STEREOSELECTIVE REACTIONS IN CARBOHYDRATE SYNTHESIS

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DOCTORAL THESIS

Supervised by

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Departament de Química Analítica i Química Orgànica

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FEM CONSTAR que aquest treball titulat "Stereoselective Reactions in Carbohydrate Synthesis" presentat per Irene Marín Ferré per a l'obtenció del títol de Doctora, ha estat realitzat sota la nostra supervisió al Departament de Química Analítica i Química Orgànica d'aquesta mateixa universitat i en altres laboratoris universitaris en el marc de col·laboracions científiques, i que compleix els requeriments per poder optar a la Menció Europea.

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Publications

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Monge, D.; Jensen, K. L.; Marín, I.; Jørgensen, K. A. **Synthesis of 1,2,4-Triazolines: Base-Catalyzed Hydrazination/Cyclization Cascade of α-Isocyano Esters and Amides.** *Org. Lett.* **2011**, *13*, 328-331 (highlighted in *SYNFACTS* **2011**, *3*, 327).

Marín, I.; Matheu, M. I.; Díaz, Y.; Castillón, S. **Stereoselective Tandem Epoxidation–Alcoholysis/Hydrolysis of Glycals with Molybdenum Catalysts.** *Adv. Synth. Catal.* **2010**, *352*, 3407-3418.

Castilla, J.; Marín, I.; Matheu, M. I.; Díaz, Y.; Castillón, S. **Short and General Procedure for Synthesizing Cis-1,2-Fused 1,3-Oxathiolan-, 1,3-Oxaselenolan-, and 1,3-Oxazolidin-2-imine Carbohydrate Derivatives.** *J. Org. Chem.* **2010**, *75*, 514-517.

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Si ja és difícil resumir el treball de quatre anys, més difícil és encara agrair a tota la gent que ha recorregut amb tu el camí. Per a mi la tesi ha sigut com una melodia. Hi hagut moments bons i no tan bons, alguns amb la pràctica han millorat i d'altres han necessitat més pràctica, però el que està clar és que les persones que m'han envoltat són les tecles que m'han permès "tocar" aquesta melodia, la melodia de la meva tesi.

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comprovat com els vostres propis llocs d'estada no eren uns llocs t'han horribles!:) Gràcies també Miri per aquests últims anys, per compartir amb mi els teus dubtes post-tesi i sobretot per la teva amistat.

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Abbreviations and Acronyms

Ac:	Acetyl
AIBN:	Azobisisobutyronitrile
AIDS:	Acquired immunodeficiency syndrome
Asn:	Asparagine
BHT:	Butylated hydroxytoluene
Bn:	Benzyl
Bz:	Benzoyl
cat.:	Catalytic
CHF:	Congestive heart failure
Conv:	Conversion
DAST:	Diethylaminosulfur trifluoride
DBP:	Dibutylphosphate
DBTO:	Dibenzothiophene 5-oxide
DCC:	Dicyclohexylcarbodiimide
DDQ:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT:	Density functional theory
DHAP:	Dihydroxyacetone phosphate
DIBAL:	Diisobutylaluminum hydride
DEAD:	Diethyl azodicarboxylate
DIAD:	Diisopropylazodicarboxylate
DMAP:	4-Dimethylaminopyridine
DMDO:	3,3-Dimethyldioxirane
DMF:	Dimethylformamide
DMSO:	Dimethyl sulfoxide
d.r.:	Diastomeric ratio
ds:	Diastereofacial selectivity
ee:	Enantiomeric excess
e.g.:	For example
equiv:	Equivalents
et al.:	And others
EWG:	Electron withdrawing group
HIV:	Human immunodeficiency virus
HMPA:	Hexamethylphosphoramide

HOMO:	Highest occupied molecular orbital
HPLC:	High-pressure liquid chromatography
IBX:	2-Iodobenzoic acid
IDCP:	Iodoniumdicollidine perchlorate
Init:	Initiator
i-Pr:	*iso*-Propyl
IR:	Infrared *Spectroscopy*
LA:	Lewis acid
Lev:	Levulinic
LG:	Leaving Group
Ln:	Ligand
LUMO:	Lowest unoccupied molecular orbital
MCBA:	*m*-Chlorobenzoic acid
MCPBA:	*m*-Chloroperbenzoic acid
MEM:	Methoxyethoxyl
Mes:	Mesityl
mixt.:	Mixture
MOM:	Methoxymethyl
MSDS:	Material Safety Data Sheet
Mp:	Melting point
MTO:	Methyltrioxorhenium
NaHMDS:	Sodium bis(trimethylsilyl)amide
NBSH	2-Nitrobenzenesulfonylhydrazide
NCX:	Na/Ca-exchanger
NIS	*N*-Iodosuccinimide
NKA:	Na^+/K^+-ATPase
NMO:	*N*-methylmorpholine-*N*-oxide
NMR:	Nuclear magnetic resonance
Np:	Naphthyl
PHP:	Pinane hydroperoxide
Piv:	Pivaloyl
PLB:	Phospholamban
PMB:	*p*-Methoxybenzyl
Pro:	Proline

PTC:	Phase-transfer catalysis
p-TSA:	*p*-Toluenesulfonic acid
Py:	Pyridine
Ref:	References
RRV:	Relative reactivity value
rt:	Room temperature
RyR:	Ryanodine-receptors
SEM:	[2-(Trimethylsilyl)ethoxy]methyl
SERCA:	Sarcoplasmatic reticulum Ca-ATPase
SOC:	Sodium open channels
SOM:	Dimethyl-*tert*-butylsilyloxy methyl
SR:	Sarcoplasmatic reticulum
TBAF:	Tetra-*n*-butylammonium fluoride
TBAI:	Tetra-*n*-butylammonium iodide
TBDPSCl:	*tert*-Butyldiphenylsilyl chloride
TBHP:	*tert*-Butyl hydroperoxide
TBSCl:	*tert*-Butyldimethylsilyl chloride
TEA:	Triethylamine
Temp:	Temperature
TFA:	Trifluoroacetic acid
Tf_2O:	Trifluoromethanesulfonyl anhydride
THF:	Tetrahydrofuran
THP:	Tetrahydropyranyl
TIPSCl	Triisopropylsilyl chloride
TLC:	Thin layer chromatography
TMEDA:	Tetramethylethylenediamine
Tol:	Tolyl
TPP:	Tetraphenylporphyrin
TS:	Transition State
TsOH:	*p*-Toluenesulfonic acid
UHP:	Hydrogen peroxide urea adduct
vs.:	Versus
WH:	Wittig-Horner

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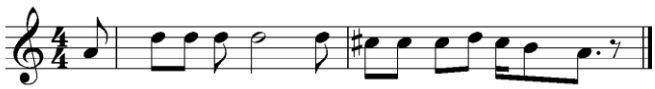

Vetusta Morla - Copenhague

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Chapter 6. *Organocatalytic and Chiral Auxiliary Approaches*

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GENERAL INTRODUCTION

Glycoproteins with *N*-glycans found on cell surfaces and in the blood serum play important roles in many biological events such as cell-cell adhesion, immune system modulation, and signal transduction. Subtle changes of the carbohydrate moieties may result in completely altered functionality of the glycoproteins. Therefore, asparagine linked *N*-glycans have gained intensive investigations.[1] Actually, only a few of these oligosaccharides can be isolated from natural sources due to their microheterogeneity.[2] These circumstances have stimulated the chemical synthesis of *N*-glycans as a method to provide sufficient quantities for further research.[3]

Manno-oligosaccharides

High mannose type oligosaccharides are ubiquitous in nature.[4] Different *N*-linked *manno*-oligosaccharides are found on the viral transmembrane glycoprotein gp120 of the human immunodeficiency virus (HIV).[5] This glycoprotein has a key role in viral attachment and initiation of infection[6] through interaction with the CD4 glycoprotein of T-lymphocytes (Figure 1).[7] The oligosaccharides of gp120 are likely to be prominent structures on the virus surface and are candidate attachment and addressing factors in the host for

1 Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Stanley, P.; Bertozzi, C. R.; Hart, G. W.; Etzler, M. E.; Eds. *Essentials of Glycobiology*, 2nd ed.; Cold Spring Harbor Laboratory Press: NY, **2009**.

2 a) Endo, T. *J. Chromatogr. A.* **1996**, *720*, 251-261. b) Rice, K. G. *Anal. Biochem.* **2000**, *283*, 10-16.

3 a) Ogawa, T.; Sugimoto, M.; Kitajima, T.; Sadozai, K. K.; Nukada, T. *Tetrahedron Lett.* **1986**, *27*, 5739-5742. b) Nukada, T.; Kitajima, T.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1992**, *228*, 157-170.

4 a) Lis, H.; Sharon, N. *J. Biol. Chem.* **1978**, *253*, 3468-3476. b) Li, E.; Kornfeld, S. *J. Biol. Chem.* **1979**, *254*, 1600-1605. c) Dorland, L.; van Halbeek, H.; Vliegenthart, J. F. G.; Lis, H.; Sharon, N. *J. Biol. Chem.* **1981**, *256*, 7708-7711.

5 Montagnier, L.; Clavel, F.; Kurst, B.; Chamaret, S.; Rey, F.; Barre-Sinoussi, F.; Chermann, J. C. *Virology* **1985**, *144*, 283-289.

6 a) McDougal, J. S.; Kennedy, M. S.; Sligh, J. M.; Cort, S. P.; Mawle, A.; Nicholson, J. K. A.; *Science* **1986**, *231*, 382-385. b) Lasky, L. A.; Nakamura, G.; Smith, D. H.; Fennie, C.; Shimasaki, C.; Patzer, E.; Berman, P.; Gregory, T.; Capon, D. J. *Cell* **1987**, *50*, 975-985.

7 a) Dalgleish, A. G.; Beverley, P. C. L.; Clapham, P. R.; Crawford, D. H.; Greaves, M. F.; Weiss, R. A. *Nature* **1984**, *312*, 763-766. b) Klatzmann, D.; Champagne, E.; Chamaret, S.; Gruest, J.; Guetard, D.; Hercend, T.; Gluckman, J.- C.; Montagnier, L. *Nature* **1984**, *312*, 767-768.

antiviral agents and vaccines.[8] Mimicking the cluster presentation of the oligomannosides on the virus surface is a strategy for designing carbohydrate-based antiviral agents.

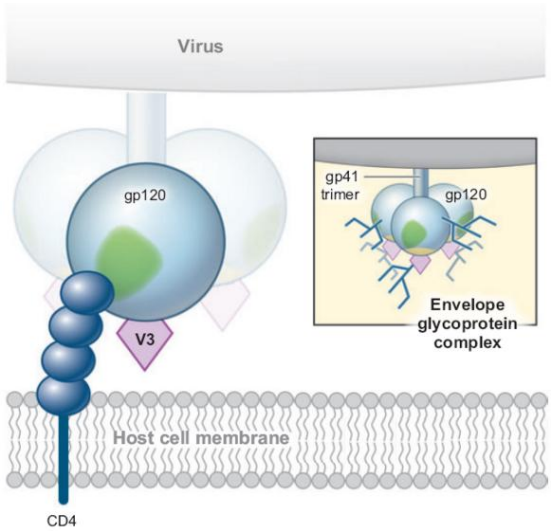


Figure 1. The HIV envelope glycoprotein complex drives viral entry into target cells.

The total synthesis of high-mannose type cell surface glycans, which are found throughout nature as *N*-linked glycoconjugates, has been explored for the past two decades,[9] but new methods of formation of the glycosidic linkage in a regio- and stereoselective way are still necessary.

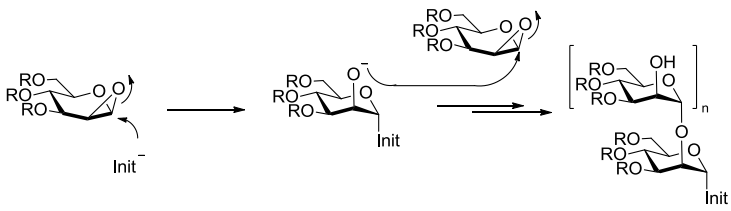
The ultimate goal of this thesis is the stereoselective obtention of *manno*-epoxides from glycals in order to use them in the synthesis of *manno*-oligosaccharides of well-defined size and low polidispersity through living anionic polymerization (Scheme 1).[10]

---

8 a) McReynolds, K. D.; Gervay-Hague, J. *Chem. Rev.* **2007**, *107*, 1533-1552. b) Scanlan, C. N.; Offer, J.; Zitzmann, N.; Dwek, R. A. *Nature* **2007**, *446*, 1038-1045.

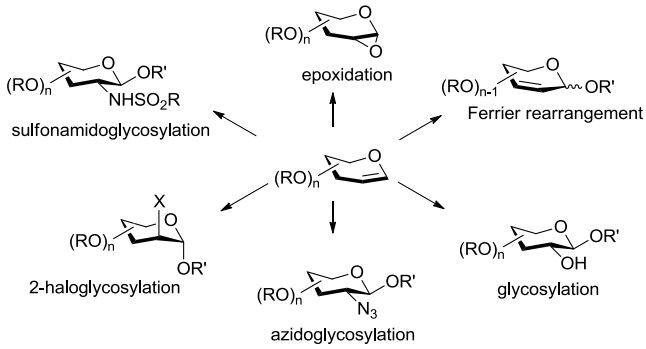
9 a) Ogawa, T.; Nukada, T. *Carbohydr. Res.* **1985**, *136*, 135-152. b) Merritt, J. R.; Naisang, E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4443-4449. c) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53-80.

10 a) Szwarc, M.; Levy, M.; Milkovich, R. *J. Am. Chem. Soc.* **1956**, *78*, 2656-2657. b) Watanabe, Y.; Aida, T.; Inoue, S. *Macromolecules*, **1990**, *23*, 2612-2617.



Scheme 1. Living anionic polymerization of *manno*-epoxides (Init: Initiator).

Glycals are versatile building blocks due to their enol ether structure. Hence, they are employed in the assembly of oligosaccharides and other glycoconjugates. By the pioneering research of Lemieux and Thiem,[11] glycals are known to act as glycosyl donors, and are activated by a variety of electrophilic reagents undergoing reactions of azidoglycosylation,[12b] sulfonamidoglycosylation,[12b] Ferrier rearrangement[12c] and particularly epoxidation[12a-b] (Scheme 2).



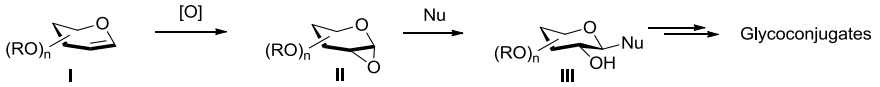
Scheme 2. Glycosyl donors by activation of glycals.

1,2-Anhydro sugars (glycal epoxides) are important intermediates in the synthesis of oligosaccharides and other anomerically-substituted carbohydrate derivatives. Moreover, liberation of the hydroxyl function at C-2, which accompanies the oxirane ring opening, provides additional synthetic perspectives. The most common route towards 1,2-anhydrosugars (**II**) is via epoxidation of

[11] a) Lemieux, R. U.; Levine, S. *Can. J. Chem.* **1964**, *42*, 1473-1480. b) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696-698.

[12] a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666. b) Seeberger, P. H.; Bilodeau, M. T.; Danishefsky, S. J. *Aldrichimica Acta* **1997**, *30*, 75-92. c) Ferrier, R. J.; Prasad, N. J. *J. Chem. Soc. C* **1969**, 570-575.

glycals (**I**) (Scheme 3), but this is not a trivial task due, among other reasons, to the sensitive nature of the epoxide, particularly in acidic media.



Scheme 3. Synthetic sequence for the use of glycals as building blocks in the construction of glycoconjugates.

This transformation is usually performed using dimethyldioxirane (DMDO).[12a] Other stoichiometric reagents have been proposed, such as MCPBA/KF,[13] but no general catalytic oxidation procedure has been reported so far for this type of transformation. Moreover, most of the epoxidation procedures of glucals provide the *gluco* derivative as the main isomer, which makes the epoxidation of glycals to give the *manno*-epoxide still a challenge.

2-Deoxyglycosides

2-Deoxy- and 2,6-dideoxyglycosides are structural units present in many natural products. Deoxysugars are defined carbohydrates with a substitution of one or more of the hydroxylic groups by another heteroatom or hydrogen. These compounds present interesting biological properties, such as the antitumor agents (anthracyclines like cyclamycin 0, aureolic acids, calicheamicin, spiramycin, angucyclines like landomycin A, indolocarbazole glycosides like the antibiotic AT2433-A1), antibiotics against Gram-positive bacteria (erithromycin, orthosomycin), antibiotic inhibitors of platelet aggregation (angucyclines), compounds used to treat the heart failure (cardiac glycosides like digitoxin), antiparasitic agents (avermectins), and appetite suppressants (like P57) (Figure 2).[14] Although the pharmacological effect of these compounds is associated to the aglycone moiety, the oligosaccharidic part is essential for the biological activity because it influences the pharmacokinetic properties, and participates in the

[13] Bellucci, G.; Catelani, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron Lett.* **1994**, *35*, 8433-8436.

[14] a) Kennedy, J. F.; White, C. A. *Bioactive Carbohydrates in Chemistry, Biochemistry, and Biology*, Chichester: Ellis Horwood, **1983**. b) Williams, N.; Wander, J. *The Carbohydrates: Chemistry and Biochemistry*, Vol. 1B; Pigman, W.; Horton, D. Eds.; Academic Press: New York, **1980**.

molecular recognition. Removing deoxysugars from these clinically important molecules often severely decreases their efficiency and/or specificity.[15] Due to this biological relevance, the development of methods for the efficient, chemo- and stereoselective construction of glycosidic linkages in deoxyglycosides has useful applications in medicinal and bioorganic chemistry by further understanding the biological mechanisms and elaborate new and less toxic drugs.

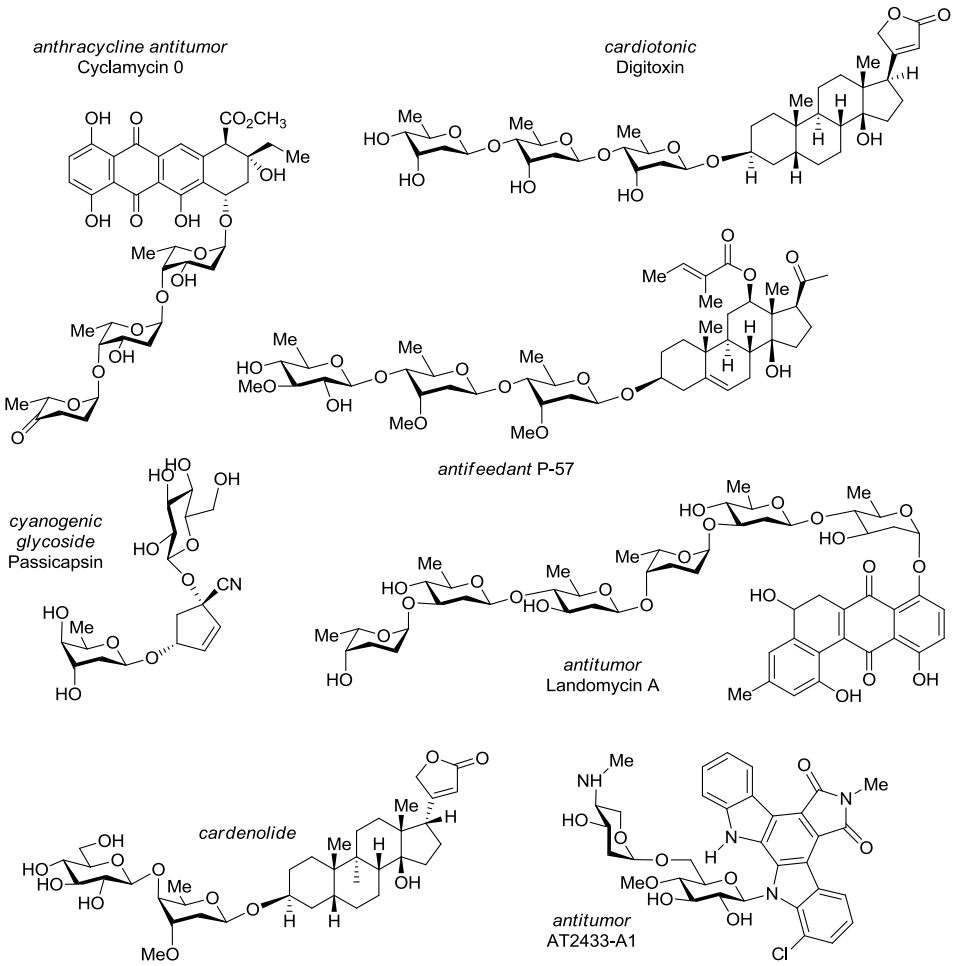


Figure 2. Examples of natural compounds with 2,6-dideoxyoligosaccharide units.

[15] Křen, V.; Martínková, L. *Curr. Med. Chem.* **2001**, *8*, 1313-1338.

The glycosylation of 2-deoxyglycosides and particularly the control of the stereoselectivity is a real challenge because of the absence of participating groups at the neighbouring position. Moreover, the absence of electron withdrawing substituents at position 2 makes the glycosidic bond more labile in acidic media, and consequently the hydrolysis and racemization is easier than in glycosides with hydroxyl groups at position 2. The synthesis of 2-deoxyglycosides has been reviewed.[16]

The stereoselective synthesis of 2-deoxyglycosides (Scheme 4), as well as 2-deoxynucleosides, is usually carried out with the help of participating groups at position 2, which are easily removed after the glycosylation. These methodologies involve the introduction of a heteroatom at position 2, which has been performed by the following procedures: a) addition of an electrophile (I^+,[11,17] H^+,[18] O,[19] SePh[20]) to the double bond of glycals (via 1). This procedure can be carried out in a *one-pot* manner by driving the reaction in the presence of the glycosyl acceptor (via 1), or by isolating first the glycosyl donor intermediate (via 1') which is further activated in a second step in the presence of a glycosyl acceptor.[21] b) From 1-thio-, or 1-seleno-*manno*-glycosides by activating a 2-OH and 1,2-migration of the anomeric group (SR,[22] SeR[23]) (via 3). Similarly, *one-pot* (via 3) or consecutive

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19 Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 1380-1419.

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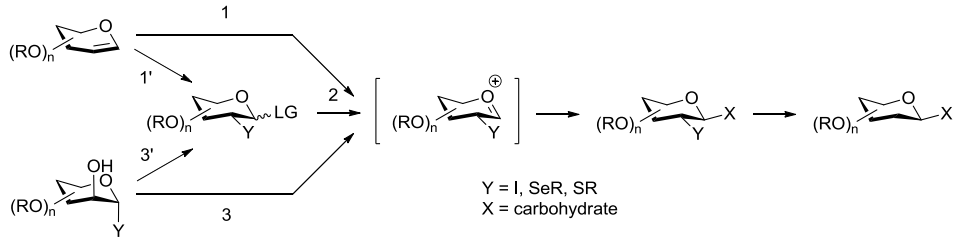
21 a) Blanchard, N.; Roush, W. R. *Org. Lett.,* **2003**, *5*, 81-84. b) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1871-1874.

22 a) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc*. **1986**, *108*, 2466-2467. b) Nicolaou, K. C.; Hummel, C. W.; Bockovich, N. J.; Wong, C.- H. *J.*

reactions (via 3') have been described.[24] c) A less common procedure for controlling the stereoselectivity of the glycosylation reaction is by a S_N2 reaction by using appropriated leaving groups (fluorides,[25] fosfites,[26] fosfates,[27] fosforamidites,[28] tetrazoles,[29] sulfoxides,[30] triflates, etc).



Scheme 4. Methodologies for the stereoselective synthesis of 2-deoxyglycosides.

Digitoxin (Figure 2), which is a metabolite present in *Digilitalis purpurea* and *Digitalis lanata*,[31] belongs to the family of cardiac glycosides.[32] They are positive inotropic substances; thus, they increase stroke volume and cardiac output and improve cardiac performance.[33] This class of compounds is characterized by an aglycone linked to a mono- to tetrasaccharide carbohydrate. It is the aglycone that possesses pharmacological activity, but the carbohydrate is thought to influence

Chem. Soc., Chem. Commun. **1991**, 870-872. c) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1874-1876. d) Zuurmond, H. M.; van der Klein, P. A. M.; van del Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993,** *49*, 6501-6514.

23 Nicolaou, K. C.; Mitchell, H. J.; Fylaktakidou, K. C.; Suzuki, H.; Rodriguez, R. M. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1089-1093.

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27 Oberthür, M.; Leimkuhler, C.; Kahne, D. *Org. Lett.* **2004**, *6*, 2873-2876.

28 Li, H.; Chan, M.; Zhao, K. *Tetrahedron Lett*. **1997**, *38*, 6143-6144.

29 Sobti, A.; Kim, K. J.; Sulikowski, G. A. *J. Org. Chem*. **1996**, *61*, 6-7.

30 Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881-6882.

31 a) Yusuf, S.; Garg, R.; Held, P.; Gorlin, R. *Am. J. Cardiol.* **1992**, *69*, 64G-70G. b) Treatment of congestive heart failure-current status of use of Digitoxin: Belz, G. G.; Breithaupt-Grogler, K.; Osowski, U. *Eur. J. Clin. Invest.* **2001**, *31*, 10-17.

32 Repke, K. R. H.; Megges, R.; Weiland, J.; Schön, J. W. R. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 282-294.

33 Joubert, P. H.; Grossman, M. *Eur. J. Clin. Invest.* **2001**, *31*, 1-4.

pharmacokinetics of the compound (absorption, distribution, metabolism and excretion).

It is known that contraction of the heart muscle is activated by a transient increase in intracellular Ca^{2+} concentration. The mechanism of action of cardiac glycosides, which is still being debated, involves inhibition of a membrane $Na^{+}K^{+}$ ATPase (NKA).[34] Recently, it was reported that digitoxigenin, its glycosides and its derivatives (Figure 2) strongly inhibit the proliferation or induced apoptosis of various malignant cell lines.[35] In response, certain carbohydrate-modified moieties have been synthesized to impair Na/K-ATPase activity and improve tumor-specific cytotoxic activity.[36]

Thus, the stereocontrolled construction of deoxyoligosaccharides scaffolds is important, but it is also a complex process for a number of reasons: a) the absence of a substituent at C-2 makes it difficult to control the stereoselectivity of the reaction; b) the 2-deoxyglycosyl donors and the glycoside products exhibit increased lability, and need to be handled with particular care; and c) the deoxyglycosidic linkage is very acid labile. Thus, these issues must be solved when developing a method for constructing such molecules.

This thesis deals with two topics connected with carbohydrate chemistry. The first part presents epoxidation and dihydroxylation reactions of glycals towards the synthesis of *manno* oligosaccharides. The second part is related to the synthesis of the cardiotonic digitoxin.

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[34] a) Heller, M. *Biochem. Pharmacol*. **1990**, *40*, 919-925. b) Lee, C. O.; Abete, P.; Pecker, M.; Sonn, J. K.; Vassalle, M. *J. Mol. Cell. Cardiol.* **1985**, *17*, 1043-1053. c) Santana, L. F.; Gomez, A. M.; Lederer, W. J. *Science*, **1998,** *279*, 1027-1033. d) Sagawa, T.; Sagawa, K.; Kelly, J. E.; Tsushima, R. G.; Wasserstrom, J. A. *Am. Journ. of Physiology-Heart and Circulatory Physiology* **2002**, *282*, H1118-H1126.

[35] a) Ueda, J.; Tezuka, Y.; Banskota, A. H.; Tran, Q. L.; Tran, Q. K.; Saiki, I.; Kadota, S. *J. Nat. Prod.* **2003**, *66*, 1427-1433. b) Laphookhieo, S.; Cheenpracha, S.; Karalai, C.; Chantrapromma, S.; Rat-a-pa, Y.; Ponglimanont, C.; Chantrapromma, K. *Phytochemistry* **2004**, *65*, 507-510. c) Lopez-Lazaro, M.; Pastor, N.; Azrak, S. S.; Ayuso, M. J.; Austin, C. A.; Cortes, F. *J. Nat. Prod.* **2005**, *68*, 1642-1645.

[36] Langenhan, J. M.; Peters, N. R.; Guzei, I. A.; Hoffmann, F. M.; Thorson, J. S. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 12305-12310.

UNIVERSITAT ROVIRA I VIRGILI
STEREOSELECTIVE REACTIONS IN CARBOHYDRATE SYNTHESIS
Irene Marin Ferré
DL: T. 161-2012

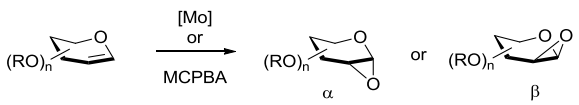
OBJECTIVES

The present work aims to develop new methodologies in carbohydrate chemistry and focuses on two different main objectives:

1. Epoxidation and dihydroxylation reactions of glycals (Part A): The work presented in this section has as a final objective developing methods for preparing 1,2-linked mannose oligomers present in glycoproteins of interest starting from *manno*-epoxides. To achieve this objective it is necessary to establish efficient protocols for accessing the starting materials. Thus, the research described in this part aims to develop new methods for the synthesis of 1,2-anhydrosugars through direct epoxidation of differently protected glycals by exploring two different approaches:

a) Catalytic: using molybdenum catalysts and *tert*-butylhydroperoxide (TBHP) as oxidizing agent (Chapter 2).

b) Stoichiometric: using *m*-chloroperbenzoic acid (MCPBA) as the oxidant (Chapter 3).



Scheme 5. Epoxidation reaction of glycals.

The following issues will be analyzed in this study:

- The effect of protecting groups and glycal configuration in the efficiency and stereoselectivity of the epoxidation reaction.

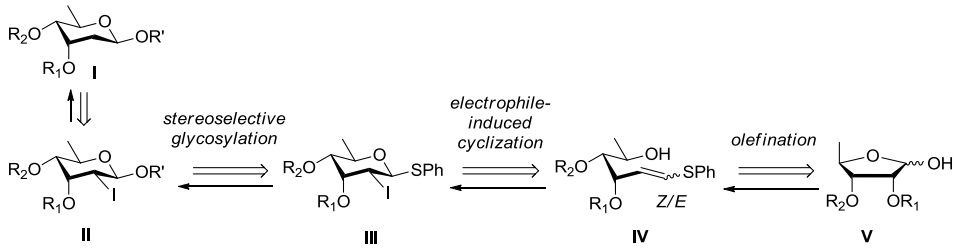
- The directing effect of free hydroxyl groups in the epoxidation reaction in order to obtain β-epoxides.

- The application of this methodology to the straightforward synthesis of orthogonally protected *manno* glycosyl donors.

2. Approaches to the synthesis of Digitoxin (Part B): The objective of this section is to develop new synthetic methodologies in order to obtain 2-deoxy-glycosides and 2-deoxy-oligosaccharides of *ribo* configuration on the way to

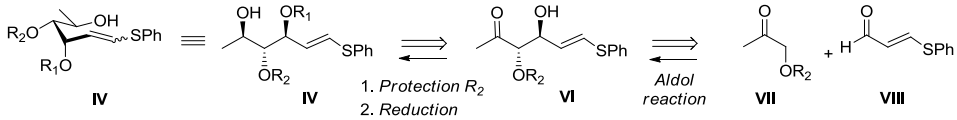
digitoxin synthesis. In connection with this purpose, the specific aims of the present work are the following:

- Synthesize 2-deoxy-glycosides **I** based on a new access to 2-deoxy-2-iodo glycosyl donors **II** from furanoses **V** through a three-step route developed in our group consisting in an olefination-cyclization-glycosylation process (Chapter 5).



Scheme 6. Proposed methodology for the synthesis of 2-deoxy-2-iodo glycosyl donors **II**.

- Develop an alternative synthesis to obtain alkenyl sulfides of type **IV** using asymmetric *anti*-aldol reaction as a key step through organocatalysis and chiral auxiliaries (Chapter 6).



Scheme 7. Alternative synthesis towards alkenyl sulfides **IV**.

*E*PART A

oxidation and dihydroxylation reactions of glycals

Introduction

CHAPTER 1

1. Biological synthesis of *manno* oligosaccharides

Nowadays, glycoconjugates are in the spotlight of chemical and biological researchers because there are a number of important biological phenomena which depend on carbohydrate-protein interactions such as immune response, inflammation, cancer and pathogen recognition.[37] This fact has spurred the study of new synthetic methodologies looking for an easy and selective access to carbohydrate-based structures and it has become one of the biggest challenges of organic synthesis. In this context, glycals are versatile building blocks for the synthesis of oligosaccharide motifs,[38] 2-deoxyglycosides,[16c-f,39] *C*-glycosides,[40] nucleosides[41] and other biologically important molecules.[42,43,44] The structural diversity present in these compounds makes them possible to be involved in a large number of inter- and intramolecular key processes. Cell-surface

[37] a) Varki, A. *Glycobiology* **1993**, *3*, 97-130. b) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321-327. c) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683-720. d) Hakomori, S. *Adv. Cancer Res.* **1989**, *52*, 257-331. e) Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, *291*, 2370-2376.

[38] a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem. Int. Ed.* **1996**, *35*, 1380-1419. b) Roberge, J. Y.; Beebe, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 3915-3927. c) McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246-4247. d) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954-958.

[39] a) Hou, D.; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1911-1940. b) Kirschning, A.; Jesberger, M.; Schöning, K.- U. *Synthesis* **2001**, 507-540. c) Castro-Palomino, J. C.; Schmidt, R.R. *Synlett* **1998**, 501-503.

[40] a) Thorn, S. N.; Gallagher, T. *Synlett* **1996,** 856-858. b) Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917-1920.

[41] a) Robles, R.; Rodríguez, C.; Izquierdo, I.; Plaza, M. T.; Mota, A. *Tetrahedron: A*symmetry **1997**, *8*, 2959-2965. b) Díaz, Y.; El-Laghdach, A.; Castillón, S. *Tetrahedron* **1997**, *53*, 10921-10938. c) Díaz, Y.; El-Laghdach, A.; Matheu, M. I., Castillón, S. *J. Org. Chem.* **1997**, *62*, 1501-1505. d) Chao, Q.; Zhang, J.; Pickering, L.; Jahnke, T. S.; Nair, V. *Tetrahedron* **1998**, *54*, 3113-3124. e) Bravo, F.; Kassou, M.; Díaz, Y.; Castillón, S. *Carbohydr. Res.* **2001**, *336*, 83-97.

[42] For use in cyclopropanation and ring expansion see: Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.*, **1997**, *62*, 7694-7703.

[43] For use in a novel class of glycosylation based in a [4+2] cycloaddition see: a) Capozzi, G.; Dios, A.; Frank, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 777-779. b) Franck, R. W.; Marzabadi, C. H. *J. Org. Chem.* **1998**, *63*, 2197-2208.

[44] For the synthesis of thionucleosides from thioglycals see: Haraguchi, K.; Nishikawa, A.; Sasakura, E.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1998**, *39*, 3713-3716.

carbohydrates act as anchoring points of other cells, bacteria, virus, toxins and other molecules.[45] Carbohydrates are intrinsically related to the origin of numerous illnesses because they are involved in molecular recognition processes. As way of illustration, it is well known that cancer cells develop an aberrant glycosylation in their own membrane.[46] These and other discoveries have encouraged scientists to study oligosaccharide synthesis and function.

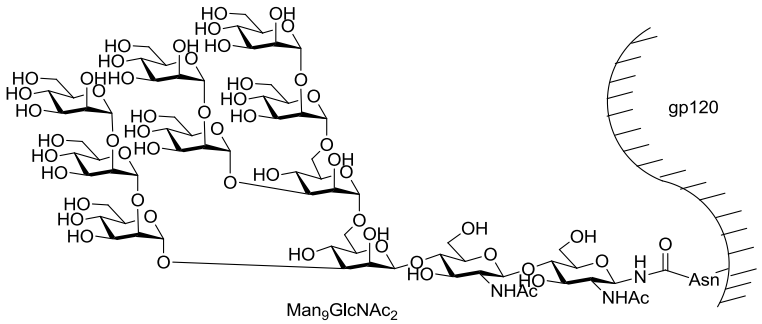


Figure 3. The high-mannose oligosaccharide ($Man_9GlcNAc_2$) is part of the glycoprotein gp120 of the viral coat of HIV-1.

There are a lot of 1,2-linkage high-mannose oligosaccharide in nature like $Man_9GlcNAc_2$.[4a] They are a member of the *N*-linked family of carbohydrates which are conjugated to glycoproteins via an *N*-acetylglucosamine unit to the amide group of an asparagine (Asn) residue on the polypeptide backbone. In particular, Mizuochi et al.[47] have shown that 29 different *N*-linked oligosaccharides are present on the envelope glycoprotein gp120 of the human immunodeficiency virus (HIV), which is known to bind with high affinity to

[45] a) Karlsson, K. A. *Trends Pharmacol. Sci.* **1991**, *12*, 265-272. b) Feizi, T.; Childs, R. A. *Biochem. J.* **1987**, *245*, 1-11. c) Varki, A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 7390-7397. d) Yuen, C.- T.; Bezouska, K.; O'Brien, J.; Stoll, M.; Lemoine, R.; Lubineau, A.; Kiso, M.; Hasegava, A.; Bockovich, N. J.; Nicolaou, K. C.; Feizi, T. *J. Biol. Chem.* **1994**, *269*, 1595-1598. e) Feizi, T. *Curr. Opin. Struct. Biol.* **1993**, *3*, 701-710.

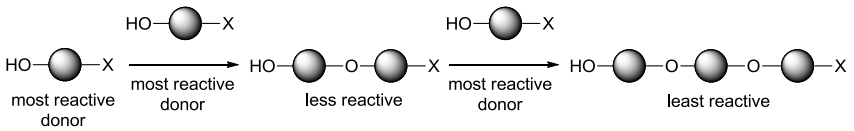
[46] Hakomori, S.- I. *Cancer Res.* **1985**, *45*, 2405-2414.

[47] Mizuochi, T.; Spellman, M. W.; Larkin, M.; Solomon, J.; Basa, L. J.; Feizi, T. *Biochem. J.* **1988**, *254*, 599-603.

human T4 lymphocytes causing AIDS (acquired immunodeficiency syndrome) (Figure 3).[48]

The chemical synthesis of segments of this binding region is of interest not only for the determination of their structure and/or conformation, but also for providing a supply of biological probes. Since gp120 has been implicated in the attachment and penetration of target cells and in the antiviral immune response,[49] it has also been anticipated that the glycans of the viral envelope are also possible targets for immunotherapy as well as vaccine development.[50] Müller et al.[51] have demonstrated the *in vitro* activity of antibodies directed against the mannose residues of HIV-1 glycoprotein gp120, and this result makes this mannan moiety an especially attractive synthetic target.

In this context, Wong developed a *one-pot* modular methodology to synthesize high-mannose oligosaccharides through self-condensation reaction.[52]



Scheme 8. Strategy for *one-pot* self-condensation synthesis.

In this type of *one-pot* synthesis, it is necessary to determine the relative reactivity value (RRV) of each monomer. This value is then used as a guide for

48 Grice, P.; Ley, S. V.; Pietruszka, J.; Osborn, H. M. I.; Priepke, H. W. M.; Warriner, S. L. *Chem. Eur. J.* **1997**, *3*, 431-440.

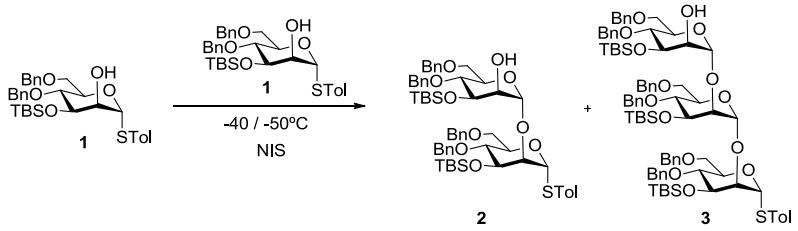
49 a) Dalgeish, A. G.; Beverely, P. C. L.; Clapham, P. R.; Crawford, D. H.; Greaves, M. F.; Weiss, R. A. *Nature* **1984**, *312*, 763-767. b) Richardson, N. E.; Brown, N. R.; Hussey, R. E.; Vaid, A.; Matthews, T. J.; Bolognesi, D. P.; Reinherz, E. L. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 6102-6106. c) Leonard, C. K.; Spellman, M. W.; Riddle, L.; Harris, R. J.; Thomas, R. N.; Gregory, T. J. *J. Biol. Chem.* **1990**, *265*, 10373-10382. d) LaRosa, G. J.; Davide, J. P.; Weinhold, K.; Waterbury, J. A.; Profy, A. T.; Lewis, J. A.; Langlois, A. J.; Dreesman, G. R.; Boswell, R. N.; Shadduck, P.; Holley, L. H.; Karplus, M.; Bolognesi, D. P.; Matthews, T. J.; Emini, E. A.; Putney, S. D. *Science* **1990**, *249*, 932-935.

50 Coffin, J. M. *Science* **1995**, *267*, 483-488.

51 Müller, W. E. G; Schröder, H. C.; Reuter, P.; Maidhof, A.; Uhlenbruck, G.; Winkler, I. *AIDS* **1990**, *4*, 159-162.

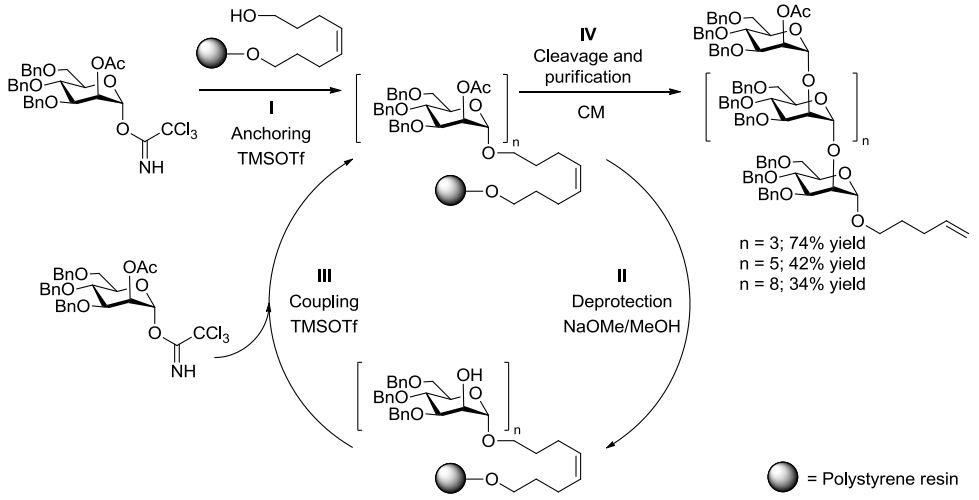
52 Lee, H. K.; Scanlan, C. N.; Huang, C. Y.; Chang, A. Y.; Calarese, D. A.; Dwek, R. A.; Rudd, P. M.; Burton, D. R.; Wilson, I. A.; Wong, C.- H. *Angew. Chem. Int. Ed.* **2004**, *43*, 1000-1003.

the selection of the reactivity order of the monomers in the synthesis. In this strategy, the most reactive monomer undergoes self-condensation to give a less-reactive dimer. The dimer then serves as an acceptor for another monomer molecule, which leads to formation of the trimer (Scheme 8). This method was applied to the synthesis of trimannose Manα1-2Manα1-2Man **3** from the mannose monomer **1** (Scheme 9).



Scheme 9. *One-pot* self-condensation synthesis of building blocks **2** and **3**.

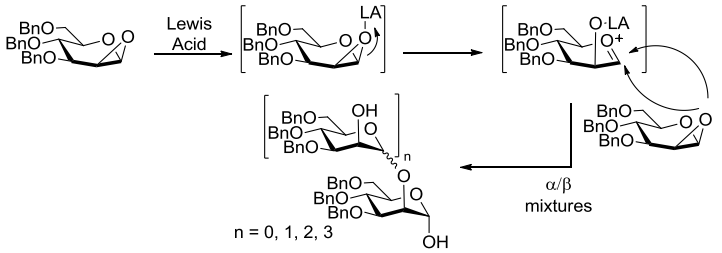
However, the necessity of a regio- and stereoselective control in the formation of the glycosidic linkage in this type of strategies often lead to laborious synthetic transformations, introduction/removal of protecting groups, mixture of glycosidic chains, and tedious isolations. All these problems make the overall synthetic process difficult and decrease the efficiency.



Scheme 10. Automated oligomannoside synthesis with trichloroacetimidates.

Seeberger investigated the synthesis of α-1,2 oligomannosides through automatic solid-phase synthesis.[53] A glycosylation (**III**)/deprotection (**II**) cycle was developed from the trichloroacetimidate donor and applied to the synthesis of a pentamer, a heptamer and a decamer of an α-1,2 mannoside (Scheme 10). The olefinic linker was readily cleaved from the solid support at the end of the synthesis by olefin cross metathesis (**IV**).

Schuerch developed another methodology to synthesize high-mannose oligosaccharides through polymerization of 1,2-anhydro-β-D-mannopyranoses in the presence of a Lewis acid, an acid catalyst or strong bases.[54] An example is shown in Scheme 11. This process leads to oligosaccharides or small polymers varying in anomeric configuration from ~90% α to 70% β. Polymerization in toluene by means of potassium alkoxide as initiator complexed with crown ethers leads to essentially stereoregular oligosaccharides (1→2)-α-D-mannopyranosides.



Scheme 11. Synthesis of (1→2)-mannopyranoside oligomers through controlled oligomerization.

2. Methods of synthesis of 1,2-Anhydrosugars

1,2-Anhydrosugars have proven to be invaluable tools for the synthesis of glycosides and oligosaccharides.[12a,55] The most common route towards 1,2-anhydrosugars is via activation of glycals.

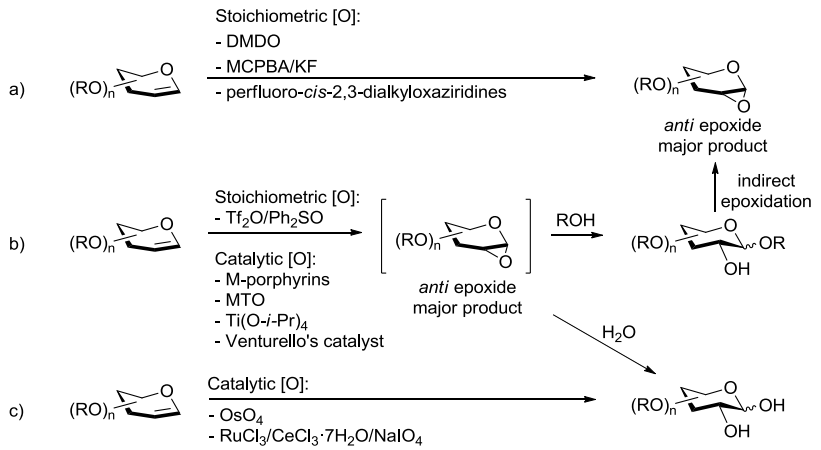
53 Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523-1527.

54 a) Yamaguchi, H.; Schuerch, C. *Biopolymers* **1980**, *19*, 297-309. b) Trumbo, D. L.; Schuerch, C. *Carbohydr. Res.* **1985**, *135*, 195-202.

55 Plante, O. J.; Andrade, R. B.; Seeberger, P. H. *Org. Lett.* **1999**, 1, 211-214.

One type of activation of glycals is via epoxidation.[12a] Thus, 1,2-anhydrosugars in the presence of Lewis acid catalysts proved to be excellent glycosyl donors in a range of glycosylation reactions.[38] In turn, 1,2-anhydrosugars can be easily employed for the installation at C-1 of functional groups that impart glycosyl donor character to the anomeric carbon atom, such as azide, amine, fluoride, phenylthiol, etc.[56] Nevertheless, the epoxidation of glycals suffers from several limitations due to the sensitive nature of the 1,2-anhydrosugar. On one hand, many epoxidation reactions lead to glycoside derivatives as a consequence of acid-catalyzed ring opening of the labile anhydrosugar initially formed. Furthermore, an efficient epoxidation reaction of glycals must render the anhydrosugar free of any by-products, since purification of the crude epoxide from a complex mixture is precluded.

The only reagents used for direct epoxidation of glycals are stoichiometric oxidant agents, such as 3,3-dimethyldioxirane (DMDO), *m*-chloroperbenzoic acid (MCPBA)/KF system and oxaziridines (Scheme 12a).

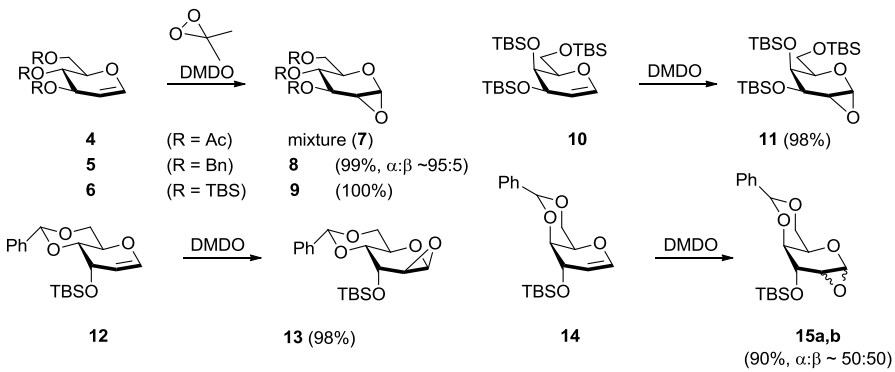


Scheme 12. a) Stoichiometric and direct methods of epoxidation of glycals. b) Tandem epoxidation-alcoholysis or epoxidation-glycosylation of glycals. c) Dihydroxylation of glycals.

The most common and wide-applied epoxidation method of glycals uses dimethyldioxirane (DMDO). This is an easy and direct way to obtain 1,2-

[56] Gordon, D. M.; Danishefsky, S. J. *Carbohydr. Res.* **1990**, *206*, 361-366.

anhydrosugars and it was discovered by Danishefsky in the 90s.[12a] In this process DMDO is prepared according to the procedure of Murray and co-workers[57] through ketone-catalyzed decomposition of potassium peroxomonosulfate ($KHSO_4$), and it is used as a solution in acetone. Reaction of tri-*O*-acetyl-D-glucal (**4**) with DMDO in methylene chloride/acetone at 0ºC affords an inseparable mixture of products (**7**) (Scheme 13). With glycals **5** and **6**, a stereospecific reaction ensues with the α-epoxide in both cases. In a similar way, galactal **10** cleanly gives rise to α-oxirane **11**. The first synthesis of a β-epoxide by direct epoxidation using this system was carried out with the allal derivative **12** obtaining **13** with a 98% yield. A mixture (ca. 50:50) of oxiranes **15a** and **15b** is generated by epoxidation of the *gulal* derivative **14**. It is observed in these results that the configuration at C-3, the size of the protecting groups, as well as the glycal configuration have a significant influence on the stereoselectivity of the epoxidation, obtaining most of the times the α-epoxide, or more precisely the epoxide *trans* to the substituent at C-3.

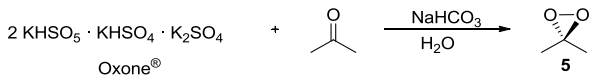


Scheme 13. Epoxidation of glycals with DMDO.

The use of DMDO gives rise to good yields and clean reactions, as well as it requires cheap and commercially available reagents. However, DMDO is unstable, has to be freshly prepared, and poses serious safety problems connected with its potential explosiveness. Therefore, the development of practical alternatives for this transformation has been highly desirable, especially for large-scale synthesis. All these reasons led Dondoni to develop glycal epoxidation with

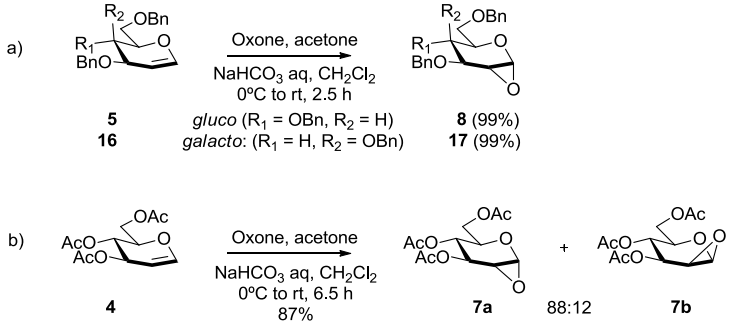
[57] Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847-2853.

in situ generated DMDO from Oxone®/acetone in a biphasic system (CH_2Cl_2/aqueous $NaHCO_3$) (Scheme 14).[58]



Scheme 14. *In situ* synthesis of DMDO.

Thus, epoxidation of 3,4,6-tri-*O*-benzyl-D-glucal (**5**) and D-galactal (**16**) in CH_2Cl_2 with Oxone, acetone and saturated aqueous $NaHCO_3$ to keep the pH of the reaction medium ≥ 8, furnishes α-epoxides **8** and **17** respectively in almost quantitative yield (99%) (Scheme 15a). In a similar way, 3,4,6-tri-*O*-acetyl-D-glucal (**4**) affords a 88:12 mixture of the corresponding *gluco* and *manno* derivatives in an 87% overall yield (Scheme 15b). This epoxidation method with *in situ* generated DMDO shows highly efficiency and serves as the basis for the large-scale preparation of 1,2-anhydro-D-glucose and D-galactose derivatives.



Scheme 15. Epoxidation of glycals with *in situ* generated DMDO.

Other stoichiometric oxidants, namely MCPBA/KF or perfluoro-cis-2,3-dialkyloxaziridines, have been described to furnish highly pure sugar epoxides free of by-products in a operationally easy way.

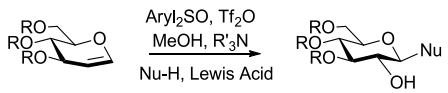
In the diastereoselective epoxidation of glycals with the MCPBA/KF system,[13] the addition of KF in the reaction medium reduces the solubility of MCPBA and MCBA (the acid formed in the reaction medium) and this fact prevent the formation of products arising from oxirane ring opening. The reaction is high

[58] Cheshev, P.; Marra, A.; Dondoni, A. *Carbohydr. Res.* **2006**, *341*, 2714-2716.

yielding when bulky substituents are placed in the glycal such as benzyloxy groups. However, the presence of acetoxy substituents in the glycal dramatically decreased the epoxidation rate, and either gives low yields or ring-opened products.

Perfluoro-*cis*-2,3-dialkyloxaziridines perform the direct epoxidation of glycals to cleanly give the corresponding 1,2-anhydrosugars with medium to complete diastereoselection.[59] The by-products of the oxidation reaction are perfluoroazaalkenes which are inert and volatile materials. However, this method has not found wide application in glycoconjugate synthesis, probably due to limited reaction scope or the use of non conventional perfluorinated solvents/reagents.

The elusive nature of 1,2-anhydrocarbohydrates has motivated the development of *one-pot* epoxidation-glycosylation or epoxidation-hydrolysis of glycals in order to obtain stable glycosides or 1,2-sugar diols, that in turn, are useful intermediates in several organic transformations (Scheme 12b). The stoichiometric system Tf_2O/diaryl sulfoxide promotes glycal oxidation via epoxidation-glycosylation processes.[60] This method for C2-hydroxyglycosylation (Scheme 16) with glycal donors, comprises a mixture of an excess of diaryl sulfoxide and Tf_2O. Initial glycal activation with this reagent combination, subsequent sequential addition of methyl alcohol and a tertiary amine (R'_3N), followed by the glycosyl acceptor (Nu-H) and a Lewis acid ($ZnCl_2$) yields C2-hydroxypyranosides in a *one-pot* procedure.



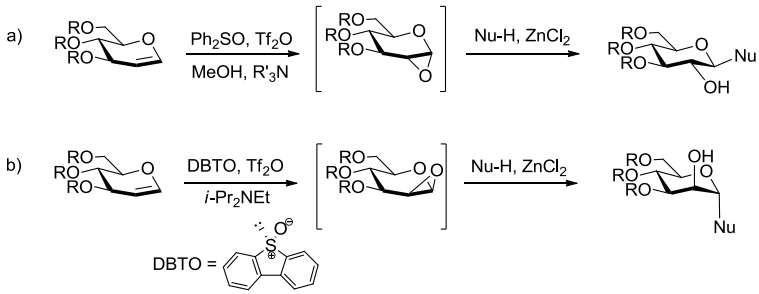
Scheme 16. C2-Hydroxyglycosylation by sulfonium-mediated oxygen transfer to glycals.

The use of Ph_2SO as the sulfoxide reagent for the C2-hydroxyglucosylation leads to the stereoselective formation of C2-hydroxy-β-glucopyranosides when

[59] Cavicchioli, M.; Mele, A.; Montanari, V.; Resnati, G. *J. Chem. Soc., Chem. Commun.* **1995**, 901-902.

[60] a) Honda, E.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 7343-7352. b) Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515-13516.

glucal donors are employed (Scheme 17a). Interestingly, a complementary manifold for C2-hydroxyglycosylation to generate α-mannopyranosides from glucal donors can be accessed when dibenzothiophene 5-oxide (DBTO) is employed as the sulfoxide reagent (Scheme 17b).[61] This remarkable reversal of diastereoselectivity with a subtle change in sulfoxide reagent allows for the direct conversion of glucal donors to mannopyranosides, a transformation that heretofore has required at least a four-step synthetic sequence.[62]



Scheme 17. C2-hydroxyglycosylation with glucal using: a) Ph_2SO/Tf_2O to lead C2-hydroxy-β-glucopyranosides and b) $DBTO/Tf_2O$ to lead C2-hydroxy-α-mannopyranosides.

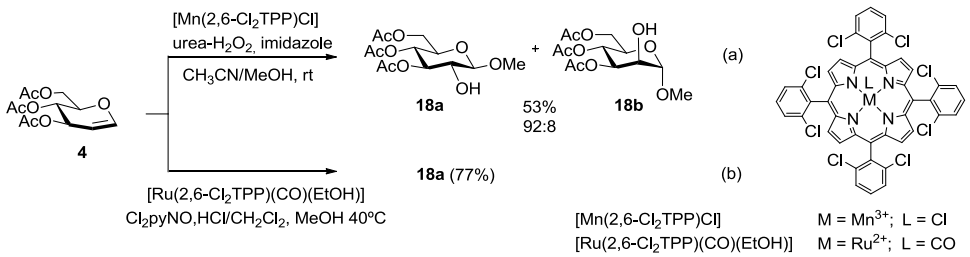
All these methods use stoichiometric amounts of reagents, resulting in large amounts of waste. However, the economic and environmental realities calling for sustainable processes are fuelling the current interest in incorporating catalysts in synthetic pathways, but so far none have been able to provide sugar epoxides. Transition metal-based catalysts have been used in the sequential epoxidation-alcoholysis or epoxidation-hydrolysis of glycals. The epoxides initially obtained are opened *in situ* in the presence of the epoxidation catalysts to give 2-hydroxy-glycosides or dihydroxyl derivatives, depending whether the reaction is carried out in the presence of alcohols or water, respectively.

Metalloporphyrins have been used to enhance poor facial selectivity resulted in epoxidation of glycals bearing small substituents such as tri-*O*-D-acetylglucal (**4**). By using metalloporphyrin [Mn(2,6-Cl_2TPP)Cl] as a catalyst, urea-H_2O_2 as

[61] Kim, J.- Y.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303-306.

[62] Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064-10072.

the oxygen source, and imidazole as an axial ligand, pyranoside derivatives **18a/18b** are obtained in a 92:8 ratio, as a consequence of epoxidation and *in situ* ring-opening (Scheme 18a).[63] The high *trans* selectivity could be attributed to the strong steric interaction between the substrates and the bulky porphyrin ligands. On the other hand, treatment of **4** with 2,6-dichloropyridine *N*-oxide (Cl_2pyNO) as the oxidant agent and [Ru(2,6-Cl_2TPP)(CO)(EtOH)] as a catalyst in methylene chloride under homogeneous conditions affords exclusively the corresponding methyl α-D-glucopyranoside **18a** (Scheme 18b).[64]



Scheme 18. Diastereoselective epoxidation-methanolysis of **4** catalyzed by metalloporphyrin [Mn(2,6-Cl_2TPP)Cl] (a) and [Ru (2,6-Cl_2TPP)(CO)(EtOH)] (b).

The development of oxidation processes which are environmentally friendly is currently the focus of much attention. Methyltrioxorhenium (MTO) has emerged in the last decade,[65,66] in combination with hydrogen peroxide as the stoichiometric oxidant, as an important catalyst for the oxidation of many classes of substrates, among which the most important and studied reactions were epoxidation of olefins. Application of this method to oxidation of glycals renders methyl glycosides via epoxidation-methanolysis reactions. The nucleophilic solvent caused the immediate ring opening of the epoxide formed *in situ* by S_N2 attack at the anomeric carbon. The facial diastereoselectivity of the oxidation ranged from satisfactory to excellent depending on the substrate and could be

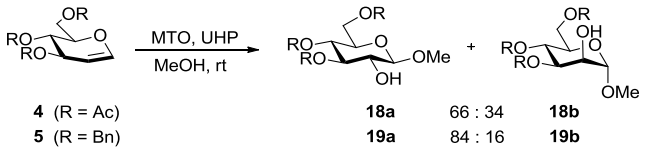
63 Chan, W.- K.; Wong, M.- K.; Che, C.- M. *J. Org. Chem.* **2005**, *70*, 4226-4232.

64 Liu, C.- J.; Yu, W.- Y.; Li, S.- G.; Che, C.- M. *J. Org. Chem.* **1998**, *63*, 7364-7369.

65 a) Soldaini, G.; Cardona, F.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 5589-5592. b) Soldaini, G.; Cardona, F.; Goti, A. *Org. Lett.* **2005**, *7*, 725-728. c) Goti, A.; Cardona, G.; Soldaini, G.; Crestini, C.; Fiani, C.; Saladito, R. *Adv. Synth. Catal.* **2006**, *348*, 476-486. d) Saladino, R.; Crestini, C.; Crucianelli, M.; Soldaini, G.; Cardona, F.; Goti, A. *J. Mol. Catal. A* **2008**, *284*, 108-115.

66 Boyd, E. C.; Jones, R. V. H.; Quayle, P.; Waring, A. J. *Green Chem.* **2003**, *5*, 679-681.

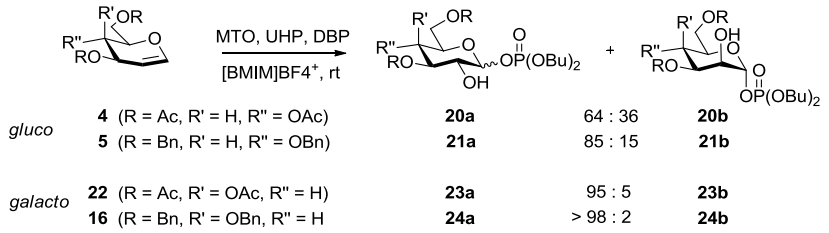
optimized by wide screening of catalysts. Reaction of glycals **4** and **5** with MTO in combination with the complex urea-H_2O_2 (UHP) as stoichiometric oxidant in MeOH as solvent gives an α/β mixture of methyl glycosides **18** and **19**, respectively (Scheme 19).



Scheme 19. Domino catalytic oxidation-nucleophilic ring opening of glucals **4** and **5** with MTO and UHP in homogeneous conditions.

The diastereoselectivity of the process is governed mainly by steric factors, with the epoxidation occurring preferentially at the face of the double bond opposite to the OR group at C-3. As expected on this basis, the epoxidation-methanolysis of tri-*O*-D-benzylglucal (**5**) affords the glucose derivative **19a** with a much higher preference compared to tri-*O*-acetyl-D-glucal (**4**).

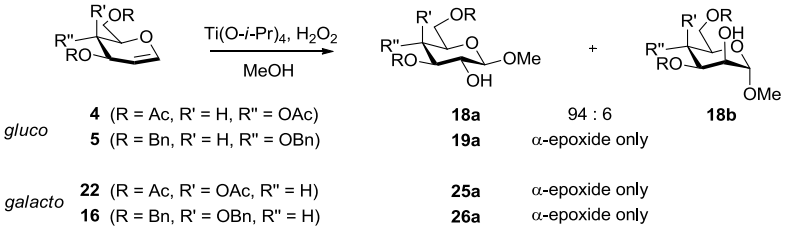
When dibutylphosphate (DBP) is introduced in the reaction mixture in the ionic liquid dimethylimidazolium tetrafluoroborate ([Bmim]BF_4), the oxidation of glucals **4** and **5**, and galactals **22** and **16** takes place, with moderate chemo- and stereoselectivity, giving the corresponding glycosyl phosphates (Scheme 20).



Scheme 20. Catalytic oxidation of glycals to glycosyl phosphates in [BMIM]BF_4 with MTO and UHP.

Since Lewis base adducts of MTO with nitrogen-containing ligands,[67] such as pyridine, pyrazole and others, are known to influence significantly the oxidation processes, for example, decreasing the formation of diols in epoxidation reactions, especially in the case of sensitive substrates, and increasing the catalytic efficiency, a series of pre-formed heterogeneous amine-MTO compounds were tested and their effectiveness as catalysts was demonstrated in both processes: epoxidation-methanolysis[65c] and epoxidation-phosphorylation[65b] of glycals. A broad screening of the homogeneous and heterogeneous catalysts allowed to define for each glycal the optimal reaction conditions, either in terms of conversion or stereoselectivity.

Other catalysts such as Venturello's phosphotungstate complex ($Q_3PW_4O_{24}^{3-}$)[68] (Q = quaternary ammonium ion) and titanium(IV) isopropoxide [Ti(O-*i*-Pr)$_4$][68] are successfully used for the epoxidation-alcoholysis of glycals using hydrogen peroxide (H_2O_2). Ti(O-*i*-Pr)$_4$ is only effective in methanol as solvent due to the formation of precipitates in ethanol or propanol, and required long reaction times. However, these drawbacks are offset by the excellent selectivity in reactions of protected glucals, which yielded predominantly or exclusively the α-epoxide derivatives (Scheme 21). On the hand, the selectivity is reversed with unprotected D-glucal to favour the β-epoxide.



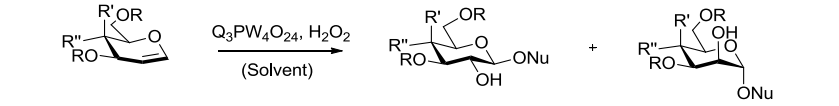
Scheme 21. Epoxidation-methanolysis of various glycals with Ti(O-*i*-Pr)$_4$.

Venturello's complex is more active and versatile as a catalyst than Ti(O-*i*-Pr)$_4$, with the former tolerating a wider range of alcohols in generally shorter

[67] a) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189-6190. b) Herrmann, W. A.; Kratzer, R. M.; Ding, H.; Thiel, W. R.; Glas, H. *J. Organomet. Chem.* **1998**, *555*, 293-295.

[68] Levecque, P.; Gammon, D. W.; Kinfe, H. H.; Jacobs, P.; De Vos, D.; Sels, B. *Adv. Synth. Catal.* **2008**, *350*, 1557-1568.

reaction times. Epoxidation from the α-face is again favoured for the fully protected glycals with this system, and α-epoxidation of galactal derivatives is exclusive achieved in selected reactions (Scheme 22).



gluco	**4** (R = Ac, R' = H, R'' = OAc)	**27a**	89 : 11	**27b**	(*n*-PrOH)
	5 (R = Bn, R' = H, R'' = OBn)	**28a**	88 : 12	**28b**	(EtOH)
galacto	**22** (R = Ac, R' = OAc, R'' = H)	**25a**	α-epoxide only		(*n*-PrOH)
	16 (R = Bn, R' = OBn, R'' = H)	**26a**	α-epoxide only		(EtOH)

Scheme 22. Epoxidation-alcoholysis of various glycals with Venturello's complex.

Biphasic conditions are applied to the Venturello's complex to allow the incorporation of long-chain alcohols or to selectively obtain sugar 1,2-diols. Due to the lower reactivity of the long aliphatic alcohols, water is a competitive nucleophile in opening the epoxide, leading to the formation of 1,2-diol as the major product.

Glycals are also activated by dihydroxylation to give protected sugar 1,2-diols (Scheme 12c), which have been used in the synthesis of *O*-glycosides,[69] *C*-glycosides[70] and in intramolecular *O*-glycosylations.[71]

Dihydroxylation of glycals with catalytic OsO_4 in the presence of *N*-methylmorpholine-*N*-oxide (NMO)[69b,c] affords the desired 1,2-diol product with facial selectivities greater than 19:1, even in the case of acetate-protected glucal. Moreover, a catalytic dihydroxylation reaction of glycals has been developed using a bimetallic oxidizing system ($RuCl_3/CeCl_3 \cdot 7H_2O/NaIO_4$)[72] to furnish sugar

[69] a) Shi, L.; Kim, Y.- J.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, 123, 6939-6940. b) Sanders, W. J.; Kiessling, L. L. *Tetrahedron Lett*. **1994**, 35, 7335-7338. c) Charette, A. B.; Marcoux, J.- F.; Cote, B. *Tetrahedron Lett*. **1991**, 32, 7215-7218.

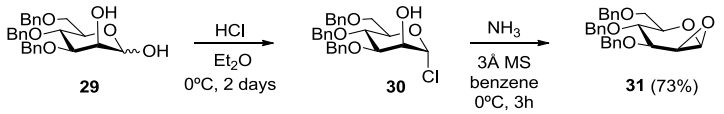
[70] a) Carpintero, M.; Nieto, I.; Fernandez-Mayoralas, A. *J. Org. Chem*. **2001**, 66, 1768-1774. b) Vidal, T.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett*. **1999**, 40, 5677-5680. c) Hung, S.- C.; Wong, C.- H. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2671-2674.

[71] a) Bols, M. *Chem. Commun*. **1992**, 913-914. b) Stork, G.; Kim, G. *J. Am. Chem. Soc*. **1992**, *114*, 1087-1088. c) Barresi, F.; Hindsgual, O. *J. Am. Chem. Soc*. **1991**, *114*, 9376-9377.

[72] Tiwari, P.; Misra, A. K. *J. Org. Chem.* **2006**, *71*, 2911-2913.

1,2-diols in a highly stereoselective manner. Sugar 1,2-diols can also be classically prepared by hydrolysis of orthoesters.[73]

Nevertheless, the synthesis of 1,2-*manno*-epoxides is still object of interest because of their difficult obtention. They can be prepared by indirect procedures in a S_N2 reaction of a free hydroxy group at C-2 and the anomeric center bearing a leaving group. Treatment of 3,4,6-tri-*O*-benzyl-D-mannopyranose (**29**) with hydrogen chloride in ether yields 3,4,6-tri-O-benzyl-α-D-mannopyranosyl chloride (**30**). This compound is highly reactive and labile due to the *trans*-diaxia1 relationship of substituents at C-l and C-2, in contrast to its D-glucopyranosyl derivative which is stable and can be readily isolated. Compound **30** gives directly epoxide **31**. The ring closure takes place using anhydrous ammonia in benzene to afford 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (**31**) in 73% yield after concentration of the benzene solution and purification (Scheme 23).[74] Similar methodology is used to prepare the α-epoxide derivative.[75]



Scheme 23. Synthesis of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (**29**).

The transition metal-catalyzed processes aforementioned mostly afford products derived of the epoxidation *trans* to the C-3 substituent. Interestingly, the dihydroxylation (epoxidation-hydrolysis) of unprotected glucal using MoO_3 as catalyst in water as solvent affords mainly mannose, in a process that involves directed β-epoxidation, probably via hydrogen bond between the neighbouring

[73] a) Lichtenthaler, F. W.; Schneider-Adams, T. *J. Org. Chem.* **1994**, *59*, 6728-6734. b) Broder, W.; Kunz, H. *Carbohydr. Res.* **1993**, *249*, 221-241. c) Schmidt, R. R.; Effenberger, G. *Carbohydr. Res.* **1987**, *171*, 59-79. d) Wu, E.; Wu, Q. *Carbohydr. Res.* **1993**, *250*, 327-333. e) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2199-2204.

[74] Sondheimer, S. J.; Yamaguchi, H.; Schuerch, C. *Carbohydr. Res.* **1979**, *74*, 327-332.

[75] Yamaguchi, H.; Schuerch, C. *Carbohydr. Res.* **1980**, *81*, 192-195.

allylic hydroxyl group and the catalyst.[76] Only the Venturello's peroxotungstate complex ($PW_4O_{24}^{3-}$)[68] provides a similar selectivity in unprotected glycals.

[76] Bilik, V.; Kucar, S. *Carbohydr. Res.* **1970**, *13*, 311-313.

Molybdenum-Catalyzed Epoxidation Reactions

CHAPTER 2

Despite molybdenum complexes being one of the most active and afficient catalysts for alkene epoxidation,[77] there is not a systematic investigation of their use in glycals epoxidation-alcoholysis or epoxidation-hydrolysis. The aim of this study was to assess the efficiency and selectivity of Mo/peroxide catalytic systems, which are cheap and really accessible, in the oxidation of glycals in order to obtain sugar epoxides.

1. Background

The general mechanism for the molybdenum-catalyzed epoxidation reaction has awakened the interest of its study.[78] The first suggestion about the mechanism of the stoichiometric epoxidation of olefins with $MoO(O_2)_2(L)$ was made by Mimoun in 1970.[79] The author interpreted the kinetic investigations in favour of a three-step process that is shown in Scheme 24 (top). According to Mimoun, the first step of the reaction involves a coordination of the olefin to the metal yielding the olefin complex **B** as a putative intermediate. The second step is a cycloinsertion of the olefin into one molybdenum-peroxo bond which leads to the metalla-2,3-dioxolane **C**, including the metal center, two carbon atoms from the olefin and the oxygen atoms from the peroxo group. In the third step, the epoxide is formed by cycloreversion of the metallacycle and the transition-metal oxide further reacts with H_2O_2 yielding the peroxo complex. However, metallocyclic intermediates similar to **C** are known only for complexes of late transition metals (e.g. Pd and Pt) and were not found in reactions involving transition metal peroxides with a d^0 configuration in the metal center.[80]

An alternative mechanism for the epoxidation reaction with molybdenum peroxo complexes was later proposed by Sharpless.[81] The author assumed that

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77 Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63-74.

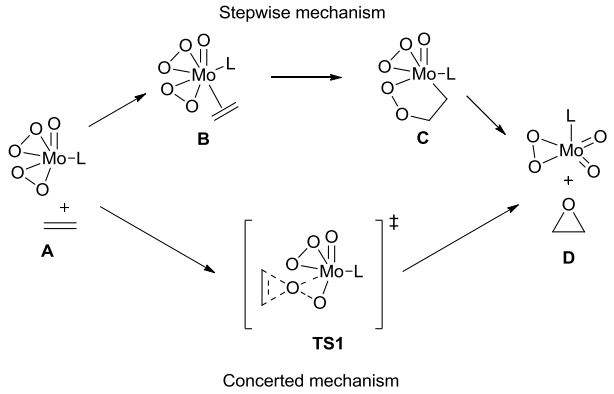
78 a) Howe, G. R.; Hiatt, R. R. *J. Org. Chem.* **1971**, *36*, 2493-2497. b) Baker, T. N.; Mains, G. J.; Sheng, M. N.; Jajacek, J. K. *J. Org. Chem.* **1973**, *38*, 1145-1148. c) Chong, A. O.; Sharpless, K. B. *J. Org. Chem.* **1977**, *42*, 1587-1590. d) Thiel, W. J. *J. Mol. Catal. A* **1997**, *117*, 449-454.

79 Mimoun, H.; de Roch, S.; Sajus, L. *Tetrahedron* **1970**, 26, 37-50.

80 a) Mimoun, H. *Pure Appl. Chem.* **1981**, *53*, 2389-2399. b) Sheldon, R. A.; Van Doorn, J. A. *J. Organomet. Chem.* **1975**, *94*, 115-129. c) Broadhurst, M. J.; Brown, J. M.; John. R. A. *Angew. Chem. Int. Ed.* **1983**, *22*, 47-48.

81 Sharpless, K. B.; Towsend, J. M.; Williams, D. R. *J. Am. Chem. Soc.* **1972**, *94*, 295-296.

olefin incorporation in the coordination sphere is not an essential condition, and suggested that the reaction takes place by a direct attack of the olefin to one of the oxygen atoms of a peroxo group in a concerted way via transition state **TS1**, which has a structure with a spiro conformation (Scheme 24, bottom). The two contradicting studies by the Mimoun[79] and Sharpless[81] laboratories led to a long-standing debate.



Scheme 24. Stepwise mechanism of epoxidation suggested by Mimoun (top) and concerted mechanism involving direct oxygen transfer suggested by Sharpless (bottom).

The mechanism of the olefin epoxidation with molybdenum diperoxo complexes was clarified with the help of modern quantum chemistry.[82,83,84] Density functional theory (DFT) calculations using the most effective exchange correlation functionals such as B3LYP level allowed to discard Mimoun mechanism of epoxidation and chose the Sharpless mechanism. The two mechanisms were compared using as example calculations for $MoO(O_2)_2L$ complexes with various basic ligands L, including OPH_3, which was used by Mimoun as HMPA model ligand in his original work.[79]

Regarding Mimoun's stepwise mechanism it was found that ethylene coordination with the metal (**A** → **B**, via **TS2**) is a 5 kcal/mol endothermic process. The calculations indicated that there was no transition state leading from

82 Di Valentin, C.; Gisdakis, P.; Yudanov, I. V.; Rösch, N. *J. Org. Chem.* **2000**, *65*, 2996-3004.
83 Deubel, D. V.; Sundermeyer, J.; Frenking, G. *J. Am. Chem. Soc*. **2000**, *122*, 10101-10108.
84 Yudanov, I. V. *J. Struct. Chem.* **2007**, *48*, S111-S124.

intermediate **B** with coordinated ethylene to the metallacycle **C**.[83] The olefin complex **B** is a dead-end street in the catalytic cycle (Figure 4). According to the calculations, ethylene incorporation into the bond between molybdenum and the peroxo oxygen and the formation of a five-membered ring occur directly from the outer coordination sphere of the complex (**A** → **C**, via **TS3**), without preliminary coordination to the metal center. However, the transition state of ethylene incorporation (**TS3**) is characterized by a high activation barrier, ~25 kcal/mol.[82,83] Moreover, it appeared that even if a metallacycle would be formed despite the high activation barrier, the decomposition product of this ring could only be an aldehyde via sigmatropic cycloreversion (**C** → **E**, via **TS4**), but not epoxide, because there is no transition state that leads to the epoxide.[83] It should be noted that the aldehyde is thermodynamically more stable than the epoxide, and the calculated C–C bond (1.52 Å) in the five-membered ring is much closer to the corresponding characteristic in the aldehyde molecule (1.51 Å) than in epoxide (1.47 Å).[84] Hence, the stepwise mechanism would lead to the wrong product.

The alternative concerted mechanism suggested by Sharpless remains as the alternative. It is characterized by a transition state in the form of a three-membered ring (**TS1**), whose product is the epoxide.[82,83] The transition state has a spiral structure, in which the axis of the C=C bond is orthogonal to the plane of the peroxo group interacting with it. The corresponding activation barrier is much lower (**A** → **TS1** → **D**) than the activation barrier of the above-discussed incorporation of ethylene, leading to the formation of a metallacycle.[82,83]

Figure 4 compares the calculated reaction profile of the epoxidation reaction of ethylene with the molybdenum diperoxo complex $[MoO(O_2)_2L]$. The concerted Sharpless mechanism is shown at the left-hand side, and the stepwise Mimoun mechanism via the organometallacycle is at the right-hand side.

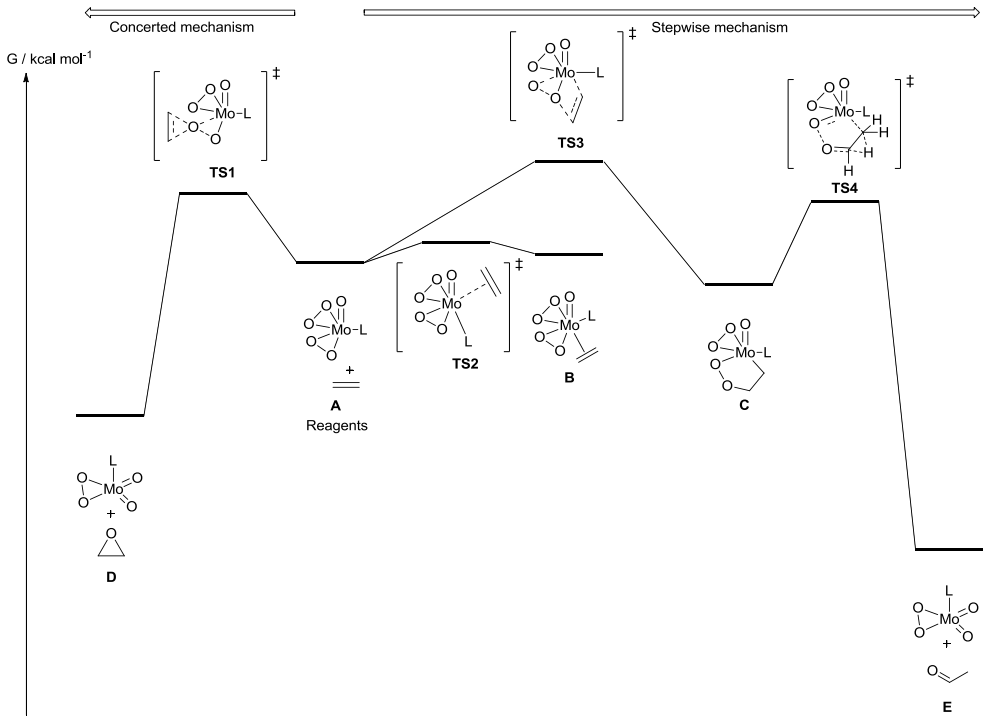


Figure 4. Theoretically predicted reaction profile for the concerted and stepwise mechanism of the epoxidation of ethylene with $[MoO(O_2)_2L]$.

Charge decomposition analysis of the transition state of the concerted mechanism, **TS1** in Figure 4, reveals the orbital interactions involved in the oxygen-transfer event. Electron donation from the π(C-C) HOMO orbital of the olefin into the σ^*(O-O) LUMO orbital of the peroxo group is found to be predominant in the transition state (Figure 5).

Figure 5. Predominant orbital interactions in the transition state.

2. Results and discussion

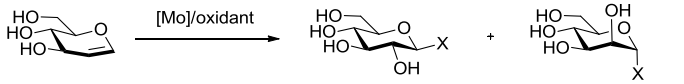
2.1 Catalytic experiments

Initially we evaluated the epoxidation of unprotected glucal (**32**) under similar conditions to those previously explored by Bilik,[76] using two molybdenum catalysts in polar solvents such as water and methanol and using different oxidizing reagents. The results are collected in Table 1. The key role of the molybdenum complex in the oxygen transfer process was first established by the lack of reactivity of the oxidant towards **32** in the absence of the molybdenum catalyst (results not displayed in Table 1).

When the reaction was carried out in water with readily available MoO_3 as a catalyst precursor and H_2O_2 as stoichiometric oxidant, mannose (**33b**) was almost exclusively obtained, in agreement with that reported by Bilik[76] et al. (Table 1, entry 1). Note that in no case the epoxide was obtained, as a consequence of the high reactivity of the anhydro sugar in the presence of metal compounds and nucleophilic solvents. The use of methanol as solvent and working in similar conditions allowed us to obtain exclusively methyl α-mannopyroside (**34b**) as consequence of an epoxidation-methanolysis process (Table 1, entries 2, 3), although the reaction rate was lower than in water. In order to seek for more general oxidation conditions that would involve protected or partially protected glycals, less polar solvents and more soluble oxidizing agents should also be explored. With this purpose in mind, oxidation reactions of **32** using *tert*-butyl hydroperoxide (TBHP) as a terminal oxidant were explored next. Reactions with this oxidant driven in methanol took place with complete conversion although they required higher temperatures than with H_2O_2 (Table 1, entries 4, 5). Interestingly, the stereoselectivity was observed to depend on the solvent for solubilizing TBHP. Thus, an almost 1:1 mixture of methyl β-glucopyranoside (**34a**) and methyl α-mannopyranoside (**34b**) was obtained when TBHP was dissolved in nonane, while the stereoselectivity was 9:91 when TBHP in water was used (Table 1, entries 4, 5). The anomeric configuration of the *gluco* derivative **34a** is β, while it is α for the *manno* derivative **34b**. This is a consequence of the selective *trans* opening of the *gluco* and *manno* epoxides initially formed under the reaction conditions. The use of TBHP with more

soluble molybdenum catalysts such as $Mo(CO)_6$ provided similar results to those from MoO_3 (Table 1, entries 6, 7).

Table 1. Tandem epoxidation-hydrolysis/glycosylation of glucal **32** with molybdenum catalysts.



Entry	Catalyst	Peroxide	Solvent	Temp (ºC)	Time (h)	Conv (%)[b,c]	Products	Ratio α/β[a,b]
1[d]	MoO_3	H_2O_2 in H_2O	H_2O	rt	48	>98	**33a / 33b**	4:96
2[d]	MoO_3	H_2O_2 in H_2O	MeOH	rt	48	50	**34b**	
3[d]	MoO_3	H_2O_2 in H_2O	MeOH	rt	96	>98	**34b**	
4[e]	MoO_3	TBHP 5.5 M in C_9H_{20}	MeOH	50	72	>98	**34a / 34b**	45:55
5[e]	MoO_3	TBHP 70 wt% in H_2O	MeOH	50	72	>98	**34a / 34b**	9:91
6[e]	$Mo(CO)_6$	TBHP 5.5 M in C_9H_{20}	MeOH	50	72	>98	**34a / 34b**	55:45
7[e]	$Mo(CO)_6$	TBHP 70 wt% in H_2O	MeOH	50	72	>98	**34a / 34b**	9:91

[a] α/β refers to products formed from the α-epoxide (*gluco*) and the β-epoxide (*manno*). See Scheme 25. [b] Determined by integration in the ^1H NMR spectrum of anomeric proton signals of compounds of the final reaction crude. [c] Selectivity > 98%. [d] *Conditions:* 1.71 mmol glycal, 1 mol % catalyst, 2.5 ml H_2O_2 (5%) in the solvent. [e] *Conditions:* 0.36 mmol glycal, 5 mol % catalyst, 1.2 ml TBHP, 2 ml MeOH.

A general trend of these epoxidation reactions with polar solvents is the long reaction times. This deactivating effect has been already observed,[79,81,85] and two reasons have been proposed, depending on the oxidant used. On the one hand, coordination of a basic ligand (solvent molecule) to a peroxo-Mo complex

[85] a) Amato, G.; Arcoria, A.; Ballisteri, F. P.; Tomaselli, G. A.; Bortolini, O.; Conte, V.; Di Furia, F.; Modena, G.; Valle, G. *J. Mol. Catal* **1986**, *37*, 165-175. b) Mimoun, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 734-750.

induces a decrease of electrophilicity of the peroxo group due to donation of electron density from the basic solvent via the metal center, thus lowering its reactivity.[86] On the other hand, the coordinating solvent may compete with the stoichiometric TBHP oxidant in the final molybdenum complex thus slowing down the generation of the catalytic species.[78b,c]

In order to assess the factors influencing the activity of the catalyst, reactivity of the starting glycals, protecting group effect and influence on the facial selectivity in product formation, a range of differently protected or partially unprotected glucals (**4**, **5**, **35**-**39**), and galactals (**16**, **22**, **40**, **41**) were prepared using standard literature procedures and used as starting materials for the epoxidation reaction (Figure 6).

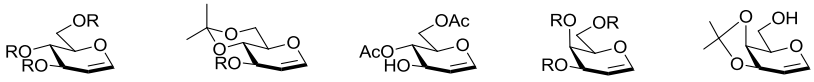
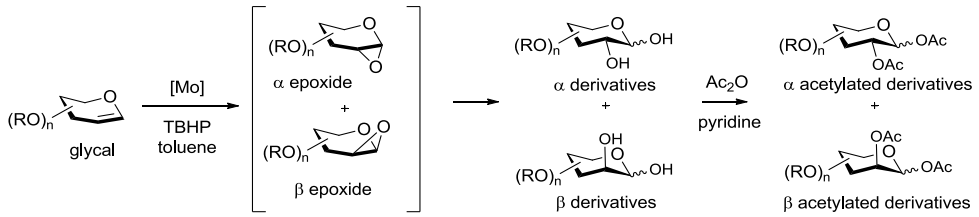


Figure 6. Structures of glycals used in Mo/TBHP dihydroxylation.

Tables 2-5 summarize the results obtained in the molybdenum-catalyzed epoxidation/hydrolysis or epoxidation/alcoholysis of protected glycals with *tert*-butyl hydroperoxide as an oxidant. Different [Mo]/TBHP catalytic systems and different solvents were explored using tri-*O*-acetyl-D-glucal (**4**) as a substrate. Thus, the reaction of **4** with $Mo(CO)_6$ in MeOH gave a mixture of compounds **18a(β)/18b(α)** in a 70:30 ratio as a consequence of a tandem epoxidation-*trans* epoxide opening process (Table 2, entry 1). The reaction needed 36h for completion, in line with the results of Table 1. The *gluco* derivative **18a** was now principally obtained, in agreement with that reported for other oxidation catalysts, and on the contrary to that observed in the reaction of unprotected glucal.[65,68,76] Neither the use of less polar solvents such as toluene nor the use of molecular sieves prevent epoxide opening of the highly reactive anhydrosugar, probably due to the Lewis acidity of the catalyst (Table 2, entries 4-7). For practical reasons, the crude reaction mixture was analyzed after acetylation of the free hydroxyl

[86] Deubel, D. V.; Sundermeyer, J.; Frenking, G. *Eur. J. Inorg. Chem.* **2001**, 1819-1827.

groups in the resulting oxidation products (Scheme 25). Thus, the diastereoselectivity of the whole process was calculated by integration of the ^{1}H NMR signals of the anomeric protons of the crude product mixture after acetylation. The spectral data obtained was assigned by comparison with those reported in the literature (see Section 2.2 of this chapter). Although the opening of epoxides is expected to be *trans*, an α/β mixture was observed in each case as a result of an anomerization process or through the formation of the oxonium ion. Two signals corresponded to *gluco* derivatives, derived from the α-epoxide (attack from the bottom face of the double bond), and other two signals to the *manno* derivatives, resulting from the β-epoxide (attack from the upper face of the double bond). In all cases epoxidation-hydrolysis reactions were carefully monitored by TLC and the reported reaction times correspond to the disappearance of starting glycal. The stereochemistry at position 2 in the final acetate products reflects the stereoselectivity in the initial epoxide formation.

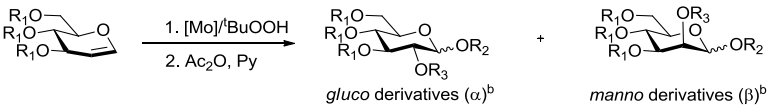


Scheme 25. Tandem epoxidation-hydrolysis of glycals with [Mo] catalysts.

The temperature conditions seemed to be crucial when $Mo(CO)_6$ was used as a catalyst in apolar solvents. Thus, temperatures of 80ºC were required for complete conversion of **4** in reasonable reaction times (Table 2, entries 5, 6). As a Mo^0 species, $Mo(CO)_6$ requires an induction period prior to any epoxidation, in which the molybdenum complex is oxidized by the alkylhydroperoxide or the oxygen peroxide to its highest oxidation state, the active Mo^{VI} species.[78a,87] Most probably, the dissociation of the carbonyl ligands in the starting complex in apolar solvents is the limiting process for activation of the complex at low temperature.

87 Haas, G. R.; Kolis, J.W. *Organometallics* **1998**, *17*, 4454-4460 and references cited therein.

Table 2. [Mo]-catalyzed oxidation of glucals (**4**, **5**, **35**, **36**).[a]



4 (R_1 = Ac)
5 (R_1 = Bn)
35 (R_1 = Piv)
36 (R_1 = TIPS)

18a (R_1 = Ac, R_2 = Me, R_3 = H) **18b**
42a (R_1 = Ac, R_2 = R_3 = Ac) **42b**
43a (R_1 = Bn, R_2 = R_3 = Ac) **43b**
44a (R_1 = Piv, R_2 = R_3 = Ac) **44b**
45a (R_1 = TIPS, R_2 = R_3 = Ac) **45b**

Entry	Substrate	Catalyst	Solvent	Temp (ºC)	Time (h)	Conv (%)[c,d]	Products	Ratio α/β[b,c]
1	**4**	$Mo(CO)_6$	MeOH	50	36	>98	**18a/18b**	70:30
2	**4**	$MoO_2(acac)_2$	MeOH	50	36	>98	**18a/18b**	70:30
3[e]	**4**	$MoO_2(acac)_2$	CH_2Cl_2	rt	6	>98	**42a/42b**	65:35
4[e]	**4**	$MoO_2(acac)_2$	toluene	30	3	>98	**42a/42b**	65:35
5[e]	**4**	$Mo(CO)_6$	toluene	40	96	>98	**42a/42b**	67:33
6[e]	**4**	$Mo(CO)_6$	toluene	80	1	>98	**42a/42b**	65:35
7[e]	**4**	MoO_2Cl_2	toluene	50	2	>98	**42a/42b**	62:38
8[e]	**5**	$Mo(CO)_6$	toluene	80	1	>98	**43a/43b**	82:18
9[e]	**5**	$MoO_2(acac)_2$	toluene	30	3	>98	**43a/43b**	75:25
10[e]	**5**	MoO_2Cl_2	toluene	50	3	>98	**43a/43b**	77:23
11[e]	**35**	$Mo(CO)_6$	toluene	80	21	>98	**44a/44b**	96:4
12[e]	**35**	$MoO_2(acac)_2$	toluene	30	24	>98	**44a/44b**	94:6
13[e]	**36**	$Mo(CO)_6$	toluene	80	21	0	**45a/45b**	--
14[e]	**36**	$MoO_2(acac)_2$	toluene	30	72	0	**45a/45b**	--

[a] *Conditions:* 0.36 mmol glycal, 5 mol % catalyst, 1.2 mmol TBHP 5.5 M in nonane, 2 ml solvent. [b] α/β refers to products formed from the α-epoxide (*gluco*) and the β-epoxide (*manno*). See Scheme 25. [c] Determined by integration in the ^{1}H NMR spectrum of anomeric proton signals of the final reaction crude. [d] Selectivity > 98%. [e] The reaction crude was acetylated to give the corresponding acetyl derivatives.

The nature of the oxidant reagent solution in the stereoselectivity outcome of the epoxidation reaction was also explored starting from **4** and using $Mo(CO)_6$ as a catalyst precursor, but there were not significant differences between the use of

TBHP 5.5 M in nonane (Table 2, entry 6) and the use of TBHP 70 wt% in water (98% conversion, 2h, *gluco*/*manno* ratio=65:35, result not displayed in Table 2).

The reaction was then tried using another soluble catalyst, $MoO_2(acac)_2$, in different solvents. In the presence of MeOH, the corresponding methyl glycosides **18a** and **18b** were obtained with a similar stereoselectivity to that from $Mo(CO)_6$ (Table 2, entry 2). Reaction in dichloromethane or toluene led to **42a/42b** with slightly lower stereoselectivities than with methanol (Table 2, entries 3, 4). Accordingly to the previous results obtained with $Mo(CO)_6$, the use of non coordinating solvents led to shorter reaction times.

Other (dioxo)Mo(VI) catalyst precursors, like MoO_2Cl_2, allowed carrying out the reaction in short reaction times but with virtually the same stereoselectivity (Table 2, entry 7). The use of MoO_3 was not considered with protected glycals as a consequence of solubility problems in non-polar solvents.

In general, epoxidation-hydrolysis from glycal **4** proceeded with moderate selectivities, probably as a consequence of steric and conformational factors. Glycals are well known to be conformationally flexible.[88] Moreover, the conformational preference between the normal half-chair ($^4H_5$ conformation) and the conformationally inverted isomer ($^5H_4$ conformation) is known to be sensitive not only to configuration but also to hydroxyl group protection.[17c,89] More importantly, this $^4H_5/^5H_4$ distribution can affect the stereoselectivity of addition reaction at the glycal alkene. In fact, reported data on electrophilic addition reactions of glycals locked in a $^4H_5$ conformation have usually shown low diastereofacial selectivities, with a slight preference for the addition from the α-face.[90] On the basis on conformational NMR-based studies, describing the $^4H_5$ half-chair as the most stable conformation in glucal **4** (and other glucal derivatives), with all its substituents in a *pseudo*-equatorial orientation,[91] low stereoselectivities should be expected, as it is the case.

88 Rico, M.; Santoro, J. *Org. Mag. Res.* **1976**, *8*, 49-55.
89 Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825-8836.
90 Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem*. **1992**, *57*, 2084-2092.
91 Chalmers, A. A.; Hall, R. H. *J. Chem. Soc. Perkin Trans. 2*, **1974**, 728-732.

In comparison, reaction with the more hindered glucal **5** afforded better stereoselectivities (Table 2, entries 8-10), obtaining *gluco* derivative **43a** as a major product. Considering that tri-*O*-benzyl derivative is conformationally more biased towards the $^4H_5$ half-chair conformation than the tri-*O*-acetyl glucal itself, the increase in α-epoxidation might be explained by steric hindrance of the protecting benzyl moiety. The existence of a π-stacking interaction of the aryl group of the benzyl group at C-3 or C-6 and the π system in the glycal thus blocking the beta face could not be discarded either.

Glucals **35**[92] and **36**,[93] with bulkier protecting groups were then tested. Glucal **35** afforded the *gluco* derivative **44a** with excellent stereoselectivity when $Mo(CO)_6$ and $MoO_2(acac)_2$ were used as catalyst (Table 2, entries 11, 12).

Unexpectedly, reaction of **36** did not occur, neither with $Mo(CO)_6$ nor with $MoO_2(acac)_2$ (Table 2, entries 13, 14). This lack of reactivity can be attributed to the significant steric demand of the bulky TIPS groups, which destabilize the $^4H_5$ conformation due to serious *gauche* interaction between the protecting groups at position 3 and 4 and force the glucal into the $^5H_4$ conformation, where the substituents at C-3, C-4 and C-5 are in a *pseudo*-axial orientation. These inhibit access of the electrophilic peroxy-molybednum species to the double bond.[68]

Following previous experiments, we decided to carry out the dihydroxylation of **4** and **5** with *N*-heterocyclic ligands-containing [Mo] complexes in order to modulate the reactivity and selectivity of the oxidation (Table 3).[65b,94] It is well known that this kind of Mo complexes presents better solubilities in apolar solvents and lower Lewis acidity, preventing the formation of diols. In our experiment, use of the complex **46**[95]/TBHP or the MoO_3/**47**[96]/TBHP catalytic system did not prevent epoxide opening and only diol derivatives were obtained as the main reaction products. Moreover, reactions were in general slower (Table

92 Matsushita, Y.; Sugamoto, K.; Kita, Y.; Matsui, T. *Tetrahedron Lett.* **1997**, *38*, 8709-8712.

93 Dötz, K. H.; Otto, F.; Nieger, M. *J. Organomet. Chem.* **2001**, *621*, 77-88.

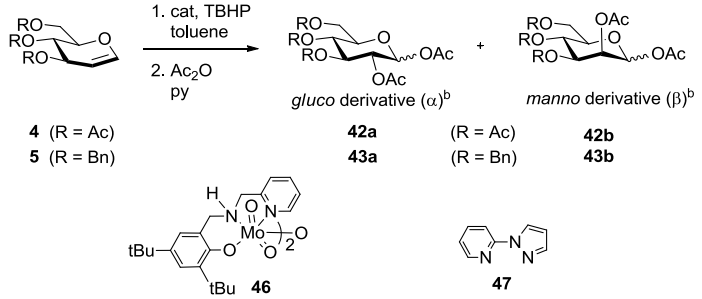
94 Ferreira, P.; Xue, W.- M.; Bencze, E.; Herdtweck, E.; Kühn, F. *Inorg. Chem*. **2001**, *40*, 5834-5841.

95 Mithcell, J. M.; Finney, N. S. *J. Am. Chem. Soc.* **2001**, *123*, 862-869.

96 Zhu, D.; Wang, R.; Mao, J.; Xu, L.; Wu, F.; Wan, B. *J. Mol. Catal. A: Chem.* **2006**,*256*, 256-260.

3 vs. Table 2) in agreement with reported epoxidation reactions catalyzed by *N*,*N*-bidentate ligand-containing Mo complexes.[97] This deactivating effect is in line with that previously stated for effect of coordinating solvents in the decrease of electrophilicity of the Mo-peroxo or alkylperoxo-Mo complex and has been also determined by theoretical studies on peroxo-Mo complexes.[82,87] Higher stereoselectivies in comparison with the unmodified catalytic systems could be obtained although catalytic performance was random. Thus, in terms of stereoselectivity, the MoO_3/**47**/TBHP catalytic system worked best with glycal **4** (Table 3, entry 2), whereas oxidation of glycal **5** was more efficient with complex **46** (Table 3, entry 3).

Table 3. Sequential epoxidation-hydrolysis of glucals **4** and **5** catalyzed by Mo/*N*-ligand catalytic systems.[a]



Entry	Substrate	Catalyst	Temp (ºC)	Time (h)	Conv (%)[c,d]	Products	Ratio α/β[b,c]
1	**4**	complex **46**	50	48	>98	**42a/42b**	55:45
2	**4**	MoO_3/**47**	80	24	>98	**42a/42b**	76:24
3	**5**	complex **46**	50	6	>98	**43a/43b**	88:12
4	**5**	MoO_3/**47**	80	24	50	**43a/43b**	nd

[a] *Conditions:* 0.36 mmol glycal, 5 mol % catalyst, 1.2 mmol TBHP 5.5 M in nonane, 2 ml solvent. [b] α/β refers to products formed from the α-epoxide (*gluco*) and the β-epoxide (*manno*). See Scheme 25. [c] Determined by integration in the ^{1}H NMR spectrum of anomeric proton signals of acetylated compounds of the crude reaction mixture. [d] Selectivity > 98%.

[97] Carreiro, E. P.; Monteiro, C.; Yong-en, G.; Burke, A. J.; Rodrigues, A. I. *J. Mol. Catal. A* **2006**, *260*, 295-298.

Epoxidation-hydrolysis reactions from differently protected glucals (**4**, **5**, **35**, **36**) showed diastereoselectivities mainly governed by steric factors, so that the initial epoxidation occurs preferentially by attack from the opposite face to the OR group at C-3. After these initial results, and taking into account that the epoxidation-hydrolysis of unprotected glucal affords mannose (see Table 1) which involves electrophilic oxygen transfer *syn* to the C-3 hydroxy moiety, we next decided to investigate the reaction of glycals containing a free hydroxyl group on that position.

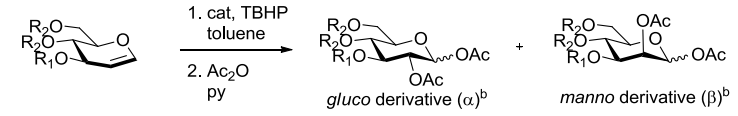
Thus, **37**[93] was treated with TBHP (Table 4, entries 1, 2) in the presence of $MoO_2(acac)_2$ and complex **46**, to obtain **48b** (*manno*) as the major product, with a stereoselectivity *gluco*:*manno* 30:70. The goal of using conformationally-restricted **37**, which is locked in a $^4H_5$ conformation on account of its isopropylidene group, is to gain insight into the parameters that govern the selectivity in oxygen transfer mechanism. Compared to results in Table 1 or Table 2, epoxidation of glucal **37** occurs with reversed selectivity, leading preferentially to a mannose derivative, thus showing the implication of the allylic hydroxy group in the oxygen transfer process. This fact was confirmed by epoxidation of the acetyl-protected derivative **38** (Table 4, entry 3). In this case, the products derived from the *gluco* epoxide **48a** were predominantly formed, as expected for an epoxidation reaction controlled by steric factors. In order to gain an insight into the association of the allylic hydroxy group in the oxygen transfer process, epoxidation of glycal **37** was developed with $VO(acac)_2$/TBHP system, which is highly used in the epoxidation of allylic alcohols (results not displayed in the table).[98] The epoxidation was carried out with 20 mol % of catalyst and 2 equiv of TBHP.[99] However, the reaction did not give rise to the epoxide or 1,2-diol products, probably due to pseudoequatorial position of allylic hydroxy group.

With the aim of testing the influence of the conformational freedom in the stereoselectivity of the epoxidation-hydrolysis, the diacetyl glucal **39**[100] was reacted under the optimized reaction conditions (Table 4, entry 4) to furnish **42a/42b** (*gluco/manno* ratio, ca 20:80) with the *manno*-configured pyranosyl

98 Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.*, **1979**, *101*, 159-169.
99 Omar, M. N. B.; Hamilton, R. J.; Moynihan, H. A. *Arkivoc* **2003**, *7*, 190-199.
100 Holla, E. W. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 220-221.

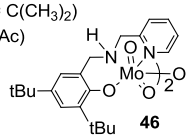
acetates as the major products. Note that the *manno* selectivity increased in comparison to the results obtained from conformationally-blocked glucal **37**, and that it is practically reversed in comparison to the obtained from compound **4** (Table 2, entry 4).

Table 4. Mo-catalyzed sequential epoxidation-hydrolysis of partially protected glycals **37-39**.[a]



37 (R_1 H, R_2 = $C(CH_3)_2$)
38 (R_1 = Ac, R_2 = $C(CH_3)_2$)
39 (R_1 = H, R_2 = Ac)

48a (R_1 = Ac, R_2 = $C(CH_3)_2$) **48b**
42a (R_1, R_2 = Ac) **42b**



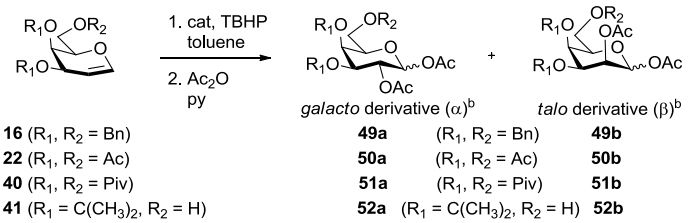
46

Entry	Substrate	Catalyst	Temp (ºC)	Time (h)	Conv (%)[c,d]	Products	Ratio α/β[b,c]
1	**37**	$MoO_2(acac)_2$	30	24	>98	**48a/48b**	30:70
2	**37**	complex **46**	50	48	50	**48a/48b**	28:72
3	**38**	$MoO_2(acac)_2$	50	53	>98	**48a/48b**	65:35
4	**39**	$MoO_2(acac)_2$	30	24	>98	**42a/42b**	20:80

[a] *Conditions:* 0.36 mmol glycal, 5 mol % catalyst, 1.2 mmol TBHP 5.5 M in nonane, 2 ml solvent. [b] α/β refers to products formed from the α-epoxide (*gluco*) and the β-epoxide (*manno*). See Scheme 25. [c] Determined by integration in the ^{1}H NMR spectrum of anomeric proton signals of acetylated compounds of the crude reaction mixture. [d] Selectivity > 98%.

To continue studying the effect of glycal configuration in the stereoselectivity, the reaction of differently protected galactals (**16**, **22**, **40**, **41**) with [Mo]/TBHP was tested. The reaction of tri-*O*-acetyl-D-galactal (**22**) with TBHP in the presence of $MoO_2(acac)_2$ afforded, after acetylation, compound **50a** as the only product (Table 5, entry 2). The reaction is much more stereoselective from galactal **22** than from glucal derivative **4** (Table 5, entry 2 vs. Table 2, entry 4). This is in agreement with that previously observed by other groups,[68] and indicates that the configuration at C-4 plays a major role in determining the degree of stereoselection, with the OR group at C-4 directing the attack of oxygen preferentially to the opposite face when it is placed in an axial position.

Table 5. Mo-catalyzed sequential epoxidation-hydrolysis of differently protected galactal derivatives **16**, **22**, **40**, **41**.[a]



16 (R_1, R_2 = Bn)
22 (R_1, R_2 = Ac)
40 (R_1, R_2 = Piv)
41 (R_1 = $C(CH_3)_2$, R_2 = H)

49a (R_1, R_2 = Bn) **49b**
50a (R_1, R_2 = Ac) **50b**
51a (R_1, R_2 = Piv) **51b**
52a (R_1 = $C(CH_3)_2$, R_2 = H) **52b**

Entry	Substrate	Catalyst	Temp (ºC)	Time (h)	Conv (%)[c,d]	Products	Ratio α/β[b,c]
1	**16**	$MoO_2(acac)_2$	30	3	>98	**49a/49b**	97:3
2	**22**	$MoO_2(acac)_2$	30	4	>98	**50a/50b**	> 98:2
3	**40**	$MoO_2(acac)_2$	30	7	>98	**51a/51b**	97:3
4	**41**	$MoO_2(acac)_2$	30	24	>98	**52a/52b**	70:30

[a] *Conditions:* 0.36 mmol glycal, 5 mol % catalyst, 1.2 mmol TBHP 5.5 M in nonane, 2 ml solvent. [b] α/β refers to products formed from the α-epoxide (*galacto*) and the β-epoxide (*talo*). See Scheme 25. [c] Determined by integration in the ^{1}H NMR spectrum of anomeric proton signals of acetylated compounds of the crude reaction mixture. [d] Selectivity > 98%.

The reaction of tri-*O*-benzyl-D-galactal (**16**) and tri-*O*-pivaloyl-D-galactal (**40**)[92] under similar conditions also provided compounds **49a** and **51a** with an excellent stereoselectivity (Table 5, entries 1, 3). Especially significant results were obtained in the reaction of galactal **41**, which has the 6-OH unprotected. The reaction was considerably slower and finished after 24h to give **52a**/**52b** with a stereoselectivity *galacto*:*talo* ratio 70:30 (Table 5, entry 4). The increase in the percentage of isomer **52b**, resulting from the epoxidation by *endo* face, may be indicative of a directing effect of the hydroxylic group at C-6.

2.2 Structure determination

As said before, two different transient epoxides resulting from the attack of the oxidizing reagent by the upper or lower face of the glycals can be formed, although they could not be isolated as a consequence of the high reactivity of the anhydro sugar in the presence of acid catalyst.

Each epoxide, after hydrolysis, affords an anomeric mixture of pyranoses. Consequently, four different diastereomers can be formed in an epoxidation-hydrolysis process: two signals corresponded to the α/β-*gluco* compounds derived from the α-epoxide (attack from the bottom face of the double bond), and other two signals to α/β-*manno* mixture resulting from the β-epoxide (attack from the upper face of the double bond). For practical reasons, the crude reaction mixture was analyzed after acetylation of the free hydroxyl groups in the resulting oxidation products. The diastereoselectivity of the epoxidation was calculated from the integrations of the anomeric protons of the acetylated products in the ^{1}H spectrum of the reaction crude, considering that each anomeric mixture coming from each epoxide. The assignments were made on the basis of signals of similar products found in the literature and on the coupling constant values.

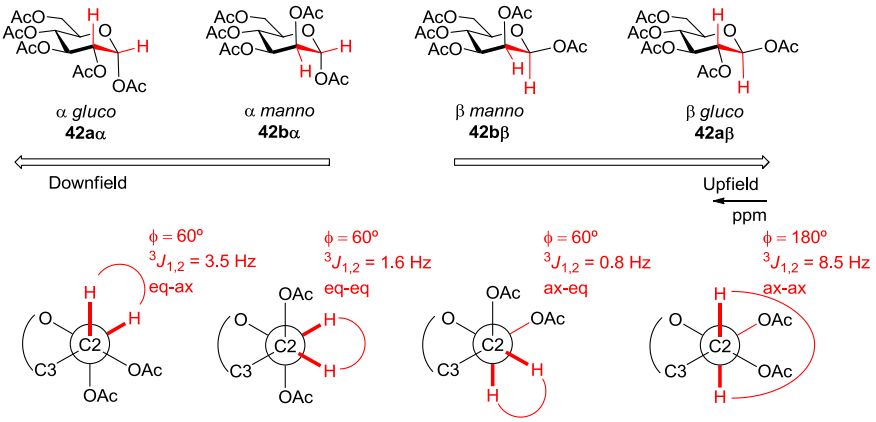


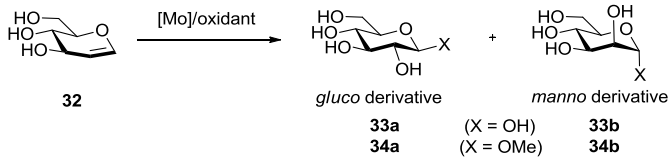
Figure 7. Anomeric configurations of *gluco* and *manno* derivatives and coupling constant $^{3}J_{1,2}$ shown in the Newman projection.

Anomeric configurations were assigned from differences in the chemical shift of H-1 and the value of the $^{3}J_{1,2}$ coupling constant (Figure 7). As a rule, the signals for known axial anomeric protons (β-glycosides) always appears upperfield than those of the equatorial protons (α-glycosides) when they are in a similar environment and the molecules are in the same conformation. Consequently, the H-1 of a α-D-configured sugar derivative displays a higher chemical shift than the H-1 of the β-D-configured analog, with chemical shift differences around 0.5 ppm. Moreover, the difference in $^{3}J_{1,2}$ is caused by different dihedral angles Φ between H-1 and H-2. The dihedral angle is 60º in the

α-*gluco* derivative (**42aα**) and 180º in the β-analog (**42aβ**). According to Karplus,[101] *trans*-diaxial hydrogens, with Φ ~ 180º have a large coupling constant (J = 7-9 Hz), whereas axial-equatorial and equatorial-equatorial orientations, both having Φ ~ 60º, have much smaller coupling constants (J = 2-4 Hz). In mannosides, with an equatorial H-2, the coupling constant between H-1 and H-2 is small for both, α- and β-mannosides as their dihedral angle is 60º in any case.

Tables 6-8 collect the chemical shifts of the anomeric protons and $^3J_{1,2}$ coupling constants of the methyl glycosides and acetylated products synthesized in this project. These data were in agreement with the reported for these products obtained by other procedures. References are given there.

Table 6. Chemical shifts of anomeric protons (δ in ppm, $^3J_{1,2}$ in Hz) of products obtained by epoxidation-hydrolysis/glycosylation of glucal **32**. Spectra recorded in CD_3OD.

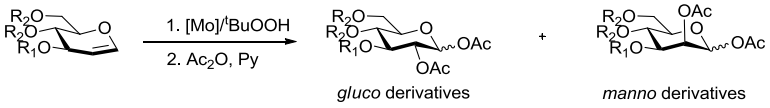


Starting Material	α *gluco*	β *gluco*	α *manno*	β *manno*	Ref
32	-	-	4.95 **33bα**	4.61 **33bβ**	[102a]
32	-	4.16 (7.8) **34aβ**	4.63 (1.3) **34bα**	4.47 **34bβ**	[102b,c]

[101] Karplus, M. *J. Chem. Phys*. **1959**, *30*, 11-13.

[102] a) Sato, K.; Akai, S.; Youda, H.; Kojima, M.; Sakuma, M.; Inaba, S.; Kurosawa, K. *Tetrahedron Lett.* **2005**, *46*, 237-243. b) Yang, M. H.; Luo, J. G.; Huang, X. F.; Kong, L. Y. *Nat. Prod. Res.* **2010**, *24*, 920-925. c) Jansson, P. E.; Lindberg, J.; Widmalm, G. *Acta Chem. Scand.* **1993**, *47*, 711-715.

Table 7. Chemical shifts of anomeric protons (δ in ppm, $^3J_{1,2}$ in Hz) of products obtained by dihydroxylation/acetylation of glucals **4**, **5, 35, 37-39**. Spectra recorded in $CDCl_3$.

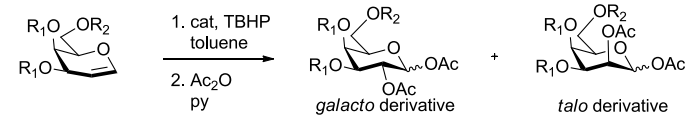


4	(R_1 = R_2 = Ac)	**42a**	(R_1 = R_2 = Ac)	**42b**
5	(R_1 = R_2 = Bn)	**43a**	(R_1 = R_2 = Bn)	**43b**
35	(R_1 = R_2 = Piv)	**44a**	(R_1 = R_2 = Piv)	**44b**
37	(R_1 = H, R_2 = $C(CH_3)_2$)	**48a**	(R_1 = Ac, R_2 = $C(CH_3)_2$)	**48b**
38	(R_1 = Ac, R_2 = $C(CH_3)_2$)	**48a**	(R_1 = Ac, R_2 = $C(CH_3)_2$)	**48b**
39	(R_1 = H, R_2 = Ac)	**42a**	(R_1 = R_2 = Ac)	**42b**

Starting Material	α *gluco*	β *gluco*	α *manno*	β *manno*	**Ref**
4	6.30 (3.6) **42aα**	5.69 (8.0) **42aβ**	6.06 (1.6) **42bα**	5.84 (1.2) **42bβ**	[72],[103a,b]
5	6.31 (3.6) **43aα**	5.62 (8.0) **43aβ**	6.14 (2.4) **43bα**	5.76 **43bβ**	[72],[103c]
35	6.31 (3.8) **44aα**	5.70 (8.3) **44aβ**	6.07 **44bα**	5.86 **44bβ**	[72]
37	6.34 (3.6) **48aα**	5.72 (8.4) **48aβ**	6.09 (1.6) **48bα**	5.87 (0.8) **48bβ**	[103d,e]
38	6.34 (3.6) **48aα**	5.72 (8.0) **48aβ**	6.10 (1.8) **48bα**	5.87 (0.7) **48bβ**	[103d,e]
39	6.33 (3.6) **42aα**	5.72 (8.2) **42aβ**	6.09 (1.7) **42bα**	5.86 (1.2) **42bβ**	[72],[103a,b]

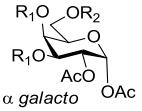
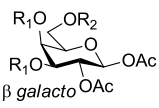
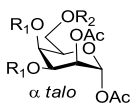
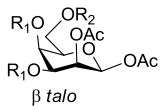
[103] a) Nóbrega, C.; Vázquez, J. T. *Tetrahedron: Asymmetry* **2003**, *14*, 2793-2801. b) Mayato, C.; Dorta, R. L.; Vázquez, J. T. *Tetrahedron: Asymmetry* **2004**, *15*, 2385-2397. c) Mayer, T. G.; Schmidt, R. R. *Eur. J. Org. Chem.* **1999**, *64*, 1153-1165. d) Cortes-Garcia, R.; Hough, L.; Richardson, A. C. *J. Chem. Soc. Trans. 1* **1981**, 3176-3181. e) Gelas, J.; Horton, D. *Carbohydr. Res.* **1978**, *67*, 371-387.

Table 8. Chemical shifts of anomeric protons (δ in ppm, $^{3}J_{1,2}$ in Hz) of products obtained by dihydroxylation/acetylation of galactals **16**, **22**, **40**, **41**. Spectra recorded in $CDCl_3$.



16 (R_1, R_2 = Bn)
22 (R_1, R_2 = Ac)
40 (R_1, R_2 = Piv)
41 (R_1 = $C(CH_3)_2$, R_2 = H)

49a (R_1 = R_2 = Bn) **49b**
50a (R_1 = R_2 = Ac) **50b**
51a (R_1 = R_2 = Piv) **51b**
52a (R_1 = $C(CH_3)_2$, R_2 = Ac) **52b**

Starting Material	 α *galacto*	 β *galacto*	 α *talo*	 β *talo*	**Ref**
16	6.35 (3.6) **49aα**	5.60 (8.4) **49aβ**	6.20 49**bα**	-	[72]
22	6.37 (1.2) **50aα**	5.69 (8.8) **50aβ**	-	-	[72],[104]
40	6.32 (3.8) **51aα**	5.70 (8.3) **51aβ**	6.07 (1.8) **51bα**	-	-
41	6.21 (3.6) **52aα**	5.55 (8.0) **52aβ**	6.01 (2.0) **52bα**	-	[103e]

Figures 8-10 display a selection of NMR spectra. There, a detail of the anomeric protons signals in the ^{1}H NMR spectrum of compounds obtained by epoxidation-hydrolysis-acetylation of glycals **4**, **37** and **40** is shown.

Poor selectivity is obtained from glycal **4** probably due to steric and conformational factors (Figure 8, ratio *gluco*/*manno*= 65:35). The epoxidation-hydrolysis-acetylation of conformationally-restricted glucal **37** rendered the *manno* derivative (**48b**) as the major product, with a stereoselectivity *gluco*:*manno* 30:70 as is shown in Figure 9. Finally, in Figure 10 the reaction of tri-*O*-pivaloyl-D-galactal (**40**) under similar conditions provided compound **51a** with an excellent stereoselectivity (ratio *galacto*/*talo*= 97:3).

[104] Roslund, M. U.; Klika, K. D.; Lehtil, R. L.; Thtinen, P.; Sillanp, R.; Leino, R. *J. Org. Chem.* **2004**, *69*, 18-25.

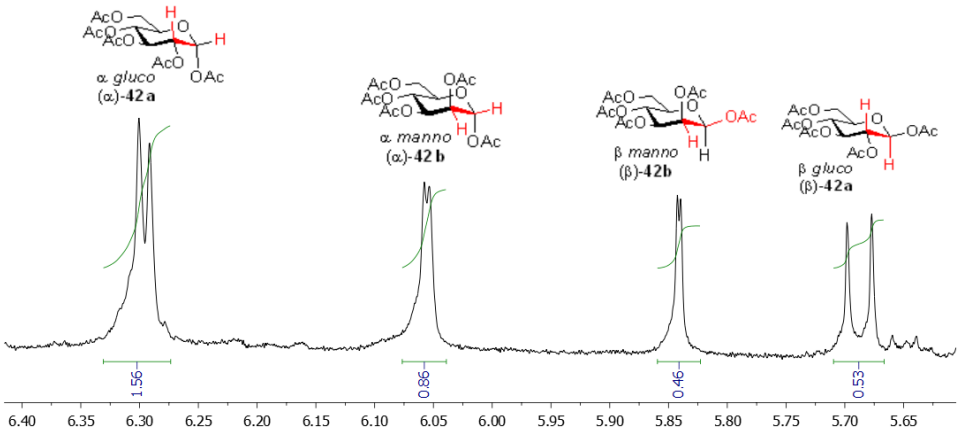


Figure 8. Anomeric protons region of products obtained by epoxidation-hydrolysis-acetylation of glucal **4**. Spectra recorded in $CDCl_3$.

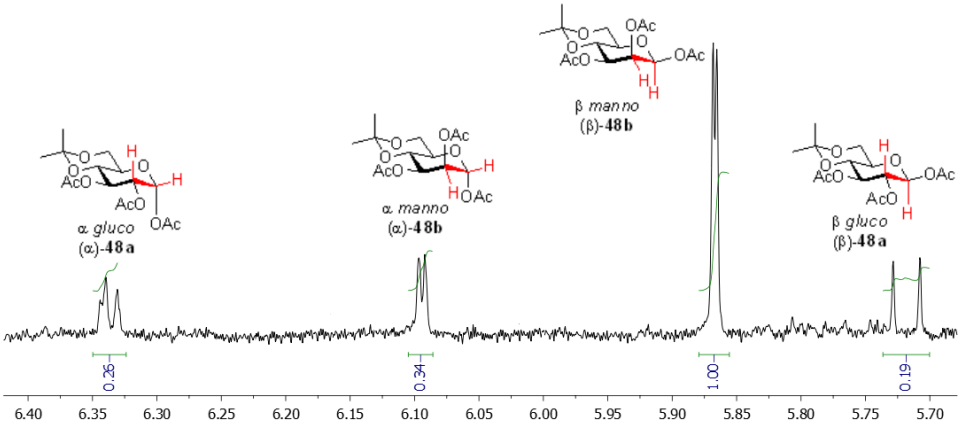


Figure 9. Anomeric protons region of products obtained by epoxidation-hydrolysis-acetylation of glucal **37**. Spectra recorded in $CDCl_3$.

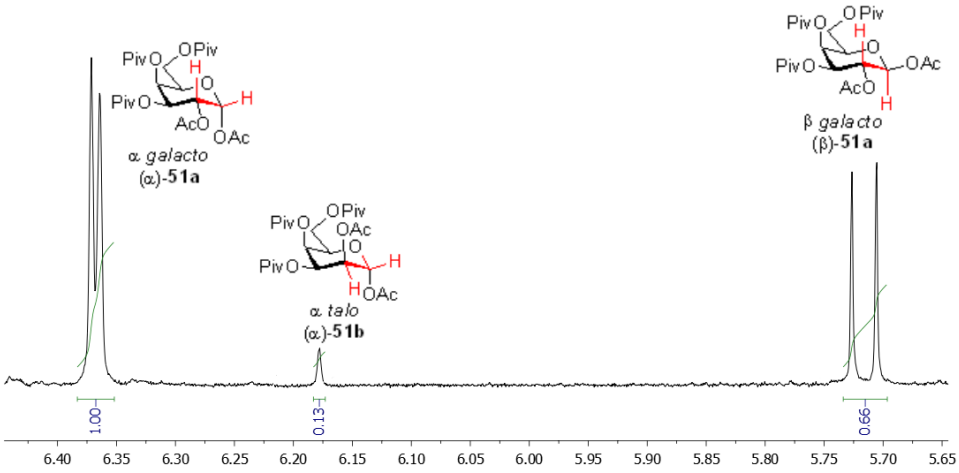


Figure 10. Anomeric protons region of products obtained by epoxidation-hydrolysis-acetylation of galactal **40**. Spectra recorded in $CDCl_3$.

2.3 Mechanistic considerations

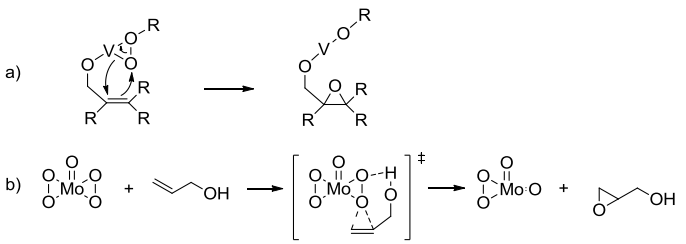
According to the literature, it seems clear that the reaction of TBHP with an oxo-Mo complex leads to the formation of an Mo(VI) alkylperoxo complex, which then transfers oxygen to the olefin.[95,105] Several studies previously attempted to isolate the intermediate Mo(VI)-*tert*-butyl peroxide complex without success.[106] In order to gain an insight into the nature of the active catalytic species in the Mo-catalyzed epoxidation of glycals, we decided to monitor the process by solution phase IR, also without success.

Another interesting issue, the role of the allylic hydroxylic group in the metal-catalyzed directed epoxidation reactions of allylic alcohols has been already

105 a) Kühn, F. E.; Groarke, M.; Bencze, É.; Herdtweck, E.; Prazeres, A; Santos, A. M.; Calhorda, M. J.; Romão, C. C.; Gonçalves, I. S.; Lopes, A. D.; Pillinger, D. *Chem. Eur. J.* **2002**, *8*, 2370-2383. b) Al-Ajlouni, A.; Valente, A. A.; Nunes, C. D.; Pillinger, M.; Santos, A. M.; Zhao, J.; Romão, C. C.; Gonçalves, I. S.; Kühn, F. E. *Eur. J. Inorg. Chem.* **2005**, 1716-1723. c) Al-Ajlouni, A.; Günyar, A.; Zhou, M.- D.; Baxter, P. N. W.; Kühn, F. E. *Eur. J. Inorg. Chem.* **2009**, 1019-1026.

106 a) Chaumette, P.; Mimoun, L.; Saussine, L.; Fischer, J.; Mitschler, A. *J. Organomet. Chem.* **1983**, *250*, 291-310. b) Groarke, M.; Gonçalves, I. S.; Herrmann, W. A.; Kühn, F. E. *J. Organomet. Chem.* **2002**, *649*, 108-112. c) see also Ref.[78d, 95]

studied.[107,108] Di Furia et al., used geraniol and linalool as probe substrates for gaining insight into the mechanism of the Mo-catalyzed epoxidation of alkenes.[108c] Based on previous experiments, the same authors had already proposed that the Mo-catalyzed epoxidation reaction of geraniol with hydrogen peroxide was consistent with an intermolecular rather than intramolecular oxygen transfer that involved the formation of a hydrogen bond between the peroxo-Mo complex and the alcohol moiety in the allylic alcohol (Scheme 26b).[109] Further experimentation led them to conclude that the moderate activation of Mo-catalyzed epoxidation of allylic alcohols compared with the very large one observed for vanadium systems might not be due to a coordinated substrate as in vanadium (Scheme 26a), but is more reasonable to propose the involvement of a transition state effect, i.e., a hydrogen-bonding assistance in the oxygen transfer process (Scheme 26b).[108c]



Scheme 26. a) Intramolecular oxygen transfer involving metal-alcoholate bonding between the peroxo-V and the coordinated substrate. b) Intermolecular oxygen transfer involving the formation of a hydrogen bond between the peroxo-Mo complex and the alcohol moiety in the allylic alcohol.

Moreover, Sheldon et al. arrived at similar conclusions when using pinane hydroperoxide (PHP) as mechanistic probes in the metal-catalyzed epoxidation of alkenes to distinguish between oxometal and peroxometal pathways.[108d] The lack of epoxidation observed with Mo/PHP in allylic alcohols suggests that

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107 Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

108 a) Sheng, M. N.; Zajacek, J. G. *J. Org. Chem*. **1970**, *35*, 1839-1843. b). Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136-6137. c) Arcoria, A.; Ballistreri, F. P.; Tomaselli, G. A.; Di Furia, F.; Modena, G. *J. Org. Chem*. **1986**, *51*, 2374-2376. d) Lempers, H. E. B.; Ripollès i Garcia, A.; Sheldon, R. E. *J. Org. Chem*. **1998**, *63*, 1408-1413. e) Adam, W.; Wirth, T. *Acc. Chem*. **1999**, *32*, 703-710.

109 Bortolini, O.; Di Furia, F., Modena, G. *J. Mol Catal*. **1983**, *19*, 319-329.

epoxidation proceeds intermolecularly and is subject to steric hindrance toward approach of the olefin to the O-O bond of the putative alkylperoxomolybdenum(VI) intermediate containing the bulky PHP.

In the late 1990s, Adam et al. proposed a transition state structure for the Ti- and Mo-TBHP epoxidation of chiral allylic alcohols, mainly dominated by ^{1,3}A strain, where the preferred dihedral angle Φ for the epoxidation of the peroxy complex lies between 70º and 90º (Figure 11a). On the basis on the similar diastereoselectivity ratios of Ti and Mo systems in the epoxidation reactions of chiral allylic alcohols and relating them with the regio- and diastereoselective epoxidation of 1-methylgeraniol with Ti, they proposed for both metals, a metal-alcoholate complex model.[108e] However, this proposal is in disagreement with the non-coordinative model proposed by Di Furia and others.

Notwithstanding, since Adam's proposal for the Mo-catalyzed transition-state structures is mainly based on the observed *erythro*/*threo* diastereoselectivities of chiral allylic alcohols, we believe that such a model can still be valid in terms of dihedral angle of the transition state, as long as the metal-alkoxo bond would be replaced with a hydrogen bond between the peroxy oxygen atom and the hydroxy group in the allylic alcohol (Figure 11b).

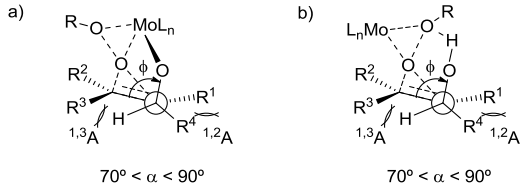


Figure 11. a) Proposed Adam's metal-alcoholate complex model for transition-state structures of the Mo-catalyzed epoxidation of allylic alcohols. b) Modified Adam's hydrogen-bond complex model for transitions-state structures of the Mo-catalyzed epoxidation of allylic alcohols.

Taking into account all these pieces of evidence, the most obvious result extracted from Table 4 is the *syn*-epoxidation of partially protected glycals with the allylic group unmasked. This is indeed indicative of some kind of directing effect by the hydroxy group. The precedent information stated above, altogether

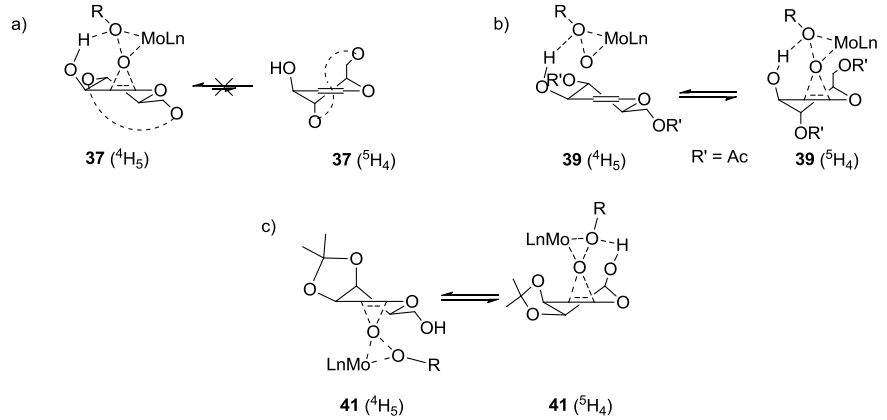
with the experimental stereoselectivity ratios obtained in this work, which are moderately high, tend to point to a hydrogen-bond assistance model rather than the coordinative metal-alkoxo model. A qualitative conformational analysis of glycal derivatives altogether with the adjustment to the previous described intermolecular Mo-catalyzed epoxidation model via hydrogen-bond activation may also give some justification of the degree of stereoselection of the process.

As stated above, the optimum dihedral angle Φ for Mo-catalyzed epoxidation transition state conformation of allylic alcohols was determined to be in the range of 70-90º, what would fit more consistently with the glycal $^5H_4$ half-chair conformation, where the allylic alcohol is in a *pseudo*-axial position, rather than in the $^4H_5$ conformation, in a *pseudo*-equatorial position. Conformationally fixed glycals (like **37**), though, cannot attain the $^5H_4$ conformation, and therefore the resulting transition state structure will not benefit from the same stabilization degree that should have in the inverted $^4H_5$ conformation (Scheme 27a).[110] On the other hand, conformational mobile glycal **39** is most likely to be preferentially in the $^4H_5$ conformation. Nevertheless, if epoxidation is agreed to proceed under Curtin-Hammet conditions, ground state conformations are not determinant of the product distribution but rather the relative energies of transition state structures. In this case, $^5H_4$ half-chair is not the most populated conformation but is the conformation that benefits from the greatest stabilization in the transition state structure, with dihedral angles in the range of what is considered an optimum value. The slight increase in the *manno* selectivity obtained with glycal **39** compared to that obtained with **37** is consistent with this appreciation (Scheme 27b).

Analogous considerations might be applied to epoxidation of galactal **41** unprotected at position 6. Simultaneous protection of hydroxyl groups at 3 and 4 as an isopropylidene acetal is not expected to prevent conformational equilibrium between half-chair conformations. On one hand, epoxidation of **41** from the most stable half-chair $^4H_5$ conformation might be expected to proceed from the α face based on the steric interaction with the isopropyliden acetal group. In such a

[110] Another experimental evidence that underscores the different mode of action between V and Mo is that the reaction of glycal **37** with $VO(acac)_2$ and TBHP did not led to even traces of epoxide product or epoxidation-hydrolysis product.

conformation, the hydroxymethyl chain in a *pseudo*-equatorial position is in a too distal position to establish any activating effect. The $^{5}H_{4}$ isomer conformation, though, may benefit from intermolecular hydrogen assistance from the hydroxymethyl moiety in a *pseudo*-axial position (Scheme 27c).



Scheme 27. Conformation equilibrium of glucals **37** (restricted, a), **39** (unrestricted, b) and galactal **41** and directed intermolecular epoxidation through hydrogen-bond assistance.

Table 9 displays a comparison of the selectivities in epoxidation/alcoholysis or epoxidation/hydrolysis of glycals obtained in this work using molybdenum catalysts, with those obtained with other catalysts, particularly MTO, Ti(O-*i*-Pr)$_4$ and Venturello's catalysts. Although glycosides or hydroxy derivatives are obtained depending on the papers, it is assumed that the *gluco*/*manno* ratio depends on the selectivity of the epoxidation step.

Stereoselectivity in the epoxidation of tri-*O*-acetyl-D-glucal (**4**) or tri-*O*-benzyl-D-glucal (**5**) is moderate with all the catalysts except with Ti(O-*i*-Pr)$_4$, which provides excellent selectivities (Table 9, entries 2, 3). An important improvement in the selectivity using MTO was obtained when the reaction was carried out in the presence of nitrogen ligands. A similar effect, although less significant was obtained with molybdenum catalysts. More important is the effect of the protecting groups. Thus, the presence of bulky protecting groups such as the pivaloyl allows us to reach very high selectivities using molybdenum catalysts (Table 9, entry 5). Curiously, no significant improvement in selectivity is

observed with Ti(O-*i*-Pr)$_4$ by replacing acetyl protecting groups by the bulkier *tert*-butyldimethylsilyl groups (Table 9, entry 4). However, the presence of bulky silyl groups precludes the reaction with molybdenum catalysts. A really different behaviour among the compared catalysts is observed in the epoxidation of unprotected glucal, MTO and Ti(O-*i*-Pr)$_4$ catalysts afforded very low selectivities, while Venturello's and molybdenum catalysts provided almost complete stereoselectivity toward the *manno* epoxide (Table 9, entry 1), which indicates a strong directing effect of hydroxyl groups in these cases. This effect is also observed with molybdenum catalysts in partially protected derivatives. Thus, compounds derived from the *manno* epoxide are mainly formed when 3-OH is unprotected (Table 9, entries 6, 7). Concerning galactal derivatives all the studied catalysts provide excellent selectivities (Table 9, entries 8-10).

Table 9. Comparison of selectivity α/β epoxide in the tandem epoxidation-glycosylation or hydrolysis with different catalysts.

Entry	Substrate	MTO[a,66]	MTO[b,65a]	MTO[c] modif[65b]	Ti(O^{i}Pr)$_4$ [a,68]	Venturello's [a,68]	[Mo]
	Glucal						
1	Unprotected (**32**)	66:33			40:60	< 2:98	< 2:98
2	3,4,6-*O*-Ac (**4**)	66:33	64:36	77:23	94:6	86:14	70:30
3	3,4,6-*O*-Bn (**5**)	86:14	85:15	93:7	> 98:2	86:14	86:14
4	3,4,6-*O*-TBS (**6**)				94:6		
5	3,4,6-*O*-Piv (**35**)						96:4
6	4,6-*O*-*i*-Propylidene (**37**)	66:33					28:72
7	4,6-*O*-Ac (**39**)						20:80
	Galactal						
8	OBn (**16**)		> 98:2	> 98:2	> 98:2	> 98:2	97:3
9	OAc (**22**)	75:25	95:5	97:3	> 98:2	> 98:2	> 98:2
10	OPiv (**40**)						97:3

[a] Reactions performed in methanol and consequently the methyl glycoside was obtained. [b] Tandem epoxidation/phosphorylation in ionic liquids. [c] Tandem epoxidation/phosphorylation in the presence of nitrogen ligands (mainly pyridine).

3. Conclusions

Highly stereoselective *one-pot* epoxidation-hydrolysis or epoxidation-alcoholysis of glucal and galactal derivatives was achieved using molybdenum catalysts and H_2O_2 or TBHP as terminal oxidants.

The stereoselectivity in the epoxidation-hydrolysis of glucal derivatives depends on the presence or absence of the protecting groups. In the absence of protecting groups the *manno* epoxide is preferably obtained. Thus, mannose (**33b**) and methyl mannopyranoside (**34b**) can be easily and stereoselectively obtained from D-glucal (**32**) using molybdenum catalysts and performing the reaction in water or methanol, respectively.

However, when the reaction is carried out in protected glucal the *trans* epoxide is mainly obtained. The best stereoselectivities in this last case were observed when pivaloyl groups were presented (**35**) obtaining a *gluco*:*manno* ratio 96:4. Modified molybdenum catalysts allowed to increase, in some cases, the stereoselectivity of the process.

In partially deprotected glycals, the hydroxy group at position 3 directs the stereoselectivity. Thus, the *gluco* derivative is obtained in fully protected glucals (*anti* attack), while the *manno* derivative is mainly obtained (*syn* attack) when 3-OH is unprotected. The best stereoselectivity was obtained in 4,6-di-acetyl glucal **39** showing a *gluco:manno* ratio 20:80.

A similar behaviour to that observed for protected glucals was stated for the protected galactal derivatives, although in this case the stereoselectivity is always good independently of the protecting groups present, and the *galacto* derivative is almost exclusively obtained in all cases.

In conclusion, molybdenum salts and complexes efficiently catalyze the epoxidation of glycals and the subsequent epoxide opening to afford glycosides or hydroxy derivatives depending on whether the solvent is an alcohol, water or other organic solvent. The stereoselectivities obtained are similar to those of the best catalysts reported. A directing effect was observed in unprotected or partially

protected glycals that seems to be consistent with a hydrogen-bond assistance model.

4. Experimental section

4.1 General methods

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2) was dried using a solvent purification system (Pure SOLV system-4®). The other solvents were purified using standard procedures.[111]

^1H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 or in a Varian® 400-MR, (both of 400 MHz and 100.6 MHz respectively) spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.27 ppm ^1H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm), unless otherwise specified. IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate.

Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F_{254} glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in a suitable developing solution.

4.2 General Procedures

General procedure for catalytic dihydroxylation using Mo(VI)/TBHP systems in water/acetylation. To a solution of glycal (1.71 mmol) in 5% aqueous or methanolic hydrogen peroxide (2.5 ml), the corresponding [Mo] catalyst (1.0 mol %) was added. After 48 h at room temperature, undissolved oxide was removed, and the excess of hydrogen peroxide was decomposed by treatment for 24 h at 22ºC with 5% palladised charcoal (5-10 mg). The filtered mixture was then evaporated in vacuo. The resulting residue was analyzed by ^1H NMR. Ratio

[111] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford, **1989**.

of isomers was determined by integration of anomeric protons of the corresponding acetyl derivatives.

General procedure for catalytic dihydroxylation using Mo(VI)/TBHP systems in organic solvents/acetylation. To a solution of glycal (0.36 mmol) in dry solvent (2 ml) the corresponding [Mo] catalyst (5.0 mol %) and TBHP (1.19 mmol) were added. The mixture was heated between 30-80ºC over a 1-96 h period. The reaction was monitored by TLC. When the reaction was completed the solution was concentrated in vacuo. The resulting residue was dissolved in pyridine (2 ml) and acetic anhydride (1 ml) was added. The resulting solution was stirred at room temperature for 2-3 h. The reaction mixture was quenched by adding MeOH. The solution was extracted with CH_2Cl_2 and washed successively with brine, saturated aqueous $NaHCO_3$ and water. The solution was dried over $MgSO_4$ and then the solvent was removed under reduced pressure. The resulting residue was analyzed by ^1H NMR. Ratio of isomers was determined by integration of anomeric protons of the corresponding acetylated products. When the solvent was methanol, the acetylation was not needed.

All products obtained in this study had been already reported in the literature and the spectroscopic data obtained from the reaction mixture matched with those reported. In the Results and discussion section (see section 2.2), the δ_1 and $J_{1,2}$ data obtained from the ^1H NMR spectra are collected (see Tables 6-8).

MCPBA-Directed Epoxidation Reactions

CHAPTER 3

As a consequence of the results obtained in the previous chapter, we present here a systematic study of the epoxidation of glycals with MCPBA in order to obtain 1,2-anhydrosugars. The idea is to use partially protected glycals with free hydroxyl groups in the allylic position in order to deliver the electrophilic oxygen to the sterically more congested glycal stereoface *syn* to the allylic alcohol, by promoting hydrogen bonding between the hydroxyl group and MCPBA. This transformation is anticipated to invert the typical stereoselectivity outcome of the oxidation reactions from fully protected glycals. The directed *syn*-oxidation of allylic alcohols with MCPBA has been widely documented, but it has not been systematically applied to unprotected glycals.[112]

1. Background

For some time it has been recognized that the hydroxy group directs the π-facial selectivity in the epoxidation of allylic alcohols for a variety of oxidazing agents,[107] providing the substrate with allylic strain.[113] The milestones during the past decades in this demanding oxidation chemistry are the Sharpless-Katsuki epoxidation[114] of allylic alcohols (Scheme 28a) and the Jacobsen-Katsuki epoxidation[115] of unfunctionalized olefins (Scheme 28b). There are a large number of selective catalytic epoxidation methods of olefins which use transition metals.[116] Ti, Mo and V systems are some of the most important for the epoxidation of allylic alcohols, meanwhile methyltrioxorhenium (MTO) and Mn(salen) complex for the epoxidation of unfunctionalized olefins. The most used stoichiometric oxidants are the peracid MCPBA and DMDO.[107]

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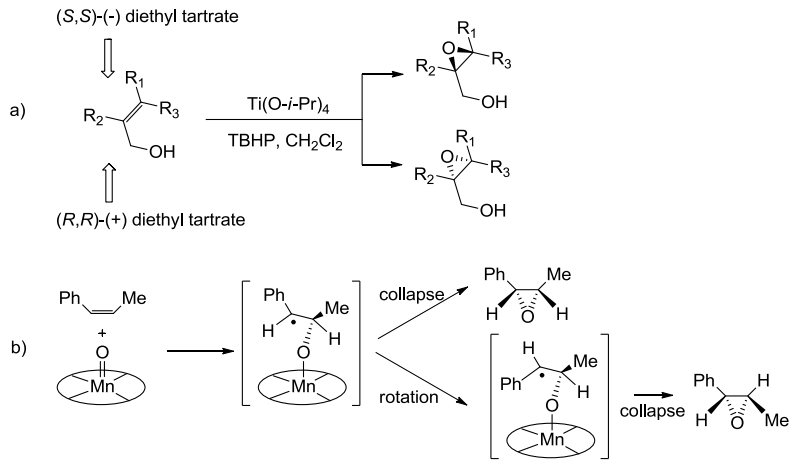
112 Only ref [13] describes two examples of *syn*-directed MCPBA/KF epoxidation starting from non-conventional ketopyranose *endo*-glycals.

113 Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841-1860.

114 Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

115 Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803.

116 a) Jorgensen, K. A. *Chem. Rev.* **1989**, *89*, 431-458. b) Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem Rev.* **2005** *105*, 1603-1662.



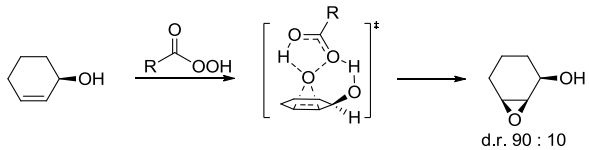
Scheme 28. a) Sharpless-Katsuki epoxidation of allylic alcohols. b) Jacobsen-Katsuki epoxidation of unfunctionalized olefins.

In this way, stereoselectivity can be controlled by optically active oxidizing species (reagent control), by optically active catalytic species (catalytic control) or it may also be controlled by substituents at stereogenic centers of chiral substrates (substrate control). In the latter case, it is important the conformation constrains on the chiral substrate and an efficient interaction (electronic, steric) with the reagent to facilitate preferential attack of one of the diastereotopic faces of the substrate.

In 1957, Henbest[117] observed a synergistic interplay between conformational control and substrate-reagent interaction through hydrogen bonding in the highly diastereoselective peracid epoxidation of cyclic allylic alcohols (Scheme 29). That hydrogen bonding between the oxygen of the peracid and the allylic alcohol of the substrate is responsible for the observed *syn* epoxidation (substrate control), and it was confirmed by the fact that on masking the hydroxy group in the form of methyl or acetyl derivatives then predominantly the *trans* epoxides were produced. The preferred *anti* attack of the peracid in this case was rationalized in terms of steric effects since hydrogen bonding by the allylic substituents with the peracid cannot apply. This concept has been extensively used in organic

[117] Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958-1965.

synthesis. However, the development of selective epoxidation requires a detailed knowledge of the transition-state structure for the oxygen-transfer process.



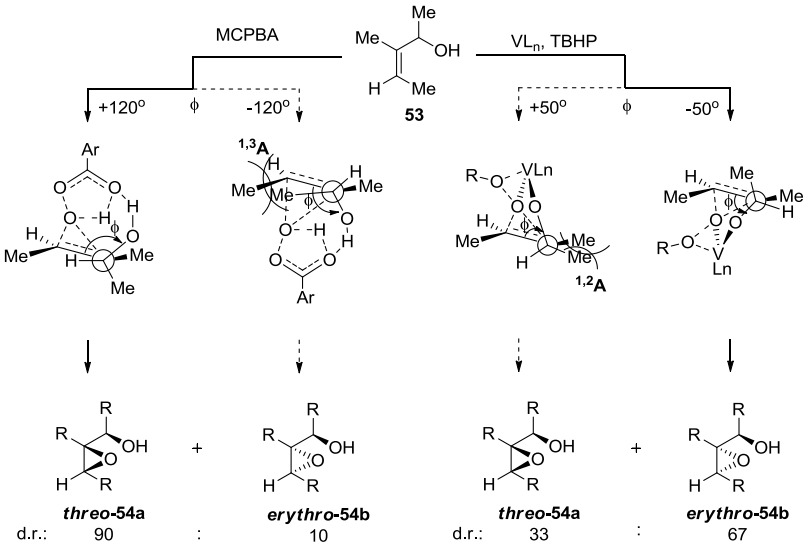
Scheme 29. Diastereoselective peracid epoxidation of cyclic allylic alcohols.

While conformational rigidity is an inherent feature of cyclic systems, such constraints do not apply to acyclic ones, unless imposed through appropriate substitution. Nevertheless, the efficiency of allylic strain (^{1,2}A and ^{1,3}A stand for 1,2- and 1,3-allylic strain) provides the necessary differentiation between the diastereotopic π faces in chiral acyclic substrates.[113] Through the proper choice of *gem* (^{1,2}A strain) and *cis* (^{1,3}A strain) substituents at the double bond of acyclic chiral alcohols, optimal dihedral angles Φ (C=C-C-OH) on the olefinic plane may be selected to test the preferred geometry of the substrate-oxidant encounter complex.[108e] From the resulting diastereoselectivities, the transition-state structure may be assessed. This is conveniently illustrated for the chiral allylic alcohol (*Z*)-3-methyl-3-penten-2-ol (**53**), which is a stereochemical probe to assess transition state in oxygen-transfer reactions (Scheme 30). In this substrate, both 1,3-allylic (^{1,3}A) and 1,2-allylic (^{1,2}A) strains are in competition. This gauges the dihedral angle about the olefinic plane and thereby aligns the hydroxyl group in a favoured conformation for hydrogen bonding with the approaching oxidant. This hydroxyl group directivity manifests itself experimentally in terms of the *threo*/*erythro* diastomeric ratio (d.r.) that is observed for the resulting epoxides.

Two oxidant agents shall serve as extreme cases to prove the importance of the dihedral angle Φ for controlling the stereochemical course in the epoxidation reaction. These are *m*-chloroperbenzoic acid (MCPBA) and $VO(acac)_2$/TBHP, for which the d.r. values are given in Scheme 30.[118] Stereoelectronic factors, as well

[118] a) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1992**, *114*, 6549-6550. b) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1993**, *34*, 5041-5049. c) Adam, W.; Nestler B. *Tetrahedron Lett.* **1993**, *34*, 611-614. d) Adam, W.; Bach, R. D.; Dmitrenko, O.; Saha-Möller, C. R. *J. Org. Chem.* **2000**, *65*, 6715-6728.

as the electronic nature of the substrate-epoxidant interaction define the favoured geometry of the oxygen-transfer process. The stereochemical differences are evident in that the epoxidation of **53** by MCPBA is *threo*-selective (***threo*-54a**), while $VO(acac)_2$/TBHP gives predominantly the *erythro* product (***erythro*-54b**). The dihedral angle (Φ) for the MCPBA transition state has been empirically estimated at ca. 120º, which is favourable for substrate-oxidant hydrogen bonding and results in *threo* diastereoselectivity, conditioned by minimal ^{1,3}A strain. In contrast, an acute dihedral angle (40º < Φ < 50º) has been estimated for $VO(acac)_2$/TBHP derived from metal-alcoholate bonding where *erythro* diastereoselectivity is favoured, imposed by minimal ^{1,2}A strain.



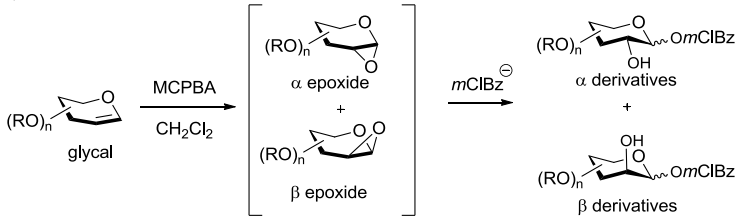
Scheme 30. Discrimination between the diastereomorphic transition states in the epoxidation of chiral allylic alcohols with peracids and a vanadium/TBHP system.

These two mechanistically distinctive epoxidants, namely, MCPBA (hydrogen bonding) vs. $VO(acac)_2$/TBHP (metal-alcoholate binding), convincingly illustrate that the diastereoselectivity in the epoxidation of allylic alcohols serves as an effective mechanistic diagnostic means to assess structural details of the transition state of oxygen transfer. Moreover, they are used as reference systems to compare the diastereoselectivity in new oxidants whose mechanism of oxygen transfer is not known.

2. Results and discussion

Taking into account first experiments developed with MCPBA in the epoxidation of glycals,[13] MCPBA/KF system was analyzed trying to obtain the epoxide and prevent the *in situ* oxirane ring-opening with *m*-chlorobenzoic acid (MCBA) generated as a subproduct of the reaction. Adding KF to the reaction medium seems to reduce the solubility of MCPBA and MCBA. In our hands, clean epoxidation only took place starting from tri-*O*-benzyl-D-glucal (**5**) to give tri-*O*-benzyl-epoxide (**8**), the rest led either to glycosides, to mixtures of sugar epoxides and glycosides or produced no glycal conversion, altogether with long reaction times.[119]

The oxidation of glycals with MCPBA in dichloromethane afforded in all cases the *m*-chlorobenzoate glycosides, as a consecuence of the *in situ* opening of the epoxides initially formed, which is induced by MCBA generated in the reaction medium (Scheme 31). Then, oxidation of tri-*O*-acetyl-D-glucal (**4**) with MCPBA in dichloromethane as the solvent afforded a mixture of *m*-chlorobenzoyl-*gluco* (**55a**) and *manno*-pyranoside (**55b**) in a ratio 80:20 (Table 10, entry 1).



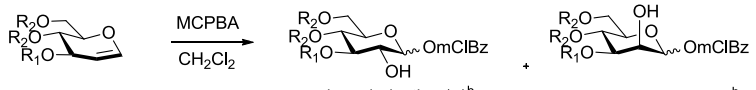
Scheme 31. MCPBA-mediated tandem epoxidation-ring opening of glycals.

When tri-*O*-benzyl-D-glucal (**5**) was tested with MCPBA, it provided a similar behaviour to acetyl derivative and the corresponding glycosides were obtained in quantitative yield and comparatively improved stereoselectivity, ratio *gluco:manno* = 84:16 (Table 10, entry 2). The use of bulkier protecting groups such as pivaloate groups in glycal **35**,[92] did not afford better stereoselectivities (Table 10, entry 3). Although α/β mixtures were obtained in all cases, the product

[119] Jordi Colavida. Experimental work, URV, Tarragona, **2011**.

derived from the α-epoxide (*gluco*), *trans* to the C-3 substituent, was the major one.

Table 10. MCPBA induced stereoselective tandem epoxidation-glycosylation of glucals **4**, **5**, **35**, **37**-**39**.[a]



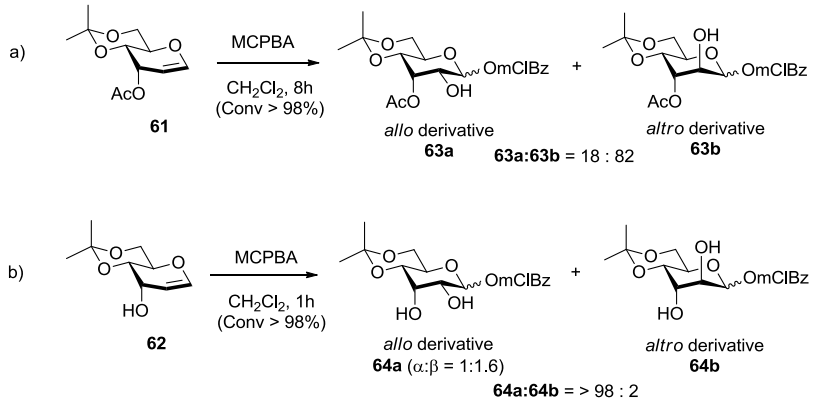
	gluco derivative (α)[b]	*manno* derivative (β)[b]
4 (R_1 = R_2 = Ac)	**55a** (R_1 = R_2 = Ac)	**55b**
5 (R_1 = R_2 = Bn)	**56a** (R_1 = R_2 = Bn)	**56b**
35 (R_1 = R_2 = Piv)	**57a** (R_1 = R_2 = Piv)	**57b**
37 (R_1 = H, R_2 = $C(CH_3)_2$)	**58a** (R_1 = H, R_2 = $C(CH_3)_2$)	**58b**
38 (R_1 = Ac, R_2 = $C(CH_3)_2$)	**59a** (R_1 = Ac, R_2 = $C(CH_3)_2$)	**59b**
39 (R_1 = H, R_2 = Ac)	**60a** (R_1 = H, R_2 = Ac)	**60b**

Entry	Substrate	Time (h)	Conv (%)[c,d]	Products	Ratio α/β[b,c]
1	**4**	1	>98	**55a/55b**	80:20[e]
2	**5**	1	>98	**56a/56b**	84:16[e]
3	**35**	5	>98	**57a/57b**	79:20[e]
4	**37**	3	>98	**58a/58b**	< 2:98[f]
5	**38**	1	>98	**59a/59b**	80:20[e]
6	**39**	1	>98	**60a/60b**	10:90[f]

[a] *Conditions:* 0.36 mmol glycal, 0.72 mmol MCPBA, 11.5 ml anhydrous CH_2Cl_2, rt. [b] α/β refers to products formed from the α-epoxide (*gluco*) and the β-epoxide (*manno*). See Scheme 31. [c] Determined by integration in the ^{1}H NMR spectrum of anomeric proton signals of the crude reaction mixture. [d] Selectivity > 98%. [e] Both compounds were obtained as α/β mixtures. [f] Only the α anomer was detected.

Oxidation of the conformationally more rigid glucal derivative **38** furnished glycosides **59a** and **59b** with similar stereoselectivity to those of the previous examples (Table 10, entry 5). In order to reverse the stereoselectivity of the process, the directing effect of a hydroxyl group at the allylic position was explored. Gratifyingly, when partially protected glucal **37**[93] reacted with MCPBA, glycoside **58b** derived from the *manno* epoxide, was exclusively obtained in 83% yield (Table 10, entry 4). In rigid systems such as this one, the directing effect can be conditioned by conformational effects. The high level of stereoselectivity obtained in **37**, however, is indicative of a directing effect where the glycal

associates with the peracid through hydrogen-bond. Actually the $^4H_5$ conformation of glycal **37** seems to fit well with the postulated transition state model for MCPBA epoxidation of allylic alcohols, where the dihedral angle ranges 120-140º (Figure 12a).[108e,118d] Oxidation of 4,6-di-*O*-acetyl-D-glucal (**39**)[100] was carried out in order to confirm the hydroxyl group directing effect in conformationally more flexible compounds (Table 10, entry 6). The product derived from the *manno* epoxide **60b** was again preferentially obtained in 76% yield with a selectivity *gluco*:*manno* 10:90.



Scheme 32. MCPBA-mediated epoxidation-acidolysis of a) protected allal **61**, and b) partially protected allal **62**.

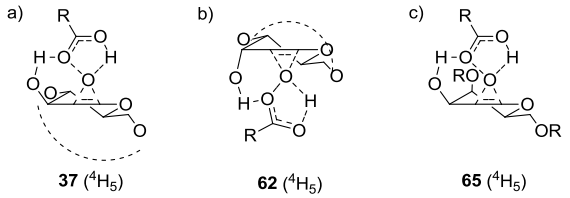


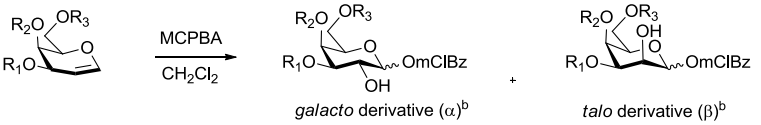
Figure 12. Proposed transition states for the 3-OH directed epoxidation with MCPBA of glucal **37** (a), allal **62** (b) and galactal **65** (c).

MCPBA oxidation of allal derivatives **61** and **62**[120], with an allylic substituent in a *pseudo*-axial position was also analyzed (Scheme 32). As expected, oxidation of fully protected allal **61** rendered *altro* glycoside **63b** as the major product, as a

[120] Kan, C.; Long, C. M.; Paul, M.; Ring, C. M.; Tully, S. E.; Rojas, C. M. *Org. Lett.* **2001**, *3*, 381-384.

consequence of epoxidation on the more accessible glycal face**.** Reaction from partially protected allal **62**, in contrast, furnished exclusively *allo* glycoside **64a** in 90% yield confirming the directing effect of the allylic hydroxyl group in the MCPBA-mediated oxidation of glycals (Figure 12b).

Table 11. MCPBA induced stereoselective tandem epoxidation-glycosylation of galactal derivatives **16**, **22**, **40**, **41**, **65**, **66**.[a]



16 ($R_1 = R_2 = R_3$ = Bn)
22 ($R_1 = R_2 = R_3$ = Ac)
40 ($R_1 = R_2 = R_3$ = Piv)
41 ($R_1 = R_2$ = $C(CH_3)_2$, R_3 = H)
65 (R_1 = H, $R_2 = R_3$ = Ac)
66 ($R_1 = R_3$ = TBS, R_2 = H)

galacto derivative (α)[b]

67a ($R_1 = R_2 = R_3$ = Bn)
68a ($R_1 = R_2 = R_3$ = Ac)
69a ($R_1 = R_2 = R_3$ = Piv)
70a ($R_1 = R_2$ = $C(CH_3)_2$, R_3 = H)
71a (R_1 = H, $R_2 = R_3$ = Ac)
72a ($R_1 = R_3$ = TBS, R_2 = H)

talo derivative (β)[b]

67b
68b
69b
70b
71b
72b

Entry	Substrate	Time (h)	Conv (%)[c,d]	Products	Ratio α/β[b,c,e]
1	**16**	1	>98	**67a/67b**	85:15
2	**22**	1	>98	**68a/68b**	82:18
3	**40**	5	>98	**69a/69b**	> 98:2
4	**41**	3	>98	**70a/70b**	72:28
5	**65**	2	>98	**71a/71b**	67:33
6	**66**	2	>98	**72a/72b**	90:10

[a] *Conditions:* 0.36 mmol glycal, 0.72 mmol MCPBA, 11.5 ml anhydrous CH_2Cl_2, rt. [b] α/β refers to products formed from the α-epoxide (*galacto*) and the β-epoxide (*talo*). See Scheme 31. [c] Determined by integration in the ^1H NMR spectrum of anomeric proton signals of the crude reaction mixture [d] Selectivity > 98%. [e] Both compounds were obtained as α/β mixtures.

The effect of glycal configuration in the stereoselectivity of MCPBA-mediated epoxidation-glycosylation was extended to galactal derivatives (Table 11). Oxidation of tri-*O*-benzyl-D-galactal (**16**) afforded galactoside **67a** as the major product (**67a/67b** ratio= 85:15) (Table 11, entry 1), similar to the selectivity obtained for the glucal analog (Table 10, entry 2). Similarly, oxidation of tri-*O*-acetyl derivative **22** furnished **68a** as the major product with a *galacto*:*talo* ratio=

82:18 (Table 11, entry 2), again similar to the selectivity obtained in the glucal analog (Table 10, entry 1). Oxidation of tri-*O*-pivaloyl-D-galactal (**40**)[92] afforded exclusively **69b** in 88% yield (Table 11, entry 3), improving the selectivity obtained with the *gluco* analog **35** (Table 10, entry 3). The axial substituent at C-4 plays a major role in the stereofacial bias of the glycal towards epoxidation, directing oxygen transfer preferentially from the opposite face.

Partially protected galactal derivatives having free hydroxyl groups at positions 3, 4 or 6 (**41, 65**, **66**) were also tested. When compound **65**,[100] with a free allylic hydroxyl group, was treated with MCPBA, the *galacto* derivative **71a** was still the major product although the percentage of the *talo* derivative **72b** increased slightly (*galacto*:*talo* ratio=67:33) (Table 11, entry 5). The presence of an axial substituent at C-4 on the same face of the directing group may destabilize the transition state that involves the complexation of MCPBA to the 3-OH (Figure 12c). Virtually the same selectivity was obtained from oxidation of glycal **41**,[121] with a free hydroxyl group at position 6 (Table 11, entry 4), although implication of a directing effect of the distal hydroxyl group might be unlikely, especially if the $^4H_5$ half-chair conformation of the glycal is considered. Oxidation of galactal **66**,[122] with a free homoallylic hydroxyl group led to the *galacto* derivative **72a** in 85% yield with an excellent stereoselectivity (**72a**/**72b** ratio= 90:10) (Table 11, entry 6). Homoallylic hydroxyl groups can direct epoxidation in cyclic systems, especially if they occupy axial positions. However, the presence of bulky groups at positions 3 and 6 probably limits the coordination of MCPBA to the hydroxyl group. Thus, the directing effect of a hydroxyl group in the oxidation of galactals is rather weak and is very sensitive to steric interferences.

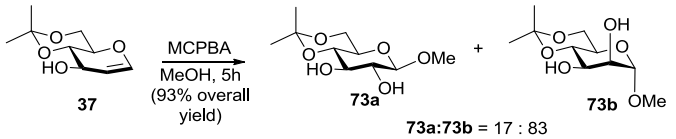
Tandem epoxidation-alcoholysis has been reported using mainly metal catalysts.[65-66,68] We explored this tandem reaction using MCPBA in methanol as a solvent. Under these conditions, methyl glycosides **73a** and **73b**[123] were obtained in a 17:83 ratio (Scheme 33), with a *manno* stereoselectivity partially eroded with respect to its analogous reaction in CH_2Cl_2 (compare with Table 10, entry 4,

121 Toyokuni, T.; Cai, S.; Dean, B. *Synthesis* **1992**, 1236-1238.

122 Jacquinet, J.- C. *Carbohydr. Res.* **1990**, *199*, 153-181.

123 a) Debost, J.- L.; Gelas, J.; Horton, D.; Mols, O. *Carbohydr. Res.* **1984**, *125*, 329-335. b) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252-3257.

where only the *manno* derivative was detected). The use of polar alcoholic solvents may partially cancel this *syn*-directing effect by disturbing the hydrogen bonding. Epoxidation-methanolysis of tri-*O*-acetyl-D-glucal with methyltrioxorhenium (MTO) or supported MTO derivatives and urea hydrogen peroxide adduct in ionic liquids have been described to give, at the best, 64:36 mixtures of the *gluco*:*manno* methyl glycosides,[65,66] whereas the analogous reaction with $Ti(O\text{-}i\text{-}Pr)_4$ provided highly stereoselectivity (*gluco*/*manno* ratio=94:6) although it required long reaction times (170 h) and did not lead to full conversion.[68]



Scheme 33. MCPBA-mediated epoxidation of partially protected glucal **37**.

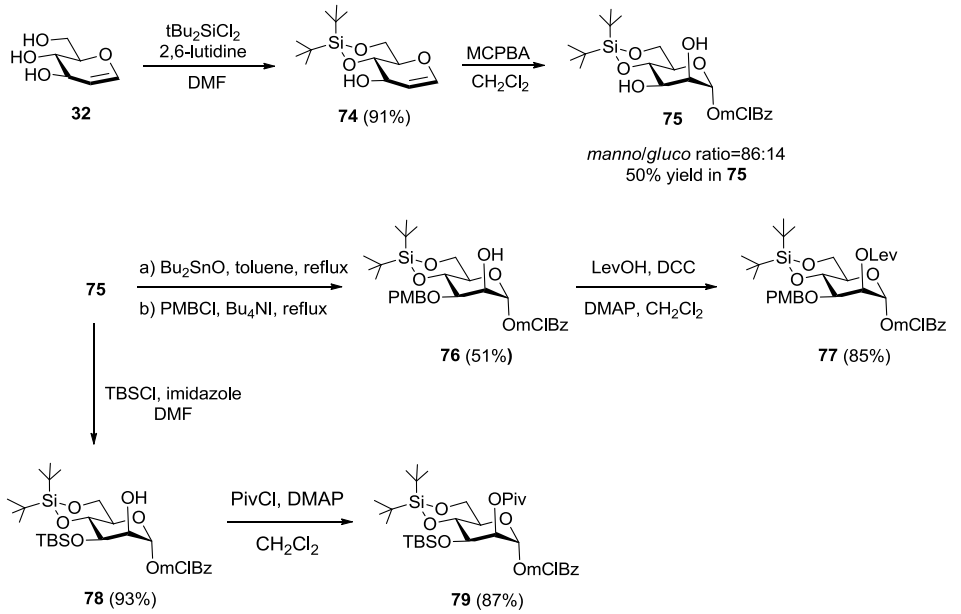
The usefulness of the directed tandem epoxidation-glycosylation procedure developed in this work was demonstrated by the straightforward synthesis of the *manno* glycosyl donors **77** and **79** (Scheme 34) and their use in glycosylation reactions. The aim of this work was to provide an easy access to orthogonally protected mannopyranoside derivatives.

Compound **74** was prepared from D-glucal (**32**) following reported procedures.[124] The reaction of **74** with MCPBA under the previously reported conditions afforded preferentially the product derived from the *manno* epoxide **75** in 50% yield with a selectivity *manno*:*gluco* 86:14. The hydroxyl group at position 3 was selectively protected as the *p*-methoxybenzyl (PMB) ether using a stannylene acetal intermediate as strategy. Reaction with dibutyltin oxide in toluene at reflux and then, PMBCl and tetrabutylammonium iodide (TBAI) gave a complete regioselective protection of that position giving compound **76**.[125] Finally, a levulinoyl ester was used to protect position 2 using levulinic acid and dicyclohexylcarbodiimide (DCC) in dichloromethane at room temperature

[124] Parker, K. A.; Georges, A. T. *Org. Lett.* **2000**, *2*, 497-499.

[125] Reina, J. J.; Díaz, I.; Nieto, P. M.; Campillo, N. E.; Páez, J. A.; Tabarani, G.; Fieschi, F.; Rojo, J. *Org. Biomol. Chem.*, **2008**, *6*, 2743-2754.

affording the orthogonally protected mannoside **77** in 43% yield (two steps).[126] Compound **79** was prepared from diol **75** via sequential silylation and pivaloylation following Seeberger procedure.[127] Orthogonally protected chlorobenzyl α-mannopyranosides **77** and **79** were synthesized in 5 and 4 steps from D-glucal in overall yields of 20% and 37%, respectively.



Scheme 34. Synthesis of orthogonally protected α-mannopyranosides building blocks **77** and **79**.

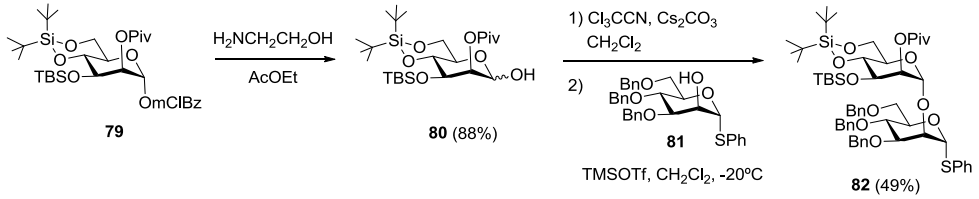
Compound **79** was then selected to test its potential use as a donor in glycosylation reactions (Scheme 35). Thus, the treatment of **79** with 2-aminoethanol afforded mannose derivative **80** in 88% yield.[128] Then, compound **80** was activated as a trichloroacetamidate and *in situ* treatment with the acceptor

[126] Compostella, F.; Ronchi, S.; Panza, L.; Mariotti, S.; Mori, L.; De Libero, G.; Ronchetti, F. *Chem. Eur. J.*, **2006**, *12*, 5587-5595.

[127] Obadiah, J. P.; Palmacci, E. R.; Seeberger, P. H. *Org. Lett.*, **2000**, *2*, 3841-3843.

[128] Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270-1277.

81 and TMSOTf as activator at -20ºC for 2h furnished the disaccharide **82** in 49% yield.[129]



Scheme 35. Synthesis of disaccharide **82**.

3. Conclusions

Partially unprotected glycals with free hydroxyl groups in the allylic position direct the stereoselectivity of the epoxidation with MCPBA to give the *syn* epoxide, which is opened *in situ* under the reaction conditions to give glycosylated compounds.

The reaction was completely stereoselective when partially protected glucal **37** and allal **62** derivatives were the starting materials giving *manno* glycoside **58b** and *allo* glycoside **64a** in 83% and 90% yield, respectively, and it was very stereoselective with di-4,6-acetylated glucal **39**, which afforded *manno* derivative **60b** in 76% yield with a selectivity *gluco*:*manno* 10:90.

Oxidation of galactal derivatives proceeded in general with much lower stereocontrol, probably due to destabilization of the transition state by the presence of an axial substituent at C-4. When the allyl hydroxyl group was protected products derived from the *anti* epoxide were obtained, achieving the better stereoselectivity with tripivaloylated galactal **40** which afforded exclusively galacto compound **69b** in 88% yield. When partially protected galactal derivatives were used, stereoselectivities decreased and weak directing effect of a hydroxyl group was observed.

[129] a) Mayer, T. G.; Kratzer, B.; Schmidt, R. R. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2177-2181. b) Mahling, J.- A.; Schmidt, R. R. *Synthesis* **1993**, *3*, 325-328.

Orthogonally protected *manno* glycosyl donors **77** and **79** have been synthesized using this procedure in only 5 and 4 steps in 20% and 37% overall yields, respectively. Compound **79** was hydrolyzed, activated as trichloroacetimidate and used as donor to afford disaccharide **82**, which demonstrates that this compound can be used as glycosyl donor.

4. Experimental Section

4.1 General methods

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), dimethylformamide (DMF) and diethyl ether were dried using a solvent purification system (Pure SOLV system-4®). The other solvents were purified using standard procedures.[111]

^1H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 or in a Varian® 400-MR, (both of 400 MHz and 100.6 MHz respectively) spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.27 ppm ^1H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm), unless otherwise specified. 2D correlation spectra (gCOSY, NOESY, TOCSY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate.

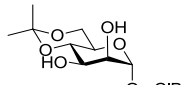
Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F_{254} glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in a suitable developing solution. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

4.2 General Procedures

General procedure for MCPBA epoxidation. To a solution of glycal (0.36 mmol) in dry CH_2Cl_2 (11.5 ml) MCPBA (180 mg, 0.72 mmol) was added. The mixture was stirred at room temperature. The reaction was monitored by TLC until the starting material was consumed. The solution was extracted with CH_2Cl_2 and washed successively with saturated aqueous $NaHCO_3$ and water. The solution was dried over $MgSO_4$ and then the solvent was removed under reduced pressure. The resulting residue was analyzed by ^1H NMR.

4.3 Compound Characterization

1-*O*-(3-Chlorobenzoyl)-4,6-*O*-isopropylidene-α-D-mannopyranose (58b).

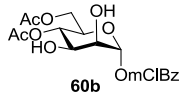


58b

Following the general procedure **37** (0.05 g, 0.27 mmol) reacted with MCPBA (0.07 g, 0.54 mmol) to furnish compound **58b** as a white solid (0.08 g, 0.22 mmol, 83%), after purification by flash chromatography (hexane/EtOAc 1:2).

Mp 175-177 ºC. **$[\alpha]^{25}_D$** +17.8 (*c* 1.18, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.99 (bs, 1H), 7.94 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.59 (ddd, 1H, *J* = 8.0, 1.2, 1.2 Hz), 7.43 (dd, 1H, *J* = 8.0, 8.0 Hz), 6.37 (d, 1H, *J* = 1.2 Hz), 4.18 (bs, 1H), 4.09 (d, 1H, *J* = 5.2 Hz), 3.91-3.76 (m, 4H), 1.54 (s, 3H), 1.45 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 163.4, 135.0, 134.0, 131.0, 130.2, 130.0, 128.3, 100.5, 94.5, 70.9, 70.2, 69.3, 66.8, 62.1, 29.3, 19.5. **FT-IR** (neat) ν in cm^{-1}: 3418, 3291, 2994, 2925, 1730, 1252, 1083, 961, 856, 744. **ESI-HRMS** *m*/*z* calcd. for $C_{16}H_{19}ClNaO_7$ [M-Na]: 381.0717, found: 381.0703.

4,6-di-*O*-Acetyl-1-*O*-(3-chlorobenzoyl)-α-D-mannopyranose (60b).

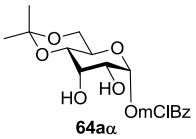


60b

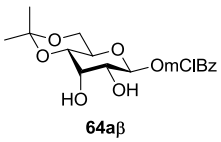
Following the general procedure **39** (0.03 g, 0.13 mmol) reacted with MCPBA (0.05 g, 0.26 mmol) to afford a 1:9 mixture of compounds **60a** and **60b**. Purification by radial chromatography (hexane/ EtOAc 1:2), afforded compound **60b** as a white solid (0.04 g, 0.10 mmol, 76%).

Mp 140-142 ºC. **[α]$^{25}_{D}$** +4.79 (*c* 0.7, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.98 (s, 1H), 7.92 (d, 1H, *J* = 8.0 Hz), 7.60 (ddd, 1H, *J* = 8.0, 1.2, 1.2 Hz), 7.44 (dd, 1H, *J* = 8.0, 8.0 Hz), 6.43 (d, 1H, *J* = 2.0 Hz), 5.19 (dd, 1H, *J* = 9.6, 9.6 Hz), 4.38 (dd, 1H, *J* = 12.4, 4.4 Hz), 4.14 (dd, 1H, *J* = 9.6, 2.0 Hz), 4.16-4.05 (m, 3H), 2.17 (s, 3H), 2.09 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 172.1, 171.1, 163.2, 134.2, 134.2, 130.9, 130.3, 130.0, 128.3, 94.0, 70.8, 70.5, 70.0, 69.5, 62.4, 21.2, 21.0. **FT-IR** (neat) ν in cm^{-1}: 3424, 3303, 2931, 1733, 1250, 1084, 964, 858, 744. **ESI-HRMS** *m/z* calcd. for $C_{17}H_{19}ClNaO_9$ [M-Na]: 425.0615, found: 425.0606.

1-*O*-(3-Chlorobenzoyl)-4,6-*O*-isopropylidene-α-D-allopyranose (64aα) and 1-*O*-(3-Chlorobenzoyl)-4,6-*O*-isopropylidene-β-D-allopyranose (64aβ).



64aα



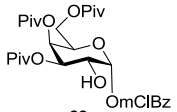
64aβ

Following the general procedure **62** (0.04 g, 0.21 mmol) reacted with MCPBA (0.11 g, 0.42 mmol) to afford **64a** (0.07 g, 0.19 mmol, 90%) as a mixture α:β = 48:52. Compound **64aβ** was obtained in a pure form by purification by radial chromatography (hexane/ EtOAc 2:1) as a white solid.

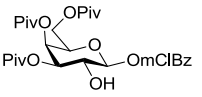
64aβ: **Mp** 88-90 ºC. **[α]$^{25}_{D}$** -15.65 (*c* 0.3, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 8.08 (dd, 1H, *J* = 1.6, 1.6 Hz), 7.99 (d, 1H, *J* = 8.0 Hz), 7.56 (ddd, 1H, *J* = 8.0, 1.2, 1.2 Hz), 7.40 (dd, 1H, *J* = 8.0, 8.0 Hz), 6.07 (d, 1H, *J* = 8.4 Hz), 4.32 (dd, 1H, *J* = 2.8, 2.4 Hz), 4.03-3.96 (m, 2H), 3.81 (dd, 1H, *J* = 8.4, 3.6 Hz), 3.77-3.69 (m, 2H), 1.53 (s, 3H), 1.46 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 164.3, 134.8, 133.9, 131.1, 130.3, 130.0, 128.5, 100. 0, 94.3, 71.3, 70.6, 69.6, 64.9, 62.3, 29.1, 19.4. **FT-IR** (neat) ν in cm^{-1}: 3390, 2941, 1734, 1250, 1066, 1024, 747. **ESI-HRMS** *m/z* calcd. for $C_{16}H_{19}ClNaO_7$ [M-Na]: 381.0717, found: 381.0679.

Spectroscopic data of **64aα** from the α/β mixture: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 8.05 (d, 1H, *J* = 1.6 Hz), 7.97 (dd, 1H, *J* = 7.6, 1.6 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.45 (dd, 1H, *J* = 8.0, 7.6 Hz), 6.56 (d, 1H, *J* = 4.0 Hz), 5.57 (dd, 1H, *J* = 3.2, 1.2 Hz), 5.41 (dd, 1H, *J* = 10.4, 3.2 Hz), 4.38 (dd, 1H, *J* = 7.2, 6.8 Hz), 4.27 (dd, 1H, *J* = 10.4, 4.0 Hz), 4.11 (dd, 1H, *J* = 10.8, 6.8 Hz), 4.05 (dd, 1H, *J* = 10.8, 7.2 Hz), 1.28 (s, 9H), 1.22 (s, 9H), 1.13 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 178.9, 178.0, 177.0, 164.0, 135.1, 134.1, 130.9, 130.3, 130.1, 128.2, 93.2, 70.7, 69.7, 67.3, 67.2, 61.1, 39.3, 39.2, 38.9, 27.4, 27.3, 27.2.

1-*O*-(3-Chlorobenzoyl)-3,4,6-tri-*O*-pivaloyl-α-D-galactopyranose (69aα) and 1-*O*-(3-Chlorobenzoyl)-3,4,6-tri-*O*-pivaloyl-β-D-galactopyranose (69aβ).



69aα



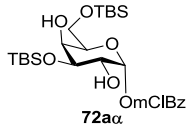
69aβ

Following the general procedure for MCPBA epoxidation **69aα** and **69aβ** were synthesized from **40** (0.08 g, 0.20 mmol) and MCPBA (0.10 g, 0.40 mmol). The final products **69aα** and **69aβ** were obtained in a ratio 21:79, respectively. Purification by radial chromatography (hexane/EtOAc 9:1), afforded compounds **69aα** (0.03 g, 0.06 mmol, 27%) and **69aβ** (0.07 g, 0.12 mmol, 61%) as colourless syrups (overall yield 88%).

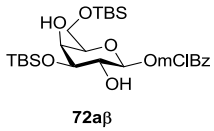
69aα: **$[\alpha]^{25}_D$** +30.5 (*c* 0.74, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 8.05 (d, 1H, *J* = 1.6 Hz), 7.97 (dd, 1H, *J* = 7.6, 1.6 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.45 (dd, 1H, *J* = 8.0, 7.6 Hz), 6.56 (d, 1H, *J* = 4.0 Hz), 5.57 (dd, 1H, *J* = 3.2, 1.2 Hz), 5.41 (dd, 1H, *J* = 10.4, 3.2 Hz), 4.38 (dd, 1H, *J* = 7.2, 6.8 Hz), 4.27 (dd, 1H, *J* = 10.4, 4.0 Hz), 4.11 (dd, 1H, *J* = 10.8, 6.8 Hz), 4.05 (dd, 1H, *J* = 10.8, 7.2 Hz), 1.28 (s, 9H), 1.22 (s, 9H), 1.13 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 178.9, 178.0, 177.0, 164.0, 135.1, 134.1, 130.9, 130.3, 130.1, 128.2, 93.2, 70.7, 69.7, 67.3, 67.2, 61.1, 39.3, 39.2, 38.9, 27.4, 27.3, 27.2. FT-IR (neat) ν in cm^{-1}: 3462, 2970, 1738, 1365, 1217. **FT-IR** (neat) ν in cm^{-1}: 3462, 2970, 1738, 1365, 1229, 1217, 1023, 748. **ESI-HRMS** *m/z* calcd. for $C_{28}H_{39}ClNaO_{10}$ [M-Na]: 593.2129, found: 593.2101.

69aβ: **$[\alpha]^{25}_{D}$** +9.39 (*c* 1.94, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 8.09 (dd, 1H, *J* = 2.0, 2.0 Hz), 8.01 (dd, 1H, *J* = 7.6, 2.0 Hz), 7.57 (dd, 1H, *J* = 8.0, 2.0 Hz), 7.41 (dd, 1H, *J* = 8.0, 7.6 Hz), 5.87 (d, 1H, *J* = 8.0 Hz), 5.48 (d, 1H, *J* = 3.2 Hz), 5.16 (dd, 1H, *J* = 10.4, 3.2 Hz), 4.24-4.03 (m, 4H), 1.29 (s, 9H), 1.20 (s, 9H), 1.18 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 178.4, 178.1, 177.0, 163.9, 134.8, 134.0, 130.9, 130.3, 130.2, 128.5, 95.2, 73.2, 72.3, 69.3, 66.9, 61.0, 39.3, 39.1, 38.9, 27.4, 27.3, 27.2**. FT-IR** (neat) ν in cm^{-1}: 3447, 2970, 1739, 1365, 1217, 1066, 746. **ESI-HRMS** *m*/*z* calcd. for $C_{28}H_{39}ClNaO_{10}$ [M-Na]: 593.2129, found: 593.2096.

3,6-Di-*O*-*tert*-butyldimethylsilyl-1-*O*-(3-chlorobenzoyl)-α-D-galactopyranose (72aα) and 3,6-Di-*O*-*tert*-butyldimethylsilyl-1-*O*-(3-chlorobenzoyl)-β-D-galactopyranose (72aβ).



72aα



72aβ

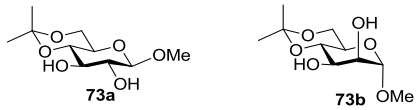
Following the general procedure **66** (0.08 g, 0.16 mmol) reacted with MCPBA (0.10 g, 0.32 mmol) to afford **72a** (0.07 g, 0.14 mmol, 85%) as a mixture α:β = 57:43, from a mixture of diastereoisomers *galacto*/*talo* = 90:10. Products **72aα** and **72aβ** were obtained in a pure form by purification by radial chromatography (hexane/EtOAc 3:1) as colourless syrups.

72aα: **$[\alpha]^{25}_{D}$** +40.57 (*c* 0.3, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.93 (dd, 1H, *J* = 2.0, 2.0 Hz), 7.86 (d, 1H, *J* = 7.6 Hz), 7.53 (ddd, 1H, *J* = 7.6, 2.0, 0.8 Hz), 7.36 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.43 (d, 1H, *J* = 4.0 Hz), 4.12-4.09 (m, 1H), 3.99-3.95 (m, 2H), 3.92-3.83 (m, 2H), 3.73 (dd, 1H, *J* = 10.0, 5.2 Hz), 2.65 (bs, 1H), 0.90 (s, 9H), 0.81 (s, 9H), 0.20 (s, 6H), 0.06 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 164.3, 134.9, 133.7, 131.8, 130.1, 130.0, 128.1, 93.7, 72.9, 72.5, 69.5, 68.7, 62.1, 26.0, 25.9, 18.5, 18.4, -4.2, -4.4, -5.2, -5.3. **FT-IR** (neat) ν in cm^{-1}: 3447, 2927, 1735, 1253, 1099, 835, 778. **ESI-HRMS** *m*/*z* calcd. for $C_{25}H_{43}ClNaO_7Si_2$ [M-Na]: 569.2134, found: 569.2123.

Spectroscopic data of **72aβ** from the reaction crude: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.96-7.87 (m, 2H), 7.64-7.55 (m, 2H), 5.77 (d, 1H, *J* = 8.0 Hz), 4.20-

3.73 (m, 6H), 0.95 (s, 9H), 0.88 (s, 9H), 0.17 (s, 6H), 0.08 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 164.3, 134.7, 133.6, 131.4, 129.9, 128.1, 128.0, 95.2, 75.4, 75.3, 71.1, 70.8, 68.8, 61.5, 26.0, 25.8, 18.4, 18.3, -4.4, -4.6, -5.1, -5.2.

Methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside (73a) and Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside (73b).

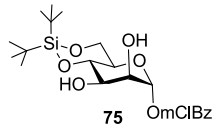


To a solution of **37** (0.06 g, 0.32 mmol) in dry MeOH (10 ml) MCPBA (144 mg, 0.64 mmol) was added. The mixture was stirred at room temperature. The reaction was monitored by TLC until the starting material was consumed. After 5h, the solution was extracted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and water. The solution was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to afford a 17:83 mixture of compounds **73a** and **73b**. Purification by radial chromatography (hexane/EtOAc 1:2), afforded compounds **73a** (0.06 g, 0.26 mmol, 80%) and **73b** (0.01 g, 0.04 mmol, 13%) as white solids (overall yield 93%).

73a: **Mp** 74-76 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 4.29 (d, 1H, *J* = 8.0 Hz), 3.95 (dd, 1H, *J* = 10.8, 5.6 Hz), 3.81 (dd, 1H, *J* = 10.8, 10.4 Hz), 3.69 (dd, 1H, *J* = 9.2, 8.8 Hz), 3.58 (dd, 1H, *J* = 10.0, 9.2 Hz), 3.57 (s, 3H), 3.46 (dd, 1H, *J* = 8.8, 8.0 Hz), 3.29 (ddd, 1H, *J* = 10.0, 10.0, 5.6 Hz), 1.52 (s, 3H), 1.45 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 104.3, 100.0, 74.9, 73.7, 73.3, 67.5, 62.2, 57.7, 29.9, 29.2.

73b: **Mp** 107-109 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 4.74 (d, 1H, *J* = 1.2 Hz), 4.02 (dd, 1H, *J* = 3.2, 1.2 Hz), 3.97-3.91 (m, 2H), 3.90-3.80 (m, 2H), 3.66-3.60 (m, 1H), 3.37 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 101.4, 100.3, 71.5, 71.1, 69.3, 63.9, 62.4, 55.2, 29.4, 19.5.

4,6-Di-*O*-(*tert*-butyl)silanediyl-1-*O*-(3-chlorobenzoyl)-α-D-mannopyranose (75).

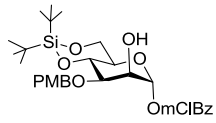


75

Following the general procedure **74** (0.68 g, 2.36 mmol) was reacted with MCPBA (1.16 g, 4.72 mmol) to afford a 14:86 mixture of compounds β-*gluco* and α-*manno* (**75**). Purification by radial chromatography (hexane/EtOAc 1:2), afforded compound **75** as a white solid (0.20 g, 0.44 mmol, 50%).

Mp 125-127 ºC. **$[\alpha]^{25}_{D}$** +31.44 (*c* 0.63, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.97 (d, 1H, *J* = 2.0 Hz), 7.91 (ddd, 1H, *J* = 8.0, 0.8, 0.8 Hz), 7.59 (ddd, 1H, *J* = 8.0, 2.0, 0.8 Hz), 7.43 (dd, 1H, *J* = 8.0, 8.0 Hz), 6.36 (d, 1H, *J* = 1.6 Hz), 4.21-4.16 (m, 2H), 4.14 (dd, 1H, *J* = 10.0, 4.8 Hz), 4.02 (dd, 1H, *J* = 9.6, 3.6 Hz), 3.97 (dd, 1H, *J* = 10.0, 10.0 Hz), 3.89 (ddd, 1H, *J* = 10.0, 9.6, 4.8 Hz), 2.90 (bs, 1H), 2.77 (bs, 1H), 1.08 (s, 9H), 1.02 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 163.2, 135.1, 134.0, 131.2, 130.2, 130.1, 128.1, 93.9, 74.3, 71.9, 69.7, 69.5, 66.3, 27.6, 27.1, 22.9, 20.2. **FT-IR** (neat) ν in cm^{-1}: 3504, 3270, 2933, 2858, 1737, 1253, 1104, 959, 855, 825, 763. **ESI-HRMS** *m/z* calcd. for $C_{21}H_{31}ClNaO_7Si$ [M-Na]: 481.1425, found: 481.1417.

4,6-Di-*O*-(*tert*-butyl)silanediyl-1-*O*-(3-chlorobenzoyl)-3-*O*-(4-methoxybenzyl)-α-D-mannopyranose (76).



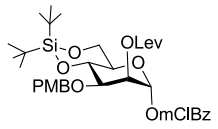
76

A mixture of **75** (137.4 mg, 0.32 mmol), dibutyltin oxide (89.2 mg, 0.35 mmol) in toluene (8.6 ml) was refluxed under Dean-Stark conditions for 3 h. The reaction mixture was allowed to cool to room temperature and DMF (0.3 ml) was added to the mixture. 4-Methoxybenzyl chloride (46 μl, 0.35 mmol) and TBAI (122.2 mg, 0.35 mmol) were added and the mixture was heated at reflux for 3h. Then, the mixture was diluted with EtOAc (5 ml), washed with H_2O (2 × 5 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure,

followed by flash chromatography on silica gel (hexane/EtOAc 3:1) affording the title compound as a colourless oil (88.9 mg, 0.16 mmol, 51%).

[α]$^{25}_{D}$ +65.6 (*c* 2.76, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ in ppm: 7.93 (s, 1H), 7.86 (d, 1H, *J* = 7.6 Hz), 7.60 (dt, 1H, *J* = 7.6, 1.0, 1.0 Hz), 7.43 (t, 1H, *J* = 7.6 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 6.90 (d, 2H, *J* = 8.4 Hz), 6.32 (d, 1H, *J* = 1.6 Hz), 4.96 (d, 1H, *J* = 11.2 Hz), 4.78 (d, 1H, *J* = 11.2 Hz), 4.39 (t, 1H, *J* = 10.0 Hz), 4.12 (dd, 1H, *J* = 10.0, 4.6 Hz), 4.02 (dd, 1H, *J* = 3.6, 1.6 Hz), 3.98 (t, 1H, *J* = 10.0 Hz), 3.88 (td, 1H, *J* = 10.0, 4.6 Hz), 3.82-3.76 (m, 4H), 2.93 (bs, 1H), 1.11 (s, 9H), 1.04 (s, 9H). **^{13}C NMR** ($CDCl_3$) δ in ppm: 162.9, 159.5, 134.6, 133.8, 131.1, 130.0, 130.0, 129.8, 129.7, 127.9, 114.5, 93.8, 76.8, 74.6, 73.5, 69.8, 69.3, 66.4, 55.3, 27.5, 27.1, 22.7, 20.0. **FT-IR** (neat) ν in cm^{-1}: 3416, 2960, 2923, 2890, 2858, 1735, 1251, 1094, 1026, 853, 823, 763. **ESI-HRMS** *m*/*z* calcd. for $C_{29}H_{39}ClNaO_8Si$ [M-Na]: 601.1995, found: 601.1937.

4,6-Di-*O*-(*tert*-butyl)silanediyl-1-*O*-(3-chlorobenzoyl)-2-*O*-levulinoyl-3-*O*-(4-methoxybenzyl)-α-D-mannopyranose (77).



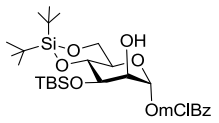
77

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (50.6 mg, 0.25 mmol) and DMAP (21.3 mg, 0.17 mmol) were added under argon to a solution of **76** (50.0 mg, 0.09 mmol) and levulinic acid (15.3 mg, 0.13 mmol) in dichloromethane (1.2 ml). The reaction mixture was stirred at room temperature overnight. Then the solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 3:1) to give the desired product as a colourless oil (37.3 mg, 0.09 mmol, 85%).

[α]$^{25}_{D}$ +33.8 (*c* 1.87, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ in ppm: 7.88 (t, 1H, *J* = 1.6 Hz), 7.77 (dt, 1H, *J* = 8.0, 1.6 Hz), 7.59 (dt, 1H, *J* = 8.0, 1.6 Hz), 7.41 (t, 1H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 6.20 (d, 1H, *J* = 1.6 Hz), 5.31 (dd, 1H, *J* = 3.6, 1.6 Hz), 4.73 (s, 2H), 4.26 (t, 1H, *J* = 9.6 Hz), 4.09 (dd, 1H, *J* = 10.0, 4.6 Hz), 3.96 (t, 1H, *J* = 10.0 Hz), 3.86-3.77 (m, 5H),

2.81-2.69 (m, 4H), 2.18 (s, 3H), 1.09 (s, 9H), 1.01 (s, 9H). **^{13}C NMR** ($CDCl_3$) δ in ppm: 206.3, 172.1, 162.7, 159.5, 134.0, 134.0, 130.9, 130.2, 130.2, 130.0, 129.7, 128.1, 114.0, 92.2, 74.8, 74.4, 72.5, 70.3, 69.3, 66.5, 55.3, 55.4, 38.2, 28.2, 27.6, 27.2, 22.9, 20.1. **FT-IR** (neat) ν in cm^{-1}: 2933, 2893, 2859, 1742, 1721, 1471, 1104, 1081, 1065, 1033, 859, 824, 1033. **ESI-HRMS** *m/z* calcd. for $C_{34}H_{45}ClNaO_{10}Si$ [M-Na]: 699.2363, found: 699.2322.

3-*O*-*tert*-Butyldimethylsilyl-4,6-di-*O*-(*tert*-butyl)silanediyl-1-*O*-(3-chlorobenzoyl)-α-D-mannopyranose (78).

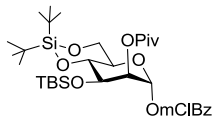


78

Compound **75** (0.26 g, 0.57 mmol) was azeotropically dried with toluene (3 x 5 ml) and taken up in DMF (7 ml). Imidazole (0.09 g, 1.43 mmol) and *tert*-butyldimethylsilyl chloride (0.10 g, 0.69 mmol) were added and the reaction mixture was stirred overnight. Diethyl ether (15 ml) was added and washed with 5 ml each: $NaHCO_3$ (aq, s), H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (from hexane/EtOAc 10:1 to 3:1) to give the desired product as a colourless oil (0.28 g, 0.53 mmol, 93%).

$[\alpha]^{25}_D$ +0.30 (*c* 4.57, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ in ppm: 7.98 (t, 1H, *J* = 1.8 Hz), 7.77 (dt, 1H, *J* = 8.0, 1.6 Hz), 7.60 (dt, 1H, *J* = 8.0, 1.6 Hz), 7.45 (t, 1H, *J* = 8.0 Hz), 6.39 (d, 1H, *J* = 1.6 Hz), 4.13 (t, 1H, *J* = 9.4 Hz), 4.12 (dd, 1H, *J* = 10.0, 4.6 Hz), 3.98 (dd, 1H, *J* = 9.4, 3.4 Hz), 3.92 (t, 1H, *J* = 9.4 Hz), 3.92 (m, 1H), 3.87 (td, 1H, *J* = 9.4, 4.6 Hz), 1.06 (s, 9H), 1.02 (s, 9H), 0.95 (s, 9H), 0.22 (s, 3H), 0.19 (s, 3H). **^{13}C NMR** ($CDCl_3$) δ in ppm: 163.2, 135.1, 133.9, 131.3, 130.2, 130.1, 128.0, 93.7, 74.5, 72.8, 71.1, 69.7, 66.5, 27.7, 27.2, 26.0, 22.9, 20.1, 18.3, -4.0, -4.7. **FT-IR** (neat) ν in cm^{-1}: 3563, 2933, 2891, 2858, 1740, 1471, 1094, 861, 837, 825, 765. **ESI-HRMS** *m/z* calcd. for $C_{27}H_{49}ClNO_7Si_2$ [M-NH_4]: 590.2736, found: 590.2741.

3-*O*-*tert*-Butyldimethylsilyl-4,6-di-*O*-(*tert*-butyl)silanediyl-1-*O*-(3-chlorobenzoyl)-2-*O*-pivaloyl-α-D-mannopyranose (79).

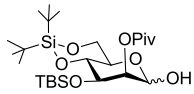


79

Compound **78** (0.29 g, 0.50 mmol) was azeotropically dried with toluene (3 x 5 ml) and taken up in CH_2Cl_2 (3.8 ml). DMAP (0.16 g, 1.30 mmol) and pivaloyl chloride (0.73 ml, 0.62 mmol) were added and the reaction was stirred for 2h. CH_2Cl_2 was added and washed with saturated $NaHCO_3$, H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (from hexane to hexane/EtOAc 15:1) to afford **77** as a colourless oil (0.28 g, 0.44 mmol, 87%).

$[\alpha]^{25}_D$ +21.43 (*c* 4.60, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ in ppm: 7.99 (t, 1H, *J* = 1.9 Hz), 7.90 (dt, 1H, *J* = 8.0, 1.2 Hz), 7.62 (ddd, 1H, *J* = 8.0, 2.2, 1.0 Hz), 7.46 (t, 1H, *J* = 8.0 Hz), 6.16 (d, 1H, *J* = 1.9 Hz), 5.21 (dd, 1H, *J* = 3.0, 2.0 Hz), 4.22 – 4.09 (m, 3H), 3.92 (t, 1H, *J* = 10.0 Hz), 3.85 (td, 1H, *J* = 8.4, 4.8 Hz), 1.26 (s, 9H), 1.08 (s, 9H), 1.01 (s, 9H), 0.92 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H). **^{13}C NMR** ($CDCl_3$) δ in ppm: 177.2, 163.0, 135.1, 134.0, 131.1, 130.3, 130.1, 127.9, 92.4, 74.7, 70.9, 70.9, 70.3, 66.9, 39.1, 27.7, 27.3, 27.2, 25.9, 23.0, 20.1, 18.4, -4.4, -4.8. **FT-IR** (neat) ν in cm^{-1}: 2932, 2894, 2859, 1741, 1473, 1113, 854, 838, 825, 746. **ESI-HRMS** *m/z* calcd. for $C_{32}H_{53}ClNaO_8Si_2$ [M-Na]: 679.2865; found: 679.2813.

3-*O*-*tert*-Butyldimethylsilyl-4,6-di-*O*-(*tert*-butyl)silanediyl-2-*O*-pivaloyl-α-D-mannopyranose (80).



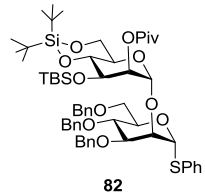
80

Compound **79** (0.25 mg, 0.42 mmol) was dissolved in EtOAc (1.7 ml). 2-Aminoethanol (84 µl, 1.43 mmol) was added and the mixture was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the crude product

was purified by column chromatography (from hexane to hexane/EtOAc 9:1) to afford **80** as a colourless oil (0.18 mg, 0.37 mmol, 88%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.00 - 4.93 (m, 2H), 4.01 (dd, 1H, *J* = 9.7, 4.7 Hz), 3.97 - 3.90 (m, 2H), 3.86 (ddd, 1H, *J* = 8.6, 8.0, 4.8 Hz), 3.82 - 3.75 (m, 1H), 2.78 (s, 1H), 1.12 (s, 9H), 0.96 (s, 9H), 0.91 (s, 9H), 0.78 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 177.8, 93.2, 75.3, 72.6, 70.2, 68.0, 67.3, 39.1, 27.8, 27.4, 27.2, 25.9, 23.1, 20.1, 18.3, -4.3, -4.7. **FT-IR** (neat) ν in cm^{-1}: 3422, 2931, 2858, 1738, 1714, 1473, 1159, 1123, 1107, 1082, 1022, 865, 838, 825. **ESI-HRMS** *m/z* calcd. for $C_{25}H_{51}O_7Si_2$ [M-NH_4]: 519.3173, found: 519.3150.

Phenyl 2-*O*-(3-*O*-*tert*-butyldimethylsilyl-4,6-di-*O*-(*tert*-butyl)silanediyl-2-*O*-pivaloyl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (82).



82

Powdered 4 Å molecular sieves (51 mg) and trichloroacetonitrile (102 µl, 0.97 mmol) were added to a solution of compound **80** (0.10 g, 0.20 mmol) in CH_2Cl_2 (2.2 ml) at room temperature. The reaction mixture was stirred for 10 min followed by the addition of cesium carbonate (0.07 g, 0.20 mmol) and stirring was continued for another 45 min. The reaction mixture was then filtered over celite and the solvent removed under reduced pressure. The crude was used in the glycosylation reaction without further purification.

A solution of trichloroacetimidate donor, thiophenyl acceptor **81** (0.33 mg, 0.61 mmol), and 4 Å molecular sieves (1.2 g) in dry CH_2Cl_2 (51 ml) was stirred at room temperature for 30 min. After cooling to -20 °C, TMSOTf (10 µl, 0.05 mmol) was added. The resulting mixture was stirred for 2 h and then diluted with CH_2Cl_2. Saturated aqueous $NaHCO_3$ was added to quench the reaction. The molecular sieves were filtered off through a Celite pad. The filtrate was washed with brine, dried over Mg_2SO_4, and concentrated. The residue was purified by

column chromatography (from hexane to hexane/CH_2Cl_2 3:2) to afford **82** (0.10 g, 0.10 mmol, 49%) as a white syrup.

$[\alpha]^{25}_D$ +0.66 (*c* 3.58, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.50 – 7.14 (m, 20H), 5.47 (d, 1H, *J* = 1.7 Hz), 5.20 (t, 1H, *J* = 2.1 Hz), 4.93 (d, 1H, *J* = 1.6 Hz), 4.84 (d, 1H, *J* = 10.7 Hz), 4.74 - 4.65 (m, 2H), 4.59 (d, 1H, *J* = 12.1 Hz), 4.53 (d, 1H, *J* = 9.5 Hz), 4.50 (d, 1H, *J* = 11.9 Hz), 4.33 - 4.26 (m, 1H), 4.20 (t, 1H, *J* = 2.3 Hz), 4.07 - 3.96 (m, 2H), 3.89 (dd, 1H, *J* = 9.0, 2.6 Hz), 3.87 - 3.64 (m, 6H), 1.20 (s, 9H), 1.04 (s, 9H), 0.95 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 177.2, 138.4, 138.3, 138.2, 134.2, 133.7, 132.1, 129.3, 128.7, 128.6, 128.5, 128.3, 128.0, 128.0, 127.8, 127.7, 126.8, 99.5, 87.8, 80.3, 75.5, 75.3, 75.1, 75.1, 73.4, 73.0, 72.6, 72.1, 70.5, 69.4, 68.6, 67.1, 39.0, 27.7, 27.4, 27.2, 25.9, 23.0, 20.1, 18.3, -4.4, -4.7. **FT-IR** (neat) ν in cm^{-1}: 3063, 3031, 2928, 2857, 1737, 1473, 1454, 1362, 1251, 1084, 1026, 864, 839. **ESI-HRMS** *m/z* calcd. for $C_{58}H_{86}NO_{11}SSi_2$ [M+NH_4]: 1060.5460, found: 1060.5

UNIVERSITAT ROVIRA I VIRGILI
STEREOSELECTIVE REACTIONS IN CARBOHYDRATE SYNTHESIS
Irene Marin Ferré
DL: T. 161-2012

A Proaches to the synthesis of Digitoxin

PART B

Introduction

CHAPTER 4

1. Deoxyglycosides

Glycoconjugates are the most functionally and structurally diverse compounds in nature. It is well established that in addition to complex polysaccharides, protein- and lipid-bound saccharides have essential roles in molecular processes.[130]

In the last 150 years the field of glycosylation chemistry has focused on creating links between sugars. In the last decade, however, that focus has changed shifted toward developing general solutions for glycosylation methods. There is now more knowledge about glycoside synthesis and formation, and more elements have been developed to control stereoselectivity.[131] However, the formation of complex oligosaccharides is still much more complicated than the synthesis of biopolymers such as peptides or nucleic acids. The increased number of possible combinations of monomers presents one of the biggest difficulties in the preparation of complex oligosaccharides, as well as, the formation of stereospecific glycosidic linkages.

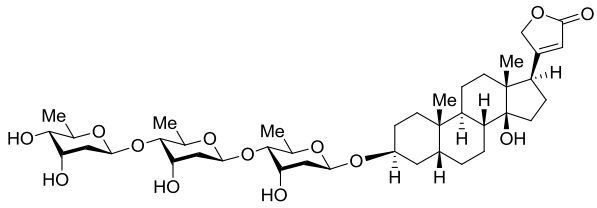


Figure 13. Chemical structure of the cardiotonic digitoxin (**83**).

Deoxysugars and deoxyoligosaccharides are an important, yet most neglected, group of biological compounds. 2-Deoxy- and 2,6-dideoxyglycoside domains are present in many natural secondary metabolites with interesting biological properties, including antibiotic, antiparasitic, anticancer and cardiotonic agents like digitoxin (**83**) (Figure 13). In addition, deoxysugars also play an important role in lipopolysaccharides, glycoproteins and glycolipids, where they act as

130 a) Boons, G.- J. *Tetrahedron* **1996**, *52*, 1095-1121. b) Meutermans, W.; Le, G. T.; Becker, B. *ChemMedChem*, **2006**, *1*, 1164-1194.

131 a) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137-2160. b) Ernst, B.; Hart, G.W.; Sinaÿ, P.; Eds. *Carbohydrates in Chemistry and Biology*, Part I; Wiley-VCH: Weinheim, **2000**.

ligands for cell-cell interactions or as targets for toxins, antibodies, and microorganisms.[132]

Once the biological importance of 2-deoxyglycosides was discovered, interest in the synthesis of these products increased. One of the ultimate goals for glycosyl chemists is to obtain 2-deoxyoligosaccharides via highly efficient and stereoselective assembly of 2-deoxy monomer (Figure 14).

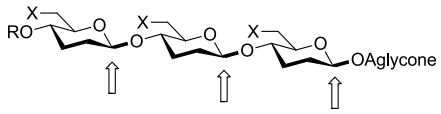


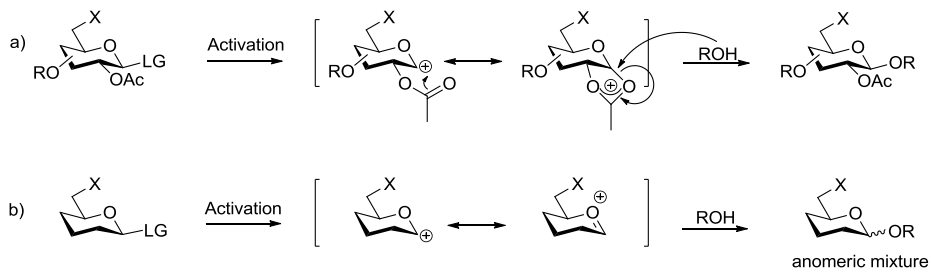
Figure 14. Glycosidic bond in 2-deoxyoligosaccharides.

The most classical method of glycosylation involves activation of an anomeric leaving-group on a glycosyl donor in the presence of an acceptor. If the glycosyl donor is acylated, excellent stereoselectivity is obtained due to the anchimeric assistance of the acyl group in the carbenium intermediate (Scheme 36a).

However, this method is of limited application to 2-deoxyglycosides. The absence of a hydroxyl group at C-2 in 2-deoxyglycosides prevents the stereocontrolled formation of the glycosidic bond (Scheme 36b), and therefore, the synthesis of 2-deoxyoligosaccharides poses a real challenge. Moreover, the absence of electron-withdrawing substituents at C-2 makes the glycosidic bond much more acid labile, giving rise to easy hydrolysis or anomerization.

In the last few decades, several strategies have been developed to address this problem.[16] Many of these methods provide good yields and stereoselectivities; however, they are usually limited to the reaction conditions and reagents. Therefore, a suitable general method for glycosylation is still missing.

[132] a) Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99-110. b) Albrecht, H. P. *Cardiac Glycosides* in *Naturally Occurring Glycosides*, Ikan, R.; Wiley, Chichester, **1999.** c) Allen, H. J.; Kisailus, E. C. *Glycoconjugates: Composition, Structure and Function* Eds.; Marcel Dekker, New York, **1992**.



Scheme 36. a) Classical method of glycosylation with stereoselective control of the acyl group in C-2. b) Glycosylation in the absence of anchimeric assistance.

2. Methods of synthesis of 2-Deoxyglycosides

Even with the aforementioned problems, there are many important antibiotic families prepared with 2-deoxyglycosidic structures. In the bibliography there are several procedures describing the synthesis of 2-deoxy-glycosides, which can be distinguished depending on the configuration of the anomeric bond, α or β.

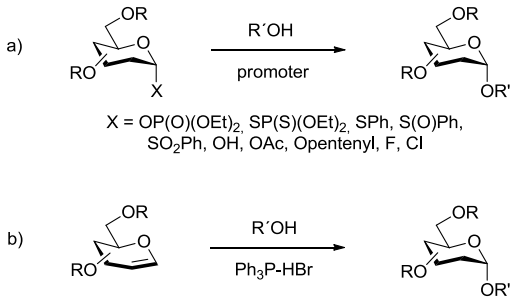
These methods are classified according to the control elements used in position C-2. When there is no control element at C-2, the ratio of α/β products depends on some combination of control elements known as *´kinetic anomeric effect´* and *´thermodynamic effect´*. These elements favour the axial linkage of nucleophilic species at C-1 and therefore produce mostly the α-product. Many anomeric leaving groups have been used in the last few decades to increase the selectivity of the glycosylation without a C-2 control element. On the other hand, the control element is usually a heteroatomic group. This strategy usually furnishes 1,2-*trans* glycosides.

2.1 Synthesis of 2-deoxy-α-glycosides

No control element at C-2

2-Deoxy-α-glycosides can be obtained from 2-deoxy glycosyl donors driving the glycosylation under thermodynamic conditions. Many different leaving groups have been tested with this purpose and the reaction takes place through an oxonium intermediate to give mainly the α-anomer, for example from a

thioether,[133] sulfoxide,[134] phenylsulfonyl group,[135] pyridylthiol, 2-pyridyl carboxylic acid,[136] fluoro glycoside,[25,137] glycosyl derivatives as *n*-pentenyl,[138] or phosphate,[139] as well as from an inactivated hydroxyl at C-1[140,141] (Scheme 37a).



Scheme 37. Selected methods for the synthesis of 2-deoxy-α-glycosides with no control element at C-2.

Another important and general method for synthesizing 2-deoxy-α-glycosides is simply the acid-catalyzed activation of glycals to form an anomeric oxonium ion intermediate in the presence of an acceptor to afford the final glycoside.[141,142] However, the acid catalyst has to be carefully chosen in order to avoid the Ferrier allylic rearrangement. A Ph_3P-HBr system is usually employed as a weak acid source (Scheme 37b).

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133 a) Ravi, D.; Kulkarni, V. R.; Mereyala, H. B. T*etrahedron Lett.* **1989**, *30*, 4287-4290. b) Toshima, K.; Nozaki, Y.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 6887-6890.

134 Ge, M.; Thomson, C.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 11014-11015.

135 Brown, D. S.; Ley, S. V.; Vile, S.; Thompson, M. *Tetrahedron* **1991**, *47*, 1329-1342.

136 Furukawa, H.; Koide, K.; Takao, K-I.; Kobayashi, K. *Chem. Pharm. Bull.* **1998**, *46*, 1244-1247.

137 Schene, H.; Waldmann, H. *Chem. Commun.* **1998**, 2759-2769.

138 Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583-5584.

139 Koch, A.; Lamberth, C.; Wetterich, F.; Giese, B. *J. Org. Chem.* **1993**, *58*, 1083-1089.

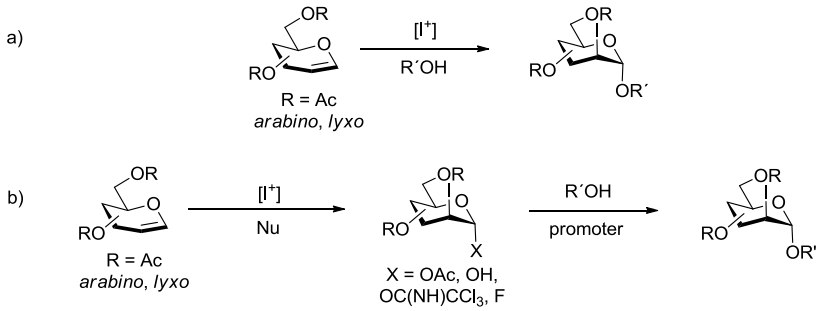
140 Takeuchi, K.; Higuchi, S.; Mukaiyama, T. *Chem. Lett.* **1997**, 969-970.

141 a) Bolitt, V.; Mioskowski, C.; Lee, S-G.; Flack, J. R. *J. Org. Chem.* **1990**, *50*, 5812-5813. b) Sabesan, S.; Neira, S. *J. Org. Chem.* **1991**, *56*, 5468-5472.

142 For some acid or metal-catalyzed strategies, see: a) Sherry, B. D.; Loy, R. N.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4510-4511. b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428-3429. c) Toshima, K.; Nagai, H.; Ushiki, Y.; Matsumara, S. *Synlett* **1998**, 1007-1009.

Control element at C-2

Glycals have been activated using a variety of electrophilic halogen and chalcogen sources. In these cases the attack of the electrophile to the enolether introduces a bulky heteroatom at C-2 which can control the stereoselectivity of the glycosylation. Usually halonium, episulfonium, and selenonium cations have been postulated as reaction intermediates being responsible for the high stereoselectivity observed in these processes. However, our group showed that the real intermediate is an oxonium cation, the observed stereoselectivity being a result of the presence of a bulky substituent at C-2.[143] The addition of *N*-iodosuccinimide (NIS) or iodoniumdicollidine perchlorate (IDCP) to glycals in the presence of an acceptor has become a routine procedure for the synthesis of α-linked disaccharides.[144] When iodine is used as electrophile, a kinetic axial attack takes place, resulting in the introduction of the iodine in the axial position, and the attack of the alcohol *trans* to the iodine. The use of this procedure for more common glycals such as D-glucal and D-galactal, results in obtaining 2-deoxy-2-iodo-α-*manno*- or *talo*-glycosides with excellent stereoselectivity (Scheme 38a).[145]



Scheme 38. Selected methods for the synthesis of 2-deoxy-α-glycosides from glycals.

143 Bravo, F.; Viso, A.; Alcázar, E.; Molas, P.; Bo, C.; Castillón S. *J. Org. Chem.* **2003**, *68*, 686-691.

144 For some approaches using glycals through a *one-pot* procedure, see: a) Ref [11],[17a],[19]. b) Fyvie, W. S.; Morton, M.; Peczuh, M. W. *Carbohydr. Res.* **2004**, *339*, 2363-2370. c) Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *Tetrahedron* **2002**, *58*, 369-375.

145 a) Thiem, J.; Kopper, S. *Tetrahedron* **1990**, *46*, 113-138. b) Kopper, S.; Thiem, J. *Carbohydr. Res.* **1994**, *260*, 219-232. c) Izumi, M.; Ichikawa, Y. *Tetrahedron Lett.* **1998**, *39*, 2079-2082.

In the last years a great number of glycosylation procedures based on an efficient leaving group/promoter couple have been reported. They allow performing glycosylation reactions in very mild conditions and enable an orthogonal activation. In this context, glycosyl donors has been prepared by reacting glycals with NIS and different nucleophiles (i.e., AcOH) which can behave as leaving groups in the next glycosylation reaction (Scheme 38b).[146]

Alternatively, when a glycal is activated with electrophilic iodonium in the presence of water, 2-deoxy-2-iodopyranoses are formed, which can be then transformed into other useful glycosyl donors such as fluorides and trichloroacetimidates. In a second step, the glycosylation is carried out by activating these new glycosyl donors under the appropriate conditions. This strategy allows a wide range of glycosylation possibilities.[147]

2.2 Synthesis of 2-deoxy-β-glycosides

No control element at C-2

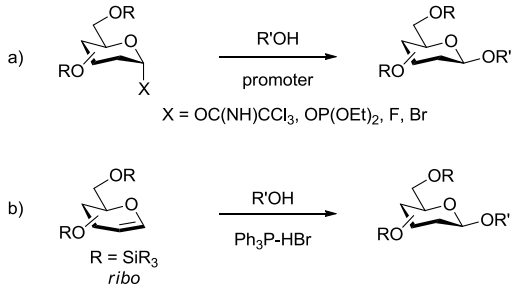
The absence of electron-withdrawing substituents on the saccharide units readily promotes the anomerization of β-glycosides under acidic glycosylation conditions. Furthermore, the non-availability of neighboring-group participation from substituents at C-2 and the enhanced conformational flexibility derived from the reduced number of substituents make it difficult to achieve glycosylation in a stereoselective manner. However, several methods are available for direct β-selective glycosylations by using 2-deoxy glycosyl donors[26a,148] such as glycosyl imidates, glycosyl phosphites and glycosyl halides (Scheme 39a). 2-Deoxy-β-glycosides can be prepared without a control element at C-2 with an inactivated

146 a) Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1990-1991. b) Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267-2274.

147 For some approaches using glycals through a two-step procedure, see: a) Kirschning, A.; Jesberger, M.; Schönberger, A. *Org. Lett.* **2001**, *3*, 3623-3626. b) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc*. **2000**, *122*, 4304-4309. c) Roush, W. R.; Narayan, S.; Bennett, C. E.; Briner, K. *Org. Lett.* **1999**, *1*, 895-897. d) Roush, W. R.; Narayan, S. *Org. Lett.* **1999**, *1*, 899-902.

148 a) Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 2505-2507. b) Binkley, R. W.; Koholic, D. J. *J. Org. Chem.* **1989**, *54*, 3577-3581.

hydroxyl group at C-1[149] using radical chemistry[150] or glycosyl fluorides[25] or the acid-catalyzed activation of glycals of *ribo* configuration[151] with Ph_3P-HBr (Scheme 39b).



Scheme 39. Selected methods for the synthesis of 2-deoxy-β-glycosides with no control element at C-2.

Control element at C-2

Although the addition of electrophiles to glycals in the presence of an acceptor has become a useful protocol for directly providing α-linked disaccharides, the same protocol is not frequently used to obtain β-glycosides.[152] Glycosyl donors bearing halogens or chalcogens at C-2 are the most commonly employed precursors for the synthesis of β-linked disaccharides and oligosaccharides.[153] The

149 Finzia, G. *J. Carbohydr. Chem.* **1998**, *17*, 75-98.

150 a) Crich, D.; Hermann, F. *Tetrahedron Lett.* **1993**, 34, 3385-3388. b) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716-8717.

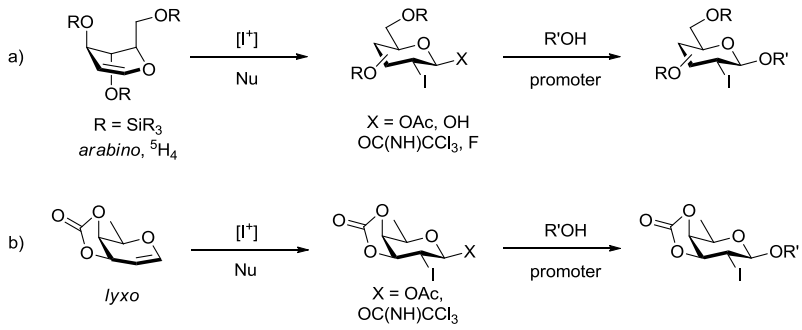
151 a) Jaunzems, J.; Kashin, D.; Schönberger, A.; Kirschning, A. *Eur. J. Org. Chem.* **2004**, 3435-3446. b) McDonald, F. E.; Wu, M. *Org. Lett*. **2002**, *4*, 3979-3981. c) McDonald, F. E.; Reddy, K. S. *Angew. Chem. Int. Ed.* **2001**, *40*, 3653-3655.

152 For some approaches using glycals through a *one-pot* procedure, see: a) Ref [90]. b) Franck, R. W.; Kaila, N. *Carbohydr. Res.* **1993**, *239*, 71-83. c) Ramesh, S.; Franck, S. W. *J. Chem. Soc., Chem. Commun.* **1989**, 960-962. d) Preuss, R.; Schmidt, R. R. *Synthesis* **1988**, 694-696. e) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 4701-4704.

153 For some approaches using glycals through a two-step procedure, see: a) Ref [89]. b) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1875-1878. c) Blanchard, N.; Roush, W. R. *Org. Lett.* **2003**, 5, 81-84. d) Chong, P. Y.; Roush, W. R. *Org. Lett*. **2002**, *4*, 4523-4526. e) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc*. **2000**, *122*, 6124-6125. f) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891-893. g) Dräger, G.; Garming, A.; Maul, C.; Noltemeyer, M.; Thiericke, R.; Zerlin, M.; Kirschning, A. *Chem. Eur. J.* **1998**, *4*, 1324-1333. h) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837-8852. i) Roush, W. R.; Briner, K.; Kesler, B. S.; Murphy, M.; Gustin, D. J. *J. Org. Chem.* **1996**, *61*, 6098-6099. j) Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc*. **1996**, *118*, 9998-9999. k) Perez, M.; Beau, J. M. *Tetrahedron*

addition of iodonium equivalent to glycals in acetic acid gives mixtures of *trans*-iodoacetates. Since iodoacetates have been successfully used as glycosyl donors for the preparation of α-glycosides, the preparation of equatorially disposed iodoacetate donors is highly desirable. Initially, Roush and Bennett performed the addition of NIS-AcOH to a 6-deoxyglycal under thermodynamic conditions.[154] Although a 1:1 mixture of α-*manno*/β-*gluco* derivatives was obtained, it was possible to separate both diastereomers. After separation, the *manno* isomer could be reduced back to the starting glycal with lithium iodide in THF. Equatorially disposed iodoacetate donors have been efficiently prepared and used as β-selective glycosyl donors from the iodoacetoxylations of glycals bearing bulky silyl ether groups with iodine reagents.[146b] The best results were obtained when the D-glycal precursor lacked oxygen at C-6, or when it was bis-silylated and could readily exist in a twisted boat conformation $^{5}H_{4}$ (Scheme 40a).

All other glycosyl donors that adopt the normal $^{4}C_{1}$ conformation and/or have deactivating heteroatom substituents at C-6, require higher temperatures. Alternatively, 2-deoxy-2-iodoglucosyl donors can be selectively prepared by opening, in acidic conditions, the corresponding 1,6-anhidro compound, which in turn can be easily obtained by iodocyclization of D-glucal.[155]



Scheme 40. Selected methods for the synthesis of 2-deoxy-β-glycosides from glycals and 2-halo glycosyl donors.

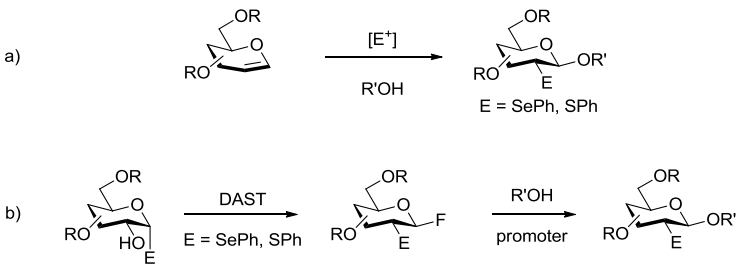
Lett. **1989**, *30*, 75-78. l) Thiem, J.; Schottmer, B. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 555-557.

154 Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541-3542.

155 a) Leteux, C.; Veyrières, A.; Robert, F. *Carbohydr. Res.* **1993**, *242*, 119-130. b) Tailler, D.; Jacquinet, J.-C.; Noirot, A.-M.; Beau, J.- M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3163-3164.

When configurations different from the *arabino* are subjected to haloalkoxylation reaction, the presence of special protecting groups can lead to the formation of the desired equatorially disposed halo-glycosyl donors in high yield. The *cis*-fusion of the cyclic 3,4-protecting group encourages the glycal to adopt the indicated boatlike conformation with the iodonium at C-2 in a pseudoaxial position, which should direct the glycosidation in a β-selective manner. Thus, Durham and Roush developed 3,4-*O*-carbonate–protected 2,6-dideoxy-2-halo-galactosyl donors that provide access to 2,6-dideoxy-β-galactosides with high diastereoselectivity (Scheme 40b).[21b]

Interestingly, electrophilic sulfur and selenium species in the presence of alcohols add to the double bond of glycals in a *trans* fashion to give glycosides. The face-selectivity of this approach may be influenced by a variety of factors including the solvent polarity, the conformation of the reacting glycal, and nature of the substituents on the glycal (Scheme 41a).



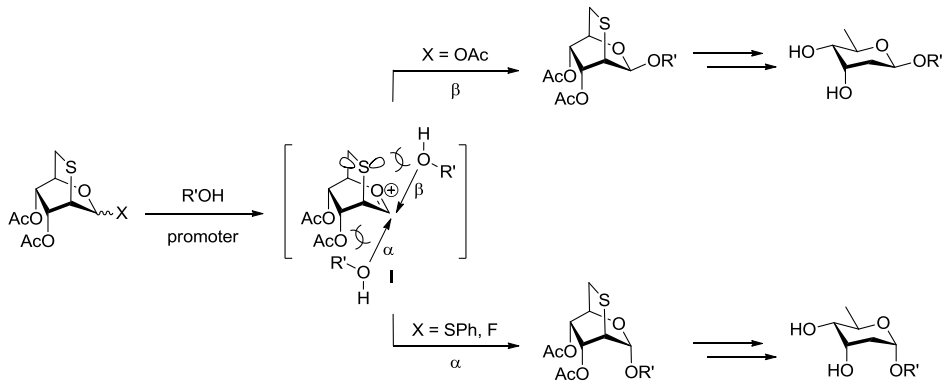
Scheme 41. Selected methods for the synthesis of 2-deoxy-β-glycosides from glycals and 2-chalcogen glycosyl donors.

Alternatively, special glycosyl donors with substituents at C-2[24,39c] acting as neighboring groups or 1,2-anhydropyranoses[156] are used followed by reductive removal of the substituents at C-2. Nicolaou and co-workers[22a,23] reported an original approach for preparing 2-deoxy-2-phenylsufanyl- and 2-phenylselenenyl-β-*gluco*-pyranosyl fluorides by reacting 1-thio-α- and 1-seleno-α-glycosides with the unprotected hydroxyl group at C-2 with diethylaminosulfur trifluoride (DAST) (Scheme 41b). DAST initially reacts with the hydroxyl group at C-2 converting it into a good leaving group and delivering a fluoride anion. A 1,2-

[156] Gervay, J.; Danishefsky, S. J. *J. Org. Chem.***1991**, *56*, 5448-5451.

migration of the group at the anomeric position and concomitant entry of fluorine at C-1 affords the 2-deoxy-2-phenylsufanyl- and 2-phenylselenenyl-β-*gluco*-pyranosyl fluorides. These compounds are excellent glycosyl donors and have allowed the synthesis of complex oligosaccharides.

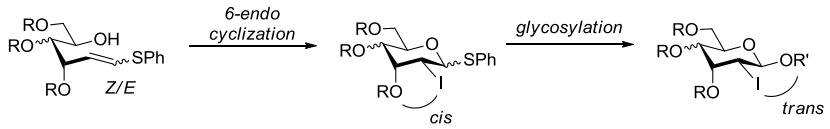
A conceptually different approach was developed by Toshima and Tatsuta whereby 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars are used for the stereocontrolled synthesis of 2,6-dideoxy-α- and -β-glycosides.[157] These new donors have a very rigid bicyclic structure (boat conformation) and the stereoselectivity of the glycosylation should not be affected by the anomeric effect in the same manner as it is with the more usual chair conformers (Scheme 42). A variety of leaving groups (X) can be used. Particularly with SPh or F, the activation under kinetic conditions produces the α-isomer in high yield and almost complete stereoselectivity. This outcome indicates that the interaction of the incoming alcohol with the sulfur electron pair in **I** is more important than the repulsion from the 3-OAc group. Alternatively, when X = OAc, the β-anomer is mainly obtained as a consequence of the evolution of the system to the more thermodynamically stable compound. In this way, both anomers can be stereoselectively obtained, depending on the reaction conditions.



Scheme 42. Synthesis of 2-deoxy-glycosides from 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars.

[157] Toshima, K. *Carbohydr. Res.* **2006**, *341*, 1282-1297 and references therein.

Our group developed a general procedure for the stereoselective synthesis of 2-deoxy-2-iodo-hexo-pyranosyl glycosides from alkenyl sulfanyl derivatives (Scheme 43).[158] The procedure involves electrophilic iodine-induced cyclization to give phenyl 2-deoxy-2-iodo-1-thio-pyranosides, a new type of glycosyl donor, and glycosylation. The cyclization reaction proceeds with complete chemo-, regio- and stereoselectivity and the stereochemistry of the iodine at C-2 is always *cis* to the neighboring alkoxy group. The yield of the cyclization is very good for substrates with a *ribo* or *xylo* configuration. In the glycosylation reaction, the glycosidic bond created in the major isomers is always *trans* to the iodine at C-2. The reaction can be carried out in a *one-pot* consecutive cyclization-glycosylation process.[158c]



Scheme 43. Proposed methodology for the stereoselective synthesis of 2-deoxy-2-iodoglycosides.

Most of the procedures described above have been applied to the synthesis of 2,6-dideoxy-D-*arabino*-hexo-pyranosides (D-olivose) and 2-deoxy-L-*fuco*-pyranosides. However, there are only a few reported examples of the synthesis of 2,6-dideoxy-D-*ribo*-hexoglycosides (D-digitoxose)[151c] and 2,6-dideoxy-D-*xylo*-hexoglycosides (D-boivinose),[159] probably because of the difficulty of obtaining the corresponding glycals. Consequently, efficient glycosylation methods, which are among the most fundamental and important reactions of carbohydrates, are of particular interest in the synthesis of these rare and biologically important configurations.

[158] a) Rodríguez, M. A.; Boutureira, O.; Arnés, X.; Matheu, M. I.; Díaz, Y.; Castillón, S. *J. Org. Chem.* **2005**, *70*, 10297-10310. b) Rodríguez, M. A.; Boutureira, O.; Benito, D.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 3564-3572. c) Rodríguez, M. A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 2470-2476.

[159] Pepito, A. S.; Dittmer, D. C. *J. Org. Chem.* **1994**, *59*, 4311-4312.

3. Chemical structure of Digitoxin

Several glycosides bearing a steroid type aglycone are used as cardiotonics in various therapies. The most important of these belong to the group of cardenolides containing aglycones with a 23-carbon core (Figure 15a). These compounds have certain specific characteristics including unsaturation, a lateral lactone chain with four carbon atoms (butenolide), and C and D rings with a conserved *cis*-configuration, with a β-oriented hydroxyl group at C-14.

These compounds come from the 5-β series, and have a C-3 hydroxyl group in the β-configuration. Other hydroxyl groups are found at C-1, C-5, C-11, C-12, C-16 and C-19. These glycosides generally contain deoxysugars linked directly to the aglycone and to D-glucose. Upon enzymatic hydrolysis during a drying up period, the parent plant yields D-glucose, whereas acid hydrolysis liberates all sugar components.

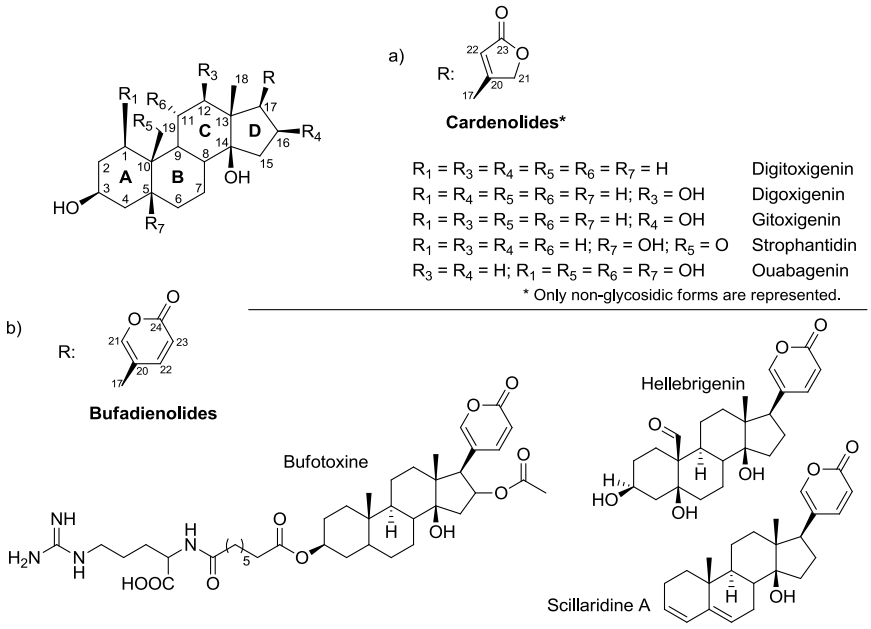


Figure 15. Structure of different cardiac steroids: (a) cardenolides and (b) bufadienolides.

A second group of aglycones are the bufadienolides, characterized by a six-membered ring lactone containing two double bonds (Figure 15b). These

glycosides are found in Scilla (star flower, *Urginea scilla*) and, in the non-glycosidic form, in toad poison (bufotoxine from *Bufo vulgaris*).

One of the principal cardiac glycosides is digitoxin (**83**), found in the foxgloves *Digitalis purpurea* and *Digitalis lanata*. Digitoxin contains a trisaccharide with three units of digitoxose (called digoxose) linked to the hydroxyl group at C-3 of the aglycone digitoxigenin (Figure 15). This important cardenolide aglycone has a steroid-like framework different from mammalian steroids. The principal characteristic structural features of digitoxin are: a *cis* C/D ring junction, a tertiary 14β-hydroxyl group, and a 17β-unsaturated lactone (see Figure 15a). The unique structure and the diverse and potent bioactivities of digitoxin have made it the focus of numerous synthetic studies and total syntheses.[160]

Although the sugars in the cardiac glycosides appear to have no therapeutic action, they have a dramatic effect on the physical, chemical and biological properties of these compounds.[160i,161] The glycan chains are molecular elements that control the pharmacokinetics of the drug and prolong their effects. For this reason, it is clear that the stereoselective formation of the *O*-glycosidic bonds between carbohydrates and the cardiac aglycones are an important issue to be considered.

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[160] Partial and/or from steroids synthesis: a) Danieli, N.; Mazur, Y.; Sondheimer, F. *Tetrahedron* **1966**, *22*, 3189-3193. b) Bach, G.; Capitaine, J.; Engel, C. R. *Can. J. Chem.* **1968**, *46*, 733-749. c) Pettit, G. R.; Houghton, L. E.; Knight, I. C.; Bruschweiler, F. *J. Org. Chem*. **1970**, *35*, 2895-2898. d) Lenz, G. R.; Schulz, J. A. *J. Org. Chem*. **1978**, *43*, 2334-2339. e) Donovan, S. F.; Avery, M. A.; McMurry, J. E. *Tetrahedron Lett.* **1979**, 3287-3290. f) Marini-Bettolo, R.; Flecker, P.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem*. **1981**, *59*, 1403-1410. g) Welzel, P.; Stein, H.; Milkova, T. *Liebigs Ann. Chem.* **1982**, 2119-2134. h) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1601-1605. i) Wiesner, K.; Tsai, T. Y. R. *Pure Appl. Chem.* **1986**, *58*, 799-810. j) Kutney, J. P.; Piotrowska, K.; Somerville, J.; Huang, S. P.; Rettig, S. J. *Can. J. Chem.* **1989**, *67*, 580-589. k) Groszek, G.; Kurek-Tyrlik, A.; Wicha, J. *Tetrahedron* **1989**, *45*, 2223-2226. l) Kocovsky, P.; Stieborova, I. *Tetrahedron Lett.* **1989**, *30*, 4295-4298. m) Hanson, J. R. *Nat. Prod. Rep*. **1993**, *10*, 313-325. n) Almirante, N.; Cerri, A. *J. Org. Chem.* **1997**, *62*, 3402-3404. o) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421-5424. For total synthesis see: p) Stork, G.; West, F.; Lee, Y. H.; Isaacs, R. C.; Manabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 10660-10661. q) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2007**, *48*, 1541-1544.

[161] Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3215-3237.

4. Previous synthesis of Digitoxin

Elderfield et al. prepared the first glycosides of digitoxigenin and digoxigenin and showed that the glycosylation reaction was specific at the secondary hydroxyl group at C-3 of the aglycones.[162] The less reactive tertiary hydroxyl group at C-14 was not glycosylated during this reaction. Nevertheless, this hydroxyl group is extremely sensitive to desiccating agents, as the aglycone tends to undergo dehydration forming anhydrodigitoxigenin derivatives.

To overcome this problem, specific methods of glycosylation have been studied, based primarily on the Koenigs-Knorr procedure.[163] These methods are not generally applicable, but have to be adapted to the specific requirements of the substrates. Thus, α-1,2-c*is*-halogenated carbohydrates have been coupled with cardenolide aglycones using azeotropic distillation,[164] Ag_2CO_3 on celite,[165] AgOTf,[166] mercuric salts,[167] Et_4NBr,[168] or by efficient disilver maleinate[169] (which provides β-products). Other glycosyl donors such as glycals,[18] 1-*O*-acetylglycosides,[170] trichloroacetimidates[168b,149] or enzymatic methods,[171] have also been used to synthesize glycosylated cardenolides.

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162 Elderfield, R. C.; Uhle, F. C.; Fried, J. *J. Am. Chem. Soc.* **1947**, *69*, 2235-2236.

163 Koenigs, W.; Knorr, E. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 957-981.

164 Takiura, K.; Yuki, H.; Okamoto, Y.; Takai, H.; Honda, S. *Chem. Pharm. Bull.* **1974**, *22*, 2263-2268.

165 Templeton, J. F.; Setiloane, P.; Sashi Kumar, V. P.; Yan, Y.; Zeglam, T. H.; LaBella, F. S. *J. Med. Chem.* **1991**, *34*, 2778-2782.

166 Thiem, J.; Köpper, S. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 779-780.

167 Templeton, J. F.; Ling, Y.; Zeglam, T. H.; Marat, K.; LaBella, F. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2503-2517.

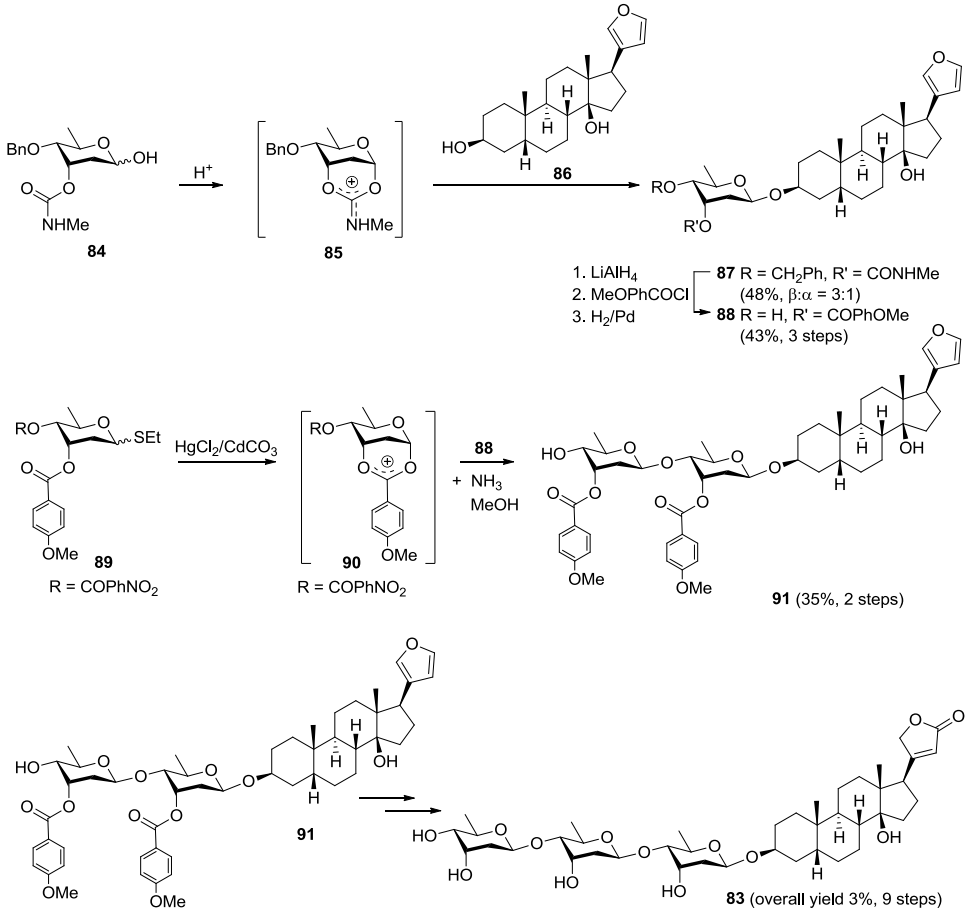
168 a) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc*. **1975**, *97*, 4056-4069. b) Rathore, H.; Hashimoto, T.; Igarashi, K.; Nukaya, H.; Fullerton, D. S. *Tetrahedron* **1985**, *41*, 5427-5438.

169 Luta, M.; Hensel, A.; Kreis, W. *Steroids* **1998**, *63*, 44-49.

170 Boivin, J.; Monneret, C.; Pais, M. *Tetrahedron Lett.* **1978**, *19*, 1111-1114.

171 a) Kawaguchi, K.; Koike, S.; Hirotani, M.; Fujihara, M.; Furuya, T.; Iwata, R.; Morimoto, K. *Phytochemistry* **1998**, *47*, 1261-1265. b) Kawaguchi, K.; Watanabe, T.; Hirotani, M.; Furuya, T. *Phytochemistry* **1996**, *42*, 667-669. c) Faust, T.; Theurer, C.; Eger, K.; Kreis, W. *Biorg. Chem.* **1994**, *22*, 140-149.

Despite the numerous procedures available for the glycosylation, only three total syntheses of digitoxin have been reported. The first[172] was the carbohydrate approach by Wiesner[160i,173] in which the β-stereoselectivity was achieved by the anchimeric assistance of an *N*-methylurethane or a *p*-methoxybenzoyl group at the C-3 position (Scheme 44). Thus, digitoxose derivative **84** and the furyl steroid **86** were treated under acidic condition to obtain **87.** The β-stereoselectivity of this method was likely due to the intermediacy of the bridged species **85**.



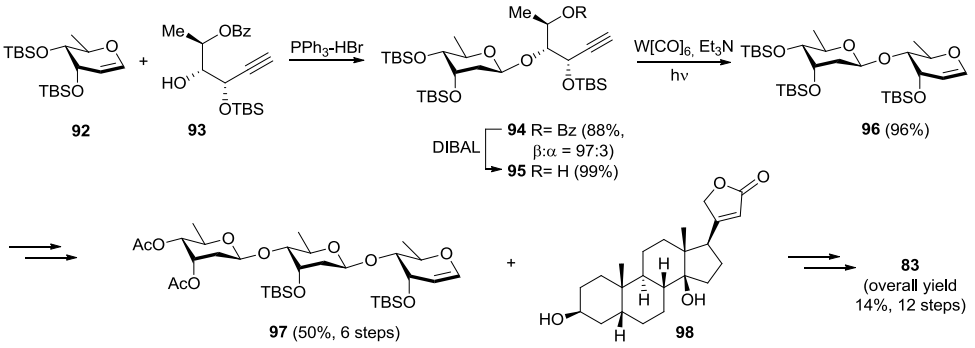
Scheme 44. Total synthesis of digitoxin (**83**) by Wiesner.

172 Digitoxose was coupled with digitoxigenin by Zorbach and Boivin groups (ref. [179]), but with poor yields and stereoselectivities: Zorbach, W.W.; Henderson, N.; Saeki, S. *J. Org. Chem.* **1964**, *29*, 2016-2017.

173 a) Jin, H.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem*. **1983**, *61*, 2442-2444. b) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300-314.

Since the urethane group was not suitable for the subsequent glycosylation steps, it was swapped, and after standard functional group manipulations, acceptor **88** was coupled with ethyl thioglycoside **89**. The β-stereoselectivity was achieved after mercury-catalyzed cleavage of **89** through intermediate **90**, which reacted with monodigitoxoside **88** to yield disaccharide **91**. A third glycosylation by using a mercury-catalyzed cleavage of ethyl thioglycoside, followed by deprotection and transformation of furyl structure provided the desired crystalline digitoxin (**83**).

The procedure of Wiesner and co-workers suffered from the requirement that the butenolide was masked as a furan derivative during glycosylation and protecting group manipulations and, thus, it needed additional final steps to obtain digitoxin. McDonald and co-workers developed a more efficient synthesis by the direct attachment of a preformed trisaccharide donor **97** to digitoxigenin (**98**) (Scheme 45).[151c] The synthesis of **97** began with protic acid-catalyzed[18] stereoselective glycosylation of alkynyl alcohol **93** with glycal **92** to provide 2,6-dideoxyglycoside **94**. Reductive debenzoylation and tungsten carbonyl-catalyzed *endo*-selective cycloisomerization[174,175] of the alkynol substrate gave disaccharide glycal **96**. Convenient protecting group manipulations and repetition of the glycosylation-cycloisomerization steps from **96** afforded the glycal **97**, which could be readily attached to digitoxigenin (**98**).[176]



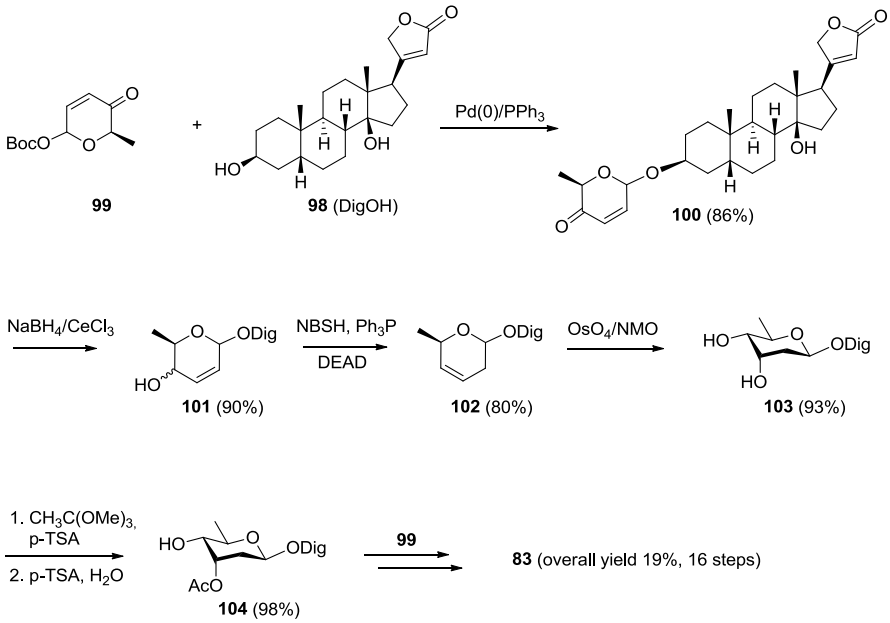
Scheme 45. Total synthesis of digitoxin (**83**) by McDonald.

174 Toshima, K.; Misawa, M.; Ohta, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1989**, *30*, 6417-6420.

175 McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* ,**1998**, *120*, 4246-4247.

176 Pongdee, R.; Wu, B.; Sulikowski, G. A. *Org. Lett.* **2001**, *3*, 3523-3525.

Recently, O'Doherty developed a linear and stereocontrolled route to the mono-, bis-, and trisaccharides of digitoxin (Scheme 46).[142b,177] This procedure began with the palladium-catalyzed glycosylation of digitoxigenin **98** with pyranone **99** to provide **100** as a single diastereomer. Luche reduction ($NaBH_4/CeCl_3$) of **100** afforded a mixture of allylic alcohols **101**, which were reduced[178] to alkene **102**. Dihydroxylation of **102** using the Uphjohn conditions (OsO_4/NMO)[179] furnished deprotected digitoxigenin monodigitoxoside **103**. Application of an ortho ester formation/hydrolysis protocol to diol **103**, acetyl-protected acceptor **104** was obtained. Repetition of these steps in iterative manner yielded disaccharide first, and eventually digitoxin (**83**).



Scheme 46. Total synthesis of digitoxin (**83**) by O'Doherty.

Both Wiesner's carbohydrate-based and O'Doherty's *de novo* synthesis of digitoxin are linear procedures which submit digitoxigenin **98** moiety to several

177 a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406-12407. b) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339-4342. c) Zhou, M. O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485-2493.

178 Myers' reductive rearrangement: Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841-4844.

179 VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973-1976.

transformations. By contrast, McDonald's *de novo* approach successfully inserts the aglycone in the final steps, and is therefore a more appealing methodology if a valuable, chemically-modified aglycone is employed.[180] However, McDonald group's final glycosylation step of glycal **97** with digitoxigenin (**98**) was accomplished in moderate yield and poor stereoselectivity (82%, β:α = 3:2).[151c]

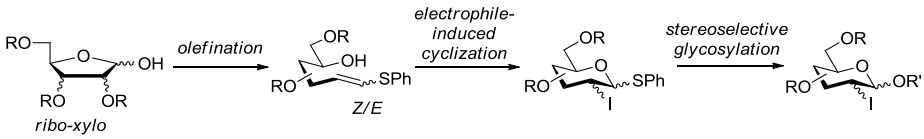
[180] Not chemically modified digitoxigenin, digoxigenin, gitoxigenin, strophanthidol and strophanthidin are available from Aldrich Chemical Company.

Olefination and Cyclization Reactions of Vinyl Thioethers

CHAPTER 5

1. Background

As introduced in the previous chapter, our group developed a new procedure for synthesising 2-deoxyglycosides and oligosaccharides based on a new access to 2-deoxy-2-iodo glycosyl donors without the limitations of availability of pyranoid glycals and the stereoselective addition of electrophiles. This new synthetic route involves three reactions: olefination of appropriately protected pentoses to obtain vinyl-thioethers, electrophilic iodine-induced cyclization to give phenyl 2-deoxy-2-iodo-1-thiopyranosides as a new type of glycosyl donor,[158,181] and finally glycosylation,[182] for the synthesis of the glycoside (Scheme 47).[183]



Scheme 47. Proposed methodology for the stereoselective synthesis of 2-deoxy-2-iodoglycosides.

The olefination of pentoses under Wittig-Horner (WH) conditions, using phosphine oxide carbanions and Li-bases, proved to be the most effective in terms of chemoselectivity, diastereoselectivity and yield of alkene formation. As expected for semistabilized carbanions, the reaction yielded *Z*/*E* alkene mixtures.[147b-c,181d,184]

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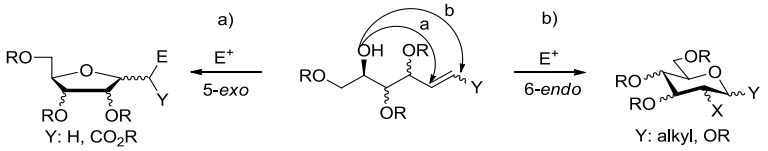
181 a) Boutureira, O.; Rodríguez, M. A.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Org. Lett.* **2006**, *8*, 673-675. b) Arnés, X.; Díaz, Y.; Castillón, S. *Synlett* **2003**, 2143-2146. c) Boutureira, O. PhD Thesis, URV, Tarragona, **2007**. d) Rodríguez, M. A. PhD Thesis, URV, Tarragona, **2007**.

182 For glycosylation methods that involve the use of 2-iodo-deoxy glycosyl donors see: a) Ref [21b],[147b],[154],[146b]. b) Kirschning, A.; Jesberger, M.; Schöning, K.- U. *Org. Lett* **2001**, *53*, 3623-3626. b) For a procedure of synthesis of glycosides involving a mercury–induced cyclization of enolethers see: Paquet, F.; Sinaÿ, P. *Tetrahedron Lett.* **1984**, *25*, 3071-3074.

183 For recent natural products incorporating pregnane 2-deoxyoligosaccharides see: a) Perrone, A.; Paza, A.; Ercolino, S. F.; Hamed, A. I.; Parente, L.; Pizza, C.; Piacente, S. *J. Nat. Prod.* **2006**, *69*, 50-54. b) Bai, H.; Li, W.; Koike, K.; Satou, T.; Chen, Y.; Nikaido, T. *Tetrahedron* **2005**, *61*, 5797-5811.

184 Arnés Novau, X. PhD Thesis, URV, Tarragona, **2003**.

The iodine-induced cyclization of the corresponding hexenyl sulfides involves activation of the double bond by an interaction of electrophilic reagents towards the intramolecular nucleophilic attack of the free hydroxyl group. The regioselectivity of these cyclizations can usually be described well by the Baldwin's rules (Scheme 48).[185] However, there are some reactions that do not follow that rules.



Scheme 48. Regioselective outcome of the electrophilic cyclization of carbohydrate-derived tetrahydroxyhexenes.

Our group has extensively studied the parameters that govern the electrophile-induced cyclization of polyhydroxylated alkenes, such as the electrophilic species, protective groups, solvent, base and kinetic or thermodynamic conditions. In particular, cyclization from alkenols with a terminal double bond (usually derived from pentoses) have been widely studied,[158,181a-b,186] and the preferred process is 5-*exo* (Scheme 48a, Y = H). Substituent at the distal terminus of the double bond has been described to control the regioselectivity of the cyclization reaction. Thus, electron-withdrawing groups such as esters[187] lead to 5-*exo* cyclizations (Scheme 48a, Y = CO_2R) to render highly substituted tetrahydrofurans, whereas electron-donating groups such as alkyl[188] and alkoxy[189] direct de process to 6-*endo*

185 Knight, D. W.; Jones, A. D.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett*. **1999**, 40, 3267-3270.

186 a) Freeman, F.; Robarge, K. D. *J. Org. Chem.* **1989**, *54*, 346-359. b) Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. *Carbohydr. Res.* **1987**, *171*, 49-57. c) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4191-4202. d) Reitz, A.B.; Nortey, S.O.; Maryanoff, B.E. *Tetrahedron Lett.* **1985**, *26*, 3915-3918. e) Nicotra, F.; Panza, L.; Ronchetti, F.; Toma, L. *Tetrahedron Lett.* **1984**, *25*, 5937-5939.

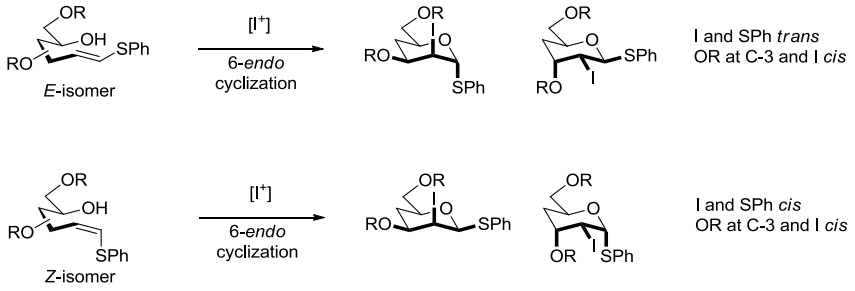
187 Guindon, Y.; Soucy, F.; Yoakim, C.; Ogilvie, W. W.; Plamondon, L. *J. Org. Chem.* **2001**, *66*, 8992-8996.

188 Jung, M. E.; Lew, W. *J. Org. Chem.* **1991**, *56*, 1347-1349.

189 a) Faivre, V.; Lila, C.; Saroli, A.; Doutheau, A. *Tetrahedron Lett.* **1989**, *45*, 7765-7782. b) Beau, J.-M.; Schauer, R. *Carbohydr. Res.* **1980**, *82*, 125-129.

cyclization products (Scheme 48b, Y = alkyl and OR). The examined reactions showed irreversibility in the presence of base.[187]

When a sulfanyl group is attached to the terminus of the double bond, the reaction is completely regioselective, and the 6-*endo* product is obtained. This regioselective outcome can be explained by stabilization of the carbocation in the α-position of the electro-donating group. Furthermore, the cyclization reaction is highly stereoselective and very predictable in terms of the stereochemical outcome. The relative stereochemistry of C-1 and C-2 in thioglycosides depends on the configuration of the starting alkene. Thus, the reaction of the *E*-alkenyl sulfide yields a cyclization product in which the iodine atom and phenylsulfanyl group are in a *trans* arrangement. Whenever the *Z*-alkene underwent cyclization, 2-iodo-thioglycosides were obtained with the substituents at C-1 and C-2 in a *cis* disposition (Scheme 49).



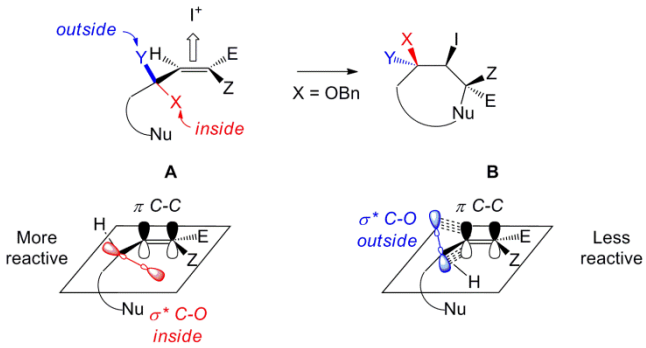
Scheme 49. Stereochemical outcome of the cyclization.

The relative stereochemistry of the new C_{sp3} in the cyclized product was studied.[190] Iodine located in the C-2 position of the final hexose was found to be situated at the *cis*-position with respect to the C-3 alkoxy substituent, the formerly allylic group in the alkene substrate (Scheme 49). This is a key point in the global process because the configuration at C-2 determines the configuration of the anomeric center in the glycosylated products. This phenomenon can be explained with the so-called *´inside-alkoxy effect´*.[191] This stereoelectronic effect directs the conformation of the alkene to the most reactive position, where the allylic alkoxy

190 Castillón, S.; Bravo, F. *Eur. J. Org. Chem.* **2001**, 507-516.

191 Houk, K. N.; Moses, S. R.; Wu, Y.- D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880-3882.

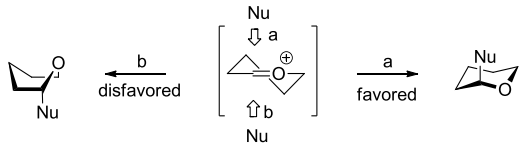
in C-3 is situated in the inner position of the plane of the double bond (inside). In this conformation, the C–O bond σ* orbital is perpendicular to the π-system of the double bond, which minimizes the electron-withdrawing effect, causing the double bond to be more electron-rich and hence more reactive towards an electrophile (Scheme 50, **A**). On the other hand, when the allylic alcoxy group is placed perpendicular to this plane (outside), the electron-withdrawing effect applies and thus the double bond is less reactive (Scheme 50, **B**).



Scheme 50. The *'inside-alkoxy effect'* by electrophile-induced cyclization.

This theory would explain the low reactivity observed with *Z*-vinyl sulfides, where the allylic alkoxy group takes an *outside* position due to a high steric hindrance in the *inside*-conformation. In this conformation, the double bound is less electron-rich and therefore the cyclization was slower and in some cases precluded (Scheme 50).

In light of previous data obtained from our group on glycosylation reactions, oxocarbenium are likely to be intermediates in these glycosylation reactions, and the stereoselectivity outcome may be explained accordingly, rather than the corresponding iodonium-ion intermediates (Scheme 51).[21b,154,181,158b] Nucleophilic attack on the oxocarbenium cation is known to take part along a pseudoaxial trajectory to maximize overlap of the nucleophile HOMO with the LUMO of the oxocarbenium, and occurs with facial preference to give a chair-like transition state (Scheme 51a), instead of higher energy twist-boat conformation (Scheme 51b).



Scheme 51. Nucleophilic attack on the oxocarbenium cation.

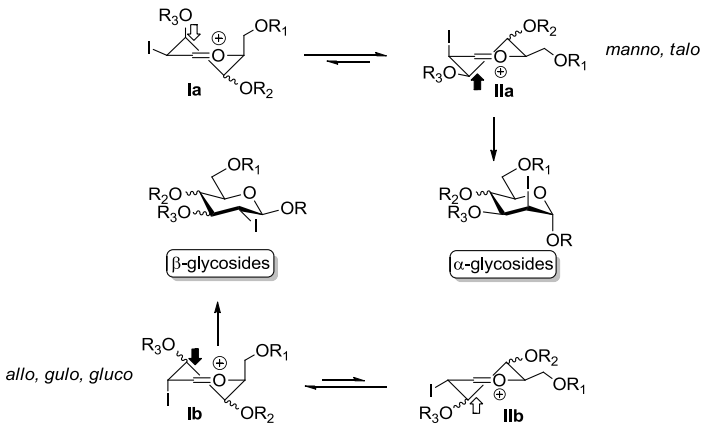
Conformational analysis of the oxocarbenium involved in this process would concern two half-chair conformations which would provide different diastereomeric products.

The selectivity observed can be determined by the nucleophilic attack on the oxocarbenium cations, the ground-state conformational preferences of these intermediates **I** and **II**, and the relative reactivity of each conformer, as mandated by Curtin-Hammett/Winstein-Holness kinetics (Scheme 52).[192]

Thus, according to the results reported by Billings and co-workers,[193] iodine-axial intermediates **IIa** (D-*manno* and D-*talo*) and **Ib** (D-*gluco*, D-*allo* and D-*gulo*) are likely to be more stable than the corresponding iodine-equatorial conformers due to stabilizing hyperconjugative interactions between $\sigma_{C\text{-}I}$ and $\pi^*_{C\text{-}O}$ of the oxocarbenium.

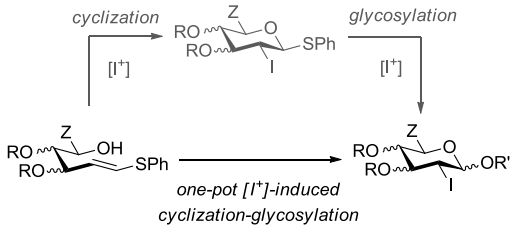
However, the selectivity obtained in the glycosylation experiments cannot only be addressed in terms of relative conformer populations; developing destabilizing interactions in the transition state (transition-state effect) should also be considered. Thus, steric interactions between the C-3 alkoxy substituent and the incoming nucleophile may affect the reactivity of the oxocarbenium conformers to nucleophilic attack.

192 a) Seemann, J. I. *Chem. Rev.* **1983**, *83*, 83-134. b) Seemann, J. I. *J. Chem. Ed.* **1986**, *63*, 42-48.
193 Billings, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171-5178.



Scheme 52. Stereochemical courses of glycosylation reactions of 2-deoxy-2-phenylselenenyl-1-thio-glycosyl donors.

This new method to synthesize 2-deoxy-2-iodo-thioglycosides has been used to apply these glycosyl donors to the synthesis of 2-deoxyglycosides with good yield and stereoselectivity as well as to easily convert these molecules into other useful glycosyl donors, such as glycals.[181] Our group refined the method to transform the sequential two-step cyclization-glycosylation process into a *one-pot* strategy, beginning with the alkenyl sulfide and finishing with the 2-deoxy-2-iodo-glycoside. This change avoids the need to isolate the glycosyl donor intermediate (which is usually unstable, especially in the 6-deoxy series) and, thus, shortens the synthetic route to 2-deoxyglycosides. This approach was possible because the conditions used in cyclization [I^+] are similar to those used in glycosylation ([I^+], TfOH). The *one-pot* procedure has higher yield than the stepwise procedure, with remarkable improvement in some cases and practically no loss of stereoselectivity in the final glycoside (Scheme 53).[158c]



Scheme 53. Refinement of the original stepwise sequential procedure into a more efficient o*ne-pot* cyclization-glycosylation process.

The method has still some limitations as for instance that derived from the different cyclization rate of the *E* and *Z* alkenes that makes the *Z* isomers unsuitable for the synthesis in some cases. The use of different substituent in sulfur (R) was explored in order to improve the percentage of *E* isomer, and bulky groups such as *t*-Bu, 2,6-di-Me-Ph, were found to afford the *E* isomer almost exclusively, but the cyclization reaction evolved slowly.[194]

This strategy is a versatile method that can produce a variety of glycosyl donors in *allo*, *manno*, *gulo* and *talo* configurations. Some of these are difficult to obtain through other approaches, such as the glycal assembly, which supports the value of this methodology (Figure 16). It would be desirable, nevertheless, to widen the scope of this reaction, as there are some configurations that are not accessible by this approach, such as *altro*, *gluco*, *ido* and *galacto* (Figure 17).

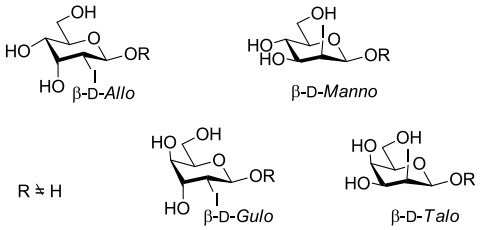


Figure 16. Accessible configurations with the strategy of olefination and cyclization (*allo*, *manno*, *gulo* and *talo*).

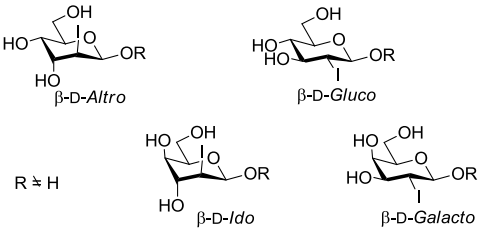


Figure 17. Configurations those are *not accessible* with olefination and cyclization (*altro*, *gluco*, *ido* and *galacto).*

[194] Köver, A. *PhD Thesis*, URV, Tarragona, **2008**.

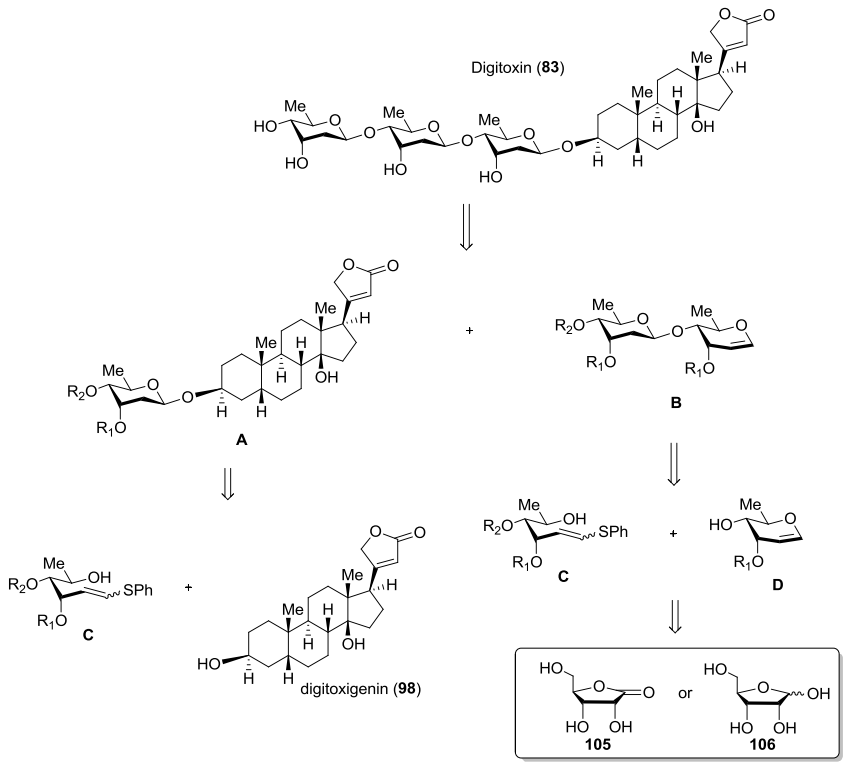
2. Results and discussion

2.1 Retrosynthetic analysis of Digitoxin

In this chapter we explore a procedure to obtain 2-deoxy-β-pyranosides and 2-deoxy-β-oligosaccharides of *ribo* configuration on the way to digitoxin synthesis. As introduced in the background section, this procedure consists of an olefination-cyclization-glycosylation process (see Scheme 47); the two latter steps can be conducted in *one-pot*. This method has been used in the synthesis of 2-deoxyglycosides, and septanosides.[181c-d,194] We next sought to employ this methodology for the convergent synthesis of digitoxin.

As Scheme 54 illustrates, we envisioned digitoxin (**83**) arising from monodigitoxoside **A** and disaccharide **B** in a convergent manner. Monodigitoxoside **A** could be prepared in a *one-pot* fashion from enol thioether **C** and commercially available digitoxigenin (**98**). Disaccharide **B** may be formed by the coupling of enol thioether **C** and glycosyl acceptor **D**. Glycal **D** could be straightforward obtained from phenyl 2-deoxy-2-iodo-thiopyranose which could be prepared from **C** by an iodine-induced cyclization. The common key intermediate **C** could subsequently be prepared from a suitably protected ribonolactone **105** or from ribofuranose **106** by an olefination reaction. Starting from the ribonolactone, it is possible to differentially protect the hydroxyls at C-2 and at C-3 since the C-2 hydroxyl is more acidic and displays similar reactivity to that of a primary hydroxyl group.[195]

[195] a) Ariza, J.; Font, J.; Ortuño, R. M. *Tetrahedron Lett.* **1990**, *46*, 1931-1942. b) Lundt, I.; Madsen, R.; *Synthesis* **1992**, 1129-1132. c) Raveendranath, P. C.; Blazis, V. J.; Agyei-Aye, K.; Hebbler, A. K.; Gentile, L. N.; Hawkins, E. S.; Johnson S. C.; Baker, D. C. *Carbohydr. Res.* **1994**, *253*, 207-223. d) Bell, A. A; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1996**, *7*, 595-606. e) Yang, W.-B.; Tsai, C.-H.; Lin, C.-H. *Tetrahedron Lett.* **2000** *41*, 2569-2572.



Scheme 54. Retrosynthesis of digitoxin (**83**).

As mentioned, the above-described routes were designed to highlight the synthesis of 2,6-dideoxy-2-iodo-pyranosides via a pentose olefination-electrophilic cyclization developed in our group. According to this strategy, either ribonolactone **105** or D-ribofuranose **106** can be used as a starting material. After the selective protection of the hydroxyl groups at C-2 and C-3 and deoxygenation at C-5, the five-membered ring of 6-deoxy-ribofuranose could be expanded to a 6-deoxy-2-iodo-allopyranoside derivative after olefination and subsequent electrophile-induced cyclization.

In order to follow this plan, the choice of the protecting groups is a key consideration, as many of the well-known protecting groups, such as esters, are cleaved under the basic conditions required for the olefination step. The ribofuranose has three hydroxyl groups that should be orthogonally protected. After a previous study, we decided to use ethers as protecting groups, allowing for a global deprotection in the final step of the synthesis. Two kinds of protecting

groups were needed: a permanent and a temporary group. A benzyl ether group was chosen as a permanent protecting group to mask the hydroxyl at C-2 of ribofuranose (R_1), to allow removal by hydrogenolysis in the final step.

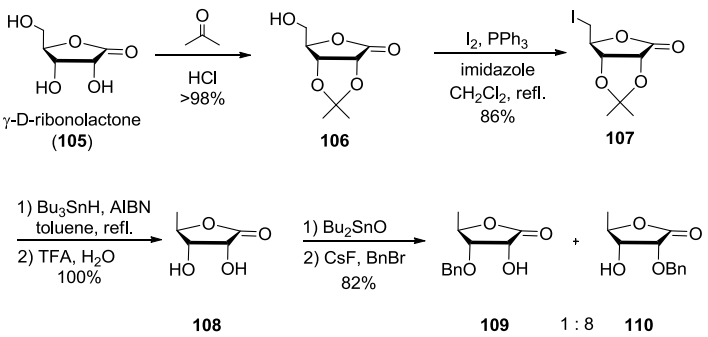
A temporary protecting group for the hydroxyl at C-3 in ribofuranose should be selectively formed and cleaved before the glycosylation step in the presence of the benzyl group. Furthermore, they should be stable under the varied conditions of the synthesis. To this end, a silyl protecting group was chosen (R_2).

Previous results come out in our group will be presented along the discussion altogether with those originally done in this project for the sake of the comparison.

2.2 Olefination and cyclization reactions

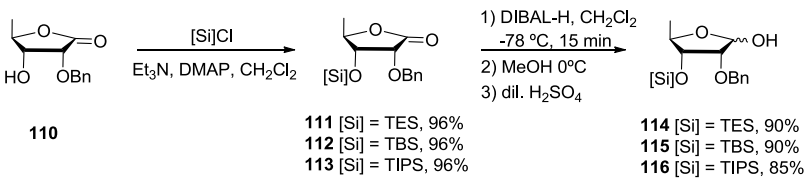
As indicated in the retrosynthetic analysis of digitoxin (Scheme 54), the synthesis of the olefinic precursors was designed to highlight the olefination-cyclization strategy developed in our group. The strategy for the synthesis of the olefinic precursors was explored by Miguel Angel Rodríguez[181d] and it began from ribonolactone **105**. This route involves initial formation of 2,3-*O*-isopropylidene derivative **106**, deoxygenation of position C-5 by iodination to provide **107**,[196] and reduction with Bu_3SnH and deprotection to afford lactone **108**.[197] Selective benzylation at the C-2 hydroxyl group of **108** was carried out by reaction with Bu_2SnO to obtain the stannyl acetal, followed by further reaction with BnBr and CsF to furnish **110** in 71% overall yield (Scheme 55).

196 Garegg, P.J.; Samuelsson, B. *J. Chem. Soc. Perkin trans. 1*, **1980**, 2866-2869.
197 Papageorgiou, C.; Benezra, C. *Tetrahedron Lett.* **1984**, 25, 6041-6044.



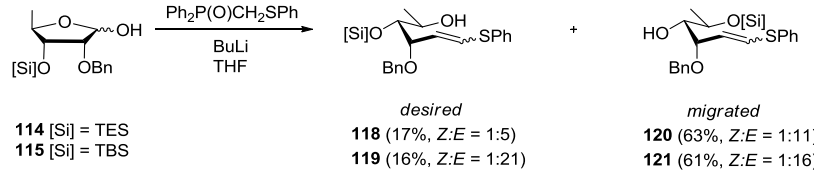
Scheme 55. Synthesis of **110**.[181d]

Some silyl ethers were chosen as temporary protecting groups for the hydroxyl group at C-3. Thus, compound **110** was transformed into 6-deoxy-*ribo* derivatives **114**, **115** and **116** by silylation and lactone reduction (Scheme 56). Moreover, TBDPS-protected furanose **117**, which was synthesized in a previous work,[194] was also used in this project.



Scheme 56. Synthesis of **114**,[194] **115**[181d] and **116**.

Starting from the less bulky TES- and TBS-protected furanoses **114** and **115**, olefination reactions were carried out under WH conditions (Scheme 57). Thus, (phenylsulfanylmethyl) diphenylphosphine oxide was treated with *n*-BuLi at -78ºC, and the solution of the appropriately protected 5-deoxy-ribofuranose was then added slowly at the same temperature. The reaction was warmed to room temperature until completion, determined by TLC analysis. The reaction was quenched by addition of a NH_4Cl saturated solution, and was then extracted with ethyl acetate to recover the alkene product, the excess of phosphine oxide and the β-hydroxyphosphine oxide intermediate. After the separation of the alkene from the reaction mixture, the β-hydroxyphosphine oxide was submitted to elimination conditions with *t*-BuOK or KH in THF to furnish the desired alkene which was combined with the one directly obtained affording good yield.



Scheme 57. WH olefination reaction of silyl-protected 5-deoxy-ribofuranoses **114** and **115**.[194]

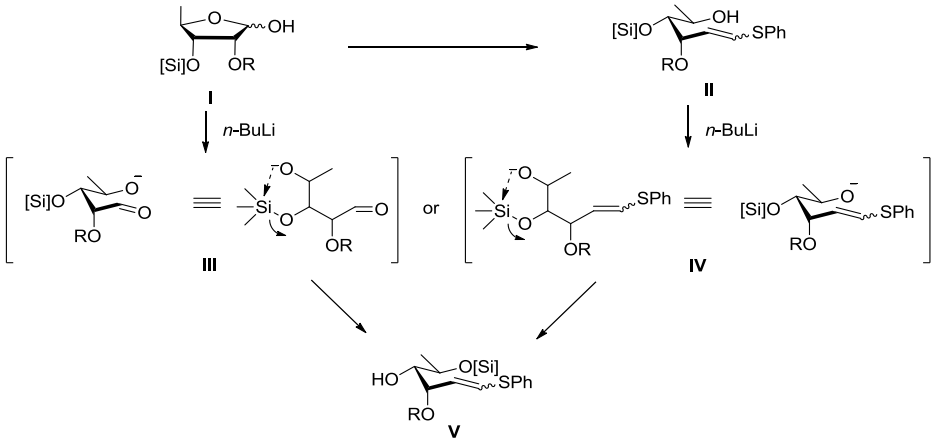
Unexpectedly, the ^{1}H NMR spectra of the reaction crude showed a mixture of four alkene products which were partially separated by chromatographic techniques. The olefinic signals in the ^{1}H NMR spectrum indicated the existence of a mixture consisting of two alkenes of *E* configuration with $J_{1,2}$ values of ca. 15 Hz and two alkenes of *Z* configuration with $J_{1,2}$ values of ca. 10 Hz. Two of the four alkenes were likely to be assigned to the desired enitols of *ribo* configuration **118** and **119** respectively, as a result of direct olefination. Structural elucidation by NMR techniques showed an interesting COSY correlation between a signal corresponding to H-4 and the free OH proton in the major *E*-isomer. The ^{1}H-NMR spectrum indicated that the signal corresponding to H-4 appeared as a *dt* instead of a *t* or *dd*, as it would be expected. On the other hand, the COSY's of the respective other *E*-isomer showed a COSY correlation between H-5 and OH, and similarly, a more complex H-5 signal was found at the ^{1}H-NMR spectrum.

Spectroscopic data allowed us to confirm the structure of the major alkenes obtained from olefination of furanose **114** and **115** corresponding to alkenes of *ribo* configuration **120** and **121** respectively, with the respective silyl groups installed at the corresponding hydroxyl groups at C-5 instead of C-4, as expected.

The mechanism of this migration is explained by the basic conditions under which olefination takes place, with formation of an intramolecular pentacoordinate silicate species either on the aldehyde substrate **I** furnishing intermediate **III**, or the alkene already formed **II** furnishing intermediate **IV** (Scheme 58).[198] The migrated product **V** could be also formed in the subsequent

[198] Examples in the literature for silyl migration: a) Furegati, S.; White, A. J. P.; Miller, A. D. *Synlett.* **2005**, 2385-2387. b) Ogilvie, K. K.; Entwistle, D. W. *Carbohydr. Res.* **1981**, *89*, 203-210. c) Mulzer, J.; Schöllhorn, B. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 431-432. d) Crich, D.; Ritchie, T. J. *Carbohydr. Res.* **1990**, *197*, 324-326. e) Friesen. R. W.; Daljeet, A. K.

elimination step of the β-hydroxyphosphine oxide intermediate with *t*-BuOK or KH. Furthermore, it is reasonable to suggest that this second step might increase the amount of migration product. The driving force for this silyl migration appears to be the increased stability of the 5-*O*-silylated product due to the steric release produced upon migration of the bulky silyl group from an inner to a more peripheral position of the molecule.

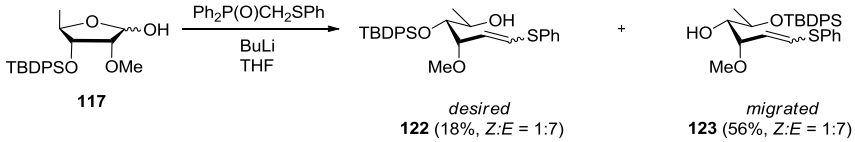


Scheme 58. Mechanism of the migration of silyl group under WH olefination reaction.

Once the silyl migration process was elucidated, the composition of the alkene mixture became clear. The four products observed by NMR in the olefination of TES- and TBS-protected furanoses **114** and **115** were assigned to a *Z*/*E* alkene mixture of the expected products **118** and **119** altogether with a *Z*/*E* alkene mixture of migration products **120** and **121**, respectively (Scheme 57).

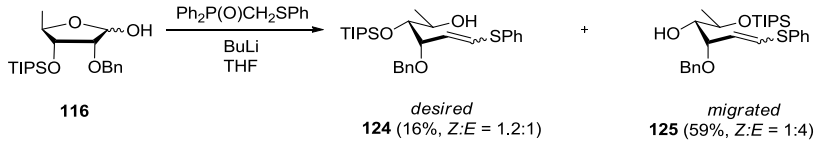
Olefination reaction of the bulky TBDPS-protected compound **117** was then carried out under WH conditions expecting a superior stability to silyl migration,[198] but once again migration alkene **123** was the major product as in the previous experiments (Scheme 59).

Tetrahedron Lett. **1990**, *31*, 6133-6236. f) Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223-2311.



Scheme 59. WH olefination reaction of silyl-protected 5-deoxy-ribofuranose **117**.[194]

In the light of unsuccessful previous experiments in the group, we decided to focus our attention into triisopropylsilyl (TIPS) group, a silyl group that has been described to be more resistant to hydroxyl migration under basic conditions.[199] Unfortunately, olefination reaction of TIPS-protected furanose **116** under WH conditions afforded again the migrated alkene **125** as the major product (Scheme 60).



Scheme 60. WH olefination reaction of silyl-protected 5-deoxy-ribofuranose **116**.

In summary, all silyl ethers derivatives studied (**114-117**) experiment silyl migration under the olefination conditions studied, and the major products obtained in all cases were the migrated compounds **120**, **121**, **123** and **125**, respectively.

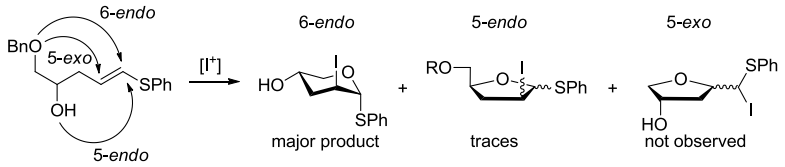
Silyl migration altered our plans to prepare the synthons for our digitoxin synthesis, but provided access to valuable alkene derivatives on which electrophilic-induced cyclization could be further studied. Although our group has extensively studied this reaction for several years,[181] we considered interesting to gain further insight into the parameters that govern this process, carrying out electrophile-induced cyclization with the C-4 free hydroxyl group alkenes generated as a consequence of silyl migration.

---

[199] a) Seela, F.; Fröhlich, T. *Helv. Chim. Acta* **1994**, *77*, 399-408. b) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031. c) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797-4798.

Despite cycloetherification being an important tool in organic synthesis, 5-*endo* electrophile-induced cyclization is not well studied in the literature.[200] The 5-*exo*-trig cyclization was described by Baldwin in 1976, and is preferred over the 6-*endo*-trig mode, although the ratio of 6-*endo* product increases with increasing electron donor substituents at the terminal olefinic carbon (see Scheme 48).

Previous studies in our group[181] on the electrophile-induced cyclization of simple alkenyl sulfides showed that whenever 6-*endo* and 5-*endo* modes are in competition, the 6-*endo* cyclization is preferred even if the hydroxyl function involved in cyclization is protected as benzyl ether. Under these conditions, the 5-*endo*-trig product was obtained in only trace quantities. On the other hand, the 5-*exo*-trig mode does not appear to compete with the *endo* mode when a phenylsulfanyl group is attached to the terminus carbon atom of the double bond, and was not observed (Scheme 61).



Scheme 61. 5-*exo*-trig vs. 5-*endo*-trig cyclization study.

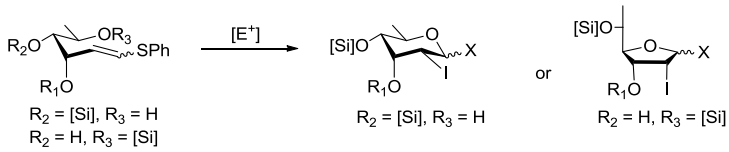
We then thought it would be interesting to implement our study with the reaction of the migrated alkenes with iodonium-electrophiles under the cyclization conditions.

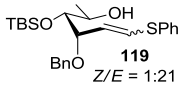
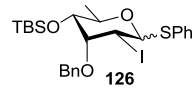
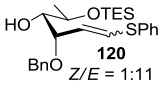
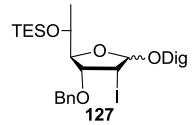
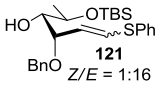
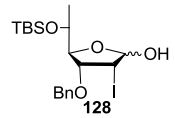
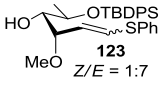
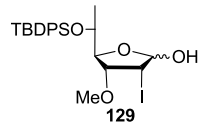
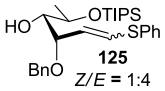
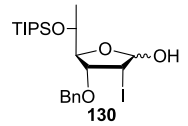
Electrophile-induced cyclization and *one-pot* cyclization-glycosylation reactions were carried out (Table 12). Standard methods of cyclization were chosen with the iodine electrophile.

---

200 Examples for the 5-*endo* cyclizations: a) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348-5349. b) Nonami, Y.; Baran, J.; Sosnicki, J.; Mayr, H.; Masoyama, A.; Nojima, M. *J. Org. Chem.* **1999**, *64*, 4060-4063. c) Alabugin, I, V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127*, 9534-9545. d) Chatgilialoglu, C.; Ferri, C.; Guerra, M.; Tomikhin, V.; Froudakis, g.; Giminiss, T. *J. Am. Chem. Soc.* **2002**, *124*, 10765-10772. e) Knight, D. W. *Progress in Heterocyclic Chemistry*, **2002**, *14*, 19-51.

Table 12. Electrophile-induced cyclization and *one-pot* cyclization-glycosylation reaction of alkenyl sulphides **119**-**121**, **123** and **125**.



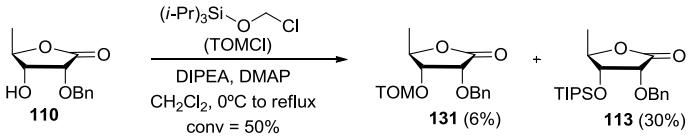
Entry	Substrate (Z/E)	Reaction Conditions	Product	Yield (%)	α/β
1[a]		IDCP CH_3CN, -35ºC		44	1.5:1
2[b]		Digitoxigenin (**98**) NIS/TFA		53	1:22
3[b]		NIS $MeCN:H_2O$ = 10:1		95	1:5
4[b]		1. NIS, $NaHCO_3$ CH_2Cl_2, -20ºC 2. $Na_2S_2O_3$ sat.sol.		63	1:15
5		NIS, $NaHCO_3$ CH_3CN, -30ºC		66	1:1.8

[a] See ref. [181d]. [b] See ref. [194].

On one hand, the electrophile-induced cyclization and the *one-pot* cyclization-glycosylation reactions of the migrated alkenes **120**, **121**, **123** and **125** furnished in all cases furanosyl derivatives as the major products, as a consequence of the 5-*endo* cyclization mode (Table 12, entries 2-5). On the other hand, iodonium-induced cyclization of the minor alkene **119** with a free-hydroxyl group at C-5 afforded pyranosyl derivative **126** as a result of a 6-*endo* cyclization reaction (Table 12, entry 1).

Silyl migration made clear that success in the synthesis of digitoxin depends on the proper selection of temporary protecting group at C-4. We were still interested in silyl-containing groups with the silyl moiety farther away from the oxygen of the hydroxyl protected in order to circumvent silyl migration through the formation of a larger silicate species. Some possible groups are [2-(trimethylsilyl)ethoxy]methyl (SEM), dimethyl-*tert*-butylsilyloxy methyl (SOM), and (triisopropylsilyloxy)methyl (TOM) ethers. Other possibilities such as methoxyethoxyl (MEM), methoxymethyl (MOM) and tetrahydropyranyl (THP) ethers should also be considered.

We decided to look further into silyl-containing groups of the alkoxymethyl ether family such as SEM or TOM. Although SEM is described to be deprotected with fluoride, some results have shown its reluctantless to deprotection under those conditions, and actually SEM is almost deprotected in acid medium.[201,202] Thus, we chose TOM group with which migration, proceeding through a seven-membered silicate species, should be more unlikely. TOM group has been extensively used for the chemical synthesis of oligoribonucleotides under standard DNA coupling conditions.[203]



Scheme 62. Protection of the hydroxyl group of lactone **110** with TOMCl in the presence of DIPEA and DMAP.

First attempt to protect hydroxyl group of lactone **110** was carried out under similar conditions of the silyl protective derivatives. Reaction of lactone **110** with

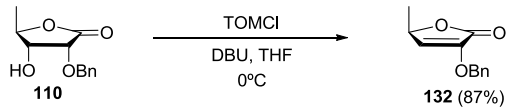
201 a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*, 4th ed.; Wiley: New York, **2006**. b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, **2003**.

202 a) Jansson, K.; Frejd, T.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1988**, *29*, 361-362. b) Pinto, B. M.; Buiting, M. M. W.; Reimer, K. B. *J. Org. Chem.* **1990**, *55*, 2177-2181. c) White, J. D. Kawasaki, M. *J. Am. Chem. Soc.* **1990**, *111***,** 4991-4993.

203 a) Pitsch, S.; Weiss, P. A.; Jenny, L.; Stutz, A.; Wu, X. *Helv. Chim. Acta* **2001**, *84*, 3773-3795. b) Serebryany, V.; Beigelman, L. *Nucleosides, Nucleotides and Nucleic Acids* **2003**, *22*, 1007-1009. c) Pitsch, S.; Weiss, P. A.; Wu, X.; Ackermanna, D.; Honeggera, T. *Helv. Chim. Acta* **1999**, *82*, 1753-1761. d) Wu, X.; Pitsch, S. *Nucleic Acids Res.* **1998**, *26*, 4315-4323.

(triisopropylsilyloxy)methyl chloride (TOMCl) in CH_2Cl_2 in the presence of DIPEA and DMAP from 0ºC to room temperature did not lead to any conversion. When the reaction was heated under reflux for three days, TOM-protected lactone **131** was obtained in a very low yield with TIPS-protected lactone **113**, and remaining starting material was recovered (Scheme 62).

Lactone **110** was then submitted to react with TOMCl in the presence of DBU.[203b] Unfortunately, elimination product **132** was obtained as the major product (Scheme 63).

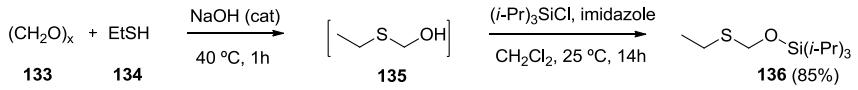


Scheme 63. Protection of the hydroxyl group of lactone **110** with TOMCl in the presence of DBU.

Alkylation of the hydroxyl in the lactone **110** was tried by first forming the tributylstannyl ether derivative with $(Bu_3Sn)_2O$ in dry toluene for 3 h at 120ºC with the purpose of increasing the nucleophilicity of the oxygen and then treating this activated intermediate with 1.2 equiv of TOMCl at room temperature for 12 h, but no perceptible conversion took place.[204]

Since the TOM group was not possible to introduce into the lactone **110** under the previous conditions, we synthesized the derivative triisopropylsilyl (ethylthio)methyl ether (**136**) (Scheme 64).[203a] The reagent TOMSEt (**136**) was synthesized by condensation of paraformaldehyde (**133**) and ethanethiol (**134**) in basic settings and subsequent silylation with TIPSCl/imidazole in CH_2Cl_2 to give TOMSEt (**136**). By distillation at 0.05 Torr, compound **136** was isolated in 85% yield.

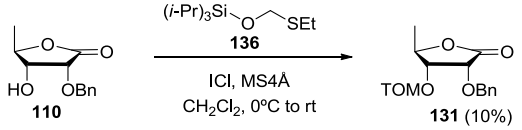
[204] a) Morales-Serna, J. A.; Boutureira, O.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 443-446. b) Vogel, K.; Sterling, J.; Herzig, Y. Nudelman, A. *Tetrahedron* **1996**, *52*, 3049-3056. c) Ogawa, T.; Nukada, T.; Matsui, M. *Carbohydr. Res.* **1982**, *101*, 263-270.



Scheme 64. Synthesis of TOMSEt (**136**).

Protection of the hydroxyl in the lactone **110** was then attempted with a combination of sulfide **136** and $CuBr_2$-Bu_4NBr in CH_2Cl_2 from 0ºC to room temperature for 12 h, but the reaction did not lead to any conversion.[205]

We then tried to couple lactone **110** with TOMSEt (**136**) by thioether activation with ICl.[206] The reaction was carried out with 10 equiv of lactone in the presence of MS4Å in CH_2Cl_2 from 0ºC to rt for 2 h. TOM-protected lactone **131** was obtained in a very poor yield (10%) (Scheme 65). Reaction under typical glycosylation conditions described for thioglycosides (NIS/TfOH)[207] did not reach any conversion.



Scheme 65. Protection of the hydroxyl group of lactone **110** with TOMSEt (**136**) by thioether activation with ICl.

The problems to obtain TOM-protected lactone **131** and the large excess of alcohol needed in the thioether activation procedure, led as to change again the protecting group.

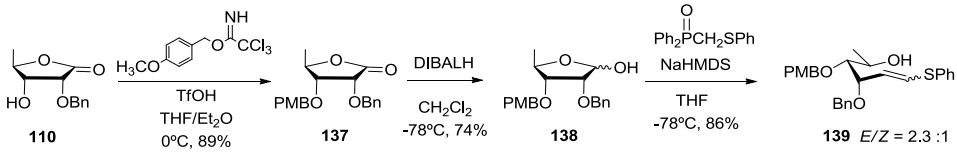
Other recommended protecting group is the *p*-methoxybenzyl (PMB) ether which can be deprotected under oxidative conditions in the presence of benzyl ethers. Since we encountered problems with the application of silyl groups in the synthesis of digitoxin, PMB was decided to be used as temporary protecting hydroxyl group at C-3. First attempt consisted in the reaction of **110** with *p*-

205 Sawada, D.; Ito, Y. *Tetrahedron Lett.* **2001**, *42*, 2501-2504.

206 a) Oikawa M.; Tanaka, T.; Kusumoto,S.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 787-790. b) Cura, P.; Aloui, M.; Kartha, K. P. R.; Field, R. A. *Synlett* **2000**, 1279-1280.

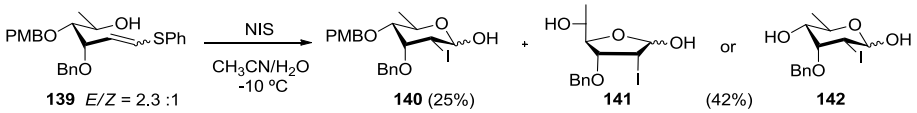
207 Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331-1334.

methoxybenzyl trichloroacetimidate and $La(OTf)_3$,[208] but after 24 h the product **137** was obtained in an only 56% yield. This poor yield could be due to a coordination of the lanthanum salt to the lactone moiety. At this point, the reaction conditions were changed and lactone **110** reacted with *p*-methoxybenzyl trichloroacetimidate and TfOH[209] to furnish lactone **137** in a 89% yield. Thus, compound **137** was transformed into 6-deoxy-*ribo* derivative **138** by lactone reduction (Scheme 66). In this case, the olefination of **138** under WH conditions afforded **139** (*E*/*Z* = 2.3:1) with excellent yield and no traces of protecting group migration.



Scheme 66. Synthesis of **139**.

The cyclization reaction of sulfanyl alkene **139** was then carried out in CH_3CN/H_2O in the presence of NIS (Scheme 67). Unexpectedly, a mixture of two compounds was obtained. The first one corresponded to the product from the 6-*endo* cyclization (**140**) and the other one obtained in major amount was not easy to identify. The ^1H NMR spectrum of the latter product showed that the PMB group had been removed but it was not clear whether it corresponded to furanose **141** (as a result of first deprotection and then 5-*endo*-trig cyclization) or to pyranose **142** (first 6-*endo*-trig cyclization and then deprotection) cyclization products.



Scheme 67. Electrophilic-induced cyclization reaction of alkenyl sulphide **139**.

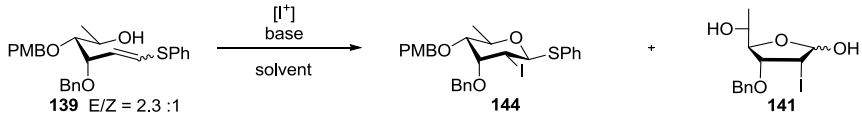
In order to clarify which product was obtained, the unknown compound was acetylated observing an increase of the chemical shift of protons linked to C-1 and C-5 and acetylated furanose **143** was obtained. This fact is in agreement with the

[208] Rai, A.N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267-2269.
[209] Ernst, A.; Schweizer, W.B.; Vasella, A. *Helv. Chim. Acta* **1998**, *81*, 2157-2189.

formation of compound **141**, which indicated that in the reaction conditions the PMB group is being deprotected first and then, with the hydroxyls in C-4 and C-5 unprotected, 5-*endo* cyclization is favoured over the 6-*endo* one.

At this point, it was decided to study different conditions of cyclization in order to avoid PMB deprotection (Table 13).

Table 13. Study of the electrophile-induced cyclization reaction of sulfanyl alkene **139**.[a]



Entry	$[I^+]$ (equiv)	Base	Solvent	Temp (ºC)	Time (h)	Products
1	NIS (2.5)	-	CH_3CN:H_2O (10:1)	-10	0.75	**141**[b]
2	NIS (1.2)	-	CH_3CN:H_2O (10:1)	-15	0.75	**141**[b]
3	NIS (1.2)	-	CH_3CN:H_2O (159:1)	-30	4	**141**[b]
4[c]	NIS (1.2)	-	CH_3CN:H_2O (159:1)	-30	4	**141**[b]
5[c]	NIS (1.5)	$NaHCO_3$	CH_3CN	-30 to -10	4	**141**[b]
6[c]	IDCP (2.2)	-	CH_3CN	-30 to -10	24	mixt.[d]
7[c]	Ipy_2BF_4 (2.2)	-	CH_3CN	-30 to -10	6	mixt.[e]
8[c]	Ipy_2BF_4 (1.2)	-	CH_3CN	-30 to -10	8	mixt.[e]
9[c]	NIS (1.2)	$NaHCO_3$	CH_2Cl_2	-78 to -10	24	mixt.[d]
10[c]	IDCP (2.2)	-	CH_2Cl_2	-78 to -10	24	mixt.[d]
11[c]	Ipy_2BF_4 (2.2)	-	CH_2Cl_2	-30 to -10	6	mixt.[d]
12[c,f]	NIS (1.2)	$NaHCO_3$	CH_3CN	-30 to -10	24	**141**[b]
13[c,g]	NIS (1.2)	$NaHCO_3$	CH_3CN	-30 to -10	5	mixt.[d]
14[c,h]	NIS (1.2)	$NaHCO_3$	CH_3CN	-30 to rt	120	mixt.[d]
15[c,i]	NIS (1.2)	$NaHCO_3$	CH_3CN	-30 to rt	120	mixt.[d]

[a] *Conditions*: Alkene (0.16 mmol), base (0.24 mmol), $[I]^+$, solvent (0.5 M). [b] Major product. [c] The reaction was protected from the light. [d] Complex mixture. [e] Mixture: **144** + glycal + mixture of alquenes. [f] Nitrobenzene (10 equiv) was added. [g] Picric acid (10 equiv) was added. [h] BHT (1.2 equiv) was added as a radical inhibitor. [i] SANTONOX (1.2 equiv) was added as a radical inhibitor.

Neither the use of less equivalents of NIS (Table 13, entry 2 vs. entry 1), nor reducing the quantity of water added to the reaction in order to decrease the

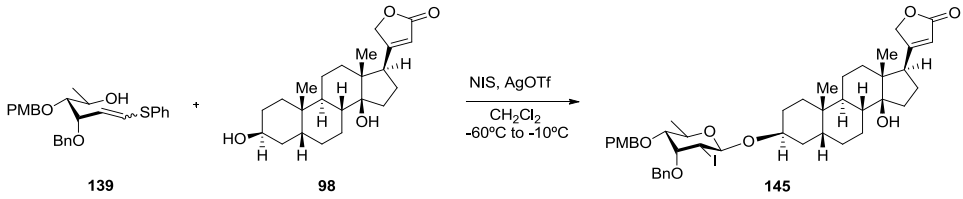
temperature from -10ºC to -30ºC (Table 13, entry 3), gave the desired product **140**. Instead, product **141** was obtained in both cases as the major one.[210]

Thinking about a radical mechanism for the deprotection of PMB, the reaction was repeated protecting it from the light but the desired product was not obtained either (Table 13, entry 4). The addition of a radical inhibitor to the reaction like BHT or SANTONOX (Table 13, entries 14, 15) resulted also unsuccessful and in any case the desired product was observed. In addition, the results obtained were the same changing the solvent to CH_3CN or adding $NaHCO_3$ as a base (Table 13, entry 5).

When different electrophilic iodonium species were used, the reaction led to complex mixtures, and in some cases the glycal derived from I and the SPh group reductive elimination could also be observed (Table 13, entries 6-8). The reaction did not improve changing the solvent to CH_2Cl_2 (Table 13, entries 9-11).

Moreover, an aromatic compound like nitrobenzene or picric acid was added to the reaction in order to prompt π-stacking interactions with the PMB group and avoid its deprotection, but it did not succeed (Table 13, entries 12, 13).

Problems to obtain pyranose **140** led us to carry out the glycosylation of digitoxigenin directly from alkene **139** in order to afford digitoxin. Thus, *one-pot* cyclization-glycosylation reaction with alkene **139** and digitoxigenin (**98**) rendered a complex mixture where distinctive signals of monodigitoxoside **145** were identified by ^{1}H NMR (Scheme 68).



Scheme 68. *One-pot* cyclization-glycosylation reactions of **139**.

[210] Selected methods of oxidative cleavage of PMB: a) Classon, B.; Garegg, P. J.; Samuelsson, B. *Acta Chem. Scand. Ser. B* **1984**, *B38*, 419-422. b) Johansson, R.; Samuelsson, B. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2371-2374. c) Vaino, A. R.; Szarek, W. A. *Synlett* **1995**, 1157-1158.

It has become clear that the choice of the proper temporary protecting group is not a trivial task. As such, digitoxin synthesis is pending in a near future, and depends upon the proper selection of temporary protecting groups at C-4. The suitable protecting group requires being compatible with the basic conditions involved in the olefination step and the oxidative conditions involved in the cyclization step.

3. Conclusions

In this chapter, we have explored the total synthesis of digitoxin. In particular, we have explored the application of an olefination-cyclization-glycosylation strategy for natural product synthesis. The relevant conclusions of this work are the following:

- Olefination, cyclization and glycosylation reactions of silyl-protected 5-deoxy-ribofuranoses **114**-**117** were studied toward the synthesis of 2,6-dideoxy oligosaccharides. Unfortunately, no desired 6-*endo* cyclization products were obtained as major products due to a competing silyl migration process during the WH olefination step.

- Olefination of PMB-protected 6-deoxy-ribose **138** was achieved satisfactorily with excellent yield. However, cyclization of sulfanyl alkene **139** furnished furanose **141**, as a consequence of first PMB group deprotection and subsequent 5-*endo*-trig cyclization.

- *One-pot* cyclization-glycosylation reaction with alkene **139** and digitoxigenin (**98**) rendered monodigitoxoside **145** with a poor yield.

- This approach to the synthesis of digitoxin has highlighted the requirement for a protecting group that is compatible with the basic conditions involved in the olefination step and with the oxidative conditions involved in the cyclization step.

4. Experimental Section

4.1 General methods

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), dimethylformamide (DMF) and diethyl ether were dried using a solvent purification system (Pure SOLV system-4®). The other solvents were purified using standard procedures.[111]

^1H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 or in a Varian® 400-MR, (both of 400 MHz and 100.6 MHz respectively) spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.27 ppm ^1H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm), unless otherwise specified. 2D correlation spectra (gCOSY, NOESY, TOCSY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate.

Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F_{254} glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in a suitable developing solution. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

4.2 General Procedures

General procedure of silylation of alcohols. To a solution of alcohol (1.00 mmol), Et_3N (1.60 mmol) and silyl chloride (3.0 mmol) in anhydrous CH_2Cl_2 (2.2 ml), DMAP (0.5 mmol) were added slowly. The mixture was vigorously stirred at

rt for 6 h and then diluted with CH_2Cl_2, extracted twice with diluted HCl, $NaHCO_3$ and finally water. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by chromatographic techniques.

General procedure of reduction of aldonolactones. DIBAL (1.5 ml, 0.1 M solution in CH_2Cl_2, 1.50 mmol) was added dropwise to a solution of lactone (1.00 mmol) in dry CH_2Cl_2 (10 ml, 0.1 M) at -78ºC. The mixture was stirred at -78ºC and the consumption of the starting material was monitored by TLC (EtOAc:hexane 1:2) (1-5 h). The reaction was quenched with MeOH (1 ml), warmed at rt, and then, diluted H_2SO_4 was added until the turbid solution became clear (pH 3-4). The mixture was extracted twice with CH_2Cl_2/H_2O. The combined organic extracts were dried and concentrated under reduced pressure. The crude product was purified by chromatographic techniques.

General procedure of WH olefination reactions. A solution of the base (4.40 mmol) was slowly added to the cold (-78ºC) solution of diphenyl(phenylthiomethyl)phosphine oxide (4.00 mmol) in anhydrous THF (13 ml) under argon atmosphere. The reaction mixture was further stirred under the same conditions for 30 min, subsequently a solution of the corresponding aldehyde (1.00 mmol) in anhydrous THF (2 ml) was transferred by cannula. The reaction mixture was warmed up to room temperature and stirred further under argon. The evolution of the reaction was followed by TLC analysis and usually after 24 h the reaction was completed. The reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with ether (3 x 20 ml). The combined ethereal layers were dried over $MgSO_4$, filtered and concentrated under vacuum. After work-up and separation of the alkene the obtained β-hydroxyphosphine oxide was further treated with KH or *t*-BuOK in THF at 40ºC for 30 minutes. Before any other purification the possible product range was checked by ^{1}H NMR. The crude of reaction was purified by chromatography (hexane to ethyl acetate) and the *E/Z* ratio was determined from ^{1}H NMR data.

General procedure for iodonium-induced cyclization

Method A. $NaHCO_3$ (0.24 mmol) was added to a 0.5 M solution of alkene (0.16 mmol) in CH_3CN. The mixture was cooled to -30ºC and left to stir at this temperature for 5 min. NIS (0.24 mmol) was then added and the reaction mixture was stirred for several hours. The reaction temperature was left to increase depending on the reactivity of the substrate (from -78ºC to room temperature). The mixture was diluted with CH_2Cl_2 and washed with a saturated solution of $Na_2S_2O_3$, extracted with ethyl acetate (3 x 20 ml). The combined organic layer was washed with water (2 x 20 ml), brine (1 x 20 ml), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by chromatographic techniques.

Method B. IDCP (0.35 mmol) was added to a 0.5 M solution of alkene (0.16 mmol) at -30 °C in CH_3CN. The reaction temperature was allowed to increase depending on the reactivity of the substrate (from -30 °C to room temperature). The mixture was diluted with dichloromethane and washed with a saturated solution of $Na_2S_2O_3$. The combined aqueous layer was extracted with dichloromethane. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by chromatographic techniques.

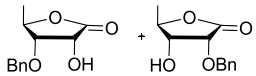
General procedure for glycosylation. A solution of the glycosyl donor (1.00 mmol) and the glycosyl acceptor (2.00 mmol) in anhydrous CH_2Cl_2 (4 ml) was stirred with 4 Å molecular sieves for 2 h. The mixture was then cooled to -78ºC, and NIS (2.20 mmol) and TfOH (0.20 mmol) were added. The mixture was allowed to warm to -40ºC and stirred until the reaction had finished. The reaction mixture was then diluted with CH_2Cl_2 and washed with a solution of $Na_2S_2O_3$ and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layer was washed with water (2 x 15 ml), brine (1 x 15 ml), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was then purified by radial chromatography.

General procedure for the o*ne-pot* cyclization-glycosylation from sulfanyl alkenes. Starting alkene (1.00 mmol), glycosyl acceptor (2.00 mmol), 4 Å molecular sieves and 25 ml (0.02 M) of anhydrous CH_2Cl_2 were stirred together at

rt during 30 min. The reaction was cooled at -65ºC and then NIS (3.00 mmol) was added. While the reaction temperature was allowed to reach -10ºC, the reaction was monitored by TLC (hexane:ethyl acetate = 3:1) and left to stir until the cyclization was complete. The reaction mixture was then cooled to -60ºC and then TfOH (0.20 mmol) was added. The reaction was left to stir at low temperature (between -40ºC and -10ºC) until the reaction was complete. The crude of the reaction was quenched with $NaHCO_3$-$Na_2S_2O_3$ solution, extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layer was washed with water (2 x 20 ml), brine (1 x 20 ml), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by chromatographic techniques.

4.3 Compound Characterization

3-*O*-Benzyl-5-deoxy-γ-D-ribonolactone (109) and 2-*O*-Benzyl-5-deoxy-γ-D-ribonolactone (110).



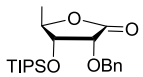
109 **110**

To a solution of 5-deoxy-γ-D-ribonolactone (**108**) (6.0 g, 45.42 mmol) in toluene (300 ml), Bu_2SnO (27.1 g, 45.42 mmol) was added. The mixture was heated at reflux for 2 h with azeotropic removal of water formed (≈ 0.8 ml in Dean-Stark trap). The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The solid crude obtained was dried for 1h under high vacuum. Under argon atmosphere, dry CsF was added (8.3 g, 54.50 mmol) and the mixture dissolved in dry DMF (260 ml). BnBr (11.8 ml, 99.92 mmol) was added dropwise and the mixture stirred for 2 days (TLC control). The reaction was quenched distilling DMF off and the crude extracted with EtOAc/H_2O. The organic phase was dried over anhydrous $MgSO_4$, concentrated, and purified by column chromatography (from hexane to EtOAc:hexane 1:2) to afford a solid mixture of **110** and **109** (ratio 8:1). This solid was recrystallized in EtOAc:hexane to afford product **110** (8.3 g, 37.35 mmol, 82%) as a bright white needles. The mother liquor was concentrated to give a mixture of **110** (0.8 g, 3.60 mmol, 8%) and **109** (0.9 g, 4.05 mmol, 9%).

110: **Mp** 134-138 ºC. **[α]$^{20}_{D}$** +92.1 (*c* 1.00, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.41-7.36 (m, 5H), 5.05 (d, 1H, *J* = 11.6 Hz), 4.80 (d, 1H, *J* = 11.6 Hz), 4.54 (qd, 1H, *J* = 6.8, 2.8 Hz), 4.19 (d, 1H, *J* = 5.2 Hz), 4.00 (m, 1H), 2.76 (d, 1H, *J* = 3.6 Hz), 1.35 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 172.9, 136.3, 128.9, 128.6, 128.1, 80.9, 73.4, 73.1, 72.6, 18.3. **ESI-HRMS** *m/z* calcd. for $C_{12}H_{18}NO_4$ [M-NH_4]: 240.1230, found: 240.1238.

Spectroscopic data of **109** from the mixture **110**/**109**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.38-7.32 (m, 5H), 4.70 (s, 2H), 4.62 (q, 1H, *J* = 6.8 Hz), 4.47 (dd, 1H, *J* = 9.0, 5.6 Hz), 3.92 (d, 1H, *J* = 5.6 Hz), 2.86 (d, 1H, *J* = 9.0 Hz), 1.33 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 185.5, 146.9, 128.9, 128.8, 128.1, 78.8, 78.4, 72.7, 68.3, 18.3.

2-*O*-Benzyl-3-*O*-triisopropylsilyl-5-deoxy-γ-D-ribonolactone (113).

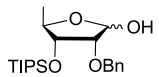


113

Following the general procedure of silylation of alcohols, 2-*O*-benzyl-5-deoxy-γ-D-ribonolactone (**110**) (3.0 g, 13.50 mmol), Et_3N (3.0 ml, 21.60 mmol), TIPSCl (8.7 ml, 40.50 mmol) and DMAP (0.8 g, 6.75 mmol) in dry CH_2Cl_2 (46 ml) were reacted at rt for 24 h. Column chromatography (1:9 EtOAc:hexane) of the reaction crude afforded **113** (4.9 g, 12.94 mmol, 96%) as a colourless syrup.

[α]$^{20}_{D}$ +49.7 (*c* 1.00, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.40-7.27 (m, 5H), 4.98 (d, 1H, *J* = 11.6 Hz), 4.76 (d, 1H, *J* = 11.6 Hz), 4.50 (dq, 1H, *J* = 6.8, 2.4 Hz), 4.20 (q, 1H, *J* = 4.8, 2.8 Hz), 4.10 (d, 1H, *J* = 4.8 Hz), 1.34 (d, 3H, *J* = 7.2 Hz), 1.05-1.03 (m, 21H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 173.1, 136.7, 127.9, 127.7, 127.4, 81.5, 73.9, 73.8, 71.8, 17.4, 12,1-11.8. **ESI-HRMS** *m/z* calcd. for $C_{21}H_{38}NO_4Si$ [M-NH_4]: 396.2570, found: 396.2552.

2-*O*-Benzyl-3-*O*-triisopropylsilyl-5-deoxy-α/β-D-ribofuranose (116).



116

The lactone **113** (3.0 g, 7.92 mmol) was reduced following the general procedure for 1h at -78ºC. Column chromatography of the residue (from EtOAc:hexane 1:5 to 1:4) afforded furanose **116** (2.6 g, 6.83 mmol, 85%) as a colourless syrup.

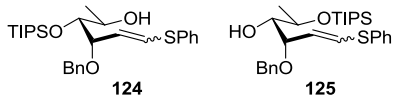
Spectroscopic data from the α/β mixture:

ESI-HRMS *m/z* calcd. for $C_{21}H_{36}NaO_4Si$ [M-Na]: 403.2281, found: 403.2254.

116α: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.39-7.26 (m, 5H), 5.31 (dd, 1H, *J* = 11.6, 4.0 Hz), 4.68 (d, 2H, *J* = 2.8 Hz), 4.50 (d, 1H, *J* = 11.6 Hz), 4.32 (qd, 1H, *J* = 6.4, 1.2 Hz), 4.01 (dd, 1H, *J* = 4.4, 1.2 Hz), 3.80 (dd, 1H, *J* = 4.4, 4.0 Hz), 1.18 (d, 3H, *J* = 6.4 Hz), 1.06-1.01 (m, 21H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 137.6, 128.4-127.7, 96.1, 81.3, 77.4, 77.3, 72.1, 20.0, 18.0, 12.2.

116β: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.39-7.26 (m, 5H), 5.34 (d, 1H, *J* = 2.8 Hz), 4.74 (d, 1H, *J* = 11.2 Hz), 4.62 (d, 1H, *J* = 11.2 Hz), 4.21 (dd, 1H, *J* = 6.8, 4.4 Hz), 4.12 (qd, 1H, *J* = 6.8, 6.8 Hz), 3.99 (m, 1H), 3.78 (dd, 1H, *J* = 4.4, 0.8 Hz), 1.37 (d, 3H, *J* = 6.8 Hz), 1.06-1.01 (m, 21H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2, 128.4-127.7, 99.5, 83.5, 78.9, 77.3, 72.2, 20.3, 18.1, 12.5.

(*E/Z*)-3-*O*-Benzyl-4-*O*-triisopropylsilyl-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (124) and (*E/Z*)-3-*O*-Benzyl-5-*O*-triisopropylsilyl-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (125).



124 **125**

According to the general procedure for WH olefination reactions, the title compound was synthesized by reaction of 2-*O*-benzyl-3-*O*-triisopropylsilyl-5-deoxy-α/β-D-ribofuranose (**116**) (0.15 g, 0.39 mmol), diphenyl(phenylthiomethyl)phosphine oxide (0.51 g, 1.58 mmol) and *n*-BuLi solution (1.1 ml, 1.73 mmol, 1.6 M in hexane) for 24 h. The reaction was monitored by TLC (hexane:EtOAc 1:1). Column chromatography (hexane:EtOAc 3:1) afforded the desired **124** (33 mg, 0.06 mmol, 16%, a *Z*/E inseparable mixture, *Z*/E = 1.2:1) as a yellowish syrup and the migrated compound **125** (124 mg, 0.23 mmol, 59%, a *Z*/E inseparable mixture, *Z*/E = 1:4) as a yellowish syrup.

Spectroscopic data from the *E:Z* mixture:

ESI-HRMS *m/z* calcd. for $C_{28}H_{42}NaO_3SSi$ [M-Na]: 509.2522, found: 509.2546.

124E: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.41-7.25 (m, 10H), 6.44 (d, 1H, *J* = 15.2 Hz), 5.82 (dd, 1H, *J* = 15.2, 8.4 Hz), 4.62 (d, 1H, *J* = 11.6 Hz), 4.38 (d, 1H, *J* = 11.2 Hz), 4.00 (dd, 1H, *J* = 8.4, 4.8 Hz), 3.94 (qd, 1H, *J* = 6.0, 4.4 Hz), 3.88 (dd, 1H, *J* = 4.8, 4.4 Hz), 2.15 (d, 1H, *J* = 4.0 Hz), 1.20 (d, 3H, *J* = 6.0 Hz), 1.06 (s, 21H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3, 134.5, 130.7, 129.4, 129.1, 128.6, 128.4, 128.1, 128.0, 127.8, 127.4, 81.1, 78.7, 70.5, 70.2, 18.5, 18.4, 18.3, 13.2.

124Z: Could not be determined.

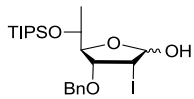
Spectroscopic data from the *E:Z* mixture:

ESI-HRMS *m/z* calcd. for $C_{28}H_{42}NaO_3SSi$ [M-Na]: 509.2522, found: 509.2504.

125E: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.42-7.24 (m, 10H), 6.41 (d, 1H, *J* = 15.2 Hz), 5.85 (dd, 1H, *J* = 15.6, 8.0 Hz), 4.66 (d, 1H, *J* = 12.0 Hz), 4.37 (d, 1H, *J* = 12.4 Hz), 4.18 (qd, 1H, *J* = 6.0, 4.4 Hz), 3.85 (dd, 1H, *J* = 8.0, 7.2 Hz), 3.69 (ddd, 1H, *J* = 7.2, 4.0, 1.8 Hz), 2.39 (d, 1H, *J* = 2.0 Hz), 1.09 (d, 3H, *J* = 6.0 Hz), 1.05 (s, 21H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 144.1, 138.2, 130.3, 129.5, 129.3, 128.8, 128.5, 128.0, 127.8, 127.2, 79.8, 76.7, 70.6, 68.9, 18.3, 17.2, 12.6.

125Z: Could not be determined.

3-*O*-Benzyl-5-*O*-triisopropylsilyl-2,6-dideoxy-2-iodo-α/β-D-*allo*-furanose (130).



130

Following the general method A for iodonium-induced cyclization, compound **125** (75 mg, 0.14 mmol, a *Z/E* inseparable mixture, *Z/E* = 1:4), NIS (48 mg, 0.21 mmol) and $NaHCO_3$ (18 mg, 0.21 mmol) were stirred in anhydrous CH_3CN (0.3 ml), from -38ºC to rt for 5 h. The reaction was monitored by TLC (hexane:EtOAc 3:1). Column chromatography (from hexane to hexane:EtOAc 7:1) afforded desired **130** (50 mg, 0.09 mmol, 66%) as a yellowish syrup.

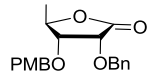
Spectroscopic data from the α/β mixture:

ESI-HRMS *m/z* calcd. for $C_{22}H_{41}INO_4S$ [M-NH_4]: 538.1850, found: 538.1825.

130α: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.45-7.13 (m, 5H), 5.52 (d, 1H, *J* = 7.6 Hz), 4.56 (d, 1H, *J* = 15.2 Hz), 4.25 (d, 1H, *J* = 15.6 Hz), 4.19 (qd, 1H, *J* = 6.8, 2.4 Hz), 3.97 (dd, 1H, *J* = 6.8, 2.4 Hz), 3.73 (dd, 1H, *J* = 6.8, 5.2 Hz), 3.65 (d, 1H, *J* = 7.6 Hz), 1.11 (d, 3H, *J* = 6.8 Hz), 1.03-0.97 (m, 21H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 137.0, 129.3-127.4, 104.5, 85.9, 74.6, 72.9, 68.1, 37.5, 20.7, 18.2, 12.8.

130β: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.45-7.13 (m, 5H), 5.08 (dd, 1H, *J* = 12.0, 4.0 Hz), 4.59 (d, 2H, *J* = 2.8 Hz), 4.29 (dd, 1H, *J* = 4.8, 4.0 Hz), 4.02 (dd, 1H, *J* = 3.6, 1.6 Hz), 3.93-3.96 (m, 1H), 3.93 (dd, 1H, *J* = 4.8, 1.6 Hz), 3.59 (d, 1H, *J* = 12.0 Hz), 1.07 (d, 3H, *J* = 6.8 Hz), 1.03-0.97 (m, 21H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 137.0, 129.3-127.4, 98.8, 87.0, 78.5, 72.4, 69.0, 32.1, 20.7, 18.2, 13.1.

2-*O*-Benzyl-3-*O*-(4-methoxybenzyl)-5-deoxy-γ-D-ribonolactone (137).



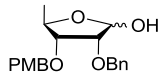
137

A solution of 2-*O*-benzyl-5-deoxy-γ-D-ribonolactone (**110**) (1.36 g, 6.12 mmol) and 4-methoxybenzyl trichloroacetimidate (1.9 ml, 9.18 mmol) in THF/Et_2O 1:1 (107 ml) was treated at 0ºC dropwise with a 0.05M solution of TfOH in Et_2O (3.7 ml, 0.19 mmol), stirred for 1h, neutralized with *Amberlite IRA-402* (OH^- form), filtered, and evaporated. Purification by flash chromatography (hexane/ EtOAc 4:1) afforded **137** still impurified. This solid was recrystallized in MeOH:water to afford product **137** (1.86 g, 5.45 mmol, 89%) as a white foam.

[α]$^{20}_D$ +93.7 (*c* 0.83, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.43-7.34 (m, 5H), 7.22 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 4.93 (d, 1H, *J* = 12.0 Hz), 4.74 (d, 1H, *J* = 12.0 Hz), 4.65-4.58 (m, 2H), 4.48 (d, 1H, *J* = 12.0 Hz), 4.09 (d, 1H, *J* = 5.2 Hz), 3.82 (s, 3H), 3.73 (dd, 1H, *J* = 5.2, 4.4 Hz), 1.33 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 172.8, 159.7, 136.8, 129.9,

129.2, 128.8, 128.6, 128.5, 114.1, 79.0, 78.7, 72.8, 72.4, 72.1, 55.5, 18.5. **ESI-HRMS** *m/z* calcd. for $C_{20}H_{22}O_5Na$ [M-Na]: 365.1365, found: 365.1361.

2-*O*-Benzyl-3-*O*-(4-methoxybenzyl)-5-deoxy-α/β-D-ribofuranose (138).



138

The lactone **137** (1.3 g, 3.80 mmol) was reduced following the general procedure for 1h at -78ºC. Column chromatography of the residue (EtOAc:hexane 1:2) afforded furanose **138** (1.2 g, 3.38 mmol, 89%) as a colourless syrup.

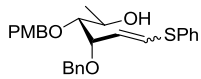
Spectroscopic data from the α/β mixture:

ESI-HRMS *m/z* calcd. for $C_{20}H_{24}O_5Na$ [M-Na]: 367.1521, found: 367.1520.

138*α*: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.39-7.33 (m, 5H), 7.26 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 5.30 (dd, 1H, *J* = 11.2, 4.4 Hz), 4.71 (d, 1H, *J* = 11.6 Hz), 4.67 (d, 1H, *J* = 11.6 Hz), 4.64 (d, 1H, *J* = 11.2 Hz), 4.55 (d, 1H, *J* = 11.2 Hz), 4.32 (qd, 1H, *J* = 6.4, 3.2 Hz), 4.26 (d, 1H, *J* = 11.2 Hz), 3.92 (dd, 1H, *J* = 4.8, 4.4 Hz), 3.82 (s, 3H), 3.62 (dd, 1H, *J* = 4.8, 3.2 Hz), 1.17 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 159.5, 137.4, 129.6, 128.6, 128.1, 128.0, 127.9, 113.9, 95.9, 81.3, 77.1, 76.8, 72.7, 72.5, 55.3, 19.7.

138β: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.39-7.33 (m, 5H), 7.26 (d, 2H, *J* = 8.8 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 5.35 (s, 1H); 4.73-4.61 (m, 2H), 4.64 (d, 1H, *J* = 11.2 Hz), 4.42 (d, 1H, *J* = 11.2 Hz), 4.21 (qd, 1H, *J* = 6.4, 0.8 Hz), 3.84 (d, 1H, *J* = 4.8 Hz), 3.81 (s, 3H), 3.77 (dd, 1H, *J* = 4.8, 0.8 Hz), 1.32 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 159.4, 137.8, 133.4, 129.5, 128.4, 128.2, 128.0, 113.8, 100.1, 82.4, 80.3, 76.8, 72.2, 72.1, 55.3, 20.5.

(*E*/*Z*)-3-*O*-Benzyl-4-*O*-(4-methoxybenzyl)-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (139).



139

According to the general procedure for WH olefination reactions, , the title compound was synthesized by reaction of 2-*O*-benzyl-3-*O*-(4-methoxybenzyl)-5-

deoxy-α/β-D-ribofuranose (**138**) (1.1 g, 3.19 mmol), diphenyl(phenylthiomethyl) phosphine oxide (4.1 g, 12.76 mmol) and hexamethyldisilazane sodium salt solution (14 ml, 14.04 mmol, 1.1 M in THF) for 4 h. The reaction was monitored by TLC (hexane:EtOAc 1:1). Column chromatography (hexane:EtOAc 4:1) afforded **139** (1.2 g, 2.74 mmol, 86%, a *Z*/E inseparable mixture, *E*/Z = 2.8:1) as a colourless syrup.

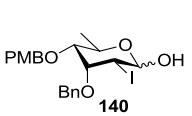
Spectroscopic data from the *E:Z* mixture:

ESI-HRMS *m/z* calcd. for $C_{27}H_{30}O_4Na$ [M-Na]: 473.1762, found: 473.1752.

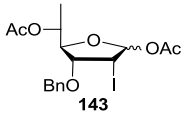
139E: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.39-7.26 (m, 10H), 7.24 (d, 2H, *J* = 8.4 Hz), 6.86 (d, 2H, *J* = 8.4 Hz), 6.52 (d, 1H, *J* = 15.2 Hz), 5.81 (dd, 1H, *J* = 15.2, 8.0 Hz), 4.68 (d, 1H, *J* = 11.6 Hz), 4.61 (d, 1H, *J* = 10.8 Hz), 4.52 (d, 1H, *J* = 10.8 Hz), 4.40 (d, 1H, *J* = 11.6 Hz), 4.02 (dd, 1H, *J* = 7.6, 7.2 Hz), 3.93 (qd, 1H, *J* = 6.4, 6.4 Hz), 3.80 (s, 3H), 3.35 (dd, 1H, *J* = 6.8, 6.4 Hz) 1.22 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 159.5, 137.8, 134.5, 130.5-128.0, 129.2, 129.1, 127.4, 114.0, 84.1, 82.0, 74.5, 70.7, 69.5, 55.5, 19.1.

139Z: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm7.39-7.26 (m, 10H), 7.24 (d, 2H, *J* = 8.4 Hz), 6.86 (d, 2H, *J* = 8.4 Hz), 6.62 (d, 1H, *J* = 9.6 Hz), 5.93 (dd, 1H, *J* = 9.6, 9.2 Hz), 4.74 (d, 1H, *J* = 11.6 Hz), 4.70 (d, 1H, *J* = 11.2 Hz), 4.64-4.59 (m, 1H), 4.53 (d, 1H, *J* = 11.2 Hz), 4.46 (d, 1H, *J* = 11.6 Hz), 3.93 (qd, 1H, *J* = 6.4, 6.4 Hz), 3.80 (s, 3H), 3.48 (dd, 1H, *J* = 6.4, 5.6 Hz), 1.26 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 159.4, 138.2, 135.8, 130.5-128.0, 129.4, 129.2, 127.4, 113.9, 84.3, 77.7, 74.3, 71.0, 69.2, 55.5, 19.4.

3-*O*-Benzyl-4-*O*-(4-methoxybenzyl)-2,6-dideoxy-2-iodo-α/β-D-*allo*-pyranoside (140) and Acetyl 5-*O*-acetyl-3-*O*-benzyl-2,6-dideoxy-2-iodo-α/β-D-*allo*-furanoside (143).



140



143

NIS (137 mg, 0.61 mmol) was added to a solution of the enitol **139** (110 mg, 0.24 mmol) in a CH_3CN/H_2O = 10:1 mixture (4.9 ml) at -10ºC. After stirring for 45 min the reaction was quenched with $Na_2S_2O_3$ and extracted with EtOAc (3 x 20 ml). The combined organic layers were washed with water (2 x 20 ml), brine

(1 x 20 ml), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexane:EtOAc = 4:1) to afford the desired pyranose **140** (30 mg, 0.06 mmol, 25%) as a colourless syrup, and the undesired furanose **141** (50 mg, 0.11 mmol, 42%) as a colourless syrup. The last one was acetylated with Ac_2O/pyridine to give **143** for an easier characterization.

Spectroscopic data from the α/β mixture:

ESI-HRMS *m/z* calcd. for $C_{21}H_{25}INaO_5$ [M-Na]: 507.0644, found: 507.0606.

140β: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.48-7.22 (m, 7H), 6.91 (d, 2H, *J* = 8.0 Hz), 5.14 (d, 1H, *J* = 7.6 Hz), 4.93 (d, 1H, *J* = 11.2 Hz), 4.78 (d, 1H, *J* = 10.4 Hz), 4.63 (d, 1H, *J* = 11.6 Hz), 4.50 (d, 1H, *J* = 11.6 Hz), 4.16-4.09 (m, 1H), 3.98 (dd, 1H, *J* = 8.8, 1.6 Hz), 3.83 (s, 3H), 3.31-3.27 (m, 1H), 3.14 (bs, 1H), 1.26 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 159.7, 138.4-127.8, 114.2, 94.5, 81.3, 78.2, 76.6, 72.2, 69.9, 55.5, 27.1, 18.2.

140α: Could not be determined.

Spectroscopic data from the α/β mixture:

ESI-HRMS *m/z* calcd. for $C_{17}H_{21}INaO_6$ [M-Na]: 471.0281, found: 471.0267.

143α: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.43-7.31 (m, 5H), 6.48 (s, 1H), 5.13 (qd, 1H, *J* = 6.5, 5.8 Hz), 4.57 (d, 1H, *J* = 10.8 Hz), 4.45 (d, 1H, *J* = 5.1 Hz), 4.34 (d, 1H, *J* = 10.8 Hz), 4.11 (dd, 1H, *J* = 7.5, 5.2 Hz), 2.07 (s, 3H), 1.99 (s, 3H), 1.25 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 170.4, 169.2, 136.6, 128.7, 128.5, 103.6, 83.9, 77.4, 72.7, 69.9, 32.3, 21.4, 21.3, 16.3.

143β: Could not be determined.

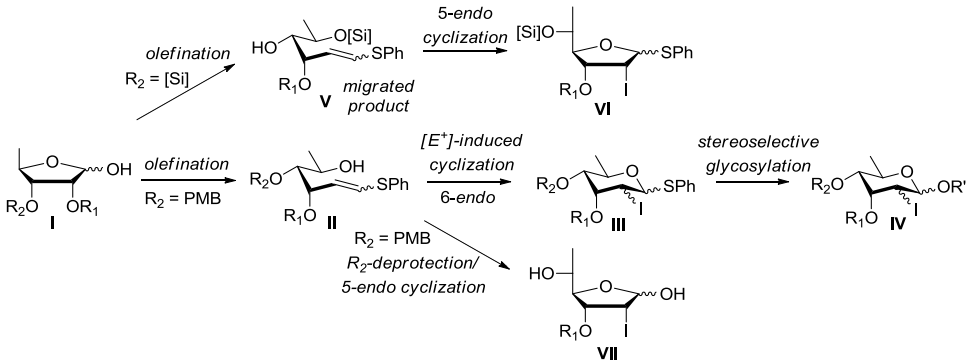
Organocatalytic and Chiral Auxiliary Approaches

CHAPTER 6

1. Introduction

Although the main topics in modern carbohydrate synthesis are associated with manipulation of readily available monosaccharides and synthesis of oligosaccharides, it has been shown in the previous chapter that accessibility to necessary synthons for the synthesis of digitoxin presents difficult access and long synthetic pathways.

The proposed methodology of olefination-cyclization-glycosylation reaction presents some drawbacks (Scheme 69). When the temporary protecting group (R_2) is a silyl ether, a silyl migration process takes place during the WH olefination step and undesirable 5-*endo* cyclization products **VI** are obtained. However, with a *p*-methoxybenzyl (PMB) ether as temporary group (R_2) olefination of corresponding ribose affords the desire alkene **II** with no traces of protecting group migration, but cyclization of alkene **II** furnishes the corresponding furanose **VII** as a consequence of PMB group deprotection and subsequent 5-*endo*-trig cyclization.

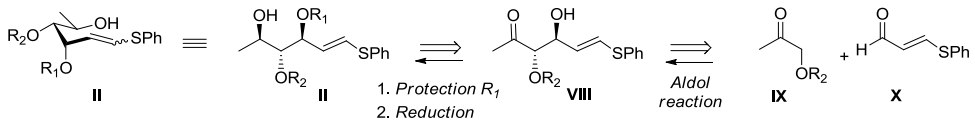


Scheme 69. Proposed methodology and drawbacks for the stereoselective synthesis of digitoxin.

On account of that, we thought in asymmetric synthesis to circumvent these problems as a powerful and easy tool to the enantioselective synthesis of rare sugars.

1.1 New retrosynthetic analysis

Connected with the synthesis of 2-deoxy- and 2,6-dideoxyglycosides, the aim of this work was to develop an alternative procedure for the synthesis of alkenylsulfides of type **II**. We chose benzyl ethers as permanent protecting groups (R_1) and silyl ethers as temporary protecting groups (R_2).



Scheme 70. New retrosynthesis of alkenylsulfides **II**.

We conceived the retrosynthetic analysis of alkenylsulfides **II** as illustrated in Scheme 70. Alkenylsulfides **II** can be obtained by protection and selective reduction of the ketone in intermediate **VIII**, which in turn can come from asymmetric *anti*-aldol reaction of a hydroxyketone **IX** and (*E*)-3-thiophenylacrolein (**X**). We envisioned asymmetric *anti*-aldol reaction through organocatalysis and with chiral auxiliaries.

With alkenylsulfides **II** in hand, the synthesis of 2,6-dideoxy-2-iodo-glycosides via electrophilic cyclization-glycosylation reaction developed in our group might be applied avoiding the problems of silyl migration.

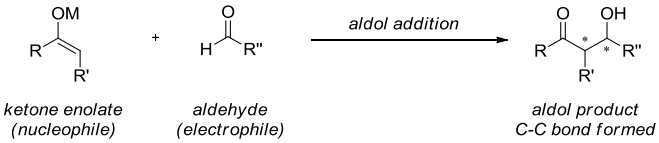
2. Background

Asymmetric synthesis is a ubiquitous catchphrase heard over and over again in the field of organic synthesis. This methodology is important in the field of pharmaceuticals because the different enantiomers or diastereomers of a molecule often present different biological activity (like the case of thalidomide).[211] This fact demands highly efficient methods of asymmetric synthesis to obtain enantiomerically pure compounds. Consequently, the need to expand the repertoire of asymmetric reactions remains a major focus of research today.

[211] a) Annas, G. J.; Elias, S. *Am. J. Public Health* **1999**, *89*, 98-101. b) Botting, J. *Drugs News & Perspectives* **2002**, *15*, 604-611.

2.1 Asymmetric aldol reaction: α-functionalization of aldehydes

The aldol reaction was discovered independently by Wurtz[212] and Borodin in 1872[213] and it combines two carbonyl compounds to form a new β-hydroxy carbonyl compound. These products are known as *aldols*, from the *ald*ehyde + alcoh*ol*, a structural motif seen in many of the products.[214]



Scheme 71. Aldol reaction.

The aldol reaction relies on the selective enolization of a carbonyl compound. The enol subsequently reacts with an acceptor, resulting in the formation of a carbon-carbon bond and up to two chiral centers (Scheme 71). The base-promoted aldol reaction, under the assistance of a stoichiometric amount of a chiral inducer, constitutes a reliable and well-documented technique.

When a trisubstituted enolate is used as the nucleophile, one can either obtain *syn* or *anti* diastereomers. In 1957, Zimmerman and Traxler proposed that some aldol reactions proceed via a six-membered chair-like transition states conformation.[215] Thus, this predicts that *E*-enolates give *anti*-aldol adducts, whereas *Z*-enolates should give *syn*-aldol adducts (Scheme 72). The factors that control selectivity are the preference for placing substituents equatorially in six-membered transition states and the avoidance of 1,3-diaxial interactions.[216] In fact, only some metals such as lithium and boron reliably follow the Zimmerman-

212 Wurtz, C. A. *Bull. Soc. Chim. Fr.* **1872**, *17*, 436-442.

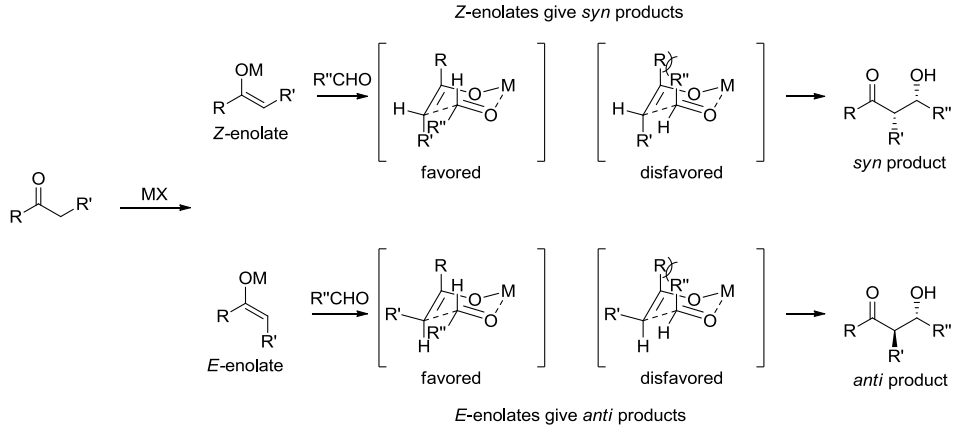
213 Borodin observed the dimerization of acetaldehyde to 3-hydroxybutanal under acidic conditions

214 a) Mukaiyama T. "The Directed Aldol Reaction". *Organic Reactions*; John Wiley & Sons, Inc., **1982**, *28*, 203-331. b) Mestres R. *Green Chem.* **2004**, *12*, 583-603. c) Braun; M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031-5034.

215 Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.

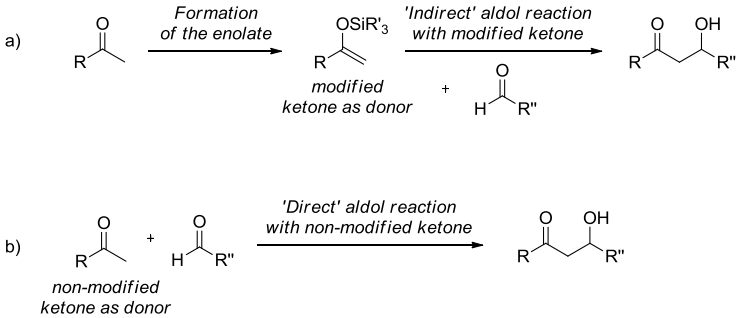
216 Heathcock, C. H.; Buse, C. T., Kleschnick W. A., Pirrung M. C., Sohn J. E., Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081.

Traxler model. In some other cases, the stereochemical outcome of the reaction may be explained through open-transition states.



Scheme 72. Zimmerman-Traxler model.

Asymmetric aldol reactions are classified into 'indirect' and 'direct aldol reactions'. 'Indirect aldol reactions' are syntheses which require a modified ketone as a starting material (Scheme 73a). For example, enolates which are prepared in a previous step starting from the ketone are often used. Syntheses which allow the 'direct' use of the ketone, in a non-activated form, as a nucleophile are defined as 'direct aldol reactions' (Scheme 73b).



Scheme 73. Classification of aldol reactions into (a) 'indirect aldol reactions' and (b) 'direct aldol reactions'.

2.1.1 Organocatalytic aldol reaction

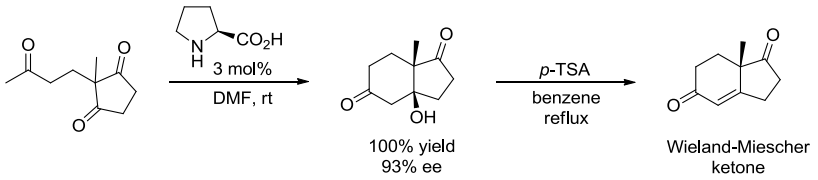
Traditionally, asymmetric catalysis was divided into two parts: metal-based and enzymatic catalysis. These two approaches are well established methodologies and good selectivities are obtained in many reactions. Recently, a new area named organocatalysis has emerged.[217] In organocatalysis, a relatively small organic molecule is applied as the catalyst; often, the amino acid proline or derivatives are used.

Organocatalysts have several advantages. They are usually robust, inexpensive, readily available and non-toxic. Many of the catalysts in the organocatalysis tool box are acquired from the chiral pool, so highly diverse structural features are accessible. Because of their inertness toward moisture and oxygen, demanding reaction conditions, for example inert atmosphere, low temperatures, dry solvents, etc., are, in many instances, not required. These properties allow most reactions to be performed in wet solvent and in air, which increases the reproducibility and operational simplicity. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds which do not tolerate metal contamination, e.g. pharmaceutical products. However, organocatalysis also suffers from several drawbacks. These are mainly related to the high catalyst loadings applied, the necessary long reaction times, and the need to have a particular starting material in excess to drive the reaction to completion.

For all these reasons, enantioselective organocatalysis has become a field of central importance within asymmetric chemical synthesis. In this field, the concept of using chiral amines to effect asymmetric bond formations has resulted in two extraordinarily powerful, and complementary, generic activation platforms. Over the last 10 years, iminium and enamine catalysis have grown from a handful of unique reactions to over 70 widely applicable enantioselective transformations, enabling unprecedented access to a host of chiral molecules.

[217] List, B. *Chem. Rev.* **2007**, *107*, 5413-5415.

In the early 1970s, the first asymmetric organocatalytic reaction was accredited to the groups of Hajos[218a] and Wiechert,[218b] who independently published the first highly enantioselective intramolecular proline-catalyzed aldol reaction in their approach toward the Wieland-Miescher ketone (Scheme 74).[219]



Scheme 74. Hajos and Wiechert's proline-catalyzed asymmetric aldol reaction.

Despite this breakthrough, it took about 30 years before the concept of organocatalysis won widespread recognition in the organic chemistry community.[220] Nowadays there are various different catalytic systems in organocatalysis, such as cinchona-alkaloid catalyst such as quinine,[221] carbine-catalyst,[222] guanidine-catalyst,[223] phase-transfer catalyst,[224] bifunctional-thiourea catalyst[225] (hydrogen-bond donor catalyst),[226] Brønsted-base catalyst,[227] Brønsted-acid catalyst,[228] small peptide catalyst,[229] nucleophile catalyst[230] and

218 a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621. b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496-497.

219 Bui, T.; Barbas III, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951-6954.

220 Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 42-47.

221 a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057-4060. b) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166-168. For reviews, see c) Kacprezak, K.; Gawroński, J. *Synthesis* **2001**, 961-998. d) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985-3012. e) Hoffmann, H. M. R.; Franckenpohl, J. *Eur. J. Org. Chem.* **2004**, 4293-4312.

222 Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606-5655.

223 Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454-1455.

224 Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656-5682.

225 a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187-1198. b) Connon, S. J. *Synlett* **2009**, 354-376.

226 Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743.

227 Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632-653.

228 Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744-5758.

229 Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759-5812.

230 Mermerian, A. H.; Fu, G. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 949-952.

aminocatalyst (chiral secondary amino catalyst).[231] The molecular structures of the mentioned organocatalysts and some additional representative ones are shown in Figure 18.

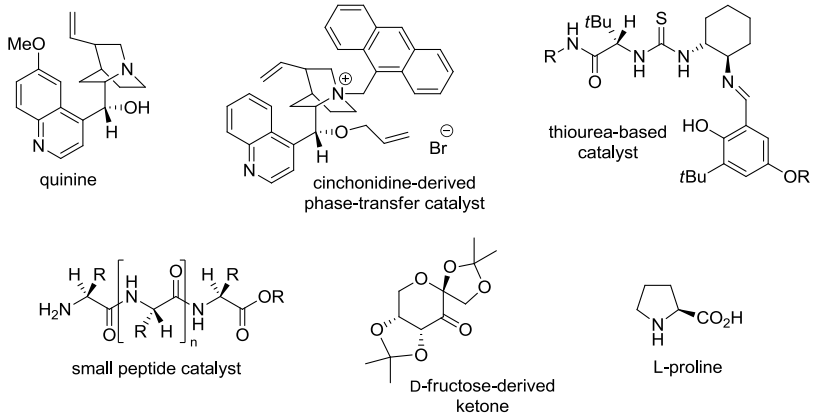


Figure 18. Molecular structure of some representative organocatalysts.

Organocatalysts can be classified in two categories depending on typical interactions between organic molecules. A general distinction can be made between processes that involve the formation of covalent adducts between catalyst and substrates within the catalytic cycle and processes that rely on noncovalent interactions such as hydrogen bonding or the formation of ion pairs (Figure 19).

The formation of covalent substrate-catalyst adducts might occur, e.g., by single step Lewis acid-Lewis base interaction or by multi-step reactions such as the formation of enamines from aldehydes and secondary amines.[231e]

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231 a) Bertelsen, S., Jørgensen, K. A. *Chem. Rev. Soc.* **2009**, *38*, 2178-2189. b) Dalko, P. L.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175. c) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, Germany, 2005. d) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719-724. e) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, B. *Drug Discovery Today* **2007**, *12*, 8-27. g) Dalko, P. I; Ed. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, Germany, **2007**. h) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267-9331. i) Jaroch, S.; Weinmann, H.; Zeitler, K. *ChemMedChem* **2007**, *2*, 1261-1264. j) Reetz, M. T.; List, B.; Jaroch, S.; Weinmann, H.; Eds. *Organocatalysis*; Springer, Heidelberg, Germany, **2008**. k) Denmark, S.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560-1638. l) Melchiore, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138-6171. m) Dondoni, A.; Massi, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638-4660. n) MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308. o) List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730-1734.

In many instances non-covalent catalysis relies on the formation of hydrogen-bonded adducts between substrate and catalyst or on protonation/deprotonation processes. Phase-transfer catalysis (PTC) by organic phase-transfer catalysts also falls into the category of 'non-covalent catalysis'.[232]

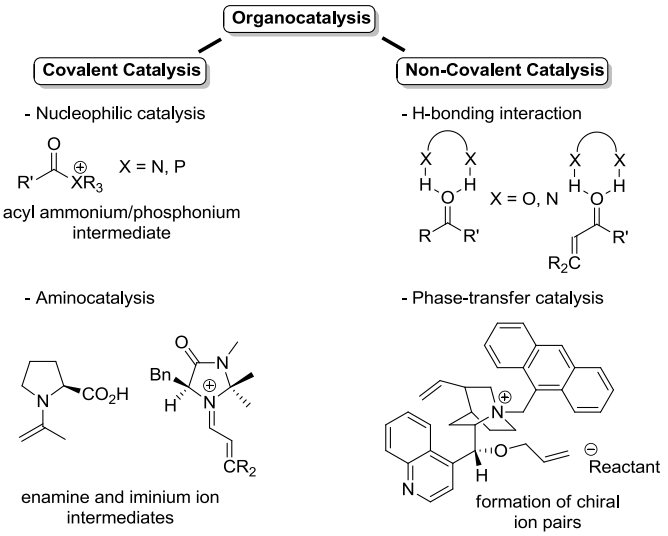


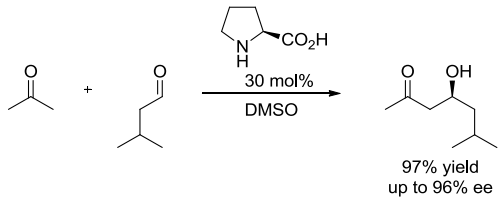
Figure 19. Organocatalysis classification into 'covalent catalysis' or 'non-covalent catalysis'.

A decade ago, the groups of List and Barbas ushered in the new era of organocatalysis with their contributions to the aldol[233] (Scheme 75) and the later Mannich[234] reactions. Since their seminal investigations in the early 2000's the field of organocatalysis has almost exploded. In particular, new methodologies for introducing heteroatoms stereoselectively to the α-position of aldehydes have been studied.

232 a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. b) Unni, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 1336-1337. c) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094-12095.

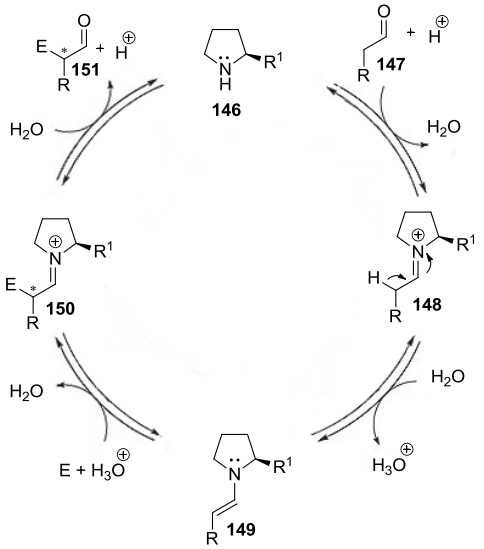
233 List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

234 List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336-9337.



Scheme 75. Aldol reaction by List and Barbas.

In 2000, List and Barbas suggested a mechanism for the organocatalytic aldol reaction involving a Zimmerman-Traxler type transition state.[215] After intense studies, this proposal was refined and the nowadays generally accepted mechanism is outline in Scheme 76. For reasons of clarity a generalized chiral secondary amine **146** is drawn as catalyst.



Scheme 76. General catalytic cycle for pyrrolidine-catalyzed α-functionalization of aldehydes (E = Electrophile).

The generalized mechanism for α-functionalization of aldehydes can be described as follows:[235] the catalytic cycle is initiated by condensation of catalyst **146** (typically a pyrrolidine derivative) and aldehyde **147**, which leads to a nucleophilic enamine intermediate **149**. In the second step, the enamine attacks an electrophile generating iminium ion **150**. Hydrolysis releases the functionalyzed

[235] List, B. *Chem. Commun.* **2006**, 819-824.

product **151** and the catalyst **146**, which reenters the catalytic cycle. In order to accelerate the catalytic cycle an acidic co-catalyst,[236] such as benzoic acid, or the addition of water[237] has often been employed and has proven to be beneficial.

Mechanistic studies by Houk's and Jørgensen's groups suggested that the stereoinduction can be controlled by at least two different ways, as outlinedin Figure 20.[238] In theory, several different isomers of enamines can be formed; however the *trans*-enamine constitutes the most stable form. When proline and its derivatives are employed as catalysts, the enamine conformation is highly controlled and reacts as follows: if the catalyst possesses a substituent which is able to form hydrogen-bond with the electrophile, *Re*-face attack is favoured (Figure 20a). In contrast, if the catalyst bears a sterically demanding substituent, the *Re*-face is blocked and attack occurs from the *Si*-face (Figure 20b).

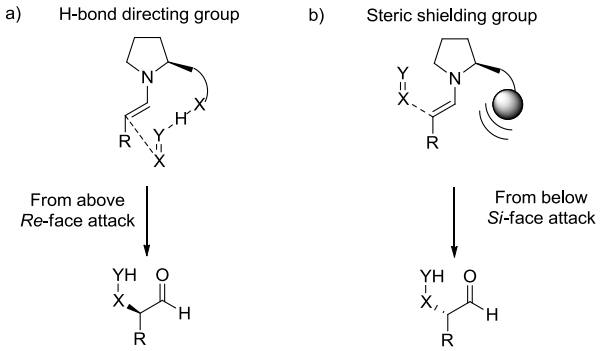


Figure 20. H-bond vs. steric shielding of enamine intermediates.

[236] a) Poe, S. L.; Bogdan, A. R.; Mason, B. P.; Steinbacher, J. L.; Opalka, S. M.; McQuade, D. T. *J. Org. Chem.* **2009**, *74*, 1574-1580. b) Bella, M.; Schietroma, D. M. S.; Cusella, P. P.; Gasperi, T.; Visca, V. *Chem. Commun.* **2009**, 597-599. c) Zotova, N.; Broadbelt, L. J.; Armstrong, A.; Blackmond, D. G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3934-3937.

[237] For recent discussions on water in organocatalysis, see: a) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 4288-4297. b) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33-57.

[238] a) Houk, K. N.; Cheong, P. H.-Y. *Nature* **2008**, *455*, 309-313. b) Dinér, P.; Kjærsgaard, A.; Lie, M. A.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 122-127.

Reactions performed with poly-substituted *N*-heterocyclic catalysts are less predictable and generally lower stereocontrol is observed. One explanation might be a diminished energy-difference between the *cis*- and *trans*-enamines.[239]

Carbohydrate synthesis via organocatalysis

The directed asymmetric assembly of simple achiral building blocks into stereochemically complex molecules like carbohydrates and polyketides has long been accomplished by enzymes in nature.[240] Like enzymes, organocatalysts can effectively catalyze aldol addition reactions providing donors for the direct coupling of aldehyde and ketone to various aliphatic and aromatic acceptors with excellent stereoselectivities. Related to that, stereoselective total synthesis of rare sugars is a challenging and practically important task.

Different carbohydrates can be accessed using only organocatalytic procedures or combined organocatalytic and Mukaiyama processes. The proline-catalyzed aldol reaction has recently paved the way for the direct assembly of carbohydrates.[241]

Enamine-catalyzed enantioselective aldol reactions were further elaborated by MacMillan and co-workers to generate a two-step carbohydrate synthesis based on the enamine-catalyzed aldol dimerization of α-oxyaldehydes, followed by a Mukaiyama-aldol-cyclization event. This protocol generated a series of differentially substituted hexoses in high yield, with excellent levels of diastereoselectivity and enantiopurity (Scheme 77).[242]

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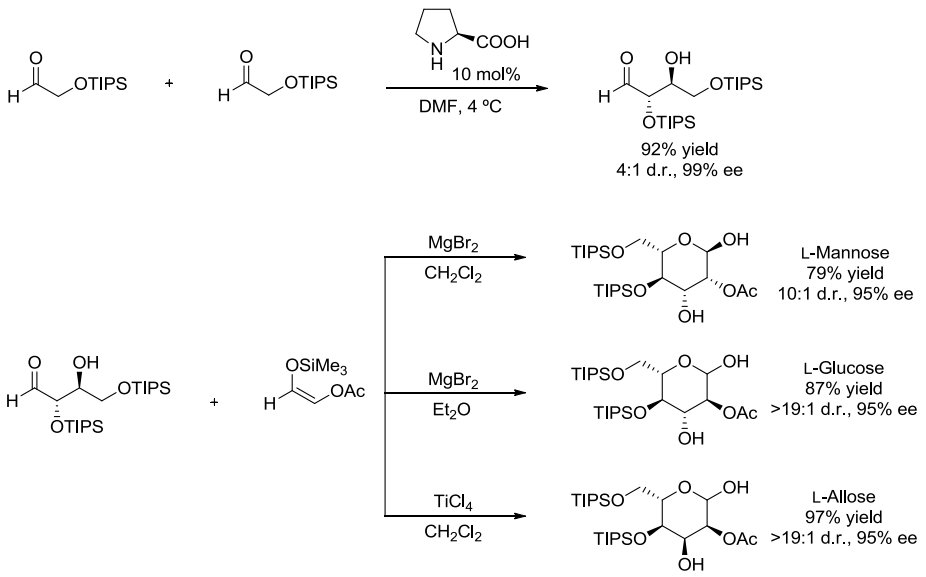
239 Chowdari, N. S.; Barbas III, C. F. *Org. Lett.* **2005**, *7*, 867-870.

240 a) Khosla, C. *J. Org. Chem.* **2000**, *65*, 8127-8133. b) Khosla, C.; Harbury, P. B. *Nature* **2001**, *409*, 247-252. c) Wu, N.; Kudo, F.; Khosla, C.; Cane, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 4847-4852. d) Boddy, C. N.; Hotta, K.; Tse, M. L.; Watts, R. E.; Khosla, C. *J. Am. Chem. Soc.* **2004**, *126*, 7436-7437, and references therein.

241 For a review see: Kazmaier, U. *Angew. Chem. Int. Ed.* **2005**, *44*, 2186-2188.

242 a) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752-1755. b) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152-2154. c) For a use in synthesis, see: Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696-3697.



Scheme 77. MacMillan's two-step organocatalytic carbohydrate synthesis.

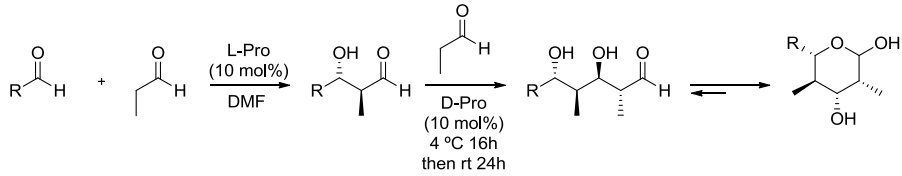
The best results were obtained with silylprotected aldehyde derivatives. However, other electron-rich *O*-alkylated derivatives could be converted with good results, whereas electron-withdrawing protecting groups (such as acetyl) suppressed the aldol reaction. These studies highlight the ability of proline to effect the clean and rapid asymmetric synthesis of stereochemically defined complex molecules using simple achiral building blocks.

Since the pioneering work of List and Barbas,[233] an expansion of the enantioselective proline catalyzed aldol began. As an example, aldol reactions between aldehydes and disubstituted dioxanones, useful building blocks, have been developed by several groups, providing a biomimetic asymmetric synthesis of various carbohydrate scaffolds in a fashion analogous to aldolase enzymes.

Cordova et al. were able to carry out MacMillan's concept employing solely proline catalysis.[243] This strategy presented a two-step sugar synthesis involving two direct amino acid catalyzed selective iterative aldol reactions with three carbonyl compounds (Scheme 78). The synthetic protocol furnishes either L- or

[243] Casas, J.; Engqvist, M.; Ibrahem, I.; Kognak, B.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1343-1345.

D-sugars in most cases with > 99% ee and allows the creation of four contiguous stereocenters with excellent stereocontrol.



Scheme 78. Two-step direct amino acid catalyzed enantioselective synthesis of hexoses.

Another approach can be borrowed from mother nature. Nature employs dihydroxyacetone phosphate (DHAP) in carbohydrate biosynthesis. The carbohydrate skeleton is assembled by an enzyme-catalyzed aldol reaction between DHAP and glyceraldehyde.[244]

Hence, the application of DHAP in carbohydrate synthesis has been investigated quite intensively employing biological methods in particular.[245] Furthermore, dihydroxyacetone and its derivatives could be employed as C3 building blocks in asymmetric synthesis using chemical methods.[246] The application of organocatalytic methods were first reported by Barbas et al. They described a direct aldol reaction of dihydroxyacetone with various aldehydes, catalyzed by proline or derivatives of the latter, but generally with moderate diastereoselectivities and low enantioselectivities.[247]

Enders investigated aldol reaction of dioxanone (the simplest ketose derivative) catalyzed by L-proline with the aim of synthesis of carbohydrates (Scheme 79).[248]

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244 Calvin, M. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 65-75.

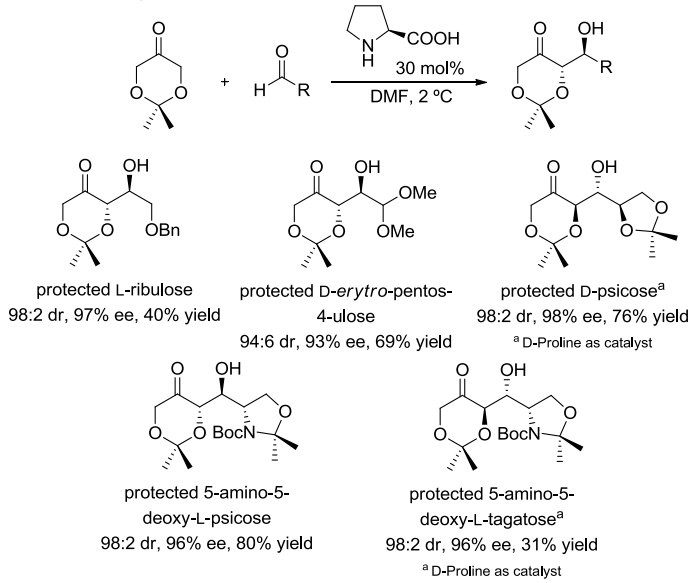
245 a) Fessner, W.- D. *Modern Aldol Reactions*; Mahrwald, R., Ed.; *Enolates, Organocatalysis, Biocatalysis and Natural Product Synthesis*; Wiley-VCH: Weinheim, **2004**; Vol. 1. b) Wong, C.- H.; Machajewski, T. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352-1375. c) Fessner, W.- D.; Walter, C. *Top. Curr. Chem.* **1996**, *184*, 97-194. d) Takayama, S.; McGarvey, G.- J.; Wong, C.- H. *Chem. Soc. Rev.* **1997**, *26*, 407-415.

246 Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1304-1325.

247 a) Córdova, A.; Notz, W.; Barbas, C. F., III *Chem. Commun.* **2002**, 3024-3025. b) Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas III, C. F., *J. Org. Chem.* **2006**, *71*, 3822-3828.

248 Enders, D.; Grondal, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1210-1212.

Stereoselective synthesis of simple protected ketose derivatives was accomplished. Organocatalysis provided a simple and direct approach to differently protected carbohydrates practically in one step, with high selectivities (88-96% dr, 93-98% ee).



Scheme 79. L-Proline-catalized aldol reaction of dioxanone towards the synthesis of carbohydrates.

All these organocatalytic methods towards the synthesis of carbohydrates afford unprotected or partially monoprotected sugars, which are not suitable for subsequent orthogonal synthetic steps.

2.1.2 Chiral auxiliary-mediated aldol reaction

The asymmetric aldol addition mediated by chiral auxiliaries is another of the most important and general methods for asymmetric carbon-carbon bond formation.[249] These methods work by temporarily creating a chiral enolate by appending a chiral auxiliary. The pre-existing chirality from the auxiliary is then transferred to the aldol adduct by performing a diastereoselective aldol reaction.

[249] a) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917-947. b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3-12. c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835-876.

Upon subsequent removal of the auxiliary, the desired aldol stereoisomer is revealed. Of the numerous chiral auxiliaries that have been developed over the past years some of the effectively applied auxiliaries are shown in Figure 21. The majority of chiral auxiliaries are derived from inexpensive, chiral natural sources and most of the diastereoselective reactions reported proceed with high levels of diastereoselection. The most widely employed auxiliary controlled reactions are the asymmetric alkylations, aldol and Diels-Alder reactions.

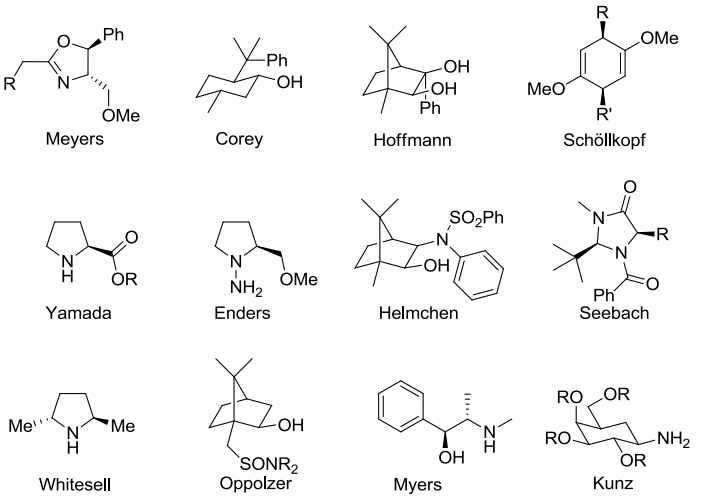


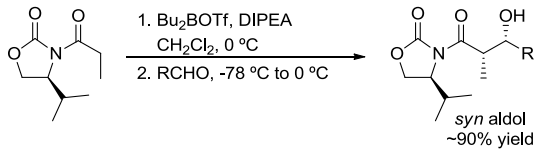
Figure 21. Selected chiral auxiliaries which have been successfully applied in asymmetric synthesis.

A widely used method is the Evans' acyl oxazolidinone method.[250] Developed in the late 1970s and 1980s, the boron-mediated aldol reaction of N-acyl oxazolidinones with aldehydes to give *syn* aldol products constitutes one of the best aldol bond construction processes (Scheme 80).[251] Conceptually, this development consists of the irreversible and quantitative generation of the *Z*-enolate that reacts with an aldehyde, presumably through a well ordered six-membered chair-like "Zimmerman-Traxler" model, to afford essentially only one diastereomeric aldol product out of four possible isomers.

250 a) Evans D. A. *Aldrichim. Acta* **1982**, *15*, 23-32. b) Gage J. R.; Evans D. A. *Org. Synth.* **1990**, *68*, 83-86; **1993**, Coll. Vol. *8*, 339-342.

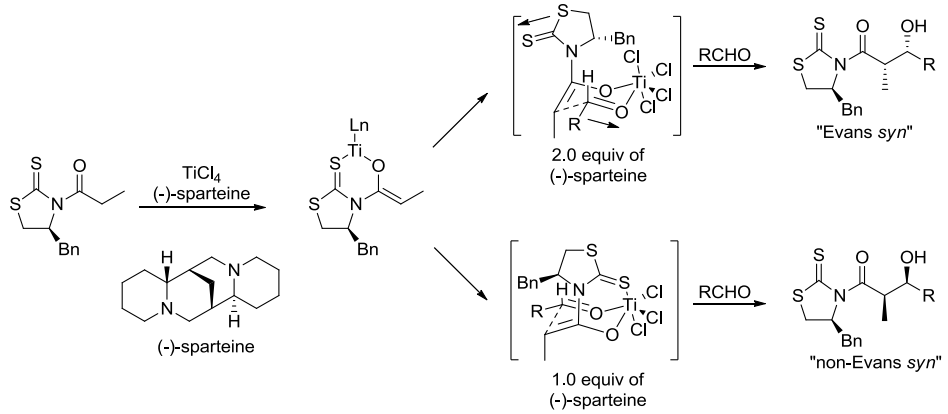
251 Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, 103, 2127-2129.

The re-usable chiral auxiliary can be efficiently recovered from the aldol adducts and the method offers a convenient access to each *syn*-isomer by simply choosing the appropriate commercially available chiral source.



Scheme 80. Boron-mediated aldol reactions of *N*-acyl 2-oxazolidinones and aldehydes to give *syn*-aldol products.

A more recent version of the Evans' auxiliary is the Crimmins thiazolidinethione.[252] This approach provides both the "Evans *syn*" and "non-Evans *syn*" from the same source of chiral information as a result of a stereodivergent control of the reaction stereochemistry by adjusting the amount of $TiCl_4$, and the amount and nature of the amine base (Scheme 81).



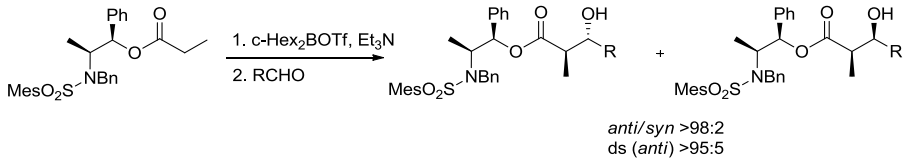
Scheme 81. Stereodivergent Crimmins thiazolidinethione aldol reaction to both *syn*-aldols from the same substrate reagent.

Use of two equivalents of sparteine produces the "Evans *syn*" isomer. Excess of base prevents coordination of the titanium center to the thiocarbonyl of the auxiliary and therefore the reaction proceeds through a TS analogous to that

[252] a) Crimmins M. T.; King B. W., Tabet A. E. *J. Am. Chem. Soc.* **1997**, *119*, 7883-7884. b) Crimmins M. T.; Chaudhary K. *Org. Lett.* **2000**, *2*, 775-777.

described for Evans' oxazolidinones where facial induction and steric interaction is determined by minimization of dipols.[251] When less base is employed, the thiocarbonyl coordinates to the titanium and exposes the transition state of the reaction to a different stereoface of the auxiliary giving the opposite isomer, the "non-Evans *syn*". Of practical importance, the reaction works efficiently at temperatures as high as 0ºC and with just one equivalent of the aldehyde substrate. The reaction is believed to proceed via six-membered, titanium-bound transition states, analogous to the proposed transition states for the Evans' auxiliary.

Despite these advances, two long standing problems associated with the aldol addition reaction in general, and the chiral auxiliary-mediated methodologies in particular, are the production of *anti* aldol products. Here, the main problem arises from the fact that *E*-configured enolates, needed in the closed transition state to give the *anti* products, are not favored. Thus, one important future direction of organic chemistry is the development of practical and inexpensive reagents which induce preferential formation of *E*-enolates.



Scheme 82. Norephedrine-derived propionate ester designed for *E*-enolate generation en route to *anti*-aldols.

One potential class of such reagents was presented by Abiko and Masamune starting from the commercially available (-)-norephedrine (Scheme 82).[253] Under optimized conditions, the boron *E*-enolate of propionate ester is obtained exclusively which subsequently reacts with a broad range of aldehyde substrates, including aliphatic, aromatic, α,β-unsaturated, and functionalyzed aldehydes, to afford *anti*:*syn* aldols in up to 99:1 selectivity ratio.

[253] a) Abiko, A.; Liu, J.- F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586-2587. b) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387-395.

The benefits derived from the use of chiral auxiliary-mediated strategies are slighty narrowed as there is the need for extra operational steps, such as the attachment/detachment of the covalently bound auxiliary from the adduct. Nevertheless, the high reliability of these methods with their often broad substrate tolerances and other practical advantages (e.g. product isolation/purification) often outweigh the above limitations.

3. Results and discussion

3.1 Organocatalytic reactions

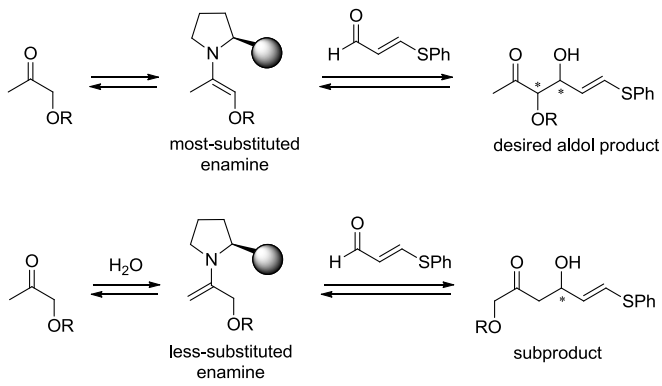
Organocatalysis presents the advantages of readily available organocatalysts for the aldol reaction, as well as simple and easy to handle operations. However, different reaction parameters should be controlled in advance in order to obtain the desire stereoselectivity:

- The most substituted enamine is needed to be formed in preference to the less-substituted enamine (Scheme 83). For this purpose, reaction conditions must be controlled. Water cannot be added to the reaction mixture because it is known to force the reaction to occur preferentially at the less substituted position. However, these reactions are usually carried out with some amount of water or with non anhydrous solvent.[254]
- The *E*-enamine is needed to afford the *anti*-aldol product, which provides the synthon with the appropriate stereochemistry for the synthesis of digitoxin (Scheme 84). Nevertheless, *E*-enamines are usually obtained from cyclic ketones,[247b,255] which cannot be used to obtain the desire synthons in this synthesis.

---

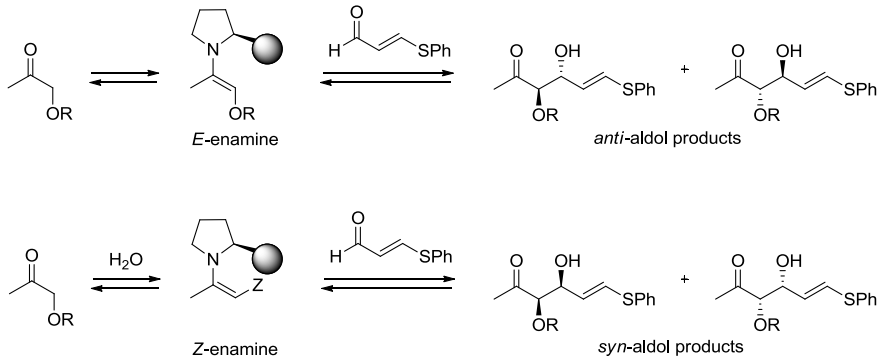
[254] The addition of water to organocatalytic reactions has often been shown to increase reaction rates and/or selectivities. For some examples see: a) Notz, W.; Tanaka, F.; Watanabe, S.- I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas III, C. F. *J. Org. Chem.* **2003**, *68*, 9624-9634. b) Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas III, C. F. *Tetrahedron Lett.* **2004**, *45*, 325-328. c) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 958-961. d) Chen, X.; Luo, S.; Tang, Z.; Cun, L.; Mi, A.; Jiang, Y.; Gong, L. *Chem. Eur. J.* **2007**, *13*, 689-701. e) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957-959. f) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 1983-1986.

[255] a) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329-337. b) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.- P. *J. Am. Chem. Soc.* **2007**, *129*, 3074-3075.

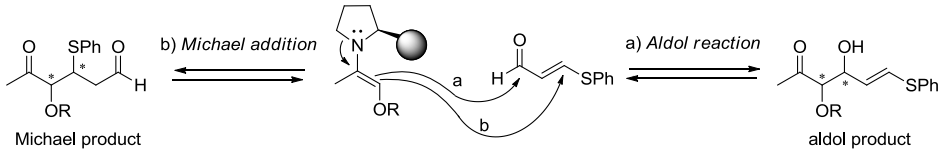


Scheme 83. Aldol reaction through the most- and less- substituted enamines.

- Moreover the reaction must be regioselective, and the enamine should attack the carbonyl carbon and not the β-carbon of the unsaturated aldehyde (Scheme 85). However, enamines are known to be good donors for Michael reactions and unsaturated aldehydes are usually poor reactive aldol acceptors.[255a]



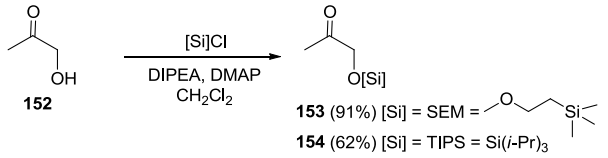
Scheme 84. Formation of the *anti*- and *syn*-aldol products from the *E*- and *Z*-enamines.



Scheme 85. Chemoselection: aldol reaction (a) vs. Michael addition (b).

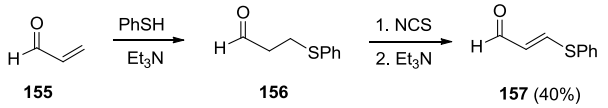
With all these obstacles in mind, first of all we decided to prepare the starting materials for the aldol reaction. As designed in the retrosynthetic analysis section, silyl-based protecting groups were chosen as the appropiated protecting groups

for R_2 in hydroxyketones. With this purpose, hydroxyacetone (**152**) was protected with 2-(trimethylsilyl)ethoxymethyl (SEM) and triisopropylsilyl (TIPS) ethers obtaining protected ketones **153** and **154** with 91% and 62% yield, respectively (Scheme 86).



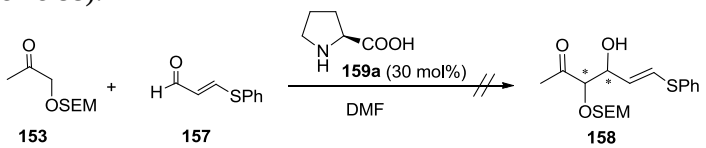
Scheme 86. Synthesis of protected ketones **153** and **154**.

The aldol acceptor (*E*)-3-thiophenylacrolein (**157**) was prepared from acrolein (**155**) according to Heathcock's work with an overall yield of 40% (Scheme 87).[256] Alternatively, propynol was attempted to be oxidised to propynal with different oxidizing agents such as CrO_3/H_2SO_4,[257a] PivCl/DMSO,[257b] or RuO_2/ZSM-5[257c] but we did not succeed in isolating the aldehyde, probably due to its volatility.



Scheme 87. Synthesis of (*E*)-3-thiophenylacrolein (**157**).

L-Proline-catalyzed *anti*-aldol reaction of ketone **153** and aldehyde **157** in DMF at 0ºC did not lead to any conversion, neither did increasing the temperature to 40ºC (Scheme 88).



Scheme 88. L-Proline-catalyzed aldol reaction of ketone **153** and aldehyde **157**.

We next explored the use of different proline derivatives as organocatalysts for the *anti*-aldol reaction of donors **153** and **154** with aldehyde **157**. The design of

256 Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173-181.

257 a) Veliev, M. G.; Guseinov, M. M. *Synthesis* **1980**, *6*, 461. b) Dubey, A.; Kandula, S. R. V.; Kumar, P. *Synth. Commun.* **2008**, *38*, 746-753. c) Qian, G.; Zhao, R.; Lu, G.; Qi, Y.; Suo, J. *Synth. Commun.* **2004**, *34*, 1753-1758.

new organocatalysts has been focused on the introduction of tunable hydrogen-bonding donor groups or sterically demanding substituents preserving the molecular scaffold created by nature as a central design element (Figure 22). A series of modifications of the structure of proline was accomplished by different research groups, who aimed mainly improving the solubility and/or enhancing the acidity of the directing acid proton.

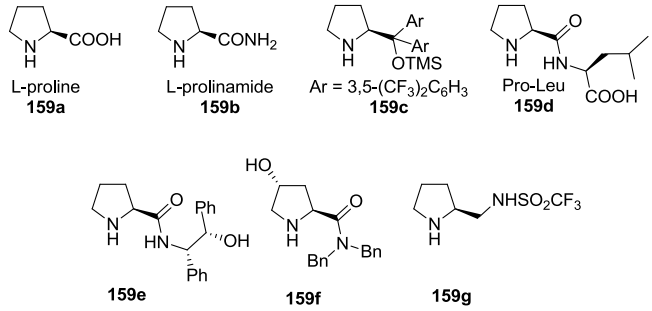


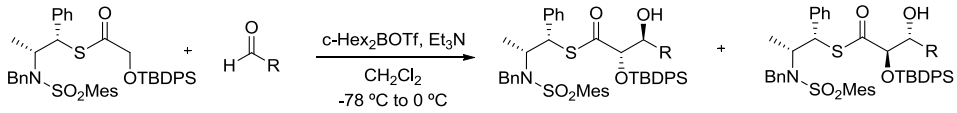
Figure 22. Catalysts screened for the aldol reaction.

Reactions were performed with 1.0 equiv of aldehyde **157**, 1.2 equiv of ketone (**153** or **154**), 30 mol % of L-proline (**159a**) or derivatives **159b-g** as catalysts using DMF or THF as solvents, beginning at 0ºC and letting the reaction mixture reach room temperature. None of these experiments gave any conversion neither with SEM-protected hydroxyacetone **153** nor with the simpler TIPS-protected **154**, and starting materials were recovered in all cases.

It is obvious from the previous results that our starting materials in the aldol reaction present low reactivity in the conditions studied. The reactants chosen do not seem to be the suitable to carry out this aldol reaction. The null reactivity of the reactants makes it clear the need for a change in the form of the starting materials. On one hand, a protected dihydroxyacetone as an aldol donor could be used in order to force the formation of only one enamine, followed by deoxygenation. In addition, a different aldol acceptor like dimethoxyacetaldehyde should also be considered in order to mask the double bond functionality.

3.2 Chiral auxiliary-based reactions

We next focused our attention in chiral auxiliary-based methodologies in which a chiral auxiliary is attached to the achiral substrate to induce chirality during the aldolization step. We focused in those methods for the selective synthesis of *anti* aldol adducts from glycolate enolates. Two chiral auxiliaries were selected for boron-mediated aldol reactions. The first one was the thiol alternative of the Abiko-Masamune norephedrine-derived chiral auxiliary **188** (Scheme 91) developed by Hulme[258]. This auxiliary had been used in the *anti* glycolate aldol reaction of different protected thiolesther such as methyl, benzyl or TBDPS, and a range of aromatic and aliphatic aldehydes in high yields (>75%) and high diastereoselectivities (88:12 to 97:3) (Scheme 89).[258a] However, although few unsaturated aldehydes had been used in this reaction, (*E*)-3-thiophenylacrolein (**157**) had not been applied. On the other hand, this auxiliary may be displaced by a range of nucleophiles (including hydride, hydroxide, methoxide, thiols, and phosphonate anions) under very mild conditions.



160

161 R = Ph
162 R = $(OCH_2O)Ph$
163 R = $CH(CH_3)_2$
164 R = $CH_2CH(CH_3)_2$
165 R = $C(CH_3)=CH_2$

166a 75%, *anti:syn* = 97:3, ds(*anti*) = 92:8 **166b**
167a 85%, *anti:syn* = >98:2, ds(*anti*) = 94:6 **167b**
168a 77%, *anti:syn* = >98:2, ds(*anti*) = 88:12 **168b**
169a 87%, *anti:syn* = >98:2, ds(*anti*) = 97:3 **169b**
170a 89%, *anti:syn* = >98:2, ds(*anti*) = 93:7 **170b**

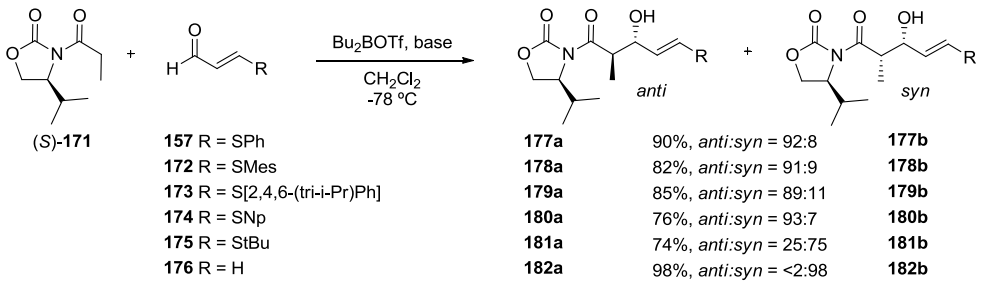
Scheme 89. *Anti-g*lycolate aldol reactions of TBDPS-protected thiolester **160** done by Hulme.[258a]

The second type of chiral auxiliary selected for the *anti* aldol reaction was Evan's oxazolidinone **194** used by Heathcock[256] which can be cleavaged through many methods.[259] Although this methodology had been applied to several 3-thiopropenals as acceptors (Scheme 90), only propionate oxazolidinones had been used as donors, thus being a challenge its application to glycolate aldol reaction. Moreover, the (*R*)-enantiomer of the oxazolidinone used by Heathcock should be

[258] a) Fanjul, S.; Hulme, A. N. *J. Org. Chem.* **2008**, *73*, 9788-9791. b) Fanjul, S.; Hulme, A. N.; White, J. W. *Org. Lett.* **2006**, *8*, 4219-4222.

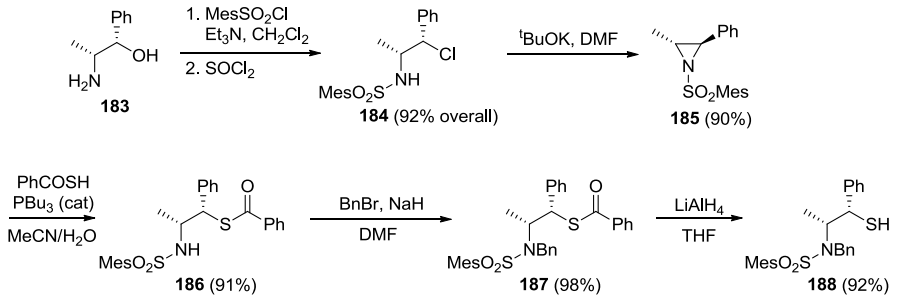
[259] Evans, D. A.; Bender S. L., Morris J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.

employed in our route in order to obtain the opposite *anti* diastereomer which is needed to the synthesis of digitoxin.



Scheme 90. *Anti*-propionate aldol reactions of oxazolidinone **171** done by Heathcock.[256]

Initially the chiral auxiliaries were prepared as described by the authors. Hulme et al. developed a high-yielding route to **188** (Scheme 91). (1*S*,2*R*)-(+)-Norephedrine (**183**) was converted into its mesitylene sulfonamide,[253] and subsequent treatment with thionyl chloride gave alkyl chloride **184** with net retention of stereochemistry.[260] The chloride was converted into aziridine **185**, which was opened regio- and stereoselectively (>95:5) with thiolbenzoic acid in the presence of catalytic PBu_3.[261] Treatment of thiolbenzoate **186** with benzyl bromide and sodium hydride gave benzyl sulfonamide **187** exclusively. Reduction of the thiolbenzoate using $LiAlH_4$ gave the thiol auxiliary **188** in excellent yield.

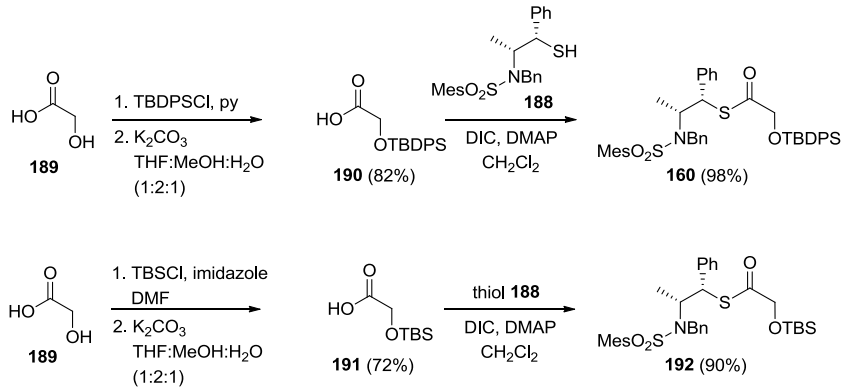


Scheme 91. Synthesis of the thiol analogue of the Abiko-Masamune auxiliary **188**.

260 Flores-Parra, A.; Suarez-Moreno, P.; Sanchez-Ruiz, S. A.; Tlahuextl, M.; Jaen-Gaspar, J.; Tlahuext, H.; Salas-Coronado, R.; Cruz, A.; Noth, H.; Contreras, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1661-1672.

261 Fan, R.- H.; Hou, X.- L. *J. Org. Chem.* **2003**, *68*, 726-730.

The preparation of TBDPS- and TBS-protected glycolate thiolesters **160** and **192** was carried out from glycolic acid **189** (Scheme 92). Protection of the hydroxy groups in **189** with the corresponding silyl chlorides and selective deprotection of the silyl esthers gave rise to protected glycolic acids **190** and **191**. These acids were coupled with thiol auxiliary **188** by a DIC/DMAP to afford TBDPS- and TBS-protected glycolate thiolesters **160** and **192** in excellent yields.[258a]

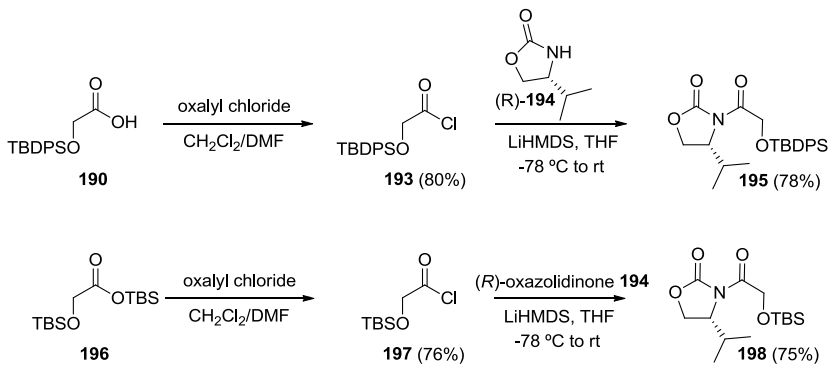


Scheme 92. Preparation of TBDPS- and TBS-protected glycolate thiolesters **160** and **192**.

N-acetyl oxazolidinones **195** and **198** were prepared as shown in Scheme 93. (*Tert*-butyldiphenylsilyloxy)acetic acid (**190**) and (*tert*-butyldimethylsilyl (*tert*-butyldimethylsilyloxy)acetate (**196**) were converted into the acyl chlorides **193** and **197** by treatment with oxalyl chloride.[262] The corresponding acid chlorides **193** and **197** were coupled with (*R*)-oxazolidinone **194** using Evans' procedure[263] in 78% and 75% yield, respectively.

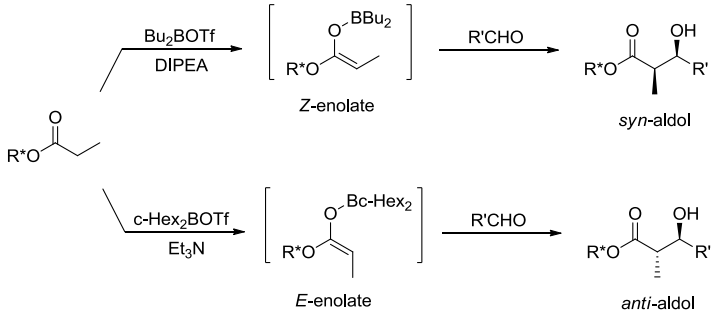
[262] Glabe, A. R; Sturgeon, K. L.; Ghizzoni, S. B.; Musker, W. K.; Takahashi, J. N. *J. Org. Chem.* **1996,** *61,* 7212-7216.

[263] Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110,* 1238-1258.



Scheme 93. Preparation of TBDPS- and TBS-protected *N*-acetyl oxazolidinones **195** and **198**.

Initial investigations focused on the boron aldol reaction of the TBDPS-protected glycolate thiolester **160**. Abiko and Masamune reported that selective enolization may be achieved in the boron-mediated aldol reaction of the norephedrine-derived auxiliary through the appropriate choice of the reagents, thus leading to either *anti*- or *syn*-aldol adducts.[253] The formation of *anti*-aldol adducts is controlled by the presence of bulky ligands on the boron [(c-Hex)$_2$BOTf] and the addition of Et_3N at low temperatures to form the kinetic *E*(*O*)-enolate. On the other hand, the combination of Bu_2BOTf and DIPEA leads to the predominant formation of the *syn*-aldol products (Scheme 94).

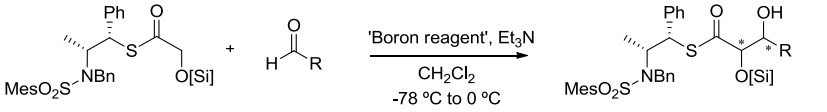


Scheme 94. Stereoselective aldol reaction.

Thus, the optimized conditions for *anti* diol production determined by Hulme (c-Hex$_2$BOTf, EtN_3, CH_2Cl_2) were aplied to TBDPS-protected glycolate thiolester **160** and (*E*)-3-thiophenylacrolein (**157**) but no reaction took place and starting materials were recovered (Table 14, entry 1). With the suspition that c-Hex$_2$BOTf

was decomposed, the glycolate aldol reaction of thiolester **160** was tested with benzaldehyde (**161**) as model substrate in order to reproduce the reaction described by Hulme[258] (Table 14, entry 2). Once again the reaction did not occur. Analysis of commercially available c-Hex_2BOTf[264] revealed the product as a two face immiscible liquid when it should be a solid (as said in its MSDS). c-Hex_2BOTf was attempted to be prepared in the laboratory following Abiko's procedure[265] without success due to the high air sensitivity of the product.

Table 14. Glycolate aldol reaction of protected thiolesters **160** and **192**.



160 [Si] = TBDPS
192 [Si] = TBS

157 R = SPh
161 R = Ph

166 R = Ph, [Si] = TBDPS
199 R = SPh, [Si] = TBDPS
200 R = SPh, [Si] = TBS
201 R = Ph, [Si] = TBS

Entry[a]	Thiol ester	Aldehyde	'boron reagent'	Conv (%)[b]
1	**160**	**157**	c-Hex_2BOTf	0
2	**160**	**161**	c-Hex_2BOTf	0
3	**160**	**157**	c-Hex_2BCl	traces
4	**160**	**161**	c-Hex_2BCl	0
5	**160**	**157**	Bu_2BOTf	0
6	**192**	**157**	c-Hex_2BCl	0
7	**192**	**161**	c-Hex_2BCl	0

[a] *Conditions:* 0.07 mmol thiol, 0.21 mmol 'boron reagent', 0.21 mmol Et_3N, 1.5 ml anhydrous CH_2Cl_2, -78ºC, 1h; then 0.21 mmol aldehyde, 0.13 ml anhydrous CH_2Cl_2, -78ºC 2h, 0ºC until finishing. [b] Determination by ^1H NMR spectroscopy.

Alternatively, c-Hex_2BCl was also used instead of c-Hex_2BOTf, for the glycolate aldol reaction of thiolester **160** with aldehyde **157** and benzaldehyde (**161**), but the corresponding reactions either led to trace product or did not

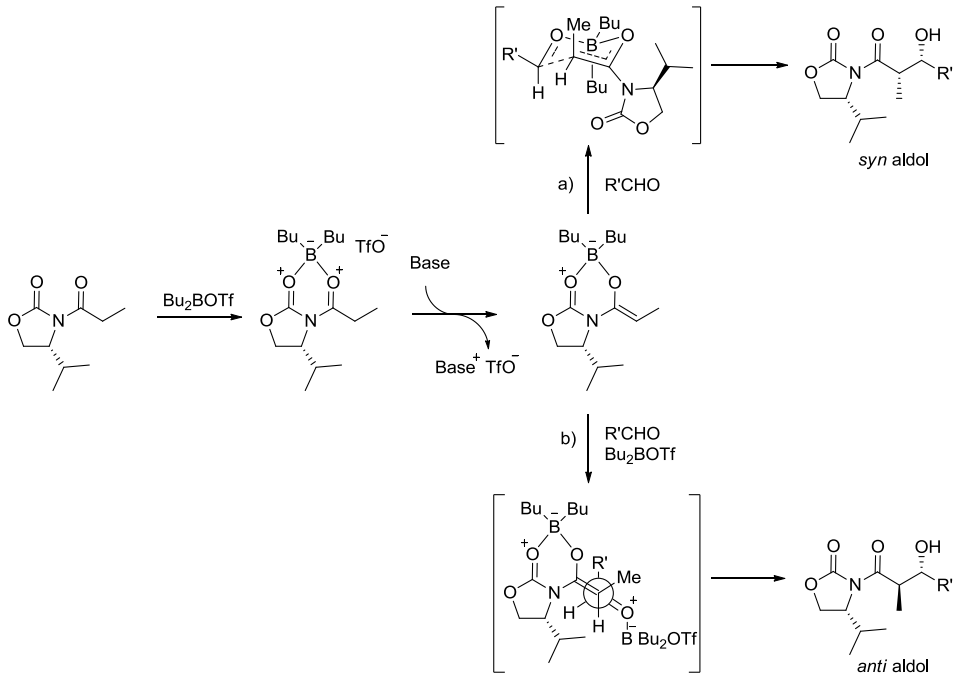
[264] Product number: 703052 - 97% (CAS-Nº: 145412-54-0), Sigma-Aldrich®, Appearance: solid.
[265] Abiko, A. *Org. Synth.* **2002**, *79*, 103-105; *Org. Synth.* **2004**, *Coll. Vol. 10*, 273-275.

proceed at all (Table 14, entries 3, 4). Furthermore, thiolester **160** was subjected to enolization in the presence of less hindered Bu_2BOTf, but the reaction did not take place (Table 14, entry 5).

On the basis of these preliminary experiments, we decided to investigate the reaction of the less bulky TBS-protected thiolesther **192** as a means to enhance reactivity (Table 14, entries 6, 7). The glycolate aldol reaction was once again tested using benzaldehyde (**177**) as substrate model, and then applied to aldehyde of interest **157**. In the presence of $c\text{-}Hex_2BCl$, the unique boron reagent which allowed some conversion in the previous experiments, neither benzaldehyde (**161**) nor aldehyde **157** gave rise to any aldol product. Since no product had been obtained, we thought that the problem could be the enolization step, but neither longer reaction periods for the glycolate and the boron reagent nor increasing the temperature led to any conversion.

In the light of the previous unsuccessful experiments, we turned our attention to the protected oxazolidinones **195** and **198** as chiral auxiliaries for the *anti*-aldol reaction. Heathcock[256] reported that selective enolization to give either *syn* or *anti* aldols depends on the amount of dibutylboron triflate used in the enolization, as well as the amine used.

According to Heathcock, when stoichiometric amounts of Bu_2BOTf and a slight excess of either DIPEA or Et_3N are used to form the boron enolate of oxazolidinone, reaction with all investigated aldehydes affords *syn* aldols as only products. Enolization with an excess of Bu_2BOTf and excess Et_3N also leads to formation of only *syn* aldols, because when an excess of amine is present only a small amount of free Bu_2BOTf should be present as the amine forms a complex with Bu_2BOTf. However, when an excess of Bu_2BOTf and DIPEA are used in the enolization, *anti* aldols are formed with aromatic aldehydes and 3-arylthio)propenals. The *syn* and *anti* aldols are formed from the same *Z*-enolate; *syn* aldols are formed via the normal closed transition state (Scheme 95a, top) and *anti* aldols are formed via an open transition state in which an excess of Bu_2BOTf functions as a Lewis acid catalyst (Scheme 95b, bottom).



Scheme 95. Mechanism of propionate aldol reaction of propionyloxazolidinone without (a) and with excess of Bu_2BOTf (b).

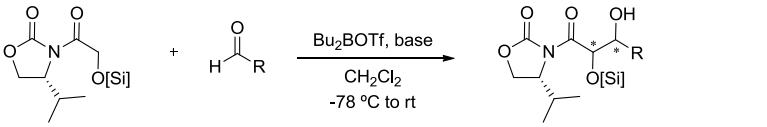
Aldehyde **157** was allowed to react with the boron enolate prepared from TBDPS-protected oxazolidinone **195** under Heathcock's conditions[256] (1.9 equiv of Bu_2BOTf, 2.2 equiv of DIPEA, 1.0 equiv of oxazolidinone, 45 min at 0ºC in CH_2Cl_2) (Table 15, entry 1). The reaction did not evolved and starting materials were recovered.

The amine used in the enolization process appears to exert a key effect on the stereochemistry of the subsequent aldol reaction.[266] For this reason, we carried out the enolization of **195** with Et_3N instead of DIPEA and Bu_2BOTf under the standard conditions described above followed by the addition of the aldehyde **157** (Table 15, entry 2). Once again the aldol reaction did not take place.

[266] a) Baker, R.; Castro, J. L.; Swain, C. J. *Tetrahedron Lett.* **1988**, *29*, 2247-2250. b) See the work of Evans and co-workers where Et_3N rather than DIPEA was essential for successful reaction: Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957-4960.

The aldol reaction with the less hindered TBS-protected oxazolidinone **195** was then tested with DIPEA and Et_3N in the presence of Bu_2BOTf, but no perceptible conversion took place (Table 15, entries 3, 4).

Table 15. Glycolate aldol reaction of protected oxazolidinones **195** and **198**.



Entry[a]	Oxazolidinone	Aldehyde	Base	Conv (%)[b]
1	**195**	**157**	DIPEA	0
2	**195**	**157**	Et_3N	0
3	**198**	**157**	DIPEA	0
4	**198**	**157**	Et_3N	0
5[c]	**198**	**161**	DIPEA	0
6[d]	**198**	**161**	DIPEA	0

[a] *Conditions:* Enolization: 1.90 mmol Bu_2BOTf, 2.20 mmol DIPEA, 1.00 mmol oxazolidinone, 45 min at 0ºC in CH_2Cl_2. Aldol reaction: 1.30 mmol aldehyde, 30 min at -78ºC then allow to raise to rt. [b] Determination by ^1H NMR spectroscopy. [c] Ratio oxazolidinone/DIPEA/Bu_2BOTf = 1 : 1.1 : 2. [d] Ratio oxazolidinone/DIPEA/Bu_2BOTf = 1 : 1.3 : 1.1.

Finally, the glycolate aldol reaction of TBS-protected oxazolidinone **198** was tested with benzaldehyde (**161**) as model substrate in the conditions described by Heathcock[256] (Table 15, entries 5, 6). The enolization of **198** was investigated with different amounts of Bu_2BOTf and DIPEA, however, the reaction did not lead to any conversion.

To sum up, it seems that (*E*)-3-thiophenylacrolein (**157**) is not a good aldol acceptor for the aldol reaction with the thiol derivative of the Abiko-Masamune auxiliary (**188**), probably because of its reactivity of low electrophilicity and

proneness to Michael reaction or nucleophilic replacement of SPh, but in our hands, none of these processes have appeared to proceed, as starting materials have been always recovered. No boron reagent has been able to efficiently enolize the glycolate and even in the presence of benzaldehyde no reaction took place.

4. Conclusions

Proline- (**159a**) and derivatives **159b-g** thereof-catalyzed aldol reaction of protected hydroxyacetones **153** and **154** and (*E*)-3-thiophenylacrolein (**157**) have been tested. Although this organocatalytic procedure has proved to be an efficient and general method for coupling ketones and aldehydes, its application to the synthesis of alkenyl sulphide synthons was unsuccesful.

Furthermore, chiral auxiliary-mediated aldol reaction with the thiol derivative of the Abiko-Masamune auxiliary (**188**) or with the Evan's oxazolidinone used by Heathcock (**194**) did not occur either.

5. Experimental Section

5.1 General methods

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), dimethylformamide (DMF) and diethyl ether were dried using a solvent purification system (Pure SOLV system-4®). The other solvents were purified using standard procedures.[111]

^1H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 or in a Varian® 400-MR, (both of 400 MHz and 100.6 MHz respectively) spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.27 ppm ^1H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm), unless otherwise specified. 2D correlation spectra (gCOSY, NOESY, TOCSY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate.

Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F_{254} glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in a suitable developing solution. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

5.2 General procedures

General procedure of silylation of hydroxyketones. To a solution of hydroxyketone (1.00 mmol) in CH_2Cl_2 (4.6 ml) at 0ºC, DIPEA was added (3.00 mmol), followed by silyl chloride (3.00 mmol). The resulting solution was

warmed to room temperature before addition of DMAP (cat.). After stirring for a further 24 h, the reaction mixture was partitioned between $NaHCO_3$ saturated aqueous solution and EtOAc, the phases separated and the aqueous extracted with EtOAc. The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatographic techniques.

General procedure for the L-proline and derivatives thereof-catalyzed aldol reaction. To a suspension of the catalyst (0.15 mmol) in DMF or THF (0.25 ml) was added the ketone (0.59 mmol) and stirred for 30 min at ambient temperature. After cooling down to 2ºC the aldehyde (0.49 mmol) was added and the suspension was stored at 2ºC. After 48–120 h, the resulting mixture was quenched with saturated aq. NH_4Cl solution and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

General procedure of DIP/DMAP-mediated coupling of protected glycolic acids and thiol auxiliary 165. To a stirred solution of freshly prepared protected glycolic acid (2.40 mmol) in CH_2Cl_2 (0.9 ml) was added a solution of thiol **165** (1.00 mmol) in CH_2Cl_2 (0.9 ml), then DMAP (0.10 mmol) and DIC (2.00 mmol). The reaction mixture was stirred at rt for 14 h. The diisopropylurea formed was removed by filtration and the filtrate was concentrated. NaCl sat aq was added and the mixture was extracted with CH_2Cl_2 and washed with NaCl, HCl 1 N, NaCl, $NaHCO_3$, and NaCl. The organics were dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude product was purified by chromatographic techniques.

General procedure of Evans of coupling acyl chlorides with oxazolidinones. To a -78 °C solution of the oxazolidinone (1.82 mmol) in THF (7.7 ml), a 1.0 M solution of LiHMDS in THF (2.00 mmol) was added via cannula. The resulting mixture was stirred at -78 °C for another 30 min, and then a solution of the acid chloride (2.00 mmol) freshly prepared in THF (4.8 ml) was added via cannula. The reaction was then slowly warmed to room temperature overnight. Saturated aq. NH_4Cl solution was then added, followed by Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (x3). The

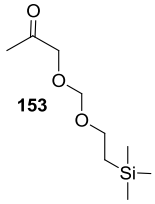
combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatographic techniques.

General procedure for the *anti*-glycolate aldol reactions of protected thiolesters 160 and 192. To a stirred solution of the protected thiolester (0.08 mmol) in CH_2Cl_2 (1.7 ml) at -78°C was added the boron reagent (0.23 mmol) and then Et_3N (0.23 mmol). The reaction mixture was stirred at -78°C for 1 h, then aldehyde (0.23 mmol) was added. The reaction was stirred at -78°C for 2 h and then at 0°C for 2 h. The mixture was quenched by the addition of pH 7 buffer and methanol and diluted with methanol to make a homogeneous solution. After careful addition of H_2O_2 (30% aq) the mixture was stirred at rt for 15 min. NaCl was added and the mixture was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude aldol product which was purified by chromatographic techniques.

General procedure for the glycolate aldol reactions of protected oxazolidinones 195 and 198. To a solution of the oxazolidinone (0.24 mmol) in CH_2C1_2 (0.5 ml) at 0ºC the base (0.52 mmol) and Bu_2BOTf (0.45 mmol) were added. After 45 min at 0ºC, the solution was cooled to -78ºC and the aldehyde (0.31 mmol) in CH_2Cl_2 (0.2 ml) was added over 20 min. After 30 min at -78ºC, the reaction was allowed to raise rt until completion by TLC. The mixture was quenched by the addition of pH 7 buffer and ether. The layers were separated and the aqueous layer was extracted with ether (x2). The combined organic layers were washed with brine and the solvent was removed under reduced pressure. The residue was dissolved in methanol and cooled to 0ºC, and H_2O_2 (30% aq) was added dropwise over 30 min. After 60 min at 0ºC, water was added and the methanol was removed under reduced pressure. The aqueous layer was extracted with ether (x3). The combined organic layers were washed with cold 5% HC1, saturated aq $NaHCO_3$, and brine and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by chromatographic techniques.

5.3 Compound characterization

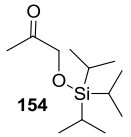
1-(2-trimethylsilylethoxymethoxy)-2-propanone (153).



Following the general procedure of silylation of hydroxyketones, hydroxyacetone (**152**) (0.5 ml, 7.30 mmol), DIPEA (3.8 ml, 21.91 mmol), SEMCl (3.9 ml, 21.91 mmol) and DMAP (cat.) in dry CH_2Cl_2 (33.6 ml) were reacted. Flash chromatography (1:9 EtOAc:hexane) of the reaction crude afforded compound **153** (1.4 g, 6.64 mmol, 91%) as a yellowish liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm 4.73 (s, 2H), 4.18 (s, 2H), 3.64 (dd, 2H, *J* = 8.8, 8.8 Hz), 2.16 (s, 3H), 0.93 (dd, 2H, *J* = 8.8, 8.8 Hz), 0.01 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 206.0, 95.0, 72.7, 65.9, 26.6, 18.2, -1.3. **FT-IR** (neat) ν in cm^{-1}: 2953, 2895, 1722, 1356, 1248, 1159, 1058, 1038, 833. **ESI-HRMS** *m/z* calcd. for $C_9H_{20}NaO_3Si$ [M-Na]: 227.1079, found: 227.1072.

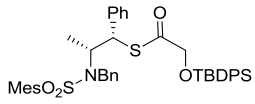
1-(triisopropylsilyloxy)-2-propanone (154).



Following the general procedure of silylation of hydroxyketones, hydroxyacetone (**152**) (0.5 ml, 7.30 mmol), DIPEA (3.8 ml, 21.91 mmol), TIPSCl (4.7 ml, 21.91 mmol) and DMAP (cat.) in dry CH_2Cl_2 (33.6 ml) were reacted. Flash chromatography (pentane) of the reaction crude afforded compound **154** (1.4 g, 6.21 mmol, 85%) as a yellowish liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm 4.20 (s, 2H), 2.23 (s, 3H), 1.16 - 0.98 (m, 21H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 209.5, 70.2, 26.3, 18.1, 12.1.

(1′*S*,2′*R*)-2′-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1′-phenylpropyl 2-(*tert*-butyldiphenylsilyloxy)thiolacetate (160).

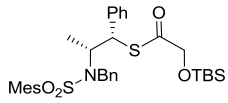


160

According to the general procedure of DIP/DMAP-mediated coupling reaction, the title compound was synthesized by reaction of TBDPS-protected glycolic acid (**190**) (512 mg, 1.63 mmol), thiol **188** (297 mg, 0.68 mmol), DMAP (9 mg, 0.07 mmol) and DIC (210 µl, 1.36 mmol). Column chromatography (hexane:EtOAc 9:1) afforded compound **160** (490 mg, 0.66 mmol, 98%) as a waxy solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm 7.67-7.56 (m, 4H), 7.48-7.23 (m, 11H), 7.17 (t, 1H, *J* = 7.4 Hz), 7.06 (t, 2H, *J* = 7.6 Hz), 6.85 (s, 2H), 6.77 (d, 2H, *J* = 7.1 Hz), 4.85 (d, 1H, *J* = 18.0 Hz), 4.82 (d, 1H, *J* = 10.4 Hz), 4.52 (d, 1H, *J* = 16.3 Hz), 4.22 (dd, 1H, *J* = 6.6, 2.1 Hz), 4.17 (d, 2H, *J* = 4.0 Hz), 2.34 (s, 6H), 2.32 (s, 3H, *J* = 4.4 Hz), 1.27 (d, 3H, *J* = 6.8 Hz), 1.08 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 198.7, 142.5, 140.3, 140.2, 137.9, 135.7, 134.5, 133.2, 132.2, 129.7, 128.3, 128.1, 127.5, 127.4, 127.3, 127.2, 126.9, 69.0, 56.3, 50.0, 47.6, 26.4, 23.6, 20.9, 19.2, 17.5.

(1′*S*,2′*R*)-2′-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1′-phenylpropyl 2-(*tert*-butyldimethylsilyloxy)thiolacetate (192).

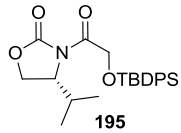


192

According to the general procedure of DIP/DMAP-mediated coupling reaction, the title compound was synthesized by reaction of TBS-protected glycolic acid (**191**) (261 mg, 1.37 mmol), thiol **188** (250 mg, 0.57 mmol), DMAP (7 mg, 0.06 mmol) and DIC (180 µl, 1.14 mmol). Column chromatography (hexane:EtOAc 9:1) afforded compound **192** (314 mg, 0.51 mmol, 90%) as a waxy solid.

$[\alpha]^{20}_D$: +38.7 (*c* 3.95, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm 7.49-7.42 (m, 2H), 7.34-7.22 (m, 3H), 7.15 (t, 1H, *J* = 7.4 Hz), 7.03 (t, 2H, *J* = 7.7 Hz), 6.84 (s, 2H), 6.74 (d, 2H, *J* = 7.3 Hz), 4.84 (d, 1H, *J* = 16.5 Hz), 4.81 (d, 1H, *J* = 9.1 Hz), 4.49 (d, 1H, *J* = 16.2 Hz), 4.21 (dd, 1H, *J* = 6.6, 2.4 Hz), 4.17 (d, 2H, *J* = 5.1 Hz), 2.32 (s, 9H, *J* = 5.6 Hz), 1.27 (d, 3H, *J* = 6.8 Hz), 0.91 (s, 9H, *J* = 2.7 Hz), 0.06 (d, 6H, *J* = 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 200.1, 142.5, 140.8, 140.5, 138.8, 132.4, 128.9, 128.6, 127.9, 127.6, 127.3, 68.9, 56.8, 50.2, 47.7, 25.9, 23.1, 21.1, 18.5, 17.7, -5.4. **FT-IR** (neat) ν in cm^{-1}: 3051, 2972, 2929, 2823, 1694, 1603, 1495, 1248, 1159, 1058, 1038, 833. **ESI-HRMS** *m/z* calcd. for $C_{33}H_{49}N_2O_4S_2Si$ [M-NH_4]: 629.2903; found: 629.2859.

(*R*)-4-Isopropyl-3-(*tert*-butyldiphenylsilanoxyacetyl)-oxazolidin-2-one (195).

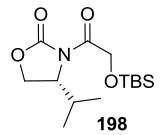


195

Following the general procedure of Evans of coupling of acid chloride and oxazolidinones, oxazolidinone **194** (235 mg, 1.92 mmol), 1.0 M solution of LiHMDS in THF (2.0 ml, 2.00 mmol), and acid chloride **193** (666 mg, 2.00 mmol) were reacted. Flash chromatography (1:9 EtOAc:hexane) of the reaction crude afforded compound **195** (637 mg, 1.50 mmol, 78%) as a yellowish liquid.

$[\alpha]^{20}_D$: -33.7 (*c* 15.30, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.78-7.69 (m, 4H, H_{Ar}); 7.49-7.35 (m, 6H, H_{Ar}); 5.00-4.83 (m, 1H, C(O)CH_2O); 4.36 (dt, *J* = 8.0, 3.5 Hz, 1H, CH_{ox}); 4.23 (t, *J* = 8.7 Hz, 1H, $CH_{2\ ox}$); 4.17 (dd, *J* = 9.2, 3.2 Hz, 1H, $CH_{2\ ox}$); 2.39-2.25 (m, 1H, CH_{iPr}); 1.16 (s, 9H, $C(CH_3)_3$); 0.88 (d, *J* = 7.0 Hz, 3H, $CH_{3\ iPr}$); 0.75 (d, *J* = 6.9 Hz, 3H, $CH_{3\ iPr}$).**^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 171.0 (C=O); 154.0 (C=O_{ox}); 135.8 (CH_{Ar}); 135.7 (CH_{Ar}), 133.0 (C_{Ar}); 133.0 (C_{Ar}); 130.0 (CH_{Ar}); 127.8 (CH_{Ar}); 127.8 (CH_{Ar}); 64.6 (C(O)$\underline{C}H_2$O); 64.3 ($CH_{2\ ox}$); 58.2 (CH_{ox}); 28.1 (CH_{iPr}); 26.9 ($C(\underline{C}H_3)_3$); 19.5 ($CH_{3\ iPr}$); 18.0 ($CH_{3\ iPr}$); 14.5 (-$\underline{C}(CH_3)_3$). **FT-IR** (neat) ν in cm^{-1}: 3072, 2961, 2931, 2858, 1778, 1720, 1427, 1389, 1260, 1209, 1143, 1112, 700. **ESI-HRMS** *m/z* calcd. for $C_{24}H_{31}NNaO_4Si$ [M-Na]: 448.1920, found: 448.1908.

(*R*)-4-Isopropyl-3-(*tert*-butyldimethylsilanoxyacetyl)-oxazolidin-2-one (198).



198

Following the general procedure of Evans of coupling of acid chloride and oxazolidinones, oxazolidinone **194** (1.26 g, 9.75 mmol), 1.0 M solution of LiHMDS in THF (10.7 ml, 10.73 mmol), and acid chloride **197** (2.24 g, 10.73 mmol) were reacted. Flash chromatography (1:9 EtOAc:hexane) of the reaction crude afforded compound **198** (2.20 g, 7.31 mmol, 75%) as a yellowish liquid.

$[\alpha]^{20}_{D}$: -35.2 (*c* 9.30, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 4.91 – 4.77 (m, 2H, $C(O)CH_2O$), 4.47 – 4.41 (m, 1H, CH_{ox}), 4.35 (td, *J* = 8.7, 1.4 Hz, 1H, $CH_{2\ ox}$), 4.26 (ddd, *J* = 9.1, 3.1, 1.5 Hz, 1H, $CH_{2\ ox}$), 2.51 – 2.37 (m, 1H, CH_{iPr}), 0.93 (s, 9H, $C(CH_3)_3$), 0.92 (d, *J* = 7.1 Hz, 3H, $CH_{3\ iPr}$), 0.87 (d, *J* = 6.9 Hz, 3H, $CH_{3\ iPr}$), 0.12 (t, *J* = 1.7 Hz, 6H, $2xCH_3$). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 171.7 (C=O); 154.1 ($C=O_{ox}$); 64.3 ($CH_{2\ ox}$); 64.3 ($C(O)\underline{C}H_2O$); 58.3 (CH_{ox}); 28.1 (CH_{iPr}); 25.8 ($C(\underline{C}H_3)_3$); 18.5 ($-\underline{C}(CH_3)_3$); 17.9 ($CH_{3\ iPr}$); 14.5 ($CH_{3\ iPr}$); -5.4 (CH_3); -5.4 (CH_3). **FT-IR** (neat) ν in cm^{-1}: 1765, 1750, 1453, 1378, 1258, 1212, 1133, 1110, 689. **ESI-HRMS** *m/z* calcd. for $C_{14}H_{28}NO_4Si$ [M-H]: 302.1788, found: 302.1754.