

Helsinki University of Technology
Department of Chemical Technology
Laboratory of Organic Chemistry

**TOWARDS THE SYNTHESIS OF THE DISACCHARIDE
FRAGMENT OF PRADIMICIN**

Tatja Maunula

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Abstract

Pradimicin is a novel antibiotic consisting of a benzo[*a*]naphthacenequinone aglycon, an amino acid and a disaccharide fragment. In this study, the α -analogue of the disaccharide derivative of pradimicin A was synthesized in its protected form.

The disaccharide moiety of pradimicin A was built up from a suitably protected, commercially available D-xylose derivative and the amino sugar part, synthesized from L-threonine. The synthesis of the target amino sugar started with the conversion of the L-threonine derived aldehyde to the desired *E*-enoate *via* a modified Horner-Wadsworth-Emmons olefination. Ruthenium-catalyzed *cis*-dihydroxylation of the double bond produced a mixture of *anti*- and *syn*-aminodiols, of which the former was lactonized under acidic conditions. Platinum-catalyzed reduction of the lactone produced a mixture of lactols, which upon treatment with DAST provided a mixture of α - and β -fluorinated amino sugar derivatives. Both the α - and β -fluorides were transformed to suitable glycosyl fluorides of pradimicin A *via* successive *N*-methylation by MeI/Ag₂O, deacetylation and regioselective benzoyl protection at the C2-position. Final coupling of the α -glycosyl fluoride with the D-xylose derived thioglycoside donor by NBS furnished the protected α -analogue of the disaccharide fragment of pradimicin A.

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Turku, December 2003

Tatja Maunula

Symbols and abbreviations

Ac	acetyl
Bn	benzyl
BOC	<i>t</i> -butoxycarbonyl
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Bz	benzoyl
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphanyl)ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Fmoc	fluorenylmethyloxycarbonyl
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate
HWE	Horner-Wadsworth-Emmons
IBAL	isobutyraldehyde

IPA	isopropyl alcohol
KHMDS	potassium hexamethyldisilazane
mCPBA	<i>m</i> -chloroperbenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PMP	<i>p</i> -methoxyphenyl
PPTS, PTSA	pyridinium <i>p</i> -toluenesulfonate
pyr	pyridine
salen	<i>N,N</i> -bis(salicylidene)ethylenediamino
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>t</i> -butyldiphenylsilyl
TBS	<i>t</i> -butyldimethylsilyl
TBSOTf	<i>t</i> -butyldimethylsilyl trifluoromethanesulfonate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
TPAP	tetra- <i>n</i> -propylammonium perruthenate

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Abstract

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Preface

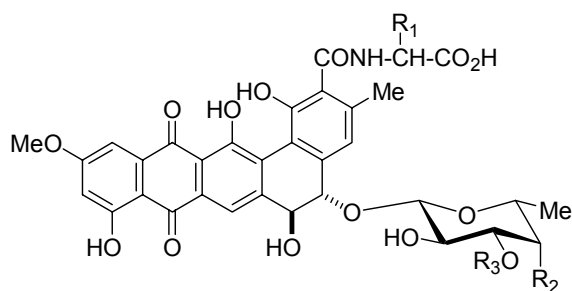
Pradimicin is a novel antifungal antibiotic first isolated from a soil sample collected in Fiji Island in the late 80's. Thus far, several pradimicin analogues have been isolated, but the entire molecule has not been totally synthesized. Because of its pharmaceutical potential, there has been strong interest towards the total synthesis of pradimicin.

In Chapter 1, the structure and biological activity of pradimicin is introduced. Chapter 2 reviews the amino acid based synthetic methods for the preparation of amino sugars and Chapter 3 presents the published synthetic approaches to pradimicin. Chapters 4 and 5 describe my own experimental work concerning the synthesis of the disaccharide fragment of pradimicin A, starting from the amino acid L-threonine.

1. Introduction to pradimicins

1.1. Structure of pradimicins

Pradimicin A is a novel antifungal antibiotic first isolated from a soil sample collected in Fiji Island in the late 80's.¹ Several pradimicin analogues, designated as pradimicin B, C, D, E etc. have been later isolated or produced biosynthetically.²⁻⁹ The pradimicin antibiotics consist of a benzo[*a*]naphthacenequinone core, an amino acid and a disaccharide (Fig. 1) In order to explore the antifungal activity of different pradimicin analogues, modifications of the original structure have been performed, including replacement of the D-alanine moiety by another amino acid¹⁰ or modification of the aglycon¹¹ or the sugar part.¹² The water-solubility of pradimicin A has been improved by modification of the amino group of the disaccharide¹³ and replacing the D-alanine moiety by D-serine.¹⁴ Some structures of the pradimicin analogues are presented in Figure 1.



Pradimicin analogue	R ₁	R ₂	R ₃
Pradimicin A	Me	NHMe	
Pradimicin B	Me	NHMe	H
Pradimicin C	Me	NH ₂	
Pradimicin D	H	NHMe	
Pradimicin E	H	NH ₂	
BMS-181184	CH ₂ OH	OH	

Figure 1. Structures of some pradimicin analogues.

1.2. Biological activity

Pradimicin A has shown moderate *in vitro* activity against a wide variety of fungi and yeasts and *in vivo* therapeutic activity against systemic fungal infections caused by *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*.^{1,15} Pradimicins have also shown inhibitory effect on human immunodeficiency virus (HIV) *in vitro*¹⁶ and antiviral activity against influenza virus.^{1a,15} The biological activities of pradimicins are attributed to the potentially specific binding to cell wall oligosaccharides of fungi or viral surfaces. At this time, the proposed mechanisms of action of pradimicins are still speculative, but it has been suggested that the pradimicins form a ternary complex with D-mannoside and calcium on the *Candida* cell wall, and this ternary complex formation results in membrane disruption and fungal cell death.¹⁷ In detail, pradimicin first

recognizes and binds to D-mannoside to produce the mannan-pradimicin conjugate, which is subsequently complexed with calcium to form a ternary complex on the cell wall. It is believed that only the free C-18 carboxyl group of pradimicin binds to calcium whereas the C-5 disaccharide moiety is essential for the stereospecific recognition of and binding to D-mannopyranoside by constructing a specific mannose-binding pocket with the pradimicin aglycon.¹⁸ The stereochemistry of the amino acid moiety in the pradimicin skeleton plays also an important role in the binding process: when the D-alanine moiety of pradimicin A was replaced by L-alanine to form 17-epipradimicin, virtually no binding to the mannose unit nor antifungal activity was observed.¹⁹ It was reasoned that the inability of L-alanine to bind to the cell surface was due to the steric factors, caused by the change in the stereochemistry.

BMS-181184 (Fig. 1), a water-soluble D-serine analogue of pradimicin A having its amino functionality of the disaccharide unit replaced by a hydroxy group²⁰ is currently targeted for clinical drug development.

2. Synthesis of amino sugars from amino acids

Amino sugars are commonly synthesized from readily available and relatively inexpensive carbohydrates as principal intermediates, usually requiring multistep synthetic transformations, but also non-carbohydrate precursors have gained interest as useful starting materials for the synthesis of deoxyaminohexoses.²¹ Some examples of the non-carbohydrate based approaches include direct amination of carbocycles,²² transformation of isoxazolines,²³ the use of hetero Diels-Alder cycloaddition,²⁴ [3+2] cycloaddition of nitrones with vinylene carbonate²⁵ and the exploitation of naturally occurring substrates such as amino acids²⁶ and lactic acid.²⁷ In this chapter, the amino acid based syntheses of amino sugars are reviewed.

2.1. Monoamino dideoxyhexoses

2.1.1. Mycaminose

In 1974, Yamada and Koga employed L-alanine as the chiral starting material in the synthesis of α -L-mycaminoside **9** (Scheme 1).²⁸ In the transformation of L-alanine to α -L-mycaminoside, the chirality of the product is inherited from the starting amino acid as shown in Figure 2.

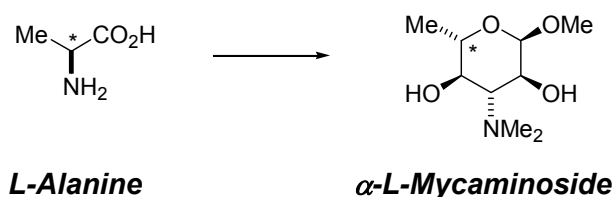
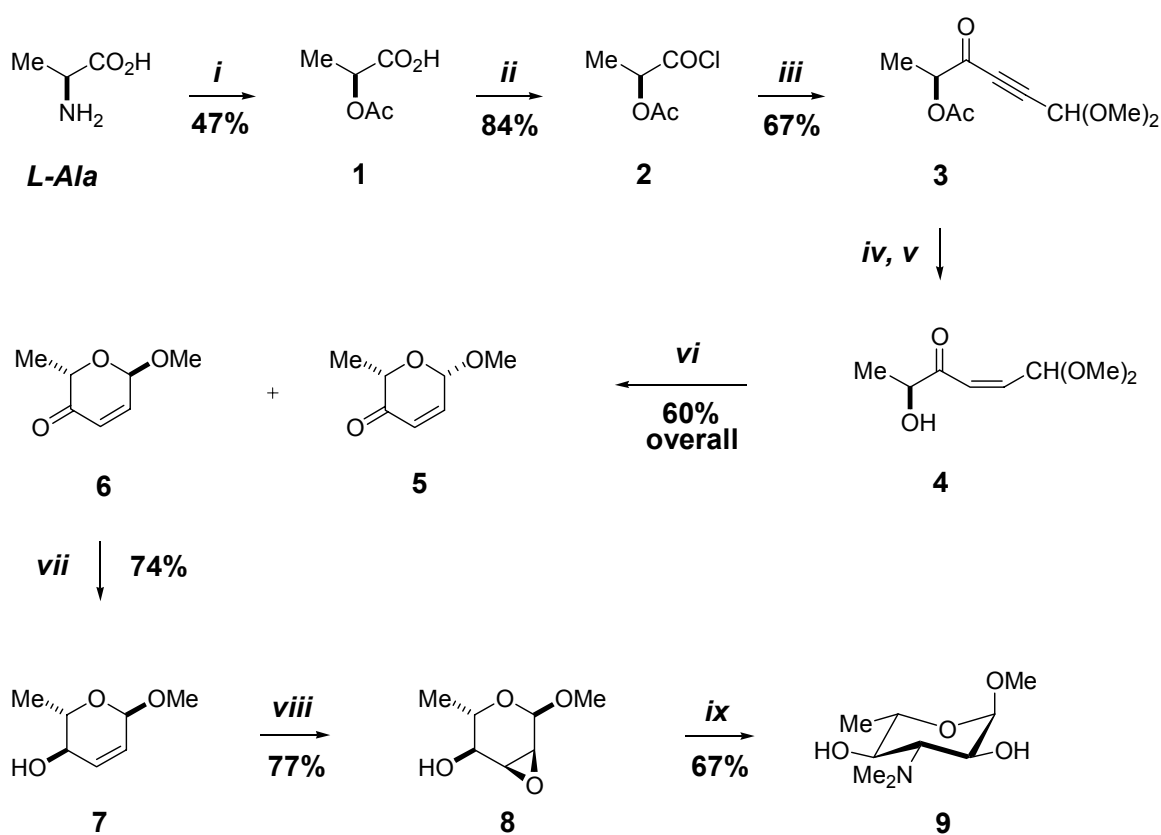


Figure 2.

The first step of the synthesis was nitrous acid deamination in acetic acid, producing 2-acetoxypropionic acid **1** with 96 % retention of configuration. Formation of acid chloride with thionyl chloride, followed by treatment with Grignard reagent provided alkyne **3**. Hydrogenation of the triple bond and subsequent deacetylation afforded *cis*-alkene **4**, which was cyclized in refluxing carbon tetrachloride in the presence of phosphoric acid to form an anomeric mixture of L-hex-2-enopyranosid-4-uloses **5** and **6** (ratio *ca.* 1:2). After purification by column chromatography and recrystallization, the optically pure α -anomer **6** was reduced by lithium aluminum hydride to give the unsaturated *anti*-alcohol **7**. Epoxidation with *m*-chloroperbenzoic acid, followed by treatment with saturated aqueous dimethylamine produced α -L-mycaminoside **9**.



Scheme 1. *i)* HNO₂, AcOH; *ii)* SOCl₂; *iii)* BrMgC≡CCH(OMe)₂; *iv)* H₂, Pd/BaSO₄, EtOAc, quinoline; *v)* NaOH, dioxane; *vi)* CCl₄, H₃PO₄, heat; *vii)* LiAlH₄, Et₂O; *viii)* *m*CPBA, benzene; *ix)* aq. Me₂NH, 80 °C.

2.1.2. Fucosamine

Polt and Sames have employed L-serine derived Schiff base **10** in the enantioselective synthesis of *N*-methyl-D-fucosamine **17** (Scheme 2)²⁹ which is the amino sugar component of the enediyne anticancer antibiotic neocarzinostatin.³⁰

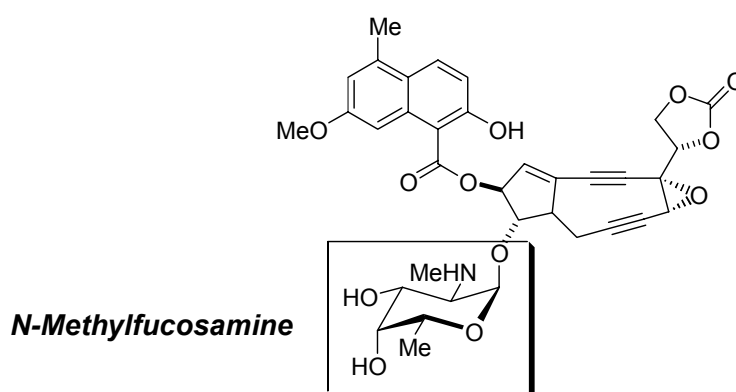
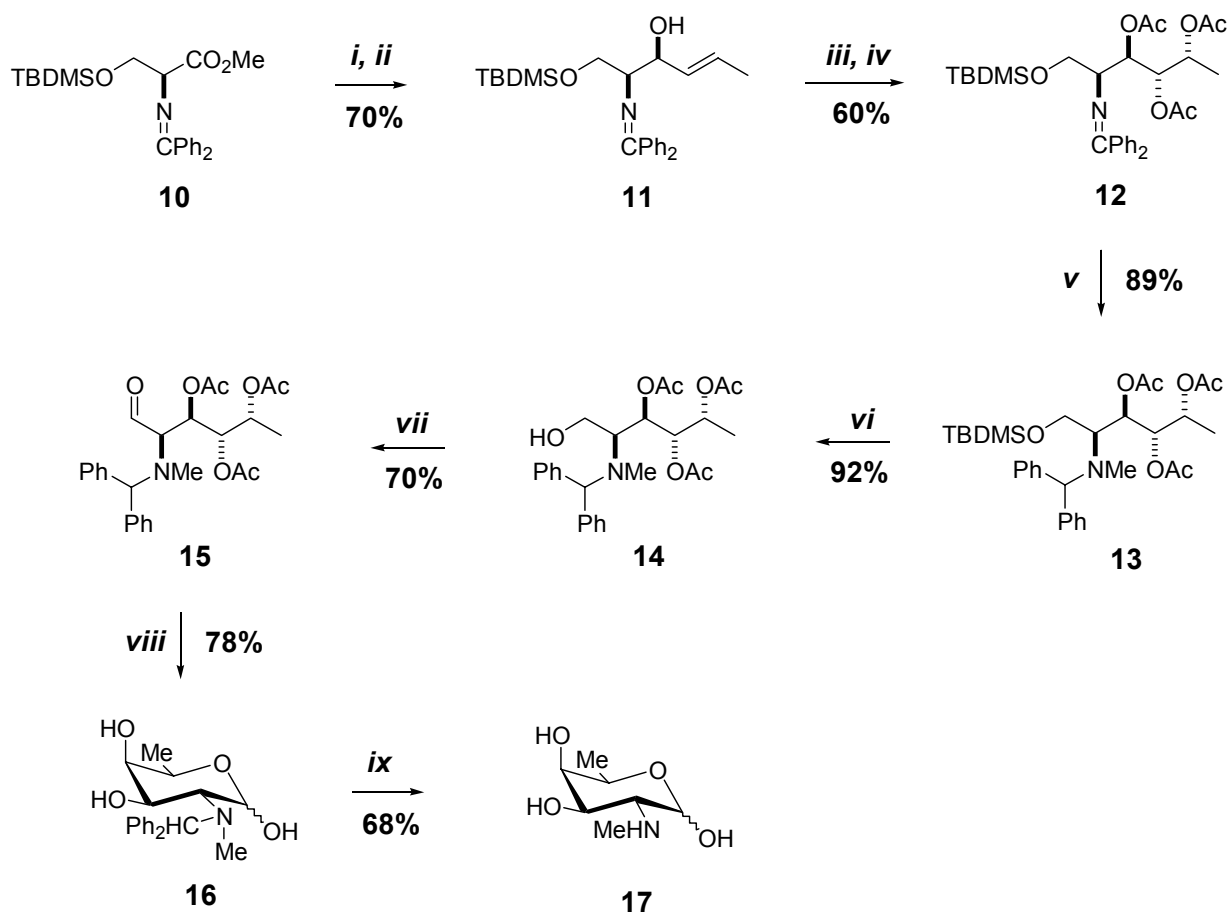


Figure 3. Neocarzinostatin chromopore.

In the beginning of the synthetic sequence, the protected L-serine derived methyl ester **10** was reduced to the corresponding aldehyde, followed by addition of alkenyllithium to form the *syn*-amino alcohol **11** with high diastereoselectivity (> 20:1). Osmium-catalyzed dihydroxylation of the double bond afforded a 6:1 mixture of *syn-anti-syn* and all-*syn*-aminotriols which were separated by chromatography after *in situ* acetylation, providing the desired triacetate **12**. Reduction of **12** to secondary amine, followed by *N*-methylation and cleavage of the silyl protection produced the primary alcohol **14**, which was converted to the α -amino aldehyde **15** by Swern oxidation. Deacetylation of **15** by weak Brønsted base potassium cyanide in anhydrous methanol gave the *N*-protected *N*-methyl-D-fucosamine intermediate **16** as a mixture of pyranose and furanose anomers. The Brønsted base was used due to the lability of aldehyde **15** towards basic reaction conditions. Finally, hydrogenolysis of the benzhydryl group of compound **16** generated *N*-methyl-D-fucosamine **17** in 13 % overall yield.

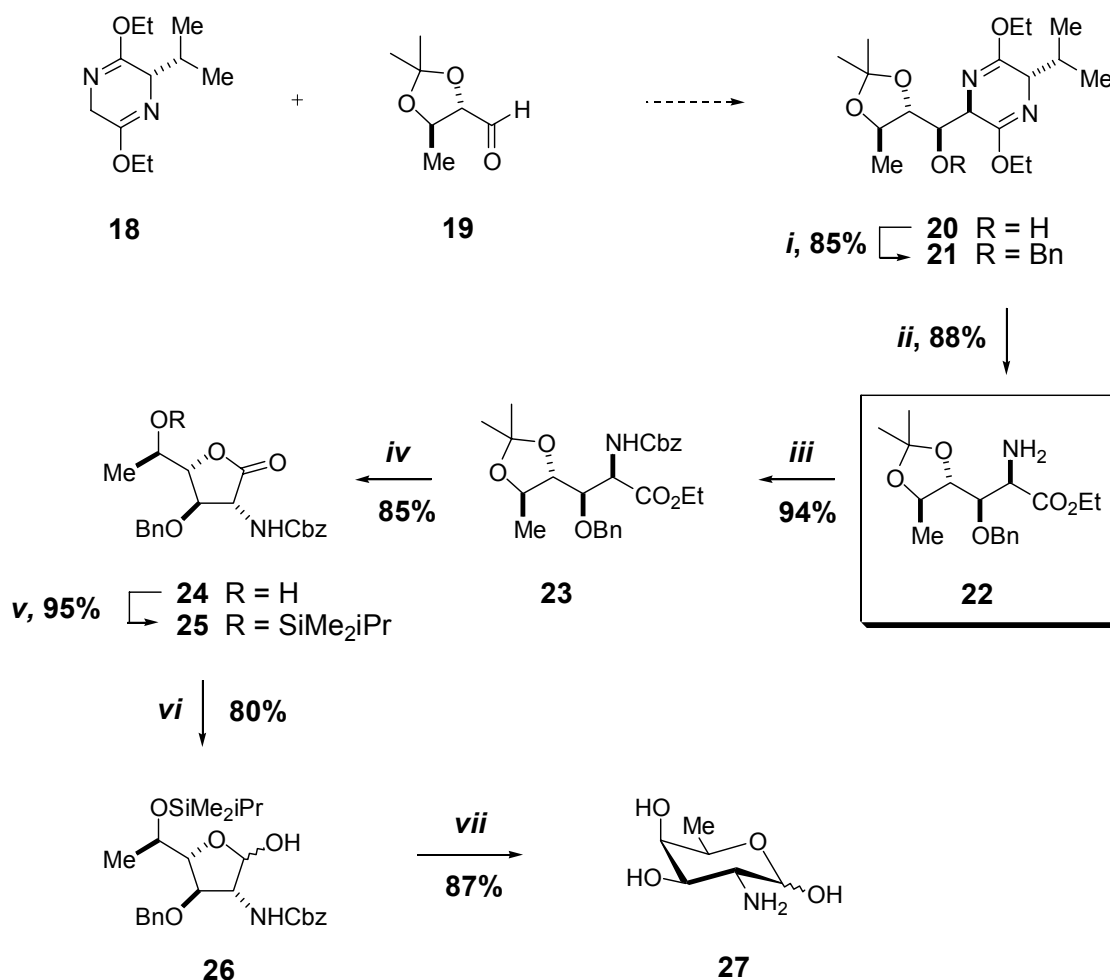


Scheme 2. *i*) DIBAL-H, TRIBAL, CH₂Cl₂, -78 °C; *ii*) LiCH=CHCH₃, toluene, -78 °C → rt; *iii*) K₂OsO₂(OH)₄, K₂CO₃/K₃Fe(CN)₆, *t*-BuOH/H₂O 1:1; *iv*) Ac₂O, pyr; *v*) NaBH₃CN, MeCN, CH₂O, pH~7; *vi*) 4 % aq. HF, MeCN; *vii*) Swern oxidation; *viii*) cat. KCN, MeOH; *ix*) H₂, Pd/C, MeOH.

Recently, Ruiz *et al.* reported the amino acid based synthesis of D-fucosamine **27** (Scheme 3) and its *N*-methyl derivative **17** (Scheme 4).³¹ The key intermediate **20** was constructed by a *syn*-aldol type reaction between Schöllkopf's bislactim ether **18**, prepared from glycine and L-valine, and the L-threonine derived 1,3-dioxolane-4-carboxaldehyde **19**. Benzyl protection of the intermediate **20**, followed by selective hydrolysis of the pyrazine moiety afforded the amino ester **22**. At this point, the synthesis routes for the two fucosamine derivatives **27** and **17** were differentiated, due to the introduction of the *N*-methyl functionality to the latter one.

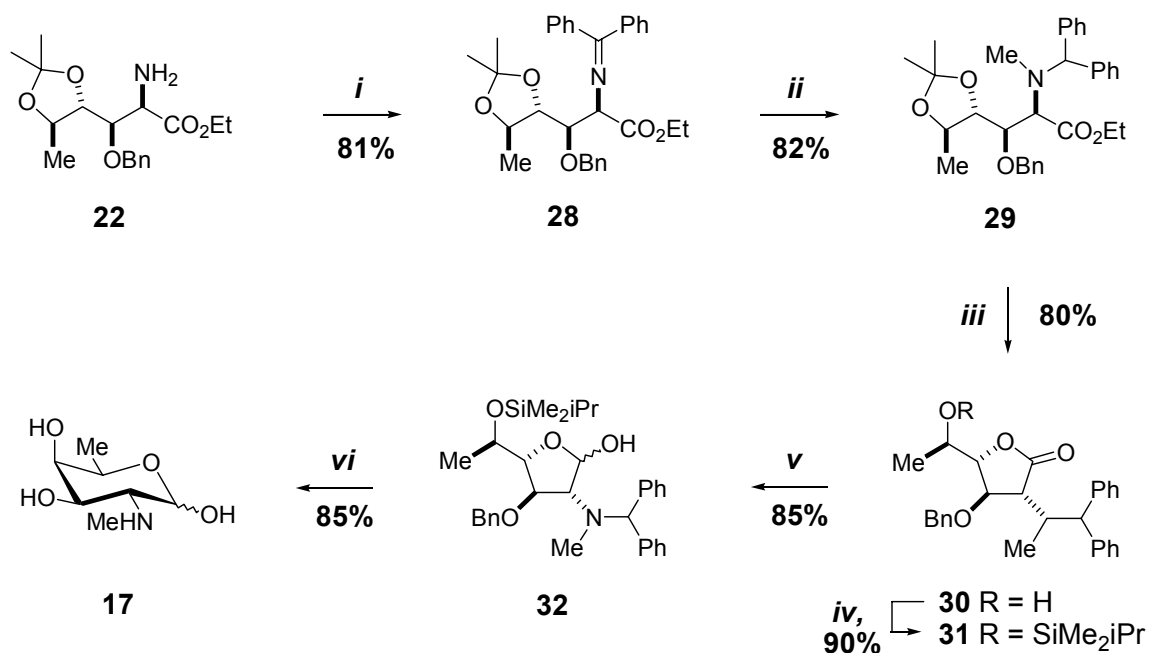
Preparation of D-fucosamine **27** proceeded *via* Cbz-protection of the amino group of **22**, followed by acidic cleavage of the acetonide, thus generating the desired lactone **24**. After

O-silylation of **24**, the fully protected lactone **25** was reduced to a mixture lactols **26**, which upon acidic deprotection furnished D-fucosamine **27**.



Scheme 3. *i*) NaH, BnBr, NBu₄I, THF, rt; *ii*) HCl, EtOH, rt; *iii*) Na₂CO₃, NaHCO₃, CbzCl, dioxane/H₂O 1:1, rt; *iv*) TFA/THF/H₂O 6:6:1, rt; *v*) *i*PrMe₂SiCl, imidazole, THF, rt; *vi*) DIBAL-H, -78 °C, toluene/THF 2:1; *vii*) H₂, Pd/C, MeOH/HCl 2:1, rt, Dowex, aq. NH₃.

For the preparation of *N*-methyl derivative **17**, the *N*-methyl moiety was brought to the molecule at the amino ester stage (Scheme 4). Treatment of the amino ester **22** with diphenylketimine and a catalytic amount of *p*-toluenesulfonic acid produced the imino ester **28**. Acidic reduction of the imine **28** to a secondary amine, followed by subsequent reductive methylation provided the monomethylamine **29**, which was converted to the target *N*-methyl-D-fucosamine **17** via similar transformations as performed for compound **23** in Scheme 3.



Scheme 4. *i*) Ph₂CNH, PTSA (cat.), CH₂Cl₂, rt; *ii*) NaBH₃CN, H₂CO, HOAc (gl.), pH~7, MeCN; *iii*) TFA/THF/H₂O 6:6:1, rt; *iv*) *i*PrMe₂SiCl, imidazole, THF, rt; *v*) DIBAL-H, -78 °C, toluene/THF 2:1; *vi*) H₂, Pd/C, MeOH/HCl 2:1, rt, then Dowex, aq. NH₃.

2.1.3. Elsaminose

Ruiz *et al.* utilized the key intermediate **20** as described for the preparation of the fucosamine derivatives **27** and **17** also in the synthesis of elsaminose **39** (Scheme 5),^{31b,32} which is the amino sugar constituent of the antitumor antibiotic elsamicin A. The amino sugar moiety makes elsamicin A remarkably water soluble and seems to have a critical role in the regulation of the biological activity of elsamicin A.³³

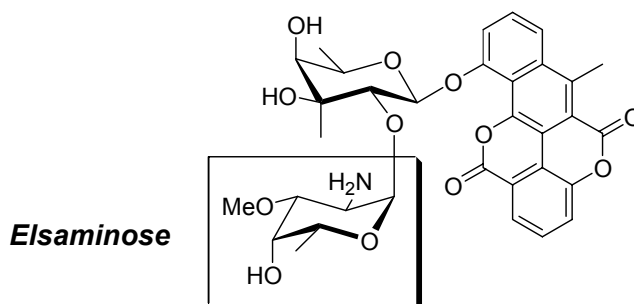
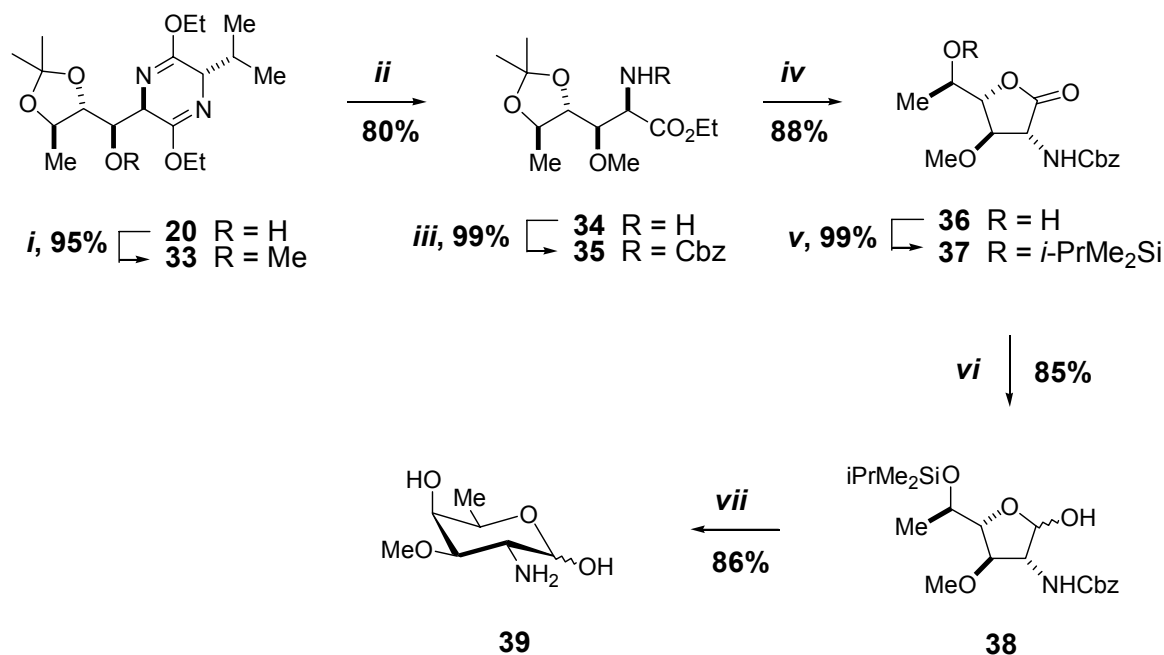


Figure 4. Elsamicin A.

The synthesis of elsaminose followed a similar pattern as reported above for the fucosamine derivatives **27** and **17**. Methylation of the free hydroxyl group of the key intermediate **20**, followed by removal of the chiral auxiliary gave the amino ester **34**, which upon Cbz- protection and cyclization in acidic media provided lactone **36**. *O*-Silylation of **36**, followed by DIBAL-H reduction afforded a mixture of furanoses **38**, which after final deprotection produced elsaminose **39**.

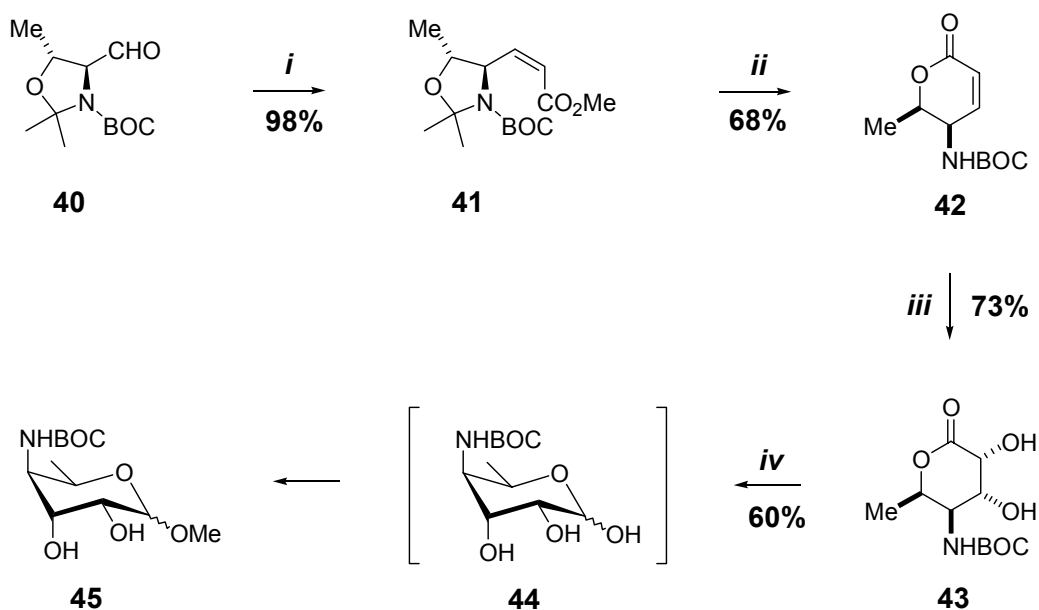


Scheme 5. *i*) NaH, MeI, THF, 0 °C \rightarrow rt; *ii*) 0.25 N HCl, EtOH, rt; *iii*) Na₂CO₃, NaHCO₃, CbzCl, dioxane/H₂O 1:1, rt; *iv*) TFA:THF:H₂O 6:6:1, rt; *v*) *i*PrMe₂SiCl, imidazole, THF, rt; *vi*) DIBAL-H, -78 °C, toluene:THF 2:1; *vii*) H₂, Pd/C, then Dowex 50x8-200, then HCl.

2.1.4. Dideoxygulopyranoside

In our group, methyl 4-amino-4,6-dideoxygulopyranoside **45** was synthesized from the L-threonine derived aldehyde **40** (Scheme 6).³⁴ The aldehyde **40** was subjected to a modified Horner-Wadsworth-Emmons olefination, producing *Z*-enoate **41** in very high yield and excellent selectivity (*Z*:*E* ratio 17:1). Simultaneous cleavage of the acetonide with cyclization in glacial acetic acid produced lactone **42**. Osmium-catalyzed *cis*-dihydroxylation afforded stereoselectively diol **43**, which was converted to the target

methyl glycoside **45** via DIBAL-H reduction and subsequent acidic methanolysis in 29 % overall yield from aldehyde **40**.



Scheme 6. *i)* MeO₂CCH₂P(O)(OCH₂CF₃)₂, K₂CO₃, 18-crown-6; toluene, -20 °C → rt; *ii)* AcOH, 60 °C; *iii)* OsO₄, NMO, *t*-BuOH/H₂O/acetone; *iv)* DIBAL-H, toluene, followed by CSA, MeOH.

2.2. Monoamino trideoxyhexoses

2.2.1. Daunosamine

Daunomycin (or daunorubicin) and adriamycin are anthracycline anticancer antibiotics which both contain an amino sugar fragment L-daunosamine.³⁵ L-Daunosamine derivatives have been synthesized from amino acids by several groups.

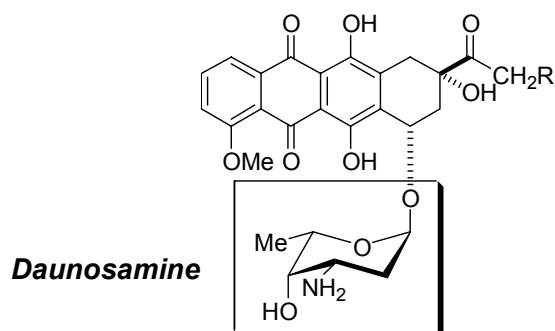
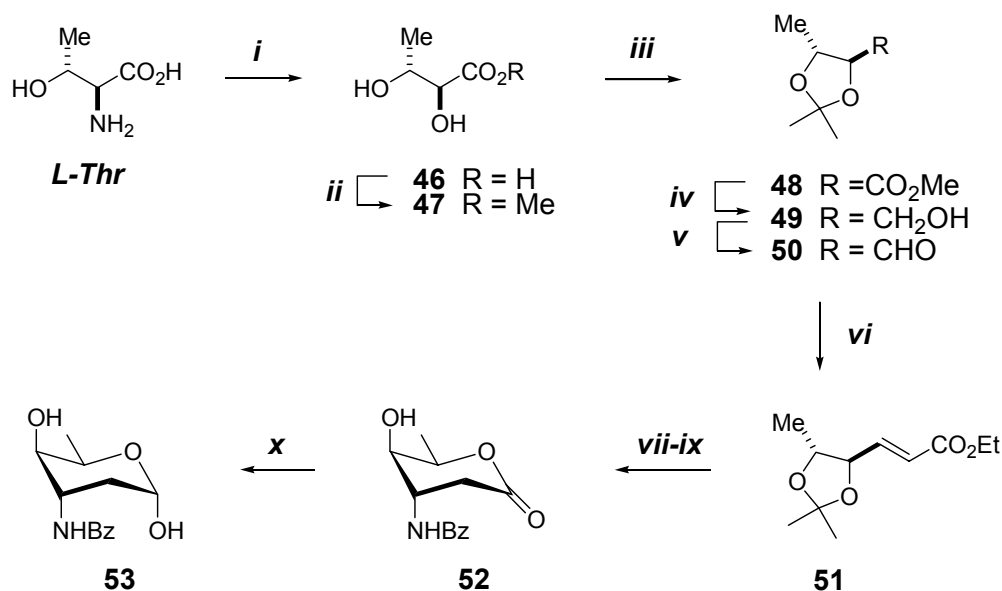


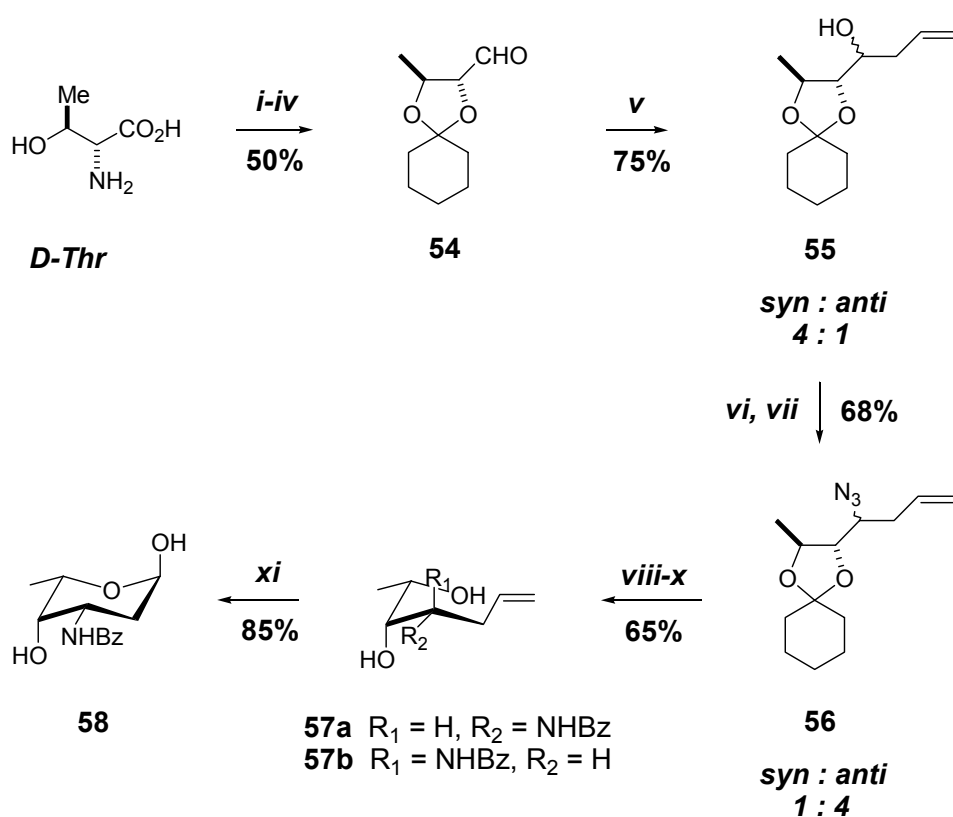
Figure 5. Daunomycin: R = H, adriamycin: R = OH.

In 1979, Fuganti and co-workers reported the synthesis of D-3-*epi*-daunosamine derivative **53** by utilizing the chirality of L-threonine (Scheme 7).³⁶ L-Threonine was converted to ester **48** *via* deamination, esterification and ketalization. Reduction of **48** by lithium aluminum hydride to the corresponding alcohol, followed by oxidation with pyridinium chlorochromate gave aldehyde **50**, which upon Wittig reaction produced the α,β -unsaturated ester **51**. Stereospecific addition of ammonia to the double bond and acidic hydrolysis of the dioxolane ring, followed by benzylation resulted in the formation of lactone **52**. Reduction of lactone to lactol furnished *N*-benzoyl-D-3-*epi*-daunosamine **53**.



Scheme 7. *i*) HNO₂; *ii*) MeOH, HCl; *iii*) DMP, PTSA (45 % overall); *iv*) LiAlH₄, Et₂O (85 %); *v*) PCC, CH₂Cl₂, AcONa, *vi*) Ph₃P=CHCO₂Et, *vii*) NH₃, MeOH; *viii*) 2*N* HCl; *ix*) BzCl, pyr/CH₂Cl₂; *x*) DIBAL-H, THF.

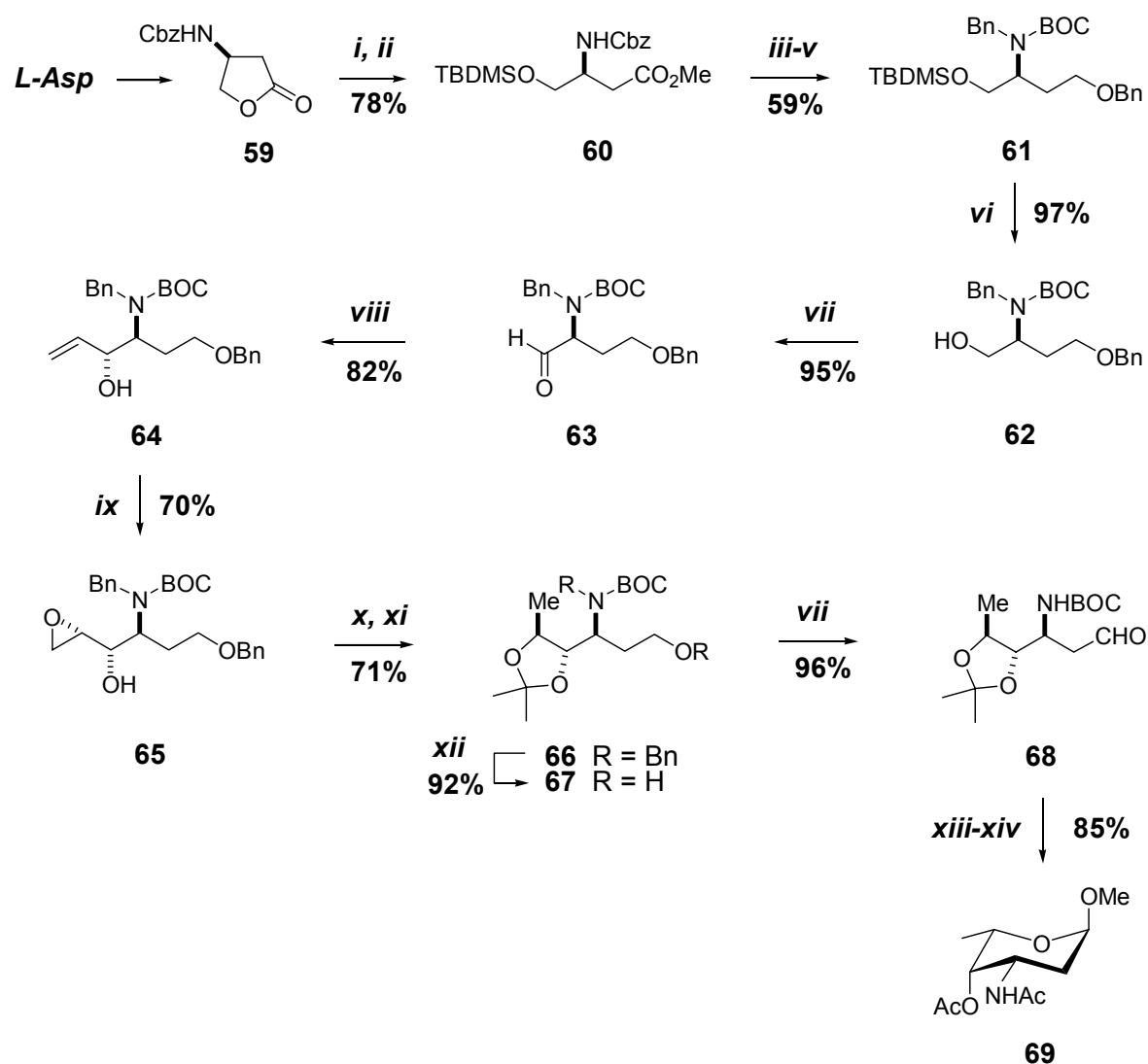
In 1981, Fuganti and co-workers prepared *N*-benzoyl-L-daunosamine **58** starting from D-threonine (Scheme 8).³⁷ D-Threonine was first converted to the dioxolane derivative **54**, which upon addition of a Grignard reagent gave an inseparable 4:1 mixture of epimeric alcohols **55** with the *syn*-isomer predominating. Transformation of the alcohol intermediates **55** to the azide derivatives **56** proceeded *via* tosylation with inversion of configuration, producing a 1:4 mixture of *syn*- and *anti*-isomers. Successive reduction, deketalization and benzoylation led to the formation of the *N*-benzoylated isomers **57**, which were separated by crystallization. Ozonolysis of **57a**, followed by treatment with dimethyl sulfide provided *N*-benzoyl-L-daunosamine **58**.



Scheme 8. *i*) $\text{NaNO}_2, \text{H}_2\text{SO}_4$; *ii*) $\text{MeOH}, \text{H}_3\text{O}^+$; *iii*) cyclohexanone, PTSA; *iv*) $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OMe})_2, \text{Et}_2\text{O}, -50^\circ\text{C}$; *v*) $\text{CH}_2=\text{CHCH}_2\text{MgBr}, \text{THF}, -78^\circ\text{C}$; *vi*) *p*TsCl, pyridine; *vii*) $\text{NaN}_3, \text{NH}_4\text{Cl}, \text{DMF}, 100^\circ\text{C}$, *viii*) $\text{LiAlH}_4, \text{Et}_2\text{O}$; *ix*) 50 % AcOH, *x*) BzCl, K_2CO_3 , acetone; *xi*) $\text{O}_3, \text{MeOH}, -20^\circ\text{C}$, then Me_2S .

Jurczak *et al.* have utilized the chirality of L-homoserinal derivative **59**, obtained from L-aspartic acid, in the synthesis of L-daunosamine (Scheme 9).³⁸ To start with, L-aspartic

acid was converted to lactone **59**, which upon transesterification and subsequent formation of the silyl ether afforded compound **60**. After replacement of the Cbz-protection of the amine by a BOC-group, reduction of the ester functionality to primary alcohol, followed by benzyl protection provided intermediate **61**. Removal of the silyl protection and oxidation of the resulting free hydroxy group generated L-homoserinal derivative **63**.

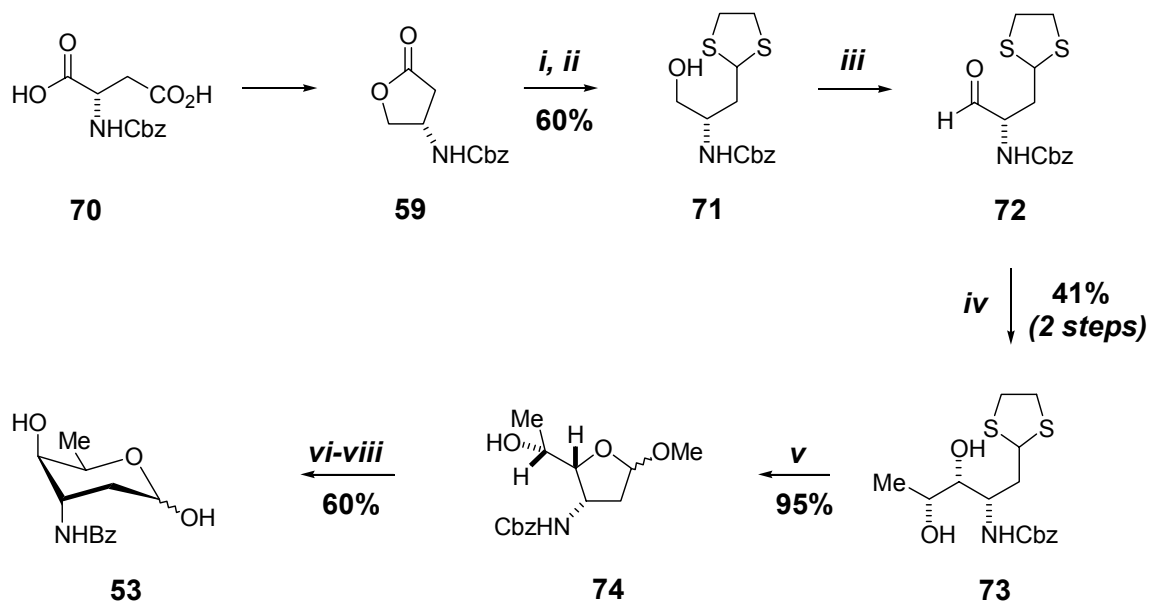


Scheme 9. *i)* DCC, MeOH, rt; *ii)* TBSCl, imidazole, DMF, 40 °C; *iii)* H₂, 5 % Pd/C, (BOC)₂O, MeOH, rt; *iv)* LiAlH₄, Et₂O, -25 °C; *v)* BnBr, NaH, DMF, -10 °C; *vi)* Bu₄NF, THF, rt; *vii)* SO₃/pyr, DMSO, rt; *viii)* vinyl-MgCl, Et₂O, -78 °C; *ix)* *m*CPBA, CH₂Cl₂, 5 °C; *x)* DIBAL-H; Et₂O, -78 °C → -40 °C; *xi)* DMP, acetone, PTSA, 0 °C → 15 °C; *xii)* Na, NH₃ (liq.); *xiii)* HCl/MeOH (pH≈1), rt; *xiv)* Ac₂O, pyr, rt.

Treatment of **63** with vinylmagnesium chloride produced the *anti*-allyl alcohol **64** in high diastereoselectivity. Epoxidation resulted in the formation of the *syn*-epoxide **65** as a single isomer. Reductive ring opening and subsequent transketalization gave the isopropylidene derivative **66**. Cleavage of the benzyl protection and oxidation of the resulting free alcohol afforded aldehyde **68**. Treatment of aldehyde **68** with acidic methanol, followed by acetylation afforded the target L-daunosamine derivative **69** as a 95:5 mixture of methyl α - and β -glycosides.

Another L-homoserinal based approach for the synthesis of daunosamine derivative was reported by Konradi and Pedersen.³⁹ They prepared *N*-benzoyl-D-3-*epi*-daunosamine **53** starting from commercially available *N*-Cbz-L-aspartic acid **70** (Scheme 10). The key step of the synthesis was pinacol cross-coupling between the α -amino aldehyde and an aliphatic aldehyde.

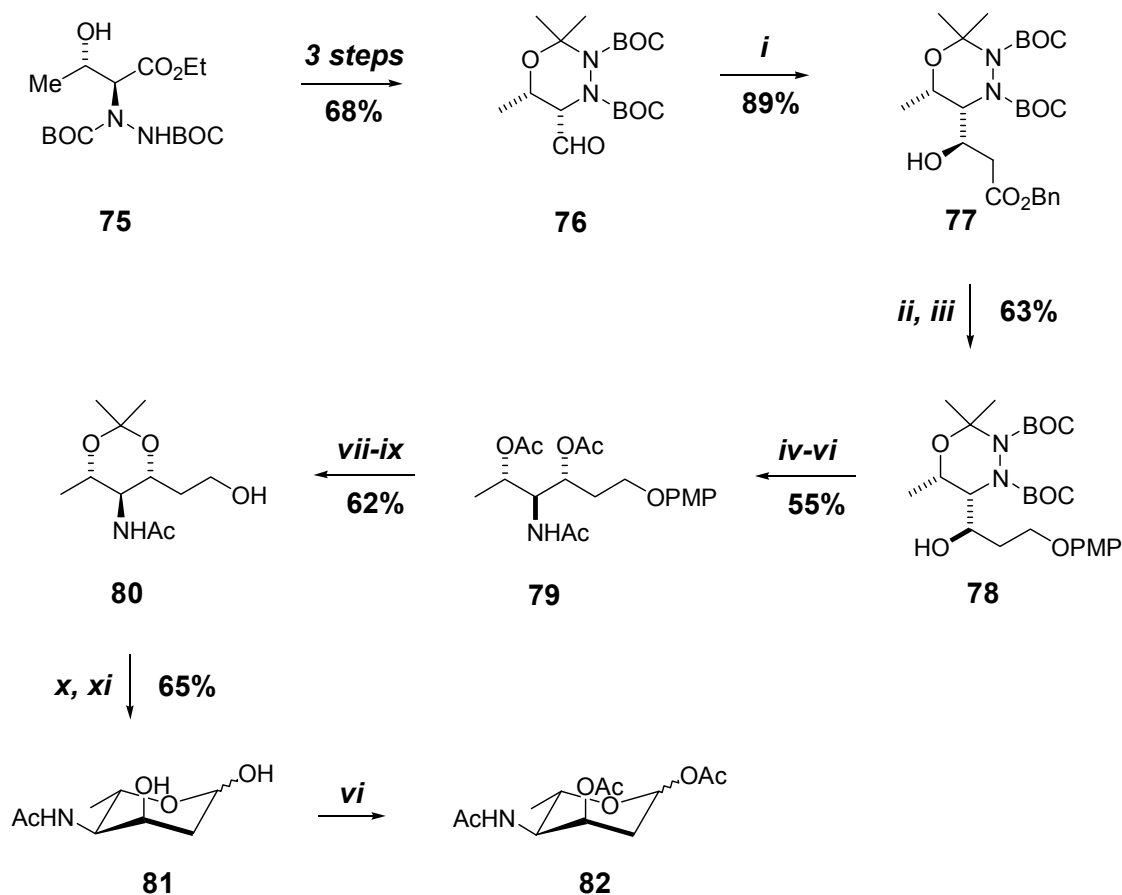
The synthesis started by conversion of *N*-Cbz-L-aspartic acid **70** into the lactone **59**, which upon DIBAL-H reduction to lactol and subsequent ring opening by 1,2-ethanedithiol in acidic media produced the hydroxydithiolane **71**. Oxidation of **71** gave the α -amino aldehyde **72**. Pinacol coupling of **72** with an excess of acetaldehyde in the presence of a vanadium(II) reagent $[V_2-Cl_3(THF)_6]_2[Zn_2Cl_6]$ afforded the cross-coupled product **73** as the major isomer. Cleavage of the dithiolane protection provided an anomeric mixture of methyl *N*-Cbz-D-furanosides **74**, which was converted to *N*-benzoyl-D-3-*epi*-daunosamine **53** in 13 % overall yield from *N*-Cbz-L-aspartic acid **70**.



Scheme 10. *i*) DIBAL-H; CH₂Cl₂, -78 °C; *ii*) (CH₂SH)₂, BF₃(Et₂O), CH₂Cl₂; *iii*) SO₃(py), DMSO, Et₃N; *iv*) MeCHO, [V₂-Cl₃(THF)₆]₂[Zn₂Cl₆], CH₂Cl₂, 0 °C; *v*) Hg(ClO₄)₂(H₂O)₃, MeOH; *vi*) LiOH, MeOH/H₂O, reflux; *vii*) PhCOCl, K₂CO₃; H₂O; *viii*) 20 % AcOH/H₂O, reflux.

2.2.2. Hollantosamine

Guanti *et al.* have synthesized the hollantosamine derivative **81** from *L-allo*-threonine synthetic equivalent **75** by a 14 step sequence in 8 % overall yield. (Scheme 11).⁴⁰ The *L-allo*-threonine derivative **75** was first converted to the aldehyde **76** in three steps, which upon condensation with the lithium enolate of benzyl acetate afforded the *anti*-alcohol **77** in excellent stereoselection. Reduction of the ester to a primary alcohol with calcium borohydride, followed by selective protection of the hydroxyl group produced compound **78**, which was converted to the triacetate **79** in three steps. A series of protecting group interchanges provided acetonide **80**. Oxidation of the free alcohol group to aldehyde and subsequent hydrolysis of the ketal generated the *N*-acetylhollantosamine **81**, which was characterized as its triacetyl derivative **82**.



Scheme 11. *i*) $\text{CH}_2=\text{C}(\text{OLi})\text{OBn}$, THF, -87°C ; *ii*) $\text{Ca}(\text{BH}_4)_2$, EtOH, THF; *iii*) 4- $\text{MeOC}_6\text{H}_4\text{OH}$, Ph_3P , DEAD; *iv*) AcOH/1N HCl 2:1, 75°C ; *v*) H_2 , PtO_2 , EtOH- H_2O ; *vi*) Ac_2O , pyr, rt; *vii*) Et_3N , MeOH, reflux; *viii*) $\text{MeOC}(\text{Me})=\text{CH}_2$, PTSA, CH_2Cl_2 , rt; *ix*) $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$, H_2O , MeCN, pyr; *x*) TPAP, NMO, 4Å molecular sieves, CH_2Cl_2 , rt; *xi*) AcOH, H_2O .

2.2.3. Kedarosamine

Kihlberg *et al.* have reported a D-threonine based diastereoselective synthesis of kedarosamine (Scheme 12), an amino sugar moiety of the enediyne antitumor antibiotic kedarcidin chromophore.⁴¹

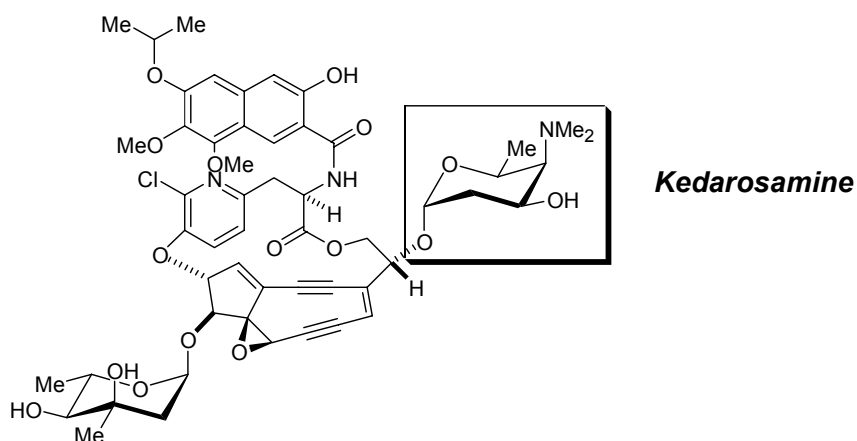
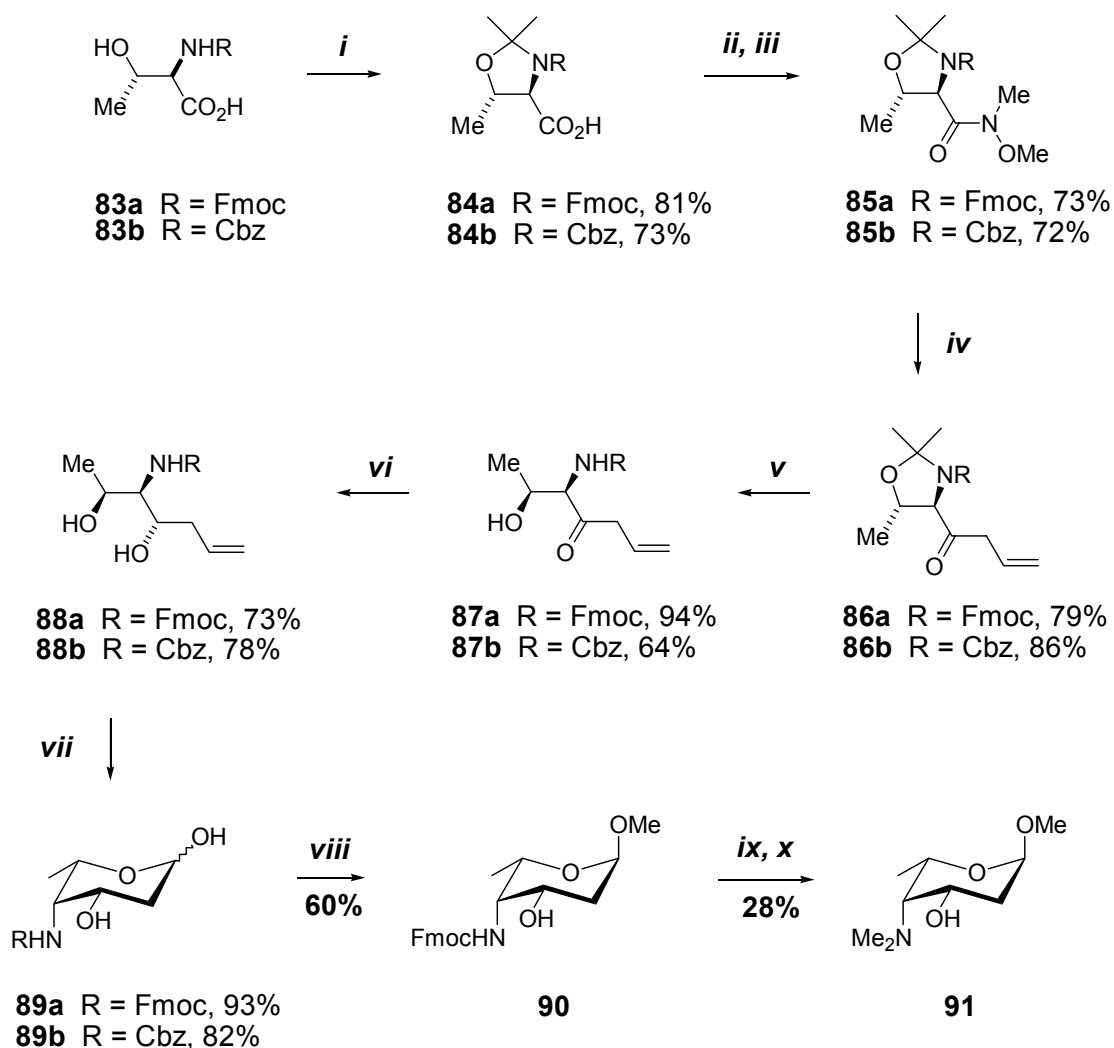


Figure 6. Kedarcidin chromophore.

Kedarosamine derivatives **89a** and **89b** were synthesized from Fmoc- or Cbz-protected D-threonine derivatives **83a** or **83b**. The synthesis route was originally developed for the Fmoc-protected derivative **89a**,^{41a} which was transformed to kedarosamine **91**, whereas the use of a Cbz instead of a Fmoc-protection was later found essential for the successful preparation of an analogue of kedarcidin chromophore.^{41b} Ketal protection of the hydroxyl and amino functionalities of **83** provided the acid **84**, which was transformed to the Weinreb amide **85** via acid chloride. Addition of allylmagnesium bromide to amide **85** provided the ketone **86**, which upon successive removal of the isopropylidene protection and reduction afforded the *anti*-alcohol **88** as a single diastereomer. Ozonolysis of **88** gave the hemiacetal **89**. Acidic methanolysis of **89a** produced a 4:1 mixture of α - and β -methyl glycosides from which the α - anomer **90** was isolated in 60 % yield. Deprotection and reductive dimethylation of the resulting amine finally gave methyl α -kedarosamine **91**.



Scheme 12. *i*) $\text{CH}_2(\text{OMe})_2$, PTSA, benzene, reflux; *ii*) cyanuric chloride, pyr, CH_2Cl_2 ; *iii*) $\text{Me}(\text{MeO})\text{NH}\cdot\text{HCl}$, pyr, CH_2Cl_2 ; *iv*) allyl-MgBr, THF, $-78\text{ }^\circ\text{C}$; *v*) TFA/MeOH 9/1; *vi*) $\text{Me}_4\text{NBH}(\text{OAc})_3$, MeCN/HOAc 1/1, $-28\text{ }^\circ\text{C}$; *vii*) O_3 , Me_2S , MeOH, $-78\text{ }^\circ\text{C}$, *viii*) PTSA, MeOH; *ix*) Pd/C, $\text{Pd}(\text{OAc})_2$, NH_4HCO_2 , MeOH; *x*) 10 % Pd/C, H_2 , HCHO, MeOH/ H_2O 1/1.

2.3. Monoamino tetraoxyhexoses

2.3.1. Tolyposamine

Guanti and co-workers also reported the synthesis of *N*-acetylated-L-tolyposamine **98**, starting from *L*-allo-threonine derivative.^{42,43} L-Tolyposamine is the carbohydrate component of antibiotic tolypomycin Y, linked by an imine group to the quinone ring.

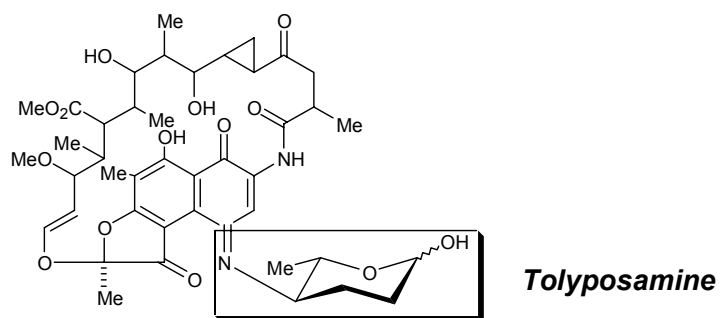
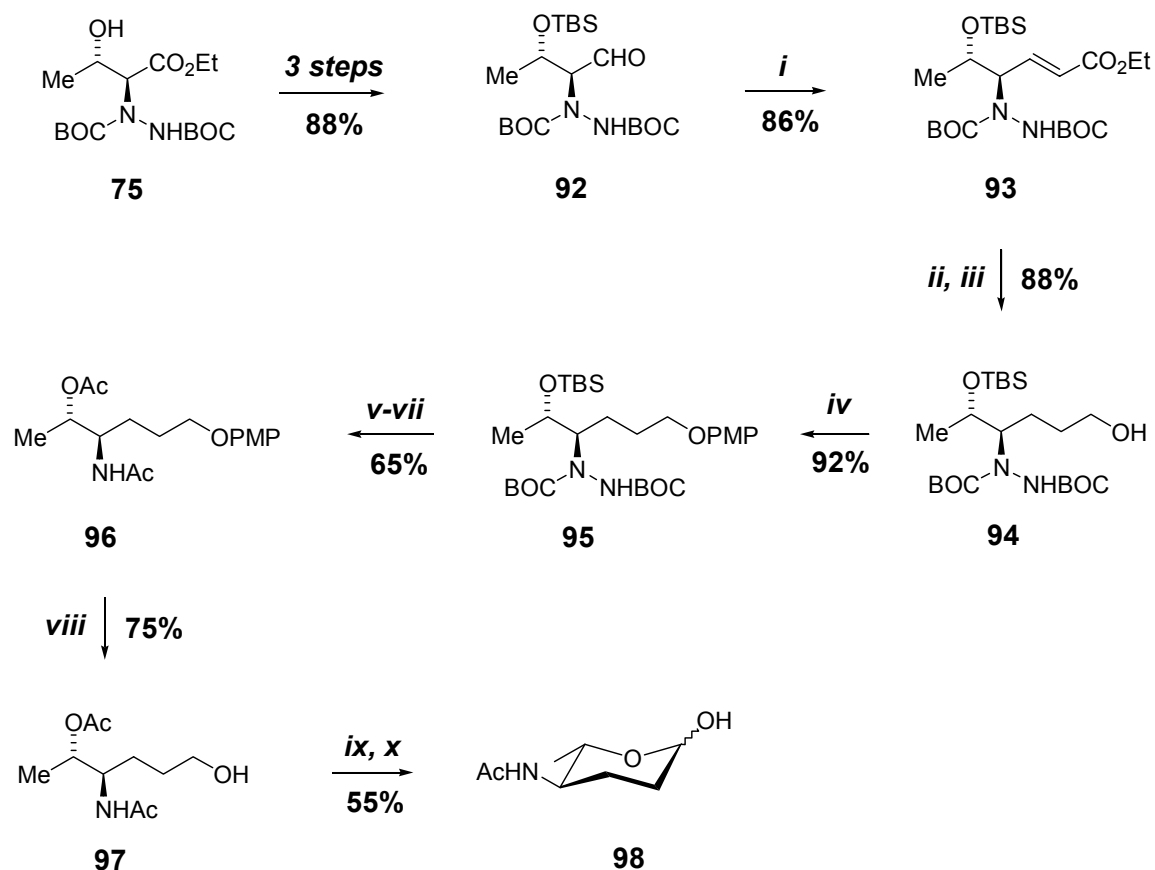


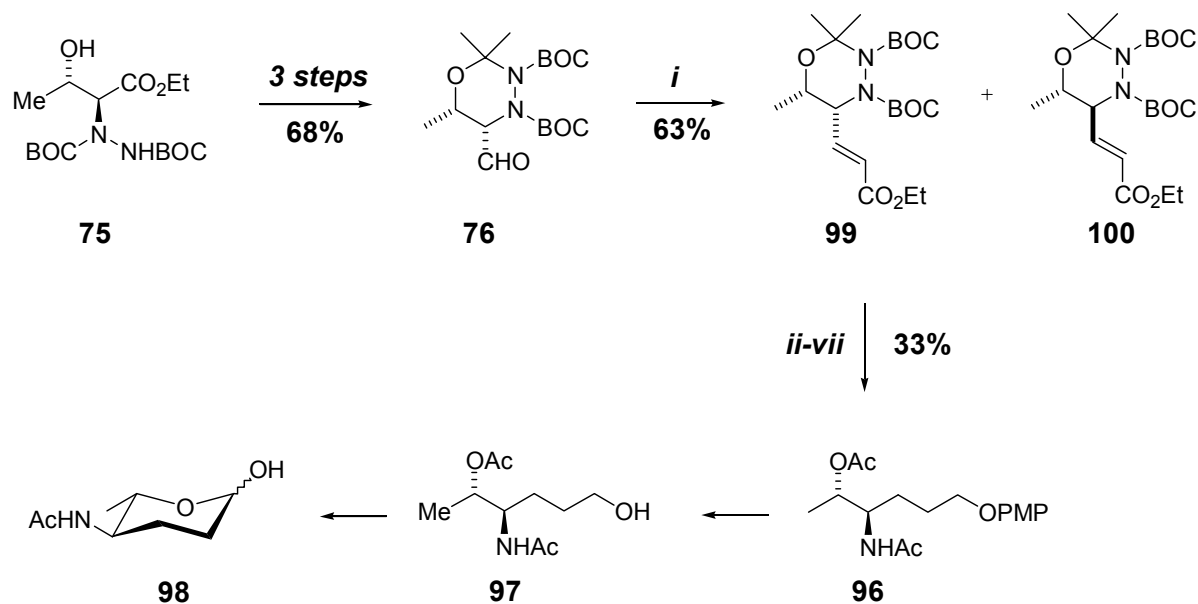
Figure 7. Tolyposamycin Y.

The preparation of the target amino sugar **98**, starting from the *L-allo*-threonine equivalent **75**, could be accomplished either *via* acyclic **92** (Scheme 13) or cyclic **76** (Scheme 14) aldehyde intermediates. The acyclic synthetic sequence started by transformation of compound **75** into aldehyde **92**, having its hydroxyl group protected as silyl ether. Wittig reaction of **92** with stabilized phosphorane afforded the unsaturated ester **93**, which was converted into alcohol **94** by hydrogenation of the double bond, followed by reduction of the ester functionality. PMP-protection of the free hydroxyl group afforded intermediate **95**, which upon replacement of the silyl ether and BOC-protections by acetates gave compound **96**. Cleavage of the PMP-group produced the primary alcohol **97**, which was transformed to the target *N*-acetyl-*L*-tolyposamine **98** *via* oxidation and selective deacetylation in 16 % overall yield from **75**.



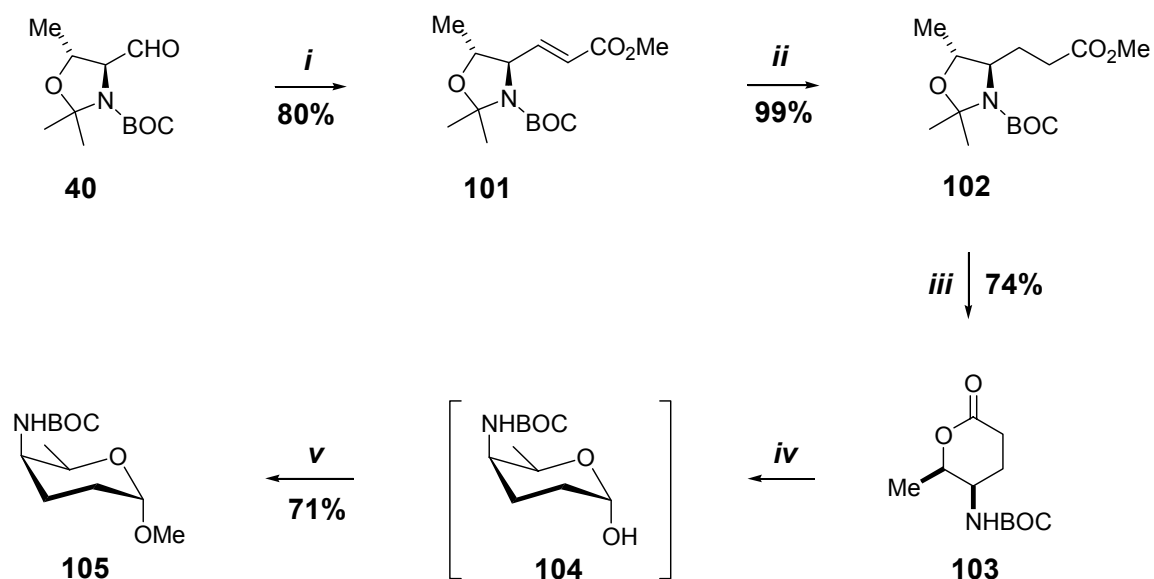
Scheme 13. *i*) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, toluene, 4Å molecular sieves, 70 °C; *ii*) H_2 , PtO_2 , EtOH, rt; *iii*) $\text{Ca}(\text{BH}_4)_2$, EtOH, THF, -20 °C → rt; *iv*) $p\text{MeOC}_6\text{H}_4\text{OH}$, Ph_3P , DEAD, CH_2Cl_2 , rt; *v*) AcOH/1N HCl 2:1, 70 °C; *vi*) H_2 , PtO_2 , EtOH- H_2O ; *vii*) Ac_2O , pyr, DMAP, rt; *viii*) $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$, H_2O , MeCN, pyr, 0 °C; *ix*) $(n\text{-Pr})_4\text{NRuO}_4$, NMO, CH_2Cl_2 , 4Å molecular sieves, rt; *x*) DBU, MeOH, 70 °C.

An attempt to convert the cyclic aldehyde intermediate **76** to the unsaturated ester **99** by the Wittig condensation resulted in epimerization to the undesired *trans* isomer **100**. Thus, by a modified procedure of the HWE olefination the *cis*- and *trans*-diastereomers **99** and **100** were generated in a 95:5 ratio, respectively. The rest of the synthesis followed similar transformations as performed for compound **93**.



Scheme 14. *i*) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, $\text{EtN}(\text{iPr})_2$, LiCl , rt, MeCN ; *ii*) H_2 , PtO_2 , EtOH , rt; *iii*) $\text{Ca}(\text{BH}_4)_2$, EtOH , THF , $-20\text{ }^\circ\text{C} \rightarrow \text{rt}$; *iv*) $p\text{MeOC}_6\text{H}_4\text{OH}$, Ph_3P , DEAD , CH_2Cl_2 , rt; *v*) $\text{AcOH}/1\text{N HCl}$ 2:1; *vi*) H_2 , PtO_2 , $\text{EtOH}-\text{H}_2\text{O}$; *vii*) Ac_2O , pyr , DMAP , rt.

The L-threonine based synthesis route developed for the dideoxy aminohexoses in our group could be adapted also for the preparation of *epi*-tolypoamine **105** (Scheme 15).³⁴ Standard Horner-Wadsworth-Emmons olefination of aldehyde **40** gave the *E*-enoate **101** as a 4:1 mixture of *E*- and *Z*-isomers, respectively. Hydrogenation of the mixture of double bond isomers followed by lactonization under acidic conditions afforded compound **103**, which upon reduction and subsequent acidic methanolysis produced the *epi*-tolypoamine derivative **105** in only five steps and with 42 % overall yield.



Scheme 15. *i*) $\text{MeO}_2\text{CCH}_2\text{P}(\text{O})(\text{OMe})_2$, K_2CO_3 , toluene; *ii*) H_2 , Pd/C, EtOAc; *iii*) AcOH, 60°C ; *iv*) DIBAL-H, toluene, -78°C ; *v*) MeOH, H^+ , $\text{HC}(\text{OMe})_3$.

2.4. Miscellaneous deoxyaminohexoses

2.4.1. Sibirosamine

Rapoport and co-workers⁴⁴ utilized *L*-allo-threonine as the chiral educt in the synthesis of methyl *L*-sibiosaminide **116** (Scheme 16). Sibirosamine is the amino sugar constituent of the potent antitumor antibiotic sibiromycin (Fig. 8).⁴⁵

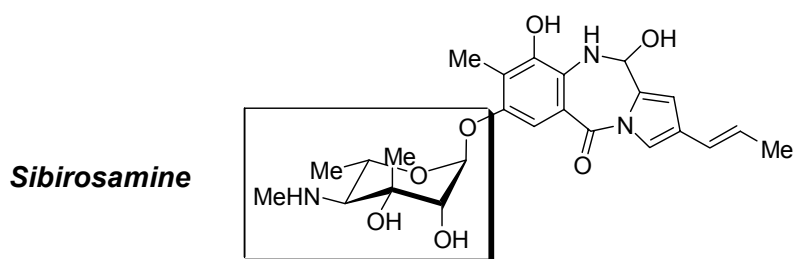
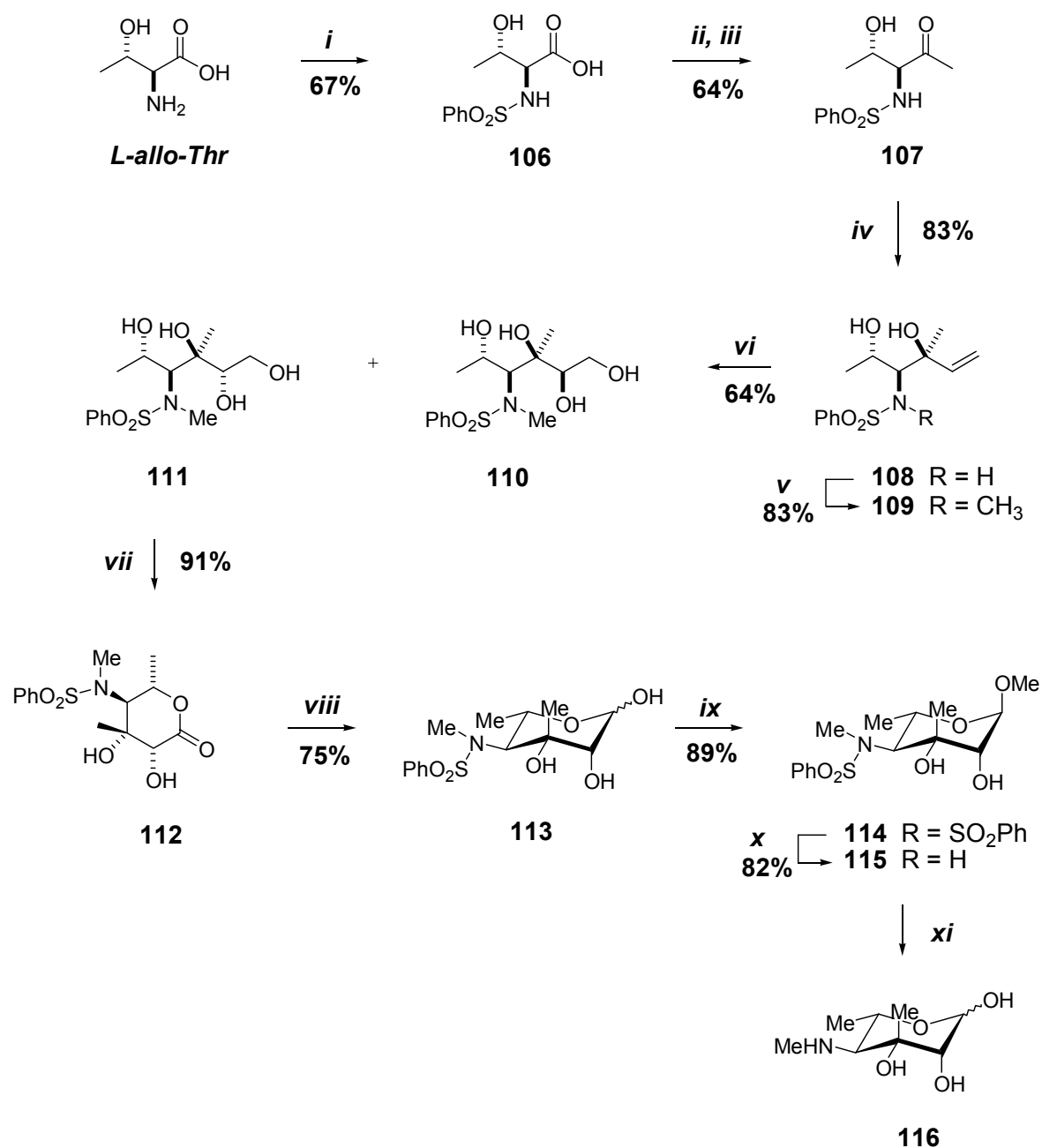


Figure 8. Sibiromycin.

L-allo-Threonine was first protected as its *N*-phenylsulfonyl derivative **106** and then converted to methyl ketone **107** via lithiation, followed by treatment with methylmagnesium iodide. The ketone **107** was then reacted with vinylmagnesium bromide

to afford the tertiary alcohol **108**, which was *N*-methylated with methyl iodide and potassium carbonate in isopropanol to give intermediate **109**. Osmium-catalyzed dihydroxylation of **109** produced a 1:4 mixture of tetraols **110** and **111**, which were separated by chromatography.



Scheme 16. *i*) PhSO₂Cl, Na₂CO₃; *ii*) MeLi, -78 °C → 0 °C; *iii*) MeMgI, 35 °C; *iv*) CH₂=CHMgBr, -10 °C → rt; *v*) K₂CO₃, MeI, IPA, 65 °C; *vi*) NMO, OsO₄; *vii*) O₂, Pt, 60 °C; *viii*) DIBAL-H, -45 °C; *ix*) MeOH, H⁺; *x*) Na, NH₃; *xi*) 6*N* HCl.

Platinum-catalyzed oxidation of the primary hydroxyl group of **111** afforded lactone **112**, which was reduced by diisobutylaluminium hydride to the anomeric mixture of lactols **113**. Acidic methanolysis of **113**, followed by reductive cleavage of the phenylsulfonyl group with sodium in liquid ammonia gave a single anomer of methyl L-sibirosaminide **115**. Acidolysis of **115** resulted in the formation of the desired free amino sugar **116**, but the product was too unstable to be isolated.

2.4.2. Purpurosamine

Kamiyama, Ohno and co-workers have reported the synthesis of 6-*epi*-D-purpurosamine B **127** (Scheme 17),⁴⁶ a component of an aminoglycoside antibiotic fortimicin A,⁴⁷ starting from L-alanine and malic acid.

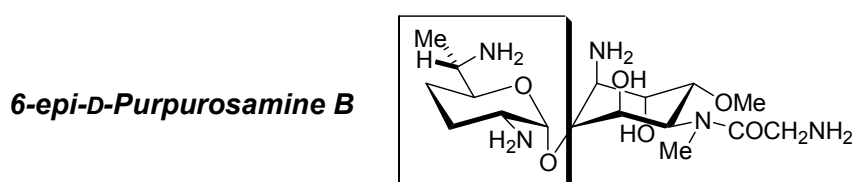
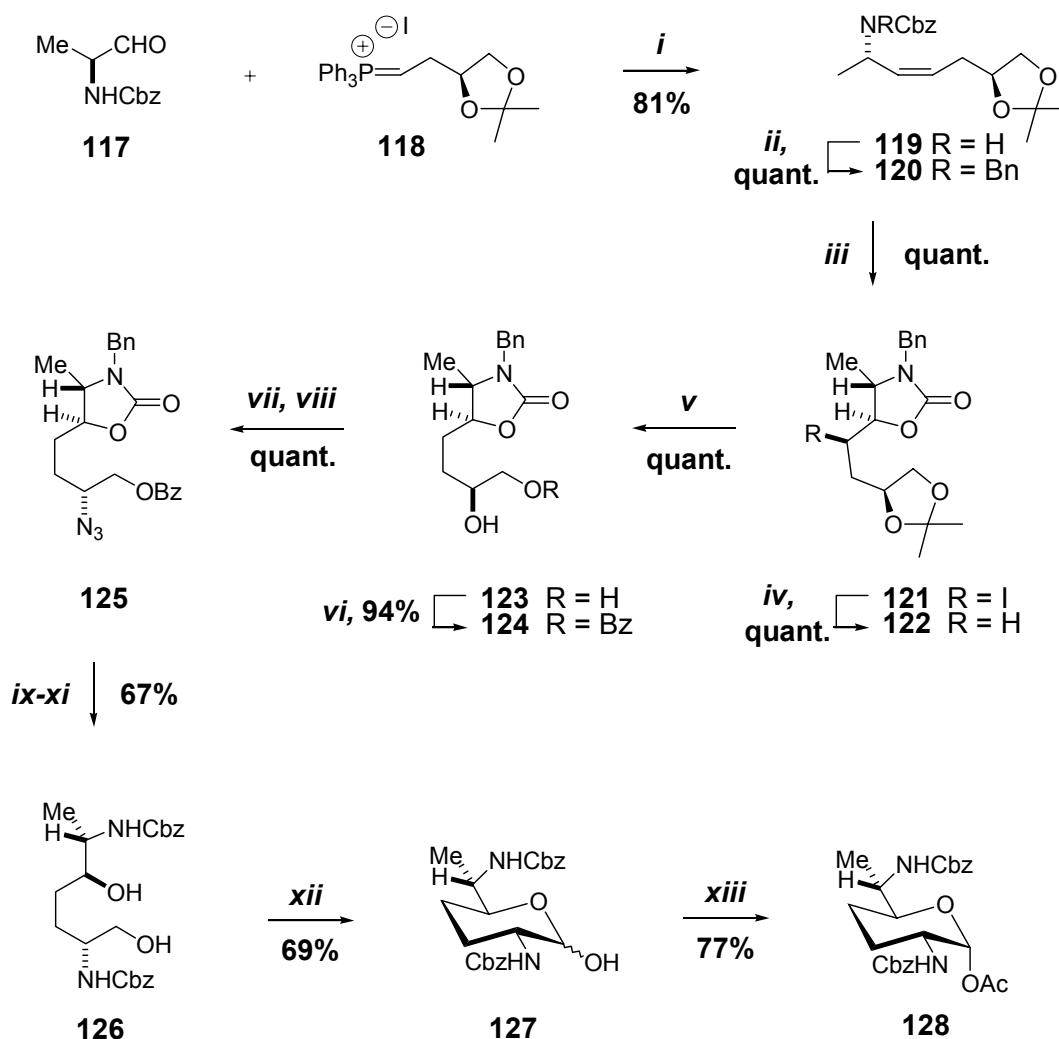


Figure 9. Fortimicin A.

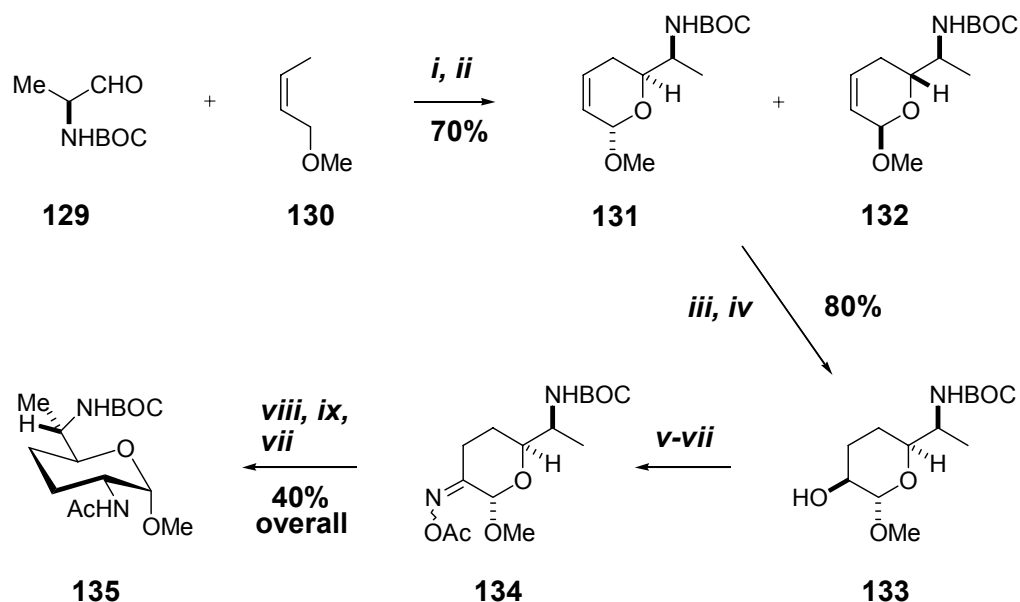
Cbz-protected L-alaninal **117** and the phosphonium salt **118**, derived from malic acid, were first coupled to form the *Z*-olefin **119**. After benzyl protection of the carbamate nitrogen, iodocyclocarbamation was carried out to form the *trans* cyclocarbamate **121** as the sole product. Successive removal of the iodo group and the acetonide moiety afforded the diol **123**. After selective benzylation of the primary hydroxyl group, the secondary hydroxyl functionality was replaced by azide with inversion of configuration to produce the azidocarbamate **125**. After transformation of **125** to diol **126**, selective oxidation for the primary hydroxyl moiety was accomplished by reaction with $\text{RuCl}_2(\text{PPh}_3)_3$ -complex to generate the protected 6-*epi*-D-purpurosamine B **127**, which was analyzed as its α -acetoxy derivative **128**.



Scheme 17. *i*) KH, THF, 0 °C; *ii*) BnBr, NaH, DMF; *iii*) I₂, CH₂Cl₂, 0 °C; *iv*) n-Bu₃SnH, benzene; *v*) 1N HCl, THF; *vi*) BzCl, Et₃N, CH₂Cl₂; *vii*) MsCl, Et₃N, CH₂Cl₂; *viii*) NaN₃, DMF; *ix*) Ba(OH)₂, dioxane/H₂O; *x*) H₂/Pd(OH)₂, MeOH/2N HCl; *xi*) CbzCl, Na₂CO₃, dioxane/H₂O; *xii*) RuCl₂·(PPh₃)₃; *xiii*) Ac₂O, pyr.

Another route to 6-*epi*-D-purpurosamine B derivative **135**, also starting from L-alanine, was reported by Jurczak *et al.* (Scheme 18).⁴⁸ Addition of diene **130** to BOC-protected L-alaninal **129** under high pressure resulted in the formation of a mixture of four diastereomers (two *cis*- and two *trans*-adducts), which upon acid catalyzed isomerization, followed by chromatographic separation afforded a 2:1 mixture of thermodynamically more stable *trans*-cycloadducts **131** and **132**. Successive hydroboration of adduct **131** by thexyl borane and oxidative work-up gave alcohol **133**. Oxidation of **133** to the corresponding ketone, followed by reaction with hydroxylamine and subsequent

acetylation yielded a 1:1 *syn-anti* mixture of oxime acetates **134**. Final reduction, acidic hydrolysis and acetylation provided methyl 2,6-di-*N*-acetyl-6-*epi*- α -D-purpurosaminide B **135** and its 2-epimer in a ratio of 6:1. The pure 6-*epi*-D-purpurosamine B **135** was obtained by recrystallization.



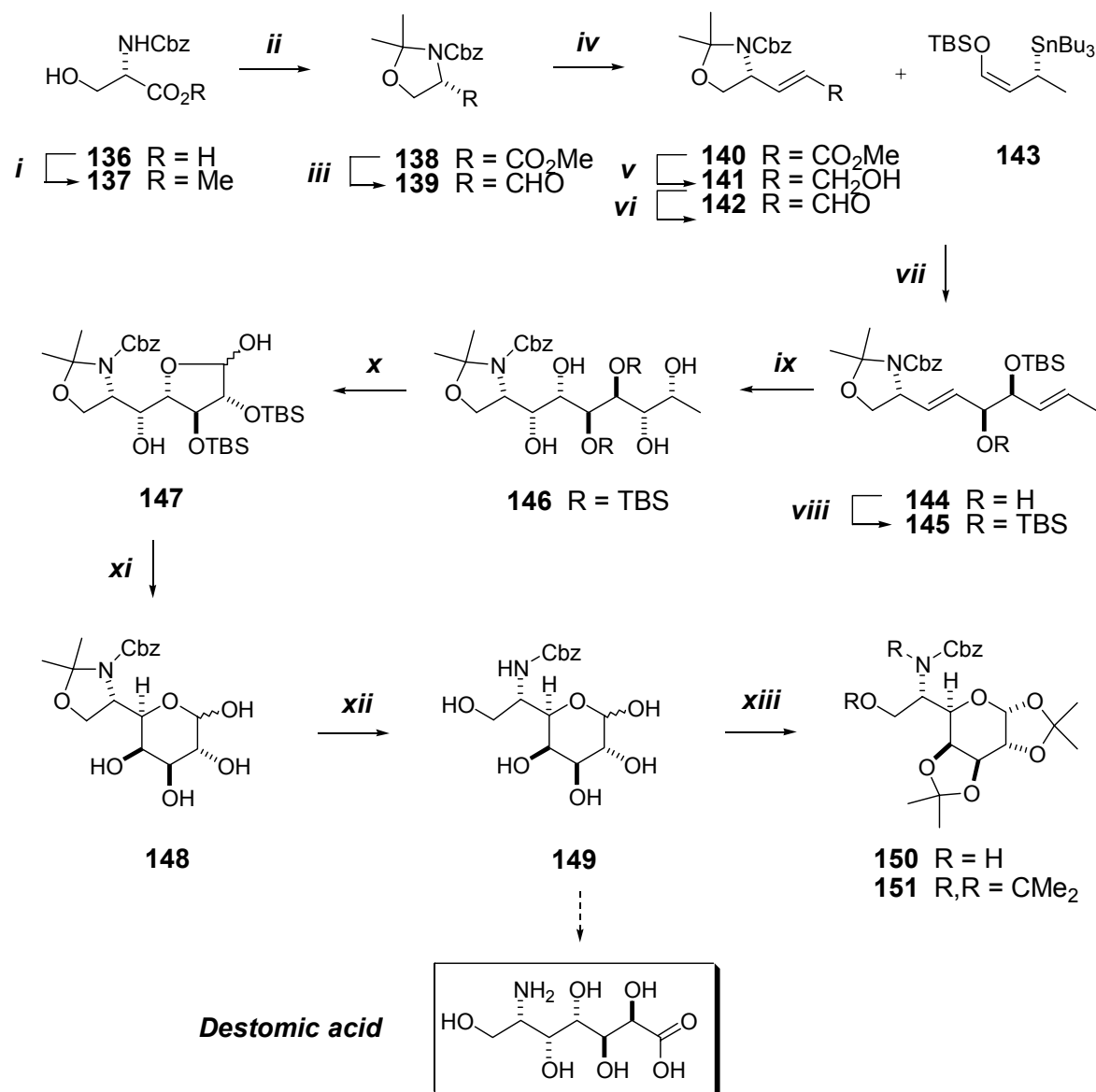
Scheme 18. *i*) 20 kbar, 2 % Eu(fod)₃, Et₂O, 50 °C; *ii*) PPTS, MeOH, rt; *iii*) ThxBH₂·DMS, Et₂O, -20 °C; *iv*) 30 % H₂O₂, 30 % NaOH aq.; *v*) PCC, 4Å molecular sieves, CH₂Cl₂, rt; *vi*) NH₂OH·HCl, K₂CO₃, MeOH, rt; *vii*) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt; *viii*) BH₃·THF, THF, -78 °C → rt; *ix*) TFA, rt.

Jurczak *et al.* have applied the methodology described above also to the syntheses of purpurosamine B⁴⁹ in enantiomerically pure form and purpurosamine C⁵⁰ in racemic form.

2.4.3. Destomic acid

Marshall and Beaudoin have used L-serine as the chiral auxiliary in the synthesis of the precursor of destomic acid,⁵¹ a component of the destomycin⁵² and hygromycin⁵³ antibiotics (Scheme 19). The synthesis of the protected destomic acid **149** started from *N*-Cbz-protected L-serine **136**, which was transformed to the corresponding aldehyde **139** via standard esterification, ketal protection and DIBAL-H reduction. Horner-Emmons reaction with triethyl phosphonoacetate afforded the *E*-enoate **140**, which was converted to enal

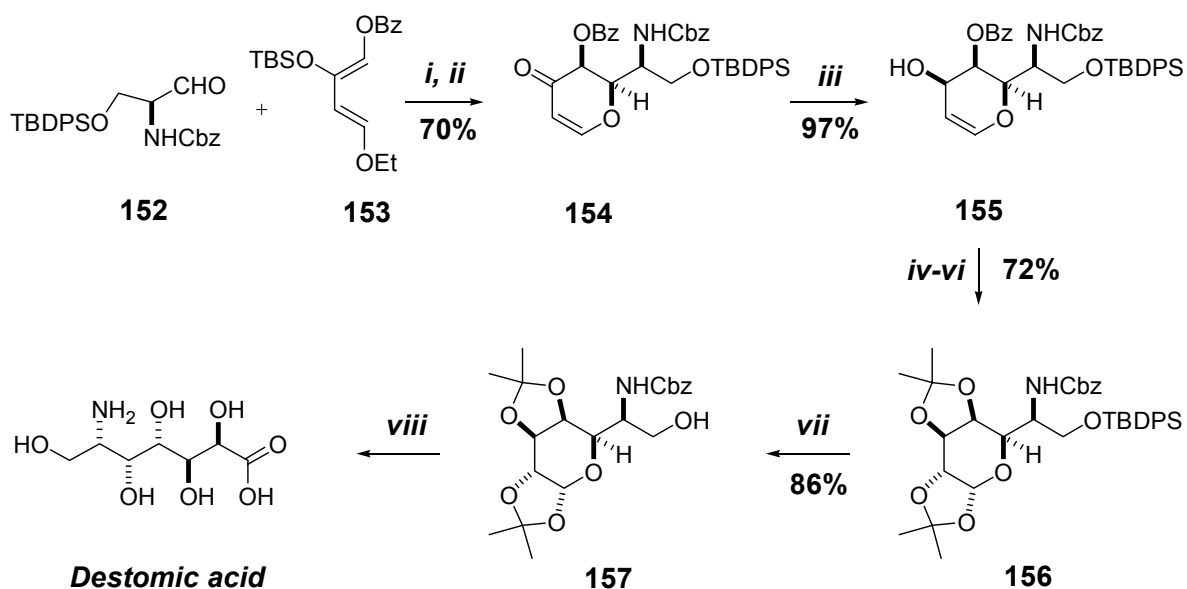
142 via successive reduction and Swern oxidation. Addition of the (*R*)-silyloxy allylic stannane **143** to **142** produced the *syn*-adduct **144** as the sole diastereomer, which after silylation was subjected to osmium-catalyzed bisdihydroxylation to form tetrol **146**.



Scheme 19. *i*) SOCl₂, MeOH, 0 °C → rt (95 %); *ii*) DMP, BF₃·OEt₂, rt (95 %); *iii*) DIBAL-H, toluene, -78 °C (75 %); *iv*) (EtO)₂POCH₂CO₂Et, NaH, THF, 0 °C (79 %); *v*) DIBAL-H/hexanes, THF, -78 °C → rt (79 %); *vi*) DMSO, Et₃N, CH₂Cl₂, -78 °C → 0 °C (90 %); *vii*) **143**, BF₃·OEt₂, CH₂Cl₂ (87 %); *viii*) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C (97 %); *ix*) NMO, acetone, H₂O, OsO₄/*t*-BuOH (68 %); *x*) H₅IO₆, THF, 0 °C (81 %); *xi*) TBAF, THF (86 %); *xii*) AcOH/H₂O 9:1, 50 °C (97 %); *xiii*) CuSO₄, H₂SO₄, acetone (46 %).

Selective oxidative cleavage of **146** gave lactol **147**. Removal of the silyl protection and acetonide hydrolysis offered the pyranose derivative **149**, which is a precursor of the destomic acid. For characterization, the sugar derivative **149** was converted to a known bis-acetonide **150** along with the formation of by-product **151**.

Another L-serine based synthesis for the destomic acid was reported by Jurczak *et al.* (Scheme 20).⁵⁴ Hetero-Diels-Alder cycloaddition of the Danishefsky-type diene **153** to L-serinal derivative **152** afforded pyrone **154** as the major product, which was separated from the other diastereomers by flash chromatography. Luche reduction of the carbonyl moiety gave intermediate **155**, which upon osmium-catalyzed dihydroxylation, followed by debenzoylation and ketal protection of the tetrol produced the diacetonide **156**. Removal of the silyl protection provided the protected precursor **157** of destomic acid.



Scheme 20. *i)* ZnBr₂, THF; *ii)* TFA, CH₂Cl₂; *iii)* NaBH₄, CeCl₃·7H₂O, MeOH; *iv)* OsO₄, NMO, THF-H₂O; *v)* K₂CO₃, MeOH; *vi)* DMP, PTSA, acetone; *vii)* *n*-Bu₄NF, THF; *viii)* Ref. 55.

2.4.4. Lincosamine

Szechner and Achmatowicz have reported a *D-allo*-threonine based synthesis of methyl- α -*D*-lincosaminide **169** (Scheme 21),⁵⁶ which is the amino sugar component of a Gram-positive glycopeptide antibiotic lincomycin.

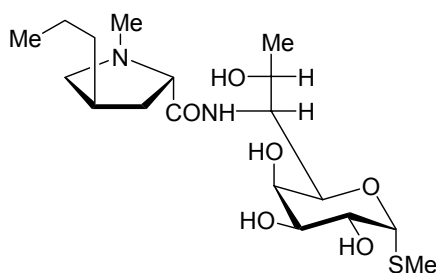
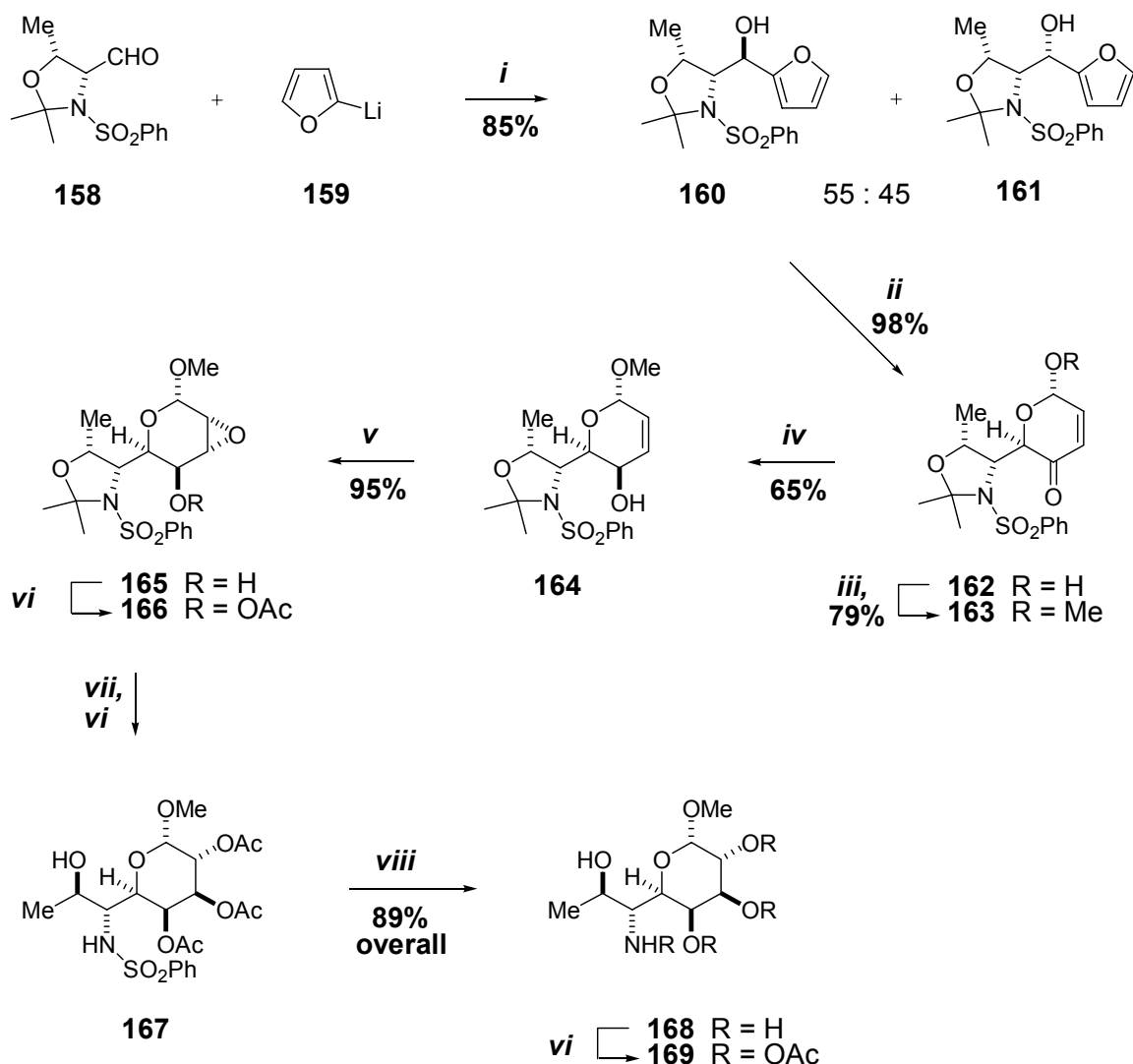


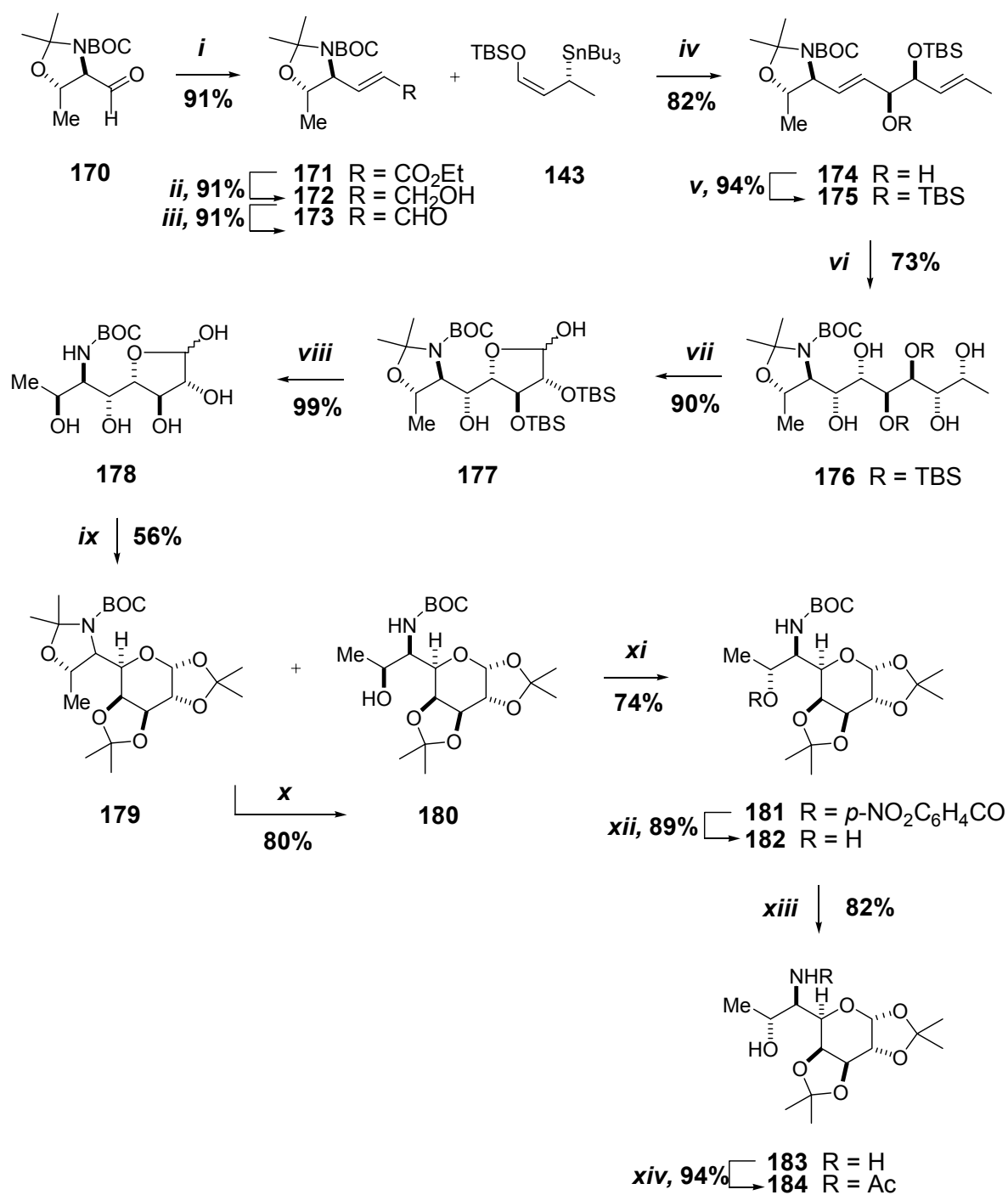
Figure 10. Lincomycin.

D-allo-Threonine was first converted to *D-allo*-threonal **158** following known procedures. Addition of furyllithium **159** to the aldehyde **158** produced the *anti*- and *syn*-alcohols **160** and **161** in a ratio of 55:45, respectively. After purification by flash chromatography, the desired *anti*-alcohol **160** was oxidized and then methylated to form the methyl α -uloside **163**. Reduction of the carbonyl group of **163** afforded the *threo* alcohol **164**, which upon epoxidation and successive acetylation gave exclusively the *gulo* epoxide **166**. Opening of the epoxide and cleavage of the isopropylidene group under acidic reaction conditions followed by acetylation provided intermediate **167**. Removal of the *N*-benzenesulfonyl group and subsequent acetate protection accomplished methyl *N*,2,3,4,7-pentaacetyl- α -*D*-lincosaminide **169** in 20 % overall yield from **158**.



Scheme 21. *i*) THF/hexane, Et₂O, -70 °C; *ii*) mCPBA, CH₂Cl₂, rt; *iii*) MeI, Ag₂O, Et₂O, rt; *iv*) NaBH₄, CeCl₃, rt; *v*) 60 % H₂O₂, MeCN, rt; *vi*) Ac₂O, pyr, DMAP; *vii*) HClO₄, H₂O, THF, 40 °C; *viii*) Na, NH₃, -70 °C → rt.

Marshall and Beaudoin have used a similar approach for the synthesis of lincosaminide derivative **184** from D-threonine as described for the preparation of the destomic acid derivative **150** from L-serine in Section 2.4.3. (Scheme 22).⁵¹ Horner-Emmons reaction of *N*-BOC-threoninal **170** produced the *E*-enoate **171**, which was converted to enal **173** via successive DIBAL-H reduction and Swern oxidation. Introduction of the (*R*)-silyloxy allylic stannane **143** generated the *syn*-adduct **174**, which after TBS-protection was bisdihydroxylated to form tetrol **176**. Lactol **177** was obtained by oxidative cleavage of **176** and transformed to a mixture of acetonides **179** and **180** after deketalization. The former acetonide was converted to the latter one under acidic conditions.



Scheme 22. *i*) (EtO)₂POCH₂CO₂Et, NaH, THF, 0 °C; *ii*) DIBAL-H/hexanes, THF, -78 °C; *iii*) DMSO, Et₃N, CH₂Cl₂, -78 °C → 0 °C; *iv*) **143**, BF₃·OEt₂, CH₂Cl₂; *v*) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C; *vi*) NMO, OsO₄, H₂O, *vii*) H₅IO₆, THF, 0 °C; *viii*) TBAF, THF, HOAc, H₂O; *ix*) acetone, CuSO₄, H₂SO₄; *x*) PTSA, MeOH; *xi*) *p*-nitrobenzoic acid, Ph₃P, DEAD, benzene; *xii*) KCN, MeOH; *xiii*) TFA, CH₂Cl₂; *xiv*) Ac₂O, MeOH, pyr.

The required inversion of configuration for the hydroxyl group at the C7-position was achieved by Mitsunobu methodology. Finally, removal of the *p*-nitrobenzoic acid moiety and the BOC-protection, followed by acetylation provided the target acetamide **184**.

2.4.5. Galantinic acid

Ohfuné and Sakai reported in 1990 the first total synthesis of galantinic acid **197**, starting from the readily available L-serinal derivative **185** (Scheme 23).⁵⁷ Galantinic acid is an amino acid constituent in a peptide antibiotic galantin I, isolated from a culture broth of *Bacillus pulvifaciens*.⁵⁸

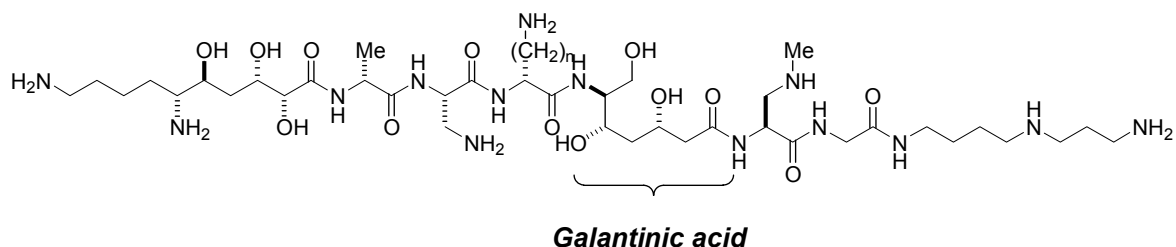
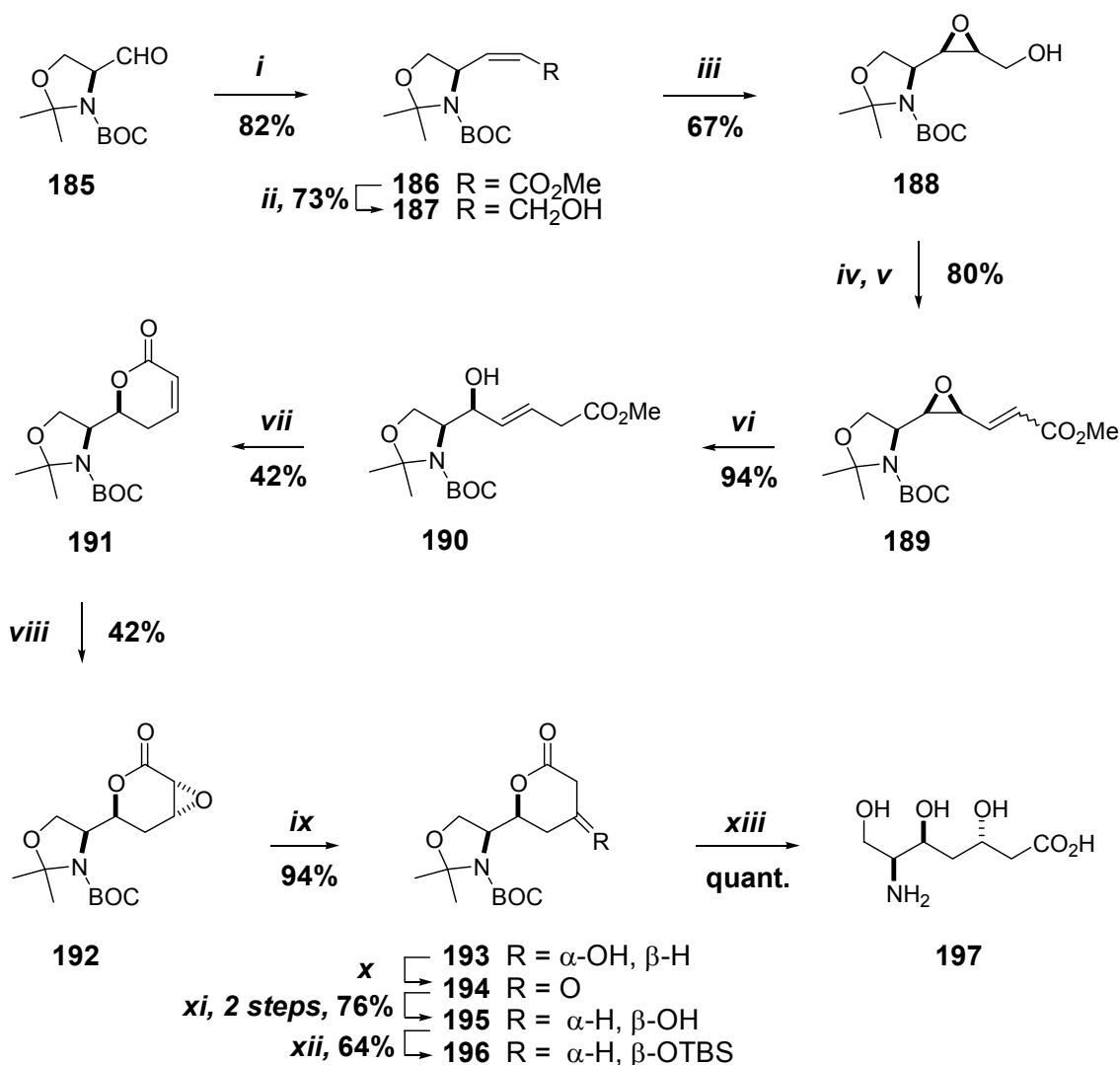


Figure 11. Galantin I.

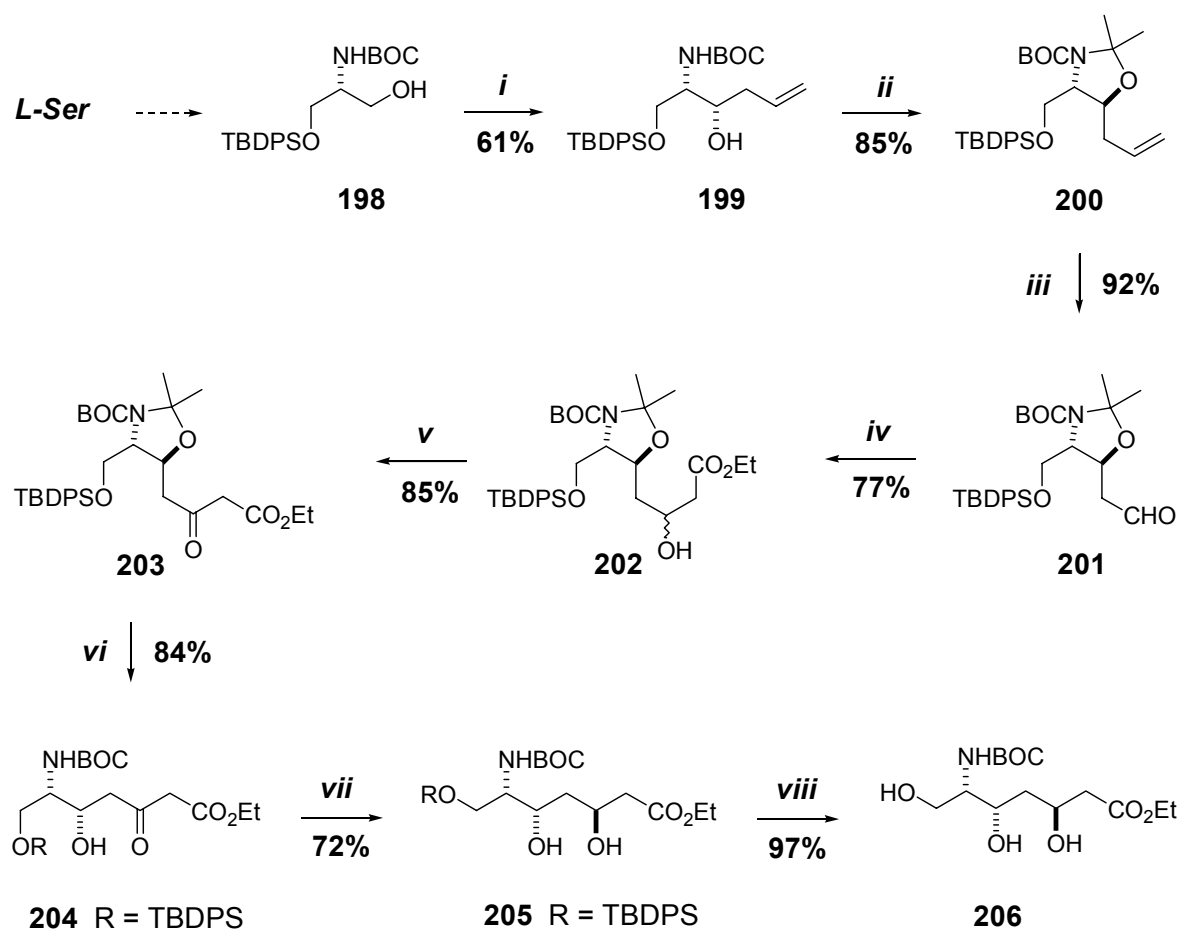
The first step of the synthesis was the conversion of the fully protected L-serinal **185**⁵⁹ to the corresponding *Z*-allyl alcohol **187** via standard procedures. Epoxidation of **187** with mCPBA afforded the *syn*-epoxy alcohol **188** exclusively, which was transformed to a 2:1 mixture of *E* and *Z* unsaturated epoxy esters **189** via Swern oxidation and subsequent Wittig olefination. Reduction of the oxirane ring was performed by employing Miyashita's reagent⁶⁰ to produce the *E* β,γ-ester **190** as a single regioisomer. Cyclization of **190** by DBU generated the unsaturated lactone **191**, which upon successive epoxidation and reduction was converted to (3*R*)-hydroxy lactone **193**. Since the natural isomer has (3*S*)-configuration, inversion of configuration for the hydroxyl group of compound **193** was carried out. Oxidation of the hydroxyl group at C3 to the corresponding ketone, followed by immediate reduction provided a 3:1 mixture of stereoisomers (3*S*)-**195** and (3*R*)-**193**, respectively. After silyl protection, the stereoisomers were chromatographically separated and the desired (3*S*)-silyl ether **196** was converted to the target (-)-galantinic acid **197** under acidic conditions.



Scheme 23. *i*) (CF₃CH₂O)₂P(O)CH₂CO₂Me, NaH, 18-crown-6, THF, -78 °C; *ii*) DIBAL-H, BF₃·OEt₂, CH₂Cl₂, -78 °C; *iii*) mCPBA, CH₂Cl₂, 0 °C; *iv*) (COCl)₂, DMSO, CH₂Cl₂, -90 °C, then Et₃N; *v*) Ph₃P=CHCO₂Me, benzene rt; *vi*) Na⁺[PhSeB(OEt)₃]⁻, EtOH, rt; *vii*) DBU, benzene, reflux; *viii*) *t*-BuOOH, Triton B (cat.), THF, 0 °C; *ix*) PhSeH, IPA, rt; *x*) TFAA, DMSO, CH₂Cl₂, -78 °C, then Et₃N, -78 °C; *xi*) NH₃·BH₃, citric acid, THF/H₂O 10:1, rt; *xii*) TBSOTf, 2,6-lutidine, CH₂Cl₂, -78 °C; *xiii*) TFA, CH₂Cl₂, rt, then Dowex 50Wx4 (elution with 1N NH₃).

Recently, another L-serine based synthesis of galantinic acid was reported with improved stereoselectivity (Scheme 24).⁶¹ Conversion of L-serine to the *N,O*-protected aminodiol **198** by a known procedure,⁶² followed by Swern oxidation and *in situ* reaction of the resulting aldehyde with allylmagnesium bromide produced the *syn*-1,2-amino

alcohol **199** in excellent stereoselectivity (*syn:anti* > 95:5). After ketal protection, Lemieux-Johnson oxidative cleavage of the double bond yielded the corresponding aldehyde **201**. Treatment of **201** with bromozincacetate resulted in the formation of the hydroxyester **202** as a 3:2 mixture of diastereomers, which upon oxidation with pyridinium dichromate afforded ketone **203**. Cleavage of the acetonide protection afforded the β -hydroxy ketone **204**, which was stereoselectively reduced to the *anti*-diol **205** by the Saksena-Evans protocol.⁶³ Desilylation of the primary alcohol group accomplished the galantinic acid derivative **206** in 16 % overall yield.



Scheme 24. *i*) Swern oxidation, then $\text{H}_2\text{C}=\text{CHCH}_2\text{MgBr}$; *ii*) $\text{Me}_2\text{C}(\text{OMe})_2$, PPTS; *iii*) OsO_4 , NMO, then NaIO_4 ; *iv*) $\text{BrZnCH}_2\text{CO}_2\text{Et}$, Et_2O ; *v*) PDC, CH_2Cl_2 ; *vi*) 80 % AcOH ; *vii*) $\text{NaB}(\text{OAc})_3\text{H}$, MeCN , AcOH , $-20\text{ }^\circ\text{C}$; *viii*) Bu_4NF , THF .

3. Pradimicin syntheses in the literature

This chapter introduces the published synthetic approaches to pradimicin. The pradimicin antibiotic has not been synthesized yet, and there exists only one total synthesis of pradimicinone, the aglycon of the pradimicin-benanomicin antibiotics (Fig. 12).⁶⁴ The syntheses of the aromatic aglycon and the disaccharide moiety of pradimicin will be presented first and the glycosylation study between the disaccharide donor and the aromatic acceptor will be discussed at the end of this chapter.

Chapter 4 will present my own work concerning the L-threonine based synthesis of the disaccharide fragment of pradimicin A, and Chapter 5 will give the full experimental data of the products prepared in this thesis.

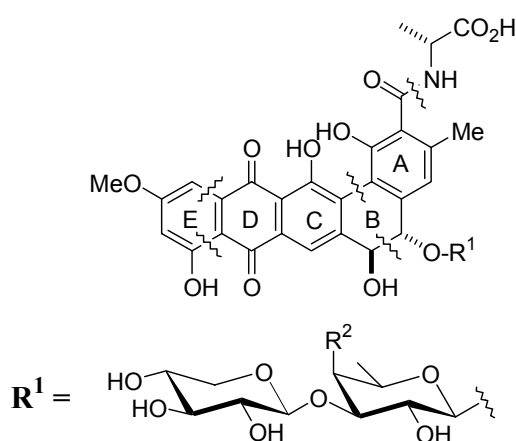


Figure 12.

$R^2 = \text{NHMe}$: pradimicin A

$R^2 = \text{NH}_2$: pradimicin C, benanomicin B

$R^2 = \text{OH}$: benanomicin A

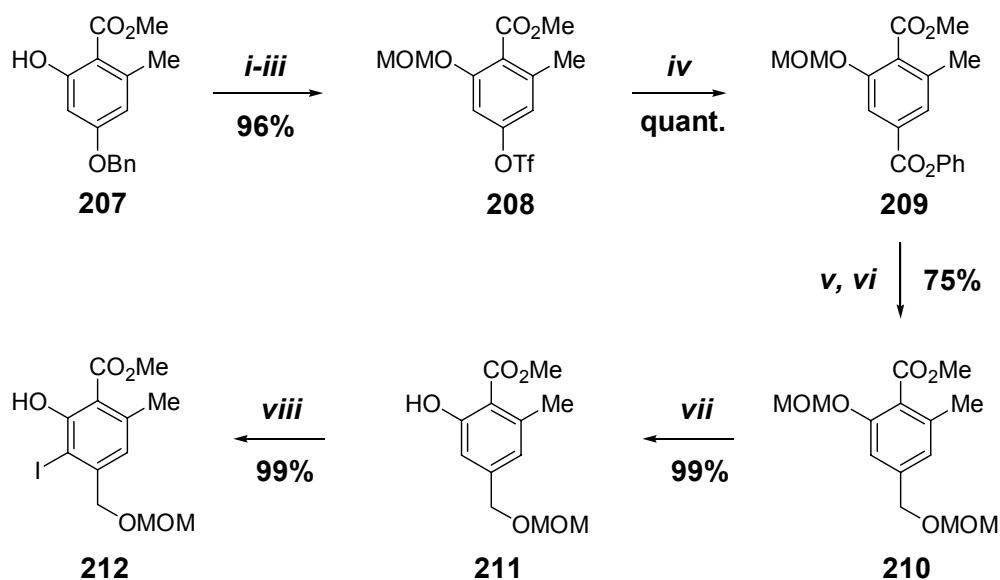
$R^1 = \text{H}$: pradimicinone, benanomicinone

3.1. Synthesis of the aromatic aglycon of pradimicin

3.1.1. Suzuki

The synthesis of benzo[*a*]naphthacene natural products has been of keen interest by several groups,⁶⁴⁻⁶⁸ but there exists only one total synthesis of the aglycon of the pradimicin-benanomicin antibiotics, reported by Suzuki *et al.*⁶⁴ Pradimicinone consists of a D-alanine moiety and a pentacycle, whose rings are named A-E (see Fig. 12). The first step in the synthesis of the aglycon part was the preparation of the A and CD rings. The B ring was created by combining the A and CD rings to form the tetracyclic structure of A-D. The final steps were the introduction of the E ring moiety to the tetracycle by a Diels-Alder reaction and final attachment of the of the D-alanine functionality by condensation.

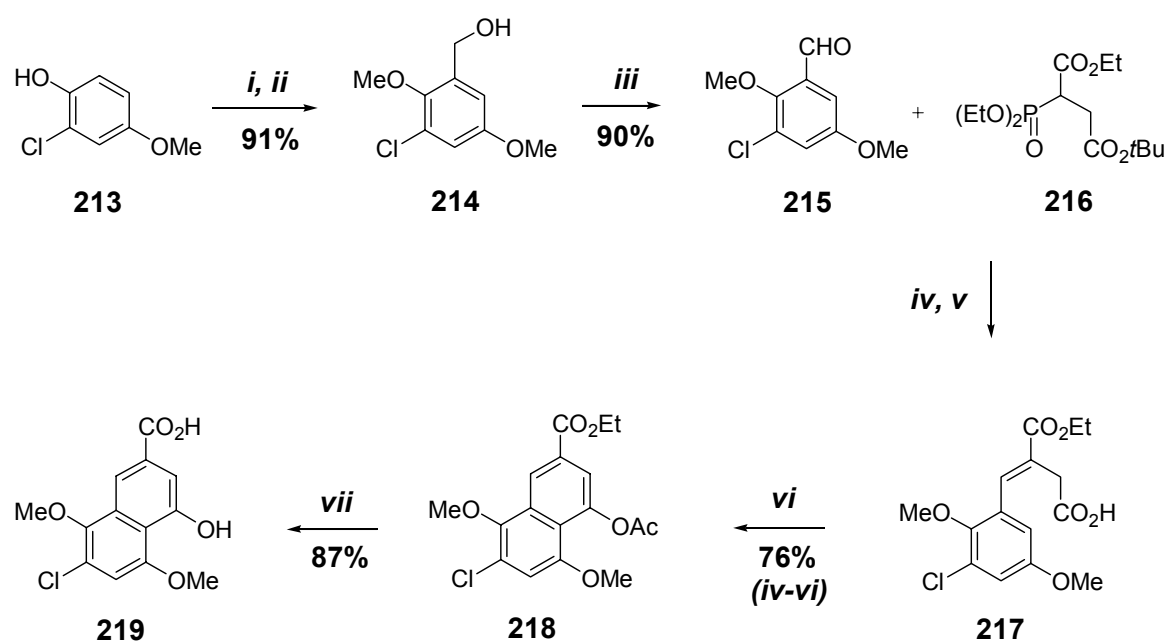
The preparation of the A ring **212** started by conversion of the orsellinic acid derivative **207** into the triflate **208** in three steps (Scheme 25). Carbonylation and subsequent selective reduction by NaBH₄ generated the primary alcohol, which was protected to produce the bis-MOM ether **210**.



Scheme 25. Synthesis of the A ring fragment: *i*) MOMCl, *i*Pr₂NEt, CH₂Cl₂, 40 °C; *ii*) H₂, Pd(OH)₂, EtOAc; *iii*) Tf₂O, *i*Pr₂NEt, CH₂Cl₂, -78 °C; *iv*) CO, PhOH, Et₃N, Pd(OAc)₂, dppf/DMF, 60-80 °C; *v*) NaBH₄, 1,4-dioxane, MeOH, 0 °C → rt; *vi*) MOMCl, *i*Pr₂NEt, CH₂Cl₂; *vii*) TFA, CH₂Cl₂, 0 °C; *viii*) I₂, Hg(OAc)₂, CH₂Cl₂, 0 °C.

Selective deprotection in acidic media, followed by iodination afforded the required A ring fragment iodophenol **212** in 71 % overall yield.

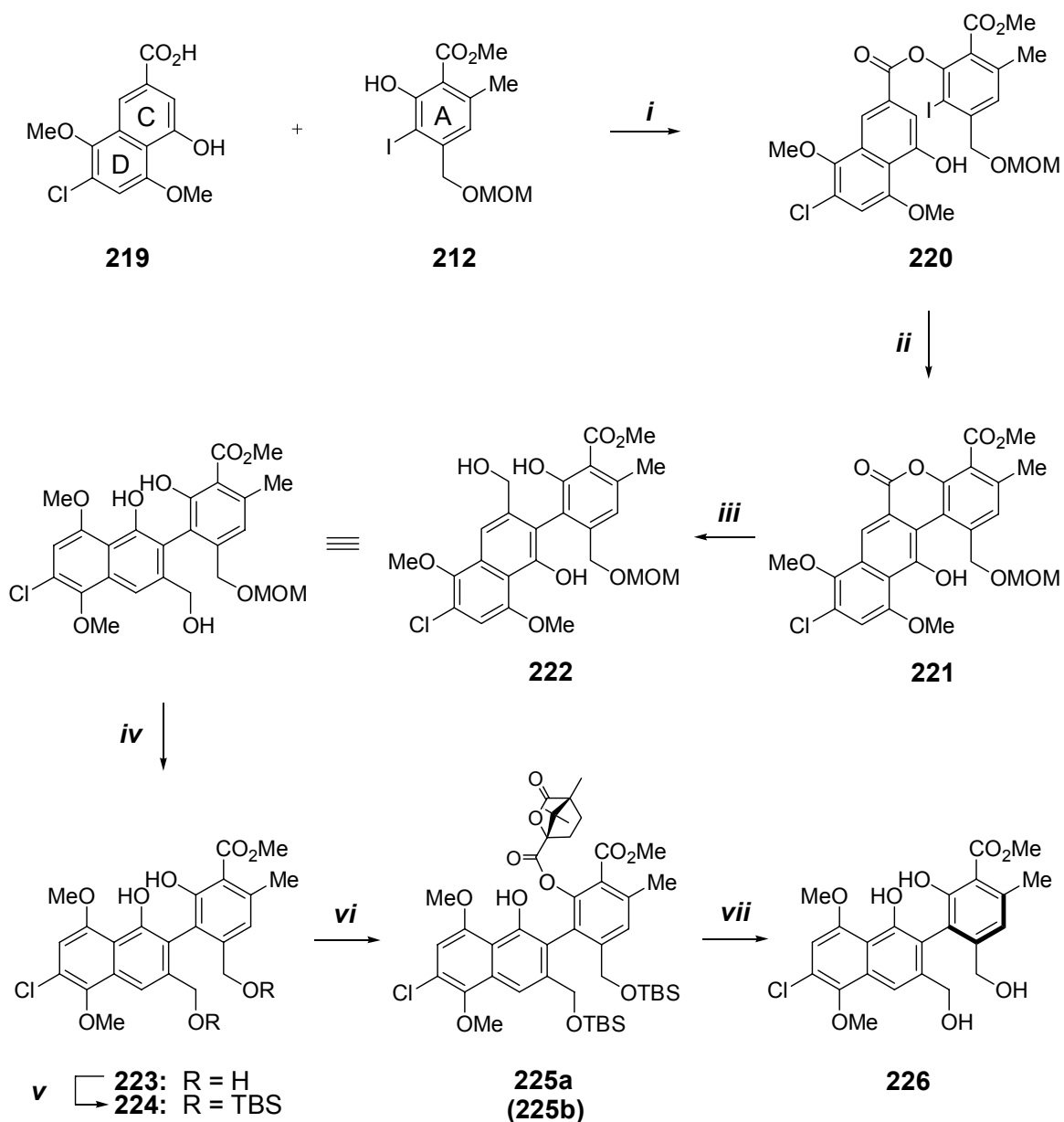
In the synthesis of the CD ring fragment **219**, the known compound **213** was first regioselectively hydroxymethylated and then *O*-methylated affording the benzyl alcohol **214** (Scheme 26). Oxidation of **214** to the corresponding aldehyde **215**, followed by HWE olefination with **216** provided the unsaturated ester, which after hydrolysis of its *tert*-butyl moiety gave the unsaturated acid **217**. Cyclization with acetic anhydride/sodium acetate led to naphthyl acetate **218**, which after deacetylation provided the desired naphthol **219** in 54 % overall yield.



Scheme 26. Synthesis of the CD ring fragment: *i*) (HCHO)_n, Me₂AlCl, CH₂Cl₂, 0 °C; *ii*) MeI, K₂CO₃, acetone, reflux; *iii*) MnO₂, CH₂Cl₂, 0 °C; *iv*) NaH, THF; *v*) TFA, H₂O; *vi*) Ac₂O, NaOAc, reflux; *vii*) NaOH (aq), THF, EtOH, 70 °C, H₃O⁺.

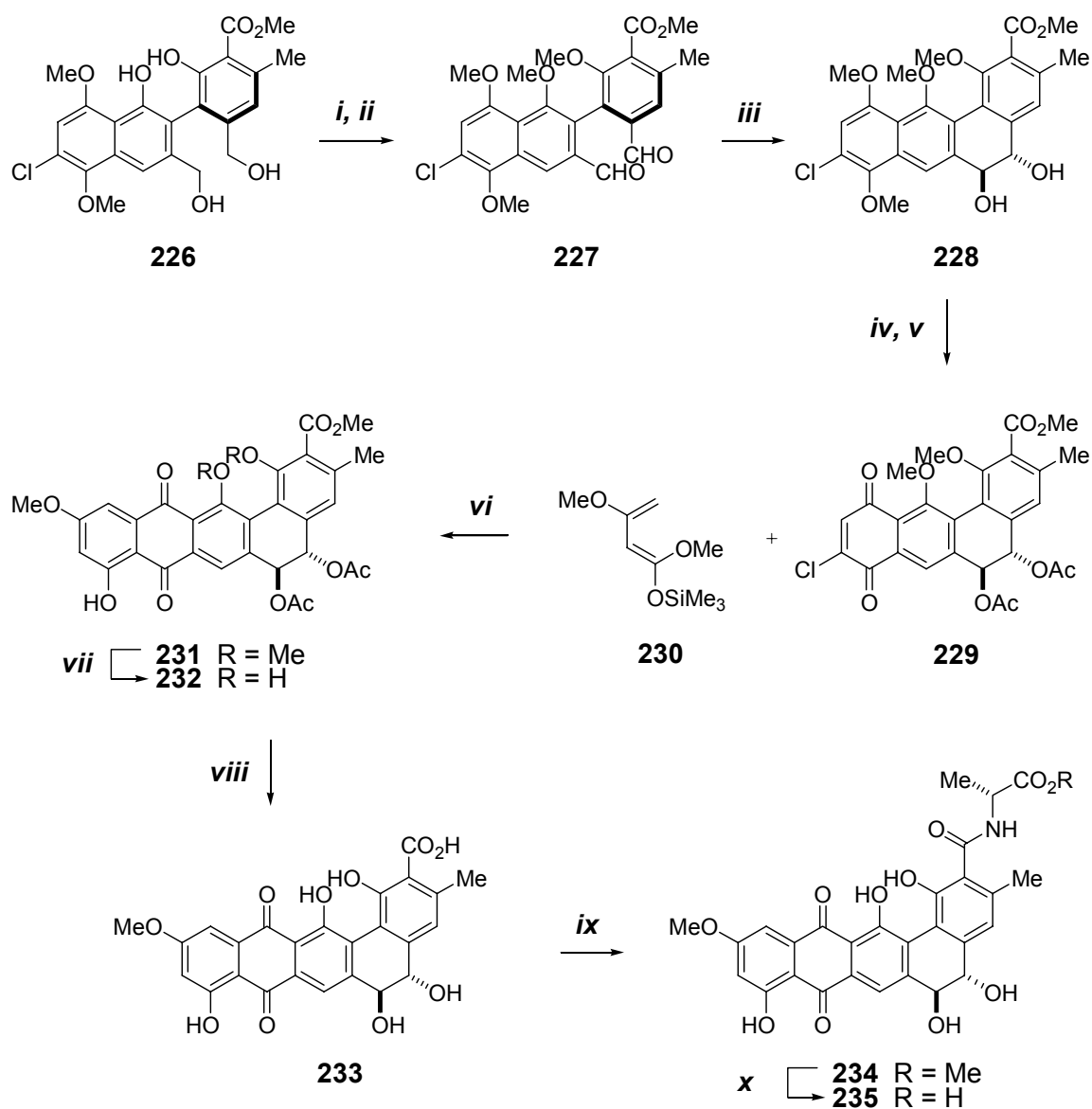
In the next stage the A and CD rings were connected *via* an ester formation using water-soluble carbodiimide as the condensing agent (Scheme 27). Palladium-catalyzed internal cyclization accomplished the tetracyclic intermediate **221**, which after reduction and cleavage of the MOM-protection gave alcohol **223**. After silylation of the primary hydroxyl groups, the enantiomers were resolved by conversion to (-)-(1*S*,4*R*)-camphanoyl esters, generating a 1:1 mixture of diastereomers **225a** and **225b** which were separated by

flash chromatography. Deprotection of **225a** furnished the enantiopure tetraol **226** in 19 % yield (from A and CD).



Scheme 27. *i*) EDCI, DMAP, CH₂Cl₂ (78 %); *ii*) Pd(OAc)₂, PPh₃, *t*BUCO₂Na, *N,N*-dimethylacetamide, 110 °C; *iii*) NaBH₄, THF, MeOH, -40 °C (2 steps, 86 %); *iv*) 6M HCl, DME, 50 °C (93 %); *v*) TBSCl, imidazole, DMF (84 %); *vi*) (-)-(1*S*,4*R*)-camphanoyl chloride, DMAP, pyr, then SiO₂ (**225a**: 38 %, **225b**: 40 %); *vii*) HF (aq.), MeCN (aq.), K₂CO₃, MeOH (97 % from **225a**).

The tetraol **226** was converted to dialdehyde **227**, which upon reductive cyclization with SmI_2 produced the enantiomerically pure *trans*-diol (*S,S*)-**228** exclusively (Scheme 28). Acetate protection of the diols and subsequent oxidation of the aromatic system afforded compound **229**, which was connected with siloxydiene **230** via Diels-Alder reaction to generate the pentacycle intermediate **231**.



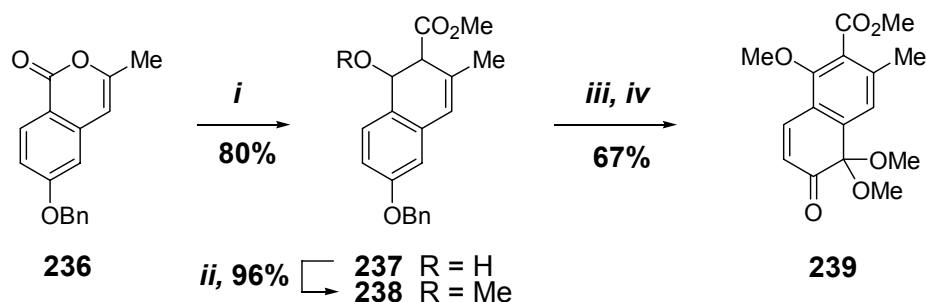
Scheme 28. Total synthesis of pradimicinone: *i*) MeI, K_2CO_3 , acetone, 40 °C (81 %); *ii*) MnO_2 , CH_2Cl_2 (79 %); *iii*) SmI_2 , THF, 0 °C (quant.); *iv*) Ac_2O , DMAP, pyr (quant.); *v*) $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$, MeCN, 0 °C (quant.); *vi*) THF, 0 °C \rightarrow rt; SiO_2 , then, K_2CO_3 , CH_2Cl_2 , THF (90 %); *vii*) BCl_3 , CH_2Cl_2 , -10 °C (99 %); *viii*) 2 M NaOH, 70 °C; H_3O^+ ; *ix*) D-Ala-OMe·HCl, BOP, Et_3N , DMF (2 steps, 80 %); *x*) 0.1 M NaOH, H_3O^+ (quant.).

Selective cleavage of the methyl ether protection, followed by deacetylation gave the fully functionalized aromatic skeleton **233**, which upon condensation with D-alanine methyl ester created the pradimicinone methyl ester **234**. Final deprotection of **234** furnished the target pradimicin aglycon **235**.

3.1.2. Hauser

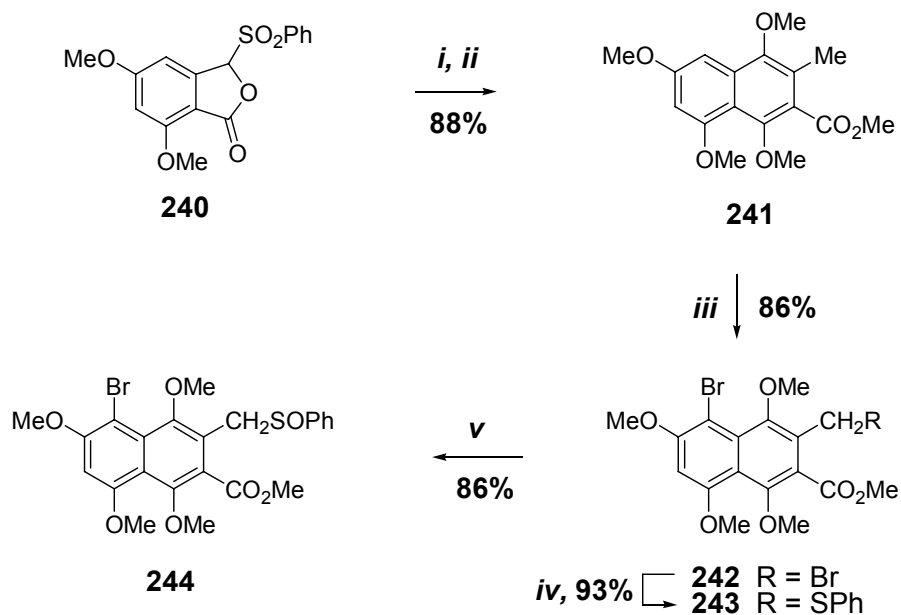
Recently, Hauser *et al.* reported a regiospecific synthesis of the benanomycinone/pradimicinone analogue **249** by condensation of the phenylsulfinyl naphthoate **244** with the *ortho*-quinone monoketal **239**.⁶⁵

The *ortho*-quinone monoketal **239** was prepared from benzyl ether protected isobenzopyranone **236**, which was first reacted with lithium enolate of methyl acetate to produce the naphthoate **237** (Scheme 29). Etherification of **237**, followed by sequential hydrogenolysis and oxidation gave the quinone ketal **239**.



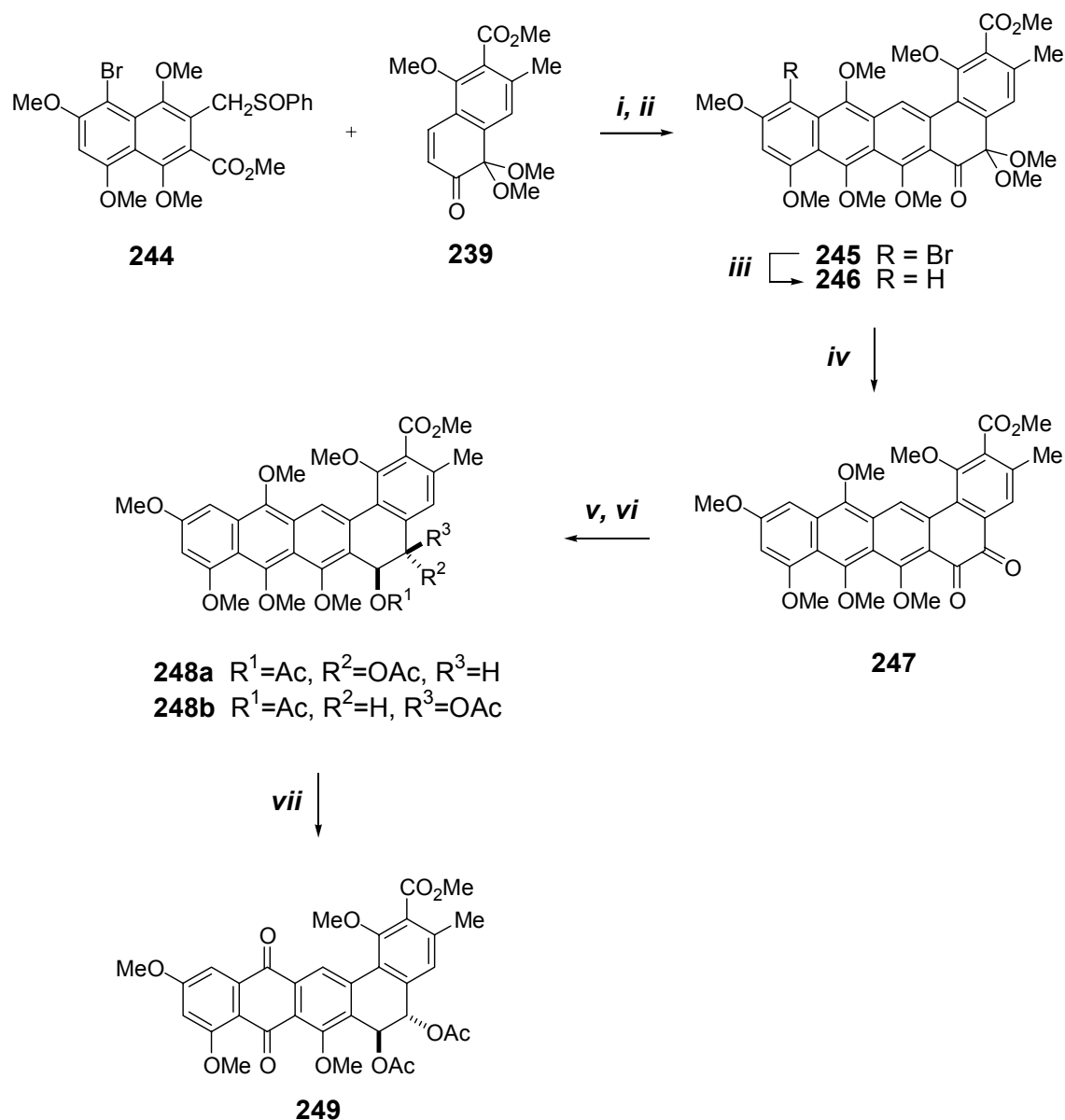
Scheme 29. *i*) LDA, THF, acetone; *ii*) (MeO)₂SO₂, acetone, K₂CO₃; *iii*) H₂/Pd-C, MeOH (98 %); *iv*) PhI(OAc)₂, MeOH (68 %).

The synthesis of *ortho*-phenylsulfinyl naphthoate **244** started by condensation of the anion of sulfone **240** with methyl crotonate, leading to formation of the naphthoate dianion, which was *in situ* methylated to yield a mixture of mono- and dimethylated regioisomers (Scheme 30). Additional methylation of the mixture provided the dimethyl ether **241**, which upon bromination gave the dibrominated product **242**. Conversion of **242** to the corresponding sulfoxide **244** was obtained *via* thiophenyl methyl ether **243**, which was oxidized by peroxyboric acid.



Scheme 30. *i*) LiOtBu, THF, methyl crotonate; *ii*) (MeO)₂SO₂, K₂CO₃, acetone; *iii*) NBS, CCl₄; *iv*) KOH, PhSH, MeOH; *v*) NaBO₃·4H₂O, AcOH.

The anion sulfoxide **244** and the quinone monoketal **239** were connected by a condensation reaction to create the pentacyclic intermediate **245** (Scheme 31). Reductive replacement of the aryl bromine proceeded by palladium-catalyzed hydrogenation affording compound **246**, which upon rapid hydrolysis (less than 15 seconds) offered the *ortho*-quinone **247**. Quinone **247** was directly reduced to a diastereomeric mixture of the corresponding diols, which after subsequent acetylation produced the *trans*- and *cis*-acetates **248a** and **248b** in a ratio of 3:1, respectively. After purification by flash chromatography, the *trans*-isomer **248a** was oxidized to the target benzo[*a*]naphthacene-8,13-quinone **249**.

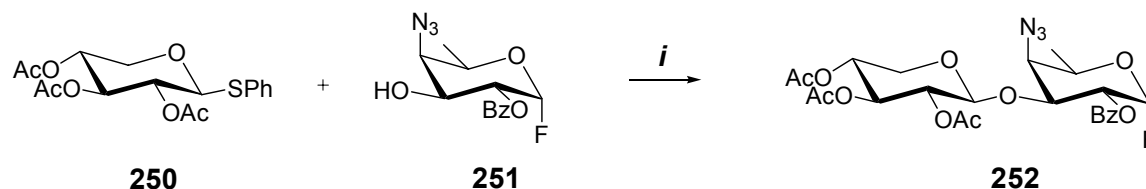


Scheme 31. *i*) *t*BuLi, THF, DMSO; *ii*) (MeO)₂SO₂, acetone, K₂CO₃ (2 steps, 31 %); *iii*) Pd/C, H₂ (97 %); *iv*) TFA, H₂O, CHCl₃; *v*) NaBH₄, EtOH; *vi*) Ac₂O, pyr, DMAP (3 steps, 85 %); *vii*) Ce(NH₄)₂(NO₃)₆, H₂O; MeCN (44 %).

3.2. Design of the suitable disaccharide donor

Suzuki *et al.* have prepared the pradimicin disaccharide fragment **252**, in which the NHMe functionality was replaced with an azide moiety (Scheme 32).⁶⁹ The synthesis strategy was based on the *orthogonal glycosylation* methodology,⁷⁰ by employing the combination of a thioglycoside donor and a glycosyl fluoride acceptor, which remain unaffected under the

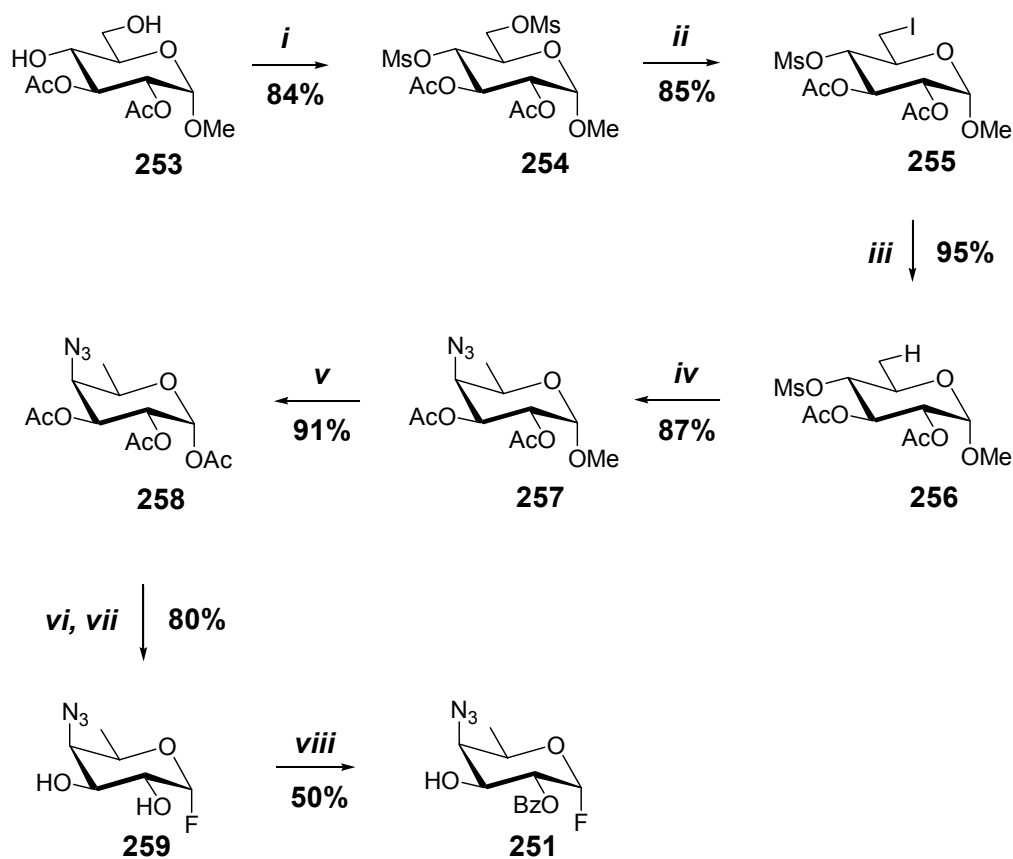
conditions required for the activation of the other. The thioglycosyl donor **250** was derived from D-xylose and the fluoride acceptor **251** was prepared from a D-glucose derivative in 8 steps (Scheme 33). The activation conditions for the glycosyl fluorides are listed in Section 3.3 and the activators for the thioglycosides will be discussed in Chapter 4.



Scheme 32. *i*) NIS, TfOH (cat.), CH₂Cl₂, -40 °C, 2 h, 93 % (α:β 1:5), then crystallization from EtOH.

The synthesis of the amino sugar acceptor **251** started from the 2,3-diacetylated D-glucose derivative **253**, which was first mesylated at its 4- and 6-positions to give compound **254**. In the next step, the primary mesylate was selectively displaced by iodine, which was subsequently removed by hydrogenolysis in the presence NaOAc buffer to produce the 6-deoxy sugar **256**. Conversion of **256** to the azide derivative **257** was accomplished by treatment with NaN₃. After acetylation of **257**, the anomeric position of **258** was fluorinated with HF·pyr complex and the acetate protection was cleaved to give the fluoride **259**. Benzoyl protection at the 2-position of **259** was carried out regioselectively by benzoyl chloride and pyridine, affording an 8:1 mixture of 2-*O*- and 3-*O*-monobenzoates. Finally, crystallization from EtOAc furnished the target 2-*O*-benzoylated α-fluoride **251** in 21 % overall yield.

The thioglycosyl donor **250** was prepared from D-xylose by standard procedures, first acetylating the free hydroxyl groups and then introducing the thiophenyl moiety at the anomeric position under acidic conditions.



Scheme 33. *i)* MsCl, pyridine; *ii)* NaI, 2-butanone, reflux; *iii)* H₂, Pd/C, NaOAc, EtOH, EtOAc; *iv)* NaN₃, *n*-Bu₄NCl, DMF, 110 °C; *v)* Ac₂O, conc. H₂SO₄; *vi)* (HF)_{*n*}/pyridine, CH₂Cl₂, -20 °C → rt; *vii)* K₂CO₃, MeOH, 0 °C; *viii)* BzCl, pyridine, 0 °C → rt.

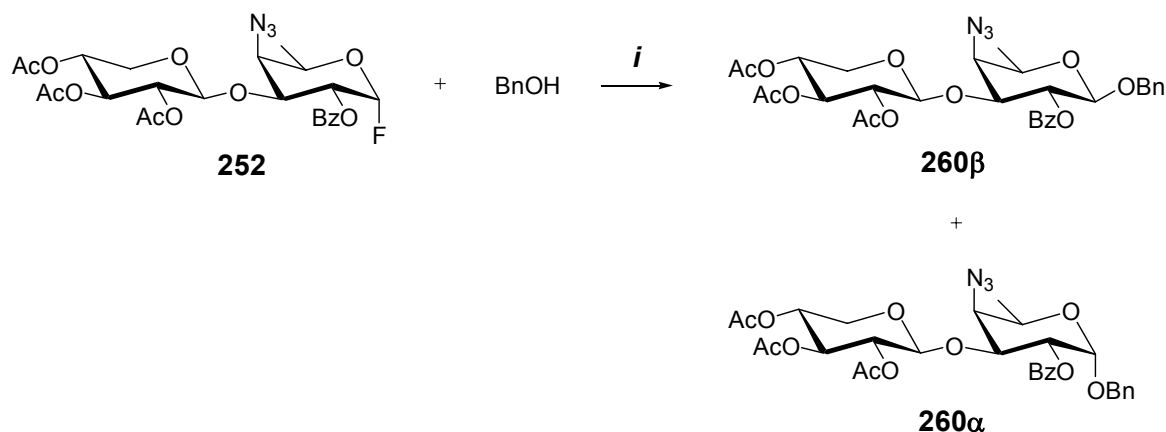
The desired pradimicin disaccharide fragment **252** was obtained *via* NIS/TfOH glycosylation.⁷¹ Treatment of the thioglycosyl donor **250** and the glycosyl fluoride acceptor **251** with NIS and a catalytic amount of TfOH in CH₂Cl₂ at -40 °C for 2 hours afforded a 1:5 mixture of α- and β-glycosylated disaccharides, from which the required β-glycoside **252** was isolated by crystallization (Scheme 32).

3.3. Glycosylation study

Common activators of glycosyl fluorides include a combination of tin chloride and silver perchlorate (SnCl₂/AgClO₄),⁷² the use of Lewis acids such as BF₃·OEt₂⁷³ or TMSOTf⁷⁴ and employment of mixtures of the (bis)cyclopentadienyl dichlorides of hafnium or zirconium with silver perchlorate or silver triflate e.g. (Cp₂HfCl₂/AgClO₄),⁷⁵ (Cp₂ZrCl₂/AgClO₄),⁷⁶

(Cp₂HfCl₂/AgOTf)⁷⁷ and (Cp₂ZrCl₂/AgOTf).⁷⁸ Particularly selective activation has been achieved with the methods involving hafnium or zirconium, although the type of protective group at the 2-position also plays a significant role in the stereochemical outcome at the glycosidic bond: a participating group such as an acetate or a benzoate will produce predominantly 1,2-*trans*-glycosides whereas a non-participating functionality like a benzyl group prefers the formation of 1,2-*cis* glycosidic linkages.

Suzuki and co-workers have performed some model glycosylation studies for the disaccharide **252** and a variety of glycosyl promoters and aromatic acceptors.⁶⁹ The α/β stereoselectivity of the glycosylation of the α -fluoride donor **252** with several promoters were examined first, employing benzyl alcohol as the model glycosyl acceptor (Scheme 34). The results of these experiments are presented in Table 1.



Scheme 34. *i*) Reaction conditions: 1 eq. of donor **252**, 1.4 eq. of acceptor BnOH, CH₂Cl₂.

The glycosylation attempts of the disaccharide **252** with BnOH employing Lewis acids (BF₃·OEt₂ or TMSOTf) resulted in complete recovery of the starting material (Entries 1 and 2). The use of the traditional SnCl₂/AgClO₄ activation procedure resulted in selective β -glycosylation but with a low yield (Entry 3). Excellent results were obtained with the zirconium- and hafnium-based promoters: the Cp₂ZrCl₂/AgClO₄ method produced the disaccharides in 97 % yield in a 7/1 β/α -ratio and the Cp₂HfCl₂/AgClO₄ process afforded stereoselectively the β -anomer in 95 % yield (Entries 4 and 5).

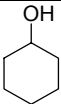

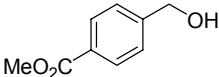
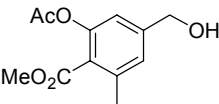
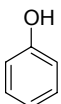
Table 1. Glycosylation of disaccharide **252** with *BnOH* by various promoters.

Entry	Promoter (eq.)	Yield (%) ^{c)}	β/α
1	$\text{BF}_3 \cdot \text{OEt}_2$ (1.3) ^{a)}	-	-
2	Me_3SiOTf (1.3) ^{a)}	-	-
3	SnCl_2 (1.3), AgClO_4 (1.3) ^{a)}	16	β
4	Cp_2ZrCl_2 (1.3), AgClO_4 (2.6) ^{b)}	97	7/1
5	Cp_2HfCl_2 (1.3), AgClO_4 (2.6) ^{b)}	95	β

a) $-78\text{ }^\circ\text{C} \rightarrow 25\text{ }^\circ\text{C}$, 10 h; b) $-78\text{ }^\circ\text{C} \rightarrow -20\text{ }^\circ\text{C}$, 30 min; c) based on **252**.

Since the hafnocene-promoter resulted in exclusive formation of the desired β -glycoside of **260**, the next experiments examining the effect of various acceptors on the glycosylation were performed by using the $\text{Cp}_2\text{HfCl}_2/\text{AgClO}_4$ activation method (Table 2). All the acceptors tested gave high yields and the reactions were complete in 30 min at low temperature. Good β -selectivity was observed with cyclohexanol, *tert*-butanol and benzyl alcohol with a methoxycarbonyl group (Entries 1, 2 and 3), whereas the use of phenol led to complete α -selectivity (Entry 5).

Table 2. Glycosylation of disaccharide **252** with various acceptors.^{a)}

Entry	Acceptor	Yield (%)	β/α ^{b)}
1		91	11/1
2		85	8.4/1
3		94	8.7/1
4		95	4.2/1
5		87	α

a) Conditions: **252**/ROH/ $\text{Cp}_2\text{HfCl}_2/\text{AgClO}_4 = 1/1.4/1.3/2.6$, 4Å molecular sieves, CH_2Cl_2 , $-78\text{ }^\circ\text{C} \rightarrow -20\text{ }^\circ\text{C}$; b) determined by ^1H NMR.

The opposite selectivity in the presence of phenol was explained as follows: 'the β -phenyl glycoside, formed if any, would be more reactive, thereby undergoing a neighbouring group-assisted departure of the phenoxide, possibly in a reverse manner, and the less reactive α -glycoside was accumulated.'⁶⁹

3.3.1. Stereochemical aspects

The final issue of the pradimicin synthesis was the examination of the conformer dependence of the diol acceptor of the aromatic aglycon. The diequatorial and diaxial (*S,S*)-phenanthrenediols **261**⁷⁹ and the mono-protected derivatives **262** and **263** were chosen as the model substrates (Fig. 13). Glycosylation experiments were performed with the disaccharide donor **252** employing the $\text{Cp}_2\text{HfCl}_2/\text{AgClO}_4$ -protocol as the promoter. The results are presented in Table 3.

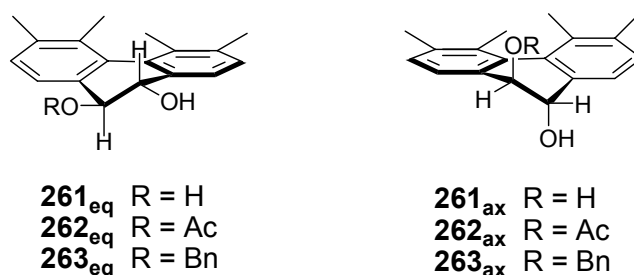


Figure 13. Structures of the *trans*-phenanthrenediol derivatives employed in the glycosylation study.

Glycosylation with diols **261eq** and **261ax** proceeded with poor yields, presumably due to internal hydrogen bonding that makes the hydroxy group less reactive (Entries 1 and 2). In the case of the diaxial **261**, only β -glycosylation took place, although the formation of bis-glycosylated product was also observed. Both the mono-protected acetates **262** and benzyl ethers **263** gave excellent yields, but the stereoselectivity was dependent on the protecting group. Glycosylation with the acetates **262** gave modest stereoselectivities, whereas better β -selectivities were obtained when using benzyl protected phenanthrenediols **263** (Entries 3-6). However, in all cases, the diaxial conformers offered higher β -selectivity than the diequatorial counterparts.

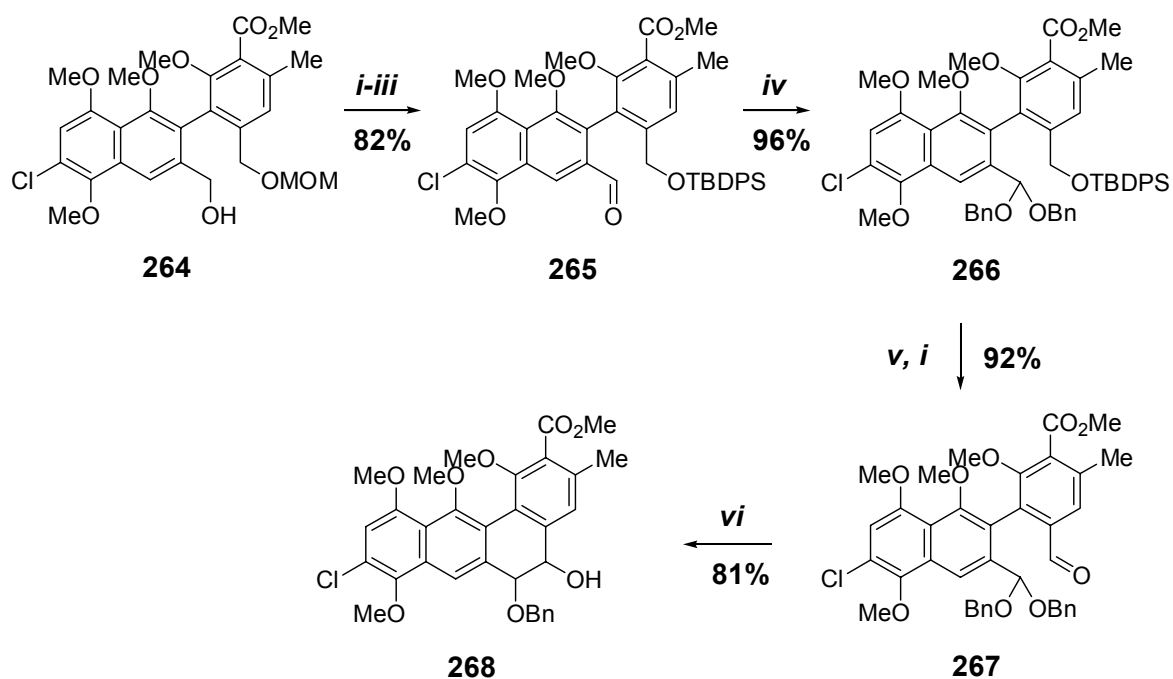
Table 3. Glycosylation of various phenanthrenediol derivatives with **252**.^{a)}

Entry	Diol	Yield (%) ^{b)}	α/β
1	261 _{eq}	69	1/4.7
2	261 _{ax}	55 (28) ^{c)}	β
3	262 _{eq}	94	1/2.6
4	262 _{ax}	91	1/4.6
5	263 _{eq}	94	1/6.7
6	263 _{ax}	90	1/7.6

a) Conditions: **252**/acceptor/CpHfCl₂/AgClO₄ = 1/1.4/1.3/2.6, MS 4Å, CH₂Cl₂, -78 °C → -20 °C; b) based on **252**; c) yield of the bis-glycosylated product.

The latest report by Suzuki and co-workers discussed the modification of the B-ring of the pradimicin aglycon in a manner that would allow selective glycosylation of the disaccharide moiety at the C5 hydroxyl group.⁸⁰ Direct glycosylation attempts between the disaccharide donor **252** and the aromatic aglycon **235** had resulted in no selectivity, due to the *trans*-configuration of the vicinal C5/C6 hydroxyls of the B-ring. In order to ensure the regioselective coupling to the C5 hydroxyl, the C6 hydroxyl group was protected. The synthesis strategy for the preparation of the suitable tetracyclic intermediate **268** is shown in Scheme 35.

Compound **264** was first oxidized to the corresponding aldehyde and the MOM-protection was replaced with a silyl group to produce compound **265**. Treatment of **265** with benzyl trimethylsilyl ether and a catalytic amount of TMSOTf gave acetal **266**, which after cleavage of the silyl protection was oxidized to the aldehyde-acetal **267**. Stereoselective reductive pinacol type cyclization of **267** by SmI₂ and BF₃·OEt₂ in THF furnished the desired C6-protected tetracycle **268** with perfect *trans*-selectivity (*trans/cis*, >99/<1).



Scheme 35. *i)* MnO₂, CH₂Cl₂; *ii)* 6 M HCl, DME (1:2), 40 °C; *iii)* TBDPCl, imidazole, DMF; *iv)* TMSOBn, TMSOTf; *v)* *n*-Bu₄NF, THF; *vi)* SmI₂, BF₃·OEt₂, THF.

In conclusion, the Suzuki group has reached closest towards the total synthesis of pradimicin A by accomplishing the synthesis of the aglycon part and performing the glycosylation studies for the attachment of the model disaccharide fragment to the aromatic skeleton.

4. Synthesis of the disaccharide fragment of pradimicin A

4.1. General

The target of my research was the synthesis of the amino sugar unit of the antibiotic pradimicin A (Fig. 14), starting from the amino acid L-threonine, and the coupling of the sugar fragment synthesized to a suitably protected, commercially available D-xylose derivative to build up the disaccharide unit of pradimicin A.

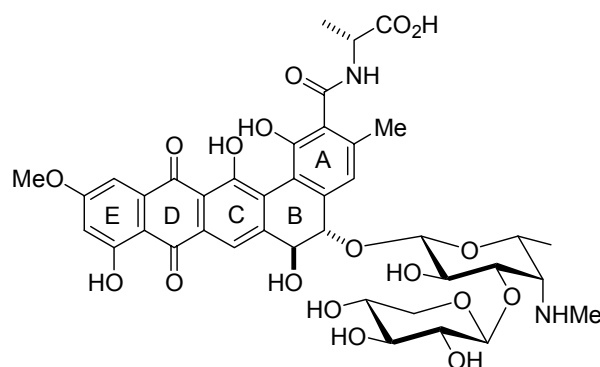


Figure 14. Pradimicin A.

Three major factors had to be taken into consideration when planning the synthesis:

- 1) preparation of the convenient glycosyl acceptor of the disaccharide *i.e.* the amino sugar unit
- 2) employment of the proper glycosyl donor
- 3) choice of suitable protective groups

A glycosidic bond is usually formed by displacement of a leaving group at the anomeric position of the glycosyl donor with the free hydroxyl group of the glycosyl acceptor (Fig. 15). Thus, glycosylation is a substitution reaction where the glycosyl acceptor acts as the nucleophile and the glycosyl donor is the electrophile. An important consideration often is that the anomeric position of the acceptor is differentially functionalized from the anomeric position of the donor in order to retain the glycosyl acceptor unaffected by the activation conditions. Another noteworthy factor is that the glycosylation reactions must be carried out under completely anhydrous conditions, since the presence of even a small amount of water will result in the formation of hydrolysis products.

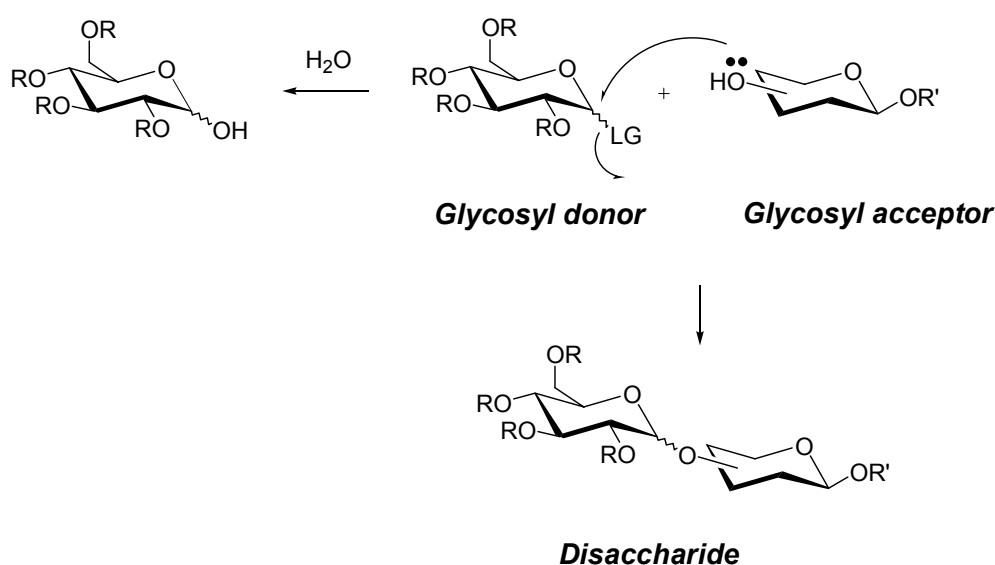


Figure 15. Formation of the glycosidic linkage. LG = leaving group.

When planning the synthesis of the disaccharide unit, the factors mentioned above had to be taken into account. In addition, the amino sugar part of the disaccharide had to be designed to function both as the acceptor and the donor, in order to facilitate the coupling of the disaccharide fragment to the pradimicin aglycon later on.

1), 2) There exist several commonly used glycosyl donors to choose from, including glycosyl bromides and fluorides, thioglycosides, selenoglycosides, sulfoxides, glycals and trichloroacetimidates. Glycosyl bromides were the first glycosyl donors used for the disaccharide formation by Koenigs and Knorr⁸¹ and are still widely employed, but they are not particularly stable and are usually generated *in situ* and employed directly after their formation. In comparison, glycosyl fluorides are much more stable and can be easily

prepared from the corresponding thioglycosides or directly from the sugars by conversion of the free anomeric hydroxyl group to fluoride. Thioglycosides are also very useful donors since they are stable and will not react until they are activated under particular conditions. Thioglycosides are easily prepared from the corresponding anomeric acetates. Since both glycosyl fluorides and thioglycosides are unaffected by the activation conditions required for the activation of the other, a partially protected glycosyl fluoride can be employed as a glycosyl acceptor with a thioglycoside donor, and *vice versa*. These are termed *orthogonal* glycosylation protocols. For this reason, a combination of glycosyl fluorides and thioglycosides was chosen for the preparation of the disaccharide fragment of pradimicin A.

3) The third crucial part in the synthesis was the choice of proper protecting groups. In a multi-step synthetic sequence, the protection has to be stable under a variety of subsequent reaction conditions, and it should be readily removed at the end of the synthesis route without affecting other functionalities or the glycosidic bond. Furthermore, the stereochemical outcome of the glycosylation can also be partly controlled by the type of protection, employing either participating or non-participating neighbouring groups at the 2-position.

Neighbouring group participation of an ester protecting group, such as an acetate or a benzoate, will result in the formation of 1,2-*trans* glycosidic linkages.⁸² Figure 16 illustrates an example of a substitution reaction of an acetylated sugar having generalized anomeric leaving group LG with a nucleophile Nu to produce a glycosidic bond. The first step of the reaction mechanism consists of an S_N1 type cleavage of the leaving group (LG) leading to the formation of the glycosyl cation. In the next stage, the glycosyl cation is stabilized by the participation of the carbonyl oxygen of the acetate at the 2-position generating the cyclic oxonium ion. Finally, an S_N2 type attack of an external nucleophile (Nu) produces the glycosidic linkage *trans* to the 2-hydroxyl group. As shown in Figure 16, a *gluco* starting sugar gives access to the β-glucoside whereas a *manno* derivative affords the α-isomer.

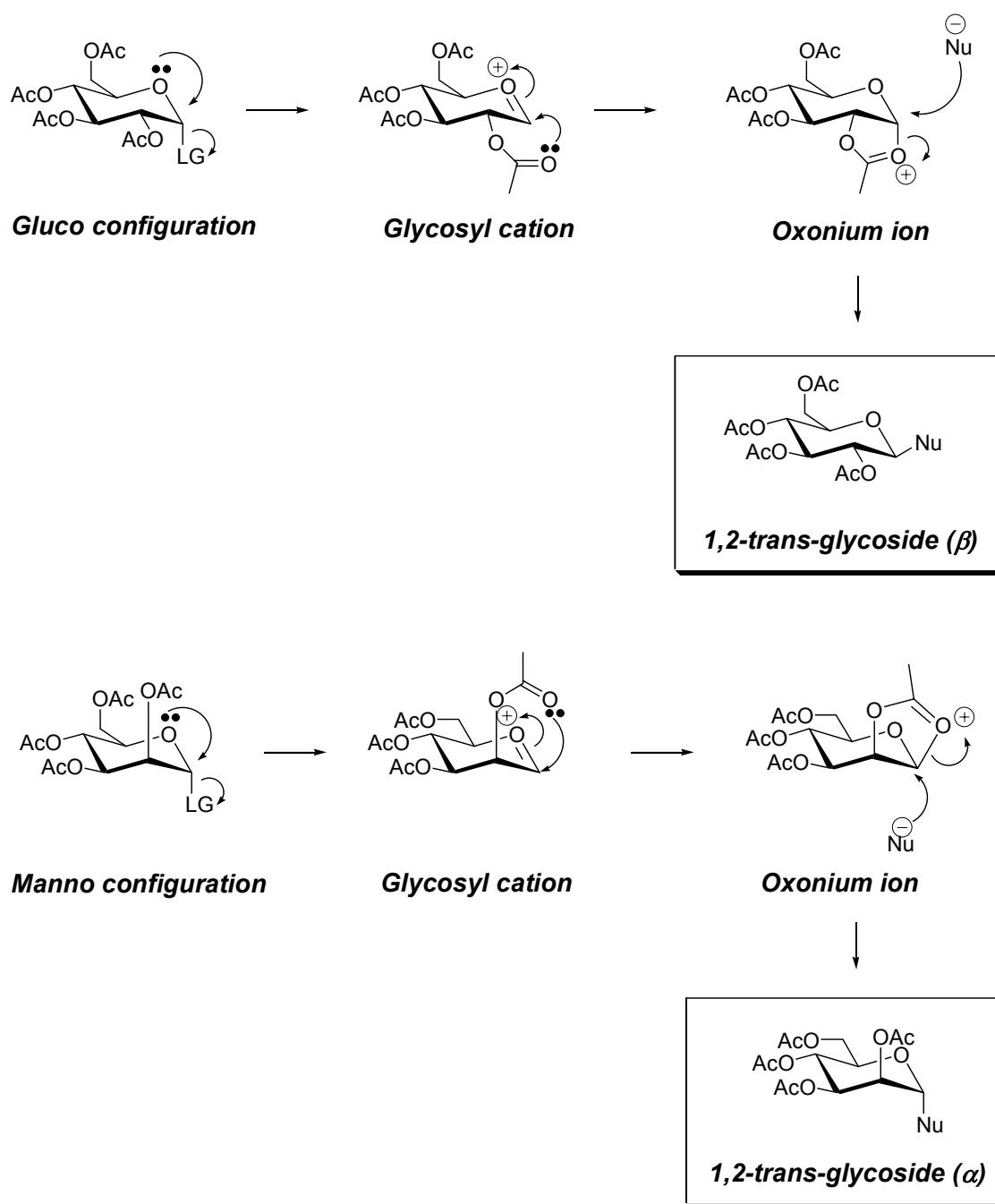


Figure 16. Neighbouring group participation in the formation of 1,2-*trans*-glycosides.

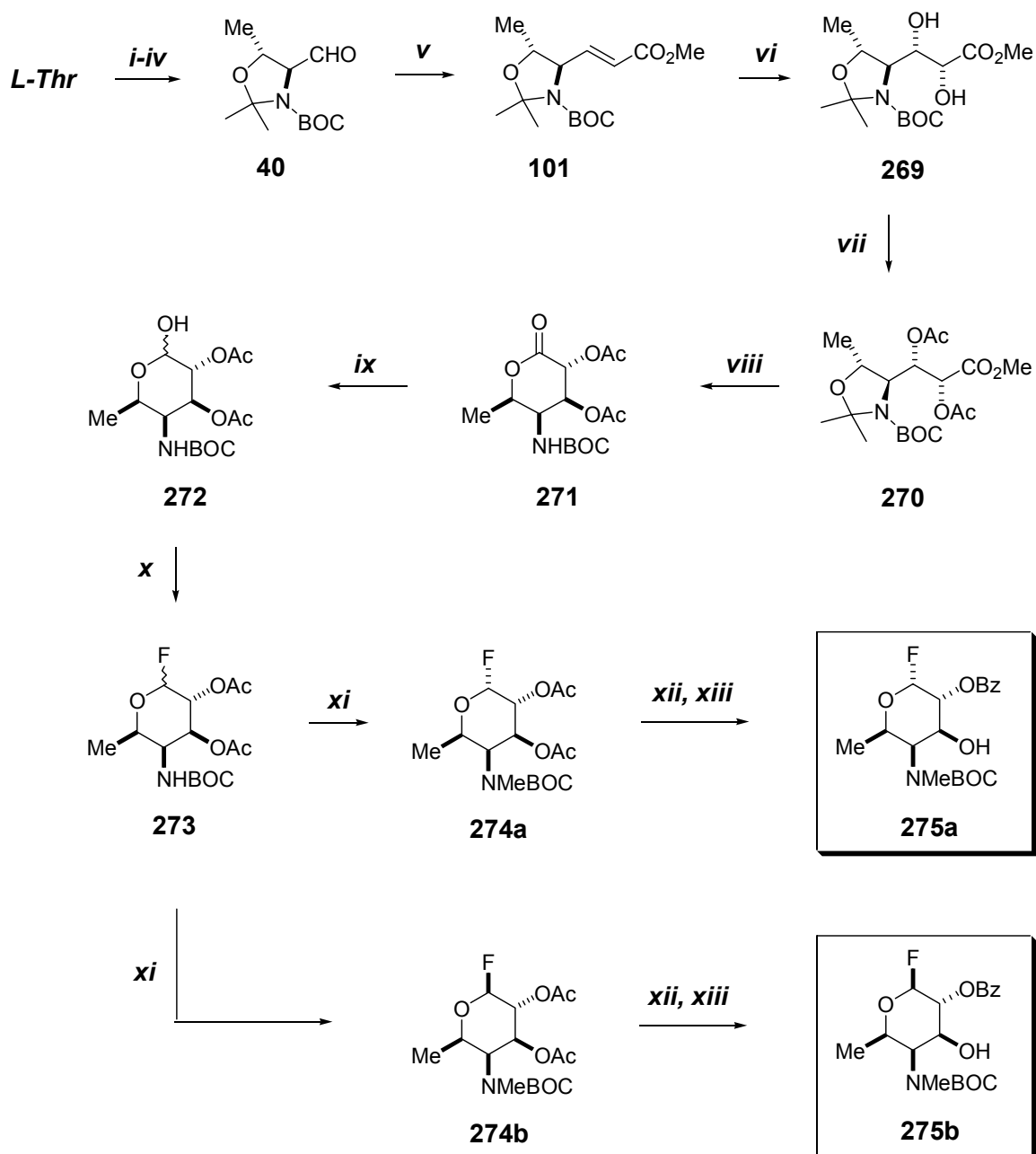
Keeping these factors in mind, the synthetic route for the preparation of the amino sugars **275**, starting from L-threonine, was designed. The synthesis path is described in general in section 4.2 and each stage of the reaction course is discussed in detail in the latter part of this chapter.

4.2. L-Threonine based approach to the synthesis of the amino sugar fragment of pradimicin A

The synthesis of the target amino sugars **275** is a multi-step process, starting from the commercially available amino acid L-threonine (Scheme 36). The work concerning the preparation of some deoxy-4-aminohexoses from L-threonine, accomplished earlier in our group,³⁴ offered the basis for the amino acid based synthesis of the deoxysugar derivatives **275a** and **275b**.

To begin with, the amino aldehyde **40** was prepared from L-threonine according to the modified procedure developed earlier in our group.³⁴ The *t*-butoxycarbonyl group (BOC) was chosen for the amine protection for two reasons: 1) the behavior of the BOC-group under the reaction conditions up to *E*-enoate **101** was already familiar and would not require any adjustments, which would have been the case when introducing a totally new protecting group, 2) it is reasonably stable under the acidic reaction conditions required during the synthesis sequence.

Conversion of the aldehyde **40** to the *E*-enoate **101** was accomplished by a modified Horner-Wadsworth-Emmons olefination, employing 18-crown-6 ether to improve the dissolution of the base used.³⁴ Ruthenium-catalyzed dihydroxylation of the double bond afforded diol **269**, which after acetate protection, was subjected to acid-catalyzed cyclization to produce lactone **271**. Reduction of lactone **271** by platinum-catalyzed hydrogenation, followed by fluorination with DAST afforded a mixture of α - and β -fluorides **273**, which were separated by flash chromatography. *N*-Methylation for both anomers, followed by deprotection and selective benzoyl protection at the 2-position furnished the target amino sugars **275a** and **275b**. The 2-position of the monosaccharides was protected by a participating benzoyl ester, in order to ensure the correct stereochemical outcome of the future glycosylation between the disaccharide fragment to be formed and the pradimicin aglycon.



Scheme 36. *i*) AcCl, MeOH, 50 °C; *ii*) Et₃N, (BOC)₂O, MeOH/CH₂Cl₂; *iii*) DMP, BF₃·OEt₂, CH₂Cl₂; *iv*) DIBAL-H, toluene, -78 °C; *v*) MeO₂CCH₂P(O)(OMe)₂, K₂CO₃, 18-c-6, toluene, rt; *vi*) NaIO₄, RuCl₃·x(H₂O), EtOAc/CH₃CN 1:1; *vii*) Ac₂O, DMAP, CH₂Cl₂; *viii*) gl. acetic acid, 60 °C; *ix*) PtO₂/H₂, EtOAc, rt; *x*) DAST, EtOAc, 0 °C → rt; *xi*) MeI, Ag₂O, DMF; *xii*) 0.1 M NaOMe, MeOH, 0 °C; *xiii*) BzCl, Bu₂SnO, Et₃N, reflux.

4.3. Formation of *E*- and *Z*-enoates via modified Horner-Wadsworth-Emmons olefination

The Horner-Wadsworth-Emmons olefination reaction can generate both the thermodynamic and kinetic olefination products *i.e.* *E*- and *Z*-enoates, respectively (Fig. 17). The process favors the formation of the thermodynamically more stable *E*-olefins, but the *E/Z* ratio can be affected by the metal cation, reaction temperature and the solvent employed.⁸³ According to the observations by Thompson and Heathcock, the alkyl substitution pattern on the aldehyde had the greatest effect on the *E/Z* ratio: the solvent, base or the reaction temperature had significant effects on the *E/Z* ratio in the reactions with mono- and disubstituted aldehydes, but olefination of the trisubstituted aldehyde produced the *E*-enoate exclusively, regardless of the reaction conditions employed.

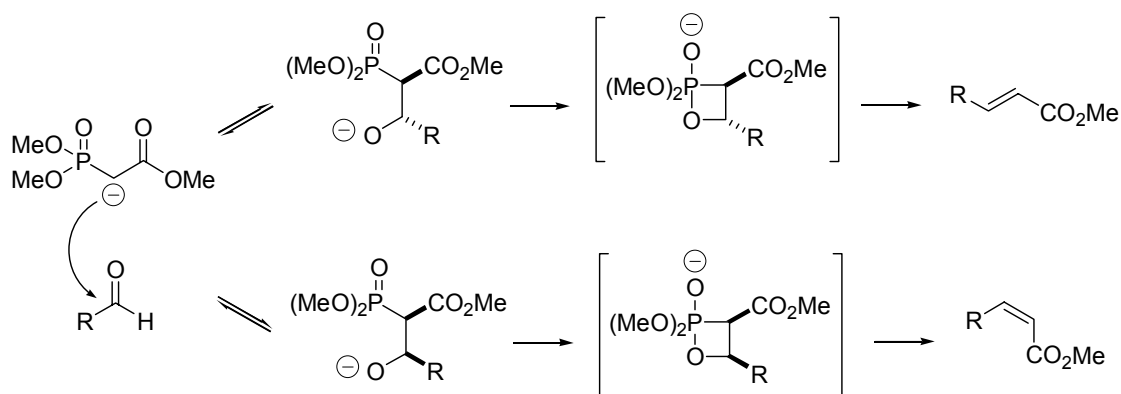
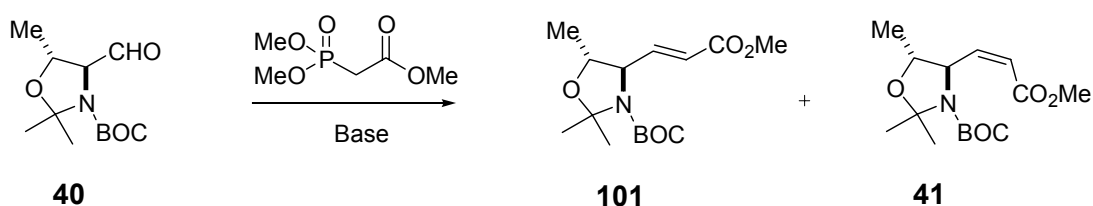


Figure 17. Mechanism for the Horner-Wadsworth-Emmons reaction.

For the olefination of the mono- and disubstituted aldehydes, among the metal cations examined were lithium, sodium and potassium. The effect of temperature (rt vs. $-78\text{ }^\circ\text{C}$) and the solvent (THF vs. DME) was greatest with the use of lithium cation and was decreased when employing sodium or potassium as the cation. At room temperature, sodium and potassium cations afforded moderated *E*-selectivities in both solvents, but the best *E/Z*-ratio for both types of aldehydes was obtained by the use of lithium at room temperature in DME.

In the synthesis towards the amino sugar derivatives **275**, the formation of the *E*-isomer was desired. The results published earlier in our group had shown that the best *E*-selectivity in the modified Horner-Wadsworth-Emmons olefination of the amino aldehyde

40 had been achieved by the combined use of trimethyl phosphonoacetate, potassium carbonate and 18-crown-6 ether in toluene, affording a 19:1 *E/Z*-ratio.³⁴ However, in order to reduce the overall costs of the synthesis sequence by avoiding the use of a large excess (200 mol-%) of the expensive 18-crown-6 ether in this particular step, we examined the effect of different bases (especially the metal cation) on the *E/Z*-selectivity in the absence of 18-crown-6. Trimethyl phosphonoacetate was used as the phosphonate carbanion and the bases examined were KHMDS, NaH and BuLi. The solvents employed were THF (for BuLi and NaH) or toluene (for KHMDS) (Scheme 37).



Scheme 37.

In a typical procedure, trimethyl phosphonoacetate and the base were combined and stirred with the solvent at ~ 0 °C for 1 h before addition of the aldehyde **40**. After addition of the aldehyde at -10 °C, the reaction was brought to rt and stirring was continued either for 1.5 h or overnight. The reactions were carried out at rt in order to produce mainly the thermodynamic *E*-olefination product **101**. The reaction time was lengthened in some experiments for comparison, in order to see whether the prolonged reaction time would increase the *E/Z*-ratio. As can be seen in Table 4, the prolonged reaction time had no effect on the stereoselectivity.

The absence of 18-crown-6 ether resulted in modest stereoselectivities, and the difference between KHMDS and NaH as the base was insignificant: the *E/Z*-ratio of the olefination products with KHMDS was 6:1 and with NaH 5:1. Olefination employing BuLi as the base afforded a 1:1 mixture of *E*- and *Z*-enoates.

The results observed for KHMDS are comparable to those recorded earlier in our group for the olefination of aldehyde **40**. The reaction of **40** with trimethyl phosphonoacetate and K_2CO_3 had afforded an *E/Z*-ratio of 6:1 in toluene and of 4:1 in acetonitrile. The effect of Na^+ and Li^+ cations on the olefination of **40** had not been reported in that study.

Table 4. The effect of base in the formation of *E*- and *Z*-enoates.

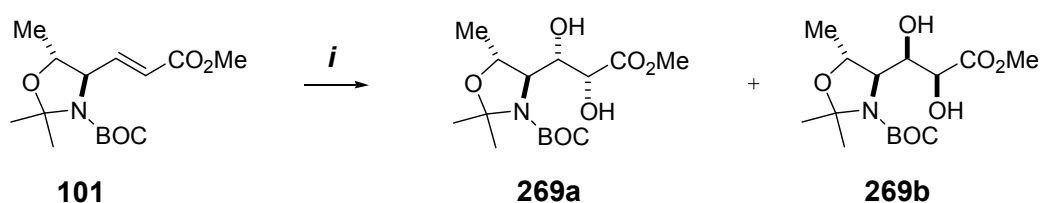
Entry	Base/Solvent	Reaction time	<i>E/Z</i> ^{a)}	Yield (%)
1	KHMDS/toluene	1.5 h	6:1	91
2	KHMDS/toluene	overnight	6:1	90
3	NaH/THF	1.5 h	5:1	95
4	NaH/THF	overnight	5:1	94
5	BuLi/THF	1.5 h	1:1	85
6	BuLi/THF	overnight	1:1	85

^{a)} The *E/Z*-ratio was determined by HPLC.

In conclusion, in order to obtain the *E*-olefin **101** in high stereoselectivity, the presence of 18-crown-6 ether in the reaction system was required. The other alternative was the awkward and time-consuming separation of the *E/Z*-mixture by flash chromatography.

4.4. Ruthenium-catalyzed *cis*-dihydroxylation of the double bond

Dihydroxylation of the *E*-enoate **101** was performed by ruthenium-catalyzed dihydroxylation, employing NaIO₄ as the oxidizing agent and RuCl₃·*x*H₂O as the catalyst.⁸⁴ The advantage of the oxidative ruthenium catalysis over the traditional, osmium tetroxide catalyzed dihydroxylation method⁸⁵ was extremely short reaction time. The reaction was essentially complete after 3 min vigorous stirring of the enoate **101** with NaIO₄ and RuCl₃·*x*H₂O in a biphasic solvent system of EtOAc/MeCN/H₂O at 0 °C. In order to avoid overoxidation, the reaction was stopped exactly after 3 minutes. The above *cis*-hydroxylation of **101** produced a 3:1 mixture of the diols **269a** and **269b**, which were purified by flash chromatography in 48 % and 18 % yield, respectively (Scheme 38).



Scheme 38. *i*) NaIO₄, cat. RuCl₃·*x*H₂O, EtOAc/MeCN/H₂O (3:3:1), 0 °C, 3 min.

The mechanism of the ruthenium-catalyzed dihydroxylation is not clear, but the *cis*-stereochemistry of the resultant diols derived from cycloalkenes suggests a cyclic intermediate.⁸⁶ Two basic mechanisms for the ruthenium- or osmium-catalyzed dihydroxylation have been proposed: the classical, concerted [3+2] cycloaddition mechanism and a stepwise [2+2] mechanism (Fig. 18). The early DFT (density functional theory) studies by Sharpless *et al.* indicated the intermediacy of the metallaoxetane intermediate *i.e.* the [2+2] mechanism⁸⁷ but more recent studies have provided strong support for the concerted [3+2] mechanism.⁸⁸

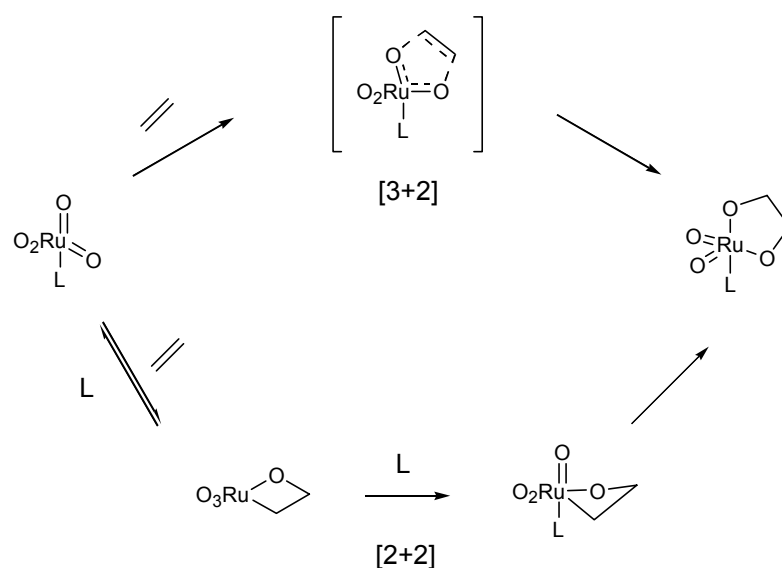
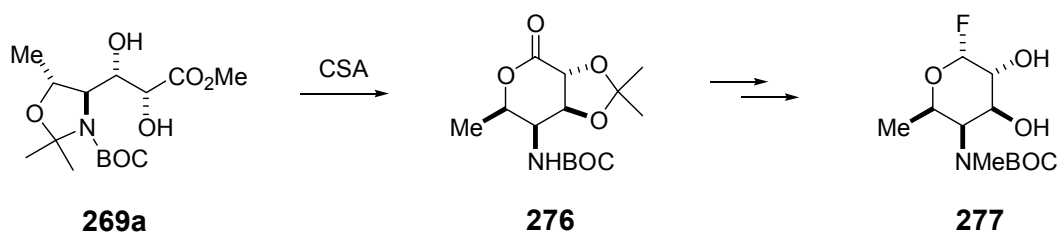


Figure 18. Possible pathways for the ruthenium-catalyzed *cis*-dihydroxylation.

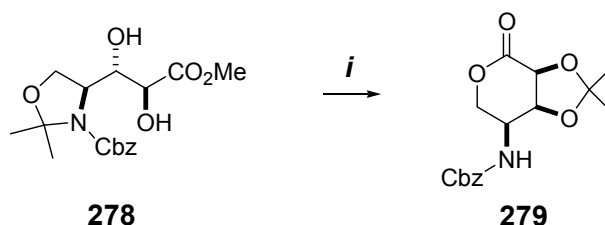
4.5. Lactonization

The original strategy to generate the desired deoxysugar **277** was to expose the diol **269a** to acid-catalyzed lactonization to form the bicyclic lactone **276**, having the two hydroxyl groups simultaneously protected. After lactonization, successive *N*-methylation, fluorination and deprotection would have followed (Scheme 39).



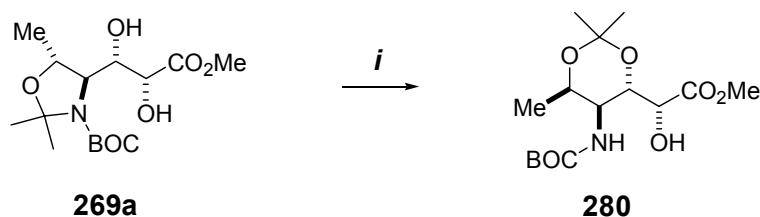
Scheme 39.

The idea to form the bicyclic lactone **276** arose from the acid-mediated lactonization results reported for the L-serine derivative **278** in our group.⁸⁹ Treatment of the Cbz-protected, L-serine derived *anti*-alcohol **278** with camphorsulfonic acid at rt for 12 h had produced the bicyclic lactone **279** (Scheme 40).



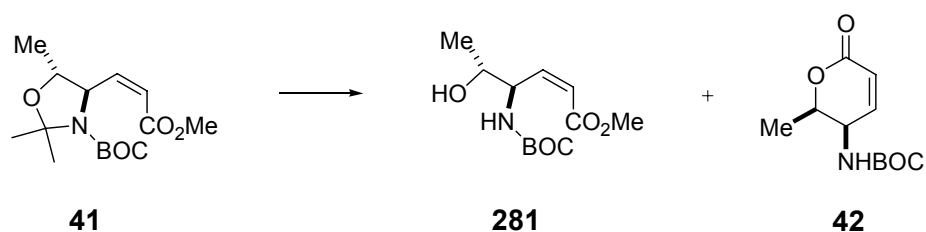
Scheme 40. *i*) CSA, CH₂Cl₂, rt.

In the case of the *syn*-diol **269a**, the reaction with CSA resulted in the formation of the O,O-acetonide **280** instead of the desired bicyclic lactone (Scheme 41). The major difference between the L-serine derived alcohol **278** and the compound **269a** is the *anti*- vs. *syn*-configuration of the starting diol. If simple molecular models built up of both of these molecules are compared, one can easily notice that the bicyclic lactone to be generated from the *syn*-derivative **269a** would have much more strain than the one formed from the *anti*-alcohol **278**.



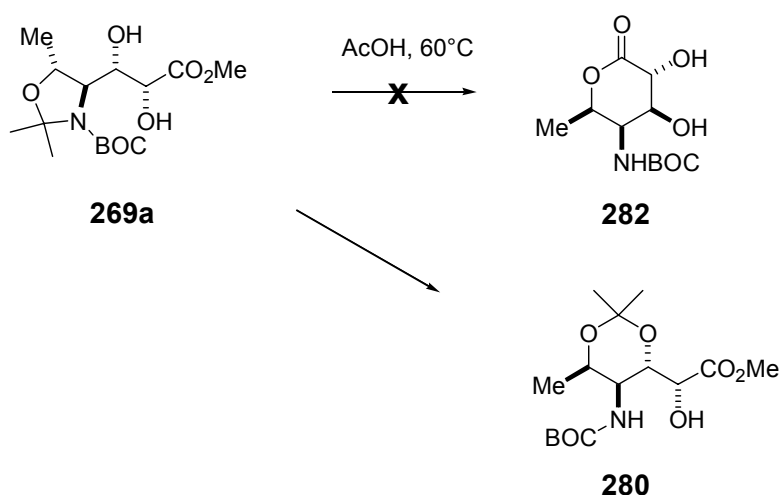
Scheme 41. *i*) CSA, CH₂Cl₂, rt.

Another attempt for the cyclization of **269a** was the application of the lactonization method developed for *Z*-enoate **41** in our group.³⁴ Several experiments to find out the most convenient acidic cyclization conditions for the *Z*-enoate **41** had been carried out, and the acids examined included formic acid, acetic acid (both 80 % and glacial), CSA, PTSA and the Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$. Most of the methods tested had afforded a mixture of the open chain product **281** and the lactone **42**, but the reaction performed in glacial acetic acid at 60 °C had produced the lactone **42** as the sole product (Scheme 42).



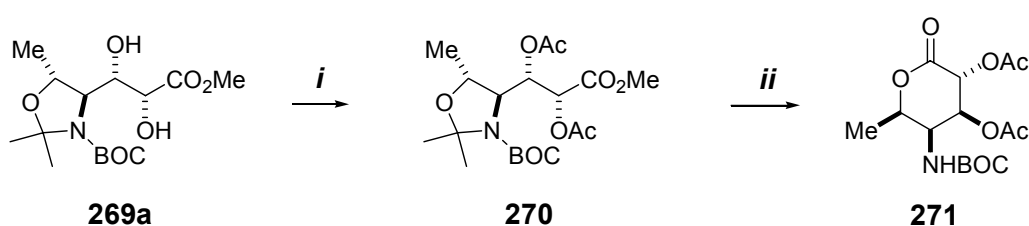
Scheme 42.

With the goal to prepare the lactone **282**, diol **269a** was subjected to the cyclization conditions employing acetic acid as the reagent and the solvent at 60 °C. However, instead of lactonization, the reaction produced the acetonide **280** (Scheme 43). Evidently, the free hydroxyl groups of the diol interfered with the lactonization process and ought to be protected before cyclization.



Scheme 43.

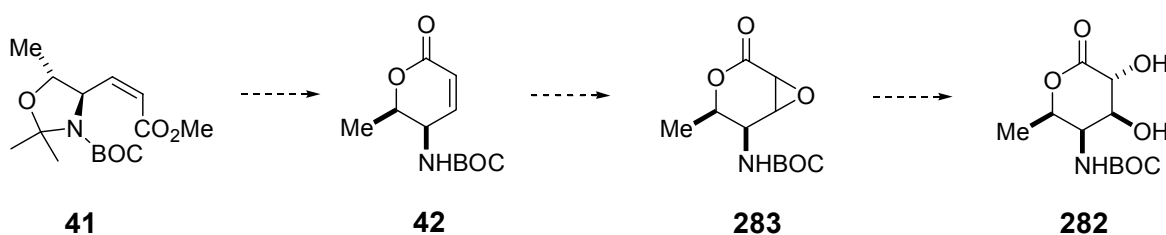
Acetate protection was chosen for the hydroxyl groups of diol **269a** due its stability under the acidic conditions required for the lactonization. Another reason was that acetylation is a simple and rapid process, leading to acetylated products in quantitative yield. Treatment of the *syn*-diol **269a** with a 20-fold excess of acetic anhydride and a catalytic amount of DMAP in CH₂Cl₂ produced the acetylated intermediate **270** after 30 min stirring at rt. Purification by flash chromatography afforded compound **270** in 99 % yield. The protected diol **270** was allowed to stir with glacial acetic acid at 60 °C for 6 days furnishing the lactone **271** together with unreacted **270**. The corrected yield for the product **271**, based on recovered starting material, was 68 % (Scheme 44).



Scheme 44. *i*) Ac₂O, DMAP, CH₂Cl₂; *ii*) Acetic acid, 60 °C.

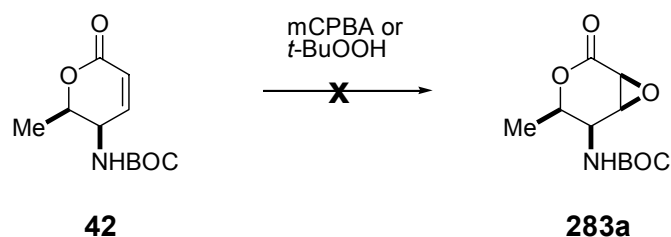
4.6. Model oxidation studies by molecular oxygen

Another possibility to obtain the desired monosaccharide derivative **282** could have been *via* epoxidation of lactone **42**, followed by ring-opening (Scheme 45).



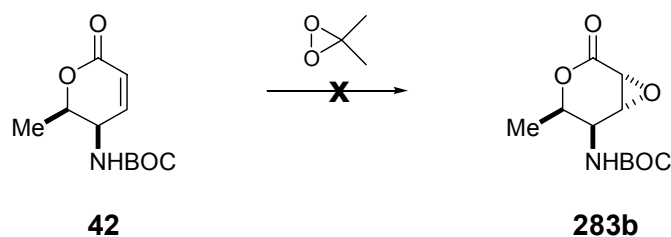
Scheme 45.

In our group, lactone **42** had been prepared from the *Z*-enoate **41** under acidic reaction conditions and several epoxidation experiments for compound **42** had been performed.⁹⁰ Epoxidation attempts with *m*-chloroperbenzoic acid or *t*-butylhydroperoxide had resulted in no reaction (Scheme 46).



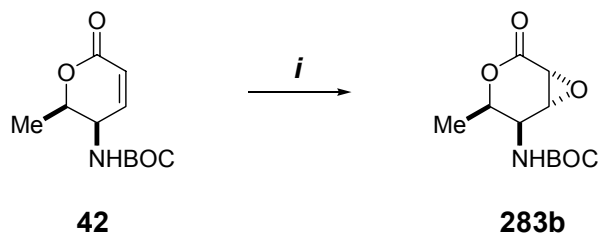
Scheme 46.

Oxidation with dioxirane had been very slow and led in decomposition of the labile oxidant, thus affording only 30 % yield after several days of oxidation (Scheme 47).



Scheme 47.

Finally, epoxidation with $t\text{-BuOO}^-\text{Li}^+$, prepared from $t\text{-BuOOH}$ and n -butyl lithium, had produced the epoxy lactone **283b** almost quantitatively, but the product had decomposed at temperatures higher than $-20\text{ }^\circ\text{C}$. It was also reported, that the epoxide **283b** had been very labile to both the acidic and basic conditions, resulting in decomposition during the work-up process.

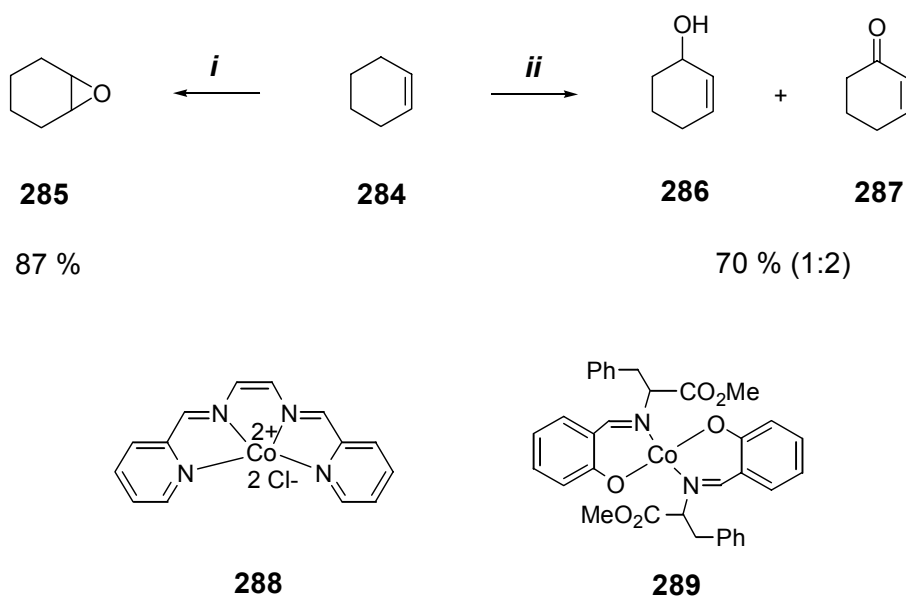


Scheme 48. *i*) $t\text{-BuOO}^-\text{Li}^+$, THF, $-20\text{ }^\circ\text{C}$.

As part of the *New Oxidation Technologies – Programme*, supported by TEKES (the National Technology Agency of Finland) and several Finnish companies, epoxidation and

allylic oxidation studies employing cyclohexene and α -pinene as model substrates were accomplished. These oxidations were carried out by molecular oxygen, using various cobalt complexes as catalysts. The research concerning the cobalt-catalyzed allylic air oxidation of α -pinene performed earlier in our group offered the basis for these oxidation experiments.⁹¹

One major topic of these cobalt-catalyzed air oxidation studies was to examine the effect of the catalyst and an additive on the direction of oxidation *i.e.* epoxidation vs. allylic oxidation. Iqbal *et al.*⁹² had reported that the direction of oxidation could be defined by a suitable cobalt catalyst. In the presence of molecular oxygen and isobutyraldehyde, several cyclic alkenes had been selectively oxidized by cobalt Schiff base complexes **288** or **289** either to the corresponding epoxides or allylic oxidation products. For example, the cobalt complex **288** had selectively catalyzed the oxidation of cyclohexene **284** to cyclohexene oxide **285** in 87 % yield, whereas the use of the catalyst **289** had produced 2-cyclohexen-1-ol **286** and 2-cyclohexen-1-one **287** as the major products in 70 % of total yield (Scheme 49).



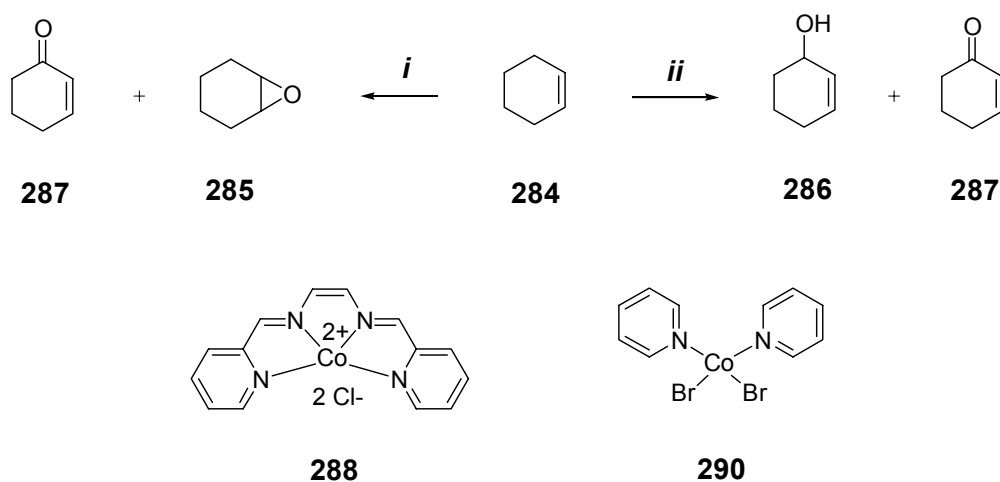
Scheme 49. *i*) O₂, **288**, IBAL, MeCN, rt, *ii*) O₂, **289**, IBAL, MeCN, rt.

Iqbal's report did not specify more precisely what factors of the cobalt catalysts defined the direction of oxidation. Our own hypothesis was that the octahedral vs. tetrahedral structure of the complex directed the oxidation *i.e.* the octahedral catalyst **288** led to

epoxidation whereas the tetrahedral complex **289** afforded allylic oxidation products. To find out whether this hypothesis was correct or not, we decided to prepare certain cobalt complexes of our own and to test them in the air oxidation experiments of our model compounds.

To start with, the literature reaction oxidizing cyclohexene in the presence of IBAL with the catalyst **288** was repeated, with expectations to produce cyclohexene oxide **285** selectively (Scheme 50). Cyclohexene and IBAL (molar ratio 1:2) were dissolved in acetonitrile in a round-bottomed flask equipped with an oxygen balloon. The cobalt Schiff base complex **288** (5 mol-%) was added to the solution and the reaction mixture was stirred at rt for 40 hours. According to the GC analysis, cyclohexene oxide **285** and 2-cyclohexen-1-one **287** were obtained as the major products in a ratio of 2.5:1, respectively, along with formation of 2-cyclohexen-1-ol **286** as the minor product.

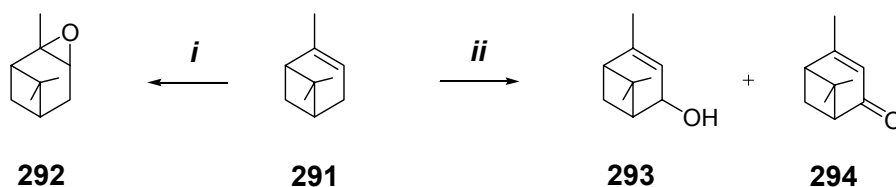
When the tetrahedral $\text{Co}(\text{py})_2\text{Br}_2$ -complex⁹³ **290** (5 mol-%) was applied to the similar oxidation of cyclohexene, the corresponding epoxide and ketone were produced as the major products in a ratio of 2:1 as well (Scheme 50). Interestingly, when only 0.13 mol-% of $\text{Co}(\text{py})_2\text{Br}_2$ -catalyst **290** was employed instead of 5 mol-%, the rate of the oxidation was accelerated and the proportion of the epoxide increased; the ratio of cyclohexene oxide **285** to 2-cyclohexen-1-one **287** was 4:1.



Scheme 50. *i*) O_2 , IBAL, MeCN, **288** or **290**, *ii*) O_2 , **288** or **290**.

Moreover, in the absence of IBAL, both the cobalt catalysts resulted in allylic oxidation of cyclohexene, affording only 2-cyclohexen-1-one **287** and 2-cyclohexen-1-ol **286** (Scheme 50).

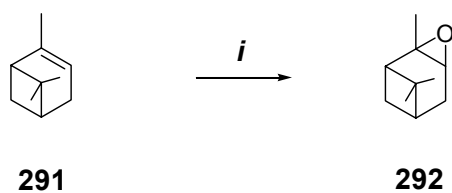
Similar results were observed in the cobalt-catalyzed oxidation of α -pinene by molecular oxygen. In the absence of any solvent or additive, $\text{Co}(\text{py})_2\text{Br}_2$ -catalyst gave mainly allylic oxidation products whereas in the presence of IBAL and $\text{Co}(\text{py})_2\text{Br}_2$, α -pinene was selectively oxidized to α -pinene oxide with no signs of allylic oxidation (Scheme 51).



Scheme 51. *i)* O_2 , IBAL, MeCN, **290**, *ii)* O_2 , **290**.

A question had also been raised whether it was necessary to employ a ready-made cobalt complex in the oxidations or whether the complex could be formed during the process provided that the reagents needed for the catalyst formation were available. Experiments for α -pinene in the absence of IBAL were performed employing either $\text{Co}(\text{py})_2\text{Br}_2$ **290** as the catalyst or by adding $\text{CoBr}_2 \cdot 6\text{H}_2\text{O}$ and pyridine separately into α -pinene in order to generate the cobalt-pyridine -complex *in situ*. The reactions were carried out at 70 °C by bubbling oxygen through a gas inlet in the bottom of a glass reactor. There were no differences between these experiments; in both the cases oxidation proceeded normally and allylic oxidation products were obtained as usual.⁹⁴ A test reaction with the plain $\text{CoBr}_2 \cdot 6\text{H}_2\text{O}$ as the catalyst was also carried out, but no reaction occurred after one day of oxidation. According to these results, the geometry of the cobalt complex did not have much effect on the oxidation of α -pinene, but the presence of pyridine was essential for the oxidation to take place.

The influence of pyridine on the oxidation of α -pinene in the presence of IBAL was also examined. When the $\text{Co}(\text{py})_2\text{Br}_2$ -complex **290** was replaced by plain $\text{CoBr}_2 \cdot 6\text{H}_2\text{O}$, the reaction proceeded smoothly as usual, yielding α -pinene oxide **292** as the sole product (Scheme 52). In the next experiment, oxidation of α -pinene in the presence of IBAL but without a catalyst was performed to find out whether any metal catalyst at all was required for the oxidation to take place. Indeed, epoxidation of α -pinene **291** to α -pinene oxide **292** was completed in 6 hours at rt (Scheme 52).



Scheme 52. *i*) O₂, IBAL, MeCN, (**290** or CoBr₂·6H₂O), rt.

Oxidation of cyclohexene in the presence of IBAL without any cobalt catalyst led to the formation of cyclohexene oxide as the major product, although the reaction rate was slightly slower compared to the experiments with the cobalt catalyst. Different from the oxidation of α -pinene, in the case of cyclohexene allylic oxidation took also place and the reaction rate was slower.

In conclusion, these experiments showed that the presence of IBAL in the oxidation of cyclohexene and α -pinene resulted mainly in epoxidation, whereas in the absence of the aldehyde, allylic oxidation products were obtained.

4.6.1. Cobalt salen and pyrrolidine complexes in the oxidation of cyclohexene

We had proposed that the octahedral structure of the cobalt Schiff base complex **288** had directed the oxidation of olefins to form epoxides. However, the experiments carried out for cyclohexene and α -pinene showed that in the absence of IBAL, the use of complex **288** resulted in allylic oxidation. Those results led to the assumption that the octahedral structure of the catalyst had changed in the substrate during the oxidation process and therefore the allylic oxidation had occurred. The effect of the positive and negative charge in the cobalt complex **288** on the oxidation process was also worthy of consideration. Since the tetrahedral Co(py)₂Br₂-catalyst was a neutral complex, it was of interest to prepare neutral, octahedral cobalt complexes in order to be able to compare the influences of the tetrahedral and octahedral structures of the catalysts on the oxidation. Cobalt salen complex **295**, one of a type of catalysts that are widely used in the epoxidation of olefins, was prepared according to the literature procedure from diamine and salicylaldehyde.⁹⁵

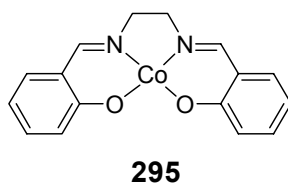
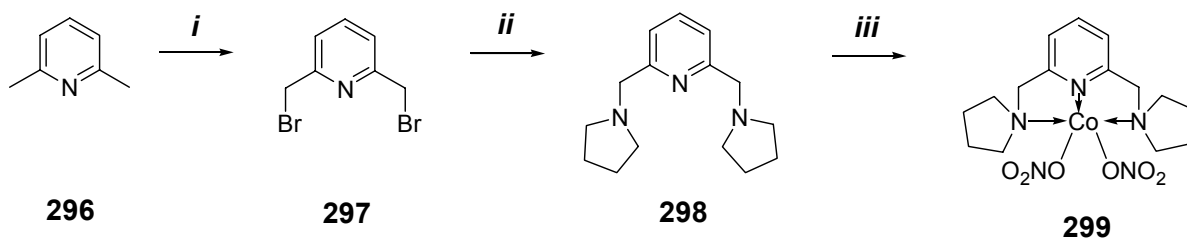


Figure 19. Cobalt(II) salen complex.

In addition, a new cobalt pyridine complex **299** was synthesized (Scheme 53). 1,3-Bis(bromomethyl)-pyridine **297** was prepared in a moderate yield (25 %) according to the literature procedure⁹⁶ by bromination of 2,6-lutidine **296** with an excess of *N*-bromosuccinimide in benzene under illumination. One equivalent of compound **297** and five equivalents of pyrrolidine in benzene reacted through nucleophilic substitution to form 1,3-bis[(pyrrolidinyl-*N*-)methyl]-pyridine **298** in a 74 % yield after Kugelrohr distillation. Compound **298** and cobalt(II) nitrate hexahydrate were stirred in absolute ethanol at rt overnight to form a purple powder. The crude product was further purified by crystallization from absolute ethanol to afford 1,3-bis[(pyrrolidinyl-*N*-)methyl]-pyridine cobalt complex **299** as large, purple crystals in a 69 % yield.



Scheme 53. *i*) NBS, AIBN, hv, benzene, *ii*) pyrrolidine, benzene, *iii*) Co(NO₃)₂·6H₂O, EtOH.

In order to see if epoxidation would take place, the cobalt catalysts **295** and **299** were employed in the air oxidation of cyclohexene in the absence of IBAL. The reactions proceeded as usual in the absence of the aldehyde, affording only allylic oxidation products of cyclohexene *i.e.* 2-cyclohexen-1-ol **286** and 2-cyclohexen-1-one **287**.

It was later determined on the basis of X-ray analysis⁹⁷ that the structure of complex **299** was rather a trigonal bipyramide than octahedral as it had been considered earlier (Fig. 20). However, the experiments performed with the neutral, octahedral cobalt salen

complex **295** indicated that epoxidation could not be directed only by the octahedral structure of the catalyst.

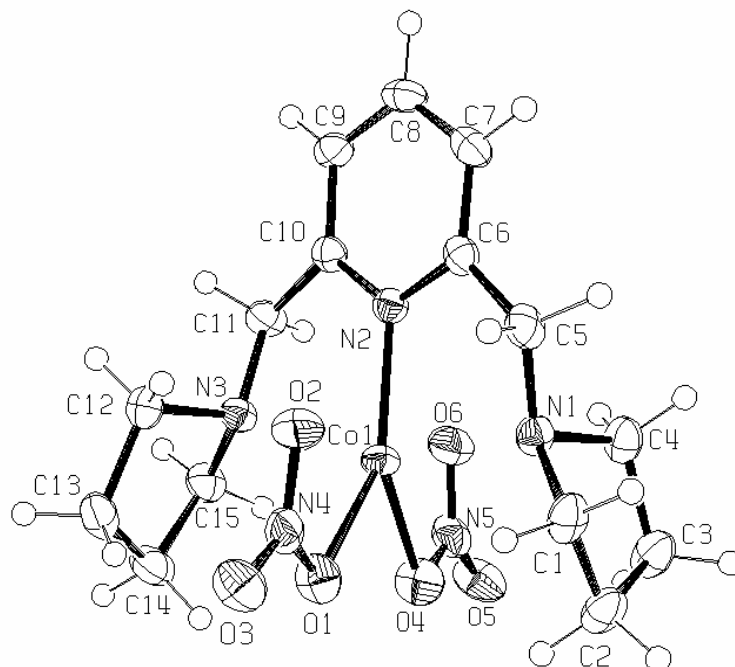


Figure 20. ORTEP plot of the molecular structure of complex **299**.

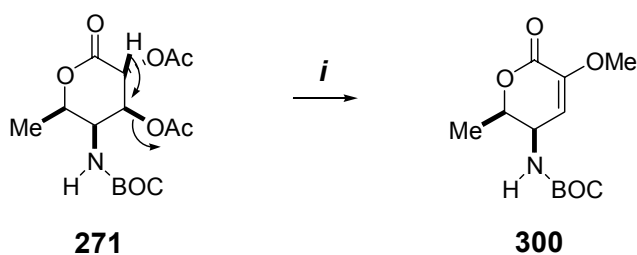
Based on the above results obtained for cyclohexene and α -pinene it was concluded that the structure of the cobalt catalyst did not seem to have a significant role in defining the direction of oxidation, but the presence or absence of the aldehyde clearly determined whether epoxidation or allylic oxidation occurred.

The cobalt-catalyzed oxidation was not applied for the epoxidation of the lactone **42** since the double bond of **42** is electron poor and therefore not easily oxidized.

4.7. *N*-Methylation attempts

N-Methylation of the lactone **271** was intended to be the next step of the synthesis. The commonly used *N*-methylating agents are methyl iodide and NaH in an appropriate solvent such as THF or DMF. Application of these methylating conditions for the lactone **271** resulted in replacement of the acetate protection at the 2-position by a methoxy group, and

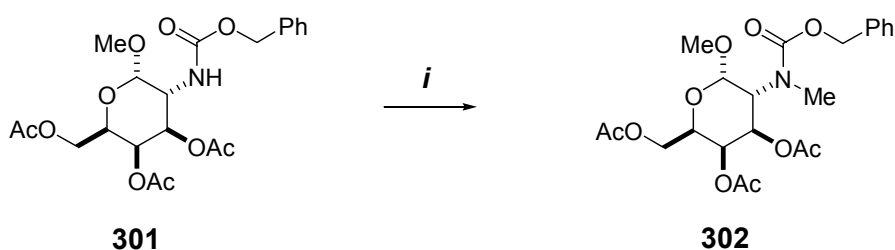
removal of the hydrogen at C-2, leading to elimination of the C-3-acetate of the lactone ring (Scheme 54).



Scheme 54. *i*) MeI, NaH, THF, rt.

Indeed, removal of the acetate protection can be accomplished under basic reaction conditions,⁹⁸ but the cleavage of the hydrogen atom at the 2-position, followed by the double bond formation was not expected. Apparently, the hydrogen atom next to the carbonyl group is slightly more acidic than the hydrogen bonded to the nitrogen.

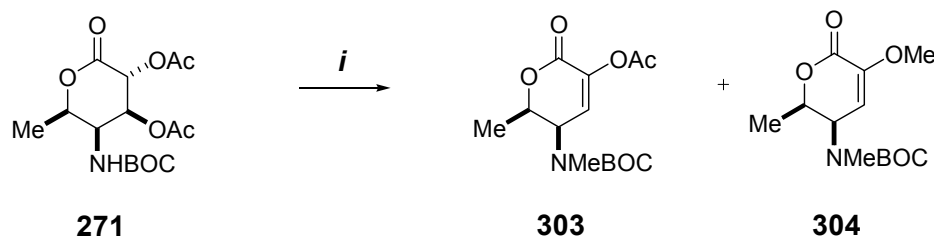
To avoid deacetylation, examples of *N*-methylation procedures under neutral reaction conditions were sought for in the literature. Kaifu and co-workers had reported of a useful *N*-methylation method for the acetylated sugar derivative **301**, by treating compound **301** with an excess of MeI and Ag₂O in DMF (Scheme 55).⁹⁹



Scheme 55. *i*) MeI, Ag₂O, DMF, rt.

This same protocol was applied for the *N*-methylation of lactone **271**. A mixture of lactone **271**, a 100-fold excess of MeI and 300 mol-% of Ag₂O in DMF was protected from light and stirred under argon at rt overnight. *N*-Methylation along with the unwanted formation of the double bond took place, producing compounds **303** and **304** in 21 % and 56 % yields, respectively (Scheme 56). The interesting point of this reaction was the partial replacement of the acetate protection at the 2-position by a methoxy group, since

the acetates were expected to remain intact under the neutral reaction conditions. It is also noteworthy, that the major product was the one having the acetate ester replaced with a methoxy group, whereas in the literature under similar reaction conditions the acetates were not influenced.



Scheme 56. *i*) MeI, Ag₂O, DMF, rt.

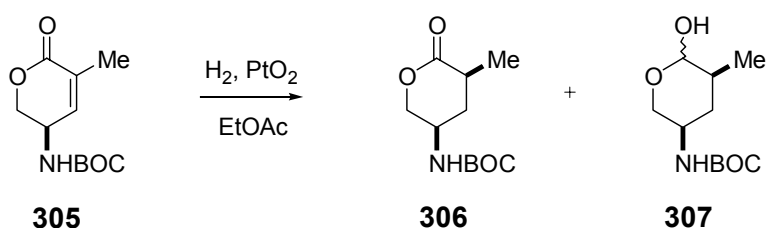
Thus, the major problem of this pathway was no longer the cleavage of the acetates, but the lactone functionality, making the α -hydrogen highly acidic thus leading to facile elimination. It became evident that the introduction of the methyl functionality to the amine at the lactone stage through this reaction path was not feasible, and a change in the synthetic strategy was required.

4.8. Platinum-catalyzed hydrogenation of the lactone

Since the lactone functionality in the molecule had been the main reason for the unsuccessful *N*-methylation attempts, the order of steps in the synthesis was rearranged. Thus, instead of introducing the methyl moiety to the molecule at the problematic lactone stage, the plan was to convert the lactone **271** first into the corresponding glycosyl fluoride, and to bring the methyl group into the molecule at the fluoride stage. The preparation of the fluoride derivative would proceed *via* hydrogenation of the lactone **271**, followed by direct fluorination of the anomeric hydroxyl group.

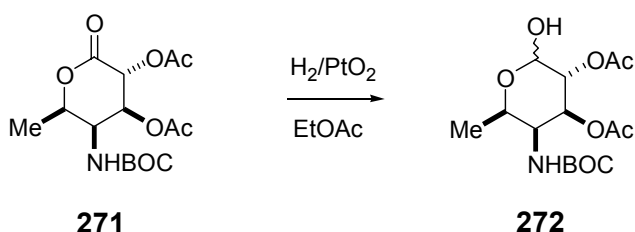
The results observed in the hydrogenation experiments accomplished for the pentenolide derivative **305** in our group¹⁰⁰ suggested the use of metal-catalyzed hydrogenation of lactone **271** instead of DIBAL-H -reduction. In addition to hydrogenation of the double bond of pentenolide **305**, platinum-catalysis had also led to simultaneous reduction of the carbonyl moiety of the molecule (Scheme 57). The

hydrogenation had been carried out under mild reaction conditions at rt and 1 atm pressure, employing a balloon filled with H₂ as the hydrogen source and PtO₂ as the catalyst.



Scheme 57.

The above hydrogenation method was applied for the reduction of lactone **271** to lactols. The process started with the reduction of platinum(II) oxide to platinum(0) by stirring the catalyst in EtOAc under hydrogen atmosphere at rt for 15 min. A solution of lactone **271** in EtOAc was added next, and the mixture was stirred under hydrogen at rt for 6 hours. Finally, the reaction mixture was filtered through a pad of Celite and the solvent removed under reduced pressure. Purification of the crude mixture by flash chromatography produced a 1:1 mixture of α - and β -lactols **272** in 76 % yield. The anomers could be separated from each other by crystallization from EtOAc/hexanes (Scheme 58).



Scheme 58.

By this simple and efficient procedure, the carbonyl group of the lactone ring was successfully reduced to a free lactol, maintaining the acetate protection intact.

4.9. Preparation of the glycosyl fluoride by direct fluorination

Glycosyl fluorides can be prepared easily under mild reaction conditions by indirect or direct methods. The indirect methods include the fluorination of the corresponding thioglycoside by a combination of DAST and NBS or HF·pyr complex and NBS.¹⁰¹ Examples of the direct fluorination procedures, in which the free anomeric hydroxyl group is replaced by fluorine, are the use of DAST,¹⁰² 2-fluoropyridinium salts,¹⁰³ hydrogen fluoride-pyridine¹⁰⁴ and hexafluoropropene-amine complex.¹⁰⁵ For the preparation of the corresponding glycosyl fluorides from the lactols **272** I chose the high-yielding, widely used DAST-method, since the reaction proceeds under mild and neutral conditions. The drawback of this procedure is the formation of α/β -anomeric mixtures of fluorides. The general mechanism for the direct fluorination of the anomeric hydroxyl group by DAST is presented in Figure 21.

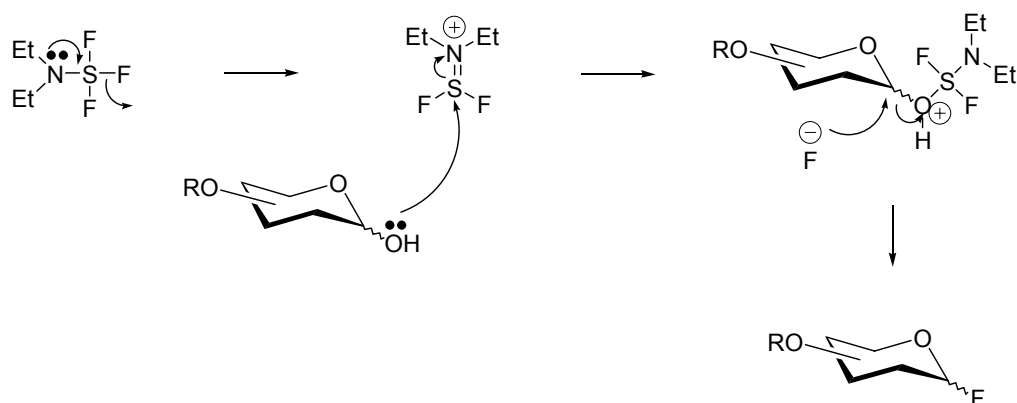
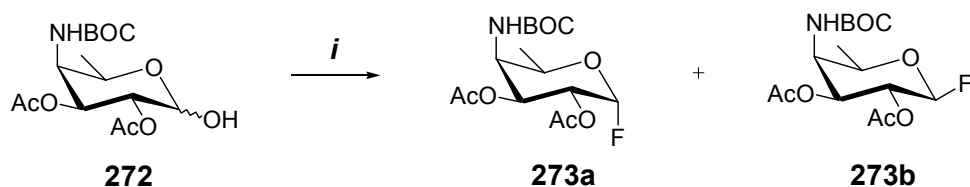


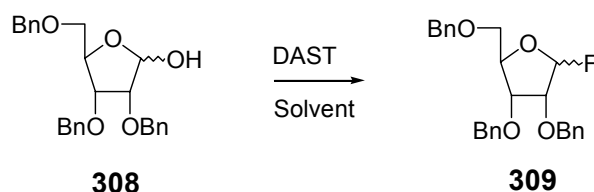
Figure 21. General mechanism for the DAST-fluorination.

In a typical experiment, 150 mol-% of DAST was added to a stirred solution of lactols **272** in THF at 0 °C. After removal of the cooling bath the reaction was stirred at rt for 30 min until TLC indicated the completion of the reaction. After standard aqueous work-up the crude mixture of fluorides was separated by flash chromatography. The ratio of the α - and β -anomers formed was to some degree dependent on the solvent employed. In order to affect the α/β -ratio, some solvent experiments were carried out. The conversion of lactols **272** to the corresponding glycosyl fluorides **273a** and **273b** by DAST is shown in Scheme 59.



Scheme 59. *i*) DAST, THF, 0 °C → rt, 30 min.

Posner and Haines have studied the effect of various solvents on the anomeric ratio of the direct fluorination of 2,3,5-tri-*O*-benzyl-D-ribofuranose **308** (Scheme 60).^{102b} All the solvents examined produced the β -fluoride **309** as the major product. The best β/α -ratio was achieved by using a polar solvent such as THF whereas CH₂Cl₂ gave the poorest selectivity (Table 5).



Scheme 60.

Table 5. Solvent effect on the fluorination of **308** by DAST.


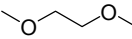
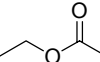


Entry	Solvent	$\beta:\alpha$
1	CH ₂ Cl ₂	2.0 : 1.0
2	Toluene	3.7 : 1.0
3	CCl ₄	4.1 : 1.0
4	Et ₂ O	4.2 : 1.0
5	DMTHF	5.7 : 1.0
6	THF	9.9 : 1.0

In the case of lactols **272**, the DAST-fluorination in THF afforded a 1:3 mixture of α - and β -anomers, respectively. The result correlated with the observations of Posner and Haines, although the selectivity was modest. In order to achieve better selectivities, the effect of a variety of solvents such as CH₂Cl₂, toluene, EtOAc, DME and 1,4-dioxane on the α/β -ratio was examined.

The expectation was that polar solvents similar to THF, such as 1,4-dioxane and DME would produce mainly the β -fluoride **273b** whereas the use of less polar solvents such as CH_2Cl_2 or toluene would increase the formation of the α -anomer **273a**. One limitation for these experiments was the insolubility of the highly polar lactols **272** in aprotic solvents; they barely dissolved in toluene. The results of the solvent experiments are listed in Table 6.

As expected, employment of less polar solvents such as toluene or CH_2Cl_2 in the direct fluorination of lactols **272** by DAST resulted in increase of the α/β -ratio from 1:3 to ~1:1 (Entries 1 and 4). Instead, the increase in the solvent polarity did not improve the β -selectivity as was expected. On the contrary, fluorination carried out in DME and 1,4-dioxane afforded a mixture of α - and β -fluorides in a ratio of 1.1:1 and 1:1.4, respectively (Entries 2 and 5). In conclusion, all the solvents studied except THF gave basically 1:1 mixture of α - and β -anomers.

Table 6. Solvent effect on the α/β -ratio of the direct fluorination of **272** by DAST.

Entry	Solvent	Yield (%)	$\alpha:\beta$
1		75	1.0 : 1.0
2		80	1.1 : 1.0
3		80	1.0 : 1.2
4	CH_2Cl_2	77	1.0 : 1.3
5		63	1.0 : 1.4
6		85	1.0 : 3.0

The $\alpha:\beta$ ratio was determined by ^1H NMR.

Since the two anomers were easily separated by flash chromatography, no more effort was put to study the α/β -selectivity of the fluorination. Keeping the future glycosylation of the pradimicin disaccharide fragment to the aromatic aglycon part in mind, it would not matter if the glycosyl donor would be the anomeric mixture of fluorides. As presented in Figure 16 on page 70, the participating neighbouring group at the 2-C-position of the glycosyl donor would favor the formation of the 1,2-*trans*-glycosidic linkage as required.

However, for clarity and to help the analyses of the following reaction steps, the two fluorides were separated at this stage. Both anomers were subjected to similar transformations in order to prepare both the α - and β -glycosyl fluorides **275a** and **275b**.

After purification of the fluorides **273a** and **273b**, I succeeded in crystallizing the β -anomer **273b** from chloroform. The crystal structure analysis was carried out and the configuration of the β -fluoride **273b** was confirmed (Fig. 22).⁹⁷

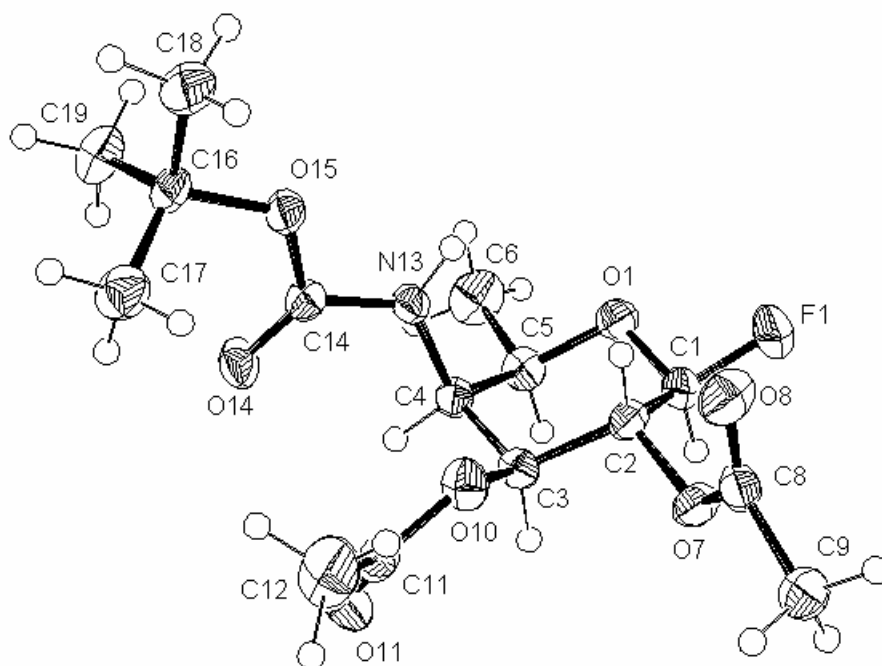


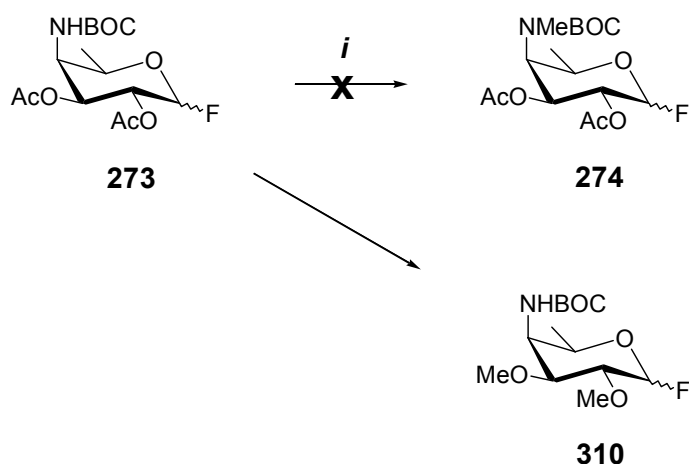
Figure 22. The crystal structure of β -fluoride **273b**.

4.10. *N*-Methylation of fluorides

N-Methylation attempts for the lactone **271** were discussed in Section 4.7. It was observed that the process had resulted in the formation of a double bond as well as replacement of the acetate ester by a methoxy group along the desired *N*-methylation. In order to avoid these problems arising from the highly acidic hydrogen atom next to the carbonyl moiety of the lactone ring, the lactone **271** was converted to the corresponding fluorides **273a** and **273b**. Both the α - and β -fluorides were *N*-methylated.

4.10.1. Attempted *N*-methylation by methyl iodide and sodium hydride

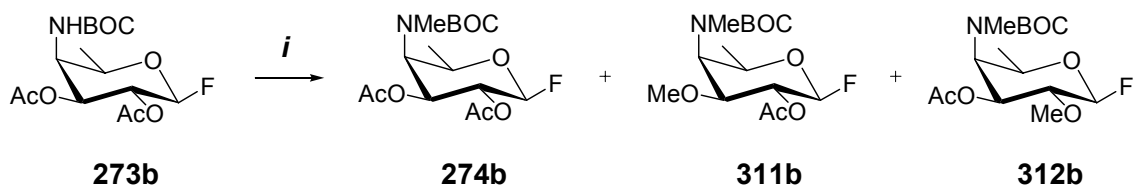
N-methylation of fluoride **273** was first attempted by the MeI/NaH-method, but no reaction occurred when 95 mol-% of NaH and 250 mol-% of MeI was used. When a large excess of both NaH (320 mol-%) and MeI (30-fold excess) were employed, the acetate protective groups were replaced by methoxy groups instead of *N*-methylation (Scheme 61). Removal of the acetate protection in the presence of NaH had been already noticed in the case of lactone **271** and therefore, no further effort was put on the MeI/NaH-method.



Scheme 61. *i*) MeI, NaH, THF, rt.

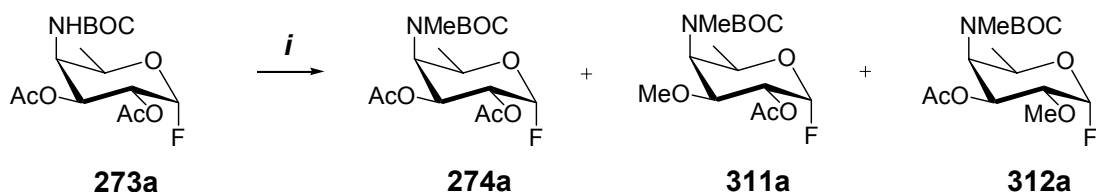
4.10.2. *N*-Methylation by methyl iodide and silver oxide

Both the α - and β -fluorides **273a** and **273b** were subjected to the *N*-methylation conditions using MeI in the presence of Ag₂O. According to the method of Kaifu *et al.*,⁹⁹ a 200-fold excess of MeI and 300 mol-% of Ag₂O were employed in the methylation process of **273b** performed in distilled DMF. The reaction mixture was protected from light and stirred at rt for 4 h. Filtration through a pad of Celite, followed by aqueous work-up afforded the desired *N*-methylated product **274b** along with the side products **311b** and **312b**. The crude product mixture was purified by flash chromatography to afford the *N*-methylated β -fluoride **274b** in 46 % yield (Scheme 62).



Scheme 62. *i)* MeI, Ag₂O, DMF, rt, dark.

N-Methylation of the α -fluoride **273a** was accomplished similarly, yielding the desired *N*-methylated product **274a**, in which both acetates had remained intact, along with the side products **311a** and **312a**, in which one of the acetates had been replaced by a methoxy functionality. The side products were not separated from each other. The yield for the α -fluoride **274a** was 42 % (Scheme 63).



Scheme 63. *i)* MeI, Ag₂O, DMF, rt, dark.

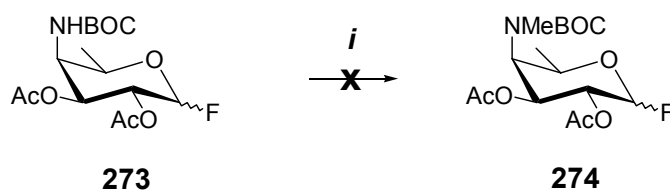
To sum up, in the case of fluorides the formation of the double bond was avoided, but the problem concerning the partial replacement of the acetate esters by a methoxy group remained. In a typical experiment, the reaction was allowed to proceed for 2-3 hours after which the amount of side products started to exceed the amount of the desired product, and the reaction was stopped despite the unreacted starting material left. If the reaction was allowed to proceed until all the starting material had been consumed, the product mixture consisted mainly of the side products.

To reduce the formation of the side products, the effect of the amount of MeI in the reaction system was examined. Thus, the amount of MeI was cut to one tenth of the original amount, but the reaction proceeded in a similar way as described above, although a bit slower. The quality of the reagents had an effect only on the reaction rate as well, not the product distribution. If a newly opened bottle of MeI was used or freshly prepared Ag₂O employed in the process, the reaction proceeded faster but resulted in the same product distribution as reported.

It was reasoned that the possible explanation for the formation of the side products was the presence of moisture in the reaction system, although the reactions were performed in distilled DMF under argon atmosphere.

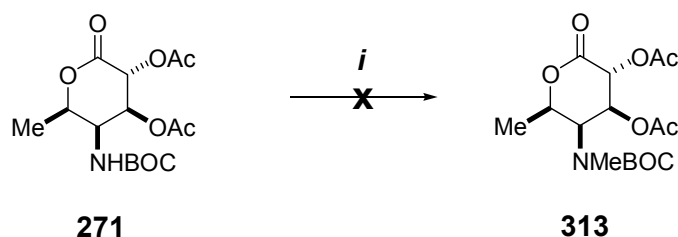
4.10.3. Attempted *N*-methylation by MeOTf and 2,6-di-*tert*-butyl-4-methylpyridine

N-Methylation for fluorides **273** was also attempted by using methyl triflate as the methylating agent in the presence of 2,6-di-*tert*-butyl-4-methylpyridine as the base (Scheme 64). It was assumed that methylation would proceed *via* an S_N2-mechanism and, therefore, nitrogen as a soft nucleophile would favor the attack of MeOTf as a soft electrophile over MeI as a harder electrophile. However, after stirring the reaction at rt overnight, the starting material was recovered unchanged.



Scheme 64. *i*) MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂, rt, overnight.

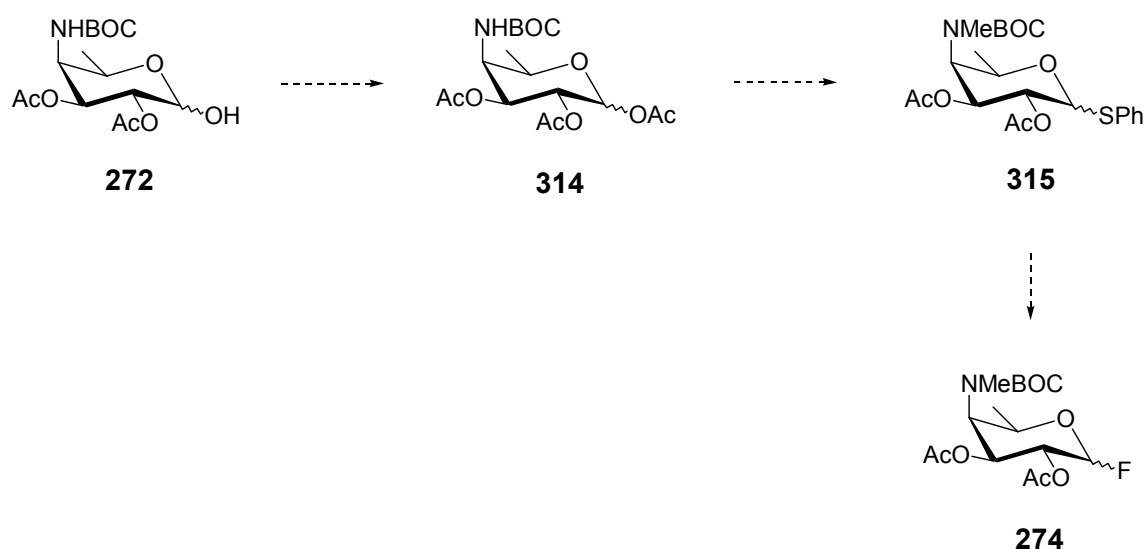
Lactone **271** was also subjected to above *N*-methylation conditions but with no success (Scheme 65).



Scheme 65. *i*) MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂, rt, overnight.

4.11. Indirect methods for the preparation of the glycosyl fluoride

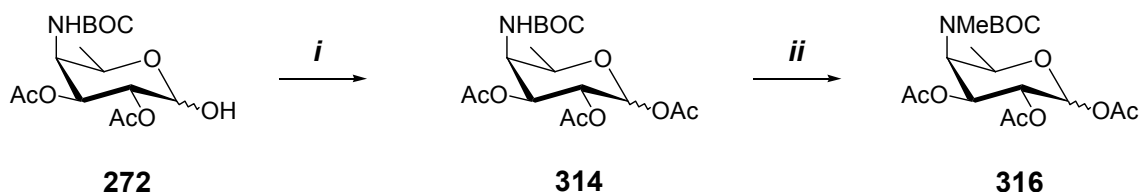
Glycosyl fluorides can be also prepared by indirect methods *via* formation of thioglycosides. In the *N*-methylation process of fluorides **273**, formation of the side products could not be avoided and the separation of the *N*-methylated product from the side products by flash chromatography had been troublesome. Therefore, it was of interest to examine also the indirect route for the preparation of the desired glycosyl fluorides and to find out, whether the thioglycoside counterparts would be easier to separate from the side products possibly formed. The aim was to acetylate the anomeric mixture of lactols **272** by standard conditions and then subject it to either *N*-methylation or thioglycosylation conditions to produce the *N*-methylated thioglycoside derivatives **315**, the precursors of the target glycosyl fluorides **274** (Scheme 66).



Scheme 66.

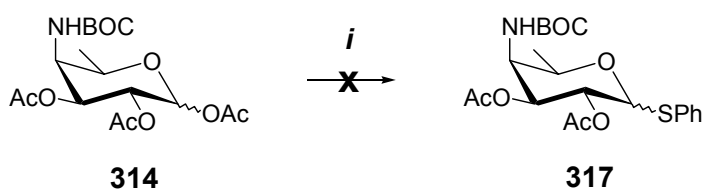
Acetylation of the anomeric position of lactols **272** by acetic anhydride and DMAP was accomplished in 30 min, producing a mixture of acetylated α - and β -anomers **314** almost in quantitative yield (Scheme 67). *N*-Methylation of the acetylated intermediate **314** was attempted by the MeI/Ag₂O-method by stirring the reaction mixture at 50 °C overnight, but most probably, a mixture of *N*-methylated product **316** and the starting material **314** was obtained. The spots of the product and the starting material were hardly separated

from each other on the TLC-plate and therefore, it was difficult to determine whether the reaction had been completed or not.



Scheme 67. *i)* Ac₂O, DMAP, CH₂Cl₂, rt, 30 min, *ii)* MeI, Ag₂O, DMF, 50 °C.

Since the *N*-methylation of **314** resulted basically in inseparable mixture of the product and the starting material and moreover, included a mixture of α - and β -anomers, I decided to convert the acetyl intermediate **314** first to its corresponding thioglycoside derivative **317** to find out whether the thioglycoside anomers could be separated from each other. Compound **314** was allowed to stir with an excess of thiophenol and BF₃·OEt₂ at rt overnight, but according to TLC-analysis, mostly baseline material had been formed, probably due to the cleavage of the BOC-protection under the acidic reaction media (Scheme 68). Thus, the indirect route for the preparation of glycosyl fluorides **274** was abandoned.



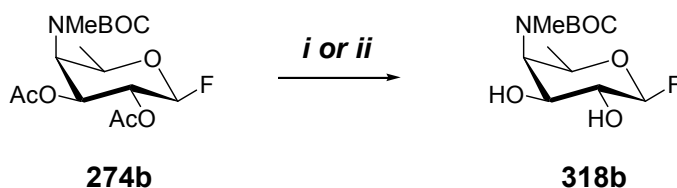
Scheme 68. *i)* SPh, BF₃·OEt₂, rt, overnight.

4.12. Deacetylation

The last steps in the preparation of the monosaccharide derivatives **275a** and **275b** were the cleavage of the acetate protection and the regioselective benzoyl protection at the 2-position of the sugar ring. A convenient way for the deacetylation is the use of basic alcoholic solution at 0 °C,⁹⁸ but it was also reported recently, that the absolute methanol

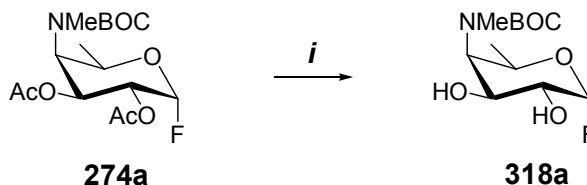
dried over 3 Å molecular sieves removes the *O*-acetyl group due to the existence of methoxy species generated by the 3 Å sieves.¹⁰⁶

Deacetylation for fluoride **274b** was accomplished in basic methanol solution, using either NaOMe or K₂CO₃ as the base (Scheme 69). In both methods, to a cooled (0 °C) solution of fluoride **274** in MeOH was added either 0.1 M solution of NaOMe in MeOH or a catalytic amount of K₂CO₃. The reaction was stirred under argon at rt for 4 hours until the starting material had been mostly consumed. If the reaction time was prolonged, decomposition products near the baseline appeared. The reaction was neutralized by filtration of the cold reaction mixture through a short pad of silica, followed by successive washes by cold MeOH. Concentration gave the crude product, which was purified by gradient flash chromatography to furnish the deacetylated amino sugar **318b** as a white solid. The yields for the β-fluoride **318b** by NaOMe- and K₂CO₃-methods were 74 % and 70 %, respectively.



Scheme 69. *i*) 0.1 M NaOMe/MeOH, MeOH, rt, 4 h, 74 %, *ii*) K₂CO₃ (cat.), MeOH, rt, 4 h, 70 %.

Deprotection for the α-anomer **274a** was performed in a similar way, employing 0.1 M solution of NaOMe in MeOH (Scheme 70). The deacetylated α-fluoride **318a** was produced in 71 % yield.

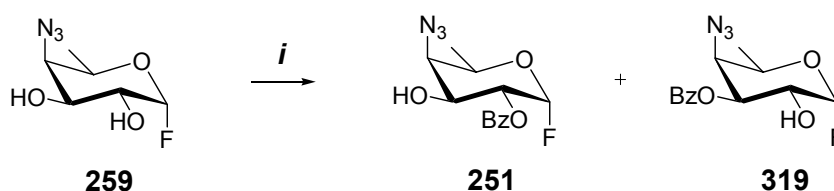


Scheme 70. *i*) 0.1 M NaOMe/MeOH, MeOH, rt, 4 h, 71 %.

4.13. Regioselective benzoyl protection

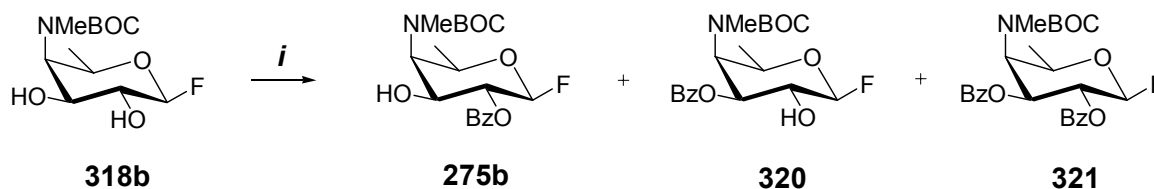
4.13.1. Attempts for the regioselective benzylation by BzCl and pyridine

In the synthesis of the amino sugar derivative **251** of pradimicin A, Kato *et al.* had selectively introduced the benzoyl group to the 2-position of the sugar using BzCl and pyridine.⁶⁹ Benzoylation of α -fluoride **259** had afforded ca. 8:1 mixture of 2-*O*- and 3-*O*-mono-benzoates **251** and **319**, giving the desired 2-*O*-benzoyl derivative in 50 % yield after recrystallization from EtOAc (Scheme 71).



Scheme 71. *i*) BzCl, pyridine, 0 °C \rightarrow rt, 15 h, 50 %.

When the β -fluoride **318b** was subjected to similar benzylation conditions employing 105 mol-% of BzCl and pyridine as the solvent, most of the starting material remained unreacted after stirring at rt overnight. When a catalytic amount of DMAP was added in order to accelerate the reaction rate, formation of mono-benzoates was observed but most of the starting material remained still unaffected. If the amount of BzCl was increased from 105 mol-% to 150 mol-%, mainly the disubstituted fluoride **321** was produced along the monosubstitution products **275b** and **320** (Scheme 72). Since in the case of the amino sugar **318b** the regioselective mono-benzylation could not be obtained by the use of BzCl and pyridine, other methods had to be considered.



Scheme 72. *i*) BzCl, pyr, DMAP, CH₂Cl₂, rt, overnight.

An interesting observation of these benzoylation experiments was that the BOC-group, usually positioned around the ppm-area of 1.40-1.48 in ^1H NMR, was transferred to 1.16 ppm in the case of the dibenzoylated product **321**! Also in the case of 3-*O*-benzoylated product **320** a similar transformation had been observed: the singlet of the BOC-group (9H) was split into two singlets (each $\sim 4.5\text{H}$), situated at 1.24 and 1.13 ppm. In the case of 2-*O*-benzoylated compound **275b** in which the benzoyl protection and the BOC-group are positioned further away from each other, the singlet of the BOC-functionality had remained in its usual position at 1.45 ppm. These observations indicate that the relatively large benzoyl protection at the 3-position, next to the bulky BOC-protection, causes major steric hindrance and thus forces the BOC-group to 'twist' from its initial position, to make room for the benzoyl-group.

4.13.2. Regioselective benzoylation via stannylene derivatives

Regioselective benzoylation of hydroxyl groups can be achieved *via* stannylene derivatives, formed by the reaction of the commercially available, polymeric dibutyltin oxide (Bu_2SnO) in an appropriate solvent.¹⁰⁷ The process involves the conversion of the dihydroxy derivatives into cyclic stannylenes along with the formation of water as a by-product, which is usually removed azeotropically from the reaction mixture by a Dean-Stark trap. The stannylenes undergo regioselective acylation upon treatment with acid chlorides, providing products of monosubstitution (Fig. 23).

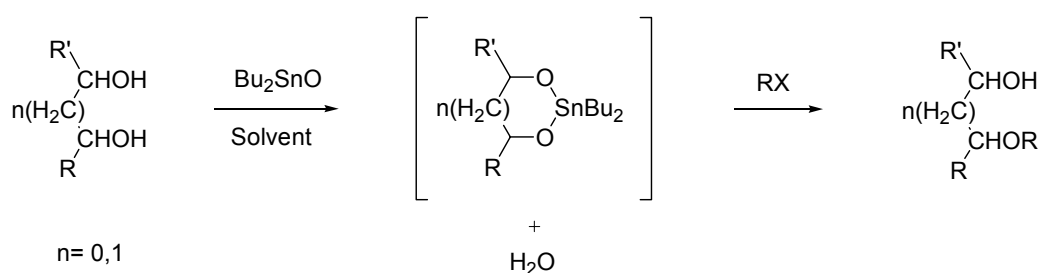


Figure 23. Regioselective acylation *via* stannylenes.

The monosubstitution is explained by the constitution of the stannylenes, which are generally considered to be dimers having in each subunit one dicoordinated and one tricoordinated oxygen.¹⁰⁸ An example of such a dimeric structure is shown in Figure 24.

The two oxygen atoms of the parent diol are differentiated in the stannylene, one at the equatorial (tricoordinated), and the other one at the apical (dicoordinated), position in a trigonal bipyramid centered on the tin atom. The regioselective acylation is thought to occur at the more nucleophilic, sterically less hindered apical oxygen rather than the electronically less enriched equatorial oxygen atom which is relatively protected by the threefold coordination. The question of which hydroxyl group of the diol will adopt the apical position in the stannylene derivative and hence undergo acylation cannot be predicted yet, although the factors affecting on the regioselective outcome of the acylation process have been studied.^{107, 109}

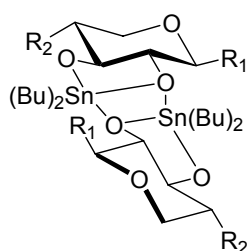
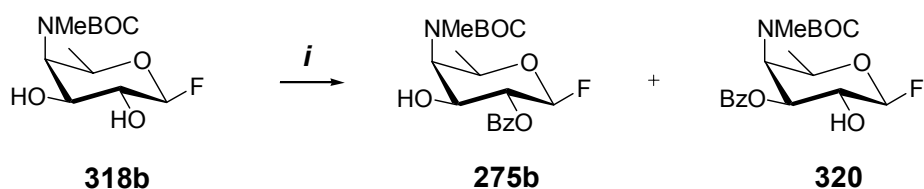


Figure 24. A dimeric structure for a stannylene intermediate.

The regioselective benzylation procedure *via* stannylene intermediates was successfully adopted for the fluorides **318a** and **318b**. The β -fluoride **318b** was heated at reflux in a round-bottomed flask with 120 mol-% of Bu_2SnO , 1000 mol-% of Et_3N and 4Å molecular sieves in benzene for 2 hours. The molecular sieves were employed for the removal of water instead of the Dean-Stark trap due to the small reaction scale. Before addition of BzCl to the mixture, the reaction vessel was lifted up from the oil bath and the mixture was allowed to cool to rt. After addition of BzCl , the reaction vessel was set back into the bath and the mixture was stirred under reflux for about 20 min until all the fluoride **318b** had reacted. Filtration and concentration gave the crude product mixture, which was purified by flash chromatography providing the monobenzoylated compounds **275b** and **320** in 70 % and 25 % yields, respectively (Scheme 73).



Scheme 73. *i)* Bu₂SnO, Et₃N, benzene, 4Å molecular sieves, reflux, then BzCl.

The position of the benzoyl protection in the monosubstituted products **275b** and **320** was deduced by the BOC-shift of the 3-*O*-benzoylated product **320** in ¹H NMR, but the final confirmation of the structures was obtained by X-ray analysis.⁹⁷ The crystal structures of the monosaccharides **275b** and **320** are shown in Figures 25 and 26.

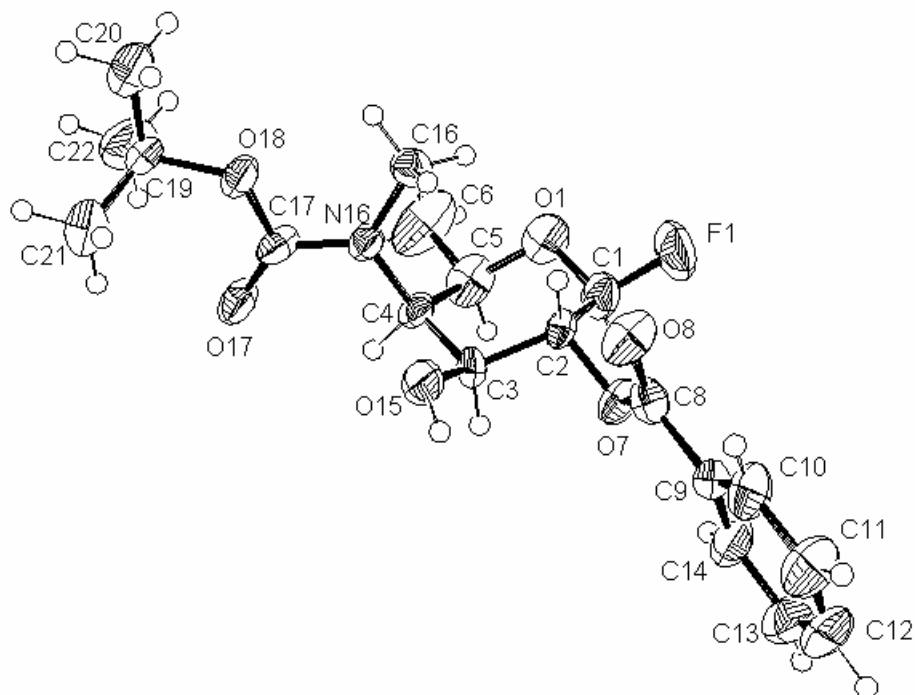


Figure 25. An ORTEP plot of molecular structure of 2-*O*-benzoylated β-fluoride **275b**.

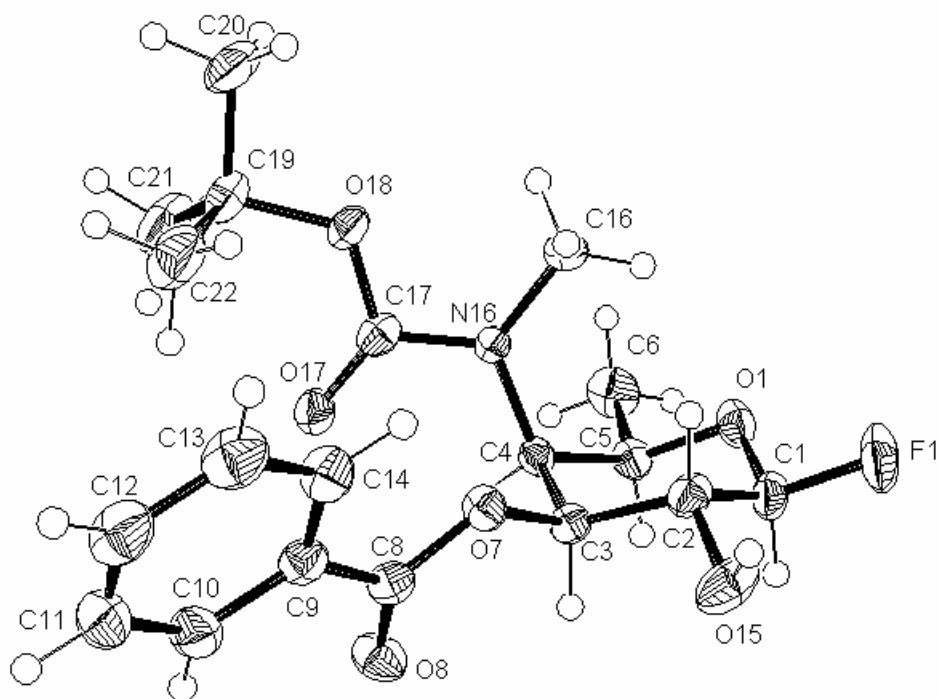
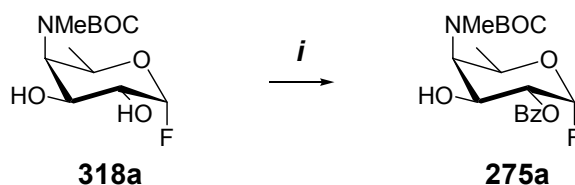


Figure 26. An ORTEP plot of molecular structure of 3-*O*-benzoylated β -fluoride **320**.

Regioselective benzoyl protection at the 2-position of the α -fluoride **318a** was carried out in a similar way as described for the β -anomer **318b** (Scheme 74). After refluxing the amino sugar **318a** with Bu_2SnO , Et_3N and 4Å molecular sieves in benzene for 2 h, the mixture was cooled down to rt and BzCl was added. Refluxing the reaction mixture for 10 min produced the 2-*O*-benzoylated fluoride **275a** in 46 % yield (corrected yield 75%; based on recovered starting material) after flash chromatography. If the reaction time after the addition of BzCl was prolonged, also the other regioisomer started to appear according to TLC. It was not possible to obtain the crystal structure of the benzoylation product **275a**, thus the position of the benzoyl group was determined on the basis of ^1H NMR analysis. Since no BOC-shift was observed in the ^1H NMR spectrum of compound **275a**, as would have expected in the case of the 3-*O*-benzoylated isomer, it was concluded that 2-*O*-benzoylated α -anomer **275a** had been formed in the process. Benzoylation of the hydroxyl group at the 2-position was also proved by the downfield shift of the corresponding ring proton from 3.9 ppm to 5.3 ppm.

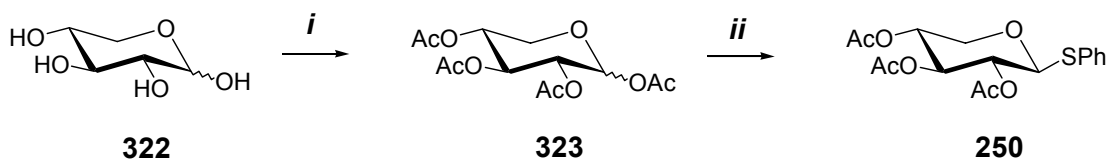


Scheme 74. *i)* Bu₂SnO, Et₃N, benzene, 4Å molecular sieves, reflux, then BzCl.

4.14. Concluding steps

The final steps of the disaccharide synthesis were the preparation of the D-xylose derived glycosyl donor **250** (Scheme 75) and its coupling with the amino sugar moiety **275** (Scheme 76). Since the glycosyl fluoride acceptors, such as the amino sugar derivative **275**, are not affected by the activation conditions required for the thioglycoside donors, we decided to convert the D-xylose **322** into a thioglycoside donor **250**.

The preparation of thioglycosides is conveniently performed *via* the corresponding acetates. To direct the required β-stereochemistry of the thioglycoside **250** to be formed, it was of interest to attach a participating ester functionality, like an acetate ester, at the 2-hydroxyl position of D-xylose ring. Thus, acetylation of D-xylose was accomplished by a convenient procedure, leading to the formation of the tetra-acetylated sugar derivative **323** in quantitative yield. Preparation of the corresponding thioglycoside by employment of thiophenol in acidic media¹¹⁰ produced a mixture of α- and β-glycoside, of which the β-anomer **250** was isolated in 63 % yield after flash chromatography (Scheme 75).

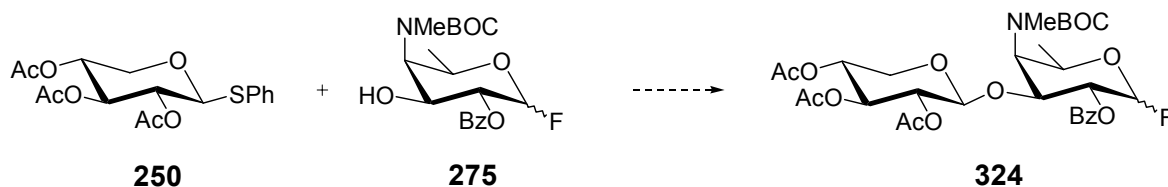


Scheme 75. *i)* Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt; *ii)* SPh, BF₃·OEt₂, CH₂Cl₂, 0 °C → rt, purification by flash chromatography.

4.14.1. Activation of the thioglycoside

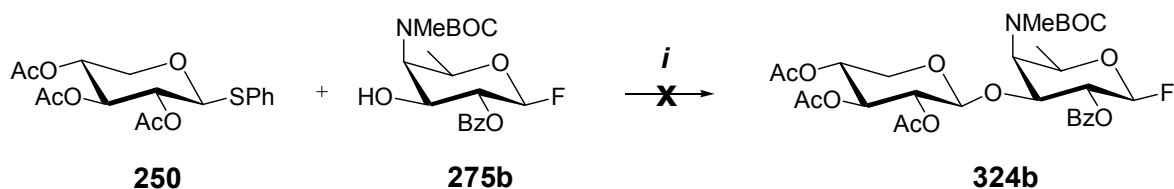
The final step of the synthesis was the formation of the disaccharide fragment of pradimicin A. A number of activators of thioglycosides are known, including bromine,¹¹¹ iodine,¹¹² *N*-bromosuccinimide (NBS),¹¹³ NBS/TMSOTf,¹¹⁴ *N*-iodosuccinimide-triflic acid (NIS/TfOH),⁷¹ methyl triflate (MeOTf),¹¹⁵ trimethylsilyl triflate (TMSOTf),¹¹⁶ iodonium dicollidine perchlorate (IDCP),¹¹⁷ dimethyl(methylthio)sulfonium triflate (DMTST),¹¹⁸ DMTST/Bu₄NBr¹¹⁹ and dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSB).¹²⁰ The activators for thioglycosides can be regarded as sources of soft electrophiles, which convert the anomeric sulfur to a leaving group.

The aim in the synthesis of the disaccharide fragment of pradimicin A was to produce the 1,2-*trans* linked β -glycoside **324** (Scheme 76). The activation method involving NIS and a catalytic amount of TfOH is perhaps the most widely used procedure for the activation of thioglycosides, including phenylthio and ethylthio derivatives. Thus, the thioglycosyl donor **250** and the amino sugar acceptor **275b** were subjected to the activation conditions promoted by NIS and TfOH (Scheme 77).



Scheme 76.

The donor **250** and the acceptor **275b** were combined and stirred in CH₂Cl₂ with 4Å molecular sieves under Ar to ensure anhydrous reaction conditions. After cooling the reaction mixture to -40 °C, NIS and a catalytic amount of TfOH were added and the mixture was stirred at cold for a few hours. TLC analysis of the reaction mixture indicated that in addition to the unreacted starting materials **250** and **275b**, some products below the acceptor **275b** and the donor **250** had formed. The reaction was stopped and the newly formed products were isolated by flash chromatography. On the basis of ¹H NMR analysis, the products isolated were not the desired disaccharide **324b**.



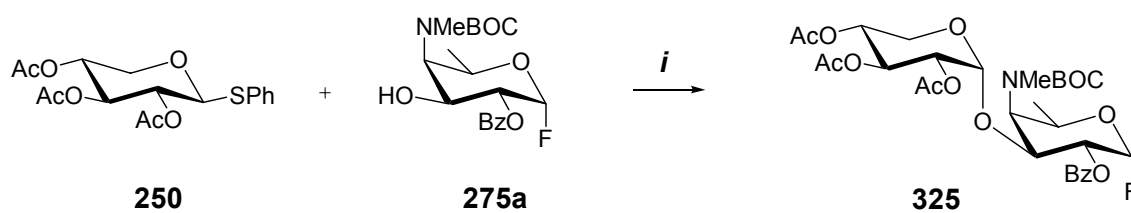
Scheme 77. *i*) NIS, TfOH (cat.), CH₂Cl₂, 4Å molecular sieves, -40 °C.

If the amount of acid in the NIS/TfOH-glycosylation process was increased, the amount of the unidentified products near the baseline was also increased, but part of the starting material remained still unreacted, even if the reaction was performed at rt. It was also presumed that the BOC-protection had not remained totally intact under the acidic reaction conditions, leading to a partial cleavage of the BOC-protection during the glycosylation. Thus, since the reaction did not seem to proceed to completion and there was a danger of ending up with a mixture of four different products by the use of acid (an α/β -mixture of BOC-disaccharides and non-BOC-disaccharides), the NIS/TfOH method was abandoned.

Preparation of the disaccharide **324b** was attempted also by applying the literature procedure published recently,¹¹⁴ employing NBS and TMSOTf. The idea was to replace the strong trifluoromethane sulfonic acid by a milder TMSOTf-promoter. However, this procedure gave similar results as obtained with the NIS/TfOH-method, affording unidentified products along the unreacted starting material.

Since there were not much of the amino sugar derivatives **275a** and **275b** left, I decided to accomplish the preparation of the target disaccharide by employing the neutral NBS-activation method. According to the procedure of Nicolaou *et al.*,¹¹³ the thioglycoside donor **250** and the α -amino sugar acceptor **275a** were combined and azeotropically dried with benzene before dissolution in freshly distilled CH₂Cl₂. After stirring the solution with pulverized 4Å molecular sieves under argon atmosphere at rt for 30 min, NBS was added and the mixture was allowed to stir at rt for 1.5 h. According to the literature,¹¹³ the formation of the glycosidic bond should have been completed in 30 min, but TLC analysis of the reaction mixture indicated a majority of unreacted acceptor **275a**. A large excess of both donor **250** and NBS were added to the mixture and stirring was continued for 1 h. Since the reaction did not seem to proceed any more, the reaction was stopped and the crude product mixture was purified by flash chromatography after aqueous work-up. Since the product could not be separated from NBS by flash chromatography, it was purified by

preparative layer chromatography to afford 6.5 mg (17 %) of the target disaccharide, tentatively assigned as the α -analogue **325** (Scheme 78).



Scheme 78. *i*) NBS, CH₂Cl₂, 4Å molecular sieves, rt.

The α -stereochemistry of the product **325** was assigned on the basis of the coupling constant of 4.8 Hz between the H₁- and H₂-protons of the xylose fragment (Figure 27). The ⁴C₁ conformation of the xylose ring was deduced by the coupling constants of $J_{\text{H}_4, \text{H}_{5\text{eq}}} = 6.6$ Hz and $J_{\text{H}_4, \text{H}_{5\text{ax}}} = 8.4$ Hz; in the case of the ¹C₄ ring conformation the corresponding coupling constants should have been 3-4 Hz. The possible ⁴C₁ and ¹C₄ conformations and the coupling constants measured for compound **325** are shown in Figure 27. The coupling constants of $J_{\text{H}_2, \text{H}_3}$ and $J_{\text{H}_3, \text{H}_4}$ could not be determined due to the rotamers.

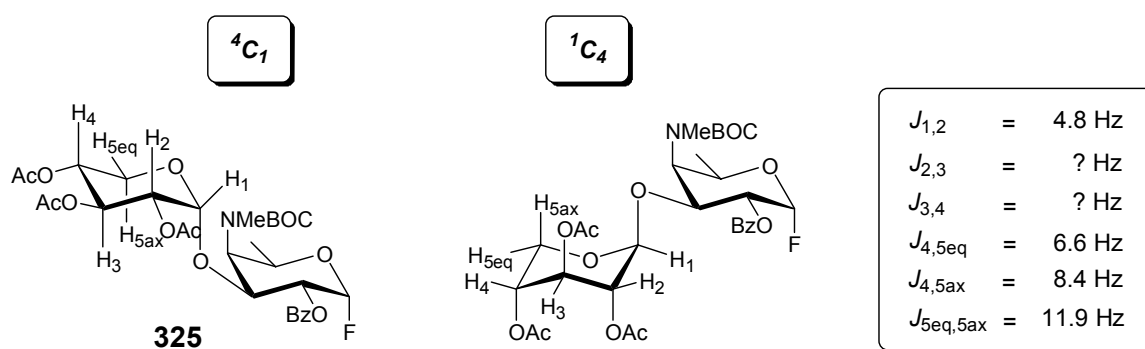


Figure 27.

The stereochemical outcome of the glycosidic bond formed was a bit confusing, since the participating acetate functionality in the 2-position of the donor **250** is a 1,2-*trans*-directing group and thus, should have produced a β -glycosidic bond as the major product. However, it was recently reported of unexpected α -stereochemical outcomes of attempted β -glycosylations in the case of acetylated thioglycosides.¹²¹

4.15. Conclusions

The α -analogue of the disaccharide fragment of pradimicin A was synthesized from the commercially available, suitably protected D-xylose derivative and the amino sugar unit, prepared from the amino acid L-threonine. L-Threonine was first converted to the fully protected L-threoinal according to known procedures. Horner-Emmons-Wadsworth olefination of the aldehyde provided the corresponding *E*-enoate, which after ruthenium-catalyzed dihydroxylation, followed by acetate protection of the hydroxyl groups, was subjected to acid-catalyzed lactonization. Attempts to introduce the *N*-methyl functionality to the molecule at the lactone stage resulted in the formation of a double bond by elimination and the replacement of the acetate protection by a methoxy group. Therefore, the lactone was transformed to the corresponding fluorides in a two-stage approach; first platinum-catalyzed hydrogenation to the corresponding lactols and DAST-fluorination. The *N*-methyl group was then attached to the molecule. In order to prepare for the coupling the disaccharide part to be formed to the pradimicin aglycon *trans*-selectively, the C-2-position of the glycosyl fluoride was protected as its benzoyl ester. Regioselective benzoylation was accomplished *via* stannylene derivatives, employing dibutyltin oxide and benzoyl chloride. The structures of both the 2-*O*- and 3-*O*-monobenzoylated products of the β -fluoride were confirmed by crystal structure analysis. The final step in the formation of the disaccharide moiety was the coupling of the amino sugar fluoride **275a** with the protected D-xylose derivative **250**. Since the acidic coupling conditions led at least partial cleavage of the BOC-protection, the glycosylation was performed under neutral conditions, producing the protected disaccharide derivative of pradimicin A, tentatively assigned as its α -analogue.

In conclusion, the amino acid based synthesis to the amino sugar fragment of pradimicin A was successfully developed, the amino sugar unit possessing the participating benzoyl protection at its C-2-position which is ideal for the intended *trans*-glycosylation of the disaccharide fragment and the aromatic aglycon. Preliminary glycosylation studies to produce the disaccharide unit of pradimicin were also performed, but further examination to adjust the stereoselectivity of the glycosylation is required.

5. Experimental

General procedures. Acetonitrile was dried by distillation from phosphorus pentoxide and methanol from magnesium methoxide. THF and dimethoxyethane were distilled prior to use from sodium/benzophenone ketyl. Toluene, benzene and triethylamine were distilled from sodium and dichloromethane from calcium hydride. Boron trifluoride diethyl etherate and DMF were distilled under reduced pressure from calcium hydride and stored under Ar. Isobutyraldehyde was dried over Na_2SO_4 and distilled. All other commercial reagents were used as obtained from the supplier, without further purification. All air or moisture sensitive reactions were performed under an atmosphere of argon with magnetic stirring. Oxidations by O_2 were performed either in a round-bottomed flask equipped with an oxygen balloon or in a glass reactor by bubbling oxygen through a gas inlet in the bottom of the reactor. The purity of the oxygen gas was 99.5 %. Oxygen flow was controlled by Brooks Mass Flow Meter Model 5850TR.

Analytical thin layer chromatography (TLC) was performed on Merck silica gel or aluminum oxide 60 F₂₅₄ plates. The TLC plates were visualized by UV light and ninhydrin or phosphomolybdic acid (PMA) or anisaldehyde/gl. AcOH/H₂SO₄/EtOH (5:1:5:90). Flash chromatography was performed using Silica gel 60 (E. Merck) as the stationary phase.

Optical rotations were measured with Perkin Elmer 343 Polarimeter. Melting points were determined with Gallenkamp melting point apparatus and are uncorrected.

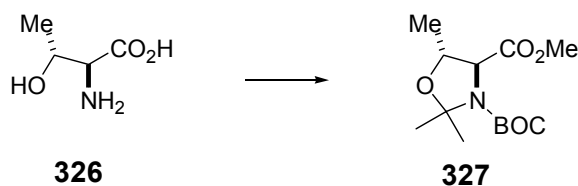
NMR spectra were recorded on Bruker 400 (¹H 400.130 MHz, ¹³C 100.613 MHz), Bruker 200 (¹H 200.13 MHz, ¹³C 50.32 MHz) or Varian 400 (¹H 399.990 MHz, ¹³C 100.587 MHz) spectrometer. Chemical shifts are reported in ppm (δ) with respect to the scale calibrated to the solvent residual signal or using tetramethylsilane (TMS) as an internal standard.

Mass spectra were determined by Jeol DX 303/DA 5000, Micromass LCT, Kratos MS 80 or BioTOF II Electrospray Time-of-Flight mass spectrometer.

HPLC analyses were performed with a Waters HPLC system using Waters 486 Tunable Absorbance Detector and Shandon Hypersil 25cm x 0.46cm column. Gas chromatograms were measured by Perkin-Elmer 8420 Capillary Gas Chromatograph (columns: DB-624, RTX-Volatiles or OV-1701).

Elemental analyses were carried out on a Perkin-Elmer 2400 instrument.

5.1. (4*S*, 5*R*)-Methyl 3-(*N*-*tert*-butoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidine-4-carboxylate **327**



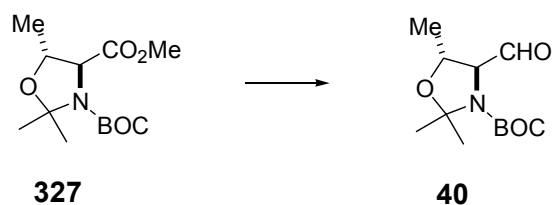
Acetylchloride (120 mL, 1.68 mol, 200 mol-%) was added dropwise to ice-cold methanol (500 mL). After the addition of L-threonine (100 g, 0.84 mol, 100 mol-%) the reaction mixture was warmed in an oil bath to 50 °C and stirred at this temperature for 2 days. Concentration afforded the crude L-threonine methyl ester hydrochloride as a yellow oil, which was used in the next step without further purification. R_f (50 % EtOAc/MeOH, ninhydrin) = 0.46. ^1H NMR (400 MHz, CD_3OD) δ 4.31-4.25 (m, 1H), 3.94 (d, 1H, $J = 4.0$ Hz), 3.85 (s, 3H), 1.33 (d, 3H, $J = 6.4$ Hz).

The crude ester hydrochloride obtained above was dissolved in a mixture of methanol (10 mL) and dichloromethane (500 mL) and the solution was cooled in an ice bath. Triethylamine (146 mL, 1.05 mol, 125 mol-%) was added dropwise, followed by addition of di-*tert*-butyl dicarbonate (183 g, 0.84 mol, 100 mol-%). The reaction mixture was allowed to warm to rt (evolution of CO_2), stirred overnight and quenched with 10 % citric acid solution (3 x 175 mL). The organic phase was washed with brine (175 mL), dried over MgSO_4 and concentrated to give the crude *N*-BOC-threonine methyl ester as a yellow oil (176 g, 90 %), which was employed in the next step without further purification. R_f (50 % EtOAc/MeOH, ninhydrin) = 0.89. ^1H NMR (400 MHz, CD_3OD) δ 5.50 (d, 1H, $J = 4.0$ Hz), 4.25-4.22 (m, 1H), 4.13 (s, 1H), 3.74 (s, 3H), 1.52-1.51 (m, 1H), 1.46 (s, 9H), 1.19 (d, 3H, $J = 6.4$ Hz).

To a solution of *N*-BOC-threonine methyl ester (176 g, 0.75 mol, 100 mol-%) in CH_2Cl_2 (320 mL) was added 2,2-dimethoxypropane (186 mL, 1.51 mol, 200 mol-%), followed by addition of $\text{BF}_3 \cdot \text{OEt}_2$ (4.8 mL, 38 mmol, 5 mol-%). The reaction mixture was stirred at rt for 24 h, washed with saturated NaHCO_3 (3 x 350 mL) and brine (350 mL), dried over MgSO_4 and concentrated. The crude product was distilled under reduced pressure (~ 100 °C, 0.5 mmHg) to give the protected ester **327** (167 g, 81 %; 73 % over three steps) as a colorless oil. R_f (30 % EtOAc/hex) = 0.83. ^1H NMR (400 MHz, CDCl_3) δ

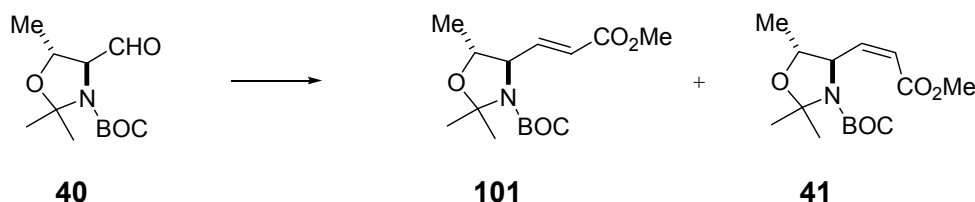
4.15-4.06 (m, 1H), 3.94, 3.85 (d, 1H, $J = 7.9$ Hz), 3.71 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H), 1.43, 1.35 (s, 9H), 1.34 (d, 3H, $J = 6.5$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 170.7, 151.8, 150.9, 95.0, 94.4, 80.7, 80.2, 73.8, 73.5, 66.1, 66.0, 52.2, 52.1, 28.1, 27.8, 26.4, 23.9, 18.8, 18.7.

5.2. (4*S*, 5*R*) 3-(*N*-*tert*-butoxycarbonyl)-2,2,5-trimethyl-4-formyl-1,3-oxazolidine **40**



To a cooled (-84 °C) solution of compound **327** (15.7 g, 57.4 mmol, 100 mol-%) in dry toluene (60 mL) was slowly added 0.1 M DIBAL-H in toluene (98 mL, 97.7 mmol, 170 mol-%). After the addition was complete the mixture was stirred at -84 °C for 5 minutes and quenched by slow addition of cold methanol (23 mL). The resulting white emulsion was poured into ice-cold 1 *N* HCl (350 mL) with stirring over 15 minutes and the aqueous mixture was then extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated to give the crude product as a colorless oil. Distillation under reduced pressure (~ 90 °C, 0.5 mmHg) afforded the pure aldehyde **40** (8.04 g, 57 %). R_f (40 % EtOAc/hex) = 0.66. ^1H NMR (400 MHz, CDCl_3) δ 9.43, 9.36 (d, 1H, $J = 3.6$ Hz), 4.04 (dq, 1H, $J = 8.5$ Hz, 6.0 Hz), 3.78, 3.68 (dd, 1H, $J = 8.5$ Hz, 3.6 Hz), 1.63 (s, 3H), 1.57, 1.55 (s, 3H), 1.48, 1.40 (s, 9H), 1.34 (d, 3H, $J = 6.0$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ 197.5, 150.9, 95.0, 81.4, 71.0, 70.1, 69.9, 28.3, 28.1, 26.2, 25.0, 17.7.

5.3. [2*E*,3(4*S*),(5*R*)]-Methyl 3-[*N*-(*tert*-butoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidin-4-yl]propenoate **101 and [2*Z*,3(4*S*),(5*R*)]-Methyl 3-[*N*-(*tert*-butoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidin-4-yl]propenoate **41****



Method 1: Potassium carbonate (0.577 g, 4.17 mmol, 200 mol-%) and 18-crown-6 (1.09 g, 4.17 mmol, 200 mol-%) were mixed with toluene (7 mL) and stirred at rt for 1 h. After cooling the mixture to $-10\text{ }^{\circ}\text{C}$, trimethyl phosphonoacetate (0.40 mL, 2.51 mmol, 120 mol-%) was added and the mixture was stirred at $-10\text{ }^{\circ}\text{C}$ for 40 min. Aldehyde **40** (0.508 g, 2.09 mmol, 100 mol-%) dissolved in toluene (1 mL) was added and the stirred reaction mixture was allowed to warm to rt overnight. The reaction was quenched with 5 % citric acid and the two layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over MgSO_4 and concentrated. The product mixture was purified by flash chromatography (silica, 10 % EtOAc/hex) to afford pure *E*-enoate **101** (0.517 g, 83 %) as a colorless oil.

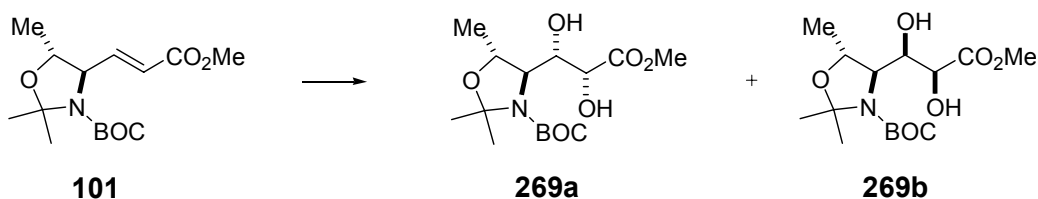
Method 2: To a cooled ($0\text{ }^{\circ}\text{C}$) suspension of NaH (460 mg, 60 % in mineral oil, 11.5 mmol, 115 mol-%) in THF (30 mL) was added trimethyl phosphonoacetate (1.78 mL, 11.0 mmol, 110 mol-%) dissolved in THF (3 mL). After stirring the mixture at $0\text{ }^{\circ}\text{C}$ for 1 h, aldehyde **40** (2.43 g, 10.0 mmol, 100 mol-%) dissolved in THF (7 mL) was added dropwise. The reaction was slowly brought to rt and stirring was continued for 1.5 h or overnight. The reaction was quenched with 5 % citric acid and the two layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over MgSO_4 and concentrated to give a mixture of *E*- and *Z*-enoates (2.86 g, 96 %). An analytical sample of *Z*-enoate **41** was separated by flash chromatography (silica, 10 % EtOAc/hex) to afford pure *Z*-enoate **41** as a white solid.

101: R_f (20 % EtOAc/hex) = 0.51. $[\alpha]_D^{20} = -27.5$ ($c = 1.00$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.74-6.71 (m, 1H), 5.89-5.85 (m, 1H), 3.84-3.81 (m, 2H), 3.70 (s, 3H), 1.56 (s, 3H), 1.48 (s, 3H), 1.41, 1.35 (s, 9H), 1.24 (d, 3H, $J = 6.0$ Hz). $^{13}\text{C NMR}$ (100 MHz,

CDCl₃) δ 166.2, 151.6, 147.4, 121.8, 94.5, 80.3, 74.4, 65.1, 51.5, 28.3, 28.2, 26.3, 25.3, 17.1.

41: R_f (20 % EtOAc/hex) = 0.57. Mp. 77-78 °C, lit.³⁴ mp. 76-78 °C. $[\alpha]_D^{20} = +72.0$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 6.02-5.97 (m, 1H), 5.86 (d, 1H, $J = 11.4$ Hz), 5.16-5.08 (m, 1H), 3.84 (m, 1H), 3.69 (s, 3H), 1.60 (s, 3H), 1.51 (s, 3H), 1.44, 1.35 (s, 9H), 1.32 (d, 3H, $J = 6.1$ Hz). ¹³C NMR (100 MHz, CDCl₃) δ 166.1, 151.9, 149.0, 120.3, 94.4, 79.9, 75.1, 60.8, 51.2, 28.3, 28.1, 26.5, 25.7, 17.7.

5.4. [2*R*,3*S*,3(4*S*),(5*R*)]-Methyl 3-[*N*-(*tert*-butoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidin-4-yl]-2,3-dihydroxypropanoate **269a and [2*S*,3*R*,3(4*S*),(5*R*)]-Methyl 3-[*N*-(*tert*-butoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidin-4-yl]-2,3-dihydroxypropanoate **269b****



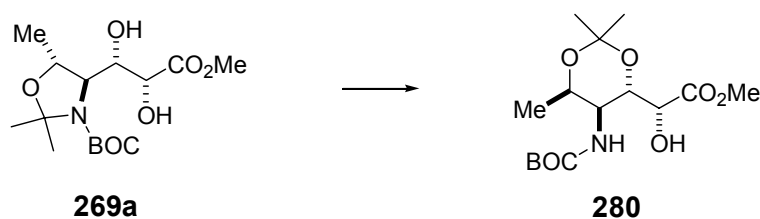
To a vigorously stirred solution of *E*-enoate **101** (1.67 g, 5.58 mmol, 100 mol-%) in EtOAc/CH₃CN (33 ml/33 mL) at 0-5 °C (ice/water bath) was added a solution of RuCl₃·*x*(H₂O) (81 mg, 0.39 mmol, 7 mol-%) and NaIO₄ (1.79 g, 8.37 mmol, 150 mol-%) in distilled water (11 mL). The two-phase mixture was stirred vigorously for 3 min and quenched with a saturated aqueous solution of Na₂S₂O₃ (55 mL). The aqueous phase was separated and extracted with EtOAc (3 x 85 mL). The combined organic layers were washed with brine (85 mL), dried over MgSO₄ and concentrated to afford a mixture of diols **269a** and **269b**. The diols were separated by flash chromatography (silica, 30 % EtOAc/hex) to give diol **269a** (0.90 g, 48 %) and diol **269b** (0.33 g, 18 %) as a colorless oil.

269a: R_f (50 % EtOAc/hex) = 0.31. $[\alpha]_D^{20} = -15.4$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz, DMSO) δ 5.16 (d, 2H, $J = 7.7$ Hz), 4.41 (dq, 1H, $J = 6.4$ Hz, 3.8 Hz), 4.13 (td, 1H, $J = 7.7$ Hz, 2.9 Hz), 4.04-3.99 (m, 1H), 3.64 (s, 3H), 3.54 (bs, 1H), 1.50 (s, 3H), 1.41, 1.39 (s, 12H), 1.22 (d, 3H, $J = 6.2$ Hz). ¹³C NMR (100 MHz, DMSO) δ 173.6, 93.7, 80.0, 73.1,

71.6, 66.9, 60.4, 52.3, 28.7, 27.5, 22.4, 21.4, 14.8. HRMS: m/z calcd for $C_{15}H_{27}NO_7$ (M - Me)⁺ 318.1553, found 318.1568.

269b: R_f (50 % EtOAc/hex) = 0.45. $[\alpha]_D^{20} = -35.3$ ($c = 1.00$, $CHCl_3$). 1H NMR (400 MHz, DMSO) δ 5.26 (d, 1H, $J = 7.9$ Hz), 4.75-4.74 (m, 1H), 4.51 (m, 1H), 4.21 (m, 1H), 4.12 (d, 1H, $J = 6.4$ Hz), 3.67 (s, 1H), 3.64 (s, 3H), 1.49 (s, 3H), 1.41 (s, 12H), 1.20 (d, 3H, $J = 6.2$ Hz). ^{13}C NMR (100 MHz, DMSO) δ 174.1, 94.2, 80.1, 73.0, 71.0, 65.7, 60.4, 52.3, 28.6, 22.5, 21.4, 14.8. HRMS: m/z calcd for $C_{15}H_{27}NO_7$ ($M+1$)⁺ 334.1866, found 334.1827.

5.5. [2*R*,2(4*S*),(5*S*),(6*R*)]-Methyl 5-[*N*-(*tert*-butoxycarbonyl)-2,2,6-trimethyl-1,3-dioxan-4-yl]ethanoate **280**

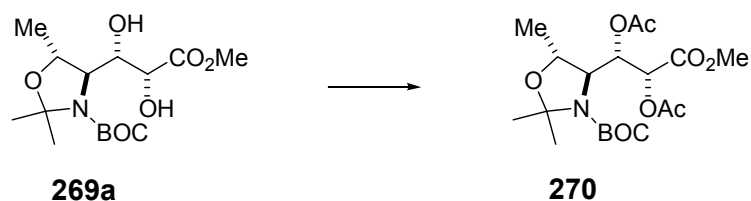


Method 1: To a solution of **269a** (384 mg, 1.15 mmol, 100 mol-%) in CH_2Cl_2 (10 mL) was added (1*S*)-(+)-10-camphorsulfonic acid (40 mg, 0.173 mmol, 15 mol-%). After stirring the reaction mixture at rt for 24 hours, saturated $NaHCO_3$ was added and the aqueous layer was extracted with Et_2O . The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product mixture was purified by flash chromatography (silica, 30 % EtOAc/hex) to give compound **280** (68 mg, 18 %) as a colorless oil.

Method 2: A solution of compound **269a** (95 mg, 0.28 mmol, 100 mol-%) in glacial acetic acid (0.85 mL) was stirred at 60 °C for 1 day. The reaction was quenched by evaporating acetic acid and dichloromethane was added. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. An analytical sample of compound **280** was purified by flash chromatography (silica, 30 % EtOAc/hex).

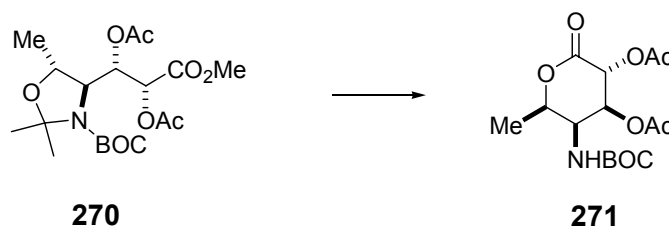
R_f (50 % EtOAc/hex) = 0.48. $[\alpha]_D^{20} = +0.4$ ($c = 1.00$, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) δ 4.81 (d, 1H, $J = 10.4$ Hz), 4.31 (dd, 1H, $J = 8.3$ Hz, 2.1 Hz), 4.22-4.16 (m, 1H), 4.04 (dq, 1H, $J = 6.6$ Hz, 4.8 Hz), 3.75 (s, 3H), 3.65 (dd, 1H, $J = 7.9$ Hz, 2.1 Hz), 3.10 (d, 1H, $J = 8.3$ Hz), 1.40 (s, 9H), 1.28 (s, 3H), 1.24 (s, 3H), 1.10 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 155.8, 101.1, 79.6, 74.4, 70.7, 66.2, 52.4, 51.5, 28.2, 24.3, 23.5, 15.0. HRMS: m/z calcd for $C_{15}H_{27}NO_7$ ($M+Na$)⁺ 356.1685, found 356.1667.

5.6. [2*R*,3*S*,3(4*S*),(5*R*)]-Methyl 3-[*N*-(*tert*-butoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidin-4-yl]-2,3-diacetoxypropanoate **270**



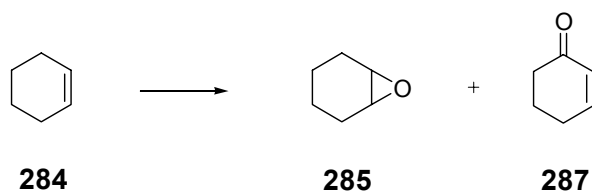
To a solution of **269a** (986 mg, 2.96 mmol, 100 mol-%) in dichloromethane (60 mL) were added pyridine (6 mL), acetic anhydride (5.61 mL, 59.1 mmol, 2000 mol-%) and 4-dimethylaminopyridine (60 mg, 49.1 mmol, 17 mol-%). The reaction mixture was stirred at rt for 30 min and washed with distilled water (2 x 15 mL) and brine (15 mL). Drying over MgSO₄ and concentration afforded the crude **270**, which was purified by flash chromatography (silica, 30 % EtOAc/hex) to give compound **270** (1.22 g, 99 %) as a colorless oil. R_f (50 % EtOAc/hex) = 0.75. $[\alpha]_D^{20} = -54.5$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.76 (bs, 1H), 5.05 (d, 1H, $J = 2.6$ Hz), 4.36 (bs, 1H), 3.73 (s, 3H), 2.18 (s, 3H), 2.08 (s, 3H), 1.59 (s, 3H), 1.48 (s, 9H), 1.43 (s, 3H), 1.33 (d, 3H, $J = 6.6$ Hz). ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 169.6, 167.7, 94.3, 81.0, 72.0, 71.7, 70.1, 64.3, 52.6, 28.2, 21.9, 20.6, 20.4, 14.1. HRMS: m/z calcd for C₁₉H₃₁NO₉ (M-Me)⁺ 402.1764, found 402.1761.

5.7. (3*R*,4*S*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3,4-diacetoxy-5-(*N*-*tert*-butoxycarbonyl)amino-6-methyl-2-pyrone **271**



Compound **270** (320 mg, 0.77 mmol, 100 mol-%) dissolved in glacial acetic acid (2.3 mL) was stirred at 60 °C for 7 days. Acetic acid was evaporated and the precipitate was dissolved in ethyl acetate (30 mL), washed with saturated NaHCO₃ (3 x 30 mL), dried over Na₂SO₄ and concentrated. Purification by flash chromatography (silica, 20 % EtOAc/hex) afforded the lactone **271** (140 mg, 51 %; corrected yield 68 %, based on recovered starting material) as a white, soft solid. R_f (30 % EtOAc/hex) = 0.33. Mp. 114-115 °C. $[\alpha]_D^{20} = +125.1$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.29 (dd, 1H, $J = 10.3$ Hz, 4.0 Hz), 5.19 (d, 1H, $J = 10.1$ Hz), 4.87 (d, 1H, $J = 9.2$ Hz), 4.74 (q, 1H, $J = 12.6$ Hz, 6.4 Hz), 4.46-4.43 (m, 1H), 2.17 (s, 3H), 2.06 (s, 3H), 1.46 (s, 9H), 1.41 (d, 3H, $J = 6.4$ Hz). ¹³C NMR (100 MHz, CDCl₃) δ 170.3, 170.2, 166.5, 155.9, 80.4, 74.9, 71.0, 68.7, 51.1, 28.2, 20.7, 20.5, 16.6. HRMS: m/z calcd for C₁₅H₂₃NO₃ (M+Na)⁺ 368.1321, found 368.1326.

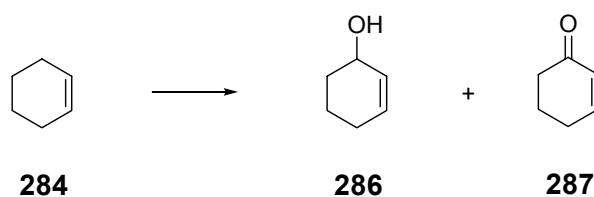
5.8. Oxidation of cyclohexene **284** in the presence of isobutyraldehyde



General procedure: Cyclohexene (205 mg, 2.5 mmol, 100 mol-%), isobutyraldehyde (360 mg, 5.0 mmol, 200 mol-%) and a catalyst, if used, were dissolved in acetonitrile (25 mL) under an atmosphere of oxygen. The amount of the cobalt catalyst was 5 mol-% or 0.13 mol-%. The solution was stirred at rt overnight or for several days producing cyclohexene oxide **285** as the main product, 2-cyclohexen-1-ol **286** and 2-cyclohexen-1-one **287**.

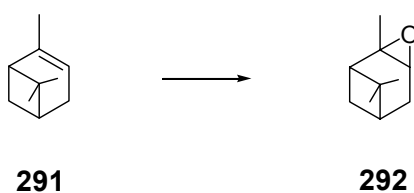
Isobutyric acid was formed as a by-product. The ratio of epoxide to ketone was dependent on the catalyst used and the amount of the catalyst. The products were identified by GC and GC/MS analysis by comparing to the authentic samples.

5.9. Oxidation of cyclohexene **284** to 2-cyclohexen-1-ol **286** and 2-cyclohexen-1-one **287**



In a typical experiment, a round-bottomed flask equipped with a reflux condenser and an oxygen balloon was charged with cyclohexene (4.0 g, 49.0 mmol, 100 mol-%) and $\text{Co}(\text{py})_2\text{Br}_2$ (24 mg, 0.06 mmol, 0.13 mol-%). The reaction mixture was stirred under oxygen at 50 °C for 18 h affording 4 % of 2-cyclohexen-1-ol **286** and 7 % of 2-cyclohexen-1-one **287**. The progress of the reaction was followed by gas chromatography. The products were determined by GC and GC/MS analysis by comparison to authentic samples.

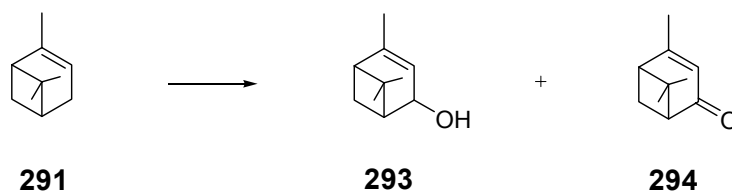
5.10. Epoxidation of α -pinene **291** to α -pinene oxide **292**



α -Pinene **291** (272 mg, 2.0 mmol, 100 mol-%) and isobutyraldehyde (288 mg, 4.0 mmol, 200 mol-%) were dissolved in acetonitrile (10 mL) in a round-bottomed flask. The reaction was stirred under an atmosphere of oxygen at rt for 6 h affording α -pinene oxide as the sole product. After evaporating the solvent, the residue was dissolved in ethyl acetate (15 mL) and washed with saturated NaHCO_3 and brine. Drying over Na_2SO_4 and concentration gave the crude product, which was purified by flash chromatography (neutral aluminium

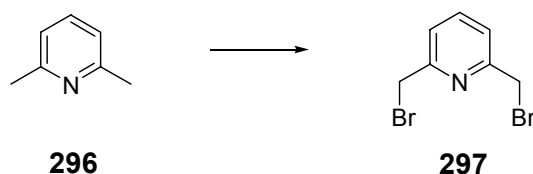
oxide, hex:EtOAc 40:1) to yield α -pinene oxide **292** (209 mg, 1.38 mmol, 69 %) as a colorless liquid. The product was identified by comparison of its NMR spectra to the literature.¹²²

5.11. Allylic oxidation of α -pinene **291**



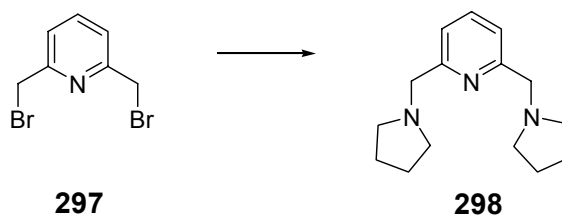
General procedure: Oxidation of α -pinene was performed in an open glass reactor by bubbling oxygen through a gas inlet in the bottom of the reactor. α -Pinene (10.0 g, 0.074 mol, 100 mol-%) and a catalyst were weighed in the reactor and the flow of oxygen was set at 5 mL/min by a mass flow meter. Oxidation was continued at 70 °C for several days.

5.12. 1,3-Bis(bromomethyl)-pyridine **297**



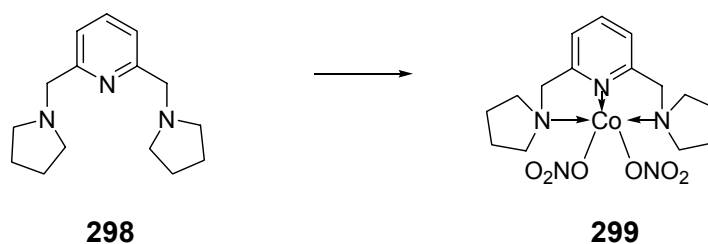
2,6-Lutidine (2.70 g, 25.0 mmol, 100 mol-%) and NBS (11.1 g, 62.5 mmol, 250 mol-%) were mixed in 100 mL of benzene in a round-bottomed flask and AIBN (0.9 g) was added. The mixture was heated at reflux under illumination (150 W bulb) for 22 hours. The reaction mixture was cooled to rt and filtered. The filtrate was collected and the solvent evaporated. The product was extracted from the residue with boiling hexanes. The crude product was recrystallized from hexane to give compound **297** (1.66 g, 6.27 mmol, 25 %) as white crystals, mp. 82-84 °C. ¹H NMR (200 MHz, CDCl₃) δ 7.71 (dd, 1H, J = 8.0 Hz, 7.4 Hz), 7.37 (d, 2H, J = 7.7 Hz), 4.54 (s, 4H). ¹³C NMR (50 MHz, CDCl₃) δ 156.8, 138.1, 122.7, 33.4. Anal. calcd for C₇H₇NBr₂ C 31.7, H 2.7, N 5.3, found C 32.4, H 2.8, N 5.4.

5.13. 1,3-Bis[(pyrrolidinyl-*N*-)methyl]-pyridine **298**



A solution of 1,3-bis(bromomethyl)-pyridine **297** (795 mg, 3.0 mmol, 100 mol-%) in benzene (20 mL) was added dropwise to a cooled (ice bath) and stirred solution of pyrrolidine (1.25 mL, 15 mmol, 500 mol-%) in benzene (8 mL). The mixture was stirred at rt for 1 h. After removing the solvent under reduced pressure diethyl ether (10 mL) and Et₃N (1.5 mL) were added. The solid was filtered off, washed with diethyl ether (5 mL) and the filtrate was evaporated. The residue was distilled by Kugelrohr to give compound **298** as a yellowish oil (54 mg, 2.2 mmol, 74 %). ¹H NMR (200 MHz, CD₃OD) δ 7.82 (dd, 1H, *J* = 7.9 Hz, 7.7 Hz), 7.43 (d, 2H, *J* = 7.7 Hz), 3.82 (s, 4H), 2.65 (m, 8H), 1.86 (m, 8H). ¹³C NMR (50 MHz, CD₃OD) δ 159.1, 138.8, 123.2, 62.5, 55.1, 24.3. HRMS: *m/z* calcd for C₁₅H₂₄N₃ MH⁺ 246.1970, found 246.1999.

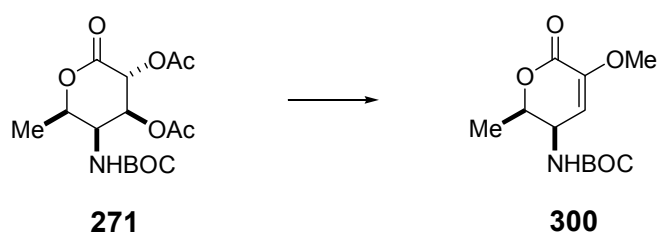
5.14. 1,3-Bis[(pyrrolidinyl-*N*-)methyl]-pyridine cobalt complex **299**



A solution of 1,3-bis[(pyrrolidinyl-*N*-)methyl]-pyridine **298** (245 mg, 1.0 mmol, 100 mol-%) and cobalt(II) nitrate hexahydrate (291 mg, 1.0 mmol, 100 mol-%) in absolute ethanol was stirred at rt overnight to form a purple solid. The solvent was filtered off and the solid washed with cold hexane affording a crude complex as a purple powder (360 mg, 0.8 mmol, 84 %). After analyses, the product remained (313 mg) was purified by crystallization from absolute EtOH yielding complex **299** (256 mg, 0.6 mmol, 69 %) as

purple crystals, mp. 192-193 °C. Anal. calcd for C₁₅H₂₃N₅O₆Co C 42.1, H 5.4, N 16.4, found C 42.1, H % 5.0, N 16.3.

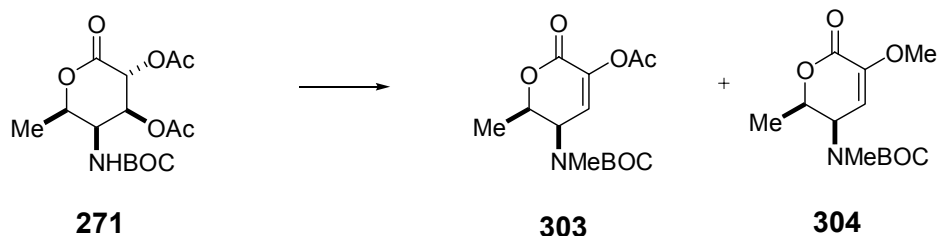
5.15. (5*S*,6*R*)-5,6-Dihydro-3-methoxy-5-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino-6-methyl-2-pyrone **300**



To a mixture of NaH (18 mg, 0.45 mmol, 155 mol-%; 60 % in mineral oil) and THF (5 mL) was added a solution of lactone **271** (100 mg, 0.29 mmol, 100 mol-%) in THF (2 mL) at 0 °C (ice-bath). After stirring the reaction mixture at rt for 45 min, MeI (45 μL, 0.72 mmol, 250 mol-%) was added at 0 °C and the mixture was stirred at rt overnight. The reaction was quenched with 1 M NH₄Cl (5 mL) and the solution was extracted with ether (25 mL). The combined organic layers were washed with water and brine, dried over Na₂SO₄ and evaporated to produce compound **300** and an unidentified product. An analytical sample of compound **300** was purified by flash chromatography (silica, 20 % EtOAc/hex).

R_f (30 % EtOAc/hex) = 0.25. ¹H NMR (400 MHz, CDCl₃) δ 5.73 (d, 1H, *J* = 6.8 Hz), 4.66 (qd, 2H, *J* = 6.6 Hz, 3.0 Hz), 4.43 (ddd, 1H, *J* = 9.8 Hz, 6.8 Hz, 3.0 Hz), 3.68 (s, 3H), 1.45 (s, 9H), 1.39 (d, 3H, *J* = 6.6 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 160.8, 155.2, 146.5, 108.3, 80.4, 76.9, 55.6, 46.5, 28.3, 16.3. HRMS: *m/z* calcd for C₁₂H₁₉NO₅ (M+Na)⁺ 280.1161, found 280.1186.

5.16. (5*S*,6*R*)-5,6-Dihydro-3-acetoxy-5-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino-6-methyl-2-pyrone **303 and (5*S*,6*R*)-5,6-Dihydro-3-methoxy-5-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino-6-methyl-2-pyrone **304****

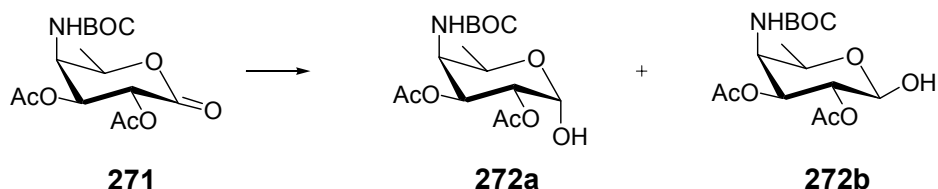


MeI (3.5 mL, 56 mmol, 100-fold excess) and Ag₂O (400 mg, 1.73 mmol, 310 mol-%) were added to a solution of **271** (193 mg, 0.56 mmol, 100 mol-%) in DMF (6 mL). The reaction was protected from light and stirred at rt overnight. The reaction mixture was filtered through a pad of Celite and rinsed with EtOAc. Water was added and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (silica, 20 % EtOAc/hex) afforded compounds **303** (38 mg, 21 %) and **304** (92 mg, 56 %) as white amorphous solids.

303 (contains a small amount of **304**): *R_f* (30 % EtOAc/hex) = 0.40. ¹H NMR (400 MHz, CDCl₃) δ 6.33 (d, 1H, *J* = 6.5 Hz), 5.18 (dd, 1H, *J* = 6.5 Hz, 4.4 Hz), 4.81 (dq, 1H, *J* = 6.6 Hz, 4.4 Hz), 2.80 (s, 3H), 2.30 (s, 3H), 1.50 (s, 9H), 1.38 (d, 3H, *J* = 6.6 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 168.4, 159.5, 155.9, 141.3, 126.8, 80.9, 77.1, 49.7, 30.5, 28.2, 20.4, 15.8. HRMS: *m/z* calcd for C₁₄H₂₁NO₆ (M+Na)⁺ 322.1267, found 322.1253.

304 (contains a small amount of **303**): *R_f* (30 % EtOAc/hex) = 0.18. ¹H NMR (400 MHz, CDCl₃) δ 5.51 (d, 1H, *J* = 6.8 Hz), 5.09 (dd, 1H, *J* = 6.8 Hz, 4.1 Hz), 4.66 (qd, 1H, *J* = 6.7 Hz, 4.1 Hz), 3.71 (s, 3H), 2.73, 2.69 (s, 3H), 1.47 (s, 9H), 1.33 (d, 3H, *J* = 6.7 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 160.9, 156.0, 148.1, 106.1, 80.5, 74.2, 55.7, 49.5, 30.1, 28.3, 16.0. HRMS: *m/z* calcd for C₁₃H₂₁NO₅ (M+Na)⁺ 294.1317, found 294.1323.

5.17. 2,3-Di-*O*-acetyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl)amino- α -D-galactopyranose **272a and 2,3-Di-*O*-acetyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl)amino- β -D-galactopyranose **272b****

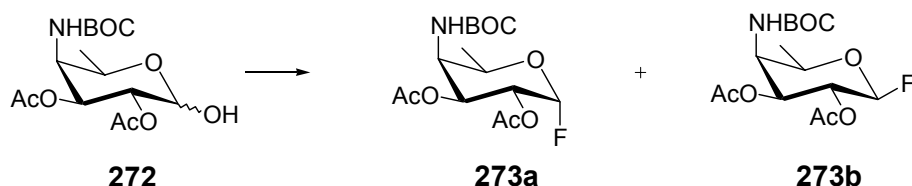


In a two-necked round-bottomed flask was placed EtOAc (2.5 mL) and PtO₂ (85 mg, 0.31 mmol, 32 mol-%). PtO₂ was reduced to Pt by filling the flask with hydrogen and stirring the mixture for 15 min at rt. Lactone **271** (340 mg, 0.98 mmol, 100 mol-%) dissolved in EtOAc (3 mL) was added and stirring was continued for 6 hours under an atmosphere of hydrogen. The reaction mixture was filtered through a pad of Celite and the solvent was evaporated under reduced pressure to afford 1:1 mixture of lactols **272a** and **272b** (260 mg, 76 %) as a white solid. The anomers were separated from each other by crystallization from EtOAc/hex.

272a (contains a small amount of **272b**): R_f (50 % EtOAc/hex) = 0.33. ¹H NMR (400 MHz, CDCl₃) δ 5.40 (t, 1H, J = 3.7 Hz), 5.26 (dd, 1H, J = 10.9 Hz, 4.0 Hz), 4.95-4.89 (m, 2H), 4.47 (dq, 1H, J = 6.5 Hz, 1.6 Hz), 4.17 (ddd, 1H, J = 10.1 Hz, 4.0 Hz, 1.6 Hz), 3.39 (dd, 1H, J = 3.7 Hz), 2.10 (s, 3H), 2.00 (s, 3H), 1.44 (s, 9H), 1.17 (d, 3H, J = 6.5 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 170.7, 170.4, 156.1, 90.3, 79.6, 68.9, 68.8, 64.2, 52.4, 28.2, 20.9, 16.4. HRMS: m/z calcd for C₁₅H₂₅NO₈ (M+Na)⁺ 370.1478, found 370.1474.

272b: R_f (50 % EtOAc/hex) = 0.28. Mp. 166-168 °C. $[\alpha]_D^{20} = +28.4$ (c = 1.00, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.10 (d, 1H, J = 9.5 Hz), 4.95-4.93 (m, 2H), 4.63 (t, 1H, J = 7.3 Hz), 4.15 (qd, 1H, J = 10.1 Hz, 3.5 Hz, 1.5 Hz), 4.00 (bs, 1H), 3.84 (dq, 1H, J = 6.4 Hz, 1.5 Hz), 2.10 (s, 3H), 2.01 (s, 3H), 1.44 (s, 9H), 1.26 (d, 3H, J = 6.4 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 170.5, 156.1, 96.0, 79.7, 72.0, 71.4, 70.0, 51.9, 28.3, 20.9, 20.8, 16.3. HRMS: m/z calcd for C₁₅H₂₅NO₈ (M+Na)⁺ 370.1478, found 370.1471.

5.18. 2,3-Di-*O*-acetyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl)amino- α -*D*-galactopyranosyl fluoride **273a and 2,3-Di-*O*-acetyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl)amino- β -*D*-galactopyranosyl fluoride **273b****

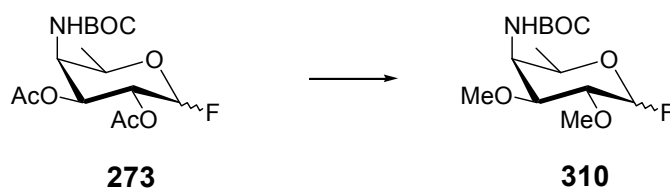


General procedure: Lactol **272** (3.09 g, 8.89 mmol, 100 mol-%) dissolved in dry THF (35 mL) was cooled to 0 °C and DAST (1.76 mL, 13.3 mmol, 150 mol-%) was added. The cooling bath was removed and the reaction mixture was stirred at rt for 30 min. After cooling the reaction to 0 °C MeOH (0.6 mL) was added and the reaction mixture was poured into ice-cold water (20 mL). Extraction with EtOAc (3 x 20 mL), drying over Na₂SO₄ and evaporation afforded the crude mixture of fluorides, which were separated by flash chromatography (silica, 10 % EtOAc/hex) to yield the α -anomer **273a** (0.70 g, 23 %) and the β -anomer **273b** (1.72 g, 55 %) as white solids.

273a: R_f (30 % EtOAc/hex) = 0.47. Mp. 119-121 °C. $[\alpha]_D^{20} = +86.5$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.69 (dd, 1H, $J = 54$ Hz, 3.0 Hz), 5.22 (dd, 1H, $J = 10.9$ Hz, 4.0 Hz), 4.96 (ddd, 1H, $J = 24$ Hz, 10.9 Hz, 3.0 Hz), 4.79 (d, 1H, $J = 9.9$ Hz), 4.38 (dq, 1H, $J = 6.5$ Hz, 1.5 Hz), 4.25 (ddd, 1H, $J = 9.9$ Hz, 4.0 Hz, 1.5 Hz), 2.11 (s, 3H), 2.02 (s, 3H), 1.44 (s, 9H), 1.23 (d, 3H, $J = 6.5$ Hz). ¹³C NMR (100 MHz, CDCl₃) δ 170.6, 170.2, 155.9, 104.0 ($J_{CF} = 228$ Hz), 79.9, 68.6, 67.8 ($J_{CF} = 25$ Hz), 67.3 ($J_{CF} = 4$ Hz), 51.8, 28.2, 20.8, 20.7, 16.2. HRMS: m/z calcd for C₁₅H₂₄FNO₇ (M+Na)⁺ 372.1435, found 372.1436.

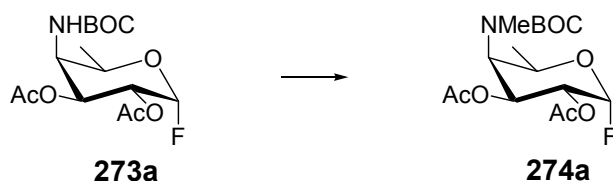
273b: R_f (30 % EtOAc/hex) = 0.31. Mp. 105-107 °C. $[\alpha]_D^{20} = +18.1$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.18 (dd, 1H, $J = 35$ Hz, 7.3 Hz), 5.12-5.08 (m, 1H), 4.92 (dd, 1H, $J = 10.3$ Hz, 4.3 Hz), 4.86 (d, 1H, $J = 10.2$ Hz), 4.16 (qd, 1H, $J = 10.2$ Hz, 4.3 Hz, 1.7 Hz), 3.89 (q, 1H, $J = 6.4$ Hz), 2.09 (s, 3H), 2.00 (s, 3H), 1.44 (s, 9H), 1.31 (d, 3H, $J = 6.4$ Hz). ¹³C NMR (100 MHz, CDCl₃) δ 170.3, 169.5, 155.8, 107.4 ($J_{CF} = 216$ Hz), 79.9, 71.5 ($J_{CF} = 11$ Hz), 70.3 ($J_{CF} = 4$ Hz), 69.1 ($J_{CF} = 25$ Hz), 51.3, 28.2, 20.7, 16.2. HRMS: m/z calcd for C₁₅H₂₄FNO₇ (M+Na)⁺ 372.1435, found 372.1432.

5.19. 2,3-Di-*O*-methyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino-D-galactopyranosyl fluoride **310**



A solution of compound **273** (19 mg, 0.05 mmol, 100 mol-%) in THF (1 ml) was added to a mixture of NaH (7 mg, 0.18 mmol, 320 mol-%; 60 % in oil) and THF (2.5 ml) at 0 °C (ice-bath). After stirring the mixture at rt for 45 min, the reaction was cooled to 0 °C and MeI (0.1 mL, 1.60 mmol, 3000 mol-%) was added. After stirring the reaction mixture at rt overnight 1 M NH₄Cl was added and the solution was extracted with ether. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and evaporated to give crude **310** as a mixture of α - and β -anomers. ¹H NMR (400 MHz, CDCl₃) δ 5.79-5.58 (dd, 1H, *J* = 53 Hz, 3.0 Hz), 5.13 (m, 1H), 5.0 (m, 1H), 4.8 (m, 1H), 4.57 (m, 1H), 4.20 (m, 1H, *J* = 6.6 Hz), 3.57, 3.55 (s, 3H), 3.45, 3.44 (s, 3H), 1.46 (s, 9H), 1.23 (d, 3H, *J* = 6.4 Hz).

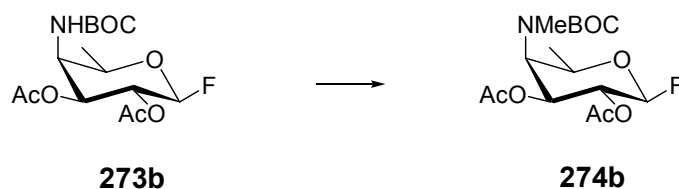
5.20. 2,3-Di-*O*-acetyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino- α -D-galactopyranosyl fluoride **274a**



MeI (16.4 mL, 263 mmol, 200-fold excess) and Ag₂O (0.915 g, 3.95 mmol, 300 mol-%) were added to a solution of **273a** (0.460 g, 1.32 mmol, 100 mol-%) in DMF (15 mL). The reaction was protected from light and stirred at rt for 2 hours. The reaction mixture was filtered through a pad of Celite and rinsed with CH₂Cl₂. Water was added and the aqueous layer was extracted with CH₂Cl₂. Drying over MgSO₄, filtration and evaporation afforded the crude product mixture which was purified by flash chromatography (silica, 10 %

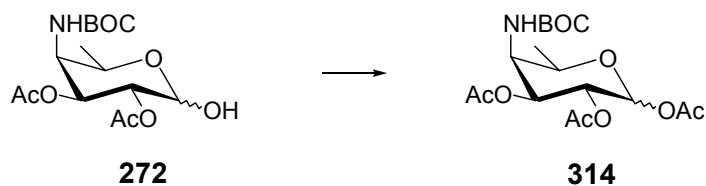
EtOAc/hex) to give compound **274a** (202 mg, 42 %) as a colorless oil. R_f (20 % EtOAc/hex) = 0.39. $[\alpha]_D^{20} = +71.5$ ($c = 1.00$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.75, 5.72 (dd, 1H, $J = 53$ Hz, 3.1 Hz), 5.46, 5.33 (dd, 1H, $J = 11.3$ Hz, 5.8 Hz), 5.22, 5.17 (ddd, 1H, $J = 23$ Hz, 11.3 Hz, 3.1 Hz), 4.71 (dd, 1H, $J = 5.8$ Hz, 3.4 Hz), 4.44, 4.38 (dq, 1H, $J = 6.7$ Hz, 3.4 Hz), 3.03, 3.02 (s, 3H), 2.07, 2.06 (s, 3H), 2.01, 1.96 (s, 3H), 1.42, 1.38 (s, 9H), 1.23, 1.20 (d, 3H, $J = 6.7$ Hz). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.4, 170.2, 169.6, 169.5, 156.90, 156.2, 104.4 ($J_{\text{CF}} = 227$ Hz), 104.2 ($J_{\text{CF}} = 228$ Hz), 80.4, 79.9, 67.9 ($J_{\text{CF}} = 4$ Hz), 67.6 ($J_{\text{CF}} = 11$ Hz), 67.2 ($J_{\text{CF}} = 20$ Hz), 54.1, 53.4, 33.1, 32.4, 28.2, 28.1, 20.7, 20.6, 16.1, 16.0. HRMS: m/z calcd for $\text{C}_{16}\text{H}_{26}\text{FNO}_7$ ($\text{M}+\text{Na}$) $^+$ 386.1591, found 386.1586.

5.21. 2,3-Di-*O*-acetyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino- β -D-galactopyranosyl fluoride **274b**



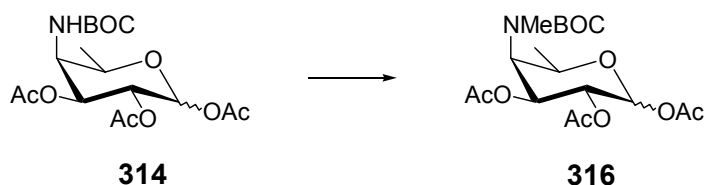
MeI (35 mL, 0.56 mol, 200-fold excess) and Ag_2O (1.96 g, 8.45 mmol, 300 mol-%) were added to a solution of **273b** (0.984 g, 2.82 mmol, 100 mol-%) in DMF (40 mL). The reaction was protected from light and stirred at rt for 4 hours. The reaction mixture was filtered through a pad of Celite and rinsed with CH_2Cl_2 . Water was added and the aqueous layer was extracted with CH_2Cl_2 . Drying over MgSO_4 , filtration and evaporation afforded the crude product mixture which was purified by flash chromatography (silica, 10 % EtOAc/hex) to give compound **274b** (0.470 g, 46 %) as a colorless oil. R_f (20 % EtOAc/hex) = 0.31. $[\alpha]_D^{20} = +3.3$ ($c = 1.00$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.47-5.31 (m, 1H), 5.27-5.00 (m, 2H), 4.68-4.59 (m, 1H), 4.02-3.94 (m, 1H), 3.10 (s, 3H), 2.08, 2.07 (s, 3H), 2.02, 1.98 (s, 3H), 1.44, 1.39 (s, 9H), 1.32, 1.30 (d, 3H, $J = 6.5$ Hz). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.7, 169.6, 169.3, 157.0, 156.1, 107.7 ($J_{\text{CF}} = 215$ Hz), 80.4, 80.0, 71.4 ($J_{\text{CF}} = 4$ Hz), 71.3 ($J_{\text{CF}} = 4$ Hz), 70.8 ($J_{\text{CF}} = 12$ Hz), 70.3 ($J_{\text{CF}} = 12$ Hz), 69.4 ($J_{\text{CF}} = 24$ Hz), 69.2 ($J_{\text{CF}} = 24$ Hz), 54.6, 53.6, 33.1, 32.5, 28.2, 20.6, 20.5, 16.2. HRMS: m/z calcd for $\text{C}_{16}\text{H}_{26}\text{FNO}_7$ ($\text{M}+\text{Na}$) $^+$ 386.1591, found 386.1613.

5.22. 1,2,3-Tri-*O*-acetyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl)amino-D-galactopyranose **314**



Acetic anhydride (0.14 mL, 1.4 mmol, 1000 mol-%) and DMAP (2.6 mg, 22 μ mol, 15 mol-%) were added to a solution of **272** (50 mg, 0.14 mmol, 100 mol-%) in CH_2Cl_2 (3 mL). The reaction was stirred at rt for 30 min and the solvent was evaporated. The crude product was directly chromatographed (silica, 30 % EtOAc/hex) to afford a mixture of α - and β -anomers **314** (54 mg, 96 %) as a white solid. R_f (50 % EtOAc/hex) = 0.70. ^1H NMR (400 MHz, CDCl_3) δ 6.24, (d, 1H, J = 3.8 Hz), 5.58 (d, 1H, J = 8.2 Hz), 5.20 (dd, 1H, J = 11.0 Hz, 3.8 Hz), 5.11 (m, 2H), 4.94 (dd, 1H, J = 10.4, 4.3 Hz), 4.88 (d, 1H, J = 9.9 Hz), 4.84 (d, 1H, J = 10.1 Hz), 4.31 (dq, 1H, J = 6.5 Hz, 1.5 Hz), 4.21 (ddd, 1H, J = 9.9 Hz, 3.8 Hz, 1.5 Hz), 4.14 (ddd, 1H, J = 10.1 Hz, 4.3 Hz, 1.2 Hz), 3.90 (dq, 1H, J = 6.3 Hz, 1.2 Hz), 2.11 (s, 3H), 2.07 (s, 3H), 2.00 (s, 12H), 1.43 (s, 18H), 1.23 (d, 3H, J = 6.3 Hz), 1.17 (d, 3H, J = 6.5 Hz). ^{13}C NMR (100 MHz, CDCl_3) δ 170.4, 170.2, 169.6, 169.0, 156.0, 155.8, 92.5, 89.6, 79.7, 72.3, 70.8, 68.9, 68.2, 67.4, 66.7, 52.0, 51.6, 28.2, 20.8, 20.7, 20.6, 20.5, 16.3, 16.2. HRMS: m/z calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_9$ ($\text{M}+\text{Na}$) $^+$ 412.1584, found 412.1588.

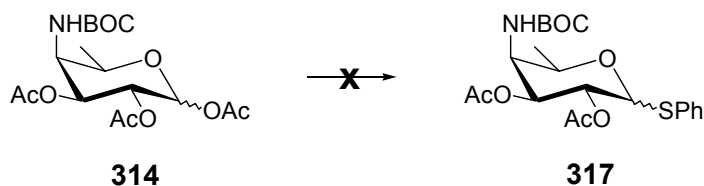
5.23. 1,2,3-Tri-*O*-acetyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino-D-galactopyranose **316**



MeI (2.2 mL, 35.3 mmol, 200-fold excess) and Ag_2O (125 mg, 0.54 mmol, 300 mol-%) were added to a solution of **314** (70 mg, 0.18 mmol, 100 mol-%) in DMF (2.5 mL). The reaction was protected from light and stirred at 50 $^\circ\text{C}$ overnight. The reaction mixture was

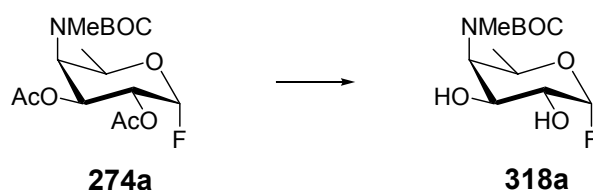
filtered through a pad of Celite and rinsed with EtOAc. Water was added and the aqueous layer was extracted with EtOAc. Drying over Na₂SO₄, filtration and evaporation afforded a mixture of product **316** and the starting material **314** which could not be separated from each other by flash chromatography.

5.24. Attempted thioglycosylation for **314**



Thiophenol (16 μ L, 0.15 mmol, 120 mol-%) and BF₃·OEt₂ (24 μ L, 0.19 mmol, 150 mol-%) were added to a solution of compound **314** (50 mg, 0.13 mmol, 100 mol-%) in dry CH₂Cl₂ (1.0 mL). The reaction was stirred at rt overnight. According to TLC-analysis, mostly baseline material had been formed, probably due to the cleavage of the BOC-protection under the acidic reaction media.

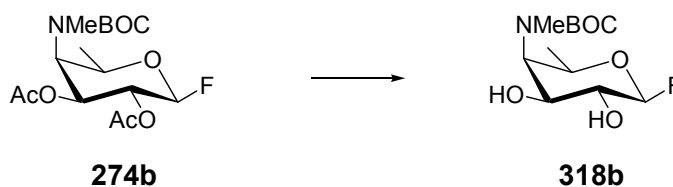
5.25. 4,6-Dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino- α -D-galactopyranosyl fluoride **318a**



To a cooled (0 °C) solution of compound **274a** (109 mg, 0.30 mmol, 100 mol-%) in MeOH (3 mL) was added NaOMe (0.50 mL, 0.1 M) and the reaction was stirred at 0 °C for 2 hours. The reaction mixture was neutralized by filtration through a pad of silica and washed with cold MeOH. Evaporation and purification by flash chromatography (silica, gradient of 20 % EtOAc/hex to 50 % EtOAc/hex) afforded compound **318a** (60 mg, 71 %) as a white solid. Crystallization from EtOAc/hex afforded white needles. R_f (50 % EtOAc/hex) = 0.15. Mp. 132-133 °C. [α]_D²⁰ = +68.2 (*c* = 1.00, MeOH). ¹H NMR (400

MHz, CD₃OD) δ 5.58 (d, 1H, J = 53 Hz), 4.51, 4.50 (dd, 1H, J = 6.3 Hz, 3.4 Hz), 4.40-4.31 (m, 1H), 4.13-3.99 (m, 1H), 3.87, 3.84 (td, 1H, J = 26 Hz, 10.6 Hz, 2.6 Hz), 2.99, 2.97 (s, 3H), 1.47, 1.46 (s, 9H), 1.20, 1.18 (d, 3H, J = 6.3 Hz). ¹³C NMR (100 MHz, CD₃OD) δ 159.4, 159.2, 109.0 (J_{CF} = 224 Hz), 81.4, 81.1, 70.1 (J_{CF} = 25 Hz), 70.0 (J_{CF} = 25 Hz), 69.6 (J_{CF} = 4 Hz), 69.0 (J_{CF} = 5 Hz), 59.4, 58.2, 34.0, 33.5, 28.7, 16.8, 16.6. HRMS: m/z calcd for C₁₂H₂₂FNO₅ (M+Na)⁺ 302.1380, found 302.1372.

5.26. 4,6-Dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino- β -D-galactopyranosyl fluoride **318b**



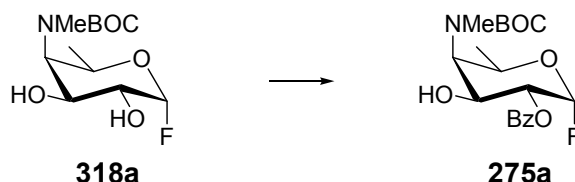
Method 1: To a cooled (0 °C) solution of compound **274b** (148 mg, 0.407 mmol, 100 mol-%) in MeOH (5 mL) was added NaOMe (0.66 mL, 0.1 M) and the reaction was stirred at 0 °C for 4 hours. The reaction mixture was neutralized by filtration through a pad of silica and washed with cold MeOH. Evaporation and purification by flash chromatography (silica, gradient of 20 % EtOAc/hex to 50 % EtOAc/hex) yielded compound **318b** (84 mg, 74 %) as a white solid. Crystallization from EtOAc/hex afforded white needles.

Method 2: To a cooled (0 °C) solution of compound **274b** (172 mg, 0.473 mmol, 100 mol-%) in MeOH (5 mL) was added K₂CO₃ (6.5 mg, 47 μ mol, 10 mol-%) and the reaction was stirred at 0 °C for 4 hours. The reaction mixture was neutralized by filtration through a pad of silica and washed with cold MeOH. Evaporation and purification by flash chromatography (silica, gradient of 20 % EtOAc/hex to 50 % EtOAc/hex) afforded compound **318b** (93 mg, 70 %) as a white solid, which was crystallized from EtOAc/hex.

R_f (50 % EtOAc/hex) = 0.16. Mp. 172-173 °C. $[\alpha]_D^{20}$ = +17.4 (c = 1.00, MeOH). ¹H NMR (400 MHz, CD₃OD) δ 5.00, 4.99 (dd, 1H, J = 53 Hz, 6.5 Hz), 4.45-4.36 (m, 1H), 4.01-3.93 (m, 1H), 3.83-3.66 (m, 2H), 3.03, 3.00 (s, 3H), 1.47, 1.46 (s, 9H), 1.25, 1.23 (d, 3H, J = 6.3 Hz). ¹³C NMR (100 MHz, CD₃OD) δ 159.4, 159.1, 112.0 (J_{CF} = 211 Hz), 81.4, 81.1, 73.3 (J_{CF} = 20 Hz), 73.2 (J_{CF} = 21 Hz), 72.9 (J_{CF} = 12 Hz), 72.3 (J_{CF} = 4 Hz), 58.9, 57.8,

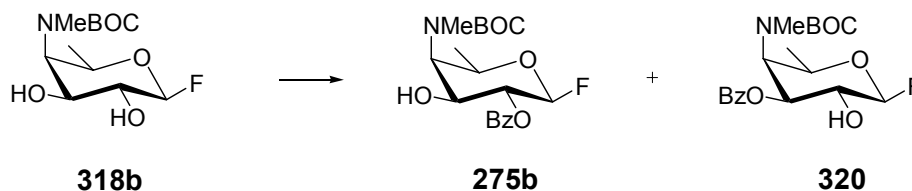
34.0, 33.5, 28.6, 16.8, 16.6. HRMS: m/z calcd for $C_{12}H_{22}FNO_5$ ($M+Na$)⁺ 302.1380, found 302.1391.

5.27. 2-*O*-Benzoyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino- α -D-galactopyranosyl fluoride **275a**



A mixture of **318a** (66 mg, 0.24 mmol, 100 mol-%), Et_3N (0.33 mL, 2.4 mmol, 1000 mol-%), Bu_2SnO (71 mg, 0.28 mmol, 120 mol-%) and 4Å molecular sieves in benzene (5 mL) was refluxed for 2 h. The reaction mixture was allowed to cool down for a while before addition of benzoyl chloride (30 μ L, 0.26 mmol, 110 mol-%). After refluxing for 10 min, the reaction mixture was filtered and evaporated to dryness to afford the crude **275a**, which was directly chromatographed (silica, 10 % EtOAc/hex) to give compound **275a** (42 mg, 46 %; corrected yield 75 % based on recovered starting material) as a white solid. R_f (30 % EtOAc/hex) = 0.58. Mp. 104-106 °C. $[\alpha]_D^{20} = +81.0$ ($c = 1.00$, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 2H, $J = 7.3$ Hz), 7.58 (t, 1H, $J = 7.5$ Hz, 7.3 Hz), 7.45 (t, 2H, $J = 7.5$ Hz), 5.86 (dd, 1H, $J = 54$ Hz, 2.9 Hz), 5.28 (dd, 1H, $J = 24$ Hz, 11.0 Hz), 4.70 (bs, 1H), 4.56-4.47 (m, 2H), 3.11 (s, 3H), 1.46 (s, 9H), 1.32 (d, 3H, $J = 6.7$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 158.7, 133.4, 129.9, 129.2, 128.4, 104.7 ($J_{CF} = 227$ Hz), 80.5, 70.9 ($J_{CF} = 24$ Hz), 67.7 ($J_{CF} = 5$ Hz), 67.1, 56.9, 33.3, 28.2, 16.3. HRMS: m/z calcd for $C_{19}H_{26}FNO_6$ ($M+Na$)⁺ 406.1642, found 406.1645.

5.28. 2-*O*-Benzoyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)-amino- β -D-galactopyranosyl fluoride 275b and 3-*O*-Benzoyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino- β -D-galactopyranosyl fluoride 320



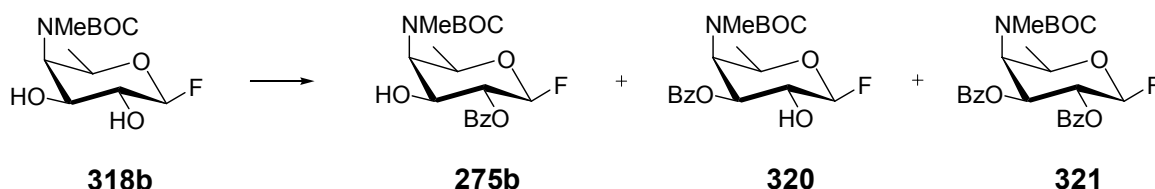
A mixture of **318b** (82 mg, 0.29 mmol, 100 mol-%), Et₃N (0.41 mL, 2.9 mmol, 1000 mol-%), Bu₂SnO (88 mg, 0.35 mmol, 120 mol-%) and 4 Å molecular sieves in benzene (4 mL) was refluxed for 2 h. The reaction mixture was allowed to cool down for a while before addition of benzoyl chloride (37 μ L, 0.32 mmol, 110 mol-%). After refluxing for another 20 min, the reaction mixture was filtered and evaporated to dryness to afford a mixture of monobenzoylated fluorides. The crude product mixture was directly chromatographed (silica, 10 % EtOAc/hex) to give compounds **275b** (79 mg, 70 %) and **320** (28 mg, 25 %) as white solids. Both the products were crystallized from EtOAc/hex to afford white needles.

275b: R_f (30 % EtOAc/hex) = 0.28. Mp. 126-127 °C. $[\alpha]_D^{20} = +6.5$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, 2H, $J = 7.3$ Hz, 1.4 Hz), 7.58 (tt, 1H, $J = 7.5$ Hz, 7.3 Hz, 1.2 Hz), 7.45 (tt, 2H, $J = 7.5$ Hz, 1.6 Hz), 5.48-5.41 (m, 1H), 5.31 (dd, 1H, $J = 52$ Hz, 7.3 Hz), 4.61 (bs, 1H), 4.17 (m, 1H), 4.01 (bs, 1H), 3.17 (s, 3H), 1.45 (s, 9H), 1.38 (d, 3H, $J = 6.5$ Hz). ¹³C NMR (100 MHz, CDCl₃) δ 166.0, 158.5, 133.4, 129.9, 129.3, 128.4, 107.8 ($J_{CF} = 214$ Hz), 80.6, 73.0 ($J_{CF} = 23$ Hz), 71.1 ($J_{CF} = 14$ Hz), 56.4, 33.4, 28.3, 16.4. HRMS: m/z calcd for C₁₉H₂₆FNO₆ (M+Na)⁺ 406.1642, found 406.1658.

320: R_f (30 % EtOAc/hex) = 0.40. Mp. 173-174 °C. $[\alpha]_D^{20} = +26.1$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, 2H, $J = 7.9$ Hz), 7.55 (q, 1H, $J = 7.2$ Hz), 7.45-7.39 (m, 2H), 5.32-5.24 (m, 1H), 5.19 (dd, 1H, $J = 52$ Hz, 7.3 Hz), 4.82-4.63 (m, 1H), 4.31-4.12 (m, 1H), 4.05-4.00 (m, 1H), 3.13, 3.10 (s, 3H), 1.33 (d, 3H, $J = 6.3$ Hz), 1.24, 1.13 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 166.0, 165.7, 156.8, 156.3, 133.5, 133.3, 129.9, 129.8, 129.4, 129.2, 128.6, 128.3, 110.2 ($J_{CF} = 212$ Hz), 110.1 ($J_{CF} = 211$ Hz), 80.5, 80.1, 73.6 ($J_{CF} = 12$ Hz), 73.2 ($J_{CF} = 12$ Hz), 71.4 ($J_{CF} = 3$ Hz), 71.2 ($J_{CF} = 4$ Hz), 70.4 ($J_{CF} = 23$ Hz),

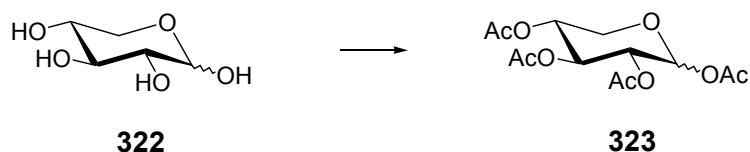
69.9 ($J_{CF} = 24$ Hz), 54.9, 53.7, 33.3, 32.8, 28.0, 27.9, 16.3, 16.2. HRMS: m/z calcd for $C_{19}H_{26}FNO_6$ ($M+Na$)⁺ 406.1642, found 406.1637.

5.29. 2,3-*O*-Dibenzoyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl)-*N*-methyl)- β -D-galactopyranosyl fluoride **321**



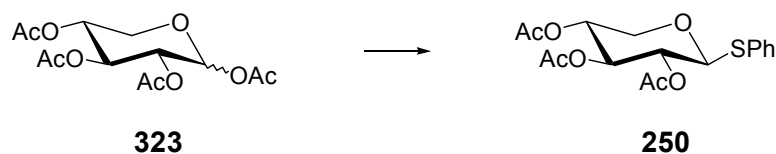
To a cooled (0 °C) solution of **318b** (62 mg, 0.22 mmol, 100 mol-%) and DMAP (3 mg, 0.02 mmol, 10 mol-%) in pyridine (1 mL) was added BzCl (39 μ L, 0.33 mmol, 150 mol-%) and the reaction was allowed to warm up to rt. After stirring at rt overnight the reaction was poured to distilled H₂O and extracted with CH₂Cl₂. The combined organic layers were washed with 1 M HCl and saturated NaHCO₃. Drying over MgSO₄ and concentration afforded a crude mixture of mono- and dibenzoylated products **275b**, **320** and **321**. An analytical sample of the dibenzoate **321** was purified by flash chromatography. R_f (30 % EtOAc/hex) = 0.52. ¹H NMR (400 MHz, CDCl₃) δ 8.00-7.93 (m, 4H), 7.55-7.47 (m, 2H), 7.42-7.34 (m, 4H), 5.95-5.82 (m, 1H), 5.59-5.46 (m, 1H), 5.44 (td, 1H, $J = 52$ Hz, 6.8 Hz), 4.97-4.78 (m, 1H), 4.18-4.12 (m, 1H), 3.28, 3.24 (s, 3H), 1.41, 1.40 (d, 3H, $J = 6.1$ Hz), 1.16 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 165.3, 165.2, 156.8, 156.1, 133.5, 133.6, 133.2, 129.8, 129.4, 129.2, 129.0, 128.7, 128.6, 128.4, 128.3, 107.9 ($J_{CF} = 216$ Hz), 80.5, 80.1, 71.7, 71.6, 71.2 ($J_{CF} = 14$ Hz), 71.1 ($J_{CF} = 12$ Hz), 69.9 ($J_{CF} = 24$ Hz), 69.7 ($J_{CF} = 23$ Hz), 55.0, 53.8, 33.3, 32.8, 28.0, 27.9, 16.3. HRMS: m/z calcd for $C_{26}H_{30}FNO_7$ ($M+Na$)⁺ 510.1904, found 510.1893.

5.30. 1,2,3,4-Tetra-*O*-acetyl-D-xylopyranose **323**



D(+)-Xylose **322** (1.00 g, 6.67 mmol, 100 mol-%), Ac₂O (3.14 mL, 33.3 mmol, 500 mol-%), Et₃N (7.43 mL, 53.3 mmol, 800 mol-%) and DMAP (163 mg, 1.33 mmol, 20 mol-%) were stirred in CH₂Cl₂ (100 mL) at rt for 3 h. Distilled water (50 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were washed with 1 M HCl (2 x 50 mL) and brine (50 mL), dried over Na₂SO₄ and concentrated. Purification by flash chromatography (silica, 50 % EtOAc/hex) afforded 2:1 mixture of α- and β-anomers **323** (2.12 g, quant.) as a colorless oil. R_f (30 % EtOAc/hex) = 0.29. ¹H NMR (400 MHz, CDCl₃) δ 6.23 (d, 1H, *J* = 3.6 Hz), 5.70 (d, 1H, *J* = 6.8 Hz), 5.44 (t, 1H, *J* = 9.9 Hz, 9.7 Hz), 5.18 (t, 1H, *J* = 8.4 Hz, 8.2 Hz), 5.04-4.92 (m, 2 x 2H), 4.12 (dd, 1H, *J* = 12.0 Hz, 5.0 Hz), 3.91 (dd, 1H, *J* = 11.1 Hz, 6.0 Hz), 3.69 (t, 1H, *J* = 11.1 Hz, 10.9 Hz), 3.50 (dd, 1H, *J* = 12.0 Hz, 8.4 Hz), 2.15 (s, 3H), 2.08 (s, 3H), 2.03, 2.02, 2.00 (s, 2 x 9H). ¹³C NMR (100 MHz, CDCl₃) δ 170.0, 169.7, 169.6, 169.2, 168.9, 92.0, 89.1, 70.9, 69.5, 69.3, 68.6, 68.3, 62.7, 60.6, 20.8, 20.7, 20.6, 20.5, 20.4.

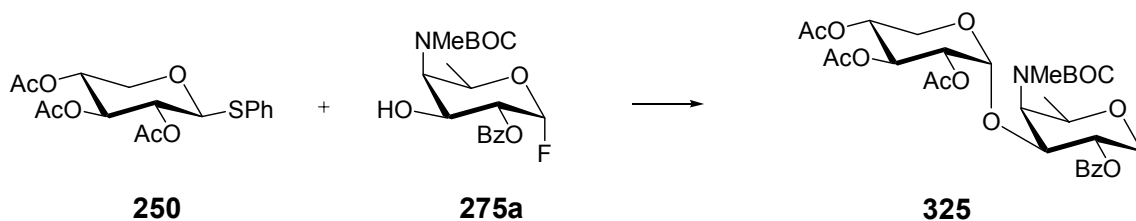
5.31. Phenyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-xylopyranoside **250**



To a solution of tetra-*O*-acetyl-D-xylopyranose **323** (504 mg, 1.58 mmol, 100 mol-%) in dry CH₂Cl₂ (2 mL) were added thiophenol (0.19 mL, 1.90 mmol, 120 mol-%) and BF₃·OEt₂ (0.60 mL, 4.75 mmol, 300 mol-%) at 0 °C under argon. The solution was stirred at rt for 2 h and then diluted with CH₂Cl₂ (2 mL). The resulting solution was washed successively with saturated NaHCO₃ (2 x 6 mL) and water (2 x 4 mL), dried over Na₂SO₄ and concentrated. Purification by flash chromatography (silica, 10 % EtOAc/hex) afforded the β-anomer **250** (370 mg, 63 %) as a white solid. R_f (30 % EtOAc/hex) = 0.40. Mp. 77-

79 °C, lit.³ mp. 77.6-77.9 °C. $[\alpha]_D^{20} = -50.2$ ($c = 1.00$, CHCl_3), lit.³ $[\alpha]_D^{20} = -54.9$ ($c = 1.00$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.49-7.45 (m, 2H), 7.32-7.28 (m, 3H), 5.19 (t, 1H, $J = 8.2$ Hz), 4.96-4.89 (m, 2H), 4.82 (d, 1H, $J = 8.4$ Hz), 4.26 (dd, 1H, $J = 11.8$ Hz, 5.0 Hz), 3.43 (dd, 1H, $J = 11.8$ Hz, 8.9 Hz), 2.08 (s, 3H), 2.03 (s, 6H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.5, 169.4, 169.0, 132.4, 132.0, 128.8, 127.9, 85.9, 71.8, 69.6, 68.2, 64.9, 20.5, 20.4.

5.32. 2,3,4-Tri-*O*-acetyl-D-xylopyranosyl-(1→3)-2-*O*-benzoyl-4,6-dideoxy-4-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino- α -D-galactopyranosyl fluoride **325**



The donor **250** (24 mg, 65 μmol , 109 mol-%) and the acceptor **275a** (23 mg, 60 μmol , 100 mol-%) were combined and azeotropically dried with benzene (3 times). CH_2Cl_2 (2 mL) and pulverized 4Å molecular sieves were added and the mixture was stirred under argon at rt for 30 min. After addition of NBS (20 mg, 113 μmol , 188 mol-%) the reaction mixture was stirred at rt for 1.5 h. TLC analysis showed that there was still plenty of unreacted acceptor **275a** left, and a large excess of both donor **250** and NBS was added to the reaction mixture. After addition the stirring was continued for 1 hour, according to TLC the reaction did not seem to proceed. The reaction was stopped by dilution with CH_2Cl_2 , the molecular sieves were filtered off and the filtrate was washed successively with saturated NaHCO_3 and brine. Drying over MgSO_4 and concentration afforded the crude product mixture, which was purified by flash chromatography (silica, 15 % EtOAc/hex) to give a mixture of disaccharide **325** and NBS. The product was separated from NBS by preparative layer chromatography affording tentatively the α -analogue **325** (6.5 mg, 17 %; corrected yield 39 % based on recovered starting material). R_f (30 % EtOAc/hex) = 0.38. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.13-8.05 (m, 2H), 7.61-7.57 (m, 1H), 7.48-7.44 (m, 2H), 5.80 (5.85) (dd, 1H, $J = 53$ Hz, 3.0 Hz), 5.78 (d, 1H, $J = 4.8$ Hz), 5.53 (ddd, 1H, $J = 24$ Hz,

11.2 Hz, 3.0 Hz), 5.12-5.10 (m, 1H), 4.84 (dd, 1H, $J = 6.2$ Hz, 3.3 Hz), 4.81-4.75 (m, 1H), 4.53 (dd, 1H, $J = 11.2$ Hz, 6.2 Hz), 4.49-4.42 (m, 1H), 4.19 (ddd, 1H, $J = 4.7$ Hz, 2.9 Hz, 1.0 Hz), 4.15-4.09 (m, 1H), 3.92 (dd, 1H, $J = 11.9$ Hz, 6.6 Hz), 3.46 (dd, 1H, $J = 11.9$ Hz, 8.4 Hz) 3.12 (3.14) (s, 3H), 2.04 (s, 6H), 1.99 (s, 3H), 1.46 (1.49) (s, 9H), 1.25 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (100 MHz, CDCl_3) (main rotamer) δ 169.8, 168.8, 165.7, 157.2, 133.6, 129.8, 129.2, 128.6, 105.0 ($J_{\text{CF}} = 226$ Hz), 96.9, 79.8, 73.4, 68.9, 68.5, 67.9, 67.7, 67.2, 59.0, 56.7, 33.6, 28.3, 22.3, 20.7, 15.9. HRMS: m/z calcd for $\text{C}_{30}\text{H}_{40}\text{FNO}_{13}$ ($\text{M}+\text{Na}$) $^+$ 664.2381, found 664.2369.

5.33. Attempts for disaccharide **324b**

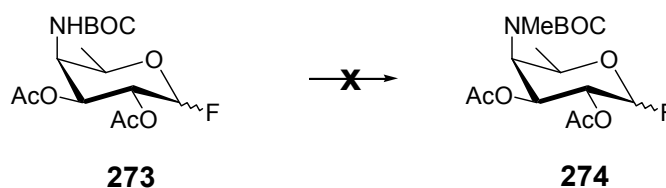
5.33.1. NIS/TfOH-method

The donor **250** (23 mg, 63 μmol , 120 mol-%) and the acceptor **275b** (20 mg, 52 μmol , 100 mol-%) were combined and stirred in CH_2Cl_2 (2 mL) with 4Å molecular sieves under argon at rt for 1 h. The reaction mixture was cooled to -40°C and NIS (18 mg, 78 μmol , 150 mol-%) and TfOH (52 μmol , 100 mol-%, 1.0 M solution in CH_2Cl_2) were added. After stirring the reaction mixture at cold for 1 h, normal aqueous work-up was performed for the crude product mixture. No disaccharide **324b** was obtained.

5.33.2. NBS/TMSOTf-method

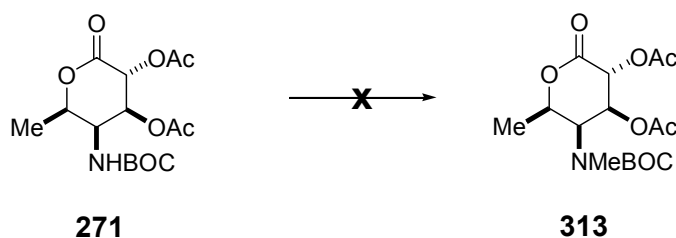
The donor **250** (34 mg, 92 μmol , 180 mol-%) and the acceptor **275b** (20 mg, 52 μmol , 100 mol-%) were combined and stirred in CH_2Cl_2 (2 mL) with 4Å molecular sieves under argon at rt for 1 h. NBS (23 mg, 130 μmol , 23 mol-%) and TMSOTf (104 μmol , 20 mol-%, 0.1 M solution in CH_2Cl_2) were added to the reaction, and the mixture was stirred at rt for 3 h. The reaction was stopped although not all the starting material had been consumed, and aqueous work-up for the crude mixture was performed. Unidentified products below the starting materials were isolated.

5.34. Attempted *N*-methylation for **273** by 2,6-di-*tert*-butyl-4-methylpyridine and MeOTf



To a cooled solution (-15 °C, ice-NaCl-bath) of compound **273** (55 mg, 0.16 mmol, 100 mol-%) in CH₂Cl₂ (2.2 mL) was added 2,6-di-*tert*-butyl-4-methylpyridine (34 mg, 0.17 mmol, 105 mol-%) dissolved in CH₂Cl₂ (1 mL). After stirring for 5 min, MeOTf (18 μL, 0.17 mmol, 105 mol-%) was added and the reaction was stirred at rt overnight. The reaction was quenched with 0.5 M H₃PO₄ and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and evaporated. Starting material was recovered unchanged.

5.35. Attempted *N*-methylation for **271** by 2,6-di-*tert*-butyl-4-methylpyridine and MeOTf



See experimental procedure as for compound **273** in 5.34. Starting material was recovered unchanged.

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