APPROACHES TO THE SYNTHESIS OF SELECTED NITROGENOUS HETEROCYCLES

by

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CHAPTER 6

EXPERIMENTAL

ABBREVIATIONS

Ac	Acetyl
BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BSA	*bis*-(Trimethylsilyl)acetamide
Bz	Benzoyl
Bzd	Benzhydrylamine
dba	Dibenzylidene acetone
DDQ	2,3-Dichloro-5,6-dicyanoquinone
DEAD	Diethyl azodicarboxylate
DHAP	Dihydroxyacetone phosphate
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMG	Directing metalation group
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone
DMSO	Dimethylsulfoxide
DoM	Directed *ortho* metalation
Et	Ethyl
FAB	Fast atom bombardment
fur	Furyl
HMDS	Hexamethyldisilizane
LDA	Lithium diisopropylamide
MCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MOM	Methoxymethyl
Ms	Mesyl
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
nOe	Nuclear Overhauser effect
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PTSA	*para*-Toluenesulfonic acid
RAMA	Rabbit muscle aldolase

TBAF	*Tetra*-Butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBS	Tributylsilyl
t-Bu	*tert*-Butyl
Tf	Triflate
TFA	Trifluoroacetic acid
Tfa	Trifluoroacetyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	N,N,N',N'-Tetramethylethylene diamine
TPAP	Tetrapropylammonium perruthenate
TPHB	Triphenylphosphine hydrobromide
TPS	Triisopropylsilyl
Tr	Trityl
Ts	*para*-Toluenesulfonyl

SYNOPSIS

The first part of the research described in this thesis involves the development of a new methodology for the synthesis of *N*-hydroxy pyrrolidines, starting from carbohydrates as building blocks. The products were identified as possible synthons for the stereocontrolled synthesis of isosteric analogues of polyhydroxylated indolizidine alkaloids. The consecutive reduction and cyclisation of selectively protected 5-*O*-mesyl hexose *O*-(*tert*-butyldiphenylsilyl) oximes to afford chiral *N*-hydroxy pyrrolidines is discussed. The mechanism involves a cascade of neighbouring group participation steps by the *O*-benzoyl protecting groups. This protocol gave rise to novel chiral *N*-hydroxy pyrrolidines in good overall yield. The choice of leaving group as well as a labile oxime protecting group proved to be of great import in the outcome of the cyclisation reactions.

The second part of the research concerns the ongoing development in our laboratories of the synthesis of analogues of biologically active compounds. In this regard, we were interested in synthesising the aza analogues of β-*C*-nucleosides and β-*C*-glycosides. Our strategy involves the synthesis of a D-ribose derived chiral cyclic nitrone as the key synthon. A facile route towards cyclic nitrones was developed starting from suitably protected hemiacetals of D-ribofuranose. Readily available tri-*O*-benzyl-D-ribofuranose was allowed to react with hydroxylamine hydrochloride to afford an acyclic oxime. Selective silylation followed by iodonation at C-5 (with inversion of configuration) furnished the cyclisation precursor. Anhydrous TBAF-mediated desilylation and subsequent intramolecular nucleophilic attack afforded a cyclic nitrone in excellent yield. Following the same protocol, 2,3-isopropylidene-5-*O*-trityl-D-ribofuranose was converted into the corresponding nitrone.

The 1,3-dipolar cycloaddition reaction of a nitrone to an alkene is an extremely powerful synthetic method for the creation of complex heterocyclic structures. The reaction of the D-ribose derived nitrones with α,β-unsaturated carbonyl compounds furnished the corresponding cycloadducts in good diastereomeric excess. The *exo*-product was isolated as the major isomer in each case. The reaction of a variety of carbon nucleophiles, including a Grignard reagent, with the nitrones led to the formation of interesting β-*C*-glycoside analogues. One of the carbohydrate nitrones was also converted into its thymine *C*-nucleoside analogue. This work clearly shows that the construction of chiral cyclic nitrones from D-ribose derivatives is an extremely efficient and simple procedure.

The final part of the work described in this thesis involve the construction of CD-ring analogues of the natural metabolite, streptonigrin. The use of metalation and palladium

catalysed cross-coupling reactions were investigated for the synthesis of highly functionalised biaryls. The synthesis and crystal structure determination of [3-(tert-butoxycarbonylamino)-4-pyridyl]-trimethyltin(IV) is discussed. The Stille cross-coupling reaction between an electron rich arylstannane and an electron poor aryl halide proved to be the most successful. The use of co-catalytic copper(I) had a dramatic effect on the overall yield and rate of this Stille cross-coupling reaction. This methodology would , in principle, allow the construction of the natural product and appropriate structural analogues.

SAMEVATTING

Die eerste deel van die navorsing wat in hierdie tesis bespreek word, behels die ontwikkeling van 'n nuwe metodologie vir die sintese van *N*-hidroksi pirrolidiene deur van koolhidrate as uitgangstowwe gebruik te maak. Hierdie produkte is geidentifiseer as moontlike sintons vir die stereogekontroleerde sintese van isosteriese analoë van poligehidroksileerde indolisidien alkaloïede. Die agteropeenvolgende reduksie en siklisering van selektief beskermde 5-O-mesiel heksose *O*-(tert-butieldifenielsiliel) oksieme na chirale *N*-hidroksi pirrolidiene word bespreek. Die meganisme behels 'n kaskade van buurgroep deelnames deur die *O*-bensoaat beskermings groepe. Hierdie protokol het aanleiding gegee tot unieke chirale *N*-hidroksi pirrolidiene in 'n hoë algehele opbrengs. Die keuse van 'n verlatende groep sowel as 'n labiele oksiem beskermings groep was van deurslaggewende belang in die siklisering reaksies.

Die tweede deel van die navorsing handel oor die aaneenlopende ontwikkeling van analoë van biologies aktiewe verbindings in ons laboratorium. In die lig hiervan was ons geïntereseerd in die sintese van aza analoë van ß-*C*-nukleosiede en ß-*C*-glikosiede. Ons strategie behels die sintese van 'n D-ribose afgeleide chirale sikliese nitroon as die sleutel sinton. 'n Effektiewe roete vir sikliese nitrone is ontwikkel deur van geskikte beskermde hemiasetale van D-ribofuranose gebruik te maak. Geredelik beskikbare tri-*O*-bensiel-D-ribofuranose is gereageer met hidroksielamienhidrochloried om 'n asikliese oksiem te lewer. Selektiewe sililering gevolg deur jodering op C-5 (met inversie van konfigurasie) het die siklisering svoorganger gelewer. Desililering met behulp van anhidriese TBAF gevolg deur intramolekulêre nukleofiliese aanval het die sikliese nitroon in hoë opbrengs gelewer. Deur dieselfde metode te volg is 2,3-isopropilideen-5-*O*-tritiel-D-ribofuranose omgeskakel na die ooreenkomstige nitroon.

Die 1,3-dipolêre sikloaddisie reaksie van 'n nitroon met 'n alkeen is 'n kragtige metode vir die sintese van komplekse heterosikliese verbindings. Die reaksie van die D-ribose afgeleide nitrone met α,ß-onversadigde karbonielverbindings het die ooreenkomstige sikloaddukte in goeie diastereomeriese oormaat gelewer. Die *ekso*-produk is in elke geval as die hoofproduk geïsoleer. Die reaksie van die nitrone met 'n verskeidenheid koolstof nukleofiele, insluitend 'n Grignard reagens, het interressante ß-*C*-glikosiedanaloë tot gevolg gehad. Een van die koolhidraatnitrone is ook omgeskakel na sy timien *C*-nukleosied. Hierdie werk toon duidelik dat die konstruksie van chirale sikliese nitrone vanaf D-ribose derivate 'n baie eenvoudige en effektiewe proses is.

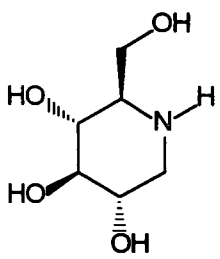
Die laaste deel van die navorsing in die tesis behels die sintese van CD-ring analoë van die natuurlike metaboliet, streptonigrin. Die gebruik van metallering en palladiumgekataliseerde kruiskoppellingsreaksies is ondersoek vir die sintese van hoogs gefunksionaliseerde biariele. Die sintese en kristalstruktuur bepaling van [3-(*tert*-butoksikarbonielamino)-4-piridiel]-arieltin(IV) word bespreek. Die Stille-kruiskoppellingsreaksie tussen 'n elektronryk arieltinverbinding en 'n elektronarm arielhalied was die meeste suksesvol. Die gebruik van ko-katalitiese koper(I) het 'n dramatiese invloed op die opbrengs van die Stille-kruiskoppelling getoon. Hierdie metodologie, kan in prinsiep gebruik word vir die konstruksie van die natuurproduk en geskikte struktuuranaloë. Die sintese- en kristalstruktuurbepaling van [3-(*tert*-butoksikarbonielamino)-4-piridiel]-arieltin(IV) word ook bespreek.

CHAPTER 1

STRATEGIES TOWARDS THE SYNTHESIS OF CHIRAL PIPERIDINE, PYRROLIDINE AND INDOLIZIDINE RING SYSTEMS: A LITERATURE SURVEY

1.1. INTRODUCTION

Polyhydroxylated piperidines and pyrrolidines constitute a class of compounds known as azasugars.[1] These compounds have received considerable attention in recent years as many have proved to be effective glycosidase inhibitors.[2] Glycosyltransferases and glycosidases modify the glycoconjugates of proteins and lipids, and are essential for normal cell growth, metabolism and development.[3] Azasugars have been succesfully employed in the treatment of several diseases, including cancer[4] and AIDS,[5] the development of which depends on specific glycosidase enzymes. As a general rule the azasugar and the parent monosaccharide should be structurally similar in order to effect inhibition of the corresponding glycosidase. Thus, the naturally occuring piperidines (+)-deoxynojirimycin (**1.1**),[6] the aza-analogue of D-glucose, and (+)-deoxymannojirimycin (**1.2**),[7] the aza-analogue of D-mannose, are specific inhibitors of glucosidases and mannosidases, respectively. A number of pyrrolidines are also known to display powerful glycosidase activity. Examples include 1,4-dideoxy-1,4-imino-D-mannitol (**1.3**),[8] which is a powerful mannosidase inhibitor, and 1,4-dideoxy-1,4-imino-D-lyxitol (**1.4**),[2b] which is an α-galactosidase inhibitor.



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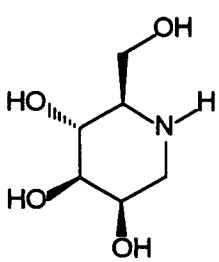

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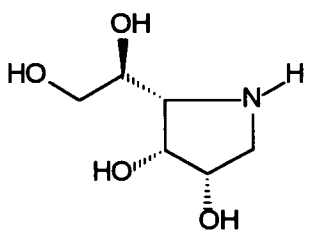

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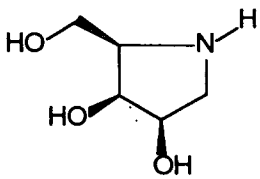
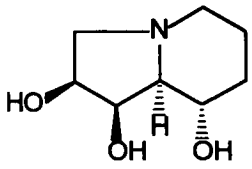


1.4

Highly substituted pyrrolidine alkaloids containing hydroxy groups, such as swainsonine **1.5**,[9] anisomycin **1.6**[10] and codonopsinine **1.7**,[11] have also been shown to display specific antiviral and anticancer activity. These compounds have been the subject of extensive synthetic efforts that have culminated in numerous syntheses of both racemic and enantiomerically pure products.



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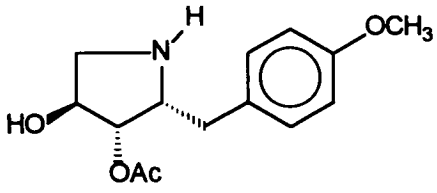

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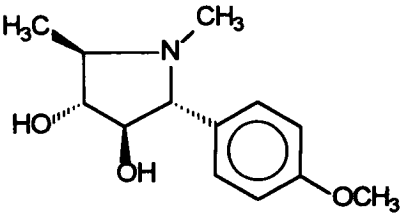


1.7

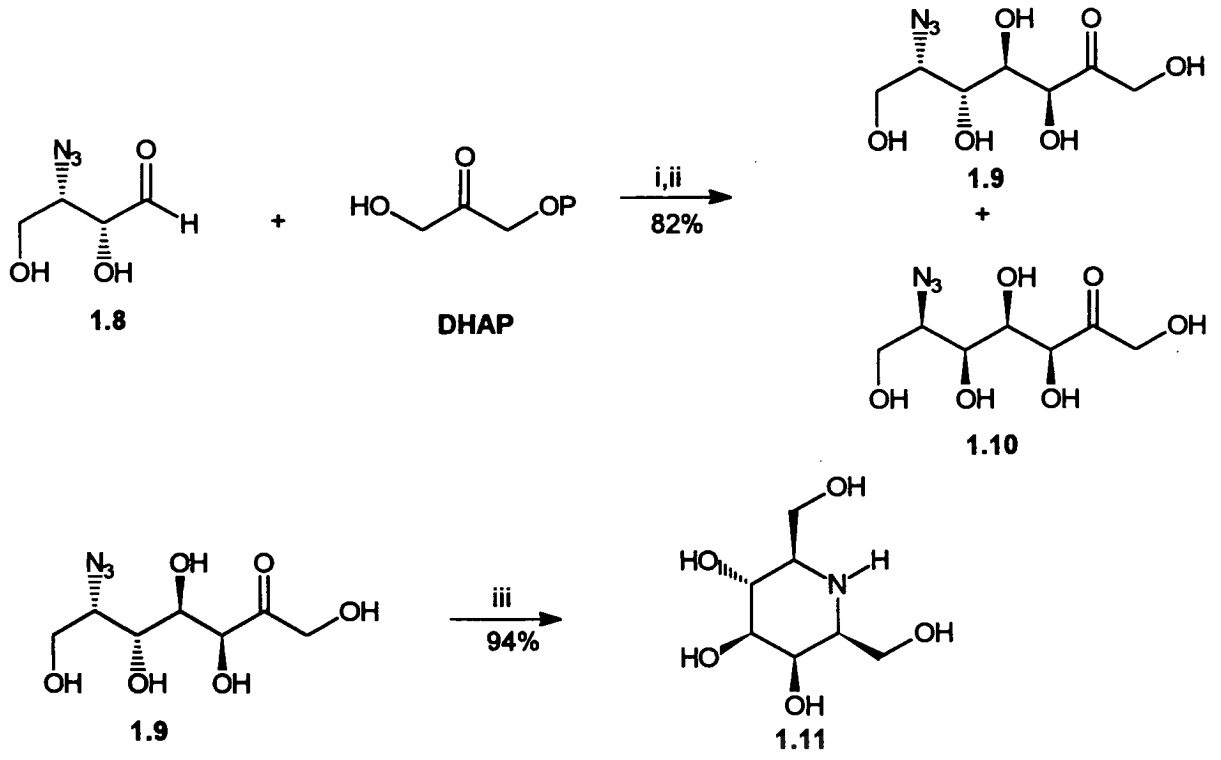
In the following sections, several of the general approaches to these piperidine and pyrrolidine ring systems will be discussed.

1.2. THE STEREOSELECTIVE CONSTRUCTION OF AZASUGARS BY ALDOLASE-CATALYZED CONDENSATION OF DIHYDROXYACETONE PHOSPHATE WITH AN AZIDOALDEHYDE

Since the first synthesis of azasugars based on fructose-1,6-diphosphate (FDP) aldolase,[12,13] the enzymatic aldol reactions of dihydroxyacetone phosphate (DHAP) with azido aldehydes followed by catalytic reductive amination has become a general and effective route to a variety of azasugars.[14,15,16] The six DHAP dependent aldolases isolated so far have shown a high degree of enantio- and diastereoselectivity in the reversible aldol reaction.[17] Systematic studies of carbon-carbon coupling reactions catalysed by aldolases showed that virtually no structural variation of the C-nucleophile (DHAP) is tolerated. However, the naturally occuring C-electrophile, D-glyceraldehyde-3-phosphate, may be replaced by a variety of substrates.[18,19]

Homoazasugars are structurally similar to other azasugars but contain an extra hydroxymethylene substituent at C-1.[20,21] A chemoenzymatic approach for the synthesis of homoazasugars was described by Wong *et al.*[22] FDP aldolase-catalysed aldol addition[23] of DHAP to racemic azidoaldehyde **1.8** (synthesised in 7 steps from the readily avilable (*Z*)-2-butene-1,4-diol) afforded the diastereomeric azidosugars **1.9** and **1.10** in a 3.5:1 ratio (Scheme 1.1). The major isomer was converted into β-D-homomannonojirimycin (**1.11**) *via* reduction of the azide group and stereoselective intramolecular reductive amination in one pot.

This synthesis has successfully demonstrated the viability of the chemoenzymatic approach. By choosing alternative four-carbon azidoaldehydes it should be possible to synthesise homoazasugar analogues by the same route.

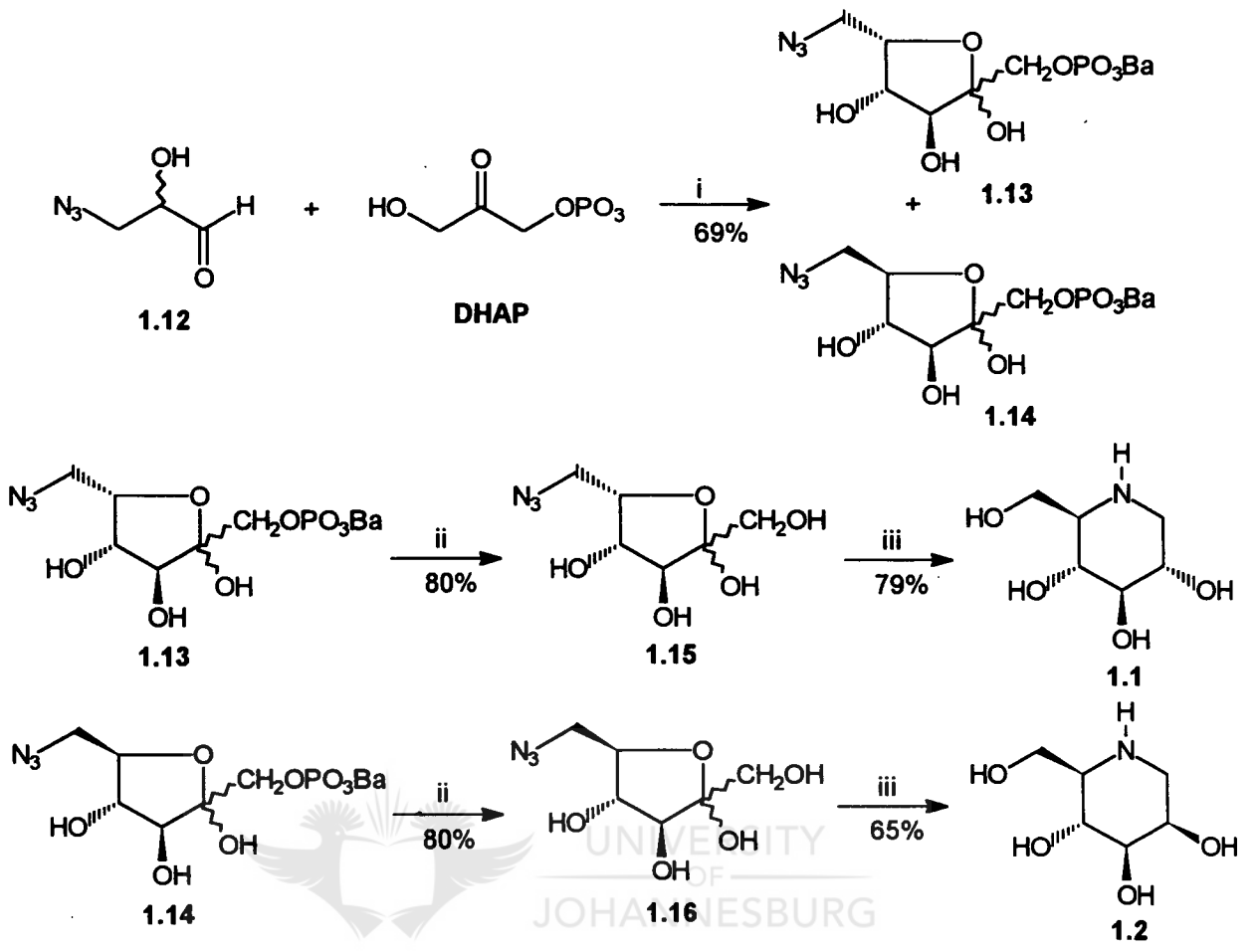


REAGENTS: i) RAMA / pH 6.7 / 25°C / 25 h ii) Acid phosphatase / pH4.5 / 48h / 37°C
iii) H_2 (50 psi) / 5% Pd-C / MeOH:H_2O (1:1) / 22h

Scheme 1.1

Straub and co-workers[24] found that rabbit muscle aldolase[25] (RAMA) catalysed the stereoselective aldol addition of DHAP to 3-azido-2-hydroxypropanal (**1.12**).[14] The resulting diastereoisomeric 6-azido-6-deoxy-D-fructose- and L-sorbose-1-phosphates, **1.13** and **1.14** respectively, were precipitated as a mixture of their barium salts, and subsequently hydrolysed with acid phosphatase (Scheme 1.2). After separation by anion-exchange chromatography, reductive amination of 6-azido-6-deoxy-D-fructose (**1.15**) and 6-azido-6-deoxy-L-sorbose (**1.16**) afforded 1-deoxynojirimycin (**1.1**) and 1-deoxymannojirimycin (**1.2**) respectively, with high diastereoselectivity.

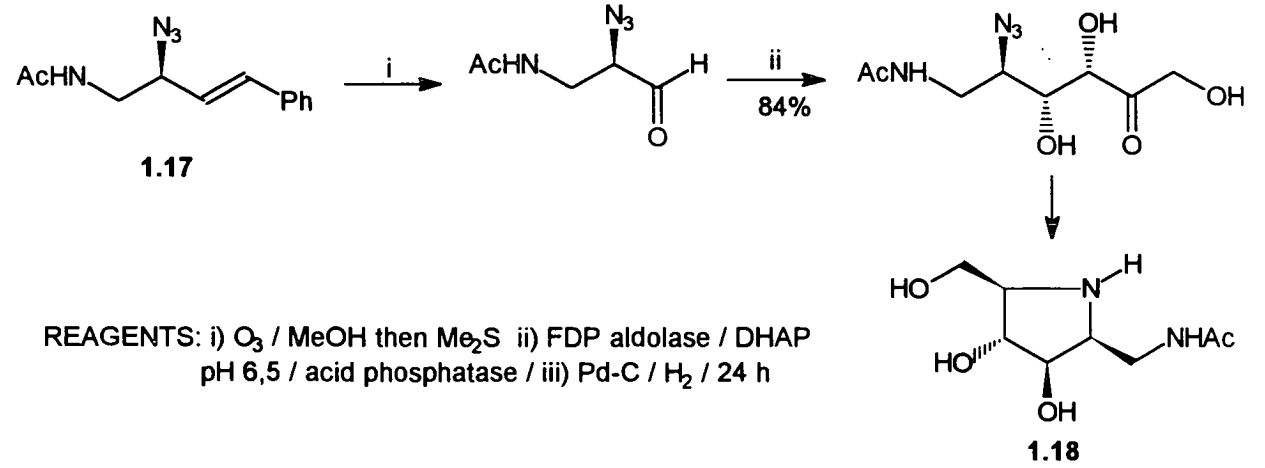
With the choice of appropriate chiral acetamidoaldehydes as acceptors, two new acetamido azasugars have been synthesised by Wong *et al.*[26] The required 2-azido-3-acetamidopropanals were prepared by ozonolysis of enantiomerically pure (R)- (**1.17**) and (S)-*N*-(4-phenyl-2-azido-3-butenyl)acetamide (**1.19**).



REAGENTS: i) a: RAMA / pH 6.5 / 25°C b: $BaCl_2$ ii) a: DOWEX 50W x $8H^+$ b: acid phosphatase (EC 3.1.3,2) c: DOWEX 1 x $8HCO_2^-$ iii) Pt-C / H_2 / H_2O / 25°C

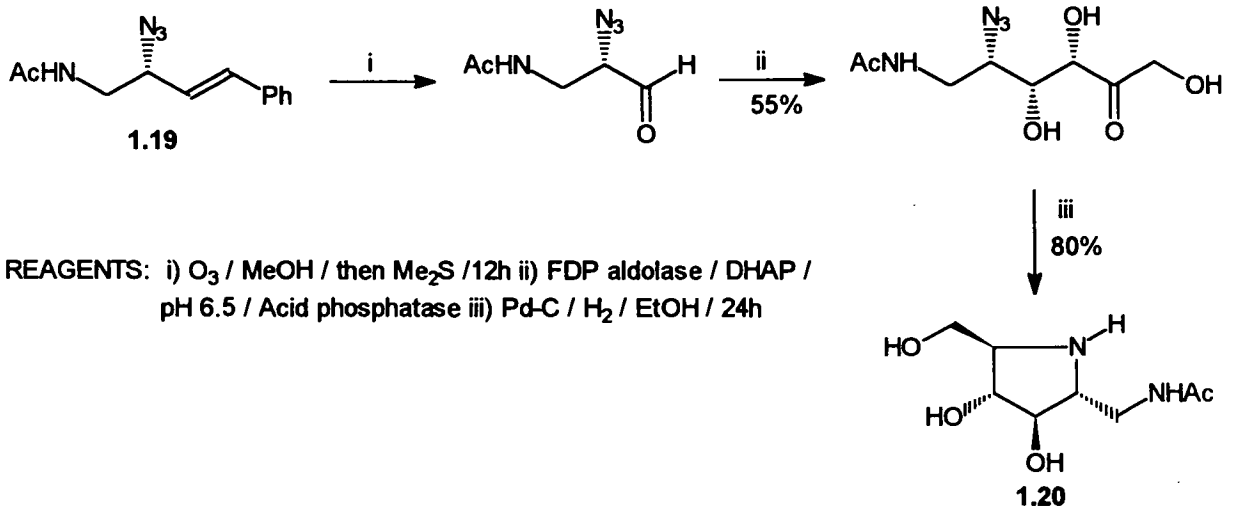
Scheme 1.2

The FDP-aldolase catalysed reaction of the aldehydes with DHAP proceeded smoothly and with high diastereoselectivity (Scheme 1.3).



REAGENTS: i) O_3 / MeOH then Me_2S ii) FDP aldolase / DHAP pH 6,5 / acid phosphatase / iii) Pd-C / H_2 / 24 h

Scheme 1.3



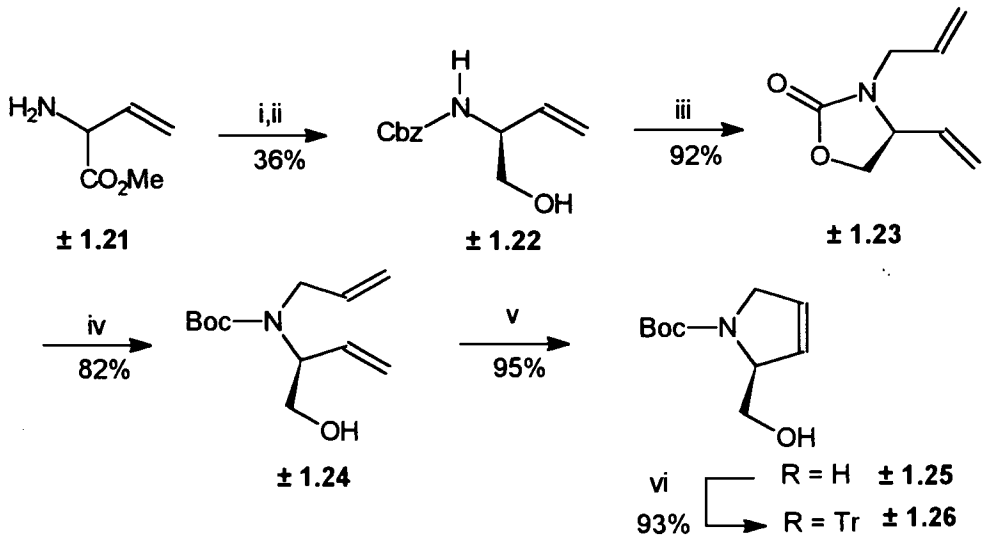
REAGENTS: i) O_3 / MeOH / then Me_2S /12h ii) FDP aldolase / DHAP / pH 6.5 / Acid phosphatase iii) Pd-C / H_2 / EtOH / 24h

Scheme 1.3 cont.

Subsequent dephosphorylation by acid phosphatase, followed by hydrogenation of the products over palladium, afforded the five-membered acetamido azasugars **1.18** and **1.20**.

1.3. SOME APPROACHES TO AZASUGARS FROM NON-CARBOHYDRATE BUILDING BLOCKS

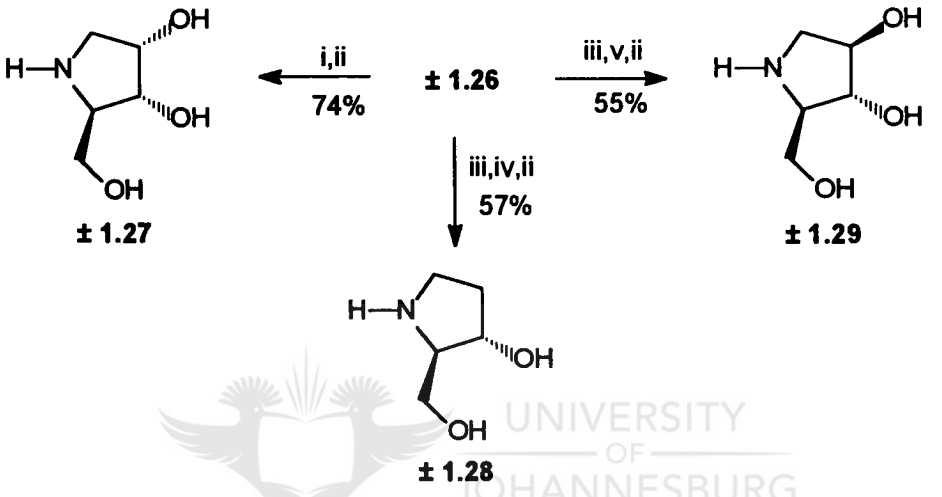
Blechert and Huwe[27] reported a novel strategy for the synthesis of enantiopure polyhydroxylated pyrrolidines starting from vinyl glycine methyl ester (**1.21**).[28] Chemoselective reduction of the ester moiety of racemic *N*-Cbz-vinylglycinol with lithium borohydride/methanol[29] afforded the amino alcohol carbamate **1.22** (Scheme 1.4).



REAGENTS: i) CbzCl / $NaHCO_3$ / CH_2Cl_2-H_2O / 30 min ii) $LiBH_4$ / CH_3OH-Et_2O / iii) NaH DME / 24h then allyl bromide / 24h iv) a: NaOH / H_2O-EtOH / 80°C b: Boc_2O Et_3N v) 4 mol% $Cl_2(PCy_3)_2Ru{=}CHCH{=}CPh_2$ vi) TrCl / Et_3N / DMAP / r.t.

Scheme 1.4

Conversion of **1.22** into *N*-allyl-4-vinyl-oxazolidin-2-one (**1.23**) was achieved in one pot by treatment with sodium hydride and then an excess of allyl bromide. Protection of the resulting amine afforded **1.24**. Olefin metathesis[30] of **1.24** with 4 mol% $Cl_2(PCy_3)_2Ru{=}CH{-}CH{=}CPh_2$ [31] in benzene afforded the *N*-Boc-2-hydroxymethyl-2,5-dihydropyrrole (**1.25**) in a yield of 95%. Protection of the primary hydroxy group was followed by stereocontrolled functionalisation of the newly formed double bond. Completion of the synthetic sequence to the azasugars **1.27**, **1.28** and **1.29** involved standard functional group transformations (Scheme 1.5).

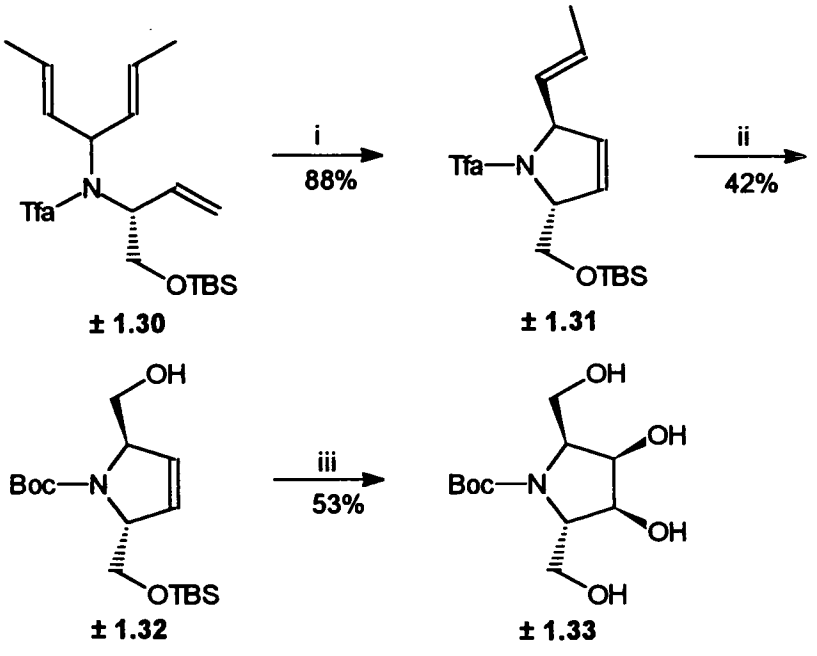


REAGENTS: i) OsO_4 / Me_3NO / pyridine-^{t}BuOH-H_2O ii) HCl / CH_3OH / AcOMe iii) *m*CPBA / Et_2O iv) $LiBH_4$ / CH_3OH / diglyme / 150°C v) KOH / H_2O / DMSO / 95°C

Scheme 1.5

This strategy was extended to the synthesis of a homoazasugar (Scheme 1.6). The metathesis precursor **1.30** was prepared in 8 steps from vinyl glycine methyl ester (**1.21**). Diastereoselective ring closing olefin metathesis with 10 mol% $Cl_2(PCy_3)_2Ru{=}CHPh$[32] in benzene afforded the unsaturated 2,5-disubstituted pyrrolidine (**1.31**). Regioselective ozonolysis of **1.31** and subsequent reductive workup with lithium aluminium hydride furnished the protected diol **1.32**. Standard functionalisation methods afforded the homoazasugar **1.33**. This synthesis may prove to be versatile as other functionalities can be introduced at the formed double bonds.[33]

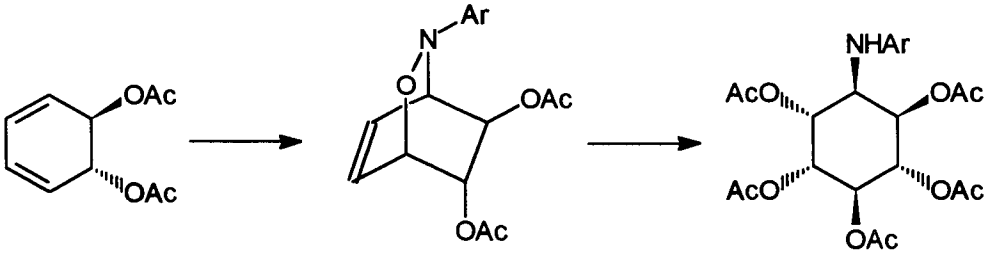
Another approach to azasugars involves the stereoselective functionalisation of conjugated dienes by means of Diels-Alder cycloaddition reactions with nitroso compounds which was first investigated by Belleau and Au-Young.[34] This was further developed by Kresze and co-workers[35]



REAGENTS: i) 10 mol % $Cl_2(PCy_3)_2Ru=CHPh$ / C_6H_6 / 2d ii) a: O_3 b: $LiAlH_4$ / THF c: Boc_2O / DMAP iii) a: OsO_4 / Me_3NO / pyridine / t-BuOH-H_2O b: HCl / CH_3OH / r.t. / 30 min

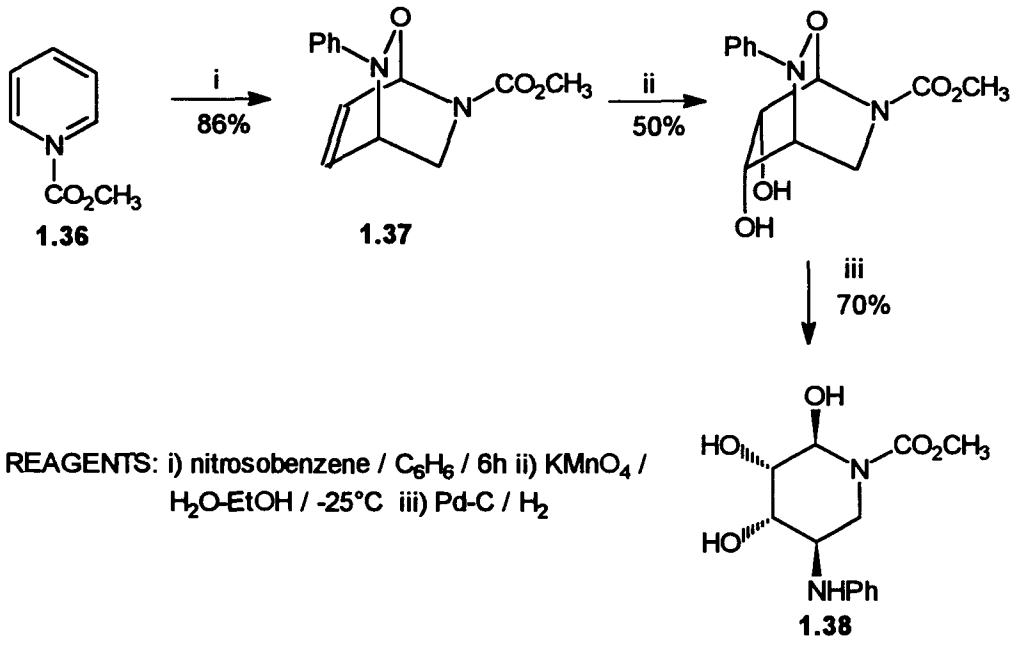
Scheme 1.6

for the synthesis of the inosamine derivative **1.35**, starting from *trans*-5,6-diacetoxy-1,3-cyclohexadiene **1.34** (Scheme 1.7).



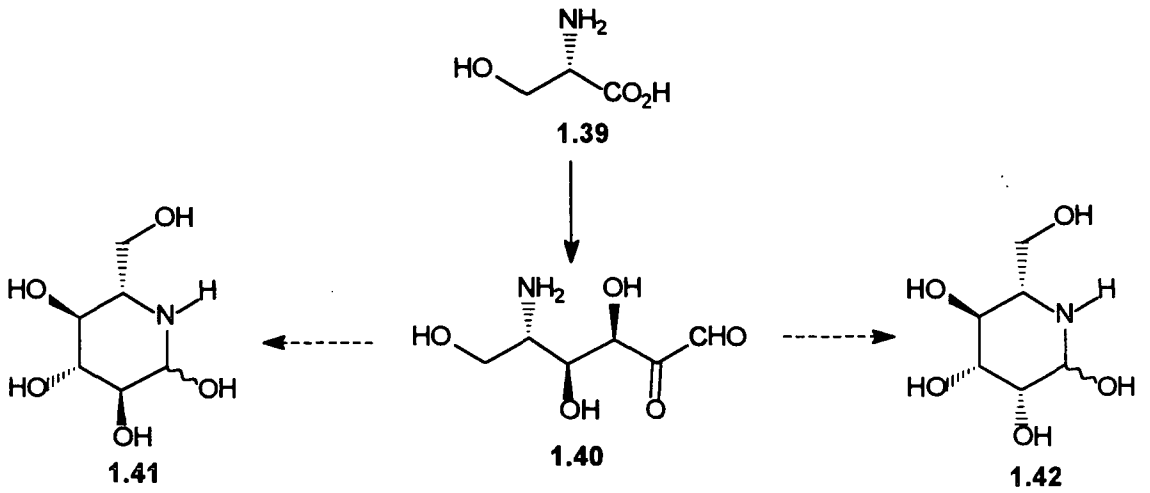
Scheme 1.7

This synthetic sequence was adapted by Streith *et al.*,[36] who employed a heterocyclic conjugated diene in the synthesis of azasugar **1.38**. The cycloaddition reaction of *N*-carbomethoxy-1,2-dihydropyridine (**1.36**)[37] with nitrosobenzene provided the bicyclic adduct **1.37** (Scheme 1.8). Consecutive *cis*-hydroxylation of **1.37** with $KMnO_4$[38] in neutral water-ethanol solution and catalytic hydrogenolysis of the endocyclic *N*-*O* bond over Pd/C afforded the monocyclic aminoazasugar **1.38** in a yield of 70%.



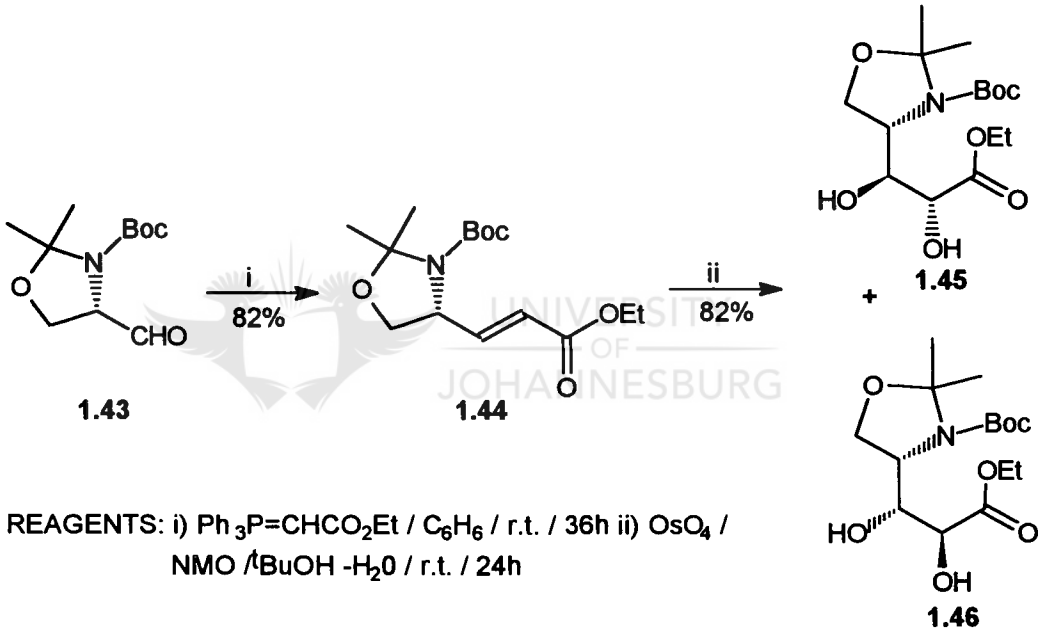
Scheme 1.9

Dondoni *et al.*[39] employed a novel and straightforward route for the stereocontrolled total synthesis of (-)-nojirimycin (**1.41**)[40] and (-)-mannojirimycin (**1.45**)[41] from the α-amino acid L-serine (**1.42**). The use of natural amino acids as starting materials was previously exploited by the same author in the synthesis of nojirimycin analogues[42] as well as the galactosidase inhibitor galactonojirimycin.[43] The α-keto aldehyde (**1.40**) was identified as a common key intermediate, which should lead to either **1.41** or **1.42** by stereocontrolled ketone reduction (Scheme 1.10).



Scheme 1.10

The synthetic equivalence of 2-substituted thiazoles to aldehydes is well documented.[44] Synthesis of a thiazole masked and protected equivalent (**1.47**) was achieved in 3 steps from the L-serinal[45] derivative **1.43**. Wittig olefination of **1.43** with ethyl (triphenylphosphoranylidene) acetate afforded the *E*-alkene **1.44** as a single isomer. Osmium tetroxide catalysed *cis*-dihydroxylation of the enoate employing *N*-methylmorpholine *N*-oxide as a reoxidant provided a 3:1 mixture of diols *anti*-(**1.45**) and *syn*- (**1.46**). The diol of the major isomer *anti* -**1.45** was protected as the acetonide derivative and reacted with 2-lithiothiazole to generate the desired 2-thiazolyl ketone intermediate **1.47**.[46] The stereocontrolled reduction of the carbonyl group to a single diastereomer of the analogous alcohol was achieved by treatment of **1.47** with sodium borohydride/methanol, to afford the desired *S*-configuration[47] at C-2 required for the synthesis of (-)-nojirimycin (**1.41**).

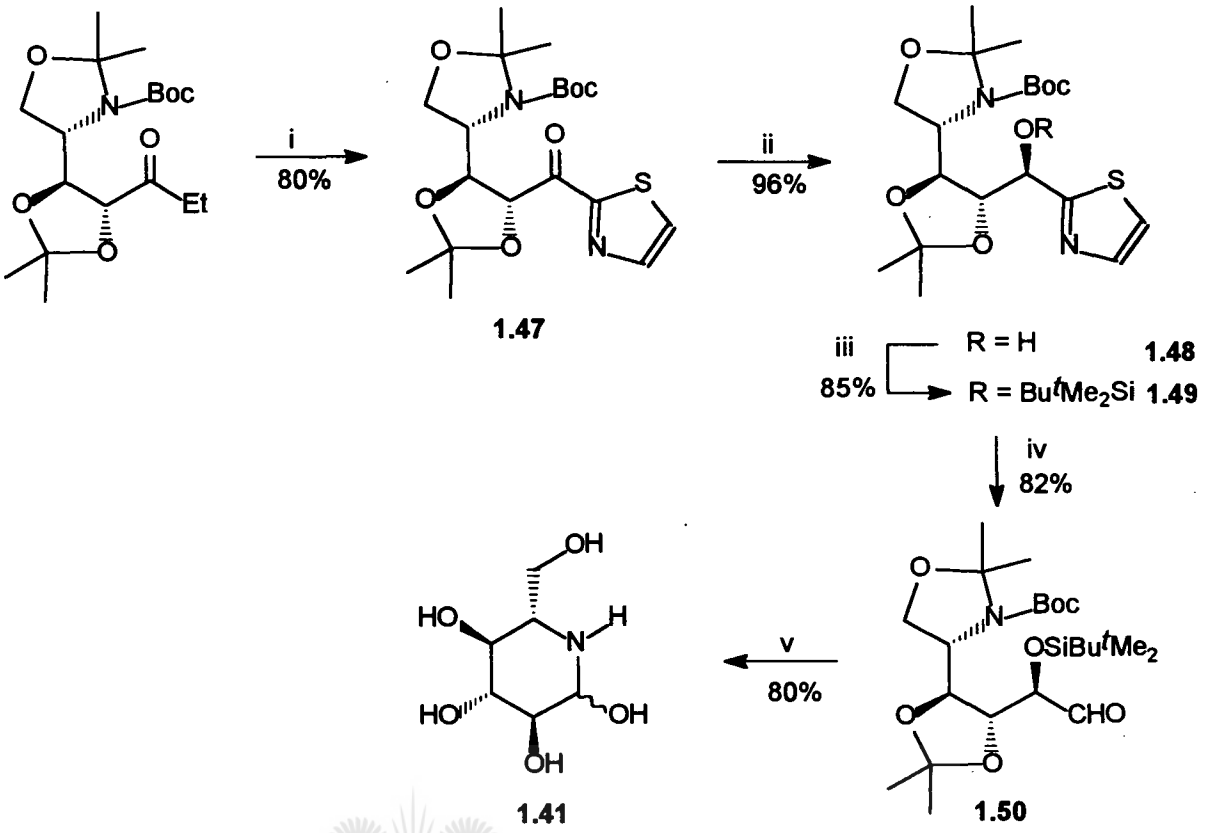


REAGENTS: i) $Ph_3P=CHCO_2Et$ / C_6H_6 / r.t. / 36h ii) OsO_4 / NMO /^{t}BuOH -H_20 / r.t. / 24h

Scheme 1.10

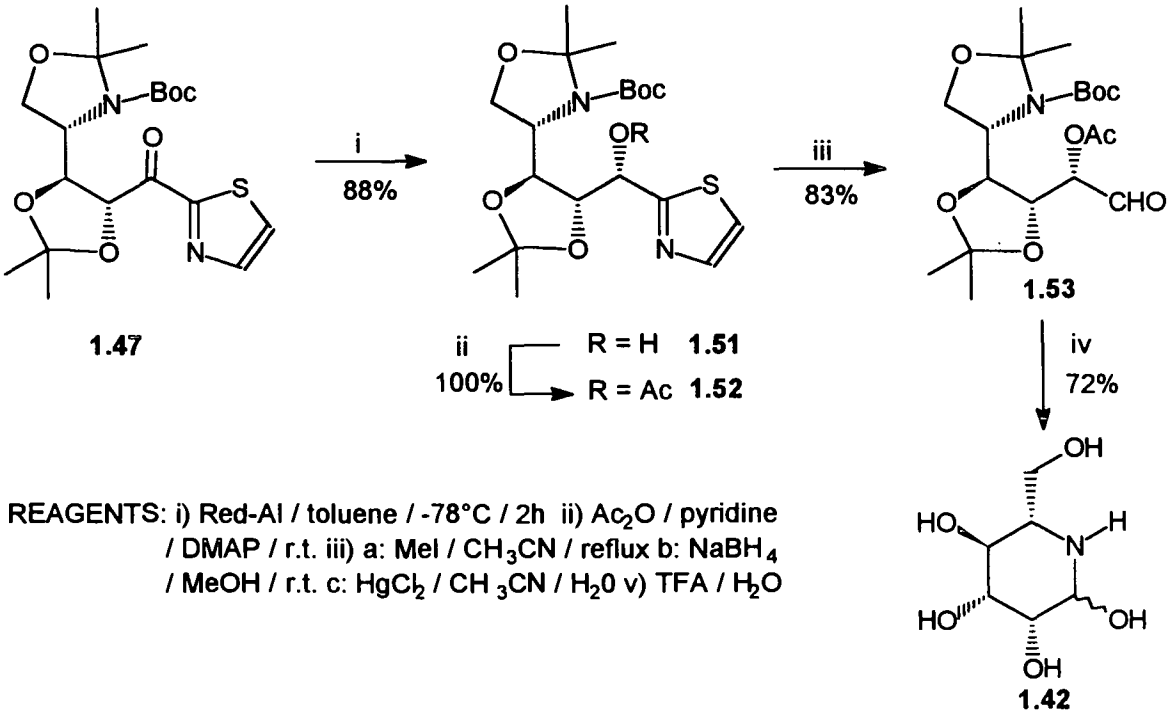
The one-pot thiazolyl-to-formyl unmasking protocol[45] (*N*-methylation, reduction and hydrolysis) was performed on the silyl-protected **1.49** to afford the aldehyde **1.50**, which upon treatment with trifluoroacetic acid-water furnished **1.41** (Scheme 1.11).

Stereoselective reduction of the carbonyl group to the *R*-alcohol **1.51** required for the synthesis of (-)-mannojirimycin (**1.42**) was achieved using Red-Al [$NaAlH_2$-(OCH_2CH_2OMe)].[48] The acetylated derivative **1.52** was subjected to the usual formyl deblocking protocol to afford the chiral aldehyde **1.53** in good yield, and the removal of all protecting groups and subsequent cyclisation with trifluoroacetic acid-water furnished the final product **1.42** (Scheme 1.12).



REAGENTS: i) 2-lithiothiazole / -45°C / 6h ii) $NaBH_4$ / MeOH / -60°C / 1h iii) ^{t}BuMe$_2$SiCl / imidazole / DMF / 80°C / 12h iv) a: MeI / CH_3CN / reflux b: $NaBH_4$ / MeOH / r.t. / 30 min. c: $HgCl_2$ / CH_3CN / H_2O / r.t. / 15 min. v) TFA / H_2O

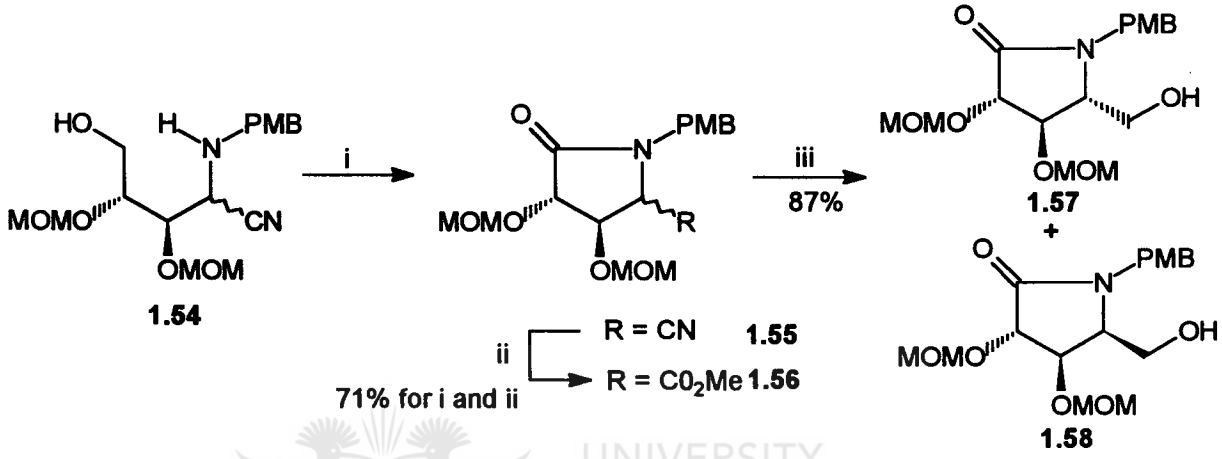
Scheme 1.11



REAGENTS: i) Red-Al / toluene / -78°C / 2h ii) Ac_2O / pyridine / DMAP / r.t. iii) a: MeI / CH_3CN / reflux b: $NaBH_4$ / MeOH / r.t. c: $HgCl_2$ / CH_3CN / H_2O v) TFA / H_2O

Scheme 1.12

Nectrisine (**1.62**),[49] a potent glycosidase inhibitor, was synthesized from D-(-)-diethyl tartrate using novel lactam intermediates (Scheme 1.13).[50] The key amino alcohol **1.54** (available in 6 steps from D-(-)-diethyl tartrate) was oxidized with tetra-*n*-propylammonium perruthenate (TPAP)[51] and *N*-methylmorpholine-*N*-oxide (NMO) to furnish the lactam **1.55**. Esterification of **1.55** with sodium methoxide in methanol afforded the methyl ester **1.56** which ,without purification, was reduced to the corresponding alcohol as a chromatographically separable mixture of diastereomers (**1.57** and **1.58** in a ratio of 56:44).



REAGENTS: i) TPAP / NMO / MS4A / CH_2Cl_2 ii) NaOMe-MeOH / 0°C to r.t / 1N HCl
iii) $LiBH_4$ / THF / 0°C to r.t.

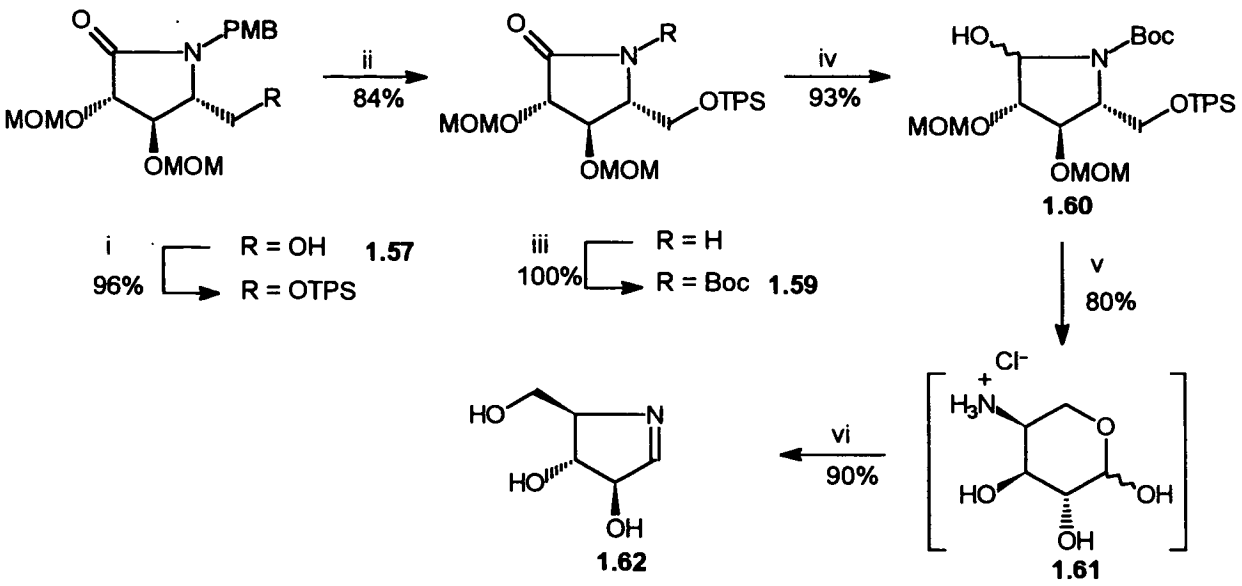
Scheme 1.13

Replacement of the PMB *N*-protecting group with the more electron-withdrawing and easily removable Boc group was crucial to effect the reduction of the corresponding lactam to an amino alcohol. Thus, reduction of the suitably protected imide **1.59** with $LiEt_3BH$ (Super Hydride)[52] in THF cleanly afforded amino alcohol **1.60** (Scheme 1.14). Removal of the protecting groups and subsequent ion exchange chromatography (Dowex resin, OH-form) of the amino sugar precursor **1.61** furnished nectrisine (**1.62**).

1.4. CONVERSION OF CARBOHYDRATES INTO AZASUGARS

1.4.1 REDUCTIVE AMINATION AT THE ANOMERIC CENTRE

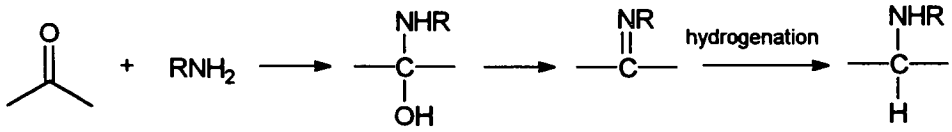
When an aldehyde or a ketone is treated with a primary- or secondary amine in the presence of hydrogen and a hydrogenation catalyst,[53] reductive amination of the carbonyl compound takes place (Scheme 1.15).



REAGENTS: i) TPSCl / imidazole / DMF / 96% ii) $(NH_4)_2Ce(NO_3)_6$ / CH_3CN-H_2O (9:1) / 0°C iii) Et_3N / $(Boc)_2O$ / DMAP / CH_2Cl_2 iv) $LiEt_3BH$ / THF / -78°C v) 6N HCl / THF / 50°C / 2h vi) Dowex 1-X2 (OH^-)

Scheme 1.14

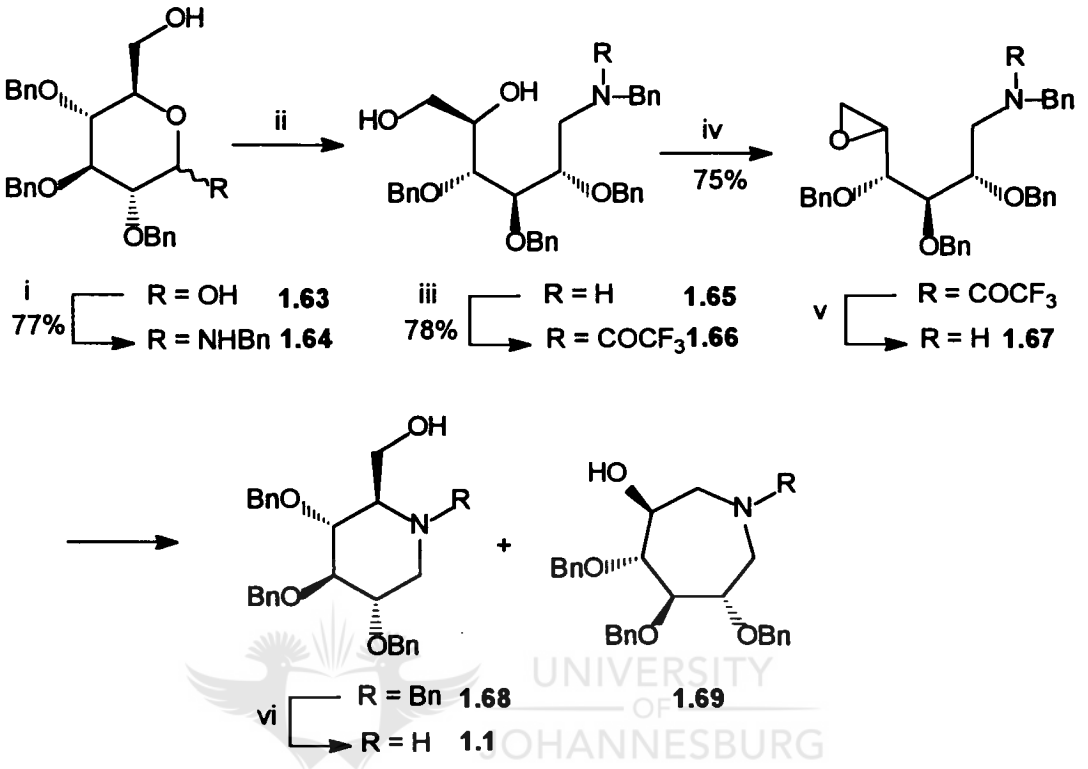
Other reducing agents can be used instead of hydrogen and a catalyst, among them zinc/HCl, sodium cyanoborohydride,[54] sodium borohydride[55] and iron pentacarbonyl/alcoholic KOH.[56]



Scheme 1.15

Ganem and Bernotas[57] reported the synthesis of (+)-deoxynojirimycin (**1.1**) based on the intramolecular cyclisation of an amine function onto an epoxide moiety (Scheme 1.16). Treatment of 2,3,4-tri-*O*-benzyl-D-glucopyranose (**1.63**)[58] with an excess of benzylamine furnished an anomeric mixture of glucosylamine (**1.64**), which was subsequently reduced with $LiAlH_4$ to the amine (**1.65**). Protection of the amine as the trifluoroacetylated amide and of the primary hydroxy group by selective silylation were important steps before epoxide formation. Subsequent mesylation followed by deprotection of the primary hydroxy group resulted in epoxide formation and the generation of **1.67** with inversion of stereochemistry at C-5. Regeneration of the amine function led to spontaneous cyclisation of the amino-epoxide in quantitative yield. Unfortunately,

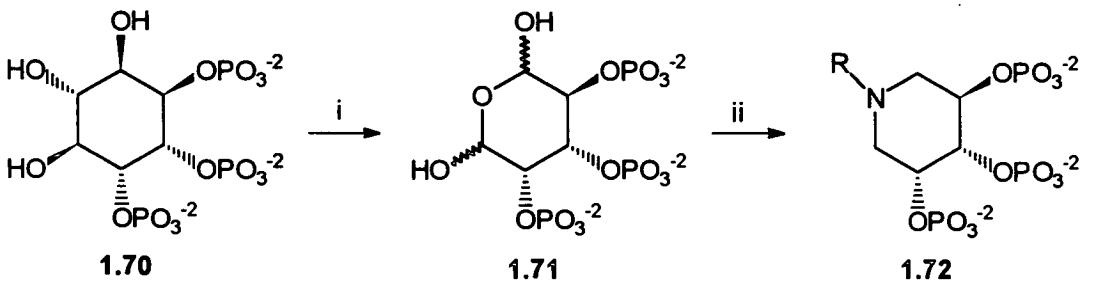
the cyclisation was not regiospecific and afforded a mixture of piperidine **1.68** (45%) and azepane **1.69** (55%). Hydrogenolysis of **1.68** furnished pure (+)-deoxynojirimycin (**1.1**).



REAGENTS: i) $PhCH_2NH_2$ (10 eq) / $CHCl_3$ ii) $LiAlH_4$ / THF / reflux / 5h iii) $(CF_3CO)_2O$ / CH_2Cl_2 iv) a: Bu^tMe_2SiCl / Imidazole b: MsCl / DMAP / NEt_3 c: Bu_4NF / THF d: CH_3ONa / CH_3OH v) $NaBH_4$ / EtOH / 40°C vi) Pd-C / H_2

Scheme 1.16

In a related approach, Malmberg and Rehnberg[59] oxidized α-trinositol **1.70** with sodium periodate and periodic acid in water to furnish the cyclic D-*arabino*-pento-aldose derivative **1.71** as a mixture of anomers[60] (Scheme 1.17).



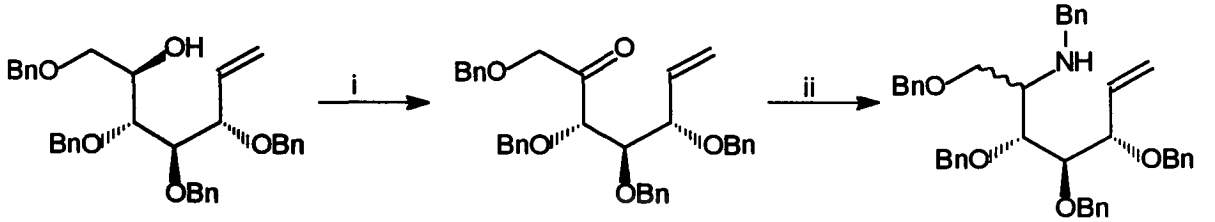
R = H, CH_3, CH_2Ph, cyclohexyl

REAGENTS: i) $NaIO_4$ (aq) / periodoc acid ii) RNH_2 / $NaBH_4$ / DME

Scheme 1.17

Reaction of **1.71** with a variety of primary amines followed by subsequent reduction with sodium borohydride afforded a range of *N*-substituted D-*arabino*-piperidinol phosphates **1.72**. Dephosphorylation of these compounds may prove to be a facile synthesis of glycosidase inhibitory *N*-substituted 1,5-dideoxy-1,5-imino-D-arabinitols.[61]

The synthesis of aza-*C*-glycosyl compounds (*i.e.*, compounds of type **1.76**) were investigated by Martin *et al.*[62] The heptenitol **1.73**[63] (available from tetra-O-benzyl D-*gluco*-hexopyranose) was oxidised using a modified Swern oxidation to furnish the unsaturated hexulose derivative **1.74** (Scheme 1.18). The nitrogen functionality was introduced at C-6 by reductive amination.[64] Thus, treatment of **1.74** with benzylamine in the presence of $NaBH_3CN$ afforded a separable mixture of aminoheptenitols **1.75**.

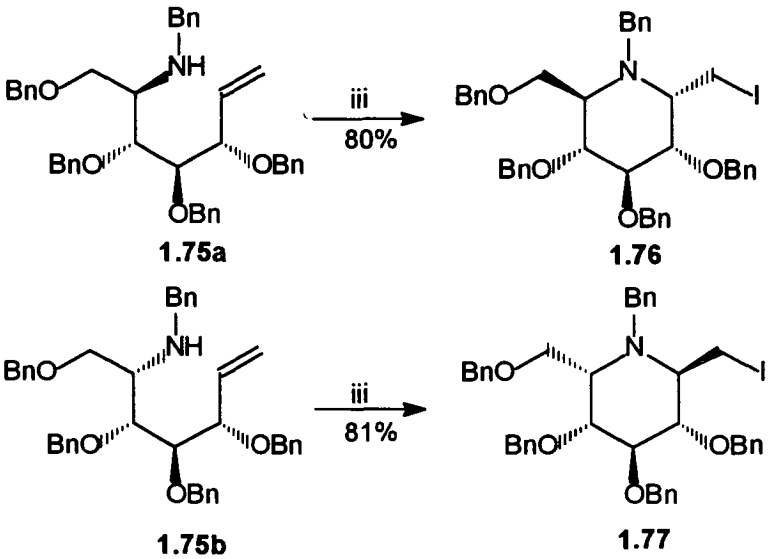


1.73 **1.74** **1.75**

REAGENTS: i) DMSO - TFAA / CH_2Cl_2 / -78°C then NEt_3 ii) $BnNH_2$ / HOAc (20 eq) / CH_3OH / r.t. then $NaBH_3CN$ / reflux 4 h

Scheme 1.18

Subsequent NIS-mediated cyclization of **1.75a** and **1.75b** afforded the novel azasugars **1.76** and **1.77** C-substituted at C-1 (Scheme 1.19).



1.75a **1.76**

1.75b **1.77**

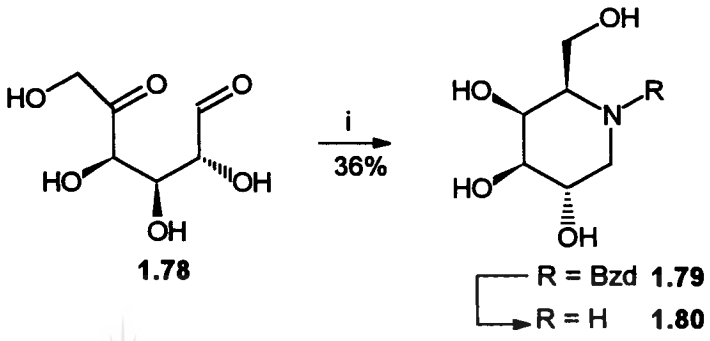
REAGENTS: i) NIS (1 equiv.) / CH_2Cl_2 / r.t. / 3 h

Scheme 1.19

These proved to be versatile precursors in the synthesis of aza-*C*-glycosyl compounds. The NIS-promoted cyclisation of the aminoheptenitols proved to be more stereoselective than the mercury-mediated cyclisation of related alkenes.[65]

1.4.2. DOUBLE REDUCTIVE AMINATION

The aminocyclisation of hexos-5-uloses[66] has proved to be a useful route to 1-deoxy-D-galactostatin **1.80**[67] and its derivatives. The synthetic intermediate, L-*arabino*-hexos-5-ulose **1.78** was readily synthesised from methyl β-D-galactopyranoside.[68]

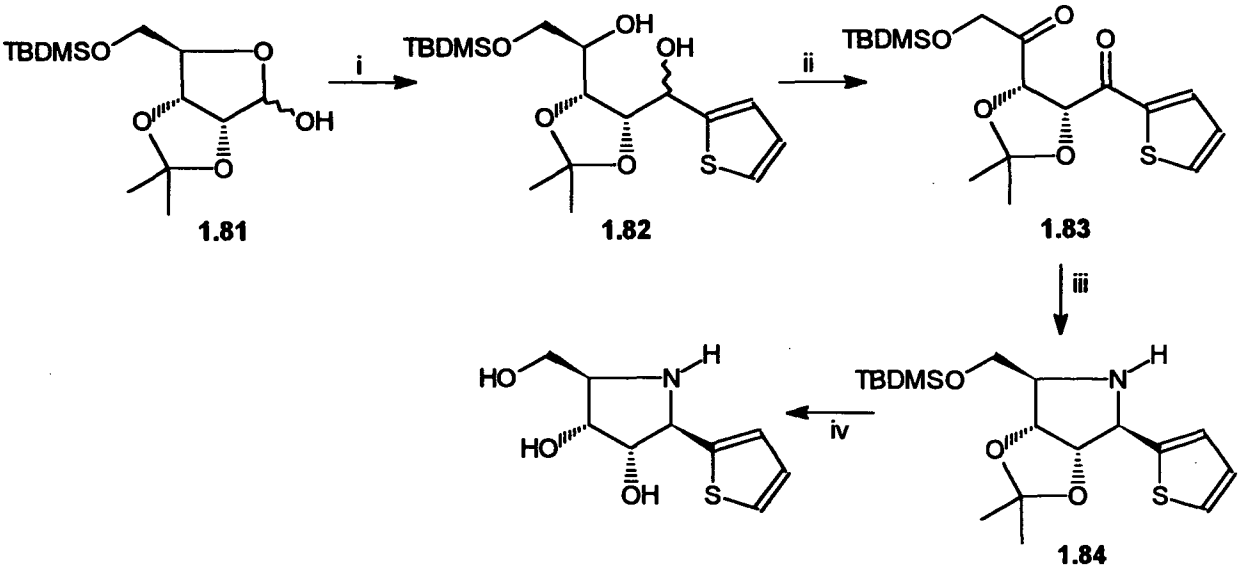


REAGENTS: i) Bzd-NH_2 / $NaBH_3CN$ / MeOH / -78°C to r.t
ii) H_2 / $Pd(OH)_2$-C / MeOH

Scheme 1.20

Unprotected **1.78** was reacted with benzhydrylamine in the presence of $NaBH_3CN$ in a double reductive amination reaction to afford the protected azasugar **1.79** (Scheme 1.20). Deprotection was achieved by hydrogenolysis with Pd on charcoal in MeOH containing an excess of HCl to avoid *N*-methylation.[69] Complete diastereoselectivity was observed for the aminocyclization of the unprotected 1,5-dicarbonyl derivative.

Yokoyama *et al.*[70] published a β-stereoselective synthesis of *C*-azanucleosides[71] based on a double reductive amination protocol. 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranose **1.81**[72] was added to a solution 2-thienyllithium in THF to furnish the aryl ribitol **1.82** (Scheme 1.21). A modified Swern oxidation of **1.82** afforded the aryl diketone **1.83**. Consecutive reduction of the 1,4-dicarbonyl derivative followed by aminocyclisation using ammonium formate afforded the protected β-*C*-azanucleoside (**1.84**) in good yield. This constitutes a reaction with remarkable stereoselectivity which has not yet been satisfactorily explained.

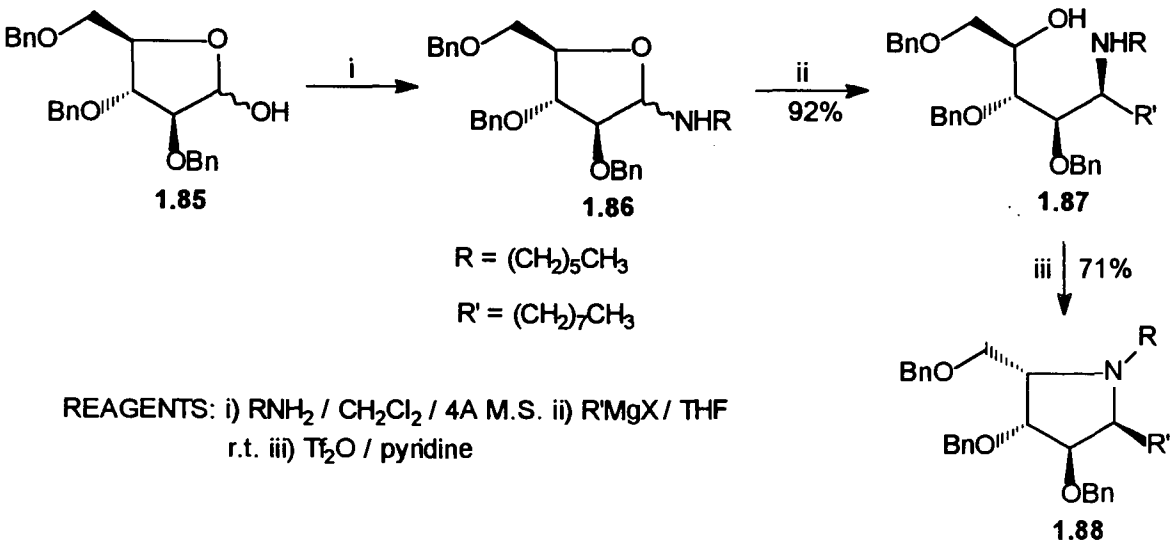


REAGENTS: i) 2-Thienyllithium / THF / r.t. ii) DMSO / TFAA / Et $_3$N / CH_2Cl_2 / -78°C to r.t.
iii) HCO_2NH_4 / $NaBH_3CN$ / MeOH / r.t. iv) 70% CF_3CO_2H / 50°C

Scheme 1.21

1.4.3. STEREOSELECTIVE C-ALKYLATION OF GLYCOSYLAMINES

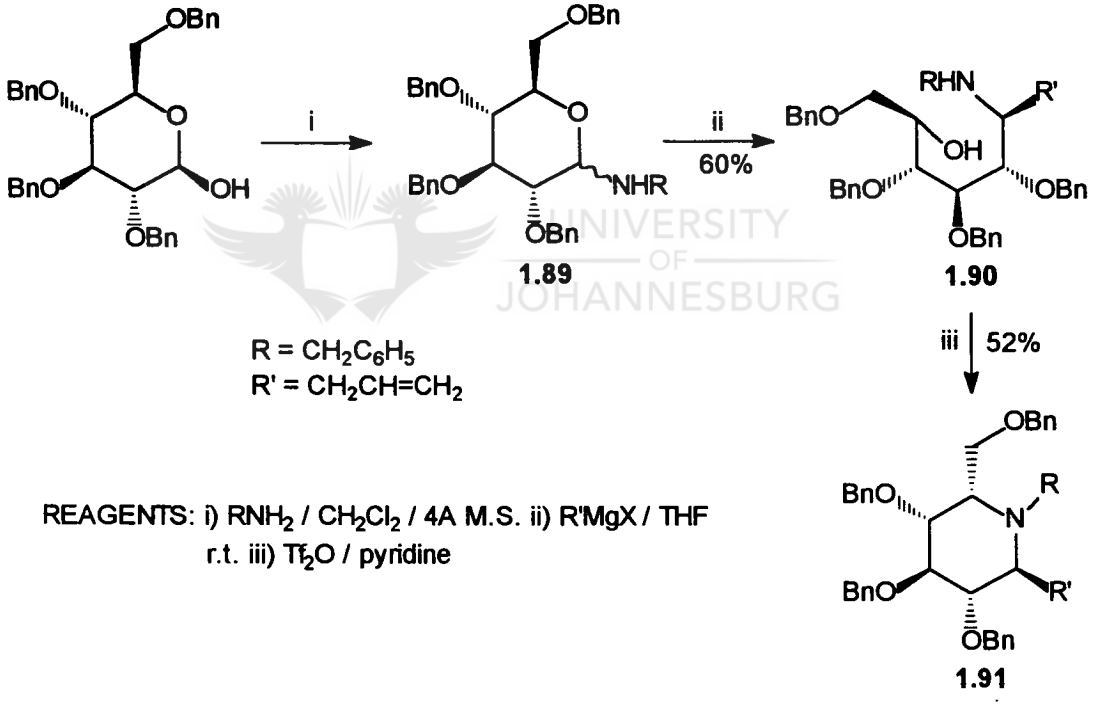
The presence of alkyl substituents on nitrogen can significantly increase the biological activity of azasugars, as in the case of *N*-butyldeoxynojirimicin.[73] Cipolla *et al.*[74] utilised the stereoselective addition of Grignard reagents to glycosylamines to synthesise a variety of *N*-substituted pyrrolidines and piperidines (Scheme 1.22).



REAGENTS: i) RNH_2 / CH_2Cl_2 / 4A M.S. ii) R'MgX / THF
r.t. iii) Tf_2O / pyridine

Scheme 1.22

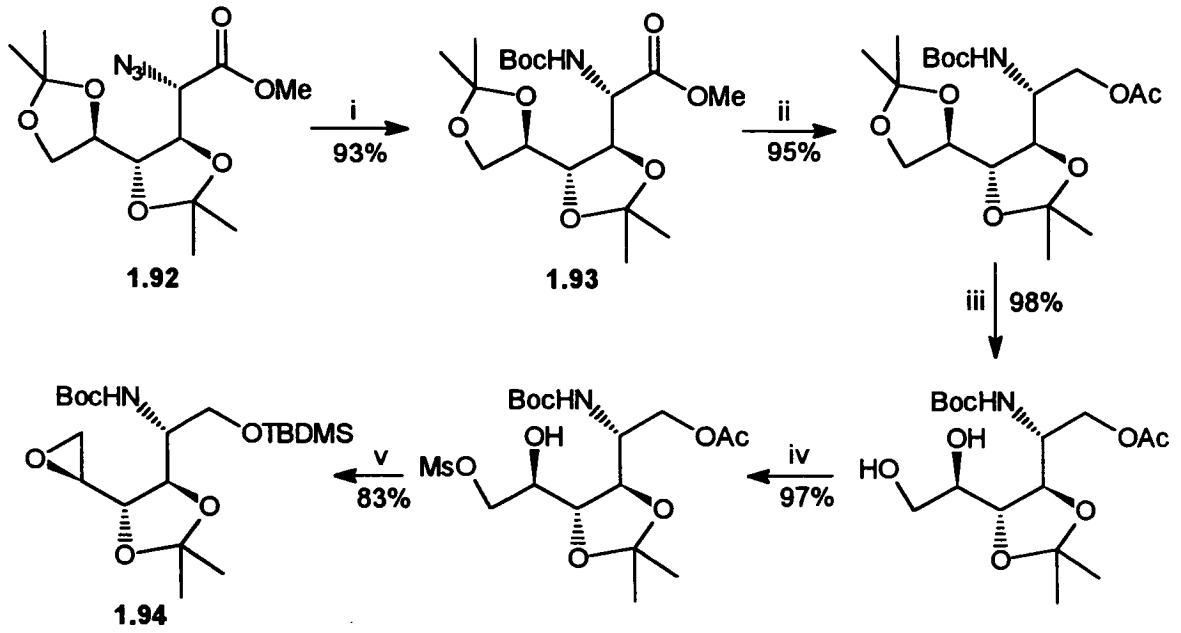
Glycosylamine formation was achieved by reaction of the aldose of a hemiacetal with an excess of a primary amine. 2,3,5-Tri-*O*-benzyl-D-arabinofuranose **1.85** was treated with hexylamine to furnish crude *N*-hexyl-2,3,5-tri-*O*-benzyl-D-arabinofuranose **1.86**, which was subsequently reacted with octylmagnesium bromide to afford adduct **1.87**. Grignard addition takes place through the corresponding aldose (which is in equilibrium with the glycosylamine) with complete diastereoselectivity to afford the *threo* product. Cyclisation was effected by treatment of **1.87** with trifluoromethanesulfonic anhydride in pyridine to provide the protected azasugar **1.88**. This procedure was also extended to pyranoses (Scheme 1.23). *N*-Benzyl-2,3-4,6-tetra-*O*-benzyl-D-glucopyranosyl amine **1.89** was reacted with allylmagnesium chloride to furnish the *threo* product **1.90**. Treatment of the aminoalcohol with Tf_2O afforded the corresponding *N*-alkylated piperidine **1.91**, which was subsequently deprotected *via* catalytic hydrogenation.



Scheme 1.23

1.4.3 CONVERSION OF A CARBOHYDRATE SECONDARY HYDROXY GROUP INTO AN AMINO GROUP

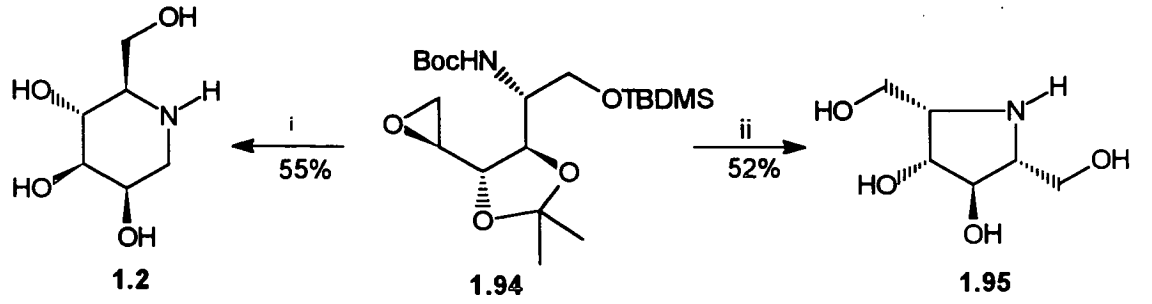
Lee *et al.*[75] synthesised the 5- and 6-membered azasugars **1.95**and **1.2** starting from suitably protected methyl 2-azido-D-mannoate **1.92**.[76] Hydrogenation of the azide and protection of the resultant amine afforded **1.93**, which was converted to epoxide **1.94** in 5 steps *via* several functional group manipulations (Scheme 1.24).



REAGENTS: i) a.10% Pd/C / H_2 / EtOAc / r.t. b: $(Boc)_2O$ / MeOH / Et_3N / r.t. ii) a: $LiAlH_4$ / THF / 0°C b: Ac_2O / pyridine / r.t. iii) Dowex 50W-X8 / 90% MeOH iv) MsCl / Et_3N / CH_2Cl_2 / -10°C v) a: NaOH / MeOH / r.t. b: TBDMSCl / imidazole / DMF / r.t.

Scheme 1.24

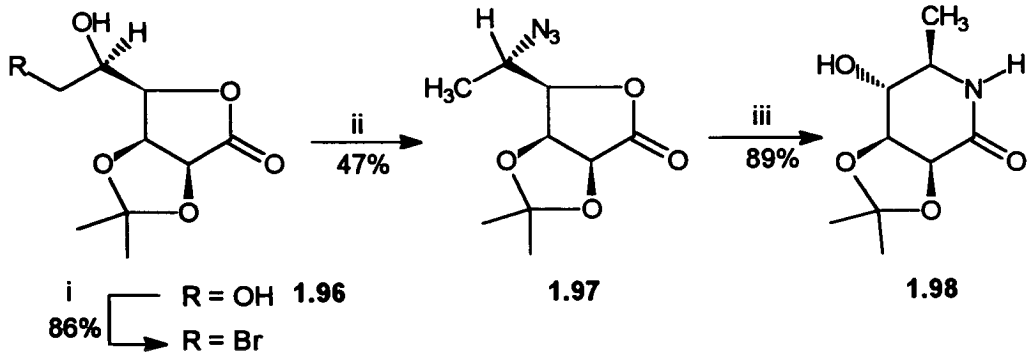
Piperidine formation resulted on selective removal of the Boc group of **1.94**, and subsequent intramolecular nucleophilic amination at C-6 of the epoxide. Alternatively, removal of both Boc and isopropylidene protecting groups on **1.94** resulted in attack of nitrogen at C-5 to furnish the pyrrolidine ring system (Scheme 1.25). It is presumed that steric strain arising from the *trans* acetal system prevents formation of a five membered ring in the first case. Subsequent deprotection afforded deoxymannojirimycin **1.2** and 2*R*,5*S*-dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine **1.95**, respectively.



REAGENTS: i) a: Me_3SiCl / PhOH / CH_2Cl_2 / r.t. - reflux b: Dowex 50-W / 90% MeOH / reflux
ii) a: $AlCl_3$ / $LiAlH_4$ / ether / r.t. - reflux b: Dowex 50W-X8 / 90% MeOH / reflux

Scheme 1.25

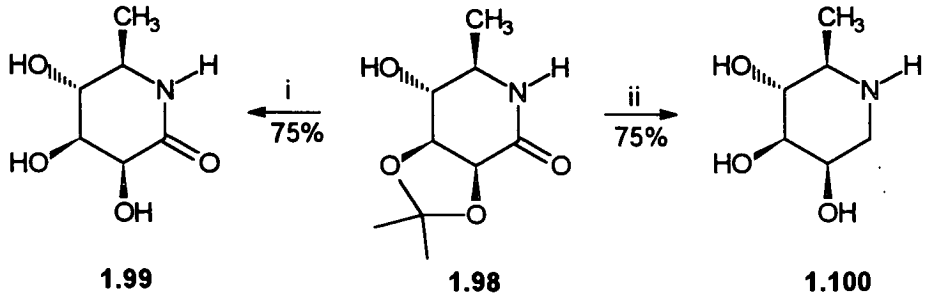
D-Deoxyrhamnojirimycin (**1.100**) and D-rhamnono-1,5-lactam (**1.99**) where prepared using a modified route first published by Fleet and co-workers,[77] starting from the monoacetonide of L-gulonolactone **1.96**.[78] The deoxygenation strategy consisted of selective bromination of the C-6 primary hydroxy group and subsequent hydrogenolysis of the C-6-Br bond (Scheme 1.26).[79] Triflation followed by nucleophilic displacement with sodium azide in DMF furnished **1.97**. Hydrogenation of **1.97** and spontaneous cyclisation of the resulting amine afforded the protected 6-deoxy-mannono-γ-lactam **1.98** in an overall yield of 36% starting from **1.96**.



REAGENTS: i) Ph_3P / CBr_4 / THF ii) a: 10% Pd/C / EtOH b: $(CF_3SO_2)_2O$ / pyridine / CH_2Cl_2 then NaN_3 / DMF iii) H_2 / 10% Pd/C / MeOH

Scheme 1.26

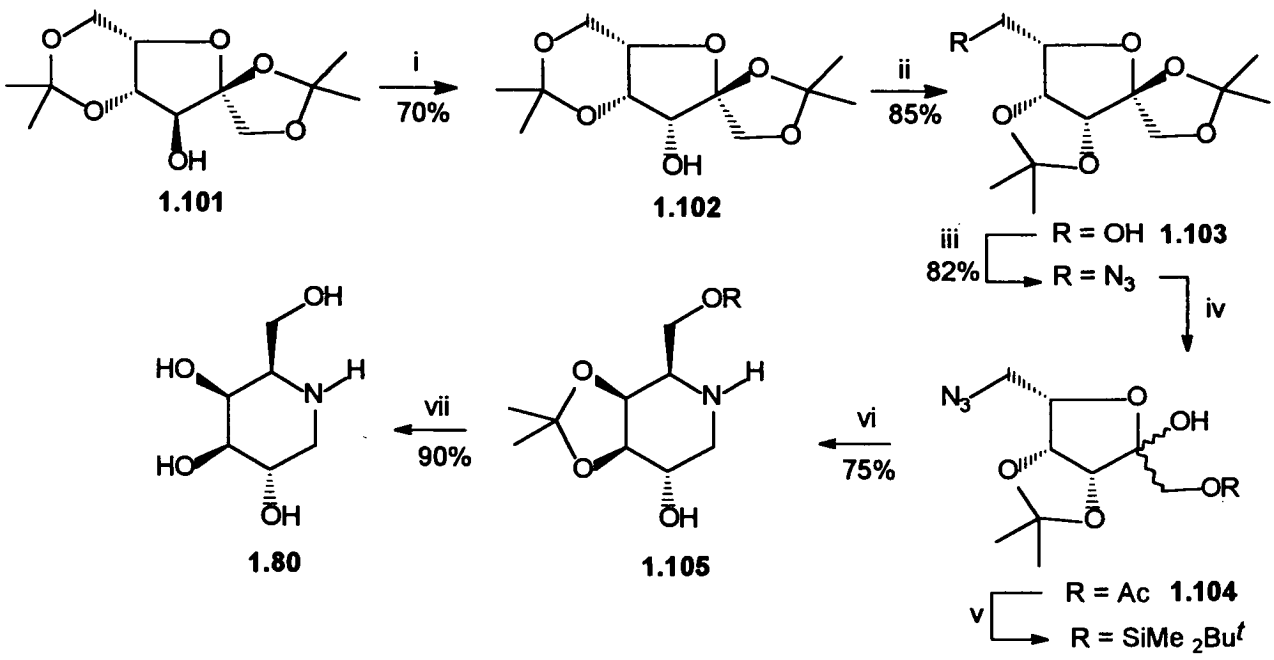
Straightforward deprotection furnished **1.99** while reduction of the lactam afforded **1.100** (Scheme 1.27).



REAGENTS: i) CF_3COOH / H_2O (2:1) ii) a: $Me_2S:BH_3$ b: aq.HCl

Scheme 1.27

Furneaux *et al.*[80] reported a facile new synthesis of 1-deoxygalactonojirimycin **1.80** starting from 1,2:4,6-di-O-isopropylidene-α-L-sorbofuranose **1.101** (Scheme 1.28).



REAGENTS: i) a: Me_2SO / Tf_2O / Et_3N b: $NaBH_4$ ii) camphorsulfonic acid / Me_2CO iii) a: MsCl / Et_3N b: NaN_3 / Me_2SO iv) 0.5% $BF_3.OEt_2$ in Ac_2O v) a: MeONa / MeOH b: $^tBuMe_2SiCl$ imidazole / DMF vi) H_2 / Pd-C vii) CF_3CO_2H:H_2O / r.t.

Scheme 1.28

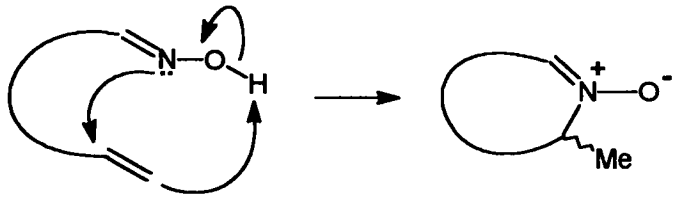
Epimerisation at C-3 was achieved *via* an oxidation-reduction sequence to afford 1,2:4,6-di-*O*-isopropylidene-α-L-tagatofuranose **1.102**. Acid catalysed isomerisation furnished the thermodynamically favoured diacetonide **1.103**, containing two five membered cyclic ketals. Conversion into the azide was accomplished in the conventional manner. The primary hydroxy group in **1.104** was selectively silylated before reduction of the azide, thereby inhibiting degradation during formation of **1.105**. Acid hydrolysis furnished **1.80**.

1.5 NITRONES AS PRECURSORS TO COMPLEX AZASUGARS

Nitrone functionality incorporated into cyclic systems has been extensively utilised to elaborate pyrrolidine and piperidine moieties which are widespread in nature.[81] These 1,3-dipoles are excellent substrates for cycloaddition reactions with alkenes, affording isoxazolidines.[82] Further manipulation of these key intermediates (reduction of the *N-O* bond, hydrogenation, rearomatisation, etc.) provides ready access to a variety of important heterocyclic ring systems.[82] The regio- and stereoselectivity of these nitrone cycloaddition reactions have earned them an important place in organic synthesis.

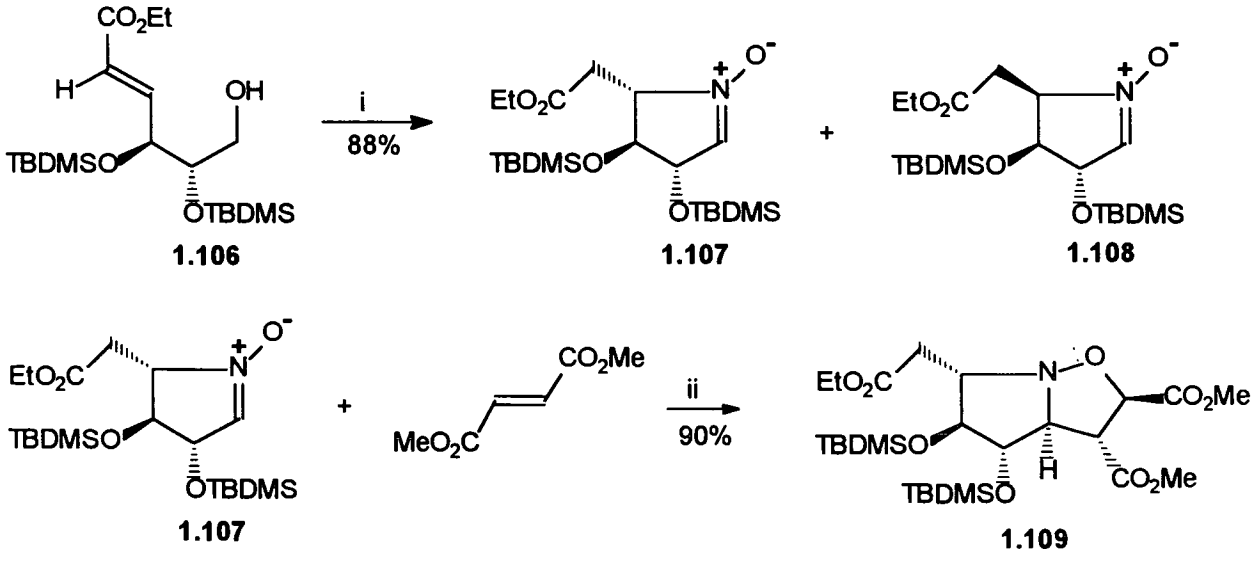
1.5.1 GENERATION OF CYCLIC NITRONES BY INTRAMOLECULAR CONJUGATE ADDITION OF OXIMES (1,3-azaprotiocyclotransfer reaction)

The intramolecular Michael addition of oximes to proximate activated alkenes results in the generation of cyclic nitrones *via* a 1,3-azaprotiocyclotransfer reaction (Scheme 1.29).[83]



Scheme 1.29

This strategy was exploited by Saito and co-workers[84] to synthesise a novel chiral cyclic nitrone which proved to be an extremely useful intermediate for heterocycle synthesis. The acyclic nitrone precursor **1.106** was synthesized in 6 steps starting from (2*S*,3*S*)-2,3-*O*-isopropylidene-L-threitol. Swern oxidation of **1.106** afforded the formyl enoate which was immediately reacted with hydroxylamine hydrochloride and triethylamine to furnish cyclic nitrone **1.107** along with a minor amount of the diastereoisomer **1.108** (Scheme 1.30).

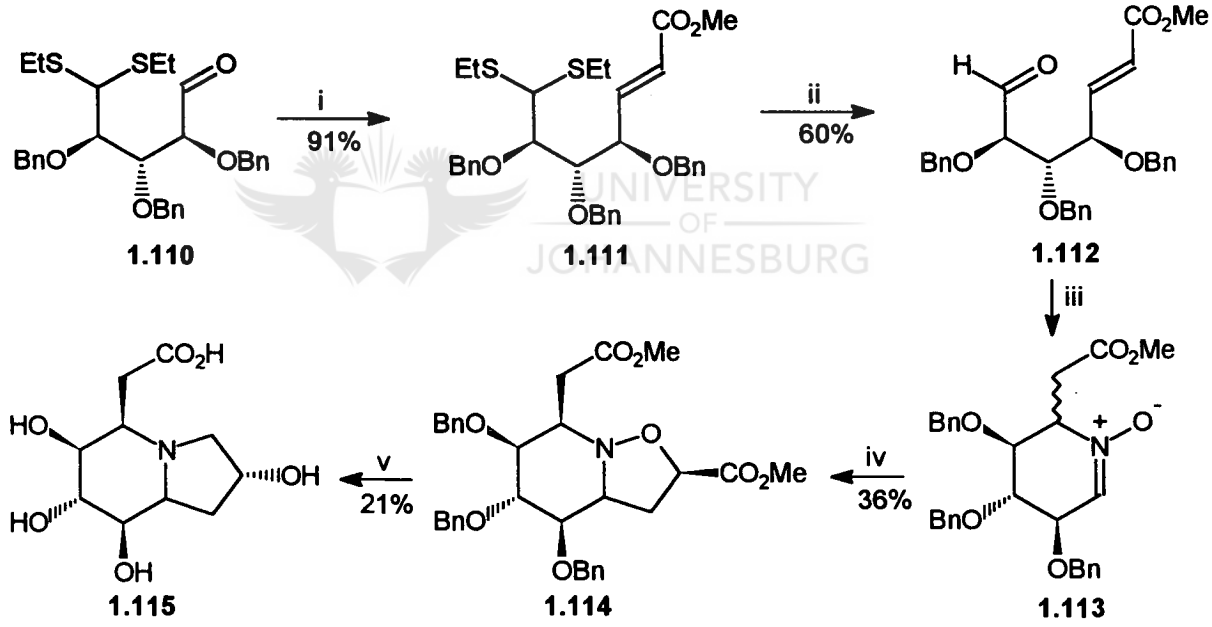


REAGENTS: i) a: Oxalyl chloride / DMSO b: $NH_2OH.HCl$
ii) benzene / reflux

Scheme 1.30

It was reasoned that cyclic nitrones of this type would provide optimal facial bias in 1,3-dipolar cycloaddition reactions with activated alkenes to afford highly substituted and stereodefined isoxazolidines. Cycloaddition of **1.107** to dimethyl fumarate afforded the corresponding cycloadduct **1.109** in very high diastereomeric excess (>99%).

Recently, the synthesis of indolizidine derivatives related to swainsonine[9] was reported, employing cyclic piperidine-based nitrones derived from a carbohydrate (Scheme 1.31).[85] The dialdose mercaptal **1.110** was synthesized from D-xylose in 5 steps.[86] Wittig reaction furnished **1.111**, which was subjected to mercury salt demercaptalisation to afford the unsaturated aldehyde **1.112**. The latter was allowed to react with hydroxylamine furnishing, after cyclisation, a diastereomeric mixture of nitrones **1.113**. Addition of methyl acrylate to the reaction mixture afforded the isoxazolidine **1.114** as the major compound. Subsequent four-step transformation of **1.114** furnished the tetrahydroxyindolizidine derivative **1.115**.



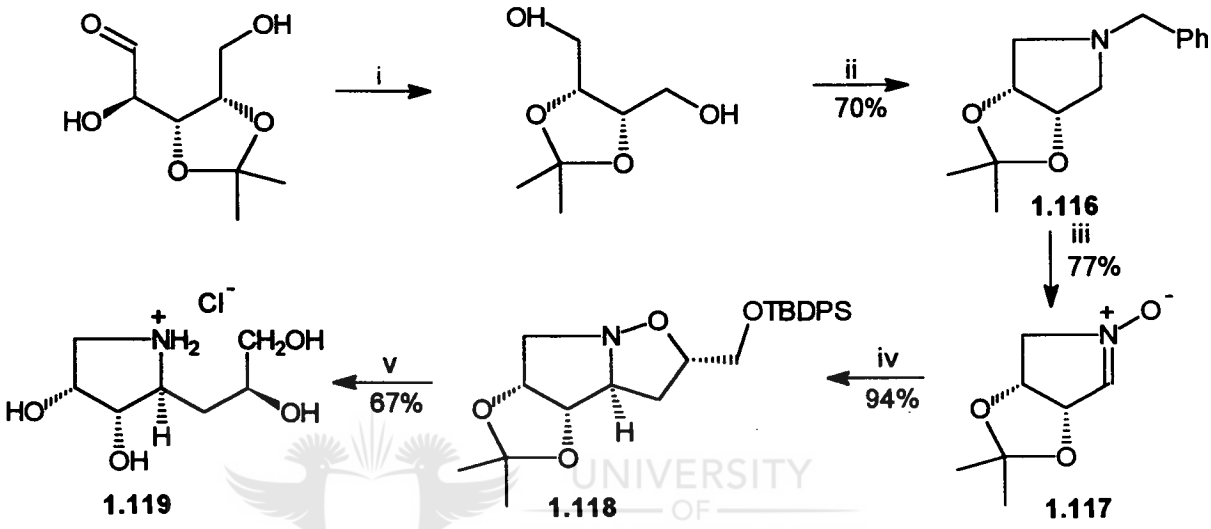
REAGENTS: i) Ph_3PCHCO_2Me / benzene / reflux ii) $HgCl_2$ / $CdCO_3$ / acetone - H_2O / r.t. iii) H_2NOH / EtOH - H_2O / r.t. iv) addition of methyl acrylate v) a: Zn / AcOH / 50°C b: $Me_2S.BH_3$ / THF / reflux c: $Ba(OH)_2$ / EtOH - H_2O / reflux, then CO_2 d: H_2 / Pd on C / AcOH

Scheme 1.31

1.5.2 SYNTHESIS OF CYCLIC NITRONES THROUGH OXIDATION OF SUITABLE PRECURSORS DERIVED FROM CARBOHYDRATES

McCaig and Wightman[87] prepared functionalised pyrroline-*N*-oxides by oxidation of C-2 symmetrical pyrrolidines (Scheme 1.32). Amine **1.116** was synthesised from 3,4-*O*-

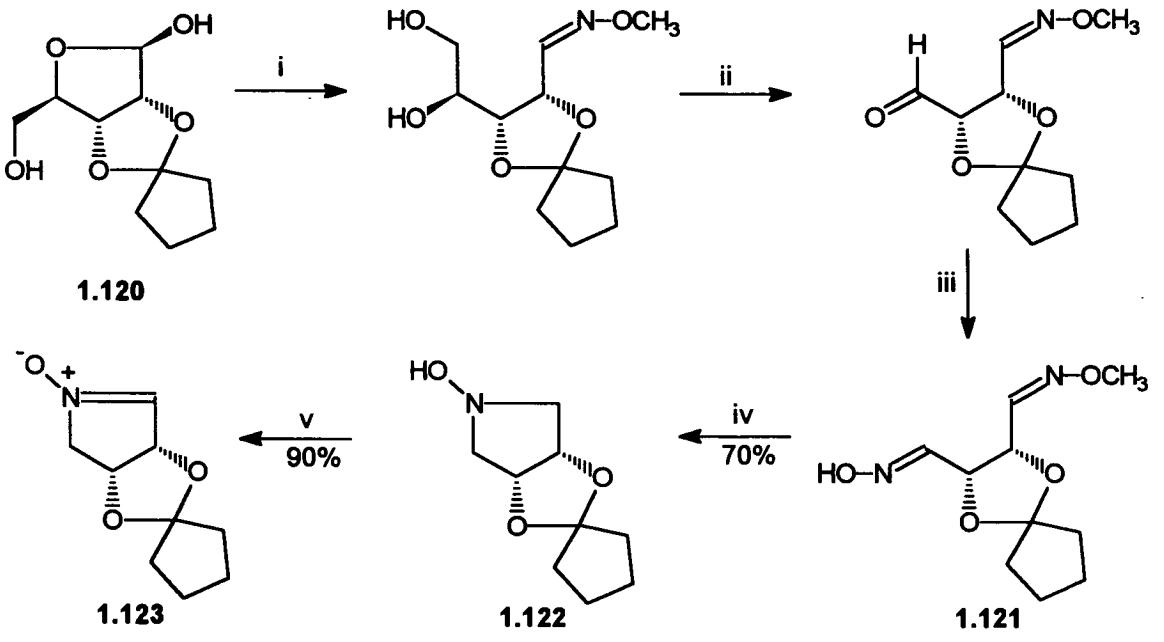
isopropylidene-D-arabinopyranose[88] in 4 steps. Hydrogenolysis of **1.116** using Pearlman's catalyst[89] furnished an unprotected amine which was immediately oxidized to the nitrone **1.117** with Davis' reagent {2-(phenylsulfonyl)-3-phenyloxaziridine}.[90] Cycloaddition of allyl *t*-butyldiphenylsilyl ether to **1.117** afforded a single cycloadduct (**1.118**). Hydrogenolysis and subsequent acid hydrolysis of **1.118** furnished 1,4,5-trideoxy-1,4-imino-D-heptitol (**1.119**) as its crystalline hydrochloride.



REAGENTS: i) a: $NaIO_4$ b: $NaBH_4$ ii) a: MsCl / Et_3N / CH_2Cl_2 b: $PhCH_2NH_2$ / 65°C / 48 h iii) a: H_2 / $Pd(OH)_2$ on C / MeOH b: 2-(phenylsulfonyl)-3-phenyloxaziridine / $CHCl_3$ iv) CH_2=$CHCH_2OTBDPS$ / toluene / reflux / 10 h v) a:H_2 / Pd on C / EtOH b: TFA - H_2O / crystallize from EtOH/HCl - Et_2O

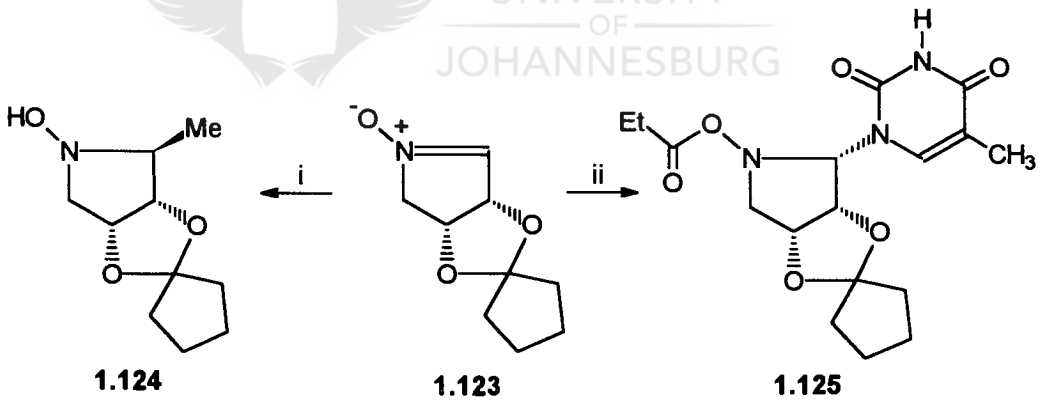
Scheme 1.32

Tronchet *et al.* [91] prepared the *meso* *N*-hydroxypyrrolidine **1.122** by reductive cyclization of dioxime **1.121**, available in 4 steps from 2,3-*O*-cyclopentylidene-α-D-ribofuranose (**1.120**)[92] (Scheme 1.33). Oxidation of **1.122** with HgO afforded the cyclic nitrone **1.123**, which constituted a useful synthetic intermediate in the synthesis of *C*-azanucleosides and *C*-azaglycosides. Reacting **1.123** with methyllithium furnished the methyl-β-*C*-glycoside analogue **1.124** in a yield of 70%, while nucleosidation afforded **1.125** (Scheme 1.34).



REAGENTS: i) $H_2NOCH_3.HCl$ / pyridine ii) a: $NaIO_4$ b: $NaBH_4$
iii) $H_2NOH.HCl$ / pyridine iv) $NaBH_3CN$ v) HgO

Scheme 1.33

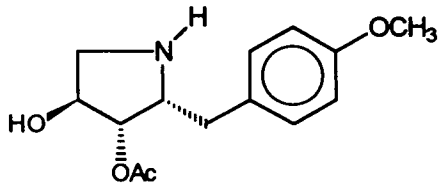


REAGENTS: i) MeLi / THF / -78°C ii) a: $(EtCO)_2O$ b: Thymine / HMDS / TMSCl
$SnCl_4$

Scheme 1.34

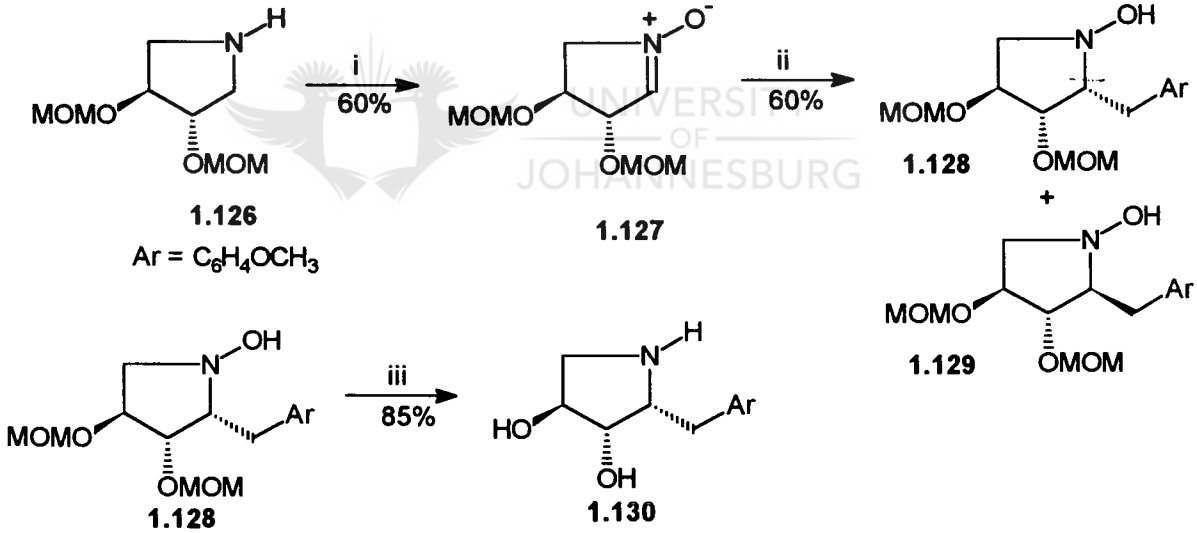
1.5.3 SYNTHESIS OF CYCLIC NITRONES THROUGH OXIDATION OF SUITABLE PRECURSORS DERIVED FROM NON-CARBOHYDRATES

Ballini *et al.* [93] reported the synthesis of the antibiotic (-)-anisomycin (**1.6**)[94] employing nitrone **1.127** as the key intermediate (Scheme 1.35). L-Tartaric acid, chosen as the precursor due to its favourable stereochemical configuration, was converted to the pyrrolidine **1.126** in 4 high



1.6

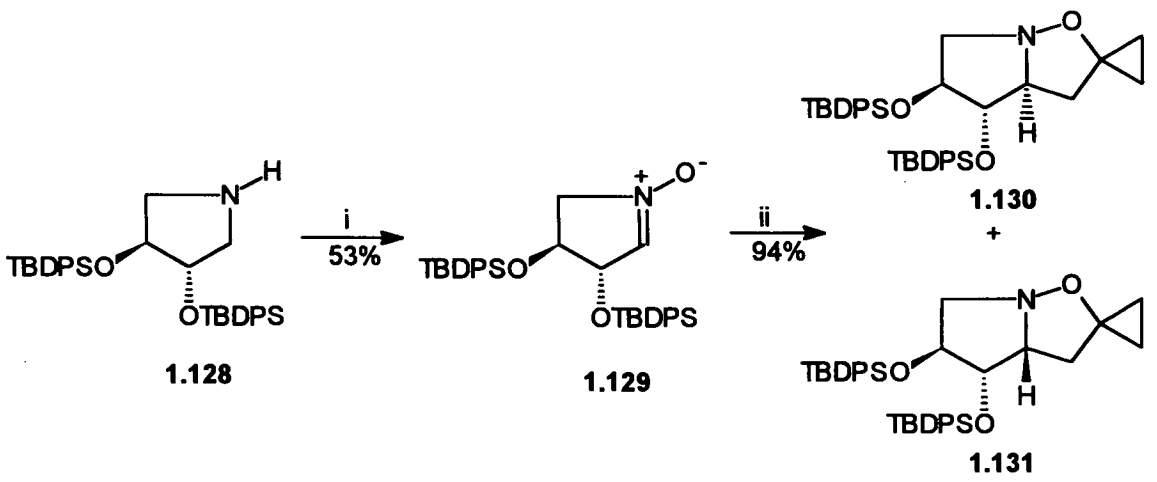
yielding steps. Oxidation of **1.126** with 30% H_2O_2 in the presence of catalytic SeO_2[95] furnished nitrone **1.127**. Several nucleophiles have been found to attack the α-carbon of nitrones to form α-substituted hydroxylamines.[96] The nitrone was therefore subsequently reacted with (4-methoxybenzyl)magnesium chloride to afford **1.128** and **1.129** in a ratio of 2:3. The diastereoselectivity could be improved to 7:3 by addition of 1 equivalent of $MgBr_2$ to the reaction mixture. It is postulated that $MgBr_2$ is capable of coordinating the nitrone oxygen, thereby forcing *cis* addition of the Grignard reagent to the double bond through a cyclic five-membered transition state. Catalytic hydrogenation of **1.128** followed by deprotection afforded deacetylanisomycin **1.130**, which has previously been converted to **1.6**.[97]



REAGENTS: i) 30% H_2O_2 / cat. SeO_2 / 0°C to rt. ii) $ArCH_2MgCl$ / CH_2Cl_2 $MgBr_2.Et_2O$ / 0°C iii) a: RaNi / H_2 b: MeOH / 6N HCl / 24 h / reflux

Scheme 1.35

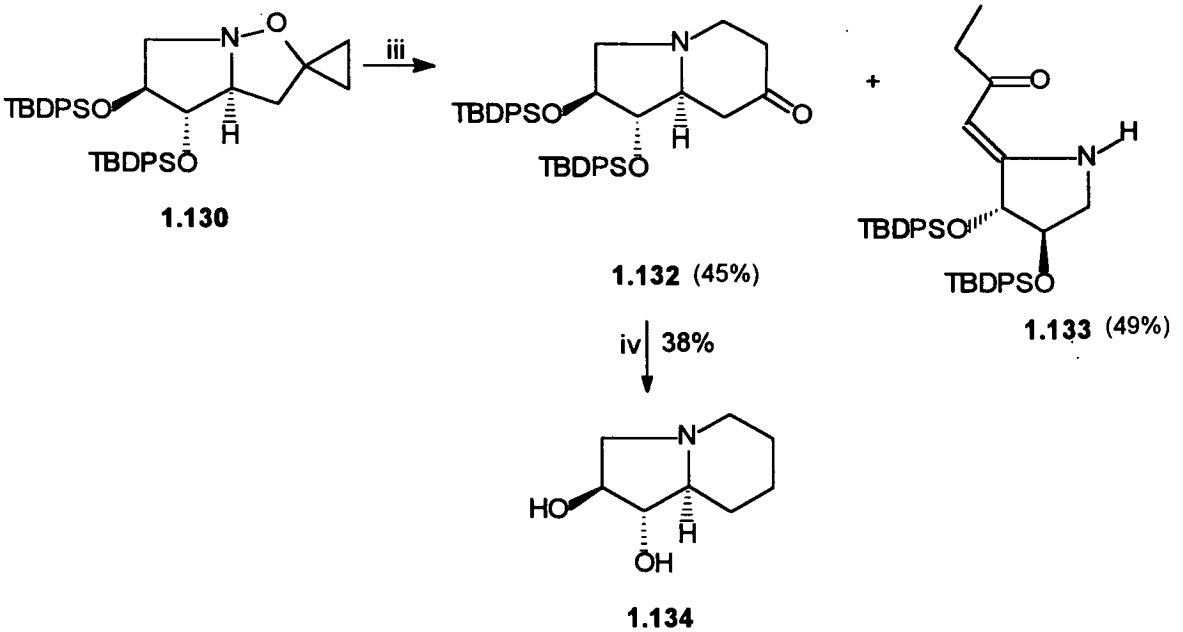
Brandi and co-workers[98] utilised the same methodology for oxidation of the pyrrolidine **1.131** to the dihydroxy nitrone **1.132** (Scheme 1.36). The L-tartrate-derived nitrone **1.132** was reacted with methylenecyclopropane in benzene to afford a separable mixture of isoxazolidines **1.133** and **1.134** (94% yield, 10:1 ratio).



REAGENTS: i) H_2O_2 / cat. SeO_2 ii) methylene cyclopropane / 35°C / 8 d

Scheme 1.36

The thermal rearrangement of strained bicyclic 5-spirocyclopropane isoxazolidines to 4-piperidone derivatives is a versatile method for the construction of the indolizidine skeleton.[99] The appropriate isomer (**1.130**) was refluxed in xylene to afford the indolizidinone **1.132** (45% yield) as well as the undesired enone **1.133** (49% yield). Reduction of the ketone **1.132** *via* its tosylhydrazone[100] and subsequent deprotection furnished (+)-lentiginosine **1.134**[101] (Scheme 1.37).



REAGENTS: iii) xylene / 150°C / 6 h iv) a: $TsNHNH_2$ / $NaBH_4$ b: aq. HF (40%) / CH_3CN

Scheme 1.37

1.7 CONCLUSION

The numerous synthetic procedures described in this chapter highlight the enormous efforts by organic chemists currently working in the field of azasugars and related compounds. The promising antiviral properties of these compounds will ensure that they remain the focus of intensive research for many years to come. In future the drive will be towards methodologies that can provide easy accses to structural analogues of azasugars. In turn, this will allow researchers to establish structure-activity relationships, hopefully leading to a better understanding of their actions.

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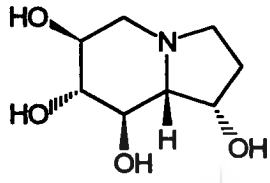
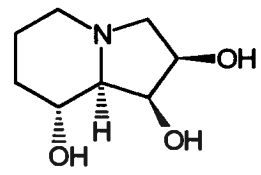
CHAPTER 2
SYNTHESIS OF CHIRAL PYRROLIDINES STARTING FROM CARBOHYDRATES

2.1 INTRODUCTION

Polyhydroxylated indolizidine alkaloids continue to attract considerable attention due to their well-established function as glycosidase inhibitors and as inhibitors of glycoprotein processing.[1] Many bind to the active site of glycosidases more strongly than the saccharides they mimic, resulting in the inhibition of the enzyme.[2] This interference of the bioprocessing of oligo- or polysaccharides may lead to therapeutic applications in viral infections, metabolic diseases and cancer. Noteworthy members among this class of compounds are castanospermine[3] (**2.1**), swainsonine[4] (**2.2**) and lentiginosine[5] (**2.3**).



2.1



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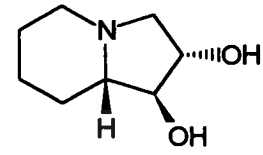
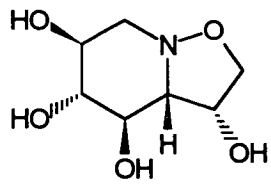
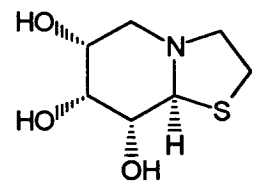


2.3

Castanospermine has generated much interest because it is a potent inhibitor of experimental metastasis of some cancers,[6] as well as various glucosidases.[7] Furthermore, it inhibits replication of the human immunodeficiency virus (HIV)[8] and other virus infections.[9] The development of general synthetic methods, which embody considerable flexibility for the construction of other stereoisomers and analogues, continues to be important to probe structure activity-correlations. Towards this end we were interested in the synthesis of isosteric analogues of polyhydroxylated indolizidine alkaloids (for example, **2.4**). The isosteric replacement of a carbon atom with a heteroatom was previously investigated by Marek *et al.*[10] who reported the synthesis of the sulfur analogue **2.5**.



2.4



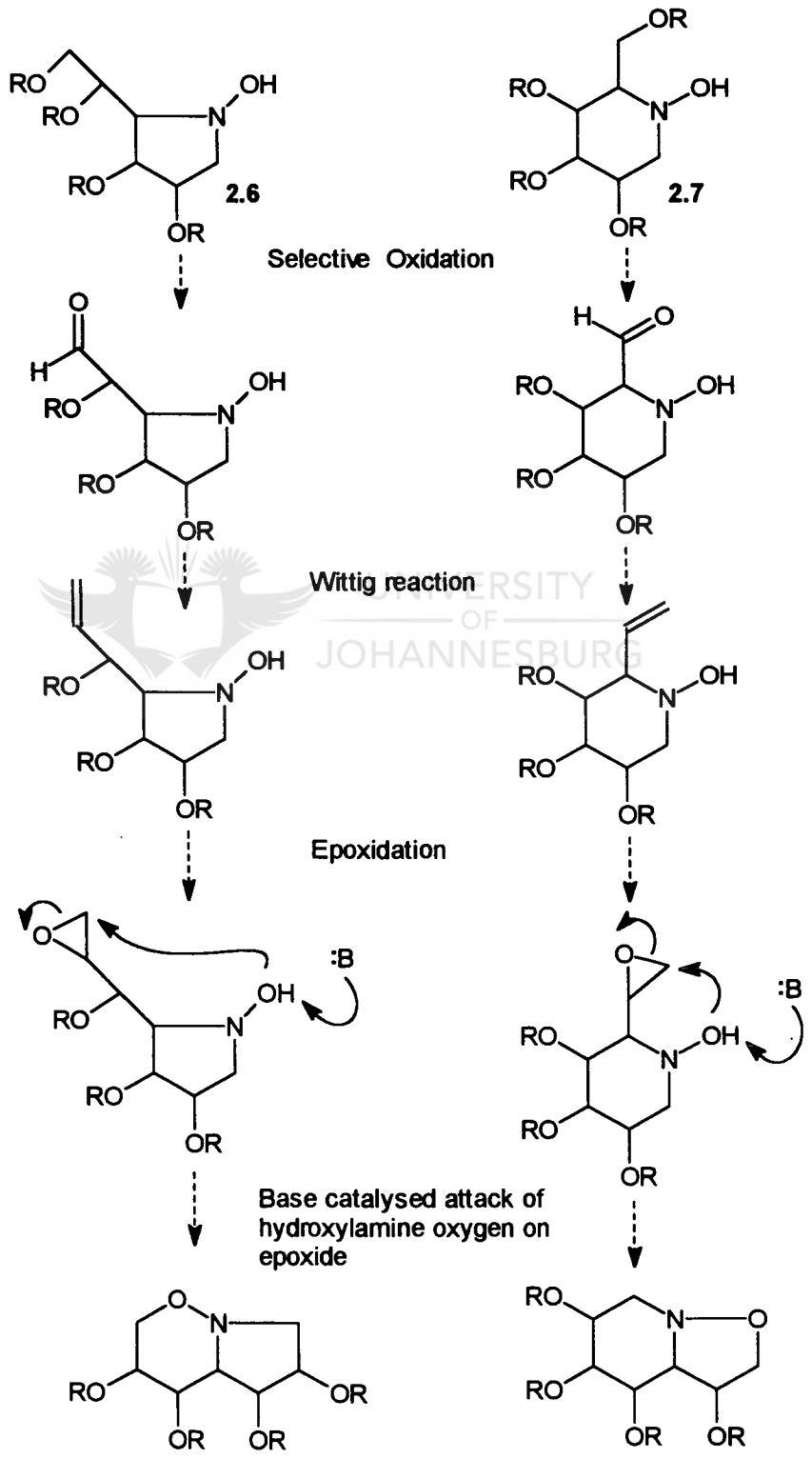
2.5

While these compounds retain their spatial relationship, which is crucial for enzyme recognition, the presence of a heteroatom can drastically alter the interaction at the active site. This can sometimes lead to an increase in physiological activity.[11] The aim of this study was to

investigate the stereocontrolled synthesis of these analogues starting from monosaccharides as chiral building blocks.

2.2 SYNTHETIC APPROACH

For the purposes of this study, the total synthesis of isosteric analogues of indolizidine



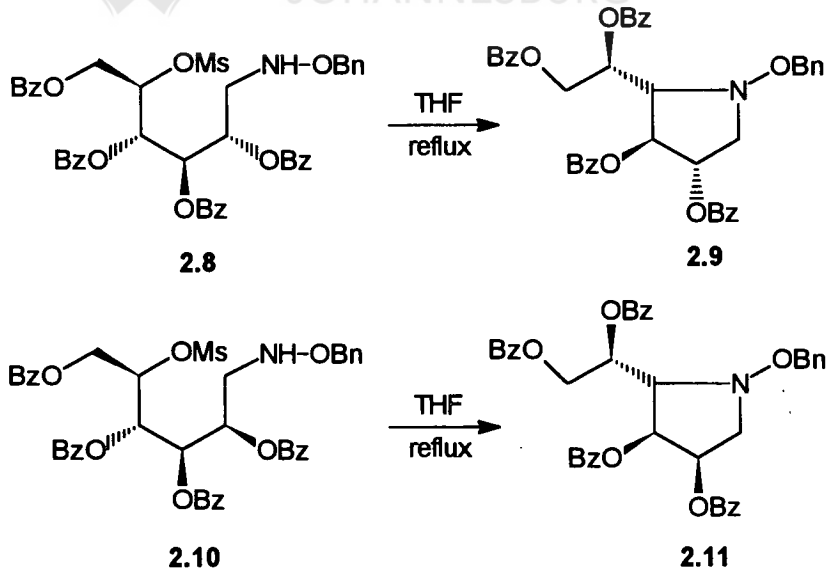
Scheme 2.1

alkaloids of type **2.4** was viewed as requiring two possible synthons: an *N*-hydroxy pyrrolidine **2.6** or an *N*-hydroxy piperidine **2.7**. These intermediates could then be transformed to the target compounds *via* the following sequence of reactions (Scheme 2.1).

a) Selective oxidation of the primary hydroxy group to an aldehyde
b) Wittig reaction to afford a terminal methylene moiety
c) Epoxidation of the formed double bond
d) Base catalysed attack of the hydroxylamine oxygen onto the epoxide to furnish the indolizidine analogue.

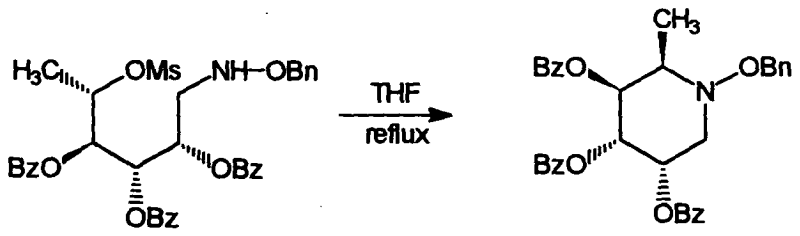
2.3 PREVIOUS WORK DONE AT RAU

Through previous work[12] which we have carried out at RAU, we had easy access to a variety of chiral pyrrolidines and piperidines. The synthetic approach involved the preparation of suitably protected hemiacetals of D-glucose, D-mannose and L-rhamnose. These compounds were used to introduce the nitrogen functionality *via* oxime formation. The *O*-benzyloxime derivatives of these selectively *O*-benzoylated hexoses were consecutively reduced and cyclised under various conditions. Unexpectedly, the 5-*O*-mesyl derivatives of the *O*-benzyl hydroxylamine hexose intermediates (**2.8** and **2.10**) furnished the *N*-benzyloxy-pyrrolidine ring systems **2.9** and **2.11** (Scheme 2.2).



Scheme 2.2

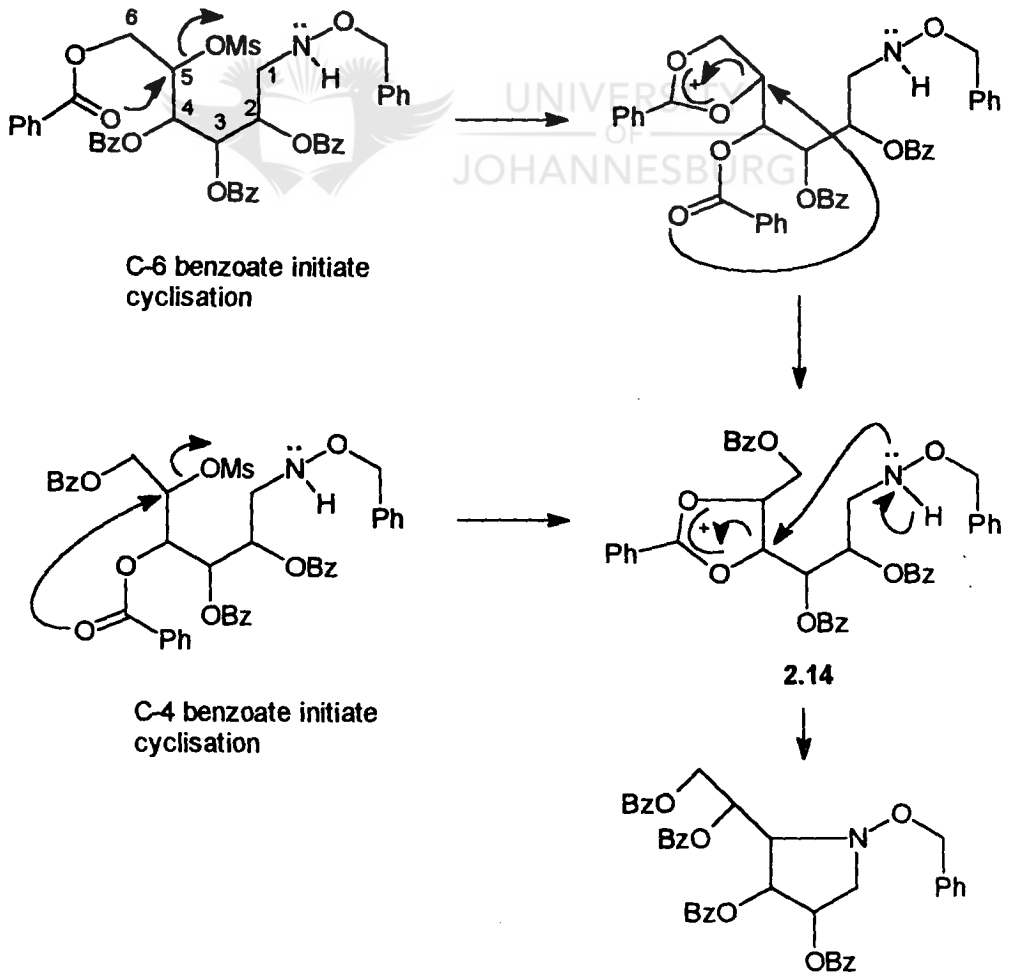
Conversely, the 5-*O*-mesyl derivative of the *O*-benzyl hydroxylamine 6-deoxy hexose analogue **2.12** furnished the piperidine ring system **2.13** (Scheme 2.3). The formation and stereochemistry of the pyrrolidine products could be explained in terms of a cascade of neighbouring group participation steps. The tendency of benzoate esters to take part in neighbouring group participation reactions is well documented.[13]



2.12 **2.13**

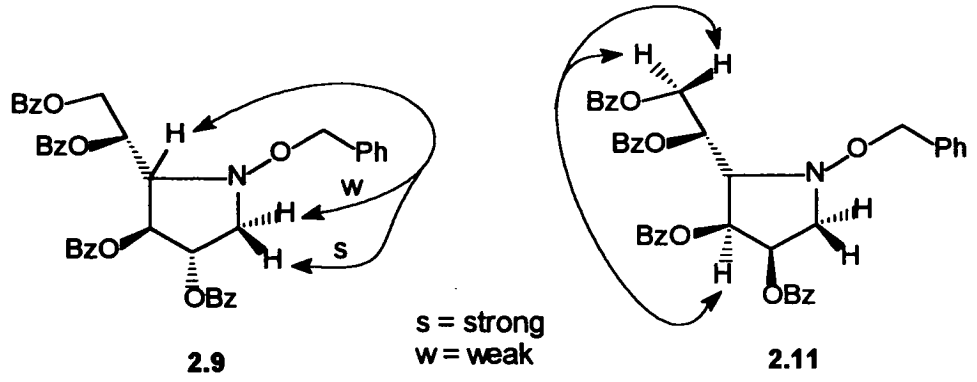
Scheme 2.3

Two possible mechanistic routes are possible (Scheme 2.4) with either the C-6 benzoate group or the C-4 benzoate group initiating the cascade reaction. Both these pathways furnish an intermediate of type **2.14** which is in turn attacked by the nitrogen lone pair to afford a five membered, rather than a six membered ring (cyclisation under kinetic control).



Scheme 2.4

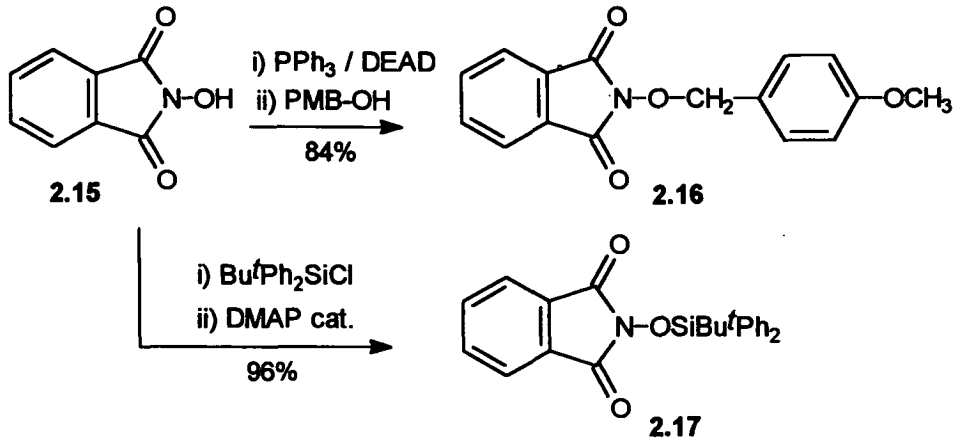
The structures of the resultant pyrrolidines were deduced on the basis of ^{1}H- and ^{13}C-NMR spectra, as well as nOe-effects established by means of ROESY spectra (Scheme 2.5). The reactions proceed with inversion of stereochemistry at C-4 and retention (double inversion) of stereochemistry at C-5. This suggests that the C-6 benzoate group initiates the cascade followed by the C-4 benzoate group. The fact that no neighbouring group participation was observed for the 6-deoxy-hexose analogue **2.12** provides further evidence for the proposed mechanism.



Scheme 2.5

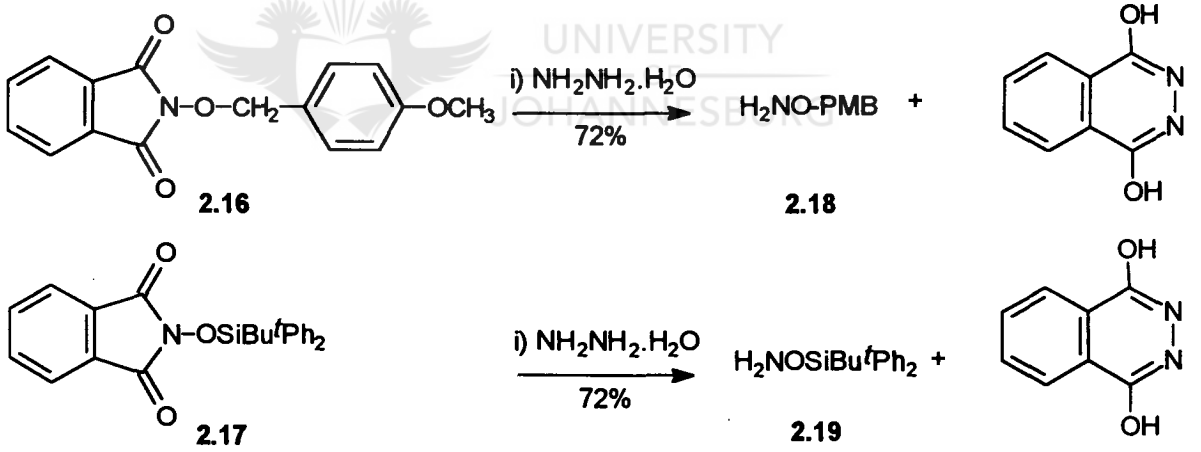
2.4 ALTERNATIVE APPROACH

The cyclisation reaction leading to the pyrrolidine ring systems is an extremely efficient and simple procedure, which we hoped to exploit in a new strategy for the synthesis of chiral *N*-hydroxy pyrrolidines. The aim was to find a labile protecting group for the oxime, which could be removed under relatively mild conditions after cyclisation. The method of choice for removal of benzyl groups is hydrogenation in the presence of a palladium catalyst.[14] However, these conditions almost always lead to the cleavage of the crucial *N-O* bond. It was decided to undertake simple model studies aimed at the development of a suitable group, which would be stable towards basic conditions, but leave the *N-O* bond intact upon deprotection. The use of methoxy-substituted benzyl ethers was considered due to their greater lability towards oxidative conditions.[15] Another option was the use of trialkylsilyl ethers that could be removed under virtually neutral conditions using fluoride ions.[16] The appropriately substituted hydroxylamines were synthesised using a method published by Grochowski and Jurczak[17] (Schemes 2.6 and 2.7).



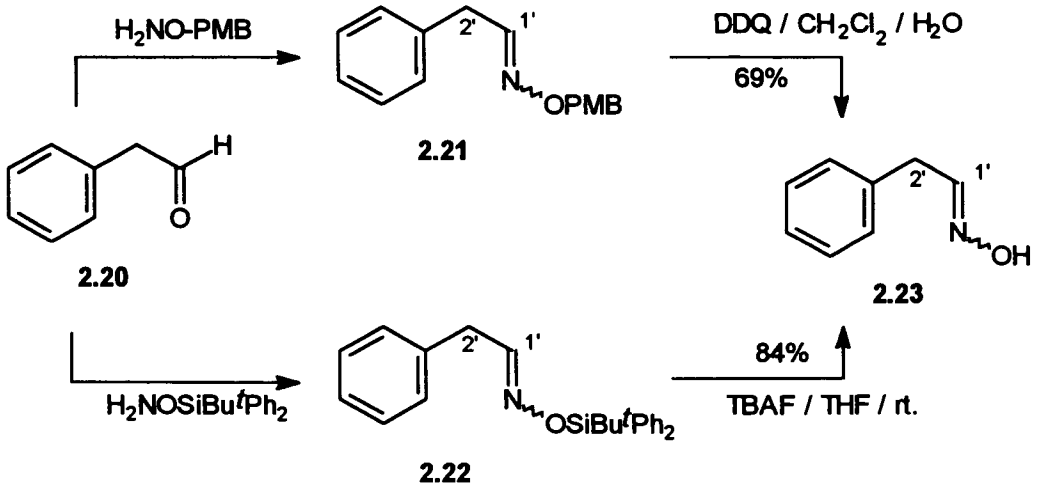
Scheme 2.6

Treatment of *N*-hydroxyphthalimide **2.15** with *p*-methoxybenzyl alcohol under Mitsunobu conditions afforded **2.16** while silylation afforded **2.17**. These compounds were reacted with hydrazine in an exchange reaction (Ing-Manske procedure)[18] to furnish the substituted hydroxylamines **2.18** and **2.19**.



Scheme 2.7

The reaction of **2.18** and **2.19** with freshly distilled phenylacetaldehyde **2.20** proceeded smoothly at room temperature to furnish the desired oximes **2.21** and **2.22**. Of the various methods available for the removal of *p*-methoxybenzyl ethers,[19] the use of 1,5 equiv. of DDQ in CH_2Cl_2-water proved to be superior.[20] The trialkylsilylethers were successfully deprotected using TBAF in THF (Scheme 2.8). The ^{13}C-NMR spectrum of the deprotected oxime **2.23** showed a shift upfield for C-1 from δ 155,7 (for **2.21**) to δ 149,5.

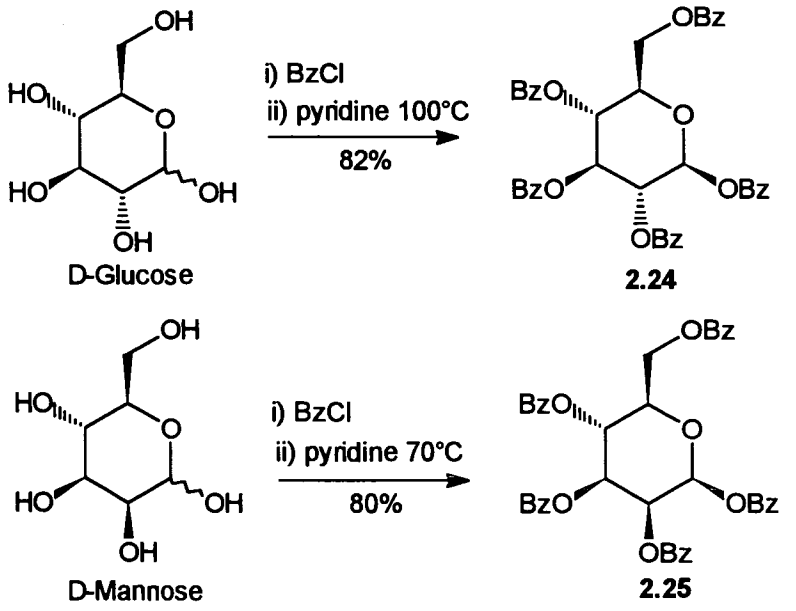


Scheme 2.8

We now had two protecting groups, which could be cleaved under essentially neutral conditions on model compounds without affecting the *N-O* bond. It was then decided to apply these results to suitably protected hemiacetals of selected hexose sugars.

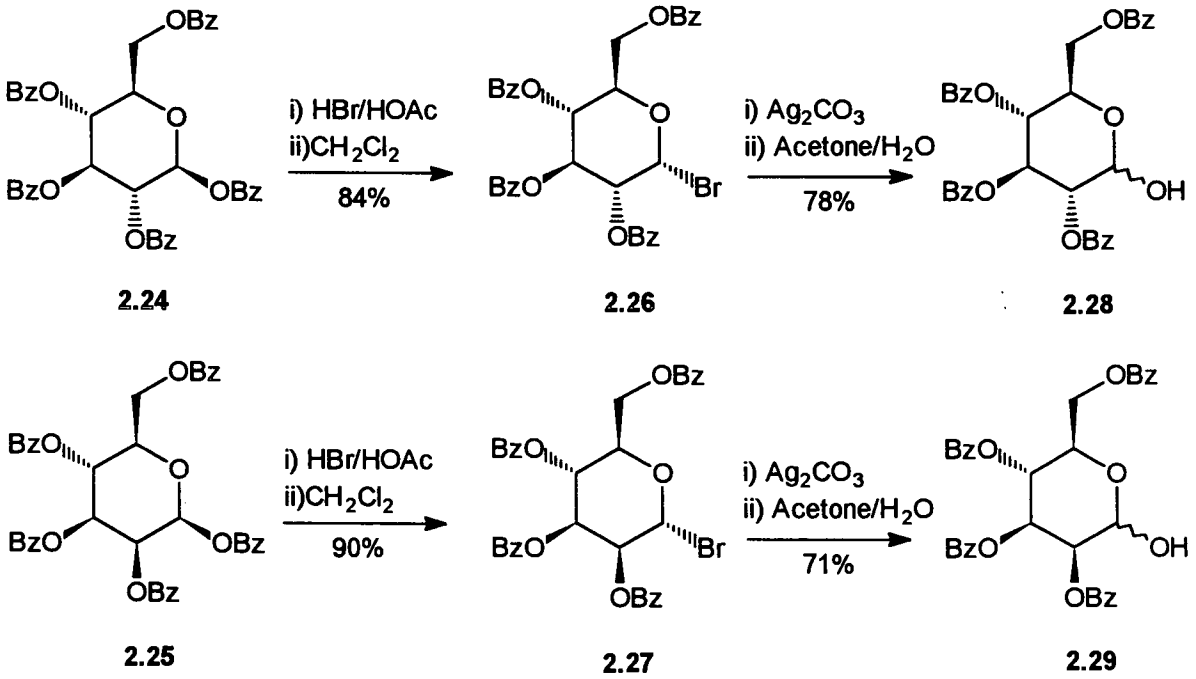
2.5. PREPARATION OF STARTING MATERIALS

The most commonly used method for the preparation of hexopyranose hemiacetals involves the hydrolysis of acylglycosyl halides in the presence of silver carbonate or silver nitrate.[21] Benzoate esters were chosen as we intended to exploit their neighbouring group participation capabilities as discussed in section 2.2. The per-benzoylated sugars were prepared according to specific methods published by Ness *et al.*[22] (Scheme 2.9).



Scheme 2.9

Any deviation from these reaction conditions resulted in complex mixtures of partially benzoylated pyranose, furanose and acyclic forms. D-Glucose was dissolved in dry pyridine and heated at 100°C for 1h after which benzoyl chloride was slowly added. The reaction mixture was maintained at 60°C for an additional 1h before work-up and chromatography furnished 1,2,3,4,6-penta-O-benzoyl-β-D-glucopyranose **2.24**. The ^{1}H-NMR spectrum of **2.24** showed a large diaxial coupling (J=7,9Hz) between H-1 and H-2 indicating that the C-1 benzoyl group is located in the equatorial position. D-Mannose was dissolved in dry pyridine and heated at 70°C for 1h before the slow addition of benzoyl chloride. The reaction mixture was maintained at this temperature for an additional 2h before workup and chromatography afforded 1,2,3,4,6-penta-O-benzoyl-β-D-mannopyranose **2.25**. The ^{1}H-NMR spectrum of **2.25** showed a small axial-equatorial coupling (J=2,1Hz) between H-1 and H-2 indicating that the C(1) benzoyl group occupies the equatorial position. The corresponding glycosyl bromides were prepared utilising an acetic acid solution of hydrogen bromide with the fully benzoylated sugars[23] (Scheme 2.10). The reaction is rapid, takes place at low temperatures, and results in the replacement of the hemiacetal ester on the anomeric carbon atom by bromine. The glycosyl halides **2.26** and **2.27** were not isolated, but immediately reacted in the next step. An analytical sample was obtained in each case by recrystallisation from an ether-hexane (2:1) solution. The ^{1}H-NMR spectra of these compounds indicated the α-anomer as the sole product. This preference for a halogen atom at C(1) to adopt the axial orientation, as the thermodynamically stable arrangement, has been termed the anomeric effect.[24]

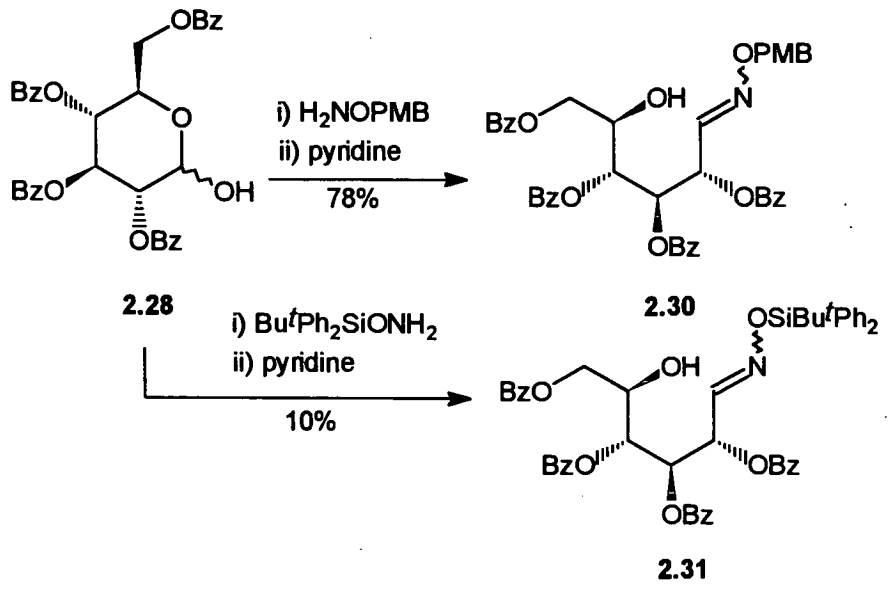


Scheme 2.10

The highly reactive pyranosyl bromides **2.26** and **2.27** were hydrolysed heterogeneously using freshly prepared silver carbonate in the presence of an equimolar amount of water.[25] The protected hemiacetals **2.28** and **2.29** were isolated as mixtures of anomers in good overall yields.

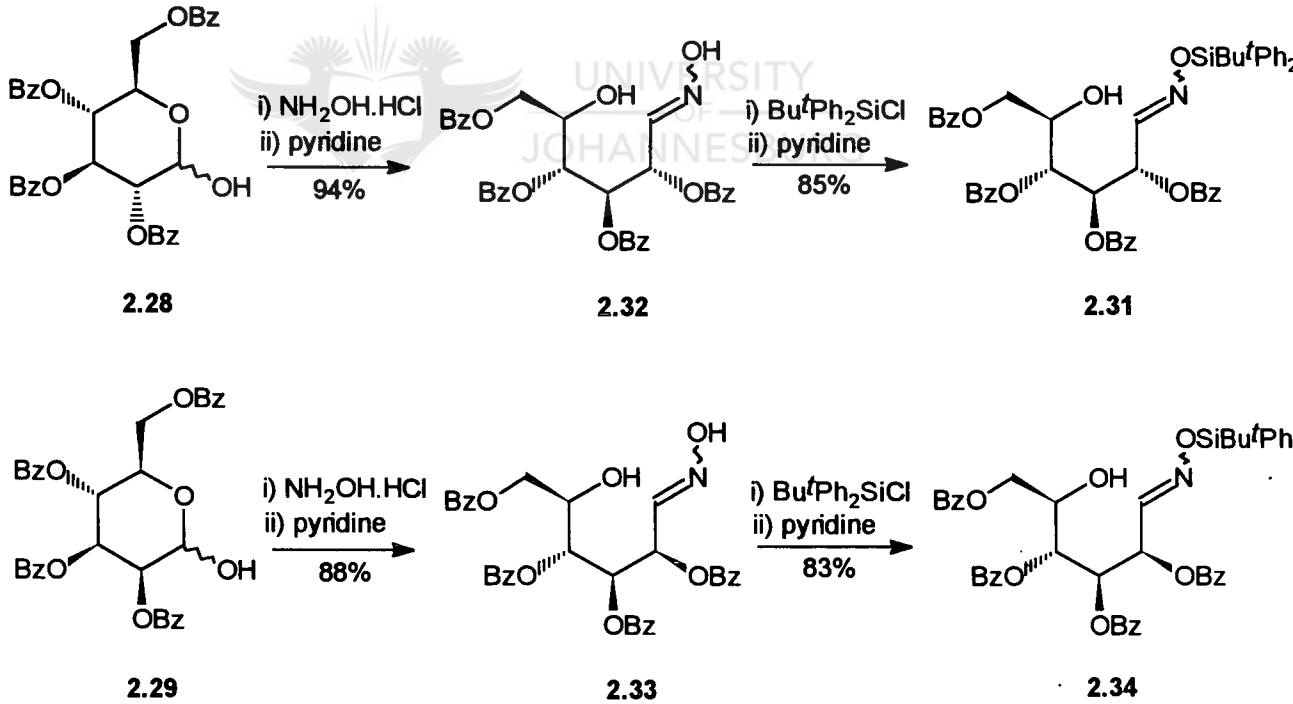
2.6 INTRODUCTION OF THE NITROGEN FUNCTIONALITY

The proposed route entails the introduction of the nitrogen functionality at C(1) *via* oxime formation. The use of oximes towards this end has been extensively developed in the past.[26] The oxime is usually reduced to the amine or dehydrated to the corresponding nitrile. The reaction of hydroxylamine with a carbohydrate hemiacetal takes place at the aldehyde functionality of the acyclic form, which only represents a small portion of the total equilibrium.[27] A solution of **2.28** and freshly prepared **2.18** in dry pyridine was stirred for 4h at room temperature after which TLC-analysis indicated the formation of a product with a higher R_f value. The ^{13}C-NMR spectrum of this compound showed C(1) resonating at δ144,41 Employing the same reaction conditions **2.28** was reacted with freshly prepared **2.19**, but only a 10% conversion to the desired product **2.31** could be achieved (Scheme 2.11). This reaction could not be optimized any further despite numerous efforts. i.e. elevated temperatures, removal of water to drive the equilibrium forward. The oximes were always isolated as mixtures of *E*- and *Z* isomers. For the sake of simplicity only the major isomer will be discussed in each case.



Scheme 2.11

In view of the failure to produce the desired protected oxime **2.31** in satisfactory yield in the manner originally envisaged, it was decided to investigate a modified approach. Treatment of **2.28** with hydroxylamine hydrochloride furnished an oxime **2.32** with two distinct hydroxy groups (Scheme 2.12). The ^{1}H-NMR spectrum of this compound showed a broad singlet resonating at δ 8,74 corresponding to the oxime hydroxy group proton, while the secondary hydroxy group on C-5 resonated as a doublet at δ 3,98 (*J*=7,5Hz). In an attempt to distinguish between the hydroxy group on the oxime and the released hydroxy group on C-5, selective silylation of **2.32** was attempted employing the sterically crowded *tert*-butyl-diphenylsilyl chloride as reagent in pyridine. The reaction mixture was stirred for 12h at room temperature after which a single product (**2.31**) was isolated. The ^{1}H-NMR spectrum of this compound showed a doublet at δ 3,48 (*J*=8,4Hz) corresponding to the C-5 hydroxy group proton, while the ^{13}C-NMR spectrum indicated a shift downfield for C-1 from δ 145,69 to δ 151,65. These results confirm the presence of the silyl group on the oxime functionality. The success attained with the glucose derivative led to the extension of this method to the mannose derivative with comparable results (Scheme 2.12).

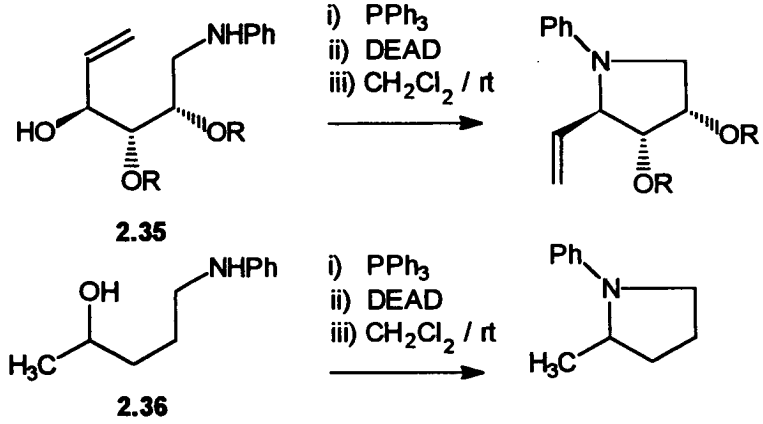


Scheme 2.12

2.7 CYCLISATION OF THE INTERMEDIATES

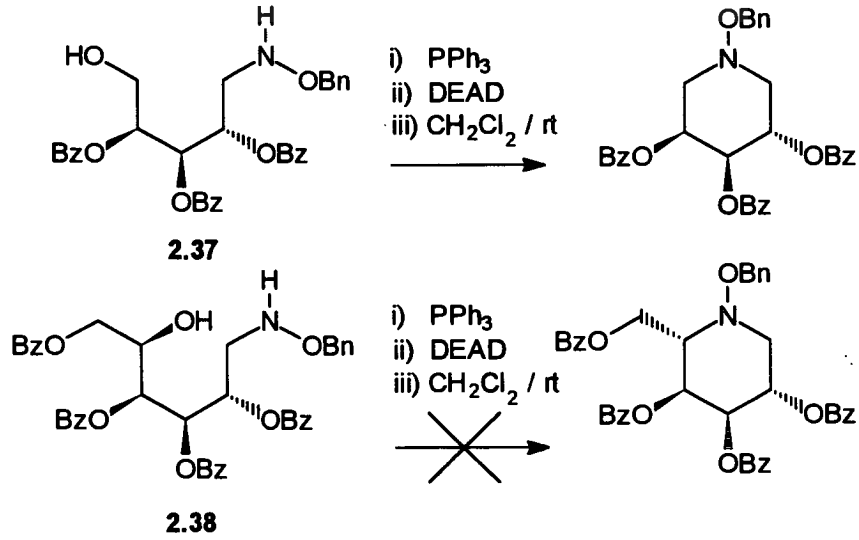
The envisaged methodology for the cyclisation of the oxime derivatives required two steps i) the conversion of the C(5) hydroxy group into a good leaving group (mesylate, tosyalte or

triflate), and ii) reduction of the oxime to the corresponding hydroxylamine followed by ring closure to furnish the desired pyrrolidines. Bernotas and Cube[28] investigated the cyclisation of related amines (Scheme 2.13). By employing Mitsunobo conditions[29] the 1,4 amino alcohols **2.35** and **2.36** were successfully cyclised in good yields.



Scheme 2.13

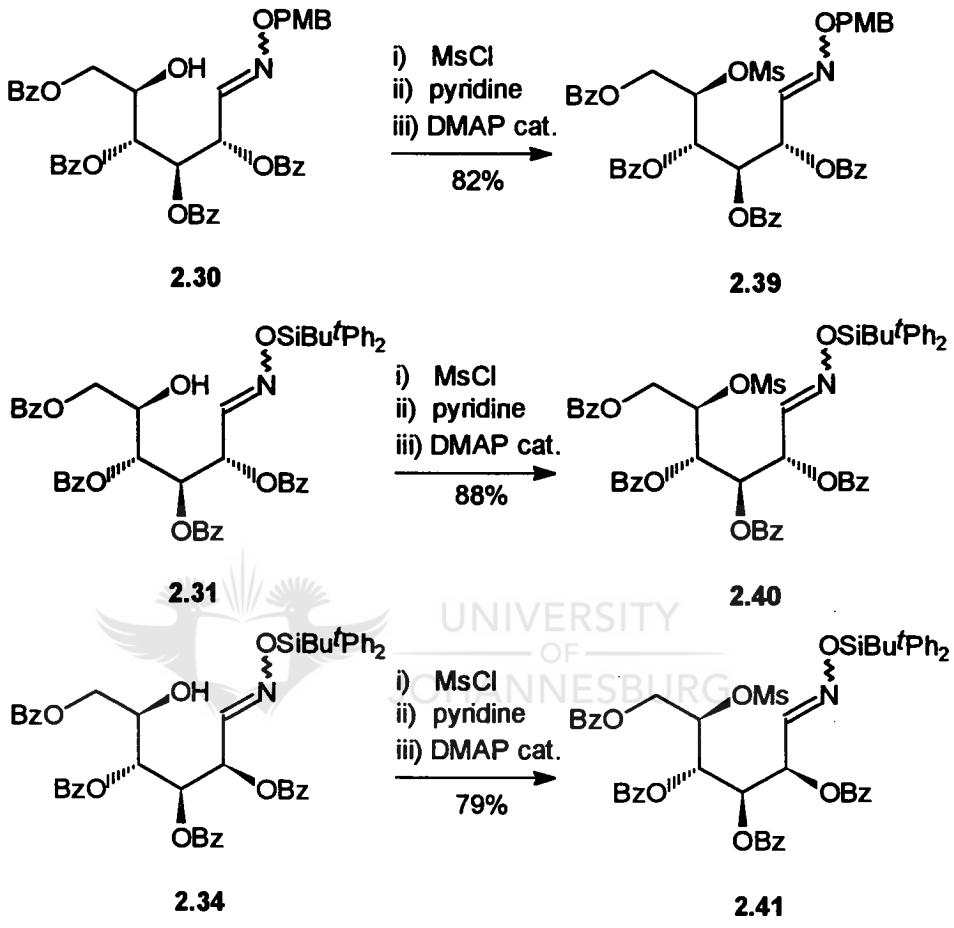
This methodology was further investigated at the RAU-laboratories on suitable carbohydrate templates.[30] It was found that activation of the primary hydroxy group in the L-arabinose derivative **2.37**, furnished a piperidine ring, while no success was achieved with **2.38** possessing a secondary hydroxy group (Scheme 2.14).



Scheme 2.14

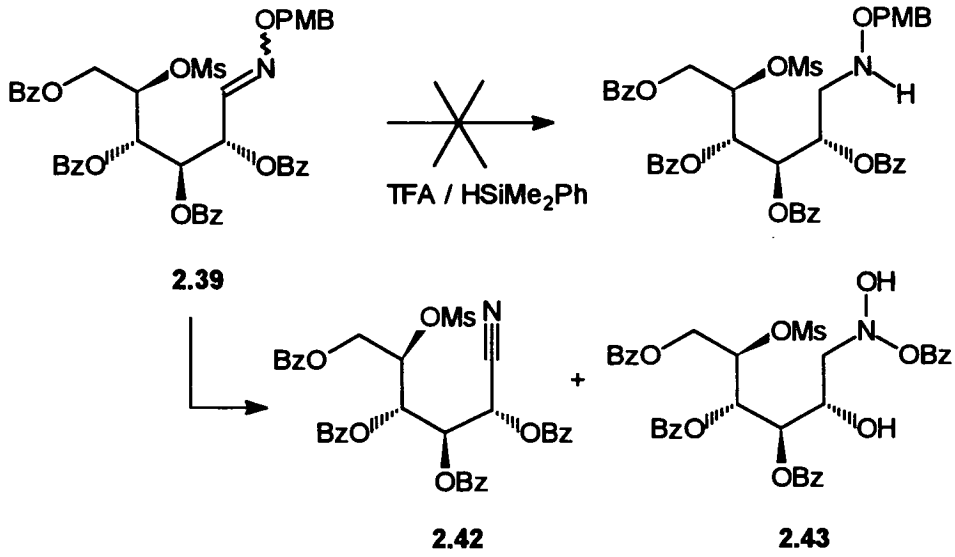
It was decided to convert the hydroxy groups of **2.30**, **2.31** and **2.34** into their corresponding mesylates. The methodology for the synthesis of sulfonic esters from alcohols is well established. Stirring a solution of mesyl chloride and pyridine for 30 min. generates an activated sulfonating complex. Addition of the latter to the sugar substrate and a catalytic

amount of 4-(dimethylamino)-pyridine resulted in the smooth conversion to the desired mesylates (Scheme 2.15). A three-proton singlet (δ 2,76) in the ^{1}H-NMR spectrum of **2.40**, was clearly indicative of the methylsulfonyl protons. In each case a considerable shift downfield was observed for H-5 while the rest of the signals remained virtually unchanged. For **2.41** the multiplet corresponding to H-5 shifted from δ 4,28 to δ 5,33.



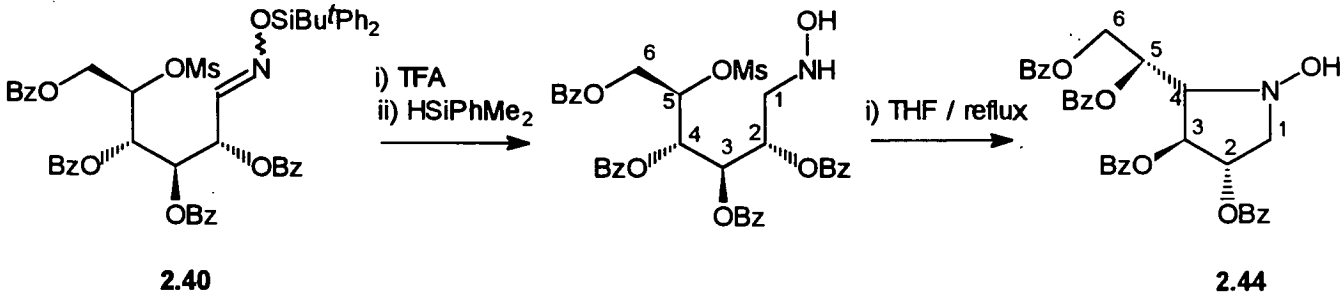
Scheme 2.15

The next step required the reduction of the oximes to the corresponding substituted hydroxylamines. The various methods known for the reduction of oximes include treatment of the oxime with ammonia in boiling ethanol, hydrogenation and reduction with lithium aluminium hydride.[31] All these methods are too drastic, as they will either result in the removal of the benzoate protecting groups or in reduction of the oximes to the corresponding unprotected amines. The acid catalysed reduction of ketones with hydrosilanes[32] was successfully modified by Fujita *et al.*[33] for the reduction of oximes to hydroxylamines. This method was further developed at the RAU laboratories[34] and it was found that the optimum conditions for reduction requires treatment of the oxime with 2.3 equivalents of dimethylphenylsilane in trifluoroacetic acid. Employing these conditions, the reduction of **2.39** was attempted (Scheme 2.16).



Scheme 2.16

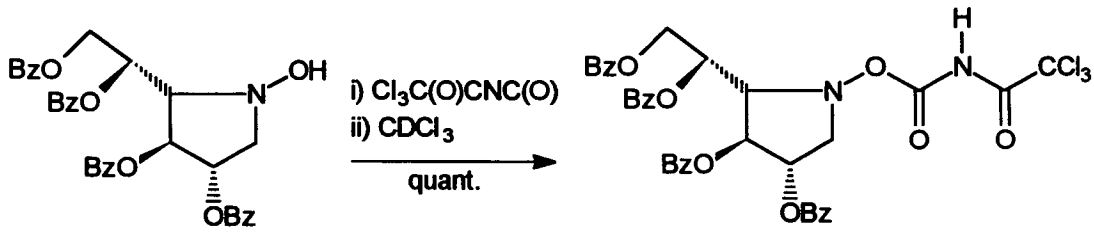
TLC-analysis of the reaction mixture indicated a wide range of products. These products could be purified to some extent and NMR studies of these mixtures provided some insight into the competing reactions at work here. The *p*-methoxy benzyl ether proved to be very labile under the acidic conditions, and one of the main products resulted from the loss of the oxime protecting group followed by dehydration to the corresponding nitrile **2.42**. The other main product **2.43** resulted from the migration of a neighbouring benzoate to the nitrogen following oxime reduction (Only compounds isolated in pure form will be discussed in the experimental section). Next, we investigated the reduction of compound **2.40** under the optimum conditions described. TLC-analysis indicated the formation of a single new product with a lower R_f-value, which proved particularly difficult to isolate. After extractive work-up the crude product was dissolved in THF and refluxed for 3h to afford compound **2.44** (Scheme 2.17).



Scheme 2.17

The FAB-MS of **2.44** showed a $[M+1]^+$ ion at m/z 596, corresponding to the cyclisation product. The ^{1}H-NMR spectrum confirmed the absence of the *tert*-butyldiphenylsilyl group.

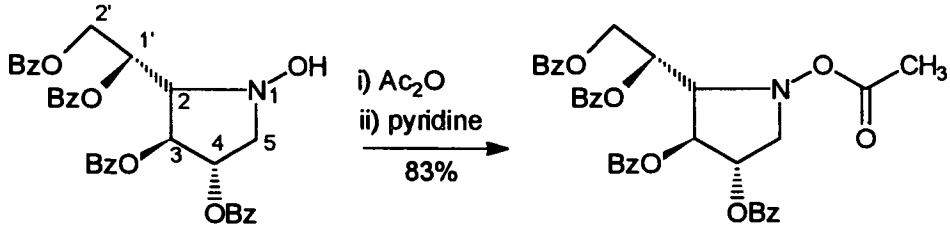
Comparing the ^{1}H-NMR spectra of **2.40** and **2.44** it is noteworthy that the doublet of doublets corresponding to H-4 shifted upfield from δ 5,89 to δ 3,56 while the chemical shift of the multiplet corresponding to H-5 shifted downfield from δ 5,23 to δ 6,05[35]. Clearly, ring closure took place on C-4 *via* the neighbouring group participation mechanism proposed in section 2.2. The addition of an equimolar amount of trichloroacetyl isocyanate to **2.44** afforded the trichloroacetyl carbamate **2.45** (Scheme 2.18).



2.44 **2.45**

Scheme 2.18

The strong electrophilic properties of this reagent allow facile reaction with alcohols and phenols (*O*-acylation) furnishing trichloroacetyl carbamates.[36] The ^{1}H-NMR spectrum of **2.45** showed a singlet resonating at δ 9,75 corresponding to the strongly deshielded amide proton. These *in situ* derivatisations are useful for the expeditious classification of alcohols by NMR-spectroscopy. Final proof of the presence of an *N*-hydroxy pyrrolidine was obtained by acetylation of **2.44** (Scheme 2.19). The ^{1}H-NMR spectrum of **2.46** indicated a diagnostic resonance for the acetyl protons (as a three-proton singlet at δ 2,01). It is also interesting to note that the two proton doublet corresponding to H(5a) and H(5b) in **2.44** was replaced by two doublet of doublets resonating at δ 3,83 and δ 3,66 in **2.46**.

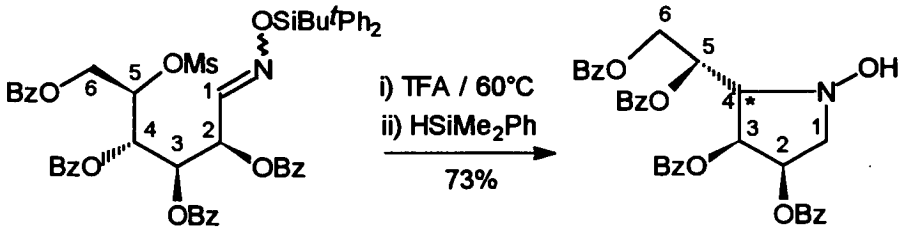


2.44 **2.46**

Scheme 2.19

Having successfully performed the reduction, deprotection and cyclisation of the D-glucose derived precursor **2.40** in two steps the corresponding one pot sequence of reactions with **2.41** was attempted. It was anticipated that although the nitrogen of the reduced intermediate will be protonated under these conditions, cyclisation would occur *via* a small equilibrium

amount of the free amine in the reaction mixture. To a solution of **2.41** in TFA at 60°C was added 2,3 equivalents of dimethylphenylsilane. TLC analysis of the reaction mixture indicated complete conversion of the starting material after 30 minutes. Chromatography afforded **2.47** in a yield of 73% (Scheme 2.20).

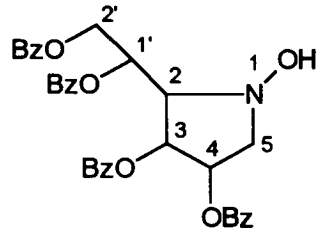


2.41 **2.47**

Scheme 2.20

The FAB-MS of **2.45** showed a $[M+1]^+$ ion at m/z 596, corresponding to the cyclisation product. Comparing the ^{1}H-NMR spectra of **2.41** and **2.47** it is again clear that ring closure took place on C-4 *via* the neighbouring group participation mechanism proposed in section 2.2. The doublet of doublets corresponding to H-4 shifted upfield from δ 6,16 to δ 4,04 while the chemical shift of the multiplet corresponding to H-5 changed from δ 5,39 to δ 6,05.

For further discussions, the cyclisation products will be named and numbered as *N*-hydroxy-1',2',3,4-tetra-*O*-benzoyl-2-(1,2-dihydroxyethyl)pyrrolidines.

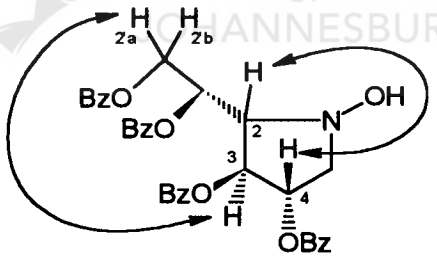


The relative stereochemistries of the novel pyrrolidine rings were deduced by direct comparison of their ^{1}H-NMR data and coupling constants with the analytical data of **2.9** and **2.11** for which the stereochemistry was known. The excellent correlation of ^{1}H-NMR data between **2.44** and compound **2.9** led us to believe that their relative stereochemistry were the same (Table 2.1). These results suggested that the cyclisation reaction leading to **2.44** proceeded with inversion of stereochemistry at C-2.

Table 2.1. Comparison of ^{1}H-NMR data for pyrrolidines derived from D-glucose

Compound **2.9**				Compound **2.44**			
H-2	δ 3,75	dd	J = 5,7 and 4,2Hz	H-2	δ 3,75	dd	J=9,8 and 3,9Hz
H-3	δ 5,89	dd	J = 5,7 and 1,6Hz	H-3	δ 5,86	dd	J=9,8 and 1,7Hz
H-4	δ 5,51	m		H-4	δ 5,52	m	
H-5a	δ 3,47	dd	J = 11,8 and 5,6Hz	H-5a	δ 3,58	d	J=6,3Hz
H-5b	δ 3,35	dd	J = 11,8 and 3,1Hz	H-5b	δ 3,58	d	J=6,3Hz
H-1'	δ 6,09	m		H-1'	δ 6,07	m	
H-2'a	δ 4,74	dd	J = 11,7 and 4,8Hz	H-2'a	δ 4,66	dd	J=12,0 and 1,8Hz
H-2'b	δ 4,65	dd	J = 11,7 and 6,6Hz	H-2'b	δ 4,62	dd	J=12,0 and 8,0Hz

This observation was confirmed by an nOe NMR-experiment which indicated a strong 1,4 nOe effect between H-3 and H2'a as well as a weak 1,3 nOe effect between H-4 and H-2 (Scheme 2.21)



2.44

Scheme 2.21

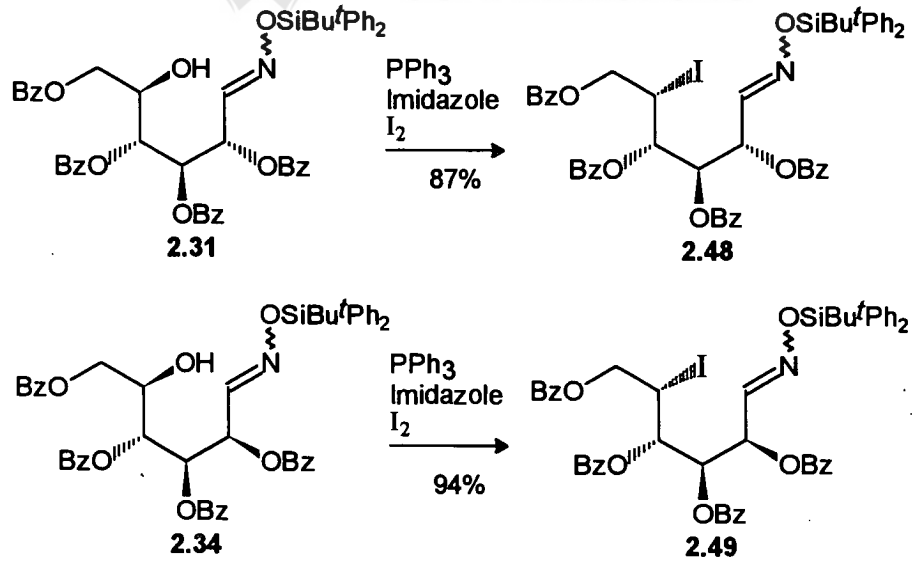
In the same manner the ^{1}H-NMR data of **2.47** and compound **2.11** showed a near perfect correlation which led us to believe that their relative stereochemistries were the same (Table 2.2). This result suggested that the cyclisation reaction leading to **2.47** proceeded with inversion of stereochemistry at C-2.

The effect of a different leaving group in the cyclisation reaction was examined next. It was decided to replace the secondary hydroxy group on C-5 of the silyl-protected oximes with iodine using methodology developed by Garegg and Samuelsson.[37]

Table 2.2. Comparison of ^{1}H-NMR data for pyrrolidines derived from D-mannose

Compound **2.11**				Compound **2.47**			
H-2	δ 4,03	dd	J=7,8 and 3Hz	H-2	δ 3,98	dd	J=6,9 and 4,2Hz
H-3	δ 5,89	dd	J=7,8 and 6Hz	H-3	δ 5,81	t	J=6,4Hz
H-4	δ 5,67	q		H-4	δ 5,53	q	
H-5a	δ 3,96	dd	J=11,9 and 5,7Hz	H-5a	δ 3,79	dd	J=11,6 and 6,2Hz
H-5b	δ 3,47	dd	J=11,9 and 5,3Hz	H-5b	δ 3,28	dd	J=11,6 and 5,8Hz
H-1'	δ 6,05	m		H-1'	δ 6,02	m	
H-2'a	δ 4,72	dd	J=11,7 and 4,8Hz	H-2'a	δ 4,72	dd	J=11,9 and 4,3Hz
H-2'b	δ 4,64	dd	J=11,7 and 7,2Hz	H-2'b	δ 4,62	dd	J=11,9 and 6,9Hz

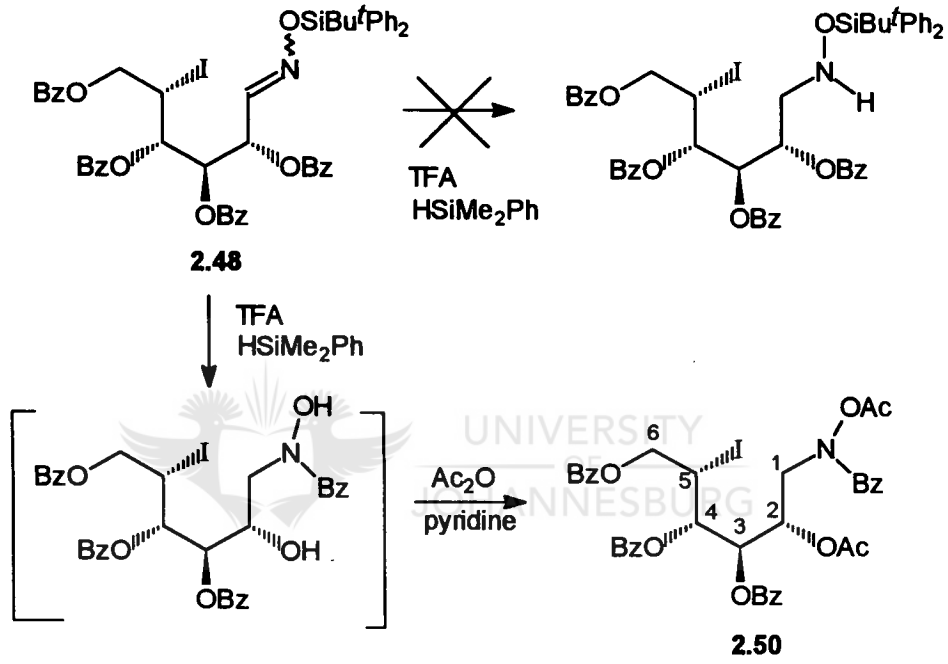
They employed a triphenylphosphine, iodine and imidazole system in toluene for the displacement with inversion of configuration of a single free hydroxy group with iodine in otherwise protected carbohydrates. Utilizing these conditions, **2.31** and **2.34** were smoothly converted into the corresponding iodo-compounds in high yields (Scheme 2.22).



Scheme 2.22

The ^{13}C-NMR spectra of **2.48** and **2.49** showed diagnostic signals at δ 26,4 and δ 32,4 respectively for the C-5 carbons. Subjecting **2.48** to the optimum conditions described earlier for reduction of the oxime only resulted in the formation of a wide range of polar products as

indicated by TLC. All attempts to cyclise **2.48** in a one pot reaction also failed. It was decided to acetylate the total reaction mixture 5 minutes after the addition of dimethylphenylsilane with the hope of trapping any possible reaction intermediates (Scheme 2.23). This strategy proved very successful, and a mixture of two isomers was isolated in a yield of 74%. It is suggested that the main isomer, identified as **2.50** resulted from migration of the neighbouring benzoate[38] on C-2 to the generated amine group. This would effectively prevent the nitrogen from participation in a cyclisation reaction, and explain the failure of **2.50** to cyclise after reduction took place.



Scheme 2.23

The fact that reduction of the oxime took place was confirmed by the ^{13}C-NMR spectrum of **2.50**, which indicated the absence of the characteristic oxime carbon at δ 151,25. Further inspection of the ^{13}C-NMR data showed the presence of the carbon bearing iodine (δ 26,51), as well as the two acetates (δ 168,41; 167,77; 18,18 and 18,13).

Several generalizations with respect to the cyclisation reaction of the various protected oxime intermediates can be made as follows:

i) The choice of leaving group was crucial to initiate the neighbouring group cascade reaction. Replacing the O-mesylate group with a poorer leaving group such as iodine prevented neighbouring group participation by the benzoate groups , clearly a

prerequisite for facile cyclisation.

ii) Performing the one-pot cyclisation reaction of **2.41** under acidic conditions greatly enhanced the speed and efficiency of the cyclisation reaction. This can possibly be ascribed to enhanced nucleofugality of the 5-*O*-mesylate group, resulting from protonation of the oxygen rich group. Even in the case of the cyclisation of **2.40** under initially neutral conditions, the cyclisation may be catalysed by methanesulphonic acid formed in the reaction.

iii) In the cases where cyclisation was slow or not observed (as for **2.39** and **2.47**) the migration of a neighbouring *O*-benzoyl group to the deprotected amine nitrogen took place. This prevents any possibility of the nitrogen taking part in the cyclisation reaction.

2.8 FUTURE WORK UTILIZING SILYL-PROTECTED OXIMES

The problem of a suitable protecting group for oximes was resolved. A variety of other protected hemiacetals are currently being investigated as possible substrates. This will give further insight into the scope and limitations of the neighbouring group cascade mechanism operating in the cyclisation reactions. The choice of a leaving group proved to be of great import and a detailed investigation into other possible groups is necessary. It is envisaged that these synthons can eventually be converted into isosteric analogues of indolizidine alkaloids *via* the proposed sequence of transformations discussed in section 2.1. The favourable results obtained in the cyclisation of the mesylated O-(*tert*-butyldiphenylsilyl) oximes provided an efficient route towards chiral *N*-hydroxypyrrolidines.

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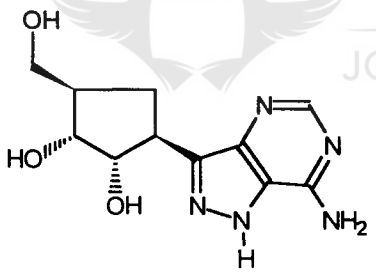
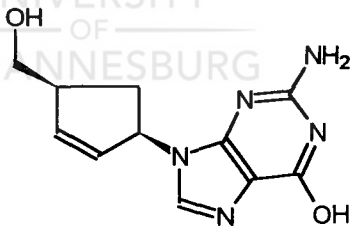
CHAPTER 3
SYNTHESIS OF CHIRAL CYCLIC NITRONES

3.1 INTRODUCTION

Nucleosides and nucleoside analogues have long been an important class of medicinal agents, possessing anticancer and antiviral activity.[1] The recent interest in modified nucleosides has centered on the development of reverse transcriptase inhibitors as potential AIDS therapies.[2] These versatile molecules have also been used in the fight against protozoan parasite infections[3]. These are a major health problem worldwide, with more than a million deaths per year from malaria, trypanosomiasis and related infections. In the search for effective and non-toxic antiviral agents, a variety of modified nucleoside analogues are currently being developed.[4] The strategies which have been employed involve several formal modifications of the naturally occuring nucleosides, particularly alteration of the carbohydrate moiety.[5] Carbocyclic nucleosides[6] are an important class of modified nucleosides in which the furanose ring has been replaced by a cyclopentane ring. The natural product aristeromycin (**3.1**),[7] obtained from *Streptomyces citricolor*, is a prominent member of this family, and has demonstrated a high degree of cytotoxicity in cell cultures while carbovir (**3.2**)[8] is an example of a synthetic cyclopentenoid nucleoside.

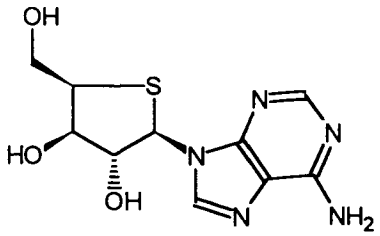


3.1



3.2

4'-Thionucleosides have also received attention in recent years due largely to the reported anti-HIV activity of the 2'-deoxy analogues.[9] In a recent publication, Hartsel and Marshall[10] reported the first synthesis of 9-β-(4-thioxylofuranosyl)adenine (**3.3**) while Kikuchi *et al.*[11] synthesised the 4'-thio analogue (**3.4**) of 9-(2',3'–dideoxy-2',3'-bis-*C*- hydroxymethyl–α-L-threofuranosyl)adenine. Diheterosubstituted nucleosides constitute a unique class of potential antiviral agents with lamivudine[12] (**3.5**) as an important example.



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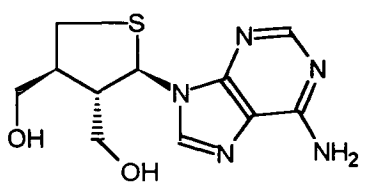

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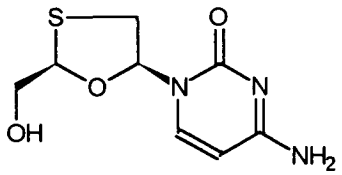
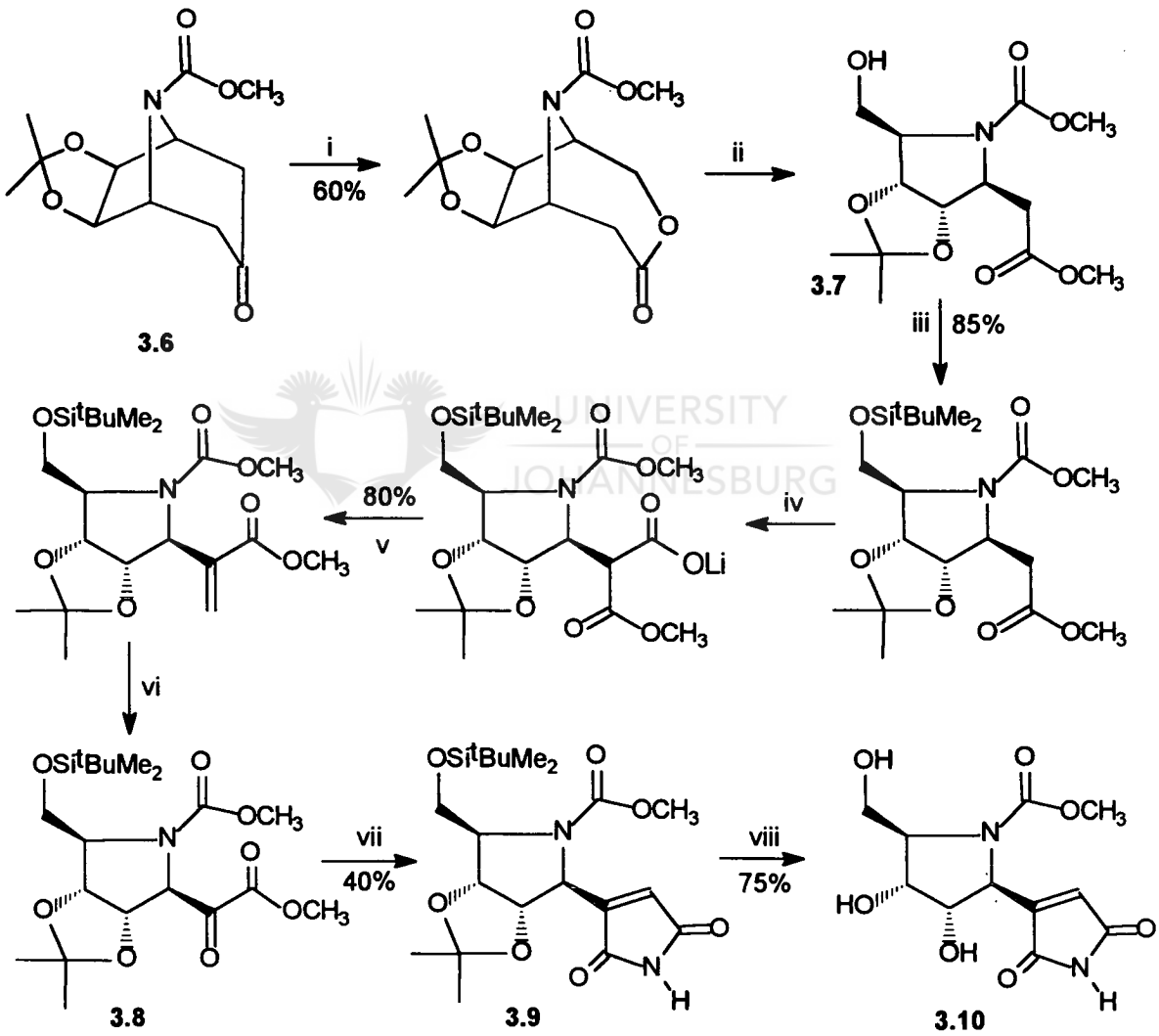


3.5

3.2 SYNTHESIS OF β-*C*-AZANUCLEOSIDES

As part of an ongoing investigation in our laboratories into the synthesis of isosteric analogues of biologically active compounds,[13] we were interested in synthesising the aza analogues of β-*C*-nucleosides and β-*C*-glycosides. Compared to the synthetic endeavours directed at the compounds discussed previously, these analogues have received little attention over the years and only a few examples could be found in the literature. Just and Donnini[14] reported the synthesis of a showdomycin analogue (**3.10**) in which an *N*-carbomethoxy group (Scheme 3.1) replaces the ribofuranosyl ring oxygen.



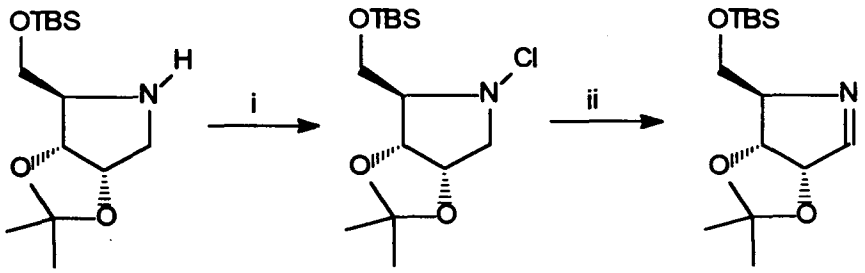
REAGENTS: i) Baeyer-Villiger oxidation ii) NaOMe iii) ^{t}BuMe$_2$SiCl / py iv) LDA / CO_2 v) aq. formaldehyde / NEt_2 vi) ozonolysis / Me_2S vii) carbamoylmethylene-triphenylphosphorane viii) aq. CF_3CO_2H

Scheme3.1

In this synthesis,the teloidinone derivative **3.6** was converted to the pyrrolidine **3.7** in two steps. The authors then proceeded to construct the heterocyclic base. The key step involves

the reaction of the α-ketoester **3.8** with carbamoyl-methylenetriphenylphosphorane in chloroform to furnish **3.9**. The maleimide **3.9** was deprotected with 50% aqueous trifluoroacetic acid to afford the triol **3.10** (overall yield of 7% starting from **3.6**).

Following a more convergent approach, Horenstein *et al.*[15] synthesised a new class of *N*-glycohydrolase transition state analogue inhibitors using the reaction between an iminoribitol and an organometallic aglycon species (Scheme 3.2). *N*-Halogenation of pyrrolidine **3.11** followed by dehydrohalogenation under kinetic control afforded imine **3.12** as the desired regioisomer.

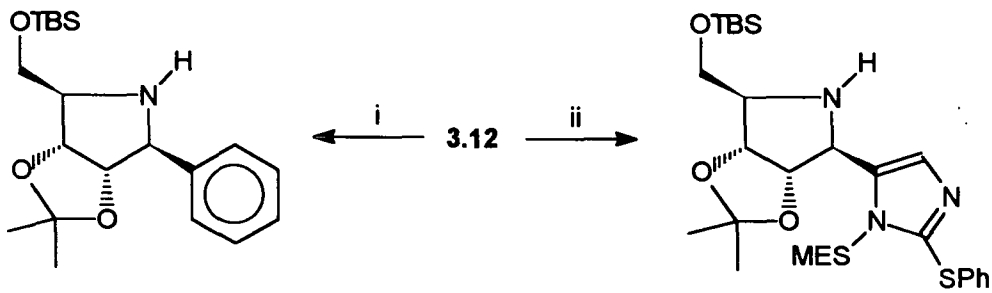


3.11 **3.12**

REAGENTS: i) *N*-Clorosuccinimide / pentane / 30 min. ii) Lithium tetramethyl piperidine / THF / -78°C / 30 min.

Scheme 3.2

This intermediate reacted with phenylmagnesiumbromide as well as lithiated imidazole to give rise to interesting nucleoside analogues **3.13** and **3.14** respectively (Scheme 3.3). Furneaux *et al.*[16] later published comparable results using the same iminoribitol **3.12** as the key intermediate.

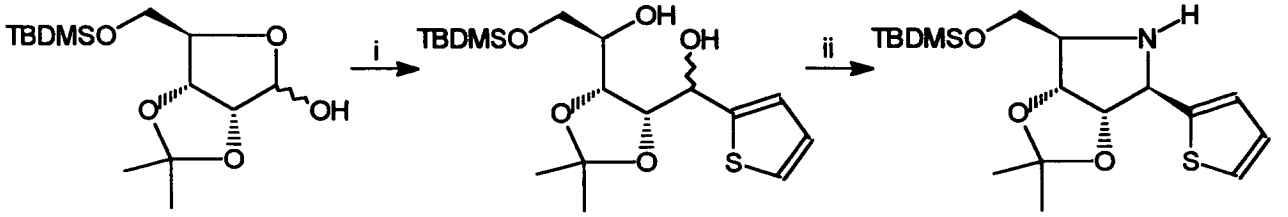


3.13 **3.14**

REAGENTS: i) 2 eq. PhMgBr / Et_2O / -78°C / 30 min. ii) lithiated heterocycle / THF / -78°C / 1h

Scheme 3.3

In a recent publication, Yokoyama *et al.*[17] reported a general β-stereoselective synthesis of *C*-azanucleosides (Chapter 1: section 1.3) based on the attack of a lithiated heterocycle on a protected ribose hemiacetal (Scheme 3.4). This method is the most elegant and economical to date as a variety of heterocycles can be introduced with moderate to good β-selectivity.



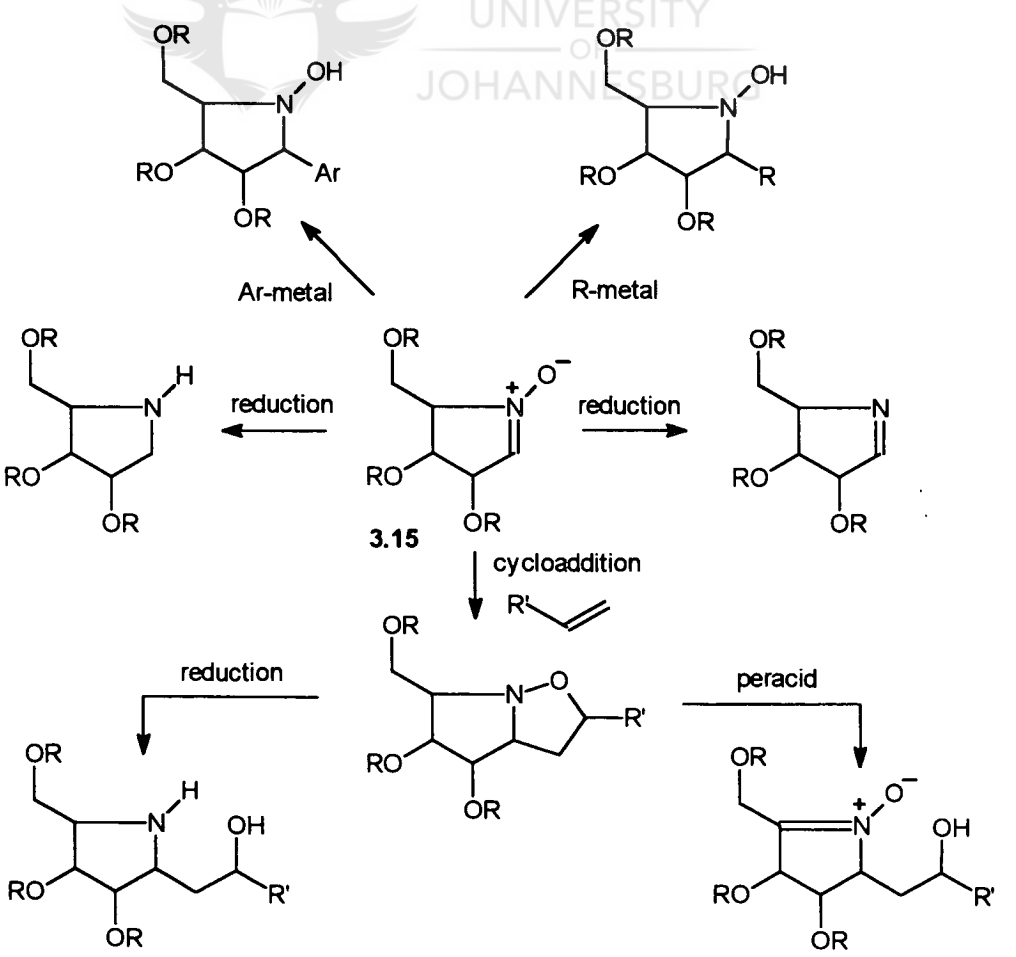
REAGENTS: i) 2-Thienyllithium / THF ii) a: DMSO / TFAA b: $NH_4^+ HCOO^-$ / $NaBH_3CN$

Scheme 3.4

3.3 CYCLIC NITRONES AS SYNTHONS FOR β-*C*-AZANUCLEOSIDE SYNTHESIS

3.3.1 STRATEGY

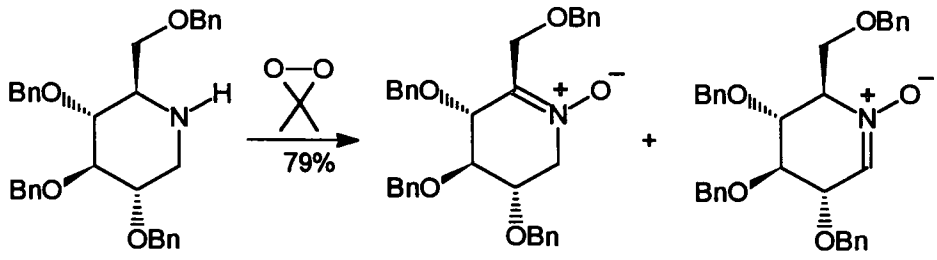
Our strategy for the synthesis of β-*C*-azanucleosides involves the use of an appropriate carbohydrate derived cyclic nitrone (**3.15**) as key intermediate (Scheme 3.5).



Scheme 3.5

A number of the envisaged chemical modifications of such a nitrone are summarised in scheme 3.5. These include the 1,3-dipolar cycloaddition reaction of a nitrone and an alkene which is an extremely powerful synthetic method for the creation of complex heterocyclic structures.[18] As a result of the labile nature of the *N-O* bond in the formed isoxazolidines,[19] they have long been used as precursors to 1,3-amino alcohols in synthesis. Furthermore, the α-carbon of a nitrone is electrophilic enough to be attacked by a variety of carbon nucleophiles, including Grignard reagents.[20] The rich chemistry displayed by these 1,3-dipoles makes them attractive targets, but the preparative methods for chiral cyclic nitrones of type **3.15** remain limited. The classical method for the synthesis of cyclic nitrones is the dehydrogenation of *N,N*-disubstituted hydroxylamines.

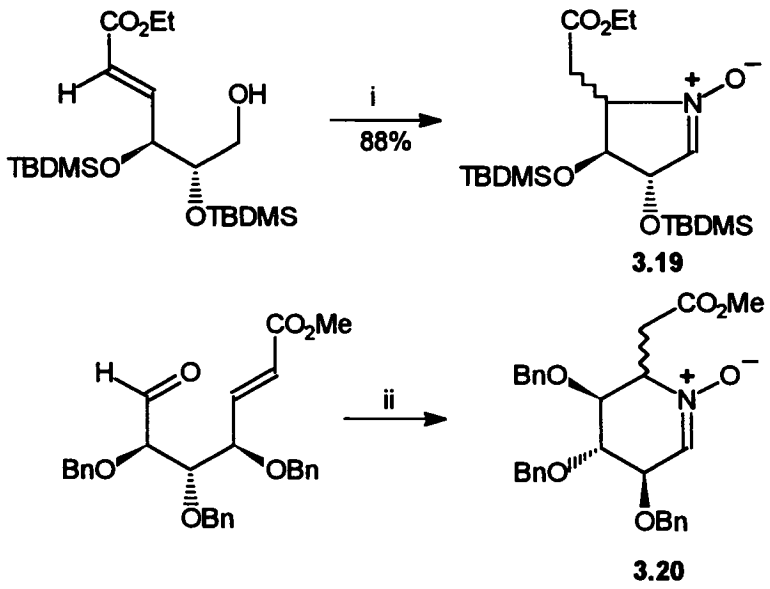
Most of the work done in this field involves the oxidation of C-2 symmetrical pyrrolidines to afford one possible regioisomer (See chapter 1,section 1.5). The oxidation agents most commonly used include H_2O_2 / SeO_2,[21] NMO / cat. TPAP[22] or HgO.[23] However, the oxidation of asymmetrical pyrrolidines and piperidines always furnishes a mixture of regioisomers. This fact was clearly demonstrated by the research of Van den Broek[24] who synthesised cyclic nitrones *via* the oxidation of protected 1-deoxynojirimycin **3.16** using 2,2-dimethyldioxirane (Scheme 3.6).



3.16 **3.17** **3.18**

Scheme 3.6

The oxidation was not regiospecific and the nitrone with the more substituted double bond was isolated as the major product (product ratio 3:1 for **3.17**:**3.18**). The isolation and separation of the isomers also proved tedious. Recently, the synthesis of pyrrolidine[25] (**3.19**) and piperidine[26] based nitrones (**3.20**) derived from carbohydrates was reported. The nitrone functionality was obtained by the intramolecular conjugate addition of an oxime[27] onto a proximate electronegative alkene. In both cases the nitrones were isolated as a mixture of diastereoisomers.



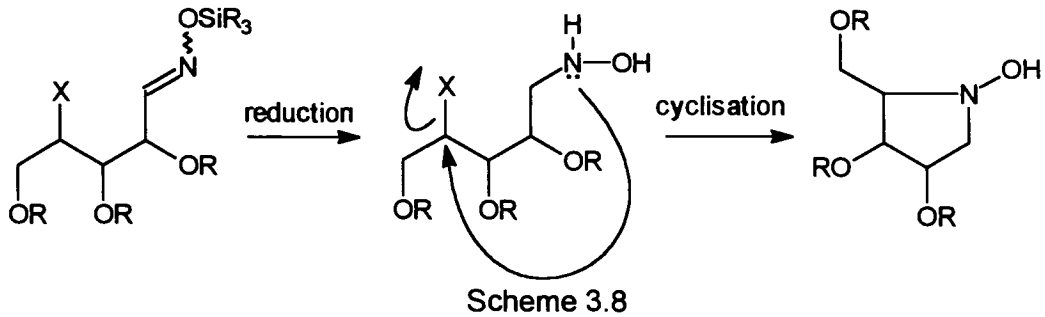
REAGENTS: i) a: Oxalyl chloride / DMSO b: $NH_2OH.HCl$
ii) NH_2OH / EtOH-H_2O / rt

Scheme 3.7

Clearly, a stereospecific synthesis for these highly versatile intermediates is lacking.

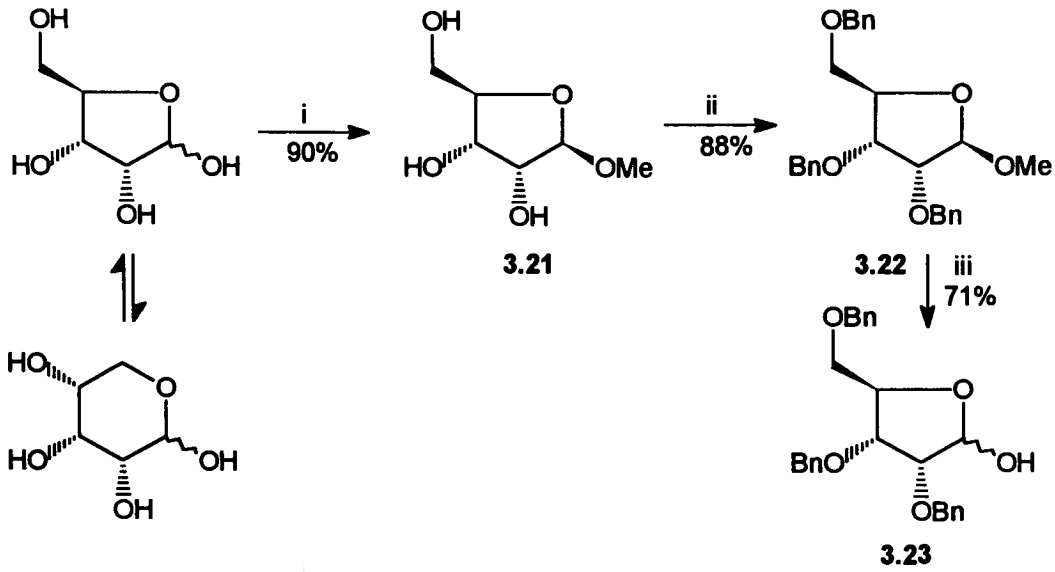
3.3.2 OXIDATION OF ASYMMETRICAL PYRROLIDINES

Our first objective was to investigate the scope of the oxidation of unsymmetrical *N*-hydroxy pyrrolidines and to investigate the possibilities of improving the regioselectivity of these reactions. We decided to utilize the same strategy as discussed in chapter 2 for protected *N*-hydroxy pyrrolidines to prepare suitable substrates. With the synthesis of nucleoside analogues in mind, pentose sugars were selected as starting materials. The choice of a protecting group was crucial as we did not envisage using the neighbouring group participation reaction to form the five membered rings in this case. Since our strategy involved the reduction of a suitably protected oxime and subsequent direct displacement of the leaving group by the nitrogen lone pair to form an *N*-hydroxy pyrrolidine (Scheme3.8), protection of the hydroxy groups as their benzylethers appeared to be appropriate.



Scheme 3.8

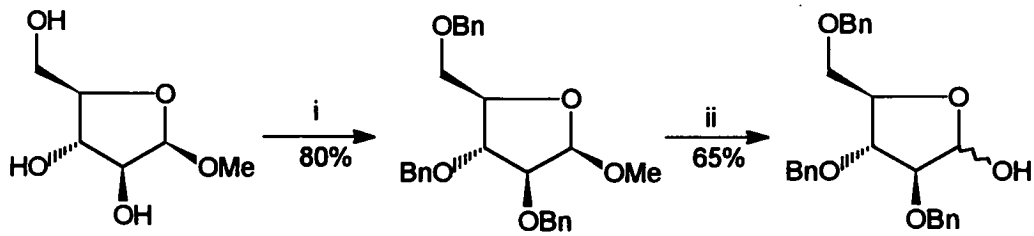
They are robust and stable to a wide range of aqueous acidic and basic conditions, and they are not readily attacked by most metal hydride reducing agents or mild oxidizing agents. A new strategy was therefore developed for the synthesis of the protected hemiacetals required in this study (Scheme 3.9).



REAGENTS: i) MeOH / H_2SO_4 / 0°C / 12 h ii) NaH 3eq / DMF / BnBr / 3 h
iii) dioxane / aq HCl / 70°C / 2h

Scheme 3.9

Natural D-ribose occurs in the furanose form. However, upon methylation a mixture of pyranosides and furanosides is generally obtained. Employing a method published by Barker and Fletcher,[28] D-ribose was converted in high yield to the crystalline methyl β-D-ribofuranoside (**3.21**). Thus, treatment of the free sugar with methanolic sulfuric acid at 0°C overnight resulted in the formation of the kinetically favoured furanose form (**3.21**) in a yield of 90%. Full *O*-benzylation of **3.21** was achieved using standard conditions. The product (**3.22**) was hydrolyzed in dioxane with aqueous hydrochloric acid to furnish 2,3,5-tri-*O*-benzyl-D-ribofuranose (**3.23**) as a mixture of anomers. Employing the same conditions D-arabinose was converted into 2,3,5-tri-*O*-benzyl-D-arabinofuranose **3.25** (Scheme 3.10). The hydrolysis of **3.24** initially proceeded very slowly, but continuous removal of the distillate and addition of fresh portions of dioxane every 10 minutes resulted in a dramatic increase in the reaction rate. As this is a reversible reaction, the removal of methanol is crucial to shift the chemical equilibrium towards formation of the desired product.

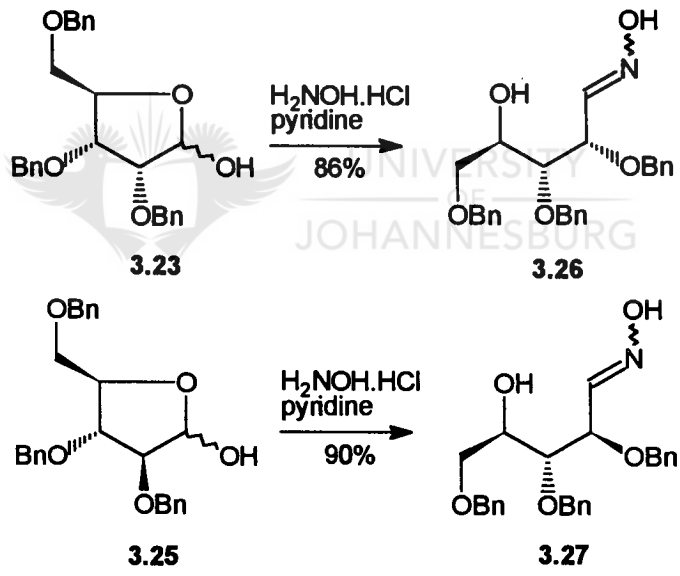


3.24 **3.25**

REAGENTS: i) NaH / DMF / BnBr ii) dioxane / aq HCl / 80°C / 4 h

Scheme 3.10

The next step required the reaction of the benzylated hemiacetals with hydroxylamine to afford the acyclic derivatives **3.26** and **3.27** (Scheme 3.11).

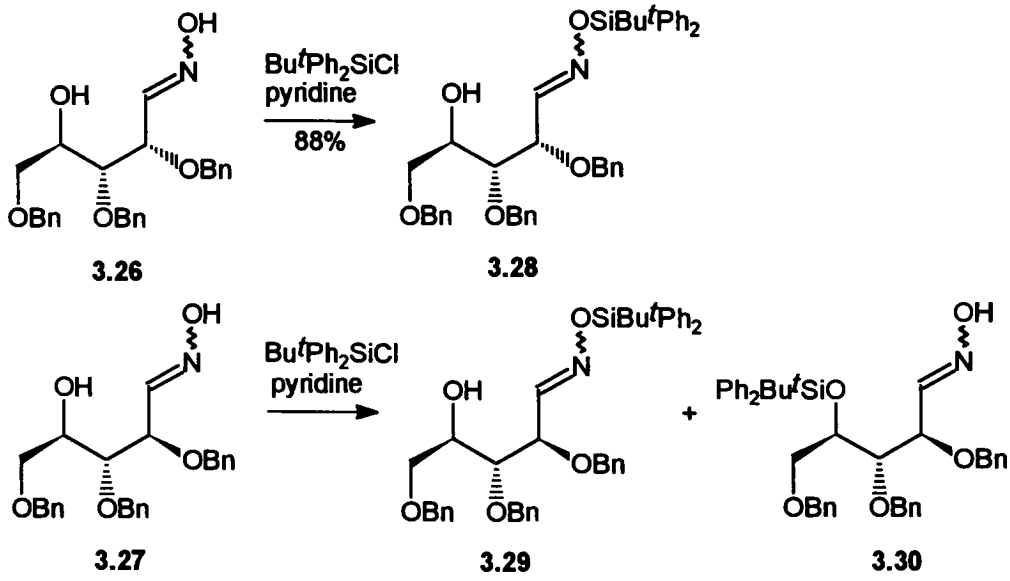


3.23 **3.26**

3.25 **3.27**

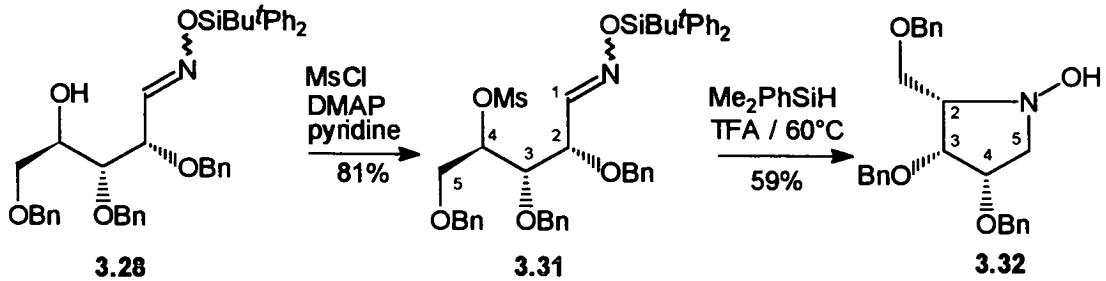
Scheme 3.11

The ^{1}H-NMR spectrum of **3.26** showed a 2:1 mixture of *syn* and *anti* isomers with the diagnostic carbon bound oxime proton of the main isomer resonating as a doublet (J=8,4Hz) at δ 7,47 and the proton of the released hydroxy group as a doublet (J=3,6Hz) at δ 3,65. The success of the synthetic route depends on the ability to distinguish between the primary hydroxy group on the oxime and the secondary hydroxy group on C(5) through selective silylation (See Chapter 2, section 2.3). The oximes **3.26** and **3.27** were allowed to react with *tert*-butyldiphenylsilyl chloride in pyridine at room temperature (Scheme 3.12). After 6 hours TLC analysis indicated the complete consumption of the starting materials and the products were purified by chromatography on silica.



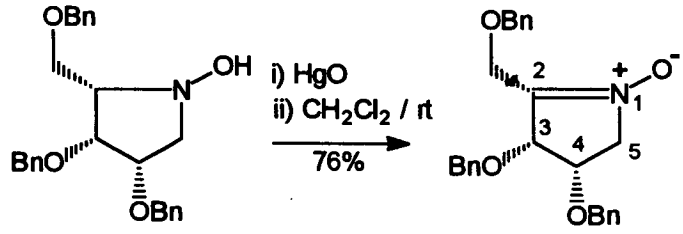
Scheme 3.12

The selective *O*-silylation of the D-ribose derived oxime was successful and **3.28** was isolated in a yield of 88%. Analysis of the NMR-spectrum of the silylated D-arabinose derived oxime **3.27** indicated a mixture of two compounds (**3.29** and **3.30**) in a 3:2 ratio. All attempts to improve the selectivity of the silylation were unsuccessful. For example, performing the reaction at –40°C as well as changing the solvent to methylene chloride with imidazole as base afforded essentially the same mixture of products. Mesylation of **3.28** was carried out using standard conditions and **3.31** was isolated in good yield. The use of optimum conditions for the one-pot reduction and cyclisation strategy of suitably protected oximes (Chapter2, section 2.4) was attempted next. Treatment of the oxime derivative **3.31** in TFA at 60°C with 2,3 equivalents of dimethylphenylsilane furnished the *N*-hydroxy pyrrolidine **3.32** in moderate yield. Non-carbohydrate nomenclature and numbering are used for **3.32** and all related cyclic compounds.



Scheme 3.13

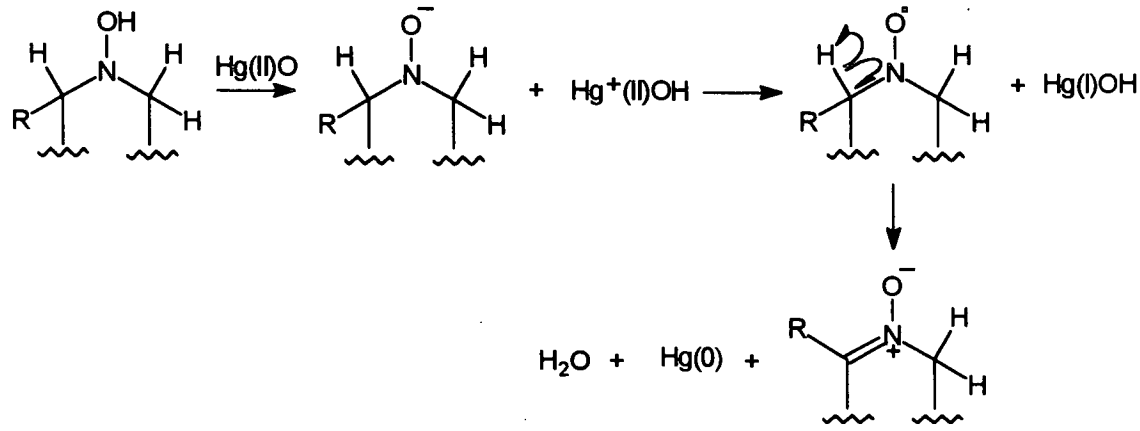
The EI-MS of **3.32** showed a molecular ion at m/z 419, corresponding to a cyclisation product. The ^{1}H-NMR spectrum of the compound showed the resonances expected for two ABX-systems corresponding to H-5a and H-5b (δ 3,80 and δ 3,71) and H-2'a and H-2'b (δ 3,48 and δ 3,18). The multiplet observed for H-4 in **3.31** (δ 5,03) was replaced by a multiplet resonating at higher field (δ 4,19) in the ^{1}H-NMR spectrum of **3.32**, confirming that cyclisation did indeed take place at C-4. The presence of an *N*-hydroxy group was confirmed by the addition of the shift reagent, trichloroacetyl isocyanate, to the NMR sample tube. The appearance of a low-field singlet (δ 8,98) in the ^{1}H-NMR spectrum was a clear indication of a free hydroxy group in **3.32**. The oxidation of the unsymmetrical *N*-hydroxy pyrrolidine **3.32** was attempted next employing HgO[29] as the oxidising agent (Scheme 3.14).



3.32 **3.33**

Scheme 3.14

The ^{1}H-NMR spectrum of the product indicated the presence of two regioisomers with the C-2 nitrone (**3.33**) representing more than 90% of the mixture. The absence of a H-2 signal indicated that the oxidation predominantly afforded the more substituted double bond. The shift of the C-2 resonance from δ 68,3 in the ^{13}C-NMR spectrum of **3.32** to δ 144,0 in **3.33** served as further evidence for nitrone formation. The oxidation with HgO is believed to involve a two-step reaction: the first step is an oxidation of the hydroxylamine anion to the corresponding radical; the second step is a hydrogen abstraction to furnish the nitrone (Scheme 3.15).

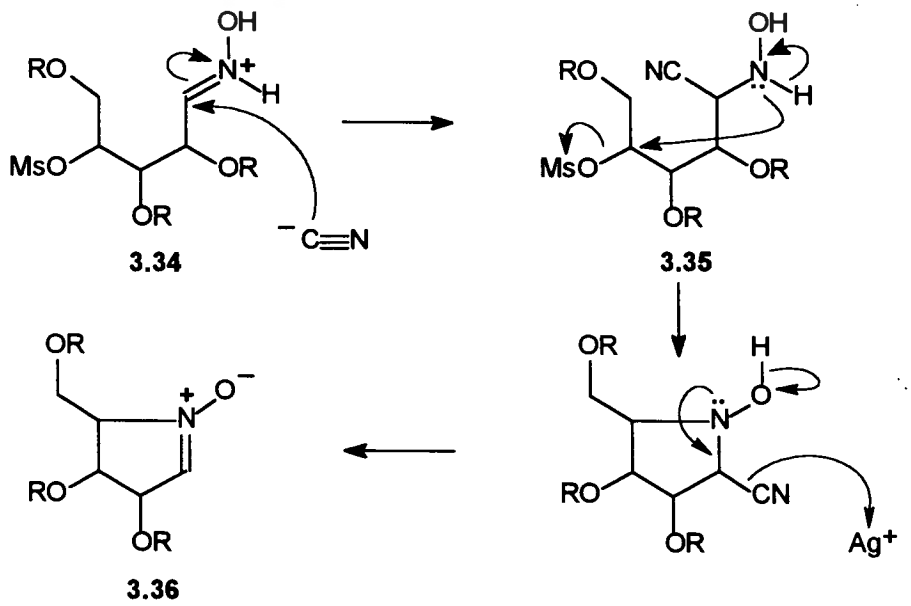


Scheme 3.15

The loss of hydrogen is thought to be a homolytic process with the more labile tertiary carbon-hydrogen bond being broken rather than the secondary carbon-hydrogen bond. This tendency is reflected in the bond dissociation energies for the series[30] CH_3-H (104kcal.mol^{-1}) > C_2H_5-H (98kcal.mol^{-1}) > *i*-C_3H_7-H (95kcal.mol^{-1}) > *t*-C_4H_9-H (92kcal.mol^{-1}). It was realised that steric or remote electronic effects do not direct the oxidation and hence it is difficult to alter the regioselectivity of the oxidation with HgO. These results once again emphasise the problem of regioselectivity in the oxidation of unsymmetrical pyrrolidines to cyclic nitrones. A number of other oxidants have also been employed for the dehydrogenation of hydroxylamines including peroxides,[31] Cu^{2+},[32] $NaIO_4$,[33] and Pd^0.[34] The exact mechanism for each of these oxidation reactions is not known, and it is possible that there may be room for improvement in the regioselectivity

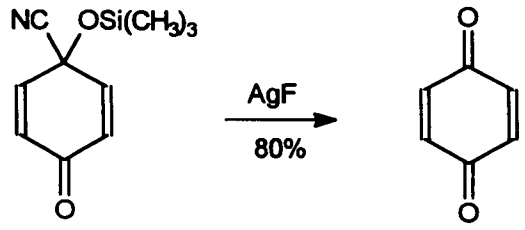
3.3.3 AN APPROACH TO CYCLIC NITRONES *VIA* A MASKED OXIME PROTOCOL

The possibility of developing a masked oxime protocol for the synthesis of cyclic nitrones was envisaged. Our strategy involved the addition of hydrogen cyanide to a carbohydrate derived oxime of type **3.34** to afford the precursor **3.35**. It was envisaged that cyclisation and subsequent silver mediated deprotection would afford the desired cyclic nitrone of type **3.36** in one pot or in two distinct steps (Scheme 3.16).



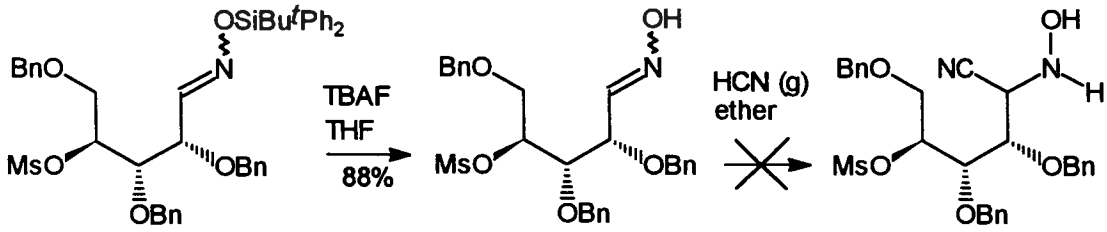
Scheme 3.16

Evans *et al* [35]studied the use of cyanosilylation as a means of protection for quinones (Scheme 3.17). The blocking group could be removed virtually instantaneously with silver fluoride in aqueous THF.



Scheme 3.17

The addition of hydrogen cyanide to Schiff bases[36] occurs readily and provides a viable route to α-amino nitriles, which can in turn be used as precursors for the synthesis (*via* hydrolysis) of α-amino acids (Strecker synthesis[37]). This reaction (which is akin to cyanohydrin formation from carbonyl compounds) is usually carried out using anhydrous hydrogen cyanide in inert solvents such as ether or benzene. Treatment of **3.31** with a molar solution of TBAF in THF at room temperature furnished the deprotected oxime in excellent yield. Treatment of **3.37** with anhydrous hydrogen cyanide in ether proceeded very slowly, and only trace amounts of a possible product could be detected on TLC after several hours (Scheme 3.18).



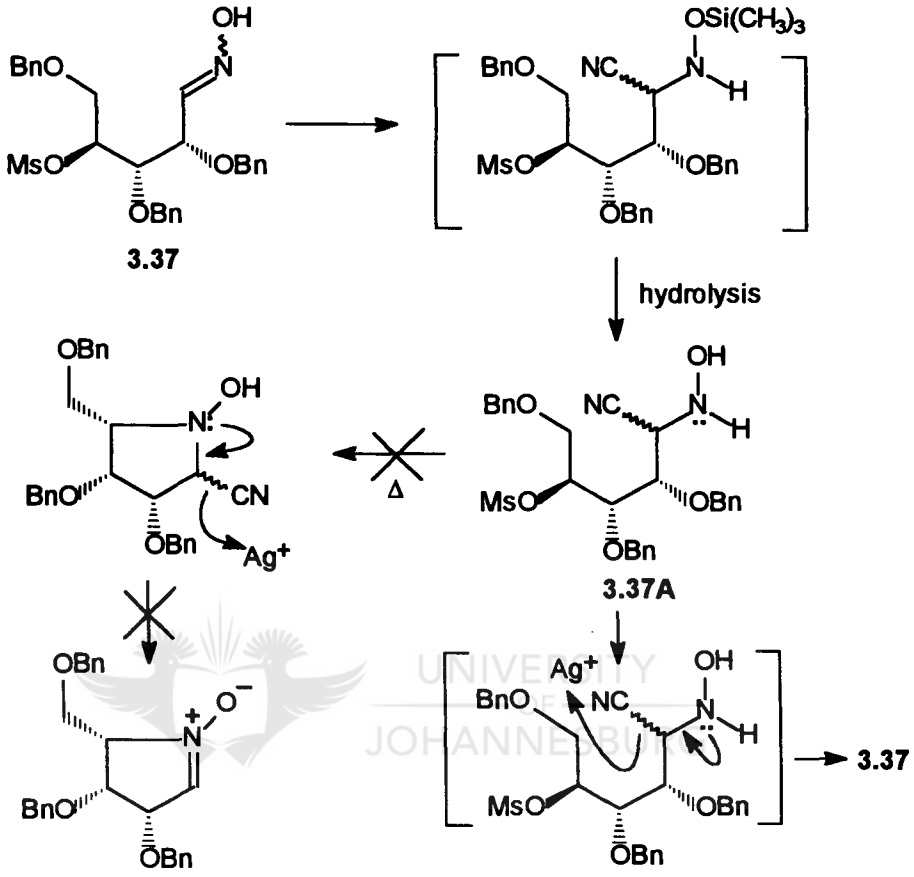
3.31 **3.37**

Scheme 3.18

This may be due to the fact that hydrogen cyanide is a weak acid and is not able to protonate the oxime nitrogen and thereby promote the addition of the cyanide nucleophile.

More recently,[38] trimethylsilyl cyanide has been recommended as a safer alternative to hydrogen cyanide in the Strecker synthesis. This reagent adds to Schiff bases in the presence of catalysts such as aluminium(III)chloride, zinc(II)iodide, or tris(acetylacetonato)aluminium, to give α-cyano-*N*-trimethylsilylamines. These are not isolated but are converted by neutral hydrolysis to α-amino nitriles in high yields. The reaction of **3.37** with trimethylsilyl cyanide in the presence of the Lewis acid ZnI_2 afforded two distinct products after hydrolysis. Compound

3.37A was identified as the desired α-hydroxyamino nitrile (Scheme 3.19). Diagnostic resonances in the ^{13}C-NMR spectrum of **3.37A** were indicative of the nitrile carbon (δ 118.7),[39] C-1 (δ 57,2) and the mesylate carbon (δ 38.6). The other product resulted from the loss of one of the O-benzyl groups under the mild acidic conditions.



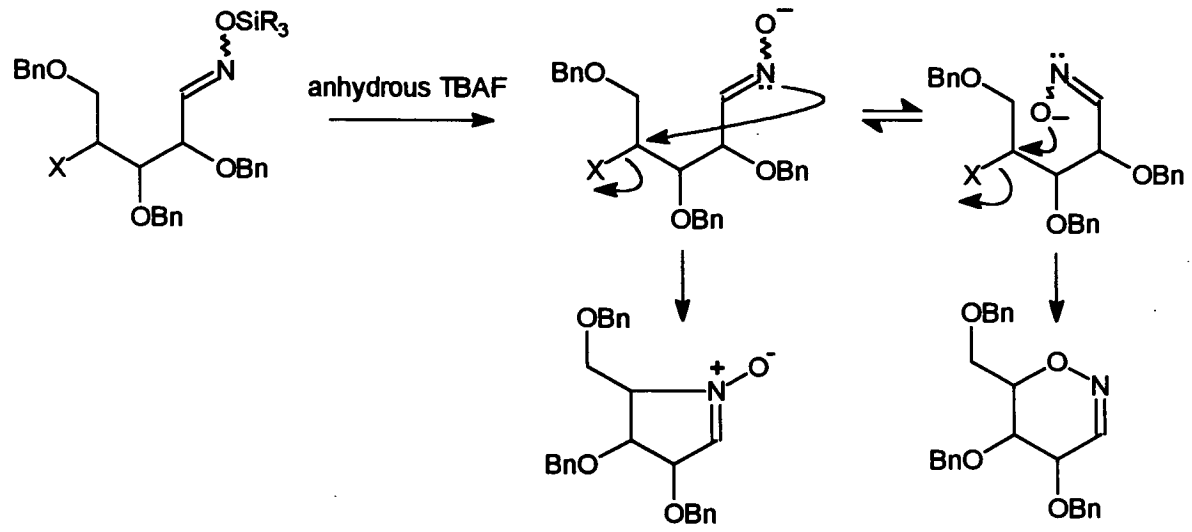
Scheme 3.19

All attempts to cyclise **3.37A** using a variety of silver salts (silver acetate, silver carbonate and silver tetrafluoroborate) only resulted in the formation of **3.37**. Failure of the reaction can probably be rationalised in terms of an unfavourable competition between ring closure and oxime formation.

3.3.4 CYCLIC NITRONES *VIA* NUCLEOPHILIC DISPLACEMENT

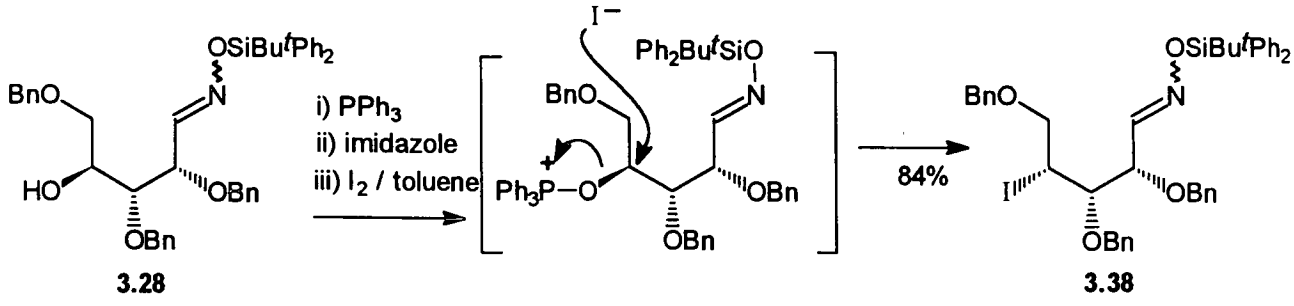
The failure of both the oxidation and the masked oxime routes to cyclic nitrones dictated a radical change in strategy. Removal of the silyl protecting group on the oxime under anhydrous conditions would generate a formal negative charge on the oxygen, thereby enhancing the nucleophilicity of the sp^2 nitrogen. It was anticipated that nitrone formation could be achieved in a direct nucleophilic displacement of the suitable leaving group X

(Scheme 3.20). We also realised that the oxime anion is a potential ambident nucleophile, but that a competition between five- and six-membered ring formation should favour the former. This proposed route offers a very simple and unexplored methodology for the formation of chiral cyclic nitrones.



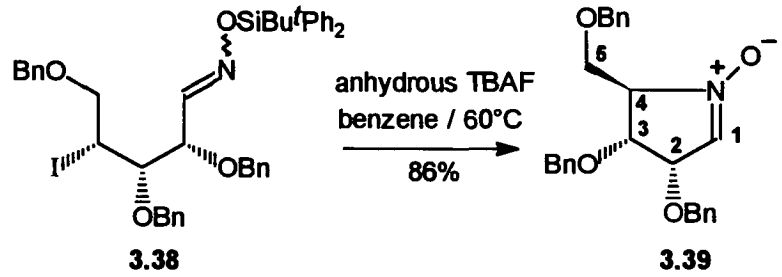
Scheme 3.20

The removal of water from commercially available tetrabutylammonium fluoride trihydrate by azeotropic distillation was carried out with great care, as anhydrous TBAF is unstable. The reagent is highly hygroscopic due to vigorous hydration of the fluoride ion, and tributylamine can be formed as a side product. Treatment of compound **3.31** with anhydrous TBAF in benzene at 60°C resulted only in the formation of a wide range of products, possibly due to competing E-2 elimination reactions which are favoured by good leaving groups such as mesylates. It was decided to convert the free hydroxy group in **3.28** to the iodide. Activation of the hydroxy group as the corresponding triphenylphosponiumoxy species followed by displacement with iodide (inversion of configuration) afforded the precursor **3.38**.



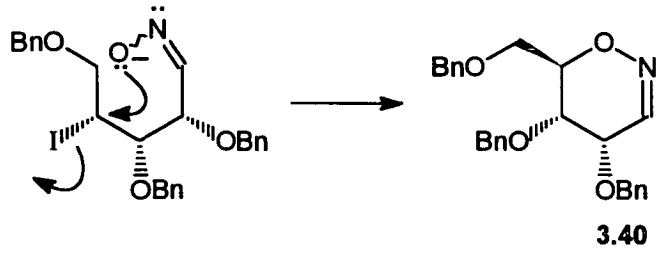
Scheme 3.21

Anhydrous TBAF was added as a 3 molar solution to **3.38** in benzene and the mixture subsequently stirred at 60°C for 30 minutes. TLC analysis indicated that all the starting material had been consumed and the formation of a distinctly polar product was observed. Column chromatography of the reaction mixture afforded the desired D-ribose derived nitrone **3.39** in a yield of 86% (Scheme 3.22).



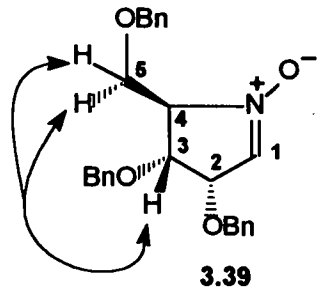
Scheme 3.22

The EI-MS of **3.39** showed a molecular ion at m/z 417 corresponding to a cyclic nitrone. The $[M-16]^+$ fragment ion at m/z 401 indicated the characteristic loss of the *N-O* oxygen.[40] The ^{1}H-NMR spectrum showed a diagnostic singlet (δ 6,90) corresponding to H-1. Characteristic signals in the ^{13}C-NMR spectrum of compound **3.39** included those of the three *ipso* aromatic benzyl carbons (δ 137,6; 137,4 and 137,2) and C-1 (δ 133,4). Further evidence for nitrone formation was obtained from a 2D-HETCOR experiment which confirmed the correlation of the singlet (δ 6,90) in the ^{1}H-NMR spectrum with the carbon at δ 133,4. It was realized from the outset that the ambident nucleophile which rapidly equilibrates between *syn* and *anti* isomers, can also attack through the oxygen and this tendency was observed when the reaction was carried out at higher temperatures. Performing the reaction at 80°-100°C resulted in the formation of trace amounts of a compound which was characterised (MS- and NMR-spectra) as the oxazine **3.40** (Scheme 3.23).



Scheme 3.23

The stereochemistry of **3.39** was confirmed by a 2D-ROESY experiment, indicating strong nOe-effects between H-3 and the side chain protons H-5a and H-5b respectively (Scheme 3.24).

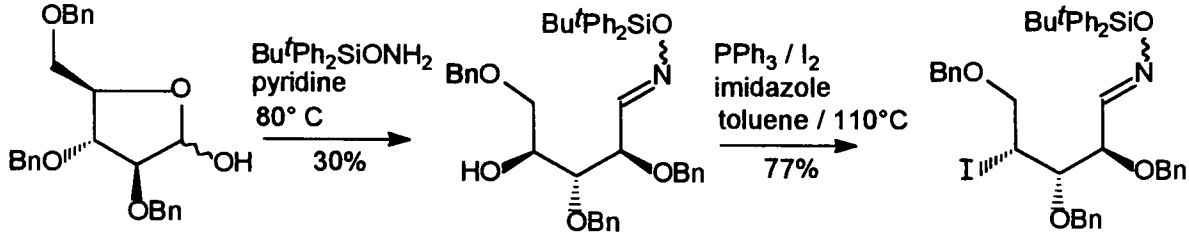


3.39

Scheme 3.24

Clearly, cyclisation took place at C-4 with inversion of configuration. The overall retention (double inversion) of the stereochemistry at C-4 also retains the ribose hydroxylation pattern and stereochemistry which is crucial for the envisaged synthesis of nucleoside analogues.

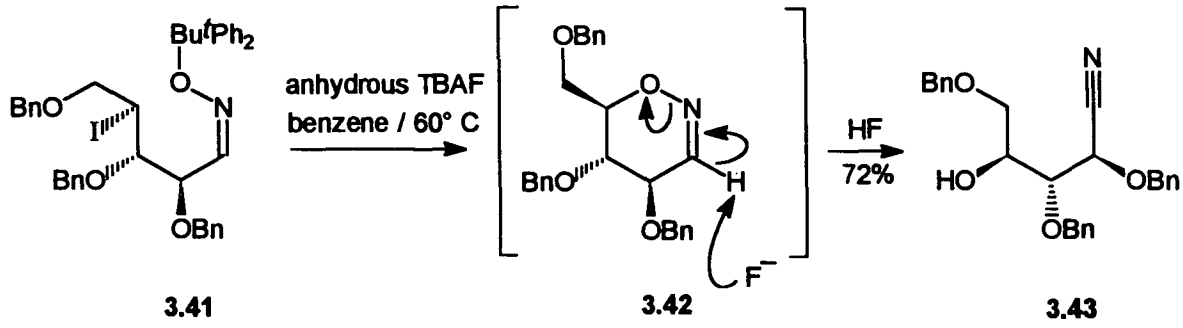
The favourable result prompted us to investigate the possibility of using the new methodology for converting a D-arabinose derivative into the corresponding cyclic nitrone. The failure to distinguish between the two distinct hydroxy groups in **3.27** by selective silylation dictated the use of the O-silylated hydroxylamine reagent synthesised previously (Chapter 2, section 2.4). The reaction of **3.25** with freshly prepared O-tert-butyldiphenylsilyl hydroxylamine in pyridine at 80°C was very slow and only a 30% conversion to the desired product **3.29** could be achieved (Scheme 3.25). This yield could be improved to roughly 55% by recycling the unreacted starting material. The hydroxy group on C-4 was converted to the iodide (inversion of stereochemistry) employing the same reaction conditions as for the synthesis of **3.38**.



3.25 **3.29** **3.41**

Scheme 3.25

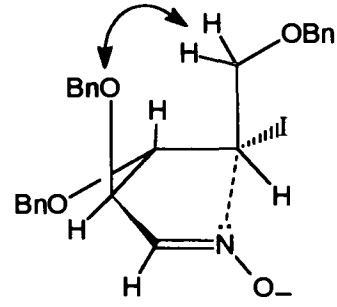
The ^{1}H-NMR spectrum of **3.41** showed a 3:1 mixture of *E*- and *Z* isomers with the multiplet corresponding to H-4 resonating at δ 3.45. The ^{13}C-NMR spectrum showed the presence of an oxime carbon (δ 157.9; main isomer) and the iodine bearing carbon (δ 31.5). Treatment of **3.41** with anhydrous TBAF in benzene at 60°C furnished a product with a slightly different polarity than the starting material as indicated by TLC. Column chromatography of the reaction mixture afforded the nitrile **3.42** in a yield of 72% (Scheme 3.26).



3.41 3.42 3.43

Scheme 3.26

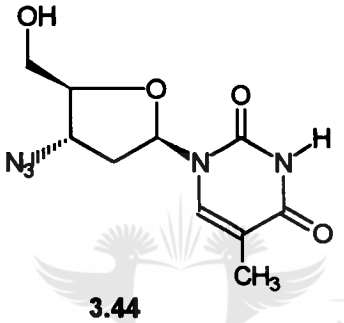
The ^{1}H-NMR spectrum of **3.43** showed H-2 resonating as a doublet (δ 4.48, *J*=2,7Hz) and H-3 as a doublet of doublets (δ 3.92, *J*=8,4 and 2,7Hz). The multiplet corresponding to H-4 shifted downfield from δ 3.43 to δ 3.82. The ^{13}C-NMR spectrum indicated the diagnostic resonance of the nitrile carbon at δ 117,5 as well as the presence of seven carbons bearing an oxygen atom (δ 77,9; 77,4; 75,0; 72,5; 71,9; 66,9 and 59,5). The presence of a hydroxy group was confirmed by the addition of the shift reagent, trichloroacetyl isocyanate to the NMR sample tube which resulted in the appearance of a low-field singlet (δ 8,25) in the ^{1}H-NMR spectrum. These results pointed to the replacement of the iodine on C-4 in **3.41** with a hydroxy group. The APT (Attached Proton Test)[41] NMR technique differentiates between $\underline{C}R_3$, $\underline{C}R_2H$, $\underline{C}RH_2$ and $\underline{C}H_3$ carbons and was used to confirm the quaternary nature of the nitrile carbon. It is postulated that **3.42** is an intermediate in the formation of **3.43**. The formation of **3.43**, like that of **3.40**, results from the attack of the oxygen atom of the deprotonated oxime on C-4 to furnish a six membered oxazine (**3.42**). Base induced/catalysed ring opening by the strongly basic fluoride counter ion would ultimately lead to the observed product. The reason for the failure of **3.41** to form a nitrone can probably be found in the transition state leading to a five membered ring (Scheme 3.27).



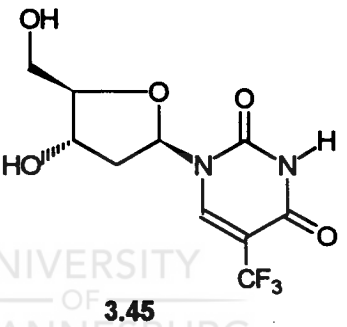
Scheme 3.27

The rigid transition state is destabilised by a 1,3-diaxial interaction. This unfavourable interaction can be reduced in the case of attack by the oxime oxygen resulting in a more flexible six membered ring transition state. We concluded that the reaction of **3.40** and **3.41** with anhydrous TBAF constituted a competition between five- and six membered ring formation. The change of the stereochemistry on C-2 in going from D-ribose to D-arabinose resulted in a complete reversal of the outcome of the competition. These two cases serve as classic examples of the competing reactions of ambident nucleophiles.

In the light of the above results the question arose as to whether other ribose derivatives could be converted into cyclic nitrones using the new methodology. The anticancer compounds retrovir[42] **3.44** and trifluridine[43] **3.45** fall under the important class of β-2'-deoxyribonucleosides.

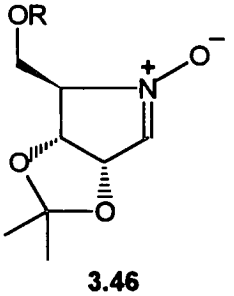


3.44



3.45

The synthesis of the aza analogues of these nucleosides *via* a nitrone must allow for differentiated functionality on the hydroxy groups. We opted for the use of a cyclic isopropylidene acetal in the protection of the 1,2-diol in a D-ribose derived nitrone of type **3.46** (Scheme 3.28).

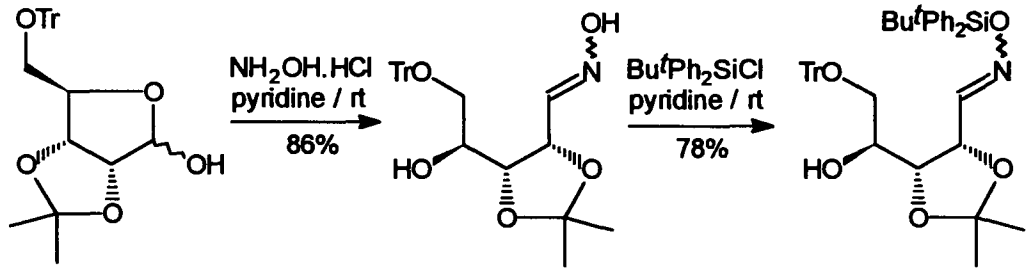


3.46

Scheme 3.28

The acetals are easily prepared and they are stable to most reaction conditions except treatment with protic and Lewis acids.[44] The use of the acetonide as a protecting group has the added advantage in that it reduces the degrees of freedom of the molecule and should result in easier cyclisation of the intermediates to form cyclic nitrones. The selective removal

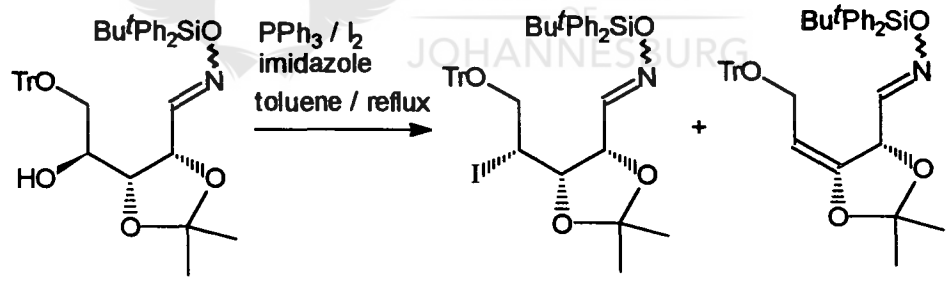
of the acetal group can be performed at any stage in the synthesis. Derivatisation of the 2'-hydroxy group, tin hydride mediated deoxygenation and deprotection would provide the desired 2'-deoxyribose skeleton.[45] The readily available 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose[46] **3.47** was chosen as starting material. Following the same methodology as before, oxime formation afforded the acyclic **3.48** which was selectively silylated at the oxime hydroxy group using *tert*-butyldiphenylsilyl chloride (Scheme 3.29).



3.47 **3.48** **3.49**

Scheme 3.29

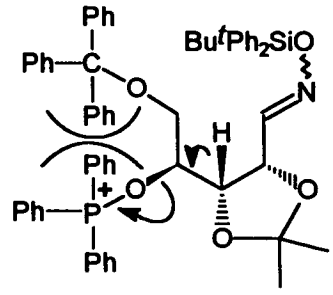
Activation of the hydroxy group in **3.49** as the corresponding triphenylphosponiumoxy species followed by displacement with iodide (inversion of configuration) afforded a mixture of two compounds **3.50** and **3.51** (Scheme 3.30).



3.49 **3.50** **3.51**

Scheme 3.30

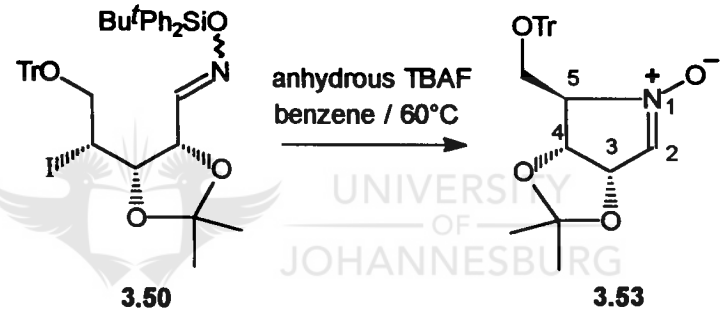
Compounds **3.50** and **3.51** could not be purified to homogeneity. The ^{1}H-NMR spectrum of the mixture showed H-1 and H-2 of the major compound resonating as two doublets (J=8,4Hz) at δ 6,95 and δ 4,96 respectively. The ^{13}C-NMR spectrum of the mixture indicated diagnostic resonances for the oxime carbon (δ 153,6), C-3 (δ 144,4), C-4 (δ 111,7) and the allylic carbon C-2 (δ 97,0), all of which correspond to **3.51**. The low yield obtained for the cyclisation precursor can be attributed to elimination of the triphenylphosponiumoxy leaving group prior to attack of the iodide nucleophile (Scheme 3.31). The neighbouring O-trityl group lends anchimeric assistance[47] and helps to expel the leaving group in the transition state **3.52** to relieve steric strain that arises from the close proximity of the large triphenylmethyl and triphenylphosphoniumoxy groups.



3.52

Scheme 3.31

The mixture of **3.51** and **3.52** was dissolved in benzene and treated with 0,5 equivalents of anhydrous TBAF to afford the desired nitrone **3.53** in a yield of 43% starting from **3.49** (Scheme 3.32).



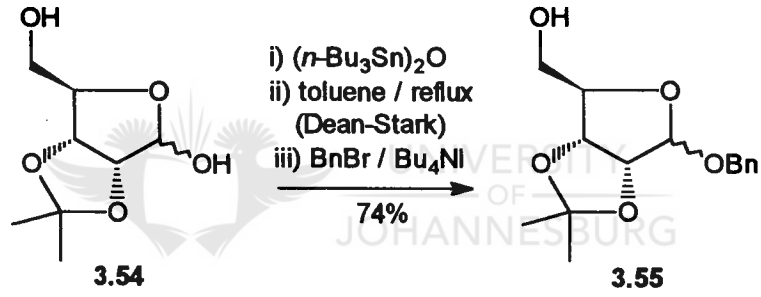
3.50 3.53

Scheme 3.32

The EI-MS of **3.53** showed a molecular ion at m/z 429 corresponding to a cyclic nitrone. The $[M-16]^+$ fragment ion at m/z 413 indicated the characteristic loss of the *N*-*O* oxygen. The ^{1}H-NMR spectrum showed a diagnostic resonance (δ 7,09) corresponding to H-2. Characteristic signals in the ^{13}C-NMR spectrum of compound **3.53** included those of C-2 (δ 143,3) and the quaternary carbons of the isopropylidene- (δ 111,7) and the trityl groups (δ 86,9).

This result highlights an important requisite for the synthetic route namely a suitable protecting group on C-5 that does not lend itself to any neighboring group effects. The trityl ether (steric effect) and the benzoyl ester (possible internal nucleophile) can thus be ruled out. The C-5 benzyl group played no detrimental role in the route to nitrone **3.39** and the use of a benzyl ether for the protection of the C-5 hydroxy group was the logical choice. The readily available 2,3-*O*-isopropylidene-D-ribofuranose **3.54** posed the problem of regioselective manipulation of the anomeric and primary hydroxy groups. In the light of the above, it was decided to utilize

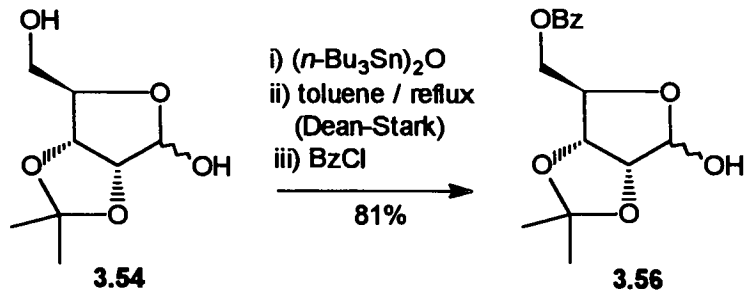
tributylstannyl ethers for the indirect selective conversion of these hydroxy groups by alkylation or acylation.[48] In carbohydrate chemistry this approach is extremely useful for regioselective acylation without the use of a blocking-deblocking technique.[49] Tributylstannyl ethers are easily prepared by refluxing a mixture of an alcohol with one equivalent of bis(tributyltin) oxide in benzene or toluene with azeotropic removal of water (Dean-Stark trap). No special precautions, such as a nitrogen atmosphere, or rigid exclusion of moisture are necessary. Their formation is practically quantitative, and more extensive purification is seldom needed. While the acylation of tributylstannyl ethers is a very fast reaction at room temperature in any solvent, alkylation is extremely slow, even with the reactive allyl or benzyl bromide. Regioselective alkylation of sugar substrates, however, can be carried out in high yield by conversion to a tributyltin ether followed by addition of the alkylating agent and a quaternary ammonium halide catalysts.[50] The attempted selective alkylation of **3.54** *via* its tributylstannyl ether using benzyl bromide and tetra-*n*-butylammonium iodide afforded the C-1 alkylated **3.55** as the sole product of the reaction after 4 hours (Scheme 3.33).



3.54 **3.55**

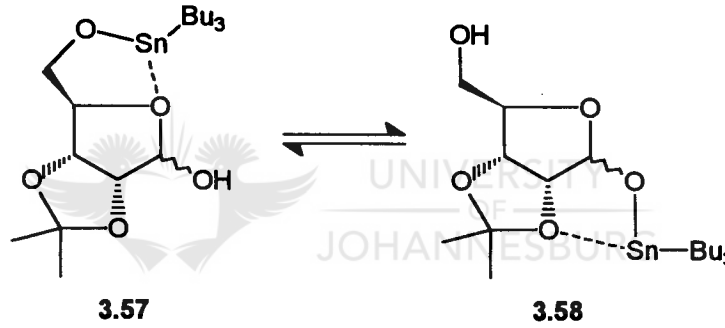
Scheme 3.33

The ^{1}H-NMR spectrum of **3.55** (main isomer) showed the diagnostic AB-system of the two protons on the benzyl methylene group resonating at δ 4,69 and H-1 resonating as a singlet at δ 5,16. The ^{13}C-NMR spectrum indicated C-1 at δ 107,9. The position of alkylation could not be established beyond reasonable doubt and it was decided to react **3.55** with hydroxylamine. After 5 hours only starting material was recovered and this unreactivity was confirmation that the benzyloxy group is on the C-1 position. The apparent higher reactivity of the anomeric oxygen under these conditions led us to believe that reaction of the tributylstannyl ether of **3.54** with benzoyl chloride in benzene at room temperature would furnish a C-1 blocked derivative. This would enable us to selectively block the C-5 position and remove the ester under basic conditions afterwards. To our surprise, compound **3.56** was isolated in a yield of 81% after 30 minutes at room temperature (Scheme 3.34).



Scheme 3.34

The ^{1}H-NMR spectrum of **3.56** showed the presence of a benzoate group as well as H-1 resonating as a singlet at δ 5,16. The anomeric proton of cyclic sugars with an ester group on C-1 characteristically resonates in the region of δ 6,5-6,0. The position of the benzoate group was assigned to C-5. This observation led us to believe that the tributylstannyl ether of **3.54** is in fact an equilibrium mixture of compounds **3.57** and **3.58** (Scheme 3.35).

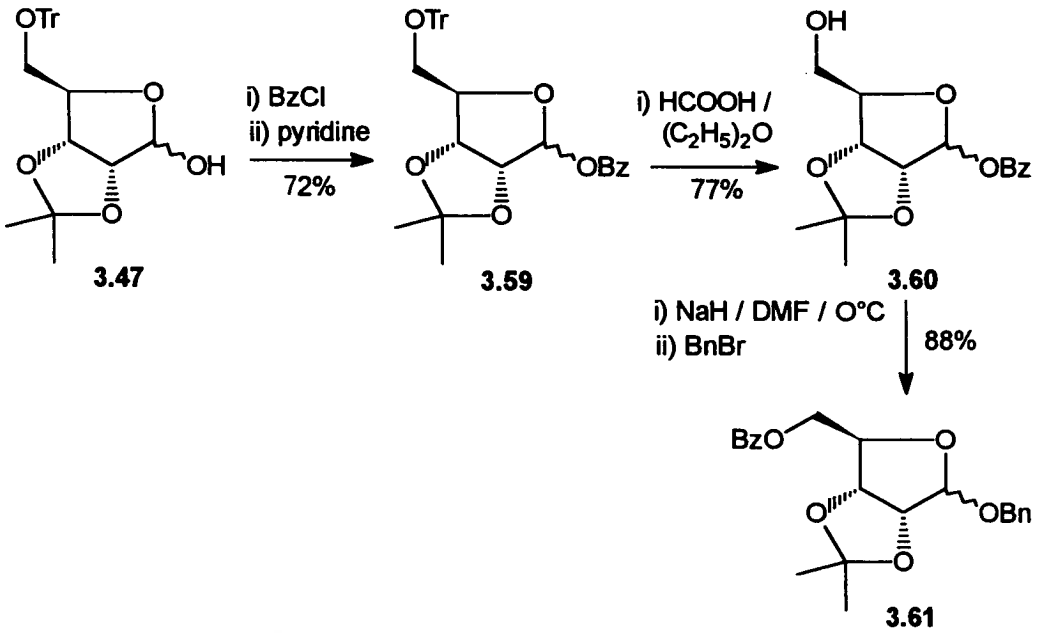


Scheme 3.35

The highly reactive benzoyl chloride reacts with intermediate **3.57** to afford the product of kinetic control (**3.56**) while the less reactive benzyl bromide in the presence of an appropriate catalyst reacts with the intermediate **3.58** to afford the product of thermodynamic control (**3.55**). Other studies carried out in the RAU laboratories confirmed the dependence of the regioselectivity of the reactions of dibutylstannyl derivatives of carbohydrates on the nature of the electrophile.[51]

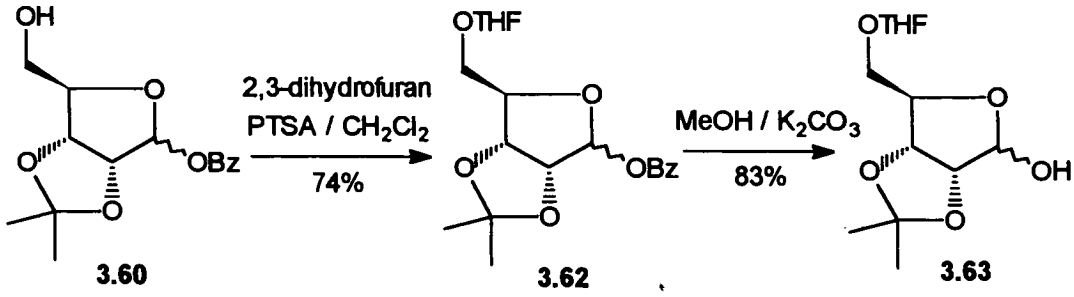
Quite clearly, the methodology stated above was unsuited for the envisaged synthesis of a nitrone of type **3.46**. The only success in discriminating between the two hydroxy groups of **3.54** was achieved *via* tritylation in pyridine to furnish **3.47**. Bessodes *et al.*[52] reported a facile method for the selective cleavage of *O*-trityl ethers in the presence of a variety of protecting groups using formic acid. Compound **3.47** was benzoylated and subsequently treated with a

3:1 mixture of formic acid and ether to furnished **3.60** in a yield of 77% after column chromatography on silica (Scheme 3.36).



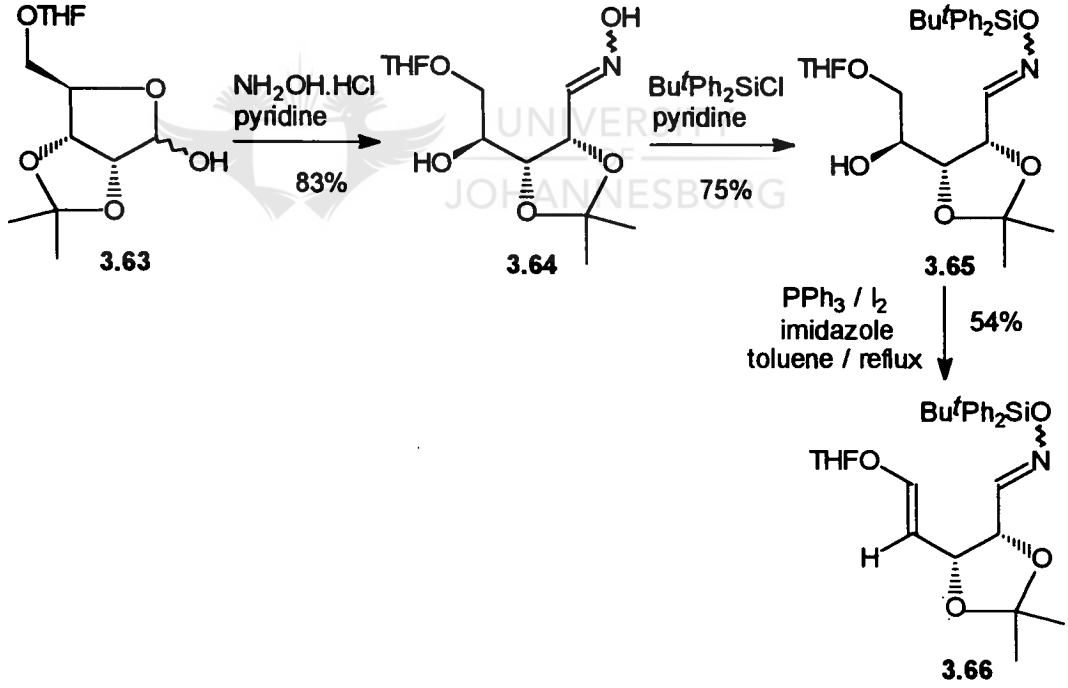
Scheme 3.36

The ^{1}H-NMR spectrum of compound **3.60** indicated a 3:1 α,β-mixture with H-1 of the major isomer resonating as a doublet (J=4,5Hz) at δ 6,45. All attempts to benzylate compound **3.60** resulted in the migration of the anomeric benzoate group to the C-5 hydroxy group and subsequent alkylation at C-1. This conclusion was justified by the considerable shift upfield observed for the anomeric proton from δ 6,45 to δ 5,21 in the ^{1}H-NMR spectrum of compound **3.61**. This result prompted us to investigate the use of an acid catalysed blocking protocol for compound **3.60**. The tetrahydropyranylation of alcohols can be affected under very mild acidic conditions and has been widely used as a hydroxy protecting strategy.[53] The reaction of a chiral alcohol with dihydropyran introduces an additional asymmetric center and hence a diastereomeric mixture is obtained. This can lead to difficulties with purification and assignment of spectral features, but does not prevent successful implementation. The treatment of **3.60** with 2,3-dihydrofuran and a catalytic amount of *p*-toluenesulfonic acid in dichloromethane at –40°C afforded **3.62**. The removal of the ester functionality under basic conditions furnished the protected hemiacetal **3.63** in good overall yield (Scheme 3.37).



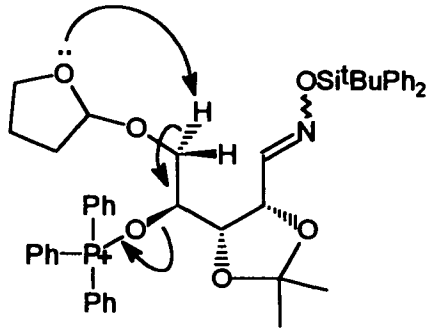
Scheme 3.37

Oximation of **3.63** proceeded smoothly at room temperature and **3.64** was obtained as a mixture of diastereoisomers. Selective silylation furnished **3.65** (Scheme 3.38). The ^{1}H-NMR spectrum of **3.65** showed diagnostic resonances for the major isomer at δ 7,76 (H-1, doublet, *J*=7,8Hz), δ 5,09 (multiplet corresponding to the anomeric proton on the protecting ether) and δ 3,16 (C-5 hydroxy proton, doublet, *J*=3,3Hz).



Scheme 3.38

The attempted conversion of the C-5 hydroxy group into an iodide resulted in the isolation of **3.66**. The ^{13}C-NMR spectrum of **3.66** showed diagnostic resonances for the double bond at δ 135,5 and δ 95,9. This product arose by elimination of the triphenylphosponiumoxy leaving group. The fact that this elimination did not take place in the case of the structurally related 5-O-benzyl derivative **3.38** suggested the intervention of neighbouring group participation in the case of **3.67** (Scheme 3.39).



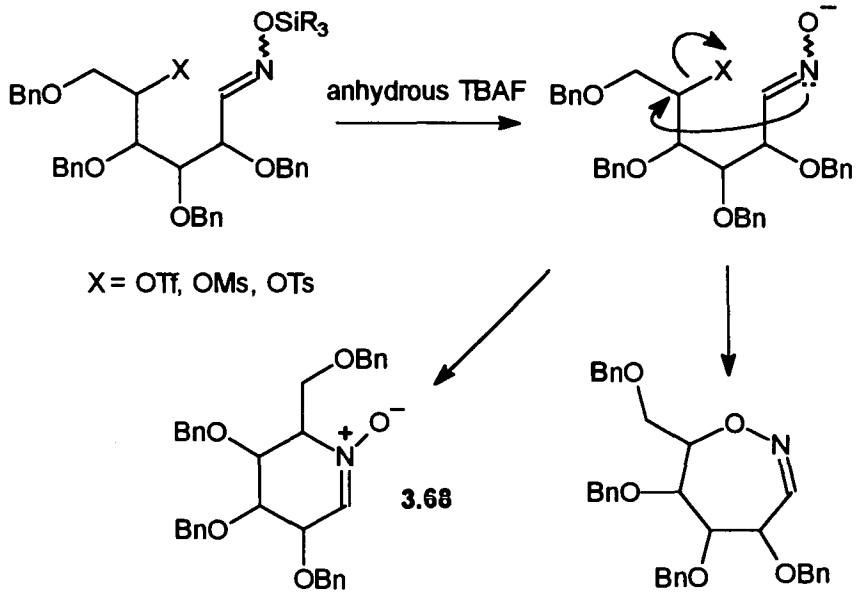
3.67

Scheme 3.39

These results proved that the choice of a protecting group for the C-5 hydroxy group in the synthesis of a nitrone of type **3.46** is crucial. Hope is still held that a method will eventually be found to provide easy access to a hemiacetal with an *O*-benzyl protecting group in the 5 position.

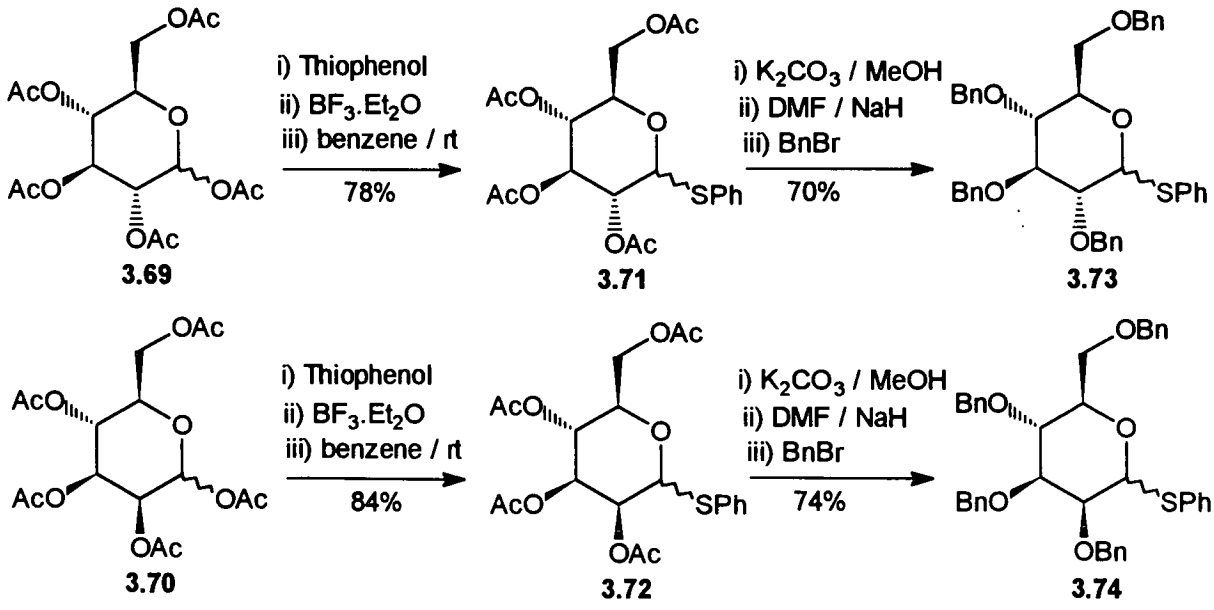
3.3.5 POSSIBLE SYNTHESIS OF SIX MEMBERED RING NITRONES

The question arose whether the methodology which was developed for the synthesis of some ribose derived five membered ring nitrones could be applied for the conversion of hexoses into six membered ring nitrones. In this regard it was anticipated that nitrone formation could be achieved by intramolecular nucleophilic displacement of a suitable leaving group X in hexose oximes (Scheme 3.40). It was realised that oximes are ambident nucleophiles, but in a competition between six- and seven membered ring formation the former would be favoured.



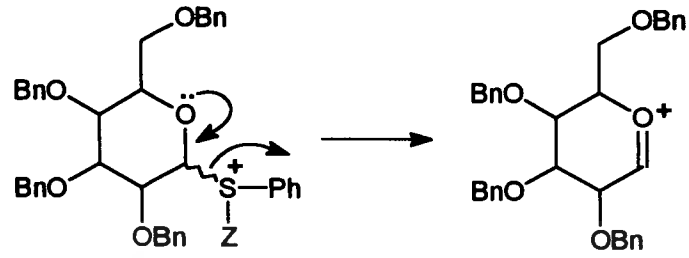
Scheme 3.40

This proposed route would, if successful, provide a facile synthesis of chiral cyclic nitrones of type **3.68**. These molecules would be valuable synthons in the synthesis of a wide variety of highly functionalised bicyclic azasugars as well as aza analogues of six membered *C*-glycosides. The established methodology required the availability of selectively *O*-benzylated hexose hemiacetals as starting materials. The classical Koenigs-Knorr reaction[54] involves the activation of the anomeric center by prior formation of a stable glycosyl bromide from which a cyclic oxocarbenium ion is generated under controlled conditions. This protocol poses problems since further manipulation of the remaining ring substituents is limited due to the labile nature of the anomeric halide under strongly basic conditions. In recent papers, Fraser-Reid *et al.*[55] reported the use of pentenyl glycosides as substrates for a wide variety of reactions occuring at the anomeric center. They are prepared by standard glycoside forming procedures and are stable to a wide variety of reaction conditions. The pentenyl protecting group is readily activated by treatment with a halonium ion. However, in this procedure the expensive *n*-pentenyl alcohol is used as both a reagent and solvent in the protection step, and the reported yields could not be repeated in our hands. Further investigations centered on the use of thioalkyl and –aryl groups for protection of the anomeric center. The ease of selectively introducing thio-aryl groups at the anomeric center[56] and the availability of several mild chemoselective methods to liberate the C-1 hydroxy group were particularly attractive. The thiolysis of readily available peracetylated D-glucose **3.69** and D-mannose **3.70** with thiophenol and a catalytic amount of boron trifluoride etherate furnished the desired thioglycosides **3.71** and **3.72** as α,β mixtures in good overall yields. Zemplén *O*-deacetylation and subsequent *O*-benzylation of the resulting polyols afforded **3.73** and **3.74** (Scheme 3.41).



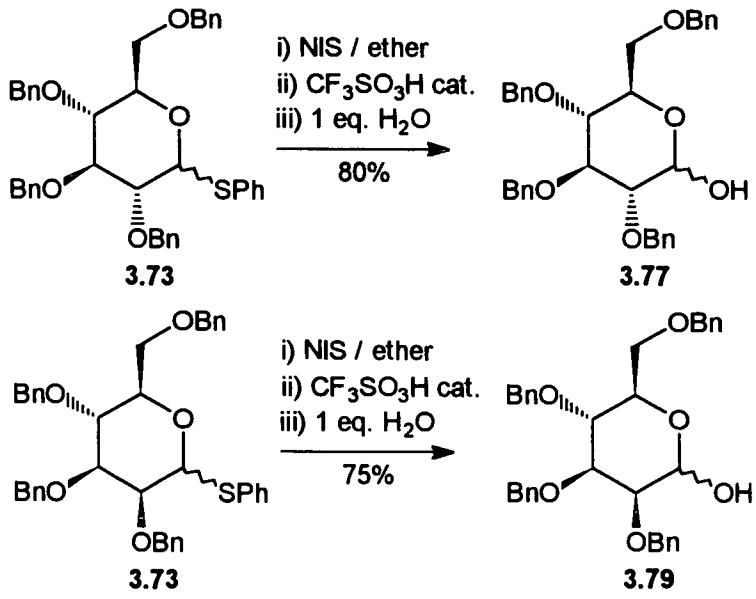
Scheme 3.41

A plausible reaction mechanism for the activation of the thioglycosides by various activators[57] is that the bivalent sulphur atom (soft base) nucleophilically attacks a soft Lewis acid to generate an unstable sulphonium species **3.75** (Scheme 3.42). Subsequent ring oxygen-assisted cleavage of the labile sulphonium group affords a reactive glycosyl cation **3.76**. This cation is stabilized by co-ordination of the counter ion (X^-) of the Lewis acid to the anomeric carbon. The nature of the counter ion plays a decisive role in determining whether, in the presence of a suitable alcohol, the oxonium species is directly converted into the corresponding *O*-glycoside. If the counter ion of the activating ion is a poor nucleophile, as in the case with NBS, then introduction of an alcohol nucleophile can take place directly. However, when thioglycosides are treated with chlorine or bromine, the labile oxonium ion is intercepted by a strongly nucleophilic halide ion to form the corresponding glycosyl halide.



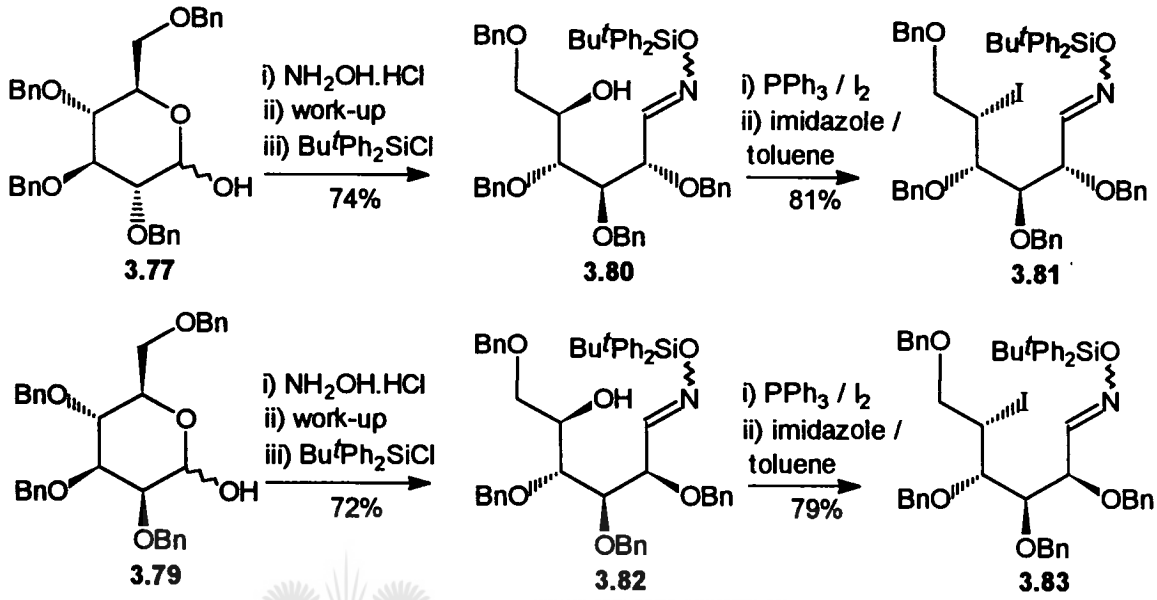
Scheme 3.42

Oxidation of the anomeric sulfur atom of **3.73** and **3.74** with *N*-iodosuccinimide and a catalytic amount of trifluoromethanesulfonic acid in the presence of water,[58] afforded the required hemiacetals **3.77** and **3.79** in very clean reactions (Scheme 3.43).



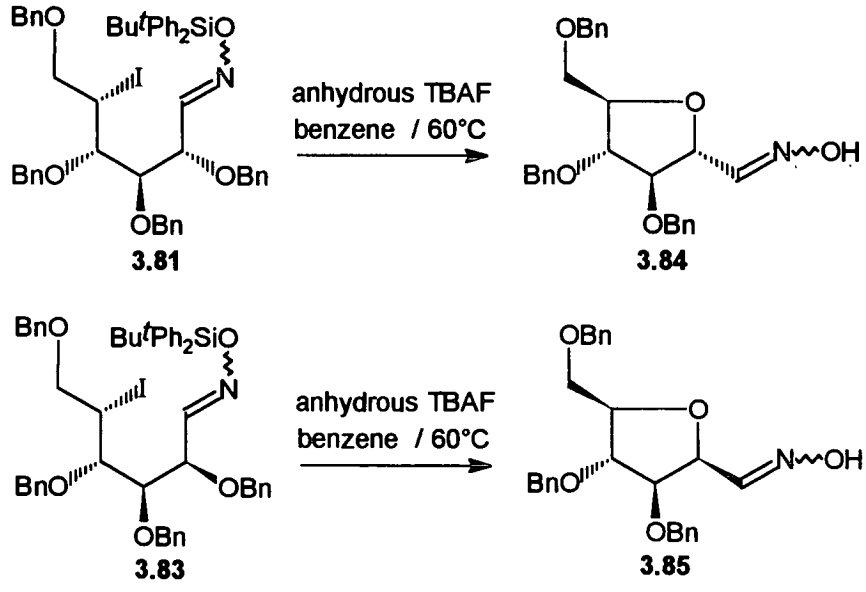
Scheme 3.43

The deprotection of the anomeric center resulted in a shift of the signal corresponding to C-1 (major isomer) from δ 87,4 to δ 97,5 in the ^{13}C-NMR spectrum of **3.77**. The sequence of oxime formation, selective *O*-silylation and subsequent conversion of the released hydroxy group on C-5 into an iodide proceeded smoothly for both the D-glucose and D-mannose derivatives (Scheme 3.44).



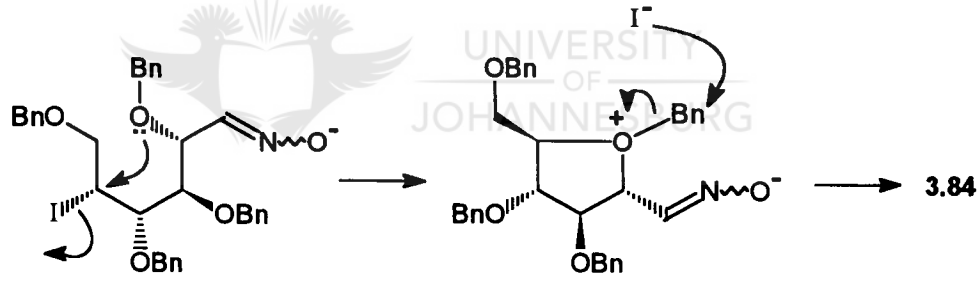
Scheme 3.44

The possible conversion of **3.81** and **3.83** into six-membered ring nitrones was investigated next. On treatment of **3.81** and **3.83** with equimolar amounts of anhydrous TBAF in benzene at 60°C, a distinctly polar product was formed within minutes in each case. Surprisingly, the isolated compounds were identified as the *C*-glycosides **3.84** and **3.85** (Scheme 3.45).



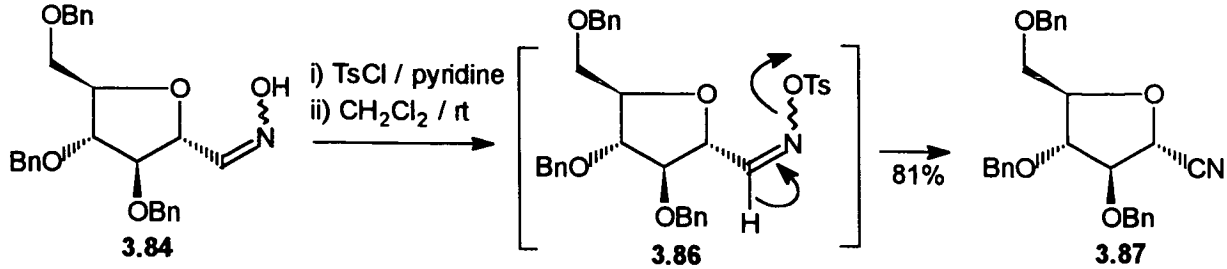
Scheme 3.45

The EI-MS of compound **3.84** showed a molecular ion at m/z 447 corresponding to a cyclisation product, as well as a fragment ion at m/z 430 due to $[M-OH]^+$. The ^{1}H-NMR spectrum of **3.84** showed a mixture of two oxime isomers with H-1 of the main isomer resonating as a doublet at δ 7,00 (J=4,2Hz). The assignment and interpretation of the spectral data proved tedious and the sample was redissolved in C_6D_6 to obtain better resolution of the ring protons. The ^{1}H-NMR spectrum indicated a doublet of doublets resonating at δ 5,06 (J=4,2 and 2,4Hz) corresponding to H-2 (major isomer). The multiplet corresponding to H-5 (major isomer) resonated at δ 4,61 compared to δ 3,95 in the starting material **3.81**. The connectivity of the product was established using proton decoupling and 2D-COSY NMR techniques. Conspicuous in the ^{13}C-NMR spectrum of **3.84** was the absence of one benzyl group as well as the carbon bearing the iodine which has a characteristic resonance at δ 26,4 in the starting material **3.81**. The structural elucidation of **3.85** followed a similar approach to that of **3.84**, making use of EI-MS, ^{1}H-NMR, ^{13}C-NMR, proton decoupling and 2D-COSY spectrometry. All these observations led us to the conclusion that cyclisation was effected by the attack of the C-2 benzyloxy substituent[59] on C-5 to afford the novel *C*-glycosides (Scheme 3.46).



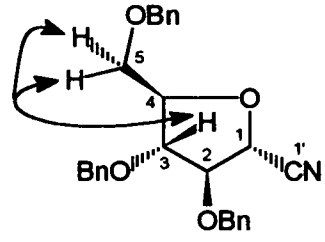
Scheme 3.46

For the purpose of unambiguously establishing the stereochemistry of the newly formed furanoid compounds, it was decided to dehydrate the mixture of aldoximes **3.84** to the corresponding nitrile. This transformation can be effected at room temperature by conversion of the oxime hydroxy group into a good leaving group by treatment of **3.84** with toluene-4-sulfonyl chloride to afford the intermediate **3.86** (Scheme 3.47). Spontaneous elimination of TsOH furnished **3.87** as a single isomer.



Scheme 3.47

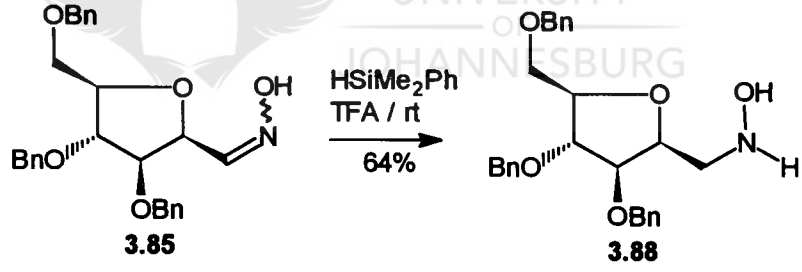
The stereochemistry of the compound was assigned on the basis of a 2D-ROESY experiment making use of pre-existing stereochemistry to determine spatial connectivity. Strong 1,3 nOe-effects were observed between H-3 and the side chain protons H-5a and H-5b respectively (Scheme 3.48).



3.87

Scheme 3.48

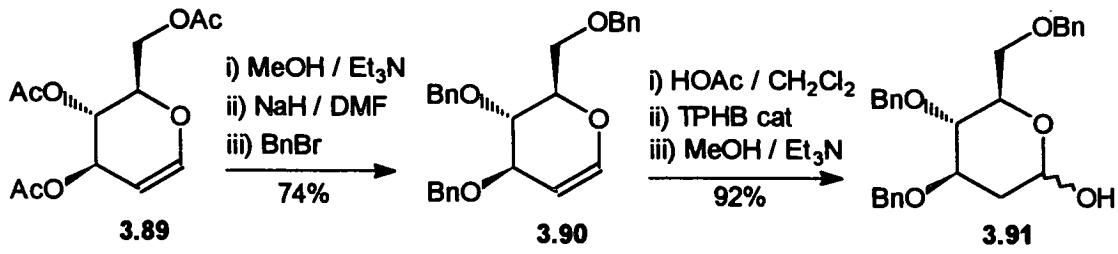
This provided confirmation that the cyclisation proceeded with inversion of stereochemistry at C-5. Final proof for the proposed structure was obtained by the reduction of the aldoxime **3.85** under standard conditions to afford the corresponding amine **3.88** in a yield of 64% (Scheme 3.49).



3.85 **3.88**

Scheme 3.49

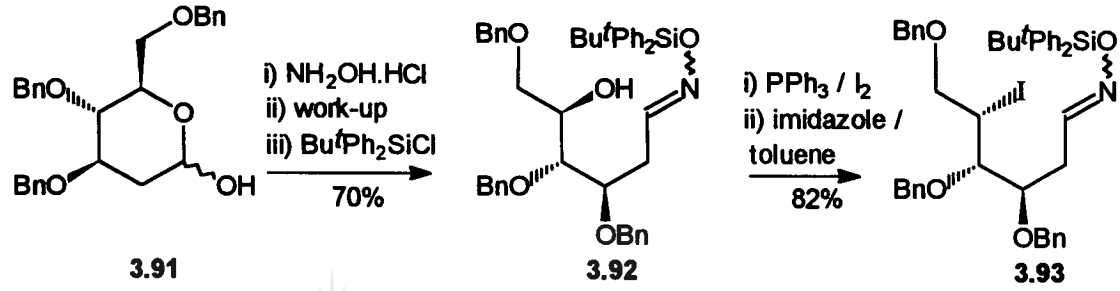
The ^{1}H-NMR spectrum showed H-1'a and H-1'b resonating as two doublets of doublets at δ 3,33 and δ 3,18 respectively. The ^{13}C-NMR spectrum indicated the diagnostic resonance of C-1 at δ 53,76. In order to gain some further insight into the mechanism proposed for the formation of these novel *C*-glycosides, it were decided to use the suitably protected 2-deoxy-hemiacetal of D-glucose (**3.91**) in our synthetic sequence. The required starting material is readily available from commercial tri-*O*-acetal-D-glucal **3.89** in a neat three-step procedure. Deprotection of **3.89** followed by standard full *O*-benzylation furnished **3.90**. The triphenylphosphine hydrobromide[60] catalysed addition of acetic acid to the double bond followed by deprotection under basic conditions afforded **3.91** in an overall yield of 68% (Scheme 3.50).



3.89 **3.90** **3.91**

Scheme 3.50

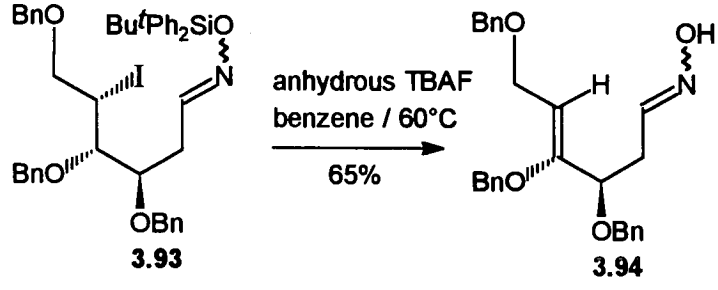
The sequence involving oxidation of **3.91**, selective silylation and subsequent conversion of the released hydroxy group of **3.92** into an iodide proceeded smoothly (Scheme 3.51).



3.91 **3.92** **3.93**

Scheme 3.51

The possible formation of a six-membered nitrone was investigated next. Treatment of **3.93** with an equimolar amount of anhydrous TBAF in benzene at 60°C furnished **3.94** in a yield of 65% (Scheme 3.52).

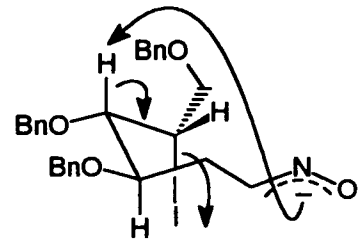


3.93 **3.94**

Scheme 3.52

The ^{1}H-NMR spectrum of **3.94** showed a mixture of two oxime isomers with H-1 of the main isomer resonating as a triplet at δ 7,49 (J=6,3Hz). The assignment and interpretation of the spectral data in $CDCl_3$ solution once again proved tedious and the sample was redissolved in C_6D_6 to obtain better resolution of the ring protons. The ^{1}H-NMR spectrum indicated a doublet of doublets resonating at δ 3,78 (J=7,2 and 5,7Hz) corresponding to H-2 (major isomer). The

^{13}C-NMR spectrum indicated diagnostic resonances for C-4 and C-5 at δ 149,3 and δ 111,4 as well as for the oxime carbon at δ 154,8. The dehydrohalogenation of **3.93** can easily be catalysed by the internally generated negative charge on the oxime functionality. Examination of the possible transition state **3.95** indicates a perfect 1,2 trans diaxial relationship between H-4 and the iodide which lends further support to the proposed elimination (Scheme 3.53).



3.95

Scheme 3.53

It was hoped that the absence of a benzyl group in the 2 position would force the molecule to form a six-membered nitrone. Clearly, the molecule can not attain the desired conformation needed for cyclisation to a six membered ring and rather eliminates HI under the reaction conditions.

3.4 CONCLUSION

This extensive study on the cyclisation reactions of a wide variety of silylated oximes under various conditions gave us a valuable insight into the multitude of competing reactions at work in these poly-functional systems under the described conditions. The fact that only the D-ribose derived intermediates cyclised to nitrones was surprising and more model studies on carbohydrate substrates is needed to grasp the scope of this reaction. The serendipitous discovery of the reactions leading to the novel C-glycosides described in section 3.3.4 opened up a new route to these highly desirable molecules and further research on this reaction is currently in progress at the RAU laboratory.

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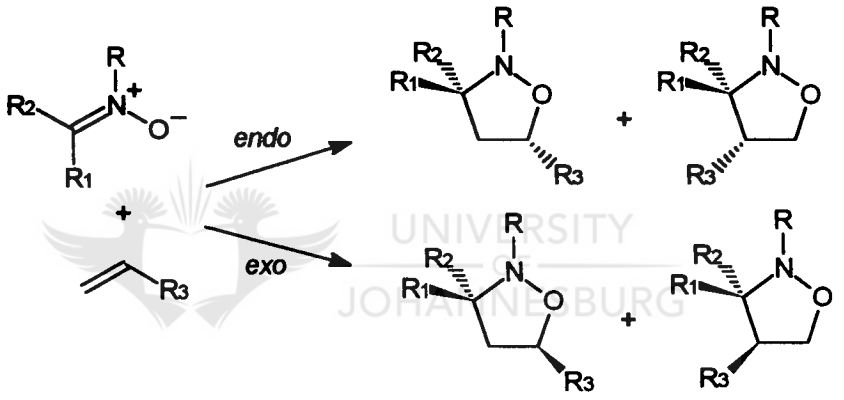
CHAPTER 4
REACTIONS AND APPLICATIONS OF D-RIBOSE DERIVED NITRONES

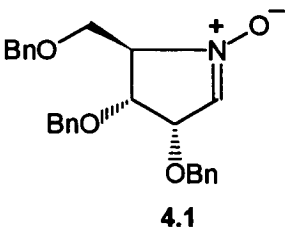
4.1 CYCLOADDITION REACTIONS OF NITRONES

Nitrones are classic examples of octet-stabilised 1,3-dipoles lacking an orthogonal double bond.[1] This makes them suitable substrates in [3+2] cycloaddition reactions with a wide variety of carbon-carbon, carbon-nitrogen and carbon-sulphur multiple bond systems to produce various five-membered heterocyclic systems.[2] In a manner analogous to the famous [4+2] cycloaddition reactions first noted by Diels and Alder,[3] nitrone-alkene cycloadditions can occur with the nitrone and alkene approaching each other in either of two possible regiochemical senses and in either an *endo*- or *exo*- fashion. This gives rise to two possible pairs of regioisomeric and diastereomeric products (Scheme 4.1).

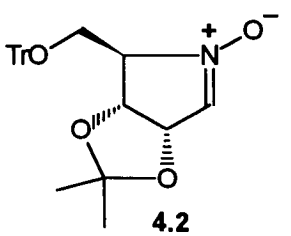


Scheme 4.1

It is generally accepted that most 1,3-dipolar cycloadditions are single step, four centered, concerted reactions, in which the two new σ-bonds are formed simultaneously, although not necessarily at equal rates.[4] Reactions of this type generally proceed in high yield by simply heating the components in an inert solvent (*e.g.* toluene), and provide a prolific source of a number of otherwise inaccessible heterocyclic systems. The 1,3-dipolar cycloaddition reaction of the D-ribose derived nitrones **4.1** and **4.2** (chapter 3, section 3.3.4) with a variety of α,β-unsaturated carbonyl compounds were investigated.

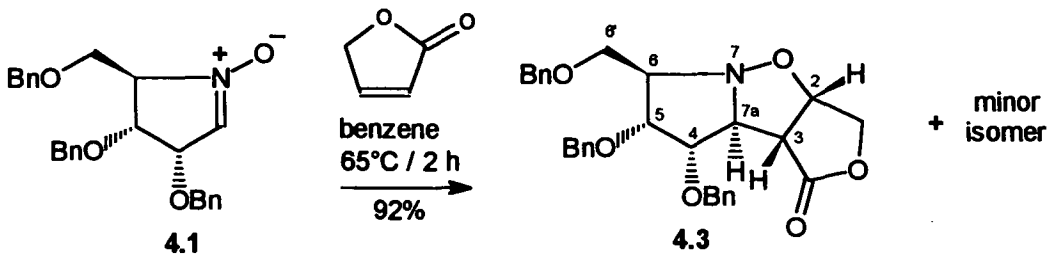


4.1



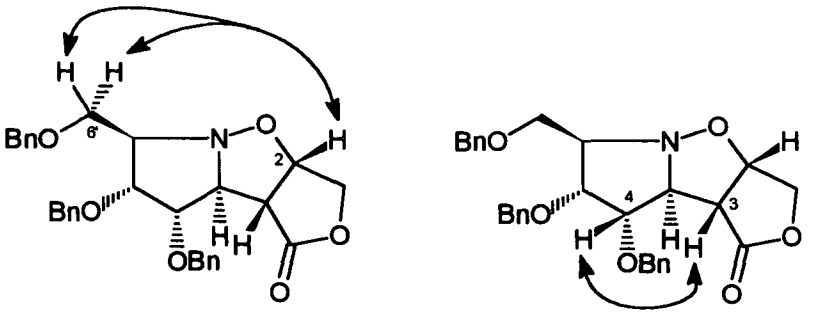
4.2

The reaction of nitrone **4.1** with 2(*5H*)-furanone in benzene at 65°C was complete within 2 hours. TLC analysis indicated the formation of two distinct products which were purified by column chromatography to afford **4.3** as the major cycloadduct (Scheme 4.2).



Scheme 4.2

The EI-MS of **4.3** indicated a molecular ion at m/z 501 which corresponded to a cycloadduct. The ^{1}H-NMR spectrum showed diagnostic resonances for H-2 (δ 4,87; doublet of triplets; *J*=5,7 and 2,0Hz), H-7a (δ 4,23; doublet of doublets; *J*=6,3 and 2,4Hz) and H-3 (δ 3,86; triplet; *J*=4,2Hz). The ^{13}C-NMR indicated the presence of the lactone carbonyl carbon (δ 177,5), three *ipso* aromatic benzyl carbons (δ 137,9; 137,7 and 137,6) and C-3 (δ 50,6). The stereochemistry of **4.3** was assigned on the basis of a 2D-ROESY experiment which indicated a strong 1,3 nOe effect between H-3 and H-4 as well as strong 1,5 nOe effects between H-2 and H-6'a and H-6'b respectively (Scheme 4.3).

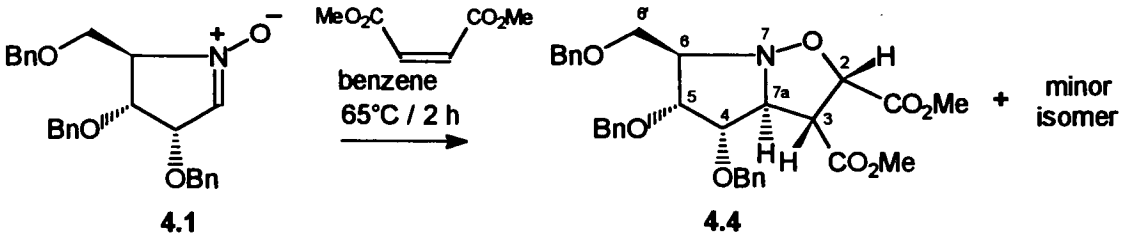


1,5-nOe interactions 1,3-nOe interaction

Scheme 4.3

These results indicate that the major product is the result of the dipolarophile approaching the β-face of the nitrone in an *exo* manner. The stereochemistry of the minor isomer could not be assigned with absolute certainty. The observed diastereomeric excess of 78% compared favourably with results reported by Ishikawa *et al.*[5] for a different cyclic nitrone.

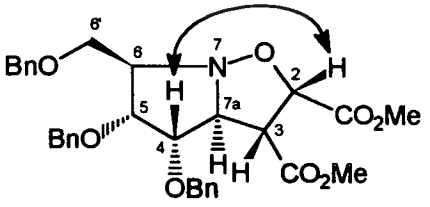
The reaction of nitrone **4.1** with dimethyl maleate in benzene at 65°C afforded two distinct products. The major compound was isolated by column chromatography to afford **4.4** in a yield of 68% (Scheme 4.3). The minor product, isolated in a yield of 24%, was also identified as a cycloadduct, but its stereochemistry has not yet been established.



4.1 **4.4**

Scheme 4.3

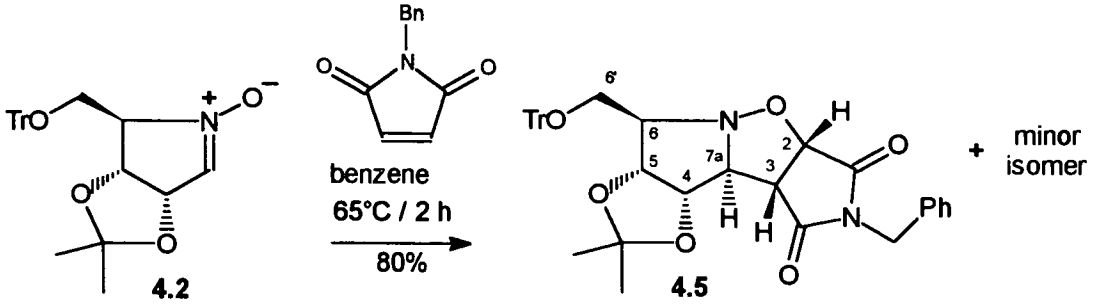
The EI-MS of **4.4** indicated a molecular ion at m/z 561 which corresponded to a cycloadduct. The ^{1}H-NMR spectrum showed diagnostic resonances for H-2 (δ 4,72; doublet; *J*=7,5) and two carbomethoxy groups (δ 3,74 and δ 3,73; two singlets). The ^{13}C-NMR indicated the presence of two ester carbonyl carbons (δ 170,8 and δ 169,1) and two ester methyl carbons (δ 52,3 and δ 51,1). The stereochemistry of **4.4** was assigned on the basis of a 2D-ROESY experiment which indicated a weak 1,4 nOe effect between H-2 and H-4 (Scheme 4.4). This result indicates that **4.4** is the *exo* product.



1,4 nOe effect

Scheme 4.4

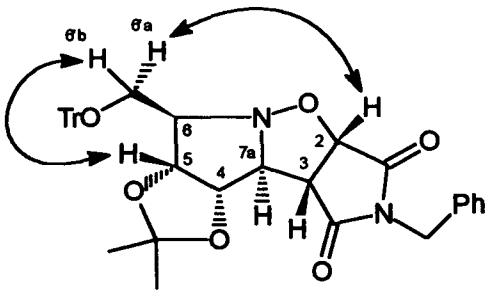
The addition of a two molar excess of *N*-benzylmaleimide to nitrone **4.2** in benzene at 65°C furnished the cycloadduct **4.5** and traces of another isomer (Scheme 4.5).



4.2 **4.5**

Scheme 4.5

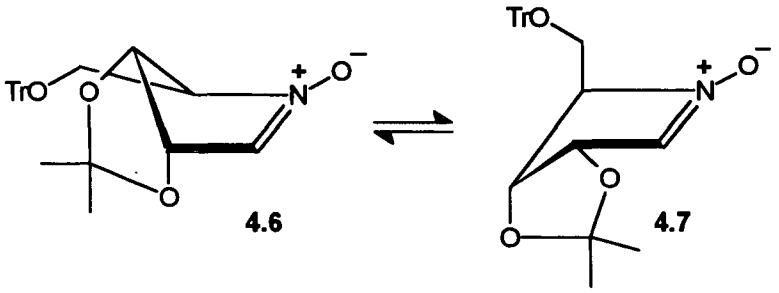
The EI-MS of **4.5** indicated a molecular ion at m/z 615 which corresponded to a cycloadduct. The ^{1}H-NMR spectrum included characteristic resonances for H-7a (δ 4,69; doublet; *J*=5,1Hz), H-3 (δ 4,81; triplet; *J*=5,1Hz) and H-4 (δ 3,95; doublet; *J*=7,5Hz). The failure of H-7a and H-4 to couple with each other can only arise from the fact that the preferred conformation of the molecule is such that H-7a and H-4 are perpendicular to each other (dihedral angle of 90°). The strong nOe effect observed between H-2 and H-6a confirmed the formation of the *exo* product (Scheme 4.6).



nOe effects

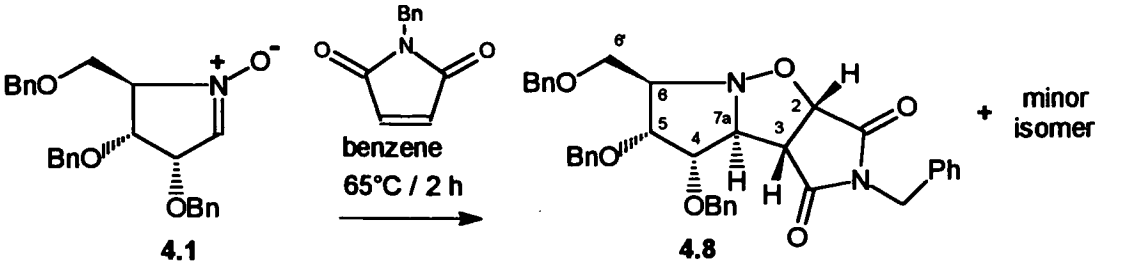
Scheme 4.6

The high yield, and therefore high diastereomeric excess came as a surprise as it was reasoned that the steric bulk of the trityl group on C-5 of the nitrone **4.2** would hinder the approach of the dipolarophile from the β-face of the molecule. Closer inspection of the preferred conformations of nitrone **4.2** confirmed that structure **4.6** is the most favourable conformation with only one substituent in an axial position (Scheme 4.7). This system would allow relatively unhindered approach of the unsaturated carbonyl compound from the β-face.



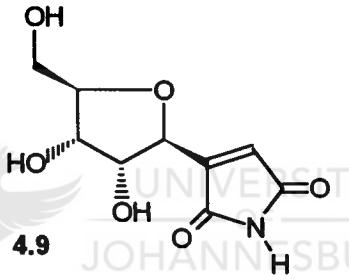
Scheme 4.7

The reaction of nitrone **4.1** with *N*-benzylmaleimide in benzene at 65°C was complete within 2 hours. TLC analysis indicated the formation of two distinct products. Column chromatography afforded **4.8** as the major cycloadduct in a yield of 60% (Scheme 4.8). The minor product, isolated in a yield of 30%, was also identified as a cycloadduct but its stereochemistry has not yet been established. As before, the structure of **4.8** was established on the basis of various NMR experiments.

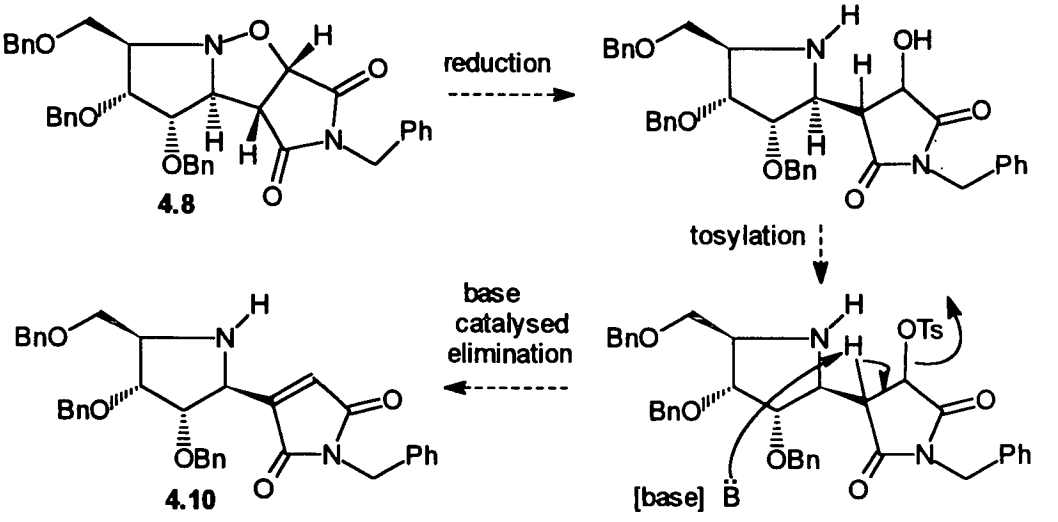


Scheme 4.8

These results prove that the 1,3-dipolar cycloadditions of the nitrones and **4.1** and **4.2** to appropriate olefins proceed smoothly in high yielding diastereoselective reactions. The labile nature of the *N-O* bond in the resultant isoxazolidines to reductive cleavage suggests that these compounds could be suitable precursors to aza analogues of β-*C*-glycosides and β-*C*-nucleosides. Thus, compound **4.8** appeared to be a protected precursor for the synthesis of the aza analogue of the antibiotic showdomycin[6] **4.9**.

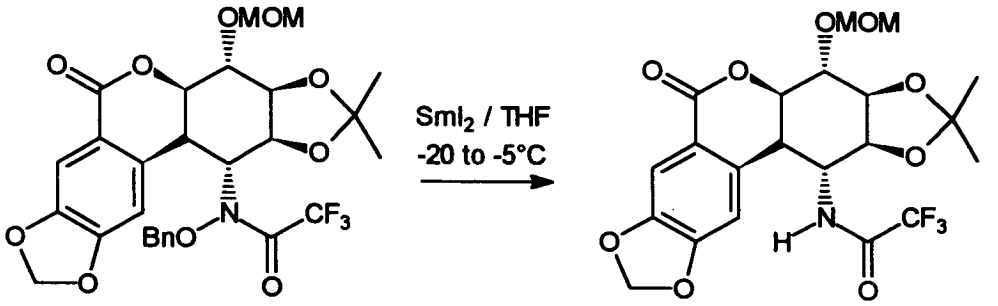


Our envisaged strategy towards an aza analogue of **4.9** involves the selective reduction of the *N-O* bond of **4.8** followed by conversion of the released hydroxy group into a leaving group (tosylation, triflation). Subsequent base catalysed elimination would furnish a protected analogue of showdomycin **4.10** (Scheme 4.9).



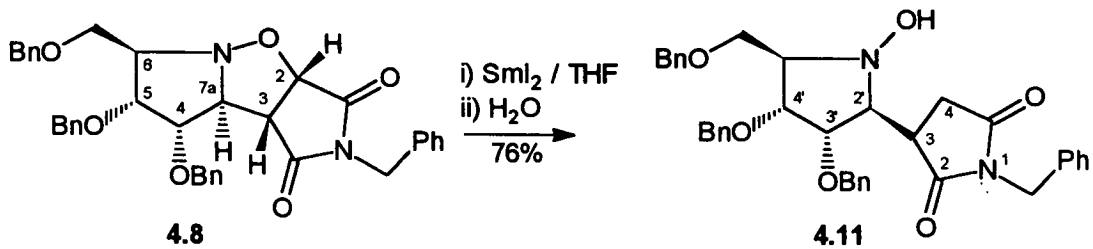
Scheme 4.9

The most common procedures for such reductive cleavage reactions employ hydrogenolysis,[7] reduction with $Mg(Hg)/TiCl_4$,[8] reduction by Al(Hg) or Na(Hg),[9] and reduction using $TiCl_3$.[10] All these procedures were considered to be too harsh for the purpose of selective reduction of the polyfunctional cycloadduct **4.8**. In a recent paper the use of SmI_2/THF was reported by Keck *et al.*[11] who employed this versatile reagent for the reductive cleavage of *N*-*O* bonds in complex hydroxylamine derivatives (Scheme 4.10).



Scheme 4.10

The choice of SmI_2 was further backed by the well-established technology developed at the RAU laboratory for the use of this reagent to convert carbohydrates into stereodefined cyclopentanoid compounds.[12] SmI_2 is a powerful one-electron reducing agent[13] whose reductive potential is increased by the presence, as co-solvent, of either a one-electron donor source, such as DMPU,[14] or a proton source. Treatment of a THF solution of **4.8** with SmI_2 (2.2 equiv. of a 0.1M solution) in the presence of deoxygenated H_2O at room temperature, however, afforded **4.11** as the only observed product in a yield of 76% (Scheme 4.11)



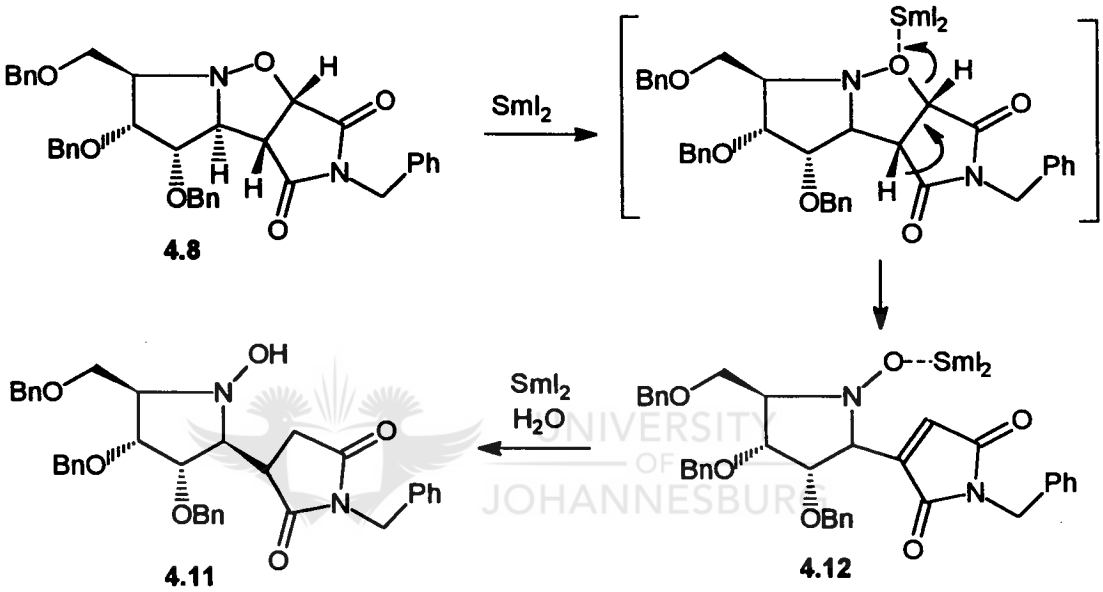
4.8 **4.11**

Scheme 4.11

The FAB-MS of **4.11** showed a molecular ion at m/z 606 corresponding to the *N*-hydroxy pyrrolidine. The ^{1}H-NMR spectrum indicated diagnostic resonances for H-2' (δ 3,95; doublet of doublets; *J*=5,7 and 3,0Hz) and a two proton singlet at δ 4,57 corresponding to the $-CH_2$ of the *N*-benzyl group. Conspicuous in the ^{1}H-NMR spectrum was the presence of the high field multiplet (δ 2,91) corresponding to H-3, as well as the ABX system corresponding to H-4a and

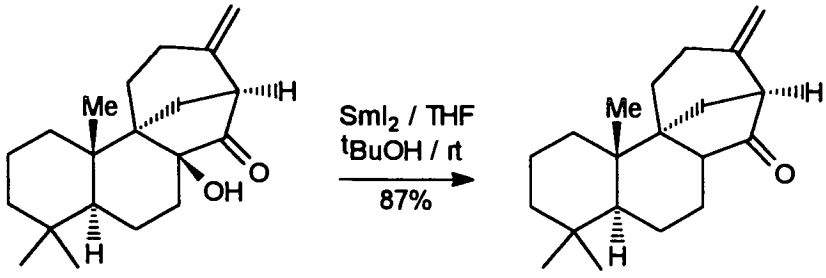
H-4b which resonated at δ 2,96 and δ 2,62. The large geminal coupling constant of 18,0Hz observed for the latter was proof that reduction afforded **4.11**. The ^{13}C-NMR spectrum indicated the presence of two amide carbonyl carbons (δ 180,0 and δ 178,1), C-4 (δ 31,6) and C-3 (δ 42,6).

The formation of **4.11** was unexpected and two possible mechanisms were proposed for this reaction. The action of SmI_2 as a weak Lewis acid could catalyse a reverse Michael reaction to form the olefin **4.12** which is subsequently reduced to **4.11** by the excess of SmI_2 in the reaction mixture (Scheme 4.12).



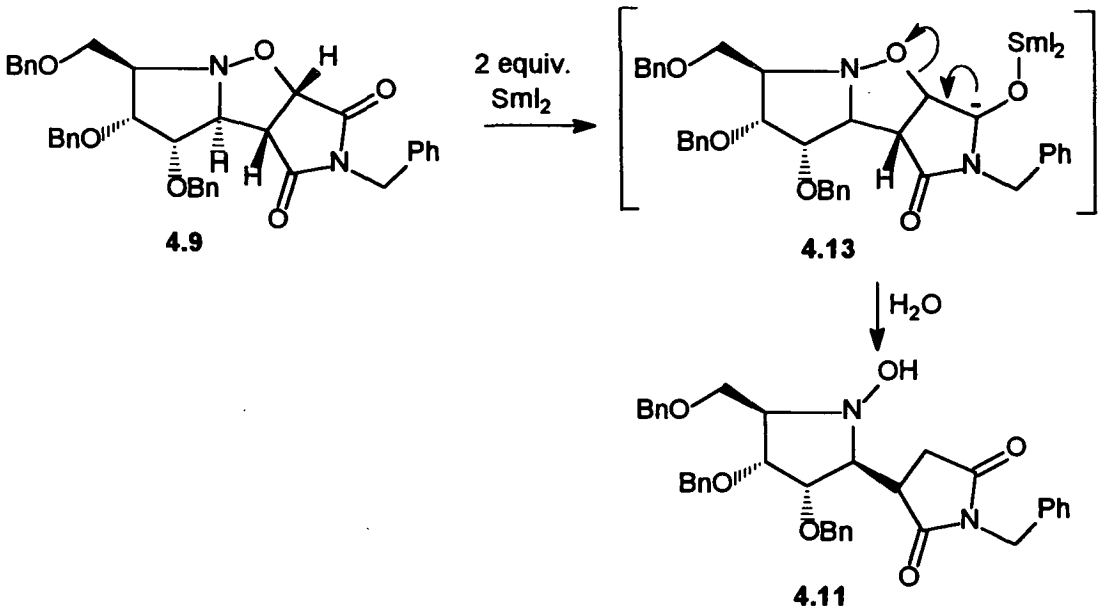
Scheme 4.12

However, the fact that only a single stereo-isomer was obtained would imply a stereospecific reduction of the double bond by SmI_2 in **4.12**. It was difficult to rationalise such perfect asymmetric induction and an alternative, direct reductive cleavage of the C(2)-O bond in **4.8** was proposed. The deoxygenation of α-hydroxy carbonyl compounds, ketones, esters etc. by the action of SmI_2 is well documented, and proceeds with high selectivity (Scheme 4.13).[15]



Scheme 4.13

It is proposed that the first equivalent of SmI_2 reduces one of the carbonyl groups of **4.8** to a radical anion. The second equivalent of SmI_2 reduces this intermediate to the formal carbanion **4.13** with subsequent ring opening to afford **4.11** (Scheme 4.14).

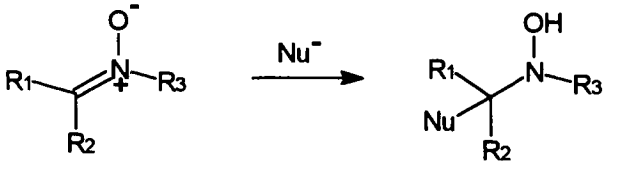


Scheme 4.14

Further investigations into the selective cleavage of the *N*-O bond of isoxazolidines is currently in progress at the RAU-laboratories.

4.2 NUCLEOPHILIC ADDITIONS TO NITRONES

Several nucleophiles attack the carbon end of the nitrone dipole and form α-substituted hydroxylamines (Scheme 4.15).

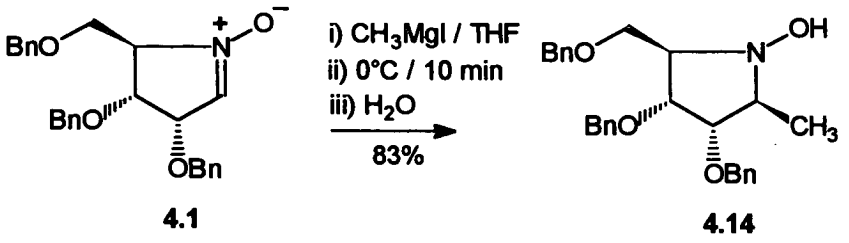


Nu^- = HO^-, RO^-, RS^-, CN^-

Scheme 4.15

Furthermore, carbanions,[16] active methylene compounds,[17] ylides[18] and organometallic compounds[19] also add readily to nitrones, making this the second most valuable type of transformation for these compounds after the [3+2] cycloaddition reactions discussed in the previous section.

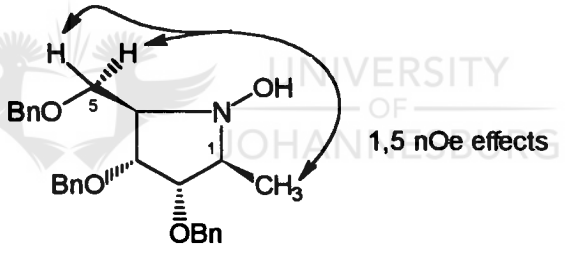
The reaction of nitrone **4.1** with freshly prepared Grignard reagent CH_3MgI proceeded smoothly in dry THF at 0°C to furnish the adduct **4.14** in a yield of 83% (Scheme 4.16).



4.1 **4.14**

Scheme 4.16

The ^{1}H-NMR spectrum of **4.14** indicated the presence of the *N*-hydroxy proton as a broad singlet at δ 6,05. The doublet of doublets (*J*=5,7 and 4,2Hz) resonating at δ 3,76 was assigned to H-1 which coupled with the doublet (*J*=5,7Hz) at δ 1,22 corresponding to a C-methyl group. The stereochemistry of the product was assigned on the basis of nOe experiments which indicated a strong 1,5 nOe effect between the methyl protons and H-5a and H-5b respectively (Scheme 4.17).

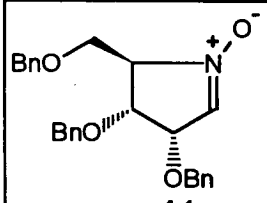
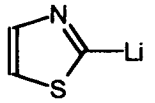
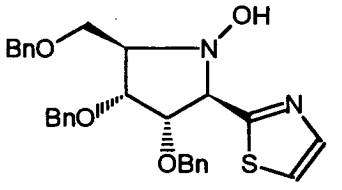
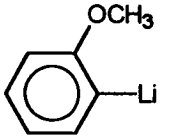
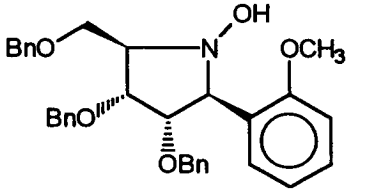
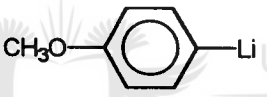
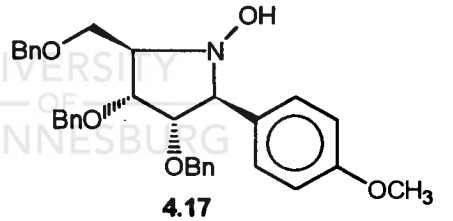


Scheme 4.17

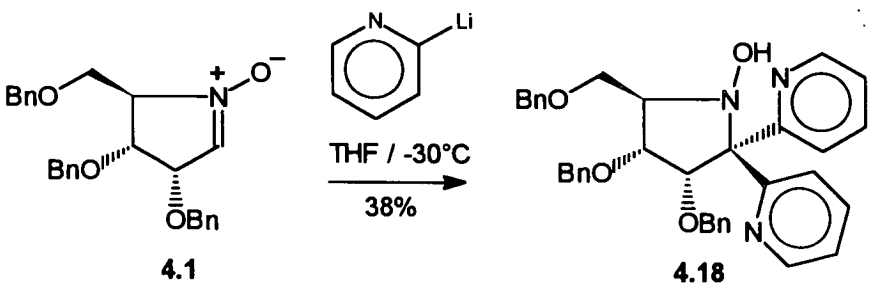
The reaction of nitrone **4.1** with a variety of lithiated aromatic compounds was investigated next. The lithiated species were prepared *in situ* by either a halogen exchange reaction or by direct deprotonation employing *n*-buthyllithium in both cases. A typical procedure involves the slow addition of a solution of the nitrone in dry THF to the lithiated species under an argon atmosphere at –78°C. The reaction mixture is allowed to warm up to –30°C and the reaction is monitored by TLC to completion. Reaction times were generally in the order of 30 minutes to 1 hour. Upon completion, the reaction mixture was quenched by the addition of an excess of saturated NH_4Cl solution. Using this methodology, three different lithiated aromatic compounds were successfully reacted with the nitrone **4.1**. The results are summarised in Table 4.1. In each case attack of the nucleophile was stereospecific, and by analogy with the reaction of the Grignard reagent and related reactions,[20] attack at the β-face of the substrate resulted in the formation of a single product together with unchanged starting material. The structures of the adducts **4.15**, **4.16** and **4.17** were established on the basis of MS, ^{1}H-NMR

and ^{13}C-NMR spectra. For example, the EI-MS of **4.15** showed a molecular ion at m/z 525 while the ^{1}H-NMR spectrum of the compound showed the diagnostic resonances of H-1 (δ 4,68; doublet; *J*=4,8Hz) and a singlet at δ 3,77 corresponding to the methoxy group.

Table 4.1 Reaction of **4.1** with carbon nucleophiles

NITRONE	REAGENT	PRODUCT	YIELD
 **4.1**		 **4.15**	**59%**
		 **4.16**	**75%**
		 **4.17**	**73%**

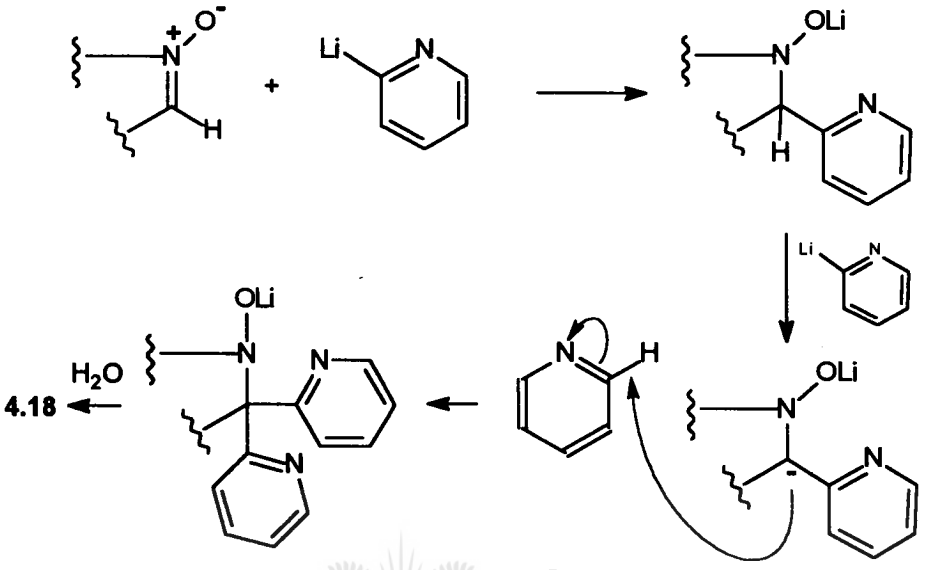
The reaction of **4.1** with 2-lithiopyridine (available *via* lithium-halogen exchange reaction employing commercially available 2-bromopyridine) in THF at –30°C afforded a number of polar products from which **4.18** could be isolated in a yield of 38% (Scheme 4.18).



4.1 **4.18**

Scheme 4.18

The EI-MS of **4.18** showed a weak molecular ion at m/z 573 corresponding to a product of double addition. The ^{1}H-NMR and ^{13}C-NMR spectra showed the signals of two pyridine groups together with those of the carbohydrate moiety. Compound **4.18** clearly arises from further reaction of the original adduct *via* i) deprotonation at C-1 of the sugar moiety by reaction with 2-lithiopyridine and ii) substitution of the released pyridine with the carbohydrate carbanion (Scheme 4.19).

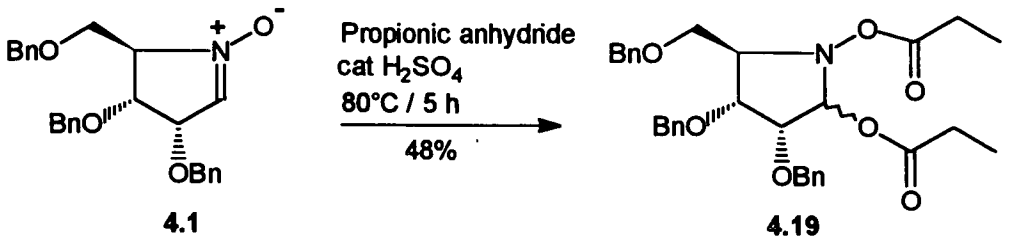


Scheme 4.19

The proposed mechanism for the formation of **4.18** is based on the known acidity of α-picolines[21] and the substitution of the α-position of pyridines with a range of carbon nucleophiles.[22]

4.3 NUCLEOSIDE SYNTHESIS

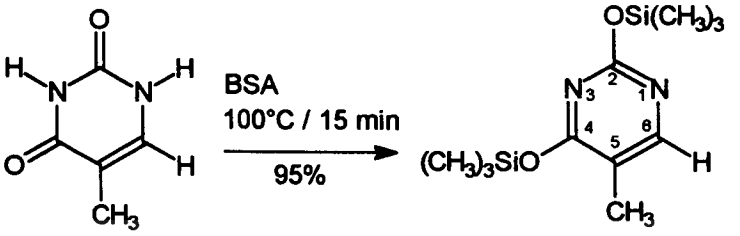
The synthesis of an aza analogue of a C-nucleoside was carried out using a procedure reported by Tronchet *et al.*[23] This method entails the reaction of silylated pyrimidine nucleosides with a suitable glycosyl donor and constitutes a modification of the Hilbert-Johnson synthesis[24] of nucleosides. The methodology is encumbered, however, by the possible formation of not only α,β-anomeric mixtures, but also the *N*-1 and *N*-3-substituted glycosyl pyrimidines.[25] The conversion of the nitrone into a suitable precursor was achieved by the reaction of **4.1** with propionic anhydride in the presence of a catalytic amount of mineral acid (H_2SO_4) at 80°C to afford **4.19** as a α,β-mixture in a yield of 48% (Scheme 4.20). This reaction was accompanied by a considerable amount of decomposition of the starting material and could not be optimized further.



4.1 **4.19**

Scheme 4.20

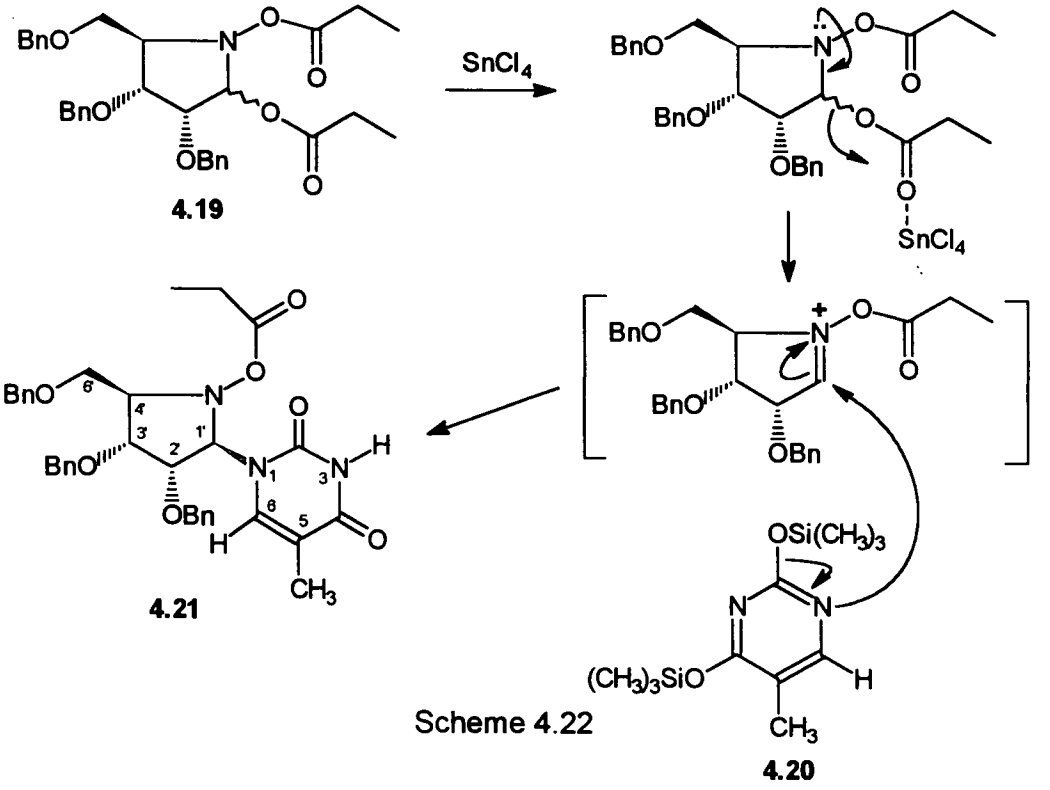
The required silylated derivatives may be prepared in excellent yields directly from pyrimidines such as cytosine, uracil or thymine. Silylation is readily accomplished with hexamethyldisilizane or *bis*-(trimethylsilyl)acetamide (BSA). Treatment of thymine with an excess of BSA at 100°C furnished **4.20** in nearly quantitative yield (Scheme 4.21). The product was purified by fractional distillation.



Thymine **4.20**

Scheme 4.21

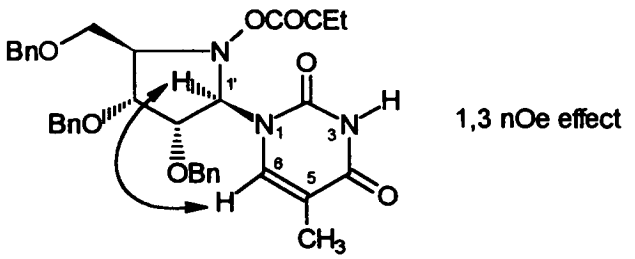
The silylated pyrimidines normally react sluggishly with the appropriate glycosyl donors and prior activation is normally provided.[26] Thus, treatment of **4.19** with *bis*-(trimethyl-silyl)thymine in the presence of a catalytic amount of the strong Lewis acid $SnCl_4$ furnished the protected nucleoside analogue **4.21** in a yield of 82% (Scheme 4.21).



4.19 **4.21** **4.20**

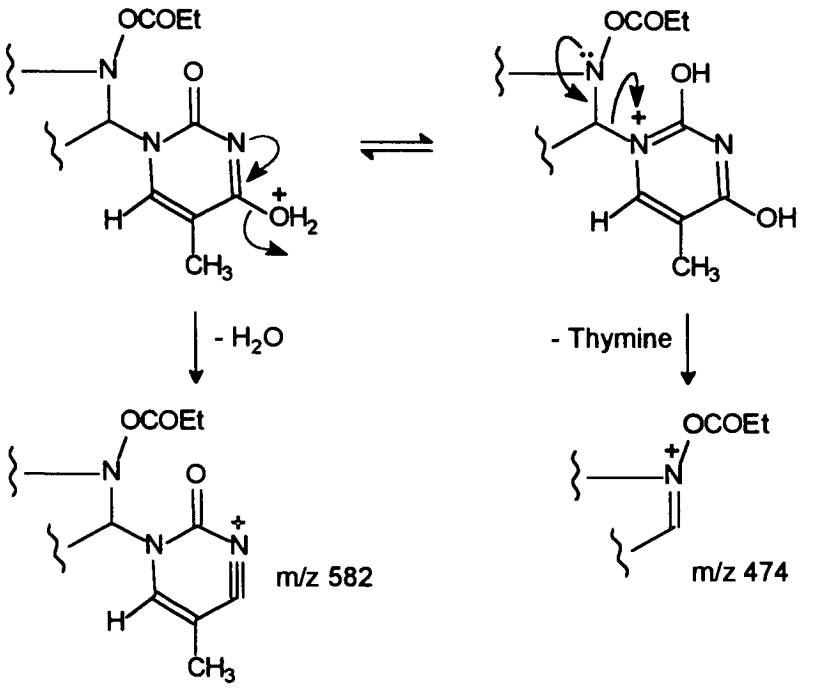
Scheme 4.22

The ^{1}H-NMR spectrum of the product showed the resonances of H-6 (δ 7,56; singlet) and the C-5 methyl protons (δ 1,93; singlet) of the thymine moiety. The resonance of H-2' appeared as a singlet (δ 6,09) indicating a dihedral angle between H-2' and H-3' close to 90° and thus that the product is the expected β-isomer. The ^{13}C-NMR spectrum showed diagnostic resonances for C-6 (δ 132,7), C-1' (δ 76,1) and the methyl carbon on C-5 (δ 13,9). The connection of the pyrrolidine moiety to *N*-1 of the pyrimidine base was confirmed by nOe experiments which indicated a strong 1,3 nOe effect between H-6 and H-2'. (Scheme 4.22). The close proximity of H-2' and H-6 can be obtained by rotation around the C-1' and N-1 bond.



Scheme 4.23

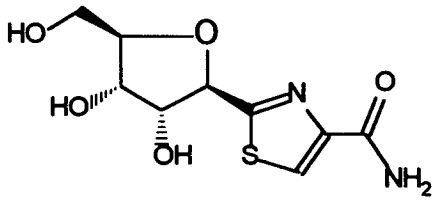
The molecular ion of **4.21** could not be detected in its EI-MS spectrum. The FAB-MS spectrum of the compound showed no [M+1] ion but prominent fragment ions were observed at m/z 582 ([M+1]-H_2O) and m/z ([M+1]-thymine moiety). The formation of the fragment ions are rationalised in scheme 4.24.



Scheme 4.24

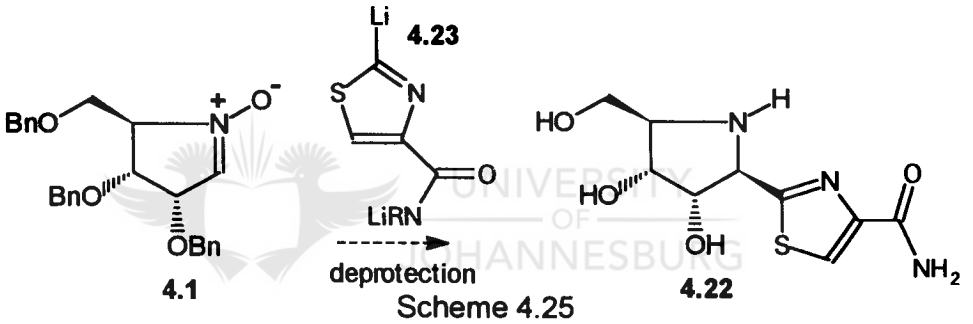
4.4 FUTURE WORK

Hope is held that the total synthesis of several aza analogues of *C*-nucleosides can be realised based on the methodology developed in these studies. The aza analogue of the antibiotic thiazofuran is an attractive target.



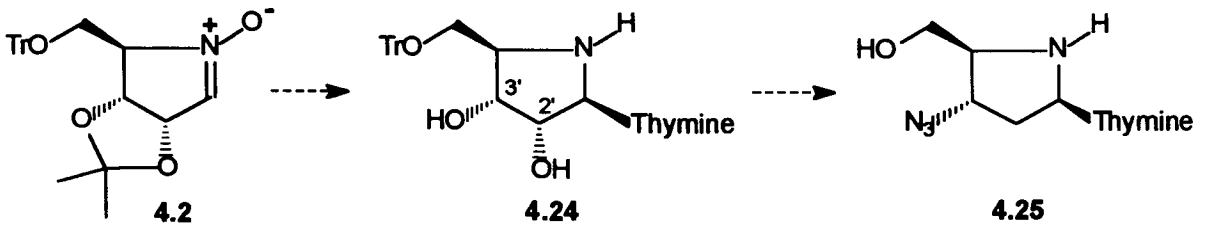
Thiazofuran

The reaction of the lithiated species **4.23** with nitrone **4.1** followed by deprotection would furnish the desired analogue **4.22** in two steps (Scheme 4.24).



Scheme 4.25

A relatively new development is that of metal ion mediated regio- and stereocontrol in nitrile oxide and nitrone dipolar cycloadditions with dipolarophiles.[27] An improvement of the diastereomeric excess obtained in the cycloadditions will further augment the synthetic value of our methodology. Furthermore, the problem of mild and selective reducing agents for the *N*-*O* bond in the polyfunctional isoxazolidines remains. The use of hydrazine and palladium on carbon for the reduction of hydroxylamines in a hydrogen transfer reaction has been reported. This method holds great promise for the mild reduction of the cycloadducts to their corresponding 1,3 amino alcohols. If successful, the proposed protocol (Section 4.1, Scheme 4.9) for the synthesis of an aza analogue of showdomycin (**4.10**) would be possible. An efficient method must also still be developed for the nucleosidation of polyhydroxylated cyclic nitrones with heterocyclic bases. This would e.g. allow the introduction of a thymine base onto nitrone **4.2**, followed by selective removal of the isopropylidene group to furnish intermediate **4.24** (Scheme 4.26).



Scheme 4.26

Selective derivatisation of the 2'-hydroxy group and subsequent tin hydride mediated deoxygenation should afford **4.25**. Replacement of the 3'-hydroxy group with an azide function would furnish an aza analogue of the anti-viral agent AZT (retrovir)[28] **4.25**. The nitrones discussed in this chapter clearly hold great potential as chiral synthons for the preparation of valuable heterocyclic compounds.

4.6 REFERENCES

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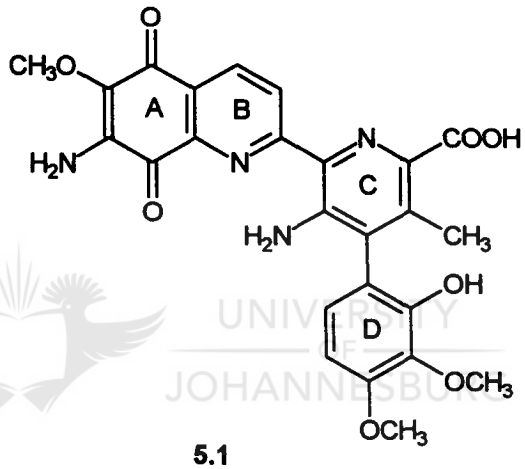
CHAPTER 5
PALLADIUM MEDIATED SYNTHESIS OF BIARYLS : APPROACHES TOWARDS CD-RING ANALOGUES OF STREPTONIGRIN

5.1 INTRODUCTION

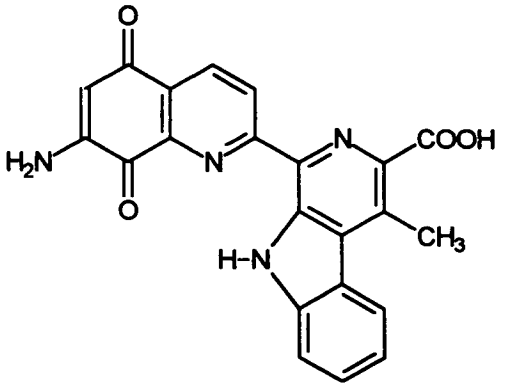
Streptonigrin[1] (**5.1**), a metabolite of a few species of *Streptomyces* and *Actinomyces*, has been found to be quite effective in the treatment of a variety of human tumors,[2] although its high toxicity has precluded general clinical use. It causes severe bone marrow depression, nausea, vomiting and chromosomal damage.[3]



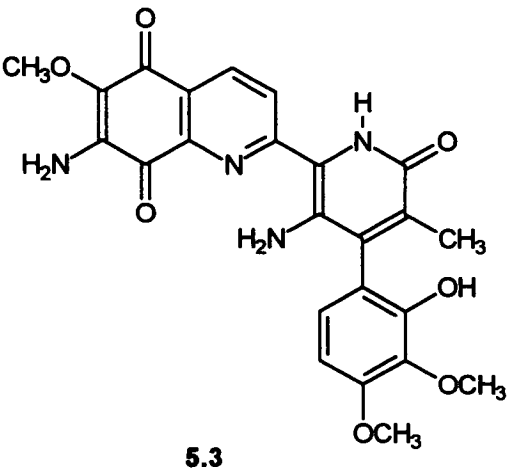
5.1

Rao, Biemann and Woodward determined the chemical structure of **5.1**, by means of spectral and degradative studies.[4] Its structure incorporates a highly substituted 2-(2-pyridyl)quinoline-5,8-dione moiety. X-ray diffraction studies[5] indicated that the A, B and C rings are almost coplanar. However, optical activity arises from a 90° twist around the C-C bond linking the C and D rings.[6] Rotation around the bond linking the two rings is prevented by steric hindrance between the amino and methyl groups of ring C and the hydroxy group of ring D. As a target for total synthesis, streptonigrin presents a major challenge with its high degree of functionalisation and tightly linked array of aromatic rings. This observation is highlighted by the fact that only three total syntheses have been reported to date in the literature.[7] Considerable work concerning the synthesis of related compounds lavendamycin[8] **5.2** and streptonigrone[9] **5.3**, as well as model studies towards the synthesis of streptonigrin itself have also been published.[10] Most of these attempts were directed solely at the synthesis of the natural products themselves and relied on chemical ring construction methods for the construction of pyridines and quinolines. The RAU organic chemistry research group is developing a different approach which would allow the construction not only of the natural

product, but of otherwise inaccessible analogues with different substituents and substitution patterns. This work is receiving support from the Cancer Research Institute of the National Institutes of Health in Washington, USA. Any new compounds which may eventually be prepared will be submitted for biological testing in the hope of identifying an antibiotic with minimum chemical functionality, optimal activity and negligible toxicity.



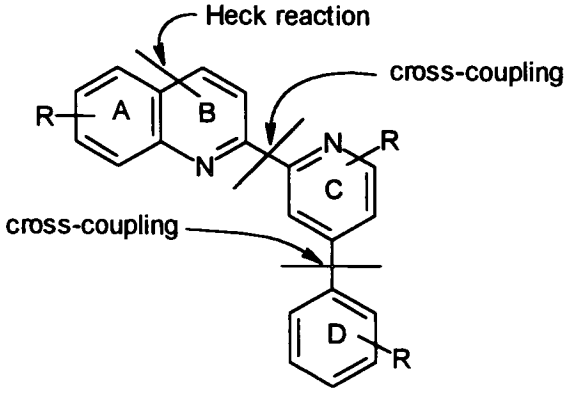
5.2



5.3

5.2 OVERALL STRATEGY TOWARDS STREPTONIGRIN

The total synthesis of streptonigrin and related compounds has been a subject of research at the RAU over the past few years. The pivotal role played by transition metal-mediated carbon-carbon bond forming reactions in organic chemistry coupled to the expertise in palladium chemistry which has been developed in our laboratories,[11] suggested their use in the overall strategy towards a convergent synthesis of the basic carbon skeleton. The retro-synthetic analysis on which this approach is based is summarised in Scheme 5.1.



Scheme 5.1

Thus, the new approach to the synthesis of **5.1** is based on the use of metalation[12] and palladium catalysed cross-coupling reactions[13] as the key steps in the synthesis. The envisaged strategy involves four stages:

i) a Heck reaction[14] of an A-ring precursor with methyl acrylate, followed by cyclisation to form the AB ring system;

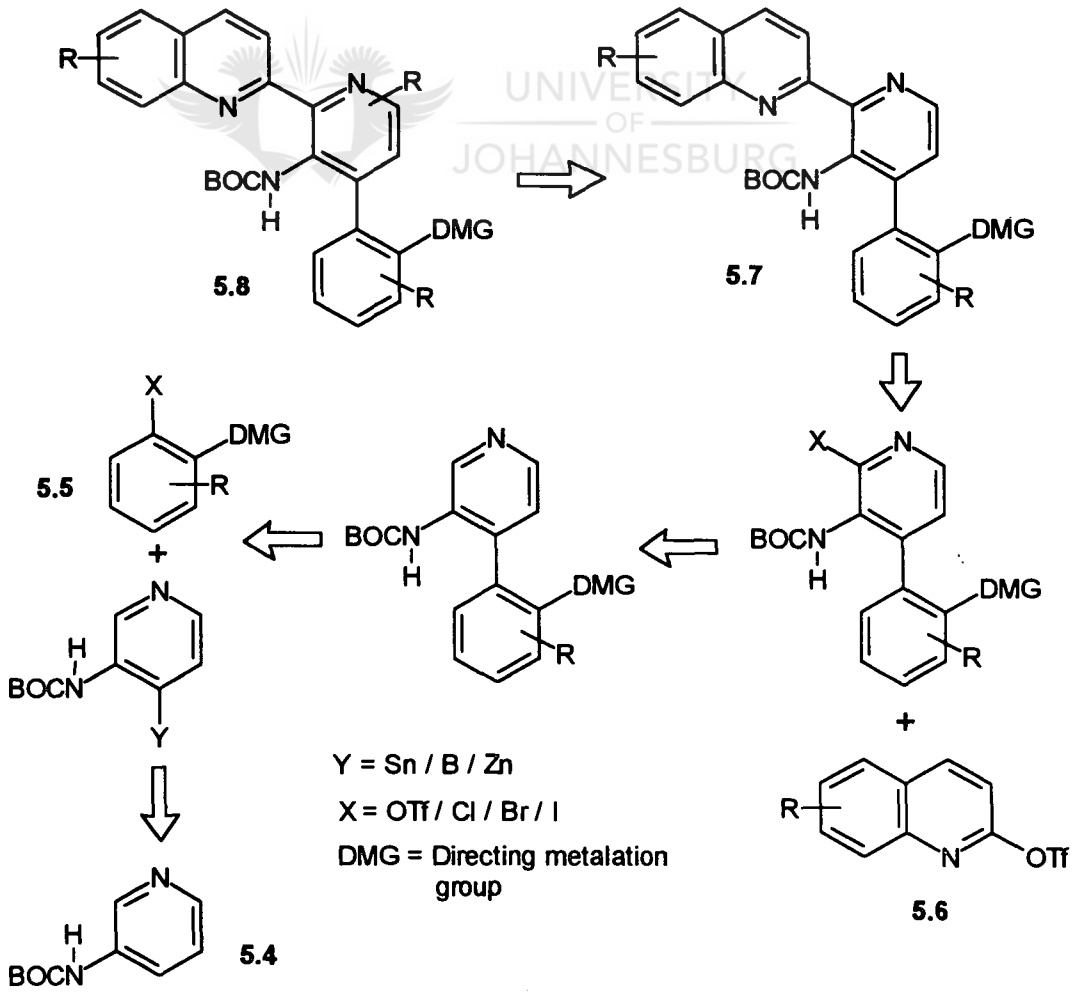
ii) a cross-coupling reaction between the appropriate C and D ring precursors;

iii) a second cross coupling reaction to link the AB and CD moieties to furnish the tetracyclic skeleton;

iv) the introduction of the remaining substituents of the C-ring *via* directed *ortho* metalation.

v) The modification of functionality eg. by oxidation to afford the final product.

The work described in this chapter will center on the development of a facile route towards CD ring models of streptonigrin.[15] The retrosynthetic route (Scheme 5.2) involves the functionalisation of *N*-(*tert*-butoxycarbonyl)-3-amino pyridine **5.4** at C-4 by metalation, followed by cross coupling with a suitably functionalised benzene **5.5**.



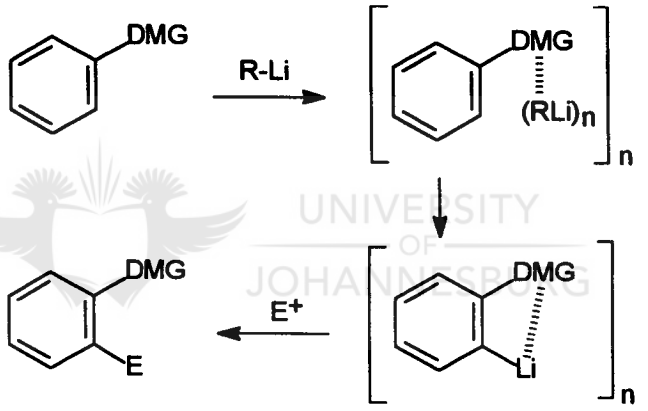
Scheme 5.2

Subsequent metalation at C-2 of the pyridine moiety followed by a second cross coupling reaction with an appropriate 2-quinolyl triflate **5.6** will furnish tetracycle **5.7**. The introduction of the remaining functionality on the C-5 and C-6 positions of the C-ring can now be accomplished *via* selective metalation with LDA and quenching with the appropriate electrophiles to afford **5.8**.

5.3 DoM AND CROSS-COUPLING STRATEGIES IN C-C BOND FORMATION

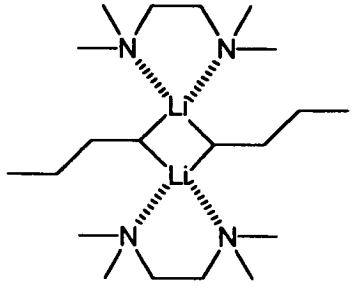
5.3.1 Directed *ortho* metalation

Directed *ortho* metalation is a useful tool in the preparation of polysubstituted aromatics.[16] Essentially it involves the deprotonation of a site *ortho* to a heteroatom-containing DMG by a strong base, usually an alkyllithium reagent. The lithium reagent coordinates to the heteroatom of the DMG and deprotonation occurs preferentially at the *ortho* position because this *ortho*-lithiated species is stabilised by coordination. Trapping of the carbanion with any electrophile affords the ortho-substituted product (Scheme 5.3).



Scheme 5.3

RLi species are believed to react as aggregates in hydrocarbon solvents, thereby decreasing the effective concentration of the base.[17] For this reason the deprotonations are usually carried out in etheral solvents (THF, ether) and in the presence of a bidentate ligand (usually TMEDA). These coordinate with the lithium and break down the aggregates into monomers and dimers thereby increasing the basicity of the RLi species (Scheme 5.4).



RLi:TMEDA aggregate

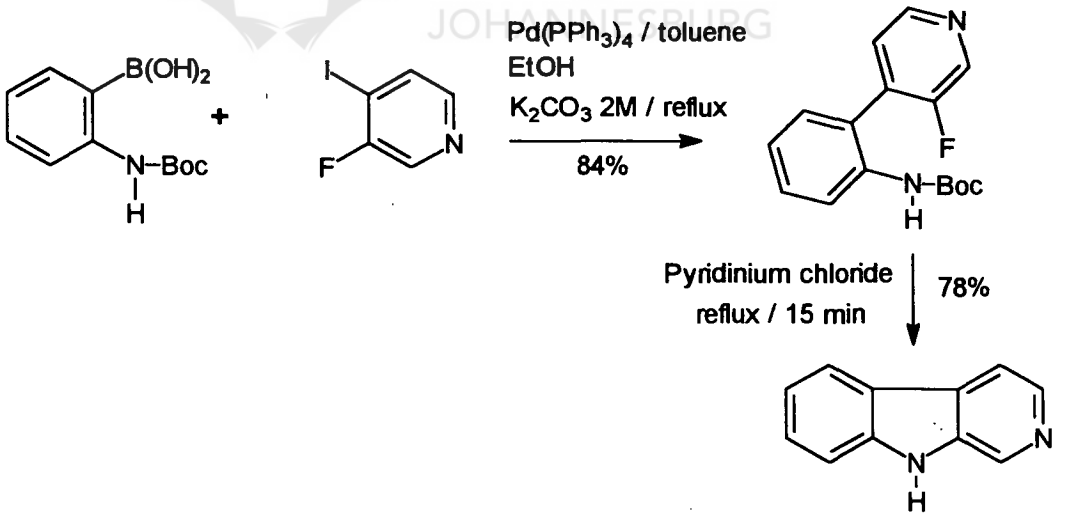
Scheme 5.4

A good DMG should have the contradictory properties of being a good coordination site for RLi but also a poor electrophilic site to prevent attack by the strong base. Some of the more commonly used DMG's are listed in Table 5.1.

Table 5.1 Directing metalation groups

$CONR_2$	Decreasing directing ability
SO_2NR_2	
$OCONR_2$	
OMOM	
NHCOR	
$NHCO_2R$	
CH_2NR_2	
OMe	

Where DoM methodology ties in strongly with the cross-coupling is that the required organotin, organozinc and organoboron compounds are generally prepared *via* this route. They may also be prepared via halogen-lithium exchange[18] of the corresponding aryl halides. A plethora of natural products have been synthesised using a combination of DoM and cross-coupling strategies.[19] Furthermore, cyclisations through the heteroatoms of the DMG's provide easy access to a number of heterocyclic compounds, for example azacarbazoles[20] (Scheme 5.5).

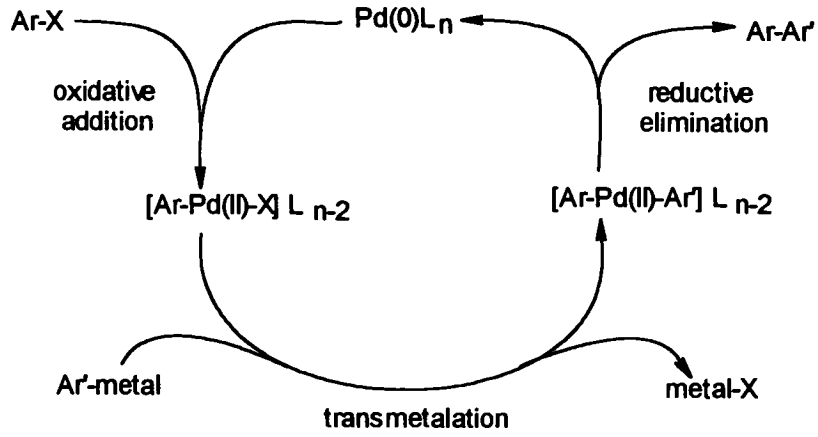


Scheme 5.5

5.3.2 Cross-coupling reactions

There are a vast selection of transition-metal catalysed cross-coupling reactions, including those based on the use of organozinc,[21] organosilicon[22] and recently organomanganese derivatives.[23] The couplings can be between sp, sp^2 and sp^3 centers or combinations of these. For the purpose of this study we concentrated on biaryl synthesis employing Stille[24] and

Suzuki[25] reactions. These involve the reaction of aryltin and arylboron compounds respectively with aryl halides or triflates using transition metal catalysts (Pt, Pd or Ni). Despite the widespread use of Stille and Suzuki cross couplings, very little is understood about the reaction mechanism. It is generally accepted that the reactions take place *via* oxidative addition, transmetalation and reductive elimination steps[26] (Scheme 5.6).



Scheme 5.6

The rate-determining step in oxidative addition is cleavage of the C-X bond. The fact that electron withdrawing groups accelerate the rate of this reaction supports a nucleophilic substitution mechanism, although single electron transfer and 3-centre concerted mechanisms have also been suggested. The exact mechanism of transmetalation is not known, but it involves the transfer of an organic group from a more electropositive metal (Sn /B) to the less electropositive palladium species. The equilibrium is driven to the right by the irreversible consumption of this species to the coupled product.

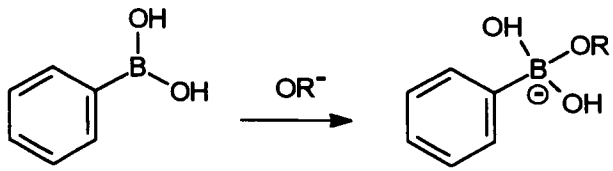
5.3.2.1 The Stille cross-coupling reaction

The palladium-catalysed coupling of organostannanes with organic electrophiles (Stille reaction) was pioneered by Migita and Stille in the late 1970's. Although it is only one within the large family of cross-coupling reactions, the Stille reaction enjoys perhaps a wider scope of application than any other cross-coupling reaction, due to the stability and low cross-reactivity of organotin compounds.[27] Unfortunately, the low reactivity of organostannanes can be a drawback. Furthermore, the high toxicity of the reagents employed in the synthesis of the organotin derivatives tends to be a limiting factor in the day to day application of this methodology in organic synthesis. The nature of the palladium ligands can have a dramatic effect on the rate of the Stille reaction.[28] Ligands of low donicity [$AsPh_3$ / $P(o\text{-}fur)_3$] are associated with faster rates as they increase the electrophilicity and therefore the reactivity of

the Pd(II) species to attack by organostannane nucleophiles. The traditional PPh_3, which is a strong donor ligand tends to inhibit the reaction rate. In a typical procedure, the catalyst was formed *in situ* by introducing the weakly coordinated tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$ and 4 equivalents (for each Pd atom) of the ligand under study. The purple colour of the dibenzylideneacetone (dba) catalyst usually turned to a pale yellow colour within 5-10 minutes to furnish the appropriate Pd(0)catalyst. Unfortunately, the use of these so-called soft ligands also produced catalysts of intermediate stability, and no definite rule of thumb could be found with which to predict the optimum catalyst for a coupling reaction.

5.3.2.2 The Suzuki cross-coupling reaction

The cross coupling of organoboron reagents with organic halides is a fairly straightforward method of carbon-carbon bond formation. It proceeds under mild conditions, is generally unaffected by the presence of water and, in probably its major advantage over Stille couplings, the reagents and by-products are generally non-toxic. This makes it one of the few cross-coupling reactions which may be employed industrially. Organoboron compounds are highly electrophilic, but this problem is overcome by the addition of a negatively charged base which coordinates to the boron to form an "ate" complex (Scheme 5.7), greatly increasing the nucleophilicity of the organic group, and facilitating transfer to the Pd(II) electrophile.[29]



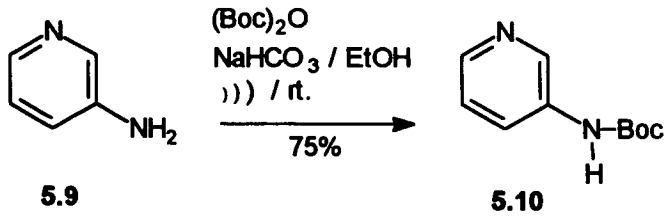
Scheme 5.7

The bases most often used are sodium and potassium carbonates, phosphates, hydroxides and alkoxides. They can be used as an aqueous solution or in suspension in an organic solvent (DME, dioxane ect.). The organoboron compounds which can be employed include the boronic acids, their ester derivatives, or borane derivatives (often bridged eg. BBN).

5.3.3 Cross-coupling reactions of π-deficient organometallic heterocycles

The key starting material for the proposed strategy (Scheme 5.2), *N*-(*tert*-butoxycarbonyl)-3-amino pyridine **5.10**, was prepared by the reaction of 3-aminopyridine **5.9** with di-*tert*-butyl

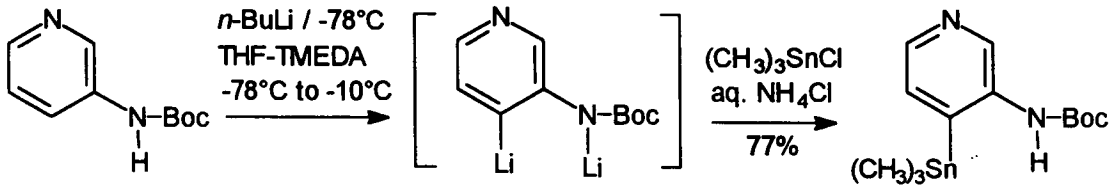
dicarbonate in an organic solvent under basic conditions (Scheme 5.8). The obtention of protected aryl amines is often more complicated than their aliphatic counterparts due largely to the decreased nucleophilicity of the aryl amine, and hence long contact times are required.[30] This can lead to a number of side reactions, including bis-carbamoylation and/or urea formation. The rate of the reaction can however be increased up to a hundred fold by sonication.[31] The ultrasonic waves accelerate the reaction by a factor depending on sound intensity, and seem to have essentially the mechanical role of increasing the reactive surface by breaking up the mineral particles. The progress of the transformation can usually be followed by the evolution of carbon dioxide.



5.9 **5.10**

Scheme 5.8

Godard *et al.*[10] showed that 3-amino-2-methoxypyridines protected as their pivaloyl amides can be efficiently lithiated at the 4-position by reaction with *n*-butyllithium. The treatment of **5.10** with 2 equivalents of n-BuLi at –78°C in a THF-TMEDA mixture afforded a monoanion which underwent a second deprotonation upon warming to –10°C generating the dianion **5.11**[32]. Subsequent recooling to -78°C and addition of 1 equivalent of trimethyltin chloride (2M solution) furnished crystalline **5.12** in a yield of 77%.



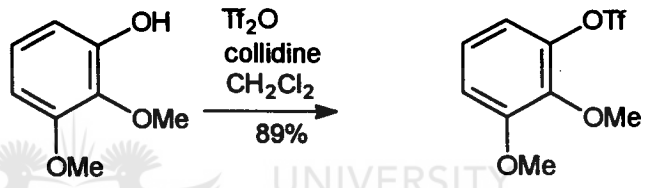
5.10 **5.11** **5.12**

Scheme 5.9

The ^{1}H-NMR spectrum of **5.12** indicated the presence of the amide proton as a broad singlet (δ 6,56), H-2 as a singlet (δ 6,56) and the trimethyltin protons as a 9 proton singlet (δ 0,32). Of great import was the amount of *n*-butyllithium used to deprotonate **5.10**. The use of any amounts in excess of 2 equivalents resulted in a dramatic decrease in the yield of the reaction. This observation can readily be explained by the fact that the Sn atom of **5.12** is a

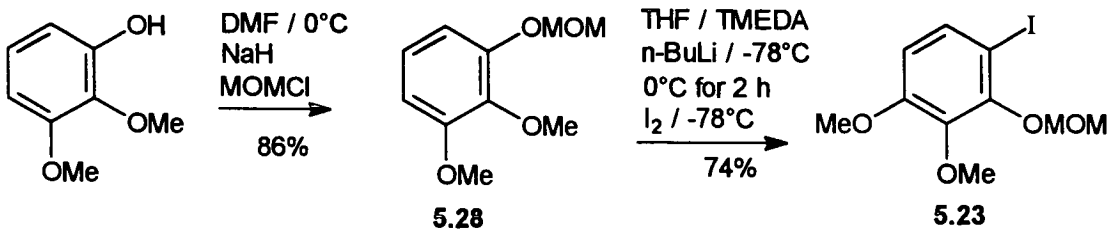
soft centre which is readily attacked by the excess of the soft nucleophile (Bu^-) in the reaction mixture.

The results of an extensive study of the Stille cross-coupling reaction of **5.12** with a variety of aryl halides and aryl triflates are summarized in Table 5.2. The phenyl triflate **5.27** were readily prepared from the corresponding phenol using a standard literature procedure[33] (Scheme 5.10). To the phenol in dry dichloromethane was added 1,2 equivalents of 2,4,6-collidine and 1,2 equivalents of triflic anhydride. The solution was stirred at room temperature until TLC analysis indicated that the reaction was complete. Evaporation of the solvent followed by extraction with pentane afforded the desired product as an oil. For the reactions involving aryltriflates, LiCl was used as a necessary additive. The *O*-triflate ion is a very weak ligand for the palladium intermediate and the addition of an additional source of a good ligand such as Cl^- is believed to increase the lifetime of the palladium catalyst.



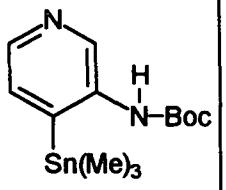
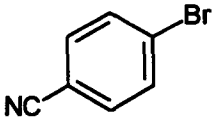
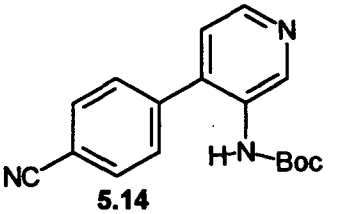
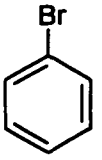
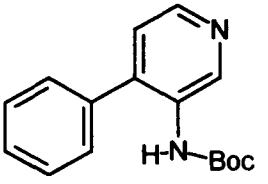
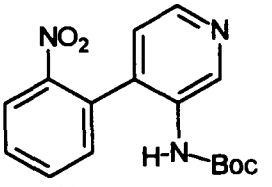
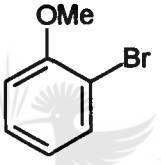
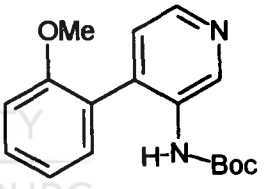
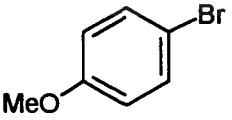
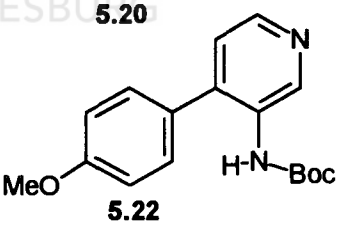
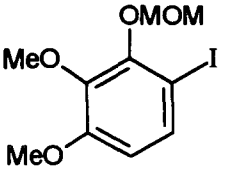
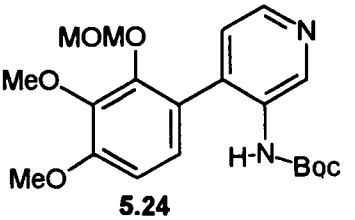
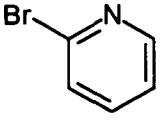
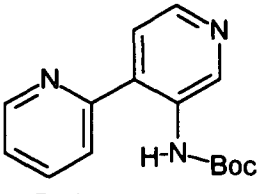
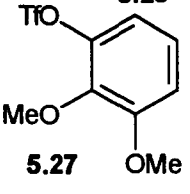
Scheme 5.10

Compound **5.23** was synthesised from the readily available 2,3-dimethoxyphenol in two high yielding reactions. The phenol was protected as its methoxymethyl ether **5.28**. The *O*-MOM group functions as a moderately strong *ortho*-directing group in lithiation reactions. Subsequent metalation using *n*-BuLi followed by quenching with iodine afforded **5.23** (Scheme 5.11).



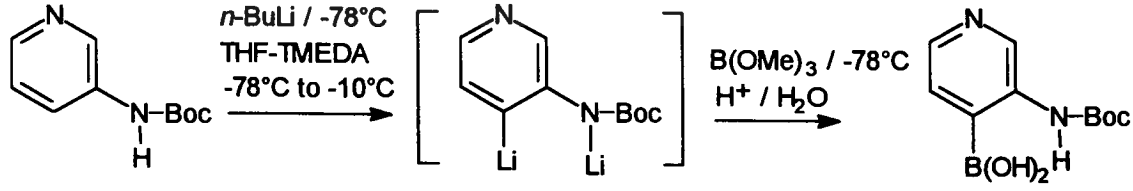
Scheme 5.11

Table 5.2 Stille cross-coupling reactions of **5.12** with aryl halides and aryl triflates

Sn-Substrate	Ar-X (X = OTf, I, Br)	Conditions	Product	Yield
 **5.12**	 **5.13**	$Pd_2(dba)_3$ $AsPh_3$ reflux 1 h	 **5.14**	88%
	 **5.15**	$Pd(PPh_3)_4$ Dioxane reflux 2 h	 **5.16**	85%
	 **5.17**	$Pd_2(dba)_3$ $AsPh_3$ Dioxane reflux 1 h	 **5.18**	80%
	 **5.19**	$Pd(PPh_3)_4$ Dioxane reflux 6 h	 **5.20**	71%
	 **5.21**	$Pd(PPh_3)_4$ Dioxane reflux 3 h	 **5.22**	68%
	 **5.23**	$Pd_2(dba)_3$ $AsPh_3$ Dioxane reflux 12 h	 **5.24**	20%
	 **5.25**	$Pd(PPh_3)_4$ Dioxane reflux 6 h	 **5.26**	58%
	 **5.27**	$Pd(PPh_3)_4$ Dioxane 2 LiCl reflux 6 h	No cross-coupling observed	

The results in Table 5.2 clearly show that the cross-coupling of **5.12** with electron poor aryl halides (**5.13** and **5.17**) proceed rapidly and in high overall yields. This is in accord with the general observation that the oxidative addition of palladium(0) is accelerated by electron withdrawing groups on the aryl moiety. As expected, the reaction of **5.12** with electron rich substrates (**5.19**, **5.21** and **5.23**) was sluggish and required longer reaction times. The low yield obtained for the Stille cross-coupling reaction of **5.12** with the hindered, electron rich **5.23** was disappointing. This highlights the fact that the Pd(0)-catalysed synthesis of hindered biaryls is limited by the presence of *ortho* substituents on either the arylstannane or the aryl halide.[34] The transmetalation step in the catalytic cycle presumably requires an electron-deficient palladium center for the nucleophilic attack by the stannane. The current synthetic route employs a stannane on the electron poor pyridine ring and an aryl halide on the electron rich aromatic ring, which represents the worst possible combination for optimal Stille cross-coupling substrates.

Following the study on the Stille cross-coupling reactions of **5.12**, the analogous organoboron compound **5.29** was synthesised *via* the metalation protocol described previously. Treatment of **5.10** with 2 equivalents of *n*-BuLi at –78°C in an THF-TMEDA mixture, deprotonation at –10°C for 2 h, subsequent recooling to -78°C followed by addition of 2 equivalents of trimethylborate afforded the crude boronic acid **5.29** after acidic workup (Scheme 5.12).



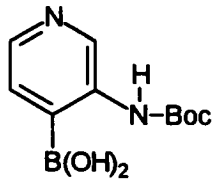
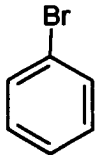
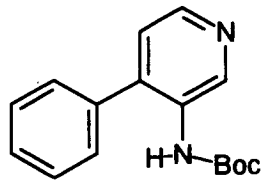
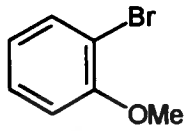
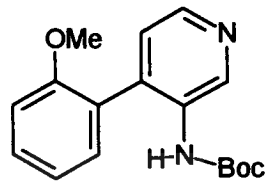
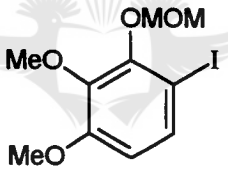
5.10 **5.29**

Scheme 5.12

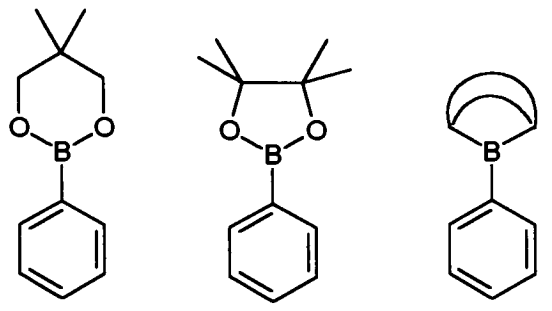
This compound was not purified further, but used immediately in Suzuki cross-coupling reactions with various aryl halides (Table 5.3). The reaction of **5.29** with the *ortho* substituted aryl halide **5.19** was accompanied by a considerable amount of dehydroboronation. This side reaction can be overcome to a reasonable extent by employing anhydrous basic conditions.[35] However, the use of anhydrous $CsCO_3$ for the attempted cross-coupling with **5.23** furnished mainly products of homocoupling and dehydroboronation (**5.10**). This result lends further support to the observations by various research groups[36] that sterically hindered arylboronic acids and those possessing electron-withdrawing groups seldomly provide satisfactory results due to competitive hydrolytic deboronation. The use of selected boronic acid esters (Scheme 5.13) has also been suggested in these cases. These esters are not easily hydrolysed and

can be chromatographed, extracted or distilled in the manner of typical organic compounds.[37] They are readily prepared by suspending the crude boronic acid in toluene and refluxing the mixture in the presence of a slight excess amount of a suitable diol such as 2,2-dimethylpropane-1,3-diol.[38]

Table 5.3 Suzuki cross-coupling reactions of **5.29** with aryl halides

Sn-Substrate	Ar-X (X = OTf, I, Br)	Conditions	Product	Yield
 **5.29**	 **5.30**	$Pd(PPh_3)_4$ aq. Na_2CO_3 EtOH / reflux	 **5.16**	80%
	 **5.19**	$Pd(PPh_3)_4$ aq. Na_2CO_3 EtOH / reflux	 **5.20**	64%
	 **5.23**	$Pd(PPh_3)_4$ $CsCO_3$ EtOH / reflux	No cross-coupling observed	

However, all attempts to derivatise **5.29** with a variety of diols only led to the formation of polymeric compounds.



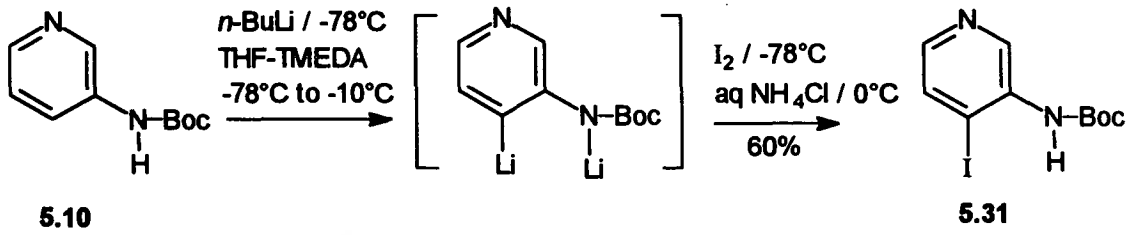
Scheme 5.13

In view of the failure to produce the desired biaryl **5.24** in good yields *via* the original protocol (Scheme 5.2), it was decided to investigate cross-coupling reactions incorporating the tin or

boron moiety on the D-ring precursor. This will provide an electronic environment which may be more conducive to the transmetalation step of the cross-coupling reactions investigated here.

5.3.4 Cross-coupling reactions of π-excessive organometallic aromatics

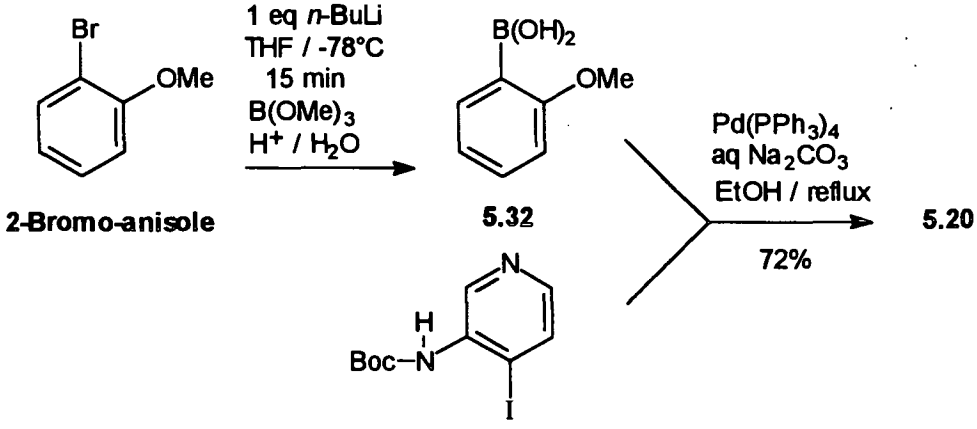
N-(*tert*-Butoxycarbonyl)-3-amino pyridine **5.10** was again used as starting material for the revised strategy. The treatment of **5.10** with 2 equivalents of *n*-BuLi at –78°C in an THF-TMEDA mixture afforded a monoanion which underwent a second deprotonation upon warming to –10°C. Subsequent recooling to -78°C and addition of 1,2 equivalents of resublimed iodine afforded the iodo-pyridine **5.31** in a yield of 60% together with unchanged starting material (Scheme 5.14).



5.10 **5.31**

Scheme 5.14

The ^{1}H-NMR spectrum of **5.31** showed the signals of H-5 and H-6 as two doublets (δ 7,88 and δ 7,67; *J*=5,1Hz) respectively. The moderate yield obtained for the iodination of metalated **5.10** is significantly lower than for other electrophiles. Other research groups[32] have also made this observation for related iodinations, but the reason for this is not known. The cross-coupling of **5.31** with the *ortho* substituted boronic acid **5.32** (available from 2-bromo-anisole *via* lithium-halogen exchange) furnished the cross-coupled product **5.20** in a yield of 72% (Scheme 5.15).

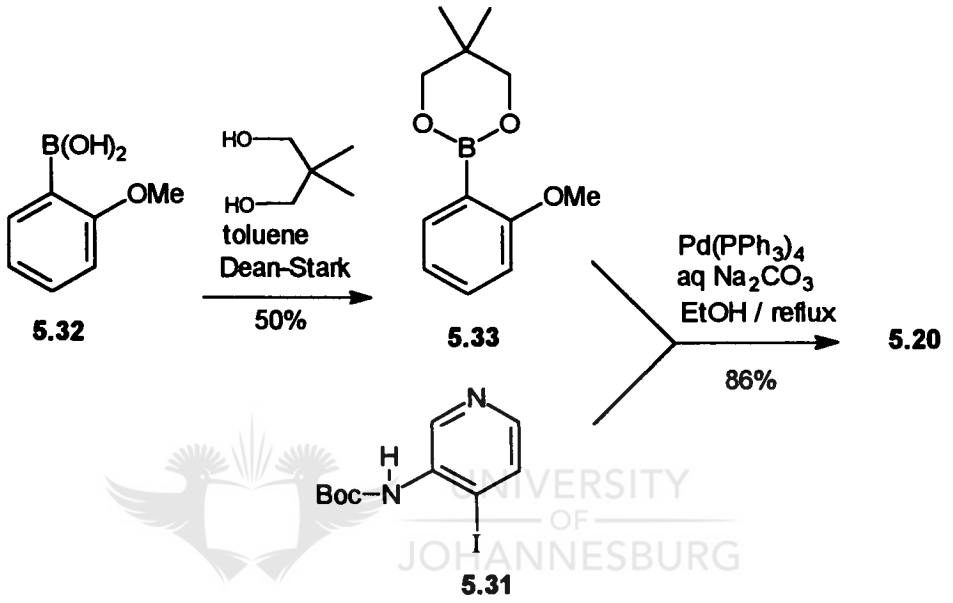


2-Bromo-anisole **5.32** **5.20**

5.31

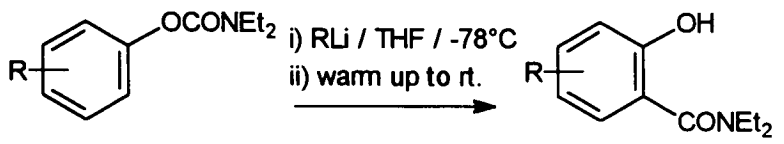
Scheme 5.15

The Suzuki cross-coupling reaction was once again plagued by hydrolytic deboronation as a competing reaction. This problem was largely overcome by first converting the boronic acid into its corresponding 2,2-dimethyl-1,3-propanediol ester **5.33** (Scheme 5.16). The ^{1}H-NMR spectrum of **5.33** showed the characteristic methyl protons as a 6-proton singlet at δ 1,02. In agreement with similar results reported by Snieckus *et al.*, the esterification of the boronic acid proceeded in low yield. This is a serious drawback for any planned total synthesis. The ester **5.33** coupled smoothly with **5.31** under standard conditions to afford the cross-coupled product **5.20** in a yield of 86%.



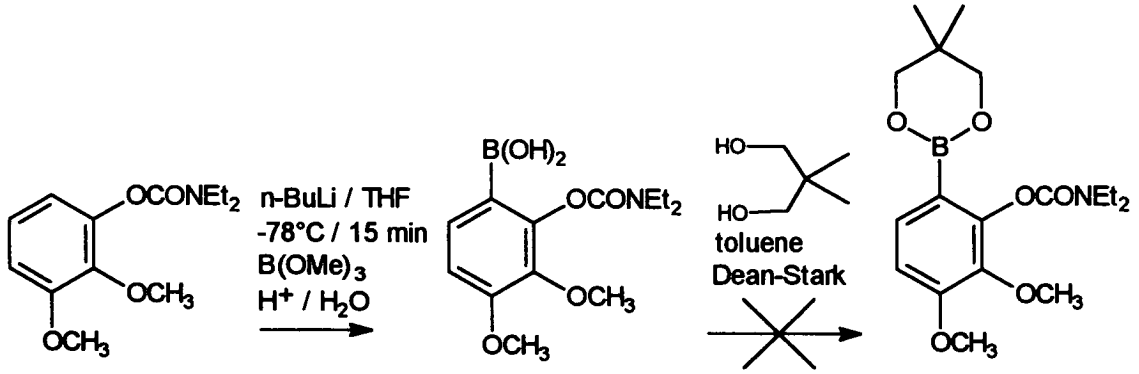
Scheme 5.16

The favourable result obtained for the cross coupling of **5.33** prompted us to attempt the coupling of a streptonigrin D-ring equivalent to **5.31**. The protection of 2,3-dimethoxyphenol as its corresponding *O*-carbamate was carried out using standard conditions. The carbamate group is one of the best directing groups in DOM-chemistry and full metalation is possible at –78°C after only a short reaction time.[12a] Care should however be taken, as these groups are prone to undergo rearrangements to *ortho*-hydroxy aromatic amides in an anionic equivalent of the *ortho*-Fries rearrangement[39] at temperatures higher than –50°C (Scheme 5.17).



Scheme 5.17

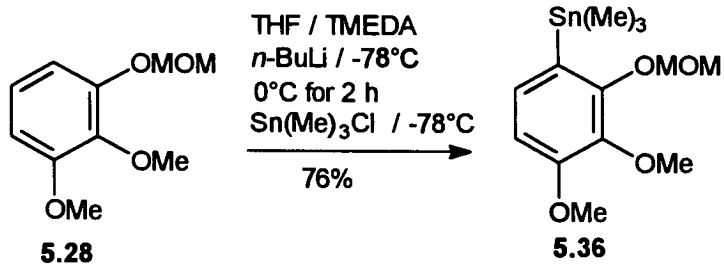
Thus, compound **5.34** was treated with *n*-BuLi for 15 min. at –78°C before quenching the reaction with an excess of trimethylborate (Scheme 5.18). TLC analysis indicated the conversion of all the starting material to a very polar product, presumably the boronic acid **5.35**. However, this compound did not undergo Suzuki cross-coupling with **5.31** while attempts to convert it to the corresponding 2,2-dimethyl-1,3-propanediol also failed.



5.34 **5.35**

Scheme 5.18

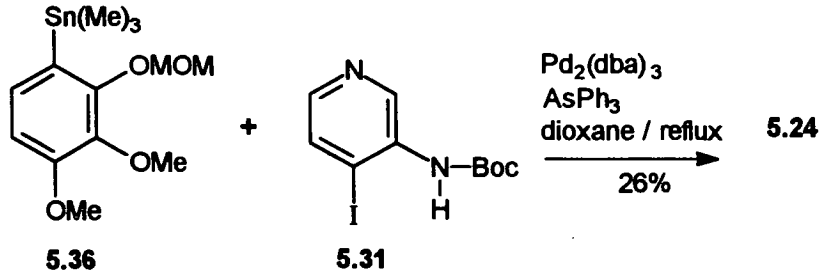
The synthesis of a corresponding electron rich trimethyltin derivative was investigated next. The MOM-ether **5.28** was metalated using 1,05 equivalents of *n*-BuLi in THF at 0°C for 2 hours. The reaction mixture turned milky white as the lithiated species formed, and quenching the reaction at –78°C with trimethyltin chloride caused the reaction mixture to gradually turn clear again, affording **5.36** in a yield of 76% (Scheme 5.19).



5.28 **5.36**

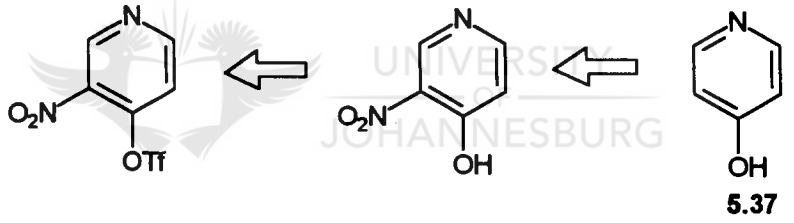
Scheme 5.19

The EI-MS of **5.36** showed a $[M\text{-}CH_3]^+$ fragment ion at m/z 345. The ^{1}H-NMR spectrum indicated the presence of the methoxymethyl ether at δ 5,15 and δ 3,51 (two singlets) and the trimethyltin moiety at δ 0,28 (singlet). The Stille cross-coupling reaction of **5.36** with **5.31** under optimised conditions furnished the desired biaryl in a yield of only 27% after a reaction time of 48 hours (Scheme 5.20).



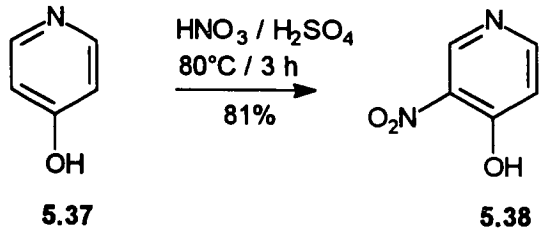
Scheme 5.20

Clearly, the placing of the trimethyltin moiety on the electron rich aromatic ring afforded no additional benefit, even though this situation would provide an organotin compound with maximum nucleophilic properties. In view of the success achieved in the Stille reaction of **5.12** with electron deficient aromatics such as **5.17** (Table 5.2), it was decided to investigate suitably substituted nitro pyridines as substrates in the cross-coupling with **5.36**. The envisaged strategy involved the nitration of readily available 4-hydroxypyridine **5.37**, triflation of the C-4 hydroxy group and subsequent Stille cross-coupling with **5.36** (Scheme 5.21).



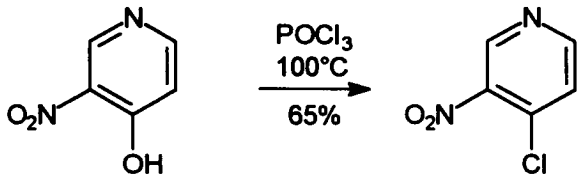
Scheme 5.21

The nitration of electron deficient aromatic rings is notoriously difficult and all attempts employing mild nitrating agents failed (claycop,[40] nitronium tetrafluoroborate,[41] etc). However, the drastic conditions employed by Wittek *et al.*[42] for the nitration of 4-hydroxy-2,3-lutidine proved very successful in this case also. Treatment of a concentrated sulfuric acid solution of **5.37** with fuming nitric acid in sulfuric acid at 80°C for 3 hours afforded the 4-hydroxy-3-nitro pyridine **5.38** in a yield of 81% after crystallisation (Scheme 5.22).



Scheme 5.22

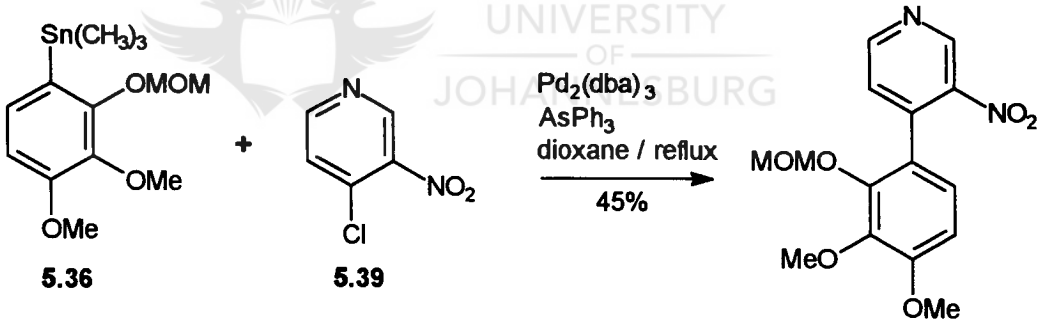
The EI-MS of **5.38** showed a molecular ion at m/z 140. All attempts to convert the 4-hydroxy group of **5.38** into the corresponding triflate employing standard conditions failed. Thus, it was decided to convert the hydroxy group of **5.38** into a chloride by the action of $POCl_3$.[43] The palladium-catalysed cross-coupling reactions of π-deficient heteroaryl chlorides have been employed with great success by Ali *et al.*[44] The treatment of **5.38** with an excess of $POCl_3$ at 100°C for 1 hour furnished **5.39** as a colourless oil in a yield of 65% (Scheme 5.23).



5.38 **5.39**

Scheme 5.23

The Stille cross-coupling reaction of **5.39** with **5.36** employing $Pd_2(dba)_3$ as catalyst and $AsPh_3$ as ligand furnished the novel biaryl **5.40** in a yield of 45% (Scheme 5.24).



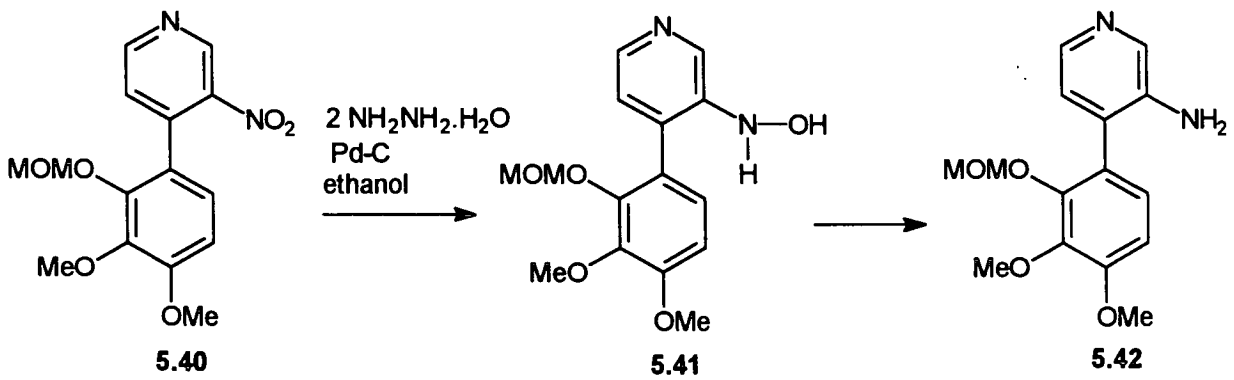
5.36 **5.39** **5.40**

Scheme 5.24

The EI-MS of **5.40** showed a molecular ion at m/z 320. The ^{1}H-NMR spectrum showed diagnostic resonances at δ 2,92; 3,84 and 3,90 (all singlets) corresponding to three methoxy groups. This result already represents a major improvement in the synthesis of a highly substituted biaryl *via* the cross-coupling protocol originally envisaged. It also provided further proof that the presence of electron withdrawing substituents on aryl halides greatly increases the rate of the oxidative addition of palladium(0). The application of a second metal salt in cross-coupling reactions has been used effectively to enhance reactivity and sometimes selectivity.[45] The use of co-catalytic copper(I) in the Stille coupling was first explored by

Liebeskind.[46] It is presumed that the Cu(I) act as a phosphine scavenger aiding in the metal-ligand dissociation required for the oxidative addition step of the catalytic cycle.[47] Alternatively, it could effect a Sn/Cu transmetallation, with the resultant organocopper species undergoing further reaction. The Stille cross-coupling reaction of **5.36** and **5.39** was repeated but with the addition of a catalytic amount (5%) of Cu(I)Br to the reaction mixture. Upon mixing of the reactants, the solution turned into a dark suspension, but turned gradually to a clear red solution as the reaction proceeded. The biaryl **5.40** was subsequently isolated in a yield of 84%. The general applicability of the copper co-catalysis concept is currently the topic of intense research and more work is currently in progress at the RAU laboratory to fully investigate the effect of Cu(I) on Stille cross-coupling reactions.

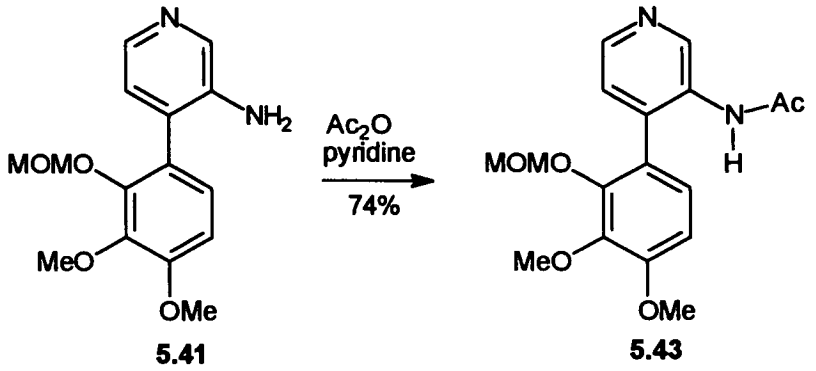
The overall success of the new strategy also depended on the selective reduction of the nitro group to the corresponding amine function. A general problem encountered with the reduction of nitro substituents on a pyridine ring is that the reduction of the π-deficient aromatic system takes precedence when reducing agents such as $SnCl_2$ are used. This problem can be overcome by the use of hydrazine in the presence of a metal catalyst, for example palladium-charcoal, platinum-charcoal or Raney-Nickel[48]. Compound **5.40** was therefore reduced with hydrazine in the presence of palladium-charcoal (Scheme 5.25). TLC analysis of the reaction mixture indicated the formation of a polar compound after 1 hour. EI-MS of the product indicated a molecular ion at m/z 306 corresponding to the hydroxylamine **5.41**. The addition of an extra equivalent of hydrazine followed by mechanical stirring for a further five hours furnished the desired amine **5.42** in nearly quantitative yield.



5.40 **5.41** **5.42**

Scheme 5.25

EI-MS of the isolated product showed a molecular ion at m/z 290 corresponding to the completely reduced derivative. These results indicate that the reduction proceeds through a hydroxylamine intermediate and that the rate of the final reduction to the free amine is considerably slower. The product **5.42** was fully characterised as the *N*-acetyl derivative **5.43** (Scheme 5.26).

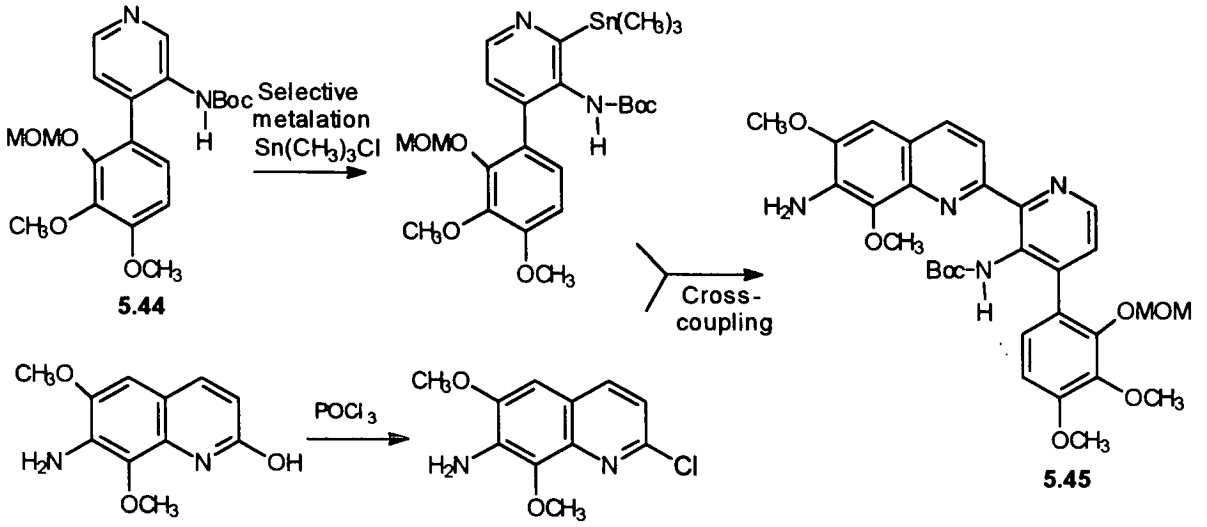


5.41 **5.43**

Scheme 5.26

5.4 FUTURE WORK

The protection of the free amine in **5.42** with di-*tert*-butyl dicarbonate would allow its conversion into **5.44** and subsequent cross-coupling with a streptonigrin AB-ring equivalent (Scheme 5.27). The preparation of a synthetic equivalent of the streptonigrin AB ring system for the coupling reaction has already been completed.[49]



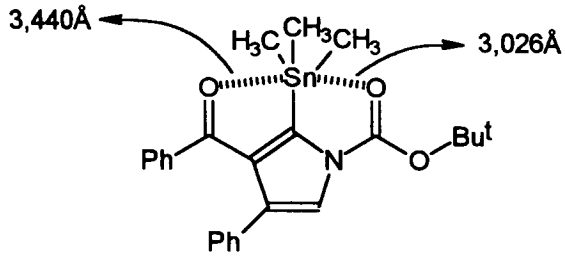
5.44 **5.45**

Scheme 5.27

Successful completion of the synthesis of the tetracyclic model **5.45** of streptonigrin would establish synthetic methodology which, in principle at least, would allow construction of the natural product and analogues of this compound.

5.5 CRYSTAL STRUCTURE DETERMINATION OF [3-(*TERT*-BUTOXYCARBONYLAMINO)-4-PYRIDYL]-TRIMETHYLTIN(IV)

The slow rate of hydrolysis and generally lower rate of reaction of **5.12** in Stille cross-coupling reactions, compared to organotin compounds lacking the 3-acylamino substituent, was tentatively ascribed to an intramolecular Sn-O stabilizing interaction. It is known that organotin compounds containing coordinating groups such as ketones, esters or amines in favourable positions sometimes extend their coordination spheres through intramolecular coordination. Crystallisation of **5.12** from hexane-ethyl acetate (1:1) furnished good quality crystals (colourless prisms) and a crystal structure determination was performed by Prof. G.J. Kruger at the RAU laboratory. The X-ray structure (Figure 5.1) showed the expected intramolecular interaction between the Sn and carbonyl O atoms, thus explaining the stability of the compound. Due to the relatively low Lewis acidity of tin in tetraorganotin compounds, known crystal structures containing pentacoordinated tin are scarce. A search of the April 1997 Cambridge Structural Database revealed only a small number of compounds containing such Sn-O or Sn-N interactions. Cases were found, however, in which the coordination of tin was increased from four to five,[50] and to six.[51] *Tert*-butyl 3-benzoyl-4-phenyl-2-(trimethyltin)-pyrrole-*N*-carboxylate **5.46** for example showed Sn-O distances of 3.026Å and 3,440Å[52] .

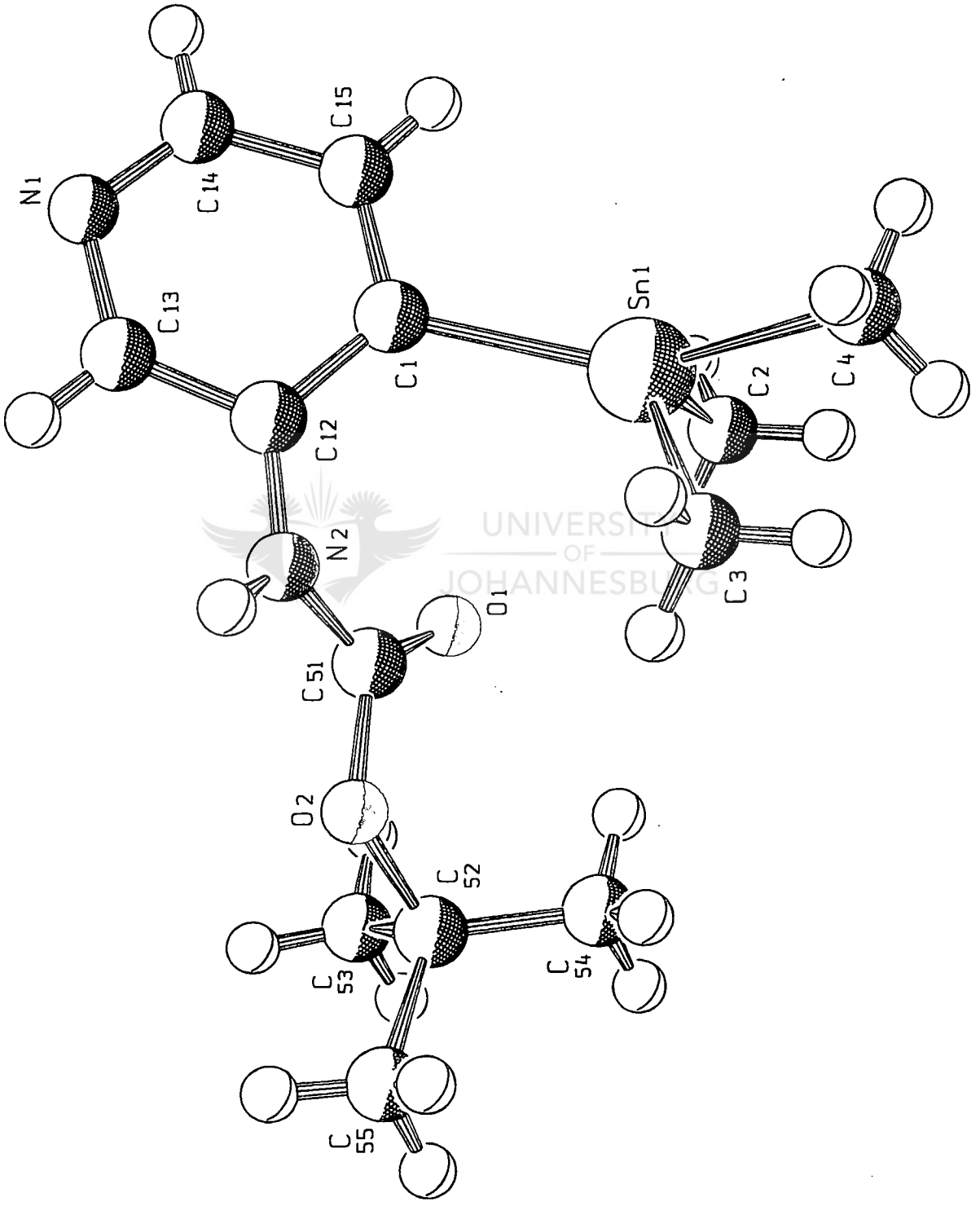


5.46

The Sn-O distance of 3.070 Å observed for **5.12** is quite long, but still within the range of distances observed in the structures quoted above (2.623-3.247Å). The presence of a definite Sn-O interaction can, however, be seen in the distortion of the Sn coordination polyhedron. If C-1 (opposite to O-1) is regarded as the apical, and C-2, C-3 and C-4 as the equatorial ligands in a trigonal-bipyramidal configuration, a measure of the deviation from tetrahedral geometry can be established by calculating the difference between the sum of the three equatorial and the sum of the three apical angles.[53] This difference turns out to be 19,63°, intermediate between the ideal value of 0° for tetrahedral and 90° for trigonal-bipyramidal coordination. The effect of additional Sn-ligand interactions on chemical reactivity, affording

unique synthetic routes to stable organotin compounds, appears to have been overlooked up to now.[54] We are currently investigating the effects on intramolecular association of ligand position and of variation of the Lewis acidity of tin by use of different substituents on the Sn atom.

Figure 5.1



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CHAPTER 6
EXPERIMENTAL

6.1 SOLVENTS

All solvents were dried from the appropriate drying agents. Ether, 1,2-dimethoxyethane (DME), tetrahydrofuran (THF), toluene, benzene, and triethylamine (Et_3N) were dried over sodium wire using benzophenone as indicator. Chloroform, *N,N*-dimethylformamide (DMF) and dichloromethane were dried over phosphorous pentoxide, pyridine over barium oxide, and ethyl acetate (EtOAc) over anhydrous potassium carbonate. Hexane was purified by distillation. All other compounds were purchased as analytical or chemically pure reagents.

6.2 CHROMATOGRAPHY

Thin layer chromatography (TLC) was performed using Merck GF_{254} pre-coated silica gel plates, having a 0,25 mm silica layer. The chromatograms where eluted using the solvent systems as indicated for column chromatography. Aromatic derivatives were detected by their fluorescence under UV light (254nm). Chromatograms were developed by spraying with a chromic acid solution, followed by heating over an open flame. "Chromatography' refers to column chromatography on Merck Kieselgel 60 (70-230 mesh), while "flash chromatography" refers to column chromatography under nitrogen pressure using Merck Kieselgel 60 (230-400 mesh), with the cited eluent mixed in a volume per volume ratio.

6.3 SPECTROSCOPIC AND SPECTROMETRIC METHODS

6.3.1 Nuclear magnetic resonance spectroscopy (NMR)

NMR-spectra were recorded in $CDCl_3$ by means of a Varian Gemini 2000, 300MHz spectrometer or a Bruker, 500MHz spectrometer unless otherwise stated. ^{1}H-NMR data are listed in the order: Chemical shift (δ, reported in ppm and referenced to the residual solvent peak of $CDCl_3$ [δ=7,24]), number of protons, multiplicity, coupling constants (*J*, in Hertz), allocation. Proton decoupling experiments were used to unequivocally assign proton signals. Where required, nuclear Overhauser effect as well as 2D-ROESY spectroscopy was employed to determine the relative stereochemistry. ^{13}C-NMR data are listed in the order: Chemical shift (δ, reported in ppm and referenced to the residual solvent peak of $CDCl_3$ [δ=77,0]), allocation. DEPT and HETCOR spectroscopy was used in certain cases to assist allocation. All resolved ^{13}C-signals are reported. In some cases the number of resolved signals

is less than the theoretical number of carbons. Since this was not required for structural elucidation, further resolution was not attempted.

6.3.2 Mass spectrometry (MS)

Electron impact (EI) mass spectra were recorded on a Finnigan-Matt 8200 spectrometer (70 eV). Major peaks listed with intensities as percentages of the base peak.

6.3.3 Infrared spectroscopy (IR)

All IR-spectra were recorded on a Perkin-Elmer 881 spectrometer, and were performed in $CHCl_3$. Only characteristic peaks are indicated in wavenumber (cm^{-1}).

6.3.4 Optical rotations

A Jasco model DIP-730 spectropolarimeter having a cell with a 10 mm path length was used to determine optical rotations. Concentration, in grams per 100 ml of solution, is given by *c*.

6.3.5 Melting points

Melting points were determined with a Reichert Thermopan microscope with Koffler hot-stage and are uncorrected.

6.4 CHEMICAL METHODS

6.4.1 General

All reactions were performed under an atmosphere of nitrogen, except for those involving the use of *n*-butyllithium, which were performed under argon. Unless otherwise stated, dry solvents were used in flamed out glass apparatus. Room temperature refers to *ca.* 20-25°C.

6.4.2 Standard work-up procedure

Unless specified to the contrary, saturated NH_4Cl (excess) was added to the reaction mixture and the aqueous phase extracted with ethyl acetate (in all cases where work-up involved extraction, termination of the process was based on TLC to ensure exhaustive extraction). The organic extract was washed with water, brine, water, dried (Na_2SO_4 or $MgSO_4$) and the solvent removed under reduced pressure at *ca.* 50°C.

6.4.3 New compounds

Some of the simple compounds described herein e.g. **2.17**, **2.18** and **2.19** are not claimed to be new, but relevant comparable physical data could not be obtained in the literature.

6.5 Synthesis of hydroxylamine reagents

N-para-methoxybenzylphthalimide (2.16)

To a solution of *N*-hydroxyphthalimide (1.0 mmol), triphenylphosphine (1.0 mmol) and *para*-methoxybenzyl alcohol (1.1 mmol) in dry THF (5 ml) was added DEAD (1,1 mmol). The solution was allowed to stir at room temperature for 12 h, after which the mixture was filtered through Celite, and the solvent removed *in vacuo*. Chromatography (6:1 hexane/ethyl acetate) afforded the title compound as white crystals.

Yield: 242mg, 84%

Mp.: 128-130°C

NMR ^{1}H : δ 7,73 (4H, m, H-aromatic); 7,43 (2H, m, H-aromatic); 6,85 (2H, m, H-aromatic); 5,12 (2H, s, $C\underline{H}_2Ph$); 3,77 (3H, s, $OC\underline{H}_3$).

NMR ^{13}C: δ 163,5 (carbonyl); 160,5 (carbonyl); 134,3; 131,5; 128,9; 125,9; 123,4 and 113,9 (C-aromatic); 79,5 ($\underline{C}H_2$-Ph); 55,2 ($O\underline{C}H_3$).

MS: m/z 458 ($[M]^+$, 22%).

N-(*tert*-butyldiphenylsilyloxy)phthalimide (2.17)

To a solution of *N*-hydroxyphthalimide (1.0 mmol) and *tert*-butyldiphenylsilyl chloride (1.1 mmol) in dry THF (5 ml) was added a catalytic amount of DMAP (0,1 mmol). The solution was allowed to stir at room temperature for 24 h, after which the mixture was filtered through Celite, and the solvent removed *in vacuo*. Chromatography (8:1 hexane/ethyl acetate) afforded the title compound as a colourless oil.

Yield: 402mg, 96%

NMR ^{1}H : δ 7,45 (5H, m, H-aromatic); 7,03 (9H, m, H-aromatic); 0,92 (9H, s, $C\underline{C}H_3$).

NMR ^{13}C: δ 161,4 (carbonyl); 160,8 (carbonyl); 133,3; 130,7; 128,9; 128,7; 125,4; 122,4 and 122,9 (C-aromatic); 25,8 ($C\underline{C}H_3$); 18,3 ($\underline{C}CH_3$).

MS: m/z 417 ($[M]^+$, 42%).

O-(*para*-methoxybenzyl)hydroxylamine (2.18)

To a solution of **2.16** (1.0 mmol) in dry dichloromethane (10 ml) was added hydrazine hydrate (1,5 mmol). The solution was refluxed until TLC showed complete consumption of the substrate. The solvent was removed *in vacuo*. and the residue was purified by flash chromatography (1:1 hexane/ethyl acetate) to afford the title compound as a colourless oil.

Yield: 110mg, 72%

NMR ^{1}H : δ 7,27 (2H, m, H-aromatic); 6,87 (2H, m, H-aromatic); 5,31 (2H, bs, $N\underline{H}_2$); 4,60 (2H, s, $C\underline{H}_2Ph$); 3,79 (3H, s, $OC\underline{H}_3$).

NMR ^{13}C: δ 159,5; 130,1; 129,5; and 113,8 (C-aromatic); 77,6 ($\underline{C}H_2$-Ph); 55,3 ($O\underline{C}H_3$).

MS: m/z 153 ($[M]^+$, 64%); 137 ($[M\text{-}NH_2]^+$, 90%).

O-(*tert*-butyldiphenylsilyl)hydroxylamine (2.19)

To a solution of **2.17** (1.0 mmol) in dry dichloromethane (10 ml) was added hydrazine hydrate (1,5 mmol). The solution was refluxed until TLC showed complete consumption of the substrate. The solvent was removed *in vacuo*. and the residue was purified by flash chromatography (1:1 hexane/ethyl acetate) to afford the title compound as a colourless oil.

Yield: 195mg, 72%

NMR ^{1}H : δ 7,73 (4H, m, H-aromatic); 7,39 (6H, m, H-aromatic); 5,22 (2H, bs, $N\underline{H}_2$); 1,09 (9H, s, $C\underline{H}_3$).

MS: m/z 271 ($[M]^+$, 13%); 137 ($[M-NH_2]^+$, 60%).

6.6 Model studies towards oxime deprotection

Phenylacetaldehyde oxime *O*-(*para*-methoxyphenyl)methyl ether (2.21 : main isomer)

To a solution of freshly distilled phenylacetaldehyde (2 mmol) in dry pyridine (5 ml) was added **2.18** (1,2 mmol). The solution was allowed to stir at room temperature for *ca*. 12 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and the resulting solution washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (1:1 hexane/ethyl acetate) afforded the title compound as a colourless oil (*E*:*Z* mixture)

Yield: 357mg, 70%

NMR ^{1}H : δ 7,31 (2H, m, H-aromatic); 7,2.5 (7H, m, H-aromatic); 6,87 (1H, t, H-1', *J*=7,8 Hz); 4,69 (2H, s, $C\underline{H}_2Ph$); 3,84 (3H, s, $OC\underline{H}_3$); 3,77 (2H, d, H-2'a and H-2'b, *J*=7,8 Hz).

MS: m/z 255 ($[M]^+$, 30%).

Phenylacetaldehyde oxime *O*-*tert*-butyldiphenylsilyl ether (2.22 : main isomer)

To a solution of freshly distilled phenylacetaldehyde (2 mmol) in dry pyridine (5 ml) was added **2.19** (1,2 mmol). The solution was allowed to stir at room temperature for *ca*. 12 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (1:1 hexane/ethyl acetate) afforded the title compound as a colourless oil (*E*:*Z* mixture)

Yield: 507 mg, 68%

NMR ^{1}H : δ 7,82-7,78 (6H, m, H-aromatic); 7,37-7,24 (10H, m, H-aromatic and H-1); 3,98 (2H, d, H-2'a and H-2'b, *J*=5,4 Hz); 1,21 (9H, s, $OC\underline{H}_3$).

MS: m/z 373 ($[M]^+$, 11%)

Phenylacetaldehyde oxime (2.23 : main isomer)

To a solution of 2.22 (1 mmol) in dry THF (2 ml) was added TBAF (1,2 mmol of a 1M solution). The solution was allowed to stir at room temperature for 1 h. Removal of the solvent followed by chromatography (1:1 hexane/ethyl acetate) afforded the title compound as a colourless oil (*E:Z* mixture)

Yield: 113 mg, 84%

NMR ^{1}H : δ 9,55 (1H, bs, =NOH); 7,37-7,27 (5H, m, H-aromatic); 6,92 (1H, t, H-1, *J*=7,8 Hz); 3,77 (2H, d, H-2'a and H-2'b, *J*=7,8 Hz).

NMR ^{13}C: δ 149,5 (C-1'); 136,6 (C-*I*-aromatic); 128,7; 128,7 and 126,6 (C-aromatic); 31,7 (C-2').

MS: m/z 135 ([M]$^{+}$, 41%), 118 ([M-OH]$^{+}$, 75%).

6.7 Synthesis of *N*-hydroxypyrrolidines

1,2,3,4,6-Penta-*O*-benzoyl-β-D-glucopyranose (2.24)

D-Glucose (5 mmol) was dissolved in dry pyridine (20 ml) and heated at 100°C for 1h. To the clear solution was slowly added benzoyl chloride (65 mmol) and the reaction mixture was allowed to stir at 60°C for 1 h. The solvent was removed *in vacuo* followed by standard work-up. The residue was purified by chromatography (5:1 hexane/ethyl acetate) to afford the title compound as white crystals.

Yield: 2,87 g, 82%

Mp.: 189-191°C[1]

$[\alpha]_D^{24}$: +24,1° (*c*=2,6)

NMR ^{1}H : δ 8,01 (10H, m, H-*o*-aromatic); 7,41 (15H, m, H-*m*- and H-*p*-aromatic); 6,31 (1H, d, H-1, $J_{1,2}$=8,0 Hz); 6,05 (1H, dd, H-3, $J_{3,2}$=$J_{3,4}$=9,3 Hz); 5,86 (1H, dd, H-2, $J_{2,1}$=7,9 Hz and $J_{2,3}$=9,1 Hz); 5,82 (1H, dd, H-4, $J_{4,3}$=$J_{4,5}$=9,4 Hz); 4,64 (1H, dd, H-6a, $J_{6a,5}$=2,6 Hz and $J_{6a,6b}$=12,2 Hz); 4,53 (1H, dd, H-6b, $J_{6b,5}$=6,1 Hz and $J_{6b,6a}$=12,2 Hz); 4,42 (1H, m, H-5).

NMR ^{13}C: δ 166,1; 165,7 (2C); 165,1 and 164,6 (carbonyl); twelve resolved C-aromatic signals 133,8; 133,5; 133,4; 133,3; 133,1; 129,8; 129,5; 129,4; 128,3; 128,1; 128,0 and 127,5; 92,7 (C-1); 73,2; 72,8; 70,8 and 69,1 (C-2, C-3, C-4 and C-5), 62,7 (C-6).

MS: m/z 595 ([M-Bz]$^{+}$, 2%); 474 ([M-OBz and Bz]$^{+}$, 4%); 105 ([C(O)Ph]$^{+}$, 100%).

1,2,3,4,6-Penta-*O*-benzoyl-β-D-mannopyranose 2.25

D-Mannose (5 mmol) was dissolved in dry pyridine (20 ml) and heated at 70°C for 1h. To the clear solution was slowly added benzoyl chloride (65 mmol) and the reaction mixture was stirred at 70°C for a further 2 h. The solvent was removed *in vacuo* followed by standard work-

up. The residue was purified by chromatography (5:1 hexane/ethyl acetate) to afford the title compound as white crystals.

Yield: 2,81 g, 80%

Mp.: 151-153°C[1]

$[\alpha]_D^{24}$: -34,2° (*c*=2,2)

NMR ^{1}H : δ 8,08 (6H, m, H-*o*-aromatic); 7,93 (4H, m, H-*o*-aromatic); 7,37 (15H, m, H-aromatic); 6,63 (1H, d, H-1, $J_{1,2}$=2,1 Hz); 6,27 (1H, dd, H-4, $J_{4,3}$=$J_{4,5}$=10 Hz); 6,07 (1H, dd, H-3, $J_{3,2}$=3,3 Hz and $J_{3,4}$=10,2 Hz); 5,92 (1H, dd, H-2, $J_{2,1}$=2,1 Hz and $J_{2,3}$=3,2 Hz); 4,72 (1H, dd, H-6a, $J_{6a,5}$=2,5 Hz and $J_{6a,6b}$=12,1 Hz); 4,59 (1H, m, H-5); 4,47 (1H, dd, H-6b, $J_{6b,5}$=3,6 Hz and $J_{6b,6a}$=12,1 Hz).

NMR ^{13}C: δ 166,0; 165,7; 165,3 165,1 and 164,6 (carbonyl); ten resolved C-aromatic signals 134,0; 133,6; 133,5; 133,3; 133,0; 129,9; 129,7; 128,6; 128,4 and 127,6; 91,4 (C-1); 71,3; 70,0; 69,5 and 66,3 (C-2, C-3, C-4 and C-5), 62,4 (C-6).

MS: m/z 595 ([M-Bz]$^+$, 9%); 105 ([C(O)Ph]$^+$, 100%).

General route to tetra-*O*-benzoyl-D-glycopyranosyl bromides:

To a solution of the D-glycopyranoside (5.0 mmol) in dry dichloromethane (10 ml) was added acetic acid saturated with HBr (40% w/w) (6 mmol). The solution was allowed to stir at room temperature for 4 h. The excess HBr-acetic acid was removed by azeotropic distillation with toluene. The residue was dissolved in hot ether (10 ml) and recrystallised by addition of hexane (3 ml) to afford the title compound as white needles.

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide 2.26

Yield: 2,77 g, 84%

Mp.: 129-130°C

$[\alpha]_D^{24}$: +123,° (*c*=2,1)

NMR ^{1}H : δ 7,97 (8H, m, H-*o*-aromatic); 7,41 (12H, m, H-aromatic); 6,86 (1H, d, H-1, $J_{1,2}$=3,9 Hz); 6,25 (1H, dd, H-3, $J_{3,2}$=$J_{3,4}$=9,8 Hz); 5,82 (1H, dd, H-4, $J_{4,3}$=$J_{4,5}$=9,9 Hz); 5,32 (1H, dd, H-2, $J_{2,1}$=4,0 Hz and $J_{2,3}$=9,9 Hz); 4,75 (1H, m, H-5); 4,67 (1H, dd, H-6a, $J_{6a,5}$=2,1 Hz and $J_{6a,6b}$=12,5 Hz); 4,52 (1H, dd, H-6b, $J_{6b,5}$=4,8 Hz and $J_{6b,6a}$=12,5 Hz).

NMR ^{13}C: δ 166,1; 165,6; 165,2 and 165,1 (carbonyl); ten resolved C-aromatic signals 133,8; 133,6; 133,3; 133,3; 130,1; 129,8; 128,5; 128,3; 128,1 and 127,8; 86,8 (C-1); 72,7; 71,5; 70,6 and 67,7 (C-2, C-3, C-4 and C-5), 61,9 (C-6).

MS: m/z 579 ([M-Br]$^+$, 30%); 105 ([C(O)Ph]$^+$, 100%).

2,3,4,6-Tetra-*O*-benzoyl-δ-D-mannopyranosyl bromide 2.27

Yield: 2,97 g, 90%

Mp.: 150-151°C

$[\alpha]_D^{24}$: +11,7° (*c*=2,8)

NMR ^1H : δ 8,07 (6H, m, H-*o*-aromatic); 7,81 (2H, m, H-*o*-aromatic); 7,45 (10H, m, H-aromatic); 7,25 (2H, m, H-*o*-aromatic); 6,57 (1H, d, H-1, $J_{1,2}$=1,5 Hz); 6,31 (1H, dd, H-3, $J_{3,2}$=3,2 Hz and $J_{3,4}$=9,6 Hz); 6,23 (1H, dd, H-4, $J_{4,3}$=$J_{4,5}$=10,1 Hz); 5,90 (1H, dd, H-2, $J_{2,1}$=1,6 Hz and $J_{2,3}$=3,2 Hz); 4,75 (1H, dd, H-6a, $J_{6a,5}$=2,4 Hz and $J_{6a,6b}$=12,1 Hz); 4,63 (1H, m, H-5); 4,54 (1H, dd, H-6b, $J_{6b,5}$=3,6 Hz and $J_{6b,6a}$=12,1 Hz).

NMR ^{13}C: δ 165,9; 165,4; 165,3 and 164,9 (carbonyl); eight resolved C-aromatic signals 133,7; 133,6; 133,3; 133,1; 129,9; 128,5; 128,2 and 127,9; 83,3 (C-1); 73,2; 73,0; 69,1 and 66,1 (C-2, C-3, C-4 and C-5), 61,8 (C-6).

MS: m/z 579 ([M-Br]$^+$, 15%); 457 ([M-BzOH and Br]$^+$, 2%); 105 ([C(O)Ph]$^+$, 100%).

General route to tetra-*O*-benzoyl-D-glycopyranosides:

To a solution of the D-glycopyranosyl bromide (2.0 mmol) in acetone (8 ml) was added freshly prepared Ag_2CO_3 (4,0 mmol) and an equimolar amount of water (*ca* 1 mmol). The solution was stirred for 1 h at room temperature after which TLC indicated consumption of all the starting material. The reaction mixture was filtered through Celite, and the solvent removed *in vacuo*. Chromatography (2:1 hexane/ethyl acetate) afforded the protected hemiacetals as colourless oils (α:β mixtures).

2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranose (2.28: α-anomer)

Yield: 931 mg, 78%

NMR ^1H : δ 7,94 (8H, m, H-*o*-aromatic); 7,38 (12H, m, H-aromatic); 6,24 (1H, dd, H-3, $J_{3,2}$=$J_{3,4}$=10,1 Hz); 5,74 (1H, dd, H-4, $J_{4,3}$=$J_{4,5}$=10,1 Hz); 5,71 (1H, dd, H-1, $J_{1,2}$=$J_{1,\sim OH}$=3,3 Hz); 5,32 (1H, dd, H-2, $J_{2,1}$=3,6 Hz and $J_{2,3}$=10,1 Hz); 4,69 (1H, m, H-5); 4,63 (1H, dd, H-6a, $J_{6a,5}$=2,4 Hz and $J_{6a,6b}$=11,9 Hz); 4,45 (1H, dd, H-6b, $J_{6b,5}$=4,4 Hz and $J_{6b,6a}$=11,9 Hz); 3,37 (1H, d, ~O<u>H</u>, $J_{\underline{OH},1}$=3,4 Hz).

NMR ^{13}C: δ 166,3; 165,9; 165,8 and 165,2 (carbonyl); seven resolved C-aromatic signals 133,4; 133,4; 133,1; 129,8; 128,4; 128,3 and 127,9; 90,5 (C-1); 72,3; 70,2; 69,5 and 67,9 (C-2, C-3, C-4 and C-5), 62,9 (C-6).

MS: m/z 579 ([M-OH]$^+$, 5%); 105 ([C(O)Ph]$^+$, 100%).

2,3,4,6-Tetra-*O*-benzoyl-D-mannopyranose (2.29: α-anomer)

Yield: 847 mg, 71%

NMR ^{1}H : δ 7,92 (8H, m, H-*o*-aromatic); 7,35 (12H, m, H-aromatic); 6,16 (1H, dd, H-4, $J_{4,3}$=$J_{4,5}$=9,8 Hz); 6,01 (1H, dd, H-3, $J_{3,2}$=3,2 Hz and $J_{3,4}$=9,8 Hz); 5,74 (1H, dd, H-2, $J_{2,1}$=1,9 Hz and $J_{2,3}$=3,2 Hz); 5,52 (1H, d, H-1, $J_{1,2}$=1,8 Hz); 4,77 (1H, dd, H-6a, $J_{6a,5}$=2,7 Hz and $J_{6a,6b}$=11,9 Hz); 4,63 (1H, m, H-5) 4,46 (1H, dd, H-6b, $J_{6b,5}$=3,6 Hz and $J_{6b,6a}$=11,9 Hz); 3,75 (1H, bs, ~O<u>H</u>).

NMR ^{13}C: δ 166,3 (2C); 165,7 and 165,5 (carbonyl); nine resolved C-aromatic signals 133,4; 133,4; 133,1; 133,0; 129,7; 128,4; 128,2; 128,0 and 127,8; 92,4 (C-1); 70,9; 69,8; 68,9 and 67,0 (C-2, C-3, C-4 and C-5), 62,8 (C-6).

MS: m/z 579 ([M-OH]$^+$, 25%); 105 ([C(O)Ph]$^+$, 100%).

General route to tetra-*O*-benzoyl-D-glyco oxime ethers:

To a solution of the D-glycopyranoside (2.0 mmol) in dry pyridine (5 ml) was added the applicable hydroxylamine (2,1 mmol). The solution was allowed to stir at room temperature for *ca.* 12 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (1:1 hexane/ethyl acetate) afforded the oximes as colourless oils (*E:Z* mixtures).

2,3,4,6-Tetra-*O*-benzoyl-D-glucose oxime *O*-(*para*-methoxyphenyl)methyl ether (2.30 : main isomer)

Yield: 1,26 g, 78%

IR: ν_{max} 1670 (C=N) cm^{-1}

NMR ^{1}H : δ 8,02 (8H, m, H-*o*-aromatic); 7,37 (17H, m, H-aromatic and H-1), 6,21 (1H, dd, H-3, $J_{3,2}$=7,2 Hz and $J_{3,4}$=2,4 Hz); 6,08 (1H, dd, H-2, $J_{2,1}$=5,3 Hz and $J_{2,3}$=7,2 Hz); 5,74 (1H, dd, H-4, $J_{4,3}$=2,4 Hz and $J_{4,5}$=8,7 Hz); 4,91 (2H, s, C<u>H</u>$_2$Ph); 4,58 (1H, dd, H-6a, $J_{6a,5}$=3,1 Hz and $J_{6a,6b}$=11,8 Hz); 4,34 (1H, dd, H-6b, $J_{6b,5}$=5,8 Hz and $J_{6b,6a}$=11,8 Hz); 4,21 (1H, m, H-5); 3,75 (3H, s, OC<u>H</u>$_3$).

NMR ^{13}C: δ 166,1 (3C) and 165,9 (carbonyl); 144,4 (C-1); nine resolved C-aromatic carbons 159,4; 133,3; 133,2; 133,0; 129,9; 128,7; 128,4; 128,0 and 127,9; 76,4 (<u>C</u>H$_2$Ph); 71,4; 71,3; 70,3 and 68,6 (C-2, C-3, C-4 and C-5), 65,5 (C-6); 55,4 (O<u>C</u>H$_3$).

MS: m/z 731 ([M]$^+$, 3%); 608 ([M-OBz]$^+$, 21%); 105 ([C(O)Ph]$^+$, 100%).

2,3,4,6-Tetra-*O*-benzoyl-D-glucose oxime *O-tert*-butyldiphenylsilyl ether (2.31: main isomer)

Yield: 170 mg, 10%

IR: ν_{max} 1670 (C=N) cm^{-1}

NMR ^1H : δ 7,94 (8H, m, H-*o*-aromatic); 7,72 – 7,24 (22H, m, H-aromatic); 7,04 (1H, d, H-1, $J_{1,2}$=4,9 Hz); 6,83 (1H, dd, H-2, $J_{2,1}$=4,9 Hz and $J_{2,3}$=3,6 Hz); 6,50 (1H, dd, H-3, $J_{3,2}$=$J_{3,4}$=3,9 Hz); 5,87 (1H, dd, H-4, $J_{4,3}$=3,9 Hz and $J_{4,5}$=8,5 Hz); 4,54 (1H, dd, H-6a, $J_{6a,5}$=2,1 Hz and $J_{6a,6b}$=11,4 Hz); 4,43 (1H, dd, H-6b, $J_{6b,5}$=2,6 Hz and $J_{6b,6a}$=11,4 Hz); 4,13 (1H, m, H-5); 3,48 (1H, d, ~O<u>H</u>, $J_{OH,5}$=8,4 Hz); 1.09 (9H, s, C-C<u>H</u>$_3$).

NMR ^{13}C: δ 166,2; 165,4; 165,3 and 165,2 (carbonyl); 151,7 (C-1); thirteen resolved C-aromatic signals 135,5; 135,1; 134,8; 133,3; 133,1; 132,8; 132,7; 129,5; 128,9; 128,4; 128,2; 128,0 and 127,8; 70,9; 69,9; 68,5 and 68,4 (C-2, C-3, C-4 and C-5); 65,5 (C-6); 26,9 (C-<u>C</u>H$_3$); 19,3 (<u>C</u>-CH$_3$).

MS: No discernible fragmentation pattern. Dominant peak: 105 ($[C(O)Ph]^+$, 100%).

2,3,4,6-Tetra-*O*-benzoyl-D-glucose oxime (2.32 : main isomer)

Yield: 1,15 g, 94%

IR: ν_{max} 1675 (C=N) cm^{-1}

NMR ^1H : δ 8,75 (1H, s, =NO<u>H</u>); 7,96 (8H, m, H-*o*-aromatic); 7,39 (13H, H-aromatic and H-1); 6,29 (1H, dd, H-3, $J_{3,2}$=10,5 Hz and $J_{3,4}$=3,9 Hz); 6,12 (1H, dd, H-2, $J_{2,1}$=8,4 Hz and $J_{2,3}$=10,5 Hz); 5,81 (1H, dd, H-4, $J_{4,3}$=3,9 Hz and $J_{4,5}$=12,7 Hz); 4,54 (1H, dd, H-6a, $J_{6a,5}$=3,5 Hz and $J_{6a,6b}$=17,2 Hz); 4,32 (1H, dd, H-6b, $J_{6b,5}$=8,4 Hz and $J_{6b,6a}$=18,1 Hz); 4,26 (1H, m, H-5); 3,98 (1H, d, ~O<u>H</u>, $J_{OH,5}$=7,5 Hz).

NMR ^{13}C: δ 166,6; 166,5; 165,4 and 165,3 (carbonyl); 145,7 (C-1); ten resolved C-aromatic signals 133,6; 133,4; 133,2; 132,9; 129,7; 128,4; 128,3; 128,0; 127,9 and 127,6; 71,3; 71,2; 70,4 and 68,6 (C-2, C-3, C-4 and C-5), 65,6 (C-6).

MS: m/z 595 ($[M-OH]^+$, 25%); 105 ($[C(O)Ph]^+$, 100%).

2,3,4,6-Tetra-*O*-benzoyl-D-mannose oxime (2.33 : main isomer)

Yield: 1,07 g, 88%

IR: ν_{max} 1675 (C=N) cm^{-1}

NMR ^1H : δ 7,94-7,82 (8H, m, H-*o*-aromatic); 7,64-7,41 (13H, m, H-aromatic and H-1); 6,22 (1H, dd, H-2, $J_{2,1}$=4,3 Hz and $J_{2,3}$=6,3 Hz); 6,01 (1H; H-3, $J_{3,2}$=$J_{3,4}$=6,3 Hz); 5,86 (1H, dd, H-4, $J_{4,3}$=2,7 Hz and $J_{4,5}$=8,4 Hz); 4,55 (1H, dd, H-6a, $J_{6a,5}$=3,9 Hz

and $J_{6a,6b}$=17,4 Hz); 4,35 (1H, dd, H-6b, $J_{6b,5}$=8,1 Hz and $J_{6b,6a}$=17,4 Hz); 4,26 (1H, m, H-5).

NMR ^{13}C: δ 166,8; 166,5; 165,1 and 165,0 (carbonyl); 145,8 (C-1); nine resolved C-aromatic signals 133,8; 133,4; 132,8; 129,4; 129,3; 128,4; 128,3; 128,0 and 127.8; 71,4; 70,6; 69,7 and 68,3 (C-2, C-3, C-4 and C-5), 65,4 (C-6).

MS: m/z 595 ([M-OH]$^+$, 40%); 105 ([C(O)Ph]$^+$, 100%).

General method for the selective silylation of tetra-*O*-benzoyl-D-glyco oxime ethers:
To a solution of the D-glyco oxime ether (2.0 mmol) in dry pyridine (5 ml) was added *tert*-butyldiphenylsilyl chloride (2,1 mmol). The solution was allowed to stir at room temperature for *ca.* 18 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (6:1 hexane/ethyl acetate) afforded the selectively silylated oximes as colourless oils (*E:Z* mixtures).

2,3,4,6-Tetra-*O*-benzoyl-D-glucose oxime *O-tert*-butyldiphenylsilyl ether (2.31: main isomer)

Yield: 1,45 g, 85%

NMR-data already reported (p.138)

2,3,4,6-Tetra-*O*-benzoyl-D-mannose oxime *O-tert*-butyldiphenylsilyl ether (2.34: main isomer)

Yield: 1,40 g, 83%

IR: ν_{max} 1670 (C=N) cm^{-1}

NMR ^{1}H : δ 8,06-7,94 (8H, m, H-*o*-aromatic); 7,75–7,24 (23H, m, H-aromatic and H-1); 6,19 (1H, dd, H-2, $J_{2,1}$=3,0 Hz and $J_{2,3}$=7,1 Hz); 6,02 (1H, dd, H-3, $J_{3,2}$=6.9 Hz and $J_{3,4}$=2,4 Hz); 5,84 (1H, dd, H-4, $J_{4,3}$=2,4 Hz and $J_{4,5}$=8,5 Hz); 4,56 (1H, dd, H-6a, $J_{6a,5}$=2,7 Hz and $J_{6a,6b}$=11,7 Hz); 4,29 (1H, dd, H-6b, $J_{6b,5}$=4,6 Hz and $J_{6b,6a}$=11,7 Hz); 4,12 (1H, m, H-5); 3,48 (1H, d, ~O<u>H</u>, $J_{OH,5}$=6,1 Hz); 1.04 (9H, s, C-C<u>H</u>$_3$).

NMR ^{13}C: δ 166,4; 165,2; 165,1 and 164,8 (carbonyl); 151,0 (C-1); twelve resolved C-aromatic signals 135,4; 134,5; 133,2; 133,1; 132,9; 132,5; 129,5; 128,9; 128,4; 128,3; 128,0 and 127,8; 70,2; 69,8; 68,9 and 68,7 (C-2, C-3, C-4 and C-5); 65,3 (C-6); 26,8 (C-<u>C</u>H$_3$); 19,2 (<u>C</u>-CH$_3$).

MS: No discernible fragmentation pattern. Dominant peak: 105 ([C(O)Ph]$^+$, 100%).

General route to tetra-*O*-benzoyl-5-*O*-mesyl-D-glyco oxime ethers:

To a solution of the protected D-glyco (alkyl or silyl) oxime ether (2.0 mmol) in dry pyridine (5 ml) was added a 1:1 mixture of mesyl chloride (3,0 mmol) and pyridine (6,0 mmol). The dark brown solution was stirred at 80°C for 6 h after which the reaction mixture was filtered through Celite. The solvent was removed *in vacuo* and the residue was redissolved in methylene chloride (10 ml), washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by flash chromatography (4:1 hexane/ethyl acetate) afforded the 5-*O*-mesylates as yellow oils (*E:Z* mixtures).

2,3,4,6-Tetra-*O*-benzoyl-5-*O*-methanesulfonyl-D-glucose oxime O-(*para*-methoxyphenyl)methyl ether (2.39 : main isomer)

Yield: 1,53 g, 82%

NMR ^{1}H : δ 8,31-7,94 (8H, m, H-*o*-aromatic); 7,71 – 7,24 (16H, m, H-aromatic); 7,0 (1H, d, H-1, $J_{1,2}$=4,4 Hz), 6,41 (1H, dd, H-3, $J_{3,4}$=2,7 Hz and $J_{3,2}$=7,7 Hz); 5,95 (1H, dd, H-2, $J_{2,3}$=7,7 Hz and $J_{2,1}$=4,4 Hz); 5,88 (1H, dd, H-4, $J_{4,3}$=2,7 Hz and $J_{4,5}$=5,2 Hz); 5,27 (1H, m, H-5); 4,91 (2H, s, C$\underline{H}_2$Ph); 4,42 (1H, dd, H-6a, $J_{6a,5}$=3,2 Hz and $J_{6a,6b}$=12,1 Hz); 4,35 (1H, dd, H-6b, $J_{6b,5}$=6,6 Hz and $J_{6b,6a}$=12,1 Hz); 3,75 (3H, s. OC$\underline{H}_3$); 2,71 (3H, s, $OSO_2C\underline{H}_3$);

NMR ^{13}C: δ 166,7; 166,4; 165,1 and 165,0 (carbonyl); 151,5 (C-1); seven resolved C-aromatic signals 135,5; 133,8; 133,4; 133,1; 129,7; 129,4 and 129,2; 76,4 (C$\underline{H}_2$Ph); 74,9; 68,3; 68,1 and 67,9 (C-2, C-3, C-4 and C-5); 60,4 (C-6); 55,4 (OC$\underline{H}_3$); 38,6 ($OSO_2C\underline{H}_3$),

MS: No discernible fragmentation pattern. Dominant peak: 105 ([C(O)Ph]$^+$, 100%).

2,3,4,6-Tetra-*O*-benzoyl-5-*O*-methanesulfonyl-D-glucose oxime *O*-*tert*-butyldiphenylsilyl ether (2.40 : main isomer)

Yield: 1,63 g, 88%

NMR ^{1}H : δ 8,12-7,85 (8H, m, H-*o*-aromatic); 7,75 – 7,24 (23H, m, H-aromatic and H-1), 6,11 (1H, dd, H-3, $J_{3,4}$=2,5 Hz and $J_{3,2}$=7,5 Hz); 5,95 (1H, dd, H-2, $J_{2,3}$=7,5 Hz and $J_{2,1}$=4,4 Hz); 5,88 (1H, dd, H-4, $J_{4,3}$=2,6 Hz and $J_{4,5}$=6,7 Hz); 5,27 (1H, m, H-5); 4,42 (1H, dd, H-6a, $J_{6a,5}$=3,1 Hz and $J_{6a,6b}$=12,6 Hz); 4,35 (1H, dd, H-6b, $J_{6b,5}$=6,6 Hz and $J_{6b,6a}$=12,6 Hz); 2,76 (3H, s, $OSO_2C\underline{H}_3$); 1.01 (9H, s, C-C$\underline{H}_3$).

NMR ^{13}C: δ 165,7; 165,4; 165,1 and 165,0 (carbonyl); 150,3 (C-1); seven resolved C-aromatic signals 135,5; 133,8; 133,4; 133,3; 133,2; 132,8 and 129,7; 75,9; 69,3; 69,1 and 69,0 (C-2, C-3, C-4 and C-5); 62,8 (C-6); 38,6 ($OSO_2C\underline{H}_3$), 26,9 (C-$\underline{C}H_3$); 19,3 ($\underline{C}$-CH_3).

MS: No discernible fragmentation pattern. Dominant peak: 105 ([C(O)Ph]$^+$, 100%).

2,3,4,6-Tetra-*O*-benzoyl-5-*O*-methanesulfonyl-D-mannose oxime *O*-*tert*-butyldiphenylsilyl ether (2.41 : main isomer)

Yield: 1,46 g, 79%

NMR ^{1}H : δ 8,24-7,95 (8H, m, H-*o*-aromatic); 7,71–7,24 (23H, m, H-aromatic and H-1), 6,93 (1H, dd, H-2, $J_{2,3}$=6,3 Hz and $J_{2,1}$=5,4 Hz); 6,07 (2H, m, H-4 and H-3); 5,33 (1H, m, H-5); 4,86 (1H, dd, H-6a, $J_{6a,5}$=2,7 Hz and $J_{6a,6b}$=12,9 Hz); 4,53 (1H, dd, H-6b, $J_{6b,5}$=5,4 Hz and $J_{6b,6a}$=12,9 Hz); 2,81 (3H, s, $OSO_2C\underline{H}_3$); 1.03 (9H, s, C-$C\underline{H}_3$).

NMR ^{13}C: δ 165,4; 165,2; 165,0 and 164,8 (carbonyl); 151,1 (C-1); eight resolved C-aromatic signals 135,5; 133,3; 133,2; 133,0; 132,8; 129,7; 129,6 and 129,4; 75,8; 74,9; 68,4 and 66,1 (C-2, C-3, C-4 and C-5); 62,5 (C-6); 38,2 ($OSO_2\underline{C}H_3$), 26,6 (C-$\underline{C}H_3$); 18,3 ($\underline{C}$-CH_3).

MS: No discernible fragmentation pattern. Dominant peak: 105 ([C(O)Ph]$^+$, 100%).

(1'*R*,*S*-2*S*,3*S*,4*S*) 1',2',3,4-tetrabenzoyloxy-2-ethyl-*N*-hydroxypyrrolidine (2.44)

To a solution of **2.40** (1.0 mmol) in TFA (1,5 ml) was added dimethylphenylsilane (2,3 mmol). The solution was stirred at room temperature for 15 min after which the reaction mixture was diluted with ethyl acetate and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was redissolved in dry THF (3 ml) and refluxed for 3 h. Removal of the solvent followed by flash chromatography (4:1 hexane/ethyl acetate) afforded the title compound as a colourless oil.

Yield: 416 mg, 70%

IR: ν_{max} 1716 (C=0) cm^{-1}

$[\alpha]_D^{24}$: +28,8° (*c*=1,2)

NMR ^{1}H : δ 8,07-7,88 (8H, m, H-*o*-aromatic); 7,51-7,23 (12H, m, H-aromatic); 6,07 (1H, m, H-1'); 5,86 (1H, dd, H-3, $J_{2,3}$=9,8 Hz and $J_{3,4}$=1,7 Hz); 5,52 (1H, m, H-4); 4,66 (1H, dd, H-2'a, $J_{2'a,1'}$=1,8 Hz and $J_{2'a,2'b}$=12,0 Hz); 4,62 (1H, dd, H-2'b, $J_{2'b,1'}$=8,0 Hz and $J_{2'a,2'b}$=12,0 Hz); 3,75 (1H, dd, H-2, $J_{2,1'}$=3,9 Hz and $J_{2,3}$=9,8 Hz); 3,58 (2H, d, H-5a and H-5b, *J*=6,3Hz).

NMR ^{13}C : δ 166,1; 165,9; 165,4 and 165,0 (carbonyl); eleven resolved C-aromatic signals 133,8; 133,5; 133,3; 133,3; 130,0; 129,8; 129,6; 128,5; 128,4; 128,3 and 128,2; 75,0 (C-3); 74,9 (C-4); 72,7 (C-2); 68,0 (C-1'); 63,1 (C-2'); 60,6 (C-5).

FAB-MS: m/z 596 ([M+1]$^+$, 56%).

The tricloroacetylisocyanate derivative (2.45)

NMR ^{1}H : δ 9,75 (1H, s, NHCO); 8,16-7,81 (8H, m, H-*o*-aromatic); 7,51-7,23 (12H, m, H-aromatic); 6,07 (1H, m, H-1'); 5,86 (1H, dd, H-3, $J_{2,3}$=9,8 Hz and $J_{3,4}$=1,7 Hz); 5,52 (1H, m, H-4); 4,66 (1H, dd, H-2'a, $J_{2'a,1'}$=1,8 Hz and $J_{2'a,2'b}$=12,0 Hz); 4,62 (1H, dd, H-2'b, $J_{2'b,1'}$=8,0 Hz and $J_{2'a,2'b}$=12,0 Hz); 3,91 (1H, dd, H-2, $J_{2,1'}$=3,5 Hz and $J_{2,3}$=9,8 Hz); 3,76 (2H, d, H-5a and H-5b, *J*=6,3Hz).

(1'*R*,*S*-2*S*,3*S*,4*S*) 1',2',3,4-tetrabenzoyloxy-2-ethyl-*N*-Acetoxypyrrolidine (2.46)

To a solution of **2.44** (1.0 mmol) in dry pyridine (1,5 ml) was added a 1:1 mixture of acetic anhydride (1,5 mmol) and pyridine (1,5 mmol). The solution was stirred at room temperature for 1 h after which the solvent was removed *in vacuo*. The residue was redissolved in ethyl acetate, washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by flash chromatography (6:1 hexane/ethyl acetate) afforded the title compound as a colourless oil.

Yield: 494 mg, 83%

IR: ν_{max} 1716 (C=0) cm^{-1}

$[\alpha]_D^{24}$: +19,1° (*c*=1,0)

NMR ^{1}H : δ 8,02-7,84 (8H, m, H-*o*-aromatic); 7,54-7,23 (12H, m, H-aromatic); 5,88 (2H, m, H-3 and H-4); 5,64 (1H, m, H-1'), 4,82 (1H, dd, H-2'a, $J_{2'a,1'}$=3,6 Hz and $J_{2'a,2'b}$=12,0 Hz); 4,74 (1H, dd, H-2'b, $J_{2'b,1'}$=6,0 Hz and $J_{2'a,2'b}$=12,0 Hz); 3,99 (1H, t, H-2, $J_{2,1'}$=$J_{2,3}$=5,7 Hz); 3,83 (1H, dd, H-5a, $J_{5a,4}$=2,7 Hz and $J_{5a,5b}$=12,6 Hz); 3,66 (1H, dd, H-5b, $J_{5b,4}$=6,6 Hz and $J_{5b,5a}$=12,6 Hz); 2,00 (3H, s, C(O)C<u>H</u>$_3$).

NMR ^{13}C : δ 168,5 (<u>C</u>(O)CH$_3$); 166,0; 165,7 and 165,1(2C) (carbonyl); eleven resolved C-aromatic signals 133,5; 133,4; 133,2; 133,1; 129,9; 129,8; 129,6; 128,5; 128,4; 128,3 and 128,1; 77,3; 71,2; 70,1; 63,4 and 61,1 (C-1'; C-2'; C-2 - C-5); 19,2 (C(O)<u>C</u>H$_3$).

MS: No discernible fragmentation pattern. Dominant peak: 105 ([C(O)Ph]$^+$, 100%).

(1'*R*,*S*-2*S*,3*S*,4*R*) 1',2',3,4-tetrabenzoyloxy-2-ethyl-*N*-hydroxypyrrolidine (2.47)

To a solution of **2.41** (1.0 mmol) in TFA (1,5 ml) was added dimethylphenylsilane (2,3 mmol). The solution was stirred at 60°C for 30 min after which the reaction mixture was diluted with ethyl acetate and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by flash chromatography (4:1 hexane/ethyl acetate) afforded the title compound as a colourless oil.

Yield: 434 mg, 73%

IR: ν_{max} 1716 (C=0) cm^{-1}

$[\alpha]_D^{24}$: +37,7° (*c*=2,1)

NMR ^{1}H : δ 8,77 (1H, bs, =NOH); 8,03-7,82 (8H, m, H-*o*-aromatic); 7,51-7,24 (12H, m, H-aromatic); 6,02 (1H, m, H-1'); 5,81 (1H, t, H-3, $J_{2,3}$=$J_{3,4}$=6,4 Hz); 5,53 (1H, q, H-4); 4,72 (1H, dd, H-2'a, $J_{2'a,1'}$=4,3 Hz and $J_{2'a,2'b}$=11,9 Hz); 4,62 (1H, dd, H-2'b, $J_{2'b,1'}$=6,9 Hz and $J_{2'a,2'b}$=11,9 Hz); 3,98 (1H, dd, H-2, $J_{2,1'}$=4,2 Hz and $J_{2,3}$=6,9 Hz); 3,79 (1H, dd, H-5a, $J_{5a,4}$=6,2 Hz and $J_{5a,5b}$=11,6 Hz); 3,28 (1H, dd, H-5b, $J_{5b,4}$=6,3 Hz and $J_{5a,5b}$=11,6).

NMR ^{13}C : δ 166,0 (2C); 165,2 and 165,1 (carbonyl); ten resolved C-aromatic signals 133,5; 133,3; 133,2; 129,9; 129,8; 129,6; 128,5; 128,4; 128,3 and 128,2; 70,7 (C-3); 69,9 (C-4); 68,7 (C-2); 68,6 (C-1'); 63,2 (C-2'); 60,6 (C-5).

FAB-MS: m/z 596 ([M+1]$^+$, 48%)

General route to tetra-*O*-benzoyl-5-iodo-D-glyco oxime ethers:

To a solution of the protected D-glyco oxime *O-tert*-butyldiphenylsilyl ether (2.0 mmol) in dry toluene (6 ml) was added PPh_3 (1,1 mmol), imidazole (2,2 mmol) and iodine (1,1 mmol). The dark solution was heated to 70°C, and stirred vigorously for 1 h, during which time the solution turned clear. The reaction mixture was allowed to cool to room temperature, after which saturated aqueous $NaHCO_3$ (5 ml) was added and the solution stirred for an additional 10 min. Iodine was carefully added until the brown colour lingered, after which the mixture was washed with saturated aqueous $Na_2S_2O_3$ until the solution became colourless, followed by water (3 x 5 ml) and brine (3 x 5 ml). Removal of the solvent followed by flash chromatography (8:1 hexane/ethyl acetate) afforded the 5-iodo oxime ethers as colourless oils (*E:Z* mixtures)

2,3,4,6-Tetra-*O*-benzoyl-5-iodo-L-idose oxime *O-tert*-butyldiphenylsilyl ether (2.48 :main isomer)

Yield: 1,67 g, 87%

NMR ^{1}H : δ 8,32-7,81 (8H, m, H-*o*-aromatic); 7,75–7,23 (22H, m, H-aromatic); 6,91 (1H, d, H-1, $J_{1,2}$=5,1 Hz); 6,77 (1H, dd, H-2, $J_{2,1}$=5,3 Hz and $J_{2,3}$=2,4 Hz); 6,46 (1H, dd, H-3, $J_{2,3}$=2,4 Hz and $J_{3,4}$=8,4 Hz) 5,64 (1H, dd, H-4, $J_{4,3}$=8,7 Hz and $J_{4,5}$=1,8 Hz); 4,72 (1H, m, H-5); 4,29 (2H, m, H-6a and H-6b); 1.17 (9H, s, C-CH_3).

NMR ^{13}C: δ 165,8; 165,5; 165,1 and 165,0 (carbonyl); 150,2 (C-1); six resolved C-aromatic signals 135,6; 135,4; 133,8; 133,6; 133,5 and 132,8; 75,8; 74,5; 69,4 and 66,1 (C-2, C-3, C-4 and C-6); 27,2 (C-5); 26,7 (C-CH_3); 19,1 (C-CH_3).

MS: m/z 901 ([M-^{t}Bu]$^+$, 75%); 838 ([M-OBz]$^+$, 24%).

2,3,4,6-Tetra-*O*-benzoyl-5-iodo-L-gulose oxime *O*-*tert*-butyldiphenylsilyl ether (2.49: main isomer)

Yield: 1,78 g, 93%

NMR ^{1}H : δ 8,39-7,78 (8H, m, H-*o*-aromatic); 7,87–7,23 (23H, m, H-aromatic and H-1); 6,89 (1H, dd, H-2, $J_{2,1}$=4,5 Hz and $J_{2,3}$=6,1 Hz); 5,76 (1H, dd, H-3, $J_{2,3}$=6,0 Hz and $J_{3,4}$=3,6 Hz); 5,95 (1H, dd, H-4, $J_{4,3}$=3,7 Hz and $J_{4,5}$=7,0 Hz); 4,73 (1H, m, H-5); 4,57 (1H, dd, H-6a, $J_{6a,5}$=5,7 Hz and $J_{6a,6b}$=12,3 Hz); 4,21 (1H, dd, H-6b, $J_{6b,5}$=7,8 Hz and $J_{6b,6a}$=12,0 Hz); 1.12 (9H, s, C-C$\underline{H}_3$).

NMR ^{13}C: δ 165,7; 165,5; 165,1 and 164,8 (carbonyl); 150,1 (C-1); six resolved C-aromatic signals 135,6; 135,5; 133,9; 133,6; 133,2 and 132,8; 75,8; 74,8; 69,4 and 66,2 (C-2, C-3, C-4 and C-6); 26,6 (C-5); 26,4 (C-$\underline{C}H_3$); 19,2 ($\underline{C}$-CH_3).

MS: No discernible fragmentation pattern. Dominant peak: 105 ([C(O)Ph]$^+$, 100%).

6.8 SYNTHESIS OF FIVE MEMBERED CYCLIC NITRONES

General route towards methyl 2,3,5-tri-*O*-benzyl-D-pentofuranosides

The D-pentose (10 mmol) was dissolved in dry methanol (30 ml) and cooled to 0°C. To the clear solution was added 0,2 ml of concentrated H_2SO_4, and the reaction mixture was allowed to stir at 0°C for 1 h. After storage at +4°C for 12 h the solution was neutralised with aqueous Na_2CO_3, dried with $MgSO_4$ and the solvent removed *in vacuo*. To the residue, dissolved in dry DMF (8 ml) and cooled to 0°C, was added NaH (30 mmol). After the evolution of hydrogen gas had ceased (30 min.), BnBr (30 mmol) was slowly added and the reaction mixture allowed to warm to room temperature and stirred for 12 h. The excess NaH was then quenched with MeOH (5 ml) and Et_3N (2 ml) added to destroy the excess BnBr. After stirring for a further 4 h, the reaction was diluted with EtOAc (20 ml) and washed with water (3 x 15 ml). The solvent was removed *in vacuo*, and the residue purified by chromatography (5:1 hexane/ethyl acetate) to afford the title compounds.

Methyl 2,3,5-tri-*O*-benzyl-β-D-ribofuranoside (3.22)

Yield: 2,97 g, 88%

$[\alpha]_D^{24}$: +11,7° (*c*=2,1); [literature +17,5°, *c*=5.8 in THF][2]

NMR ^{1}H : δ 7,30 (15H, m, H-aromatic); 4,91 (1H, d, H-1, $J_{1,2}$=0,9 Hz); 4,65-4,42 (6H, m, C$\underline{H}_2$Ph); 4,34 (1H, m, H-4); 4,01 (1H, dd, H-3, $J_{3,2}$=4,8 Hz and $J_{3,4}$=7,2 Hz); 3,83 (1H, dd, H-2, $J_{2,1}$=0,9 Hz and $J_{2,3}$=4,8 Hz); 3,60 (1H, dd, H-5a, $J_{5a,4}$=3,6 Hz and $J_{5a,5b}$=10,3 Hz); 3,49 (1H, dd, H-5b, $J_{5b,4}$=5,7 Hz and $J_{5b,5a}$=10,3 Hz); 3,31 (3H, s, OC$\underline{H}_3$).

NMR ^{13}C: eight resolved C-aromatic signals δ 138,3; 137,8; 128,4; 128,3; 127,9; 127,8; 127,7 and 127,6; 106,3 (C-1); 80,4; 79,6 and 78,3 (3 x $\underline{C}H_2$Ph); 73,1; 72,4; 72,3 and 71,3 (C-2, C-3, C-4 and C-5), 55,0 (O$\underline{C}H_3$).

MS: m/z 434 ([M]$^+$, 5%); 402 ([M$^+$-MeOH], 10%); 91 ([CH_2Ph]$^+$, 100%)

Methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranoside (3.24 α- isomer)

Yield: 2,97 g, 80%

NMR ^{1}H : δ 7,34 (15H, m, H-aromatic); 4,87-4,62 (7H, m, C$\underline{H}_2$Ph and H-1); 4,02 (1H, dd, H-2, $J_{2,1}$=9,6 Hz and $J_{2,3}$=3,3 Hz); 3,88 (1H, dd, H-3, $J_{3,2}$=3,3 Hz and $J_{3,4}$=8,9 Hz); 3,75 (1H, m, H-4); 3,64 (1H, dd, H-5a, $J_{5a,4}$=2,4 Hz and $J_{5a,5b}$=12,1 Hz); 3,61 (1H, dd, H-5b, $J_{5b,4}$=1,5 Hz and $J_{5b,5a}$=12,1 Hz); 3,54 (3H, s, OC$\underline{H}_3$).

NMR ^{13}C: ten resolved C-aromatic signals δ 138,7; 138,6; 138,4; 128,4; 128,3; 128,0; 127,9; 127,6; 127,5 and 127,4; 99,3 (C-1); 77,2; 76,3 and 74,0 (3 x $\underline{C}H_2$Ph); 73,7; 72,8; 71,7 (C-2, C-3 and C-4); 60,1 (C-5), 55,4 (O$\underline{C}H_3$).

MS: m/z 434 ([M]$^+$, 2%); 343 ([M$^+$-Bn], 20%); 91 ([CH_2Ph]$^+$, 100%)

General route towards 2,3,5-tri-*O*-benzyl-D-ribofuranoses

To a solution of the protected β-D-pentofuranoside (5.0 mmol) in dioxane (40 ml) was added 0,1*N* hydrochloric acid (10 ml). The solution was boiled gently for 2 h, with 10 ml of distillate being collected. The solution was made up to its original volume with dioxane and boiled gently for an additional 1 h after which the excess acid was neutralised with solid Na_2CO_3 and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate (20 ml) and washed with water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (1:1 hexane/ethyl acetate) afforded the title compounds as colourless oils (α:β mixtures).

2,3,5-tri-*O*-benzyl-D-ribofuranose (3.23)

Yield: 1,49 g, 71% (for α:β-mixture)

NMR ^{1}H : main isomer: δ 7,35-7,26 (15H, m, H-aromatic); 5,33 (1H, m, H-1); 4,70-4,41 (6H, m, C$\underline{H}_2$Ph); 4,37 (1H, m, H-4); 3,99 (1H, dd, H-3, $J_{3,2}$=5,1 Hz and $J_{3,4}$=2,1 Hz); 3,97 (1H, dd, H-2, $J_{2,1}$=3,8 Hz and $J_{2,3}$=5,1 Hz); 3,66 (1H, dd, H-5a, $J_{5a,4}$=2,7 Hz and $J_{5a,5b}$=10,2 Hz); 3,46 (1H, dd, H-5b, $J_{5b,4}$=4,8 Hz and $J_{5b,5a}$=10,2 Hz).

NMR ^{13}C: main isomer: nine resolved C-aromatic signals δ 137,8; 137,7; 137,5; 128,4; 127,9; 127,8; 127,7; 127,6 and 127,5; 96,2 (C-1); 81,1; 80,8 and 77,7 (3 x $\underline{C}H_2$Ph); 73,5; 72,8; 72,4 and 70,0 (C-2, C-3, C-4 and C-5).

MS: No discernible fragmentation pattern. Dominant peak: m/z 91 ([CH_2Ph]$^+$, 100%).

2,3,5-tri-*O*-benzyl-D-arabinofuranose (3.25)

Yield: 1,37 g, 65% (for α,β-mixture)

NMR ^{1}H : main isomer: δ 7,33-7,30 (15H, m, H-aromatic); 5,16 (1H, s, H-1); 4,79-4,49 (7H, m, C<u>H</u>$_2$Ph and H-4); 3,85 (2H, m, H-2 and H-3), 3,64 (2H, m, H-5a and H-5b); 3,17 (1H, bs, ~O<u>H</u>).

NMR ^{13}C: main isomer: seven resolved C-aromatic signals δ 138,1; 137,9; 137,5; 128,5; 128,4; 127,6 and 127,5; 93,8 (C-1); 76,7; 76,2 and 75,5 (3 x <u>C</u>H$_2$Ph); 73,7; 73,1 and 71,5 (C-2, C-3 and C-4); 60,9 (C-5).

MS: m/z 343 ([M$^+$-Ph]; 55%) 91 ([CH$_2$Ph]$^+$, 100%)

General route towards 2,3,5-tri-*O*-benzyl-D-pentose oximes

To a solution of the protected D-pentofuranoside (3.0 mmol) in dry pyridine (5 ml) was added hydroxylamine hydrochloride (3,1 mmol). The solution was allowed to stir at room temperature for *ca.* 12 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (1:1 hexane/ethyl acetate) afforded the oximes as colourless oils (*E:Z* mixtures)

2,3,5-tri-*O*-benzyl-D-ribose oxime (3.26)

Yield: 1,12 g, 86% (for *E:Z* mixture)

IR: ν_{max} 1670 (C=N) cm^{-1}

NMR ^{1}H : main isomer: δ 7,47 (1H, d, H-1, $J_{1,2}$=8,4 Hz); 7,32-7,21 (15H, m, H-aromatic); 4,82 (1H, m, H-2); 4,71-4,41 (7H, m, C<u>H</u>$_2$Ph and H-3); 3,90 (1H, m, H-4), 3,79 (1H, dd, H-5a, $J_{5a,4}$=1,8 Hz and $J_{5a,5b}$=9,2 Hz); 3,65 (1H; d, ~O<u>H</u>, J=3,6 Hz); 3,39 (1H, dd, H-5b, $J_{5b,4}$=7,5 Hz and $J_{5b,5a}$=9,2 Hz).

NMR ^{13}C: main isomer: δ 149,3 (C-1); seven resolved C-aromatic signals 138,1; 138,0; 136,8; 128,4; 128,3; 127,6 and 127,4; 80,7; 78,4 and 74,3 (3 x <u>C</u>H$_2$Ph); 73,8; 73,2 and 71,3 (C-2, C-3 and C-4); 68,8 (C-5).

MS: No discernible fragmentation pattern. Dominant peak: m/z 91 ([CH$_2$Ph]$^+$, 100%).

2,3,5-tri-*O*-benzyl-D-arabinose oxime (3.27)

Yield: 1,17 g, 90% (for *E:Z* mixture)

IR: ν_{max} 1675 (C=N) cm^{-1}

NMR ^{1}H : main isomer: δ 8,68 (1H, bs, ~NO<u>H</u>); 7,46 (1H, d, H-1, $J_{1,2}$=8,1 Hz); 7,31 (15H, m, H-aromatic); 4,71-4,32 (6H, m, 3 x C<u>H</u>$_2$Ph); 4,26 (1H, dd, H-2, $J_{2,3}$=4,5 Hz and $J_{2,1}$=8,1 Hz) 3,82 (3H, m, H-3; H-5a and H-5b), 3,69 (1H, m, H-4); 2,51 (1H; bs, ~O<u>H</u>).

NMR ^{13}C: main isomer: δ 150,1 (C-1); nine resolved C-aromatic signals 137,7; 137,4; 128,5; 128,4; 128,3; 128,2; 127,9; 127,6 and 127,4; 79,9; 78,6 and 77,1 (C-2, C-3 and C-4); 74,9; 71,8 and 71,1 (3 x $\underline{C}H_2Ph$); 60,3 (C-5).

MS: No discernible fragmentation pattern. Dominant peak: m/z 91 ($[CH_2Ph]^+$, 100%).

2,3,5-Tri-*O*-benzyl-D-ribose oxime *O-tert*-butyldiphenylsilyl ether (3.28 :main isomer)

To a solution of **3.26** (2.0 mmol) in dry pyridine (5 ml) was added *tert*-butyldiphenylsilyl chloride (2,1 mmol). The solution was allowed to stir at room temperature for *ca.* 18 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (6:1 hexane/ethyl acetate) afforded the selectively silylated oxime as a colourless oil (*E:Z* mixtures).

Yield: 1,18 g, 88% (for *E:Z* mixture)

NMR ^1H : main isomer: δ 7,72 (1H, d, H-1, $J_{1,2}$=8,1 Hz); 7,66 (4H, m, H-*ortho*-aromatic); 7,45-7,28 (21H, m, H-aromatic); 5,39 (1H, dd, H-2, $J_{2,3}$=1,8 Hz and $J_{2,1}$=8,1 Hz); 4,75 (1H, d, C$\underline{H}_2$Ph, *J*=11,8 Hz); 4,70 (1H, d, C$\underline{H}_2$Ph, *J*=11,8 Hz); 4,41 (1H, d, C$\underline{H}_2$Ph, *J*=12,0 Hz); 4,35 (1H, d, C$\underline{H}_2$Ph, *J*=12,0 Hz); 4,33 (1H, d, C$\underline{H}_2$Ph, *J*=11,8 Hz); 4,28 (1H, d, C$\underline{H}_2$Ph, *J*=11,9 Hz); 4,27 (1H, dd, H-3, $J_{2,3}$=1,8 Hz and $J_{3,4}$=5,1 Hz); 3,79 (1H, m, H-4); 3,66 (2H, d, H-5a and H-5b, *J*=3,4 Hz); 2,66 (1H, d, C[4]-O$\underline{H}$, *J*=5,7 Hz); 1,12 (9H, s, Si(C$\underline{H}_3$)$_3$).

NMR ^{13}C: main isomer: δ 156,2 (C-1); sixteen resolved C-aromatic signals 138,1; 137,7; 137,6; 135,5; 135,4; 133,4; 133,2; 129,8; 129,7; 128,4; 128,3; 128,2; 127,9; 127,8; 127,7 and 127,4; 80,3 (C-2); 73,9; 73,3; and 73,2 (3 x $\underline{C}H_2Ph$); 70,7 and 70,5 (C-3 and C-4); 71,0 (C-5); 27,0 (SiC($\underline{C}H_3$)$_3$); 19,3 (Si$\underline{C}$(CH$_3$)$_3$).

MS: m/z 675 ($[M]^+$, 20%); 91 ($[CH_2Ph]^+$, 100%).

2,3,5-Tri-*O*-benzyl-4-*O*-methanesulfonyl-D-ribose oxime *O-tert*-butyldiphenylsilyl ether (3.31 :main isomer)

To a solution of **3.28** (2.0 mmol) in dry pyridine (5 ml) was added a 1:1 mixture of mesyl chloride (3,0 mmol) and pyridine (6,0 mmol). The dark brown solution was stirred at 80°C for 6 h after which the reaction mixture was filtered through Celite. The solvent was removed *in vacuo* and the residue was redissolved in methylene chloride (10 ml), washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by flash chromatography (4:1 hexane/ethyl acetate) afforded the 5-O-mesylate as a yellow oil (*E:Z* mixture).

Yield: 1,22 g, 81% (for *E:Z* mixture)

IR: ν_{max} 1677 (C=N) cm^{-1}

NMR ^{1}H : main isomer: δ 7,78 (4H, m, H-*ortho*-aromatic); 7,66 (1H, d, H-1, $J_{1,2}$=7,9 Hz); 7,41-7,23 (21H, m, H-aromatic); 5,03 (1H, m, H-4); 4,76 (1H, d, C$\underline{H}_2$Ph, *J*=11,1 Hz); 4,74 (1H, d, C$\underline{H}_2$Ph, *J*=11,1 Hz); 4,65 (2H, s, C$\underline{H}_2$Ph); 4,46 (1H, d, C$\underline{H}_2$Ph, *J*=11,2 Hz); 4,44 (1H, d, C$\underline{H}_2$Ph, *J*=11,2 Hz); 4,25 (1H, d, H-3, $J_{4,3}$=8,4 Hz); 3,87 (1H, d, H-2, $J_{2,1}$=7,9 Hz); 3,77 (1H, dd, H-5a, $J_{5a,5b}$=11,1 Hz and $J_{5a,4}$=6,9 Hz); 3,59 (1H, dd, H-5b, $J_{5a,5b}$=11,1 Hz and $J_{5b,4}$=3,1 Hz); 2,83 (3H, s, $SO_2C\underline{H}_3$); 1,18 (9H, s, $SiC(C\underline{H}_3)_3$).

NMR ^{13}C: main isomer: δ 153,5 (C-1); sixteen resolved C-aromatic signals 137,6; 137,5; 137,3; 135,6; 135,4; 133,2; 133,0; 129,7; 128,5; 128,4; 128,3; 128,1; 127,9; 127,8; 127,6 and 127,5; 81,4 (C-2); 74,8; 74,2; and 73,8 (3 x $\underline{C}H_2$Ph); 73,2 (C-3); 70,2 (C-4); 68,2 (C-5); 38,2 ($SO_2\underline{C}H_3$); 26,9 ($SiC(\underline{C}H_3)_3$); 19,1 ($Si\underline{C}(CH_3)_3$).

MS: m/z 571 ([M]$^+$, 25%); 693 ([M$^+$ -*t*Bu], 40%); 586 ([M$^+$ -OBn], 12%); 91 ([CH_2Ph]$^+$, 100%).

(2*S*,3*R*,4*S*) 3,4-Dibenzyloxy-2-benzyloxymethyl-*N*-hydroxypyrrolidine (3.32)

To a solution of **2.31** (1.0 mmol) in TFA (1,5 ml) was added dimethylphenylsilane (2,3 mmol). The solution was stirred at 60°C for 30 min after which the reaction mixture was diluted with ethyl acetate and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by flash chromatography (4:1 hexane/ethyl acetate) afforded the title compound as a colourless oil.

Yield: 0,25 g, 59%

$[\alpha]_D^{24}$: -17,7° (*c*=1,5)

NMR ^{1}H : δ 7,30-7,27 (15H, m, H-aromatic); 4,71 (1H, d, C$\underline{H}_2$Ph, *J*=12,1 Hz); 4,57 (1H, d, C$\underline{H}_2$Ph, *J*=12,1 Hz); 4,53 (2H, s, C$\underline{H}_2$Ph); 4,48 (1H, d, C$\underline{H}_2$Ph, *J*=12,0 Hz); 4,46 (1H, d, C$\underline{H}_2$Ph, *J*=12,0 Hz); 4,19 (2H, m, H-3 and H-4); 3,80 (1H, dd, H-5a, $J_{5a,5b}$=9,1 Hz and $J_{5a,4}$=7,3 Hz); 3,71 (1H, dd, H-5b, $J_{5a,5b}$=9,1 Hz and $J_{5b,4}$=6,7 Hz); 3,45 (1H, dd, H-2'a, $J_{2'a,2'b}$=16,8 Hz and $J_{2'ab,2}$=7,5 Hz); 3,35 (1H, m, H-2); 3,15 (1H, dd, H-2'b, $J_{2'a,2'b}$=16,9 Hz and $J_{2'b,2}$=9,5 Hz).

NMR ^{13}C: ten resolved C-aromatic signals δ 138,4; 138,2; 138,0; 129,7; 128,5; 128,3; 128,1; 127,9; 127,8; and 127,5; 77,3; 76,8; and 73,5 (3 x $\underline{C}H_2$Ph); 73,4 (C-3); 72,0 (C-4); 70,4 (C-1); 68,3 (C-2); 60,7 (C-5).

MS: m/z 419 ([M]$^+$, 10%); 107 ([OCH_2Ph]$^+$, 100%).

(3*S*,4*R*) 3,4-Dibenzyloxy-2-benzyloxymethyl-1-pyrroline *N*-oxide (3.33)

To a solution of **2.32** (0.5 mmol) in CH_2Cl_2 (2,0 ml) was added HgO (0,55 mmol). The solution was stirred at room temperature for 10 minutes after which the reaction mixture was filtered

through a pad of celite. Removal of the solvent followed by flash chromatography (1:1 hexane/ethyl acetate) afforded the title compound as a colourless oil.

Yield: 0,16 g, 76%

$[\alpha]_D^{24}$: +7,1° (*c*=1,0)

NMR ^{1}H : δ 7,31-7,24 (15H, m, H-aromatic); 4,68 (1H, d, C$\underline{H}_2$Ph, *J*=12,0 Hz); 4,65 (1H, d, C$\underline{H}_2$Ph, *J*=12,0 Hz); 4,61 (1H, d, H-3, $J_{3,4}$=4,3 Hz); 4,58 (2H, s, C$\underline{H}_2$Ph); 4,51 (1H, d, C$\underline{H}_2$Ph, *J*=11,8 Hz); 4,47 (1H, d, C$\underline{H}_2$Ph, *J*=11,8 Hz); 4,24 (1H, dd, H-5a, $J_{5a,5b}$=14,1 Hz and $J_{5a,4}$=2,3 Hz); 4,13-4,05 (3H, m, H-2'a; H-2'b and H-4); 3,83 (1H, dd, H-5b, $J_{5a,5b}$=14,3 Hz and $J_{5a,4}$=8,3 Hz)

NMR ^{13}C: δ 144,0 (C-2); nine resolved C-aromatic signals 137,5; 137,4; 136,9; 128,6; 128,4; 128,2; 128,1; 128,0 and 127,8; 77,3; 73,8; and 72,7 (3 x $\underline{C}H_2$Ph); 72,1 (C-3); 71,6 (C-4); 65,6 (C-2'); 62,3 (C-5).

MS: No discernible fragmentation pattern. Dominant peak: m/z 91 ([CH_2Ph]$^+$, 100%).

2,3,5-Tri-*O*-benzyl-4-*O*-methanesulfonyl-D-ribose oxime (3.37 :main isomer)

To a solution of **3.31** (2.0 mmol) in dry THF (5 ml) was added TBAF (2.1 ml of a 2 M solution in THF). The solution was stirred at room temperature for 10 minutes after which the solvent was removed *in vacuo*. The residue was redissolved in methylene chloride (10 ml), washed with water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by flash chromatography (1:1 hexane/ethyl acetate) afforded the 4-*O*-mesylate as a yellow oil (*E:Z* mixture).

Yield: 0,95 g, 88% (for *E:Z* mixture)

IR: ν_{max} 1680 (C=N) cm^{-1}

NMR ^{1}H : main isomer: δ 7,41-7,23 (16H, m, H-aromatic and H-1); 5,03 (1H, m, H-4); 4,68 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,65 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,59 (1H, d, C$\underline{H}_2$Ph, J=11,3 Hz); 4,43 (1H, d, C$\underline{H}_2$Ph, *J*=10,7 Hz); 4,42 (1H, d, C$\underline{H}_2$Ph, *J*=10,7 Hz); 4,36 (1H, d, C$\underline{H}_2$Ph, J=11,4 Hz); 4,05 (1H, dd, H-2; $J_{2,3}$=6,6 Hz and $J_{2,1}$=7,5 Hz); 3,98 (1H, dd, H-3, $J_{2,3}$=6,5 Hz and $J_{4,3}$=3,9 Hz); 3,72 (1H, dd, H-5a, $J_{5a,5b}$=11,1 Hz and $J_{5a,4}$=7,2 Hz); 3,56 (1H, dd, H-5b, $J_{5a,5b}$=11,1 Hz and $J_{5b,4}$=2,7 Hz); 2,96 (3H, s, $SO_2C\underline{H}_3$).

NMR ^{13}C: main isomer: δ 149,3 (C-1); nine resolved C-aromatic signals 137,5; 137,2; 137,1; 128,6; 128,4; 128,2; 128,1; 127,9; and 127,5; 81,3 (C-2); 78,8 (C-4); 75,4; 74,1; and 73,3 (3 x $\underline{C}H_2$Ph); 70,7 (C-2); 68,3 (C-5); 38,5 ($SO_2\underline{C}H_3$).

MS: m/z 542 ([M]$^+$, 3%); 451 ([M$^+$ -Bn], 50%); 91 ([CH_2Ph]$^+$, 100%).

General route to tri-*O*-benzyl-4-iodo-D-pentose oxime ethers:

To a solution of the protected D-pentose oxime *O-tert*-butyldiphenylsilyl ether (2.0 mmol) in dry toluene (6 ml) was added PPh_3 (1,1 mmol), imidazole (2,2 mmol) and iodine (1,1 mmol). The dark solution was heated to 70°C, and stirred vigorously for 1 h, during which time the solution turned clear. The reaction mixture was allowed to cool to room temperature, after which saturated aqueous $NaHCO_3$ (5 ml) was added and the solution stirred for an additional 10 min. Iodine was carefully added until the brown colour lingered, after which the mixture was washed with saturated aqueous $Na_2S_2O_3$ until the solution became clear, followed by water (3 x 5 ml) and brine (3 x 5 ml). Removal of the solvent followed by flash chromatography (6:1 hexane/ethyl acetate) afforded the 4-iodo oxime ethers as colourless oils (*E:Z* mixtures).

2,3,5-Tri-*O*-benzyl-4-iodo-L-lyxose oxime *O-tert*-butyldiphenylsilyl ether (3.38 :main isomer)

Yield: 1,32 g, 84% (for *E:Z* mixture)

IR: ν_{max} 1670 (C=N) cm^{-1}

NMR ^1H : main isomer: δ 7,76 (4H, m, H-*ortho*-aromatic); 7,64 (1H, d, H-1, $J_{1,2}$=8,1 Hz); 7,45-7,28 (21H, m, H-aromatic); 4,76 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,70 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,60 (1H, m, H-4); 4,49 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,47 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,46 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,36 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,11 (1H, dd, H-2, $J_{2,3}$=6,9 Hz and $J_{2,1}$=8,1 Hz); 3,80 (1H, dd, H-5a, $J_{5a,5b}$=10,2 Hz and $J_{5a,4}$=8,4 Hz); 3,75 (1H, dd, H-5b, $J_{5a,5b}$=10,2 Hz and $J_{5b,4}$=4,8 Hz); 3,59 (1H, dd, H-3, $J_{2,3}$=6,9 Hz and $J_{3,4}$=3,3 Hz); 1,17 (9H, s, SiC(C$\underline{H}_3$)$_3$).

NMR ^{13}C: main isomer: δ 153,8 (C-1); sixteen resolved C-aromatic signals 137,9; 137,5; 137,4; 135,5; 135,4; 133,6; 133,2; 129,7; 128,5; 128,4; 128,3; 128,2; 127,9; 127,8; 127,6 and 127,4; 78,8 (C-2); 77,4; 74,3; and 72,7 (3 x $\underline{C}H_2$Ph); 72,3 (C-3); 71,0 (C-5); 33,6 (C-4); 26,9 (SiC($\underline{C}H_3$)$_3$); 19,2 (Si$\underline{C}$(CH$_3$)$_3$).

MS: No discernible fragmentation pattern. Dominant peak: m/z 91 ([CH_2Ph]$^+$, 100%).

2,3,5-Tri-*O*-benzyl-4-iodo-L-xylose oxime *O-tert*-butyldiphenylsilyl ether (3.41 :main isomer)

Yield: 1,21 g, 77% (for *E:Z* mixture)

IR: ν_{max} 1670 (C=N) cm^{-1}

NMR ^1H : main isomer: δ 7,74 (4H, m, H-*ortho*-aromatic); 7,40-7,23 (21H, m, H-aromatic); 5,31 (1H, dd, H-2, $J_{2,3}$=2,1 Hz and $J_{2,1}$=5,7 Hz); 4,75 (1H, d, C$\underline{H}_2$Ph, *J*=11,8 Hz); 4,71 (1H, d, C$\underline{H}_2$Ph, *J*=11,8 Hz); 4,49 (1H, d, C$\underline{H}_2$Ph, *J*=11,5 Hz); 4,47 (1H, d, C$\underline{H}_2$Ph, *J*=11,5 Hz); 4,39 (1H, d, C$\underline{H}_2$Ph, *J*=11,8 Hz); 4,36 (1H, d, C$\underline{H}_2$Ph,

J=11,8 Hz); 4,11 (1H, dd, H-3, $J_{2,3}$=2,1 Hz and $J_{3,4}$=7,8 Hz); 3,65 (2H, m, H-5a and H-5b); 3,42 (1H, m, H-4); 1,12 (9H, s, SiC(C<u>H</u>$_3$)$_3$).

NMR ^{13}C: main isomer: δ 157,9 (C-1); sixteen resolved C-aromatic signals 137,8; 137,4; 137,3; 135,6; 135,4; 133,6; 133,4; 129,7; 128,6; 128,3; 128,2; 128,1; 127,9; 127,8; 127,6 and 127,4; 81,2 (C-2); 78,2; 74,3; and 73,8 (3 x <u>C</u>H$_2$Ph); 71,1 (C-3); 67,5 (C-5); 31,5 (C-4); 26,9 (SiC(<u>C</u>H$_3$)$_3$); 19,2 (Si<u>C</u>(CH$_3$)$_3$).

MS: m/z 657 ([M$^+$ -I], 15%); 91 ([CH$_2$Ph]$^+$, 100%).

(3*S*,4*R*,5*R*)-3,4-Dibenzyloxy-5-benzyloxymethyl-1-pyrroline *N*-oxide (3.39)

To a solution of **3.38** (2.0 mmol) in benzene (3 ml) was added anhydrous TBAF (0,66 ml of a 3 M solution in benzene). The reaction mixture was stirred at 60°C for 30 minutes. Removal of the solvent under reduced pressure and chromatography (1:2 hexane:ethyl acetate) of the residue afforded the title compound as a colourless oil.

Yield: 0,72 g, 86%

$[\alpha]_D^{24}$: +5,6° (c=1,5)

IR: ν_{max} 1670 (C=N) cm^{-1}

NMR ^{1}H : δ 7,31-7,18 (15H, m, H-aromatic); 6,90 (1H, s, H-1); 4,69 (1H, d, C<u>H</u>$_2$Ph, J=11,7 Hz); 4,62 (1H, d, C<u>H</u>$_2$Ph, J=11,7 Hz); 4,61 (1H, d, H-2, $J_{2,3}$=3,6 Hz); 4,59 (1H, d, C<u>H</u>$_2$Ph, J=11,7 Hz); 4,51 (1H, d, C<u>H</u>$_2$Ph, J=11,7 Hz); 4,49 (1H, d, C<u>H</u>$_2$Ph, J=11,7 Hz); 4,44 (1H, dd, H-3, $J_{2,3}$=3,6 Hz and $J_{3,4}$=2,9 Hz); 4,40 (1H, d, C<u>H</u>$_2$Ph, J=11,8 Hz); 4,12 (1H, dd, H-5a, $J_{5a,5b}$=10,7 Hz and $J_{5a,4}$=2,7 Hz); 4,07 (1H, m, H-4); 3,61 (1H, dd, H-5b, $J_{5a,5b}$=10,7 Hz and $J_{5b,4}$=2,1 Hz).

NMR ^{13}C: δ 133,4 (C-1); eleven resolved C-aromatic signals 137,6; 137,4; 137,2; 128,6; 128,5; 128,4; 128,2; 128,1; 128,0; 127,8 and 127,6; 76,3 (C-4); 75,3 (C-3); 74,6; 73,4; and 72,4 (3 x <u>C</u>H$_2$Ph); 72,1 (C-2); 64,7 (C-5).

MS: m/z 417 ([M]$^+$, 60%); 401 ([M$^+$ -O], 12%); 91 ([CH$_2$Ph]$^+$, 100%).

(4*S*,5*R*,6*R*)-3,4-Di-*O*-benzyl-6-benzyloxymethyl-1,2-oxazine (3.40)

Yield: 0,083 g, 10%

NMR ^{1}H : δ 7,33-7,28 (16H, m, H-aromatic and H-1); 4,77 (1H, d, C<u>H</u>$_2$Ph, J=11,5 Hz); 4,67 (1H, d, C<u>H</u>$_2$Ph, J=11,5 Hz); 4,63 (1H, d, H-2, $J_{2,3}$=4,2 Hz); 4,62 (1H, d, C<u>H</u>$_2$Ph, J=11,5 Hz); 4,61 (1H, d, C<u>H</u>$_2$Ph, J=11,6 Hz); 4,58 (1H, d, C<u>H</u>$_2$Ph, J=11,5 Hz); 4,54 (1H, d, C<u>H</u>$_2$Ph, J=11,7 Hz); 4,22 (1H, m, H-4); 3,94 (1H, dd, H-3, $J_{2,3}$=4,2 Hz and $J_{3,4}$=9,3 Hz); 3,86 (1H, dd, H-5a, $J_{5a,5b}$=11,1 Hz and $J_{5a,4}$=3,6 Hz); 3,82 (1H, dd, H-5b, $J_{5a,5b}$=11,1 Hz and $J_{5b,4}$=4,1 Hz).

NMR ^{13}C: δ 147,2 (C-1); 137,9; 137,6 and 137,5 (C-*Ipso*-aromatic); 128,6; 128,5; 128,4; 128,3; 128,1; 128,0; 127,9; 127,7 and 127,6 (C-aromatic); 75,6 (C-3); 73,6 (C-4); 72,7; 72,1; and 71,2 (3 x $\underline{C}H_2Ph$); 67,4 (C-2); 65,3 (C-5).

MS: m/z 417 ($[M]^+$, 20%); 326 ($[M^+ -Bn]$, 90%); 91 ($[CH_2Ph]^+$, 100%).

2,3,5-Tri-*O*-benzyl-D-arabinose oxime *O*-*tert*-butyldiphenylsilyl ether (3.29 :main isomer)

To a solution of **3.27** (2.0 mmol) in dry pyridine (5 ml) was added freshly prepared *O*-(*tert*-butyldiphenylsilyl)hydroxylamine (2,1 mmol). The solution was stirred at 80°C for *c.a.* 12 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (1:1 hexane/ethyl acetate) afforded the title compound as a colourless oil (*E*:*Z* mixture).

Yield: 0,40 g, 30% (for *E*:*Z* mixture)

NMR ^1H : main isomer: δ 7,64-7,58 (4H, m, H-*ortho*-aromatic); 7,44-7,28 (22H, m, H-aromatic and H-1); 4,68 (2H, s, $C\underline{H}_2Ph$); 4,49 (1H, d, $C\underline{H}_2Ph$, *J*=11,9 Hz); 4,32 (1H, d, $C\underline{H}_2Ph$, *J*=11,9 Hz); 4,25 (1H, d, $C\underline{H}_2Ph$, *J*=11,8 Hz); 4,24 (1H, d, $C\underline{H}_2Ph$, *J*=11,9 Hz); 4,20 (1H, d, $C\underline{H}_2Ph$, *J*=11,9 Hz); 4,15 (1H, dd, H-2, $J_{2,3}$=4,8 Hz and $J_{2,1}$=8,1 Hz); 3,74 (3H, m, H-3; H-5a and H-5b); 3,57 (1H, m, H-4); 1,11 (9H, s, $SiC(C\underline{H}_3)_3$).

NMR ^{13}C: main isomer: δ 154,5 (C-1); sixteen resolved C-aromatic signals 137,8; 137,7; 137,4; 135,6; 135,5; 133,4; 133,2; 129,8; 128,7; 128,5; 128,2; 128,1; 127,9; 127,8; 127,6 and 127,3; 79,9 (C-3); 78,2 (C-4); 77,0 (C-2); 74,9; 71,7 and 70,7 (3 x $\underline{C}H_2Ph$); 60,3 (C-5); 27,0 ($SiC(\underline{C}H_3)_3$); 19,2 ($Si\underline{C}(CH_3)_3$).

MS: m/z 617 ($[M^+ -t\text{Bu}]$, 80%); 91 ($[CH_2Ph]^+$, 100%).

(2*R*,3*R*,4*S*)-Tri-*O*-benzyl-D-arabinonitrile (3.43)

To a solution of **3.41** (2.0 mmol) in benzene (3 ml) was added anhydrous TBAF (0,66 ml of a 3 M solution in benzene). The reaction mixture was stirred at 60°C for 30 minutes. Removal of the solvent under reduced pressure and chromatography (1:2 hexane:ethyl acetate) of the residue afforded the title compound as a colourless oil.

Yield: 0,60 g, 72%

$[\alpha]_D^{24}$: +29,1° (*c*=1,0)

IR: ν_{max} 2245 (nitrile) cm^{-1}

NMR ^1H : δ 7,30-7,27 (15H, m, H-aromatic); 4,91 (1H, d, $C\underline{H}_2Ph$, *J*=11,9 Hz); 4,86 (1H, d, $C\underline{H}_2Ph$, *J*=11,9 Hz); 4,51 (1H, d, $C\underline{H}_2Ph$, *J*=12,0 Hz); 4,48 (1H, d, H-2, $J_{2,3}$=2,7 Hz); 4,47 (1H, d, $C\underline{H}_2Ph$, *J*=11,9 Hz); 4,28 (1H, d, $C\underline{H}_2Ph$, *J*=11,9 Hz); 4,20 (1H, d, $C\underline{H}_2Ph$, *J*=11,9 Hz); 3,92 (1H, dd, H-3, $J_{2,3}$=2,7 Hz and $J_{3,4}$=8,4 Hz); 3,81 (1H,

m, H-4); 3,74 (1H, dd, H-5a, $J_{5a,5b}$=8,6 Hz and $J_{5a,4}$=3,0 Hz); 3,69 (1H, dd, H-5b, $J_{5a,5b}$=8,6 Hz and $J_{5b,4}$=3,1 Hz).

NMR ^{13}C: eleven resolved C-aromatic signals δ 137,4; 136,9; 135,5; 128,7; 128,6; 128,5; 128,3; 128,1; 127,9; 127,8 and 127,5; 117,4 (C-1); 77,9 (C-3); 77,4 (C-4); 75,0; 72,5; and 71,9 (3 x $\underline{C}H_2Ph$); 66,9 (C-2); 59,5 (C-5).

MS: No discernible fragmentation pattern. Dominant peak: m/z 91 ([CH_2Ph]$^+$, 100%).

2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranose (3.47)

To a solution of D-ribose (15 mmol) in dry acetone (50 ml) was added anhydrous $CuSO_4$ (1 g) and concentrated H_2SO_4 (0.1 ml). The suspension was stirred at room temperature for 24 h. The reaction mixture was filtered through a pad of celite to remove the solids, diluted with ethyl acetate (35 ml), and washed with saturated aqueous $NaHCO_3$ (3 x 15 ml). The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo.* The resulting syrup consisted mainly of **3.54** (2,3 g) and was dissolved in pyridine (20 ml). To this solution was added TrCl (15 mmol) and the resulting suspension was stirred at 65°C for 12 h after which all the reagent had dissolved. Removal of the solvent *in vacuo* and chromatography (6:1 hexane:ethyl acetate) of the residue afforded the title compound as a yellow syrup.

Yield: 4,65 g, 71% (starting from D-ribose)

NMR ^{1}H : δ 7,42-7,24 (15H, m, H-aromatic); 5,33 (1H, d, H-1, $J_{1,OH}$=9,0 Hz); 4,76 (1H, dd, H-3, $J_{4,3}$=0,6 Hz and $J_{3,2}$=6,3 Hz); 4,64 (1H, d, H-2, $J_{2,3}$=6,3 Hz); 4,34 (1H, m, H-4); 3,94 (1H, d, ~O$\underline{H}$, $J_{1,OH}$=9,0 Hz); 3,39 (1H, dd, H-5a, $J_{5a,5b}$=10,5 and $J_{5a,4}$=3,0 Hz); 3,32 (1H, dd, H-5b, $J_{5a,5b}$=10,5 and $J_{5b,4}$=3,9 Hz); 1,47 (3H, s, C$\underline{H}_3$, isopropylidene); 1,34 (3H, s, C$\underline{H}_3$, isopropylidene).

NMR ^{13}C: δ 142,8 (C-*Ipso*-aromatic); 128,7 (C-*ortho*-aromatic); 128,1 (C-*meta*-aromatic); 127,5 (C-*para*-aromatic); 112,2 ($\underline{C}(CH_3)_2$, isopropylidene); 103,5 (C-1); 88,1 ($\underline{C}$[Ph]$_3$, trityl); 86,9 (C-3); 86,0 (C-4); 81,9 (C-2); 64,9 (C-5); 26,4 and 24,9 ($\underline{C}H_3$, isopropylidene).

MS: m/z 432 ([M]$^+$, 60%); 355 ([M$^+$ -Ph], 80%).

2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribose oxime (3.48)

To a solution of **3.47** (3.0 mmol) in dry pyridine (5 ml) was added hydroxylamine hydrochloride (3,1 mmol). The solution was allowed to stir at room temperature for *c.a.* 12 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (1:1 hexane/ethyl acetate) afforded the oxime as a colourless oil (*E:Z* mixture).

Yield: 1,15 g, 86%

NMR ^{1}H : δ 8,58 (1H, bs, N-O<u>H</u>); 7,47-7,23 (16H, m, H-aromatic and H-1); 4,77 (1H, dd, H-2, $J_{2,3}$=6,3 Hz and $J_{1,2}$=7,2 Hz); 4,22 (1H, d, H-3, $J_{2,3}$=6,3 Hz and $J_{3,4}$=7,8 Hz); 3,75 (1H, m, H-4); 3,37 (1H, dd, H-5a, $J_{5a,5b}$=10,0 and $J_{5a,4}$=2,1 Hz); 3,32 (1H, dd, H-5b, $J_{5a,5b}$=10,0 and $J_{5b,4}$=5,2 Hz); 2,88 (1H, d, [C4]-O<u>H</u>, J=2,7 Hz); 1,38 (3H, s, C<u>H</u>$_3$, isopropylidene); 1,33 (3H, s, C<u>H</u>$_3$, isopropylidene).

NMR ^{13}C: δ 148,5 (C-1); 143,7 (C-*Ipso*-aromatic); 128,7 (C-*ortho*-aromatic); 127,9 (C-*meta*-aromatic); 127,2 (C-*para*-aromatic); 109,8 (<u>C</u>(CH$_3$)$_2$, isopropylidene); 88,8 (<u>C</u>[Ph]$_3$, trityl); 77,5 (C-2); 75,2 (C-3); 68,8 (C-4); 64,8 (C-5); 27,6 and 25,3 (<u>C</u>H$_3$, isopropylidene).

MS: m/z 447 ([M]$^+$, 20%); 430 ([M$^+$ -OH], 55%); 370 ([M$^+$ -Ph], 70%).

2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribose oxime *O*-*tert*-butyldiphenylsilyl ether (3.49)

To a solution of **3.48** (3.0 mmol) in dry pyridine (5 ml) was added *tert*-butyldiphenylsilyl chloride (3,1 mmol). The solution was allowed to stir at room temperature for *ca*. 18 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (6:1 hexane/ethyl acetate) afforded the selectively silylated oxime as a colourless oil (*E:Z* mixture).

Yield: 1,60 g, 78%

NMR ^{1}H : δ 7,73-7,68 (4H, m, H-aromatic); 7,46-7,23 (22H, m, H-aromatic and H-1); 4,74 (1H, dd, H-2, $J_{2,3}$=6,3 Hz and $J_{1,2}$=8,1 Hz); 4,17 (1H, d, H-3, $J_{2,3}$=6,3 Hz and $J_{3,4}$=9,0 Hz); 3,67 (1H, m, H-4); 3,34 (2H, m, H-5a and H-5b); 2,25 (1H, d, [C4]-O<u>H</u>, J=5,1 Hz); 1,38 (3H, s, C<u>H</u>$_3$, isopropylidene); 1,30 (3H, s, C<u>H</u>$_3$, isopropylidene); 1,11 (9H, s, Si-C(C<u>H</u>$_3$)$_3$).

NMR ^{13}C: δ 153,6 (C-1); seven resolved C-aromatic signals 143,8; 135,5; 135,2; 129,7; 128,5; 127,9 and 127,2; 109,9 (<u>C</u>(CH$_3$)$_2$, isopropylidene); 86,8 (<u>C</u>[Ph]$_3$, trityl); 77,5 (C-2); 75,2 (C-3); 68,8 (C-4); 65,0 (C-5); 27,6 (<u>C</u>H$_3$, isopropylidene);.26,9 (Si-C(<u>C</u>H$_3$)$_3$); 24,9 (<u>C</u>H$_3$, isopropylidene); 19,2 (Si-<u>C</u>(CH$_3$)$_3$).

MS: No discernible fragmentation pattern.

(3*S*,4*R*,5*R*)-3,4-Isopropylidenedioxy-5-trityloxymethyl-1-pyrroline *N*-oxide (3.53)

To a solution of **3.49** (2.0 mmol) in dry toluene (6 ml) was added PPh_3 (1,1 mmol), imidazole (2,2 mmol) and iodine (1,1 mmol). The dark solution was heated to 70°C, and stirred vigorously for 1 h, during which time the solution turned clear. The reaction mixture was allowed to cool to room temperature, after which saturated aqueous $NaHCO_3$ (5 ml) was added and the solution stirred for an additional 10 min. Iodine was carefully added until the brown colour lingered, after which the mixture was washed with saturated aqueous $Na_2S_2O_3$

until the solution became clear, followed by water (3 x 5 ml) and brine (3 x 5 ml). Removal of the solvent and filtration through a silica plug afforded a mixture of **3.50** and **3.51**. The mixture was dissolved in benzene (5 ml) and anhydrous TBAF (0,66 ml of a 3 M solution in benzene) was added. The reaction mixture was stirred at 60°C for 30 minutes. Removal of the solvent under reduced pressure and chromatography (1:2 hexane:ethyl acetate) of the residue afforded the title compound as a colourless oil.

Yield: 0,37 g, 43%

$[\alpha]_D^{24}$: +15,9° (*c*=1,0)

IR: ν_{max} 1680 (C=N) cm^{-1}

NMR ^1H : δ 7,33-7,24 (15H, m, H-aromatic); 7,09 (1H, s, H-2); 5,35 (1H, d, H-3, $J_{2,3}$=6,3 Hz); 4,52 (1H, d, H-4, $J_{2,3}$=6,0 Hz); 4,08 (1H, dd, H-5'a, $J_{5'a,5'b}$=10,2 and $J_{5'a,4}$=2,7 Hz); 4,02 (1H, m, H-5); 3,15 (1H, dd, H-5'b, $J_{5'a,5'b}$=10,2 and $J_{5'b,4}$=2,4 Hz); 1,42 (3H, s, C$\underline{H}_3$, isopropylidene); 1,31 (3H, s, C$\underline{H}_3$, isopropylidene).

NMR ^{13}C: δ 143,3 (C-2); 133,3 (C-*Ipso*-aromatic); 128,5 (C-*ortho*-aromatic); 128,1 (C-*meta*-aromatic); 127,4 (C-*para*-aromatic); 111,7 ($\underline{C}(CH_3)_2$, isopropylidene); 86,9 ($\underline{C}[Ph]_3$, trityl); 79,2 (C-3); 79,1 (C-4); 77,4 (C-5); 59,5 (C-5'); 27,3 ($\underline{C}H_3$, isopropylidene);.25,8 ($\underline{C}H_3$, isopropylidene).

MS: m/z 429 ($[M]^+$, 15%); 413 ($[M^+ -O]$, 20%).

Benzyl 2,3-*O*-isopropylidene-α,β-D-ribofuranoside (3.55)

To a solution of **3.54** (1.0 mmol) in toluene (5 ml) was added $(Bu_3Sn)_2O$ (1.1 mmol). The solution was refluxed for 1 h with the continuous removal of water (Dean-Stark trap). The reaction mixture was allowed to cool to room temperature and BnBr (1.1 mmol) and Bu_4NI (1.1 mmol) was added. The reaction was refluxed for an additional 4 h after which the solvent was removed *in vacuo*. Chromatography (1:1 hexane:ethyl acetate) of the residue afforded the title compound as a colourless syrup.

Yield: 0,21 g, 74%

NMR ^1H : (main isomer) δ 7,32-7,28 (5H, m, H-aromatic); 5,16 (1H, s, H-1); 4,83 (1H, d, H-3, $J_{2,3}$=6,0 Hz); 4,73 (1H, d, C$\underline{H}_2$Ph, *J*=11,7 Hz); 4,65 (1H, d, H-2, $J_{2,3}$=6,0 Hz); 4,52 (1H, d, C$\underline{H}_2$Ph, *J*=11,7 Hz); 4,43 (1H, m, H-4); 3,64 (2H, m, H-5a and ~O$\underline{H}$); 3,16 (1H, dd, H-5b, $J_{5a,5b}$=9,3 and $J_{5b,4}$=3,1 Hz); 1,46 (3H, s, C$\underline{H}_3$, isopropylidene); 1,29 (3H, s, C$\underline{H}_3$, isopropylidene).

NMR ^{13}C: (main isomer) δ 136,3 (C-*Ipso*-aromatic); 128,6 (C-*ortho*-aromatic); 128,2 (C-*meta*-aromatic); 128,1 (C-*para*-aromatic); 111,1 ($\underline{C}(CH_3)_2$, isopropylidene); 107,9 (C-1); 88,4 (C-3); 85,8 (C-2); 81,4 ($\underline{C}H_2Ph$); 70,1 (C-4); 63,9 (C-5); 26,2 ($\underline{C}H_3$, isopropylidene);.24,5 ($\underline{C}H_3$, isopropylidene).

MS: m/z 279 ($[M]^+$, 80%); 188 ($[M^+ -Bn]$, 45%); 91 ($[Bn]^+$, 100%).

5-*O*-Benzoyl-2,3-*O*-isopropylidene-D-ribofuranose (3.56)

To a solution of **3.54** (1.0 mmol) in toluene (5 ml) was added $(Bu_3Sn)_2O$ (1.1 mmol). The solution was refluxed for 1 h with the continuos removal of water (Dean-Stark trap). The reaction mixture was allowed to cool to room temperature and BzCl (1.1 mmol) was added. The reaction was stirred for an additional 30 minutes after which the solvent was removed *in vacuo*. Chromatography (1:1 hexane:ethyl acetate) of the residue afforded the title compound as white crystals.

Yield: 0,24 g, 81%

Mp: 110-112°C

NMR ^{1}H : (main isomer) δ 7,32-7,24 (5H, m, H-aromatic); 5,16 (1H, s, H-1); 4,83 (1H, d, H-3, $J_{2,3}$=6,0 Hz); 4,64 (1H, d, H-2, $J_{2,3}$=6,0 Hz); 4,44 (1H, m, H-4); 3,65 (2H, m, H-5a and ~O<u>H</u>); 3,09 (1H, dd, H-5b, $J_{5a,5b}$=10,2 and $J_{5b,4}$=4,2 Hz); 1,46 (3H, s, C<u>H</u>$_3$, isopropylidene); 1,29 (3H, s, C<u>H</u>$_3$, isopropylidene).

NMR ^{13}C: (main isomer) δ 165,1 (ester carbonyl); 136,4 (C-*Ipso*-aromatic); 128,8 (C-*ortho*-aromatic); 128,5 (C-*meta*-aromatic); 128,1 (C-*para*-aromatic); 112,1 (<u>C</u>(CH$_3$)$_2$, isopropylidene); 108,1 (C-1); 85,9 (C-3); 81,5 (C-2); 70,2 (C-4); 64,0 (C-5); 26,3 (<u>C</u>H$_3$, isopropylidene); 24,6 (<u>C</u>H$_3$, isopropylidene).

MS: m/z 293 ([M]$^+$, 20%).

1-*O*-Benzoyl-2,3-*O*-isopropylidene-D-ribofuranose (3.60)

To a solution of **3.47** (5.0 mmol) in dry pyridine (10 ml) was added BzCl (5.1 mmol). The solution was stirred at room temperature for 2 h after which TLC analysis indicated the complete formation of a product with higher R_f-value. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (10 ml), washed with water (3 x 10 ml), dried over $MgSO_4$, and concentrated to a syrup containing mostly **3.59**. The crude mixture of compound **3.59** was dissolved in ether and a 3:1 mixture (3 ml) of formic acid and ether was added. The reaction mixture was stirred at room temperature for 10 minutes after which the acid was neutralised with an aqueous NH_4Cl solution. Separation of the organic phase, drying over $MgSO_4$, and chromatography (2:1 hexane:ethyl acetate) afforded the title compound as a colourless oil.

Yield: 0,81 g, 55% (starting from **3.47**)

NMR ^{1}H : (main isomer) δ 7,96-7,91 (2H, m, H-aromatic); 7,54-7,36 (3H, m, H-aromatic); 6,45 (1H, s, H-1); 4,81 (2H, m, H-3 and H-2); 4,43 (1H, t, H-4, *J*=7,7 Hz); 3,69 (2H, d, H-5a and H-5b, *J*=7,7 Hz); 2,78 (1H, bs, ~O<u>H</u>); 1,49 (3H, s, C<u>H</u>$_3$, isopropylidene); 1,31 (3H, s, C<u>H</u>$_3$, isopropylidene).

NMR ^{13}C: (main isomer) δ 164,7 (ester carbonyl); 133,5 (C-*Ipso*-aromatic); 129,5 (C-*ortho*-aromatic); 129,2 (C-*meta*-aromatic); 128,5 (C-*para*-aromatic); 112,9

($\underline{C}(CH_3)_2$, isopropylidene); 103,1 (C-1); 88,7 (C-3); 85,5 (C-2); 81,1 (C-4); 63,4 (C-5); 26,3 ($\underline{C}H_3$, isopropylidene); 24,8 ($\underline{C}H_3$, isopropylidene).

MS: m/z 293 ($[M]^+$, 5%); 172 ($[M^+ -OBz]$, 84%).

5-*O*-Benzoyl-1-*O*-benzyl-2,3-*O*-isopropylidene-D-ribofuranose (3.61)

To a solution of **3.60** (1.0 mmol) in dry DMF (5 ml) at 0°C was added NaH (1.1 mmol, 1.1 equiv.). After the evolution of hydrogen gas had ceased (30 min.), BnBr (1.1 mmol) was slowly added and the reaction mixture allowed to warm to room temperature and stirred for 5 h. The excess NaH was then quenched with MeOH (1 ml) and Et_3N (1 ml) added to destroy the excess BnBr. After stirring for a further 1 h, the reaction was diluted with EtOAc (10 ml) and washed with water. The solvent was removed *in vacuo*, and the residue purified by chromatography (5:1 hexane: EtOAc) to afford the title compound.

Yield: 0,44 g, 88%

NMR ^1H : (main isomer) δ 8,07-8,03 (2H, m, H-aromatic); 7,54-7,30 (3H, m, H-aromatic); 7,29-7,22 (5H, m, H-aromatic); 5,21 (1H, s, H-1); 4,78 (1H, d, H-3, $J_{3,2}$=6,3 Hz); 4,69 (2H, s, $C\underline{H}_2Ph$); 4,23 (1H, m, H-4); 3,74 (2H, m, H-5a and H-5b); 1,49 (3H, s, $C\underline{H}_3$, isopropylidene); 1,32 (3H, s, $C\underline{H}_3$, isopropylidene).

NMR ^{13}C: (main isomer) δ 166,1 (ester carbonyl); seven resolved C-aromatic signals 136,8; 133,1; 129,6; 129,4; 128,3; 128,1 and 127,8; 112,6 ($\underline{C}(CH_3)_2$, isopropylidene); 107,4 (C-1); 85,4 (C-2); 84,5 (C-3); 81,9 (C-4); 69,4 ($\underline{C}H_2Ph$); 65,1 (C-5); 26,4 ($\underline{C}H_3$, isopropylidene); 24,9 ($\underline{C}H_3$, isopropylidene).

MS: m/z 293 ($[M^+$-Bn], 26%).

1-*O*-Benzoyl-2,3-*O*-isopropylidene-5-*O*-(2-oxolanyl)-D-ribofuranose (3.62)

To a solution of **3.60** (5 mmol) in methylene chloride (5 ml) at –40°C was added 2,3-dihydrofuran (10.0 mmol) and *p*-toluenesulfonic acid (0.1 mmol). The solution was stirred for 30 minutes at –40°C before being quenched with an aqueous NH_4Cl solution. Separation of the organic phase, drying over $MgSO_4$, and chromatography (8:1 hexane:ethyl acetate) afforded the title compound as a mixture of diastereoisomers.

Yield: 1,35 g, 74%

NMR ^1H : (main isomer) δ 8,04 (2H, m, H-aromatic); 7,55 (1H, m, H-aromatic); 7,39 (2H, m, H-aromatic); 6,41 (1H, d, H-1, $J_{1,2}$=4,5 Hz); 5,06 (1H, m, H-oxolanyl); 4,82 (2H, m, H-3 and H-4); 4,93 (1H, m, H-oxolanyl); 3,79 (2H, m, H-4 and H-oxolanyl); 3,66 (1H, dd, H-5a, $J_{5a,5b}$=10,2 Hz and $J_{5a,4}$=8,4 Hz); 3,43 (1H, dd, H-5b, $J_{5a,5b}$=10,2 Hz and $J_{5a,4}$=7,5 Hz); 1,87-1,73 (4H, m, H-oxolanyl); 1,51 (3H, s, $C\underline{H}_3$, isopropylidene); 1,33 (3H, s, $C\underline{H}_3$, isopropylidene).

NMR ^{13}C: (main isomer) δ 165,1 (ester carbonyl); 133,1 (C-*ipso*-aromatic); 129,7 (C-*ortho*-aromatic); 129,6 (C-*meta*-aromatic); 128,4 (C-*para*-aromatic); 113,0 ($\underline{C}(CH_3)_2$, isopropylidene); 104,3 (C-1); 103,4 (C-oxolanyl); 86,7 (C-2); 85,4 (C-3); 81,9 (C-4); 67,6 (C-oxolanyl); 66,9 (C-5); 32,2 and 26,4 (2 x C-oxolanyl); 26,3 ($\underline{C}H_3$, isopropylidene); 24,1 ($\underline{C}H_3$, isopropylidene).

MS: m/z 259 ([M^+-Bz], 6%).

2,3-*O*-Isopropylidene-5-*O*-(2-oxolanyl)-D-ribose oxime (3.64)

To a solution of **3.62** (2.0 mmol) in MeOH (10 ml) was added solid K_2CO_3 (0.05 g). The suspension was stirred at room temperature for 5 h after which it was filtered through celite to remove the solids. The solvent was removed *in vacuo* to furnish crude **3.63**. The resulting syrup was dissolved in dry pyridine (5 ml) and hydroxylamine hydrochloride (2,1 mmol) was added. The solution was allowed to stir at room temperature for *c.a.* 12 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (4:1 hexane/ethyl acetate) afforded the oxime as a colourless oil (*E:Z* mixture).

Yield: 0,37 g, 68% (starting from **3.62**)

NMR ^1H : (main isomer) δ 8,61 (1H, bs, N-O$\underline{H}$); 7,48 (1H, d, H-1, $J_{1,2}$=8,1 Hz); 5,11 (1H, m, H-oxolanyl); 4,78 (2H, m, H-3 and H-4); 4,24 (1H, m, H-oxolanyl); 3,88-3,69 (4H, m, H-4, H-oxolanyl, H-5a and H-5b); 1,94-1,71 (4H, m, H-oxolanyl); 1,55 (3H, s, $C\underline{H}_3$, isopropylidene); 1,29 (3H, s, $C\underline{H}_3$, isopropylidene).

NMR ^{13}C: (main isomer) δ 148,6 (C-1); 109,9 ($\underline{C}(CH_3)_2$, isopropylidene); 104,7 (C-oxolanyl); 75,3 (C-2); 70,7 (C-3); 68,7 (C-4); 67,4 (C-oxolanyl); 67,2 (C-5); 32,2 and 27,7 (2 x C-oxolanyl); 25,3 ($\underline{C}H_3$, isopropylidene); 23,1 ($\underline{C}H_3$, isopropylidene).

2,3-*O*-Isopropylidene-5-*O*-(2-oxolanyl)-D-ribose oxime *O*-*tert*-butyldiphenylsilyl ether (3.65)

To a solution of **3.64** (2.0 mmol) in dry pyridine (5 ml) was added *tert*-butyldiphenylsilyl chloride (2,1 mmol). The solution was allowed to stir at room temperature for *ca.* 18 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (6:1 hexane/ethyl acetate) afforded the selectively silylated oxime as a colourless oil (*E:Z* mixture).

Yield: 0,77 g, 75%

NMR ^{1}H : (main isomer) δ 7,78 (1H, d, H-1, $J_{1,2}$=7,8 Hz); 7,69-7,66 (4H, m, H-aromatic); 7,40-7,31 (6H, m, H-aromatic); 5,09 (1H, m, H-oxolanyl); 4,75 (1H, dd, H-2, $J_{2,1}$=7,8 and $J_{2,3}$=6,3 Hz); 4,06 (1H, dd, H-3; $J_{2,3}$=6,3 and $J_{3,4}$=4,2 Hz); 3,88-3,57 (4H, m, H-4, H-oxolanyl, H-5a and H-5b); 3,15 (1H, d, ~O<u>H</u>, *J*=3,3 Hz); 1,94-1,62 (4H, m, H-oxolanyl); 1,56 (3H, s, C<u>H</u>$_3$, isopropylidene); 1,32 (3H, s, C<u>H</u>$_3$, isopropylidene); 1,09 (9H, s, Si-OC(CH$_3$)$_3$).

NMR ^{13}C: (main isomer) δ 153,7 (C-1); 135,6; 133,5; 129,7; 127,6 and 127,5 (C-aromatic); 109,9 (<u>C</u>(CH$_3$)$_2$, isopropylidene); 104,6 (C-oxolanyl); 75,3 (C-2); 70,6 (C-3); 68,9 (C-4); 67,1 (C-oxolanyl); 67,0 (C-5); 32,3 and 27,7 (2 x C-oxolanyl); 26,9 (Si-C(<u>C</u>H$_3$)$_3$); 25,3 (<u>C</u>H$_3$, isopropylidene); 23,1 (<u>C</u>H$_3$, isopropylidene); 19,3 (Si-<u>C</u>(CH$_3$)$_3$).

6.9 Attempted synthesis of six-membered cyclic nitrones

General route to thiophenyl glycosides

To a solution of the peracetylated D-hexose sugar (10 mmol) in benzene (20 ml) was added thiophenol (10,5 mmol) and $BF_3.Et_2O$ (0.1 mmol). The solution was stirred at room temperature for 10 h. The reaction mixture was washed with aqueous Na_2CO_3 (3 x 10 ml), the organic phase concentrated and chromatographed (5:1 hexane:ethyl acetate) to afford the title compounds as α,β-anomeric mixtures.

Thiophenyl 2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside (3.71)

Yield: 3,43 g, 78%

NMR ^{1}H : (β-anomer) δ 7,48 (2H, m, H-aromatic); 7,31-7,24 (3H, m, H-aromatic); 5,20 (1H, t, H-3, *J*=9,3 Hz); 5,01 (1H, t, H-4, *J*=9,3 Hz); 4,94 (1H, t, H-2, *J*=9,0 Hz); 4,66 (1H, d, H-1, *J*=9,0 Hz); 4,17 (2H, m, H-6a and H-6b); 3,69 (1H, m, H-5); 2,06 (3H, s, C[O]C<u>H</u>$_3$); 2,05 (3H, s, C[O]C<u>H</u>$_3$); 1,99 (3H, s, C[O]C<u>H</u>$_3$); 1,96 (3H, s, C[O]C<u>H</u>$_3$).

NMR ^{13}C: δ 170,7; 170,2; 169,5 and 169,3 (ester carbonyl); 133,1; 131,6; 128,9 and 128,5 (C-aromatic); 85,7 (C-1); 75,7 (C-3); 73,9 (C-2); 69,8 (C-4); 68,1 (C-5); 62,1 (C-6); 20,7 and 20,5 (4 x (C[O]<u>C</u>H$_3$).

MS: m/z 440 ([M]$^+$, 35%); 331 ([M$^+$ -SPh], 78%).

Thiophenyl 2,3,4,6-tetra-*O*-acetyl-D-mannopyranoside (3.72)

Yield: 3,69 g, 84%

NMR ^{1}H : (main-anomer) δ 7,46 (2H, m, H-aromatic); 7,28-7,24 (3H, m, H-aromatic); 5,46 (2H, m, H-1 and H-3); 5,28 (2H, m, H-4 and H-2);4,51 (1H, m, H-5); 4,26 (1H, dd, H-6a, $J_{6a,6b}$=12,3 and $J_{6a,5}$=6,0 Hz); 4,05 (1H, dd, H-6b, $J_{6a,6b}$=12,3 and

$J_{6b,5}$=2,4 Hz); 2,11 (3H, s, C[O]C$\underline{H}_3$); 2,05 (3H, s, C[O]C$\underline{H}_3$); 1,99 (3H, s, C[O]C$\underline{H}_3$); 1,95 (3H, s, C[O]C$\underline{H}_3$).

NMR ^{13}C: δ 169,9; 169,8; 169,5 and 169,1 (ester carbonyl); 132,6; 132,0; 129,2 and 128,1 (C-aromatic); 85,6 (C-1); 70,8 (C-3); 69,4 (C-2); 69,1 (C-4); 68,1 (C-5); 62,3 (C-6); 20,7 and 20,5 (4 x (C[O]$\underline{C}$H$_3$).

MS: m/z 440 ([M]$^+$, 58%); 331 ([M$^+$ -SPh], 70%).

General route to thiophenol tetra-*O*-benzyl glycosides

To a solution of the thiophenyl tetra-*O*-acetyl-D-glycoside (5 mmol) in dry methanol (10 ml) was added triethylamine (1 ml). The solution was allowed to stir at room temperature for 12 h and the solvent was removed *in vacuo*. To a solution of the residue in dry DMF (10 ml) at 0°C was added NaH (22.5 mmol, 4.5 equiv.). After the evolution of hydrogen gas had ceased (30 min.), BnBr (22.5 mmol, 4.5 equiv.) was slowly added and the reaction mixture allowed to warm to room temperature and stirred for 12 h. The excess NaH was then quenched with MeOH (5 ml) and Et_3N (5 ml) added to destroy the excess BnBr. After stirring for a further 4 h, the reaction was diluted with EtOAc (20 ml) and washed with water. The solvent was removed *in vacuo*, and the residue purified by chromatography (5:1 hexane: EtOAc) to afford the title compounds as syrups.

Thiophenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (3.73)

Yield: 2,21 g, 70%

NMR ^{1}H : (main-anomer) δ 7,66-7,59 (2H, m, H-aromatic); 7,35-7,24 (23H, m, H-aromatic); 4,94-4,83 (2H, m, C$\underline{H}_2$Ph); 4,91 (1H, d, H-1, $J_{1,2}$=8,5 Hz); 4,77-4,54 (9H, m, 3 x C$\underline{H}_2$Ph, H-2, H-3 and H-4); 3,83-3,64 (3H, m, H-5, H-6a, H-6b).

NMR ^{13}C: five resolved C-aromatic signals δ 138,4; 138,3; 138,0; 133,8 and 131,9; 87,3 (C-1); 86,7; 80,7; 79,0 and 77,7 (4 x $\underline{C}$H$_2$Ph); 75,7 (C-5); 75,4 (C-2); 75,0 (C-3); 73,3 (C-4); 68,9 (C-6).

MS: m/z 633 ([M+1]$^+$, 5%); 523 ([M$^+$ -SPh], 80%); 91 ([Bn]$^+$, 100%).

Thiophenyl 2,3,4,6-tetra-*O*-benzyl-D-mannopyranoside (3.73)

Yield: 2,34 g, 74%

NMR ^{1}H : (main-anomer) δ 7,61-7,57 (2H, m, H-aromatic); 7,35-7,23 (23H, m, H-aromatic); 5,62 (1H, d, H-1, $J_{1,2}$=1,8 Hz); 4,94-4,83 (2H, m, C$\underline{H}_2$Ph); 4,92 (1H, d, C$\underline{H}_2$Ph, J=10,8 Hz); 4,71 (1H, d, C$\underline{H}_2$Ph, J=11,0 Hz); 4,63 (1H, d, C$\underline{H}_2$Ph, J=12,0 Hz); 4,60 (1H, d, C$\underline{H}_2$Ph, J=12,0 Hz); 4,51-4,43 (4H, m, C$\underline{H}_2$Ph); 4,29 (1H, m, H-5); 4,07 (1H, t, H-4, $J_{4,5}$=$J_{4,3}$=9,6 Hz); 4,00 (1H, dd, H-2, $J_{2,1}$=1,8 and $J_{2,3}$=3,0 Hz); 3,88 (1H, dd, H-3, $J_{3,4}$=9,6 and $J_{3,2}$=3,0 Hz); 3,84 (1H, dd, H-6a, $J_{6a,6b}$=11,1 and $J_{6a,5}$=5,3 Hz); 3,74 (1H, dd, H-6b, $J_{6a,6b}$=11,1 and $J_{6b,5}$=2,1 Hz).

NMR ^{13}C: seven resolved C-aromatic signals δ 138,4; 138,3; 138,1; 137,8; 134,4; 131,7 and 130,6; 85,7 (C-1); 80,1; 76,1; 75,2 and 74,9 (4 x $\underline{C}H_2Ph$); 73,7 (C-5); 73,1 (C-2); 71,4 (C-3); 71,3 (C-4); 69,1 (C-6).

MS: m/z 633 ($[M+1]^+$, 12%); 523 ($[M^+ -SPh]$, 60%); 91 ($[Bn]^+$, 100%).

General route to tetra-*O*-benzyl-D-glycopyranoses

To a solution of the thiophenyl tetra-*O*-benzyl-D-glycoside (2.5 mmol) in diethyl ether (5 ml) was added *N*-iodosuccinimide (2.8 mmol, 1,1 equiv), trifluoromethanesulfonic acid (0.25 mmol) and H_20 (2,8 mmol). The solution was allowed to stir at room temperature for 3 h. The reaction mixture was diluted with water (15 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were washed with aqueous saturated $Na_2S_2O_4$ (2 x 5 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded the crude product which was purified by chromatography (3:1 hexane:ethyl acetate).

2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (3.77)

Yield: 1,08 g, 80%

NMR ^1H : (main-anomer) δ 7,31-7,29 (20H, m, H-aromatic); 5,22 (1H, s, H-1); 4,96-4,46 (11H, m, 4 x $C\underline{H}_2Ph$, H-2, H-3 and H-4); 4,01 (1H, m, H-5); 3,76-3,53 (2H, m, H-6a and H-6b).

NMR ^{13}C: four resolved C-aromatic signals δ 138,7; 138,6; 138,4 and 138,2 (C-*ipso*-aromatic); 97,5 (C-1); 84,6; 83,1; 81,7 and 79,9 (4 x $\underline{C}H_2Ph$); 75,9 (C-5); 73,8 (C-2); 73,4 (C-3); 70,3 (C-4); 68,6 (C-6).

MS: m/z 540 ($[M]^+$, 6%); 522 ($[M^+ -H_20]$, 85%); 91 ($[Bn]^+$, 100%).

2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (3.79)

Yield: 1,01 g, 75%

NMR ^1H : (main-anomer) δ 7,30-7,28 (20H, m, H-aromatic); 5,21 (1H, d, H-1, $J_{1,2}$=1,8 Hz); 4,89 (1H, d, $C\underline{H}_2Ph$, J=10,5 Hz); 4,69 (2H, s, $C\underline{H}_2Ph$); 4,63-4,51 (5H, m, $C\underline{H}_2Ph$); 4,01 (1H, t, H-4, J=9,6 Hz); 3,74-3,61 (4H, m, H-2, H-3, H-6a and H-6b); 3,55 (1H, m, H-5).

NMR ^{13}C: four resolved C-aromatic signals δ 138,4; 138,2; 138,1 and 137,9 (C-*ipso*-aromatic); 93,3 (C-1); 80,1; 76,3; 76,2 and 75,9 (4 x $\underline{C}H_2Ph$); 75,8 (C-5); 73,9 (C-2); 72,5 (C-3); 72,0 (C-4); 68,9 (C-6).

MS: m/z 540 ($[M]^+$, 20%); 522 ($[M^+ -H_20]$, 90%); 91 ($[Bn]^+$, 100%).

General route to 2,3,4,6-tetra-*O*-benzyl-D-glyco oxime O-tert-butyldiphenylsilyl ethers

To a solution of the protected hemiacetal (2.0 mmol) in dry pyridine (5 ml) was added hydroxylamine hydrochloride (2,1 mmol). The solution was allowed to stir at room temperature for *c.a.* 12 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent afforded the crude oxime as a colourless oil. To a solution of the crude D-glyco oxime ether in dry pyridine (5 ml) was added *tert*-butyldiphenylsilyl chloride (2,1 mmol). The solution was allowed to stir at room temperature for *ca.* 18 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (10:1 hexane/ethyl acetate) afforded the selectively silylated oximes as
colourless oils (*E*,*Z* mixtures).

2,3,4,6-tetra-*O*-benzyl-D-glucose oxime *O-tert*-butyldiphenylsilyl ether (3.80)

Yield: 1,17 g, 74% (starting from **3.77**)

IR: ν_{max} 1680 (C=N) cm^{-1}

NMR ^1H : (main-anomer) δ 7,73 (1H, d, H-1, $J_{1,2}$=8,0 Hz); 7,70-7,62 (2H, m, H-aromatic); 7,34-7,28 (28H, m, H-aromatic); 4,72 (9H, m, 4 x C$\underline{H}_2$Ph, H-2); 3,92-3,86 (3H, m, H-3; H-4 and H-5); 3,52 (2H, d, H-6a and H-6b, *J*=4,5 Hz); 2,62 (1H, d, ~O$\underline{H}$, *J*=3,5 Hz); 1,08 (9H, s, Si-C(C$\underline{H}_3$)$_3$).

NMR ^{13}C: δ 154,5 (C-1); seven resolved C-aromatic signals 138,0; 137,8; 137,5; 137,0; 135,6; 135,5 and 133,1; 80,1; 78,4; 78,2 and 74,9 (4 x $\underline{C}H_2$Ph); 74,8 (C-5); 73,9 (C-2); 71,4 (C-3); 71,1 (C-4); 68,9 (C-6); 26,9 (Si-C($\underline{C}H_3$)$_3$); 19,1 (Si-$\underline{C}$(CH$_3$)$_3$).

MS: m/z 793 ([M]$^+$, 2%); 91 ([Bn]$^+$, 100%).

2,3,4,6-tetra-*O*-benzyl-D-mannose oxime *O-tert*-butyldiphenylsilyl ether (3.82)

Yield: 1,14 g, 72% (starting from **3.79**)

IR: ν_{max} 1680 (C=N) cm^{-1}

NMR ^1H : (main-anomer) δ 7,75-7,61 (3H, m, H-aromatic and H-1); 7,34-7,23 (28H, m, H-aromatic); 4,79-4,41 (9H, m, 4 x C$\underline{H}_2$Ph, H-2); 4,11 (1H, dd, H-3, $J_{3,2}$=3,0 and $J_{3,2}$=6,91 Hz); 4,00 (1H, m, H-5); 3,77 (1H, dd, H-4, $J_{4,5}$=7,8 and $J_{3,4}$=3,0 Hz); 3,64 (1H, dd, H-6a, $J_{6a,6b}$=10,5 and $J_{6a,5}$=2,8 Hz); 3,57 (1H, dd, H-6b, $J_{6a,6b}$=10,5 and $J_{6a,5}$=5,1 Hz); 2,62 (1H, d, ~O$\underline{H}$, *J*=5,7 Hz); 1,15 (9H, s, Si-C(C$\underline{H}_3$)$_3$).

NMR ^{13}C: δ 154,9 (C-1); seven resolved C-aromatic signals 138,1; 137,9; 137,8; 137,5; 135,6; 135,3 and 133,0; 78,8; 78,4; 78,1 and 75,8 (4 x $\underline{C}H_2$Ph); 74,2 (C-5); 72,1 (C-2); 71,4 (C-3); 70,6 (C-4); 69,5 (C-6); 26,9 (Si-C($\underline{C}H_3$)$_3$); 19,1 (Si-$\underline{C}$(CH$_3$)$_3$).

MS: No discernible fragmentation pattern

General route towards 2,3,4,6-tetra-*O*-benzyl-5-iodo-D-glycose oxime O-*tert*-butyldiphenylsilyl ethers

To a solution of the silylated oxime (1.0 mmol) in dry toluene (6 ml) was added PPh_3 (1,1 mmol), imidazole (2,2 mmol) and iodine (1,1 mmol). The dark solution was heated to 70°C, and stirred vigorously for 1 h, during which time the solution turned clear. The reaction mixture was allowed to cool to room temperature, after which saturated aqueous $NaHCO_3$ (5 ml) was added and the solution stirred for an additional 10 min. Iodine was carefully added until the brown colour lingered, after which the mixture was washed with saturated aqueous $Na_2S_2O_3$ until the solution became clear, followed by water (3 x 5 ml) and brine (3 x 5 ml). Removal of the solvent followed by chromatography (10:1 hexane:ethyl acetate) afforded the title compounds as yellow syrups.

2,3,4,6-tetra-*O*-benzyl-5-iodo-L-idose oxime *O-tert*-butyldiphenylsilyl ether (3.81)

Yield: 0,73 g, 81%

IR: ν_{max} 1688 (C=N) cm^{-1}

NMR ^1H : (main-anomer) δ 7,79 (1H, d, H-1, $J_{1,2}$=8,1 Hz); 7,69-7,62 (2H, m, H-aromatic); 7,36-7,28 (28H, m, H-aromatic); 4,72-3,81 (11H, m, 4 x C$\underline{H}_2$Ph, H-2, 3H, H-4); 4,00 (1H, m, H-5); 3,70 (2H, d, H-6a and H-6b, *J*=6,3 Hz); 1,08 (9H, s, Si-C(C$\underline{H}_3$)$_3$).

NMR ^{13}C: δ 154,1 (C-1); seven resolved C-aromatic signals 138,8; 138,5; 137,9; 137,8; 135,7; 135,5 and 133,4; 81,3; 79,7; 78,2 and 75,5 (4 x $\underline{C}H_2$Ph); 72,4 (C-2); 72,1 (C-3); 68,4 (C-4); 68,3 (C-6); 26,9 (Si-C($\underline{C}H_3$)$_3$); 26,4 (C-5); 19,2 (Si-$\underline{C}$(CH$_3$)$_3$).

MS: No discernible fragmentation pattern. Dominant peak m/z 91 ([Bn]$^+$, 100%).

2,3,4,6-tetra-*O*-benzyl-5-iodo-L-gulose oxime *O-tert*-butyldiphenylsilyl ether (3.83)

Yield: 0,70 g, 79%

IR: ν_{max} 1680 (C=N) cm^{-1}

NMR ^1H : (main-anomer) δ 7,81 (1H, d, H-1, $J_{1,2}$=7,8 Hz); 7,71-7,62 (2H, m, H-aromatic); 7,30-7,18 (28H, m, H-aromatic); 4,70-4,26 (11H, m, 4 x C$\underline{H}_2$Ph, H-2, 3H, H-5); 4,01 (1H, dd, H-4, *J*=3,3 and 1,2 Hz); 3,78 (2H, m, H-6a and H-6b); 1,16 (9H, s, Si-C(C$\underline{H}_3$)$_3$).

NMR ^{13}C: δ 155,9 (C-1); seven resolved C-aromatic signals 138,2; 138,1; 137,6; 137,4; 135,5; 135,2 and 133,2; 85,1; 82,4; 80,7 and 78,5 (4 x $\underline{C}H_2$Ph); 72,4 (C-2); 72,2 (C-3); 68,9 (C-4); 68,3 (C-6); 27,1 (Si-C($\underline{C}H_3$)$_3$); 26,9 (C-5); 19,2 (Si-$\underline{C}$(CH$_3$)$_3$).

MS: No discernible fragmentation pattern. Dominant peak m/z 91 ([Bn]$^+$, 100%).

General route towards formyl 2,3,5-tri-*O*-benzyl-D-glycofuranoside oximes

To a solution of the iodo oxime (0.5 mmol) in benzene (2 ml) was added anhydrous TBAF (0,17 ml of a 3 M solution in benzene). The reaction mixture was stirred at 60°C for 30 minutes. Removal of the solvent under reduced pressure and chromatography (1:2 hexane:ethyl acetate) of the residue afforded the title compounds as colourless oils (*E,Z*-mixtures).

1-*C*-Formyl 2,3,5-tri-*O*-benzyl-α-D-glucofuranoside oxime (3.84)

Yield: 0,14 g, 66%

IR: ν_{max} 1675 (C=N) cm^{-1}

NMR ^1H: (C_6D_6):(main-anomer) δ 7,84 (1H, d, oxime proton, *J*=4,2 Hz); 7,39-7,23 (15H, m, H-aromatic); 5,05 (1H, dd, H-1, *J*=4,2 and $J_{2,1}$=2,5 Hz); 4,66 (1H, m, H-4); 4,44-4.13 (6H, m, 3 x C$\underline{H}_2$Ph); 3,95 (1H, dd, H-2, $J_{3,2}$=1,8 and $J_{2,1}$=2,5 Hz); 3,78 (1H, dd, H-3, $J_{2,3}$=1,8 and $J_{4,3}$=5,5 Hz); 3,68 (2H, m, H-5a and H-5b).

NMR ^{13}C: δ 149,4 (C=N); nine resolved C-aromatic signals 138,1; 137,6; 137,4; 128,6; 128,5; 128,4; 128,3; 127,8 and 127,4; 83,2; 81,8 and 81,4 (3 x $\underline{C}H_2$Ph); 79,7; 77,7; 73,5; 72,3; (C-1, C-2, C-3, and C-4); 68,2 (C-5).

MS: m/z 447 ([M]+, 40%); 430 ([M^+ -OH], 45%); 91 ([Bn]$^+$, 100%).

1-*C*-Formyl 2,3,5-tri-*O*-benzyl-α-D-mannofuranoside oxime (3.85)

Yield: 0,13 g, 60%

IR: ν_{max} 1670 (C=N) cm^{-1}

NMR ^1H: (C_6D_6):(main-anomer) δ 7,47 (1H, d, oxime proton, *J*=7,2 Hz); 7,31-7,23 (15H, m, H-aromatic); 5,20 (1H, dd, H-1, J_1=7,2 and $J_{2,1}$=5,7 Hz); 4,68-4.33 (7H, m, 3 x C$\underline{H}_2$Ph and H-4); 4,05 (1H, dd, H-2, $J_{3,2}$=2,8 and $J_{2,1}$=5,7 Hz); 3,78-3,62 (3H, m, H-3, H-5a and H-5b).

NMR ^{13}C: δ 150,5 (C=N); nine resolved C-aromatic signals 138,1; 138,0; 137,8; 128,9; 128,6; 128,4; 128,3; 127,9 and 127,5; 82,2; 81,2 and 81,1 (3 x $\underline{C}H_2$Ph); 80,1; 77,6; 74,9; 72,3; (C-1, C-2, C-3, and C-4); 68,2 (C-5).

MS: m/z 447 ([M]+, 10%); 430 ([M^+ -OH], 55%); 91 ([Bn]$^+$, 100%).

1-*C*-Cyano (1*R*,2*R*,3*S*,4*R*) 2,3,5-tri-*O*-benzyl-α-D-glucofuranoside (3.87)

To a solution of **3.84** (1.0 mmol) in a mixture of methylene chloride (2 ml) and dry pyridine (2 ml) was added TsCl (1.1 mmol). The solution was stirred at room temperature for 1 h. Removal of the solvent *in vacuo* and chromatography (8:1 hexane:ethyl acetate) afforded the title compound as a colourless oil.

Yield: 0,29 g, 81%

$[\alpha]_D^{24}$: +30,8° (*c*=2,0)

IR: ν_{max} 2240 (nitrile) cm^{-1}

NMR ^1H: δ 7,33-7,23 (15H, m, H-aromatic); 4,83 (1H, d, H-1, $J_{2,1}$=4,8 Hz); 4,59-4.38 (7H, m, 3 x $C\underline{H}_2Ph$ and H-5); 4,11 (1H, dd, H-3, $J_{3,4}$=2,3 and $J_{2,3}$=4,8 Hz); 4,04 (1H, dd, H-4, $J_{3,4}$=2,3 and $J_{4,5}$=4,1 Hz); 3,67 (1H, dd, H-6'a, $J_{6a,6b}$=10,1 and $J_{6a,5}$=5,1 Hz); 3,65 (1H, dd, H-6'b, $J_{6a,6b}$=10,1 and $J_{6b,5}$=3,5 Hz).

NMR ^{13}C: nine resolved C-aromatic signals δ 137,1; 137,0; 136,8; 128,9; 128,6; 128,4; 128,3; 127,9 and 127,8; 115,8 (C-1); 81,2; 81,0 and 80,9 (3 x $\underline{C}H_2Ph$); 73,1; 72,9; 72,6; 69,8; (C-2, C-3, C-4, and C-5); 67,4 (C-6).

MS: m/z 429 ([M]+$^+$, 80%); 338 ([M+$^+$ -Bn], 50%); 91 ([Bn]$^+$, 100%).

1-*C*-(Hydroxyamino)methyl (1*R*,2*R*,3*S*,4*R*)-2,3,5-tri-*O*-benzyl-α-D-glucofuranoside (3.88)

To a solution of **3.85** (1.0 mmol) in TFA (1 ml) was added $HSiMe_2Ph$ (2.3 mmol). The solution was stirred at room temperature for 30 minutes. Removal of the solvent *in vacuo* and chromatography (1:1 hexane:ethyl acetate) afforded the title compound as a colourless oil.

Yield: 0,26 g, 64%

NMR ^1H: δ 10,3 (1H, bs, N-O$\underline{H}$); 7,35-7,28 (15H, m, H-aromatic); 4,55-4,42 (8H, m, $C\underline{H}_2Ph$, H-1, H-3); 4,30 (1H, m, H-4); 3,67 (1H, dd, H-5a, $J_{5a,5b}$=10,5 and $J_{5a,4}$=5,1 Hz); 3,65 (1H, dd, H-5b, $J_{5a,5b}$=10,5 and $J_{5b,4}$=4,1 Hz); 3,31 (1H, dd, H-1'a, $J_{1'a,1'b}$=12,9 and $J_{1'a,2}$=7,2 Hz); 3,22 (1H, dd, H-1'b, $J_{1'a,1'b}$=12,9 and $J_{1'b,2}$=3,0 Hz);.

NMR ^{13}C: nine resolved C-aromatic signals δ 139,8; 137,1; 136,9; 128,7; 127,6; 128,4; 128,3; 127,9 and 127,8; 115,8 (C-1); 81,2; 81,0 and 80,9 (3 x $\underline{C}H_2Ph$); 73,1; 73,0; 72,6; 68,9; (C-2, C-3, C-4); 68,7 (C-5); C-1' (53,7).

MS: m/z 449 ([M]+, 40%); 91 ([Bn]$^+$, 100%).

3,4,6-Tri-*O*-benzyl-D-glucal (3.90)

To a solution of 3,4,6-tri-*O*-acetal-D-glucal (5 mmol) in dry methanol (10 ml) was added triethylamine (1 ml). The solution was allowed to stir at room temperature for 12 h and the solvent was removed *in vacuo*. To a solution of the residue in dry DMF (10 ml) at 0°C was added NaH (17.5 mmol, 3.5 equiv.). After the evolution of hydrogen gas had ceased (30 min.), BnBr (17.5 mmol, 3.5 equiv.) was slowly added and the reaction mixture allowed to warm to room temperature and stirred for 12 h. The excess NaH was then quenched with MeOH (3 ml) and Et_3N (3 ml) added to destroy the excess BnBr. After stirring for a further 4 h, the reaction was diluted with EtOAc (20 ml) and washed with water. The solvent was removed *in vacuo*, and the residue purified by chromatography (5:1 hexane: EtOAc) to afford the title compound.

Yield: 1,55 g, 74%

NMR ^{1}H : δ 7,35-7,29 (15H, m, H-aromatic); 6,41 (1H; dd; H-1; $J_{1,2}$ =6.3 and J=1.2 Hz); 4,86 (1H; dd; H-2; $J_{1,2}$ =6,3 and $J_{2,3}$ =3,0 Hz); 4,87-4,23 (6H, m, C$\underline{H}_2$Ph); 4,19 (1H, m, H-4); 4,05 (1H, m, H-3); 3,85 (1H, dd, H-6a, $J_{6a,6b}$=9,9 and $J_{6a,5}$=6,3 Hz) 3,78-3,72 (2H, m, H-6b and H-5);

NMR ^{13}C: δ 144,7 (C-1); nine resolved C-aromatic signals 138,3; 138,1; 137,9; 128,5; 128,4; 128,3; 128,2; 127,9 and 127,6; 99,9 (C-2); 76,7; 75,6 and 74,4 (3 x $\underline{C}H_2$Ph); 73,7; 73,5 and 70,4 (C-3, C-4 and C-5); 68,5 (C-6).

MS: m/z 325 ([M-CH_2Ph]$^+$, 10%); 91 ([CH_2Ph]$^+$, 100%).

2-Deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranose (3.91)

To a solution of the *O*-protected-D-glucal **3.90** (1 mmol) in CH_2Cl_2 (5 ml) was added, triphenylphosphine hydrobromide (0.1 mmol, 0.1 equiv.) and AcOH (5 mmol), and the solution heated to reflux for 3 h. The reaction mixture was allowed to cool to room temperature and quenched with saturated aqueous $NaHCO_3$ (5 ml), extracted with EtOAc (3x5 ml) and washed with water (3x5 ml). The combined extracts were dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The residue was redissolved in dry methanol (10 ml) and triethylamine (1 ml) was added. The solution was allowed to stir at room temperature for 10 h. Removal of the solvent and chromatography (2:1 hexane:EtOAc) afforded the title compound as a colourless oil.

Yield: 0,44 g, 92%

NMR ^{1}H : (main isomer) δ 7,32-7,23 (15H, m, H-aromatic); 6,23 (1H, dd, H-1, $J_{1,2a}$=5,4 and $J_{1,2b}$=2,7 Hz); 4,95 (4H, m, C$\underline{H}_2$Ph); 4,61 (2H, s, C$\underline{H}_2$Ph); 4,49 (1H, dd, H-4, $J_{4,3}$=4,1 and $J_{4,5}$=1,4 Hz); 4,22 (1H, m, H-3); 4,10 (1H, dd, H-6a, $J_{6a,6b}$=11,2 and $J_{6a,5}$=6,1 Hz) 3,97 (1H, m, H-6b, $J_{6a,6b}$=11,2 and $J_{6a,5}$=2,6 Hz); 3.71 (1H, m, H-5); 2,45-2,41 (2H, m, H-2a and H-2b).

NMR ^{13}C: (main isomer) nine resolved C-aromatic signals δ 138,4; 138,2; 138,0; 128,7; 128,6; 128,4; 128,2; 127,9 and 127,8; 90,7 (C-1); 74,4; 74,2 and 73,4 (3 x $\underline{C}H_2$Ph); 73,1; 72,8 and 72,5 (C-3, C-4 and C-5); 69,9 (C-6); 34,2 (C-2).

MS: m/z 417 ([M-OH]$^+$, 2%); 343 ([M-CH_2Ph]$^+$, 12%); 91 ([CH_2Ph]$^+$, 100%).

2-Deoxy-3,4,6-tri-*O*-benzyl-D-glucose oxime *O-tert*-butyldiphenylsilyl ether (3.92)

To a solution of the D-glyco oxime ether (2.0 mmol) in dry pyridine (5 ml) was added *tert*-butyldiphenylsilyl chloride (1,1 mmol). The solution was allowed to stir at room temperature for *ca*. 18 h after which the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10 ml) and washed with aqueous $NaHCO_3$ (3 X 10 ml), water (3 x 10 ml) and dried over $MgSO_4$. Removal of the solvent followed by chromatography (6:1 hexane/ethyl acetate) afforded the selectively silylated oximes as a colourless oil (*E*:*Z* mixture).

Yield: 1,11 g, 70%

NMR ^{1}H : (main isomer) δ 7,32-7,23 (25H, m, H-aromatic); 7,05 (1H, t, H-1, $J_{1,2}$ =8,1 Hz); 6,23 (1H, dd, H-1, $J_{1,2a}$=5,4 and $J_{1,2b}$=2,7 Hz); 4,95 (4H, m, C$\underline{H}_2$Ph); 4,55 (2H, s, C$\underline{H}_2$Ph); 4,49 (1H, dd, H-4, $J_{4,3}$=4,1 and $J_{4,5}$=1,4 Hz); 4,22 (1H, m, H-3); 4,10 (1H, dd, H-6a, $J_{6a,6b}$=10,2 and $J_{6a,5}$=6,9 Hz) 3,97 (1H, m, H-6b, $J_{6a,6b}$=10,2 and $J_{6a,5}$=3,1 Hz); 3.66 (1H, m, H-5); 2,45-2,43 (2H, m, H-2a and H-2b); 1,15 (9H, s, Si-C(C$\underline{H}_3$)$_3$).

NMR ^{13}C: (main isomer) δ 155,1 (C-1); ten resolved C-aromatic signals 138,3; 137,8; 137,5; 128,7; 128,6; 128,4; 128,3; 128,2; 127,9 and 127,8; 75,8; 74,8 and 73,1 (3 x $\underline{C}$H$_2$Ph); 72,7; 72,5 and 72,1 (C-3, C-4 and C-5); 67,5 (C-6); 30,2 (C-2); 26,4 (Si-C($\underline{C}$H$_3$)$_3$); 19,1 (Si-$\underline{C}$(CH$_3$)$_3$).

MS: No discernible fragmentation pattern

6.10 Reactions of D-ribose derived nitrones

(2*S*,3*R*,4*S*,5*R*,6*R*,7a*S*) 4,5-Dibenzyloxy-6-benzyloxymethyl-2-methyl-hexahydropyrrolo-[1,2-*b*]-isoxazole-3,2'-carbolactone (4.3)

To a solution of **4.1** (1.0 mmol) in dry benzene (1,5 ml) was added 2(*5H*)-furanone (3 mmol). The solution was stirred at 65°C for 2 h after which the solvent was removed *in vacuo*. The residue was purified by flash chromatography (3:1 hexane/ethyl acetate) to afford the title compound as fine white crystals.

Yield: 0,46 g, 92% (total cycloadduct yield)

Mp: 63-64°C

IR: ν_{max} 1755 (C=0) cm^{-1}

$[\alpha]_D^{24}$: +0,58° (*c*=2,4)

NMR ^{1}H : δ 7,34-7,27 (15H, m, H-benzyl-aromatic); 4,87 (1H, dt, H-2, $J_{2,2'a/b}$=2,0 Hz and $J_{2,3}$=5,7 Hz), 4,68 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,67 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,62 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,57 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,53 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,50 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,34 (2H, d, H-2'a and H-2'b, $J_{2',2}$=2,1 Hz); 4,23 (1H, dd, H-7a, $J_{7a,4}$=6,3 Hz and $J_{7a,3}$=2,4 Hz); 4,11 (1H, dd, H-4, $J_{4,7a}$=6,3 Hz and $J_{4,5}$=4,5 Hz); 3,94 (1H, dd, H-3, $J_{3,2}$=6,0 Hz and $J_{3,7a}$=2,4 Hz); 3,85 (1H, m, H-5); 3,54 (1H, m, H-6); 3,46-3,43 (2H, m, H-6'a and H-6'b).

NMR ^{13}C : δ 177,5 (lactone carbonyl); 137,9; 137,7; and 137,5 (C-i-aromatic); 128,5; 128,4 and 128,3 (C-*o*-aromatic); 127,8 and 127,7 (C-aromatic); 78,6 (C-2); 78,3 (C-5); 76,7 (C-4); 73,4; 72,7 and 72,5 ($\underline{C}$H$_2$Ph); 71,1 (C-6); 70,7 (C-7a); 69,9 (C-6'); 69,7 (C-2'); 50,6 (C-3).

MS: m/z 501 ([M]$^+$, 20%); 410 ([M$^+$ -Bn], 65%); 91 ([Bn]$^+$, 100%).

Dimethyl (2*S*,3*R*,4*S*,5*R*,6*R*,7a*S*)-4,5-dibenzyloxy-6-benzyloxymethyl-hexahydropyrrolo-[1,2-*b*]isoxazole-2,3-dicarboxylate (4.4)

To a solution of **4.1** (1.0 mmol) in dry benzene (1,5 ml) was added dimethyl maleate (3.0 mmol). The solution was stirred at 65°C for 2 h after which the solvent was removed *in vacuo*. The residue was purified by flash chromatography (3:1 hexane/ethyl acetate) to afford the title compound as a colourless oil.

Yield: 0,52 g, 92% (total cycloadduct yield)

IR: ν_{max} 1750 (C=0) cm^{-1}

$[\alpha]_D^{24}$: +12,58° (*c*=2,0)

NMR ^1H : δ 7,34-7,23 (15H, m, H-aromatic); 4,76 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,71 (1H, d, H-2, $J_{2,3}$=5,1 Hz), 4,61 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,59 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,57 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,50 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,39 (1H, dd, H-7a, $J_{7a,3}$=6,9 Hz and $J_{7a,4}$=1,5 Hz); 4,34 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,34 (1H, dd, H-3, $J_{3,7a}$=6,9 Hz and $J_{3,2}$= 5,1 Hz); 3,84 (1H, dd, H-5, $J_{5,4}$=4,8 Hz and $J_{5,6}$=8,4 Hz); 3,79 (2H, m, H-6'a and H-6), 3,74 (3H, s, OC$\underline{H}_3$); 3,73 (3H, s, OC$\underline{H}_3$); 3,67 (1H, dd, H-4, $J_{4,7a}$=1,5 Hz and $J_{4,5}$=4,8 Hz); 3,09 (1H, dd, H-6'b, $J_{6'a,6'b}$=10,1 Hz and $J_{6'b,6}$=2,3 Hz).

NMR ^{13}C : δ 169,6 and 169,2 (ester carbonyl); ten resolved C-aromatic signals 138,6; 137,7; 137,6; 128,4; 128,3; 128,2; 127,9; 127,8; 127,6 and 127,4; 79,4 (C-2); 77,8 (C-4); 76,7 (C-5); 72,9; 72,2 and 70,8 (C$\underline{H}_2$Ph); 70,2 (C-6); 68,3 (C-7a); 66,6 (C-6'); 54,6 (C-3); 52,5 (OC$\underline{H}_3$); 52,4 (OC$\underline{H}_3$).

MS: m/z 561 ([M]$^+$, 5%); 530 ([M$^+$ -OCH_3], 70%); 91 ([Bn]$^+$, 100%).

***N*-Benzyl-(2*S*,3*R*,4*S*,5*R*,6*R*,7a*S* 4,5-isopropylidenedioxy-6-trityloxymethyl-hexahydropyrrolo[1,2-*b*]isoxazole-2,3-dicarboximide (4.5)**

To a solution of **4.2** (1.0 mmol) in dry benzene (1,5 ml) was added *N*-benzylmaleimide (2.0 mmol). The solution was stirred at 65°C for 2 h after which the solvent was removed *in vacuo*. The residue was purified by flash chromatography (3:1 hexane/ethyl acetate) to afford the title compound as a colourless oil.

Yield: 0,49 g, 80% (main cycloadduct yield)

IR: ν_{max} 1755 (C=0) cm^{-1}

$[\alpha]_D^{24}$: +6,48° (*c*=1,0)

NMR ^1H : δ 7,36-7,20 (20H, m, H-aromatic); 4,81 (1H, t, H-3, $J_{2,3}$=$J_{3,7a}$=5,1 Hz), 4,73 (2H, s, N-C$\underline{H}_2$Ph); 4,69 (1H, d, H-7a, $J_{7a,3}$=5,1 Hz); 4,18 (1H, d, H-2, $J_{2,3}$=5,1 Hz); 3,95 (1H, d, H-4, $J_{4,5}$=7,5 Hz); 3,91 (2H, m, H-5 and H-6); 3,24 (1H, dd, H-6'a, $J_{6'a,6'b}$=9,9 Hz and $J_{6'b,6}$=4,2 Hz); 3,14 (1H, dd, H-6'a, $J_{6'a,6'b}$=9,9 Hz and $J_{6'b,6}$=4,2 Hz); 1,41 (3H, s, isopropylidene C$\underline{H}_3$); 1,25 (3H, s, isopropylidene C$\underline{H}_3$).

NMR ^{13}C : δ 175,8 and 175,1 (amide carbonyl); six resolved C-aromatic signals 143,3; 135,3; 128,7; 128,5; 127,9 and 127,2; 113,1 ($\underline{C}(CH_3)_2$ isopropylidene); 87,5 ($\underline{C}(Ph)_3$ trityl); 85,9 (C-2); 82,8 (C-4); 75,7; 72,8 and 71,5 (C-5; C-6 and C-7a); 63,5 (C-6'); 50,2 (N-$\underline{C}H_2Ph$); 42,5 (C-3); 26,3 and 24,0 (2 x isopropylidene $\underline{C}H_3$).

MS: m/z 615 ($[M]^+$, 25%); 373 ($[M^+ -Tr]$, 5%); 342 ($[M^+-OTr]$, 50%).

_N_-Benzyl-(2_S_,3_R_,4_S_,5_R_,6_R_,7a_S_)-4,5-dibenzyloxy-6-benzyloxymethyl-hexahydropyrrolo-[1,2-_b_]isoxazole-2,3-dicarboximide (4.8)

To a solution of **4.1** (1.0 mmol) in dry benzene (1,5 ml) was added *N*-benzylmaleimide (2.0 mmol). The solution was stirred at 65°C for 2 h after which the solvent was removed *in vacuo*. The residue was purified by flash chromatography (3:1 hexane/ethyl acetate) to afford the title compound as a colourless oil.

Yield: 0,53 g, 90% (total cycloadduct yield)

IR: ν_{max} 1640 (C=0) cm^{-1}

$[\alpha]_D^{24}$: +3,22° (*c*=1,5)

NMR ^1H : δ 7,35-7,26 (15H, m, H-aromatic); 4,85 (1H, d, H-2, $J_{2,3}$=7,2 Hz); 4,76 (1H, d, $C\underline{H}_2Ph$ *J*=11,7 Hz); 4,65 (1H, d, $C\underline{H}_2Ph$ *J*=11,7 Hz); 4,64 (2H, s, N-$C\underline{H}_2Ph$); 4,60 (1H, d, $C\underline{H}_2Ph$ *J*=11,7 Hz); 4,57 (1H, d, $C\underline{H}_2Ph$ *J*=11,7 Hz); 4,48 (1H, d, $C\underline{H}_2Ph$ *J*=11,7 Hz); 4,44 (1H, d, $C\underline{H}_2Ph$); 4,17 (1H, dd, H-3, $J_{2,3}$=7,2 Hz and $J_{3,7a}$=2,1 Hz); 4,11 (2H, m, H-4 and H-5); 3,97 (1H, t, H-7a, $J_{3,7a}=J_{7a,4}$=2,1 Hz); 3,56 (1H, m, H-6); 3,50-3,47 (2H, m, H-6'a and H-6).

NMR ^{13}C : δ 176,1 and 172,5 (carbonyl); 137,8; 137,5; and 137,4 (C-i-aromatic); 135,1 (C-i-aromatic); 128,7; 128,5; 128,4 and 128,2 (C-*o*-aromatic); 127,9; 127,8; 127,7 and 127,5 (C-aromatic); 79,5 (C-2); 77,4 (C-4); 77,2 (C-5); 73,3; 72,8 and 72,6 ($\underline{C}H_2Ph$); 71,8 (C-7a); 70,0 (C-6); 69,7 (C-6'); 51,4 (C-3); 42,4 (N-$\underline{C}H_2Ph$).

MS: m/z 590 ($[M]^+$, 3%); 499 ($[M^+ -Bn]$, 20%); 91 ($[Bn]^+$, 100%).

1-Benzyl-3-[(2_S_,3_R_,4_S_,5_R_)-3,4-dibenzyloxy-5-benzyloxymethyl-1-hydroxy-2-pyrrolidinyl]-succinimide (4.11)

Compound **4.8** (0.5 mmol) was dissolved in degassed THF (5 ml) and the solvent removed by vacuum distillation to ensure an oxygen-free system. The residue was dissolved in THF (5 ml) and this solution was slowly added to a solution of freshly prepared SmI_2 in THF (1.1 mmol; 11 ml of a 0.1M solution) and deoxygenated water (0,05 ml). The solution was stirred at room temperature for 0.5 h after which it was diluted with ethyl acetate (10 ml) and filtered through a pad of celite to remove the precipitated Sm(III) salts. The solvent was removed *in vacuo* and

the residue purified by flash chromatography (5:1 hexane/ethyl acetate) to afford the title compound as a colourless oil.

Yield: 0,23 g, 76%

$[\alpha]_D^{24}$: +20,1° (*c*=1,0)

NMR ^{1}H : δ 7,30-7,26 (20H, m, H-aromatic); 4,84 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,76 (1H, d, C$\underline{H}_2$Ph, *J*=11,7 Hz); 4,62 (1H, d, C$\underline{H}_2$Ph *J*=11,4 Hz); 4,57 (2H, s, N-C$\underline{H}_2$Ph); 4,52 (1H, d, C$\underline{H}_2$Ph *J*=11,4 Hz); 4,48 (1H, d, C$\underline{H}_2$Ph *J*=11,4 Hz); 4,42 (1H, d, C$\underline{H}_2$Ph *J*=11,4 Hz); 4,38 (1H, d, C$\underline{H}_2$Ph, *J*=11,4 Hz); 4,13 (1H, dd, H-3', $J_{2',3'}$=5,7 Hz and $J_{3',4'}$=4,2 Hz); 3,94 (1H, dd, H-2', $J_{2',3}$=5,7 Hz and $J_{2',3}$=3,0 Hz); 3,84 (1H, dd, H-4', $J_{4',3}$=4,2 Hz and $J_{5',4'}$=8,1 Hz); 3,52 (1H, dd, H-6'a, $J_{6'a,6'b}$=9,7 Hz and $J_{6'a,5'}$=3,3 Hz); 3,47 (1H, dd, H-6'b, $J_{6'a,6'b}$=9,7 Hz and $J_{6'b,5'}$=3,5 Hz); 3,29 (1H, m, H-5'); 2,96 (1H, dd, H-4a, $J_{4a,4b}$=18,0 Hz and $J_{4a,3}$=4,5 Hz); 2,91 (1H, m, H-3); 2,62 (1H, dd, H-4b, $J_{4a,4b}$=18,0 Hz and $J_{4b,3}$=8,4 Hz).

NMR ^{13}C : δ 180,0 and 178,1 (amide carbonyls); ten resolved C-aromatic signals 138,4; 138,0; 137,9; 136,1; 128,6; 128,5; 128,4; 127,8; 127,7 and 127,7; 80,9 (C-4'); 78,8 (C-3'); 73,6; 73,2 and 72,8 (C$\underline{H}_2$Ph); 68,3 (C-5'); 60,4 (C-6'); 58,1 (C-2'); 42,6 (C-3); 42,1 (N-C$\underline{H}_2$Ph); 31,6 (C-4).

MS: (FAB) m/z 606 ([M]$^+$, 80%).

(2*R*,3*R*,4*S*,5*R*)-3,4-Dibenzyloxy-2-benzyloxymethyl-*N*-hydroxy-2-methylpyrrolidine (4.14)

To a solution of **4.1** (0.5 mmol) in dry THF (2 ml) at 0°C was added freshly prepared CH_3MgI (0.8 mmol, 0,27 ml of a ~3 M solution in diethyl ether). The solution was stirred at 0°C for 10 minutes and then quenched with excess water (2 ml). The reaction mixture was extracted with diethyl ether (3 x 10 ml), the combined extracts dried over $MgSO_4$,and concentrated under reduced pressure. Chromatography (2:1 hexane:ethyl acetate) of the residue furnished the title compound as white crystals.

Yield: 0,18 g, 83%

Mp: 121-123°C

$[\alpha]_D^{24}$: +10,8° (*c*=1,1)

NMR ^{1}H : δ 7,28-7,23 (15H, m, H-aromatic); 6,05 (1H, bs, N-O$\underline{H}$); 4,60 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,56 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,51 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,46 (1H, d, C$\underline{H}_2$Ph *J*=12,1 Hz); 4,41 (1H, d, C$\underline{H}_2$Ph *J*=12,0 Hz); 4,38 (1H, d, C$\underline{H}_2$Ph, *J*=12,1 Hz); 3,76 (1H, dd, H-5, $J_{5,4}$=4,2 Hz and $J_{5,Me}$=5,7 Hz); 3,53 (2H, m, H-2 and H-3); 3,32 (1H, dd, H-2'a, $J_{2'a,2'b}$=10,2 Hz and $J_{2'a,2}$=5,1 Hz); 3,27 (1H, dd, H-2'b, $J_{2'a,2'b}$=10,2 Hz and $J_{2'b,2}$=5,7 Hz); 3,21 (1H, m, H-5); 1,22 (3H, d, C$\underline{H}_3$, *J*=5,7 Hz).

NMR ^{13}C : eleven resolved C-aromatic signals δ 138,1; 138,0; 137,9; 128,4; 128,3; 128,2; 128,1; 127,8; 127,7; 127,6 and 127,5; 79,5 (C-3); 75,3 (C-4); 73,2; 72,8 and 71,7 ($\underline{C}H_2Ph$); 71,3 (C-2); 69,5 (C-2'); 65,7 (C-5); 16,6 ($\underline{C}H_3$).

MS: m/z 416 ([M^+ -OH], 30%); 326 ([M^+ -OBn], 68%); 91 ([Bn]$^+$, 100%).

(2*R*,3*S*,4*R*,5*R*)-3,4-Dibenzyloxy-5-benzyloxymethyl-*N*-hydroxy-2-(thiazol-2-yl)pyrrolidine (4.15)

To a solution of thiazole (1.5 mmol) in dry THF (3 ml) at –78°C was slowly added *n*-BuLi (1.5 mmol, 15% solution in THF) over a period of 5 minutes under an argon atmosphere. The solution was stirred at –78°C for 30 minutes. A solution of nitrone **4.1** (1.3 mmol) in dry THF (2 ml) was slowly added at –78°C and the reaction mixture was allowed to warm up to –30°C. The reaction was followed by TLC to completion (30 minutes) after which the reaction mixture was quenched with an excess of a saturated NH_4Cl solution. Extraction of the aqueous phase with diethyl ether (3 x 10 ml), drying of the combined extracts over anhydrous $MgSO_4$ and chromatography (4:1 hexane:ethyl acetate) furnished the title compound as a orange oil.

Yield: 0,36 g, 59%

$[\alpha]_D^{24}$: +32,5° (*c*=1,4)

NMR ^1H : δ 7,76 (1H, d, H-thiazolyl, *J*=3,3 Hz); 7,74 (1H, d, H-thiazolyl, *J*=3,3 Hz); 7,32-7,06 (15H, m, H-benzyl-aromatic); 4,68 (1H, d, H-2, $J_{2,3}$=4,5 Hz); 4,61 (1H, d, $C\underline{H}_2Ph$ *J*=12,0 Hz); 4,55 (1H, d, $C\underline{H}_2Ph$ *J*=12,0 Hz); 4,53 (1H, d, $C\underline{H}_2Ph$ *J*=12,0 Hz); 4,50 (1H, d, $C\underline{H}_2Ph$ *J*=12,0 Hz); 4,44 (1H, d, $C\underline{H}_2Ph$ *J*=12,0 Hz); 4,38 (1H, d, $C\underline{H}_2Ph$, *J*=12,0 Hz); 3,94 (1H, m, H-5); 3,92 (1H, dd, H-4, $J_{4,3}$=3,9 Hz and $J_{5,4}$=5,4 Hz); 3,86 (1H, dd, H-3, $J_{2,3}$=4,5 Hz and $J_{3,4}$=3,9 Hz); 3,66 (1H, dd, H-6a, $J_{6a,6b}$=9,6 Hz and $J_{6a,5}$=3,6 Hz); 3,61 (1H, dd, H-6b, $J_{6a,6b}$=9,6 Hz and $J_{6b,5}$=5,7 Hz).

NMR ^{13}C : δ 171,3 (C-1' thiazolyl); 141,6 (C-3' thiazolyl); thirteen resolved C-aromatic signals 138,6; 138,1; 138,0; 128,3; 128,2; 128,1; 127,6; 127,5; 127,4 and 127,3; 120,7 (C-4' thiazolyl); 85,6 (C-2); 80,7 (C-3); 73,8; 73,0 and 72,4 ($\underline{C}H_2Ph$); 72,3 (C-5); 71,8 (C-4); 60,2 (C-6).

MS: m/z 502 ([M]$^+$, 2%); 411 ([M^+ -Bn]; 36%); 91 ([Bn]$^+$, 100%).

(2*S*,3*S*,4*R*,5*R*)-3,4-Dibenzyloxy-5-benzyloxymethyl-*N*-hydroxy-2-(2-methoxyphenyl)-pyrrolidine (4.16)

To a solution of 2-bromoanisole (1.5 mmol) in dry THF (3 ml) at –78°C was slowly added *n*-BuLi (1.5 mmol, 15% solution in THF) over a period of 5 minutes under an argon atmosphere. The solution was stirred at –78°C for 30 minutes. A solution of nitrone **4.1** (1.3 mmol) in dry THF (2 ml) was slowly added at –78°C and the reaction mixture was allowed to warm up to –

30°C. The reaction was followed by TLC to completion (50 minutes) after which the reaction mixture was quenched with an excess of a saturated NH_4Cl solution. Extraction of the aqueous phase with diethyl ether (3 x 10 ml), drying of the combined extracts over anhydrous $MgSO_4$ and chromatography (4:1 hexane:ethyl acetate) furnished the title compound as white crystals.

Yield: 0,51 g, 75%

Mp: 84-85°C

$[\alpha]_D^{24}$: +5,9° (*c*=2,1)

NMR ^1H : δ 7,43-7,19 (17H, m, H-aromatic); 6,87 (2H, m, H-aromatic); 5,28 (1H, bs, N-O<u>H</u>); 4,68 (1H, d, H-2, $J_{2,3}$=4,8 Hz), 4,64 (1H, d, C<u>H</u>$_2$Ph *J*=9,3 Hz); 4,61 (1H, d, C<u>H</u>$_2$Ph *J*=9,2 Hz); 4,56 (1H, d, C<u>H</u>$_2$Ph *J*=9,3 Hz); 4,48 (1H, d, C<u>H</u>$_2$Ph *J*=10,2 Hz); 4,46 (1H, d, C<u>H</u>$_2$Ph *J*=10,2 Hz); 4,42 (1H, d, C<u>H</u>$_2$Ph, *J*=9,3 Hz); 3,90 (1H, dd, H-4, $J_{4,3}$=4,9 Hz and $J_{5,4}$=7,5 Hz); 3,83 (1H, t, H-3, $J_{3,2}$=$J_{4,3}$=4,9 Hz); 3,77 (3H, s, OC<u>H</u>$_3$); 3,76 (1H, dd, H-6a, $J_{6a,6b}$=10,2 Hz and $J_{6a,5}$=3,9 Hz); 3,66 (1H, dd, H-6b, $J_{6a,6b}$=10,2 Hz and $J_{6b,5}$=4,2 Hz); 3,60 (1H, m, H-5).

NMR ^{13}C : δ 157,5 (C-2'); thirteen resolved C-aromatic signals 138,5; 138,4; 138,2; 128,8; 128,6; 128,4; 128,3; 128,0; 127,9; 127,8; 127,6; 127,5 and 127,4; 120,6 (C-6'); 110,6 (C-5'); 80,0 (C-2) 75,3 (C-3); 73,2; 71,6 and 71,1 (<u>C</u>H$_2$Ph); 71,0 (C-5); 70,4 (C-4); 69,1 (C-6); 55,3 (O<u>C</u>H$_3$).

MS: m/z 525 ([M]$^+$, 40%); 494 ([M$^+$ -OCH$_3$], 13%); 434 ([M$^+$ -Bn], 90%); 91 ([Bn]$^+$, 100%).

(2*S*,3*S*,4*R*,5*R*)-3,4-Dibenzyloxy-5-benzyloxymethyl-*N*-hydroxy-2-(4-methoxyphenyl)-pyrrolidine (4.17)

To a solution of 4-bromoanisole (1.5 mmol) in dry THF (3 ml) at –78°C was slowly added *n*-BuLi (1.5 mmol, 15% solution in THF) over a period of 5 minutes under an argon atmosphere. The solution was stirred at –78°C for 30 minutes. A solution of nitrone **4.1** (1.3 mmol) in dry THF (2 ml) was slowly added at –78°C and the reaction mixture was allowed to warm up to –30°C. The reaction was followed by TLC to completion (30 minutes) after which the reaction mixture was quenched with an excess of a saturated NH_4Cl solution. Extraction of the aqueous phase with diethyl ether (3 x 10 ml), drying of the combined extracts over anhydrous $MgSO_4$ and chromatography (6:1 hexane:ethyl acetate) furnished the title compound as a colourless oil.

Yield: 0,49 g, 73%

$[\alpha]_D^{24}$: +17,1° (*c*=1,0)

NMR ^1H : δ 7,32-7,29 (17H, m, H-aromatic); 7,04 (1H, m, H-aromatic); 6,85 (1H, d, H-aromatic, *J*=8,7 Hz); 4,91 (1H, bs, N-O<u>H</u>); 4,62 (2H, s, C<u>H</u>$_2$Ph); 4,55 (1H, d,

$C\underline{H}_2Ph$ J=12,3 Hz); 4,54 (1H, d, $C\underline{H}_2Ph$ J=12,3 Hz); 4,35 (1H, d, $C\underline{H}_2Ph$ J=12,0 Hz); 4,29 (1H, d, $C\underline{H}_2Ph$ J=12,0 Hz); 4,21 (1H, d, H-2, $J_{2,3}$=8,7 Hz); 3,84 (1H, dd, H-4, $J_{4,3}$=3,9 Hz and $J_{5,4}$=5,7 Hz); 3,80 (3H, s, $OC\underline{H}_3$); 3,62 (1H, dd, H-6a, $J_{6a,6b}$=10,2 Hz and $J_{6a,5}$=4,8 Hz); 3,59 (1H, dd, H-3, $J_{3,2}$=8,7 Hz and $J_{4,3}$=3,9 Hz); 3,57 (1H, dd, H-6b, $J_{6a,6b}$=10,2 Hz and $J_{6b,5}$=5,1 Hz); 3,45 (1H, m, H-5).

NMR ^{13}C : δ 159,3 (C-4'); 138,3; 138,2 and 137,8 (C-*I*-aromatic); 131,8 (C-1'); 129,0 (C-5' and C-3'); six resolved C-aromatic signals 128,4; 128,3; 128,2; 128,1; 127,7 and 127,5; 113,8 (C-6' and C-2'); 80,4 (C-2) 75,6 (C-3); 73,8; 73,3 and 72,3 ($\underline{C}H_2Ph$); 71,8 (C-5); 71,4 (C-4); 69,9 (C-6); 55,3 ($O\underline{C}H_3$).

MS: m/z 525 ($[M]^+$, 14%); 434 ($[M^+ -Bn]$, 29%); 418 ($[M^+ -Bn]$, 29%); 91 ($[Bn]^+$, 100%).

(2*S*,3*S*,4*R*,5*R*)-3,4-Dibenzyloxy-5-benzyloxymethyl-*N*-hydroxy-2-di-(2-pyridyl)pyrrolidine (4.18)

To a solution of 2-bromopyridine (1.5 mmol) in dry THF (3 ml) at –78°C was slowly added *n*-BuLi (1.5 mmol, 15% solution in THF) over a period of 5 minutes under an argon atmosphere. The solution was stirred at –78°C for 30 minutes. A solution of nitrone **4.1** (1.3 mmol) in dry THF (2 ml) was slowly added at –78°C and the reaction mixture was allowed to warm up to –30°C. The reaction was followed by TLC to completion (1 h) after which the reaction mixture was quenched with an excess of a saturated NH_4Cl solution. Extraction of the aqueous phase with diethyl ether (3 x 10 ml), drying of the combined extracts over anhydrous $MgSO_4$ and chromatography (6:1 hexane:ethyl acetate) furnished the title compound as a orange oil.

Yield: 0,28 g, 38% (contaminated with ~3% of possible monoadduct)

NMR ^1H : δ 8,49 (2H, m, pyridine H-aromatic); 7,78 (1H, d, pyridine H-aromatic, J=8,1 Hz); 7,61 (1H, d, pyridine H-aromatic, J=8,0 Hz); 7,49 (2H, m, pyridine H-aromatic); 7,31-7,10 (15H, m, benzyl H-aromatic); 6,86 (2H, m, pyridine H-aromatic); 5,29 (1H, d, H-3, $J_{3,4}$=2,7 Hz); 4,67 (1H, d, $C\underline{H}_2Ph$, J=11,7 Hz); 4,62 (1H, d, $C\underline{H}_2Ph$ J=11,5 Hz); 4,49 (1H, d, $C\underline{H}_2Ph$ J=11,7 Hz); 4,47 (1H, d, $C\underline{H}_2Ph$ J=11,7 Hz); 4,43 (1H, d, $C\underline{H}_2Ph$ J=11,6 Hz); 4,40 (1H, d, $C\underline{H}_2Ph$ J=11,6 Hz); 3,83 (2H, m, H-4 and H-5); 3,54 (1H, dd, H-6a, $J_{6a,6b}$=9,3 Hz and $J_{6a,5}$=3,0 Hz); 3,42 (1H, dd, H-6b, $J_{6a,6b}$=9,3 Hz and $J_{6b,5}$=5,4 Hz).

NMR ^{13}C : δ 164,9 and 160,5; 147,8 and 147,7 (pyridine C-aromatic); 138,8; 138,4 and 136,9 (C-*ipso*-aromatic); 136,4 and 135,7 (pyridine C-aromatic); 128,2; 128,1; 127,9 and 127,7 (C-aromatic); 127,5; 127,4; 127,3 and 127,1 (C-aromatic); 123,1; 122,9; 122,0 and 121,6 (pyridine C-aromatic); 121,1 (C-2); 84,1 (C-3); 82,4 (C-4); 74,7 (C-5); 73,7; 72,8 and 72,6 ($\underline{C}H_2Ph$); 59,8 (C-6).

MS: m/z 573 ($[M]^+$, 2%); 556 ($[M^+ -OH]$, 35%); 91 ($[Bn]^+$, 90%).

(3*R*,4*S*,5*S*)-3,4-Dibenzyloxy-5-benzyloxymethyl-*N*,2-bis(ethylcarboxy)pyrrolidine (4.19)

To a solution of nitrone **4.1** (3 mmol) in propionic anhydride (3.8 ml; 30 mmol) was added concentrated H_2SO_4 (0,015 ml). The solution was stirred at 80°C for 5 h. The reaction mixture was diluted with ethyl acetate (10 ml) and the acid neutralised with an aqueous $NaHCO_3$ solution. The organic phase was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (3:1 hexane:ethyl acetate) to afford the title compound as a pale yellow oil.

Yield: 0,78 g, 48%

NMR ^{1}H : (main isomer) δ 7,30-7,26 (15H, m, H-aromatic); 6,06 (1H, d, H-2, $J_{2,3}$=3,9 Hz); 4,65-4,45 (6H, m, 3 x C$\underline{H}_2$Ph); 3,87 (2H, m, H-3 and H-4), 3,69 (1H, m, H-5); 3,58 (2H, m, H-6'a and H-6'b); 2,32 (2H, qt, C[O]C$\underline{H}_2$CH$_3$); 2,19 (2H, qt, C[O]C$\underline{H}_2$CH$_3$); 1,07 (3H, t, C[O]CH$_2$C$\underline{H}_3$, *J*=7,5 Hz); 1,02 (3H, t, C[O]CH$_2$C$\underline{H}_3$, *J*=7,2 Hz).

NMR ^{13}C : δ 173,7 and 173,2 (ester carbonyl); nine resolved C-aromatic signals 138,1; 137,5; 137,4; 128,5; 128,4; 128,3; 128,0; 127,9 and 127,6; 93,0 (C-2); 77,4 (C-3); 74,4; 73,5 and 71,8 (3 x $\underline{C}$H$_2$Ph and C-5); 69,3 (C-4); 68,1 (C-6); 27,5 and 25,7 (2 x C[O]$\underline{C}$H$_2$CH$_3$); 8,8 and 8,7 (2 x C[O]CH$_2\underline{C}$H$_3$).

MS: No discernible fragmentation pattern. Dominant peak: 108 ([Bn-OH]$^+$, 100%).

Bis-(trimethylsilyloxy)thymine (4.20)

Thymine (5.0 mmol) was suspended in excess *bis*-(trimethylsilyl)acetamide (5 ml, 20 mmol). The reaction mixture was stirred at 100°C for 15 min. upon which all the thymine dissolved. Fractional distillation of the crude reaction mixture afforded the title compound as a colourless oil.

Yield: 1,28 g, 95%

NMR ^{1}H : δ 7,89 (1H, s, H-5); 1,87 (3H, s, C$\underline{H}_3$); 0,26 (9H, s, Si(C$\underline{H}_3$)$_3$); 0,24 (9H, s, Si(CH3)3).

NMR ^{13}C : δ 167,9 (C-2); 161,6 (C-4); 158,6 (C-5); 112,4 (C-6) 11,9 (C$\underline{H}_3$); 0,019 (Si(C$\underline{H}_3$)$_3$); 0,018 (Si(C$\underline{H}_3$)$_3$).

MS: m/z 270 ([M$^+$], 75%); 255 ([M$^+$ - CH$_3$], 80%).

1-[(2*S*,3*S*,4*R*,5*R*)-3,4-Dibenzyloxy-5-benzyloxymethyl-1-ethylcarboxy-2-pyrrolidinyl]-thymine (4.21)

To a solution of **4.19** (0.5 mmol) in dry CH_2Cl_2 (1.5 ml) was added $SnCl_4$ (0.05 mmol) and *bis*-(trimethylsilyloxy)thymine (0.55 mmol). The solution was stirred at room temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (10 ml) followed by the addition of a saturated

NH_4Cl solution (5 ml). Separation of the organic phase, drying over anhydrous $MgSO_4$ and chromatography (5:1 hexane:ethyl acetate) afforded the title compound as a yellow oil.

Yield: 0,25 g, 82%

IR: ν_{max} 1716 (C=0) cm^{-1}

$[\alpha]_D^{24}$: +30,1° (*c*=1,0)

NMR ^1H : δ 7,56 (1H, s, H-6); 7,32-7,29 (15H, m, H-aromatic); 6,09 (1H, s, H-2'); 4,71-4,32 (6H, m, 3 x C$\underline{H}_2$Ph); 4,29 (3H, m, H-3; H-4 and H-5), 3,33 (2H, d, H-6'a and H-6'b, *J*=6,9 Hz); 2,27 (2H, qt, C[O]C$\underline{H}_2$CH$_3$); 1,93 (3H, s, C$\underline{H}_3$ thymine); 1,09 (3H, t, C[O]CH$_2$C$\underline{H}_3$, *J*=6,9 Hz).

NMR ^{13}C : δ 174,9 (ester carbonyl); 172,2 and 158,5 (amide carbonyl); 136,7; 135,7 and 135,2 (C-*Ipso*-aromatic); 132,7 (C-6); six resolved C-aromatic signals 128,8; 128,7; 128,6; 128,5; 128,2 and 127,9; 119,1 (C-5); 78,6 (C-3'); 76,1 (C-2'); 73,6; 72,7 and 69,1 (3 x $\underline{C}$H$_2$Ph); 68,1 (C-4' and C-5'); 64,2 (C-6'); 26,1 (C[O]$\underline{C}$H$_2$CH$_3$); 13,9 ($\underline{C}$H$_3$ thymine); 8,4 (C[O]CH$_2\underline{C}$H$_3$).

MS: (FAB) m/z 582 ([M^{+1} -H_2O], 90%); 474 ([M^{+1} - thymine], 20%).

6.11 Palladium mediated synthesis of biaryls

N-(*tert*-Butoxycarbonyl)-3-aminopyridine (5.10)

To a solution of 3-aminopyridine (10 mmol) in dry ethanol (20 ml) was added di-*tert*-butyldicarbonate (15 mmol) and solid sodium bicarbonate (15 mmol). The solution was placed in a sonic bath at room temperature and allowed to react until the evolution of CO_2 had ceased. The reaction mixture was filtered to remove the excess sodium bicarbonate and the solvent removed *in vacuo*. Chromatography of the residue (1:1 hexane:ethyl acetate) afforded the title compound as fine yellow crystals.

Yield: 1,45 g; 75%

Mp: 114-115°C (lit. 115-116°C)[3]

IR: ν_{max} 1688 (amide carbonyl) cm^{-1}

NMR ^1H : δ 8,45 (1H, d, H-2, $J_{2,6}$=2,3 Hz); 8,25 (1H, dd, H-6, $J_{6,5}$=4,6 and $J_{6,2}$=2,3 Hz); 8,01 (1H, d, H-4, $J_{4,5}$=8,5 Hz); 7,65 (1H, s, N-H), 7,21 (1H, dd, H-5, $J_{5,4}$=8,5 and $J_{5,6}$=4,6 Hz); 1,48 (9H, s, 3 x C$\underline{H}_3$).

NMR ^{13}C : δ 152,8 (carbonyl); 143,7 (C-6); 139,9 (C-2); 135,6 (C-3); 125,7 (C-4); 123,6 (C-5); 80,9 ($\underline{C}$(CH$_3$)$_3$); 28,2 (C($\underline{C}$H$_3$)$_3$).

MS: m/z 194 ([M]$^+$, 75%); 137 ([M^+ -*t*Bu], 12%.

[3-(*tert*-Butoxycarbonylamino)-4-pyridyl]trimethyltin (5.12)

To a solution of **5.10** (5.0 mmol) in dry THF (7 ml) was added TMEDA (10.0 mmol). The solution was cooled to –78°C and *n*-BuLi (10.0 mmol, 15% solution in THF) was slowly added

over a period of 5 min. The solution was allowed to warm up to –10°C and maintained at this temperature for 2 h. The solution was cooled back to –78°C and trimethyltin chloride (5.0 mmol, 2M solution in THF) was slowly added over a period of 1 min. The reaction mixture was maintained at –78°C for an additional 1 h and then quenched with an excess of a saturated NH_4Cl solution. Extraction of the aqueous phase with ethyl acetate (3 x 10 ml), drying of the combined extracts over anhydrous $MgSO_4$ and flash chromatography (3:1 hexane:ethyl acetate) afforded the title compound as fine white crystals.

Yield: 1,37 g, 77%

Mp: 134-135°C

NMR ^1H : δ 8,48 (1H, s, H-2); 8,26 (1H, d, H-6, $J_{6,5}$=4,5 Hz); 7,31 (1H, d, H-5, $J_{5,6}$=4,5 Hz); 6,56 (1H, s, N-H); 1,46 (9H, s, 3 x C-C$\underline{H}_3$); 0,32 (9H, s, 3 x Sn-C$\underline{H}_3$).

NMR ^{13}C : δ 154,1 (carbonyl); 145,1 (C-6); 144,2 (C-3); 140,0 (C-2); 131,1 (C-5); 123,5 (C-4); 81,0 ($\underline{C}(CH_3)_3$); 28,2 ($C(\underline{C}H_3)_3$); 8,5 ($Sn(\underline{C}H_3)_3$.

MS: m/z 356 ([M]$^+$, 60%); 193 ([M$^+$ -$Sn(CH_3)_3$], 95%).

2,3-Dimethoxyphenyl triflate (5.27)

To a solution of 2,3-dimethoxyphenol (1.0 mmol) in dry CH_2Cl_2 (5 ml) was added 2,4,6-collidine (1.2 mmol) and triflic anhydride (1.2 mmol). The solution was stirred at room temperature for 1 h. Removal of the solvent *in vacuo* followed by extraction with *n*-pentane (3 x 10 ml) afforded the title compound as a colourless oil.

Yield: 0,25 g, 89%

NMR ^1H : δ 7,04 (1H, t, H-5, $J_{5,6}$=$J_{5,4}$=8,4 Hz); 6,89 (1H, dd, H-6, $J_{6,5}$=8,4 Hz and $J_{6,4}$=1,5 Hz); 6,81 (1H, dd, H-4, $J_{4,5}$=8,4 Hz and $J_{4,6}$=1,5 Hz); 3,93 (3H, s, OC$\underline{H}_3$); 3,87 (3H, s, OC$\underline{H}_3$).

NMR ^{13}C : δ 154,1 ($\underline{C}F_3$); 142,9 (C-3); 141,6 (C-2); 123,6 (C-5); 113,9 (C-4); 112,3 (C-6); 61,2 (O$\underline{C}H_3$); 56,1 (O$\underline{C}H_3$).

MS: m/z 286 ([M]$^+$, 84%).

2,3-Dimethoxy-1-(methoxymethoxy)benzene (5.28)

To a solution of 2,3-dimethoxyphenol (5.0 mmol) in dry DMF (10 ml) at 0°C was added NaH (5.1 mmol). After the evolution of hydrogen gas had ceased (30 min.), MOMCl (5.1 mmol) was slowly added and the reaction mixture allowed to warm to room temperature and stirred for 12 h. The excess NaH was then quenched with MeOH (3 ml) and Et_3N (3 ml) added to destroy the excess MOMCl. After stirring for a further 4 h, the reaction was diluted with EtOAc (20 ml) and washed with water. The solvent was removed *in vacuo*, and the residue purified by chromatography (3:1 hexane:ethyl acetate) to afford the title compound as a colourless oil.

Yield: 0,85 g, 86%

NMR ^{1}H : δ 6,94 (1H, t, H-5, $J_{5,6}$=$J_{5,4}$=8,4 Hz); 6,75 (1H, dd, H-6, $J_{6,5}$=8,4 Hz and $J_{6,4}$=1,5 Hz); 6,59 (1H, dd, H-4, $J_{4,5}$=8,4 Hz and $J_{4,6}$=1,5 Hz); 5,18 (2H, s, $OC\underline{H}_2OCH_3$); 3,84 (3H, s, $OC\underline{H}_3$); 3,83 (3H, s, $OC\underline{H}_3$); 3,48 (3H, s, $OCH_2OC\underline{H}_3$).

NMR ^{13}C : δ 153,7 (C-3); 150,9 (C-1); 139,1 (C-2); 123,6 (C-5); 109,4 (C-6); 106,2 (C-4); 95,3 ($O\underline{C}H_2OCH_3$); 60,7 ($O\underline{C}H_3$); 56,1 ($O\underline{C}H_3$); 55,8 ($OCH_2O\underline{C}H_3$).

MS: m/z 198 ([M]$^+$, 78%); 167 ([M$^+$-OCH_3], 25%).

3,4-Dimethoxy-1-iodo-2-(methoxymethoxy)benzene (5.23)

To a solution of **5.28** (5.0 mmol) in dry THF (5 ml) was added TMEDA (10.0 mmol). The solution was cooled to –78°C and *n*-BuLi (10.0 mmol, 15% solution in THF) was slowly added over a period of 5 min. The solution was allowed to warm up to 0°C and maintained at this temperature for 2 h. The solution was cooled back to –78°C and I_2 (5.0 mmol solution in dry THF) was slowly added over a period of 1 min. The reaction mixture was maintained at –78°C for an additional 1 h and then quenched with an excess of a saturated NH_4Cl solution. The mixture was washed with saturated NaS_2O_3 until the brown solution became colourless. Extraction of the aqueous phase with ethyl acetate (3 x 10 ml), drying of the combined extracts over anhydrous $MgSO_4$ and flash chromatography (6:1 hexane:ethyl acetate) afforded the title compound as a yellow oil.

Yield: 1,19 g, 74%

NMR ^{1}H : δ 7,41 (1H, d, H-5, $J_{5,6}$=8,7 Hz); 6,46 (1H, d, H-6, $J_{6,5}$=8,7 Hz); 5,17 (2H, s, $OC\underline{H}_2OCH_3$); 3,81 (3H, s, $OC\underline{H}_3$); 3,79 (3H, s, $OC\underline{H}_3$); 3,63 (3H, s, $OCH_2OC\underline{H}_3$).

NMR ^{13}C : δ 154,5 (C-4); 150,4 (C-2); 142,3 (C-3); 133,1 (C-6); 109,8 (C-5); 99,2 ($O\underline{C}H_2OCH_3$); 81,3 (C-1); 60,7 ($O\underline{C}H_3$); 58,3 ($O\underline{C}H_3$); 56,1 ($OCH_2O\underline{C}H_3$).

MS: m/z 324 ([M]$^+$, 21%); 197 ([M$^+$-I], 75%).

General method for the Stille cross-coupling of 5.12 with various aryl halides employing $Pd_2(dba)_3$ / $AsPh_3$ as catalyst

To a solution of **5.12** (1.0 mmol) in dry dioxane (2.5 ml) at room temperature was added $Pd_2(dba)_3.CHCl_3$ (0.1 mmol) and $AsPh_3$ (0.8 mmol). The resulting purple solution was stirred for 10 min. until it turned yellow, indicating the formation of the appropriate Pd(0) catalyst. To the solution was added the appropriate aryl halide (1.0 mmol) and the reaction mixture refluxed at 120°C. The reactions were followed by TLC until completion, after which the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (10 ml), washed with water (3 x 10 ml), dried over anhydrous $MgSO_4$, and concentrated. Chromatography of the crude product (2:1 hexane:ethyl acetate) afforded the title compounds.

3-*tert*-Butoxycarbonylamino-4-(4-cyanophenyl)pyridine (5.14)

Yield: 0,26 g, 88% (colourless oil)

NMR ^{1}H : δ 9,12 (1H, s, H-2); 8,40 (1H, d, H-6, $J_{6,5}$=5,1 Hz); 7,78 (2H, d, H-3' and H-5', $J_{5',6'}=J_{3',2'}$=8,1 Hz); 7,50 (2H, d, H-2' and H-6', $J_{6',5'}=J_{2',3'}$=7,8 Hz); 7,10 (1H, d, H-5, $J_{5,6}$=5,1 Hz); 6,31 (1H, bs, N-H); 1,41 (9H, s, C-(C$\underline{H}_3$)$_3$).

NMR ^{13}C : δ 152,5 (carbonyl); 145,4 (C-2); 144,4 (C-6); 140,9 and 138,3 (C-*i*-aromatic); 133,0 (C-3' and C-5'); 131,4 (C-*i*-aromatic); 129,4 (C-2' and C-6'); 123,8 (C-5); 118,2 (nitrile carbon); 112,8 (C-*i*-aromatic); 81,6 (C(CH$_3$)$_3$); 28,1 (C($\underline{C}$H$_3$)$_3$)

MS: m/z 296 ([M]$^+$, 51%); 239 ([M$^+$-^{t}Bu], 49%)

3-*tert*-Butoxycarbonylamino-4-(2-nitrophenyl)pyridine (5.18)

Yield: 0,25 g, 80% (yellow oil)

NMR ^{1}H : δ 9,03 (1H, s, H-2); 8,38 (1H, d, H-6, $J_{6,5}$= 5,1Hz); 8,06 (1H, dd, H-3', $J_{3',4'}$=6,9 Hz and $J_{3',5'}$=1,2 Hz); 7,72 (1H, dt, H-4', $J_{4',5'}=J_{4',3'}$=6,9 Hz and $J_{4',6'}$=1,5 Hz); 7,61 (1H, dt, H-5', $J_{5',4'}=J_{5',6'}$=6.8 Hz and $J_{5',3}$=1.2 Hz) 7,35 (1H, dd, H-6', $J_{6',5'}$=6,8 Hz and $J_{6',4'}$=0.8 Hz); 7,02 (1H, d, H-5, $J_{5,6}$=5,1 Hz); 6,07 (1H, bs, N-H); 1,38 (9H, s, C-(C$\underline{H}_3$)$_3$).

NMR ^{13}C : δ 152,6 (carbonyl); 148,4 (C-2'); 145,3 (C-2); 144,7 (C-3); 138,0 (C-*i*-aromatic); 133,7 (C-6); 132,1 (C-3'); 130,9 (C-*i*-aromatic); 130,0 (C-4'); 124,9 (C-5'); 123,1 (C-5); 81,4 (C(CH$_3$)$_3$); 28,0 (C($\underline{C}$H$_3$)$_3$).

MS: m/z 316 ([M]$^+$, 70%); 270 ([M$^+$-NO$_2$], 10%).

3-*tert*-Butoxycarbonylamino-4-[3,4-dimethoxy-2-(methoxymethoxy)phenyl])pyridine (5.24)

Yield: 0,078 g, 20% (yellow oil)

NMR ^{1}H : δ 9,02 (1H, s, H-2); 8,34 (1H, d, H-6, $J_{6,5}$=4,8 Hz); 7,15 (1H, d, H-5, $J_{5,6}$=4,8 Hz); 6,94 (1H, d, H-5', $J_{6',5'}$=8,3 Hz); 6,79 (1H, d, H-6', $J_{5',6'}$=8,3 Hz); 6,65 (1H, bs, N-H); 4,92 (2H, s, OC$\underline{H}_2$OCH$_3$); 3,90 (6H, s, 2 x OC$\underline{H}_3$); 2,92 (3H, s, OCH$_2$OC$\underline{H}_3$); 1,49 (9H, s, C-(C$\underline{H}_3$)$_3$).

NMR ^{13}C : δ 154,4 (carbonyl); 147,7 (C-2); 145,1 (C-6); 143,9 and 142,3 (C-*i*-aromatic); 133,43 and 132,8 (C-*i*-aromatic); 125,2 (C-5); 125,1 (C-6'); 123,5 (C-*i*-oaromatic)108,7 (C-5'); 99,3 (O$\underline{C}$H$_2$OCH$_3$); 80,8 ($\underline{C}$(CH$_3$)$_3$); 60,8 (O$\underline{C}$H$_3$); 56,3 (O$\underline{C}$H$_3$); 55,9 (OCH$_2$O$\underline{C}$H$_3$); 28,1 (C($\underline{C}$H$_3$)$_3$).

MS: m/z 390 ([M]$^+$, 12%); 359 ([M$^+$ -OCH$_3$], 20%).

General method for the Stille cross-coupling of 5.12 with various aryl halides employing $Pd(PPh_3)_4$ as catalyst

To a solution of **5.12** (1.0 mmol) in dry dioxane (2.5 ml) at room temperature was added $Pd(PPh_3)_4$ (0.1 mmol) and the appropriate aryl halide (1.0 mmol). The reaction mixture was stirred at room temperature for 10 min. and then refluxed at 120°C. The reactions were followed by TLC until completion, after which the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (10 ml), washed with water (3 x 10 ml), dried over anhydrous $MgSO_4$, and concentrated. Chromatography of the crude product (2:1 hexane:ethyl acetate) afforded the title compounds as oils.

3-*tert*-Butoxycarbonylamino-4-phenylpyridine (5.16)

Yield: 0,23 g, 85% (colourless oil)

NMR ^{1}H : δ 9,26 (1H, s, H-2); 8,34 (1H, d, H-6, $J_{6,5}$=4,8 Hz); 7,51-7,44 (3H, m, H-3', H-4' and H-5'); 7,37-7,33 (2H, m, H-6' and H-2'); 7,09 (1H, d, H-5, $J_{5,6}$=4,8 Hz); 6,37 (1H, bs, N-H); 1,45 (9H, s, C-(C$\underline{H}_3$)$_3$).

NMR ^{13}C : δ 152,5 (carbonyl); 144,5 (C-2); 142,9 (C-6); 138,8 (C-3); 135,9 and 131,9 (C-*i*-aromatic); 129,3 and 128,5 (C-2', C-3', C-5' and C-6'); 128,8 (C-4'); 123,1 (C-5); 81,2 (C$\underline{C}$(CH$_3$)$_3$); 28,2 (C(C$\underline{H}_3$)$_3$).

MS: m/z 270 ([M]$^+$, 14%); 196 ([M$^+$-^{t}BuOH], 10%).

3-*tert*-Butoxycarbonylamino-4-(2-methoxyphenyl)pyridine (5.20)

Yield: 0,20 g, 71% (colourless oil)

NMR ^{1}H : δ 9,12 (1H, s, H-2); 8,32 (1H, d, H-6, $J_{6,5}$=6,5 Hz); 7,44 (1H, dt, H-4', $J_{4',5'}$=$J_{4',3'}$=5,4 Hz and $J_{4',6'}$=1,2 Hz); 7,19 (1H, dd, H-3', $J_{3',4'}$=6,1 Hz and $J_{3',5'}$=0.9 Hz); 7,11 (1H, d, H-6', $J_{6',5'}$=4,1 Hz); 7,10 (1H, d, H-5, $J_{5,6}$=6,5 Hz); 7,04 (1H, t, H-5', $J_{5',4'}$=$J_{5',6'}$=4,0 Hz); 6,44 (1H, bs, N-H); 3,81 (3H, s, OC$\underline{H}_3$); 1,38 (9H, s, C-(C$\underline{H}_3$)$_3$).

NMR ^{13}C : δ 155,9 (carbonyl); 152,8 (C-2'); 144,3 (C-2); 144,2 (C-3); 143,5 (C-6); 132,9 (C-*i*-aromatic); 131,3 (C-3'); 130,5 (C-4'); 125,9 (C-*i*-aromatic); 124,9 (C-5); 121,6 (C-6'); 111,5 (C-5'); 80,8 (C$\underline{C}$(CH$_3$)$_3$); 55,7 (OC$\underline{H}_3$); 29,6 (C(C$\underline{H}_3$)$_3$).

MS: m/z 284 ([M]$^+$, 63%); 227 ([M$^+$-*t*Bu], 9%).

3-*tert*-Butoxycarbonylamino-4-(4-methoxyphenyl)pyridine (5.22)

Yield: 0,19 g, 68% (colourless oil)

NMR ^{1}H : δ 9,23 (1H, s, H-2); 8,29 (1H, d, H-6, $J_{6,5}$=5,2 Hz); 7,28 (2H, d, H-5' and H-3', $J_{2',3'}$=$J_{5',6'}$=5,4 Hz) 7,07 (1H, d, H-5, $J_{6,5}$=5,2 Hz); 6,99 (2H, d, H-2' and H-6', $J_{2',3'}$= $J_{6',5'}$=5,4 Hz); 6,42 (1H, bs, N-H); 3,85 (3H, s, OC$\underline{H}_3$); 1,44 (9H, s, C-(C$\underline{H}_3$)$_3$).

NMR ^{13}C : δ 160,1 (C-4'); 152,6 (carbonyl); 144,4 (C-2); 144,1 (C-6); 142,7 (C-3); 138,0 (C-*i*-aromatic); 129,8 (C-2' and C-6'); 127,8 (C-*i* -aromatic); 124,2 (C-5); 114,8 (C-3' and C-5'); 81,2 ($\underline{C}(CH_3)_3$); 55,3 ($OC\underline{H}_3$); 28,2 ($C(\underline{C}H_3)_3$).

MS: m/z 284 ([M]$^+$, 41%); 253 ([M$^+$ -OCH_3], 70%).

3-*tert*-Butoxycarbonylamino-4-(2-pyridyl)pyridine (5.26)

Yield: 0,15 g, 58% (yellow oil)

NMR ^1H : δ 8,84 (1H, s, H-2); 8,33 (1H, d, H-3', $J_{3',4}$=2,5 Hz); 8,26 (3H, m, H-4', H-5' and H-6'); 8,19 (1H, d, H-6, $J_{6,5}$=5,2); 7,06 (1H, d, H-5, $J_{5,6}$=5,2 Hz); 6,52 (1H, bs, N-H); 1,48 (9H, s, C-($C\underline{H}_3)_3$).

NMR ^{13}C : δ157,1 (C-1'); 152,9 (carbonyl); 144,8 (C-2); 144,1 (C-6); 140,3 (C-3); 140,0 (C-4); 138,8 (C-5'); 133,6 (C-3'); 133,4 (2C; C-4' and C-6'); 125,3 (C-5); 84,5 ($\underline{C}(CH_3)_3$); 28,3 ($C(\underline{C}H_3)_3$).

MS: m/z 200 ([M$^+$ -*t*Bu], 45%).

[3-(*tert*-Butoxycarbonylamino)-4-pyridyl]boronic acid (5.29)

To a solution of **5.10** (5.0 mmol) in dry THF (7 ml) was added TMEDA (10.0 mmol). The solution was cooled to –78°C and *n*-BuLi (10.0 mmol, 15% solution in THF) was slowly added over a period of 5 min. The solution was allowed to warm up to –10°C and maintained at this temperature for 2 h. The solution was cooled back to –78°C and trimethylborate (5.0 mmol) was slowly added over a period of 1 min. The reaction mixture was maintained at –78°C for an additional 1 h, quenched with water and allowed to warm up to room temperature. The reaction mixture was acidified and the aqueous phase extracted with diethyl ether (3 x 10 ml). Drying of the combined extracts over anhydrous $MgSO_4$ and removal of the solvent *in vacuo* afforded the crude boronic acid which was not purified any further, but used immediately in Suzuki cross-coupling reactions.

General method for the Suzuki cross-coupling reactions of 5.29 with aryl halides

To a solution of **5.29** (1.0 mmol) in ethanol (2 ml) was added $Pd(PPh_3)_4$ (0.05 mmol), Na_2CO_3 (1.1 mmol, 2M solution in H_2O) and the appropriate aryl halide (1.0 mmol). The reaction mixture was stirred at room temperature for 10 min. and then refluxed at 100°C. The reactions were followed by TLC until completion, after which the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (10 ml), washed with water (3 x 10 ml), dried over anhydrous $MgSO_4$, and concentrated. Chromatography of the crude products (3:1 hexane:ethyl acetate) afforded the title compounds.

3-*tert*-Butoxycarbonylamino-4-phenylpyridine (5.16)

Yield: 0,22 g, 80% (colourless oil)

3-*tert*-Butoxycarbonylamino-4-(2-methoxyphenyl)pyridine (5.20)

Yield: 0,18 g, 64% (colourless oil)

3-*tert*-Butoxycarbonylamino-4-iodopyridine (5.31)

To a solution of **5.10** (5.0 mmol) in dry THF (7 ml) was added TMEDA (10.0 mmol). The solution was cooled to –78°C and *n*-BuLi (10.0 mmol, 15% solution in THF) was slowly added over a period of 5 min. The solution was allowed to warm up to –10°C and maintained at this temperature for 2 h. The solution was cooled back to –78°C and I_2 (5.0 mmol, solution in THF) was slowly added over a period of 1 min. The reaction mixture was maintained at –78°C for an additional 1 h, quenched with water and allowed to warm up to room temperature. The mixture was washed with saturated NaS_2O_3 until the brown solution became colourless. Extraction of the aqueous phase with ethyl acetate (3 x 10 ml), and drying of the combined extracts over anhydrous $MgSO_4$ followed by flash chromatography (3:1 hexane:ethyl acetate) afforded the title compound as a yellow oil.

Yield: 0,96 g, 60%

NMR ^{1}H : δ 9,11 (1H, s, H-2); 7,86 (1H, d, H-6, $J_{6,5}$=5,4 Hz); 7,64 (1H, d, H-5, $J_{5,6}$=5,4 Hz); 6,66 (1H, bs, N-H), 1,51 (9H, s, 3 x C<u>H</u>$_3$).

NMR ^{13}C : δ 152,1 (carbonyl); 144,4 (C-2); 142,0 (C-6); 136,4 (C-3); 133,5 (C-5); 99,6 (C-4); 81,8 (<u>C</u>(CH$_3$)$_3$); 28,2 (C(<u>C</u>H$_3$)$_3$).

MS: m/z 320 ([M]$^+$, 14%).

(2,2-Dimethoxypropane-1,3-dioxy)(2-methoxyphenyl)borane (5.33)

A round bottomed flask equipped with a Dean-Stark apparatus was charged with a solution of **5.32** (1.0 mmol) in dry benzene (10 ml) and 2,2-dimethyl-1,3-propanediol (1.5 mmol). The solution was refluxed at 70°C for 4 h. Concentration of the reaction mixture followed by flash chromatography (7:1 hexane:ethyl acetate) afforded the title compound as a colourless oil.

Yield: 0,12 g, 50%

NMR ^{1}H : δ 7,62 (1H, dd, H-6, $J_{6,5}$=11,3 Hz and $J_{6,4}$=2,9 Hz); 7,34 (1H, dt, H-4, $J_{4,5}$= $J_{4,3}$=11,0 Hz and $J_{4,6}$=2,9 Hz); 6,92 (1H, dt, H-5, $J_{5,6}$=$J_{5,4}$=11,2 Hz and $J_{5,3}$=1,2 Hz); 6,88 (1H, dd, H-3, $J_{3,4}$=11.0 Hz and $J_{3,5}$=1,2 Hz), 3,89 (3H, s, OC<u>H</u>$_3$); 3,77 (4H, s, 2 x OC<u>H</u>$_2$-C); 1,02 (6H, s, 2 x C-C<u>H</u>$_3$).

NMR ^{13}C : δ 163,6 (C-1); 135,7 (C-3); 131,6 (C-5); 120,2 (C-3); 110,4 (C-6); 72,5 (2 x O<u>C</u>H$_2$-C); 55,7 (O<u>C</u>H$_3$); 31,7 (quaternary C); 21,8 (2 x C(<u>C</u>H$_3$).

MS: No discernible fragmentation pattern.

2,3-Dimethoxyphenyl *N,N*-diethylcarbamate (5.34)

To a solution of 2,3-dimethoxyphenol (2.0 mmol) in dry DMF (6 ml) at 0°C was added NaH (2.1 mmol). After the evolution of hydrogen gas had ceased (30 min.), diethylcarbamoyl chloride (2.1 mmol) was slowly added and the reaction mixture allowed to warm to room temperature and stirred for 12 h. The excess NaH was then quenched with MeOH (3 ml) and Et_3N (3 ml) added to destroy the excess diethylcarbamoyl chloride. After stirring for a further 4 h, the reaction was diluted with EtOAc (20 ml) and washed with water. The solvent was removed *in vacuo*, and the residue purified by chromatography (5:1 hexane:ethyl acetate) to afford the title compound as a colourless oil.

Yield: 0,43 g, 84%

NMR ^{1}H : δ 6,97 (1H, t, H-5, $J_{5,6}$=$J_{5,4}$=12,5 Hz); 6,76 (1H, dd, H-6, $J_{6,5}$=12,5 Hz and $J_{6,4}$=2,4 Hz); 6,69 (1H, dd, H-4, $J_{4,5}$=12,5 Hz and $J_{4,6}$=2,1 Hz); 3,83 (3H, s, $OC\underline{H}_3$); 3,81 (3H, s, $OC\underline{H}_3$); 3,38 (4H, m, 2 x $NC\underline{H}_2CH_3$); 1,21 (6H, m, 2 x $NCH_2C\underline{H}_3$).

NMR ^{13}C : δ 154,1 (carbonyl); 153,6; 145,1 and 141,6 (C-*i*-aromatic); 123,1 (C-5); 115,7 (C-4); 109,6 (C-6); 60,6 ($O\underline{C}H_3$); 56,0 ($O\underline{C}H_3$); 42,1 (2 x $N\underline{C}H_2CH_3$); 13,9 and 13,4 (2 x $NCH_2\underline{C}H_3$).

MS: m/z 253 ([M]$^+$, 25%).

[3,4-Dimethoxy-2-(methoxymethoxy)-1-phenyl]trimethyltin (5.36)

To a solution of **5.28** (5.0 mmol) in dry THF (5 ml) was added TMEDA (10.0 mmol). The solution was cooled to –78°C and *n*-BuLi (10.0 mmol, 15% solution in THF) was slowly added over a period of 5 min. The solution was allowed to warm up to 0°C and maintained at this temperature for 2 h. The solution was cooled back to –78°C and trimethyltin chloride (5.0 mmol, 2M solution in THF) was slowly added over a period of 1 min. The reaction mixture was maintained at –78°C for an additional 1 h and then quenched with an excess of a saturated NH_4Cl solution. Extraction of the aqueous phase with diethyl ether (3 x 10 ml), drying of the combined extracts over anhydrous $MgSO_4$ and filtration through a short silica plug furnished the title compound as a colourless oil.

Yield: 1,37 g, 76%

NMR ^{1}H : δ 7,01 (1H, d, H-5, $J_{5,6}$=7,7 Hz); 6,69 (1H, d, H-6, $J_{5,6}$=7,7 Hz); 5,15 (2H, s, $OC\underline{H}_2OCH_3$); 3,83 (3H, s, $OC\underline{H}_3$); 3,81 (3H, s, $OC\underline{H}_3$); 3,51 (3H, s, $OCH_2OC\underline{H}_3$); 0,27 (9H, s, $Sn(C\underline{H}_3)_3$).

NMR ^{13}C : δ 154,9 (C-4); 154,8 (C-2); 140,8 (C-3); 130,8 (C-6); 123,7 (C-1); 108,2 (C-5); 98,9 ($O\underline{C}H_2OCH_3$); 60,6 ($O\underline{C}H_3$); 57,5 ($O\underline{C}H_3$); 55,9 ($OCH_2O\underline{C}H_3$); 8,7 ($Sn(\underline{C}H_3)_3$).

MS: m/z 345 ([M^+-CH_3], 85%); 299 ([M^+-OCH_2OCH_3], 64%).

4-Hydroxy-3-nitropyridine (5.38)

To a solution of **4**-hydroxypyridine (10 mmol) in concentrated sulfuric acid (10 ml) was slowly added a mixture of fuming nitric acid (5 ml) and sulfuric acid (10 ml) over a period of 1 h at 80°C. The reaction mixture was maintained at 60°C for an additional 3 h before being poured onto crushed ice. The excess acid was neutralised with a 25% ammonia solution and left to stand at room temperature overnight upon which the title compound crystallised out of the solution as fine yellow crystals.

Yield: 1,13 g, 81%

NMR ^{1}H : δ 8,62 (1H, s, H-2); 7,67 (1H, d, H-5, $J_{5,6}$=6,9 Hz); 6,26 (1H, d, H-6, $J_{6,5}$=6.9 Hz); 3,49 (1H, bs, C[4]-O<u>H</u>).

NMR ^{13}C : δ 169,0 (C-4); 147,2 (C-2); 146,9 (C-6); 122,3 (C-5).

MS: m/z 140 ([M]$^+$, 95%); 94 ([M$^+$-NO_2], 60%).

4-Chloro-3-nitropyridine (5.39)

Compound **5.38** (2 mmol) was dissolved in $POCl_3$ (10 ml). The solution was refluxed at 120°C for 4 h. The reaction mixture was concentrated, cooled to 0°C in an ice bath, and water was carefully added to the solution. Extraction of the aqueous phase with ethyl acetate (3 x 10 ml), drying of the combined extracts over anhydrous $MgSO_4$ and chromatography (1:1 hexane:ethyl acetate) furnished the title compound as a light yellow oil.

Yield: 0,21 g, 65%

NMR ^{1}H : δ 9,10 (1H, s, H-2); 8,67 (1H, d, H-5, $J_{5,6}$=5,4 Hz); 7,52 (1H, d, H-6, $J_{6,5}$=5,4 Hz).

NMR ^{13}C : δ 153,3 (C-2); 146,7 (C-6); 137,5 (C-4); 126,4 (C-5).

MS: m/z 158 ([M]$^+$, 20%); 112 ([M$^+$-NO_2], 15%).

3-Nitro-4-[3,4-dimethoxy-2-(methoxymethoxy)phenyl]pyridine (5.40)

To a solution of **5.39** (1.0 mmol) in dry dioxane (2.5 ml) at room temperature was added $Pd_2(dba)_3.CHCl_3$ (0.1 mmol) and $AsPh_3$ (0.8 mmol). The resulting purple solution was stirred for 10 min. until it turned yellow, indicating the formation of the appropriate Pd(0) catalyst. To the solution was added **5.36** (1.0 mmol) and the reaction mixture was refluxed at 120°C. The reaction was followed by TLC until completion (4 h), after which the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (10 ml), washed with water (3 x 10 ml), dried over anhydrous $MgSO_4$, and concentrated. Chromatography of the crude product (1:1 hexane:ethyl acetate) afforded the title compounds as yellow crystals.

Yield: 0,14 g, 45%

IR: – ν_{max} 1520 (N=0) cm^{-1}

NMR ^{1}H : δ 9,13 (1H, s, H-2); 8,78 (1H, d, H-6, $J_{5,6}$=5,1 Hz); 7,40 (1H, d, H-5, $J_{6,5}$=5,1 Hz); 7,03 (1H, d, H-5', $J_{5',6}$=8,7 Hz); 6,80 (1H, d, H-6', $J_{6',5'}$=8,7 Hz); 4,93 (2H, s, $OC\underline{H}_2OCH_3$); 3,90 (3H, s, $OC\underline{H}_3$); 3,84 (3H, s, $OC\underline{H}_3$); 2,93 (3H, s, $OCH_2OC\underline{H}_3$).

NMR ^{13}C : δ 170,2 (C-3'); 155,4 (C-2'); 152,9 (C-2); 148,3 (C-4'); 145,2 (C-6); 141,2 (C-3); 132,2 (C-1'); 126,5 (C-5); 123,6 (C-5'); 122,7 (C-4); 108,3 (C-6'); 99,4 ($O\underline{C}H_2OCH_3$); 61,0 ($O\underline{C}H_3$); 56,8 ($O\underline{C}H_3$); 56,1 ($OCH_2O\underline{C}H_3$).

MS: m/z 320 ([M]$^+$, 90%); 274 ([M$^+$-NO_2], 45%).

Synthesis of 3-Nitro-4-(3,4-dimethoxy-2-methoxymethylphenyl)pyridine (5.40) using co-catalytic copper(I)

To a solution of **5.39** (1.0 mmol) in dry dioxane (2.5 ml) at room temperature was added $Pd_2(dba)_3.CHCl_3$ (0.1 mmol) and $AsPh_3$ (0.8 mmol). The resulting purple solution was stirred for 10 min. until it turned yellow, indicating the formation of the appropriate Pd(0) catalyst. To the solution was added **5.36** (1.0 mmol) and Cu(I)Br (0.05 mmol) after which the reaction mixture was refluxed at 120°C. The reaction was followed by TLC until completion, after which the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (10 ml), washed with water (3 x 10 ml), dried over anhydrous $MgSO_4$, and concentrated. Chromatography of the crude product (1:1 hexane:ethyl acetate) afforded the title compound as yellow crystals.

Yield: 0,27 g, 84%

3-Acetamido-4-(3,4-dimethoxy-2-methoxymethylphenyl)pyridine (5.43)

To a solution of **5.40** (0.5 mmol) in absolute ethanol (2 ml) was added hydrazine hydrate (1.0 mmol) and palladium on carbon (0.05 mmol). The suspension was stirred at room temperature for 6 h. Filtration to remove the insoluble material and concentration *in vacuo* furnished the crude amine **5.42** as a white solid. This material was redissolved in a mixture of pyridine (2 ml) and acetic anhydride (2 ml). The reaction mixture was stirred at room temperature for 2 h after which the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (5 ml), washed with water (3 x 5 ml), dried over anhydrous $MgSO_4$, and concentrated. Chromatography of the crude product (1:2 hexane:ethyl acetate) afforded the title compound as yellow crystals.

Yield: 0,12 g, 74% (starting from **5.40**)

Mp: 145°C

IR: ν_{max} 1700 (C=O) cm^{-1}

NMR ^{1}H : δ 9,12 (1H, s, H-2); 8,39 (1H, d, H-6, $J_{5,6}$=5,1 Hz); 7,64 (1H, bs, N-$\underline{H}$); 7,19 (1H,

d, H-5, $J_{6,5}$=5,0 Hz); 6,92 (1H, d, H-5', $J_{5',6'}$=8,4 Hz); 6,81 (1H, d, H-6', $J_{6',5'}$=8,7 Hz); 4,95 (2H, s, $OC\underline{H}_2OCH_3$); 3,90 (3H, s, $OC\underline{H}_3$); 3,89 (3H, s, $OC\underline{H}_3$); 2,92 (3H, s, $OCH_2OC\underline{H}_3$); 2,03 (3H, s, $NHC[O]C\underline{H}_3$).

NMR ^{13}C : δ 168,6 (carbonyl); 154,6 (C-3'); 147,5 (C-2'); 145,9 (C-2); 145,7 (C-6); 142,2 (C-4); 138,8 (C-4'); 132,1 (C-3); 125,4 (C-5); 125,2 (C-5'); 123,6 (C-1'); 108,9 (C-6'); 99,7 ($O\underline{C}H_2OCH_3$); 60,9 ($O\underline{C}H_3$); 56,9 ($O\underline{C}H_3$); 56,1 ($OCH_2O\underline{C}H_3$); 24,1 ($NHC[O]\underline{C}H_3$).

MS: m/z 332 ($[M]^+$, 70%); 317 ($[M^+-CH_3]$, 25%).

6.12 REFERENCES

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