UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

The Total Synthesis of (–)-Luminacin D

And

The Synthesis of Tetrafluorinated Heptoses and Octoses

by

Julien Malassis

Thesis for the degree of Doctor of Philosophy

October 2015

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ABSTRACT

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Chemistry

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THE TOTAL SYNTHESIS OF (–)-LUMINACIN D
AND
THE SYNTHESIS OF TETRAFLUORINATED HEPTOSES AND OCTOSES

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Luminacin D belongs to a family of bioactive compounds isolated from the fermentation broth of soil bacteria. This molecule was shown to exhibit potent angiogenesis inhibitory activity in several *in vitro* assays. In addition, *in vivo* assays performed on another Luminacin member with similar structure showed that this molecule operates by an unusual mechanism of action. Hence, the development of a synthesis giving access to sufficient quantity of luminacin D to enable further research is of interest. Recently, our group developed a highly stereoselective synthesis of luminacin D. This involved the introduction of the epoxide moiety at an early stage of the synthesis, and exploiting its stereochemistry for the construction of an adjacent stereocentre, *via* a chelation-controlled allylation reaction. However, while excellent selectivity was achieved for this reaction, inversion of the obtained stereocentre was required. The first part of this thesis describes the efforts undertaken in the development of a second generation synthesis that allows direct access to the desired stereochemistry.

Lipopolysaccharides (LPS) are the main components of the surface of gram negative bacteria and are involved in their resistance. The inner core of LPS is constituted of a certain number of specific carbohydrates, namely Kdo (3-deoxy-D-manno-oct-2-ulosonic) and heptoses (L-*glycero*-D-*manno*-heptose), which play a key role in the bacterial virulence. In this context, we have been interested in the preparation of tetrafluorinated analogues of heptose and Kdo, as potential probes or inhibitors to investigate the LPS biosynthesis pathway. The introduction of hydrophobic perfluoroethylene group into carbohydrate backbone has indeed recently emerged as a strategy to improve the typically low protein-carbohydrate affinity, through the so-called "polar hydrophobicity" effect. The synthesis of tetrafluorinated heptoses and Kdo has been successfully achieved, and will be described in the second part of this thesis.

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DECLARATION OF AUTHORSHIP

I, Julien Malassis

declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

'The Total Synthesis of (–)-Luminacin D and the Synthesis of Tetrafluorinated Heptoses and Octoses'

I confirm that:

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3. Where I have consulted the published work of others, this is always clearly attributed;
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7. None of this work has been published before submission
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Acknowledgements

First of all, I would like to thank Pr. Bruno Linclau, for giving me the opportunity to undertake a PhD under his supervision. I would also like to acknowledge his guidance, support and constant encouragement throughout the last three years.

I would like to thank all the members of the Linclau group I had the chance to meet over these years. This includes, in no particular order Carole, Clément, Sam, Craig, Nathan, Lewis, Leona, Stéphanie, Guillaume, Florent, Lucas, Gert-Jan aka Jean-Jacques, Gemma, Jo, Bobby, Kane, and all the people I forgot to mention here. Thank you guys for making the lab a friendly place to work, and for all the memorable times spent together, inside and outside the lab.

I am also grateful to all the people from the chemistry building, for being always helpful in providing chemicals, equipments and assistance when needed. Special thanks go to Thomas, who was almost like my wife over these three years. I would also like to thank Shamim, Ayham, Marc, Victor and Alexandre for always being nice and friendly over these years.

I don't forget all the University staff, in particular Neil for performing the numerous NMR analyses I requested, John and Julie for running all the MS analyses, Mark Light for providing the X-ray structures, and also Karl, Keith and Mark for running the chemical store so well and for always being nice. I also would like to thank Sally for all the administrative help she provided throughout these years.

I am very grateful to the INTERREG programme for the funding of this work, and I would also like to thank all the people in France and UK involved in the project, and especially Karin and Robin from the University of Southampton.

Lastly, I would like to thank my family for being constantly supportive during all my studies. I would also like to thank my friends, outside and inside chemistry, who also helped making these years way more bearable. I would finally like to thank Agnès, who is currently squatting my flat, for the enormous support she provided during all these years, and much more.

Definitions and Abbreviations

ADP	adenosine diphosphate
AMAP-1	AMY-1-binding protein 1
aq.	aqueous
ar	anomeric ratio
Ar	aryl
ax.	axial
Bn	benzyl
CMP	cytidine monophosphate
COSY	correlation spectroscopy
CTP	cytidine triphosphate
d.r	diastereomeric ratio
DCM	dichloromethane
DCE	dichloroethane
DIPEA	di*iso*propylethylamine
DIBAL-(H)	di*iso*butylaluminium hydride
DMP	dess-Martin Periodinane
DMF	dimethylformamide
e.r.	enantiomeric ratio
eq.	equatorial
equiv.	equivalent
-f	furanose
FAD	flavin adenine dinucleotide
HldD	gene encoding for ADP-L-glycero-D-manno-heptose-6-epimerase
HMBC	heteronuclear multiple bond correlation
J	coupling constant
Kdo	3-deoxy-D-*manno*-oct-2-ulosonic acid
LDA	lithium di*iso*propyl amide
LPS	lipopolysaccharide
Lum D	luminacin D
m-CPBA	*meta*-chloroperbenzoic acid
Mer-VD1207	designated bacterial strain number
MOM	methoxymethylene
MS	mass spectrometry
MsCl	methanesulfonyl chloride

NAP	2-naphtylmethyl
NADP	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromo succinimide
NMR	nuclear magnetic resonance
NMO	*N*-methymorpholine *N*-oxide
nOe	nuclear Overhauser effect
Nu	nucleophile
OMe	methoxy
-p	pyranose
Ph	phenyl
PPTS	pyridinium *para*-toluenesulfonate
PTSA	*para*-toluene sulfonic acid
rt	room temperature
sp.	species
Src	sarcoma
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TCCA	trichloroisocyanuric Acid
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TMS	trimethylsilyl
TLC	Thin Layer Chromatography
UDP	uridine diphosphate
UGM	UDP-galactopyranose mutase
WaaC	gene encoding for LPS heptosyl transferase I

Chapter 1: Luminacin D: Introduction

1.1 Angiogenesis

Angiogenesis refers to the formation of new blood vessels from the pre-existing vascular network.[1] In mammals, the process is of fundamental importance for the foetal development, reproductive system and wound repair. However, unregulated angiogenesis contributes to the development of numerous pathologies. Hence, in the case of arthritis, the over-production of capillary blood vessels induced by uncontrolled angiogenesis leads to joint inflammation and can damage cartilage.[2] The abnormal proliferation of blood vessels in the retina, or ocular neovascularisation is associated to the development of several ocular diseases, including proliferative diabetic retinopathy, age-related macular degenerative and retinopathy of prematurity.[3] In cancer, angiogenesis is known to play a crucial role in the tumor development and metastasis.[2,4] The growth process is indeed related to the ability of the tumor to stimulate the production of capillary blood vessels. In addition, these novel blood vessels constitute the principal route by which cancer cells can exit the primary tumor and propagate in the body through the blood circulation. In this context, targeting key mechanisms involved in the angiogenesis regulation has emerged as an effective strategy for the treatment of associated diseases.[5]

1.2 Luminacins

1.2.1 Overview

The luminacins are natural products originally isolated from the fermentation broth of the soil bacterial strain *Streptomyces sp.* Mer-VD1207.[6] As depicted in Figure 1-1, the 14 members of the luminacin family share common structural features, including a polysubstituted aromatic ring connected to a highly oxygenated fragment.

Numerous luminacin members have shown to exhibit potent anti-angiogenic activities in several *in vitro* assays. Wakabayashi *et* al. showed that luminacins operate by blocking the initial stages of the capillary tube formation, with luminacin D being the most active among the 12 members tested.[6] Later on, additional *in vivo* studies using luminacin C2 revealed that this molecule effectively inhibited the phosphorylation activity of Src

tyrosine kinases, and was found to exert its unique mode of action by disrupting Src mediated protein-protein interactions.[7,8] Src tyrosine kinases play key roles in the regulation of numerous processes associated to angiogenesis, including growth, differentiation, migration and survival.[9] In addition, luminacin C2 was also found to inhibit breast cancer cell invasion and metastasis *in vitro* by disrupting the AMAP1-cortactin binding (protein-protein interactions).[10] The recent isolation of two cancer cell migration inhibitors of similar structure (migracins A and B, Figure 1-1), highlighted once more the therapeutic potential of these molecules.[11]

Despite its promising anti-angiogenesis activity revealed by the original work of Wakabayashi, luminacin D was less extensively studied in comparison with some other members of its family, and little information can be found regarding its mode of action and biological functions. Given the poor yield obtained from bacterial fermentation, the development of an efficient chemical synthesis is required to enable further biological investigations. This has not been achieved so far, despite numerous efforts towards this goal.

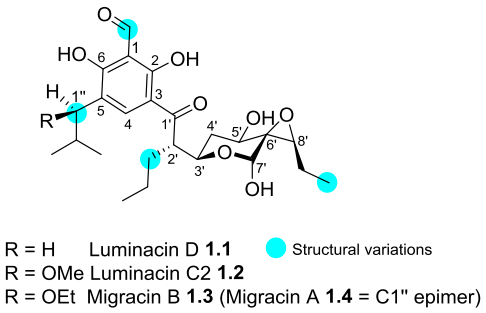


Figure 1-1: Structures of luminacins

1.3 Previous syntheses of luminacin derivatives

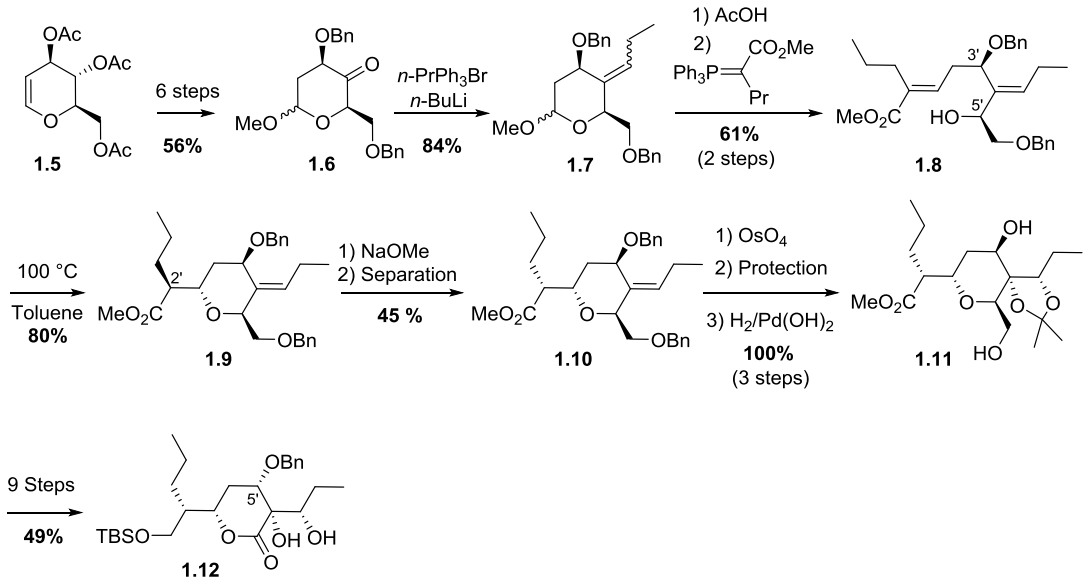
Several syntheses of luminacins C1, and C2 and D have been already reported in the literature. In general, the strategy of synthesis involves the construction of the aromatic and aliphatic fragments separately, before joining them *via* a coupling reaction. In this chapter the different strategies applied for the synthesis of the luminacin derivatives will be described.

1.3.1 The synthesis of unnatural luminacins C1 and C2 (Tatsuta, 2001)

The first total synthesis of a luminacin derivative was achieved in 2001 by Tatsuta and co-workers.[12] Although the reported route was lengthy (43 total steps, resulting in 0.35 % overall yield), it enabled assignment of the luminacin absolute configuration.

1.3.1.1 Aliphatic fragment

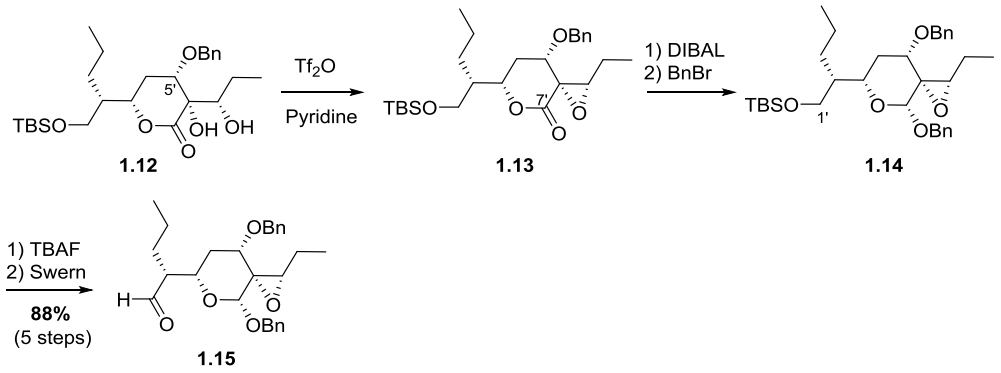
As depicted in Scheme 1-1, the synthesis of the aliphatic fragment started from the enantiopure D-glucal **1.5**, which was converted to the ketone **1.6** in 6 steps. A Wittig reaction afforded the alkene **1.7**, and subsequent anomeric deprotection allowed a second Wittig olefination to give the unsaturated ester **1.8**. The cyclisation of **1.8** *via* an intramolecular Michael addition provided the compound **1.9** with undesired configuration at C2', which was subsequently isomerised using sodium methanolate to give a 1:1 mixture of C2' epimers **1.9** and **1.10**. The desired epimer **1.10** was isolated in 45% yield after column chromatography. The exocyclic alkene was then hydroxylated using OsO_4, leading to compound **1.11** after diol protection and hydrogenolysis. Following this, the formation of the lactone **1.12** was achieved after 9 further transformations, including the inversion of the alcohol at C5'.



Scheme 1-1: Synthesis of the aliphatic fragment

In order to complete the aliphatic fragment synthesis, the diol was effectively converted to the corresponding epoxide **1.13** upon triflation and subsequent displacement with

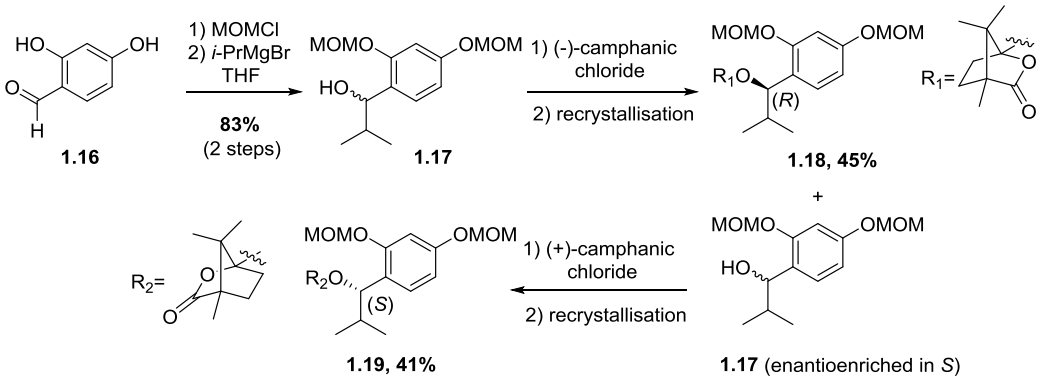
inversion (Scheme 1-2). The lactone was then reduced to the corresponding hemiacetal using DIBAL, to give the compound **1.14** after its benzylation. Finally, TBAF mediated TBS cleavage followed by Swern oxidation of the resulting alcohol afforded the aliphatic fragment **1.15** in good overall yield.



Scheme 1-2: Completion of the aliphatic fragment

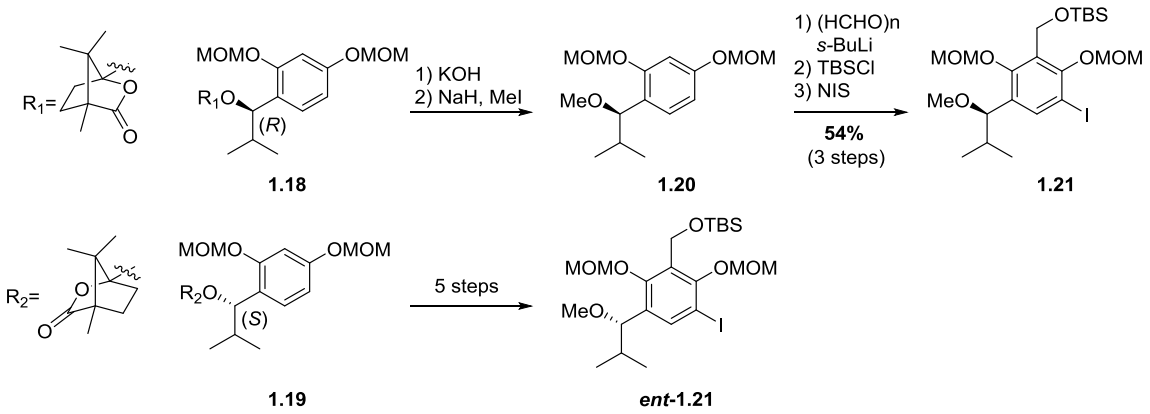
1.3.1.2 Aromatic fragment

The synthesis of the aromatic fragment was achieved starting from the commercially available β-resorcinol aldehyde **1.16** (Scheme 1-3). At first, the protection of the phenolic groups followed by Grignard addition provided the alcohol **1.17** as a racemic mixture. From **1.17**, a kinetic resolution was successfully achieved *via* esterification using (–)-camphanic chloride, which enabled isolation of the enantiopure (*R*)-isomer **1.18** in 45% after recrystallisation. The remaining starting material **1.17** enriched in (*S*)-isomer was then treated with the (+)-camphanic chloride, giving the pure (S)-isomer **1.19** in 41% after recrystallisation.



Scheme 1-3: Kinetic resolution

At this stage, the enantiopure **1.18** was hydrolysed and *O*-methylated to give the intermediate **1.20** (Scheme 1-4). The latter was then subjected to hydroxymethylation, alcohol protection, and finally iodination to give the aromatic fragment **1.21** possessing the suitable C1'' configuration for the synthesis of (+)-luminacin C1. The same synthetic pathway was applied on compound **1.19** and enabled the formation of the aromatic derivative ***ent*-1.21** for the synthesis of (–)-luminacin C2.

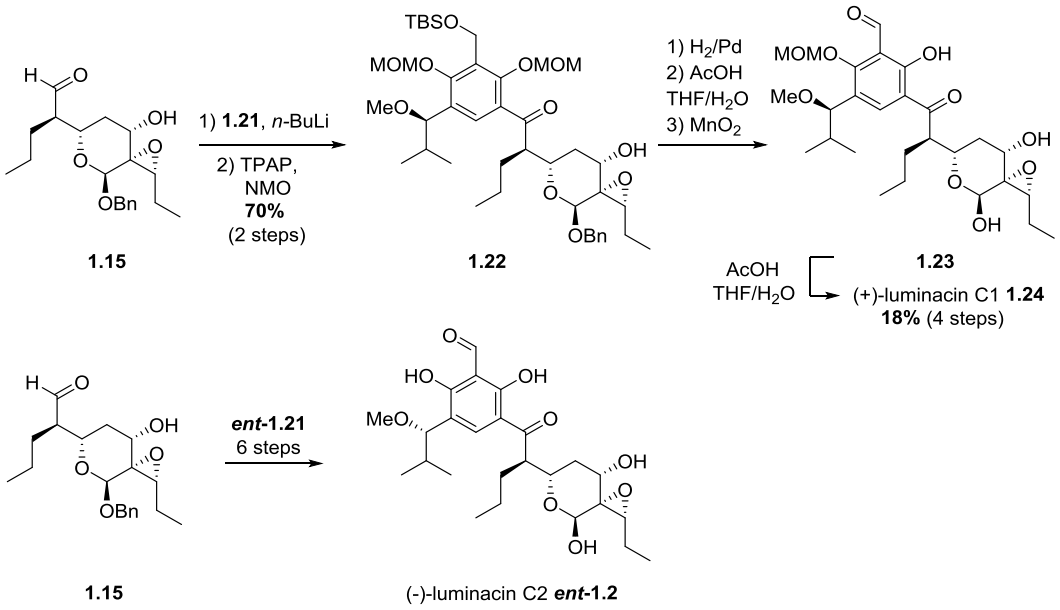


Scheme 1-4: Completion of the aromatic fragment

1.3.1.3 Completion of the synthesis

The iodo-arene **1.21** was treated with *n*-BuLi to generate the corresponding aryllithium intermediate, which was added to the aldehyde fragment **1.15** to yield the corresponding ketone **1.22** after oxidation step. Subsequent hydrogenolysis, acidic treatment and benzylic oxidation led to the partly deprotected intermediate **1.23**, which, upon final MOM hydrolysis, afforded (+)-luminacin C1 **1.24**. The same synthetic pathway was applied to the aromatic intermediate ***ent*-1.21**, leading to the formation of (–)-luminacin C2 ***ent*-1.2**.

Even though the natural luminacins C1 and C2 could be accessible by the same route starting from the corresponding L-glucal ***ent*-1.5**, the number of steps required for the formation of the final product made the synthesis unattractive. In particular, the required inversion of configuration at C2' and at C5' is one of the main drawback of this synthesis.



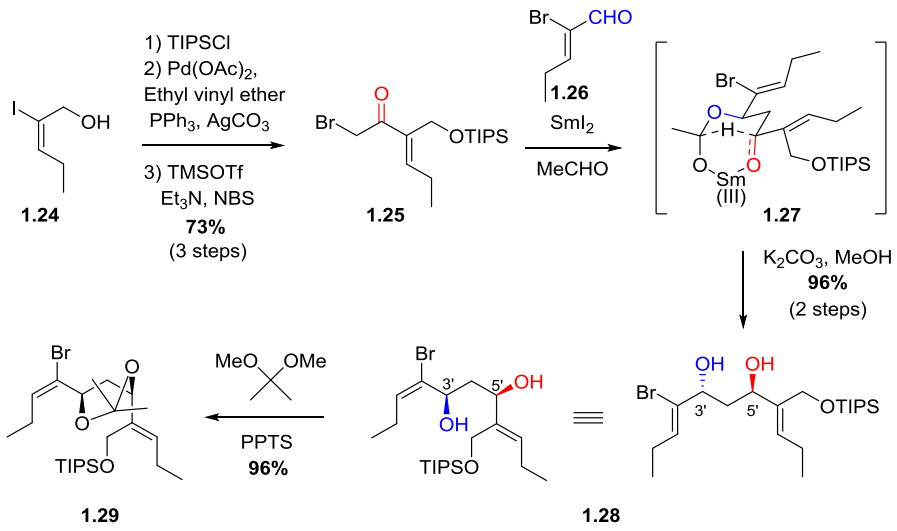
Scheme 1-5: Completion of the synthesis of unnatural luminacins C1 and C2

1.3.2 The racemic synthesis of luminacin D (Wood, 2002)

The following year, Wood and co-worker published a diastereoselective synthesis of (±)-luminacin D.[13] The synthesis is concise, proceeding in 13 linear steps (19 steps total) and good overall yield (5.3 %), although this route only allows access to the racemic product.

1.3.2.1 Aliphatic fragment

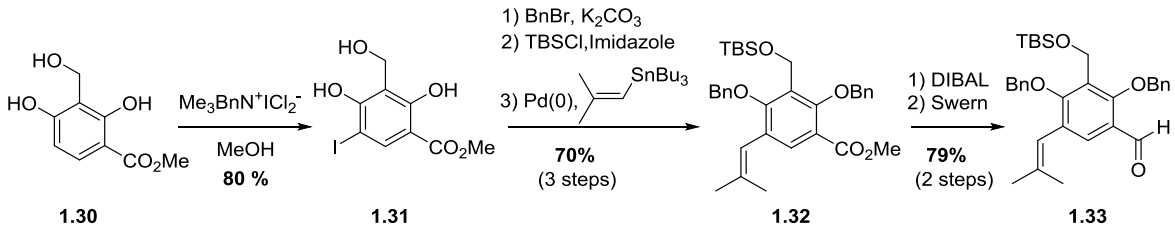
The synthesis of the aliphatic fragment started from the known vinyl iodide **1.24**, which was converted to the α-bromoketone **1.25** in 3 steps *via* protection, Heck type acylation reaction and α-bromination (Scheme 1-6). Following this, a SmI_2-mediated tandem Evans aldol/Tishchenko reaction was used as key step to give, after basic treatment, the 1,3-*anti* diol **1.28** as a single diastereoisomer. The reaction is thought to proceed through an 8-membered ring transition state **1.27**, with intramolecular hydride delivery explaining the diastereoselectivity observed. The diol **1.28** was then protected as the acetal **1.29**, to be used later on as substrate for the coupling reaction.



Scheme 1-6: Aliphatic Synthesis

1.3.2.2 Aromatic fragment

The synthesis of the aromatic fragment began with the electrophilic iodination of the known derivative **1.30**, leading to compound **1.31** in good yield (Scheme 1-7). The latter was then protected in two steps prior to Stille cross-coupling with (tributyl)-*iso*-butenylstannane, affording the intermediate **1.32**. The aromatic fragment **1.33** was finally obtained after DIBAL reduction followed by Swern oxidation.

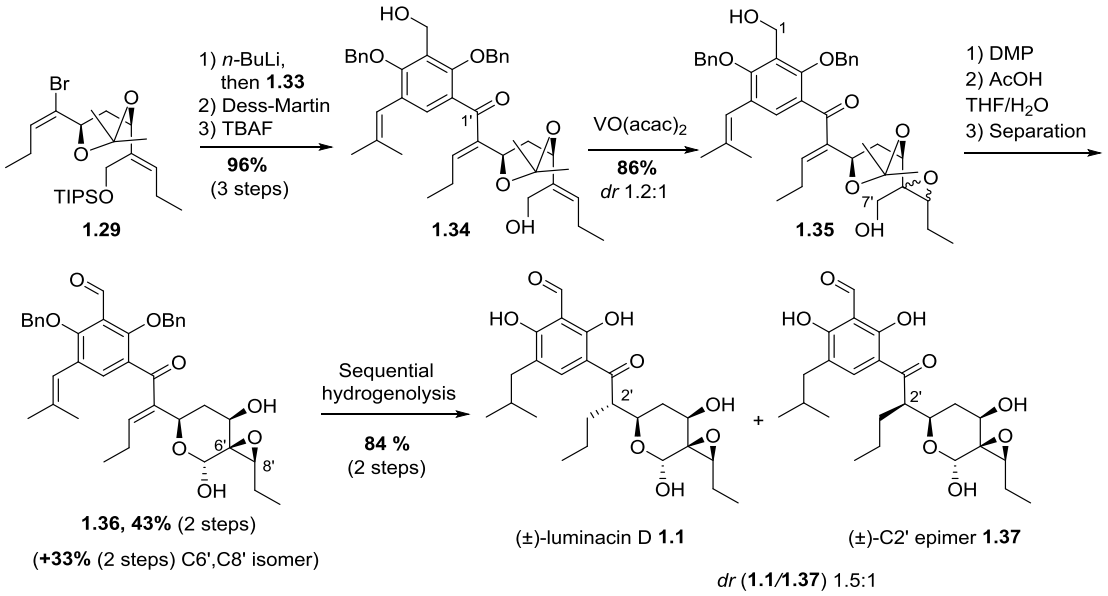


Scheme 1-7: Aromatic synthesis

1.3.2.3 Completion of the synthesis

After coupling of the aromatic and aliphatic fragments, the resulting intermediate **1.34** was obtained through oxidation at C1' and TBAF treatment (Scheme 1-8). The subsequent epoxidation using vanadyl acetylacetonate proved to be poorly selective, resulting only in a *dr* of 1.2:1 in favour of the desired isomer **1.35**. The synthesis was however pursued with the isomer mixture. Subsequent oxidation at C1 and C7', followed by acetal deprotection, led to the formation of the intermediate **1.36**, which could be separated at this stage from the C6',C8' epoxide isomer. Finally, two consecutive hydrogenation

reactions enabled benzylic deprodection and alkene reduction, yielding the (±)-luminacin D **1.1** and its C2' epimer **1.37** in 84%. Both isomers could be separated by preparative TLC (isolated yields not mentioned).



Scheme 1-8: Completion of the synthesis

Although this synthesis is quite straightforward, the poor selectivity encountered during the epoxidation and C2'-hydrogenation significantly reduces its efficiency. In addition, it can be noted that the overall yield (5.3 %) given by the authors not only includes the yield of the (±)-luminacin D **1.1**, but also the cumulated yields of the C6',C8' epoxide isomer and the C2' isomer **1.37**.

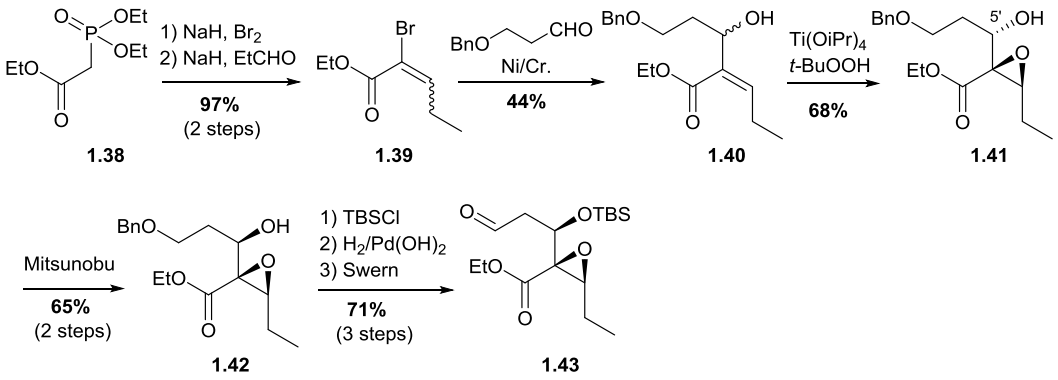
1.3.3 Alternative racemic synthesis of luminacin D (Fang, 2003)

In 2003, the Official Gazette for Patents (uspto) published a patent from the Eisai company, in which an alternative synthesis of the racemic luminacin D is described.[14]

1.3.3.1 Aliphatic synthesis

As described in Scheme 1-9, the synthesis started by α-bromination of the sulfonate **1.38**, which then reacted with propionaldehyde in the presence of a base to give the vinyl bromide **1.39** *via* a HWE reaction. Subsequent Ni/Cr-mediated coupling reaction provided the racemic allyl alcohol **1.40**, which was subjected to epoxidation to afford the *anti*-α-epoxy alcohol **1.41**, corresponding to the undesired diastereoisomer. Inversion of the

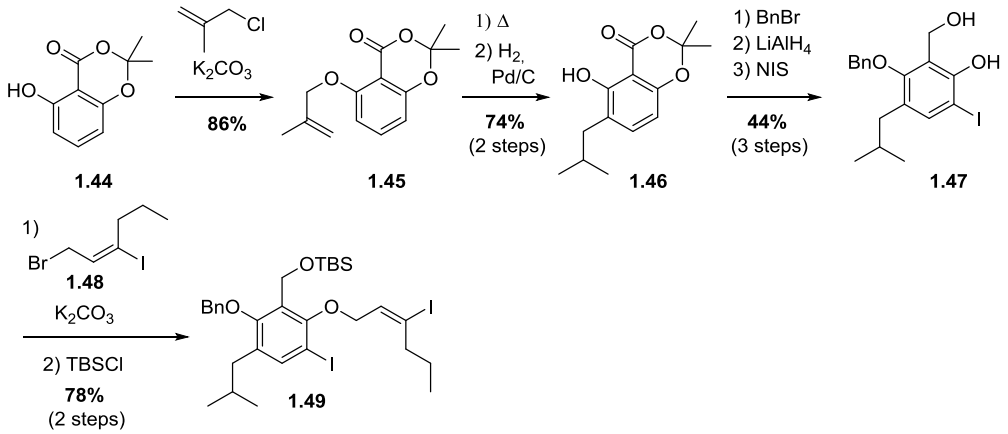
alcohol at C5' was achieved through a Mitsunobu/deprotection process, and the resulting compound **1.42** was converted to the protected aldehyde **1.43** in 3 steps.



Scheme 1-9: Synthesis of aliphatic fragment

1.3.3.2 Aromatic fragment

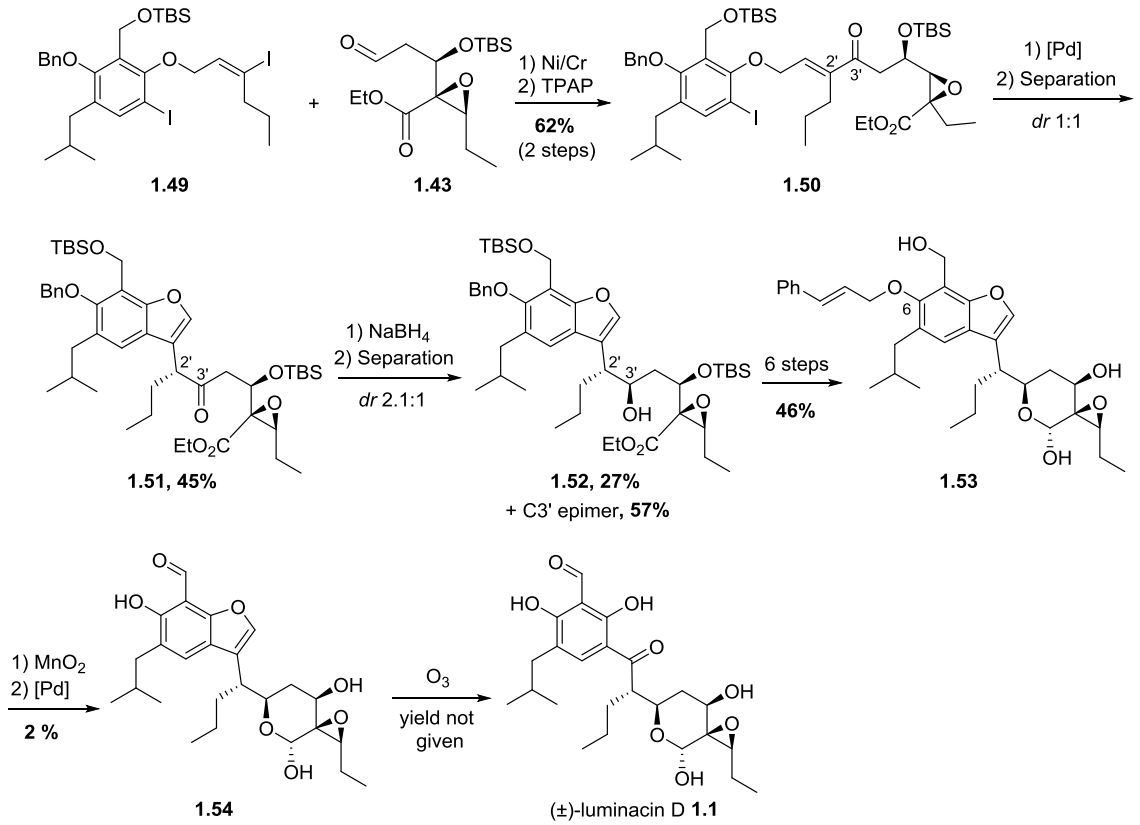
The synthesis of the fragment **1.49** was achieved in 8 steps starting from the known compound **1.44** (Scheme 1-10). In a first step, alkylation of the free phenolic alcohol with methallyl chloride led to **1.45**. The latter rearranged at high temperature to give, upon alkene reduction, the isobutyl derivative **1.46**. Compound **1.46** was then successively subjected to benzylation, reduction and electrophilic iodination, leading to the formation of **1.47**. Final *O*-alkylation using the alkyl bromide **1.48**, followed by TBS protection provided the aromatic derivative **1.49**.



Scheme 1-10: Synthesis of the aromatic fragment

1.3.3.3 Final coupling reactions and completion of the synthesis

A second Ni/Cr-mediated coupling reaction involving the vinyl iodide **1.49** and the aldehyde **1.43** (Scheme 1-11) led to the formation of an allylic alcohol, which was oxidised in the next step to give the corresponding unsaturated ketone **1.50**. The latter underwent an intramolecular Heck reaction, giving the benzofuran derivative as a mixture of C2' epimers (*dr* 1:1), and the desired diastereoisomer **1.51** was isolated by column chromatography in 45% yield. The subsequent reduction of the ketone at C3' gave once again a mixture of stereoisomers, with the desired compound **1.52** isolated as the minor product (27%, *dr* 2.1:1). The intermediate **1.53** was then obtained from **1.52** in 6 steps. The main transformation of this sequence involved the construction of the hemiacetal *via* a lactonisation/reduction process. It can be noted that the cinnamyl group introduced at C6 is used as protecting group. From **1.53**, the benzylic alcohol was then oxidised using MnO_2, and the cinnamyl group was subsequently removed via a Tsuji-Trost reaction to yield the aldehyde **1.54** in extremely low yield (2% over 2 steps). Finally, oxidative cleavage of the furan enabled the formation of (±)-luminacin D **1.1** (procedure described on less than 1 mg scale).



Scheme 1-11: Completion of the synthesis

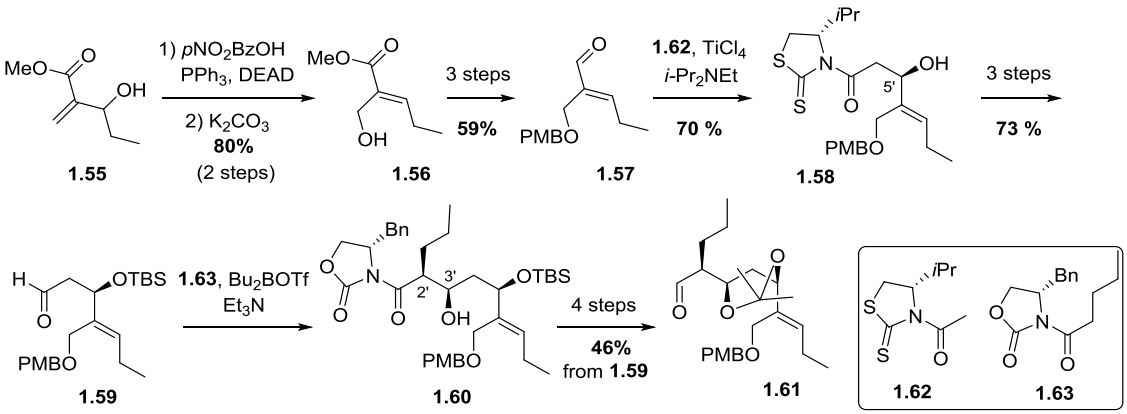
In general, the efficiency of the synthesis is affected by numerous diastereoselectivity issues, and one very low yielding sequence. Nevertheless, one interesting feature of this synthesis is the early-stage epoxidation of the allylic alcohol, which proceeded in good selectivity, although a Mitsunobu reaction was required for the continuation of the synthesis.

1.3.4 The enantioselective synthesis of luminacin D (Maier, 2006)

In 2006, Maier and coworkers reported the first enantioselective synthesis of (–)-luminacin D. The strategy involved the construction of the aliphatic fragment *via* successive aldol reactions, as well as the late stage introduction of the spiro epoxide. The synthesis of the final product was accomplished in 20 linear steps, for an overall yield of 2.1%.[15]

1.3.4.1 Aliphatic fragment

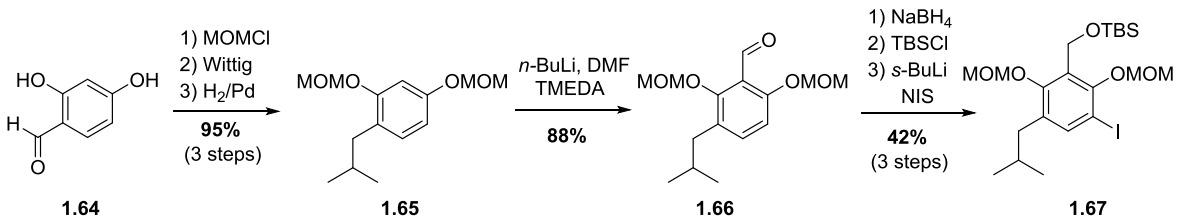
The aliphatic fragment synthesis was achieved in 14 steps from the known Bayliss-Hillman product **1.55**. At first, a Mitsunobu/deprotection process led to the formation of the intermediate **1.56** *via* a S_N2' mechanism (Scheme 1-12). This compound was converted in 3 steps to the corresponding aldehyde **1.57**, which was subsequently engaged in $TiCl_4$-mediated Nagao aldol reaction with the thiazolidinethione **1.62**, leading to the adduct **1.58**. After protection of the secondary alcohol, the chiral auxiliary was removed by reduction, and the resulting alcohol was oxidised to the aldehyde **1.59**. The subsequent Evans-aldol reaction with **1.63** enabled the formation of the *syn* C2',C3' product **1.60**, which finally gave the fragment **1.61** after 4 steps.



Scheme 1-12: Aliphatic synthesis

1.3.4.2 Aromatic fragment

The synthesis of the aromatic fragment started from the resorcinol derivative **1.64**, which was protected in the first step using MOMCl. The resulting product was successively subjected to Wittig reaction and hydrogenation, leading to the intermediate **1.65** (Scheme 1-13). The subsequent formylation using DMF and *n*-BuLi proceeded in excellent yield to the corresponding aldehyde **1.66**. The latter was reduced to the alcohol, protected and subjected to iodination to yield the aromatic fragment **1.67**.



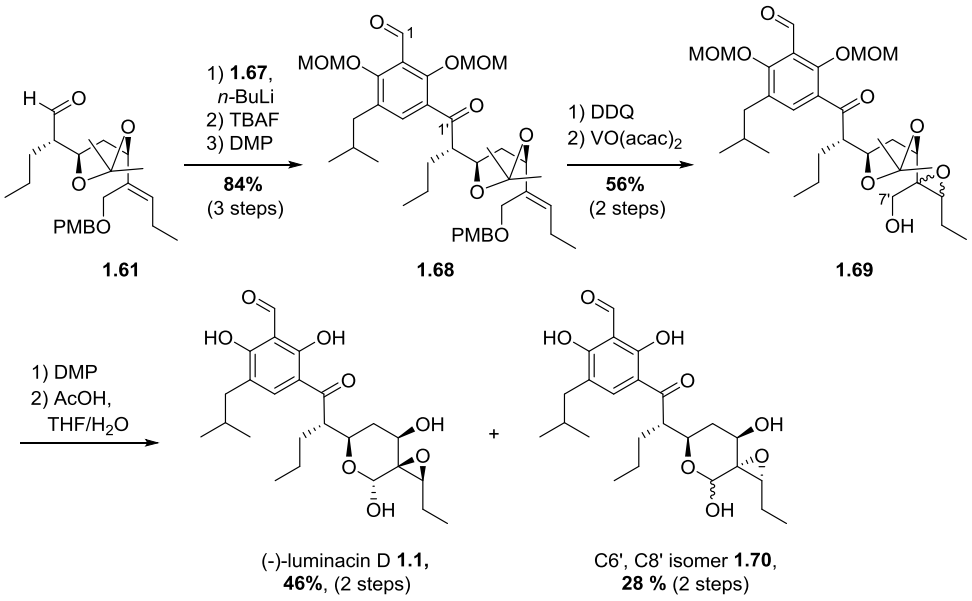
Wittig : $Me_2CHPPh_3^+I^-$, *n*-BuLi

Scheme 1-13: Aromatic synthesis

1.3.4.3 Completion of the synthesis

As depicted in Scheme 1-14, the combination of both fragments was achieved by conventional arylation of the aldehyde **1.61** using the aryl iodide **1.67**. The resulting product was desilylated at C1, which enabled the benzylic oxidation at both C1 and C1' to form the intermediate **1.68** in good yield. The latter was then treated with DDQ to remove the PMB group, and the resulting allylic alcohol was subjected to epoxidation using $VO(acac)_2$, giving the intermediate **1.69** in low diastereoselectivity. Finally, oxidation at C7' and subsequent acetal deprotection furnished the final compound **1.1**, alongside with its epoxide isomer **1.70**, which were separated by column chromatography.

Although the authors stated that the luminacin D was successfully synthesised, the reported ^{1}H and ^{13}C NMR data of the final product showed however some significant differences with the data reported by Wakabayashi on the natural product. Nevertheless, in relation with the synthesis of Wood and co-workers, it can be noted that this synthesis also suffers from selectivity issues regarding the epoxidation step.



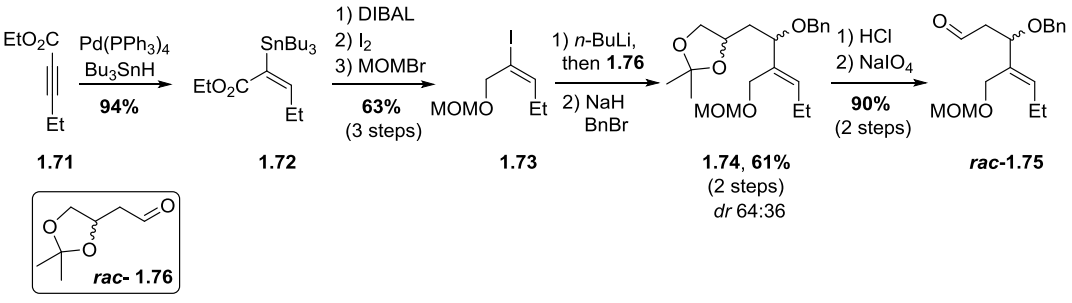
Scheme 1-14: Completion of the synthesis

1.3.5 Other racemic synthesis of luminacin D (Shipman, 2007)

In 2006, a new attempted synthesis of luminacin D was reported by Shipman and co-workers in 16 linear steps, for an overall yield of 0.64%.

1.3.5.1 Aliphatic fragment

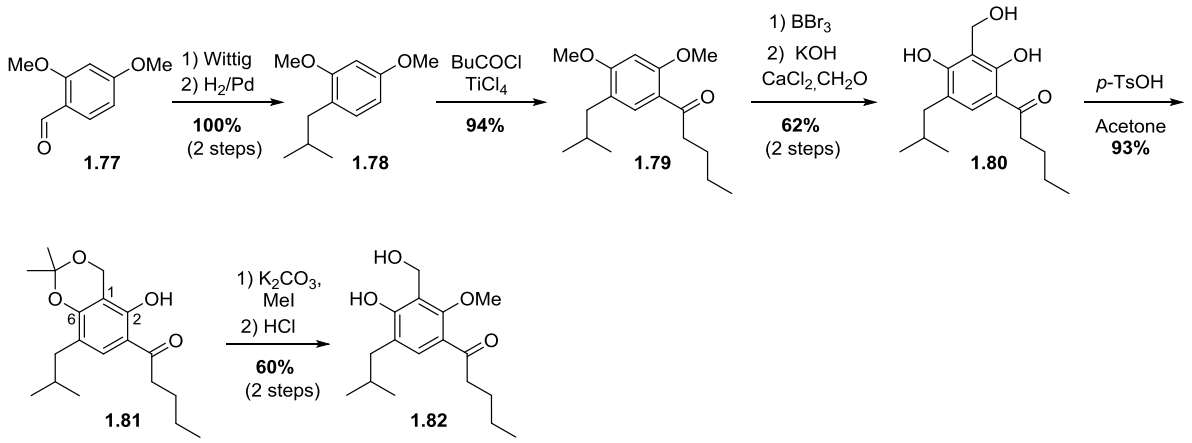
As shown in Scheme 1-15, the aliphatic fragment synthesis started with the hydrostannylation of the alkyne **1.71**, which proceeded in excellent yield and selectivity for the (*E*)-Alkene **1.72**. The latter was then subjected to sequential reduction, iodination and MOM protection to afford the intermediate **1.73**. Subsequent lithiation of **1.73**, followed by addition of the aldehyde **1.76** provided the coupling product **1.74** after a benzylation step. Hydrolysis of the acetal followed by oxidative cleavage of the diol using sodium periodate furnished the aldehyde **1.75** as a racemic mixture.



Scheme 1-15: Aromatic synthesis

1.3.5.2 Aromatic fragment

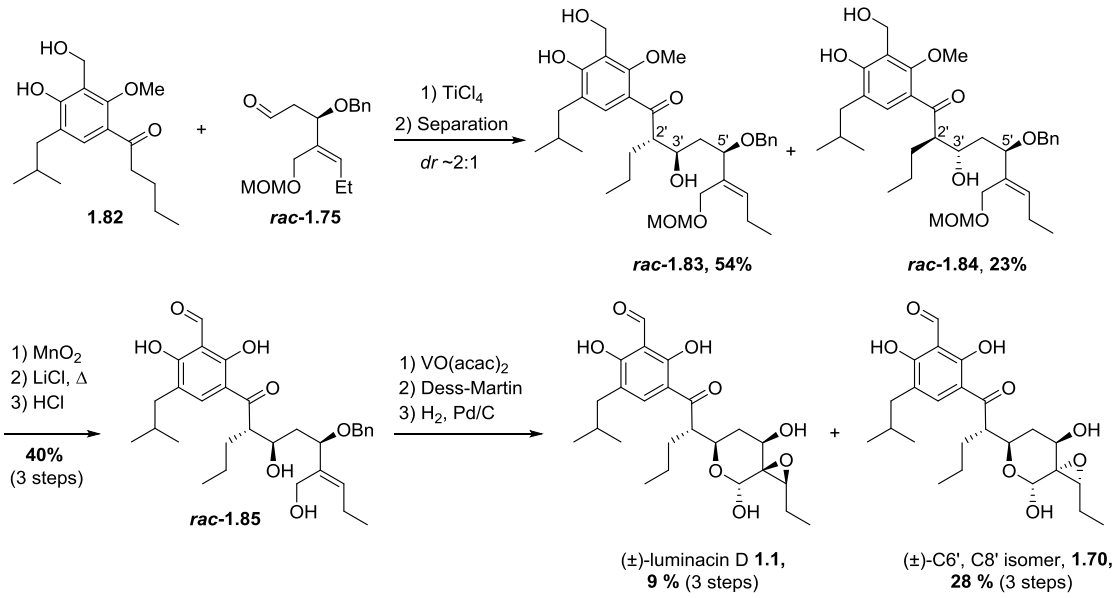
As described in Scheme 1-16, the synthesis of the aromatic fragment was achieved in 8 steps from the resorcinol derivative **1.77**.[16] At first, the 4-isobutyl resorcinol **1.78** was obtained in 2 steps according to a similar procedure as used by Maier. Then, Friedel-Craft acylation using valeroyl chloride led to the formation of the compound **1.79**, which was subsequently deprotected with BBr_3 prior to hydroxymethylation reaction, affording compound **1.80**. Selective acetal formation at C1 and C6 enabled *O*-methylation at C2, to give the final compound **1.82** after subsequent acidic treatment.



Scheme 1-16: Synthesis of the aromatic fragment

1.3.5.3 Aldol condensation and final steps of the synthesis

With access to compound **1.75** and **1.82**, a $TiCl_4$-mediated aldol reaction was carried out, which enabled the formation of the desired 2',3'-*syn*-3',5'-*anti* **1.83** in moderate diastereoslectivity (*dr* ~2:1). The C5' epimer **1.84** could be isolated by column chromatography. The diasteroisomer **1.83** was then subjected to benzylic oxidation with MnO_2, demethylation of the phenolic alcohol and MOM hydrolysis to afford the intermediate **1.85**. The subsequent allylic epoxidation of **1.85** resulted in the formation of two epoxide isomers (*dr* 3:1), which were not separable at this stage. The synthesis was then completed on the mixture of isomers, and the final products were separated by column chromatography, which enabled assignment of the major product as the undesired (±)-C6',C8' epimer **1.70** (28% over 3 steps), and the minor isomer as the (±)-luminacin D **1.1** (9% over 3 steps). The authors mentioned that other epoxidation reagents (*m*-CPBA, oxone) were tried to resolve the selectivity issues, but none of their attempts proved successful.



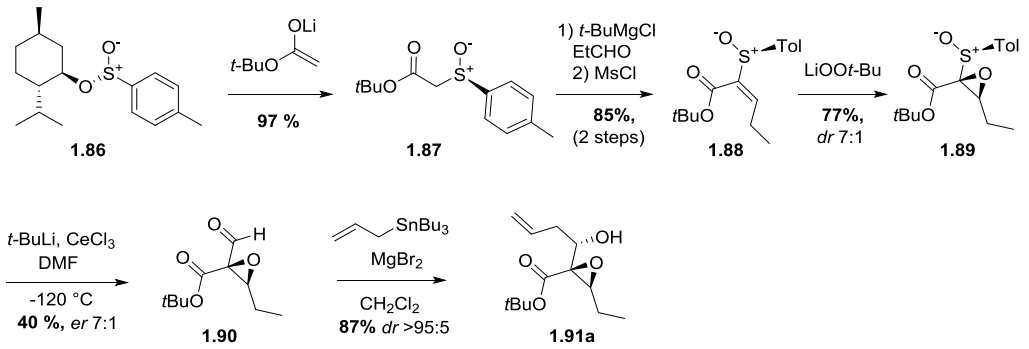
Scheme 1-17: Completion of the synthesis

1.3.6 The most recent synthesis of luminacin D (Linclau, 2014)

Recently, our group reported a highly diastereoselective synthesis of (–)-luminacin D.[17] The synthesis was achieved in 19 linear steps from a commercially available material, in an overall yield of 2.5 %. The strategy involved the diastereoselective introduction of the epoxide moiety at an early stage of the synthesis, and exploited its stereochemistry for the selective construction of the aliphatic fragment.

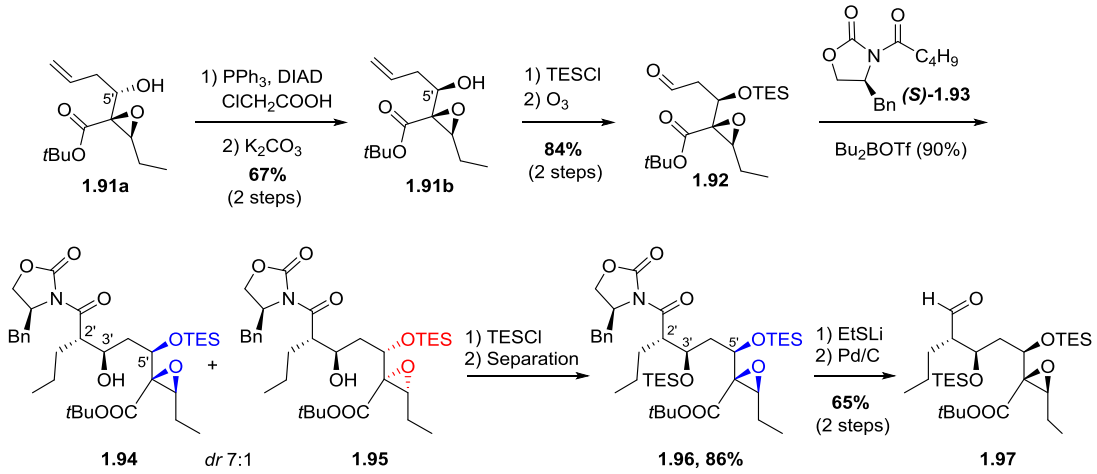
1.3.6.1 Aliphatic fragment

As shown in Scheme 1-18, the synthesis started with the formation of the enantiopure β-sulfoxy ester **1.87**, which was synthesised in one step from the commercially available menthyl sulfinyl ester **1.86**. A two-step Knoevenagel condensation led to the formation of **1.88** as *E*-isomer, which was then subjected to a de la Pradilla type epoxidation[18] to give **1.89** in good yield and diastereoselectivity towards the desired *syn*-product (*dr* 7:1). Following this, the formylation of the oxiranyl ion generated from **1.89** led to the corresponding aldehyde **1.90**, which thus was obtained in a 7:1 enantiomeric ratio. Subsequent allylation afforded the α-epoxy alcohol **1.91a** in excellent yield and diastereoselectivity. The allylation reaction proceeded through a 1,3-chelation controlled transition state, which will be discussed in the following section.



Scheme 1-18: Synthesis of the aromatic fragment (early steps)

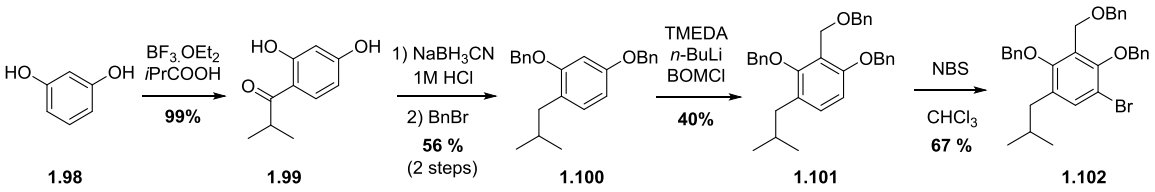
In order to complete the synthesis of the aliphatic fragment, an inversion of configuration at C5' was required, which was achieved *via* a Mitsunobu/deprotection process (Scheme 1-19). Following this, the intermediate **1.91b** was successively protected with TESCl and subjected to ozonolysis to give the aldehyde **1.92** in excellent yield. The latter was subsequently engaged in an Evans-aldol reaction with the chiral oxazolidinone **1.93**, leading to the 2',3'-*syn*-3',5'-*anti* aldol **1.94** as major product in excellent diastereoselectivity. A minor isomer **1.95** was also obtained, resulting from the *syn* Evans-aldol reaction of the oxazolidinone **1.93** with the enantiomer of **1.92**, since an enantioenriched mixture was used (*er* 7:1). After treatment with TESCl, both isomers could be separated by preparative HPLC, and the desired product **1.96** was isolated in 86% yield. Removal of the chiral auxiliary using lithium thioethanolate followed by palladium catalysed reduction of the thioester afforded the aldehyde derivative **1.97** in 65% yield over 2 steps, which will be used as substrate for the coupling reaction with the aromatic fragment.



Scheme 1-19: Completion of the aliphatic fragment

1.3.6.2 Aromatic fragment

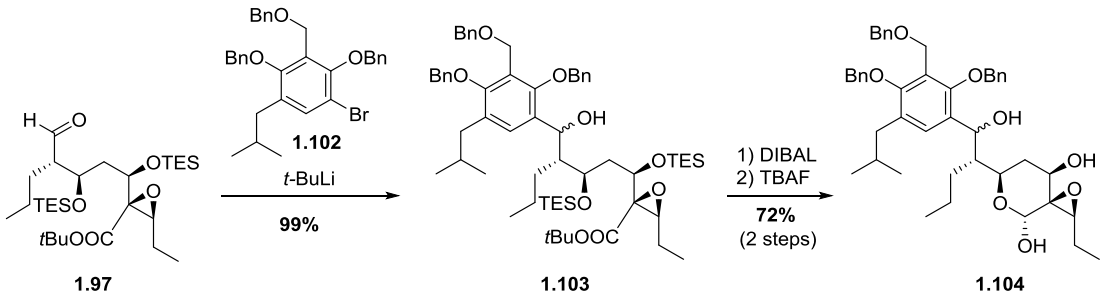
The aromatic fragment was synthesised in 5 steps from the commercially available resorcinol **1.98** (Scheme 1-20). In a first step, Friedel-Craft reaction using isobutyric acid provided the isobutyrophenone **1.99** in quantitative yield. The latter was then reduced to the alkane using sodium cyanoborohydride in acidic medium, to give the intermediate **1.100** after benzyl protection of the phenolic alcohols. The benzyl protected primary alcohol was then introduced in one step through *ortho*-lithiation of the aromatic ring and reaction with BOMCl, leading to compound **1.101** in moderate yield. Finally, **1.101** was brominated to yield compound **1.102**, which was used as substrate for the coupling reaction.



Scheme 1-20: Synthesis of aromatic fragment

1.3.6.3 Completion of the synthesis

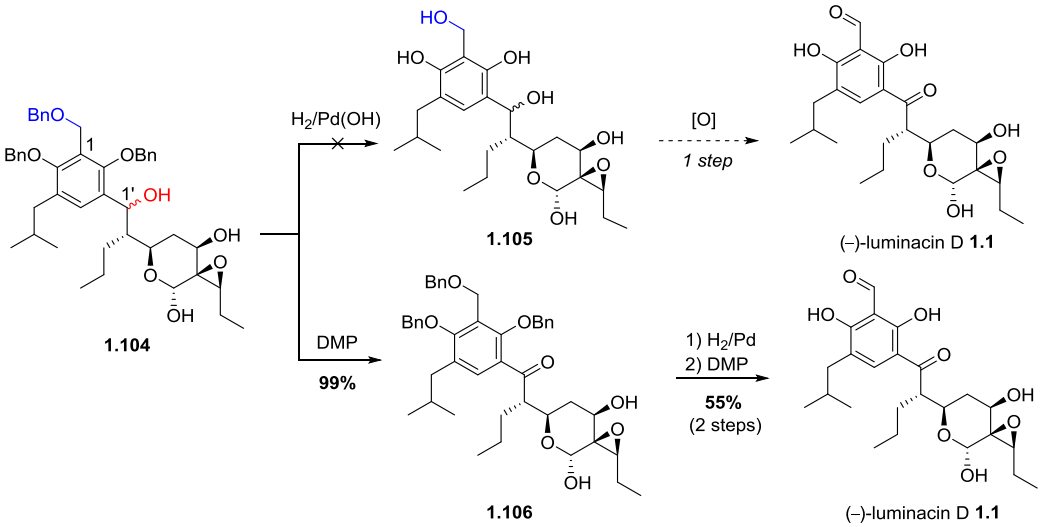
As shown in Scheme 1-21, the combination of the aliphatic and aromatic fragments was achieved *via* lithiation of **1.102** using *t*-BuLi, followed by addition to the aldehyde **1.97**, giving the intermediate **1.103** in almost quantitative yield. The *t*-butyl ester was then converted to the corresponding aldehyde using DIBAL, and the subsequent silyl cleavage/ring closure was performed with TBAF to afford the hemiacetal **1.104** in excellent yield.



Scheme 1-21: Coupling reaction and hemiacetal formation

At this stage, the simultaneous deprotection of the three benzyl ethers to give the intermediate **1.105** was envisaged, which would enable the synthesis of luminacin D **1.1**

in one step after oxidation of the two benzylic alcohols (Scheme 1-22). However, the hydrogenation attempts were associated with numerous selectivity issues.[19] In particular, the benzyl alcohol formed after deprotection of phenolic benzyl ether could be easily reduced to the methyl group, while the secondary benzyl alcohol was found to be labile, leading to compound decomposition. The selectivity and degradation issues were overcome by performing the oxidation of the secondary benzylic alcohol first, giving the compound **1.106**, which was then successfully debenzylated. A final oxidation using DMP afforded (–)-luminacin D **1.1**, in 55% yield. All spectral data and optical rotation of the final product fully corresponded with the data provided by Wakabayashi on the natural substrate.



Scheme 1-22: Completion of the synthesis

To date, this synthesis is probably the most efficient way to produce luminacin D, since it proceeds in high overall diastereoselectivity and yield and allows access to the enantiopure material. However, the requisite inversion of configuration at C5', and the deprotection issues encountered in the last steps suggest that improvements are still possible.

1.4 Nucleophilic addition of α-substituted carbonyl compounds

1.4.1 Asymmetric induction

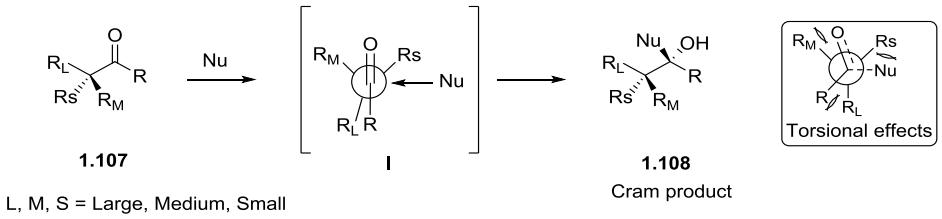
The presence of a chiral centre in proximity to a carbonyl group is known to influence the facial selectivity of nucleophilic addition. In this context, numerous models have been

proposed to predict and explain the asymmetric induction, considering a combination of steric and electronic factors.[20,21]. In this section, the Cram, Felkin-Anh, Cornforth-Evans and Cram-chelate models will be described.

1.4.2 1,2-Asymmetric induction - Acyclic models

1.4.2.1 Cram rules

The first remarkable contribution in the field of asymmetric induction was made by Cram and co-workers in 1952.[22,23] According to their proposed model (Scheme 1-23), the α-chiral carbonyl **1.107** is assumed to adopt the eclipsed conformation **I**, in which the largest substituent in α-position is antiperiplanar to the carbonyl group. The nucleophilic attack will preferentially occur on the least hindered face, leading to the formation of the Cram product **1.108**. It can be noted that the torsional effect induced by the eclipsed conformation adopted in the transition state is not considered, and that a 90 ° angle of attack is assumed.



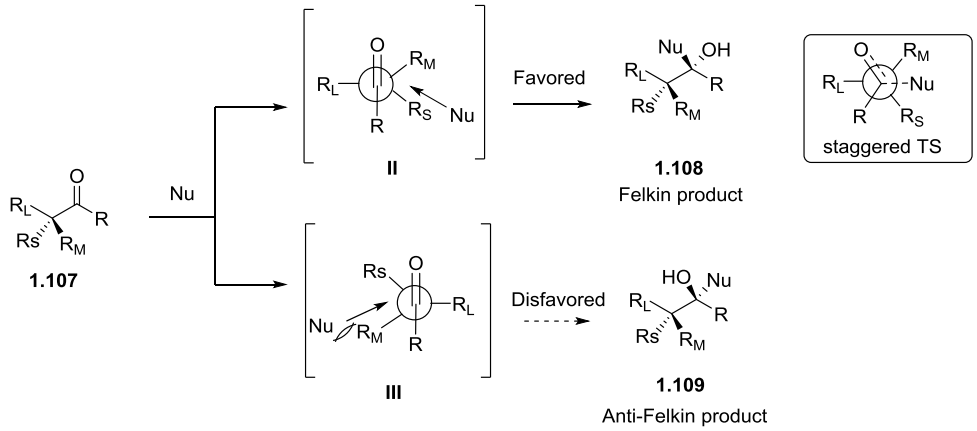
Scheme 1-23: The cram model

The Cram model has proved to be effective in explaining the selectivity outcome for nucleophilic additions to carbonyl groups (particulary to aldehydes) possessing a non-polar α-substituents. However, in the case of addition reactions to aldehydes bearing α-polar substituents such as Cl or OTMS, the model predictions are in contradiction with the experimental results. Later on, more sophisticated models were proposed.

1.4.2.2 Felkin-Anh model

As a consequence of the work of Felkin,[24] which was subsequently completed by Anh and Eisentein,[25,26,27] a new induction model was devised (Scheme 1-24). The so called Felkin-Anh model is first based on the assumption that a staggered conformation is preferred in the transition state, due to the aforementioned torsional effects. In addition, the largest

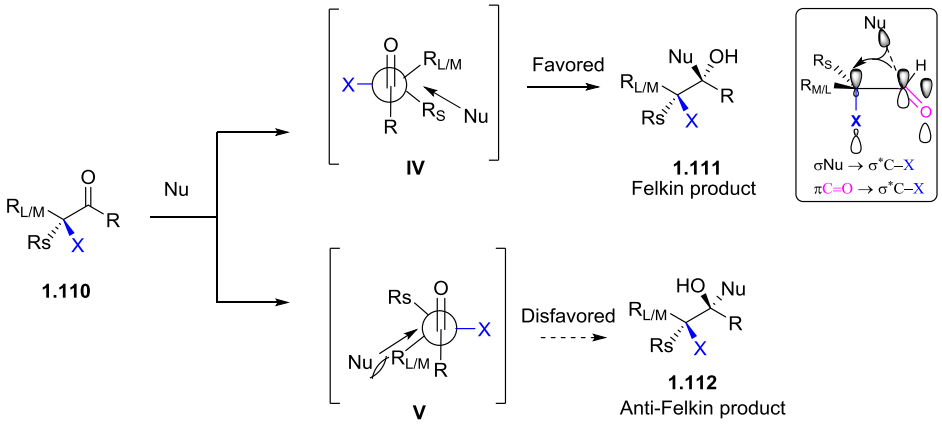
R_L group is assumed to be positioned orthogonal to the carbonyl plane, in order to minimise the steric interactions with the upcoming nucleophile. The combination of these two criteria leads to considering the conformations **II** and **III** as the two possiblereactive conformers. Further contribution made by Bürgi and Dunitz,[28,29] stating that the nucleophilic approach is not perpendicular but aligned with the $\pi_{C=O}$* (corresponding to an attack angle of 107°) gave a new element to distinguish between the two conformers. Hence, it was assumed that the nucleophilic attack from the least hindered face of conformer **III** is disfavoured in comparison with **II**, since the nucleophile has to approach with close proximity to the medium-sized group R_M in the case of conformer **III**, while the steric constraint related to the nucleophilic approach is reduced in the transition state **II**.



Scheme 1-24: The Felkin-Anh model

In the case where the carbonyl compound possesses an adjacent heteroatom substituent, Felkin stated that "polar effects stabilize those transition states in which the separation between the incoming nucleophile and the electronegative group is greatest",[24] corresponding to the conformers **IV** and **V** (Scheme 1-25). Anh and Elsentein proposed later on an explanation for this "polar effect" based on orbital interactions, giving the polar Felkin-Anh model (PFA).[25,26,27] According to their calculations, the alignment of the π bond of the carbonyl with the antibonding orbital of the best acceptor (σ_{C-X}*) is expected to stabilise the transition state, since the hyperconjugative delocalisation is maximised. This is the case when the X substituent is perpendicular to the carbonyl plane. In addition, the hyperconjugative delocalisation of the forming bond (σ_{Nu}) with the σ_{C-X}* orbital of the best vicinal acceptor (C-X) can be also considered. This interaction is maximised when the X-substituent and the upcoming nucleophile are antiperiplanar. Finally, in order to distinguish between the conformers **IV** and **V**, similar steric considerations related to the

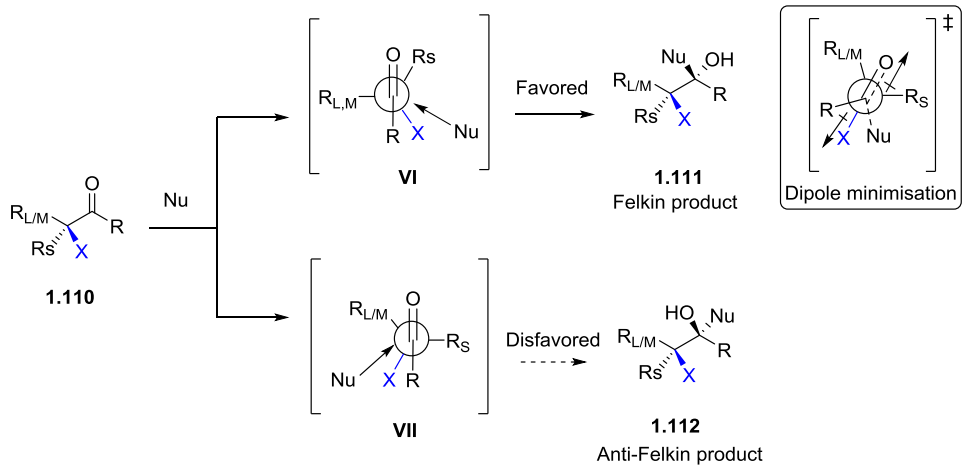
nucleophilic approach can be made, which supposes the formation of product **1.111** *via* nucleophilic attack from the least hindered face of transition state **IV**.



Scheme 1-25: The Polar Felkin-Anh model

1.4.2.3 Cornforth Evans model

Like the polar Felkin-Anh, the Cornforth-Evans (CE) model is used to predict the facial selectivity of nucleophilic addition involving an aldehyde substituted with a heteroatom (Scheme 1-26). This model is first based on Cornforth's assumption that the determining factor stabilising the transition state is the minimisation of electrostatic repulsion, corresponding to an antiperiplanar orientation between the carbonyl and the X-substituent.[30] In addition, the Felkin argument in favour of a staggered conformation in the transition state and the Bürgi-Dunitz trajectory were integrated by Evans, leading to two possible reactive conformers **VI** and **VII**, which can be further distinguished by steric considerations.[31,32] Thus, in the case of conformer **VII**, the nucleophile has to approach in between the hetereoatom and the largest group $R_{L/M}$, while the steric constraints related to the nucleophilic approach are reduced in the conformer **VI**, thus leading to the formation of the preferred Felkin product **1.111**.

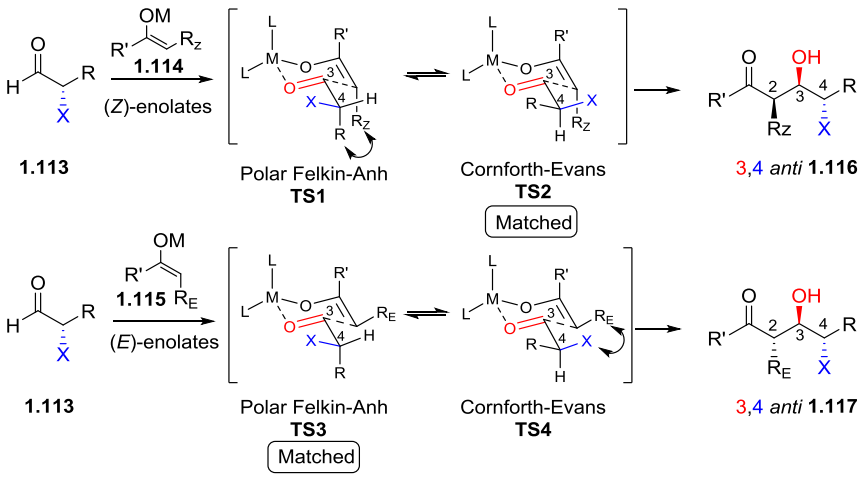


Scheme 1-26: The Cornforth-Evans model

1.4.2.4 Experimental and computational evidence to distinguish between the PFA and CE models

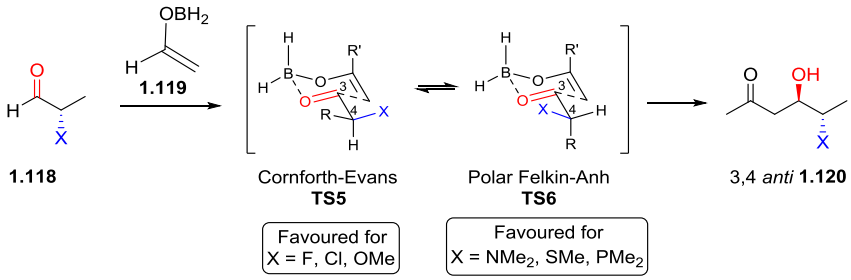
Experimental distinction between the PFA and CE models is difficult as the same selectivity outcome is predicted. Experimentally, both models can only be distinguished for carbonyl additions in which a conformational constraint is imposed on the α-stereocentre. This distinction was first demonstrated by Evans *et al*. with the comparative study of aldol reactions between the substituted metal (*Z*)- and (*E*)- enolates and α-alkoxy aldehydes (Scheme 1-27).[31] When combined with a Zimmerman-Traxler transition state, the PFA and CE models can be differentiated by taking steric constraints into consideration. Hence, in the case of (*Z*)-enolates **1.114**, the conformation induced by the PFA model would cause destabilising steric repulsions between the R and R_Z substituents (**TS1**), while such repulsions are absent in the case of (*E*)-enolates **1.115** (**TS3**). On the other hand, the conformation imposed by the CE model would imply a steric repulsion between the polar substituent X and the R_E group for the (*E*)-enolates **1.115** (**TS4**), while no such constraint would be imposed by the CE model with (*Z*)-enolates **1.114** (**TS2**). Thus, it was assumed that a PFA stabilisation should impart superior levels of 3,4-*anti* selectivity with (*E*)-enolates **1.115** than with the corresponding (*Z*)-enolates **1.114**, because of the aforementioned steric effects. Conversely, the CE model would predict higher levels of 3,4-*anti* selectivity with (*Z*)-enolates **1.114**, compared to (*E*)-enolates **1.115** for the same reasons. The experiments were conducted with various α-alkoxy aldehydes **1.113** and lithium and boron (*Z*)-(*E*) enolates **1.114** and **1.115**, and

demonstrated higher levels of 3,4-*anti* selectivity for the (*Z*)- compared to (*E*)-enolates, in agreement with the Cornforth-Evans model.



Scheme 1-27: Comparative study involving aldol reactions[31]

Later on, a theoretical study based on the addition of enolboranes **1.119** with several α-heteroatom substituted aldehydes **1.118** was reported by Cramer and Evans (Scheme 1-28).[32] The results showed that the relative energies of the PFA and CE transition states are dependent of the nature of the α-heteroatom substituent. Hence, the highly electronegative substituents (F, Cl, OMe) were found to favour the Cornforth type transition states, while the less electronegative substituents (PMe_2, SMe, NMe_2) favour the polar Felkin-Anh type transition states. Importantly, the study of the energetic profiles for the different α-substituted aldehydes also showed that the $\sigma^*_{C\text{-}X}$ - σ_{Nu} interaction is of little influence for the reactions involving enolborane nucleophiles. The preferred orthogonal orientation observed in the case of less electronegative substituent (PMe_2, SMe) was found to be due to a highly stabilised π - $\sigma^*_{C\text{-}X}$ interaction.



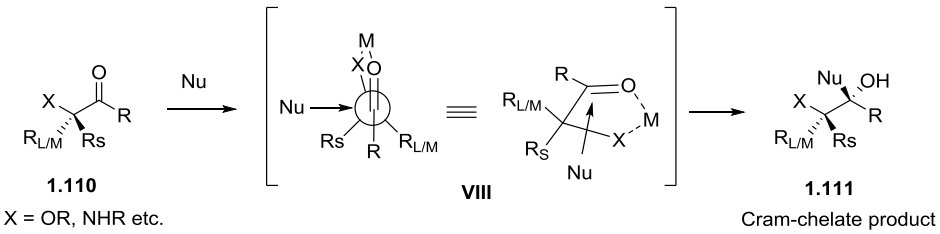
Scheme 1-28: Additions of enolboranes to various aldehydes. In order to simplify the study, only the PFA and CE transition states leading to the formation of the 3,4 *anti* product were considered.

As a complement to Evans' work, Marco and co-workers also exploited the destabilising *syn*-pentane interaction in an aldol Zimmerman-Traxler transition state, in order to distinguish between the PFA and CE transition states according to the product outcome.[33,34]

1.4.3 Cyclic transition state

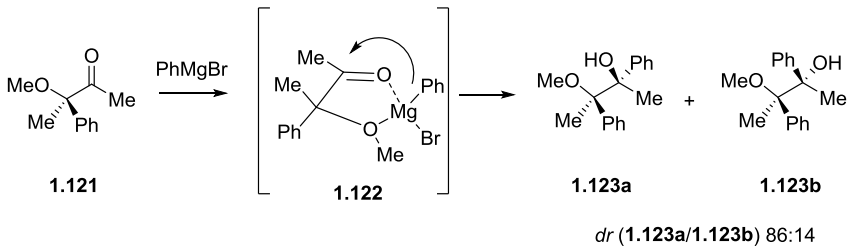
1.4.3.1 1,2-Chelation (Cram-chelate model)

In his seminal paper on the control of asymmetric induction, Cram noticed that if the carbonyl compound possesses an adjacent heteroatom substituent capable of coordinating with a chelating metal, the addition reaction proceeded with opposite selectivity compared to his model's predictions. Hence, an alternative model, coined the "Cram-chelate" model, was proposed (Scheme 1-29).[35] Thus, chelation involving the metal, the carbonyl group, and the α-heteroatom substituent gives rise to the 5-membered ring transition state **VIII**, in which the α-substituents R_S and $R_{L/M}$ are positioned on opposite sides of the carbonyl group. The nucleophilic attack will then preferentially occur from the least hindered face, giving the Cram-chelate product **1.111**.



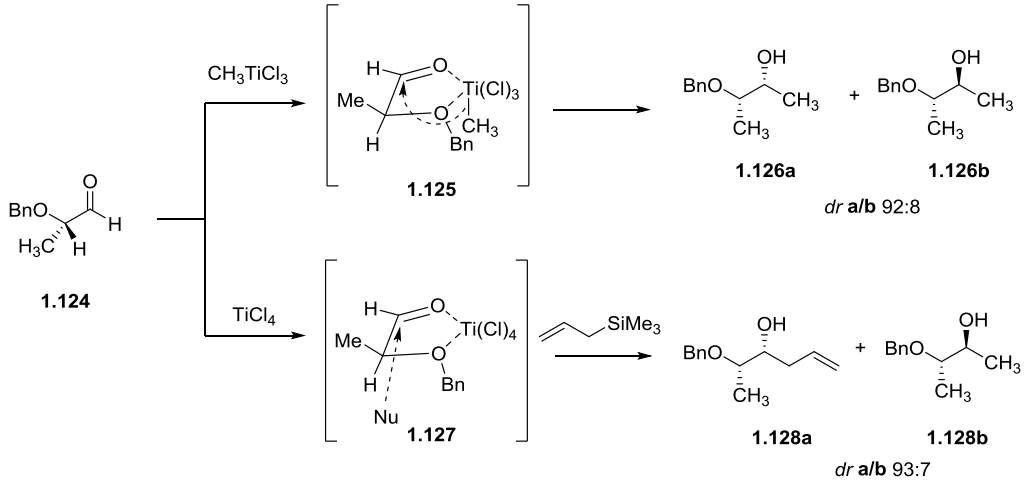
Scheme 1-29: The Cram-chelate model

Early examples were reported by Cram and Stocker with the addition of Grignard or organilithium reagents to α-alkoxy carbonyl compounds (Scheme 1-30).[22,35,36] These reactions were assumed to proceed through the formation of a chelated transition state involving the organometallic reagent with the carbonyl group and the α-alkoxy substituent, such as **1.122**. The nucleophile is then delivered in an intramolecular manner on the least hindered face, to give the Cram-chelate product **1.123a**. The level of selectivity observed for these reactions can vary from excellent (*dr* 96:4) to poor (*dr* 55:45) according to the substrate and organometallic reagents used.



Scheme 1-30: Addition of Grignard to α-methoxy ketone

Reetz and co-workers showed that organotitanium reagents ($RTiCl_3$) can be employed for the chelation controlled addition to α-alkoxy aldehydes, leading to excellent selectivity towards the Cram-chelate product (Scheme 1-31). As a continuation of this work, they also found that $TiCl_4$ can be used to generate the chelated intermediate **1.127**, which can subsequently react with mild C-nucleophilic reagents, such as dialkylzinc, allylsilanes, silyl enol ether and allylstananes, in an intermolecular manner (Scheme 1-31).[20,37] This methodology was further on extended to a vast range of bidentate Lewis acids.[20]



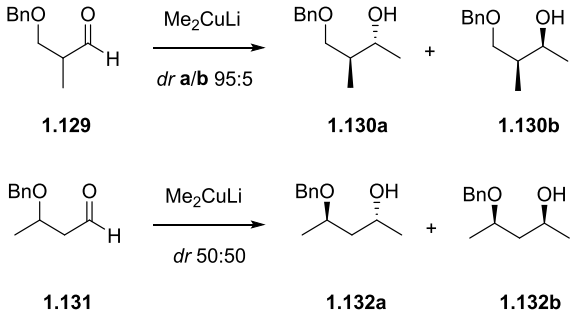
Scheme 1-31: 1,2-chelation-controlled addition with $RTiCl_3$ or $TiCl_4$/nucleophiles

The Cram-Chelate model has proved to be a reliable tool to predict the selectivity of addition reactions to carbonyl compounds under 1,2-chelation control. Furthermore, the unambiguous experimental evidence for formation of the Cram-chelate intermediate came from X-ray analysis [38] and NMR studies.[39]

1.4.3.2 1,3-Chelation

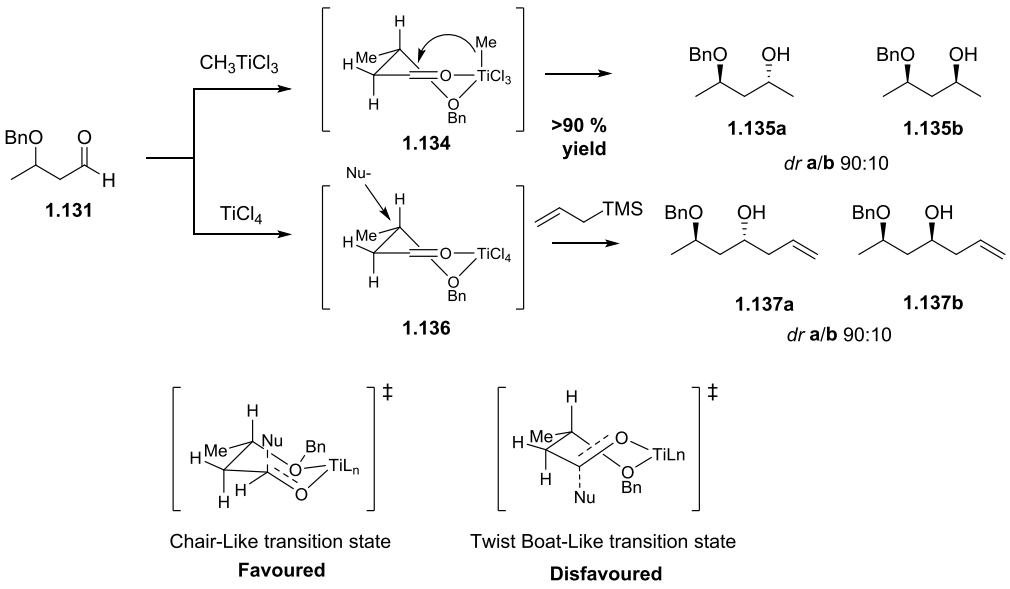
In contrast with the results obtained for α-alkoxy aldehydes, Still and co-workers showed that the addition of organolithiums or Grignard to β-alkoxyaldehydes proceeded with low

selectivity.[40] However, organocuprates, and in particular Me_2CuLi, proved efficient to alkylate the β-alkoxy-α-methylated **1.129** in excellent diastereoselectivity for the Cram-chelate product **1.130a** (Scheme 1-32). Surprisingly, the reaction of Me_2CuLi with the β-substituted aldehyde **1.131** gave no selectivity.



Scheme 1-32: Addition of organocuprate to β-alkoxy aldehydes

Reetz et *al.* demonstrated that their alkylation methodology developed with α-alkoxy-aldehydes and organotitanium reagents ($RTiCl_3$ or $TiCl_4$/nucleophiles) was applicable to 1,3-chelation controlled addition involving β-alkoxy-aldehydes **1.131** (Scheme 1-33).[41] Indeed, excellent selectivity was observed for the 1,3-*anti* diols **1.135a** and **1.137a** using CH_3TiCl_3 or the combination of $TiCl_4$/allylsilane, respectively. The methodology also proved efficient with other nucleophiles, such as dialkylzinc, silyl enol ethers or allylstananes. In order to rationalise the stereochemical outcome, Reetz proposed the formation of the chelate intermediates **1.134** and **1.136**, in which the largest β-substituent is positioned in *pseudo* equatorial position.[20] The nucleophile is proposed to attack from the face *anti* to the methyl substituent, leading to the observed diastereosectivity for the 1,3-*anti*-products. The facial selectivity can further be explained by invoking a chair like transition state (See Scheme 1-33).

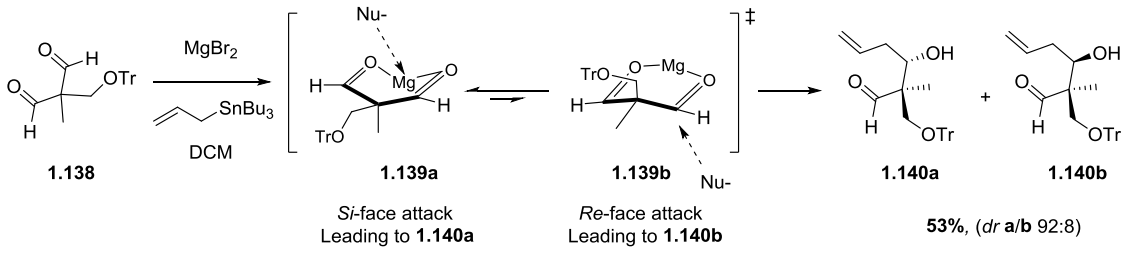


Scheme 1-33: The Cram-Reetz model

1.4.4 1,3-Chelation-controlled nucleophilic addition to carbonyl compounds possessing an α-stereocentre

1.4.4.1 Carbonyl compound possessing an α-*All*-C quarternary centre

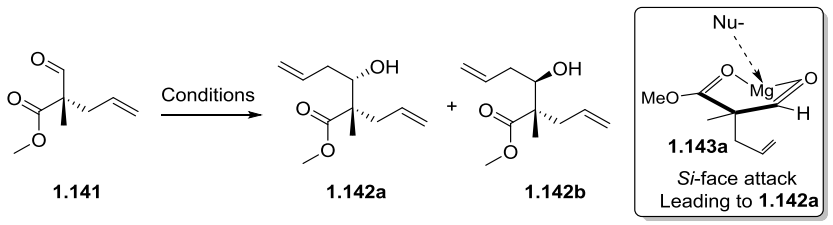
As previously mentioned in section 1.3.6.1, our group has developed a diastereoselective allylation methodology as key step to achieve the synthesis of luminacin D. This step was inspired by precedent work of the group showing that high level of stereocontrol can be achieved through allylation reaction of 1,3-dialdehydes such as **1.138** under 1,3-chelation control, with stereochemical bias provided by the α-quaternary centre (Scheme 1-34).[42] Thus, using allyltributylstannane under $MgBr_2$ activation, excellent diastereoselectivity was observed towards the formation of **1.140a**. The diastereochemical outcome was consistent with the formation of the "open book" transition state **1.139a** under 1,3-chelation control, with the non-chelating trityloxymethyl group positioned on *pseudo* equatorial position, which is thought to be due to electronic factors. Nucleophilic attack from the least hindered *Si*-face of **1.139a** would lead to the formation of **1.140a**, as observed experimentally. On the other hand, the formation of the minor isomer **1.140b** was assumed to arise from the higher energy conformer **1.139b**, with the nucleophilic attack occurring from the least congested *Re*-face.



Scheme 1-34: $MgBr_2$ promoted allylation reaction to 1.3 dialdehydes

In relation to this work, Mulzer and co-workers previously reported similar allylation methodology with α-formyl ester **1.141**, proceeding in good diastereoselectivity towards **1.142a** (Table 1-1, Entry 1).[43] The selectivity outcome is consistent with the formation of the transition state **1.143a**.[19] Furthermore, additional experiments demonstrated that the selectivity of the reaction could be reverted in the presence of non-chelating Lewis acids (Entry 2 and 3), which strongly suggests that a chelation control is operative when $MgBr_2$ is used.

Table 1-1: Allylation reaction of **1.141** under different conditions

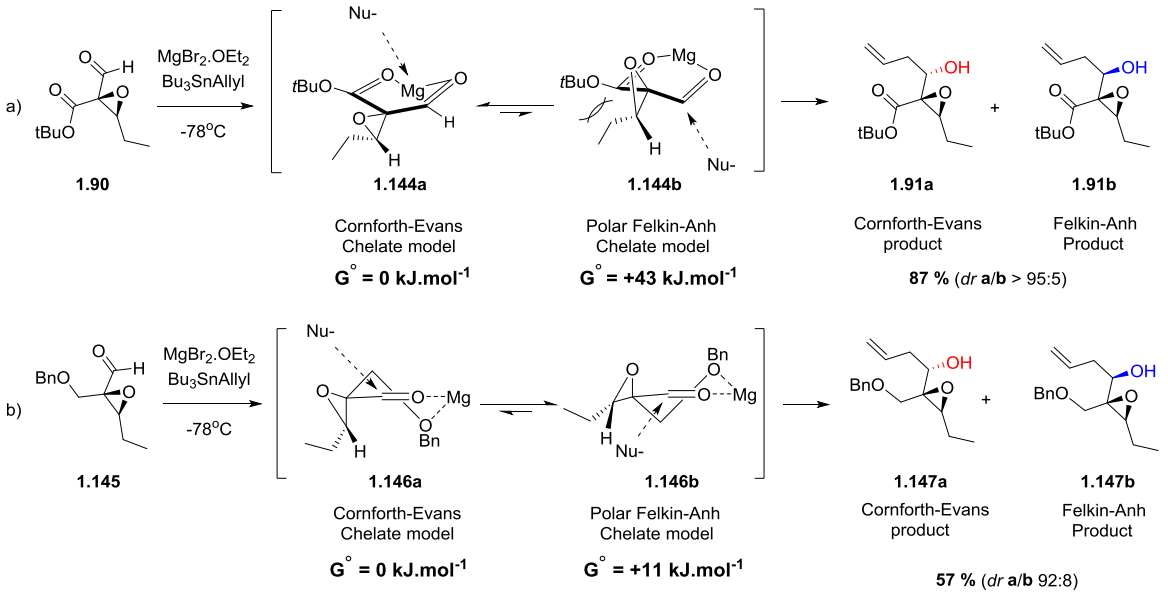


Entry	Allyl reagent	Lewis Acid	Yield (%)	*dr* **a/b**
1	$AllylSnBu_3$	$MgBr_2$	87	7:1
2	AllylTMS	$BF_3.Et_2O$	84	<1:19
3	Brown allylation [(+)-Ipc]	-	Quant.	1:20

1.4.4.2 Carbonyl compounds possessing an α-polar substituent

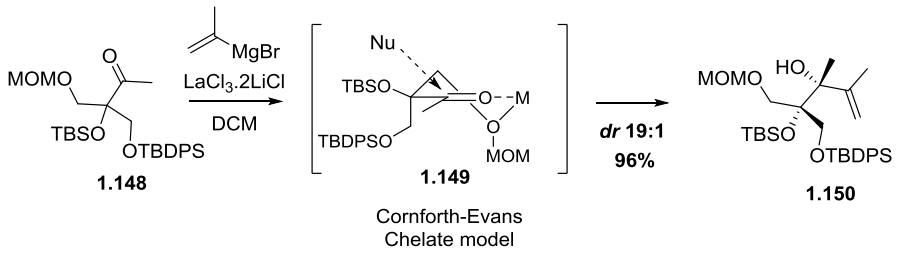
The chelation-controlled allylation methodology was further investigated with α-formyl ester **1.90** and benzyloxy-aldehyde **1.145** possessing a quaternary epoxide centre, in the course of the luminacin D synthesis (Scheme 1-35).[17] Again, the reaction proceeded with excellent selectivity in both cases, giving the *anti*-diastereoisomer **1.91a** and **1.147a** as

major products, respectively (Scheme 1-35). The stereochemical outcome of the allylation reaction was explained as follows: as already observed, chelation induced by $MgBr_2$ between the two carbonyl groups of compound **1.90** leads to two interconverting "open book" structures **1.144a** and **1.144b**, which can be distinguished by the epoxide C-O bond orientation. The conformer **1.144a**, in which the C-O bond is positioned antiperiplanar to carbonyl dipoles, can be related to a Cornforth-Evans type model, whereas conformer **1.144b**, with the C-O bond perpendicular to the carbonyl groups, is akin to a polar Felkin-Anh type model. In this case, the two models can be distinguished as they predict opposite stereochemical results. Thus, a nucleophilic attack on the least hindered *Si*-face of the Cornforth-Evans conformer **1.144a** would result in the formation of the *anti*-product **1.91a**, while the polar Felkin-Anh conformer **1.144b** would lead to the formation of the *syn*-product **1.91b** through addition of the nucleophile on the least congested *Re*-face. The experimental results showed here that the Cornforth-Evans conformer corresponds to the lowest energy transition state, with almost exclusive formation of the Cornforth-Evans product **1.91a** (*dr* > 95:5). This was corroborated by DFT calculations, which confirmed that **1.144a** is much more stable than **1.144b**, by 43 $kJ.mol^{-1}$. In the case of the β-benzyloxy aldehyde **1.145**, similar considerations can be made to distinguish between the CE and PFA conformers **1.146a** and **1.146b**, with the chair-like transition state dictating the facial selectivity (Scheme 1-35). The experimental results confirmed that a CE stabilisation is also operative in that case, though a lower *dr* towards **1.147a** was obtained compared to the previous example. This result is consistent with the computational analyses, showing a lower energy difference between the CE and PFA conformers **1.146a** and **1.146b** (ΔG = +11 $kJ.mol^{-1}$). Apart from the obvious conformational differences between an "open book" and a half-chair transition states, the higher level of selectivity observed for compound **1.90** is thought to arise from steric repulsions (allylic strain) destabilizing the PFA conformer **1.144b**, while no such repulsions are present in conformer **1.144a**. The chelation controlled allylation reaction was also investigated with β-benzyloxy aldehydes possessing an α-OTBS substituent instead of the quaternary epoxide, which also led to the preferred formation of the Cornforth-Evans product.[17]



Scheme 1-35: Allylation reaction proceeding *via* a CE type transition state

In relation with the above example, Castle and co-workers demonstrated that the 1,3 – chelation controlled addition to analogous ketones such as **1.148** proved also efficient for the diastereoselective formation of **1.150** (Scheme 1-36).[44] The stereochemical outcome is consistent with the chelated transition state **1.149**, in which the α-OTBS substituent is positioned in accordance with the Cornforth-Evans model.



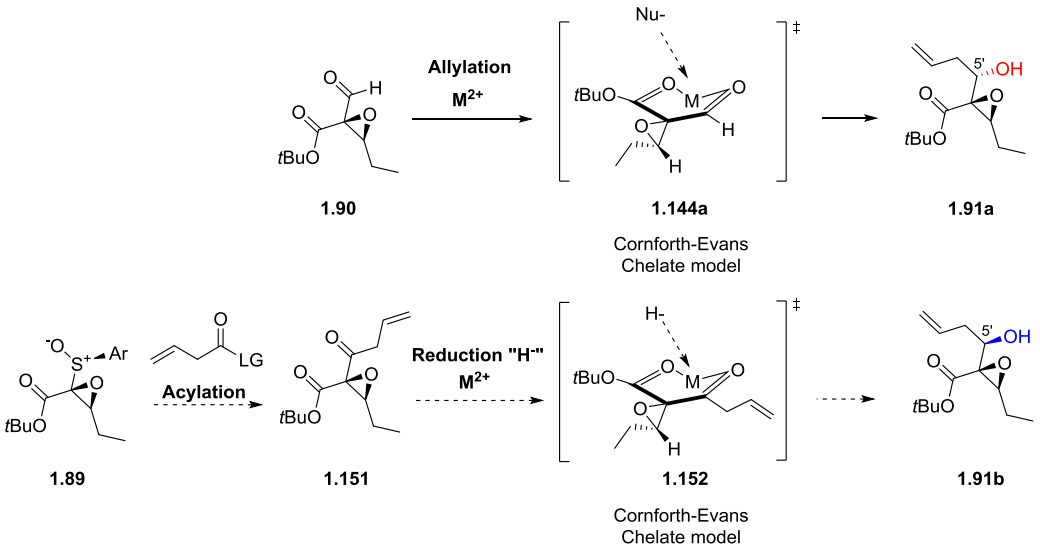
Scheme 1-36: Chelation-controlled addition to ketones

1.5 Aim of this project

The general objective of this work was to improve the total synthesis of luminacin D developed in our laboratory. In this matter, two main modifications of the reported route were investigated.

1.5.1 New methodology

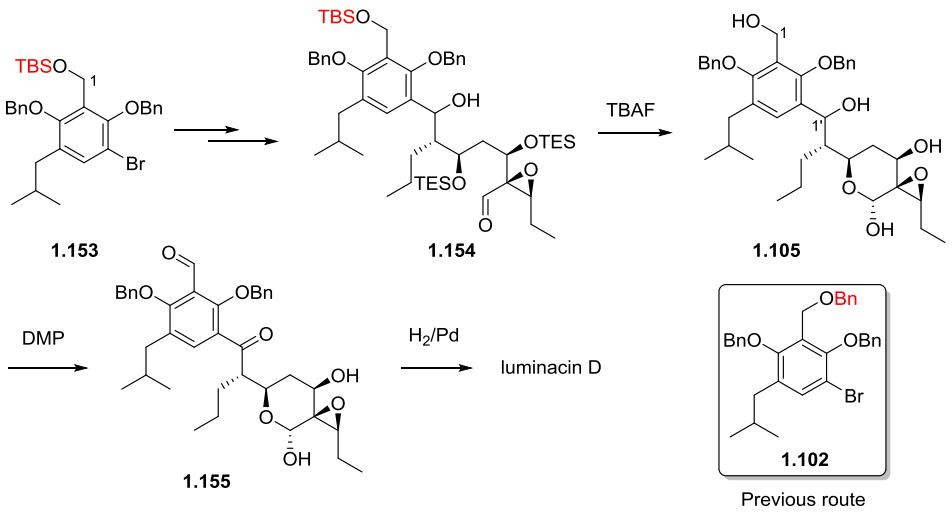
The $MgBr_2$-promoted allylation reaction of aldehyde **1.90** has proved highly selective, and was used as key step for the synthesis of luminacin D (Scheme 1-37). However, the reaction led to the formation of the diastereoisomer **1.91a** possessing the undesired configuration at C5', and thus inversion of this stereocentre was required to complete the synthesis of the natural product. In this context, the aim of this work was to develop a diastereoselective methodology allowing direct access to the desired alcohol **1.91b**, thus avoiding the requisite Mitsunobu inversion. In order to achieve this, the metal mediated diastereoselective reduction of the 1,3-keto ester intermediate **1.151** was envisaged. By assuming the formation of the transition state **1.152**, in which a Cornforth-Evans type stabilisation is operative, the hydride attack of the least congested *Si*-face would lead to desired product **1.91b**. The formation of the β-keto-ester **1.151** was envisaged *via* acylation reaction of the sulfoxide derivative **1.89.**



Scheme 1-37: New strategy

1.5.2 New protecting group strategy

In relation with the difficulties encountered in the last step of the synthesis (cf section 1.3.6.3), the second objective of this work is to modify the protecting group strategy on the aromatic fragment (Scheme 1-38). Thus, the formation of the bromo-arene **1.153**, in which the benzyl alcohol is protected with a TBS group (instead of benzyl group) was envisaged**,** which would enable formation of the intermediate **1.154** following the current synthetic pathway. Subsequent TBAF deprotection would allow access to intermediate **1.105**, which could be oxidised at the two benzylic positions in one step to give the keto aldehyde **1.155**. Finally, the cleavage of the phenolic benzyl ethers would lead to the formation of luminacin D. This new protecting group strategy would shorten the synthetic route by one step compared to the current synthesis. The synthesis of the bromo-arene **1.153** will be detailed later.

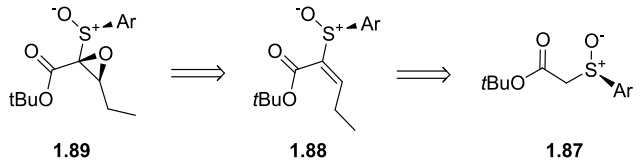


Scheme 1-38: Modification of the protecting group strategy

Chapter 2: Synthesis of epoxide precursors

2.1 Target

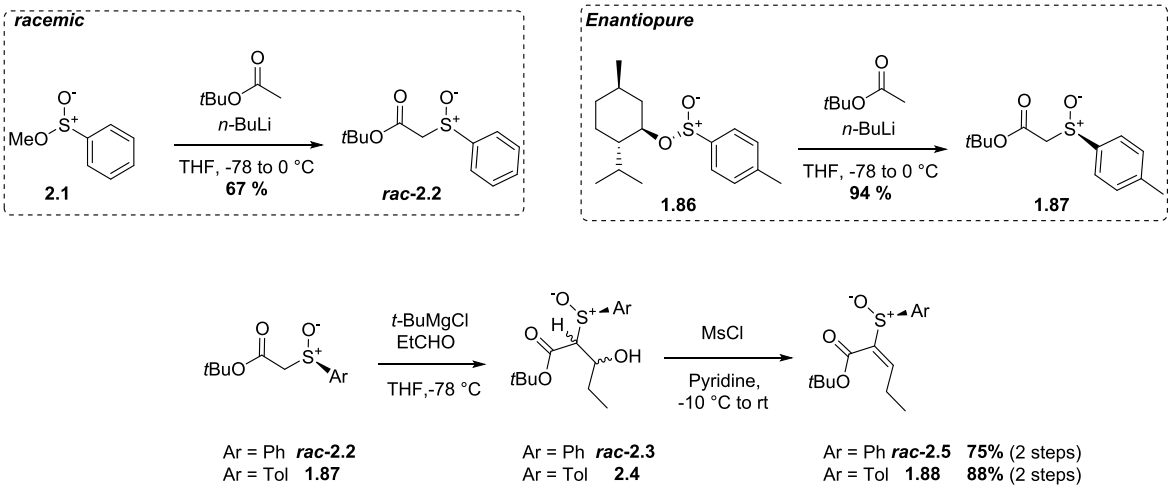
In this chapter, the synthesis of the epoxide precursor **1.89** will be described, (Scheme 2-1), including optimisation of the epoxidation conditions to improve both the reported yield and diastereoselectivity (**77%**, *dr* 7:1).



Scheme 2-1: Retrosynthetic analysis of epoxide **1.89**

2.1.1 Early steps

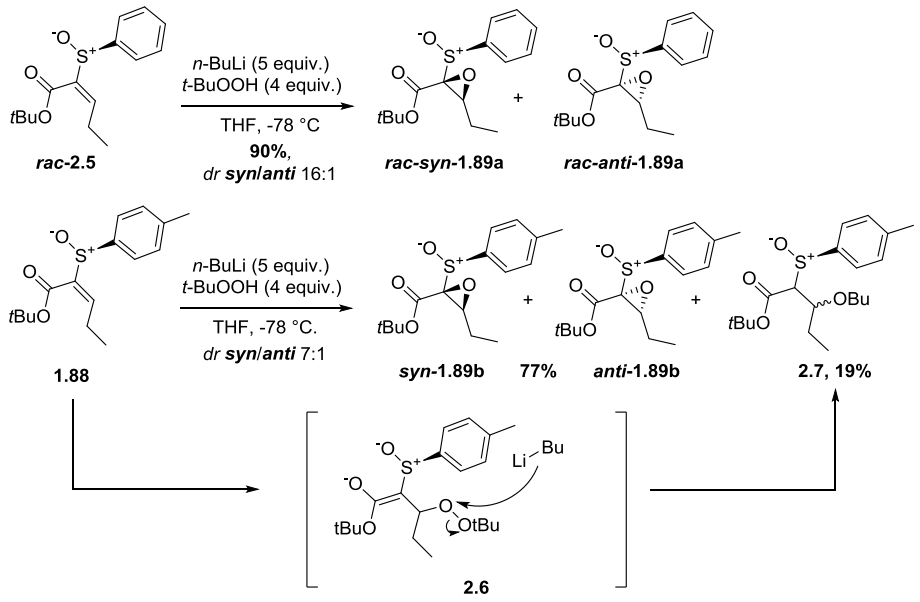
Following the original work of Nathan Bartlett, the synthesis of the racemic and enantiopure α,β-unsaturated alkenes **2.5** and **1.88** was performed in 3 steps (Scheme 2-2). Nucleophilic substitution of the preformed enolate of *t*-butylacetate onto the methyl benzyl sulfinate **2.1** afforded the racemic α-sulfoxy ester **2.2** in 67% yield. The same procedure, applied to the enantiopure and commercially available (1*R*,2*S*,5*R*)-(–)-menthyl-(S_S)-*p*-toluenesulfinate **1.86** furnished the enantiopure ester **1.87** in excellent yield. Subsequent two step Knoevenagel type condensation led to the phenyl and tolyl derivatives **2.5** and **1.88** as pure *E*-isomers, in 77% and 88% yield respectively. These compounds will be used in an undifferentiated way for the optimisation studies.



Scheme 2-2: Formation of alkenes **2.5** and **1.88**

2.1.2 Epoxidation reaction

The formation of epoxides **1.89a-b** had been achieved in a diastereoselective manner in the previous synthesis, using a procedure deriving from De La Pradilla's vinyl sulfoxide methodology (Scheme 2-3).[18] The reaction proceeded in excellent yield and diastereoselectivity with the phenyl derivative **2.5** (90%, *dr* 16:1), while the same reaction conditions applied with tolyl derivative **1.88** led to lower yield and diastereoselectivity (77%, *dr* 7:1). In addition, the product **2.7** was obtained in 19% yield as mixture of diastereoisomers. The latter was thought to arise from the nucleophilic attack of *n*BuLi onto the Michael intermediate **2.6**, since an excess of *n*-BuLi was used compared to *t*-BuOOH (5 *vs* 4 equiv., respectively).

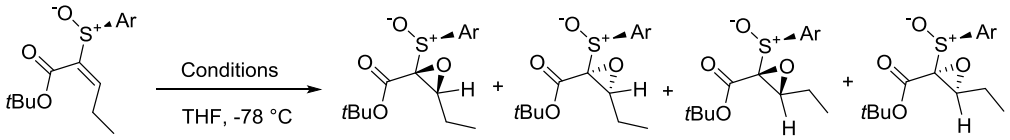


Scheme 2-3: Epoxidation reaction

The reaction conditions were then modified in order to improve both yield and diastereoselectivity (Table 2-1). The first experiment was carried out with **1.88** by using an excess of *t*-BuOOH compared to *n*-BuLi (Entry 1). Although the reaction proceeded without any formation of **2.7** (Scheme 2-3), the formation of undesired by-products could be observed by ^{1}H NMR, alongside with the expected *trans*-epoxides ***syn*-1.89b** and ***anti***. After column chromatography, both *trans*-epoxides were isolated as a mixture of diastereoisomers in moderate yield (60%, *dr* ***syn*-1.89b**/***anti*-1.89b** 95:5). A mixture of the two undesired by-products was also isolated in 16% yield, which allowed their assignment as the *cis*-epoxide isomers ***syn*-2.8b and *anti***. Following this, it was found that using a 1:1

ratio of *t*-BuOOH and *n*-BuLi, and reducing the reaction time allowed to minimise the formation of the *cis*-epoxides **2.8b** (Entry 2). Epoxide **1.89b** was isolated in both excellent yield and diastereselectivity under these conditions (82 %, *dr* ***syn*-1.89b**/***anti*-1.89b** 91:9). Interestingly, the replacement of *n*-BuLi by NaH with the racemic derivative **2.5** resulted in promoting the formation of *cis*-isomers **2.8a**, with a good selectivity towards the *syn*-epoxide ***syn*-2.8b** (Entry 3). The same outcome was observed when an excess of NaH compared to *t*-BuOOH was used with the tolyl derivative **1.88** (Entry 4).

Table 2-1: Optimisation of the epoxidation reaction. Prefixes *syn*/*anti* refer to the relative position of the aryl group.compared to the epoxide function. Prefixes trans/cis (used in the text) refer to the relative arrangement of the epoxide substituents.



Ar = Ph **2.5**
Ar = Tol **1.88**

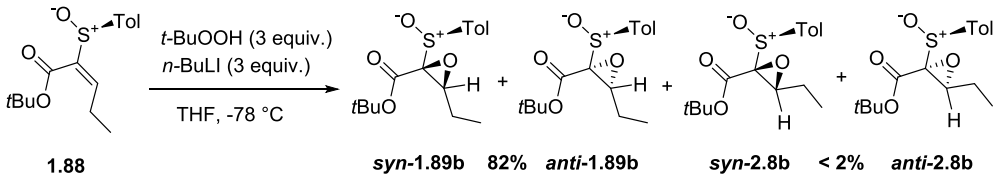
***syn*-1.89a** **+** ***syn*-1.89b** | ***anti*-1.89a** **+** ***anti*-1.89b** | ***syn*-2.8a** **+** ***syn*-2.8b** | ***anti*-2.8a** **+** ***anti*-2.8b**

Entry	Ar	Base (equiv.)	*t*-BuOOH (equiv.)	t (h)	*dr* ***syn*-1.89**/***anti*-1.89**/ ***syn*-2.8**/***anti*-2.8**[c]	Overall Yield (%)[d]	Yield **1.89**[d]	Yield **2.8**[d]
1	Tol	*n*-BuLi (4)	4.9 – 6[a]	1.5	72 : 4 : 16 : 8	91	60	16
2	Tol	*n*-BuLi (3)	3[b]	0.4	81 : 8 : 6 : 6	88	82	NI
3	Ph	NaH (2.5)	3.2 -3.9[a]	0.4	35 : 4 : 54 : 7	78	23	53
4	Tol	NaH (3.2)	3[b]	0.4	45 : 2 : 50 : 3	78	NI	25

[a]A commercial solution of *t*-BuOOH in decane (5M-6M) was used; [b]A commercial solution of *t*-BuOOH in decane (5.5 M) was used; [c]Determined by ^{1}H NMR; [d]Isolated yield; NI: not isolated

The epoxidation reaction was carried out on 3 g scale (10 mmol) with the tolyl derivative **1.88** using the optimised conditions, and enabled isolation of the expected *trans*-epoxides **1.89b** in a slightly improved yield and diastereoselectivity compared to the reported procedure (Scheme 2-4, 82%, *dr* ***syn***/***anti*** 92:8 *vs* 77% *dr* ***syn***/***anti*** 7:1). A minor quantity of the *cis*-epoxides **2.8b** was also obtained in 2% yield. An expansion of the ^{1}H NMR

showing the characteristic peaks used for determination of the diastereoselectivity is given in Figure 2-1.



dr (***syn*-1.89b**/***anti*-1.89b**/***syn*-2.8b**/***anti*-2.8b**) : 86 : 7 : 4 : 3

Scheme 2-4: synthesis of epoxides **1.89b** and **2.8b** on 3g scale

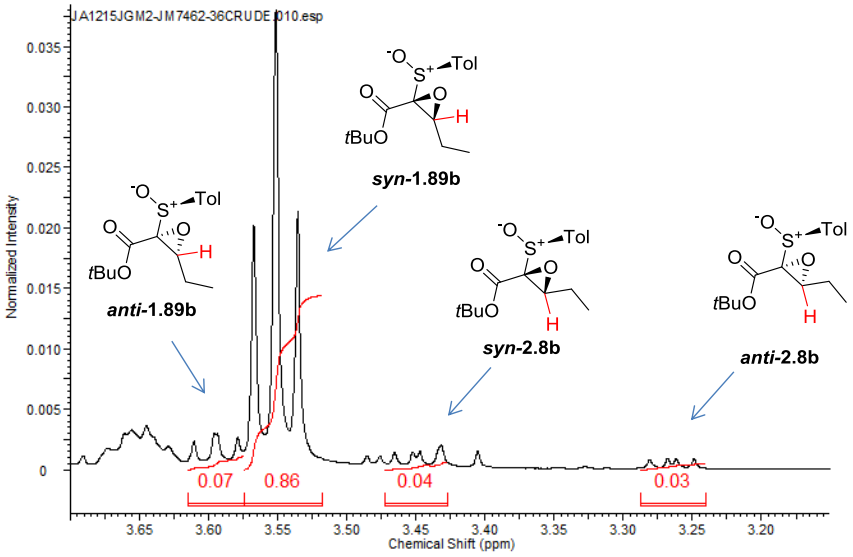
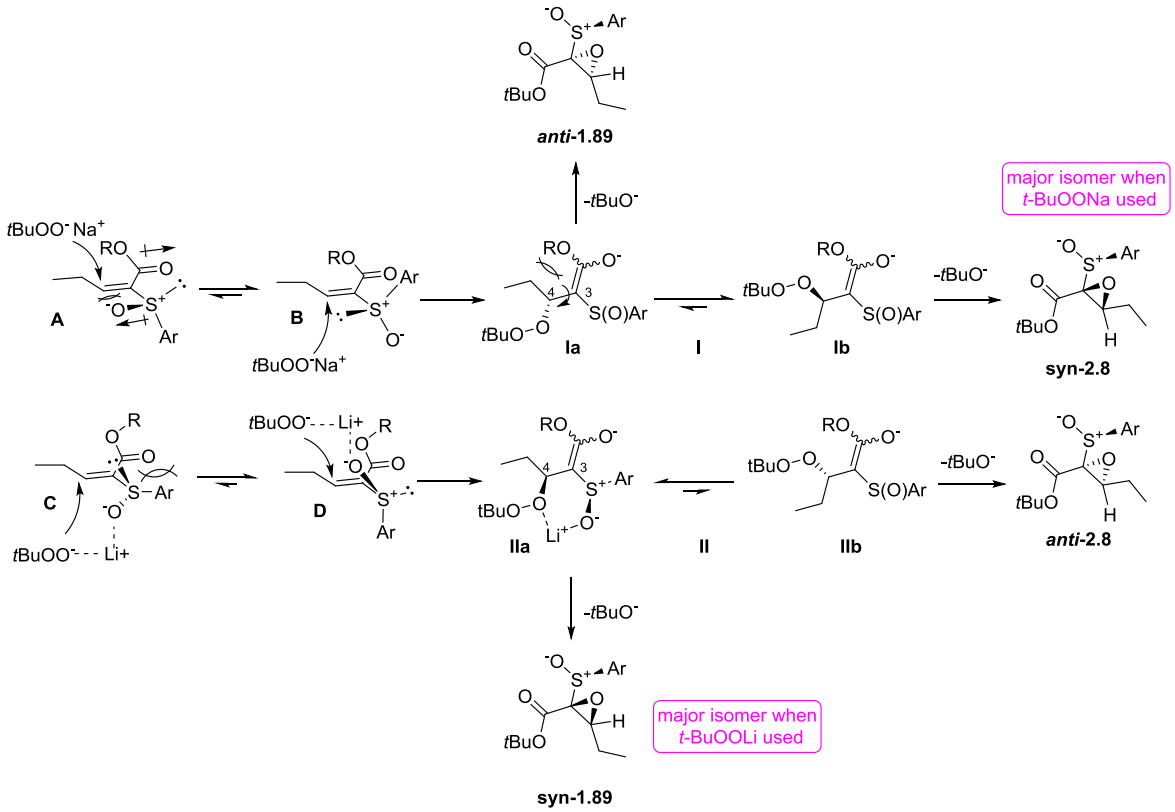


Figure 2-1: NMR expansion of 3.7-3.1 ppm zone of the crude NMR- The protons used for the *dr* determination is indicated in red

The formation of the different epoxide isomers and the selectivity observed for the nucleophilic attack can be rationalised as follows (Scheme 2-5).[45] If *t*-BuOONa is employed, the equilibrium between the two most stable conformers **A** and **B** is slightly shifted towards the conformer **B**, in which steric interactions are minimised (Scheme 2-5). Nucleophilic attack on the least hindered bottom face would give intermediate **Ia**, which can either lead to the formation of the *anti*-epoxide ***anti*-1.89** after ring closure, or to the *cis syn*-epoxide ***syn*-2.8** through rotation of the C3-C4 bond and subsequent ring closure. The presence of allylic strain in **Ia** is thought to favour the formation of **Ib**, leading to the observed formation of ***syn*-2.8** as major product.

If *t*-BuOOLi is employed, the diastereoselectivity observed would be consistent with the formation of the transition state **D**, in which the coordination of the Li cation with the sulfinyl oxygen directs the addition of the *t*-BuOO$^-$ anion towards the top face of the alkene (Scheme 2-5),[45] leading to intermediate **II**, then to epoxides ***syn*-1.89** and ***anti*-2.8**. In this case, chelation involving the sulfoxide and the oxygen at C4 in intermediate **IIa** is assumed to prevent the C3-C4 rotation, which could explain the observed formation of ***syn*-1.89** as major product.



Scheme 2-5: Rationalisation of the selectivity outcome

The assignment of configuration of the different epoxides was achieved thanks to X-ray crystallographic analysis of the crystalline compounds ***syn*-1.89b** and ***syn*-2.8a** (Figure 2-2). In addition, the oxidation of a mixture of isomers ***syn*-2.8b** and ***anti*-2.8b** (*dr* 1:1) led to the sulfone **2.9** as a single product, which allowed assignment of ***anti*-2.8b** as the *cis-anti*-epoxide (Scheme 2-6).

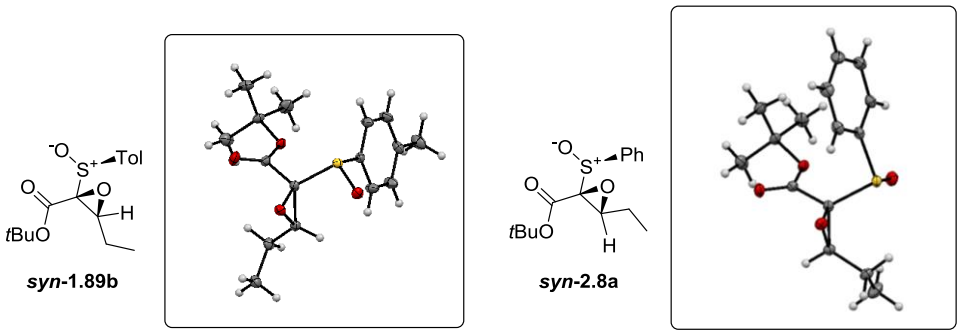
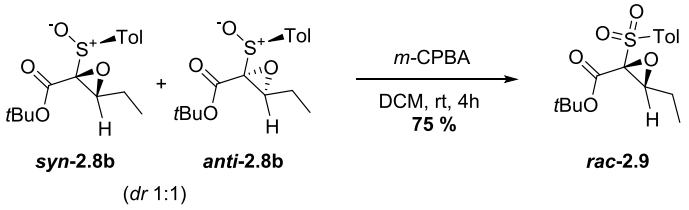


Figure 2-2: X-ray structures obtained for ***syn*-1.89b** and ***syn*-2.8a.** Epoxide ***syn*-1.89b** was obtained as enantiopure material by recrystallisation performed on an analytical sample. Large scale recrystallisation was however not attempted.



Scheme 2-6: Oxidation of ***syn*-2.8b** and ***anti*-2.8b**

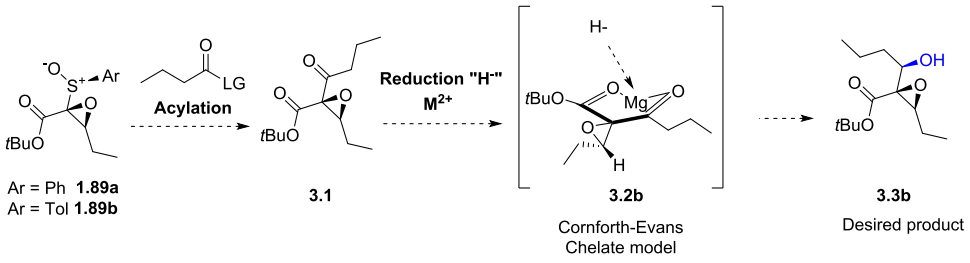
2.2 Summary

The synthesis of the epoxide precursors was achieved in 4 steps from a commercially available starting material. Optimisation of reaction conditions for the epoxidation step was conducted, which enabled to improve yield and diastereoselectivity. From these intermediates, investigations were directed towards the development of new diastereoselective methodologies, which will be described in the next chapters.

Chapter 3: Acylation and diastereoselective reduction

3.1 Aim of this chapter

With access to epoxides **1.89a** and **1.89b**, the acylation/diastereoselective reduction approach was investigated. In order to simplify the optimisation work, the acylation reaction was initially developed with a saturated ester or equivalent, leading to compound **3.1** (Scheme 3-1). This keto-ester will be used as model substrate for the diastereoselective reduction (formation of alcohols **3.3**). The optimised conditions will be then applied towards the synthesis of luminacin D.

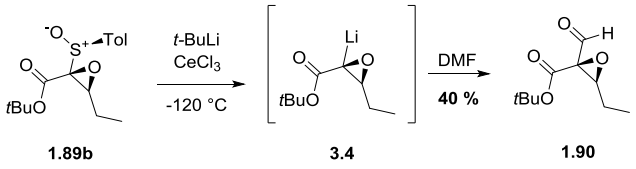


Scheme 3-1: Acylation/reduction approach Acylation reaction

3.2 Acylation

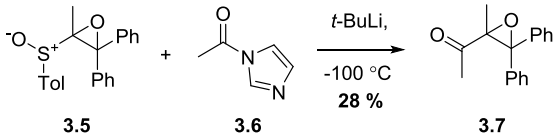
3.2.1 Background

In the previous route, our group reported the synthesis of the α-epoxy aldehyde **1.90** from the sulfoxide derivate **1.89b** (Scheme 3-2).[17] The reaction involved the generation of the oxiranyl anion species **3.4** through sulfoxide-lithium exchange mediated by *t*-BuLi, which was then added to DMF to give, upon hydrolysis, the corresponding aldehyde **1.90**. The procedure is however low-yielding, even when conducted at -120 °C under anhydrous conditions to stabilise the oxiranyl ion intermediate.



Scheme 3-2: Oxiranyl ion formation

Regarding the formation of α-keto epoxide from α-sulfoxy epoxide derivatives, only one example has been reported in the literature, by Satoh and co-workers (Scheme 3-3).[46] Thus, treatment of **3.5** with *t*-BuLi and the acetyl imidazole **3.6** afforded the corresponding ketone **3.7** in low yield. No justifications were given in the paper to explain the use of the unusual carbonyl imidazole derivative as acetylating agent.



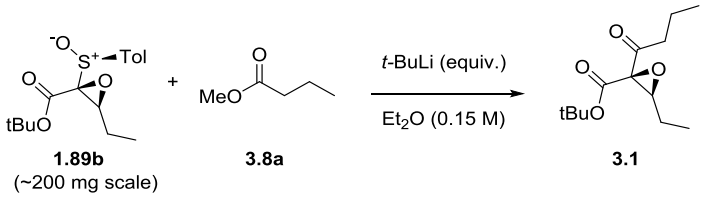
3.5 **3.6** **3.7**

Scheme 3-3: Acetylation of **3.5**

3.2.2 Acylation reaction – Optimisation

With the epoxide precursors in hand, the formation of the model substrate **3.1** was investigated using the commercially available methyl butanoate **3.8a** as acyl donor. Results of the different experiments are summarised in Table 3-1. The generation of the oxiranyl anion was first attempted with *t*-BuLi added prior to the addition of methyl butanoate **3.8a** (Entry 1). This led to consumption of the starting material, though no evidence of the formation of the product was observed by ^{1}H NMR. Modifying the order of addition of the reagents enabled isolation of the product in modest yield and conversion (Entry 2). A significant improvement of yield was obtained by reducing the excess of ester **3.8a**, keeping the same amount of *t*-BuLi used(Entry 3,4). In contrast, the use of a large excess of **3.8a** led mainly to the recovery of the starting material (Entry 5). Interestingly, no yield improvement was obtained when $CeCl_3$ or TMEDA were added to the mixture to stabilise the oxiranyl ion intermediate (Entry 6,7).

Table 3-1: Optimisation of the conditions for the acylation reaction



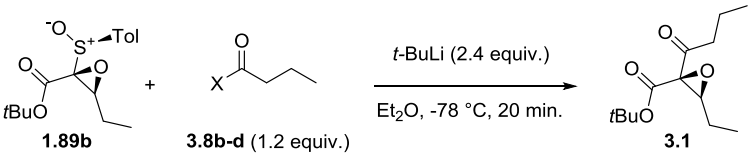
1.89b (~200 mg scale) **3.8a** **3.1**

Entry	T (°C)	**3.8a** (equiv.)	*t*-BuLi (equiv.)	Conditions	Conversion (%)[a]	Yield **3.1** (%)[b]
1	-100	3.6	2.6	**1.89b** in Et_2O, *t*-BuLi added dropwise and **3.8a** immediately added	100	Complex mixture
2	-78	2.4	2.4	**1.89b**+ **3.8a** in Et_2O, *t*-BuLi added dropwise	38	20[b]
3	-78	1.6	2.4	**1.89b** + **3.8a** in Et_2O, *t*-BuLi added dropwise	88	31[b]
4	-78	1.2	2.4	**1.89b** + **3.8a** in Et_2O, *t*-BuLi added dropwise	100	38[b]
5	-78	5.0	2.4	**1.89b** + **3.8a** in Et_2O, *t*-Buli added dropwise	15	Traces
6	-78	1.2	2.4	**1.89b** + **3.8a** + $CeCl_3$ (1 equiv.) in Et_2O, *t*-Buli added dropwise	100	35[b]
7	-78	1.2	2.4	**1.89b** + **3.8a** + TMEDA (1.2 equiv.) in Et_2O, *t*-Buli added dropwise	100	27[b]

[a]Determined by ^1H NMR. Defined as the ratio between the product obtained **3.1** and the starting material **1.89b**. Other by-products not included. [b]Isolated yield.

The influence of the leaving group on the acylation reaction was then examined with diverse carbonyl compounds **3.8b-d**, (Table 3-2). No product was obtained when using the more reactive phenolic ester **3.8b**[47] (entry 1). On the other hand, the use of Weinreb or dimethyl amide derivatives **3.8c**[48] (Entry 2) and **3.8d**[49] (Entry 3) enabled formation of the coupling adduct **3.1**, though no yield improvement was obtained compared to the reference conditions.

Table 3-2: Influence of the leaving group in the coupling reaction



Entry	Allyl reagent	Conversion (%)[a]	Yield **3.1** (%)[b]
ref	OMe **3.8a**	100	38
1	OPh **3.8b**	100	Complex mixture
2	N(OMe)(Me) **3.8c**	100	36
3	$N(Me)_2$ **3.8d**	100	32

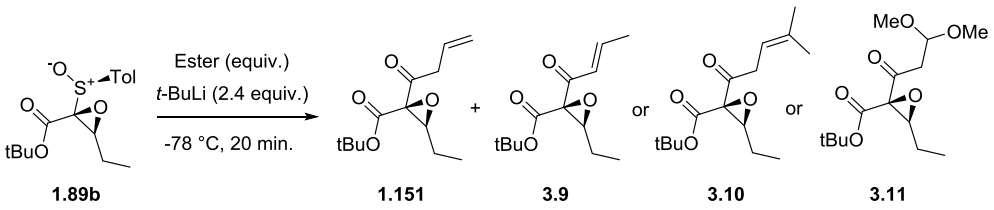
[a]Determined by ^{1}H NMR. Defined as the ratio between the product obtained **3.1** and the starting material **1.89b**. Other by-products not included. [b]Isolated yield.

3.2.3 Acylation reaction – Application to functionalised esters

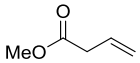
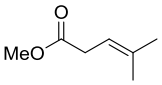
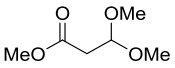
As a continuation of this work, the acylation reaction was investigated with several functionalised esters (Table 3-3) towards the luminacin D synthesis. Using methyl butenoate **3.12**,[50] an inseparable mixture of isomers **1.151** and **3.9** was isolated in moderate yield (33 %, Entry 1). However, only the desired compound **1.151** could be observed in the crude ^{1}H NMR, suggesting that the alkene isomerisation occurred during column chromatography. The trisubstituted alkene **3.13**[51] was then investigated in the coupling reaction to overcome the isomerisation issue (Entry 2). Unexpectedly, no characteristic peaks indicating the formation of the coupling adduct **3.10** were found by ^{1}H NMR. The same outcome was observed when dimethoxy acetal ester **3.14** was employed as substrate (Entry 3).

Since the acylation using methyl butanoate **3.12** gave the expected product **1.151**, but proved unstable to silica gel chromatography, the development of an acylation/reduction procedure involving no intermediate purification was envisaged. Investigations conducted on this approach will be described in the following section.

Table 3-3: Acylation reaction with functionalised esters



1.89b **1.151** **3.9** **3.10** **3.11**

Entry	Ester (equiv.)	Outcome
1	 **3.12** (1.6 equiv.)	33% of an impure mixture of isomers **1.151**/**3.9** (25:75) isolated. Only **1.151** observed in the crude ^{1}H NMR.
2	 **3.13** (1.6 equiv.)	Complex mixture
3	 **3.14** (1.2 equiv.)	Complex mixture

3.3 Diastereoselective reduction

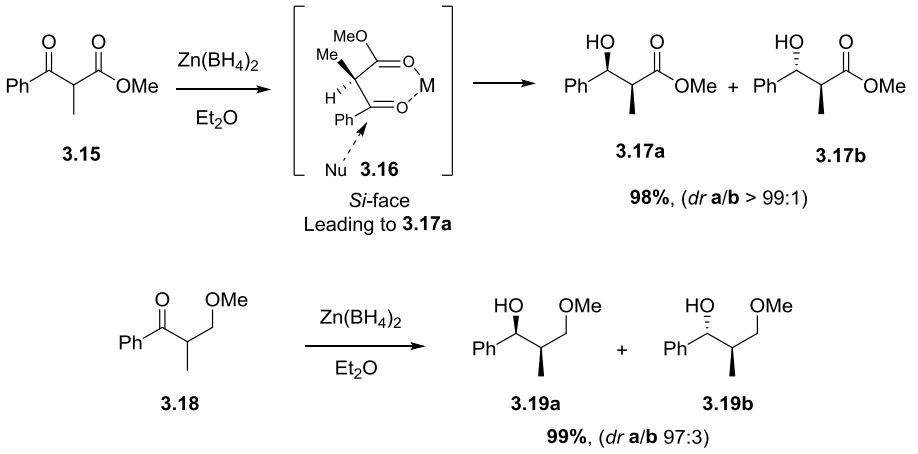
3.3.1 Background

Methodology for diastereoselective chelation-controlled reduction has been described, and an overview of the reduction of β-keto esters, β-hydroxy ketones and α-epoxy ketones will be given in this section.

3.3.1.1 Reduction of β-keto esters and β-hydroxy ketones

In 1983, Yamaguchi *et al.* described the diastereoselective reduction of β-keto esters such as **3.15** using $Zn(BH)_4$ as reducing agent.[52] This led to the almost exclusive formation of the *syn*-product **3.17a** in excellent yield (Scheme 3-4). The reaction was assumed to proceed *via* the chelated transition state **3.16**, with the nucleophile attacking on the face *anti* to the α-methyl substituent. Canceill et *al.* had previously reported that the reduction of **3.15** with $LiAlH_4$ afforded the *syn*-alcohol **3.17a** predominantly (*dr* **3.17a**/**3.17b** 90:10), while the use KBH_4 produced the *anti*-alcohol **3.17b** as major product (*dr* **3.17a**/**3.17b** 27:73).[53] These results showed that the selectivity outcome is related to the coordination capacity of the cation associated to the borohydride. In relation to this work, Nakata et *al.*

demonstrated that the reduction of the analogous β-methoxy ketone **3.18** gave the *syn*-product **3.19a** in excellent selectivity using similar methodology (Scheme 3-4).[54]



Scheme 3-4: Reduction of β-keto-ester

The structure of $Cp_2Nb(CO)H\text{-}Zn(BH_4)_2$ **3.20** has been established by X-ray crystallography (Figure 3-1), showing that Zn^{2+} is linked with BH_4^- through a pair of hydrogen bonds.[55] Based on these data, the bidentate covalent structure **3.21** was proposed by Nakata and co-workers as reacting species.[54] Thus, the formation of the chelated transition state **3.22** and **3.23** was proposed to explain the diastereoselectivity observed with **3.15** and **3.18**, respectively. The hydride is thought to be delivered on the *Re*-face in an intramolecular manner.

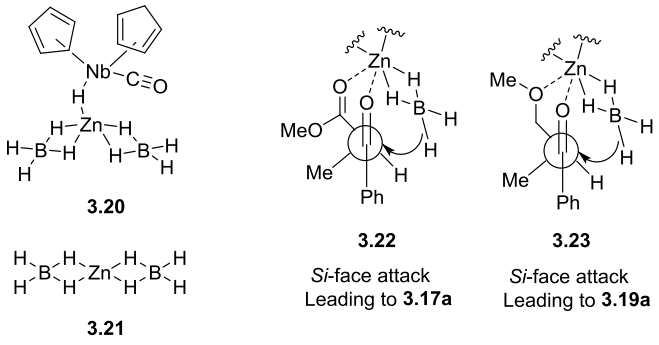
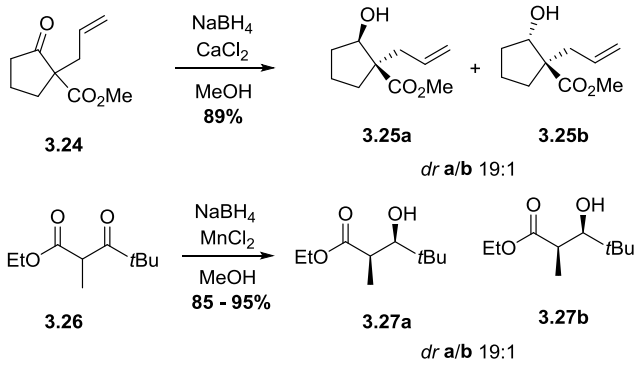


Figure 3-1: Transition states proposed by Nakata

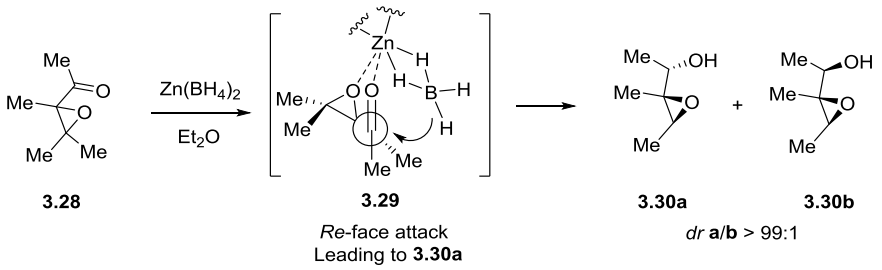
Barreiro *et al.* reported an efficient diastereoselective reduction methodology to cyclic β-keto esters such as **3.24**, using $NaBH_4$ and $CaCl_2$ (Scheme 3-5).[56,57] This led to the formation of the *syn*-compound **3.25a** in excellent diastereoselectivity. A chelated transition state was invoked to explain the selectivity outcome. In addition, the use of $MnCl_2$ in combination with $NaBH_4$ proved also efficient for the diastereoselective reduction of acyclic β-keto esters **3.26**.[58]



Scheme 3-5: diastereoselective reduction of β-keto esters with $NaBH_4$ /$CaCl_2$ or $MnCl_2$

3.3.1.2 Reduction of α-epoxy ketones

The reduction of α-epoxy ketones such as **3.28** was also investigated by Nakata and coworkers using $Zn(BH_4)_2$, which resulted in the formation of the *anti*-product **3.30a** with high diastereoselectivity (Scheme 3-6).[59] The reaction was assumed to proceed through the chelated transition state **3.29**, with the hydride being delivered in an intramolecular manner to the *Re*-face, since the hydride source is bound with the chelating centre.[54]

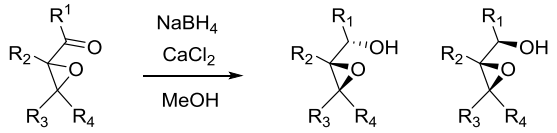


Scheme 3-6: reduction of α-epoxy ketone with $Zn(BH_4)_2$

A complementary methodology was developed by Fuji and co-workers using $NaBH_4$ and $CaCl_2$, leading to the same selectivity outcome (Table 3-4).[60] In order to evidence the formation of calcium complex in solution, NMR experiments were carried out by varying the molar ratio **3.31d**/$CaCl_2$ in CD_3OD, and the influence on the chemical shift on $COCH_3$ and the α-proton substituent (H_2) was studied (Figure 3-2). The results showed that the chemical shift of $COCH_3$ and H_2 moved downfield as long as the concentration of $CaCl_2$ increased, which indicates that the calcium coordinates with **3.31d** in CD_3OD (Figure 3-2). The formation of the complex **3.33** was suggested, with the hydride attack occurring on the *Re*-face**,** leading to the observed diastereoselectivity for the compound ***anti*-3.32**. However, if we consider that the transition state **3.33** is operative, the selectivity of the reaction is expected to decrease when the size of the α-substituent R^2 increases, which is

not the case here (Table 3-4, Entry 1 and 2). Alternatively, Utimoto et *al.* suggested the formation of the transition state **3.34** in order to explain the selectivity (Figure 3-2). By measuring the volume of hydrogen gas released upon mixing $NaBH_4$ and $CaCl_2$ in MeOH, they showed that the presence of $CaCl_2$ catalyses the hydrolysis of $NaBH_4$. Thus, the reacting species were thought to be alkoxyborohydrides $NaBH_{4-n}(OMe)_n$, and the coordination between a Ca^{2+} and the methoxy group of the borohydride species would direct the hydride attack to the *Re*-face.[61]

Table 3-4: Reduction of α,β-epoxy ketones **3.27** with $NaBH_4/CaCl_2$



3.31 ***anti*-3.32** ***syn*-3.32**

Entry	Compound	R_1	R_2	R_3	R_4	*dr* ***anti*-3.28**/***syn*-3.28**
1	**3.31a**	*n*-Bu	H	H	H	85:15
2	**3.31b**	*n*-Bu	Me	H	H	95:5
3	**3.31c**	Me	Me	Me	H	92:8
4	**3.31d**	Me	H	Me	Me	97:3

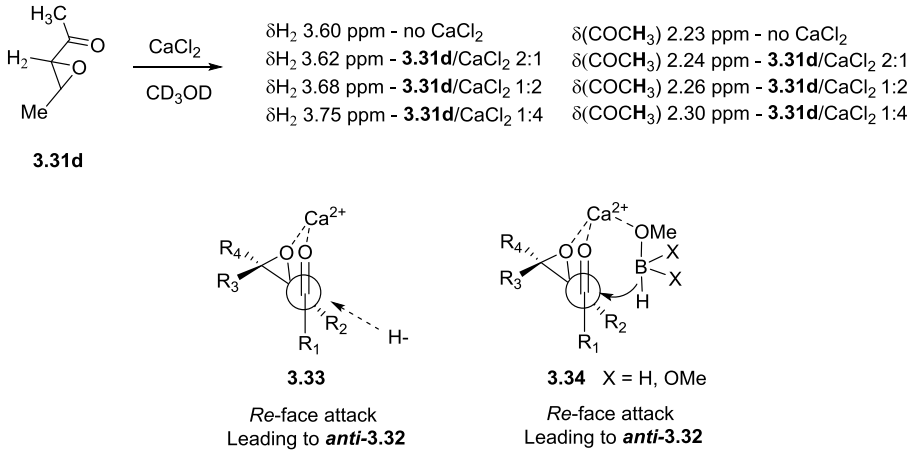


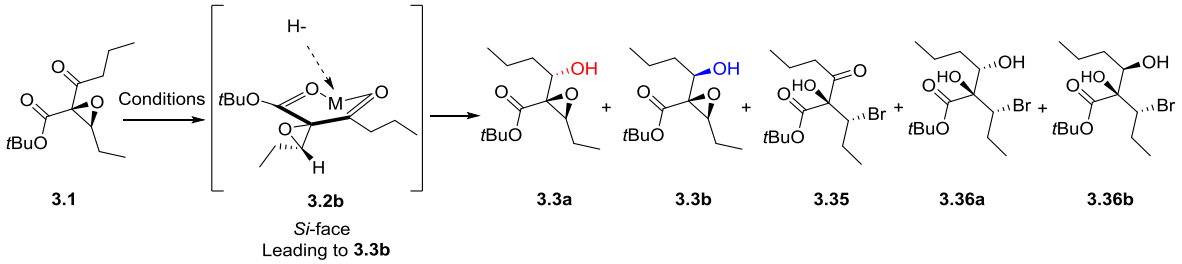
Figure 3-2: NMR experiments and models proposed by Fuji (**3.33**) and Utimoto (**3.34**)

3.4 Optimisation of the reduction reaction and application to luminacin D

3.4.1 Reduction reaction

Despite a modest yield obtained for the acylation step, the potential development of a diastereoselective reduction made this approach promising nonetheless. Several trials involving a Lewis acid to induce chelation-control were undertaken (Table 3-5). As a first experiment, **3.1** was treated with $NaBH_4$ as reducing agent and $MgBr_2$ as chelating metal salt, in a mixture of THF/DCM (Entry 1). Although the starting material was completely consumed, no evidence of the formation of the alcohols **3.3** was observed by ^{1}H NMR. Instead, these conditions resulted in the epoxide opening to form the bromohydrin **3.35,** which was isolated in 48% yield, and the reduced bromohydrin **3.36** was also observed by ^{1}H NMR as a mixture of diastereoisomers (*dr* **3.36a**/**3.36b** 93:7). The *anti*-product **3.36a** was isolated in 9% yield. The epoxide opening issue was overcome by performing the reaction at 0 °C in MeOH, and the expected alcohols **3.3** were then observed by ^{1}H NMR as a mixture of diastereoisomers. To our surprise, the undesired *anti*-diastereoisomer **3.3a** was obtained as major product (*dr* **3.3a**/**3.3b** 71:29, Entry 2). This result suggests that the 1,3-chelated transition state **3.2b** is not operating in these conditions, since it would lead to the predominant formation of the *syn*-diastereoisomer **3.3b**. Replacing $MgBr_2$ by $CaCl_2$ as chelating metal[56,57] resulted in a similar outcome, with **3.3a** obtained in good isolated yield and excellent diastereoselectivity (70%, *dr* **3.3a**/**3.3b** 97:3, Entry 3). Following this, the use of Et_3SiH or L-selectride as reducing agents with $MgBr_2$ was also attempted at -78 °C, though both conditions led to the exclusive formation of the bromohydrin **3.35** (Entry 4 and 5). Since the involvement of $MgBr_2$/$CaCl_2$ led to undesired diastereoselectivity or unexpected reactivity, the reduction of the ketone **3.1** was attempted using L-selectride only (Entry 6). This time, the reaction proceeded in good yield and excellent diastereoselectivity towards the desired *syn*-product **3.3b** (Entry 6, 90%, *dr* **3.3a**/**3.3b** 1:9). Interestingly, employing the more hindered LS-selectride (Figure 3-3) led to a drop of diastereoselectivity and conversion (Entry 7).

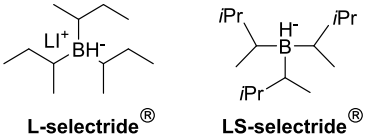
Table 3-5: Optimisation of the reduction reaction



Si-face
Leading to **3.3b**

Entry	Conditions	Yield **3.3** (%)	Yield **3.35** (%)	Yield **3.36** (%)
1	$NaBH_4$ (1.05 equiv.), $MgBr_2$ (1.6 equiv), DCM/THF 2:1, -78 °C to rt, 3 h	-	78[a] (48)	22[a] (9) (*dr* **3.36a**/**3.36b** 93:7)[a]
2	$NaBH_4$ (1.2 equiv.), $MgBr_2$ (2 equiv.), MeOH, 0 °C, 30 min.	100[a] (*dr* **3.3a**/**3.3b** 71:29)[a]	-	-
3	$NaBH_4$ (0.6 equiv.), $CaCl_2$ (2 equiv.), MeOH, 0 °C, 30 min.	100[a] (72)[b] (*dr* **3.3a**/**3.3b** 97:3)[a]	-	-
4	Et_3SiH (1.05 equiv.), $MgBr_2$ (1.6 equiv), DCM, -78 °C, 2 h	-	83[a] (64)[b]	-
5	L-selectride (1.05 equiv.), $MgBr_2$ (1.6 equiv), DCM, -78 °C, 2 h	-	100[a]	-
6	L-selectride (1.05 equiv.), THF, -78 °C, 30 min.	100[a] (90)[b] (*dr* **3.3a**/**3.3b** 1:9)[b]	-	-
7	LS-selectride (1.3 equiv.), THF, -78 °C, 45 min.	48[a] (*dr* **3.3a**/**3.3b** 33:67)[a]	-	-

[a]Determined by ^1H NMR; [b]Isolated yield



L-selectride® **LS-selectride®**

Figure 3-3: representation of L and LS selectride

In order to rationalise the selectivity outcome, it can be noted that the selectivity observed when $NaBH_4$ and $CaCl_2/MgBr_2$ were employed corresponds to the selectivity obtained by Fuji and Umimoto for the reduction of α-epoxy ketones. Thus, the 1,2-chelation-controlled transition state **3.37** can be proposed to explain the facial selectivity (Figure 3-4).[61] On the other hand, the models **3.2b** or **3.38** are consistent with the selectivity observed when L or LS-selectride are employed, assuming that the Li cation is able to chelate between the carbonyl groups (model **3.2b**) or between the carbonyl group and the epoxide (model **3.38**). Nucleophilic attack from the least hindered *Si*-face in both cases would lead to the observed formation of the *syn*-compound **3.3b**. The excellent yield and diastereoselectivity observed for the desired diastereoisomer **3.3b** using L-selectride made the acylation/reduction suitable for the luminacin D synthesis.

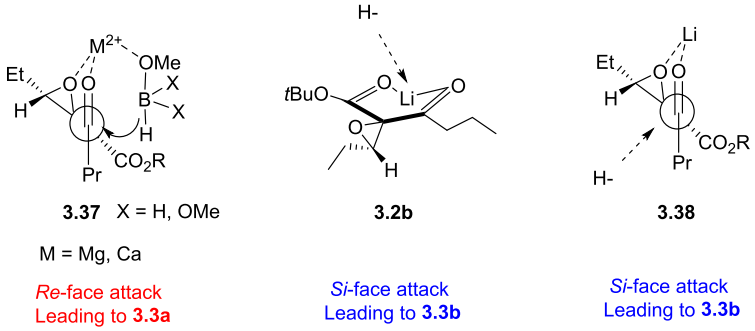
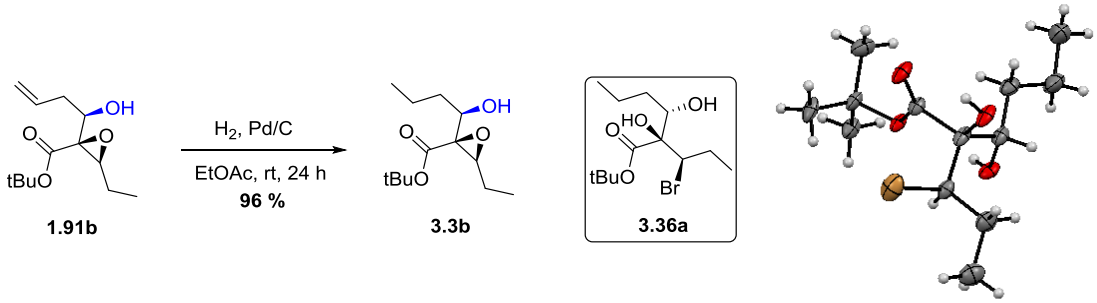


Figure 3-4: Rationalisation of the diastereoselectivity

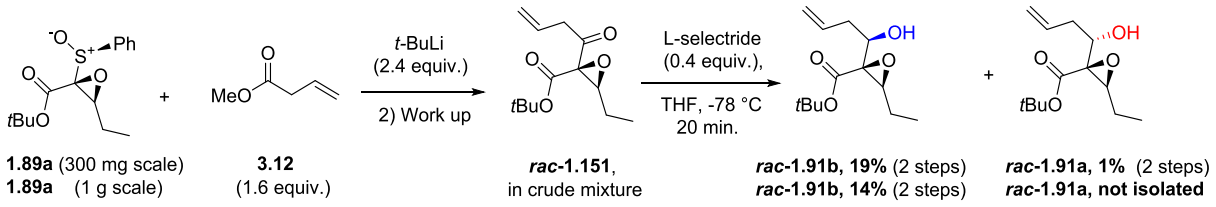
The relative configuration of **3.3a** and **3.3b** was assigned by NMR comparison with the *anti*-alcohol, which was obtained after reduction of the double bond of the previously synthesised **1.91b** (Scheme 3-7). The regioselectivity of the epoxide opening on **3.35** was confirmed by HMBC. The relative configuration of **3.36a** was determined by XRD analysis (Scheme 3-7).



Scheme 3-7: Reduction of **1.91b** and X-ray structure of **3.36a**

3.4.2 Application to the luminacin D synthesis

The reduction methodology was then applied towards the formation of the key intermediate **1.91**, using methyl butenoate **3.12** (Scheme 3-8). Since the intermediate **1.151** proved unstable to purification on silica gel, the reduction was attempted on the crude material, immediately after work-up. A first experiment was conducted on small scale with the racemic epoxide **1.89a** and L-selectride as reducing agent. The *syn*-α-epoxy alcohol **1.91b** was obtained as major product in an encouraging yield (19 % over 2 steps), together with a minor quantity of the *anti*-diastereoisomer **1.91a** (1% over 2 steps), with separation achieved by column chromatography. Since a large number of by-products was formed during the process, the determination of the *dr* on the crude mixture proved difficult. However, the *syn*-diastereoisomer appeared clearly predominant in the crude ^{1}H NMR (Scheme 3-8), which is consistent with the diastereoselectivity observed for the reduction of the model substrate **3.1** using L-selectride (cf. section 3.4.1). The relative configuration of **1.91a** and **1.91b** was confirmed by comparison of the NMR data already reported by our group for these two compounds.[17] Unfortunately, the reaction proved less efficient on 1 g scale, resulting in a drop of yield (14% for **1.91b** over 2 steps). Several parameters, including the volatility of intermediate **1.151** and the purification issues induced by the formation of numerous by-products over the 2 steps, made the process cumbersome. Therefore, no further investigations were carried out on this approach.



Scheme 3-8: Formation of **1.91** *via* the acylation/reduction approach

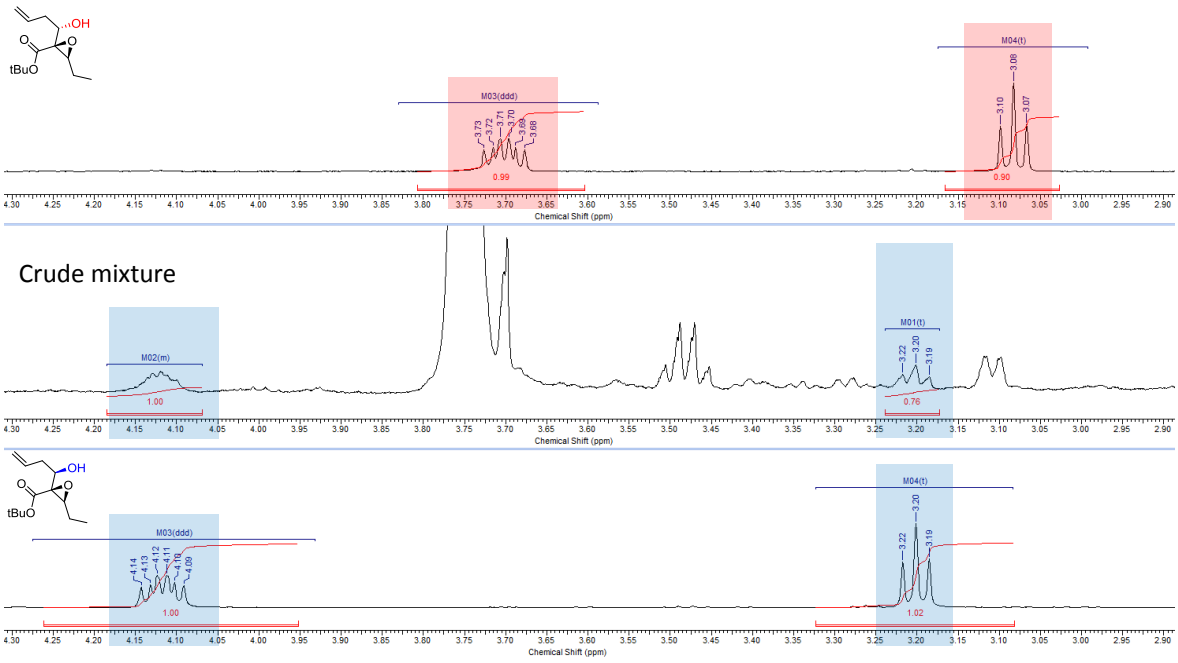
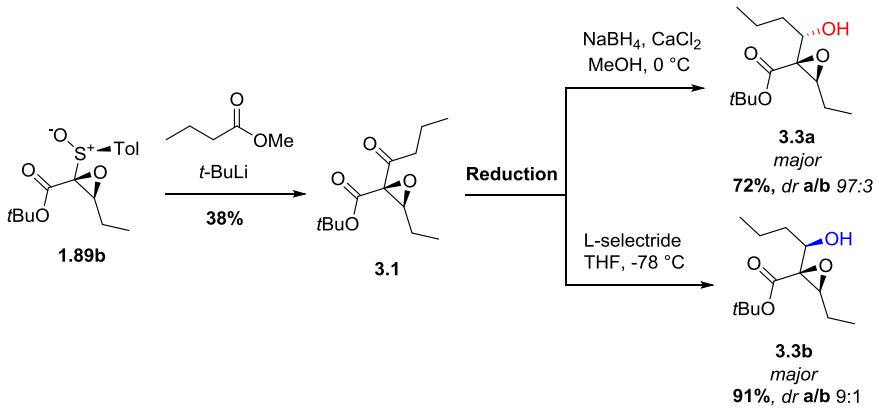


Figure 3-5: ^{1}H NMR comparison of the crude mixture after reduction of **1.151** (middle spectrum) with the clean compounds **1.91a** (top spectrum) and **1.91b** (bottom spectrum). Characteristics features are highlighted in red for **1.91a**, and blue for **1.91a**.

3.5 Summary

The optimisation conducted with model substrate **3.1** highlighted some interesting results (Scheme 3-9). Thus, when $NaBH_4$ was associated with $CaCl_2$, an excellent selectivity was obtained towards the formation of the *anti*-allyl alcohol **3.3a**. On the other hand, it was possible to reverse the facial selectivity of the reaction by using L-selectride only, leading to the desired *syn*-alcohol **3.3b** as major diastereoisomer. While transition states could be proposed, the origin of this selectivity remains unsure.

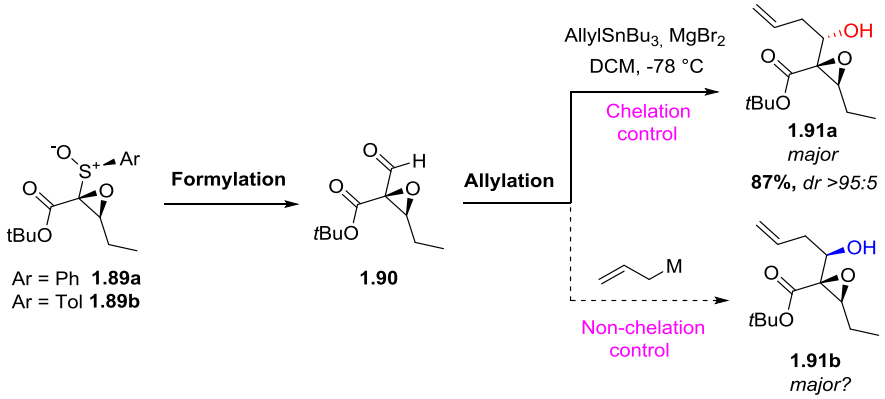


Scheme 3-9: Summary of results

When applied towards the luminacin D synthesis, although excellent diastereoselectivity towards the desired product was obtained using L-selectride, the process proved cumbersome, and a poor overall yield was obtained. Thus, an alternative approach was investigated.

Chapter 4: Alternative approach

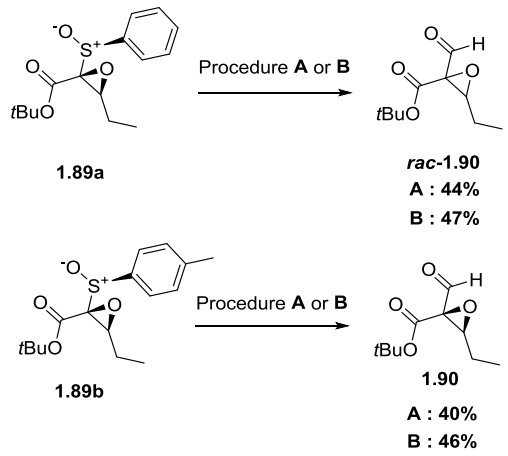
As mentioned in section 1.3.4.1, a study of Mulzer and co-workers involving the allylation reaction of α-formyl esters showed that the aldehyde facial selectivity could be reversed, depending on whether the reaction was carried out under chelation-control or not.[43] Inspired by this work, the allylation of the aldehyde **1.90** under conditions of non-chelation control was re-examined, with the aim of reversing the diastereoselectivity compared to the metal-mediated allylation reaction already reported by our group, which led to the undesired **1.91a** (Scheme 4-1).



Scheme 4-1: New approach

4.1 Oxiranyl anion Formylation

In order to study the allylation reaction, the first task was to resynthesise the key aldehyde **1.90** (and ***rac*-1.90**), which was achieved from the epoxide precursors **1.89a-b,** applying similar conditions as used for the acylation procedure (Procedure **B**, Scheme 4-2). The reaction proceeded in an improved yield compared to the previous procedure **A**, and is generally more efficient as it can be conducted at -78 °C (previously -120 °C) without the need of $CeCl_3$, which had to be dried under vacuum prior to the reaction and made the work up difficult.



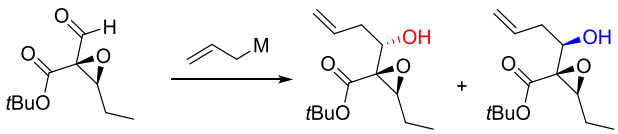
Procedure **A**: DMF (2 equiv.), *t*BuLi (2 equiv.) $CeCl_3$ (0.8 equiv.), Et_2O, -120 °C
Procedure **B:** DMF (1.5 equiv.), *t*BuLI (2.4 - 2.8 equiv.), Et_2O, -78 °C

Scheme 4-2: Comparison between the reported procedure (**A**) and the new procedure (**B**)

4.2 **Allylation reaction**

With access to aldehyde **1.90**, the allylation reaction was investigated (Table 4-1). In relation with the work of Mulzer and Prantz, investigations were directed towards the use of non-chelating conditions for the allylation reaction (Table 4-1). Given the presence of an epoxide function in the substrate, the use of strong Lewis acids was avoided. In a first experiment, the reaction was carried out in DCM using allyl trimethyl silane and a sub-stoichiometric amount of TBAF, according to a reported procedure (Entry 1).[62] However, the reaction did not proceed in these conditions, and aldehyde **1.90** was recovered after 48 h at rt. The allylation of **1.90** finally occurred using the more reactive pinacolyl allylboronate in DCM, by raising the temperature from -78 °C to rt overnight (entry 2).[63] As predicted, the non-chelation control promoted the formation of the desired *syn*-diastereoisomer **1.91b**, in an excellent diastereoselectivity and isolated yield (80%, *dr* **1.91b**/**1.91a** >95:5). The NMR expansion of the crude mixture, showing the characteristic peaks used for the *dr* determination in comparison with the pure products **1.91a** and **1.91b** is shown in Figure 4-1.

Table 4-1: Optimisation of the allylation reaction



***rac*-1.90** ***rac*-1.91a** ***rac*-1.91b**

Entry	M =	Conditions	Conversion (%)[a]	*dr* **1.91a/1.91b**[a]	Yield **1.91a** (%)[b]	Yield **1.91b** (%)[b]
Ref	$SnBu_3$ (1.05 equiv.)	$MgBr_2$ (1.6 equiv.), DCM (0.2 M), -78 °C, 2 h	n.d	> 95:5	87	-
1	TMS (1.05 equiv.)	TBAF (0.1 equiv.), MS 4Å, DCM (0.05 M), rt, 48 h	s.m. recovered	-	-	-
2	 (1.05 equiv.)	DCM (0.3 M), -78 °C to rt, 16 h	100	< 5:95	2	80

[a]Determined by ^{1}H NMR; [b]Isolated yield.

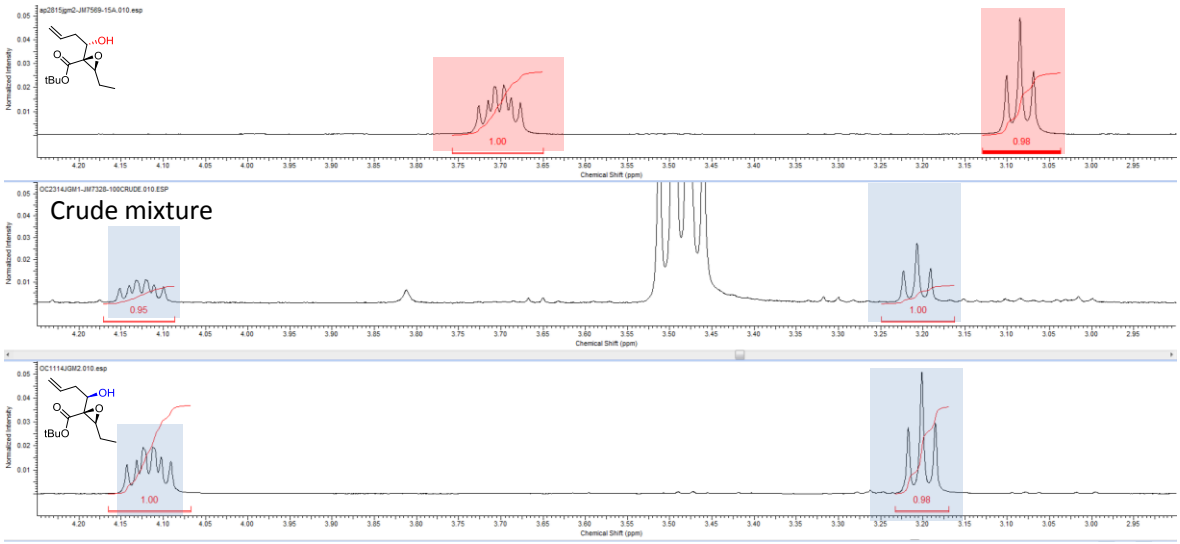


Figure 4-1: NMR comparison of the crude mixture after allllylation of **1.90** (middle spetrum) with the clean compounds **1.91a** (top spectrum) and **1.91b** (bottom spectrum). Characteristics features are highlighted in red for **1.91a**, and blue for **1.91b**.

Since the reaction with allyl boronate substrates proceeds *via* a classic Zimmerman-Traxler transition state (Figure 4-2), and the allyl reagent is achiral, the observed diastereoselectivity must have arisen through excellent substrate control.

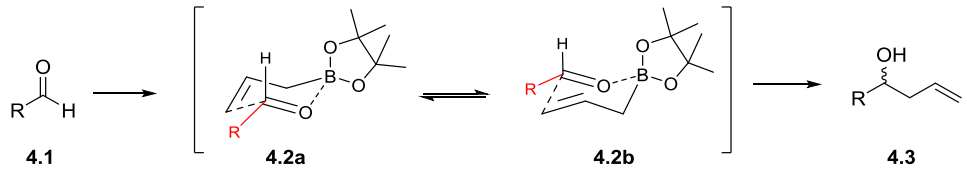


Figure 4-2: Allylation mechanism

By considering all the possible conformations of **1.90** (Figure 4-3), the facial selectivity can only be explained by invoking the transition states **4.4a** or **4.4b**, which would lead to the observed formation of **1.91b** through a nucleophilic attack from the least hindered *Re*-face. Indeed, all the other possible transition states would promote the formation of the *anti*-alcohol **1.91a** *via* attack from the opposite face. It can be noted that the conformers **4.4a** and **4.4b** are related to the Cornforth-Evans and the polar Felkin-Anh transition states respectively, assuming that the C-O bond of the epoxide acts as the "polar substituent" in preference to the ester.

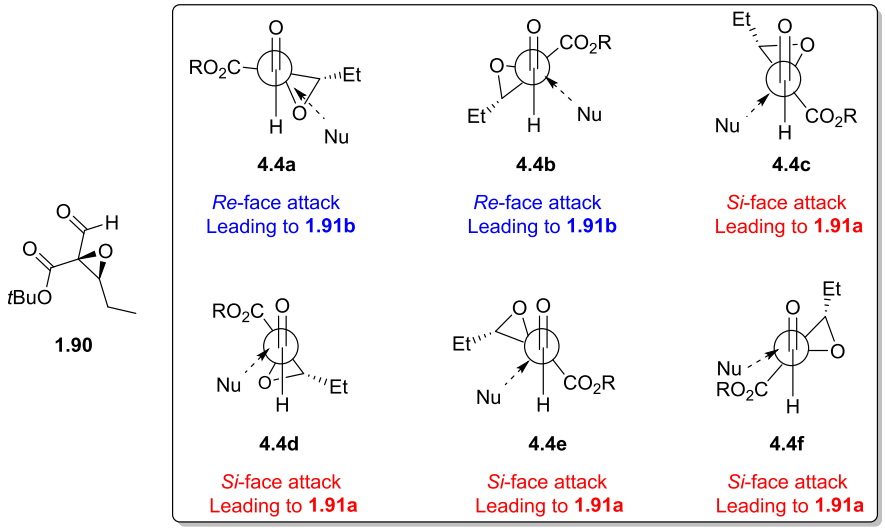
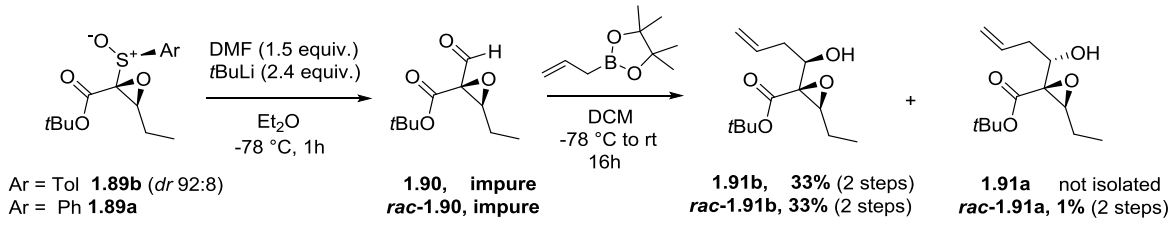


Figure 4-3: Possible conformers of **1.90**

Given the excellent results obtained with this approach on small scale, the procedure was attempted on larger scale for the synthesis of luminacin D.

4.3 Application on large scale

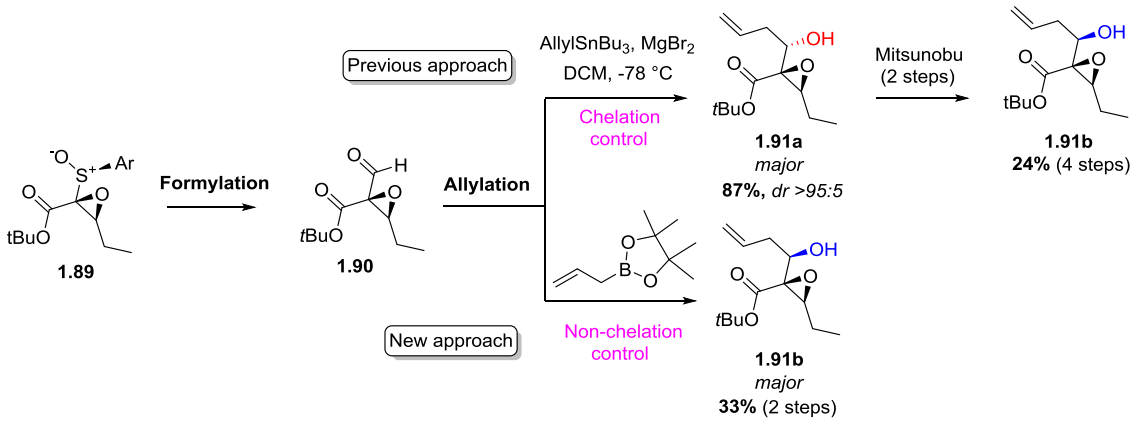
The optimised procedure was then carried out on 1.5 g scale of sulfoxide **1.89b** (*dr* 92:8) (Scheme 4-3). The slow addition of *t*-BuLi to the mixture *via* syringe pump over a period of 1 h was found to give the best results for the formylation reaction. After column chromatography, the aldehyde **1.90** was obtained in a mixture with minor impurities. Subsequent treatment with the pinacolyl allylboronate using the optimised conditions enabled isolation of the *syn*-alcohol **1.91b** as major product in 33 % yield over 2 steps, together with the minor *anti*-diastereoisomer **1.91a**, isolated in 1% yield. Although an accurate *dr* determination was not possible by ^{1}H NMR due to the presence of impurities, the ratio of isolated yields of **1.91a** and **1.91b** is consistent with that observed on small scale. Similar results were obtained when the racemic phenyl epoxide **1.89a** was used as starting material (Scheme 4-3).



Scheme 4-3: Formylation/allylation approach

4.4 Summary

A two-step methodology was successfully developed to synthesise the intermediate **1.91b** from **1.89** in high diastereoselectivity (Scheme 4-4). In the context of the luminacin D synthesis, this new procedure represents a significant improvement compared to the previous route reported by our laboratory, which required two extra steps for the formation of **1.91b**, in a lower overall yield (Scheme 4-4).

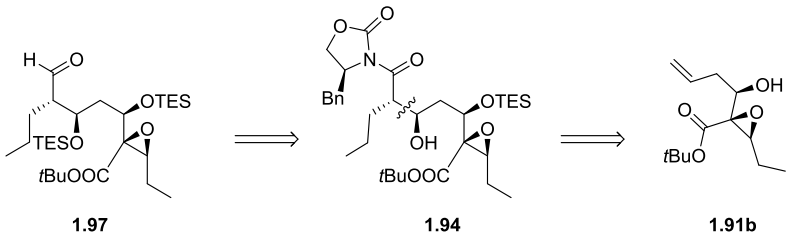


Scheme 4-4: Comparison of the new methodology compared to the previous approach

Chapter 5: Completion of the Synthesis

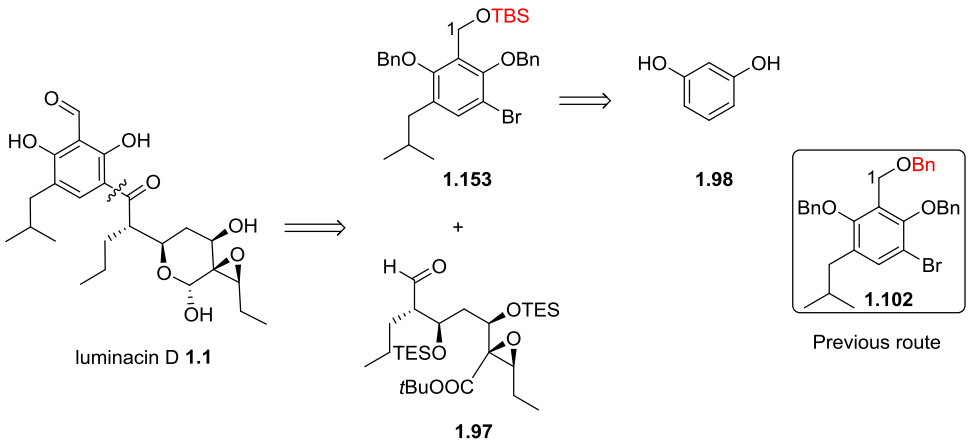
5.1 Aim

With access to the key intermediate **1.91b**, the synthesis of the aliphatic fragment **1.97** was pursued, following the reported route (Scheme 5-1). This involved the formation of the key intermediate **1.94** *via* Evans-aldol reaction.



Scheme 5-1: Synthesis of the aliphatic fragment

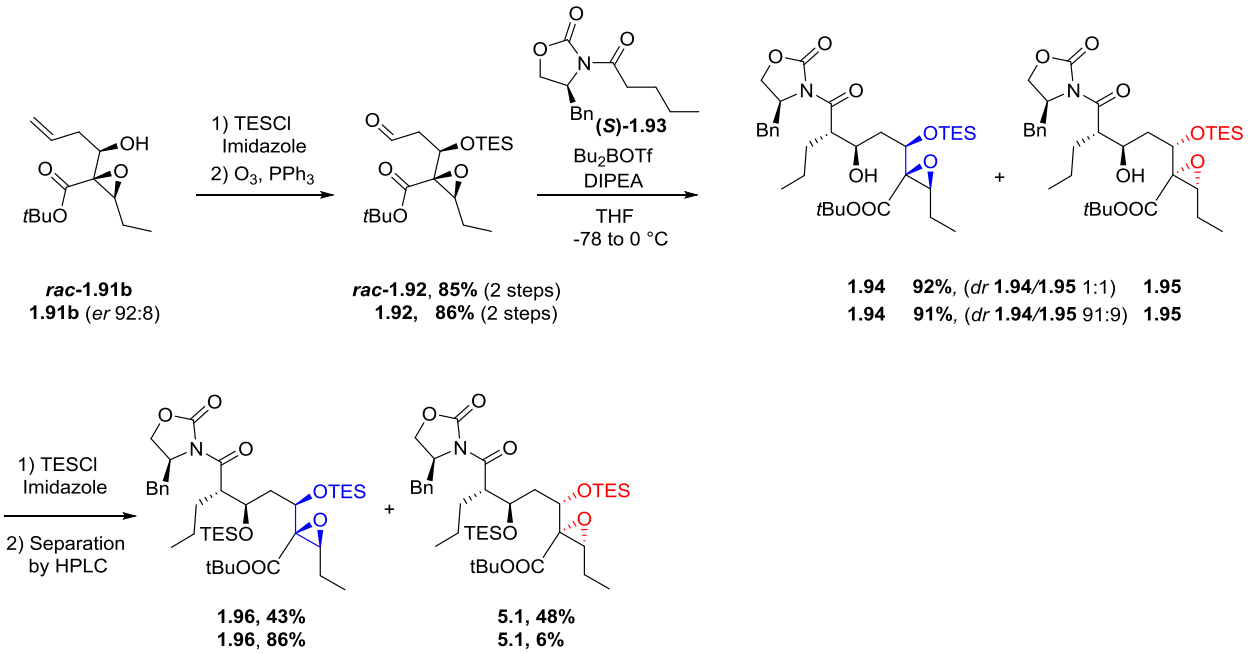
Following this, the synthesis of the aromatic fragment **1.153** was investigated (Scheme 5-2). The latter can be distinguished from the previous aromatic fragment **1.102** by the choice of protecting group for the benzylic alcohol. The completion of the luminacin D synthesis was then attempted with this new protecting group strategy. The synthesis of the aromatic fragment **1.153** was envisaged from the commercially available resorcinol **1.98**.



Scheme 5-2: New aromatic group strategy

5.2 Evans aldol reaction

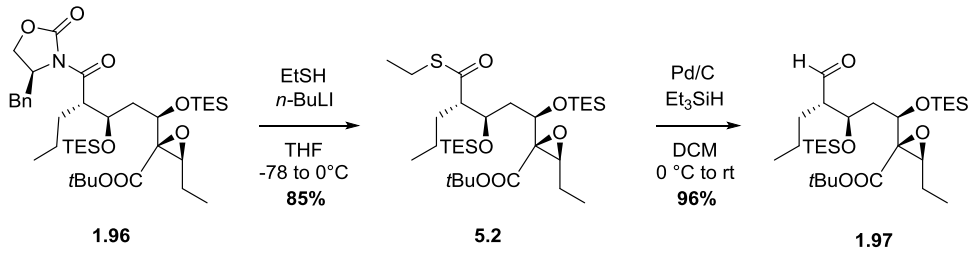
The enantioenriched intermediate **1.91b** (*er* 92:8) was converted to the corresponding aldehyde **1.92** after protection of the alcohol function and subsequent ozonolysis (Scheme 5-3). The same procedure, applied to the racemic compound ***rac*-1.91b**, enabled formation of ***rac*-1.92** in similar yield. Following this, the aldehyde **1.92** (*er* 92:8) was engaged in Evans-aldol reaction with the acyl chiral oxazolidinone **1.93**, according to the procedure reported by our group.[17] After 4h, analysis by TLC indicated full consumption of the starting material, and the formation of two aldol adducts was evidenced by ^{1}H NMR, in a 91:9 diastereomeric ratio. The two isomers could be separated by preparative HPLC after TES protection of the formed alcohol, which allowed assignment of the major product **1.96** as the expected C2',C3' *syn*-diastereoisomer thanks to NMR comparison with the reported data.[17] The minor product **1.95**, which was previously observed by Nathan Bartlett but not characterised, is thought to result from the Evans aldol reaction of the oxazolidinone **1.93** with the enantiomer of **1.92**, since an enantioenriched material was employed (*er* 92:8). The exclusive formation of the aldol products **1.94** and **1.95** in a 1:1 *dr*, which was observed using the racemic aldehyde ***rac*-1.92**, provided further evidence of the configuration assignment. From that mixture, alcohol protection and HPLC separation allowed isolation of **1.96** and **5.1** in 43 and 48% yields, respectively.



Scheme 5-3: Evans aldol reaction and separation of the diastereoisomers

5.3 Synthesis of the aliphatic fragment

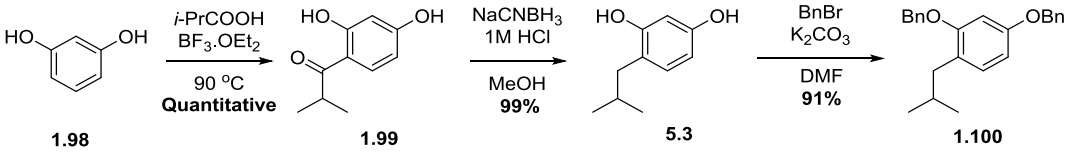
The formation of the aliphatic fragment **1.97** was achieved in 2 steps from the enantiopure diastereoisomer **1.96** (Scheme 5-4). In the first step, the chiral oxazolidinone was removed using ethyl thiolate, giving the corresponding thioester **5.2** in 85% yield. The subsequent palladium-mediated reduction reaction produced the final aldehyde fragment **1.97**. The yield of the reduction was significantly increased by adding the reagents at 0 °C rather than rt as reported in the previous procedure (96% *vs* 75%)



Scheme 5-4: Completion of the aliphatic fragment

5.4 Aromatic synthesis[1]

In order to synthesise the aromatic fragment, the methodology used by Nathan Bartlett on the previous aromatic synthesis (described in section 1.3.6.2) was reproduced for the formation of the intermediate **1.100** (Scheme 5-5). Thus, acylation and subsequent reduction afforded the isobutyl resorcinol **5.3**, which was then benzylated to give **1.100** in excellent yield.

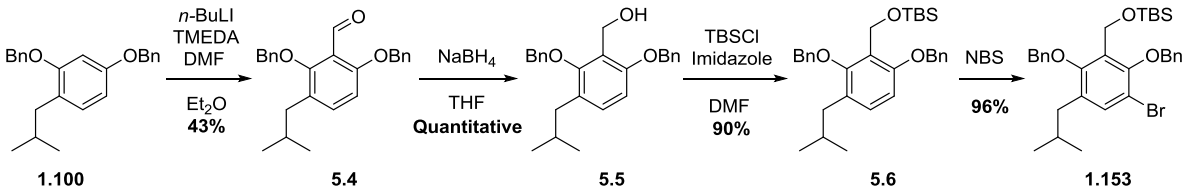


Scheme 5-5: Synthesis of the intermediate **1.100**

To complete the synthesis of the aromatic fragment, the compound **1.100** was subjected to formylation using *n*-BuLi and DMF, giving the aromatic aldehyde **5.4** in moderate yield (Scheme 5-6). The aldehyde was then reduced to the alcohol **5.5**, which was subsequently

[1] The synthesis of the aromatic fragment was achieved by Kane Hands (MSc student) under direct supervision.

protected with TBSCl to give the intermediate **5.6**. Finally, monobromination provided the expected compound **1.153** in excellent yield.

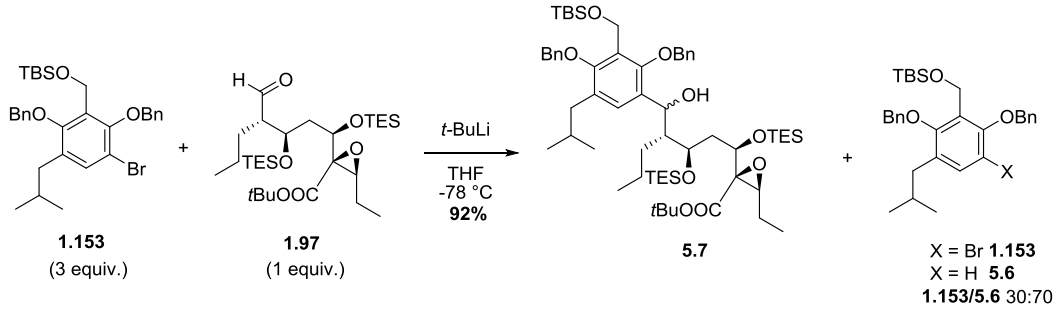


Scheme 5-6: Completion of the aromatic synthesis

5.5 Completion of the luminacin D synthesis

5.5.1 Coupling reaction

The aromatic fragment **1.153** was then used as substrate for the coupling reaction with **1.97**, which was carried out according to the procedure reported by our group (Scheme 5-7).[17] Pleasingly, the benzylic TBS ether was found to be stable in the coupling conditions, as the expected coupling adduct **5.7** was obtained as a mixture of epimers in excellent yield. In addition, the excess of aromatic compound could be recovered by column chromatography as an inseparable mixture of compounds **5.6** and **1.153**, and was recycled for the next coupling reaction by treatment with NBS.

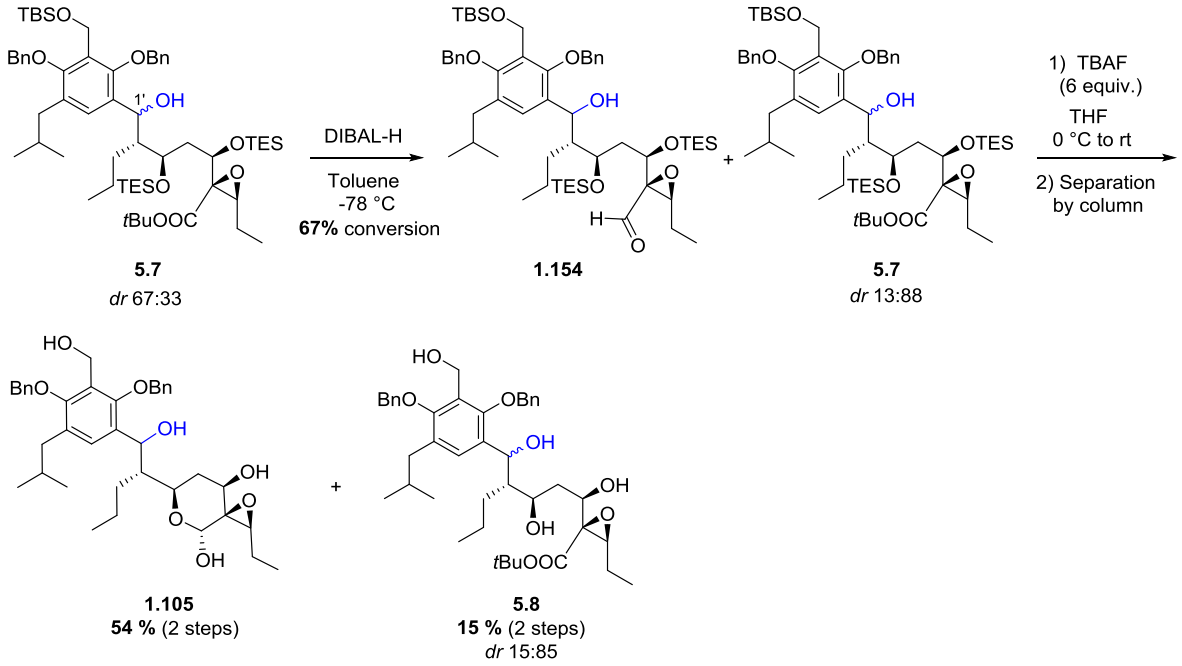


Scheme 5-7: Coupling reaction

5.5.2 Hemiacetal formation

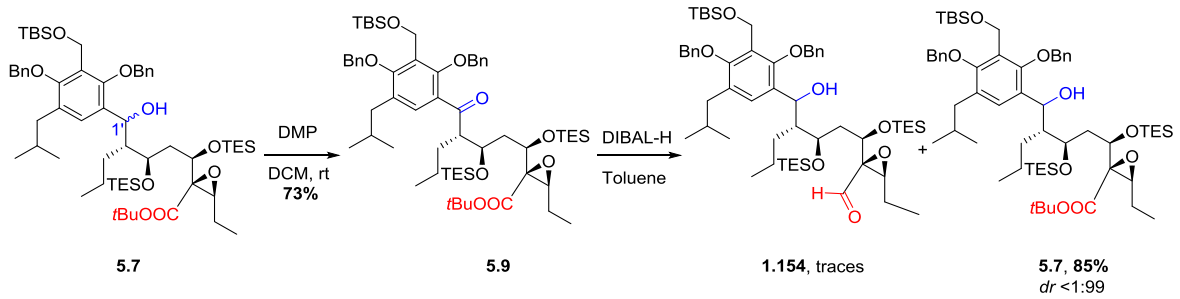
The mixture of epimers **5.7** (*dr* 67:33) was then subjected to DIBAL-H reduction, which resulted in the incomplete conversion of the *t*-butyl ester to the corresponding aldehyde **1.154** (Scheme 5-8). Surprisingly, the minor epimer was found to be unreactive towards reduction, as the aldehyde **1.154** was obtained as a single diastereoisomer, together with the remaining starting material **5.7** (*dr* 13:88, the alcohol configuration at C1' was not

determined). The formation of the hemiacetal **1.105** was then achieved *via* TES deprotection of **1.154** with TBAF, followed by spontaneous cyclisation. Hemiacetal **1.105** could be separated with some difficulties from the residual starting material **5.8** by column chromatography.



Scheme 5-8: Hemiacetal formation

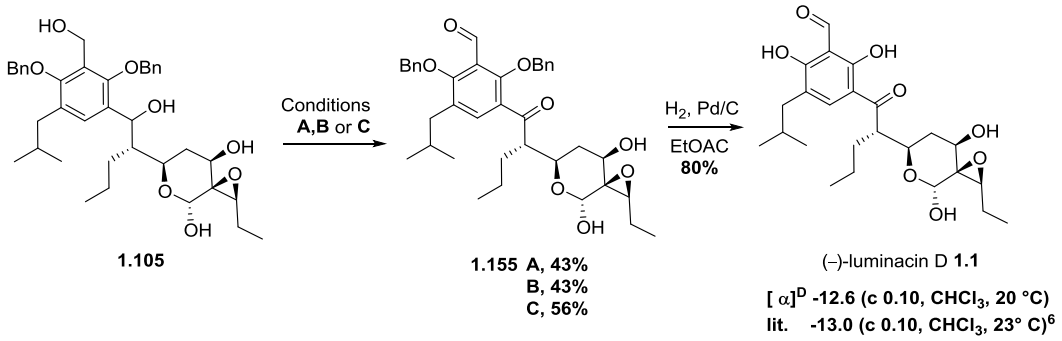
Assuming that the lack of reactivity observed for the minor epimer **5.7** was due to conformational restrictions imposed by the alcohol configuration at C1', a sequential oxidation/reduction process towards the formation of **1.154** was attempted (Scheme 5-9). Thus, the benzylic alcohol was oxidised using Dess-Martin periodinane in 73% yield, and the resulting ketone **5.9** was then treated with an excess of DIBAL-H. Although the benzylic ketone in C1' was effectively reduced, only trace amount of the aldehyde **1.154** could be observed by NMR. Instead, the compound **5.7** was obtained as a single epimer, whose configuration unfortunately corresponds to that of the previously observed unreactive isomer towards reduction (cf. Scheme 5-8). Following this, no further investigation was attempted on this sequence, and the synthesis was pursued on the major epimer **1.105**.



Scheme 5-9: Attempted sequential oxidation/reduction process

5.5.3 Completion of the synthesis

With access to hemiacetal **1.105**, the formation of luminacin D was achieved in 2 further steps (Scheme 5-10). At first, the treatment of **1.105** using DMP in the presence of $NaHCO_3$ enabled oxidation of the benzylic alcohols to give **1.155** in moderate yield. The oxidation step proved cumbersome and would necessitate further investigations. Indeed, the procedure giving the best yield (56%) required termination of the reaction prior to completion (5 min), separation of the product from the starting material, and treatment of the remaining starting material a second time with DMP. Finally, subsequent deprotection provided (–)-luminacin D **1.1** in 80% yield after column chromatography and HPLC purification.



Scheme 5-10: Completion of the synthesis

As shown in Figure 5-1 and Figure 5-2, the ^{1}H and ^{13}C NMR spectra of luminacin D synthesised *via* this new modified route were found to match with the spectra reported by our laboratory on the previous approach.[17] In addition the value of the optical rotation found was similar as the previously reported values.[6,17] This work enabled to produce 17 mg of natural product.

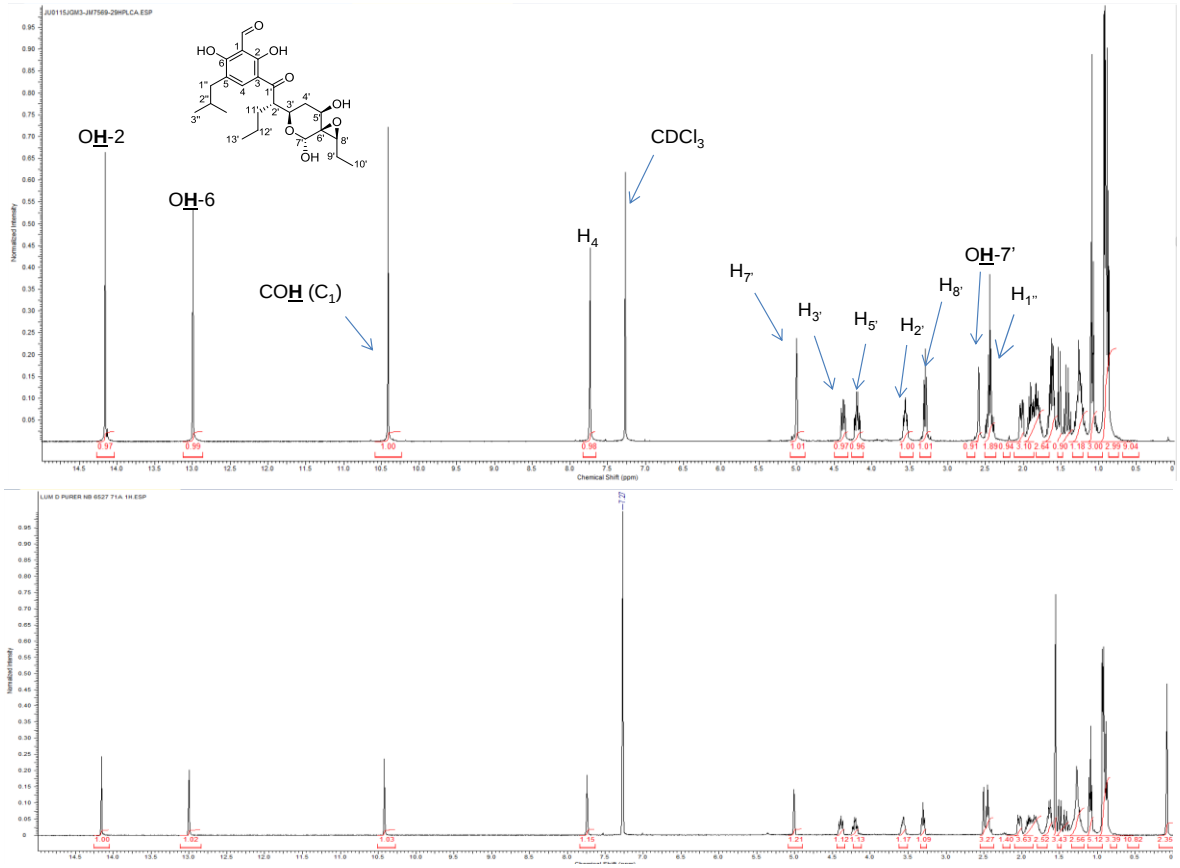


Figure 5-1: ^{1}H NMR comparison of the final product. The top spectrum was obtained through this work. The bottom spectrum correspond to the previous work of our laboratory.

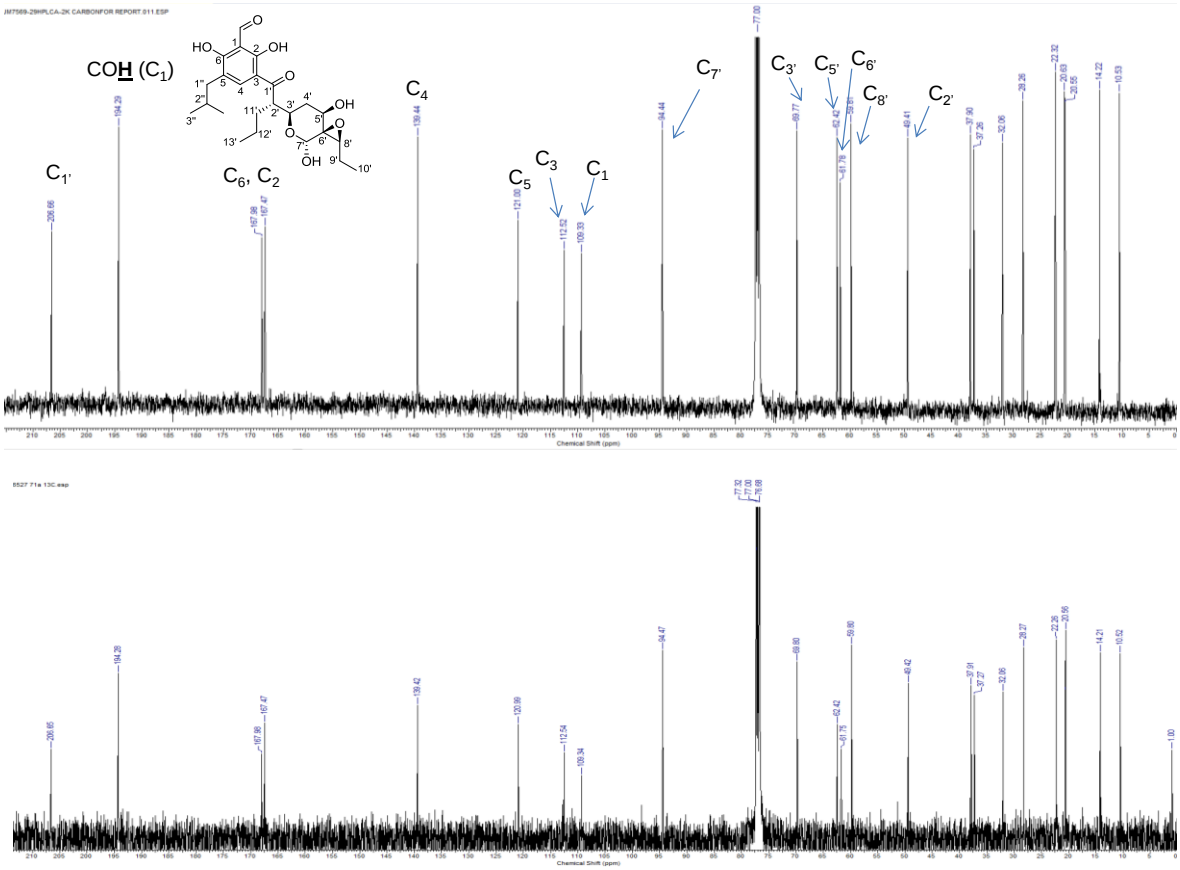


Figure 5-2: ^{13}C NMR comparison of the final product. The top spectrum was obtained through this work. The bottom correponds to the previous work of our laboratory.

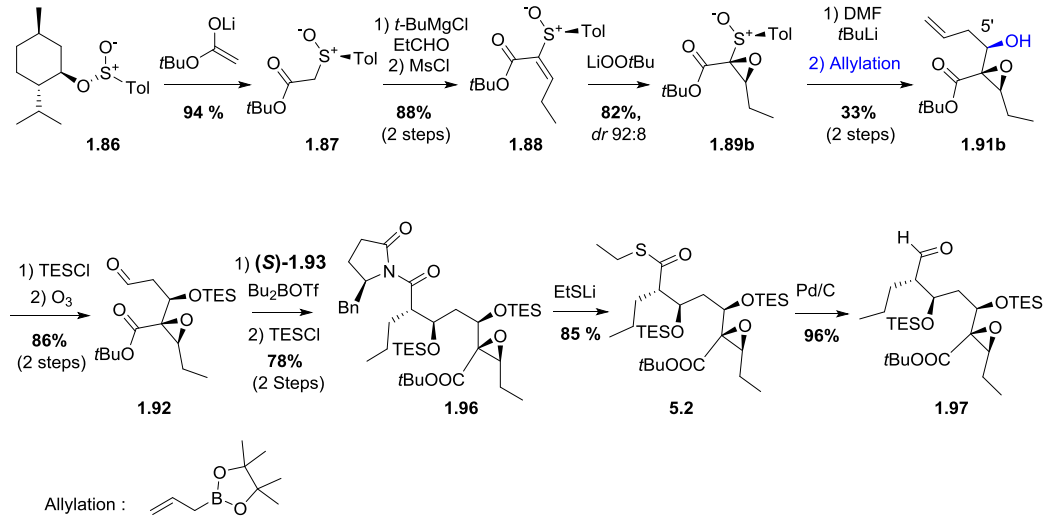
Chapter 6: Luminacin D: conclusions

From a general perspective, this second generation synthesis of (–)-luminacin D represents a good improvement over the previously reported route. The final product is now accessible in 17 steps (previously 20 steps) from a commercially available material, with an overall yield of 2.7 % (previously 2.5%).

6.1.1 Aliphatic synthesis

Regarding the synthesis of the aliphatic fragment (Scheme 6-1), the main modification compared to the reported route involves the development of a new diastereoselective allylation procedure, which allowed the direct formation of the desired diastereoisomer **1.91b**. The previous allylation procedure led to the predominant formation of the C5'-epimer of **1.91b**, therefore a Mitsunobu inversion/deprotection process was required to pursue the synthesis.

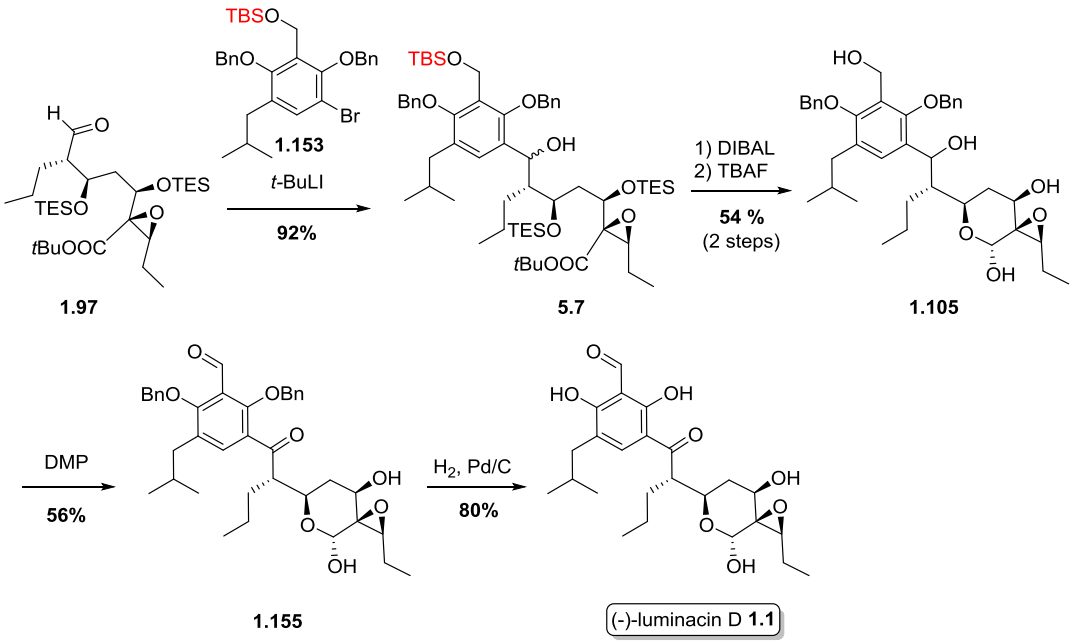
Considering the other steps of the aliphatic synthesis, it can be noted that a significant yield improvement was obtained for the thioester reduction step compared to the reported procedure (95% *vs* 75% previously). This apart, the yields and selectivity obtained were similar to those reported by Nathan Bartlett. The aliphatic fragment **1.97** was achieved by this modified route in 12 steps for an overall yield of 12.3% (previously 14 steps, 6.4% overall yield).



Scheme 6-1: New synthesis of the aliphatic fragment

6.1.2 New protecting group strategy

The new aromatic protecting group strategy was successfully applied to the final steps of the synthesis, which enabled the formation of luminacin D in 5 steps from the coupling reaction (Scheme 6-2). In comparison, the previous route required one extra deprotection step to achieve the synthesis of the natural product. However, this new route would need to be further optimised, as it resulted in a decrease of yield compared to the previous one (22% yield over 5 steps *vs* 40% over 6 steps previously).



Scheme 6-2: Completion of the synthesis

Chapter 7: Fluorinated carbohydrates: Introduction

7.1 Properties of fluorinated compounds

7.1.1 Fluorine - Overview

Fluorine is the most electronegative element in the periodic table.[64] This property confers a strong ionic character to the C-F bond, and is also responsible for the low polarisability and the relatively small size of the fluorine atom, as its three non-bonding electron pairs are held tightly to the nucleus.[65]

Due to its high level of polarisation, the presence of a C-F bond has an influence on the molecular conformation (Figure 7-1). This can arise from dipole interactions, as observed in the case of α-fluoroamides such as **7.1**, in which the C-F bond adopts an orientation *anti* to the carbonyl bond, in order to minimise electrostatic repulsions. In addition, the C-F bond can also induce conformational preferences through hyperconjugative interaction (gauche effect), or electrostatic stabilisation or electrostatic stabilisation of proximal cations, resulting in both cases in a gauche conformation.[65,66,67,68]

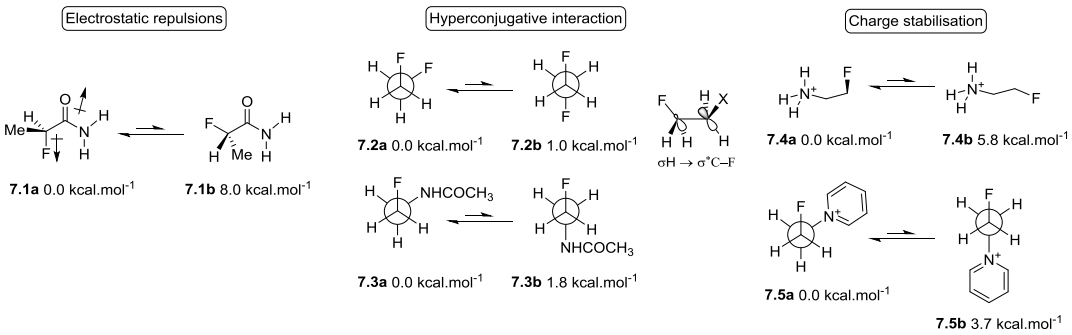
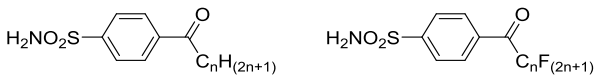


Figure 7-1: Conformational changes induced by fluorine

Apart from the aforementioned structural effects, fluorination of bioactive compounds has also proved to have substantial effects on many other molecular properties.[69] In particular, the high chemical stability of the C-F bond is often exploited to prevent metabolisation processes, which generally leads to an improved bioavailability.[69] In addition, fluorine is known to influence the lipohilicity of a molecule, but also the Brønsted acidity and hydrogen bond properties of adjacent functional groups.[70,71]

7.1.2 Polyfluorination strategy to improve the binding affinity

The hydrophobic effect refers to the tendency of hydrophobic molecules to aggregate in aqueous media, in order to minimise the contact surface with water molecules.[72] This phenomenon plays a major role in molecular recognition, as the desolvation of hydrophobic surface areas of ligand and receptor prior to binding is energetically favourable, and is generally the main driving force of the process. In this context, the incorporation of hydrophobic regions in a polar ligand is of interest to enhance its binding affinity for a protein. As a proof of concept, Whitesides *et al.* developed two series of carbonic anhydrase inhibitors **7.6** and **7.7**, containing a hydrocarbon or fluorocarbon chain of varying length (Figure 1).[73] For both series, a correlation could be established between the binding strength for the enzyme and the length of the hydrophobic group. In addition, for a similar chain length, fluorinated compounds **7.7** have shown to display a better affinity for the enzyme than its hydrocarbon analogue **7.6**. Thus, although intrinsic hydrophobicity of hydrocarbon is similar than perfluorocarbon, the latter displays a larger hydrophobic surface area, which explains the better affinity observed. Interestingly, Whitesides also established that the mechanism of hydrophobic desolvation is essentially the same for both types of groups.[74]



7.6 **7.7**

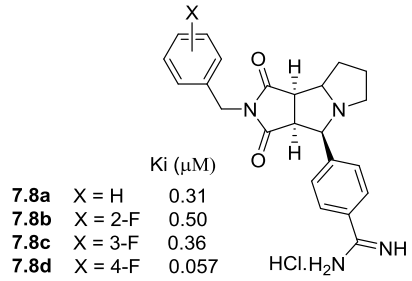
Figure 7-2 : carbonic anhydrase inhibitors **7.6** and **7.7**

7.1.3 Fluorine involvement in H-bond and dipolar interactions

Although the C-F bond appears to possess favourable characteristics to act as H-bond acceptor, such as its high level of polarisation and the presence of 3 lone pairs, it is commonly accepted that the fluorine atom can only be involved in weak hydrogen bond interactions. Inspections of the Cambridge Structural Database (CSD) indicated that only 0.6% of C-F bonds are in close contact with the hydrogen of an H-X bond (O,N), thus corresponding to a potential H-bonding interaction.[75,76] Interestingly, this proportion rises up to 10% in the Protein Data Bank,[77] which tends to demonstrate that these interactions play a non-negligible role for the protein/ligand affinity. In addition, despite the controversy regarding the real existence of these interactions, the formation of H-bond

involving fluorine could be unambiguously evidenced in the absence of competitive H-bond acceptors.[78,79]

Perhaps more importantly, the ionic C-F bond can also be engaged in dipole-dipole interactions. This was demonstrated in an enzymatic context from a study of Diederich and co-workers, in which a fluorine scan of thrombose inhibitors **7.8** was performed (Figure 7-3).[80,81] In this work, they observed that the fluorinated analogues **7.8b-d**, which only differs from each other by the position of the fluorine atom on the aromatic residue, showed important differences in term of inhibition potency for the studied enzyme (thrombose). Thus, while *ortho* and *meta*-fluorinated derivatives **7.8b** and **7.8c** displayed comparable activity levels as their non-fluorinated parent **7.8a**, the *para*-fluorinated analogue **7.8d** was five-fold more potent than **7.8a**.



		Ki (μM)
7.8a	X = H	0.31
7.8b	X = 2-F	0.50
7.8c	X = 3-F	0.36
7.8d	X = 4-F	0.057

Figure 7-3: Activities of thrombose inhibitors **7.8**

The introduction of a fluorine atom is expected to decrease the polarisability of the aromatic ring, making it more hydrophobic, thus should lead to a binding enhancement. Since the fluorinated anologues **7.8b-c** show similar binding affinity compared to **7.8a**, it can be assumed that the gain in desolvation energy induced by the fluorine substitution must be compensated by unfavourable electrostatic repulsions within the binding site. On the other hand, increase of the affinity observed with compound **7.8d** should result from beneficial electrostatic interactions.

X-ray analysis of the compound **7.8d** in complex with the enzyme provided insights on the nature of these interactions (Figure 7-4). Thus, a close contact between fluorine and an H-C_α-C=O moiety could be observed within the enzymatic pocket. An F•••H interaction was established, but also F•••C_α and an orthogonal F•••C=O interaction. Later on, an extensive study of the protein database conducted by the same group showed that F•••C=O and analogous F•••CN interactions could be observed in numerous crystallographic structures.[82,83]

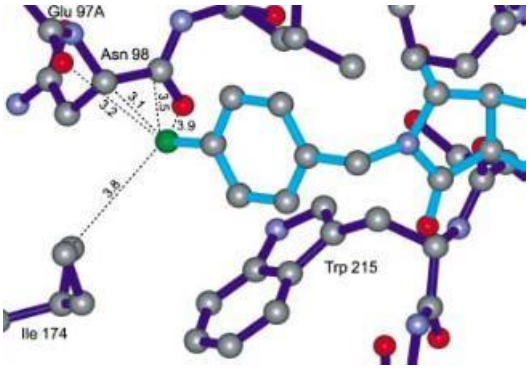


Figure 7-4 Cristal structure of **7.8d** in complex with thrombin.
F-protein close contact are indicated with dotted lines

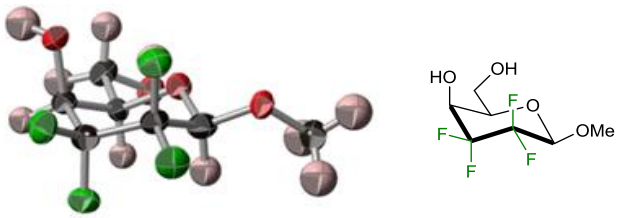
By classifying the fluorinated ligands found in the protein data bank, Vulpetti and Dalvit managed to evidence an empirical correlation between the chemical shift measured in ^{19}F NMR, related to the fluorine electron density, and the nature of fluorine-protein interaction. Thus, while shielded or electron rich fluorines (such as $-CH_2F$) were more prone to interact with H-bond donors, unshielded or electron-poor fluorines (such as $-OCF_3$) were more frequently involved in hydrophobic or dipolar interactions. This is of great relevance for the development of new drugs, as it gives insights in order to select the appropriate fluorinated motif able to effectively influence the binding interaction.[84,85]

7.1.4 Polyfluorinated carbohydrates

Carbohydrates are ubiquitous across a wide range of biological processes.[86] As part of glycolipids, glycoproteins and other conjugates, they play essential functions in the regulation of many cellular recognition events occurring at the cell surface, including growth, differentiation, inflammation, and immune response.[87,88,89] As a consequence, the malfunctioning of processes involving carbohydrates is often associated with the development of numerous disorders. In addition, by mediating host-pathogen interactions, carbohydrates also contribute to the virulence of pathogenic agents, such as bacteria or viruses.[87,90] In this context, targeting specific enzymes involved in carbohydrate biosynthesis is a promising strategy to develop new therapeutic tools, or more generally to understand biological processes.

Importantly, carbohydrates themselves typically display low affinity to proteins, which is essentially attributed to their high hydrophilic character.[87,88] In this context, Di Magno *et*

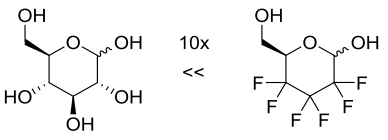
al. proposed the introduction of polyfluorinated regions into carbohydrates as a strategy to improve the low protein-carbohydrate affinity.[91,92] The introduction of hydrophobic CF_2 groups into carbohydrate backbone is indeed expected to enhance the binding affinity due to a gain in desolvation energy. In addition, as described in the previous section, the C-F bond can be involved in favourable electrostatic interaction within the enzymatic receptor. The combination of both effects was coined by Di Magno as "polar hydrophobicity".[91,92] It can also be noted that the introduction of a polyfluorinated motif does not induce major conformational changes, as was shown by Di Magno[91,92] and our group in the example of β-methyl-galactopyranoside **7.9**[93] (Figure 7-5), which was found to adopt a typical $^4C_1$ chair conformation.



7.9

Figure 7-5: conformation of β-methyl-galactopyranoside **7.9**

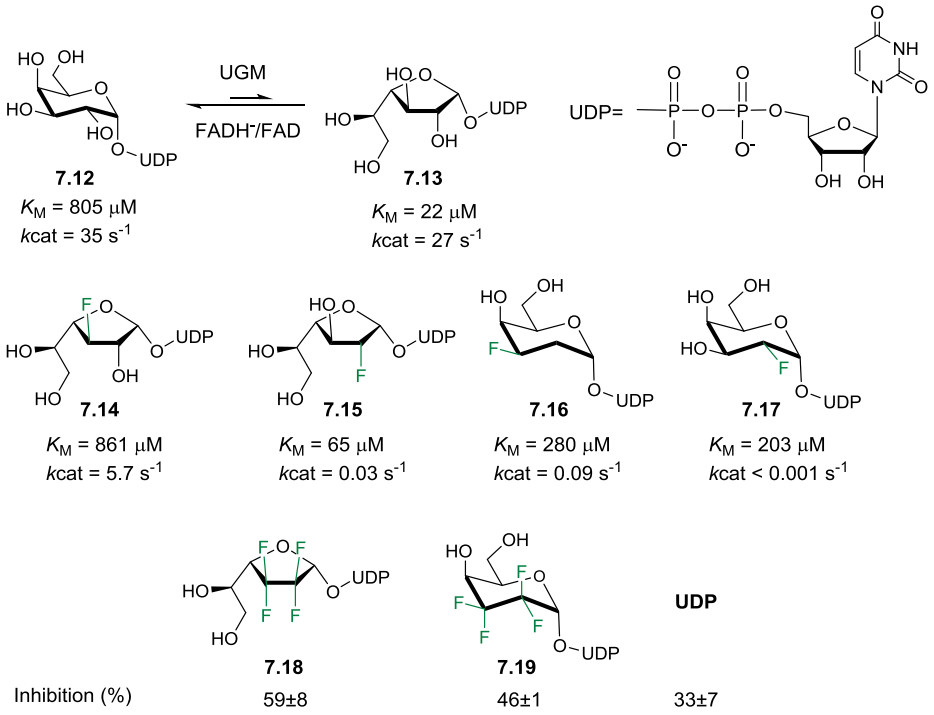
As a first illustration of the concept, transport study of the hexafluoropyranose **7.11** (Figure 7-6) across the red blood cell membrane was carried out. It was found that **7.11** was transported ten-fold faster than glucose itself **7.10**, this despite the loss of stereochemical information. This result was attributed to an enhanced affinity of **7.11** with the erythrocyte glucose transporter protein (GLUT-1).[91]



7.10 **7.11**

Figure 7-6: Representation of glucose **7.10** and hexafluoropyranose **7.11**

The first clear evidence of binding enhancement involving polyfluorinated sugars has emerged from the binding study of the UDP-F_4-galactofuranose **7.18** (UDP-F_4-gal*p*) and pyranose **7.19** (UDP-F_4-gal*f*) with the UDP-galactopyranose mutase (UGM), [94] an enzyme involved in the biosynthesis of the mycobacterial cell wall. This enzyme catalyses the conversion of UDP-gal*p* **7.12** to UDP-gal*f* **7.13**, using FAD as cofactor (Scheme 7-1).



Scheme 7-1: Enzymatic reaction and fluorinated analogues synthesised

The synthesis of monofluorinated UDP-Gal analogues **7.14-17** and their biological activity against the enzyme had been previously reported. In general, results showed that the enzyme has a high level tolerance towards fluorine incorporation into the carbohydrate moiety, since the four analogues were found to be substrates of UGM. However, the position of fluorine substitution resulted in significant differences in term of binding affinity and catalytic activity, especially for the furanose analogues **7.14** and **7.15**. Thus, the values of K_M, which are related to the binding affinity of a ligand for an enzyme, revealed that the 3F-gal*f* **7.14** has a considerably lower affinity for UGM than its fluorinated analogue **7.15**. This would suggest that the 3-OH is involved in a favourable electrostatic interaction or that the fluorine incorporation in position 3 leads to electrostatic repulsions in the binding site. On the other hand, the values of k_{cat} observed for UDP-2F-gal*f* **7.15** showed that fluorination in position 2 dramatically decreases the catalytic activity compared to its non-fluorinated parent **7.13**. This result was consistent with a cationic transition state, which the incorporation of fluorine is indeed known to destabilise. Based on these indications, the highly electron-withdrawing CF_2-CF_2 moiety in UDP-F_4-gal*f* **7.18** and gal*p* **7.19** was expected to prevent their processing by the enzyme. By incubating either **7.18** or **7.19** with UDP, at high enzymatic concentration, no interconversion could be observed by HPLC, confirming that neither UDP-F_4-gal*f* **7.18** nor gal*p* **7.19** is a substrate for the enzyme. Their ability to act as inhibitor was further

assessed by competition assays against UDP-gal*f* **7.13**. The UDP moiety, which is a known inhibitor of UGM, was used reference for the assay. Significantly, the tetrafluorinated analogues **7.18** and **7.19** were found to be better inhibitors than UDP, with the furanose **7.18** displaying the most inhibition percentage. In complement to this study, STD-NMR and competitive STD-NMR experiments provided support that UDP-F_4-gal*f* **7.18** displays a significant binding enhancement for the enzyme, compared to the natural substrate UDP-gal*f* **7.13**. From these experiments, a dissociation constant K_d value of 5-10 µM could be determined for UDP-F_4-gal*f* **7.18**, which when compared to the K_d value available for its non-fluorinated parent **7.13** (K_d 400-800 µM) provided further insights about the gain in affinity induced by the polyfluorination.

Later on, crystal structures of UDP-gal*p* **7.12** and UDP-F_4-gal*p* **7.19** in complex with UGM could be obtained (Figure 7-7).[95] Thus, comparison of both structures showed that the F_4-Gal*p* moiety of **7.19** adopted a similar position and orientation than the non-fluorinated Gal*p* moiety in the binding pocket. In addition, conformation and orientation of the UDP moiety was also found identical in **7.12** and **7.19**, the combination of which indicates a similar mode of binding for the two ligands. Remarkably, the equatorial C-F and C-O bonds were shown to similarly interact with protein residues, as well as with water molecules (indicated by a red cross), in the enzymatic pocket. Equatorial C-F bonds were also found to establish additional favourable multipolar interactions compared to the C-O bonds, as observed by Diederich *et al*. In addition, axial C-F bonds, which substitute the C-H bonds of the natural substrate, seem to further contribute to the binding affinity, through intermolecular interactions with protein residues and water molecules. The combination of all these interactions, as well as a potential gain in hydrophobic desolvation, is likely to explain the observed binding enhancement. Similar observations could be made from the crystal structure comparison of the furanose analogues UDP-gal*f* **7.13** and UDP-F_4-gal*p* **7.18**.

This study demonstrated the great potential of the polyfluorination strategy to improve the protein-carbohydrate binding. As a continuation of this work, our project is aimed at further investigating the use of tetrafluorinated sugars as ligands of improved binding in other biological processes.

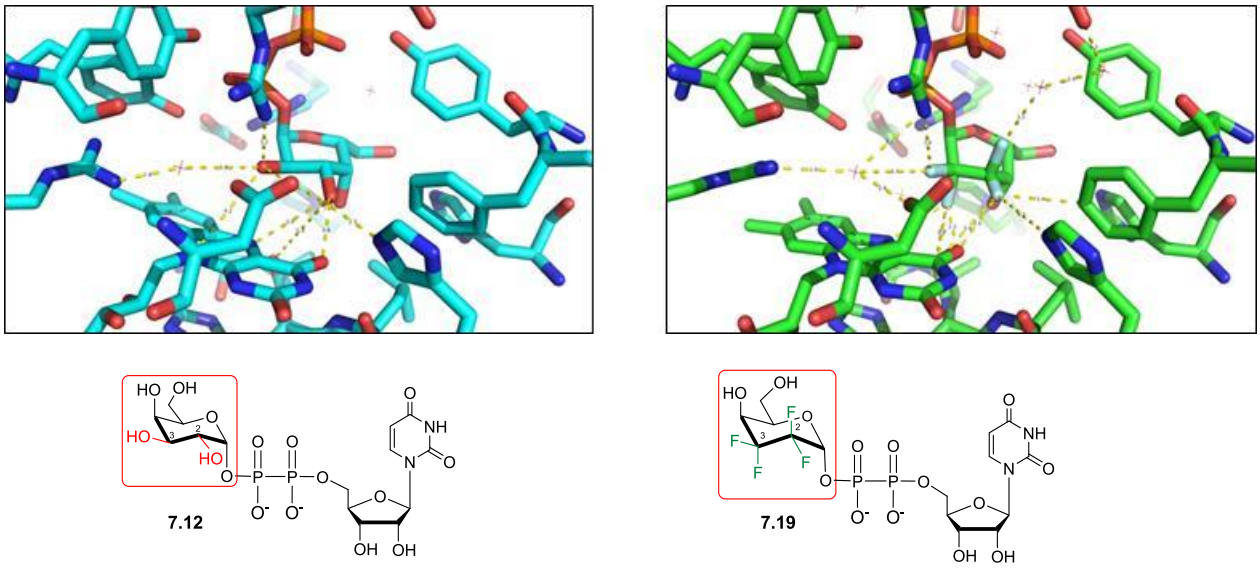


Figure 7-7: Crystal structures of UDP-gal*p* **7.12** (left) and UDP-F4-gal*p* **7.19** (right) in complex with UGM. F-and O close contacts with water molecule or protein residues are indicated with dotted line. Water molecules are represented by a red cross.

7.2 Lipopolysaccharide

7.2.1 Overview

Lipopolysaccharides (LPS) are the main component of the outer membrane of gram negative bacteria. These macromolecules are involved in the protection of bacteria against external attack of hydrophobic molecules, and therefore contribute to bacterial virulence.[96] LPS can be divided into three main parts: the lipid A, the oligosaccharide core and the *O*-antigen. The oligosaccharide core of LPS can be further decomposed into the inner core, constituted of Kdo **7.20** (3-deoxy-D-manno-oct-2-ulosonic acid) and heptoses **7.21** (L-*glycero*-D-*manno*-heptose, Figure 7-8), and the outer core, composed of hexoses. The presence of lipid A and at least one molecule of Kdo is required for bacterial growth and to maintain cell viability.[97,98] In addition, gram negative bacteria lacking heptoses are more sensitive to immune system attack, detergents or hydrophobic antibiotics.[96,99] Therefore, a strategy to alter the structural integrity of gram negative bacteria is to target the biosynthetic pathway of these carbohydrates.

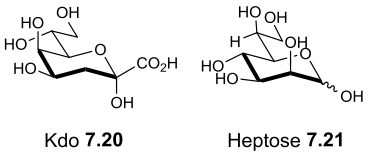
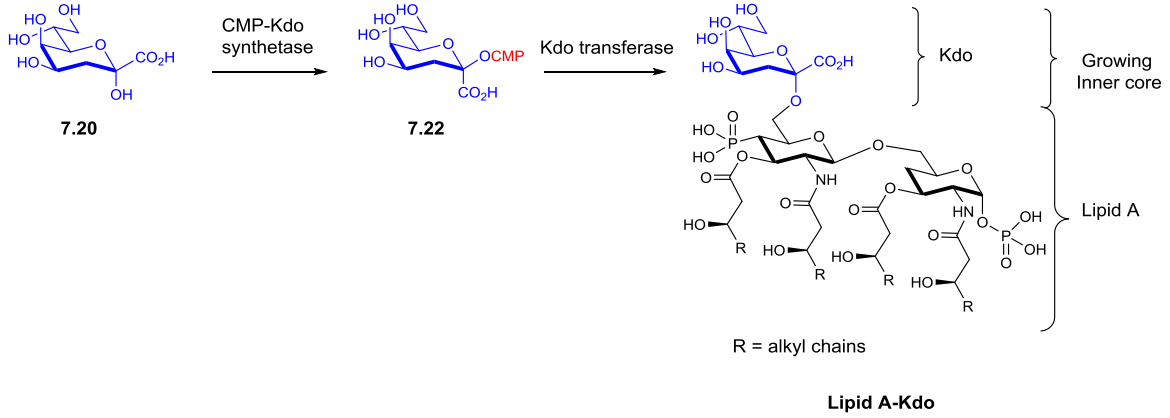


Figure 7-8: Structures of Kdo and heptose

7.2.2 Kdo biosynthesis

7.2.2.1 Background

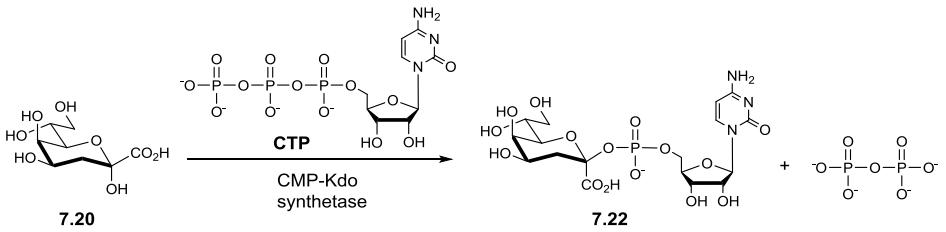
Due to its importance for bacterial integrity, the Kdo biosynthesis has been extensively studied, which enabled to identify the different enzymatic stages of the process.[97,100-102] Two key steps are depicted in Scheme 7-2. At first, Kdo **7.20** is converted to CMP-Kdo **7.22** by the CMP-Kdo synthetase. The Kdo moiety of **7.22** is then transferred to lipid A *via* action of Kdo transferase, and constitutes the first motif of the growing inner core of LPS. The next part will be focused on the CMP-Kdo synthetase.



Scheme 7-2: Biosynthesis of Lipid A-Kdo

7.2.2.2 CMP-Kdo synthetase

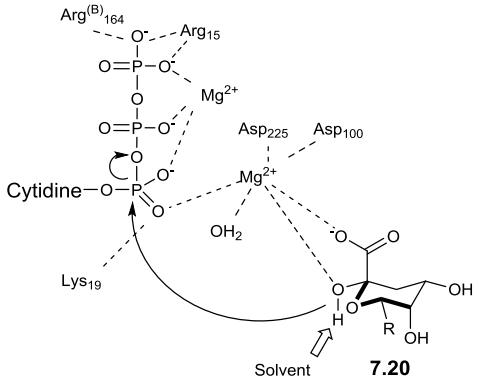
As previously mentioned, CMP-Kdo synthetase catalyses the addition of CMP (from CTP) to the anomeric centre of Kdo (Scheme 7-3).[97,100] Interestingly, this transformation constitutes the rate determining step of the LPS biosynthesis.[103]



Scheme 7-3: CMP-Kdo synthetase

The crystal structures of diverse substrates/inhibitors with the CMP-Kdo synthetase have been solved, which provided details on the enzymatic mechanism (Scheme 7-4).[97,104] Hence, the reaction is thought to proceed *via* nucleophilic attack of the anomeric alcohol

upon the α-phosphate of cytidine, in a S_N2 mechanism. The enzymatic process would require the presence of two Mg^{2+} ions, which are involved in the correct positioning of both substrates in the enzymatic pocket. Those ions also would play a role in the activation of the two reactive sites (anomeric alcohol and α-phosphate). It can also be noted that inversion of the anomeric configuration of **7.20** occurs upon binding with the enzyme.



Scheme 7-4: Proposed mechanism of action for CMP-Kdo synthetase

Several mimics of Kdo have been designed in order to inhibit the enzymatic activity. As pioneering work, 2-deoxy-α and β-Kdo **α-7.23** and **β-7.23** were synthesised and tested against CMP-Kdo synthetase (Figure 7). While compound **α-7.23** displayed no activity against the enzyme, its epimer **β-7.23** has shown potent inhibitory activity.[105] This compound has however proved inefficient *in vivo* due to its inability to cross the outer membrane.[106,107] So far, **β-7.23** is still one of the most potent *in vitro* inhibitors of CMP-Kdo synthetase, and no *in vivo* inhibitors have been reported in the literature.[100]

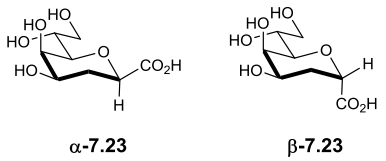


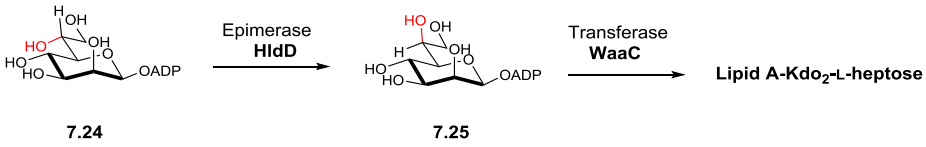
Figure 7-9: Representation of 2-deoxy-α and β-Kdo **α-7.23** and **β-7.23**

7.2.3 Study of bacterial Heptose biosynthesis

7.2.3.1 Background

As in the case of Kdo, the enzymatic processes involved in the heptoside biosynthesis have been identified.[101] This study will focus on the two last enzymatic steps on this

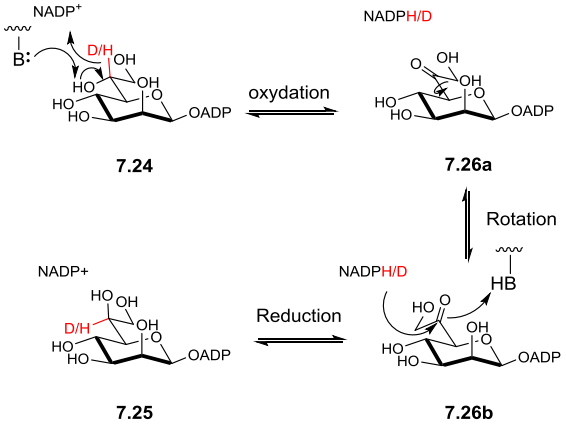
biosynthesis (Scheme 7-5). At first, adenosine diphosphate (ADP)-D-heptose **7.24** is converted to (ADP)-L-heptose **7.25** by HldD epimerisase. The heptose moiety is then incorporated to the growing core of LPS through action of the WaaC transferase (Lipid A-Kdo-2-heptose).



Scheme 7-5: Enzymatic reactions studied in the heptose biosynthesis

7.2.3.2 HldD epimerase

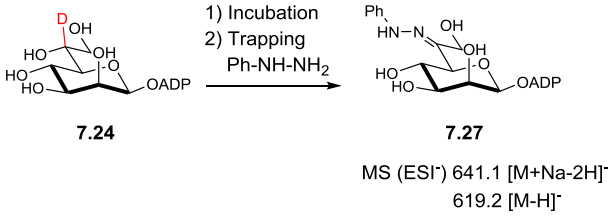
HldD epimerase is a member of the short-chain dehydrogenase reductase (SRD) family. This enzyme uses a tightly bound NADP(H) as cofactor for catalysis.[108,109] As depicted in Scheme 7-6, the proposed mechanism involves a direct oxidation of the hydroxyl group at C6, generating the ketone intermediate **7.26**. Rotation of the C5-C6 bond of **7.26** then occurs, which enables the hydride on the bound NADPH to attack the opposite face of the carbonyl group, leading to the (ADP)-L-heptose **7.25**.



Scheme 7-6: Proposed enzymatic mechanism for the epimerisation reaction

The enzymatic mechanism has been supported by numerous experimental evidence.[110,111,112,113,114] Tanner and co-workers notably showed that the deuterated analogue of **7.24** could be converted to its L-epimer **7.25** with retention of deuterium at the C-6 hydroxyl group (Scheme 7-7).[110] This is consistent with a direct oxidation/reduction mechanism in which an hydride exchange occurs between NADP(H) and C6-hydroxyl of

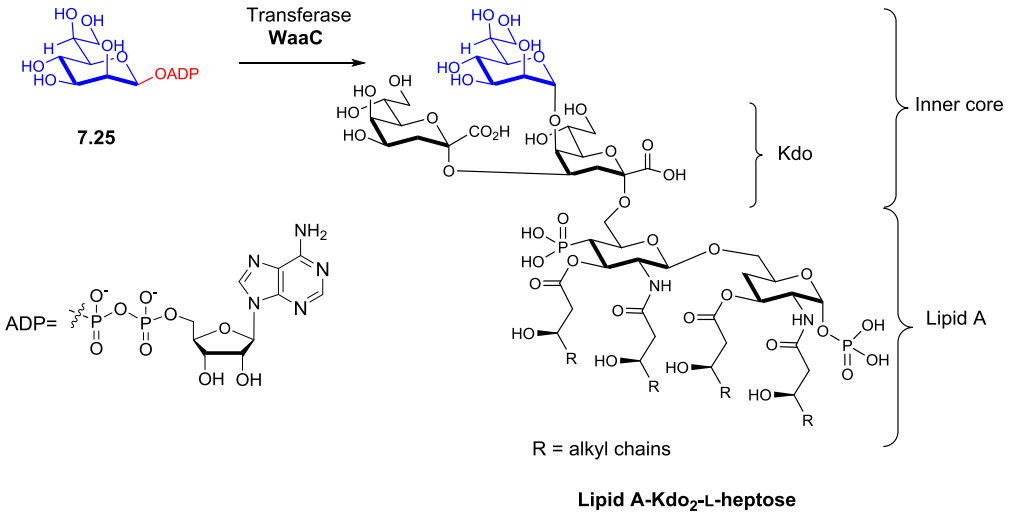
the substrate. The same group also observed that deoxy-analogues of **7.24** at C-4 and C-7 are also processed by the enzyme, thus excluding any alternative pathway involving the transient oxidation at these positions.[112] Later on, an isotopic crossover experiment demonstrated that the hydride transfer is "intramolecular", meaning that the carbonyl group moves from the first active site (oxidation) to the other (reduction) without any dissociation between the substrate and the enzyme.[113] In an additional experiment, by incubating the deuterated analogue **7.24** with the enzyme for an extended period of time, little released (keto) intermediate was however detected by trapping with phenyl hydrazine (Scheme 7-7).[113] Interestingly, mass spec analysis of hydrazone **7.27** indicated that no deuterium atom is present in the structure, which provided further evidence for the proposed mechanism involving the direct oxidation of the alcohol at C-6. Furthermore, crystal structures of the enzyme have also been obtained, giving structural details about its enzymatic pocket.[109,112] Nevertheless, despite all the information available on this enzyme, no inhibitors of the HldD epimerase have been so far reported in literature.



Scheme 7-7: Trapping of intermediate release with phenyhydrazone

7.2.3.3 WaaC transferase

WaaC transferase catalyzes the transfer of the heptose moiety of ADP-L-heptose **7.25** to a molecule of Kdo located in the growing core of LPS (Scheme 7-8). As for HldD, enzymatic structure and mechanism have been extensively studied. In 2000, Kosma *et al.* reported the first synthesis of ADP-L-heptose **7.25** and its α-anomer analogue, which enabled the determination of the anomeric configuration of the natural substrate as **7.25**.[115]



Scheme 7-8: WaaC transferase

A major progress in the investigation of the enzymatic process has been accomplished with the synthesis of ADP-2F-L-heptose **7.28**, which was found to be a potent inhibitor of the WaaC transferase (Figure 7-10).[116] Its inhibitory activity was thought to arise from the strong electron withdrawing character of the fluorine atom, destabilising the proposed oxocarbenium transition state (Figure 7-10).[117] Remarkably, the enzyme was able to accommodate ADP-2F-L-heptose **7.28**, although the C2-fluorine assumes a different orientation compared to the C2-hydroxyl in the natural substrate **7.25** (equatorial F *vs* axial OH).

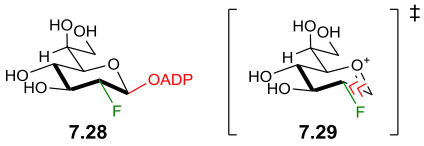


Figure 7-10: ADP-2F-L-heptose **7.28** and oxonium transition state **7.29**

In addition to this work, the crystal structure of the WaaC transferase in a complex with **7.28** could be obtained (Figure 7-11).[117] As observed in the previous examples, the C-F bond was found to be involved in an orthogonal interaction with a carbonyl dipole in the binding site. This supposes that the fluorine also contributes to the binding with the enzyme.

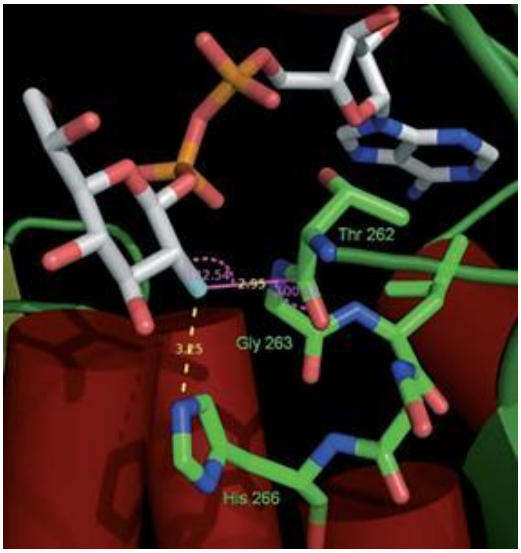


Figure 7-11: Cristal structure of WaaC in a complex with **7.28**. Structure shows a close contact between fluorine in turquoise and the C=O of Thr 262 (2.65 Å, θ = 100°).

7.3 Aim and Strategy of Synthesis

7.3.1 Aim

The first objective of this project was to synthesise and investigate 3,3,4,4-tetrafluoro-Kdo (F_4-Kdo) **7.30** as potential probe or inhibitor of the CMP-Kdo synthetase (Figure 7-12). As mentioned in section 7.1.4, the potential gain in desolvation energy induced by the tetrafluorethylene moiety combined with the strong polarity of the C-F bond is expected to enhance the binding affinity towards the enzymatic receptor. In addition, from a mechanistic aspect (see Scheme 7-4), the presence of the strongly electron withdrawing CF_2-CF_2 moiety should reduce the coordination of the anomeric alcohol with Mg^{2+}, making it less prone to react with the α-phosphate. Furthermore, the requisite inversion of anomeric configuration upon binding is still expected to occur with **7.30**, since previous examples from our laboratory showed that tetrafluoropyranoses underwent mutarotation in solution. In a second phase, the synthesis of 2-β-deoxy-3,3,4,4-tetrafluoro-Kdo (β-deoxy-F_4-Kdo) **β-7.31** was envisaged. The introduction of fluorine should improve the bioavailability of this compound compared to its non-fluorinated analogue **β-7.23** (See Figure 7-9).

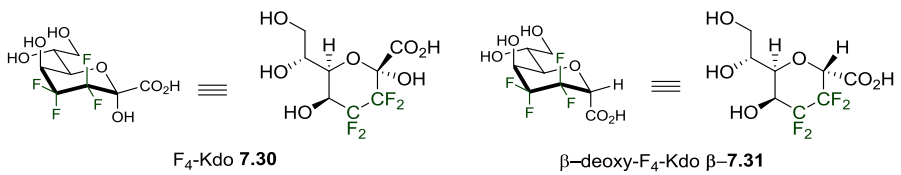


Figure 7-12: Representation of **7.30** and **β-7.31**

The second objective is to synthesize ADP-D- and L-2,2,3,3-tetrafluorinated heptoses (F_4-heptoses) **7.32** and **7.33**, and to investigate them as probes or inhibitors of HldD epimerase and WaaC transferase (Figure 7-13). HldD epimerase is indeed viewed as a good model to investigate the polyfluorination strategy, since the oxidation/reduction sequence is expected to proceed without any dissociation between the enzyme and the substrate, as described in section 7.2.3.2. In the case of the WaaC transferase, apart from the gain in binding affinity expected from the polar hydrophobicity effect, the strong electron withdrawing effect of the adjacent tetrafluoroethylene moiety in **7.33** should exacerbate the destabilisation of the cationic transition state already observed with ADP-2F-L-heptose **7.28** (see Figure 7-10), thus making it a potential inhibitor of the enzyme.

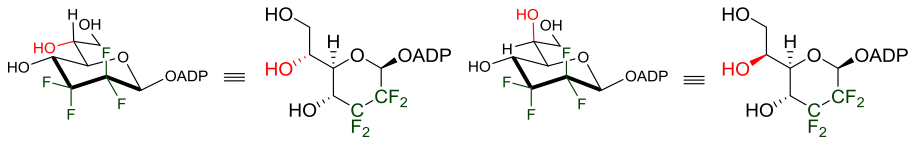
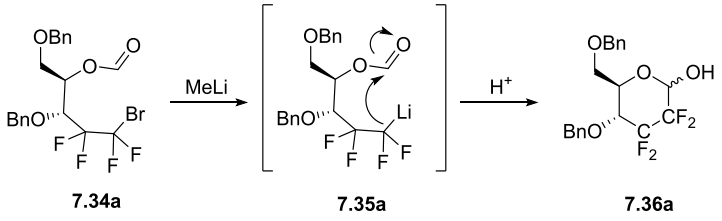


Figure 7-13: Representation of **7.32** and **7.33**

7.3.2 Strategy of synthesis

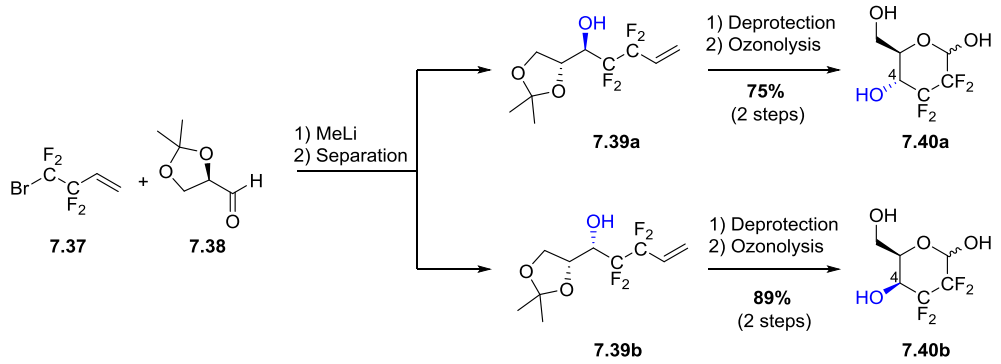
7.3.2.1 Background

The preparation of a large number of tetrafluorinated carbohydrates has been achieved by the Linclau group.[94,118,119,120] As shown in the example of D-tetrafluoroglucose **7.36a** (Scheme 7-9), the key step involves an intramolecular coupling reaction between the perfluoroalkylidene lithium and the formate ester of intermediate **7.35a**, giving, upon acidic work up, the protected carbohydrate **7.36a**. The intermediate **7.35a** was formed *in situ via* a halogen-lithium exchange between the brominated species **7.34a** and MeLi.



Scheme 7-9: Intramolecular coupling reaction

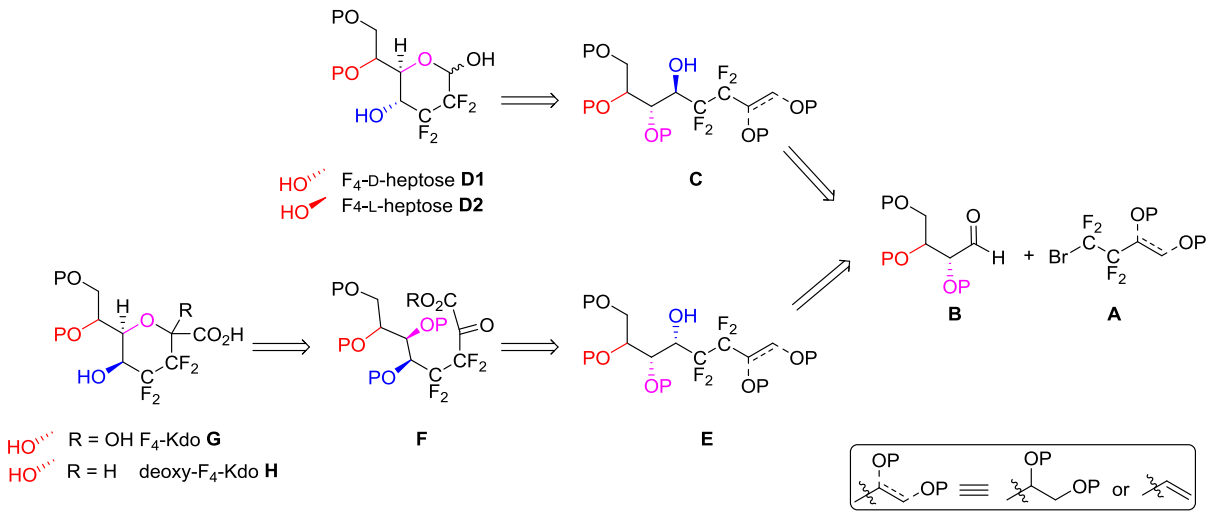
Recently, Konno *et al.* have developed an alternative approach for the preparation of tetrafluorosugars, involving an intermolecular coupling reaction between the commercially available bromo-derivative **7.37** and a homochiral aldehyde as key step.[121] As shown in Scheme 7-10 with the synthesis of tetrafluororinated-D-glucose **7.40a** and D-galactose **7.40b**, the MeLi-mediated coupling reaction between **7.37** and glyceraldehyde **7.38** afforded **7.39a** and **7.39b** as a mixture of diastereoisomers, which could be separated by column chromatography. Finally, subsequent diol deprotection and ozonolysis provided tetrafluororinated-D-glucose **7.40a** and D-galactose **7.40b** in good overall yield**.** This approach allows access to both C-4 epimers from the same starting materials.



Scheme 7-10: Synthesis of **7.40a** and **7.40b**

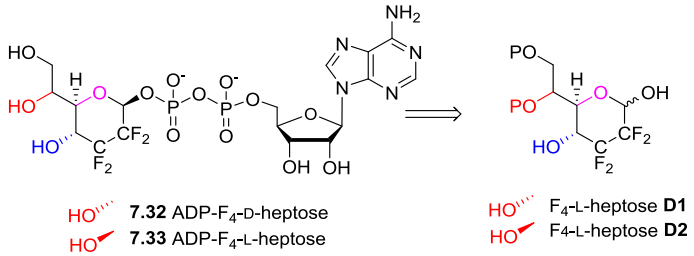
7.3.2.2 Retrosynthetic approach

With regards to this project, the methodology developed by Konno appears to be the most convenient approach, as shown in Scheme 7-11. Thus, the synthesis of F_4-D,L-heptoses **D1** and **D2** was envisaged *via* oxidative cleavage and cyclisation of intermediate **C**, which would result from the intermolecular coupling reaction of the homochiral C-4 aldehyde **B** and the brominated derivative **A**. The tetrafluorinated-Kdo **G** would be synthesised from the α-keto-acid **F**, which would be obtained from the intermediate **E**, also formed during the coupling reaction between **B** and **A**. Finally, the deoxy-F_4-Kdo **H** could be accessible from the intermediate **G** through deoxygenation reaction.



Scheme 7-11: Retrosynthetic analysis

With potential access to heptoses **D1** and **D2**, The preparation of the ADP-D- and L-glycoside analogues **7.32** and **7.33** would be investigated, in collaboration with Pr. Stephane Vincent (University of Namur, Belgium, Scheme 7-12). The strategy of synthesis will be detailed later.

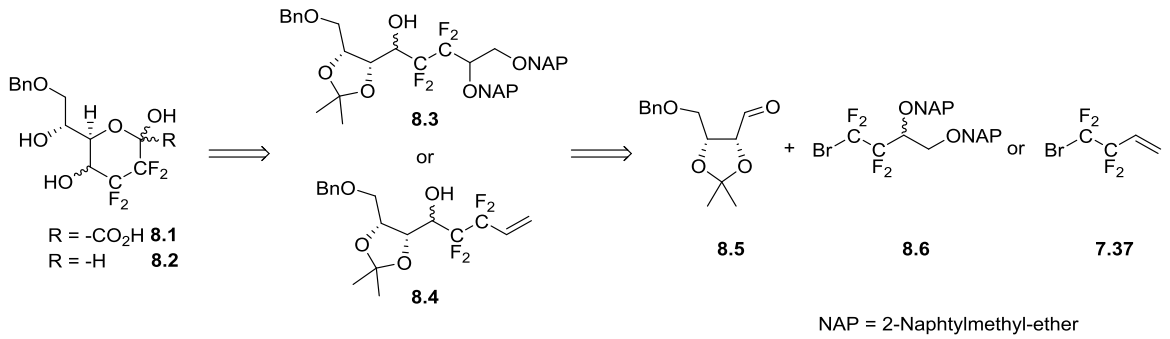


Scheme 7-12: ADP-D- and L-glycosides **7.32** and **7.33**

Chapter 8: Synthesis of fluorinated tetrafluoro heptoses and octoses

8.1 Investigation of the coupling reaction

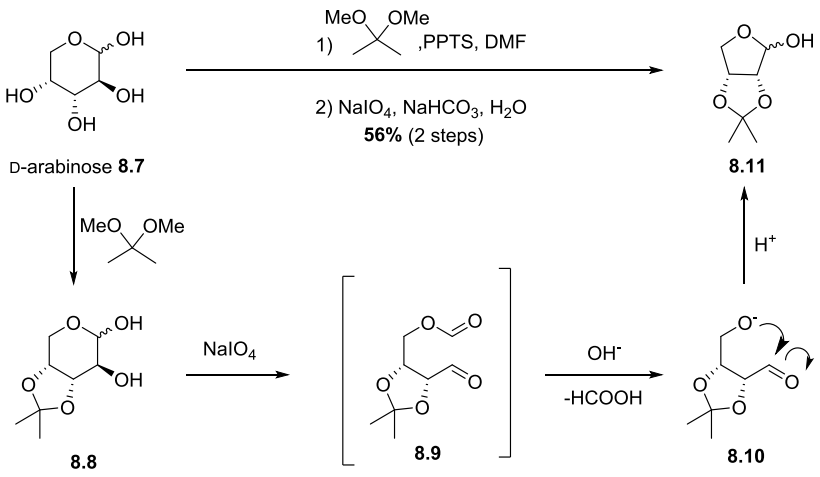
In this section, a first approach regarding the formation of **8.3** as key intermediates towards the synthesis of the protected F_4-Kdo **8.1** and F_4-D-heptose **8.2** will be described (Scheme 8-1). This includes the synthesis of aldehyde precursor **8.5**, as well as the fluorinated building block **8.6**, from which will follow optimisation of the coupling conditions and the first synthesis of D-heptose.



Scheme 8-1: Retrosynthetic analysis

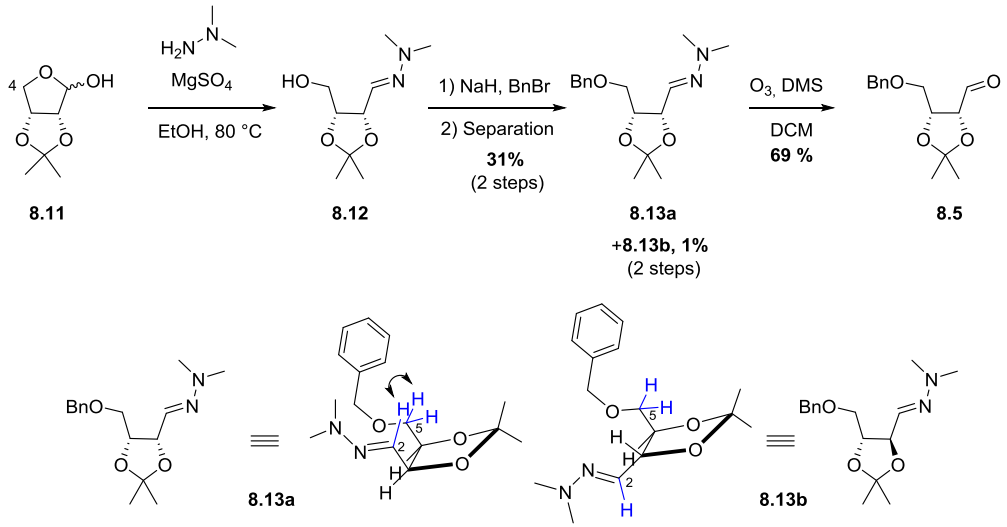
8.1.1 Synthesis of aldehyde precursor

The synthesis of the aldehyde precursor **8.5** was achieved in 5 steps from the commercially available D-arabinose **8.7**. The latter was first converted to the erythrose acetal **8.11**, according to the procedure reported by Blanchet-Cadeddu *et al* (Scheme 8-2).[122] In a first step, treatment of **8.7** with an excess of 2,2-dimethoxypropane and PPTS as catalyst afforded the protected arabinose **8.8**. Subsequent oxidative cleavage with sodium periodate led to the formation of dicarbonyl intermediate **8.9**. Base mediated hydrolysis of the formate ester followed by spontaneous cyclisation of the resulting alkoxy-aldehyde **8.10** furnished the sugar derivative **8.11** in 56% yield.



Scheme 8-2: Synthesis of erythrose **8.11**

In order to enable protection of the primary alcohol, erythrose **8.11** was first converted to the ring-opened hydrazone derivative **8.12**, as reported by Bepary and co-workers (Scheme 8-3).[123] The latter was then treated with an excess of benzyl bromide and sodium hydride. After 16h, analysis by TLC indicated full consumption of the starting material, and two hydrazones isomers could be isolated by column chromatography, in 31% and 1% yield. NMR data, supported by NOE enabled assignment of the major compound as the desired *syn*-hydrazone **8.13a**, and the minor compound as the *anti*-diastereoisomer **8.13b** (Scheme 8-3). Finally, oxidative cleavage of the hydrazine **8.13a** led to the enantiopure aldehyde **8.5**. The *syn*-configuration was confirmed by ^{1}H NMR comparison with the data of 4-*O*-benzyl-2,3-*O*-isopropylidene erythrose (*syn*) and threose (*anti*) reported in the literature (Table 8-1).[124]



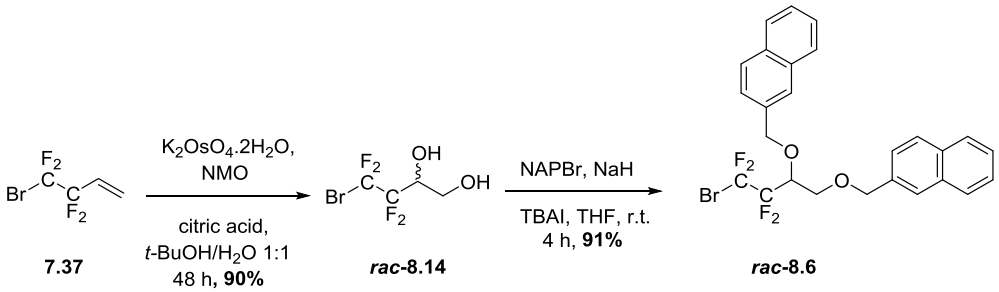
Scheme 8-3: Formation of aldehyde **8.5** and spatial representations of **8.13a** and **8.13b**. Irradiation at H2 resulted in a nOe effect at H5 in compound **8.13a**, while no such effect could be observed in the case of **8.13b**.

Table 8-1: NMR comparison between 4-*O*-Benzyl-2,3-*O*-isopropylidene erythrose[124] and threose[124]

	δ (ppm)								
Compound **8.5**	1,41	1,6	3,52	3,68	4,45	4,49	4,59	7.39-7.30	9,66
	3H, s	3H, s	1H, dd	1H, dd	1H, dd	2H, s	1H, apparent dt	5H, m	1H, d
4-*O* -Benzyl-2,3-*O* -*iso* propylidene D-erythrose	1,42	1,64	3,53	3,7	4,47	4,5	4,61	7,34	9,67
	3H, s	3H, s	1H, dd	1H, dd	1H, dd	2H, m	1H, ddd	5H, m	1H, d
4-*O* -Benzyl-2,3-*O* -*iso* propylidene D-threose	1,46	1,52	3,58		4,18	4,21	4,53	7,28	9,58
	3H, s	3H, s	2H, m		1H, dd	1H, m	2H, br s	5H, m	1H, d

8.1.2 Synthesis of F-building block

Since the commercially available 4-bromo-3,3,4,4-tetrafluorobut-1-ene **7.37** is volatile, it was initially envisaged to use the protected diol **8.6** as substrate for the coupling reaction, in order to facilitate the optimisation studies. As shown in Scheme 8-4, the latter could be prepared in two steps from **7.37**. At first**,** dihydroxylation of **7.37** was carried out at with a catalytic amount of K_2OsO_4 and NMO, giving **8.14** as a racemic mixture in excellent yield.[118,120] Subsequent treatment of **8.14** with NaH and NAPBr afforded the 1,2-*bis*-naphtylmethyl ether **8.6** in 91% yield.

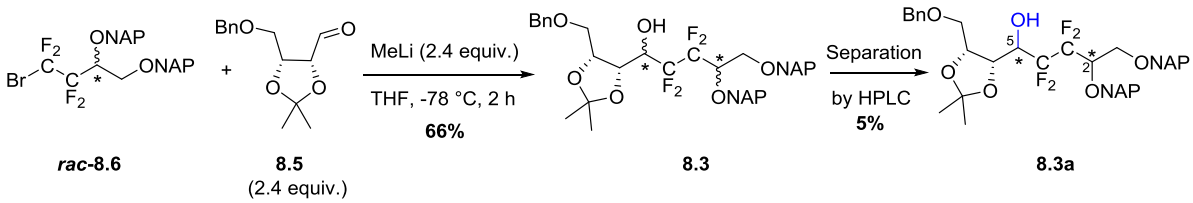


Scheme 8-4: Synthesis of F-building block 28

8.1.3 Coupling reaction

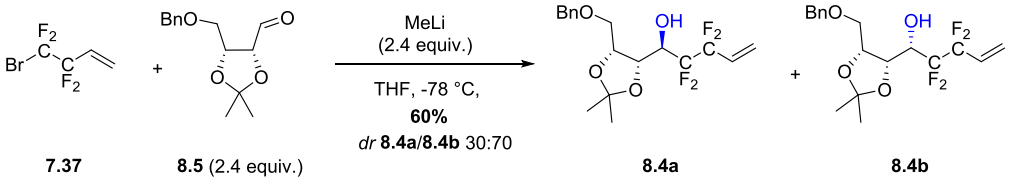
With access to the different precursors, MeLi-mediated coupling reaction was investigated, according to the procedure reported by Konno and co-workers (Scheme 8-5).[121] After 2h, analysis of the crude ^{19}F NMR indicated full consumption of the bromo-derivative **8.6**, and signals suggesting the formation of coupling adducts **8.3** could be observed in the expected chemical shift area (-110 – -130 ppm), although the presence of four diastereoisomers and potential by-products made the NMR analysis complex. An inseparable mixture of products was obtained after column chromatography, in 66% yield. Subsequent HPLC purification however enabled isolation and characterisation of

the single diastereoisomer **8.3a**. The configuration at C-2 and C-5 was nonetheless not determined.



Scheme 8-5: First attempt in coupling reaction

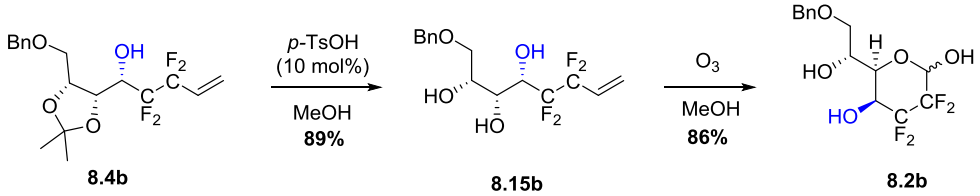
Given this encouraging result, the reaction was trialled using the tetrafluoro-alkene **7.37** as starting material, in order to minimise the number of diastereoisomers formed during the coupling reaction (Scheme 8-6). This time, the expected formation of the two adducts isomers **8.4** could be unambiguously evidenced by ^{19}F NMR, and these products were obtained as a mixture of diastereoisomers after column chromatography. Further purification steps enabled isolation of pure fractions of **8.4a** and **8.4b**. Assignment of the relative stereochemistry will be described later.



Scheme 8-6: Coupling reaction with **7.37** and **8.5**

8.1.4 First synthesis of F_4-D-heptose

For availability reasons, the synthesis of D-heptose was pursued with the major diasteroisomer **8.4b** (50 mg scale), in order to validate the strategy of synthesis (Scheme 8-7). Deprotection of the diol group in the presence of a catalytic amount of *p*-TsOH led to **8.15b** in excellent yield. The galacto-configured F_4-heptose **8.2b** was then obtained in 86% yield after ozonolysis and spontaneous hemiacetal formation.



Scheme 8-7: Synthesis of **8.2b**

8.1.5 Investigation of configuration

The configuration at C-4 could be assigned based on ^{13}C NMR data. Hence, the relative orientation of an electronegative substituent with an adjacent fluorine has shown to influence the magnitude of $^{2}J_{CF}$, as depicted in Figure 8-1.[125]

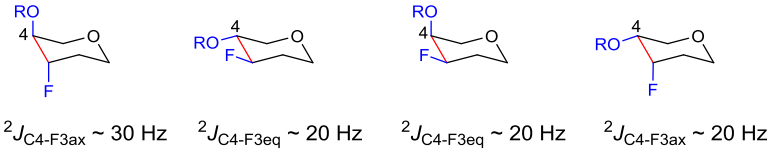


Figure 8-1: Values of $^{2}J_{C4\text{-}F3}$ according to the relative orientation

Thus, a value of $^{2}J_{C4\text{-}F}$ ~ 30 Hz is indicative of a *trans*-diaxial arrangement, while *a* gauche-dihedral angle displays a value of $^{2}J_{C4\text{-}F}$ ~ 20 Hz. In the case of compound **8.2b**, both signals corresponding to C-4 for α and β anomers (Figure 8-2) overlapped in the ^{13}C spectrum, and prevented the direct assignment by NMR analysis. Therefore, the separation of both anomers was required to obtain relevant NMR data. Given spontaneous equilibration of the hemiacetal form, per-acetylation followed by anomeric separation was envisaged.

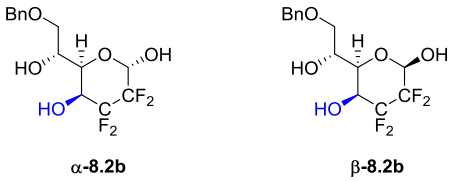
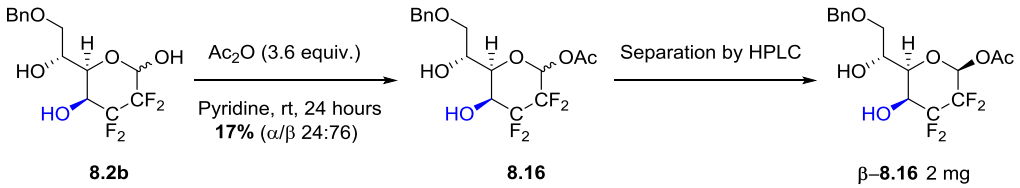


Figure 8-2: Representation of α and β anomers

F_4-D-heptose **8.2b** was then treated with an excess of acetic anhydride in pyridine. After 24 h reaction time, the crude ^{19}F NMR indicated the formation of several products, presumably a mixture of tri-, di- and mono- acetylated compounds, from which only the acetylated derivative **8.16** could be isolated in 17% yield (α/β 24:76 after purification) (Scheme 8-8). Despite the poor results obtained from the acetylation reaction, the isolation of the β pure anomer **β-8.16** however enabled assignment of the relative stereochemistry.



8.2b **8.16** **β–8.16** 2 mg

Scheme 8-8: Acetylation of **8.2b**

The ^{13}C NMR of **β-8.16** is shown below (Figure 8-3). The largest coupling constant $^{2}J_{CF}$ observed for C-4 (30 Hz) is indicative of a *trans*-diaxial orientation, which allowed to confirm the galacto-configuration at C-4. The relative configuration of C-1 was assigned the same way. In that case, the presence of the vicinal ring oxygen atom increases the magnitude of $^{2}J_{CF}$. Thus, values of couplings constant $^{2}J_{CF}$ observed for C-1 (28.8; 18.0 Hz) are indicative of an equatorial position of the substituent (i.e. β anomer). On the other hand, a *trans*-diaxial arrangement (i.e. α anomer) would display $^{2}J_{CF}$ value of approximately 35-40 Hz for the highest coupling constant.

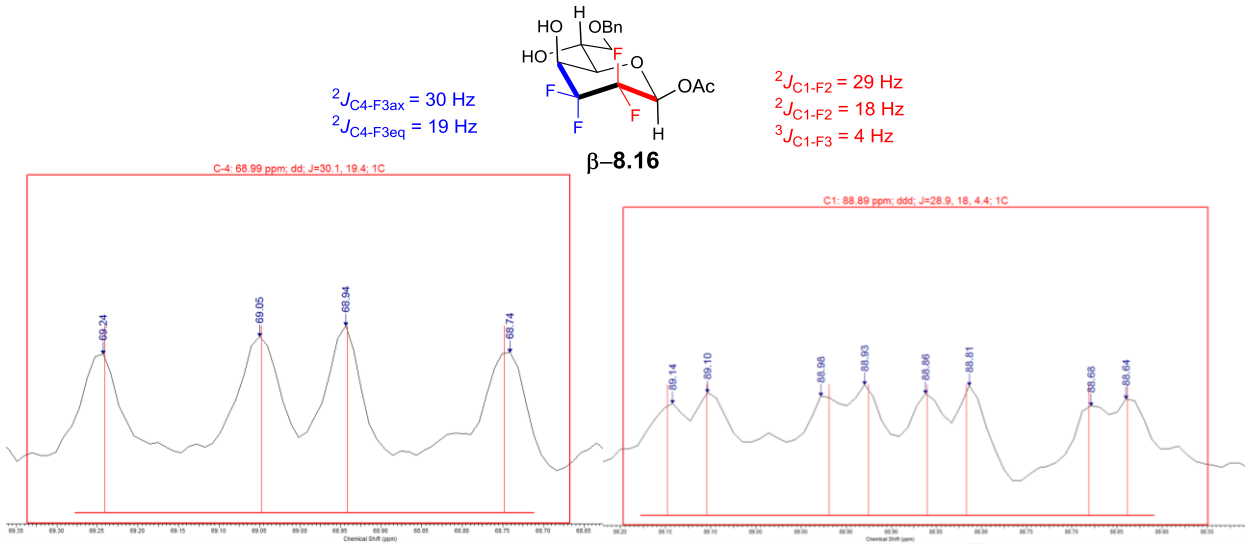


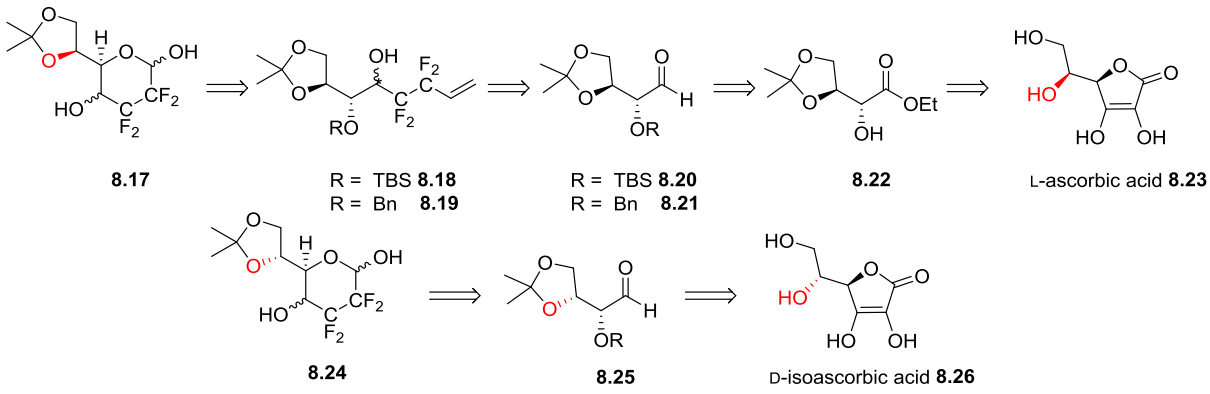
Figure 8-3: Configuration assignment

The first synthesis of F_4-D-heptose has been successfully achieved in this first part, which showed that intermolecular approach is suitable for the preparation of tetrafluorinated "higher-carbon sugar" analogues. Nevertheless, the poor overall yield obtained for the synthesis of the homochiral aldehyde **8.5** (12% over 5 steps), and the separation problems encountered while purifying the coupling adducts led to reconsider the aldehyde synthesis and the protecting group strategy.

8.2 Alternative approach and synthesis of L,D-heptoses

8.2.1 Background

With regards to the precedent work, efforts were directed towards the synthesis of protected aldehydes **8.20** and **8.21** as potential substrates for the coupling reaction (Scheme 8-9). The latter would be synthesised from the corresponding α-alkoxy ester **8.22**, which is accessible from the commercially available L-ascorbic acid **8.23**, as described by Abushanab *et al*.[126] Interestingly, the same methodology would allow access to F_4-D-heptoses **8.24**, starting from the D-isoascorbic acid **8.26**.[126] For availability reasons, the methodology was first attempted on the L-ascorbic acid **8.23**.

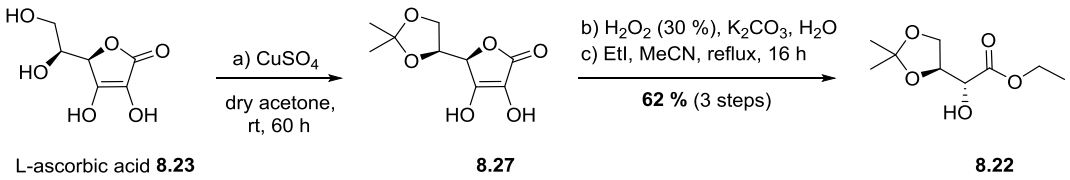


Scheme 8-9: Alternative approach with new protecting group strategy

8.2.2 Synthesis of F_4-L-heptoses

8.2.2.1 Synthesis of α-alkoxy ester

The preparation of α-alkoxy ester **8.22** as precursor of homochiral aldehydes was achieved in 3 steps from L-ascorbic acid **8.23** (Scheme 8-10).[126] At first, treatment of **8.23** with copper sulfate in dry acetone afforded the correponding acetonide **8.27**. Subsequent oxidative cleavage of the double bond using hydrogen peroxide, followed by treatment of the corresponding carboxylate with ethyl iodide provided the α-alkoxy ester **8.22** in 62% yield overall.

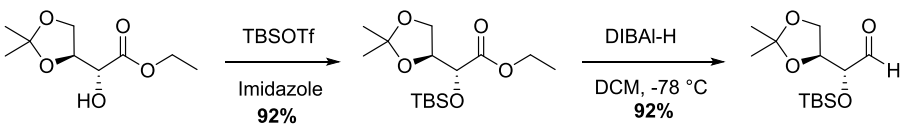


L-ascorbic acid **8.23** **8.27** **8.22**

Scheme 8-10: Synthesis of ester **8.22**

8.2.2.2 Synthesis of L-heptoses from the TBS-protected aldehyde

Protection of the α-alkoxy group was first envisaged using a TBDMS group in order to prevent any potential epimerisation issues on this position, since its formation does not require the use of a strong base. Thus, treatment of **8.22** with TBSOTf and imidazole enabled the formation of the protected α-alkoxy ester **8.28**, which was subsequently converted to the corresponding aldehyde **8.20** in excellent yield (Scheme 8-11).[127]

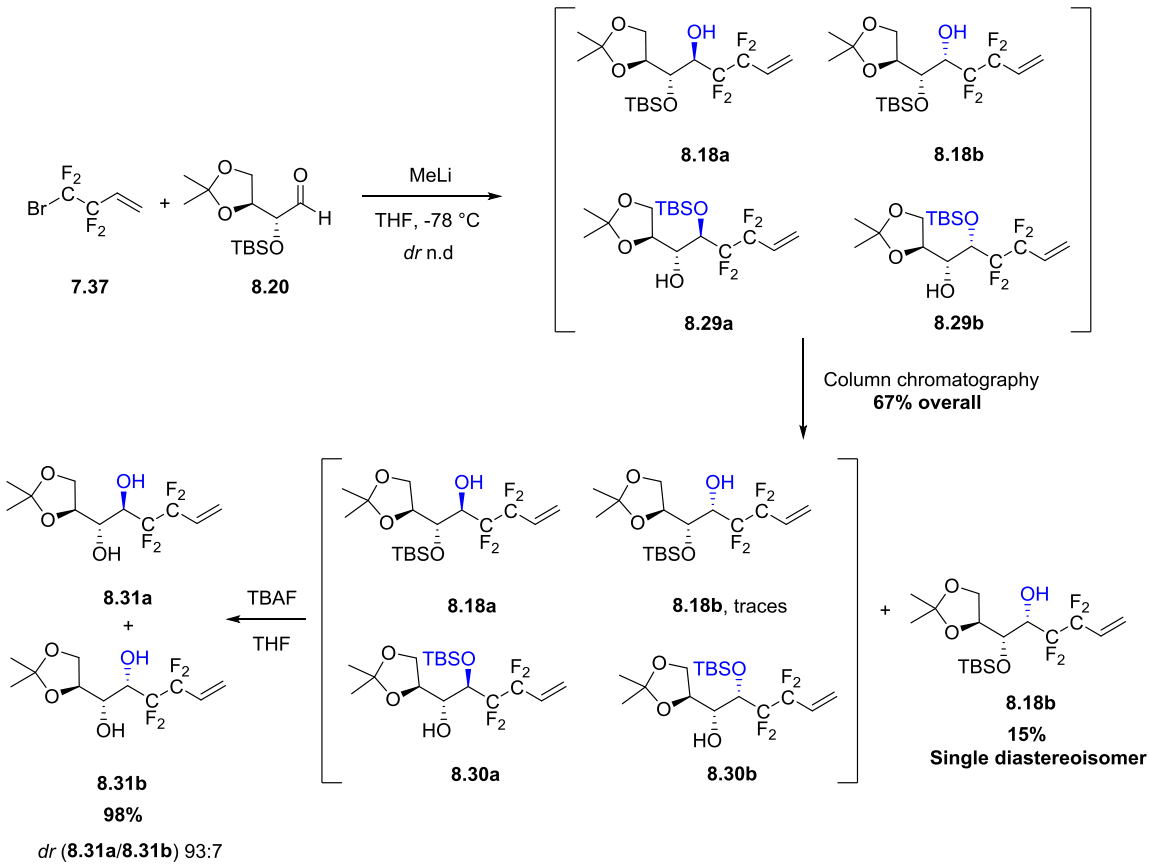


8.22 **8.28** **8.20**

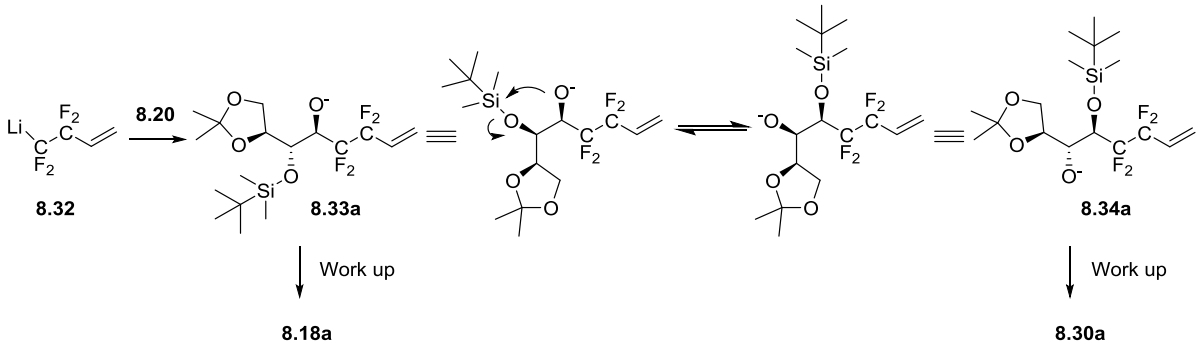
Scheme 8-11: Synthesis of TBS protected aldehyde

With access to protected aldehyde **8.20**, the MeLi-mediated coupling reaction was carried out using the reported conditions (Scheme 8-12).[121] Unexpectedly, analysis of the crude ^{19}F NMR showed the presence of more than two products in the diagnostic chemical shift area corresponding to the coupling adducts formation. After column chromatography, the desired **8.18a** was isolated as a single diastereoisomer, alongside with an inseparable mixture containing **8.18a** (trace amounts) and **8.18b**, and preasumably isomers **8.29a** and **8.29b**, resulting from silyl migration on the vicinal alcohol. After treatment of the mixture of products with TBAF, analysis of the crude ^{19}F NMR indeed indicated the presence of only two products, which were isolated as an inseparable mixture in 98% yield, and identified as compounds **8.31a** and **8.31b**.

The proposed mechanism for the formation of **8.31a** and **8.31b** is shown in Scheme 8-13. After addition of the lithiated species **8.32** to aldehyde **8.20**, leading to alcoholate **8.33a**, the TBS group can migrate towards the vicinal oxyanion, giving, upon aqueous work up, the silylated isomer **8.30a**.



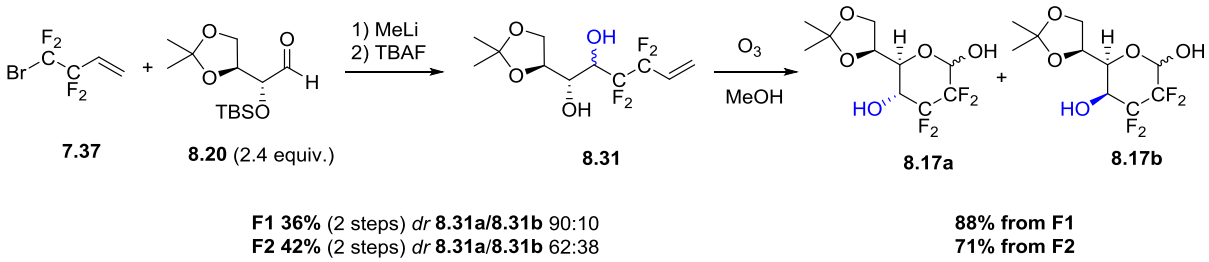
Scheme 8-12: Coupling reaction and deprotection



Scheme 8-13: Silyl migration

Since the silyl migration made the separation of the coupling adducts cumbersome, the synthesis was repeated on gram scale (2g of aldehyde) and pursued towards the preparation of the ring closed products (Scheme 8-14). Thus, coupling reaction led once again to the formation of the adduct isomers in very good yield, which were isolated by column chromatography as two fractions with different ratios. Both fractions were independently subjected to deprotection, giving in both cases the intermediate **8.31** as an inseparable mixture of diastereoisomers in good overall yield. Subsequent ozonolysis afforded a mixture of gluco and galacto configured F_4-L-heptoses **8.17a** and **8.17b**, for which any attempted separations by column chromatography proved unsuccessful.

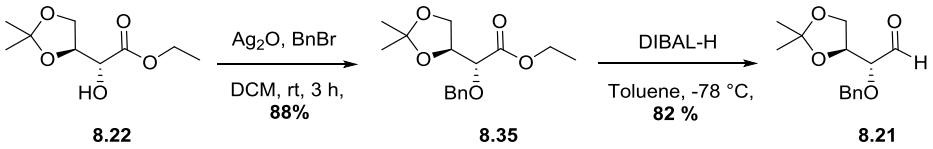
Therefore, it was envisaged to replace the TBS protecting group in α-position by a benzyl group, in order to overcome the migration issues, and hopefully facilitate the separation of diastereoisomers at an earlier stage.



Scheme 8-14: Formation of heptoses **8.17** from **8.20**

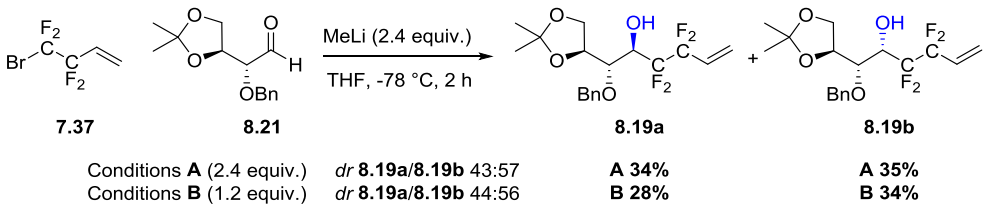
8.2.2.3 Synthesis of L-heptoses from the Bn-protected aldehyde

Following the procedure described by Sasaki and co-workers, the benzylation reaction was carried out using Ag_2O as mild base, giving the expected product **8.35** in excellent yield (Scheme 8-15).[128,129] Interestingly, no epimerisation at C-2 was detected by ^1H NMR. Subsequent DIBAL reduction afforded the aldehyde **8.21** in 78% yield.



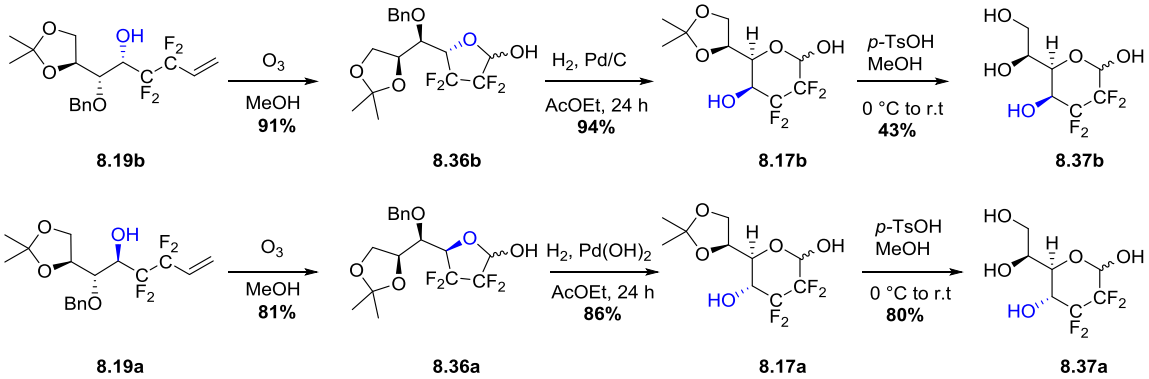
Scheme 8-15: Synthesis of benzyl aldehyde **8.21**

With the aldehyde **8.21** in hand, the coupling reaction was carried out according to the conditions previously described (Scheme 8-16, conditions **A**).[121] This time, separation by column chromatography followed by preparative HPLC enabled isolation of the two diastereoisomers **8.19a** and **8.19b** in similar yield (34% and 35% respectively). Given the formation of the aldehyde requires 5 steps from L-ascorbic acid, the coupling reaction was then investigated with a reduced amount of this substrate (Scheme 8-16, conditions **B**). These conditions led to a slight decrease of the reaction yield (69 to 62% overall), but enabled to access a higher absolute quantity of adducts, considering the amount of **8.21** used.



Scheme 8-16: Coupling reaction

For selectivity reasons, the change of protecting group has necessitated a slight modification of the synthetic route (Scheme 8-17). Thus, the *syn* and *anti*-diastereoisomer **8.19b** and **8.19a** were first subjected to ozonolysis to afford the furanose derivatives **8.36b** and **8.36a** after spontaneous cyclisation. Formation of the galacto-configured heptose acetal **8.17b** was then achieved through hydrogenolysis of the benzyl ether using Pd/C, followed by spontaneous isomerisation to the thermodynamically favoured pyranose. Regarding the gluco-configured analogue **8.17a**, while the use of Pd/C as catalyst gave the desired product in 77% yield, the same reaction using Pearlman's catalyst $Pd(OH)_2$ led to **8.17a** in an improved 86% yield. The 6-membered ring structure of **8.17b** and **8.17a** was confirmed by HMBC and COSY experiments. Finally, subsequent acetal methanolysis afforded the fully deprotected galacto and gluco F_4-heptose analogues **8.37b** and **8.37a** in 43 and 80% yield, respectively.



Scheme 8-17: Formation of heptoses **8.37**

8.2.2.4 Conformational and configurational analysis

Recrystallisation of the F_4-heptose **8.17a** from a hexane/Et_2O mixture afforded suitable crystals for XRD analysis. As shown in Figure 8-4, this compound crystallised in its α-anomer form, and was found to adopt a $^4C_1$ chair conformation with minimal distortion. This confirmed that the introduction of the tetrafluoroethylene moiety does not

drastically affect the shape compared to natural carbohydrates. In addition, the hydroxyl group at C-4 was shown to assume an equatorial orientation, thus enabling assignment of **8.17a** as the gluco-configured heptose.

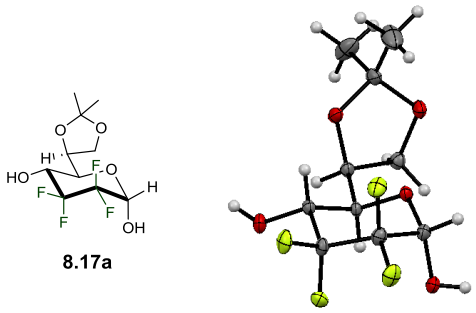


Figure 8-4: X-ray structure of **8.17a**

The configuration at C-4 could also be determined on the final products **8.37a** and **8.37b** by comparing the J_{CF} values between C-4 and both F-3ax and F-3eq observed in ^{13}C NMR.[125] For both anomers of **8.37b**, the values of $^{2}J_{CF}$ observed for C-4 (dd, $^{2}J_{C4\text{-}F3ax}$ 31 Hz, $^{2}J_{C4\text{-}F3eq}$ 20 Hz, average values for both anomers) are indicative of an axial position of the alcohol, and therefore a galacto configuration (Figure 8-5). In contrast, the C-4 signal for the two anomers of compound **8.37a** perfectly overlapped to give an apparent triplet, with a $^{2}J_{CF}$ value of 19 Hz indicating an equatorial position of the alcohol, and thus a gluco-configuration (Figure 8-6).

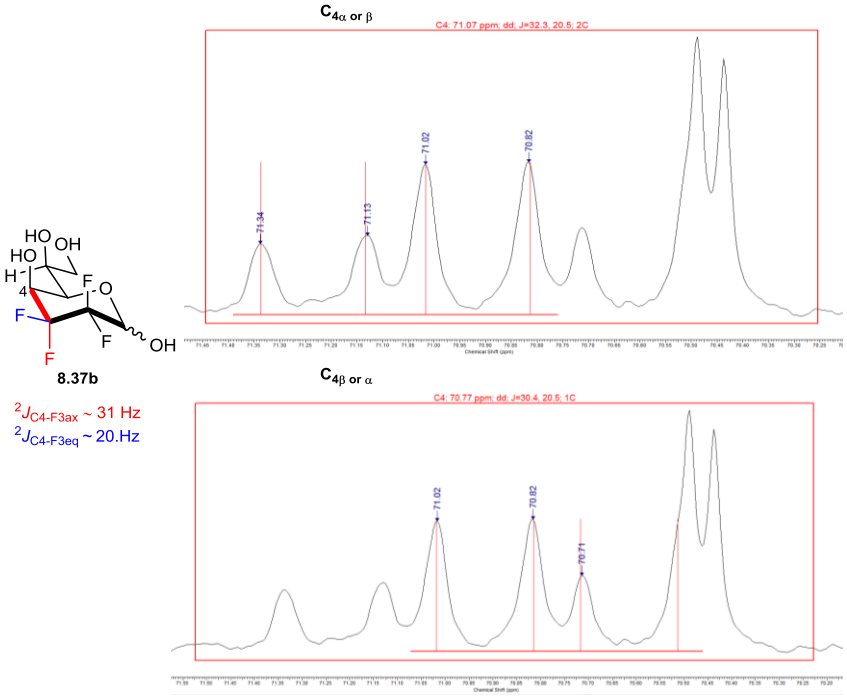


Figure 8-5: C-4 assignment by ^{13}C NMR analysis of **8.37b**

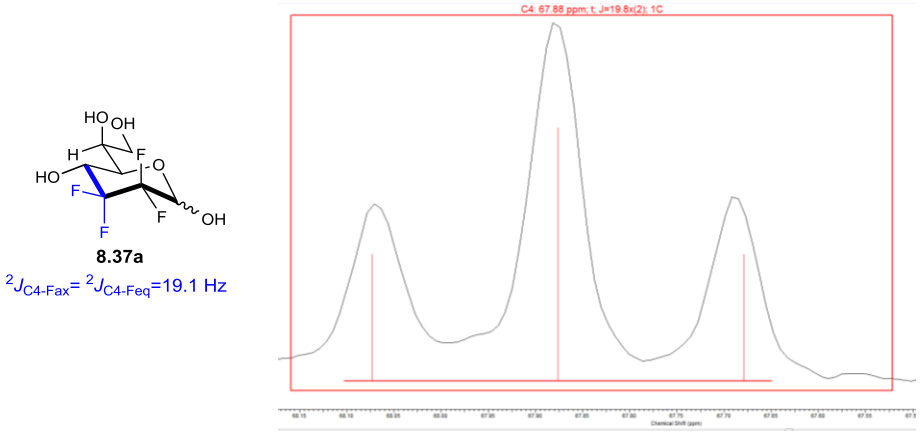
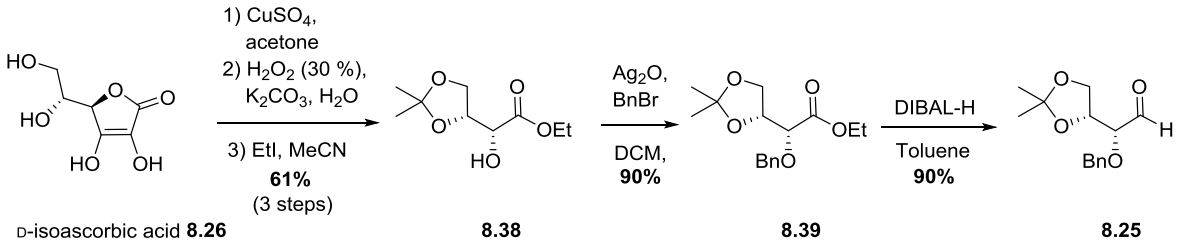


Figure 8-6: assignment by ^{13}C NMR analysis for **8.37a**

8.2.3 Synthesis of D-heptose

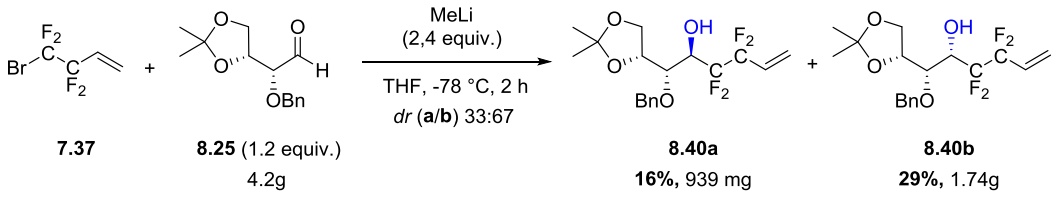
8.2.3.1 Coupling reaction and configurational analysis

The optimised conditions were then applied to the synthesis of the D-heptose analogue, starting from D-isoascorbic acid **8.26** (Scheme 8-18). Formation of the α-alkoxy ester **8.39** was achieved in similar yield as previously.[126] Subsequent protection of the C-2 hydroxyl, followed by DIBAL reduction furnished the protected aldehyde **8.25** in 81% yield over 2 steps.



Scheme 8-18: Synthesis of homochiral aldehyde **8.25**

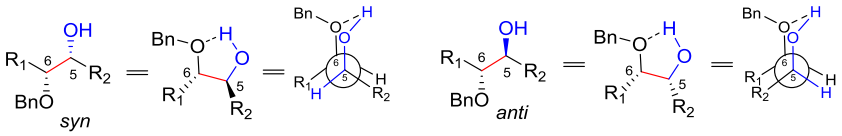
The coupling reaction was then carried out with a reduced excess of aldehyde **8.25**, as described in section 8.2.2.3 (Scheme 8-19). Interestingly, the reaction proceeded in an improved *anti*-selectivity compared to the precedent coupling reaction described in section 8.2.2.3. Both compounds could be separated by column chromatography and preparative HPLC, affording **8.40a** and **8.40b** in 16 and 29% yield, respectively.

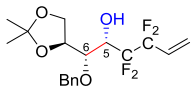
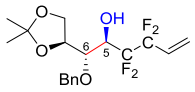
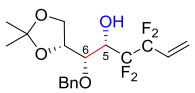
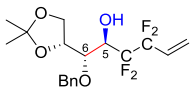


Scheme 8-19: Coupling reaction

This time, the C-4 assignment of **8.40a** and **8.40b** was achieved by ^{1}H NMR comparison with the previously synthesised diastereoisomers **8.19a** and **8.19b**. β-Hydroxy ethers are indeed known to adopt a specific cyclic conformation through intramolecular hydrogen bonding.[130] In this context, the *syn* or *anti*-configuration can be reflected in the values of coupling constants $^{3}J_{H5\text{-}H6}$ and $^{3}J_{H5\text{-}OH}$ (Table 8-2). Since the configuration of **8.19a** and **8.19b** was previously determined, $^{3}J_{H5\text{-}H6}$ and $^{3}J_{H5\text{-}OH}$ values of these compounds were compared with the corresponding values of the two isomers **8.40** (Table 8-2). In the case of compound **8.19b**, a null value was found for $^{3}J_{H5\text{-}H6}$, and a relatively high value was observed for $^{3}J_{H5\text{-}OH}$ (10.2 Hz). On the other hand, compound **8.19a** displays a value of 3.7 Hz for $^{3}J_{H5\text{-}H6}$ as well as a relatively low value for $^{3}J_{H5\text{-}OH}$ (7.7 Hz). Relatively similar sets of coupling constants were found for the two diastereoisomers **8.40** obtained from the coupling reaction, which allowed their assignment as **8.40b** and **8.40a**. Following this, the synthesis was pursued on the *anti*-diastereoisomer **8.40a** possessing the suitable C-4 configuration towards the synthesis of the gluco configured D-heptose, and diastereoisomer **8.40b** will be used as key intermediate in the synthesis of F_4-Kdo (cf. section 8.4).

Table 8-2: Tentative assignment of *syn* and *anti*-β-hydroxy ethers.
NMR analyses were carried out in $CDCl_3$ (conc. *ca.* 0.1 M)

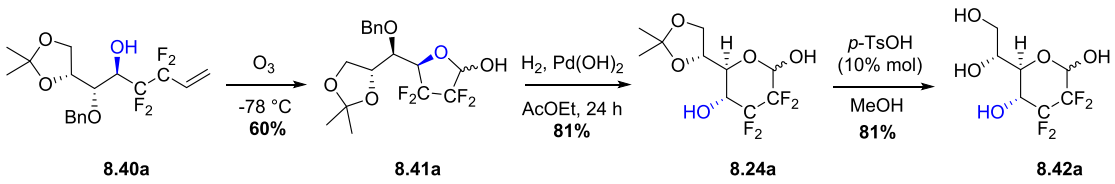


Compound		$^{3}J_{H5\text{-}H6}$ (Hz)[a]	$^{3}J_{H5\text{-}OH}$ (Hz)
8.19b		0	10.2
8.19a		3.7	7.7
8.40b		0	11.1
8.40a		3.5	6.2

[a]Values observed after D_2O shake and fluorine decoupling

8.2.3.2 Completion of the synthesis

The thus assigned *anti*-diastereoisomer **8.40a** was then submitted to ozonolysis to afford the furanose derivative **8.41a** in moderate yield (Scheme 8-20). Subsequent debenzylation of **8.41a** in the presence of Pearlman catalyst and spontaneous furanose/pyranose isomerisation enabled the formation of the D-tetrafluoroheptose **8.24a** in 81% yield. Finally, the gluco configured F_4-heptose **8.42a** was obtained in 80% yield after acetal methanolysis. The values of coupling constants $^3J_{C4\text{-}F}$ observed for C-4 (t, *ca.* 19.0 Hz for both α and β anomers) are consistent with an equatorial orientation of the alcohol,[125] and therefore a gluco configuration (Figure 8-7), thus confirming the previous tentative assignment.



8.40a **8.41a** **8.24a** **8.42a**

Scheme 8-20: Completion of the D-heptose synthesis

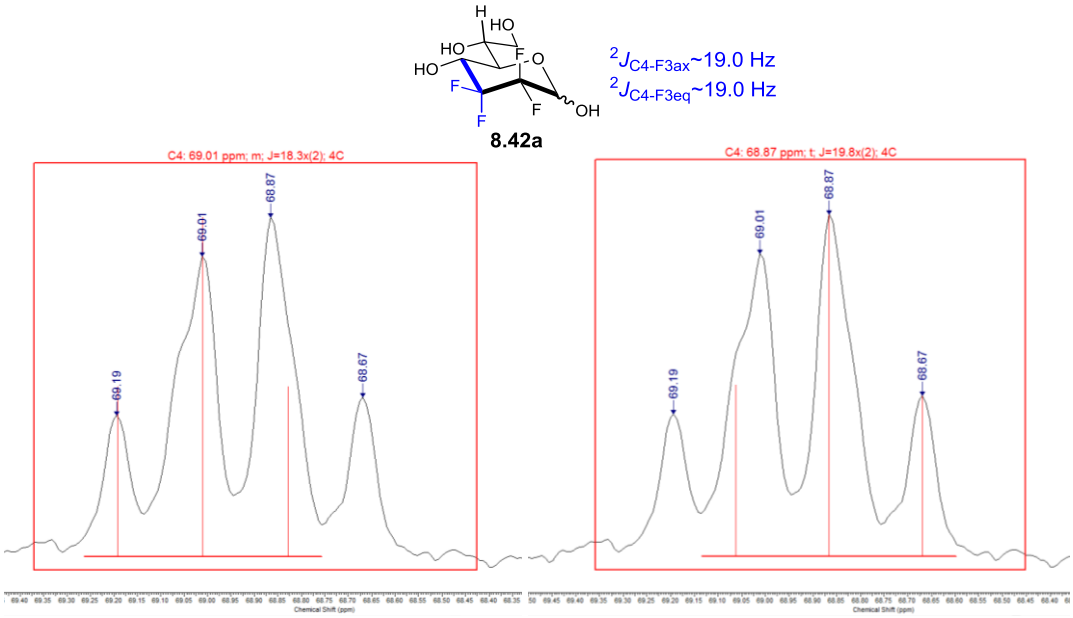


Figure 8-7: Details of the ^{13}C NMR centred on C-4 for α and β anomers

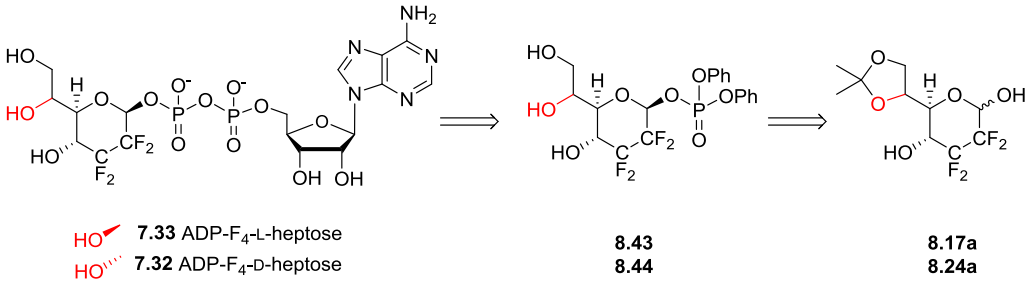
In summary, a reported methodology giving easily access to protected C-4 homochiral aldehydes from L-ascorbic or D-isoascorbic acid was successfully applied for the synthesis of F_4-heptoses. This new approach enabled to produce sufficient quantity of material to

continue investigations towards the formation of ADP-nucleotide sugars analogues, which will be described in the following section.

8.3 Towards the synthesis of ADP-L- and D-F_4-heptoses

8.3.1 Background

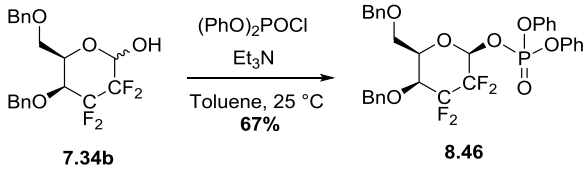
With access to L- and D-heptoses **8.17a** and **8.24a**, the synthesis of the ADP-L- and D-glycoside analogues **7.33** and **7.32** was investigated (Scheme 8-21). This involves the formation of the β-heptosyl monophosphates **8.43** and **8.44** as key intermediates, and their conversion to nucleotide sugars will be performed by the team of Pr. Stephane Vincent (University of Namur, Belgium).



Scheme 8-21: Retrosynthetic approach

8.3.2 Optimisation of the phosphorylation reaction

In prior investigations carried out in our group, it was found that the protected tetrafluorogalactose **7.34b** could be efficiently converted to the phosphorylated intermediate **8.46** in good yield and total β-selectivity (Scheme 8-22).[131] The reaction involves first deprotonation of the anomeric alcohol using Et_3N, followed by nucleophilic attack of the resulting alcoholate species to diphenyl phosphoryl chloride.

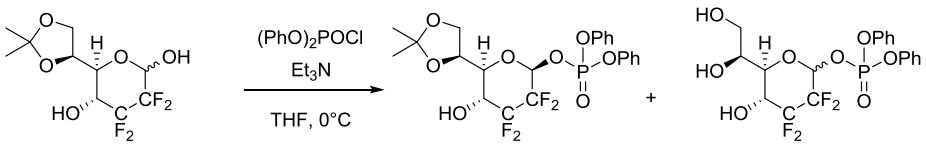


Scheme 8-22 Phosphorylation of galactose derivative

Inspired by this result, the phosphorylation of **8.17a** was trialled under similar conditions (Table 8-3). It was however decided to use THF as solvent instead of toluene for solubility

reasons, and to perform the reaction at 0 °C in order to avoid potential phosphorylation at C-4. The first experiment was thus carried out using 1.1 equiv Et_3N and $(PhO)_2POCl$ (Entry 1). After 3 h reaction time, the formation of only one phosphorylated product was evidenced by ^{19}F and ^{31}P NMR in 86% conversion. This product could be isolated by column chromatography and characterised as the phosphorylated β-anomer **8.47** (42% yield). By increasing the excess of Et_3N and $(PhO)_2POCl$, the starting material was almost entirely consumed, and the phosphorylated compound **β-8.47** was obtained in an improved 65% yield (Entry 2). These conditions were then applied on larger scale (Entry 3). This time, the desired compound **β-8.47** was isolated in 21% yield, and the deprotected compound **β-8.43** was also obtained in a mixture with the undesired α-anomer **α-8.43** (41%, α/β 15:85). Anomeric separation was not possible at this stage.

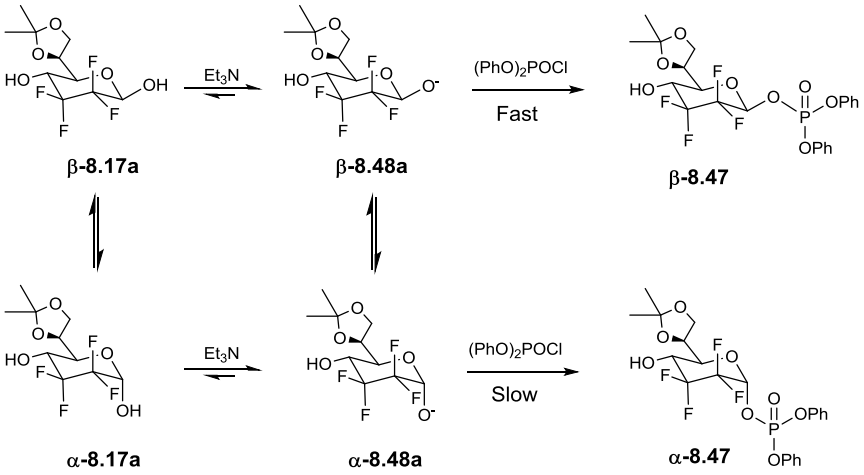
Table 8-3: Optimisation of the phosphorylation conditions



Entry	Scale **8.17a** (mg)	Et_3N (equiv.)	$(PhO)_2POCl$ (equiv.)	Conversion (%)[a]	Yield **8.47** (%)[b]	α/β[a]	Yield **8.43** (%)[b]	α/β[a]
1	71	1.1	1.1	86	42%	0/100	0	-
2	68	1.3	1.3	97	65%	0/100	0	-
3	222	1.3	1.3	100	21%	0/100	41	15/85

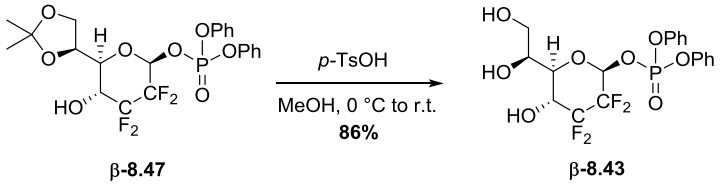
[a]Determined by ^{19}F NMR; [b]Isolated yield

The observed selectivity can be explained as follows (Scheme 8-23). At 0 °C, both α and β-anomers of **8.17a** are expected to be in fast interconversion. In these conditions, addition of the phosphorylating agent will preferentially occur on the most reactive species, corresponding to the β-oxy-anion **β-8.48a**.



Scheme 8-23: Equilibrium and difference of reactivity between both anomers of **8.17a**

Finally, acetal methanolysis of the β-anomer **β-8.47** (obtained in small scale) using *p*-TsOH afforded the β-heptosyl monophosphate **β-8.43** in 86% yield (Scheme 8-24). The magnitude of coupling constant $^{2}J_{CF}$ observed between F-2ax/eq and C-1 (24.9; 22.0 Hz), indicating an equatorial orientation of the phosphate group, confirmed the assignment of the product as the β-anomer. This also allowed to confirm the gluco configuration at C-4 (Figure 8-8).[125]



Scheme 8-24: Deprotection of the phosphorylated intermediate **β-8.47**

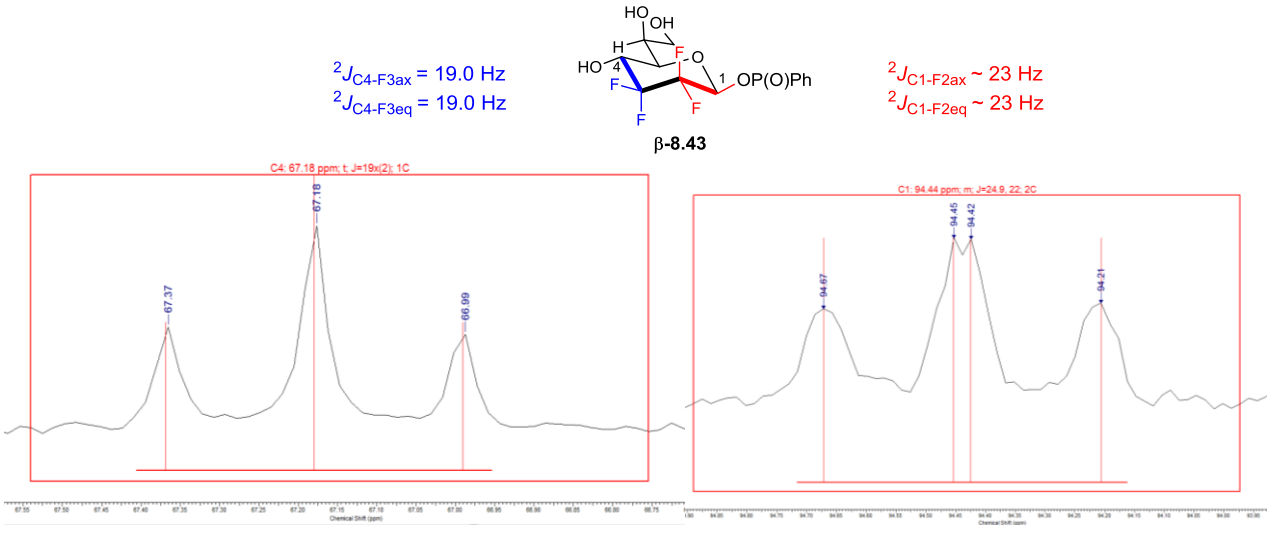
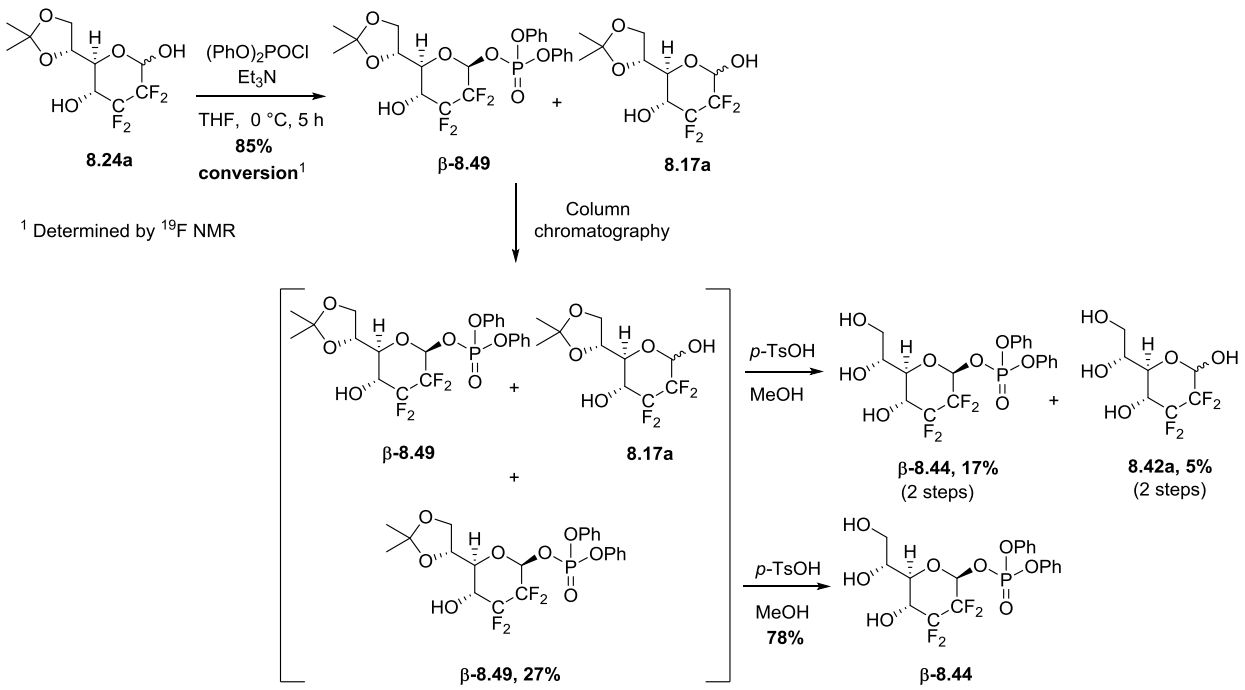


Figure 8-8: Details of the ^{13}C NMR centred on C-4 (left) and C-1 (right) for compound **β-8.43**

Following this, the optimised conditions were applied for the D-heptose **8.24a**, which led to incomplete conversion into the corresponding heptosyl phosphate derivative **β-8.49** (Scheme 8-25). Purification by chromatography enabled isolation of the phosphorylated compound **β-8.49** in 27% yield, alongside with a fraction of **β-8.49** in a mixture with the remaining starting material **8.17a**. Both fractions were independently subjected to acetal methanolysis using a catalytic amount of *p*-TsOH, giving the final D-heptose derivative **β-8.44** (38% yield combined over 2 steps) and the deprotected fluoroheptose **8.42a** in 5% yield over 2 steps. Once again, the magnitude of $^{2}J_{CF}$ observed for C-1 (t, 23.5 Hz) and C-4 (t, 19 Hz) is consistent with an equatorial electronegative substituent (i.e β anomer for C-1 and gluco-configuration for C-4, Figure 8-9).[125] As mentioned at the beginning of the section, continuation of the synthesis will be carried out by Pr. Stéphane Vincent and co-workers, who has the expertise needed in the field of nucleotide sugar synthesis.



Scheme 8-25: Phosphorylation and deprotection of D-heptose **8.24a**

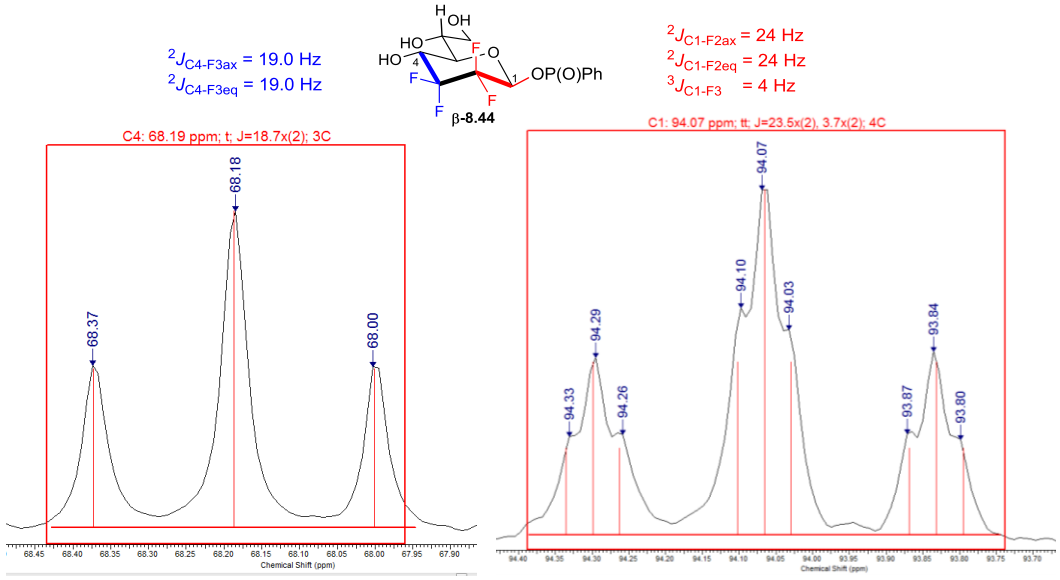
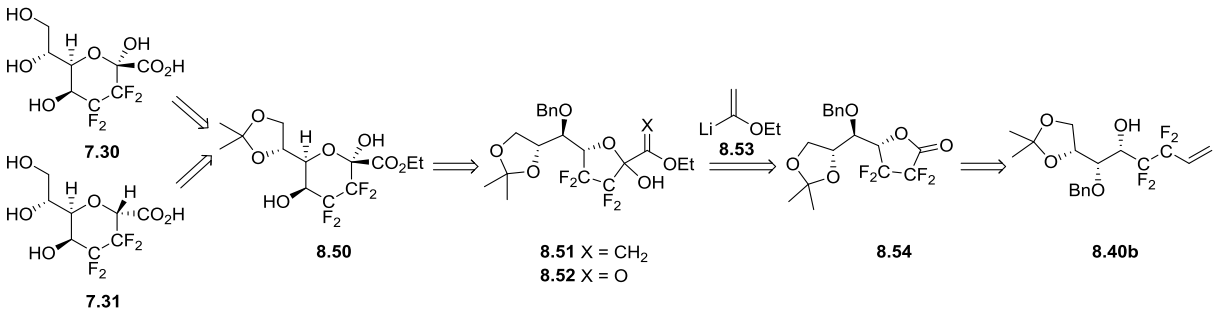


Figure 8-9: Details of the 13C NMR centred on C-4 (left) and C-1 (right) for compound **β-8.44**

8.4 Synthesis of F4-octoses and 2β-deoxy-Kdo

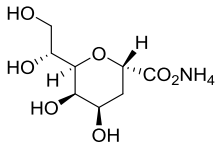
8.4.1 Strategy of synthesis

As final part of this project, the synthesis of F_4-Kdo **7.30** and deoxy-F_4-Kdo **7.31** was examined. As depicted in Scheme 8-26, both final products could be accessible from the common intermediate **8.50** after successive deprotections and anomeric deoxygenation in the case of the deoxy-F_4-Kdo. The key step of the synthesis would involve the addition of the vinyl ether moiety **8.53** to the lactone **8.54** to give the furanose **8.51**, from which oxidative cleavage of the alkene would reveal the ester **8.52**.[132] The synthesis of lactone **8.54** was envisaged *via* successive oxidation steps from intermediate **8.40b**, whose synthesis was described in section 9.2.2.3.



Scheme 8-26: Retrosynthetic approach

Furthermore, the synthesis of 2β-deoxy-Kdo **β-7.23**, which was previously reported as a potent inhibitor of CMP-Kdo synthetase, (see section 8.2) was also investigated. This compound would be used as control for the enzymatic studies (Figure 8-10).[105,133]



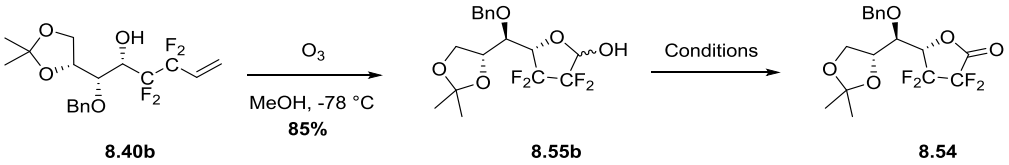
β-7.23

Figure 8-10: representation of 2β-deoxy Kdo **β-7.23**

8.4.2 Synthesis of F_4-Kdo

As a first step towards the formation of F_4-Kdo, intermediate **8.40b** was converted to the lactol **8.55b** in good yield through ozonolysis of the alkene, followed by spontaneous cyclisation (Table 8-4). Several oxidising agents were then investigated towards the formation of lactone **8.54** (Table 8-4). In a first attempt, hemiacetal **8.55b** was treated with PDC in DCM for 15 h. These conditions led however to the degradation the starting material (Entry 1).[134] When IBX was employed instead of PDC, no reaction occurred and the lactol **8.55b** was recovered (Entries 2 and 3).[135] The use of TEMPO with TCCA as co-oxidant finally enabled the formation of the desired lactone **8.54** in excellent yield (93%, entry 4).[136]

Table 8-4: Ozonolysis and attempts in the lactone formation

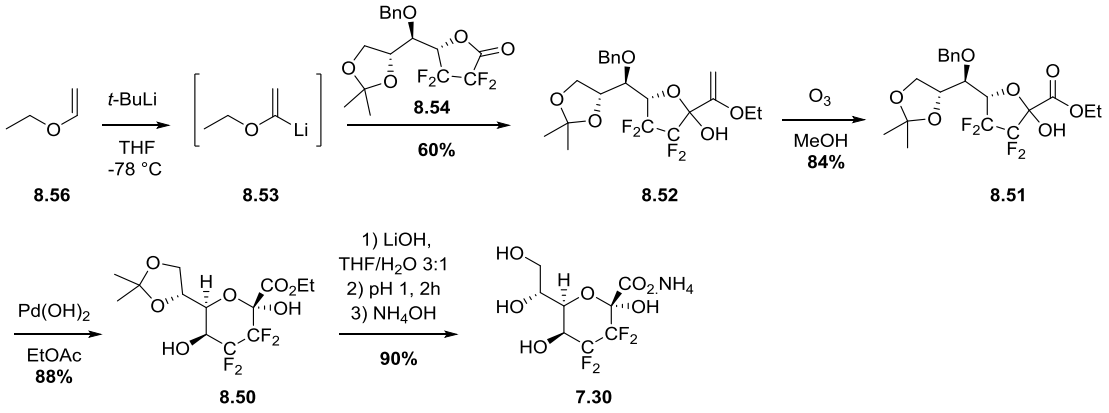


8.40b **8.55b** **8.54**

Entry	Solvent	Reagents (equiv.)	T (°C)	Reaction time (h)	Yield **8.54** (%)[a]
1	DCM	PDC (2.5)	rt	16	degradation
2	DCM	IBX (2)	rt	24	s.m recovered
3	EtOAc	IBX (2)	Reflux	3	s.m recovered
4	DCM	TEMPO(0.02)/ TCCA (2)	0 °C to rt	16	93%

[a]Isolated yield

With lactone **8.54** in hand, the coupling reaction could be performed (Scheme 8-27). Thus, formation of the vinyl lithium **8.53** by treatment of **8.56** with *t*-BuLi, followed by addition of the lactone **8.54** furnished the expected coupling adduct **8.52** in good yield. The latter was then subjected to ozonolysis, leading to the formation of the ester **8.51** in 84% yield. Subsequent debenzylation of **8.51** in the presence of Pearlman's catalyst $Pd(OH)_2$ followed by spontaneous furanose/pyranose isomerisation afforded he D-tetrafluorooctose **8.50** in 88% yield as a single anomer. Formation of the ammonium F_4-Kdo **7.30** was finally achieved after hydrolysis of the ester, spontaneous acetal methanolysis during the acidic work-up and treatment with NH_4OH. Again, ^{13}C NMR analysis enabled assignment of the C-5 and C-2 configurations (Figure 8-11). The highest coupling constant $^2J_{CF}$ observed for C-2 (36.0 Hz) and C-5 (30.8 Hz) are indeed both indicative of an axial orientation of the alcohol function (i.e α anomer for C-2 and galacto configuration for C-5).[125]



Scheme 8-27: Synthesis of F_4-Kdo

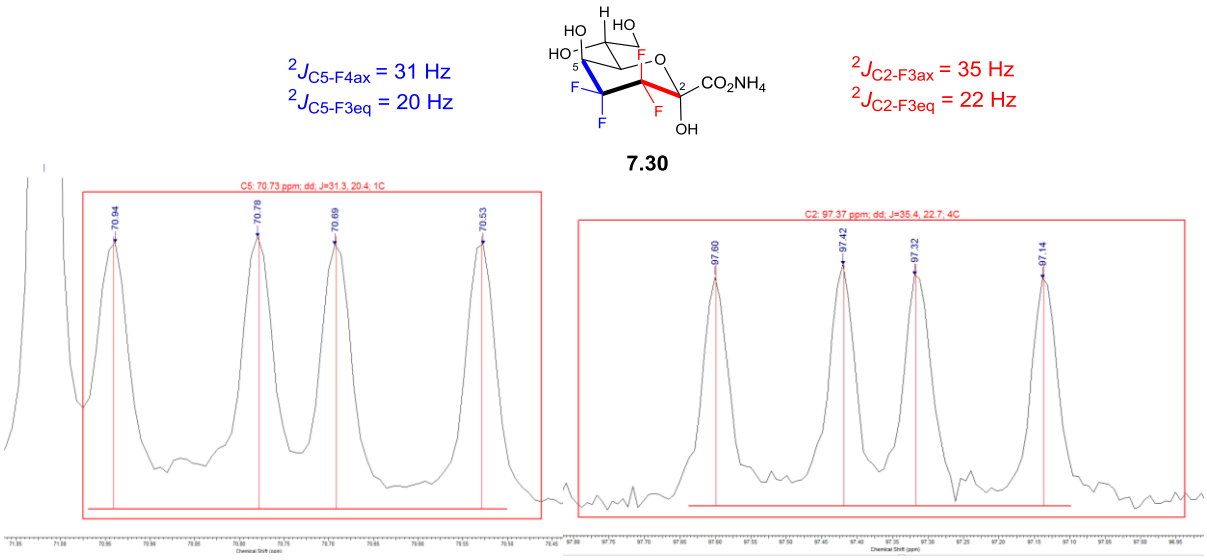
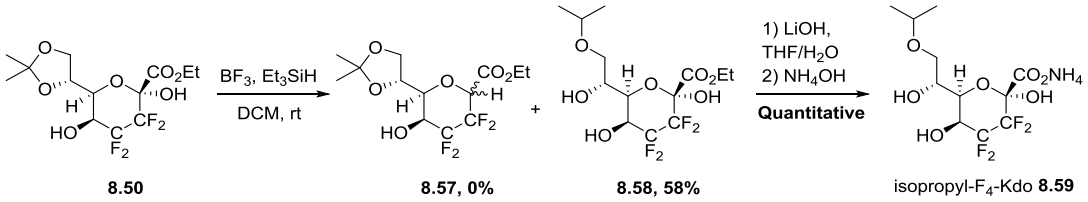


Figure 8-11: Details of the ^{13}C NMR centred on C-5 (left) and C-2 (right) for compound **7.30**

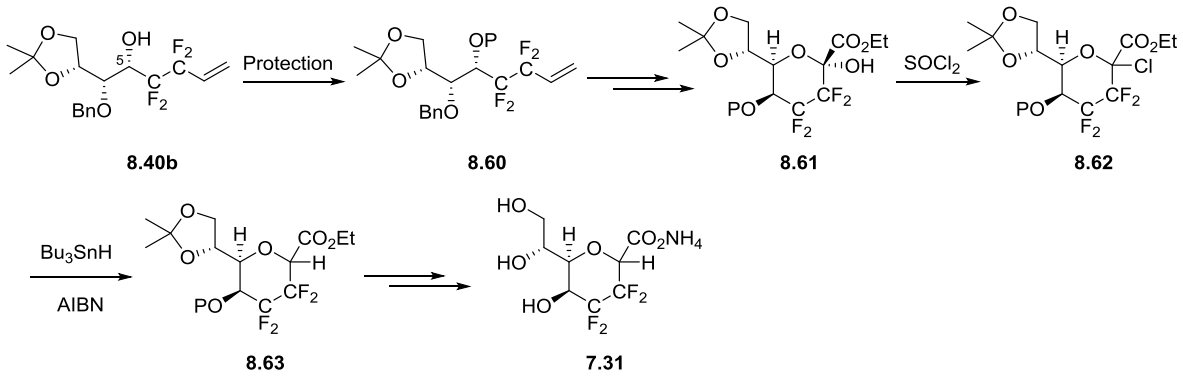
8.4.3 Attempts in the synthesis of 2-F_4-deoxy-Kdo

The formation of the 2-deoxy-F_4-derivative **8.57** was trialled following the deoxygenation methodology developed by Gouverneur et *al*. on a tetrafluoropentose.[134] However, treatment of **8.50** with $BF_3.Et_2O$ and Et_3SiH did not lead to the desired outcome. Instead, the isopropyl-ether derivative **8.58** resulting from the acetal opening/oxonium reduction was obtained in 58% yield (Scheme 8-28). The latter was finally hydrolyzed and converted to the ammonium salt **8.59** in quantitative yield. This compound was also tested against the CMP-Kdo synthetase. By lack of time, no further investigations were carried out towards the synthesis of F_4-deoxy-Kdo.



Scheme 8-28: Attempts in the deoxygenation reaction

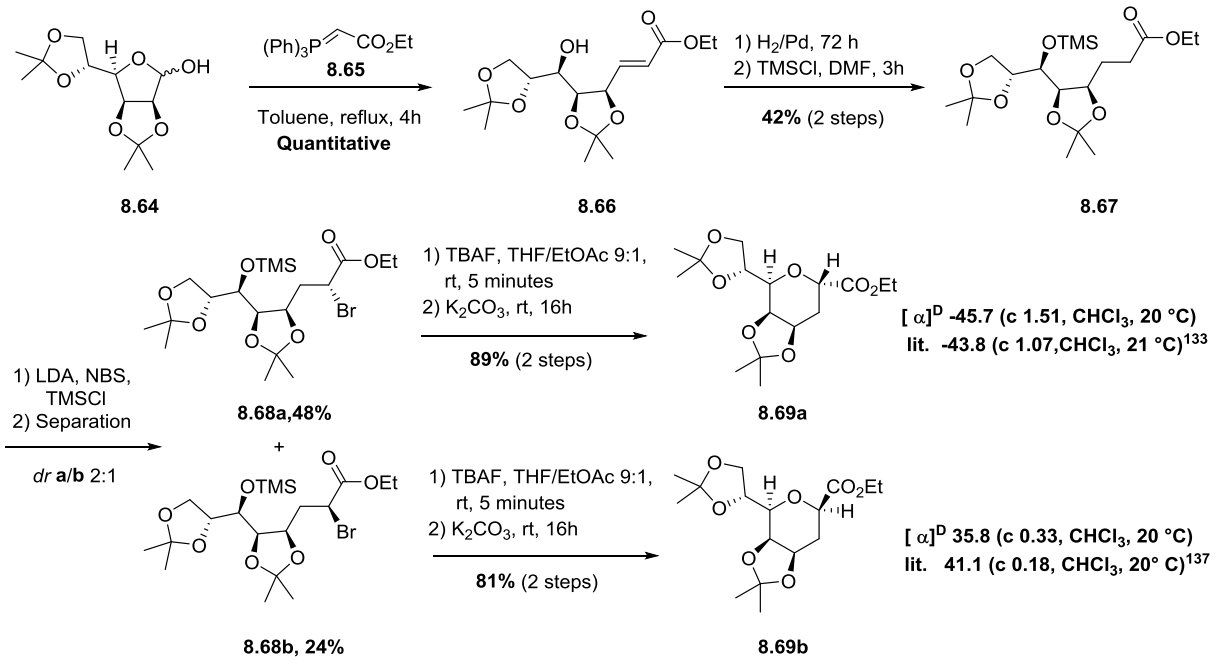
A possible alternative to the the previous strategy is shown in Scheme 8-29. This would involve protection of the free alcohol after the coupling step to give the intermediate **8.60**, which could then be converted to the furanose **8.61** following the current synthetic route. With access to intermediate **8.61**, an anomeric halogenation/reductive dehalogenation sequence could be investigated, which might enable formation of the expected product **7.31** after successive deprotections.



Scheme 8-29: Proposed alternative route for the preparation of deoxy Kdo

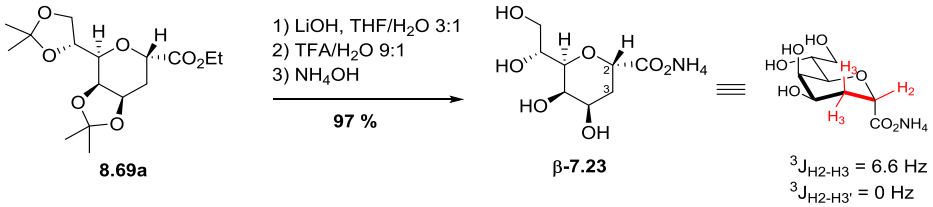
8.4.4 Synthesis of 2-β-deoxy-Kdo

The preparation of the protected 2-β-deoxy Kdo **8.69a** was achieved according to the procedure published by Claesson *et al.* (Scheme 8-30).[133] At first, Wittig reaction involving the stabilised ylide **8.65** and the commercially available D-mannose acetonide **8.64** led to the formation of the unsaturated ester **8.66** in quantitative yield. Subsequent alkene hydrogenation, followed by TMS protection of the secondary alcohol afforded intermediate **8.67** in moderate yield (42 % over 2 steps). Following this, α-bromination of the ester using NBS was preferred to the iodination procedure described by Claesson, which enabled formation of diasteroisomers **8.68a** and **8.68b** in similar yield and slightly higher diastereoselectivity compared to the initial procedure (71% *vs* 65-85%, *dr* **8.68a**/**8.68b** 2:1 *vs* 3:2).[133] Both diastereoisomers could be separated by column chromatography, and their configuration at C-2 was deduced later on from the assignment of the ring closed products. Subsequent treatment of **8.68a** and **8.68b** with TBAF, followed by base mediated cyclisation furnished the furan derivatives **8.69a** and **8.69b** in 89 and 81%, respectively. Comparison of NMR data and optical rotations reported in the literature for these products enabled assignment of **8.69a** and **8.69b** as the β and α protected Kdo, respectively.[133,137]



Scheme 8-30: Synthesis of protected β and α-deoxy Kdo **8.69a** and **8.69b**

The expected ammonium 2β-deoxy Kdo **β-7.23** was finally obtained from **8.69a** in almost quantitative yield after successive deprotections steps and treatment in aqueous ammonia (Scheme 8-31). The anomeric configuration was confirmed by ^{1}H NMR using the values of coupling constants $^{3}J_{H2\text{-}H3}$ observed for H_2 ($^{3}J_{H2\text{-}H3}$ 6.6 Hz, $^{3}J_{H2\text{-}H3'}$ 0 Hz (lit. 6.5, 1.1 Hz)[137]), indicating an axial position of the carboxylate group.

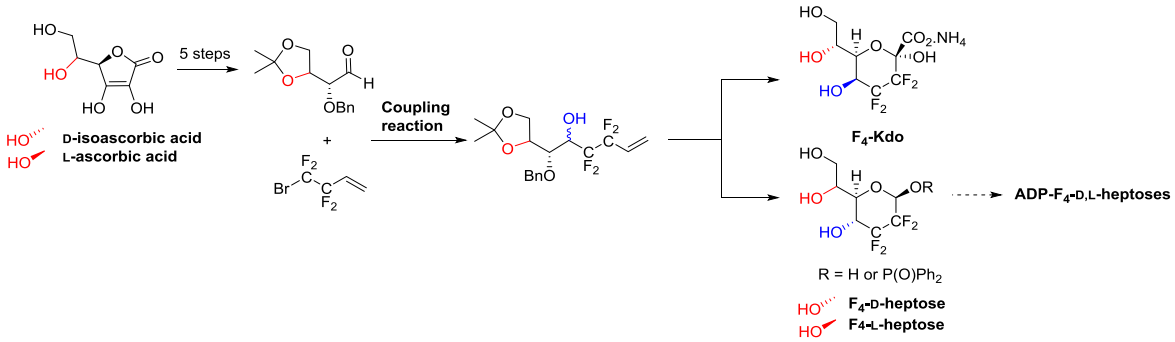


Scheme 8-31: Final deprotections leading to β-deoxy Kdo **β-7.23**

Chapter 9: Fluorinated carbohydrates: Conclusion

9.1 Overview

A divergent synthesis has been successfully developed for the preparation of D,L-F_4-heptoses and F_4-Kdo in 8 and 12 steps, respectively from D-isoascorbic and L-ascorbic acid (Scheme 9-1). The key step involves the formation of a common intermediate *via* an intermolecular coupling reaction between a C-4 protected homochiral aldehyde and the commercially available tetrafluorinated building blocks, according to the methodology developed by Konno and co-workers.[121] Furthermore, anomeric phophsorylation of these D,L-F_4-heptoses was successfully achieved in a diastereoselective manner. Their conversion to ADP-glycoside analogues is currently being examined by Pr. Stephane Vincent and co-workers (University of Namur), before investigating them as probes or inhibitors in the lipopolysaccharide pathway.



Scheme 9-1: Summary of the synthesis

9.2 Early enzymatic results

The enzyme kinetics and inhibitor studies of F_4-Kdo **7.30**, isopropyl-F_4-Kdo **8.59** and 2β-deoxy Kdo **8.55** have been conducted *in vitro* by dr. Kevin Smyth (Centre for Biological Sciences, University of Southampton) on the *E. coli* KdsB protein (CMP-Kdo synthetase). The 2β-deoxy Kdo **8.55** has shown inhibitions properties consistent with those reported in the literature (*K*i 19.4 µM).[138] However, the same enzymatic assays, supported by NMR studies suggested that the F_4-Kdo **7.30** and *iso*propyl-F_4-Kdo **8.59** are neither substrates nor inhibitors of the enzyme (does not interact with the enzyme). We are currently examining the use of F_4-Kdo or derivative as probes or inhibitors for other enzymatic targets.

Chapter 10: Experimental

10.1 General conditions

Chemical reagents were obtained from commercial sources and used without further purification, unless stated otherwise. All air/moisture sensitive reactions were carried out under inert atmosphere (Ar) in flame-dried glassware. THF (from Na and benzophenone), toluene (from Na), DCM, Et_3N and MeCN (from CaH_2) were distilled prior to use, and when appropriate, other reagents and solvents were purified by standard techniques.

Reactions were monitored by TLC (MERCK Kieselgel 60 F_{254}, aluminium sheet), visualised under UV light (254 nm), and by staining with $KMnO_4$ (10% aq.) or vanillin. Column chromatography was performed on silica gel (MERCK Geduran 60 Å, particle size 40-63 µm). All reported solvent mixtures are volume measures. Preparative HPLC was carried out using Biorad Bio-Sil D 90-10 columns (250 × 10 at 10 mL.min^{-1} and 1250 × 22 mm at 20 mL min^{-1}).

^{1}H, ^{19}F and ^{13}C NMR spectra were recorded in $CDCl_3$, acetone-d_6, methanol-d_4 or D_2O using a BRUKER AV300 (300, 75 and 282 MHz respectively) and AV400 (400, 101 and 376 MHz respectively) spectrometers. ^{1}H and ^{13}C chemical shifts (δ) are quoted in ppm relative to residual solvent peaks as appropriate. ^{19}F spectra were externally referenced to $CFCl_3$. The coupling constants (*J*) were recorded in Hertz (Hz). The proton NMR signals signals were designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), spt (septet), m (multiplet), or a combination of the above. The coupling constants have not been averaged.

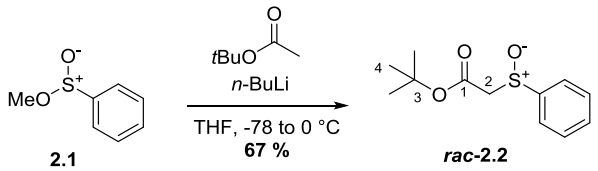
Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected on a PerkinElmer Spectrum one FT6IR fitted with an ATR accessory using neat samples (solid or liquids). The abbreviations s (strong), m (medium) w (weak), and br (broad, combined with s,m,w when appropriate) were used for the reported data.

Electrospray mass spectra were obtained from a Waters 2700 sample manager ESI, and recorded in m/z (abundance pourcentage). HRMS was obtained from a Bruker APEX III FT-ICR-MS. Samples were run in HPLC methanol or MeCN.

Optical rotations were recorded on an Optical Activity POLAAR 2001 at 589 nm with samples dissolved in $CHCl_3$, MeOH or D_2O.

10.2 Synthesis of epoxide precursors

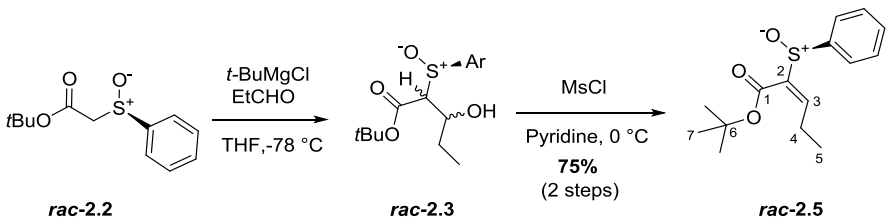
10.2.1 Synthesis of *rac*-*t*-butyl-2-(phenylsulfinyl)acetate *rac*-2.2



To a solution of diisopropyl amine (34.7 mL, 247 mmol, 1.54 equiv) in THF (300 mL) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 98.8 mL, 247 mmol, 1.54 equiv) dropwise *via* dropping funnel. The solution was stirred at -78 °C for 15 min before adding *t*-butyl acetate (51.3 mL, 380 mmol, 2.38 equiv) dropwise. After stirring for a further 1 h at -78 °C, a solution of methyl benzene sulfinate **2.1** (25.0 g, 160.0 mmol, 1 equiv) in THF (60 mL) was added *via* cannula. The solution was warmed to 0 °C, and stirring was continued for 1 h. The reaction was then quenched with a saturated solution of NH_4Cl (100 mL), and diluted with H_2O (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2×200 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/EtOAc 8:2 to 7:3) afforded ***rac*-2.2** as a pale oil (26.3 g, 67 %).

IR (neat) 3025 (w), 2978 (w, br.), 1720 (s), 1284 (s, br.), 1155 (s, br.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.63 (2H, m, H_{Ar}), 7.59 – 7.45 (3H, m, H_{Ar}), 3.80 (1H, d, $^3J_{HH}$ 13.6 Hz, H_2), 3.60 (1H, $^3J_{HH}$ 13.6 Hz, $H_{2'}$), 1.40 (9H, s, H_4); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.7 (C_1), 143.3 (C_{qAr}), 131.6 (CH_{Ar}), 129.3 (2C, CH_{Ar}), 124.4 (2C, CH_{Ar}), 83.2 (C_3), 62.6 (C_2), 27.7 (C_4) ppm; NMR spectra correspond with the reported data;[139] **MS** (ESI^+) (m/z) 241 $[M+H]^+$, 185 [M-*t*Bu + 2H]$^+$; **HRMS** (ESI^+) for $C_{12}H_{16}O_3S$ $[M+Na]^+$ calcd. 263.0712, found. 263.0712.

10.2.2 Synthesis of *rac*-(*E*)-*t*-butyl-2-(*p*-tolylsulfinyl)pent-2-enoate (*rac*-2.5)

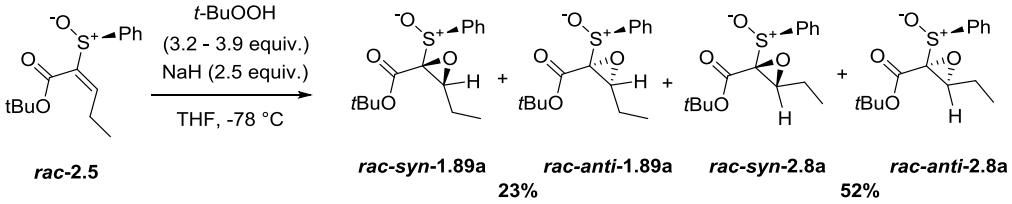


To a solution of *t*-BuMgCl (1.6 M in THF, 100 mL, 160.7 mmol, 1.5 equiv) in THF (150 mL) at -78 °C was added ***rac*-2.2** (25.7 g, 107.1 mmol, 1 equiv) in THF (150 mL) at -78 °C *via* dropping funnel. The mixture was then stirred at -78 °C for 1 h before propionaldehyde (97%, 24.5 mL, 331.7 mmol, 3.1 equiv) was added dropwise. The reaction was then stirred for a further 2 h at -78 °C. The reaction mixture was then allowed to warm up to 0 °C before quenching with a saturated solution of NH_4Cl (200 mL), and H_2O (100 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (2×300 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/EtOAC 8:2 to 5:5) afforded 30.3 g of the impure addition product ***rac*-2.3** as a mixture of diastereoisomers and as a white solid, which was directly used in the next step.

The impure addition product ***rac*-2.3** (30.3g) was dissolved in pyridine (200 mL), and MsCl (23.7 mL, 306 mmol, 3.2 equiv.) was added dropwise at 0 °C. The reaction was stirred at this temperature for 24 h, before quenching with a solution of HCl (1M, 400 mL). The mixture was extracted with Et_2O (3×800 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/EtOAc 8:2) afforded ***rac*-2.5** as a yellow oil (22.4 g, 75% over 2 steps, *E* isomer only).

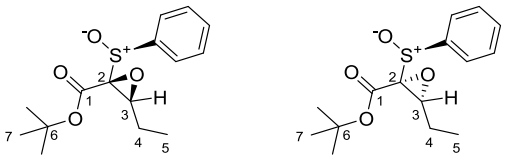
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.61 (2H, m, H_{Ar}), 7.55 – 7.40 (3H, m, H_{Ar}), 7.05 (1H, t, $^3J_{HH}$ 7.7 Hz, H_3), 2.88 – 2.65 (2H, m, H_4, $H_{4'}$), 1.30 (9H, s, H_7), 1.18 (3H, t, $^3J_{HH}$ 7.6 Hz, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5 (C_1), 148.3 (C_3), 144.0 (C_2 or C_{qAr}), 136.6 (C_2 or C_{qAr}), 131.6 (CH_{Ar}), 129.7 (2C, CH_{Ar}), 126.4 (2C, CH_{Ar}), 83.0 (C_6), 27.9 (C_7), 22.8 (C_4), 13.3 (C_5) ppm. NMR spectra correspond with the reported data.[17]

10.2.3 Synthesis of racemic epoxides *rac*-1.89a and *rac*-2.8a

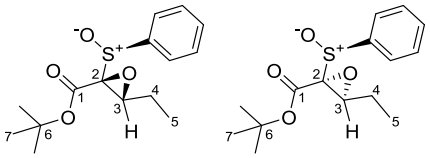


dr ***syn*-1.89a**/***anti*-1.89a**/***syn*-2.8s**/***anti*-2.8a** 35 : 4 : 54 : 7

To a solution of *t*-BuOOH (5-6 M in decane, 480 µL, 2.6 mmol, 3.2 - 3.9 equiv.) in THF (12 mL) at -78 °C was added NaH (60 % dispersion in mineral oil, 75.2 mg, 1.88 mmol, 2.5 equiv.) portionwise. The resulting suspension was allowed to warm up to rt and stirred at this temperature for 20 min. The suspension was then cooled to -78 °C before adding a solution of ***rac*-2.5** (211 mg, 0.75 mmol, 1 equiv.) in THF (8 mL) *via* cannula. The reaction mixture was then stirred at -78 °C for 20 min, and was quenched at this temperature with a saturated solution of $Na_2S_2O_3$ (10 mL). The mixture was allowed to warm up to 0 °C, and was extracted at this temperature with Et_2O (2×10 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated *in vacuo*, yielding the crude epoxides ***rac*-1.89a** and ***rac*-2.8a** (*dr* ***syn*-1.89a**/***anti*-1.89a**/***syn*-2.8s**/***anti*-2.8a** 35: 4: 54: 7). Purification *via* column chromatography (pentane/Et_2O 9:1 to 5:5) and preparative HPLC (pentane/Et_2O 7:3) afforded *trans*-epoxides **1.89a** as a viscous oil (52 mg, 23%) and *cis*-epoxides **2.8a** as a white solid (117 mg, 53%). An analytical sample of **2.8a** was recrystallised from hot pentane (few drops of Et_2O added) to give the pure epoxide ***syn*-2.8a**.

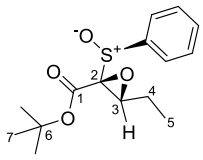


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.70 (4H, m, H_{Ar}, *syn and anti*), 7.65 – 7.42 (6H, m, H_{Ar}, *syn and anti*), 3.64 – 3.53 (1H, m, H_3, *anti*), 3.58 (1H, t, $^3J_{HH}$ 6.4 Hz, H_3, *syn*), 1.83 – 1.62 (4H, m, H_4, *syn and anti*), 1.38 (9H, m, H_7, *anti*), 1.34 (9H, m, H_7, *syn*), 1.11 (3H, t, $^3J_{HH}$ 7.6 Hz, H_5, *syn*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.3 (C_1), 140.5 (C_{qAr}), 131.8 (CH_{Ar}), 129.0 (2C, CH_{Ar}), 125.5 (2C, CH_{Ar}), 84.5 (C_6), 75.2 (C_2), 61.6 (C_3), 27.8 (C_7), 21.7 (C_4), 10.0 (C_5) ppm. NMR spectra correspond with the reported data.[17]



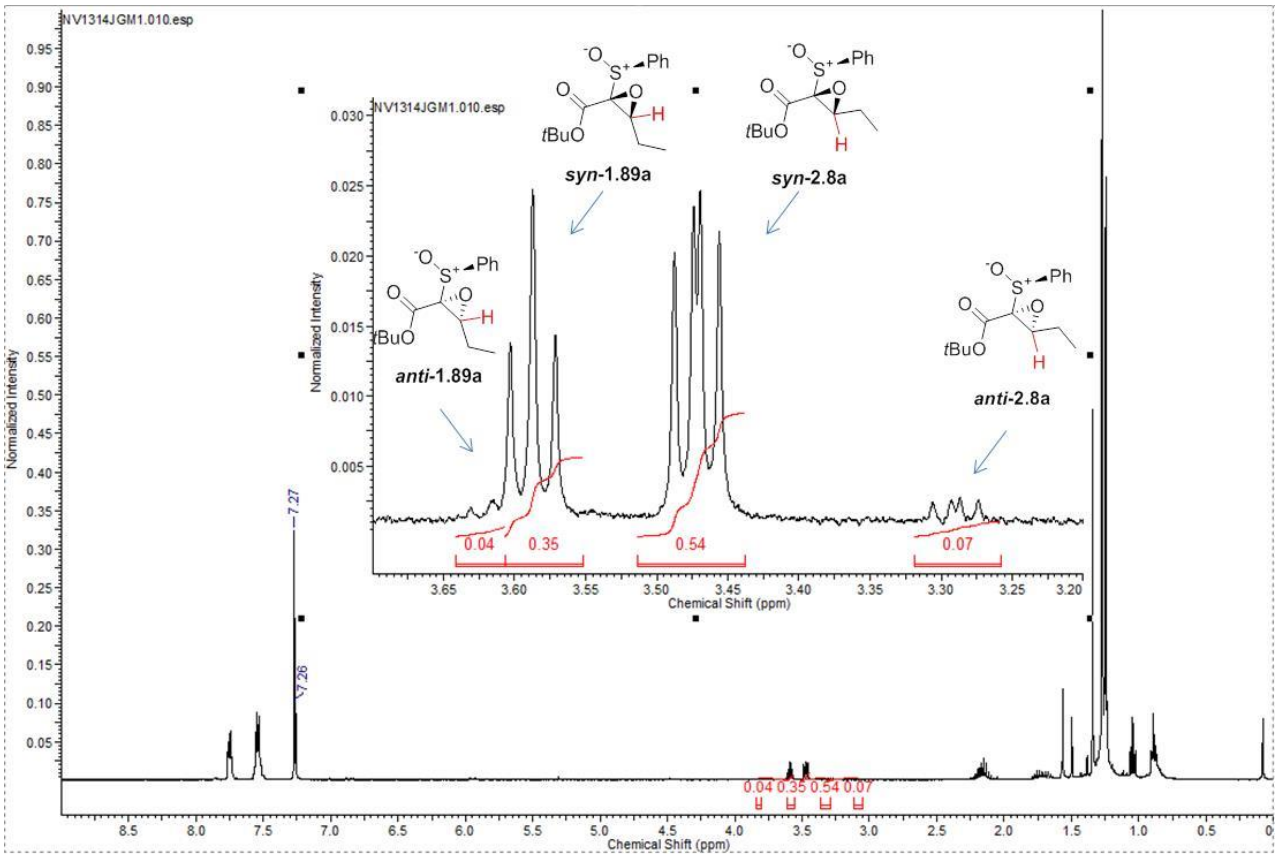
syn-2.8a *anti*-2.8a

IR (neat) 3080 (w), 2983 (w, br.), 1737 (m), 1373 (m), 1158 (s), 1088 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.80 (2H, m, H_{Ar}, *anti*), 7.79 – 7.67 (2H, m, H_{Ar}, *syn*), 7.60 – 7.44 (6H, m, H_{Ar}, *syn and anti*), 3.47 (1H, dd, $^{3}J_{HH}$ 7.3 Hz, $^{3}J_{HH}$ 5.4 Hz, H_3, *syn*), 3.29 (1H, dd, $^{3}J_{HH}$ 7.6 Hz, $^{3}J_{HH}$ 5.2 Hz, H_3, *anti*), 2.33 – 2.07 (4H, m, H_4, *syn and anti*), 1.247 (3H, t, $^{3}J_{HH}$ 7.3 Hz, H_5, *syn*), 1.240 (9H, s, H_7, *syn*), 1.235 (9H, s, H_7, *anti*), 1.19 (3H, t, $^{3}J_{HH}$ 7.5 Hz, H_5, *anti*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.7 (C_1, *anti*), 163.2 (C_1, *syn*), 141.5 (C_{qAr}, *anti*), 140.3 (C_{qAr}, *syn*), 132.3 (CH_{Ar}, *anti*), 131.1 (CH_{Ar}, *syn*), 129.1 (2C, CH_{Ar}, *anti*), 128.9 (2C, CH_{Ar}, *syn*), 127.3 (2C, CH_{Ar}, *anti*), 124.7 (2C, CH_{Ar}, *syn*), 84.5 (C_6, *anti*), 84.2 (C_6, *syn*), 74.4 (C_2, *anti*), 73.0 (C_2, *syn*), 65.9 (C_3, *anti*), 65.3 (C_3, *syn*), 27.6 (C_7, *syn and anti*), 21.3 (C_4, *anti*), 19.5 (C_4, *syn*), 11.0 (C_5, *anti*), 10.6 (C_5, *syn*) ppm. **MS** (ESI^+) (m/z) (peak 1) 241 $[M\text{-}t\text{Bu}+2H]^+$; (peak 2) 241 $[M\text{-}t\text{Bu}+2H]^+$; **HRMS** ($ESI^+$) $C_{15}H_{20}O_4S$ $[M+Na]^+$ calcd. 319.0975, found. 333.0979.

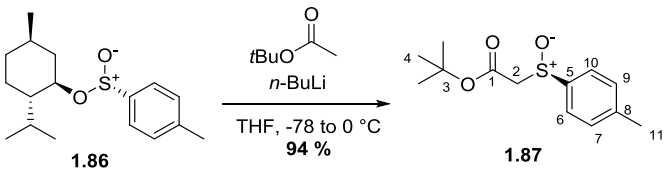


syn-2.8a

mp: 108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.67 (2H, m, H_{Ar}), 7.60 – 7.44 (3H, m, H_{Ar}), 3.47 (1H, dd, $^{3}J_{HH}$ 7.2 Hz, $^{3}J_{HH}$ 5.4 Hz, H_3), 2.25 – 2.07 (2H, m, H_4), 1.247 (3H, t, $^{3}J_{HH}$ 7.3 Hz, H_5), 1.242 (9H, s, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.2 (C_1), 140.4 (C_{qAr}), 131.1 (CH_{Ar}), 128.9 (2C, CH_{Ar}), 124.7 (2C, CH_{Ar}), 84.2 (C_6), 73.0 (C_2), 65.4 (C_3), 27.6 (C_7), 21.4 (C_4), 10.6 (C_5) ppm.



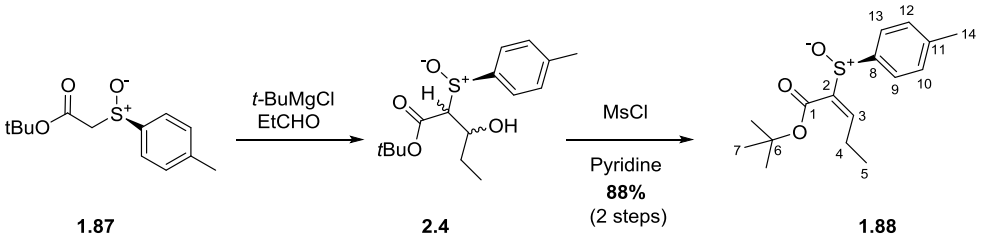
10.2.4 Synthesis of (R_S)-*t*-butyl 2-(*p*-tolylsulfinyl)acetate 1.87



To a solution of diisopropylamine (19.1 mL, 135.8 mmol, 2 equiv) in THF (510 mL) at -78 °C was added *n*-BuLi (2.5 m in hexanes, 54.3 mL, 135.8 mmol, 2 equiv) dropwise *via* dropping funnel. The solution was stirred for 15 min, before adding *t*-butyl acetate (27.5 mL, 204 mmol, 3 equiv) dropwise at -78 °C. After stirring for a further 1 h at -78 °C, a solution of (1*R*,2*S*,5*R*)-(–)-menthyl-(S_S)-*p*-toluenesulfinate **1.86** (20.0 g, 67.9 mmol, 1 equiv) in THF (70 mL) was added *via* cannula. The solution was warmed to 0 °C before stirring for 1 h. The reaction was then quenched with a saturated solution of NH_4Cl (100 mL), and diluted with H_2O (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2×200 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/EtOAc 8:2 to 7:3) afforded compound **1.87** as a pale oil (16.2 g, 94 %).

$[\alpha]_D$ 122.9 (c 0.82, $CHCl_3$, 20 °C), lit. 135.2 (c 0.56, $CHCl_3$, 31 °C)[17]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (2H, d, $^3J_{HH}$ 8.1 Hz, H_6, H_{10}), 7.34 (2H, d, $^3J_{HH}$ 7.9 Hz, H_7, H_9), 3.80 (1H, d, $^3J_{HH}$ 13.5 Hz, H_2), 3.58 (1H, $^3J_{HH}$ 13.7 Hz, $H_{2'}$), 2.43 (3H, s, H_{11}), 1.41 (9H, s, H_4); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.8 (C_1), 142.2 (C_5 or C_{11}), 140.1 (C_{11} or C_5), 130.0 (C_7 and C_9), 124.5 (C_6 and C_{10}), 83.1 (C_3), 62.7 (C_2), 27.9 (C_4), 21.5 (C_{11}) ppm. NMR spectra correspond with the reported data.[17]

10.2.5 Synthesis of (*S*,*E*)-*t*-butyl 2-(*p*-tolylsulfinyl)-pent-2-enoate 1.88



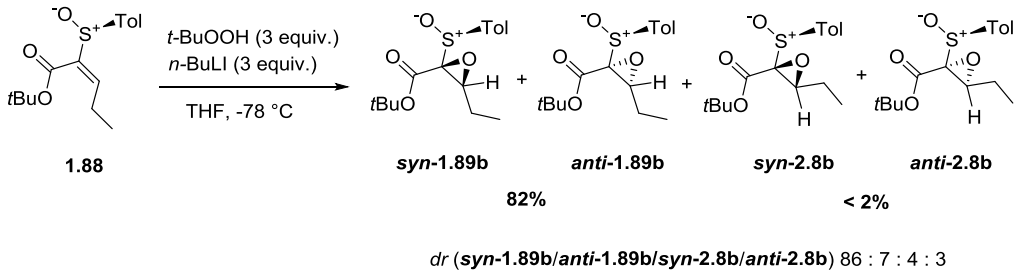
1.87 **2.4** **1.88**

To a solution of *t*-BuMgCl (1.7 M in THF, 66 mL, 112.8 mmol, 1.5 equiv) in THF (150 mL) at -78 °C was added **1.87** (19.13 g, 75.2 mmol, 1 equiv) in THF (350 mL) *via* dropping funnel. The mixture was then stirred at -78 °C for 1 h before propionaldehyde (97%, 17.2 mL, 233.2 mmol, 3.1 equiv) was added dropwise. The reaction was then stirred for a further 1.5 h at -78 °C. The reaction mixture was then allowed to warm up to 0 °C before quenching with a saturated solution of NH_4Cl (200 mL) and H_2O (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×250 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/EtOAC 8:2 to 5:5) afforded 24.5 g of the impure addition product **2.4** as mixture of diastereoisomers and as a white solid, which was directly used in the next step.

The addition product **2.4** (24.5 g) was dissolved in pyridine (250 mL), and MsCl (17.5 mL, 225.7 mmol, 3 equiv.) was added dropwise, by keeping the temperature between -10 and 0 °C for 40 min. The reaction mixture was stirred for 16 h without removing the ice bath (T=10 °C after 16 h), before quenching with a solution of HCl (1M, 500 mL) dropwise at 0 °C. The mixture was extracted with Et_2O (3×600 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/EtOAc 8:2) afforded compound **1.88** as a yellow oil (19.6 g, 88% over 2 steps).

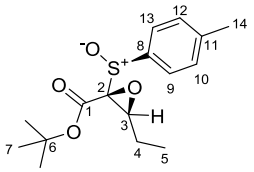
$[\alpha]_D$ 236.4 (c 0.40, $CHCl_3$, 21 °C), lit. 195.6 (c 0.26, $CHCl_3$, 26 °C)[17]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (2H, d, $^3J_{HH}$ 8.1 Hz, H_9, H_{13}), 7.26 (2H, d, $^3J_{HH}$ 7.8 Hz, H_{10}, H_{12}), 7.03 (1H, t, $^3J_{HH}$ 7.9 Hz, H_3), 2.86 – 2.65 (2H, m, H_4, $H_{4'}$), 2.39 (3H, s, H_{14}), 1.30 (9H, s, H_7), 1.18 (3H, t, $^3J_{HH}$ 7.6 Hz, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6 (C_1), 148.0 (C_3), 142.1 (C_2 or C_8 or C_{11}), 140.8 (C_2 or C_8 or C_{11}), 136.6 (C_2 or C_8 or C_{11}), 129.7 (C_9 and C_{13}), 125.6 (C_{10} and C_{12}), 82.8 (C_6), 27.9 (C_7), 22.8 (C_4), 21.5 (C_{14}), 13.3 (C_5) ppm. NMR spectra correspond with the reported data.[17]

10.2.6 Synthesis of epoxides 1.89b and 2.8b

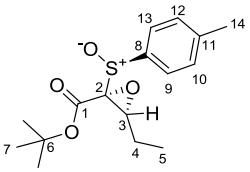


To a solution of *t*-BuOOH (5.5M in decane, dried over MS 4Å, 5.4 mL, 29.8 mmol, 3 equiv.) in THF (290 mL) at -78 °C was added *n*-BuLi (2.45 M in hexane, 12.1 mL, 29.8 mmol, 3 equiv.) dropwise *via* cannula. The resulting solution was stirred at the same temperature for 20 min, before adding a solution of **1.88** (2.92 g, 9.91 mmol, 1 equiv.) in THF (80 mL) dropwise *via* cannula. The reaction mixture was then stirred at -78 °C for a further 25 min, and was quenched at this temperature with a saturated solution of $Na_2S_2O_3$ (200 mL). The mixture was allowed to warm up to 0 °C, and was extracted at this temperature with EtOAc (3×200 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated *in vacuo*, yielding a mixture of crude epoxides **1.89b** and **2.8b** (*dr* ***syn*-1.89b/*anti*-1.89b/*syn*-2.8b/*anti*-2.8b** 86: 7 : 4 : 3). Purification *via* column chromatography (pentane/Et_2O 8:2 to 6:4) afforded *trans*-epoxides **1.89b** as a white solid (2.52 g, 82%) and the impure *cis*-epoxides **2.8b** as colourless oil (68 mg, isolated with minor impurity, <2%). An analytical mixture of **1.89b** was recrystallised from hot pentane (few drops of Et_2O added) to give the pure epoxide ***syn*-1.89b**.

N.b: ***syn*-2.8b** and ***anti*-2.8b** were obtained as pure products on small scale.

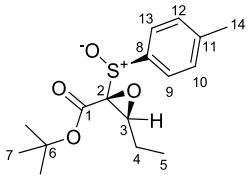


***syn*-1.89b**



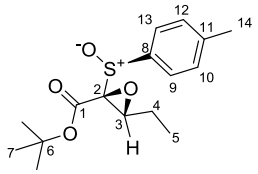
***anti*-1.89b**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (4H, d, $^{3}J_{HH}$ 8.1 Hz, H_9, H_{13}, *syn and anti*), 7.33 (4H, d, $^{3}J_{HH}$ 8.1 Hz, H_{10}, H_{12}, *syn and anti*), 3.59 (1H, t, $^{3}J_{HH}$ 6.4 Hz, H_3, *anti*), 3.55 (1H, $^{3}J_{HH}$ 6.4 Hz, H_3, *syn*), 2.42 (3H, s, H_{14}, *syn*), 2.40 (3H, s, H_{14}, *anti*), 1.81 – 1.60 (4H, m, H_4, *syn and anti*), 1.38 (9H, m, H_7, *anti*), 1.35 (9H, m, H_7, *syn*), 1.10 (3H, t, $^{3}J_{HH}$ 7.6 Hz, H_5, *anti*), 1.03 (3H, t, $^{3}J_{HH}$ 7.6 Hz, H_5, *syn*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.4 (C_1), 142.5 (C_8 or C_{11}), 137.1 (C_{11} or C_8) , 129.7 (C_9 and C_{13}), 125.6 (C_{10} and C_{12}), 84.4 (C_6), 75.3 (C_2), 61.2 (C_3), 27.8 (C_7), 21.7 (C_4), 21.5 (C_{14}) 10.0 (C_5) ppm. NMR spectra correspond to the reported data.[17]

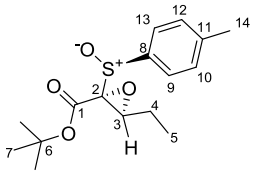


***syn*-1.89b**

$[\alpha]_D$ 49.2 (c 1.4, $CHCl_3$, 23 °C); **mp:** 56 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (2H, d, $^{3}J_{HH}$ 8.1 Hz, H_9, H_{13}), 7.32 (2H, d, $^{3}J_{HH}$ 8.1 Hz, H_{10}, H_{12}), 3.54 (1H, t, $^{3}J_{HH}$ 6.4 Hz, H_3), 2.41 (3H, s, H_{14}), 1.81 – 1.60 (4H, m, H_4), 1.34 (9H, m, H_7), 1.03 (3H, t, $^{3}J_{HH}$ 7.5 Hz, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.4 (C_1), 142.5 (C_8 or C_{11}), 137.1 (C_{11} or C_8), 129.7 (C_9 and C_{13}), 125.6 (C_{10} and C_{12}), 84.4 (C_6), 75.3 (C_2), 61.1 (C_3), 27.8 (C_7), 21.7 (C_4), 21.5 (C_{14}) 10.0 (C_5) ppm. NMR spectra correspond to the reported data (previously only described in a mixture with ***anti*-1.89b**).[17]



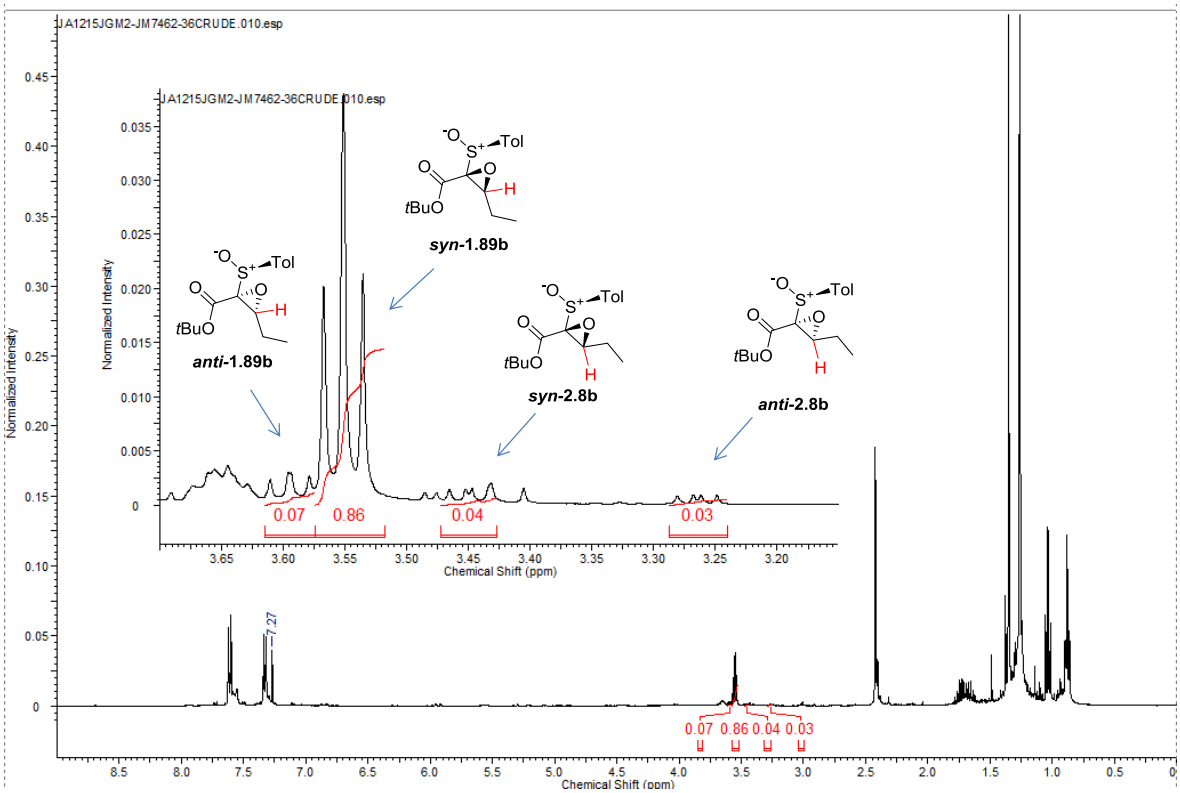
***syn*-2.8b**



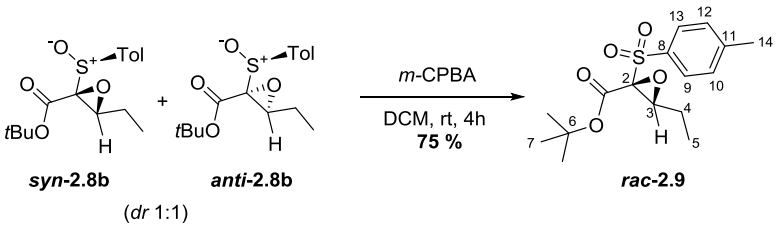
***anti*-2.8b**

IR (neat) 2971 (w, br.), 1743 (m), 1716 (m), 1251 (m), 1096 (s), 1062 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (2H, d, $^{3}J_{HH}$ 7.8 Hz, H_9, H_{13}, *anti*), 7.62 (2H, d, $^{3}J_{HH}$ 8.6 Hz, H_9, H_{13}, *syn*), 7.38 – 7.28 (4H, m, H_{10}, H_{12}, *syn and anti*), 3.45 (1H, dd, $^{3}J_{HH}$ 7.3 Hz, $^{3}J_{HH}$ 5.5 Hz, H_3, *syn*), 3.26 (1H, dd, $^{3}J_{HH}$ 7.5 Hz, $^{3}J_{HH}$ 5.1 Hz, H_3, *anti*), 2.42 (3H, s, H_{14}, *syn*), 2.41 (3H, s, H_{14}, *anti*),

2.32 – 2.00 (4H, m, H_4, *syn and anti*), 1.27 (9H, s, *syn*), 1.244 (9H, s, H_7, *anti*), 1.236 (3H, t, $^3J_{HH}$ 7.3 Hz, H_5, *syn*), 1.17 (3H, t, $^3J_{HH}$ 7.5 Hz, H_5, *anti*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.7 (C_5, *anti*), 163.2 (C_5, *syn*), 142.9 (C_8 or C_{11}, *syn or anti*), 141.5 (C_8 or C_{11}, *syn or anti*), 138.3 (C_8 or C_{11}, *syn or anti*), 136.9 (C_8 or C_{11}, *syn or anti*), 129.7 (C_{10} and C_{12}, *syn or anti*), 129.6 (C_{10} and C_{12}, *syn or anti*), 127.3 (C_9 and C_{13}, *anti*), 124.7 (C_9 and C_{13}, *syn*), 84.4 (C_6, *anti*), 84.1 (C_6, *syn*), 74.3 (C_2, *anti*), 73.0 (C_2, *syn*), 65.9 (C_3, *anti*), 65.4 (C_3, *syn*), 27.64 (C_7, *syn*), 27.59 (C_7, *anti*), 21.5 (C_{14}, *anti*), 21.4 (C_{14}, *syn*), 21.3 (C_4, *syn*), 19.5 (C_4, *anti*), 10.9 (C_5, *anti*), 10.6 (C_5, *syn*) ppm; **MS** (ESI^+) (m/z) (peak 1) 311 $[M+H]^+$, 255 [M - *t*Bu + 2H]$^+$; (peak 2) 311 $[M+H]^+$, 255 $[M-tBu+2H]^+$; **HRMS** (ESI^+) for $C_{16}H_{22}O_4S$ $[M+Na]^+$ calcd. 333.1131, found. 333.1136.



10.2.7 Oxidation of sulfoxide derivatives 2.8b to give 2.9



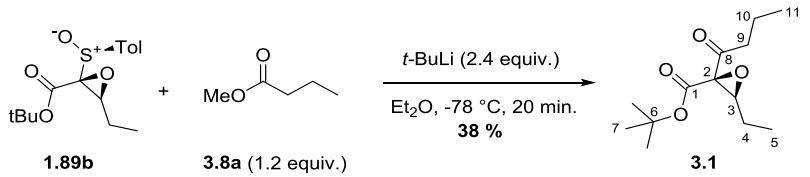
syn-2.8b **anti-2.8b** (*dr* 1:1) **rac-2.9**

To a solution of sulfoxides **2.8b** (*dr* ***syn***/***anti*** 1:1, 243 mg, 0.78 mmol, 1 equiv.) in DCM (5 mL) at rt was added portionwise *m*-CPBA (77%, 192 mg, 0.86 mmol, 1.1 equiv.). The resulting suspension was stirred at this temperature for 4 h, before quenching with saturated solution of $Na_2S_2O_3$ (5 mL). The layers were separated, and the aqueous phases were extracted with Et_2O (3×5 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* column chromatography (pentane/Et_2O 8:2) afforded sulfone **rac-2.9** as viscous oil (192 mg, 75%).

IR (neat) 2978 (w, br.), 1736 (m), 1331 (m), 1253 (m), 1140 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (2H, d, $^3J_{HH}$ 8.3 Hz, H_9 and H_{13}), 7.37 (2H, d, $^3J_{HH}$ 8.0 Hz, H_{10} and H_{12}), 3.28 (1H, dd, $^3J_{HH}$ 7.5 Hz, $^3J_{HH}$ 5.2 Hz, H_3), 2.46 (3H, s, H_{14}), 2.33 – 2.11 (2H, m, H_4), 1.28 (9H, s, H_7), 1.19 (3H, t, $^3J_{HH}$ 7.5 Hz, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.7 (C_1), 145.4 (C_8 or C_{11}), 135.9 (C_8 or C_{11}), 129.6 (C_{10} and C_{12}), 128.9 (C_9 and C_{13}), 84.9 (C_6), 74.3 (C_2), 66.3 (C_3), 27.5 (C_7) , 21.7 (C_{14}), 20.4 (C_4), 10.9 (C_5) ppm; **MS** (ESI^+) (m/z) 344 $[M+NH_4]^+$, 349 $[M+Na]^+$; **HRMS** (ESI^+) for $C_{16}H_{22}O_5S$ $[M+Na]^+$ calcd. 349.1080, found. 349.1079.

10.3 Acylation and diastereoselective reduction

10.3.1 Acylation reaction: synthesis of model substrate 3.1



1.89b **3.8a** (1.2 equiv.) **3.1**

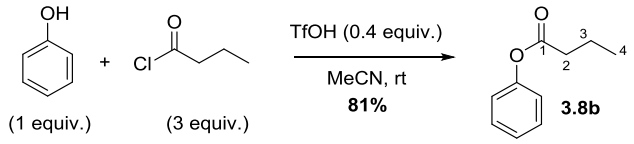
To compound **1.89b** (217 mg, 0.70 mmol, 1 equiv.), dissolved in Et_2O (4.7 mL), was added methyl butanoate **3.8a** (95 µL, 0.84 mmol, 1.2 equiv.) at rt. The mixture was cooled to -78 °C and stirred for 10 min, before adding a solution of *t*-BuLi (1.9 M in pentane, 880 µL, 1.69 mmol, 2.4 equiv.) dropwise for 5 min. The resulting mixture was stirred at this

temperature for 20 min, and was quenched at -78 °C with a saturated solution of NH_4Cl (2 mL). The mixture was then extracted with Et_2O (3×5 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure (30 °C, < 500 mbar) to minimise losses through compound evaporation. Purification *via* column chromatography (pentane/Et_2O 95:5 to 9:1) afforded the compound **3.1** as colourless oil (67 mg, 91 % purity with 9% Et_2O, 65 mg calculated, 38%).

IR (neat) 2972 (w, br.), 1743 (s), 1716 (s), 1369 (m), 1253 (m), 1163 (m), 1136 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.24 (1H, t, $^3J_{HH}$ 6.1 Hz, H_3), 2.58 (1H, dt, $^2J_{HH}$ 17.9 Hz, $^3J_{HH}$ 7.1 Hz, H_9), 2.40 (1 H, dt, $^2J_{HH}$ 17.4 Hz, $^3J_{HH}$ 6.8 Hz, $H_{9'}$), 1.71 - 1.56 (4H, m, H_4, H_{10}), 1.53 (9H, s, H_7), 1.10 (3 H, t, $^3J_{HH}$ 7.5 Hz, H_5 or H_{11}), 0.92 (3 H, t, $^3J_{HH}$ 7.5 Hz, H_{11} or H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.0 (C_8), 164.6 (C_1), 83.5 (C_6), 65.9 (C_2), 63.1 (C_3), 39.5 (C_9), 28.0 (C_6), 22.7 (C_4 or C_{10}), 16.7 (C_{10} or C_4), 13.6 (C_5 or C_{11}), 10.1 (C_{11} or C_5) ppm; **MS** (ESI^+) (m/z) 265 $[M+Na]^+$, 260 $[M+NH_4]^+$, 187 $[M-t\text{Bu}+2H]^+$; **HRMS** (ESI^+) for $C_{13}H_{22}O_4$ $[M+Na]^+$ calcd. 265.1416, found. 265.1410.

10.3.2 Synthesis of acyl donors

10.3.2.1 Synthesis of phenyl butanoate 3.8b

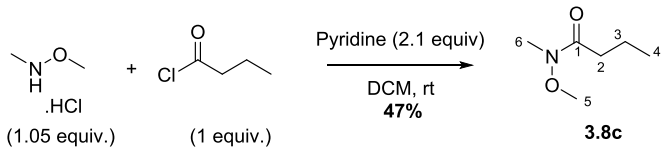


To a solution of phenol (590 mg, 6.3 mmol, 1 equiv.) in MeCN at rt was added butanoyl chloride (2.0 mL, 18.3 mmol, 2.9 equiv.), followed by TfOH (230 µL, 2.6 mmol, 40 mol%) dropwise. The resulting solution was stirred at rt for 1 h. The mixture was then poured into a mixture of Et_2O/H_2O (1:1, 200 mL). The layers were separated, and the organic phase was successively washed with HCl (1M, 100 mL) and a saturated solution of $NaHCO_3$ (3×100 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure, yielding phenyl butyrate **3.8b** as colourless oil (834 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 750 (2H, m, H_{Ar}), 7.47 – 7.36 (1H, m, H_{Ar}), 7.32 – 7.21 (2H, m, H_{Ar}), 2.72 (2H, t, $^3J_{HH}$ 7.4 Hz, H_2), 1.98 (2H, sxt, $^3J_{HH}$ 7.4 Hz, H_3), 1.23 (3H, t, $^3J_{HH}$ 7.4 Hz, H_4); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.1 (C_1), 150.8 (C_{qAr}), 129.4 (2C, CH_{Ar}), 125.7 (CH_{Ar}),

121.6 (2C, CH_{Ar}), 36.2 (C_2), 18.5 (C_3), 13.6 (C_4) ppm. NMR spectra correspond with the reported data.[140,141]

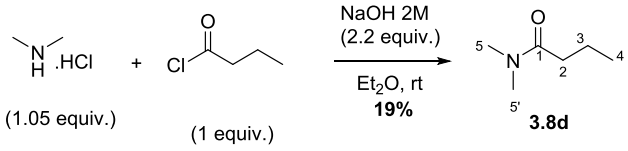
10.3.2.2 Synthesis of *N*-Methoxy-*N*-methylbutanamide 3.8c



To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (975 mg, 10 mmol, 1.05 equiv.) and butanoyl chloride (1 mL, 9.6 mmol, 1 equiv.) in DCM (20 mL) at 0 °C was added pyridine (1.6 mL, 20.2 mmol, 2.1 equiv.) dropwise. The resulting solution was stirred at rt for 2 h. The mixture was then diluted in Et_2O (100 mL), and was successively washed with a saturated solution of $NaHCO_3$ (100 mL), HCl (1M, 100 mL) then brine (100 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure, yielding compound **3.8c** as a colourless oil (590 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (3H, s, H_6 or H_5), 3.18 (3H, s, H_5 or H_6), 2.40 (2H, t, $^3J_{HH}$ 7.5 Hz, H_2), 1.66 (2H, sxt, $^3J_{HH}$ 7.5 Hz, H_3), 0.96 (3H, t, $^3J_{HH}$ 7.5 Hz, H_4); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.6, 61.2, 33.8, 32.2, 18.0, 13.9 ppm. NMR spectra correspond with the reported data.[48]

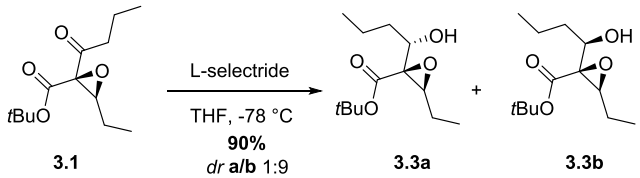
10.3.2.3 Synthesis of *N*,*N*-dimethylbutanamide 3.8d



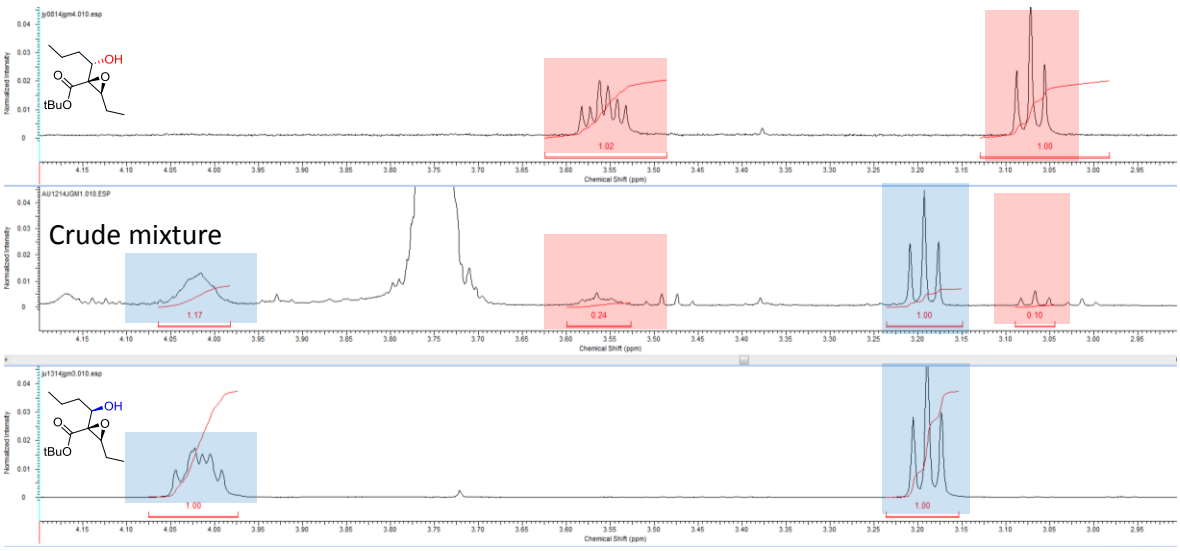
To a suspension of dimethylamine hydrochloride (2.5 g, 31.0 mmol, 1.08 equiv.) and butanoyl chloride (3 mL, 28.7 mmol, 1 equiv.) in Et_2O (100 mL) at rt was added NaOH (2M in H_2O, 31 mL, 62 mmol, 2.16 equiv.) dropwise *via* dropping funnel, and the resulting emulsion was stirred at this temperature for 3 h, before extracting with Et_2O. The layers were separated, and the organic phase was dried over $MgSO_4$, and concentrated under reduced pressure (30 °C, < 500 mbar), yielding **3.8d** as a yellowish oil (692 mg, 86 % purity with 14% Et_2O, 626 mg calculated, 19%).

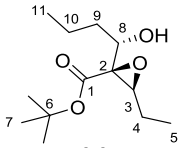
IR (neat) 2961 (w, br.), 1636 (s), 1396 (m), 1153 (m), 1070 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.96 (3H, s, H_5 or $H_{5'}$), 2.89 (3H, s, $H_{5'}$ or H_5), 2.24 (2H, t, $^{3}J_{HH}$ 7.5 Hz, H_2), 1.61 (2H, sxt, $^{3}J_{HH}$ 7.5 Hz, H_3), 0.91 (3H, t, $^{3}J_{HH}$ 7.4 Hz, H_4); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.0 (C_1), 37.2 (C_5 or $C_{5'}$), 35.2 (C_2 and $C_{5'}$ or C_5), 18.4 (C_3), 13.8 (C_4) ppm; **MS** (ESI^+) (m/z) 231 $[2M+H]^+$, 179 $[M+Na+CH_3CN]^+$; **HRMS** (ESI^+) for $C_6H_{13}NO$ $[M+Na]^+$ calcd. 138.0889, found. 138.0887.

10.3.3 Diastereoselective reduction using L-selectride (*syn*- selective)



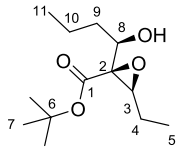
To a solution of **3.1** (129 mg, 0.53 mmol, 1 equiv.) in THF (4 mL) at -78 °C was added L-selectride (1M solution in THF, 560 µL, 0.56 mmol, 1.05 equiv.) dropwise. The mixture was stirred for 30 min at -78 °C, before quenching with a saturated solution of NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×5 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated *in vacuo*, yielding the crude alcohol as a mixture of diastereoisomers (*dr* **3.3a**/**3.3b** 1:9). Purification *via* column chromatography (petroleum ether/EtOAc 8:2 to 7:3) allowed isolation of the *anti*-α-epoxy alcohol **3.3a** (10 mg, 8%) as well as the *syn*-α-epoxy alcohol **3.3b** (78 mg, 60%). A mixture of both diastereoisomers was also obtained (28 mg, 22%, *dr* **3.3a**/**3.3b** 15:85). Overall yield: 116 mg, 90%.





3.3a

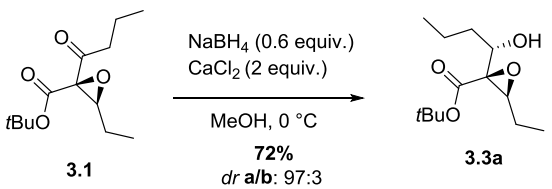
IR (neat) 3519 (w, br.), 2975 (w, br.), 1735 (s, br.), 1376 (m), 1266 (s), 1142 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.56 (1H, td, $^3J_{HH}$ 8.1 Hz, $^3J_{HH}$ 3.9 Hz, H_8), 3.07 (1H, t, $^3J_{HH}$ 6.5 Hz, H_3), 2.46 (1H, d, $^3J_{HH}$ 7.8 Hz, O<u>H</u>-8), 1.83 – 1.31 (6H, m, H_4, H_9, H_{10}), 1.53 (9H, s, H_7), 1.07 (3 H, t, $^3J_{HH}$ 7.3 Hz, H_5 or H_{11}), 0.95 (3 H, t, $^3J_{HH}$ 7.1 Hz, H_{11} or H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2 (C_1), 83.3 (C_6), 72.5 (C_8), 64.6 (C_2), 62.4 (C_3), 35.7 (C_4 or C_9 or C_{10}), 28.1 (C_7), 21.6 (C_4 or C_9 or C_{10}), 18.7 (C_4 or C_9 or C_{10}), 14.0 (C_5 or C_{11}), 10.2 (C_{11} or C_5) ppm; **MS** (ESI^+) (m/z) 511 $[2M+Na]^+$, 267 $[M+Na]^+$, 189 $[M-t\text{Bu}+2H]^+$; **HRMS** (ESI^+) for $C_{13}H_{24}O_4$ $[M+Na]^+$ calcd. 267.1567, found. 267.1573.



3.3b

IR (neat) 3455 (w, br.), 2968 (m, br.), 1746 (s), 1372 (s), 1244 (s), 1134 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.16 – 3.90 (1H, m, H_8), 3.19 (1H, t, $^3J_{HH}$ 6.4 Hz, H_3), 1.69 – 1.52 (6H, m, H_4, H_9, H_{10}), 1.50 (9H, s, H_7), 1.05 (3 H, t, $^3J_{HH}$ 7.5 Hz, H_5 or H_{11}), 0.95 (3 H, t, $^3J_{HH}$ 7.0 Hz, H_{11} or H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5 (C_1), 82.6 (C_6), 69.6 (C_8), 66.0 (C_2), 60.5 (C_3), 35.8 (C_4 or C_9 or C_{10}), 28.0 (C_7), 21.4 (C_4 or C_9 or C_{10}), 18.6 (C_4 or C_9 or C_{10}), 13.9 (C_5 or C_{11}), 10.2 (C_{11} or C_5) ppm; **MS** (ESI^+) (m/z) 511 $[2M+Na]^+$, 267 $[M+Na]^+$, 189 $[M - t\text{-Bu} + 2H]^+$; **HRMS** (ESI^+) for $C_{13}H_{24}O_4$ $[M+Na]^+$ calcd. 267.1567, found. 267.1565.

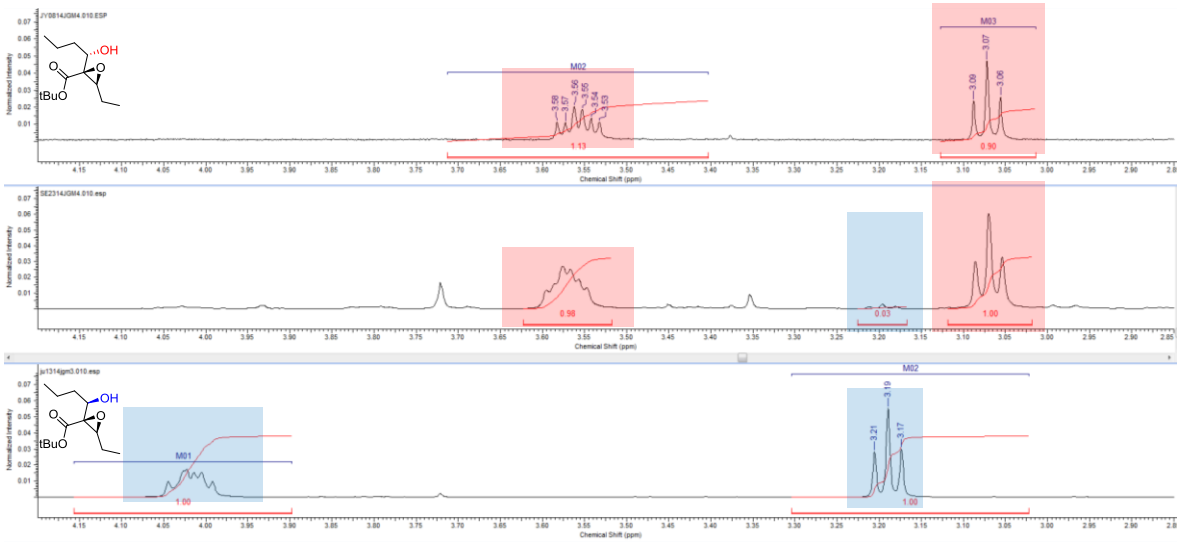
10.3.4 Diastereoselective reduction using $NaBH_4/CaCl_2$ (*anti*-selective)



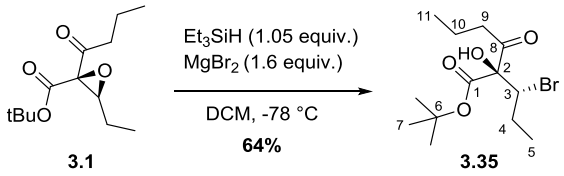
3.1 **3.3a**

To a solution of **3.1** (120 mg, 0.50 mmol, 1 equiv.) in MeOH (4 mL) at rt was added $CaCl_2$ (111 mg, 1 mmol, 2 equiv.). The mixture was stirred at this temperature for 5 min (dissolution of $CaCl_2$), and was cooled down to 0 °C. $NaBH_4$ (11 mg, 0.3 mmol, 0.6 equiv.)

was then added, and the resulting solution was stirred at this temperature for 20 min, before quenching with a saturated solution of NH_4Cl (3 mL). The mixture was extracted with Et_2O (3×20 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated *in vacuo*, yielding the crude alcohol as a mixture of disatereoisomers (*dr* **3.3a**/**3.3b** 97:3). Purification *via* column chromatography (petroleum ether/EtOAc 8:2 to 7:3) afforded the *anti*-product **3.3a** (87 mg, 72%).



10.3.5 Synthesis of bromohydrin 3.35

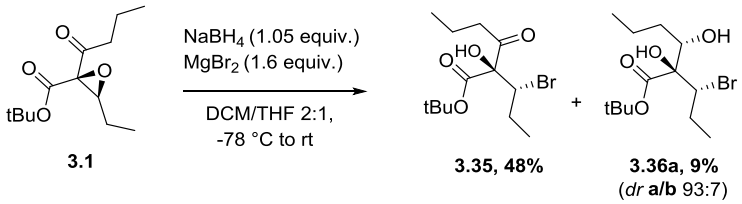


To a suspension of magnesium granules (20 mg, 0.85 mmol, 1.6 equiv) in Et_2O (2 mL) at rt was added 1,2-dibromoethane (73 µL, 0.85 mmol, 1.6 equiv). The mixture started to spontaneously reflux and was stirred for approximately 2 h until complete dissolution of the magnesium. Et_2O was then evacuated from the flask under vacuum to yield a white solid which was dissolved in DCM (3 mL). Separately, a flask containing compound **3.31** (128 mg, 0.53 mmol, 1 equiv.) in DCM (2 mL) was prepared and added to $MgBr_2$ suspension *via* syringe. In another flask, Et_3SiH (88 µL, 0.55 mmol, 1.05 equiv.) was dissolved in DCM (2 mL). All flasks were then cooled down at -78 °C and stirred for 10 min, after which the solution of Et_3SiH was then transferred *via* syringe followed by stirring for 2 h at -78 °C. The mixture was then quenched with a saturated solution of

$NaHCO_3$ (2 mL) and diluted with H_2O (10 mL). The layers were separated and the aqueous phase was extracted with DCM (3×10 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* column chromatography (pentane/Et_2O 97:3) afforded the bromohydrin **3.35** as white solid (109 mg, 64%).

mp: 44 °C; **IR** (neat) 3478 (w, br.), 2956 (w, br.), 1716 (s, br.), 1376 (m), 1281 (m), 1259 (m), 1153 (s), 1123 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.68 (1H, dd, $^3J_{HH}$ 10.8 Hz, $^3J_{HH}$ 2.2 Hz, H_3), 4.19 (1H, s, O<u>H</u>-2, disappeared upon D_2O exchange), 2.72 (1H, dt, $^2J_{HH}$ 18.2 Hz, $^3J_{HH}$ 6.9 Hz, H_9), 2.45 (1H, dt, $^2J_{HH}$ 18.2 Hz, $^3J_{HH}$ 7.3 Hz, $H_{9'}$), 1.85 − 1.70 (1H, m, H_4), 1.69 − 1.53 (3H, m, $H_{4'}$, H_{10}), 1.57 (9H, s, H_7), 1.07 (3 H, t, $^3J_{HH}$ 7.2 Hz, H_5), 0.89 (3 H, t, $^3J_{HH}$ 7.3 Hz, H_{11}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.3 (C_8), 167.9 (C_1), 87.3 (C_2 or C_6), 85.2 (C_6 or C_2), 61.3 (C_3), 40.3 (C_6), 27.7 (C_7), 26.7 (C_4), 16.7 (C_{10}), 13.5 (C_{11}), 12.8 (C_5) ppm; **MS** (ESI^+) (m/z) 347 [M(^{81}Br)+Na]$^+$, 345 [M(^{79}Br)+Na]$^+$; **HRMS** (ESI^+) for $C_{13}H_{23}{}^{79}BrO_4$ [M+Na]$^+$ calcd. 345.0672, found. 345.0669.

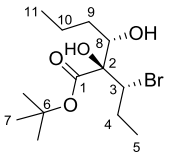
10.3.6 Synthesis of bromohydrins 3.35 and 3.36



3.1 **3.35, 48%** **3.36a, 9%** (*dr* **a**/**b** 93:7)

To a suspension of magnesium granules (23 mg, 0.94 mmol, 1.6 equiv) in Et_2O (2 mL) was added 1,2-dibromoethane (80 µL, 0.94 mmol, 1.6 equiv) at rt. The mixture started to spontaneously reflux and was stirred for approximately 2 h until complete dissolution of the magnesium. Et_2O was then evacuated from the flask under vacuum to yield a white solid which was dissolved in DCM (3 mL). Separately, a flask containing **3.1** (142 mg, 0.59 mmol, 1 equiv.) in DCM (2 mL) was prepared and added to $MgBr_2$ suspension via syringe. In another flask, $NaBH_4$ (23 mg, 0.62 mmol, 1.05 equiv.) was dissolved in THF (2 mL). All flasks were then cooled down at -78 °C and stirred for 10 min, after which the solution of $NaBH_4$ was then transferred *via* syringe, followed by stirring at this temperature for 1 h. The reaction mixture was then allowed to warm up to rt, and stirring was continued for 1 h, before quenching with $NaHCO_3$ (2 mL), and diluting with H_2O (10 mL). The layers were separated and the aqueous phase was extracted with DCM (3×10 mL). Organic phases

were combined, dried over Na_2SO_4 and concentrated *in vacuo*, yielding the crude bromohydrin **3.35** and the reduced bromohydrin **3.36** as a mixture of diastereoisomers (*dr* **3.36a**/**3.36b** 7:93). Purification *via* column chromatography (pentane/Et_2O 97:3 to 8:2) afforded the bromohydrin **3.35** as white solid (91 mg, 48%) and the *anti*-diol **3.36a** as a white solid (18 mg, 9%).

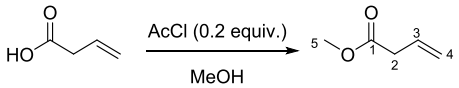


3.36a

mp: 102 °C; **IR** (neat) 3561 (w), 3402 (w, br.), 2964 (w, br.), 1739 (s), 1372 (m), 1153 (s), 1130 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.47 (1H, dd, $^3J_{HH}$ 11.3 Hz, $^3J_{HH}$ 2.5 Hz, H_3), 3.74 (1H, ddd, $^3J_{HH}$ 12.0 Hz, $^3J_{HH}$ 10.5 Hz, $^3J_{HH}$ 2.0 Hz, H_8), 3.53 (1H, s, O<u>H</u>-2), 2.09 (1H, dqd, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 2.3 Hz, H_4), 1.94 (1H, d, $^3J_{HH}$ 12.0 Hz, O<u>H</u>-8), 1.85 − 1.70 (2H, m, $H_{4'}$, H_9), 1.69 − 1.59 (1H, m, H_{10}), 1.56 (9H, s, H_7), 1.48 − 1.33 (1H, m, $H_{10'}$), 1.16 – 1.01 (1H, m, $H_{9'}$), 1.11 (3H, t, $^3J_{HH}$ 7.2 Hz, H_5), 0.94 (3H, t, $^3J_{HH}$ 7.3 Hz, H_{11}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0 (C_1), 84.8 (C_2 or C_6), 81.2 (C_6 or C_2), 73.6 (C_8), 63.3 (C_3), 34.8 (C_9), 28.0 (C_7), 24.9 (C_4), 19.5 (C_{10}), 13.9 (C_{11}), 12.8 (C_5) ppm; **MS** (ESI^+) (m/z) 349 [M(^{81}Br)+Na]$^+$, 347 [M(^{79}Br)+Na]$^+$; **HRMS** (ESI^+) for $C_{13}H_{25}{}^{79}BrO_4$ [M+Na]$^+$ calcd. 345.0828, found. 347.0836.

10.3.7 Synthesis of functionalised esters

10.3.7.1 Methyl-but-3-enoate 3.12

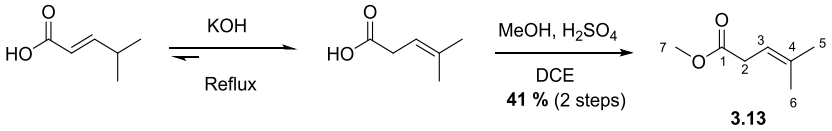


3.12

To a solution of 3-butenoic acid (5 mL, 56.9 mmol, 97% purity), in methanol (40 mL) at rt was added acetyl chloride (813 µL, 11.4 mmol, 0.2 equiv.) dropwise. After 15 h stirring at rt, a saturated solution of $NaHCO_3$ was added (10 mL, pH 8). The mixture was then extracted with pentane (3×50 mL), and dried over $MgSO_4$. The solvent was removed by distillation, to give methyl-but-3-enoate **3.12** as a colourless oil (2.8 g, 79 % purity with 21 % pentane, 2.35 g calculated, 41 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 – 5.85 (1H, m, H_3), 5.30 – 5.07 (2H, m, H_4), 3.71 (3H, s, H_5), 3.17 – 3.06 (2H, m with the presence of J_{HH} 7 Hz, H_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0 (C_1), 130.2 (C_4), 118.6 (C_3), 51.8 (C_2), 38.9 (C_5) ppm. NMR spectra correspond to the reported data.[142]

10.3.7.2 Methyl-4-methyl-3-pentenoate 3.13

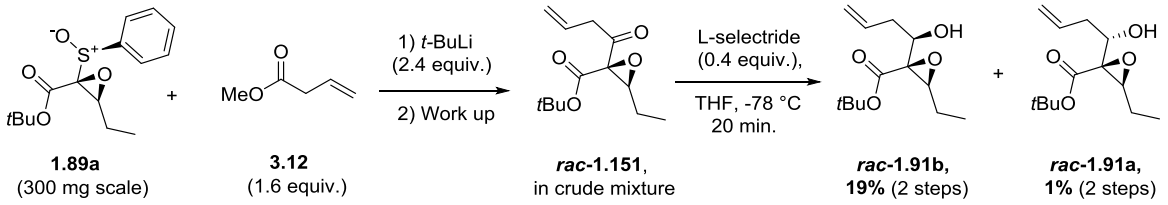


3.13

4-Methyl-2-pentenoic acid (5 mL, 42.0 mmol, 1 equiv.) was dissolved in a solution of KOH (10.3 $mmol.L^{-1}$, 50 mL, 11.6 equiv.) at rt, and the resulting mixture was refluxed for 24 h. The mixture was then neutralised with HCl (6M, 80 mL), and was extracted with EtOAc (4×100 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure, yielding 4.3 g of a mixture of 4-methyl-2-pentenoic acid and of 4-methyl-3-pentenoic (ratio 17:83 respectively). The mixture of acids (4 g, 37.7 mmol) was then dissolved in MeOH (4.5 mL) and DCE (11 mL), after which concentrated H_2SO_4 (100 µL) was added. The mixture was refluxed until the solution became cloudy (10 min). Refluxing was continued for further 10 min at 800 mbar. The mixture was then allowed to warm up to rt. The layers were separated, and the organic phase was washed with a saturated solution of $NaHCO_3$ (3×10 mL), dried over $MgSO_4$. A first distillation at atmospheric pressure was first carried out to remove the excess of solvent, and the residue was then redistilled at reduced pressure, yielding the 4-methyl-3-pentenoate **3.13** as a colourless liquid (bp 115 °C (850 mbar), 2.2 g, 41% over 2 steps).

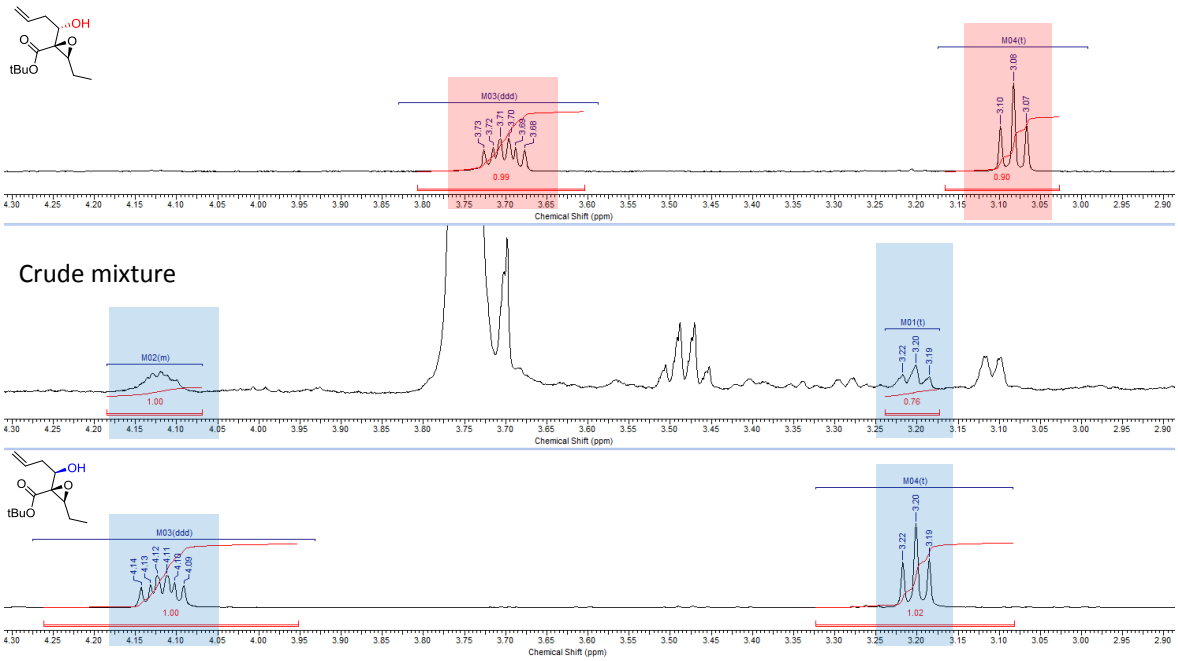
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 – 5.25 (1H, m, H_3), 3.68 (3H, s, H_7), 3.04 (2H, d, $^{3}J_{HH}$ 7.1 Hz, H_2), 1.75 (3H, s, H_5 or H_6), 1.64 (3H, s, H_6 or H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9 (C_1), 135.6 (C_4), 115.8 (C_3), 51.7 (C_2), 33.6 (C_7), 25.6 (C_5 or C_6), 17.9 (C_5 or C_6) ppm. NMR spectra correspond to the reported data.[143]

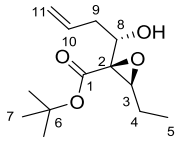
10.3.8 Two step procedure to give the α-epoxy alcohols *rac*-1.91



To a solution of **1.89a** (265 mg, 0.89 mmol, 1 equiv.) in Et_2O (6.0 mL) at rt was added methyl-but-3-enoate **3.12** (dried over molecular sieves 4Å, 21% pentane, 163 mg, 1.43 mmol, 1.6 equiv.). The mixture was cooled down at -78 °C and stirred for 10 min, before adding dropwise a solution of *t*-BuLi (1.8 M in pentane, 1.2 mL, 2.13 mmol, 2.4 equiv.) for 5 min. The resulting mixture was stirred -78 °C for 20 min, and was quenched at this temperature with a saturated solution of NH_4Cl (5 mL). The mixture was then extracted with Et_2O (3×10 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure (30 °C, < 500 mbar) to give the crude β-keto ester ***rac*-1.151**.

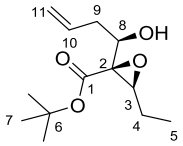
The crude product ***rac*-1.151** was then dissolved in THF (3 mL), and L-selectride (1M solution in THF, 0.36 mmol, 360 µL, 0.4 equiv.) was added to the mixture dropwise at -78 °C. The resulting solution was stirred at this temperature for 10 min, before quenching with a saturated solution of NH_4Cl (3 mL). The mixture was extracted with Et_2O (3×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure, giving the crude α-epoxy allylic alcohol as a mixture of diastereoisomers (*dr* n.d. due to complexity of the crude mixture, but only the *syn*-alcohol was observed by ^1H NMR). Purification *via* column chromatography (pentane/Et_2O 9:1 to 6:4) afforded the *anti*-α-epoxy alcohol ***rac*-1.91a** as a colourless oil (2 mg, isolated with unknown impurities, ~1% over 2 steps) and the *syn*-α-epoxy alcohol ***rac*-1.91b** as a colourless oil (41 mg, 19% over 2 steps).





***rac*-1.91a**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 – 5.71 (1H, m, H_{10}), 5.34 – 4.85 (2H, m, H_{11}), 3.70 (1H, ddd, $^{3}J_{HH}$ 7.7 Hz, $^{3}J_{HH}$ 7.2 Hz, $^{3}J_{HH}$ 4.4 Hz, H_8), 3.08 (1H, t, $^{3}J_{HH}$ 6.4 Hz, H_3), 2.58 (1H, d, $^{3}J_{HH}$ 7.2 Hz, O<u>H</u>-8), 2.57 – 2.48 (1H, m, H_9), 2.40 – 2.25 (1H, m, $H_{9'}$), 1.75 – 1.56 (2H, m, H_4, $H_{4'}$), 1.53 (9H, s, H_7), 1.06 (3H, t, $^{3}J_{HH}$ 7.6 Hz, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.0 (C_1), 133.8 (C_{10}), 117.8 (C_{11}), 83.4 (C_6), 71.9 (C_8), 64.2 (C_2), 62.3 (C_3), 37.9 (C_9), 28.1 (C_7), 21.5 (C_4), 10.2 (C_5) ppm. NMR spectra correspond to the reported data.[17]

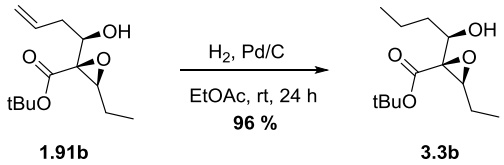


***rac*-1.91b**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 – 5.71 (1H, m, H_{10}), 5.29 – 4.99 (2H, m, H_{11}), 4.12 (1H, ddd, $^{3}J_{HH}$ 8.8 Hz, $^{3}J_{HH}$ 7.7 Hz, $^{3}J_{HH}$ 4.6 Hz, H_8), 3.20 (1H, t, $^{3}J_{HH}$ 6.4 Hz, H_3), 2.52 – 2.30 (2H, m, H_9), 1.84 (1H, d, $^{3}J_{HH}$ 8.8 Hz, O<u>H</u>-8), 1.71 – 1.57 (2H, m, H_4, $H_{4'}$), 1.51 (9H, s, H_7), 1.05 (3H, t, $^{3}J_{HH}$ 7.5 Hz, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.4 (C_1), 133.5 (C_{10}), 118.7 (C_{11}), 82.8 (C_6),

68.9 (C_8), 65.5 (C_2), 60.3 (C_3), 38.4 (C_9), 28.0 (C_7), 21.4 (C_4), 10.2 (C_5) ppm. NMR spectra correspond to the reported data.[17]

10.3.9 Hydrogenation of the *syn* α-epoxy alcohol 1.91b to give 3.3b

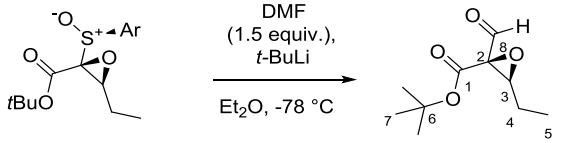


1.91b **3.3b**

Compound **1.91b** (60 mg, 0.25 mmol, 1 equiv.) was dissolved in EtOAc (4 mL). Pd/C (10% wt, 26 mg, 26 µmol, 10 mol%) was added and the resulting mixture was flushed with H_2. Stirring under an atmosphere of H_2 at rt was continued for 24 h, before the mixture was filtered through a pad of silica and concentrated *in vacuo*, yielding the *syn*-alcohol **3.3b** as a colourless oil (58 mg, 96%).

10.4 Alternative approach

10.4.1 Synthesis of α-epoxy aldehyde 1.90 (Small scale)



Ar = Tol **1.89b**
Ar = Ph **1.89a**

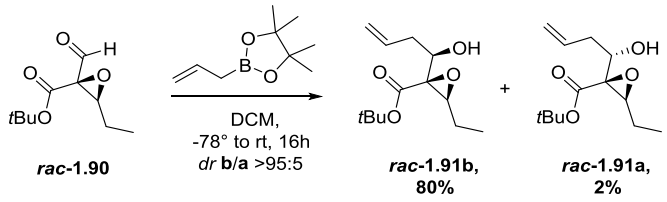
1.90, 46%
***rac*-1.90, 47%**

To compound **1.89a** (410 mg, 1.38 mmol, 1 equiv.), dissolved in Et_2O (9 mL) was added DMF (dried over molecular sieves 4Å, 160 µL, 2.07 mmol, 1.5 equiv.) at rt. The mixture was cooled down at -78 °C and stirred for 10 min, before adding a solution of *t*-BuLi (1.7 M in pentane, 2.3 mL, 3.86 mmol, 2.8 equiv.) dropwise for 15 min. The resulting mixture was stirred for further 20 min at -78 °C and was quenched with a saturated solution of NH_4Cl (5 mL). The mixture was then extracted with Et_2O (3×10 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure (30 °C, <500 mbar). Purification *via* column chromatography (pentane/Et_2O 8:2 to 7:3) afforded the α-epoxy aldehyde ***rac*-1.90** as a colourless oil (133 mg, 94% purity with 6% Et_2O, 130 mg calculated, 47%).

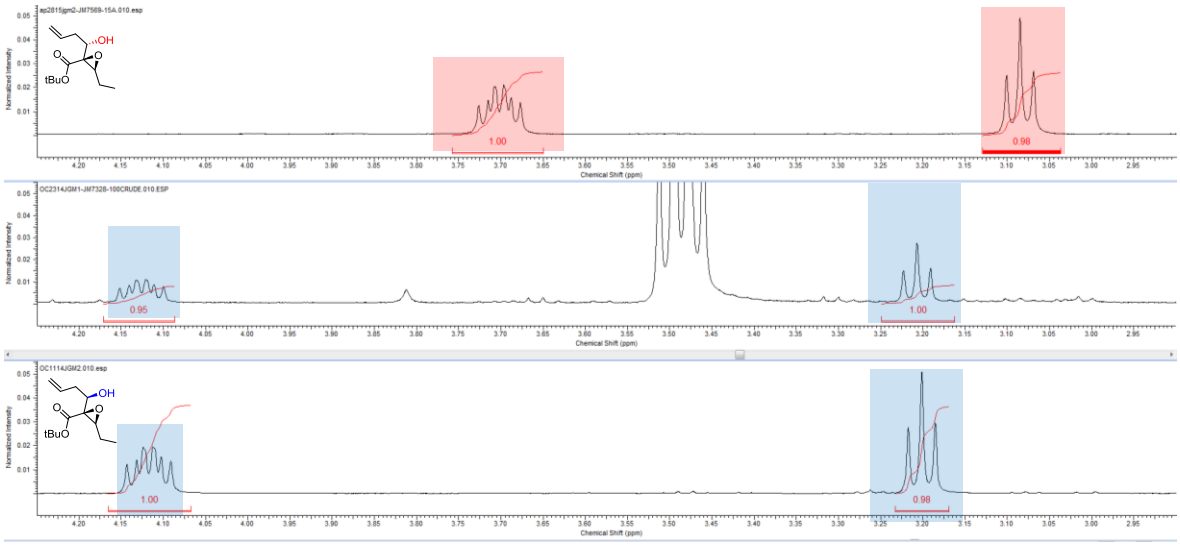
The same procedure was carried out with **1.89b** (297 mg, 0.96 mmol, 1 equiv.), to give **1.90** as a colourless oil (103 mg, 70% purity with 30% Et_2O, 89 mg calculated, 46%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (1H, s, H_8), 3.25 (1H, t, $^3J_{HH}$ 6.2 Hz, H_3), 1.81 – 1.60 (2H, m, H_4, $H_{4'}$), 1.53 (9H, s, H_7), 1.08 (3 H, t, $^3J_{HH}$ 7.6 Hz, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.8 (C_8), 163.8 (C_1), 84.2 (C_6), 64.9 (C_3), 63.9 (C_2), 28.0 (C_7), 21.6 (C_4), 9.9 (C_5) ppm. NMR spectra correspond to the reported data.[17]

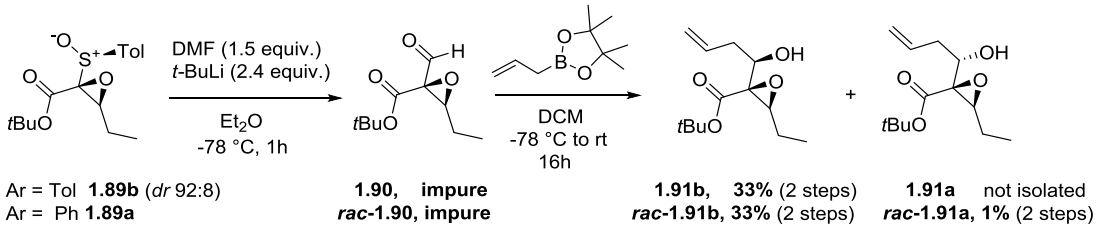
10.4.2 Allylation of *rac*-1.90 (small scale)



Aldehyde ***rac*-1.90** (129 mg, 0.64 mmol, 1 equiv.) was dissolved in DCM (2.1 mL) at rt. The solution was cooled to -78 °C, after which allylboronic acid pinacol ester (97%, 135 µL, 0.70 mmol, 1.1 equiv.) was added dropwise at -78 °C. The reaction was allowed to warm up for 14 h (without removing the dry ice bath, T = 10 °C after 14 h). The mixture was then quenched at rt with H_2O (5 mL) and stirring was continued for 5 min. The layers were separated, and the aqueous phase was extracted with Et_2O (3×10 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated in *vacuo* to give the crude α-epoxy alcohol as a mixture of diatereoisomers (*dr* **1.91b**/**1.91a** >95:5). Purification *via* column chromatography (pentane/Et_2O 8:2 to 7:3) afforded the *anti* α-epoxy alcohol ***rac*-1.91a** as colourless oil (3 mg, 2%) and the *syn*-α-epoxy alcohol ***rac*-1.91b** as a colourless oil (125 mg, 80%).



10.4.3 Two step synthesis of α-epoxy alcohols 1.91a and 1.91b (Large scale)



Ar = Tol **1.89b** (*dr* 92:8)
Ar = Ph **1.89a**

1.90, impure
***rac*-1.90, impure**

1.91b, 33% (2 steps)
***rac*-1.91b, 33%** (2 steps)

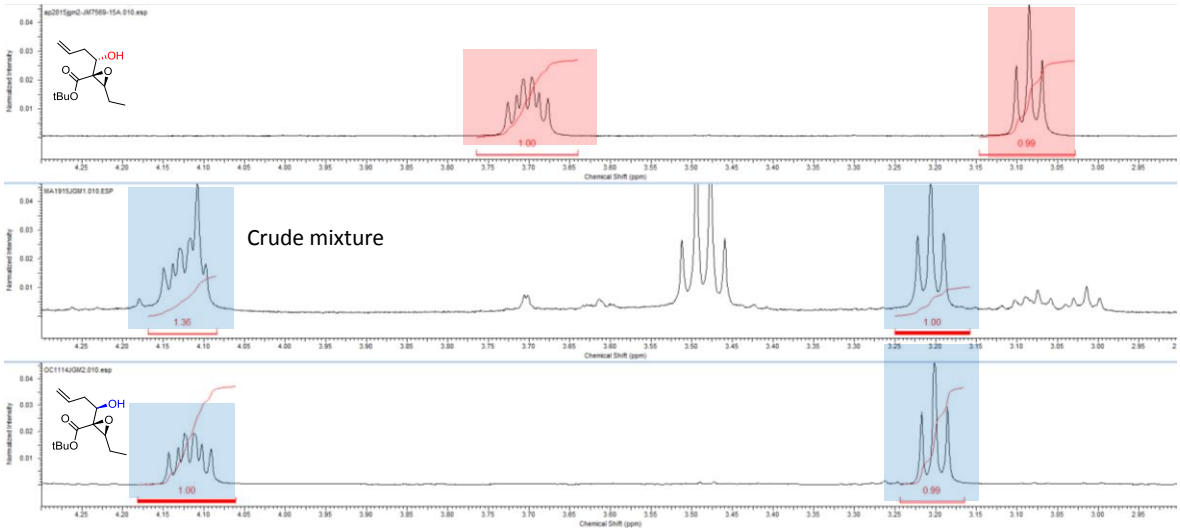
1.91a not isolated
***rac*-1.91a, 1%** (2 steps)

To compound **1.89b** (1.58 g, 5.1 mmol, 1 equiv.), dissolved in Et_2O (33 mL) was added DMF (dried over molecular sieves 4Å, 588 µL, 7.6 mmol, 1.5 equiv.). The mixture was cooled down at -78 °C and stirred for 10 min, before adding a solution of *t*-BuLi (1.9 M in pentane, 6 mL, 12.0 mmol, 2.4 equiv.) dropwise *via* syringe pump for 1 h. The resulting mixture was stirred at -78 °C for 20 min and was quenched at this temperature with a saturated solution of NH_4Cl (25 mL). The mixture was then extracted with Et_2O (3×30 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure (30 °C, <500 mbar). Purification *via* column chromatography (pentane/Et_2O 8:2 to 7:3) afforded the impure α-epoxy aldehyde **1.90** as a colourless oil (483 mg, *ca*. 28% of Et_2O), which was used in the next step without further purification.

The mixture was dissolved in DCM (8 mL) and cooled down at -78 °C, after which allylboronic acid pinacol ester (475 µL, 2.53 mmol, 0.5 equiv.) was added dropwise. The reaction was then allowed to warm up for 16 h (without removing the dry ice bath, T ~ 15 °C after 16 h). The mixture was then quenched at rt with H_2O (8 mL), and stirring was

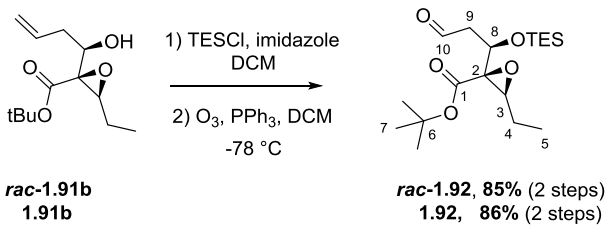
continued for 5 min. The layers were separated, and the aqueous phase was extracted with Et_2O (3×20 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated in *vacuo* to give the crude α-epoxy alcohol as a mixture of diastereoisomers (*dr* **n.d** due to complexity of the crude mixture, see copy of ^1H NMR spectrum below). Purification *via* column chromatography (pentane/Et_2O 8:2 to 7:3) afforded the *anti* α-epoxy alcohol **1.91a** as colourless oil (11 mg, 1% over 2 steps) and the *syn* α-epoxy alcohol **1.91b** as a colourless oil (400 mg, 33% over 2 steps).

The same procedure was carried out with the phenyl derivative **1.89a** (1.67 g, 5.63 mmol, 1 equiv.), giving *syn*-α-epoxy alcohol ***rac*-1.91b** as a colourless oil (454 mg, 33% over 2 steps).



10.5 Completion of the synthesis

10.5.1 Synthesis of aldehyde 1.92



***rac*-1.91b**
1.91b

***rac*-1.92, 85%** (2 steps)
1.92, 86% (2 steps)

Compound **1.91b** (465 mg, 1.92 mmol, 1 equiv.) was dissolved in DCM (19 mL) at rt. The resulting solution was cooled to 0 °C, after which imidazole (326 mg, 4.79 mmol, 2.5

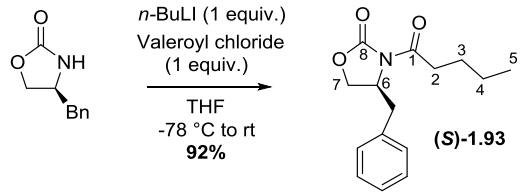
equiv.) was added in one portion, followed by chlorotriethylsilane (645 µL, 3.84 mmol, 2 equiv.) dropwise. The reaction was then stirred at rt for 16 h, before quenching with a saturated solution of NH_4Cl (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3×20 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* column chromatography (pentane/Et_2O 96:4) afforded the impure protected allyl alcohol (811 mg, 83% purity with 17% of TESOH), which was engaged in the next step without further purification.

Ozone was bubbled through a solution of impure protected allyl alcohol (811 mg) in DCM (61 mL) at -78 °C until the solution became blue (*ca.* 15 min). The excess of ozone was purged from the solution by bubbling oxygen through for 20 min. Triphenylphosphine (587 mg, 2.1 mmol, 1.1 equiv.) was then added dropwise, and stirring was continued for 1h at -78 °C, before allowing to warm up to rt over 1h. The resulting mixture was then concentrated under vacuum. Purification *via* column chromatography (crude loaded in DCM; pentane/Et_2O 85:15 to 80:20) afforded TES protected aldehyde **1.92** as a colourless oil (593 mg, 86% over 2 steps).

The same procedure was carried out with ***rac*-1.91b** (720 g, 2.97 mmol, 1 equiv.), giving aldehyde ***rac*-1.92** as a colourless oil (930 mg, 85% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, t, $^3J_{HH}$ 1.7 Hz, H_{10}), 4.26 (1H, dd, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 5.0 Hz, H_8), 3.05 (1H, t, $^3J_{HH}$ 6.4 Hz, H_3), 2.97 (1H, ddd, $^2J_{HH}$ 16.9 Hz, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 1.8 Hz, H_9), 2.80 (1H, ddd, $^2J_{HH}$ 16.9 Hz, $^3J_{HH}$ 5.0 Hz, $^3J_{HH}$ 1.7 Hz, $H_{9'}$), 1.71 – 1.59 (1H, m, H_4), 1.55 – 1.39 (1H, m, $H_{4'}$), 1.51 (9H, s, H_7), 1.03 (3H, t, $^3J_{HH}$ 7.6 Hz, H_5), 0.95 (9H, t, $^3J_{HH}$ 7.9 Hz, $C\underline{H}_{3TES}$), 0.69 – 0.60 (6H, m, $C\underline{H}_{2TES}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.3 (C_{10}), 166.7 (C_1), 82.8 (C_6), 69.6 (C_8), 66.5 (C_2), 61.5 (C_3), 49.3 (C_9), 28.0 (C_7), 21.7 (C_4), 10.1 (C_5), 6.7 ($\underline{C}H_{3TES}$), 4.6 ($\underline{C}H_{2TES}$) ppm. NMR spectra correspond to the reported data.[17]

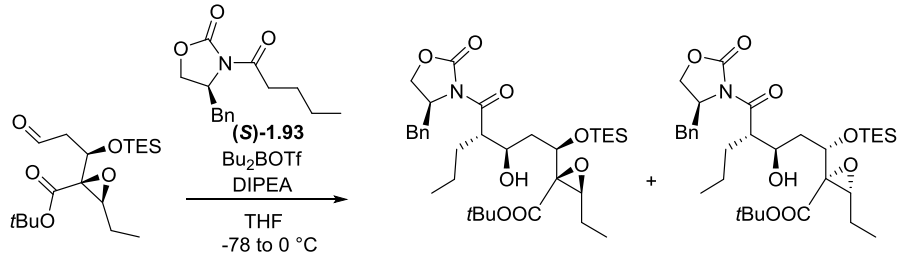
10.5.2 Synthesis of 3-(1-Oxopentyl-4(*S*)-(benzyl)-2-oxazolidinone ((*S*)-1.93)



To a suspension of (*S*)-4-benzyl-2-oxazolidinone (1.83 g, 10.3 mmol, 1 equiv.) in THF (14 mL) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 4.12 mL, 10.3 mmol, 1 equiv.) dropwise. The resulting solution was stirred for 15 min at this temperature, before adding valeroyl chloride (1.2 mL 10.3 mmol, 1 equiv.) dropwise at -78 °C. The mixture was allowed to warm up to rt and stirred for 2 h, before quenching with a saturated solution of NH_4Cl (12 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3×12mL). Organic phases were combined, washed with a saturated solution of $NaHCO_3$ (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* a short pad of silica (petroleum ether/EtOAc 5:5) afforded compound **(*S*)-1.93** as a viscous oil (2.48 g, 92%).

$[\alpha]_D$ 101.3 (c 2.07, MeOH, 23 °C), lit. 103.4 (c 2.05, MeOH, 25 °C)[144]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (3H, m, H_{Ar}), 7.24 – 7.19 (2H, m, H_{Ar}), 4.67 (1H, ddt, $^3J_{HH}$ 9.9 Hz, $^3J_{HH}$ 6.8 Hz, $^3J_{HH}$ 3.3 Hz, H_6), 4.22 – 4.12 (2H, m, H_7), 3.29 (1H, dd, $^2J_{HH}$ 13.4 Hz, $^3J_{HH}$ 3.2 Hz, CH**H**Ph), 3.02 – 2.84 (2H, m, H_2), 2.77 (1H, dd, $^2J_{HH}$ 13.4 Hz, $^3J_{HH}$ 9.6 Hz, C**H**HPh), 1.76 – 1.60 (2H, m, H_3), 1.41 (2H, sxt, $^3J_{HH}$ 7.4 Hz, H_4), 0.96 (3H, t, $^3J_{HH}$ 7.34 Hz, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.3 (C_1), 153.4 (C_8), 135.3 (C_{qAr}), 129.3 (2C, CH_{Ar}), 128.9 (2C, CH_{Ar}), 127.2 (CH_{Ar}), 66.1 (C_7), 55.1 (C_6), 37.8 (**C**H_2Bn), 35.2 (C_2), 26.3 (C_3), 22.2 (C_4), 13.8 (C_5) ppm. NMR spectra correspond with the reported data.[145]

10.5.3 Evans aldol reaction



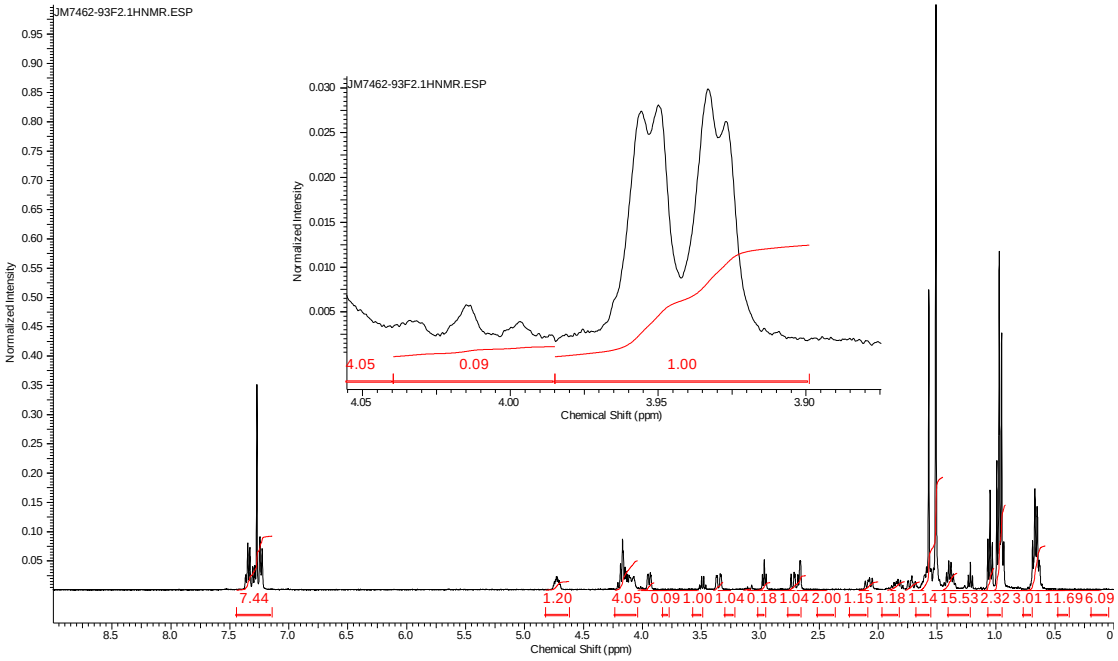
***rac*-1.92**
1.92 (*er* 92:8)

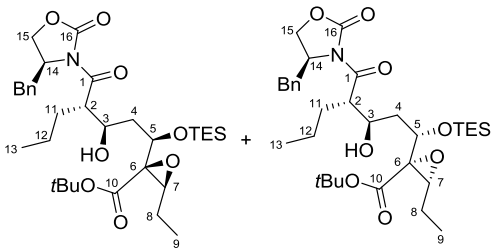
1.94 **92%**, (*dr* **1.94**/**1.95** 1:1) **1.95**
1.94 **91%**, (*dr* **1.94**/**1.95** 92:8) **1.95**

10.5.3.1 From enantioenriched aldehyde 1.92

To a solution of **(*S*)-1.93** (864 mg, 3.30 mmol, 2 equiv) in DCM (3 mL) at 0 °C was added Bu_2BOTf (1M in CH_2Cl_2, 3.3 mL, 3.30 mmol, 2 equiv) dropwise to give an orange solution. The mixture was stirred for 5 min, then DIPEA (575 µL, 3.30 mmol, 2 equiv.) was added dropwise and the solution became yellow. After another 5 min stirring at this temperature, the mixture was cooled down to -78 °C and transferred *via* cannula to a solution of enantioenriched aldehyde **1.92** (*er* 92:8, 593 mg, 1.65 mmol, 1 equiv.) in DCM (3 mL) at -78 °C. The resulting mixture was stirred at this temperature for 3.5 h, then allowed to warm up at 0 °C and stirred for further 1.5 h. The reaction mixture was quenched at 0 °C with a mixture of H_2O_2/phosphate buffer pH 7 (1:1, 20 mL). The mixture was extracted with DCM (3×20mL). Organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* column chromatography (pentane/Et_2O 8:2 to 5:5) afforded the inseparable mixture of aldol adducts **1.94** and **1.95** as a colourless viscous oil (943 mg, 88% purity with 12% Et_2O, 927 mg calculated, 91%, *dr* **1.94**/**1.95** 92:8).

^{1}H NMR (after column chromatography)





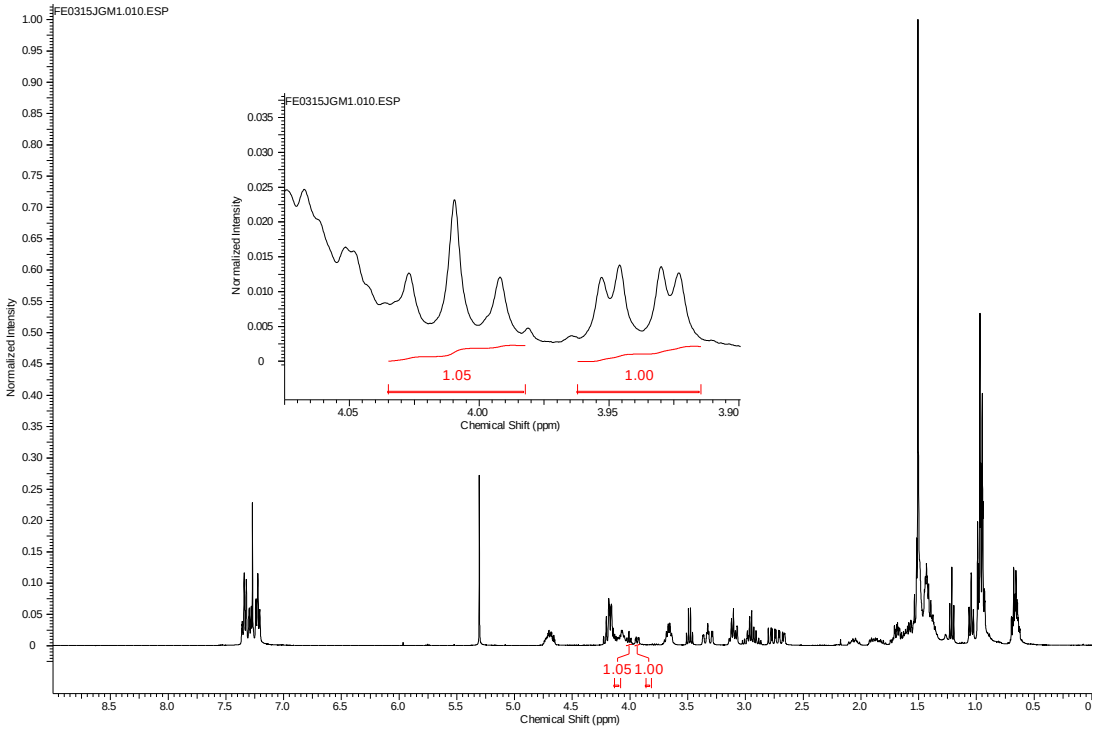
1.94 *dr* **1.94**/**1.95** 92:8 **1.95** *minor*

^{1}H NMR (400 MHz, $CDCl_3$) 7.41 – 7.20 (5H, m, H_{Ar}), 4.73 (1 H, ddt, $^{3}J_{HH}$ 10.1 Hz, $^{3}J_{HH}$ 6.8 Hz, $^{3}J_{HH}$ 3.32, H_{14}), 4.23 – 4.05 (4H, m, H_2, H_3, H_{15}, $H_{15'}$), 4.01 (1H, t, $^{3}J_{HH}$ 7.0 Hz, H_5, minor), 3.94 (1H, dd, $^{3}J_{HH}$ 9.1 Hz, $^{3}J_{HH}$ 2.4 Hz, H_5), 3.35 (1H, dd, $^{2}J_{HH}$ 13.3 Hz, $^{3}J_{HH}$ 2.8 Hz, C**H**HPh), 3.11 (1H, t, $^{3}J_{HH}$ 6.4 Hz, H_7, *minor*), 3.07 (1H, br. S, O**H**-3, minor), 2.97 (1H, t, $^{3}J_{HH}$ 6.4 Hz, H_7), 2.71 (1H, dd, $^{2}J_{HH}$ 13.2 Hz, $^{3}J_{HH}$ 10.1 Hz, CH**H**Ph), 2.66 (1H, d, $^{3}J_{HH}$ 2.0 Hz, O**H**-3), 2.08 (1 H, dd, $^{2}J_{HH}$ 14.0 Hz, $^{3}J_{HH}$ 9.5 Hz, H_4), 1.91 – 1.78 (1H, m, H_{11}), 1.71 (1 H, ddd, $^{2}J_{HH}$ 14.0 Hz, $^{3}J_{HH}$ 10.9 Hz, $^{3}J_{HH}$ 2.6 Hz, $H_{4'}$), 1.64 – 1.47 (3H, m, H_8, $H_{8'}$, $H_{11'}$), 1.51 (9H, s, C(C**H**$_3$)$_3$), 1.45 – 1.34 (2H, m, H_{12}, $H_{12'}$), 1.05 (3H, t, $^{3}J_{HH}$ 7.5 Hz, H_9), 1.01 – 0.91 (12H, m, H_{13}, C**H**$_{3TES}$), 0.73 – 0.60 (6H, m, C**H**$_{2TES}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.5 (C_1), 167.1 (C_{10}), 153.8 (C_{16}), 135.3 (C_{qAr}), 129.4 (2C, CH_{Ar}), 129.0 (2C, CH_{Ar}), 127.4 (CH_{Ar}), 82.3 (**C**$(CH_3)_3$), 71.8 (C_5), 68.9 (C_3), 67.1 (C_6), 65.9 (C_{15}), 61.1 (C_7), 55.6 (C_{14}), 47.9 (C_2), 38.5 (C_4), 38.0 (**C**H_2Ph), 30.1 (C_8 or C_{11}), 28.1 (C(**C**H_3)$_3$), 21.9 (C_8 or C_{11}), 20.8 (C_{12}), 14.3 (C_{13}), 10.4 (C_9, *minor*), 10.2 (C_9), 6.8 (**C**H_3 TES), 4.8 (**C**H_2 TES), 4.7 (**C**H_2 TES, *minor*). NMR spectra correspond with the reported data.[17]

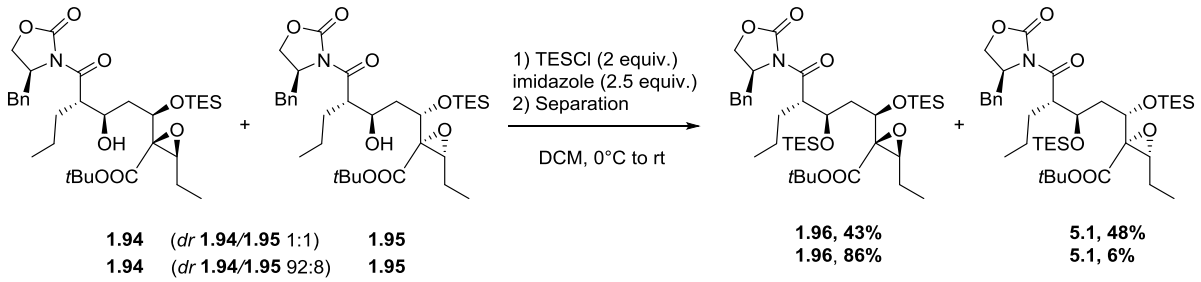
10.5.3.2 From racemic aldehyde *rac*-1.92

To a solution of (*S*)-4-benzyl-3-pentanoyloxazolidin-2-one **(*S*)-1.93** (1.34 g, 5.12 mmol, 2 equiv) in DCM (4.6 mL) at 0 °C was added Bu_2BOTf (1M in CH_2Cl_2, 5.10 mL, 5.12 mmol, 2 equiv) dropwise to give an orange solution. The mixture was stirred for 5 min, then DIPEA (890 µL, 5.12 mmol, 2 equiv.) was added dropwise and the solution became yellow. After another 5 min stirring at this temperature, the mixture was cooled down to -78 °C and transferred *via* cannula to a solution of racemic aldehyde **1.92** (918 mg, 2.56 mmol, 1 equiv.) in DCM (5.6 mL) at -78 °C. The resulting mixture was stirred at this temperature for 3.5 h, then allowed to warm up at 0 °C and stirred for further 1.5 h. The reaction mixture was quenched at 0 °C with a mixture of H_2O_2/phosphate buffer pH 7 (1:1, 30 mL) and was extracted with DCM (3×20mL). Organic layers were combined, dried over Na_2SO_4 and concentrated under pressure to give the crude mixture of aldol products **1.94** and **1.95** (*dr* 1:1). Purification *via* column chromatography (pentane/Et_2O 8:2 to 5:5) afforded the mixture of aldol adducts as colourless resin (1.3 g, 80% purity with 20% Et_2O, 1.26 g calculated, 78%, dr **1.94**/**1.95** 36:64). A fraction of the diastereoisomer **1.95** was also obtained (208 mg, 86% purity with 14 % Et_2O, 203 mg calculated, 13%, trace amount of **1.94** was detected by ^{1}H NMR).

Crude ^{1}H NMR



10.5.4 Synthesis of the protected aldol adducts 1.96 and 5.1



1.94 (*dr* **1.94**/**1.95** 1:1) **1.95**
1.94 (*dr* **1.94**/**1.95** 92:8) **1.95**

1.96, 43%
1.96, 86%

5.1, 48%
5.1, 6%

10.5.4.1 From a 92:8 mixture of diastereoisomers

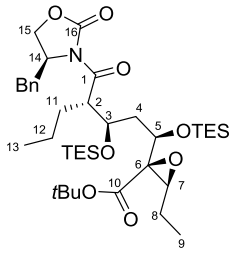
To a solution of aldols **1.94** and **1.95** (*dr* 92:8, 935 mg, 1.51 mmol, 1 equiv.) in DCM (15 mL) at 0 °C was added imidazole (257 mg, 3.77 mmol, 2.5 equiv.) in one portion, followed by the dropwise addition of chlorotriethylsilane (507 µL, 3.02 mmol, 2 equiv.). The reaction was then stirred for 16 h at rt before quenching with a saturated solution of NH_4Cl (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3×20 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* column chromatography (petroleum ether/EtOAC 96:4) followed by HPLC (hexane/EtOAc 93:7) afforded **1.96** (950 mg, 86%), and **5.1** (66 mg, 6%) as colourless viscous oils.

10.5.4.2 From a 1:1 mixture of diastereoisomers

To a solution of aldols **1.94** and **1.95** (*dr* 36:64, 1.23 g, 1.98 mmol, 1 equiv.) in DCM (20 mL) at 0 °C was added imidazole (336 mg, 3.77 mmol, 2.5 equiv.) in one portion, followed by the dropwise addition of chlorotriethylsilane (670 µL, 3.02 mmol, 2 equiv.). The reaction was then stirred for 16 h at rt before quenching with a saturated solution of NH_4Cl (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3×20 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* column chromatography (petroleum ether/EtOAC 96:4) followed by HPLC purifications (hexane/EtOAc 93:7) afforded **1.96** (566 mg, 39%), and **5.1** (728 mg, 50%) as colourless viscous oils.

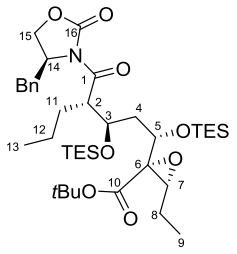
The same procedure was applied with the diastereoisomer **1.95** (198 mg, 0.32 mmol). Purification *via* column chromatography (pentane/EtOAC 96:4) afforded the protected **5.1** as a colourless resin (233 mg, 99%).

Cumulated yield of the two fractions: **1.96** (728 mg, 43%) and **5.1** (799 mg, 48%).



1.96

[α]$_D$ 33.5 (c 0.63, $CHCl_3$, 19 °C), lit. 31.9 (c 0.63, $CHCl_3$, 25 °C)[17]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.18 (5H, m, H_{Ar}), 4.67 (1H, ddt, $^3J_{HH}$ 9.7 Hz, $^3J_{HH}$ 6.2 Hz, $^3J_{HH}$ 3.0 Hz, H_{14}), 4.22 – 4.08 (3H, m, H_2, H_{15}, $H_{15'}$), 4.00 (1H, ddd, $^3J_{HH}$ 7.5 Hz, $^3J_{HH}$ 5.0 Hz, $^3J_{HH}$ 2.1 Hz, H_3), 3.54 (1H, dd, $^3J_{HH}$ 9.5 Hz, $^3J_{HH}$ 1.9 Hz, H_5), 3.34 (1H, dd, $^2J_{HH}$ 13.3 Hz, $^3J_{HH}$ 3.0 Hz, C**H**HPh), 2.85 (1H, t, $^3J_{HH}$ 6.3 Hz, H_7), 2.73 (1H, dd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 10.0 Hz, CH**H**Ph), 2.37 (1H, ddd, $^2J_{HH}$ 15.0 Hz, $^3J_{HH}$ 9.6 Hz, $^3J_{HH}$ 2.2 Hz, H_4), 1.87 (1H, ddd, $^2J_{HH}$ 15.0 Hz, $^3J_{HH}$ 8.0 Hz, $^3J_{HH}$ 2.0 Hz, $H_{4'}$), 1.82 – 1.72 (1 H, m, H_{11}), 1.62 – 1.50 (3H, m, H_8, $H_{8'}$ $H_{11'}$), 1.52 (9H, s, C(C**H**$_3$)$_3$), 1.46 – 1.32 (2H, m, H_{12}, $H_{12'}$), 1.05 (3H, t, $^3J_{HH}$ 7.5 Hz, H_9), 1.02 – 0.91 (21H, m, H_{13}, C**H**$_{3TES}$, C**H**$_3$'$_{TES}$), 0.77 – 0.58 (12H, m, C**H**$_{2TES}$, C**H**$_2$'$_{TES}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.3 (C_1), 166.6 (C_{10}), 153.2 (C_{16}), 135.6 (C_{qAr}), 129.4 (2C, CH_{Ar}), 128.9 (2C, CH_{Ar}), 127.2 (CH_{Ar}), 82.0 (**C**Me$_3$), 74.1 (C_5), 71.5 (C_3), 67.3 (C_6), 65.7 (C_{15}), 61.4 (C_7), 55.8 (C_{14}), 48.3 (C_2), 41.3 (C_4), 37.9 (**C**H$_2$Ph), 31.6 (C_{11}), 28.1 (C(**C**H$_3$)$_3$), 21.8 (C_8), 20.4 (C_{12}), 14.2 (C_{13}), 10.3 (C_9), 6.98 (**C**H$_{3TES}$), 6.92 (**C**H$_3$'$_{TES}$), 5.4 (**C**H$_{2TES}$), 5.1 (**C**H$_2$'$_{TES}$) ppm. NMR spectra correspond to the reported data.[17]

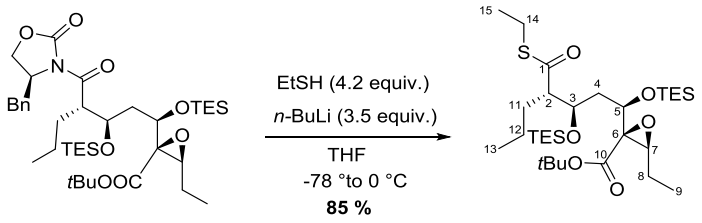


5.1

[α]$_D$ 25.7 (c 0.88, $CHCl_3$, 23 °C); **IR** (neat) 2966 (w, br.), 1772 (m), 1749 (s), 1697 (s), 1455 (s), 1387 (s), 1205 (m), 1092 (m, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (5H, m, H_{Ar}), 4.73 – 4.61 (1H, m, H_{14}), 4.21 – 4.12 (3H, m, H_2, H_{15}, $H_{15'}$), 4.05 – 3.99 (1H, m, H_3), 3.76 (1H, dd, $^3J_{HH}$ 8.6 Hz, $^3J_{HH}$ 4.1 Hz, H_5), 3.37 (1H, dd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 2.9 Hz, C**H**HPh), 2.96 (1H, t, $^3J_{HH}$ 6.4 Hz, H_7), 2.73 (1H, dd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 10.1 Hz, CH**H**Ph), 2.19 (1H, ddd, $^2J_{HH}$ 14.8 Hz, $^3J_{HH}$ 7.4 Hz, $^3J_{HH}$ 4.1 Hz, H_4), 1.99 (1H, ddd, $^2J_{HH}$ 14.7 Hz, $^3J_{HH}$ 8.7 Hz, $^3J_{HH}$ 4.0 Hz, $H_{4'}$), 1.89 – 1.77 (1 H, m, H_{11}), 1.71 – 1.57 (2H, m, H_8, $H_{11'}$), 1.50 (9H, s, C(C**H**$_3$)$_3$), 1.53 –

1.42 (1H, m, $H_{8'}$) , 1.41 – 1.33 (2H, m, H_{12}, $H_{12'}$), 1.06 (3H, t, $^3J_{HH}$ 7.5 Hz, H_9), 1.02 – 0.91 (21H, m, H_{13}, C**H**$_{3TES}$, C**H**$_3$'$_{TES}$), 0.73 – 0.58 (12H, m, C**H**$_{2TES}$, C**H**$_2$'$_{TES}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.8 (C_1), 166.9 (C_{10}), 153.1 (C_{16}), 135.6 (C_{qAr}), 129.4 (2C, CH_{Ar}), 128.9 (2C, CH_{Ar}), 127.3 (CH_{Ar}), 82.2 (**C**Me$_3$), 72.3 (C_5), 70.6 (C_3), 67.0 (C_6), 65.8 (C_{15}), 61.1 (C_7), 56.1 (C_{14}), 48.3 (C_2), 41.8 (C_4), 37.9 (**C**H$_2$Ph), 30.8 (C_{11}), 28.1 (C(**C**H$_3$)$_3$), 21.9 (C_8), 20.8 (C_{12}), 14.3 (C_{13}), 10.2 (C_9), 6.95 (**C**H$_{3\ TES}$), 6.92 (**C**H$_3$'$_{TES}$), 5.0 (**C**H$_{2TES}$), 4.9 (**C**H$_2$'$_{TES}$) ppm; **MS** (ESI$^+$) (m/z) 756.5 [M+Na]$^+$; **HRMS** (ESI$^+$) for $C_{39}H_{67}NO_8Si_2$ [M+Na]$^+$ calcd 756.4297; found 756.4287.

10.5.5 Synthesis of thioester 5.2



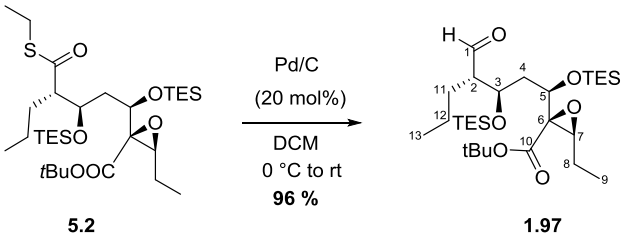
1.96 **5.2**

To a solution of ethanethiol (96 µL, 1.30 mmol, 4.2 equiv.) in THF (1.5 mL) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 436 µL, 1.09 mmol, 3.5 equiv.) dropwise. The mixture was stirred at -78 °C for 5 min, then warmed up to 0 °C. A solution of **1.96** (228 mg, 0.31 mmol, 1 equiv.) in THF (2.5 mL) was then added *via* syringe to the mixture. The resulting reaction was stirred for 6 h at 0 °C, before quenching with Et_2O (8 mL), and a saturated solution of $NaHCO_3$ (4 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×8 mL). Organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* column chromatography (pentane/Et_2O 95:5) afforded thioester **5.2** as a colourless oil (164 mg, 85%).

[α]$_D$ 19.8 (c 0.51, $CHCl_3$, 19 °C), lit. 20.3 (c 0.48, $CHCl_3$, 27 °C)[17]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.93 (1H, dt, $^3J_{HH}$ 7.6 Hz, $^3J_{HH}$ 3.8 Hz, H_3), 3.47 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^3J_{HH}$ 2.4 Hz, H_5), 2.87 (2H, q, $^3J_{HH}$ 7.4 Hz, H_{14}), 2.84 (1H, t, $^3J_{HH}$ 6.4 Hz, H_7), 2.72 (1H, dt, $^3J_{HH}$ 9.9 Hz, $^3J_{HH}$ 3.8 Hz, H_2), 2.26 (1H, ddd, $^2J_{HH}$ 14.9 Hz, $^3J_{HH}$ 9.2 Hz, $^3J_{HH}$ 3.4 Hz, H_4), 1.82 – 1.72 (2H, m, $H_{4'}$,H_{11}), 1.67 – 1.60 (1H, m, H_8), 1.51 (9H, s, C(C**H$_3$**)$_3$), 1.49 – 1.34 (3H, m, $H_{8'}$, $H_{11'}$, H_{12}), 1.34 – 1.28 (1H, m, $H_{12'}$), 1.25 (3H, t, $^3J_{HH}$ 7.4 Hz, H_{15}), 1.06 – 0.89 (24H, m, H_9, H_{13}, C**H$_3$** TES, C**H$_3$**$'$ TES), 0.75 – 0.58 (12H, m, C**H$_2$** TES, C**H$_2$**$'$ TES); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.5 (C_1), 166.4 (C_{10}), 82.1 (**C**Me$_3$), 74.4 (C_5), 71.9 (C_3), 67.4 (C_6), 61.3 (C_7), 60.5 (C_2), 41.9 (C_4), 30.4 (C_{11}),

28.1 (C(**C**H$_3$)$_3$), 23.3 (C_{14}), 21.9 (C_8), 20.9 (C_{12}), 14.7 (C_{15}), 14.2 (C_9), 10.1 (C_{13}), 6.9 (**C**H$_{3TES}$), 7.0 (**C**H$_3$'$_{TES}$), 5.4 (**C**H$_{2TES}$), 5.1 (**C**H$_2$'$_{TES}$). NMR spectra correspond to the reported data.[17]

10.5.6 Synthesis of aldehyde 1.97

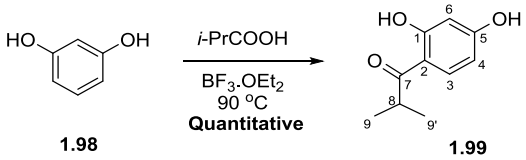


5.2 **1.97**

To a solution of thioester **5.2** (170 mg, 0.27 mmol, 1 equiv.) in DCM (1.5 mL) at 0 °C was added Et_3SiH (129 µL, 0.81 mmol, 3 equiv.) and Pd/C (10% wt, 57 mg, 54 µmol, 20 mol%) in one portion. The mixture was then stirred for 20 min at rt, before adding DCM (0.75 mL). The suspension was stirred for further 18 h, before filtering through celite, washing with DCM (15 mL), and concentrating under reduced pressure. Purification *via* column chromatography (pentane/Et_2O 98:2 to 95:5) afforded compound **1.97** as a colourless oil (145 mg, 96%).

[α]$_D$ 40.0 (c 0.68, $CHCl_3$, 23 °C), lit.39.4 (c 0.30, $CHCl_3$, 25 °C)[17]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.81 (1H, d, $^3J_{HH}$ 2.1 Hz, H_1), 4.09 (1H, dt, $^3J_{HH}$ 7.7 Hz, $^3J_{HH}$ 3.8 Hz, H_3), 3.61 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^3J_{HH}$ 2.6 Hz, H_5), 2.86 (1H, t, $^3J_{HH}$ 6.4 Hz, H_7), 2.45 (1H, dtd, $^3J_{HH}$ 8.1 Hz, $^3J_{HH}$ 4.0 Hz, $^3J_{HH}$ 2.1 Hz, H_2), 2.21 (1H, ddd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 9.2 Hz, $^3J_{HH}$ 3.9 Hz, H_4), 1.80 – 1.58 (3H, m, $H_{4'}$, H_8, H_{11}), 1.49 (9H, s, C(C**H$_3$**)$_3$), 1.47 – 1.24 (4H, m, $H_{8'}$, $H_{11'}$, H_{12}, $H_{12'}$), 1.03 (3H, t, $^3J_{HH}$ 7.6 Hz, H_9), 1.00 – 0.90 (21H, m, H_{13}, C**H**$_{3TES}$, C**H**$_3$'$_{TES}$), 0.76 – 0.57 (12H, m, CH_{2TES}, C**H**$_2$'$_{TES}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.1 (C_1), 166.5 (C_{10}), 82.3 (**C**Me$_3$), 73.6 (C_5), 70.5 (C_3), 67.2 (C_6), 61.5 (C_7), 57.7 (C_2), 41.0 (C_4), 28.1 (C(**C**H$_3$)$_3$), 26.6 (C_{11}), 21.8 (C_8), 21.0 (C_{12}), 14.2 (C_{13}), 10.1 (C_9), 6.92 (**C**H$_{3TES}$), 6.87 (**C**H$_3$'$_{TES}$), 5.3 (**C**H$_{2TES}$), 5.0 (**C**H$_2$'$_{TES}$) ppm. NMR spectra correspond to the reported data.[17]

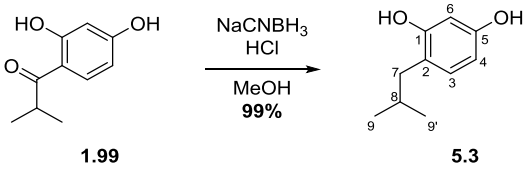
10.5.7 Synthesis of 4-isobutanoyl resorcinol 1.99



To a solution of resorcinol **1.98** (10.0 g, 90.8 mmol, 1 equiv.) in $BF_3.OEt_2$ (60 mL) was added isobutyric acid (9.27 mL, 90.8 mmol, 1 equiv) in one portion. The reaction mixture was heated to 90 °C for 1.5 h and then cooled to rt. The reaction mixture was added dropwise to an aqueous solution of 10% NaOAc (400 mL) and was stirred for 4 h. The mixture was extracted with EtOAc (3x100 mL) and the combined organic phases were washed with saturated solution of $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/Et_2O 7:3) afforded **1.99** as a brown oil (16.35 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.13 (1H, s, OH), 7.70 (1H, d, $^3J_{HH}$ 8.4 Hz, H_4), 6.92 (1H, br. s., OH), 6.66 – 6.30 (2H, m, H_3, H_6), 3.52 (1H, spt, $^3J_{HH}$ 6.7 Hz, H_8), 1.24 (6H, d, $^3J_{HH}$ 6.7 Hz, H_9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 209.6 (C_7), 165.5 (C_1 or C_5), 162.9 (C_5 or C_1), 132.3 (C_3), 112.4 (C_2), 108.0 (C_4 or C_6), 103.7 (C_6 or C_4), 34.6 (C_8), 19.4 (C_9 and $C_{9'}$) ppm. NMR spectra correspond to the reported data.[17]

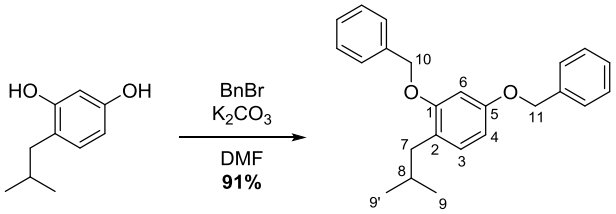
10.5.8 Synthesis of 4-isobutyl resorcinol 5.3



To a solution of ketone **1.99** (3.0 g, 16.7 mmol, 1 equiv.) in MeOH (15 mL) at rt was added $NaCNBH_3$ (3.2 g, 50.9 mmol, 3 equiv.) in one portion with a pinch of methyl orange as indicator. HCl (1M) was added dropwise at a rate to maintain the acidified red colour of methyl orange (pH ≈ 3-4). The reaction mixture was stirred overnight (until effervescence has stopped), then was diluted with H_2O (15 mL) and extracted with DCM (3x10 mL). The combined organic phases were washed with brine, acidified with a few drops of HCl (2M, 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/Et_2O 5:5) afforded **5.3** as a brown oil (2.75 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, d, $^3J_{HH}$ 8.7 Hz, H_5), 6.69 (1H, br. s., OH), 6.38 (2H, app. br. s, H_4, H_6), 6.05 (1H, br. s., OH), 2.40 (2H, d, $^3J_{HH}$ 7.1 Hz, H_7), 1.87 (1H, tspt, $^3J_{HH}$ 7.1 Hz $^3J_{HH}$ 6.7 Hz, H_8), 0.90 (6H, d, $^3J_{HH}$ 6.7 Hz, H_9, $H_{9'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.7 (C_1 or C_5), 154.5 (C_5 or C_1), 131.7 (C_3), 119.7 (C_2), 107.4 (C_4 ord C_6), 102.8 (C_6 ord C_4), 38.6 (C_7), 29.0 (C_8), 22.4 (C_9 and $C_{9'}$) ppm. NMR spectra correspond to the reported data.[17]

10.5.9 Synthesis of *O,O*-dibenzyl-4-isobutyl resorcinol 1.100

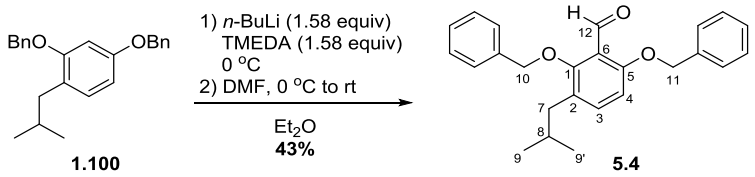


5.3 **1.100**

To a solution of **5.3** (5.69 g, 34.2 mmol 1 equiv) in DMF (175 mL) at rt was added K_2CO_3 (23.80 g, 171.2 mmol, 5 equiv.) in one portion followed by the dropwise addition of benzyl bromide (20.42 mL, 171.2 mmol, 5 equiv.). The reaction was stirred vigorously overnight, before quenching with HCl (1M). The mixture was extracted with ether (2x50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/Et_2O 98:2) afforded compound **1.100** as a yellow oil (10.8 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.37 (8H, m, H_{Ar}), 7.30 – 7.36 (2H, m, H_{Ar}), 7.02 (1H, d, $^3J_{HH}$ 8.2 Hz, H_3), 6.60 (1H, d, $^4J_{HH}$ 2.3 Hz, H_6), 6.52 (1H, dd, $^3J_{HH}$ 8.3, $^4J_{HH}$ 2.4 Hz, H_4), 5.04 (2H, s, H_{10} or H_{11}), 5.03 (2H, s, H_{10} or H_{11}), 2.50 (2H, d, $^3J_{HH}$ 7.0 Hz, H_7), 1.93 (1H, tspt, $^3J_{HH}$ 7.0, $^3J_{HH}$ 6.6 Hz, H_8), 0.91 (6H, d, $^3J_{HH}$ 6.6 Hz, H_9, $H_{9'}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.1 (C_1 or C_5), 157.5 (C_1 or C_5), 137.4 (C_{qAr}), 137.2 (C_{qAr}), 131.0 (C_3), 128.6 (2C, CH_{Ar}), 128.5 (2C, CH_{Ar}), 127.9 (CH_{Ar}), 127.63 (CH_{Ar}), 127.57 (2C, CH_{Ar}), 126.9 (2C, CH_{Ar}), 123.3 (C_2), 105.1 (C_4 or C_6), 100.5 (C_6 or C_4), 70.2 (C_{10} or C_{11}), 69.8 (C_{10} or C_{11}), 39.0 (C_7), 28.9 (C_8), 22.5 (C_9 and $C_{9'}$) ppm. NMR spectra correspond to the reported data.[17]

10.5.10 Formylation of 1.100 to give aldehyde 5.4

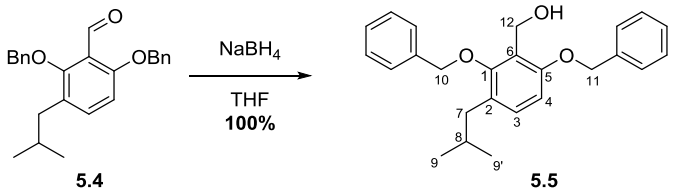


1.100 **5.4**

To a solution of **1.100** (3.0 g, 8.2 mmol, 1 equiv.) in Et_2O (25 mL) at rt was added TMEDA (1.9 mL, 13.0 mmol, 1.58 equiv.) and the solution was cooled to 0 °C. Following this, *n*-BuLi (1.6 M in hexanes, 8.1 mL, 13.0 mmol, 1.58 equiv.) was added dropwise and the mixture was stirred at 0 °C for 15 min. DMF (1.50 mL, 19.0 mmol, 2.3 equiv.) was then added dropwise at 0 °C and the reaction mixture was stirred for a further h. The reaction mixture was allowed to warm to rt slowly and was quenched with H_2O (20 mL). The mixture was extracted with ether (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* column chromatography (hexane/Et_2O 90:10) afforded compound **5.4** as a yellow oil (1.33 g, 43%).

mp 88-90 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.59 (1H, s, H_{12}), 7.54 – 7.29 (11H, m, H_{Ar}, H_3, H_6), 6.80 (1H, d, $^3J_{HH}$ 8.6 Hz, H_4), 5.18 (2H, s, H_{10} or H_{11}), 4.94 (2H, s, H_{10} or H_{11}), 2.41 (2H, d, $^3J_{HH}$ 7.2 Hz, H_7), 1.90 (1H, tspt, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 6.6 Hz, H_8), 0.86 (6H, d, $^3J_{HH}$ 6.6 Hz, H_9, $H_{9'}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.6 (C_{12}), 160.0 (C_1 or C_5), 158.8 (C_1 or C_5), 137.13 (C_3), 137.09 (C_{qAr}), 136.3 (C_{qAr}), 128.7 (2C, CH_{Ar}), 128.51 (C_2), 128.48 (2C, CH_{Ar}), 128.2 (2C, CH_{Ar}), 128.1 (2C, CH_{Ar}), 127.2 (2C, CH_{Ar}), 119.4 (C_6), 108.5 (C_4), 77.3 (C_{10} or C_{11} (DEPT 135)), 70.9 (C_{10} or C_{11}), 38.6 (C_7), 29.1 (C_8), 22.4 (C_9 and $C_{9'}$) ppm. NMR spectra correspond to the reported data.[19]

10.5.11 Reduction of aldehyde 5.4 to give alcohol 5.5

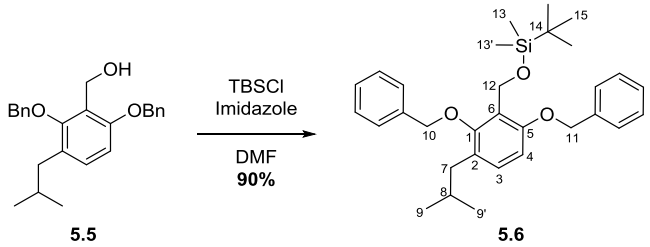


5.4 **5.5**

To a solution of aldehyde **5.4** (1.0 g, 2.7 mmol, 1 equiv.) in THF (20 mL) at rt was added $NaBH_4$ (220 mg, 5.9 mmol, 2.2 equiv.) in one portion. The reaction mixture was stirred for 1.5 h at this temperature, before quenching with H_2O (10 mL), followed by dropwise addition of HCl (0.5 M, 5 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was re-extracted with Et_2O (2x25 mL) and the combined organic phases were washed with a saturated solution of NH_4Cl (20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*, to give compound **5.5** as a pale oil (1.02 g, 100%) which was used without further purification.

IR (neat) 3031 (w), 2952 (m), 2866 (m), 1600 (m), 1483 (s), 1453 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.32 (10H, m, H_{Ar}), 7.08 (1H, d, $^3J_{HH}$ 8.4 Hz, H_3), 6.75 (1H, d, $^3J_{HH}$ 8.4 Hz, H_4), 5.12 (2H, s, H_{10} or H_{11}), 4.92 (2H, s, H_{11} or H_{10}), 4.83 (2H, d, $^3J_{HH}$ 6.3 Hz, H_{12}), 2.54 (1H, t, $^3J_{HH}$ 6.4 Hz, O<u>H</u>-12), 2.48 (2H, d, $^3J_{HH}$ 7.2 Hz, H_7), 1.95 (1H, tspt, $^3J_{HH}$ 7.2, $^3J_{HH}$ 6.6 Hz, H_8), 0.90 (6H, d, $^3J_{HH}$ 6.6 Hz, H_9, $H_{9'}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.4 (C_1 or C_5), 156.3 (C_1 or C_5), 137.4 (C_{qAr}), 136.8 (C_{qAr}), 130.5 (C_3), 128.7 (2C, CH_{Ar}), 128.5 (2C, CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (C_2 or C_6), 127.7 (2C, CH_{Ar}), 127.4 (2C, CH_{Ar}), 122.9 (C_6 or C_2), 107.8 (C_4), 76.8 (C_{10} or C_{11}), 70.5 (C_{10} or C_{11}), 56.2 (C_{12}), 39.2 (C_7), 29.3 (C_8), 22.5 (C_9 and $C_{9'}$) ppm. **MS** (ESI^+) (m/z) 399 $[M+Na]^+$, 359 $[M\text{-}OH^-]^+$; **HRMS** (ESI^+) for $C_{25}H_{28}O_3$ $[M+Na]^+$ calcd. 399.1931; found. 399.1927.

10.5.12 Synthesis of 2,6-bis(benzyloxy)-3-isobutylbenzyloxy-*t*-butyldimethylsilane 5.6

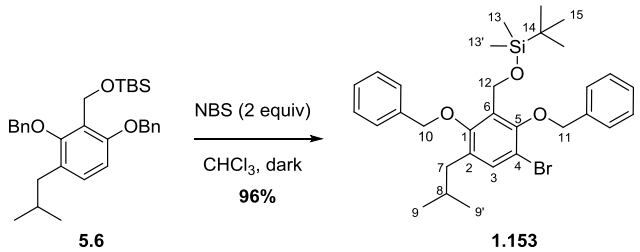


5.5 **5.6**

To a solution of **5.5** (1.0 g, 2.7 mmol, 1 equiv.) in DMF (25 mL) at rt was added TBSCl (0.48 g, 3.2 mmol, 1.2 equiv.), and imidazole (0.43 g, 6.4 mmol, 2.4 equiv.) in one portion. The reaction mixture was stirred for 1 h before quenching with H_2O (20 mL), and stirred for additional 15 min. The mixture was extracted with Et_2O (3x25 mL), the combined organic phases were washed with brine (20 mL) dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* column chromatography (hexane/Et_2O 80:20) afforded compound **5.6** as a yellow oil (1.18 g, 90%).

IR (neat) 3031 (w), 2952 (m), 2866 (m), 1600 (m), 1483 (m), 1347 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.30 (10H, m, H_{Ar}), 7.05 (1H, d, $^3J_{HH}$ 8.4 Hz, H_3), 6.70 (1H, d, $^3J_{HH}$ 8.4 Hz, H_4), 5.09 (2H, s, H_{11} or H_{10}), 5.05 (2H, s, H_{11} or H_{10}), 4.84 (2H, s, H_{12}), 2.46 (2H, d, $^3J_{HH}$ 7.2 Hz, H_7), 1.93 (1H, tspt, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 6.6 Hz H_8), 0.89 (6H, d, $^3J_{HH}$ 6.7 Hz, H_9, $H_{9'}$), 0.84 (9H, s, H_{15}), -0.01 (6H, s, H_{13}, $H_{13'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4 (C_1 or C_5), 156.7 (C_5 or C_1), 138.2 (C_{qAr}), 137.3 (C_{qAr}), 130.5 (C_3), 128.4 (3 or 4C, CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (2 or 3C, CH_{Ar}), 127.44 (C_2 or C_6), 127.41 (2C, CH_{Ar}), 122.9 (C_6 or C_2), 107.9 (C_4), 76.8 (C_{10} or C_{11}), 70.5 (C_{10} or C_{11}), 55.2 (C_{12}), 39.2 (C_8), 29.3 (C_7), 26.0 (C_{15}), 22.6 (C_9 and $C_{9'}$), 18.4 (C_{14}), -5.4 (C_{13} and $C_{13'}$) ppm; **MS** (ESI^+) (*m/z*) 513 $[M+Na]^+$; **HRMS** (ESI^+) for $C_{31}H_{42}O_3Si$ $[M+Na]^+$ calcd. 513.2975; found. 513.2976.

10.5.13 Synthesis of the aromatic derivative 1.153

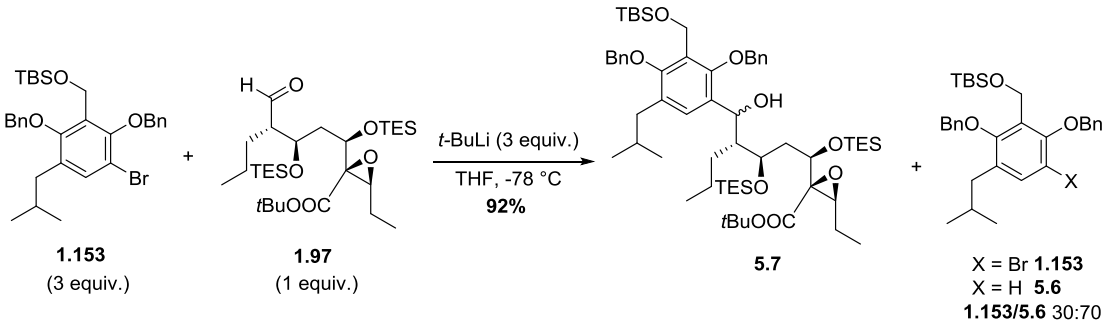


5.6 1.153

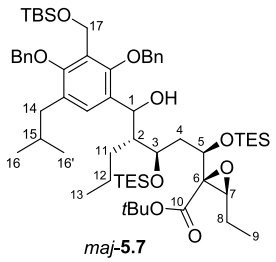
To a solution of protected triol **5.6** (998 mg, 2.0 mmol, 1 equiv.) in dry $CHCl_3$ (20 mL) at rt was added NBS (724 mg, 4.0 mmol, 2 equiv.) and the reaction mixture was stirred overnight in the dark. At completion the reaction mixture was concentrated *in vacuo* and extracted with Et_2O (30 mL) and H_2O (30 mL). The aqueous layer was re-extracted with ether (30 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* column chromatography (hexane/Et_2O 97:3) afforded compound **1.153** as a yellow oil (1.11 g, 96%).

mp 65-66 ^{o}C; **IR** (neat) 2954 (s), 2928 (m), 2856 (w), 1497 (w), 1448 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 –7.53 (2H, m with the presence of $^{3}J_{HH}$ 7.0 Hz, H_{Ar} and/or H_3), 7.49 – 7.31 (9H, m, H_{Ar} and/or H_3), 5.13 (2H, s, H_{11} or H_{10}), 5.00 (2H, s, H_{11} or H_{10}), 4.77 (2H, s, H_{12}), 2.45 (2H, d, $^{3}J_{HH}$ 7.2 Hz, H_7), 1.94 (1H, tspt, $^{3}J_{HH}$ 7.2 Hz, $^{3}J_{HH}$ 6.6 Hz, H_8), 0.90 (6H, d, $^{3}J_{HH}$ 6.7 Hz, H_9, $H_{9'}$), 0.84 (9H, s, H_{15}), -0.01 (6H, s, H_{13}, $H_{13'}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.6 (C_1 or C_5), 153.8 (C_1 or C_5), 137.6 (C_{qAr}), 137.3 (C_{qAr}), 134.3 (C_3), 133.1 (C_4 or C_6), 130.0 (C_4 or C_6), 128.5 (2C, CH_{Ar}), 128.3 (2C, CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (2C, CH_{Ar}), 127.1, (2C, CH_{Ar}), 112.5 (C_2), 76.8 (C_{10} or C_{11}), 76.1 (C_{10} or C_{11}), 55.8 (C_{12}), 39.0 (C_7), 29.3 (C_8), 25.9 (C_{15}), 22.5 (C_9 and $C_{9'}$), 18.1 (C_{14}), -5.4 (C_{13} and $C_{13'}$) ppm; **MS** (ESI^+) (m/z) 593 $[M(^{81}Br)+Na]^+$, 591 $[M(^{79}Br)+Na]^+$; **HRMS** (ESI^+) $C_{31}H_{41}{}^{79}BrO_3Si$ $[M+Na]^+$ calcd. 591.1901, found. 591.1882.

10.5.14 Coupling reaction

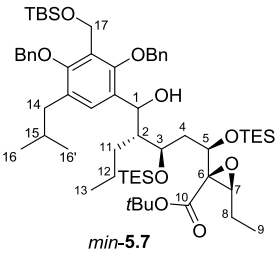


To a solution of **1.153** (427 mg, 0.75 mmol, 3 equiv.) in THF (2.5 mL) at -78 °C was added *t*-BuLi (1.86 M in pentane, 400 µL, 0.75 mmol, 3 equiv.) dropwise. The mixture was stirred at this temperature for 10 min, after which a solution of **1.97** (142 mg, 0.25 mmol, 1 equiv.) in THF (9 mL), was added at -78 °C, and the flask was washed with THF (2 mL). The resulting solution was stirred at -78 °C for 45 min, before quenching at this temperature with H_2O (10 mL). The mixture was then allowed to warm up to rt before extracting with Et_2O (3×20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* column chromatography (pentane/Et_2O 9:1) gave the coupling product **5.7** as a mixture of epimers (245 mg, 92%, *dr* 63:37), alongside with an inseparable mixture of aromatic derivatives **1.153** and **5.6** (206 mg, **1.153/5.6** 30:70). A preparative HPLC (pentane/EtOAc 98:2) was then performed on an analytical mixture of the pure **5.7** (80 mg) which allowed separation of epimers *maj*-**5.7** (52 mg) and *min*-**5.7** (27 mg) for characterisation purpose (***maj*-5.7** eluted first). The configuration at C1 was not determined.



maj-**5.7**

[α]$_D$ 18.6 (c 1.26, $CHCl_3$, 22°C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 - 7.29 (11H, m, H_{Ar}), 5.22 – 5.17 (2H, m, H_1, C**H**HPh), 5.15 – 5.09 (2H, m, C**H**$_2$Ph), 5.00 – 4.93 (1H, m, CH**H**Ph), 4.83 – 4.72 (2H, m, H_{17}), 4.07 – 3.99 (1H, m, H_3), 3.43 (1H, d, $^3J_{HH}$ 1.3 Hz, O**H**-1), 3.32 (1 H, dd, $^3J_{HH}$ 7.0 Hz, $^3J_{HH}$ 5.1 Hz, H_5), 2.71 (1H, t, $^3J_{HH}$ 6.4 Hz, H_7), 2.55 (1H, dd, $^3J_{HH}$ 13.3 Hz, $^3J_{HH}$ 7.4 Hz, H_{14}), 2.39 (1 H, dd, $^3J_{HH}$ 13.4 Hz, $^3J_{HH}$ 7.1 Hz, $H_{14'}$), 2.23 (1 H, dt, $^2J_{HH}$ 14.7 Hz, $^3J_{HH}$ 7.4 Hz, H_4), 2.09 – 1.95 (2H, m, $H_{4'}$, H_{15}), 1.83 – 1.75 (1H, m, H_2), 1.63 – 1.40 (2H, m, H_8, H_{11}), 1.48 (9H, s, C(C**H**$_3$)$_{3\ ester}$), 1.39 – 1.16 (4H, m, $H_{8'}$, $H_{11'}$, H_{12}, $H_{12'}$), 1.00 – 0.85 (27H, m, H_9, H_{16}, $H_{16'}$, C**H**$_{3TES}$), 0.80 (9H, s, C(C**H**$_3$)$_{3TBS}$), 0.73 (3H, t, $^3J_{HH}$ 6.6 Hz, H_{13}), 0.69 – 0.55 (12H, m, C**H**$_{2TES}$), -0.03 (3H, s, C**H**$_{3TBS}$), -0.06 (3H, s, C**H**$_{3'TBS}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4 (C_{10}), 156.4 (**C**OBn), 154.1 (**C**OBn), 138.1 (C_{qAr}), 137.7 (C_{qAr}), 132.6 (C_{qAr}), 130.6 (C_{qAr}), 129.0 (CH_{Ar}), 128.4 (2C, CH_{Ar}), 128.3 (2C, CH_{Ar}), 127.7 (CH_{Ar}), 127.5 (CH_{Ar}), 127.2 (2C, CH_{Ar}), 127.1 (C_{qAr}), 126.9 (2C, CH_{Ar}), 82.1 ((CH$_3$)$_3$**C**$_{ester}$), 77.3 (**C**H$_2$Ph (DEPT 135)), 76.6 (**C**H$_2$Ph), 75.9 (C_3), 74.9 (C_5), 71.4 (C_1), 67.0 (C_6), 61.1 (C_7), 55.4 (C_{17}), 47.3 (C_2), 41.3 (C_4), 39.3 (C_{14}), 29.5 (C_{15}), 28.0 (C(**C**H$_3$)$_{3\ ester}$), 25.8 (C(**C**H$_3$)$_{3TBS}$), 24.7 (C_{11}), 23.0 (C_{12}), 22.6 (C_{16} or $C_{16'}$), 22.4 (C_{16} or $C_{16'}$), 21.9 (C_8), 18.0 ((CH$_3$)$_3$**C**$_{TBS}$), 14.6 (C_{13}), 10.1 (C_9), 6.9 (**C**H$_{3TES}$, **C**H$_3$'$_{TES}$), 5.36 (**C**H$_{2TES}$), 4.88 (**C**H$_2$'$_{TES}$), -5.5 (**C**H$_{3TBS}$), -5.7 (**C**H$_3$'$_{TBS}$) ppm; **MS** (ESI$^+$) (m/z) 1071.65 $[M+Na]^+$.

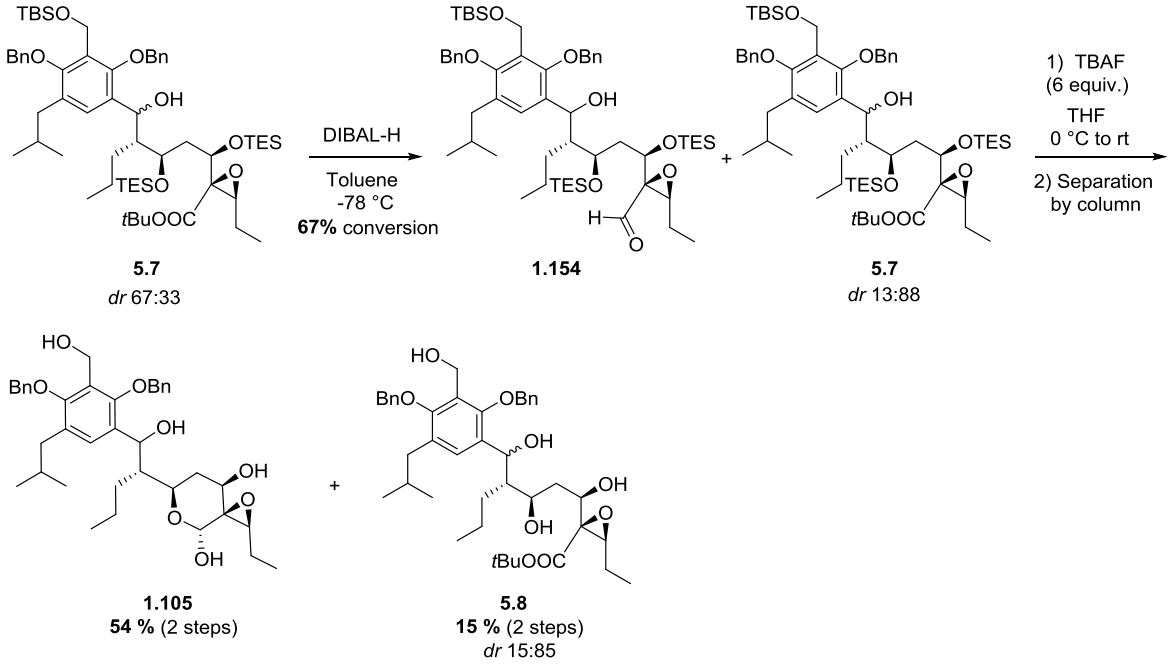


min-**5.7**

[α]$_D$ 13.6 (c 0.69, $CHCl_3$, 22°C); **IR** (neat) 3477 (w, br.), 2958 (s, br.), 1749 (m,br.), 1471 (w), 1356 (m), 1245 (m), 1095 (s) cm^{-1} ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 − 7.28 (11 H, m, H_{Ar}), 5.19 − 5.12 (2H, m, H_1, C**H**HPh), 5.11 (1H, d, $^3J_{HH}$ 4.5 Hz, CH**H**Ph), 5.08 (1H, d, $^3J_{HH}$ 4.3 Hz, C**H**HPh), 5.00 – 4.94 (1H, m, CH**H**Ph), 4.92 − 4.89 (1H, m, O**H**-1), 4.81 (1H, d, $^3J_{HH}$ 9.6

Hz, H_{17}), 4.75 (1 H, d, $^3J_{HH}$ 9.7 Hz, $H_{17'}$), 4.10 (1H, app. d, *J* 9 Hz, H_3 or H_5), 3.52 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^3J_{HH}$ 1.5 Hz, H_5 or H_3), 2.80 (1H, t, $^3J_{HH}$ 6.3 Hz, H_7), 2.59 (1H, dd, $^2J_{HH}$ 13.5 Hz, $^3J_{HH}$ 7.0 Hz, H_{14}), 2.44 – 2.31 (2H, m, H_4, $H_{14'}$), 2.09 – 1.91 (3H, m, H_2, $H_{4'}$, H_{15}), 1.66 – 1.57 (1H, m, H_8), 1.53 – 1.45 (1H, m, $H_{8'}$), 1.36 (9H, s, C(C**H**$_3$)$_{3\ ester}$), 1.22 – 1.10 (1H, m, H_{11} or H_{12}), 1.08 – 0.93 (24H, m, H_9, , $H_{11'}$, $H_{12'}$, C**H**$_{3TES}$, H_{12} or H_{11}), 0.90 (3H, d, $^3J_{HH}$ 6.5 Hz, H_{16} or $H_{16'}$), 0.89 (3H, d, $^3J_{HH}$ 6.6 Hz, H_{16} or $H_{16'}$), 0.79 (9H, s, C(C**H**$_3$)$_{3TBS}$), 0.77 – 0.60 (15H, m, H_{13}, C**H**$_{2TES}$), -0.075 (3H, s, C**H**$_{3TBS}$), -0.079 (3H, s, C**H**$_{3TBS}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ166.3 (C_{10}), 156.7 (**C**OBn), 155.1 (**C**OBn), 138.2 (C_{qAr}), 138.0 (C_{qAr}), 132.3 (C_{qAr}), 131.2 (C_{qAr}), 130.0 (CH_{Ar}), 128.34 (2C, CH_{Ar}), 128.28 (2C, CH_{Ar}), 127.5 (CH_{Ar}), 127.4 (CH_{Ar}), 127.3 (C_{qAr}), 127.2 (2C, CH_{Ar}), 126.9 (2C, CH_{Ar}), 82.1 ((CH$_3$)$_3$**C**$_{ester}$), 77.7 (**C**H$_2$Ph), 76.5 (**C**H$_2$Ph), 74.5 (C_3 or C_5), 73.6 (C_3 or C_5), 70.1 (br. s, C_1), 67.2 (C_6), 61.4 (C_7), 55.4 (C_{17}), 49.2 (C_2), 39.4 (C_4 or C_{14}), 39.2 (C_4 or C_{14}), 29.8 (C_{12} or C_{11}), 29.2 (C_{15}), 27.9 (C(**C**H$_3$)$_{3ester}$), 25.8 (C(**C**H$_3$)$_{3TBS}$), 22.6 (C_{16} or $C_{16'}$), 22.5 (C_{16} or $C_{16'}$), 21.7 (C_8), 21.0 (C_{11} or C_{12}), 17.9 ((CH$_3$)$_3$**C**$_{TBS}$), 14.1 (C_{13}), 10.2 (C_9), 6.9 (**C**H$_{3\ TES}$, **C**H$_{3'TES}$), 5.4 (**C**H$_{2TES}$), 5.1 (**C**H$_{2TES}$),-5.5 (**C**H$_{3TBS}$),-5.6 (**C**H$_{3'TBS}$) ppm; **MS** (ESI$^+$) (m/z) 1071.66 [M+Na]$^+$.

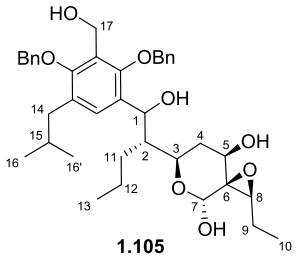
10.5.15 Reduction/Deprotection leading to hemiacetal 1.105, and deprotected ester 5.8.



To a solution of **5.7** (107 mg, 0.10 mmol, *dr* 67:33, 1 equiv.) in toluene (3.2 mL) at -78 °C was added DIBAL-H (1M in heptane, 400 µL, 0.40 mmol, 4 equiv.) dropwise. The resulting mixture was stirred for 1 h at this temperature, before quenching with MeOH (3 mL) at -78 °C. The solution was allowed to warm up to 0 °C after which H_2O (3 mL) was added and the resulting mixture was stirred for further 1 h at 0 °C. The mixture was filtered through a pad of celite®, washed with EtOAc (24 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification *via* column chromatography (pentane/Et_2O 95:5 to 9:1) followed by preparative HPLC (hexane/Et_2O 9:1) gave a mixture of aldehyde **1.154** and starting material **5.7** (86 mg), which was used in the next step without further purification.

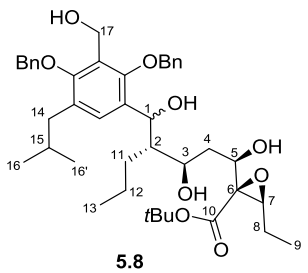
The mixture (86 mg) was then dissolved in THF (3 mL), and TBAF (1M in THF, 520 µL, 0.52 mmol, 5.2 equiv.) was added dropwise at 0 °C. The resulting solution was stirred for 1 h at 0 °C, then the mixture was allowed to warm up to rt, and stirring was continued for 2.5 h at this temperature, before evaporating under reduced pressure. Purification *via* column chromatography (pentane/acetone 8:2 to 7:3) gave the hemiacetal *maj*-**1.105** as a single epimer and as a colourless oil (35 mg, isolated with 5% of **5.8**, 54% over 2 steps), as well as an impure mixture of deprotected ester **5.8**, which was repurified by preparative HPLC

(hexane/acetone 7:3) to give the pure by-product **5.8** as a colourless oil (10.9 mg, 15% over 2 steps, *dr* 85:15).



1.105

$[\alpha]_D$ 31.8 (c 0.23, $CHCl_3$, 21 °C); **IR** (neat) 3408 (m, br.), 2955 (s, br.), 2353 (m, br.), 1458 (s), 1212 (m), 1098 (s), 1019 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 − 7.35 (10H, m, H_{Ar}), 7.32 (1H, s, H_{Ar}), 5.11 (1H, d, $^3J_{HH}$ 5.8 Hz, H_1), 5.05 (1H, d, $^2J_{HH}$ 10.9 Hz, C**H**HPh), 5.00 − 4.92 (3H, m, C**H**HPh, C**H**$_2$Ph), 4.84 (1H, s, H_7), 4.73 (2H, app. d, $^3J_{HH}$ 4.9 Hz, H_{17}), 4.02 (1H, td, $^3J_{HH}$ 11.3 Hz, $^3J_{HH}$ 5.1 Hz, H_3 or H_5), 3.85 (1 H, d, $^3J_{HH}$ 11.4 Hz, H_5 or H_3), 3.35 − 3.28 (1H, m, O**H**-7), 3.24 (1H, dd, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 5.8 Hz, H_8), 2.60 (1H, dd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 7.1 Hz, H_{14}), 2.52 (1 H, dd, $^2J_{HH}$ 13.3 Hz, $^3J_{HH}$ 7.3 Hz, $H_{14'}$), 2.29 (1 H, t, $^3J_{HH}$ 5.5 Hz, O**H**-17), 2.25 – 2.18 (1H, m, O**H**-1), 2.06 – 1.94 (1H, m, H_{15}), 1.76 – 1.67 (1H, m, H_4), 1.67 – 1.48 (6H, m, H_2, $H_{4'}$, H_9, $H_{9'}$, H_{11}, $H_{11'}$), 1.37 – 1.19 (2H, m, H_{12}), 1.06 (3H, t, $^3J_{HH}$ 7.5 Hz, H_{10}), 0.92 (3H, d, $^3J_{HH}$ 6.8 Hz, H_{16} or $H_{16'}$), 0.91 (3H, d, $^3J_{HH}$ 6.8 Hz, H_{16} or $H_{16'}$), 0.82 (3H, t, $^3J_{HH}$ 7.3 Hz, H_{13}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.1 (**C**OBn), 152.8 (**C**OBn), 137.2 (C_{qAr}), 136.6 (C_{qAr}), 133.0 (C_{qAr}), 131.9 (C_{qAr}), 129.1 (CH_{Ar}), 128.7 (4C, CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (2C, CH_{Ar}), 128.2 (CH_{Ar}), 127.7 (2C, CH_{Ar}), 127.4 (C_{qAr}), 94.3 (C_7), 77.7 (**C**H_2Bn), 76.5 (**C**H_2Bn), 71.1 (C_1), 69.8 (C_3 or C_5), 63.0 (C_5or C_3), 61.8 (C_6), 59.6 (C_8), 56.3 (C_{17}), 49.0 (C_2), 39.4 (C_{14}), 37.3 (C_4), 29.3 (C_{15}), 26.6 (C_{11}), 23.3 (C_{12}), 22.6 (C_{16} or $C_{16'}$), 22.4 (C_{16} or $C_{16'}$), 20.6 (C_9), 14.5 (C_{13}), 10.6 (C_{10}); **MS** (ESI^+) (m/z) 657 $[M+Na]^+$; **HRMS** (ESI^+) for $C_{38}H_{50}O_8$ $[M+Na]^+$ calcd 657.3398, found 657.3385.

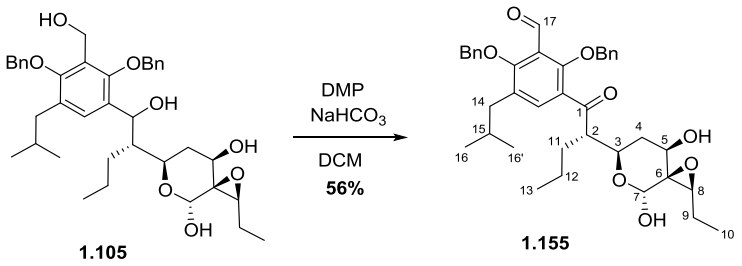


5.8

IR (neat) 3395 (m, br.), 2966 (s, br.), 1724 (m), 1457 (m), 1370 (m), 1247 (m), 1098 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 − 7.33 (20H, m, H_{Ar}, *major and minor*), 7.32 (1H, s, H_{Ar}, *minor*), 7.26 (1H, s, H_{Ar}, *major*), 5.11 − 5.08 (1H, m, H_1, *minor*), 5.04 (2H, d, $^2J_{HH}$ 11.1 Hz,

C**H**HPh, *major and minor*), 5.00 − 4.92 (6H, m, C**H**$_2$Ph, CH**H**Ph, *major and minor*), 4.75 (2H, app. d, $^3J_{HH}$ 5.9 Hz, H_{17}, *major*), 4.41 (1H, ddd, $^3J_{HH}$ 9.1 Hz, $^3J_{HH}$ 6.5 Hz, $^3J_{HH}$ 3.0 Hz, H_3 or H_5, *major*), 4.31 − 4.20 (2H, m, H_3 or H_5, *major and minor*), 4.17 − 4.09 (1H, m, H_3 or H_5, *minor*), 3.73 – 3.65 (1H, m, O**H**-3 or O**H**-5, *major*), 3.27 (1H, t, $^3J_{HH}$ 6.4 Hz, H_7, *major and minor*), 3.14 − 3.08 (1H, m, OH, *minor*), 3.04 – 2.97 (1H, d, $^3J_{HH}$ 8.8 Hz, O**H**-5 or O**H**-3, *major*), 2.86 (1H, br. d, $^3J_{HH}$ 9.5 Hz, OH, *minor*), 2.66 – 2.42 (3H, m, H_{14}, $H_{14'}$,O**H**-17, *major*), 2.06 − 1.89 (3H, m, H_2, H_4, H_{15}, *major*), 1.69 − 1.51 (3H, m, $H_{4'}$, H_8, $H_{8'}$, O**H**-1, *major*), 1.48 (9H, s, (C**H**$_3$)$_3$C, *major*), 1.44 (9H, s, (C**H**$_3$)$_3$C, *minor*), 1.32 – 1.10 (2H, m, H_{12}), 1.09 – 0.98 (2H, m, H_{11}), 1.06 (3H, t, $^3J_{HH}$ 7.7 Hz, H_9, *major*), 0.908 (3H, d, $^3J_{HH}$ 6.3 Hz, H_{16} or $H_{16'}$, *major*), 0.904 (3H, d, $^3J_{HH}$ 6.2 Hz, H_{16} or $H_{16'}$, *major*), 0.73 (3 H, t, $^3J_{HH}$ 7.1 Hz, H_9, *major*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.8 (C_{10}), 156.4 (**C**OBn), 153.3 (**C**OBn), 137.1 (C_{qAr}), 136.6 (C_{qAr}), 132.4 (C_{qAr}), 131.7 (C_{qAr}), 129.3 (CH_{Ar}), 128.72 (CH_{Ar}), 128.66 (br. s, CH_{Ar}), 128.60 (CH_{Ar}) 128.53 (CH_{Ar}), 128.48 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (C_{qAr}), 82.6 ((CH$_3$)$_3$**C**), 77.6 (**C**H$_2$Bn), 76.4 (**C**H$_2$Bn), 72.6 (C_1 or C_3 or C_5, *minor*), 72.4 (C_1 or C_3 or C_5, *minor*), 71.0 (C_1), 70.4 (C_3), 67.4 (C_5), 65.9 (C_6), 59.8 (C_7), 56.5 (C_{17}), 48.1 (C_2), 39.3 (C_{14}), 34.6 (C_4), 29.2 (C_{15}), 29.1 (C_{11}), 28.0 (C(**C**H$_3$)$_3$), 27.9 (C(CH$_3$)$_3$, minor), 22.6 (C_{16}), 22.5 ($C_{16'}$), 21.4 (C_8), 20.7 (C_{12}), 14.1 (C_{13}), 10.3 (C_9) ppm; **MS** (ESI$^+$) (m/z) (peak 1) 729 [M+Na]$^+$, (peak 2) 729 [M+Na]$^+$; **HRMS** (ESI$^+$) for $C_{42}H_{58}O_9$ [M+Na]$^+$ calcd 729.3973; found 729.3964.

10.5.16 Bis-benzylic oxidation of 1.105 to give 1.155



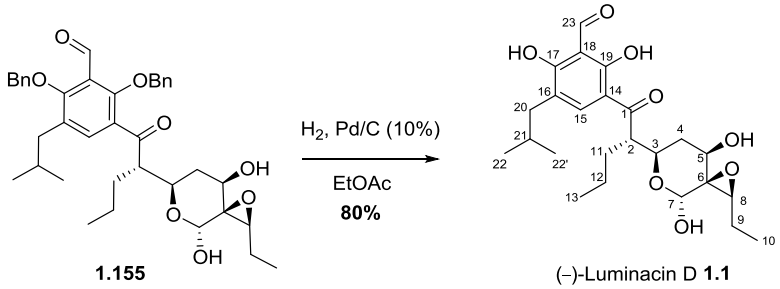
1.105 **1.155**

To a solution of **1.105** (18.5 mg, 29.1 µmol, 1 equiv.) in DCM (2 mL) at 0 °C were successively added $NaHCO_3$ (24.4 mg, 29.1 µmol, 10 equiv.) and Dess-Martin periodinane (25.3 mg, 59.7 µmol, 2.05 equiv.). The mixture was stirred at rt for 5 min, before filtering through a pad of silica (pentane/Et_2O 5:5) to give 8 mg of impure keto aldehyde **1.155**. A mixture of mono-oxidised product and starting material **1.105** (9.1 mg, *ca.* 2:1) was also isolated. The mixture of starting material **1.105** and mono-oxidised product (9.1 mg) was

redissolved in DCM (1 mL), and $NaHCO_3$ (13 mg) was added at 0 °C, followed by Dess-Martin periodinane (8 mg). The resulting suspension was then stirred at rt for 8 min, before filtering through a pad of silica (pentane/Et_2O 5:5) to give 3 mg of impure keto aldehyde, which was combined with the first fraction and purified *via* column chromatography (pentane/Et_2O 5:5) to give the pure benzyl protected luminacin D **1.155** (10.3 mg, 56 %) as a colourless oil.

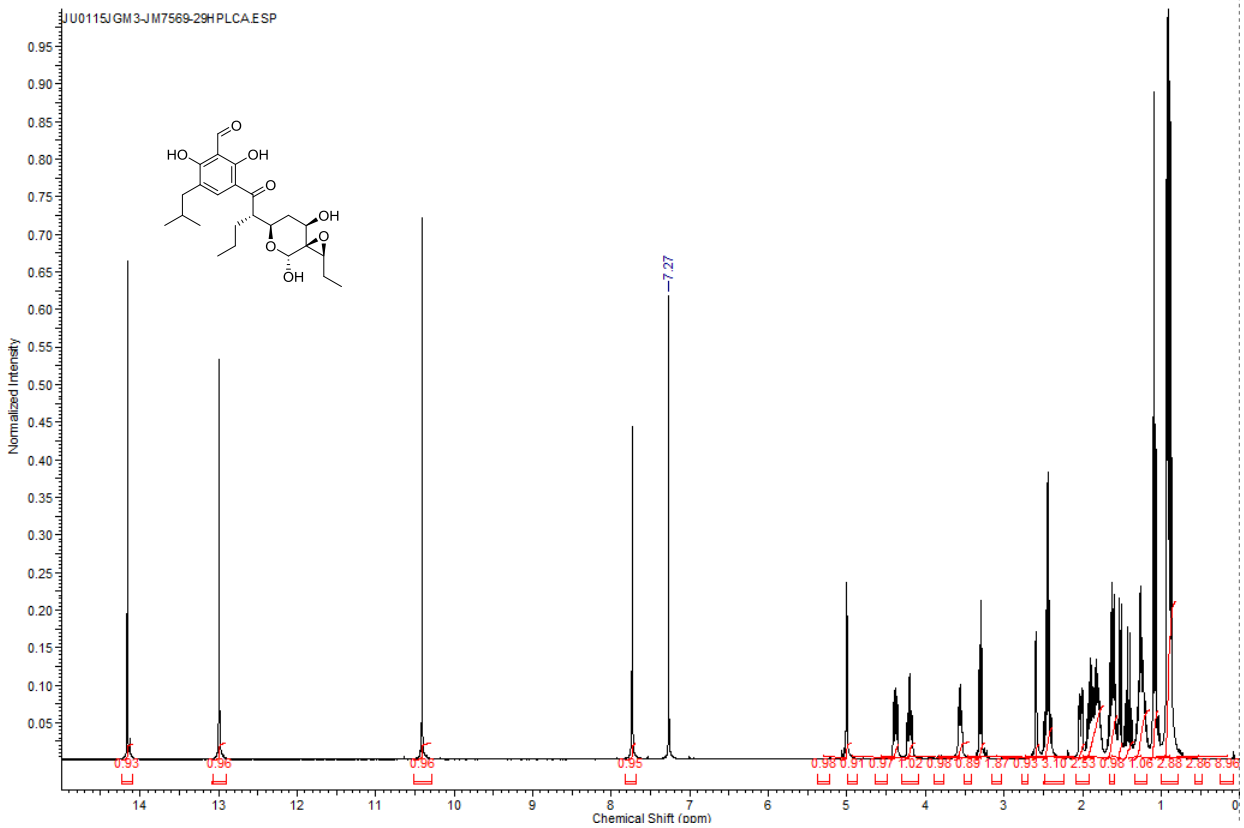
IR (neat) cm^{-1} 3432 (br., m), 2957 (m, br.), 1690 (s), 1556 (m), 1556 (m), 1369 (m), 1094 (s, br.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.33 (1H, s, H_{17}), 7.52 − 7.33 (11H, m, H_{Ar}), 5.07 (1H, d, $^2J_{HH}$ 10.3 Hz, C**H**HPh), 5.04 (1H, d, $^2J_{HH}$ 10.1 Hz, CH**H**Ph), 4.98 (1H, d, $^2J_{HH}$ 11.5 Hz, C**H**HPh), 4.95 (1H, d, $^2J_{HH}$ 11.3 Hz, CH**H**Ph), 4.66 (1H, d, $^3J_{HH}$ 2.3 Hz, H_7), 4.39 (1H, ddd, $^3J_{HH}$ 11.7 Hz, $^3J_{HH}$ 4.8 Hz, $^3J_{HH}$ 1.3 Hz, H_3), 4.11 (1H, td, $^3J_{HH}$ 11.6 Hz, $^3J_{HH}$ 4.9 Hz, H_5), 3.36 (1H, dt, $^3J_{HH}$ 8.7 Hz, $^3J_{HH}$ 4.3 Hz, H_2), 3.22 (1H, t, $^3J_{HH}$ 6.5 Hz, H_8), 2.49 (2H, d, $^3J_{HH}$ 7.2 Hz, H_{14}), 2.47 (1H, d, $^3J_{HH}$ 2.8 Hz, O**H**-7), 2.01 − 1.85 (3H, m, H_4, H_{11}, H_{15}), 1.59 − 1.45 (4H, m, $H_{4'}$, H_9, $H_{9'}$, $H_{11'}$), 1.44 – 1.29 (1H, m, H_{12}), 1.29 – 1.15 (1H, m, $H_{12'}$), 1.03 (3H, t, $^3J_{HH}$ 7.5 Hz, H_{10}), 0.92 − 0.85 (9H, m, H_{13}, H_{16}, $H_{16'}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.6 (C_{17}), 189.1 (C_1), 161.3 (**C**OBn), 156.7 (**C**OBn), 136.1 (C_{qAr}), 135.81 (C_{qAr}), 135.77 (CH_{Ar}), 132.7 (C_{qAr}), 132.4 (C_{qAr}), 128.9 (2C, CH_{Ar}), 128.68 (CH_{Ar}), 128.65 (2C, CH_{Ar}), 128.60 (2C, CH_{Ar}), 128.5 (CH_{Ar}), 128.2 (2C, CH_{Ar}), 124.3 (C_{qAr}), 94.3 (C_7), 80.2 (**C**H_2Bn), 78.2 (**C**H_2Bn), 67.5 (C_3), 62.8 (C_5), 61.5 (C_6), 59.5 (C_8), 54.9 (C_2), 38.7 (C_{14}), 36.8 (C_4), 29.1 (C_{15}), 28.1 (C_{11}), 22.5 (C_{16} or $C_{16'}$), 22.3 (C_{16} or $C_{16'}$), 20.9 (C_8), 20.5 (C_{12}), 14.3 (C_{13}), 10.5 (C_{10}) ppm; **MS** (ESI^+) (m/z) 653 $[M+Na]^+$; **HRMS** (ESI^+) for $C_{38}H_{46}O_8$ $[M+Na]^+$ calcd 653.3085; found 635.3091.

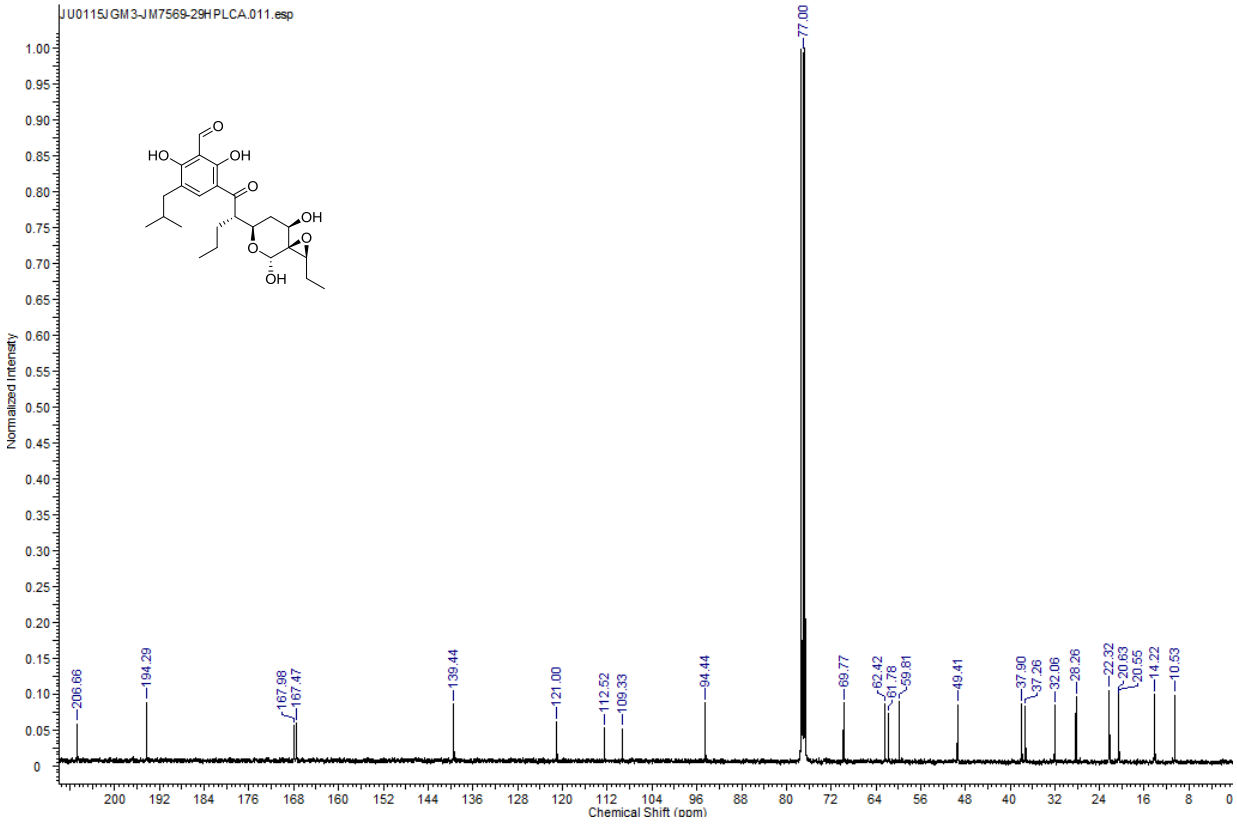
10.5.17 Luminacin D formation



The benzyl protected luminacin D **1.155** (12.6 mg, 20.5 µmol, 1 equiv.) was dissolved in EtOAc (8 mL). Pd (10% wt, 5 mg, 21 µmol, 10 mol%) was added and the resultant mixture was flushed with H_2. Stirring under an atmosphere of H_2 was continued at rt for 24 h, before the mixture was filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (hexane/EtOAc 70:30) followed by preparative HPLC (hexane/EtOAc 65:35) afforded (–)-Luminacin D **1.1** as a pale yellow residue (7.2 mg, 80%).

$[\alpha]_D$ -12.6 (c 0.10, $CHCl_3$, 20 °C), lit -13.0 (c 0.10, $CHCl_3$, 23 °C)[6]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 14.16 (1H, s, O<u>H</u>-19), 12.99 (1H, s, O<u>H</u>-17), 10.41 (1H, s, H_{23}), 7.74 (1H, s, H_{15}), 5.00 (1H, d, $^3J_{HH}$ 2.0 Hz, H_7), 4.38 (1H, ddd, $^3J_{HH}$ 11.6 Hz, $^3J_{HH}$ 8.0, $^3J_{HH}$ 1.6 Hz, H_3), 4.20 (1H, td, $^3J_{HH}$ 11.6 Hz, $^3J_{HH}$ 4.8 Hz, H_5), 3.56 (1H, td, $^3J_{HH}$ 8.5 Hz, $^3J_{HH}$ 4.2 Hz, H_2), 3.30 (1H, dd, $^3J_{HH}$ 6.6 Hz, $^3J_{HH}$ 6.5 Hz, H_8), 2.59 (1H, d, $^3J_{HH}$ 2.6 Hz, O<u>H</u>-7), 2.47 (1H, dd, $^2J_{HH}$ 13.6 Hz, $^3J_{HH}$ 7.2 Hz, H_{20}), 2.42 (1H, dd, $^2J_{HH}$ 13.6 Hz, $^3J_{HH}$ 7.2 Hz, $H_{20'}$), 2.03 (1H, ddd, $^2J_{HH}$ 12.3 Hz, $^3J_{HH}$ 4.8 Hz, $^3J_{HH}$ 1.4 Hz, H_4), 1.96 – 1.75 (3H, m, H_{11}, H_{21}), 1.69 – 1.56 (2H, m, H_9), 1.52 (1H, d, $^3J_{HH}$ 11.6 Hz, O<u>H</u>-5), 1.42 (1H, q, $^2J_{HH}$, $^3J_{HH}$ 11.9 Hz, $H_{4'}$), 1.35 – 1.14 (2H, m, H_{12}), 1.09 (3H, t, $^3J_{HH}$ 7.5 Hz, H_{10}), 0.93 (3H, d, $^3J_{HH}$ 6.7 Hz, H_{22}), 0.92 (3H, d, $^3J_{HH}$ 6.7 Hz, $H_{22'}$), 0.88 (3H, t, $^3J_{HH}$ 7.3 Hz, H_{13}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.7 (C_1), 194.3 (C_{23}), 168.0 (C_{19}), 167.5 (C_{17}), 139.4 (C_{15}), 121.0 (C_{16}), 112.5 (C_{14}), 109.3 (C_{18}), 94.4 (C_7), 69.8 (C_3), 62.4 (C_5), 61.8 (C_6), 59.8 (C_8), 49.4 (C_2), 37.9 (C_{20}), 37.3 (C_4), 32.1 (C_{11}), 28.3 (C_{21}), 22.32 (C_{22}), 22.26 ($C_{22'}$), 20.63 (C_9 or C_{12}), 20.55 (C_9 or C_{12}), 14.2 (C_{13}), 10.5 (C_{10}) ppm. NMR spectra correspond with the reported data.[17]


JU0115JGM3-JM7569-29HPLCA.ESP
Normalized Intensity
Chemical Shift (ppm)
7.27
HO
OH
O
OH
O
OH


JU0115JGM3-JM7569-29HPLCA.011.esp
Normalized Intensity
Chemical Shift (ppm)
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206.66
194.29
167.98
167.47
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112.52
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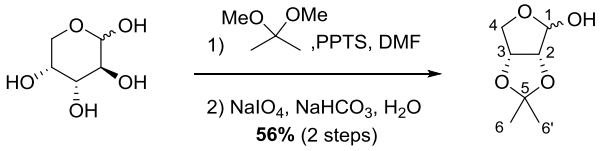
69.77
62.42
61.78
59.81
49.41
37.90
37.26
32.06
28.26
22.32
20.63
20.55
14.22
10.53
HO
OH
O
OH
O
OH

10.6 Synthesis of terafluoroheptoses and octoses

10.6.1 Synthesis of 2,3-*O*-isopropylidene-D-erythrose 8.11

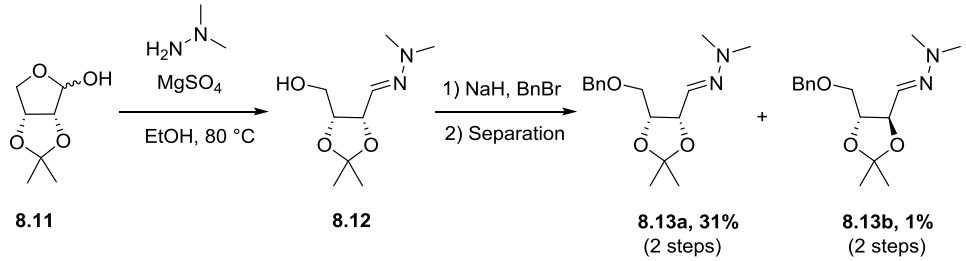


D-arabinose **8.7** → **8.11** *major and minor*

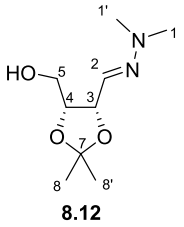
To D-arabinose **8.7** (5.0 g, 33.3 mmol, 1 equiv.), dissolved in dry DMF (60 mL) at rt, was added 2,2-dimethoxypropane (12.5 mL, 101.6 mmol, 3.05 equiv.) followed by pyridinium *p*-toluenesulfonate (82 mg, 0.33 mmol, 1 mol%), and stirring was continued for 16 h. Following this, the solvent was removed under vacuum and the residue was dissolved in a warm mixture of H_2O/petroleum ether (2:1, 45 mL). The layers were separated, then sodium periodate (14.2 g, 66.6 mmol, 2 equiv.), followed by $NaHCO_3$ (4.2 g, 50.0 mmol, 1.5 equiv.) was added to the aqueous phase at 0 °C. The mixture was stirred for 12 h at rt. The resulting precipitate was then filtered through celite and washed with water, Et_2O and DCM. The combined organic phases were washed several times with a saturated solution of Na_2CO_3, dried over $MgSO_4$ and concentrated under reduced pressure to give **8.11** as yellow oil, which was used without further purification (2.98 g, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (1H, s, H_1, *major*), 5.00 (1H, dd, $^2J_{HH}$ 11.5 Hz, $^3J_{HH}$ 3.6 Hz, H_1, *minor*), 4.84 (1H, dd, $^3J_{HH}$ 5.9 Hz, $^3J_{HH}$ 3.6 Hz, H_3, *major*), 4.76 (1H, dd, $^3J_{HH}$ 6.1 Hz, $^3J_{HH}$ 3.4 Hz, H_3, *minor*), 4.58 (1H, d, $^3J_{HH}$ 5.9 Hz, H_2, *major*), 4.49 (1H, dd, $^3J_{HH}$ 6.2 Hz, $^3J_{HH}$ 3.6 Hz, H_2, *minor*), 4.08 (1H, dd, $^3J_{HH}$ 10.4 Hz, $^3J_{HH}$ 3.6 Hz, H_4, *major*), 4.03 (1H, d, $^3J_{HH}$ 10.4 Hz, $H_{4'}$, *major*), 3.98 (1H, d, $^3J_{HH}$ 10.8 Hz, H_4, *minor*), 3.90 (1H, d, $^3J_{HH}$ 11.6 Hz, O<u>H</u>-1, *minor*), 3.55 (1H, dd, $^3J_{HH}$ 11.1 Hz, $^3J_{HH}$ 3.7 Hz, $H_{4'}$, *minor*), 2.82 (1H, br. s, O<u>H</u>-1, *major*), 1.55 (3H, s, H_6 or $H_{6'}$, *minor*), 1.47 (3H, s, H_6 or $H_{6'}$, *major*), 1.38 (3H, s, H_6 or $H_{6'}$, *minor*), 1.32 (3H, s, H_6 or $H_{6'}$, *major*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 113.5 (C_5, *minor*), 112.3 (C_5, *major*), 101.8 (C_1, *major*), 97.5 (C_1, *minor*), 85.2 (C_2, *major*), 80.0 (C_3, *major*), 79.6 (C_2, *minor*), 78.3 (C_3, *minor*), 72.0 (C_4, *major*), 67.7 (C_4, *minor*), 26.2 (C_6 or $C_{6'}$, *major*), 26.0 (C_6 or $C_{6'}$, *minor*), 24.9 (C_6 or $C_{6'}$, *minor*), 24.8 (C_6 or $C_{6'}$, *major*) ppm. NMR spectra correspond with the reported data.[146,147]

10.6.2 Synthesis of benzylated hydrazones 8.13a and 8.13b.



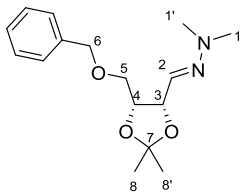
2,3-*O*-Isopropylidene-D-erythrose **8.11** (503 mg, 3.14 mmol, 1 equiv.) was dissolved in absolute ethanol and poured into a sealed tube. $MgSO_4$ (755 mg, 6.28 mmol, 2 equiv.) and N,N-dimethylhydrazine (354 µL, 4.71 mmol, 1.5 equiv.) were then consecutively added, and the mixture was vigorously stirred for 6.5 h at 80 °C. The reaction mixture was allowed to cool down at rt, before filtering through a sintered funnel, and concentrating *in vacuo*. The crude mixture was subjected to column chromatography (pentane/EtOAc 7:3) to give the impure hydrazone **8.12** as a yellow oil (451 mg), which was engaged in the next step without further purification.



8.12

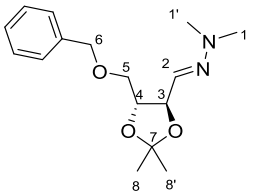
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (1H, d, $^3J_{HH}$ 6.6 Hz, H_2), 4.80 (1H, dd appeared as t, $^3J_{HH}$ 6.6 Hz, H_3), 4.32 (1H, ddd appeared as dt, $^3J_{HH}$ 7.0 Hz, $^3J_{HH}$ 5.3 Hz, H_4), 3.69 (1H, dd, $^2J_{HH}$ 11.6 Hz, $^3J_{HH}$ 4.8 Hz, H_5 or $H_{5'}$), 3.62 (1H, dd, $^2J_{HH}$ 11.7 Hz, $^3J_{HH}$ 5.6 Hz, $H_{5'}$ or H_5), 2.82 (6H, s, H_1 and $H_{1'}$) 1.52 (3H, s, H_8 or $H_{8'}$), 1.39 (3H, s, H_8 or $H_{8'}$) ppm. NMR spectra correspond to the reported data.[123]

To a solution of NaH (60% dispersion in mineral oil, 89 mg, 2.23 mmol, 0.7 equiv.) in THF (9 mL) at rt was added dropwise a solution of impure **8.12** (451 mg) in THF (4 mL) over 10 min. The reaction mixture was stirred at rt for 30 min, before adding BnBr (344 µL, 2.9 mmol, 1.3 equiv.) dropwise. The resulting mixture was stirred at rt for 16 h, then quenched with H_2O (10 mL). The mixture was extracted with EtOAc (3×10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/EtOAc 90:10 to 80:20) afforded compound **8.13a** (285 mg, 31% over 2 steps) and **8.13b** (4 mg, <1% over 2 steps) as yellow oils.



8.13a

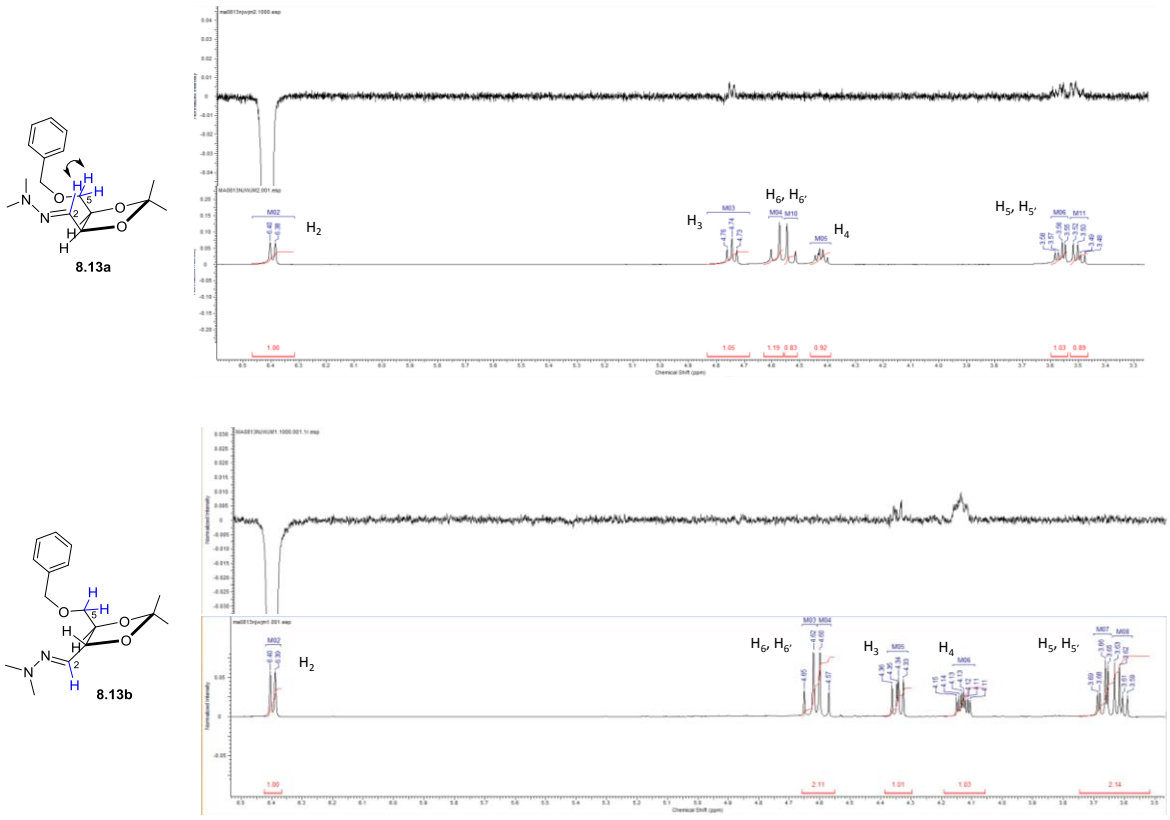
[α]$_D$ -53.0 (c 1.1, $CHCl_3$, 19 °C); **IR** (neat) 2850 (w, br.), 1959 (w), 1459 (w), 1376 (m), 1217.1 (m), 1081 (s), 1013 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.20 (5H, m, H_{Ar}), 6.39 (1H, d, $^3J_{HH}$ 7.2 Hz, H_2), 4.74 (1H, dd appeared as t, $^3J_{HH}$ 7.0 Hz, H_3), 4.59 (1H, d, $^2J_{HH}$ 12.2 Hz, H_6),. 4.53 (1H, d, $^2J_{HH}$ 12.2 Hz, $H_{6'}$), 4.42 (1H, ddd appeared as td, $^3J_{HH}$ 6.3 Hz, $^3J_{HH}$ 4.5 Hz, H_4), 3.56 (1H, dd, $^2J_{HH}$ 10.2 Hz, $^3J_{HH}$ 4.5 Hz, H_5), 3.50 (1H, dd, $^2J_{HH}$ 10.1 Hz, $^3J_{HH}$ 6.3 Hz, H_5), 2.78 (6H, s, H_1, $H_{1'}$), 1.52 (3H, s, $H_{8'}$ or H_8), 1.39 (3H, s, H_8 or $H_{8'}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.0 (C_{qAr}), 130.2 (C_2), 128.3 (2C, CH_{Ar}), 127.61 (2C, CH_{Ar}), 127.57 (CH_{Ar}), 108.9 (C_7), 78.1 (C_3), 76.9 (C_4), 73.4 (C_6), 69.3 (C_5), 42.5 (C_1 and $C_{1'}$), 27.7 (C_8 or $C_{8'}$), 25.2 ($C_{8'}$ or C_8) ppm; only ^{1}H NMR spectrum reported, our data correspond with the reported data.[123] **MS** (ESI^+) (m/z) 293 $[M+H]^+$; **HRMS** (ESI^+) for $C_{16}H_{24}N_2O_3$ $[M+Na]^+$ calcd 315.1685, found. 315.1679.



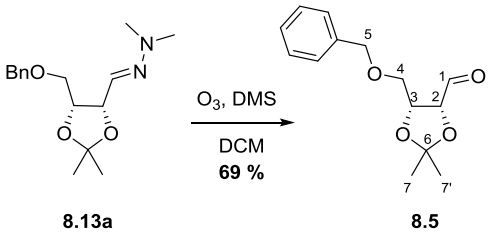
8.13b

[α]$_D$ 44.5 (c 0.1, $CHCl_3$, 19 °C); **IR** (neat) 2986 (w), 2859 (w, br.), 1454 (w), 1379 (w, br.), 1245 (m), 1214 (m), 1080 (s, br.), 1014 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.25 (5H, m, H_{Ar}), 6.40 (1H, d, $^3J_{HH}$ 6.3 Hz, H_2), 4.64 (1H, d, $^2J_{HH}$ 12.1 Hz, H_6), 4.58 (1H, d, $^2J_{HH}$ 12.4 Hz, $H_{6'}$), 4.34 (1H, dd, $^2J_{HH}$ 8.6 Hz, $^3J_{HH}$ 6.4 Hz, H_3), 4.13 (1H, ddd, $^3J_{HH}$ 8.7 Hz, $^3J_{HH}$ 6.1 Hz, $^3J_{HH}$ 3.1 Hz, H_4), 3.67 (1H, dd, $^2J_{HH}$ 10.5 Hz, $^3J_{HH}$ 3.2 Hz, H_5), 3.61 (1H, dd, $^2J_{HH}$ 10.4 Hz, $^3J_{HH}$ 6.3 Hz, $H_{5'}$), 2.83 (6H, s, H_1, $H_{1'}$), 1.47 (3H, s, $H_{8'}$ or H_8), 1.45 (3H, s, H_8 or $H_{8'}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.1 (C_{qAr}), 130.3 (C_2), 128.3 (2C, CH_{Ar}), 127.7 (2C, CH_{Ar}), 127.5 (CH_{Ar}), 109.5 (C_7), 78.9 (C_4), 78.7 (C_3), 73.5 (C_6), 70.0 (C_5), 42.5 (C_1 and $C_{1'}$), 27.1 (C_8 or $C_{8'}$), 27.0 ($C_{8'}$ or C_8) ppm; **MS** (ESI^+) (m/z) 293 $[M+H]^+$; **HRMS** (ESI^+) for $C_{16}H_{24}N_2O_3$ $[M+H]^+$ calcd 293.18620, found 293.18597.

Comparison of NOE experiments. Irradiation at H_2 resulted in a nOe effect at H5 in compound **8.13a**, while no such effect could be observed in the case of **8.13b**. On the other hand, a nOe effect is observed between H_2 and H_4 in the case of **8.13b**.



10.6.3 Synthesis of 4-O-benzyl-2,3-*O*-*iso*propylidene-D-erythrose 8.5

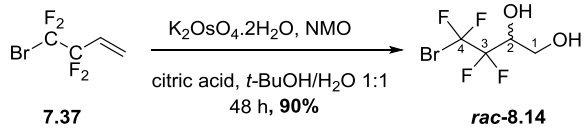


8.13a 8.5

Ozone was bubbled through a solution of **8.13a** (485 mg, 1.66 mmol, 1 equiv.) in DCM (10 mL) at -78 °C until the solution became red (10 min). The excess of ozone was purged from the solution by bubbling oxygen through for 10 min. Dimethyl sulfide (815 µL, 11.1 mmol, 7 equiv.) was then added, and the resulting mixture was allowed to warm to rt, and stirring was continued for 1 h at this temperature. The resulting mixture was then concentrated *in vacuo*. Filtration over silica (petroleum ether/EtOAc 8:2) afforded aldehyde **8.5** as a colourless oil (286 mg, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (1H, d, $^{3}J_{HH}$ 2.1 Hz, H_1), 7.39–7.25 (5H, m, H_{Ar}), 4.59 (1H, ddd appeared as dt, $^{3}J_{HH}$ 7.8 Hz, $^{3}J_{HH}$ 4.0 Hz, H_3), 4.49 (2H, s, H_5), 4.45 (1H, dd, $^{3}J_{HH}$ 7.7 Hz , $^{3}J_{HH}$ 2.3 Hz, H_2), 3.68 (1H, dd, $^{2}J_{HH}$ 10.6 Hz, $^{3}J_{HH}$ 3.9 Hz, H_4), 3.52 (1H, dd, $^{2}J_{HH}$ 10.6 Hz, $^{3}J_{HH}$ 4.0 Hz, $H_{4'}$), 1.60 (3H, s, H_8 or $H_{8'}$), 1.41 (3H, s, $H_{8'}$ or H_8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.4 (C_1), 137.4 (C_{qAr}), 128.4 (2C, CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (2C, CH_{Ar}), 111.0 (C_6), 80.8 (C_2), 78.2 (C_3), 73.4 (C_5), 67.4 (C_4), 26.9 ($C_{7'}$ or C_7), 25.0 (C_7 or C_7') ppm. NMR spectra correspond with the reported data.[124]

10.6.4 Synthesis of *rac*-4-bromo-3,3,4,4-tetrafluorobutane-1,2-diol 8.14

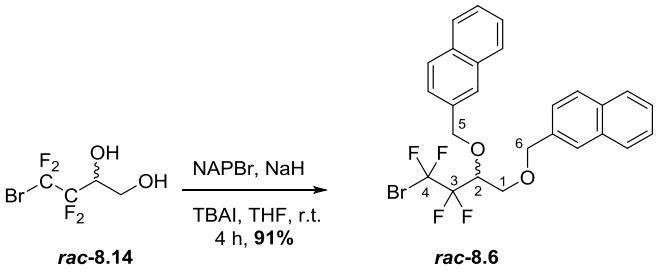


7.37 ***rac*-8.14**

To citric acid (7.6 g, 36.2 mmol, 0.75 equiv.), dissolved in a mixture of H_2O/*t*-BuOH (1:1, 50 mL) at rt, were successively added **7.37** (6.15 mL, 48.3 mmol, 1 equiv.), $K_2OsO_4.2H_2O$ (17.8 mg, 48 µmol, 0.1 mol%) and NMO (50% w/w in H_2O, 11 mL, 36.2 mmol, 1.1 equiv.). The mixture was stirred at rt for 48 h, before concentrating *in vacuo*. The resulting residue was then dissolved in HCl (1M, 60 mL), and extracted with ether (2×50 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure, to give diol ***rac*-8.14** as a colourless oil (10.5 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (1H, br. s, OH), 4.34 – 4.18 (1H, m, H_2), 3.98 – 3.78 (2H, m, H_1, $H_{1'}$), 3.67 – 3.46 (1H, m, OH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 117.0 (dddd appeared as tt, $^{1}J_{CF}$ 313.2 Hz, $^{2}J_{CF}$ 39.6 Hz, C_3 or C_4), 114.3 (dddd appeared as ddt, $^{1}J_{CF}$ 262.0 Hz, $^{1}J_{CF}$ 257.8 Hz, $^{2}J_{CF}$ 30.8 Hz, C_3 or C_4), 70.0 (dd, $^{2}J_{CF}$ 27.9 Hz, $^{2}J_{CF}$ 22.0 Hz, C_2), 61.0 (C_1) ppm; **^{19}F NMR** (386 MHz, $CDCl_3$) δ -63.4 (1F, dd, $^{2}J_{FF}$ 180.3 Hz, *J* 6.9 Hz), -64.3 (1F, dd, $^{2}J_{FF}$ 182.1, *J* 5.2 Hz), -116.2 (1F, ddd appeared as dt, $^{2}J_{FF}$ 272.2 Hz, ^{3}J 6.9 Hz), -122.8 (1F, ddd appeared as dt, $^{2}J_{FF}$ 272.2 Hz, ^{3}J 17.3 Hz, ^{3}J 6.9 Hz) ppm. NMR spectra correspond with the reported data.[120]

10.6.5 Synthesis of *rac*-1,2-bis-(napht-2-ylmethyloxy)-3,3,4,4-tetrafluorobutane *rac*-8.6

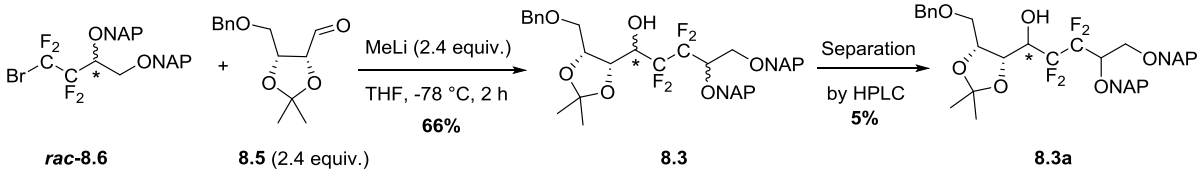


rac-8.14 *rac*-8.6

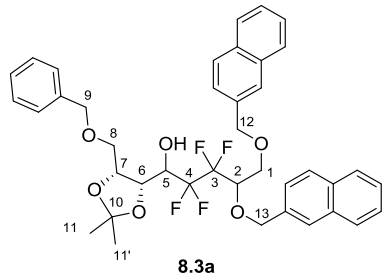
To a solution of ***rac*-8.14** (2.32 g, 9.6 mmol, 1 equiv.) and 2-naphthylmethyl bromide (7.10 g, 30.8 mmol, 3.2 equiv.) in THF (55 mL) at rt was added portionwise NaH (60% dispersion in mineral oil, 2.45 g, 61.3 mmol, 6.4 equiv.), followed by the addition of TBAI (0.96 g, 2.6 mmol, 0.27 equiv.) in one portion. The resulting mixture was stirred at rt for 4 h, before quenching at 0 °C with a saturated solution of NH_4Cl. The aqueous mixture was extracted three times with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc 98:2) gave ***rac*-8.6** as a yellow solid (4.57 g, 91 %).

mp: 66 °C; **IR** (neat) 3054 (w), 2918 (w), 2869 (w), 1123 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.75 (8H, m, H_{Ar}), 7.58 – 7.41 (6H, m, H_{Ar}), 5.01 (1H, d, $^2J_{HH}$ 11.5 Hz, H_5 or H_6), 4.97 (1H, d, $^2J_{HH}$ 11.5 Hz, $H_{5'}$ or $H_{6'}$), 4.75 (2H, br. s., H_5, $H_{5'}$ or H_6, $H_{6'}$), 4.38 (dddd appeared as dtd, ^3J 15.4 Hz, ^3J 7.7 Hz, ^3J 3.0 Hz, H_2), 4.00 – 3.94 (m, 1H, H_1), 3.93 – 3.84 (m, 1H, $H_{1'}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.0, 134.3, 133.24, 133.17, 133.14, 133.07, 128.3, 128.2, 128.0, 127.9, 127.71, 127.68, 127.1, 126.5, 126.2, 126.11, 126.07, 126.01, 125.6, 76.70 (dd, $^2J_{CF}$ 26.4 Hz, $^2J_{CF}$ 22.0 Hz, C_2 (DEPT 135)), 74.7 (C_6 or C_5), 73.8 (C_5 or C_6), 69.0 (br. s, C_1), CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.4 (1F, dd, $^2J_{FF}$ 178.4 Hz, $^3J_{FF}$ 6.5 Hz), -63.1 (1F, d, $^2J_{FF}$ 180.5 Hz), -112.3 (1F, d, $^2J_{FF}$ 277.2 Hz), -120.15 (1F, ddd, $^2J_{FF}$ 272.9, $^3J_{HF}$ 15.0, $^3J_{FF}$ 6.5 Hz) ppm; **HRMS** (ESI^+) for $C_{26}H_{21}{}^{79}BrF_4O_2$ $[M+Na]^+$ calcd 543.0553, found 543.0551.

10.6.6 Synthesis of coupling product 8.3a



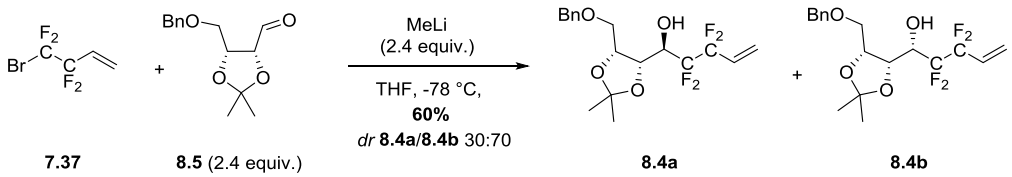
Compounds ***rac*-8.6** (190 mg, 0.37 mmol, 1 equiv.) and **8.5** (220 mg, 0.879 mmol, 2.4 equiv.) were dissolved in THF (1.5 mL) at rt. The resulting solution was cooled to -78 °C and stirred for 10 min at this temperature, after which a solution of MeLi (1.5 M in Et_2O, 586 µL, 0.879 mmol, 2.4 equiv.) was added dropwise. The mixture was stirred at -78 °C for further 2 h, and was quenched at this temperature with a saturated solution of NH_4Cl. The reaction mixture was extracted with Et_2O three times. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. In order to enable separation of the coupling adducts from the remaining aldehyde, the residue was dissolved in EtOH (8 mL), and $NaBH_4$ (49 mg, 1.33 mmol, 1.5 equiv.) was added at 0 °C. The reaction mixture was stirred for 2 h at rt, and then quenched with a saturated solution of NH_4Cl. The mixture was extracted with EtOAc three times. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. Column chromatography (petroleum ether/EtOAc 85:15) gave the coupling adduct **8.3** as a mixture of diastereoisomers (167 mg, 66 %). HPLC (hexane/EtOAc 82:18) was performed on an analytical sample of this mixture (62 mg) and enabled isolation of **8.3a** (13 mg, 5%) as a single diastereoisomer and as a colourless oil. The configuration at C-2 and C-5 was not determined.



$[\alpha]_D$ -25.8 (c 0.44, $CHCl_3$, 21 °C); **IR** (neat) 3512 (w, br.), 3054 (w), 2922 (w, br.), 1111 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.73 (8H, m, H_{Ar}), 7.54 – 7.41 (6H, m, H_{Ar}) , 7.36 – 7.20 (5H, m, H_{Ar}), 4.98 (2H, s, H_9 or H_{12} or H_{13}), 4.72 (2H, s, H_9 or H_{12} or H_{13}), 4.53 (1H, app. d, *J* 6.8 Hz, H_6), 4.45 – 4.31 (5H, m, H_5, H_7, H_2, H_9 or H_{12} or H_{13}), 3.97 (1H, dd, $^2J_{HH}$

10.7 Hz, $^{3}J_{HH}$ 1.9 Hz, H_8). 3.83 (1H, dd, $^{2}J_{HH}$ 10.7 Hz, $^{3}J_{HH}$ 8.1 Hz, $H_{8'}$), 3.64 – 3.59 (2H, m, H_1), 3.20 (1H, d, $^{3}J_{HH}$ 9.9 Hz, O<u>H</u>-5), 1.50 (3H, s, H_{11} or $H_{11'}$), 1.39 (3H, s, $H_{11'}$ or H_{11}) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.4, 135.3, 134.9, 133.24, 133.20, 133.1, 133.0, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 126.9, 126.4, 126.11, 126.07, 126.0, 125.9, 125.6, 77.9 (dd appeared as t, $^{2}J_{CF}$ 24.9 Hz, C_2 or C_5 (DEPT 135)), 75.5 (C_7), 74.9 (C_9, C_{13} or C_{14}), 73.7 (C_9, C_{13} or C_{14}), 73.5 (C_9, C_{13} or C_{14}), 72.4 (C_6), 69.2 (C_8), 68.6 (C_1), 66.6 (dd, $^{2}J_{CF}$ 27.8 Hz, $^{2}J_{CF}$ 22.0 Hz, C_2 or C_5), 26.6 (C_{11} or $C_{11'}$), 24.4 ($C_{11'}$ or C_{11}) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -119.0 (1F, dd, $^{2}J_{FF}$ 279.4 Hz, ^{3}J 12.9 Hz), -119.2 (1F, d, $^{2}J_{FF}$ 275.1 Hz) , -121.0 (1F, dd, $^{2}J_{FF}$ 279.4 Hz, ^{3}J 12.9 Hz), -126.5 (1F, dd, $^{2}J_{FF}$ 275.1 Hz, ^{3}J 21.5 Hz) ppm; **HRMS** (ESI^+) for $C_{40}H_{40}F_4O_6$ $[M+Na]^+$ calcd 715.2653, found 715.2661.

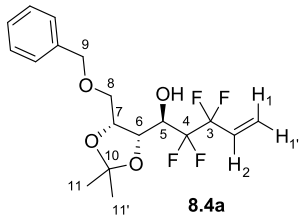
10.6.7 Synthesis of coupling products 8.4a and 8.4b.



7.37 **8.5** (2.4 equiv.) **8.4a** **8.4b**

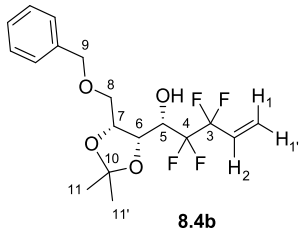
Compounds **7.37** (87 µL, 0.68 mmol, 1 equiv.) and **8.5** (407 mg, 1.63 mmol, 2.4 equiv.) were dissolved in THF (2.5 mL) at rt. The resulting solution was cooled to -78 °C and stirred for 10 min at this temperature, after which a solution of MeLi (1.5 M in Et_2O, 1.1 mL, 1.63 mmol, 2.4 equiv.) was added dropwise at -78 °C. The mixture was stirred at -78 °C for further 2 h, and was quenched at this temperature with a saturated solution of NH_4Cl (5 mL). The reaction mixture was extracted with EtOAc three times. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. In order to enable separation of the coupling adducts from the remaining aldehyde, the residue was dissolved in EtOH (16 mL), and $NaBH_4$ (46 mg, 1.22 mmol, 1.8 equiv.) was added at 0 °C. The reaction mixture was stirred for further 2 h at rt, and then quenched with a saturated solution of NH_4Cl. The mixture was extracted with EtOAc three times. The combined organic phases were dried over $MgSO_4$ and concentrated under vacuo to give the coupling adducts as mixture of diastereoisomers (*dr* **8.4a**/**8.4b** 30:). The crude mixture was subjected to column chromatography (petroleum ether/EtOAc 90:10), giving **8.4a-b** as a mixture of diastereoisomers (153 mg, 60 % overall). Subsequent HPLC (hexane/EtOAc 82:18) followed by a second column chromatography (petroleum

ether/Et_2O 85:15) enabled isolation of both diastereoisomers **8.4a** as and **8.4b** as colourless oil.



8.4a

$[\alpha]_D$ -1.4 (c 0.29, $CHCl_3$,21 °C); **IR** (neat) 3385 (w, br.), 2899 (w), 2922 (w, br.), 1221 (m), 1093 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.29 (5H, m, H_{Ar}), 6.15 – 6.00 (1H, m, H_2), 5.91 – 5.82 (1H, m with the presence of $^3J_{HHtrans}$ 17.6 Hz, H_1), 5.62 (1H, m with the presence of $^3J_{HHcis}$ 11.6 Hz, $H_{1'}$), 4.64 (1H, d, $^3J_{HH}$ 11.6 Hz, H_9), 4.56 (1H, d, $^3J_{HH}$ 11.6 Hz, $H_{9'}$), 4.53 – 4.46 (2H, m, H_6 and O<u>H</u>-5), 4.40 (1H, ddd, $^2J_{HH}$ 9.0 Hz, $^3J_{HH}$ 5.3 Hz, $^3J_{HH}$ 3.3 Hz, H_7), 4.24 (1H, dddd appeared as ddt, ^3J 19.2 Hz, ^3J 9.9 Hz, ^3J 4.2 Hz, H_5), 3.73 (1H, dd appeared as t, $^2J_{HH,}$ $^3J_{HH}$ 9.5 Hz, H_8), 3.54 (1H, dd, $^2J_{HH}$ 9.5 Hz, $^3J_{HH}$ 3.4 Hz, $H_{8'}$), 1.42 (3H, s, $H_{11'}$ or H_{11}), 1.37 (3H, s, H_{11} or $H_{11'}$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.1 (C_{qAr}), 128.7 (2C, CH_{Ar}), 128.5 (CH_{Ar}), 128.2 (2C, CH_{Ar}), 127.9 (t, $^2J_{CF}$ 23.4 Hz, C_2), 122.7 (t, $^3J_{CF}$ 9.5 Hz, C_1), 109.5 (C_{10}), 75.5 (C_7), 75.0 (d, $^3J_{CF}$ 2.9 Hz, C_6), 74.2 (C_9), 68.23 (dd, $^2J_{CF}$ 27.8 Hz, $^2J_{CF}$ 23.4 Hz, C_5), 68.20 (C_8), 27.9 ($C_{11'}$ or C_{11}), 25.4 (C_{11} or $C_{11'}$) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.3 (1F, dd, $^2J_{FF}$ 262.2 Hz, ^3J 12.9 Hz), -115.2 (1F, dd, $^2J_{FF}$ 262.2 Hz, ^3J 12.9 Hz), -118.5 (1F, d, $^2J_{FF}$ 275.1 Hz), -129.1 (1F, dd, $^2J_{FF}$ 275.1 Hz, ^3J 17.2 Hz) ppm; **HRMS** (ESI^+) for $C_{18}H_{22}F_4O_4$ $[M+Na]^+$ calcd 401.1346, found 401.1345.

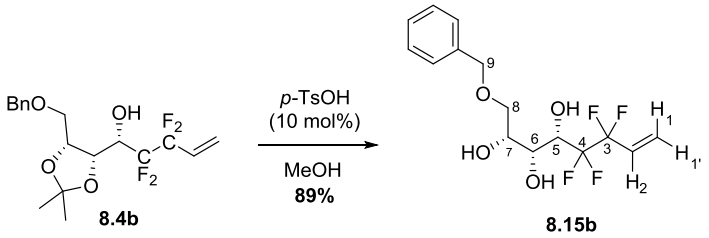


8.4b

mp 56 °C; **$[\alpha]_D$** -29.7 (c 0.62, $CHCl_3$,20 °C); **IR** (neat) 3523 (w, br.), 3032 (w), 2989 (w, br.), 2926 (w, br.), 1214 (m), 1100 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (5H, m, H_{Ar}), 6.16 – 5.98 (1H, m, H_2), 5.91 – 5.82 (1H, m, with the presence of $^3J_{HHtrans}$ 17.3 Hz, H_1), 5.65 (1H, d, $^3J_{HHcis}$ 11.0 Hz, $H_{1'}$), 4.62 – 4.53 (3H, m, H_7 and H_9), 4.48 (1H, td, $^3J_{HH}$ 6.9 Hz, $^3J_{HH}$ 5.1 Hz, H_6), 4.31 (1H, ddd, $^3J_{HF}$ 21.6 Hz, $^3J_{HH}$ 9.9 Hz, $^3J_{HH}$ 4.7 Hz, H_5), 3.78 (1H, dd, $^2J_{HH}$ 9.7 Hz, $^3J_{HH}$ 6.8 Hz, H_8), 3.71 (1H, dd, $^2J_{HH}$ 9.7 Hz, $^3J_{HH}$ 5.2 Hz, $H_{8'}$), 3.05 (1H, d, $^3J_{HH}$ 9.9 Hz,

OH-5), 1.53 (3H, s, $H_{11'}$ or H_{11}), 1.41 (3H, s, H_{11} or $H_{11'}$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.4 (C_{qAr}), 128.5 (2C, CH_{Ar}), 127.9 (3C, CH_{Ar}), 127.3 (t, $^2J_{CF}$ 24.9 Hz, C_2), 123.2 (t, $^3J_{CF}$ 10.2 Hz, C_1), 109.3 (C_{10}), 75.5 (C_7), 73.8 (C_9), 72.5 (d, $^3J_{CF}$ 2.9 Hz, C_6), 68.7 (C_8), 66.1 (dd, $^2J_{CF}$ 27.8 Hz, $^2J_{CF}$ 23.4 Hz, C_5), 26.6 ($C_{11'}$ or C_{11}), 24.4 (C_{11} or $C_{11'}$) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.5 (1F, dd, $^2J_{FF}$ 262.2 Hz, ^3J 12.9 Hz), -115.6 (1F, dd, $^2J_{FF}$ 262.2 Hz, ^3J 12.9 Hz), -120.9 (1F, d, $^2J_{FF}$ 270.8 Hz), -128.8 (1F, dd, $^2J_{FF}$ 270.8 Hz, ^3J 21.5 Hz) ppm; **HRMS** (ESI^+) for $C_{18}H_{22}F_4O_4$ $[M+Na]^+$ calcd 401.1346, found 401.1347.

10.6.8 Synthesis of triol 8.15b

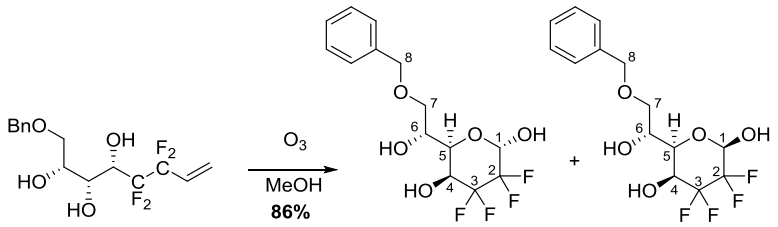


To a solution of **8.4b** (106 mg, 0.28 mmol, 1 equiv.) in MeOH (6 mL) at 0 °C was added *p*-TsOH (6 mg, 0.028 mmol, 10 mol%). The reaction mixture was stirred at rt for 16 h, after which the mixture was cooled back to 0 °C, and an additional amount of *p*-TsOH (6 mg, 0.028 mmol, 10 mol%) was added. Stirring was continued for 6 h at rt, before quenching with a saturated solution of $NaHCO_3$ and extracting three times with EtOAc. Organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/acetone 7:3) afforded compound **8.15b** as a white solid (84 mg, 89%, isolated with 6% of unknown fluorinated material).

$[\alpha]_D$ 0.2 (c 0.23, $CHCl_3$, 22 °C); **IR** (neat) 3252 (w, br.), 1329 (w), 1104 (s), 1050 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (5H, m, H_{Ar}), 6.15 – 6.00 (1H, m, H_2), 5.93 – 5.84 (1H, m with $^3J_{HHtrans}$ 16.9 Hz, H_1), 5.69 (1H, d, $^3J_{HHcis}$ 11.4 Hz, $H_{1'}$), 4.61 (1H, d, $^2J_{HH}$ 11.9 Hz H_9), 4.57 (1H, d, $^2J_{HH}$ 11.9 Hz $H_{9'}$), 4.38 (1H, ddd, $^3J_{HF}$ 20.7 Hz, $^3J_{HH}$ 9.1 Hz, $^3J_{HF}$ 6.3 Hz), 4.17 – 4.08 (1H, m with $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 6.2 Hz, H_6), 3.88 – 3.79 (1H, m, H_7), 3.73 (1H, dd, $^2J_{HH}$ 9.6 Hz, $^3J_{HH}$ 3.9 Hz, H_8), 3.70 (1H, dd, $^2J_{HH}$ 9.6 Hz, $^3J_{HH}$ 5.2 Hz, H_8), 3.12 (1H, d, $^3J_{HH}$ 9.2 Hz, OH-5), 2.59 (1H, d, $^3J_{HH}$ 6.4 Hz OH-7), 2.55 (1H, d, $^3J_{HH}$ 6.2 Hz, OH-6) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.4 (C_{qAr}), 128.6 (2C,CH_{Ar}), 128.1 (CH_{Ar}), 127.9 (2C, CH_{Ar}), 127.0 (t, $^2J_{CF}$ 23.4 Hz,

C_2), 123.2 (t, $^3J_{CF}$ 10.2 Hz, C_1), 73.7 (C_9), 70.7 (C_8), 69.6 (C_7), 68.9 (br. s, C_6), 67.2 (dd, $^2J_{CF}$ 27.8 Hz, $^2J_{CF}$ 22.0 Hz, C_5) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.8 (1F, dd, $^2J_{FF}$ 262.2 Hz, ^3J 12.9 Hz), -115.3 (1F, dd, $^2J_{FF}$ 262.2 Hz, ^3J 8.6 Hz), -121.3 (1F, d, $^2J_{FF}$ 270.8 Hz), -128.8 (1F, dd, $^2J_{FF}$ 270.8 Hz, ^3J 17.2 Hz) ppm; **HRMS** (ESI^+) for $C_{15}H_{18}F_4O_4$ $[M+Na]^+$ calcd 361.1033, found 361.1035.

10.6.9 Synthesis of galacto configured D-heptose 8.2b



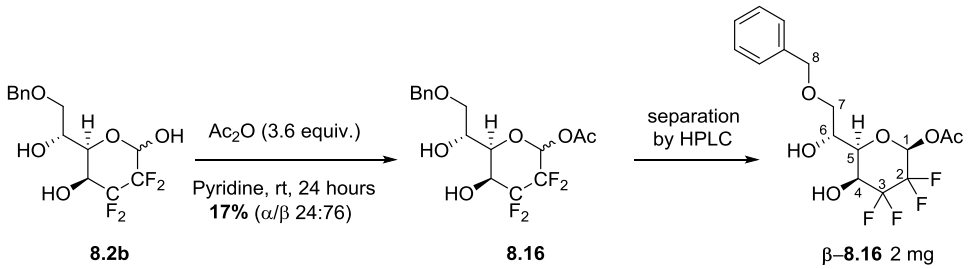
8.15b α–**8.2b** β–**8.2b**

Ozone was bubbled through a solution of **8.15b** (78 mg, 0.23 mmol, 1 equiv.) in MeOH (10 mL) at -78 °C until the solution became blue (5 min). The excess of ozone was purged from the solution by bubbling oxygen through for 10 min. Dimethyl sulfide (180 µL, 2.44 mmol, 10.6 equiv.) was added and the reaction was allowed to warm to rt over a period of 1 h. The resulting mixture was then concentrated *in vacuo*. Filtration over silica (petroleum ether/acetone 6:4) gave heptose **8.2b** as a mixture of anomers and as a white solid (67 mg, 86%, *ar* 48:52).

IR (neat) 3606 (w, br), 3164 (w), 3003 (w), 2944 (w), 2253 (m), 1443 (m, br), 1375 (m) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6, D_2O shake) δ 7.42 – 7.17 (10H, m, H_{Ar}), 5.25 (1H, dd, $^3J_{HF}$ 9.1 Hz, $^3J_{HF}$ 6.6 Hz, $H_{1\alpha}$), 4.96 – 4.87 (1H, m, $H_{1\beta}$), 4.62 – 4.50 (4H, m, $H_{8\alpha+\beta}$), 4.34 – 4.20 (3H, m, $H_{4\alpha+\beta,}$ $H_{5\alpha}$ or $H_{5\beta}$), 4.11 – 4.02 (2H, m, $H_{6\alpha+\beta}$), 3.79 – 3.67 (3H, m, $H_{7\alpha+\beta}$, $H_{5\alpha}$ or $H_{5\beta}$), 3.63 (1H, dd, $^2J_{HH}$ 10.2 Hz, $^3J_{HH}$ 5.4 Hz, $H_{7'\alpha}$ or $H_{7'\beta}$), 3.60 (1H, dd, $^2J_{HH}$ 10.1 Hz, $^3J_{HH}$ 5.8 Hz, $H_{7'\beta}$ or $H_{7'\alpha}$) ppm; **^{13}C NMR** (100 MHz, acetone-d_6, D_2O shake) δ 139.7 (2C, br. s, $C_{qAr\text{-}\alpha+\beta}$), 129.11 (2C, CH_{Ar}), 129.08 (2C, CH_{Ar}), 128.4 (4C, CH_{Ar}), 128.23 (CH_{Ar}), 128.20 (CH_{Ar}), 92.0-93.5 (m, $C_{1\alpha+\beta}$), 74.3 (d, $^4J_{CF}$ 5.9 Hz, $C_{5\alpha\text{ or }\beta}$), 73.9 (br. s., $C_{8\alpha+\beta}$), 69.6 – 68.7 (m, $C_{4\alpha+\beta}$), 69.13 (d, $^4J_{CF}$ 4.4 Hz, $C_{5\alpha\text{ or }\beta}$), 68.5 ($C_{6\alpha\text{ or }\beta}$), 68.2 ($C_{6\alpha\text{ or }\beta}$) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, acetone-d_6, D_2O shake) δ -112.2 – -113.5 (1F, d, $^2J_{FF}$ 266.5 Hz, $F_{\alpha or\beta}$), -113.5 – -114.8 (1F, m with the presence of $^2J_{FF}$ 266.5 Hz, $F_{\alpha\text{ or }\beta}$), -115.6 (1F, d, $^2J_{FF}$ 266.5 Hz, $F_{\alpha\text{ or }\beta}$), -125.6 – -124.1 (1F, m with the presence of $^3J_{FF}$ 266.5 Hz, $F_{\alpha\text{ or }\beta}$), -127.8 – - 126.4 (1F, m,

with the presence of $^{2}J_{FF}$ 266.5 Hz, $F_{\alpha \text{ or } \beta}$) , -128.8 – -128.1 (1F, m, with the presence of $^{3}J_{FF}$ 266.5 Hz, $F_{\alpha \text{ or } \beta}$), -132.36 – -132.0 (2F, m, $F_{\alpha \text{ or } \beta}$) ppm; **MS** ($ESI^-$) (m/z) 375.0 $[M.HCl\text{-}H]^-$, 339 $[M\text{-}H]^-$; **HRMS** (ESI^+) for $C_{14}H_{16}F_4O_5$ $[M+Na]^+$ calcd 363.08261, found 363.08234.

10.6.10 Synthesis of 1-*O*-acetyl-D-heptose 8.16



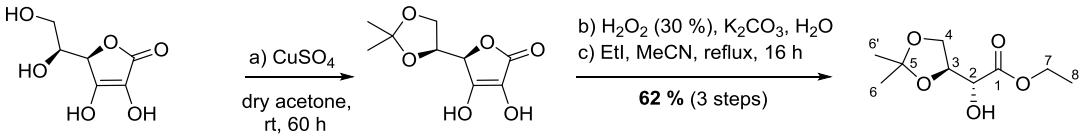
8.2b **8.16** β–**8.16** 2 mg

To a solution of D-heptose **8.2b** (62 mg, 0.18 mmol, 1 equiv.), in pyridine (1 mL), was added Ac_2O (62 µL, 0.66 mmol, 3.2 equiv.) at 0 °C. The reaction mixture was stirred at rt for 16 h, before quenching with EtOH at 0 °C. The mixture was then concentrated to dryness, and was subsequently co-evaporated with toluene and $CHCl_3$. Purification by flash chromatography (petroleum ether/acetone 80:20) gave **8.16** as a white solid (12 mg, 17%, α/β 24:76). Subsequent HPLC (hexane/EtOAc 65:35) enabled isolation of **β-8.16** as a pale yellow solid (2 mg, 0.5%).

$[\alpha]_D$ 12.8 (c 0.13, $CHCl_3$, 21 °C); **IR** (neat) 3432 (w, br.), 2922 (w, br.), 1765 (m), 1119 (s, br.), 1017 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (5H, m, H_{Ar}), 5.82 (1H, dd , $^{3}J_{HF}$ 15.5 Hz, $^{3}J_{HF}$ 4.0 Hz, simplified as s upon fluorine decoupling, H_1), 4.61 (1H, d, $^{2}J_{HH}$ 11.7 Hz, H_8), 4.57 (1H, d, $^{2}J_{HH}$ 11.7 Hz, $H_{8'}$), 4.42 – 4.33 (1H, m, simplified as dd, $^{3}J_{HH}$ 6.6 Hz, $^{3}J_{HH}$ 1.1 Hz upon fluorine decoupling, H_4), 4.17 – 4.08 (1H, m, H_6), 3.94 – 3.87 (1H, m, simplified as dd, $^{3}J_{HH}$ 8.3 Hz, $^{3}J_{HH}$ 1.2 Hz upon fluorine decoupling, H_5), 3.71 (1H, dd, $^{2}J_{HH}$ 9.8 Hz, $^{3}J_{HH}$ 3.4 Hz, H_7), 3.66 (1H, dd, $^{2}J_{HH}$ 9.8 Hz, $^{3}J_{HH}$ 4.3 Hz, $H_{7'}$), 2.77 (1H, d, $^{3}J_{HH}$ 6.7 Hz, O<u>H</u>-4), 2.62 (1H, d, $^{3}J_{HH}$ 7.1 Hz, O<u>H</u>-6), 2.24 (3H, s, C<u>**H**</u>$_{3OAc}$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2 (C_9), 137.4 (C_{qAr}), 128.6 (2C, CH_{Ar}), 128.1 (CH_{Ar}), 127.9 (2C, CH_{Ar}), 88.9 (ddd, $^{3}J_{CF}$ 28.9 Hz, $^{3}J_{CF}$ 18.0 Hz, $^{4}J_{CF}$ 4.4 Hz, C_1), 73.8 (d, $^{4}J_{CF}$ 4.9 Hz, C_5), 73.7, 69.6, 69.0 (dd, $^{3}J_{CF}$ 30.1 Hz, $^{3}J_{CF}$ 19.4 Hz, C_4), 67.8, 20.6 (<u>**C**</u>H_{3OAc}) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -120.8 (1F, d, $^{2}J_{FF}$ 275.1 Hz), -134.6 – -131.9 (2F, m), -135.9 – -137.8 (1F, m) ppm; **HRMS** (ESI^+) for for $C_{16}H_{18}F_4O_6$ $[M+Na]^+$ calcd 405.0932, found 405.0934.

10.7 Synthesis of F_4-L-heptoses *via* an alternative approach

10.7.1 Synthesis of ethyl (2*R*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate 8.22

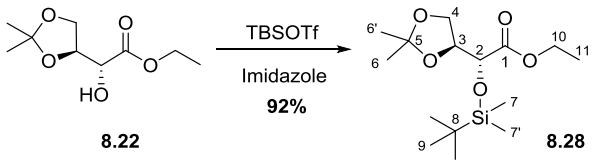


L-ascorbic acid **8.23** **8.27** **8.22**

To a suspension of L-ascorbic acid **8.23** (10 g, 57 mmol, 1 equiv.) in dry acetone at rt was added anhydrous $CuSO_4$ (18 g, 114 mmol, 2 equiv.). The resulting mixture was vigourously stirred at this temperature for 24 h, after which an additional amount of anhydrous $CuSO_4$ (18 g, 114 mmol, 2 equiv.) was added, and stirring was continued for 36 h. The reaction mixture was then filtered and evaporated under reduced pressure, leading to (2*R*,3*S*)-3,4-*O*-isopropylidene-L-ascorbic acid **8.27** (12.2 g, 99 %). The isopropylidene derivative **8.27** was then dissolved in H_2O (60 mL) containing 20 g of K_2CO_3. The solution was cooled in an ice bath and stirred while 30 % H_2O_2 (18 mL) was added. The solution was stirred overnight at rt and concentrated *in vacuo*. The solid was extracted in boiling ethanol, filtered and concentrated under reduced pressure, to give 11.5 g of material. The crude salt was then dissolved in MeCN (75 mL), and EtI (5.7 mL, 71.1 mmol, 1.25 equiv.) was added. The resulting mixture was stirred under reflux for 24 h. The reaction mixture was then filtered and concentrated under reduced pressure. Purification by filtration over silica (petroleum ether/acetone 6:4) gave **8.22** as yellow oil (7.74 g, 62 % over 3 steps).

$[\alpha]_D$ 17.6 (c 1.5, MeOH, 26 °C) lit. 4.2 (c 1.5, MeOH, 21 °C)[127]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.38 (1H, ddd appeared as td, $^3J_{HH}$ 6.8 Hz, $^3J_{HH}$ 2.9 Hz, H_3) , 4.32 – 4.22 (2H, m, H_7), 4.13 – 4.06 (2H, m, H_4 and H_2), 4.01 (1H, dd, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 7.0 Hz, $H_{4'}$), 2.96 (1H, d, $^3J_{HH}$ 8.1 Hz, O<u>H</u>-2), 1.43 (3H, s, H_6 or $H_{6'}$), 1.35 (3H, s, $H_{6'}$ or H_6), 1.32 (3H, t, $^3J_{HH}$ 7.1 Hz, H_8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0 (C_1), 109.9 (C_5), 76.3 (C_3), 70.3 (C_2), 65.6 (C_4), 61.9 (C_7), 26.0 (C_6), 25.3 ($C_{6'}$), 14.1 (C_8) ppm. NMR spectra correspond to the reported data.[127]

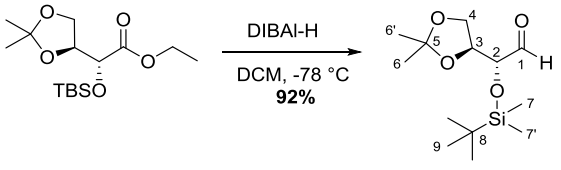
10.7.2 Synthesis of α-TBS-protected ester 8.28



To a stirred solution of **8.22** (2.09 g, 10.2 mmol) in DMF (4 mL) at 0 °C were succesively added imidazole (833 mg, 12.2 mmol, 1.2 equiv.) and TBSOTf (2.5 mL, 10.7 mmoL, 1.05 equiv.). The mixture was stirred at rt for 6 h, before partitioning between H_2O (20 mL) and EtOAc (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2×20 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Filtration over silica (petroleum ether/EtOAc 6:4) afforded **8.28** as colourless oil (2.98 g, 92 %)

$[\alpha]_D$ 29.9 (c 0.97, CH_2Cl_2, 21 °C), lit. 28 (c 4.65, CH_2Cl_2, 21 °C)[127]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.33 (1H, ddd appeared as td, $^3J_{HH}$ 6.4 Hz, $^3J_{HH}$ 5.6 Hz, H_3), 4.26 – 4.18 (3H, m, H_2 and H_{10}), 4.05 (1H, dd, $^3J_{HH}$ 8.5 Hz, $^3J_{HH}$ 6.6 Hz, H_4), 3.96 (1H, dd, $^3J_{HH}$ 8.6 Hz, $^3J_{HH}$ 6.3 Hz, $H_{4'}$), 1.41 (3H, s, H_6 or $H_{6'}$), 1.35 (3H, s, $H_{6'}$ or H_6), 1.30 (3H, t, $^3J_{HH}$ 7.1 Hz, H_{11}), 0.93 (9H, s, H_9), 0.11 (3H, s, H_7 or $H_{7'}$), 0.09 (3H, s, $H_{7'}$ or H_7) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1 (C_1), 109.7 (C_5), 77.2 (C_3), 73.4 (C_2), 65.6 (C_4), 61.0 (C_{10}), 26.3 (C_6 or $C_{6'}$), 25.7 (C_9), 25.4 ($C_{6'}$ or C_6), 18.3 (C_8), 14.2 (C_{11}), -5.0 (C_7 or $C_{7'}$), -5.2 ($C_{7'}$ or C_7) ppm. NMR spectra correspond with the reported data.[127]

10.7.3 Synthesis of α-TBS-protected aldehyde 8.20

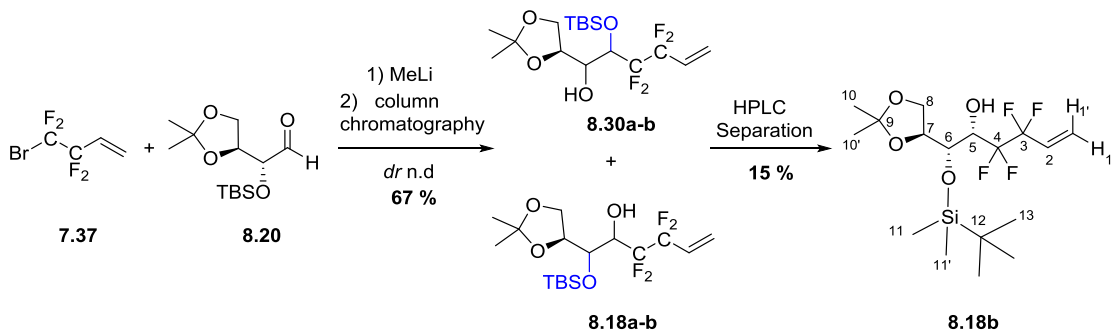


To a stirred solution of **8.28** (682 mg, 2.14 mmol) in DCM (10 mL) at -78 °C was added DIBAL (1.0 M in heptane, 3.21 mL, 3.21 mmol, 1.5 equiv) over a period of 20 min. The reaction mixture was stirred at this temperature for further 6 h, before quenching with a solution of NaOH 2% at -78°C. The mixture was allowed to warm up at rt, after which H_2O and DCM were added to the mixture, followed by a saturated solution of sodium potassium tartrate. The aqueous phase was extracted with DCM, and the combined organic layers were washed with water, dried over $MgSO_4$ and concentrated *in vacuo*.

Filtration over silica (petroleum ether/EtOAc 92:8) gave aldehyde **8.20** as colourless oil (587 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (1H, d, $^{3}J_{HH}$ 1.3 Hz, H_1), 4.31 (1H, ddd appeared as td, $^{3}J_{HH}$ 6.2 Hz, $^{3}J_{HH}$ 4.7 Hz, H_3), 4.07 (1H, dd, $^{3}J_{HH}$ 8.7 Hz, $^{3}J_{HH}$ 6.7 Hz, H_4), 4.05 (1H, dd, $^{3}J_{HH}$ 4.8 Hz, $^{3}J_{HH}$ 1.3 Hz, H_2), 3.94 (1H, dd, $^{3}J_{HH}$ 8.7 Hz , $^{3}J_{HH}$ 6.2 Hz, $H_{4'}$), 1.42 (3H, s, H_6 or $H_{6'}$), 1.34 (3H, s, $H_{6'}$ or H_6), 0.93 (9H, s, H_8), 0.11 (3H, s, H_7 or $H_{7'}$), 0.09 (3H, s, $H_{7'}$ or H_7) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.3 (C_1), 109.8 (C_5), 77.8 (C_2 or C_3), 76.5 (C_3 or C_2), 65.1 (C_4), 26.1 (C_6 or $C_{6'}$), 25.7 (C_8), 25.1 ($C_{6'}$ or C_6), 18.3 (C_9), -4.7 (C_7 or $C_{7'}$), -5.1 ($C_{7'}$ or C_7) ppm. NMR spectra correspond with the reported data.[127]

10.7.4 Coupling reaction with the α-TBS-protected aldehyde

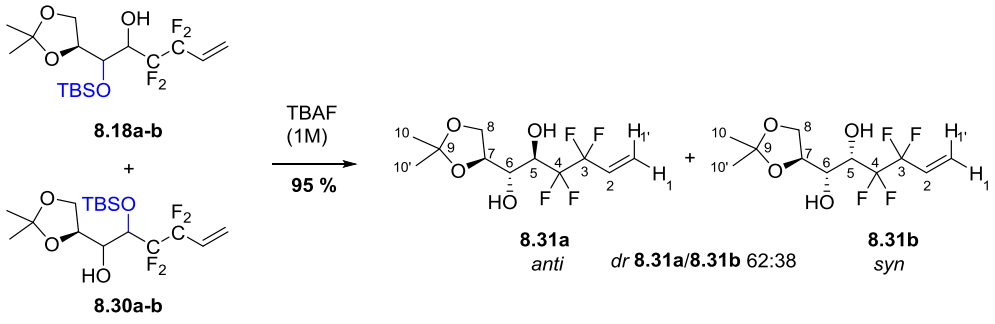


Compounds **7.37** (94 µL, 0.74 mmol, 1 equiv.) and **8.20** (486 mg, 1.78 mmol, 2.4 equiv.) were dissolved in THF (3 mL) at rt. The resulting solution was cooled to -78 °C and stirred for 10 min at this temperature, after which a solution of MeLi (1.5 M in Et_2O, 1.2 mL, 1.78 mmol, 2.4 equiv.) was added dropwise at -78 °C. The mixture was stirred at -78 °C for further 2 h, and was quenched at this temperature with a saturated solution of NH_4Cl. The reaction mixture was extracted with EtOAc three times. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. In order to enable separation of the coupling adducts from the remaining aldehyde, the residue was dissolved in EtOH, and an excess of $NaBH_4$ was added at 0 °C. The reaction mixture was stirred overnight at rt, and was then quenched with a saturated solution of NH_4Cl. The mixture was extracted with EtOAc three times. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/EtOAc 90:10) gave a mixture of adducts **8.18a** and **8.18b**, **8.30a** and

8.30b (201 mg, 67% overall). Subsequent HPLC (hexane/EtOAc 92:8) enabled isolation of **8.18b** as a single isomer (46 mg, 15 %).

[α]$_D$ -19.1 (c 0.76, $CHCl_3$, 21°C); **IR** (neat) 3501 (w, br.), 2933 (w, br.), 2858 (w), 1255 (m), 1119 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.16 – 5.98 (1H, m, H_2), 5.94 – 5.80 (1H, m, with the presence of $^3J_{HHtrans}$ 17.0 Hz, $H_{1'}$), 5.67 (1H, d, $^3J_{HHcis}$ 11.0 Hz, H_1), 4.24 (1H, dd, $^3J_{HH}$ 5.7 Hz, $^3J_{HH}$ 1.5 Hz, H_6), 4.17 (1H, app. q, *J* 6.5 Hz, H_7), 4.08 – 3.89 (1H, m, H_4) , 4.00 (1H, dd, $^2J_{HH}$ 8.6 Hz, $^3J_{HH}$ 6.4 Hz, H_8), 3.93 (1H, dd, $^2J_{HH}$ 8.6 Hz, $^3J_{HH}$ 7.0 Hz, $H_{8'}$), 3.33 (1H, d, $^3J_{HH}$ 10.2 Hz, O<u>H</u>-5), 1.45 (3H, s, H_{10} or $H_{10'}$), 1.36 (3H, s, H_{10} or $H_{10'}$), 0.91 (9H, s, H_{13}), 0.18 (3H, s, H_{11} or $H_{11'}$), 0.14 – 0.13 (3H, m, H_{11} or $H_{11'}$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 127.3 (t, $^2J_{CF}$ 24.9 Hz, C_2), 123.2 (t, $^2J_{CF}$ 9.5 Hz, C_1), 109.6 (C_9), 76.6 (C_7), 68.6 (C_6), 66.3 (dd, $^2J_{CF}$ 29.3 Hz, $^2J_{CF}$ 20.5 Hz, C_5), 65.2 (C_8), 26.3 (C_{10} or $C_{10'}$), 25.8 (C_{13}), 25.0 (C_{10} or $C_{10'}$), 18.1 (C_{12}), -4.2 (C_{11} or $C_{11'}$), -5.3 (C_{11} or $C_{11'}$) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.9 (1F, dd, $^2J_{FF}$ 262.2 Hz, $^3J_{FH}$ 9.7 Hz, simplified as d, $^2J_{FF}$ 262.2 Hz upon proton decoupling), -115.7 (1F, ddd, $^2J_{FF}$ 263.3 Hz, $^3J_{FH}$ 11.8 Hz, $^3J_{FF}$ 6.5 Hz, simplified as dd, $^2J_{FF}$ 263.3 Hz, $^3J_{FF}$ 6.5 Hz upon proton decoupling), -122.3 (1F, br. d, $^2J_{FF}$ 270.8 Hz, appeared as dd, $^2J_{FF}$ 270.8 Hz, $^3J_{FF}$ 6.5 Hz upon proton decoupling), -129.7 (1F, dd, $^2J_{FF}$ 270.8 Hz, $^3J_{FH}$ 22.6 Hz, simplified as d, $^2J_{FF}$ 270.8Hz, upon proton decoupling) ppm; **HRMS** (ESI^+) for $C_{17}H_{30}F_4O_4Si$ $[M+Na]^+$ calcd 425.1742, found 425.1750.

10.7.5 TBAF treatment of the mixture of coupling adducts

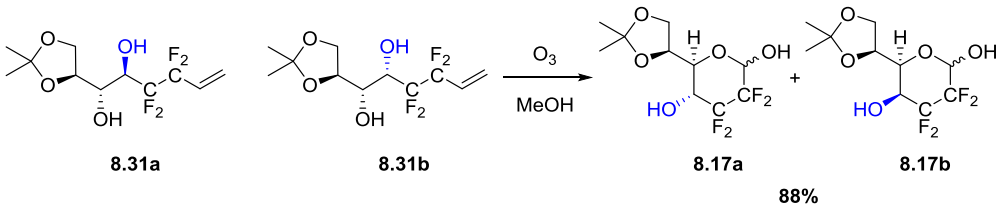


To a mixture of **8.19a**, **8.19b** **8.30a** and **8.30b** (*dr* n.d, 585 mg, 1.45 mmol, 1equiv.), dissolved in THF (6 mL) was added dropwise a solution of TBAF (1 M in THF, 2.2 mL, 2.18 mmol, 1.5 equiv.) at rt. The mixture was stirred at this temperature for 2 h, and was then concentrated *in vacuo* to give the crude products **8.31** as a mixture of diastereoisomers

(*dr* **8.31a**/**8.31b** 62:38). Purification by column chromatography (pentane/acetone 9:1) afforded diols **8.31a** and **8.31b** as a mixture of diastereoisomers (398 mg, 95 %).

IR (neat) 3444 (w, br.), 2990 (w), 2933 (w, br.), 1217 (m, br.), 1066 (s, br.), 1062 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.17 – 5.98 (2H, m, $H_{2,}$ *syn and anti*), 5.95 – 5.84 (2H, m, $H_{1',}$ *syn and anti*), 5.71 (1H, d, $^{3}J_{HHcis}$ 10.6 Hz, H_1, *anti*), 5.69 (1H, d, $^{3}J_{HHcis}$ 10.2 Hz, H_1, *syn*), 4.50 (1H, ddd appeared as td, $^{3}J_{HH}$ 6.7 Hz, $^{3}J_{HH}$ 2.3 Hz, H_7, *anti*), 4.39 – 4.22 (2H, m, H_5, *anti*, H_7, *syn*), 4.14 – 3.94 (5H, m, H_5 *syn*, H_8, $H_{8'}$, *syn and anti*), 3.94 – 3.86 (2H, m, H_6, *syn and anti*), 3.36 (1H, d, $^{3}J_{HH}$ 9.3 Hz, OH, *anti*), 3.32 (1H, d, $^{3}J_{HH}$ 7.6 Hz, OH, *syn*), 2.83 – 2.70 (2H, m, OH, *syn and anti*), 1.47 (6H, s, H_{10} or H_{10}, *syn and anti*), 1.39 (6H, s, $H_{10'}$ or $H_{10'}$, *syn and anti*) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 127.1 (t, $^{2}J_{CF}$ 24.0 Hz, $C_{2,}$ *syn*), 126.7 (t, $^{2}J_{CF}$ 24.0 Hz, $C_{2,}$ *anti*), 123.8 (t, $^{2}J_{CF}$ 10.2 Hz, $C_{2,}$ *anti*), 123.5 (t, $^{2}J_{CF}$ 24.0 Hz, $C_{2,}$ *syn*), 110.2 (C_9, *syn*), 110.1 (C_9, *anti*), 76.9 (C_7, *syn* (DEPT 135)), 75.9 (C_7, *anti*), 72.0 (dd, $^{2}J_{CF}$ 27.8 Hz, $^{2}J_{CF}$ 22.0 Hz, C_5, *anti*), 69.0 (dd, $^{2}J_{CF}$ 29.3 Hz, $^{2}J_{CF}$ 23.4 Hz, C_5, *syn*), 67.8 (C_6, *syn*), 67.2 (C_6, *anti*), 66.0 (C_8, *anti*), 65.7 (C_8, *syn*), 26.5 (C_{10} or $C_{10'}$, *syn*), 26.1 (C_{10} or $C_{10'}$, *anti*), 25.2 (C_{10} or $C_{10'}$, *syn*), 25.0 (C_{10} or $C_{10'}$, *anti*) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.7 (1F, dd, $^{2}J_{FF}$ 263.3 Hz, $^{3}J_{FH}$ 11.8 Hz, simplified as d, $^{2}J_{FF}$ 263.3 Hz upon proton decoupling, *syn*), -114.2 (1F, dd, $^{2}J_{FF}$ 264.3 Hz, $^{3}J_{FH}$ 11.9 Hz, simplified as d, $^{2}J_{FF}$ 264.3 Hz upon proton decoupling, *anti*), -115.55 (1F, ddd, $^{2}J_{FF}$ 263.3 Hz, $^{3}J_{FH}$ 11.3 Hz, $^{3}J_{FF}$ 4.8 Hz, simplified as dd, $^{2}J_{FF}$ 263.3 Hz, $^{3}J_{FF}$ 4.8 Hz, upon proton decoupling, *syn*), -115.7 (1F, ddd, $^{2}J_{FF}$ 262.2 Hz, $^{3}J_{FH}$ 11.5 Hz, $^{3}J_{FF}$ 4.3 Hz simplified as dd, $^{2}J_{FF}$ 262.2 Hz, $^{3}J_{FF}$ 4.3 Hz, *anti*), -121.4 (1F, br. d, $^{2}J_{FF}$ 275.1 Hz, appeared as dd, $^{2}J_{FF}$ 274.0 Hz, $^{3}J_{FF}$ 6.5 Hz upon proton decoupling, *syn*), -123.6 (1F, br. d, $^{2}J_{FF}$ 274.0 Hz, appeared as dd, $^{2}J_{FF}$ 274.0 Hz, $^{3}J_{FF}$ 5.4 Hz upon proton decoupling, *anti*), -126.3 (1F, dd, $^{2}J_{FF}$ 275.1 Hz, $^{3}J_{FH}$ 20.4 Hz, simplified as d, $^{2}J_{FF}$ 275.1 Hz upon proton decoupling, *anti*), -128.3 (1F, dd, $^{2}J_{FF}$ 274.0 Hz, $^{3}J_{FH}$ 20.4 Hz, simplified as d, $^{2}J_{FF}$ 274.0 Hz upon proton decoupling, *syn*) ppm; **HRMS** (ESI^+) for $C_8H_{12}F_4O_4$ (loss of acetal group) $[M+Na]^+$ calcd 271.0564, found 271.0558.

10.7.6 Formation of 8.31a and 8.31b from 8.17a and 8.17b

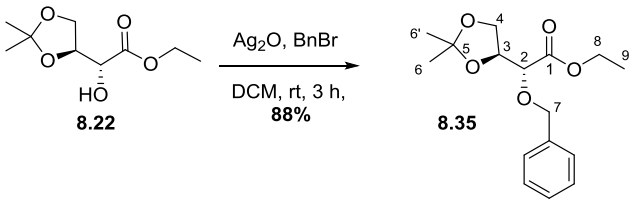


8.31a **8.31b** **8.17a** **8.17b**

88%

Ozone was bubbled through a solution of containing a mixture of **8.31a** and **8.31b** (*dr* **8.31a**/**8.31b** 90:10, 306 mg, 1.06 mmol, 1 equiv.) in MeOH (20 mL) at -78°C until the solution became blue (15 min). The excess of ozone was purged from the solution by bubbling oxygen through for 15 min. Dimethyl sulfide (560 µL, 7.6 mmol, 7 equiv.) was then added and the reaction was allowed to warm to rt over 1 h. The resulting mixture was then concentrated *in vacuo*. Purification by column chromatography (petroleum ether/Et_2O 55:45) gave a non-separable mixture of L-heptoses **8.17a** and **8.17b** (271 mg, 88 %).

10.7.7 Synthesis of α-Bn-protected ester 8.35



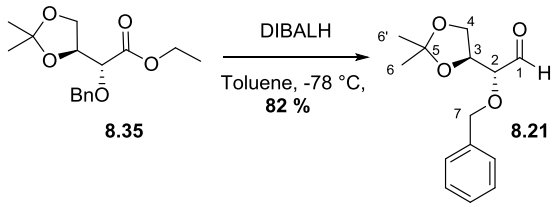
8.22 **8.35**

To a stirred solution of **8.22** (2.75 g, 13.5 mmol, 1 equiv.) in DCM (39 mL) at rt was added freshly prepared Ag_2O (4.7 g, 20.3 mmol, 1.5 equiv.) in one portion, followed by BnBr (1.9 mL, 16.2 mmol, 1.2 equiv.) dropwise. The mixture was stirred at this temperature for 3 h, before filtering through celite, and concentrating *in vacuo*. Purification by column chromatography (petroleum ether/EtOAc 90:10) afforded **8.35** as colourless oil (3.5 g, 88 %).

$[\alpha]_D$ 59 (c 1.6, $CHCl_3$, 26 °C), lit. 60 (1.6, $CHCl_3$, T not mentioned)[148]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.26 (5H, m, H_{Ar}), 4.79 (1H, d, $^2J_{HH}$ 12.0 Hz, H_7), 4.54 (1H, d, $^2J_{HH}$ 12.0 Hz, $H_{7'}$), 4.40 (1H, dd, $^3J_{HH}$ 12.3 Hz, $^3J_{HH}$ 5.9 Hz, H_3), 4.29 – 4.15 (2H, m, H_8), 4.06 – 3.92 (3H, m, H_2 and H_4), 1.41 (3H, s, H_6 or $H_{6'}$), 1.36 (3H, s, $H_{6'}$ or H_6), 1.31 (3H, br. t, *J* 7.2 Hz, H_9) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0 (C_1), 137.1 (C_{qAr}), 128.4 (2C, CH_{Ar}), 128.1 (2C, CH_{Ar}),

127.9 (CH_{Ar}), 109.8 (C_5), 78.6 (C_2), 75.9 (C_3), 72.7 (C_7), 65.5 (C_4), 61.1 (C_8), 26.3 (C_6), 25.3 ($C_{6'}$), 14.2 (C_9) ppm. NMR spectra correspond with the reported data.[148]

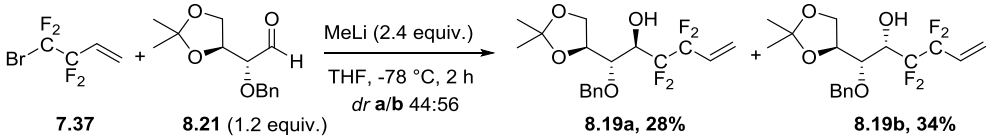
10.7.8 Synthesis of α-Bn-protected aldehyde 8.21



To a stirred solution of **8.35** (3.15 g, 10.7 mmol, 1 equiv.) in toluene (57 mL) at -78 °C was added DIBAL (1.2 M in toluene, 18.7 mL, 22.47 mmol, 2.1 equiv) dropwise. The reaction mixture was stirred at this temperature for 20 min, before immediately quenching with MeOH (5 mL). The mixture was allowed to warm up to rt, and a saturated solution of sodium potassium tartrate (5 mL) was added, followed by EtOAc (30 mL). The mixture was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then dissolved in DCM (50 mL), and a solution of NaOH was added (2%, 10 mL), as well as followed by a saturated solution of sodium potassium tartrate (10 mL). The resulting emulsion was stirred for 5 min at rt. The layers were then separated, and the aqueous phase was extracted with DCM (3×40 mL). Organic layers were combined, dried over $MgSO_4$ and concentrated. Filtration over silica (petroleum ether/EtOAc 80:20) gave aldehyde **8.21** as colourless oil (2.19 g, 82 %).

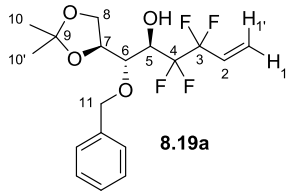
$[\alpha]_D$ 55 (c 1.04, $CHCl_3$, 23 °C), lit. 44 (c 1.1, $CHCl_3$, T not mentioned)[148]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.73 (1H, d, $^3J_{HH}$ 1.6 Hz, H_1), 7.62 – 7.21 (5H, m, H_{Ar}), 4.79 (1H, d, $^2J_{HH}$ 12.0 Hz, H_7), 4.67 (1H, d, $^2J_{HH}$ 11.9 Hz, $H_{7'}$), 4.38 (1H, ddd, $^3J_{HH}$ 6.7 Hz, $^3J_{HH}$ 6.1 Hz, $^3J_{HH}$ 5.4 Hz, H_3), 4.07 (1H, dd, $^2J_{HH}$ 8.4 Hz, $^3J_{HH}$ 6.7 Hz, H_4), 3.96 (1H, dd, $^2J_{HH}$ 8.8 Hz, $^3J_{HH}$ 6.7 Hz, $H_{4'}$), 3.86 (1H, dd, $^3J_{HH}$ 5.4 Hz, $^3J_{HH}$ 1.6 Hz, H_2), 1.44 (3H, s, H_6 or $H_{6'}$), 1.36 (3H, s, $H_{6'}$ or H_6) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.9 (C_1), 136.9 (C_{qAr}), 128.5 (2C, CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (2C, CH_{Ar}), 109.8 (C_5), 82.8 (C_2), 75.3 (C_3), 73.3 (C_7), 65.3 (C_4), 26.1 (C_6), 25.0 ($C_{6'}$) ppm. NMR spectra correspond with the reported data.[148]

10.7.9 Coupling reaction with the α-Bn-protected aldehyde



7.37 **8.21** (1.2 equiv.) **8.19a, 28%** **8.19b, 34%**

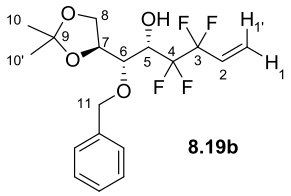
Compounds **7.37** (922 µL, 7.25 mmol, 1 equiv.) and **8.21** (2.17 g, 8.7 mmol, 1.2 equiv.) were dissolved in THF (29 mL). The resulting solution was cooled to -78 °C and stirred for 10 min at this temperature, after which a solution of MeLi (1.6 M in Et_2O, 10.9 mL, 17.4 mmol, 2.4 equiv.) was added at -78 °C during 30 min, using a syringe pump. The mixture was stirred at -78 °C for further 2 h, and was quenched at this temperature with a saturated solution of NH_4Cl. The reaction mixture was extracted with EtOAc three times. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. In order to enable separation of the coupling adducts from the remaining aldehyde, the residue was dissolved in EtOH, and $NaBH_4$ (274 mg, 7.25 mmol, 1 equiv.) was added at 0 °C. The reaction mixture was stirred overnight at rt, and then quenched with a saturated solution of NH_4Cl. The mixture was extracted with EtOAc three times. The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum to give the crude coupling adducts as a mixture of diastereoisomers (*dr* **8.19a/8.19b** 44:56). Purification by column chromatography (hexane/EtOAc 80:20) followed by HPLC (hexane/EtOAc 85:15) afforded compounds **8.19a** (775 mg, 28%), and **8.19b** (936 mg, 34 %) as colourless oils.



8.19a

$[\alpha]_D$ 24.1 (c 0.41, $CHCl_3$, 20 °C); **IR** (neat) 3421 (w, br.), 2983 (w), 2896 (w), 1127 (m), 1096 (s, br.), 1077 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (5H, m, H_{Ar}), 6.18 – 6.00 (1H, m, H_2), 5.93 –5.84 (1H, m with the presence of $^3J_{HHtrans}$ 17.2 Hz, $H_{1'}$), 5.69 (1H, d, $^3J_{HHcis}$ 11.6 Hz, H_1), 4.77 (1H, d, $^2J_{HH}$ 11.5 Hz, H_{11}), 4.57 (1H, d, $^2J_{HH}$ 11.6 Hz, $H_{11'}$), 4.52 (1H, ddd appeared as td, $^3J_{HH}$ 6.7 Hz, $^3J_{HH}$ 3.0 Hz, H_7), 4.50 – 4.39 (1H, m, H_5), 4.09 (1H, d, $^3J_{HH}$ 7.7 Hz, O<u>H</u>-5), 4.01 (1H, dd, $^2J_{HH}$ 8.1 Hz, $^3J_{HH}$ 6.7 Hz, H_8), 3.95 (1H, dd, $^2J_{HH}$ 8.3 Hz, $^3J_{HH}$ 7.0 Hz, $H_{8'}$), 3.77 – 3.73 (1H, m, H_6), 1.48 (3H, s, H_{10} or $H_{10'}$), 1.37 (3H, s, H_{10} or $H_{10'}$) ppm; **^{13}C NMR** (100

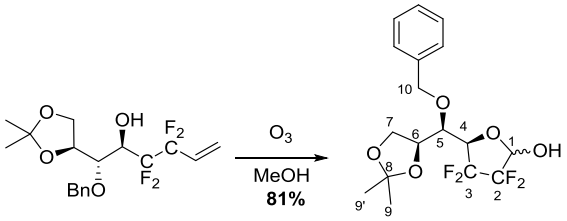
MHz, $CDCl_3$) δ 137.2 (C_{qAr}), 128.5 (2C, CH_{Ar}), 128.0 (3C, CH_{Ar}), 127.1 (t, $^2J_{CF}$ 24.9 Hz, C_2), 123.3 (t, $^2J_{CF}$ 9.5 Hz, C_1), 110.2 (C_9), 77.7 (C_7, (DEPT 135)), 74.0 (C_6), 72.5 (C_{11}), 69.5 (dd, $^2J_{CF}$ 26.4 Hz, $^2J_{CF}$ 22.0 Hz, C_5), 65.7 (C_8), 25.9 (C_{10} or $C_{10'}$), 25.5 ($C_{10'}$ or C_{10}) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.8 (1F, dd, $^2J_{FF}$ 263.3 Hz, $^3J_{HF}$ 11.8 Hz, simplified as d, $^2J_{FF}$ 263.3 Hz upon proton decoupling), -115.7 (1F, ddd, $^2J_{FF}$ 263.3 Hz, $^3J_{HF}$ 12.9 Hz, $^3J_{FF}$ 6.5 Hz, simplified as dd, $^2J_{FF}$ 263.3 Hz, $^3J_{FF}$ 6.5 Hz upon proton decoupling), -123.0 (1F, br. d, $^2J_{FF}$ 270.8 Hz, appeared as dd, $^2J_{FF}$ 270.8 Hz, $^3J_{FF}$ 6.4 Hz upon proton decoupling), -126.4 (1F, dd, $^2J_{FF}$ 270.8 Hz, $^3J_{FF}$ 21.5 Hz, simplified as d, $^2J_{FF}$ 270.8 Hz upon proton decoupling) ppm; **HRMS** (ESI^+) for $C_{18}H_{22}F_4O_4$ $[M+Na]^+$ calcd. 401.1346, found. 401.1353.



8.19b

[α]$_D$ -1.0 (c 0.49, $CHCl_3$, 20 °C); **IR** (neat) 3516 (w, br.), 2975 (w), 2933 (w, br.), 2205 (m, br.), 1221 (m), 1107 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (5H, m, H_{Ar}), 6.19 – 5.99 (1H, m, H_2), 5.94 – 5.83 (1H, m, $^3J_{HH}$*trans* 17.2 Hz, $H_{1'}$), 5.68 (1H, d, $^3J_{HH}$*cis* 11.0 Hz, H_1), 4.80 (1H, d, $^2J_{HH}$ 10.9 Hz, H_{11}), 4.72 (1H, d, $^2J_{HH}$ 10.6 Hz, $H_{11'}$), 4.33 (1H, dd, $^3J_{HH}$ 12.9 Hz, $^3J_{HH}$ 6.40 Hz, H_7), 4.11 – 3.86 (2H, m, H_5 and H_6), 4.04 (1H, dd, $^2J_{HH}$ 8.5 Hz, $^3J_{HH}$ 6.6 Hz, H_8), 3.91 (1H, dd, $^2J_{HH}$ 8.7 Hz, $^3J_{HH}$ 6.4 Hz, $H_{8'}$), 3.26 (1H, d, $^3J_{HH}$ 10.2 Hz, O<u>H</u>-5), 1.46 (3H, s, H_{10} or $H_{10'}$), 1.38 (3H, s, H_{10} or $H_{10'}$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.2 (C_{qAr}), 128.5 (2C, CH_{Ar}), 128.3 (2C, CH_{Ar}), 128.2 (CH_{Ar}), 127.3 (t, $^2J_{CF}$ 24.6 Hz, C_2), 123.3 (t, $^2J_{CF}$ 9.5 Hz, C_1), 109.8 (C_9), 76.0 (C_7), 75.0 (C_6), 74.3 (C_{11}), 67.2 (dd, $^2J_{CF}$ 30.7 Hz, $^2J_{CF}$ 23.4 Hz, C_5), 65.5 (C_8), 26.5 (C_{10} or $C_{10'}$), 25.1 ($C_{10'}$ or C_{10}) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.6 (1F, dd, $^2J_{FF}$ 263.3 Hz, $^3J_{HF}$ 10.8 Hz, simplified as d, $^2J_{FF}$ 263.3 upon proton decoupling), -115.6 (1F, ddd, $^2J_{FF}$ 263.3 Hz, $^3J_{FH}$ 12.9 Hz, $^3J_{FF}$ 6.3 Hz, simplified as dd, $^2J_{FF}$ 263.3 Hz, $^3J_{FF}$ 6.3 Hz upon proton decoupling), -121.2 (1F, br. d, $^2J_{FF}$ 270.8 Hz appeared as dd, $^2J_{FF}$ 270.8 Hz, $^3J_{FF}$ 6.5 Hz, upon proton decoupling), -129.6 (1F, dd, $^2J_{FF}$ 270.8 Hz, $^3J_{FF}$ 21.5 Hz, simplified as d, $^2J_{FF}$ 270.8Hz upon proton decoupling) ppm; **HRMS** (ESI^+) for $C_{18}H_{22}F_4O_4$ $[M+Na]^+$ calcd. 401.1346, Found. 401.1355.

10.7.10 Synthesis of L-2,2,3,3-tetrafluoro-heptofuranose 8.36a



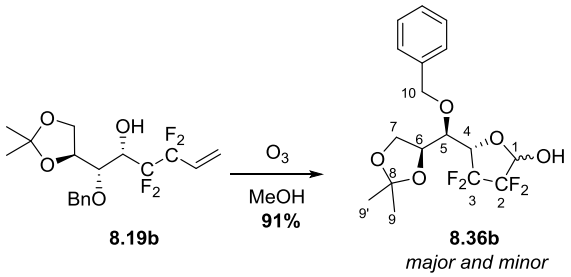
8.19a **8.36a** *major and minor*

Ozone was bubbled through a solution of **8.19a** (278 mg, 0.73 mmol, 1 equiv.) in MeOH (13 mL) at -78 °C until the solution became blue (5 min). The excess of ozone was purged from the solution by bubbling oxygen through for 20 min. Dimethyl sulfide (270 µL, 3.65 mmol, 5 equiv.) was added and the reaction was allowed to warm to rt over 1 h. The resulting mixture was then concentrated *in vacuo*. Filtration over silica (petroleum ether/acetone 8:2) gave heptofuranose **8.36a** as a white solid (224 mg, 81%, *ar* 55:45).

IR (neat) 3327 (w, br), 2983 (w), 2937 (w, br.), 2359 (w, br.), 1134 (m, br), 1066 (s), 1032 (s) cm^{1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.46 – 7.23 (10H, m, H_{Ar}, *major and minor*), 7.16 – 6.90 (2H, m, OH-1, *major and minor*), 5.56 (1H, dd, $^{3}J_{HF}$ 7.8 Hz, $^{3}J_{HF}$ 3.3 Hz, H_1, *major*), 5.46 (1H, dd, $^{3}J_{HF}$ 8.0 Hz, $^{3}J_{HF}$ 2.4 Hz, H_1, *minor*), 4.96 – 4.89 (2H, m, $H_{10,}$ *major and minor*), 4.76 – 4.68 (2H, m, $H_{10,}$ *major and minor*), 4.47 – 4.17 (4H, m, H_4 and H_6, *major and minor*), 4.09 (1H, dd, $^{2}J_{HH}$ 8.7 Hz, $^{3}J_{HH}$ 6.3 Hz, H_7, *minor*), 4.08 (1H, dd, $^{2}J_{HH}$ 8.8 Hz, $^{3}J_{HH}$ 6.4 Hz, H_7, *major*), 3.94 (1H, dd, $^{2}J_{HH}$ 8.8 Hz, $^{3}J_{HH}$ 7.1 Hz, $H_{7'}$, *minor*), 3.91 (1H, dd, $^{2}J_{HH}$ 8.7 Hz, $^{3}J_{HH}$ 6.8 Hz, $H_{7'}$, *major*), 3.87 (1H, dd, $^{3}J_{HH}$ 9.4 Hz, $^{3}J_{HH}$ 5.7 Hz, H_5, *minor*), 3.82 (1H, dd, $^{3}J_{HH}$ 9.4 Hz, $^{3}J_{HH}$ 4.9 Hz, H_5, *major*), 1.39 (6H, s, H_9 or $H_{9'}$, *major and minor*), 1.33 (6H, s, H_9 or $H_{9'}$, *major and minor*) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 139.32 (C_{qAr}, *minor*), 139.25 (C_{qAr}, *major*), 129.0 (4C, CH_{Ar}, *major and minor*), 128.6 (4C, CH_{Ar}, *major and minor*), 128.4 (2C, CH_{Ar}, *major and minor*), 122.5 – 113.0 (4C, m, CF_2, *major and minor*), 109.7 (C_8, *major*), 109.5 (C_8, *minor*), 95.4 (2C, dd, $^{3}J_{CF}$ 39.5 Hz, $^{3}J_{CF}$ 22.0 Hz, C_1, *major and minor*), 78.7 – 76.8 (6C, m, C_4, C_5, C_6, *major and minor*), 75.2 (C_7, *major*), 75.1 (C_7, *minor*), 66.7 (C_{10}, *minor*), 66.6 (C_{10}, *major*), 26.6 (2C, C_9, *major and/or minor*), 26.04 ($C_{9'}$, *major or minor*), 26.01 ($C_{9'}$, *major or minor*) ppm; **^{19}F NMR** (286 MHz, acetone-d_6) δ -113.8 (1F, dd, $^{2}J_{FF}$ 240.7 Hz, $^{3}J_{FF}$ 8.6 Hz, *major*), -122.5 (1F, d, $^{2}J_{FF}$ 245.0 Hz, *minor*), -123.97 – -125.12 (1F, m with the presence of $^{2}J_{FF}$ 245 Hz, *minor*), -125.29 – -127.51 (1F, m with the presence of $^{2}J_{FF}$ 245 Hz, *minor*), -126.8 (1F, dd, $^{2}J_{FF}$ 245 Hz, ^{3}J 8.6 Hz, *major*), -129.0 (1F, d, $^{2}J_{FF}$ 245.0 Hz, *major*), -131.9 (1F, dd, $^{2}J_{FF}$ 240.7 Hz, ^{3}J 17.2 Hz, *minor*), -136.2 (1F, d, $^{2}J_{FF}$ 245.0 Hz, *major*)

ppm; **MS** (ESI^-) (m/z) 415 $[M.HCl-H]^-$; **HRMS** (ESI^+) for $C_{17}H_{20}F_4O_5$ $[M+Na]^+$ calcd 403.1139, found 403.1140.

10.7.11 Synthesis of L-2,2,3,3-tetrafluoro-heptofuranose 8.36b



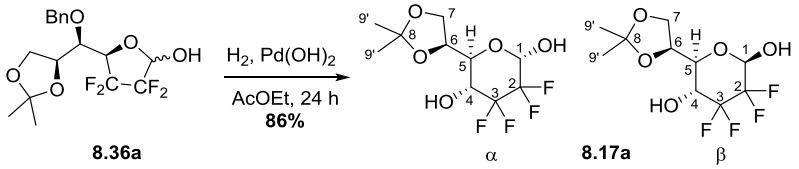
8.19b → **8.36b** *major and minor*

Ozone was bubbled through a solution of **8.19b** (144 mg, 0.38 mmol, 1 equiv.) in MeOH (7 mL) at -78 °C until the solution became blue (4 min). The excess of ozone was purged from the solution by bubbling oxygen through for 10 min. Dimethyl sulfide (140 µL, 1.9 mmol, 5 equiv.) was added and the reaction was allowed to warm to rt over 1 h. The resulting mixture was then concentrated in vacuo. Filtration over silica (petroleum ether/acetone 8:2) gave heptofuranose **8.36b** as a white solid (133 mg, 91 %, *ar* 68:32).

IR (neat) 3357 (w, br), 2990 (w), 2930 (w, br.), 1121 (m, br), 1128 (s, br), 1069 (s, br.), 1016 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.50 – 7.20 (10H, m, H_{Ar}, *major and minor*), 6.93 (1H, d, $^3J_{HH}$ 5.8 Hz, OH-1, *major*), 6.63 (1H, d, $^3J_{HH}$ 8.5 Hz, OH-1, *minor*), 5.66 – 5.56 (1H, m, H_1, *major*), 5.44 (1H, dddd appeared as tt, $^3J_{HF}$, $^3J_{HH}$ 8.7 Hz, $^3J_{HF}$, $^4J_{HF}$ 2.4 Hz, H_1, *minor*), 4.88 (1H, d, $^2J_{HH}$ 11.2 Hz, H_{10}, *minor*), 4.81 (1H, d, $^2J_{HH}$ 11.1 Hz, $H_{10'}$, *minor*), 4.80 (1H, d, $^2J_{HH}$ 11.4 Hz, H_{10}, *major*), 4.76 (1H, d, $^2J_{HH}$ 11.2 Hz, $H_{10'}$, *major*), 4.63 (1H, ddd, $^3J_{HF}$ 15.6 Hz, *J* 11.3 Hz, *J* 5.5 Hz, H_4), 4.56 – 4.44 (1H, m, H_4, *minor*), 4.43 – 4.32 (2H, m, H_6, *major and minor*), 4.07 (1H, dd, $^2J_{HH}$ 8.5 Hz, $^3J_{HH}$ 6.6 Hz, H_8, *minor*), 4.05 (1H, dd, $^2J_{HH}$ 8.3 Hz, $^3J_{HH}$ 6.7 Hz, H_8, *major*), 3.99 (1H, dd, $^2J_{HH}$ 8.2 Hz, $^3J_{HH}$ 6.8 Hz, $H_{8'}$, *major*), 3.97 (1H, dd, $^2J_{HH}$ 8.3 Hz, $^3J_{HH}$ 7.0 Hz, $H_{8'}$, *minor*), 3.94 – 3.90 (2H, m, H_5, *major and minor*), 1.40 – 1.37 (6H, s, H_9 or $H_{9'}$, *major and minor*), 1.34 – 1.30 (6H, s, $H_{9'}$ or H_9, *major and minor*) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 139.5 (C_{qAr}, *major*), 139.1 (C_{qAr}, *minor*) 129.2 (CH_{Ar}, *major and/or minor*), 129.1 (CH_{Ar}, *major and/or minor*), 129.0 (CH_{Ar}, *major and/or minor*), 128.7 (CH_{Ar}, *major and/or minor*), 128.4 (CH_{Ar}, *major and/or minor*), 110.3 (C_8, *minor*), 110.2 (C_8, *major*), 96.2 (dd, $^3J_{CF}$ 41.0 Hz, $^3J_{CF}$ 20.5 Hz, C_1, *minor*), 95.8 (dd, $^3J_{CF}$ 39.5 Hz, $^3J_{CF}$ 20.5 Hz, C_1, *minor*), 79.3 (dd, $^3J_{CF}$ 27.8 Hz, $^3J_{CF}$ 22.0 Hz, C_4, *minor*), 78.7 (dd, $^3J_{CF}$ 27.8 Hz, $^3J_{CF}$ 22.0 Hz, C_4, *minor*), 77.2 (C_5, *minor*), 76.7 (C_5, *major*), 76.1 (C_6, *minor*), 75.9 (C_6, *major*), 75.6 (C_{10},

minor), 75.2 (C_{10}, *major*), 66.2 (C_7, *major and minor*), 26.7 (C_9 or $C_{9'}$, *major and minor*), 25.85 (C_9 or $C_{9'}$, *minor*), 25.80 (C_9 or $C_{9'}$, *major*) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, acetone-d_6) δ -115.5 (1F, dd, $^2J_{FF}$ 245.0 Hz, ^3J 12.0 Hz, *major*), -122.7 (1F, d, $^2J_{FF}$ 245.0 Hz, ^3J 12.9 Hz, *minor*), -125.8 – -128.4 (3F, m, 2F *minor*, 1F *major*), -130.4 (1F, d, $^2J_{FF}$ 240.7 Hz, *major*), -131.7 (1F, dd, $^2J_{FF}$ 240.7 Hz, ^3J 17.2 Hz, *major*), -133.9 (1F, d, $^2J_{FF}$ 249.3 Hz, *major*) ppm; **MS** (ESI^-) (m/z) 379 $[M-H]^-$; **HRMS** (ESI^+) for $C_{17}H_{20}F_4O_5$ $[M+Na]^+$ calcd 403.1139, found 403.1143.

10.7.12 Synthesis of gluco configured L-heptopyranose 8.17a

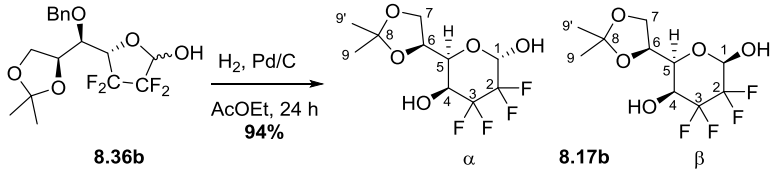


Heptofuranose **8.36a** (376 mg, 0.99 mmol, 1 equiv.) was dissolved in EtOAc (8 mL). $Pd(OH)_2/C$ (20% wt, 140 mg, 0.2 mmol, 20 mol%) was added and the resultant mixture was flushed with H_2. Stirring under an atmosphere of H_2 was continued at rt for 24 h, before the mixture was filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/acetone 7:3) gave heptopyranose **8.17a** as a white solid (247 mg, 86%, *ar* 52:48).

IR (neat) 3323 (m, br.), 2912 (w), 1107 (s, br.). 1070 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 6.84 (1H, d, $^3J_{HH}$ 8.3 Hz, OH-1β), 6.71 (1H, d, $^3J_{HH}$ 5.1 Hz, OH-1α), 5.53 (1H, d, $^3J_{HH}$ 7.1 Hz, OH-4β), 5.43 (1H, d, $^3J_{HH}$ 6.4 Hz, OH-4α), 5.36 (1H, ddd appeared as dt, $^3J_{HF}$ 8.7 Hz, $^3J_{HH}$, $^3J_{HF}$ 4.7 Hz, $H_{1\alpha}$), 5.04 (1H, ddd, $^3J_{HF}$ 15.5 Hz, $^3J_{HH}$ 8.2 Hz, $^3J_{HF}$ 2.7 Hz, $H_{1\beta}$), 4.50 (1H, ddd appeared as td, $^3J_{HH}$ 6.8 Hz, $^3J_{HH}$, 2.3 Hz, $H_{6\alpha}$), 4.44 (1H, ddd appeared as td, $^3J_{HH}$ 6.9 Hz, $^3J_{HH}$, 2.9 Hz, $H_{6\beta}$), 4.13 – 4.02 (5H, m, $H_{4\alpha+\beta,}$ $H_{5\alpha}$, $H_{7\beta}$, $H_{7'\beta}$), 3.99 (1H, dd, $^2J_{HH}$ 8.1 Hz, $^3J_{HH}$ 7.0 Hz, $H_{7\alpha}$), 3.93 (1H, dd, $^2J_{HH}$ 8.0 Hz, $^3J_{HH}$ 6.7 Hz, $H_{7'\alpha}$), 3.59 (1H, dd, $^3J_{HH}$ 10.0 Hz, $^3J_{HH}$ 2.9 Hz, $H_{5\beta}$), 1.35 – 1.32 (6H, m, $H_{9\alpha+\beta}$) , 1.29 (6H, s, $H_{9'\alpha+\beta}$) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 109.98 ($C_{8\alpha\ or\ \beta}$), 109.95 ($C_{8\alpha\ or\ \beta}$), 93.0 – 91.9 ($C_{1\alpha+\beta}$), 74.35 ($C_{1\beta}$), 74.30 ($C_{1\alpha}$), 73.6 (d, $^4J_{CF}$ 2.9 Hz, $C_{5\beta}$), 69.5 (d, $^4J_{CF}$ 4.4 Hz, $C_{5\alpha}$), 68.8 (t, $^3J_{CF}$ 19 Hz, $C_{4\alpha\ or\ \beta}$), 68.7 (t, $^3J_{CF}$ 19 Hz, $C_{4\alpha\ or\ \beta}$), 65.8 ($C_{7\alpha+\beta}$), 26.4 ($C_{9\alpha\ or\ \beta}$), 26.1 ($C_{9\alpha\ or\ \beta}$), 26.0 ($C_{9'\alpha+\beta}$) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, acetone-d_6) δ -120.20 (1F, d, $^2J_{FF}$ 266.5 Hz, $F_{\alpha\ or\ \beta}$), -128.5 – -130.9 (2F, m, $F_{\alpha\ or\ \beta}$), -131.5 – -133.3 (2F, m, $F_{\alpha\ or\ \beta}$), -133.9 (1F, ddd appeared as dt, $^2J_{FF}$ 266.5 Hz, ^3J

12.9 Hz, $F_{\alpha or \beta}$), -136.8 (1F, ddd appeared as dt, $^2J_{FF}$ 258.0 Hz, ^3J 12.9 Hz, $F_{\alpha \text{ or } \beta}$), -138.9 – -140.9 (1F, m with the presence of $^2J_{FF}$ 258.0 Hz, $F_{\alpha \text{ or } \beta}$) ppm; **MS** ($ESI^-$) (m/z) 325 $[M.HCl-H]^-$; **HRMS** (ESI^+) for $C_{10}H_{14}F_4O_5$ $[M+Na]^+$ calcd 313.0670, found 313.0666.

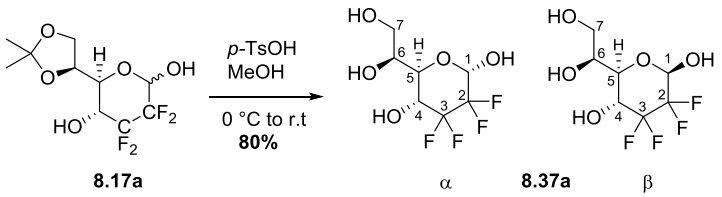
10.7.13 Synthesis of galacto configured L-heptopyranose 8.17b



Heptofuranose **8.36b** (110 mg, 0.29 mmol, 1 equiv.) was dissolved in EtOAc (5 mL). Pd/C (10% wt, 52 mg, 50 µmol, 17 mol%) was added and the resultant mixture was flushed with H_2. Stirring under an atmosphere of H_2 was continued at rt for 24 h before the mixture was filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/acetone 6:4) gave heptopyranose **8.17b** as a white solid (79 mg, 94%, *ar* 55:45).

IR (neat) 3372 (m, br.), 2983 (w), 2930 (w, br.), 1372 (m). 1215 (m), 1117 (s, br.), 1048 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 6.83 (1H, d, $^3J_{HH}$ 8.3 Hz, O<u>H</u>-1β), 6.74 (1H, ddd appeared as dt, $^3J_{HH}$ 5.3 Hz, *J* 1.6 Hz O<u>H</u>-1α), 5.36 (1H, ddd appeared as dt, $^3J_{HF}$ 9.4 Hz, $^3J_{HF}$, $^3J_{HH}$ 5.7 Hz, $H_{1\alpha}$), 5.12 (1H, d, $^3J_{HH}$ 5.9 Hz, O<u>H</u>-4α or β), 5.03 (1H, ddd, $^3J_{HF}$ 12.0 Hz, $^3J_{HH}$ 8.0 Hz, $^3J_{HH}$ 3.9 Hz, $H_{1\beta}$), 5.00 (1H, d, $^3J_{HH}$ 5.7 Hz, O<u>H</u>-4α or β), 4.48 – 4.37 (2H, m, $H_{6\alpha+\beta}$), 4.37 – 4.30 (1H, m, $H_{5\alpha \text{ or } \beta}$), 4.19 – 4.06 (4H, m, $H_{7\alpha+\beta}$, $H_{4\alpha+\beta}$), 3.89 (1H, dd, $^2J_{HH}$ 7.3 Hz, $^3J_{HH}$ 1.9 Hz, $H_{7'\alpha \text{ or } \beta}$), 3.87 (1H, dd, $^2J_{HH}$ 7.2 Hz, $^3J_{HH}$ 1.8 Hz, $H_{7'\alpha \text{ or } \beta}$), 3.84 – 3.78 (1H, m, $H_{5\alpha \text{ or } \beta}$), 1.36 (3H, s, $H_{9\alpha \text{ or } \beta}$), 1.35 (3H, s, $H_{9\alpha \text{ or } \beta}$), 1.34 – 1.30 (6H, $H_{9'\alpha+\beta}$) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 110.32 ($C_{8\alpha \text{ or } \beta}$), 110.25 ($C_{8\alpha \text{ or } \beta}$), 93.2 – 92.1 ($C_{1\alpha+\beta}$), 76.2 ($C_{6\alpha \text{ or } \beta}$), 76.1 ($C_{6\alpha \text{ or } \beta}$), 76.0 (d, $^4J_{CF}$ 5.9 Hz, $C_{5\alpha \text{ or } \beta}$), 71.1 – 70.1 (m, $C_{4\alpha+\beta}$), 70.8 (d, $^4J_{CF}$ 5.9 Hz, $C_{5\alpha \text{ or } \beta}$), 66.2 ($C_{7\alpha \text{ or } \beta}$), 66.1 ($C_{7\alpha \text{ or } \beta}$), 26.92 ($C_{9\alpha \text{ or } \beta}$), 26.89 ($C_{9\alpha \text{ or } \beta}$), 26.01 ($C_{9'\alpha \text{ or } \beta}$), 25.95 ($C_{9'\alpha \text{ or } \beta}$) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282MHz, acetone-d_6) δ -117.1 – -117.8 (1F, m, $F_{\alpha \text{ or } \beta}$), -118.1 – -118.7 (1F, m, $F_{\alpha \text{ or } \beta}$), -119.5 (1F, d, $^2J_{FF}$ 266.5 Hz, $F_{\alpha \text{ or } \beta}$), -129.1 – -130.6 (1F, m, $F_{\alpha \text{ or } \beta}$), -131.4 – -132.8 (1F, m, $F_{\alpha \text{ or } \beta}$), -132.8 – -134.1 (1F, m, $F_{\alpha \text{ or } \beta}$), -135.7 – -138.0 (2F, m, $F_{\alpha \text{ or } \beta}$) ppm; **HRMS** ($ESI^+$) for $C_{10}H_{14}F_4O_5$ $[M+Na]^+$ calcd 313.0670, found 313.0670.

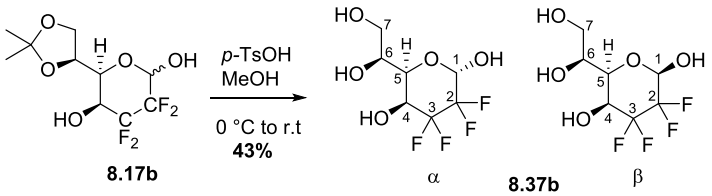
10.7.14 Synthesis of the fully deprotected L-heptose 8.37a



To a solution of **8.17a** (109 mg, 0.38 mmol, 1 equiv.) in MeOH (6 mL) at 0°C was added *p*-TsOH (11 mg, 60 µmol, 15 mol%). The mixture was stirred at rt for 16 h, then quenched with $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (EtOAc 100%) gave L-heptose **8.37a** as a white solid (76 mg, 80%, *ar* 54:46).

IR (neat) 3265 (m, br.), 2945 (w, br.), 1107 (s), 1064 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, methanol-d_4) δ 5.19 (1H, dd, $^3J_{FH}$ 8.3 Hz, $^3J_{FH}$ 4.2 Hz, $H_{1\alpha}$), 4.88 (1H, ddd appeared as t, $^3J_{FH}$ 15.5 Hz, $^3J_{FH}$, $^4J_{FH}$ 2.5 Hz, $H_{1\beta}$ (signal partially overlapped with the solvent peak)), 4.16 – 4.00 (3H, m, $H_{4\alpha+\beta}$, $H_{5\alpha\ or\ \beta}$), 3.96 (1H, ddd appeared as br. t, $^3J_{HH}$ 6.8 Hz, $H_{6\alpha}$), 3.91 (1H, ddd appeared as td, $^3J_{HH}$ 7.0 Hz, $^3J_{HH}$ 1.2 Hz, $H_{6\beta}$), 3.69 – 3.56 (5H, m, $H_{5\alpha\ or\ \beta}$, $H_{7\alpha+\beta}$) ppm; **^{13}C NMR** (100 MHz, methanol-d_4) δ 92.9 (d, $^2J_{CF}$ 36.7 Hz, $^2J_{CF}$ 27.1 Hz, $C_{1\alpha}$), 93.1 (d, $^2J_{CF}$ 27.1 Hz, $^2J_{CF}$ 19.1 Hz, $C_{1\beta}$), 74.1 (d, $^4J_{CF}$ 4.4 Hz, $C_{5\alpha\ or\ \beta}$), 70.3 – 70.0 (2C, m, $C_{5\alpha\ or\ \beta}$, $C_{6\alpha\ or\ \beta}$), 69.8 ($C_{6\alpha\ or\ \beta}$), 67.9 (app. t, $^3J_{CF}$ 19.8 Hz, $C_{4\alpha+\beta}$), 64.2 ($C_{7\alpha\ or\ \beta}$), 63.5 ($C_{7\alpha\ or\ \beta}$) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (376 MHz, methanol-d_4) δ -120.6 – -121.1 (1F, m with the presence of $^2J_{FF}$ 267.0 Hz, $F_{\alpha\ or\ \beta}$, simplified as dd, $^2J_{FF}$ 267.0 Hz, $^3J_{FF}$ 10.4 Hz upon proton decoupling), -131.4 – -129.7 (2F, m, $F_{\alpha\ or\ \beta}$ appeared as two distinct signals upon proton decoupling:-130.1 (1F, ddd appeared as dt, $^2J_{FF}$ 254.9 Hz, $^3J_{FF}$ 12.1 Hz), -131.6 (1F, dd, $^2J_{FF}$ 254.9 Hz, $^3J_{FF}$ 15.6 Hz)), -133.0 (1F, dddd appeared as dq, $^2J_{FF}$ 256.6 Hz, $^3J_{FF,}$ $^3J_{FH}$ 10.4 Hz, $F_{\alpha\ or\ \beta}$ simplified as dt, $^2J_{FF}$ 256.6 Hz, $^3J_{FF}$ 10.4 Hz upon proton decoupling), -133.7 (1F, ddd appeared as dt, $^2J_{FF}$ 254.9 Hz, *J* 15.6 Hz, $F_{\alpha\ or\ \beta}$, appeared as m, with the presence of $^2J_{FF}$ 254.9 Hz upon proton decoupling, -135.2 (1F, ddd, $^2J_{FF}$ 267.0 Hz, $^3J_{FF}$ 14.8 Hz, $^3J_{FF}$ 11.0 Hz, $F_{\alpha\ or\beta}$), -138.1 (1F, ddd, $^2J_{FF}$ 257.0 Hz, *J* 13.9 Hz, *J* 10.4 Hz $F_{\alpha\ or\ \beta}$ appeared as br. dt $^2J_{FF}$ 258.4 Hz, $^3J_{FF}$ 12.5 Hz upon proton decoupling), 141.23 – -140.40 (1F, m, $F_{\alpha\ or\ \beta}$, simplified as dd $^2J_{FF}$ 258.4 Hz, $^3J_{FF}$ 12.1 Hz upon proton decoupling) ppm; **HRMS** (ESI^+) for $C_7H_{10}F_4O_5$ $[M+Na]^+$ calcd 273.0357, found 273.0359.

10.7.15 Synthesis of the fully deprotected L-heptose 8.37b

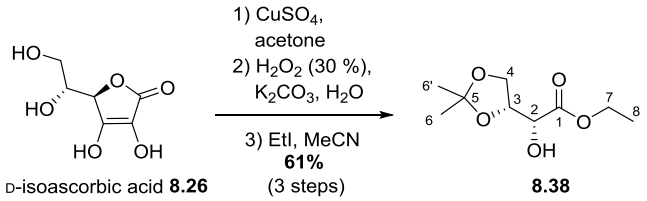


To a solution of **8.17b** (69 mg, 0.24 mmol, 1 equiv.) in MeOH (4 mL) at 0 °C was added *p*-TsOH (5 mg, 24 µmol, 10 mol%). The mixture was stirred at rt for 16 h, then quenched with $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (EtOAc 100%) gave L-heptose **8.37b** as a white solid (26 mg, 43%, *ar* 52:48).

IR (neat) 3318 (m, br.), 2922 (w, br.), 1149 (m), 1018 (s), 1065 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, methanol-d_4) δ 5.24 (1H, dd, $^3J_{FH}$ 9.5 Hz, $^3J_{FH}$ 6.5 Hz, $H_{1\alpha}$), 4.90 – 4.85 (1H, app. t, $^3J_{FH}$ 3.4 Hz, half of the signal overlapped with the solvent peak, $H_{1\beta}$), 4.38 – 4.33 (1H, m, $H_{5\alpha\ or\ \beta}$), 4.15 – 4.06 (2H, m, $H_{4\alpha+\beta}$), 3.96 – 3.89 (2H, m, $H_{6\alpha+\beta}$), 3.81 – 3.75 (1H, m, $H_{5\alpha\ or\ \beta}$), 3.72 (1H, dd, $^2J_{HH}$ 11.7 Hz, $^3J_{HH}$ 3.9 Hz, $H_{7\alpha or\beta}$), 3.71 (1H, dd, $^2J_{HH}$ 11.6 Hz, $^3J_{HH}$ 3.9 Hz, $H_{7\alpha or\beta}$), 3.65 (2H, dd, $^2J_{HH}$ 11.7 Hz, $^3J_{HH}$ 4.8 Hz, $H_{7'\alpha+\beta}$) ppm; **^{13}C NMR** (100 MHz, methanol-d_4) δ 94.2 – 92.7 (m, $C_{1\alpha+\beta}$), 76.0 (d, $^4J_{CF}$ 5.9 Hz, $C_{5\alpha\ or\ \beta}$), 72.7 (d, $^5J_{CF}$ 1.8 Hz, $C_{6\alpha\ or\ \beta}$), 72.5 (d, $^5J_{CF}$ 2.2 Hz, $C_{6\alpha\ or\ \beta}$), 71.1 (dd, $^3J_{CF}$ 32.3 Hz, $^3J_{CF}$ 20.5 Hz, $C_{4\alpha\ or\ \beta}$), 70.8 (dd, $^3J_{CF}$ 30.8 Hz, $^3J_{CF}$ 19.8 Hz, $C_{4\alpha\ or\ \beta}$), 70.5 (d, $^4J_{CF}$ 5.1 Hz, $C_{5\alpha\ or\ \beta}$), 63.6 ($C_{7\alpha\ or\ \beta}$), 63.5 ($C_{7\alpha\ or\ \beta}$) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (376 MHz, methanol-d_4) δ -120.3 – 119.01 (2F, m, $F_{\alpha\ or\ \beta}$, appeared as two distinct signals upon proton decoupling: -119.5 (1F, ddd, $^2J_{FF}$ 267.0 Hz, $^3J_{FF}$ 17.3 Hz, $^3J_{FF}$ 8.7 Hz), -119.9 (1F, ddd, $^2J_{FF}$ 268.8 Hz, $^3J_{FF}$ 13.9 Hz, $^3J_{FF}$ 6.9 Hz), -121.9 – -121.0 (1F, m, $F_{\alpha\ or\ \beta}$ simplified as ddd $^2J_{FF}$ 268.8 Hz, $^3J_{FF}$ 10.4 Hz, $^3J_{FF}$ 5.2 Hz upon proton decoupling), -132.3– -131.4 (1F, m, $F_{\alpha\ or\ \beta}$ simplified as ddd, $^2J_{FF}$ 268.8 Hz, $^3J_{FF}$ 17.3 Hz, $^3J_{FF}$ 10.4 Hz upon proton decoupling), -134.6 – -133.7 (1F, m, $F_{\alpha\ or\ \beta}$ simplified as ddd, $^2J_{FF}$ 268.8 Hz, $^3J_{FF}$ 15.6 Hz, $^3J_{FF}$ 10.4 Hz upon proton decoupling), -135.81 – -134.83 (1F, m, $F_{\alpha\ or\ \beta}$ simplified as ddd, $^2J_{FF}$ 267.0 Hz, $^3J_{FF}$ 13.9 Hz, $^3J_{FF}$ 10.4 Hz upon proton decoupling), -138.78 – -137.88 (m, 1F, $F_{\alpha or\beta}$ simplified as ddd appeared as dt, $^2J_{FF}$ 260.1 Hz, $^3J_{FF}$ 10.4 Hz upon proton decoupling), -139.81 – -138.80 (m, 1F, $F_{\alpha or\beta}$ simplified as ddd, $^2J_{FF}$ 260.1, $^3J_{FF}$ 15.6 Hz, $^3J_{FF}$ 5.2 Hz upon proton decoupling) ppm; **HRMS** (ESI^+) for $C_7H_{10}F_4O_5$ $[M+Na]^+$ calcd 273.0357, found 273.0362.

10.8 Synthesis of F_4-D-heptoses *via* an alternative approach

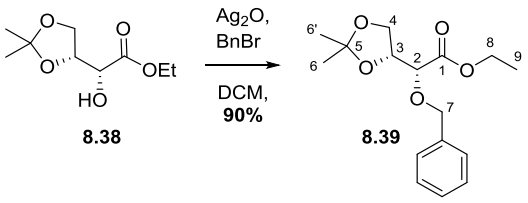
10.8.1 Synthesis of ethyl (*2R,3R*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate 8.38



To a suspension of D-ascorbic acid **8.26** (20 g, 114 mmol, 1 equiv.) in dry acetone was added anhydrous $CuSO_4$ (36 g, 228 mmol, 2 equiv.) at rt. The reaction was vigourously stirred at rt for 24 h, after which an additional amount of anhydrous $CuSO_4$ (36 g, 114 mmol, 2 equiv.) was added to the mixture, and stirring was continued for 36 h. The reaction mixture was then filtered and evaporated under reduced pressure, leading to (2*R*,3*R*)-3,4-*O*-isopropylidene-D-ascorbic acid (24.6 g, 100%). The isopropylidene derivative was then dissolved in H_2O (120 mL) containing 40 g of K_2CO_3. The solution was chilled in an ice bath and stirred while 30 % H_2O_2 (36 mL) was added. The solution was stirred overnight at rt and concentrated *in vacuo*. The solid was extracted in boiling ethanol, filtered and concentrated under reduced pressure, to give 20 g of material. The crude salt was then dissolved in MeCN (150 mL), and EtI (11.4 mL, 142.2 mmol, 1.25 equiv.) was added. The resulting mixture was stirred under reflux for 24 h. The reaction mixture was then filtered and concentrated under reduced pressure to give **8.38** as a brown oil (14.3 g, 61 % over 3 steps).

$[\alpha]_D$ -26.9 (c 3.8, $CHCl_3$, 22 °C), lit. -23.6 (c 3.9, $CHCl_3$, 25°C)[149]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.37 – 4.19 (4H, m, H_2, H_3. H_7, $H_{7'}$), 4.03 (1H, dd, $^2J_{HH}$ 8.5 Hz, $^3J_{HH}$ 5.7 Hz, H_4), 3.99 (1H, dd, $^2J_{HH}$ 8.4 Hz, $^3J_{HH}$ 6.9 Hz, $H_{4'}$), 3.10 – 2.99 (1H, m, OH), 1.42 (3H, s, H_6 or $H_{6'}$), 1.34 (3H, s, $H_{6'}$ or H_6), 1.30 (3H, t, $^3J_{HH}$ 7.1 Hz, H_8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.9 (C_1), 109.7 (C_5), 76.8 (C_3), 71.0 (C_2), 64.9 (C_4), 61.5 (C_7), 26.1 (C_6 or $C_{6'}$), 24.9 ($C_{6'}$ or C_6), 13.9 (C_9) ppm. NMR spectra correspond with the reported data.[149]

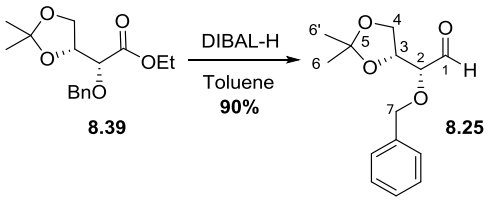
10.8.2 Synthesis of α-Bn-protected ester 8.39.



To a stirred solution of **8.38** (5.17 g, 25.3 mmol, 1 equiv.) in DCM (100 mL) at rt was added freshly prepared Ag_2O (8.8 g, 38 mmol, 1.5 equiv.) in one portion, followed by BnBr (3.6 mL, 30.4 mmol, 1.2 equiv.) dropwise. The mixture was stirred at this temperature for 3 h, before filtering through celite, and concentrating *in vacuo*. Purification by column chromatography (petroleum ether/EtOAc 85:15) gave compound **8.39** as pale yellow oil (6.67 g, 90%).

$[\alpha]_D$ 37.0 (c 0.79, $CHCl_3$, 20 °C), lit. 37.0 (c 2.0, $CHCl_3$, 20 °C)[150]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (5H, m, H_{Ar}), 4.69 (1H, d, $^2J_{HH}$ 11.6 Hz, H_7), 4.51 (1H, d, $^2J_{HH}$ 11.5 Hz, $H_{7'}$), 4.35 (1H, td, $^3J_{HH}$ 6.2 Hz, $^3J_{HH}$ 5.3 Hz, H_3), 4.26 (1H, dq, $^2J_{HH}$ 10.7 Hz, $^3J_{HH}$ 7.2, H_8), 4.22 (1H, dq, $^2J_{HH}$ 10.7 Hz, $^3J_{HH}$ 7.2, $H_{8'}$), 4.05 (1H, dd, $^2J_{HH}$ 8.9 Hz, $^3J_{HH}$ 6.1 Hz, H_7), 4.01 (1H, dd, $^2J_{HH}$ 8.7 Hz, $^3J_{HH}$ 5.1 Hz, $H_{7'}$), 3.96 (1H, d, $^3J_{HH}$ 6.4 Hz, H_2), 1.43 (3H, s, H_6 or $H_{6'}$), 1.35 (3H, s, $H_{6'}$ or H_6), 1.30 (3H, t, $^3J_{HH}$ 7.1 Hz, H_9) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4 (C_1), 137.0 (C_{qAr}), 128.4 (2C, CH_{Ar}), 128.1 (2C, CH_{Ar}), 128.0 (CH_{Ar}), 109.9 (C_5), 79.1 (C_2), 76.0 (C_3), 72.8 (C_7), 66.2 (C_4), 61.1 (C_8), 26.6 (C_6 or $C_{6'}$), 25.3 (C_6 or $C_{6'}$), 14.2 (C_9) ppm. NMR spectra correspond with the reported data.[151]

10.8.3 Synthesis of α-Bn-protected aldehyde 8.25.

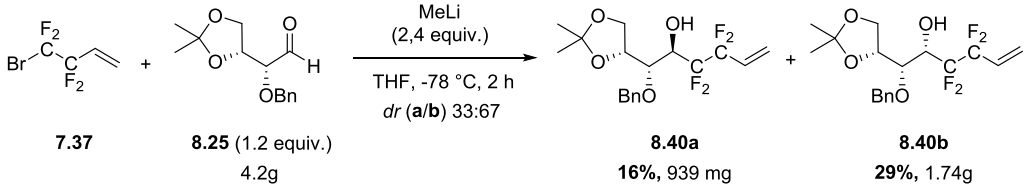


To a stirred solution of **8.39** (6.21 g, 21.0 mmol, 1 equiv.) in toluene (100 mL) at -78 °C under argon was added DIBAL (1.2 M in toluene, 32 mL, 38 mmol, 1.8 equiv.) over a period of 15 min. The reaction mixture was stirred at this temperature for 20 min, and the excess of DIBAL was quenched with a solution of NaOH 2% at -78 °C. The mixture was allowed to warm to rt, after which H_2O and DCM were added to the mixture, followed by

a saturated solution of sodium potassium tartrate. The aqueous phase was extracted with DCM, and the combined extracts were washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. Filtration over silica (petroleum ether/EtOAc 8:2) gave aldehyde **8.25** as colourless oil (4.76 g, 90 %).

$[\alpha]_D$ 44.5 (c 1.14, $CHCl_3$, 21 °C), lit. 28.7 (c 1.0, $CHCl_3$, 20 °C)[152]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.71 (1H, d, $^3J_{HH}$ 2.1 Hz, H_1), 7.43 – 7.28 (5H, m, H_{Ar}), 4.74 (1H, d, $^2J_{HH}$ 11.7 Hz, H_7), 4.62 (1H, d, $^2J_{HH}$ 12.0 Hz, $H_{7'}$), 4.36 (1H, dd, $^3J_{HH}$ 12.2 Hz , $^3J_{HH}$ 6.2 Hz, H_3), 4.08 (1H, dd, $^3J_{HH}$ 8.7 Hz , $^3J_{HH}$ 6.3 Hz, H_4), 3.93 (1H, dd, $^3J_{HH}$ 8.8 Hz , $^3J_{HH}$ 5.7 Hz, $H_{4'}$), 3.83 (1H, dd, $^3J_{HH}$ 6.2 Hz, $^3J_{HH}$ 2.1 Hz, H_2), 1.44 (3H, s, H_6 or $H_{6'}$), 1.36 (3H, s, H_6 or $H_{6'}$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.3 (C_1), 136.8 (C_{qAr}), 128.6 (2C, CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (2C, CH_{Ar}), 110.1 (C_5), 83.1 (C_2), 75.0 (C_3), 73.3 (C_7), 66.2 (C_4), 26.4 (C_6 or $C_{6'}$), 25.1 ($C_{6'}$ or C_6) ppm. NMR spectra correspond with the reported data.[152]

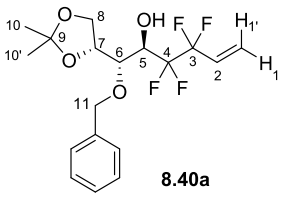
10.8.4 Coupling reaction with the α-Bn-protected aldehyde 8.25.



7.37 | **8.25** (1.2 equiv.) 4.2g | **8.40a** **16%,** 939 mg | **8.40b** **29%,** 1.74g

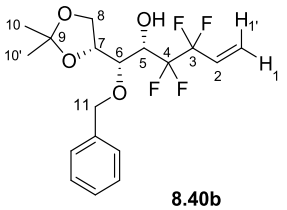
Compounds **7.37** (2.0 mL, 16.0 mmol, 1 equiv.) and **8.25** (4.72 g, 19.0 mmol, 1.2 equiv.) were dissolved in THF (64 mL). The resulting solution was cooled to -78 °C and stirred for 10 min at this temperature, after which a solution of MeLi (1.6 M in Et_2O, 24.0 mL, 38.4 mmol, 2.4 equiv.) was added at -78 °C during 1 h, using a syringe pump. The mixture was stirred at -78 °C for further 2 h, and was quenched at this temperature with a saturated solution of NH_4Cl. The reaction mixture was extracted with EtOAc three times. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. In order to enable separation of the coupling adducts from the remaining aldehyde, the residue was dissolved in EtOH, and $NaBH_4$ (605 mg, 16 mmol, 1 equiv.) was added at 0 °C. The reaction mixture was stirred overnight at rt, and then quenched with a saturated solution of NH_4Cl. The mixture was extracted with EtOAc three times. The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum to give the crude coupling adduct **8.40** as a mixture of diastereoisomers (*dr* **8.40a**/**8.40b** 33:67).

Purification by column chromatography (hexane/EtOAc 85:15) followed by HPLC (hexane/EtOAc 90:10) afforded compound compounds **8.40a** (939 mg, 16 %), and **8.40b** (1.74 g, 29 %) as colourless oils.



8.40a

[α]$_D$ 18.3 (c 1.63, $CHCl_3$, 23 ^oC); **IR** (neat) 3395 (w, br.), 2986 (w), 2930 (w, br.), 1212 (m), 1102 (s, br.), 1071 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (5H, m, H_{Ar}), 6.13 – 5.97 (1H, m, H_2), 5.93 − 5.84 (1H, m with the presence of $^3J_{HH\textit{trans}}$ 17.3 Hz, $H_{1'}$), 5.69 (1H, d, $^3J_{HH\textit{cis}}$ 10.8 Hz, H_1), 4.74 (1H, d, $^2J_{HH}$ 11.3 Hz, H_{11}), 4.69 (1H, d, $^2J_{HH}$ 11.3 Hz, $H_{11'}$), 4.42 – 4.28 (1H, m, H_7), 4.34 (1H, dddd appeared as ddt, $^3J_{HF}$ 21.6 Hz, $^3J_{HH}$ 6.2 Hz, $^3J_{HF}$, $^3J_{HH}$ 4.6 Hz, H_5), 4.11 (1H, dd, $^2J_{HH}$ 8.6 Hz, $^3J_{HH}$ 6.4 Hz, H_8), 4.05 – 3.98 (2H, m, H_6, $H_{8'}$), 2.99 (1H, d, $^3J_{HH}$ 6.2 Hz , O<u>H</u>-5), 1.44 (3H, s, H_{10} or $H_{10'}$), 1.36 (3H, s, H_{10} or $H_{10'}$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.6 (C_{qAr}), 128.5 (2C, CH_{Ar}), 128.04 – 127.93 (3C, m, CH_{Ar}), 126.9 (t, $^2J_{CF}$ 23.9 Hz, C_2), 123.6 (t, $^2J_{CF}$ 9.5 Hz, C_1), 120.4 – 110.9 (2C, m, CF_2), 108.9 (C_9), 77.4 (C_6), 76.0 (C_7), 74.1 (C_{11}), 71.0 (dd, $^2J_{CF}$ 28.6 Hz, $^2J_{CF}$ 22.0 Hz, C_5), 66.0 (C_8), 26.3 (C_{10} or $C_{10'}$), 25.2 ($C_{10'}$ or C_{10}) ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.5 (1F, dd, $^2J_{FF}$ 262.7 Hz, $^3J_{HF}$ 10.4 Hz, simplified as d, $^2J_{FF}$ 262.7 Hz upon proton decoupling), -114.6 (1F, ddd, $^2J_{FF}$ 263.6 Hz, $^3J_{HF}$ 12.1 Hz, ^3J 3.5 Hz, simplified as br. d, $^2J_{FF}$ 262.2 Hz, upon proton decoupling), -120.8 (1F, ddd appeared as dt, $^2J_{FF}$ 275.3 Hz, $^3J_{FF}$, $^3J_{HF}$ 5.2 Hz, simplified as dd, $^2J_{FF}$ 275.3 Hz, $^3J_{FF}$ 5.2 Hz upon proton decoupling), -126.7 (1F, dd, $^2J_{FF}$ 275.7 Hz, $^3J_{FH}$ 22.5 Hz, simplified as d, $^2J_{FF}$ 275.7 Hz, upon proton decoupling) ppm; **HRMS** (ESI^+) $C_{18}H_{22}F_4O_4$ $[M+Na]^+$ calcd. 401.1346, found. 401.1346.

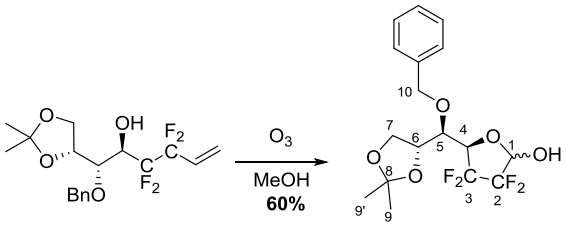


8.40b

[α]$_D$ 17.0 (c 1.65, $CHCl_3$, 23 °C); **IR** (neat) 3444 (w, br.), 2986 (w), 2918 (w, br.), 1215 (m), 1103 (s, br.), 1071 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.30 (5H, m, H_{Ar}), 6.18 – 6.02 (1H, m, H_2), 5.96 – 5.86 (1H, m with the presence of $^3J_{HH\textit{trans}}$ 17.5 Hz, $H_{1'}$), 5.70 (1H, d, $^3J_{HH\textit{cis}}$ 11.1 Hz, H_1), 4.76 (1H, d, $^2J_{HH}$ 10.5 Hz, H_{11}), 4.67 (1H, d, $^2J_{HH}$ 10.6 Hz, $H_{11'}$), 4.25 (1H,

ddd, $^{2}J_{HF}$ 22.6 Hz, $^{3}J_{HH}$ 11.0 Hz, $^{3}J_{HF}$ 4.4 Hz, H_5), 4.21 – 4.15 (1H, m, H_7), 4.07 (1H, dd, $^{2}J_{HH}$ 8.6 Hz, $^{3}J_{HH}$ 6.2 Hz, H_8), 3.97 (1H, dd, $^{3}J_{HH}$ 7.1 Hz, $^{3}J_{HH}$ 1.4 Hz, H_6), 3.88 (1H, dd, $^{2}J_{HH}$ 8.7 Hz, $^{3}J_{HH}$ 5.3 Hz, $H_{8'}$), 2.99 (1H, d, $^{3}J_{HH}$ 11.1 Hz, OH-5), 1.43 (3H, s, H_{10} or $H_{10'}$), 1.36 (3H, s, H_{10} or $H_{10'}$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.1 (C_{qAr}), 128.5 (2C, CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (2C, CH_{Ar}), 127.2 (t, $^{2}J_{CF}$ 24.2 Hz, C_2), 123.4 (t, $^{2}J_{CF}$ 9.5 Hz, C_1), 112.22 – 119.87 (2C, m, CF_2), 109.4 (C_9), 75.7 (C_6), 75.4 (C_7), 74.6 (d, $^{5}J_{CF}$ 3.7 Hz, C_{11}), 67.2 (dd, $^{2}J_{CF}$ 29.3 Hz, $^{2}J_{CF}$ 21.3 Hz, C_5), 66.2 (C_8), 26.7 (C_{10} or $C_{10'}$), 25.3 ($C_{10'}$ or C_{10}) ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.9 (1F, dd, $^{2}J_{FF}$ 263.6 Hz, $^{3}J_{HF}$ 12.1 Hz, simplified as d, $^{2}J_{FF}$ 263.6 upon proton decoupling), -115.8 (1F, ddd, $^{2}J_{FF}$ 261.8 Hz, $^{3}J_{HF}$ 12.1 Hz, $^{3}J_{FF}$ 6.9 Hz, simplified as dd, $^{2}J_{FF}$ 261.8 Hz, $^{3}J_{FF}$ 6.9 Hz upon proton decoupling), -121.1 (1F, d, $^{2}J_{FF}$ 270.5 Hz), -129.0 (1F, dd, $^{2}J_{FF}$ 268.8Hz, $^{3}J_{HF}$ 22.5 Hz, simplified as d, $^{2}J_{FF}$ 268.8Hz upon proton decoupling), ppm; **HRMS** (ESI^+) for $C_{18}H_{22}F_4O_4$ $[M+Na]^+$ calcd. 401.1346, found. 401.1345.

10.8.5 Synthesis of D-2,2,3,3-tetrafluoro-heptofuranose 8.41a



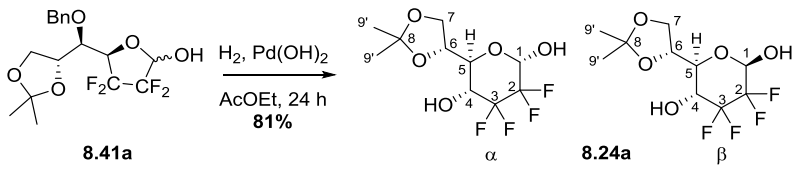
8.40a **8.41a**
major and minor

Ozone was bubbled through a solution of **8.40a** (860 mg, 2.27 mmol, 1 equiv.) in MeOH (45 mL) at -78 °C until the solution became blue (10 min). The excess of ozone was purged from the solution by bubbling oxygen through for 10 min. Dimethyl sulfide (833 µL, 11.35 mmol, 5 equiv.) was added and the reaction was allowed to warm to rt for 1 h. The resulting mixture was then concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether/EtOAc/DCM 75:20:5) followed by preparative HPLC (hexane/EtOAc 88:12) and recrystallisation in Et_2O/Hexane 3:1 gave heptofuranose **8.41a** as a white solid (520 mg, 60 %, *ar* 62:38).

IR (neat) 3327 (w, br), 2983 (w), 2933 (w, br.), 1121 (m, br), 1133 (s), 1064 (s, br.), 1023 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.43 – 7.24 (10H, m, H_{Ar}, *major and minor*), 7.16 – 6.99 (2H, m, OH-1, *major and minor*), 5.59 (1H, dd, *J* 7.8 Hz, *J* 3.3 Hz, H_1, *major*), 5.51 – 5.45 (1H, m with the presence of *J* 8.2 Hz, H_1, *minor*), 4.97 (1H, d, $^{2}J_{HH}$ 11.1 Hz, $H_{10,}$ *minor*), 4.91 (1H, d, $^{2}J_{HH}$ 11.1 Hz, $H_{10,}$ *major*), 4.74 (1H, d, $^{2}J_{HH}$ 11.0 Hz, $H_{10,}$ *major*), 4.70

(1H, d, $^{2}J_{HH}$ 10.9 Hz, $H_{10,}$ *minor*), 4.47 (1H, ddd appeared as td, $^{3}J_{HH}$ 7.2 Hz, $^{3}J_{HH}$ 2.2 Hz, H_7 *minor*), 4.43 – 4.31 (2H, m, H_4 *major or minor*, H_6 *major*), 4.25 – 3.96 (7H, m, H_4 *major or minor*, H_5 *major and minor*, H_7, $H_{7'}$, *major and minor*), 1.43 – 1.38 (6H, m, H_9 or $H_{9'}$, *major and minor*), 1.35 – 1.30 (6H, s, H_9 or $H_{9'}$, *major and minor*) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 139.35 (C_{qAr}, *minor*), 139.26 (C_{qAr}, *major*), 129.12 (2C, CH_{Ar}, *major*), 129.10 (2C, CH_{Ar}, *minor*), 128.64 (2C, CH_{Ar}, *major*), 128.61 (2C, CH_{Ar}, *minor*), 128.50 (CH_{Ar}, *major*), 128.45 (CH_{Ar}, *minor*), 122.0 – 114.5 (4C, m, CF_2, *major and minor*), 109.8 (C_8, *major*), 109.6 (C_8, *minor*), 95.7 (ddd, $^{3}J_{CF}$ 37.4 Hz, $^{3}J_{CF}$ 22.0 Hz, $^{4}J_{CF}$ 2.2 Hz, C_1, *minor*), 95.5 (dd, $^{3}J_{CF}$ 38.9 Hz, $^{3}J_{CF}$ 22.0 Hz, C_1, *major*), 78.5 – 77.6 (2C, m, C_4, *major and minor*), 77.0 (C_6, *minor*), 76.6 (C_6, *major*), 76.3 (d, $^{4}J_{CF}$ 2.9 Hz, C_5, *minor*), 76.1 (d, $^{4}J_{CF}$ 2.3 Hz, C_5, *major*), 75.5 (C_{10}, *major*), 75.4 (C_{10}, *minor*), 65.2 (C_7, *major*), 64.6 (C_7, *minor*), 26.72 (C_9 or $C_{9'}$, *major*), 26.66 (C_9 or $C_{9'}$, *minor*), 25.4 (C_9 or $C_{9'}$, *major and minor*) ppm; **^{19}F NMR** (376 MHz, acetone-d_6) δ -112.2 (1F, dd, $^{2}J_{FF}$ 242.8 Hz, $^{3}J_{FH}$ 10.4 Hz, *major*, simplified as d, $^{2}J_{FF}$ 242.8 Hz, upon proton decoupling), -122.0 – -121.1 (1F, m with the presence of $^{2}J_{FF}$ 244.5 Hz, *minor*, simplified as ddd appeared as dt $^{2}J_{FF}$ 244.5 Hz, $^{3}J_{FF}$ 5.2 Hz, upon proton decoupling), -125.3 (1F, ddd, $^{2}J_{FF}$ 244.5 Hz, $^{3}J_{HF}$ 12.1 Hz, $^{3}J_{FF}$ 6.9 Hz *minor*, dd, $^{2}J_{FF}$ 244.5 Hz, $^{3}J_{FF}$ 6.9 Hz, upon proton decoupling), -126.2 (1F, ddd appeared as dt, $^{2}J_{FF}$ 244.5 Hz, $^{2}J_{FF}$, $^{3}J_{HF}$ 6.9 Hz, *minor*, simplified as dd $^{2}J_{FF}$ 244.5 Hz, $^{3}J_{FF}$ 6.9 Hz, upon proton decoupling), -126.7 (1F, dd, $^{2}J_{FF}$ 242.8, $^{3}J_{HF}$ 6.9 Hz, *major* simplified as d, $^{2}J_{FF}$ 242.8, upon proton decoupling), -129.5 – -130.4 (1H, m with the presence of $^{2}J_{FF}$ 242.8 Hz, *major*, simplified as ddd appeared as dt, $^{2}J_{FF}$ 242.8 Hz, $^{3}J_{FF}$ 5.2 Hz, upon proton decoupling), -132.5 (1F, br. dd, $^{2}J_{FF}$ 242.8 Hz, *J* 13.9 Hz, *major*, appeared as dd, $^{2}J_{FF}$ 242.8 Hz, $^{3}J_{FF}$ 3.5 Hz, upon proton decoupling), -135.7 (1F, ddd appeared as dt, $^{2}J_{FF}$ 242.8 Hz, $^{3}J_{FF}$ 5.2 Hz, *minor*) ppm; **HRMS** (ESI^+) for $C_{14}H_{16}F_4O_5$ (loss of acetal group) $[M+Na]^+$ calcd. 363.0826, found. 363.0834.

10.8.6 Synthesis of gluco configured D-heptopyranose 8.24a

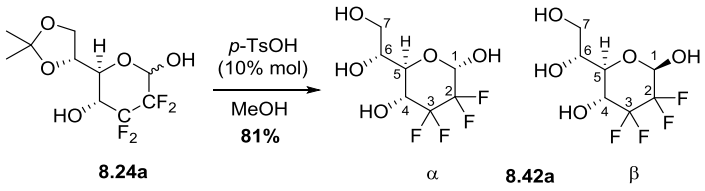


Heptofuranose **8.41a** (378 mg, 0.99 mmol, 1 equiv.) was dissolved in EtOAc (8 mL). $Pd(OH)_2$ (20% wt, 140 mg, 0.2 mmol, 10 mol%) was added and the resultant mixture was flushed with H_2. Stirring under an atmosphere of H_2 was continued at rt for 24 h, before

the mixture was filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/acetone 75:25) gave heptopyranose **8.24a** as a white solid (233 mg, 81 %, *ar* 57:43).

IR (neat) 3383 (m, br.), 2986 (w), 2930 (w), 1113 (s, br.). 1059 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 6.92 (1H, d, $^{3}J_{HH}$ 8.0 Hz, O<u>H</u>-1β), 6.85 (1H, d, $^{3}J_{HH}$ 5.1 Hz, O<u>H</u>-1α), 5.40 – 5.31 (1H, m, $H_{1\alpha}$), 5.24 (1H, d, $^{3}J_{HH}$ 6.2 Hz, O<u>H</u>-4β), 5.12 (1H, d, $^{3}J_{HH}$ 6.5 Hz, O<u>H</u>-4α), 5.07 (1H, br. dd, $^{3}J_{HF}$ 15.8 Hz, $^{3}J_{HH}$ 8.0 Hz, $H_{1\beta}$), 4.48 – 4.41 (2H, m, $H_{6\alpha+\beta}$), 4.23 (1H, dd, $^{3}J_{HH}$ 10.2 Hz, $^{3}J_{HH}$ 3.7 Hz, $H_{5\alpha}$), 4.09 – 3.89 (6H, m, $H_{4\alpha+\beta}$, $H_{7\alpha+\beta}$, $H_{7'\alpha+\beta}$), 3.76 (1H, dd, $^{3}J_{HH}$ 10.1 Hz, $^{3}J_{HH}$ 3.5 Hz, $H_{5\beta}$), 1.37 (6H, br. s, $H_{9\alpha+\beta}$) , 1.31 (6H, br. s, $H_{9'\alpha+\beta}$) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 119.2 – 111.9 (4C, m, $CF_{2\alpha+\beta}$), 110.3 ($C_{8\beta}$), 110.2 ($C_{8\alpha}$), 92.4 (d, $^{3}J_{CF}$ 26.4 Hz, $^{3}J_{CF}$ 21.3 Hz, $C_{1\beta}$), 92.2 (d, $^{3}J_{CF}$ 36.7 Hz, $^{3}J_{CF}$ 26.4 Hz, $C_{1\alpha}$), 76.5 ($C_{6\alpha}$), 76.4 ($C_{6\beta}$), 73.6 (dd appeared as t, $^{4}J_{CF}$ 3.3 Hz, $C_{5\beta}$), 69.9 (t, $^{3}J_{CF}$ 19.0 Hz, $C_{4\alpha}$), 69.8 (t, $^{3}J_{CF}$ 19.0 Hz, $C_{4\ \beta}$), 69.5 – 69.4 (m, $C_{5\beta}$), 65.6 ($C_{7\alpha}$), 65.4 ($C_{7\beta}$), 26.6 ($C_{9\alpha}$), 26.5 ($C_{9\beta}$), 25.73 ($C_{9'\beta}$), 25.66 ($C_{9'\alpha}$) ppm; **^{19}F NMR** (376 MHz, acetone-d_6) δ -119.2 – -121.2 (1F, m, F_α, simplified as dd, $^{2}J_{FF}$ 265.3 Hz, $^{3}J_{FF}$ 8.8 Hz, upon proton decoupling), -128.5 – -130.9 (2F, m, F_β, appeared as 2 signals upon proton decoupling: -129.5 (dd, $^{2}J_{FF}$ 255.0 Hz, $^{3}J_{FF}$ 14.2 Hz), -130.2 (ddd, $^{2}J_{FF}$ 254.9 Hz, $^{3}J_{FF}$ 12.1 Hz, $^{3}J_{FF}$ 8.7 Hz)), -132.3 – -133.1 (2F, m, F_α), -134.1 (1F, dt, $^{2}J_{FF}$ 265.3 Hz, $^{3}J_{FF}$ 12.6 Hz, F_α), -136.9 (1F, ddd appeared as dt, $^{2}J_{FF}$ 257.5 Hz, $^{3}J_{FF}$ 13.0 Hz, F_β), -139.7 (1F, dd, $^{2}J_{FF}$ 256.2 Hz, ^{3}J 13.9 Hz, F_β) ppm; **MS** (ESI^-) (m/z) 289 $[M-H]^-$; **HRMS** (ESI^+) for $C_{10}H_{14}F_4O_5$ $[M+Na]^+$ calcd 313.0670; found 313.0667.

10.8.7 Synthesis of fully deprotected D-heptose 8.42a

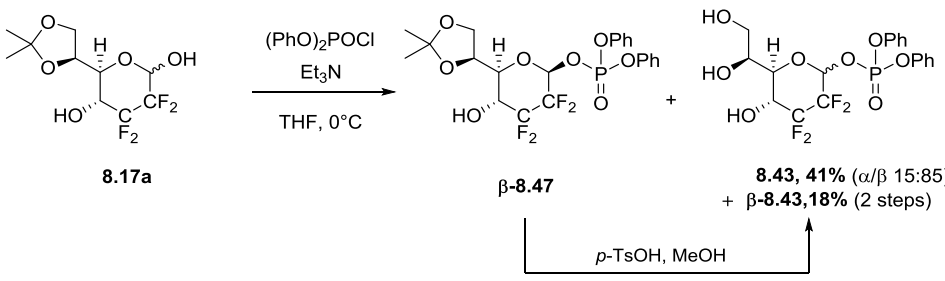


To a solution of **8.24a** (83 mg, 0.29 mmol, 1 equiv.) in MeOH (6 mL) was added *p*-TsOH (5.5 mg, 29 µmol, 10 mol%) at 0 °C. The reaction mixture was stirred at rt for 16 h and then quenched with a saturated solution of $NaHCO_3$. The mixture was extracted 3 times with EtOAc. Organic layers were combined, dried over $MgSO_4$ and concentrated under *vacuo*. Column chromatography (DCM/MeOH 9:1) gave D-heptose **8.42a** as a colourless oil (58 mg, 81 %, *ar* 55:45).

IR (neat) 3274 (m, br.), 2930 (w, br.), 1131 (s), 10692 (s, br.), 1032 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, methanol-d_4) δ 5.18 (1H, dd, $^{3}J_{HF}$ 8.0 Hz, $^{3}J_{HF}$ 2.9 Hz, $H_{1\alpha}$), 4.95 – 4.80 (1H, m with the presence of $^{3}J_{FH}$ 15.3 Hz, $H_{1\beta}$, signal partially overlapped with the solvent peak), 4.19 – 3.92 (5H, m, $H_{4\alpha+\beta}$, $H_{5\alpha\ or\ \beta}$, $H_{6\alpha+\beta}$), 3.374 (1H, dd, $^{2}J_{HH}$ 11.3 Hz, $^{3}J_{HH}$ 4.8 Hz, $H_{7\alpha\ or\ \beta}$), 3.373 (1H, dd, $^{2}J_{HH}$ 11.6 Hz, $^{3}J_{HH}$ 4.5 Hz, $H_{7\alpha\ or\ \beta}$), 3.67 (1H, dd, $^{2}J_{HH}$ 11.3 Hz, $^{3}J_{HH}$ 6.7 Hz, $H_{7'\alpha\ or\ \beta}$), 3.66 (1H, dd, $^{2}J_{HH}$ 11.5 Hz, $^{3}J_{HH}$ 7.2 Hz, $H_{7'\alpha\ or\ \beta}$), 3.63 (1H, dd, *J* 8.1 Hz, $^{3}J_{HH}$ 2.6 Hz, $H_{5\alpha\ or\ \beta}$) ppm; **^{13}C NMR** (100 MHz, methanol-d_4) δ 120.0 – 109.8 (4C, m, $CF_{2\alpha+\beta}$), 93.0 (d, $^{2}J_{CF}$ 27.1 Hz, $^{2}J_{CF}$ 19.1 Hz, $C_{1\beta}$), 92.8 (d, $^{2}J_{CF}$ 36.7 Hz, $^{2}J_{CF}$ 26.4 Hz, $C_{1\alpha}$), 76.0 (br. s, $C_{5\alpha\ or\ \beta}$), 73.7 ($C_{6\alpha}$), 73.5 ($C_{6\beta}$), 71.5 (br. s, $C_{5\alpha\ or\ \beta}$), 69.0 (dd appeared as t, $^{3}J_{CF}$ 18.3 Hz, $C_{4\alpha\ or\ \beta}$), 68.9 (dd appeared as t, $^{3}J_{CF}$ 19.8 Hz, $C_{4\alpha\ or\ \beta}$), 63.8 ($C_{7\alpha}$), 63.5 ($C_{7\beta}$) ppm; **^{19}F NMR** (376 MHz, methanol-d_4) δ -121.4 (1F, dddd appeared as dtd, $^{2}J_{FF}$ 266.2 Hz, $^{3}J_{FF,}$ $^{3}J_{FH}$ 9 Hz, $^{3}J_{HF}$ 4.4 Hz, F_{α} simplified as dd, $^{2}J_{FF}$ 266.2 Hz, $^{3}J_{FF}$ 9 Hz upon proton decoupling), -130.5 (1F, ddd appeared as dt, $^{2}J_{FF}$ 256.1 Hz, $^{3}J_{FF,}$ $^{3}J_{FH}$ 14.3 Hz, $F_{\alpha\ or\ \beta}$ simplified as dd, $^{2}J_{FF}$ 256.1 Hz, $^{3}J_{FF}$ 14.3 Hz, upon proton decoupling), -131.8 – -130.9 (1F, m, $F_{\alpha\ or\ \beta,}$ simplified as ddd $^{2}J_{FF}$ 256.1 Hz, $^{3}J_{FF}$ 11.2 Hz, $^{3}J_{FF}$ 9.2 Hz upon proton decoupling), -134.4 – -132.9 (2F, m, $F_{\alpha\ or\ \beta}$), -135.5 (ddd, $^{2}J_{FF}$ 266.5 Hz, $^{3}J_{FF}$ 14.6 Hz, $^{3}J_{FF}$ 11.5 Hz, $F_{\alpha\ or\ \beta}$), -138.3 (1F, ddd appeared as dt, $^{2}J_{FF}$ 258.1 Hz, $^{3}J_{FF}$ 11.8 Hz, $F_{\alpha\ or\ \beta}$), -141.4 – -140.4 (1F, m, $F_{\alpha\ or\ \beta}$ simplified as dt $^{2}J_{FF}$ 258.4 Hz, $^{3}J_{FF}$ 3.4 Hz upon proton decoupling) ppm; **MS** (ESI^{-}) (m/z) 249 $[M-H]^{-}$; **HRMS** (ESI^{+}) for $C_7H_{10}F_4O_5$ $[M+Na]^{+}$ calcd 273.0357, found 273.0358.

10.9 Towards the synthesis of ADP-L- and D-F_4-heptoses

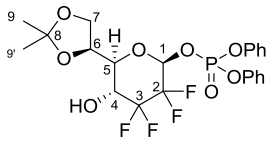
10.9.1 Synthesis of L-phosphorylated heptoses β-8.47 and 8.43



To a solution of heptose **8.17a** (222 mg, 0.76 mmol, 1equiv) in THF (5 mL) at 0 °C was added Et_3N (138 µL, 0.99 mmol, 1.3 equiv.). The mixture was stirred at this temperature for 10 min, and a solution of diphenyl phosphoryl chloride (207 µL, 0.99 mmol, 1.3 equiv.) in THF (2 mL) was added *via* syringe over a period of 15 min. Stirring was then continued

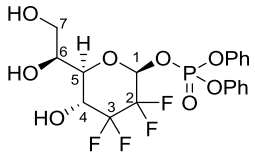
for 7 h at 0 °C, after which the mixture was quenched with H_2O. The mixture was then extracted 3 times with EtOAc. Organic layers were combined, dried over $MgSO_4$ and concentrated under *vacuo*. Purification *via* column chromatography (petroleum ether/acetone 7:3) enabled isolation of componds **β-8.47** (83 mg, 21%, α/β 0:100) and **β-8.43** (149 mg, 41 %, α/β 15:85) as colourless oils.

Following this, **β-8.47** (83 mg, 0.16 mmol, 1 equiv.) was dissolved in MeOH (4 mL), and *p*-TsOH (3 mg, 16 µmol, 10 mol%) was added at 0 °C. The reaction mixture was stirred at rt for 16 h and then quenched with a saturated solution of $NaHCO_3$. The mixture was extracted 3 times with EtOAc. Organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petroleum ether/acetone 7:3) gave **β-8.43** as a colourless oil (66 mg, 86%, 18% over 2 steps, α/β 0:100).



β-8.47

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.24 (4H, m), 7.23 – 7.09 (6H, m), 5.49 (1H, td, *J* 9.1 Hz, *J* 2.8 Hz), 4.36 (1H, td, *J* 6.6 Hz, *J* 2.6 Hz), 4.21 – 4.03 (1H, m), 3.99 – 3.85 (1H, m), 3.62 – 3.37 (2H, m with the presence of *J* 9.9 Hz, *J* 2.4 Hz), 1.28 (6H, s) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -132.2 – -134.2 (2F, m), -136.4 – -137.7 (1F, m), -137.7 – -139 (1F, m) ppm; **^{31}P NMR** (282 MHz, $CDCl_3$) δ -13.13 (d, *J* 6.7 Hz) ppm.

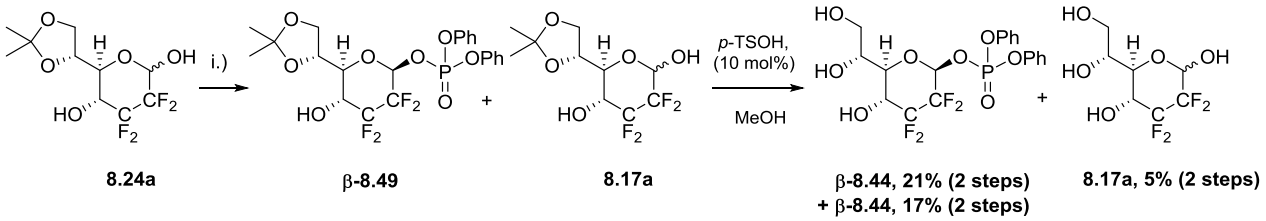


β-8.43

$[\alpha]_D$ 2.0 (c 0.48, $CHCl_3$, 23°C); **IR** (neat) 3363 (m, br.), 2926 (w, br.), 1489 (m), 1287 (m, br.), 1184 (m, br.), 1163 (w, br.), 1102 (s, br.) cm-^{1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.49 – 7.40 (4H, m, H_{Ar}), 7.38 – 7.22 (6H, m, H_{Ar}), 5.80 – 5.74 (1H, m, H_1), 5.71 (1H, d, $^3J_{HH}$ 7.5 Hz, O<u>H</u>-4, disappeared upon D_2O exchange), 4.44 – 4.25 (1H, m, H_4), 4.07 – 3.97 (3H, m, H_5, H_6, O<u>H</u>-6), 3.92 (1H, t, $^3J_{HH}$ 5.7 Hz, O<u>H</u>-7, disappeared upon D_2O exchange), 3.72 – 3.61 (2H, m, H_7, $H_{7'}$) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 151.3 (d, $^2J_{CP}$ 7.3 Hz, C_{qAr}), 151.2 (d, $^2J_{CP}$ 7.3 Hz, C_{qAr}), 131.0, 126.92, 126.87, 121.21, 121.15, 121.1, 94.4 (dd, $^2J_{CF}$ 24.9 Hz,

$^{2}J_{CF}$ 22.0 Hz, C_1), 75.1 (br. s, C_5), 69.3 (C_6), 67.2 (t, $^{2}J_{CF}$ 19.0 Hz, C_4), 63.1 (C_7) ppm, CF_2CF_2 are not observed; **^{19}F NMR** (282 MHz, acetone-d_6) δ -130.6 – -133.2 (2F, m), -133.6 – -138.5 (2F, m) ppm; **^{31}P NMR** (282 MHz, acetone-d_6) δ -12.4 (d, *J* 6.7 Hz) ppm; **MS** (ESI^+) (m/z) 505 $[M+Na]^+$; **HRMS** (ESI^+) for $C_{19}H_{19}F_4O_8P$ $[M+Na]^+$ calcd 505.0646, found 505.0648.

10.9.2 Synthesis of D-phosphorylated heptoses β-8.49 and β-8.17

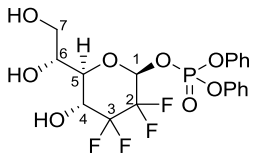


i.) $(PhO)_2POCl$, Et_3N

To a solution of **8.24a** (211 mg, 0.73 mmol, 1equiv) in THF (5 mL) at 0 °C was added Et_3N (132 µL, 0.95 µmol, 1.3 equiv.). The mixture was stirred for 10 min, and a solution of diphenyl phosphoryl chloride (200 µL, 0.95 mmol, 1.3 equiv.) in THF (1.9 mL) was added *via* syringe over a period of 15 min. Stirring was then continued for 7 h at 0 °C, after which the mixture was quenched with H_2O (1 mL). The mixture was then extracted 3 times with EtOAc. Organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/acetone 7:3) afforded a mixture of **β-8.49** and **8.17a** (123 mg, **β-71/53a** 78:22), alongside with the pure **β-8.49** (104 mg, 27 %), as colourless oils.

The pure **β-8.49** (104 mg, 0.2 mmol, 1 equiv.) was dissolved in MeOH (5 mL) and *p*-TsOH (4 mg, 20 µmol, 10 mol%) was added at 0 °C. The reaction mixture was stirred at rt for 16 h and then quenched with a saturated solution of $NaHCO_3$. The mixture was extracted 3 times with EtOAc. Organic layers were combined, dried over $MgSO_4$ and concentrated under *vacuo*. Purification *via* column chromatography (petroleum ether/acetone 7:3) afforded **β-8.44** as colourless oil (75 mg, 78%, 21% over 2 steps, 99% purity).

The same procedure was applied for the mixture of **β-8.49** and **8.17a** (123 mg), *p*-TsOH (4 mg) and MeOH (6 mL). Purification *via* column chromatography (petroleum ether/EtOAc 7/3) followed by HPLC (DCM/MeOH 9:1) enabled isolation of **β-8.44** (63 mg, 17% over 2 steps, 97% purity) and **8.17a** (10 mg, 5% over 2 steps) as colourless oils.

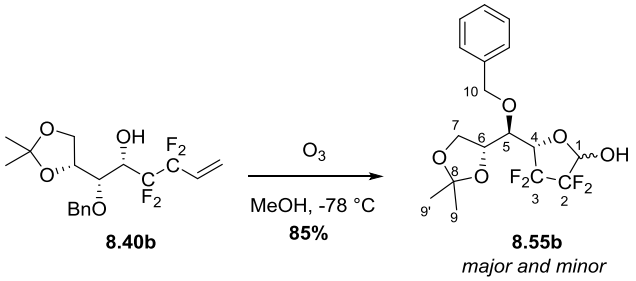


β-8.44

[α]$_D$ 4.0 (c 0.41, $CHCl_3$, 20 °C); **IR** (neat) 3378 (w, br.), 2918 (w, br.), 1488 (m), 1182 (m), 1161 (m), 1098 (s, br.), 1069 (s, br.) cm-^{1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.50 – 7.40 (4H, m, H_{Ar}), 7.39 – 7.24 (6H, m, H_{Ar}), 5.86 – 5.67 (1H, m, OH, disappeared upon D_2O exchange), 5.78 (1H, app. qd, *J* 7.2 Hz, *J* 2.5 Hz, H_1), 4.66 – 4.53 (1H, m, OH, disappeared upon D_2O exchange), 4.44 – 4.30 (1H, m, H_4), 4.28 – 4.12 (1H, m, OH, disappeared upon D_2O exchange), 4.10 – 4.02 (1H, m, H_6), 3.99 (1H, dd, $^{3}J_{HH}$ 9.9 Hz, $^{3}J_{HH}$ 2.5 Hz, H_5), 3.77 (1H, dd, $^{3}J_{HH}$ 11.3 Hz, $^{3}J_{HH}$ 5.0 Hz, H_7), 3.70 (1H, dd, $^{3}J_{HH}$ 11.4 Hz, $^{3}J_{HH}$ 5.8 Hz, $H_{7'}$) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 151.2 (d, $^{2}J_{CP}$ 7.3 Hz, C_{qAr}), 151.1 (d, $^{2}J_{CP}$ 7.3 Hz, C_{qAr}), 130.96, 130.92, 126.9, 126.8, 121.20, 121.16, 121.04, 120.99, 119.1 – 108.5 (2C, m, CF_2), 94.1 (tt, $^{2}J_{CF}$ 23.5 Hz, $^{3}J_{CF}$ 3.7 Hz, C_1), 76.4 (1H, d, $^{3}J_{CF}$ 4.4 Hz, C_5), 73.2 (C_6), 68.2 (t, $^{2}J_{CF}$ 18.7 Hz, C_4), 63.5 (C_7) ppm; **^{19}F NMR** (376 MHz, acetone-d_6) δ -131.6 (1F, ddd appeared as dt, $^{3}J_{HH}$ 256.6 Hz, *J* 3.5 Hz), -132.5 (1F, ddd appeared as dt, $^{3}J_{FF}$ 258.4 Hz, *J* 12.1 Hz), -137.86 – -136.38 (2F, m) ppm; **^{31}P NMR** (376 MHz, acetone-d_6) δ -12.8 (d, *J* 7.5 Hz) ppm; **MS** (ESI^+) (m/z) 505 $[M+Na]^+$; **HRMS** (ESI^+) for $C_{19}H_{19}F_4O_8P$ $[M+Na]^+$ calcd 505.0646, found 505.0647.

10.10 Synthesis of F4-octoses

10.10.1 Synthesis of D-2,2,3,3-tetrafluoro-heptofuranose 8.55b



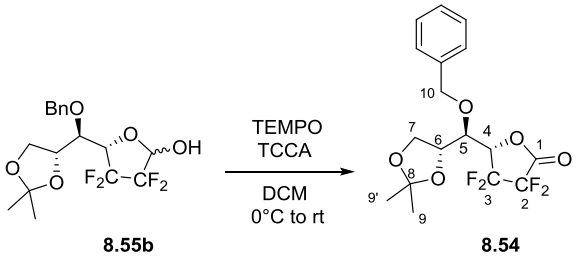
8.40b → **8.55b** *major and minor*

Ozone was bubbled through a solution of **8.40b** (315 mg, 0.83 mmol, 1 equiv.) in MeOH (15 mL) at -78 °C until the solution became blue (10 min). The excess of ozone was purged from the solution by bubbling oxygen through for 10 min. Dimethyl sulfide (305 µL, 4.2 mmol, 5 equiv.) was added and the reaction was allowed to warm to rt for 1 h. The

resulting mixture was then concentrated *in vacuo*. Purification *via* column chromatography (DCM/EtOAc 95:5) afforded heptofuranose **8.55b** as a white solid (269 mg, 85 %, *dr* 70:30).

IR 3338 (w, br), 2990 (w), 1147 (m, br), 1070 (s), 1018 (s) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.44 – 7.23 (10H, m, H_{Ar}, *major and minor*), 6.92 (1H, d, $^{3}J_{HH}$ 5.4 Hz, O<u>H</u>-1 *major*), 6.22 (1H, d, $^{3}J_{HH}$ 9.3 Hz, O<u>H</u>-1 *minor*), 5.64 – 5.55 (1H, m, H_1, *major*), 5.38 (1H, dddd appeared as tdd, $^{3}J_{HF}$, $^{3}J_{HH}$ 9.2 Hz, *J* 2.3 Hz, *J* 1.71 Hz, H_1, *minor*), 4.88 (1H, d, $^{2}J_{HH}$ 10.5 Hz, H_{10}, *minor*), 4.80 (1H, d, $^{2}J_{HH}$ 10.8 Hz, H_{10}, *major*), 4.78 (1H, d, $^{2}J_{HH}$ 10.3 Hz, $H_{10'}$, *minor*), 4.72 (1H, d, $^{2}J_{HH}$ 11.2 Hz, $H_{10'}$, *major*), 4.62 – 4.43 (1H, m, H_4, *minor*), 4.54 (1H, ddd appeared as td, *J* 13.5 Hz, *J* 3.2 Hz, H_4, *major*), 4.33 – 4.25 (2H, m, H_6, *major and minor*), 4.12 (1H, dd appeared as t, $^{3}J_{HH}$ 4.2 Hz, H_5, *minor*), 4.10 – 3.97 (5H, m, H_5, *major*, H_7, $H_{7'}$, *major and minor*), 1.40 (3H, s, H_9 or $H_{9'}$, *minor*), 1.38 (3H, s, $H_{9'}$ or H_9, *major*), 1.34 – 1.31 (6, m, $H_{9'}$ or H_9, *major and minor*) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 139.3 (C_{qAr}, *major*), 138.5 (C_{qAr}, *minor*), 129.3 (CH_{Ar}, *major and/or minor*), 129.1 (CH_{Ar}, *major and/or minor*), 128.9 (CH_{Ar}, *minor*), 128.6 (CH_{Ar}, *major and/or minor*), 128.4 (CH_{Ar}, *major and/or minor*), 122.0 – 113.5 (4C, m, CF_2, *major and minor*), 109.51 (C_8, *major and minor*), 96.4 (dd, $^{2}J_{CF}$ 38.9 Hz, $^{2}J_{CF}$ 21.3 Hz, C_1, *minor*), 95.8 (dd, $^{2}J_{CF}$ 38.9 Hz, $^{2}J_{CF}$ 21.3 Hz, C_1, *major*), 80.0 (dd, $^{2}J_{CF}$ 30.8 Hz, $^{2}J_{CF}$ 23.4 Hz, C_4, *minor*), 79.2 (dd, $^{2}J_{CF}$ 29.3 Hz, $^{2}J_{CF}$ 22.7 Hz, C_4, *major*), 76.9 (3C, C_6, *major and minor*, C_5 *major*), 76.8 (C_5, *minor*), 76.1 (d, $^{5}J_{CF}$ 1.5 Hz, C_{10}, *minor*), 75.5 (d, $^{5}J_{CF}$ 2.9 Hz, C_{10}, *major*), 66.3 (C_7, *minor*), 66.1 (C_7, *major*), 26.80 (C_9 or $C_{9'}$, *major*), 26.75 (C_9 or $C_{9'}$, *minor*), 25.7 (C_9 or $C_{9'}$, *major*), 25.6 (C_9 or $C_{9'}$, *minor*) ppm; **^{19}F NMR** (376 MHz, acetone-d_6) δ -112.8 (1F, dd, $^{2}J_{FF}$ 243.6 Hz, $^{3}J_{FH}$ 13.9 Hz, *major*, simplified as d, $^{2}J_{FF}$ 243.6 Hz, upon proton decoupling), -119.7 (1F, dd, $^{2}J_{FF}$ 245.8 Hz, $^{3}J_{FH}$ 13.9 Hz *minor*, simplified as d $^{2}J_{FF}$ 245.8 Hz upon proton decoupling), -124.4 – -125.3 (1F, m, *minor*, simplified as dd, $^{2}J_{FF}$ 246.2 Hz, $^{3}J_{FF}$ 5.6 Hz upon proton decoupling), -125.4 – -127.0 (2F, m, *major and minor*), -129.3 (1F, dd, $^{2}J_{FF}$ 243.6 Hz, $^{3}J_{HF}$ 11.3 Hz, *major*, simplified as dd, $^{2}J_{FF}$ 243.6 Hz, upon proton decoupling), -130.1 – -131.5 (1F, m, *minor*), -131.1 (d, $^{2}J_{FF}$ 241.5 Hz, *major*) ppm; **HRMS** (ESI^+) for $C_{14}H_{16}F_4O_5$ (loss of acetal group) $[M+Na]^+$ calcd 363.0826, found 363.0835.

10.10.2 Synthesis of lactone 8.54

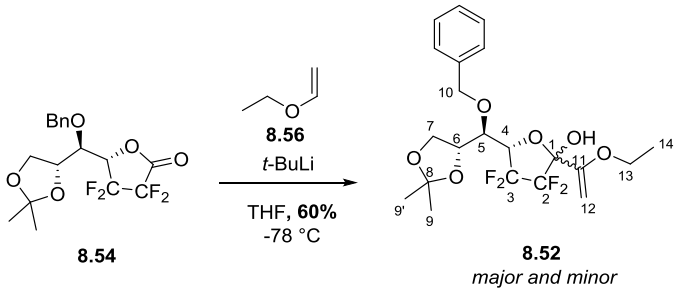


8.55b **8.54**

To a solution of heptofuranose **8.55b** (498 mg, 1.31 mmol, 1 equiv.) in DCM (23 mL) at rt were added TCCA (608 mg, 2.62 mmol, 2 equiv.), followed by TEMPO (4 mg, 26 µmol, 2 mol%) at 0 °C. The reaction mixture was stirred at rt for 16 h, before filtering through a pad of celite. The resulting solution was washed with brine (1×30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford lactone **8.54** as a colourless oil (462 mg, 93%).

IR (neat) 2998 (w, br.), 2937 (w), 1829 (s), 1177 (s), 1147 (s), 1102 (s), 1071 (s) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.49 – 7.24 (5H, m, H_{Ar}), 5.43 (1H, br. d, $^3J_{HF}$ 16.9 Hz, H_4), 4.85 (1H, d, $^2J_{HH}$ 11.1 Hz, H_{10}), 4.72 (1H, d, $^2J_{HH}$ 11.1 Hz, $H_{10'}$), 4.40 – 4.29 (2H, m, H_5, H_6), 4.17 – 4.09 (1H, m, H_7), 4.04 – 3.94 (1H, m, $H_{7'}$), 1.38 (3H, s, H_9 or $H_{9'}$), 1.33 (3H, s, $H_{9'}$ or H_9) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 161.5 (ddd appeared as td, $^2J_{CF}$ 31.5 Hz, $^2J_{CF}$, $^3J_{CF}$ 20.5 Hz, C_1), 138.3 (C_{qAr}), 129.2 (2C, CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (2C, CH_{Ar}), 115.2 (dddd appeared as ddt, $^1J_{CF}$ 269.2 Hz, $^1J_{CF}$ 260.4 Hz, $^2J_{CF}$ 22.0 Hz, CF_2), 109.8 (C_8), 106.0 (dddd appeared as ddt, $^1J_{CF}$ 267.0 Hz, $^1J_{CF}$ 264.1 Hz, $^2J_{CF}$ 22.7 Hz, CF_2), 82.7 (dd, $^2J_{CF}$ 31.5 Hz, $^2J_{CF}$ 24.2 Hz, C_4), 76.4 (C_6), 75.8 (d, $^3J_{CF}$ 4.4 Hz, C_5), 75.3 (C_7), 66.5 (C_{10}), 26.8 (C_9 or $C_{9'}$), 25.5 (C_9 or $C_{9'}$) ppm; **^{19}F NMR** (376 MHz, acetone-d_6) δ -115.7 (1F, ddd, $^2J_{FF}$ 253.2 Hz, $^3J_{FH}$ 17.3 Hz, $^3J_{FF}$ 8.7 Hz, simplified as dd, $^2J_{FF}$ 253.2 Hz, $^3J_{FF}$ 8.7 Hz upon proton decoupling), -122.1 (1F, ddd, $^2J_{FF}$ 284.4 Hz, $^3J_{FF}$ 8.7 Hz, $^3J_{FF}$ 5.2 Hz), -125.5 (1F, dd, $^2J_{FF}$ 286.1 Hz, $^3J_{FF}$ 6.9 Hz), -127.1 (1F, m, simplified as ddd appeared as dt, $^2J_{FF}$ 253.2 Hz, $^3J_{FF}$ 5.2 Hz upon proton decoupling) ppm; **MS** (ESI^-) (m/z) 395 $[M+H_2O-H]^-$, 394 $[M+NH_3-H]^-$; **HRMS** (ESI^+) for $C_{17}H_{18}F_4O_5$ $[M+Na]^+$ calcd 401.0983, found 401.0984; for $C_{17}H_{20}F_4O_5$ (hydrate) $[M+Na]^+$ calcd 419.1088, found 419.1081.

10.10.3 Coupling reaction with lactone 8.52

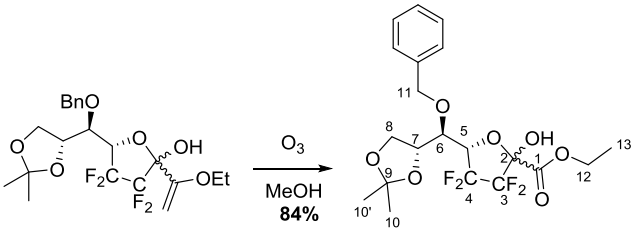


To a solution of ethyl vinyl ether **8.56** (686 µL, 7.14 mmol, 6 equiv.) in THF (6 ml) at -78 °C was added dropwise *t*-BuLi (1.6 M in pentane, 4.3 mL, 6.9 mmol, 5.8 equiv.). The mixture was stirred at this temperature for 10 min, then warmed up to -5 °C, and stirred for further 30 min. Following this, the mixture was cooled down to -78 °C, and a solution of lactone **8.54** (452 mg, 1.19 mmol, 1 equiv.) in THF (6 ml) was added *via* syringe. The resulting mixture was stirred at -78 °C for 2 h, after which a solution of ethyl vinyl ether **8.56** (228 µL, 2.38 mmol, 6 equiv.) and *t*-BuLi (1.6 M in pentane, 1.4 mL, 2.26 mmol, 1.9 equiv.) in THF (2 mL), prepared as previously, was added to the mixture at -78 °C. The resulting mixture was stirred at -78 °C for 1 h, before quenching at this temperature with a saturated solution of NH_4Cl, and extracting with EtOAc (3×10 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification via column chromatography (petroleum ether/EtOAc 80:20) afforded compound **8.52** as a yellow oil (320 mg, 60%, *ar* 75:25).

IR (neat) 3315 (w, br), 2986 (w, br.), 1746 (w, br.), 1641 (w), 1149 (s, br.), 1065 (s, br.), 1028 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.54 – 7.12 (10H, m, H_{Ar}, *major and minor*), 6.71 (1H, s, O<u>H</u>-1 *major*), 6.37 (1H, s, O<u>H</u>-1 *minor*), 4.86 – 4.75 (4H, m, H_{10}, H_{10}', *major and minor*), 4.68 – 4.63 (2H, m, H_{12}, *major and minor*), 4.59 – 4.44 (1H, H_4, *minor*), 4.54 (1H, ddd appeared as td, $^3J_{HF}$ 14.0 Hz, *J* 3.4 Hz, H_4, *major*), 4.36 – 4.26 (4H, m, H_6, $H_{12'}$, *major and minor*), 4.16 – 3.99 (6H, m, H_5, H_7, $H_{7'}$, *major and minor*), 3.90 – 3.72 (4H, m, H_{13}, *major and minor*), 1.39 (3H, s, H_9 or $H_{9'}$, *minor*), 1.37 (3H, s, $H_{9'}$ or H_9, *major*), 1.33 (6, s, $H_{9'}$ or H_9, *major and minor*), 1.31 – 1.25 (6H, m, H_{14}, *major and minor*) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 157.3 (C_{11}, *minor*), 156.5 (C_{11}, *major*), 139.6 (C_{qAr}, *major*), 138.9 (C_{qAr}, *minor*), 129.2 (CH_{Ar}, *minor*), 129.0 (CH_{Ar}, *major and/or minor*), 128.7 (CH_{Ar}, *minor*), 128.4 (CH_{Ar}, *major and/or minor*), 128.3 (CH_{Ar}, *major and/or minor*), 123.0 – 113.0 (4C, m,

CF_2, *major and minor*), 109.6 (C_8, *major and minor*), 98.9 (dd, $^2J_{CF}$ 32.3 Hz, $^2J_{CF}$ 21.3 Hz, C_1, *minor*), 99.5 (dd, $^2J_{CF}$ 30.1 Hz, $^2J_{CF}$ 20.5 Hz, C_1, *major*), 86.1 (C_{12}, *major*), 85.8 (C_{12}, *minor*), 79.5 (ddd, $^2J_{CF}$ 27.9 Hz, $^2J_{CF}$ 23.5 Hz, $^3J_{CF}$ 2.2 Hz, C_4, *minor*), 78.8 (ddd, $^2J_{CF}$ 30.1 Hz, $^2J_{CF}$ 23.5 Hz, $^3J_{CF}$ 2.2 Hz, C_4, *major*), 77.4 (C_5, *minor*), 77.0 (C_6, *major*), 76.6 (C_6, *minor*), 76.3 (C_5, *major*), 76.0 (C_{10}, *minor*), 75.3 (d, $^5J_{CF}$ 2.9 Hz, C_{10} *major*), 66.3 (C_7, *major*), 66.0 (C_7, *minor*), 64.56 (C_{13}, *minor*), 64.50 (C_{13}, *major*), 26.76 (C_9 or $C_{9'}$, *major*)m 26.72 (C_9 or $C_{9'}$, *minor*), 25.7 (C_9 or $C_{9'}$, *major*), 25.6 (C_9 or $C_{9'}$, *minor*), 14.5 (C_{14}, *major and minor*) ppm; **^{19}F NMR** (376 MHz, acetone-d_6) δ -108.2 (1F, ddd, $^2J_{FF}$ 241.0 Hz, $^3J_{FH}$ 13.9 Hz, $^3J_{FF}$ 3.5 Hz *major*, simplified as dd, $^2J_{FF}$ 241.0 Hz, $^3J_{FF}$ 3.5 Hz upon proton decoupling), -121.9 (1F, dddd appeared as ddt, $^2J_{FF}$ 242.8 Hz, $^3J_{FH}$ 12.1 Hz, $^3J_{FF}$ 6.9 Hz *minor*, simplified as dt $^2J_{FF}$ 242.8 Hz, $^3J_{FF}$ 6.9 Hz upon proton decoupling), -123.0 (1F, dddd appeared as ddt, $^2J_{FF}$ 242.8 Hz, $^3J_{FH}$ 13.9 Hz, $^3J_{FF}$ 8.7 Hz *minor*, simplified as dt $^2J_{FF}$ 242.8 Hz, $^3J_{FF}$ 8.7 Hz upon proton decoupling), -125.5 (1F, dd, $^2J_{FF}$ 239.3 Hz, $^3J_{FF}$ 6.9 Hz *minor*), -125.9 (1F, d, $^2J_{FF}$ 234.1 Hz, *major*), -129.7 (1F, ddd appeared as dt, $^2J_{FF}$ 232.4 Hz, $^3J_{FH}$, $^3J_{FF}$ 5.2 Hz, *major*, simplified as dd, $^2J_{FF}$ 232.4 Hz, $^3J_{FF}$ 5.2 Hz upon proton decoupling), -129.8 (1F, ddd appeared as dt, $^2J_{FF}$ 239.9 Hz, $^3J_{FF}$ 6.9 Hz, *minor*), -129.9 (1F, ddd, $^2J_{FF}$ 241.0 Hz, $^3J_{FH}$ 15.6 Hz, $^3J_{FF}$ 5.2 Hz, *major*, simplified as dd, $^2J_{FF}$ 241.0 Hz, $^3J_{FF}$ 5.2 Hz upon proton decoupling) ppm; **MS** (ESI^-) (m/z) 449 $[M-H]^-$; **HRMS** (ESI^+) for $C_{21}H_{26}F_4O_6$ $[M+Na]^+$ calcd 473.1558, found 475.1561.

10.10.4 Ozonolysis of intermediate 8.52 to give 8.51



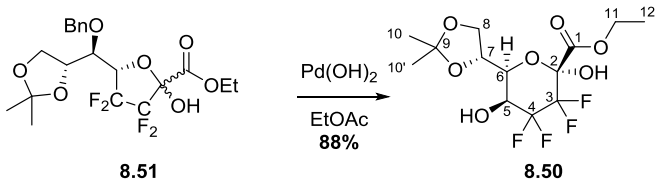
8.52 **8.51** *major and minor*

Ozone was bubbled through a solution of **8.52** (304 mg, 0.67 mmol, 1 equiv.) in MeOH (12 mL) at -78° C until the solution became blue (10 min). The excess of ozone was purged from the solution by bubbling oxygen through for 10 min. Dimethyl sulfide (250 µL, 3.4 mmol, 5 equiv.) was added and the reaction was allowed to warm to rt for 1 h. The resulting mixture was then concentrated in vacuo. Purification *via* column

chromatography (pentane/acetone 8:2) gave ester **8.51** as a white solid (256 mg, 84 %, *dr* 68:34).

IR (neat) 3296 (w, br), 2983 (w), 1752 (s), 1250 (m), 1213 (m), 1134 (m), 1049 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.56 (1H, s, OH-2 *major*), 7.45 – 7.21 (10H, m, H_{Ar}, *major and minor*), 7.08 (1H, s, OH-2 *minor*), 4.90 – 4.76 (1H, m, H_{11}, *minor*), 4.86 (1H, d, $^{2}J_{HH}$ 10.8 Hz, $H_{11'}$, *minor*), 4.82 (1H, d, $^{2}J_{HH}$ 11.2 Hz, H_{11}, *major*), 4.78 (1H, d, $^{2}J_{HH}$ 11.2 Hz, $H_{11'}$, *major*), 4.72 – 4.52 (1H, H_5, *minor*), 4.59 (1H, ddd appeared as td, $^{3}J_{HF}$ 13.4 Hz, *J* 4.3 Hz, H_5, *major*), 4.35 – 4.24 (6H, m, H_7, H_{12}, H_{12}, *major and minor*), 4.14 (1H, t, $^{3}J_{HH}$ 4.6 Hz, H_6, *minor*), 4.12 – 3.98 (5H, m, H_6, *major*, H_8, $H_{8'}$, *major and minor*), 1.40 (3H, s, H_{10} or $H_{10'}$, *minor*), 1.38 (3H, s, $H_{10'}$ or H_{10}, *major*), 1.33 (3, s, $H_{10'}$ or H_{10}, *minor*), 1.32 (3, s, $H_{10'}$ or H_{10}, *major*), 1.29 (3H, t, $^{3}J_{HH}$ 7.2 Hz, H_{13}, *minor*), 1.28 (3H, t, $^{3}J_{HH}$ 7.1 Hz, H_{13}, *major*) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 165.3 (C_1, *minor*), 164.7 (C_1, *major*), 139.4 (C_{qAr}, *major*), 138.7 (C_{qAr}, *minor*), 129.2 (CH_{Ar}, *minor and/or minor*), 129.0 (CH_{Ar}, *major and/or minor*), 128.8 (CH_{Ar}, *minor*), 128.5 (CH_{Ar}, *major and/or minor*), 128.3 (CH_{Ar}, *major and/or minor*), 121.6 – 113.1 (4C, m, CF_2, *major and minor*), 109.7 (C_9, *major and minor*), 98.7 (dd, $^{2}J_{CF}$ 33.0 Hz, $^{2}J_{CF}$ 20.5 Hz, C_2, *minor*), 97.9 (dd, $^{2}J_{CF}$ 32.3 Hz, $^{2}J_{CF}$ 20.5 Hz, C_2, *major*), 80.9 – 79.3 (C_5, *major and minor*), 77.0 (br. s, C_6, *minor*), 76.8 (C_7, *major*), 76.6 (C_7, *minor*), 76.3 (br. s, C_6, *major*), 76.0 (d, $^{5}J_{CF}$ 1.5 Hz, C_{11}, *minor*), 75.3 (d, $^{5}J_{CF}$ 2.2 Hz, C_{11}, *major*), 66.4 (C_8, *major*), 66.2 (C_8, minor), 63.4 (C_{12}, *minor*), 63.2 (C_{12}, *minor*), 26.7 (C_{10} or $C_{10'}$, *major and minor*), 25.6 (C_{10} or $C_{10'}$, *major and minor*), 14.3 (C_{13}, *major and minor*) ppm; **^{19}F NMR** (376 MHz, acetone-d_6) δ -108.9 (1F, ddd, $^{2}J_{FF}$ 242.8 Hz, ^{3}J 13.9 Hz, ^{3}J 3.5 Hz *major*), -120.9 (1F, dddd, $^{2}J_{FF}$ 244.5 Hz, ^{3}J 12.1 Hz, ^{3}J 6.9 Hz, ^{3}J 5.2 Hz, *minor*), -123.9 (1F, ddd, $^{2}J_{FF}$ 246.2 Hz, ^{3}J 13.9 Hz, ^{3}J 6.9 Hz *minor*), -125.3 (1F, dd, $^{2}J_{FF}$ 242.8 Hz, ^{3}J 5.2 Hz *minor*), -126.7 (1F, d, $^{2}J_{FF}$ 237.6 Hz, *major*), -129.7 – -128.8 (m, 2F, *major and minor*), -130.2 (1F, ddd, $^{2}J_{FF}$ 243.0 Hz, ^{3}J 12.0 Hz, ^{3}J 6.9 Hz, *major*) ppm; **MS** (ESI^-) (m/z) 449 $[M-H]^-$; **HRMS** (ESI^+) for $C_{20}H_{24}F_4O_7$ $[M+Na]^+$ calcd 475.1350, Found 475.1362.

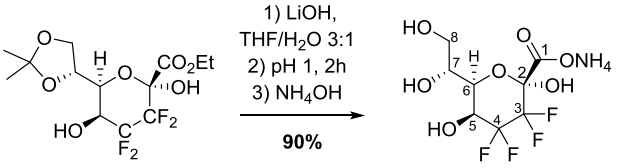
10.10.5 Synthesis of 7,8-*O*-*iso*propylidene-F_4-Kdo-ester 8.50



Octofuranose **8.51** (255 mg, 0.57 mmol, 1 equiv.) was dissolved in EtOAc (15 mL). $Pd(OH)_2$ (20% wt, 8 mg, 11 µmol, 2 mol%) was added and the resultant mixture was flushed with H_2. Stirring under an atmosphere of H_2 was continued at rt for 24 h, before the mixture was filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (pentane/acetone 75:25) followed by preparative HPLC (hexane/acetone 65:35) afforded the F_4-Kdo-ester derivative **8.50** as a white solid (185 mg, 93% purity with 7% DCM, 182 mg calculated, 88 %).

$[\alpha]_D$ 23.9 (c 0.51, $CHCl_3$, 18 ^oC); **IR** (neat) 3361 (w, br.), 2986 (w, br.), 1746 (m), 1682 (w), 1182 (m), 1131 (s), 1069 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.20 (1H, s, OH-2), 5.34 (1H, d, $^3J_{HH}$ 6.1 Hz, OH-5), 4.43 (1H, ddd, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 6.0 Hz, $^3J_{HH}$ 4.6 Hz, H_7), 4.32 – 4.17 (2H, m, H_5, H_6), 4.27 (2H, app. qd, $^3J_{HH}$ 7.0 Hz, *J* 0.9 Hz, H_{11}, $H_{11'}$), 4.09 (1H, dd, $^2J_{HH}$ 8.7 Hz, $^3J_{HH}$ 6.1 Hz, H_8), 3.99 (1H, dd, $^2J_{HH}$ 8.7 Hz, $^3J_{HH}$ 4.4 Hz, $H_{8'}$), 1.37 (3H, s, H_{10} or $H_{10'}$), 1.30 (3H, s, H_{10} or $H_{10'}$), 1.27 (3H, t, $^3J_{HH}$ 7.1 Hz, H_{12}) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 165.4 (C_1), 117.5 – 108.0 (2C, m, CF_2), 110.1 (C_9), 95.2 (dd, $^2J_{CF}$ 31.5 Hz, $^2J_{CF}$ 24.2 Hz, C_2), 73.2 (C_7), 71.8 (d, $^3J_{CF}$ 5.9 Hz, C_6), 69.2 (dd, $^2J_{CF}$ 30.8 Hz, $^2J_{CF}$ 20.5 Hz, C_5), 67.4 (C_8), 63.1 (C_{11}), 27.3 (C_{10} or $C_{10'}$), 25.6 (C_{10} or $C_{10'}$), 14.3 (C_{12}) ppm; **^{19}F NMR** (386 MHz, acetone-d_6) δ -118.3 (1F, ddddd appeared as ddtd, $^2J_{FF}$ 266.7 Hz, $^3J_{FF}$ 14.3 Hz, $^3J_{FH}$, $^3J_{FF}$ 8.6 Hz, $^3J_{FH}$ 2.9 Hz, simplified as ddd, $^2J_{FF}$ 266.7 Hz, $^3J_{FF}$ 14.3 Hz, $^3J_{FF}$ 8.6 Hz upon proton decoupling), -121.2 (1F, ddd, $^2J_{FF}$ 264.7 Hz, $^3J_{FF}$ 17.2 Hz, $^3J_{FF}$ 8.6 Hz), -129.7 (1F, ddddd, $^2J_{FF}$ 266.5 Hz, $^3J_{FF}$ 16.9 Hz, $^3J_{FF}$ 11.8 Hz, $^3J_{FH}$ 5.2 Hz, $^3J_{FH}$ 2.9 Hz, simplified as ddd, $^2J_{FF}$ 266.5 Hz, $^3J_{FF}$ 16.9 Hz, $^3J_{FF}$ 11.8 Hz upon proton decoupling), -134.9 (1F, dddd, $^2J_{FF}$ 265.3 Hz, $^3J_{FF}$ 13.5 Hz, $^3J_{FF}$ 12.0 Hz, $^3J_{FH}$ 5.7 Hz, simplified as ddd, $^2J_{FF}$ 266.3 Hz, $^3J_{FF}$ 13.5 Hz, $^3J_{FF}$ 12.0 Hz upon proton decoupling) ppm; **MS** (ESI^+) (m/z) 363 $[M+H]^+$, 380 $[M+Na]^+$; **HRMS** (ESI^+) for $C_{13}H_{18}F_4O_7$ $[M+Na]^+$ calcd 385.08712; Found 385.08809; $[M+K]^+$ calcd 401.06108, found 401.06108.

10.10.6 ;lmSynthesis of F_4-Kdo 7.30

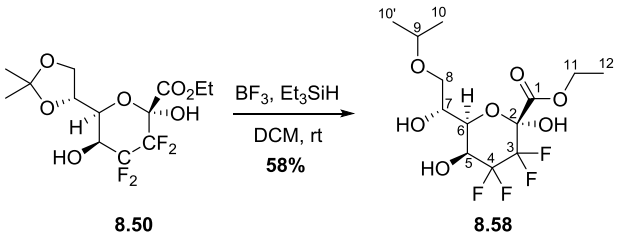


8.50 **7.30**

To a solution of **8.50** (47 mg, 0.13 mmol, 1 equiv.) in THF/H_2O (3:1, 3 mL) at rt was added LiOH (12 mg, 0.52 mmol, 4 equiv.). The mixture was stirred at rt for 1.5 h. A solution of HCl (2M, ~500 µL) was then added to the mixture until pH 1-2, and the resulting mixture was stirred for futher 2.5 h. The organic phase was extracted with EtOAc (5×10 mL), dried over $MgSO_4$ and concentrated in *vacuo*. The resulting oil was then dissolved in NH_4OH (2 mL), and concentrated under reduced pressure to give the ammonium F_4-Kdo **7.30** as a white powder (36 mg, 90%).

$[\alpha]_D$ 47.9 (c 0.39, MeOH, 20 °C); **IR** (neat) 3222 (s, br.), 1630 (s), 1413 (m, br.), 1124 (s), 1056 (s, br.) cm^{-1}; **^{1}H NMR** (500MHz, D_2O) δ 4.37 – 4.25 (1H, m, H_5), 4.23 – 4.14 (1H, H_6), 3.94 (1H, ddd, $^3J_{HH}$ 9.0 Hz, $^3J_{HH}$ 5.9 Hz, $^3J_{HH}$ 2.8 Hz, H_7), 3.82 (1H, dd, $^2J_{HH}$ 12.1 Hz, $^3J_{HH}$ 2.7 Hz, H_8), 3.64 (1H, dd, $^2J_{HH}$ 12.1 Hz, $^3J_{HH}$ 5.6 Hz, $H_{8'}$) ppm; **^{13}C NMR** (126 MHz, D_2O) δ 173.1 (C_1), 120.0 – 109.5 (2C, m, CF_2), 97.4 (dd, $^2J_{CF}$ 35.4 Hz, $^2J_{CF}$ 22.7 Hz, C_2), 71.8 (d, $^3J_{CF}$ 5.5 Hz, C_6), 71.0 (C_7), 70.7 (dd, $^2J_{CF}$ 31.3 Hz, $^2J_{CF}$ 20.4 Hz, C_5), 65.4 (C_8) ppm.; **^{19}F NMR** (376 MHz, D_2O) δ -117.8 (1F, dddd appeared as ddt, $^2J_{FF}$ 269.5 Hz, $^3J_{FF}$ 13.8 Hz, $^3J_{FH}$, $^3J_{FF}$ 8.3 Hz, simplified as ddd, $^2J_{FF}$ 269.5 Hz, $^3J_{FF}$ 13.8 Hz, $^3J_{FF}$ 8.3 Hz upon proton decoupling), -120.6 (1F, ddd, $^2J_{FF}$ 268.5 Hz, $^3J_{FF}$ 17.5 Hz, $^3J_{FF}$ 8.3 Hz), -128.5 (1F, dddd, $^2J_{FF}$ 269.0 Hz, $^3J_{FF}$ 16.6 Hz, $^3J_{FF}$ 12.0 Hz, $^3J_{FH}$ 5.4 Hz, simplified as ddd, $^2J_{FF}$ 269.0 Hz, $^3J_{FF}$ 16.6 Hz, $^3J_{FF}$ 12.0 Hz upon proton decoupling) -133.9 (1F, dddd, $^2J_{FF}$ 268.5 Hz, $^3J_{FF}$ 15.5 Hz, $^3J_{FF}$ 12.0 Hz, $^3J_{FH}$ 5.4 Hz, simplified as ddd, $^2J_{FF}$ 268.9 Hz, $^3J_{FF}$ 15.5 Hz, $^3J_{FF}$ 12.0 Hz upon proton decoupling) ppm; **MS** (ESI^-) (m/z) 293 $[M\text{-}NH_3\text{-}H]^-$; **HRMS** ($ESI^+$) for $C_8H_{13}F_4NO_7$ (ammonium salt) $[M+H]^+$ calcd 312.0701, found 312.0702; for $C_8H_{10}F_4O_7$ (carboxylic acid) $[M+Na]^+$ calcd 317.0255, found 317.0255.

10.10.7 Synthesis 8-*O*-isopropyl–F_4-Kdo ester 8.58

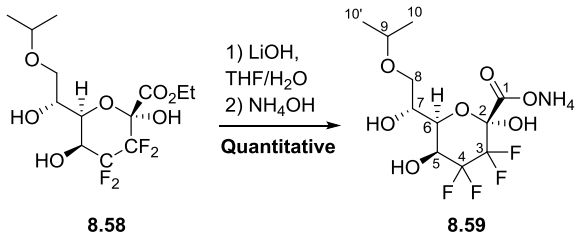


8.50 **8.58**

To a solution of **8.50** (40 mg, 0.11 mmol, 1 equiv.) in DCM at -78 °C was added $BF_3.Et_2O$ (48%, 60 µL, 0.22 mmol, 2 equiv.) and Et_3SiH (35 µL, 0.22 mmol, 2 equiv.) dropwise. The reaction mixture was stirred at this temperature for 1 h, before warming up to rt and stirring for 2.5 h. The mixture was then partitioned between EtOAc (10 mL) and a saturated solution of $NaHCO_3$ (10 mL), and stirred for 15 min. The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (pentane/acetone 65:35) followed by preparative HPLC (hexane/acetone 65:35) afforded compound **8.58** as a pale oil (23 mg, 58%).

$[\alpha]_D$ 53.4 (c 0.95, $CHCl_3$, 19 °C); **IR** (neat) cm^{-1} 3364 (w, br.), 2971 (w, br.), 1746 (m), 1376 (w), 1304 (w), 1149 (m), 1105 (s), 1062 (s, br.); **^{1}H NMR** (400 MHz, acetone-d-6) δ 7.08 (1H, s, OH-2), 5.17 (1H, d, $^3J_{HH}$ 5.7 Hz, OH-5), 4.39 – 4.20 (2H, m, H_5, H_6), 4.28 (2H, app. qd, $^3J_{HH}$ 7.2 Hz, *J* 2.6 Hz, H_{11}, $H_{11'}$), 4.18 – 4.04 (2H, m, H_7, OH-7), 3.70 (1H, dd, $^2J_{HH}$ 9.7 Hz, $^3J_{HH}$ 2.8 Hz, H_8), 3.63 (1H, spt, $^3J_{HH}$ 6.1 Hz, H_9), 3.53 (1H, dd, $^2J_{HH}$ 9.8 Hz, $^3J_{HH}$ 5.2 Hz, $H_{8'}$), 1.29 (3H, t, $^3J_{HH}$ 7.1 Hz, H_{12}), 1.131 (3H, d, $^3J_{HH}$ 6.2 Hz, H_{10} or $H_{10'}$), 1.125 (3H, d, $^3J_{HH}$ 6.2 Hz, H_{10} or $H_{10'}$) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 165.6 (C_1) 95.2 (dd, $^2J_{CF}$ 34.5 Hz, $^2J_{CF}$ 23.5 Hz, C_2), 72.7 (C_9), 70.9 (d, $^3J_{CF}$ 5.9 Hz, C_6), 69.9 (C_8), 69.3 (dd, $^2J_{CF}$ 31.5 Hz, $^2J_{CF}$ 19.8 Hz, C_5), 68.7 (C_7), 63.0 (C_{11}), 22.45 (C_{10} or $C_{10'}$), 22.38 (C_{10} or $C_{10'}$), 14.3 (C_{12}), CF_2CF_2 are not observed; **^{19}F NMR** (376 MHz, acetone-d-6) δ -116.7 (1F, ddddd appeared as ddtd, $^2J_{FF}$ 265.9 Hz, $^3J_{FF}$ 14.3 Hz, $^3J_{FH}$, $^3J_{FF}$ 8.7 Hz, $^3J_{FH}$ 2.6 Hz, simplified as ddd, $^2J_{FF}$ 265.9 Hz, $^3J_{FF}$ 14.3 Hz, $^3J_{FF}$ 8.7 Hz upon proton decoupling), -119.54 (1 F, ddd, $^2J_{FF}$ 265.0 Hz, $^3J_{FF}$ 16.9 Hz, $^3J_{FF}$ 8.9 Hz), -128.0 (1F, ddddd, $^2J_{FF}$ 266.3 Hz, $^3J_{FF}$ 17.2 Hz, $^3J_{FF}$ 11.8 Hz, $^3J_{FH}$ 5.2 Hz, $^3J_{FH}$ 2.0 Hz, simplified as ddd, $^2J_{FF}$ 266.3 Hz, $^3J_{FF}$ 17.2 Hz, $^3J_{FF}$ 11.8 Hz upon proton decoupling), -133.4 (1F, dddd, $^2J_{FF}$ 264.2 Hz, $^3J_{FF}$ 14.3 Hz, $^3J_{FF}$ 11.8 Hz, $^3J_{FH}$ 6.0 Hz, simplified as ddd, $^2J_{FF}$ 264.2 Hz, $^3J_{FF}$ 14.3 Hz, $^3J_{FF}$ 11.8 Hz upon proton decoupling); **MS** (ESI^+) (m/z) 365 $[M+H]^+$, 387 $[M+Na]^+$; **HRMS** (ESI^+) for $C_{13}H_{20}F_4O_7$ $[M+Na]^+$ calc. 387.1031, found 387.1037.

10.10.8 Synthesis 3,3,4,4-tetrafluoro-8-*O*-isopropyl–Kdo 8.59



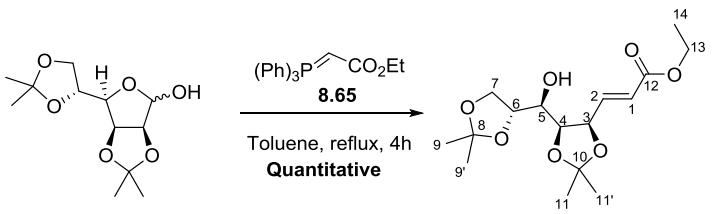
8.58 **8.59**

To a solution of **8.58** (19 mg, 0.052 mmol, 1 equiv.) in THF/H_2O (3:1, 2.6 mL) at rt was added LiOH (5 mg, 0.2 mmol, 4 equiv.). The mixture was stirred at rt for 1.5 h. A solution of HCl (2M) was then added to until pH 1-2, and the resulting mixture was stirred for 5 min. The organic phase was extracted with EtOAc (5×10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was then dissolved in NH_4OH (2 mL), concentrated under reduced pressure to give **8.59** as a white powder (19 mg, quantitative yield).

$[\alpha]_D$ 49.8 (c 0.26, MeOH, 19 °C); **IR** (neat) 3364 (w, br.), 2971 (w, br.), 1746 (m), 1376 (w), 1304 (w), 1149 (m), 1105 (s), 1062 (s, br.) cm^{-1}; **^{1}H NMR** (400 MHz, D_2O) δ 4.36 – 4.26 (1H, m, H_5), 4.23 – 4.14 (1H, m, H_6), 4.00 (1H, ddd, $^2J_{HH}$ 8.9 Hz, $^3J_{HH}$ 6.2 Hz, $^3J_{HH}$ 2.5 Hz, H_7), 3.78 (1H, dd, $^2J_{HH}$ 11.1 Hz, $^3J_{HH}$ 2.6 Hz, H_8), 3.55 (1H, spt, $^3J_{HH}$ 6.1 Hz, H_9), 3.55 (1H, dd, $^2J_{HH}$ 11.1 Hz, $^3J_{HH}$ 6.0 Hz, $H_{8'}$), 1.142 (3H, d, $^3J_{HH}$ 6.1 Hz, H_{10}), 1.138 (3H, d, $^3J_{HH}$ 6.2 Hz, $H_{10'}$); **^{13}C NMR** δ (100 MHz, D_2O) 170.1 (C_1), 116.5 – 107.2 (CF_2), 94.5 (dd, $^2J_{CF}$ 36.2 Hz, $^2J_{CF}$ 22.9 Hz, C_2), 73.3 (C_9), 69.2 (d, $^3J_{CF}$ 3.8 Hz, C_6), 68.7 (C_8), 67.9 (dd, $^2J_{CF}$ 30.5 Hz, $^2J_{CF}$ 21.0 Hz, C_5), 67.3 (C_7), 21.14 (C_{10} or $C_{10'}$), 21.08 (C_{10} or $C_{10'}$); **^{19}F NMR** (386 MHz, D_2O) δ -117.9 (1F, dddd appeared as ddt, $^2J_{FF}$ 269.2 Hz, $^3J_{FF}$ 14.9 Hz, $^3J_{FH}$, $^3J_{FF}$ 7.7 Hz, simplified as ddd, $^2J_{FF}$ 269.2 Hz, $^3J_{FF}$ 14.9 Hz, $^3J_{FF}$ 7.7 Hz upon proton decoupling), -120.5 (1 F, ddd, $^2J_{FF}$ 268.1 Hz, $^3J_{FF}$ 17.6 Hz, $^3J_{FF}$ 8.3 Hz), -128.6 (1F, ddddd, $^2J_{FF}$ 269.3 Hz, $^3J_{FF}$ 16.1 Hz, $^3J_{FF}$ 11.5 Hz, $^3J_{FH}$ 5.5 Hz, $^3J_{FH}$ 1.4 Hz, simplified as ddd, $^2J_{FF}$ 269.3 Hz, $^3J_{FF}$ 16.1 Hz, $^3J_{FF}$ 11.5 Hz upon proton decoupling), -133.8 (1F, dddd, $^2J_{FF}$ 267.9 Hz, $^3J_{FF}$ 14.6 Hz, $^3J_{FF}$ 11.8 Hz, $^3J_{FH}$ 5.7 Hz, simplified as ddd, $^2J_{FF}$ 267.9 Hz, $^3J_{FF}$ 14.6 Hz, $^3J_{FF}$ 11.8 Hz upon proton decoupling) ppm; **MS** (ESI^-) (m/z) 335 [M-NH_3-H]$^-$.

10.11 **Synthesis of 2β-deoxy-Kdo**

10.11.1 Synthesis of ester 8.66

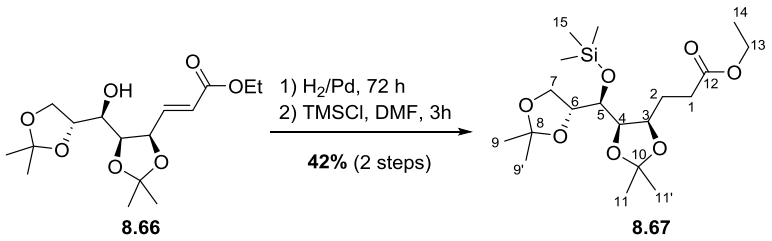


8.64 **8.66**

A solution of 2,3,5,6-di-*O*-isopropylidene-α-D-mannofuranose **8.64** (4.2 g, 16.3 mmol, 1 equiv.) and **8.65** (6.8 g, 19.5 mmol, 1.2 equiv.) in toluene (100 mL) was stirred under reflux for 4 h. The reaction mixture was then filtered through a pad of silica and concentrated *in vacuo*. Purification via column chromatography (pentane/EtOAc 7:3) afforded compound **8.66** as a colourless oil (5.4 g, quantitative yield, E/Z 94:6). An analytical sample was purified by HPLC (hexane/EtOAc 75:25) for characterisation purpose (E/Z 98:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, dd, $^{3}J_{HH}$ 15.7 Hz, $^{3}J_{HH}$ 6.1 Hz, H_2), 6.10 (1H, dd, $^{3}J_{HH}$ 15.7 Hz, $^{3}J_{HH}$ 1.5 Hz, H_1), 4.83 (1H, ddd, $^{3}J_{HH}$ 7.5 Hz, $^{3}J_{HH}$ 6.2 Hz, $^{3}J_{HH}$ 1.5 Hz, H_3), 4.46 (1H, dd, $^{3}J_{HH}$ 7.5 Hz, $^{3}J_{HH}$ 2.1 Hz, H_4), 4.21 (2H, app. qd, *J* 7.1 Hz, *J* 1.8 Hz, H_{13}), 4.14 − 4.07 (1H, m, H_7), 4.03 – 3.96 (2H, m, H_6, $H_{7'}$), 3.49 − 3.40 (1H, m with the presence of *J* 7.8 Hz, *J* 2.2 Hz, H_5), 2.15 (1H, d, $^{3}J_{HH}$ 7.6 Hz, O<u>H</u>-5), 1.55 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.42 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.41 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.35 (3 H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.30 (3H, t, $^{3}J_{HH}$ 7.1 Hz, H_{14}) ppm; **^{13}C NMR** δ (100 MHz, $CDCl_3$) 165.7 (C_{12}), 143.2 (C_1), 123.6 (C_2), 109.5 (C_8 or C_{10}), 109.3 (C_8 or C_{10}), 77.4 (C_4, (DEPT 135)), 76.7 (C_3), 76.1 (C_6), 70.5 (C_5), 67.2 (C_7), 60.6 (C_{13}), 26.75 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 26.72 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 25.2 (C_9 or $C_{9'}$ or C_{11} or C_{11}), 24.8 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 14.2 (C_{14}) ppm. NMR spectra correspond to the reported data.[153]

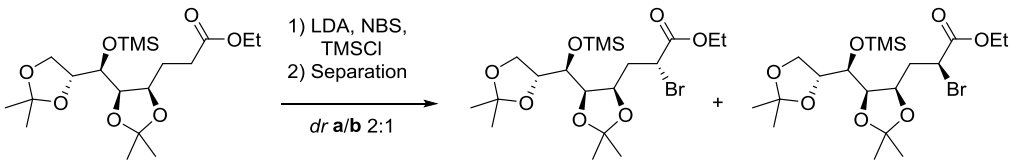
10.11.2 Synthesis of protected ester 8.67



Compound **8.66** (5.4 g, 16.3 mmol, 1 equiv.) was dissolved in EtOAc (100 mL). Pd/C (10% wt, 1.0 g, 1.0 mmol, 6 mol%) was added and the resultant mixture was flushed with H_2. Stirring under an atmosphere of H_2 was continued for 48 h at rt, before the mixture was filtered through a pad of silica and concentrated *in vacuo*, to give 4.66 g of crude mixture, which was engaged in the next step without any purification. The crude mixture was dissolved in DMF (53 mL) and imidazole (1.1 g, 16.1 mmol, 0.86 equiv.) as well as TMSCl (1.8 mL, 14.1 mmol, 0.86 equiv.) were added at 0 °C. The resulting solution was stirred for 2 h at rt and an additional amount of TMSCl (850 µL, 7.0 mmol, 0.43 equiv.) was added. The mixture was then partitioned between H_2O (100 mL) and EtOAC (100 mL). The layers were separated, and the aqueous phase was extracted with EtOAC (3×100 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated in *vacuo*. Purification *via* column chromatography (pentane/acetone 95:5) afforded compound **8.67** as a pale oil (2.8 g, 42% over 2 steps).

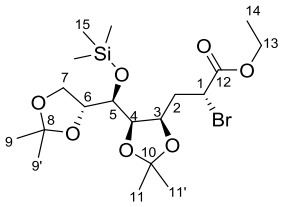
$[\alpha]_D$ 52.1 (c 1.1, $CHCl_3$, 19 °C), lit. 38.7 (c 1.04, $CHCl_3$, 20 °C)[133]; **IR** (neat) 2977 (w, br), 2017 (w, br.), 1742 (m), 1375 (m), 1250 (s), 1220 (s), 1160 (s), 1060 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.16 – 4.03 (2H, m, H_3, H_7), 4.13 (2H, q, $^3J_{HH}$ 7.3 Hz, H_{13}), 4.00 – 3.90 (2H, m, H_4 or H_5, H_6), 3.90 – 3.82 (2H, m, H_4 or H_5, $H_{7'}$), 2.54 (1H, ddd, $^2J_{HH}$ 16.1 Hz, $^3J_{HH}$ 9.1 Hz, $^3J_{HH}$ 5.6 Hz, H_1), 2.36 (1 H, ddd, $^2J_{HH}$ 16.0 Hz, $^3J_{HH}$ 9.2, $^3J_{HH}$ 6.9 Hz, $H_{1'}$), 1.99 – 1.88 (1H, m, H_2), 1.82 – 1.70 (1H, m, $H_{2'}$), 1.44 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.41 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.34 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.32 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.26 (3H, t, $^3J_{HH}$ 7.1 Hz, H_{14}), 0.15 (9 H, s, H_{15}) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4 (C_{12}), 109.4 (C_8 or C_{10}), 107.7 (C_8 or C_{10}), 79.86 (C_4 or C_5 or C_6), 77.02 (C_4 or C_5 or C_6 (DEPT 45)), 76.6(C_3), 71.8 (C_4 or C_5 or C_6), 67.0 (C_7), 60.3 (C_{13}), 30.7 (C_1), 28.1 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 26.2 (2C, C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 26.1 (C_2), 25.2 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 12.4 (C_{14}), 0.7 (C_{15}) ppm. Only ^{13}C NMR reported in the literature, our data match the literature data.[154] **MS** (ESI^+) (m/z) 427.2 $[M+Na]^+$; **HRMS** (ESI^+) for $C_{19}H_{36}O_7Si$ $[M+Na]^+$ calcd 427.2123, found 427.2132.

10.11.3 Synthesis of α-brominated esters 8.68



8.67 **8.68a, 48%** **8.68b, 24%**

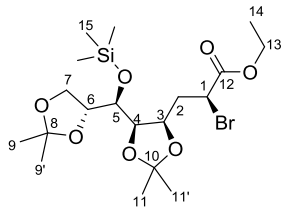
To a stirred solution of LDA (prepared from *n*-BuLi (1.6M in hexanes, 1.1 mL, 1.7 mmol, 1.3 equiv.) and diisopropylamine (240 µL, 1.7 mmol, 1.3 equiv.) in THF (5 mL) at -78 °C) was added a solution of TMSCl (300 µL, 2.3 mmol, 1.8 equiv.) and ester **8.67** (528 mg, 1.3 mmol, 1 equiv.) in THF (5 mL) at -78 °C. The mixture was stirred for 1 h at this temperature, after which *N*-bromosuccinimide (276 mg, 1.56 mmol, 1.2 equiv.) was added portionwise. The resulting mixture was then stirred at 0 °C for 1 h, then quenched with a saturated solution of $NaHCO_3$ (5 mL). The mixture was then partitioned between EtOAc (10 mL) and H_2O (10 mL). The aqueous phase was extracted with EtOAc (3×10 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated in *vacuo* to give α-brominated ester **8.68** as a mixture of diastereoisomers (*dr* **8.68a**/**8.68b** 2:1). Purification *via* column chromatography (pentane/acetone 95:5 to 85:15) afforded compound **8.68a** (299 mg, 48%) and **8.68b** (150 mg, 24%) as pale oils.



8.68a

[α]$_D$ 72.7 (c 0.77, $CHCl_3$, 21 °C); **IR** (neat) 2979 (w, br), 1739 (m), 1372 (m), 1247 (s), 1213 (s), 1151 (s), 1096 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.49 (1H, dd, $^3J_{HH}$ 11.0 Hz, $^3J_{HH}$ 3.4 Hz, H_1), 4.39 (1H, ddd, $^3J_{HH}$ 10.8 Hz, $^3J_{HH}$ 5.2 Hz, $^3J_{HH}$ 2.1 Hz, H_3), 4.24 (2H, q, $^3J_{HH}$ 7.3 Hz, H_{13}), 4.12 (1H, dd, $^2J_{HH}$ 8.2 Hz, $^3J_{HH}$ 6.5 Hz, H_7), 4.04 (1H, dd, $^3J_{HH}$ 8.4 Hz, $^3J_{HH}$ 5.3 Hz, H_4), 3.96 (1H, dd, $^3J_{HH}$ 13.5 Hz, $^3J_{HH}$ 7.0 Hz, H_6), 3.81 (1H, dd, $^2J_{HH}$ 8.1 Hz, $^3J_{HH}$ 7.1 Hz, $H_{7'}$), 3.77 – 3.70 (1 H, m, H_5), 2.33 (1H, ddd, $^2J_{HH}$ 14.2 Hz, $^3J_{HH}$ 11.0 Hz, $^3J_{HH}$ 2.2 Hz, H_2), 2.05 (1 H, ddd, $^2J_{HH}$ 14.2 Hz, $^3J_{HH}$ 10.9, $^3J_{HH}$ 3.2 Hz, $H_{2'}$), 1.45 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.43 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.37 – 1.33 (6H, m, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.31 (3H, t, $^3J_{HH}$ 7.2 Hz, H_{14}), 0.14 (9 H, s, H_{15}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0 (C_{12}), 110.0 (C_8 or C_{10}), 108.0 (C_8

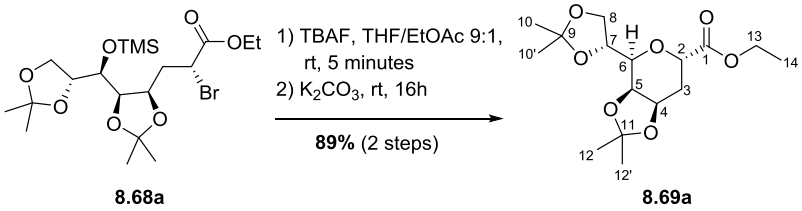
or C_{10}), 80.3 (C_4), 77.0 (C_6), 74.7 (C_3), 72.2 (C_5), 67.9 (C_7), 62.0 (C_{13}), 44.3 (C_1), 35.4 (C_2), 28.3 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 26.3 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 26.1 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 25.2 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 13.9 (C_{14}), 0.7 (C_{15}) ppm; **MS** (ESI^+) (m/z) 507 $[M(^{81}Br) + Na]^+$, 505 $[M(^{79}Br) + Na]^+$; **HRMS** (ESI^+) for $C_{19}H_{35}{}^{79}BrO_7Si$ $[M+Na]^+$ calcd 505.1228, found 505.1235.



8.68b

$[\alpha]_D$ 27.1 (c 0.64, $CHCl_3$, 21 °C); **IR** (neat) 2983 (w, br), 1742 (s), 1372 (m), 1250 (s), 1221 (s), 1152 (s), 1105 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.50 (1H, dd, $^3J_{HH}$ 11.5 Hz, $^3J_{HH}$ 3.7 Hz, H_1), 4.31 – 4.17 (2H, m, H_{13}), 4.11 – 4.02 (1H, m, H_3), 4.08 (1H, dd, $^2J_{HH}$ 8.1 Hz, $^3J_{HH}$ 6.4 Hz, H_7), 3.99 – 3.91 (2H, m, H_4, H_6), 3.87 – 3.81 (1H, m with the presence of *J* 7.6 Hz, $H_{7'}$), 3.78 (1H, dd, $^3J_{HH}$ 8.0, $^3J_{HH}$ 6.7 Hz, H_5), 2.58 (1H, ddd, $^2J_{HH}$ 13.4 Hz, $^3J_{HH}$ 11.3 Hz, $^3J_{HH}$ 2.5 Hz, H_2), 2.11 (1H, ddd, $^2J_{HH}$ 13.3 Hz, $^3J_{HH}$ 11.4, $^3J_{HH}$ 3.7 Hz, $H_{2'}$), 1.47 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.46 (3H, s, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.36 (3H, m, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.32 (3H, m, H_9 or $H_{9'}$ or H_{11} or $H_{11'}$), 1.31 (3H, t, $^3J_{HH}$ 7.0 Hz, H_{14}), 0.16 (9H, s, H_{15}) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.4 (C_{12}), 109.8 (C_8 or C_{10}), 108.1 (C_8 or C_{10}), 80.1 (C_4 or C_6), 76.9 (C_6 or C_4), 74.7 (C_3), 71.9 (C_5), 67.3 (C_7), 61.9 (C_{13}), 41.4 (C_1), 37.0 (C_2), 28.3 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 26.2 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 26.0 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 25.3 (C_9 or $C_{9'}$ or C_{11} or $C_{11'}$), 14.0 (C_{14}), 0.7 (C_{15}) ppm. **MS** (ESI^+) (m/z) 507 $[M(^{81}Br)+Na]^+$, 505 $[M(^{79}Br)+Na]^+$; **HRMS** (ESI^+) for for $C_{19}H_{35}{}^{79}BrO_7Si$ $[M+Na]^+$ calcd 505.1228, found 505.1235.

10.11.4 Synthesis of protected 2β-deoxy-Kdo 8.69a

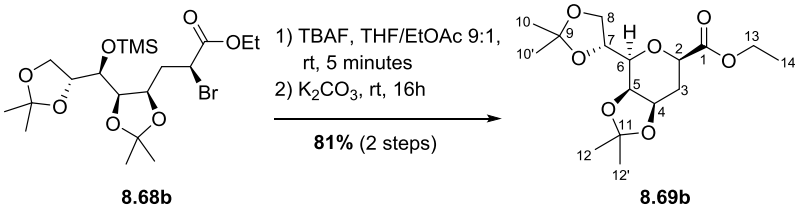


8.68a **8.69a**

To a solution of **8.68a** (278 mg, 0.57 mmol, 1 equiv.) in EtOAc/EtOH (9:1, 5.7 mL) at rt was added TBAF (1M in THF, 520 µL, 0.52 mmol, 0.9 equiv.) dropwise. The mixture was stirred at rt for 5 min., after which K_2CO_3 (336 mg, 1.7 mmol, 3 equiv.) was added. The resulting suspension was stirred for 16 h, then partitioned between H_2O (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3×10 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated. Purification via column chromatography (pentane/Et_2O 6:4) followed by preparative HPLC (hexane/EtOAc 8:2) afforded compound **8.69a** as a colourless oil (168 mg, 89%).

$[\alpha]_D$ -45.7 (c 1.51, $CHCl_3$, 21 °C), lit. -43.8 (c 1.07, $CHCl_3$, 21 °C)[133]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.59 (1H, ddd appeared as dt, $^3J_{HH}$ 7.8 Hz, $^3J_{HH}$ 2.9 Hz, H_4), 4.53 (1H, dd, $^3J_{HH}$ 11.4 Hz, $^3J_{HH}$ 6.0 Hz, H_2), 4.34 (1H, dd, $^3J_{HH}$ 8.1 Hz, $^3J_{HH}$ 1.5 Hz, H_5), 4.26 – 4.17 (4H, m, H_{13}, H_7 and H_8 or H_8 and $H_{8'}$), 4.16 – 4.07 (1H, H_7 or H_8), 3.51 (1H, dd, $^3J_{HH}$ 8.1 Hz, $^3J_{HH}$ 1.5 Hz, H_6), 2.31 (1H, ddd, $^2J_{HH}$ 15.0 Hz, $^3J_{HH}$ 5.9 Hz, $^3J_{HH}$ 2.7 Hz, H_3), 1.86 (1H, ddd, $^2J_{HH}$ 14.7 Hz, $^3J_{HH}$ 11.7, $^3J_{HH}$ 2.8 Hz, $H_{3'}$), 1.49 (3H, s, H_{10} or $H_{10'}$ or H_{12} or $H_{12'}$), 1.42 (3H, s, H_{10} or $H_{10'}$ or H_{12} or $H_{12'}$), 1.38 (3H, s, H_{10} or $H_{10'}$ or H_{12} or $H_{12'}$), 1.37 (3H, s, H_{10} or $H_{10'}$ or H_{12} or $H_{12'}$), 1.29 (3H, t, $^3J_{HH}$ 7.2 Hz, H_{14}) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9 (C_1), 109.4 (C_9 or C_{11}), 109.3 (C_9 or C_{11}), 73.7 (C_7), 72.8 (C_6), 72.2 (C_5), 69.8 (C_2), 68.4 (C_4), 67.2 (C_8), 61.0 (C_{13}), 27.0 (C_{10} or $C_{10'}$ or C_{12} or $C_{12'}$), 26.7 (C_3), 26.2 (C_{10} or $C_{10'}$ or C_{12} or $C_{12'}$), 25.1 (C_{10} or $C_{10'}$ or C_{12} or $C_{12'}$), 24.9 (C_{10} or $C_{10'}$ or C_{12} or $C_{12'}$), 14.2 (C_{14}) ppm. NMR spectra correspond with the reported data.[137]

10.11.5 Synthesis of protected 2α-deoxy-Kdo-ester 8.69b

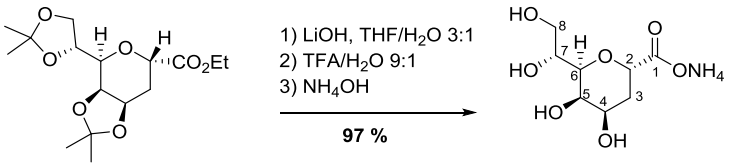


8.68b **8.69b**

To a solution of **8.68b** (130 mg, 0.27 mmol, 1 equiv.) in EtOAc/EtOH 9:1 (2.7 mL) at rt was added TBAF (1M in THF, 240 µL, 0.24 mmol, 0.9 equiv.) dropwise. The mixture was stirred at rt for 5 min, after which K_2CO_3 (111 mg, 0.8 mmol, 3 equiv.) was added. The resulting suspension was stirred for 16 h, then partitioned between H_2O (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3×10 mL). Organic phases were combined, dried over $MgSO_4$ and concentrated. Purification via column chromatography (pentane/Et_2O 45:55) afforded compound **8.69b** as a white solid (72 mg, 81%).

$[\alpha]_D$ 35.8 (c 0.33, $CHCl_3$, 20 °C), lit. 41.1 (c 0.18, $CHCl_3$, 20 °C)[137]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.44 – 4.32 (2H, m, H_4, H_7), 4.29 – 4.15 (3H, m, H_5, H_{13}), 4.14 – 4.10 (2H, m, H_8, $H_{8'}$), 4.03 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^3J_{HH}$ 3.9 Hz, H_2), 3.55 (1H, dd, $^3J_{HH}$ 7.8 Hz, $^3J_{HH}$ 2.0 Hz, H_6), 2.18 (1H, ddd, $^2J_{HH}$ 13.9 Hz, $^3J_{HH}$ 5.4 Hz, $^3J_{HH}$ 4.2 Hz, H_3), 1.99 (1 H, ddd, $^2J_{HH}$ 13.9 Hz, $^3J_{HH}$ 9.1 Hz, $^3J_{HH}$ 8.1 Hz, $H_{3'}$), 1.50 (3H, s, H_{10} or $H_{10'}$ or H_{12} or $H_{12'}$), 1.44 (3H, s, H_{10} or $H_{10'}$ or H_{12} or $H_{12'}$), 1.38 (3H, s, H_{10} or $H_{10'}$ or H_{12} or $H_{12'}$), 1.37 (3H, s, H_{10} or $H_{10'}$ or H_{12} or $H_{12'}$), 1.29 (3H, t, $^3J_{HH}$ 7.1 Hz, H_{14}) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.6 (C_1), 109.6 (C_9 or C_{11}), 109.3 (C_9 or C_{11}), 75.8 (C_7), 74.3 (C_6), 72.5 (C_5), 71.3 (C_2), 71.2 (C_4), 66.9 (C_8), 61.1 (C_{13}), 30.6 (C_3), 27.5 (C_{10} or $C_{10'}$ or C_{12} or $C_{12'}$), 27.0 (C_{10} or $C_{10'}$ or C_{12} or $C_{12'}$), 26.0 (C_{10} or $C_{10'}$ or C_{12} or $C_{12'}$), 25.4 (C_{10} or $C_{10'}$ or C_{12} or $C_{12'}$), 14.1 (C_{14}) ppm. NMR spectra correspond with the reported data.[137]

10.11.6 Synthesis of 2β-deoxy-Kdo β-7.23



8.69a **β-7.23**

To a solution of **8.69a** (49 mg, 0.15 mmol, 1 equiv.) in THF/H_2O (3:1, 6 mL) at rt was added LiOH (7 mg, 0.3 mmol, 2 equiv.), and the mixture was stirred at this temperature for 90 min. A solution of HCl 2M was then added until pH 1-2, and the resulting mixture was stirred for 5 min. The organic phase was extracted with EtOAc (5×10 mL), dried over $MgSO_4$ and concentrated in *vacuo*, to give 46 mg of crude acid, which was then dissolved in TFA/H_2O (9:1, 6 mL) and stirred for 90 min The mixture was then concentrated in *vacuo*, co-evaporated with toluene, dissolved in H_2O and filtered through cotton wool. The resulting oil was freeze-dried for 48 h, to give 33 mg of acid (isolated with 1 mol% of TFA (fluorobenzene used as internal reference)). The acid was then dissolved in NH_4OH (2 mL), concentrated in *vacuo* and freeze-dried for 48 h, to give the 2β-deoxy Kdo **β-7.23** as a white solid (35 mg, 97% over 2 steps).

$[\alpha]_D$ 52.1 (c 0.3, H_2O, 24 °C), lit. 68.6 (c 1.02, H_2O, 20 °C)[137]; **^{1}H NMR** (400 MHz, D_2O) δ 4.28 (1H, d, $^3J_{HH}$ 6.6 Hz, H_2), 3.91 (1H, br. s, H_5), 3.81 – 3.57 (4H, m, H_4, H_7, H_8, $H_{8'}$), 3.47 (1H, d, $^3J_{HH}$ 8.3 Hz, H_6), 2.14 (1H, dd, $^2J_{HH}$ 13.0 Hz, $^3J_{HH}$ 4.9 Hz, H_3), 1.95 (1 H, ddd appeared as td, $^2J_{HH}$, $^3J_{HH}$ 12.6 Hz, $^3J_{HH}$ 6.8 Hz, $H_{3'}$) ppm; **^{13}C NMR** (100 MHz, D_2O) δ 178.6 (C_1), 74.2, 73.8, 69.1, 66.9, 66.3, 64.0 (C_8), 28.5 (C_3) ppm. NMR spectra correspond with the reported data.[137]

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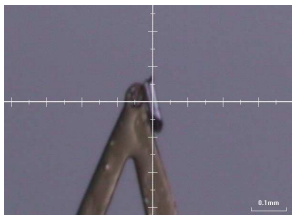
Chapter 11: Appendices

Submitted by: **Malassis, J.**
Supervisor: **Linclau, B.L.**
Solved by: **Light, M.E.**
Sample ID: ***syn*-1.89b** (JM7196-87recryst)



Crystal Data and Experimental

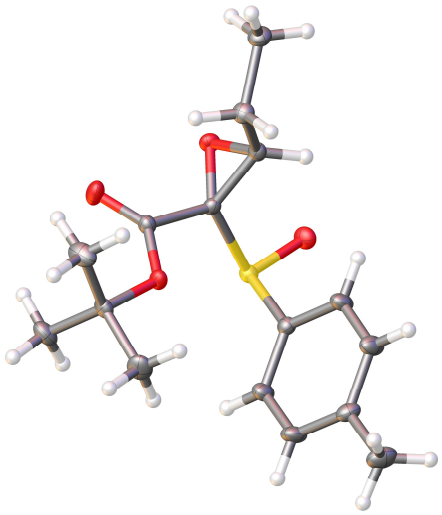


Figure 1. Thermal ellipsoids drawn at the 50 % probability level.

Experimental. Single clear colourless rod-shaped crystals of (**2014sot0048**) were recrystallised from a mixture of pentane and ethanol by slow evaporation. A suitable crystal (0.16 × 0.03 × 0.02 mm^3) was selected and mounted on a MITIGEN holder in perfluoroether oil a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the ShelXT (Sheldrick, 2008) structure solution program, using the Direct Methods solution method. The model was refined with version of **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

Crystal Data. $C_{16}H_{22}O_4S$, M_r = 310.39, orthorhombic, $P2_12_12_1$ (No. 19), a = 5.88884(12) Å, b = 12.3215(3) Å, c = 22.2795(5) Å, $\alpha = \beta = \gamma$ = 90 °, V = 1616.58(6) Å^3, T = 100(2) K, Z = 4, Z' = 1, μ (MoK$_\alpha$) = 0.213, 17203 reflections measured, 5362 unique (R_{int} = 0.0242) which were used in all calculations. The final wR_2 was 0.0755 (all data) and R_1 was 0.0312 (I > 2(I)).

Compound	**2014sot0048**
Formula	$C_{16}H_{22}O_4S$
$D_{calc.}$/ g cm^{-3}	1.275
μ/mm^{-1}	0.213
Formula Weight	310.39
Colour	clear colourless
Shape	rod
Max Size/mm	0.16
Mid Size/mm	0.03
Min Size/mm	0.02
T/K	100(2)
Crystal System	orthorhombic
Flack Parameter	0.05(2)
Hooft Parameter	0.044(18)
Space Group	$P2_12_12_1$
a/Å	5.88884(12)
b/Å	12.3215(3)
c/Å	22.2795(5)
α/°	90
β/°	90
γ/°	90
V/Å^3	1616.58(6)
Z	4
Z'	1
Θ_{min}/°	2.465
Θ_{max}/°	32.306
Measured Refl.	17203
Independent Refl.	5362
Reflections Used	4890
R_{int}	0.0242
Parameters	195
Restraints	0
Largest Peak	0.294
Deepest Hole	-0.186
GooF	1.066
wR_2 (all data)	0.0755
wR_2	0.0730
R_1 (all data)	0.0370
R_1	0.0312

Experimental Extended. A clear colourless rod-shaped crystal with dimensions 0.16 × 0.03 × 0.02 mm^3 was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T = 100(2)$ K.

Data were measured using profile data from ω-scans of 1.0° per frame for 10.0 s using MoK_α radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\Theta = 32.306$.

Cell parameters were retrieved using the CrysAlisPro (Agilent, V1.171.37.35, 2014) software and refined using CrysAlisPro (Agilent, V1.171.37.35, 2014) on 10959 reflections, 64 of the observed reflections.

Data reduction was performed using the CrysAlisPro (Agilent, V1.171.37.35, 2014) software which corrects for Lorentz polarisation. The final completeness is 99.80 out to 32.306 in Θ. The absorption coefficient (MU) of this material is 0.213 and the minimum and maximum transmissions are 0.96303 and 1.00000.

The structure was solved by Direct Methods using the ShelXT (Sheldrick, 2008) structure solution program and refined by Least Squares using version of **ShelXL** (Sheldrick, 2008).

The structure was solved in the space group $P2_12_12_1$ (# 19). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

There is no entry for the cif item _refine_special_details

Citations

CrystalClear, Rigaku, ?(?).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

groupsite.soton.ac.uk/Research/xray/ | light@soton.ac.uk | 02380599429

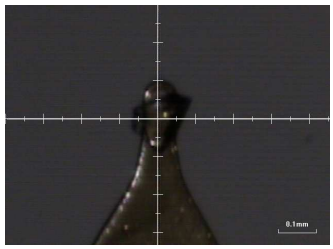
Submitted by: **Julien J Malassis**

Supervisor: **Bruno Linclau**

Solved by: **Mark Edward Light**

Sample ID: ***syn*-2.8a** (JM7462-15F1-recryst)

d min	0.67	I/σ	34.4	Rint	2.76%	complete at 2θ=64°	91%
Shift/esd	-0.001	Max Peak	0.4	Min Peak	-0.3	GooF	1.040



Crystal Data and Experimental

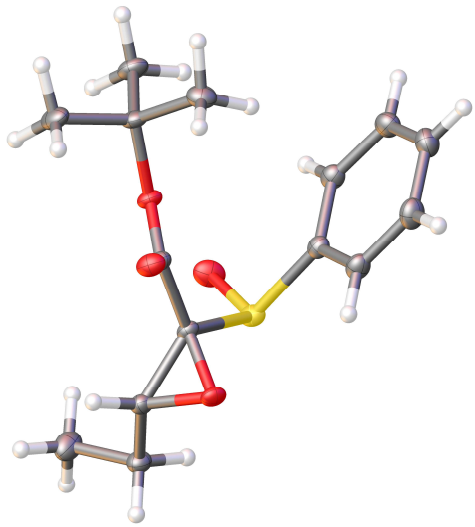


Figure 1. Thermal ellipsoids drawn at the 50 percent probability level.

Experimental. Single clear colourless Fragment-shaped crystals of (**2014sot0062**) were recrystallised from a mixture of pentane and Et2O by slow evaporation. A suitable crystal (0.14 × 0.10 × 0.03) was selected and mounted on a Lindemann tube in perfluoroether oil a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the ShelXT (Sheldrick, 2008) structure solution program, using the Direct Methods solution method. The model was refined with version of **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

Crystal Data. $C_{15}H_{20}O_4S$, M_r = 296.37, monoclinic, $P2_1/n$ (No. 14), a = 8.82630 Å, b = 15.6858 Å, c = 11.5156 Å, β = 106.331(2)°, α = γ = 90°, V = 1529.98(5) Å^3, T = 100(2) K, Z = 4, Z' = 1, μ(MoK$_\alpha$) = 0.221, 18422 reflections measured, 4826 unique (R_{int} = 0.0276) which were used in all calculations. The final wR_2 was 0.0835 (all data) and R_1 was 0.0315 (I > 2(I)).

Compound	**2014sot0062**
Formula	$C_{15}H_{20}O_4S$
$D_{calc.}$/ g cm^{-3}	1.287
μ/mm^-1	0.221
Formula Weight	296.37
Colour	clear colourless
Shape	Fragment
Max Size/mm	0.14
Mid Size/mm	0.10
Min Size/mm	0.03
T/K	100(2)
Crystal System	monoclinic
Space Group	$P2_1/n$
a/Å	8.82630(17)
b/Å	15.6858(3)
c/Å	11.5156(2)
α/°	90
β/°	106.331(2)
γ/°	90
V/Å^3	1529.98(5)
Z	4
Z'	1
Θ_{min}/°	2.254
Θ_{max}/°	32.001
Measured Refl.	18422
Independent Refl.	4826
Reflections Used	4243
R_{int}	0.0276
Parameters	185
Restraints	0
Largest Peak	0.409
Deepest Hole	-0.264
GooF	1.040
wR_2 (all data)	0.0835
wR_2	0.0799
R_1 (all data)	0.0372
R_1	0.0315

Experimental Extended. A clear colourless Fragment-shaped crystal with dimensions 0.14 × 0.10 × 0.03 was mounted on a Lindemann tube in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T = 100(2)$ K.

Data were measured using profile data from ω-scans of 1.0° per frame for 10.0 s using MoK_α radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\theta = 32.001$.

Cell parameters were retrieved using the CrysAlisPro (Agilent, V1.171.37.35, 2014) software and refined using CrysAlisPro (Agilent, V1.171.37.35, 2014) on 14213 reflections, 77 of the observed reflections.

Data reduction was performed using the CrysAlisPro (Agilent, V1.171.37.35, 2014) software which corrects for Lorentz polarisation. The final completeness is 99.80 out to 32.001 in θ. The absorption coefficient (μ) of this material is 0.221 and the minimum and maximum transmissions are 0.94219 and 1.00000.

The structure was solved by Direct Methods using the ShelXT (Sheldrick, 2008) structure solution program and refined by Least Squares using version of **ShelXL** (Sheldrick, 2008).

The structure was solved in the space group $P2_1/n$ (# 14). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

There is no entry for the cif item _refine_special_details

Citations

CrystalClear, Rigaku, ? (?).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

groupsite.soton.ac.uk/Research/xray/ | light@soton.ac.uk | 02380599429

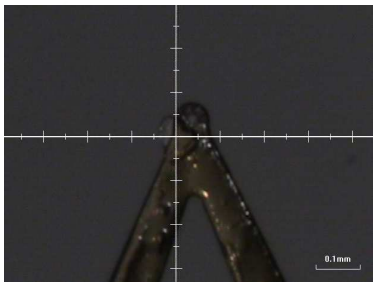
d min	0.69	I/σ	15.1	Rint	3.38%	complete at 2θ=62°	61%
Shift/esd	0.000	Max Peak	1.0	Min Peak	-0.4	GooF	0.982

Submitted by: **Malassis, J.**

Supervisor: **Linclau, B.**

Solved by: **Light, M.**

Sample ID: **3.36a** (JM7196-97F2)



Crystal Data and Experimental

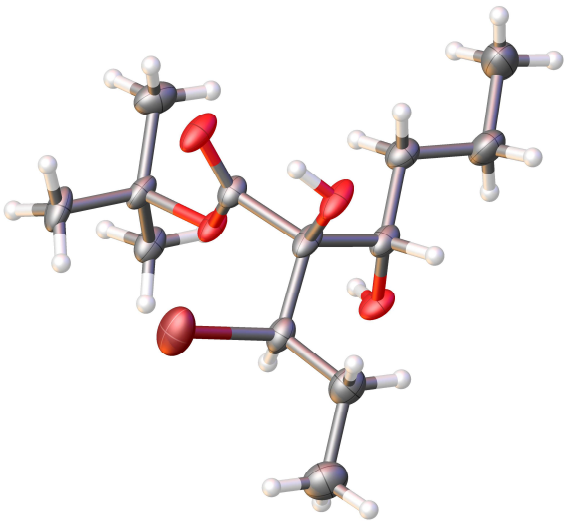


Figure 1. Thermal ellipsoids drawn at the 50 percent probability level.

Experimental. Single clear colourless plate-shaped crystals of (**2014sot0049**) were recrystallised from a mixture of pentane and Et2O by slow evaporation. A suitable crystal (0.11 × 0.05 × 0.01 mm^3) was selected and mounted on a MITIGEN holder in perfluoroether oil a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the ShelXT (Sheldrick, 2008) structure solution program, using the Direct Methods solution method. The model was refined with version of **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

Crystal Data. $C_{13}H_{25}BrO_4$, M_r = 325.24, triclinic, P1 (No. 1), a = 6.0963(3) Å, b = 8.7014(8) Å, c = 8.7050(8) Å, α = 66.516(9)°, β = 73.360(6)°, γ = 87.831(6)°, V = 404.26(6) Å^3, T = 100(2) K, Z = 1, Z' = 1, μ (MoK$_\alpha$) = 2.547, 4082 reflections measured, 3019 unique (R_{int} = 0.0338) which were used in all calculations. The final wR_2 was 0.1220 (all data) and R_1 was 0.0486 (I > 2(I)).

Compound	2014sot0049
Formula	$C_{13}H_{25}BrO_4$
$D_{calc.}$/ g cm^{-3}	1.336
μ/mm^{-1}	2.547
Formula Weight	325.24
Colour	clear colourless
Shape	plate
Max Size/mm	0.11
Mid Size/mm	0.05
Min Size/mm	0.01
T/K	100(2)
Crystal System	triclinic
Flack Parameter	0.003(14)
Hooft Parameter	0.114(6)
Space Group	P1
a/Å	6.0963(3)
b/Å	8.7014(8)
c/Å	8.7050(8)
α/°	66.516(9)
β/°	73.360(6)
γ/°	87.831(6)
V/Å^3	404.26(6)
Z	1
Z'	1
Θ_{min}/°	2.562
Θ_{max}/°	30.841
Measured Refl.	4082
Independent Refl.	3019
Reflections Used	2470
R_{int}	0.0338
Parameters	174
Restraints	5
Largest Peak	1.024
Deepest Hole	-0.415
GooF	0.982
wR_2 (all data)	0.1220
wR_2	0.1152
R_1 (all data)	0.0619
R_1	0.0486

Experimental Extended. A clear colourless plate-shaped crystal with dimensions 0.11 × 0.05 × 0.01 mm^3 was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T = 100(2)$ K.

Data were measured using profile data from ω-scans of 1.0° per frame for 10.0 s using MoK_α radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\Theta = 30.841$.

Cell parameters were retrieved using the CrysAlisPro (Agilent, V1.171.37.35, 2014) software and refined using CrysAlisPro (Agilent, V1.171.37.35, 2014) on 2489 reflections, 61 of the observed reflections.

Data reduction was performed using the CrysAlisPro (Agilent, V1.171.37.35, 2014) software which corrects for Lorentz polarisation. The final completeness is 99.80 out to 30.841 in Θ. The absorption coefficient (MU) of this material is 2.547 and the minimum and maximum transmissions are 0.82030 and 1.00000.

The structure was solved by Direct Methods using the ShelXT (Sheldrick, 2008) structure solution program and refined by Least Squares using version of **ShelXL** (Sheldrick, 2008).

The structure was solved in the space group P1 (# 1). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

The short inter D-H..H-D (H3..H4) contact of 2.03Ang is an unavoidable consequence of the packing. The highest residual electron density peak may be a result of very minor whole molecule disorder in relation to the bromine position. H3 and H4 (hydroxyl hydrogens) were refined with a distance restraint (0.84Angs) and a thermal parameter tied to 1.5 that of its parent atom.

The Flack parameter was refined to 0.003(14), confirming the absolute stereochemistry. Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.114(6). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

Citations

CrystalClear, Rigaku, ?(?).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

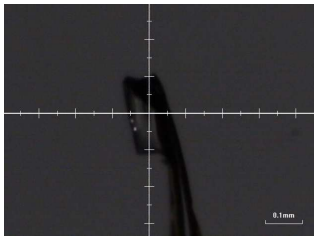
groupsite.soton.ac.uk/Research/xray/ | light@soton.ac.uk | 02380599429

Submitted by: **Julien J Malassis**

Supervisor: **Bruno Linclau**

Solved by: **Mark Edward Light**

Sample ID: **8.17a** (JM6867-61)



Crystal Data and Experimental

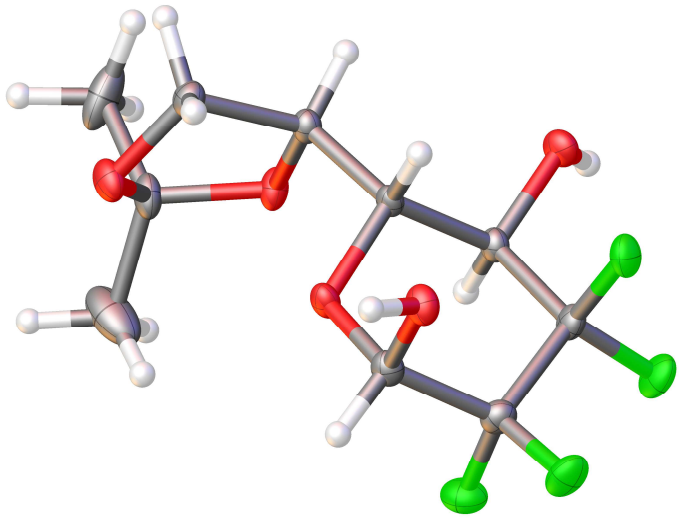


Figure 1. Thermal ellipsoids drawn at the 50 percent probability level.

Experimental. Single clear colourless prism-shaped crystals of (**2014sot0053**) were recrystallised from a mixture of hexane and Et2O by slow evaporation. A suitable crystal (0.23 × 0.18 × 0.15) was selected and mounted on a MITIGEN holder in perfluoroether oil a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the ShelXT (Sheldrick, 2015) structure solution program, using the Direct Methods solution method. The model was refined with version of **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

Crystal Data. $C_{10}H_{14}F_4O_5$, M_r = 290.21, monoclinic, $P2_1$ (No. 4), a = 10.3974 Å, b = 21.0683 Å, c = 11.4465 Å, β = 102.014(2)°, α = γ = 90°, V = 2452.50(9) Å^3, T = 100(2) K, Z = 8, Z' = 4, μ(MoK$_\alpha$) = 0.161, 27648 reflections measured, 14504 unique (R_{int}# = 0.0313) which were used in all calculations. The final wR_2 was 0.1256 (all data) and R_1 was 0.0453 (I > 2(I)).

Compound	2014sot0053
Formula	$C_{10}H_{14}F_4O_5$
$D_{calc.}$/ g cm^{-3}	1.572
μ/mm^-1	0.161
Formula Weight	290.21
Colour	clear colourless
Shape	prism
Max Size/mm	0.23
Mid Size/mm	0.18
Min Size/mm	0.15
T/K	100(2)
Crystal System	monoclinic
Flack Parameter	-0.2(3)
Hooft Parameter	-0.46(11)
Space Group	$P2_1$
a/Å	10.3974(2)
b/Å	21.0683(4)
c/Å	11.4465(2)
α/°	90
β/°	102.014(2)
γ/°	90
V/Å^3	2452.50(9)
Z	8
Z'	4
Θ_{min}/°	2.973
Θ_{max}/°	30.503
Measured Refl.	27648
Independent Refl.	14504
Reflections Used	13598
R_{int}	0.0313
Parameters	701
Restraints	1
Largest Peak	1.742
Deepest Hole	-0.498
GooF	1.025
wR_2 (all data)	0.1256
wR_2	0.1234
R_1 (all data)	0.0481
R_1	0.0453

Experimental Extended. A clear colourless prism-shaped crystal with dimensions 0.23 × 0.18 × 0.15 was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at $T = 100(2)$ K.

Data were measured using profile data from ω-scans of 1.0° per frame for 10.0 s using MoK_α radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was $\theta = 30.503$.

Cell parameters were retrieved using the CrysAlisPro (Agilent, V1.171.37.35, 2014) software and refined using CrysAlisPro (Agilent, V1.171.37.35, 2014) on 25122 reflections, 91 of the observed reflections.

Data reduction was performed using the CrysAlisPro (Agilent, V1.171.37.35, 2014) software which corrects for Lorentz polarisation. The final completeness is 99.60 out to 30.503 in θ. The absorption coefficient (μ) of this material is 0.161 and the minimum and maximum transmissions are 0.92979 and 1.00000.

The structure was solved by Direct Methods using the ShelXT (Sheldrick, 2015) structure solution program and refined by Least Squares using version of **ShelXL** (Sheldrick, 2008).

The structure was solved in the space group $P2_1$ (# 4). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

The 2 high residual electron density peaks probably result from minor disorder of the OH and H on C307 and C407.

Citations

CrystalClear, Rigaku, ? (?).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.