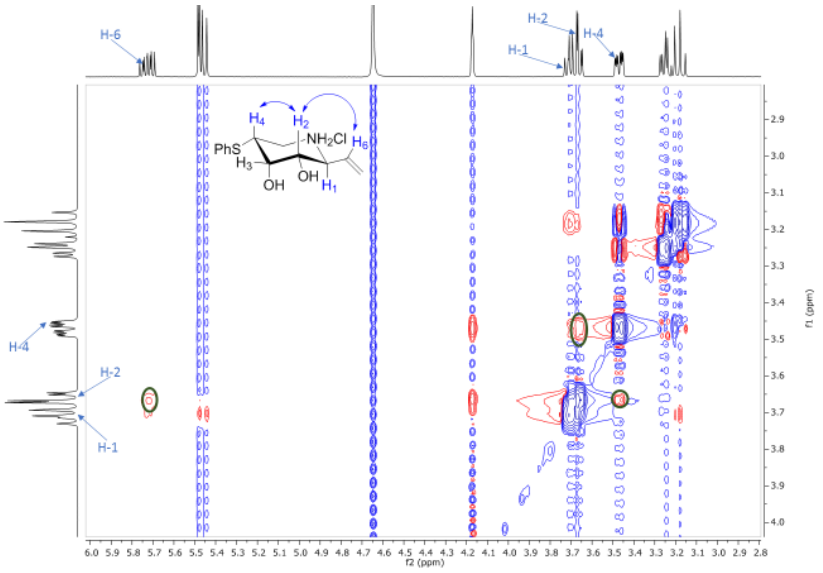


Figure 5.7 NOESY experiments of **118**

In the case of **109**, HMBC (Figure 5.8) showed correlations between C-1 to H-4 indicating pyrrolidine formation. Stereochemistry of the 5-membered rings were addressed in a similar fashion to the equivalent 6-membered systems.

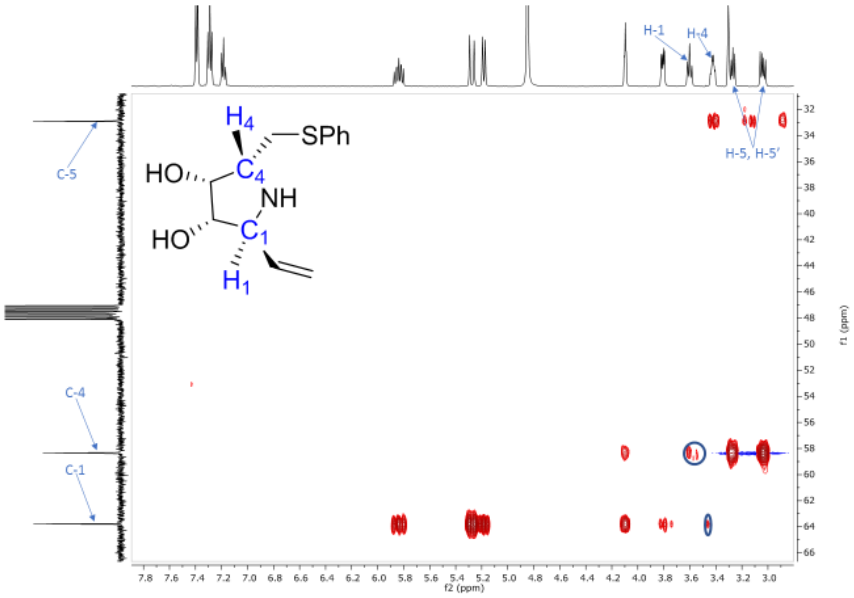


Figure 5.8 HMBC experiment for **109**

Using 1D NOESY experiments (Figure 5.9) it was possible to see correlations between H-2 and H-4 indicating the methylthiophenyl group at C-4 is facing downwards. There is a correlation between H-6 and H-2, indicating the vinyl group is facing upwards.

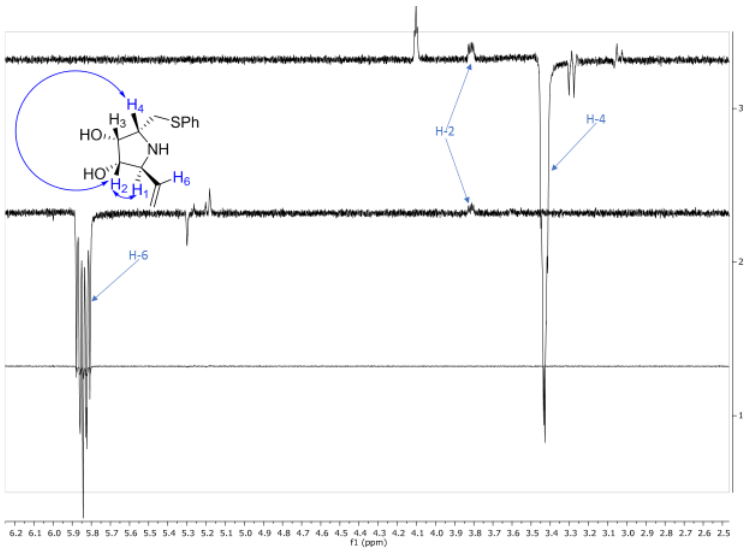


Figure 5.9 1D NOESY experiment for **109**

The orientation of **109** at C-1 and C-4 could be further confirmed by comparison of the ^{13}C NMR of **119** & **115**. As shown in Table 5.4, there is no dramatic difference in the shifts of ^{13}C spectra except for C-5. This outlier could be rationalized by the attached Se and S substituents.

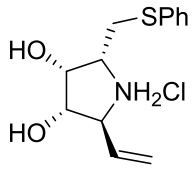
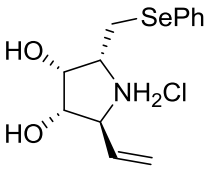
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7
 **115**	63.16	75.47	70.59	59.52	30.59	130.82	122.35
 **119**	63.32	75.51	70.72	60.47	22.83	130.87	122.30

Table 5.4 ^{13}C NMR shifts of **115** & **119**

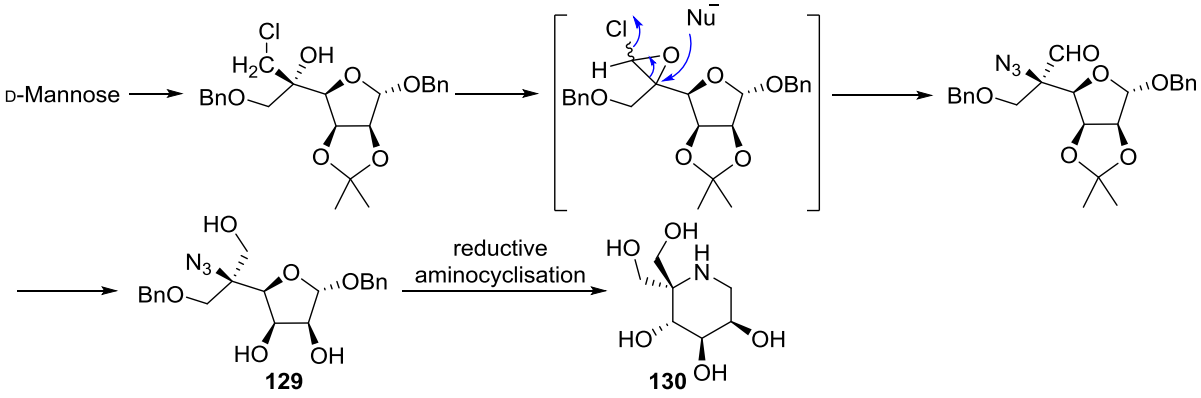
5.3 Conclusion

In summary, this chapter has described our efforts to synthesise C-glycosyl pyrrolidines using the tandem allylic azide rearrangement and the 1,3-dipolar Huisgen cycloaddition. Stereo- and regioselectivity were not as selective as previously reported[184] during the formation of pyrrolidines. However, we have shown capability to manipulate the regioselectivity of the reaction by nucleophile alteration. The orientation at C-1 can be rationalized on the basis of steric hindrance. X-ray crystal structures of **119** and **125** confirmed the preferred stereo-orientation at C-4 and C-1. It has also been established that a diol protecting group is not required for the cycloaddition to proceed with the highest yields achieved from deprotected azide **96**.

Chapter 6 Quaternary-centered iminosugars from D-mannose

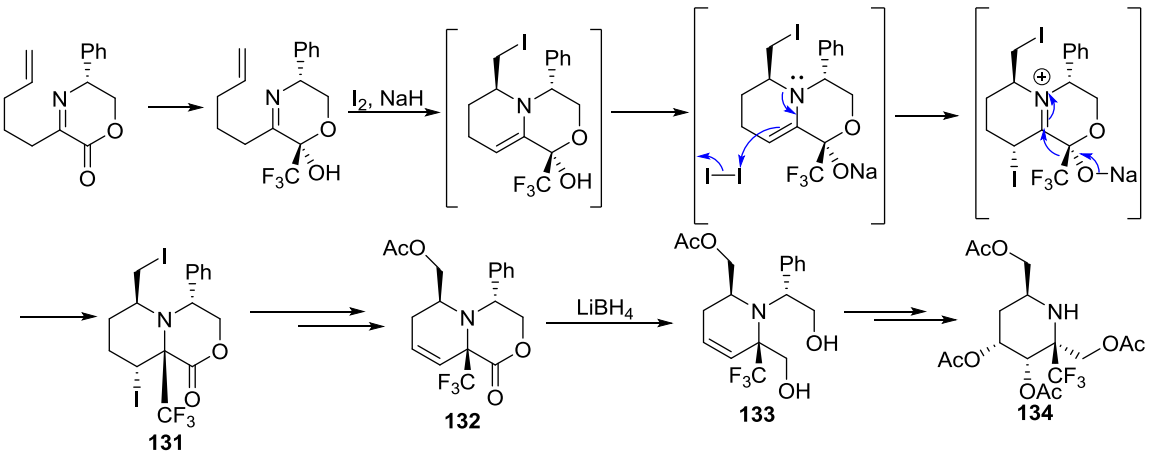
6.1 Introduction

The number of synthetic routes to quaternary-centered piperidine iminosugars derivatives are limited based on the relatively sparse literature published in this area. In 2012, Dhavale[93] reported the first synthesis of α-geminal di(hydroxymethyl)substituted piperidine iminosugars from D-mannose (Scheme 6.1). The α-quaternary piperidine framework **130** could be accessed *via* a one pot transformation of **129** involving: (i) hydrogenolysis at C-1 and C-6 of *O*-benzyl substituents to afford mixtures of hemiacetals, (ii) azide reduction to yield the primary amine and (iii) intramolecular reductive amino cyclisation at C-1 aldehyde and C-5 amine.



Scheme 6.1 Preparation of piperidine iminosugars with a quaternary-centre α to the N-atom by Dhavale and co-workers

In the same year, Aceña and co-workers[94] also prepared a *C*-glycosyl iminosugar based on chiral iminolactones using a carbon trifluoride rearrangement to yield quaternary-centered bicyclic lactone **131** (Scheme 6.2). Subsquent manipulations afforded **132**. The lactone moiety of **132** was then reduced to yield **133**. Relevant manipulations of **133** afforded the acetylated piperidine iminosugar **134** as efforts to isolate the deprotected tetrahydroxylated piperidines proved difficult.



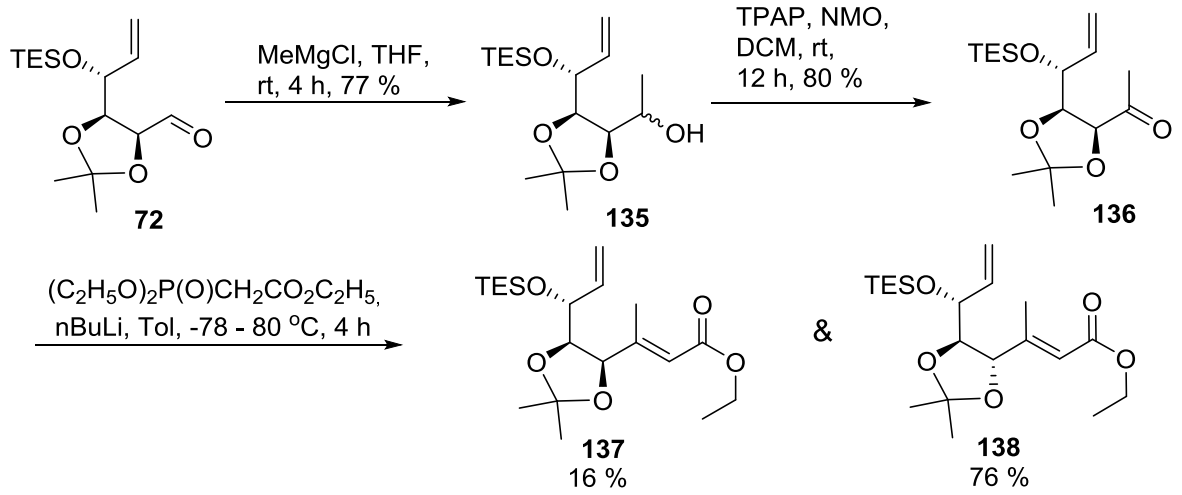
Scheme 6.2 Preparation of peracetylated quaternary centre *C*-glycosyl iminosugars

This chapter describes our attempts to synthesise iminosugars with a quaternary-centre at the anomeric carbon. From existing work by Sharpless and co-workers[178], it was expected that some difficulties would be encountered in the isolation of products forming from tertiary azides (Chapter 3). The synthetic route envisaged was based on procedures that have been previously discussed in Chapter 4 and 5.

6.2 Results and discussion

6.2.1 Preparation of key ester intermediates 137 & 138

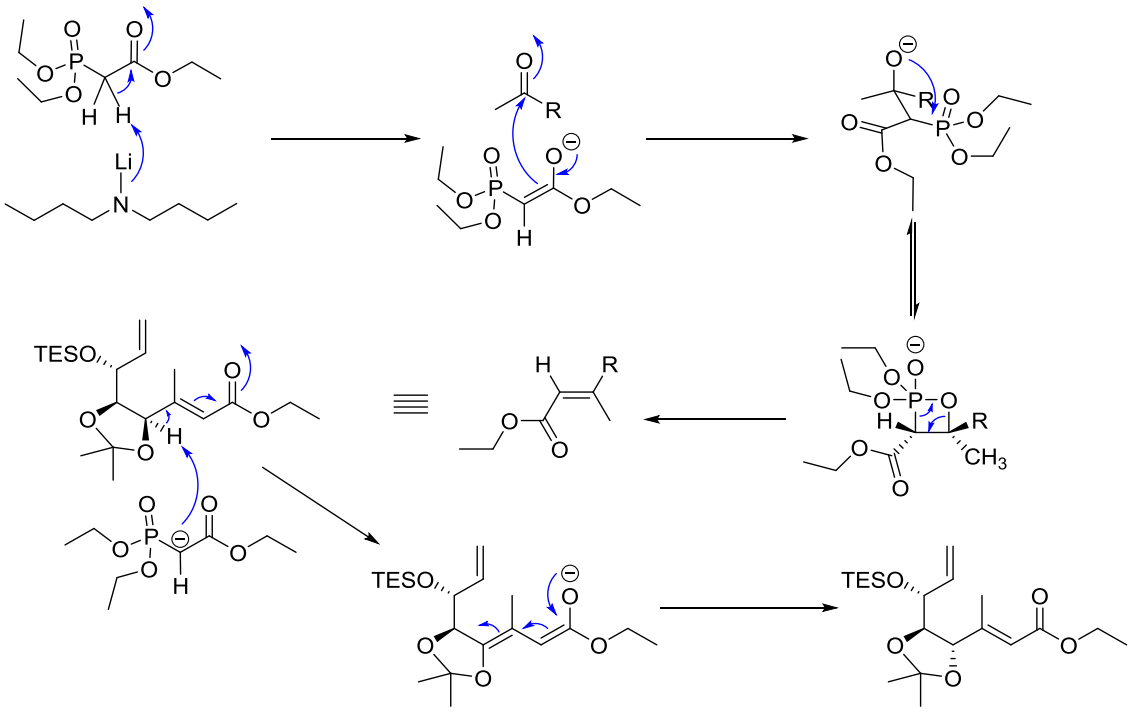
As discussed in Chapter 4, the aldehyde **72** can be easily accessed from methyl D-mannopyranoside in 4 steps. This aldehyde was treated with the Grignard reagent MeMgCl in THF to afford **135** as a mixture of diastereoisomers (45:55). The alcohol **135** was subsequently oxidised to ketone **136** using the Ley-Griffith oxidation reaction.[207] Ketone **136** was then investigated in the preparation of alkene **137**. Both Wittig and Horner Wadsworth Emmons (HWE) reactions were investigated and this included testing various bases (K_2CO_3, NaH, NaHDMS, nBuLi) and temperatures with a view to optimise preparation of **137**. The highest yield of **137** (16 %) could be obtained from the reaction of triethylphosphonacetate with n-butylithium at -78 °C followed by addition of **136** and subsequent heating to 80 °C. The *E*-olefin geometry of the esters was confirmed using 1D NOESY experiments. The diastereoisomer **138**, which resulted from epimerisation of the carbon atom α to ketone was found to be formed in high yield (76%).



Scheme 6.3 Preparation of ester intermediates **137** and **138**

In attempt to understand the mechanism of this transformation, **136** was heated to 80 °C in toluene for 8 h and ^{1}H NMR spectroscopic analysis did not show any evidence that epimerisation had occurred at the carbon atom α to ketone by simply heating alone. This suggests that epimer **138** does not result from simple heating of **136**. As basic conditions were the most likely source of the epimer **138**, base-sensitive Masamune-Roush conditions[208] were employed (using 1 equiv. of DBU or DIPEA in combination with LiCl). In this case, the epimerised **138** was the only product observed. Based on

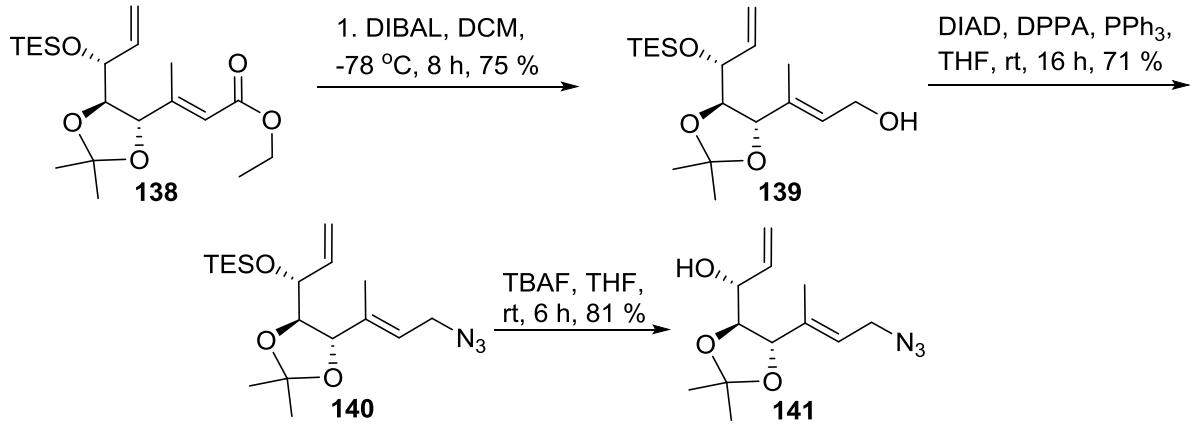
these findings it was possible to deduce that a plausible mechanism for this HWE reaction is as shown in Scheme 6.4. The epimerisation at carbon α to the ester could happen as a result of the HWE reagent. The capability of the HWE reaction to induce epimerisation has previously been reported by Etayo and Gálvez.[209] With ester intermediates **137** and **138** in hand it was decided to attempt the synthesis of both glucose and mannose configured iminosugars from these precursors.



Scheme 6.4 Mechanism for epimerisation at C_2 in the HWE reaction

6.2.2 Preparation and cycloaddition of azide 141 with isopropylidine restraint anchored on the 2,3-diol

As outlined in Scheme 6.5, reduction of **138** in the presence of dibal-H afforded **139**. Mitsunobu type conditions[181] were utilised to displace -OH moiety and yield azide **140**. TBAF was then employed to remove the triethylsilane protecting group providing access to the precursor azide **141.**



Scheme 6.5 Preparation of precursor azide **141**

Heating of **141** in both DMF and toluene lead to formation of cyclised triazoline intermediate (previously discussed in Chapter 5) on the basis of TLC analysis. Attempts to isolate these intermediates were not successful, as attempts to do so only led to recovering of the starting material azide. Higher temperatures were investigated (105-120 °C) to promote completion of the cycloaddition, however these conditions led to decomposition. As the triazoline intermediates could not be isolated, cycloaddition to the piperidine was attempted in the presence of acetic acid as the nucleophile and the results from **141** are summarised in Table 6.1.

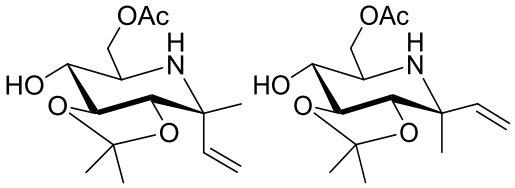
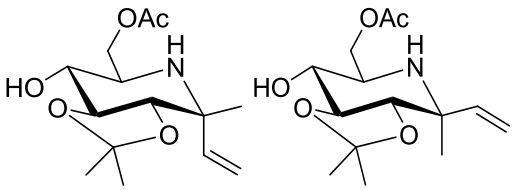
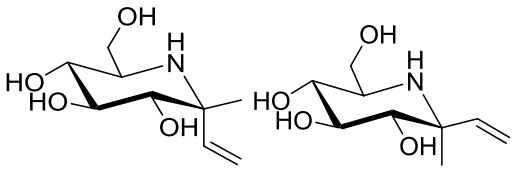
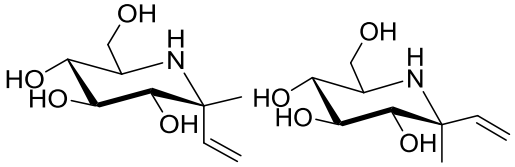
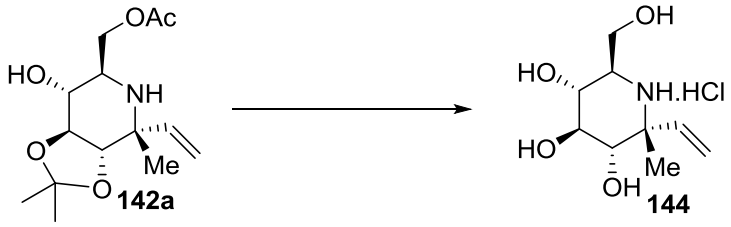
Entry	Reaction Conditions	Products and isolated yields
1	1. AcOH (5 equiv), Tol, 100 °C, 4.5 days	 **142a** 30 % **142b** 4 %
2	1. AcOH (5 equiv), DMF, 100 °C, 4.5 days	 **142a** 15 % **142b** 2 %
3	1. AcOH (5 equiv), Tol, 100 °C, 4.5 days 2. 2M HCl, 12 h	 **143a** **143b** 0.79 : 0.21 55 %
4	1. AcOH (5 equiv), DMF, 100 °C, 4.5 days 2. 2M HCl, 12 h	 **143a** **143b** 0.79 : 0.21 30 %

Table 6.1 Cycloaddition of azide **141**

DMF and toluene were both investigated as solvents for the reaction (Table 6.1). Higher yields were observed using toluene. Monitoring of the reaction by TLC indicated that removal of the protecting group was occurring competitively during the cycloaddition. Prolonged exposure to high temperatures and acidic conditions were thought to be the reason for protecting group cleavage as evidenced by low

yielding transformations (Table 6.1, entries 1 and 2). Thus, it was considered that removing the acetyl and isopropylidene protecting groups immediately after the cycloaddition could limit loss of product and give higher yields of piperidine. As shown (entry 3, Table 6.1) this approach yielded iminosugars **143a** & **143b** in a higher total yield of 55% compared to entries 1 & 2, although inseparable mixtures of stereoisomers were obtained. It is important to note that maintaining of temperature ≤100 °C for the cycloaddition proved to be important, as heating over this temperature led to significantly reduced yields. Treatment of **142a** in aqueous HCl at rt for 16 h and subsequent removal of solvent under reduced pressure afforded salt **144** as yellow foam.



Scheme 6.6 Preparation of salt **144**

The stereochemical outcome of the cycloaddition reaction could be rationalised using Newman projections (Figure 6.1) and by considering the substituent A-value[210,211] which is 1.7 for a methyl group and 1.52 for a vinyl group, indicating that the methyl group is bulkier. Therefore, on the basis of steric hindrance of the transition state structures, the major product should place the methyl group upwards to minimise gauche interactions in the transition structure.

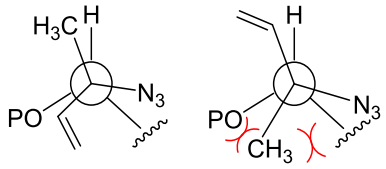


Figure 6.1 Newman Projections of potential stereoisomers from tertiary allylic azide **141**

NOESY experiments were used to support the stereochemical assignment at the anomeric carbon. In spectra of **142b** (Figure 6.2), strong cross peaks between -CH_3, H-3 and H-5 indicated the methyl group at the anomeric carbon is downwards facing.

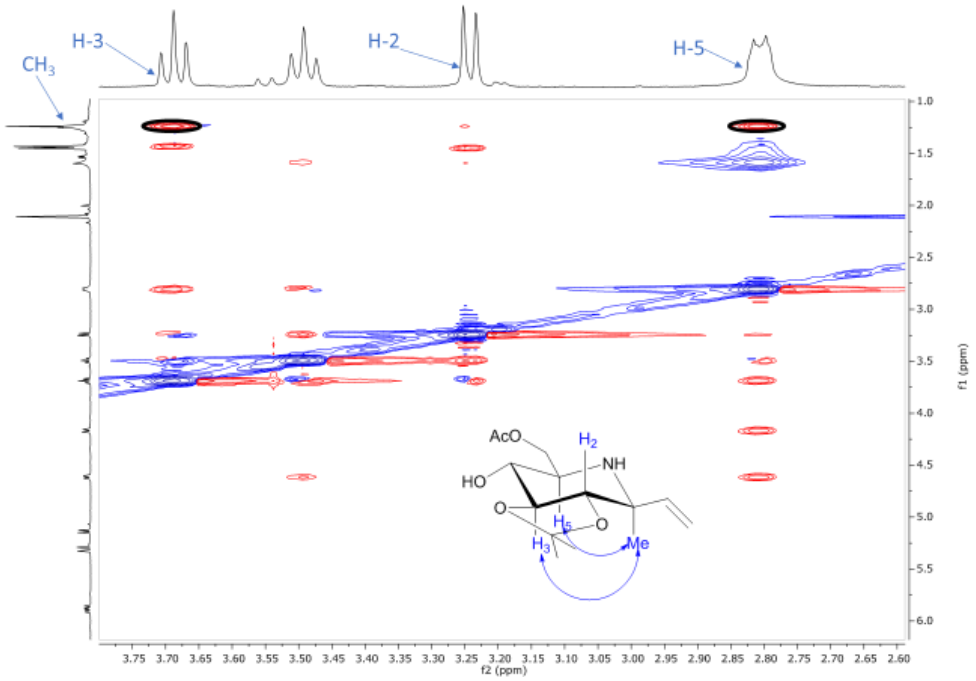


Figure 6.2 NOESY experiment for **142b**

In contrast NOESY experiments for **142a** (Figure 6.3) showed strong crosspeak correlations between H-2 and -CH_3, indicating the methyl group is facing upwards. This was further confirmed by crosspeaks between H-5 and H-8 and H-7. The latter correlation signifying the axial orientation of the vinylic substituent.

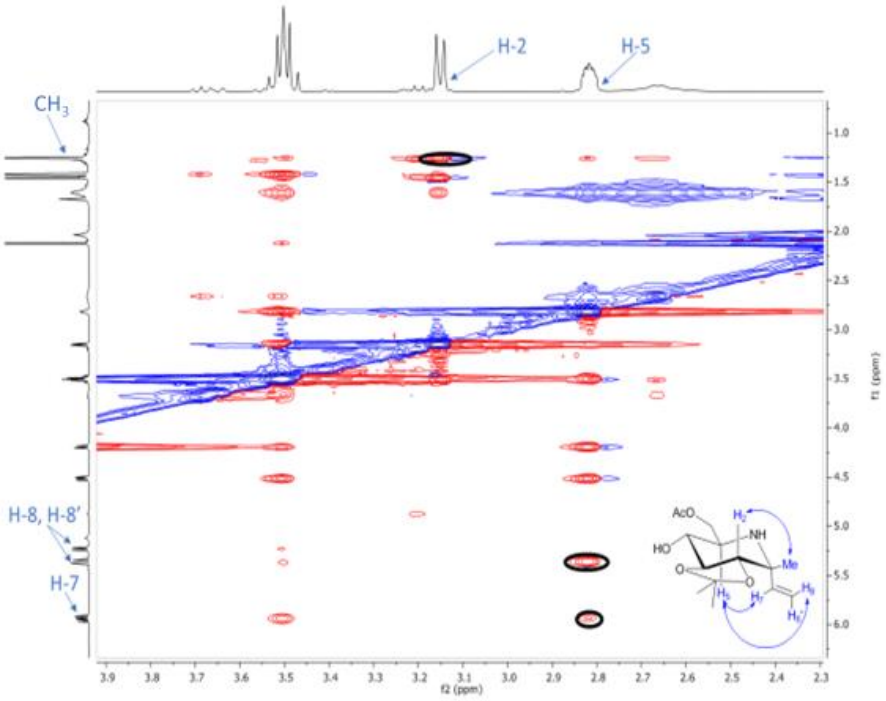
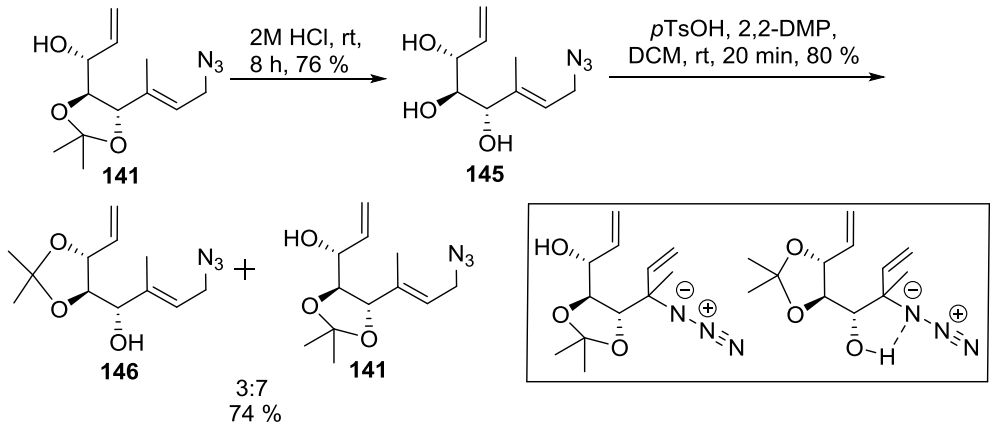


Figure 6.3 NOESY experiment for **142a**

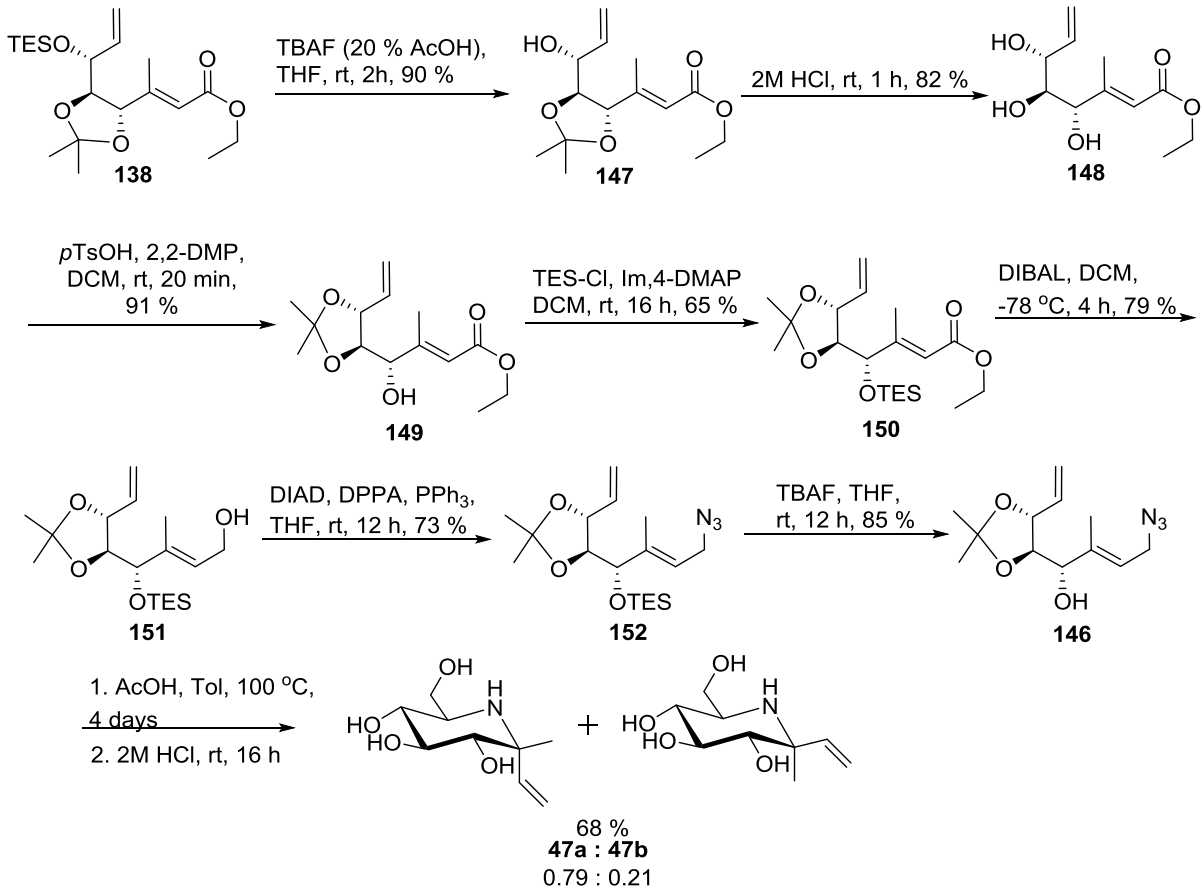
6.2.3 Preparation and cycloaddition of azide 141 anchored with an *trans* isopropylidine restraint on the 3,4-diol

While efforts of the cycloaddition from **141** were promising, modification of the position of the isopropylidine on azide **141** was proposed with a view to investigating if a higher yielding reaction occurred. Based on previous literature reports[177,178] and our results from Chapter 5, placing the free -OH group in closer proximity to the N_3 functionality was expected to increase the amount of hydrogen bonding thus promoting conversion of primary azide to the tertiary counterpart (Scheme 6.7). Initially, azide **141** was deprotected by treatment with dilute HCl to afford **145**. Attempts to install the isopropylidine group on the 3,4-diol were non-selective with a mixture of the acetonide products **141** and **145** observed.



Scheme 6.7 Non-stereoselective protection of azide **145** and reacting conformers from **141** and **146**

In an attempt to synthesise the desired *trans* 3,4-isopropyl protected diol it was expected an electron-withdrawing substituent should be implemented near C-2 to prevent anchoring of the isopropyl substituent on the 2,3-diol. To achieve this, ester **138** was deprotected using a combination of TBAF/acetic acid to attain **147**. This ester was subjected to 2M HCl to provide **148**. Selective installation of the acetonide protecting group on the 3,4-diol was subsequently observed by treating **148** with a catalytic amount of acid in 2,2-DMP and DCM. The -OH group at C-2 of **149** was then protected with triethylsilane to yield **150**. Ester **150** was subsequently subjected to the same conversions as **138** *via*. **151**-**152** to afford azide **146**. This azide was treated using similar conditions as optimised previously (Table 6.1) to afford the desired iminosugars as a mixture of isomers (0.79:0.21) with higher yields (68 %).

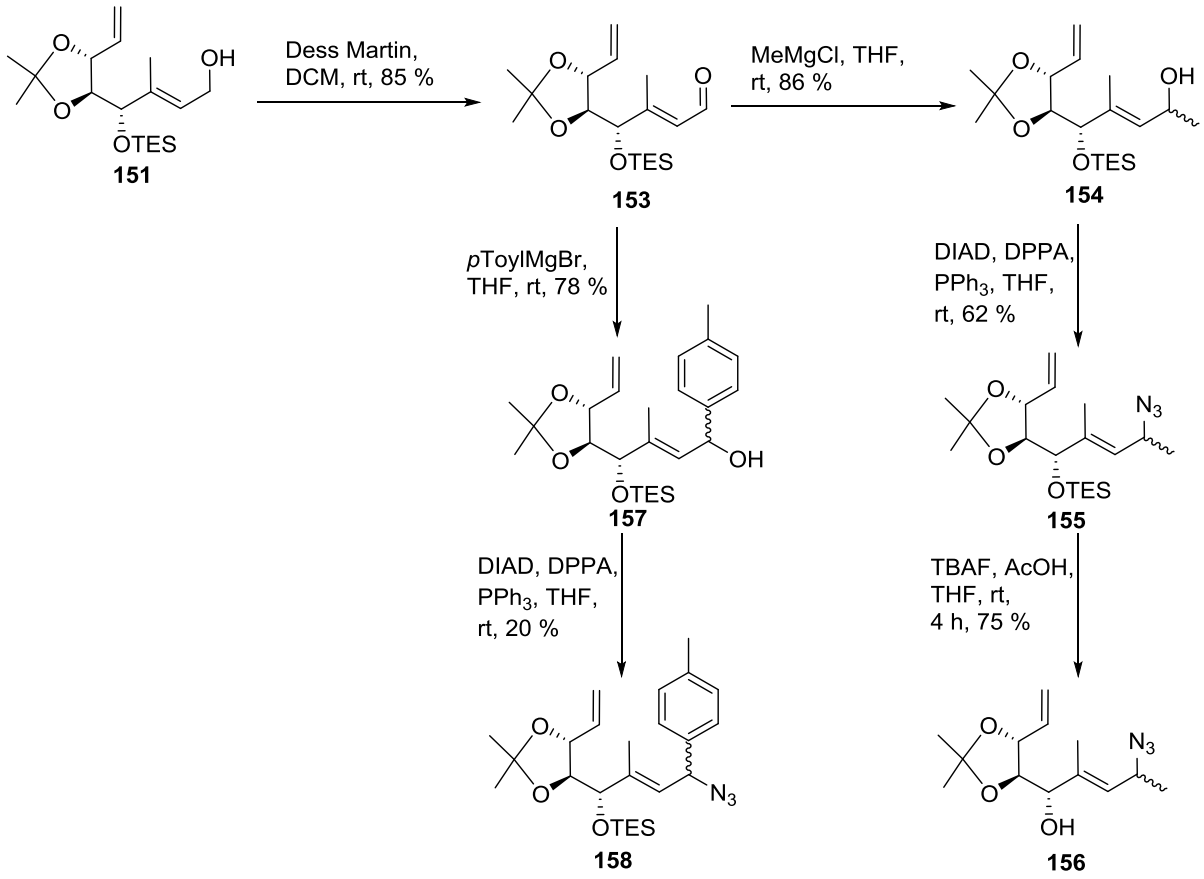


Scheme 6.8 Preparation of piperidine derivatives from *trans* 3,4-acetonide protected diol **146**

6.2.4 Preparation and cycloaddition of substituted azides

Attempts to improve reaction times, yields and selectivities were further investigated. Based on previous reports[178], 2° azides could be utilised as a means of improving conversion rates to the 3° counterpart. Moynihan[181] in her PhD thesis work had previously attempted this strategy to increase reaction yields however it was found to be unsuccessful.

Alcohol **151** was subjected to Dess Martin oxidation and afforded **153**. The aldehyde **153** was subsequently subjected to the Grignard reaction conditions to achieve formation of **154** as a mixture of stereoisomers. Alcohol **154** underwent the same transformations as **151** to afford **156** *via*. **155**. Similar reaction conditions as previously shown (Table 6.1) were implemented and this gave the iminosugar products (Table 6.2), which were isolated after hydrogenation reaction using Pd-C and H_2.



Scheme 6.9 Preparation of azides **158** and **156**

As shown, various protected iminosugars **159a**, **159b** and **160** were isolated but in lower yields in comparison to the cycloaddition from **146**. It is possible this result can be attributed to cleavage of the acetonide protecting group under the acidic reaction conditions of the cycloaddition. The formation of **159a** and **159b** could be rationalised by the migration of the acetonide protecting group. Products **161a** and **161b** were also formed from the conversion of azide **156** without any chromatographic purification pre-deprotection and after acetate and acetonide removal using aq. HCl. This led to an improvement in yield compared to that in entry 1.

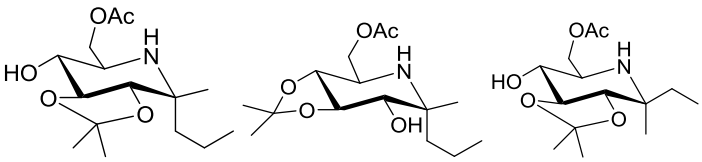
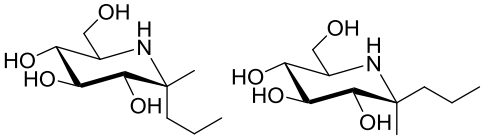
Entry	Reaction Conditions	Results
1	AcOH (4 equiv), Tol, 100 °C, 4 days Pd-C, MeOH, H_2, 2 h	 0.45 : 0.36 : 0.19 **159a**: **160** : **159b** (30 %)
2	AcOH (4 equiv), Tol, 100 °C, 4 days Pd-C, MeOH, H_2, 2 h 2M HCl, 16 h	 71 : 29 **161a** : **161b** (44 %)

Table 6.2 Cycloaddition of **156**

NOESY experiments were used to verify the stereochemical assignments of the products. As shown in Figure 6.4, a strong crosspeak exists between -CH_3 and H-2 in the major product. This correlation suggests the major product has the methyl substituent equatorially orientated. The minor product shows a strong crosspeak between -CH_3 and H-3, H-5. This indicates the methyl group is axially orientated in the minor product.

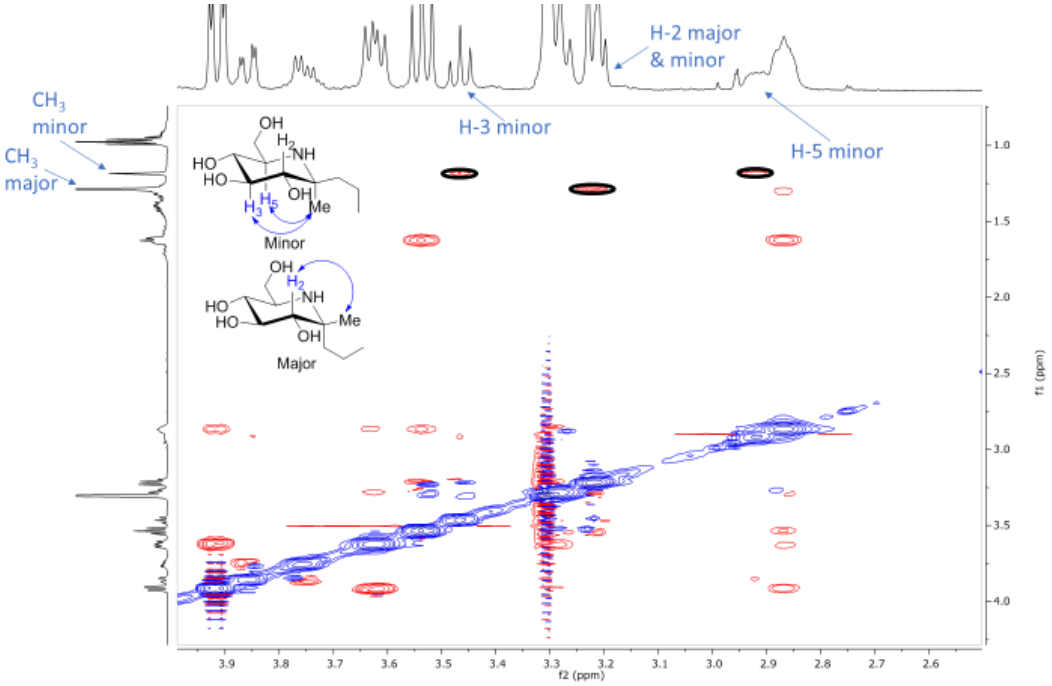


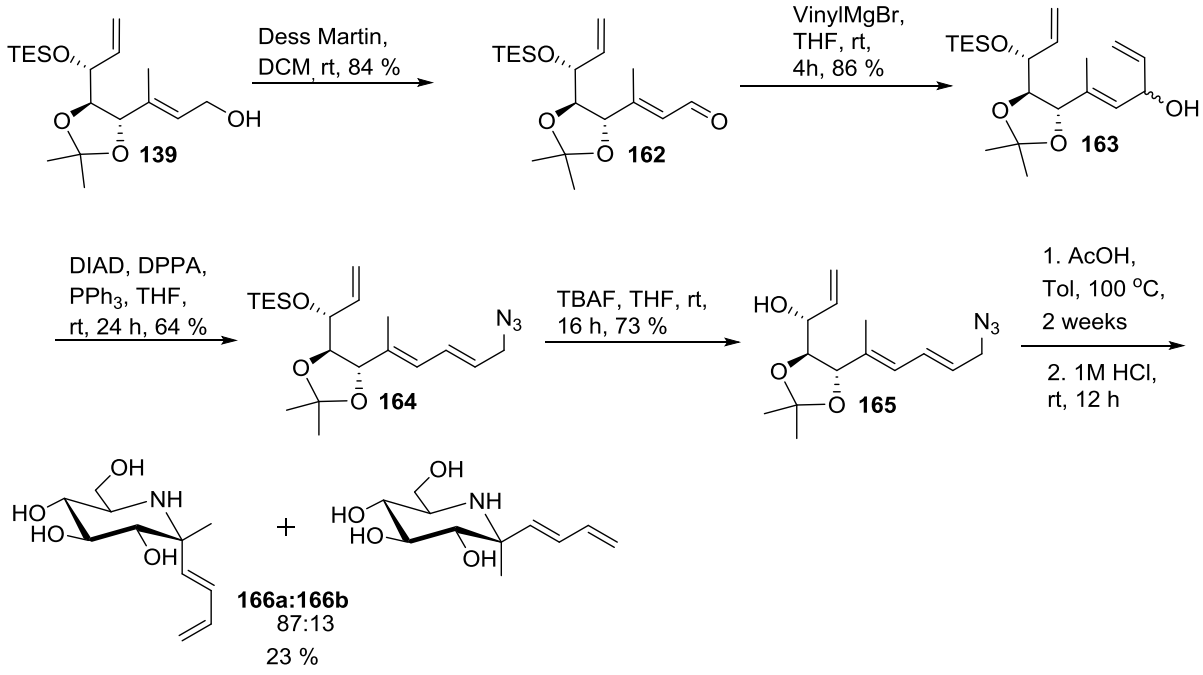
Figure 6.4 NOESY experiments of **161a** and **161b**

In an attempt to further promote the conversion of the azide, a *p*-toluoyl group was employed. To synthesise the toluoyl moiety, aldehyde **153** was reacted with the appropriate Grignard reagent to afford **157** as a mixture of isomers. Further transformations using Mitsunobu type conditions to afford azide **158** were undertaken. However, this azide reacted at room temperature and attempts to convert it to piperidines were made but no productive product could be identified upon NMR analysis. While the reaction did not give rise to piperidines, it was encouraging that transformation to the intermediates of the rearrangement and cycloaddition could be achieved at room temperature as observed by ^{1}H-NMR analysis.

The use of diene **165** was also investigated as to whether it would undergo the tandem rearrangement-cycloaddition. This azide was synthesised from **139** (through intermediates **162-164**) as shown in Scheme 6.6, using similar conditions to those previously discussed for the preparation of azide **156**.

The rearrangement-cycloaddition of **165** was investigated and TLC analysis showed that even after prolonged heating (2 weeks) of **165** in toluene in the presence of acetic acid, starting material was still remaining. Due to degradation of intermediates (as observed by TLC) the cycloaddition was stopped at

this point and subsequent treatment with HCl (aq), yielded **166a** the desired iminosugar with a minor impurity, suggested to be the minor anomer **166b**. These anomers were inseparable.



Scheme 6.6 Preparation of azide **165** and cycloaddition to form **166a** & **166b**

The use of NOESY experiments supported this structural assignment. As shown in Figure 6.5, in the major product there is a stronger cross peak between H-3 and H-7 in comparison to the cross peak between H-7 and overlapping H-2 and H-4. This suggests H-7 is downwards facing thus the diene substituent would be axial orientated in the major product. In the minor product, no cross peak is observed between H-7 and H-3 but a strong cross peak exists between H-7 and the overlapping H-2 and H-4 signal. This verifies the diene substituent as upwards facing in the minor product. Although the yield and reaction time were poor for this cycloaddition, the selectivity observed was higher than other examples shown above.

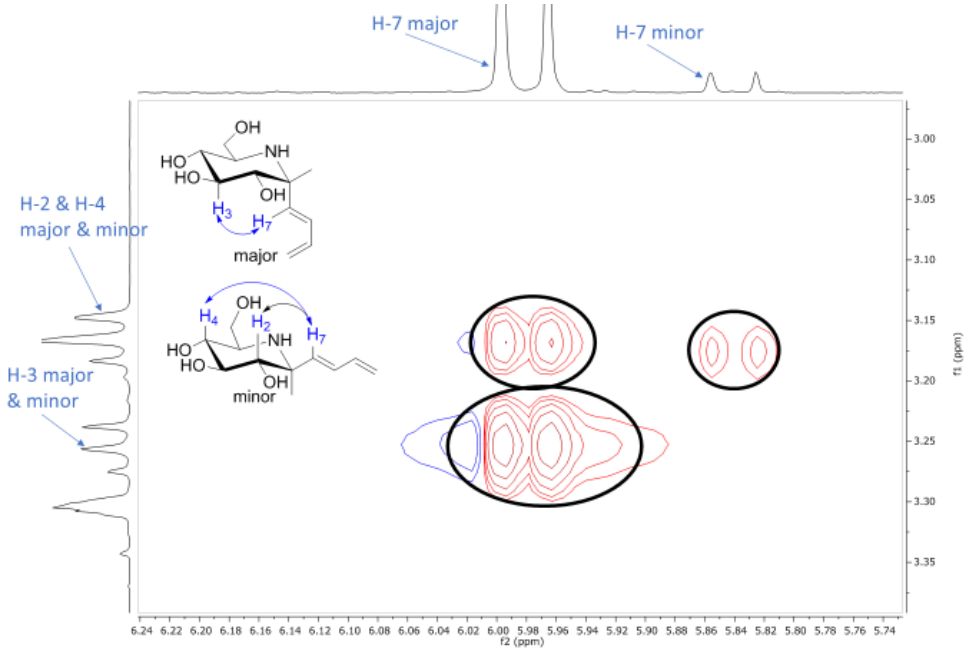
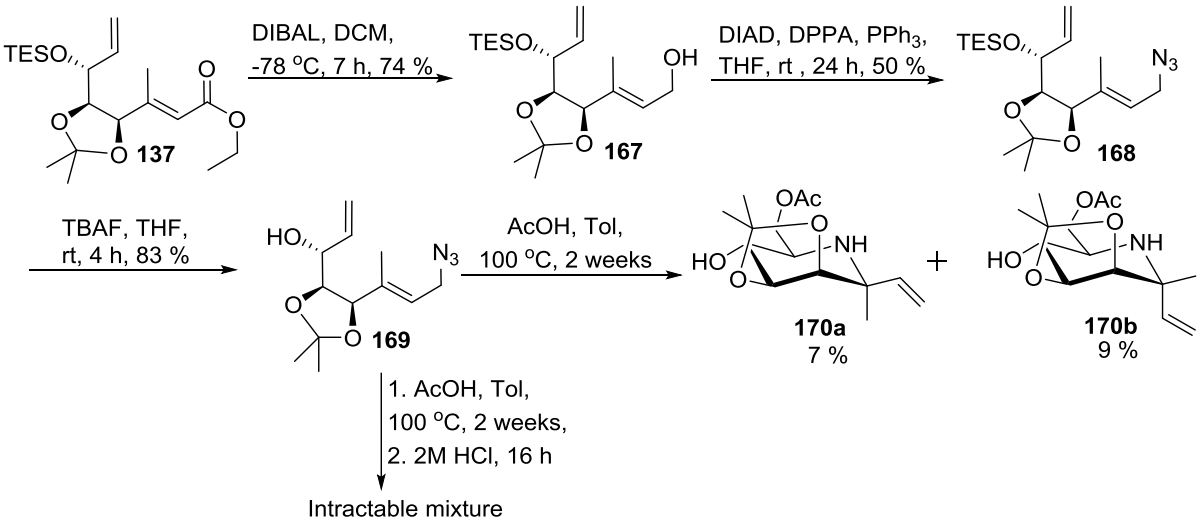


Figure 6.5 NOESY experiment of **166a & 166b**

6.2.5 Preparation and cycloaddition of mannose substrates 169 and 172

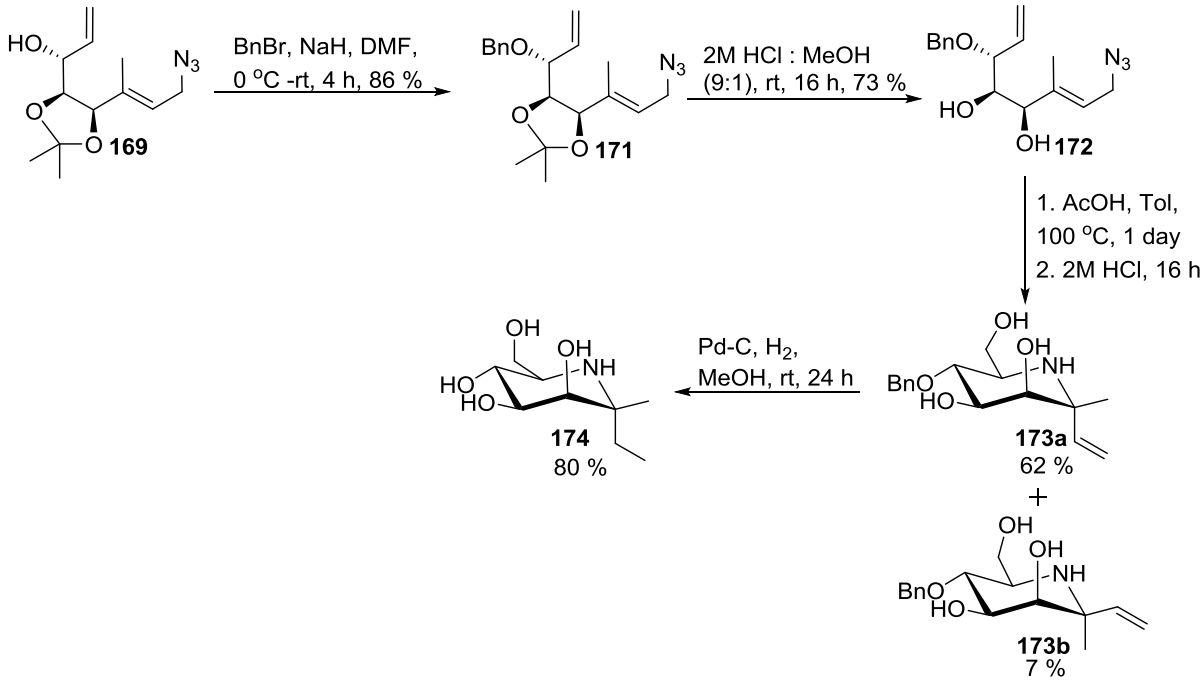
Due to the success of the allylic azide rearrangement coupled to the Huisgen azide-alkene cycloaddition to synthesise quaternary-centre containing iminosugars with glucose configuration, **137** was subjected to a similar reactions **138** (through intermediates **167-169**) in an attempt to achieve the analogous mannose derivatives. Isolation of the protected iminosugar intermediates **170a** and **170b** was achieved but the reaction was low yielding and slow. The analysis of the reaction using TLC indicated incomplete conversion of **169**. Poor selectivities were also observed for this cycloaddition. Conversion of azide **165** under conditions that would give the fully deprotected iminosugar (without any purification pre-deprotection) led to intractable mixtures.



Scheme 6.7 Preparation and cycloaddition of azide **169**

Due to the poor yields, reaction times and selectivities obtained in the preparation of the mannose derivatives, it was decided to explore a different substrate. In the previous chapter, it was shown that removal of the acetonide conformational restraint could lead to improved Huisgen cycloaddition (Chapter 5, Table 5.2). It was also envisaged (based on previous results, see Chapter 5) that selection of a non-polar solvent such as toluene, could suppress products resulting from the S_{N1} pathway. As such precursor azide **172** was prepared with a benzyl moiety inplace, to increase the solubility of the precursor azide in toluene. Furthermore, the isopropylidine restraint was removed in an attempt to improve formation and breakdown of the triazoline intermediate.

To synthesise the azide precursor **172**, a benzyl group was initially installed on **169**. The isopropylidene protecting group was subsequently removed from **171** to yield **172**. Notably, the cycloaddition of **172** proceeded with increased yields, selectivity and shorter reaction times. However, the stereochemistry observed at C-1 was unexpected based on previous observations in the formation of mannose derivatives where the bulkier group (CH_3) showed a preference to be axial in the piperidine product. Based on previous results from **169** (Scheme 6.7**)**, **173b** might have been predicted to be the major product. It is uncertain why this transformation is an outlier. Hydrogenation of **173a** provided access to the deprotected iminosugar **174**.



Scheme 6.8 Preparation and cycloaddition of **172**

2D NOESY experiments and ^{1}H NMR *J* values were used to determine the stereochemical assignment of **173a** and **173b**. Upon analysis of the ^{1}H NMR spectrum of **173a**, the signal for H-4 (δ 3.64 (t, J = 9.7 Hz, 1H)) and H-5 (δ 2.70 (ddd, J = 10.1, 4.2, 2.8 Hz, 1H)) indicated the $J_{4,5}$ as approximately 9.9 Hz. A *J* value of this magnitude could only be possible if the orientation of H-5 is axially orientated.

Subsequent 2D NOESY experiments showed a cross peaks between H-5 and H-7, H-8 & H-8', indicating the vinylic substituent is downwards facing. A weak cross peak was also evidence between CH_3 and H-4 equatorial orientation of the methyl substituent at the anomeric carbon.

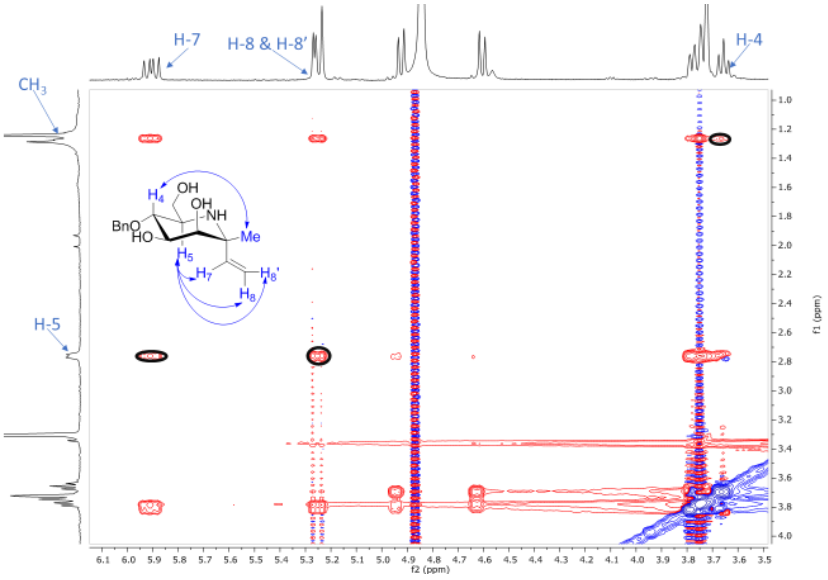


Figure 6.6 2D NOESY experiment for **173a**

In the case of the contending minor anomer **173b**, the ^{1}H NMR spectrum showed signals for H-4 (δ 3.69 (t, J = 9.8 Hz, 1H)) indicating the $J_{4,5}$ as 9.8 Hz. As mentioned previously, a J value of this magnitude could only be possible if the H-5 is downwards facing. 2D NOESY experiments were also performed on the minor anomer **173b**. As shown in Figure 6.7, strong correlations were observed between the methyl substituent on the anomeric carbon and H-2, H-3 and H-5, indicating the methyl substituent is downwards facing in **173b**.

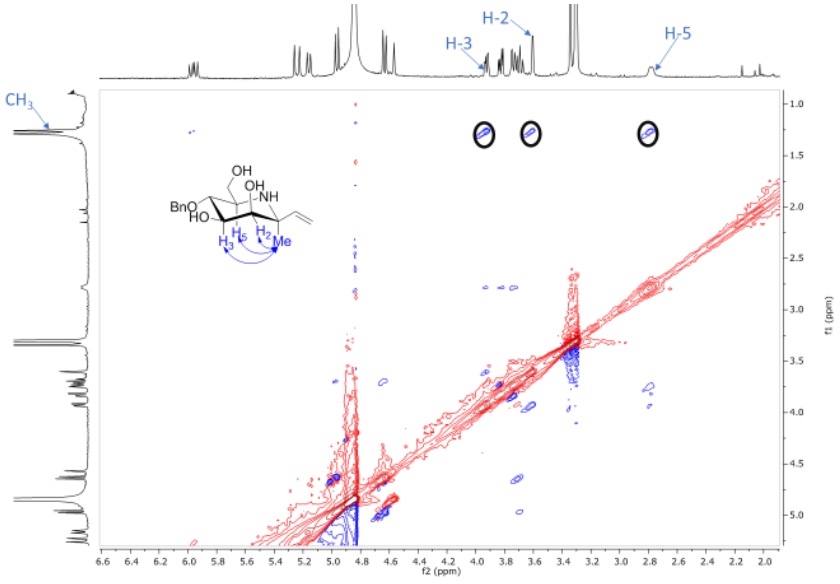
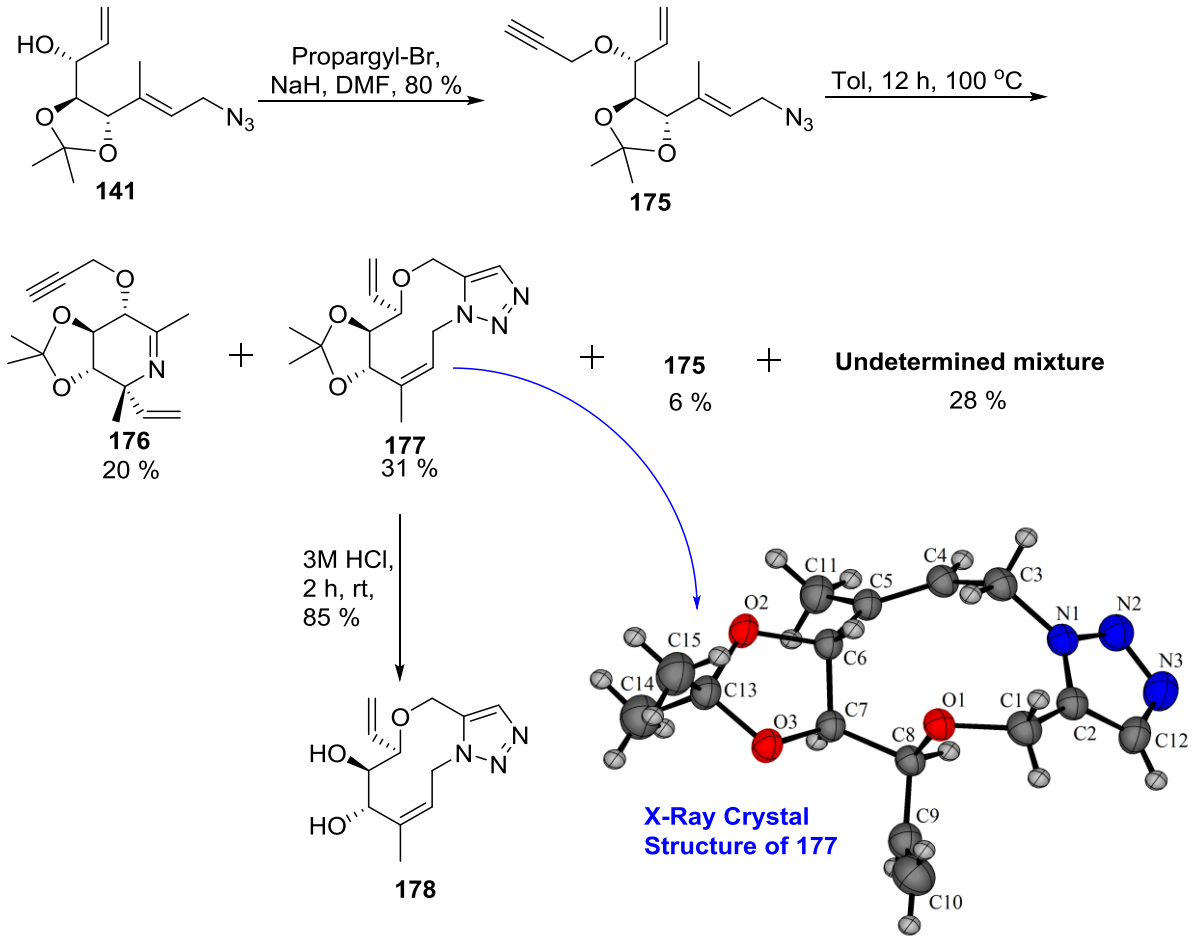


Figure 6.7 2D NOESY experiment for **173b**

6.2.6 Competitive reaction: azide-alkyne vs. azide-alkene

A couple of easily accessible compounds containing the allylic azide with both alkyne and alkene functionalities were also prepared with a view to determining the relative reactivities of dipolarphiles in the intramolecular Huisgen cycloaddition reaction with azides. The azide precursor **175** was synthesised by protection of free -OH in **141** with a propargyl group. Heating of the azide for 12 h in toluene lead to a number of products. The major product obtained was the 10-membered ring **177** (31 %). X-ray crystallography was used to confirm the structure of **177** (Scheme 6.9). The imine **176** and unreacted azide **175** were also isolated. The stereochemical assignment of imine **176** was determined using 2D NOESY experiments. The 10-membered ring system **177** was deprotected using dil HCl to provide **178**.

This particular model suggests reactivity of the alkyne is greater than that of the alkene. However, this example could have been affected by a decreased conversion rate of primary to teritary azide as no -OH group was available for intramolecular H-bonding with the azide functionality.



Scheme 6.9 Cycloaddition of azide **175** and X-ray crystal structure of main cycloaddition product **177**

To further investigate this model, azide **181** was prepared (Scheme 6.10). Alcohol **149** was treated with sodium hydride and propargyl bromide to afford the alkyne **179**. This alkyne was subjected reduction

with dibal-H to yield **180** which was subsequently subjected to Mitsunobu-type reaction conditions to achieve the synthesis of **181**. However, upon cycloaddition of the azide 2 isomeric products were obtained **182a** and **182b**. The stereorientation of these products could be confirmed using 2D NOESY experiments and the preference could be explained using Newman projections (Figure 6.8).

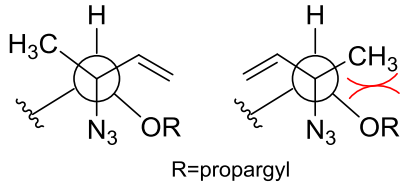
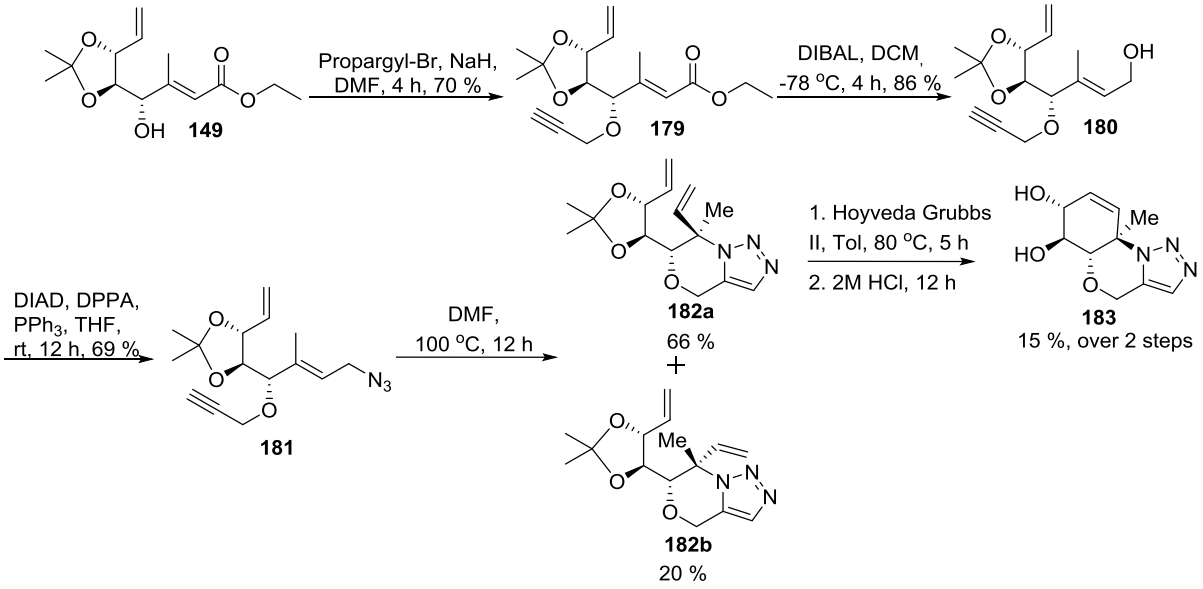


Figure 6.8 Newman projections of potential tertiary allylic azides from **87**

Diene **182a** was then subjected to ring closing metathesis conditions. Both Grubbs II and Hoyveda catalysts were reacted with a view to maximising the yield of the ring-closed product. Neither catalyst carried out the transformation with high yields due to poor conversion of the starting material. The addition of of additive 2,6-dichloro-1,4-benzoquinone in combination with Hoyveda-Grubbs II enabled formation of the *cis*-isomer selectively, as observed by ^{1}H NMR analysis of the crude product. This residue was treated with 2M HCl and subsequently purified using flash chromatography to give novel scaffold **183** as a white solid. Based on this model, it was possible to confirm the higher reactivity of alkynes with azides in comparison to the alkene dipolarphile.



Scheme 6.10 Cycloaddition of **181** to form new scaffold

6.2.7 Hemiacetal formation from aldehyde intermediate 72

Aldehyde **72** was a molecule of interest as hemiacetal formation arises in the presence of carbonyl and alcohol functionalities. With this mind, it was found that treatment of the aldehyde with Pd-C primarily reduced the alkene (as visualised by TLC), but progressed rapidly to remove the triethylsilane protecting

group with subsequent intramolecular nucleophilic attack of the alcohol on the aldehyde yielding hemiacetal **184**.

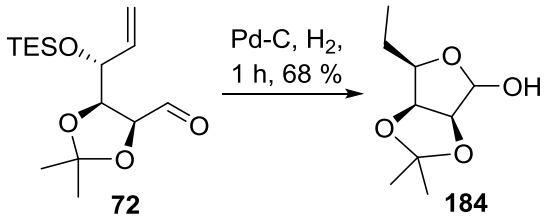


Figure 6.9 Hemiacetal formation from aldehyde **184**

6.3 Conclusion

This chapter explored formation of α,α-disubstituted iminosugars using the allylic azide rearrangement coupled to the Huisgen cycloaddition with subsequent decomposition of the resulting triazoline. It was established that while the presence of a restraint hindered the formation of the manno-configured compounds, removal of the conformational restraint resulted in increased yield, efficiency and reduced reaction times yielding the piperidine quaternary centred derivatives. Stereochemistry of all α,α-disubstituted iminosugars prepared were determined using 2D NOESY experiments. Competitive reactions between dipolarphiles, alkenes and alkynes, with azides showed alkynes as the more reactive functionality in the 1,3-dipolar cycloaddition. During these studies, novel 10-membered and bicyclic fused-scaffolds, **178** and **183**, were prepared. The olefin geometry of the 10-membered triazole was verified by X-ray crystallography of intermediate **177**.

A note on summary and future work

This thesis consisted of two main components; (i) the preparation of macrocycles derived from glucuronic acid as a means of accessing potent inhibitors of tumour cell migration and (ii) the exploration of the Huisgen cycloaddition in tandem with the allylic azide rearrangement to access piperidines, pyrrolidines and α,α-disubstituted piperidines.

From the first part of this work, two inhibitors of tumour cell migration were identified. Further work in this area to access more potent analogues could come from the preparation of galacto- and manno-configured derivatives.

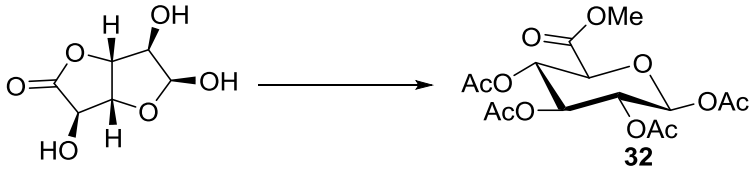
The latter component raised questions regarding the source of stereoselectivity of the reaction and the requirement of a conformational restraint for the cycloaddition. To explore these ideas further, azide substrates with different protecting groups should be explored as a means of further understanding the transition state pathways that can potentially occur in the cyclisation. This route has also identified the Huisgen cycloaddition as a potential route to 10-membered heterocyclic scaffolds. Further investigations could be undertaken to explore the limitations of this 1,3-dipolar cycloaddition in the formation of 10-ring systems of this nature.

Experimental

7.1 Experimental introduction

NMR spectra were recorded with a 500 and 600 MHz spectrometer. Chemical shifts are reported relative to internal Me_4Si in $CDCl_3$ (δ 0.0) or $CDCl_3$ (δ 7.26), HOD for D_2O (δ 4.65) and CD_2HOD (δ 3.31) for ^1H and $CDCl_3$ (δ 77.16), CD_3OD (δ 49.0) for ^{13}C. NMR spectra were analysed using MestReNova software. ^1H NMR signals were assigned with the aid of COSY. ^{13}C signals were assigned with the aid of HSQC and HMBC. Coupling constants are reported in Hertz. Low and high resolution mass spectra were measured on a Waters LCT Premier XE Spectrometer in positive/negative mode as indicated using solvents; ACN, H_2O and/or MeOH. FTIR Spectra were recorded with a Perkin Elmer Spectrum 100 FTIR Spectrometer with a polarized UATR accessory. TLC was performed on aluminium sheets pre-coated with Silica Gel 60 (HF_{254}, E. Merck) and spots visualised by UV and charring with cerium (IV) molybdate, ninhydrin and phosphomolybdic acid solutions. Flash chromatography was generally employed and was carried out using silica gel 60 (0.040-0.0630 mm, Aldrich) using a stepwise solvent polarity gradient correlated with TLC mobility. Chromatography solvents used were petroleum ether (40-60 °C, Fischer Scientific), diethyl ether, EtOAc, CH_2Cl_2 and MeOH (Sigma Aldrich). Ion exchange chromatography was carried out using DOWEX-50WX8 (200-400 mesh) resin. THF, toluene, CH_2Cl_2, DMF, Et_2O and methanol were used as obtained from a Pure-Solv^{TM} solvent purification. All previously published experimental data from Chapter 4 can be accessed from reference 181 and/or 184. All other experimental data is provided.

7.2 Experimental Data for Chapter 2



32

1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranosiduronic acid, methyl ester 32[64]

Glucuronolactone (10.0 g, 56.8 mmol) was suspended in dry MeOH (160 mL) and triethylamine (0.1 mL) subsequently added dropwise. The reaction mixture was stirred at rt for 16 h. The solvent was then removed under reduced pressure, followed by the addition of acetic anhydride (50 mL) and sodium acetate (5 g, 61.0 mmol). The reaction was shaken for 2 days, poured onto ice (300 mL) and stirred overnight. The β-acetate was separated by filtration and recrystallisation from EtOH afford **32** as a white solid (7.63 g, 35 %).

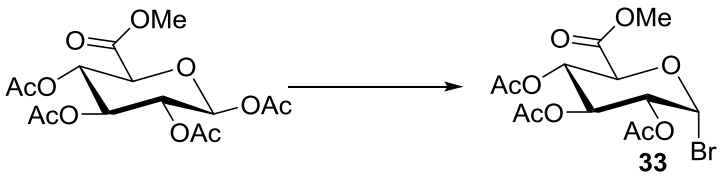
R_f = 0.52 (EtOAc-hexanes, 1:1)

FTIR 2955, 1752, 1455, 1443, 1371, 1265, 1206, 1144, 1115, 1088, 1077, 1038, 980, 934, 906, 890, 779, 736, 692 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (d, *J* = 7.8 Hz, 1H, H-1), 5.31 (t, *J* = 9.1 Hz, 1H, H-3), 5.24 (t, *J* = 9.5 Hz, 1H, H-4), 5.14 (d, *J* = 8.3 Hz, 1H, H-2), 4.18 (d, *J* = 9.6 Hz, 1H, H-5), 3.74 (s, 3H, CH_3), 2.12 (s, 3H, OAc), 2.04 (s, 6H, 2 x OAc), 2.03 (s, 3H, OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.4, 169.1, 168.8, 166.8 (C=O), 91.3 (C-1), 73.0 (C-5), 71.8 (C-3), 70.1 (C-2), 68.9 (C-4), 53.0 (OMe), 20.8, 20.6, 20.5, 20.5 (each OAc)

HRMS (ESI): m/z calc for $C_{15}H_{20}O_{11}Na$: 399.0903, found: 339.0906 $[M+Na]^+$



33

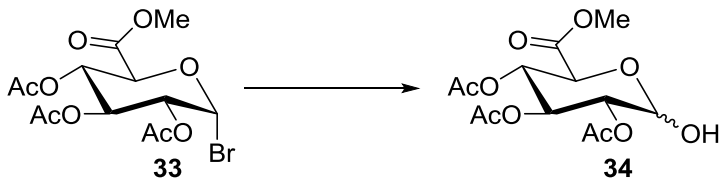
1-Bromo-1-deoxy-2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronic acid, methyl ester 33[212]

Methyl ester **32** (5.0 g, 13 mmol) was dissolved in CH_2Cl_2 and solution cooled to 0 °C. HBr (33 % in AcOH, 20 mL) was added and solution stirred at 0 °C for 7 h. Ice water was added and the organic layer separated. The organic layer was washed with H_2O, sat. $NaHCO_3$ solution (x 2), brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to give bromide **33** (3.7 g, 70 %).

R_f = 0.6 (EtOAc-hexanes, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (d, *J* = 4.0 Hz, 1H, H-1), 5.61 (t, *J* = 9.7 Hz, 1H, H-3), 5.24 (t, *J* = 9.9 Hz, 1H, H-4), 4.85 (dd, *J* = 9.9, 4.0 Hz, 1H, H-2), 4.58 (d, *J* = 10.3 Hz, 1H, H-5), 3.76 (s, 3H, OMe), 2.10 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.05 (s, 3H, OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 169.6, 169.4, 166.6 (each C= O), 85.3 (C-1), 72.0 (C-5), 70.3 (C-2), 69.3 (C-3), 68.5 (C-4), 53.1 (OMe), 20.6 (2 x OAc), 20.4 (OAc)



2,3,4-Tri-*O*-acetyl-α-D-glucopyranuronic acid, methyl ester 34[213]

Bromide **33** (9.5 g, 13.0 mmol) was dissolved in acetone (200 mL) and water (20 mL). The reaction vessel was then wrapped in tinfoil and Ag_2CO_3 (1.8 g, 6.5 mmol) then added. The reaction mixture stirred at rt for 16 h. The reaction was filtered through celite, washed with CH_2Cl_2 and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded the mixture of hemiacetals **34** (1:0.35) as a white solid (3.1 g, 71 %).

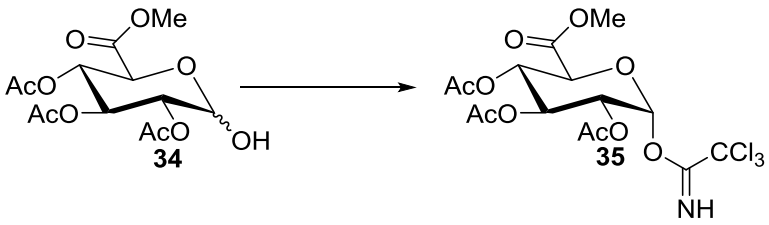
R_f = 0.3 (EtOAc-hexanes, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 – 5.52 (m, 2H, overlapping signals, H-1 & H-2), 5.30 (td, *J* = 9.4, 1.5 Hz, 1H, C-H*), 5.26 – 5.14 (m, 2H, overlapping signals H-4 & C-H*), 4.94 – 4.87 (m, 2H, overlapping signals H-2 & C-H*), 4.79 (dd, *J* = 7.7, 1.4 Hz, 1H, C-H*), 4.58 (dd, *J* = 10.1, 1.4 Hz, 1H, H-5), 4.14 – 4.07 (m, 1H, C-H*), 3.75 (d, *J* = 1.4 Hz, 1H, OMe*), 3.74 (d, *J* = 1.5 Hz, 3H, OMe), 2.09 – 2.06 (m, 6H, 2 x overlapping OAc signals), 2.03 – 2.00 (m, 12H, 4 x overlapping OAc signals)

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 170.0, 169.6, 168.3 (each C=O), 95.6 (C-H*), 90.3 (C-1), 72.9 (C-H*), 72.6 (C-H*), 71.3 (C-H*), 70.7 (C-2), 69.5 (C-4), 69.4 (C-H*), 69.0 (C-3), 68.1 (C-5), 53.0 (-CH_3*), 52.9 (-CH_3), 20.6, 20.5 (6 x OAc peaks)

HRMS (ESI): m/z calc for $C_{13}H_{18}O_{10}Na$: 357.0798, found: 357.0789 $[M+Na]^+$

* = minor product



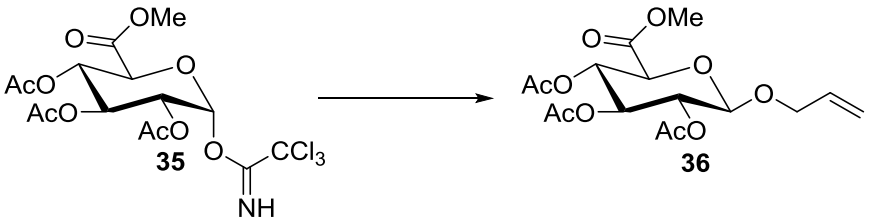
2,3,4-Tri-*O*-acetyl-1-(2,2,2-trichloroethanimidate)-α-D-glucopyranuronic acid, methyl ester 35[65]

Hemiacetal **34** (10 g, 29.9 mmol) was dissolved CH_2Cl_2 (500 mL). The solution was cooled to 0 °C, followed by the addition of Cl_3CCN (30 mL, 299.15 mmol) and DBU (0.1 mL). The reaction was stirred at 0 °C for 5 h. The solvent was removed under reduced pressure and flash chromatography (EtOAc-hexanes, 3:2) afforded trichloroacetimidate **35** (10.7 g, 75 %) as a white solid.

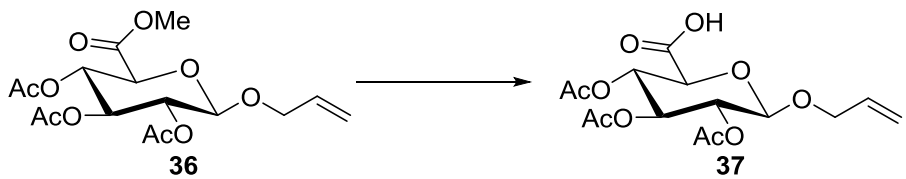
R_f = 0.4 (hexanes-EtOAc, 1:1)

FTIR 3325, 2957, 1750, 1678, 1438, 1368, 1286, 1205, 1150, 1038, 969, 909, 834, 795, 728 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H, N-H), 6.62 (d, *J* = 3.6 Hz, 1H, H-1), 5.67 – 5.54 (m, 1H, H-3), 5.32 – 5.20 (m, 1H, H-4), 5.14 (ddd, *J* = 10.2, 3.7, 1.1 Hz, 1H, H-2), 4.48 (d, *J* = 10.3 Hz, 1H, H-5), 3.74 (d, *J* = 1.2 Hz, 3H, -OMe), 2.05 – 2.02 (m, 6H, 2 x OAc), 2.00 (s, 3H, OAc)
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7 (C=O), 169.7 (C=O), 169.4 (C=O), 167.1 (C=O), 160.5 (C=N), 92.6 (C-1), 70.4 (C-5), 69.4 (C-2), 69.1 (C-4), 68.9 (C-3), 53.0 (OMe), 20.6 (OAc), 20.5 (OAc), 20.4 (OAc)
HRMS (ESI): m/z calc for $C_{15}H_{18}NO_{10}NaCl_3$: 499.9894, found 499.9878 $[M+Na]^+$



2,3,4-Tri-*O*-acetyl-1-*O*-allyl-β-D-glucopyranuronic acid, methyl ester 36[214]
Trichloroacetimide **35** (10.0 g, 20.9 mmol) was dissolved in CH_2Cl_2 (250 mL). 4 Å Molecular sieves were added followed by allyl alcohol (1.85 mL, 27.2 mmol). The solution was stirred at rt for 30 mins and then BF_3Et_2O (1.3 mL, 10.5 mmol) charged. The reaction mixture adjusted to rt and solution stirred for 3 h. Reaction mixture was quenched upon addition of satd. $NaHCO_3$ solution, organic layer separated, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 7:3) afforded the ester **36** (4.5 g, 58 %).
R_f = 0.23 (hexanes-EtOAc, 7:3)
FTIR 2952, 1752, 1436, 1370, 1212, 1163, 1092, 1072, 1045, 980, 953, 897, 781, 695, 669 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 16.5, 10.7, 5.2 Hz, 1H, H-7), 5.32 – 5.18 (m, 4H, overlapping signals H-8, H-8', H-4 & H-3), 5.04 (t, *J* = 8.1 Hz, 1H, H-2), 4.60 (d, *J* = 7.7 Hz, 1H, H-1), 4.36 (dd, *J* = 13.3, 4.7 Hz, 1H, H-6), 4.10 (dd, *J* = 13.2, 6.2 Hz, 1H, H-6), 4.03 (d, *J* = 8.8 Hz, 1H, H-5), 3.76 (s, 3H, OMe), 2.04 (s, 3H, OAc), 2.02 (s, 6H, OAc)
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 169.3, 169.2, 167.2 (C=O), 133.1 (C-7), 117.8 (C-8), 99.5 (C-1), 72.6 (C-5), 72.1 (C-H), 71.2 (C-2), 70.1 (C-6), 69.4 (C-H), 52.9 (OMe), 20.6 (OAc), 20.6 (OAc), 20.5 (OAc)
HRMS (ESI) m/z calc for $C_{16}H_{22}O_{10}Na$: 397.1122, Found 397.1111 $[M+Na]^+$



2,3,4-Tri-*O*-acetyl-1-*O*-allyl-α-D-glucopyranuronic acid 37

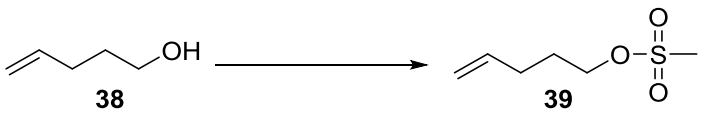
Ester **36** (3.8 g, 10.2 mmol) was dissolved in dry EtOAc (20 mL), and lithium iodide (12.23 g, 91.36 mmol) charged. The solution was refluxed for 9 h and the reaction mixture then diluted with EtOAc. The organic layer was washed with 1M HCl and this acidic aqueous layer was back-extracted with EtOAc (x 2). The combined organic layers were then washed with satd. $Na_2S_2O_3$ solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford the desired acid **37** as a pale-yellow solid (2.9 g, 79 %).

FTIR 3303, 3255, 2953, 1737, 1697, 1432, 1409, 1381, 1368, 1266, 1242, 1199, 1164, 1119. 1076, 1024, 926, 889, 838, 766, 704, 670 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (dddd, *J* = 17.0, 10.8, 6.2, 4.8 Hz, 1H, H-7), 5.32 – 5.17 (m, 4H, overlapping peaks H-3, H-4, H-8 & H-8'), 5.07 – 4.98 (m, 1H, H-2), 4.64 (d, *J* = 7.5 Hz, 1H, H-1), 4.39 – 4.34 (m, 1H, H-6), 4.16 – 4.06 (m, 2H, overlapping signals H-6' & H-5), 2.04 (s, 3H, -OAc), 2.03 (s, 3H, -OAc), 2.01 (s, 3H, -OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 170.3, 169.7, 169.4 (C=O), 133.0 (C-7), 118.0 (C-8), 99.4 (C-1), 72.0 (C-H), 71.9 (C-5), 71.1 (C-2), 70.3 (C-8), 69.1 (C-H), 20.6 (OAc), 20.6 (OAc), 20.5 (OAc)

HRMS (ESI): m/z calc for $C_{15}H_{19}O_{10}$: 359.0978, found 359.0964 $[M-H]^-$



38 **39**

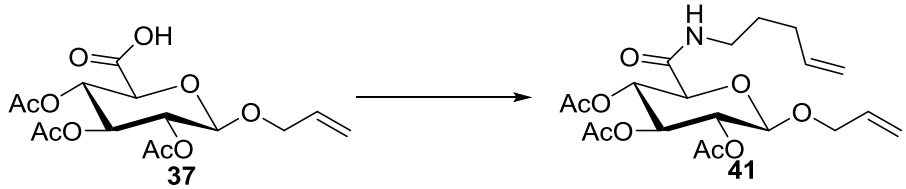
1-(methylsulfonyl)pent-4-ene 39

Alcohol **38** (1.0 mL, 9.8 mmol) was dissolved in dry CH_2Cl_2 and triethylamine (2.17 mL, 19.7 mmol) charged. The solution was cooled to 0 °C, followed by the addition of methanesulfonyl chloride (1.14 mL, 14.7 mmol). The reaction mixture was stirred for a further 2 h at 0 °C and subsequently poured onto an ice-cold solution of 1M HCl. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford the mesylate **39** (1.3 g, 80 %) as a pale-yellow oil.

FTIR 2942, 1348, 1869, 958, 915, 830, 771, 724 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H-4), 5.11 – 4.99 (m, 2H, H-5 & H-5'), 4.24 (t, *J* = 6.5 Hz, 2H, H-1 & H-1'), 3.00 (s, 3H, $-CH_3$), 2.24 – 2.13 (m, 2H, overlapping signals H-3 & H-3'), 1.90 – 1.81 (m, 2H, overlapping signals H-2 & H-2')

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6 (C-4), 116.1 (C-5), 69.2 (C-1), 37.4 (CH_3), 29.4 (C-3), 28.2 (C-2)



37 **41**

2,3,4-Tri-*O*-acetyl-1-*O*-allyl-β-D-glucopyranuronic acid, amide 41

Mesylate **39** (2.73 g, 16.7 mmol) was dissolved in MeOH (7 mL) and aq NH_3 (7 mL) was subsequently added. The solution was stirred at 60 °C for 2 days and the reaction then quenched with the addition of water. This mixture was diluted with CH_2Cl_2, and the organic layer separated. The organic layer was then dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford the intermediate amine **40** as a yellow oil.

Simultaneously, acid **37** (2.0 g, 5.6 mmol) was dissolved in THF (60 mL), followed by the addition of HBTU (4.2 g, 11.1 mmol) and DIEA (0.79 g, 6.11 mmol). The reaction mixture was stirred for 10 min and amine (approx. 3 equiv) was subsequently added. The reaction was stirred at rt overnight and then quenched upon addition of 1% HCl. The organic layer was separated and aqueous layer extracted with CH_2Cl_2. The combined organic layers were then washed with satd. $NaHCO_3$ solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 3:2) afforded amide **41** (2.14 g, 82 %) as a white solid.

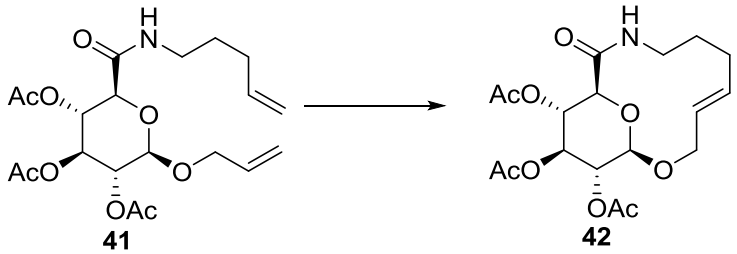
R_f = 0.45 (hexanes-EtOAc, 3:2)

FTIR 3355, 3330, 2166, 1746, 1666, 1541, 1435, 1409, 1368, 1291, 1243, 1218, 1171, 1083, 1036, 997, 917, 903, 772, 677 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 6.43 (t, *J* = 6.0 Hz, 1H, N-H), 5.93 – 5.71 (m, 2H, overlapping peaks H-7 & H-12), 5.32 – 5.20 (m, 3H, overlapping peaks H-8, H-8' & H-3), 5.13 – 4.95 (m, 4H, overlapping peaks H-4, H-2, H-13 & H-13'), 4.60 (d, *J* = 8.0 Hz, 1H, H-1), 4.33 (dd, *J* = 13.3, 4.9 Hz, 1H, H-6), 4.18 – 4.09 (m, 1H, H-6), 3.88 (d, *J* = 9.8 Hz, 1H, H-5), 3.24 (dh, *J* = 27.0, 6.8 Hz, 2H, H-9), 2.12 – 2.04 (m, 2H, H-11), 2.06 (s, 3H, -OAc), 2.05 (s, 3H, -OAc), 2.01 (s, 3H, -OAc), 1.62 (p, *J* = 7.2 Hz, 2H, H-10)

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.7, 169.3, 166.5 (each C=O), 137.6 (C-12), 133.0 (C-7), 118.0 (C-8), 115.4 (C-13), 99.6 (C-1), 72.6 (C-5), 72.0 (C-3), 71.1 (C-2), 70.7 (C-6), 69.7 (C-4), 38.6 (C-9), 31.0 (C-11), 28.3 (C-10), 20.7 (OAc), 20.6 (OAc), 20.6 (OAc)

HRMS (ESI): m/z calc for $C_{20}H_{29}NO_9Na$: 450.1740, found 450.1755 $[M+Na]^+$



2,3,4-Tri-*O*-acetyl-β-D-Macrolactam 42

Amide **41** (0.1 g, 0.2 mmol) was dissolved anhydrous degassed toluene (500 mL). The solution was heated to 80 °C, followed by the addition of 2,6-dichloro-1,4-benzoquinone (16 mg, 0.1 mmol) and Hoyveda-Grubbs II (14.0 mg, 0.02 mmol). The reaction mixture was stirred at 80 °C for 5 h. The

solvent was removed under reduced pressure and flash chromatography (hexanes-EtOAc, 1:1) afforded macrocycle **42** (50 mg, 57 %) as a white solid.

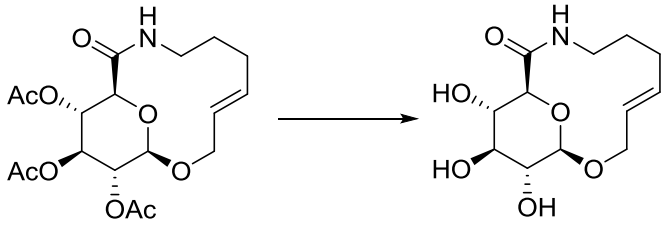
R_f = 0.3 (hexanes-EtOAc, 1:1)

FTIR 3367, 2920, 1660, 1559, 1526, 1408, 1347, 1269, 1230, 1084, 1039, 1026, 980, 970, 961, 867, 818, 791, 667 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 5.6 Hz, 1H, N-H), 5.86 – 5.76 (m, 1H, H-7), 5.69 (ddd, *J* = 15.0, 9.1, 4.8 Hz, 1H, H-8), 5.46 (dd, *J* = 10.6, 9.0 Hz, 1H, H-4), 5.13 (dd, *J* = 9.0, 5.4 Hz, 1H, H-3), 4.95 (t, *J* = 5.1 Hz, 1H, H-2), 4.79 (d, *J* = 4.8 Hz, 1H, H-1), 4.61 – 4.52 (m, 1H, H-6), 3.95 (d, *J* = 10.6 Hz, 1H, H-5), 3.88 (dd, *J* = 13.3, 9.0 Hz, 1H, H-6'), 3.54 – 3.45 (m, 1H, H-11), 3.22 (ddt, *J* = 13.9, 10.5, 3.7 Hz, 1H, H-11), 2.44 – 2.36 (m, 1H, H-9), 2.20 (dt, *J* = 15.2, 9.9 Hz, 1H, H-9'), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.80 (ddq, *J* = 14.9, 10.4, 6.2, 5.1 Hz, 1H, H-10'), 1.66 – 1.55 (m, 1H, H-10')

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 169.9, 169.3, 166.4 (each C=O), 136.1 (C-8), 129.4 (C-7), 100.5 (C-1), 73.1 (C-6), 73.0 (C-3), 72.6 (C-2), 71.2 (C-5), 68.3 (C-4), 40.4 (C-11), 31.8 (C-9), 27.3 (C-10), 20.8 (OAc), 20.7 (OAc), 20.7 (OAc)

HRMS (ESI): m/z calc for $C_{18}H_{25}O_9NNa$: 422.1427, found 422.1427 $[M+Na]^+$



2,3,4-Tri-*O*-hydroxy-β-D-Macrolactam 43

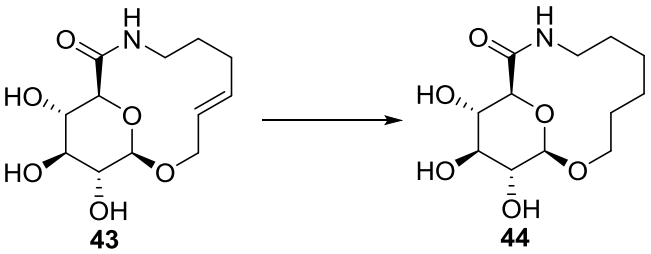
Macrolactam **42** (20 mg, 0.05 mmol) was dissolved in MeOH, and Ambersep900OH resin (100 mg) was subsequently added. The reaction mixture was shaken at rt for 1 h. The resin was then filtered and solvent removed under reduced pressure. Flash chromatography (CH_2Cl_2-MeOH, 9:1) afforded the deprotected macrolactam **43** (11 mg, 86 %) as a white solid.

R_f = 0.1 (CH_2Cl_2-MeOH, 9:1)

^{1}H NMR (500 MHz, CD_3OD) δ 5.72 (dddd, *J* = 15.1, 9.2, 3.7, 1.9 Hz, 1H, H-7), 5.62 (dddd, *J* = 15.2, 9.7, 4.0, 1.2 Hz, 1H, H-8), 4.54 (d, *J* = 6.0 Hz, 1H, H-1), 4.52 – 4.47 (m, 1H, H-6), 4.33 (d, *J* = 7.8 Hz, 1H, H-1*) , 3.96 (dd, *J* = 13.2, 9.3 Hz, 1H, H-6'), 3.88 (d, *J* = 9.5 Hz, 1H, H-5*). 3.72 (d, *J* = 9.7 Hz, 1H, H-5), 3.61 (dd, *J* = 9.8, 8.3 Hz, 1H, H-4), 3.53 (dt, *J* = 13.4, 4.0 Hz, 1H, H-11), 3.43 – 3.35 (m, 2H, overlapping signals H-2 & H-3), 3.16 (ddd, *J* = 13.9, 11.3, 3.2 Hz, 1H, H-11), 2.48 – 2.39 (m, 1H, H-9), 2.22 – 2.12 (m, 1H, H-9), 1.84 – 1.76 (m, 1H, H-10), 1.72 – 1.59 (m, 1H, H-10)

^{13}C NMR (126 MHz, CD_3OD) δ 134.1 (C=O), 129.8 (C-8), 110.0 (C-7), 103.6 (C-1), 76.8 (C-3), 74.2 (C-2), 73.4 (C-5), 72.3 (C-6), 71.2 (C-4), 39.8 (C-11), 31.2 (C-9), 27.5 (C-10)

HRMS (ESI): m/z calc for $C_{14}H_{22}N_2O_6Na$: 337.1376, found 337.1367 $[M+Na+ACN]^+$



2,3,4-Tri-*O*-hydroxy-β-D-Macrolactam 44

Macrolactam **43** (4.0 mg, 0.2 mmol) was dissolved in MeOH, followed by the addition of Pd-C (0.015 mmol, 10 % wt Pd on carbon) and a H_2 balloon. The solution was reacted at rt for 10 min. The reaction mixture was filtered through a pad of celite and washed with MeOH. The solvent then was removed under reduced pressure and flash chromatography (CH_2Cl_2-MeOH, 9:1) afforded macrolactam **44** as a white solid (3.3 mg, 81 %).

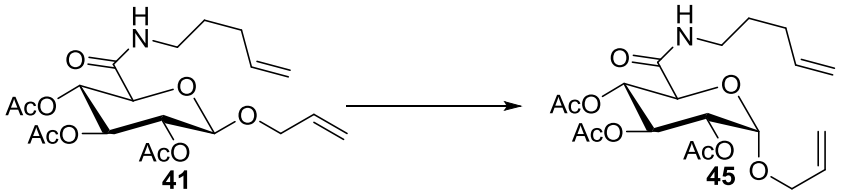
R_f = 0.14 (CH_2Cl_2-MeOH, 9:1)

^{1}H NMR (500 MHz, D_2O) δ 4.62 (d, *J* = 3.5 Hz, 1H, H-1), 4.50 (d, *J* = 7.9 Hz, 1H, H-1*), 4.14 (d, *J* = 9.9 Hz, 1H, H-5*), 4.05 – 3.99 (m, 2H, overlapping signals H-4 & H-5), 3.81 – 3.69 (m, 2H, H-6 & H-4*), 3.59 – 3.38 (m, 4H, overlapping signals H-2, H-3, H-6, H-11 & H-3*), 3.24 – 3.16 (m, 1H, H-2*), 2.93 (ddd, *J* = 13.7, 6.3, 4.7 Hz, 1H, H-11), 1.63-1.50 (m, 2H, overlapping signals H-10 & H-7), 1.45 (dtd, *J* = 14.7, 7.6, 6.7, 3.2 Hz, 1H, H-10), 1.40 – 1.22 (m, 3H, overlapping signals H-7, H-9 & H-9'), 1.17 (qd, *J* = 8.4, 8.0, 3.5 Hz, 2H, H-8 & H-8')

^{13}C NMR (126 MHz, D_2O) δ 172.1 (C=O), 104.2 (C-1), 77.5 (C-5), 74.1, 73.6 (each C-3, C-2), 69.0 (C-4), 67.6 (C-6), 37.9 (C-11), 27.0 (C-7), 24.5 (C-10), 22.1 (C-9), 21.4 (C-8)

HRMS (ESI): m/z calc for $C_{14}H_{24}N_2O_6Na$: 339.1532, found 339.1519 $[M+Na+ACN]^+$

* = minor



2,3,4-Tri-*O*-acetyl-1-*O*-allyl-α-D-glucopyranuronic acid, amide 45

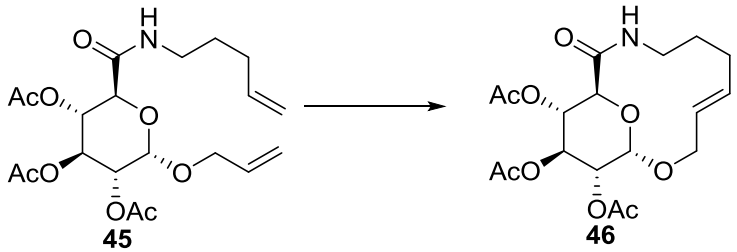
Amide **41** (70.0 mg, 0.16 mmol) was dissolved in dry CH_2Cl_2, followed by the addition of $SnCl_4$ (0.41 mL, 1M in CH_2Cl_2). The reaction mixture was stirred at rt for 16 h and subsquently quenched upon addition of $NaHCO_3$. This mixture was diluted with EtOAc and washed with satd. $NaHCO_3$ solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 3:2) yielded the α-anomer **45** as a white solid (61 mg, 88 %).

R_f = 0.37 (hexanes-EtOAc, 3:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (t, *J* = 5.9 Hz, 1H, N-H), 5.82 (m, 2H, overlapping signals H-7 & H-12), 5.57 (t, *J* = 9.9 Hz, 1H, H-3), 5.31 (dd, *J* = 17.2, 1.7 Hz, 1H, H-8), 5.24 (d, *J* = 10.5 Hz, 1H, H-8'), 5.18 (d, *J* = 3.8 Hz, 1H, H-1), 5.12 – 5.05 (m, 2H, overlapping signals H-4 & H-13), 5.05 – 4.95 (m, 1H, H-13), 4.83 (dd, *J* = 10.3, 3.7 Hz, 1H, H-2), 4.23 (d, *J* = 10.2 Hz, 1H, H-5), 4.19 (dd, *J* = 13.0, 5.2 Hz, 1H, H-6), 4.01 (dd, *J* = 13.0, 6.1 Hz, 1H, H-6'), 3.36 – 3.17 (m, 2H, H-9 & H-9'), 2.12 – 2.06 (m, 2H, overlapping signals H-11 & H-11'), 2.08 (s, 6H, 2 x OAc), 2.02 (s, 3H, -OAc), 1.62 (p, *J* = 7.3 Hz, 2H, H-10 & H-10')

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 169.8, 169.8, 167.2 (each C=O), 137.6 (C-12), 132.7 (C-7), 118.5 (C-8), 115.3 (C-13), 94.8 (C-1), 70.8 (C-2), 69.9 (C-4), 69.3 (C-3, C-6), 68.3 (C-5), 38.6 (C-9), 31.0 (C-11), 28.4 (C-10), 20.7 (OAc), 20.7 (2 x OAc)

HRMS (ESI): m/z calc for $C_{20}H_{29}NO_9Na$: 450.1740, found 450.1753 $[M+Na]^+$



2,3,4-*O*-acetyl-α-*O*-D-Macrolactam 46

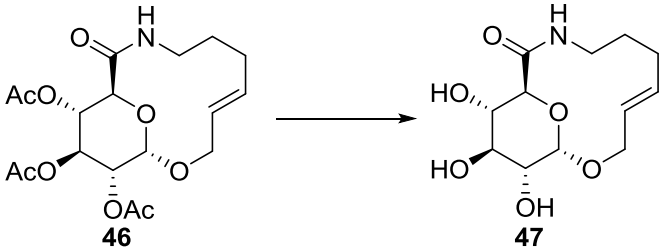
Amide **45** (0.07 g, 0.16 mmol) was dissolved anhydrous degassed toluene (350 mL). The solution was heated to 80 °C, followed by the addition of 2,6-dichloro-1,4-benzoquinone (11 mg, 0.064 mmol) and Hoyveda-Grubbs II (10 mg, 0.016 mmol). The reaction mixture was then stirred at 80 °C for 5 h. The solvent was removed under reduced pressure and flash chromatography (hexanes-EtOAc, 3:7) afforded macrocycle **46** (13 mg, 20 %) and starting material (28 mg, 40 %) as white solids.

R_f = 0.32 (hexanes-EtOAc, 3:7)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, *J* = 9.1 Hz, 1H, N-H), 5.70 – 5.59 (m, 2H, overlapping signals H-7 & H-8), 5.46 (t, *J* = 9.0 Hz, 1H, H-3), 5.24 (d, *J* = 4.2 Hz, 1H, H-1), 5.19 (t, *J* = 9.2 Hz, 1H, H-4), 4.80 (dd, *J* = 9.3, 4.2 Hz, 1H, H-2), 4.54 (dt, *J* = 13.0, 2.8 Hz, 1H, H-6), 4.26 (d, *J* = 9.7 Hz, 1H, H-5), 3.81 – 3.66 (m, 2H, overlapping signals H-6' & H-11), 3.19 – 3.04 (m, 1H, H-11'), 2.37 (dd, *J* = 14.8, 7.6 Hz, 1H, H-9), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.03 – 1.92 (m, 1H, H-9'), 1.84 (ddt, *J* = 14.9, 7.2, 3.5 Hz, 1H, H-10), 1.68 – 1.57 (m, 1H, H-10')

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 170.1, 169.5, 166.6 (each C=O), 138.8, 125.6 (C-7, C-8), 97.0 (C-1), 73.5 (C-6), 71.2 (C-2), 70.3 (C-3), 68.4 (C-4), 66.1 (C-5), 40.4 (C-11), 30.8 (C-9), 28.1 (C-10), 20.8 (OAc), 20.7 (OAc), 20.6 (OAc)

HRMS (ESI): m/z calc for $C_{18}H_{25}NO_9Na$: 422.1427, found 422.1429 $[M+Na]^+$



46 **47**

2,3,4-*O*-hydroxy-α-*O*-D-Macrolactam 47

Macrolactam **46** (16.0 mg, 0.04 mmol) was dissolved in MeOH, followed by the addition of ambersep900OH resin (80 mg). The reaction mixture was stirred at rt for 1 h. The resin was then filtered and solvent removed under reduced pressure. Flash chromatography (CH_2Cl_2-MeOH, 9:1) afforded the deprotected macrolactam **47** as a white solid (9 mg, 84 %).

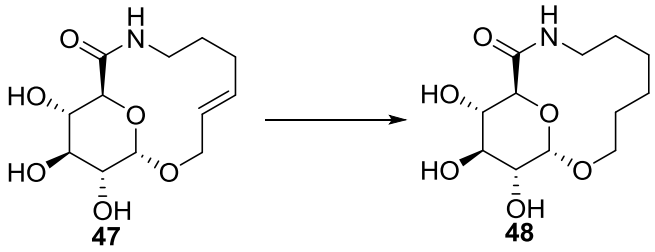
R_f = 0.13 (CH_2Cl_2-MeOH, 9:1)

^{1}H NMR (500 MHz, CD_3OD) δ 6.02 – 5.91 (m, 2H, overlapping signals H-7*), 5.77 (ddd, *J* = 13.0, 9.4, 3.2 Hz, 1H, H-8 & H-8*), 5.73 – 5.65 (m, 1H, H-7), 4.99 (d, *J* = 4.0 Hz, 1H, H-1), 4.92 (d, *J* = 4.2 Hz, 1H, H-1*), 4.67 (d, *J* = 7.9 Hz, 1H, H-5*), 4.50 – 4.43 (m, 1H, H-6), 4.32 (t, *J* = 10.8 Hz, 1H, H-6*), 4.02 (d, *J* = 7.3 Hz, 1H, H-5), 3.92 – 3.81 (m, 1H, overlapping signals H-6' & H-6'*), 3.62 – 3.57 (m, 2H, overlapping signals H-4 & H-3), 3.49 (ddd, *J* = 21.7, 10.8, 4.5 Hz, 2H, overlapping signals H-11 & H-2), 3.32 – 3.18 (m, 1H, H-11), 3.15 (d, *J* = 14.9 Hz, 1H, H-11*), 2.43 – 2.30 (m, 1H, H-10), 2.17 (d, *J* = 14.9 Hz, 2H, overlapping signals CH_2*), 1.99 (td, *J* = 15.2, 12.8, 6.5 Hz, 1H, H-10'), 1.87 – 1.73 (m, 2H, overlapping signals H-9 & H-9')

^{13}C NMR (126 MHz, CD_3OD) δ 170.7 (C=O), 138.3 (C-8), 134.5 (C-8*), 130.6 (C-7*), 125.8 (C-7), 101.3 (C-1*), 100.1 (C-1), 75.1 (C-3), 72.4 (C-6), 72.1 (C-2), 70.9 (C-4), 70.4 (C-6), 68.7 (C-5), 65.4 (C-5*), 40.2 (C-11), 39.7 (C-11*), 30.4 (C-10), 26.9 (C-9)

HRMS (ESI): m/z calc for $C_{14}H_{22}O_6N_2Na$: 337.1376, found 337.1376 $[M+Na+ACN]^+$

* = minor



47 **48**

2,3,4-*O*-hydroxy-α-*O*-Macrolactam 48

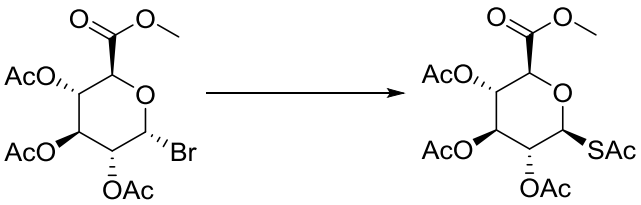
Macrocycle **47** (6 mg, 22 mmol) was dissolved in MeOH (2 mL), followed by the addition of Pd-C (2.2 mmol, 10% wt on carbon) and a H_2 balloon. The reaction mixture was stirred at rt for 1 h. The solution was then filtered and solvent removed under reduced pressure. Flash Chromatography (CH_2Cl_2-MeOH, 9:1) afforded macrocycle **48** (4.8 mg, 80 %) as a white solid.

R_f = 0.2 (CH_2Cl_2-MeOH, 9:1)

^{1}H NMR (500 MHz, D_2O) δ 4.81 (d, *J* = 4.1 Hz, 1H, H-1), 4.54 (d, *J* = 9.9 Hz, 1H, H-5), 3.70 – 3.59 (m, 3H, overlapping signals H-6, H-6' & H-3), 3.56 – 3.46 (m, 3H, overlapping signals H-2, H-4 & H-11), 3.07 (dt, *J* = 15.5, 3.4 Hz, 1H, H-11), 1.85 (td, *J* = 13.9, 4.2 Hz, 1H, H-7), 1.68 – 1.49 (m, 2H, overlapping signals H-10 & H-8), 1.41 – 1.30 (m, 2H, overlapping signals H-10 & H-7), 1.24 (m, 3H, overlapping signals H-9, H-8 & H-8'), 1.14 (dt, *J* = 13.8, 7.0 Hz, 1H, H-9)

^{13}C NMR (126 MHz, D_2O) δ 172.7 (C=O), 98.1 (C-1), 73.3 (C-3), 71.2 (C-4), 70.9 (C-2), 65.4 (C-5), 65.1 (C-6), 39.0 (C-11), 29.1 (C-10), 27.2 (C-7), 22.0 (C-8), 18.6 (C-9)

HRMS (ESI): m/z calc for $C_{14}H_{24}O_6NaN_2$: 399.1532, found 399.1547 $[M+Na+ACN]^+$



33 **49**

1-*S*-Acetyl-2,3,4-tri-*O*-acetyl-1-β-thio-D-glucopyranuronic acid, methyl ester 49

Bromide **33** (3.0 g, 7.6 mmol) was dissolved in DMF (25 mL). The solution was charged with KSAc (1.0 g, 9.0 mmol) and reaction mixture stirred for 4 h at rt. The reaction mixture was diluted with Et_2O and satd. NH_4Cl solution subsequently added. The organic layer was back extracted with Et_2O (x 2) and the combined organic layers were washed with satd. NH_4Cl solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. The crude residue was purified *via*. flash chromatography (hexanes-EtOAc, 1:1) to afford the thiol as a brown solid. Recrystallisation from EtOH yielded **49** (1.18 g, 40 %) as an off-white solid.

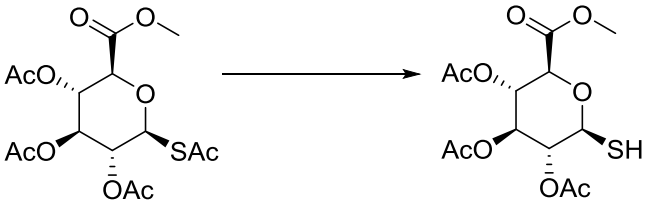
R_f = 0.6 (Hexane-EtOAc, 1:1)

FTIR 2944, 1753, 1712, 1439, 1373, 1244, 1208, 1108, 1090, 1073, 1049, 1034, 978, 958, 900, 892, 824, 769, 719, 678, 656 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 – 5.19 (m, 2H, overlapping signals H-3 & H-1), 4.99 (t, 1H, H-4), 4.57 (t, *J* = 10.0 Hz, 1H, H-2), 4.04 (d, *J* = 9.7 Hz, 1H, H-5), 3.75 (s, 3H, -OCH_3), 2.38 (d, *J* = 10.0 Hz, 3H, -SAc), 2.07 (s, 3H, OAc), 2.02 (s, 3H, -OAc), 2.01 (s, 3H, -OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.5, 169.3, 166.7 (each C=O), 79.0 (C-1), 76.6 (C-5), 73.2 (C-3), 72.7 (C-4), 69.3 (C-2), 53.0 (OMe), 20.7 (SAc), 20.6 (2s, 2 x OAc), 20.4 (OAc)

HRMS (ESI): m/z calc for $C_{15}H_{20}O_{10}SNa$: 415.0675, found 415.0683 $[M+Na]^+$



49 **50**

2,3,4-Tri-*O*-acetyl-1-β-thio-D-glucopyranosiduronic acid, methyl ester 50

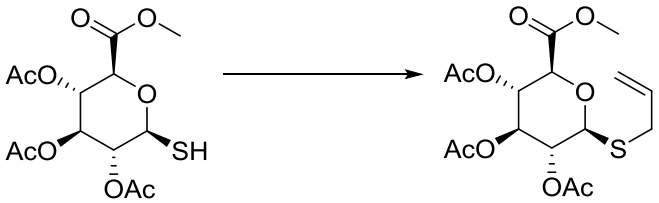
Thioacetate **49** (400 mg, 1.01 mmol) was dissolved in $CHCl_3$-MeOH (1:1, 10 mL) and cooled to 0 °C. Nitrogen was bubbled through the solution for 10 min, followed by addition of NaSMe (70 mg, 1.0 mmol). The reaction was stirred at 0 °C for 10 min and subsequently poured onto 1% HCl (aq). The reaction mixture was then diluted with CH_2Cl_2 and organic layer separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were then washed with brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Recrystallisation from EtOH yielded thiol **50** (195 mg, 55 %) as an off-white solid.

R_f = 0.2 (hexanes-EtOAc, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 – 5.19 (m, 2H, overlapping peaks H-3 & H-4), 4.99 (t, 1H, H-2), 4.57 (t, *J* = 10.0 Hz, 1H, H-1), 4.04 (d, *J* = 9.7 Hz, 1H, H-5), 3.75 (s, 3H, -OCH_3), 2.38 (d, *J* = 10.0 Hz, 1H, SH), 2.07 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.5, 169.3, 166.7 (each C=O), 79.0 (C-1), 76.6 (C-5), 73.2 (C-2), 72.7, 69.3 (C-3, C-4), 53.0 (OMe), 20.7 (OAc), 20.6 (OAc), 20.4 (OAc)

HRMS (ESI): m/z calc for $C_{15}H_{21}NO_9SNa$: 414.0835, found 414.0821 $[M+Na+ACN]^+$



2,3,4-Tri-*O*-acetyl-1-*S*-allyl-β-D-glucopyranuronic acid, methyl ester 51

Thiol **50** (0.17 g, 0.49 mmol) was dissolved in DMF (4 mL). The solution was cooled to 0 °C and NaH (0.02 g, 60 % in mineral oil, 0.49 mmol) charged portionwise. The reaction mixture was stirred at 0 °C for 10 min, followed by the addition of allyl bromide (0.05 mL, 0.59 mmol). The reaction mixture was adjusted to rt overnight. This mixture was then diluted with Et_2O and satd. NH_4Cl solution added. The organic layer was separated and the aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with satd. NH_4Cl solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 1:1) afforded ester **51** (86 mg, 45 %) as a white solid.

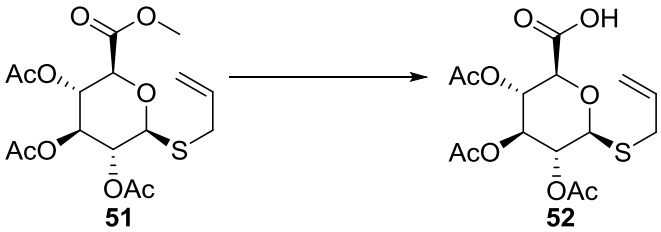
R_f = 0.63 (hexanes-EtOAc, 1:1)

FTIR 2949, 1746, 1432, 1377, 1302, 1216, 1091, 1054, 1038, 995, 978, 909, 892, 863, 828, 767, 736, 681 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 – 5.74 (m, 1H, H-7), 5.30 – 5.13 (m, 5H, overlapping signals, H-8, H-8', H-3 & H-4), 5.11 – 5.05 (m, 1H, H-2), 4.51 (d, *J* = 10.1 Hz, 1H, H-1), 3.98 (d, *J* = 9.4 Hz, 1H, H-5), 3.76 (s, 3H, -OMe), 3.40 (dd, *J* = 13.6, 8.3 Hz, 1H, H-6), 3.24 (dd, *J* = 13.5, 6.1 Hz, 1H, H-6'), 2.05 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 169.3, 169.3, 166.9 (each C=O), 133.1 (C-7), 118.3 (C-8), 82.3 (C-1), 76.1 (C-5), 73.1 (C-H), 69.6 (C-H), 69.4 (C-H), 52.9 (-OMe), 32.9 (C-6), 20.7 (OAc), 20.6 (OAc), 20.5 (OAc)

HRMS (ESI): m/z calc for $C_{16}H_{22}O_9SNa$: 413.0882, found 413.0887 $[M+Na]^+$



2,3,4-Tri-*O*-acetyl-1-*S*-allyl-β-D-glucopyranuronic acid 52

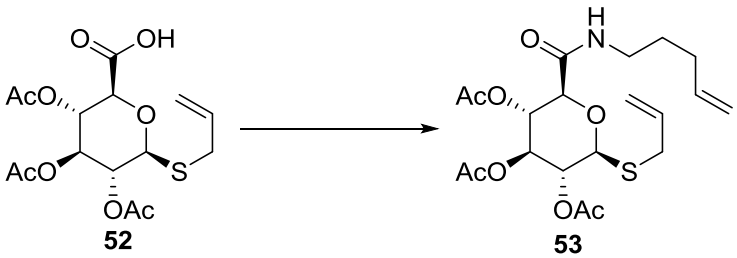
Ester **51** (200 mg, 0.5 mmol) was dissolved in EtOAc (5 mL), followed by the addition of lithium iodide (0.6 g, 4.6 mmol). The reaction mixture was refluxed for 12 h, and subsequently poured onto a 1M HCl solution. The organic layer was separated and the acidic aqueous layer was back-extracted with EtOAc (x 2). The combined organic layers were then washed with satd, $Na_2S_2O_3$ solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford the desired acid **52** as a pale-yellow solid (154 mg, 83 %).

FTIR 3262, 3249, 3082, 2165, 1763, 1742, 1706, 1636, 1417, 1378, 1315, 1262, 1214, 1181, 1077, 1094, 1063, 1033, 1020, 1000, 956, 932, 890, 878, 822, 741, 687, 676, 661 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 – 5.72 (m, 1H, H-7), 5.35 – 5.20 (m, 2H, overlapping signals H-4 & H-3), 5.20 – 5.12 (m, 2H, overlapping signals H-8 & H-8'), 5.08 (t, *J* = 9.3 Hz, 1H, H-2), 4.56 (d, *J* = 10.1 Hz, 1H, H-1), 4.03 (d, *J* = 9.3 Hz, 1H, H-5), 3.41 (dd, *J* = 13.6, 8.3 Hz, 1H, H-6), 3.25 (dd, *J* = 13.6, 6.1 Hz, 1H, H-6'), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.02 (s, 3H, OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 170.2, 169.7, 169.4 (each C=O), 133.1 (C-7), 118.3 (C-8), 82.3 (C-1), 75.3 (C-5), 73.2 (C-H), 69.5 (C-2), 69.1 (C-H), 33.0 (C-6), 20.6 (OAc), 20.6 (OAc), 20.5 (OAc)

HRMS (ESI): m/z calc for $C_{15}H_{19}O_9S$: 375.0750, found 375.0764 $[M-H]^-$



2,3,4-Tri-*O*-acetyl-1-*S*-allyl-β-D-glucopyranuronic acid, amide 53

Acid **52** (290 mg, 0.77 mmol) was dissolved in THF (30 mL), followed by the addition of HBTU (0.36 g, 0.94 mmol) and DIEA (27 mL, 0.20 mmol). Amine **40** (approx. 3 eq.) was subsequently

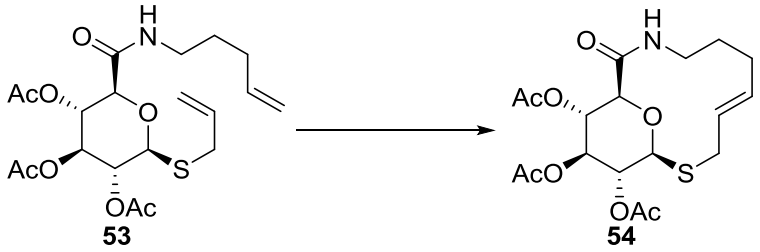
added and solution stirred at rt for 16 h. The reaction mixture was quenched upon addition of 1% HCl. The organic layer was then separated and aqueous layer extracted with CH_2Cl_2. The combined organic layers were then washed with satd. $NaHCO_3$ solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 3:2) afforded amide **53** (280 mg g, 81 %) as a white solid.

R_f = 0.35 (hexane-EtOAc, 3:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (t, *J* = 6.1 Hz, 1H, N-H), 5.87 – 5.66 (m, 2H, overlapping signals H-7 & H-13), 5.26 (t, *J* = 9.3 Hz, 1H, H-3), 5.18 – 5.12 (m, 2H, overlapping signals H-8 & H-8'), 5.10 – 4.96 (m, 4H, H-13, H-13', H-4 & H-2), 4.53 (d, *J* = 9.9 Hz, 1H, H-1), 3.84 (d, *J* = 10.0 Hz, 1H, H-5), 3.35 (dd, *J* = 14.0, 8.3 Hz, 1H, H-6), 3.24 (tq, *J* = 13.8, 7.0 Hz, 3H, H-6', H-9 & H-9'), 2.12 – 2.06 (m, 2H, H-11, H-11'), 2.05 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.61 (p, *J* = 7.2 Hz, 2H, H-10, H-10')

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.6, 169.4, 166.4 (each C=O), 137.6 (C-12), 133.5 (C-7), 118.1 (C-8), 115.4 (C-13), 82.3 (C-1), 76.1 (C-5), 73.0 (C-3), 69.6, 69.6 (C-2, C-4), 38.6 (C-9), 33.4 (C-6), 31.0 (C-11), 28.4 (C-10), 20.7 (OAc), 20.6 (OAc), 20.6 (OAc)

HRMS (ESI): m/z calc for $C_{20}H_{29}O_8NSNa$: 466.1512, found 466.1502 $[M+Na]^+$



2,3,4-Tri-*O*-acetyl-β-*S*-D-Macrolactam 54

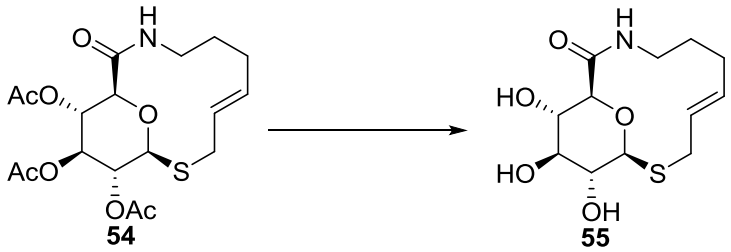
Amide **53** (0.09 g, 0.20 mmol) was dissolved anhydrous degassed toluene (400 mL). The solution was heated to 80 °C, followed by the addition of 2,6-dichloro-1,4-benzoquinone (14.0 mg, 0.078 mmol) and Hoyveda-Grubbs II (17.0 mg, 0.020 mmol). The reaction mixture was stirred at 80 °C for 5 h. The solvent was then removed under reduced pressure and flash chromatography (hexanes-EtOAc, 3:2) afforded macrocycle **54** (56 mg, 65 %) as a white solid.

R_f = 0.3 (hexanes-EtOAc, 3:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 6.4 Hz, 1H, NH), 5.66 – 5.58 (m, 1H, H-7), 5.52 (dt, *J* = 15.4, 6.8 Hz, 1H, H-8), 5.26 (t, *J* = 9.3 Hz, 1H, H-3), 5.11 (m, 2H, overlapping peaks H-4 & H-2), 4.66 (d, *J* = 9.7 Hz, 1H, H-1), 3.89 (d, *J* = 9.8 Hz, 1H, H-5), 3.48 (dd, *J* = 15.7, 7.2 Hz, 1H, H-6), 3.42 – 3.26 (m, 2H, H-11s), 3.13 (ddt, *J* = 15.8, 6.4, 1.6 Hz, 1H, H-6), 2.41 – 2.21 (m, 2H, H-9s), 2.07 (s, 3H, -OAc), 2.05 (s, 3H, -OAc), 2.01 (s, 3H, -OAc), 1.73 – 1.58 (m, 2H, H-10s)

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 169.7, 169.4, 165.7 (C=O), 134.0 (C-8), 130.1 (C-7), 82.0 (C-1), 74.6 (C-5), 72.9 (C-3), 69.4 (C-H), 69.2 (C-H), 40.0 (C-11), 33.2 (C-6), 31.7 (C-9), 27.9 (C-10), 20.7 (OAc), 20.6 (OAc), 20.6 (OAc)

HRMS (ESI): m/z calc for $C_{18}H_{25}NO_8SNa$: 438.1199, found 438.1184 $[M+Na]^+$



2,3,4-Tri-*O*-hydroxy-β-*S*-D-Macrolactam 55

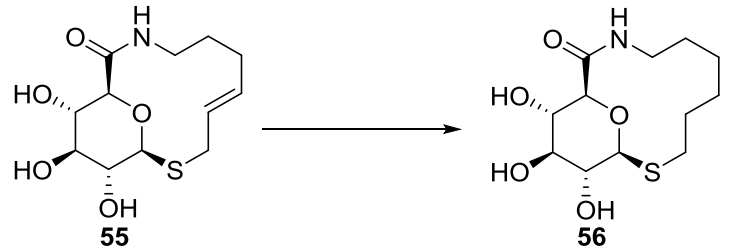
Macrolactam **54** (25.0 mg, 0.06 mmol) was dissolved in MeOH., followed by the addition of ambersep900OH resin (80 mg). The reaction mixture was shaken at rt for 30 mins. The resin was then filtered and solvent removed under reduced pressure. Flash chromatography (CH_2Cl_2-MeOH, 9:1) afforded the deprotected macrolactam **55** (14 mg, 79 %) as a white solid.

R_f = 0.15 (CH_2Cl_2-MeOH, 9:1)

^{1}H NMR (500 MHz, CD_3OD) δ 5.62 (dddd, *J* = 15.2, 7.7, 4.3, 2.7 Hz, 1H, H-7), 5.50 (dt, *J* = 15.0, 6.8 Hz, 1H, H-8), 4.59 (d, *J* = 9.3 Hz, 1H, H-1), 3.68 (d, *J* = 9.2 Hz, 1H, H-5), 3.52 – 3.46 (m, 1H, H-11), 3.44 – 3.37 (m, 3H, overlapping signals H-4, H-3 & H-6), 3.34 (s, 1H, H-2), 3.28 – 3.19 (m, 2H, overlapping signals H-11 & H-6), 2.36 (dddd, *J* = 12.5, 8.0, 5.6, 2.5 Hz, 1H, H-9), 2.25 (dtd, *J* = 16.1, 8.6, 2.9 Hz, 1H, H-9'), 1.73 – 1.60 (m, 2H, H-10 & H-10')

^{13}C NMR (126 MHz, CD_3OD) δ 169.7 (C=O), 132.8 (C-8), 130.8 (C-7), 85.1 (C-1), 77.5 (C-3), 76.1 (C-5), 72.6 (C-2), 72.1 (C-4), 39.7 (C-11), 32.9 (C-6), 31.2 (C-9), 27.7 (C-10)

HRMS (ESI): m/z calc for $C_{14}H_{22}O_5N_2SNa$: 353.1147, found 353.1140 $[M+Na+ACN]^+$



2,3,4-Tri-*O*-hydroxy-β-*S*-D-Macrolactam 56

Compound **55** (5.0 mg, 0.03 mmol) was dissolved in MeOH (3 mL), followed by ambersep900OH resin (25 mg) was added and solution shaken at rt for 30 mins. The resin was filtered and the solution concentrated. The crude residue was purified *via*. flash chromatography (CH_2Cl_2-MeOH, 9:1) to achieve macrocycle **56** (4.5 mg, 89 %).

R_f = 0.13 (CH_2Cl_2-MeOH, 9:1)

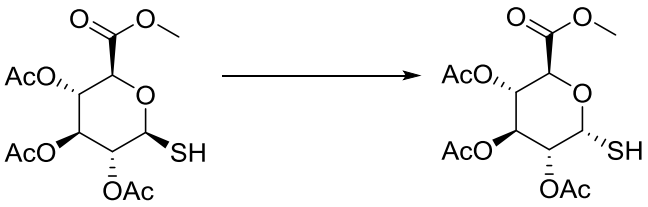
^{1}H NMR (500 MHz, CD_3OD) δ 4.60 (d, *J* = 9.8 Hz, 1H, H-1*), 4.57 (d, *J* = 8.8 Hz, 1H, H-1), 4.07 (d, *J* = 9.5 Hz, 1H, H-5*), 3.82 (t, *J* = 9.3 Hz, 1H, H-4*), 3.78 (d, *J* = 9.2 Hz, 1H, H-4), 3.65 (d, *J* = 9.6 Hz, 1H, H-5), 3.58 (dt, *J* = 13.9, 4.3 Hz, 1H, H-11), 3.43 (t, *J* = 8.9 Hz, 1H, H-3*), 3.37 (t, *J* = 8.8 Hz,

1H, H-3), 3.35 – 3.27 (m, 1H, H-2), 3.20 (t, *J* = 9.3 Hz, 1H, H-2*), 2.95 – 2.84 (m, 1H, H-11), 2.85 – 2.80 (m, 1H, H-6*), 2.67 (dt, *J* = 14.9, 7.6 Hz, 1H, H-6), 2.60 – 2.53 (m, 1H, overlapping signals H-6 & H-6*), 1.63 (ddd, *J* = 22.6, 11.8, 6.0 Hz, 2H, overlapping signals H-7 & H-7'), 1.56 – 1.30 (m, 6H, overlapping signals H-8. H-8', H-9, H-9', H-10 & H-10')

^{13}C NMR (126 MHz, CD_3OD) δ 170.2 (C=O), 85.9 (C-1), 79.0 (C-5), 77.6 (C-3), 74.5 (C-2), 69.5 (C-4), 39.3 (C-11), 30.5 (C-7), 28.9 (C-6), 26.8 (C-8), 26.5, 22.9 (each C-10, C-9)

HRMS (ESI): m/z calc for $C_{12}H_{22}O_5NS$: 292.1219, found 292.1218 $[M+H]^+$

* = minor



50 **57**

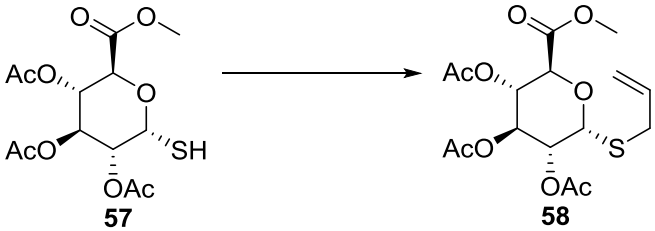
2,3,4-Tri-*O*-acetyl-1-α-*S*-D-glucopyranosiduronic acid, methyl ester 57

Thiol **50** (0.07 g, 0.20 mmol) was dissolved in CH_2Cl_2 (2 mL), followed by the dropwise addition of $TiCl_4$ (55 µL, 0.5 mmol). The reaction mixture was stirred at rt for 10 min and then cooled to 0 °C for 16 h. The reaction was then quenched upon addition of satd. NH_4Cl (aq) and the organic layer separated. The aqueous layer was back extracted with CH_2Cl_2. The combined organic layers were then washed with H_2O, brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to yield the α-anomer **57** (42 mg, 60 %) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (t, *J* = 5.7 Hz, 1H, H-1), 5.35 (t, *J* = 9.0 Hz, 1H, H-3), 5.17 – 5.09 (m, 1H, H-4), 4.98 (dd, *J* = 9.4, 5.2 Hz, 1H, H-2), 4.72 (d, *J* = 9.2 Hz, 1H, H-5), 3.72 (s, 3H, OMe), 2.05 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.00 (s, 3H, OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 169.5, 169.4, 167.7 (each C=O), 76.5 (C-1), 69.8 (C-2), 69.4 (C-5), 68.9 (C-4), 68.6 (C-3), 52.9 (OMe), 20.6 (OAc), 20.6 (OAc) 20.5 (OAc)

HRMS (ESI): m/z calc for $C_{13}H_{17}O_9S$: 349.0593, found 349.0596 $[M-H]^-$



57 **58**

2,3,4-Tri-*O*-acetyl-1-*S*-allyl-α-D-glucopyranuronic acid, methyl ester 58

Thiol **57** (0.27 g, 0.77 mmol) was dissolved in DMF (20 mL). The solution was cooled to 0 °C, followed by the portionwise addition of NaH (0.05 g, 60 % in mineral oil, 1.16 mmol). The reaction mixture was stirred at 0 °C for 10 min, and allyl bromide (0.2 mL, 2.3 mmol) was subsequently charged. The reaction mixture was adjusted to rt for 16 h, and then diluted with Et_2O. The reaction

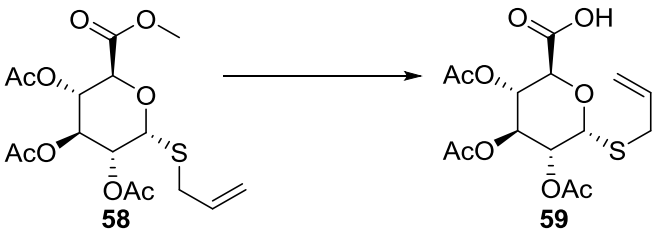
was quenched with satd. NH_4Cl solution and the organic layer was separated. The aqueous layer was back-extracted with Et_2O and the combined organic layers were washed with satd. NH_4Cl solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 1:1) afforded ester **58** (141 mg, 47 %) as a white solid.

R_f = 0.55 (hexanes-EtOAc, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 – 5.70 (m, 1H, H-7), 5.66 (d, *J* = 5.6 Hz, 1H, H-1), 5.38 (t, *J* = 9.4 Hz, 1H, H-3), 5.20 – 5.11 (m, 3H, overlapping peaks H-8, H-8' & H-4), 5.04 (dd, *J* = 9.8, 5.6 Hz, 1H, H-2), 4.74 (d, *J* = 9.6 Hz, 1H, H-5), 3.76 (s, 3H, OMe), 3.22 (dd, *J* = 13.9, 8.5 Hz, 1H, H-6), 3.15 (dd, *J* = 13.9, 5.8 Hz, 1H, H-6'), 2.06 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.03 (s, 3H, OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 169.6, 169.5, 168.0 (each C=O), 132.5 (C-7), 118.6 (C-8), 80.6 (C-1), 70.0 (C-2), 69.7 (C-3), 69.4 (C-4), 68.8 (C-5), 52.8 (OMe), 32.4 (C-6), 20.7 (OAc), 20.6 (OAc), 20.5 (OAc)

HRMS (ESI): m/z calc for $C_{18}H_{25}NO_9SNa$: 454.1148, found 454.1147 $[M+Na]^+$



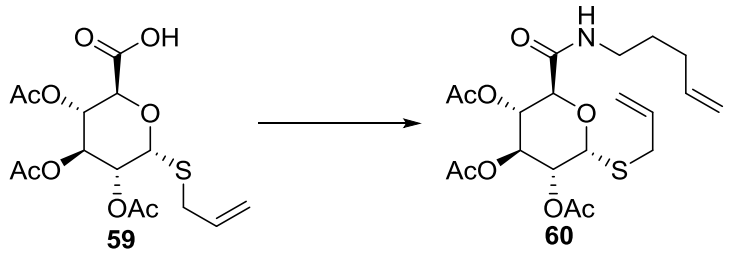
2,3,4-Tri-*O*-acetyl-1-*S*-allyl-α-D-glucopyranuronic acid 59

Thiol **58** (0.07 g, 0.19 mmol) was dissolved in EtOAc, followed by the addition of lithium iodide (0.23 g, 1.68 mmol). The reaction mixture was refluxed for 12 h and subsequently poured onto 1M HCl. The organic layer was separated and the acidic aqueous layer was back-extracted with EtOAc (x 2). The combined organic layers were washed with satd. $Na_2S_2O_3$ solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford the acid **59** as a pale-yellow solid (56 mg, 79 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dddd, *J* = 16.6, 10.1, 8.5, 5.9 Hz, 1H, H-7), 5.66 (d, *J* = 5.5 Hz, 1H, H-1), 5.39 (t, *J* = 9.4 Hz, 1H, H-3), 5.23 – 5.12 (m, 3H, overlapping peaks H-4, H-8 & H-8'), 5.04 (dd, *J* = 9.8, 5.5 Hz, 1H, H-2), 4.75 (d, *J* = 9.6 Hz, 1H, H-5), 3.23 (dd, *J* = 13.9, 8.3 Hz, 1H, H-6), 3.16 (dd, *J* = 13.7, 6.0 Hz, 1H, H-6), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.02 (s, 3H, OAc)

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 169.7, 169.7, 169.7 (C=O), 132.6 (C-7), 118.6 (C-8), 80.7 (C-1), 70.0 (C-2), 69.7 (C-3), 69.3 (C-4), 68.4 (C-5), 32.5 (C-6), 20.7 (OAc), 20.6 (OAc)

HRMS (ESI): m/z calc for $C_{15}H_{19}O_9S$: 375.0750, found 375.0748 $[M-H]^-$



2,3,4-Tri-*O*-acetyl-1-*S*-allyl-α-D-glucopyranuronic acid, amide 60

Acid **59** (0.07 g, 0.19 mmol) was dissolved in THF (5 mL), followed by the addition of HBTU (0.14 g, 0.37 mmol) and DIEA (0.040 mL, 0.223 mmol). The reaction mixture was stirred added for 10 min at rt. Amine **40** (3 equiv., as previously prepared) was added and solution stirred at rt overnight. The reaction was quenched upon addition of 1M HCl. The organic layer was separated and aqueous layer back extracted with EtOAc. The combined organic layers were washed with satd. $NaHCO_3$ solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 3:2) afforded amide **60** (63 mg, 75 %) as a white solid.

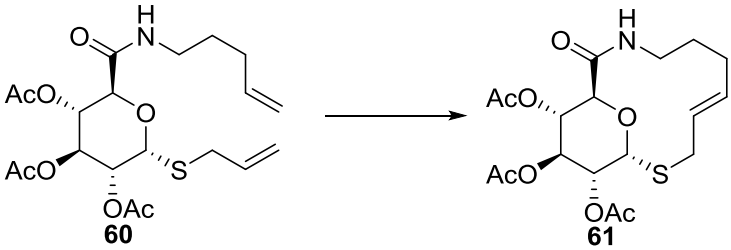
R_f = 0.32 (hexanes-EtOAc, 3:2)

FTIR 3353, 3080, 2943, 1743, 1667, 1640, 1537, 1435, 1368, 1213, 1033, 911, 817, 739, 712, 673 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (t, *J* = 6.0 Hz, 1H, N-H), 5.85 – 5.68 (m, 2H, overlapping signals H-7 & H-12), 5.65 (d, *J* = 5.8 Hz, 1H, H-1), 5.41 (t, *J* = 9.8 Hz, 1H, H-3), 5.16 – 4.95 (m, 6H, overlapping signals H-8, H-8', H-13, H-13', H-2 & H-4), 4.59 (d, *J* = 10.0 Hz, 1H, H-5), 3.35 – 3.17 (m, 2H, overlapping signals H-9 & H-9'), 3.16 – 3.08 (m, 2H, H-6 & H-6'), 2.13 – 2.03 (m, 2H, H-11 & H-11'), 2.08 (s, 3H, -OAc), 2.06 (s, 3H, -OAc), 2.02 (s, 3H, -OAc), 1.63 – 1.60 (m, 2H, H-10 & H-10')

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.8, 169.6, 167.0 (each C=O), 137.6 (C-12), 132.7 (C-7), 118.3 (C-8), 115.4 (C-13), 80.8 (C-1), 70.5 (C-H), 69.8 (C-H), 69.8 (C-3), 68.5 (C-5), 38.6 (C-9), 32.7 (C-6), 31.0 (C-11), 28.4 (C-10), 20.7 (OAc), 20.7 (OAc), 20.62 (OAc)

HRMS (ESI): m/z calc for $C_{22}H_{32}O_8N_2SNa$: 507.1777, found 507.1763 $[M+Na+ACN]^+$



2,3,4-Tri-*O*-acetyl-α-*S*-D-Macrolactam 61

Amide **60** (0.015 g, 0.034 mmol) was dissolved anhydrous degassed toluene (50 mL). The solution was heated to 80 °C, followed by the addition of 2,6-dichloro-1,4-benzoquinone (0.0025 g, 0.0135 mmol) and Hoyveda-Grubbs II (0.0021 g, 0.0034 mmol). The reaction mixture was stirred at 80 °C

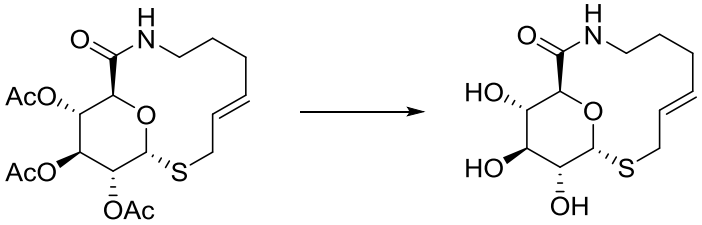
for 5 h. The solvent was removed under reduced pressure and flash chromatography (hexanes-EtOAc, 1:1) afforded macrocycle **61** (7.3 mg, 52 %) as a white solid.

R_f = 0.11 (hexanes-EtOAc, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, 1H, N-H), 5.54 (dd, *J* = 7.3, 3.7 Hz, 3H, overlapping signals H-7, H-8 & H-1), 5.34 (t, *J* = 6.8 Hz, 1H, H-4), 5.28 (t, *J* = 6.9 Hz, 1H, H-3), 4.95 (dd, *J* = 7.2, 4.5 Hz, 1H, H-2), 4.64 (d, *J* = 6.7 Hz, 1H, H-5), 3.48 (dddd, *J* = 14.8, 11.1, 7.2, 3.5 Hz, 1H, H-11), 3.40 (dq, *J* = 13.3, 4.0 Hz, 1H, H-11), 3.33 (dt, *J* = 15.0, 3.2 Hz, 1H, H-6), 3.15 (dd, *J* = 14.7, 8.0 Hz, 1H, H-6), 2.39 (dd, *J* = 14.5, 8.1 Hz, 1H, H-9), 2.10 (s, 6H, 2 x OAc), 2.09 – 1.99 (m, 1H, H-9), 2.03 (s, 3H, OAc), 1.80 (dd, *J* = 16.2, 6.4 Hz, 1H, H-10), 1.62 (d, *J* = 13.2 Hz, 1H, H-10)

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 169.7, 169.0, 166.3 (each C=O), 136.0 (C-H alkene), 127.1 (C-H alkene), 80.8 (C-1), 70.3 (C-5, C-2), 68.6 (C-3), 67.0 (C-4), 40.5 (C-11), 34.9 (C-6), 31.3 (C-9), 27.7 (C-10), 20.9 (OAc), 20.7 (OAc), 20.6 (OAc)

HRMS (ESI): m/z calc for $C_{18}H_{25}NO_8SNa$: 438.1199, found 438.1187 $[M+Na]^+$



2,3,4-Tri-*O*-hydroxy-α-*S*-D-Macrolactam 62

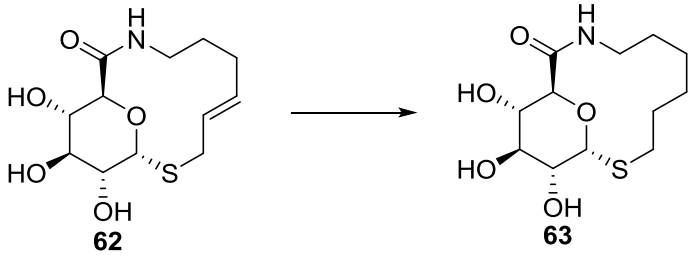
Compound **61** (20.0 mg, 0.48 mmol) was dissolved in MeOH, followed by the addition ambersep900OH resin (100 mg). The reaction mixture was shaken at rt for 1 h. The resin was removed by filtration and the solvent was removed under reduced pressure. Flash chromatography (CH_2Cl_2-MeOH, 9:1) afforded macrocycle **62** (13 mg, 92 %) as a white solid.

R_f = 0.27 (CH_2Cl_2-MeOH, 9:1)

^{1}H NMR (500 MHz, D_2O) δ 5.47 (d, *J* = 5.4 Hz, 1H, H-1), 5.43 – 5.41 (m, 2H, overlapping signals H-7 & H-8), 4.36 (d, *J* = 8.9 Hz, 1H, H-5), 3.76 (dd, *J* = 8.7, 5.4 Hz, 1H, H-2), 3.61 (t, *J* = 8.6 Hz, 1H, H-4), 3.52 (t, *J* = 8.4 Hz, 1H, H-3), 3.40 (dt, *J* = 13.5, 3.5 Hz, 1H, H-11), 3.28 – 3.22 (m, 1H, H-6), 3.10 – 3.00 (m, 2H, overlapping peaks H-11' & H-6'), 2.22 (dd, *J* = 15.1, 7.5 Hz, 1H, H-9), 1.88 (ddd, *J* = 14.3, 11.1, 8.0 Hz, 1H, H-9'), 1.70 – 1.49 (m, 2H, overlapping peaks H-10 & H-10')

^{13}C NMR (126 MHz, D_2O) δ 169.8 (C=O), 135.8 (C-H alkene), 126.8 (C-H alkene), 86.3 (C-1), 73.6 (C-3), 71.6 (C-5), 71.4 (C-2), 69.6 (C-4), 40.5 (C-11), 34.1 (C-6), 30.2 (C-9), 25.8 (C-10)

HRMS (ESI) m/z calc for $C_{14}H_{22}N_2O_5SNa$: 353.1147, found 353.1157 $[M+Na+ACN]^+$



2,3,4-Tri-*O*-hydroxy-α-*S*-D-macrolactam 63

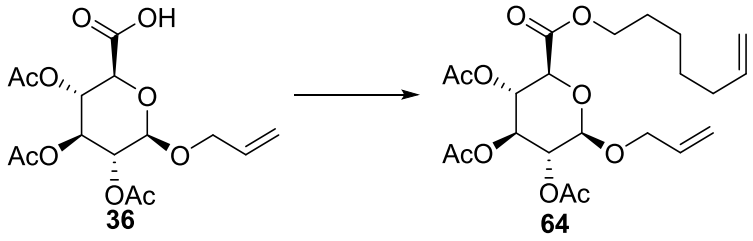
Compound **63** (0.008 g, 0.027 mmol) was dissolved in MeOH (3 mL), followed by the addition of ambersep900OH resin (40 mg). The reaction mixture was shaken at rt for 1 h. The resin was filtered and the solvent removed under reduced pressure. Flash chromatography (CH_2Cl_2-MeOH, 4:1) to afforded macrocycle **63** (6.3 mg, 80 %) as a white solid.

R_f = 0.4 (CH_2Cl_2-MeOH, 4:1)

^{1}H NMR (500 MHz, CD_3OD) δ 5.27 (d, *J* = 5.5 Hz, 1H, H-1), 5.16 (d, *J* = 3.0 Hz, 1H, H-1*), 4.88 (d, *J* = 9.6 Hz, 1H, H-5), 4.50 (d, *J* = 4.8 Hz, H-5*), 3.91 (t, *J* = 5.0 Hz, 1H, H-4*), 3.81 – 3.72 (m, 2H, overlapping peaks H-2 & H-7), 3.68 (t, *J* = 9.2 Hz, 1H, H-4), 3.53 (t, *J* = 9.3 Hz, 1H, H-3), 3.03 (dt, *J* = 14.6, 4.9 Hz, 1H, CH_2), 2.77 – 2.71 (m, 2H, CH_2), 2.12 – 2.00 (m, 1H, CH_2), 1.75 – 1.56 (m, 3H, CH_2), 1.55 – 1.46 (m, 1H, CH_2), 1.44 – 1.36 (m, 1H, CH_2), 1.35 – 1.24 (m, 2H, CH_2)

^{13}C NMR (126 MHz, CD_3OD) δ 171.7 (C=O), 87.6 (C-1), 74.0 (C-3), 71.5 (C-4), 71.3 (C-2), 67.0 (C-5), 39.1 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 26.2 (CH_2), 22.2 (CH_2), 21.1 (CH_2)

HRMS (ESI): m/z calc for $C_{12}H_{22}NO_5S$: 292.1219, found 292.1218 $[M+H]^+$



2,3,4-Tri-*O*-acetyl-1-*O*-allyl-β-D-glucopyranuronic acid, methyl ester 64

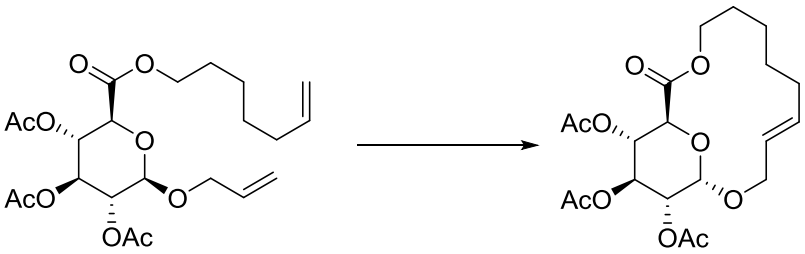
Compound **36** (0.5 g, 1.4 mmol) was dissolved in DMF (10 mL), followed by the addition of $NaHCO_3$ (0.23 g, 2.78 mmol) and 7-bromo-1-heptene (0.63 mL, 4.16 mmol). The reaction mixture was heated to 110 °C for 1 h. The solution was then diluted with Et_2O and satd. NH_4Cl solution added. The organic layer was separated and aqueous layer back extracted with Et_2O (x 2). The combined organic layers were washed with satd. NH_4Cl solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 4:1) afforded ester **64** (570 mg, 90 %) as a clear oil.

R_f = 0.33 (hexanes-EtOAc, 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 – 5.74 (m, 2H, overlapping peaks H-7 & H-14), 5.31 – 5.17 (m, 4H, overlapping peaks, H-3, H-4, H-8 & H-8'), 5.07 – 5.01 (m, 2H, overlapping peaks H-2 & H-13), 5.00 – 4.92 (m, 1H, H-13'), 4.60 (d, *J* = 7.7 Hz, 1H, H-1), 4.39 – 4.32 (m, 1H, H-6), 4.17 (dt, *J* = 10.8, 6.8 Hz, 1H, H-9), 4.13 – 4.06 (m, 2H, H-6' & H-9'), 4.04 – 4.00 (m, 1H, H-5), 2.10 – 2.01 (m, 2H, H-13), 2.05 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.65 (p, *J* = 6.9 Hz, 2H, H-10 & H-10'), 1.45 – 1.32 (m, 4H, overlapping peaks H-11, H-11', H-12 & H-12')

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 169.2, 169.2, 166.8 (C=O), 138.6 (C-14), 133.1 (C-7), 117.8 (C-8), 114.6 (C-13), 99.5 (C-1), 72.8 (C-5), 72.3 (C-3), 71.2 (C-2), 70.0 (C-6), 69.4 (C-4), 66.1 (C-9), 33.5 (C-13), 28.4, 28.2 (each C-10,C-12), 25.2 (C-11), 20.6 (OAc), 20.6 (OAc), 20.6 (OAc)

HRMS (ESI): m/z calc for $C_{22}H_{32}O_{10}Na$: 479.1893, found 479.1889 $[M+Na]^+$



2,3,4-Tri-*O*-acetyl-1-*O*-allyl-β-D-macrolactam 65

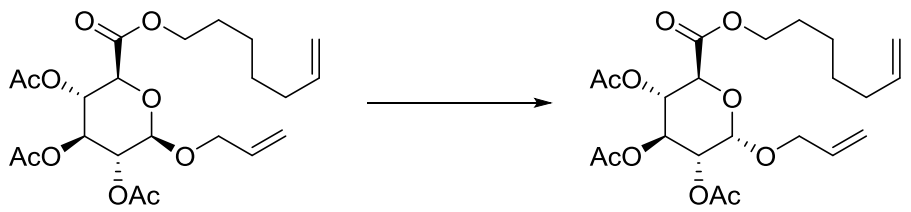
Ester **64** (0.08, 0.18 mmol) was dissolved degassed anhydrous toluene (250 mL). The solution was heated to 80 °C and Grubbs II (0.015 g, 0.018 mmol) was subsequently added. The solution was stirred at 80 °C for 1 h. Upon reaction completion, the toluene was removed under reduced pressure and flash chromatography (hexanes-EtOAc, 4:1) afforded macrocycle **65** (64 mg, 83 %) as a white solid.

R_f = 0.3 (hexanes-EtOAc, 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (ddd, *J* = 15.6, 7.8, 5.1 Hz, 1H, H-7), 5.51 (dt, *J* = 15.3, 6.8 Hz, 1H, H-8), 5.32 (t, *J* = 9.7 Hz, 1H, H-4), 5.19 (t, *J* = 9.3 Hz, 1H, H-3), 5.02 (dd, *J* = 9.4, 7.7 Hz, 1H, H-2), 4.60 (d, *J* = 7.5 Hz, 1H, H-1), 4.49 (dd, *J* = 13.6, 4.7 Hz, 1H, H-6), 4.28 (ddd, *J* = 10.8, 6.9, 4.0 Hz, 1H, H-13), 4.20 (ddd, *J* = 11.0, 7.5, 3.6 Hz, 1H, H-13'), 3.99 (d, *J* = 10.0 Hz, 1H, H-1), 3.91 (dd, *J* = 13.5, 7.6 Hz, 1H, H-6'), 2.15 – 2.05 (m, 1H, H-9), 2.04 (s, 3H, -OAc), 2.00 (s, 3H, -OAc), 1.99 (s, 3H, -OAc), 1.97 – 1.92 (m, 1H, H-9), 1.76 – 1.66 (m, 1H, H-10), 1.60 – 1.42 (m, 3H, overlapping peaks H-10, H-11 & H-12), 1.37 – 1.25 (m, 2H, overlapping peaks H-11 & H-12)

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 169.3, 169.2, 166.5 (C=O), 132.3 (C-8), 129.1 (C-7), 103.2 (C-1), 73.9 (C-6), 72.7 (C-5), 72.6 (C-3), 71.5 (C-2), 68.8 (C-4), 64.4 (C-13), 30.3 (C-9), 26.9 (C-10), 25.8, 21.7 (each C-11, C-12) 20.7 (OAc), 20.6 (OAc), 20.6 (OAc)

HRMS (ESI): m/z calc for $C_{20}H_{28}O_{10}Na$: 451.1580, found 451.1588 $[M+Na]^+$



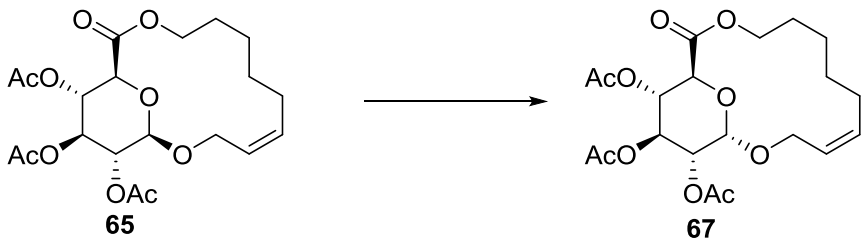
2,3,4-Tri-*O*-acetyl-1-*O*-allyl-α-D-glucopyranuronic acid, methyl ester 66

Ester **64** (68 µmol) was dissolved in anhydrous $CDCl_3$ (0.75 mL), and $SnCl_4$ in $CDCl_3$ (0.1 mL of 0.34 M, 34 µmol) subsequently charged. Upon reaction completion, satd. $NaHCO_3$ solution was added. The mixture was diluted with $CDCl_3$ and the organic layer separated, washed with brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to achieve **66** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H, H-7), 5.78 (tt, *J* = 13.3, 5.1 Hz, 1H, H-14), 5.56 (t, *J* = 9.7 Hz, 1H, H-3), 5.33 (d, *J* = 17.2 Hz, 1H, H-8), 5.28 – 5.18 (m, 3H, overlapping signals, H-4, H-8' & H-1), 5.06 – 4.91 (m, 3H, overlapping signals H-2, H-15 & H-15'), 4.38 (d, *J* = 10.2 Hz, 1H, H-5), 4.30-4.17 (m, *J* 2H, overlapping signals H-6 & H-9), 4.15-4.05 (m, 2H, overlapping signals H-6 & H-9), 2.09 (s, 3H, OAc), 2.10 – 2.02 (m, 2H, overlapping signals H-13 & H-13'), 2.04 (s, 6H, 2 x OAc), 1.64 (p, *J* = 7.3 Hz, 2H, H-10 & H-10'), 1.46 – 1.31 (m, 4H, overlapping signals H-11, H-11', H-12 & H-12')

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.3, 170.0, 168.7 (C=O), 138.5 (C-14), 132.7 (C-7), 118.6 (C-8), 114.6 (C-15), 95.1 (C-1), 70.5 (C-2), 69.7 (C-4), 69.4 (C-3), 69.3 (C-6), 68.4 (C-5), 66.7 (C-9), 33.5 (C-13), 28.4 (CH_2), 28.1 (CH_2), 25.2 (CH_2), 20.8 (2 x OAc), 20.7 (OAc)

HRMS (ESI): m/z calc for $C_{22}H_{32}O_{10}Na$: 479.1893, found 479.1890 $[M+Na]^+$



2,3,4-Tri-*O*-acetyl-1-α-D-*O*-macrolactam 67

Ester **65** (68 µmol) was dissolved in anhydrous $CDCl_3$ (0.75 mL), followed by the addition of the $SnCl_4$ in $CDCl_3$ (0.1 mL of 0.34 M, 34 µmol). Upon reaction completion, satd. $NaHCO_3$ solution was added. The mixture was diluted with $CDCl_3$ and organic layer separated, washed with brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to achieve **67** as a clear oil.

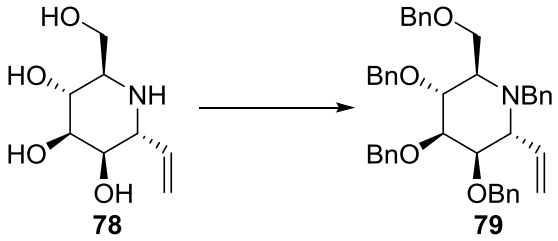
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 – 5.68 (m, 1H, H-7), 5.63 – 5.53 (m, 1H, H-8), 5.51 – 5.43 (m, 1H, H-2), 5.28 – 5.21 (m, 2H, overlapping peaks H-1 & H-4), 4.84 (dd, *J* = 10.2, 3.9 Hz, 1H, H-3), 4.55 – 4.50 (m, 1H, H-6), 4.49 (d, *J* = 10.2 Hz, 1H, H-5), 4.35 (ddd, *J* = 10.8, 7.9, 4.6 Hz, 1H, H-13), 4.15 – 4.10 (m, 1H, H-13), 3.88 (dd, *J* = 13.1, 8.8 Hz, 1H, H-6), 2.07 (s, 3H, OAc), 2.10 – 2.00 (m,

2H, H-9 & H-9'), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.67 – 1.55 (m, 2H, H-12), 1.53 – 1.36 (m, 4H, overlapping peaks H-10, H-10', H-11 & H-11')

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 170.1, 169.5, 167.8 (C=O), 134.5 (C-8), 128.0 (C-7), 98.1 (C-1), 74.1 (C-6), 70.8 (C-3), 69.9 (C-2), 69.2 (C-4), 68.2 (C-5), 65. (C-13), 29.4 (C-9), 25.8 (C-12), 25.7 (C-10), 22.3 (C-11), 20.7 (2 x OAc), 20.6 (OAc)

HRMS (ESI): m/z calc for $C_{20}H_{28}O_{10}Na$: 451.1580, found 451.1592 $[M+Na]^+$

7.3 Experimental Data for Chapter 4



78 **79**

***N*-benzyl-2,3,4,6-tetra-*O*-benzyl-5-deoxy-1-vinyl-1,5-piperidine**

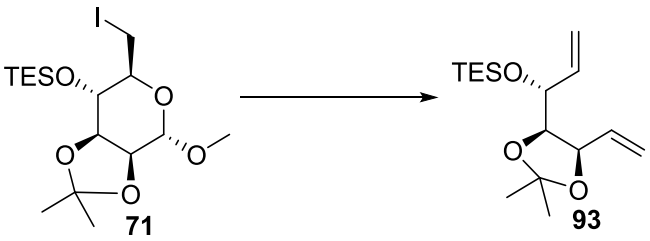
Compound **78** (60.0 mg, 0.32 mmol) was dissolved in DMF (4 mL) and cooled to -78 °C. NaH (70.0 mg, 60 % in mineral oil) was added and reaction mixture warmed to 0 °C. The solution was stirred at 0 °C for a further 10 min and benzyl bromide (0.29 mL, 2.4 mmol) subsequently added. The reaction mixture was adjusted to rt and stirred for 12 h. Upon reaction completion, the mixture was diluted with water and organic layer exracted with EtOAc. The combined organic layers were then dried over Na_2SO_4, filtered and solvent removed under reduced pressure to achieve **79** (122 mg, 60 %) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.13 (m, 25H, overlapping aromatic peaks), 5.84 (dt, *J* = 17.8, 9.1 Hz, 1H, H-7), 5.20 (d, *J* = 10.6 Hz, 1H, H-8'), 5.02 (d, *J* = 17.1 Hz, 1H, H-8'), 4.81 (d, *J* = 11.2 Hz, 1H, Ar-CH_2), 4.58 – 4.49 (m, 4H, Ar-CH_2 X 4), 4.44 – 4.34 (m, 3H, Ar-CH_2 X 3), 4.23 (d, *J* = 14.2 Hz, 1H, N-CH_2), 3.94 (t, *J* = 8.0 Hz, 1H, H-4), 3.82 (d, *J* = 4.0 Hz, 2H, H-5 & H-5'), 3.74 (dd, *J* = 8.2, 3.1 Hz, 1H, H-3), 3.62 (d, *J* = 15.0 Hz, 2H, H-2, N-CH_2), 3.54 (dd, *J* = 8.1, 4.3 Hz, 1H, H-1), 3.09 (dt, *J* = 8.4, 4.1 Hz, 1H, H-5)

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.56, 138.76, 138.56, 138.50, 138.40 (QC Ar-C), 134.41 (C-6), 128.52, 128.28, 128.24, 128.23, 128.14, 128.01, 127.92, 127.83, 127.74, 127.59, 127.44, 127.42, 127.39, 127.34 (Ar-C), 119.16 (C-8), 79.45 (C-3), 76.83 (C-2), 76.15 (C-4), 74.21, 72.91, 71.68, 71.16 (Ar-CH_2) , 68.81 (C-5), 60.22 (C-1), 59.27 (C-5), 52.88 (N-CH_2)

HRMS (ESI): m/z calc for $C_{43}H_{45}NO_4Na$: 662.3246, found: 662.3251 $[M+H]^+$

7.4 Experimental Data for Chapter 5



(3R,4R,5R)-3,4-*O*-isopropylidine-1,2,6,7-tetradeoxy-5-*O*-triethylsilyl-1,6-heptadiene 93

Compound **71** (2.5 g, 5.45 mmol) was dissolved in THF and cooled to -78 °C. nBuLi (1.1 mL, 2.5 M in hexanes) was added and solution stirred until full conversion to the aldehyde was complete as observed by TLC. In a separate vessel methyltriphenylphosphonium iodide (4.43 g, 10.9 mmol) was suspended in THF (26 mL) and cooled to -78 °C and to this nBuLi (2.7 mL, 2.5 M in hexanes) was slowly added and solution stirred at -78 °C for a further 15 min. The solution containing the in-situ generated aldehyde was transferred to the second vessel and reaction allowed to attain room temp over 2 h. Satd. NH_4Cl (aq) was added and the mixture then extracted with EtOAc, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (EtOAc-hexane, 1:40) gave **93** (1.62 g, 80 %) as a clear oil.

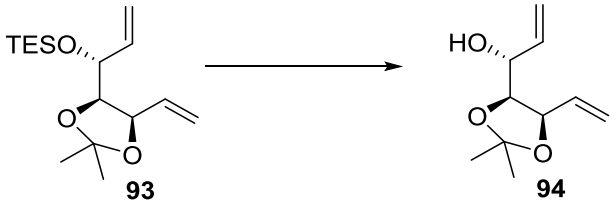
R_f = 0.48 (EtOAc-hexane, 1:20)

FTIR: 2986, 2954, 2877, 1458, 1415, 1379, 1369, 1238, 1216, 1146, 1123, 1092, 1036, 1003, 973, 927, 869, 844, 778 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 5.96 (ddd, *J* = 17.8, 10.3, 8.2 Hz, 1H), 5.87 (ddd, *J* = 16.6, 10.5, 5.6 Hz, 1H), 5.36 – 5.27 (m, 2H, overlapping signals), 5.23 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.15 (dt, *J* = 10.5, 1.8 Hz, 1H), 4.45 (dd, *J* = 8.2, 6.9 Hz, 1H), 4.16 (t, *J* = 6.3 Hz, 1H), 3.98 (t, *J* = 6.5 Hz, 1H), 1.50 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$), 0.96 (t, *J* = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.61 (m, *J* = 7.9, 3.0 Hz, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$): δ 136.9, 134.5, 118.6, 116.5 (alkene CH/CH_2), 108.6 (-*C*$(CH_3)_2$), 81.7 (CH-O), 79.0 (CH-O) 72.4 (CH-O), 27.7 ($C(CH_3)_2$), 25.5 ($C(CH_3)_2$), 6.7 ($Si(CH_2CH_3)_3$), 5.0 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{16}H_{31}O_3Si$: 299.2042, found: 299.2044 $[M+H]^+$



(3R,4S,5R)-5-hydroxy-3,4-*O*-isopropylidene-1,2,6,7-tetradeoxy-5-*O*-triethylsilyl-1,6-heptadiene 94

Compound **93** (3.80 g, 12.7 mmol) was dissolved in anhydrous THF (100 mL). TBAF (38 mL, 1 M in THF) was charged slowly and solution stirred at room temp overnight. Reaction mixture was then quenched with 3M NaOH (50 mL) and stirred for 15 min. The organic layer was separated and aqueous layer extracted with EtOAc. Combined organic layers were washed with 3M NaOH, H_2O, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexane, 4:1) gave alkene **94** (1.92 g, 82 %) as a clear oil. The NMR spectroscopic data (400 MHz, 100 MHz) published previously[215] showed agreement with those data (500 MHz, 126 MHz) obtained for **94** prepared here.

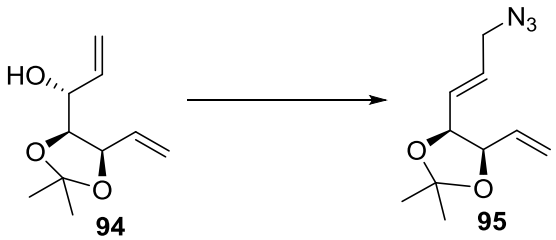
R_f = 0.56 (EtOAc-hexanes, 1:4)

FTIR 3482, 2987, 2936, 1644, 1457, 1428, 1380, 1214, 1165, 1146, 1110, 992, 925, 869, 804, 690, 662 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (ddd, *J* = 17.7, 10.3, 7.8 Hz, 1H), 5.85 (ddd, *J* = 16.6, 10.5, 5.4 Hz, 1H), 5.43 – 5.34 (2H, overlapping signals), 5.30 (d, *J* = 10.2 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.61 (t, *J* = 7.3 Hz, 1H), 4.17 – 4.05 (2H, overlapping signals), 2.30 (d, *J* = 5.3 Hz, 1H, OH), 1.54 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$): δ 136.7, 133.9, 119.4, 117.0 (alkene CH&CH_2), 108.7 ($C(CH_3)_2$), 80.6, 78.9, 70.5 (each CH-O), 27.3 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$)

HRMS (ESI): m/z calc for $C_{10}H_{17}O_3$:185.1178, found: 185.1186 $[M+H]^+$



(5E,3R,4S)-7-azido-3,4-*O*-isopropylidene-1,2,5,6,7-pentadeoxy-1,5-heptadiene 95

Compound **94** (0.4 g, 2.17 mmol) was dissolved in anhydrous THF (13 mL) and then PPh_3 (0.97 g, 3.69 mmol) was added and solution cooled to 0˚C. DIAD (0.73 mL, 3.69 mmol) and DPPA (0.8 mL, 3.69 mmol) were charged slowly and solution allowed to adjust to room temp overnight. The solvent was removed under reduced pressure. Flash chromatography (hexane-EtOAc, 40:1) gave azide **95** (0.34 g, 74 %) as a clear oil.

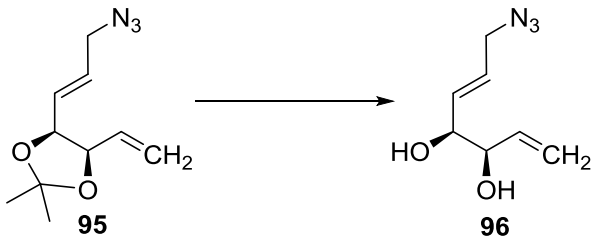
R_f = 0.31 (EtOAc-hexane, 1:20)

FTIR 2987, 2936, 2097, 1455, 1380, 1371, 1245, 1214, 1163, 1114, 1043, 1018, 972, 929, 871, 792, 663 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.86 – 5.63 (m, 3H, overlapping signals), 5.33 (d, *J* = 17.3 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.67 (t, *J* = 6.8 Hz, 1H), 4.63 (t, *J* = 7.0 Hz, 1H), 3.82-3.74 (m, 2H), 1.54 (s, 3H,-$C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 133.9, 131.2, 126.7, 118.5 (alkene CH&CH_2), 109.9 ($C(CH_3)_2$), 79.7, 78.5 (each CH), 52.0 (CH_2N_3), 27.9 ($C(CH_3)_2$), 25.4 ($C(CH_3)_2$)

HRMS (ESI): m/z calc for $C_{10}H_{16}N_3O_2$: 210.1243, found: 210.1245 $[M+H]^+$



(5E,3R,4S)-7-azido-3,4-hydroxy-1,2,5,6,7-pentadeoxy-1,5-heptadiene 96

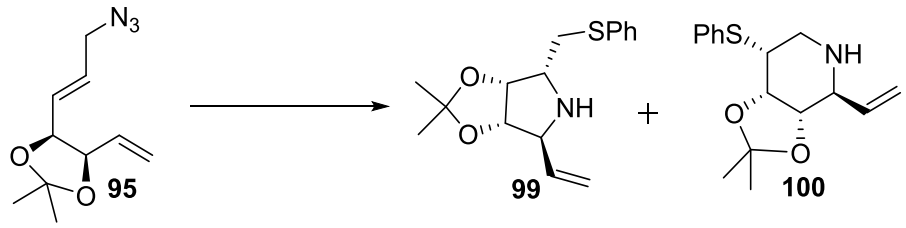
Compound **95** (0.1, 0.48 mmol**)** was dissolved in dil. HCl (2 mL) and the mixture was stirred at room temp for 30 min. The solution was extracted with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash chromatography (hexane-EtOAc, 1:1) gave **96** (58 mg, 72 %) as a pale-yellow oil.

R_f = 0.29 (hexane-EtOAc, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 – 5.70 (3H, overlapping signals), 5.39 (d, *J* = 16.2 Hz, 1H), 5.30 (d, *J* = 10.6 Hz, 1H), 4.27 (t, *J* = 4.5 Hz, 1H), 4.23 (t, *J* = 5.0 Hz, 1H), 3.82 (d, *J* = 5.0 Hz, 2H), 2.26 (s, 1H, OH), 2.17 (s, 1H, OH)

^{13}C NMR (126 MHz, $CDCl_3$): δ 135.6, 132.8, 126.2, 117.9 (alkene CH/CH_2), 75.4 (CH-O), 74.1 (CH-O), 52.1 (CH_2N_3)

HRMS (ESI): m/z calc for $C_7H_{11}N_3O_2Cl$: 204.0540, found: 204.0544 $[M+Cl]^-$



(1S,2S,3R,4R)-1-ethenyl-2,3-*O*-isopropylidene--1,4,5,6,7-pentadeoxy-5-thiophenyl-1,4-pyrrolidine 99 (1S,2S,3S,4R)-1-ethenyl-2,3-*O*-isopropylidene--1,4,5,6,7-pentadeoxy-4-thiophenyl-1,5-piperidine 100

Azide **95** (0.075 g, 0.36 mmol) was dissolved in DMF (30 mL) and the solution was heated to 100 °C and stirred until TLC analysis showed the azide was consumed (1-3 h). Then PhSH (0.18 mL, 1.79 mmol) was added and solution allowed to attain room temp and left overnight. The reaction mixture was then diluted with Et_2O and washed with aqueous satd. NH_4Cl, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (hexane-EtOAc, 7:3) gave **99** (26 mg, 25 %) and **100** (12 mg, 11 %), both as clear oils

Data for **99**

R_f = 0.34 (EtOAc-hexane, 2:3)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.4 Hz, 2H, aromatic H), 7.31 – 7.24 (m, 2H, aromatic H), 7.18 (t, *J* = 7.3 Hz, 1H, aromatic H), 5.72 (ddd, *J* = 17.4, 10.6, 5.0 Hz, 1H), 5.24 (dt, *J* = 17.0, 1.6 Hz, 1H), 5.11 (dt, *J* = 10.6, 1.7 Hz, 1H), 4.63 – 4.53 (m, 2H), 3.74 (dd, *J* = 4.9, 2.3 Hz, 1H), 3.23 – 3.11 (m, 3H), 1.50 (s, 3H, $C(CH_3)_2$), 1.32 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4 (aromatic C), 136.0 (alkene CH), 129.1 (2 aromatic CH), 128.8 (2 aromatic CH), 126.0 (aromatic CH), 115.9 (alkene CH_2), 111.2($C(CH_3)_2$), 85.8 (CH-O), 81.2 (CH-O), 65.0 (CH-N), 60.0 (CH-N), 32.7 (CH_2S), 26.0 ($C(CH_3)_2$), 24.1 ($C(CH_3)_2$)

HRMS (ESI): m/z calc for $C_{16}H_{22}NSO_2$: 292.1371, found: 292.1365 $[M+H]^+$

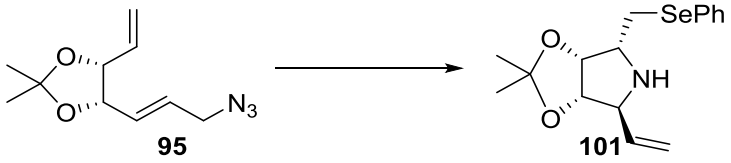
Data for **100**

R_f = 0.22 (EtOAc-hexanes, 2:3)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H, aromatic H), 7.32 – 7.21 (m, 3H, aromatic H), 5.85 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 4.46 (t, *J* = 4.1 Hz, 1H), 3.80 (dd, *J* = 8.9, 4.5 Hz, 1H), 3.53 (dt, *J* = 9.4, 4.5 Hz, 1H), 3.19 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.07 (dd, *J* = 12.0, 5.2 Hz, 1H), 2.96 (t, *J* = 11.8 Hz, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.0 (alkene CH) 134.1 (aromatic C), 131.7 (2 aromatic CH), 129.0 (2 aromatic CH), 127.3 (aromatic CH), 117.1 (alkene CH_2), 109.6 ($C(CH_3)_2$), 77.4 (CH-O), 74.7 (CH-O), 60.8 (CHN), 46.5 (CH_2N), 45.6 (CH-S), 28.3 ($C(CH_3)_2$), 26.3 ($C(CH_3)_2$)

HRMS (ESI): m/z calc for $C_{16}H_{22}NSO_2$: 292.1371, found: 292.1363 $[M+H]^+$



95 **101**

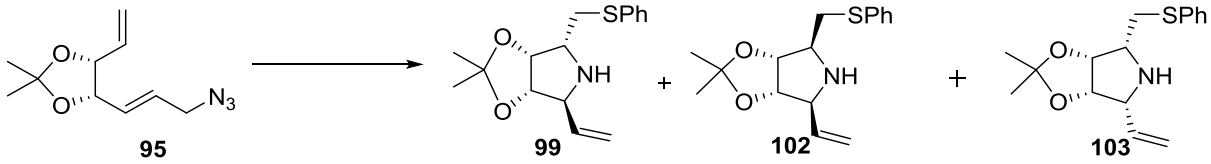
(1S,2S,3R,4R)-1-ethenyl-2,3-*O*-isopropylidene-1,4,5,6,7-pentadeoxy-5-selenaylphenyl-1,4-pyrrolidine 101

Diphenyl diselenide (0.373 g, 1.195 mmol) was dissolved in degassed DMF (15 mL) and heated to 60 °C. $NaBH_4$ (0.045 g, 1.195 mmol) was added and solution stirred at 60 °C for 30 mins. This reaction mixture was subsequently heated to 110 °C for 1 h. In a separate vessel the azide **12** (0.050 g, 0.239 mmol) was dissolved in degassed DMF (5 mL) and heated to 100 °C until TLC analysis showed consumption of the azide **95** (1-3 h). Under inert conditions, the contents of the latter vessel were then transferred to the mixture containing in situ generated sodium phenylselenolate. The mixture was allowed to attain room temp and stirred for 12 h. This mixture was diluted with Et_2O and washed with aqueous satd. NH_4Cl solution, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexane-EtOAc, 7:3) gave **101** (40 mg, 50 %)

R_f = 0.35 (EtOAc-hexane, 3:7)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.0 Hz, 2H, aromatic H), 7.29 – 7.18 (m, 3H, aromatic H), 5.72 (ddd, *J* = 16.4, 10.6, 5.0 Hz, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 5.11 (d, *J* = 10.6 Hz, 1H), 4.59 (s, 2H), 3.75 (d, *J* = 4.9 Hz, 1H), 3.24 – 3.14 (m, 2H), 3.11 (dd, *J* = 11.9, 7.0 Hz, 1H), 1.50 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.13 (alkene CH), 132.51 (2 aromatic CH), 130.68 (aromatic C), 129.01(2 aromatic CH), 126.84 (aromatic CH), 115.90 (alkene CH_2), 111.19 ($C(CH_3)_2$), 86.07 (CH-O), 81.61 (CH-O), 65.07 (CH-N), 60.70 (CH-N), 26.52 (CH_2Se), 26.00 ($C(CH_3)_2$), 24.11 ($C(CH_3)_2$)
HRMS (ESI): m/z calc for $C_{16}H_{22}NO_2Se$: 340.0816, found: 340.0822 $[M+H]^+$



(1S,2S,3R,4R)-1-ethenyl-2,3-*O*-isopropylidene--1,4,5,6,7-pentadeoxy-5-thiophenyl-1,4-pyrrolidine 99 (1S,2S,3R,4S)-1-ethenyl-2,3-*O*-isopropylidene--1,4,5,6,7-pentadeoxy-5-thiophenyl-1,4-pyrrolidine 102 (1R,2S,3R,4R)-1-ethenyl-2,3-*O*-isopropylidene--1,4,5,6,7-pentadeoxy-5-thiophenyl-1,4-pyrrolidine 103

Compound **95** (0.075 g, 0.36 mmol) was dissolved in toluene (30 mL) and the mixture was heated to 100 ^{o}C and then stirred for 1 h. Thiophenol (0.18 mL, 1.79 mmol) was subsequently added and solution allowed to attain room temp and left overnight. The solvent was removed under reduced pressure and flash chromatography (hexane-EtOAc, 3:2) gave **99** (27 mg, 30 %), **102** (7 mg, 7 %) & **103** (10 mg, 10 %), all as clear oils.

Data for **103**

R_f = 0.43 (EtOAc-hexane, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.7 Hz, 2H, aromatic H), 7.31 – 7.25 (m, 2H, aromatic H), 7.18 (t, *J* = 7.4 Hz, 1H, aromatic H), 5.93 (ddd, *J* = 17.4, 10.5, 6.8 Hz, 1H), 5.29 (d, *J* = 17.3 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.65 (t, *J* = 4.9 Hz, 1H), 4.58 (t, *J* = 4.9 Hz, 1H), 3.34 – 3.30 (m, 1H), 3.25 – 3.12 (m, 2H), 3.00 (td, *J* = 6.9, 3.9 Hz, 1H), 1.48 (s, 3H, $C(CH_3)_2$), 1.32 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.30 (aromatic C), 133.72 (C-6), 129.08 (2 aromatic CH), 128.91 (2 aromatic CH), 126.01 (aromatic CH), 117.68 (alkene CH_2), 111.24 ($C(CH_3)_2$), 83.08 (CH-O), 81.30 (CH-O), 64.89 (CH-N), 61.36 (CH-N), 32.18 (CH_2S), 25.68 ($C(CH_3)_2$), 24.21 ($C(CH_3)_2$)
HRMS (ESI): m/z calc for $C_{16}H_{22}NSO_2$: 292.1371, found: 292.1382 $[M+H]^+$

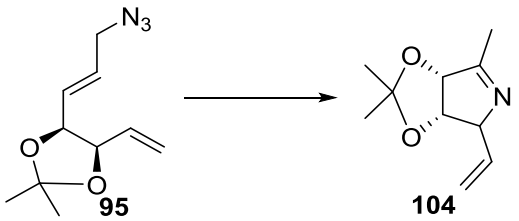
Data for **102**

R_f = 0.64 (EtOAc-hexane, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.7 Hz, 2H, aromatic H), 7.28 (dd, *J* = 13.9, 6.3 Hz, 2H, aromatic H), 7.19 (t, *J* = 7.3 Hz, 1H, aromatic H), 5.88 (ddd, *J* = 17.0, 10.2, 6.3 Hz, 1H), 5.30 (d, *J* = 17.5 Hz, 1H), 5.14 (d, *J* = 10.3 Hz, 1H), 4.46-4.34 (m, 2H), 3.62 (dd, *J* = 6.4, 3.9 Hz, 1H), 3.36 (ddd, *J* = 8.3, 5.6, 3.2 Hz, 1H), 3.21 (dd, *J* = 13.2, 5.5 Hz, 1H), 3.00 (dd, *J* = 13.2, 7.8 Hz, 1H); ^{1}H-NMR (500 MHz, CD_3OD) δ 7.41 (d, *J* = 7.8 Hz, 2H), 7.30 (td, *J* = 8.3, 7.9, 1.9 Hz, 2H), 7.20 (dd, *J* = 8.3, 6.5 Hz, 1H), 5.94 – 5.79 (m, 1H), 5.28 (d, *J* = 16.8 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 4.43 (dt, *J* = 5.9, 3.0 Hz, 1H), 4.38 (dd, *J* = 7.0, 4.7 Hz, 1H), 3.53 (t, *J* = 6.0 Hz, 1H), 3.26 – 3.20 (m, 1H), 3.12 – 3.00 (m, 2H), 1.45 (s, 3H), 1.29 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.15 (alkene CH), 135.80 (aromatic C), 129.49 (2 aromatic CH), 128.96 (2 aromatic CH), 126.24 (aromatic CH), 116.44 (alkene CH_2), 113.65 ($C(CH_3)_2$), 85.08, 84.32 (each CH-O), 66.66 (CH-N), 63.20 (CH-N), 38.01 (CH_2S), 27.21 ($C(CH_3)_2$), 25.17 ($C(CH_3)_2$); ^{13}C NMR (126 MHz, CD_3OD) δ 137.39 (CH), 135.61 (C) 129.56 (2 C), 128.65 (2 C), 126.06 (C), 115.79 (CH_2), 84.93 (CH), 84.55 (CH), 66.74 (CH1), 63.10 (CH), 36.67 (CH), 26.04 (CH_3), 23.92 (CH_3)

HRMS (ESI): m/z calc for $C_{16}H_{22}NSO_2$: 292.1371, found: 292.1374 $[M+H]^+$



(2S,3R)-1-ethenyl-*O*-2,3-isopropylidine-4-methyl-1,4,5,6-tetradeoxy-1,4-imine-1,4-pyrrolidine 104

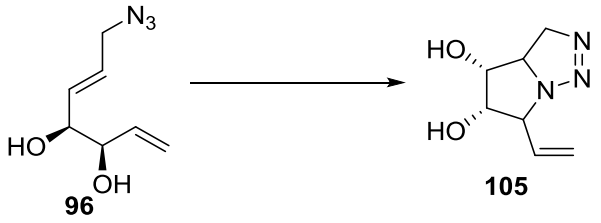
Compound **95** (50 mg, 0.24 mmol) was dissolved in toluene (5 mL) and heated at reflux for 12 h. The solvent was removed and chromatography (hexane-EtOAc, 3:2) gave imine **104** (4 mg, 10 %) as a clear oil

R_f = 0.38 (EtOAc-hexane, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.0, 10.4, 6.2 Hz, 1H), 5.19 – 5.10 (m, 2H), 4.89 (d, *J* = 5.4 Hz, 1H), 4.67 (d, *J* = 6.0 Hz, 1H), 4.45 (d, *J* = 5.4 Hz, 1H), 2.14 (s, 3H, CH_3), 1.37 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.35 (C=N), 136.08 (alkene CH), 116.38 (alkene CH_2), 112.13 ($C(CH_3)_2$), 86.82 (CHO), 82.48 (CHO), 77.82 (CH-N), 26.94 ($C(CH_3)_2$), 25.91 ($C(CH_3)_2$), 16.95 (CH_3)

HRMS (ESI): m/z calc for $C_{10}H_{16}NO_2$: 182.1181, found: 182.1189 $[M+H]^+$

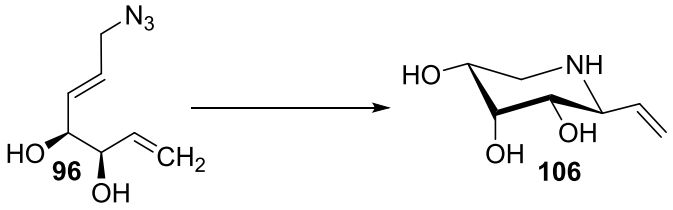


(2S,3R)-1-ethenyl-2,3-hydroxy-1,4,5,6,7-pentadeoxy-4-[1,2,3]-triazoline-1,4-piperidine 105

Azide **96** (0.03 g) was dissolved in DMF and heated to 90 °C for 30 mins. Solvent was removed under reduced pressure to obtain **105** as a pale-yellow residue

^{1}H NMR (500 MHz, DMF) δ 6.31 (ddd, *J* = 16.7, 10.3, 6.0 Hz, 1H), 5.59 (dt, *J* = 17.1, 1.7 Hz, 1H), 5.37 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.29 (d, *J* = 7.2 Hz, 1H, OH), 5.21 (d, *J* = 3.3 Hz, 1H, OH), 4.73 (dd, *J* = 16.5, 4.2 Hz, 1H), 4.30 – 4.22 (m, 2H), 4.13 (td, *J* = 7.6, 3.5 Hz, 1H), 3.96 – 3.88 (m, 2H)

^{13}C NMR (126 MHz, DMF) δ 138.66 (alkene CH), 115.12 (alkene CH_2), 78.30 (CH-O), 72.05 (CHO), 67.08 (CH-N), 66.49 (CH-N), 58.47 (CH-N)



(1S,2S,3R,4R)-1-ethenyl-2,3,4-trihydroxy-1,5-piperidine-2,3,4-triol 106

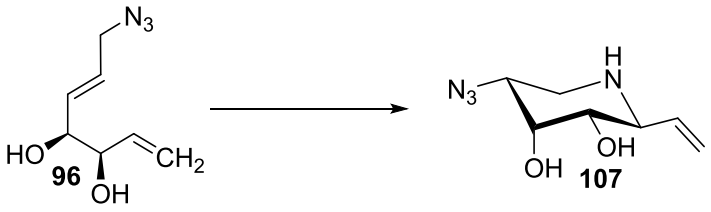
Compound **96** (50 mg, 0.296 mmol) was dissolved in DMF (5 mL) and stirred at 90 ˚C for 30 mins. AcOH (85µL, 1.47 mmol) was then added followed by water (25 mL) after 10 mins and the solvent was removed under reduced pressure. The residue was then stirred in dilute HCl overnight and volatile materials removed under reduced pressure. Flash chromatography (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:0.1:0.1) gave the free amine **106** (42 mg, 91 %) as a yellow foam. The ^{13}C-NMR spectroscopic data for **106** was in good agreement with those reported (75 MHz) previously by Wrodnigg and co-workers[216].

R_f = 0.2 (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:0.1:0.1)

^{1}H NMR (500 MHz, D_2O) δ 5.71 (ddd, *J* = 17.6, 10.3, 7.4 Hz, 1H, H-6), 5.44 – 5.35 (m, 2H, overlapping signals H-7 & H-7'), 4.04 (d, *J* = 2.5 Hz, 1H, H-3), 3.83 (ddd, *J* = 11.7, 5.1, 2.6 Hz, 1H, H-4), 3.62 – 3.48 (m, 2H, overlapping signals H-1 & H-2), 3.05 (dd, *J* = 12.1, 5.0 Hz, 1H, H-5), 2.92 (t, *J* = 11.8 Hz, 1H, H-5')

^{13}C NMR (126 MHz, D_2O) δ 131.08 (alkene CH), 123.28 (alkene CH_2), 69.96 (CH-O), 68.96 (CH-O), 65.36 (CH-O), 56.23 (CH-N), 41.83 (CH-N)

HRMS (ESI) *m/z* calc for $C_7H_{14}NO_3$: 160.0974, Found: 160.0965 $[M+H]^+$



(1S,2S,3R,4R)-4-azido-1-ethenyl-2,3-dihydroxy-1,5-piperidine 107

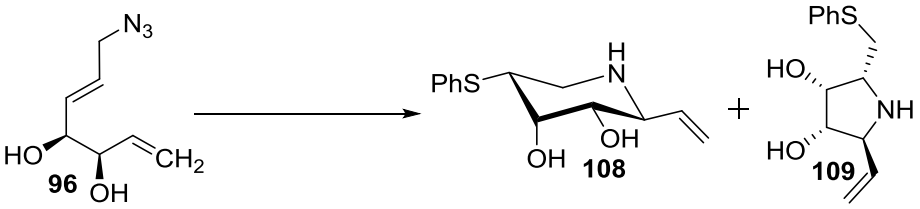
Compound **96** (50 mg, 0.296 mmol) was dissolved in DMF (5 mL) and stirred at 90 ˚C for 30 mins. NaN_3 (95 mg, 1.47 mmol) and AcOH (25µL, 0.44 mmol) were added and water (25 mL) was added after 10 mins and the solvent was removed under reduced pressure. Flash chromatography (EtOAc-aq NH_3, 100:1) gave the title compound **107** (19 mg, 35 %) as a yellow foam.

R_f = 0.6 (EtOAc-aq NH_3, 100:1)

^{1}H NMR (500 MHz, CD_3OD): δ 5.89 (ddd, *J* = 17.4, 10.7, 6.5 Hz, 1H), 5.27 (d, *J* = 17.7 Hz, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 4.10 (d, *J* = 2.7 Hz, 1H), 3.30 – 3.25 (2H, overlapping signals), 3.17 (dd, *J* = 9.8, 2.8 Hz, 1H), 2.98 (t, *J* = 11.7 Hz, 1H), 2.86 (dd, *J* = 12.1, 4.9 Hz, 1H)

^{13}C NMR (126 MHz, CD_3OD) δ 137.18 (alkene CH), 115.98 (alkene CH_2), 72.46 (CH-O), 70.48 (CH-O), 59.38 (CH-N_3), 56.83 (CH-N), 41.75 (CH_2-N)

HRMS (ESI): m/z calc for $C_7H_{13}N_4O_2$: 185.1039, found: 185.1045 $[M+H]^+$



(1S,2S,3S,4R)-2,3-dihydroxy-1-ethenyl-4-(thiophenyl)-1,5-piperidine 108 (1S,2S,3R,4R)-2,3-dihydroxy-5-(thiophenyl)-1,4-pyrrolidine 109

Compound **96** (0.05 g, 0.296 mmol) was dissolved in DMF (5 mL) and stirred at 90 ˚C for 30 mins. Thiophenol (0.15 mL, 1.47 mmol) was then added followed by H_2O (25 mL) after 10 mins and the solvent was removed under reduced pressure. Flash chromatography (EtOAc-aq NH_3, 100:1) gave the title compounds **108** (35 mg, 48%) and **109** (24 mg, 32 %) as white solids.

Data for **108**

R_f = 0.64 (EtOAc-aq NH_3, 100:1)

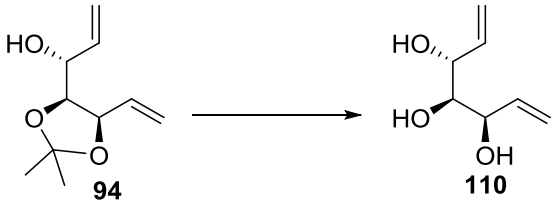
^{1}H NMR (500 MHz, CD_3OD) δ 7.47 – 7.41 (m, 2H, aromatic H), 7.34 – 7.26 (m, 2H, aromatic H), 7.26 – 7.20 (m, 1H, aromatic H), 5.90 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H), 5.26 (dt, *J* = 17.5, 1.5 Hz, 1H), 5.18 (dt, *J* = 10.6, 1.4 Hz, 1H), 4.10 (t, *J* = 2.6 Hz, 1H), 3.38 – 3.25 (2H, overlapping signals), 3.22 (dd, *J* = 10.0, 2.8 Hz, 1H), 2.96 (t, *J* = 12.2 Hz, 1H), 2.86 (dd, *J* = 12.5, 4.7 Hz, 1H)

^{13}C NMR (126 MHz, CD_3OD): δ 137.43 (alkene CH), 135.07 (aromatic C), 130.94 (2 aromatic CH), 128.68 (2 aromatic CH), 126.49 (aromatic CH), 115.81 (alkene CH_2), 73.42 (CH-O), 70.75 (CH-O), 57.03 (CH-N), 49.94 (CH-S), 44.40 (CH_2N)
HRMS (ESI): *m/z* calc for $C_{13}H_{18}NO_2S$: 252.1058, found: 252.1051 $[M+H]^+$

Data for **109**

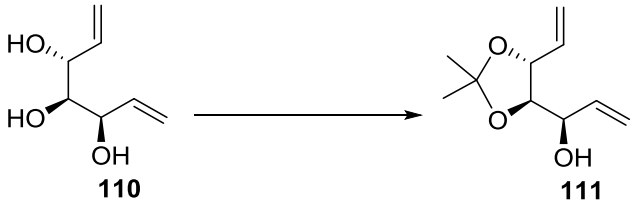
R_f = 0.31 (EtOAc-aq NH_3, 100:1)
^{1}H NMR (500 MHz, CD_3OD): δ 7.39 (d, *J* = 7.6 Hz, 2H, aromatic H), 7.29 (t, *J* = 7.7 Hz, 2H, aromatic H), 7.18 (t, *J* = 7.4 Hz, 1H, aromatic H), 5.84 (ddd, *J* = 17.7, 10.2, 7.9 Hz, 1H), 5.28 (d, *J* = 16.9 Hz, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 4.10 (t, *J* = 3.9 Hz, 1H), 3.81 (dd, *J* = 8.6, 4.0 Hz, 1H), 3.60 (t, *J* = 8.2 Hz, 1H), 3.42 (td, *J* = 7.1, 3.6 Hz, 1H), 3.33 – 3.24 (m, 1H), 3.04 (dd, *J* = 13.3, 7.1 Hz, 1H)

^{13}C NMR (126 MHz, CD_3OD): δ 136.8 (alkene CH), 135.9 (aromatic C), 129.0 (2 aromatic CH), 128.6 (2 aromatic CH), 125.8 (aromatic CH), 116.9 (alkene CH_2), 77.3 (CH-O), 71.7 (CH-O), 63.7 (CH-N), 58.3 (CH-N), 32.9 (CH_2S)
HRMS (ESI): m/z calc for $C_{13}H_{18}NO_2S$: 252.1058, found: 252.1056 $[M+H]^+$



94 **110**

Compound **94** (1 g, 5.43 mmol) was dissolved in 2M HCl and MeOH (10:1, 10 mL) and the mixture stirred at room temp for 1 h. The solution was then extracted with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under diminished pressure. Flash chromatography (EtOAc-petroleum ether bp 40-60 °C, 7:3) gave the intermediate diol **110** (0.65 g, 83 %) as a clear oil.
R_f = 0.3, (EtOAc-hexane, 7:3)
FTIR 3341, 3082, 2983, 2912, 1644, 1425, 1265, 1091, 1031, 990, 922, 853, 763 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 – 5.78 (m, 2H,), 5.46 – 5.37 (m, 2H,), 5.37 – 5.21 (m, 2H), 4.48 – 4.28 (m, 2H), 3.56 (t, *J* = 3.9 Hz, 1H)
^{13}C NMR (126 MHz, $CDCl_3$) δ 137.0 (alkene CH), 136.4 (alkene CH), 117.4 (alkene CH_2), 117.1 (alkene CH_2), 74.8 (CH-O), 74.7 (CH-O), 72.2 (CH-O)
HRMS (ESI): m/z calc for $C_7H_{13}O_3$: 145.0865, found: 145.0873 $[M+H]^+$



110 **111**

(3R,4R,5R)-3-hydroxy-4,5-*O*-isopropylidene-1,2,6,7-tetradeoxy-1,6-heptadiene ol 111

Triol **110** (0.5 g, 3.47 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 ˚C. *p*-TsOH (0.12 g, 0.69 mmol) was added and the mixture was stirred for a further 10 min. Then 2,2-DMP (0.85 mL, 6.94 mmol) was added & reaction mixture stirred at room temp for 15 min. Triethylamine (0.48 mL, 3.47 mmol) was added and the solvent was then removed under reduced pressure. Flash chromatography (hexane-EtOAc, 7:3) gave **111** (0.5 g, 70 %) as a clear oil.

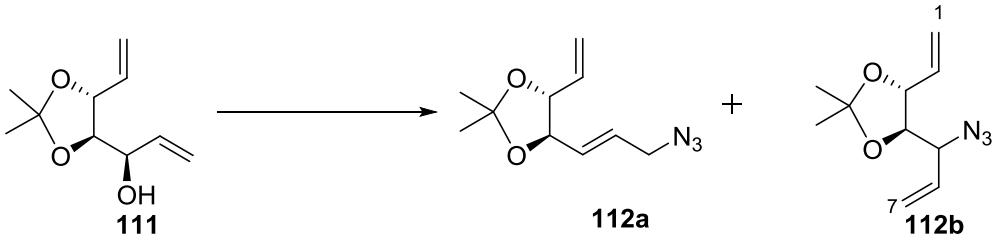
R_f = 0.54 (hexane-EtOAc, 7:3)

FTIR 3460, 2987, 2882, 1646, 1427, 1371, 1214, 1168, 1122, 1052, 987, 923, 873, 812, 744 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 5.90-5.78 (m, 2H), 5.44 – 5.33 (m, 2H), 5.27 – 5.21 (m, 2H), 4.45 – 4.34 (m, 2H), 3.82 (dd, J = 8.2, 3.8 Hz, 1H), 2.18 (d, J = 3.1 Hz, 1H, OH), 1.45 (s, 3H, $C(CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 135.2, 118.3), 117.1 (alkene CH&CH_2), 109.1 ($C(CH_3)_2$), 82.7, 77.4, 71.5 (each CH-O), 26.8 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$)

HRMS (ESI): *m/z* calc for $C_{10}H_{16}NaO_3$: 207.0997, found: 207.0990 $[M+Na]^+$



(E,4R,5R)-7-azido-3,4-*O*-isopropylidene-1,2,5,6,7-pentadeoxy-1,5-heptadiene 112a

(4R,5R)-5-azido-3,4-*O*-isopropylidene-1,2,5,6,7-pentadeoxy-1,6-heptadiene 112b

Compound **111** (0.28 g, 1.52 mmol) was dissolved in anhydrous THF (10 mL) and PPh_3 (0.71 g, 2.58 mmol) was added and solution cooled to 0˚C. DIAD (0.4 mL, 2.58 mmol) and DPPA (0.66 mL, 2.58 mmol) were charged slowly and solution allowed to adjust to room temp overnight. The reaction mixture was concentrated and then flash chromatography (hexane-EtOAc, 40:1) gave **112a** (0.179 g, 56 %) and a 31:69 mixture of **112a** and **112b** (48 mg, 15%) as clear oils.

Data for **112a:**

R_f = 0.15 (EtOAc-hexane, 1:80)

^1H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.75 (m, 3H), 5.39 (d, J = 17.1 Hz, 1H), 5.29 (d, J = 10.0 Hz, 1H), 4.18 – 4.04 (m, 2H), 3.81 (t, J = 5.5 Hz, 2H), 1.46 (s, 3H, $C(CH_3)_2$), 1.46 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 133.7, 130.9, 127.3, 119.3 (alkene CH/CH_2), 109.4 ($C(CH_3)_2$), 82.5 (CH-O), 80.9 (CH-O), 51.9 (CH_2N_3), 26.9 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$)

HRMS (ESI): m/z calc for $C_{10}H_{16}N_3O_2$: 210.1243, found: 210.1237 $[M+H]^+$

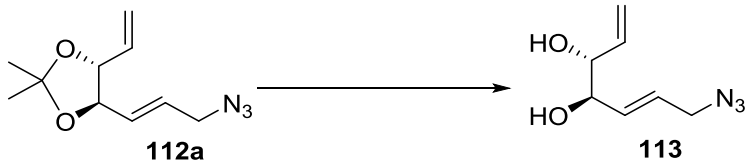
Data for mixture of **112a** and **112b**:

^1H NMR **112a** & **112b** (500 MHz, $CDCl_3$) δ 5.95 – 5.73 (m, 6H, overlapping signals H-2_a, H-2_b, H-5_a, H-6_a & H-6_b), 5.47 – 5.36 (m, 7H, overlapping signals H-1_b, H-$1'_b$, H-7_b, H-$7'_b$, H-1_a), 5.29 (d, 1H, H-

1'$_a$) 4.36 (t, J = 7.6 Hz, 1H, H-3$_b$), 4.12 (m, 2H, overlapping signals H-4$_a$ & H-3$_a$) 3.85 (dd, J = 7.9, 5.0 Hz, 1H, H-5$_b$), 3.81 (t, J = 5.39, 2H, H-7$_a$) 3.77 (dd, J = 7.9, 4.9 Hz, 1H, H-4$_b$), 1.49 (s, 3H, C(CH$_3$)$_2$), 1.46 (s, 3H, C(CH$_3$)$_2$), 1.46 (s, 3H, C(CH$_3$)$_2$), 1.45 (s, 3H, C(CH$_3$)$_2$)

^{13}C NMR **22a** & **22b** (126 MHz, $CDCl_3$) δ 134.91 (C-2b), 133.76(C-2a), 131.82 (C-6b), 130.92 (C-5a), 127.34 (C-6a), 120.54 (C-7b), 119.54 (C-1b), 119.31 (C-1a), 109.93 (C(CH$_3$)$_2$b), 109.43 (*C*(CH$_3$)$_2$a), 82.58 (C-3a), 82.06 (C-4b), 80.93 (C-4a), 79.27 (C-3b), 64.10 (C-5b), 51.94 (C-7a), 27.04 (C(*C*H$_3$)$_2$b), 26.99(C(*C*H$_3$)$_2$a), 26.95(C(*C*H$_3$)$_2$a), 26.75(C(*C*H$_3$)$_2$b)

HRMS (ESI): m/z calc for $C_{10}H_{16}N_3O_2$: 210.1243, found: 210.1239 $[M+H]^+$



112a **113**

(E,4R,5R,)-1-azidohepta-2,6-heptadiene-4,5-diol 113

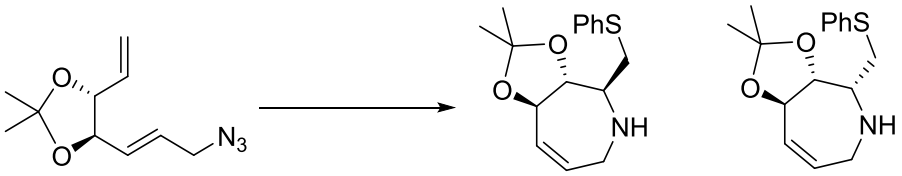
Compound **112a** (0.3 g, 1.43 mmol) was suspended in 2M HCl for 1 h and the mixture was then extracted with EtOAc, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash chromatography (hexane-EtOAc, 3:2) gave **113** (0.24 g, 78 %) as a clear oil.

R_f = 0.27 (hexane-EtOAc, 7:3)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 – 5.81 (m, 3H), 5.40 (d, J = 17.3 Hz, 1H), 5.30 (d, J = 10.7 Hz, 1H), 4.09 (t, J = 5.9 Hz, 1H), 4.04 (t, J = 6.2 Hz, 1H), 3.82 (d, J = 5.8 Hz, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.3, 133.4, 126.1, 117.9 (alkene CH/CH_2), 75.8 (CH-O), 74.5 (CH-O), 52.1 (CHN_3)

HRMS (ESI): *m/z* calc for $C_7H_{11}N_3O_2Cl$: 204.0540, found: 204.0549 $[M+Cl]^-$



112a **114a** **114b**

(4R,5R,6S,Z)-2,3-*O*-isopropylidine-1,2,3,6,7-pentadeoxy-7-thiophenyl-1,6-azepane 114a

(4R,5R,6R,Z)-2,3-*O*-isopropylidine-1,2,3,6,7-pentadeoxy-7-thiophenyl-1,6-azepane 114b

Compound **112a** (0.05 g, 0.239 mmol) was dissolved in DMF (20 mL) and the solution was heated to 110 ^{o}C and stirred for 2 h. PhSH (0.12 mL, 1.2 mmol) was then added and the mixture was allowed to attain room temp and left overnight. The reaction mixture was then diluted with Et_2O and washed with satd NH_4Cl, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash chromatography (hexane-EtOAc, 4:1) gave **114a** (23 mg, 33 %) and **114b** (4 mg, 5 %), both as clear oils.

Data for **114a**

R_f = 0.21 (hexane-EtOAc, 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 2H, aromatic H), 7.30 – 7.25 (m, 2H, aromatic H), 7.17 (t, *J* = 7.4 Hz, 1H, aromatic H), 5.99 (dt, *J* = 10.7, 2.2 Hz, 1H), 5.95 – 5.90 (m, 1H), 4.58 – 4.43 (m, 1H), 3.54 – 3.42 (2H, overlapping signals), 3.35 (t, *J* = 8.8 Hz, 1H), 3.20 (dd, *J* = 16.2, 5.0 Hz, 1H), 3.04 (td, *J* = 9.1, 2.4 Hz, 1H), 2.94 (dd, *J* = 13.4, 9.2 Hz, 1H), 1.40 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$): δ 136.10 (aromatic C), 131.33 (alkene CH), 130.53 (alkene CH), 129.00 (2 aromatic CH), 128.89 (2 aromatic CH), 125.93 (aromatic CH), 109.16 ($C(CH_3)_2$), 80.97 (CH-O), 79.03, (CH-O) 60.73 (CH-N), 44.63 (CH_2-N), 37.00 (CH_2-S), 26.98 ($C(CH_3)_2$), 26.80 ($C(CH_3)_2$)

HRMS (ESI): m/z calc for $C_{16}H_{22}NO_2S$: 292.1371, found: 292.1366 $[M+H]^+$

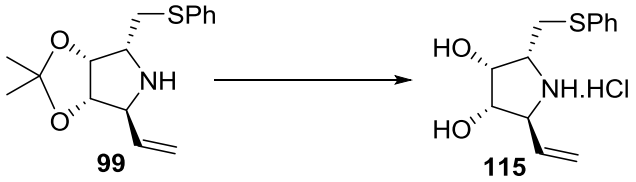
Data for **114b**

R_f = 0.13 (hexane-EtOAc, 4:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.2 Hz, 2H, aromatic H), 7.29 (t, *J* = 7.6 Hz, 2H, aromatic H), 7.19 (q, *J* = 6.6, 5.8 Hz, 1H, aromatic H), 5.85 (d, *J* = 11.1 Hz, 1H), 5.75 (ddt, *J* = 10.9, 5.6, 2.3 Hz, 1H), 4.86 (d, *J* = 9.1 Hz, 1H), 4.04 (dd, *J* = 9.5, 6.9 Hz, 1H), 3.58 – 3.49 (2H, overlapping signals), 3.46 (ddd, *J* = 10.1, 6.9, 2.5 Hz, 1H), 3.32 (dq, *J* = 17.9, 2.9 Hz, 1H), 2.80 (dd, *J* = 13.7, 10.7 Hz, 1H), 1.43 (s, 3H, $C(CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.70 (aromatic C), 131.46 (alkene CH), 129.41 (2 aromatic CH), 128.99 (2 aromatic CH), 128.23 (alkene CH), 126.19 (aromatic CH), 109.13 ($C(CH_3)_2$), 80.90 (C-5), 75.13 (C-4), 53.93 (C-6), 45.87 (C-1), 34.60 (C-7), 27.18 ($C(CH_3)_2$), 26.73 ($C(CH_3)_2$)

HRMS (ESI): m/z calc for $C_{16}H_{22}NSO_2$: 292.1371, found: 292.1363 $[M+H]^+$



(1S,2S,3R,4R)-1-ethenyl-2,3-dihydroxy-5-thiophenyl-1,4-pyrrolidine hydrochloride 115

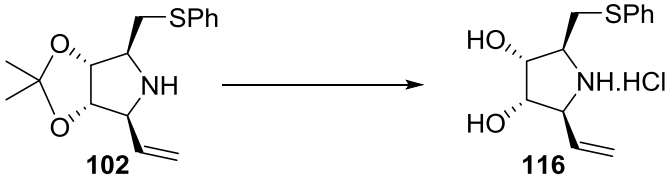
Compound **99** (10 mg, 0.034 mmol) was dissolved in 2M HCl (5 mL) and the mixture stirred at rt overnight. Removal of the volatile materials under reduced pressure gave **115** (9 mg) as a white solid.

$[\alpha]_D^{20}$ -58.8 (***c*** 0.35, H_2O)

^{1}H NMR (500 MHz, CD_3OD) δ 7.46 (d, *J* = 7.7 Hz, 2H, aromatic 2H), 7.35 (t, *J* = 7.6 Hz, 2H, aromatic H), 7.27 (t, *J* = 7.3 Hz, 1H, aromatic H), 5.93 (ddd, *J* = 17.0, 10.2, 8.7 Hz, 1H, alkene H), 5.52 (d, *J* = 17.0 Hz, 1H, alkene H), 5.49 (d, *J* = 10.3 Hz, 1H, alkene H), 4.20 (t, *J* = 3.4 Hz, 1H), 4.07 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.96 (t, *J* = 9.0 Hz, 1H), 3.75 (ddd, *J* = 9.1, 6.2, 3.2 Hz, 1H), 3.46 (dd, *J* = 14.3, 6.1 Hz, 1H), 3.22 (dd, *J* = 14.2, 8.7 Hz, 1H)

^{13}C NMR (126 MHz, CD_3OD) δ 133.95 (aromatic C), 130.82 (alkene CH), 129.80 (2 aromatic CH), 129.02 (2 aromatic CH), 126.82 (aromatic CH), 122.35 (alkene CH_2), 75.37 (CH-O), 70.59 (CH-O), 63.16 (CH-N), 59.52 (CH-N), 30.59 (CH_2S)

HRMS (ESI): m/z calc for $C_{13}H_{17}NO_2SCl$: 286.0669, found: 286.0676 $[M-H]^-$



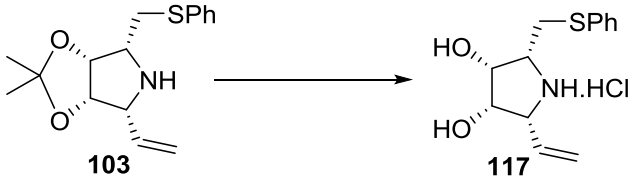
(1S,2S,3R,4S)-1-ethenyl-2,3-dihydroxy-5-thiophenyl-1,4-pyrrolidine hydrochloride 116

Compound **102** (4 mg, 0.01 mmol) was treated with 2M HCl as described for **115** and this gave the **116** (3 mg) as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.54 – 7.39 (m, 2H, aromatic H), 7.37 (dd, *J* = 8.5, 7.0 Hz, 2H, aromatic H), 7.35 – 7.25 (m, 1H, aromatic H), 5.96 (ddd, *J* = 17.1, 10.3, 8.4 Hz, 1H, alkene H), 5.58 – 5.48 (overlapping signals, 2H, alkene H), 4.09 (t, *J* = 5.0 Hz, 1H), 4.05 (dd, *J* = 6.5, 4.8 Hz, 1H), 4.00 – 3.93 (m, 1H), 3.56 – 3.44 (2H, overlapping signals), 3.17 (dd, *J* = 14.5, 9.7 Hz, 1H)

^{13}C NMR (126 MHz, CD_3OD) δ 133.291 (1 aromatic C), 130.29 (2 aromatic CH), 130.16 (alkene CH), 129.11 (2 aromatic C), 127.15 (aromatic C), 122.58 (alkene CH_2), 73.67 (CH-O), 72.95 (CH-O), 65.20 (CH-N), 62.57 (CH-N), 33.79 (CH_2S)

HRMS (ESI): m/z calc for $C_{13}H_{17}NO_2SCl$: 286.0669, found: 286.0660 $[M-H]^-$



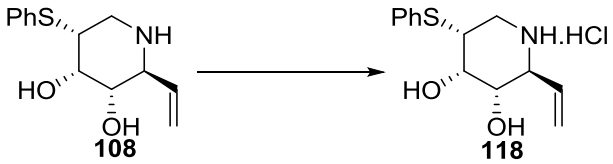
(1R,2S,3R,4R)-1-ethenyl-2,3-dihydroxy-5-thiophenyl-1,4-pyrrolidine hydrochloride 117

Compound **103** (5 mg, 0.034 mmol) was treated with 2M HCl as described for **115** and gave **117** (4 mg) as a white solid.

^{1}H NMR (500 MHz, CD_3OD) δ 7.50 – 7.44 (m, 2H, aromatic H), 7.35 (dd, *J* = 8.5, 6.9 Hz, 2H, aromatic H), 7.27 (t, *J* = 7.4 Hz, 1H, aromatic H), 6.10 (ddd, *J* = 17.1, 10.4, 9.0 Hz, 1H, alkene H), 5.54 – 5.45 (overlapping signals, 2H, alkene CH_2), 4.35 (dd, *J* = 6.2, 4.1 Hz, 1H), 4.26 (dd, *J* = 5.3, 4.2 Hz, 1H), 4.00 (dd, *J* = 9.1, 5.3 Hz, 1H), 3.65 (dt, *J* = 10.6, 5.4 Hz, 1H), 3.49 (dd, *J* = 14.6, 4.6 Hz, 1H), 3.22 – 3.15 (m, 1H)

^{13}C NMR (126 MHz, CD_3OD) δ 134.00 (aromatic C), 129.94 (2 aromatic C), 129.37 (alkene CH), 129.01(2 aromatic CH), 126.81 (aromatic CH), 122.57 (alkene CH_2), 72.07 (CH-O), 70.76 (CH-O), 63.04 (CH-N), 59.32 (CH-N), 31.35 (CH_2S)

HRMS (ESI): m/z calc for $C_{13}H_{17}NO_2SCl$: 286.0669, found: 286.0681 $[M-H]^-$



(1S,2S,3S,4R)-1-ethenyl-2,3-dihydroxy-4-thiophenyl-1,5-piperidine hydrochloride 118

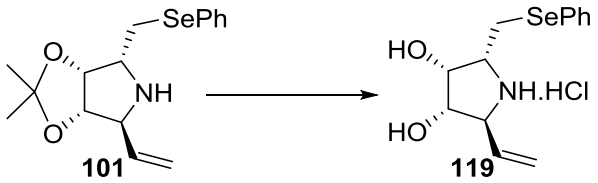
Reaction of **108** (11 mg, 0.044 mmol) with 2M HCl as described for **115** gave **118** (11 mg) as a white solid.

$[\alpha]_D^{20}$ -10.0 (***c*** 0.1, H_2O)

^{1}H NMR (500 MHz, D_2O) δ 7.49 – 7.41 (m, 2H, aromatic H), 7.36 – 7.26 (m, 3H, aromatic H), 5.73 (ddd, *J* = 17.1, 10.6, 7.8 Hz, 1H, alkene H), 5.49 – 5.43 (overlapping signals, 2H, alkene CH_2), 4.17 (t, *J* = 2.4 Hz, 1H), 3.71 (dd, *J* = 10.7, 7.8 Hz, 1H), 3.66 (dd, *J* = 10.6, 2.4 Hz, 1H), 3.47 (ddd, *J* = 12.7, 4.8, 2.2 Hz, 1H), 3.26 (dd, *J* = 12.7, 4.7 Hz, 1H), 3.23 – 3.14 (m, 1H)

^{13}C NMR (126 MHz, D_2O) δ 132.48 (2 aromatic CH), 131.46 (aromatic C), 129.68 (alkene CH), 129.55 (2 aromatic CH), 128.48 (aromatic CH), 124.59 (alkene CH_2), 69.19 (CH-O), 68.54 (CH-O), 56.16 (CHN), 45.49 (CH-S), 41.73 (CH_2N)

HRMS (ESI): *m/z* calc for $C_{13}H_{17}NO_2SCl$: 286.0669, found: 286.0671 $[M-H]^-$



(1S,2S,3R,4R)-1-ethenyl-2,3-dihydroxy-5-selenaylphenyl-1,4-pyrrolidine hydrochloride 119

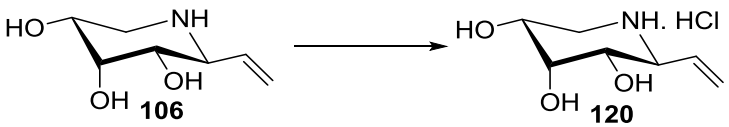
Reaction of **101** (20 mg, 0.06 mmol) with 2M HCl as described for **115** gave **119** (18 mg) as a white solid

$[\alpha]_D^{20}$ -38.0 (***c*** 0.1, H_2O)

^{1}H NMR (500 MHz, CD_3OD) δ 7.79 – 7.41 (m, 2H, aromatic H), 7.40 – 7.11 (m, 3H, aromatic H), 5.95 (ddd, *J* = 17.0, 10.2, 8.6 Hz, 1H, alkene H), 5.51 (d, *J* = 16.9 Hz, 1H, alkene H), 5.48 (d, *J* = 10.2 Hz, 1H, alkene H), 4.23 (t, *J* = 3.3 Hz, 1H), 4.09 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.97 (t, *J* = 9.0 Hz, 1H), 3.78 (td, *J* = 7.6, 3.1 Hz, 1H), 3.35 (dd, *J* = 13.0, 7.7 Hz, 1H), 3.14 (dd, *J* = 13.0, 7.6 Hz, 1H)

^{13}C NMR (126 MHz, CD_3OD) δ 132.80 (2 aromatic CH), 130.87 (alkene CH), 129.15 (2 aromatic CH), 128.31 (aromatic C), 127.45 (aromatic CH), 122.30 (alkene CH_2), 75.51 (CH-O), 70.72 (CH-O), 63.32 (CH-N), 60.47 (CH-N), 22.83 (CH_2Se)

HRMS (ESI): m/z calc for $C_{13}H_{17}NO_2SeCl$: 334.0113, found: 334.0120 $[M-H]^-$



(1S,2S,3R,4R)-1-ethenyl-2,3,4-trihydroxy-1,5-piperidine-hydrochloride 120

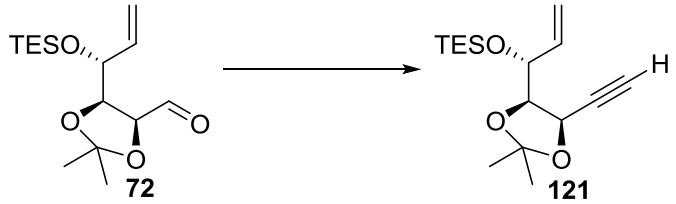
Compound **106** (10 mg, 0.063 mmol) with 2M HCl gave the title hydrochloride salt **25** (10 mg, 85 %) as a yellow foam. The ^{13}C-NMR spectroscopic data for this HCl salt were in good agreement with those reported (75 MHz) previously by Wrodnigg and co-workers[216].

$[\alpha]_D^{20}$ +5.51 (***c*** 0.29, H_2O)

^{1}H NMR (500 MHz, D_2O) δ 5.80 – 5.65 (m, 1H, alkene H), 5.52 – 5.41 (2H, overlapping alkene H), 4.07 (br s, 1H), 3.90 (dddd, *J* = 11.6, 5.0, 2.6, 0.9 Hz, 1H), 3.67 – 3.64 (2H, overlapping signals), 3.16 (dd, *J* = 12.1, 4.9 Hz, 1H), 3.02 (t, *J* = 11.9 Hz, 1H)

^{13}C NMR (126 MHz, D_2O) δ 129.51 (alkene CH), 124.68 (alkene CH_2), 69.59 (CH-O), 68.18 (CH-O), 64.55 (CH-O), 56.09 (CH-N), 41.34 (CH_2N)

HRMS (ESI): m/z calc for $C_7H_{13}NO_3Cl$: 194.0584, found: 194.0590 $[M-H]^-$



(3R,4R,5R)-3,4-*O*-isopropylidine-5-triethylsilyl-6-hepten-1-ynl 121

$TMSCH_2N_2$ (12.5 mL, 2 M in Et_2O) was added slowly to LDA in THF (25.0 mL of 1 M in THF) at -78 °C under argon and the mixture stirred for 1 h. The aldehyde **72** (1 g, 3.33 mmol) in anhydrous THF (60 mL) was subsequently added to this and the mixture stirred at -78 ˚C for a further hour. The reaction was allowed to attain 0 ˚C and then stirred for 30 min. Satd. NH_4Cl solution (100 mL) was added and the mixture stirred for 2 h and was subsequently concentrated. EtOAc (75 mL) was added to the concentrate which was then washed with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 x 75 mL) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent then removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:40) gave alkyne **35** (0.65 g, 55 %, two steps) as a clear oil.

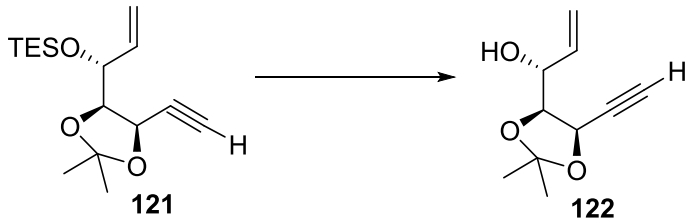
R_f = 0.58 (EtOAc-hexane, 1:20)

FTIR 3310, 2987, 2954, 2877, 1458, 1415, 1380, 1370, 1338, 1227, 1145, 1123, 1078, 1046, 1004, 973, 930, 866, 839, 780, 726, 690, 671 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.0, 10.5, 5.2 Hz, 1H, alkene H), 5.47 (dt, *J* = 17.1, 1.9 Hz, 1H, alkene H), 5.20 (dt, *J* = 10.8, 1.6 Hz, 1H, alkene H), 4.58 (dd, *J* = 5.2, 2.2 Hz, 1H) 4.48 (ddt, J = 8.3, 5.2, 1.5 Hz, 1H), 3.84 (dd, *J* = 8.3, 5.3 Hz, 1H), 2.51 (d, *J* = 2.0 Hz, 1H, alkyne H), 1.54 (s, 3H, $C(CH_3)_2$), 1.33 (s, 3H, $C(CH_3)_2$), 0.97 (t, *J* = 7.8 Hz, 9H, $Si(CH_2CH_3)$), 0.70 – 0.59 (m, 6H, $Si(CH_2CH_3)$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.3 (alkene CH), 117.1 (alkene CH_2), 110.6 ($C(CH_3)_2$), 81.5 (CH-O), 80.5 (alkyne C), 75.4 (alkyne CH), 73.2 (CH-O), 67.0 (CH-O), 27.6 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$), 6.7 ($Si(CH_2CH_3)_3$), 4.9 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{16}H_{27}O_3Si$:295.1729, found: 295.1739 $[M-H]^-$



(3R,4S,5R)-5-hydroxy-3,4-*O*-isopropylidene-6-hepten-1-ynl 122

To **121** (1.3 g, 4.38 mmol) in anhydrous THF (35 mL), TBAF in THF (13.2 mL, 1 M in THF) was charged slowly and solution stirred at room temp overnight. The mixture was then treated with 3M NaOH (20 mL) and stirred for 15 min. The layers were separated and aqueous layer extracted with EtOAc. All the organic portions were combined and then dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexane, 1:4) gave the alcohol **122** (0.63 g, 79 %) as a clear oil.

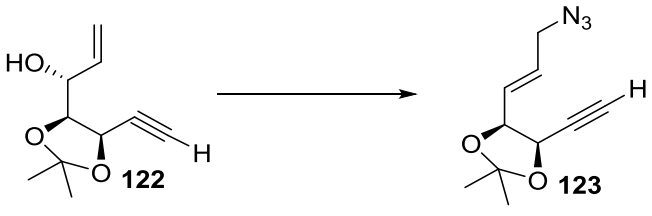
R_f = 0.16 (EtOAc-hexane, 1:4)

FTIR 3475, 3282, 2988, 2937, 1456, 1421, 1372, 1341, 1225, 1162, 1133, 1075, 994, 929, 864, 798 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 16.8, 10.7, 5.7 Hz, 1H), 5.52 (d, *J* = 17.1 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 4.72 (dd, *J* = 5.8, 2.2 Hz, 1H), 4.57 – 4.48 (m, 1H), 3.98 (dd, *J* = 7.6, 5.7 Hz, 1H), 2.58 (d, *J* = 2.3 Hz, 1H), 2.28 (d, *J* = 3.0 Hz, 1H, OH), 1.58 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, -$C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1 (alkene CH), 118.1 (alkene CH_2), 110.9 ($C(CH_3)_2$), 80.7 (CH-O), 79.6 (alkyne C), 76.2 (alkyne CH), 72.2 (CH-O), 66.9 (CH-O), 27.4 ($C(CH_3)_2$), 26.0 ($C(CH_3)_2$)

HRMS (ESI): *m/z* calc for $C_{10}H_{14}NaO_3$: 205.0841, found: 205.0850 $[M+Na]^+$



(E,3R,4S)-7-azido-3,4-*O*-isopropylidene-6-hepten-1-ynl 123

To alcohol **122** (0.76 g, 4.17 mmol) in THF (25 mL), PPh_3 (1.86 g, 7.10 mmol) was added and mixture was cooled to 0 °C. DIAD (1.4 mL, 7.10 mmol) and DPPA (1.53 mL, 7.10 mmol) were then charged slowly and solution allowed to attain room temp and left overnight. the solvent was removed

under reduced pressure and then flash chromatography (hexane-EtOAc, 40:1) gave the title compound **123** (0.52 g, 60 %) as a clear oil.

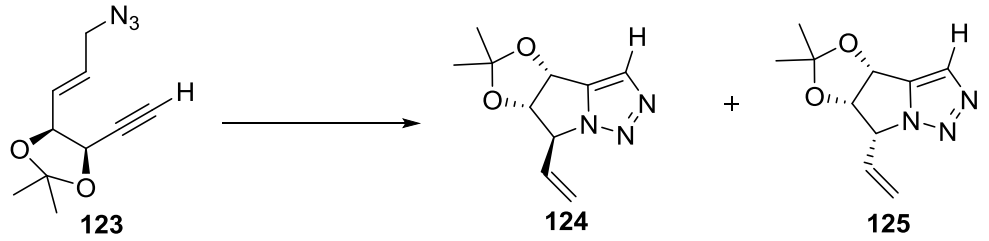
R_f = 0.4 (EtOAc-hexane, 1:20)

FTIR 3295, 2988, 2935, 2099, 1371, 1223, 1160, 1118, 1045, 971, 863, 781 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$) δ 6.03 – 5.87 (2H, overlapping signals, alkene H), 4.82 (dd, J = 5.8, 2.2 Hz, 1H), 4.60 (t, J = 6.3 Hz, 1H), 3.84 (d, J = 5.5 Hz, 2H), 2.56 (d, J = 2.2 Hz, 1H, alkyne H), 1.58 (s, 3H, $(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.0 (alkene CH), 128.7 (alkene CH), 110.7 (-*C*$(CH_3)_2$), 79.4 (alkyne C), 78.0 (CH-O), 76.5 (alkyne CH), 69.1 (CH-O), 52.0 (CH_2N_3), 27.6 (C(*C*$H_3)_2$), 26.0 (C(*C*$H_3)_2$)

HRMS (ESI): m/z calc for $C_{20}H_{27}N_6O_4$:415.2094, found: 415.2079 $[2M+H]^+$



(1S,2S,3R)-1-ethenyl-2,3-*O*-isopropylidene-1,4,5,6,7-pentadeoxy-1,4-[1,2,3]-triazole-1,4-pyrrolidine 124 (1R,2S,3R)-1-ethenyl-2,3-*O*-isopropylidene-1,4,5,6,7-pentadeoxy-1,4-[1,2,3]-triazole-1,4-pyrrolidine 125

Allylic azide **123** (0.33 g, 1.59 mmol) was heated in toluene at 100 ˚C for 3 h and the solvent was removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 3:2) gave **124** (0.13 g, 40 %) as a clear oil and **125** (79 mg, 24 %) as a clear waxy solid.

Data for **124**

R_f = 0.52 (EtOAc-hexane, 1:1)

FTIR 2989, 2939, 1376, 1259, 1210, 1182, 1155, 1128, 1096, 1058, 989, 929, 868, 825, 804, 688 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.70 (s, 1H, triazole H), 5.94 (ddd, J = 16.9, 10.5, 6.3 Hz, 1H, alkene H), 5.56 (d, J = 5.5 Hz, 1H, alkene H), 5.39 (d, J = 10.5 Hz, 1H), 5.24 – 5.18 (2H, overlapping signals), 5.15 (d, J = 5.8 Hz, 1H), 1.42 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.1 (triazole C), 131.9 (alkene CH), 128.6 (triazole CH), 119.8 (alkene CH_2), 113.7 (*C*$(CH_3)_2$), 89.7 (CH-O), 71.7 (CH-O), 66.7 (CH-N), 27.0 (C(*C*$H_3)_2$), 25.8 (C(*C*$H_3)_2$)

HRMS (ESI): m/z calc for $C_{10}H_{14}N_3O_2$: 208.1086, found: 208.1085 $[M+H]^+$

Data for **125**

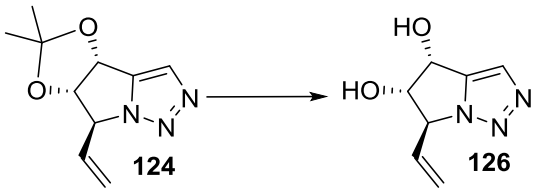
R_f = 0.35 (EtOAc-hexane, 1:1)

FTIR 3111, 2994, 1450, 1371, 1212, 1154, 1128, 1100, 1083, 1055, 1003, 986, 952, 888, 846, 709, 689 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H, triazole H), 6.05 (ddd, J = 17.8, 10.2, 8.1 Hz, 1H, alkene H), 5.66 (d, J = 17.2 Hz, 1H, alkene H), 5.59 (d, J = 10.3 Hz, 1H, alkene H), 5.57 (d, J = 5.7 Hz, 1H), 5.41 (t, J = 5.6 Hz, 1H), 5.02 (dd, J = 8.0, 5.3 Hz, 1H), 1.42 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.60 (triazole C), 129.25 (alkene CH), 128.78 (triazole CH), 122.60 (alkene CH_2), 113.95 ($C(CH_3)_2$), 86.21 (CH-O), 72.05 (CH-O), 64.51 (CH-N), 26.85 ($C(CH_3)_2$), 25.84 ($C(CH_3)_2$)

HRMS (ESI): m/z calc for $C_{10}H_{14}N_3O_2$: 208.1086, found: 208.1081 $[M+H]^+$



(1S,2S,3R)-1-ethenyl-2,3-dihydroxy-1,4-[1,2,3]-triazole-1,4-pyrrolidine 126

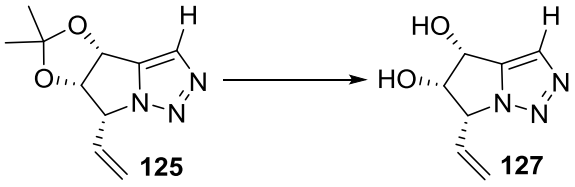
Compound **124** (84.0 mg, 0.40 mmol) was dissolved in 1M HCl (10 mL) and the mixture stirred for 1 h. The solvent was removed under reduced pressure and flash chromatography (CH_2Cl_2-MeOH, 17:3) gave the triazole **126** (61 mg, 90 %) as a white solid.

R_f = 0.1 EtOAc); $[\alpha]_D^{20}$ -4.53 (***c*** 0.75, $CHCl_3$)

^1H NMR (500 MHz, CD_3OD) δ 7.73 (s, 1H, triazole H), 6.02 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H, alkene H), 5.57 – 5.45 (2H, overlapping signals, alkene H), 5.06 (d, *J* = 5.1 Hz, 1H), 4.88 (d, *J* = 6.9 Hz, 1H), 4.48 (t, *J* = 5.6 Hz, 1H)

^{13}C NMR (126 MHz, CD_3OD) δ 141.21 (triazole C), 132.00 (alkene CH), 128.08 (triazole CH), 120.24 (alkene CH_2), 80.70 (CH-O), 66.57 (CH-O), 63.96 (CH-N)

HRMS (ESI): m/z calc for $C_7H_{10}N_3O_2$:168.0773, found: 168.0778 $[M+H]^-$



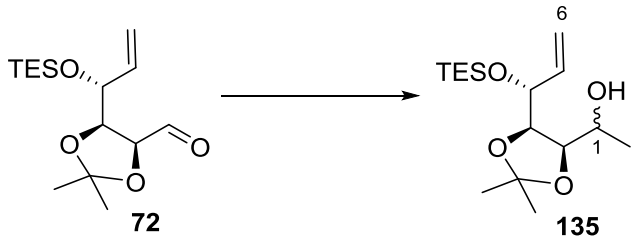
(1R,2S,3R)-1-ethenyl-2,3-dihydroxy-1,4-[1,2,3]-triazole-1,4-pyrrolidine 127

Compound **125** (34 mg, 0.16 mmol) was dissolved in 1M HCl (5 mL) and the mixture stirred for 1 h. The removal of the solvent under reduced pressure and subsequent flash chromatography (CH_2Cl_2:MeOH, 17:3) gave **127** (25 mg, 92 %) as a clear oil.

R_f = 0.15 (EtOAc); $[\alpha]_D^{20}$ -15.66 (***c*** 0.83, MeOH)

^{1}H NMR (500 MHz, CD_3OD) δ 7.70 (s, 1H, triazole H), 6.06 (ddd, *J* = 17.8, 10.3, 8.3 Hz, 1H, alkene H), 5.50 (d, *J* = 17.2 Hz, 1H, alkene H), 5.45 (d, *J* = 10.4 Hz, 1H, alkene H), 5.19 – 5.08 (2H, overlapping signals), 4.81 (t, *J* = 5.6 Hz, 1H)
^{13}C NMR (126 MHz, CD_3OD) δ 141.58 (triazole C), 131.61 (alkene CH), 127.75 (triazole CH), 120.43 (alkene CH_2), 77.47 (CH-O), 65.14 (CH-O), 64.84 (CH-N)

7.4 Experimental Data for Chapter 6



(2S,3R,4R)-2,3-*O*-Isopropylidene-4-*O*-triethylsilyl-hept-5-en-1-ol 135

Compound **72** (4.0 g, 13.3 mmol) was dissolved in THF (170 mL). The solution was cooled to 0˚C and MeMgCl (13.3 mL, 3M in THF) charged slowly. The solution was adjusted to rt and stirred for 4 h. Upon reaction completion, the solution cooled to 0 ˚C and reaction quenched with satd. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash chromatography (EtOAc-Hexane, 1:20) afforded **135** (3.2 g, 77 %)as a mixture of diastereoisomers (0.45:0.55) and as a clear oil.

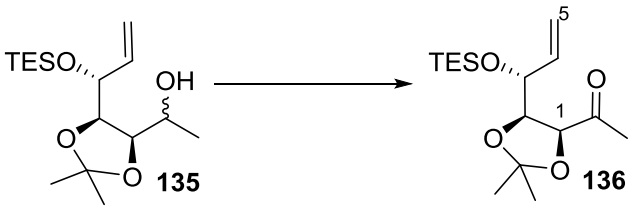
R_f = 0.11 (EtOAc-Hexane, 1:20)

FTIR 3474, 2956, 2912, 2877, 1458, 1414, 1369, 1241, 1214, 1128, 1056, 1006, 928, 872, 851, 831, 802 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (ddd, *J* = 17.4, 10.7, 5.2 Hz, 1H, H-5_{major}), 6.02 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H, H-5_{minor}), 5.39 (dt, *J* = 17.3, 1.9 Hz, 1H, H-6_{major}), 5.32 (d, *J* = 17.2 Hz, 1H, H-6_{minor}), 5.26 (dt, *J* = 10.4, 1.9 Hz, 1H, H-6'$_{major}$), 5.21 (d, *J* = 10.4 Hz, 1H, H-6'$_{minor}$), 4.41 (dd, *J* = 7.2, 4.8 Hz, 2H, overlapping peaks H-4_{major} & H-4_{minor}), 4.30 (dd, *J* = 8.8, 2.4 Hz, 1H, H-3_{major}), 4.25 (ddt, *J* = 9.7, 6.2, 3.1 Hz, 1H, H-1_{major}), 4.11 – 4.06 (m, 1H, H-1_{minor}), 4.04 (dd, *J* = 6.5, 4.9 Hz, 1H, H-3_{minor}), 4.00 (dd, *J* = 9.3, 6.4 Hz, 1H, H-2_{major}), 3.92 (dd, *J* = 6.4, 3.9 Hz, 1H, H-2_{minor}), 2.68 (d, *J* = 4.2 Hz, 1H, OH), 1.54 (s, 3H, $C(CH_3)_2$), 1.46 (s, 3H, $C(CH_3)_2$), 1.37 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$), 1.26 – 1.22 (m, 6H, overlapping peaks CH_{3major} & CH_{3minor}), 1.03 – 0.92 (m, 18H, overlapping peaks $Si(CH_2CH_3)_{3\ minor}$ & $Si(CH_2CH_3)_{3major}$), 0.75 – 0.54 (m, 12H, overlapping peaks $Si(CH_2CH_3)_{3\ minor}$ & $Si(CH_2CH_3)_{3\ major}$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2 (C-5_{minor}) , 136.4 (C-5_{major}), 117.0 (C-6_{minor}), 116.5 (C-6_{major}), 108.1 ($C(CH_3)_2$), 108.1 ($C(CH_3)_2$), 83.1 (C-2_{major}), 81.0 (C-2_{minor}), 80.4 (C-3_{minor}), 79.0 (C-3_{major}), 74.4 (C-4_{major}), 73.0 (C-4_{minor}), 65.3 (C-1_{minor}), 64.6 (C-1_{major}), 26.6 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$), 25.1 ($C(CH3)_{2major}$), 24.6($C(CH_3)_{2minor}$), 20.6 (CH_{3major}), 20.1 (CH_{3minor}), 6.7 ($Si(CH_2CH_3)_3$), 6.6 ($Si(CH_2CH_3)_3$), 5.0 ($Si(CH_2CH_3)_3$), 4.5 ($Si(CH_2CH_3)_3$)

HRMS (ESI): *m/z* calc for $C_{16}H_{33}O_4Si$:317.2148, found: 317.2137 $[M+H]^+$



(2S,3R,4R)-1,2-*O*-Isopropylidene-3-*O*-triethylsilyl-hept-4-en-1a-one 136

Compound **135** (4.5 g, 14.2 mmol) & NMO (2.5 g, 21.3 mmol) were dissolved in CH_2Cl_2 (300 mL) and stirred with 4 Å molecular sieves for 30 mins at rt. The solution was cooled to 0 ˚C. After stirring for a further 15 min, TPAP (0.5 g, 1.4 mmol) was added and solution then stirred at rt for 12 h. The solution was filtered through a pad of celite and rinsed thoroughly with CH_2Cl_2. The solvent was removed under reduced pressure to yield ketone **136** (3.6 g, 80 %) as a clear oil.

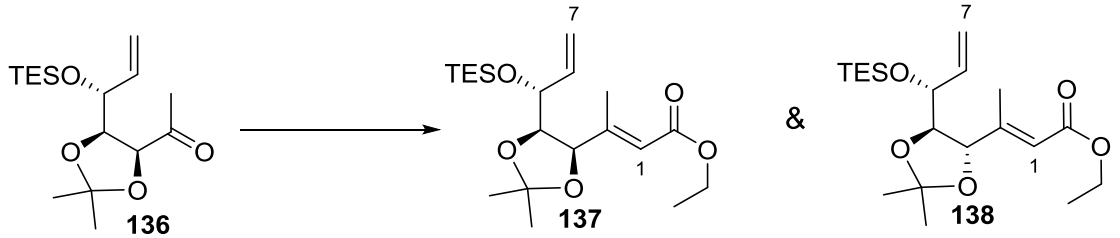
R_f = 0.44 (hexanes:EtOAc, 10:1)

FTIR 2954, 2914, 2878, 1716, 1458, 1417, 1380, 1353, 1241, 1211, 1166, 1123, 1063, 1000, 928, 906, 885, 841, 724, 671 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (ddd, *J* = 17.6, 10.3, 7.7 Hz, 1H, H-4), 5.27 (dd, *J* = 16.6, 1.6 Hz, 1H, H-5), 5.17 (dd, *J* = 10.2, 1.6 Hz, 1H, H-5'), 4.45 (d, *J* = 7.6 Hz, 1H, H-1), 4.33 – 4.22 (m, 2H, overlapping peaks H-2 & H-3), 2.30 (s, 3H, CH_3), 1.60 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 0.94 (t, *J* = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.57 (q, *J* = 7.8 Hz, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.7 (C=O), 137.9 (C-4), 117.1 (C-5), 109.8 ($C(CH_3)_2$), 82.7 (C-2), 81.2 (C-1), 72.9 (C-3), 28.6 (CH_3), 26.4 ($C(CH_3)_2$), 25.0 ($C(CH_3)_2$), 6.7 ($Si(CH_2CH_3)_3$), 5.1 ($Si(CH_2CH_3)_3$)

HRMS (ESI): *m/z* calc for $C_{16}H_{31}O_4Si$: 315.1992, found: 315.1980 $[M+H]^+$



(E,2R,3R,4R)-3,4-*O*-isopropylidene-5-*O*-triethylsilyl-octa-dien-1,6-oate 137 (E,2S,3R,4R)-3,4-*O*-isopropylidene-5-*O*-triethylsilyl-octa-dien-1,6-oate 138

Triethylphosphonoacetate (2.50 mL, 12.7 mmol) was dissolved in toluene, cooled to – 78 ˚C and stirred for 15 min. Next, nBuLi (6.9 mL, 1.6 M in hexanes) was charged slowly and the reaction was stirred for a further 30 min. The ketone **136** (2.66 g, 8.46 mmol) in THF (12 mL) was then added and the reaction mixture was warmed to 80 ˚C. The mixture was maintained at this temperature for 3 h. The solution was cooled to rt and satd. NH_4Cl (aq) added. The organic layer was separated and the aqueous layer was then back extracted with EtOAc. The combined organic layers were then dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash

chromatography (hexanes:EtOAc, 40:1) afforded diastereoisomers **138** (2.45 g, 76 %) & **137** (0.52 g, 16 %) as clear oils**.**

Analytical data for 138

R_f = 0.14 (hexanes:EtOAc, 40:1)

FTIR 2956, 2878, 1718, 1655, 1458, 1406, 1379, 1370, 1314, 1219, 1150, 1074, 1040, 1004, 924, 868, 828, 810, 687 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 – 5.92 (m, 2H, overlapping peaks H-1 & H-6), 5.34 (dt, *J* = 17.4, 1.9 Hz, 1H, H-7), 5.25 (dt, *J* = 10.4, 1.6 Hz, 1H, H-7'), 4.41 (d, *J* = 7.4 Hz, 1H, H-3), 4.34 (td, *J* = 4.3, 1.7 Hz, 1H, H-5), 4.17 (m, 2H, CH_2), 3.86 (dd, *J* = 7.6, 4.1 Hz, 1H, H-4), 2.17 (d, *J* = 1.4 Hz, 3H, CH_3), 1.45 (s, 3H, $C(CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3), 0.95 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.61 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4 (C=O), 155.1 (C-2), 136.9 (C-6), 117.8 (C-1), 116.6 (C-7), 109.7 ($C(CH3)_2$), 82.7 (C-4), 81.0 (C-3), 72.8 (C-5), 59.7 (CH_2), 27.0 ($C(CH_3)_2$), 27.0 ($C(CH_3)_2$), 14.6 (CH_3), 14.2 (CH_3), 6.7 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{20}H_{36}O_5SiNa$:407.2230, found: 407.2223 $[M+Na]^+$

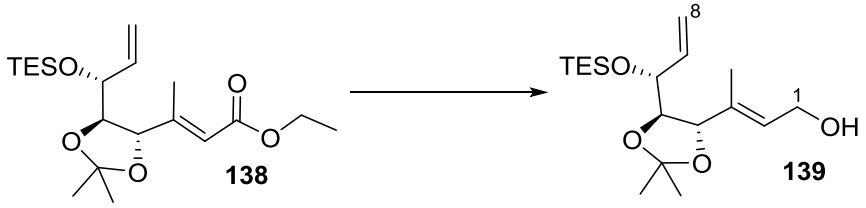
Analytical data for 137

FTIR 2955, 2877, 1717, 1655, 1458, 1405, 1379, 136, 1324, 1219, 1151, 1072, 1039, 1004, 924, 867, 841, 811, 725 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (t, *J* = 1.4 Hz, 1H, H-1), 5.87 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H, H-6), 5.23 (dt, *J* = 17.1, 1.5 Hz, 1H, H-7), 5.14 (dt, *J* = 10.4, 1.2 Hz, 1H, H-7'), 4.59 (dd, *J* = 6.9, 1.3 Hz, 1H, H-3), 4.22 – 4.14 (m, 3H, overlapping signals CH_2 & H-4), 4.09 (dd, *J* = 6.8, 5.5 Hz, 1H, H-5), 2.19 (d, *J* = 1.3 Hz, 3H, CH_3), 1.56 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, $C(CH_3)_2$), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3), 0.94 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.59 (q, *J* = 7.6 Hz, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3 (C=O), 153.0 (C-2), 137.4 (C-6), 117.8 (C-1), 117.0 (C-7), 108.8 ($C(CH_3)_2$), 81.4 (C-4), 81.0 (C-3), 73.5 (C-5), 59.6 (CH_2), 26.4 ($C(CH_3)_2$), 25.2 ($C(CH_3)_2$), 17.4 (CH_3), 14.3 (CH_3), 6.7 ($Si(CH_2CH_3)_3$), 4.9 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{20}H_{36}O_5SiNa$: 407.2230, found: 407.2239 $[M+Na]^+$



(E,4S,5R,6R)-4,5-*O*-isopropylidene-6-*O*-triethylsilyl-octa-dien-2,7-an-1-ol 139

Compound **138** (2.88 g, 7.48 mmol) was dissolved in CH_2Cl_2. The solution was cooled to -78 ˚C and dibal-H (22.5 mL, 1M in CH_2Cl_2) added slowly. The reaction mixture was subsequently stirred at -78 ˚C for 8 h. Upon completion, MeOH was added slowly to quench the reaction. The solution was warmed to rt and stirred with satd. potassium tartrate (aq) until clear. The organic layer was

separated and subsequently washed with H_2O, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to obtain the desired alcohol **139** (1.92 g, 75 %) as a clear oil.

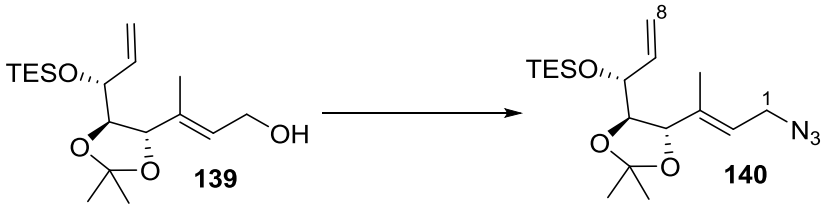
R_f = 0.57 (EtOAc:hexanes, 3:2)

FTIR 3422, 2954, 2877, 1458, 1414, 1378, 1368, 1238, 1166, 1132, 1067, 1003, 923, 887, 831, 811, 725, 688 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (ddd, J = 17.0, 10.5, 6.1 Hz, 1H, H-7), 5.73 (t, J = 6.5 Hz, 1H, H-2), 5.29 (dt, J = 17.3, 1.6 Hz, 1H, H-8), 5.18 (dt, J = 10.4, 1.5 Hz, 1H, H-8'), 4.35 (d, J = 8.2 Hz, 1H, H-4), 4.30 – 4.14 (m, 3H, overlapping peaks H-1, H-1' & H-6), 3.78 (dd, J = 8.2, 4.3 Hz, 1H, H-5), 1.70 (s, 3H, CH_3), 1.44 (s, 3H, ($C(CH_3)_2$), 1.41 (s, 3H, ($C(CH_3)_2$), 0.95 (t, J = 8.0 Hz, 9H, $Si(CH_2CH_3)_2$), 0.60 (q, J = 7.9 Hz, 6H, $Si(CH_2CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3 (C-7), 135.2 (C-3), 128.7 (C-2), 116.2 (C-8), 108.8 ($C(CH_3)_2$), 81.8, 81.8, (each C-5, C-4), 73.2 (C-6), 59.2 (C-1), 27.2 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 11.9 (CH_3), 6.7 ($Si(CH_2CH_3)_2$), 4.9 ($Si(CH_2CH_3)_2$)

HRMS (ESI): m/z calc for $C_{18}H_{35}O_4Si$: 343.2305, found: 343.2309 $[M+H]^+$



(E,4S,5R,6R)-1-azido-4,5-*O*-isopropylidene-6-*O*-triethylsilyl-octa-2,7-ene 140

Compound **139** (2.32 g, 6.77 mmol) was dissolved in anhydrous THF (50 mL) and PPh_3 (3.0 g, 12 mmol) was added. The solution was cooled to 0˚C, followed by the addition of DIAD (2.27 mL, 11.5 mmol) and DPPA (2.47 mL, 11.5 mmol). The solution was adjusted and stirred for 16 h. The reaction mixture was concentrated and then purified using flash chromatography (hexanes:EtOAc, 40:1) to afford azide **140** (1.64 g, 71 %) as a clear oil.

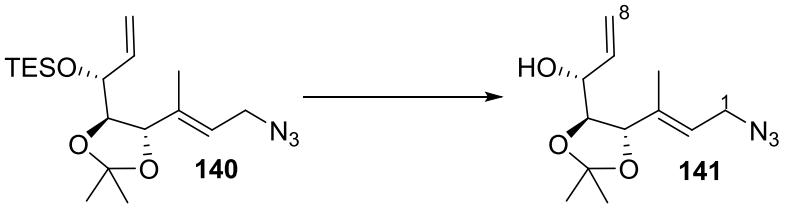
R_f = 0.31 (EtOAc:hexanes, 1:20)

FTIR 2955, 2877, 2094, 1457, 1415, 1379, 1369, 1239, 1167, 1132, 1068, 1033, 1055, 925, 880, 831, 726, 686 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (ddd, J = 17.0, 10.5, 6.2 Hz, 1H, H-7), 5.66 (t, J = 7.2 Hz, 1H, H-2), 5.31 (dt, J = 17.3, 1.6 Hz, 1H, H-8), 5.21 (dt, J = 10.2, 1.5 Hz, 1H, H-8'), 4.39 (d, J = 8.1 Hz, 1H, H-4), 4.24 (dd, J = 6.0, 4.4 Hz, 1H, H-6), 3.84 (m, J = 7.0 Hz, 2H, H-1), 3.78 (dd, J = 8.0, 4.2 Hz, 1H, H-5), 1.74 (s, 3H, -CH_3), 1.44 (s, 3H, -$C(CH_3)_2$), 1.42 (s, 3H, -$C(CH_3)_2$), 0.96 (t, J = 8.0 Hz, 9H, $Si(CH_2CH_3)_2$), 0.61 (q, J = 8.0 Hz, 6H, $Si(CH_2CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1 (C-3), 137.5 (C-7), 122.2 (C-2), 116.5 (C-8), 109.2 ($C(CH_3)_2$), 82.4 (C-5), 81.7 (C-4), 73.4 (C-6), 47.9 (C-1), 27.3 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 12.3 (CH_3), 6.9 ($Si(CH_2CH_3)_2$), 5.0 ($Si(CH_2CH_3)_2$)

HRMS (ESI): m/z calc for $C_{18}H_{34}N_3O_3Si$: 368.2369, found: 368.2378 $[M+H]^+$



(E,4S,5S,6R)-1-azido-6-hydroxy-4,5-*O*-isopropylidene-octa-2,7-ene 141

Compound **140** (1.6 g, 4.4 mmol) was dissolved in anhydrous THF (30 mL) and TBAF (3.1 mL, 1 M in THF) charged slowly. The reaction mixture was stirred at rt for 6 h and subsequently quenched upon addition of 3M NaOH. The organic layer was separated and aqueous layer back extracted with EtOAc. Combined organic layers were then dried over Na_2SO_4, filtered and solvent removed under reduced pressure. The crude residue was then columned by flash chromatography (EtOAc:hexanes, 1:4) to afford azide **141** (0.89 g, 81 %) as a clear oil.

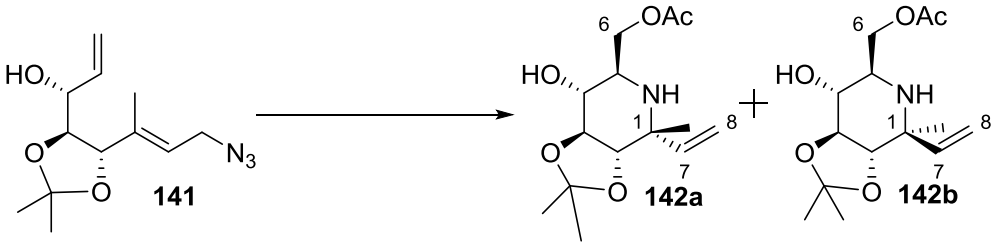
R_f = 0.59 (EtOAc:hexanes, 1:1)

FTIR 3472, 2987, 2935, 2095, 1644, 1456, 1371, 1218, 1165, 1135, 1106, 1060, 991, 928, 874, 825, 743 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 16.6, 10.6, 5.5 Hz, 1H, H-7), 5.70 (t, *J* = 7.2 Hz, 1H, H-2), 5.38 (d, *J* = 17.1 Hz, 1H, H-8), 5.24 (d, *J* = 10.4 Hz, 1H, H-8'), 4.44 (d, *J* = 8.3 Hz, 1H, H-4), 4.14 – 4.05 (m, 1H, H-6), 3.89 (dd, *J* = 14.1, 7.6 Hz, 1H, H-1), 3.84 – 3.73 (m, 2H, overlapping peaks H-5 & H-1), 2.19 (d, *J* = 7.8 Hz, 1H, OH peak), 1.76 (s, 3H, CH_3), 1.47 (s, 3H, $C(CH_3)_2$), 1.46 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5 (C-3), 137.4 (C-7), 122.8 (C-2), 117.0 (C-8), 109.8 ($C(CH_3)_2$), 82.2, 81.4, (each C-4, C-5), 71.4 (C-6), 47.7 (C-1), 27.3 (2 x($C(CH_3)_2$), 12.1 (CH_3)

HRMS (ESI): m/z calc for $C_{12}H_{20}N_3O_3$: 254.1505 found: 254.1515 $[M+H]^+$



(1R,2S,3S,4R,5R)-6-*O*-acety-1,5-dideoxy-1-ethenyl-4-hydroxy-2,3-*O*-isopropylidene-1-methyl-1,5-imino-D-glucitol 142a & (1S,2S,3S,4R,5R)-6-*O*-acety-1,5-dideoxy-1-ethenyl-4-hydroxy-2,3-*O*-isopropylidene-1-methyl-1,5-imino-D-glucitol 142b

Compound **141** (0.050 g, 0.197 mmol) was dissolved in toluene (20 mL) and acetic acid (56.0 µL, 0.98 mmol) was subsequently charged. The solution was stirred at 98 ˚C for 4.5 days. The solvent was then removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 1:1) yielded a mixture of **142a** (17 mg, 30 %) and **142b** (3 mg, 4 %) as clear oils.

Data for **142a**

R_f = 0.23 (hexanes:EtOAc, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 – 5.89 (m, 1H, H-7), 5.35 (dd, *J* = 17.7, 1.8 Hz, 1H, H-8), 5.22 (dd, *J* = 11.1, 1.8 Hz, 1H, H-8'), 4.50 (dd, *J* = 11.5, 4.6 Hz, 1H, H-6), 4.19 (dd, *J* = 11.4, 2.4 Hz, 1H, H-6), 3.55 – 3.44 (m, 2H,overlapping peaks H-3 & H-4), 3.15 (d, *J* = 8.7 Hz, 1H, H-2), 2.81 (ddd, *J* = 8.8, 4.4, 2.4 Hz, 1H, H-5), 2.12 (s, 3H, OAc), 1.45 (s, 3H, $C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (C=O), 136.9 (C-7), 114.8 (C-8), 110.2 ($C(CH_3)_2$), 83.3 (C-2), 79.1, 72.4 (each C-3, C-4), 63.9 (C-6), 57.0 (C-1) 55.7 (C-5), 28.2 (CH_3), 27.0 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$), 20.9 (OAc)

HRMS (ESI): m/z calc for $C_{14}H_{24}NO_5$: 286.1654 found: 286.1663 $[M+H]^+$

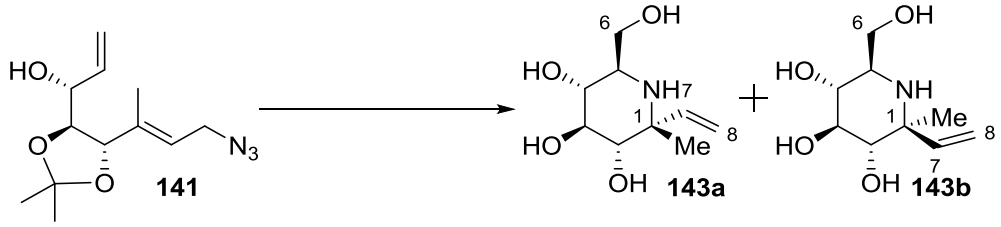
Data for **142b**

R_f = 0.17 (hexanes:EtOAc, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.6, 10.8, 1.3 Hz, 1H, H-7), 5.31 (d, *J* = 17.4 Hz, 1H, H-8), 5.14 (d, *J* = 10.8 Hz, 1H, H-8'), 4.62 (dd, *J* = 11.5, 4.0 Hz, 1H, H-6), 4.17 (dd, *J* = 11.4, 2.4 Hz, 1H, H-6), 3.69 (td, *J* = 9.5, 1.3 Hz, 1H, H-3), 3.49 (t, *J* = 9.4 Hz, 1H, H-4), 3.24 (dd, *J* = 9.4, 1.3 Hz, 1H, H-2), 2.95 – 2.61 (m, 2H, H-5), 2.11 (d, *J* = 1.3 Hz, 3H, OAc), 1.45 (s, 3H, $C(CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$), 1.24 (d, *J* = 1.1 Hz, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6 (C=O), 143.39 (C-7), 113.65 (C-7), 110.12 ($C(CH_3)_2$), 81.13 (C-2), 78.20 (C-3), 72.09 (C-4), 63.73 (C-6), 56.50 (C-1), 55.60 (C-5), 26.95 ($C(CH_3)_2$), 26.55 ($C(CH_3)_2$), 20.86 (OAc), 16.50 (CH_3)

HRMS (ESI): m/z calc for $C_{14}H_{24}NO_5$: 286.1654 found: 286.1661$[M+H]^+$



(1R,2S,3S,4R,5R)-1,5-dideoxy-1-ethenyl -1-methyl-1,5-imino-D-glucitol 143a & (1S,2S,3S,4R,5R)-1,5-dideoxy-1-ethenyl-1-methyl-1,5-imino-D-glucitol 143b Azide **141** (0.05 g, 0.19 mmol) was dissolved in toluene (20 mL) and acetic acid (56.0 µL, 0.98 mmol) subsequently charged. The reaction mixture was stirred at 98 ˚C for 4.5 days and the solvent then removed under reduced pressure. The crude residue was subsequently treated with 1M HCl (5 mL) for 12 h. The solvent was then removed under reduced pressure. Flash Chromatography (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:0.1:0.1) afforded **143** (21 mg, 55 %) as a mixture of isomers (79:21, **143a**:**143b**) and a yellow foam.

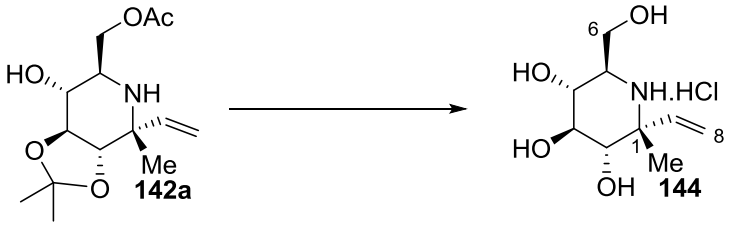
R_f = 0.11 (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:1:1)

^{1}H NMR (500 MHz, CD_3OD) δ 6.12 (dd, *J* = 18.0, 11.2 Hz, 1H, H-7), 5.98 (dd, *J* = 17.6, 10.8 Hz, 1H, H-7*), 5.30 – 5.20 (m, 2H, H-8 & H-8'), 5.13 (d, *J* = 11.1 Hz, 2H, H-8* & H-8'*), 3.84 (dd, *J* = 10.8, 3.0 Hz, 1H, H-6 & H-6*), 3.67 – 3.63 (m, 1H, H-6*), 3.55 (dd, *J* = 10.9, 7.0 Hz, 1H, H-6), 3.45 (t, *J* = 9.3 Hz, 1H, H-3*), 3.25 (d, *J* = 9.3 Hz, 1H, H-3), 3.22 – 3.19 (m, 1H, H-4*), 3.16 (m, 3H, overlapping signals H-2, H-4 & H-2*), 2.84 (ddd, *J* = 9.9, 6.8, 3.0 Hz, 1H, H-5), 2.81 – 2.77 (m, 1H, H-5*), 1.23 (s, 3H, CH_3), 1.22 (s, 3H, CH_3*)

^{13}C NMR (126 MHz, CD_3OD) δ 143.84 (C-7*), 138.12 (C-7), 113.63 (C-8), 112.40 (C-8*), 77.82 (C-2), 76.28 (C-2*), 75.59 (C-3), 75.10 (C-3*), 72.85 (C-4), 72.33 (C-4*), 61.99 (C-6*), 61.50 (C-6*), 58.39 (C-1), 57.74 (C-1*), 55.86 (C-5), 55.53 (C-5*), 26.90 (CH_3), 15.37 (CH_3*)

HRMS (ESI): *m/z* calc for $C_9H_{18}NO_4$: 204.1236 found: 204.1243 $[M+H]^+$

* = minor



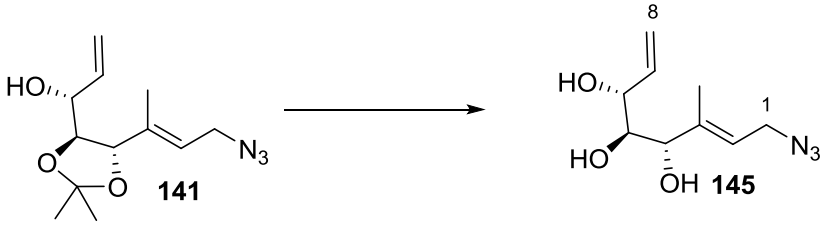
(1R,2S,3S,4R,5R)-1,5-dideoxy-1-ethenyl -1-methyl-1,5-imino-D-glucitol hydrochloride 144

Compound **142a** (0.025 mg, 0.088 mmol) was stirred in 1M HCl (1 mL) for 16 h. The solvent was removed under reduced pressure to yield **144** (18 mg, 86 %) as a white solid.

^{1}H NMR (500 MHz, D_2O) δ 6.01 (dd, *J* = 17.6, 11.4 Hz, 1H, H-7), 5.54 (d, *J* = 11.4 Hz, 1H, H-8'), 5.47 (d, *J* = 17.6 Hz, 1H, H-8), 3.82 (dd, *J* = 12.8, 3.0 Hz, 1H, H-6), 3.77 (dd, *J* = 12.7, 5.3 Hz, 1H, H-6), 3.56 – 3.49 (m, 2H, overlapping signals H-3 & H-4), 3.45 – 3.41 (m, 1H, H-2), 3.37 – 3.32 (m, 1H, H-5), 1.49 (s, 3H, CH_3)

^{13}C NMR (126 MHz, D_2O) δ 130.6 (C-7), 122.0 (C-8), 74.2 (C-2), 72.9, 68.2 (each C-3, C-4), 62.0 (C-1), 57.6 (C-6), 56.0 (C-5), 21.9 (CH_3)

HRMS (ESI):m/z calc for $C_9H_{17}NO_4Cl$: 238.0846 found: 238.0843 $[M-H]^-$



(E,4S,5S,6R)-1-azido-octa-2,7-diene-4,5,6-triol 141

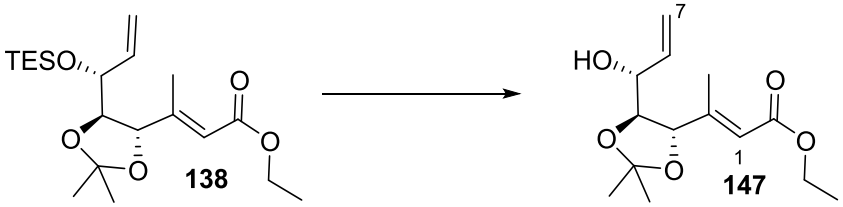
Compound **141** (0.3 g, 1.2 mmol) was suspended in 2M HCl and stirred for 8 h. The reaction mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and solvent evaporated under reduced pressure. Flash chromatography (hexanes-EtOAc, 3:2) afforded **145** (0.19 g, 76 %) as a clear oil.

R_f = 0.42 (hexanes-EtOAc, 3:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 – 5.91 (m, 1H, H-7), 5.77 – 5.71 (m, 1H, H-2), 5.41 (dt, *J* = 17.2, 1.4 Hz, 1H, H-8), 5.31 (dt, *J* = 10.3, 1.3 Hz, 1H, H-8'), 4.24 (dt, *J* = 8.3, 4.4 Hz, 2H, overlapping signals H-6 & H-4), 3.93 – 3.86 (m, 2H, H-1 & H-1'), 3.57 (q, *J* = 4.2 Hz, 1H, H-5), 2.71 (d, *J* = 4.4 Hz, 1H, OH peak), 2.56 (d, *J* = 5.6 Hz, 1H, OH peak), 2.42 – 2.34 (m, 1H, OH peak), 1.76 (s, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1 (C-3), 137.2 (C-7), 120.2 (C-2), 117.6 (C-8), 76.2 (C-4), 73.9 (each C-5, C-6), 47.6 (C-1), 13.3(CH_3)

HRMS (ESI): **141** m/z calc for $C_9H_{16}N_3O_3$: 214.1192 found: 214.1203 $[M+H]^+$



(E,3S,4S,5R)-5-hydroxy-3,4-*O*-isopropylidene-octa-dien-1,6-oate 147

Compound **138** (2.12 g, 5.51 mmol) was dissolved in anhydrous THF (40 mL) and TBAF (11.0 mL, 1 M in THF buffered with 20 % AcOH) charged slowly. The reaction mixture was stirred at rt for 2 h, followed by the addition of pH buffer 7 solution (30 mL). The aqueous layer was back extracted with EtOAc. The combined organic layers were then dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 3:7) afforded ester **147** (1.34 g, 90 %) as a clear oil.

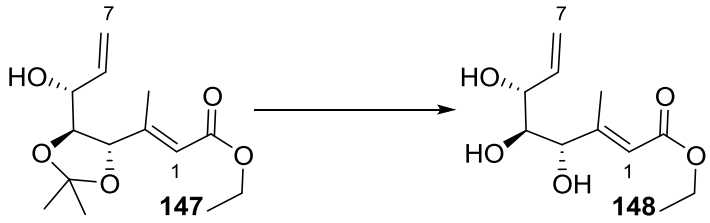
R_f = 0.63 (EtOAc-hexanes, 3:7)

FTIR 3488, 2985, 2936, 1715, 1653, 1445, 1371, 1219, 1154, 1038, 992, 926, 865, 819, 746 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 – 5.97 (apt m, 1H, H-1), 5.90 (ddd, J = 17.2, 10.5, 5.6 Hz, 1H, H-6), 5.40 (dt, J = 17.2, 1.5 Hz, 1H, H-7), 5.27 (dt, J = 10.9, 1.4 Hz, 1H, H-7'), 4.48 (d, J = 7.9 Hz, 1H, H-3), 4.18 (q, J = 7.2 Hz, 2H, CH_2), 4.15 – 4.10 (m, 1H, H-5), 3.82 (dd, J = 8.1, 3.0 Hz, 1H, H-4), 2.18 (d, J = 1.2 Hz, 3H, CH_3), 1.48 (s, 3H, $C(CH_3)_2$), 1.48 (s, 3H, $C(CH_3)_2$), 1.30 (t, J = 7.1 Hz, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2 (C=O), 153.7 (C-2), 137.2 (C-6), 118.2 (C-1), 116.9 (C-7), 110.2 ($C(CH_3)_2$), 81.9 (C-4), 81.3 (C-3), 71.1 (C-5), 59.9 (CH_2), 27.1 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 14.3 (CH_3), 14.2 (CH_3)

HRMS (ESI): m/z calc for $C_{16}H_{25}O_5NNa$: 334.1630, found 334.1630 $[M+Na+ACN]^+$



(E,3S,4S,5R)-3,4,5-triol-octa-dien-1,6-oate 147

Compound **147** (1.25 g, 4.62 mmol) was dissolved in 2M HCl (10 mL) and stirred at rt for 1 hr. The solution was extracted with EtOAc, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 7:3) afforded **148** (0.88 g, 82 %) as a clear oil.

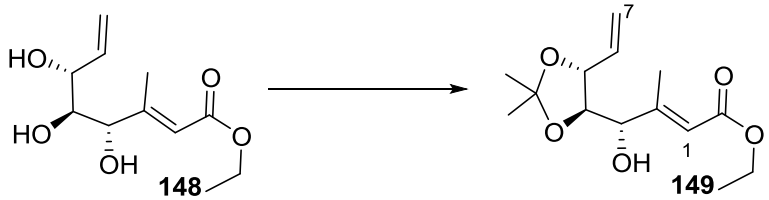
R_f = 0.53 (hexanes-EtOAc, 7:3)

FTIR 3387, 2921, 2093, 1643, 1385, 1249, 1091, 1045, 992, 925, 886, 743 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (s, 1H, H-1), 5.94 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1H, H-6), 5.42 (d, *J* = 17.1 Hz, 1H, H-7), 5.31 (d, *J* = 10.4 Hz, 1H, H-7'), 4.31-4.05 (m, 4H, overlapping signals - CH_2, H-3 & H-5), 3.60 (t, *J* = 3.9 Hz, 1H, H-4), 2.14 (s, 3H, CH_3), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.51 (C=O), 156.40 (C-2), 136.84 (C-6), 118.13 (C-7), 116.78 (C-1), 75.93, 74.25 (C-3, C-5), 73.35 (C-4), 59.85 (CH_2), 15.59 (CH_3) , 14.25 (CH_3)

HRMS (ESI): m/z calc for $C_{11}H_{18}O_5Cl$: 265.0843, found 265.0841 $[M+Cl]^-$



(E,3S,4R,5R)-3-hydroxy-4,5-*O*-isopropylidene-octa-dien-1,6-oate 149

Compound **148** (2.67 g, 11.6 mmol) was dissolved in CH_2Cl_2 (30 mL). The solution was cooled to 0 ˚C and *p*-TsOH (0.4 g, 2.3 mmol) added. After stirring for 10 mins, 2,2-DMP (2.85 mL, 23.2 mmol) was added. The reaction mixture was subsequently stirred at rt for a further 15 mins and triethylamine (1.60 mL, 11.6 mmol) charged. The solvent was then removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 7:3) afforded ester **149** (2.85 g, 91 %) as a clear oil.

R_f = 0.72 (hexanes-EtOAc, 7:3)

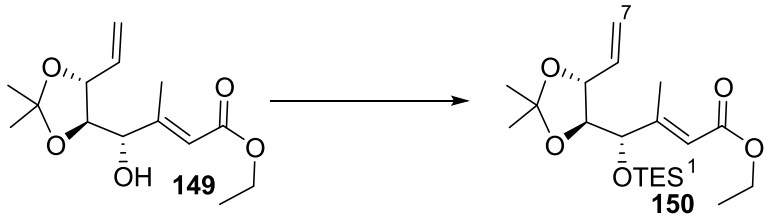
FTIR 3484, 2986, 2936, 1714, 1654, 1446, 1371, 1212, 1151, 1115, 1063, 1039, 989, 929, 871, 817, 753 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (s, 1H, H-1), 5.82 (ddd, *J* = 17.3, 10.3, 7.4 Hz, 1H, H-6), 5.42 (d, *J* = 17.0 Hz, 1H, H-7), 5.32 (d, *J* = 10.4 Hz, 1H, H-7'), 4.39 (t, *J* = 7.9 Hz, 1H, H-5), 4.18 (q, *J* = 7.2 Hz, 3H, -CH_2), 3.99 (dd, *J* = 8.4, 2.6 Hz, 1H, H-3), 3.82 (dd, *J* = 8.3, 2.6 Hz, 1H, H-4), 2.58

(d, *J* = 8.6 Hz, 1H, -OH signal), 2.15 (s, 3H, CH_3), 1.46 (s, 3H, $C(CH_3)_2$), 1.45 (s, 3H, $C(CH_3)_2$), 1.30 (t, *J* = 7.1 Hz, 3H, (CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3 (C=O), 156.5 (C-2), 134.4 (C-6), 119.9 (C-7), 116.7 (C-1), 109.9 ($C(CH_3)_2$), 80.8 (C-4), 79.4 (C-5), 73.6 (C-3), 59.8 (CH_2), 27.1 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 15.2 (CH_3), 14.2 (CH_3)

HRMS (ESI): m/z calc for $C_{14}H_{22}O_5Na$: 293.1365, found 293.1354 $[M+Na]^+$



(E,3S,4S,5R) -4,5-*O*-isopropylidene-3-*O*-triethylsilyl-octa-dien-1,6-oate 150

Compound **149** (2.61 g, 9.65 mmol) was dissolved in CH_2Cl_2 (35 mL) followed by the addition of imidazole (1.25 g, 18.3 mmol), triethylsilane chloride (1.85 mL, 11.9 mmol) & 4-DMAP (0.12 g, 0.97 mmol) were subsequently charged and solution stirred for 4 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and quenched with H_2O (50 mL). The organic layer was separated & aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (Hexanes-EtOAc, 9:1) afforded silylated ester **150** (2.41 g, 65%) and starting material **149** (0.4 g, 11%) as clear oils.

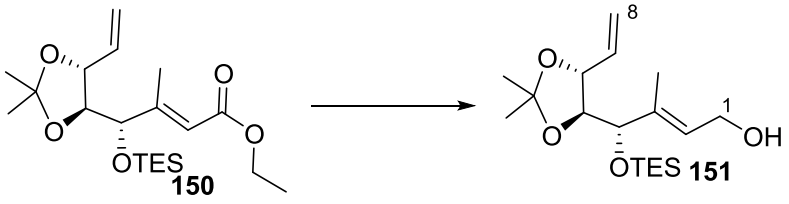
Data for **150**

R_f = 0.72 (hexanes-EtOAc, 9:1)

FTIR 2956, 2878, 1718, 1651, 1458, 1379, 1369, 1323, 1213, 1154, 1073, 1043, 1005, 929, 881, 826, 804, 726, 675 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (d, J = 1.5 Hz, 1H, H-1), 5.77 (ddd, J = 17.4, 10.3, 7.0 Hz, 1H, H-6), 5.31 (dt, J = 17.3, 2.5 Hz, 1H, H-7), 5.21 (dd, J = 10.3, 2.4 Hz, 1H, H-7'), 4.26 (t, J = 7.6 Hz, 1H, H-5), 4.16 (qd, J = 7.1, 2.2 Hz, 2H, CH_2), 4.12 (d, J = 4.6 Hz, 1H, H-3), 3.76 (dd, J = 8.2, 4.8 Hz, 1H, H-4), 2.12 (d, J = 1.4 Hz, 3H, CH_3), 1.40 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$) 1.29 (t, J = 7.1 Hz, 3H, CH_3), 0.95 (t, J = 7.9 Hz, 9H, $Si(CH_2CH_3)_2$), 0.61 (q, J = 8.8, 8.3 Hz, 6H, $Si(CH_2CH_3)_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3 (C=O), 157.5 (C-2), 135.5 (C-6), 118.4 (C-7), 117.3 (C-1), 109.2 ($C(CH_3)_2$), 82.7 (C-4), 78.4 (C-5), 77.1 (C-3), 59.7 (CH_2), 27.0 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 15.7 (CH_3) 14.2 (CH_3) , 6.7 ($Si(CH_2CH_3)_2$), 4.7 ($Si(CH_2CH_3)_2$)

HRMS (ESI): m/z calc for $C_{22}H_{39}O_5SiNa$: 448.2495, found 448.2483 $[M+Na+ACN]^+$



(E,3S,4S,5R) -4,5-*O*-isopropylidene-3-*O*-triethylsilyl-oct-1,6-ene-1-ol 151

Compound **150** (2.3 g, 6.0 mmol) was dissolved in CH_2Cl_2. The solution was cooled to -78 ˚C and dibal-H (17.9 mL, 1M in THF) was added slowly and solution stirred at -78 ˚C for a further 4 h. The reaction was then quench with the slow addition of MeOH. The solution was warmed to rt and stirred with potassium tartrate (aq) until clear. The organic layer was separated and subsequently washed with H_2O, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford the desired alcohol **151** (1.62 g, 79 %) as a clear oil.

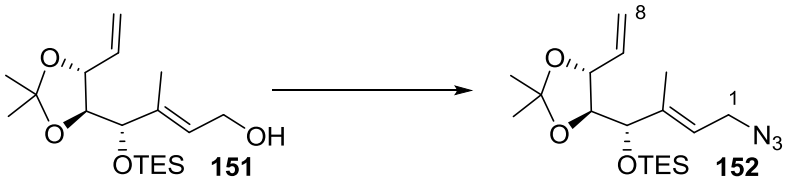
R_f = 0.57 (EtOAc-hexanes, 3:2)

FTIR 3434, 2954, 2877, 1458, 1413, 1378, 1239, 1214, 1170, 1095, 1059, 1004, 927, 884, 834, 725, 671 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddd, J = 17.2, 10.3, 7.0 Hz, 1H, H-7), 5.62 (t, J = 6.4 Hz, 1H, H-2), 5.29 (d, J = 17.0 Hz, 1H, H-8), 5.19 (d, J = 10.1 Hz, 1H, H-8'), 4.24 – 4.17 (m, 2H, overlapping signals H-6 & H-1), 4.14 (dt, J = 12.7, 6.1 Hz, 1H, H-1'), 4.04 (d, J = 6.0 Hz, 1H, H-4), 3.75 (dd, J = 8.1, 6.0 Hz, 1H, H-5), 1.63 (s, 3H, CH_3), 1.41 (s, 3H, $C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$), 0.95 (t, J = 7.9 Hz, 9H, $Si(CH_2CH_3)_2$), 0.60 (qd, J = 7.9, 2.9 Hz, 6H, $Si(CH_2CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3 (C-3), 136.0 (C-7), 126.5 (C-2), 118.2 (C-8), 109.0 ($C(CH_3)_2$), 83.1 (C-5), 78.9 (C-6), 78.5 (C-4), 59.1, (C-1) 27.0 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 12.8 (CH_3), 6.7 ($Si(CH_2CH_3)_2$), 4.8 ($Si(CH_2CH_3)_2$)

HR-MS (ESI): m/z calc for $C_{18}H_{34}O_4SiCl$: 377.1915, found 377.1929 $[M+Cl]^-$



(E,3S,4S,5R)-1-azido-4,5-*O*-isopropylidene-3-*O*-triethylsilyl-octa-2,7-diene 152

Compound **151** (0.6 g, 1.8 mmol) was dissolved in anhydrous THF (10 mL) and PPh_3 (0.78 g, 2.98 mmol) was then added. The solution was cooled to 0˚C, followed by the addition of DIAD (0.59 mL, 2.98 mmol) and DPPA (0.64 mL, 2.98 mmol). The solution was then adjusted to rt and stirred for 12 h. The solvent was removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 40:1) afforded azide **152** (0.46 g, 73 %) as a clear oil.

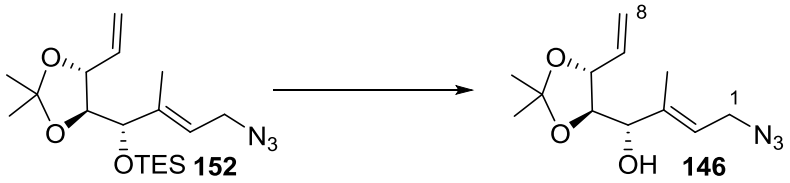
R_f = 0.3 (hexanes-EtOAc, 40:1)

FTIR 2955, 2877, 2094, 1457, 1370, 1215, 1170, 1098, 1006, 928, 884, 837, 726, 674 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.2, 10.4, 7.1 Hz, 1H, H-7), 5.58 (t, J = 7.0 Hz, 1H, H-2), 5.30 (dd, J = 17.1, 1.4 Hz, 1H, H-8), 5.21 (dd, J = 10.2, 1.4 Hz, 1H, H-8'), 4.21 (t, J = 7.5 Hz, 1H, H-6), 4.09 (d, J = 5.5 Hz, 1H, H-4), 3.86 (dd, J = 14.0, 7.2 Hz, 1H, H-1), 3.79 – 3.70 (m, 2H, H-1 & H-5), 1.69 (s, 3H, CH_3), 1.41 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 0.95 (t, J = 7.9 Hz, 9H, $Si(CH_2CH_3)_2$), 0.61 (qd, J = 7.9, 2.1 Hz, 6H, $Si(CH_2CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2 (C-3), 136.3 (C-7), 120.8 (C-2), 118.7 (C-8), 109.6 ($C(CH_3)_2$), 83.6 (C-5), 79.2 (C-6), 78.2 (C-4), 48.2 (C-1), 27.5 ($C(CH_3)_2$), 27.3 ($C(CH_3)_2$), 13.7 (CH_3), 7.18 ($Si(CH_2CH_3)_2$), 5.22 ($Si(CH_2CH_3)_2$)

HRMS (ESI): m/z calc for $C_{18}H_{34}O_3SiN_3$: 368.2369, found 368.2361 $[M+H]^+$



(E,3S,4S,5R)-1-azido-3-hydroxy-4,5-*O*-isopropylidene-oct-2,7-ene-4-ol 146

Compound **152** (0.49 g, 1.33 mmol) was dissolved in anhydrous THF (16 mL) and TBAF (4.0 mL, 1 M in THF) was charged slowly. The solution was stirred at rt for 12 h. The reaction mixture was then quenched with 3M NaOH and stirred for a further 15 min. The organic layer was separated and aqueous layer back extracted with EtOAc. Combined organic layers were then dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded azide **146** (0.28 g, 85 %) as a clear oil.

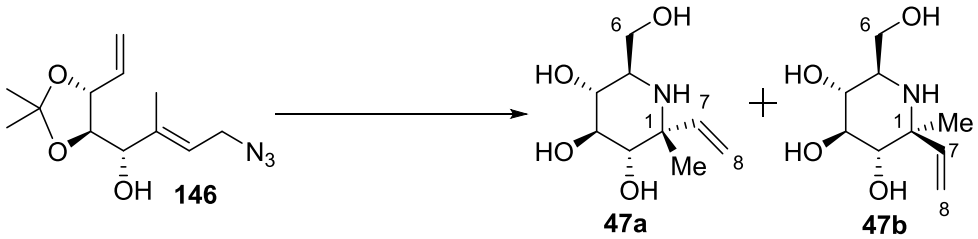
R_f = 0.8 (EtOAc-hexanes, 1:1)

FTIR 3460, 2987, 2094, 1455, 1372, 1215, 1168, 1056, 988, 939, 878, 817 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 – 5.74 (ddd, J = 17.4, 10.3, 7.3 Hz, 1H, H-7), 5.67 – 5.62 (m, 1H, H-2), 5.37 (dt, J = 17.1, 2.4 Hz, 1H, H-8), 5.28 (dd, J = 10.3, 1.7 Hz, 1H, H-8'), 4.31 (t, J = 7.8 Hz, 1H, H-6), 4.00 (dd, J = 7.0, 4.2 Hz, 1H, H-4), 3.84 (d, J = 7.2 Hz, 1H, H-1, H-1'), 3.79 (dd, J = 8.2, 4.1 Hz, 1H, H-5), 1.71 (d, J = 1.3 Hz, 3H, CH_3), 1.46 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.7 (C-3), 134.8 (C-7), 120.6 (C-2), 119.5 (C-8), 109.7 ($C(CH_3)_2$), 81.5 (C-5), 79.4 (C-6), 75.0 (C-4), 47.7 (C-1), 27.1 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 12.9 (CH_3)

HRMS (ESI): m/z calc for $C_{12}H_{19}O_3N_3Cl$: 288.1115, found 288.1123 $[M+Cl]^-$



(1R,2S,3S,4R,5R)-1,5-dideoxy-1-ethenyl -1-methyl-1,5-imino-D-glucitol 47a & (1S,2S,3S,4R,5R)-1,5-dideoxy-1-ethenyl-1-methyl-1,5-imino-D-glucitol 47b

Azide **146** (50 mg, 0.20 mmol) was dissolved in toluene (20 mL) and acetic acid (56 µL, 0.98 mmol) subsequently charged. The reaction mixture was stirred at 98 ˚C for 4 days. The solvent was then removed under reduced pressure and 2M HCl (5 mL) added to the resultant residue. This mixture was stirred for a further 16 h. The solvent was then removed under reduced pressure. Flash

chromatography (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:0.1:0.1) afforded **47a** & **47b** (27 mg, 84:16, 47a:47b, 68 %) as a yellow foam.

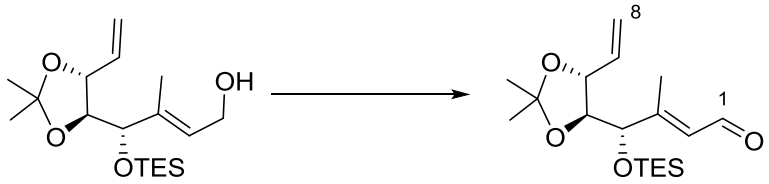
R_f = 0.11 (CH_2Cl_2-MeOH-aq NH_3-H_2O, 8:2:0.1:0.1)

^{1}H NMR (500 MHz, CD_3OD) δ 6.12 (dd, *J* = 18.0, 11.2 Hz, 1H, H-7), 5.98 (dd, *J* = 17.6, 10.8 Hz, 1H, H-7*), 5.30 – 5.20 (m, 2H, H-8 & H-8'), 5.13 (d, *J* = 11.1 Hz, 2H, H-8* & H-8'*), 3.84 (dd, *J* = 10.8, 3.0 Hz, 1H, H-6 & H-6*), 3.67 – 3.63 (m, 1H, H-6*), 3.55 (dd, *J* = 10.9, 7.0 Hz, 1H, H-6), 3.45 (t, *J* = 9.3 Hz, 1H, H-3*), 3.25 (d, *J* = 9.3 Hz, 1H, H-3), 3.22 – 3.19 (m, 1H, H-4*), 3.16 (m, 3H, overlapping signals H-2, H-4 & H-2*), 2.84 (ddd, *J* = 9.9, 6.8, 3.0 Hz, 1H, H-5), 2.81 – 2.77 (m, 1H, H-5*), 1.23 (s, 3H, CH_3), 1.22 (s, 3H, CH_3*)

^{13}C NMR (126 MHz, CD_3OD) δ 143.8 (C-7*), 138.1 (C-7), 113.6 (C-8), 112.4 (C-8*), 77.8 (C-2), 76.3 (C-2*), 75.6 (C-3), 75.1 (C-3*), 72.9 (C-4), 72.3 (C-4*), 62.0 (C-6*), 61.5 (C-6*), 58.4 (C-1), 57.7 (C-1*), 55.9 (C-5), 55.5 (C-5*), 26.9 (CH_3), 15.4 (CH_3*)

HRMS (ESI): m/z calc for $C_9H_{18}NO_4$: 204.1236 found: 204.1243 $[M+H]^+$

* = minor



151 **153**

(E,4S,5S,6R)-5,6-*O*-isopropylidene-4-*O*-triethylsilyl-oct-2,7-ene-1-al 153

Compound **151** (1.32 g, 3.85 mmol) was dissolved in CH_2Cl_2. The solution was cooled to 0 ˚C and Dess Martin periodinane (2.45 g, 5.78 mmol) added. The reaction mixture was stirred at rt for 1 h. The solution was subsequently diluted with Et_2O and stirred with aqueous $Na_2S_2O_3$ (1 g/L) containing $NaHCO_3$ (100 g/L). The organic layer was separated and washed with H_2O, brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to yield aldehyde **153** (1.11 g, 85 %) as a clear oil.

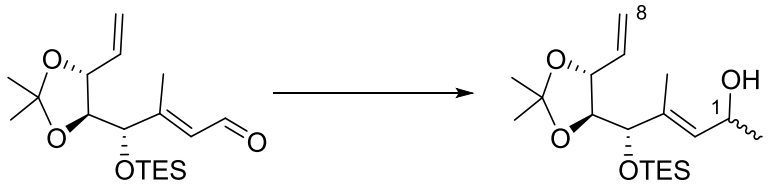
R_f = 0.31 (EtOAc-hexanes, 1:20)

FTIR 2955, 2877, 1677, 1457, 1413, 1379, 1239, 1215, 1170, 1104, 1066, 1005, 929, 844, 832, 802, 726, 673 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (d, *J* = 7.9 Hz, 1H, H-1), 6.07 (d, *J* = 8.0 Hz, 1H, H-2), 5.79 (ddd, *J* = 17.4, 10.3, 7.1 Hz, 1H, H-7), 5.33 (d, *J* = 17.1 Hz, 1H, H-8), 5.24 (d, *J* = 10.3 Hz, 1H, H-8'), 4.29 (apt t, *J* = 7.6 Hz, 1H, H-6), 4.20 (d, *J* = 4.3 Hz, 1H, H-4), 3.78 (dd, *J* = 8.0, 4.4 Hz, 1H, H-5), 2.18 (d, *J* = 1.3 Hz, 3H, CH_3), 1.40 (s, 6H, 2 x $C(CH_3)_2$), 0.95 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.61 (q, *J* = 8.7, 8.3 Hz, 6H, $Si(CH_2CH_3)_3$

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.1 (C-1), 161.5 (C-3), 135.4 (C-7), 127.5 (C-2), 118.9 (C-8), 109.4 ($C(CH_3)_2$), 82.7 (C-5), 78.3 (C-6), 76.2 (C-4), 27.0 ($C(CH_3)_2$), 26.6 ($C(CH_3)_2$), 14.5 (CH_3), 6.7 ($Si(CH_2CH_3)_3$), 4.7 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{18}H_{32}O_4NaSi$: 363.1968, found 363.1958 $[M+Na]^+$



153 **154**

(E,4S,5S,6R)-5,6-*O*-isopropylidene-4-*O*-triethylsilyl-non-2,7-ene-1-ol 154

Compound **153** (0.65 g, 1.91 mmol) was dissolved in THF (50 mL) and methyl magnesium chloride (1.9 mL, 3M in Et_2O) subsequently charged. The solution was stirred at rt for 4 h. The reaction mixture was quenched with satd. NH_4Cl (aq), extracted with EtOAc, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 9:1) afforded alcohol **154** (0.55 g, 86 %) as a clear oil.

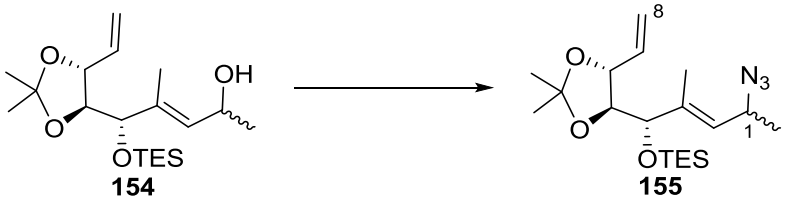
R_f = 0.27 (hexanes-EtOAc, 9:1)

FTIR 3420, 2955, 2877, 1457, 1413, 1369, 1239, 1213, 1170, 1053, 1005, 927, 886, 823, 803, 726, 671 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 – 5.69 (m, 2H, overlapping signals H-7 & H-7m), 5.46 (d, *J* = 8.4 Hz, 1H, H-2m), 5.43 (d, *J* = 8.5 Hz, 1H, H-2), 5.34 (dt, *J* = 17.1, 1.2 Hz, 1H, H-8), 5.28 (dt, *J* = 17.1, 1.5 Hz, 1H, H-8m), 5.23 – 5.17 (m, 2H, overlapping signals H-8'm & H-8'), 4.60 – 4.50 (m, 2H, overlapping signals H-1 & H-1m), 4.13-4.26 (m, 2H, overlapping peaks H-6 & H-6m), 4.00 (apt d, *J* = 6.0 Hz, 2H, overlapping peaks H-4 & H-4m), 3.80 – 3.71 (m, 2H, overlapping signals H-5 & H-5m), 1.70 – 1.62 (m, 6H, overlapping peaks CH_3 & CH_3m), 1.41 (apt s, 12H, overlapping signals –$C(CH_3)_2$ & $C(CH_3)_2$m), 1.25 (d, *J* = 6.3 Hz, 3H, CH_3), 1.22 (d, *J* = 6.4 Hz, 3H, CH_3m), 0.99 – 0.89 (m, 18H, overlapping peaks $Si(CH_2CH_3)_3$ & $Si(CH_2CH_3)_3$m), 0.47-0.70 (m, 12H, overlapping peaks $Si(CH_2CH_3)_3$ & $Si(CH_2CH_3)_3$m)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7 (C-3) , 136.7 (C-3m) , 136.7 (C-7), 136.1 (C-7m), 135.9 (C-2), 131.9 (C-2m), 118.3 (C-8), 118.1 (C-8m), 109.0 ($C(CH_3)_2$), 109.0 ($C(CH_3)_2$), 83.2 (C-5), 83.1 (C-5m), 78.8 (C-6), 78.7 (C-6m), 78.7 (C-4), 78.6 (C-4m), 64.3 (C-1), 64.2 (C-1m), 27.0 ($C(CH_3)_2$), 27.0 ($C(CH_3)_2$m), 26.9 ($C(CH_3)_2$m), 26.8 ($C(CH_3)_2$), 23.1 (CH_3), 22.9 (CH_3m) , 12.8 (CH_3), 12.8 (CH_3m), 6.7 ($Si(CH_2CH_3)_3$m), 6.7 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$m), 4.7 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{19}H_{36}O_4NaSi$: 379.2281, found 379.2287 $[M+Na]^+$



(E,4S,5S,6R)-1-azido-5,6-*O*-isopropylidene-4-*O*-triethylsilyl-non-2,7-diene 155

Compound **154** (0.54 g, 1.51 mmol) and PPh_3 (0.68 g, 2.57 mmol) were dissolved in anhydrous THF (75 mL). The solution was cooled to 0˚C, followed by the slow addition of DIAD (0.51 mL, 2.57 mmol) and DPPA (0.55 mL, 2.57 mmol). The solution was allowed to adjust to rt overnight. The solvent was removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 80:1) afforded azide **155** (0.41 g, 62 %) as a clear oil.

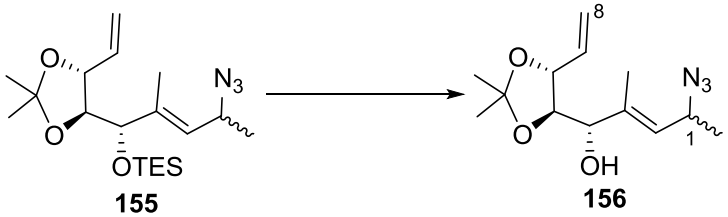
R_f = 0.16 (hexanes-EtOAc, 80:1)

FTIR 2955, 2877, 2097, 1457, 1413, 1378, 1236, 1170, 1068, 1005, 988, 927, 882, 839, 822, 804, 726, 670 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.83 – 5.70 (m, 2H, H-7 & H-7m), 5.42 (apt d, *J* = 9.1 Hz, 2H, H-2 & H-2m), 5.35 (d, *J* = 17.2 Hz, 1H, H-8m), 5.29 (d, *J* = 17.1 Hz, 1H, H-8), 5.23 – 5.14 (m, 2H, overlapping signals H-8' & H-8'm), 4.32 – 4.23 (m, 2H, H-1 & H-1m), 4.23 – 4.16 (m, 2H, H-6 & H-6m), 4.07 (apt t, *J* = 6.0 Hz, 2H, H-4 & H-4m), 3.79 – 3.72 (m, 2H, overlapping signals H-5 & H-5m), 1.71 (d, *J* = 1.5 Hz, 3H, CH_3), 1.69 (d, *J* = 1.4 Hz, 3H, CH_3m), 1.41 (s, 3H, $C(CH_3)_2$), 1.40 (s, 9H, $C(CH_3)_2$), 1.27 (d, *J* = 6.7 Hz, 3H, CH_3m), 1.21 (d, *J* = 6.7 Hz, 1H, CH_3), 0.99 – 0.92 (m, 12H, $Si(CH_2CH_3)_3$), 0.68 – 0.56 (m, 18H, $Si(CH_2CH_3)_3$

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8 (C-3), 139.3 (C-3m), 135.9 (C-7), 135.9 (C-7m), 127.0 (C-2m), 126.9 (C-2), 118.3 (C-8m), 118.2 (C-8), 110.0 ($C(CH)_3$m), 109.1($C(CH)_3$), 83.3 (C-5m), 83.2 (C-5), 78.7 (C-6), 78.6 (C-6m), 78.1 (C-4), 78.0 (C-4m), 54.6 (C-1m), 54.5 (C-1), 27.0 ($C(CH_3)_2$ x 2), 26.9 ($C(CH_3)_2$ x 2), 20.3 (CH_3), 20.2 (CH_3m), 13.4 (CH_3m), 13.3 (CH_3), 6.8 (2 x $Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{19}H_{36}N_3O_3Si$: 382.2526, found 382.2539 $[M+H]^+$



(E,4S,5R,6R)-1-azido-4-hydroxy-5,6-*O*-isopropylidene-non-2,7-ene-4-ol 156

Compound **156** (0.41 g, 1.07 mmol) was dissolved in THF (8 mL) and TBAF (2.15 mL, 1M in THF) prebuffered with 20% AcOH was subsequently added. The solution was stirred at rt for 4 h and the reaction mixture then quenched with slow addition of 3M NaOH, and stirred for a further 15 mins. The organic layer was extracted with EtOAc, dried over Na_2SO_4, filtered and solvent

removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded azide **156** (0.21 g, 75 %) as a clear oil.

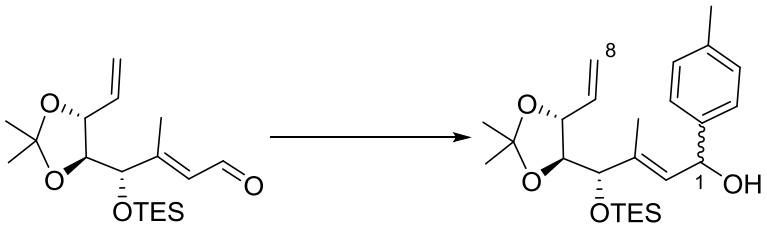
R_f = 0.85 (EtOAc-hexanes, 1:1)

FTIR 3454, 2986, 2097, 1454, 1373, 1217, 1168, 1038, 988, 928, 877, 813, 683 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.70 (m, 2H, overlapping signals H-7 & H-7m), 5.52 – 5.42 (m, 2H, overlapping signals H-2 & H-2m), 5.41 (d, *J* = 17.5 Hz, 1H, H-8m), 5.36 (d, *J* = 17.2 Hz, 1H, H-8), 5.30 – 5.24 (m, 2H, overlapping signals H-8 & H-8m'), 4.33 – 4.23 (m, 4H, overlapping signals H-5, H-5m, H-1 & H-1m), 3.97 (apt t, *J* = 5.4 Hz, 2H, overlapping signals H-4 & H-4m), 3.82 – 3.75 (m, 2H, overlapping peaks H-3 & H-3m), 2.50 (d, *J* = 6.4 Hz, 1H, OHm), 2.47 (d, *J* = 6.3 Hz, 1H, -OH), 1.72 (s, 3H, CH_3 x 2), 1.47 – 1.42 (m, 12H, $C(CH_3)_2$ x 4), 1.28 (d, *J* = 6.6 Hz, 3H, CH_3m), 1.24 (d, *J* = 6.5 Hz, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8 (C-3m), 138.8 (C-3), 135.0 (C-7) , 134.8 (C-7m), 127.3 (C-2m), 126.9 (C-2), 119.5 (C-7m), 119.5 (C-7), 109.7 ($C(CH_3)_2$), 109.7 ($C(CH_3)_2$m), 82.0 (C-5m), 81.6 (C-5), 79.5 (C-6m), 79.4 (C-6), 75.6 (C-4), 75.4 (C-4m), 54.5 (C-1m), 54.5 (C-1), 27.2 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 27.0 ($C(CH_3)_2$), 27.0 ($C(CH_3)_2$), 20.3 (CH_3m), 20.3 (CH_3), 13.2 (CH_3), 12.8 (CH_3)

HRMS (ESI): m/z calc for $C_{13}H_{22}N_3O_3$: 268.1661, found 268.1675 $[M+H]^+$



(E,4S,5R,6R)-5,6-*O*-isopropylidene-1-methylphenyl-4-triethylsilyl-oct-2,7-ene-1-ol 157

Compound **153** (0.65 g, 1.91 mmol) was dissolved in THF (50 mL), followed by the addition of *p*-Tolylmagnesium bromide (11.5 mL, 0.5 M in Et_2O). The solution was stirred at rt for 4 h and the reaction mixture then quenched with satd. NH_4Cl (aq), extracted with EtOAc, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 9:1) afforded alcohol **157** (0.62 g, 78 %) as a clear oil.

R_f = 0.39 (hexanes-EtOAc, 9:1)

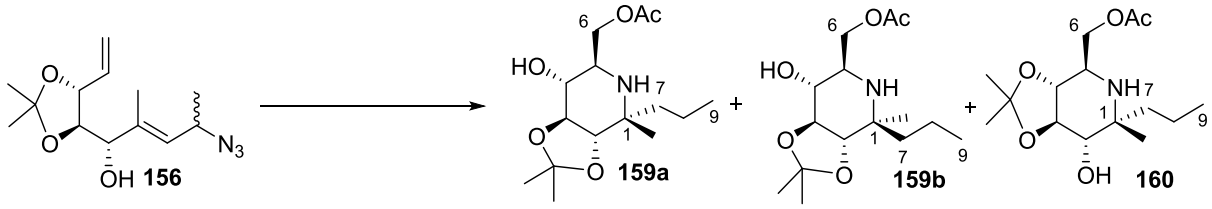
FTIR 3418, 2954, 2876, 1742, 1513, 1457, 1413, 1378, 1239, 1213, 1170, 1091, 1058, 1005, 931, 884, 814, 741, 725, 675 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 4H, overlapping Ar-H signals), 7.17-7.13 (m, 4H, overlapping Ar-H signals), 5.79 (ddd, *J* = 17.2, 10.4, 7.1 Hz, 1H, H-7), 5.67 (m, 2H, H-2 & H-2m), 5.52 (ddd, *J* = 17.3, 10.4, 7.0 Hz, 1H, H-7m), 5.43 – 5.39 (m, 2H, H-1 & H-1m), 5.35 (d, *J* = 17.2 Hz, 1H, H-8), 5.22 (d, *J* = 10.3 Hz, 1H, H-8'), 4.94 (d, *J* = 10.3 Hz, 1H, H-8'm), 4.87 (d, *J* = 17.0 Hz, 1H, H-8m), 4.23 (t, *J* = 7.6 Hz, 1H, H-6), 4.06 – 4.00 (m, 3H, overlapping peaks H-6m, H-4 &

H-4m), 3.78 (dd, *J* = 8.1, 5.9 Hz, 1H, H-4), 3.72 (dd, *J* = 7.9, 6.3 Hz, 1H, H-4m), 2.36 – 2.30 (m, 6H, Ar-CH_3 x 2), 1.74 (d, *J* = 1.5 Hz, 3H, CH_3m), 1.72 (d, *J* = 1.4 Hz, 3H, CH_3), 1.41 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, $C(CH_3)_2$), 1.37 (s, 6H, 2 x $C(CH_3)_2$), 0.94 (t, *J* = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$m), 0.88 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.64 – 0.56 (m, 6H, $Si(CH_2CH_3)_3$m), 0.56 – 0.48 (m, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4 (Ar-C), 137.5 (C-3 & C-3m), 137.2 (Ar-C), 136.0 (C-7), 136.0 (C-7m), 130.3 (C-2 & C-2m), 129.2 (Ar-Cm), 129.1 (Ar-C), 126.0 (Ar-C_m), 125.9 (Ar-C), 118.4 (C-8), 118.0 (C-8m), 109.0 ($C(CH_3)_2$m), 109.0 ($C(CH_3)_2$), 83.3 (C-5), 83.3 (C-5), 78.8 (C-5), 79.0, 78.8, 78.6, 78.6 (C-4, C-4m, C-6, C-6m), 70.4 (C-1m), 70.2 (C-1), 27.1 ($C(CH_3)_2$m), 27.0 ($C(CH_3)_2$m), 26.9 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 21.1 (2 x Ar-CH_3), 13.3 ($C(CH_3)_2$), 12.9 ($C(CH_3)_2$m), 6.8 ($Si(CH_2CH_3)_3$), 6.7 ($Si(CH_2CH_3)_3$m), 4.8 ($Si(CH_2CH_3)_3$m), 4.7 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{25}H_{41}O_4Si$: 433.2774, found 433.2779 $[M+H]^+$



(1R,2S,3S,4R,5R)-6-*O*-acetyl-4-hydroxy-2,3-*O*-isopropylidene-1-methyl-1-propyl-1,5-D-iminoglucitol 159a (1S,2S,3S,4R,5R)-6-*O*-acetyl-4-hydroxy-2,3-*O*-isopropylidene-1-methyl-1-propyl-1,5-D-iminoglucitol 159b (1R,2S,3R,4R,5R)-6-*O*-acetyl-2-hydroxy-3,4-*O*-isopropylidene-1-methyl-1-propyl-1,5-D-iminoglucitol 160

Compound **156** (0.070 g, 0.262 mmol) was dissolved in toluene (35 mL) and acetic acid (75 µL, 1.3 mmol) subsequently charged. The solution was then stirred at 98 ˚C for 4 days and solvent then removed under reduced pressure. The crude residue was redissolved in MeOH (3 mL) and subsequently treated with Pd-C (10 %) under H_2 for 2 h. The reaction mixture was then passed through a pad of celite and solvent removed under reduced pressure. Flash Chromatography (hexanes-EtOAc, 1:1) afforded a mixture of compounds **159a** & **159b** & **160** (23 mg, 159a:159b:160, 0.45:0.19:0.36, 30 %) as a clear oil.

R_f = 0.23 (hexanes-EtOAc, 1:1)

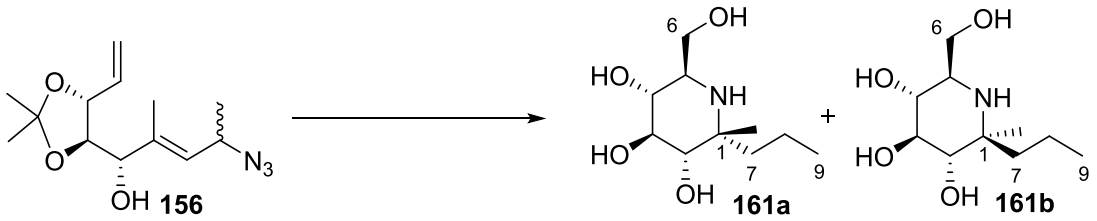
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (dd, *J* = 11.5, 4.0 Hz, 1H, H-6_C), 4.53 (dd, *J* = 11.4, 4.3 Hz, 1H, H-6_B), 4.32 (dd, *J* = 11.3, 3.0 Hz, 1H, H-6_D), 4.19 – 4.11 (m, 2H, overlapping peaks H-$6_{B\&C}$), 4.02 (dd, *J* = 11.2, 6.6 Hz, 1H, H-6_D), 3.73 (t, *J* = 9.4 Hz, 1H, H-3_B), 3.70 -3.60 (m, 2 H, overlapping peaks H-$3_{D\&C}$), 3.53 – 3.41 (m, 3H, overlapping peaks H-4_B & H-4_A & H-2_D), 3.14 (t, *J* = 9.3 Hz, 1H, H-4_D), 3.10 (d, *J* = 9.6 Hz, 1H, H-2_B), 3.09 (d, *J* = 9.4 Hz, 1H, H-2_C), 3.02 (ddd, *J* = 9.8, 6.6, 3.0 Hz, 1H, H-5_D), 2.76 (dt, *J* = 9.0, 3.3 Hz, 1H, H-5_C), 2.69 (ddd, *J* = 9.3, 4.3, 2.5 Hz, 1H, H-5_B), 2.11 (s, 3H, OAc_C), 2.10 (s, 3H, OAc_B), 2.07 (s, 3H, OAc_D), 1.55 – 1.46 (m, 4H, overlapping peaks CH_{2D}, CH_{2B}), 1.44 – 1.41 (m, 18H, overlapping peaks 2 x $C(CH_3)_2)_{B,C\&D}$), 1.41 –

1.23 (m, 8H, overlapping peaks CH_{2D}, CH_{2B} & 2 x CH_{2C}), 1.17 (s, 3H, CH_{3D}), 1.16 (s, 3H, CH_{3B}), 1.11 (s, 3H, CH_{3C}), 0.97 – 0.90 (m, 9H, $CH_{3B,C\&D}$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 ($C{=}O_C$), 171.5 ($C{=}O_B$), 170.7 ($C{=}O_D$), 110.8 ($C(CH_3)_{2D}$), 109.8 ($C(CH_3)_{2C}$), 109.7 ($C(CH_3)_{2B}$), 84.7 (C-2_B), 82.3 (C-2_C), 79.8 (C-3_D), 78.4 (C-2_D), 78.3 (C-3_C), 77.9 (C-3_B), 77.3 (C-4_D), 72.3 (C-4_B), 72.2 (C-4_C), 65.0 (C-6_D), 63.9 (C-6_B), 63.9 (C-6_C), 57.7 (C-1_D), 55.5 (C-5_C), 55.4 (C-5_B), 54.8 (C-1_C), 54.7 (C-1_B), 52.0 (C-5_D), 44.8 (C-7_C) , 32.4 (CH_{2B}), 32.2 (CH_{2D}), 27.0 ($C(CH)_3$), 26.9 ($C(CH)_3$), 26.6 ($C(CH)_3$), 25.8, 25.5 (2x $CH_{3B\&D}$), 20.9, 20.8 (OAc x 3), 16.4 (CH_{3C}), 16.3 (CH_2), 16.2 (CH_2), 15.7 (CH_{2D}), 14.9 (C-9_B), 14.8 (C-9_D), 14.6 (C-9_C)

HRMS (ESI): m/z calc for $C_{15}H_{28}NO_5$: 302.1967, found 302.1954 $[M+H]^+$

B=**65a**, C=**65b**, D=**66**



(E,1R,2S,3S,4R,5R) -1-methyl-1-propyl-2,3,4,6-tetrahydroxy- 1,5-D-iminoglucitol 161a & (E,1S,2S,3S,4R,5R) -1-methyl-1-propyl-2,3,4,6-tetrahydroxy- 1,5-D-iminoglucitol 161b

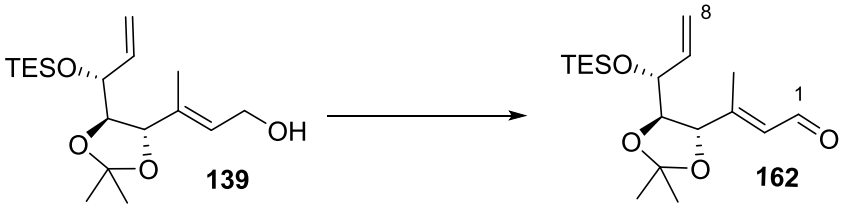
Compound **156** (40 mg, 0.15 mmol) was dissolved in toluene (20 mL) and acetic acid (43 µL, 0.75 mmol) charged. The solution was stirred at 98 ˚C for 4 days and solvent then removed under reduced pressure. The crude mixture was redissolved in MeOH (3 mL) and subsequently treated with Pd-C (10 %) under H_2 for 2 h. The reaction mixture was passed through a pad of celite and concentrated. The residue was then treated with 2M HCl (5 mL) for 16 h and solvent subsequently removed under reduced pressure. Flash Chromatography (CH_2Cl_2-MeOH- aq NH_3-H_2O, 8:2:0.1:0.1) afforded a mixture of **161a** & **161b** (14 mg, **161a**:**161b**, 71:29, 44 %) as a clear oil.

R_f = 0.11 (CH_2Cl_2-MeOH aq NH_3-H_2O, 8:2:0.1:0.1)

^{1}H NMR (500 MHz, CD_3OD) δ 3.91 (dd, *J* = 11.3, 3.1 Hz, 1H, H-6), 3.86 (dd, *J* = 11.3, 3.0 Hz, 1H, H-6m), 3.81 – 3.72 (m, 1H, H-6'm), 3.62 (dd, *J* = 11.3, 6.8 Hz, 1H, H-6'), 3.54 (t, *J* = 9.2 Hz, 1H, H-3), 3.47 (t, *J* = 9.3 Hz, 1H, H-3m), 3.31 – 3.25 (m, 2H, overlapping signals H-4 & H-4m), 3.25-3.18 (m, 2H, overlapping signals H-2 & H-2m), 2.96 – 2.90 (m, 1H, H-5m), 2.90 – 2.83 (m, 1H, H-5), 1.76 – 1.65 (m, 1H, H-7m), 1.62 (ddt, *J* = 11.0, 7.6, 4.0 Hz, 2H, H-7 & H-7'), 1.61 – 1.51 (m, 1H, H-7'm), 1.50 – 1.24 (m, 7H, overlapping signals CH_3, H-8, H-8m, H-8' & H-8'm), 1.19 (s, 3H, CH_3), 1.01 – 0.93 (m, 6H, CH_3)

^{13}C NMR (126 MHz, CD_3OD) δ 77.3 (C-2), 75.4 (C-2m), 74.5 (C-3m), 74.3 (C-3), 70.9 (C-4, C-4m), 60.2 (C-6), 59.8 (C-6m), 58.6 (C-1), 58.5 (C-1m), 56.0 (C-5), 55.9 (C-5m), 41.8 (C-7m), 31.5 (C-7), 22.3 (CH_3), 15.3 (CH_3m), 14.9 (C-8, C-8m), 13.5 (-C-9m) , 13.5 (C-9)

HRMS (ESI): m/z calc for $C_{10}H_{22}NO_4$: 220.1549, found 220.1564 $[M+H]^+$



(E,4S,5R,6R)-1,2,3,7,8-pentadeoxy-4,5-*O*-isopropylidene-6-*O*-triethylsilyl-oct-2-enal 162

Compound **139** (3.0 g, 8.8 mmol) was dissolved in CH_2Cl_2. The solution was cooled to 0 ˚C and Dess Martin periodinane (7.43 g, 17.5 mmol) charged. The reaction mixture was then stirred at rt for 4 h. The solution was subsequently diluted with Et_2O and stirred with aqueous $Na_2S_2O_3$ (1 g/L) containing $NaHCO_3$ (100 g/L). The organic layer was separated and washed with H_2O, brine, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to yield aldehyde **162** (2.5 g, 84 %) as a clear oil.

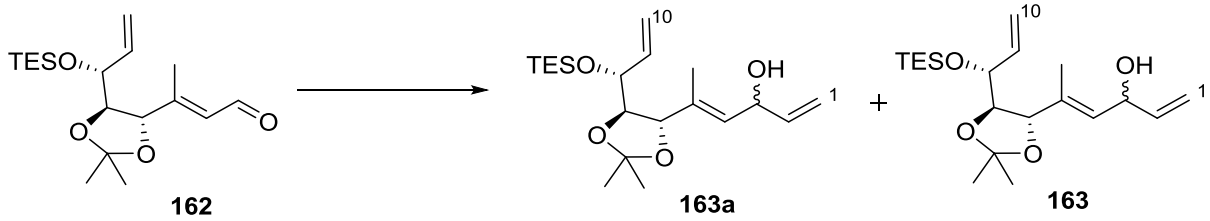
R_f = 0.81 (hexanes:EtOAc, 3:2)

FTIR 2955, 2877, 1677, 1457, 1406, 1380, 1238, 1166, 1126, 1072, 1005, 926, 878, 827 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 10.06 (d, *J* = 7.9 Hz, 1H, H-1), 6.14 (d, *J* = 7.8 Hz, 1H, H-2), 5.95 (ddd, *J* = 16.5, 10.5, 5.5 Hz, 1H, H-7), 5.34 (d, *J* = 17.5 Hz, 1H, H-8), 5.26 (d, *J* = 10.5 Hz, 1H, H-8'), 4.44 (d, *J* = 7.6 Hz, 1H, H-4), 4.37 (t, *J* = 4.9 Hz, 1H, H-6), 3.87 (dd, *J* = 7.7, 4.1 Hz, 1H, H-5), 2.19 (s, 3H, CH_3), 1.43 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 0.94 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.60 (q, *J* = 8.0 Hz, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.1 (C-1), 159.3 (C-3), 136.5 (C-7), 127.8 (C-2), 116.9 (C-8), 110.0 ($C(CH_3)_2$) , 83.0 (C-5), 80.4 (C-4), 72.6 (C-6), 27.0 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 13.6 (CH_3) , 6.7 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{18}H_{33}O_4Si$: 341.2148 Found: 341.2153 $[M+H]^+$



(E,6S,7R,8R)-6,7-*O*-isopropylidene-8-*O*-triethylsilyl-dec-1,4,9-triene-3-ol 163a & 163b

Compound **162** (1.5 g, 4.4 mmol) was dissolved in THF (70 mL) and vinylMgBr (4.4 mL, 3M in Et_2O) charged. The reaction mixture was stirred at rt for 4 h and subsequently quenched with satd. NH_4Cl (aq), extracted with EtOAc, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 10:1) obtained isomers **163a** (0.67 g, 41 %) & **163b** (0.76 g, 42 %) as clear oils.

Data for 163a

R_f = 0.11 (hexanes-EtOAc, 10:1)

FTIR 3429, 2985, 2955, 2877, 1641, 1457, 1414, 1378, 1369, 1239, 1132, 1166, 1067, 1004, 921, 887, 828, 725, 687 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.96 – 5.84 (m, 2H, overlapping signals H-2 & H-9), 5.53 (d, *J* = 8.2 Hz, 1H, H-4), 5.33 – 5.23 (m, 2H, overlapping signals H-10 & H-1), 5.19 (dd, *J* = 10.5, 1.6 Hz, 1H, H-9'), 5.11 (dt, *J* = 10.3, 1.5 Hz, 1H, H-1'), 4.91 (t, *J* = 7.0 Hz, 1H, H-3), 4.34 (d, *J* = 7.9 Hz, 1H, H-6), 4.25 – 4.22 (m, 1H, H-8), 3.78 (dd, *J* = 8.0, 4.2 Hz, 1H, H-7), 1.73 (d, *J* = 1.4 Hz, 3H, CH_3), 1.43 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 0.95 (t, *J* = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.61 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9 (C-2), 137.5 (C-9), 135.2 (C-5), 130.4 (C-4), 116.3 (C-10), 114.8 (C-1), 108.9 ($C(CH_3)_2$), 82.2 (C-7), 81.7 (C-6), 73.3 (C-8), 69.7 (C-3), 27.2 ($C(CH_3)_2$), 27.0 ($C(CH_3)_2$), 12.4 (CH_3), 6.8 ($Si(CH_2CH_3)_3$), 4.9($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{20}H_{37}O_4Si$: 369.2461; found: 369.2473 $[M+H]^+$

Data for 163b

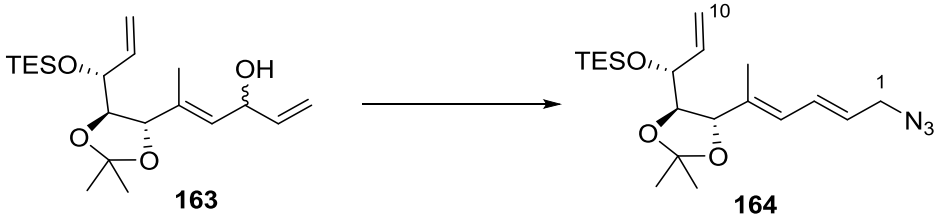
R_f = 0.9 (hexanes-EtOAc, 10:1)

FTIR 3391, 2985, 2954, 2877, 1688, 1457, 1414, 1378, 1369, 1238, 1167, 1132, 1065, 1005, 989, 922, 890, 827, 809, 687 cm^{-1}

69 ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 – 5.79 (m, 2H, overlapping signals H-2 & H-9), 5.54 (d, *J* = 8.4 Hz, 1H, H-4), 5.34 – 5.22 (m, 2H, overlapping signals H-1 & H-10), 5.16 (d, *J* = 10.5 Hz, 1H, H-10'), 5.11 (d, *J* = 10.5 Hz, 1H, H-1'), 4.92 (t, *J* = 7.3 Hz, 1H, H-3), 4.32 (dd, *J* = 8.1, 1.9 Hz, 1H, H-6), 4.20 (t, *J* = 5.3 Hz, 1H, H-8), 3.76 (ddd, *J* = 7.7, 4.4, 1.9 Hz, 1H, H-7), 1.73 (s, 3H, CH_3), 1.43 (s, 3H, $(C(CH_3)_2)$, 1.40 (s, 3H, $C(CH_3)_2$), 0.98 – 0.91 (m, 9H, $Si(CH_2CH_3)_3$), 0.64 – 0.57 (m, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7 (C-2), 137.4 (C-9), 134.9 (C-5), 131.1 (C-4), 116.2 (C-10), 114.8 (C-1), 108.9 ($C(CH_3)_2$), 82.0, 81.9 (C-6, C-7), 73.5 (C-8), 69.6 (C-3), 27.2 ($C(CH_3)_2$) , 27.0 ($C(CH_3)_2$) , 12.1 (CH_3) , 6.8 ($Si(CH_2CH_3)_3$), 4.90 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{20}H_{37}O_4Si$: 369.2461; found: 369.2450 $[M+H]^+$



(E,E,6S,7R,8R)-1-azido-6,7-*O*-isopropylidiene-8-*O*-triethylsilyl-dec-2,4,9-ene 164

Compound **163** (1.2 g, 3.2 mmol) was dissolved in anhydrous THF (160 mL) and PPh_3 (1.43 g, 5.44 mmol) charged. The solution was cooled to 0˚C, followed by the addition of DIAD (1.1 mL, 5.4 mmol) and DPPA (1.17 mL, 5.55 mmol) and solution allowed to stir at rt for 24 h. The solvent

was then removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 160:1) afforded azide **164** (0.8 g, 64 %) as a clear oil.

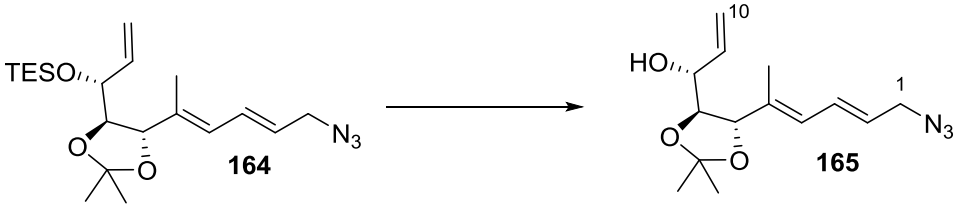
R_f = 0.47 (EtOAc-hexanes, 1:10)

FTIR 2985, 2955, 2877, 2098, 1657, 1457, 1414, 1378, 1369, 1237, 1167, 1138, 1068, 1030, 1005, 966, 924, 878, 828, 810, 739, 725, 686 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 14.9, 11.0 Hz, 1H, H-3), 6.11 (d, *J* = 10.8 Hz, 1H, H-4), 5.92 (ddd, *J* = 16.8, 10.5, 6.0 Hz, 1H, H-9), 5.71 (dt, *J* = 14.5, 6.8 Hz, 1H, H-2), 5.30 (d, *J* = 17.2 Hz, 1H, H-10), 5.19 (d, *J* = 10.5 Hz, 1H, H-10'), 4.38 (d, *J* = 8.1 Hz, 1H, H-6), 4.25 (t, *J* = 5.2 Hz, 1H, H-8), 3.84 (d, *J* = 6.7 Hz, 2H, H-1), 3.79 (dd, *J* = 8.2, 4.3 Hz, 1H, H-7), 1.81 (s, 3H, CH_3), 1.44 (s, 3H, ($C(CH_3)_2$), 1.41 (s, 3H, ($C(CH_3)_2$), 0.95 (t, *J* = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.60 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3 (C-9), 136.2 (C-5), 130.2 (C-3), 127.3(C-4), 126.0 (C-2), 116.1 (C-10), 108.9 ($C(CH_3)_2$), 82.0, 81.9 (each C-6, C-7), 73.1 (C-8), 52.8 (C-1), 27.1 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 12.3 (CH_3), 6.7 ($Si(CH_2CH_3)_3$), 4.9 ($Si(CH_2CH_3)_3$);

HRMS (ESI): m/z calc for $C_{20}H_{36}N_3O_3Si$: 394.2526 found: 394.2520 $[M+H]^+$



(E,E,6S,7R,8R)-1-azido-8-hydroxy-6,7-*O*-isopropylidiene-8-*O*-triethylsilyl-dec-2,4,9-en-8-ol

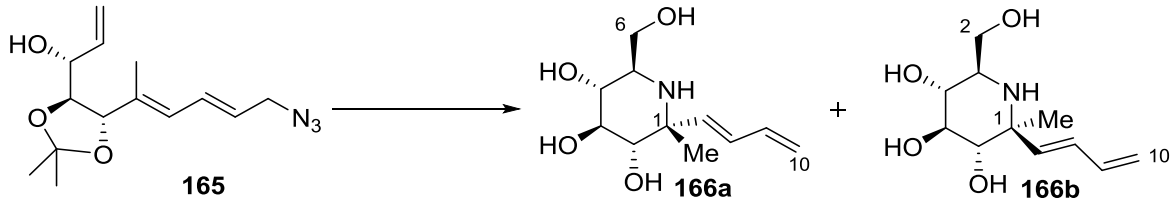
165 Compound **164** (0.68 g, 1.73 mmol) was dissolved in anhydrous THF (20 mL), followed by the addition of TBAF (3.5 mL, 1 M in THF). The reaction mixture was stirred at rt for 16 h and subsequently quenched with 3M NaOH (10 mL), and stirred for a further 15 mins. The organic layer was separated and aqueous layer back extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded azide **165** (0.35 g, 73 %) as a clear oil.

R_f = 0.7 (EtOAc-hexanes, 1:1)

^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (dd, *J* = 14.8, 11.0 Hz, 1H, H-3), 6.16 (d, *J* = 10.8 Hz, 1H, H-4), 5.86 (ddd, *J* = 16.7, 10.7, 5.4 Hz, 1H, H-9), 5.74 (dt, *J* = 14.2, 6.6 Hz, 1H, H-2), 5.37 (d, *J* = 17.1 Hz, 1H, H-10), 5.23 (d, *J* = 10.7 Hz, 1H, H-10'), 4.43 (d, *J* = 8.4 Hz, 1H, H-6), 4.07 (apt broad s, 1H, H-8), 3.85 (d, *J* = 6.7 Hz, 2H, H-1), 3.78 (dd, *J* = 8.6, 3.1 Hz, 1H, H-7), 2.19 (d, *J* = 7.9 Hz, 1H, OH peak), 1.82 (s, 3H, CH_3), 1.47 (s, 3H, $C(CH_3)_2$), 1.45 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4 (C-9), 134.9 (C-5), 129.8 (C-3), 127.9 (C-4), 126.9 (C-2), 116.5 (C-10), 109.5 ($C(CH_3)_2$), 82.5 (C-6), 81.0 (C-7), 71.1 (C-8), 52.8 (C-1), 27.1 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 12.1 (CH_3)

HRMS (ESI): m/z calc for $C_{14}H_{22}N_3O_3$: 280.1661, found: 280.1648 $[M+H]^+$



(E,1R,2S,3S,4R,5R)-1-but-7,9-ene-1-methyl-2,3,4,6-tetrahydroxy-1,5-piperidine 166a
(E,1S,2S,3S,4R,5R)-1-but-7,9-ene-1-methyl-2,3,4,6-tetrahydroxy-1,5-piperidine 166b

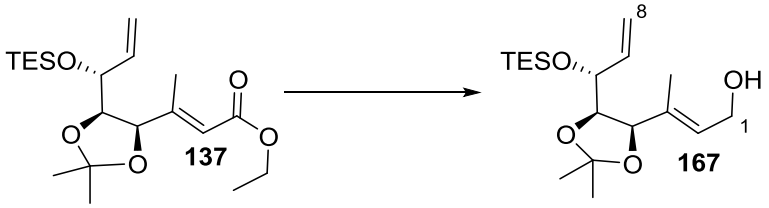
Compound **165** (76 mg, 0.27 mmol) was dissolved in toluene (30 mL), followed by the addition of acetic acid (75 µL, 1.4 mmol). The solution was stirred at 100 ˚C for 14 days and solvent was then removed under reduced pressure. The crude residue was treated with 1M HCl (5 mL) for 12 h. Upon reaction completion solvent was removed under reduced pressure. Flash chromatography afforded **166** (17mg, 23 %) as a mixture of isomers (**166a**:**166b**, 87:13) and as a clear oil.

R_f = 0.23 (CH_2Cl_2-MeOH, 4:1)

^{1}H NMR (500 MHz, CD_3OD) δ 6.43 – 6.25 (m, 4H, overlapping signals H-8, H-8m, H-9 & H-9m), 5.98 (d, *J* = 15.6 Hz, 1H, H-7), 5.84 (d, *J* = 15.3 Hz, 1H, H-7m), 5.24 – 5.13 (m, 2H, overlapping signals H-10 & H-10m), 5.08 – 5.05 (m, 1H, H-10'm), 5.03 (dd, *J* = 10.0, 1.7 Hz, 1H, H-10), 3.84 (apt dd, *J* = 10.8, 3.1 Hz, 2H, H-6 & H-6m), 3.65 (dd, *J* = 10.9, 6.1 Hz, 1H, H-6'm), 3.56 (dd, *J* = 10.8, 6.8 Hz, 1H, H-6'), 3.45 (t, *J* = 9.2 Hz, 1H, H-3m), 3.29-3.23 (m, 1H, H-3) 3.22 – 3.11 (m, 4H, overlapping signals H-4, H-4m, H-2 & H-2m), 2.84 – 2.74 (m, 2H, H-5 & H-5m), 1.25 (s, 3H, CH_3 & CH_3m)

^{13}C NMR (126 MHz, CD_3OD) δ 139.6 (C-7m), 137.1 (C-9), 137.0 (C-9m), 134.4 (C-7), 130.6 (C-8), 129.3 (C-8m), 116.0 (C-10m), 115.2 (C-10), 78.0 (C-2), 76.5 (C-2m), 75.7 (C-3), 75.1 (C-3m), 72.9 (C-4), 72.3 (C-4m), 62.0 (C-6), 61.5 (C-6m), 57.9 (C-1), 57.4 (C-1m), 56.0 (C-5), 55.6 (C-5m), 26.8 (CH_3), 15.8 (CH_3m)

HRMS (ESI): m/z calc for $C_{11}H_{20}NO_4$: 230.1392, found: 230.1387 $[M+H]^+$



(E,4R,5R,6R)-4,5-*O*-isopropylidene-6-*O*-triethylsilyl-oct-2,7-diene-1-ol 167

Compound **137** (0.86 g, 2.24 mmol) was dissolved in CH_2Cl_2. The solution was cooled to -78 ˚C and dibal-H (6.7 mL, 1M in CH_2Cl_2) was added slowly. The reaction mixture was then stirred at -78 ˚C for 7 h followed by quenching with the slow addition of MeOH. The solution was warmed to rt and stirred with potassium tartrate (aq) until clear. The organic layer was separated and subsequently washed with H_2O, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to obtain alcohol **167** (0.57 g, 74 %) as a clear oil.

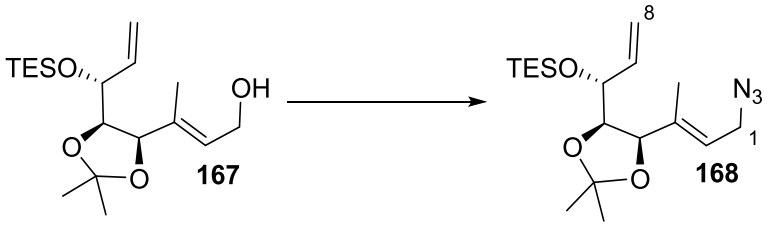
R_f = 0.33 (EtOAc-hexanes, 3:7)

FTIR 3401, 2954, 2912, 2876, 1458, 1414, 1380, 1368, 1262, 1240, 1211, 1148, 1066, 1035, 1003, 927, 877, 836, 805, 725, 690, 670 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 – 5.80 (m, 1H, H-7), 5.69 (dd, *J* = 7.4, 5.9 Hz, 1H, H-2), 5.30 (dt, *J* = 17.4, 1.9 Hz, 1H, H-8), 5.12 (dt, *J* = 10.5, 1.4 Hz, 1H, H-8'), 4.47 (d, *J* = 6.5 Hz, 1H, H-4), 4.27 – 4.17 (m, 2H, overlapping signals H-1 & H-1'), 4.17 – 4.11 (m, 1H, H-6), 4.11 – 4.05 (m, 1H, H-5), 1.73 (s, 3H, CH_3), 1.53 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 1.02 – 0.87 (m, 9H, $Si(CH_2CH_3)_3$), 0.67 – 0.56 (m, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.2 (C-7), 134.8 (C-3), 128.4 (C-2), 116.5 (C-8), 108.1 ($C(CH_3)_2$), 81.7, 81.6 (each C-4, C-5), 72.5 (C-6), 59.2 (C-1), 26.5 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$), 14.5 (CH_3), 6.8 ($Si(CH_2CH_3)_3$), 5.0 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{18}H_{34}O_4NaSi$: 365.2124, found: 365.2111 $[M+Na]^+$



(E,4R,5R,6R)-1-azido-4,5-*O*-isopropylidene-6-*O*-triethylsilyl-oct-2,7-diene 168

Compound **167** (0.58 g, 1.70 mmol) was dissolved in anhydrous THF (60 mL) and PPh_3 (0.76 g, 2.89 mmol) was subsequently charged. The solution was then cooled to 0˚C, followed by addition of DIAD (0.57 mL, 2.89 mmol) and DPPA (0.62 mL, 2.89 mmol). The reaction mixture was allowed to adjust to rt and stirred for 24 h. The solvent was removed under reduced pressure and flash chromatography (hexanes-EtOAc, 80:1) afforded azide **168** (0.31 g, 50 %) as a clear oil.

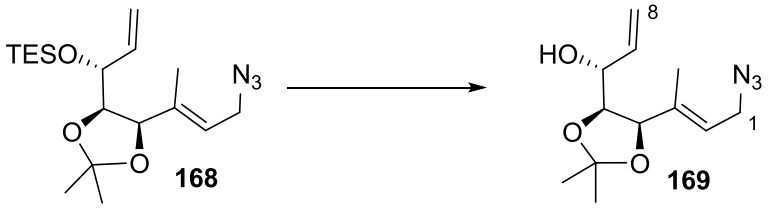
R_f = 0.35 (EtOAc-hexanes, 1:20)

FTIR 2954, 2912, 2877, 2095, 1458, 1414, 1380, 1368, 1262, 1241, 1211, 1148, 1122, 1065, 1032, 1006, 971, 928, 871, 829, 805, 739, 726 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 16.4, 10.4, 5.1 Hz, 1H, H-7), 5.63 (t, *J* = 7.1 Hz, 1H, H-2), 5.30 (d, *J* = 16.8 Hz, 1H, H-8), 5.14 (d, *J* = 10.5 Hz, 1H, H-8'), 4.50 (d, *J* = 6.3 Hz, 1H, H-4), 4.16 – 4.08 (m, 2H, overlapping signals H-5 & H-6), 3.87 (dd, *J* = 14.0, 7.4 Hz, 1H, H-1), 3.80 (dd, *J* = 14.1, 6.9 Hz, 1H, H-1'), 1.76 (s, 3H, CH_3), 1.54 (s, 3H, $C(CH_3)_2$), 1.37 (s, 3H, $C(CH_3)_2$), 0.95 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.66 – 0.56 (m, 6H, $Si(CH_2CH_3)_3$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.02 (C-3), 136.99 (C-7), 122.31 (C-2), 116.70 (C-8), 108.24 ($C(CH_3)_2$), 81.57 (C-H), 81.40 (C-4), 72.49 (C-H), 47.90 (C-1), 26.46 ($C(CH_3)_2$), 24.92 ($C(CH_3)_2$), 14.72 (CH_3), 6.76 ($Si(CH_2CH_3)_3$), 4.96 ($Si(CH_2CH_3)_3$)

HRMS (ESI): m/z calc for $C_{18}H_{34}N_3O_3Si$: 368.2369, found 368.2357 $[M+H]^+$



(E,4R,5R,6R)-1-azido-6-hydroxy-4,5-*O*-isopropylidene-6-*O*-triethylsilyl-oct-2,7-diene-6-ol 169

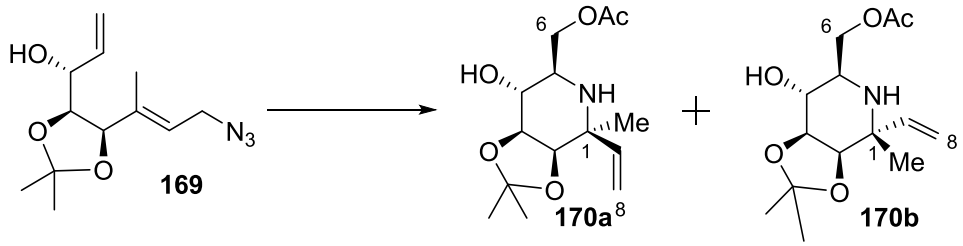
Compound **168** (0.42 g, 1.14 mmol) was dissolved in THF (25 mL) and TBAF (3.42 mL, 1M in THF) was subsequently charged. The reaction mixture was stirred at rt for 4 h and subsequently quenched upon addition of 3M NaOH. The solution was diluted with EtOAc and organic layer separated, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:4) afforded azide **169** (0.24 g, 83 %).as a clear oil.

R_f = 0.41 (EtOAc-hexanes, 1:4)

^{1}H NMR (500 MHz, CDCl) δ 5.84 – 5.70 (m, 2H, overlapping signals H-2 & H-7), 5.35 (d, *J* = 17.4 Hz, 1H, H-8), 5.22 (d, *J* = 10.4 Hz, 1H, H-8'), 4.63 (d, *J* = 6.4 Hz, 1H, H-4), 4.09 (t, *J* = 6.5 Hz, 1H, H-5), 4.04 (t, *J* = 6.3 Hz, 1H, H-6), 3.91 – 3.80 (m, 2H, H-1s), 2.17 (d, *J* = 0.7 Hz, 1H, OH signal), 1.74 (s, 3H, CH_3), 1.58 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6 (C-7), 136.4 (C-3), 120.9 (C-2), 117.7 (C-7), 108.7 ($C(CH_3)_2$), 80.3 (C-4), 80.3 (C-5), 70.4 (C-6), 47.7 (C-1), 27.1 ($C(CH_3)_2$), 25.2 ($C(CH_3)_2$), 15.2 (CH_3)

HRMS (ESI): m/z calc for $C_{12}H_{20}N_3O_3$: 254.1505, found 254.1516 $[M+H]^+$



(1S,2R,3S,4R,5R)-6-*O*-acetyl-1-ethenyl-4-hydroxy-2,3-*O*-isopropylidene-1-methyl-1,5-D-mannitol 170a & (1R,2R,3S,4R,5R)-6-*O*-acetyl-1-ethenyl-4-hydroxy-2,3-*O*-isopropylidene-1-methyl-1,5-D-mannitol 170b

Compound **169** (0.04 g, 0.16 mmol) was dissolved in toluene (20 mL), followed by the addition of acetic acid (45.0 µL, 1.06 mmol) The reaction mixture was stirred at 100 ˚C for 2 weeks. The solvent was then removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 3:7, **170a** R_f 0.23 **170b** R_f 0.13) to achieve **170a** (4 mg, 7 %) and **170b** (3 mg, 9 %) as clear oils.

Data for 170a

R_f = 0.23 (hexanes-EtOAc, 3:7)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (dd, *J* = 17.5, 10.8 Hz, 1H, H-7), 5.31 (d, *J* = 17.3 Hz, 1H, H-8), 5.17 (d, *J* = 11.2 Hz, 1H, H-8'), 4.56 (dd, *J* = 11.3, 4.0 Hz, 1H, H-6), 4.17 (dd, *J* = 11.3, 2.8 Hz,

1H, H-6'), 4.07 (dd, *J* = 7.5, 4.7 Hz, 1H, H-3), 3.96 (d, *J* = 4.8 Hz, 1H, H-2), 3.40 (ddd, *J* = 10.8, 7.5, 3.0 Hz, 1H, H-4), 2.85 (dt, *J* = 10.7, 3.5 Hz, 1H, H-5), 2.63 (d, *J* = 3.5 Hz, 1H, OH signal), 2.10 (s, 3H, OAc), 1.50 (s, 3H, ($C(CH_3)_2$)), 1.36 (s, 3H, ($C(CH_3)_2$)), 1.29 (s, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (C=O), 142.3 (C-7), 113.1 (C-8), 109.4 ($C(CH_3)_2$), 79.9 (C-2), 77.2 (C-3), 71.3 (C-4), 64.7 (C-6), 55.3 (C-1), 52.5 (C-5), 28.5 ($C(CH_3)_2$), 26.6 ($C(CH_3)_2$), 24.1 (CH_3), 20.8 (OAc)

HRMS (ESI): m/z calc for $C_{14}H_{24}NO_5$: 286.1654, found 286.1648 $[M+H]^+$

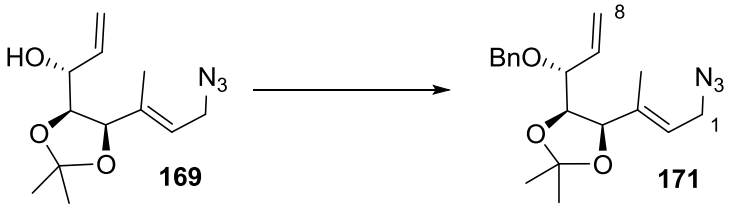
Data for 170b

R_f = 0.13 (hexanes-EtOAc, 3:7)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (dd, *J* = 17.7, 10.9 Hz, 1H, H-7), 5.26 – 5.17 (m, 2H, overlapping signals H-8 & H-8'), 4.48 (dd, *J* = 11.3, 4.3 Hz, 1H, H-6), 4.15 – 4.10 (m, 2H, overlapping signals H-6 & H-2), 3.95 (dd, *J* = 7.6, 4.7 Hz, 1H, H-3), 3.38 (dd, *J* = 10.6, 7.5 Hz, 1H, H-4), 2.75 (dt, *J* = 10.6, 3.7 Hz, 1H, H-5), 2.11 (s, 3H, OAc), 1.52 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (C=O), 142.6 (C-7), 114.8 (C-8), 108.7 ($C(CH_3)_2$), 79.5 (C-3), 79.0 (C-2), 71.4 (C-4), 64.6 (C-6), 56.1 (C-1), 52.8 (C-4), 28.6 ($C(CH_3)_2$), 26.6 ($C(CH_3)_2$), 26.3 (CH_3), 20.8 (OAc)

HRMS (ESI): m/z calc for $C_{14}H_{24}NO_5$: 286.1654, found 286.1642 $[M+H]^+$



(E,4R,5S,6R)-1-azido-6-*O*-benzyl-4,5-*O*-isopropylidene-oct-2,7-diene 171

Compound **169** (0.18 g, 0.71 mmol) was dissolved in DMF (6 mL). The solution was cooled to 0 ˚C and NaH (31 mg, 60 % in mineral oil) charged portionwise. The reaction mixture was stirred at 0 ˚C for 30 min followed by the addition of BnBr (0.25 mL, 2.13 mmol). The solution was then adjusted to rt and stirred for a further 3.5 h. Upon reaction completion, water was added and product extracted using Et_2O (x 2). The combined organic layers were washed with satd. NH_4Cl (aq), dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded **171** (0.21 g, 86 %) as a clear oil.

R_f = 0.81 (EtOAc-hexanes, 1:1)

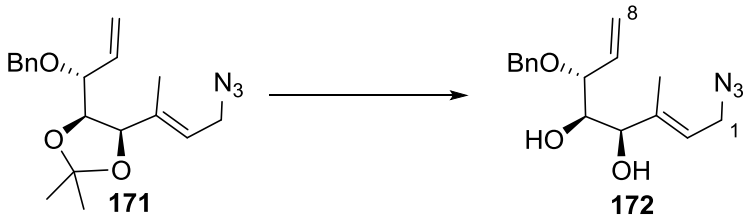
FTIR 2984, 2935, 2093, 1497, 1454, 1379, 1368, 1246, 1212, 1160, 1118, 1063, 1028, 993, 929, 871, 808, 735, 697 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 4H, Ar-H), 7.28 – 7.24 (m, 1H, Ar-H), 5.75 (ddd, *J* = 17.7, 10.6, 7.6 Hz, 1H, H-7), 5.65 (t, *J* = 7.3 Hz, 1H, H-2), 5.37 – 5.24 (m, 2H, overlapping signals H-8 & H-8'), 4.61 (d, *J* = 12.0 Hz, 1H, H-9), 4.55 (d, *J* = 6.7 Hz, 1H, H-4), 4.37 (d, *J* =

12.1 Hz, 1H, H-9), 4.27 (t, *J* = 6.7 Hz, 1H, H-5), 3.82 – 3.73 (m, 3H, overlapping signals H-1, H-1' & H-6), 1.67 (s, 3H, CH_3), 1.54 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3 (Ar-C), 137.3 (C-3), 134.8 (C-7), 128.2 (Ar-CH x 2), 127.7 (Ar-CH x 2), 127.3 (Ar-CH), 121.4 (C-2), 119.6 (C-8), 108.8 ($C(CH_3)_2$), 81.1 (C-4), 80.2 (C-5), 78.5 (C-6), 70.0 (C-9), 47.9 (C-1), 26.6 ($C(CH_3)_2$), 25.2 ($C(CH_3)_2$), 14.8 (CH_3)

HRMS (ESI): m/z calc for $C_{19}H_{25}N_3O_3Na$: 366.1794, found 366.1794 $[M+Na]^+$



(E,4R,5R,6R)-1-azido-6-*O*-benzyl-4,5-dihydroxy-oct-2,7-diene-4,5-diol 172

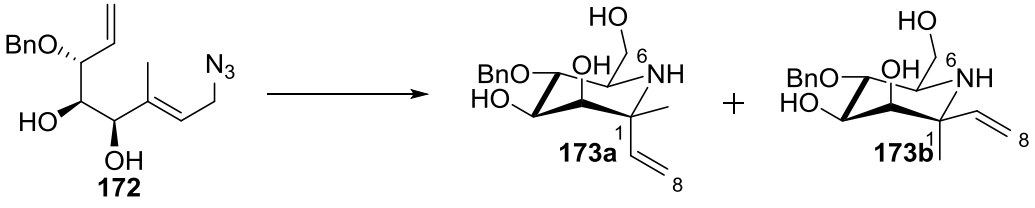
Compound **171** (0.2 g, 0.6 mmol) was dissolved in MeOH (2 mL) and 2M HCl (10 mL). The solution was stirred at rt for 16 h and CH_2Cl_2 was added. The organic layer was separated, dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) afforded **172** (0.13 g, 73 %) as a clear oil.

R_f = 0.61 (EtOAc-hexanes, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 5H, Ar-H), 5.97 (ddd, *J* = 17.7, 10.4, 7.9 Hz, 1H, H-7), 5.62 (t, *J* = 7.3 Hz, 1H, H-2), 5.47 – 5.33 (m, 2H, overlapping peaks H-8 & H-8'), 4.63 (d, *J* = 11.3 Hz, 1H, H-9), 4.33 (d, *J* = 11.4 Hz, 1H, H-9), 4.18 (t, *J* = 5.4 Hz, 1H, H-4), 4.05 (dd, *J* = 7.9, 3.1 Hz, 1H, H-6), 3.82 (m, *J* = 7.1 Hz, 2H, overlapping peaks H-1 & H-1'), 3.64 (m, *J* = 2.9 Hz, 1H, H-5), 2.99 (d, *J* = 6.2 Hz, 1H, OH), 2.57 (d, *J* = 7.6 Hz, 1H, OH), 1.71 (s, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4 (C-3), 137.4 (Ar-C), 134.9 (C-7), 128.6 (Ar-CH x 2), 128.2 (Ar-CH x 2), 128.1 (Ar-CH), 120.1 (C-2), 119.8 (C-8), 79.9 (C-6), 77.7 (C-4), 73.3 (C-5), 70.5 (C-9), 47.6 (C-1), 13.0 (CH_3)

HRMS (ESI): m/z calc for $C_{16}H_{21}N_3O_3Na$: 326.1481, Found 326.1480 $[M+Na]^+$



(1R,2R,3R,4R,5R)-4-(benzyloxy)-5-(hydroxymethyl)-1-methyl-1-vinylpiperidine-2,3-diol 173a

(1S,2R,3R,4R,5R)-4-(benzyloxy)-5-(hydroxymethyl)-1-methyl-1-vinylpiperidine-2,3-diol 173b

Compound **172** (45.0 mg, 0.15 mmol) was dissolved in toluene (20 mL) and acetic acid (43.0 µL, 0.75 mmol) charged. The reaction mixture was stirred at 100 °C for 24 h. The solvent was then evaporated under reduced pressure and 2M HCl (5 mL) added to the crude residue. The solution

was stirred at rt for 16 h. The solvent was then removed under reduced pressure and flash chromatography (CH_2Cl_2-MeOH-H_2O-aq NH_3, 20:1:0.1:0.1) afforded **173a** (27 mg, 62 %) and **173b** (3 mg, 7 %) as clear oils.

Data for 173a

R_f = 0.13 (CH_2Cl_2-MeOH-H_2O-aq NH_3, 20:1:0.1:0.1)

^{1}H NMR (500 MHz, CD_3OD) δ 7.36 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.31 (ddd, *J* = 7.7, 6.4, 1.5 Hz, 2H, Ar-H), 7.25 (td, *J* = 7.4, 1.6 Hz, 1H, Ar-H), 5.91 (ddd, *J* = 18.0, 11.1, 1.5 Hz, 1H, H-7), 5.29 – 5.20 (m, 2H, H-8 & H-8'), 4.92 (dd, *J* = 11.0, 1.5 Hz, 1H, H-9), 4.61 (dd, *J* = 11.2, 1.5 Hz, 1H, H-9'), 3.82 – 3.69 (m, 4H, H-2, H-3, H-6 & H-6'), 3.66 (t, *J* = 9.5 Hz, 1H, H-4), 2.76 (d, *J* = 10.2 Hz, 1H, H-5), 1.24 (s, 3H, CH_3)

^{13}C NMR (126 MHz, CD_3OD) δ 141.2 (C-7), 138.9 (Ar-C), 127.8 (Ar-CH x 2), 127.6 (Ar-CH x 2), 127.1 (Ar-CH), 114.0 (C-8), 76.8 (C-4), 75.5 (C-2), 74.5 (C-9), 73.1 (C-3), 60.6 (C-6), 58.7 (C-1), 55.8 (C-5), 25.3 (CH_3)

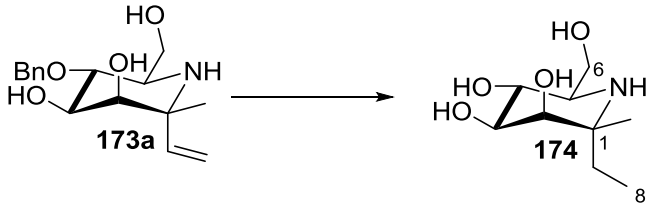
HRMS (ESI): m/z calc for $C_{16}H_{24}NO_4$: 294.1705, found 294.1716 $[M+H]^+$

Data for 173b

R_f = 0.21 (CH_2Cl_2-MeOH-H_2O-aq NH_3, 20:1:0.1:0.1)

^{1}H NMR (500 MHz, CD_3OD) δ 7.39 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.32 (t, *J* = 7.4 Hz, 2H, Ar-H), 7.26 (t, *J* = 7.1 Hz, 1H, Ar-H), 5.96 (dd, *J* = 17.6, 11.1 Hz, 1H, H-7), 5.24 (d, *J* = 17.6 Hz, 1, H-8), 5.16 (d, *J* = 11.1 Hz, 1H, H-8'), 4.97 (d, *J* = 10.9 Hz, 1H, H-9), 4.63 (d, *J* = 10.9 Hz, 1H, H-9'), 3.92 (dd, *J* = 9.4, 3.0 Hz, 1H, H-3), 3.83 (dd, *J* = 11.1, 3.9 Hz, 1H, H-6), 3.74 (dd, *J* = 11.0, 2.6 Hz, 1H, H-6'), 3.69 (t, *J* = 9.8 Hz, 1H, H-4), 3.60 (d, *J* = 3.0 Hz, 1H, H-2), 2.78 (d, *J* = 10.1 Hz, 1H, H-5), 1.26 (s, 3H, CH_3)

HRMS (ESI): m/z calc for $C_{16}H_{24}NO_4$: 294.1705, found 294.1711 $[M+H]^+$



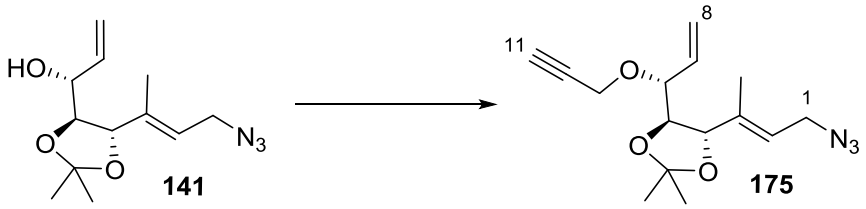
(1S,2R,3S,4R,5R)-1-ethyl-5-(hydroxymethyl)-1-methylpiperidine-2,3,4-triol 174

Compound **173a** (0.015 g, 0.051 mmol) was dissolved in MeOH (5 mL), followed by addition of Pd-C. A H_2 balloon was then added to the reaction system and solution stirred at rt for 24 h. The reaction mixture was filtered through a pad of celite and the solvent removed under reduced pressure. Flash chromatography afforded **80** (8 mg, 80 %) as a clear oil.

^{1}H NMR (500 MHz, D_2O) δ 3.85 (td, *J* = 12.2, 2.9 Hz, 2H, overlapping signals C-H & H-6), 3.79 (d, *J* = 2.9 Hz, 1H, C-H), 3.77 – 3.69 (m, 2H, overlapping peaks C-H & H-6), 3.22 (td, *J* = 7.3, 6.3, 3.8 Hz, 1H, C-H), 1.80 (dq, *J* = 14.8, 7.3 Hz, 1H, H-7), 1.65 (dq, *J* = 15.1, 7.7 Hz, 1H, H-7'), 1.31 (s, 3H, -CH_3), 0.87 (t, *J* = 7.5 Hz, 3H, H-8s)

^{13}C NMR (126 MHz, D_2O) δ 71.1 (C-H), 69.8 (C-H), 65.6 (C-H), 63.3 (C-1), 58.1 (C-6), 55.8 (C-H), 25.1 (C-7), 19.4 (CH_3), 6.6 (C-8)

HRMS (ESI): m/z calc for $C_9H_{20}NO_4$: 206.1392, found 206.1385 $[M+H]^+$



(E,4S,5S,6R)-1-azido-4,5-*O*-isopropylidene-6-*O*-propargyl-octa-2,7-diene 175

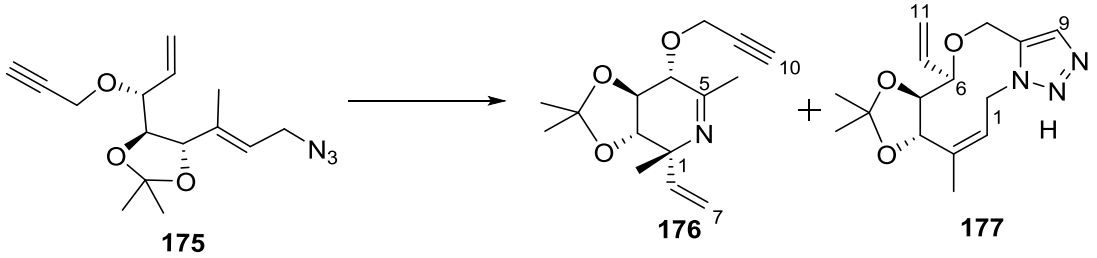
Compound **141** (1.0, 3.95 mmol) was dissolved in anhydrous DMF. The solution was cooled to 0 °C and NaH (0.2 g, 60% in mineral oil, 5.13 mmol) charged portionwise. The reaction mixture was stirred for 30 min and propargyl bromide (0.8 mL, 80 wt. % in toluene, 7.10 mmol) then added. The reaction mixture was warmed to rt and stirred for 16 h. The solution was diluted with Et_2O and subsquently quenched with satd. NH_4Cl (aq). The organic layer was separated, dried over Na_2SO_4, filtered & solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 4:1) afforded alkyne **175** (0.92 g, 80 %) as a clear oil.

R_f = 0.51 (hexanes-EtOAc, 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 – 5.68 (m, 2H, overlapping signals H-2 & H-7), 5.40 – 5.34 (m, 2H, overlapping signals H-8 & H-8'), 4.48 (d, *J* = 8.2 Hz, 1H, H-4), 4.29 (dd, *J* = 16.0, 2.4 Hz, 1H, H-9), 4.11 – 4.06 (dd, *J* = 16.2, 2.2 Hz, 1H, H-9'), 4.05 (dd, *J* = 8.3, 4.2 Hz, 1H, H-6), 3.89 (dd, *J* = 13.9, 7.7 Hz, 1H, H-1), 3.83 (dd, *J* = 8.2, 4.3 Hz, 1H, H-5), 3.77 (dd, *J* = 14.0, 6.7 Hz, 1H, H-1'), 2.42 (t, 2.4 Hz, 1H, H-11), 1.74 (s, 3H, CH_3), 1.45 (s, 6H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4 (C-3), 133.7 (C-7), 122.9 (C-2), 120.7 (C-8), 109.6 ($C(CH_3)_2$), 81.7 (C-4), 80.7 (C-5), 79.6 (C-10), 78.1 (C-6), 74.5 (C-11), 55.2 (C-9), 47.7 (C-1), 27.1 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 11.8 (CH_3)

HRMS (ESI): m/z calc for $C_{15}H_{22}N_3O_3$: 292.1661 found: 292.1665 $[M+H]^+$



Imine 176 & Triazole 177

Compound **175** (100 mg, 0.343 mmol) was dissolved in toluene (20 mL) and heated at 100 ˚C for 12 h. The solvent was evaporated under reduced pressure and flash chromatography (hexanes-EtOAc, 1:1) afforded **176** (18 mg, 20 %) as a clear oil, **177** (31mg, 31 %) as a crystalline solid and starting material **175** (6 mg, 6 %) as a clear oil.

Data for 177

R_f = 0.74 (EtOAc-hexanes, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H, H-9), 5.94 – 5.84 (m, 2H, overlapping signals H-2 & H-10), 5.39 (dd, *J* = 9.8, 1.3 Hz, 1H, H-11), 5.35 – 5.29 (m, 2H, overlapping signals H-1 & H-4), 5.19 – 5.12 (m, 1H, H-11), 4.91 (dd, *J* = 13.6, 5.7 Hz, 1H, H-1), 4.86 (d, *J* = 14.3 Hz, 1H, H-7), 4.76 (d, *J* = 14.2 Hz, 1H, H-7), 3.62 (dd, *J* = 8.8, 3.3 Hz, 1H, H-5), 3.46 (dd, *J* = 8.3, 3.3 Hz, 1H, H-6), 1.78 (t, *J* = 1.3 Hz, 3H, CH_3), 1.50 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2 (C-3), 133.9 (C-9), 132.4 (C-10), 131.6 (C-8), 123.0 (C-2), 120.6 (C-11), 109.4 ($C(CH_3)_2$), 79.5 (C-5), 74.1 (C-4), 73.5 (C-6), 58.1 (C-7), 45.5 (C-1), 27.0 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 18.3 (CH_3)

HRMS (ESI): m/z calc for $C_{15}H_{22}N_3O_3$: 292.1661 found: 292.1669 $[M+H]^+$

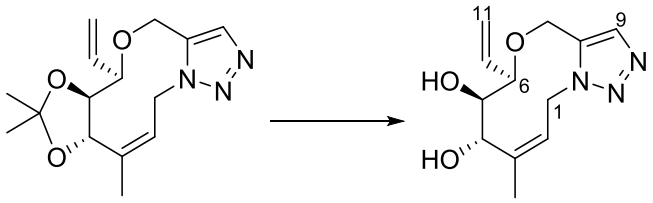
Data for 176

R_f = 0.67 (EtOAc-hexanes, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 17.4, 10.9 Hz, 1H, H-6), 5.15 (dd, *J* = 10.8, 1.4 Hz, 1H, H-7'), 4.95 (dd, *J* = 17.5, 1.4 Hz, 1H, H-7), 4.43 (dd, *J* = 15.8, 2.5 Hz, 1H, H-8), 4.34 (dd, *J* = 15.6, 2.3 Hz, 1H, H-8'), 4.13 (d, *J* = 8.8 Hz, 1H, H-4), 3.70 – 3.62 (m, 1H, H-3), 3.22 (d, *J* = 10.2 Hz, 1H, H-2), 2.48 (t, *J* = 2.4 Hz, 1H, H-10), 2.17 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.43 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8 (C-5), 138.9 (C-6), 115.6 (C-7), 110.4 ($C(CH_3)_2$), 81.2 (C-4), 80.7 (C-2), 79.4 (C-9), 76.2 (C-3), 74.9 (C-10), 64.0 (C-1), 58.0 (C-8), 27.8 (CH_3), 27.0 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 23.1 (CH_3)

HRMS (ESI): m/z calc for $C_{15}H_{22}NO_3$: 264.1600 found: 264.1611 $[M+H]^+$



177 **178**

Triazole 178

Compound **177** (30 mg, 0.10 mmol) was stirred in 3M HCl (5 mL) for 2 h. The solvent was removed under reduced pressure and flash chromatography (Et_2O-Acetone, 1:1) afforded triazole **178** (21 mg, 85 %) as a white solid.

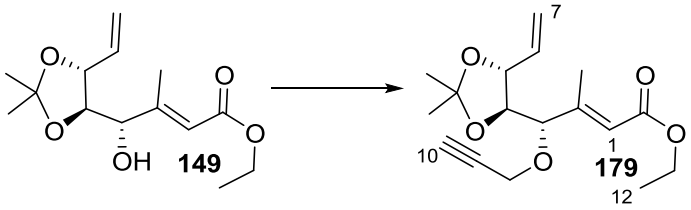
R_f = 0.43 (Et_2O-Acetone, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H, H-9), 5.90 (ddd, *J* = 17.3, 10.3, 8.1 Hz, 1H, H-10), 5.81 – 5.67 (m, 1H, H-2), 5.44 (dd, *J* = 10.3, 1.4 Hz, 1H, H-11), 5.32 (dd, *J* = 13.6, 11.7 Hz, 1H, H-1), 5.24 – 5.12 (m, 1H, H-11), 5.01 (d, *J* = 9.1 Hz, 1H, H-4), 4.99 – 4.93 (m, 1H, H-1), 4.85 (d, *J* =

14.8 Hz, 1H, H-7), 4.75 (d, *J* = 14.8 Hz, 1H, H-7'), 3.55 – 3.46 (m, 2H, overlapping signals H-5 & H-6), 1.75 (t, *J* = 1.3 Hz, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6 (C-3), 133.2 (C-9), 132.5 (C-10), 131.7 (C-8), 123.4 (C-2), 121.5 (C-11), 76.3, 75.1 (each C-6, C-5), 71.0 (C-4), 58.1 (C-7), 46.3 (C-1), 18.3 (CH_3)

HRMS (ESI): m/z calc for $C_{12}H_{18}N_3O_3$: 252.1348 found: 252.1359 $[M+H]^+$



(E,3S,4S,5R)-4,5-*O*-isopropylidene-3-*O*-propargyl-octa-1,6-diene-1a-oate 179

Compound **149** (0.93, 3.44 mmol) was dissolved in anhydrous DMF (30 mL). The solution was cooled to 0 °C and NaH (0.19 g, 60% in mineral oil, 4.81 mmol) charged portionwise. The reaction mixture was stirred for a further 30 min and propargyl bromide (0.7 mL, 80 wt. % in toluene, 6.19 mmol) added, reaction mixture warmed to rt and stirred for 4 h. The solution was quenched with satd. NH_4Cl (aq), extracted with EtOAc, dried over Na_2SO_4, filtered & solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 4:1) afforded the desired alkyne **179** (0.74 g, 70 %) as a clear oil.

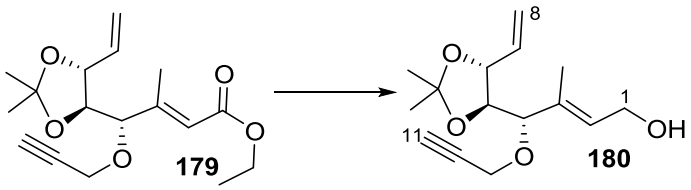
R_f 0.4 (hexanes-EtOAc, 4:1)

FTIR 3263, 2986, 2936, 1715, 1654, 1445, 1370, 1213, 1153, 1120, 1075, 1043, 989, 931, 874, 840, 809, 660 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (s, 1H, H-1), 5.77 (ddd, *J* = 17.3, 10.3, 7.3 Hz, 1H, H-6), 5.35 (d, *J* = 17.2 Hz, 1H, H-7), 5.25 (d, *J* = 10.8 Hz, 1H, H-7'), 4.34 (t, *J* = 7.7 Hz, 1H, H-5), 4.30 (dd, *J* = 16.1, 2.4 Hz, 1H, H-8), 4.19 (q, *J* = 7.0 Hz, 3H, H-11s), 4.04 – 3.99 (m, 2H, overlapping signals H-3 & H-8'), 3.84 (dd, *J* = 8.1, 5.2 Hz, 1H, H-4), 2.43 (q, *J* = 2.5 Hz, 1H, H-10), 2.11 (s, 3H, CH_3), 1.45 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$), 1.30 (t, *J* = 7.1 Hz, 3H, H-12s)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8 (C=O), 153.4 (C-2), 135.1 (C-6), 119.9 (C-1), 119.4 (C-7), 109.7 ($C(CH_3)_2$), 82.2 (C-3), 81.0 (C-4), 79.0 (C-9), 78.9 (C-5), 75.1 (C-10), 60.0 (C-11), 56.1 (C-8), 27.0 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 15.3 (CH_3), 14.3 (C-12);

HRMS (ESI): m/z calc for $C_{18}H_{29}O_6$: 341.1964, found 341.1971 $[M+H+CH_3OH]^+$



(E,3S,4S,5R)-4,5-*O*-isopropylidene-3-*O*-propargyl-octa-1,6-diene-1-ol 180

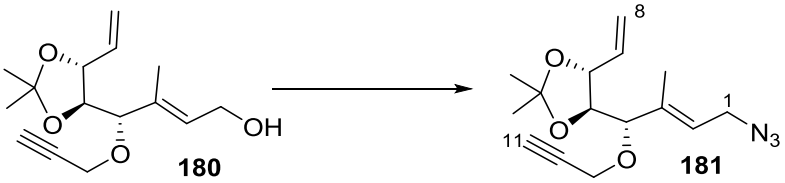
Compound **179** (0.4 g, 1.3 mmol) was dissolved in CH_2Cl_2 (5 mL). The solution was cooled to -78 ˚C and dibal-H (3.9 mL, 1M in THF) charged slowly. The solution was then stirred at -78 ˚C for 4 h and the reaction was subsequently quenched with the slow addition of MeOH. The solution was warmed to rt and stirred with potassium tartrate (aq) until clear. The organic layer was separated and subsequently washed with H_2O, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford alcohol **180** (0.3 g, 86 %) as a clear oil.

FTIR 3266, 2986, 2923, 1644, 1371, 1256, 1214, 1170, 1060, 1015, 930, 877, 802, 665 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.80 – 5.73 (m, 2H, overlapping signals H-2 & H-7), 5.33 (dt, *J* = 17.2, 1.1 Hz, 1H, H-8), 5.23 (dd, *J* = 10.1, 1.9 Hz, 1H, H-8’), 4.30 – 4.21 (m, 3H, overlapping signals H-6, H-1 & H-9), 4.18 (dt, *J* = 12.6, 5.8 Hz, 1H, H-1), 4.03 (dd, *J* = 16.1, 2.4 Hz, 1H, H-9), 3.97 (d, *J* = 6.6 Hz, 1H, H-4), 3.86 (dd, *J* = 8.1, 6.6 Hz, 1H, H-5), 2.41 (apt t, *J* = 2.4 Hz, 1H, H-11), 1.60 (s, 3H, CH_3), 1.46 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5 (C-7), 133.8 (C-3), 130.8 (C-2), 118.9 (C-8), 109.5 ($C(CH_3)_2$), 83.9 (C-4), 81.2 (C-5), 79.5 (C-10), 79.3 (C-6), 74.5 (C-11), 59.0 (C-1), 55.2 (C-9), 27.0 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 12.5 (CH_3)

HRMS (ESI): m/z calc for $C_{15}H_{21}O_4$: 265.1440, found 265.1436 $[M-H]^-$



(E,3S,4S,5R)-1-azido-4,5-*O*-isopropylidene-3-*O*-propargyl-octa-1,6-diene 181

Compound **180** (0.3 g, 1.1 mmol) was dissolved in anhydrous THF (6 mL) and PPh_3 (0.53 g, 1.92 mmol) charged. The solution was cooled to 0 ˚C, followed by the addition of DIAD (0.38 mL, 1.92 mmol) and DPPA (0.4 mL, 1.9 mmol). The reaction mixture was adjusted to rt and stirred for a further 12 h. The solvent was then removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 10:1) afforded azide **181** (0.22, 69 %) as a clear oil.

R_f = 0.75 (EtOAc-hexanes, 1:4)

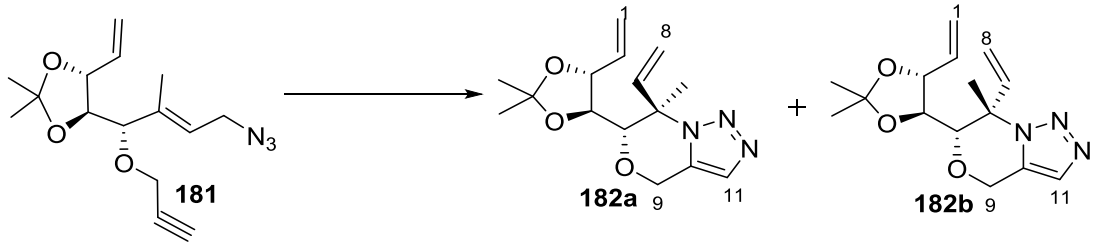
FTIR 3414, 2983, 1712, 1654, 1372, 1214, 1151, 1097, 1040, 994, 928, 873, 764 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddd, *J* = 17.5, 10.3, 7.4 Hz, 1H, H-7), 5.69 (t, *J* = 7.1 Hz, 1H, H-2), 5.34 (d, *J* = 17.1 Hz, 1H, H-8), 5.25 (d, *J* = 10.2 Hz, 1H, H-8’), 4.33 – 4.24 (m, 2H, overlapping signals H-6 & H-9), 4.08 – 3.99 (m, 2H, overlapping signals H-4 & H-9), 3.92 (dd, *J* =

14.1, 7.2 Hz, 1H, H-1), 3.85 (dd, *J* = 8.1, 6.3 Hz, 1H, H-5), 3.79 (dd, *J* = 14.1, 6.9 Hz, 1H, H-1'), 2.42 (apt t, *J* = 2.2 Hz, 1H, H-11), 1.66 (s, 3H, CH_3), 1.46 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5 (C-3), 135.4 (C-7), 124.2 (C-2), 119.1 (C-8), 109.6 ($C(CH_3)_2$), 83.1 (C-4), 81.2 (C-5), 79.2 (C-10), 79.1 (C-6), 74.7 (C-11), 55.4 (C-9), 47.7 (C-1), 27.0 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 12.8 (CH_3)

HRMS (ESI): m/z calc for $C_{15}H_{22}O_3N_3$: 292.1661, found 292.1650 $[M+H]^+$



Triazole 182a & Triazole 182b

Compound **181** (0.14 g, 0.41 mmol) was dissolved in DMF (5 mL) and heated for 12 h. Water was added and product extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes,1:1) afforded **182a** (92.8 mg, 66 %) as a white solid and **182b** (27.5 mg, 20 %) as a clear oil.

Data for 182a

R_f = 0.3 (EtOAc-hexanes, 1:1)

^{1}H NMR **52** (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 1.9 Hz, 1H, H-11), 5.93 (ddd, *J* = 17.2, 10.8, 2.0 Hz, 1H, H-7), 5.80 (dddd, *J* = 17.7, 9.9, 7.8, 2.0 Hz, 1H, H-2), 5.61 – 5.49 (m, 2H, overlapping signals H-8 & H-8'), 5.39 (d, *J* = 17.1 Hz, 1H, H-1), 5.31 (d, *J* = 10.3 Hz, 1H, H-1'), 5.23 (dd, *J* = 14.8, 2.0 Hz, 1H, H-9), 4.84 (dd, *J* = 14.7, 1.9 Hz, 1H, H-9'), 4.49 (m, 1H, H-3), 3.85 (dd, *J* = 8.5, 1.9 Hz, 1H, H-4), 3.48 (d, *J* = 1.8 Hz, 1H, H-5), 1.79 (d, *J* = 2.1 Hz, 3H, CH_3), 1.44 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0 (C-7), 134.8 (C-2), 129.7 (C-10), 127.8 (C-11), 120.4 (C-1), 120.1 (C-8), 110.2 ($C(CH_3)_2$), 79.4 (C-3), 77.2 (C-4), 76.8 (C-5), 65.1 (C-6), 62.9 (C-9), 27.2 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$), 20.8 (CH_3)

HRMS (ESI): m/z calc for $C_{15}H_{22}N_3O_3$: 292.1661, found 292.1649 $[M+H]^+$

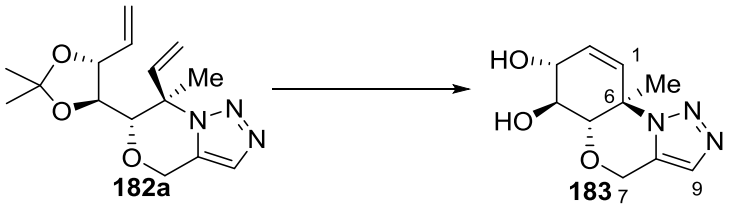
Data for 182b

R_f = 0.35 (EtOAc-hexanes, 1:1)

^{1}H NMR **53** (600 MHz, $CDCl_3$) δ 7.50 (s, 1H, H-11), 6.28 (dd, *J* = 17.1, 10.6 Hz, 1H, H-7), 5.85 (ddd, *J* = 17.6, 10.2, 7.5 Hz, 1H. H-2), 5.41 (d, *J* = 16.9 Hz, 1H, H-1), 5.33 (d, *J* = 10.2 Hz, 1H, H-1'), 5.24 (d, *J* = 15.0 Hz, 1H, H-9), 5.20 (d, *J* = 10.7 Hz, 1H, H-8'), 4.87 (d, *J* = 15.1 Hz, 1H, H-9), 4.61 (d, *J* = 17.0 Hz, 1H, H-8), 4.53 (t, *J* = 8.1 Hz, 1H, H-3), 3.96 (d, *J* = 8.4 Hz, 1H, H-4), 3.48 (d, *J* = 3.4 Hz, 1H, H-5), 1.88 (s, 3H, -CH_3), 1.44 (m, 6H, -$C(CH_3)_2$)

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.3 (C-7), 134.7 (C-2), 130.2 (C-10), 127.8 (C-11), 120.3 (C-1), 116.0 (C-8), 110.3 ($C(CH_3)_2$), 79.1 (C-3), 78.5 (C-5), 77.4 (C-4), 65.0 (C-6), 62.7 (C-9), 27.0 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$), 21.9 (CH_3)

HRMS (ESI): *m/z* calc for $C_{15}H_{22}N_3O_3$: 292.1661, found 292.1665 $[M+H]^+$



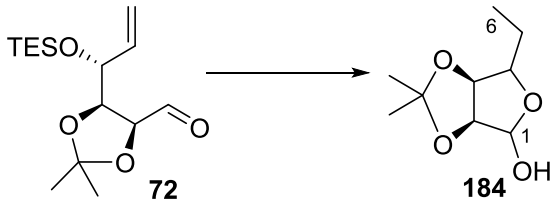
Triazole 183

Compound **182a** (0.05 g, 0.17 mmol) was dissolved in anhydrous degassed toluene (150 mL). The solution was heated to 80 ˚C, followed by the addition of 2,6-dichloro-1,4-benzoquinone (0.012 g ,0.069 mmol) and Hoyveda-Grubbs II (0.011 g, 0.017 mmol). The reaction mixture was stirred at 80 °C for 5 h. The solvent was subsequently removed under reduced pressure and crude residue treated with 2M HCl for 12 h. Flash chromatography (CH_2Cl_2-MeOH, 9:1) afforded triazole **183** (6 mg, 15 %) as a white solid

^{1}H NMR (500 MHz, CD_3OD) δ 7.54 (d, *J* = 0.9 Hz, 1H, H-9), 6.66 (dd, *J* = 10.2, 2.1 Hz, 1H, H-1), 5.79 (dd, *J* = 10.2, 2.9 Hz, 1H, H-2), 5.23 (dd, *J* = 15.4, 0.7 Hz, 1H, H-7), 4.98 (dd, *J* = 15.3, 1.0 Hz, 1H, H-7), 4.18 (ddd, *J* = 6.9, 2.9, 2.1 Hz, 1H, H-3), 3.92 (dd, *J* = 10.9, 6.8 Hz, 1H, H-4), 3.70 (d, *J* = 10.9 Hz, 1H, H-5)

^{13}C NMR (126 MHz, CD_3OD) δ 130.9 (C-8), 130.5 (C-2), 128.1 (C-9), 127.1 (C-1), 79.7 (C-5), 73.7 (C-3), 72.0 (C-4), 62.6 (C-7), 61.8 (C-6)

HRMS (ESI): m/z calc for $C_{10}H_{14}N_3O_3$: 224.1035, found 224.1028 $[M+H]^+$



(2S,3S,4R)-4-ethyl-1-hydroxy-2,3-*O*-isopropylidene-1,5-furanose 184

Compound **72** (0.55 g, 1.67 mmol) was dissolved in MeOH and Pd-C (0.18 g, 0.1666 mmol) then charged. A H_2 balloon was added to the reaction system and solution stirred at rt for 1 h. The reaction mixture was subsquently filtered through a pad of celite and solvent removed under reduced pressure. Flash chromatography (hexanes:EtOAc, 1:1) afforded **184** (210 mg, 68 %) as a clear oil.

R_f 0.58 (hexanes-EtOAc, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (s, 1H, H-1), 4.67 (dd, *J* = 5.9, 3.5 Hz, 1H, H-3), 4.60 (d, *J* = 5.9 Hz, 1H, H-2), 4.06 (td, *J* = 7.1, 3.5 Hz, 1H, H-4), 1.75 (dtd, *J* = 15.1, 7.5, 6.1 Hz, 3H, CH_2), 1.46 (s, 3H, $C(CH_3)_2$), 1.33 (s, 3H, $C(CH_3)_2$), 1.01 (t, *J* = 7.4 Hz, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ 112.3 ($C(CH_3)_2$), 100.9 (C-1), 85.7 (C-2), 81.9 (C-4), 80.2 (C-3), 26.1 ($C(CH_3)_2$), 25.0 ($C(CH_3)_2$), 21.6 (C-5), 10.5 (C-6)

HRMS (ESI): m/z calc for $C_9H_{17}O_4$: 189.1127, found 189.1115 $[M+H]^+$

References

(1) John, J. E. *Curr. Sci.* **2009**, *96* (6), 753.

(2) Rungsung, W.; Ratha, K. K.; Dutta, S.; Dixit, A. K.; Hazra, J. *World J. Pharm. Res.* **2015**, *4* (7).

(3) Achan, J.; Talisuna, A. O.; Erhart, A.; Yeka, A.; Tibenderana, J. K.; Baliraine, F. N.; Rosenthal, P. J.; D'Alessandro, U. *Malar. J.* **2011**, *10*, 144.

(4) Meshnick, S. R.; Dobson, M. J. In *Anti-malarial Chemotherapy*; Rosenthal, P. J., Ed.; Humana Press: New York, 2001; pp 15–25.

(5) Tu, Y. *Nat Med* **2011**, *17* (10), 1217–1220.

(6) Wang, M.-Y. *Asian Pac. J. Trop. Biomed.* **2016**, *6* (6), 461–467.

(7) Johnson, I. S.; Wright, H. F.; Svoboda, G. H.; Vlantis, J. *Cancer Res.* **1960**, *20* (7 Part 1), 1016–1022.

(8) Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N. Y. Acad. Sci.* **1958**, *76* (3), 882–894.

(9) Cragg, G. M. *Med. Res. Rev.* **1998**, *18* (5), 315–331.

(10) Yvon, A.-M. C.; Wadsworth, P.; Jordan, M. A. *Mol. Biol. Cell* **1999**, *10* (4), 947–959.

(11) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88* (16), 3888–3890.

(12) Sugawara, K.; Nishiyama, Y.; Toda, S.; Komiyama, N.; Hatori, M.; Moriyama, T.; Sawada, Y.; Kamei, H.; Konishi, M.; Oki, T. *J. Antibiot. (Tokyo).* **1992**, *45* (9), 1433–1441.

(13) Micoine, K.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132* (40), 14064–14066.

(14) Nakae, K.; Yoshimoto, Y.; Sawa, T.; Homma, Y.; Hamada, M.; Takeuchi, T.; Imoto, M. *J. Antibiot. (Tokyo).* **2000**, *53* (10), 1130–1136.

(15) Nakae, K.; Yoshimoto, Y.; Sawa, T.; Homma, Y.; Hamada, M.; Takeuchi, T.; Imoto, M. *J. Antibiot. (Tokyo).* **2000**, *53* (10), 1228–1230.

(16) Takemoto, Y.; Tashiro, E.; Imoto, M. *J Antibiot* **2006**, *59* (7), 435–438.

(17) Woo, E. J.; Starks, C. M.; Carney, J. R.; Arslanian, R.; Cadapan, L.; Zavala, S.; Licari, P. *J. Antibiot. (Tokyo).* **2002**, *55* (2), 141–146.

(18) Ju, J.; Lim, S.-K.; Jiang, H.; Shen, B. *J. Am. Chem. Soc.* **2005**, *127* (6), 1622–1623.

(19) Ju, J.; Lim, S.-K.; Jiang, H.; Seo, J.-W.; Her, Y.; Shen, B. *Org. Lett.* **2006**, *8* (25), 5865–5868.

(20) Hochlowski, J. E.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot. (Tokyo).* **1994**, *47* (8), 870–874.

(21) Ju, J.; Rajski, S. R.; Lim, S.-K.; Seo, J.-W.; Peters, N. R.; Hoffmann, F. M.; Shen, B. *J. Am. Chem. Soc.* **2009**, *131* (4), 1370–1371.

(22) Giralt, E.; Lo Re, D. *Molecules* **2017**, *22* (2).

(23) Cancer in Ireland 2013 : Annual report of the National Cancer Registry http://www.ncri.ie/sites/ncri/files/pubs/CancerinIreland2013AnnualReportoftheNationalCancerRegistry.pdf (accessed Feb 27, 2017).

(24) Steeg, P. S. *Nat Med* **2006**, *12* (8), 895–904.

(25) Takemoto, Y.; Nakae, K.; Kawatani, M.; Takahashi, Y.; Naganawa, H.; Imoto, M. *J. Antibiot. (Tokyo).* **2001**, *54* (12), 1104–1107.

(26) Nakamura, H.; Takahashi, Y.; Naganawa, H.; Nakae, K.; Imoto, M.; Shiro, M.; Matsumura, K.; Watanabe, H.; Kitahara, T. *J. Antibiot. (Tokyo).* **2002**, *55* (4), 442–444.

(27) Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43* (50), 9039–9042.

(28) Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125* (20), 6042–6043.

(29) Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X.-Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126* (4), 1038–1040.

(30) Gaul, C.; Njardarson, J. T.; Shan, D.; Dorn, D. C.; Wu, K.-D.; Tong, W. P.; Huang, X.-Y.; Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126* (36), 11326–11337.

(31) Shan, D.; Chen, L.; Njardarson, J. T.; Gaul, C.; Ma, X.; Danishefsky, S. J.; Huang, X.Y. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102* (10), 3772–3776.

(32) Oskarsson, T.; Nagorny, P.; Krauss, I. J.; Perez, L.; Mandal, M.; Yang, G.; Ouerfelli, O.; Xiao, D.; Moore, M. A. S.; Massagué, J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132* (9), 3224–3228.

(33) Lecomte, N.; Njardarson, J. T.; Nagorny, P.; Yang, G.; Downey, R.; Ouerfelli, O.; Moore, M. a S.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108* (37), 15074–15078.

(34) Chen, L.; Yang, S.; Jakoncic, J.; Zhang, J. J.; Huang, X.-Y. *Nature* **2010**, *464* (7291), 1062–1066.

(35) Nagorny, P.; Krauss, I.; Njardarson, J. T.; Perez, L.; Gaul, C.; Yang, G.; Ouerfelli, O.; Danishefsky, S. J. *Tetrahedron Lett.* **2010**, *51* (30), 3873–3875.

(36) Majchrzak, K.; Lo Re, D.; Gajewska, M.; Bulkowska, M.; Homa, A.; Pawowski, K.; Motyl, T.; Murphy, P. V.; Krol, M. *PLoS One* **2013**, *8* (10).

(37) Lo Re, D.; Zhou, Y.; Nobis, M.; Anderson, K. I.; Murphy, P. V. *ChemBioChem* **2014**, *15* (10), 1459–1464.

(38) Thiery, J. P.; Acloque, H.; Huang, R. Y. J.; Nieto, M. A. *Cell* **2017**, *139* (5), 871–890.

(39) Christofori, G. *EMBO J.* **2010**, *29* (11), 1787–1789.

(40) David, J. M.; Rajasekaran, A. K. *Cancer Res.* **2012**, *72* (12), 2917–2923.

(41) Lecomte, N.; Njardarson, J. T.; Nagorny, P.; Yang, G.; Downey, R.; Ouerfelli, O.; Moore, M. a S.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, 1–5.

(42) Krauss, I. J.; Mandal, M.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46* (29), 5576–5579.

(43) Metaferia, B. B.; Chen, L.; Baker, H. L.; Huang, X.-Y.; Bewley, C. A. *J. Am. Chem. Soc.* **2007**, *129* (9), 2434–2435.

(44) Yan, D. Synthesis of macrocycles and divalent ligands based on carbohydrates, University College Dublin, 2010.

(45) Edward, J. T. *Chem. Ind.* **1955**, 1102–1104.

(46) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25* (3), 527.

(47) Bauerfeldt, G. F.; Cardozo, T. M.; Pereira, M. S.; da Silva, C. O. *Org. Biomol. Chem.* **2013**, *11* (2), 299–308.

(48) Pacsu, E. *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.* **1928**, *61* (1), 137–144.

(49) Pacsu, E. *J. Am. Chem. Soc.* **1930**, *52* (6), 2568–2571.

(50) Lindberg, B. *Acta Chem. Scand.* **1949**, *3* (1), 1153–1169.

(51) Lemieux, R. U. In *Molecular Rearrangements*; Mayo, P. De, Ed.; Interscience: New York, 1964; pp 709–769.

(52) Lemieux, R. U.; Shyluk, W. P. *Can. J. Chem.* **1955**, *33* (1), 120–127.

(53) Murphy, P. V. In *Carbohydrate Chemistry: Volume 41*; The Royal Society of Chemistry, 2016; Vol. 41, pp 90–123.

(54) Tosin, M.; Murphy, P. V. *Org. Lett.* **2002**, *4* (21), 3675–3678.

(55) Poláková, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Angew. Chem. Int. Ed.* **2004**, *43* (19), 2518–2521.

(56) O'Brien, C.; Poláková, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Chem. Eur. J.* **2007**, *13* (3), 902–909.

(57) Pilgrim, W.; Murphy, P. V. *J. Org. Chem.* **2010**, *75* (20), 6747–6755.

(58) Pau, J. K.; Ruggera, M. B.; Kim, J. K.; Caserio, M. C. *J. Am. Chem. Soc.* **1978**, *100* (13), 4242–4248.

(59) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39* (4), 259–265.

(60) O'Reilly, C.; Murphy, P. V. *Org. Lett.* **2011**, *13* (19), 5168–5171.

(61) Farrell, M.; Zhou, J.; Murphy, P. V. *Chem. Eur. J.* **2013**, *19* (44), 14836–14851.

(62) McDonagh, A. W.; Mahon, M. F.; Murphy, P. V. *Org. Lett.* **2016**, *18* (3), 552–555.

(63) André, S.; Velasco-Torrijos, T.; Leyden, R.; Gouin, S.; Tosin, M.; Murphy, P. V; Gabius, H.-J. *Org. Biomol. Chem.* **2009**, *7* (22), 4715–4725.

(64) Graf von Roedern, E.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118* (42), 10156–10167.

(65) T. Brown, R.; Scheinmann, F.; V. Stachulski, A. *J. Chem. Res.* **1997**, No. 10, 370–371.

(66) Igarashi, K. Tipson, R. S., Horton, D., Eds.; Advances in Carbohydrate Chemistry and Biochemistry; Academic Press, 1977; Vol. 34, pp 243–283.

(67) Mayato, C.; Dorta, R. L.; Vázquez, J. T. *Tetrahedron Lett.* **2008**, *49* (8), 1396–1398.

(68) McDonagh, A. W.; Murphy, P. V. *Tetrahedron* **2014**, *70* (19), 3191–3196.

(69) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127* (49), 17160–17161.

(70) Kajetanowicz, A.; Milewski, M.; Rogińska, J.; Gajda, R.; Woźniak, K. *European J. Org. Chem.* **2017**, *2017* (3), 626–638.

(71) MacDougall, J. M.; Zhang, X. D.; Polgar, W. E.; Khroyan, T. V.; Toll, L.; Cashman, J. R. *J. Med. Chem.* **2004**, *47* (23), 5809–5815.

(72) Wallace, O. B.; Springer, D. M. *Tetrahedron Lett.* **1998**, *39* (18), 2693–2694.

(73) Bradley, H.; Fitzpatrick, G.; Glass, W. K.; Kunz, H.; Murphy, P. V. *Org. Lett.* **2001**, *3* (17), 2629–2632.

(74) Sweeney, S. Design and Synthesis of Macrocycles, Peptides and Coiled Coils with Sugar Connections, NUI Galway, 2016.

(75) Al-Horani, R. A.; Desai, U. R. *Tetrahedron* **2012**, *68* (8), 2027–2040.

(76) Smith, A. B.; Chruma, J. J.; Han, Q.; Barbosa, J. *Bioorganic Med. Chem. Lett.* **2004**, *14* (7), 1697–1702.

(77) Moraczewski, A. L.; Banaszynski, L. A.; From, A. M.; White, C. E.; Smith, B. D. *J. Org. Chem.* **1998**, *63* (21), 7258–7262.

(78) Kleckner, I. R.; Foster, M. P. *Biochim. Biophys. Acta - Proteins Proteomics* **2011**, *1814* (8), 942–968.

(79) Compain, P.; Martin, O. R. *Iminosugars: From Synthesis to Therapeutic Applications*; Wiley: Chichester, 2008.

(80) Paulsen, H. *Angew. Chemie Int. Ed. English* **1962**, *1* (8), 454.

(81) Paulsen, H. *Angew. Chemie Int. Ed. English* **1962**, *1* (11), 597.

(82) Jones, J. K. N.; Turner, J. C. *J. Chem. Soc.* **1962**, 4699–4703.

(83) Jones, J. K. N.; Szarek, W. A. *Can. J. Chem.* **1963**, *41* (3), 636–640.

(84) Inouye, S.; Tsuruoka, T.; Nida, T. *J. Antibiot. (Tokyo).* **1966**, *19* (6), 288—292.

(85) Horne, G.; Wilson, F. X. Lawton, G., Witty, D. R., Eds.; Progress in Medicinal Chemistry; Elsevier, 2011; Vol. 50, pp 135–176.

(86) Kondo, K.; Adachi, H.; Shitara, E.; Kojima, F.; Nishimura, Y. *Bioorg. Med. Chem.* **2001**, *9* (5), 1091–1095.

(87) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11* (8), 1645–1680.

(88) Kite, G. C.; Fellows, L. E.; Fleet, G. W. J.; Liu, P. S.; Scofield, A. M.; Smith, N. G. *Tetrahedron Lett.* **1988**, *29* (49), 6483–6485.

(89) Kite, G. C.; Horn, J. M.; Romeo, J. T.; Fellows, L. E.; Leest, D. C.; Scofield, A. M.; Smith, N. G. *Phytochemistry* **1990**, *29* (1), 103–105.

(90) Asano, N.; Nishida, M.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *J. Nat. Prod.* **1997**, *60* (2), 98–101.

(91) Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *J. Nat. Prod.* **1998**, *61* (5), 625–628.

(92) Asano, N.; Nishida, M.; Kato, A.; Kizu, H.; Matsui, K.; Shimada, Y.; Itoh, T.; Baba, M.; Watson, A. A.; Nash, R. J.; Lilley, P. M. de Q.; Watkin, D. J.; Fleet, G. W. J. *J. Med. Chem.* **1998**, *41* (14), 2565–2571.

(93) Pawar, N. J.; Parihar, V. S.; Chavan, S. T.; Joshi, R.; Joshi, P. V; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *J. Org. Chem.* **2012**, *77* (18), 7873–7882.

(94) Fustero, S.; Albert, L.; Mateu, N.; Chiva, G.; Mirõ, J.; González, J.; Aceña, J. L. *Chem. Eur. J.* **2012**, *18* (12), 3753–3764.

(95) Welter, A.; Jadot, J.; Dardenne, G.; Marlier, M.; Casimir, J. *Phytochemistry* **1976**, *15* (5), 747–749.

(96) Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V; Fellows, L. E.; Nash, R. J.

Tetrahedron Lett. **1985**, *26* (26), 3127–3130.

(97) Molyneux, R. J.; Pan, Y. T.; Tropea, J. E.; Elbein, A. D.; Lawyer, C. H.; Hughes, D. J.; Fleet, G. W. J. *J. Nat. Prod.* **1993**, *56* (8), 1356–1364.

(98) Watson, A. A.; Nash, R. J.; Wormald, M. R.; Harvey, D. J.; Dealler, S.; Lees, E.; Asano, N.; Kizu, H.; Kato, A.; Griffiths, R. C.; Cairns, A. J.; Fleet, G. W. J. *Phytochemistry* **1997**, *46* (2), 255–259.

(99) Hiranuma, S.; Shimizu, T.; Nakata, T.; Kajimoto, T.; Wong, C. H. *Tetrahedron Lett.* **1995**, *36* (45), 8247–8250.

(100) Shibano, M.; Nakamura, S.; Akazawa, N.; Kusano, G. *Chem. Pharm. Bull. (Tokyo).* **1998**, *46* (6), 1048–1050.

(101) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem. Int. Ed.* **2003**, *42* (48), 5987–5990.

(102) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem. Eur. J.* **2006**, *12* (25), 6607–6620.

(103) Asano, N.; Nishida, M.; Miyauchi, M.; Ikeda, K.; Yamamoto, M.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Phytochemistry* **2000**, *53* (3), 379–382.

(104) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2* (3), 199.

(105) Asano, N. *Glycobiology* **2003**, *13* (10), 93–104.

(106) Wardrop, D. J.; Waidyarachchi, S. L. *Nat. Prod. Rep.* **2010**, *27* (10), 1431–1468.

(107) Wong, C. H.; Dumas, D. P.; Ichikawa, Y.; Koseki, K.; Danishefsky, S. J.; Weston, B. W.; Lowe, J. B. *J. Am. Chem. Soc.* **1992**, *114* (18), 7321–7322.

(108) Bols, M.; Hazell, R. G.; Thomsen, I. B. *Chem. Eur. J.* **1997**, *3* (6), 940–947.

(109) Heightman, T. D.; Vasella, A.; Tsitsanou, K. E.; Zographos, S. E.; Skamnaki, V. T.; Oikonomakos, N. G. *Helv. Chim. Acta* **1998**, *81* (5–8), 853–864.

(110) Horenstein, B. A.; Zabinski, R. F.; Schramm, V. L. *Tetrahedron Lett.* **1993**, *34* (45), 7213–7216.

(111) Moriyama, H.; Tsukida, T.; Inoue, Y.; Yokota, K.; Yoshino, K.; Kondo, H.; Miura, N.; Nishimura, S.-I. *J. Med. Chem.* **2004**, *47* (8), 1930–1938.

(112) de Melo, E. B.; da Silveira Gomes, A.; Carvalho, I. *Tetrahedron* **2006**, *62* (44), 10277–10302.

(113) Koshland, D. E.; Stein, S. S. *J. Biol. Chem.* **1954**, *208* (1), 139–148.

(114) Strutz, A. E. *Iminosugars as glycosidase inhibitors : Nojirimycin and beyond*; Wiley-VCH: Weinheim; Cambridge, 1999.

(115) Koshland, D. E. *Biol. Rev.* **1953**, *28* (4), 416–436.

(116) Sinnott, M. L. *Chem. Rev.* **1990**, *90* (7), 1171–1202.

(117) Cerqueira, Nuno; Brás, Natércia; Ramos, Maria João; Fernandes, P. A. In *Carbohydrates - Comprehensive Studies on Glycobiology and Glycotechnology*; Chang, C.-F., Ed.; InTech, 2012.

(118) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56* (3), 265–295.

(119) Brás, N. F.; Cerqueira, N. M.; Ramos, M. J.; Fernandes, P. A. *Expert Opin. Ther. Pat.* **2014**, *24* (8), 857–874.

(120) Hanahan, D.; Weinberg, R. A. *Cell* **2017**, *144* (5), 646–674.

(121) Potapenko, I. O.; Haakensen, V. D.; Luders, T.; Helland, A.; Bukholm, I.; Sorlie, T.; Kristensen, V. N.; Lingjaerde, O. C.; Borresen-Dale, A.-L. *Mol. Oncol.* **2010**, *4* (2), 98–118.

(122) Dimitroff, C. J.; Sharma, A.; Bernacki, R. J. *Cancer Invest.* **1998**, *16* (4), 279–290.

(123) Hadwiger, A.; Niemann, H.; Kabisch, A.; Bauer, H.; Tamura, T. *EMBO J* **1986**, *5* (4), 689–694.

(124) Humphries, M. J.; Matsumoto, K. M.; White, S. L. W.; Olden, K. O. *Cancer Res.* **1986**, *46* (10), 5215–5222.

(125) Ostrander, G. K.; Scribner, N. K.; Rohrschneider, L. R. *Cancer Res.* **1988**, *48* (5), 1091–1094.

(126) Pili, R.; Chang, J.; Partis, R. A.; Mueller, R. A.; Chrest, F. J.; Passaniti, A. *Cancer Res.* **1995**, *55* (13), 2920–2926.

(127) Wrodnigg, T. M.; Steiner, A. J.; Ueberbacher, B. J. *Anticancer. Agents Med. Chem.* **2008**, *8* (1), 77–85.

(128) Shaheen, P. E.; Stadler, W.; Elson, P.; Knox, J.; Winquist, E.; Bukowski, R. M. *Invest New Drugs* **2005**, *23* (6), 577–581.

(129) Nishimura, Y.; Shitara, E.; Adachi, H.; Toyoshima, M.; Nakajima, M.; Okami, Y.; Takeuchi, T. *J. Org. Chem.* **2000**, *65* (1), 2–11.

(130) Brown, J. R.; Nishimura, Y.; Esko, J. D. *Bioorg. Med. Chem. Lett.* **2006**, *16* (3), 532–536.

(131) Heyman, B.; Yang, Y. *Exp. Hematol.* **2017**, *44* (11), 1002–1012.

(132) Nguyen, M.; Folkman, J.; Bischoff, J. *J. Biol. Chem.* **1992**, *267* (36), 26157–26165.

(133) Kallander, L. S.; Lu, Q.; Chen, W.; Tomaszek, T.; Yang, G.; Tew, D.; Meek, T. D.; Hofmann, G. A.; Schulz-Pritchard, C. K.; Smith, W. W.; Janson, C. A.; Ryan, M. D.; Zhang, G.-F.; Johanson, K. O.; Kirkpatrick, R. B.; Ho, T. F.; Fisher, P. W.; Mattern, M. R.; Johnson, R. K.; Hansbury, M. J.; Winkler, J. D.; Ward, K. W.; Veber, D. F.; Thompson, S. K. *J. Med. Chem.* **2005**, *48* (18), 5644–5647.

(134) Selvakumar, P.; Lakshmikuttyamma, A.; Dimmock, J. R.; Sharma, R. K. *Biochim. Biophys. Acta Rev. Cancer* **2006**, *1765* (2), 148–154.

(135) Zhao, Y.; Zhou, Y.; O'Boyle, K. M.; Murphy, P. V. *Bioorg. Med. Chem.* **2008**, *16* (12), 6333–6337.

(136) Zhou, Y.; Zhao, Y.; O' Boyle, K. M.; Murphy, P. V. *Bioorganic Med. Chem. Lett.* **2008**, *18* (3), 954–958.

(137) Zhao, Y.; Liu, W.; Zhou, Y.; Zhang, X.; Murphy, P. V. *Bioorg. Med. Chem. Lett.* **2010**, *20* (24), 7540–7543.

(138) Zois, C. E.; Harris, A. L. *J. Mol. Med.* **2016**, *94* (2), 137–154.

(139) Bour, S.; Geleziunas, R.; Wainberg, M. A. *Microbiol. Rev.* **1995**, *59* (1), 63–93.

(140) Brik, A.; Wong, C.-H. *Org. Biomol. Chem.* **2003**, *1*, 5–14.

(141) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330* (6143), 74–77.

(142) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci.U.S.A* **1987**, *84* (22),

8120–8124.

(143) Tyms, A. S.; Berrie, E. M.; Ryder, T. A.; Nash, R. J.; Hegarty, M. P.; Taylor, D. L.; Mobberley, M. A.; Davis, J. M.; Bell, E. A.; Jeffries, D. J.; Taylor-Robinson, D.; Fellows, L. E. *Lancet* **2017**, *330* (8566), 1025–1026.

(144) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237* (1–2), 128–132.

(145) Karpas, A.; Fleet, G. W.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A* **1988**, *85* (23), 9229–9233.

(146) Fischer, P. B.; Karlsson, G. B.; Dwek, R. A.; Platt, F. M. *J. Virol.* **1996**, *70* (10), 7153–7160.

(147) Fischl, M. A.; Resniek, L.; Coombs, R.; Kremer, A. B.; Pottage, J. C. J.; Fass, R. J.; Fife, K. H.; Powderly, W. G.; Collier, A. C.; Aspinall, R. L.; Smith, S. L.; Kowalski, K. G.; Wallemark, C.-B. *J. Acquir. Immune Defic. Syndr.* **1994**, *7* (2).

(148) Cook, C. S.; Karabatsos, P. J.; Schoenhard, G. L.; Karim, A. *Pharm. Res.* **1995**, *12* (8), 1158–1164.

(149) Murphy, P. V. *European J. Org. Chem.* **2007**, *2007* (25), 4177–4187.

(150) Chagnault, V.; Lalot, J.; Murphy, P. V. *ChemMedChem* **2008**, *3* (7), 1009.

(151) Barron, S.; Murphy, P. V. *Med. Chem. Commun.* **2014**, *5* (8), 1150–1158.

(152) Chery, F.; Cronin, L.; O'Brien, J. L.; Murphy, P. V. *Tetrahedron* **2004**, *60* (31), 6597–6608.

(153) Varrot, A.; Tarling, C. A.; Macdonald, J. M.; Stick, R. V; Zechel, D. L.; Withers, S. G.; Davies, G. J. *J. Am. Chem. Soc.* **2003**, *125* (25), 7496–7497.

(154) Murphy, P. V; Dunne, J. L. *Curr. Org. Synth.* **2006**, *3* (4), 403–437.

(155) Gouin, S. G.; Murphy, P. V. *J. Org. Chem.* **2005**, *70* (21), 8527–8532.

(156) Specker, E.; Böttcher, J.; Lilie, H.; Heine, A.; Schoop, A.; Müller, G.; Griebenow, N.; Klebe, G. *Angew. Chem. Int. Ed.* **2005**, *44* (20), 3140–3144.

(157) Schwank, G.; Koo, B.-K.; Sasselli, V.; Dekkers, J. F.; Heo, I.; Demircan, T.; Sasaki, N.; Boymans, S.; Cuppen, E.; van der Ent, C. K.; Nieuwenhuis, E. E. S.; Beekman, J. M.; Clevers, H. *Cell Stem Cell* **2017**, *13* (6), 653–658.

(158) Leonard, A.; Lebecque, P.; Dingemanse, J.; Leal, T. *J. Cyst. Fibros.* **2012**, *11* (3), 231–236.

(159) Norez, C.; Antigny, F.; Noel, S.; Vandebrouck, C.; Becq, F. *Am. J. Respir. Cell Mol. Biol.* **2009**, *41* (2), 217–225.

(160) Best, D.; Jenkinson, S. F.; Saville, A. W.; Alonzi, D. S.; Wormald, M. R.; Butters, T. D.; Norez, C.; Becq, F.; Blériot, Y.; Adachi, I.; Kato, A.; Fleet, G. W. J. *Tetrahedron Lett.* **2010**, *51* (32), 4170–4174.

(161) Compain, P.; Chagnault, V.; Martin, O. R. *Tetrahedron: Asymmetry* **2009**, *20* (6–8), 672–711.

(162) Smith, L. I. *Chem. Rev.* **1938**, *23* (2), 193–285.

(163) Huisgen, R. *Angew. Chem. Int. Ed. English* **1963**, *2* (10), 565–598.

(164) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41* (14), 2596–2599.

(165) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67* (9), 3057–3064.

(166) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130* (28), 8923–8930.

(167) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40* (11), 2004–2021.

(168) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem Int. Ed.* **2005**, *44* (33), 5188–5240.

(169) Wolff, H. In *Organic Reactions*; John Wiley & Sons, Inc, 2011; pp 307–336.

(170) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37* (3), 437–472.

(171) Shilvock, J. P.; Hsia, K. Y.; Nash, R. J.; Lloyd, J. D.; Winters, A. L.; Asano, N.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9* (23), 4157–4164.

(172) Carstensen, E. V; Duynstee, H. I.; van der Marel, G. A.; van Boom, J. H.; Nielsen, J.; Overkleeft, H. S.; Overhand, M. *J. Carbohydr. Chem.* **2003**, *22* (3–4), 241–252.

(173) Zhou, Y.; Murphy, P. V. *Org. Lett.* **2008**, *10* (17), 3777–3780.

(174) Kumar, I.; Mir, N. A.; Rode, C. V; Wakhloo, B. P. *Tetrahedron: Asymmetry* **2012**, *23* (3–4), 225–229.

(175) Arora, I.; Kashyap, V. K.; Singh, A. K.; Dasgupta, A.; Kumar, B.; Shaw, A. K. *Org. Biomol. Chem.* **2014**, *12* (35), 6855–6868.

(176) Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82* (22), 5956–5957.

(177) Trost, B. M.; Pulley, S. R. *Tetrahedron Lett.* **1995**, *36* (48), 8737–8740.

(178) Feldman, A. K.; Colasson, B.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127* (39), 13444–13445.

(179) Liu, R.; Gutierrez, O.; Tantillo, D. J.; Aubé, J. *J. Am. Chem. Soc.* **2012**, *134* (15), 6528–6531.

(180) Vekariya, R. H.; Liu, R.; Aubé, J. *Org. Lett.* **2014**, *16* (7), 1844–1847.

(181) Moynihan, L. Synthesis of Iminosugar C-Glycosides *via* Tandem Allylic Azide Rearrangement - Huisgen Cycloaddition, NUI Galway, 2013.

(182) Kato, A.; Kato, N.; Adachi, I.; Hollinshead, J.; Fleet, G. W. J.; Kuriyama, C.; Ikeda, K.; Asano, N.; Nash, R. J. *J. Nat. Prod.* **2007**, *70* (6), 993–997.

(183) Fleet, G. W. J.; Namgoong, S. K.; Barker, C.; Baines, S.; Jacob, G. S.; Winchester, B. *Tetrahedron Lett.* **1989**, *30* (33), 4439–4442.

(184) Moynihan, L.; Chadda, R.; McArdle, P.; Murphy, P. V. *Org. Lett.* **2015**, *17* (24), 6226–6229.

(185) Shilvock, J. P.; Wheatley, J. R.; Nash, R. J.; Watson, A. a.; Griffiths, R. C.; Butters, T. D.; Müller, M.; Watkin, D. J.; Winkler, D. a.; Fleet, G. W. J. *J. Chem. Soc. Perkin Trans. 1* **1999**, 2735–2745.

(186) Garegg, P. J. *Pure Appl. Chem.* **1984**, *56* (7), 845–858.

(187) Garegg, P. J.; Johansson, R.; Ortega, C.; Samuelsson, B. *J. Chem. Soc. Perkin Trans. 1* **1982**, No. 0, 681–683.

(188) Garegg, P. J.; Regberg, T.; Stawinski, J.; Stromberg, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, No. 3, 271–274.

(189) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62* (7), 2400–2410.

(190) Skaanderup, P., Hyldtoft, L. & Madsen, R. *Monatshefte fuer Chemie* **2002**, *133* (4), 467–472.

(191) Skaanderup, P. R.; Poulsen, C. S.; Hyldtoft, L.; Jørgensen, M. R.; Madsen, R. *Synthesis (Stuttg).* **2002**, *12* (12), 1437–210.

(192) Card, P. J.; Hitz, W. D. *J. Org. Chem.* **1985**, *50* (6), 891–893.

(193) García-Moreno, M. I.; Aguilar, M.; Ortiz Mellet, C.; García Fernández, J. M. *Org. Lett.* **2006**, *8* (2), 297–299.

(194) Ayers, B. J.; Ngo, N.; Jenkinson, S. F.; Martínez, R. F.; Shimada, Y.; Adachi, I.; Weymouth-Wilson, A. C.; Kato, A.; Fleet, G. W. J. *J. Org. Chem.* **2012**, *77* (18), 7777–7792.

(195) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13* (7), 1594–1597.

(196) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9* (4), 723–726.

(197) Wang, Y.; Liang, Y.; Jiao, L.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2006**, *71* (18), 6983–6990.

(198) Kadaba, P. K.; Stevenson, P. J.; P-Nnane, I.; Damani, L. A. *Bioorganic Med. Chem.* **1996**, *4* (2), 165–178.

(199) Chadda, R.; McArdle, P.; Murphy, P. V. *Synthesis (Stuttg).* No. EFirst.

(200) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(201) Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4* (7), 1195–1201.

(202) Barrows, S. E.; Eberlein, T. H. *J. Chem. Educ.* **2005**, *82* (9), 1334–1339.

(203) Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* **1999**, *40* (49), 8575–8578.

(204) Waldvogel, S. R. *Synthesis (Stuttg).* **2010**, *2010* (5), 892–892.

(205) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103* (18), 5568–5570.

(206) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, No. 5, 151–152.

(207) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis (Stuttg).* **1994**, 639–666.

(208) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25* (21), 2183–2186.

(209) Etayo, P.; Badorrey, R.; Díaz-de-Villegas, M. D.; Gálvez, J. a. *Chem. Commun.* **2006**, No. 32, 3420–3422.

(210) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199–222.

(211) Eliel, E. L., Wilen, S. H., Doyle, M. P. *Basic Organic Stereochemistry*; Wiley, 2001.

(212) Bollenback, G. N.; Long, J. W.; Benjamin, D. G.; Lindquist, J. A. *J. Am. Chem. Soc.* **1955**, *77* (12), 3310–3315.

(213) Tietze, L. F.; Seele, R. *Carbohydr. Res.* **1986**, *148* (2), 349–352.

(214) Tosin, M.; Gouin, S. G.; Murphy, P. V. *Org. Lett.* **2005**, *7* (2), 211–214.

(215) Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69* (11), 3993–3996.

(216) Zoidl, M.; Santana, A. G.; Torvisco, A.; Tysoe, C.; Siriwardena, A.; Withers, S. G.; Wrodnigg, T. M. *Carbohydr. Res.* **2016**, *429*, 62–70.

Appendix

Appendices