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STEREOSELECTIVE SYNTHESIS OF OLIGOSACCHARIDES BY *DE NOVO* SACCHARIDE WELDING

BY

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Doctor of Philosophy

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ABSTRACT

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Carbohydrates play important roles in biological recognition and regulation processes; as a result, carbohydrates have become the focus of intense synthetic efforts. Although great advances have been made in the synthesis of carbohydrates from monosaccharide precursors, this traditional chemical synthesis of carbohydrates is limited to the range of available naturall monosaccharide building blocks. Moreover, this method suffers from laborious protection and glycosylation strategies.

The aim of this thesis was to develop an alternative strategy to construct the carbohydrate linchpin between two carbohydrate building blocks via the direct *de novo* synthesis of the central monosaccharide unit. The advantage of such a strategy is that in the coupling step, there is no need to control the stereochemistry and the position of glycosidic linkages. Moreover, the strategy is not limited to the natural carbohydrate building blocks.

The first strategy employed in this work was to construct the carbohydrate linchpin using a two-step aldol methodology; this approach was unsuccessful because of low yields and unstability of the products in the first aldol addition step. The next strategy for the synthesis of di- and trisaccharides was to use a one-step hetero-Diels–Alder (HDA) reaction. In this method, functionalized monosaccharide building blocks that already included the glycosidic linkages were welded together using a metal-catalyzed HDA reaction to generate a new monosaccharide unit between them. The highest yields and selectivities in the HDA reaction were obtained with Jacobsen's chiral Schiff base chromium complexes. Disaccharide products were accessible by reaction of Danishefsky's diene with acetyl- and benzyl-protected galactose-derived aldehydes. For the synthesis of trisaccharide products, acetyl-protected glucose or galactose-derived dienes were fused with monosaccharide-derived aldehydes using chromium complexes. The desired 4,6-linked trisaccharide products were obtained in moderate to good yields (32-68%) with excellent stereoselectivity (dr > 30:1). The central pyranulose B-ring generated in the process possessed an L-galactal-type configuration according to NMR and modeling studies.

Moreover, in this work, a short introduction to the carbohydrate chemistry, *in vivo* synthesis of monosaccharides, and the previously published *de novo* methodologies for aldohexoses are reviewed.

Keywords: carbohydrate synthesis, *de novo* saccharide synthesis, aldol, hetero-Diels –Alder, salen, chromium

TIIVISTELMÄ

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Hiilihydraatit ovat tärkeässä roolissa biologisissa tunnistus- ja säätelytehtävissä, ja siksi niiden synteesistä on tullut tärkeä tutkimuskohde. Kuitenkin hiilihydraattien perinteistä synteesiä vaikeuttaa työläs suojaryhmien käyttö. Myös muodostuvan sidoksen stereokemian ja sijainnin säätely on haasteellista. Lisäksi menetelmä on rajoittunut lähtöaineiden osalta luonnossa esiintyviin hiilihydraattirakenteisiin.

Tämän väitöskirjan tavoitteena oli kehittää vaihtoehtoinen menetelmä hiilihydraattien synteesiin. Tässä menetelmässä uusi hiilihydraattiosa muodostetaan kahden toiseensa kytkettävän hiilihydraattirakenteen väliin *de novo* synteesillä. Tämän menetelmän etuna on, että kytkentävaiheessa ei tarvitse kontrolloida glykosidisidoksen stereokemiaa eikä sijaintia. Lisäksi menetelmä ei ole rajoittunut lähtöaineiden osalta hiilihydraattirakenteisiin.

Tässä työssä yritettiin aluksi muodostaa uusi hiilihydraattiosa kaksivaiheisella aldolimenetelmällä. Tämä menetelmä osoittautui kuitenkin toimimattomaksi ensimmäisen aldolivaiheen huonojen saantojen ja tuotteiden epästabiilisuuden vuoksi. Tämän jälkeen tutkittiin uuden hiilihydraattiosan muodostamista yksivaiheisella hetero-Diels–Alder (HDA) -reaktiolla. Metallikatalysoidun HDA-reaktion avulla valmistettiin di- ja trisakkarideja muodostamalla uusi hiilihydraattiosa toisiinsa kytkettävien funktionaalisten monosakkaridiosien väliin. Korkein saanto ja selektiivisyys HDA-kytkennässä saavutettiin käyttämällä katalyyttinä Jacobsenin kiraalisen Schiff emäksen ja kromin kompleksia. Disakkarideja valmistettiin Danishefskyn dieenin sekä asetyyli- ja bentsyylisuojatun galaktoosipohjaisen aldehydin välisellä HDA-reaktiolla. Trisakkaridien synteesissä käytettiin asetyyli-suojatun galaktoosi- ja glukoosipohjaisen dieenin sekä monosakkaridipohjaisen aldehydin välistä HDA-reaktiota. Tässä kromikompleksin katalysoimassa reaktiossa 4,6-kytkettyjen trisakkaridien saanto vaihteli kohtalaisesta hyvään (32-68%) ja stereoselektiivisyys oli erittäin korkea (dr > 30:1). Kytkennässä muodostuneen pyranuloosi-renkaan (B) stereokemia määritettiin L-galaktoosityyppiseksi NMR-tutkimuksella ja molekyylimallinnuksella.

Tässä työssä esitetään lisäksi lyhyt johdanto hiilihydraattikemiaan, monosakkaridien luonnossa tapahtuvaan *in vivo* synteesiin sekä yhteenveto aiemmin julkaistuista aldoheksoosien *de novo* synteesimenetelmistä.

Asiasanat: hiilihydraattien synteesi, sakkaridien *de novo* synteesi, aldoli, hetero-Diels –Alder, salen, kromi

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PREFACE

This work was carried out at the Department of Chemical Technology, Aalto University (formerly the Helsinki University of Technology, TKK) and the Department of Chemistry, University of Jyväskylä, between 2007 and 2011.

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I am grateful to my supervisor, Prof. Petri Pihko, for taking me into his research group and introducing me to the exciting field of saccharide chemistry. Petri, thanks for a supportive, yet independent, research environment and for your encouragement through these years!

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Espoo, September 2012
Jatta Himanen

AUTHOR'S CONTRIBUTION

The author designed and carried out the experiments and analyses presented in this work, and interpreted the results together with Prof. Petri Pihko. This work is also written by the author.

ABBREVIATIONS AND DEFINITIONS

Ac	acetyl
AcOH	acetic acid
AD	asymmetric dihydroxylation
AD-mix-α	$K_2OsO_4 \cdot 2H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3
AD-mix-β	$K_2OsO_4 \cdot 2H_2O$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3
AE	asymmetric epoxidation
ATP	adenosine-5'-triphosphate
aq	aqueous
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*t*-butyloxycarbonyl
br	broad
Bu	butyl
*t*Bu	*tert*-butyl
BIPHEP	bis[di(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl
BOX	bisoxazoline
BQ	benzoquinone
Bz	benzoyl
calcd	calculated
cat.	catalytic amount
CBB cycle	Calvin–Benson-Bassham cycle
COT	cyclooctatetraene
*m*CPBA	*meta*-chloroperbenzoic acid
CTAB	cetyltrimethylammonium bromide
d	day
DA	Diels-Alder reaction
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarbozylate
DET	diethyl tartrate
DHA	dihydroxyacetone
DHAP	dihydroxyacetone phosphate
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutyl aluminum hydride
DIG	digitoxigenin
DMAP	4-dimethylaminopyridine
DMCC	dimethylcarbamoyl chloride
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide

DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
E	entgegen (opposite, *trans*)
EDTA	ethylenediaminetetraacetic acid
er	enantiomeric ratio
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
G3P	D-glyceraldehyde-3-phosphate
h	hour
HDA	hetero-Diels –Alder
KHMDS	potassium hexamethyldisilazane
LDA	lithium diisopropylamide
m	*meta*
Me	methyl
MPM	4-methoxybenzyl
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves
NADPH	nicotinamide adenine dinucleotide phosphate
Naph	naphthyl
NBS	*N*-bromosuccinimide
NBSH	2-nitrobenzenesulfonylhydrazide
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
p	page
p	*para*
PCC	pyridinium chlorochromate
PGA	phosphoglyceric acid
PHAL	phthalazine
Ph	phenyl
Piv	pivaloyl
PNBOH	*p*-nitrobenzoic acid
PPTS	pyridinium *p*-toluenesulfonate
*i*Pr	iso-propyl
Pro	proline
py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
$[Rh(cod)_2]BARF$	bis(cyclooctadiene)rhodium(I)(tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate)
rt	room temperature
SEM	2-trimethylsilylethoxymethoxy
S_N2	bimolecular nucleophilic substitution
TBAF	tetrabutylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl

TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFDO	methyl(trifluoromethyl)dioxirane
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMS	trifluoromethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	toluene-4-sulfonyl
*p*TSOH	*para*-toluenesulfonic acid
Z	zusammen (together, *cis*)
quant.	quantitative

TABLE OF CONTENTS

1 INTRODUCTION

Carbohydrates have the empirical formula $C_x(H_2O)_y$ (with x and y equal to or greater than three). Thus, they have the same hydrogen:oxygen atom ratio (2:1) as water (H_2O), which explains the origin of their name. Carbohydrates are also called saccharides, in accordance with the Greek word meaning sugar. They are polyhydroxylated aldehydes and ketones, and are termed aldoses and ketoses, respectively. The carbonyl group normally does not occur as such, but is combined with hydroxyl groups to form hemiacetal or acetal linkages and ring forms of saccharide. The most common monosaccharides are pentoses and hexoses, which contain five and six carbon atoms, respectively. Two monosaccharides can be attached to each other via a glycosidic bond to form disaccharide. Mono- and disaccharides, the smallest of all carbohydrates, are also colloquially called sugars. Saccharides with two to nine monosaccharides are called oligosaccharides. More detailed information on carbohydrates is available. (1) (2)

Of the three main classes of biopolymers — proteins, nucleic acids and carbohydrates — the carbohydrates are structurally the most complex and hence form the extreme diverse class of organic compounds in nature. As each monosaccharide unit possesses multiple attachment sites, they can be linked in a variety of linear or branched fashions. Carbohydrates are essential for life, and carry out numerous roles in living organisms. In addition storing energy and acting as structural components, they also form the backbone of the genetic molecules, DNA and RNA. Moreover, carbohydrates and their derivatives are the key molecules in biological recognition and regulation processes, as well as in fertilization and development. (1) (2) (3) (4) (5)

Hence, the synthesis of carbohydrates and their analogues has become of considerable interest in organic chemistry. The chemical synthetic strategies for saccharides may be divided into two broad categories: 1) strategies involving the transform and assembly of naturally occurring carbohydrates into new (oligo)saccharide structures, and 2) strategies that afford the targeted compound via manipulation of non-saccharide precursors. The first strategy is used in the traditional chemical synthesis of oligosaccharides. In addition, naturally occurring monosaccharides can be modified into rare or unnatural sugar structures. However, this strategy obviously suffers from laborious protection/deprotection and activation/deactivation procedures due to difficulties in controlling the stereochemistry and position of glycosidic linkages. Moreover, this approach is limited to the range of available monosaccharide building blocks. (6) (7) (8) (9) (10) (11)

On the other hand, the second strategy, also known as *de novo* synthesis of carbohydrates, offers many advantages. It often enables the synthesis of either enantiomer of the target saccharide with a choice of starting materials, whereas from natural sources the D-

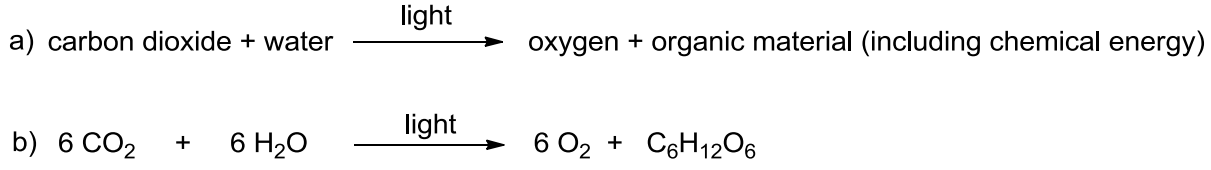
monosaccharides are more common than their L-counterparts. Thus, in the *de novo* synthesis there is a much wider range of available starting materials, meaning that more saccharide structures can be achieved. Moreover, a well designed *de novo* synthesis requires fewer steps because less protection and activation procedures are needed. Finally, this strategy enables easier access to ^{13}C-labeled oligosaccharides. However, for the *de novo* strategy to be competitive with the traditional strategy, a high degree of stereoselectivity at the newly formed stereocenters must be achieved. As a result, a wide variety of asymmetric approaches to synthetic saccharides have been developed. (6) (7) (8) (9) (10)

In Chapter 2, a short discussion of the formation of saccharides in nature is presented. Comprehensive reviews of the *de novo* syntheses of carbohydrates, and of the prior approaches to *de novo* synthesis of aldohexoses, are presented in Chapter 3. It should be stressed that the published methods have been directed almost exclusively to the synthesis of different *mono*saccharides, and thus, only a few examples of methodologies affording *oligo*saccharides are available. Even though monosaccharides are also fascinating and have readily available starting materials and sources of chirality for asymmetric synthesis, their further modifications are outside the scope of this review. Comprehensive reviews of carbohydrate-based chiral synthesis of natural products are available elsewhere. (12) (13) (14) (15)

In Chapter 4, my own work to extend the *de novo* methodology for the construction of more complex *oligo*saccharide units is presented. This is followed by the conclusion (Chapter 5), and finally, the experimental section (Chapter 6).

2 *IN VIVO* SYNTHESIS OF MONOSACCHARIDES

Saccharides, such as cellulose in cotton and glucose and fructose in honey, have been utilized early days of the human race. However, the understanding what carbohydrates are, and how they are produced, came much later. The first observations of understanding of plant grow date back to Greek philosopher Aristotle (384-322 B.C.) as he suggested that soil provided the substance for plant growth. (16) However, in 1648 van Helmont a Dutch alchemist, concluded from his experiments that in fact Aristotele must have been wrong. He presented that most of the weight of a plant did not come from the soil, but from water. (17) Later, in 1727 Hales, an English minister and naturalist, postulate that plants are nourished mostly by air. (18) In the beginning of the 1770's, Priestley, an English chemist, found out that green plants make and absorb gases. He noticed that plants were able to restore the healthy, life-sustaining capacities of air fouled by burning candles or breathing animals. As a result he discovered that plants produce oxygen (known then as 'dephlogisticated' or 'vital' air). (17) In 1779 Ingenhousz, a Dutch physiologist, biologist and chemist, discovered the action of ligh in plant grow. He noticed that in the presence of light, plants give off bubbles from their green parts while, in the shade, the bubbles eventually stop. He identified the gas as oxygen and leaves as the sites of this reaction. (19) (20) (21) (22) In 1796, Senabier, a Swiss pastor and naturalist, demonstrated that green plants consume carbon dioxide. Later, in 1845, Mayer, a German doctor and one of the codiscoverers of the law of conservation of energy, realized that ''plants absorb one form of energy, light, and put forth another, chemical''. (18) With all those discoveries, the equation of process used by plants to convert light energy to chemical energy, photosynthesis, became finally complete (see Scheme 1a). (23)



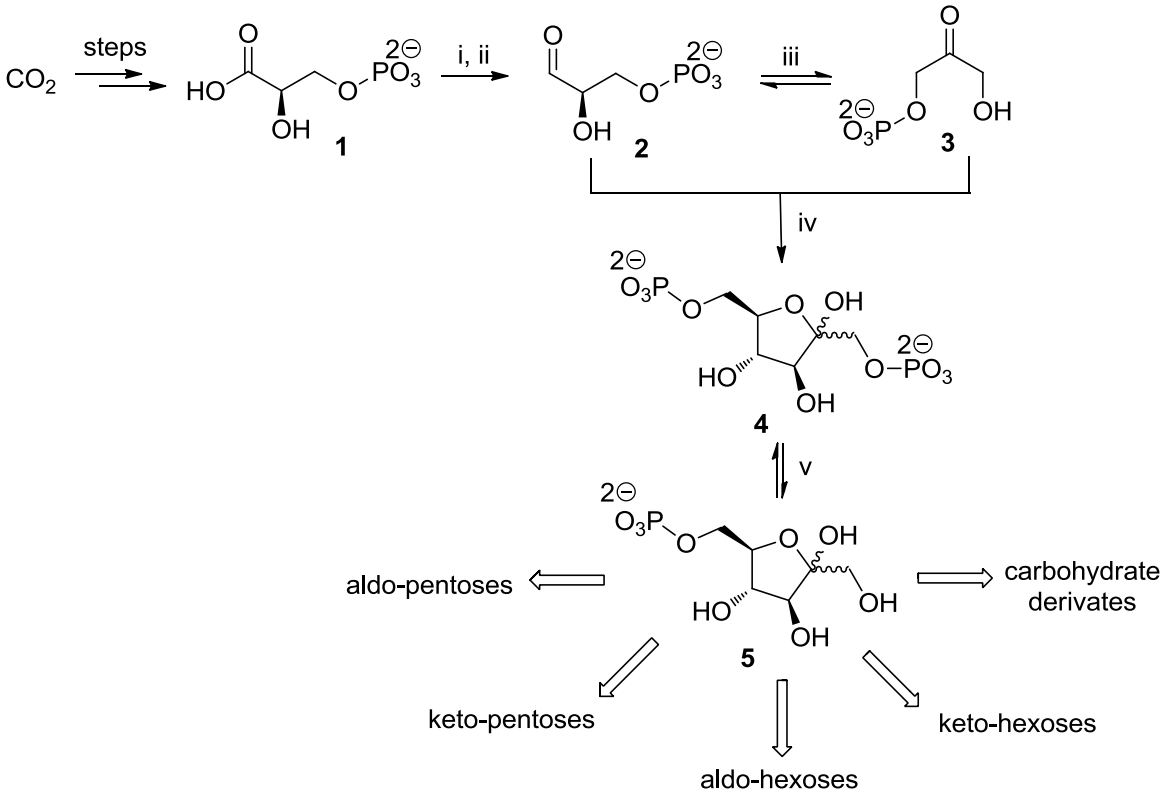
Scheme 1. The early (a) and general (b) equations of photosynthesis.

The presence of starch in leaves was recognized by von Mohl in 1837. However, it was not until 1893 when Brown and Morris suggested that most leaves contain sugars, for example sucrose, glucose and fructose. (24) In 1943 Smith established that the major products of photosynthesis were disaccharides (sucrose). (25)

Attempts to break photosynthesis into partial processes turned out to be troublesome. Photosynthesis involves the storage of chemical energy and the formation of highly unstable intermediates that undergo rapid enzymatic stabilization, ending in the liberation of oxygen and the formation of carbohydrates. Therefore, the mechanism of photosynthesis was long based on pure speculation. In 1870 it was proposed by von Baeyer, a German chemist, that photosynthesis occurs through a formaldehyde model consisting of two consecutive steps. In this model, carbon dioxide is first reduced to formaldehyde. Subsequent polymerization of formaldehyde would then yield carbohydrates. (26) However, attempts to test this hypothesis failed and later this model was shown to be in error. (27)

The key discoveries in understanding the reaction pathway of photosynthesis were made by Niel, a Dutch American microbiologist, in 1931: he demonstrated that photosynthesis is a light-dependent redox reaction. In this process, hydrogen from water reduces carbon dioxide. Oxygen, which plants produce during photosynthesis, is derived from water, not from carbon dioxide. (9) During the late 1940s and early 1950s Benson, Calvin, Bassham and coworkers determined the photosynthetic carbon dioxide reduction cycle in plants, known as the Calvin–Benson-Bassham (CBB) cycle. (28) (25) Currently, photosynthesis is known to consist of two separate series of interconnected biochemical reactions: the light reactions and the dark reactions (the latter is known also as the CBB cycle). The light reactions convert light energy to chemical energy by forming labile energy-storage molecules, ATP and NADPH. In the second stage, the dark reactions use these molecules to convert carbon dioxide and water into carbohydrates. (16)

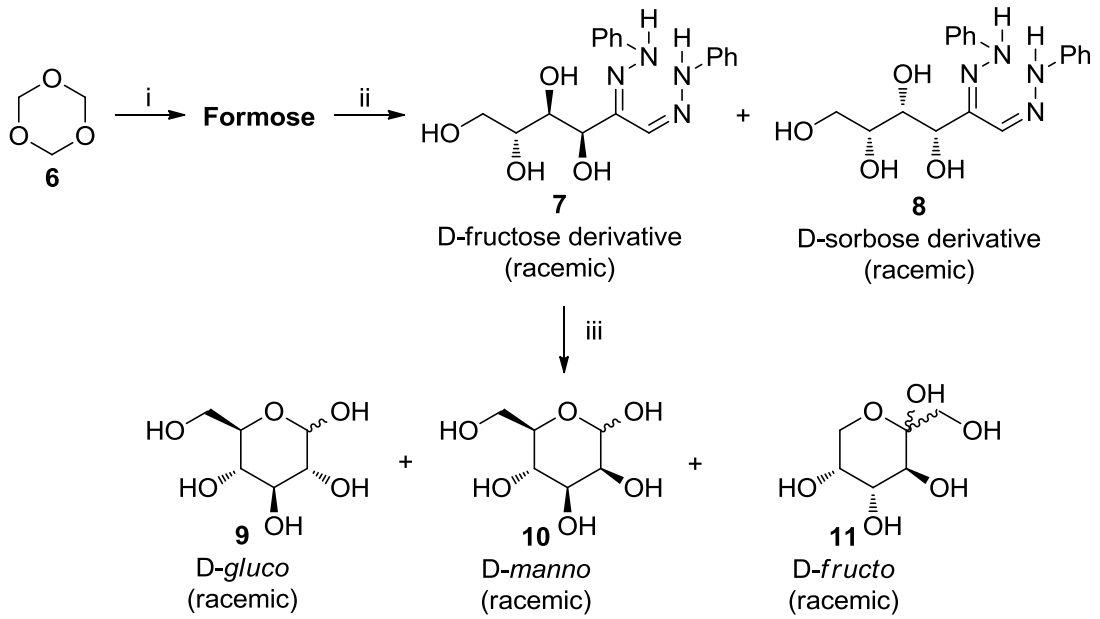
In this second stage, CO_2 is first incorporated into phosphoglyceric acid (PGA) **1** (Scheme 2). The subsequent phosphorylation and reduction of **1** affords D-glyceraldehyde-3-phosphate (G3P) **2**, which is isomerized to dihydroxyacetone phosphate (DHAP) **3**. G3P **2** and DHAP **3** undergo a stereoselective aldol reaction catalyzed by aldolase to give D-fructose-1,6-diphosphate **4**. Dephosphorylation affords D-fructose-1-phosphate **5**, which is then transformed to various carbohydrates and carbohydrate derivatives. Thus, many naturally occurring saccharides are produced via ketohexose intermediates. (28) (29) (30)



Scheme 2. Carbon pathway to saccharides during the Calvin cycle: i) ATP (phosphorylation); ii) NADPH (reduction); iii) triose phosphate isomerase; iv) fructose aldolase; v) fructose-1,6-bisphosphatase.

3 *DE NOVO* SYNTHESIS OF ALDOHEXOSES

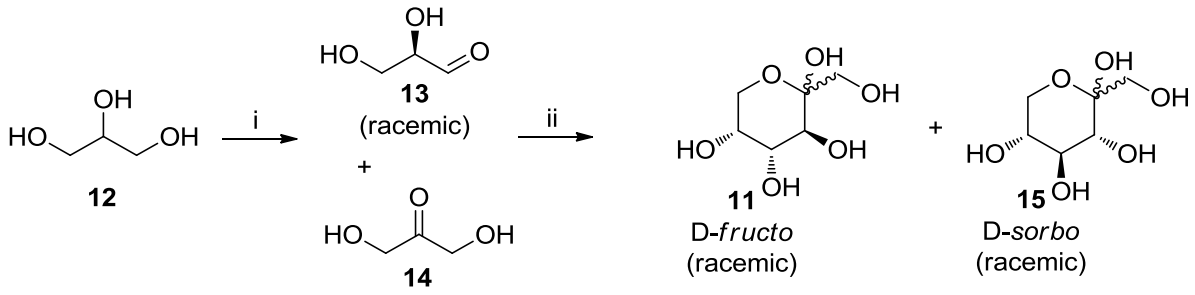
The first documented synthesis of sugars from non-carbohydrate substrates was reported in 1861, when the Russian chemist Butlerov presented his empirical findings. He had noticed that by heating a condensation product of formaldehyde, trioxan **6**, in basic conditions, a viscous fluid that had some of the properties of sugar could be produced (Scheme 3). (31) The product, known as formose, was shown by Emil Fischer to consist of a mixture of saccharides and the main components had the molecular formula $C_6H_{12}O_6$. (32) Two components of formose were identified as racemic fructose and sorbose via the preparation of the phenylosazones **7** and **8**, respectively. The fructose derivative **7** was subsequently transformed to racemic glucose, mannose and fructose by chemical and enzymatic transformations. (33) (34) (35) (36)



Scheme 3. Synthesis of racemic hexoses from formose by Fischer and Tafel. The structure of D-form is presented. Reagents and conditions: i) $Ca(OH)_2$, H_2O; ii) $PhNHNH_2$; iii) chemical and enzymatic transformations.

Fischer and Tafel also carried out a synthesis of two racemic ketohexoses via methodology that resembled naturally occurring saccharide production (see Schemes 2 and 4). The synthesis commenced with the oxidation of glycerol **12** by bromine to a mixture of

racemic glyceraldehyde **13** and dihydroxyacetone **14**. (33) When a mixture of **13** and **14** was allowed to stand in a dilute NaOH solution, two racemic hexoses, **11** and **15,** were obtained; Fischer named these α- and β-acrose, respectively. Fisher soon established that α-acrose was identical to fructose, with the exception that it was optically inactive. Thus, α-acrose was racemic fructose. On the other hand, β-acrose corresponded to racemic sorbose. (37) (38)



Scheme 4. Synthesis of two ketohexoses from glycerol by Fischer and Tafel. Reagents and conditions: i) Br_2, aq Na_2CO_3; ii) aq NaOH, 5 days.

The saccharide syntheses presented later in this review are based on the elegant and versatile work on the chemistry, stereochemistry and synthesis of saccharides by Fischer. In addition to the syntheses described above, he also established the configurational assignment of glucose, galactose, mannose, fructose, arabinose and xylose with the help of the Fischer projection. Fischer also established the nomenclature of monosaccharides: they were named after the number of carbon atoms as *tri*oses, *tetr*oses, *pent*oses, *hex*oses, *hept*oses, etc. He also established that the symbols "D" and "L" should be used only according to the spatial orientation of the substituents, independent of the direction of rotation. Excellent tributes to the achievements of Fischer have been published (39) (40) (41) and a compilation of the articles published by Fischer and his students describing their research on carbohydrates and related products carried out from 1884 to 1908 is available (42).

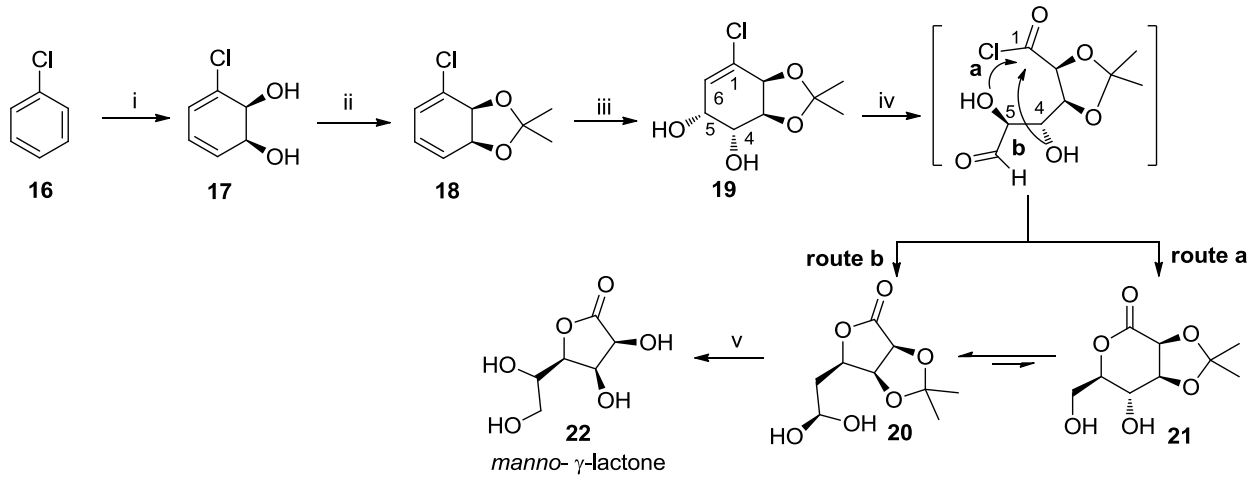
Although the *de novo* synthesis of carbohydrates has attracted organic chemists since these pioneering findings, in the first half of the 1900s only a few papers concerning the total synthesis of sugars (mostly DL-tetroses) were published. In those pioneering works, saccharides were obtained mostly as pure diastereomers in racemic form. A significant increase in the number of papers published on the topic since 1950 was the result of many important developments in stereoselective synthesis, separation techniques and methods for structural determination. The past 40 years have witnessed a rapid development of methods leading to saccharides of desired structure and stereochemistry in a highly chemo- and stereoselective manner. (6)

This review is focused mostly on the *de novo* synthesis of *aldo*hexoses. Methodologies are divided into two categories according to the type of substrate utilized: the syntheses relying on either stereoselective modification of cyclic frameworks, or assembly of acyclic carbon frameworks. Both strategies can be further subdivided according to the type of bond formed and the reaction type used in the key reaction step.

3.1 Stereoselective Modification of Cyclic Carbon Framework

The *de novo* synthesis of carbohydrates based on the stereoselective modification of cyclic substrates is based on knowledge of selective transformations of five- and six-membered rings. Although the use of cyclic stereocontrol is certainly an attractive strategy, relatively few applications of this strategy have been published. Comprehensive reviews of the use of cyclic species in the synthesis of carbohydrate derivates are available. (6) (43)

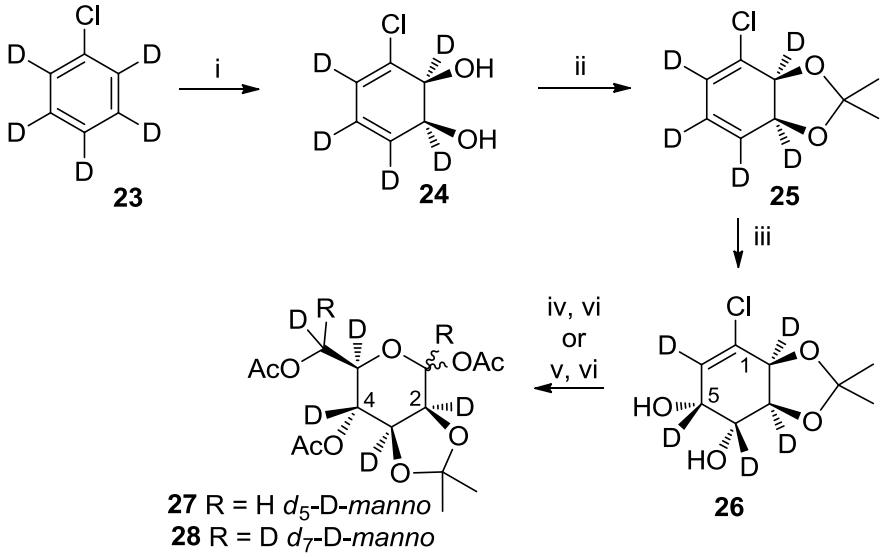
Hudlicky and coworkers developed a concise synthesis of monosaccharides and monosaccharide derivatives by using an oxidative ring cleavage and concomitant cyclization as key step. (44) (45) The synthesis of the mannopyranose derivative **22** was initiated by the formation of the key intermediate chlorocyclohexa-*cis*-diene **17**, from halogenated benzene **16** by means of a bacterial dioxygenase, *Pseudomonas putida* (Scheme 5). (46) Comprehensive reviews of halocyclohexadiene-*cis*-diols have been published. (47) (48) Next, the diol **17** was protected by acetonide formation. The subsequent oxidation with permanganate gave the *cis*-diol **19** in 85% overall yield. (44) The rationale for the use of permanganate instead of OsO_4 was the authors' desire to use a method that was more environmentally benign. Oxidative cleavage of the C_1 - C_6 olefinic bond in diol **19** by ozonolysis and a concomitant cyclization afforded protected D-mannolactones **20** and **21**, in which **21** rapidly isomerized to the more stable 5-membered lactone **20**. Finally, acid-catalyzed deprotection of the acetonide gave D-manno- γ-lactone **22** over five steps from **16**.



Scheme 5. Synthesis of D-manno-γ-lactone via microbial oxidation of chlorobenzene by Hudlicky. Reagents and conditions: i) *Pseudomonatas. putida* 39, **17** (er > 99:1, ~1 g/L); ii) 2,2-dimethoxypropane, *p*TSOH, CH_2Cl_2; iii) $KMnO_4$, $MgSO_4$, **19** (85% from **17**); iv) O_3, MeOH, -78 °C; then Pd/C, H_2, rt, **20** (32%); v) TFA, H_2O, **22** (not reported).

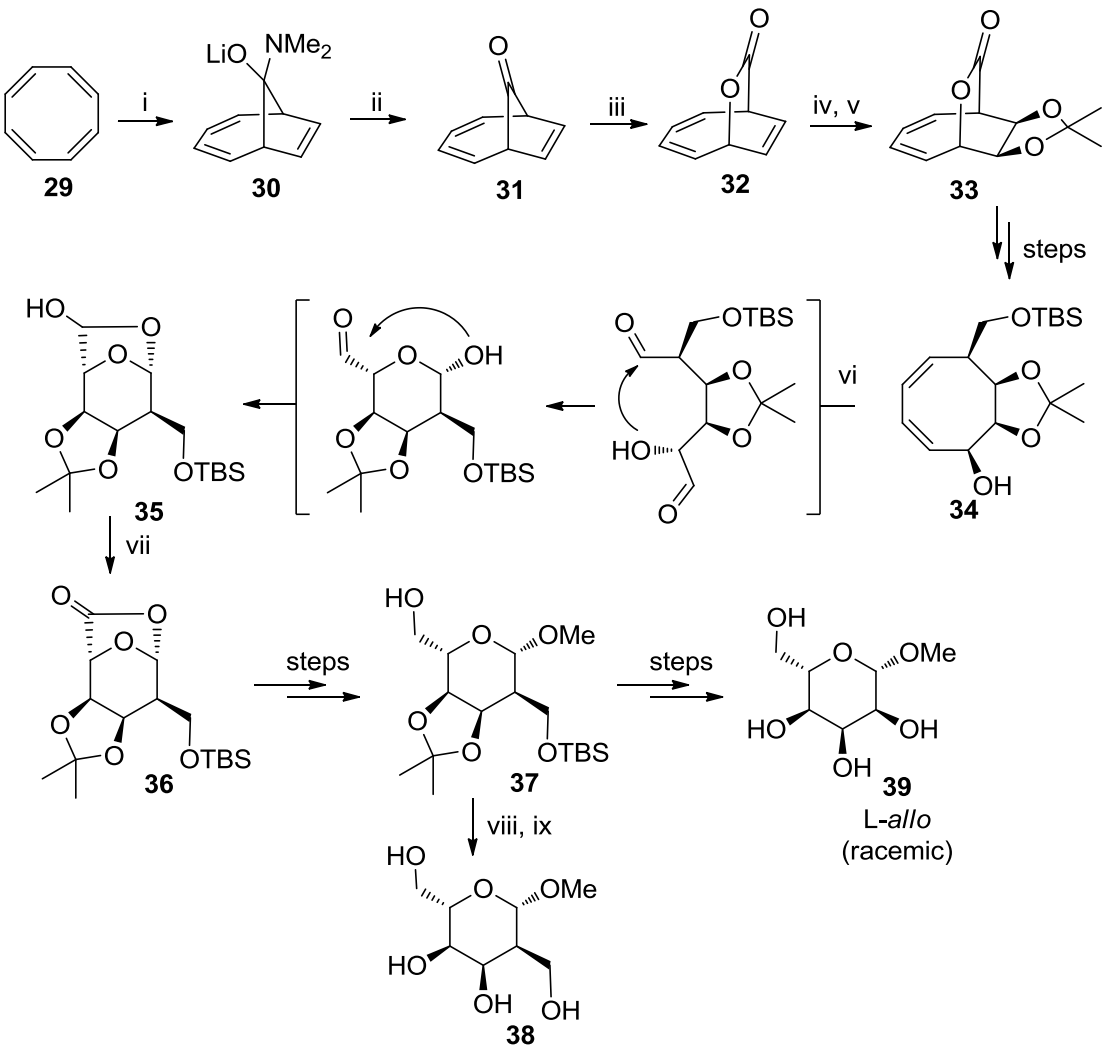
Hudlicky and coworkers also applied this method to the syntheses of fully and partially deuterated d_5- and d_7-mannopyranosides **27** and **28** (Scheme 6). (45) The intermediate **25** was prepared in the same synthetic manner as described above. Subjection of *cis*-diol **25** to ozonolysis and a reductive workup with $NaBH_4$ or $NaBD_4$, followed by acetyl-protection, gave d_5- and d_7-D-mannopyranosides **27** and **28**, respectively. Although the routes for mannopyranose and mannopyranoside derivatives were short, the total yields of **27** and **28** were low, mainly due to the low productivity of the oxidative cleavage and concomitant cyclization step. However, the use of this methodology should, in principle, allow the synthesis other aldohexoses. The D-gluco and D-galacto configuration could be afforded by inversion of the stereochemistry at C_2, and D-talo configuration by inversion at C_4.

Furthermore, the synthesis of L-hexoses should be possible by using a *cis*-diol with the opposite stereochemistry. (44) It should be added that, although the microbially-produced, enantiomerically-enriched dienediols should be versatile starting materials in the synthesis of a wide variety of monosaccharides, their use in the synthesis of monosaccharides derivatives (e.g., azasugars (49), aminosugars (50) and pseudosugars (51)), has received much more attention.



Scheme 6. Synthesis of deuterated D-mannopyranosides via microbial oxidation of d_5-chlorobenzene by Hudlicky. Reagents and conditions: i) *Pseudomonatas putida* 39 or *Escherichia coli* JM109, **24** (~1 g/L); ii) 2,2-dimethoxypropane, *p*TSOH, CH_2Cl_2; iii) OsO_4, *t*BuOH, H_2O, **26** (85% from **24**); iv) O_3, MeOD, -78 °C, then $NaBH_4$, 0 °C to rt; v) O_3, MeOD, -78 °C, then $NaBD_4$, 0 °C to rt; vi) Ac_2O, pyridine, CH_2Cl_2, **27** (α:β 3:2, 7% from **26**), **28** (35% from **26**).

Mehta and Pallavi used a cyclic polyene, cyclooctatetraene (COT) **29**, in the synthesis of racemic DL-allopyranoside **39** and its C_2-branched counterpart **38** (Scheme 7). (52) The synthesis was conducted using Baeyer–Villiger oxidation (53) and catalytic OsO_4 dihydroxylation as key steps. First, bicyclic ketone **31** was prepared via dilithium cyclooctatetraenide, which was transformed to adduct **30** by adding dimethylcarbamoyl chloride. Hydrolysis with aqueous sulfuric acid afforded bicyclic ketone **31**. (54) Subsequent Baeyer-Villiger oxidation of ketone **31** afforded lactone **32** in 60% yield. (55) This was followed by a catalytic dihydroxylation by OsO_4, and acetonide protection, affording **33** with a complete regio- and stereo-control. Further elaboration yielded derivative **34**, which was transformed to lactol **35** via ozonolysis. Then, lactone **36** was obtained via PCC oxidation. The lactone **36** was further processed to derivative **37**, which was the common intermediate for both **38** and **39**. The deprotection of **37** led directly to the DL-allopyranoside derivative **38**. Alternatively, derivative **37** could be converted to DL-allopyranoside **39**. However, this route used by Mehta and Pallavi was very laborious and overall yields of **39** and **38** from COT **29** were very low (0.3% and 1%, respectively). In addition, this methodology yielded only racemic allopyranose products.



Scheme 7. Synthesis of racemic DL-allopyranose and its C_2-branched homologue starting from cyclooctatetraene by Mehta and Pallavi. Reagents and conditions: i) Li, Et_2O; -70 °C, then DMCC; ii) H_2SO_4, **31** (76% from **29**); iii) *m*CPBA, CH_2Cl_2, **31** (60%); iv) OsO_4, NMO; v) 2,2-dimethoxypropane, acetone, camphorsulfonic acid, **33** (49% from **32**); vi) O_3, CH_2Cl_2, MeOH, then Me_2S; vii) PCC, NaOAc, CH_2Cl_2, **36** (40% from **35**); viii) TBAF, THF; ix) Amberlyst-15 ion exchange resin, MeOH, **38** (46% from **37**).

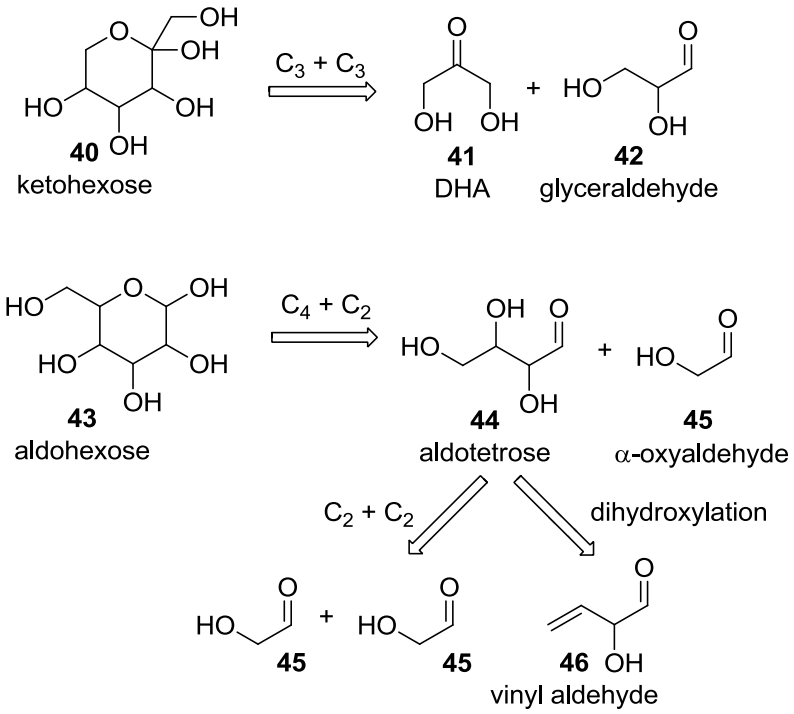
3.2 Stereoselective Assembly of Acyclic Carbon Framework

In the following discussion, the *de novo* synthesis of carbohydrates based on the assembly of an acyclic carbon framework is subdivided into two categories according to the type of bond formed in the key synthetic step(s): syntheses relying on either 1) stereoselective carbon-carbon (Chapter 3.2.1-3.2.3) or 2) carbon-heteroatom formation (Chapters 3.2.4-3.2.6). Both categories are further organized according to the type of reaction used in the key synthetic step. A comprehensive review of the use of acyclic species in the synthesis of carbohydrate derivatives has been published. (7)

3.2.1 Strategies Relying on Stereoselective Carbon-Carbon Bond Formation

One of the most common stereoselective carbon-carbon bond formation strategies involves the addition of a carbon-bearing reagent to a carbonyl compound. The most commonly used reactions for the synthesis of monosaccharides are based on aldol and cycloaddition reactions.

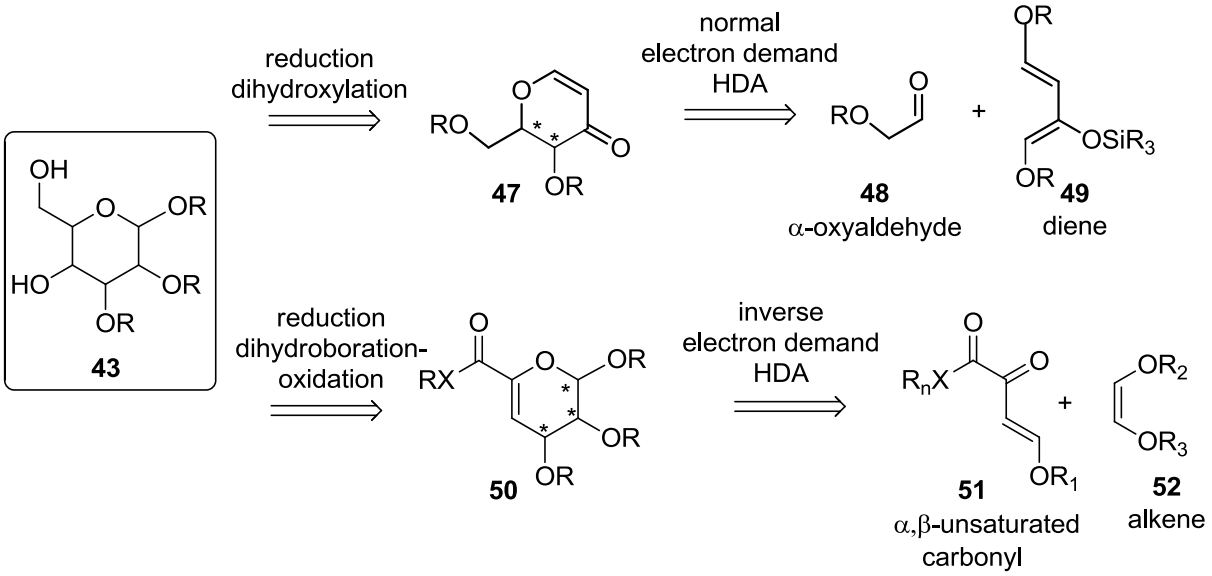
The asymmetric aldol reaction is an effective way of forming carbon-carbon bonds. Two new stereogenic centers can be formed in a predictable *syn*- or *anti*-fashion because the relationship between enolate geometry and product configuration is generally well defined, especially if the reaction proceeds via a cyclic transition state. (56) There are two subcategories of the aldol strategy for synthesizing hexoses (Scheme 8). The synthesis based on a $C_3 + C_3$ protocol leads to ketohexoses, while aldohexoses can be obtained via a $C_4 + C_2$ protocol (Scheme 8). The $C_3 + C_3$ protocol mimics natural biosynthesis of the D-fructose derivative, a common intermediate for naturally occurring saccharides (see Scheme 2, p. 23). This efficient one-step protocol employs a common intermediate, dihydroxyacetone (DHA) **41**, as a C_3 building block. This protocol has inspired chemists for a long time, and in 2005 Enders and Grondal published an elegant organocatalytic method for the synthesis of ketohexoses from DHA derivatives. (57) As the protocol only affords the direct synthesis of ketoses, a redox reaction sequence is needed to obtain aldoses. Therefore, this protocol is outside the scope of this review. However, the direct synthesis of aldohexoses is possible via a $C_4 + C_2$ protocol. A possible starting material is a vinyl aldehyde **46** (a C_4 building block) and a α-oxyaldehyde derivative **45** (a C_2 building block). A more common strategy is a $C_2 + C_2 + C_2$ protocol, in which the synthesis of a C_4 building block is based on an iterative aldol sequence via α-oxyaldehyde **45**. Comprehensive reviews of the use of aldol addition in the synthesis of carbohydrates have been published by Kazmaier (58), Mahrwald (59) and Mlynarski (60).



Scheme 8. Retrosynthetic aldol strategy for hexose synthesis: $C_3 + C_3$ and $C_4 + C_2$ /$C_2 + C_2 + C_2$ protocols.

As an alternative to the aldol strategy, the hetero-Diels–Alder (HDA) reaction is a very powerful method for constructing optically active six-membered heterocycles. The pyran

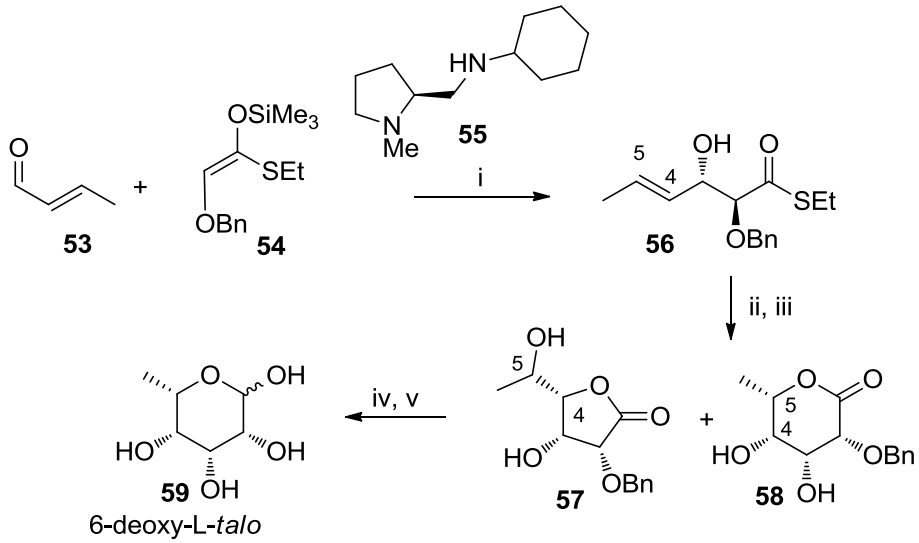
substructures encountered in carbohydrates are accessible via either normal or inverse electron demand HDA reactions (Scheme 9). The normal electron demand HDA reaction between oxy-aldehyde **48** and diene **49** gives a dihydropyranone **47**, whereas the inverse HDA between *α,β*– unsaturated carbonyl compound **51** and electron-rich alkene **52** gives dihydropyran **50**. In both cases, the stereochemistry of newly formed stereocenters can be controlled in a single step. Then, the products **47** and **50** can easily be transformed into different monosaccharides **43**. (61) (62) (63) Comprehensive reviews of the HDA method for the synthesis of carbohydrate derivates are available. (64) (10)



Scheme 9. Retrosynthetic HDA strategy for hexose synthesis: a normal electron demand (top) and inverse electron demand (bottom) hetero-Diels-Alder protocols.

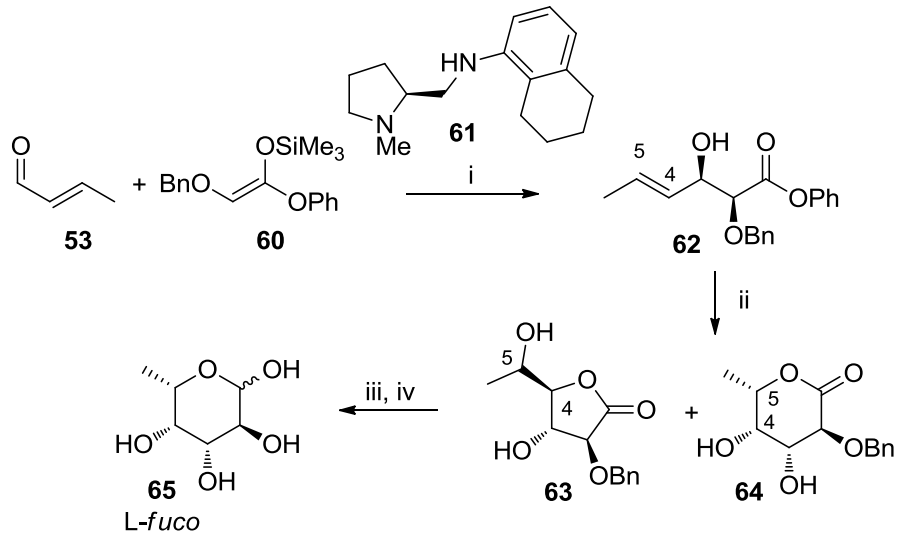
3.2.2 Methodologies Based on Aldol Reaction

Although stereoselective C_2 + C_4 aldol additions for the synthesis of monosaccharides were developed in the 1980s (7), it was not until 1990 that Mukaiyama, Kobayashi and coworkers utilized a catalytic version of this transformation. They combined a chiral diamine–tin(II) catalyzed asymmetric Mukaiyama aldol reaction (65) (66) with a diastereoselective dihydroxylation step. This led to the rapid synthesis of 6-deoxy-L-aldohexoses. As an example, the 6-deoxy-L-talopyranose **59** was commenced with an aldol reaction between crotonaldehyde **53** and the silyl enol ethers of α-benzyloxy thioesters **54** in the presence of Sn(II) and chiral diamine **55** (Scheme 10). (67) The corresponding *anti*-aldol adduct **56** was obtained in 85% yield with a 99:1 enantiomeric ratio. Dihydroxylation of **56** by using a catalytic amount of OsO_4 afforded lactone **57** and its 4,5-isomer **58** directly. Subsequent reduction of the mixture of lactones with DIBALH and deprotection of the benzyl group gave the 6-deoxy-L-talopyranose **59** in five steps and 43% overall yield from aldehyde **53**.



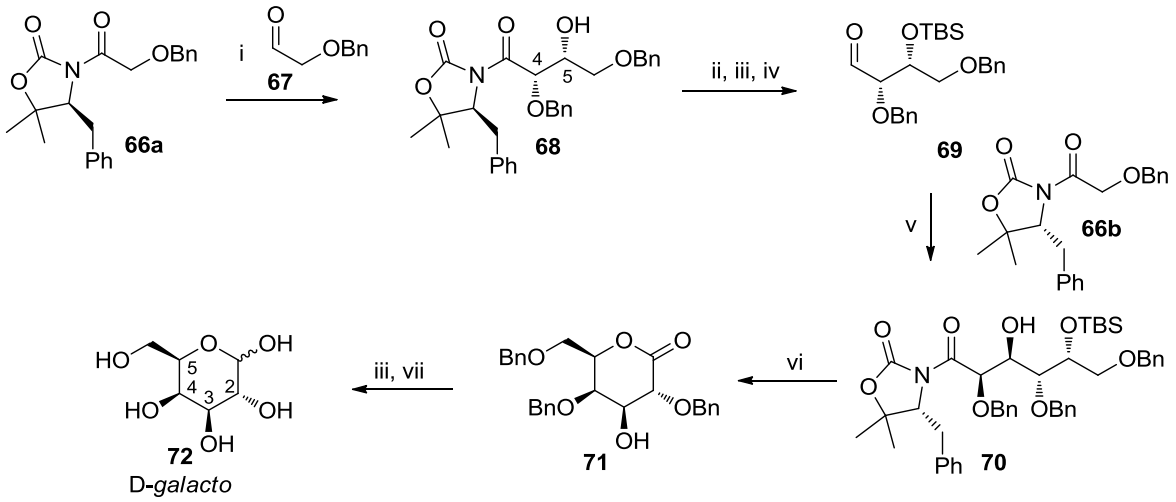
Scheme 10. Synthesis of 6-deoxy-L-talose via a catalytic Mukaiyama aldol reaction by Mukaiyama and Kobayashi. Reagents and conditions: i) **55**, $Sn(OTf)_2$, $Bu_2Sn(OAc)_2$, C_2H_5CN, -78 °C, **56** (*anti*:*syn* 98:2, er 99:1 (*anti*), 85%); ii) OsO_4, NMO, acetone, H_2O, 0 °C; iii) H_2S gas, **57** and **58** (**57**:**58** 72:28, **57**+**58** 72%); iv) DIBALH, CH_2Cl_2, -78 °C; v) Pd/C, H_2, MeOH, **59** (71% from **57**+**58**).

Later, in 1993, Kobayashi and coworkers extended this methodology to the synthesis of L-fucopyranose (6-deoxy-L-galactopyranose) **65** by using somewhat modified reaction conditions (Scheme 11). (68) In the aldol reaction, a more reactive ketene silyl acetal **60** with stereochemistry opposite to that of **54** was used in the presence of Sn(II) and chiral diamine **61**. The *syn*-aldol adduct **62** was obtained in 87% yield with a 96:4 enantiomeric ratio. Then, the olefin functionality of **62** was dihydroxylated using a catalytic amount of OsO_4 to afford lactone **63** and its 4,5-isomer **64**. Subsequent reduction and deprotection in the same manner as described above gave L-fucopyranose **65** in 56% overall yield over four steps. As both enantiomers of chiral diamine **61** are available, this protocol should, in principle, be applicable to the synthesis of deoxy- D-aldohexoses.



Scheme 11. Synthesis of L-fucose via a catalytic Mukaiyama aldol reaction by Mukaiyama and Kobayashi. Reagents and conditions: i) **61**, $Sn(OTf)_2$, SnO, C_2H_5CN, -78 °C, **62** (*anti*:*syn* 97:3, er 96:4 (*anti*), 87%); ii) OsO_4, NMO, acetone, H_2O, 0 °C **,** **63** and **64** (**63:64** 92:8, **63**+**64** 83%); iii) DIBALH, CH_2Cl_2, -78 °C; iv) Pd/C, H_2, MeOH, **65** (77% from mixture of **63**+**64**).

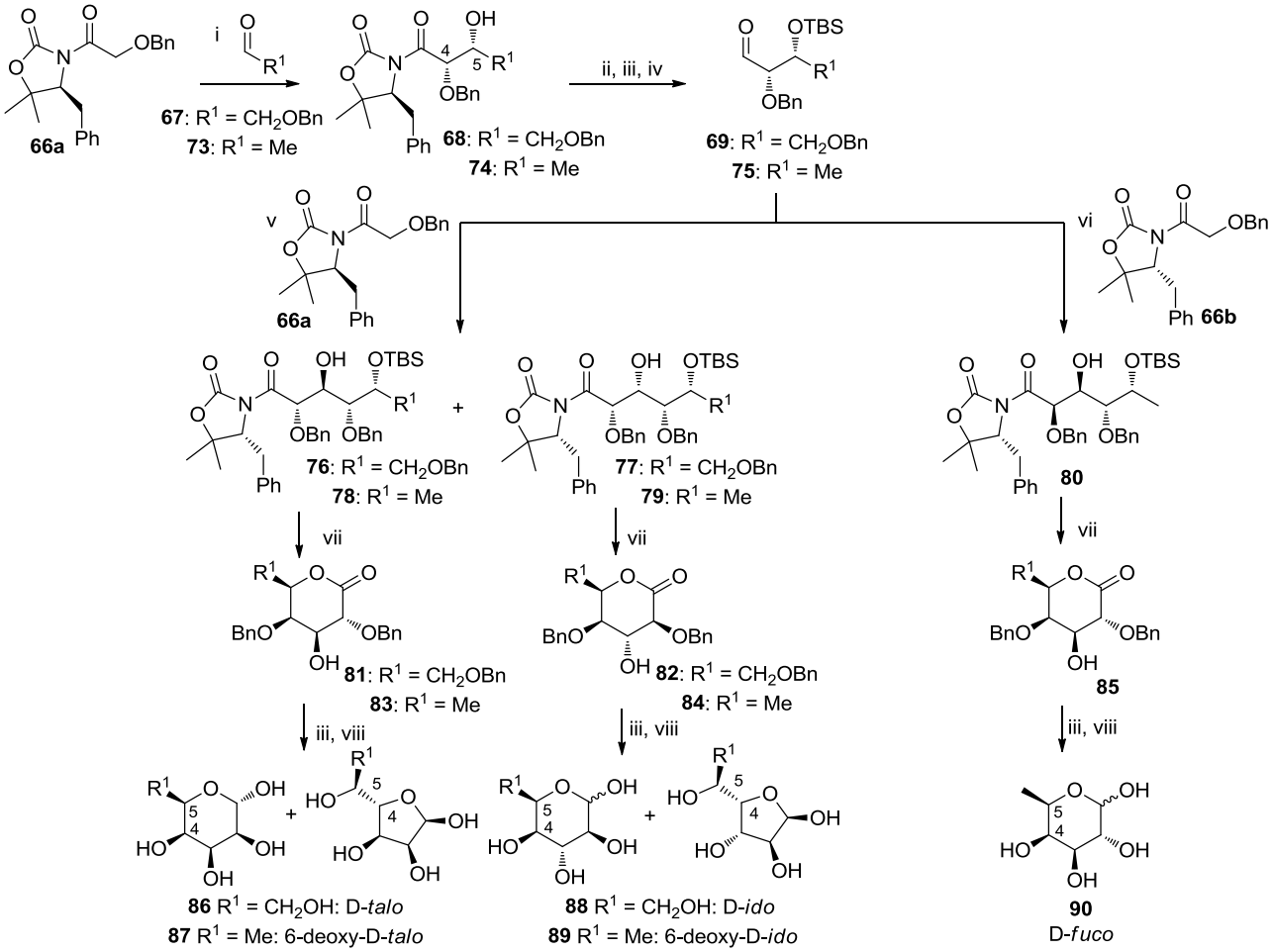
In 2002, Davies and coworkers synthesized D-galactopyranose **72** by utilizing chiral auxiliaries via a diastereoselective glycolate aldol protocol (Scheme 12). (69) The first boron-mediated aldol reaction was carried out between (*S*)-*N*-acyl oxazolidinone **66a** and benzyloxyacetalde **67**. The corresponding *syn*-aldol adduct **68** was obtained in 73% yield with a 97:3 diastereomeric ratio. Subsequent silyl protection and reduction with DIBALH afforded D-threose **69**. Iteration of the aldol procedure by using a boron enolate derived from (*R*)-N-acyl oxazolidinone **66b** yielded the *syn*-aldol product **70** in a 98:2 diastereomeric ratio. Desilylation led to the cleavage of the oxazolidinone group, affording lactone **71**. Subsequent reduction by DIBALH and deprotection of the benzyl group gave D-galactopyranose **72** over eight steps and in 14% overall yield from **66a**.



Scheme 12. Synthesis of D-galactose via an iterative aldol protocol by Davies. Reagents and conditions: i) **67**, Et_2BOTf, *i*Pr_2NEt, THF, -78 °C, **68** (dr 97:3, 73%); ii) TBSCl, imidazole, DMAP, DMF, rt; iii) DIBALH, CH_2Cl_2; iv) K_2CO_3, MeOH-H_2O, rt, **69** (49% from **68**); v) **66b**, Et_2BOTf, *i*Pr_2NEt,THF, -78 °C, **70** (dr 98:2, 63%); vi) TBAF, AcOH, THF, rt, **71** (98%); vii) Pd/C, H_2, EtOAc, EtOH, **72** (65% from **71**).

Later in 2004, Davies and coworkers applied this boron-mediated glycolate aldol protocol to the synthesis of five other D-aldo- and 6-deoxy-D-aldohexoses having the D-galacto stereochemistry at C_4 and C_5 (Schemes 12 and 13). (70) Thus, the first aldol reaction was carried out using (*S*)-N-acyl oxazolidinone **66a** in the same manner as described above, with the exception that acetaldehyde **73** was used in the synthesis of deoxyaldohexoses. The corresponding *syn*-aldol adducts **68** and **74** were obtained in 77% and 79% yields, respectively, with high diastereomeric ratios. Since the D-fucopyranose (6-deoxy-D-galactose) **90** and D-galactose **72** are stereochemically identical, iteration of the aldol procedure for **69** was carried out by using (*R*)-oxazolidinone **66b** to give **80** in 53% yield with a 98:2 diastereomeric ratio. After subsequent fragmentation of the oxazolidinone group, followed by reduction and deprotection, D-fucopyranose **90** was obtained in 9% overall yield from **66a**. For the pyranoses **86-89**, the second aldol reaction was carried out with **69** and **75** by using (*S*)-*N*-acyl oxazolidinone **66a**. The *syn*-stereoselectivity of this mismatched aldol reaction was low and it gave a mixture of aldol products (*anti*-**76**:*syn*-**77** 23:77, 9% and 46%, respectively; *anti*-**78**:*syn*-**79** 31:69, 19% and 58%, respectively). Next, the diastereomers were separated, and after subsequent cleavage of the oxazolidinone group, followed by reduction and deprotection, α-D-talopyranose **86** (4%), 6-deoxy-D-talopyranose **87** (6%), D-idopyranose **88** (22%) and 6-deoxy-D-idopyranose **89** (17%) were obtained as a mixture of pyranose and furanose forms in 4-22% overall yields from **66a**. As both (*R*)- and (*S*)-enantiomers of oxazolidinone (**66a** and **66b**) are available, this methodology should be equally applicable to the synthesis of L-aldohexoses.

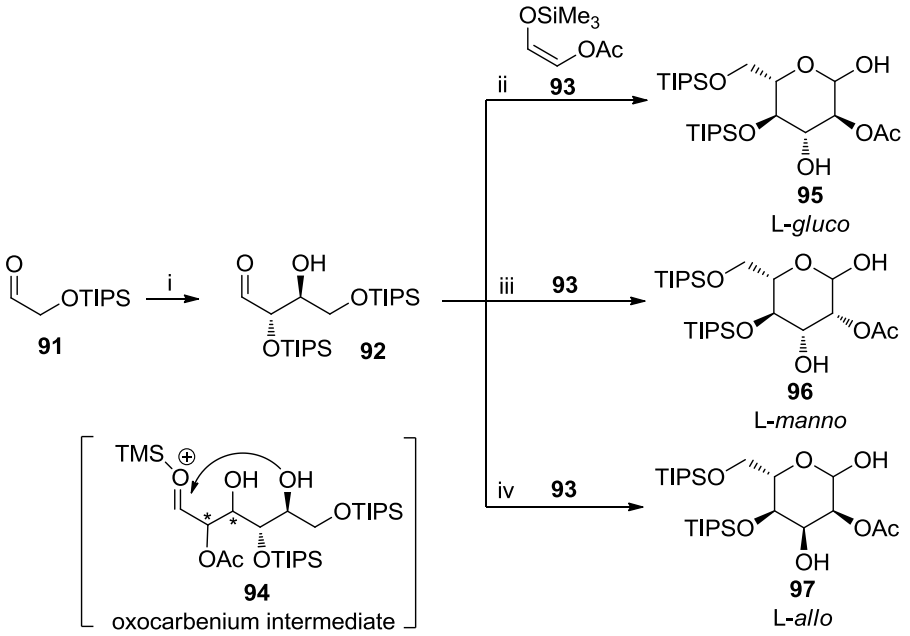
There are a number of issues with this iterative aldol strategy that could be considered weaknesses: the requirement of protective group manipulations, the need for iterative oxidation-state adjustments, and a long synthetic pathway leading to relatively low overall yields.



Scheme 13. Synthesis of D-talose, D-idose, their deoxy derivatives and D-fucose via an iterative aldol strategy by Davies. Reagents and conditions: i) **67** or **73**, Et_2BOTf, *i*Pr_2NEt, THF, -78°C, **68** (dr 97:3, 77% from **67**), **74** (dr 89:11, 79% from **73**); ii) TBSCl, imidazole, DMAP, DMF, rt; iii) DIBALH, CH_2Cl_2; iv) K_2CO_3, MeOH-H_2O, rt, **69** (49% from **68**), **75** (57% from **74**); v) **66a**, Et_2BOTf, *i*Pr_2NEt, THF, -78 °C, **76** (dr 98:2, 9% from **69**), **77** (dr 98:2, 46% from **69**), **78** (dr 98:2, 19% from **75**), **79** (dr 98:2, 58% from **75**); vi) **66b**, Et_2BOTf, *i*Pr_2NEt, THF, -78 °C, **80** (dr 98:2, 53%); vii) TBAF, HOAc, THF, rt, **85** (dr 98:2, 73%); viii) Pd/C, H_2, EtOAc, EtOH, **86** (not reported), **87** (not reported), **88** (79% from **82**), **89** (86% from **84**), **90** (53% from **85**).

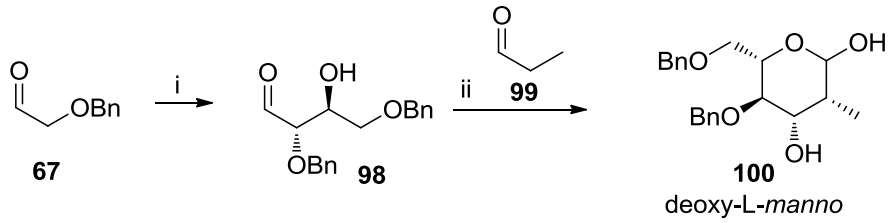
In the same year (2004), MacMillan and Northrup applied proline catalysis to the synthesis three L-aldohexoses. (71) (72) The straightforward synthesis route consisted of two steps: 1) an organocatalytic aldol addition, and 2) a Lewis acid-catalyzed Mukaiyama aldol addition. (66) The first L-proline-catalyzed aldol dimerization of silyl-protected α-oxyaldehyde **91** gave *anti*-threose **92** with high enantio- and moderate diastereoselectivity (er 98:2 (*anti*) 4:1 *anti*:*syn*) (Scheme 14). The aldol adduct **92** was then converted to three different L-hexoses with high stereochemical purity via a Mukaiyama aldol addition followed by lactol formation. The stereochemistry of the Mukaiyama aldol product was controlled by changing the solvent and Lewis acid. As such, reaction of **92** with enol ether **93** by using $MgBr_2{\cdot}OEt_2$ in Et_2O or in CH_2Cl_2 afforded partially protected L-glucopyranose **95** and L-mannopyranose **96**, respectively. Instead, L-allopyranose **97** was obtained when $TiCl_4$ was used as a Lewis acid.

The overall yields of the pyranose products were high (58-64% over two steps) in this concise protocol. As both L- and D-enantiomers of proline are available, this protocol is equally applicable to the synthesis of D-aldohexoses. The reaction sequence also efficiently enables the production of structural variants such as 2-amino– and 2-thio–substituted derivatives. Moreover, even though MacMillan and Northrup did not extend this methodology to the whole serie of L-aldohexoses, a recent discussion of the *de novo* synthesis of monosaccharides by organocatalyzed aldol reactions suggested that this series could be completed by choosing appropriate reaction conditions. (59)



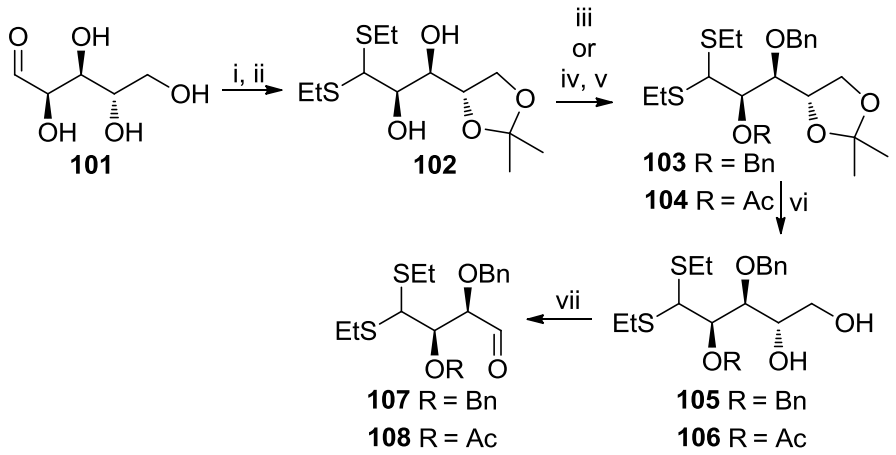
Scheme 14. Synthesis of L-gluco-, L-allo- and L-mannopyranose via aldol reactions by MacMillan and Northrup. Reagents and conditions: i) L-Pro, DMF, 2 days, rt, **92** (*anti*:*syn* 4:1, er 98:2 (*anti*), 92%); ii) **93**, $MgBr_2OEt_2$, Et_2O, **95** (dr 10:1, er 98:2, 79%); iii) **93**, $MgBr_2OEt_2$, CH_2Cl_2, **96** (dr > 19:1, er 98:2, 87%; iv) **93**, $TiCl_4$ CH_2Cl_2 **97** (dr >19:1, er 98:2, 87%).

In 2005 Cordova and coworkers described a completely amino acid-controlled aldol methodology for the synthesis of protected saccharide derivatives. (73) (74) In the synthesis of 2-deoxy-2-methyl-L-mannopyranose **100**, a benzyl-protected α-oxyaldehyde **67** was used as a starting material (Scheme 15). L-Proline mediated the direct asymmetric formation of *anti*-threose **93**, which was inert to further proline-catalyzed enolization. (60) Thus, **98** was isolated prior to the second aldol reaction, which was carried out with propanal **99** and catalyzed by D-proline to give L-mannopyranose derivative **100** in 39% total yield and with an enantiomeric ratio greater than 99:1. The reaction sequence in which the proline catalysts were used in the opposite order (first D-proline, then L-proline) yielded the opposite enantiomer of the sugar (D-**100**).



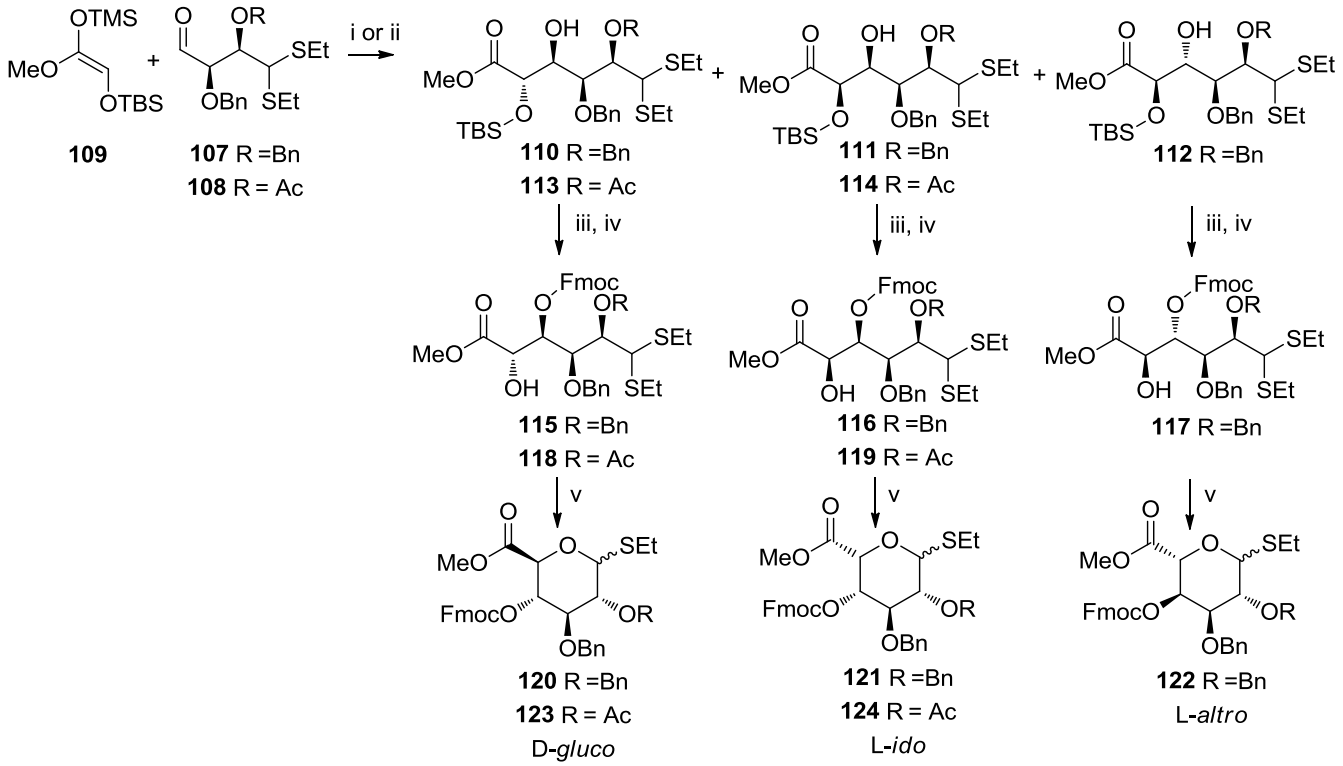
Scheme 15. Synthesis of an L-mannopyranose derivative via aldol reactions by Cordova. Reagents and conditions: i) L-proline, DMF, rt; ii) **99**, D-proline, DMF, rt, **100** (dr > 99:1, 39% from **67**).

In 2005 Seeberger and coworkers presented a protocol to orthogonally protected aldohexose derivatives, uronic acid thioglycosides, via a Mukaiyama-type aldol reaction (66) of silyl enol ether and a thioacetal-containing aldehyde. (75) The synthesis of thioacetal-aldehydes **107** and **108** was commenced with conversion of L-arabinose **101** into the corresponding thioacetal (Scheme 16). (76) Subsequent protection with 2,2-dimethoxypropane gave acetonide **102** in 63% overall yield. The reaction of **102** with NaH in the presence of benzyl bromide gave dibenzyl-product **103**. Alternatively, orthogonally protected product **104** was obtained via tin ketal formation of **102** and subsequent monobenzylation and acetylation (46% overall yield, also 2-*O*-benzyl-3-*O*-acetyl regioisomer was formed 45%). The following deprotection of the acetal groups in **103** and **104** and cleavage of the resulting diol with periodate gave the thioacetal-containing aldehydes **107** and **108** (in 42% and 21% yields from **101**), respectively.



Scheme 16. Synthesis of protected of saccharide precursors. Reagents and conditions: i) EtSH, aq. HCl; ii) 2,2-dimethoxypropane, pyridinium *p*-toluenesulfonate (cat.), acetone, **102** (63% from **101**); iii) BnBr, TBAI (cat.), NaH, DMF, 0 °C, **103**; iv) nBu$_2$SnO, toluene, Dean-Stark trap; then BnBr, CsF, TBAI (cat.), DMF; v) Ac_2O, pyridine, **104** (46% from **102**); vi) AcOH, H_2O, 50 °C, **105** (81% from **102**), **106** (92% from **104**); vii) $NaIO_4$, H_2O, THF, 0 °C, **107** (82%), **108** (80%).

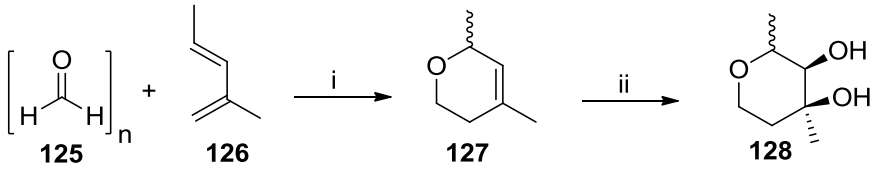
The $BF_3 \cdot Et_2O$-mediated aldol reaction (77) of the aldehydes **107** and **108** with silyl enol ether **109** (78) led to the aldol product(s) (Scheme 17). The aldol reaction conducted in toluene at -78 °C to -30 °C gave single *anti*-diastereomers **110** and **113** in high yields (quant. and 98%, respectively). The stereoselectivity was explained by the preference for an open transition state. In contrast, a mixture of *anti*- and *syn*-products was afforded when the reaction was conducted in CH_2Cl_2 at 0 °C (**110**:**111**:**112** 1:1:1 from **107** and **113**:**114** 3:2 from **108**). The individual products were isolated and the free hydroxy group was first transformed into 9-fluorenylmethyl carbonates followed by cleavage of the silyl ether to give the alcohols **16-20** in good overall yields (76-89%). Finally, NIS-promoted cyclization of the thioacetal in the alcohols **115-119** led to the formation of pyranoside derivatives **120-124**. Thus, the D-glucuronic acids **120** and **123** were available from *anti*-aldol products **110** and **113** in 35% and 16% overall yields from **101**, respectively. However, the yields of L-iduronic acids **121** and **124** and L-altruronic acid **122** were lower because of low selectivity in aldol reaction towards pecursors **111**, **112** and **114** (overall yields of **121** and **122**: 11% and of **124**: 5% from **101**).



Scheme 17. Synthesis of protected D-glucuronic, L-iduronic and L-altruronic acid via a aldol reaction by Seeberger. Reagents and conditions: i) $BF \cdot OEt_2$, CH_2Cl_2, 0 °C, **110**-**112** (R = Bn, **110**:**111**:**112** 1:1:1, 93%), **113**-**114** (R = Ac, **113**:**114** 3:2, 95%); ii) $BF \cdot OEt_2$, toluene, -78 °C → -30 °C, only **110** (quant.), $BF \cdot OEt_2$, toluene, -78 °C → -30 °C, only **113** (98%); iii) FmocCl, pyridine, rt; iv) HF·pyridine, THF, rt, **115** (83% from **110**), **116** (89% from **111**), **117** (84% from **112**), **118** (79% from **113**), **119** (76% from **114**); v) NIS, CH_2Cl_2, **120** (α, quant.), **121** (β, quant.), **122** (α, quant.), **123** (α:β 1 :1, quant.), **124** (α:β 1 :1, quant.).

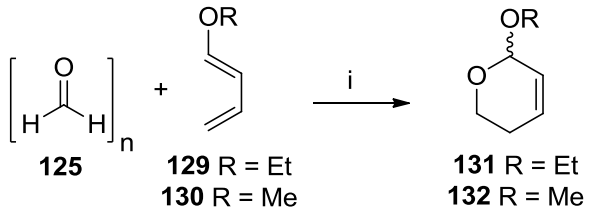
3.2.3 Methodologies Based on Hetero-Diels-Alder Reaction

In 1949 Gresham and Steadman reported the first example of a carbonyl group acting as a dienophile in a HDA reaction. (79) The cycloaddition proceeded with 2-methyl-1,3-pentadiene **126** and paraformaldehyde **125**, yielding racemic 2,4-dimethyl-5,6-dihydro-1,2-pyran **127** (Scheme 18). The subsequent hydroxylation of the double bond with potassium permanganate yielded *cis*-3,4-dihydroxy-2,4-dimethyl-5,6-dihydro-l,2-pyran **128** in 16% overall yield over two steps. Although this reaction did not directly yield an aldohexose, it was nevertheless an important precedent for later development in HDA-based monosaccharide syntheses.



Scheme 18. Synthesis of hydropyran structure via a HDA raction by Gresham and Steadman. Reagents and conditions: i) pressure vessel, 185 °C, **127** (61%); ii) $KMnO_4$, rt, **128** (26%).

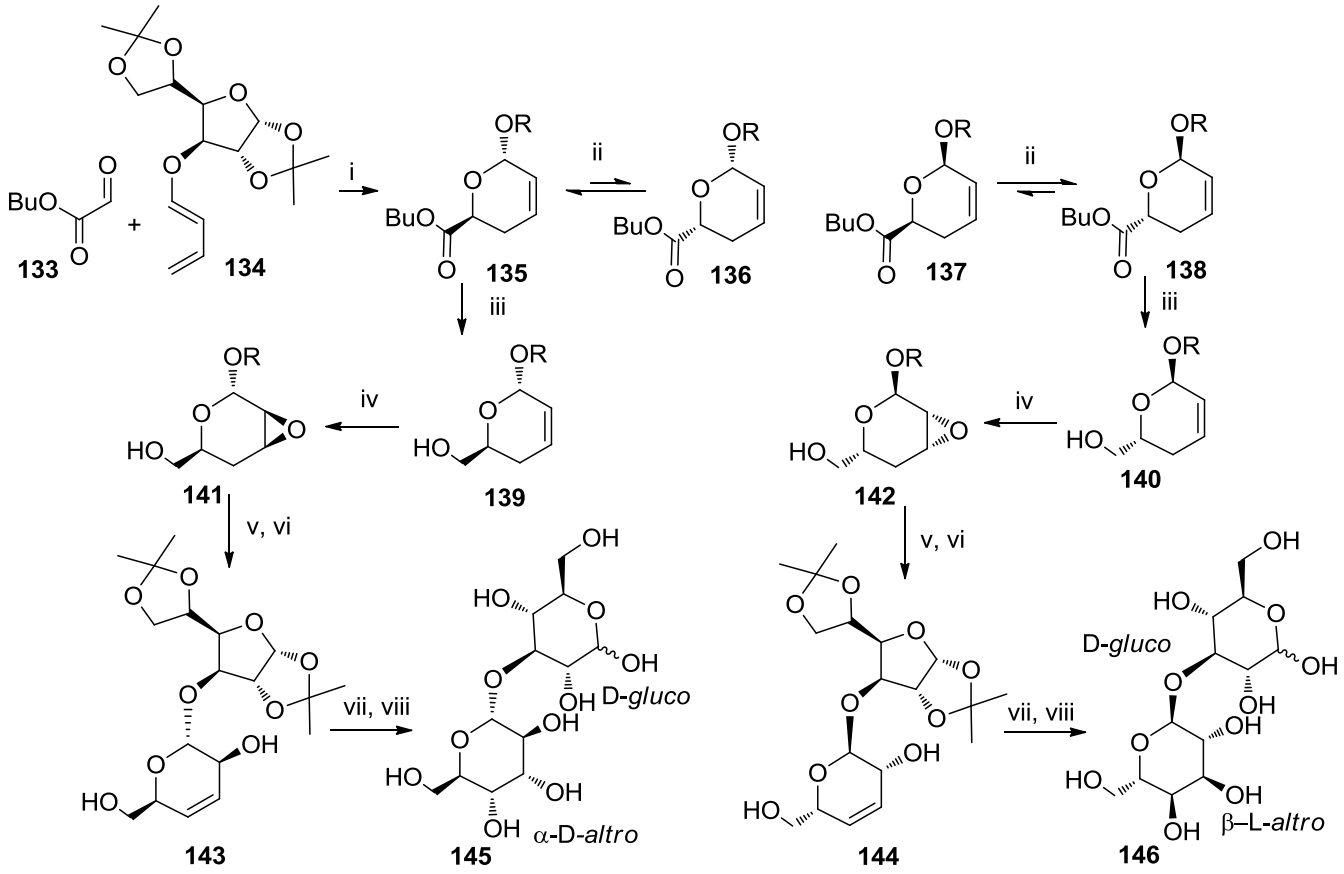
Later, Kubler found that an alkoxy group on the 1-position of a diene provides sufficient activation to permit the HDA reaction with paraformaldehyde. (80) In 1962, he reported the first successful example of a HDA reaction of 1-alkoxybutadienes **129** and **130** with paraformaldehyde **125** to give alkoxy-5,6-dihydro-2*H*-pyrans **131** and **132** in 56% and 62% yields, respectively (Scheme 19). However, Kubler did not extend the synthesis to saccharide structures.



Scheme 19. Synthesis of dihydro-2*H*-pyrans via a HDA reaction by Kubler. Reagents and conditions: i) hydroquinone, 180°C, **131** (56%), **132** (62%).

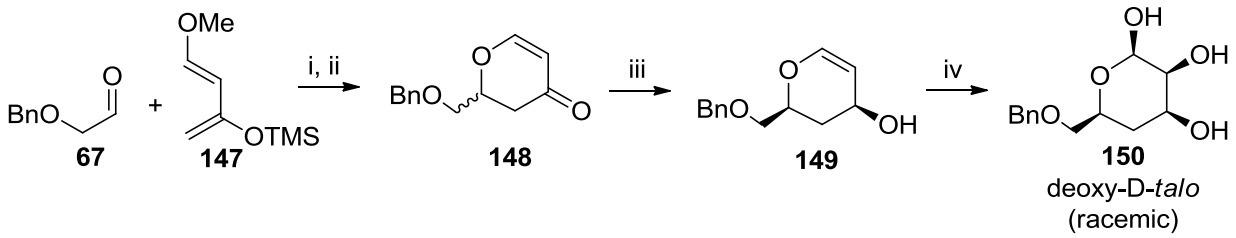
In 1974, diene-aldehyde cycloaddition reactions were extended to saccharide structures by David and coworkers as they achieved a total synthesis of D- and L-altropyranoses. (81) (82) Moreover, they developed the methodology that allowed the synthesis of (1-3)-linked *di*saccharide products by using a starting material that already incorporated a glycosylated carbohydrate building block. Cycloaddition of the D-glucose-derived diene **134** with *n*-butyl glyoxylate **133** afforded the HDA products **135–138** as a mixture of stereoisomers (**135**:**136**:**137**:**138** 13:60:18:9) in 93% overall yield (Scheme 20). The *endo*/*exo* -selectivity of the cycloaddition was moderate, favoring the (*endo*) *cis*-products **136** and **137**. Purification of the reaction mixture afforded two inseparable *cis*-*trans*- mixtures (**135** + **136** and **137** + **138**), which were isomerized to the more stable *trans*-forms **135** and **138** by sodium butoxide. However, complete conversion into a single diastereomer could not be achieved in either case. Then, **135** and **138** were reduced to unsaturated primary alcohols **139** and **140** by $LiAlH_4$. Epoxidation of **139** and **140** with benzonitrile and hydrogen peroxide gave **141** and **142**, respectively. Then, the opening of epoxides **141** and **142** with selenophenol and consecutive oxidation/selenoxide elimination with hydrogen peroxide (83) gave the allylic alcohols **143** and **144**. *Cis*-hydroxylation with OsO_4 and hydrolysis of the ketal protective groups by trifluoroacetic acid

gave the free disaccharides, *O*-α-D-altropyranosyl-(1→3)-D-glucopyranose **145** and *O*-β-L-altropyranosyl-(1→3)-D-glucopyranose **146**, over eight steps. Although the number of steps required for the disaccharide assembly was modest, the stereoselectivity of the key step, the HDA reaction, was low.

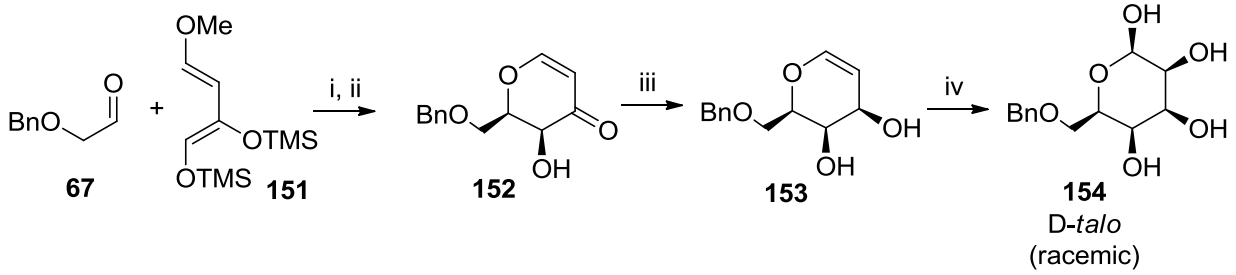


Scheme 20. Synthesis of disaccharides via a HDA reaction by David. Reagents and conditions: i) 60 °C, 3 days, **135** (αD, 12%), **136** (βL, 56%), **137** (βD, 17%), **138** (αL, 9%); ii) NaOBu, BuOH, rt, **135** (not reported), **138** (not reported); iii) $LiAlH_4$, Et_2O, rt, **139** (not reported), **140** (89%); iv) PhCN, H_2O_2, **141** (52%), **142** (not reported); v) PhSeH; vi) H_2O_2, **143** (76% from **9**), **144** (not reported); vii) OsO_4 ; viii) TFA, H_2O, $CHCl_3$, **145** (95% from **135**), **146** (not reported).

The HDA methodology was further developed by Danishefsky and coworkers. In 1982, they demonstrated significant advances by presenting Lewis acid promoted HDA reaction of highly oxygen-substituted diene with aldehyde. (61) This methodology was successfully applied to the synthesis of racemic 4-deoxy-talopyranose **150** and talopyranose **154** (Schemes 21 and 22). The synthesis of **150** was commenced by the HDA reaction of silyloxy diene **147** (also known as Danishefsky's diene) with benzyloxyacetalaldehyde **67** by using $ZnCl_2$ catalysis. After treatment with TFA, the reaction produced racemic dihydropyranone **148** in 87% yield. Treatment of **148** with DIBALH afforded *cis*-glycal **149**. Dihydroxylation of the double bond was conducted by MoO_3 and hydrogen peroxide, yielding 4-deoxy-DL-talopyranose **150**. For the synthesis of DL-talopyranose **154**, the trioxygenated diene **151** was employed. Reaction of **151** with benzyloxyacetalaldehyde **67** was carried out using $BF_3{\cdot}OEt_2$. The resulting product was treated with TFA to afford dihydropyranone **152** in a 42% yield. Reduction of **152** with DIBALH afforded the glycal **153**, which upon dihydroxylation by MoO_3 and hydrogen peroxide, afforded the DL-talopyranose **154**.

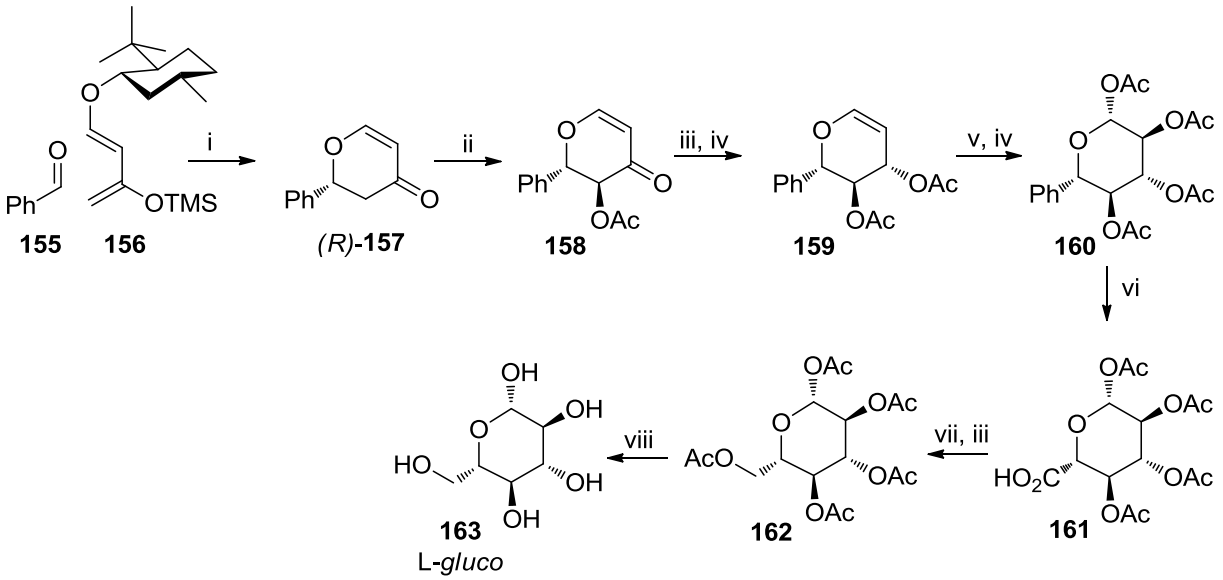


Scheme 21. Synthesis of racemic 4-deoxy-talopyranose via a HDA reaction by Danishefsky. Reagents and conditions: i) $ZnCl_2$, ii) TFA, THF, rt, **148** (87%); iii) DIBALH, benzene, **149** (86%); iv) MoO_3 H_2O_2, **150** (racemic, not reported).



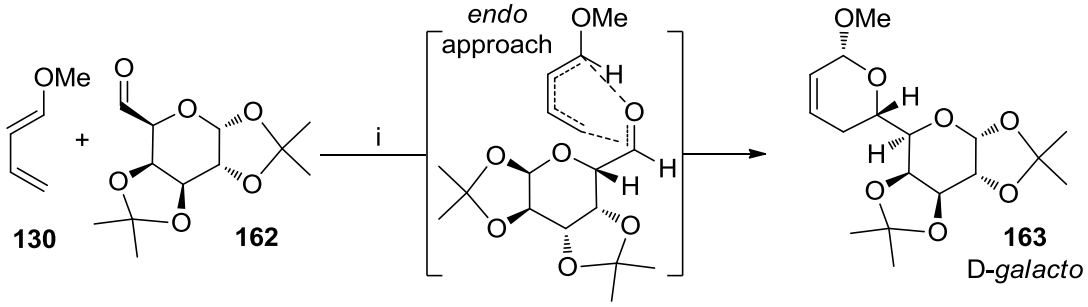
Scheme 22. Synthesis of racemic talopyranose via a HDA reaction by Danishefsky. Reagents and conditions: i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C; ii) TFA, THF, rt, **152** (racemic, 42% from **67**); iii) DIBALH, benzene, **153** (not reported); iv) MoO_3 H_2O_2, **154** (not reported).

Later, Danishefsky and coworkers devised a highly selective route for the asymmetric synthesis of L-glucopyranose by combining the use of a chiral Lewis acid and a 1-phenyl–D-menthoxy auxiliary on the diene (Scheme 23). (84) (85) Reaction of benzaldehyde **155** with diene **156** gave after treatment with TFA dihydropyranone (*R*)-**157**, with high streoselectivity (*R*:*S* 25:1). The missing C_4 oxygen was introduced by oxidation of dihydropyranone **157** with manganese(III) acetate in a highly *anti*-stereoselective reaction. The reduction of **158** with $NaBH_4$ in the presence of cerium(III) chloride and subsequent acetylation afforded intermediate **159**. Dihydroxylation of the double bond with OsO_4 followed by acetylation gave saccharide precursor **160**. The phenyl substituent was then converted to the hydroxymethyl function required for the saccharide structure. Treament of **160** with ozone followed by treatment with hydrogen peroxide led to the protected L-glucuronic acid **161**. Reduction of **161** with borane-THF followed by acetylation provided peracetylated L-glucopyranose **162**. Deprotection gave free L-glucopyranose **163**. Although this methodology offered high stereoselectivities, ten steps were required for the construction of the single monosaccharide unit, and accordingly the overall yield was relatively low (6% from **155**).



Scheme 23. Synthesis of L-glucose via an auxiliary-controlled HDA reaction by Danishefsky. Reagents and conditions: i) (+)-Eu(hfc)$_3$, hexane, -20 °C; then TFA, rt, (*R*)-**157** (er 98:2, 52% from **155**); ii) Mn(OAc)$_3$, CH_2Cl_2, 90 °C, **158** (52%); iii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, -78 °C → 0 °C; iv) Ac_2O, Et_3N, DMAP (cat.), rt, CH_2Cl_2, **159** (80% from **158**), **160** (β:α 5:1, 80% from **159**); v) OsO_4, NMO, *t*BuOH, H_2O, THF, rt; vi) O_3, AcOH, rt; then H_2O_2, H_2O, rt, **161** (42%); vii) BH_3-THF, rt; viii) NaOMe, MeOH, rt; then DOWEX-H ion exchange resin, **163** (86% from **161**).

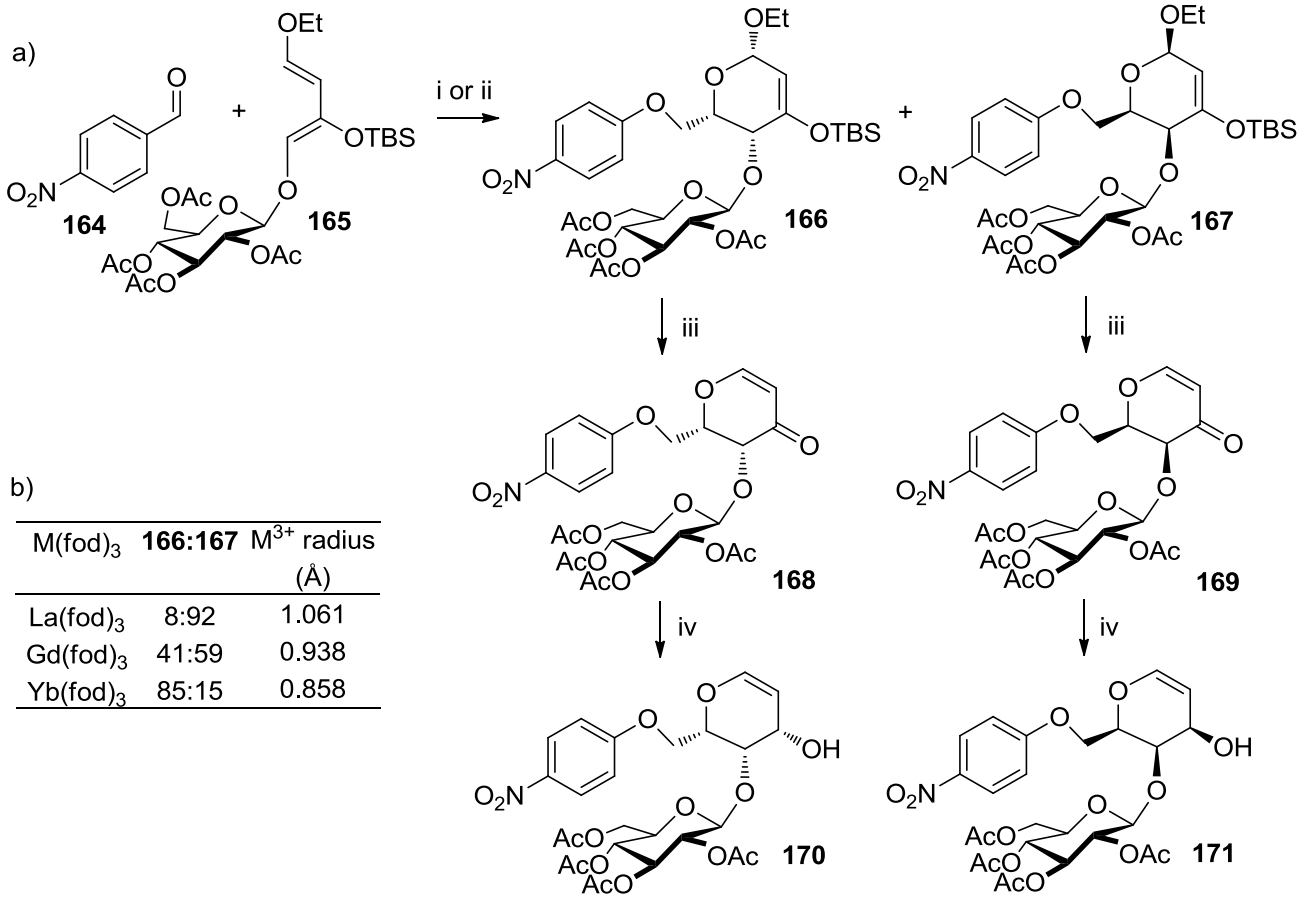
Diene-aldehyde cycloadditions with a starting material that already incorporated a glycosylated building block were studied further by Jurczak and coworkers. (86) (87) To overcome the slow reaction rates usually obtained with less reactive substrates such as **130**, the cycloaddition was conducted at high pressure (20 kbar) (Scheme 24). Under these conditions, 1-metoxybutadiene **130** reacted with D-galactopyranose-derived aldehyde **162** to give dihydropyran structure **163** with a complete stereoselectivity. When the reaction was carried out at 11 kbar in the presence of Eu(fod)$_3$ as a catalyst, a 98:2 ratio of the cycloadducts was obtained, in which **163** was the major product. The diastereoselectivity of the reaction was consistent with a Felkin-Anh transition state in which the diene approaches the formyl group from the less hindered face, in the *endo* mode.



Scheme 24. Synthesis of a disaccharide precursor via a HDA reaction by Jurczak. Reagents and conditions: i) 20 kbar, 53 °C, Et_2O, **163** (72%).

In 2002, Cousins and coworkers reported access to disaccharide precursors with the help of a carbohydrate-derived diene. (88) Their method afforded (1-4)-linked disaccharide derivatives by utilizing the versatile technology of Danishefsky (see Schemes 21 and 22, p. 39). La(fod)$_3$ and Yb(fod)$_3$ promoted a HDA reaction of an aromatic aldehyde **164** with D-glucopyranose-derived diene **165**, giving *cis*-enulopyranoses **166** and **167** with good

diastereoselectivity (**166:167** 10:90 and 82:18, respectively) (Scheme 25). A clear correlation between the stereochemistry of the product and the cationic radius of the lanthanide metal was observed: as the radius decreased, the stereoselectivity switched from **166** toward **167** (see Scheme 23b). Treatment of **166** and **167** with TFA and fractional crystallization afforded **168** and **169** as single diastereomers in 68% and 52% yields, respectively. Luche reduction ($NaBH_4$, $CeCl_3$) (89) afforded the glycals **170** and **171** in 75% and 55% yields, respectively. In principle, the newly formed glycal **170** could be could be converted both to L-talo- and L-galactopyranose structures, while glycal **171** is a precursor for D-talo- and D-galactopyranoses. (62) The major drawback of this method was the relatively low yield of the D-glucopyranose-derived diene **165**. Although the diene **165** reacted with two other heteroaryl aldehydes, the *p*-nitrophenyl protection of aldehyde was essential.



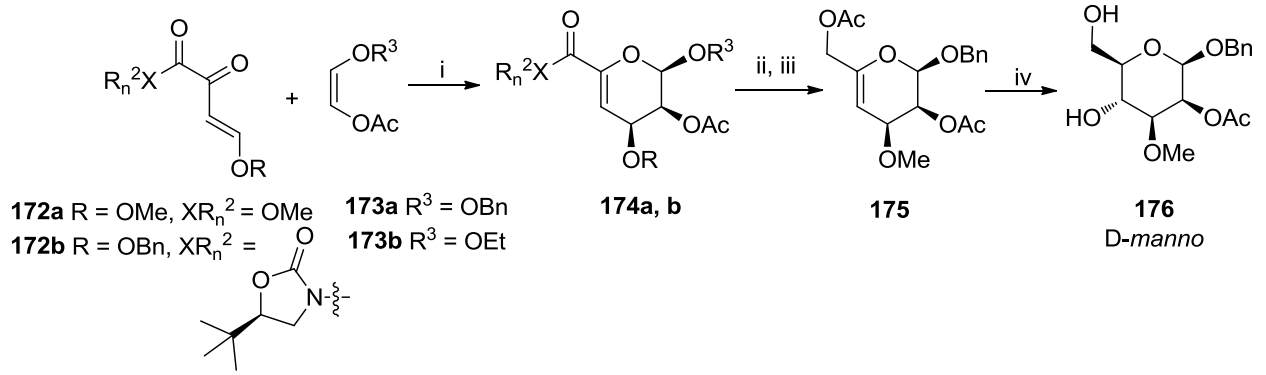
b)

$M(fod)_3$	**166:167**	M^{3+} radius (Å)
$La(fod)_3$	8:92	1.061
$Gd(fod)_3$	41:59	0.938
$Yb(fod)_3$	85:15	0.858

Scheme 25. a) Synthesis of protected glycals **166** and **167** via a HDA reaction by using the glucose-derived diene **165** by Cousins. Reagents and conditions: i) $La(fod)_3$, 1,2-dichloroethane, **166**:**167** 8:92; or ii) $Yb(fod)_3$, 1,2-dichloroethane, **166**:**167** 85:15; iii) TFA, rt, **168** (68%), **169** (52%); iv) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH–THF (1:1), **170** (75%) **171** (55%). b) Effect of M^{3+} radius on the reaction of the diene **165** with aldehyde **164**.

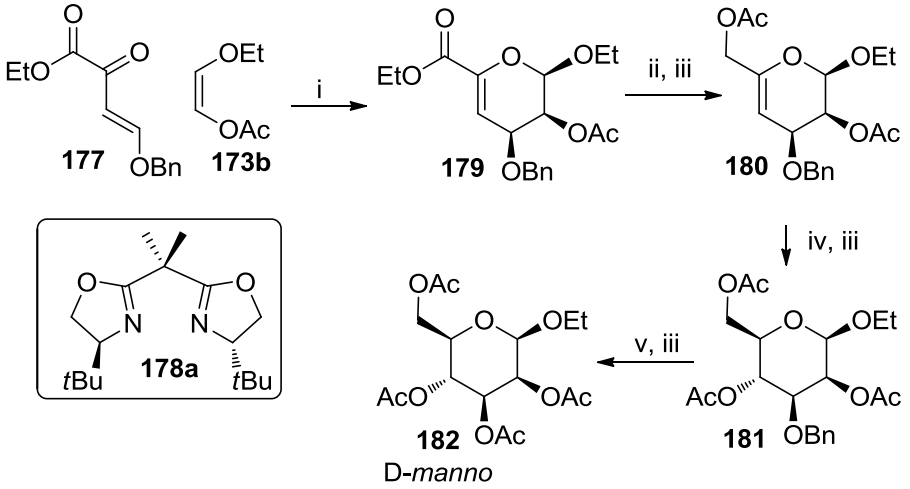
In addition to the normal electron demand HDA reactions, the inverse electron demand HDA reaction has also been used in the synthesis of saccharides. In 1988, Boger and coworkers presented the synthesis of DL-mannopyranoside via a highly *endo*-selective HDA reaction (Scheme 26). (63) In 1994 Tietze and coworkers made important advances in this methodology. They developed a highly diastereo- and enantioselective version of the *endo*-selective inverse electron demand HDA reaction by using a diene bearing a chiral acyl oxazolidinone moiety (**172b**). (90) Reverse facial differentiation was achieved by variation of

the Lewis acid (chelating or nonchelating) that enabled the selective formation of either *endo* diastereoisomer from the same chiral auxiliary. Simple transformations of HDA products afforded the desired L- and D-mannopyranoses diastereoselectively and in good yield.



Scheme 26. Synthesis of protected D-mannopyranoside via an inverse electron demand HDA reaction by Boger. Reagents and conditions: i) **172a**, **173a**, 13 kbar, 25 °C, 72 h, **174a** (racemic, 50%), or **172b**, **173b**, $AlMe_2Cl_2$, CH_2Cl_2, -35 °C , **174b** (*endo*:*exo* > 50:1, 97%,); ii) $LiAlH_4$, Et_2O, 0 °C → rt; iii) Ac_2O, pyridine, rt, **175** (65% from **174a**); iv) BF_3SMe_2, THF, rt, then NaOH, H_2O_2, THF, 70 °C, **176** (56% from **175**).

In 2000, Evans and coworkers presented a catalytic and highly diastereo- and enantioselective version of this HDA reaction, where the bis(oxazoline)-Cu(II) complexes were used as catalysts. (91) In 2002, Jørgensen and coworkers further extended this methodology to the catalytic, enantio- and diastereoselective synthesis of D-mannopyranoside. (92) HDA reaction of *β,γ*–unsaturated α-keto ester **177** with electron-rich alkene **173b** catalyzed by chiral bisoxazoline **178a**-$Cu(OTf)_2$ complex gave the *endo*-product **179** as the only diastereomer in 60% yield and with a 98:2 enantiomeric ratio (Scheme 27). The ester functionality of **179** was reduced and the resulting alcohol was protected with an acetate group to give compound **180** in 92% overall yield. Hydroboration of the double bond in **180** gave the protected D-mannopyranoside **181** in moderate yield. Finally, tetraacetate **182** was obtained after debenzylation and acetylation. Thus, **182** was prepared in five steps and 19% overall yield from **177**.



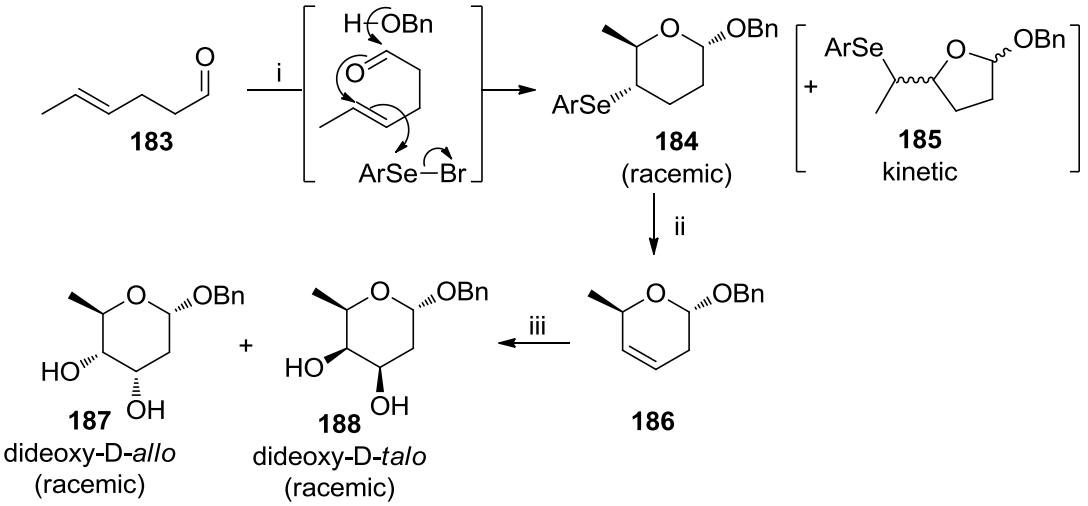
Scheme 27. Synthesis of protected D-mannopyranoside via an inverse electron demand HDA reaction by Jørgensen. Reagents and conditions: i) **178a**-$Cu(OTf)_2$, Et_2O, rt, **179** (dr 98:2 (*endo*), 60%); ii) $LiAlH_4$, THF, 0 °C → rt; iii) Ac_2O, pyridine, **180** (92% from **179**), **181** (35% from **180**), **182** (92% from **181**); iv) BF_3SMe_2, THF, 0 °C → rt, then NaOH, H_2O_2, THF, 60 °C; v) $Pd(OAc)_2$, H_2, EtOH, rt.

3.2.4 Strategies Relying on Stereoselective Carbon-Heteroatom Bond Formation

De novo synthesis of carbohydrates relying on stereoselective carbon-heteroatom formation begins with the assembly of a carbon framework. Then, the required heteroatoms are stereoselectively attached in the key synthetic step(s). The stereoselectivity of the heteroatom insertion step(s) is almost without exception based on pi-facial discrimination of an olefin, leading to a carbon-oxygen or carbon-nitrogen bond. In this review, only methods affording carbon-oxygen bonds are discussed. The methodologies are organized according to the reaction type by which the oxygen atoms are introduced: oxidative cyclization of an acyclic precursor, dihydroxylation and epoxidation.

3.2.5 Methodologies Based on Oxidative Cyclization

In an oxidative cyclization, an unsaturated, acyclic starting material is activated towards intermolecular ring formation with an electrophilic oxidant. In 1978 Current and Sharpless utilized this methodology in the synthesis of racemic 2,6-dideoxy-glucopyranosides (Scheme 28). (93) A three-component condensation of *trans*-4-hexenal **183**, benzyl alcohol and (*p*-chlorophenyl)selenyl bromide gave a mixture of selenides **184** and **185**, and the desired six-membered **184** was the main product under equilibrating conditions (62%). Selenoxide elimination afforded the dihydropyran **186**, which was then subjected to dihydroxylation. The mixture of isomers **187** and **188** was obtained in 25% and 13% yields, respectively.



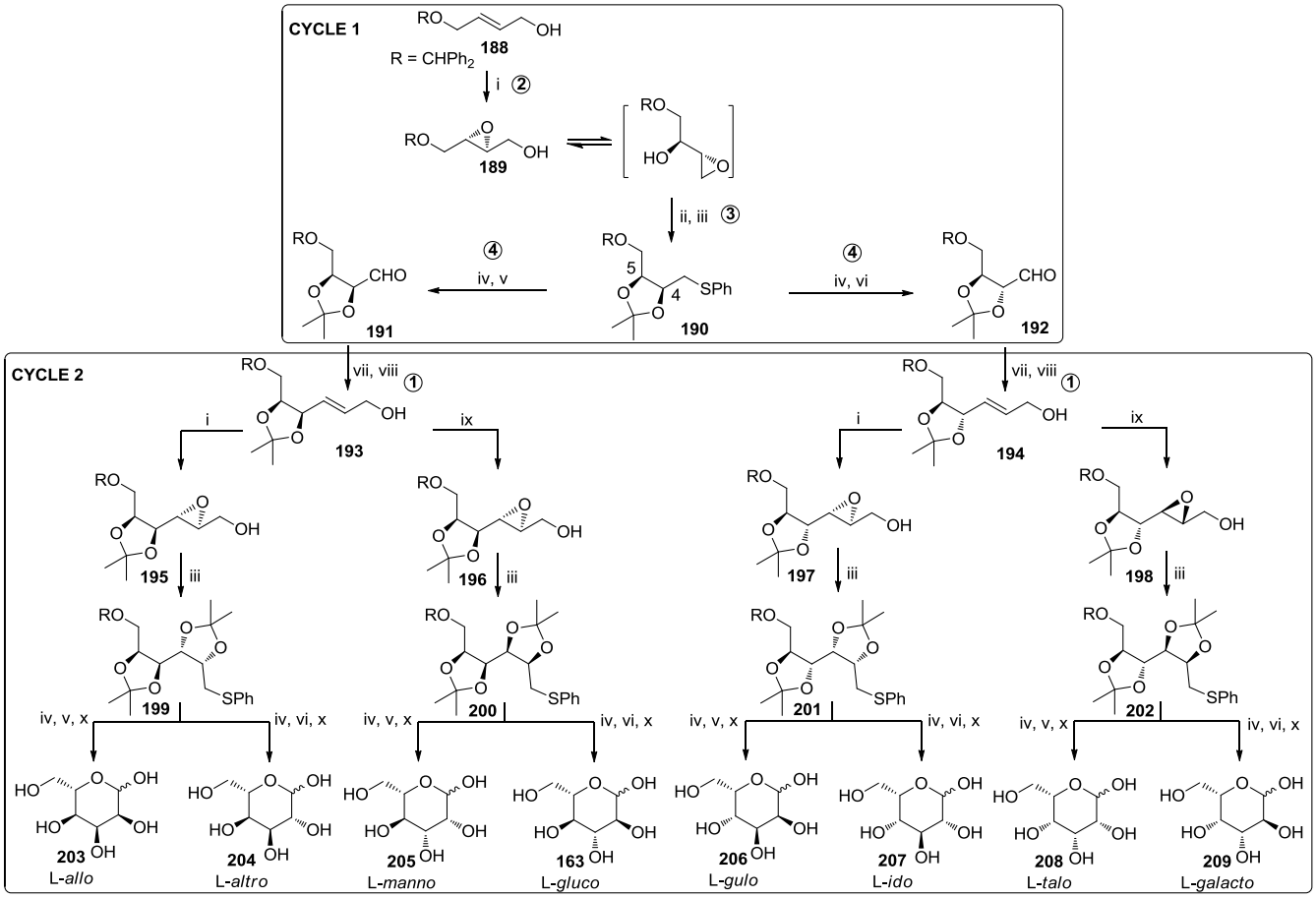
Scheme 28. Synthesis of 2,6-dideoxyglucosides via selenyl halide promoted cyclofunctionalization by Current and Sharpless. Reagents and conditions: i) benzyl alcohol, (*p*-chlorophenyl)selenyl bromide, **184** (62%); ii) H_2O_2 (30%), CCl_4, pyridine, **186** (80%); iii) OsO_4, H_2O_2, **187** (25%), **188** (13%).

3.2.6 Methodologies Based on Asymmetric Epoxidation and Dihydroxylation

Asymmetric epoxidation (AE) and asymmetric dihydroxylation (AD) are highly useful tools in the *de novo* synthesis of carbohydrates. Many stereoselective AE reactions, especially those influenced by allylic heteroatoms, have emerged since 1980s (94) (95) (96) and comprehensive reviews on the preparation and reactions of epoxides are available. (97) (98) (99) In the cases which an AD reaction is utilized for hydroxyl function attachment, the Sharpless AD is the most commonly used. (100) (101)

Sharpless and Masamune were the first to report the stereoselective *de novo* synthesis methodology for the synthesis of all eight L-aldohexoses in 1983. (102) (103) The

stereoselectivity was based on Katsuki-Sharpless asymmetric epoxidation. (104). The synthesis route consisted of a repetitive two-carbon extension cycle. One cycle included four steps: 1) conversion of an aldehyde into its corresponding *E*-allylic alcohol; 2) AE reaction of allylic alcohol; 3) opening of the resulting epoxy alcohol by thiophenol followed by acetonide protection; 4) oxidation of the thiol to generate aldehyde with or without inversion of the C_2 center (Scheme 29). As the synthesis could be commenced directly from monoprotected butenediol **188**, only one two-carbon extension step (1) was needed. AE of **188** in the presence of (+)-DET ligand gave epoxide **189** with a high enantiomeric ratio and yield (er > 20:1, 92%). Payne rearrangement (105) of **189** with thiophenolate followed by acetonide protection of diol led to the protected thiol **190**. Then, oxidation and Pummerer rearrangement (106) (107) of the sulfide followed by the net hydrolysis of the resulting *gem*-acetoxysulfide with or without inversion of the C_2 center yielded aldehydes **191** and **192**, respectively. The second cycle was commenced with the conversion of aldehydes **191** and **192** into their corresponding *E*-allylic alcohols **193** and **194**. The subsequent steps 2-4 were conducted in the same manner as described above. Finally, deprotection yielded all eight L-aldohexoses: **163** and **203-209**. Although this methodology was the first to enable the synthesis of all eight possible diastereomers of L-aldohexoses, the method is not without limitations. The synthesis route is quite long and the overall yields of the hexoses are low (ranging from 17% for L-allopyranose **203**, to 3% for L-galactopyranose **209** 3%, starting from **188**). In addition, the regioselectivity of the Payne rearrangement is not always high. Finally, isomerization of thiols (**190**, **199**, **200**, **201** and **202**) is critical for the synthesis of aldehyde **192** and L-hexoses **204**, **163**, **207** and **209** because of the inability to obtain *cis*-epoxy alcohols with high optical purity. (108)

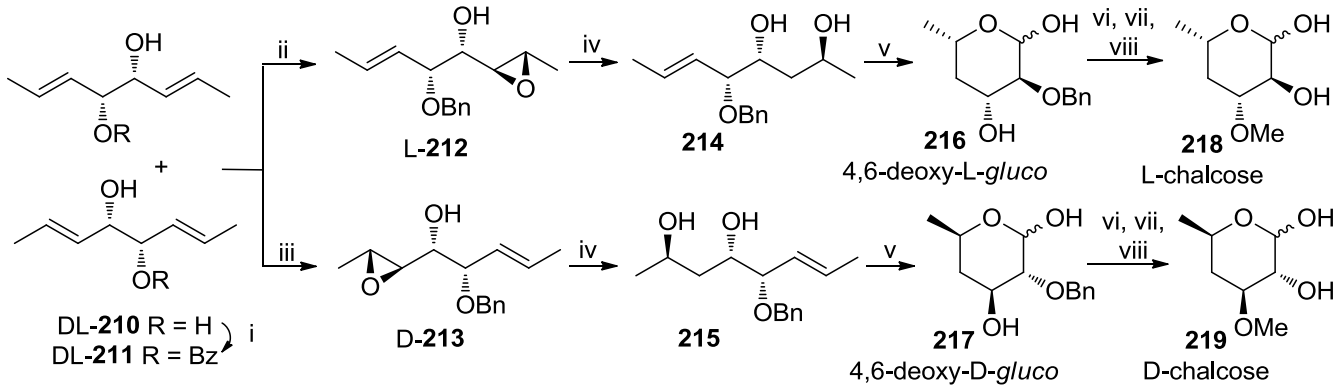


Scheme 29. Synthesis of all eight L-hexoses by Masamune and Sharpless. Reagents and conditions: i) (+)-DET, Ti(*i*Pr)$_4$, *t*BuO$_2$H, CH_2Cl_2, -20 °C, **189** (er > 20:1, 92%), **195** (er > 20:1, 76%), **197** (er > 20:1, 71%); ii) NaOH, reflux, *t*BuOH**,** then thiophenol; iii) 2,2-dimethoxypropane, phosphorus oxychloride, CH_2Cl_2, rt, **190** (8:2; 71% from **189**), **199** (er 16:1, 77%, from **195**), **200** (er 7:3, 63% from **196**), **201** (er 7:1, 79% from **197**), **202** (er 15:1, 86% from **198**); iv) *m*CPBA, CH_2Cl_2, -78 °C; v) DIBALH, CH_2Cl_2, -78°C, **191** (>20:1, 86%); vi) K_2CO_3, MeOH, **192** (>20:1, 99%); vii) formylmethylenetriphenylphosphorane, benzene, rt; viii) $NaBH_4$, MeOH, -40 °C → -10 °C, **193** (80%), **194** (not reported); ix) (-)-DET, Ti(*i*Pr)$_4$, *t*BuO$_2$H, -20 °C, CH_2Cl_2, **196** (er > 20:1, 84%); **198** (er > 20:1, 86%); x) TFA, H_2O, rt, then Pd/C, H_2, MeOH, rt, **203** (66% from **199**), **204** (26% from **199**), **205** (77% from **200**), **163** (11% from **200**), **206** (59% from **201**), **207** (49% from **201**), **208** (33% from **202**), **209** (8% from **202**).

Later, some improvements to this methodology were disclosed. Miyashita and coworkers reported the synthesis of aldopentoses involving two stereospecific epoxide-opening reactions. (109) This reaction sequence consisted of a ring-opening reaction of epoxy sulfides with phenylboronic acid (110) and the stereospecific interconversion of *trans*- and *cis*-epoxy sulfides (111). However, as this methodology was directed only towards aldopentoses, it is outside the scope of this review.

In 1986 Schmidt and coworkers presented the synthesis of enatiomerically pure dideoxy hexoses via asymmetric epoxidation reaction starting from racemic divinylglycols. (112) The racemic DL-dipropenyl glycol **210** (obtained by reductive dimerization of crotonaldehyde (113) and separation of diastereomers) was reacted with bezyl bromide to give monobenzylated DL-**211** (Sheme 30). Katsuki-Sharpless AE (104) of DL-**211** leaded to kinetic resolution and thus the formation of enantimerically pure epoxides L-**212** and D-**213**. Next, the epoxide ring of L-**212** was opened regioselectively with Red-Al to afford **214** in 86% yield. The following ozonolysis gave partially protected 4,6-dideoxy-L-glucose **216** in only four steps, but in low overall yield

(6%) from DL-**210**. Then, **216** was benzylated at anomeric position, 3-*O*-methylated and finally, hydrogenolytically debenzylated to afford L-chalcose **218** in 52% yield over three steps. 4,6-dideoxy-D-glucose **217** and D-chalcose **219** were prepared in the enantiomeric sequence for L-serie hexoses **216** and **218**. In addition to *gluco*-serie of hexoses, this route shoud be applicable for *galacto*-serie by starting from *erythro*-dipropenyl glycol.

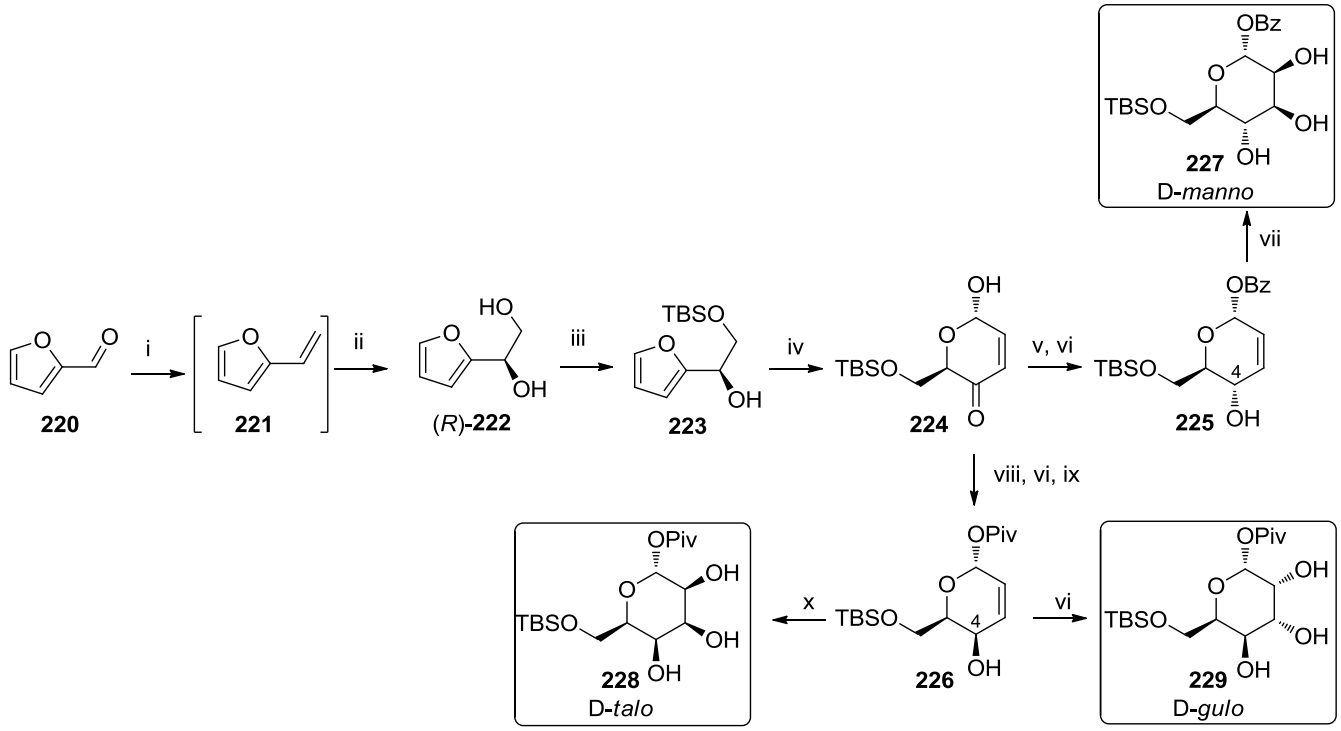


Scheme 30. Synthesis of deoxyhexoses from divinylglycols by Schmidt. Reagents and conditions: i) BnBr, DMF, BaO, $Ba(OH)_2$, DL-**211** (46%); ii) (+)-DET, $Ti(iPr)_4$, $tBuO_2H$, CH_2Cl_2, L-**212** (35%); ii) (-)-DET, $Ti(iPr)_4$, $tBuO_2H$, CH_2Cl_2, D-**213** (35%); iv) Red-Al, THF, L-**214** (86%), **215** (not reported); v) O_3, MeOH, CH_2Cl_2, then Me_2S, **216** (81%), **217** (not reported); vi) BnOH, HCl; vii) MeI, NaH, DMF; viii) Pd/C, H_2, EtOAc, **218** (52% from **216**), **219** (not reported).

In 1999, O'Doherty and coworkers presented the stereoselective synthesis of manno-, gulo-, and talopyranosides via asymmetric dihydroxylation to afford the D- and L-configuration of saccharides depending on the ligand used. (114) The synthesis started with the conversion of furfural **220** to vinylfuran **221**, which was directly dihydroxylated to diol **222** using a catalytic asymmetric dihydroxylation developed by the Sharpless group (100) (101) and pioneered for this system by Ogasawara (Scheme 31) (115). The use of AD-mix-α gave diol (*R*)-**222** with a 95:5 enantiomeric ratio and in 85% yield from **220**, and the enantiomeric diol (*S*)-**222** was readily obtained in similar yield and selectivity by the use of AD-mix-β. Diol (*R*)-**222** was selectively protected with TBSCl to give furan **223** (90%); this was treated with NBS to initiate a smooth Achmatowicz oxidative rearrangement (116) to hemiacetal **224**, which existed as an equilibrating mixture of anomers. To separate the anomers, the higher reactivity of the pseudoaxial α–anomer was used to an advantage when **224** was treated with benzoyl chloride. The isolated benzoyl product was then reduced under Luche conditions ($NaBH_4$, $CeCl_3$) (89) and afforded alcohol **225** as the only observable stereoisomer. Finally, a second AD reaction afforded the partially protected D-mannopyranoside **227** in 90% yield (overall yield over five steps from furfural **220** was 39%).

For the synthesis of D-talo- and D-gulopyranosides **228** and **229**, the C_4 isomer of **225** was needed. This could be obtained via a Mitsunobu isomerization. (117) More reproducible results were observed when pivalate protection was used in anomeric oxygen. Thus, hemiacetal **224** was protected with the pivaloyl group and the resulting pyranone was reduced under the Luche conditions to yield an allylic alcohol (similar to **225**, not shown). Exposure of this material to the Mitsunobu reaction conditions (PPh_3, DEAD, *p*-nitrobenzoic acid) (117) resulted in the formation of an intermediate *p*-nitrobenzoic ester, which was selectively hydrolyzed with Et_3N/MeOH to yield the axial alcohol **226**. Treatment of **226** with OsO_4 and NMO afforded the protected D-gulopyranoside **229** in 80% yield. The protected D-talopyranoside **228** was selectively produced upon treatment of **226** with the TMEDA adduct

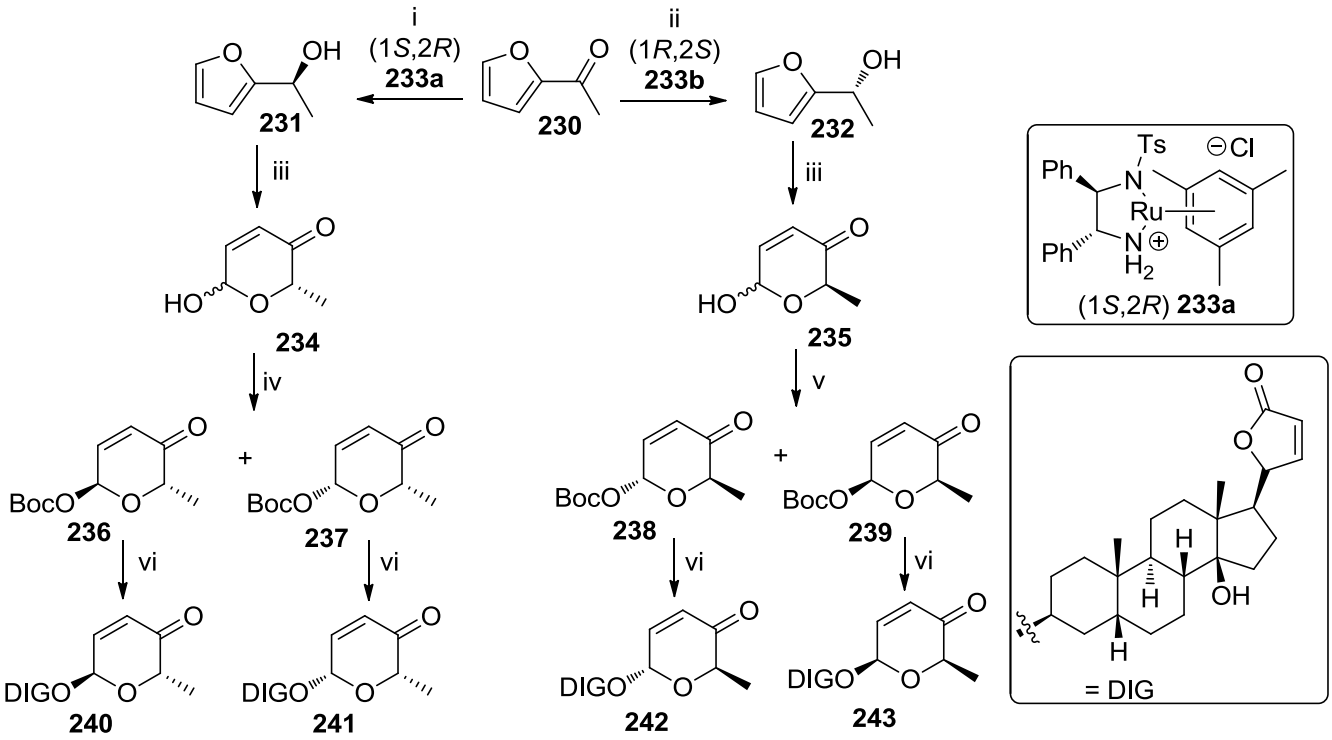
of OsO_4 (80%). The overall yield of **228** and **229** over seven steps from furfural **220** was *ca.* 19%. This practical methodology is equally applicable to the synthesis of L-series saccharides. The high cost of osmium and the ligands may be prohibitive for a large-scale synthesis, however.



Scheme 31. Synthesis of protected D-manno-, D-gulo-, and D-talopyranose by O'Doherty. Reagents and conditions: i) $TMSCH_2MgCl$, Et_2O, then HCl; ii) AD-mix-α, *t*BuOH, H_2O, (*R*)-**222** (ee 90%, 85%), or AD-mix-β, *t*BuOH, H_2O, (*S*)-**222** (ee 92%, 85%); iii) TBSCl, Et_3N, DMAP, 0 °C, **223** (90%); iv) NBS, H_2O, 0 °C; v) BzCl, -78 °C; vi) $NaBH_4$, $CeCl_3$, -78 °C, **225** (α:β > 20:1, 80% from **224**); vii) OsO_4, NMO, 0 °C, **227** (62%), **229** (80%); viii) PivCl, Et_3N; ix) PPh_3, DEAD, PNBOH, then Et_3N, MeOH, **226** (31% from **223**); x) OsO_4, TMEDA, **228** (80%).

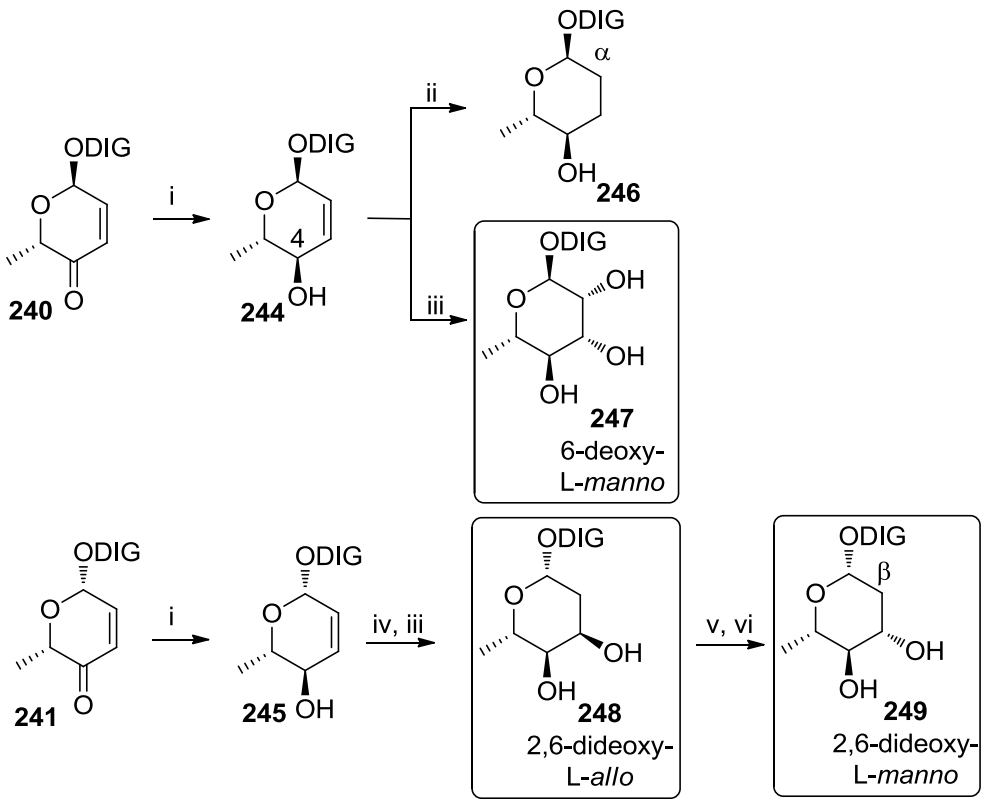
Later, O'Doherty and coworkers applied this methodology to the synthesis of protected D- and L-gulo-δ-lactone, and L-allo-δ-lactone, which were obtained in eight steps and with 20% overall yield from furfural. (118) They also presented the syntheses of D- and L-galacto-1,4-lactone over three steps and with 51% overall yield starting from 2,4-dienoates. (119)

Moreover, in 2011 O'Doherty and coworkers presented a practical methodology to 6-deoxyhexose derivatives via Noyori asymmetric reduction (120) and AD reactions. (121) They synthetized digitoxin derivatives, which consisted of digitoxigenin (DIG) and deoxyhexose moieties, as digitoxin is known to play a crucial role in cell growth inhibition and tumor cell death. (122) The synthesis was commenced with the Noyori asymmetric reduction of acylfuran **230** to afford furanyl alcohols **231** and **232** with high enantioselectivity (ee > 98%) (Scheme 32). Thus, the methodology allowed the synthesis of both D- and L-serie of hexoses depending on the ligand used. An Achmatowicz oxidative rearrangement (116) of **231** and **232** and subsequent diastereoselective Boc-protection gave mixtures of α- and β- anomers, which were separated, and thus pyranones **236-239** were obtained. The following Pd-catalyzed glycosylation converted each sugar building block **236-239** to the desired digitoxin monosaccharide precursors **240-243** with excellent yield and stereoretention at the anomeric center.



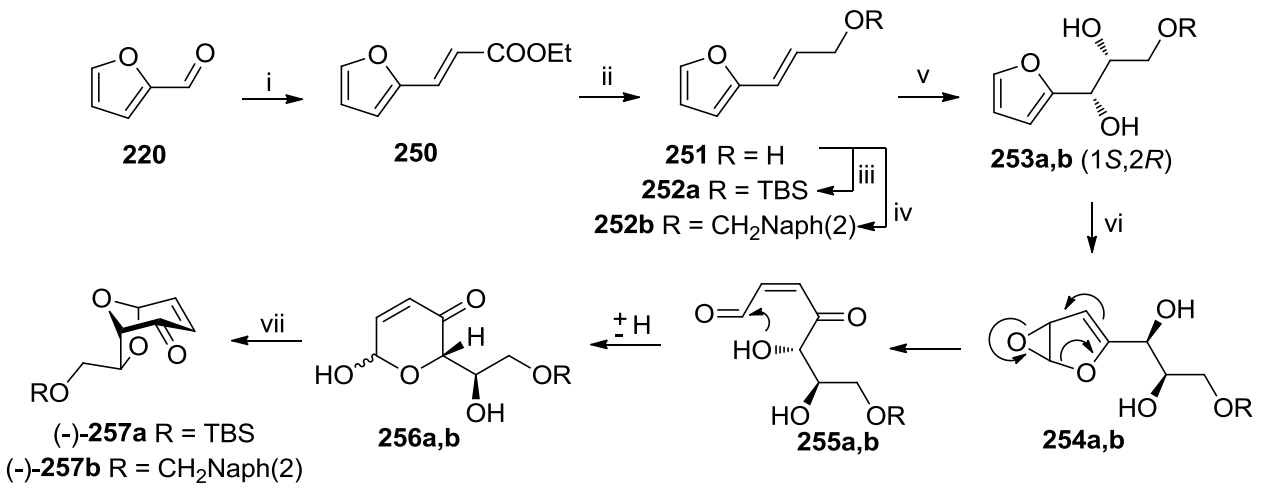
Scheme 32. Synthesis of key intermediate for hexose synthesis by O'Doherty. Reagents and conditions: i) HCO_2Na, CTAB, (1*S*,2*R*) **233a** (cat.), H_2O, rt; ii) HCO_2Na, (1*R*,2*S*) **233b** (cat.), CTAB, H_2O, rt; iii) NBS, $NaHCO_3$, NaOAc, THF, H_2O, 0 °C; iv) $(Boc)_2O$, DMAP, CH_2Cl_2, -78 °C to – 30 °C, **236** (48% from **230**) + **237** (16% from **230**); v) $(Boc)_2O$, NaOAc, benzene, 80 °C, **238** (28% from **230**) + **239** (43% from **230**); vi) DIGOH, $Pd(PPh_3)_2$ (cat.), 0 °C, **240** (82%), **241** (85%), **242** (88%), **243** (86%).

Pyranones **240** and **241** were the precursors for α-L- and β-L-hexoses, while pyranones **242** and **243** were used to afford α-D- and β-D-hexoses, respectively. In this review, only the synthesis of L-hexoses is presented, but the enantiomeric sequence was used to afford corresponding D-hexoses. Thus, α-deoxy- and trideoxy-L-mannopyranose derivatives were synhetized from **240**. To afford the desired stereochemistry at C_4, pyranone **240** was diastereoselectively reduced under Luche conditions ($NaBH_4/CeCl_3$, −78 °C) (89) to afford alcohol **244** as a single isomer (Scheme 33). Then, the olefinic group of **244** was reduced under a facile diimide condition to generate trideoxypyranoside **246**. The use of NMM as solvent improved the overall yield of this reaction. (123) Alternatively, olefin **244** was dihydrolyzed (OsO_4/NMO) to afford α–6-deoxy-L-mannopyranoside (α-L-rhamnose) **247** (80%, the overall yield 28% from acylfuran **230**). Alternatively, β-dideoxy-L-mannopyranose derivative **249** was synthesized from **241**. A reduction of pyranone **241** under Luche conditions (89) followed by Myers reductive rearrangement (NBSH, PPh_3/DIAD, NMM) (124) and dihydroxylation gave exclusively dideoxypyranoside **248** with 63% yield in three steps. Then, the C_3-alcohol **248** was inverted via Mitsunobu reaction (DIAD/PPh_3, *p*-nitrobenzoic acid) (117) and subsequently hydrolyzed with K_2CO_3 to generate β–2,6-dideoxy-L-mannopyranoside (β-L-olivose) **249** (the overall yield 7% from acylfuran **230**).



Scheme 33. Synthesis of deoxypyranosides by O'Doherty. Reagents and conditions: i) $NaBH_4$, $CeCl_3$, -78 °C, **244** (90%); ii) NBSH, Et_3N, NMM, -30 °C to rt, **246** (92%); iii) OsO_4, NMO, H_2O, 0 °C, **247** (80%), **248** (63% from **241**); iv) PPh_3, *p*-nitrobenzoic acid, DIAD, THF, rt; vi) K_2CO_3, **249** (79% from **248**).

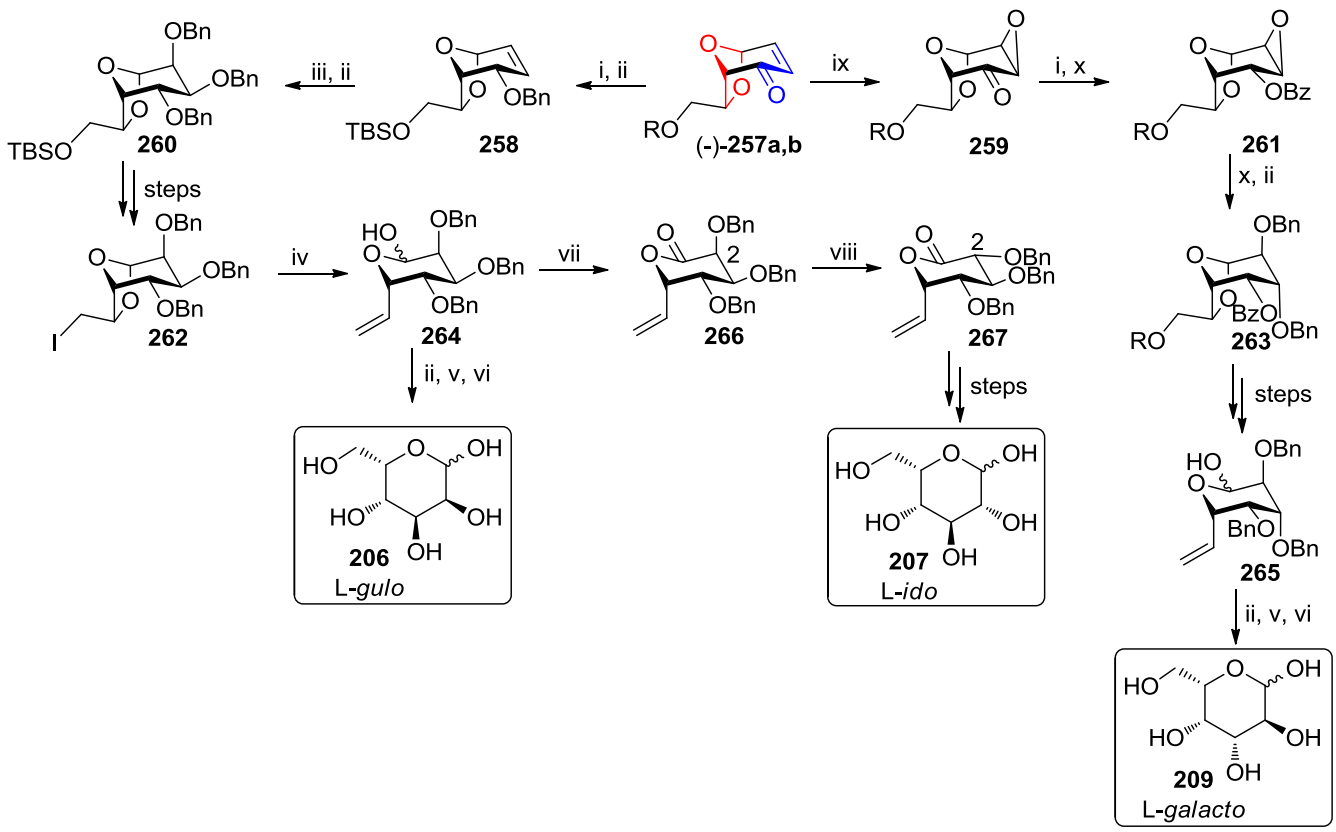
Ogasawara and coworkers presented in 2000 a versatile stereocontrolled methodology to synthesize both enantiomers of all eight aldohexoses. (125) (126) This procedure employed the Sharpless AD as a key step. Only a single asymmetric chiral induction step was needed, as the stereochemical background of L-glucose-type key intermediate (-)-**257a,b** could be utilized in the subsequent synthetic steps (Scheme 34). The synthesis commenced with the Horner-Wadsworth-Emmons olefination (127) (128) (129) of furfural **220** with ethyl diethylphosphonoacetate in the presence of NaH to afford the (*E*)-α,β-unsaturated ester **250** stereoselectively in 97% yield. Reduction of **250** with $LiAlH_4$, followed by TBS protection of the allylic alcohol **251** gave **252a** in excellent yield. Alternatively, treatment of **250** with 2-bromomethyl-naphthalene afforded **252b**. The alkene **252a** was then subjected to the AD reaction using AD-mix-β reagent in the presence of methanesulfonamide to afford the chiral diol **253a** in 94% yield with an enantiomeric ratio greater than 99:1. Then, **253a** was oxidized with *m*CPBA to initiate the ring-expansion, producing the pyranone **256a** as a mixture of two epimers which, without separation, was treated with acid to give the bicyclic enone (-)-**257a** as a single isomer in five steps and with 60% overall yield from **220**. Enone (-)-**257b** was prepared **i**n the same synthetic manner as described for (-)-**257a**.



Scheme 34. Synthesis of key intermediate for hexose synthesis by Ogasawara. Reagents and conditions: i) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 °C → rt, **250** (97%); ii) $LiAlH_4$, Et_2O, 0 °C, **251** (97%); iii) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, **252a** (98%); iv) 2-bromomethyl-naphthalene, NaH (60%), Bu_4NI, THF, 0 °C, **252b** (95%); v) AD-mix-β, $MeSO_2NH_2$, *t*BuOH, H_2O, **253a**(1*S*,2*R*) (er > 99:1, 94%), **253b**(1*S*,2*R*) (74%); vi) *m*CPBA, $NaHCO_3$, 0 °C → rt; vii) *p*TsOH, EtOAc, (-)-**257a** (69% from **253a**), (-)-**257b** (68% from **253b**).

Then, the key intermediates (-)-**257a,b** could be directly used as the starting material for the synthesis of L-gulo-, L-ido- and L-galactopyranoses **206**, **207** and **209** by stereoselective modification of the enone functionality (blue) and regioselective cleavage of the dioxolane moiety (red) (Scheme 35). Reduction of (-)-**257a** under Luche conditions (89) proceeded stereoselectively to give, after benzyl protection, the single product **258**. Then, **258** was dihydroxylated and benzyl-protected to give compound **260**. The dioxolane ring was cleaved by converting **260** into iodide compound **262** via primary alcohol and mesylate intermediates. The subsequent treatment of **262** with zinc in acetic acid afforded six-membered hemiacetal **264** as an epimeric mixture. Next, benzyl protection of **264**, sequential cleavage and reduction of vinyl functionality, and lastly debenzylation, afforded L-gulopyranose **206** in 57% overall yield from (-)-**257a** (34% from **220**).

To obtain L-iodopyranose **207**, the hemiacetal **264** was oxidized with TPAP in the presence of NMO to give the δ-lactone **266**. Epimerization at C_2 with DABCO afforded the isomeric δ-lactone **267** as a single product. Reduction of **267** and further elaboration afforded L-iodopyranose **207** in 20% overall yield from (-)-**257a** (12% from **220**). On the other hand, to obtain L-galactopyranose **209**, epoxidation of (-)-**257b** with alkaline hydrogen peroxide afforded the single *exo*-epoxide **259**. Reduction of **259** under Luche conditions (89) proceeded stereoselectively to give, after benzoyl protection, the single benzoate **261**. The epoxide group was then stereoselectively cleaved utilizing neighboring group participation of the benzoate functionality by treating **261** with BF_3OEt_2 to give, after benzyl protection, the single product **263**. After cleavage of the dioxolane ring and manipulation of the protection groups, L-galactopyranose **209** was obtained in 37% overall yield from (-)-**257b** (22% from **220**).



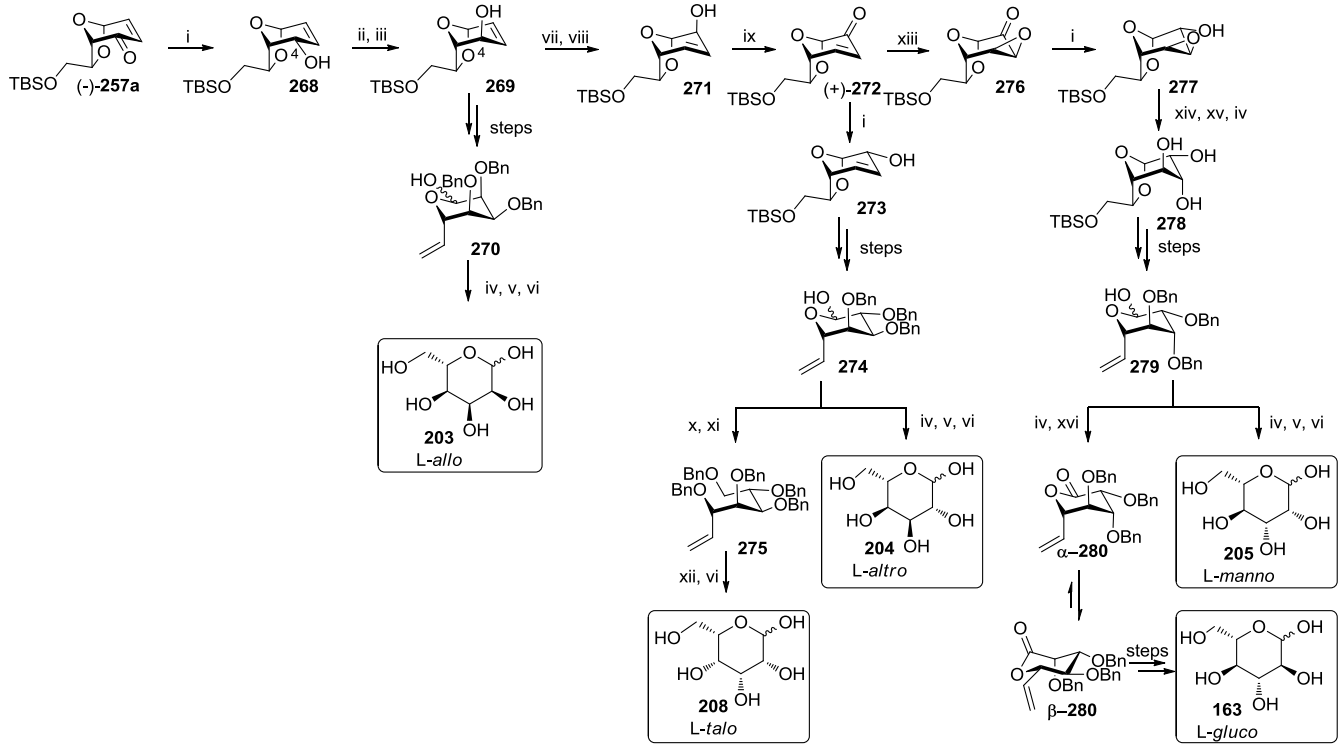
Scheme 35. Synthesis of L-gulo-, L-ido- and L-galactopyranose by Ogasawara. Reagents and conditions: i) $NaBH_4$, $CeCl_3$, MeOH, 0 °C; ii) BnBr, NaH, **258** (91%from (-)-**257a**), **260** (86%from **258**); iii) OsO_4 (cat.), NMO, THF, H_2O; iv) Zn, AcOH, rt, **264** (97%); v) O_3, MeOH, CH_2Cl_2, -78 °C, then $NaBH_4$; vi) H_2, $Pd(OH)_2$, **206** (95% from **264**), **209** (79% from **265**); vii) TPAP, NMO, **266** (84%); viii) DABCO, **267** (74%); ix) (-)-**257b**, H_2O_2, aq. NaOH, THF, **259** (87% from (-)-**257b**, R = CH_2Naph(2)); x) BzCl, pyridine, **261** (87% from **259**).

However, for the synthesis of the L-allopyranose **203,** inverted alcohol **269** was needed (Scheme 36). For this purpose, the enone (-)-**257a** was selectively reduced under Luche conditions (89). Mitsunobu inversion (117) of **268** with formic acid followed by methanolysis of the resulting formate gave the inverted alcohol **269**. Then, **269** was protected, diastereoselectively dihydroxylated, and the dioxolane ring was cleaved to afford the vinyl hemiacetal **270**. After further elaboration, L-allopyranose **203** was obtained in 25% overall yield from (-)-**257a** (15% from **220**). The alcohol intermediate **269** was further utilized for the construction of the isomeric bicyclic enone (+)-**272**, which was the key intermediate for the formation of four remaining L-aldohexoses, L-altro-, L-talo-, L-manno- and L-glucopyranoses **204**, **208**, **205** and **163**. Thus, the inverted alcohol **269** was mesylated and then refluxed with aqueous calcium carbonate to afford isomeric alcohol **271** via a regio- and diastereoselective S_N2 type rearrangement. Oxidation with PCC gave the isomeric enone (+)-**272**. Then, (+)-**272** was reduced diastereoselectively into the alcohol **273**. After further manipulation the vinyl hemiacetal **274** was obtained, which was directly transformed into the L-altropyranose **204** in 15% overall yield from (-)-**275a** (9% from **220**).

For the synthesis of L-talopyranose **208**, the vinyl hemiacetal **274** was further reduced and protected as the pentabenzyl ether **275**. Subsequent oxidation and benzyl group removal afforded L-talopyranose **208** in 15% overall yield from (-)-**257a** (9% from **220**). On the other hand, the enone (+)-**272** was converted diastereoselectively to the epoxide **276** by treatment with sodium hypochlorite in pyridine. Then, the ketone functionality was reduced to give the alcohol **277** as the single product. Further elaboration resulted in the vinyl hemiacetal **279**,

which was directly transformed into the L-mannopyranose **205** in 20% overall yield from (-)-**257a** (12% from **220**). For the synthesis of L-glucopyranose **163**, the vinyl hemiacetal **279** was first oxidized with TPAP to give the equilibrium mixture of α- and β-lactones **280**. This mixture was again epimerized with DABCO. After further modification, L-glucopyranose **163** was obtained in 9% overall yield from (-)-**257a** (5% from **220**).

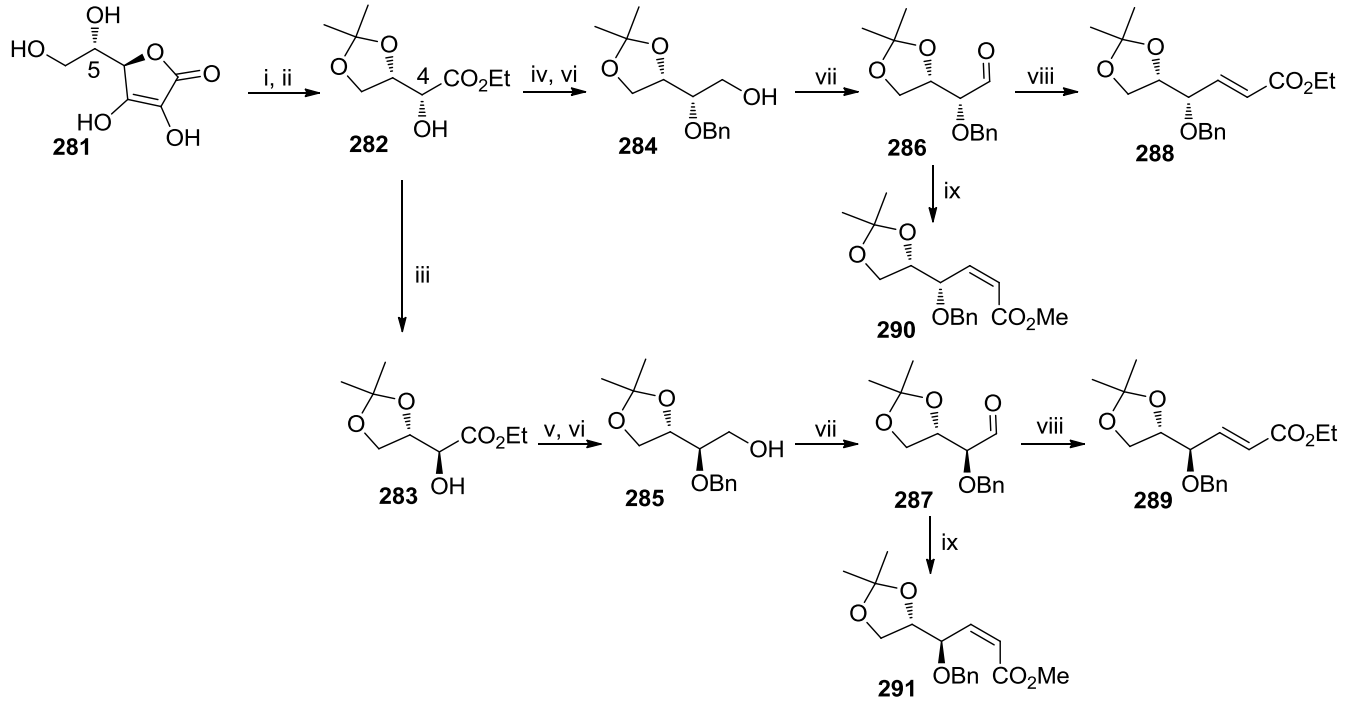
Although this versatile methodology enables the synthesis of both enantiomers of all eight aldohexoses, in some cases the route is quite laborious (for example, for L-glucose, 23 steps were needed starting from **220**) and overall yields are quite low.



Scheme 36. Synthesis of L-allo-, L-talo-, L-altro-, L-manno- and L-glucopyranose by Ogasawara. Reagents and conditions: i) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, **268** (93%), **273** (99% from (+)-**272**), **277** (57% from **276**); ii) HCO_2H, DIAD, PPh_3, THF, 40 °C; iii) K_2CO_3, MeOH, **269** (70% from **268**); iv) BnBr, NaH, THF, reflux, **278** (94% from **277**); v) O_3, MeOH, CH_2Cl_2, -78 °C, then $NaBH_4$; vi) H_2, $Pd(OH)_2$, **203** (79% from **270**), **208** (86% from **275**), **204** (83% from **274**), **205** (78% from **279**); vii) MesCl, Et_3N, CH_2Cl_2; viii) $CaCO_3$, H_2O, reflux; ix) PCC, NaOAc, 4 Å MS, CH_2Cl_2, (+)-**272** (50% from **269**); x) $LiAlH_4$, THF, 0 °C; xi) BnBr, NaH, Bu_4NI (cat.), THF, **275** (83% from **274**); xii) OsO_4 (cat.), NMO, THF, H_2O, then $NaIO_4$; xiii) NaOCl, pyridine, 0 °C; xiv) BzCl, pyridine, CH_2Cl_2; xv) $BF_3{\cdot}OEt_2$, benzene, then NaOMe, MeOH; xvi) TPAP (cat.), NMO, 4Å MS, CH_2Cl_2, **280** (84% from **279**).

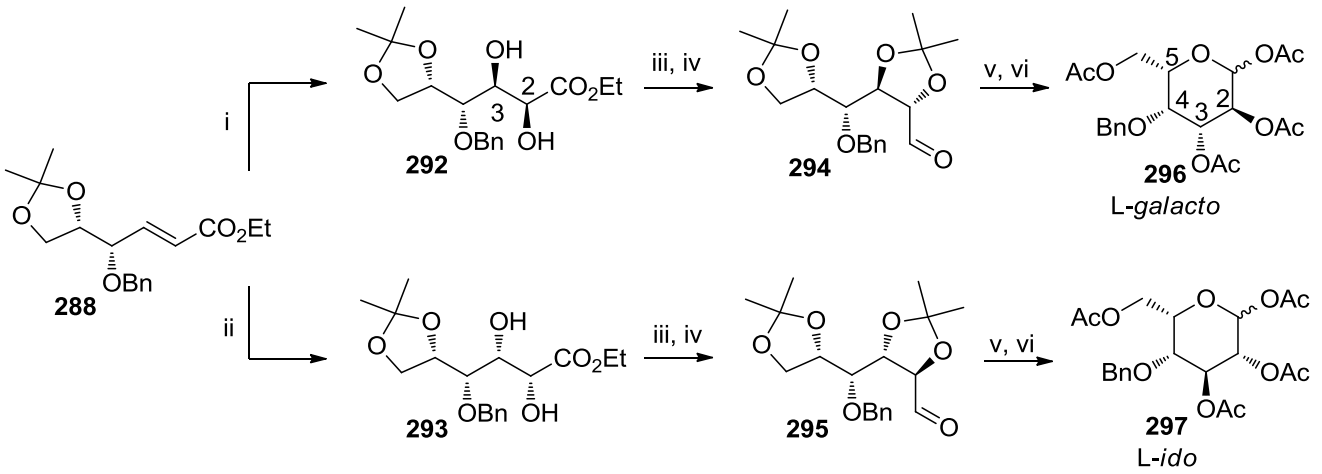
In 2006, Sasaki and coworkers presented a versatile stereoselective *de novo* synthesis methodology to afford all eight L-hexoses. (130) They employed the Sharpless AD as a key step and used L-ascorbic acid **281** as a single starting material, as this compound already incorporated the C_5 stereochemistry required for the final products (Schemes 37, 38 and 39). The key intermediate, ethyl trihydroxybutanoate **282**, was prepared from **281** in two steps (Scheme 37). (131) (132) Inversion of the configuration at C_4 in **282** was crucial to afford the precursor for the synthesis of L-series gluco-, altro-, allo- and mannopyranoses. This was accomplished via the Mitsunobu inversion (117) followed by acetate hydrolysis to give trihydroxybutanoate **283** in 65% yield. Next, the free hydroxyl groups of **282** and **283** were protected and ester functionality was reduced with $LiBH_4$ to give the alcohols **284** and **285**, respectively. Subsequent Swern oxidation (133) afforded the aldehydes **286** and **287**, which

were used directly in the subsequent olefination step. Wittig reaction of **286** and **287** with the stabilized phosphonate, triethylphosphonoacetate (134), resulted in the *E*-unsaturated esters **288** and **289** in high selectivity and yield (*E*:*Z* 98:2, 80% and 83%, respectively). For the *Z*-unsaturated esters, the Still modification of the Horner-Wadsworth-Emmons reaction (135) was used to afford nearly exclusive *Z*-unsaturated esters **290** and **291** (*E*:*Z* > 99:1, 85% and 80%, respectively). Thus, the synthesis of enoates **288-291** was conducted in a total of six to seven steps and with 21-23% overall yields from the **281**.



Scheme 37. Synthesis of key intermediates for hexose synthesis by Sasaki. Reagents and conditions: i) AcCl, acetone, rt; ii) H_2O_2, K_2CO_3, H_2O, then EtI, MeCN, reflux, **282** (59%); iii) $ClCH_2COOH$, Ph_3P, DIAD, THF, then Et_3N, EtOH, **283** (65%); iv) BnBr, Ag_2O, CH_2Cl_2, rt; v) BnBr, Ag_2O, CH_3CN, reflux; vi) $LiBH_4$, Et_2O, 0 °C, **284** (81% from **282**), **285** (76% from **283**); vii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C, **286** (95%), **287** (95%); viii) $(C_2H_5O)_2POCH_2CO_2Et$, NaH, benzene, rt, **288** (*E*:*Z* 98:2, 80%), **289** (*E*:*Z* 98:2, 83%); ix) $(CF_3CH_2O)_2POCH_2CO_2Me$, 18-crown-6, $KN(TMS)_2$, THF, -78 °C, **290** (*E*:*Z* 1:99, 85%), **291** (*E*:*Z* 1:99, 80%).

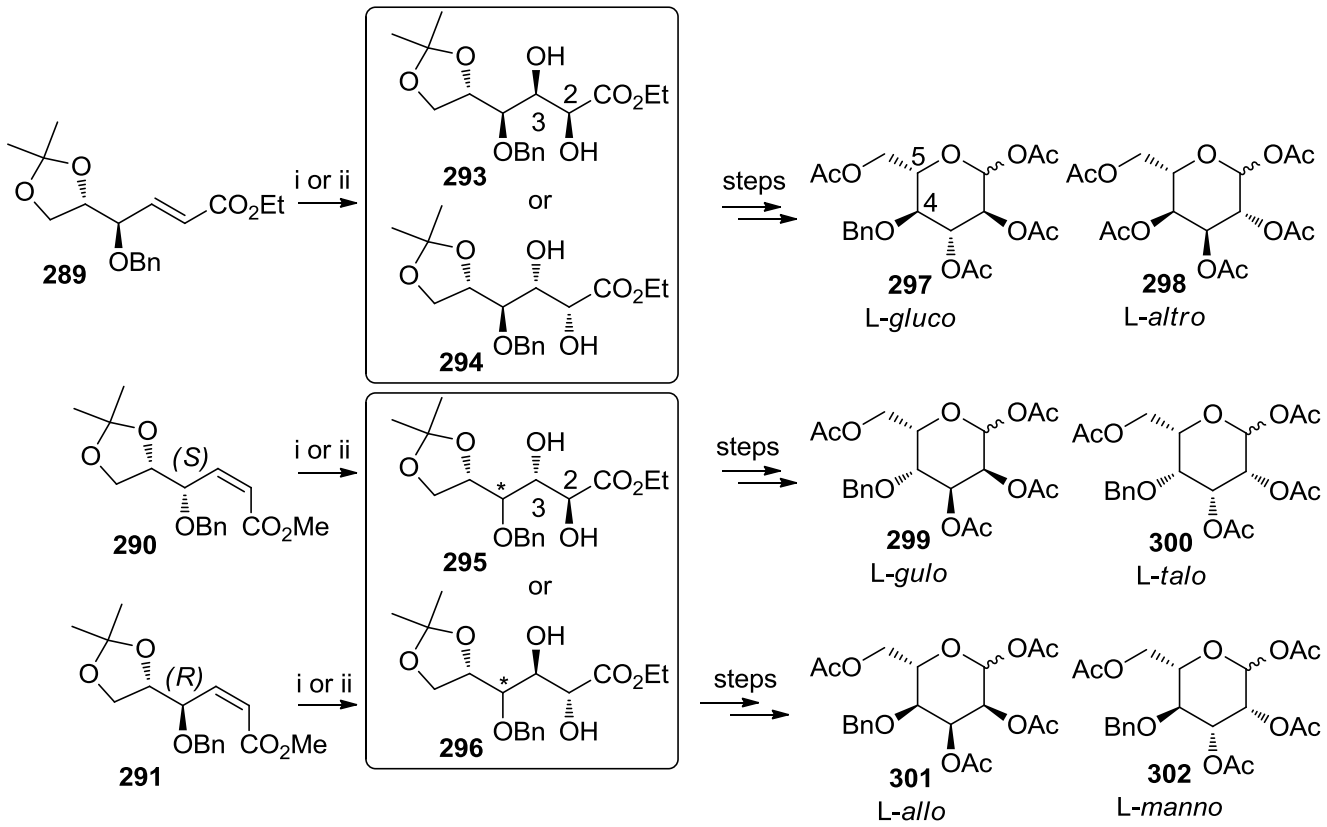
With a carbon framework already assembled (i.e., the enoates **288-291**), the remaining two stereogenic centers were installed by the osmium-catalyzed Sharpless AD. For L-galacto-, L-ido-, L-gluco- and L-altropyranosides, the *syn*-stereochemistry at newly formed OH-2 and OH-3 was needed. Thus, their synthesis was conducted by hydroxylation of *E*-enoates **288** and **289** (Schemes 38 and 39). Dihydroxylation of *E*-enoate **288** in the presence of β- and α-directing ligans gave diols **292** and **293** in high selectivity (dr 99:1 and 98:2, respectively) and high yield (90%) (Scheme 38). After acetonide protection and DIBALH reduction, aldehydes **294** and **295** were obtained in excellent yield (95%). Deprotection of the acetonide and subsequent acetylation afforded protected L-galacto- and L-idopyranosides **296** and **297** as mixtures of α- and β-anomers in five steps and in 49% overall yield from the **288** (10% from the **281**).



Scheme 38. Synthesis of L-galacto- and L-idopyranosides by Sasaki. Reagents and conditions: i) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*BuOH, H_2O, **292** (dr 99:1, 90%); ii) OsO_4, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*BuOH, H_2O, **293** (dr 95:5, 90%); iii) DMP, acetone; iv) DIBALH, toluene, **294** (90% from **292**), **295** (90% from **293**); v) AcOH; vi) Ac_2O, Et_3N, DMAP, CH_2Cl_2, **296** (α:β 22:78, 60% from **294**), **297** (α:β 4:6, 60% from **295**).

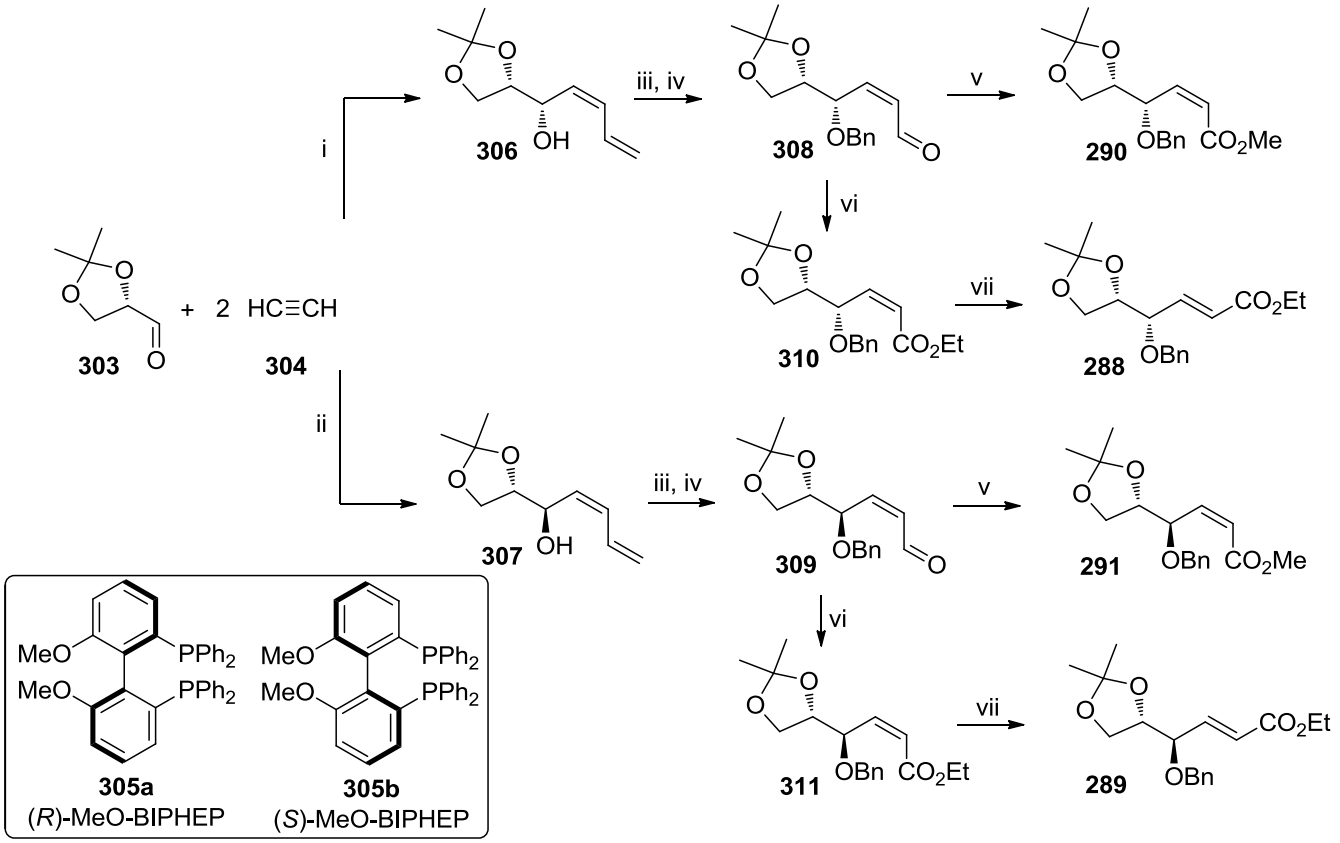
L-gluco- and L-altropyranosides are the epimers of L-galacto- and L-idopyranoses in C_4, respectively. Thus, their synthesis was initiated by dihydroxylation of *E*-enoate **289** to yield diols **293** and **294** in high selectivity (dr 98:2 and 99:1, respectively) (Scheme 39). Further elaboration of the diols in the same manner as described above resulted in the protected L-gluco- and L-altropyranoses **297** and **298** as mixture of α- and β-anomers in 59% and 51% overall yields from **289**, respectively. For the synthesis of L-gulo-, L-talo-, L-allo- and L-mannopyranosides, *trans*-stereochemistry at the newly formed OH-2 and OH-3 was needed. Thus, for their synthesis, the route started from *Z*-enoates **290** and **291**, leading to *trans*-diols **295** and **296** with slightly lower selectivity than that obtained with *E*-enoates. The resulting diols were then carried through the rest of the sequence, resulting in the formation of protected L-gulo-, L-talo-, L-allo- and L-mannopyranosides **299**-**202**.

An interesting point worth noting is that the starting material, L-ascorbic acid **288** (known as vitamin C), is biosynthesized by many organisms from D-glucose. (136) Moreover, the industrial preparation of L-ascorbic acid is initiated from D-glucose. (137)



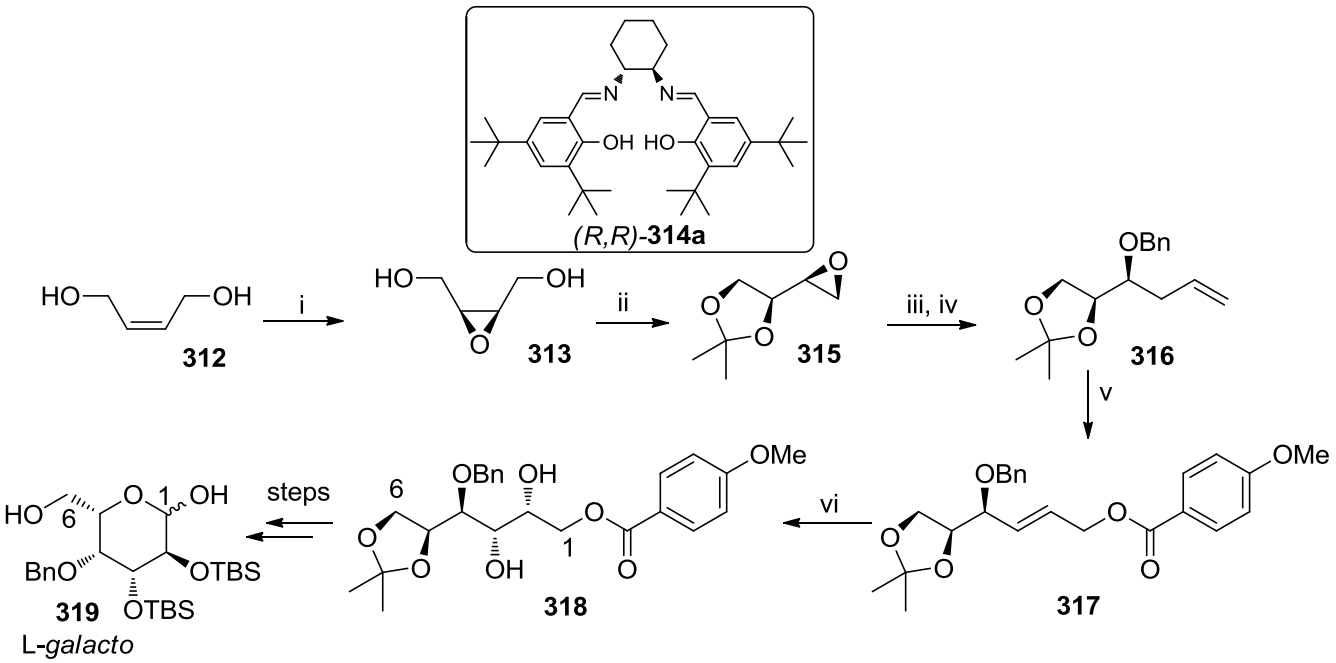
Scheme 39. Synthesis of L-gluco-, L-altro-, L-gulo-, L-talo-, L-allo- and L-mannopyranosides by Sasaki. Reagents and conditions: i) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*BuOH, H_2O, **293** (dr 98:2, 90%), *(S)*-**295** (dr 91:9, 90%), *(R)*-**295** (dr 87:13, 90%); ii) OsO_4, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*BuOH, H_2O, **294** (dr 99:1, 90%), *(S)*-**296** (dr 84:16, 90%), *(R)*-**296** (dr 84:6, 90%).

Later, in 2008, Krische and coworkers presented the synthesis of saccharide precursors **288–291** by a catalytic enantioselective hydrogenative C-C coupling of acetylene as a key step. (138) The synthesis was commenced with hydrogenative coupling of acetylene **304** to L-glyceraldehyde **303** (Scheme 40). To induce enantioselectivity, a chiral rhodium catalyst ligated by (*S*)-MeO-BIPHEP **305b** was used, and these conditions afforded the diene **306** in high selectivity and good yield (dr > 20:1, 78 %, respectively). When the enantiomeric rhodium (*R*)-MeO-BIPHEP **305a** complex was used, an inversion of diastereofacial selectivity was observed. Thus, the adduct **307** was obtained, but the selectivity was unfortunately lower (dr 7:1). Protection of the allylic alcohol and regioselective oxidative cleavage of the terminal double bond of **306** and **307** gave aldehydes **308** and **309** in good overall yields (76% and 71%, respectively). Then, the aldehydes **308** and **309** were oxidized into their corresponding methyl- and ethylesters by treatment with manganese dioxide and sodium cyanide in methanol or ethanol to give the *Z*-unsaturated esters **290** or **310** and **291** or **311**, respectively. The stereochemistry of the *Z*-olefin moieties of **290** and **291** was retained by means of the cyanide anion acting as a nucleophilic catalyst. The corresponding ethyl *E*-unsaturated esters **288** and **289** were obtained by exposing the *Z*-unsaturated ethyl esters **310** and **311** to trimethylphosphine. Thus, the synthesis route of Krische to the unsaturated esters **288-291** was shorter (four to five steps) and the overall yields were higher (43-55%from **303**) than those obtained using the methodology of Sasaki and coworkers presented above. (130)



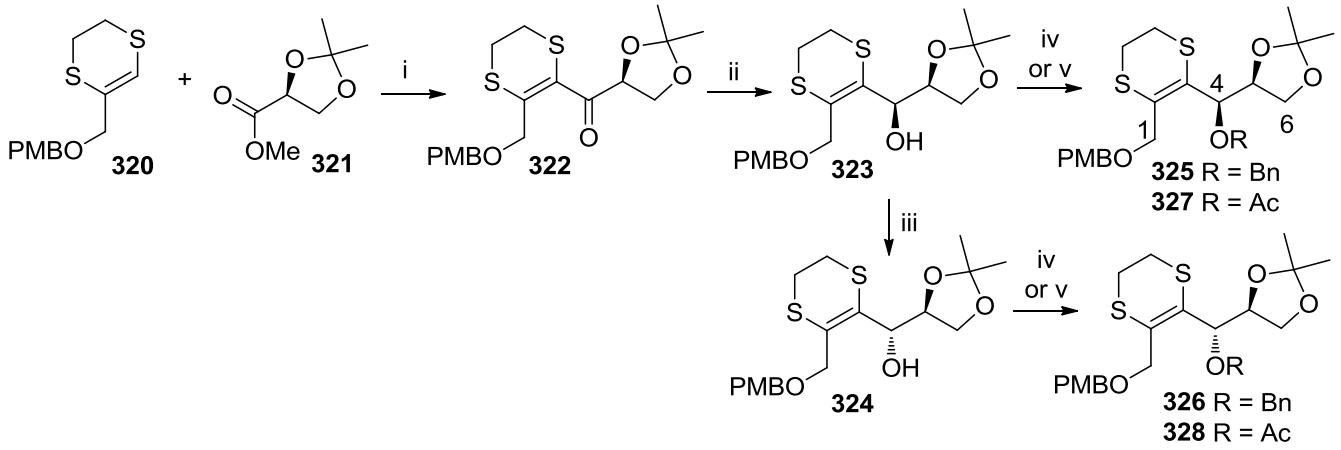
Scheme 40. Synthesis of unsaturated esters for hexose precursors by Krische. Reagents and conditions: i) $[Rh(cod)_2]BARF$, (*S*)-MeO-BIPHEP **255b**, pentafluorobenzoic acid, Na_2SO_4, toluene, 25 °C, H_2, **306** (dr > 20:1, 78%); ii) (*R*)-MeO-BIPHEP **255a**, **307** (dr > 7:1, 83%); iii) NaH, BnBr, DMF, 0°C; iv) OsO_4, $NaIO_4$, THF, H_2O, 25 °C, **308** (76% from **306**), **309** (71% from **307**); v) MnO_2, NaCN, AcOH, MeOH, 25 °C, **290** (93%), **291** (87%); vi) MnO_2, NaCN, AcOH, EtOH, 25°C, **310** (86%), **311** (79%); vii) PMe_3, *t*BuOH, 35 °C, **288** (92%), **289** (92%).

White and coworkers presented the synthesis of L-saccharide based on an enantioselective Payne rearrangement (105) and asymmetric dihydroxylation in 2006. (139) The synthesis started with the epoxidation of butene-1,4-diol **312** with *m*-chloroperbenzoic acid to give the *meso*-epoxide **313** in 74% yield (Scheme 41). Then, the epoxide **313** was desymmetrized by Payne rearrangement in the presence of oligomeric salen–chromium complex (*R,R*)-**314a** using the method developed by Jacobsen (140). The intermediate diol (not shown) was protected as an acetonide, giving the chiral epoxyketal **315**. Regioselective opening of **315** at the terminal position with vinylcuprate and subsequent protection of the intermediate alcohol gave the benzyl-protected allylic alcohol **316** with high enantiomeric purity and in 54% overall yield over three steps. The allylic oxidation of **316** with *p*-anisic acid using a palladium catalyst under the optimized reaction conditions (by using DIPEA as a non-coordinating base additive and phenyl-*p*-benzoquinone as an oxidant) (141) gave the **317** in 71% yield as essentially one isomer. Asymmetric dihydroxylation of **317** furnished polyoxygenated **318** with a diastereomeric ratio of over 20:1 and in 96% yield. Protection of **318** as the silyl ether, followed by removal of the *p*-methoxybenzoate ester, Swern oxidation (133), and removal of the isopropylidene ketal group, gave the protected L-galactopyranose **319** in 74% yield over four steps. Thus the enantioselective synthesis of **319** was conducted in a total of ten steps and with 20% overall yield from the **312**.



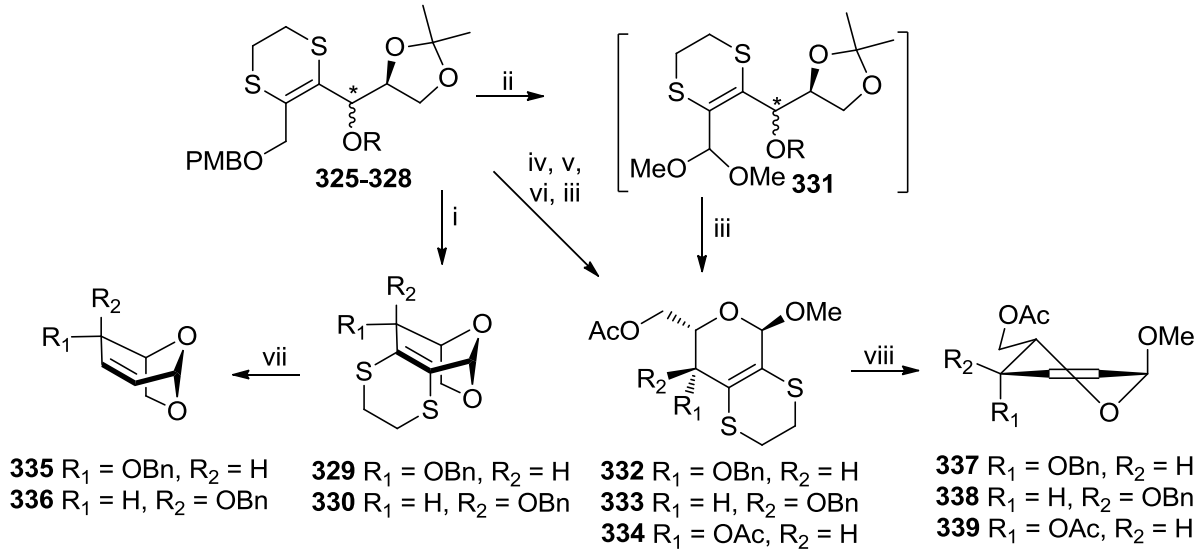
Scheme 41. Synthesis of protected L-galactopyrase by White. Reagents and conditions: i) *m*CPBA, CH_2Cl_2, 0 °C → rt, **313** (74%); ii) oligomeric (*R,R*)-(salen)-**314a**-Co(III)OTf, CH_3CN, then 2-methoxypropene, *p*TsOH·H_2O, 0 °C; iii) CuBr, CH_2=CHMgBr, THF, -40 °C; iv) NaH, TBAI, DMF, 0 °C, then BnBr, 0 °C → rt, **316** (99% ee, 54% from **315**); v) *p*-anisic acid, $[Pd(CH_3CN)_4](BF_4)_2$, PhBQ, DIPEA, MS, DMSO, CH_2Cl_2, 41 °C, **317** (linear/branched > 300:1, *E*/*Z* = 36:1, 71%); vi) AD-mix-β, $MeSO_2NH_2$, *t*BuOH, H_2O, 0 °C, **318** (dr > 20:1, 96%); four steps **319** (74%).

Guaragna and coworkers described in 2010 a versatile route to afford all eight L-hexoses. (142) (143) (144) The methodology consisted of three major steps: construction of the carbon framework by a coupling reaction, cyclization of the framework by an acid catalyzed domino reaction and suitable double-bond functionalization by stereoselective dihydroxylation or epoxidation reactions. The key intermediates were prepared starting from heterocyclic **320**, which was prepared from methyl pyruvate (145). Coupling of **320** with the L-glycerate **321** gave ketone **322** in 96% yield (Scheme 42). Then, **322** was stereoselectively reduced from the less hindered face using $NaBH_4$ to give the *syn*-alcohol **323** in 98% yield. To synthesize the full series of aldohexoses, *anti*-alcohol **324** (with a reverse stereochemistry at C_4) was needed. Attempts to reduce ketone **322** with a reverse stereoselectivity were unsuccessful, but a Mitsunobu inversion (117) gave a better result. Thus, *syn*-**323** was treated with PPh_3, DIAD and *p*-nitrobenzoic acid. Subsequent alkaline hydrolysis of the resulting benzoate gave *anti*-**324** in a 75% overall yield. Protection of the secondary hydroxyl with a benzyl or acetyl group afforded **325** and **326** (R = Bn) or **327** and **328** (R = Ac), respectively, in high yields.



Scheme 42. Synthesis of saccharide precursors by Guaragna. Reagents and conditions: i) BuLi, THF, -78 °C, **322** (96%); ii) $NaBH_4$, MeOH, -60 °C, **323** (dr > 99:1%, 98%); iii) PPh_3, DIAD, *p*NO_2BzOH, THF, 0 °C, then Et_3N, MeOH, **324** (75% from **32**); iv) BnBr, NaH, DMF, rt, **325** (98%), **326** (95%); v) Ac_2O, pyridine, rt, **327** (95%), **328** (97%).

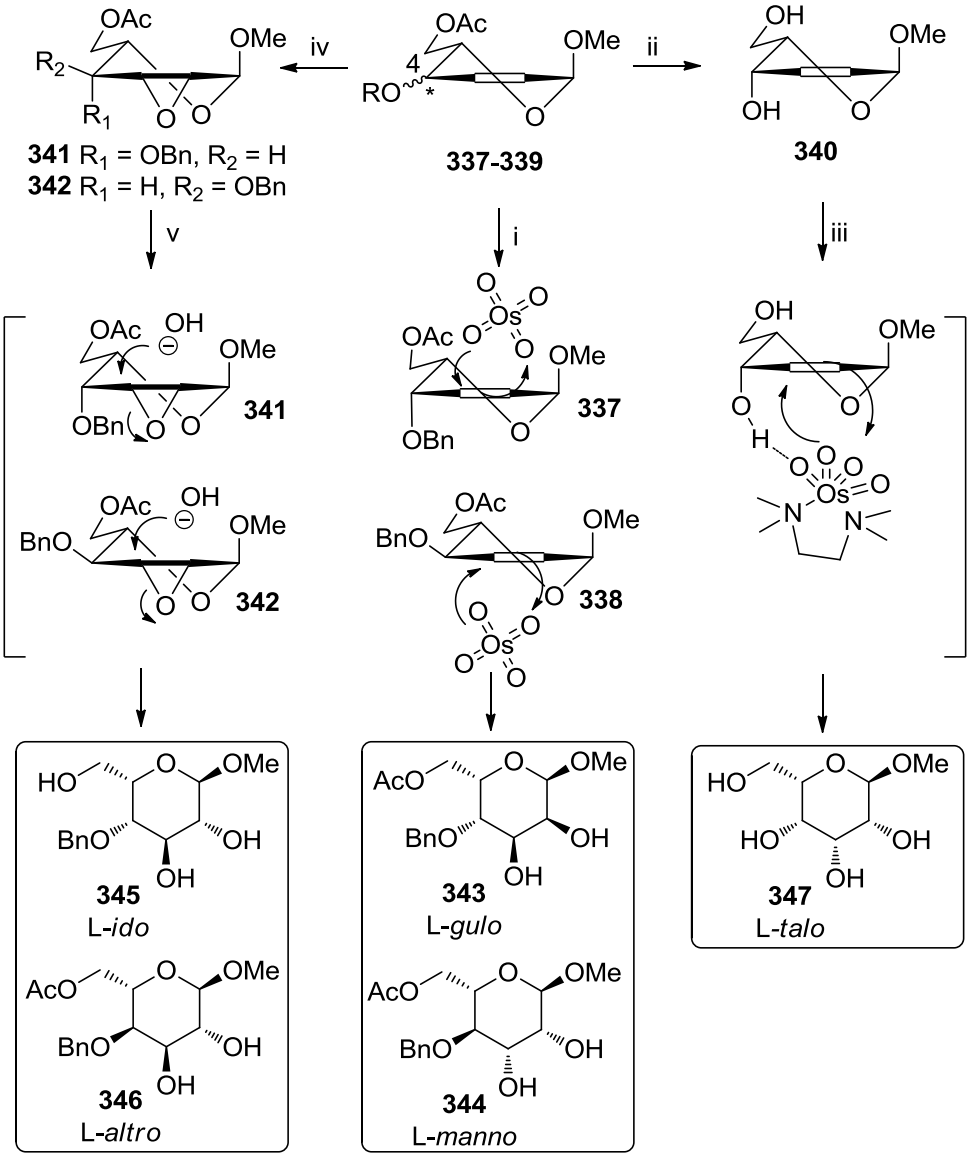
Next, with the carbon framework assembled, the key intermediates (1,6-anhydro compound **335** and **336** and 2,3-dideoxy compound **337-339**) were prepared by cyclization of the carbon framework with an acid catalyzed multistep domino reaction (Scheme 43). In this step, the oxidant, DDQ, served several purposes. Initially, DDQ removed the PMB protection of **325-328**. When an excess of DDQ was used, the resulting alcohol was oxidized to an aldehyde. Then, isopropylidene group removal and a subsequent two-step ring closure produced 1,6-anhydro olefins **329** and **330** in 88% and 94% overall yields, respectively. Alternatively, inclusion of methanol in the DDQ oxidation and subsequent acetylation of the intermediate gave the methyl glycosides **332** and **334** in 86-89% overall yield. Previously, **333** had been prepared by a stepwise route, where the overall yield was lower (67%) and the route was also more laborious. Thus, the use of the domino reaction sequence saved –three to four steps and increased the efficiency of the entire route in comparison with the stepwise route. To remove the dithioethylene bridge, the olefins **329** and **330** and **332-334** were desulfurized with Raney-Ni in acetone or in THF to afford the unsaturated pyranoses **335** and **336** or **337–339**, respectively, in good yields (75-82%).



Scheme 43. Synthesis of saccharide precursors by Guaragna. Reagents and conditions: i) DDQ, CH_2Cl_2:H_2O 18:1, reflux, **329** (88% from **325**), **330** (94% from **326**); ii) DDQ, CH_2Cl_2:MeOH 3:1, rt; iii) Ac_2O, pyridine, rt, **332** (86% from **325**), **333** (67% from **326**), **334** (89% from **327**); iv) DDQ, CH_2Cl_2:H_2O 18:1, rt; v) PCC, pyridine, celite, rt; vi) Amberlyst 15 ion-exchange resin, MeOH, rt; vii) Raney-Ni, acetone, 0 °C → rt, **335** and **336** (75-78%); viii) Raney-Ni, THF, 0 °C, **337**– **339** (75-82%).

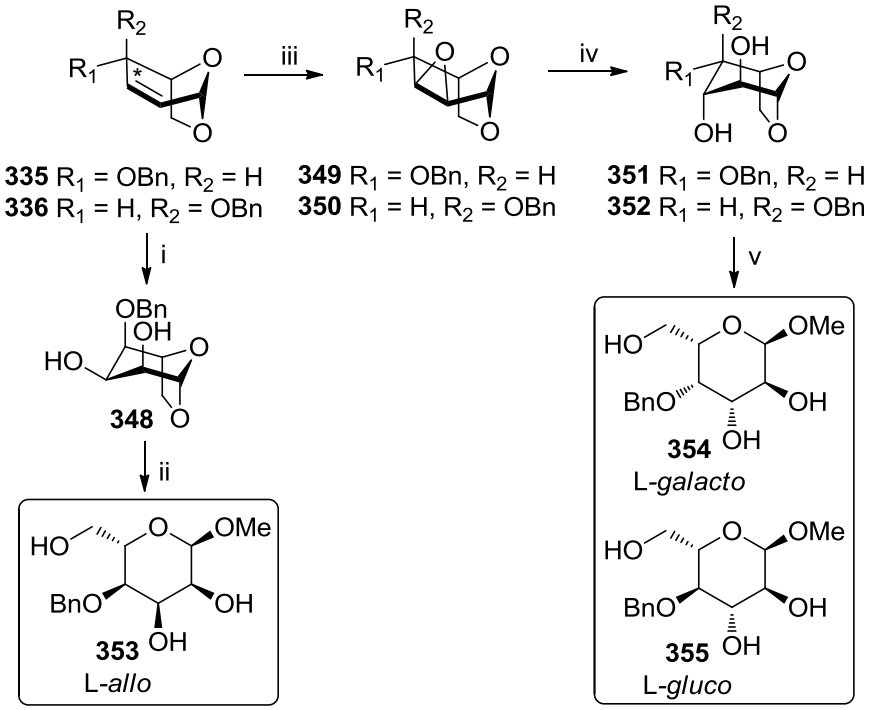
Subsequent *syn*-dihydroxylation of olefins **337** and **338** was readily achieved with catalytic OsO_4 in the presence of NMO (Scheme 44). The reaction proceeded *anti* to the neighboring benzyloxy group (at C_4), yielding partially protected L-gulopyranoside **343** (48% overall from **320**) and L-mannopyranoside **344** (51% overall from **320**), respectively. Alternatively, the selectivity of the dihydroxylation could be reversed by means of the hydrogen bond formation. Thus, olefin **339** was deacetylated, and treatment of the resulting diol **340** with OsO_4 in the presence of TMEDA yielded methyl-L-talopyranoside **347** (38% overall from **320**).

Finally, *anti*-diols derived from the olefin could be obtained via epoxidation. Thus, treatment of olefins **337** and **338** with *in situ*-generated dioxirane (TFDO) led to the epoxides **341** and **342** with good yield (79-80%) and diastereoselectivity (dr 9:1). Ring opening under alkaline conditions (refluxing 1 N KOH) afforded partially protected L-idopyranoside **345** (40% overall yield from **320**) and partially protected L-altropyranoside **346** (43% overall yield from **320**), respectively.



Scheme 44. Synthesis of L-ido-, L-altro-, L-gulo-, L-manno- and L-talopyranosides by by Guaragna. Reagents and conditions: i) OsO_4, NMO, *t*BuOH, acetone, H_2O, rt, **343** (84% from **337**), **344** (82% from **338**); ii) NaOMe, MeOH, rt, **340** (98% from **339**); iii) OsO_4, TMEDA, CH_2Cl_2, -78 °C, **347** (80%); iv) O_3, trifluoroacetone, Na_2EDTA (aq), $NaHCO_3$, MeCN, 0 °C, **341** (dr 9:1, 79% from **337**), **342** (92% from **338**); v) KOH (1N), reflux, **345** (99% from **341**), **346** (90% from **342**).

For the preparation of the remaining epimers of aldohexoses, the 1,6-anhydro derivatives **335** and **336** fulfilled the stereochemical requirements. Stereoselective *syn*-dihydroxylation on the less hindered face of the olefin **335** with OsO_4 in pyridine gave **348** with complete selectivity and in 91% yield (Scheme 45). Treatment of **348** with a catalytic amount of TMSOTf in MeOH allowed smooth acetal cleavage to give the partially protected L-allopyranoside **353** (52% overall yield from **320**). Again, the *anti*-diols were obtained via double bond epoxidation. Treatment of olefins **335** and **336** with *in situ* -generated dioxirane (TFDO) led to the epoxides **349** and **350** with good yields (85-92%) Subsequent epoxide ring opening by KOH solution yielded the dihydroxylated products **351** and **352**. Cleavage of the internal acetal was achieved with catalytic TMSOTf in MeOH and led to the partially protected L-galactopyranoside **354**(48% overall yield from **320**) and L-glucopyranoside **355** (59% overall yield from **320**), respectively.



Scheme 45. Synthesis of L-allo-, L-galacto- and L-glucopyranosides by by Guaragna. Reagents and conditions: i) OsO_4, pyridine, rt, **337** (91% from **335**); ii) TMSOTf, MeOH, 50 °C, **353** (92%); iii) O_3, trifluoroacetone, Na_2EDTA (aq), $NaHCO_3$, MeCN, 0 °C, **349** (85%), **350** (92%); iv) KOH (1N), reflux; v) TMSOTf, MeOH, 50 °C, **354** (90% from **349**), **355** (93% from **350**).

3.3 Summary

The *de novo* synthesis of carbohydrates offers many advantages. It often enables the synthesis of either enantiomer of the target saccharide when the starting materials are carefully selected. Accordingly, a variety of saccharide structures can be accessed. Moreover, a well designed *de novo* synthesis requires only a few synthetic steps because laborious protection and activation procedures are not needed. Finally, this strategy enables access to ^{13}C-labeled oligosaccharides. As a result, a wide variety of asymmetric approaches to synthetic saccharides have been developed. (6) (7) (8) (9) (10)

Methodologies used in *de novo* synthesis can be categorized according to the type of substrate utilized, into syntheses relying on 1) stereoselective modification of cyclic frameworks, or 2) assembly of acyclic carbon frameworks. The methodologies based on latter strategy are more abundant and can be further subdivided according to the type of bond formed in the key synthetic step(s). The most important methodologies based on stereoselective carbon-carbon formation rely on aldol and hetero-Diels-Alder reactions. On the other hand, the syntheses based on stereoselective carbon-oxygen formation normally rely on asymmetric epoxidation and dihydroxylation reactions.

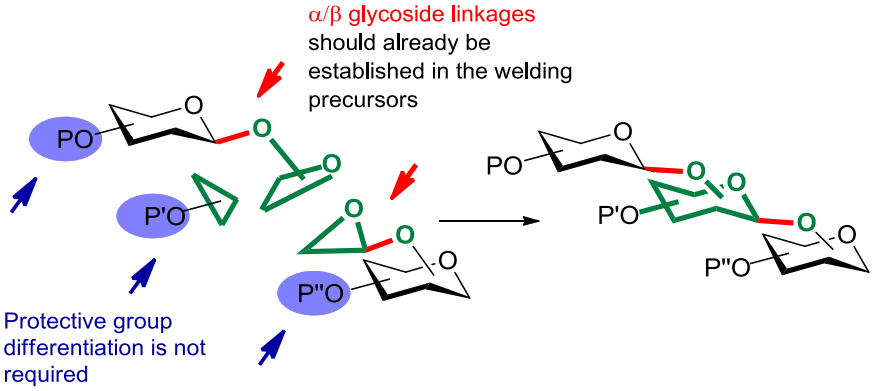
There are few versatile strategies that enable the *de novo* synthesis of the whole series of aldohexoses. In 1983, Sharpless and Masamune reported the first stereoselective synthesis of all eight L-hexoses based on asymmetric epoxidation. (102) (103) More recently, Ogasawara (1999-2000) (125) (126), Sasaki (2006) (130) and Guaragna (2010) (144) introduced the enantioselective synthesis of all eight L-hexoses based on asymmetric dihydroxylation and asymmetric epoxidation reactions. It should also be added that although MacMillan and

Northrup (2004) applied proline and Lewis acid-catalyzed aldol additions to the synthesis of only three protected L-hexoses (71) (72), it has been suggested that carefully selected reaction conditions would enable the completion of the series using this methodology. (59)

In conclusion, the recent *de novo* synthesis of carbohydrates is based on only a few catalytic symmetric transformation types. They have been used nearly exclusively in the synthesis of different *mono*saccharides by using non-saccharide precursors, and few examples of methodologies affording oligosaccharide derivatives are available (82) (88). Thus, there is a demand for new catalytic symmetric transformation types that could be utilized in the *de novo* construction of carbohydrates. Moreover, there is also a need for methodologies that can be utilized in the *de novo* construction of oligosaccharide units by using starting materials that already incorporate glycosylated carbohydrate building blocks.

4 THE SYNTHESIS OF OLIGOSACCHARIDES BY DE NOVO SACCHARIDE WELDING

As stated above, *de novo* construction of saccharides offers many advantages (see pp. 19-20). Although versatile chemical *de novo* methodologies of the whole series of aldohexoses are presented by Sharpless (102) (103), Ogasawara (125) (126), MacMillan (71) (72), Sasaki (130) and Guaragna (144), these have been used without exception for the synthesis of different *mono*saccharides by using non-saccharide precursors. Thus, only a few examples of methodologies affording *oligo*saccharides are available. (82) (88). The aim of this study was to extend the *de novo* methodology to the construction of more complex oligosaccharide units by using starting materials that already incorporate glycosylated carbohydrate building blocks (Scheme 46). In our saccharide welding strategy, the new central monosaccharide unit (green) is constructed by coupling those saccharide building blocks together.

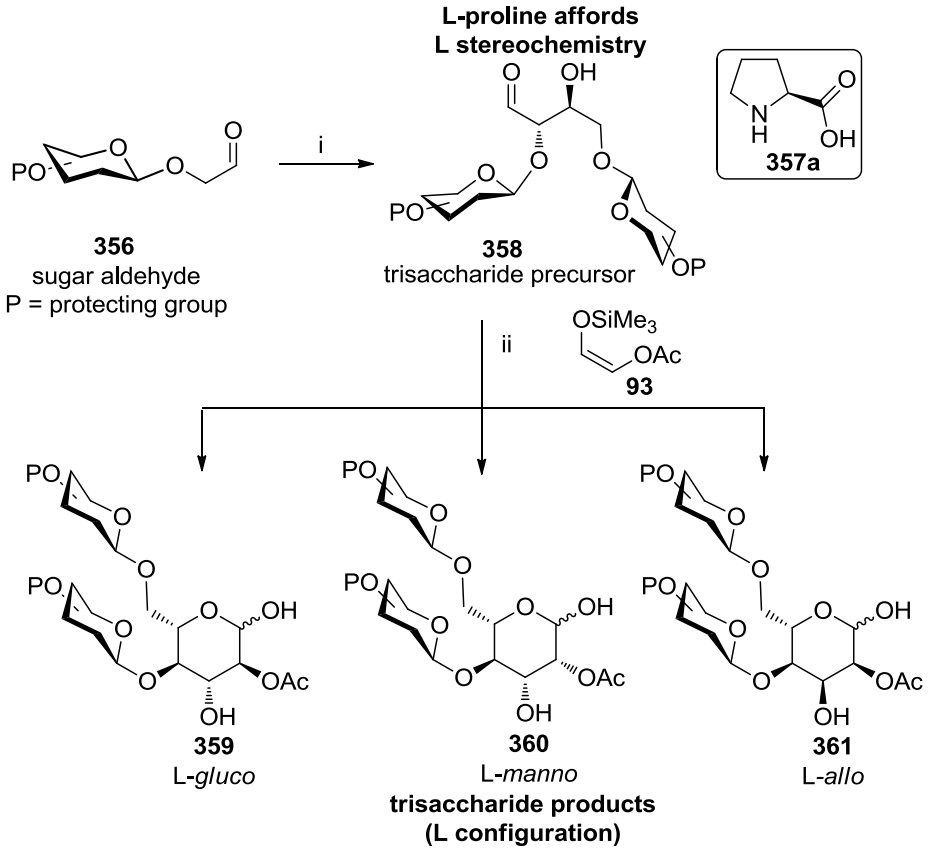


Scheme 46. *De novo* saccharide welding of oligosaccharides.

4.1 Aldol Strategy

Our first strategy for the *de novo* synthesis of oligosaccharides was based on a two-step aldol methodology. Previously, our group has used this methodology in the synthesis of prelactone B. (146) MacMillan and coworkers have also used a similar methodology in the synthesis of different monosaccharides. (71) (72) (See pages 30-36 for a discussion of the precedents used in the synthesis of monosaccharides by using an aldol method, and related references.) In this

study, our aim was to extend this methodology to the construction of oligosaccharide units by using starting aldehydes that already incorporate carbohydrate building blocks. The basic idea behind this method is presented in Scheme 47. In the first step of the synthesis, disaccharide intermediate **358** could be accessed via aldol dimerization of saccharide-derived aldehyde **356** by using a proline catalyst. Enantiomeric catalysts (D- or L-form) should result in the formation of two different diastereomers of the products according to the List-Houk model. (56) This could be used to our advantage, since we could then, in principle, access both D- and L-configured monosaccharide units. The dimeric adduct might be then transformed into different trisaccharides **359**, **360** and **361** via Mukaiyama aldol chemistry. (66) The stereochemistry of the product might be controlled by the selection of the solvent and the Lewis acid. (71) (72)



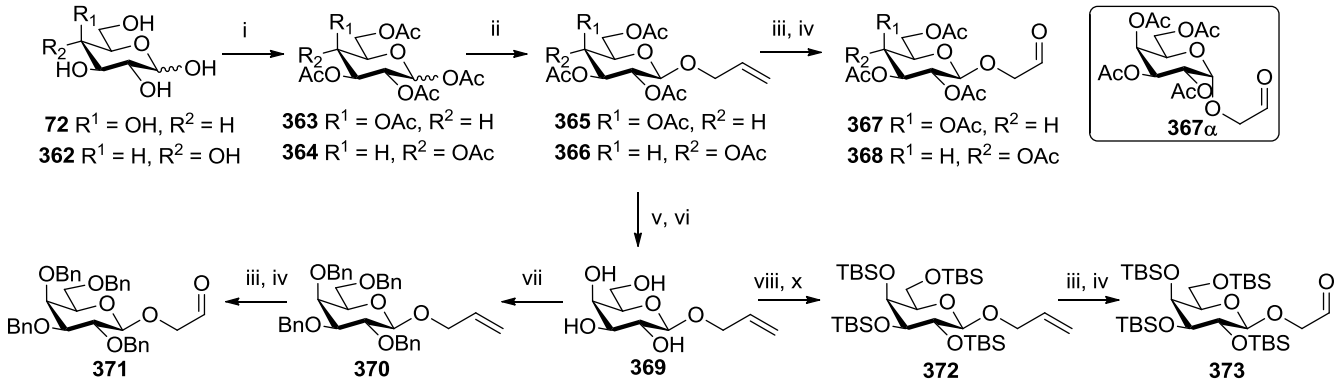
Scheme 47. The synthesis of trisaccharides by two stereoselective aldol additions. Reagents: i) L–proline **357a**; ii) **93**, Lewis acid.

We initiated the work with the construction of the aldehyde building blocks.

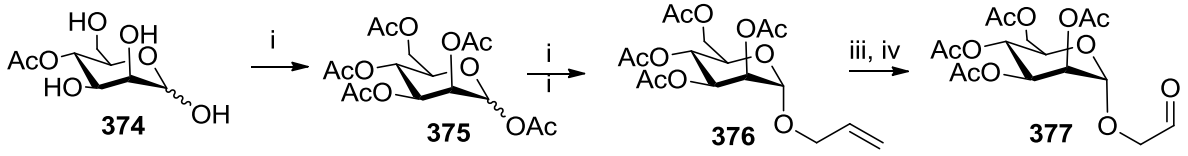
4.1.1 Synthesis of Aldehydes

The synthesis of acetyl-protected D-galactose-, D-glucose- and D-mannose-derived monosaccharide aldehydes **367**, **368** and **377** was carried out according to a method described previously for the synthesis of mannose aldehyde **377**. (147) (148) The synthesis commenced with the preparation of peracetylated galacto-, gluco- and mannopyranosides **363**, **364** and **375** (Schemes 48 and 49). (149) (150) Glycosylation of allyl alcohol promoted by $BF_3 \cdot OEt_2$ led to the pyranosides **365**, **366** and **376** in moderate yields. (151) In this step, the formation of unidentified side products lowered the yields. Moreover, the α-form of peracetylated glucopyranosides **364** turned out to be nonreactive in these reaction conditions. Next, the

alkene functionality was oxidatively cleaved (OsO_4; then $NaIO_4$) to give aldehydes **367**, **368** and **377** in good yields over two steps. (148) (152) (153) Moreover, aldehyde formation by ozonolysis was attempted, but an extremely impure product was obtained under these conditions. Generally, the purity of the allyl pyranoside starting materials **365**, **366** and **367** was important, because delaying the purification at the aldehyde stage led to a dramatic decrease in yields.



Scheme 48. Synthesis of galacto-and glucopyranoside aldehydes. Reagents and conditions: i) NaOAc, acetic anhydride, 100 °C, **363** (α:β > 1:30, 47%), **364** (α:β 1:3, 80%); ii) allyl alcohol, $BF_3 \cdot OEt_2$, molecular sieves (4 Å), CH_2Cl_2, 0 °C to rt, **365** (pure β, 61%), **366** (pure β, 52%); iii) OsO_4, NMO, *t*BuOH, THF, H_2O, rt; iv) $NaIO_4$, (Na_2CO_3), THF, pH 7-buffer, 0 °C, **367** (88%), **368** (92%), **371** (94%), **373** (86%); v) NaOMe/MeOH, rt; vi) DOWEX-50WX8 (H+ form) ion exchange resin, rt, **369** (71%); vii) BnCl, NaH, 115-130°C, **370** (40%); viii),TBSCl, imidazole, I_2, MeCN, DMF; ix) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, **372** (71% from **369**).



Scheme 49. Synthesis of mannopyranoside aldehyde. Reagents and conditions: i) NaOAc, acetic anhydride, 100 °C, **375** (α:β 5:1, quant); ii) allyl alcohol, $BF_3 \cdot OEt_2$, molecular sieves (4 Å), CH_2Cl_2, 0 °C to rt, **376** (pure α, 35%); iii) OsO_4, NMO, *t*BuOH, THF, H_2O, rt; iv) $NaIO_4$, Na_2CO_3, THF, pH 7-buffer, 0 °C, **377** (93%).

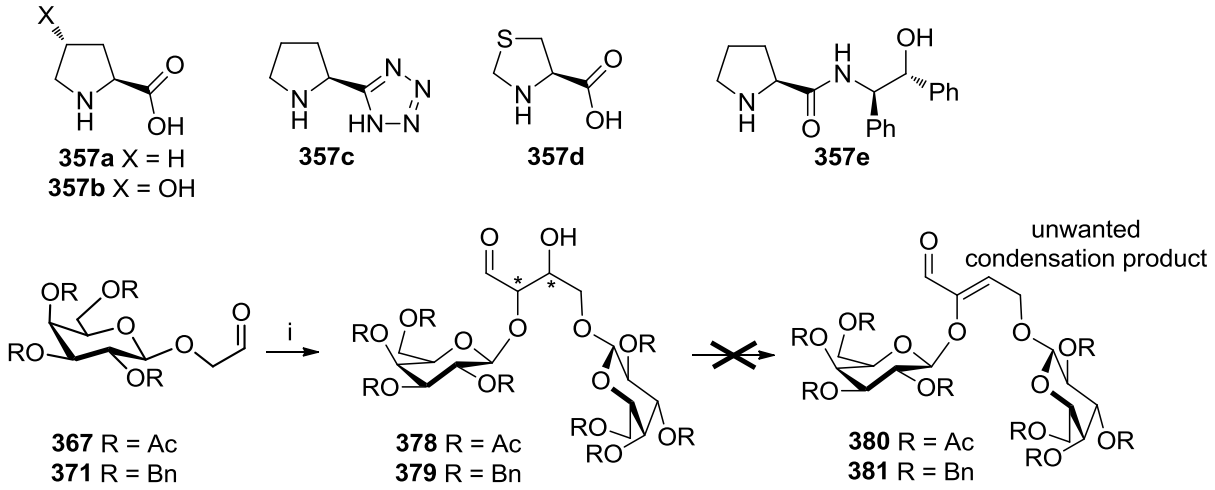
In the case of benzyl- and TBS-protected monosaccharide derivatives, the protective groups were modified after the allylation step (Scheme 48). Deacetylation of allyl galactopyranoside **365** under Zemplén conditions afforded galactopyranoside **369**. (154) (155) (156) Treatment of **369** with BnCl and NaH afforded galactopyranoside **370**. (157) For TBS-protection, a two-stage silylation with TBSCl followed by completion of silylation with TBSOTf afforded the desired tetrasilylated galactopyranoside **372**. (158) (159) (160) TBS-protection was first attempted with TBSCl alone as the silylating agent, but only incomplete silylated products were obtained (the yields of trisilylated and disilylated products were 45% and 42%, respectively, the latter being a mixture of two regioisomers). Complete silylation was achieved by treating the mixture of the incomplete silylated products with TBSOTf and 2,6-lutidine. The alkene functionality of **370** and **372** was cleaved as described above to give aldehydes **371** and **377**, respectively, in good yields over two steps. α-Anomer of acetyl-protected galactose aldehyde **367α** was prepared according to methods described in the literature (Scheme 43). (149) (150) (161)

4.1.2 Aldol Dimerization

We began the aldol dimerization studies by using acetyl- and benzyl-protected galactose aldehydes **367** and **371** and proline catalysts (Scheme 50). Unfortunately, the aldol dimerization easily favored the formation of condensation products **380** and **381** (Scheme 45), but this could be minimized by optimization of the reaction conditions. In the case of acetyl-protected **367**, DMF was the best choice for the solvent. However with benzyl-protected **371**, reaction in CH_2Cl_2 using an H_2O additive (100 mol-%) decreased the formation of **381**. In both cases, formation of the condensation product could not be completely avoided (in all cases conversion to the condensation product remained over 12%). We also tested different proline-derivatives, but these failed to improve the reaction. When *trans*-4-hydroxy-L-proline **357b** and (*S*)-(–)-5-(2-pyrrolidinyl)-1*H*-tetrazole **357c** were used, conversion to the dimer product was lower. With (2S)-N-[(1S,2S)-2-hydroxy-1,2-diphenylethyl]-2-pyrrolidinecarboxamide **357e** the stereoselectivity of the reaction deteriorated, and by using (4*R*)-1,3-thiazolidine-carboxylic acid **357d** no dimer product was formed.

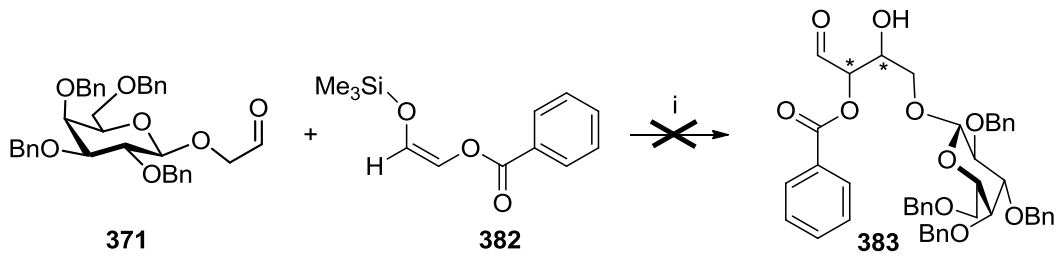
We found that in aldol dimerization, the enantiomeric catalysts (D- or L-proline) indeed led to different diastereomers of the dimer product. With acetyl-protected **367** only one diasteromer of the dimer was produced, but with benzyl-protected **371** a small amount of another diastereomer was present. Although the relative stereochemistry of the product was not determined, we presume the stereochemistry of the products followed the Houk-List stereochemical model. (56) (162)

However, when we tried to isolate the dimer products, we found that 80-90 mol-% of the starting materials **367** and **371** decomposed during the reaction, and less than 20 mol-% reacted via an aldol pathway. The dimer products were also extremely susceptible to decomposition and they could not be isolated in a pure form.



Scheme 50. The aldol dimerization studies of acetyl- and benzyl-protected galactose aldehydes **367** and **371**. For proline, only the L-enantiomer of the catalyst is shown.Reagents and conditions: i) catalyst (20 to 35 mol%); for **367** (R = Ac): solvent DMF; for **371** (R = Bn): solvent CH_2Cl_2, H_2O additive (100 mol-%), rt, 2 days.

Moreover, we attempted to use the Mukaiyma aldol methodology (Scheme 51). Unfortunately, product **383** was not observed under any of the conditions used ($TiCl_4$, $BF_3{\cdot}OEt_2$ and $MgBr_2{\cdot}OEt_2$). Faced with these setbacks, we decided to discontinue the aldol approach and to search for an alternative strategy.

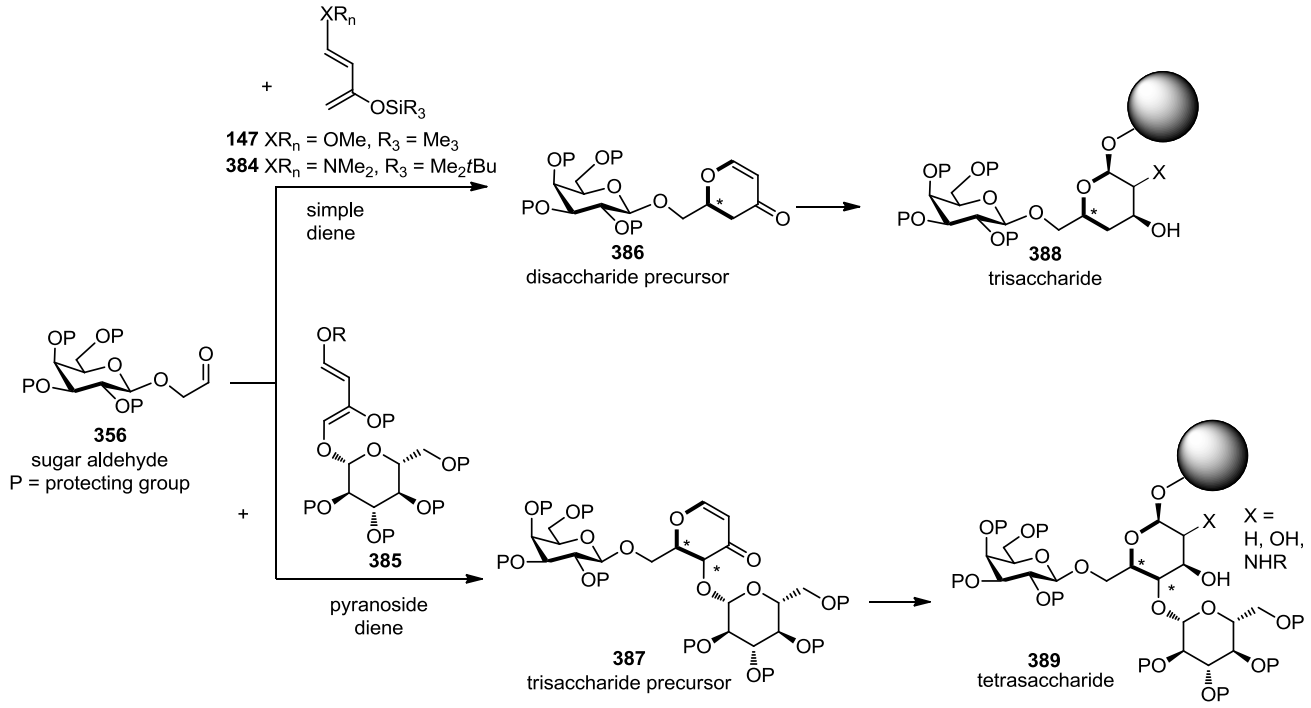


Scheme 51. The Mukaiyama aldol studies of benzyl-protected galactose aldehydes **371**. Reagents and conditios: i) $TiCl_4$, BF_3OEt_2 or $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, -78 °C → -20 °C, 1-2 days.

4.2 Hetero- Diels-Alder– Strategy

An alternative strategy for the generation of the central monosaccharide unit is based on a hetero-Diels-Alder (HDA) welding of functionalized monosaccharide units. (Comprehensive reviews of the HDA method for the synthesis of carbohydrate derivates are available. (10) (64) See pp. 37-42 for a discussion of the precedents used in the synthesis of hexoses by using an HDA method, and related references.) In our study, the aim was to extend the HDA strategy to the construction of oligosaccharide units by using starting materials that already incorporate glycosylated carbohydrate building blocks.

The basic idea behind this study is presented in Scheme 52. Starting from the common glycosylated aldehyde precursor **356**, both di- and trisaccharide products could be accessed via the HDA reaction by using a suitable diene. The disaccharide products could be obtained from Danishefsky's or Rawal's diene **147** or **384** with aldehydes **356**. Furthermore, this method could also be expanded to the synthesis of trisaccharides by using a more functionalized diene **385** that already incorporates a mono- or oligosaccharide. In both cases, the HDA products can easily be transformed into different trisaccharides **388** and tetrasaccharides **389**. (61) (62) Moreover, after reduction of the keto group, the glycals derived from **386** and **387** could be used as glycosyl donors. (163)



Scheme 52. A hetero-Diels-Alder (HDA) strategy to the *de novo* synthesis of oligosaccharides.

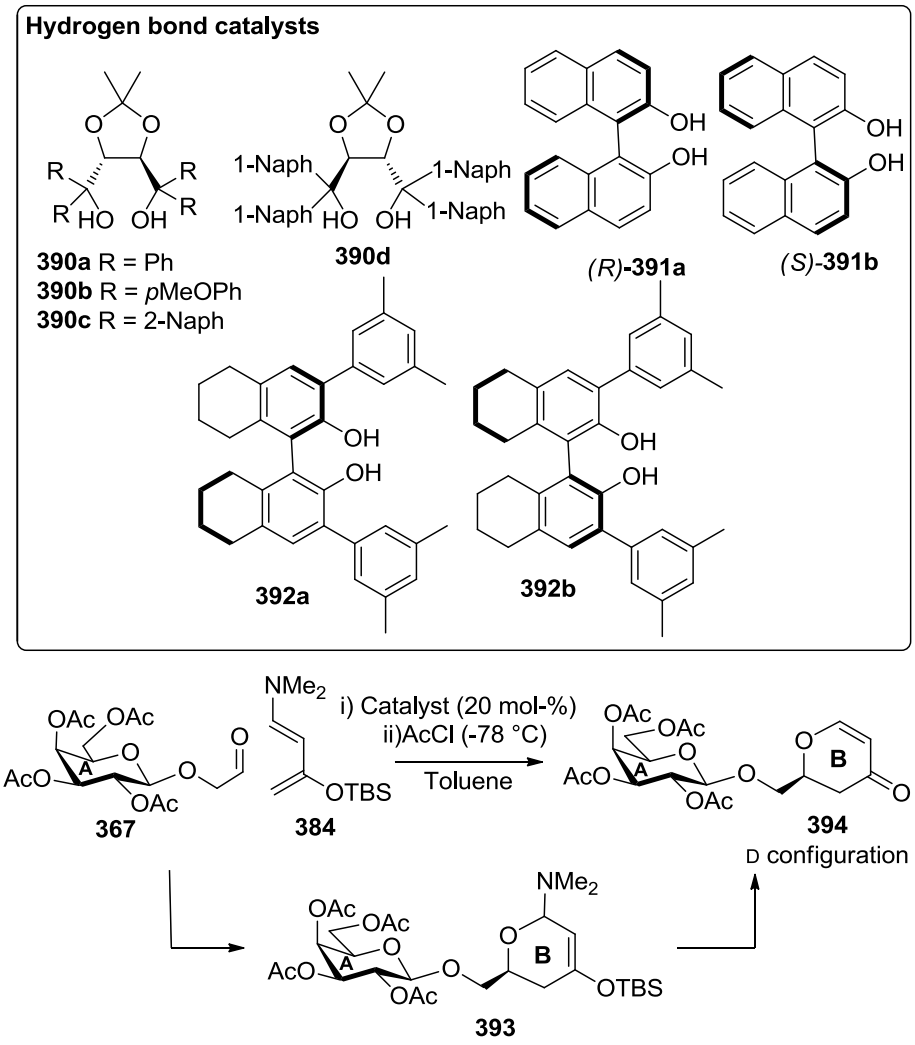
Furthermore, as aldehyde dienophiles, the aldehyde building blocks that were already screened in the aldol methodology could be used.

4.3 Synthesis of Disaccharide Products

In our *de novo* saccharide welding methodology, the stereoselective HDA reaction was the key step to constructing the central monosaccharide unit. We began the HDA reaction studies with the synthesis of disaccharide products. In initial screens, Rawal's diene **384** was employed due to its high reactivity. (164) (165) (166) As such, we anticipated that only very mild activation, such as a hydrogen-bond donor catalyst, would be required for catalysis. Previously, the Rawal group had demonstrated the efficiency of both TADDOL-type (167) (168) and BAMOL-type (169) catalysts in HDA reactions with simple aldehydes and diene **384**.

Table 1 summarizes the results obtained with **384** and galactose-derived aldehyde **367**. In a control reaction without a catalyst, we found that **367** did not exhibit any stereochemical bias and as such a chiral catalyst was needed (entry 1). This could be used to our advantage, however, since we could then, in principle, access both D- and L-configured monosaccharide units. Although moderate selectivities were obtained with TADDOL catalysts **390a -390c** when the reaction was carried out at -20 °C, the yields of the product were only moderate. Other catalysts gave lower selectivities. The low yields were mainly due to the pyranone formation step since the intermediate **393** was obtained with good NMR conversion (> 70%). Increasing the amount of AcCl, or the use of alternative conditions (TFA, chloroacetic acid) also failed. Another reason for the low yield was the partial decomposition of diene **384**. Even though a higher yield was obtained with an excess of aldehyde **367** (entry 7), this was not an economical option because of the more laborious synthesis of **367**. As such this approach was abandoned.

Table 1. HDA reaction of acetyl protected galactose aldehyde **367** with Rawal's diene **384**.



Entry	Catalyst	T (°C)	t (h)	Yield[a] (%)	dr (D:L)[b]
1	-	-20	120	Trace	50:50
2	**390a**	-78	72	Trace	n. d.
3	**390a**	-40	20	10	63:37
4	**390a**	-20[c]	23	51	80:20
5	**390b**	-20[c]	16	29	71:29
6	**390c**	-20[c]	16	35	80:20
7	**390d**	-20[c]	18	68[d]	58:42
8	**391a**[e]	-20[c]	25	15	67:33
9	**391b**[e]	-20[c]	25	60	63:37
10	**392a**	-20[c]	20	trace	64:36
11	**392b**	-20[c]	20	trace	45:55

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy after purification. The absolute stereochemistry of the B ring was assigned by analogy with the literature precedents. (170) (171) (172) (173) (174) In cases where a non-optimal catalyst combination is described, the dr of the product was not determined accurately and therefore is not reported (n. d.). [c] Reaction started at -78 °C and allowed to warm to -20 °C during the reported reaction time. [d] Aldehyde **367** used 200 mol-%. [e] Catalyst loading 40%.

The next diene in our tests was the less reactive Danishefsky's diene **147**. (175) The asymmetric catalytic HDA reaction of **147** with a variety of aromatic and aliphatic aldehydes has been used to give corresponding dihydriopyranones. Comprehensive reviews of HDA reactions using Danishefsky's diene have been published. (176) (177) For example, chiral bisoxazoline(BOX)-copper(II) (178), BINOL-titanium (IV) (170) and tetradentate salen Schiff base chromium(III) complexes (172) have been employed for asymmetric HDA reactions in good to excellent enantioselectivity. Additionally, other metal and chiral ligand combinations have been used successfully in this HDA reaction. (179) (180) With less nucleophilic dienes, the chiral indanol-based Schiff base chromium(III) complexes, pioneered by Jacobsen, have been very popular. (181) (182) (183) In general, **147** and related dienes typically require Lewis acid activation for the heterodienophile. Preliminary screens with aldehyde **367**, diene **147**, and Lewis acids (such as $ZnCl_2$, $MgBr_2$, $La(OTf)_3$, $Yb(OTf)_3$ or $Sc(OTf)_3$) resulted in product formation but without selectivity, pointing to the need for a chiral catalyst. However, the Lewis acids could theoretically bind to the multifunctionalized aldehydes in several sites, and as such we decided to study the feasibility of different chiral catalysts by using an achiral model dienophile **395** containing an acetal unit. (Figure 1).

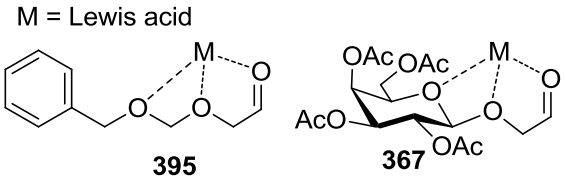
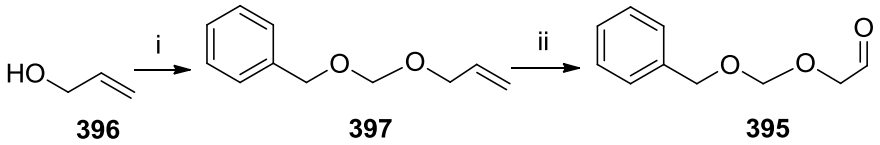


Figure 1. Possible binding mode of an oxophilic metal catalyst to the aldehydes **395** and **367**.

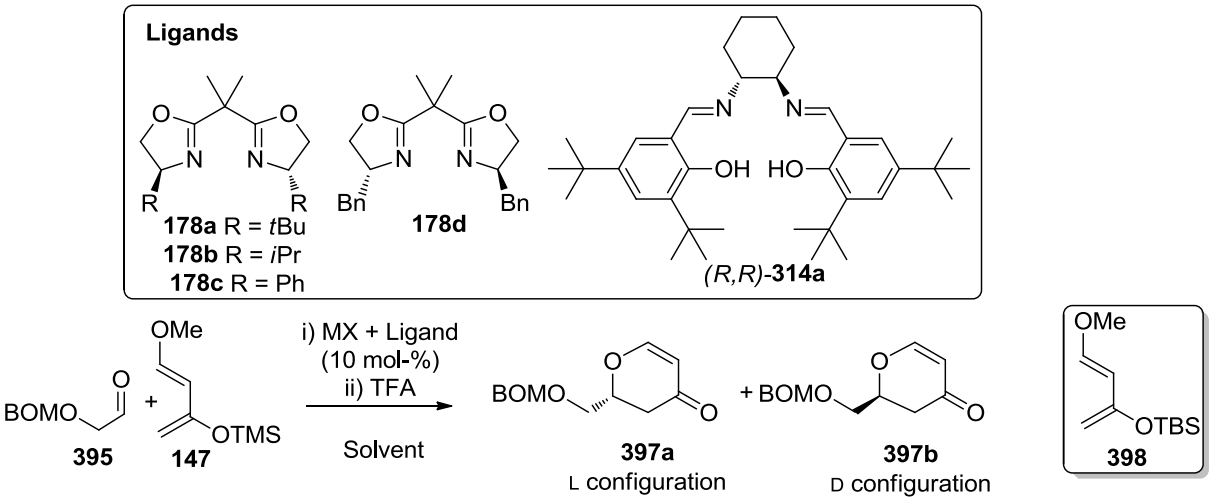
The model dienophile **395** was prepared according to methods described in the literature (Scheme 53). (184) (185)



Scheme 53. Synthesis of the model dienophile. Reagents and conditions: i) *i*Pr_2NEt, Bu_4NI, BOMCl, THF, 0 °C to rt, **397** (78%); ii) O_3, CH_2Cl_2, MeOH, then Me_2S, -78 °C, **395** (83%).

Table 2 summarizes the results obtained with **147** and model dienophile **395**. Different BOX-copper(II) complexes gave only low selectivities (ligands **178a - 178d**, OTf^- counter anion). The stereoselectivities at rt and at 0 °C were unsatisfying, whereas at a lower reaction temperature (-20 °C) the reactivity of the starting materials was too low. Attempts at improving the selectivity and reactivity by changing the counterion (OTf^- → SbF_6^-) were unsuccessful, as no formation of the desired product **397a,b** was observed. However, high selectivities were obtained with BINOL-titanium complexes (ligands **396a** and **396b** in reaction conditions) (entries 7 and 8). Replacing the diene **147** with the more stable diene **398** failed to bring any improvement, as both the stereoselectivity and the yield of the reaction were low (45:55 and 32%, respectively). In addition, neither slow addition nor greater excess (120% → 160%) of the diene **147** were successful. Different BINOL-zinc and BINOL- magnesium complexes gave lower selectivities (entries 9 and 10). However, the use of salen-chromium complex (ligand **314a**) turned out to be promising considering both stereoselectivity and yield of the reaction (entries 11 and 12).

Table 2. HDA reaction of model aldehyde **395** with Danishefsky's diene **147**.



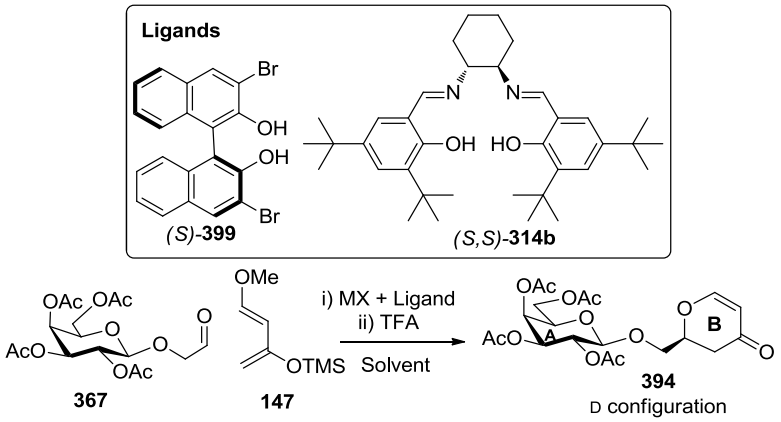
Entry	Metal	Anion	Ligand	Solvent	T (°C)	Time (h)	Yield[a] (%)	er (D:L)[b]
1	Zn^{2+}[c]	Cl^-	-	CH_2Cl_2	rt	1	69	50:50
2	Cu^{2+}	OTf^-	**178b**	CH_2Cl_2	-20→0[d]	138	32	38:62
3	Cu^{2+}	OTf^-	**178a**	CH_2Cl_2	-20→0[d]	138	40	54:46
4	Cu^{2+}	OTf^-	**178c**	CH_2Cl_2	-20→0[d]	138	n. d.	42:58
5	Cu^{2+}	OTf^-	**178d**	CH_2Cl_2	0	41	42	62:38
6	Cu^{2+}	OTf^-	**178d**	CH_2Cl_2	rt	4	37	51:49
7	Ti^{4+}[e]	O*i*Pr$^-$	**391a**	toluene	0	1	23	5:95
8	Ti^{4+}[e]	O*i*Pr$^-$	**391b**	toluene	0	1	19	95: 5
9	$ZnEt_2$	-	**391a**	toluene	rt[f]	43	70	65:35
10	$MgBu_2$	-	**391a**	toluene	rt[f]	47	41	68:32
11	Cr^{3+} [g]	BF_4^-	**314a**	Et_2O	-20[h]	17	70	14:86
12	Cr^{3+} [g]	SbF_6^-	**314a**	Et_2O	-20	22	31	39:61

[a] Yield of isolated product. In cases where a non-optimal catalyst combination is described, the yield of the product was not determined accurately and therefore is not reported (n.d.). [b] Determined by hplc after purification (IPA:hex 10%, 0.7 ml/min, λ = 254 nm, t_R (D-isomer) = 38 min ja t_R (L-isomer) = 45 min). The absolute stereochemistry of the newly formed ring was assigned by analogy with the literature precedents. (170) (171) (172) (173) (174) [c] Catalyst loading 20%. [d] Reaction stirred for 96 h at -20 °C and 42 h at 0 °C. [e] Catalyst loading 20%. [f] Reaction was stirred at 0 °C for 20 h, after which it was transferred to rt. [g] Catalyst loading 5%. [h] Reaction started at – 40 °C and allowed to warm to -20 °C overnight.

With the results of the preliminary catalyst screening at hand, the optimization was continued with acetyl-protected galactose-derived aldehyde **367** (Table 3). The use of BINOL-titanium complexes (ligands **391a** and **391b**, see Table 1) afforded a good level of stereoselectivity, but the yields were low (entries 6 and 7). Fortunately, the salen chromium complexes (ligands **314a** and **314b**) were determined once again to be better choices with respect to both the stereoselectivity and the yield of the reaction. Interestingly, both ligand enantiomers led to the same diastereomer of the product (entries 11 and 13). Although the tetrafluoroborate counter anion gave better selectivities, the chloride complex turned out to be a more reproducible and stable catalyst. The absolute stereochemistry in the the newly formed

B-ring (D- and L-form) has been assigned by analogy with the literature precedents (170) (171) (172) (173) (174) but has not been experimentally confirmed.

Table 3. HDA reaction of acetyl protected galactoside derivative **367** with Danishefsky's diene **147**.

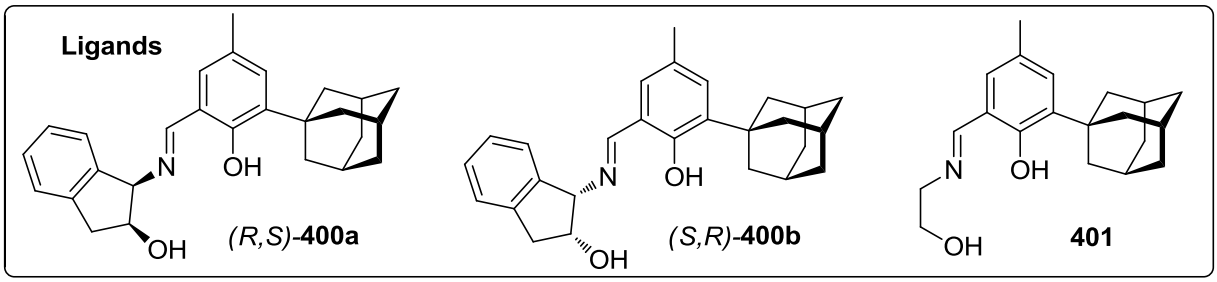


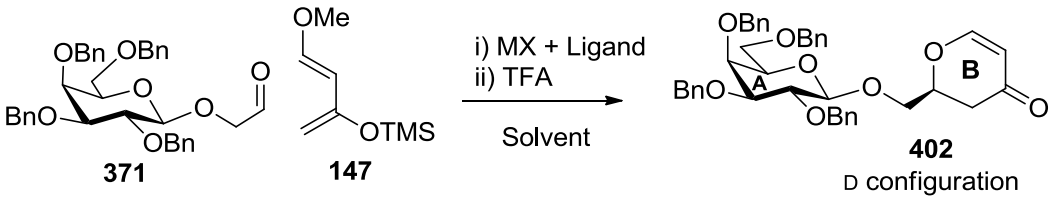
Entry	Metal	Anion	Ligand	MX (+Ligand) (%)	Solvent	T (°C)	Time (h)	Yield[a] (%)	dr (D:L) [b]
1	Zn^{2+}	Cl^-	-	120	CH_2Cl_2	rt	10 min	76	50:50
2	Zn^{2+}	Br^-	-	120	CH_2Cl_2	rt	0.5	35	50:50
3	Mg^{2+}	Br^-	-	120	CH_2Cl_2	rt	0.5	35	45:55
4	Mg^{2+}	Br^-	-	120	CH_2Cl_2	-78	24	n. d	67:33
5	Zn^{2+}	Br^-	**178b**	40	Et_2O	rt	24	20	50:50
6	Ti^{4+}	*i*PrO$^-$	**391a**	20	toluene	0	1	33	18:82
7	Ti^{4+}	*i*PrO$^-$	**391b**	20	toluene	0	1	37	92:8
8	$ZnEt_2$		**391b**	10	toluene	0	17	n. d.	50:50
9	Zn*i*Pr$_2$		**391b**	10	toluene	0	17	n. d	50:50
10	$ZnEt_2$		**399**	10	toluene	0[c]	137	n. d	55:45
11	Cr^{3+}	Cl^-	**314a**	5	Et_2O	-20	18.5	59	59:41
12	Cr^{3+}	BF_4^-	**314a**	5	Et_2O	-44	41	52	70:30
13	Cr^{3+}	Cl^-	**314b**	5	Et_2O	-20	18.5	59	78:22
14	Cr^{3+}	BF_4^-	**314b**	5	Et_2O	-20	45	27	81:19

[a] The isolated product. In case where a non-optimal catalyst combination is described, the yield of the product was not determined accurately and therefore not reported (n.d.). [b] Determined by ^{1}H NMR spectroscopy after purification. The absolute stereochemistry of the B ring was assigned by analogy with the literature precedents. (170) (171) (172) (173) (174) [c] Reaction stirred for 65 h at 0 °C and 72 h at rt.

In addition to the acetyl-protected aldehyde **367**, a more lipophilic benzyl-protected galactose-derived aldehyde **371** was also studied, in part due to concerns about the possibility of Lewis-acid-mediated acetyl deprotection. The most optimal conditions from Table 3 were selected, and the results are summarized in Table 4. The use of tridentate indanol-type chromium complexes (ligands **400a** and **400b**) yielded the highest level of stereoselectivity (entries 6 and 7). Moreover, in this case, enantiomeric catalysts resulted in the formation of two different diastereomers of the products. Unfortunately, the yields of reaction were still moderate.

Table 4. HDA reaction of benzyl protected galactoside derivative **371** with Danishefsky's diene **147**.





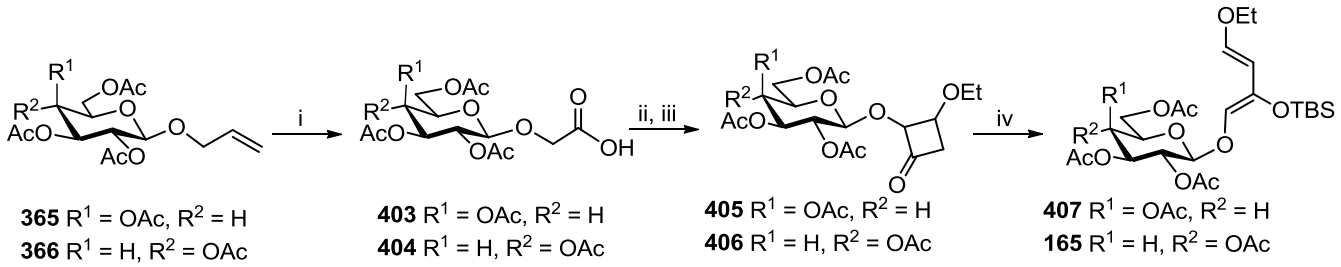
Entry	Metal	Anion	Ligand	MX (+Ligand) (%)	Solvent	T (°C)	Time (h)	Yield[a] (%)	dr (D:L)[b]
1	Ti^{4+}	*i*PrO$^-$	**391a**	20	toluene	0	2.5	49	16:84
2	Ti^{4+}	*i*PrO$^-$	**391b**	20	toluene	0	2.5	30	89:11
3	Cr^{3+}	Cl^-	**314a**	5	Et_2O	-20	18.5	48	61: 39
4	Cr^{3+}	Cl^-	**314b**	5	Et_2O	-20	18.5	54	81:19
5	Cr^{3+}	BF_4^-	**314b**	5	Et_2O	-20	45	59	88:12
6	Cr^{3+}	Cl^-	**400a**	1	Et_2O	-20	43.5	54	19:81
7	Cr^{3+}	Cl^-	**400b**	1	Et_2O	-20	43.5	59	94:6

[a] The yield of isolated product. [b] Determined by ^1H NMR spectroscopy after purification. The absolute stereochemistry of the B-ring was assigned by analogy with the literature precedents. (170) (171) (172) (173) (174)

4.4 Synthesis of Saccharide Based Dienes

To expand the *de novo* saccharide welding to the synthesis of trisaccharide products, more complex dienes incorporating the monosaccharide unit were needed. We decided to use Scheeren's methodology for their synthesis (186), because a similar method was previously described for the synthesis of saccharide diene **165**. (88) Danishefsky and coworkers also described a method for accessing 1,3,4-trioxygenated 1,3-dienes, but the method suffers from low *Z*/*E* stereoselectivities. (61) (187) The synthesis of dienes **407** and **165** was initiated by the preparation of allylic galacto- and glucopyranosides **365** and **366** as described above (Scheme 54) and by oxidation of the pendant alkene functionality to the corresponding carboxylic acids **403** and **404** (Scheme 6). (188) The acids **403** and **404** were then transformed to the corresponding ketenes via treatment of the derived acid chlorides with Et_3N. The ketene intermediate was subjected to [2+2] cycloaddition with ethyl vinyl ether. In our initial attempts, these conditions afforded the cyclobutanones **405** and **406** in variable yields (24-58%, Table 5, entries 5 and 7), comparable with results given in the literature. (186) (189) We noticed

that it was crucial to carefully remove the hydrogen chloride released in the formation of the acid chloride intermediates. Otherwise, only ethyl esters of **403** and **404** were formed in subsequent reaction with ethyl vinyl ether.



365 R^1 = OAc, R^2 = H
366 R^1 = H, R^2 = OAc

403 R^1 = OAc, R^2 = H
404 R^1 = H, R^2 = OAc

405 R^1 = OAc, R^2 = H
406 R^1 = H, R^2 = OAc

407 R^1 = OAc, R^2 = H
165 R^1 = H, R^2 = OAc

Scheme 54. Synthesis of saccharide dienes. Reagents and conditions: i) $RuCl_3 \cdot H_2O$, CH_2Cl_2, MeCN, H_2O, AcOH, rt, **403** (quant), **404** (95%); ii) oxalyl chloride, DMF (cat), CH_2Cl_2, 0 °C to rt; iii) ethyl vinyl ether, *i*PrNEt$_2$, MeCN, $NaIO_4$, 0 °C to 70 °C, **405** (74%), **406** (80%); iv) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to rt, **407** (56%), **165** (40%).

4.4.1 Optimization of Cyclobutanone Synthesis

Due to low and variable yields, we optimized the cyclobutane synthesis by using phenoxyacetic acid. Among the conditions screened (Table 5, entries 1-4), the use of *i*Pr$_2$NEt as the base afforded the desired model cyclobutane **409** reproducibly and in higher yield (60%, entry 4, 93:7 *trans*/*cis* ratio). Evidence for the *trans*-configuration of the major product is summarized in Figure 2. (186) (190) In known compound **408**, the H^1 – H^4 coupling constant ($J_{H1\text{-}H4}$) in the *trans*- isomer is smaller (~5 Hz) than in the corresponding *cis*– isomer (~6.5-10 Hz). (186) (190) In our synthesized cyclobutanone **409**, the major isomer exhibited $J_{H1\text{-}H4}$ = 5.4 Hz and the minor isomer $J_{H1\text{-}H4}$ = 6.1 Hz. Furthermore, in cyclobutanone **409**, the chemical shift difference between the two H_2 protons was smaller in the *trans*- isomer than in the *cis*– isomer. Taken together, these data indicate that the major isomer of cyclobutanone **309** should be the *trans*- isomer (main isomer: $\delta(H_2)$ = 3.09 ppm and 2.95 ppm, Δ = 0.14 ppm; minor isomer: $\delta(H_2)$ = 3.16 ppm and 2.81 ppm, Δ = 0.35 ppm).

The *i*Pr$_2$NEt conditions were then employed with monosaccharide acids **403** and **404**, affording cyclobutanoses **405** and **406** in good yields (74% and 80%, respectively; entries 6 and 8). In both cases, a complex mixture of diastereomers was formed. Fortunately, the stereochemistry of isolated cyclobutanones **405** and **406** had no effect on the next step, because treatment of the cyclobutanones with excess Et_3N converted them completely to the *trans*-isomers (as described by Aben and Scheeren (186)). After treatment with TBSOTf, the pyranoside dienes **407** and **165** were obtained in moderate yields (56% and 40%, respectively) (Scheme 49). Purification of the dienes **407** and **165** by flash chromatography lowered the yields significantly even though base in the eluent (Et_3N) and very short columns were used. Because the final ring opening is a concerted and conrotary process, only the *trans*- isomers of the diene products were eventually formed. (186)

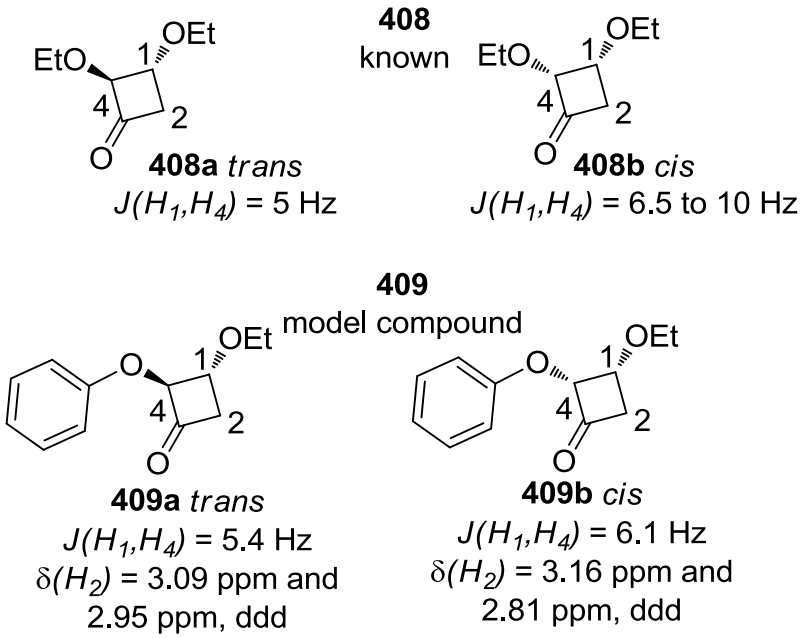
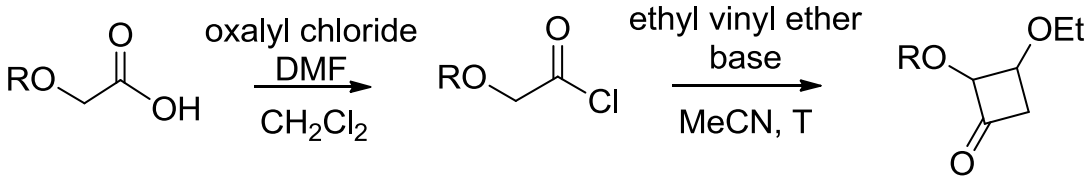
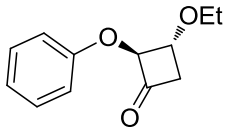
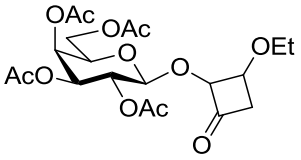
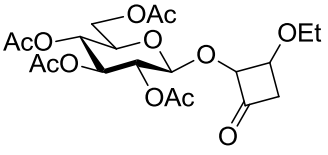


Figure 2. ^{1}H NMR coupling constants and chemical shifts of cyclobutanones **408** and **409**.

Table 5. Optimization of cyclobutanone synthesis with **409** and synthesis of the monosaccharide cyclobutanones **405** and **406**.



Entry	Product	Base (%) (additive)	Time (h)	T (°C)	Yield (%)
1	 **409** (racemic)	Et_3N (150)	16	65	43
2		Et_3N (150) (+$ZnCl_2$ 70%)	16	21	25
3		DABCO (150)	2.5	65	0
4		iPr$_2$NEt (150)	**2.5**	**65**	**60**
5	 **405**	Et_3N (150)	1.5 – 2.5	65	24 - 48
6		iPr$_2$NEt (120)	**2.5**	**65**	**74**
7	 **406**	Et_3N (150)	1.5 – 2.5	65	35 - 58
8		iPr$_2$NEt (150)	**2.5**	**65**	**80**

4.5 Synthesis of Trisaccharide Products

As discussed above, the HDA strategy can also be expanded to enable the synthesis of trisaccharides by using the pyranoside building blocks containing diene **385** (see: Scheme 52, p. 68). During initial screening, we used acetyl-protected glucose- or galactose-derived dienes **407** and **165** with monosaccharide aldehyde derivatives **367**, **368**, **371**, **373** and **377** (see: Schemes 48 and 49, p. 65). The results are summarized in Tables 6 and 7. In the absence of a catalyst, the reaction did not proceed, and only slow decomposition of the diene was observed after six days. With catalytic $MgBr_2 \cdot OEt_2$, the yields were moderate (47-57%), but a mixture of diastereomers was formed.

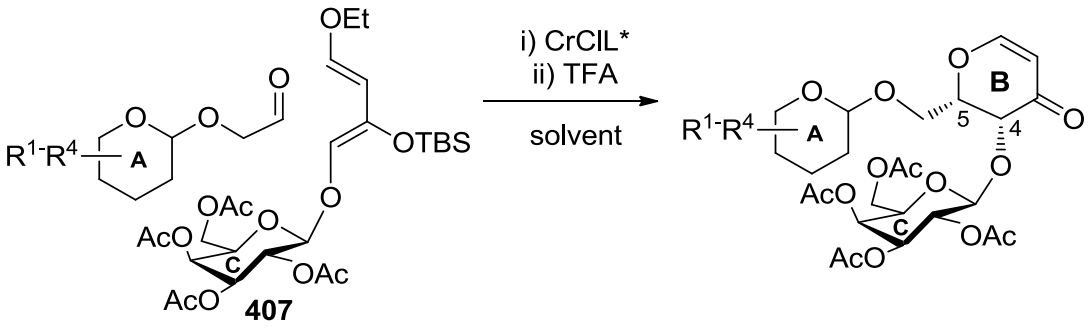
After obtaining the screening results for the disaccharide system, further screens were carried out using the Cr(III) catalysts (Table 4, ligands **400a** and **400b**). The yield and stereoselectivity of the reaction in CH_2Cl_2 and in Et_2O were equivalent. However, CH_2Cl_2 was used because the solubility of the dienes in Et_2O was problematic. Significantly, regardless of the catalyst configuration, single diastereomers of the trisaccharide products were obtained with both acetyl- and benzyl-protected β-galacto- and β-glucopyranoside-derived aldehydes **367**, **368** and **371**. The highest yields were obtained in the reaction of acetyl-protected galactoside-derived aldehyde **367** with glucoside diene **165** (Table 7, entries 1 and 2). On the other hand, tetrasilylated aldehyde **373** failed to undergo the desired reaction.

Attempts to further improve the yields by raising the temperature, prolonging the reaction time, changing the counterion ($Cl^- \rightarrow SbF_6^-$) or slowly adding the components were unsuccessful. However, increasing the amount of catalyst did improve the yield slightly. In the reaction of acetyl-protected glucopyranoside aldehyde **368** with acetyl-protected glucopyranoside diene **165**, the yields of product **416** with 6 mol-% and 15 mol-% catalyst loadings were 45% and 51%, respectively. As such, in further screens higher catalyst loadings (9-15%) were used.

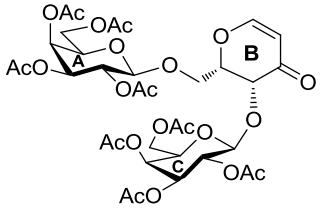
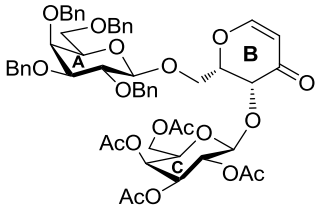
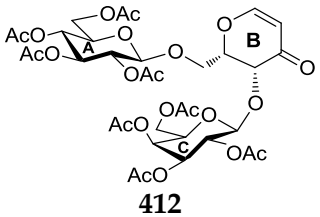
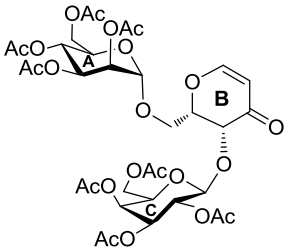
Since both chiral catalysts afforded the same trisaccharide diastereomers with high dr, we also screened an achiral catalyst based on ligand **401** (see Table 4). Catalyst **411**·CrCl was synthesized according to a modified procedure based on the literature. (179) (180) Indeed, when this catalyst was employed in the HDA reaction of galactopyranoside aldehyde **367** and galactopyranosideside diene **356**, we again obtained the same diastereomer of product **410**. However, the yield of **410** was lower (~ 30%) and the reactions were sluggish. As such, although the use of a chiral catalyst was not essential for the diastereoselectivity of the HDA reaction, the higher reactivity of the chiral catalysts necessitated their use.

We also checked the influence of the anomeric centre of aldehyde **367** on the reactivity and stereoselectivity. These studies were initially conducted with acetyl-protected α-galactopyranoside-derived aldehyde **367α** (Scheme 2). Aldehyde **367α** turned out to be much more unreactive than its β-anomer **367**. The catalyst with ligand **400a** was more efficient in this context, but the highest yield of the corresponding trisaccharide product was still significantly lower than in the case of the corresponding β-anomer **367** (i.e., with diene **165**, the α-anomer afforded a 16% yield, compared to 68% with the β-anomer). In the case of the corresponding mannopyranoside, the α-anomer **377** was also not an optimal substrate for the HDA reaction because the products were formed as a mixture of diastereomers. With glucopyranoside diene **165** the yields were low (15% and 7% for ligands **400a** and **400b**, respectively), but with galactopyranoside diene **407** somewhat higher yields (31-48%) were obtained (Tables 6 and 7, entries 7 and 8).

Table 6. Reaction of monosaccharide aldehydes **367**, **368**, **371** and **377** with the galactose-derived diene **407**.

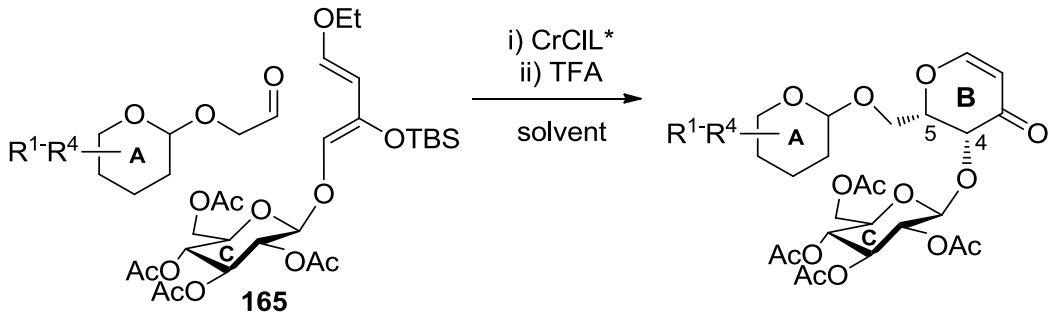


407

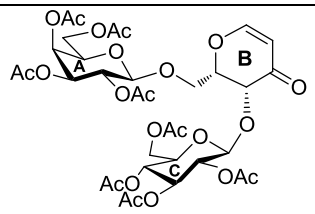
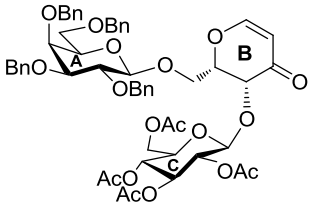
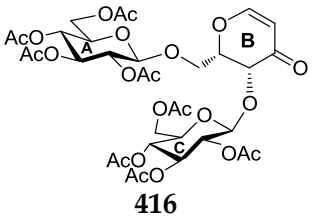
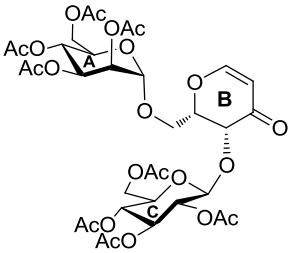
Entry	Product	Ligand[a]	Solvent	Yield[b] (%)	dr[c]
1		**400a**	CH_2Cl_2	44	>30:1
2		**400b**	CH_2Cl_2	41	>30:1
	410				
3		**400a**	CH_2Cl_2	41	>30:1
4		**400b**	CH_2Cl_2	40	>30:1
	411				
5		**400a**	CH_2Cl_2	39	>30:1
6		**400b**	CH_2Cl_2	35	>30:1
	412				
7		**400a**[d]	CH_2Cl_2	48	63:31:3:3
8		**400b**[d]	CH_2Cl_2	31	66:19:10:5
	413				

[a] Catalyst loading 5-9%. [b] The isolated product. [c] Determined by ^{1}H NMR spectroscopy after purification. [d] Catalyst loading 12%.

Table 7. Reaction of monosaccharide aldehydes **367**, **368**, **371** and **377** with the glucose-derived diene **165**.



165

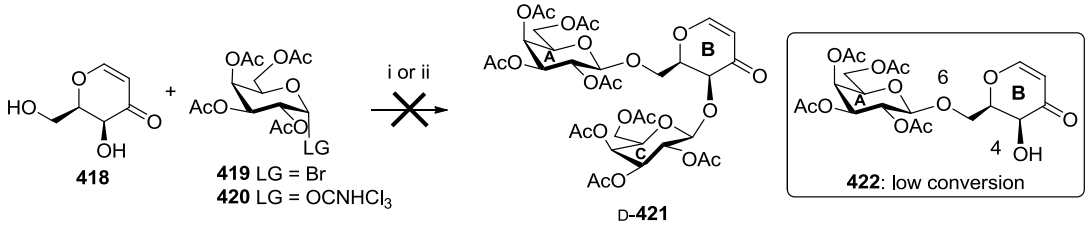
Entry	Product	Ligand[a]	Solvent	Yield[b] (%)	dr[c]
1		**400a**	CH_2Cl_2	63	>30:1
2		**400b**	Et_2O	68[d]	>30:1
	414				
3		**400a**	CH_2Cl_2	29	>30:1
4		**400b**	CH_2Cl_2	32	>30:1
	415				
5		**400a**[e]	CH_2Cl_2	51	>30:1
6		**400b**	Et_2O[f]	39	>30:1
	416				
7		**400a**[g]	CH_2Cl_2	15	92:4:4
8		**400b**[g]	CH_2Cl_2	7	Mixture n.d. [h]
	417				

[a] Catalyst loading 6-9%. [b] The isolated product. [c] Determined by ^{1}H NMR spectroscopy after purification. [d] Aldehyde **367** used 200 mol-%. [e] Catalyst loading 15%. [f] CH_2Cl_2 used as a co-solvent. [g] Catalyst loading 11%. [h] Not determined.

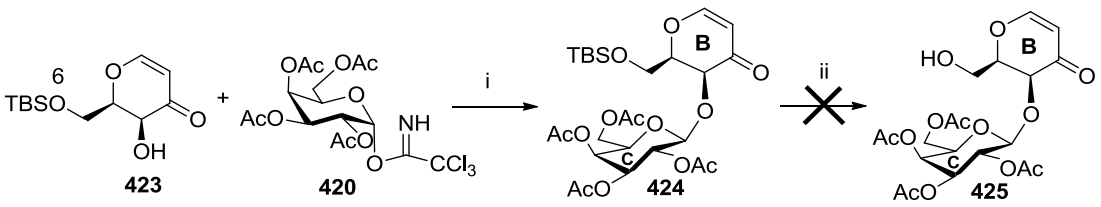
4.5.1 Stereochemistry of the Trisaccharide Products

In the major products **410-417**, the relative stereochemistry of the central ulose-ring (B-ring) formed in the HDA reaction was confirmed by ^{1}H NMR data. Comparison with the literature regarding related enulose rings indicated that the H^4–H^5 coupling constant ($J_{H4\text{-}H5}$) of the *trans*- isomer is larger (10.4-13.2 Hz) than that of the *cis*–isomer (0.6-6.0 Hz) (see Tables 6 and 7). (191) (192) (193) In the products **410-417**, the B-ring showed $J_{H4\text{-}H5}$ = 1.4-1.9 Hz, indicating a *cis*-configuration (*galacto*- stereochemistry) (see Figure 5).

In order to assign the full absolute stereochemistry, we initially attempted the traditional synthesis of the trisaccharide product by using either bromide or trichloroacetimidate donor and the corresponding galactal-derived enones to allow comparison of products with known stereochemistries. For the glycosylation reaction of enulose **418** with the bromide donor **419**, $AgCO_3$, $AgPF_6$, AgOTf and $InCl_3$ activation was used. With the trichloroacetimidate donor **369**, glycosylation reaction was attempted by using both $BF_3{\cdot}OEt_2$ and TMSOTf activation. Unfortunately, in all cases either the glycosylation did not occur or it only occurred at position 6 in low conversion leading to product **422** (Scheme 55). However, donor **420** in combination with $BF_3{\cdot}OEt_2$ activation turned out to be the most promising. At this point, we decided to protect the enulose **418** in its 6-position to afford compound **423**, and then attempted to couple at the free 4-position (Scheme 56). Unfortunately, even though some glycosylation occurred at position 4 (according to HRMS analysis), the conversion to the product **424** was low (< 5%). Moreover, attempts to remove the silyl protection led only to the unreacted **424** (with TBAF) or to the decomposition of **424** (with HF/pyridine). Thus, the desired products could not be obtained, mainly due to the relatively low reactivity of the enulose-type acceptor.



Scheme 55. Attempts at the traditional synthesis of the trisaccharide product **359** by using donors **419** and **420**. Reagents and conditions: i) **419**, Lewis acid: $AgCO_3$, $AgPF_6$ (+2,6-lutidine additive), AgOTf (+tetramethylurea additive), or $InCl_3$, MS, CH_2Cl_2, rt; ii) **420**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, - 78 °C → rt.



Scheme 56. Attempts at the traditional synthesis of the trisaccharide product by using protected ulose **423**. Reagents and conditions: i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, - 78 °C → rt; ii) TBAF or HF, pyridine.

We also attempted the crystallization of the trisaccharide product for crystallographic analysis. Thus, the glucose-derived HDA product **416** (as we expected that this derivative might crystallize most easily) was subjected to different combinations of solvents (Et_2O, EtOAc and MeOH) and the mixture was cooled, but no crystals were afforded. Alternatively, we assumed that an unprotected HDA product would crystallize more easily or it might be possible to make more crystalline derivatives of HDA product for example by benzoate protection. Thus, removal of acetyl protection for galactose derived **410** was attempted. However, when Zemplén conditions (NaOMe/MeOH) were used, only decomposition of **410** occurred. Also the use of Et_3N/MeOH was attempted, but no reaction was observed. An attempt to convert HDA products to other derivatives, for example by reduction to the deoxysugars, might have helped, by this was not tried.

Therefore, the stereochemistry of the products has been assigned by extensive ^{1}H NMR NOE and NOESY experiments (Figures 3 and 4). For the product **416**, which displayed the cleanest separation of ^{1}H NMR signals, a more complete conformational analysis was carried out via a combination of a Monte Carlo conformational search using initially force field (MMFFs) methods, and DFT (6-311G**/B3LYP) methods for further optimization and energy calculations. Both D- and L- isomers and both conformers of the linking B-ring (4-*O*-axial and 4-*O*-equatorial) were examined (Figure 3). Of the minimum energy structures thus obtained, the only one that clearly matched the NMR data was the L- isomer with an axial 4-*O* substituent. In this case, the distance between H_{B4} and H_{2A} was short enough to explain the observed ^{1}H NMR NOE enhancements and the corresponding NOESY cross-peaks. For the L- isomer, this 4-*O*-axial conformation was also more stable than the 4-*O*-equatorial conformation by 20.7 kJ/mol. A similar conformational analysis was carried out for the product **414**.

Taken together, the evidence pointed towards an L-*cis* configuration in the newly generated B-ring. In the case of disaccharides (Table 4), the enantiomeric ligands **400a** and **400b** afforded products of opposite stereochemistry in the newly formed B ring. However, we believe that it is the stereochemical bias of the C-ring diene (perhaps in combination with the A-ring aldehyde) that dictates the stereochemical outcome in the case of trisaccharides, because the enantiomeric ligands **400a** and **400b** both afforded the same trisaccharide

product diastereomer. As such, we believe that the stereochemical outcome from the disaccharide experiments cannot be used to predict the stereochemistry of the trisaccharide products.

The configurations of the other products **410-414** have been assigned by analogy. The coupling constants of the B4 proton in all products **410-416** were virtually identical and similar NOE enhancements were observed for the products **414** and **410** (see Figures 3-5).

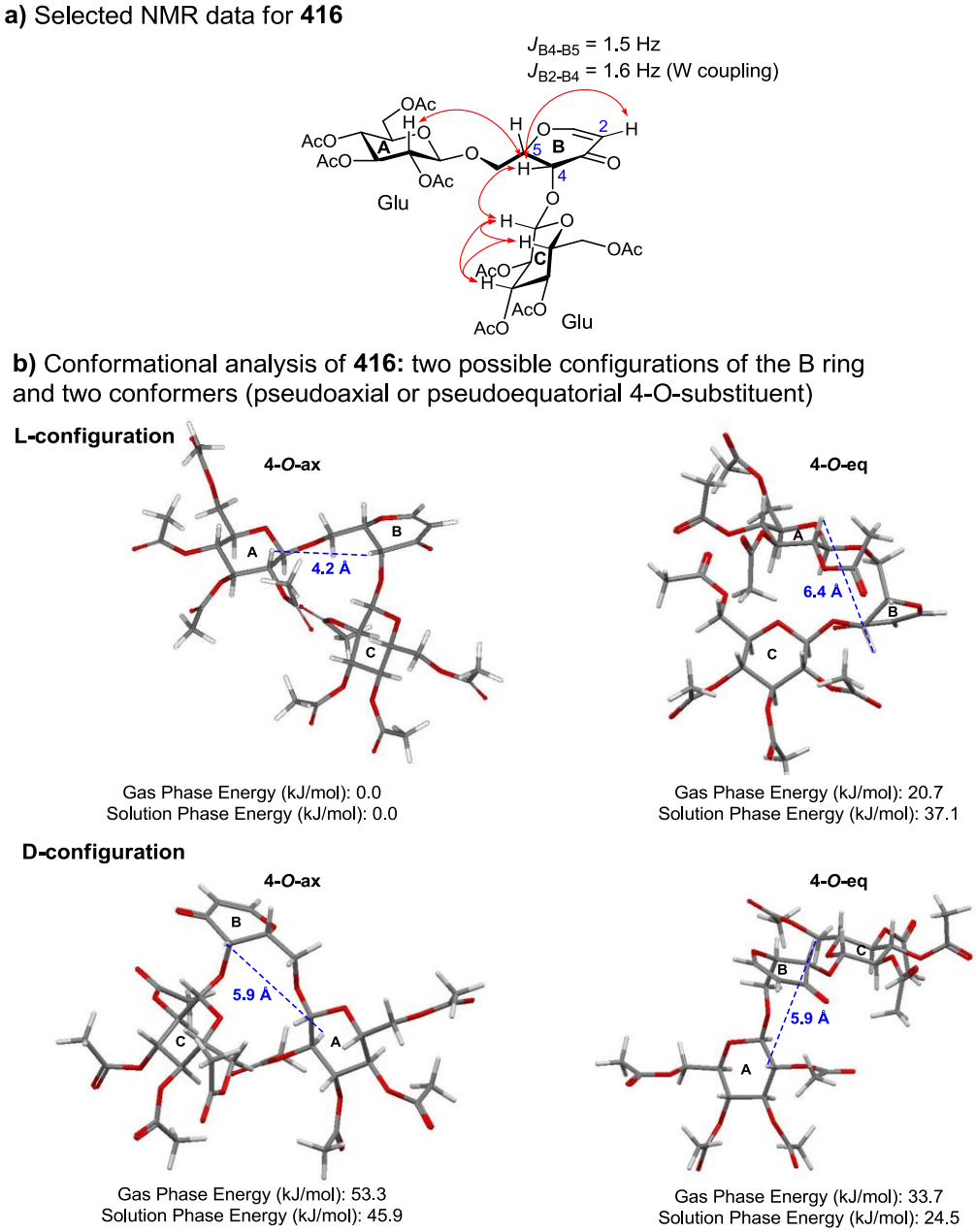


Figure 3. NMR and computational evidence (energies calculated at the DFT (6-311G**/B3LYP) level of theory) for the configuration of **416**.

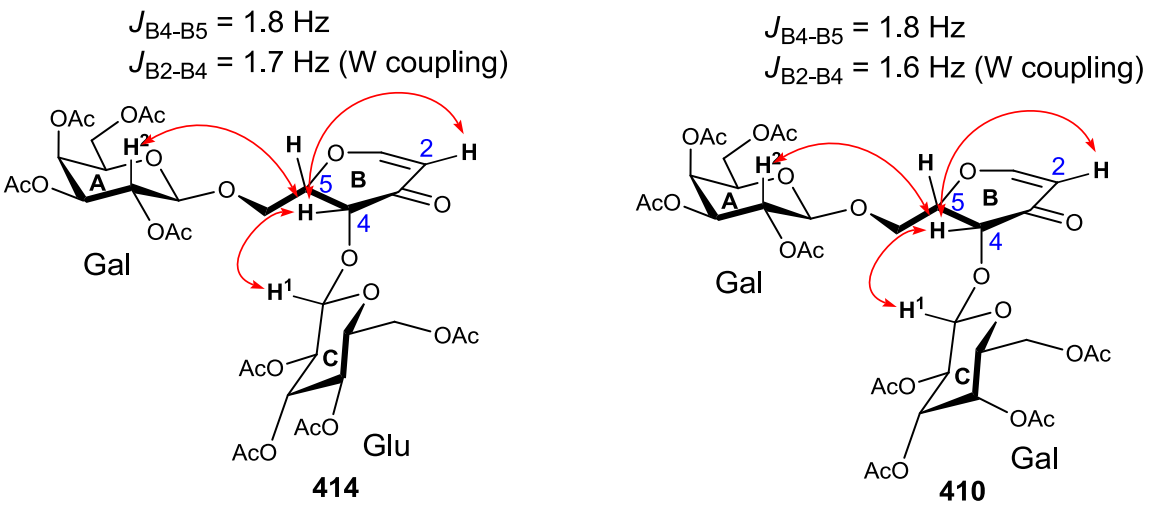


Figure 4. Further 1D NOE and 2D NOESY evidence for the configuration of **414** and **410**. Other trisaccharides have been assigned by analogy.

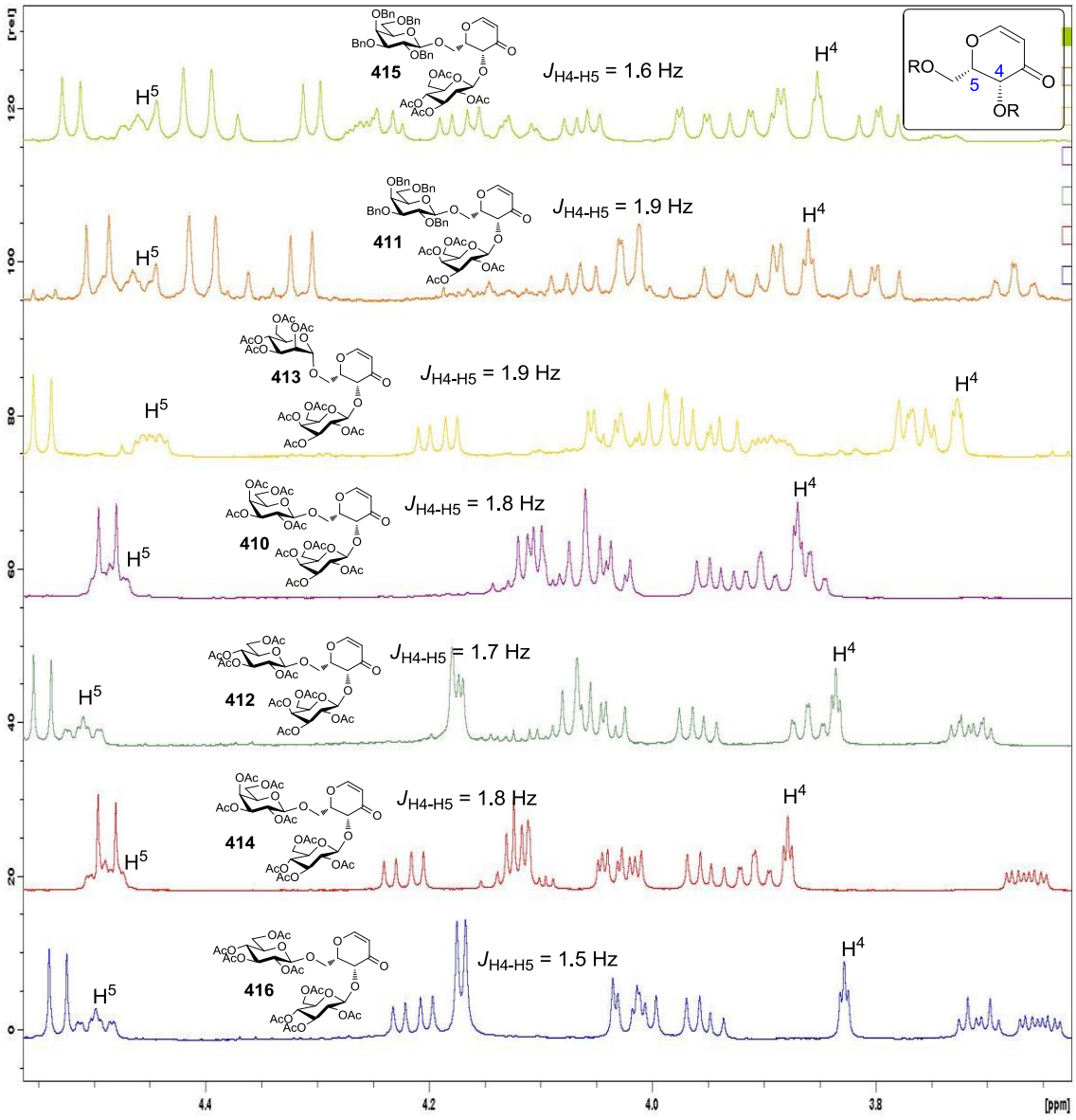


Figure 5. ^{1}H NMR shifts and coupling constants of the B4 and B5 protons were virtually identical in all products **410–416**.

5 SUMMARY AND CONCLUSIONS

The objective of this work was *de novo* construction of oligosaccharides by saccharide welding. To achieve this objective, functionalized monosaccharide building blocks that already included the glycosidic linkages were prepared. Unfortunately, saccharide welding via a two-step aldol methodology using saccharide-derived aldehydes was unsuccessful, as most of the aldehyde decomposed during the reaction, and less than 20% reacted via the aldol pathway. The dimer product was also extremely susceptible to decomposition and it could not be isolated as a pure form. Nevertheless, the aldol strategy could work if the unstable dimers could be processed rapidly to the saccharide products.

Our next strategy was to use one-step hetero-Diels-Alder (HDA) coupling. The same aldehyde building blocks as in the aldol methodology could were used as the aldehyde dienophiles. This HDA protocol provided a viable strategy for a selective saccharide welding. Disaccharide products were accessible by reaction of Danishefsky's diene with acetyl- and benzyl-protected galactoside aldehydes. The highest yields and selectivities were obtained with chiral Schiff base chromium complexes.

For the synthesis of trisaccharide products, acetyl-protected glucose and galactose–derived dienes were synthesized. Their fusion with saccharide-derived aldehydes by using the chiral Schiff base chromium complex catalyzed HDA reaction gave the desired 4,6-linked trisaccharide products in moderate to good yields (32-68%) with excellent stereoselectivity (> 30:1). The HDA protocol appears to tolerate different protective groups provided they are not too bulky. The reaction fully preserves the glycosidic linkage already present in the precursor units. Interestingly, an L-configured galactal-type pyranulose linking unit (B-ring) is stereoselectively generated in the welding process. The assignment of the B-ring stereochemistry of the trisaccharidic HDA-products was based on NMR techniques and molecular modeling studies. The reasons for the use those assignment methods were that it was not possible to obtain crystals for crystallographic analysis or to synthesize HDA-products by

traditional glycosylation methods. However, an attempt to convert HDA products to other derivatives, for example by reduction to the deoxysugars, might have helped, but this was not tried.

As discussed in the reviews of the *de novo* syntheses of aldohexoses (see: Chapter 3), and as supported by the somewhat limited but nonetheless promising results presented in the research component of this thesis, it can be concluded that *de novo* synthesis of *oligo*saccharides provides an interesting alternative approach to saccharide synthesis. Although the primary objective of this research was realized, at the same time many new questions arose. Could our strategy enable the synthesis of both enantiomers of the fused saccharide part with a different type of catalyst? Is it possible to extend the strategy to the construction of products other than 4,6-linked trisaccharides? Could the inverse electron demand HDA reaction be utilized in a comparable manner to construct oligosaccharides? Or could the other methodologies presented in review part (for example aldol, asymmetric epoxidation or dihydroxylation methodologies) permit *de novo* synthesis of oligosaccharides? Thus far, as described in this thesis, only the HDA methodology has been utilized in the *de novo* construction of oligosaccharides.

6 EXPERIMENTAL SECTION

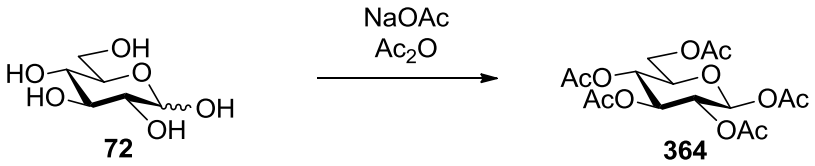
6.1 General Experimental

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. The reaction temperatures refer to the temperatures of the cooling or warming baths. When needed, nonaqueous reagents were transferred under argon via syringe or cannula and dried prior to use. Acetonitrile, dichloromethane, diethyl ether, tetrahydrofuran (THF) and toluene and used were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system). DMF was distillated from molecular sieves (4 Å). Et_3N, *i*-Pr_2Net and 2,6-lutidine were distillated from CaH_2. DMF was distillated from molecular sieves (4 Å). Other solvents and reagents were used as obtained from supplier, unless otherwise noted. TBSOTf was prepared with Corey's procedure. (158) Analytical TLC was performed using Merck silica gel F254 (230-400 mesh) plates and analyzed by UV light or by staining upon heating with vanillin solution (6 g vanillin, 5 mL conc. H_2SO_4, 3 mL glacial acetic acid, 250 mL EtOH). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230-400 mesh) and p.a. grade solvents unless otherwise noted. The ^{1}H NMR and ^{13}C NMR spectra were recorded in either in $CDCl_3$, CD_3CN or CD_3OD on Bruker Avance 500, 400 or 250 spectrometers. The chemical chifts are reported in ppm relative to $CHCl_3$ (δ 7.26), CD_3CN δ (δ 1.94) or CD_3OD (δ 3.31) for ^{1}H NMR. For the ^{13}C NMR spectra, the residual $CDCl_3$ (δ 77.0), CD_3CN (δ 1.32) or CD_3OD (δ 49.0) were used as the internal standard. The enantiomeric ratios (er) of the products were determined by HPLC in comparison to the racemic samples using Waters 501 pump and Waters 486 detector. Melting points (mp) were determined in open capillaries using either Gallenkamp melting point Apparatus or Bibbly Stuart Scientific (SMP3) melting point Apparatus. IR spectra were recorded on either Perkin-Elmer Spectrum One FT-IR spectrometer or Bruker Optics Tensor 27 FT-IR spectrometer. Optical

rotations were obtained with a Perkin-Elmer 343 polarimeter. High resolution mass spectrometric data were measured by using Micromass (ESI-TOF) spectrometer.

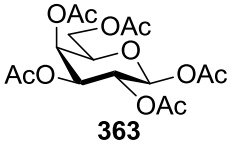
6.2 Synthesis of Aldehydes

6.2.1 General Procedure for the Preparation of Acetyl Protected Saccharides (149) (150)



Monosaccharide **72** (62.7 g, 348 mmol) and NaOAc (50.1 g, 609 mmol; 175 mol-%) were grinded together in a porcelain crucible and dissolved to Ac_2O (410 ml, 4.34 mol, 1250 mol-%) under an air atmosphere. The reaction mixture was stirred at 100 °C for 2 h 15 min until it was allowed to cool to rt. During this time, the mixture turned brown, with a white solid precipitate. Crushed ice (300 g), H_2O (100 mL) and CH_2Cl_2 (300 mL) were added and the phases were separated. The aq. phase was extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with H_2O (200 mL) and aq. sat. $NaHCO_3$ (200 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by crystallization (EtOH, repeted twice) afforded the desired product **364**.

6.2.2 1,2,3,4,6-Penta-*O*-acetyl-β-D-galactopyranoside 363

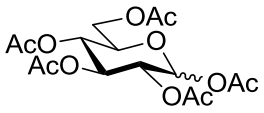


Prepared according to the general procedure. White crystals (41.3 g, 47%). ^1H NMR showed > 30:1 ratio of β- and α-anomer, respectively, the data of the major β-anomer being in agreement with those reported in the literature. (194) (195)

R_f (50% EtOAc/hexanes) = 0.46; mp = 133 - 134 °C; $[\alpha]_D$ = +30.8° (c 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2984, 2941, 1750, 1537, 1433, 1370, 1221, 1068, 1045; ^1H NMR (250 MHz, $CDCl_3$) δ 5.70 (d, 1H *J* = 8.3 Hz), 5.42 (dd, 1H, *J* = 3.4 Hz, 1.0 Hz), 5.33 (dd, 1H, *J* = 10.4 Hz, 8.3 Hz), 5.08 (dd, 1H, *J* = 10.4 Hz, 3.4 Hz), 4.17-4.01 (m, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.03 (s, 6H), 1.99 (s, 3H); ^{13}C NMR (63 MHz, CDCl3): δ 170.5, 170.2, 170.1, 169.5, 169.1, 92.3, 71.9, 71.0, 68.0, 67.0, 61.2, 20.9, 20.8, 20.76 (2C),

20.73; HMRS (ESI+): m/z calcd for [$C_{16}H_{22}O_{11}Na$] 413.1060, found 413.1068, Δ = 1.9 ppm.

6.2.3 1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranoside 364

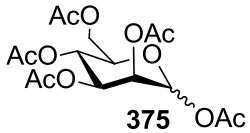


364

Prepared according to the general procedure. White crystals (108.3 g, 80%). ^{1}H NMR showed a 2:5 ratio of the α- and β-anomers, respectively, the data of the major β-anomer being in agreement with those reported in the literature. (194) (195)

R_f (80% EtOAc/hexanes) = 0.66; mp = 98-104 °C; IR (film, cm^{-1}): 2984, 2942, 1748, 1648, 1434, 1371, 1227, 1126, 1070; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.72 (d, 1H, *J* = 8.1 Hz), 5.30–5.07 (m, 3H), 4.29 (dd, 1H, *J* = 12.5 Hz, 4.5 Hz), 4.12 (dd, 1H, *J* = 12.5 Hz, 2.3 Hz), 3.84 (ddd, 1H, *J* = 9.9 Hz, 4.5 Hz, 2.3 Hz), 2.12 (s, 3H), 2.09 (s, 3H), 2.03 (s, 6H) , 2.01 (s, 3H); Characteristic peaks for α-anomer: δ 6.33 (d, 1H, *J* = 3.6 Hz), 5.48 (dd, 1H, *J* = 10.0 Hz, 9.5 Hz), 2.18 (s, 3H), 2.09 (s, 3 H), 2.04 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.5, 170.0, 169.3, 169.2, 168.9, 91.7, 72.8, 72.7, 70.2, 67.8, 61.4, 20.7, 20.6, 20.5 (3C); Characteristic peaks for α-anomer: δ 170.1, 169.6, 168.7, 89.0, 69.8, 69.2, 67.9, 20.8, 20.6, 20.4); HRMS (ESI$^+$): *m/z* calcd. for [$C_{16}H_{22}O_{11}Na$] 413.1060; found 413.1064, Δ = 0.1 ppm.

6.2.4 1,2,3,4,6-Penta-*O*-acetyl-D-mannopyranoside 375

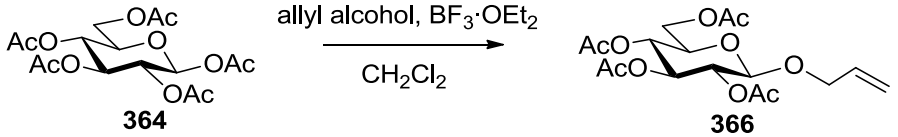


375

Prepared according to the general procedure with the exception that the product was not crystallizated. Yellowish foam (52.1 g, quant.). ^{1}H NMR showed a 5:1 ratio of the α- and β-anomers, respectively, the data of the major α-anomer being in agreement with those reported in the literature. (194) (195)

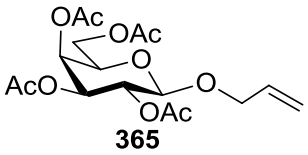
R_f (50% EtOAc/hexanes) = 0.35; IR (film, cm^{-1}): 2991, 2965, 1752, 1434, 1371, 1223, 1150, 1088, 1054, 1028; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.01 (d, 1H, *J* = 1.7 Hz), 5.28-5.17 (m, 3H), 4.27-4.17 (m, 1H), 4.07 (dd, 1H, *J* = 10.0 Hz, 2.5 Hz), 4.03-3.95 (m, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.8, 169.2, 169.0, 168.8, 167.4, 90.0, 70.0, 68.2, 67.8, 65.0, 61.5, 20.1, 20.01, 19.95, 19.92, 19.88; HRMS (ESI$^+$): *m/z* calcd. for [$C_{16}H_{22}O_{11}$·Na] 413.1060; found 413.1073, Δ = 3.2 ppm.

6.2.5 General Procedure for the Preparation of Saccharide Based Allyl Compounds (151)



To a stirred solution of glucopyranoside **364** (12.4 g, 31.7 mmol, 100 mol-%) and molecular sieves (4 Å, 16.5 g) in CH_2Cl_2 (75 mL) was added allyl alcohol (8.25 mL, 7.01 g, 121 mmol, 400 mol-%). The mixture was cooled to 0 °C and $BF_3 \cdot OEt_2$ (15.0 ml, 17.0 g, 119 mmol, 380 mol-%) was added dropwise during 4 h 15 min. The mixture was allowed to warm to rt and stirred for additional 16 h The mixture was filtered trough celite, washed with CH_2Cl_2 (80 mL) and concentrated in vacuo. The residue was dissolved to CH_2Cl_2 (100 ml), extracted with H_2O (100 mL) and aq. sat. NaCl (100 mL). The organic extract was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (initially 30% EtOAc/hexanes, finally 60% EtOAc/hexanes) afforded desired product **366**.

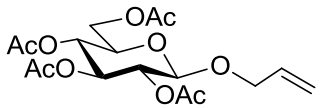
6.2.6 1-*O*-Allyl-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside 365



Prepared according to the general procedure. White foam (5.061 g, 61%). ^{1}H NMR-data matched those reported in the literature. (196)

R_f (50% EtOAc/hexanes) = 0.37; mp = 53-56 °C; $[\alpha]_D$ = -11.4° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2984, 2940, 2879, 1751, 1648, 1432, 1371, 1224, 1174, 1056; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.84 (dddd, 1H, *J* = 16.6 Hz, 10.5 Hz, 5.8 Hz, 5.0 Hz), 5.37 (dd, 1H, *J* = 3.4 Hz, 0.8 Hz), 5.29-5.16 (m, 3H), 5.00 (dd, 1H, *J* = 10.4 Hz, 3.4 Hz), 4.51 (d, 1H *J* = 7.9 Hz), 4.34 (ddt, 1H, *J* = 13.2 Hz, 5.0 Hz, 1.4 Hz), 4.21-4.05 (m, 3H), 3.89 (td, 1H, *J* = 6.5 Hz, 0.8 Hz), 2.13 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.8, 169.7, 168.8, 133.1, 116.9, 99.7, 70.5, 70.2, 69.4, 68.5, 66.8, 60.9, 20.2, 20.1 (2C), 20.0; HMRS (ESI^+): *m/z* calcd for [$C_{17}H_{24}O_{10}Na$] 411.1267, found 411.1265, Δ = -0.5 ppm.

6.2.7 1-*O*-Allyl 2,3,4,6-penta-*O*-acetyl-β-D-glucopyranoside 366

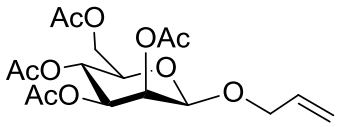


366

Prepared according to the general procedure. White crystals (6.35 g, 52%). ^{1}H and ^{13}C NMR-data matched those reported in the literature. (196) (197)

R_f (50% EtOAc/hexanes) = 0.66; mp = 86-87 °C (CH_2Cl_2); $[\alpha]_D$ = -22.1 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2962, 2882, 1755, 1647, 1433, 1369, 1228, 1170, 1042; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.84 (dddd, 1H, *J* = 17.1 Hz, 10.5 Hz, 6.1 Hz, 5.0 Hz) 5.27 (dq, 1H, *J* = 17.1 Hz, 1.6 Hz), 5.25-5.18 (m, 1H), 5.21 (app t, 1H, *J* = 9.3 Hz), 5.09 (app t, 1H, *J* = 9.6 Hz), 5.02 (dd, 1H, *J* = 9.4 Hz, 7.9 Hz), 4.55 (d, 1H, *J* = 7.9 Hz), 4.32 (ddt, 1H, *J* = 13.2 Hz, 5.0 Hz, 1.6 Hz), 4.25 (dd, 1H, *J* = 12.2 Hz, 4.7 Hz), 4.12 (dd, 1H, *J* = 12.2 Hz, 2.5 Hz), 4.08 (ddt, 1H, *J* = 13.2 Hz, 6.1 Hz, 1.3 Hz), 3.67 (ddd, 1H, *J* = 9.8 Hz, 4.7 Hz, 2.5 Hz), 2.07 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.2, 169.9, 169.1, 168.9, 133.1, 117.2, 99.3, 72.6, 71.5, 71.0, 69.7, 68.2, 61.7, 20.4, 20.32, 20.26 (2C); HRMS (ESI$^+$): *m/z* calcd. for [$C_{17}H_{24}O_{10}$Na] 411.1267, found 411.1265, Δ = -0.5 ppm.

6.2.8 1-*O*-Allyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside 375

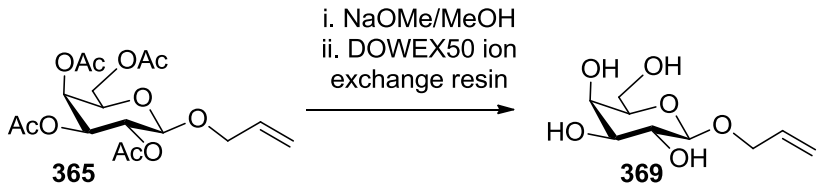


375

Prepared according to the general procedure. Yellow oil (1.776 g, 35%). ^{1}HNMR-data matched those reported in the literature. (147)

R_f (50% EtOAc/hexanes) = 0.42; $[\alpha]_D$ = +42.1 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 30083, 2985, 2959, 2940, 1751, 1649, 1432, 1371, 1227, 1136, 1083, 1050; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.84 (dddd, 1H, *J* = 16.7 Hz, 10.4 Hz, 6.2 Hz, 5.3 Hz), 5.34-5.15 (m, 5H), 4.81 (d, 1H, *J* = 1.7 Hz), 4.23 (dd, 1H, *J* =12.2 Hz, 5.3 Hz), 4.14 (ddt, 1H, *J* = 12.8 Hz, 5.3 Hz, 1.4 Hz), 4.05 (dd, 1H, *J* = 12.2 Hz, 2.5 Hz), 4.02-3.92 (m, 2H), 2.09 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.0, 169.5, 169.3, 169.2, 132.7, 117.9, 96.2, 69.2, 68.7, 68.24, 68.21, 65.8, 62.1, 20.4, 20.27, 20.24, 20.21; HRMS (ESI$^+$): *m/z* calcd. for [$C_{17}H_{24}O_{10}$·Na] 411.1267; found 411.1271, Δ = 0.9 ppm.

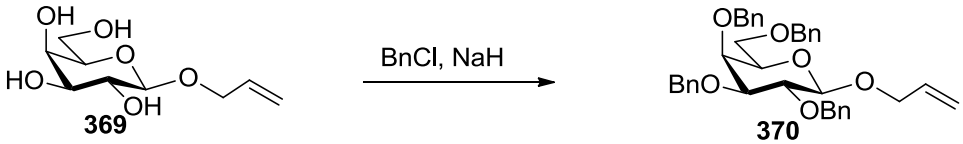
6.2.9 Acetyl Deprotection: 1-*O*-Allyl-β-D-galactopyranoside 369 (154)



To galactopyranoside **365** (320 mg, 0.77 mmol, 100 mol-%) was added NaOMe in MeOH (1M, 3.9 mL). The mixture was stirred for 3 h until all starting material was used. DOWEX-50WX8 (H^+ form) ion exchange resin (2.28 g) was added. The mixture was stirred for additional 17 h, and then filtered trough celite with MeOH (10 mL). The filtrate was concentrated in vacuo to afford **369** as a yellowish oil (121mg, 71%). ^{1}H NMR-data matched those reported in the literature. (198)

R_f (50% H_2O/*i*PrOH) = 0.80; $[\alpha]_D$ = -16.6° (*c* 1.00, MeOH); IR (film, cm^{-1}): 3384 (broad), 2928, 2886, 1653, 1410, 1284, 1143, 1074; ^{1}H NMR (250 MHz, MeOD) δ 4.48 (dddd, 1H, *J* = 17.2 Hz, 10.4 Hz, 6.0 Hz, 5.2 Hz), 3.84 (app. dq, 1H, *J* = 17.2 Hz, 1.6 Hz,), 3.67 (app. dd, 1H, *J* = 10.4 Hz, 1.4 Hz), 2.89 (ddt, 1H, *J* = 12.9 Hz, 5.2 Hz, 1.6 Hz), 2.77 (d, 1H, *J* = 7.3 Hz), 2.66 (ddt, 1H, *J* = 12.9 Hz, 6.0 Hz, 1.4 Hz), 2.35 (dd, 1H, *J* = 3.2 Hz, 1.0 Hz), 2.27 (d, 1H, *J* = 2.3 Hz), 2.24 (d, 1H, *J* = 1.0 Hz), 2.05 (dd, 1H, *J* = 9.7 Hz, 7.3 Hz), 2.00 (app td, 1H, *J* = 5.4 Hz, 1.1 Hz), 1.96 (dd, 1H, *J* = 9.7 Hz, 3.2 Hz), 1.82 (pent. 1H, *J* = 1.6 Hz), 1.51 (s, 1H), 1.37 (d, 1H, *J* = 0.6 Hz); ^{13}C NMR (63 MHz, MeOD): δ 135.7, 117.4, 103.8, 76.4, 74.8, 72.4, 70.9, 70.1, 62.3; HMRS (ESI^+): *m/z* calcd for [$C_9H_{16}O_6Na$] 243.0845, found 243.0848, Δ = 1.4 ppm.

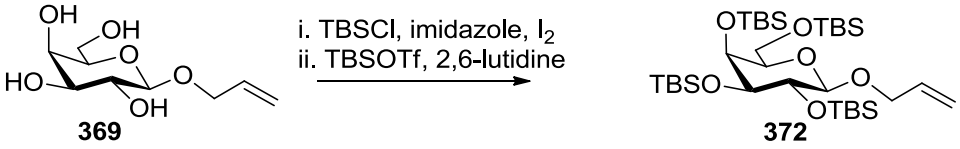
6.2.10 Benzyl protection: 1-*O*-Allyl-2,3,4,6-tetra-O-benzyl-β-D-galactopyranoside 370 (157)



To a strirred solution of galactopyranoside **369** (2.03 g, 9.22 mmol, 100 mol-%) in BnCl (31.3 ml, 272 mmol, 2950 mol-%) at rt was added NaH (60% dispersion in mineral oil, 2.07 g, 86.2 mmol, 940 mol-%). The mixture was stirred for 1 h 30 min at 115-130 °C and allowed to cool to rt. Filtered through celite and with toluene (100 mL). Majority of toluene was removed in vacuo and the residual toluene and BnCl were removed by distillation (85 °C, bath 120 °C). Purification of the residue by flash chromatography (initially 20% EtOAc/hexanes, finally 40% EtOAc/hexanes) afforded product **370** as a yellow oil (2.12 g, 40%). ^{1}H NMR-data matched those reported in the literature. (199)

R_f (80% EtOAc/hexanes) = 0.89; mp = 75-78 °C; $[\alpha]_D$ = +5.59° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3063, 3030, 2915, 2867, 1496, 1454, 1363, 1209, 1156, 1099, 1075, 1028; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.25 (m, 20H), 5.95 (dddd, 1H, *J* = 17.2 Hz, 10.5 Hz, 6.0 Hz, 5.2 Hz), 5.32 (app dq, 1H, *J* = 17.2 Hz, 1.7 Hz), 5.18 (app d, 1H, *J* = 10.5 Hz), 4.95 (d, 1H, *J* = 11.7 Hz), 4.94 (d, 1H, *J* = 10.9 Hz), 4.78 (d, 1H, *J* = 10.9 Hz), 4.77 (d, 1H, *J* = 11.9 Hz), 4.72 (d, 1H, *J* = 11.9 Hz), 4.63 (d, 1H, *J* = 11.7 Hz), 4.47 (d, 1H, *J* = 11.8 Hz), 4.43 (d, 1H, *J* = 11.8 Hz), 4.42 (d, 1H, *J* = 7.7 Hz), 4.41 (ddt, 1H, *J* = 13.0 Hz, 5.2 Hz, 1.7 Hz), 4.13 (ddt, 1H, *J* = 13.0 Hz, 6.0 Hz, 1.4 Hz), 3.90 (dd, 1H, *J* = 2.9 Hz, 0.6 Hz), 3.86 (dd, 1H, *J* = 9.8 Hz, 7.7 Hz), 3.62 (d, 1H, *J* = 0.8 Hz), 3.61 (s, 1H), 3.54 (dt, 1H, *J* = 6.3 Hz, 0.8 Hz), 3.53 (dd, 1H, *J* = 9.8 Hz, 2.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 138.7, 138.6, 138, 134.3, 128.4 (2C), 128.33 (2C), 128.27 (2C), 128.23 (2C), 128.20 (2C), 128.1 (2C), 127.8 (2C), 127.7, 127.52 (3C), 127.50, 127.47, 117.0, 103.0, 82.3, 79.6, 75.2, 74.5, 73.7, 73.6, 73.5, 73.1, 70.2, 68.9; HMRS (ESI^+): *m/z* calcd for $[C_{37}H_{40}O_6Na]$ 603.2723, found 603.2723, Δ = 0.0 ppm.

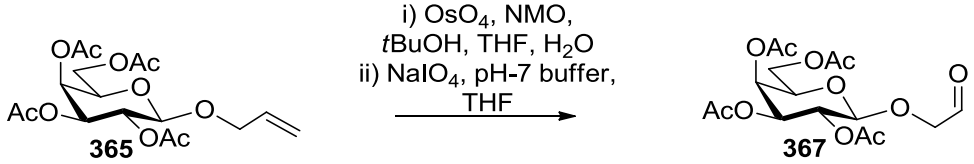
6.2.11 TBS protection: 1-*O*-Allyl-2,3,4,6-tetra-*O*-*t*-butyldimethylsilyl-β-D-galactopyranoside 372 (158) (160)



To a strirred solution of galactopyranoside **369** (349 mg, 1.59 mmol, 100 mol-%) in MeCN (2.5 mL) and DMF (2.0 mL) at rt were added imidazole (1.019 g, 15.9 mmol, 1000 mol-%), I_2 (1.025 g, 7.95 mmol, 500 mol-%) and TBSOCl (1.180 g, 7.95 mmol, 500 mol-%). The mixture was stirred for 20 h and then concentrated. The residue was dissolved to EtOAc (10 mL), washed with sat. aq. $NaHCO_3$ (10 mL), dried over Na_2SO_4 and and concentrated. Purification of the residue by flash chromatography (initially 10% EtOAc/hexanes, finally 40% EtOAc/hexanes) afforded partially silylated products as colourless oil and white crystals (tot. 891 mg, 87%). To a stirred solution of combined products in CH_2Cl_2 (5 mL) was added 2,6-lutidine (693 mg, 0.69 mL, 5.97 mmol, 250 mol-%). The mixture was cooled to 0 °C and TBSOTf (1.26 g, 1.1 mL, 4.77 mmol, 200 mol-%) was added during 5 min. After 10 min at 0 °C the mixture was allowed to warm to rt and stirred for additional 16 h. Because there was still starting materials left, the mixture was cooled to 0 °C and 2,6-lutidine (693 mg, 0.69 mL, 5.97 mmol, 250 mol-%) and TBSOTf (1.26 g, 1.1 mL, 4.77 mmol, 200 mol-%) were added . The resulting mixture was stirred for additional 7 h at rt, and then diluted with CH_2Cl_2 (10 mL), washed with sat. aq. $NaHCO_3$ (20 mL), sat. aq. NaCl (20 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (3% EtOAc/hexanes) afforded product **372** as a colourless oil (862 mg, 71%).

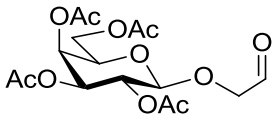
R_f (10% EtOAc/hexanes) = 0.58; $[\alpha]_D$ = -15.7° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3083, 2930,2887, 2858, 1472, 1463, 1390, 1362, 1255, 1166, 1104, 1005; ^1H NMR (500 MHz, CD_3CN, 78 °C): δ 5.97 (dddd, 1H, *J* = 17.0 Hz, 10.5 Hz, 6.3 Hz, 5.4 Hz), 5.27 (dq, 1H, *J* = 17.0 Hz, 1.5 Hz), 5.15 (app dq, 1H, *J* =10.5 Hz, 1.5 Hz), 4.35-4.33 (m, 1H), 4.32 (ddt, 1H, *J* = 12.8 Hz, 5.4 Hz, 1.4 Hz), 4.16 (br s, 1H), 4.05 (ddt, 1H, *J* = 12.8 Hz, 6.3 Hz, 1.1 Hz), 3.91 (br s, 1H), 3.89 (dd, 1H, *J* = 7.5 Hz, 5.6 Hz), 3.78 (dd, 1H, *J* = 10.5 Hz, 5.6 Hz), 3.69 (dd, 1H, *J* = 7.5 Hz, 1.8 Hz), 3.57 (br s, 1H), 0.97 (s, 9H), 0.96 (s, 9H), 0.94 (s, 9H), 0.93 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, CD_3CN, 78 °C): δ 136.4, 117.4, 104.0, 78.0, 77.2, 74.2, 72.1, 70.9, 63.7, 27.4 (3C), 27.1 (3C), 27.0 (3C), 26.7 (3C), 19.7, 19.6, 19.23, 19.17, -2.5, -2.9, -3.3, -3.4 (2C), -3.7, -4.5, -4.6; HRMS (ESI^-): *m/z* calcd. for $[C_{33}H_{72}O_6Si_4Na]$ 699.4304; found 699.4324, Δ = 2.9 ppm.

6.2.12 General Procedure for the Preparation of Saccharide Based Aldehydes (152) (153)



To a stirred solution of galactopyranoside **365** (5.587 g, 14.39 mmol, 100 mol-%) in a mixture of *t*BuOH (160 mL), THF (64 mL) and H_2O (16 mL) at rt were added NMO (2.004 g, 17.1 mmol, 120 mol-%) and OsO_4 (2.5% solution in *t*BuOH, 6.48 g, 0.64 mmol, 4 mol-%). The mixture was stirred for 24 h and then poured into sat. aq. NH_4Cl (300 mL). The phases were separated and the aq. phase was extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in THF (200 mL) and pH 7 buffer (25 mL), cooled to 0 °C and $NaIO_4$ (7.701 g, 36.0 mmol, 250 mol-%) was added. The mixture was stirred for 1 h, after which sat. aq. $Na_2S_2O_3$ (200 mL) was added. The phases were separated and aq. phase was extracted with EtOAc (2 x 150 ml). The combined organic extracts were washed with brine (200 mL) and dried over Na_2SO_4. Concentration in vacuo afforded the desired product **367**.

6.2.13 2-[(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosyl)oxy]-acetaldehyde 367

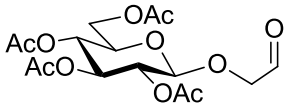


367

Prepared according to the general procedure. White foam (4.95 g, 88%). ^{1}H and ^{13}C NMR-data matched those reported in the literature. (200)

R_f (50% EtOAc/hexanes) = 0.09; mp = 65-66 °C; $[\alpha]_D$ = -12.0° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2942, 1748, 1433, 1371, 1223, 1177, 1136, 1060; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (m, 1H), 5.40 (dd, 1H, *J* = 3.4 Hz, 0.6 Hz), 5.30 (dd, 1H, *J* = 10.4 Hz, 8.0 Hz), 5.04 (dd, 1H, *J* = 10.4 Hz, 3.4 Hz), 4.47 (d, 1H, *J* = 8.0 Hz), 4.29 (dd, 1H, *J* = 17.5 Hz, 0.6 Hz), 4.20 (dd, 1H, *J* = 17.5 Hz, 1.5 Hz), 4.16 (dd, 1H, *J* = 11.2 Hz, 6.8 Hz), 4.10 (dd, 1H, *J* = 11.2 Hz, 6.4 Hz), 3.92 (ddd, 1H, *J* = 6.8 Hz, 6.4 Hz, 0.6 Hz), 2.17 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 170.2, 170.0, 169.9, 169.5, 101.2, 73.8, 70.90, 70.5, 68.2, 66.8, 61.1, 60.2, 20.9, 20.6, 20.5, 20.4; HMRS (ESI^+): *m/z* calcd for $[C_{16}H_{22}O_{11}Na]$ 445.1322, found 445.1320, Δ = -0.4 ppm.

6.2.14 2-[(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]-acetaldehyde 368

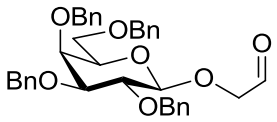


368

Prepared according to the general procedure. White foam (5.67 g, 92%). ^{1}H NMR-data matched those reported in the literature. (153)

R_f (50% EtOAc/hexanes) = 0.09; mp = 55-56 °C; $[\alpha]_D$ = -2.71° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2960, 1754, 1434, 1396, 1226, 1173, 1039; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (dd, 1H, *J* = 1.6 Hz, 1.0 Hz), 5.20 (app t, 1H, *J* = 9.5 Hz), 5.06 (dd, 1H, *J* = 9.9 Hz, 7.9 Hz), 5.05 (app t, 1H, *J* = 9.5 Hz), 4.57 (d, 1H, *J* = 7.9 Hz), 4.23 (dd, 1H, *J* = 17.5 Hz, 1.0 Hz), 4.21, (dd, 1H, *J* = 12.4 Hz, 5.2 Hz), 4.16 (dd, 1H, *J* = 17.5 Hz, 1.6 Hz), 4.08 (dd, 1H, *J* = 12.4 Hz, 2.5 Hz), 3.70 (ddd, 1H, *J* = 10.0 Hz, 5.2 Hz, 2.5 Hz), 2.050 (s, 3H), 2.049 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.7, 170.5, 170.0, 169.33, 169.28, 100.9, 74.0, 72.1, 70.9, 68.3, 61.7, 20.6 (2C), 20.5 (2C); HRMS (ESI^+): *m/z* $[C_{16}H_{22}O_{11}Na]$ 445.1322, found 445.1330, Δ = 1.8 ppm.

6.2.15 2-[(2′,3′,4′,6′-Tetra-*O*-benzyl-β-D-galactopyranosyl)oxy]-acetaldehyde 371

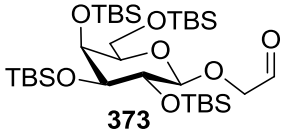


371

Prepared according to the general procedure. Yellowish oil (940 mg, 94%).

R_f (50% EtOAc/hexanes) = 0.47; $[\alpha]_D$ = +2.43° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3088, 3063, 3030, 2914, 2869,1734, 1497, 1454, 1363, 1209, 1099, 1071, 1028; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (dd, 1H, *J* = 1.6 Hz, 1.2 Hz), 7.40-7.28 (m, 20H), 4.97 (d, 1H, *J* = 11.6 Hz), 4.96 (d, 1H, *J* = 11.0 Hz), 4.85 (d, 1H, *J* = 11.0 Hz), 4.79 (d, 1H, *J* = 11.8 Hz), 4.75 (d, 1H, *J* = 11.8 Hz), 4.64 (d, 1H, *J* = 11.6 Hz), 4.46 (d, 1H, *J* = 11.8 Hz), 4.43 (1H, d, *J* = 7.6 Hz), 4.42 (d, 1H, *J* = 11.8 Hz), 4.26 (dd, 1H, *J* = 17.4 Hz, 1.6 Hz), 4.20 (dd, 1H, *J* = 17.4 Hz, 1.1 Hz), 3.94 (dd, 1H, *J* = 9.8 Hz, 7.6 Hz), 3.93 (d, 1H, *J* = 2.9 Hz), 3.55-3.60 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.1, 138.55, 138.47, 138.3, 137.8, 128.41 (2C), 128.36 (2C), 128.27 (2C), 128.26, (2C), 128.2 (2C), 128.1 (2C), 127.83 (2C), 127.80, 127.6 (3C), 127.5 (2C), 104.2, 82.0, 79.3, 75.3, 74.6, 74.5, 73.7, 73.5, 73.4, 73.1, 68.6; HMRS (ESI^+): *m/z* calcd for $[C_{36}H_{38}O_7Na]$ 605.2515, found 605.2511, Δ = -0.7 ppm.

6.2.16 2-[(2′,3′,4′,6′-Tetra-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl)oxy]acetaldehyde 373

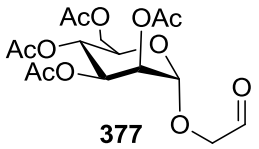


373

Prepared according to the general procedure with the exception that Na_2CO_3 (650 mol-%) was used in the diol cleavagee step. Colourless liquid (691 mg, 86%).

R_f (50% EtOAc/hexanes) = 0.82; $[\alpha]_D$ = -17.1° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2956, 2930, 2887, 2858, 1739, 1473, 1464, 1390, 1256, 1167, 1005; ^1H NMR (500 MHz, CD_3CN, 78 °C): δ 9.70 (app. t, 1H, *J* = 1.3 Hz), 4.43 (d, 1H, *J* = 5.2 Hz), 4.24 (dd, 1H, *J* = 17.4 Hz, 1.4 Hz), 4.19 (t, 1H, *J* = 2.4 Hz), 4.16 (dd, 1H, *J* = 17.4 Hz, 1.2 Hz), 4.00 (dd, 1H, *J* = 7.4 Hz, 5.3 Hz), 3.95-3.92 (m, 1H), 3.79 (dd, 1H, *J* = 10.6 Hz, 5.8 Hz), 3.72 (dd, 1H, *J* = 7.4 Hz, 2.2 Hz), 3.64-3.61 (m, 1H), 0.98 (s, 9H), 0.97 (s, 9H), 0.95 (s, 9H), 0.93 (s, 9H), 0.20 (s, 3H), 0.18 (s, 6H), 0.17 (s, 3H), 0.151 (s, 3H), 0.146 (s, 3H), 0.084 (s, 3H), 0.078 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN, 78 °C): δ 201.7, 104.8, 78.1, 76.9, 75.2, 74.0, 71.8, 63.5, 27.3 (3C), 27.0 (3C), 26.9 (3C), 26.7 (3C), 19.7, 19.5, 19.2, 19.1, -2.6, -3.0, -3.4, -3.5, -3.6, -3.8, -4.6, -4.7; HRMS (ESI^-): *m/z* calcd. for $[C_{32}H_{70}O_7Si_4+H]$ 679.4277; found 679.4297, Δ = 3.0 ppm.

6.2.17 2-[(2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-mannopyranosyl)oxy]-acetaldehyde 377

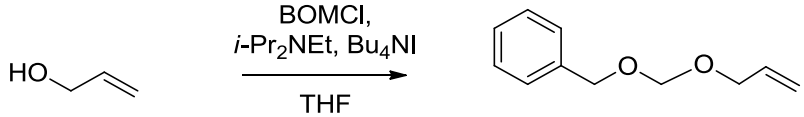


377

Prepared according to the general procedure with the exception that Na_2CO_3 (320 mol-%) was used in the diol cleavagee step. Brown foam (1.379 g, 93%). ^{1}H and ^{13}C NMR-data matched those reported in the literature. (148)

R_f (80% EtOAc/hexanes) = 0.41; $[\alpha]_D$ = +13.2 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3063, 2959, 2848, 1748, 1434, 1371, 1228, 1144, 1050; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.65 (t/dd, 1H, *J* = 0.7/0.8 Hz), 5.30 (dd, 1H, *J* = 9.5 Hz, 3.5 Hz), 5.29 (dd, 1H, *J* = 3.5 Hz, 1.8 Hz), 5.22 (app. t, 1H, *J* = 9.5 Hz), 4.82 (d, 1H, *J* = 1.5 Hz), 4.20 (dd, 1H, *J* = 17.7 Hz, 0.7 Hz), 4.21-4.18 (m, 1H), 4.15 (dd, 1H, *J* = 17.7 Hz, 1.0 Hz), 4.05-4.02 (m, 2H), 2.08 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.0, 170.3, 169.64, 169.59, 169.45, 98.1, 72.9, 69.1, 69.0, 68.6, 65.8, 62.2, 20.6, 20.43 (2C), 20.39; HRMS (ESI$^+$): *m/z* calcd. for [$C_{16}H_{22}O_{11}$·Na] 413.1060; found 413.1040, Δ = -4.8 ppm.

6.2.18 Allyloxymethyl benzyl ether 397 (184)



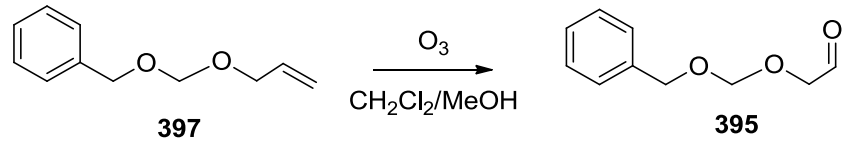
396 **397**

To a stirred solution of allyl alcohol **396** (0.59 mL, 498 mg, 8.58 mmol, 100 mol-%) in THF (13 mL) at 0 °C were added *i*-Pr_2NEt (2.99 mL, 2.19 g, 17.2 mmol, 200 mol-%) and Bu_4NI (254 mg, 0.687 mmol, 8 mol-%). After 5 min, BOMCl (60 % solution, 2.4 mL, 17.2 mmol, 200 mol-%) was added via dropping funnel during 15 min. Funnel was rinsed with THF (7 mL). The reaction mixture was allowed to warm at rt and stirring was continued for additional 18 h. The mixture was poured to sat. aq. NH_4Cl (200 mL). Et_2O (50 mL) was added and phases were separated. Aq. phase was exracted with Et_2O (2 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (initially 10% EtOAc/hexanes, finally 20% EtOAc/hexanes), followed by distillation under reduced pressure (0.1 mbar, bp. 75 °C, oil bath 130-140 °C) afforded product **397** as a colourless liquid (1.19 g, 78%). ^{1}H and ^{13}C NMR-data matched those reported in the literature. (185)

R_f (50% EtOAc/hexanes)= 0.77; bp = 75 °C (0.1 mbar); IR (film, cm^{-1}): 3066, 3032, 2940, 2883, 1727, 1648, 1606, 1497, 1455, 1381, 1173, 1107, 1050; ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.95 (ddt, 1H, *J* = 17.2 Hz, 10.4 Hz, 5.6 Hz), 5.32 (app. dq, 1H, *J* = 17.2 Hz, 1.6 Hz), 5.22 (app. dq, 1H, *J* = 10.4 Hz, 1.6 Hz), 4.80 (s, 2H), 4.64 (s, 2H), 4.14 (dt, 2H, *J* = 5.6 Hz, 1.4 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 137.8, 134.3, 128.3 (2C), 127.8 (2C), 127.6, 117.0, 93.7, 69.3, 68.3; HMRS (ESI^+): *m/z* calcd for [$C_{11}H_{14}O_2Na$] 201.0891, found 201.0887, Δ = -2.0 ppm.

6.2.19 Benzyloxymethoxy acetaldehyde 395 (185)



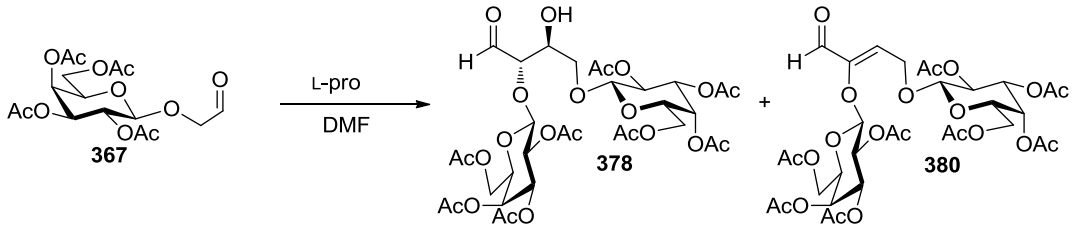
397 **395**

To a stirred solution of **397** (517 mg, 2.8 mmol, 100 mol-%) in CH_2Cl_2 (8 mL) and MeOH (8 mL) at -78 °C, ozone was bubbled through solution until light blue colour was obtained (*ca.* 3 min). Oxygen gas was then bubbled through solution until solution was again colourless (*ca.* 3 min). Me_2S (0.16 mg, 2.2 mmol, 78 mol-%) was added. Mixture was stirred at -78 °C for additional 1 h before solvents were evaporated. Purification of the residue by flash cromatography (initially 30% EtOAc/hexanes, finally 50% EtOAc/hexanes) afforded aldehyde **395** as colourless liquid (422 mg, 83%).

R_f (50% EtOAc/hexanes)= 0.48; IR (film, cm^{-1}): 3064, 3032, 2945, 2888, 1736, 1455, 1383, 1172, 1120, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (br s, 1 H), 7.39-7.29 (m, 5H), 4.85 (s, 2H), 4.66 (s, 2H), 4.23 (d, 2H, *J* = 0.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 137.2, 128.5 (2C), 127.91, 127.86 (2C), 95.0, 73.3, 70.0; HMRS (ESI^+): *m/z* calcd for [$C_{10}H_{12}O_3Na$] 203.0684, found 203.0683, Δ = - 0.5 ppm.

6.3 General Procedures for Aldol Dimerization of Aldehydes

6.3.1 General Procedure for Aldol Dimerization of Aldehyde 367



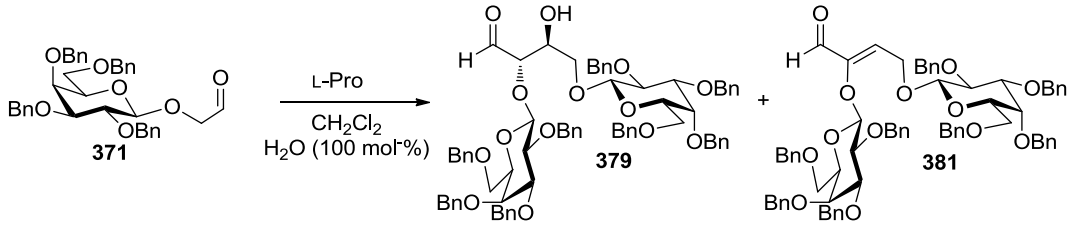
367 **378** **380**

To a stirred solution of **367** (57 mg, 0.128 mmol, 100 mol-%) in DMF (0.15 mL) at rt was added L-proline (2.0 mg, 0.013 mmol, 10 mol-%). The mixture was stirred and progress of reaction was monitored by ^{1}H NMR. After two days, percentage of compounds in reaction mixture was: aldehyde **367** 24%, dimer

product **378** 67% and condensation product **380** 9%. (When longer reaction time was used, the portion of dimer product **378** decreased while the portion of condensation product **380** increased.) The reaction was quenched by adding H_2O (5 mL). Aq. phase was extracted with Et_2O (3 x 5 mL), dried over Na_2SO_4, and concentrated in vacuo. The aq. phase was extracted with Et_2O (3 x 5 mL), dried over Na_2SO_4, and concentrated in vacuo. However, the product **378** could not be isolated in a pure form by silica gel chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): characteric peaks for dimer **378**: δ 9.49 (s, 1H), aldehyde **367**: δ 9.70 (m, 1H), condensation product **380**: 9.26 (s, 1H), 6.21 (dd, 1H, *J* = 6.4 Hz , 5.3 Hz); HRMS (ESI$^+$): *m/z* calcd. for [$C_{32}H_{44}O_{22}$·Na] 803.2222; found 803.2230, Δ = -2.4 ppm.

6.3.2 General Procedure for Aldol Dimerization of Aldehyde 371

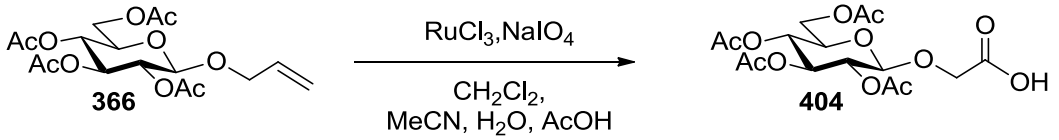


To stirred solution of **371** (18 mg, 0.031 mmol, 100 mol-%) in CH_2Cl_2 (0.15 mL) at rt was added L-proline (1.0 mg, 0.009 mmol, 29 mol-%) and H_2O (0.63 µL, 0.61 mg, 0.035 mmol, 100 mol-%). The mixture was stirred and progress of reaction was monitored by ^{1}H NMR. After two days, percentage of compounds in reaction mixture was: aldehyde **371** 17% dimer product **379** 73% and condensation product **381** 10%. When longer reaction time was used, the portion of dimer product **379** decreased while the portion of condensation product **381** increased. The reaction was quenched by adding H_2O (5 mL). Aq. phase was extracted with Et_2O (3 x 5 mL), dried over Na_2SO_4, and concentrated in vacuo. The aq. phase was extracted with Et_2O (3 x 5 mL), dried over Na_2SO_4, and concentrated in vacuo. However, the product **379** could not be isolated in a pure form by silica gel chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): characteric peaks for dimer **379**: δ 9.61 (d, 1H, *J* = 1.4 Hz), aldehyde **371**: δ 9.74 (m, 1H), condensation product **381**: 9.19 (s, 1H), 6.21 (dd, 1H, *J* = 6.5 Hz, 5.2 Hz); HRMS (ESI$^+$): *m/z* calcd. for [$C_{72}H_{76}O_{14}$·Na] 1187.5133; found 1187.5140, Δ = 0.6 ppm.

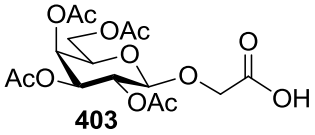
6.4 Synthesis of Saccharide Based Dienes

6.4.1 General Procedure for the Preparation of Saccharide Based Carboxylic Acids (188)



To a stirred solution of **366** (3.91 g, 10.1 mmol, 100 mol-%) in MeCN (25 mL), CH_2Cl_2 (20 mL), H_2O (10 mL) and AcOH (10mL) at rt was added $NaIO_4$ (10.1 g, 47.3 mmol, 470 mol-%), followed by addition of $RuCl_3 \cdot H_2O$ (103 mg, 0.403 mmol, 4 mol-%) over 5 min. The mixture became brown and heat formation was observed. The mixture was stirred under an air atmosphere for 1.5 h, and then concentrated in vacuo. The residue was suspended with CH_2Cl_2 (20 mL) and filtered trough celite with CH_2Cl_2 (20 mL). The filtrate was extracted with H_2O (2 x 20 mL) and brine (20 mL), and dried over Na_2SO_4. Concentration in vacuo afforded desired product **404**. The crude product was used in the next reaction step without further purification.

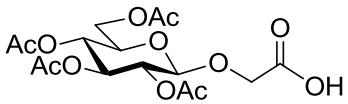
6.4.2 2-Acetic acid-2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranoside 403



Prepared according to the general procedure. White foam (1.82 g, quant.).

R_f (50% EtOAc/hexanes) = 0.28; $[\alpha]_D$ = -129° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3444 (broad), 2982, 2941, 1748, 1644, 1334, 1371, 1226, 1176, 1081; 1H NMR (400 MHz, CDCl3): δ 5.41 (dd, 1H, J = 3.4 Hz, 1.0 Hz), 5.25 (dd, 1H, J = 10.5 Hz, 8.0 Hz), 5.06 (dd, 1H, J = 10.5 Hz, 3.4 Hz), 4.62 (d, 1H, J = 8.0 Hz), 4.37 (s, 1H), 4.36 (s, 1H) 4.18 (dd, 1H, J = 11.4 Hz, 6.7 Hz), 4.13 (dd, 1H, J = 11.4 Hz, 6.7 Hz), 3.96 (td, 1H, J = 6.6 Hz, 1.0 Hz), 2.17 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 170.4, 170.2, 170.1, 169.8, 100.7, 71.0, 70.5, 68.4, 66.9, 64.9, 61.2, 20.7, 20.57, 20.56, 20.5; HRMS (ESI^+): *m/z* calcd. for $[C_{16}H_{22}O_{12} \cdot Na]$ 429.1009; found 429.0989, Δ = -4.5 ppm.

6.4.3 2-Acetic acid-2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranoside 404

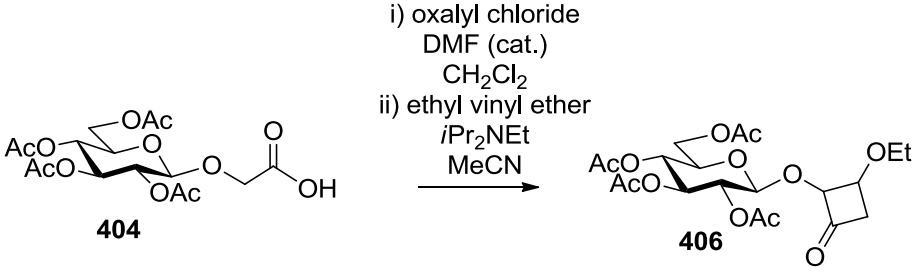


404

Prepared according to the general procedure. White crystals (3.87 g, 95%). ^{1}H and ^{13}C NMR data matched those reported in the literature. (201)

R_f (80% EtOAc/hexanes) = 0.09 ; mp = 138 - 139 °C; $[\alpha]_D$ = -186° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3493, 3210, 2962, 2925, 1754, 1643, 1435, 1371, 1223, 1170, 1064, 1041; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.25 (app. t, 1H, *J* = 9.4 Hz), 5.09 (app. t, 1H, *J* = 9.8 Hz), 5.05 (dd, 1H, *J* = 9.5 Hz, 7.8 Hz), 4.66 (d, 1H, *J* = 7.8 Hz), 4.34 (s, 2H), 4.26 (dd, 1H, *J* = 12.4 Hz, 4.8 Hz), 4.15 (dd, 1H, *J* = 12.4 Hz, 2.5 Hz), 3.73 (ddd, 1H, *J* = 9.8 Hz, 4.8 Hz, 2.5 Hz), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 173.1, 170. 7, 170.2, 169.6, 169.4, 100.1, 72.4, 71.8, 70.8, 68.2, 64.7, 61.7, 20.5, 20.4, 20.3 (2C); HRMS (ESI^-): *m/z* calcd. for [$C_{16}H_{22}O_{12}$-1H] 405.1033; found 405.1035, Δ = 0.5 ppm.

6.4.4 General Procedure for the Preparation of Saccharide Based Cyclobutanones (186) (88)

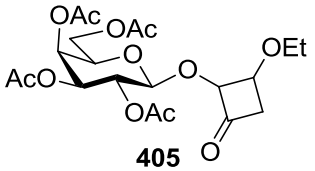


404 **406**

To a stirred solution of acid **404** (1.68 g, 4.14 mmol, 100 mol-%) in CH_2Cl_2 (20 mL) at rt was added DMF (0.10 mL, 94 mg, 1.29 mmol, 30 mol-%). The solution was cooled to 0 °C and oxalyl chloride (1.44 mL, 2.15 g 16.6 mmol, 400 mol-%) was added over 10 min. Gas formation was observed. The reaction mixture was stirred for 20 min and then allowed to warm to rt. The mixture was stirred for additional 2 h 10 min and then concentrated in vacuo. Toluene (20 mL) and CH_2Cl_2 (20 mL) were added, and the resulting solution was concentrated. This procedure was repeated twice while maintaining the mixture under an argon atmosphere all the time. To the stirred solution of residue in MeCN (8 mL) at 0 °C was added a mixture of ethyl vinyl ether (0.90 mL, 680 mg, 9.36 mmol, 230 mol-%) and *i*PrNEt$_2$ (0.87 mL, 643 mg, 4.97 mmol, 120 mol-%) in MeCN (1 mL) dropwise over a period of 10 min. The formation of white fog was observed. The mixture was stirred for 5 min, heated to 70 °C and stirred for additional 30 min. During this time, the mixture turned first orange and then darker brown. The reaction mixture was allowed to cool to rt and then concentrated in vacuo.

The residue was suspended with Et_2O (3 x 15 mL) and filtered trough celite with Et_2O (5 mL). The filtrate was concentrated and purification of the residue by flash chromatography (initially 50% EtOAc/hexanes, finally 80% EtOAc/hexanes) afforded cyclobutanone **406** (1.52 g, 80%) as a yellowish foam.

6.4.5 2-Ethoxy-4-oxocyclobutoxy-2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranoside 405

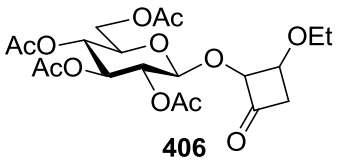


405

Prepared according to the general procedure. Flash chromatography: 20% EtOAc/hexanes was used. Tan oil (800 mg, 89%). ^{1}H NMR-data showed a mixture of two diastereomers, which were both assumed to possess the *trans*-configuration. Analytical data was obtained for pure isomers, but a mixture of isomers was used in the next step as the absolute stereochemistry of the cyclobutane ring was inconsequential.

R_f (50% EtOAc/hexanes) = 0.21 (first eluting isomer), 0.18 (second eluting isomer); IR (film, cm^{-1}): 3483, 2979, 2938, 1791, 1750, 1371, 1225, 1079, 1061; ^{1}H NMR (400 MHz, $CDCl_3$): First eluting isomer δ 5.39 (dd, 1H, *J* = 3.4 Hz, 1.1 Hz), 5.20 (dd, 1H, *J* = 10.5 Hz, 8.0 Hz), 5.01 (dd, 1H, *J* = 10.5 Hz, 3.4 Hz), 4.90 (ddd, 1H, *J* = 5.3 Hz, 3.5 Hz, 2.3 Hz), 4.73 (d, 1H, *J* = 8.0 Hz), 4.13 (d, 1H, *J* = 6.6 Hz), 4.20-4.14 (m, 2H), 3.91 (dt, 1H, *J* = 6.6 Hz, 1.1 Hz), 3.67-3.56 (m, 2H), 2.95 (ddd, 1H, *J* = 17.6 Hz, 8.0 Hz, 2.3 Hz), 2.83 (ddd, 1H, *J* = 17.6 Hz, 7.4 Hz, 3.5 Hz), 2.14 (s, 3H), 2.07 (s, 3H) 2.04 (s, 3H) 1.97 (s, 3H), 1.24 (t, 3H, *J* = 7.0 Hz). Second eluting isomer: δ 5.37 (dd, 1H, *J* = 3.5 Hz, 1.1 Hz), 5.21 (dd, 1H, *J* = 10.4 Hz, 8.0 Hz), 5.00 (dd, 1H, *J* = 10.4 Hz, 3.5 Hz), 4.88 (ddd, 1H, *J* = 5.7 Hz, 3.5 Hz, 2.3 Hz), 4.75 (d, 1H, *J* = 8.0 Hz), 4.25-4.08 (m, 3H), 3.88 (dt, 1H, *J* = 6.6 Hz, 1.1 Hz), 3.63 (dd, 1H, *J* = 9.4 Hz, 7.1 Hz), 3.57 (dd, 1H, *J* = 9.4 Hz, 7.1 Hz), 2.92 (ddd, 1H, *J* = 17.7 Hz, 8.2 Hz, 2.4 Hz), 2.75 (ddd, 1H, *J* = 17.7 Hz, 7.0 Hz, 3.7 Hz), 2.15 (s, 3H), 2.06 (s, 3H) 2.04 (s, 3H) 1.97 (s, 3H), 1.25 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): First eluting isomer δ 201.6, 170.3, 170.1, 170.0, 169.7, 100.7, 91.1, 70.9, 70.7, 70.2, 68.5, 66.8, 65.7, 61.1, 45.8, 20.7, 20.6 (2C), 20.5, 15.1. Second eluting isomer δ 200.0, 170.3, 170.2, 170.0, 169.3, 99.0, 91.4, 70.9 (2C), 70.7, 68.6, 66.9, 65.8, 61.4, 44.7, 20.7, 20.6 (2C), 20.5, 15.1; HRMS (ESI$^+$): *m/z* calcd. for [$C_{20}H_{28}O_{12}$·Na] 483.1478; found 483.1476, Δ = -0.4 ppm.

6.4.6 2-Ethoxy-4-oxocyclobutoxy- 2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranoside 406

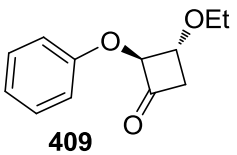


406

Prepared according to the general procedure. Yellowish foam (1.52 g, 80%). ^{1}H NMR-data showed a mixture of two diastereomers, which were both assumed to possess the *trans*-configuration. Analytical data was obtained for pure isomers, but a mixture of isomers was used in the next step as the absolute stereochemistry of the cyclobutane ring was inconsequential.

R_f (80% EtOAc/hexanes) = 0.51 (first eluting isomer), 0.48 (second eluting isomer); IR (film, cm^{-1}): 3062, 2977, 2941, 2897, 1751, 1628, 1435, 1370, 1225, 1042; ^{1}H NMR (500 MHz, $CDCl_3$): First eluting isomer δ 5.16 (app t, 1H, *J* = 9.5 Hz), 5.03 (dd, 1H, *J* = 10.0 Hz, 9.6 Hz), 4.95 (dd, 1H, *J* = 9.6 Hz, 8.0 Hz), 4.86 (ddd, 1H, *J* = 5.3 Hz, 3.7 Hz, 2.5 Hz), 4.76 (d, 1H, *J* = 8.0 Hz), 4.19 (dd, 1H, *J* = 12.3 Hz, 4.6 Hz), 4.14-4.10 (m, 2H), 3.68 (ddd, 1H, *J* = 10.0 Hz, 4.6 Hz, 2.7 Hz), 3.62 (dd, 1H, *J* = 9.5 Hz, 7.0 Hz), 3.54 (dd, 1H, *J* = 9.5 Hz, 7.0 Hz), 2.90 (ddd, 1H, *J* = 17.6 Hz, 8.2 Hz, 2.5 Hz), 2.79 (ddd, 1H, *J* = 17.6 Hz, 7.3 Hz, 3.7 Hz), 2.03 (s, 3H), 2.00 (s, 3H) 1.97 (s, 3H) 1.95 (s, 3H), 1.19 (t, 3H, *J* = 7.0 Hz). Second eluting isomer δ 5.16 (app t, 1H, *J* = 9.4 Hz), 5.03 (dd, 1H, *J* = 10.0 Hz, 9.5 Hz), 4.97 (dd, 1H, *J* = 9.5 Hz, 8.0 Hz), 4.85 (ddd, 1H, *J* = 5.5 Hz, 3.8 Hz, 2.4 Hz), 4.82 (d, 1H, *J* = 8.0 Hz), 4.21-4.13 (m, 3H), 3.64 (ddd, 1H, *J* = 10.0 Hz, 5.0 Hz, 2.8 Hz), 3.60 (dd, 1H, *J* = 9.5 Hz, 7.0 Hz), 3.54 (dd, 1H, *J* = 9.5 Hz, 7.0 Hz), 2.90 (ddd, 1H, *J* = 17.7 Hz, 8.2 Hz, 2.4 Hz), 2.72 (ddd, 1H, *J* = 17.7 Hz, 6.9 Hz, 3.8 Hz), 2.05 (s, 3H), 2.02 (s, 3H) 1.99 (s, 3H) 1.96 (s, 3H), 1.22 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): First eluting isomer δ 201.3, 170.3, 169.9, 169.3, 169.2, 99.8, 90.8, 72.5, 72.0, 71.0, 70.1, 68.2, 65.6, 61.7, 45.7, 20.53, 20.49, 20.4 (2C), 15.0. Second eluting isomer δ 200.1, 170.4, 170.0, 169.3, 169.1, 98.1, 91.0, 72.7, 71.9, 71.1, 70.9, 68.3, 65.7, 61.8, 44.7, 20.6, 20.5, 20.4 (2C), 15.0; HRMS (ESI$^+$): *m/z* calcd. for [$C_{20}H_{28}O_{12}$·Na] 483.1478; found 483.1486, Δ = 1.7 ppm.

6.4.7 2-phenoxy-3-ethoxy-cyclobutanone 409

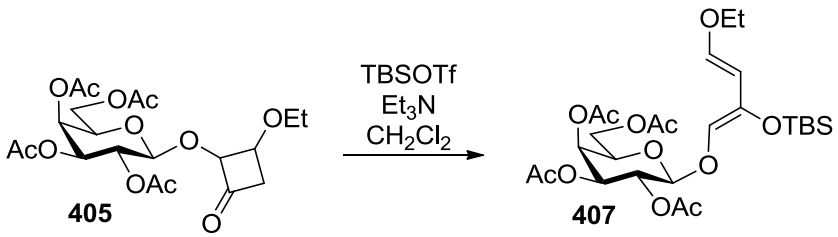


409
(racemic)

Prepared according to the according to the general procedure. Flash chromatography: 20% EtOAc/hexanes was used. Tan oil (800 mg, 89%). ^{1}H NMR-data showed a 93: 7 ratio of the *trans*- and *cis* -diastereomers, respectively.

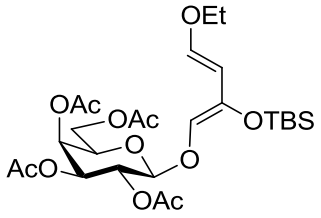
For the major *trans*-isomer: R_f (50% EtOAc/hexanes) = 0.60; IR (film, cm^{-1}): 2978, 2929, 2894, 1798, 1598, 1591, 1495, 1242, 1226, 1119, 1104, 1026; ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (dd, 2H, *J* = 8.7 Hz, 7.4 Hz), 7.06 (dd, 2H, *J* = 8.7 Hz, 0.9 Hz), 7.02 (tt, 1H, *J* = 7.4 Hz, 0.9 Hz), 5.28 (ddd, 1H, *J* = 5.4 Hz, 3.7 Hz, 2.5 Hz), 4.31 (ddd, 1H, *J* = 8.0 Hz, 7.2 Hz, 5.4 Hz), 3.65 (dd, 1H, *J* = 7.0 Hz, 2.5 Hz), 3.62 (dd, 1H, *J* = 7.0 Hz, 2.5 Hz), 3.09 (ddd, 1H, *J* = 17.6 Hz, 8.0 Hz, 2.5 Hz), 2.95 (ddd, 1H, *J* = 17.6 Hz, 7.2 Hz, 3.7 Hz), 1.28 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.8, 157.2, 129.5 (2C), 122.2, 115.7 (2C), 91.0, 70.5, 66.0, 45.8, 15.1; HRMS (ESI^+): *m/z* calcd. for $[C_{12}H_{14}O_3Na]$ 229.0841; found 229.0835, Δ = -2.4 ppm. For the minor *cis*-isomer: R_f (50% EtOAc/hexanes) = 0.48; ^1H NMR (250 MHz, $CDCl_3$): δ 7.30 (dd, 2H, *J* = 9.2 Hz, 8.0 Hz), 7.06-6.98 (m, 3H), 5.17 (ddd, 1H, *J* = 6.1 Hz, 4.3 Hz, 1.8 Hz), 4.53 (app. td, 1H, *J* = 6.1 Hz, 2.1 Hz), 3.65 (dd, 1H, *J* = 7.0 Hz, 2.5 Hz), 3.62 (dd, 1H, *J* = 7.0 Hz, 2.5 Hz), 3.16 (ddd, 1H, *J* = 17.7 Hz, 6.3 Hz, 4.3 Hz), 2.81 (app. dt, 1H, *J* = 17.7 Hz, 1.8 Hz), 1.28 (t, 3H, *J* = 7.0 Hz); HRMS (ESI^-): *m/z* calcd. for $[C_{12}H_{14}O_3H]$ 207.1021; found 207.1017, Δ = -2.2 ppm.

6.4.8 General Procedure for the Preparation of Saccharide Dienes (88)



To a stirred solution of cyclobutanone **405** (1.07 g, 2.33 mmol, 100 mol-%) in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (1.33 mL, 0.966 g, 9.55 mmol, 410 mol-%), followed by the addition of TBSOTf (1.07 mL, 1.32 g, 4.66 mmol, 200 mol-%) over 5 min. The reaction mixture was yellowish, but became slowly reddish. After 15 min, the reaction mixture was allowed to warm to rt and stirred for additional 45 min. Then, Et_3N (5.0 mL) and sat. aq. $NaHCO_3$ (20 mL) were added and the phases were separated. The organic phase was washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 30% EtOAc/hexanes containing 2 *v*-% Et_3N, finally 40% EtOAc/hexanes containing 2 *v*-% Et_3N) afforded diene **407** (752 mg, 56%) as a yellowish solid.

6.4.9 (1*E*,3*Z*)- 1-Ethoxy-3-(*tert*-butyl-dimethylsilanyloxy)buta-1,3-dien-1-yl -4- (2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranoside 407

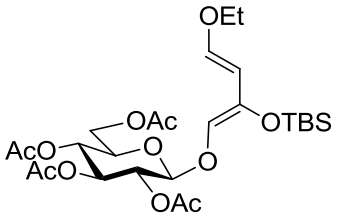


407

Prepared according to the general procedure. Yellowish solid (752 mg, 56%).

R_f (50% EtOAc/hexanes) = 0.54; $[\alpha]_D$ = +86.1° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2956, 2932, 2887, 2859, 1753, 1627, 1370, 1250, 1221, 1079; ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (d, 1H, *J* = 12.3 Hz), 5.70 (s, 1H), 5.36 (app d, 1H, *J* = 3.1 Hz), 5.27 (dd, 1H, *J* = 10.2 Hz, 8.0 Hz), 5.17 (d, 1H, *J* = 12.3 Hz), 5.00 (dd, 1H, *J* = 10.2 Hz, 3.4 Hz), 4.67 (d, 1H, *J* = 8.0 Hz), 4.16-4.09 (m, 2H), 3.92 (td, 1H, *J* = 6.7 Hz, 0.8 Hz), 3.74 (q, 2H, *J* = 7.1 Hz), 2.14 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.26 (t, 3H, *J* = 7.1 Hz), 0.94 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 170.13, 170.05, 169.0, 146.8, 134.9, 125.4, 101.4, 100.4, 71.3, 70.9, 68.5, 66.9, 65.5, 61.1, 25.9 (3C), 20.7, 20.6 (2C) 20.5, 18.4, 14.7, -4.37, -4.43; HRMS (ESI^+): *m/z* calcd. for [$C_{26}H_{42}O_{12}SiNa$] calcd. 597.2343; found 597.2347, Δ = 0.7 ppm.

6.4.10 ((1*E*,3*Z*)- 1-Ethoxy-3-(*tert*-butyl-dimethylsilanyloxy)buta-1,3-dien-1-yl -4- (2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranoside 165



165

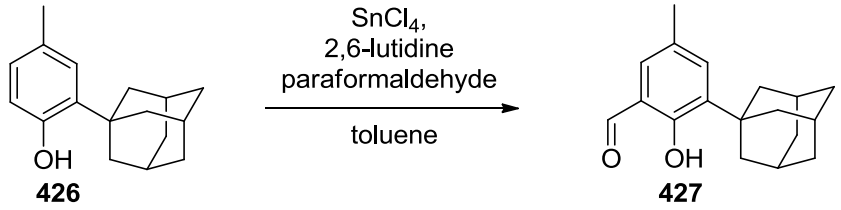
Prepared according to the general procedure. Yellowish solid (535 mg, 40%).

R_f (50% EtOAc/hexanes) = 0.68; mp = 113-115 °C; $[\alpha]_D$ = +35.2° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2957, 2932, 2859, 1759, 1637, 1366, 1222, 1164, 1127, 1069, 1042; ^1H NMR (250 MHz, $CDCl_3$): δ 6.65 (d, 1H, *J* = 12.2 Hz), 5.71 (s, 1H), 5.23-5.04 (m, 4H), 4.71 (d, 1H, *J* = 7.6 Hz), 4.24 (dd, 1H, *J* = 12.3 Hz, 4.5 Hz), 4.14 (dd, 1H, *J* = 12.3 Hz, 2.6 Hz), 3.74 (q, 1H, *J* = 7.0 Hz), 3.75-3.68 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.27 (t, 3H, *J* = 7.0 Hz), 0.94 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.4, 170.0, 169.1, 168.9, 146.7, 134.7, 125.4, 101.2, 99.8, 73.0, 71.9, 71.0, 67.9, 65.4, 61.6, 25.8 (3C), 20.50, 20.48, 20.4 (2C),

18.3, 14.6, -4.48, -4.53; HRMS (ESI$^+$): *m/z* calcd. for [$C_{26}H_{42}O_{12}SiNa$] 575.2524; found 575.2529, Δ = 0.9 ppm.

6.5 Synthesis of Chromium Catalysts (183) (181)

6.5.1 3-Adamantyl-2-hydroxy-5-methyl-benzaldehyde 427

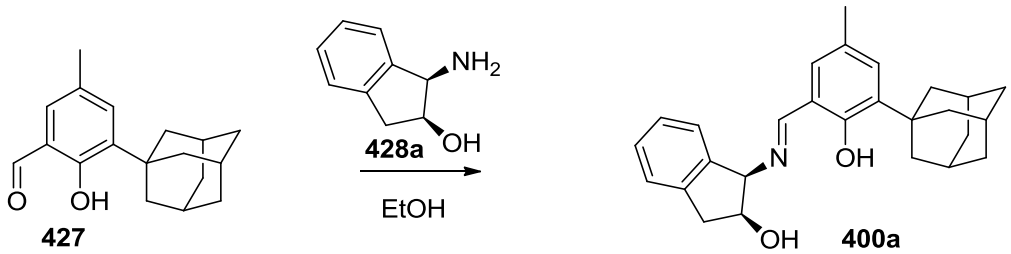


426 **427**

To a stirred solution of 2-adamantyl-4-methyl phenol **426** (805 mg, 3.32 mmol, 100 mol-%) and 2,6-lutidine (0.3 mL, 283 mg, 2.64 mmol, 80 mol-%) in toluene (15 mL) at rt was added $SnCl_4$ (80 µL, 172 mg, 0.66 mmol, 20 mol-%) during 10 min. The colourless solution turned yellow and yellow precipitate formed during addition. The mixture was stirred for 20 min, before paraformaldehyde (1.19 g, 13.2 mmol, 400 mol-%) was added. The mixture was stirred additional 10 min, and then heated to 90-95 °C. Stirring was continued for 5 h 30 min, until the mixture was allowed to cool to rt. The reaction mixture was filtered trough mixture of celite and silica gel (1:2) with EtOAc (100 mL). The organic filtrate was washed with H_2O (50 mL), HCl (1M, 30 mL) and brine (30 mL), and dried over Na_2SO_4. Concentration of the residue afforded aldehyde **427** as yellowish crystals (870 mg, 98%). The crude product **427** was used in the next reaction without further purification. IR-, ^1H and ^{13}C NMR-data matched those reported in the literature. (183) (181)

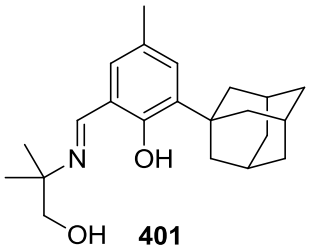
R_f (20% EtOAc/hexanes) = 0.69; mp =135-136 °C; IR (film, cm^{-1}): 3419, 2904, 2849, 1646, 1454, 1326, 1245; ^1H NMR (400 MHz, $CDCl_3$) δ 11.64 (br s, 1H), 9.82 (s, 1H), 7.27 (d, 2H, *J* = 2.2 Hz), 7.16 (dd, 1H, *J* = 2.2 Hz, 0.8 Hz), 2.32 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 2.09 (br s, 3H), 1.79-1.78 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 159.4, 138.1, 135.4, 131.2, 128.2, 120.3, 40.1 (3C), 36.95, 36.87 (3C), 28.9 (3C), 20.5; HRMS (ESI$^-$): *m/z* calcd. for [$C_{18}H_{21}O_2$ = M-H] calcd. 269.1542; found 269.1541, Δ = -0.2048 ppm.

6.5.2 General Prosedure for the Preparation of Imino Ligands



A stirred solution of aldehyde **427** (540 mg, 2.00 mmol, 100 mol-%) in EtOH (15 mL) was heated to 75 °C until complete dissolution occurred. (1*R*,2*S*)-amino-2-indanol **428a** (316 mg, 2.09 mmol, 105 mol-%) was added. The reaction mixture was stirred at 80 °C for 45 min, allowed to cool to rt, and allowed to stand for 3 h. Isolation of solid material by filtration, washing with cold EtOH (15 mL), and drying in vacuum afforded **400a** as yellow crystals (538 mg, 67%).

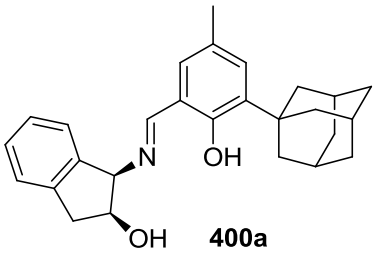
6.5.3 2-Adamantyl-[(1-hydroxy-2-methylpropan-2-yl)imino]methyl-4-methylphenol 401



Prepared according to the general procedure. Flash chromatography: 20% EtOAc/hexanes was used. Yellow foam (351 mg, 67%).

R_f (50% EtOAc/hexanes) = 0.74; IR (film, cm^{-1}): 3424, 2969, 2904, 2849, 1630, 1455, 1270, 1250, 1048; ^1H NMR (250 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.08 (d, 1H, *J* = 2.0 Hz), 6.94 (dd, 1H, *J* = 2.0 Hz, 0.5 Hz), 3.59 (s, 2H), 2.29 (s, 3H), 2.19-2.18 (m, 6H), 2.09 (br s, 3H), 1.81 (br s, 6H), 1.31 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.2, 158.7, 137.5, 130.5, 129.7, 126.5, 118.3, 71.2, 60.7, 40.5, 40.3 (3C), 37.1 (3C), 36.9, 29.0 (3C), 23.6, 20.6; HRMS (ESI^+): *m/z* calcd. for $[C_{22}H_{31}NO_2+H]$ 342.2433 ; found 342.2427, Δ = -1.8 ppm.

6.5.4 (1*R*,2*S*)-1-[3-Adamantyl]-2-hydroxy-5-methylbenzyliden-amino]indan-2-ol 400a

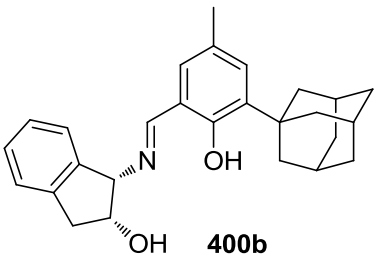


400a

Prepared according to the general procedure. Yellow crystals (538 mg, 67%). IR- and NMR-data matched those reported in the literature. (183) (181)

R_f (20% EtOAc/hexanes) = 0.31; mp = 120 – 122 °C; $[\alpha]_D^{20}$ = 71.8° (*c* 0.5, CH_2Cl_2); IR (film, cm^{-1}): 3443, 2905, 2849, 1653, 1455, 1247, 1087; ^1H NMR (400 MHz, $CDCl_3$) δ 13.06 (br s, 1H), 8.56 (s, 1H), 7.33-7.27 (m, 2H), 7.23 (td, 1H, *J* = 6.8 Hz, 0.8 Hz), 7.18-7.16 (m, 1H), 7.11 (d, 1H, *J* = 2.0 Hz), 6.98 (d, 1H, *J* = 1.5 Hz), 4.79 (d, 1H, *J* = 5.3 Hz), 4.69 (pentet, 1H, *J* = 5.6 Hz), 3.26 (dd, 1H, *J* = 16.0 Hz, 5.9 Hz), 3.13 (dd, 1H, *J* = 16.0 Hz, 5.0 Hz), 2.30 (s, 3H), 2.143-2.136 (m, 6H), 2.06 (br s, 3H), 1.77 (br s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.0, 158.3, 140.9, 140.8, 137.6, 131.2, 130.0, 128.5, 127.1, 127.0, 125.5, 124.9, 118.3, 75.8, 75.2, 40.3 (3C), 39.7 (3C), 37.1, 37.0, 29.1 (3C), 20.7; HRMS (ESI^+): *m/z* calcd. for $[C_{27}H_{31}NO_2H]$ calcd. 402.2433; found 402.2431, Δ = -0.50 ppm.

6.5.5 (1*S*,2*R*)-1-[3-Adamantyl]-2-hydroxy-5-methylbenzyliden-amino]indan-2-ol 400b



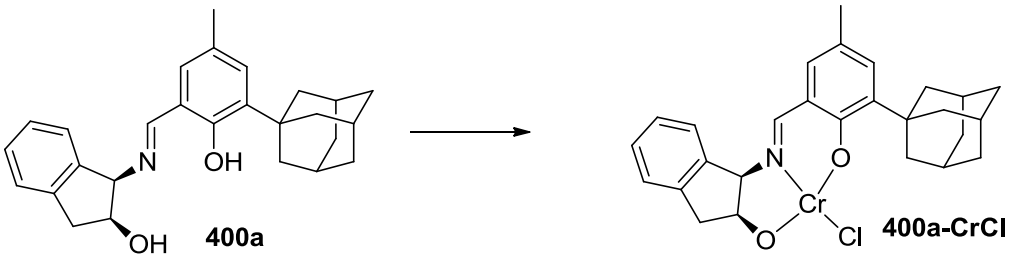
400b

Prepared according to the general procedure. Yellow crystals (450 mg, 70%). IR- and NMR-data matched those reported in the literature. (183) (181)

R_f (20% EtOAc/hexanes) = 0.31; mp = 123-124 °C; $[\alpha]_D^{20}$ = - 69.6° (*c* 0.5, CH_2Cl_2); IR (film, cm^{-1}): 3453, 2906, 2850, 1644, 1455, 1249, 1087; ^1H NMR (250 MHz, $CDCl_3$) δ 13.08 (br s, 1H), 8.56 (s, 1H), 7.34-7.29 (m, 2H), 7.23 (m, 2H), 7.11 (d, 1H, *J* = 2.0 Hz), 6.99-6.98 (m, 1H, *J* = 1.5 Hz), 4.79 (d, 1H, *J* = 5.3 Hz), 4.69 (pentet, 1H, *J* = 5.6 Hz), 3.27 (dd, 1H, *J* = 16.0 Hz, 5.9 Hz), 3.13 (dd, 1H, *J* = 16.0 Hz, 5.0 Hz), 2.31 (s, 3H), 2.17-2.14 (m, 7H), 2.06 (br s, 3H), 1.77 (br s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 158.3, 140.9, 140.8, 137.6, 131.2, 130.0, 128.4, 127.1, 127.0, 125.5, 124.9, 118.2, 75.8, 75.2, 40.3 (3C), 39.6 (3C), 37.1, 37.0, 29.1 (3C), 20.7; HRMS

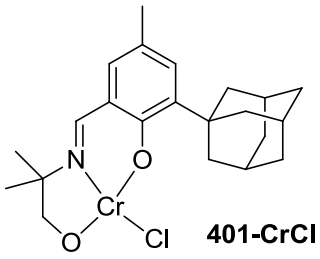
(ESI$^+$): *m/z* calcd. for [$C_{27}H_{31}NO_2H$] calcd. 402.2433; found 402.2434, Δ = 0.25 ppm.

6.5.6 General Prosedure for the Preparation of Tridentate Schiff Base Chromium(III) Catalysts (181)



To a stirred solution of **400a** (313 mg, 0.779 mmol, 100 mol-%) in CH_2Cl_2 (6 mL) at rt was added $CrCl_3{\cdot}(THF)_3$ (292 m g, 0.779 mmol, 100 mol-%) followed with dropwise addition of 2,6-lutidine (0.18 mL, 167 mg, 1.556 mmol, 200 mol-%). The mixture become brown and little bit greenish. The mixture was stirred for 3 h until diluted with CH_2Cl_2 (20 mL). The mixture was washed with H_2O (3x20mL) and brine (20 mL). Dried over Na_2SO_4 and concentrated. The residue was triturated with acetone (2 mL), filtered, and washed with acetone (5 mL). The crystals thus obtained were dried under an air atmosphere overnight affording catalyst complex **400a-CrCl** as brown crystals (180 mg, 62%).

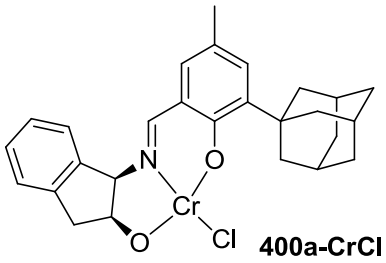
6.5.7 2-Adamantyl-[(1-hydroxy-2-methylpropan-2-yl)imino]methyl-4-methylphenol Chromium(III) Complex 401-CrCl



Prepared according to the general procedure. Brown solid (207 mg, 74%).

IR (film, cm^{-1}): 3424, 2967, 2904, 2849, 1619, 1540, 1433, 1302, 1231, 1167, 1036.

6.5.8 (1*R*,2*S*)-1-[3-Adamantyl]-2-hydroxy-5-methylbenzyliden-amino]indan-2-ol Chromium(III) Complex 400a-CrCl

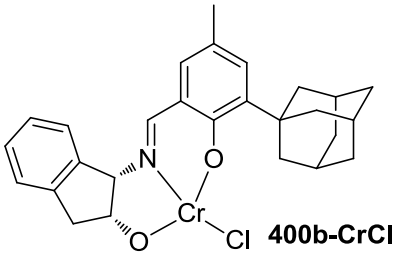


400a-CrCl

Prepared according to the general procedure. Brown crystals (180 mg, 62%)

IR (film, cm^{-1}): 3424, 2903, 2848, 1620, 1538, 1434, 1308, 1264, 1229, 1078.

6.5.9 (1*S*,2*R*)-1-[3-Adamantyl]-2-hydroxy-5-methylbenzyliden-amino]indan-2-ol Chromium(III) Complex 400b-CrCl



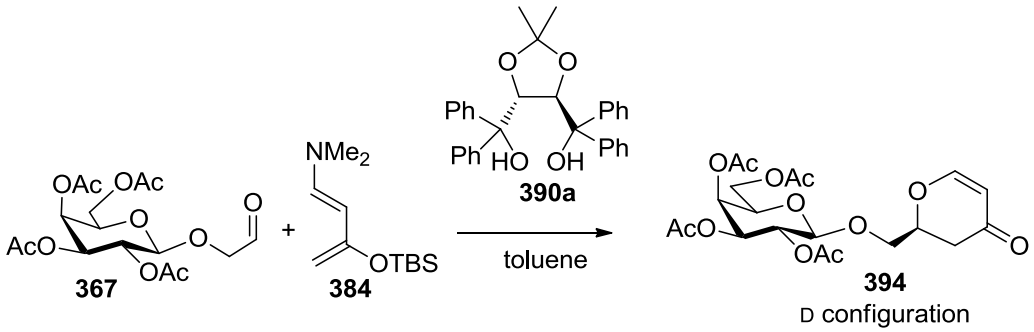
400b-CrCl

Prepared according to the general procedure. Brown crystals (137 mg, 47%)

IR (film, cm^{-1}): 3424, 2903, 2848, 1620, 1538, 1434, 1308, 1264, 1229, 1078.

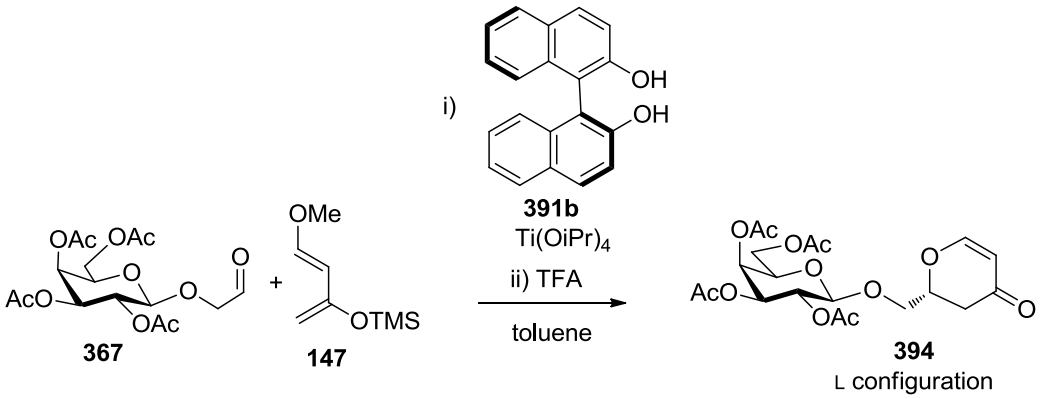
6.6 General Procedures for HDA Reactions

6.6.1 General Procedure for the HDA Reaction of Aldehyde 367 with Rawal's Diene 384



To a solution of aldehyde **367** (100 mg, 0.256 mmol, 100 mol-%) and TADDOL **390a** (24.2 mg, 0.005 mmol, 20 mol-%) in toluene (1.8 mL) at -78 °C was added dropwise Rawal's diene **384** (84 µl, 71.6 mg, 0.310 mmol, 120 mol-%). The reaction mixture was stirred for 5 h and allowed to warm to -20 °C during 18 h. The mixture was cooled back to -78 °C, AcCl (17.5 µl, 24.3 mg, 0.307 mmol, 120 mol-%) was added, and stirred for additional 4 h. The mixture was diluted with Et_2O (2 mL) and brine (3 mL), and allowed to warm to rt. Phases were separated and aq. phase was extracted with Et_2O (3 x 5 mL). Combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (initially 70% EtOAc/hexanes, finally 80% EtOAc/hexanes) afforded **394** as a yellowish oil (60 g, 51%) ^1H NMR showed a 80:20 ratio of the D- and L-diastereomers, respectively.

6.6.2 General Procedure for the HDA Reaction of Danishefsky's Diene 147 by Using BINOL Titanium Complexes

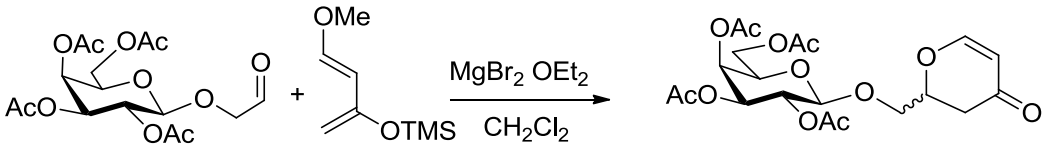


A mixture of $Ti(OiPr)_4$ (1M in CH_2Cl_2, 51 µL, 14.3 mg, 0.051 mmol, 21 mol-%), (*S*)-BINOL **391b** (16.2 mg, 0.057 mmol, 24 mol-%) and crushed molecular sieves (4Å, 100 mg) in toluene (0.8 mL) was stirred at 40 °C for 1 h until cooled to rt and solution of aldehyde **367** (94 mg, 0.24 mmol, 100 mol-%) in toluene (1.0 mL)

was added. The mixture was stirred at 0 °C and diene **147** (66 µL, 66 mg, 0.38 mmol, 160 mol-%) was added dropwise. The mixture was stirred for additional 50 min until TFA (0.03 µL, 45 mg, 0.39 mmol, 160 mol-%) in dry toluene (1.0 mL) was added. The stirring was continued for additional 2 h, until the reaction was quenched by adding sat. aq. $NaHCO_3$ (3 mL). Phases were separated and aq. phase was extracted with CH_2Cl_2 (3 x 4 mL). Combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (initially 60% EtOAc/hexanes, finally 80% EtOAc/hexanes) afforded **394** as a yellowish oil (41 g, 37%). ^1H NMR showed a 92:8 ratio of the D- and L-diastereomers, respectively.

The same procedure was used for aldehydes **371** and **395**.

6.6.3 General Procedure for the HDA Reaction of Danishesky's Diene 147 by Using Achiral Lewis Acids

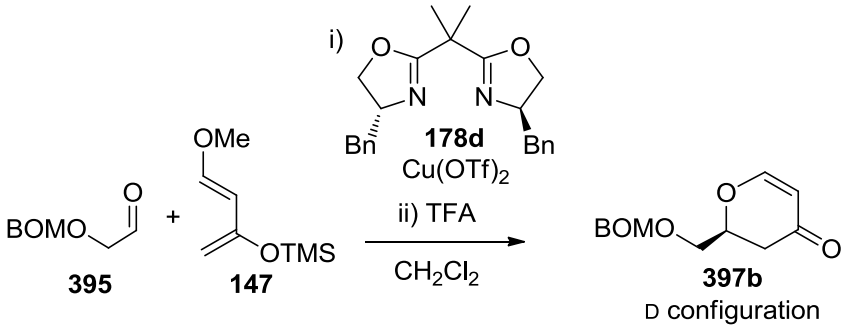


367 **147** **394**

To a stirred solution of aldehyde **367** (142 mg, 0.36 mmol, 100 mol-%) and $MgBr_2{\cdot}OEt_2$ (93 mg, 0.36 mmol, 100 mol-%) in CH_2Cl_2 (2.5 mL) at 0 °C was added Danishesky's diene **147** (140 µL,124 mg, 0.72 mmol, 200 mol-%). The reaction mixture was stirred for 30 h and allowed to warm to rt. The mixture was stirred for 2 h, until the reaction was quenched by adding sat. aq. NaCl (5 mL). Phases were separated and aq. phase was extracted with EtOAc (3 x 5 mL). Combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (initially 70% EtOAc/hexanes, finally 80% EtOAc/hexanes) afforded **394** as a yellowish oil (58 mg, 35%). ^1H NMR showed a 45:55 ratio of the D- and L-diastereomers, respectively.

The same procedure was used for aldehyde **371**.

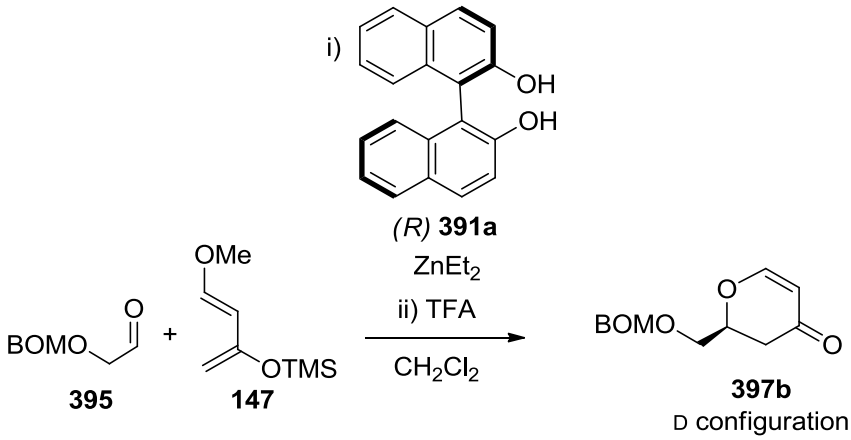
6.6.4 General procedure for the HDA Reaction of Danishesky's Diene 147 by using Bisoxazoline Copper Complexes



A mixture of $Cu(OTf)_2$ (19.1 mg, 0.053 mmol, 9.5 mol-%) and bisoxazoline **178d** (24.1 mg, 0.067 mmol, 12 mol-%) in CH_2Cl_2 (0.5 mL) was stirred at rt for 1 h 15 min until it was cooled to 0 °C, and BOM aldehyde **395** (100 mg, 0.56 mmol, 100 mol-%) in CH_2Cl_2 (0.75 mL) and Danishesky's diene **147** (200 µL, 177 mg, 0.93 mmol, 170 mol-%) were added. The reaction mixture was stirred for 41 h and TFA (150 µL, 240 mg, 2.1 mmol, 380 mol-%) in CH_2Cl_2 (5 mL) was added. The stirring was continued for additional 2 h, until the reaction was quenched by adding sat. aq. $NaHCO_3$ (5 mL). Phases were separated and aq. phase was extracted with CH_2Cl_2 (3 x 5 mL). Combined organic phases were was washed brine (10 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 30% EtOAc/hexanes, finally 40% EtOAc/hexanes) afforded **397a,b** as a yellowish oil (61 mg, 42%). The isolated material was determined to be 62:38 ratio of the D- and L-enantiomers, respectively by chiral HPLC analysis (Daicel Chiralpak OD, IPA:hex 10 %, 0.7 ml/min, λ = 254 nm, t_R(first eluting D-enantiomer) = 38 min, t_R(second eluting L- enantiomer) =45 min).

The same procedure was used for aldehyde **367** with exeption that the ratio of diastereomers was determined by ^{1}H NMR.

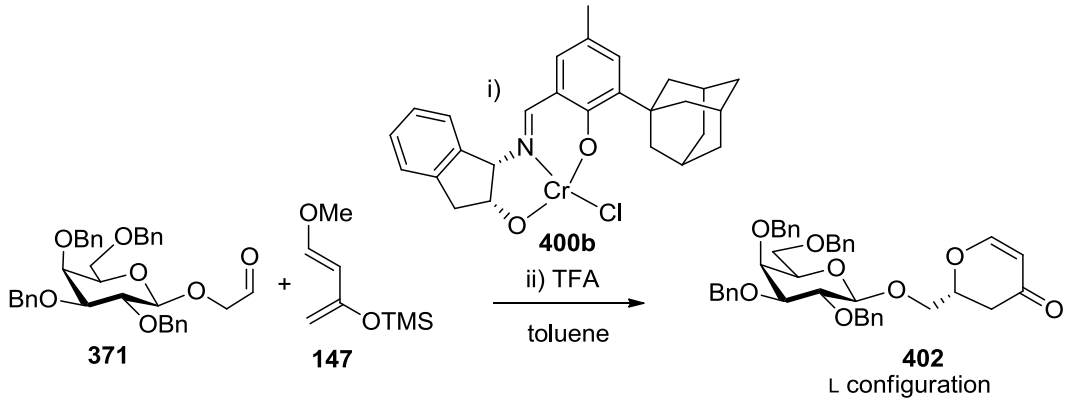
6.6.5 General procedure for the HDA Reaction of Danishesky's Diene 147 by using BINOL ZnR_2 or MgR_2 Complexes



A mixture of $ZnEt_2$ (1M in hexane) (28 µL 19.1 mg, 0.028 mmol, 10 mol-%), BINOL **391a** (8 mg, 0.028 mmol, 10 mol-%) and cruched molecular sieves (4 Å, 120 mg) in toluene (1 mL) was stirred at rt for 50 min until BOM aldehyde **395** (50 mg, 0.28 mmol, 100 mol-%) in toluene (0. 5 mL) was added. The mixture was cooled to 0°C and Danishesky's diene **147** (100 µL, 89 mg, 0.42 mmol, 150 mol-%) was added. The mixture was stirred at 0 °C for 20 h, allowed to warm to rt and stirred for additional 23 h. Then, TFA (40 µL, 62 mg, 0.54 mmol, 190 mol-%) in Et_2O (3 mL) was added. The stirring was continued for additional 3 h, until the reaction was quenched by adding sat. aq. $NaHCO_3$ (4 mL). Phases were separated and aq. phase was extracted with Et_2O (3 x 5 mL). Combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 30% EtOAc/hexanes, finally 40% EtOAc/hexanes) afforded **397a,b** as a yellowish oil (48 mg, 70%). The isolated material was determined to be 65:35 ratio of the D- and L-enantiomers, respectively by chiral HPLC analysis (Daicel Chiralpak OD, IPA:hex 10 %, 0.7 ml/min, λ = 254 nm, t_R(first eluting D-enantiomer) = 38 min, t_R(second eluting L-enantiomer) =45 min).

The same procedure was used for aldehyde **367**.

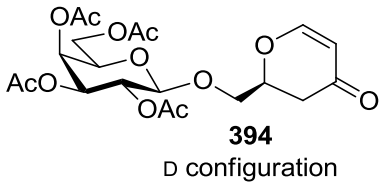
6.6.6 General Procedure for the HDA Reaction of Danishefsky's Diene 147 by Using Schiff Base Chromium Complexes (Ligands 314a, 314b, 400a or 400b)



To a stirred solution of aldehyde **371** (53 mg, 0.091 mmol, 100 mol), **400b**-CrCl complex (0.7 mg, 0.01 mmol, 2 mol-%) and crushed molecular sieves (4Å, 30 mg) in Et_2O (0.2 mL) at -20 °C was added diene **147** (22 µL, 18 mg, 0.10 mmol, 110 mol-%). The mixture was stirred for 43.5 h, and TFA (0. 30 µL, 45 mg, 0.392 mmol, 430 mol-%) in dry Et_2O (1.0 mL) was added. The mixture was strirred for additional 3 h. The reaction was quenched by adding sat. aq. $NaHCO_3$ (3 mL). Et_2O (3 mL) was added and phases were separated. Aq. phase was extracted with Et_2O (3 x 4 mL) and combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (initially 50% EtOAc/hexanes) afforded **402** as a yellowish oil (35 mg, 59%). ^1H NMR showed a 94:6 ratio of the D- and L-diastereomers, respectively.

The same procedure was used for aldehyde **367** and **395**.

6.6.7 2-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-1,3-dihydro-4*H*-pyran-4-one 394

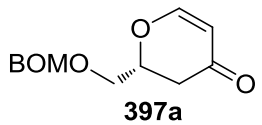


Prepared according to the general procedure by using BINOL-Titanium Complex (ligand **391b**). Yellow oil (41 g, 37%). ^1H NMR showed a 92: 8 ratio of the D- and L-diastereomers, respectively.

R_f (50% EtOAc/hexanes) = 0.09 (L-diastereomer), 0.06 (D-diastereomer); IR (film, cm^{-1}): 3062, 2937, 2856, 1751, 1676, 1663, 1596, 1407, 1371, 1227, 1176, 1075, 1049; ^1H NMR (400 MHz, $CDCl_3$) L-diastereomer δ 7.34 (d, 1H), J = 6.0 Hz), 5.42 (dd, 1H, J = 6.0 Hz, 1.1 Hz), 5.40 (dd, 1H, J = 3.4 Hz, 1.0 Hz), 5.23 (dd, 1H, J = 10.5 Hz,

8.0 Hz), 5.03 (dd, 1H, *J* = 10.5 Hz, 3.4 Hz), 4.60-4.54 (m, 1H), 4.56 (d, 1H, *J* = 8.0 Hz), 4.19 (dd, 1H, *J* = 11.2 Hz, 6.6 Hz), 4.13 (dd, 1H, *J* = 11.2 Hz, 6.7 Hz), 4.04 (dd, 1H, *J* = 11.4 Hz, 4.4 Hz), 3.92 (ddd, 1H, *J* = 6.7 Hz, 6.6 Hz, 1.0 Hz), 3.85 (dd, 1H, *J* = 11.4 Hz, 4.0 Hz), 2.73 (dd, 1H, *J* = 16.7 Hz, 14.2 Hz), 2.43 (ddd, 1H, *J* = 16.7 Hz, 3.6 Hz, 1.1 Hz), 2.16 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), D-diastereomer δ 7.35 (d, 1H), *J* = 6.0 Hz), 5.43 (dd, 1H, *J* = 6.0 Hz, 1.1 Hz), 5.40 (dd, 1H, *J* = 3.4 Hz, 1.0 Hz), 5.24 (dd, 1H, *J* = 10.4 Hz, 8.0 Hz), 5.03 (dd, 1H, *J* = 10.4 Hz, 3.4 Hz), 4.59 (app ddd, 1H, *J* = 14.0 Hz, 6.0 Hz, 3.4 Hz,), 4.55 (d, 1H, *J* = 8.0 Hz), 4.19 (dd, 1H, *J* = 11.3 Hz, 6.6 Hz), 4.13 (dd, 1H, *J* = 11.3 Hz, 6.6 Hz), 4.09 (dd, 1H, *J* = 11.4 Hz, 3.4 Hz), 3.92 (td, 1H, *J* = 6.6 Hz, 1.0 Hz), 3.79 (dd, 1H, *J* = 11.4 Hz, 6.0 Hz), 2.65 (dd, 1H, *J* = 16.8 Hz, 14.0 Hz), 2.39 (ddd, 1H, *J* = 16.8 Hz, 3.4 Hz, 1.1 Hz), 2.16 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) L-diastereomer δ 191.7, 170.3, 170.2, 170.1, 169.3, 162.5, 107.2, 101.4, 77.7, 70.8, 70.7, 69.5, 68.5, 66.9, 61.2, 38.0, 20.7, 20.62, 20.61, 20.5, D-diastereomer δ 191.4, 170.3, 170.2, 170.1, 169.3, 162.6, 107.2, 101.4, 77.8, 70.9, 70.7, 70.0, 68.5, 66.9, 61.2, 37.9, 20.7, 20.62, 20.60, 20.5; HRMS (ESI$^+$): *m/z* calcd. for [$C_{20}H_{26}O_{12}Na$] 481.1322, found 481.1331 (L-diastereomer), Δ = -1.9 ppm, 481.1321, Δ = -0.1 ppm (D-diastereomer).

6.6.8 2-Benzyloxymethyloxymethyl-1,3-dihydro-4*H*-pyran-4-one 397



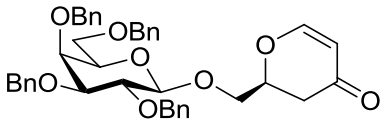
397a

L configuration

Prepared according to the general procedure by using BINOL Titanium complex (Ligand **391a**). Flash chromatography: gradient of 30% to 40% EtOAc/hexanes was used. Yellow oil (35 mg, 23%). The isolated material was determined to be 5: 95 ratio of the D- and L-enantiomers, respectively by chiral HPLC analysis (Daicel Chiralpak OD, IPA:hex 10 %, 0.7 ml/min, λ = 254 nm, t_R(first eluting D-enantiomer) = 38 min, t_R(second eluting L-enantiomer) =45 min).

R_f (50% EtOAc/hexanes) = 0.31; IR (film, cm^{-1}): 3064, 3032, 2935, 2888, 1723, 1678, 1595, 1455, 1406, 1283, 1226, 1169, 1110, 1044, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 6H), 5.432 (dd, 1H, *J* = 6.0 Hz, 1.1 Hz), 4.84 (d, 1H, *J* = 6.8 Hz), 4.82 (d, 1H, *J* = 6.8 Hz), 4.63 (s, 2H), 4.58 (dddd, 1H, *J* = 14.0 Hz, 7.1 Hz, 3.6 Hz 3.6 Hz), 3.85 (dd, 1H, *J* = 11.2 Hz, 3.6 Hz), 3.80 (dd, 1H, *J* = 11.2 Hz, 5.4 Hz), 2.72 (dd, 1H, *J* = 16.7 Hz, 14.0 Hz), 2.40 (ddd, 1H, *J* = 16.7 Hz, 3.6 Hz, 1.1 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 191.6, 162.6, 137.3, 128.3 (2C), 127.70 (2C), 127.67, 106.9, 94.6, 77.9, 69.5, 68.1, 38.0; HRMS (ESI$^+$): *m/z* calcd. for [$C_{14}H_{16}O_4H$] 249.1127, found 249.1122, Δ = -2.0 ppm.

6.6.9 2-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-2,3-dihydropyran-4-one 402

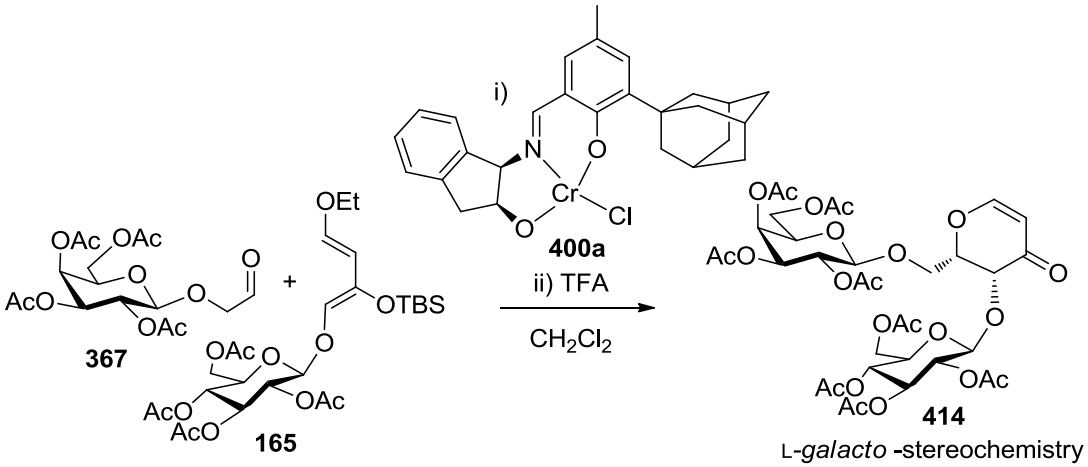


402
D configuration

Prepared according to the general procedure by using Schiff base Chromium Complex (Ligand **391b**). Yellow oil (35 mg, 59%). ^{1}H NMR showed a 94:6 ratio of the D- and L-diastereomers, respectively.

R_f (50% EtOAc/hexanes) = 0.31 (L-diastereomer), 0.28 (D-diastereomer); IR (film, cm^{-1}): 3088, 3063, 3031, 2920, 2872, 1723, 1677, 1596, 1454, 1364, 1276, 1099, 1071, 1028;^{1}H NMR (500 MHz, $CDCl_3$) (L-diastereomer) δ 7.37-7.26 (m, 21H), 5.38 (dd, 1H, *J* = 6.0 Hz, 1.1 Hz), 4.95 (d, 1H, *J* = 11.6 Hz), 4.89 (d, 1H, *J* = 10.9 Hz), 4.79 (d, 1H, *J* = 10.9 Hz), 4.75 (d, 1H, *J* = 10.7 Hz), 4.73 (d, 1H, *J* = 10.7 Hz), 4.63 (d, 1H, *J* = 11.6 Hz), 4.57 (app dq, 1H, *J* = 14.3 Hz, 4.0 Hz), 4.46 (d, 1H, *J* = 11.9 Hz), 4.43 (d, 1H, *J* = 11.9 Hz), 4.42 (d, 1H, *J* = 7.7 Hz), 4.07 (dd, 1H, *J* = 11.3 Hz, 4.5 Hz), 3.90 (d, 1H, *J* = 2.9 Hz), 3.85 (dd, 1H, *J* = 9.8 Hz, 7.7 Hz), 3.82 (dd, 1H, *J* = 11.3 Hz, 4.0 Hz), 3.60-3.53 (m, 3H), 3.54 (dd, 1H, *J* = 9.8 Hz, 2.9 Hz), 2.78 (dd, 1H, *J* = 16.9 Hz, 14.3 Hz), 2.44 (ddd, 1H, *J* = 16.9 Hz, 3.5 Hz, 1.1 Hz); (D-diastereomer) δ 7.38-7.25 (m, 21H), 5.41 (dd, 1H, *J* = 6.0 Hz, 1.0 Hz), 4.95 (d, 1H, *J* = 11.6 Hz), 4.90 (d, 1H, *J* = 10.8 Hz), 4.78 (d, 1H, *J* = 10.8 Hz), 4.77 (d, 1H, *J* = 11.8 Hz), 4.73 (d, 1H, *J* = 11.8 Hz), 4.62 (d, 1H, *J* = 11.6 Hz), 4.62 (m, 1H), 4.45 (d, 1H, *J* = 11.7 Hz), 4.41 (d, 1H, *J* = 11.7 Hz), 4.41 (d, 1H, *J* = 7.7 Hz), 4.07 (dd, 1H, *J* = 11.2 Hz, 3.2 Hz), 3.90 (d, 1H, *J* = 2.9 Hz), 3.85 (dd, 1H, *J* = 9.7 Hz, 7.7 Hz), 3.79 (dd, 1H, *J* = 11.2 Hz, 6.6 Hz), 3.59-3.55 (m, 3H), 3.53 (dd, 1H, *J* = 9.7 Hz, 2.9 Hz), 2.63 (dd, 1H, *J* = 16.8 Hz, 14.0 Hz), 2.41 (ddd, 1H, *J* = 16.8 Hz, 3.7 Hz, 1.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) (L-diastereomer) δ; 191.9, 162.7, 138.6, 138.5, 138.4, 137.9, 128.42 (2C), 128.36 (2C), 128.33 (2C), 128.28 (2C), 128.2 (2C), 128.1, 128.0 (2C), 127.84 (2C), 127.8, 127.6 (2C), 127.5 (2C), 107.1, 104.1, 82.2, 79.3, 78.0, 75.2, 74.6, 73.7, 73.6, 73.5, 73.1, 69.9, 68.9, 38.5; (D-diastereomer) δ 191.5, 162.7, 138.63, 138.55, 138.4, 137.9, 128.44 (2C), 128.38 (2C), 128.33 (2C), 128.30 (2C), 128.2 (2C), 128.1 (2C), 127.9 (2C), 127.8, 127.62 (2C), 127.60, 127.5 (2C), 107.1, 104.3, 82.2, 79.3, 78.3, 75.2, 74.6, 73.7, 73.6, 73.5, 73.1, 70.5, 68.9, 38.3; HRMS (ESI$^+$): *m/z* [$C_{40}H_{42}O_8Na$] 673.2777, found 673.2803, Δ = - 4.9 ppm (L-diastereomer), 673.2770, Δ = -1.1 ppm (D-diastereomer).

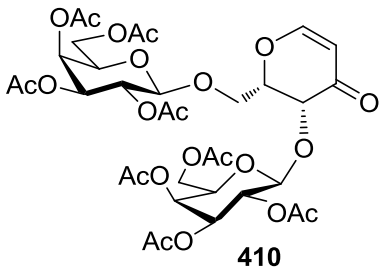
6.6.10 General Procedure for HDA Reaction of Saccharide Dienes 406 and 165



To a stirred solution of **367** (30 mg, 0.077 mmol, 100 mol-%), **400a**-CrCl complex (2.7 mg, 0.006 mmol, 6 mol-%) and crushed molecular sieves (4Å, 47 mg) in CH_2Cl_2 (0.2 mL) at rt was added **165** (47 m g, 0.091 mmol, 120 mol-%) in CH_2Cl_2 (0.2 mL). The reaction mixture was stirred for 18 h. Then, TFA (0.03 mL, 45 mg, 0.392 mmol, 510 mol-%) in dry CH_2Cl_2 (1.0 mL) was added and the reaction mixture was stirred for additional 2 h. The reaction was quenched by adding sat. aq. $NaHCO_3$ (3 mL). CH_2Cl_2 (3 mL) was added and phases were separated. The aq. phase was extracted with CH_2Cl_2 (3 x 4 mL) and the combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 60% EtOAc/hexanes, finally 70% EtOAc/hexanes) afforded **414** as yellowish oil (39 g, 63%).

The same procedure was used for aldehydes **367α**, **368**, **371**, **373** and **377**.

6.6.11 4,6-di-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-1,5-anhydro-2-deoxy-L-threo-hex-1-en-3-ulose 410

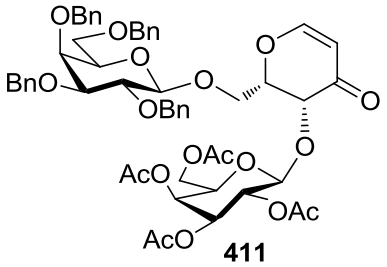


Prepared according to the general procedure. Yellow oil (48 mg, 44%).

R_f (80% EtOAc/hexanes) = 0.35; $[\alpha]_D$ = +19.8° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3064, 2982, 2940, 1751, 1688, 1599, 1371, 1227, 1175, 1078, 1061; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, 1H, $J_{1\text{-HB, 2-HB}}$ = 6.1 Hz, $J_{1\text{-HB, 5-HB}}$ = 0.5 Hz, 1-H_B), 5.40

(dd, 1H, $J_{1\text{-HB, 2-HB}}$ = 6.1 Hz, $J_{\text{2-HB, 4-HB}}$ = 1.6 Hz, 2-H_B), 5.37 (dd, 1H, J = 3.4 Hz, 1.0 Hz), 5.34 (dd, 1H, J = 3.5 Hz, 1.0 Hz), 5.18 (dd, 1H, $J_{\text{2-HC, 3-HC}}$ = 10.2 Hz, $J_{\text{1-HC, 2-HC}}$ = 8.1 Hz, 2-H_C), 5.16 (dd, 1H, 1H, $J_{\text{2-HA, 3-HA}}$ = 10.4 Hz, $J_{\text{1-HA, 2-HA}}$ = 8.0 Hz, 2-H_A), 5.02 (dd, 1H, J = 10.2 Hz, 3.5 Hz), 5.00 (dd, 1H, J = 10.4 Hz, 3.4 Hz), 4.62 (d, 1H, $J_{\text{1-HC, 2-HC}}$ = 8.1 Hz, 1-H_C), 4.49 (d, 1H, $J_{\text{1-HA, 2-HA}}$ = 8.0 Hz, 1-H_A), 4.48 (ddd, 1H, $J_{\text{5-HB, 6-HB}}$ = 7.7 Hz, $J_{\text{5-HB, 6-HB}}$ = 5.8 Hz, $J_{\text{5-HB, 4-HB}}$ = 1.8 Hz, 5-H_B) 4.13-4.02 (m, 4H, 2x6-H_A, 2x6-H_C, 6-H_B), 4.04 (dd, 1H, J = 6.6 Hz, 4.3 Hz), 3.95 (dd, 1H, $J_{\text{6-HB, 6-HB}}$ = 10.8 Hz, $J_{\text{5-HB, 6-HB}}$ = 5.8 Hz, 6-H_B), 3.90 (app td, 1H, J = 6.9 Hz, 1.0 Hz), 3.87 (app t, 1H, $J_{\text{2-HB, 4-HB, 5-HB}}$ = 1.8 Hz, 4-H_B), 3.86 (app td, 1H, J = 6.6 Hz, 1.0 Hz), 2.17 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.050 (s, 3H),2.048 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 170.4, 170.22, 170.15, 170.1, 170.0, 169.9, 169.4, 169.1, 161.8, 105.7, 102.0, 10.8, 79.0, 75.7, 71.1, 71.0, 70.8, 70.7, 68.9, 68.7, 67.0, 66.9, 66.3, 61.3, 60.9, 20.68, 20.65 (2C) , 20.61, 20.57, 20.52, 20.47, 20.45; HRMS (ESI$^+$): *m/z* [$C_{34}H_{44}O_{22}Na$] 827.2222, found 827.2248, Δ = 3.2 ppm.

6.6.12 4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-1,5-anhydro-2-deoxy-L-threo-hex-1-en-3-ulose 411



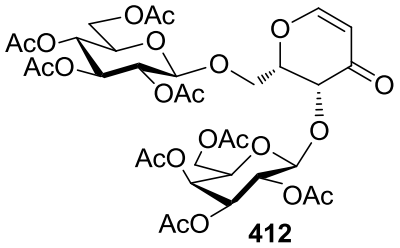
411

Prepared according to the general procedure. Flash chromatography: gradient of 50% to 60% EtOAc/hexanes was used. Yellow oil (32 mg, 41%).

R_f (50% EtOAc/hexanes) =0.24; $[\alpha]_D$ = +16.5° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3064, 3031, 2926, 2871, 1771, 1686, 1598, 1454, 1369, 1224, 1076; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 21H) 5.36 (dd, 1H, J = 6.1 Hz, 1.6 Hz), 5.30 (dd, 1H, J = 3.5 Hz, 1.0 Hz), 5.16 (dd, 1H, J = 10.4 Hz, 8.0 Hz), 4.93 (dd, 1H, J = 10.4 Hz, 3.5 Hz), 4.92 (d, 1H, J = 11.5 Hz), 4.83 (d, 1H, J = 11.1 Hz), 4.79 (d, 1H, J = 11.1 Hz), 4.71 (s, 2H), 4.61 (d, 1H, J = 11.5 Hz), 4.50 (d, 1H, J = 8.1 Hz), 4.47 (ddd, 1H, J = 8.3 Hz, 5.6 Hz, 1.7 Hz), 4.43 (d, 1H, J = 11.8 Hz) 4.38 (d, 1H, J = 11.8 Hz), 4.31 (d, 1H, J = 7.7 Hz), 4.07 (dd, 1H, J = 10.4 Hz, 5.6 Hz), 4.03 (s, 1H), 4.01 (s, 1H), 3.93 (dd, 1H, J = 10.4 Hz, 8.3 Hz), 3.89 (d, 1H, J = 2.9 Hz), 3.86 (app t, 1H, J = 1.7 Hz), 3.80 (dd, 1H, J = 9.7 Hz, 7.7 Hz), 3.68 (td, 1H, J = 6.4 Hz, 1.0 Hz), 3.55-3.51 (m, 3H), 3.49 (dd, 1H, J = 9.7 Hz, 2.9 Hz), 2.10 (s, 3H), 2.08 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 188.5, 170.4, 170.2, 169.9, 169.3, 162.0, 138.4, 138.3, 138.1, 137.7, 128.4 (2C), 128.35 (4C), 128.33 (3C), 128.2 (2C), 127.84 (3C), 127.79 (2C), 127.6 (2C), 127.5 (2C), 105.4, 104.1, 100.8, 82.1, 79.11, 79.07, 77.2,

75.9, 75.2, 74.5, 73.6, 73.5, 73.1, 72.8, 70.8, 68.73, 68.67, 66.9, 65.6, 60.8, 20.72, 20.66, 20.6, 20.5; HRMS (ESI$^+$): *m/z* calcd. for [$C_{54}H_{60}O_{18}Na$] 1019.3677, found 1019.3647, Δ = - 2.9 ppm.

6.6.13 4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,5-anhydro-2-deoxy-L-threo-hex-1-en-3-ulose 412

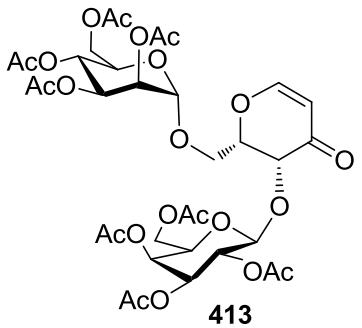


412

Prepared according to the general procedure. Yellow oil (41 mg, 39%).

R_f (80% EtOAc/hexanes) = 0.32; $[\alpha]_D$ = +8.32° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3064, 2960, 1753, 1688, 1599, 1371, 1229, 1173, 1061; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, 1H, $J_{1\text{-HB, 2-HB}}$ = 6.1 Hz, $J_{1\text{-HB, 5-HB}}$ = 0.5 Hz, 1-H_B), 5.40 (dd, 1H, $J_{1\text{-HB, 2-HB}}$ = 6.1 Hz, $J_{2\text{-HB, 4-HB}}$ = 1.6 Hz, 2-H_B), 5.35 (dd, 1H, $J_{3\text{-HC, 4-HC}}$ = 3.5 Hz, $J_{4\text{-HC, 5-HC}}$ = 1.1 Hz, 4-H_C), 5.19 (app t, 1H, $J_{3\text{-HA, 4-HA, 5-HA}}$ = 9.6 Hz, 3-H_A), 5.18 (dd, 1H, $J_{2\text{-HC, 3-HC}}$ = 10.4 Hz, $J_{1\text{-HC, 2-HC}}$ = 8.1 Hz, 2-H_C), 5.06 (app t, 1H, 1H, $J_{3\text{-HA, 4-HA, 5-HA}}$ = 9.6 Hz, 4-H_A), 5.02 (dd, 1H, $J_{2\text{-HC, 3-HC}}$ = 10.4 Hz, $J_{3\text{-HC, 4-HC}}$ = 3.5 Hz, 3-H_C), 4.98 (dd, 1H, $J_{2\text{-HA, 3-HA}}$ = 9.6 Hz, $J_{1\text{-HA, 2-HA}}$ = 7.9 Hz, 2-H_A), 4.62 (d, 1H, $J_{1\text{-HC, 2-HC}}$ = 8.1 Hz, 1-H_C), 4.55 (d, 1H, $J_{1\text{-HA, 2-HA}}$ = 7.9 Hz, 1-H_A), 4.51 (ddd, 1H, $J_{5\text{-HB, 6-HB}}$ = 7.9 Hz, $J_{5\text{-HB, 6-HB}}$ = 5.9 Hz, $J_{5\text{-HB, 4-HB}}$ = 1.7 Hz, 5-H_B), 4.18 (s, 1H, 6-H_A), 4.17 (d, 1H, *J* = 2.0 Hz, 6-H_A), 4.10-4.03 (m, 2H, 6-H_C), 4.04 (dd, 1H, $J_{6\text{-HB, 6-HB}}$ = 10.8 Hz, $J_{5\text{-HB, 6-HB}}$ = 7.9 Hz, 6-H_B), 3.96 (dd, 1H, $J_{6\text{-HB, 6-HB}}$ = 10.8 Hz, $J_{5\text{-HB, 6-HB}}$ = 5.9 Hz, 6-H_B), 3.86 (app td, 1H, $J_{5\text{-HC, 6-HC}}$ = 6.6 Hz, $J_{4\text{-HC, 5-HC}}$ = 1.1 Hz, 5-H_C), 3.83 (app t, 1H, $J_{2\text{-HB, 4-HB, 5-HB}}$ = 1.7 Hz, 4-H_B), 3.71 (ddd, 1H, $J_{4\text{-HA, 5-HA}}$ = 10.0 Hz, $J_{5\text{-HA, 6-HA}}$ = 4.5 Hz, $J_{5\text{-HA, 6-HA}}$ = 3.4 Hz, 5-H_A), 2.12 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.055 (s, 3H), 2.049 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 170.5, 170.4, 170.2, 170.1, 169.9, 169.5, 169.3, 169.1, 161.8, 105.7, 101.5, 100.8, 79.0, 75.7, 72.6, 72.1, 71.3, 71.1, 70.8, 70.0, 68.3, 67.1, 66.5, 61.8, 61.0, 20.7 (2C), 20.6 (3C), 20.5 (3C); HRMS (ESI$^+$): *m/z* calcd. for [$C_{34}H_{44}O_{22}Na$] 827.2222, found 827.2240, Δ = 2.2 ppm.

6.6.14 4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-1,5-anhydro-2-deoxy-L-threo-hex-1-en-3-ulose 413

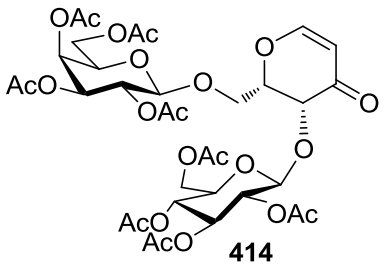


413

Prepared according to the general procedure. Flash chromatography: 60% EtOAc/hexanes was used. Yellow oil (37 mg, 48%).

For major diastereomer: R_f (50% EtOAc/hexanes) = 0.34; $[\alpha]_D$ = +37.6° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2959, 2940, 1750, 1687, 1599, 1370, 1226, 1139, 1079, 1049; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, 1H, *J* = 6.1 Hz), 5.44 (dd, 1H, *J* = 6.1 Hz, 1.4 Hz), 5.35 (dd, 1H, *J* = 3.5 Hz, 0.9 Hz), 5.31-5.26 (m, 3H), 5.18 (dd, 1H, *J* = 10.4 Hz, 8.1 Hz), 4.99 (dd, 1H, *J* = 10.4 Hz, 3.5 Hz), 4.90 (d, 1H, *J* = 1.5 Hz), 4.63 (d, 1H, *J* = 8.1 Hz), 4.52 (app ddd, 1H, *J* = 6.0 Hz, 3.3 Hz, 1.9 Hz), 4.27 (dd, 1H, *J* = 12.2 Hz, 5.2 Hz), 4.14-4.01 (m, 4H), 3.97 (ddd, 1H, J = 8.4 Hz, 5.2 Hz, 2.6 Hz), 3.86-3.83 (m, 2H), 3.81 (t, 1H, *J* = 1.9 Hz), 2.16 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 2.082 (s, 3H), 2.075 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.6, 170.5, 170.4, 170.2, 169.90, 169.87, 169.8, 169.6, 169.2, 162.3, 105.5, 100.8, 98.5, 79.7, 76.6, 71.3, 70.8, 69.2, 69.1, 68.76, 68.76, 67.0, 66.3, 66.2, 62.6, 61.0, 20.8, 20.71, 20.66 (2C), 20.62, 20.60 (2C), 20.5; HRMS (ESI^+): *m/z* calc. for $[C_{34}H_{44}O_{22}Na]$ 827.2222, found 827.2213, Δ = -1.1 ppm. For minor diastereomer: R_f (50% EtOAc/hexanes) = 0.37; HRMS (ESI^+): *m/z* calc. for $[C_{34}H_{44}O_{22}Na]$ 827.2222, found 827.2183, Δ = -4.7 ppm.

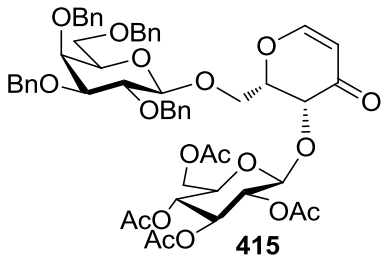
6.6.15 4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,5-anhydro-2-deoxy-L-threo-hex-1-en-3-ulose 414



414

Prepared according to the general procedure. Yellow oil (42 mg, 68%).
R_f (80% EtOAc/hexanes) =0.40; $[\alpha]_D$ = +14.2° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3064, 2960, 2892, 1753, 1688, 1599, 1371, 1228, 1174, 1058; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, 1H, $J_{1\text{-HB, 2-HB}}$ = 6.1 Hz, $J_{1\text{-HB, 5-HB}}$ = 0.6 Hz, 1-H_B), 5.42 (dd, 1H, $J_{1\text{-HB, 2-HB}}$ = 6.1 Hz, $J_{2\text{-HB, 4-HB}}$ = 1.7 Hz, 2-H_B), 5.38 (dd, 1H, $J_{3\text{-HA, 4-HA}}$ = 3.5 Hz, $J_{4\text{-HA, 5-HA}}$ = 1.1 Hz, 4-H_A), 5.19 (app t, 1H, $J_{2\text{-HC, 3-HC, 4-HC}}$ = 9.5 Hz, 3-H_C), 5.17 (dd, 1H, $J_{2\text{-HA, 3-HA}}$ = 10.5 Hz, $J_{1\text{-HA, 2-HA}}$ = 7.9 Hz, 2-H_A), 5.01 (app t, 1H, 1H, $J_{3\text{-HC, 4-HC, 5-HC}}$ = 9.5 Hz, 4-H_C), 5.00 (dd, 1H, $J_{2\text{-HA, 3-HA}}$ = 10.5 Hz, $J_{3\text{-HA, 4-HA}}$ = 3.5 Hz, 3-H_A), 4.99 (dd, 1H, $J_{2\text{-HC, 3-HC}}$ = 9.5 Hz, $J_{1\text{-HC, 2-HC}}$ = 8.1 Hz, 2-H_C), 4.68 (d, 1H, $J_{1\text{-HC, 2-HC}}$ = 8.1 Hz, 1-H_C), 4.49 (ddd, 1H, $J_{5\text{-HB, 6-HB}}$ = 7.9 Hz, $J_{5\text{-HB, 6-HB}}$ = 5.5 Hz, $J_{4\text{-HB, 5-HB}}$ = 1.8 Hz, 5-H_B), 4.48 (d, 1H, $J_{1\text{-HA, 2-HA}}$ = 7.9 Hz, 1-H_A), 4.23 (dd, 1H, $J_{6\text{-HC, 6-HC}}$ = 12.3 Hz, $J_{5\text{-HC, 6-HC}}$ = 5.5 Hz, 6-H_C), 4.14-4.10 (m, 2H, 2 x 6-H_A), 4.031 (dd, 1H, $J_{6\text{-HC, 6-HC}}$ = 12.3 Hz, $J_{5\text{-HC, 6-HC}}$ = 2.5 Hz, 6-H_C), 4.030 (dd, 1H, $J_{6\text{-HB, 6-HB}}$ = 10.7 Hz, $J_{5\text{-HB, 6-HB}}$ = 7.9 Hz, 6-H_B), 3.96 (dd, 1H, $J_{6\text{-HB, 6-HB}}$ = 10.7 Hz, $J_{5\text{-HB, 6-HB}}$ = 5.5 Hz, 6-H_B), 3.91 (td, 1H, $J_{5\text{-HA, 6-HA}}$ = 6.4 Hz, $J_{4\text{-HA, 5-HA}}$ = 1.1 Hz, 5-H_A), 3.88 (app t, 1H, $J_{2\text{-HB, 4-HB, 5-HB}}$ = 1.8 Hz, 4-H_B), 3.67 (ddd, 1H, $J_{4\text{-HC, 5-HC}}$ = 10.1 Hz, $J_{5\text{-HC, 6-HC}}$ = 5.5 Hz, $J_{5\text{-HC, 6-HC}}$ = 2.5 Hz, 5-H_C), 2.18 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 188.2, 170.6, 170.3, 170.14, 170.09, 170.0, 169.4, 169.2 (2C), 105.7, 102.0, 100.3, 79.0, 75.6, 72.8, 72.0, 71.3, 71.1, 70.7, 68.7, 68.7, 68.4, 66.9, 66.2, 61.6, 61.3, 20.8, 20.7, 20.64, 20.55 (4C), 20.49; HRMS (ESI^+): HRMS (ESI^+): *m/z* calcd. for [$C_{34}H_{44}O_{22}Na$] 827.2222, found 827.2253, Δ = 3.8 ppm.

6.6.16 4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-1,5-anhydro-2-deoxy-L-threo-hex-1-en-3-ulose 415

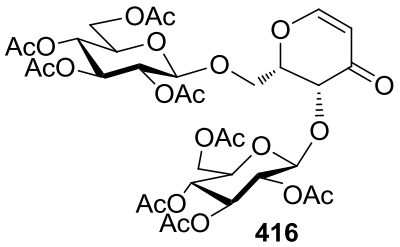


415

Prepared according to the general procedure Flash chromatography: gradient of 40% to 50% EtOAc/hexanes was used. Yellow oil (46 mg, 32%).

R_f (50% EtOAc/hexanes) = 0.15; $[\alpha]_D$ = +163.5° (*c* 2.00, CH_2Cl_2); IR (film, cm^{-1}): 3031, 3007, 2938, 2874, 1754, 1688, 1598, 1454, 1368, 1229, 1158, 1056; ^1H NMR (500 MHz, $CDCl_3$) δ; 7.34-7.25 (m, 21H) 5.36 (dd, 1H, *J* = 6.1 Hz, 1.7 Hz), 5.12 (app t, 1H, *J* = 9.5 Hz), 4.97 (app t, 1H, *J* = 9.5 Hz), 4.96 (dd, 1H, *J* = 9.5 Hz, 8.1 Hz), 4.92 (d, 1H, *J* = 11.5 Hz), 4.82 (d, 1H, *J* = 11.2 Hz), 4.79 (d, 1H, *J* = 11.2 Hz), 4.71 (s, 2H), 4.60 (d, 1H, *J* = 11.5 Hz), 4.52 (d, 1H, *J* = 8.1 Hz), 4.46 (ddd, 1H, *J* = 8.5 Hz, 5.7 Hz, 1.6 Hz), 4.43 (d, 1H, *J* = 11.9 Hz) 4.39 (d, 1H, *J* = 11.9 Hz), 4.30 (d, 1H, *J* = 7.7 Hz), 4.18 (dd, 1H, *J* = 12.3 Hz, 5.5 Hz), 4.07 (dd, 1H, *J* = 10.4 Hz, 5.7 Hz), 3.96 (dd, 1H, *J* = 12.3 Hz, 2.3 Hz), 3.91 (dd, 1H, *J* = 10.4 Hz, 8.5 Hz), 3.89 (d, 1H, *J* = 2.8 Hz), 3.85 (app t, 1H, *J* = 1.6 Hz), 3.80 (dd, 1H, *J* = 9.7 Hz, 7.7 Hz), 3.55-351 (m, 3H), 3.50-3.46 (m, 1H), 3.49 (dd, 1H, *J* = 9.6 Hz, 2.8 Hz), 2.10 (s, 3H), 2.09 (s, 3H), 1.98 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 188.5, 170.6, 170.1, 169.4, 169.2, 162.0, 138.5, 138.4, 138.1, 137.8, 128.40 (2C), 128.39 (2C), 128.37 (2C), 128.3 (2C), 128.2 (2C), 127.84 (2C), 127.83 (2C), 127.80, 127.67, 127.65 (2C), 127.6 (2C), 105.4, 104.2, 100.3, 82.2, 79.1, 75.9, 75.3, 74.6, 73.7, 73.5, 73.2, 72.9, 71.8, 71.1, 69.9, 68.8, 68.5, 67.2, 65.9, 61.5, 20.7, 20.63, 20.58, 20.5; HRMS (ESI^+): *m/z* [$C_{54}H_{60}O_{18}Na$] 1019.3677, found 1019.3652, Δ = -2.5 ppm.

6.6.17 4,6-di-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,5-anhydro-2-deoxy-L-threo-hex-1-en-3-ulose 416

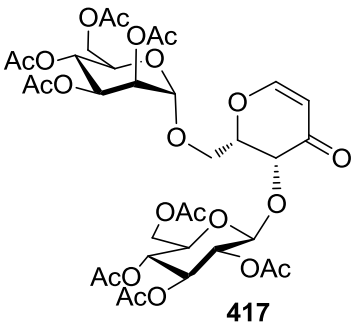


416

Prepared according to the general procedure. Yellow oil (37 mg, 51%).

R_f (80% EtOAc/hexanes) = 0.33; $[\alpha]_D$ = +4.84° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3063, 2961, 1755, 1688, 1599, 1370, 1227, 1171, 1040; ^1H NMR (500 MHz, $CDCl_3$) δ; 7.29 (dd, 1H, $J_{1\text{-HB, 2-HB}}$ = 6.1 Hz, $J_{1\text{-HB, 5-HB}}$ = 0.6 Hz, 1-H_B), 5.41 (dd, 1H, $J_{1\text{-HB, 2-HB}}$ = 6.1 Hz, $J_{2\text{-HB, 4-HB}}$ = 1.7 Hz, 2-H_B), 5.185 (app t, 1H, *J* = 9.5 Hz), 5.183 (app t, 1H, *J* = 9.5 Hz), 5.05 (app t, 1H, $J_{3\text{-HA, 4-HA, 5-HA}}$ = 10.0 Hz, 4-H_A), 5.01 (app t, 1H, $J_{3\text{-HC, 4-HC, 5-HC}}$ = 9.5 Hz, 4-H_C), 4.99 (dd, 1H, $J_{2\text{-HC, 3-HC}}$ = 9.5 Hz, $J_{1\text{-HC, 2-HC}}$ = 8.1 Hz, 2-H_C), 4.97 (dd, 1H, $J_{2\text{-HA, 3-HA}}$ = 9.5 Hz, $J_{1\text{-HA, 2-HA}}$ = 7.9 Hz, 2-H_A), 4.66 (d, 1H, $J_{1\text{-HC, 2-HC}}$ = 8.1 Hz, 1-H_C), 4.43 (d, 1H, $J_{1\text{-HA, 2-HA}}$ = 7.9 Hz, 1-H_A), 4.50 (ddd, 1H, $J_{5\text{-HB, 6-HB}}$ = 8.0 Hz, $J_{5\text{-HB, 6-HB}}$ = 6.0 Hz, $J_{5\text{-HB, 4-HB}}$ = 1.5 Hz, 5-H_B), 4.22 (dd, 1H, $J_{6\text{-HC, 6-HC}}$ = 12.2 Hz, $J_{5\text{-HC, 6-HC}}$ = 5.5 Hz, 6-H_C), 4.18 (d, 2H, $J_{5\text{-HA, 6-HA}}$ = 3.9 Hz, 2 x 6-H_A) 4.021 (dd, 1H, $J_{5\text{-HC, 6-HC}}$ = 12.2 Hz, $J_{6\text{-HC, 6-HC}}$ = 2.2 Hz, 6-H_C), 4.016 (dd, 1H, $J_{6\text{-HB, 6-HB}}$ = 10.7 Hz, $J_{5\text{-HB, 6-HB}}$ = 8.6 Hz, 6-H_B), 3.96 (dd, 1H, *J* = 10.7 Hz, 6.0 Hz, 6-H_B), 3.83 (app t, 1H, $J_{2\text{-HB, 4-HB, 5-HB}}$ = 1.5 Hz, 4-H_B), 3.71 (app dt, 1H, $J_{4\text{-HA, 5-HA, 6-HA}}$ = 10.1 Hz, $J_{5\text{-HA, 6-HA}}$ = 3.9 Hz, 5-H_A), 3.66 (ddd, 1H, $J_{4\text{-HC, 5-HC}}$ = 10.1 Hz, $J_{5\text{-HC, 6-HC}}$ = 5.5 Hz, $J_{5\text{-HC, 6-HC}}$ = 2.4 Hz, 5-H_C), 2.11 (s, 3H), 2.060 (s, 3H), 2.055 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.002 (s, 3H), 1.998 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.0, 170.6, 170.5, 170.12, 170.05, 169.4, 169.28, 169.26, 169.1, 161.8, 105.7, 101.4, 100.3, 78.9, 75.6, 72.8, 72.6, 72.1, 72.0, 71.3, 71.2, 68.4, 68.3, 66.3, 61.8, 61.6, 20.7, 20.59 (2C), 20.56, 20.54 (2C), 20.51 (2C); HRMS (ESI^+): *m/z* calcd. for [$C_{34}H_{44}O_{22}Na$] 827.2222, found 827.2215, Δ = -0.8 ppm.

6.6.18 4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-1,5-anhydro-2-deoxy-L-threo-hex-1-en-3-ulose 417



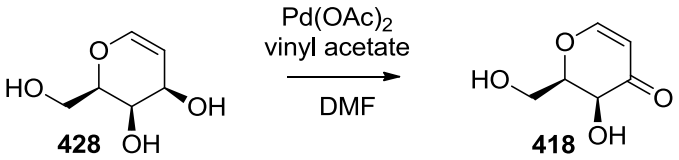
417

Prepared according to the general procedure. Yellow oil (17 mg, 15%).

HRMS (ESI$^+$): *m/z* [$C_{34}H_{44}O_{22}Na$] 827.2222, found 827.2191, Δ = -3.7 ppm.

6.7 Attempts at the Traditional Synthesis of the Trisaccharide Product 410

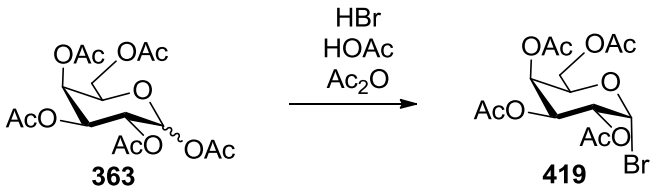
6.7.1 1,5-Anhydro-2-deoxy-D-threo-hex-l-en-3-ulose 418 (202)



To a stirred solution of galactal **428** (501 mg, 3.42 mmol, 100 mol-%) in DMF (10 mL) at rt were added vinyl acetate (1.0 mL, 884 mg, 10.3 mmol, 300 mol-%) and $Pd(OAc)_2$ (38 mg, 0.171 mmol, 5 mol-%). The mixture was brown and become slowly darker. It was stirred for 68 h, and then filtered trough celite with EtOAc (15 mL). DMF was removed in vacuo as a azeotrope with toluene. Purification of the residue by flash chromatography (100% EtOAc) afforded **418** as yellow oil (365 mg, 74%). IR, ^{1}H and ^{13}C NMR-data matched those reported in the literature. (202)

R_f (EtOAc) = 0.27; $[\alpha]_D$ = +118 (*c* 1.00, MeOH); IR (film, cm^{-1}): 3416 (br s), 2946, 1667, 1597, 1413, 1267, 1252, 1120, 1044; ^{1}H NMR (250 MHz, CD_3OD) δ 7.52 (d, 1H, *J* = 6.0 Hz), 5.38 (dd, 1H, *J* = 6.0 Hz, 1.0 Hz), 4.79 (s, 2H), 4.42 (ddd, 1H, *J* = 7.3 Hz, 4.9 Hz, 3.4 Hz), 4.06 (dd, 1H, *J* = 3.4 Hz, 1.0 Hz), 3.96 (dd, 1H, *J* = 12.0 Hz, 7.3 Hz), 3.85 (dd, 1H, *J* = 12.0 Hz, 4.9 Hz); ^{13}C NMR (63 MHz, CD_3OD) δ 194.0, 165.0, 105.3, 84.2, 70.0, 60.3; HRMS (ESI$^+$): *m/z* calcd. for [$C_6H_8O_4Na$] 167.0320, found 167.0324, Δ = 2.1 ppm.

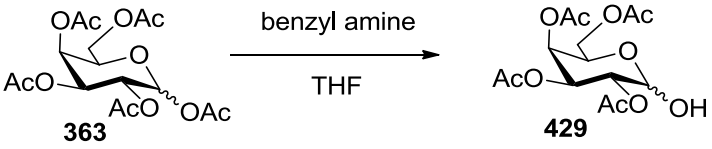
6.7.2 2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosyl bromide 419 (203)



To a stirred solution of saccharide **363** (4.05 g, 10.3 mol, 100 mol-%) in AcOH (8 mL) and Ac_2O (8 mL) at rt was added HBr (33% in AcOH, 86 mL, 61.6 g, 251 mmol, 2430 mol-%). The mixture was stirred at rt for 3 h 10 min, before it was diluted with CH_2Cl_2 (800 mL). Phases were separated and organic phase was washed with H_2O (3 x 150 mL), sat. aq. $NaHCO_3$ (200 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated in vacuo. Removal of residual AcOH by coevaporating with toluene afforded **419** as brown oil (3.00 g, 71%). Product was used in the next step without further purification. ^{1}H NMR-data matched those reported in the literature. (204)

R_f (EtOAc/hexanes) = 0.75; $[\alpha]_D$ = +190° (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3483 (br s), 2963, 1750, 1648, 1433, 1373, 1222, 1128, 1081, 1055; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.69 (d, 1H, *J* = 4.0 Hz), 5.51 (dd, 1H, *J* = 3.3 Hz, 1.3 Hz), 5.40 (dd, 1H, *J* = 10.7 Hz, 3.3 Hz), 5.04 (dd, 1H, *J* = 10.7 Hz, 4.0 Hz), 4.48 (tdd, 1H, *J* = 6.3 Hz, 1.3 Hz, 0.7 Hz), 4.18 (dd, 1H, *J* = 11.4 Hz, 6.3 Hz), 4.09 (dd, 1H, *J* = 11.4 Hz, 3.3 Hz), 2.14 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.0, 169.7, 169.6, 169.4, 88.0, 70.8, 67.7, 67.5, 66.7, 60.6, 20.4, 20.3, 20.2 (2C); HRMS (ESI^+): *m/z* calcd. for [$C_{14}H_{19}O_9$ 79BrNa] 433.0110, found 433.0128, Δ = 4.1 ppm. *m/z* calcd. for [$C_{14}H_{19}O_9$ 81BrNa] 435.0090, found 435.0088, Δ = -0.4 ppm.

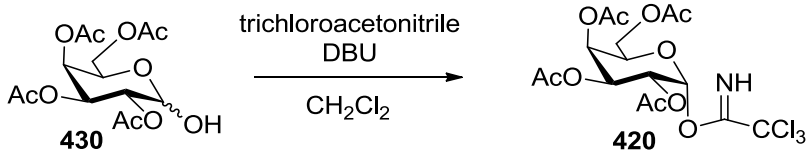
6.7.3 2,3,4,6-Tetra-*O*-D-galactopyranose 429 (205)



To a stirred solution of saccharide **363** (12.04 g, 30.84 mmol, 100 mol-%) in THF (70 mL) at rt was added benzyl amine (4.7 mL, 4.61 g, 43.03 mmol, 140 mol-%). The mixture was stirred for 20 h before it was concentrated. The residue was dissolved in CH_2Cl_2 (150 mL), and then washed with HCl (1 M, 2 x 200 mL) and H_2O (100 mL), dried over $NaSO_4$ and concentrated. Purification of the residue by flash chromatography (initially 60% EtOAc/hexanes, finally 100% EtOAc) afforded **429** as yellowish foam (6.87 g, 64%). Product was used in the next step without further purification. ^{1}H NMR showed a 3:1 ratio of the α- and β-anomers, respectively, the data of the major α-anomer being in agreement with those reported in the literature. (204)

R_f (50 % EtOAc/hexanes) = 0.19; IR (film, cm^{-1}): 3465 (br s), 2970, 2941, 1748, 1663, 1435, 1373, 1232, 1156, 1128, 1052; ^1H NMR (250 MHz, $CDCl_3$) δ 5.47 (d, 1H, *J* = 3.6 Hz), 5.44 (dd, 1H, *J* = 3.5 Hz, 1.2 Hz), 5.39 (dd, 1H, *J* = 10.6 Hz, 3.5 Hz), 5.11 (dd, 1H, *J* =10.6 Hz, 3.6 Hz), 4.45 (app. td, 1H, *J* = 6.6 Hz, 0.9 Hz), 4.13 - 4.05 (m, 2H), 2.11 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (MHz, $CDCl_3$) δ; HRMS (ESI^+): *m/z* calcd. for [$C_{14}H_{20}O_{10}Na$] 371.0954, found 371.0946, Δ = -2.1 ppm.

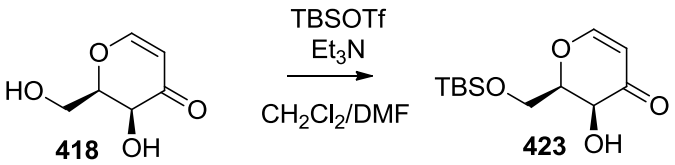
6.7.4 2,3,4,6-Tetra-*O*-α-D-galactopyranosyl trichloroacetimidate 420 (206)



To a stirred mixture of saccharide **430** (2.17 g, 6.15 mmol, 100 mol-%) and molecular sieves (4 Å, 2.60 g) in CH_2Cl_2 (25 mL) at 0 °C was added trichloroacetonitrile (6.6 mL, 9.50 g, 65.8 mmol, 1070 mol-%). The mixture was stirred for 50 min before DBU (0.2 mL, 204 mg, 1.34 mmol, 22 mol-%) was added. Stirring was continued for additional 1 h 20 min, after which time the mixture was filtered through celite with CH_2Cl_2 (25 mL) and concentrated in vacuo. Purification of the residue by flash chromatography (initially 20% EtOAc/hexanes, finally 60% EtOAc/hexanes) afforded **420** as a white solid (2.19 g, 72%). ^1H and ^{13}C NMR-data matched those reported in the literature. (207)

R_f (50% EtOAc/Hex) = 0.56; mp 118-119 °C; $[\alpha]_D$ = 108° (*c* 2.00, CH_2Cl_2); IR (film, cm^{-1}): 3443 (br s), 3343, 2973, 1752, 1677, 1433, 1372, 1226, 1150, 1073, 1035; ^1H NMR (500 MHz, $CDCl_3$) δ; 8.65 (s, 1H), 6.57 (d, 1H, *J* = 3.6 Hz), 5.53 (dd, 1H, *J* = 3.2 Hz, 1.2 Hz), 5.40 (dd, 1H, *J* = 10.9 Hz, 3.2 Hz), 5.33 (dd, 1H, *J* = 10.9 Hz, 3.6 Hz), 4.41 (app. td, 1H, *J* =6.6 Hz, 0.7 Hz), 4.14 (dd, 1H, *J* = 11.3 Hz, 6.6 Hz), 4.05 (dd, 1H, *J* = 11.3 Hz, 6.6 Hz), 2.13 (s, 3H), 1.99 (s, 3H), 1.984 (s, 3H), 1.979 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 169.95, 169.91, 169.8, 160.8, 93.5, 90.7, 69.0, 67.4, 67.3, 66.9, 61.2, 20.52, 20.49, 20.46, 20.4; HRMS (ESI^+): *m/z* calcd. for [$C_{16}H_{20}O_{10}N^{35}Cl_3Na$] 514.0050, found 514.0067, Δ = 3.2 ppm, calcd. for [$C_{16}H_{20}O_{10}N^{35}Cl_2{}^{37}ClNa$] 516.0021, found 516.0016, Δ = -1.0 ppm, calcd. for [$C_{16}H_{20}O_{10}N^{35}Cl^{37}Cl_2Na$] 517.9991, found 517.9984, Δ = -1.4 ppm.

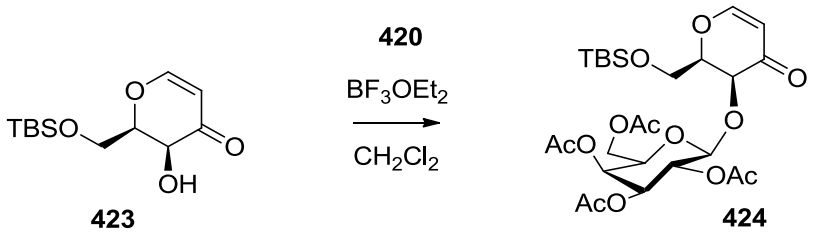
6.7.5 6- *O-Tert*-butyldimethylsilyl-1,5-Anhydro-2-deoxy-D-threo-hex-l-en-3-ulose 423



To a stirred solution of **418** (161 mg, 1.12 mmol, 100 mol-%) in CH_2Cl_2 (3.0 mL) and DMF (0.3 mL) at 0 °C was added Et_3N (0.39 mL, 283 mg, 2.79 mmol, 250 mol-%), followed by slow addition of TBSOTf (0.33 mL, 384 m g, 1.45 mmol, 130 mol-%) during 5 min. The reaction was stirred for 2 h 20 min before it was diluted with CH_2Cl_2 (20 mL). Et_3N (2 drops) and sat. aq. $NaHCO_3$ (20 mL) were added and the phases were separated. The organic phase was washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (30% EtOAc/hexanes) afforded **423** as yellowish oil (535 mg, 40%).

R_f (50% EtOAc/hexanes) = 0.79; $[\alpha]_D$ = +162 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3425, 2955, 2930, 2857, 1680, 1597, 1471, 1410, 1256, 1122, 1051; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, 1H, *J* = 6.0 Hz), 5.36 (d, 1H, *J* = 6.0 Hz), 4.65 (ddd, 1H, *J* = 6.5 Hz, 5.0 Hz, 3.1 Hz), 4.51 (d, 1H, *J* = 6.5 Hz), 4.02 (dd, 1H, *J* = 11.7 Hz, 5.0 Hz), 3.93 (dd, 1H, *J* = 11.7 Hz, 3.1 Hz), 3.57 (br s, 1H), 0.87 (s, 9H), 0.044 (s, 3H), 0.037 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.9, 162.6, 103.4, 81.9, 69.0, 60.8, 25.7 (3C), 18.2, -5.6 (2C); HRMS (ESI^+): *m/z* calcd. for $[C_{12}H_{22}O_4SiNa]$ 281.1185, found 281.1188, Δ = 1.2 ppm.

6.7.6 4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-6-*O*-*tert*-butyldimethylsilyl-1,5-anhydro-2-deoxy-D-threo-hex-1-en-3-ulose 424



To a stirred solution of ulose **423** (105 mg, 0.36 mmol, 100 mol-%) and molecular sieves (4 Å, 92 mg) in CH_2Cl_2 (1.5 mL) at -78 °C were added $BF_3{\cdot}OEt_2$ (20 µL, 17 mg, 0.12 mmol, 32 mol-%) and **420** (220 mg, 0.45 mmol, 120 mol-%). The mixture was allowed to warm at rt and stirred for 16 h before Et_3N (4 drops) was added. The mixture was filtered through celite with CH_2Cl_2 (10 mL) and concentrated in vacuo. Purification of the residue by flash chromatography (30%

EtOAc/hexanes) afforded impure **424** as yellowish oil (11 mg, 5%). This product was used in the next step without further purification.

R_f (50% EtOAc/Hex) = 0.31; HRMS (ESI^+): *m/z* calcd. for [$C_{26}H_{40}O_{13}SiNa$] 611.2136, found 611.2131, Δ = -0.7 ppm.

6.7.7 Attempts to Crystallize and Deprotect the HDA Products

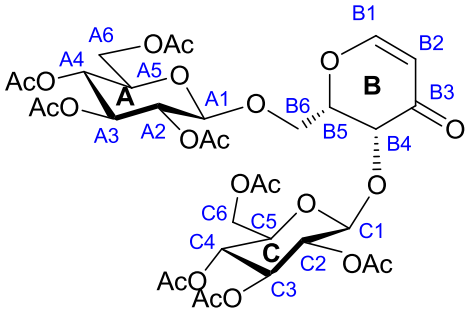
HDA product **416** (50 mg, 0.06 mmol) was dissolved in small portion of MeOH (0.2 mL). Different combination of Et_2O and EtOAc was added (total volume 0.5-2 mL). The mixture was cooled to -20 °C, but no crystals were got.

Also removal of acetyl protection of HDA product **410** was tried. However, when Zemplén conditions (NaOMe in MeOH, 1 M, 0.32 mL, 1000 mol-%) at rt were used, only decomposition of **410** (25 mg, 0.032 mmol, 100 mol%) occurred. Also the use of Et_3N (7 µL, 4.8 mg, 100 mol-%) as the base in CH_2Cl_2 (1 mL) was attempted, but no reaction of **410** (38 mg, 0.047 mmol, 100 mol%) was observed (at rt, 7 days).

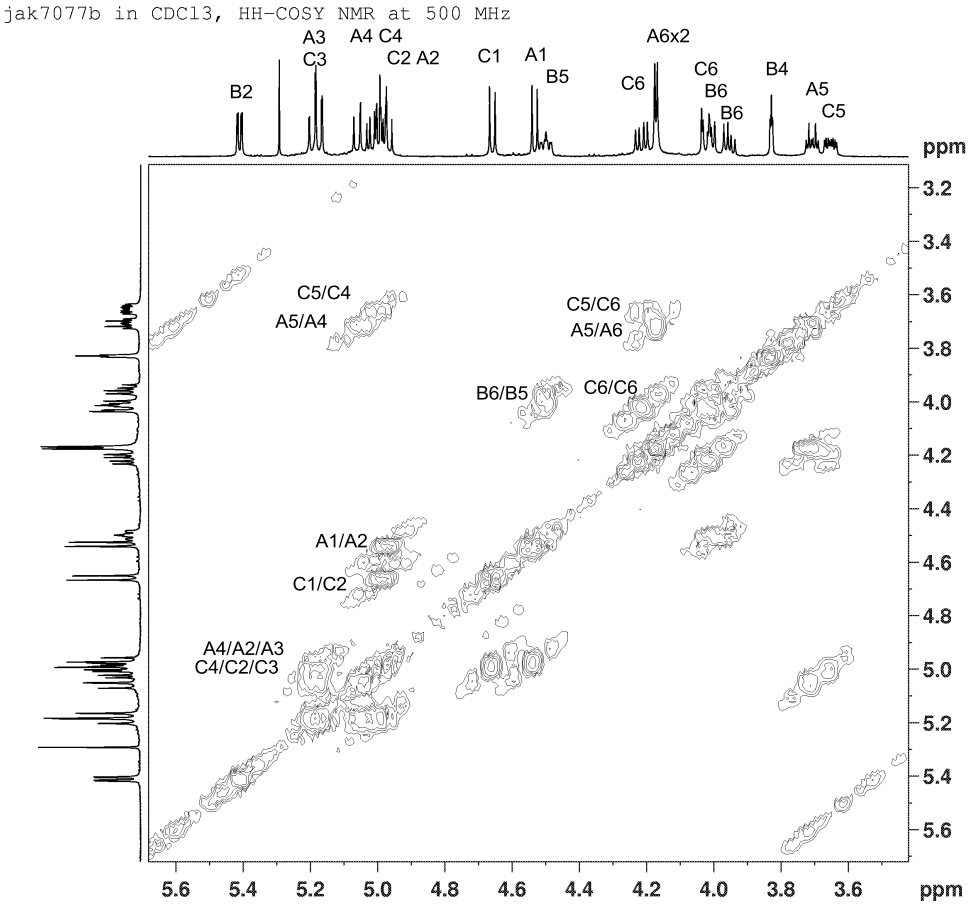
6.7.8 1D NOE and 2D NOESY Experiments of Compound 416

The details of the structural assignment are provided here for the glucose-derived trisaccharide **416** as this compound displayed the best separation of key signals for the assignment. For the details of other compounds, the reader is referred to the Supporting Information of (208). The NMR spectra were recorded in $CDCl_3$ at a concentration of 5 mg/0.6 mL $CDCl_3$.

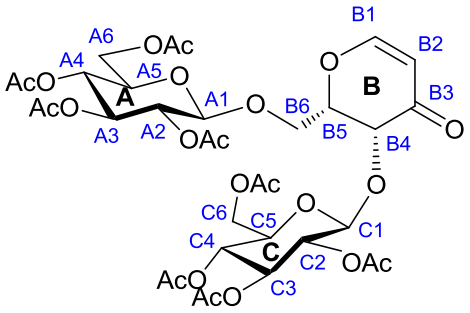
416: ^{1}H-^{1}H COSY



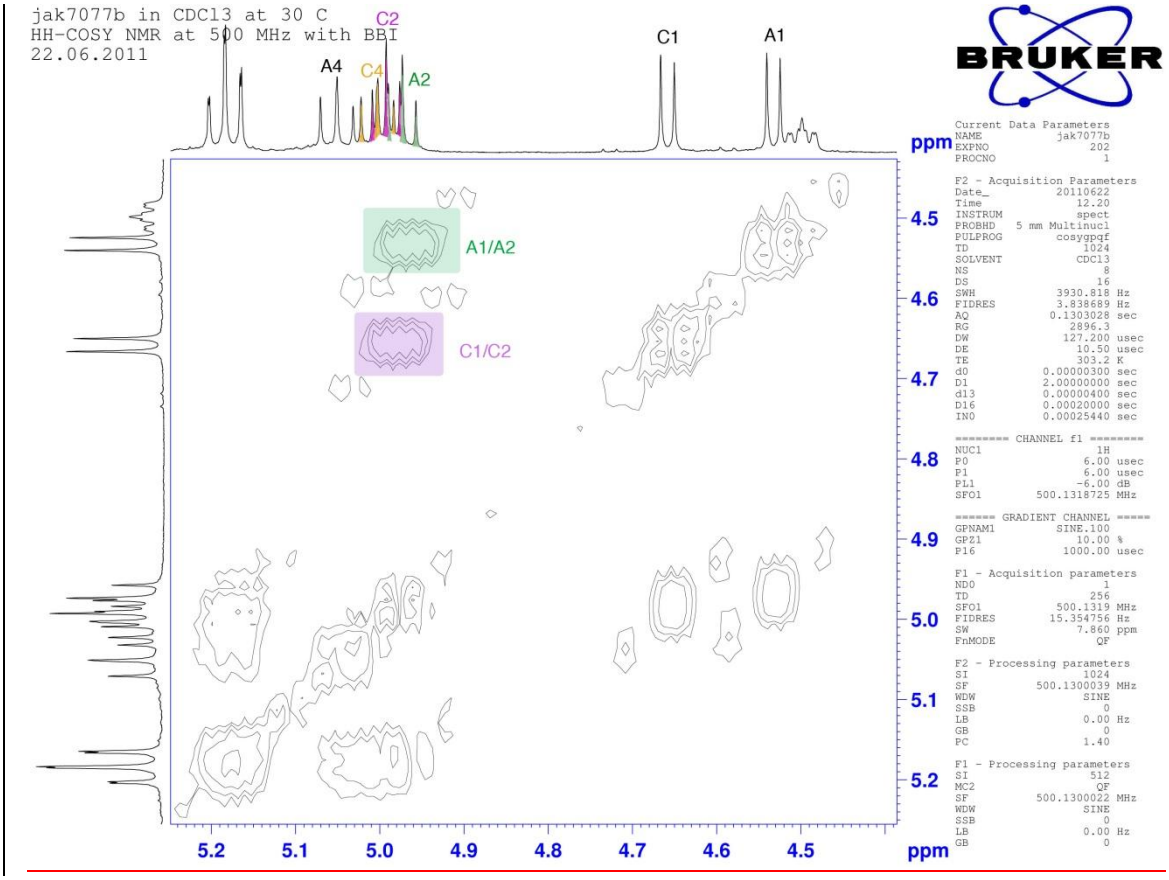
416



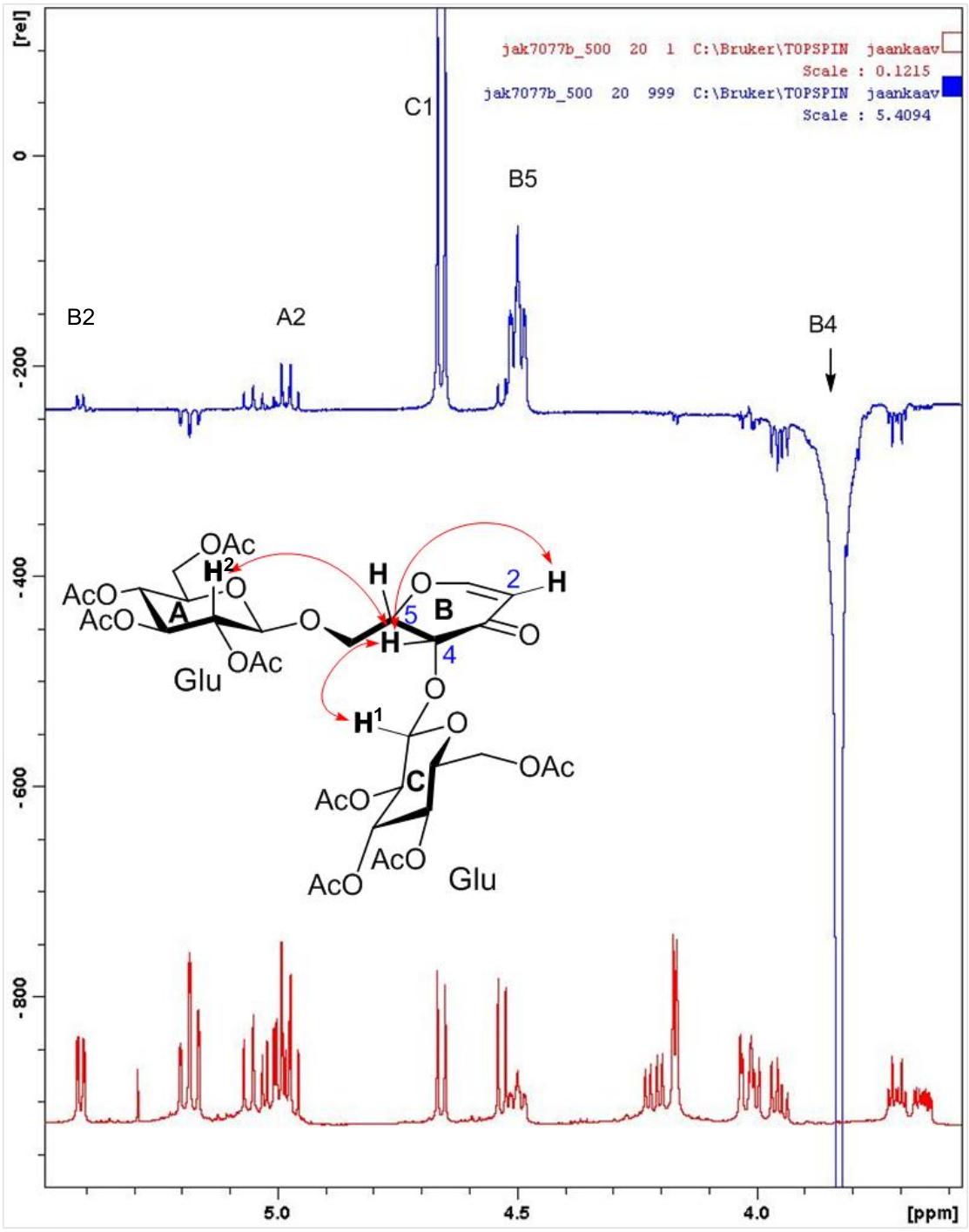
For the assignment of the A4, C4, C2, and A2 protons, please see the following expansion of the COSY spectrum:



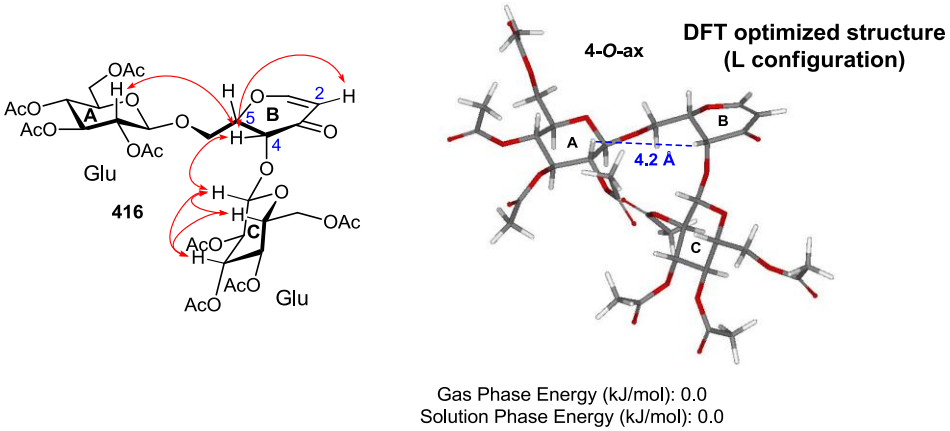
416

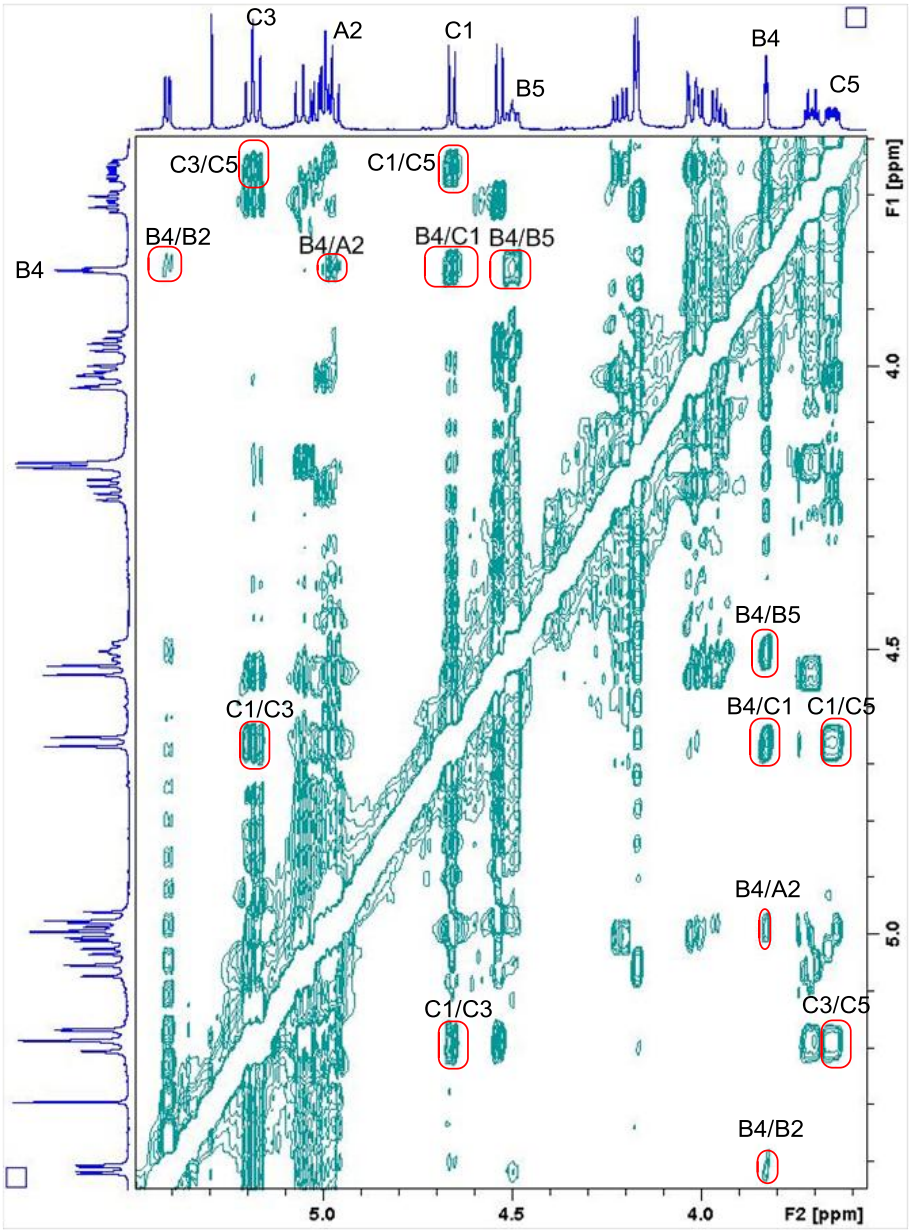


1D NOE experiment with **416** allows the clear assignment of C1 proton and also illustrates a key NOE between B4 and A2 protons.



Finally, a 2D NOESY experiment (mixing time 0.6 s) confirms the B4/A2 NOE.





6.7.9 Computational Details

The initial structures for the geometry optimizations were generated in an extensive Monte Carlo conformational search using MMFF94s force field as implemented in the *MacroModel* software. [*Macromodel embedded in Maestro suite (Version 9.1)*; Schrödinger, Inc.: Portland, OR, **2010**.] Both L and D configurations of the central B ring, as well as both pseudoaxial and pseudoequatorial conformers of the 4-oxygen substituent were considered. For each cluster, ten lowest non-redundant conformers were further were further optimized by density functional theory (DFT) optimization (B3LYP/6-311G**) (for the 6-31G* basis set, see: (209) (210) (211) (212) (213)) in the Jaguar module of the Maestro suite and ranked by both gas phase as well as solution phase energy. The lowest energy conformers of each cluster are shown in Figure 3 at p. 81. Significantly, the isomer L-4OAx that also matches the NOE data lies significantly lower in energy than all other identified conformers.

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