Departamento de Química Analítica y Química Orgánica

Stereoselective Synthesis of 2-Deoxyoligosaccharides — New Approaches to the Synthesis of Digitoxin and P57

Memoria presentada por
Andrea Kövér
Para optar al título de
Doctor en Química
Tarragona, Abril 2008

UNIVERSITAT ROVIRA I VIRGILI
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Química Analítica y Química Orgánica de la Universitat Rovira i Virgili.

CERTIFICAN:

Que el trabajo titulado: "**Stereoselective Synthesis of 2-Deoxyoligosaccharides – New Approaches to the Synthesis of Digitoxin and P57**" presentado por Andrea Kövér para optar al grado de Doctor, ha estado realizado bajo su inmediata dirección en los laboratorios de Química Orgánica del Departamento de Química Analítica y Química Orgánica de la Universitat Rovira i Virgili.

Tarragona, Abril de 2008

Sergio Castillón Miranda

Yolanda Díaz Giménez

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AGRADECIMIENTOS

"Querer es tener valor de
chocar con los obstáculos."

Stendhal, novelista francés

para Ferran

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Éste es el punto donde tradicionalmente va la sección de agradecimientos, pero es tanto lo que debo, y a tantas personas, que es realmente difícil expresarlo en unas pocas líneas.

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En resumen, a todos los integrantes del área de Química Orgánica y en general de Universitat Rovira i Virgili por haber aportado cada uno su granito de arena y hacer que me sintiera como en casa.

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Por último, a la persona que ha estado a mi lado todo este tiempo sufriendo y disfrutando todos los momentos juntos. Gracias Ferran.

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"Los grandes acontecimientos
no corresponden
a nuestros momentos
bulliciosos, sino a nuestros
momentos de tranquilidad."

F. Nietzsche, filósofo alemán

ABBREVIATIONS

"Experiencia es el
nombre que damos a
nuestras equivocaciones."

Oscar Wilde, escritor irlandés

Ac	Acetyl
ACE	Angiotensin-Converting-Enzyme
AcOEt	Ethyl Acetate
AcOH	Acetic Acid
AIBN	2,2´-Azobisisobutyronitrile
All	Allyl
Bn	Benzyl
Bp	Boiling Point
Bu	Butyl
Bz	Benzoyl
CAN	Ceric Ammonium Nitrate
Cat.	Catalytic, Catalyst
cc.	Concentrated
CHF	Congestive Heart Failure
COSY	Correlation Spectroscopy
CSA	Camphore Sulfonic Acid
CSIR	South African Council for Scientific and Industrial Research
d	Doublet
dd	Double Doublet
ddd	Doublet of Double Doublet
δ	Chemical Shift
DAST	Diethylaminosulfur Trifluoride
DCM	Dichloromethan
DDQ	2,3-Dichloro-5,6-Dicyano-1,4-Benzoquinone
DEAD	Diethyl Azodacarboxylate
DFT	Density Functional Theory
DIBAL	Diisobutylaluminium Hydride
DMF	*N,N*-Dimethylformamide
DMAP	4-(Dimethylamino)pyridine
DNA	Deoxy Nucleic Acid
Et	Ethyl
FT–IR	Furier Transform – Infra Red Spectroscopy
HMBC	Heteronuclear Multiple Bond Correlation
HOMO	Highest Occupied Molecular Orbital
HR-MAS	High Resolution Magic Angel Spinning
HSQC	Heteronuclear Single-quantum Correlation

hv	Irradiation (λ = Wavelength)
Hz	Hertz
IDCP	Iodonium Di(*sym*-collidine)perchlorate
IR	Infra Red Spectroscopy
LDA	Lithium Diisopropylamide
LUMO	Lowest Occupied Molecular Orbital
m	Multiplet
MALDI	Matrix Assisted Laser Desorption/Ionization
Me	Methyl
MEM	2-Methoxyethoxymethyl
MOM	Methoxymethyl
MS	Mass Spectroscopy
MS	Molecular Sieve
NBS	*N*-Bromosuccinimide
NCX	Na/Ca Exchange
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine-*N*-Oxide
NMR	Nuclear Magnetic Resonance
NKA	Na/K ATPase
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
PDE	Inhibitors of the Phosphodiesterase
Ph	Phenyl
PMB	*p*-Methoxyphenyl
ppm	Parts Per Million
pyr	Pyridine
q	Quartet
R_f	Retention Factor
RCM	Ring–Closing Metathesis
Refl.	Reflux
rt	Room Temperature
RyR	Ryanodine Receptor
s	Singlet
SEM	2-(Thimethylsilyl)ethoxymethyl
SERCA	SR Ca–ATPase

SOC	Sodium Open Channels
SMOM	(Phenyldimethylsilyl)methoxymethyl
SR	Sarcoplasmatic Reticulum
t	Triplet
TBABr	*tetra*-Butylammonium Bromide
TBAF	*tetra*-Butylammonium Fluoride
TBAI	*tetra*-Butylammonium Iodine
TBDPS	*tert*-Butyldiphenylsilyl
TBS (TBDMS)	*tert*-Butyldimethylsilyl
TEA	Triethyl Amine
TEG	Triethyleneglycol
TES	Triethylsilyl
TFA	Triflouroacetic Acid
TfOH	Triflic Acid
THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl Trifluoromethane Sulfonate
TOF	Time of Flight
TOCSY	Total Correlation Spectroscopy
Ts	Tosyl
TSA	Toluen Sulfonic Acid
UV	Ultraviolet Light

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FIRST Chapter: **Introduction and Goals**

"Si conociéramos
el verdadero fondo de todo,
tendríamos compasión
hasta de las estrellas."

Graham Greene, escritor inglés

1.1 Introduction

1.1.1 Deoxyglycosides

Glycoconjugates are the most functionally and structurally diverse compounds in the nature. It is well established that in addition to complex polysaccharides, protein– and lipid–bound saccharides haveessential roles in molecular processes.[1]

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 selectivity.[2] However, the formation of complex oligosaccharides is still much more complicated than the synthesis of biopolymers such as peptides or nucleic acids. The increased numbed of possible combinations of monomers presents one of the biggest difficulties in the preparation of complex oligosaccharides. In addition, glycosydic linkages must be formed stereospecifically.

Deoxysugars and deoxyoligosaccharides belong to the most important, yet most neglected, group of biological compounds. Deoxysugars are defined carbohydrates with a substitution of one or more of the hydroxylic groups with another heteroatom or hydrogen. They provide a challenge not only for synthesis, but also for the study of their various biological functions.

These compounds are frequently found in natural secondary metabolites, including anticancer agents, antibiotics against Gram–positive bacteria (erythromycins **3**, orthosomycins **1**), antibiotics inhibitors of platelet aggregation (angucyclines) drugs used in the treatment of cardiac insufficiency (cardiac glycosides, digitoxin **5**), antiparasitic agents (avermictins **7**), and appetite suppressants (P57, **4**) (Figure 1.1).[3] It has been shown that aglycon parts of these molecules mediate their therapeutic effects; the glycosydic parts, however, are essential for the reagulation of its biological activity (interaction with nucleic acids, for example). There are deoxysugars in a large number of bioactive carbohydrates in lipopolysaccharides. The development of methods for the efficient and stereoselective construction of deoxyglycosidic linkages will likely lead to useful application in medicinal and bioorganic chemistry by helping to elucidate the biological mechanisms and to develop of new and less toxic drugs.[4]

---

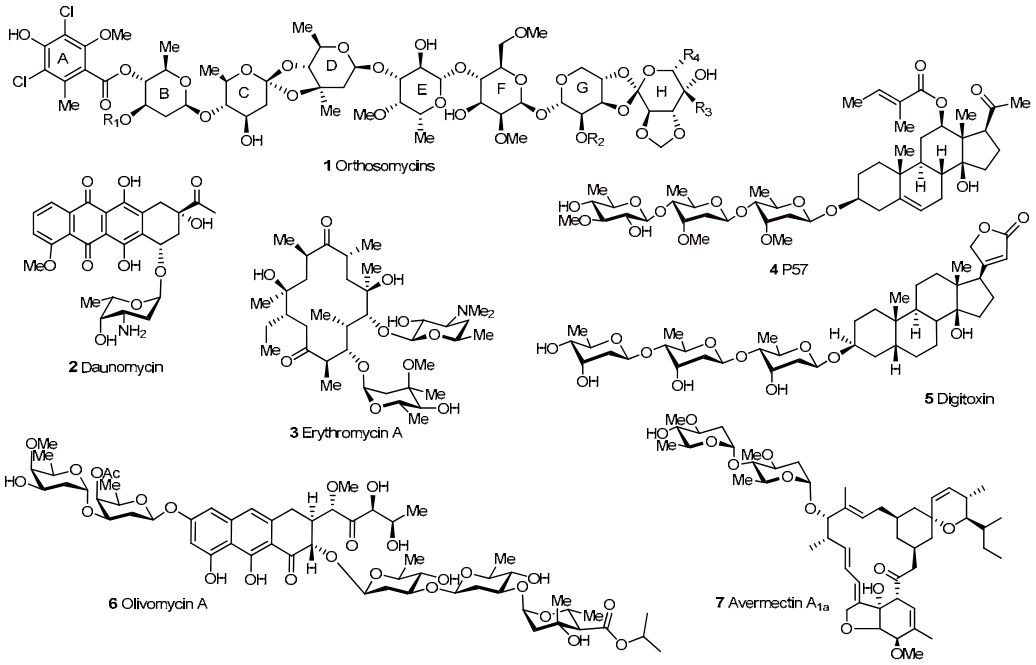
1 (a) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095. (b) Meutermans, W.; Le, G. T.; Becker, B. *ChemMedChem*, **2006**, *1*, 1164.

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

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

4 Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Bioorganic Chemistry Models and Applications* **1996**.

Figure 1.1 Natural 2,6-Dideoxyglycosides



1.1.2 Biological Background for the Cardiac Glycosides. Digitoxin

Congestive heart failure (CHF) is a condition in which the heart cannot pump enough blood to the body's other organs. It causes shortness of breath, fluid retention, swelling (edema), exercise intolerance, left ventricular dysfunction and, in the most severe cases, arrhythmias and sudden death. This highly lethal condition currently affects over nine million Americans, Europeans, and Japanese. Furthermore, CHF incidences are expected to continue increasing as the populations of these countries age.[5]

Several compounds[6] have been used to treat CHF, including diuretics (eg. furosemide [*Lasix*]),[7] natriuretic peptides,[8] inhibitors of the angiotensin–converting–enzyme (ACE),[9] inhibitors of the

[5] (a) National Health and Nutrition Examination Survey III (NHANES III) pp. 1988; American Center for Disease Control (CDC)/NCHS data 1979. (b) Reddy, S.; Benatar, D.; Gheorghiade, M. *Curr. Opin. Cardiol.* **1997**, *12*, 233. (c) American Heart Association; Heart and Stroke Statistical Update. Dallas: AHA, **2002**. (d) Yusuf, S.; Garg, R.; Held, P.; Gorlin, R. *Am. J. Cardiol.* **1992**, *69*, 64G-70G. (d) National Institute for Clinical Excellence. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. Clinical Guideline 5. London: National Institute for Clinical Excellence; **2003** Jul. (e) 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*(S2) 10.

[6] (a) Grupp, G. *Mol. Cell. Biochem*. **1987**, *76*, 97. (b) http://www.cardiologychannel.com/chf/treatment.shtml

phophodiesterase (PDE),[10] *β*-blockers[11] (e.g., carvedilol [*Coreg*®], metoprolol [*Lopressor*®, *Toprol XL*®]) and blood thinners (e.g., warfarin [*Coumadin*®]). Even with these recently developed treatments, CHF continues to cause a 5-year mortality rate of 50%. Unfortunately, only diuretics, inhibitors of the ACE, and digitalis fulfill at last some of the criteria for a first–line agent for treating CHF. None of these drugs satisfies all of the desired characteristics, however, and none can optimally manage the heart failure state when used alone. Thus, digitalis and cardiac glycosides continue to be the first choice in CHF treatment.[5c-e]

Cardiac glycosides have been used as therapeutic agents for a very long time: they can be traced back to 1600 BC when ancient Egyptian manuscripts describe the medicinal prescription of the squill bulb, which contains cardienolides. Prescription of the squill bulb was again reported two centuries later in the *Corpus Hippocraticum*, for diuresis. In the medieval times, Welsh physicians write about *Digitalis purpurea*. In 1785, Withering was the first physician to describe the efficacy of digitalis in treating edema (dropsy).[12] It wasn´t until 1869, however, that the different components, and particularly digoxin, were purified by Nativelle. In 1875 it was Johann Schmiedeberg who isolated the principal active constituent of digitalis, the glycoside digitoxin (**5**, Figure 1.1).[13]

Cardiac glycosides[14] are positive inotropic substances; thus, they increase stroke volume and cardiac output and improve cardiac performance.[15] This class of compounds is characterized by an aglycon (genin) linked to a glycon (a carbohydrate, mono- to tetrasaccharide). It is the aglycon that possesse pharmacological activity, but the carbohydrate is thought to influence pharmacokinetics of the compound (absorption, distribution, metabolism, and excretion).

---

7 Kramer B. K, Schweda F, Riegger G. A. Diuretic treatment and diuretic resistance in heart failure. *Am J Med.* **1999**. *106*. 90.

8 Sagnelli; G. A. *Cardiovascular Research* **2001**, *51*, 416.

9 Krum H, Carson P, Farsang C, et al. Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT. *Eur J Heart Fail* **2004**; *6*(7):937.

10 (a) Monrad, E.; Bain, D. S.; Smith, H. *Circulation* **1985**, *71*, 972. (b) Cuffe, M. S.; Califf, R. M.; Adam, K. R. Jr. *JAMA* **2002**, *287*, 1541.

11 (a) Pritchett, A. M.; Redfield, M. M. "Beta–blockers: new standard therapy for heart failure". *Mayo Clin. Proc.* **2002**, *77* (8), 839 (b) Pritchett, A. M.; Redfield, M. M. "Beta–blockers: new standard therapy for heart failure". *Mayo Clin. Proc.* **2002**, *77* (8), 845. c) Hjalmarson, A.; Goldstein, S.; Fagerberg, B. *et al* "Effects of controlled–release metoprolol on total mortality, hospitalizations, and well–being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group". *JAMA* **2000**, *283* (10), 129.

12 Whitering, W. *"An Account of The Foxglove, And Some Of Its Medical Uses; With Practical Remarks On Dropsy, And Other Diseases"* Robinson, London, **1785**.

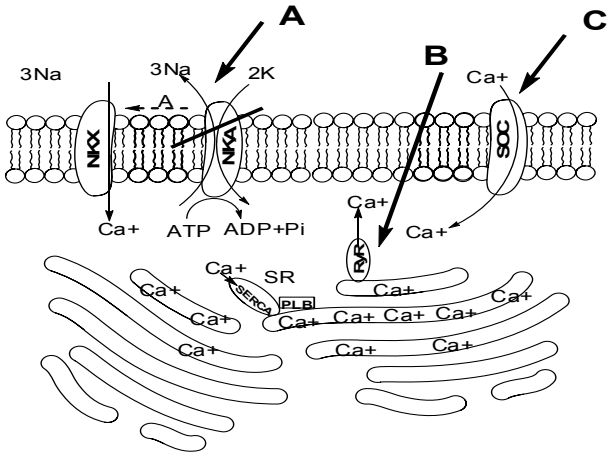
13 (a) Schmiedeberg J. E. O. Untersuchungen über die pharmakologisch wirksamen Bestandteile der *Digitalis purpurea*. *Arch Exp Path Pharmak* **1875**, *3*, pp. 16. (b) Greef, K.; Schadewalt H. C*ardiac Glycosides Part I Exp. Pharmacology* (Ed. Grieff, K. *Handb. Exp. Pharmacol.* **1981**, *56*/I, pp. 1

14 (a) Barhmann, H.; Greeff, K. in C*ardiac Glycosides Part I Exp. Pharmacology* (Ed. Grieff, K. *Handb. Exp. Pharmacol.* **1981**, *56*/I, pp. 124). (b) Repke, R. H.; Megges, R.; Weiland, J.; Schön, R. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 282.

15 Joubert, P. H.; Grossman, M. *Eur. J. Clin. Invest.* **2001**, *31* (S2), 1.

It is known that contraction of the heart muscle is activated by a transient increase in intracellular Ca^{2+} concentration. It is thought, though there is still debate, that cardiac glycosides act by inhibiting a membrane $Na^{+}K^{+}$ ATPase (NKA),[16] causing less Ca^{2+} to be exported from the cell. Consequently, more Ca^{2+} accumulates in the sarcoplasmatic reticulum and is available during subsequent contractions, leading to an increased contraction force (Figure 1.2, via A).[17] In contrast, Santana et al.[18] found that cardiac glycosides may induce a slip-mode conductance through Na–channels (SOC), allowing Ca–ions to enter the cell via these channels (Figure 1.2, via C). Other researchers[19] have found that cardiac glycosides enhance the release of Ca from the sarcoplasmatic reticulum (SR) by increasing single channel activity of ryanodine–receptors (RyR), which release Ca ions to the cytoplasm (Figure 1.2, via B).

Figure 1.2 Mode of Action of Cardiac Glycosides[20]



NCX = Na/Ca exchanger; NKA = Na/K ATPase; SOC = Sodium open channels; RyR = Ryanodine receptor; SR = Sarcoplasmatic Reticulum; SERCA = SR Ca–ATPase; PLB = phospholamban

Recently, it was reported that digitoxigenin, its glycosides, and its derivatives (Figure 1.1) strongly inhibit the proliferation or induced apoptosis of various malignant cell lines.[21] In response,

16 Heller, M. *Biochem. Pharmacol.* **1990**, *40*, 919.
17 Lee, C. O.; Abete, P.; Pecker, M.; Sonn, J. K.; Vassalle, M. *J. Mol. Cell. Cardiol.* **1985**, *17*, 1043.
18 Santana, L. F.; Gomez, A. M.; Lederer, W. J. *Science,* **1998,** *279*, 1027.
19 Sagawa, T.; Sagawa, K.; Kelly, J. E.; Tsushima, R. G.; Wasserstrom, J. A. *Am. Journ. of Physiology-Heart and Circulatory Physiology* ,**2002,** *282*, H1118.
20 Adapted from: Schwinger, R. H. G.; Bundgaard, H.; Müller-Ehmsen, J.; Kjeldsen, K. *Cardiovascular Research,* **2003**, *57*, 913.
21 (a) Ueda, J.; Tezuka, Y.; Banskota, A. H.; Tran, Q. L.; Tran, Q. K.; Saiki, I.; Kadota, S. *J. Nat. Prod.* **2003**, *66*, 1427. (b) Laphookhieo, S.; Cheenpracha, S.; Karalai, C.; Chantrapromma, S.; Rat-a-pa, Y.; Ponglimanont, C.;

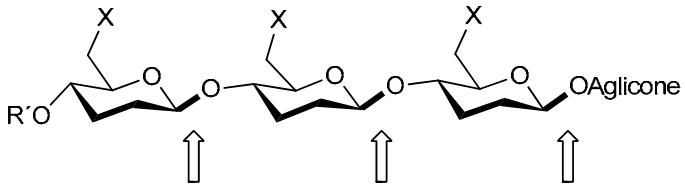
certain carbohydrate–modified moieties have been synthesized to impair Na/K ATPase activity and improve tumor–specific cytotoxic activity.[22]

1.1.3 Challenges in the Synthesis of 2-Deoxyglycosides

Once the biological importance of 2-deoxyglycosides was discovered, interest in the synthesis of these products increased. The ultimate goal for glycosyl chemists is to obtain 2-deoxyoligosaccharides in a highly efficient and stereoselective manner.

The target of the synthesis of 2-deoxyglycosides is obtaining oligosaccharides by glycosylation, starting with 2-deoxymonomers in a highly stereoselective fashion. (Figure 1.3)

Figure 1.3 Problems of the Glycosylic Bond Formation



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 1.1).

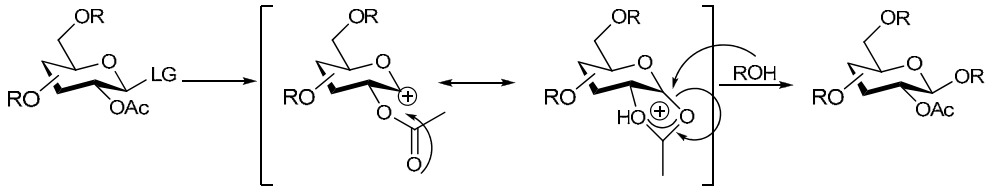
However, the application of this method is limited; it cannot be effectively used for the synthesis of 2-deoxyglycosides. Another problem associated with 2-deoxyglycoconjugates is that the absence of a hydroxyl group at C-2 makes the glycosyl bond much more labile to acid hydrolysis. This is the drawback of several carbohydrate drugs that are administered as oral medications.

In the absence of an ester group to serves as a stereodirecting neighbouring group at C-2, there is low stereoselectivity at the glycosylation step and an α/β mixture of glycosides is obtained (Scheme 1.2).

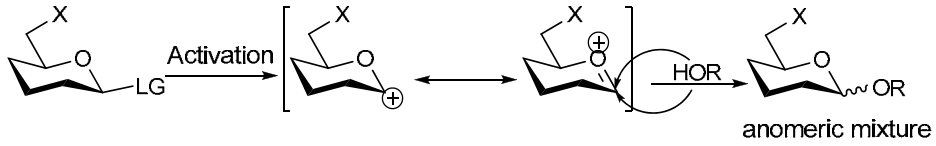
Chantrapromma, K. *Phytochemistry* **2004**, *65*, 507. (c) Kamano, Y.; Kotake, A.; Hashima, H.; Inoue, M.; Morita, H.; Takeya, K.; Itokawa, H.; Nandachi, N.; Segawa, T.; Yukita, A.; Saitou, K.; Katsuyama, M.; Pettit, G. R. *Bioorg. Med. Chem.* **1998**, *6*, 1103. (d) Lopez-Lazaro, M.; Pastor, N.; Azrak, S. S.; Ayuso, M. J.; Austin, C. A.; Cortes, F. *J. Nat. Prod.* **2005**, *68,* 1642.

[22] 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.

Scheme 1.1 Stereoselective Control of the Acyl Group



Scheme 1.2 Glycosylation Products without Stereoselective Assistant



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

1.1.4 Methods for the Synthesis of 2-Deoxyglycosides

Even with the above mentioned problems, there are many important antibiotic families prepared with 2-deoxyglycosyl structures. In the past few years, many synthetic strategies that allow for the synthesis of 2-deoxyglycosides have been published.[23] The objective of this chapter is to briefly review these methods, which are classified according to the control elements used in position C-2 and the leaving group strategy. The selectivities of these synthesis methods will also be compared.

1.1.4.1 No Control Element at C-2

When there is no control element at position C-2, the ratio of α/β products depends on some combination of control elements known as *´kinetic anomeric effect´* and *´thermodynamic effect´*. These favour axial linkage of nucleophilic species at C-1 and so produce mostly the α-product. Many

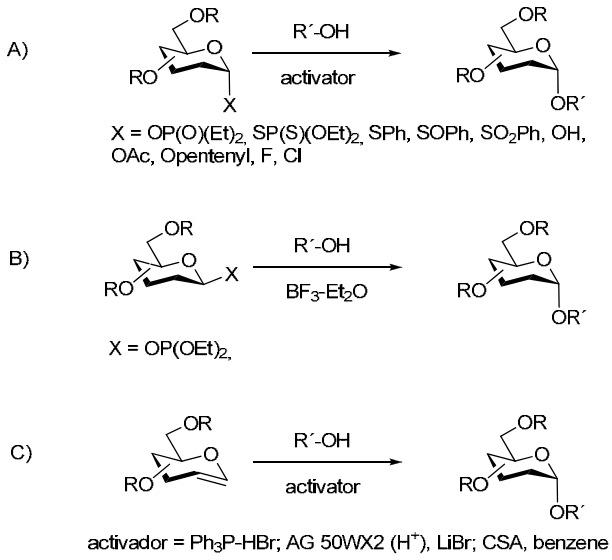
[23] (a) Marzabadi, C. H.; Franck, R. W. *Tetrhadron* **2000**, *56*, 8385. (b) Kirschning, A.; Bechtold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1.

anomeric leaving groups have been used at C-1 in the last few decades to increase the selectivity of the glycosylation without a C-2 control element.

Synthesis of 2-Deoxy-α-glycosides

2-Deoxy-α-glycosides can be obtained from 2-deoxy glycosyl donors driving the glycosylation under thermodynamic conditions. 2-Deoxy-α-glycosides can be prepared without a control element at C-2 from a thioether,[24] sulfoxide,[25] phenylsulfonyl group,[26] pyridylthiol, 2-pyridyl carboxylic acid,[27] fluoro glycoside,[28] glycosyl derivatives as *n*-pentenyl,[29] or phosphate,[30] as well as from an inactivated hydroxyl at C-1,[31] or by starting with glycals[32] (Scheme 1.3, A).

Scheme 1.3 Selected Methods for the Synthesis of 2-Deoxy-α-glycosides without a Control Element at C-2



[24] (a) Ravi, D.; Kulkarni, V. R.; Mereyala, H. B. T*etrahedron Lett.* **1989**, *30*, 4287. (b) Toshima, K.; Nozaki, Y.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 6887.

[25] Ge, M.; Thomson, C.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 11014.

[26] Brown, D. S.; Ley, S. V.; Vile, S.; Thompson, M. *Tetrahedron* **1991**, *47*, 1329.

[27] Furukawa, H.; Koide, K.; Takao, K-I.; Kobayashi, K. *Chem. Pharm. Bull.* **1998**, *46*, 1244.

[28] (a) Junneman, J.; Lundt, I.; Thiem, J. *Liebigs Ann Chem*. **1991**, 759. (b) Schene, H.; Waldmann, H. *Chem. Commun.* **1998**, 2759.

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

[30] Koch, A.; Lamberth, C.; Wetterich, F.; Giese, B. *J. Org. Chem.* **1993**, *58*, 1083.

[31] Takeuchi, K.; Higuchi, S.; Mukaiyama, T. *Chem. Lett.* **1997**, 960.

[32] (a) Bolitt, V.; Mioskowski, C.; Lee, S-G.; Flack, J. R. *J. Org. Chem.* **1990**, *50*, 4576. (b) Nicolaou, K. C.; Trujillo, J. I.; Chibale, K. *Tetrahedron* **1997**, *53*, 8751. (c) Sabesan, S.; Neira, S. *J. Org. Chem. 1991*, *56*, 5468. (d) Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 3471. (e) Thiem, J.; Kopper, S. *Tetrahedron* **1990**, *46*, 113. (f) Izumi, M.; Ichikawa, Y. *Tetrahedron Lett.* **1998**, *39*, 2079.

α-Products were also obtained from β-configured glycosyl phosphites[33] (Scheme 1.3, B). Another important and general method for synthesizing 2-deoxy-α-glycosides is simply the acid–catalyzed activation of glycals in the presence of an acceptor to afford the final glycoside.[34] However, the acid catalyst has to be carefully chosen to avoid the Ferrier allylic rearrangement. A Ph_3P–HBr system is usually employed as a weak acid source (Scheme 1.3, C).

Synthesis of 2-Deoxy-β-glycosides

The absence of electron–withdrawing substituents on the saccharide units readily promotes the anomerization of β-glycosides under acidic glycosylation conditions. Furthermore, it is difficult to achieve glycosylation in a stereoselective manner when neighbouring–group participation from substituents at C-2 is unavailable and an enhanced conformational flexibility owing to a reduced number of substituents. However, several methods are available for direct β-selective glycosylations using 2-deoxy glycosyl donors[35] (Scheme 1.4, A). 2-Deoxy-β-glycosides can be prepared without a control element at C-2 with an inactivated hydroxyl group at C-1[36] using radical chemistry[37] or β-fluoro glycosides[38] (Scheme 1.4, B) or the acid–catalyzed activation of glycals[39] with Ph_3P–HBr (Scheme 1.4, C).

Alternatively, Zhou and O'Doherty have developed a linear and stereocontrolled route to the mono-, di-, and trisaccharide of Digitoxin.[40] This *de novo* procedure starts with the palladium–catalyzed glycosylation of digitoxigenin **II** with pyranone **I** to render product **III,** a single diastereoisomer. Further reduction, rearrangement, and dihydroxylation produces deprotected monodigitoxoside **IV**. Repetition of these procedures in an iterative manner yields the disaccharide first and, eventually, Digitoxin (Scheme 1.5).

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33 Paterson, I.; McLeod, M. D. *Tetrahedron Lett.* **1995**, *36*, 9065.

34 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. (b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc*. **2004**, *126*, 3428. (c) Toshima, K.; Nagai, H.; Ushiki, Y.; Matsumara, S. *Synlett*, **1998**, 1007.

35 (a) Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 2505. (b) Pongdee, R.; Wu, B.; Sulikowski, G. A. *Org. Lett*. **2001**, *3*, 3523. (c) Hashimoto, S. I.; Sano, A.; Sakamoto, H.; Nakajima, I.; Yanagiya, Y.; Ikegami, S. *Synlett* **1995**, 1271. (d) Toshima, K.; Misawa, M.; Ohta, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1989**, *30*, 6417. (e) Binkley, R. W.; Koholic, D. J. *J. Org. Chem.* **1989**, *54*, 3577.

36 Finzia, G. J. *Carbohyd. Chem.* **1998**, *17*, 75.

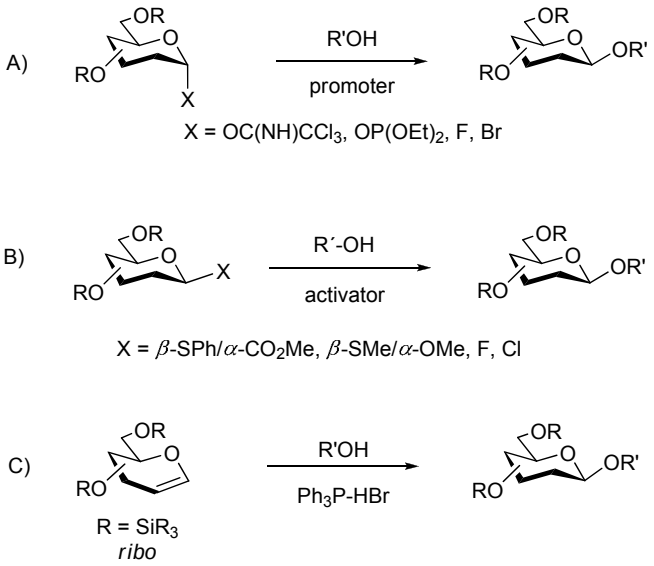
37 (a) Crich, D.; Hermann, F. *Tetrahedron Lett.* **1993**, *34*, 3385. (b) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716.

38 Junneman, J.; Lundt, I.; Thiem, J. *Liebigs Ann. Chem*. **1991**, 759.

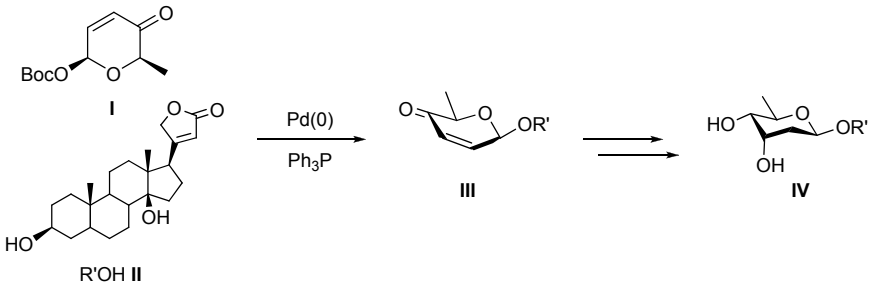
39 (a) Jaunzems, J.; Kashin, D.; Schönberger, A.; Kirschning, A. *Eur. J. Org. Chem.* **2004**, 3435. (b) McDonald, F. E.; Wu, M. *Org. Lett*. **2002**, *4*, 3979. (c) McDonald, F. E.; Reddy, K. S. *Angew. Chem. Int. Ed.* **2001**, *40*, 3653. (d) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc*. **2000**, *122*, 4304.

40 (a) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485. (b) Zhou, M.; O'Doherty, G. A. *Org. Lett*. **2006**, *8*, 4339.

Scheme 1.4 Selected Methods for the Synthesis of 2-Deoxy-β-glycosides (from 2-Deoxy Glycosyl Donors and Acid–catalyzed Strategies)



Scheme 1.5 Selected Method for the Synthesis of 2-Deoxy-β-glycosides (*de Novo* Metal–Catalyzed Strategy)



1.1.4.2 Control Element at C-2

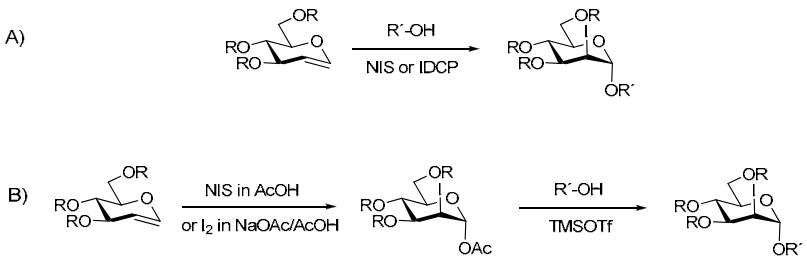
When a control element is present at C-2, it is usually a heteroatomic group. The advantage of this approach is that once the anomeric group is activated, the group at C-2 can act as a Lewis base, controlling the stereoselectivity of the glycosylation. This strategy furnishes 1,2-*trans* glycosides.

Synthesis of 2-Deoxy-α-glycosides

Halogens have been found to add to the top face of D-glycals; the oxonium intermediates[41] afford *trans*-diaxial products. Attack of the intermediates by alcohol nucleophiles produces mainly *trans*-2-halo-glycosides. The rate of diastereomers formed in the reaction is highly dependent on the halogen. It was observed that iodine has the best selectivity, with decreasing selectivity from bromine to chlorine. One of the main advantages of these halogen groups is that they can be removed easily to form 2-deoxyglycosides.

There are several examples of halogen–controlled glycosylation in the literature. In this chapter, examples are classified by the reaction strategy. Two strategies can be distinguished: a) glycal is activated with an electrophilic halogen source in the presence of a glycosyl donor to give the 2-iodo-2-deoxy glycoside in a so called *´one-pot´* reaction, such α-glycosides were obtained starting directly from glycals, as described by Thiem (Scheme 1.6, A);[32e,42] or b) the 2-halogenated glycosyl donor is isolated and subsequently activated in the presence of an alcohol acceptor,[43] α-glycosides were obtained in two steps, through 2-iodoglycosyl donors, as described by Roush (Scheme 1.6, B).[44]

Scheme 1.6 Synthesis 2-α-Deoxy-glycosides from Glycals



Synthesis of 2-Deoxy-β-glycosides

Although the addition of electrophiles to glycals in the presence of an acceptor has become a useful protocol for directly providing α-linked disaccharides, this same protocol is not frequently used

[41] (a) Bravo, F.; Viso, A.; Alcazar, E.; Molas, P.; Bo, C.; Castillon, S. *J. Org. Chem.* **2003**, *68*. 686. (b) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel. K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521.

[42] (a) Kopper, S.; Thiem, J. *Carbohydr. Res.* **1994**, *260*, 219. (b) Izumi, M.; Ichikawa, Y. *Tetrahedron Lett.* **1998**, *39*, 2079.

[43] Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1990.

[44] Kirschinng, A. *Eur. J. Org. Chem.* **1998**, 2267.

to obtain *β*-glycosides.[45] Glycosyl donors bearing halogens or chalcogens at C-2 are the more commonly employed precursors for the synthesis of *β*-linked disaccharides and oligosaccharides.[46] The addition of any electrophilic iodine 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.[47] 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 hypervalent iodine reagents.[44] The best results were obtained when the D-glycal precursor lacked oxygenation at C-6, or when it was *bis*-silylated and could readily exist in a twisted boat conformation $^{5}H_{4}$ (Scheme 1.7, A).

All other glycosyl donors that adopt the normal $^{4}C_{1}$ conformation and/or have deactivating heteroatom substituents at C-6 require higher temperature. 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[48] (Scheme 1.7, B).

When configurations that are 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. 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 1.7, C).[49]

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45 For some approaches using glycals through a *´one-pot´* procedure, see: (a) Franck, R. W.; Kaila, N. *Carbohydr. Res.* **1993**, *239*, 71. (b) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084. (c) Ramesh, S.; Franck, S. W. *J. Chem. Soc., Chem. Commun.* **1989**, 960. (d) Preuss, R.; Schmidt, R. R. *Synthesis* **1988**, 694. (e) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 4701.

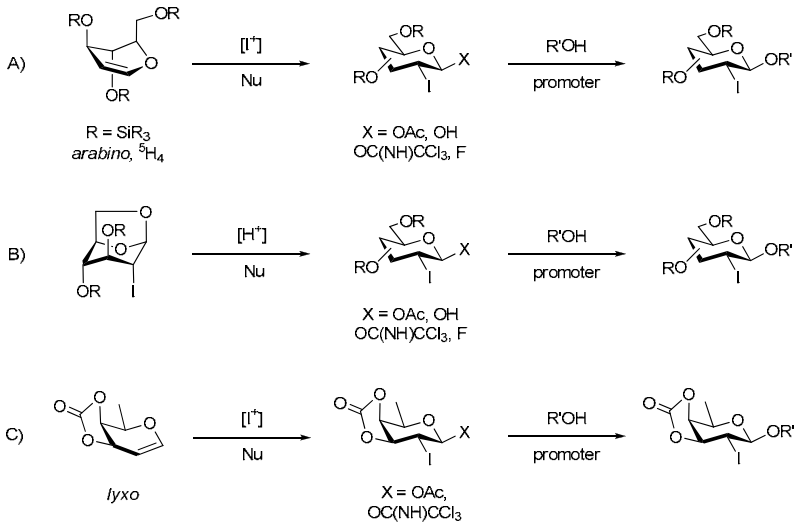
46 For some approaches using glycals through a two-step procedure, see: (a) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1875. (b) Blanchard, N.; Roush, W. R. *Org. Lett.* **2003**, 5, 81. (c) Chong, P. Y.; Roush, W. R. *Org. Lett*. **2002**, *4*, 4523. (d) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc*. **2000**, *122*, 6124. (e) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891. (f) Dräger, G.; Garming, A.; Maul, C.; Noltemeyer, M.; Thiericke, R.; Zerlin, M.; Kirschning, A. *Chem. Eur. J.* **1998**, *4*, 7. (g) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837. (h) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825. (i) Roush, W. R.; Briner, K.; Kesler, B. S.; Murphy, M.; Gustin, D. J. *J. Org. Chem.* **1996**, *61*, 6098. (j) Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc*. **1996**, *118*, 9998. (k) Perez, M.; Beau, J. M. *Tetrahedron Lett.* **1989**, *30,* 75. (l) Thiem, J.; Schottmer, B. *Angew. Chem, Int. Ed, Engl.* **1987**, *26*, 555.

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

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

49 Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1871.

Scheme 1.7 Selected Methods for the Synthesis of 2-Deoxy-*β*-glycosides (from Glycals and 2-Halo Glycosyl Donors)



Interestingly, in the presence of alcohols, electrophilic sulfur and selenium species 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, conformation of the reacting glycal, and nature of the substituents on the glycal (Scheme 1.8, A). For D-glycals that exist in the normal $^4H_5$ conformation, sulfonium species have been observed to attack predominately from below the plane of the glycal. The good selectivities obtained from electrophilic sulfur reagents have given rise to their extensive use for the preparation of 2-deoxy-2-thio-*β*-glycosides. The sulfur group at C-2 is easily removed to afford the 2-deoxy-*β*-glycosides. In addition, different face–selectivity approaches are observed for the two electrophiles, sulfur and selenium.

Alternatively, special glycosyl donors with substituents at C-2[50] acting as neighboring groups or 1,2-anhydropyranoses[51] are used, followed by reductive removal of the substituents at C-2. Nicolaou and co-workers[52] reported an original approach for preparing 2-deoxy-2-phenylsufanyl- and 2-phenylselelenenyl-*β*-glucopyranosyl fluorides whereby 1-thio-*α*- and 1-seleno-*α*-glycosides are reacted with the unprotected hydroxyl group at C-2 with diethylaminosulfur trifluoride (DAST) (Scheme 1.8, B). DAST first reacts with the hydroxyl group at C-2 converting it into a good leaving group and

[50] (a) Yu, B.; Yang, Z. *Org. Lett.* **2001**, *3*, 377. (b) Castro-Palomino, J. C.; Schmidt, R. R. *Synlett* **1998**, 501.

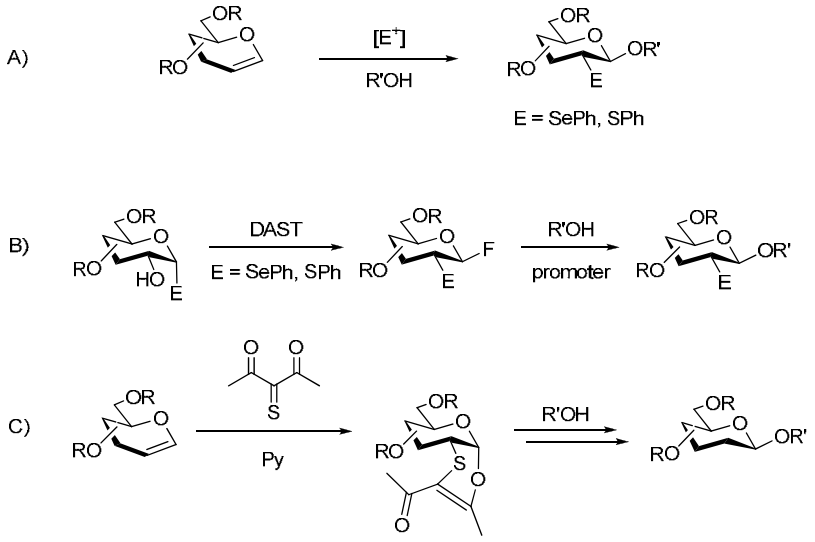
[51] Gervay, J.; Danishefsky, S. J. *J. Org. Chem.***1991**, *56*, 5448.

[52] (a) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466. (b) Nicolaou, K. C.; Mitchell, H. J.; Fylaktakidou, K. C.; Suzuki, H.; Rodríguez, R. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 1089.

delivering a fluoride anion. A 1,2-migration of the group at the anomeric position and concomitant entry of fluorine at position C-1 produces the 2-deoxy-2-phenylsufanyl- and 2-phenylselenenyl-*β*-glucopyranosyl fluorides. These compounds are excellent glycosyl donors and have allowed for the synthesis of complex oligosaccharides.

In a novel approach, following the elegant synthesis of 2-aminosugar glycosides by [4+2] cycloaddition of azodicarboxylates to glycals,[53] Franck and co-workers[54] developed new bicyclic donors for the synthesis of 2-deoxy-*β*-glycosides. The cycloaddition appears to be a reaction with inverse electron demand, since the smallest differences in energy are between the HOMO of the glycal dienophile and the low–lying LUMO of the heterodiene (Scheme 1.8, C).

Scheme 1.8 Selected Synthesis of 2-Deoxy-*β*-glycosides with sulfur and Selenium as Control Elements at C-2



β-Glycosides have been prepared in modest yields from various derivates of *N*-formylglucosamine. Intermediate oxazolinium ions are thought to give rise to a high level of *β*-selectivity in these glycosylation reactions (Scheme 1.9).[55]

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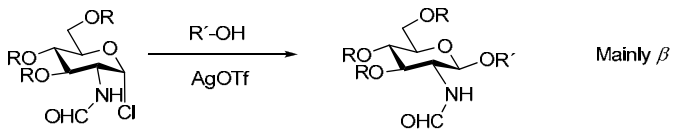
53 Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995.

54 (a) Dios, A.; Nativi, C.; Capozzi, G.; Franck, R. W. *Eur. J. Org. Chem.* **1999**, 1869. (b) Dios, A.; Geer, A.; Marzabadi, C. H.; Franck, R. W. *J. Org. Chem.* **1998**, *63*, 6673. (c) Marzabadi, C. H.; Franck, R. W. *J. Org. Chem.* **1998**, *63*, 2197.

55 Capozzi, G. Dios, A.; Franck, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Ang. Chem. Int. Ed. Engl.* **1996**, *35*, 777.

Scheme 1.9 Selected Synthesis of 2-Deoxy-β-glycosides with Oxygen and Nitrogen as Control Elements at C-2

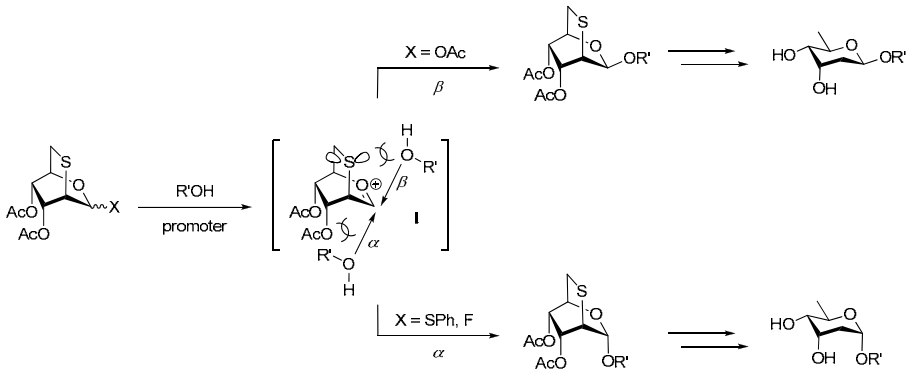


Synthesis of 2-Deoxy-α-glycosides or 2-Deoxy-β-glycosides by Stereocontrol

Toshima and Tatsuta developed a conceptually different approach, 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.[56] 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 1.10).

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.

Scheme 1.10 Selected Synthesis of 2-Deoxy-α- or 2-Deoxy-β-glycosides from 2,6-Anhydro-2,6-dideoxy-2,6-dithio Sugars



[56] Toshima, K. *Carbohydr. Res.* **2006**, *341*, 1282 and references therein.

In this way, both anomers can be stereoselectively obtained, depending on the reaction condition. However, when the 3-*O*-substituent is equatorial, no 1,3-diaxial interaction is present and the *α*-glycoside is thermodynamically stable. The high reactivity of 2,6-anhydro-2-thioglycosyl donors is due to the electro–donating nature of the bridging sulfur atom. Indeed, the derived sulfoxides and sulfones have no glycosylating power and can thus be implied in block synthesis exploiting the armed–disarmed effect.

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) and no reports of the synthesis of 2,6-dideoxy-D-*xylo*-hexoglycosides (D-boivinose), probably because of the difficulty of obtaining the corresponding glycals. Consequently, efficient methods for glycosylation, which are among the most fundamental and important reactions performed with carbohydrates, are of particular interest in the synthesis of these rare and biologically important configurations.

1.1.5 Synthesis of 2-Deoxyglycosides from Furanoses through an Olefination – Cyclization – Glycosylation Process

Our group presented a new method for the synthesis of 2-desoxyglycosides 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 to yield an alkenyl derivative, electrophilic iodine–induced cyclization to give phenyl 2-deoxy-2-iodo-1-thiopyranosides as a new type of glycosyl donor,[57] and finally glycosylation[44,47,49,58] for synthesis of the natural product[59] (Scheme 1.11 and Scheme 1.12).

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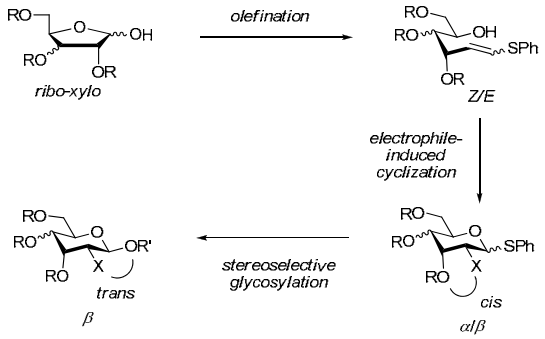
[57] Boutureira, O.; Rodríguez, M. A.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Org. Lett.* **2006**, *8*, 673. (b) Rodríguez, M. A.; Boutureira, O.; Arnés, X.; Matheu, M. I.; Díaz, Y.; Castillón, S. *J. Org. Chem.* **2005**, *70*, 10297. (c) Arnés, X.; Díaz, Y.; Castillón, S. *Synlett* **2003**, 2143. d) Boutureira, O. Tesis Doctoral, Tarragona, **2007**. e) Rodríguez, M. A. Tesis Doctoral, Tarragona, **2007**.

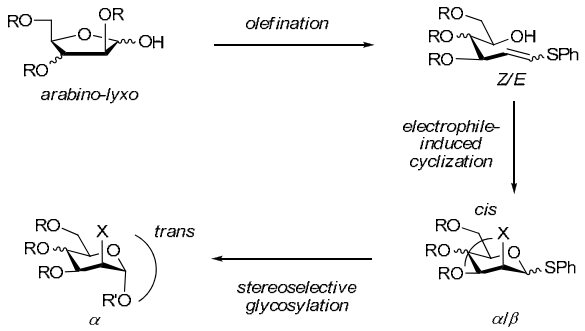
[58] For glycosylation methods that involve the use of 2-iodo-deoxy glycosyl donors see: (a) Kirschning, A.; Jesberger, M.; Schöning, K-U. *Org. Lett* **2001**, *53*, 3623. (b) Roush, W. R.; Narayan, S.; Bennett, C. E.; Briner, K. *Org. Lett.* **1999***, 1*, 895. (c) Roush, W. R.; Narayan, S. *Org. Lett*. **1999**, *1*, 899. (d) For a procedure of synthesis of glycosides involving a mercury–induced cyclization of enolethers see: Paquet, F.; Sinaÿ, P. *Tetrahedron Lett.* **1984**, *25*, 3071.

[59] 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. (b) Bai, H.; Li, W.; Koike, K.; Satou, T.; Chen, Y.; Nikaido, T. *Tetrahedron* **2005**, *61*, 5797.

Scheme 1.11 General Scheme for the Synthesis of 2-Deoxy-2-iodo-pyranosylglycosides from *Ribo*/*Xilo* pentofuranoses



Scheme 1.12 General Scheme for the Synthesis of 2-Deoxy-2-iodo-pyranosylglycosides from *Arabino*/*Lyxo* Pentofuranoses



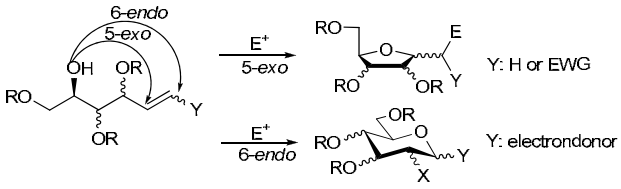
The olefination of pentoses under Wittig–Horner (WH) conditions, using phosphine oxide carbanoins and Li–bases, proved the most effective for chemoselectivity, diastereoselectivity, and yield of alkene formation. As expected for semistabilized carbanions, the reaction yielded *Z*/*E* alkene mixtures.[57c-e,60]

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

[60] Arnés Novau, X. Tesis Doctoral, Tarragona, **2003**.

the Baldwin's rules (Scheme 1.13);[61] however, there are some reactions that do not follow the Baldwin's rules. Our group has extensively studied the parameters that govern the electrophile–induced cyclization of alkenols, such as the electrophilic species, protective groups, solvent, and base, kinetic or thermodynamic conditions. When terminal double bonds are involved in the reaction, the *exo*-cyclization mode is usually favoured. The examined reactions show irreversibility in the presence of base.[62]

Scheme 1.13 The Effect of Y Group by Electrophile–Induced Cyclization



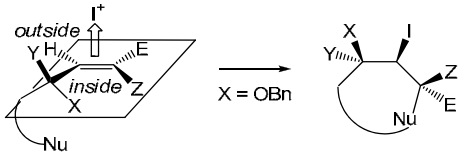
When a sulfanyl group is attached to the terminus of the double bond, however, the reaction is completely regioselective, and the 6-*endo* product is obtained. This regiochemical outcome can be explained by stabilization of the carbocation in the α-position of the electro–donating group. In contrast, the presence of an electron–withdrawing group favours the *exo*-attack, which could be considered a Michael reaction.

The effect of an iodine electrophile and an allylic substituent on the stereoselectivity of the cyclization was also studied.[63] It was found that the iodine, which is located in the C-2 position of the final hexose, as a result of electrophilic induced cyclization, was situated at the *cis*-position with respect to the C-3 alkoxy substituent, the formerly allylic group in the alkene substrate. This phenomenon can be explained with the so-called *´inside-alkoxy effect´*.[64] This stereoelectronic effect directs the conformation of the alkene to the most reactive position, where the allylic alkoxy is situated in the inner position of the plane of double bond and there is a minimum overlap between the double bond π orbital and the C–O bond σ* orbital. In such a conformation, therefore, the electron–withdrawing effect of the alkoxy group over the double bond is minimized, and the latter is then most reactive towards an electrophile (Scheme 1.14).

61 Knight, D. W.; Jones, A. D.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett*. **1999**, 40, 3267
62 Guindon, Y.; Soucy, F.; Yoakim, C.; Ogilvie, W. W.; Plamondon L. *J. Org. Chem*. **2001**, *66*, 8992.
63 Castillón, S.; Bravo, F. *Eur. J. Org. Chem.* **2001**, *507.*
64 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.

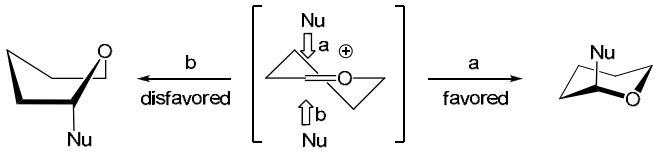
This theory would explain the low reactivity observed with *Z*-vinyl sulfides, where the allylic alkoxy group takes an *outside* position due to a high steric hindrance in the *inside*-conformation. In this conformation, the double bound is less electron-rich and therefore the cyclization was slower and in some classes precluded (Scheme 1.14).

Scheme 1.14 The *Inside-Alkoxy Effect* by Electrophile–Induced Cyclization



In light of previous data obtained from our group on glycosylation reactions, it was thought that the oxocarbenium intermediates play an important role in the stereoselectivity of these glycosylation reactions, rather than the corresponding iodonium–ion intermediates (Scheme 1.15).[42,46,49,57,65]

Scheme 1.15 Nucleophilic Attack on the Oxocarbenium Cations



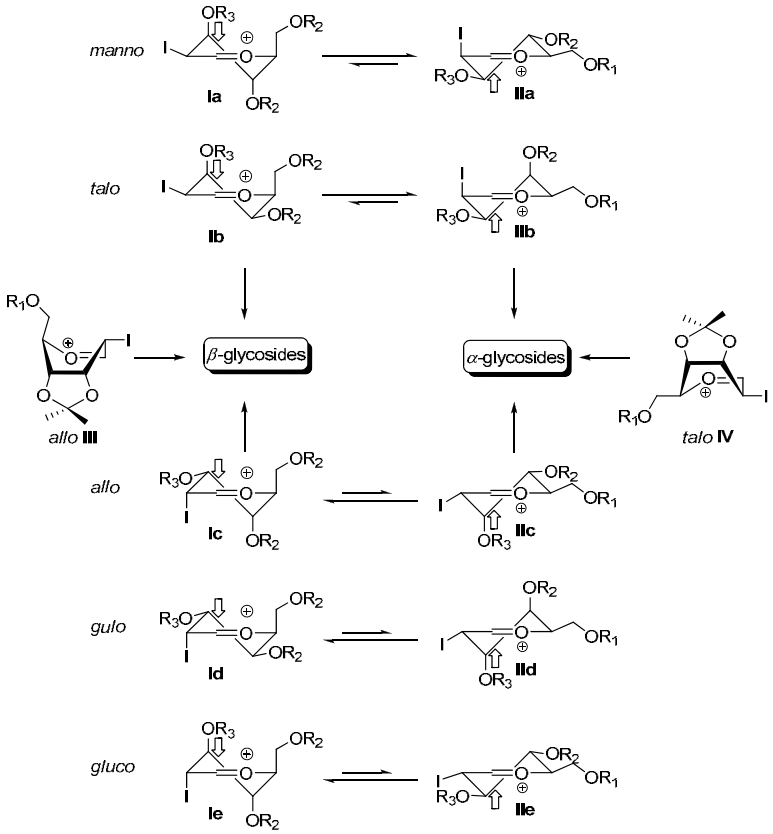
The selectivity observed would be determined by the nucleophilic attack on the oxocarbenium cations, the ground-state conformational preferences of these intermediates **Ia-e** and **IIa-e**, and the relative reactivity of each conformer, as mandated by Curtin–Hammet/Winstein–Holmess kinetics (Scheme 1.16).[66] Thus, according to the results reported by Billings and co-workers,[42b,67] I-axial intermediates **IIa,b** (D-*manno* and D-*talo*) and **Ic-e** (D-*gluco*, D-*allo* and D-*gulo*) are likely to be more stable than the corresponding I-equatorial conformers due to stabilizing hyperconjugative interactions between $\sigma_{C\text{-}I}$ and $\pi^*_{C\text{-}O}$ of the oxocarbenium. Additionally, it is known that nucleophilic attack on the

[65] Boutureira, O.; Rodríguez, M. A.; Benito, D.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 3564.
[66] Seemann, J. I. *Chem. Rev.* **1983**, *83*, 83.
[67] Billings, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171.

oxocarbenium cations along a pseudoaxial trajectory to maximize overlap of the nucleophile HOMO with the LUMO of the oxocarbenium ion occurs with a facial preference to give a chair–like transition state. According to this stereoelectronic effect, the reaction of each conformer is expected to provide a different diastereomer of the product. 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.

Consistent with this idea, glycosylation of D-*manno* and D-*gulo* derivatives provide excellent α- and β-selectivities, respectively; by far the more stable axial I conformers **IIa** (D-*manno*) and **Id** (D-*gulo*) are also more reactive towards nucleophilic attack. The D-*allo* derivative shows moderate β-selectivity. When compared to the D-*gulo* derivative, the lower selectivity magnitude obtained could be explained by ground–state conformational preference variations.

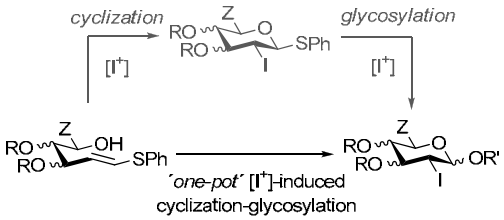
Scheme 1.16 Stereochemical Courses of Glycosylation Reactions of 2-Deoxy-2-phenylselenenyl-1-thio-glycosyl Donors



In the D-*allo* derivative, the more reactive conformer **Ic** is also the more stable one (axial I); however, in this case the 1,3-diaxial interactions between I and the C-4 alkoxy group may increase its energy with respect to the case of D-*gulo* derivative, where such destabilizing interactions do not exist. The D-*gluco* donor provides no selectivity, probably because the reactivity of the more stable I-axial conformer **Ie** is seriously attenuated by steric interactions of the incoming nucleophile with the pseudoaxial C-3 substituent. Finally, to rationalize the observed β- and α-face approach of donors D-*allo* and D-*talo* with restricted (3,4-*O*-isopropylidene) protecting groups, respectively, it was thought that the reaction might operate by way of a constrained conformation[44,68] such as **III** and **IV** (Scheme 1.16). However, β-selectivity in the 3,4-*O*-isopropylidene protected D-*tallo* derivative is lower than observed in the benzyl protected D-*tallo* derivative, suggesting that the relative enhancement of α-selectivity is, in this case, predominantly a temperature effect.

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.[57] 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 eliminates 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 1.17).[69]

Scheme 1.17 Refinement of the Original Stepwise Sequential Procedure into a More Efficient *´One-pot´* Cyclization–Glycosylation Process



[68] For a recent review dealing with the use of cyclic bifunctional protecting group in oligosaccharide synthesis, see: Litjens, R. E. J. N.; van den Bos, L. J.; Codée J. D. C.; Overkleeft, H. S.; van der Marel, G. A. *Carbohydr. Res.* **2007**, *342*, 419.

[69] Rodríguez, M. A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 2470.

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 our methodology (Figure 1.4). 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 1.5).

Figure 1.4 *Accessible* Configurations with the Strategy of Olefination and Cyclization (*allo*, *manno*, *gulo*, and *talo*)

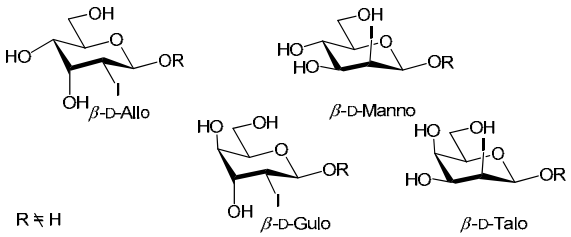
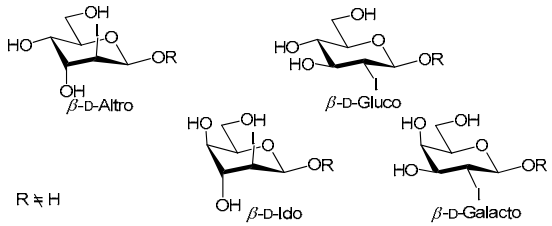


Figure 1.5 Configurations that are *not Accessible* with Olefination and Cyclization (*altro*, *gluco*, *ido*, and *galacto)*



The elimination of the iodine moiety could follow two synthetic strategies, depending on the application, sensibility of the compounds intermediates, and the glycosides.

Based on data presented in the literature and work already discussed in this section, it can be concluded that 2-deoxyglycosides can be successfully prepared from furanoses through an olefination–cyclization–glycosylation process.

As an initial step in this process, the WH olefination reaction can be used to successfully synthesize the desired sulfanyl alkenes with good to excellent yields, although usually in *E*/*Z* mixtures.

Our group has studied in depth the electrophilic cyclization reactions with different electrophiles. Iodine was found to be an appropriate electrophile in these reactions, since it efficiently induces

cyclizations, is effective in controlling the stereoselectivity of the reaction, and can be easily removed to yield 2-deoxyglycosides. Other electrophiles, such as selenium and sulfur derivatives, may be also considered.

These cyclization reactions are limited by the usual presence of *Z*-alkenes, since under conditions applied, these molecules cyclize significantly more slowly, as in the case of sulfanyl alkenes from ribofuranose, or not at al, as in the case of sulfanyl alkenes from arabinofuranose.

As thioglycosides have been successfully used in glycosylation strategies,[70] the 2-deoxy-2-iodo thioglycosides synthesized in our group were used as glycosyl donors in the stereoselective synthesis of 2-deoxy-2-iodo glycosides. Glycosylation proceeds with good to excellent yields and stereselectivities. The *´one-pot´* cyclization–glycosylation procedure starting from the alkenyl sulfide, also provides good yields of 2-deoxy-2-iodo-glycoside with practically no loss of stereoselectivity.

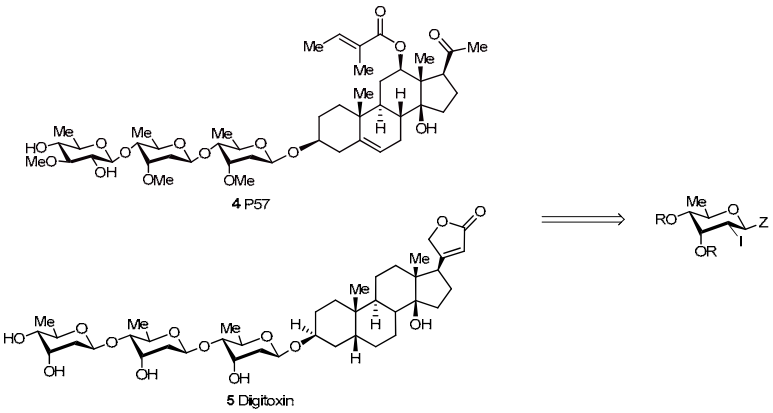
1.2 Goals

The specific aims of this work are:

1. Since *Z*-alkenes are rather reluctant to cyclization in the context of our synthetic olefination–cyclization–glycosylation strategy, it is necessary to improve *E*-alkene selectivity in the olefination reaction in order to increase the overall yield of final glycoside. For this reason, we designed the preparation of a library of sulfanylphosphine oxides with different SR bulky groups. The Second Chapter describes a new and simple method for the synthesis of sulfanylphosphine oxides and their use in the Wittig–Horner olefination reaction of pentoses to furnish 2-deoxy-2-iodo thioglycosides and subsequent stereoselective glycosylation of different glycosyl acceptors with the latter. The electronic and steric effects of SR group are studied not only in relation to the olefination reaction but also to cyclization and glycosylation.
2. Although our group obtained good results with the olefination reactions of furanoses and subsequent 6-*endo* cyclization reactions furnishing 2-deoxy-2-iodo-1-thiopyranosides, we had no previous evidence to determine whether this strategy would also be successful for the ring expansion of pyranoses to obtain heptoses *via* olefination and subsequent 7-*endo* cyclization reaction of the corresponding heptenyl sulfide. In the Third Chapter, the synthesis study of septanosides is described.

[70] Thio–Glycosides are useful glycosyl donors, see for instance: (a) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 172. (b) Codeé, J. D. C.; Litjens, R. E. J. N.; van der Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769.

3. The novel synthetic process developed in our group needs to be applied to natural product synthesis. Hence, two natural products were selected with similar structural 2,6-dideoxy-glycosidic units: Digitoxin and the appetite suppressant P57.
4. In Fourth Chapter an approach for the synthesis of the desired structural units is described.

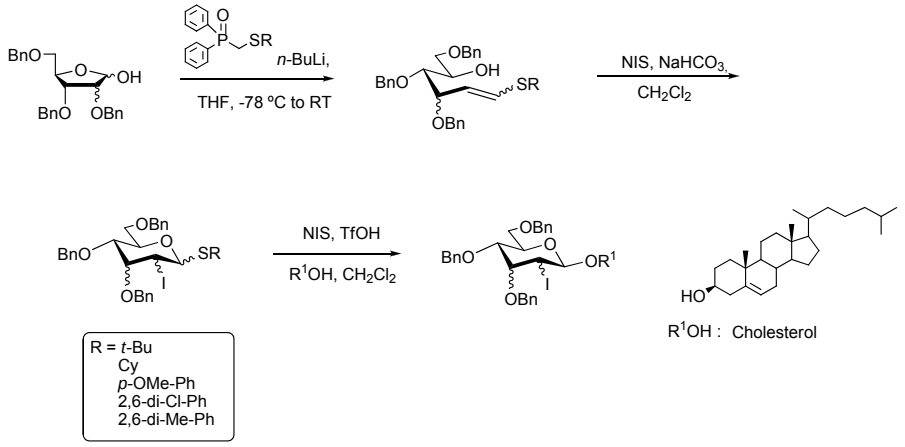


UNIVERSITAT ROVIRA I VIRGILI
STEREOSELECTIVE SYNTHESIS OF 2-DEOXYOLIGOSACCHARIDES.NEW APRROACHES TO THE SYNTHESIS OF DIGITOXIN AND P-57
Andrea Köver
978-84-691-9523-9 /DL: T-1261-2008

SECOND Chapter: Study of the Olefination, Cyclization and Glycosylation of *Ribo* and *Arabino* Derivatives

Abstract:

Phopshine oxides with general formula $Ph_2P(O)CH_2SR$ (R = *t*-butyl, cyclohexyl, *p*-methoxyphenyl, 2,6-dichlorophenyl, 2,6-dimethylphenyl) were used in the olefination reaction with 2,3,5-tri-*O*-benzyl-α,β-D-ribose and -arabinose to study the effect of a bulky R group in the stereoselective formation of desired alkenes or in electrophile–cyclization and glycosylation reactions.



"Nunca se da tanto como
cuando se dan esperanzas."

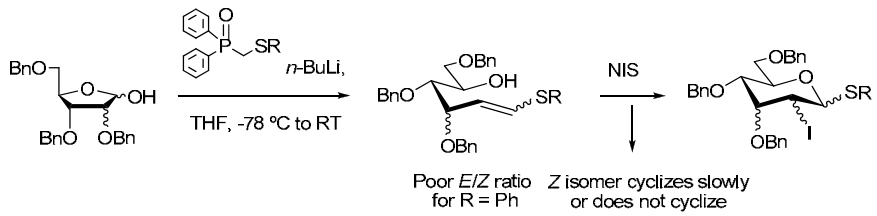
Anatole France, escritor francés

2.1 Introduction

2.1.1 The Need for Synthesis of Novel Phosphine Oxides

As discussed in the general introduction, our group has developed a general two-step procedure for synthesizing 2-deoxy-2-iodo-thioglycosides from furanoses. The first step is an olefination of furanoses to obtain sulfanylalkene derivatives, which undergoes a NIS–induced cyclization reaction to give 2-deoxy-2-iodo-1-thioglycosides in a regio- and stereoselective manner. In our previous work,[57] we observed that the *Z*-isomer cyclizes much more slowly than the *E*-isomer or not at all. Various reagents have been used in the olefination reactions of furanoses, including Wittig,[71] Wittig–Horner (WH),[72] Horner–Wadsworth–Emmons[73] and Peterson olefination.[74] We tested all these procedures and obtained the best results in chemoselectivity, diastereoselectivity, and yield of alkene formation under WH conditions,[74] that is using phosphine oxide carbanions formed by Li–bases. However, as expected for semistabilized carbanions, the WH olefination reaction produced *Z*/*E* alkene mixtures (Scheme 2.1). To increase the stereoselectivity of olefination and, consequently, the efficiency of cyclization, we studied the influence of different SR groups on the *E/Z*-ratio, where R can be a phenyl, substituted phenyl, *tert*-butyl, cyclohexyl, etc. For this study, we synthesized the (sulfanylmethyl)-diphenylphosphine oxides because many of these phosphine oxides had not been described in the literature.

Scheme 2.1 General Scheme for the Synthesis of Sulfanyl Glycosides from Furanoses



[71] Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

[72] (a) Warren, S.; Grayson, J. I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2263. (b) Clayden, J.; Warren, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 241. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1999**, *89*, 863.

[73] Corey, E. J.; Shulman, J. I. *J. Org. Chem.* **1970**, *35*, 777.

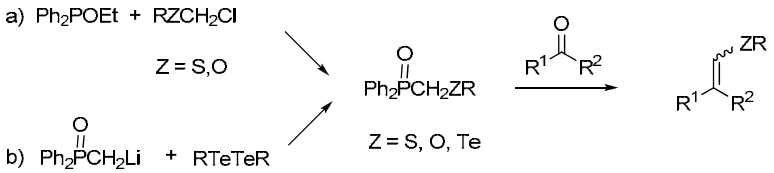
[74] Corey, F. A.; Court, A. S.; *J. Org. Chem.* **1972**, *37*, 939.

2.1.2 Previous Methods for the Synthesis of (Sulfanylmethyl)phosphine Oxides

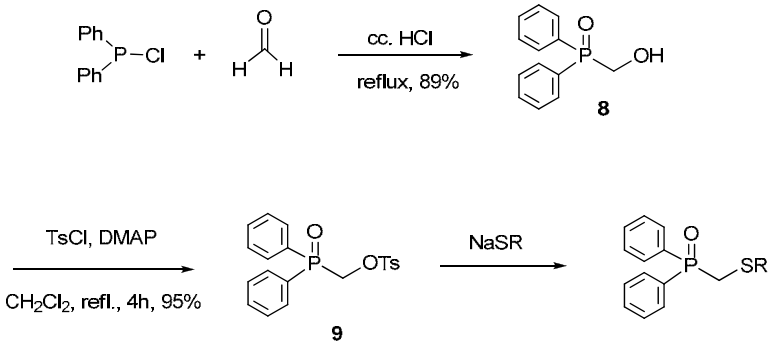
The most common procedure for preparing (sulfanylmethyl)phosphine oxide derivatives is the Arbuzov reaction,[75] which consists of reacting *O*-ethyl-diphenylphosphinite with a sulfanyl halide. The Arbuzov reaction with available chloromethyl thioethers[76] produce (sulfanylmethyl)phosphine oxides (Scheme 2.2a). The limitation of this reaction is that the required reagents for the Arbuzov reaction, $RSCH_2Cl$ are usually difficult to prepare and unstable.

An alternative procedure involves obtaining the α-heteroatom substituted derivative methylphosphine oxide by a reaction with *n*-BuLi and an electrophilic reagent. These reagents are often not available and must be specifically prepared (Scheme 2.2b).[77]

Scheme 2.2 Synthesis of Diphenylphosphine Oxides a) by Arbuzov Reaction, b) by Alkylation Reaction



Scheme 2.3 Synthetic Strategy of (Sulfanylmethyl)diphenylphosphine Oxide Derivatives



[75] Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev*., **1981**, *81*, 415.
[76] Dilworth, B. M.; McKervey, M. A. *Tetrahedron* **1986**, *42*, 3731.
[77] Silviera, C. C.; Benini, M. L.; Boeck, P.; Braga, A. L. *Synthesis*, **1997**, 221.

(Sulfanylmethyl)diphenylphosphine oxides[78] have been prepared from (tosyloxymethyl)-diphenylphosphine oxide **9** in a substitution reaction with a sulfide salt.[79,80] Tosyl derivative **9** can be prepared from the (hydroxymethyl)diphenylphosphine oxide **8**, which is obtained by reacting diphenylchlorophosphine with aqueous formaldehyde in concentrated hydrochloric acid. This procedure was considered more convenient for preparing a variety of (sulfanylmethyl)diphenylphosphine oxide derivatives since more common thiols or thiolates are used as nucleophilic reagents (Scheme 2.3).

2.2 Results and Discussion

2.2.1 Synthesis of (Sulfanylmethyl)diphenylphosphine Oxides and Sulfanyl Alkenes

To explore the steric effect of substitutions at the sulfur atom on the stereoselectivity of the WH reaction, we prepared various substituted (sulfanylmethyl)diphenylphosphine oxide derivatives using the procedure showed in Scheme 2.3. *p*-MeOPh derivatives were also prepared to obtain thioglycosides to be used in orthogonal glycosylations. Starting from (tosyloxymethyl)diphenylphosphine oxide **9**, phosphine oxides **10**–**15** were prepared in excellent yields in a reaction with thiolate anions, which were prepared from the corresponding thiols by treatment with NaH (Table 2.1).

We first explored the olefination of benzaldehyde using the phosphine oxides **10**–**15** to give sulfanyl alkenes **16**–**21**. Highly hindered sulfanyl alkenes **17**–**20** were obtained with good to excellent yields (entries 2–5, Table 2.1). High stereoselectivities (*E*/*Z* >10:1) were reached when sulfur substituted alkyl groups were used, and when there were 2,6-disubstituted arylsubstituents. The formation of β-hydroxyphosphine oxide intermediates was not observed in these syntheses.

Phosphine oxides **11** and **13** were treated with cyclohexanone in the presence of *n*-BuLi to give sulfanyl alkenes **22** and **23**, respectively, in excellent yields. Phosphine oxide **14**, which has a *tert*-butyl group, was made to react with acetophenone to give the sulfanyl alkene **24** with excellent yield and stereoselectivity (Table 2.2). The exact structure of compound **24** was not possible to confirm with 2D NMR studies so it is only a proposal.

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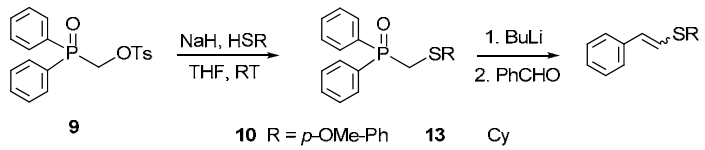
78 (a) Otten, P. A.; Davies, H. M.; Steenis, J. H.; Gorter, S.; van der Gen, A. *Tetrahedron*, **1997**, *53*, 10527. (b) Otten, P. A, Davies, H. M.; Van der Gen, A. *Phosphorus, Sulfur and Silicon and the Related Elements* **1996**, 109.

79 (a) De Wit, P. P.; van der Steeg, M.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 307. (b) Wegener, W. *Z. Chem.* **1971**, *11*, 262.

80 Marmor, R. S.; Seyferth, D. *J. Org. Chem.* **1969**, *34*, 748.

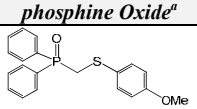
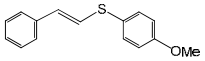
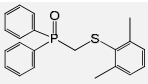
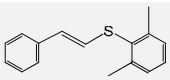
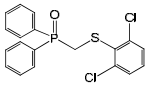
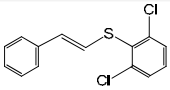
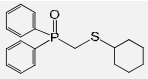
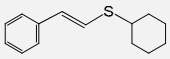
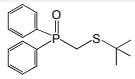
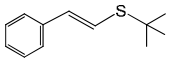
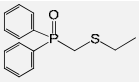
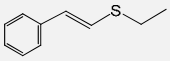
Table 2.1 Synthesis of (Sulfanylmethyl)diphenylphosphine Oxides **10**–**15** and Sulfanyl Alkenes **16**–**21**.



9

10 R = *p*-OMe-Ph
11 2,6-di-Me-Ph
12 2,6-di-Cl-Ph
13 Cy
14 *t*-Bu
15 Et

16 R = *p*-OMe-Ph
17 2,6-di-Me-Ph
18 2,6-di-Cl-Ph
19 Cy
20 *t*-Bu
21 Et

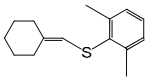
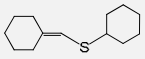
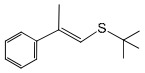
Entry	*(Sulfanylmethyl)diphenyl-phosphine Oxide*[a]	*Yield (%)*	*Sulfanyl Alkenes*[b]	*Yield (%)*	*E/Z Ratio*
1	 **10**	89	 **16**	93	1.3:1
2	 **11**	78	 **17**	75	11:1
3	 **12**	72	 **18**	63	15:1
4	 **13**	98	 **19**[c]	86	10:1
5	 **14**	89	 **20**	93	9:1
6	 **15**	79	 **21**	96	10:1

a) Conditions: NaSR (10.5 mmol), **9** (10 mmol), THF, 2h.
b) Conditions: Phosphine oxide (2.0 mmol), *n*-BuLi (3.5 mmol) in THF at –78 ºC, 0.5 h, then benzaldehyde (1.0 mmol), and warm up to room temperature.
c) LDA (3.5 mmol) was used.

2.2.2 Synthesis of Diphenylphosphine Oxides with General Formula $Ph_2P(O)CH_2XR$

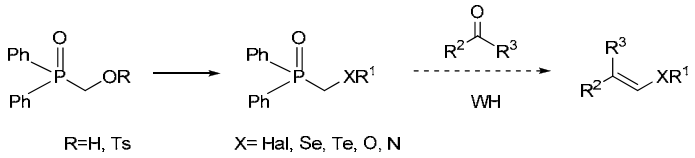
In Section 2.1, the (tosyloxymethyl)diphenylphosphine oxide **9** was shown to be an excellent starting material to obtain a variety of sulfanyl derivatives. We believed that this compound and its hydroxyl derivative **8** could be appropriate starting materials for synthesizing hetero-substituted methyldiphenylphosphine oxide derivatives of the general formula $Ph_2P(O)CH_2X$ (X = Hal, SR, SeR, OR, NR_2). These phosphine oxide derivatives could react with aldehydes and ketones under WH conditions to give a new access to halo, sulfanyl, selelenenyl and telluro alkenes, enol ethers and enamines.

Table 2.2 Synthesis of Sulfanyl Alkenes **22–24** by the Reaction of Ketones with (Sulfanylmethyl)diphenylphosphine Oxides **11**, **13** and **14**.

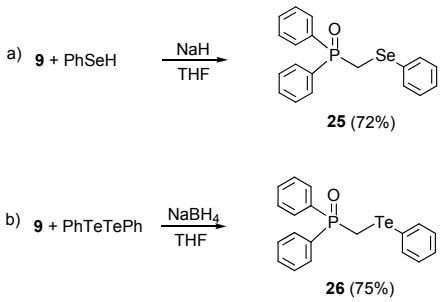
Entry	*(Sulfanylmethyl)diphenylphosphine Oxide*[a]	*Ketone*	*Sulfanyl Alkenes*[b]	*Yield (%)*	*E/Z ratio*
1	**11**		 **22**	89	-
2	**13**		 **23**	93	-
3	**14**		 **24**	92	10:1

a) Conditions: NaSR (10.5 mmol), **9** (10 mmol), THF, 2h.
b) Conditions: Phosphine oxide (2.0 mmol), *n*-BuLi (3.5 mmol) in THF at –78 ºC, 0.5 h, then ketone (1.0 mmol), and warm up to room temperature.

Scheme 2.4 General Scheme for the Synthesis of Hetero-Substituted Methyldiphenylphosphine Oxide Derivatives and Hetero–Substituted Alkenes

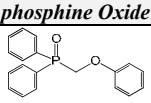
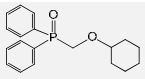
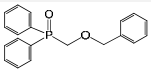
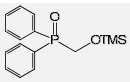
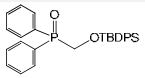
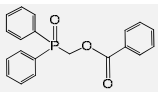
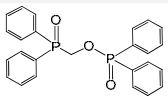
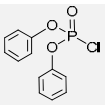
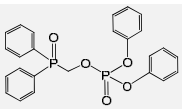


Scheme 2.5 Synthesis of (Phenylselelenylmethyl)- and (Phenyltelluromethyl)diphenylphosphine Oxides **25** and **26**



Thus, the (phenylselelenylmethyl)diphenylphosphine oxide **25**[81] was synthesized in 72% yield by the reaction of **9** with PhSeH in basic medium (Scheme 2.5, a). Similarly, the reaction of **9** with PhTeTePh/$NaBH_4$ produced phosphine oxide **26** in 75% yield (Scheme 2.5, b).[77]

Table 2.3 Synthesis of (Oxymethyl)diphenylphosphine Oxides **27**–**34** from Compounds **8** and **9**

Entry	*Starting Material*	*Reagents*	*(Oxymethyl)diphenyl-phosphine Oxide*	*Yield (%)*
1	**9**		 **27**	65
2	**9**		 **28**[a]	95
3	**9**		 **29**[a]	93
4	**8**	TMSCl	 **30**[b]	90
5	**8**	TBDPSCl	 **31**[b]	93
6	**8**		 **32**[b]	89
7	**8**		 **33**[b]	95
8	**8**		 **34**[b]	92

a) Conditions: Alcohol (10.5 mmol), NaH (10.5 mmol), **9** (10 mmol), THF, 2h, room temperature.
b) Conditions: **8** (10 mmol), RCl (R = TMS, TBDPS, Bz, Diphenylphosphinic, Diphenyl Phosphoryl) (10.5 mmol), imidazol (10.5 mmol), DMAP (0.5 mmol), CH_2Cl_2.

Despite enol ethers having an important role in organic synthesis, only a few examples of the synthesis of these compounds by Wittig,[82] WH,[57,83] and Julia[84] olefination procedures have been

[81] Arbuzov reaction using $PhSeCH_2Cl$ allows obtaining compound **25** but in a poorest yield of 39%. Ref. 67.

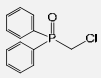
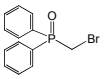
reported. In the case of the WH reaction, the (alkoxymethyl)diphenylphosphine oxides were prepared by reacting the unstable alkoxymethyl chlorides with ethyl diphenylphosphinite.

Starting from **8**, different ester and silyl ethers can be easily prepared, generating the entry to a new family of WH reagents. Compounds **30** and **31** were prepared from **8** by reaction with TMSCl and TBDPSCl, respectively (Table 2.3, Entries 4 and 5). In addition, benzoate **32** was synthesized in a reaction of **8** with benzoyl chloride with an 89% yield after recrystallization (Table 2.3, Entry 6). Phosphinate **33** and phosphate **34** were also synthesized in excellent yields in a reaction of **8** with $Ph_2P(O)Cl$ and $(PhO)_2P(O)Cl$,, respectively (Table 2.3, Entries 7 and 8).

(Halomethyl)diphenylphosphine oxides, except for the chloro and fluoro derivatives, are rarely reported, in spite of halo vinyl ethers being widely used in organic synthesis, particularly in cross–coupling reactions.

(Fluoromethyl)diphenylphosphine oxide **35** was already prepared from compound **9** and used in olefination reactions.[80] In a similar fashion, treatment of compound **9** with either potassium chloride, potassium bromide, or potassium iodide in triethyleneglycol at 150 ºC generated phosphine oxides **35**–**38** in excellent yields (Table 2.4).

Table 2.4 Synthesis of (Halomethyl)diphenylphosphine Oxides **35**–**38** from Compound **9**

Entry	*(Halomethyl)diphenyl-phosphine Oxide*	*Yield (%)*
1	 **35**	85
2	 **36**	92
3	 **37**	98
4	 **38**	95

a) Conditions: Compound **9** (1 mmol), KX (X = F, Cl, Br, I; 10 mmol), TEG, 150 ºC. 15 to 60 min.

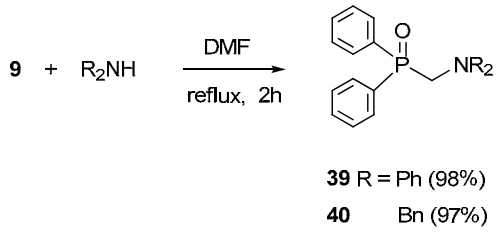
[82] (a) Kulkarni, M. G.; Pendharkar, D. S.; Rasne, R. M. *Tetrahedron Lett.* **1997**, *38*, 1459. (b) Wollenberg R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365. (c) Kluge, A. F. Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847.

[83] (a) Suzuki, K.; Mukaiyama, T. *Chem Lett.* **1982**, 683. (b) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. C. S. Perkin I.* **1979**, 3099.

[84] Surprenant S.; Chan, W. Y.; Brethelette C. *Org. Lett.* **2003**, *5*, 4851.

There are only a few reports describing the synthesis of (aminomethyl)diphenylphosphine oxides with an Arbuzov reaction.[85] Therefore, it would be interesting to explore the preparation of enamines following the same methodology used for enol ethers. Thus, (aminomethyl)-diphenylphosphine oxides **39**[86] and **40**[87] were easily prepared from **9** in a reaction with diphenyl- and dibenzylamine in almost quantitative yields after recrystallization (Scheme 2.6).[88]

Scheme 2.6 Synthesis of (Aminomethyl)diphenylphosphine Oxides



39 R = Ph (98%)
40 Bn (97%)

2.2.3 WH Olefination Reactions of Furanoses with Novel Sulfanyl Phosphine Oxides

As the first target, 2,3,5-tri-*O*-benzyl-α,β-D-ribose **41** was reacted with (sulfanylmethyl)-diphenylphosphine oxides **10**–**14** and the yield and stereoselectivity was compared to that observed for the pilot reaction with compound **42** (Table 2.5, entry 1). To drive the reaction, the phosphine oxide stabilized carbanion was formed at –78 ºC in the presence of *n*-BuLi or LDA, at –78 ºC in the presence of *n*-BuLi or LDA, in the case of (cyclohexylsulfanylmethyl)-diphenylphosphine oxide, and then a solution of the *ribo* derivative was added slowly. The reaction mixture was warmed to room temperature and left until the completion of the reaction. After the usual work-up the *E*/*Z* ratio was checked by ^{1}H NMR before further purification. WH olefination reaction of **41** with the *tert*-butyl derivative **14** produced the sulfanyl alkene **44** with a 65% yield and an excellent *E/Z* ratio of 25:1 (Table 2.5, Entry 2).

---

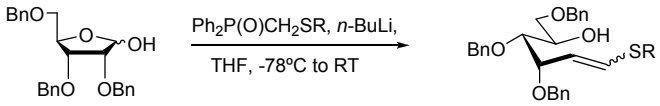
85 (a) Bakker, B. H.; Tjin A-Lim, D. S.; Van der Gen, A. *Tetrahedron Lett.* **1984**, *25*, 4259. (b) Broekhof, N. L. J. M.; Jonkers, F. L.; Van der Gen, A. *Tetrahedron Lett.* **1980**, *21*, 2671. (c) Broekhof, N. L. J. M.; Jonkers, F. L.; Van der Gen, A. *Tetrahedron Lett.* **1979**, *20*, 2433.

86 Abu-Gnim, C.; Amer, I. *J. Organometal. Chem.* **1996**, *516*, 235.

87 Broekhof, N. L. J. M.; *J. Royal Nether. Chem. Soc.* **1984**, *103,* 312.

88 Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690.

Table 2.5 Olefination Reactions from *Ribo* Derivative **41**.[a]



41

43 R = Ph **46** *p*-OMe-Ph
44 *t*-Bu **47** 2,6-di-Me-Ph
45 Cy **48** 2,6-di-Cl-Ph

Entry	*(Sulfanylmethyl)diphenyl-phosphine Oxide (R)*		*Sulfanyl Alkenes*	*Yield %*	*E/Z Ratio*[b]
1	**42**	(Ph)	**43**	72	4:1[c]
2	**14**	(*t*-Bu)	**44**	65	25:1
3	**13**	(Cy)[d]	**45**	47	7:1
4	**10**	(*p*-MeO-Ph)	**46**	22	9:1
5	**11**	(2,6-di-MePh)	**47**	83	50:1
6	**12**	(2,6-di-Cl-Ph)	**48**	17	2:1

a) Conditions: Phosphine oxide (2.0 mmol), *n*-BuLi (3.5 mmol) in THF at –78 ºC, 0.5 h, then aldehyde (1.0 mmol), and warm up to room temperature.
b) Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture.
c) Reference 57b.
d) LDA (3.5 mmol) was used.

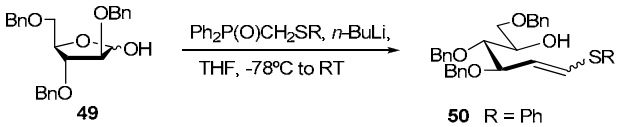
Better yield and stereoselectivity (83%, *E/Z* = 50:1) was obtained from the 2,6-di-methyl derivative **11** to give the sulfanyl alkene **47** (Table 2.5, Entry 5). The cyclohexyl derivative **13** furnished the desired sulfanyl alkene **45** with a 47% yield and a moderate stereoselectivity (Table 2.5, Entry 3). WH reactions with the *p*-methoxy derivative **10** (Table 2.5, Entry 4) and the 2,6-di-chloro-phenyl derivative **12** (Table 2.5, Entry 6) generated the corresponding products in low yields and selectivities.

We conclude that increased stereoselectivities were obtained in almost all WH reactions with the phosphine oxides **10–14** compared to the (phenylsulfanylmethyl)diphenylphosphine oxide (**42**) (Table 2.5, Entry 1); although, these reactions were not optimized. It is particularly relevant that the *E/Z* ratios of 25:1 and 50:1 were obtained with the phosphine oxides **14** and **11** (Table 2.5, Entries 2 and 5).

The olefination reactions of 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranose **49** with (sulfanylmethyl)-diphenylphosphine oxides **10–12,** and **14** was further explored. As mentioned in the introduction, only the *E*-isomers of the sulfanylalkenyl-*arabino* derivatives cyclize. For this reason, in the olefination of derivatives, it is very important to use (sulfanylmethyl)diphenylphosphine oxide derivatives that are able to provide the highest percentage of *E*-isomer. This choice will not only reduce the reaction time

but also allow for a better yield of the cyclization product. The results of the olefination reactions are presented in Table 2.6.

Table 2.6 Olefination Reactions of *Arabino* Derivative **49**.[a]



50 R = Ph
51 *t*-Bu
52 *p*-OMe-Ph
53 2,6-di-Me-Ph
54 2,6-di-Cl-Ph

Entry	*(Sulfanylmethyl)diphenyl-phosphine Oxide (R)*	*Sulfanyl Alkenes*	*Yield (%)*	*E/Z ratio*[b]
1	**42** (Ph)	**50**	100	1:1.5[c]
2	**14** (*t*-Bu)	**51**	93	8:1
3	**10** (*p*-MeO-Ph)	**52**	32	3:1
4	**11** (2,6-di-Me-Ph)	**53**	64	12:1
5	**12** (2,6-di-Cl-Ph)	**54**	78	6:1

a) Conditions: THF, 2h. Phosphine oxide (2.0 mmol), *n*-BuLi, (3.5 mmol) in THF at –78 ºC, 0.5 h, then aldehyde (1.0 mmol), and warming to room temperature.
b) Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture.
c) Reference 57b.

WH olefination reactions of **49** with the *tert*-butyl derivative **14** afforded compound **51** in excellent yield and with improved *E*-selectivity (Table 2.6, Entry 2) compares to those obtained with phenyl derivative (Table 2.6, Entry 1). In this case, the best stereoselectivity (*E/Z* = 12:1) was obtained with the 2,6-di-methyl derivative **11**, although the yield was comparably lower than that for **51** (Table 2.6, Entry 4). WH olefination reactions with **12** furnished the sulfanyl alkene **54**, but resulted in worse yield and stereoselectivity than the previous examples (Table 2.6, Entry 5). In this case, the WH reaction with the *p*-methoxy derivative **10** (Table 2.6, Entry 3) produced the sulfanyl alkene **52** with poor yield and stereoselectivity.

In all cases except when **10** was used, *E*-isomers were principally obtained with higher stereoselectivities than that of the reference compound **50** (Table 2.6, Entry 1), confirming our initial hypothesis. Among the different derivatives, the *tert*-butyl derivative **14** seems to combine better yields and stereoselectivies.

2.2.4 6-*Endo* Cyclization Reactions from Sulfanyl Alkenes 44, 47 and 51, 53

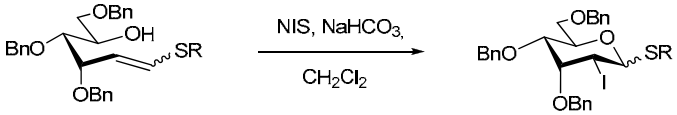
The prepared sulfanyl-hex-1-enitols were tested in electrophile–induced cyclization reactions to study whether the presence of the different sulfanyl alkyl or aryl groups influence the yield and the selectivity of the 6-*endo* cyclization reaction.

We selected for the cyclization study the sulfanyl *ribo*-hex-1-enitols **44** and **47**, *tert*-butyl and 2,6-dimethylphenyl groups respectively, that were obtained with the best *E/Z* ratio in the olefination experiments. The cyclization reaction was conducted under standard conditions, with NIS in the presence of sodium bicarbonate in DCM, starting at –60 ºC, and allowing the temperature to increase until the cyclization reactions started. Results are shown in Table 2.7.

When compound **44** was placed under cyclization conditions, the 1-thioglycoside **56,** resulting from a *6-endo* cyclization, was obtained with 57% yield and an α/β ratio of 1:13. The ratio α/β (*cis/trans* ratio for substitutions at positions C-1 and C-2) was lower that in the reference reaction (Table 2.7, Entry 1) reflecting the higher percentage of *E*-isomer in the starting sufanyl-alkene. Unexpectedly, however, the yield decreased, showing that bulkier groups at the sulfur position negatively influence the cyclization reaction.

A similar result was obtained in the cyclization of **47** to give the 1-thioglycoside **57**, although yields were even lower in this case.

Table 2.7 Cyclization of *Ribo*-hex-1-enitols[a]



43 R = Ph
44 R = *t*-Bu
47 R = 2,6-di-Me-Ph

55 R = Ph
56 R = *t*-Bu
57 R = 2,6-di-Me-Ph

Entry	Ribo-*hex-1-enitols* (*R*)	*Compound*	*Yield %*	α/β *ratio*[b]
1	**43** (Ph)	**55**	77	1:9[c]
2[d]	**43** (Ph)	**55**	64	1:41
3[e]	**44** (*t*-Bu)	**56**	57	1:13
4[e]	**47** (2,6-di-Me-Ph)	**57**	49	1:25

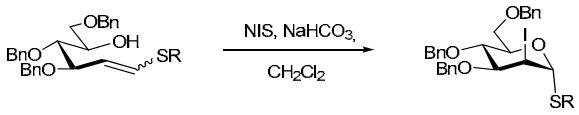
a) Conditions: *Ribo*-hex-1-enitol (1.0 eq), NIS (1.5 eq), $NaHCO_3$ (1.5 eq), solvent: CH_3CN, –30 ºC to room temperature, 15h.
b) Determined by integration of the anomeric proton signals in the ^1H NMR spectrum of the crude reaction mixture.
c) Reference 57b.
d) Solvent: CH_2Cl_2; temperature: –78 ºC to room temperature; time: 19.5h.
e) Solvent: CH_2Cl_2; temperature: –78 ºC to –10 ºC; time: 18h.

The α/β-selectivity of the cyclization reaction depended on the solvent. Thus, cyclization reactions with compound **43** carried out in acetonitril produced compound **55** with α/β ratio of 1:9 in 77 % yield, while in DCM, the same reaction gave the cyclization product **55** with α/β ratio of 1:43 in 64 % yield.

Subsequently, we studied the cyclization reactions of *arabino*-hex-1-enitols **51** and **53** (Table 2.8, Entries 2 and 3), which had produced the best results in the olefination reaction. When compound **51** was put under cyclization conditions, compound **59** was obtained as an inseparable mixture with glycal resulting from the elimination of iodine and *tert*-butylsulfanyl group (ratio 2:1) with a 57% yield and with an estimated yield of compound **59** of 64% (Table 2.8, Entry 2). A similar elimination reaction had been observed when 2-deoxy-2-iodo-pyranoses were put under dehydrative glycosylation conditions.[89] Cyclization of compound **53** did not yield the expected compound **60,** even at room temperature after several days of reaction.

The relative stereochemistry of the cyclization products **55**–**59** was initially deduced by ^{1}H, ^{13}C, COSY and HSQC NMR analysis, taking into account the general rules observed for the coupling constants $J_{1,2}$ and $J_{2,3}$ of the different configurations of 2-deoxy-2-iodo-glycosides (Figure 2.1).

Table 2.8 Cyclization of *Arabino*-hex-1-enitols **51**, **53**[a]



50 R = Ph
51 R= *t*-Bu
53 R= 2,6-di-Me-Ph

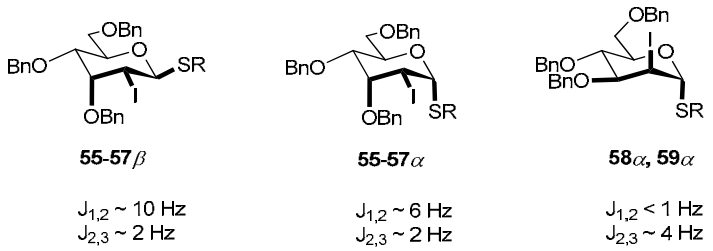
58 R = Ph
59 R= *t*-Bu
60 R= 2,6-di-Me-Ph

Entry	Arabino-*hex-1-enitols* (R)	*Compound*	*Yield %*	α/β *ratio*[b]
1	**50** (Ph)	**58**	36	1:0[c]
2[d]	**51** (*t*-Bu)	**59**	57 (64)[e]	1:0
3[f]	**53** (2,6-di-Me-Ph)	**60**	-	-

a) Conditions: *Arabino*-hex-1-enitol (1.0 eq), NIS (1.5 eq), $NaHCO_3$ (1.5 eq), 4Å MS, solvent: CH_3CN, 0 ºC, 18h.
b) Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture.
c) Reference 57b.
d) Solvent: CH_2Cl_2; temperature: –78 ºC to 0 ºC; time: 20h.
e) Yield estimated.
f) Solvent: CH_2Cl_2; temperature: –78 ºC to room temperature; time: 3d.

[89] Rodríguez, M. A.; Boutureira, O.; Díaz, Y.; Matheu, M. I.; Castillón, S.; Seeberger. P. *J. Org. Chem.* **2007**, *72*, 8998.

Figure 2.1 Assignment of the Configuration in 2-Deoxy-2-iodo-1-thioglycosides **55**–**59**.



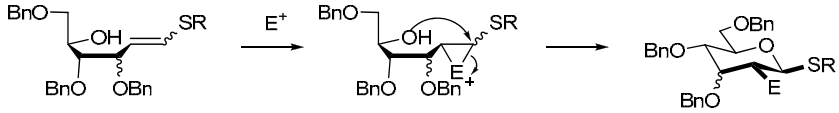
55-57β — $J_{1,2}$ ~ 10 Hz, $J_{2,3}$ ~ 2 Hz

55-57α — $J_{1,2}$ ~ 6 Hz, $J_{2,3}$ ~ 2 Hz

58α, **59**α — $J_{1,2}$ < 1 Hz, $J_{2,3}$ ~ 4 Hz

This series of experiments confirmed that hexenyl-1-enitols **44** and **47**, as well as **51** and **53,** undergo a complete 6-*endo* regioselective electrophilic iodine–induced cyclization. The normal 5-*exo* course observed in analogue hexenols is biased to the 6-*endo* cyclization by the presence of the sulfanyl group (Scheme 2.7).[90]

Scheme 2.7 Mechanism of Electrophile–Induced Cyclization of Vinyl Sulfides



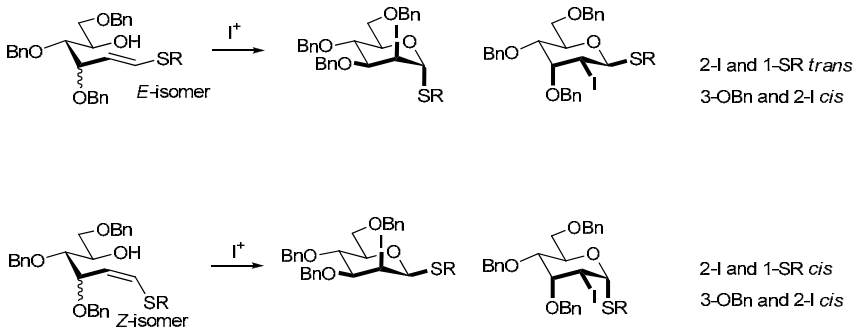
Furthermore, the cyclization reactions of *ribo*- **43**, **44**, and **47** and *arabino*-hex-1-enitols **50**, **51**, and **53** studied are highly stereoselective and have a very predictable stereochemical outcome. The relative stereochemistry of C-1 and C-2 in thioglycosides depends on the configuration of the starting alkene. Thus, the reaction of the *E*-alkene sulfides of compounds **43**, **44**, **50**, and **51** yields a cyclization product in which the iodine atom and the respective sulfanyl group are in a *trans* arrangement; although, unexpectedly, compound **53***E* did not yield the cyclization product. The *Z*-alkenes of compounds **43**, **44**, **47**, **50**, and **51** underwent cyclization only in the case of the *allo* derivatives **43**, **44**, and **47** and did not take place in the case of *manno* derivatives **50**, **51**, and **53** (Scheme 2.8).

Another important issue associated with stereoselectivity is the formation of cyclized products where the iodo group at C-2 is *cis* with respect to the benzyloxy group at C-3 (see Scheme 1.14). The stereoselectivity observed for the alkenes considered here is consistent with that reported for alkenols

[90] For possible electrophilic–induced 6-*endo* cyclization assisted by sulfur, see: Galluci, J. C.; Ha, D.-H.; Hart, D. J. *Tetrahedron Lett.* **1989**, *45*, 1989.

with an allylic alkoxy group[91] and is determined by a stereoelectronic effect known as the *inside-alkoxy effect*.[92,57] This effect favours cyclization from the most reactive conformation, in which the benzyloxy group is situated inside the plane that configures the framework of the double bond. In this conformation, the σ* C–O orbital is perpendicular to the π-system of the double bond, which minimizes the electron–withdrawing effect and causes the double bond to be more electron–rich and hence more reactive toward the electrophile (see Chapter 1.1.5).

Scheme 2.8 Cyclization Products with Iodine Electrophiles of *E*- and *Z*-Alkenes



This stereodirecting role of the allylic group can be observed in the cyclization reaction of *ribo* derivatives **43**, **44**, and **47** and *arabino* derivative compounds **50**, **51**, and **53**. For *ribo* derivatives, the most stable conformer is the one that leads to the preferred transition state for cyclization, which is the conformation where the large alkyl group is anti to the incoming electrophile and the allylic alkoxy group occupies the inside position. As a result, the cyclization proceeds readily (Scheme 2.9). In contrast, for *arabino* derivatives the preferred *outside-alkoxy* conformation is not the one that favours cyclization, and a conformational change must occur for cyclization to proceed. For these molecules, the transition state has a boat-like conformation, which is higher in energy than the transition state of the *ribo* derivatives. Consequently, the cyclization is slower for the *arabino* derivative and longer reaction times are needed than for the *ribo* derivatives.

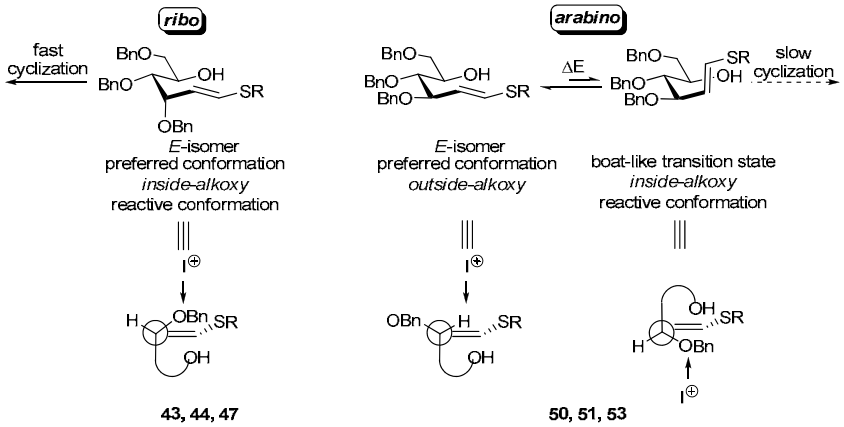
The *inside-alkoxy effect* may well explain why *Z*-thioether is less reactive than the corresponding *E*-isomer. Specifically, the *inside-alkoxy* conformation of the *Z*-alkenes is sterically crowded, and, therefore, the activation energy that must be overcome to reach the transition state for cyclization will

[91] (a) Arnés, X.; Díaz, Y.; Castillón, S. *Synlett.* **2003**, 2143. (b) Landais, Y.; Panchenault, D. *Synlett.* **1995**, 1191.

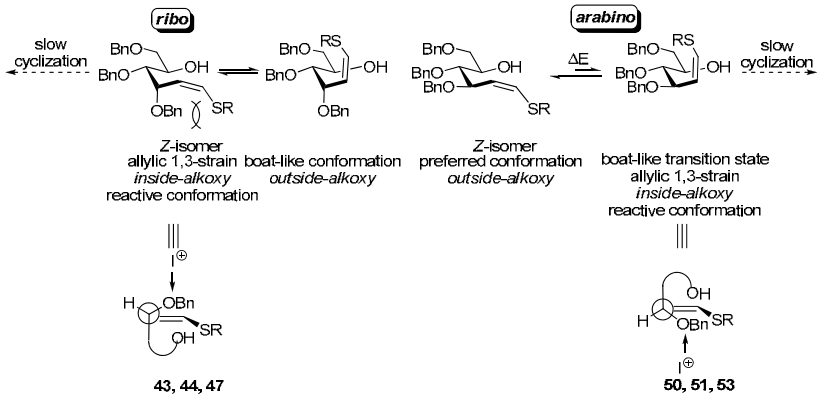
[92] Halter, J.; Strassner, T.; Houk, K. N. *J. Am. Che. Soc.* **1997**, *119*, 8031. (b) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Che. Soc.* **1984**, *106*, 3880. (c) Strock, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951.

be higher than for the corresponding *E*-alkenes. For *arabino* derivatives **50**, **51,** and **53** the activation energy is sufficiently high to preclude cyclization. Although these compounds could also undergo cyclization *via outside-alkoxy* conformation, this conformation is insufficiently reactive to promote cyclization (Scheme 2.10).

Scheme 2.9 Proposed Models for the Electrophile–Induced Cyclization Reactions of *E*-Hydroxy-Alkenyl Sulfides with *Ribo* Configurations **43**, **44,** and **47** and *Arabino* Configurations **50**, **51,** and **53**



Scheme 2.10 Proposed Models for the Electrophile–Induced Cyclization Reactions of *Z*-Hydroxy-Alkenyl Sulfides with *Ribo* Configurations **43**, **44,** and **47**, and with *Arabino* Configurations **50**, **51,** and **53**



2.2.5 Glycosylation of Cholesterol with the Glycosyl Donors 56 and 57

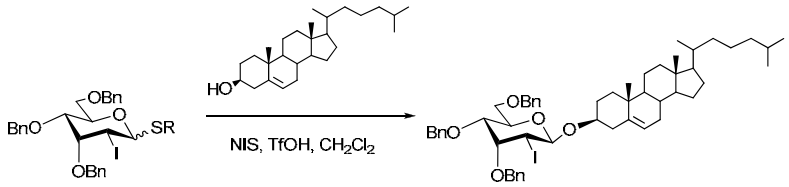
Glycosylation reactions were carried out using cholesterol as acceptor and NIS and TfOH as promoter systems. The reaction was started at –60 ºC and then warmed until glycosylation was finished. Only the *allo* derivatives **56** and **57** were used since the *manno* derivatives either were not obtained in pure form (**59** forming an inseparable mixture with the secondary product, glycal) or were not obtained at all (**60**).

When *tert*-butyl 1-thio-glycoside **56** was used as a glycosyl donor, compound **61** was obtained with an excellent 95% yield. The ratio α/β = 1:7 was slightly higher than that obtained when starting from the phenyl 1-thio-glycoside **55**.

The glycosyl donor **57** (and 2,6-di-methyl-phenyl 1-thio-glycoside) also yielded the glycoside **61** when it was reacted with cholesterol. Although the stereoselectivity was slightly better in this case, the yield was significantly lower (Table 2.9, Entry 3).

The relative stereochemistry of the glycosylation product **61** was deduced by ^{1}H, ^{13}C, COSY, and HSQC NMR analysis. The $J_{1,2}$ value of 9.0 Hz and $J_{2,3}$ value of 2.8 Hz for the major isomer clearly shows that the β-anomer was preferably obtained.

Table 2.9 Glycosylation Reactions with *tert*-Butyl and 2,6-di-Methyl Phenyl Sulfanyl Groups[a]



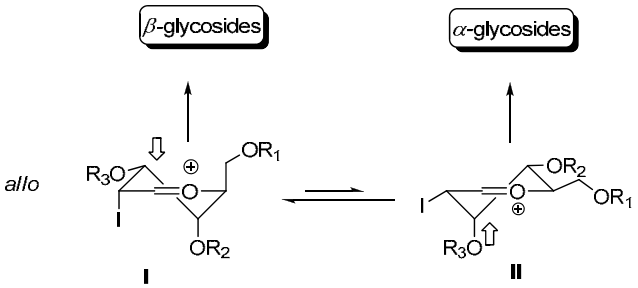
55 R = Ph
56 R = *t*-Bu
57 R = 2,6-di-Me-Ph

61

Entry	Ribo-*hex-1-enitols* (R)		α/β *ratio*[a]	*Compound*	*Yield %*	α/β *ratio*[b]
1	**55**	(Ph)	1:1.5	**61**	81	1:9 [c]
2[d]	**56**	(*t*-Bu)	1:13	**61**	95	1:7
3[d]	**57**	(2,6-di-Me-Ph)	1:25	**61**	60	1:10

a) Conditions: Glycosyl donor (1.0 eq), Cholesterol (2.0 eq), NIS (2.2 eq), TfOH (20 mol%), 4Å MS, solvent: CH_2Cl_2, –40 ºC, 2h.
b) Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture.
c) Reference 57b.
d) Temperature: from –78 ºC to –40 ºC; time: 4h.

Scheme 2.11 Stereochemical Courses of Glycosylation Reactions of 2-Deoxy-2-iodo-1-thio-*allo*-glycosyl Donors



For years, the preferred *trans* selectivity obtained in glycosylation with 2-deoxy-2-halo-glycosyl donors was explained by the formation of a cyclic halonium cation intermediate. Based on the data that show that α/β mixtures are always obtained and the DFT calculations made by our group, it was suggested that the real intermediate was an oxonium cation and not the halonium (bromonium or iodonium).[93] Recently, Billings and Woerpel have demonstrated, theoretically and experimentally, that the intermediate in these cases is the oxonium cation and that the more stable conformer is **I**, in which iodine occupies and axial disposition (See Chapter 1.1.5 and Scheme 1.16).[57] This is due to an hyperconjugative interactions between σ_{C-I} and π^*_{C-O} of the oxocarbenium. This more stable conformation is also the most reactive towards nucleophilic attack. This is because incoming nucleophile (Nu) from the upper β-face finds significantly less nonbonding interactions than the corresponding Nu attack from the α-face in **II**, where there appears to be significant non–bonding interactions between C-3–Nu (Scheme 2.11) resulting from attack of the glycosyl acceptor on the upper side to give mainly theβ-derivative. This preferred reaction path may be affected by steric interactions between the C-3 (OR_3) and C-6 (OR_1) alkoxy substituents and the incoming nucleophile.

2.3 Conclusions

In this chapter we have explored the synthesis of 2-deoxy-2-iodo-glycosides from furanoses in three steps: olefination of furanoses with (sufanylmethyl)diphenylphosphine oxides to give sulfanylalkenes, elctrophilic iodine–induced cyclization, and glycosylation. In particular, we have

[93] Bravo, F.; Viso, A.; Alcazár, E.; Molas, P.; Bo, C.; Castillón, S. *J. Org. Chem.* **2003**. *68*. 686.

explored the effect of bulky substitutions at the sulfur on the yield and stereoselectivity of olefination and cyclization. The most relevant conclusions of this work are:

-The (tosyloxymethyl)diphenylphosphine oxide **9** is an appropriate starting material for accessing the (sulfanylmethyl)diphenylphosphine oxide required for the olefination reaction.

- The (tosyloxymethyl)diphenylphosphine oxide **9** and its (hydroxymethyl)diphenylphosphine oxide precursors **8** are appropriate starting materials to prepare a series of phosphine oxide derivatives with general formula $Ph_2P(O)CH_2X$ (X = Hal, SR, SeR, OR, NR_2). This procedure is an alternative to the Arbuzov procedure and opens the way for synthesizing heteroatom-substituted alkenes with the WH reaction.

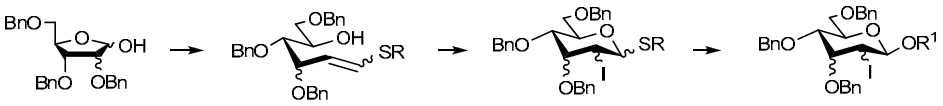
-The use of phosphine oxide derivatives $Ph_2P(O)CH_2X$ (X= *t*-Bu, 2,6-di-Me-Ph) provided good yields and excellent *E* selectivities in the WH olefination reaction of both ribo- and arabinofuranoses and were selected as possible candidates for improving the efficiency of the process.

- The presence of these bulky substitutions decreases the yield of cyclization reactions starting from *ribo*-hex-1-enitols and increases the cyclization of the *tert*-butyl *arabino*-hex-1-enitol derivative. However, no cyclization product was obtained starting from the 2,6-di-methyl phenyl *arabino*-hex-1-enitol derivative.

- Glycosylation reactions were studied starting from 2-deoxy-2-iodo-1-thio-*allo*-glycosides **56** and **57**, which have *t*-Bu and 2,6-di-Me-Ph groups, respectively, at the sulfur. It can be concluded that the yield increases with *tert*-butyl without affecting stereoselectivity much. With a 2,6-di-methyl phenyl group, however, the stereoselectivity is increased but yield decreased.

- Table 2.10 shows the results of the three steps using *t*-Bu and 2,6-di-Me-Ph groups bonded to sulfur in comparison with the reference PhS group. From this data, it can be concluded that none of the groups explored were an improvement of the previous results, but the *t*-BuS group appears to be a promising group in this process.

Table 2.10 The Results of Olefination – Cyclization – Glycosylation Reactions of *tert*-Butyl and 2,6-di-Methyl Phenyl Sulfanyl Groups Compared to Phenyl Group



Entry	*(Sulfanylmethyl)diphenyl-phosphine Oxide (R)*	*Olefination (%)*	E/Z *ratio*	*Cyclization (%)*	α/β *ratio*	*Glycosylation (%)*	α/β *ratio*	*Overall yield (%)*
1[a]	**42** (Ph)	72	4:1	77	1:9	81	1:9	45
2	**14** (*t*-Bu)	65	25:1	57	1:13	95	1:7	35
3	**11** (2,6-di-Me-Ph)	83	50:1	49	1:25	60	1:10	24

a) Reference 57b

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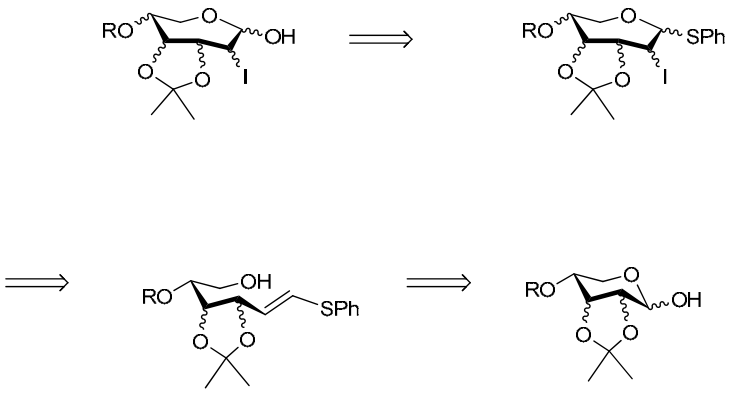
STEREOSELECTIVE SYNTHESIS OF 2-DEOXYOLIGOSACCHARIDES.NEW APRROACHES TO THE SYNTHESIS OF DIGITOXIN AND P-57
Andrea Köver
978-84-691-9523-9 /DL: T-1261-2008

THIRD Chapter: Oxepane Synthesis by 7-*endo* Electrophile–Induced Cyclization of Alkenylsulfides

Abstract

7-*Endo* electrophile–induced cyclizations of sulfanyl alkenes were studied, and applied toward the synthesis of septanosides. The sulfanyl alkenes were obtained by a Wittig–Horner WH olefination reaction of the corresponding pyranoses and furanoses.



"Sabio es aquel que
constantemente se maravilla."

André Gide, escritor francés

3.1 Introduction

The Septanosides are ring-expanded analogues of pyranosides that are characterized by a seven-membered ring.[94] The use of septanose glycosides in a biological setting relies on the efficient synthesis of these compounds. It has been shown that septanoside derivatives bind the lectin protein concanavalin A,[95] are glycosidase inhibitors[96] along with their aza analogs,[97] and have been used to define new types of protein–carbohydrate interactions.[98] Further, pharmacological investigations have shown that they have ion–change blocking,[99] antiviral,[100] and antifungal activities.[101] Septanosides may be able to effectively adopt distorted conformations in glyco–enzyme binding sites,[102] and as such, have been used to define new types of protein–carbohydrate interactions.[103] These α-D-septenosyl glycosides have been prepared using an S-phenyl septanoside donor. [104]

Although considerable progress has been made in the synthesis of the septanoses, most of the strategies have relied on the cyclization of a natural pyranose through the C-6 hydroxyl group rather than C-5 hydroxyl group. Septanoses have been synthesized[105] through the ring expansion of a cyclopropanated galactal (Scheme 3.1a).[106] The sequential acid–catalyzed cyclization–elimination of hydroxy–acetals (Scheme 3.1b),[107] and the ring–closing metathesis of dienes (Scheme 3.1c)[108] have been shown to directly furnish 1,2-anhydro-septanose derivatives (glycals). These 1,2-anhydro-

94 Pakulski, Z. *Pol. J. Chem*. **1996,** *70,* 667.

95 Castro, S.; Duff, M.; Snyder, N. L.; Morton, M.; Kumar, C. V.; Peczuh, M. W. *Org. Biomol. Chem.* **2005**, *3*, 3869.

96 Tauss, A.; Steiner, A. J.; Stütz, A. E.; Tarling, C. A.; Whiters, S. G.; Wrodnigg, T. M. *Tetrahedron: Asymmetry* **2006**, *17*, 234.

97 (a) Martínez-Mayorga, K.; Medina-Franco, J. L.; Mari, S., Cañada, F. J.; Rodríguez-García, E.; Vogel, P.; Li, H.; Blériot, P.; Sinaÿ, P.; Jiménez-Barbero, J. *Eur. J. Org. Chem.* **2004**, 4119. (b) Morís-Varas, F.; Qian, X.-H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 7647.

98 Benner, S.A.; Sismour, A. M. *Nat. Rev. Genet.* **2005**, *6*, 533.

99 Candenas, M. L.;Pinto, F. M.; Cintado, C. G.; Morales, E. Q.; Brouard, I.; Diaz, M. T.; Rico, M.; Rodriquez, R.; Rodriguez, P. M.; Perez, R.; Perez, R. L.; Martin, J. D. *Tetrahedron*, **2002**, *58*, 1921.

100 Venkateswarlu, Y.; Reddy, M. V. R.; Ramesh, P.; Rao, J. V. *Indian J. Chem., Sect. B* **1999**, *38*, 254.

101 Edrada, R. A.; Proksch, P.; Wray, V.; Witte, L.; Ofwegen, L. *J. Nat. Prod.* **1998**. *61*, 358.

102 (a) Martínez-Mayora, K.; Medina-Franco, J. L.; Mari, S.; Cañada, F. J; Rodríguez-Garcia, E.; Vogel, P.; Li, H.; Blériot, Y.; Sinaÿ, P.; Jiménez-Barbero, J. *Eur. J. Org. Chem.* **2004**, 4119. (b) Morís-Varas, F.; Quian, X.-H., Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7647.

103 Benner, S. A. *Nature* **2003**, *421*, 118.

104 Castro, S.; Fyvie, W. S.; Hatcher, S. A.; Peczuh, M. W. *Org. Lett.* **2005**, 16, 4709.

105 For more information in this field see: Snyder, N. L.; Haines, H. M.; Peczuh, M. W. *Tetrahedron*, **2006**, *62*, 9321.

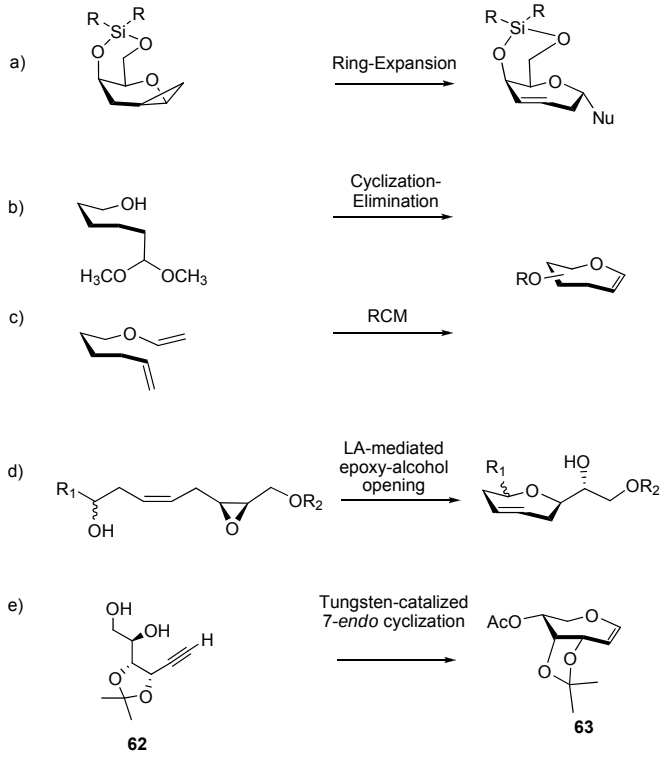
106 Batchelor, R.; Hoberg, J. O. *Tetrahedron Lett.* **2003**, *44*, 9043.

107 (a) Castro, S.; Peczuh, M. W. *J. Org. Chem.* **2005**, *70*, 3312. (b) McAuliffe, J. C.; Hindsgaul, O. *Synlett*, **1998**, 307.

108 (a) Peczuh, M. W.; Snyder, N. L. *Tetrahedron Lett.* **2003**, *44*, 4057. (b) Peczuh, M. W.; Snyder, N. L.; Fyvie, W. S. *Carbohydr. Res.* **2004**, *339*, 1163.

septanose derivatives were later modified by epoxidation and nucleophilic opening of the anhydroseptanose furnishing novel septanoside derivatives.[109] Oxepines have also been prepared by Lewis–acid mediated opening of epoxy alcohols (Scheme 3.1d).[110] Recently, oxepine **63** was synthesized by a tungsten–catalyzed cyclization of alkyne **62** (Scheme 3.1e).[111] Under these conditions, the presence of an isopropylidene protecting group was required to favor the formation of the seven-member ring.

Scheme 3.1 Synthesis of Septanoses (a) by Ring Expansion; (b) by Sequential Cyclization–Elimination; (c) by Ring–Closing Metathesis of Dienes: (d) by Lewis–Acid Mediated Epoxy-alcohol Opening; (e) Tungsten–catalyzed 7-*endo* Cyclization



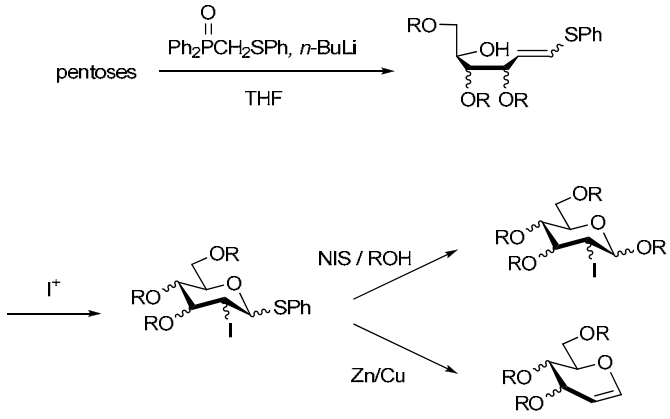
[109] (a) DeMatteo, M. P.; Snyder, N. L.; Morton, M.; Baldisseri, D. M.; Hadad, C. M.; Peczuh, M. W. *J. Org. Chem.* **2005**, *70*, 24. (b) Fyvie, W. S.; Morton, M.; Peczuh, M. W. *Carbohydr. Res.* **2004**, *339*, 2363.

[110] Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* **1998**, *54*, 21.

[111] Alcázar, E.; Pletcher, J. M.; McDonald, F. W. *Org. Lett.* **2004**, *6*, 3877.

In the Second Chapter we discussed the optimization of the synthesis[57] of phenyl 2-deoxy-2-iodo-1-thio-pyranosyl glycosides[2b,70a,112] from pentoses through a two-step procedure involving initial WH olefination to provide the requisite sulfanylalkenes, followed by iodonium–induced cyclization to the desired glycoside (Scheme 3.2).

Scheme 3.2 Synthetic Strategy of 2-Deoxy-2-iodo-1-thiopyranosyl Glycosides



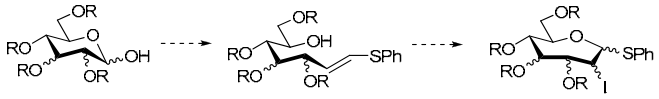
The 1-thio-pyranosides were useful glycosyl donors for the stereocontrolled synthesis of 2-deoxy-2-iodo-disaccharides, and this procedure was particularly efficient for the synthesis of 2-deoxy-β-hexo-glycosides of both *allo* or *gulo* configuration.[57] 1-Thio-glycosides were also efficiently transformed into glycals (Scheme 3.3).

In order to expand the scope of this strategy, we chose to explore an olefination-electrophile-induced cyclization strategy as a direct route to 2-deoxy-2-iodo-septanosides (Scheme 3.3). There are few examples for the formation of oxepane rings by electrophile-induced cyclization, and those that have been reported involve the formation of lactones through a 7-*exo* cyclization.[113] is one example of the formation of oxepanes by iodine–induced cyclization of hydroxyl-enolethers through a 7-*endo* cyclization Herein, we detail our results on the synthesis of heptenyl thioethers derived from protected *hexo*-pyranoses and pentoses, and the subsequent study of electrophile–induced cyclizations.

[112] 2-deoxy-thioglycosides have recently been used as glycosyl donors in a solid-phase–assisted synthesis of 2-deoxyconjugates: Jaunzems, J.; Hofer, E.; Jesberger, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1166.

[113] (a) Rousseau, G.; Homsi, F. *Chem. Soc. Rev.* **1997**, 453. (b) Simonot, B.; Rousseau, G. *J. Org. Chem.* **1994**, *59*, 5912.

Scheme 3.3 Synthetic Strategy of 2-Deoxy-2-iodo-1-thio-septanosyl Glycosides



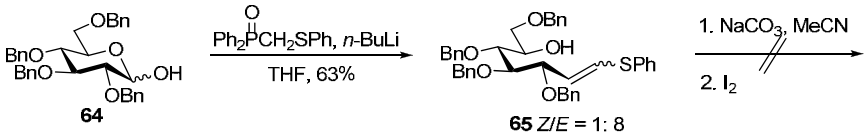
3.2 Results and Discussion

3.2.1 Synthesis of Sulfanyl-alkenyl Derivatives from 2,3,4,6-tetra-*O*-Benzyl-D-glucopyranose

As shown in previous studies, the conditions of the WH reaction for the synthesis of sulfanylalkenes displayed optimal chemoselectivity, diastereoselectivity, and yield[107] when employing phosphine oxide carbanions and Li bases. The selected olefination reagent (phenylsulfanylmethyl)diphenylphosphine oxide (**42**) was prepared by an Arbuzov reaction in 94% yield starting from ethyl diphenylphosphinite and chloromethylphenyl sulfide,[75] or in a similar yield by nucleophilic substitution of (tosyloxymethyl)diphenylphosphine oxide **(9**) by NaSPh, as shown in the Second Chapter.

When the WH reaction was carried out starting from 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranose (**64**) and **42**, the desired alkene **65** was obtained in 63% yield as an inseparable mixture of diastereomers (*Z*/*E* = 1:8). This was expected for such semi-stabilized carbanions. Subsequently, the cyclization of alkenylsulfanyl derivative **65** was studied. Initially, the standard conditions reported by Barlett and co-workers[114] employing iodine in acetonitrile in presence of $NaHCO_3$, were examined. Under these conditions, however, only the starting material was recovered. An increase of the reaction temperature to 40 ºC, or substitution of NIS for iodine as an electrophile was also ineffective (Scheme 3.4).

Scheme 3.4 WH Olefination Reaction of **64**

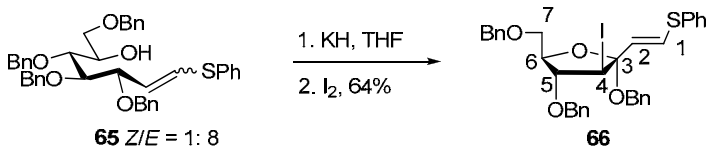


[114] Barlett, P. A.; Mayerion, J. *J. Am. Chem. Soc*. **1978**, *100*, 3950.

We next examined increasing the nucleophilicity of the hydroxylic oxygen by first forming the requisite alkoxide. Treatment of **65** with KH and iodine[115] in ether at –78 ºC did not provide the oxepane ring, but rather afforded compound **66** that was isolated in 64 % yield (Scheme 3.5).

The structure of compound **66** was determined by ^{1}H NMR, ^{13}C NMR, COSY, HMQC, TOCSY and NOESY. By analysis of this data, we made the following observations: a) the number of aromatic protons changed during the course of the reaction indicating the loss of one aromatic ring; b) the presence of two independent spin systems formed by protons H-1* and H-2 and H-4, H-5, H-6 and H-7 was observed by a TOCSY experiment; c) two doublets were found at 6.8 ppm (J = 15.0 Hz) and 5.64 ppm (J = 15.0 Hz) characteristic of protons of a *E*-configured double bond, assigned to H-1 and H-2; d) the presence of two carbons (CHs) at 129.5 and 124.6 ppm correlate with protons H-1 and H-2, and were consequently assigned to C-1 and C-2; e) the presence of a doublet at 4.2 ppm (J = 6.6 Hz) was assigned to H-4, and correlates with the signal at 33.9 characteristic of carbon bound to iodine; f) the presence of an acetalic quaternary carbon at 105.5 ppm was assigned as C-3; g) the relative configurations of the C-3 and C-4 were assigned by NOESY experiments.

Scheme 3.5 Cyclization Reaction of **65** in the Presence of KH and Iodine



65 *Z*/*E* = 1: 8 **66**

We next attempted to form the requisite alkoxide by reaction of **65** with *n*-BuLi. Interestingly, the subsequent treatment with iodine afforded compound **67** in 62% yield (Scheme 3.6).

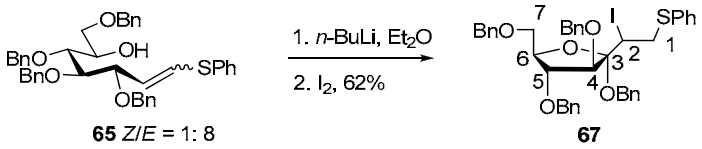
The structure of compound **67** was determined by ^{1}H NMR, ^{13}C NMR, COSY, HMQC, TOCSY and NOESY. By analysis of this data, we made the following observations: a) the presence of two independent spin systems formed by protons H-1, H-1', H-2* and H-4, H-5, H-6 and H-7 was observed by a TOCSY experiment; b) the number of aromatic protons did not change during the course of the reaction; c) H-2 appeared at 4.18 ppm as a double of doublets (J = 10.8, 3.2 Hz) and correlated with a signal at 41.9 ppm in the ^{13}C NMR spectrum, indicating that it is bound to iodine, and was subsequently assigned to C-2; e) the presence of a signal at 105.3 ppm, characteristic of an acetalic quaternary

[115] Lipshutz, B. H.; Tirado, R. *J. Org. Chem.* **1994**, *59*, 8307.

* For the sake of clarity hydrogen and carbon atoms have been numbered according to the respective alkene starting material.

carbon, was attributed to C-3; f) the configuration of the C-3 and C-4 was assigned by NOESY experiments.

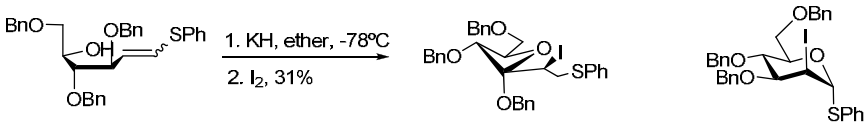
Scheme 3.6 Cyclization Reaction of **65** in the Presence of *n*-BuLi and Iodine



65 *Z*/*E* = 1: 8 **67**

A similar behavior was previously observed in the cyclization reaction of tri-*O*-benzyl-*arabino* derivative **50** in the presence of KH,[114] which led to the formation of oxetane **68** in 31% yield (Scheme 3.7). However, in the presence of a weak base (such as $NaHCO_3$), cyclization product **58** was preferentially formed.[57a]

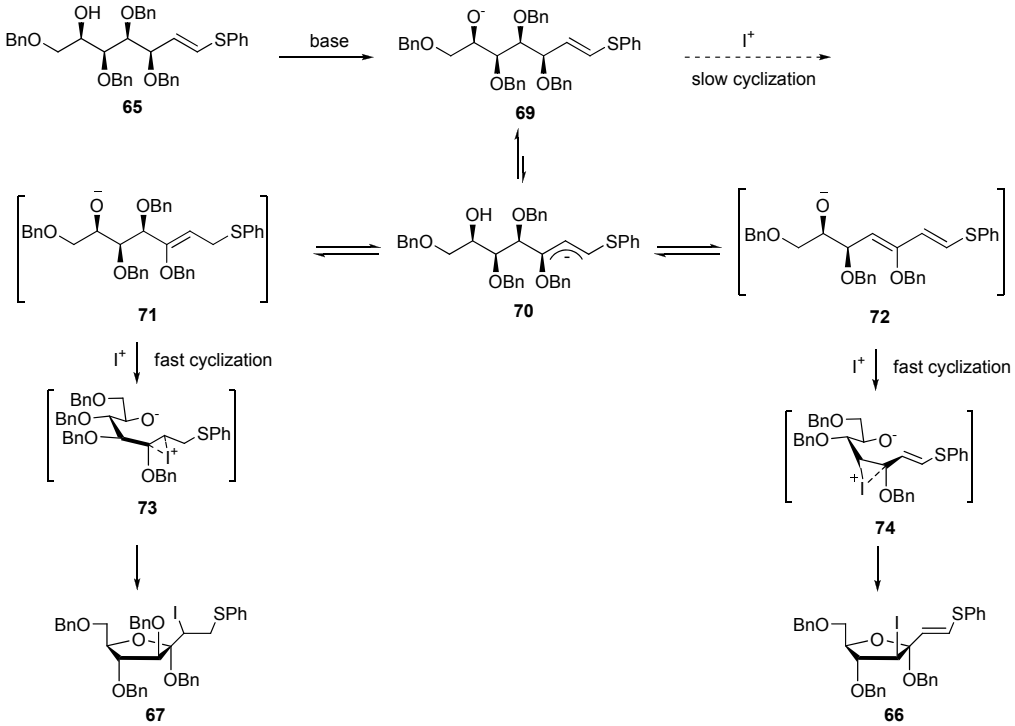
Scheme 3.7 Cyclization Reaction of **50** in the Presence of KH and Iodine



50 **68** **58**

This unexpected outcome occurred when cyclization of **65** was attempted using either *n*-BuLi or KH as bases in ether. Under strongly basic conditions, the more nucleophilic alkoxide **69** was expected to be formed, and eventually cyclize. However, as studied previously[57a] (see also SECOND Chapter), the preferred conformations in the *arabino* and *gluco* derivatives do not favour cyclization because the allylic benzyloxy group does not occupy an *inside*-position with respect to the C=C double bond As such, an alternative reaction pathway predominates. One possible pathway consists of an initial proton transfer to provide allylic anion **70** that could be reprotonated to provide enol ether **71**. This is a considerably more electron rich species that would be more prone toward cyclization than the starting thioenol ether **69** (Scheme 3.8). Reaction with iodine would then afford compound **67** through intermediate **73**. In this manner, the configurations of C-2 and C-3 would be determined by the reaction mechanism. At the same time under the alternate KH/THF conditions, anion **72** could be formed from **70** by elimination of a benzyloxy group. Iodine induced-cyclization of **72** would provide **66** through intermediate **74** (Scheme 3.8).

Scheme 3.8 Proposed Mechanism of Cyclization Reaction of **65** by Treatment with *n*-BuLi or KH in the Presence of Iodine



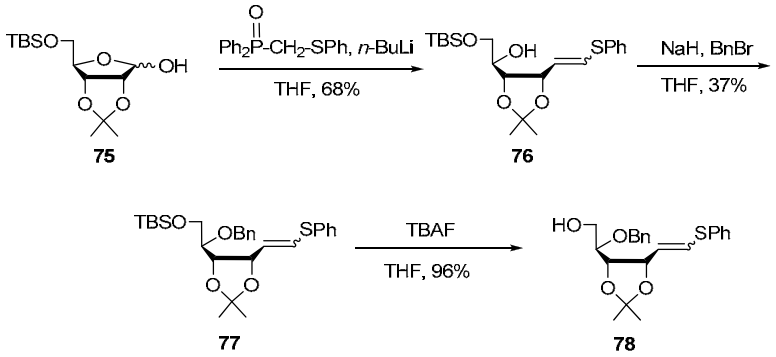
3.2.2 Synthesis of Oxepanes Starting from 75 and 83

Recently, McDonald demonstrated that the presence of an isopropylidene protecting group in the alkynol structure was necessary for the 7-*endo* cyclization (See Scheme 3.1e).[111] To test whether the presence of a dioxolane in the starting material would favor the desired cyclization, we prepared sulfanyl alkene **76** through the WH reaction of *ribo* derivative **75** with $Ph_2P(O)CH_2SPh$ in the presence of *n*-BuLi. Treatment of **76** with benzyl bromide afforded **77**, which was subsequently treated with TBAF to provide **78** (Scheme 3.9).

Compound **79,**[116] with hydroxyl groups at C-5 and C-6, was also prepared from **76** to study the competition between 6-*endo* and 7-*endo* cyclizations (Scheme 3.10).

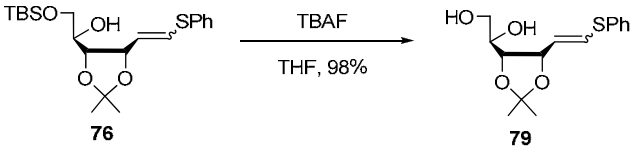
[116] Aucagne, V.; Tatibouët, A.; Rollin, P. *Tetrahedron* **2004**, *60*, 1817.

Scheme 3.9 Synthesis of **78**



75 76 77 78

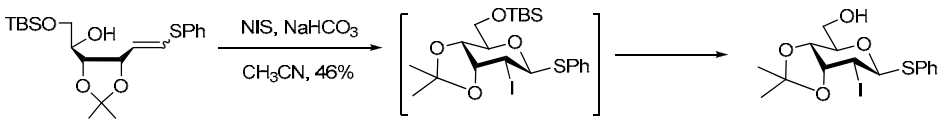
Scheme 3.10 Synthesis of **79**



76 79

When **76** was treated with NIS in a basic medium at low temperatures, compound **81** was isolated in 46% yield, as a result of a 6-*endo* cyclization through putative compound **80**, followed by concomitant loss of the silyl protecting group (Scheme 3.11). The stereochemical outcome of the reaction was similar to that previously observed for related compounds lacking the isopropylidene protecting groups.[2b,70a]

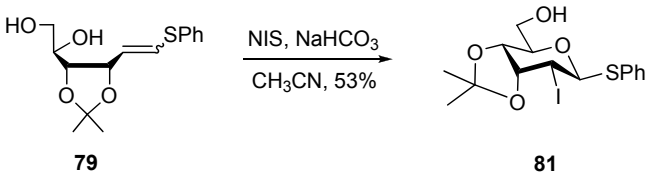
Scheme 3.11 Cyclization Reaction of **76**



76 80 81

Compound **81** was also exclusively obtained starting from **79** in 53% yield, indicating that the 6-*endo* cyclization is preferred over the 7-*endo* cyclization (Scheme 3.12).

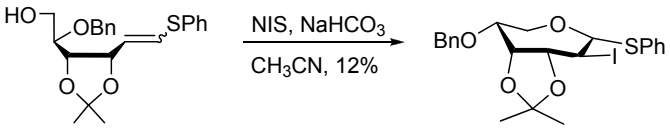
Scheme 3.12 Cyclization Reaction of **79**



79 **81**

When alkene **78** was employed as a starting material, the reaction proceeds more slower, and required extended periods of elevated temperature. After 24 hours at 35 ºC, compound **82** was isolated in 12% yield (Scheme 3.13), with 40% recovered starting material. The structure of **82** was determined according to the following data: a) the signals of H-1 and C-1, which appear at chemical shifts δ = 5.56 ppm and 93.0 ppm, respectively, are characteristic of the anomeric proton and carbon, and a $J_{6a,6b}$ value of 13 Hz indicates that cyclization had taken place; b) the presence of iodine at position 2 was confirmed by the correlation of H-2 with a ^{13}C signal at δ = 32 ppm (see Table 4.1); c) the obtained $J_{1,2}$ and $J_{2,3}$ values confirmed an equatorial disposition for the substituents at these positions; d) the presence of H-2 on the bottom face of the molecule was confirmed by a significant NOE with the signal at δ = 3.81 ppm, corresponding to axial H-6.

Scheme 3.13 Synthesis of **82**



78 **82**

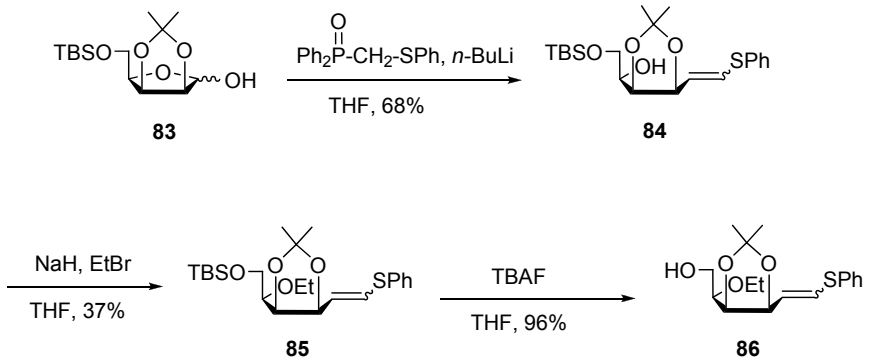
It should be noted that the relative stereochemistry of the iodine and the neighboring alkoxy group is *trans*, which is the opposite of that observed for the cyclizations yielding pyranoses (Scheme 3.13, see previous Chapter as well), where the relative stereochemistry was always *cis* as a result of

cyclization under the influence of the *alkoxy-inside effect*.[61,117] In the more reactive conformer, this effect sets the alkoxy chain at an *inside*-conformation with respect to the double bond. The observed low reactivity is likely due to the high degree of substitution of the chain, which limits the number of reactive conformations. It may also be due to the fact that cyclization of compound **78** takes place through the less reactive *alkoxy-outside* conformer.

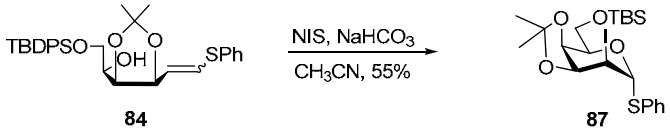
In our laboratory, compound **84** had been previously prepared by olefination of *lyxo* derivative **83** (Scheme 3.14),[57] and we observed that benzyl ethers reacted in electrophile–induced cyclizations.[61] In order to avoid this possibility, compound **84** was protected as ethyl ether (**85**), which was treated with TBAF to afford **86** (Scheme 3.14).

Iodine–induced cyclization of **84** provided 2-deoxy-2-iodo-1-thio-pyranoside (**87)** in 55% yield (Scheme 3.15).[57]

Scheme 3.14 Synthesis of **86**



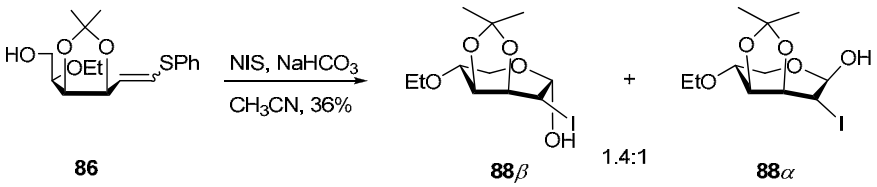
Scheme 3.15 Synthesis of **87**



[117] (a) Landais, Y.; Panchenault, D. *Synlett* **1995**, 1191. (b) Stork, G.; Kahn, M. *Tetrahedron Lett*. **1983**, *24*, 3951. (c) 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. (d) Halter, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc*. **1997**, *119*, 8031.

When **86** was treated with NIS and $NaHCO_3$, the reaction slowly evolved an anomeric α/β mixture of compounds **88**β and **88**α in 36% yield (32% of the starting material was also recovered), resulting from a 7-*endo* cyclization followed by hydrolysis of the anomeric phenylsulfanyl group (Scheme 3.16). This hydrolysis has been observed in other similar reaction when the cyclization was slow, due to competing activation of the 1-thiophenyl group by NIS.[57] More relevant spectroscopic features allowing for the structural elucidation of **88**α,β include following: a) the ^{13}C chemical shifts at δ = 96.9 and 98.1 ppm for C-1, and at δ = 35.4 and 32.5 ppm for C-2, for **88**β and **88**α, respectively, together with the absence of aromatic carbons, confirms the presence of a hydroxyl group at C-1 and an iodine at C-2 (Table 3.1); b) the existence of acetalic carbons and the $J_{6a,6b}$ value of 13 Hz confirms that the compounds are acyclic; c) for compound **88**β, the $J_{2,3}$ value of 10.0 Hz indicates that these protons are in a *trans*-diaxial disposition, and the NOE cross peak observed between protons H-2 and H-5 confirms that iodine is on the α-face. This suggests that for compound **88**β a 7-*endo* cyclization has taken place under an *alkoxy-outside* control. The configuration of the minor product **88**α could not be fully elucidated, but $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ values suggest that it would be tentatively aasigned to **88**α.

Scheme 3.16 Synthesis of septanoses **88**β and **88**α



86 **88**β **88**α

Table 3.1 Selected ^1H NMR Data for Compounds **82, 88**β, and **88**α (δ in ppm, J in Hz)

	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
82	5.56	5.13	4.65	4.49	4.13	4.58	3.81	8.8	8.8	7.6	2.0	1.0	5.2	13.6
88β	5.48	4.18	4.72	4.25	3.47	3.95	3.57	1.2	10	8.0	7.2	9.6	2.0	13.2
88α	5.41	4.10	4.41	4.32	3.75	4.33	3.45	8.0	11.2	7.6	9.2	nd	nd	nd

nd: not determined

Table 3.2 Selected ^{13}C NMR Data for Compounds **82, 88**β, and **88**α (δ in ppm, J in Hz)

	C-1	C-2	C-3	C-4	C-5	C-6
82	93.0	32.0	80.1	76.9	77.8	63.5
88β	96.9	35.4	76.5	80.4	78.8	60.7
88α	98.1	32.5	77.0	78.5	78.1	62.0

3.3 Conclusions

In this chapter, we have explored the synthesis of 2-deoxy-2-iodo-1-thio-septanosyl glycosides through an olefination–cyclization strategy. The most relevant conclusions of this work include following:

- Septanosides **82** and **88** were obtained in low-to-moderate yields from pentoses through a two–step procedure. A WH olefination of pentoses **75** and **83** provided phenylsulfanyl derivatives **76** and **84**, and further protection and deprotection afforded alkenes **78** and **86** that underwent NIS–induced 7-*endo* cyclization to give provide **82** and **88**. 7-*endo* cyclization took place preferentially under *alkoxy-outside* control when an isopropylidene protecting group was employed in the starting alkene. This was the first example of a 7-*endo* iodine–induced cyclization to yield highly substituted oxepanes.

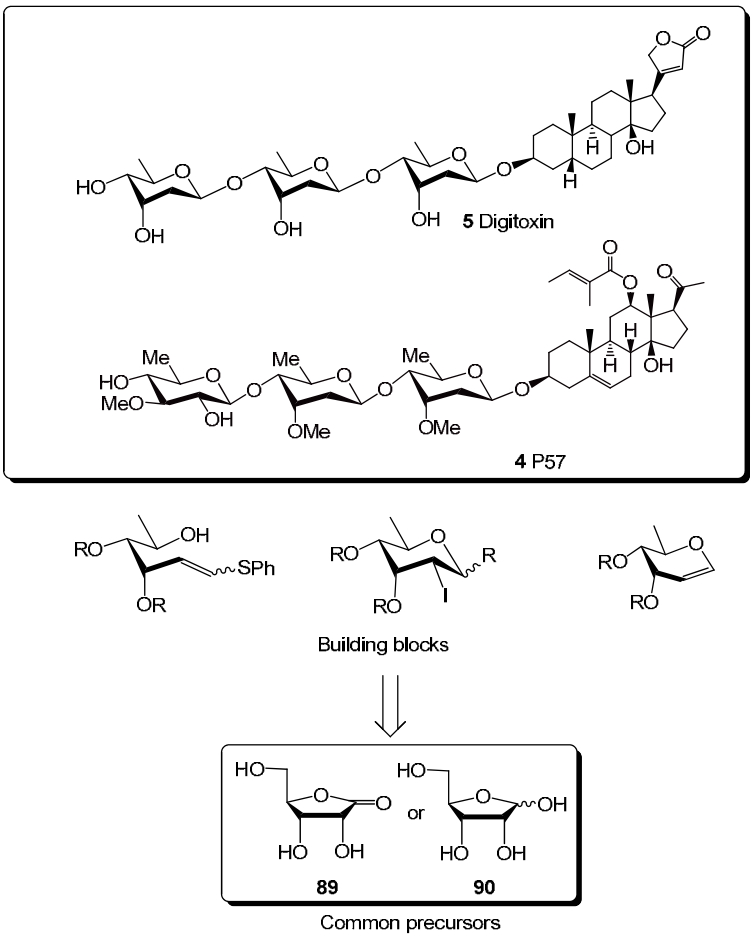
- In the absence of an isopropylidene protecting group, the cyclization did not take place, and when more basic reaction conditions were employed, an alternate reaction took place, providing compounds **66** and **67**.

FOURTH Chapter: Synthesis of 2,6-Dideoxyoligosaccharides. Approaches to the Synthesis of Digitoxin and P57

Abstract:

Cardiac glycosides, specifically digitoxin, are used for the treatment of congestive heart failure (CHF), and as inhibitors for tumor cells.

In this chapter, we employ previously-developed procedures such as furanose olefination, alkene iodonium–induced cyclization (Second Chapter), glycosylation from alkenyl sulfanyl derivatives (*´One-pot´*) toward the synthesis of digitoxin and P57.



"A veces sentimos que lo que hacemos es
tan solo una gota en el mar, pero si ésta
no estuviera, Él la echaría de menos."

Teresa de Calcutta, Premio Nobel de Paz

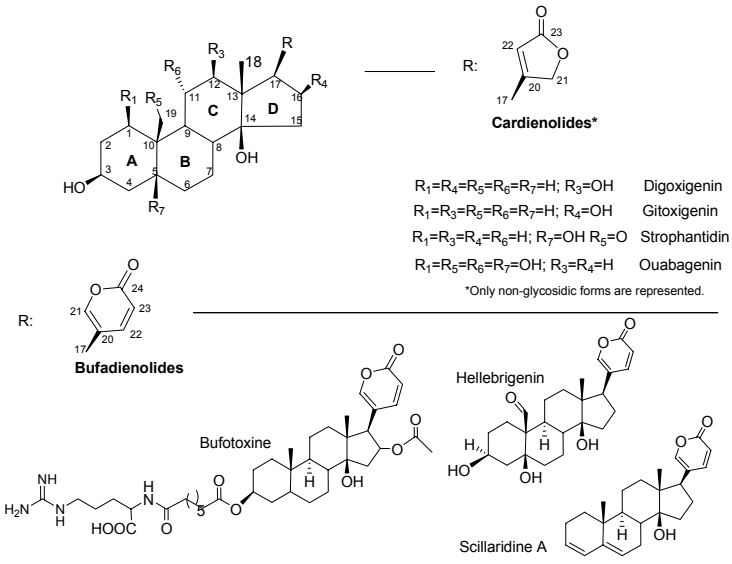
4.1 Introduction

4.1.1 Chemical Structure of the Digitoxin

Several glycosides bearing a steroid type aglycon are used as cardiotonics in various therapies (Figure 1.1). The most important of these belong to the group of cardenolides containing aglycons with a 23-carbon core. 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 aglycon and to D-glucose. Upon enzymatic hydrolysis during a drying up period, the parent plant yields D-glucose, whereas acid hydrolysis liberates all sugars components.

Figure 4.1 Structure of Different Cardiac Steroids



A second group of aglycons is of the "bufadienolides," characterized by a six-membered ring lactone containing two double bonds. 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 (**5**, Scheme 1.1), found in *Digitalis purpurea* (Figure 4.2) and *Digitalis lanata* (Figure 4.3).

Figure 4.2 Picture of the Plant *Digitalis purpurea*

Figure 4.23 Picture of the Plant *Digitalis lanata*

Digitoxin contains a trisaccharide with three digitoxose (called digoxose) units linked to the hydroxyl group at C-3 of the aglycon digitoxigenin. However, this important aglycon has a steroid–like framework that shows differences with mammalian steroids and other cardienolides. The principal characteristic structural features of digitoxin are a) a *cis* C/D ring junction, b) a tertiary 14β-hydroxyl group, and c) a 17β-unsaturated lactone (see Figure 4.1). The unique structure and the diverse and potent bioactivities of digitoxin have made it the focus of numerous synthetic studies and total syntheses.[118]

[118] Partial and/or from steroids synthesis: (a) Danieli, N.; Mazur, Y.; Sondheimer, F. *Tetrahedron* **1966**, *22*, 3189. (b) Bach, G.; Capitaine, J.; Engel, C. R. *Can. J. Chem.* **1968**, *46*, 733. (c) Pettit, G. R.; Houghton, L. E.; Knight, I. C.; Bruschweiler, F. *J. Org. Chem*. **1970**, *35*, 2895. (d) Lenz, G. R.; Schulz, J. A. *J. Org. Chem*. **1978**, *43*, 2334. (e) Donovan, S. F.; Avery, M. A.; McMurry, J. E. *Tetrahedron Lett.* **1979**, 3287. (f) Marini-Bettolo, R.; Flecker, P.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem*. **1981**, *59*, 1403. (g) Welzel, P.; Stein, H.; Milkova, T. *Liebigs Ann. Chem.* **1982**, 2119. (h) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**,

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.[118i,119] The glycan chains are molecular elements that control the pharmacokinetics of the drug, and prolong their effects.

4.1.2 Previous Syntheses of Digitoxin

Elderfield et al. prepared the first glucosides of digitoxigenin and digoxigenin and showed that the glycosylation reaction was specific at the secondary hydroxyl group at C-3 of the aglycons.[120] 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 aglycon tends to undergo dehydration forming anhydrodigitoxigenin derivatives.

To overcome this problem, specific methods of glycosylation have been studied, based primarily on the Knoenigs–Knorr procedure. These methods are not generally applicable, but have to be adapted to the specific requirements of the substrates. α-1,2-cis-halogenated carbohydrates have been coupled with cardenolide aglycons using azeotropic distillation,[121] $AgCO_3$ on celite,[122] AgOTf,[123] mercuric salts,[124] Et_4NBr,[125] or by efficient disilver maleinate[126] (which provide β-products). Other glycosyl donors such as glycals,[123] 1-*O*-acetylglycosides,[127] trichloroacetimidates,[125b,128] or enzymatic methods,[129] have also been used to synthesize glycosylated cardienolides.

1601. (i) Wiesner, K.; Tsai, T. Y. R. *Pure Appl. Chem.* **1986**, *58*, 799. (j) Kutney, J. P.; Piotrowska, K.; Somerville, J.; Huang, S. P.; Rettig, S. J. *Can. J. Chem.* **1989**, *67*, 580. (k) Groszek, G.; Kurek-Tyrlik, A.; Wicha, J. *Tetrahedron* **1989**, *45*, 2223. (l) Kocovsky, P.; Stieborova, I. *Tetrahedron Lett.* **1989**, *30*, 4295. (m) Hanson, J. R. *Nat. Prod. Rep*. **1993**, *10*, 313. (n) Almirante, N.; Cerri, A. *J. Org. Chem.* **1997**, *62*, 3402. (o) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421. For total synthesis see: (p) Stork, G.; West, F.; Lee, Y. H.; Isaacs, R. C.; Manabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 10660. (q) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2007**, *48*, 1541.

119 Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3215.

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

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

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

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

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

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

126 Luta, M.; Hensel, A.; Kreis, W. *Steroids* **1998**, *63*, 44.

127 Boivin, J.; Monneret, C.; Pais, M. *Tetrahedron Lett.* **1978**, *19*, 1111.

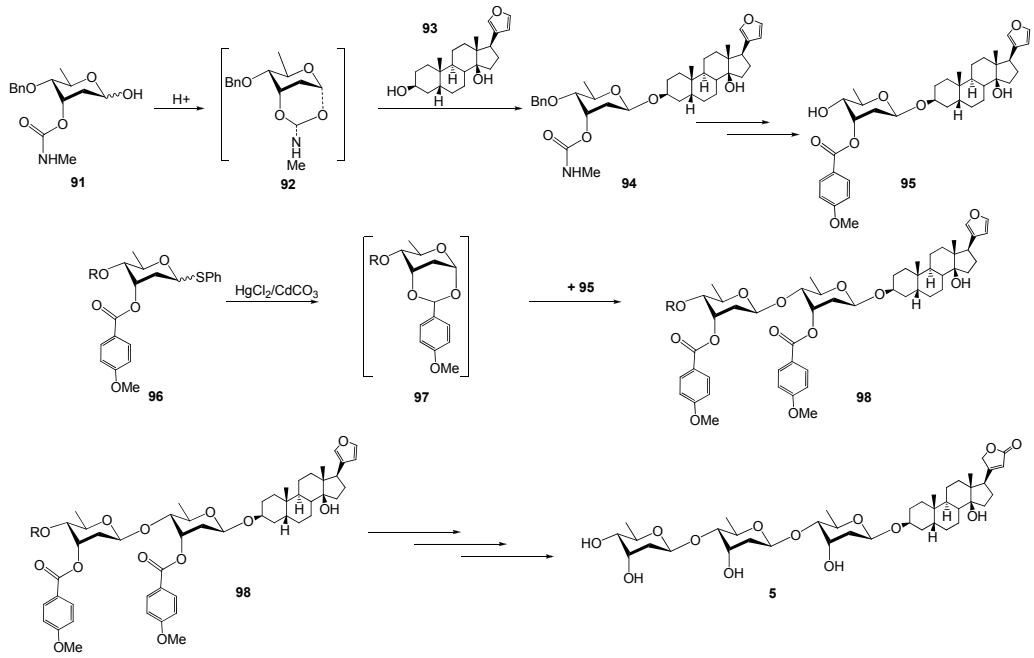
128 Finizia, G. *J. Carbohydr. Chem.* **1998**, *17*, 75.

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

Despite the numerous procedures available for the glycosylation, only three total syntheses of digitoxin have been reported. The first[130] was the carbohydrate approach by Wiesner[131] 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 4.1). Thus, digitoxose derivative **91** and the furyl steroid **93** were treated under acidic condition to obtain **94.** The β-stereoselectivity of this method was likely due to the intermediacy of the bridged species **92**.

Since the urethane group was not suitable for the subsequent glycosylation steps, it was swapped out, and after standard functional group manipulations, acceptor **95** was coupled with ethyl thioglycoside **96**. The β-stereoselectivity was achieved after mercury–catalyzed cleavage of **96** through intermediate **97,** which reacted with monodigitoxoside **95** to yield disaccharide **98**. A third glycosylation by use a mercury–catalyzed cleavage of ethyl thioglycoside, followed by deprotection and transformation of furyl structure provided the desired crystalline digitoxin (**5**).

Scheme 4.1 Total Synthesis of Digitoxin by Wiesner

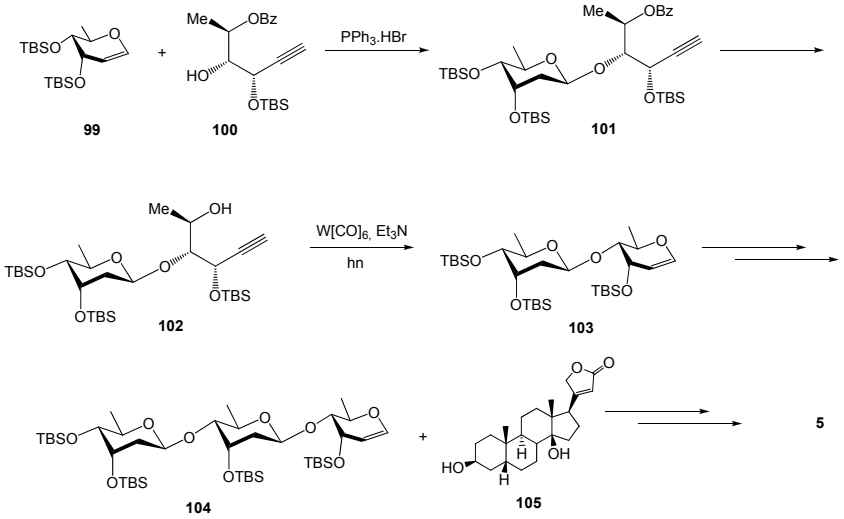


[130] Digitoxose was coupled with digitoxigenin by Zorbach and Boivin groups (ref. 137), but with poor yields and stereoselectivities: Zorbach, W.W.; Henderson, N.; Saeki, S. *J. Org. Chem.* **1964**, *29*, 2016.

[131] (a) Jin, H.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem*. **1983**, *61*, 2442. (b) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300. (c) Wiesner, K.; Tsai, T. Y. R. *Pure Appl. Chem*. **1986**, *58*, 799.

The procedure of Wiesner and co-workers suffered from the requirement that the butenolide be masked as a furan derivative during glycosylation, as well as excessive protecting group manipulations. As such, it required additional final steps to obtain digitoxin. McDonald and co-workers developed a more efficient synthesis by the direct attachment of a preformed trisaccharide donor **104** to digitoxigenin **105** (Scheme 4.2).[132] The synthesis of **104** began with protic acid–catalyzed[133] stereoselective glycosylation of alkynyl alcohol **100** with glycal **99** to provide 2,6-dideoxyglycoside **101**. Reductive debenzoylation and tungsten carbonyl–catalyzed *endo*-selective cycloisomerization[35d,134] of the alkynol substrate gave disaccharide glycal **103**. Convenient protecting group manipulations and repetition of the glycosylation–cycloisomerization steps from **103** afforded the glycal **104**, which could be readily attached to digitoxigenin (**105**)[35b]

Scheme 4.2 Total Syntheses of Digitoxin by McDonald



Recently, O'Doherty developed a linear and stereocontrolled route to the mono-, bis-, and trisaccharides of digitoxin (Scheme 4.3).[135] This procedure began with the palladium–catalyzed glycosylation of digitoxigenin **105** with pyranone **106** to provide **107** as a single diasteroisomer. Luche reduction ($NaBH_4/CeCl_3$) of **107** afforded a mixture of allylic alcohols **108**, which were reduced[136] to

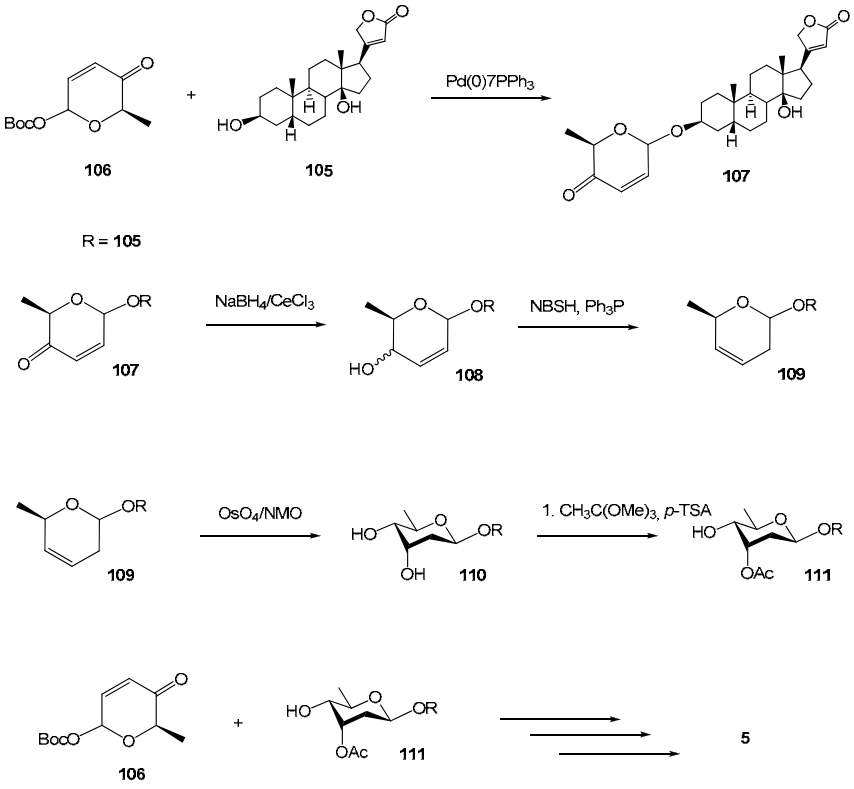
[132] McDonald, F. E.; Reddy, K. S. *Angew. Chem. Int. Ed.* **2001**, *40*, 3653.
[133] Bolitt,V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.
[134] McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* ,**1998**, *120*, 4246.
[135] (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406. (b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428. (c) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339. d) Zhou, M. O'Doherty, G. A. *J. Org. Chem.*, **2007**, ASAP DOI: 10.1021/jo062534+
[136] Myers' reductive rearrangement: Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841.

rearrange into alkene **109**. Dihydroxylation of **109** using the Uphjohn conditions (OsO_4/NMO)[137] furnished deprotected digitoxin monodigitoxoside **110**. Application of an ortho ester formation/hydrolysis protocol to diol **110**, afforded acetyl–protected acceptor **111**. Repetition of these steps in iterative manner yielded disaccharide first, and eventually digitoxin (**5**).

Both Wiesner's carbohydrate-based and O'Doherty's *de novo* synthesis of digitoxin are high yielding linear procedures which submit digitoxigenin **105** moiety to several transformations. By contrast, McDonald's *de novo* approach successfully inserts the aglycon in the final steps, and is therefore a more appealing methodology if a valuable, chemically–modified aglycon is employed.[138]

However, the final glycosylation step of glycal **106** with digitoxigenin derivative **111** was accomplished in poor yield and stereoselectivity.[135]

Scheme 4.3 Total Syntheses of Digitoxin by O'Doherty



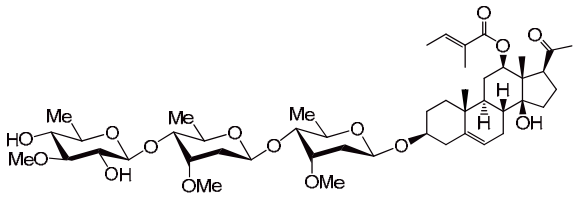
[137] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

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

4.1.3 Chemical Stucture of P57

P57 (**4,** Scheme 4.4) (3-*O*-[-*β*-D-thevetopyranosyl-(1→4)-*β*-D-cymaropyranosyl-(1→4)-*β*-D-cymaro-pyranosyl]-12*β*-*O*-tigloyloxy-14-hydroxy-14*β*-preg-50-en-20-one; $C_{47}H_{74}O_{15}$;M^+:878, Scheme 4.4) is a stereoidal glycoside that was extracted from the African plant of the genus *Trichocaulon* or of the genus *Hoodia* (Figure 4.4) and isolated by the South African Council for Scientific and Industrial Research (CSIR) in 1977. This compound is directly related to stereoidal glycosides with appetite suppressant activities. This activity has been harnessed from the cactus *Hoodia*, and used by the African population to bear hunger during heavy drought seasons. A synthetic approach to P57 was patented by Van Heerden *et al*. in collaboration with Phytopharm and Pfizer, in 1998.[139] Shortly thereafter, Pfizer released the synthesis of P57 due to the difficult synthetic approach involved. Today, the *Hoodia* extract has become popular with consumers with obesity problems.

Scheme 4.4 Structure of P57



4 P57

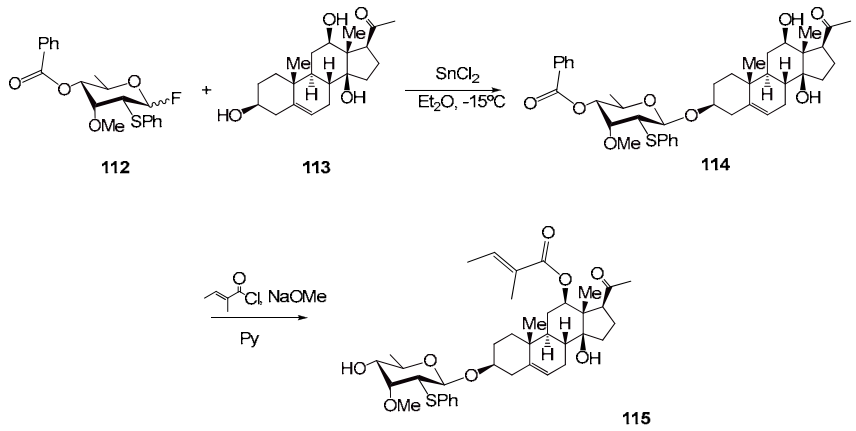
Figure 4.4 Picture of the African Plant of the Genus *Hoodia Gordonii*

[139] Van Heerden, F.; Vleggar, R.; Learmonth. R.; Maharaj, V.; Whittal, R. WO 98/46243

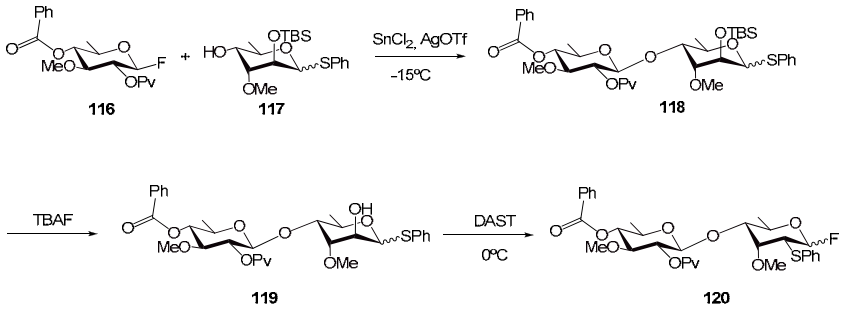
4.1.4 Previous Synthesis of P57

The key considerations in the synthesis of 2,6-dideoxy-oligosaccharides are the appropriate selection of protecting groups, deoxygenation of positions C-2 and C-6, and the execution of a stereoselective glycosylation procedure. The glycosylation can be linear or convergent, and both strategies were explored in the Van Heerden synthesis.[139] In the convergent strategy, the glycosyl fluoride **112** was reacted with aglycon **113** in the presence of $SnCl_2$ furnishing **114**, the "right–half" of the molecule (Scheme 4.5). A subsequent esterification provided **115.**

Scheme 4.5 The Convergent Synthesis of the "Right–half" of the P57



Scheme 4.6 The Convergent Synthesis of the "Left–half" of the P57

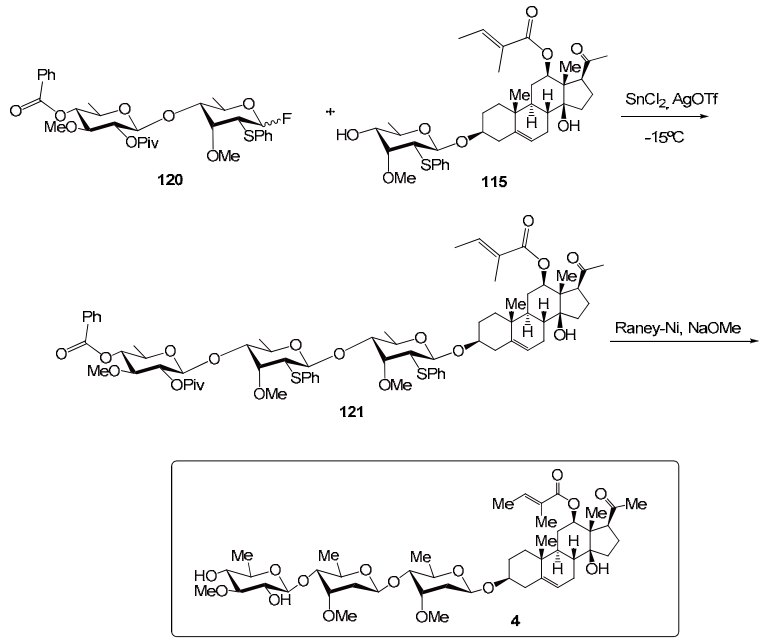


Disaccharide **120**, the "left–half" of the molecule, was prepared by reaction of the glycosyl acceptor **117** with the glycosyl fluoride **116** as donor, using $SnCl_2$. This provided disaccharide **118**, which was reacted with TBAF to deprotect the hydroxyl at C-2. Subsequent reaction with DAST

afforded **120**, through a reaction sequence involving OH activation, 1,2-migration of PhS group, and incorporation of fluorine at the anomeric position (Scheme 4.6).

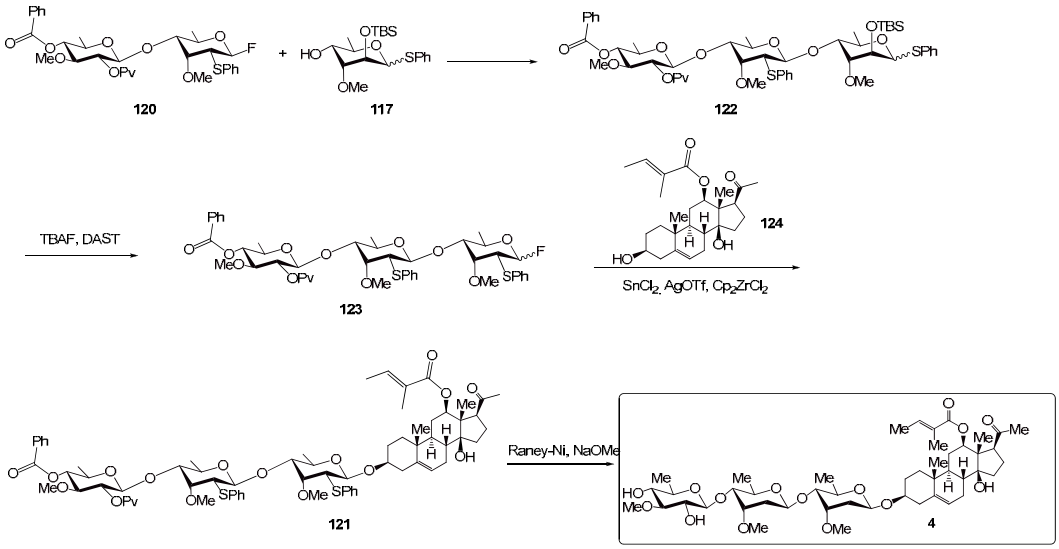
The two halves of P57 (**120** and **115**) were linked by glycosylation of **115** with the glycosyl donor **120** using $SnCl_2$ and AgOTf as activators. Finally the thiophenyl moiety at C-2 of the 1st and 2nd synthons were reduced with Raney–Ni, and the ester protecting groups were cleaved with NaOMe to furnish the desired compound, **4** (Scheme 4.7).

Scheme 4.7 End Game in the Convergent Synthesis of **4**



Applying the linear strategy mentioned earlier, trisaccharide chain **123** was prepared by reaction of the disaccharide **120** with the glycosyl acceptor **117**, to furnish **122**. This was treated with DAST to obtain the fluorine donor **123**. Finally, aglycon **124** was glycosylated with fluorine trisaccharide **123** using $SnCl_2$, AgOTf and Cp_2ZrCl_2 as activators. Reduction of the thiophenyl moiety and removal of all protecting groups with NaOMe furnished **4** (Scheme 4.8).

Scheme 4.8 End Game in the Linear Synthesis of **4**



4.2 Results and Discussion

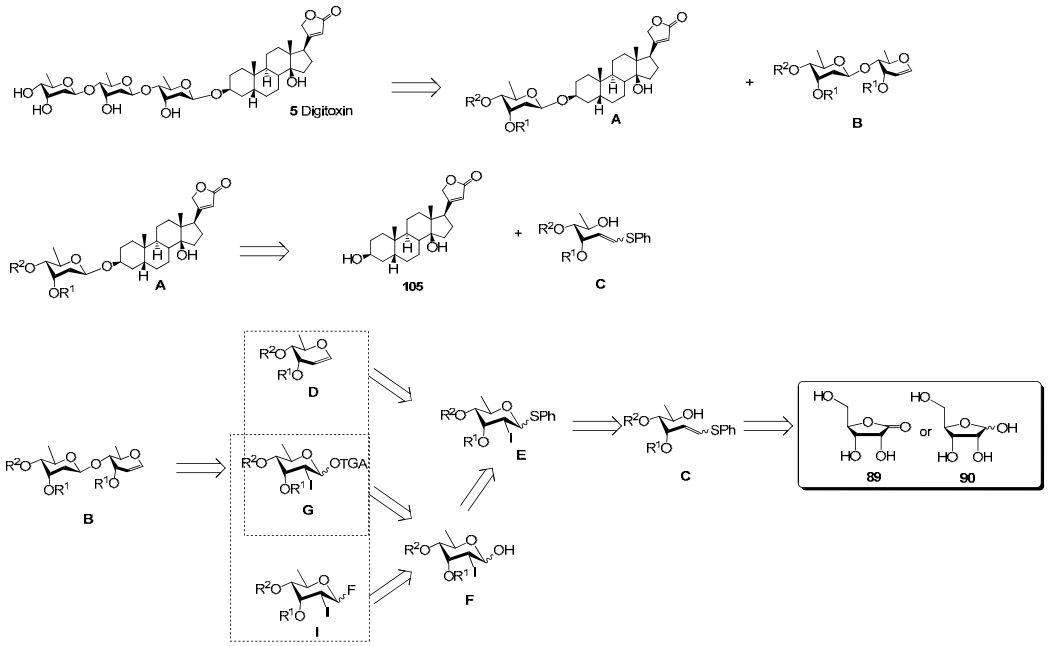
4.2.1 Retrosynthetic Analysis of Digitoxin and P57

In the previous chapters we have presented a new method for the synthesis of 2-deoxyglycosides from furanoses. This three-step sequence involves olefination with (phenylsulfanylmethyl)phosphine oxides, NIS–induced intramolecular cyclization, and glycosylation; the two latter steps can be conducted in´*one-pot*´. This method has been used in the synthesis of 2-deoxyglycosides (Introduction and Second Chapter), and septanosides (Third Chapter). We next sought to employ use this methodology for the convergent synthesis of digitoxin and P57. As such, our strategy should highlight the key coupling step with the aglycon in good yield and high stereoselectivity, together with a non–iterative reaction sequence over the cardenolide moiety.

As illustrates in Scheme 4.9, we envisioned digitoxin (**5**) 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 **105**. Disaccharide **B** may be formed either by the coupling of the glycoside donor **G** and glycal acceptor **D**, form **G** and acceptor **I**, or from donor **I** and acceptor **D**, that is, disaccharide **B** can be obtained by combining **D, G** and **I** as donors or acceptors**.** We envisioned preparing Glycal **D** from **E** by a reductive elimination. Compound **E** could also be transformed into 2-deoxy-2-iodopyranose **F** from which the trichloroacetimidate donor **G** or fluoride donor **I** could be straightforward obtained. The key synthon, **E**, could be prepared from **C** by

an iodine–induced cyclization**.** The common key intermediate **C** could subsequently be prepared from a suitably protected ribonolactone such as **89** or from ribofuranose **90** by an olefination reaction. Starting from the ribonolactone **89**, 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.[140]

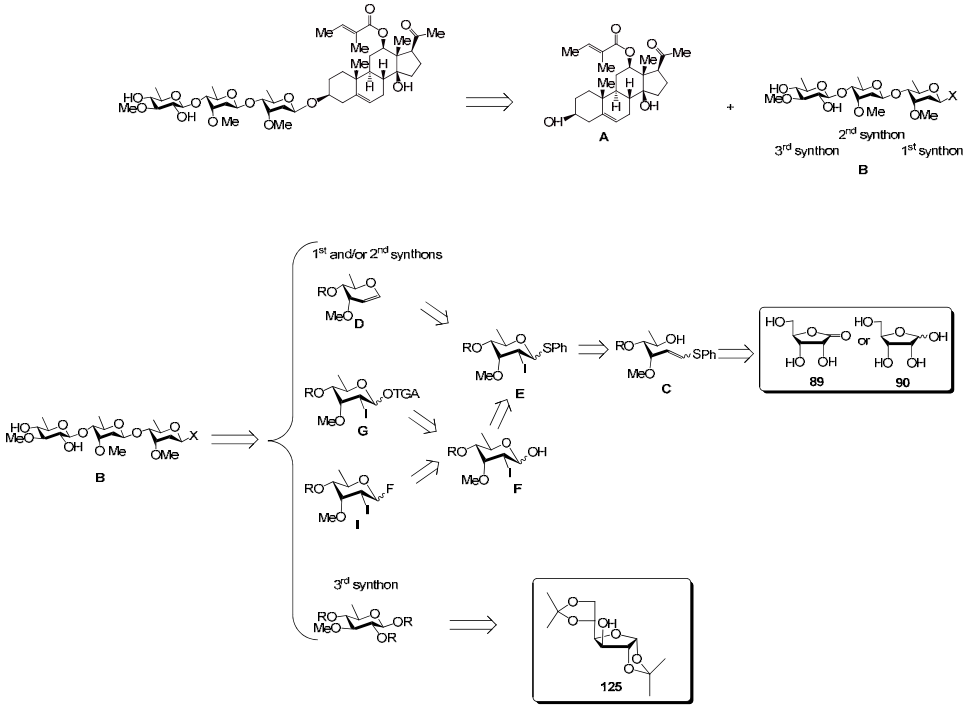
Scheme 4.9 Retrosynthesis of Digitoxin



Unfortunately, a convergent approach to P57 was not applicable since the requisite aglycon was not available. Therefore, we were compelled to design a linear synthesis of the trisaccharide moiety of P57. In this case, the non-reductive end (3rd synthon) of trisaccharide **B** is different from the two other units (1st and 2nd synthon) (Scheme 4.10). The third synthon could arise from diacetone-D-glucose **125** after selective protection at C-3 and reduction at C-6, in a manner similar to that previously reported. The two identical units (1st and 2nd synthons) could be prepared in a similar manner to that described above in the synthesis of digitoxin, by combining **D**, **E**, **G** or **I** as acceptors or donors, all of which can be obtained from intermediate **C**. Compund **C** is readily available from 1,4-D-ribonolactone **89** or α,β-D-ribofuranose **90**.

[140] (a) Ariza, J.; Font, J.; Ortuño, R. M. *Tetrahedron Lett.* **1990**, *46*, 1931. (b) Lundt, I.; Madsen, R.; *Synthesis* **1992**, 1129. (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. (d) Bell, A. A; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **1996**, *7*, 595. (e) Yang, W.-B.; Tsai, C.-H.; Lin, C.-H. *Tetrahedron Letters*, **2000** *41*, 2569.

Scheme 4.10 Retrosynthesis of P57



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 D-ribofuranose or ribonolactone 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 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 in order to elaborate them the core. After a previous study, we decided to use ethers as protecting groups for all three hydroxyl groups, allowing for a global deprotection in the final step of the synthesis. For the synthesis of digitoxin, a benzyl ether group was chosen to mask the hydroxyl group at C-3 of the 1st and 2nd synthons and the hydroxyls at C-3 and C-4 of the 3rd synthon, to allow for hydrogenolytic cleavage in the final step.

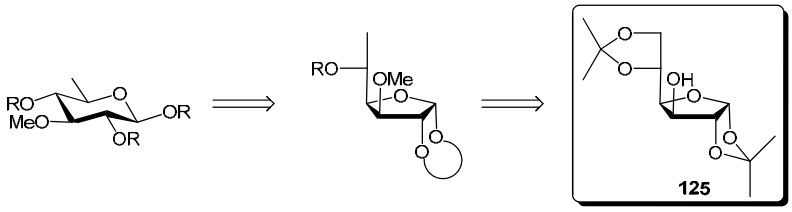
In the case of P57, a methyl ether group was selected to protect the hydroxyl at C-3 of the 1st and 2nd synthons, as it is required in the target product, P57. A temporary protecting group for the hydroxyl

at C-4 of the 1st and 2nd synthons in both digitoxin and P57 should be selectively formed and cleaved before the glycosylation steps in the presence of benzyl group. Furthermore, they should be stable under the varied conditions of the synthesis. To this end, a silyl protecting group were chosen.

4.2.2 Synthesis of the 3rd Synthon of P57

Unlike the 1st and 2nd synthons of P57, the 3rd synthon of P57 is not a 2-deoxymonosaccharide and its synthesis could be envisioned to involve the classical manipulation of glucose. The limitation imposed by the presence of a methyl ether at the hydroxyl group at C-3 validates the use of commercially available diacetone-D-glucose **125**, where the only free hydroxyl group is that of C-3 (Scheme 4.11).

Scheme 4.11 Restrosynthetic Approach for 3rd Synthon

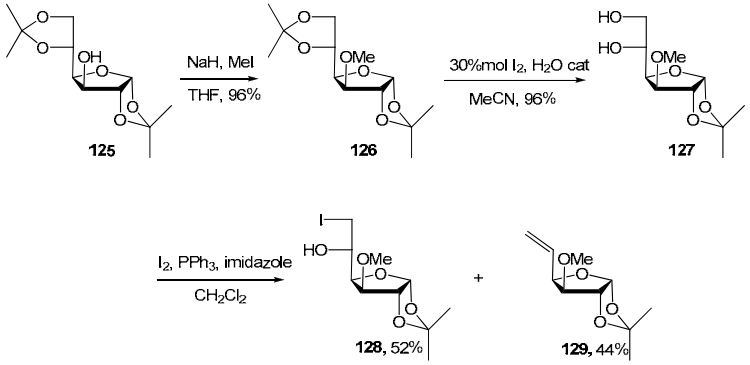


Thus, compound **125** was methylated with MeI in the presence of NaH in anhydrous THF to furnish **126** in 96% yield. The 5,6-*O*-isopropylidene group was selectively hydrolyzed with iodine in the presence of water to provide diol **127** in 96% yield. The primary hydroxyl in compound **127** was next converted to iodide by reaction with iodine-triphenylphosphine (Appel type reaction)[141] to afford compound **128** in 52% isolated yield together with considerable quantities of elimination product **129**, isolated in 44% yield (Scheme 4.12).

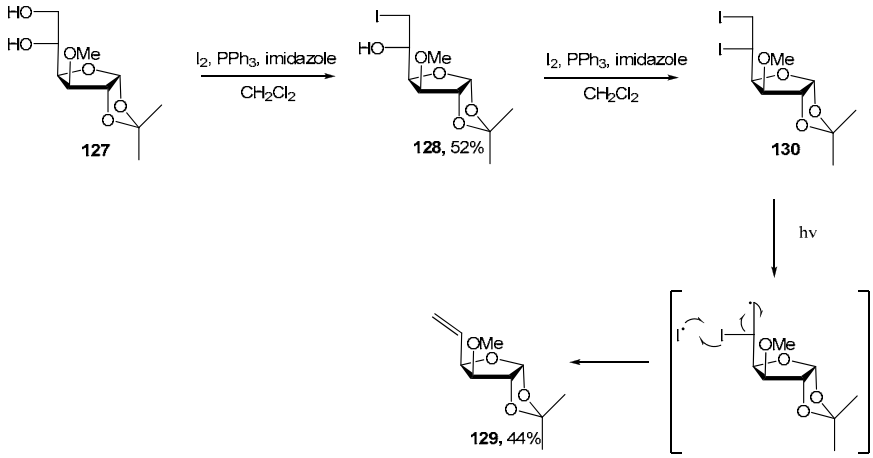
The formation of compound **129** likely proceeds trough the formation of diiodide **130** followed by subsequent radical elimination in the presence of the UV light (Scheme 4.14). When this reaction was initially tested on a 100-mg scale under the same conditions and reaction time, the formation of the secondary product was minimal relative to a 4-g scale reaction (Scheme 4.13).

[141] Papageorgiou, C.; Benezra, C. *Tetrahedron Lett.* **1984**, *25*, 6041.

Scheme 4.12 Synthesis of **129**

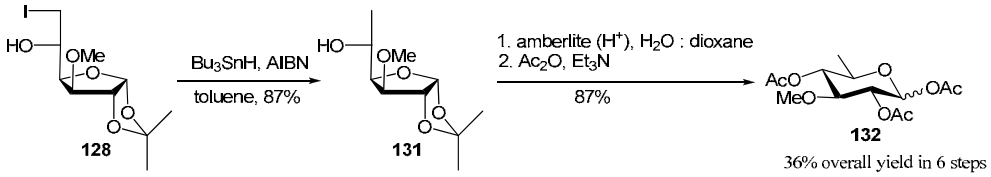


Scheme 4.13 Proposed Mechanism of the Formation of Compound **129**



Compounds **128** and **129** were separated by column chromatography, and the synthesis continued with the deiodination of **128** with Bu_3SnH/AIBN to furnish **131** in 87% yield.[141] The isopropilydene moiety was then hydrolyzed with an acidic resin to obtain 6-deoxy-3-*O*-methyl-α,β-D-glucopyranose, which was subsequently acetylated to provide **132** in 87% yield as an α/β mixture (α/β = 3:1). The structure of these compounds was confirmed with 1D and 2D NMR methods, including HMBC and NOESY (Scheme 4.14).

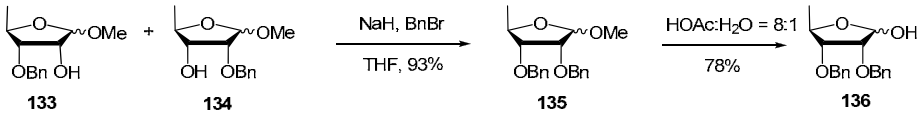
Scheme 4.14 Synthesis of **132** as a Possible 3rd Synthon of P57



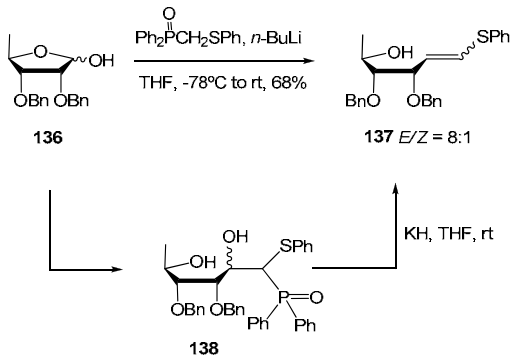
4.2.3 Synthesis of the 3rd Synthon of Digitoxin

The third synthon of digitoxin is a 2,6-dideoxy-2-iodo-allopyranose residue placed at the non-reducing end of the oligosaccharide moiety, and consequently it must only act as a glycosyl donor in the glycosylation step for monosaccharide assembly. As such, it does not require a temporarily protected hydroxyl group at C-4. Consequently, the hydroxyl groups at C-3 and C-4 were both protected as benzyl ethers. 2,3-di-*O*-Benzyl-5-deoxy-α,β-D-ribofuranose (**136)** was prepared by benzylation of **133** and **134** (the syntheses of which were described in section 2.4) in the presence of NaH in anhydrous THF, to provide **135** in 93% yield. Hydrolyzis of **135** in HOAc/H_2O = 8:1 at 80 ºC for 4 hours rendered **136** in 78% yield (Scheme 4.15).

Scheme 4.15 Synthesis of **136**



Scheme 4.16 Synthesis of **137**

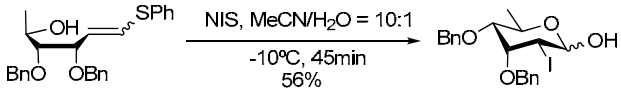


Olefination of 6-deoxy-ribofuranose **136** furnished **137** in 68% yield as an inseparable *E/Z* diastereoisomeric mixture (*E/Z* = 8:1). Significant amounts of *β*-hydroxyphosphine oxide **138** were also isolated, and were transformed into alkene **137** by treatment with KH in tetrahydrofuran (Scheme 4.16).

Next, the mixture of enitols **137** was employed in cyclization reaction in the presence of NIS in the mixture of MeCN/H_2O = 10:1 at –10 ºC for 45 minutes to furnish 2-iodo-*α,β*-D-allopyranoside (**139**) in 56% yield. The outcome of the reaction reveals that the thioglycoside initially formed from cyclization is further activated *in situ* by [I^+] to provide the final hemiacetal **139** (Scheme 4.17). **139** was next treated with DAST to afford an 96% isolate yield of the glycosyl fluoride **140** (the targeted synthon **I** in Scheme 4.10, $R^1 = R^2$ = Bn, Scheme 4.18).

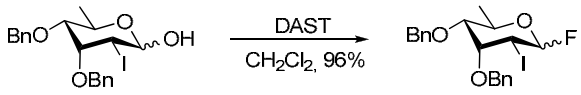
NMR data of phenylsulfanyl alkene **137** and related compounds are collected in Table 1, and NMR data of cyclized compounds are included in Table 4.2, in order to facilitate comparison of spectroscopic trends in these families of compounds.

Scheme 4.17 Synthesis of **139**



137 *E/Z* = 8:1 **139**

Scheme 4.18 Synthesis of **140**



139 **140**

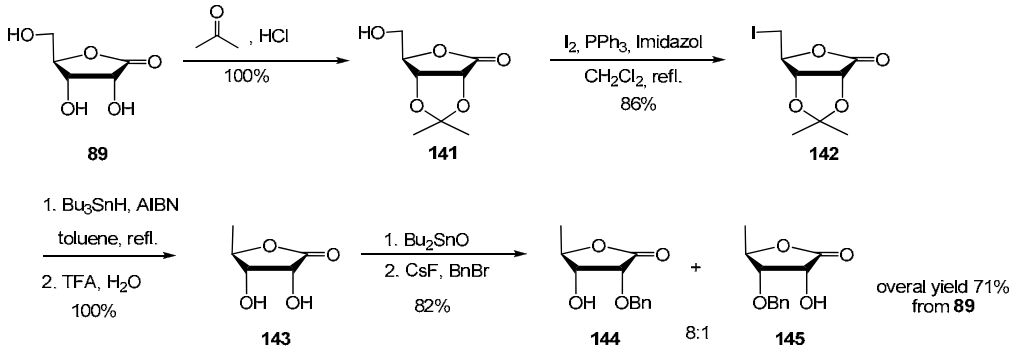
4.2.4 Synthesis of the 1st and 2nd Synthons of Digitoxin and P57

4.2.4.1 Synthesis of Olefination Precursors

As indicated in the retrosynthesic analysis of digitoxin and P57 (Schemes 4.9 and 4.10), the synthesis of all olefinic precursors was designed to highlight the olefination–cyclization strategy developed in our group. Two strategies for the synthesis of precursors were developed. The first was explored by Miguel Angel Rodríguez, and begins from ribonolactone **89**. This route involves initial formation of 2,3-*O*-isoprpylidene derivative **141**, deoxygenation of position C-5 by iodination to

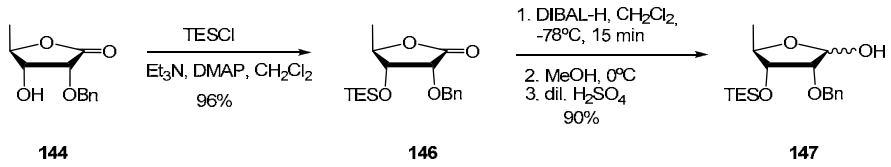
provide **142**, and reduction with Bu_3SnH to afford **143**.[141] Selective benzylation of at the C-3 hydroxyl group in **143** was carried out by reaction with Bu_2SnO to obtain the stannyl acetal, followed by further reaction with BnBr and CsF furnished **144** in 71% overall yield (Scheme 4.19).

Scheme 4.19 Synthesis of **144**[57e]

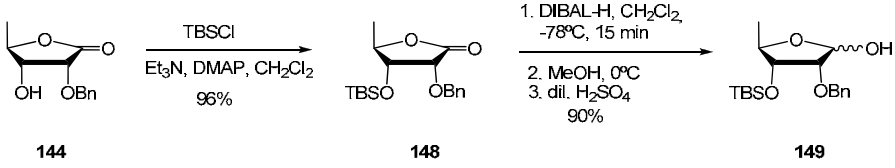


In order to account for the acid–sensitivity of the digitoxin aglycon, TES or TBS ethers were chosen as temporary protecting groups for the hydroxyl group at C-3. Thus, compound **144** was transformed into 6-deoxy-*ribo* derivatives **147** (Scheme 4.12) and **149** (Scheme 4.20) by silylation and lactone reduction (Scheme 4.21).

Scheme 4.20 Synthesis of **147**[142]



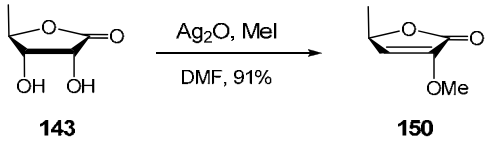
Scheme 4.21 Synthesis of **149**[142]



[142] Prepared and described by Miguel Angel Rodrígez.

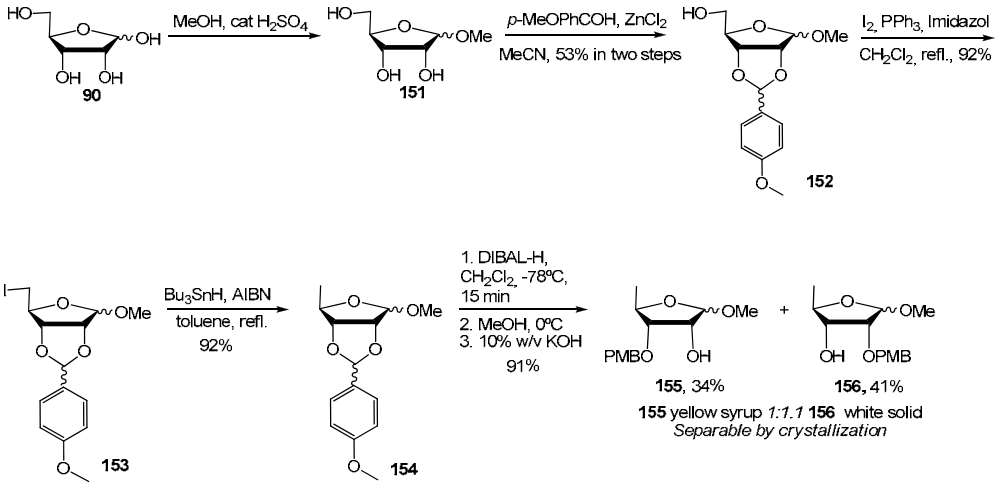
Although this synthetic process was successful for the synthesis of digitoxin precursors **147** and **149** with benzyl protecting groups at C-2, it was not useful for the synthesis of the corresponding P57 precursor with a methoxy group at C-2, as treatment of **143** with Bu_2SnO and CsF, or with Ag_2O and MeI in DMF provided only elimination product **150** (Scheme 4.22). This result was accounted for in the literature by the basic reaction conditions and the use of polar solvent, which leads to β-elimination in aldonolactones *via* an ElcB mechanism.[143]

Scheme 4.22 Reaction of **143** with Ag_2O and MeI[142]



We decided to explore an alternate approach starting from α,β-D-ribofuranose **90** for the synthesis of P57. Treatment of **90** with anhydrous methanol and catalytic H_2SO_4 afforded the methyl glycoside **151**. Next, protection of the hydroxyl groups at C-2 and C-3 as a *p*-methoxybenzylidene derivative with *p*-methoxy benzaldehyde in the presence of anhydrous $ZnCl_2$ rendered **152** in 45% yield over the two steps. This yield could be increased to 53% using an ultrasound treatment during the second step.[144]

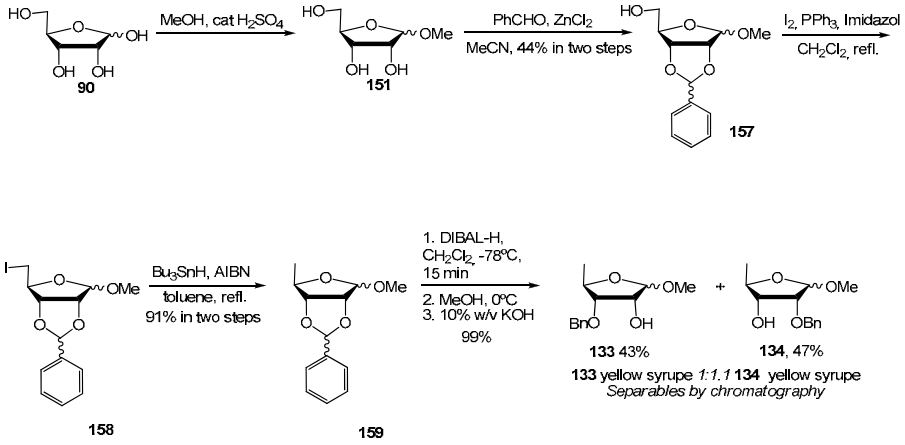
Scheme 4.23 Synthesis of **156**



[143] Jeronic, L. O.; Sznaidman, M. L.; Cirelli, A. F.; de Lederkremer, R. M. *Carbohydr. Res.* **1989**, *1989*, 130.
[144] Dhimitruka, I.; SantaLucia, J. Jr. *Org. Lett.* **2006**, *8*, 47.

Ribofuranoside **152** was deoxygented at C-5 in two steps by iodination to intermediate **153** followed by radical hydrogenolysis with Bu_3SnH/AIBN to compound **154**.[141] Compound **154** was then reduced with DIBAL-H to provide a mixture of **155** and **156**, which were separated by recrystallization (Scheme 4.23).[145] This process was repeated to obtain compounds **133** and **134** using benzaldehyde at the second synthetic step (Scheme 4.24).

Scheme 4.24 Synthesis of **133** and **134**

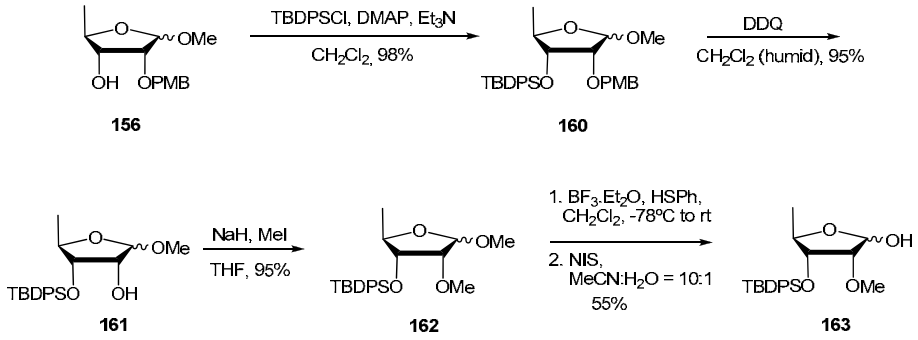


Since we encountered problems with the application of TES and TBS groups in the synthesis developed by Rodriguez, we decided to use a more stable silyl protecting group under the basic conditions required for the olefination reaction. We considered both TIPS and TBDPS protecting groups, and selected the latter due to it superior stability. Silylation of the secondary hydroxyl at C-3 of **156** using TBDPSCl in the presence of TEA and DMAP in anhydrous DCM furnished **160** in near quantitative yield. The PMB group was then deprotected by oxidation with DDQ in wet DCM, and subsequent etherification on the unmasked hydroxyl group with NaH and MeI in THF provided the desired methoxy ether **162**. Traditional methods for acidic hydrolysis to afford the olefination precursors were unsuccessful, because the silyl ether at C-3 was deprotected faster than the anomeric hydrogenolysis. We discovered, however, that thiophenol in the presence of BF_3•Et_2O furnished a

[145] Riley, A. M.; Jenkins, D. J.; Marwood, R. D.; Potter, B. V. L. *Carbohydr. Res.* **2002**, *337*, 1067.

thioglycoside[146] that was easily hydrolyzed by NIS in MeCN/H_2O = 10:1 to furnish **163** (Scheme 4.25).[147]

Scheme 4.25 Synthesis of **163**



4.2.4.2 Olefination Reactions

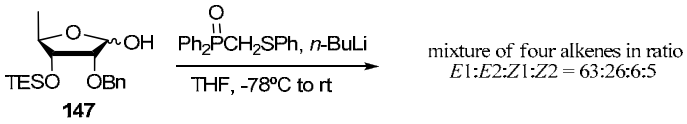
Starting from the previously prepared precursors, olefination reactions were carried out under WH conditions. Thus, (phenylsulfanylmethyl)diphenylphosphine oxide was treated with *n*-BuLi at –78 ºC, and the solution of the appropriately protected 5-deoxy-ribofuranose was then added slowly at the same temperature. The reaction was warmed to room temperature until complete as determined by TLC analysis, by a colour change from orange to yellow, and by the formation of a solid precipitate. The reaction was quenched by addition of a saturated solution of ammonium chloride, and was then extracted with ethyl acetate to recover the desired product the alkene and excess phosphine oxide, and the *β*-hydroxyphosphine oxide intermediate. After the separation of the reaction mixture, the *β*-hydroxyphosphine oxide was eliminated with *t*-BuOK or KH in THF to furnish the desired alkene in good yield.

The olefination reaction for TES–protected 5-deoxy-ribofuranose **147** was first performed by Rodríguez. Unlike the analogous olefination reactions of ribofuranoses, where the ^{1}H NMR spectra showed a mixture of two products corresponding to the *E*/*Z* alkenes, the *E*-alkene being the major one, the ^{1}H NMR spectrum of the alkene mixture obtained from olefination reaction of **147** indicated 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

[146] Viso, A.; Pooppeiko, N.; Castillón, S. *Tetrahedron Lett.* **2000**, *41*, 407.
[147] Dinkelaar, J.; Witte, M. D.; van der Bos, L.; Overkleeft, H. S.; van der Marel, G. A. *Carbohydr. Res.* **2006**, *341*, 1723.

the four alkenes were likely to be assigned to the desired enitols of *ribo* configuration as a result of direct olefination of **147**. However, the structure of the other *Z/E* alkene pair was unclear at that moment. In view of the difficulty of determining the structure of the alkene products, we decided to continue with the synthetic route in order to carry out structural elucidation employing the corresponding cyclized products (Scheme 4.26).

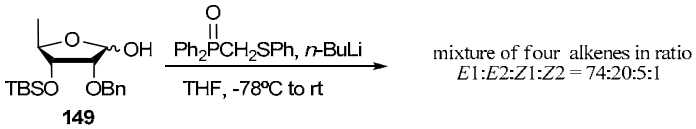
Scheme 4.26 Olefination Products of **147** from the ^{1}H NMR[142]



The cyclization reactions from the different isolated fractions were carried out to confirm the exact structure of the respective alkenes. NMR analysis of the cyclized products obtained by Rodríguez suggested that the unknown major *E*-alkene isomer corresponded to that of the *arabino* configuration, as a result of extensive epimerization at C-4 of the corresponding *ribo* derivative under the basic condition of olefination.

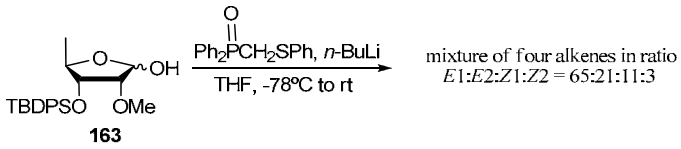
Faced with the challenge of selectively obtaining enough synthetic amounts of *ribo* alkene, Rodríguez decided to reconsider the protecting group strategy and replace the TES group by the more robust TBS group that should minimize epimerization. Following an analogous process to that used for TES derivatives **147**, TBS–protected 5-deoxy-*ribo* derivative **149** was synthesized and subsequently submitted to WH olefination. Four major alkene compounds were again observed in the ^{1}H NMR spectrum, with no change in the product distribution. From structural elucidation of the partially separated products, it was deduced that the *ribo* alkene was formed in 61% yield as an inseparable mixture of isomers (*Z*/*E*= 1:16) and that the epimerized *arabino* product represented only a 16% yield (Scheme 4.27).

Scheme 4.27 Olefination Products of **149** from the ^{1}H NMR[142]



Due to these results, we decided to implement Rodriguez' work with the use of bulkier TBDPS ether at C-3. However, the WH olefination reaction on TBDPS–protected ribose **163** also furnished a mixture of four alkenes with one major *E*-alkene in a 66% ratio based on ^{1}H NMR analysis (Scheme 4.28).

Scheme 4.28 Olefination Products of **163** from the ^{1}H NMR



Previous experiments on 6-deoxy-furanosides in our group had provided variable amounts of epimerized alkene products, particularly in the presence of benzyl protecting groups. Interestingly, furanosides proved to be resistant to this process. To gain insight into this problem, the complex alkene mixture obtained from olefination of **163** was purified and the two major alkenes were analyzed. For complete structural elucidation, it was necessary to submit these two products to cyclization in order to elucidate the structure of the cyclized products. All products obtained were analyzed by standard ^{1}H and ^{13}C NMR techniques, as well as by COSY, and, wherever possible, by HMBC, TOCSY, and NOESY experiments. The obtained spectroscopic data were compared with those obtained by Rodriguez from the TES– and TBS–protected derivatives that were tentatively assigned as the epimerized products. The results of this study are detailed in Tables 4.1 and 4.2.

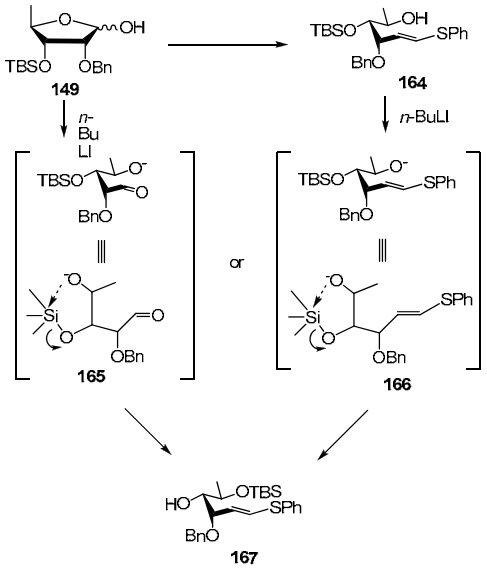
The ^{1}H NMR features of the two major isomers in all cases showed many similarities. Signals corresponding to olefinic protons H-1 and H-2 were found at similar chemical shifts and with similar $^{3}J_{1,2}$ values of 15.6 Hz. Further similarities were found comparing coupling constants between other protons. The ^{13}C NMR spectra of these alkenes showed only slightly more pronounced differences. However, for the determination of the exact structure of the alkenes further analysis was necessary.

The existence of a correlation between the free hydroxyl proton with the proton in the neighbouring carbon in the COSY spectrum allowed us to directly address our problem. This correlation is often not observed or only with a big expansion. The major *E*-isomer of TBDPS–protected alkene showed an interesting COSY correlation between a signal corresponding to H-4 and that corresponding to the free OH proton. The ^{1}H-spectrum indicated that the signal corresponding to H-4 appeared as a *dt* instead of a *t* or *dd,* be expected. The same observation was made with one of the *E*-isomers in the TES– and TBS–derivatives, as well. The COSY's of the respective other *E*-isomers in TES–, TBS– and TBDPS–derivatives, on the contrary, showed a COSY correlation between H-5 and

OH, and similarly, a more complex H-5 signal was found at the ^{1}H-spectra. Furthermore, the NMR spectrum pattern of these other *E*-isomers was nearly identical, with similar chemical shifts and coupling constants, regardless of the protecting group installed.

Spectroscopic data allowed us to confirm the structure of the major alkenes obtained from olefination corresponding to alkenes of *ribo* configuration **167**, **169** and **173**, with the respective silyl groups installed at the corresponding hydroxyl groups at C-5 instead of C-4, as expected.

Scheme 4.29 Mechanism of the Migration of Silyl Group under WH Olefination Reaction

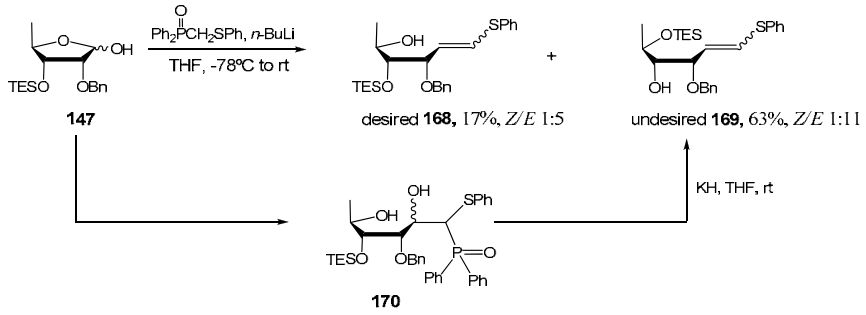


The mechanism of this migration is explained by the basic conditions under which olefination takes place, with formation of an intramolecular pentacoordinate silicate species either on the aldehyde substrate **149** furnishing intermediate **165**, or the alkene already formed **164** furnishing intermediate **166** (Scheme 4.29).[148] The migrated product **167** could be also formed in the subsequent elimination step of the β-hydroxyphosphine oxide intermediate with *t*-BuOK or KH. Furthermore, it is reasonable to suggest that this second step may 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.

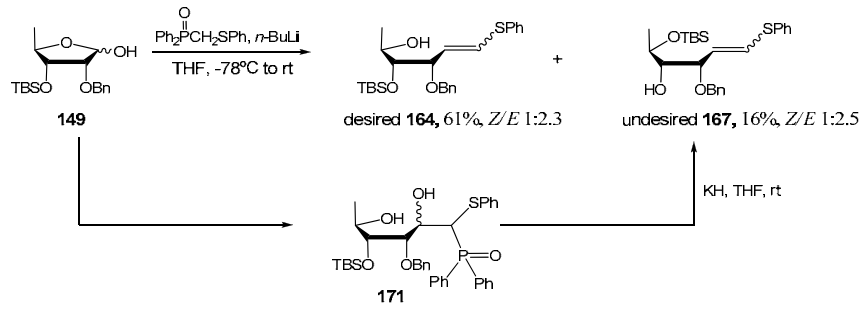
[148] Examples in the literature for silyl migration: a) Furegati, S.; White, A. J. P.; Miller, A. D. *Synlett.* **2005**, *15*, 2385. b) Ogilivie, K. K.; Entwistle, D. W. *Carbohydr. Res.* **1981**, *203*, 89. c) Mulzer, J.; Schöllhorn, B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 431. d) Crich, D.; Ritchie, T. J. *Carbohydr. Res.* **1990**, *29*, 324. e) Friesen. R. W. Daljeet, *Tetrahedron Lett.* **1990**, *31*, 6133. f) Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223.

Once the silyl migration process was elucidated, the composition of the alkene mixture became clear. The four products observed by NMR in all olefination experiments were assigned to a *Z*/*E* alkene mixture of the expected products **164**, **168** and **172** altogether with a *Z*/*E* alkene mixture of migration products **167**(Scheme 4.30), **169** (Scheme 4.31), and **173** (Scheme 4.32), respectively

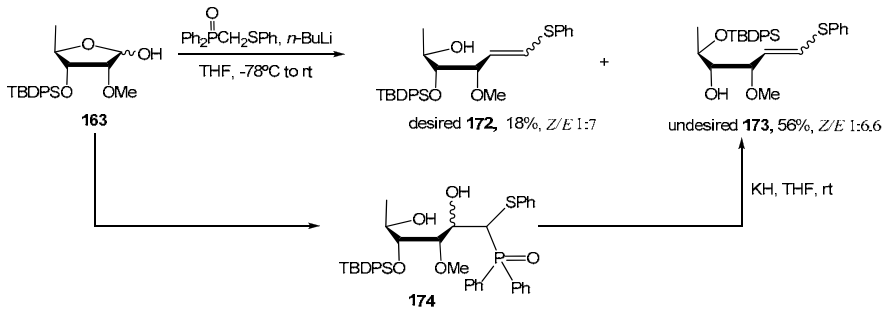
Scheme 4.30 WH Olefination Reaction of **147**[142]



Scheme 4.31 WH Olefination Reaction of **149**[142]

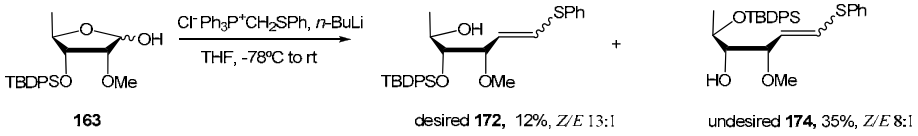


Scheme 4.32 WH Olefination Reaction of **163**



In order to mitigate the basicity of the olefinating reagent, thereby minimizing silyl group migration, a Wittig olefination reaction was tested for compound **163**. Under such conditions, however, the migrated *Z*-isomer **173** was again predominantly formed together with smaller amounts of the desired *Z*-isomer **172**, with only traces of *E*-isomers (Scheme 4.33).

Scheme 4.33 Wittig Olefination Reaction of **163**



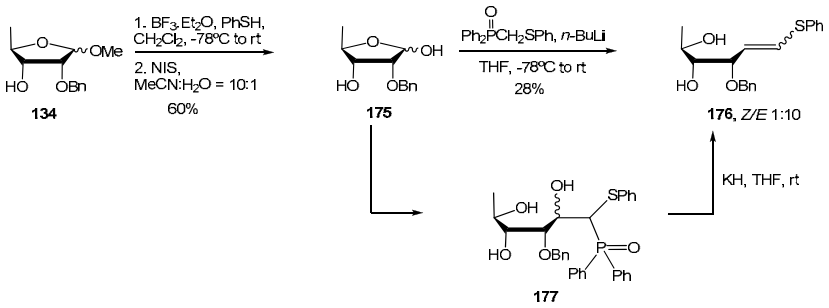
163 desired **172**, 12%, *Z*/*E* 13:1 undesired **174**, 35%, *Z*/*E* 8:1

In summary, all silyl ethers derivatives studied experiment silyl migration under the olefination conditions studied. With TES and TBDPS protecting groups, the major products were the migrated compounds, whereas, with TBS the desired protected on hydroxyl at C-4 ether was produced in the same proportion to the silyl migration alkene. This result contrasts with the literature data on this issue that describe that TBDPS ethers are more stable to migrations than TBS.[148]

In view of the outcome of these olefination reactions, it is clear that none of the well–known silyl ethers would be able to tolerate the strong basic conditions of the olefination reaction. We decided to assay the olefination reaction without protecting hydroxyl group at C-3. For this reason, 2-*O*-benzyl-6-deoxy-α,β-D-ribofuranose **175** was prepared from the ribofuranoside **134**. The ribofuranose **175** obtained was submitted to the standard olefination reaction under WH conditions with (phenylthiomethyl)diphenylphosphine oxide anion. The evolution of the reaction was monitored by TLC analysis. After work-up with ammonium chloride, the higher R_f olefination product was separated from the low R_f mixture of starting material, and the formed β-hydroxyphosphine oxide derivative. The β-hydroxyphosphine oxide derivative was then eliminated with KH to increase the yield of alkene (Scheme 4.34).

The olefination reaction of **175** furnished **176** in a poor yield, but good selectivity (28%, *E*/*Z* = 10:1). The NMR data of compound **176** are included in Table 4.1 for comparison.

Scheme 4.34 Synthesis of **176**



4.2.4.3 Cyclization and Glycosylation Reactions: Study of the 5-*Endo* Cyclization Mode

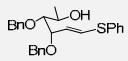
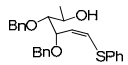
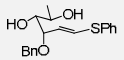
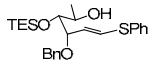
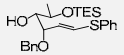
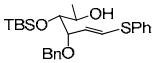
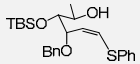
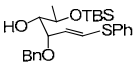
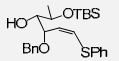
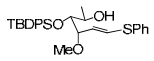
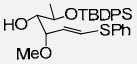
Silyl migration altered our plans to prepare the synthons for our Digitoxin and P57 syntheses, but provided access to valuable alkene derivatives on which electrophilic–induced cyclization could be further studied. Although our group has extensively studied this reaction for several years,[57] we considered it interesting to gain further insight into the parameters that govern this process, carrying out electrophile–induced cyclization with the free hydroxyl group at C-6 alkenes generated as a consequence of silyl migration.

Despite cycloetherification being an important tool in organic synthesis, 5-*endo* electrophile–induced cyclization is not well studied in the literature.[149] 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 section 1.1.5, Scheme 1.13).

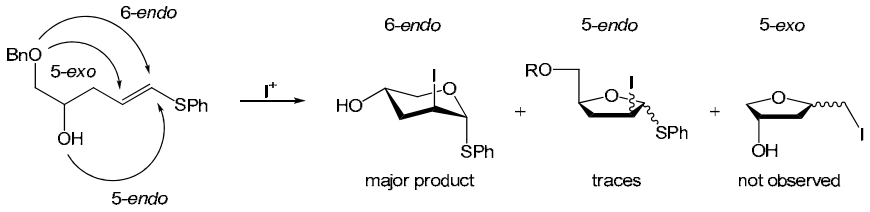
Previous studies in our group[57] on the electrophile–induced cyclization of simple alkenyl sulfides showed that whenever 6-*endo* and 5-*endo* modes are in competition, the 6-*endo* cyclization is preferred even if the hydroxyl function involved in cyclization is protected as benzyl ether. Under these 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 4.35).

[149] 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. b) Nonami, Y.; Baran, J.; Sosnicki, J.; Mayr, H.; Masoyama, A.; Nojima, M. *J. Org. Chem.* **1999**, *64*, 4060. c) Alabugin, I, V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127*, 9534. d) Chatgilialoglu, C.; Ferri, C.; Guerra, M.; Tomikhin, V.; Froudakis, g.; Giminiss, T. *J. Am. Chem. Soc.* **2002**, *124*, 10765. e) Knight, D. W. *Progress in Heterocyclic Chemistry*, **2002**, *14*, 19.

Table 4.1 NMR Dates of 6-Deoxy Alkenes with Different Protecting Groups

Entry		δ *(ppm)*						J *(Hz)*						δ *(ppm)*					
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*1,2*	*2,3*	*3,4*	*4,5*	*5, 6*	*Hx-OH*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
1		6.50	5.81	4.03	3.36	3.93	1.21	15.2	8.4	6.8	6.0	6.4	4.0 H5-OH	129.3	129.0	81.8	84.5	69.3	19.1
2		6.59	5.92	4.92	3.49	3.93	1.23	9.2	9.2	5.6	6.4	6.8	4.0 H5-OH	129.4	129.2	77.6	84.7	69.1	19.3
3		6.52	5.77	3.97	3.56	3.89	1.18	15.2	8.0	6.4	5.6	6.8	OH Broad	130.2	127.9	81.5	76.3	68.7	18.9
4		6.45	5.76	3.93	4.65	3.86	1.17	15.2	8.0	6.0	5.6	6.4	4.0 H5-OH	128.1	128.7	81.7	78.3	69.9	18.8
5		6.48	5.84	3.92	3.62 *dt*	3.94	1.10	14.8	8.0	6.0	5.6	6.4	2.4 H4-OH	128.1	129.3	79.8	77.0	68.6	18.3
6		6.42	5.73	3.93	3.63	3.86	1.15	15.6	8.0	6.8	5.6	6.0	4.8 H5-OH	128.6	129.4	81.5	78.2	69.8	18.8
7		6.55	5.84	4.50	3.75	3.86	1.2	9.6	9.2	4.8	5.2	6.4	4.8 H5-OH	129.2	129.3	77.2	78.4	69.7	19.0
8		6.50	5.84	3.93	3.75 *dt*	3.62	1.10	15.2	7.6	6.4	5.6	6.0	2.4 H4-OH	128.9	128.7	79.6	76.9	68.9	18.2
9		6.64	5.86	4.34	3.71 *dd* broad	4.08	1.10	9.6	8.4	8.0	4.0	6.8	H4-OH OH-broad	130.1	129.2	75.9	76.3	69.0	17.1
10		6.17	5.51	3.88	3.71	3.86	1.15	15.6	8.0	6.8	5.6	6.4	H5-OH OH-broad	128.5	129.1	83.7	79.3	69.9	19.0
11		6.35	5.68	3.75	3.68	3.95	1.05	15.6	8.0	6.8	5.6	6.0	COSY H4-OH	128.9	128.2	82.3	76.6	70.2	18.2

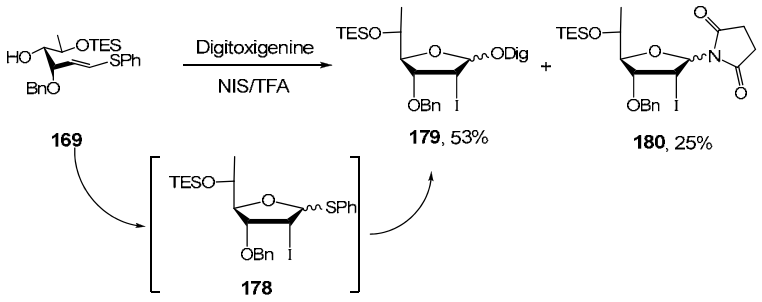
Scheme 4.35 5-*exo*-trig *versus* 5-*endo*-trig Cyclization Study



The migrated alkenes have an analogous structure to those studied by Arnes. Therefore, we though it would be interesting to implement our study with the reaction of the former with NIS under the typical conditions of cyclization.

To solve the problem of the structural elucidation of the alkenes obtained from olefination described above, electrophile–induced cyclization and *´one-pot´* cyclization–glycosylation reactions were carried out. These structures are beneficial because the coupling constants of six-membered mannopyranosides and allopyranosides have been well-studied in our group. Standard methods of cyclization were chosen with the iodine electrophile.

Scheme 4.36 Synthesis of **180**[142]

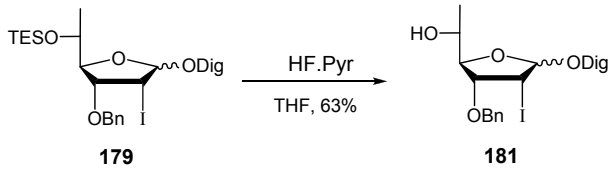


First, the major TES–protected enitol **169** was studied in glycosylation and cyclization reactions to elucidate the exact compound structure. Following our overall plan, a *´one-pot´* cyclization–glycosylation reaction was carried out by reaction with Digitoxigenine as a glycosyl acceptor. The enitol and the Digitoxigenine were stirred in the presence of NIS at –78 ºC. The reaction mixture was warmed to –20 ºC for 8 h, to promote the cyclization. The reaction mixture was then cooled to –60 ºC, and TFA was added to promote glycosylation of Digitoxigenine by activation of the thioglycoside intermediate **178**. The reaction mixture was then warmed –30 ºC. After stirring for 15 hours,

digitoxigenyl glycoside **179** was obtained in 53% yield, together with the *N*-succinimide glycoside (Scheme 4.36).

TES deprotection from **179** was studied with HF·Pyr to evaluate the stability of the glycosidic linkage towards desilylation. The reaction provided **181** in 63% yield (Scheme 4.37).

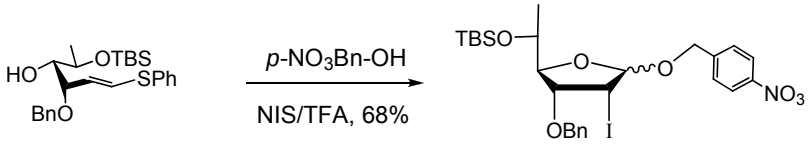
Scheme 4.37 Synthesis of **181**[142]



179 **181**

The *´one-pot´* cyclization–glycosylation from **167** and *p*-nitro-benzyl alcohol furnished the *p*-nitrobenzyl furanoside **182** in 68% yield (Scheme 4.38).

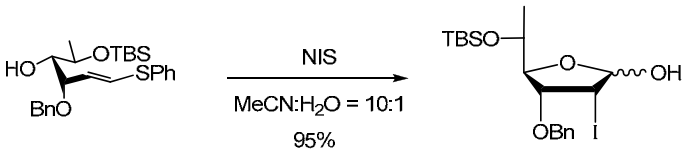
Scheme 4.38 Synthesis of **182**[142]



167 **182**

The cyclization reaction from the TBS–protected enitol **167** in the presence of NIS in MeCN/H_2O = 10:1 led to compound **183** in 95% yield in only 45 minutes at –10 ºC (Scheme 4.39).

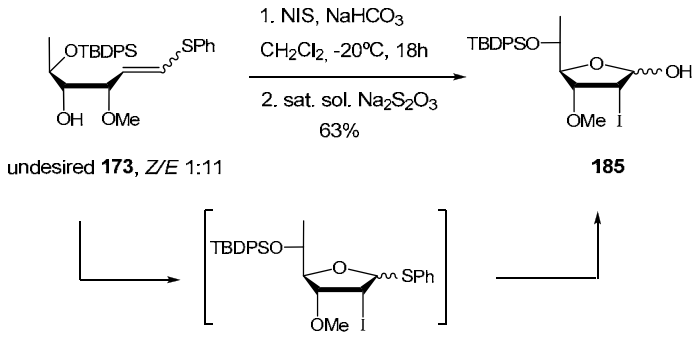
Scheme 4.39 Synthesis of **183**[142]



167 **183**

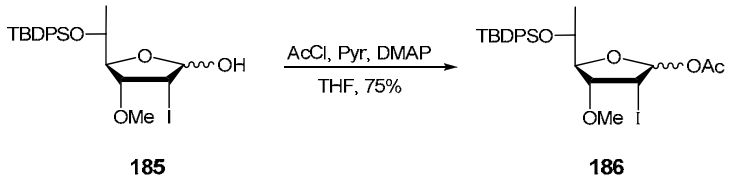
Correspondingly, the TBDPS–protected enitol **173** was cyclized in the presence of NIS and $NaHCO_3$ in DCM to afford furanose **185** in 63% yield (Scheme 4.40).

Scheme 4.40 Synthesis of **185**



To confirm the structure of compound **185**, it was acetylated with acetyl chloride in the presence of pyridine and DMAP in THF to give **186** in 75% yield (Scheme 4.41).

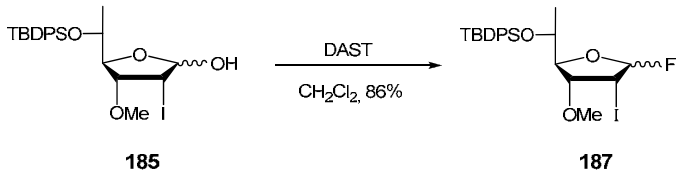
Scheme 4.41 Synthesis of **186**



2-Iodofuranose **185**, in turn, was transformed into the glycosyl fluoride with DAST to furnish **187** in 86% yield (Scheme 4.42).

When these cyclization experiments were carried out, we were excited to be working with 4-*O*-silyl akenyl sulfides with a free hydroxyl function at C-5, leading to cyclization experiments that would provide direct access pyranosides.

Scheme 4.42 Synthesis of **187**



When these cyclization experiments were carried out we were in the conviction to be working with 4-*O*-silyl akenyl sulfides with a free hydroxyl function at C-5 and therefore that the cyclization experiments would render pyranosides.

The ^{1}H and the ^{13}C NMR of fluoride **187**, however, provided an important piece of information in the determination of the structure of the previously described five-membered cyclized products and eventually of the olefination products.

It shows a signal at a relatively high chemical shift (δ = 6.11 ppm) identified from the HSQC spectrum as H-1 in the form of a doublet with $^{2}J_{1,F}$ of 66.4 Hz, a value that is far from the typical value located in pyranosyl fluorides (ca. 53 Hz). The related C-1 of compound **187** was found at δ = 116.49 ppm with a $^{1}J_{1,F}$ = 228.1 Hz, a chemical shift that is also relatively high for a typical anomeric carbon in a pyranosyl fluoride (ca. 110 ppm).[150] This was the first clue that made us suspect that we were working with an incorrect structural hypothesis. Further interesting data included the form of the signal of H-4 (qd), the coupling constant between H-4 and F ($^{4}J_{4,F}$ = 9.6 Hz), and H-2 in the form of double doublet with coupling constants ($^{3}J_{2,F}$ = 8.0 Hz, $^{3}J_{2,3}$ = 5.2 Hz) that was correlated in the ^{13}C NMR spectrum with a signal at high field (δ = 33.32 ppm). This is characteristic of a carbon atom attached to iodine (C-2) with the form of a doublet ($J_{C2,F}$ = 22.7 Hz). TOCSY, HMBC, and NOESY experiments were also carried out. TOCSY allowed identification of the spin system of the proton atoms in the ring framework. More interestingly, HMBC showed a correlation between the signal at 6.11 ppm in the ^{1}H NMR spectrum and a signal at 87.5 ppm in the ^{13}C NMR spectrum, assigned to H-1 and C-4, respectively. HMBC correlations are expected when the nuclei involved are 2 or 3 bonds apart, and therefore, the H-1–C-4 correlation should not be observed in a pyranosyl fluoride. No HMBC correlation was observed between H-1 and C-5 or H-5 and C-1.

NMR data of fluoride **187** and the previously described cyclized products were included in a table with the other six-membered allopyranoside derivatives for the sake of comparison. This allowed for the identification of common spectroscopic trends either in five- and six-membered *allo* derivatives. Results of this study are provided in Table 4.2. In the case of allopyranosides, α- and β-isomers can be distinguished by the coupling constant between H-1 and H-2 (in case of α-isomers, $J_{1,2}$ ranges from 0.0 to 2.8 Hz, while in the case of β-isomers $J_{1\text{-}2}$ ranges from 8.8 to 11.2 Hz). The coupling constants between other protons are comparable. This issue is not so clear for five-membered derivatives where the $^{3}J_{1,2}$ values do not follow a regular trend.

Chemical shifts of H-6 and C-6 also experience significant changes depending on the size of the ring. In the the ^{1}H NMR spectra, proton H-6 signals appear in furanosides at lower fields (δ = 1.20 to 1.35 ppm) than those in the corresponding pyranosides (δ = 0.96 to 1.16 ppm), whereas the general

[150] Dax, K.; Albert, M.; Ortner, J.; Paul, B. J. *Carbohydr. Res.* **2000**, *327*, 47.

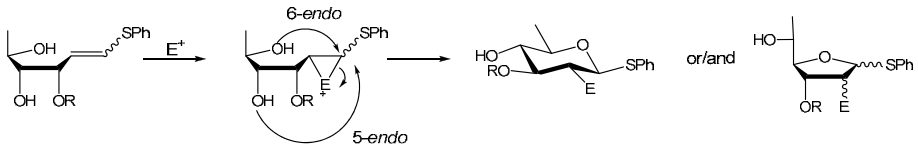
trend in the ^{13}C NMR spectra is the opposite, as the C-6 signals appear at lower chemical shifts (δ = 17.9 – 18.3 ppm) in furanosides than those in pyranosides (δ = 19.4 to 23.9 ppm).

Chemical shifts of C-4 and C-5 are also interesting because they depend on the size of the ring. Signals assigned to C-4 have chemical shifts between δ = 86 to 88 ppm in furanosides, whereas the analogous ones in pyranosides appear in the range between 70 and 82 ppm. Signals assigned to C-5 in furanosides appear nearly invariably at around δ = 69 ppm, whereas in pyranosides, the chemical shift values are considerably more irregular.

These spectroscopic evidences allowed us to confirm the furanosidic nature of the cyclized products **179**, **180, 181**, **182**, **183**, **185**, **186**, and **187** in detriment to the pyranoside hypothesis, and eventually allowed us to establish the connection with their migrated alkene precursors **167**, **169**, and **173**, respectively.

To understand whether 5-*endo* or 6-*endo* cyclization would be favoured, we carried out a cyclization reaction with an enitol from 6-deoxy-ribofuranose with two free secondary hydroxyls at C-4 and C-5 (Scheme 4.43).

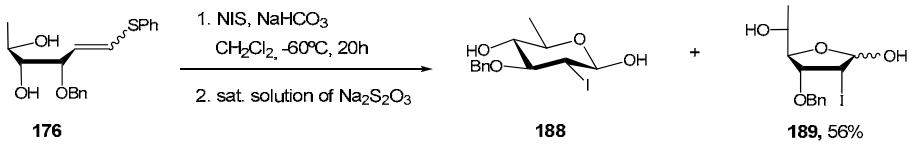
Scheme 4.43 Cyclization 6-*endo* versus 5-*endo*



After the preparation of enitol **176** by WH olefination reaction, cyclization reaction was carried out DCM in the presence of NIS (1.5 equiv), $NaHCO_3$ (1.1 equiv), and 4Å MS at –60 ºC. After 30 minutes, TLC analysis indicated that more than one cyclization product was formed with R_f higher than the respective enitol. The reaction was stopped after 20 hours by addition of a solution of $Na_2S_2O_3$. The compounds obtained were separated by column chromatography, and one major compound was obtained in a 56% yield, and at least three minor products were obtained as an inseparable mixture (Scheme 4.44).

The major compound was analyzed by ^1H and ^{13}C NMR and 2D NMR techniques, compared with other cyclization products prepared previously, and finally assigned as compound **189.** As such, the 5-*endo* mode was clearly favoured over the 6-*endo* cyclization.

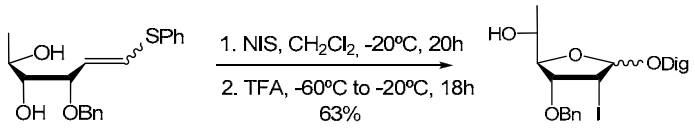
Scheme 4.44 Cyclization Reaction of **176**



176 **188** **189,** 56%

We were also interested in elucidating whether it was possible to obtain the desired 6-*endo* cyclized product at higher temperatures in a *´one-pot´* reaction. The *´one-pot´* cyclization–glycosylation from alkenyl sulfide **176** in the presence of Digitoxigenine as glycosyl acceptor was thus studied. The reaction mixture was stirred at –20 ºC in the presence of NIS to promote the cyclization event. When starting material disappeared as indicated by TLC analysis, the reaction mixture was cooled –60 ºC, and TFA was added to promote glycosylation. The resulting mixture warmed to –20 ºC and stirred for 18 hours. The reaction products was isolated and analyzed with ^{1}H and ^{13}C NMR and 2D NMR techniques. Comparison of the spectroscopic data with those of the other cyclized products prepared previously allowed assignment the product to that of 5-*endo* cyclization–glycosylation product **182**, obtained in a 63% yield starting from (Scheme 4.45).

Scheme 4.45 *´One-pot´* Reaction of 1**76**



176 **182**

The silyl migration process was an obstacle that prevented synthesis of the monosaccharide moieties for digitoxin and P57 syntheses. However, they provided us with unexpected cyclization modes that were studied to gain further insight into a process we have studied for many years. As such, digitoxin and P57 syntheses are pending in a near future, and depend upon the proper selection of temporary protecting groups at C-4. One recommended group is the PMB ether that can be deprotected under oxidative conditions, or alternatively dimethyl-*t*-butylsilyloxy methyl ethers that can be deprotected by treatment with TBAF. This group should, however, circumvent the undesired migration. Other possibilities such as THP, MOM, MEM and SEM ethers should also be considered.

Table 4.2 ^{1}H and ^{13}C NMR Dates of Cyclization Products with Different Protecting Groups.

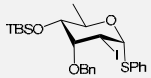
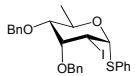
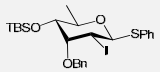
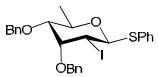
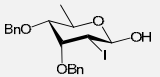
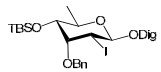
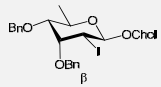
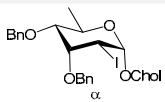
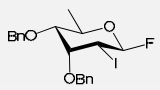
Entry		δ *(ppm)*						J *(Hz)*								δ *(ppm)*					
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*1,2*	*2,3*	*3,4*	*4,5*	*5, 6*	*1,F*	*2,F*	*H,F*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
1		5.45	4.88	3.89	4.28	4.63	1.31	0.0	2.8	2.4	9.2	6.0				88.6	28.3	80.5	70.7	67.0	18.1
2		5.46	4.92-4.39	4.00	3.97	4.92-4.39	1.36	0.0	3.6	2.8	9.2	6.4				89.5	27.5	75.8	76.4	65.7	18.0
3		5.09	4.09	3.95	3.47	4.06	1.22	10.8	2.4	2.0	9.2	6.4				84.7	32.4	82.4	75.7	73.5	18.5
4		5.10	4.03	4.18	3.23	4.11	1.27	11.2	2.6	2.2	9.6	6.4				84.6	32.4	78.5	81.9	72.6	18.4
5		5.29	4.61	4.16	3.29	4.71	1.26	5.2	2.6	2.4	9.6	6.0				90.0	27.7	77.9	82.2	64.6	17.9
6		4.79	4.08	3.93	3.57	4.00	1.19	8.8	2.4	2.4	9.2	6.4				98.4	33.9	82.4	75.9	70.2	18.3
7		4.85	4.00	4.16	3.29	4.08	1.26	8.8	2.4	2.0	9.2	nd				98.9	33.9	78.3	82.0	69.4	18.3
8		5.12	4.46	3.97	3.76	4.36	126	2.4	4.4	3.0	7.4	nd				99.5	28.7	78.0	76.0	65.4	18.3
9		5.55	3.99	4.14	3.35	4.10	1.35	8.8	6.0	2.4	9.2	6.0	52.4	8.4	3.6 $_{H3,F}$	107.7 *d*, $J_{F,C1}$= 209.8	29.6 *d*, $J_{F,C2}$= 82.3	77.9 *d*, $J_{F,C3}$= 6.8	81.3	70.4 *d*, $J_{F,C5}$= 4.6	18.0

Table 4.2 ^{1}H and ^{13}C NMR Dates of Cyclization Products with Different Protecting Groups (Continued).

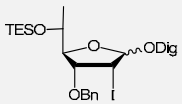
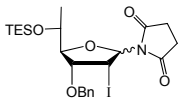
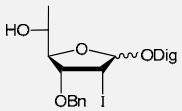
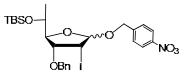
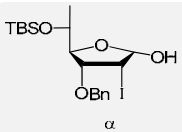
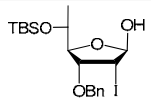
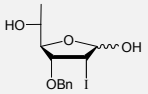
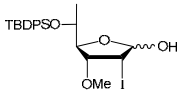
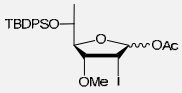
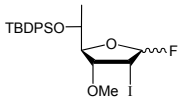
Entry		δ *(ppm)*						J *(Hz)*								δ *(ppm)*					
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*1,2*	*2,3*	*3,4*	*4,5*	*5, 6*	*1,F*	*2,F*	*H,F*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
10		5.37	4.12	4.48	3.87	3.96	1.15	2.8	3.6	4.8	4.4	6.4				109.8	28.5	87.5	87.5	73.6	20.5
11		5.93	5.20	4.63	4.08	3.99	1.10	9.0	7.8	6.6	2.4	6.8				88.1	21.6	85.1	86.1	68.3	19.4
12		5.42	4.15	3.93	4.47	3.99	1.15	1.2	2.4	6.0	3.0	6.4				109.7	28.4	86.5	86.9	66.5 with OH free	23.9
13		5.45	4.37	3.73	3.98	3.88	1.14	3.6	5.6	5.2	4.8	6.0				110.0	31.9	77.8	86.9	69.2	20.4
14	 α	5.61	4.23	3.81	4.58	4.05	1.12	4.4	4.0	nd	nd	nd				95.8	27.0	78.5	87.2	68.5	20.6
15	 β	5.43	4.18	3.81	3.93	3.65	1.16	7.6	5.2	3.2	5.2	6.4				93.4	30.8	78.6	88.0	68.7	20.7

Table 4.2 ^{1}H and ^{13}C NMR Dates of Cyclization Products with Different Protecting Groups (Continued).

Entry		δ *(ppm)*						J *(Hz)*								δ *(ppm)*					
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*1,2*	*2,3*	*3,4*	*4,5*	*5, 6*	*1,F*	*2,F*	*H,F*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
16		5.29	4.38	3.88	3.91	3.84	1.07	0.0	4.8	0.8	7.6	7.2				108.9	35.6	76.5	83.8	73.6	17.7
17		5.45	3.86	3.48	3.89	3.72	1.09	7.2	5.2	3.2	6.8	6.8				93.2	30.1	81.0	87.3	69.8	20.7
18		6.17	4.28	3.78	4.03	4.04	1.03	4.8	6.4	2.4	6.8	6.8				96.8	26.2	79.0	88.8	69.2	20.2
19		6.08	4.49	3.55	4.00	4.16	0.96	0.0	5.2	7.2	3.6	6.4	66.1	8.0	9.6 $_{H4,F}$	116.5 $J_{C1,F}$= 228.1	33.3 $J_{C2,F}$= 22.7	77.7	87.2	69.0	19.4

4.3 Conclusions

In this chapter, we have explored the total syntheses of digitoxin and P57. 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:

- The 3rd Synthon of P57 **132** was synthesized from the commercially available compound **125** in 6 steps. Compound **132** can be used directly in glycosylation reaction, or can be readily converted to other glycosyl donors depending on the desired synthetic strategy.

- The 3rd Synthon of digitoxin was synthesized through an olefination reaction from dibenzylated ribose derivative **136**, followed by iodonium–induced cyclization to provide 2-iodo-*allo*-pyranose **139** as a versatile agent for the preparation of glycosylation agents. Compound **139** was eventually converted into the corresponding glycosyl fluoride **140** in good yield.

- Olefination, cyclization, and glycosylation reactions were studied toward the synthesis of 2,6-didexy 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. Since the structural elucidation of migrated products was complicated, subsequent cyclization and glycosylation steps were necessary.

- The cyclization reaction without a protecting group on the hydroxyl at C-4 furnished one major product that was determined to be the 5-*endo* product, along with an inseparable mixture of various cyclic products.

- This approach to the synthesis of digitoxin and P57 has highlighted the requirement for a protecting group that is compatible with the basic conditions involved in the olefination step. Protecting groups such as PMB, THP, MOM, MEM and SEM or SOM ethers will be analyzed, and our results will be disclosed in due course.

UNIVERSITAT ROVIRA I VIRGILI
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SUMMARY

"Uno no se da cuenta de lo que ha hecho,
sino de lo que queda por hacer."

Marie Curie, Premio Nobel de Física

In the present work, a complete study for the synthesis of 2-deoxy-glycosides is described, applying a strategy previously developed in our group for the preparation of 2-deoxy-2-iodo-pyranoses. This strategy, that involves Wittig–Horner olefination from fully protected furanoses to give alkenyl sulfides, electrophilic–induced cyclization to furnish 2-deoxy-2-iodo-pyranosyl thioglycosides, gives access to a new type of glycosyl donor that can be used in glycosylation reactions of the desired glycosyl acceptors to give 2-deoxy-2-iodo-glycosides.

This method is based, on one hand, in the availability of sulfanylmethylphosphine oxides to perform the olefination reaction over the furanoses. The usual access to these reagents is the Arbuzov reaction, that requires chloroderivatives as starting materials that are not easy to prepare and in many cases are unstable. Furthermore, the efficiency of the cyclization is limited by the obtaintion of *E*/Z alkene mixtures in the olefination step, because *Z* alkenes were proved to be reluctant to cyclization.

To increase the efficiency of the whole process, two implementations were studied in this work. Firstly, a new approach for the preparation of sulfanylmethylphosphine oxides was investigated starting from (tosyloxymethyl)phosphine oxide. The method was also extended to heteroatomic substituted methylphosphine oxides (X, Se, Te, NR_2, etc).

Application of these novel sulfanylmethylphosphine oxides in the olefination of ribo- and arabinofuranoses resulted in the formation of the corresponding sulfanyl alkenes with increased *E*/*Z* stereoselectivity.

The sulfanyl *ribo* and *arabino* alkenes were investigated in the iodonium–induced cyclization reaction. The effect of the bulkiness of the substituent at sulfur was studied and the results of cyclization compared to that of phenyl at the phenylsulfanyl parent compound. Cyclization of the *arabino* derivatives led to 6-*endo* cyclization products in lower yields whereas the *t*-butylsulfanyl *arabino*-1-hex-enitol proceeded in higher yield. No cyclization took place from 2,6-dimethylphenyl *arabino*-1-hex-enitol.

Glycosylation of some of the thioglycosides synthesized were explored and compared with those obtained from phenylsulfanyl parent thioglycoside. *t*-Butyl thioglycoside was reacted with cholesterol to render glycosylated product in higher yield without almost affecting the stereoselectivity whereas with 2,6-dimethylphenyl thioglycoside the stereoselectivity increased but the yield was lower.

The synthesis of septanosides was studied starting from pyranosides with the strategy of Wittig–Horner olefination and subsequent electrophile–induced cyclization reaction, but the desired 7-*endo* cyclization did no work with secondary alcohols. To overcome this problem, starting from conformationally–restricted 2,3-O-isopropylidenefuranosides, hex-1-enitols with a free primary hydroxyl function were prepared, from which 7-*endo* cyclization reaction took place to furnish the desired oxepanes with moderate yields.

The total syntheses of 2,6-dideoxyoligosaccharides digitoxin and appetite suppressant P57, with common 2,6-dideoxypyranose units, were explored, applying the three-step (olefination–cyclization–

glycosylation) methodology. For the synthesis of common intermediate **C**, two different permanent protecting groups for free hydtoxyl group at C-3 were used: benzyl ethers for digitoxin and methyl ethers for P57. Different silyl groups (TBS, TES and TBDPS) were used for hydroxyl at C-4 that required temporary protection. Olefination of the different 6-deoxyribofuranoses rendered the corresponding 5-*O*-silyl hex-1-enitols (**167**, **169**, and **173**) as a consequence of silyl migration from hydroxyl at C-4 to C-5, altogether with the expected 4-*O*-silyl hex-1-enitols (**164**, **168**, and **172**). These products were analyzed by 1D and 2D NMR techniques.

5-*O*-TES, 5-*O*-TBS or 5-*O*-TBDPS protected hex-1-enitols were submitted to iodonium–induced cyclization reactions to afford exclusively 5-*endo* cyclization products. Furthermore, 5-*endo* cyclization product 2-iodofuranose **189** was formed as a major product by cyclization from the C-4 unprotected enitol **176**.

Digitoxin and P57 synthesis will be reconsidered in a near future using other protecting groups that do not migrate under the basic conditions of the olefination.

EXPERIMENTAL SECTION

"Una conciencia tranquila
nos hace serenos."

Lord Byron, poeta británica

General Remarks

All chemicals used were reagent grade and used as supplied. HPLC grade dichloromethene (DCM), tetrahydrofurane (THF) and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLV system-400). Optical rotations were measured at room temperature in 10 cm cells in a Perkin–Elmer 241 polarimeter. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using a Varian Gemini 300 MHz (300 MHz and 75 MHz respectively) and 400 MHz (400 MHz and 100 MHz respectively) apparatus, with $CDCl_3$ as solvent, with chemical shift (δ) referenced to intermal standards $CDCl_3$ (δ = 7.26 ppm ^{1}H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (δ = 0.00 ppm ^{1}H), and H_3PO_4 (^{31}P) as external standard. Elemental analyses were performed using a Carlo–Erba Microanalyzer. Flash column chromatography was performed using silica gel 60 A CC (230–400 mesh). Radial chromatography was performed on 1, 2 or 4 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Medium–pressure chromatography (MPLC) was performed using silica gel 60 A CC (6–35 μm).

General Methods

General Methods for the Synthesis of Diphenylphosphine Oxides

General Method A: **Synthesis of 10–15, 25, 26, 27–29.** The respective thiol, selenol, tellurol or alcohol, (10.5 mmol) was added to a suspension of sodium hydride (60% in mineral oil, 10.5 mmol) in anhydrous THF (42 ml) at 0 ºC under argon atmosphere. The reaction mixture was warmed up to room tempeature and stirred for an hour. Subsequently, a solution of **9** (10.0 mmol) in anhydrous THF (20 ml) was added at 0 ºC. The reaction mixture was warmed up to room temperature and stirred for 2 hours. After quenching with the addition of saturated solution of NH_4Cl the reaction mixture was extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The white solid obtained was recrystallized from ethyl acetate – hexane and in general white crystals were obtained.

General Method B: **Synthesis of 30–34.** The respective chloro derivative (10.5 mmol) was added to a solution of **8** (10.0 mmol) in anhydrous DCM (40 ml), imidazol (10.5 mmol) and DMAP (0.5 mmol) finally the reaction mixture that was heated to reflux overnight. The reaction was quenched with saturated NH_4Cl, and extracted with ethyl acetate (3x25 ml). The combined organic layer was washed with water (2x25 ml), brine (1x25 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The obtained crude product was recrystallized from ethyl acetate – hexane.

General Method C: **Synthesis of 35–38.** Compound **9** (4.0 mmol) and the respective potassium halide (40.0 mmol) were dissolved in triethylenglycol (80 ml). The reaction mixture was warmed up to 160 ºC for 15 to 60 minutes depending on the halide. Then the reaction mixture was cooled to room temperature, quenched with NH_4Cl and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20ml), brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified with flash chromatography (ethyl acetate: hexane = 1:1 to ethyl acetate).

General Method D: **Synthesis of 39–40.** The corresponding amine (12.0 mmol) was added to a solution of **9** (10.0 mmol) in anhydrous DMF (40 ml) in a round flask, subsequently the reaction mixture was heated to reflux overnight. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate (3x25 ml). The combined organic layer was washed with water (2x25 ml), brine (1x25 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The obtained crude product was recrystallized from ethyl acetate – hexane.

The Michaelis-Arbuzov Reaction

Ethyl diphenylphosphinite (1.0 mmol) and the corresponding halo methyl derivative (1.05 mmol) were stirred at 150 ºC under argon atmosphere. The evolution of the reaction was monitored by TLC. After the completion of the reaction the mixture was cooled to room temperature and purified by recrystallization or by flash chromatography using hexane: ethyl acetate = 2:1 as eluent.

General Methods of WH Olefination Reactions

A *n*-BuLi solution (2.2 ml, 3.5 mmol, 3.5 eq, 1.6 M in hexane) was slowly added to the cold (–78 ºC) solution of (alkylsulfanyl- or arylsulfanylmethyl)diphenylphosphine oxide (2.0 mmol) in anhydrous THF (13 ml) under argon atmosphere. The reaction mixture was further stirred under the same conditions for 30 minutes, subsequently a solution of the corresponding aldehyde (1.0 mmol) in anhydrous THF (5 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 ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on $MgSO_4$, 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 40 ºC 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.[114] $NaHCO_3$ (0.24 mmol) was added to a 0.5 M solution of alkene (0.16 mmol) in CH_3CN. The mixture was cooled to –30 ºC and left to stir at this temperature for 5 min. NIS (0.24 mmol) was then added and the reaction mixture stirred for several hours. The reaction temperature was left to increase depending on the reactivity of the substrate (from –78 ºC to room temperature). The mixture was diluted with dichloromethene and washed with a saturated solution of $Na_2S_3O_3$, extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by chromatographic techniques.

Method B.[115] A solution of the alkene (1.0 mmol) in anhydrous Et_2O (7 ml) was added to a solution of KH 30% (1.3 mmol) at –30 ºC. The mixture was left to stir at this temperature for 20 minute until solution turned yellow, by the time the mixture was cooled to –78 ºC and a solution of I_2 in anhydrous Et_2O (7 ml) was then added. The reaction was monitored by TLC (hexane: ethyl acetate = 3:1) and left to stir until the cyclization was completed, warming gently if necessary. The reaction was quenched by adding Et_2O and $Na_2S_2O_3$, and the aqueous layer was extracted with ethyl acetate (3x20 ml). The combined organic layer was dried over $MgSO_4$, and concentrated under vacuum. The crude was purified by chromatographic techniques.

General Procedure for Glycosylation

A solution of the glycosyl donor (1.0 mmol) and the glycosyl acceptor (2.0 mmol) in anhydrous DCM (4 ml) was stirred with 4Å molecular sieves for 2 h. The mixture was then cooled to –78 ºC, and NIS (2.2 mmol) and TfOH (0.2 mmol) were added. The mixture was allowed to warm to –40 ºC and stirred until the reaction had finished. The reaction mixture was then diluted with DCM and washed with a solution of $Na_2S_3O_3$ and the aqueous layer was extracted with DCM (3x20 ml). The combined organic layer was washed with water (2x15 ml), brine (1x15 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The residue was then purified by radial chromatography.

General Procedure for the *´One-pot´* Cylization – Glycosylation from Sulfanyl Alkenes

Starting alkene (1 mmol), glycosyl acceptor (2 mmol), 4Å molecular sieves and 25 ml (0.02 M) of anhydrous DCM were stirred together at rt during 30 min. The reaction was cooled at –65 ºC and then NIS (3.0 mmol) was added. While the reaction temperature was allowed to reach at –10 ºC, 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 –60 ºC and then TfOH (0.2 mmol) was added. The reaction was left to stir at low temperature (between –40 ºC and –10 ºC) until the reaction was complete. The

crude of the reaction was quenched with $NaHCO_3$–$Na_2S_2O_3$ solution, extracted with DCM (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum.The crude was purified by chromatographic techniques.

General Procedure of Silylation of Alcohols

To a solution of alcohol (1.00 eq), imidazol (1.50 eq) and silyl chloride (1.05 eq) in anhydrous DCM (2.0 ml, 0.5 M), DMAP (0.20 eq) were added slowly. The mixture was vigorously stirred at rt for 6 h and then diluted with ethyl acetate, quenched with NH_4Cl, extracted with DCM (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by chromatographic techniques.

General Procedure of Oxidation of PMB Group

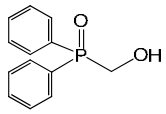
To a solution of PMB protected compound (1.00 eq) in humid DCM DDQ (1.05 eq) was added and the reaction was left to react at rt for 8 h. The reaction mixture was then quenched with $NaHCO_3$, extracted with ethyl acetate, quenched with NH_4Cl solution, extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by chromatographic techniques.

General Procedure of Demethylation

Ribofuranoside (1.0 eq) and PhSH (1.5 eq) are dissolved in anhydrous DCM (20 ml, 0.2 M) and was added $BF_3.Et_2O$ (1.5 eq) at –78 ºC and was warmed up to rt. The mixture was reacted at rt for 8 h and was quenched with TEA, concentrated and filtered on silice. The crude of the reaction was treated with NIS (1.2 eq) in $MeCN/H_2O$ = 10:1 and in 10 minutes quenched with the solution of $Na_2S_2O_3$, extracted with DCM (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by chromatographic techniques.

Synthesis of Compounds

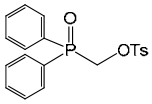
(Hydroxymethyl)diphenylphosphine Oxide (8).[78]



In a 1–L round flask diphenylchlorophosphine (20 g, 90.64 mmol), aqueous formaldehyde (158 ml, 35%, 2.00 mol) and concentrated hydrochloric acid (163 ml, 37%, 2.00 mol) were heated to reflux overnight. The reaction mixture was then quenched with a saturated solution of sodium bicarbonate, concentrated under vacuum, and extracted with ethyl acetate (4x100 ml). The combined organic layer was washed with water (2x100 ml), brine (1x100 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The white solid obtained was recrystallized from ethyl acetate – hexane to afforded compound **8** (18.72 g, 89%) as white crystals.

Mp: 135.0 – 136.0 ºC (Lit. 136.0 – 136.5 ºC)

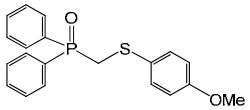
(Tosyloxymethyl)diphenylphosphine Oxide (9).[151]



In a 1-L round flask previously filled with argon **8** (18.56 g, 80.00 mmol) was dissolved in anhydrous DCM (200 ml) and toluene-4-sulfonyl chloride (16.01 g, 84.00 mmol) and DMAP (11.73 g, 96.00 mmol) were added. The reaction mixture was heated to reflux for four hours. After quenching with a saturated solution of NH_4Cl the DCM was removed under vacuum, the aqueous layer extracted with ethyl acetate (3x80 ml), and the combined organic layer washed with water (2x80 ml) and brine (1x80 ml), dried over $MgSO_4$, filtered and concentrated under vacuum. Compound **9** was obtained in quantitative yield and was pure enough to be used in the next reactions without further purification.

Mp: 123.0 – 124.0 ºC (Lit. 124.0 – 125.0 ºC)

(4-Methoxyphenylsulfanylmethyl)diphenylphosphine Oxide (10).



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium hydride (60% in mineral oil, 420 mg, 10.50 mmol) and methoxythiophenol (930 μl, 10.50 mmol) were reacted in anhydrous THF (40 ml) at 0 ºC under argon atmosphere, then a solution of compound **9** (3.86 g,

[151] van Steenis, J. H.; van der Gen, A. *Eur. J. Org. Chem.* **2001**, 897.

10.00 mmol) in anhydrous THF (20 ml) was added and the reaction was monitored by TLC for 2 hours. General work-up and recrystallization from ethyl acetate – hexane afforded compound **10 (**3.16 g, 89%) as white solid.

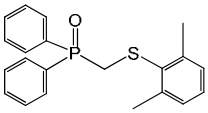
Mp: 71.0 – 72.0 ºC.

IR: ν (C=C): 1436.8 cm^{-1}; ν (P=O): 1185.0 cm^{-1}.

Anal. Calcd for $C_{20}H_{19}O_2PS$: 67.78 C, 5.40 H, 9.05 S. Found: 67.44 C, 5.24 H, 8.93 S.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.77 (m, 4H, $H_{aromatic}$); 7.52 (m, 2H, $H_{aromatic}$); 7.45 (m, 4H, $H_{aromatic}$); 7.27 (m, 2H, $H_{aromatic}$); 6.74 (d, 2H, $J_{H,H}$ = 8.8 Hz, $H_{aromatic}$); 3.76 (s, 2H, CH_3); 3.63 (d, 2H, $J_{H,P}$ = 8.8 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 159.6, 132.4, 132.3, 128.8 ($C_{aromatic}$); 134.1, 132.2, 131.4, 128.7, 114.8 ($\underline{C}H_{aromatic}$); 55.5 ($O\underline{C}H_3$); 35.9 (d, $\underline{C}H_2$, $J_{C,P}$ = 67.9 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 28.74 (s, P=O).

(2,6-Dimethylphenylsulfanylmethyl)diphenylphosphine Oxide (11).



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium hydride (60% in mineral oil, 168 mg, 4.20 mmol) and 2,6-dimethylbenzenethiol (559 μl, 581 mg, d = 1.038 g/ml, 4.20 mmol) were reacted in anhydrous THF (16 ml) at 0 ºC under argon atmosphere, then a solution of compound **9** (1.54 g, 4.00 mmol) in anhydrous THF (8 ml) was added and the reaction was monitored for 3 hours. General work-up and recrystallization from ethyl acetate – hexane afforded compound **11** (2.74 g, 7.79 mmol, 78%) as white crystals.

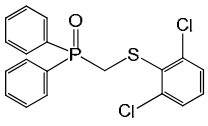
Mp: 119.0 – 120.0 ºC.

IR: ν (C=C): 1436.7 cm^{-1}; ν (P=O): 1189.9 cm^{-1}.

Anal. Calcd for $C_{21}H_{21}OPS$: 71.57 C, 6.01 H, 9.10 S. Found: 71.93 C, 5.96 H, 9.73 S.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.76 (m, 4H, $H_{aromatic}$); 7.54 (m, 2H, $H_{aromatic}$); 7.46 (m, 4H, $H_{aromatic}$); 7.07 (m, 2H, $H_{aromatic}$); 7.01 (m, 1H, $H_{aromatic}$); 3.45 (d, 2H, $J_{H,P}$ = 9.6 Hz, CH_2); 2.35 (s, 3H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 142.1, 142.0, 139.2, 131.2, 131.1 ($C_{aromatic}$); 134.1, 132.2, 131.4, 130.4, 128.7 ($\underline{C}H_{aromatic}$); 34.5 (d, $J_{C,P}$ = 67.1 Hz, $\underline{C}H_2$); 22.0 ($\underline{C}H_3$). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 28.94 (s, P=O).

(2,6-Dichlorophenylsulfanylmethyl)diphenylphosphine Oxide (12).



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium hydride (60% in mineral oil, 420 mg, 10.50 mmol) and 2,6-dichlorobenzenethiol (1.88 g, 10.50 mmol) were reacted in anhydrous THF (40 ml) at 0 ºC under argon atmosphere, then a solution of compound **9** (3.86 g, 10.00 mmol) in THF (20 ml) was added and the reaction was monitored for 4 hours. After general work-up and recrystallization from ethyl acetate – hexane afforded compound **12** (2.84 g, 7.22 mmol, 72%) as white crystals.

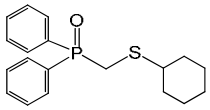
Mp: 181.5 – 183.0 ºC.

IR: ν (C=C): 1436.7 cm^{-1}; ν (P=O): 1188.9 cm^{-1}.

Anal. Calcd for $C_{19}H_{15}Cl_2OPS$: 58.03 C, 3.84 H, 8.15 S. Found: 57.92 C, 3.57 H, 8.06 S.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.80 (m, 4H, $H_{aromatic}$); 7.52 (m, 2H, $H_{aromatic}$); 7.45 (m, 4H, $H_{aromatic}$); 7.27 (m, 2H, $H_{aromatic}$); 7.14 (m, 1H, $H_{aromatic}$); 3.74 (d, 2H, $J_{H,P}$ = 8.8 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 142.1, 142.0, 141.4, 131.2, 131.1 ($C_{aromatic}$); 132.4-128.7 ($\underline{C}H_{aromatic}$); 33.4 (d, $\underline{C}H_2$, $J_{C,P}$ = 67.10 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 28.54 (s, P=O).

(Cyclohexylsulfanylmethyl)diphenylphosphine Oxide (13).[78]



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium hydride (60% in mineral oil, 420 mg, 10.50 mmol) and cyclohexylthiol (1.56 ml, 1.22 g, d = 0.78 g/ml, 10.50 mmol) were reacted in anhydrous THF (42 ml) at 0 ºC under argon atmosphere, then a solution of compound **9** (3.86 g, 10.00 mmol) in THF (20 ml) was added and the reaction was monitored for 2 hours. After general work-up and recrystalization from ethyl acetate – hexane afforded compound **13** (3.25 g, 9.84 mmol, 98%) as white crystals.

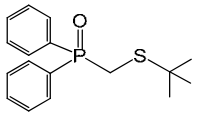
Mp: 100.0 – 101.0 ºC.

IR: ν (C=C): 1436.7 cm^{-1}; ν (P=O): 1183.1 cm^{-1}.

Anal. Calcd for $C_{19}H_{23}OPS$: 69.06 C, 7.02 H, 9.70 S. Found: 68.95 C, 7.11 H, 9.73 S.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.79 (m, 4H, $H_{aromatic}$); 7.59 (m, 2H, $H_{aromatic}$); 7.51 (m, 4H, $H_{aromatic}$); 3.28 (d, 2H, $J_{H,P}$ = 9.6 Hz, CH_2); 2.64 (m, 1H, CH); 1.90 (m, 4H, CH_2); 1.80 (m, 4H, CH_2); 1.49 (m, 2H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 142.05, 131.3, 131,2 ($C_{aromatic}$); 132.3, 131.4, 129.9, 128.8, 128.4 ($\underline{C}H_{aromatic}$); 45.6 ($\underline{C}H$); 33, 2 ($\underline{C}H_2$); 28.5 (d, $\underline{C}H_2$, $J_{C,P}$ = 94.46 Hz); 26.1 ($\underline{C}H_2$); 25.9 ($\underline{C}H_2$). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 29.86 (s, P=O).

(*tert*-Butylsulfanylmethyl)diphenylphosphine Oxide (14).[78]



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium hydride (60% in mineral oil, 168 mg, 4.20 mmol) and 2-methylpropane-2-thiol (473 μl, 379 mg, d = 0.8 g/mol, 4.20 mmol) were reacted in anhydrous THF (16 ml) at 0 ºC under argon atmosphere, then a solution of compound **9** (1.54 g, 4.00 mmol) in THF (8 ml) was added and the reaction was monitored for 2 hours. After general work-up and recrystalization from ethyl acetate – hexane afforded compound **14** (1.08 g, 3.55 mmol, 89%) as white crystals.

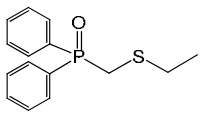
Mp: 155.5 – 157.0 ºC.

IR: ν (C=C): 1436.7 cm^{-1}; ν (P=O): 1183.1 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}OPS$: 67.08 C, 6.95 H, 10.53 S. Found: 67.37 C, 7.01 H, 10.35 S.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.81 (m, 4H, $H_{aromatic}$); 7.53 (m, 2H, $H_{aromatic}$); 7.48 (m, 4H, $H_{aromatic}$); 3.31 (d, 2H, $J_{H,P}$ = 12.4 Hz, CH_2); 1.27 (s, 9H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 131.2, 131.1 ($C_{aromatic}$); 132.3, 131.6, 128.7 ($\underline{C}H_{aromatic}$); 50.2 (C); 34.4 (d, $\underline{C}H_2$, $J_{C,P}$ = 67.20 Hz); 21.9 ($\underline{C}H_3$). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 30.12 (s, P=O).

(Ethylsulfanylmethyl)diphenylphosphine Oxide (15).[152]



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium ethylthiolate (883 mg, 10.50 mmol) was diluted in anhydrous THF (40 ml) and a solution of compound **9** (3.86 g, 10.00 mmol) in THF (8 ml) at 0 ºC under argon atmosphere was added and the reaction was monitored for 2 hours. After general work-up and recrystalization from ethyl acetate – hexane afforded compound **15** (2.18 g, 7.90 mmol, 79%) as white crystals.

Mp: 88.0 – 89.0 ºC.

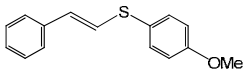
IR: ν (C=C): 1436.70 cm^{-1}; ν (P=O): 1178.3 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}OPS$: 65.20 C, 6.20 H, 11.60 S. Found: 65.04 C, 5.94 H, 11.36 S.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.79 (m, 4H, $H_{aromatic}$); 7.56 (m, 2H, $H_{aromatic}$); 7.49 (m, 4H, $H_{aromatic}$); 3.26 (d, 2H, $J_{H,P}$ = 8.4 Hz, CH_2); 2.64 (m, 1H, CH_2); 1.20 (m, 3H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 132.7, 132.3 ($C_{aromatic}$); 132.3, 131.4, 128.8 ($\underline{C}H_{aromatic}$); 31.1 ($\underline{C}H_2$); 29.9 (d, $\underline{C}H_2$, $J_{C,P}$ = 70.92 Hz); 14.4 ($\underline{C}H_3$). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 30.05 (s, P=O).

[152] (a) Vanifatova, N. G.; Zolotov, Y. A.; Medved, T. Y. *Zhurnal Neorganicheskoi Khimii* **1977**, *22(11)*, 3103. (b) Legin, G. Y. *Zhurnal Obshei Khimii* **1976**, *43(3)*, 545.

***E*/*Z*-4-Methoxyphenyl-styryl-sulfane (16).**[153]



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **10 (**709 mg, 2.00 mmol) in anhydrous THF (13 ml) that was then reacted with previously distilled benzaldehyde (102 μl, 106 mg, 1.0 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **16** (225 mg, 0.93 mmol, 93%, an *E*/*Z* inseparable mixture, *E*/*Z* = 1.3:1) as a light yellow oil.

R_f (hexane: ethyl acetate = 6:1): 0.83.

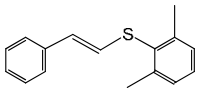
Anal. Calcd for $C_{15}H_{14}OS$: 74.34 C, 5.82 H, 13.23 S. Found: 74.04 C, 5.94 H, 13.36 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

16*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.70 (m, 2H, $H_{aromatic}$); 7.42 (m, 3H, $H_{aromatic}$); 6.76 (d, 1H, $J_{H,H}$ = 15.6 Hz, CH); 6.56 (d, 1H, $J_{H,H}$ = 15.6 Hz, CH); 2.98 (m, 1H, CH); 1.79 (m, 4H, CH_2); 1.57 (m, 6H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 159.5, 136.1, 124.3 ($C_{aromatic}$); 133.9, 128.7, 128.4, 127.6, 114.6 ($\underline{C}H_{aromatic}$); 131.7 ($\underline{C}H$); 125.7 ($\underline{C}H$); 55.2 ($\underline{C}H_3$).

16*Z***:** RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.81 (m, 2H, $H_{aromatic}$); 7.42 (m, 3H, $H_{aromatic}$); 6.43 (d, 1H, $J_{H,H}$ = 10.8 Hz, CH); 6.33 (d, 1H, $J_{H,H}$ = 10.8 Hz, CH); 2.98 (m, 1H, CH); 1.79 (m, 4H, CH_2); 1.57 (m, 6H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 159.9, 136.16, 127.1 ($C_{aromatic}$); 133.9, 128.7, 128.4, 127.6, 114.5 ($\underline{C}H_{aromatic}$); 131.9 ($\underline{C}H$); 127.1 ($\underline{C}H$); 55.2 ($\underline{C}H_3$).

***E*/*Z*-2,6-Dimethylphenyl-styryl-sulfane (17).**[153b,154]



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (1.9 ml, 3.06 mmol, 1.6 M in hexane) was added to a solution of **11 (**616 mg, 1.75 mmol) in anhydrous THF (12 ml) that was then reacted with previously distilled benzaldehyde (89 μl, 93 mg, 0.88 mmol) in anhydrous THF (3 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **17** (180 mg, 0.75 mmol, 75%, an *E*/*Z* inseparable mixture, *E*/*Z* = 11:1) as a colourless oil.

R_f (hexane: ethyl acetate = 6:1): 0.80.

Anal. Calcd for $C_{16}H_{16}S$: 79.95 C, 6.71 H, 13.34 S. Found: 80.02 C, 6.94 H, 13.35 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

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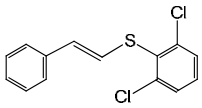
[153] (a) Leardini, R.; Nanni, D.; Zanardi, G. *J. Org. Chem.* **2000**, *65*, 2763. b) Marino, J. P.; Zou, N. Org. *Lett*, **2005**, *7(10)*, 1915. (c) Sridhar, R.; Surendra, K.; Srilakshmi, Krishnaveni, N.; Srinivas, B.; Rama Rao, K. *Synlett*, **2006**, 3497.

[154] Baliah, V.; Rathinasamy, T. K. *Indian J. Chem.* **1971**, *9*, 220.

17*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.14 (m, 6H, $H_{aromatic}$); 7.00 (m, 2H, $H_{aromatic}$); 6.65 (d, 1H, $J_{H,H}$ = 15.2 Hz, CH); 5.96 (d, 1H, $J_{H,H}$ = 15.2 Hz, CH); 2.49 (m, 3H, CH_3); 2.22 (s, 3H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 143.6, 143.5, 137.2, 134.9 ($C_{aromatic}$); 128.6, 128.4, 128.1, 127.3, 125.3 ($\underline{C}H_{aromatic}$); 128.5 ($\underline{C}H$); 124.7 ($\underline{C}H$); 21.9 ($\underline{C}H_3$); 21.7 ($\underline{C}H_3$).

17*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.14 (m, 6H, $H_{aromatic}$); 7.00 (m, 2H, $H_{aromatic}$); 6.61 (d, 1H, $J_{H,H}$ = 11.2 Hz, CH); 6.43 (d, 1H, $J_{H,H}$ = 11.2 Hz, CH); 2.47 (m, 3H, CH_3); 2.19 (s, 3H, CH_3). RMN ^{13}C ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

***E*/*Z*-2,6-Dichlorophenyl-styryl-sulfane (18).**



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **12** (787 mg, 2.00 mmol) in anhydrous THF (13 ml) and was then reacted with previously distilled benzaldehyde (102 μl, 106 mg, 1.0 mmol) in anhydrous THF (5 ml). General work-up and chromatography (hexane to ethyl acetate) afforded compound **18** (177 mg, 0.63 mmol, 63%, an *E*/*Z* inseparable mixture, *E*/*Z* = 15:1) as a white solid.

R_f (hexane: ethyl acetate = 6:1): 0.83.

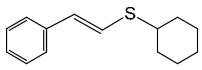
Anal. Calcd for $C_{14}H_{10}Cl_2S$: 59.80 C, 3.58 H, 11.40 S. Found: 59.75 C, 3.55 H, 11.45 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

18*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.47 (m, 2H, $H_{aromatic}$); 7.29 (m, 4H, $H_{aromatic}$); 7.22 (m, 2H, $H_{aromatic}$); 6.65 (d, 1H, $J_{H,H}$ = 15.6 Hz, CH); 6.40 (d, 1H, $J_{H,H}$ = 15.6 Hz, CH). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 137.2, 135.5, 135.4, 134.9 ($C_{aromatic}$); 132.9, 131.8, 128.7, 128.1, 127.8 ($\underline{C}H_{aromatic}$); 128.5 ($\underline{C}H$); 120.5 ($\underline{C}H$).

18*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.47 (m, 2H, $H_{aromatic}$); 7.29 (m, 4H, $H_{aromatic}$); 7.22 (m, 2H, $H_{aromatic}$); 6.57 (d, 1H, $J_{H,H}$ = 11.2 Hz, CH); 6.00 (d, 1H, $J_{H,H}$ = 11.2 Hz, CH). RMN ^{13}C ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

***E*/*Z*-Cyclohexyl-styryl-sulfane (19).**[153b, 155]



Following the *general method B* of *the WH olefination reactions*, LDA solution (7.7 ml, 3.50 mmol in 5 ml THF) was added to a solution of **13 (**660 mg, 2.00 mmol,) in anhydrous THF (13 ml) an

[155] (a) Bates, C. G.; Saejueng, P: Doherty, M. Q.; Venkataramen, D. *Org. Lett.* **2004**, *6(26)*, 5005. (b) Yatsumonji, Y.; Okada, O.; Tsubouchi, A.; Takeda, T. *Tetrahedron*, **2006**, *62*, 9981.

and was reacted with previously distilled benzaldehyde (102 μl, 106 mg, 1.0 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **19** (188 mg, 0.86 mmol, 86%, an *E*/*Z* inseparable mixture, *E*/*Z* = 11:1) as a colourless oil.

R_f (hexane: ethyl acetate = 6:1): 0.83.

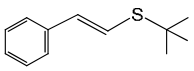
Anal. Calcd for $C_{14}H_{18}S$: 77.01 C, 8.31 H, 14.68 S. Found: 76.95 C, 8.35 H, 14.54 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

19*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.23 (m, 3H, $H_{aromatic}$); 7.17 (m, 2H, $H_{aromatic}$); 6.76 (d, 1H, $J_{H,H}$ = 15.6 Hz, CH); 6.56 (d, 1H, $J_{H,H}$ = 15.6 Hz, CH); 2.97 (m, 1H, CH); 2.02 (m, 4H, CH_2); 1.79 (m, 4H, CH_2); 1.63 (m, 2H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 137.4 ($C_{aromatic}$); 128.8 (CH); 128.8, 127.9, 125.8 ($CH_{aromatic}$); 124.3 (CH); 45.5 (CH); 33.9 (CH_2); 33.8 (CH_2); 30.0 (CH_2); 26.3 (CH_2); 25.9 (CH_2).

19*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.23 (m, 3H, $H_{aromatic}$); 7.17 (m, 2H, $H_{aromatic}$); 6.42 (d, 1H, $J_{H,H}$ = 11.2 Hz, CH); 6.32 (d, 1H, $J_{H,H}$ = 11.2 Hz, CH); 2.89 (m, 1H, CH); 2.02 (m, 4H, CH_2); 1.79 (m, 4H, CH_2); 1.63 (m, 2H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 137.4 ($C_{aromatic}$); 128.8, 127.9, 125.8 ($C_{aromatic}$); 128.4 (CH); 125.2 (CH); 48.0 (CH); 34.0 (CH_2); 33.9 (CH_2); 28.8 (CH_2); 26.0 (CH_2); 25.9 (CH_2).

***E*/*Z*-*tert*-Butyl-styryl-sulfane (20).**[153b,154,156]



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (1.9 ml, 3.06 mmol, 1.6 M in hexane) was added to a solution of **14 (**532 mg, 1.75 mmol) in anhydrous THF (12 ml) and then was reacted with previously distilled benzaldehyde (89 μl, 93 mg, 0.88 mmol) in anhydrous THF (3 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **20** (179 mg, 0.93 mmol, 93%, an *E*/*Z* inseparable mixture, *E*/*Z* = 3:1) as a colourless oil.

R_f (hexane: ethyl acetate = 8:1): 0.53.

Anal. Calcd for $C_{12}H_{16}S$: 74.94 C, 8.39 H, 16.67 S. Found: 74.75 C, 8.33 H, 16.53 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

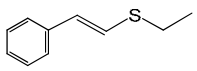
20*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.78 (m, 2H, $H_{aromatic}$); 7.52 (m, 1H, $H_{aromatic}$); 7.23 (m, 2H, $H_{aromatic}$); 6.87 (d, 1H, $J_{H,H}$ = 15.6 Hz, CH); 6.72 (d, 1H, $J_{H,H}$ = 15.6 Hz, CH); 1.40 (s, 9H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 135.6 ($C_{aromatic}$); 131.5 (CH); 129.7, 128.5, 127.9 ($CH_{aromatic}$); 122.0 (CH); 44.3 (C); 31.1 (CH_3).

20*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.78 (m, 2H, $H_{aromatic}$); 7.52 (m, 1H, $H_{aromatic}$); 7.23 (m, 2H, Ar); 6.45 (d, 1H, $J_{H,H}$ = 11.2 Hz, CH); 6.36 (d, 1H, $J_{H,H}$ = 11.2 Hz, CH); 1.28 (m, 2H, CH_3).

[156] Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J.-L.; Oshima, K.; Utimoto, K. *Chem. Lett.*, **1987**, 1647.

RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 135.3 ($C_{aromatic}$); 131.2 (CH); 129.7, 128.5, 127.9 ($CH_{aromatic}$); 124.2 (CH); 43.2 (C); 31.0 (CH_3).

_E/Z_-Ethyl-styryl-sulfane (21).[155b,157]



Following the *general method of the WH olefination reacti*ons, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **15 (**552 mg, 2.00 mmol) in anhydrous THF (13 ml) and then was reacted with previously distilled benzaldehyde (102 μl, 106 mg, 1.00 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **21** (184 mg, 0.96 mmol, 96%, an *E*/*Z* inseparable mixture, *E*/*Z* = 10:1) as a colourless oil.

R_f (hexane: ethyl acetate = 8:1): 0.63.

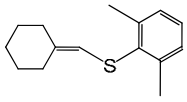
Anal. Calcd for $C_{10}H_{12}S$: 73.12 C, 7.36 H, 19.52 S. Found: 72.95 C, 7.33 H, 19.53 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

21*E*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.78 (m, 2H, $H_{aromatic}$); 7.35 (m, 3H, $H_{aromatic}$); 6.73 (d, 1H, $J_{H,H}$ = 15.2 Hz, CH); 6.46 (d, 1H, $J_{H,H}$ = 15.2 Hz, CH); 2.82 (ddd, 2H, $J_{H,H}$ = 14.4, 7.4, 7.2 Hz, CH_2); 1.35 (dd, 3H, $J_{H,H}$ = 14.4, 7.2 Hz, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 137.2 ($C_{aromatic}$); 128.6, 128.5, 128.2 ($CH_{aromatic}$); 131.6 (CH) ; 125.0 (CH); 26.7 (CH_2); 14.7 (CH_3).

21*Z*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.78 (m, 2H, $H_{aromatic}$); 7.35 (m, 3H, $H_{aromatic}$); 6.45 (d, 1H, $J_{H,H}$ = 10.8 Hz, CH); 6.26 (d, 1H, $J_{H,H}$ = 10.8 Hz, CH); 2.80 (m, 2H, CH_2); 1.32 (m, 3H, CH_3). RMN ^{13}C ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

Cyclohexylidenemethyl-2,6-dimethylphenyl-sulfane (22).



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **11 (**705 mg, 2.00 mmol) in anhydrous THF (13 ml) that was then reacted with cyclohexanone (104 μl, 98 mg, 1.0 mmol) in anhydrous THF (5 ml). General work-up and chromatography (hexane to ethyl acetate) afforded compound **22** (207 mg, 0.89 mmol, 89%) as light yellow oil.

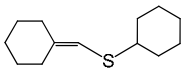
R_f (hexane: ethyl acetate = 9:1): 0.9.

Anal. Calcd for $C_{15}H_{20}S$: 77.53 C, 8.67 H, 13.80 S. Found: 77.45 C, 8.53 H, 13.59 S.

[157] (a) Nguyen, V.-H.; Nishino, H.; Kajikawa, S.; Kurosawa, K. *Tetrahedron*, **1998**, *54*, 11445. (b) Tiecco, M.; Testferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *J. Org. Chem.* **1983**, *48*, 4795.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.10 (m, 2H, $H_{aromatic}$); 7.00 (d, 1H, $J_{H,H}$ = 7.6 Hz, $H_{aromatic}$), 5.36 (s, 1H, CH), 2.49 (s, 3H, CH_3); 2.38 (d, 2H, J = 5.6 CH_2); 2.23 (s, 3H, CH_3); 2.10 (d, 2H, J = 5.6 CH_2); 1.56 (m, 4H, CH_2); 1.25 (s, 2H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 143.6, 142.7, 142.3, 128.5 ($C_{aromatic}$); 129.5, 128.3 ($\underline{C}H_{aromatic}$); 115.2 ($\underline{C}H$); 36.4 ($\underline{C}H_2$); 30.3 ($\underline{C}H_2$); 28.5 ($\underline{C}H_2$); 27.4 ($\underline{C}H_2$); 26.7 ($\underline{C}H_2$); 22.3 ($\underline{C}H_3$); 21.9 ($\underline{C}H_3$).

Cyclohexyl-cyclohexylidenemethyl-sulfane (23).[158]



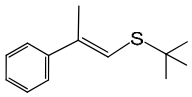
Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **13 (**660 mg, 2.00 mmol) in anhydrous THF (13 ml) that was then reacted with cyclohexanone (104 μl, 98 mg, 1.00 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **23 (**202 mg, 0.93 mmol, 93%) as a colourless oil.

R_f (hexane:ethyl acetate = 6:1): 0.75.

Anal. Calcd for $C_{13}H_{22}S$: 74.22 C, 10.54 H, 15.24 S. Found: 74.34 C, 10.47 H, 15.33 S.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 5.60 (d, 1H, $J_{H,H}$ = 15.6 Hz, CH); 2.68 (m, 1H, CH); 2.21 (m, 4H, CH_2); 2.10 (m, 4H, CH_2); 1.79 (m, 4H, CH_2); 1.57-1.18 (m, 8H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 143.0 (C); 113.1 ($\underline{C}H$); 45.7 ($\underline{C}H$); 37.4 ($\underline{C}H_2$); 33.7 ($\underline{C}H_2$); 30.4 ($\underline{C}H_2$); 28.4 ($\underline{C}H_2$); 27.2 ($\underline{C}H_2$); 26.5 ($\underline{C}H_2$); 26.1 ($\underline{C}H_2$).

***E*/*Z*-*tert*-Butyl-2-phenylprop-1-enyl-sulfane (24).**



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **14 (**608 mg, 2.00 mmol) in anhydrous THF (13 ml) that was then reacted with acetophenone (117 μl, 120 mg, 1.00 mmol) in anhydrous THF (5 ml). General work-up and chromatography (hexane to ethyl acetate) afforded compound **24** (189 mg, 0.92 mmol, 92%, an *E*/*Z* inseparable mixture, *E*/*Z* = 10:1) as a colourless oil.

R_f (hexane: ethyl acetate = 10:1): 0.70.

Anal. Calcd for $C_{13}H_{18}S$: 75.67 C, 8.79 H, 15.54 S. Found: 75.75 C, 8.83 H, 15.53 S.

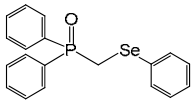
Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

[158] Harpp, D. N.; Aida, T.; Chan, T. H. *Tetrahedron Lett.*, **1985**, *26*, 1795.

24*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.38 (m, 5H, $H_{aromatic}$); 6.42 (s, 1H, CH); 2.06 (s, 3H, CH_3); 1.34 (s, 9H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 135.1 ($C_{aromatic}$); 128.5-125.0 ($\underline{C}H_{aromatic}$); 128.3 ($\underline{C}H$); 120.0 ($\underline{C}H$); 44.3 (C); 31.3 ($\underline{C}H_3$); 17.9 ($\underline{C}H_3$).

24*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.38 (m, 5H, $H_{aromatic}$); 6.11 (s, 1H, CH); 2.10 (s, 3H, CH_3); 1.28 (s, 9H, CH_3). RMN ^{13}C ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

(Phenylselenenylmethyl)diphenylphosphine Oxide (25).



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium hydride (60% in mineral oil, 560 mg, 14.00 mmol) and commercial benzeneselenol (2.0 g, 12.73 mmol) were reacted in anhydrous THF (51 ml) at 0 ºC under argon atmosphere. Then a solution of compound **9** (4.92 g, 12.73 mmol) in THF (25 ml) was added. General work-up and flash chromatography with ethyl acetate: hexane = 1:1 to ethyl acetate afforded compound **25** (3.12 g, 9.17 mmol, 72%) as white crystals.

R_f: 0.625 in ethyl acetate.

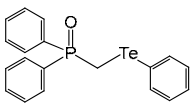
Mp: 121.5 – 123.0 ºC.

IR: ν (C=C): 1434.78 cm^{-1}; ν (P=O): 1187.94 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}OPSe$: 61.47 C, 4.62 H. Found: 61.96 C, 4.48 H.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.76 (m, 4H, $H_{aromatic}$); 7.53 (m, 2H, $H_{aromatic}$); 7.44 (m, 6H, $H_{aromatic}$); 7.20 (m, 3H, $H_{aromatic}$); 3.60 (d, 2H, $J_{H,P}$ = 7.6 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 139.6, 131.3, 131.1 ($C_{aromatic}$); 134.4, 132.6, 130.2, 128.8, 128.1, 127.8 ($\underline{C}H_{aromatic}$); 25.6 (d, $\underline{C}H_2$, $J_{C,P}$ = 68.71 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 29.16 (s, P=O).

(Phenyltelluromethyl)diphenylphosphine Oxide (26).[77]



Diphenyl ditelluride (1.3 g, 3.18 mmol) and KBH_4 (515 mg, 9.54 mmol) were reacted in anhyrous THF (32 ml) at room temperature under argon until the dark red colour of the diphenyl telluride became more clear. After the formation of the telluride anion, following the *general method A for the synthesis of diphenylphosphine oxides*, a solution of compound **9** (2.33g, 6.04 mmol) in THF (12 ml) was added. After general work-up and recrystalization from ethyl acetate – hexane afforded compound **26** (1.66 g, 3.93 mmol, 65%) as yellowish crystals.

R_f: 0.81 in ethyl acetate.

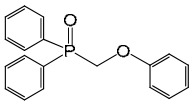
Mp: 122.5 – 123.5 ºC. (Lit: 123-124 ºC).

IR: ν (C=C): 1431.89 cm^{-1}; ν (P=O): 1180.22 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}OPTe$: 54.35 C, 4.08 H. Found: 54.56 C, 4.28 H.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.74 (m, 7H, $H_{aromatic}$); 7.50 (m, 4H, $H_{aromatic}$); 7.22 (m, 4H, $H_{aromatic}$); 3.58 (d, 2H, $J_{H,P}$ = 13.2 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6, 132.8, 131.7 ($C_{aromatic}$); 131.4, 130.6, 130.5, 128.8, 128.2, 128.1, 127.8, 111.6 ($\underline{C}H_{aromatic}$); 4.9 (d, $\underline{C}H_2$, $J_{C,P}$ = 68.0 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 30.74 (s, P=O).

(Phenyloxymethyl)diphenylphosphine Oxide (27).[159]



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium hydride (60% in mineral oil, 420 mg, 10.50 mmol) and phenol (0.99 g, 10.50 mmol) were reacted in anhydrous THF (42 ml) at 0 ºC under argon atmosphere, then a solution of compound **9** (3.86 g, 10.00 mmol) in THF (20 ml) was added. After general work-up and recrystalization from ethyl acetate – hexane afforded compound **27** (2.93 g, 9.52 mmol, 95%) as white solid.

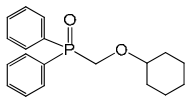
Mp: 102.0 – 103.0 ºC.

IR: ν (C=C): 1435.74 cm^{-1}; ν (P=O): 1180.22 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}O_2P$: 74.02 C, 5.56 H. Found: 73.96 C, 5.48 H.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.89 (m, 4H, $H_{aromatic}$); 7.58 (m, 2H, $H_{aromatic}$); 7.50 (m, 4H, $H_{aromatic}$); 7.29 (m, 2H, $H_{aromatic}$); 7.29 (m, 1H, $H_{aromatic}$); 6.99 (m, 2H, $H_{aromatic}$); 4.73 (d, 2H, $J_{H,P}$ = 8.0 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 163.8, 131.1, 130.9 ($C_{aromatic}$); 132.7, 131.7, 129.7, 128.8, 122.2, 114.7 ($\underline{C}H_{aromatic}$); 66.0 (d, $\underline{C}H_2$, $J_{C,P}$ = 88.43 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 27.87 (s, P=O).

(Cyclohexyloxymethyl)diphenylphosphine Oxide (28).



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium hydride (60% in mineral oil, 840 mg, 21.00 mmol) and cyclohexanol (2.0 ml, 21.00 mmol) were reacted in anhydrous THF (84 ml) at 0 ºC under argon atmosphere for 1h, then a solution of compound **9** (7.72 g,

[159] (a) Chaunov, V. A.; Studnev, Y. N.; Rudnitskaya, L. S. Fokin, A. V. *Zhournal Obschei Khimii*, **1986**, *56(11)*, 2553. (b) Patsanovskii, I. I.; Ishmaeva, E. A.; Sundukova, E. N.; Yarkevich, A. N.; Tsvetkov, E. N. *Zhournal Obschei Khimii*, **1986**, *56(3)*, 2563.

20.00 mmol) in THF (40 ml) was added. After general work-up and recrystalization the crystals of unreacted starting material were recovered, finally flash chromatography (ethyl acetate: hexane = 1:1 to ethyl acetate) afforded 4.15 g (13.22 mmol, 65%) compound **28** as orange oil that was crystallized from DCM.

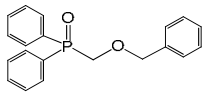
R_f: 0.56 in ethyl acetate.

Mp: 65 – 67 ºC. IR: ν (C=C): 1437.67 cm^{-1}; ν (P=O): 1182.91 cm^{-1}.

Anal. Calcd for $C_{19}H_{23}O_2P$: 72.59 C, 7.37 H. Found: 72.96 C, 7.48 H.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.85 (m, 4H, $H_{aromatic}$); 7.53 (m, 2H, $H_{aromatic}$); 7.46 (m, 4H, $H_{aromatic}$); 4.24 (d, 2H, $J_{H,P}$ = 7.6 Hz, CH_2); 3.31 (m, 1H, CH); 1.79 (m, 4H, CH_2); 1.62 (m, 4H, CH_2); 1.45 (m, 2H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 140.1, 131.0, 130.9 ($C_{aromatic}$); 132.2, 131.7, 128.4 ($\underline{C}H_{aromatic}$); 80.44 (d, $\underline{C}H$, $J_{C,P}$ = 9.96 Hz); 66.45 (d, $\underline{C}H_2$, $J_{C,P}$ = 90.04 Hz); 31.54 ($\underline{C}H_2$); 25.77 ($\underline{C}H_2$); 23.70 ($\underline{C}H_2$). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 28.35 (s, P=O).

(Benzyloxymethyl)diphenylphosphine Oxide (29).



Following the *general method A for the synthesis of diphenylphosphine oxides*, sodium hydride (60% in mineral oil, 420 mg, 10.50 mmol) and benzyl alcohol (1.1 ml, 1.14 g, d = 1.05 g/ml, 10.50 mmol) were reacted in anhydrous THF (42 ml) at 0 ºC under argon atmosphere, then a solution of compound **9** (3.86 g, 10.00 mmol) in THF (20 ml) was added. General work-up and recrystallization from ethyl acetate – hexane afforded compound **29** (2.99 g, 9.29 mmol, 93%) as white solid.

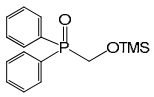
Mp: 105.0 – 106.0 ºC.

IR: ν (C=C): 1437.67 cm^{-1}; ν (P=O): 1177.33 cm^{-1}.

Anal. Calcd for $C_{20}H_{19}O_2P$: 74.52 C, 5.94 H. Found: 73.96 C, 5.68 H.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.80 (m, 4H, $H_{aromatic}$); 7.50 (m, 6H, $H_{aromatic}$); 7.30 (m, 3H, $H_{aromatic}$); 7.19 (m, 2H, $H_{aromatic}$); 4.61 (s, 2H, CH_2); 4.23 (d, 2H, $J_{H,P}$ = 6.6 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 136.7, 133.0, 131.7 ($C_{aromatic}$); 132.3, 131.7, 131.6, 128.7, 128.6, 128.2 ($\underline{C}H_{aromatic}$); 75.7 (d, $\underline{C}H_2$, $J_{C,P}$ = 11.47 Hz); 68.1 (d, $\underline{C}H_2$, $J_{C,P}$ = 88.4 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 28.22 (s, P=O).

(Trimethylsilyloxymethyl)diphenylphosphine Oxide (30).



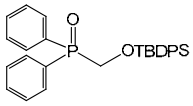
Following the *general method B for the synthesis of diphenylphosphine oxides*, **8** (2.32 g, 10.00 mmol) and trimethylsilyl chloride (1.3 ml, 1.09 g, d = 0.859 g/ml, 11.00 mmol) were reacted in anhydrous DCM (40 ml) in the presence of imidazol (715 mg, 10.50 mmol) and DMAP (244 mg, 2.00 mmol) at room temperature under argon atmosphere. After general work-up and recrystallization from ethyl acetate – hexane afforded compound **30** (2.75 g, 9.04 mmol, 90%) as white solid.

IR: ν (C=C): 1437.67 cm^{-1}; ν (P=O): 1183.13 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}O_2PSi$: 63.13 C, 6.95 H. Found: 62.96 C, 6.86 H.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.80 (m, 4H, $H_{aromatic}$); 7.48 (m, 6H, $H_{aromatic}$); 4.31 (d, 2H, $J_{H,P}$ = 6.9 Hz, CH_2); 0.15 (s, 9H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 132.4, 132.0 ($C_{aromatic}$); 134.1, 132.4, 128.0, ($\underline{C}H_{aromatic}$); 62.3 (d, $\underline{C}H_2$, $J_{C,P}$ = 91.13 Hz); 2.3 ($\underline{C}H_3$). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 29.19 (s, P=O).

(*tert*-Butyldiphenylsilyloxymethyl)diphenylphosphine Oxide (31).



Following the *general method B for the synthesis of diphenylphosphine oxides*, **8** (2.32 g, 10.00 mmol) and *tert*-butyldiphenylsilyl chloride (2.7 ml, 2.89 g, d = 1.057 g/ml, 10.50 mmol) were reacted in anhydrous DCM (40 ml) in the presence of imidazol (715 mg, 10.50 mmol) and DMAP (244 mg, 2.00 mmol) at room temperature under argon atmosphere. General work-up and recrystallization from ethyl acetate – hexane afforded compound **31** (4.37 g, 9.29 mmol, 93%) of as white solid.

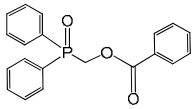
Mp: 135.0 – 136.0 ºC.

IR: ν (C=C): 1437.67 cm^{-1}; ν (P=O): 1182.25 cm^{-1}.

Anal. Calcd for $C_{29}H_{31}O_2PSi$: 74.01 C, 6.64 H. Found: 73.96 C, 6.48 H.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.85 (m, 4H, $H_{aromatic}$); 7.57 (m, 2H, $H_{aromatic}$); 7.49 (m, 4H, $H_{aromatic}$); 7.41 (m, 6H, $H_{aromatic}$); 7.29 (m, 4H, $H_{aromatic}$); 4.33 (d, 2H, $J_{H,P}$ = 7.20 Hz, CH_2); 0.95 (s, 9H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 136.5, 136.3, 132.4, 132.0 ($C_{aromatic}$); 135.8, 132.4, 132.0, 130.2, 128.6, 128.0 ($\underline{C}H_{aromatic}$); 62.5 (d, $\underline{C}H_2$, $J_{C,P}$ = 92.25 Hz), 26.8 ($\underline{C}H_3$). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 30.17 (s, P=O).

Diphenylphosphoryl-methyl Benzoate (32).



Following the *general method B for the synthesis of diphenylphosphine oxides*, **8** (2.32 g, 10.00 mmol) and benzoyl chloride (950 μl, 1.48 g, d = 1.553 g/ml, 10.50 mmol) were reacted in anhydrous

DCM (40 ml) in the presence of imidazol (715 mg, 10.50 mmol) and DMAP (244 mg, 2.00 mmol) at room temperature under argon atmosphere. After general work-up and recrystallization from ethyl acetate – hexane afforded compound **32** (3.00 g, 8.93 mmol, 89%) as a white solid.

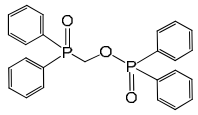
Mp: 137.0 – 138.0 ºC.

IR: ν (C=O): 1723.09 cm^{-1}; ν (C=C): 1436.71 cm^{-1}; ν (P=O): 1188.90 cm^{-1}.

Anal. Calcd for $C_{20}H_{17}O_3P$: 71.42 C, 5.09 H. Found: 71.39 C, 5.01 H.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.84 (m, 6H, $H_{aromatic}$); 7.53 (m, 6H, $H_{aromatic}$); 7.39 (m, 3H, $H_{aromatic}$); 5.10 (d, 2H, $J_{H,P}$ = 5.2 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 169.4, 140.3, 134.3, 134.2 ($C_{aromatic}$); 133.7, 132.8, 131.6, 130.0, 129.1, 128.7 ($\underline{C}H_{aromatic}$); 64.0 (d, $\underline{C}H_2$, $J_{C,P}$ = 88.4 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 29.19 (s, P=O).

Diphenylphosphoryl-methyl Diphenylphosphinate (33).[160]



Following the *general method B for the synthesis of diphenylphosphine oxides*, **8** (1.16 g, 5.00 mmol) and diphenylphosphinic chloride (1.0 ml, 1.24 g, d = 1.24 g/mol, 5.25 mmol) were reacted in anhydrous DCM (20 ml) in the presence of imidazol (0.68 g, 10.00 mmol) and DMAP (30 mg, 0.25 mmol) at room temperature under argon atmosphere. After general work-up and recrystalization from ethyl acetate – hexane afforded compound **33** (2.05 g, 4.76 mmol, 95%) as white solid.

Mp: 132.5 – 134.0 ºC.

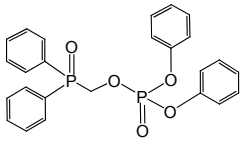
IR: ν (C=C): 1437.67 cm^{-1}; ν (P=O): 1219.76 cm^{-1}; ν (P=O): 1184.06 cm^{-1}.

Anal. Calcd for $C_{25}H_{22}O_3P_2$: 69.44 C, 5.13 H. Found: 69.55 C, 5.24 H.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.81 (m, 4H, $H_{aromatic}$); 7.60 (m, 5H, $H_{aromatic}$); 7.50 (m, 6H, $H_{aromatic}$); 7.38 (m, 5H, $H_{aromatic}$); 4.68 (t, 2H, $J_{H,P}$ = 5.6 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 140.0 ($C_{aromatic}$); 134.2, 132.8, 132.4, 132.2, 129.3, 128.7 ($\underline{C}H_{aromatic}$); 60.8 (dd, $\underline{C}H_2$, $J_{C,P}$ = 87.02, 7.65 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 35.79 (d, $J_{P,P}$ = 37.91 Hz, P=O); 28.26 (d, $J_{P,P}$ = 37.91 Hz, P=O).

[160] Frey, G.; Lesiecki, H.; Lindner, E.; Vordermaier, S. *Chem. Ber.* **1979**, *112(2)*, 763.

Diphenylphosphoryl-methyl Diphenyl Phosphate (34).



Following the *general method B for the synthesis of diphenylphosphine oxides*, **8** (1.86 g, 8.00 mmol) and diphenyl phosphoryl chloride (1.74 ml, 2.26 g, d = 1.299 g/mol, 8.40 mmol) were reacted in anhydrous DCM (32 ml) in the presence of imidazol (571 mg, 8.40 mmol,) and DMAP (49 mg, 0.40 mmol) at room temperature under argon atmosphere. General work-up and recrystallization from ethyl acetate – hexane afforded compound **34** (3.42 g, 7.36 mmol, 92%) as white solid.

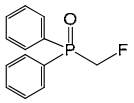
Mp: 113.0 – 114.5 ºC.

IR: ν (C=C): 1437.67 cm^{-1}; ν (P=O): 1291.11 cm^{-1}; ν (P=O): 1183.11 cm^{-1}.

Anal. Calcd for $C_{25}H_{22}O_5P_2$: 64.66 C, 4.78 H. Found: 65.02 C, 4.55 H.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.75 (m, 4H, $H_{aromatic}$); 7.59 (m, 2H, $H_{aromatic}$); 7.47 (m, 4H, $H_{aromatic}$); 7.32 (m, 4H, $H_{aromatic}$); 7.18 (m, 2H, $H_{aromatic}$); 7.04 (m, 4H, $H_{aromatic}$); 4.91 (dd, 2H, $J_{H,P}$ = 6.0, 6.0 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 150.1, 150.0, 130.5, 130.5 ($C_{aromatic}$); 132.8, 132.2, 131.1, 128.7, 122.3, 120.3 ($\underline{C}H_{aromatic}$); 64.6 (dd, $\underline{C}H_2$, $J_{C,P}$ = 85.51, 9.15 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 26.9 (d, $J_{P,P}$ = 30.7 Hz, P=O); 28.26 (d, $J_{P,P}$ = 30.7 Hz, P=O).

(Fluoromethyl)diphenylphosphine Oxide (35).[151]



Following the *general method C for the synthesis of diphenylphosphine oxides*, **8** (1.54 g, 4.00 mmol) and potassium fluoride (2.32 g, 40.00 mmol) were reacted in triethylenglycol (32 ml, without anhydrousing) at 160 ºC for 15 minutes. After general work-up and flash chromatography (hexane: ethyl acetate = 1:1 to ethyl acetate) afforded compound **35** (801 mg, 3.42 mmol, 85%) as white crystals.

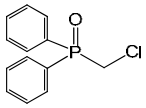
R_f (hexane: ethyl acetate = 1:1): 0.32.

Mp: 95.0 – 96.5 ºC. (Lit.: 95.0 – 95.5 ºC).

IR: ν (C=C): 1437.67 cm^{-1}; ν (P=O): 1183.11 cm^{-1}.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.82 (m, 4H, $H_{aromatic}$); 7.61 (m, 2H, $H_{aromatic}$); 7.53 (m, 4H, $H_{aromatic}$); 5.18 (dd, 2H, $J_{H,F}$ = 46.8; $J_{H,P}$ = 3.2 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 139.1 ($C_{aromatic}$); 134.2, 132.9, 128.6 ($\underline{C}H_{aromatic}$); 80.5 (dd, $\underline{C}H_2$, $J_{C,F}$ = 188.4; $J_{C,P}$ = 83.9 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 25.75 (d, $J_{P,F}$ = 64.8 Hz, P=O). RMN ^{19}F ($CDCl_3$, 376 MHz) δ in ppm: -242.7 (dd, J = 125.96, 62.79 Hz).

(Chloromethyl)diphenylphosphine Oxide (36).[161]



Following the *general method C for the synthesis of diphenylphosphine oxides*, **8** (1.54 g, 4.00 mmol) and potassium chloride (2.98 g, 40.00 mmol) were reacted in triethylenglycol (32 ml, without anhydrousing) at 160 ºC for 30 minutes. After general work-up and flash chromatography (ethyl acetate: hexane = 1:1 to ethyl acetate) afforded compound **36** (920 mg, 3.68 mmol, 92%) as white crystals.

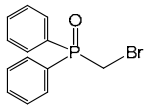
Mp: 126.0 – 127.5 ºC.

IR: ν (C=C): 1435.74 cm^{-1}; ν (P=O): 1193.72 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}ClOP$: 62.29 C, 4.83 H. Found: 61.98 C, 5.02 H.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.81 (m, 4H, $H_{aromatic}$); 7.58 (m, 2H, $H_{aromatic}$); 7.51 (m, 4H, $H_{aromatic}$); 4.06 (d, 2H, $J_{H,P}$ = 6.6 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 142.3 ($C_{aromatic}$); 134.2, 132.7, 128.5 ($CH_{aromatic}$); 37.9 (d, $\underline{C}H_2$, $J_{C,P}$ = 73.7 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 28.95 (s, P=O).

(Bromomethyl)diphenylphosphine Oxide (37).[162]



Following the *general method C for the synthesis of diphenylphosphine oxides*, **8** (1.54 g, 4.00 mmol) and potassium bromide (4.12 g, 40.00 mmol) were reacted in triethylenglycol (32 ml, without anhydrousing) at 160 ºC for 45 minutes. After general work-up and flash chromatography (ethyl acetate: hexane = 1:1 to ethyl acetate) afforded compound **37** (1.16 g, 3.92 mmol, 98%) as white crystals.

Mp: 165.5 – 167.0 ºC.

IR: ν (C=C): 1434.78 cm^{-1}; ν (P=O): 1192.76 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}BrOP$: 52.91 C, 4.10 H. Found: 52.86 C, 4.21 H.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.81 (m, 4H, $H_{aromatic}$); 7.55 (2H, m, $H_{aromatic}$); 7.53 (m, 4H, $H_{aromatic}$); 3.81 (d, 2H, $J_{H,P}$ = 6.0 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 142.0, 135.3, 135.1 ($C_{aromatic}$); 1134.2, 32.8, 128.9 ($\underline{C}H_{aromatic}$); 23.6 (d, $\underline{C}H_2$, $J_{C,P}$ = 69.6 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 27.71 (s, P=O).

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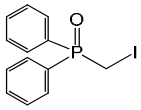
[161] Lawrence, N. J.; Liddle, J.; Jackson, D. *J. Chem. Soc. Perkin I.*, **2002**, 2260.

[162] Tkachenko, S. E; Yarkevich, A. N.; Timfeev, S. V.; Tsvetkov, E. N. *Zhurnal Obshchei Khimii* **1988**, *58(3)*, 531.

(Iodomethyl)diphenylphosphine Oxide (38).[163]



Following the *general method C for the synthesis of diphenylphosphine oxides*, **8** (1.54 g, 4.00 mmol) and potassium iodine (6.64 g, 40.00 mmol) were reacted in triethylenglycol (32 ml, without anhydrousing) at 160 ºC for 1 hour. After general work-up and flash chromatography (ethyl acetate: hexane = 1:1 to ethyl acetate) afforded compound **38** (1.31 g, 3.82 mmol, 95%) of as white, light-sensitive crystals.

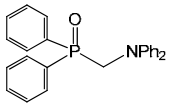
Mp: 172.0 – 173.0 ºC.

IR: ν (C=C): 1436.71 cm^{-1}; ν (P=O): 1188.90 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}IOP$: 45.64 C, 3.54 H. Found: 45.76 C, 3.21 H.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.79 (m, 4H, $H_{aromatic}$); 7.48 (m, 2H, $H_{aromatic}$); 7.51 (m, 4H, $H_{aromatic}$), 3.60 (d, 2H, $J_{H,P}$ = 5.6 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 143.9 135.4, 135.0 ($C_{aromatic}$); 134.2, 132.7, 128.9 ($\underline{C}H_{aromatic}$); –4.8 (d, $\underline{C}H_2$, $J_{C,P}$ = 67.1 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 28.04 (s, P=O).

(Diphenylaminomethyl)diphenylphosphine Oxide (39).[164]



Following the *general method D for the synthesis of diphenylphosphine oxides*, **8** (3.86 g, 10.00 mmol) and diphenyl amine (2.03 g, 12.00 mmol) were reacted in anhydrous DMF (40 ml) at 70 ºC in 2 days under argon atmosphere. After general work-up and recrystalization from ethyl acetate – hexane afforded compound **39** (3.70 g, 9.64 mmol, 96%) as dark crystals.

Mp: 44.0 – 45.0 ºC.

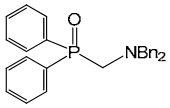
IR: ν (C=C): 1437.67 cm^{-1}; ν (P=O): 1172.51 cm^{-1}.

Anal. Calcd for $C_{25}H_{22}NOP$: 78.31 C, 5.78 H, 3.65 N. Found: 77.95 C, 5.93 H, 3.82 N.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.63 (m, 4H, $H_{aromatic}$); 7.51 (m, 2H, $H_{aromatic}$); 7.39 (m, 4H, $H_{aromatic}$); 7.17 (m, 4H, $H_{aromatic}$); 6.98 (m, 4H, $H_{aromatic}$); 6.84 (m, 2H, $H_{aromatic}$); 4.52 (d, 2H, $J_{H,P}$ = 7.2 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 145.7, 143.2, 130.2, 129.6 ($C_{aromatic}$); 133.0, 131.6, 129.3, 128.3, 121.1, 117.9 ($\underline{C}H_{aromatic}$); 64.9 (dd, $\underline{C}H_2$, $J_{C,P}$ = 82.4 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 26.62 (s, P=O).

[163] Dielmann, C. B.; Matt, D.; Jones, P. G. *J. Organometallic Chem.* **1997**, *545-546*, 461.
[164] Abu-Gnim, C.; Amer, I. *J. Organometallic Chem.* **1996**, *516(1-2)*, 235.

(Dibenzylaminomethyl)diphenylphosphine Oxide (40).[165]



Following the *general method D for the synthesis of diphenylphosphine oxides*, **8** (3.86 g, 10.00 mmol) and dibenzyl amine (2.36 g, 12.00 mmol) were reacted in anhydrous DMF (40 ml) at 70 ºC for 2 days under argon atmosphere. After general work-up and recrystalization from ethyl acetate – hexane afforded compound **40** (3.99 g, 9.70 mmol, 97%) as white crystals.

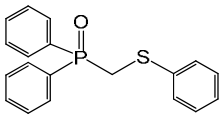
Mp: 130.0 – 131.0 ºC.

IR: ν (C=C): 1435.74 cm^{-1}; ν (P=O): 1180.22 cm^{-1}.

Anal. Calcd for $C_{27}H_{26}NOP$: 78.831 C, 6.37 H, 3.40 N. Found: 78.95 C, 6.23 H, 3.62 N.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.55 (m, 6H, $H_{aromatic}$); 7.40 (m, 4H, $H_{aromatic}$); 7.26 (m, 6H, $H_{aromatic}$); 7.14 (m, 4H, $H_{aromatic}$); 3.82 (s, 4H, CH_2); 3.32 (d, 2H, $J_{H,P}$ = 6.0 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.8, 138.8, 132.9, 131.2 ($C_{aromatic}$); 131.9, 131.4. 129.4, 128.6, 128.4, 127.2, ($\underline{C}H_{aromatic}$); 60.4 (dd, $\underline{C}H_2$, $J_{C,P}$ = 7.6 Hz); 53.0 (dd, $\underline{C}H_2$, $J_{C,P}$ = 86.2 Hz). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 29.84 (s, P=O).

(Phenylsulfanylmethyl)diphenylphosphine Oxide (42)



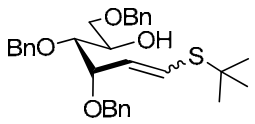
Following *the general procedure of the Michaelis–Arbuzov*, the mixture of 10 g (43.4 mmol) of commercially available ethyl diphenylphosphinite and 7.2 g (45.6 mmol) of commercially available chloromethyl-phenyl-sulfane was stirred at 150 ºC under argon atmosphere for 3 hours. The evolution of the reaction was monitored by TLC analysis. After the completion of the reaction the mixture was cooled down to room temperature and was purified by recrystallization from ether petroleum – ethyl acetate to obtain the corresponding compound **42** (13.3 g, 94%).

Bp: 101 – 2ºC. [lit. 101-2 ºC].

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.81 – 7.16 (m, 15H, $H_{aromatic}$); 3.73 (d, 2H, $J_{H,P}$ = 9.2 Hz, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 135.9-127.1 ($C_{aromatic}$, $CH_{aromatic}$), 34.1 (d, $J_{C,P}$ = 68.3 Hz, $\underline{C}H_2$). RMN ^{31}P ($CDCl_3$, 162 MHz) δ in ppm: 29.4 (s, P=O).

[165] (a) Frolovskii, V. A.; Studnev, Y. N.; Rozantsev, G. G. *Zhurnal Obshei Khimii* **1996**, *66(4)*, 692. (b) Broekhof, N. L. J. M.; *J. of the Royal Neth. Chem. Soc.* **1984**, *103/11*. 312.

(*E*/*Z*)-3,4,6-tri-*O*-Benzyl-1,2-dideoxy-1-*tert*-butylsulfanyl-D-*ribo*-hex-1-enitol (44).



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (1.91 ml, 3.06 mmol, 1.6 M in hexane) was added to a solution of **14 (**532 mg, 1.75 mmol) in anhydrous THF (10 ml) and then was reacted with a solution of 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranose (368 mg, 0.88 mmol) in anhydrous THF (5 ml). After general work-up and radial chromatography (hexane to ethyl acetate) afforded compound **44** (288 mg , 0.57 mmol, 65%, an *E*/*Z* inseparable mixture, *E*/*Z* = 25:1) as a light yellow oil.

R_f (hexane: ethyl acetate = 3:1): 0.60.

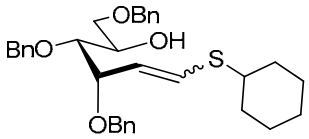
Anal. Calcd for $C_{31}H_{38}O_4S$: 73.48 C, 7.56 H, 6.33 S. Found: 73.37 C, 7.43 H, 6.27 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

44*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.33 – 7.21 (m, 15H, $H_{aromatic}$); 6.44 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.90 (dd, 1H, $J_{2,3}$ = 8.4 Hz, H-2); 4.76 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.65 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.56 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.49 (d, 2H, J_{AB} = 11.2 Hz, CH_2Ph); 4.36 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.17 (dd, 1H, $J_{3,4}$ = 4.2, Hz, H-3); 3.81 (m, 1H, H-5); 3.68 (dd, 1H, $J_{4,5}$ = 8.4, Hz, H-4); 3.61 (2H, m, H-6a, H-6b); 2.89 (bs, 1H, OH); 1.35 (s, 9H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.51, 138.41, 138.15 ($C_{aromatic}$); 128.99, 128.57, 128.53, 128.42, 128.30, 128.03, 127.90, 127.82, 127.75; 127.71 ($\underline{C}H_{aromatic}$, C-1, C-2); 81.75 (CH, C-3); 80.98 (CH, C-4); 74.30 ($\underline{C}H_2$, CH_2Ph); 73.43 ($\underline{C}H_2$, CH_2Ph); 71.14 ($\underline{C}H_2$, CH_2Ph); 70.99 (CH, C-5); 70.31 ($\underline{C}H_2$, C-6); 43.82 (C); 31.03 ($\underline{C}H_3$).

44*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

(*E*/*Z*)-3,4,6-tri-*O*-Benzyl-1,2-dideoxy-1-cyclohexylsulfanyl-D-*ribo*-hex-1-enitol (45).



Following the *general method of the WH olefination reactions*, an LDA solution (diisopropyl ammine (490 μl, 354 mg, 3.50 mmol in 5ml of THF and *n*-BuLi solution 2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **13** (660 mg, 2.00 mmol) in anhydrous THF (8 ml) that was then reacted with a solution of 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranose (420 mg, 1.00 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **45** (253 mg, 0.47 mmol, 47 an *E*/*Z* inseparable mixture, *E*/*Z* = 7:1) as a light yellow oil.

R_f (hexane: ethyl acetate = 3:1): 0.63.

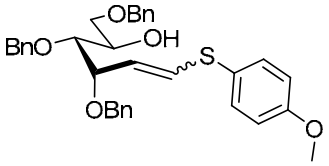
Anal. Calcd for $C_{33}H_{40}O_4S$: 74.40 C, 7.57 H, 6.02 S. Found: 74.03 C, 7.52 H, 6.07 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

45*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.27 – 7.13 (m, 15H, $H_{aromatic}$); 6.23 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.61 (dd, 1H, $J_{2,3}$ = 8.4 Hz, H-2); 4.67 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.55 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.48 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph; 4.41 (d, 2H, J_{AB} = 11.2 Hz, CH_2Ph); 4.27 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.10 (dd, 1H, $J_{3,4}$ = 4.4 Hz, H-3); 3.72 (m, 1H, H-5); 3.59 (dd, 1H, $J_{4,5}$ = 8.4 Hz, H-4); 3.42 (s, 1H, H-6a); 3.52 (d, 1H, J = 2.8 Hz, H-6b); 2.77 (m, 1H, CH); 2.70 (d, 1H, $J_{OH,5}$ = 4.8 Hz, OH); 1.89 (m, 2H, CH_2); 1.66 (m, 2H, CH_2); 1.53 (m, 1H, CH_2); 1.18 (m, 5H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.56, 138.48, 138.13 ($C_{aromatic}$); 129.49, 128.56, 128.51, 128.42, 128.36, 128.25, 128.03, 127.98, 127.90, 127.83, 127.79, 127.74, 127.66, 125.02 ($\underline{C}H_{aromatic}$, C-1, C-2); 82.11 ($\underline{C}H$, C-3); 81.05 ($\underline{C}H$, C-4); 74.36 ($\underline{C}H_2$, CH_2Ph); 73.55 ($\underline{C}H_2$, CH_2Ph); 71.16 ($\underline{C}H_2$, CH_2Ph); 71.14 ($\underline{C}H$, C-6); 70.32 ($\underline{C}H_2$, C-5); 44.82 ($\underline{C}H$); 33. 64 ($\underline{C}H_2$); 33.59 ($\underline{C}H_2$), 26.15 ($\underline{C}H_2$); 25.80 ($\underline{C}H_2$).

45*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

(*E*/*Z*)-3,4,6-ttri-*O*-Benzyl-1,2-dideoxy-1-*p*-methoxyphenylsulfanyl-D-*ribo*-hex-1-enitol (46).



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **10 (**709 mg, 2.00 mmol) in anhydrous THF (13 ml) that was then reacted with a solution of 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranose (420 mg, 1.00 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **46** (125 mg, 0.22 mmol, 22%, an *E*/*Z* inseparable mixture, *E*/*Z* = 9:1) as an oil. Starting matherial (120 mg, 0.28 mmol, 28%) was recovered.

R_f (hexane: ethyl acetate = 3:1): 0.65.

Anal. Calcd for $C_{34}H_{36}O_5S$: 73.35 C, 6.52 H, 5.76 S. Found: 73.20 C, 6.32 H, 5.67 S.

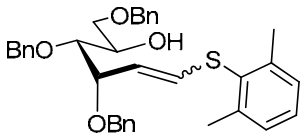
Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

46*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.27 – 7.13 (m, 19H, $H_{aromatic}$); 6.23 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.61 (dd, 1H, $J_{2,3}$ = 8.4 Hz, H-2); 4.67 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.55 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.48 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph; 4.41 (d, 2H, J_{AB} = 11.2 Hz, CH_2Ph); 4.27 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.10 (dd, 1H, $J_{3,4}$ = 4.4 Hz, H-3); 3.72 (m, 1H, H-5); 3.59 (dd, 1H, $J_{4,5}$ = 8.4 Hz, H-4); 3.42 (s, 1H, H-6a); 3.52 (d, 1H, $J_{6b,5}$ = 2.8 Hz, H-6b); 2.77 (m, 1H, CH); 2.70 (d, 1H, $J_{OH,5}$ = 4.8 Hz, OH); 1.89 (m, 2H, CH_2); 1.66 (m, 2H, CH_2); 1.53 (m, 1H, CH_2); 1.18 (m, 5H, CH_2). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.56, 138.48, 138.13 ($C_{aromatic}$); 129.49, 128.56, 128.51, 128.42,

128.36, 128.25, 128.03, 127.98, 127.90, 127.83, 127.79, 127.74, 127.66, 125.02 ($\underline{C}H_{aromatic}$, C-1, C-2); 82.11 ($\underline{C}H$, C-3); 81.05 ($\underline{C}H$, C-4); 74.36 ($\underline{C}H_2$, CH_2Ph); 73.55 ($\underline{C}H_2$, CH_2Ph); 71.16 ($\underline{C}H_2$, CH_2Ph); 71.14 ($\underline{C}H$, C-6); 70.32 ($\underline{C}H_2$, C-5); 55.09 ($\underline{C}H_3$).

46*Z*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

(*E*/*Z*)-3,4,6-tri-*O*-Benzyl-1,2-dideoxy-1-(2,6-dimethylphenyl)sulfanyl-D-*ribo*-hex-1-enitol (47).



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (1.75 ml, 3.05 mmol, 1.6 M in hexane) was added to a solution of **11 (**616 mg, 1.75 mmol) in anhydrous THF (10 ml) that was then reacted with a solution of 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranose (368 mg, 0.88 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **47** (403 mg, 0.73 mmol, 83%, an *E*/*Z* inseparable mixture, *E*/*Z* = 50:1) as a light yellow oil.

R_f (hexane: ethyl acetate = 3:1): 0.65.

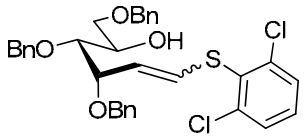
Anal. Calcd for $C_{35}H_{38}O_4S$: 75.78 C, 6.90 H, 5.78 S. Found: 75.63 C, 6.85 H, 5.67 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

47*E*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.31 – 7.09 (m, 18H, $H_{aromatic}$); 6.23 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.17 (dd, 1H, $J_{2,3}$ = 8.8 Hz, H-2); 4.65 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.57 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.48 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.46 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.43 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.29 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.10 (dd, 1H, $J_{3,4}$ = 4.4 Hz, H-3); 3.76 (m, 1H, H-5); 3.57 (m, 3H, H-4, H-6a, H-6b); 2.82 (d, 1H, $J_{OH,5}$ = 3.6 Hz, OH); 2.45 (m, 6H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 143.22, 138.55, 138.31, 138.10 ($C_{aromatic}$); 129.78, 129.41, 129.29, 128.50, 128.47, 128.32, 127.94, 127.91, 127.81, 127.73, 127.62, 127.56 ($\underline{C}H_{aromatic}$, C-1), 122.29 ($\underline{C}H$, C-2); 81.44 ($\underline{C}H$, C-3); 81.10 ($\underline{C}H$, C-3); 74.02 ($\underline{C}H_2$, CH_2Ph); 73.43 ($\underline{C}H_2$, CH_2Ph); 71.10 ($\underline{C}H_2$, CH_2Ph); 71.06 ($\underline{C}H$, C-5); 70.22 ($\underline{C}H_2$, C-6); 21.79 ($\underline{C}H_3$).

47*Z*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

(*E*/*Z*)-3,4,6-tri-*O*-Benzyl-1,2-dideoxy-1-(2,6-dichlorophenyl)sulfanyl-D-*ribo*-hex-1-enitol (48).



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **12 (**787 mg, 2.00 mmol) in anhydrous THF (13 ml)

that was then reacted with a solution of 2,3,5-tri-*O*-benzyl-α,β-D-ribofuranose (420 mg, 1.00 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **48** (103 mg, 0.17 mmol, 17%, an *E*/*Z* inseparable mixture, *E*/*Z* = 2:1) as a light yellow oil. Starting matherial was recovered (302 mg, 0.72 mmol. 72%) after 2 days of reaction time.

R_f (hexane: ethyl acetate = 3:1): 0.65.

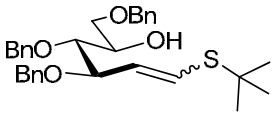
Anal. Calcd for $C_{33}H_{32}O_4S$: 66.55 C, 5.42 H, 10.75 S. Found: 65.93 C, 5.32 H, 10.27 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

48*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.43 – 7.15 (m, 18H, $H_{aromatic}$); 6.25 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.50 (dd, 1H, $J_{2,3}$ = 8.4 Hz, H-2); 4.82 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.74 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.68 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.53 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.50 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.35 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.14 (dd, 1H, $J_{3,4}$ = 4.4 Hz, H-3); 3.82 (m, 1H, H-5); 3.66 (m, 3H, H-4, H-6a, H-6b); 2.78 (d, 1H, $J_{OH,5}$ = 4.0 Hz, OH). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 141.19, 138.50, 138.21, 138.15 ($C_{aromatic}$); 130.89, 129.07, 128.60, 128.58, 128.53, 128.46, 128.06, 127.98, 127.93, 127.90, 127.78, 127.77, 125.72 ($\underline{C}H_{aromatic}$, C-1, C-2); 81.36 ($\underline{C}H$, C-4), 80.95 ($\underline{C}H$, C-3); 74.33 ($\underline{C}H_2$, CH_2Ph); 73.57 ($\underline{C}H_2$, CH_2Ph); 71.24 ($\underline{C}H_2$, CH_2Ph); 71.05 ($\underline{C}H$, C-5); 70.47 ($\underline{C}H_2$, C-6).

48*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.43 – 7.15 (m, 18H, $H_{aromatic}$); 6.22 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1): 5.90 (t(dd), 1H, $J_{2,3}$ = 10.4 Hz, H-2); 4.82 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.74 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.68 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.53 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.50 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.35 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.06 (dd, 1H, $J_{3,4}$ = 4.4 Hz, H-3); 3.95 (m, 1H, H-5); 3.57 (m, 3H, H-4 H-6a, H-6b); 2.89 (d, 1H, $J_{OH,5}$ = 4.0 Hz, OH). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 140.61, 138.50, 138.21, 138.15 ($C_{aromatic}$); 130.54, 130.48, 129.92, 129.76, 128.97, 128.58, 128.41, 128.21, 128.02, 127.98, 127.93, 127.66, 127.32 ($\underline{C}H_{aromatic}$, C-1, C-2); 81.36 ($\underline{C}H$, C-4); 81.07 ($\underline{C}H$, C-3); 77.42 ($\underline{C}H_2$, CH_2Ph); 74.38 ($\underline{C}H_2$, CH_2Ph); 71.35 ($\underline{C}H_2$, CH_2Ph); 71.27 ($\underline{C}H$, C-5); 71.22 ($\underline{C}H_2$, C-6).

(*E*/*Z*)-3,4,6-tri-*O*-Benzyl-1,2-dideoxy-1-*tert*-butylsulfanyl-D-*arabino*-hex-1-enitol (51).



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (1.91 ml, 3.06 mmol, 1.6 M in hexane) was added to a solution of **14** (609 mg, 2.00 mmol) in anhydrous THF (13 ml) that was then reacted with a solution of 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranose (420 mg, 1.00 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate)

afforded compound **51** (472 mg, 0.93 mmol, 93%, an *E*/*Z* inseparable mixture, *E*/*Z* = 8:1) as a light yellow oil.

R_f (hexane: ethyl acetate = 3:1): 0.60.

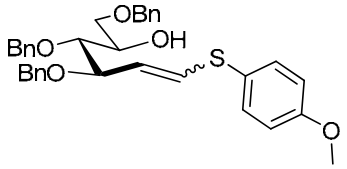
Anal. Calcd for $C_{31}H_{38}O_4S$: 73.48 C, 7.56 H, 6.33 S. Found: 73.39 C, 7.32 H, 6.27 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

51*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.33 – 7.20 (m, 15H, $H_{aromatic}$); 6.39 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.89 (dd, 1H, $J_{2,3}$ = 7.6 Hz, H-2); 4.64 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.61 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.52 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.47 (s, 2H, CH_2Ph); 4.36 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.14 (dd, 1H, $J_{3,4}$ = 4.0, Hz, H-3); 4.00 (m, 1H, H-5); 3.61 – 3.54 (m, 3H, H-4, H-6a, H-6b); 2.79 (d, 1H, $J_{OH,5}$ = 5.2 Hz, OH); 1.34 (m, 9H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.17, 138.10, 137.93 ($C_{aromatic}$); 128.97; 128.53, 128.49, 128.40, 128.31, 128.25, 128.22, 127.99, 127.89, 127.81, 126.59 ($\underline{C}H_{aromatic}$, C-1, C-2); 80.90 ($\underline{C}H$, C-4); 79.49 ($\underline{C}H$, C-3); 74.37 ($\underline{C}H_2$, CH_2Ph); 73.47 ($\underline{C}H_2$, CH_2Ph); 71.04 ($\underline{C}H_2$, CH_2Ph), 70.67 ($\underline{C}H_2$, C-6); 70.30 ($\underline{C}H$, C-5); 43.93 (C); 31.05 ($\underline{C}H_3$).

51*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.33 – 7.20 (m, 15H, $H_{aromatic}$); 6.49 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1); 5.83 (t(dd), 1H, $J_{2,3}$= 9.6 Hz, H-2); 4.66 (dd, 1H, $J_{3,4}$ = 4.0 Hz, H-3); 4.64 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.61 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.52 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.47 (s, 2H, CH_2Ph); 4.36 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.00 (m, 1H, H-5); 3.64 (dd, 1H, $J_{4,5}$ = 6.4 Hz, H-4); 3.61 – 3.54 (m, 2H, H-6a, H-6b); 2.96 (d, 1H, $J_{OH,5}$ = 5.2 Hz, OH); 1.34 (m, 9H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: Could not be determined.

(*E*/*Z*)-3,4,6-tri-*O*-Benzyl-1,2-dideoxy-1-*p*-methoxyphenylsulfanyl-D-*arabino*-hex-1-enitol (52).



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **10 (**709 mg, 2.00 mmol) in anhydrous THF (13 ml) that was then reacted with a solution of 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranose (420 mg, 1.0 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **52** (176 mg, 0.32 mmol, 32%, an *E*/*Z* inseparable mixture, *E*/*Z* = 3:1) as a light yellow oil. Starting matherial was recovered (152 mg, 0.36 mmol, 36%).

R_f (hexane: ethyl acetate = 3:1): 0.53.

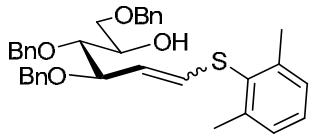
Anal. Calcd for $C_{34}H_{36}O_5S$: 73.35 C, 6.52 H, 5.76 S. Found: 73.19 C, 6.35 H, 5.56 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

52*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.51 – 7.32 (m, 17H, $H_{aromatic}$); 6.99 (d, 2H, J_{AB} = 11.6 Hz, $H_{aromatic}$); 6.40 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.73 (dd, 1H, $J_{2,3}$ = 8.0 Hz, H-2); 5.04 – 4.56 (m, 5H, CH_2Ph); 4.50 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.26 (dd, 1H, $J_{3,4}$ = 4.0 Hz, H-3); 4.11 (m, 1H, H-5); 3.92 (s, 3H, OMe); 3.83 – 3.70 (m, 3H, H-4, H-6a, H-6b); 2.87 (d, 1H, $J_{OH,5}$ = 4.8 Hz, OH). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 159.84, 138.18, 138.15, 138.13, 127.43 ($C_{aromatic}$); 134.12, 130.16, 128.51 – 127.66 ($CH_{aromatic}$, C-1); 125.26 (CH, C-2); 114.98 ($CH_{aromatic}$); 80.93 (CH, C-4); 79.44 (CH, C-3); 74.39 (CH_2, CH_2Ph); 73.51 (CH_2, CH_2Ph); 71.87 (CH_2, CH_2Ph); 71.01 (CH, C-5); 70.69 (CH, C-6); 55.50 (OCH_3).

52*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.51 – 7.32 (m, 17H, $H_{aromatic}$); 6.99 (d, 2H, J_{AB} = 11.6 Hz, $H_{aromatic}$); 6.57 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1); 5.97 (t(dd), 1H, $J_{2,3}$ = 9.2 Hz, H-2); 5.04 - 4.56 (m, 6H, CH_2Ph); 4.40 (dd, 1H, $J_{3,4}$ = 4.8 Hz, H-3); 4.08 (m, 1H, H-5); 3.96 (s, 3H, OMe); 3.83 – 3.70 (m, 3H, H-4, H-6a, H-6b); 3.12 (d, 1H, $J_{OH,5}$ = 4.4 Hz, OH). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: Could not be determined.

(*E*/*Z*)-3,4,6-tri-*O*-Benzyl-1,2-dideoxy-1-(2,6-dimethylphenyl)sulfanyl-D-*arabino*-hex-1-enitol (53).



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.0 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **11 (**705 mg, 2.00 mmol) in anhydrous THF (13 ml) that was then reacted with a solution of 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranose (420 mg, 1.00 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **53** (357 mg, 0.64 mmol, 64%, an *E*/*Z* inseparable mixture, *E*/*Z* = 12:1) as a light yellow oil. Starting matherial was recovered (128 mg, 0.30 mmol, 30%).

R_f (hexane: ethyl acetate = 3:1): 0.65.

Anal. Calcd for $C_{35}H_{38}O_4S$: 75.78 C, 6.90 H, 11.54 S. Found: 75.62 C, 6.87 H, 11.39 S.

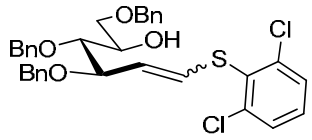
Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

53*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.39 – 7.10 (m, 18H, $H_{aromatic}$); 6.20 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.12 (dd, 1H, $J_{2,3}$ = 8.8 Hz, H-2); 4.58 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.47 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.42 (s, 2H, CH_2Ph); 4.41 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.30 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.06 (dd, 1H, $J_{3,4}$ = 3.6 Hz, H-3); 3.91 (m, 1H, H-5); 3.52 (d, 2H, $J_{6,5}$ = 4.4 Hz, H-6a, H-6b); 3.47 (dd, 1H, $J_{4,5}$ = 7.2 Hz, H-4); 2.66 (d, 1H, $J_{OH,5}$ = 5.6 Hz, OH); 2.47 (m, 6H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 143.37, 138.22, 138.17, 137.98 ($C_{aromatic}$); 129.55, 128.96, 128.66, 128.59, 128.57, 128.43, 128.29, 128.22, 128.05, 127.93, 127.89, 127.81 ($CH_{aromatic}$, C-1); 121.75 (CH,

C-2); 81.42 (CH, C-4); 79.59 (CH, C-3); 74.49 (CH_2, CH_2Ph), 73.48 (CH_2, CH_2Ph); 70.95 (CH_2, CH_2Ph); 70.32, 70.31 (CH, C-5; CH_2, C-6); 21.82 (CH_3).

53*Z*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.39 – 7.10 (m, 18H, $H_{aromatic}$); 6.03 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1); 5.78 (dd, 1H, $J_{2,3}$ = 8.8 Hz, H-2); 4.72 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3); 4.58 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.47 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.42 (s, 2H, CH_2Ph); 4.41 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.30 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 3.91 (m, 1H, H-5); 3.74 (dd, 1H, $J_{4,5}$ = 3.6 Hz, H-4); 3.65 (d, 2H, $J_{6,5}$ = 4.0 Hz, H-6a, H-6b); 3.02 (d, 1H, $J_{OH.5}$ = 5.6 Hz, OH); 2.46 (m, 6H, CH_3). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: Could not be determined.

(*E*/*Z*)-3,4,6-tri-*O*-Benzyl-1,2-dideoxy-1-(2,6-dichlorophenyl)sulfanyl-D-*ribo*-hex-1-enitol (54).



Following the *general method of the WH olefination reactions*, a *n*-BuLi solution (2.2 ml, 3.50 mmol, 1.6 M in hexane) was added to a solution of **12 (**787 mg, 2.00 mmol) in anhydrous THF (13 ml) that was then reacted with a solution of 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranose (420 mg, 1.00 mmol) in anhydrous THF (5 ml). After general work-up and chromatography (hexane to ethyl acetate) afforded compound **54** (464 mg, 0.778 mmol, 78%, an *E*/*Z* inseparable mixture, *E*/*Z* = 6:1) as a light yellow oil.

R_f (hexane: ethyl acetate = 3:1): 0.45.

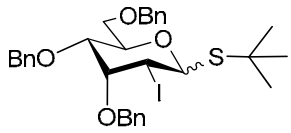
Anal. Calcd for $C_{33}H_{32}Cl_2O_4S$: 66.55 C, 5.42 H, 5.38 S. Found: 66.61 C, 5.32 H, 5.27 S.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

54*E*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.42 – 7.17 (m, 18H, $H_{aromatic}$); 6.21 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.40 (dd, 1H, $J_{2,3}$ = 8.4 Hz, H-2); 4.62 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.54 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.45 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.46 (s, 2H, CH_2Ph); 4.34 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.11 (dd, 1H, $J_{3,4}$ = 7.2 Hz, H-3); 3.97 (m, 1H, H-5); 3.54 – 3.52 (m, 2H, H-6a, H-6b); 3.51 (dd, 1H, $J_{4,5}$ = 3.6 Hz, H-4); 2.62 (d, 1H, $J_{OH,5}$ = 5.2 Hz, OH). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 141.41, 138.27, 138.18, 137.92 ($C_{aromatic}$); 131.08, 130.15, 129.12, 128.62, 128.48, 128.22, 128.09, 127.99, 127.84, 127.56, 126.58, 125.15 ($CH_{aromatic}$, C-1, C-2), 81.29 (CH, C-4); 79.16 (CH, C-3); 74.53 (CH_2, CH_2Ph); 73.51 (CH_2, CH_2Ph); 70.98 (CH_2, CH_2Ph); 70.58 (CH_2, C-6), 70.25 (CH, C-5).

54*Z*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

tert-Butyl 3,4,6-tri-*O*-Benzyl-2-deoxy-2-iodo-1-thio-α,β-D-allopyranoside (56).



As described in *general method A of the iodium–induced cyclization*, compound **44** (253 mg, 0.50 mmol, 1.0 eq; mixture of *E/Z* = 8:1), NIS (169 mg, 0.75 mmol, 1.2 eq) and $NaHCO_3$ (63 mg, 0.75 mmol, 1.5 eq) were stirred in anhydrous DCM (10 ml) from –78 ºC to –10 °C for 18 h. The reaction was monitored by TLC (hexane: ethyl acetate = 3:1). Chromatographic purification (hexane → hexane: ethyl acetate = 3:1) afforded compound **56** (181 mg, 0.29 mmol, 57%, an α/β inseparable mixture, α/β = 1:12) as a yellowish syrup.

R_f(hexane: ethyl acetate = 3:1): 0.45.

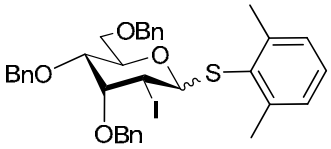
Anal. Calcd for $C_{31}H_{37}IO_4S$: 58.86 C, 5.90 H, 10.12 S. Found: 59.02 C, 5.72 H, 10.13 S.

Spectroscopic data obtained from α/β mixture.

56β: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.48 – 7.23 (m, 15H, $H_{aromatic}$); 5.05 (d, 1H, $J_{1,2}$ = 10.8 Hz, H-1); 4.92 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.78 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.64 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.58 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.52 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.50 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.19 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3); 4.16 (td, 1H, $J_{5,6a}$ = 9.6 Hz, $J_{5,6b}$ = 6.4 Hz, H-5); 4.14 (dd, 1H, $J_{2,3}$ = 2.8 Hz, H-2); 3.69 (m, 2H, $J_{6a,6b}$ = 9.6 Hz, H-6a, H-6b); 3.63 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4); 1.37 (s, 9H, $3CH_3$). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.53, 137.76, 134.22 ($C_{aromatic}$); 129.70, 128.69, 128.45, 128.34, 128.20, 128.16, 128.02, 127.83, 127.91, 127.66 ($\underline{C}H_{aromatic}$); 81.86 (C-1); 78.78 (C-3); 76.77 (C-4); 75.94 (C-5); 75.65 ($\underline{C}H_2Ph$); 73.55 ($\underline{C}H_2Ph$); 72.31 ($\underline{C}H_2Ph$); 69.91 (C-6); 44.84 (C); 32.31 (C-2); 31.62 ($3\underline{C}H_3$).

56α: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

Dimethyl-phenyl 3,4,6-tri-*O*-Benzyl-2-deoxy-2-iodo-1-thio-α,β-D-allopyranoside (57).



As described in *general method A of the iodium–induced cyclization*, compound **47** (203 mg, 0.37 mmol, 1.0 eq, an *E/Z* inseparable mixture, *E/Z* = 1:50), NIS (193 mg, 0.86 mmol, 1.2 eq) and $NaHCO_3$ (47 mg, 0.56 mmol, 1.5 eq) were stirred in anhydrous DCM (10 ml), from –78 ºC to –10 °C for 18 h. The reaction was monitored by TLC (hexane: ethyl acetate = 3:1). Chromatographic purification (hexane → hexane: ethyl acetate = 2:1) afforded compound **57** (123 mg, 0.18 mmol, 49%, an α/β inseparable mixture, α/β = 1:25) as a yellowish syrup.

R_f (hexane: ethyl acetate = 3:1): 0.45.

Anal. Calcd for $C_{35}H_{37}IO_4S$: 61.76 C, 5.48 H, 9.40 S. Found: 62.03 C, 5.32 H, 9.27 S.

Spectroscopic data obtained from α/β mixture.

57β: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.42 – 7.04 (m, 18H, $H_{aromatic}$); 4.90 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.88 (d, 1H, $J_{1,2}$ = 10.8 Hz, H-1); 4.77 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.63 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.53 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.47 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.41 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.27 (dd, 1H, $J_{2,3}$ = 2.0 Hz, H-2); 4.17 (dd, 1H, $J_{3,4}$ = 1.6 Hz, H-3); 3.89 (td, 1H, $J_{5,6a}$ = 9.6 Hz, $J_{5,6b}$ = 6.4 Hz, H-5); 3.76 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4); 3.57 (m, 2H, $J_{6a,6b}$ = 11.2 Hz, H-6a, H-6b); 1.37 (s, 9H, $3CH_3$). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 144.66, 138.48, 138.46; 137.83, 131.76 ($C_{aromatic}$); 129.13, 128.67, 128.46, 128.31, 128.26, 128.14, 128.08, 128.03; 127.86, 127.75, 127.69 ($\underline{C}H_{aromatic}$); 86.60 (C-1); 79.04 (C-3); 76.48 (C-4); 75.87 (C-5); 75.76 ($\underline{C}H_2Ph$); 73.67 ($\underline{C}H_2Ph$); 72.38 ($\underline{C}H_2Ph$); 69.63 (C-6); 31.42 (C-2); 23.03 ($3\underline{C}H_3$).

57α: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

***tert*-Butyl 3,4,6-tri-*O*-Benzyl-2-deoxy-2-iodo-1-thio-α,β-D-mannopyranoside (59).**

As described in *general method A of the iodium–induced cyclization*, compound **51** (253 mg, 0.50 mmol, 1.0 eq, an *E/Z* inseparable mixture, *E/Z* = 8:1), NIS (169 mg, 0.75 mmol, 1.2 eq) and $NaHCO_3$ (63 mg, 0.75 mmol, 1.5 eq) were stirred in anhydrous DCM (10 ml), from –78 ºC to 0 °C for 20 h. The reaction was monitored by TLC (hexane: ethyl acetate = 1:3). Chromatographic purification (hexane → hexane: ethyl acetate = 1:3) afforded compound **59** (179 mg, 0.28 mmol, 57%, an α/β inseparable mixture, α/β = 1:0) as a yellowish syrup.

R_f (hexane: ethyl acetate = 3:1): 0.46.

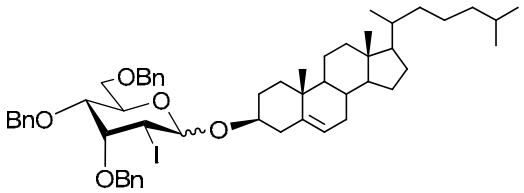
Anal. Calcd for $C_{31}H_{37}IO_4S$: 58.86 C, 5.90 H, 5.07 S. Found: 58.07 C, 5.89 H, 4.99 S.

Spectroscopic data obtained from α/β mixture.

59α: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.55 – 6.99 (m, 15H, $H_{aromatic}$); 5.72 (s, 1H, H-1); 4.85 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.79 (d, $J_{2,3}$ = 3.6 Hz, H-2); 4.75 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.64 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.58 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.52 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.45 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.29 (m, 1H, H-5); 3.99 (dd, 1H, $J_{4,3}$ = 8.8, $J_{4,5}$ = 8.4 Hz, H-4); 3.86 (dd, 1H, $J_{6a,6b}$ = 10.8 Hz, $J_{6a,5}$= 4.8 Hz, H-6a); 3.73 (dd, 1H, $J_{6a,6b}$ = 10.8 Hz, $J_{6a,5}$= 2.0 Hz, H-6b); 3.10 (dd, 1H, $J_{3,4}$ = 8.4 Hz, $J_{3,2}$ = 3.6 Hz, H-3); 1.37 (s, 9H, $3CH_3$). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.53, 137.76, 134.22 ($C_{aromatic}$); 129.70, 128.69, 128.45, 128.34, 128.20, 128.16, 128.02, 127.83, 127.91, 127.66 ($\underline{C}H_{aromatic}$); 89.86 (C-1); 77.78 (C-3); 76.77 (C-4); 75.54 (C-5); 75.65 ($\underline{C}H_2Ph$); 73.55 ($\underline{C}H_2Ph$); 71.31 ($\underline{C}H_2Ph$); 68.91 (C-6); 44.84 (C); 35.00 (C-2); 31.62 ($3\underline{C}H_3$).

59β: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

Cholesteryl 3,4,6-tri-*O*-Benzyl-2-deoxy-2-iodo-α,β-D-allopyranoside (61).



Starting from **56**: *Following the general procedure for glycosylation*, **56** (144 mg, 0.23 mmol, 1.0 eq, an α/β inseparable mixture, α/β = 1:12), NIS (113 mg, 0.50 mmol, 2.2 eq), cholesterol (106 mg, 0.27 mmol, 1.2 eq), 4Å molecular sieves (160 mg), and TfOH (1 drop) in anhydrous DCM (6.1 ml) were allowed to react at –78 ºC for 1 h and then at –40 ºC for 3 h. TLC (hexane: ethyl acetate = 3:1). Radial chromatography (hexane → hexane: ethyl acetate = 2:1) afforded **61** (202 mg, 0.22 mmol, 95%, inseparable an α/β inseparable mixture, α/β = 1: 7) as a pale yellow solid.

Starting from **57**: *Following the general procedure for glycosylation*, **57** (98 mg, 0.14 mmol, 1.0 eq, an α/β inseparable mixture, α/β = 1:25), NIS (71 mg, 0.32 mmol, 2.2 eq), cholesterol (67 mg, 0.17 mmol, 1.2 eq), 4Å molecular sieves (100 mg), and TfOH (1 drop) in anhydrous DCM (4.0 ml) were allowed to react at –78 ºC for 1 h and then at –40 ºC for 3 h. TLC (hexane ethyl: acetate = 1:3). Radial chromatography (hexane → hexane: ethyl acetate = 2:1) afforded **61** (81 mg, 0.09 mmol, 60%, an α/β inseparable mixture, α/β = 1:10) a pale yellow solid.

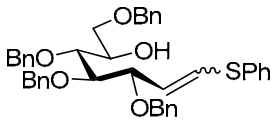
R_f (hexane: ethyl acetate = 3:1): 0.62.

Spectroscopic data obtained from α/β mixture.

Anal. Calcd for $C_{54}H_{73}IO_5$: 69.81 C, 7.92 H. Found: 69.87 C, 7.89 H.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.47 – 7.06 (m, 15H, $H_{aromatic}$); 5.35 (d, 1H, J = 5.2 Hz, CH=$_{cholesteryl}$); 4.87 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph); 4.86 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1); 4.77 (d, J_{AB} = 10.4 Hz, CH_2Ph); 4.66 – 4.50 (m, 4H, $2CH_2Ph$); 4.18 – 4.11 (m, 2H, H-3, H-5); 4.02 (dd, 1H, $J_{1,2}$ = 9.0 Hz, $J_{2,3}$ = 2.8 Hz, H-2); 3.73 – 3.64 (d, 2H, H-4, H-6a, H-6b); 3.48 (m, 1H, $HCOR_{cholesteryl}$); 2.39 – 0.67 (m, 44H, $H_{cholesteryl}$). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 143.6 – 127.7 ($C_{aromatic}$, =C $_{cholesteryl}$); 122.0 (=CH $_{cholesteryl}$); 99.3 (C-1); 79.9 ($CHOR_{cholesteryl}$); 78.6 (C-3); 76.9 (C-4); 75.8, 73.5 (CH_2Ph); 73.2 (C-5); 72.4 (CH_2Ph); 69.6 (C-6); 57.0, 56.3, 50.3, 42.5, 40.0, 39.7, 38.7, 37.4, 36.9, 36.4, 36.0, 32.2, 32.0, 29.7, 28.4, 28.2, 24.5, 24.0, 23.0, 22.8, 21.2, 19.6, 18.9, 12.15 ($24C_{cholesteryl}$) [166]; 33.4 (C-2).

(*Z/E*)-3,4,5,7-tetra-*O*-Benzyl-1,2-dideoxy-1-phenylsulfanyl-D-*gluco*-hept-1-enitol (65).



Folloing the *general method of the WH olefination reactions*, *n*-BuLi (2.6 ml, 4.20 mmol, 1.6 M in hexane) was slowly added to a solution of (phenylsulfanylmethyl)diphenylphosphine oxide (**42**) (1.3 g, 4.00 mmol) in anhydrous THF (27 ml, 0.15 M) at –78 ºC. The resulting solution was stirred under argon atmosphere until an intensive orange colour appeared (1hour aprox.). Then a THF solution of the 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranose (**64**) (1.00 mmol in 2.0 ml THF, 0.5 M) was added. The evolution of the reaction was monitored by TLC. The reaction did not evolve at –78 ºC and the solution was warmed up to room temperature. After full conversion (24 h) and work-up, the product was purified by flash chromatography (hexane: ethyl acetate = 3:1) to obtain compound **65** (406 mg, 0.63 mmol, 63%, an *E*/*Z* inseparable mixture, *E*/*Z* = 8:1) as an oil.

Spectroscopic data obtained from **65** *E*/*Z* diastereoisomeric mixture.

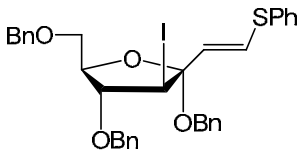
65*E*: R_f (hexane: ethyl acetate = 2:1): 0.7.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.52 – 7.16 (m, 25H, $H_{aromatic}$); 6.30 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.70 (dd, 1H, $J_{2,3}$ = 8.0 Hz, H-2); 4.80 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.71 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.67 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.62 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.64 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.50 (s, 2H, CH_2Ph); 4.48 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.24 (dd, 1H, $J_{3,4}$ = 5.6 Hz, H-3); 4.01 (m, 1H, H-5); 3.72 (m, 2H, H-4, H-6); 3.60 (s, 1H, H-7a), 3.58 (d, 1H, $J_{6,7b}$ = 2.0 Hz, H-7b), 2.82 (d, 1H, $J_{OH,6}$ = 6.0 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.5, 138.3, 138.2, 138.1, 134.4 ($C_{aromatic}$);130.6 – 127.4 ($\underline{C}H_{aromatic}$); 128.6 ($\underline{C}H$, C-1); 128.4 ($\underline{C}H$, C-2); 81.6 ($\underline{C}H$, C-4); 81.0 ($\underline{C}H$, C-3); 78.6 ($\underline{C}H$, C-6); 75.0, 73.5, 73.3 ($\underline{C}H_2Ph$); 71.2 ($\underline{C}H_2$, C-7); 71.0 ($\underline{C}H_2Ph$); 70.5 ($\underline{C}H$, C-5).

65*Z*: R_f (hexane: ethyl acetate = 2:1): 0.6.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.35 – 7.18 (m, 25H, $H_{aromatic}$); 6.50 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1); 5.89 (dd, 1H, $J_{2,3}$ = 8.8 Hz, H-2); 4.80 – 4.40 (m, 8H, CH_2Ph); 4.24 (m, 1H, H-3), 4.0 (m, 1H, H-5); 3.82 (m, 2H, H-4, H-6); 3.60 (s, 1H, H-7a); 3.58 (d, 1H, $J_{6,7b}$ = 2.0 Hz, H-7b); 2.87 (d, 1H, $J_{OH,6}$ = 5.2 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: Could not be determined.

(2S,3S,4R,5R)-2,4-Bis(benzyloxy)-5-(benzyloxymethyl)-3-iodo-2-((*E*)-2-(phenylthio)vinyl)tetrahydrofuran (66).

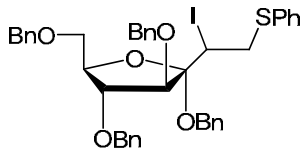


A solution of **65** (194 mg, 0.3 mmol) in 3.5 ml (0.085 M) of anhydrous THF was added to the mixture of potassium hydroxide (52 mg, 0.39 mmol) and 2.2 ml (0.175 M) of anhydrous THF at 0 ºC. The resulting mixture was stirred for an hour under argon atmosphere and was cooled down to –78 ºC. A solution of iodine (228 mg, 0.9 mmol) in anhydrous THF (2.1 ml, 0.43 M) was then added. TLC analysis was made and the completion of the reaction was observed in a half an hour. The mixture was quenched with $Na_2S_2O_3$, and after the separation of the organic layer, it was extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), with brine (1x20 ml), dried on anhydrous $MgSO_4$, and concentrated under vacuum. After the purification with radial chromatography (hexane → hexane: ethyl acetate = 1:2) compound **66** (127 mg, 0.191 mmol, 64%) was obtained.

66*E*: R_f (hexane: ethyl acetate = 2:1): 0.46.

^{1}H-RMN[167] ($CDCl_3$, 300 MHz) δ in ppm: 7.3 – 7.2 (m, 20H, $H_{aromatic}$); 6.80 (d, 1H, $J_{1,2}$ = 15.0 Hz, H-1); 5.64 (d, 1H, $J_{2,1}$ = 15.0 Hz, H-2); 4.89 (dd, 1H, J_{AB} = 11.4, 1.6 Hz, CH_2Ph); 4.72 (dd, 1H, J_{AB} = 11.4, 1.6 Hz, CH_2Ph); 4.6 – 4.5 (4H, CH_2Ph); 4.45 (dd, H, $J_{6,5}$ = 8.4 Hz, $J_{5,4}$ = 6.3 Hz, H-5); 4.33 (m, $J_{5,6}$ = 8.4 Hz, H-6); 4.2 (d, H, $J_{4,5}$ = 6.3 Hz, H-4); 3.52 (m, 2H, H-7a, H-7b). ^{13}C-RMN ($CDCl_3$, 75.46 MHz) δ in ppm: 138.68, 137.94, 133.62 ($C_{aromatic}$); 131.5-125.03 ($\underline{C}H_{aromatic}$, C-1, C-2); 105.54 (C, C-3); 87.70 ($\underline{C}H$, C-5); 82.70 ($\underline{C}H$, C-6); 73.70, 73.56 ($\underline{C}H_2Ph$); 71.80 ($\underline{C}H_2$, C-7); 64.65 ($\underline{C}H_2Ph$); 33.97 ($\underline{C}H$, C-4).

(2R,3S,4R,5R)-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)-2-(1-iodo-2-(phenylthio)ethyl)tetrahydrofuran (67).



As described in *general method A of the iodium–induced cyclization*, *n*-BuLi (53 μl, 0.08 mmol, 1.6 M in hexane) were added to a solution of **65** (55 mg, 0.08 mmol) in anhydrous diethyl ether (1.0 ml, 0.08 M) at –78 ºC. The mixture was stirred for one hour at this temperature under an argon atmosphere. Subsequently, a solution of I_2 (65 mg, 0.22 mmol) in 2.0 ml (0.43 M) of diethyl ether was added. TLC analysis showed the completion of the reaction after 5 min. The reaction was quenched with $Na_2S_2O_3$, and the aqueous layer was extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), with brine (1x20 ml), dried on anhydrous $MgSO_4$, and concentrated under vacuum. After purification by radial chromatography methods (hexane → hexane: ethyl acetate = 1:2) compound **67** (41 mg, 0.05 mmol, 62%) as an oil was obtained.

R_f (hexane: ethyl acetate = 2:1): 0.67.

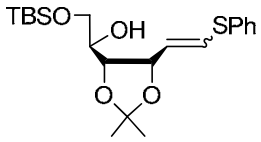
[167] For the sake of clarity hydrogen and carbon atoms have been numbered according to the respective alkene starting material.

$[\alpha]_D^{25}$ –21.5 (*c* 0.40, DCM).

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.25 – 7.13 (m, 25H, $H_{aromatic}$); 4.81 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.65 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.61 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.58 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.56 (d, 1H, $J_{4,5}$ = 6.4 Hz, H-4); 4.49 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.46 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.44 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.38 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.30 (dd, 1H, $J_{5,6}$ = 7.2 Hz, H-5); 4.18 (dd, 1H, $J_{2,1a}$ = 10.8 Hz, $J_{2,1b}$ = 2.8 Hz, H-2); 4.12 (m, 1H, H-6); 3.86 (dd, 1H, $J_{1a,1b}$ = 14.8 Hz, $J_{1a,2}$ = 2.8 Hz, CH_2, H-1a); 3.69 (dd, 1H, $J_{7a,7b}$ = 10.8 Hz, $J_{7a,6}$ = 2.8 Hz, H-7a); 3.53 (dd, 1H, $J_{7a,7b}$ = 10.8 Hz, $J_{7b,6}$ = 3.6 Hz, H-7b); 3.22 (dd, 1H, $J_{7b,6}$ = 14.8 Hz, $J_{7a,7b}$ = 10.8 Hz, CH_2, H-1b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 139.0, 138.4, 138.4, 138.1, 136.0 ($C_{aromatic}$); 129.6-125.3 ($\underline{C}H_{aromatic}$); 105.3 (C, C-3); 87.2 ($\underline{C}H$, C-4); 82.9 ($\underline{C}H$, C-5); 80.6 ($\underline{C}H$, C-6); 73.8, 73.1, 72.9 ($\underline{C}H_2Ph$); 69.5 ($\underline{C}H_2$, C-7); 65.8 ($\underline{C}H_2Ph$); 41.9 ($\underline{C}H$, C-2); 40.1 ($\underline{C}H_2$, C-1).

HRMS (TOF MS ES+): calcd for $C_{41}H_{41}O_5NaSI$ (MNa+) 795.1617; found, 795.1600.

(*Z*/*E*)-6-*O*-*tert*-Butyldimethylsilyl-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (76).



Folloing the *general method of the WH olefination reactions*, *n*-BuLi (8.6 ml, 13.80 mmol, 1.6 M in hexane) was slowly added to a solution of (phenylsulfanylmethyl)diphenylphosphine oxide (**42**) (4.26 g, 13.10 mmol) in anhydrous THF (13 ml, 0.25 M) at –78 ºC and the solution was stirred under an argon atmosphere until the intensive orange colour occurred. The reaction mixture was stirred for an hour at this temperature, then the solution of **75** (1.0 g, 3.30 mmol) in anhydrous THF (2.0 ml, 0.5 M) was added. After full conversion (24 h) and work-up, the product was purified by flash chromatography (hexane: ethyl acetate = 6:1) to obtain compound **76** (920 mg, 2.24 mmol, 68%, an *E*/*Z* inseparable mixture, *E*/*Z* = 11:1) as an oil.

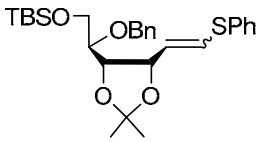
Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

76*E*: R_f (hexane: ethyl acetate = 6:1): 0.62.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.51 – 7.20 (m, 5H, $H_{aromatic}$); 6.50 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 6.00 (dd, 1H, $J_{2,3}$ = 6.4 Hz, H-2); 4.77 (dd, 1H, $J_{3,4}$ = 6.0 Hz, H-3); 4.05 (dd, 1H, $J_{4,5}$ = 9.2 Hz, H-4); 3.81 (dd, 1H, $J_{6a,6b}$ = 9.6 Hz, $J_{6a,5}$ = 3.2 Hz, H-6a); 3.68 (dd, 1H, $J_{6a,6b}$ = 9.6 Hz, $J_{6b,5}$ = 5.2 Hz, H-6b); 3.64 (m, 1H, H-5); 2.50 (d, 1H, $J_{OH,5}$ = 6.0 Hz, OH); 1.46 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 0.92 (s, 9H, CH_3); 0.12 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 139.2 ($C_{aromatic}$); 130.0 – 127.0 ($\underline{C}H_{aromatic}$); 127.3 ($\underline{C}H$, C-1); 126.7 ($\underline{C}H$, C-2); 109.5 (C); 78.5 ($\underline{C}H$, C-3); 76.9 ($\underline{C}H$, C-4); 69.0 ($\underline{C}H_2$, C-6); 64.6 ($\underline{C}H$, C-5); 28.1 ($\underline{C}H_3$); 26.1 ($\underline{C}H_3$); 25.6 ($\underline{C}H_3$).

76*Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

(*Z/E*)-6-*O*-*tert*-Butyldimethylsilyl-5-*O*-benzyl-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (77).



A solution of compound **76** (820 mg, 2.00 mmol) in anhydrous THF (8.0 ml, 0.25 M) was added to a suspension of sodium hydride (84 mg, 2.10 mmol) in THF, at room temperature. The reaction mixture was further stirred for an hour and benzyl bromide (250 μl, 2.1 mmol) was slowly added. The reaction mixture was stirred overnight, and the evolution of the reaction was followed by TLC analysis. The reaction was quenched by saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3x20 ml), the combined organic layer was washed with water (2x20 ml), with brine (1x20 ml) and dried on $MgSO_4$, filtered and concentrated under vacuum. The resulting mixture was purified by chromatography (hexane → hexane: ethyl acetate = 3:1) to obtain compound **77** (361 mg, 0.74 mmol, 37%, an *E*/*Z* inseparable mixture, *E*/*Z* = 11:1) as a light yellow oil.

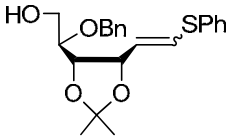
Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

77*E*: R_f (hexane: ethyl acetate = 8:1): 0.51.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40 – 7.22 (m, 10H, $H_{aromatic}$); 6.52 (d, 1H, $J_{1,2}$ = 15.6 Hz, H-1); 5.86 (dd, 1H, $J_{2,3}$ = 6.4 Hz, H-2); 4.77 (d, 1H, J_{AB} = 11.2 Hz CH_2Ph); 4.74 (dd, 1H, $J_{3,4}$ = 5.6 Hz, H-3); 4.40 (d, 1H, J_{AB} = 11.2 Hz CH_2Ph); 4.26 (dd, 1H, $J_{4,5}$ = 8.8 Hz, H-4); 3.86 (dd, 1H, $J_{6a,6b}$ = 10.0 Hz, $J_{6a,5}$ = 2.0 Hz, H-6a); 3.68 (dd, 1H, $J_{6a,6b}$ = 10.0 Hz, $J_{6a,5}$ = 5.2 Hz, H-6b); 3.61 (m, 1H, H-5); 1.45 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 0.92 (s, 9H, CH_3); 0.12 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 139.0, 134.5 ($C_{aromatic}$); 130.0 – 127.0 ($\underline{C}H_{aromatic}$); 127.3 ($\underline{C}H$, C-1); 126.7 ($\underline{C}H$, C-2); 109.5 (C); 78.5 ($\underline{C}H$, C-3); 76.9 ($\underline{C}H$, C-4); 72.3 ($\underline{C}H_2Ph$); 69.8 ($\underline{C}H_2$, C-6); 64.6 ($\underline{C}H$, C-5); 28.1 ($\underline{C}H_3$); 26.1 ($\underline{C}H_3$); 25.6 ($\underline{C}H_3$).

77*Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

(*Z/E*)-5-*O*-Benzyl-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (78).



Compound **77** (361 mg, 0.74 mmol) was dissolved in THF (3.0 ml) and *tetra*-butylammonium fluoride (275 mg, 0.78 mmol) was added. The reaction mixture was stirred at room temperature and the

reaction was monitored by TLC analysis. After an hour, the reaction was quenched with a saturated solution of sodium carbonate. The aqueous layer was extracted with ethyl acetate (3x20 ml), and the combined organic layer was washed with water (2x20 ml), with brine (1x20 ml) dried on $MgSO_4$, filtered and concentrated under vacuum. The mixture was separated by chromatography (hexane → hexane: ethyl acetate = 1:1) and compound **78** (276 mg, 0.71 mmol, 96%, inseparable mixture of *Z/E* = 11:1) was obtained as a light yellow oil.

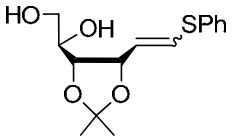
Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

78*E*: R_f (hexane: ethyl acetate = 4:1): 0.46.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.43 – 7.20 (m, 10H, $H_{aromatic}$); 6.50 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.88 (dd, 1H, $J_{2,3}$ = 6.8 Hz, H-2); 4.77 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph); 4.76 (dd, 1H, $J_{3,4}$ = 6.0, H-3); 4.40 (d, 2H, J_{AB} = 10.8 Hz, CH_2Ph); 4.26 (dd, 1H, $J_{4,5}$ = 8.8 Hz, H-4); 3.86 (d, 1H, $J_{6a,6b}$ = 10.4 Hz, H-6a); 3.66 (dd, 1H, $J_{6a,6b}$ = 10.4 Hz, $J_{6b,5}$ = 5.2 Hz, H-6b); 3.65 (m, 1H, H-5); 1.45 (s, 3H, CH_3); 1.35 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4, 134.79 ($C_{aromatic}$); 130.3 – 126.5 ($\underline{C}H_{aromatic}$); 127.3 ($\underline{C}H$, C-1); 126.7 ($\underline{C}H$, C-2); 108.9 (C); 78.4 ($\underline{C}H$, C-3); 77.3 ($\underline{C}H$, C-5); 76.9 ($\underline{C}H$, C-4); 72.3 ($\underline{C}H_2Ph$); 70.6 ($\underline{C}H_2$, C-6); 29.8 ($\underline{C}H_3$); 28.9 ($\underline{C}H_3$).

78*Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

(*Z/E*)-1,2-Dideoxy-3,4-*O*-isopropylidene-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (79).



Compound **76** (410 mg, 1.00 mmol) was dissolved in THF (4.0 ml, 0.25 M) and *tetra*-butylammonium fluoride (331 mg, 1.05 mmol) was added. The reaction mixture was stirred at room temperature and the reaction was monitored by TLC analysis. After an hour, the reaction was quenched with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (3x20 ml), the combined organic layer was washed with water (2x20 ml), with brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The mixture was separated by chromatography (hexane → hexane: ethyl acetate = 1:1) and was obtained compound **79** (244 mg, 0.82 mmol, 98%, an *E*/*Z* inseparable mixture, *E*/*Z* = 11:1) as a light yellow oil.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

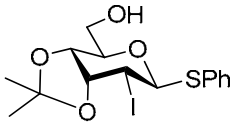
79*E*: R_f (hexane: ethyl acetate = 6:1): 0.62.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.97 – 7.23 (m, 5H, $H_{aromatic}$); 6.58 (d, 1H, $J_{1,2}$ = 14.8 Hz, H-1); 5.90 (dd, 1H, $J_{2,3}$ = 6.8 Hz, H-2); 4.78 (dd, 1H, $J_{3,4}$ = 6.0 Hz, H-3); 4.09 (dd, 1H, $J_{4,5}$ = 8.8 Hz, H-4); 3.86 (d, 1H, $J_{6a,6b}$ = 10.4 Hz, H-6a); 3.68 (m, 1H, H-5); 3.66 (dd, 1H, $J_{6a,6b}$ = 10.4 Hz, $J_{6b,5}$ =5.2 Hz, H-6b); 1.40 (s, 3H, CH_3); 1.30 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.5 ($C_{aromatic}$);

130.4 – 127.3 ($\underline{C}H_{aromatic}$); 128.0 ($\underline{C}H$, C-1); 126.9 ($\underline{C}H$, C-2); 109.2 (C); 78.2 ($\underline{C}H$, C-3); 76.8 ($\underline{C}H$, C-5); 74.84 ($\underline{C}H$, C-4); 70.0 ($\underline{C}H_2$, C-6); 27.8 ($\underline{C}H_3$); 25.4 ($\underline{C}H_3$).

79*Z*: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

Phenyl 2-Deoxy-2-iodo-3,4-*O*-isopropylidene-1-thio-β-D-allopyranoside (81).

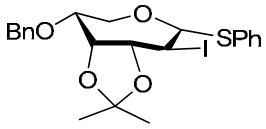


As described in *general method A of the iodium–induced cyclization*, compound **76** (264 mg, 0.50 mmol) was dissolved in acetonitrile (9.4 ml, 0.05 M) and the solution was cooled to –30 ºC. Sodium bicarbonate (59 mg, 0.70 mmol) and NIS (159 mg, 0.70 mmol) were then added. The reaction was monitored by TLC. After half an hour, full conversion was observed and the reaction was stopped by the addition of a saturated solution of $Na_2S_2O_3$. The aqueous layer was extracted with ethyl acetate (3x20 ml), the combined organic layer was washed with water (2x20 ml), with brine (1x20 ml) dried on $MgSO_4$, filtered and concentrated under vacuum. The crude reaction mixture was purified by chromatography (hexane → hexane: ethyl acetate = 1:1) and compound **81** (101 mg, 0.24 mmol, 47%) was obtained as a light yellow oil.

R_f (hexane: ethyl acetate = 4:1): 0.62.

81*β*: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.51 – 7.26 (m, 5H, $H_{aromatic}$); 5.60 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 4.64 – 4.57 (m, 2H, H-2, H-3); 4.43 (d, 1H, $J_{4,5}$ = 9.6 Hz, $J_{4,3}$ = 5.6 Hz, H-4); 4.29 (m, 1H, H-5); 3.93 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{6a,5}$ = 2.8 Hz, CH_2, H-6a); 3.79 (dd, 1H, $J_{6a,6b}$ = 12.0, $J_{6b,5}$ = 5.2 Hz, CH_2, H-6b); 1.60 (s, 3H, CH_3); 1.37 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.2 ($C_{aromatic}$); 132.1 – 128.1 ($\underline{C}H_{aromatic}$); 111.60 (C); 89.51 ($\underline{C}H$, C-1); 78.23 ($\underline{C}H$, C-3); 71.19 ($\underline{C}H$, C-5); 70.41 ($\underline{C}H$, C-4); 62.97 ($\underline{C}H_2$, C-6); 28.37 ($\underline{C}H_3$), 26.77 ($\underline{C}H_3$), 25.59 ($\underline{C}H$, C-2).

Phenyl 5-*O*-Benzyl-2-deoxy-2-iodo-3,4-*O*-isopropylidene-1-thio-α-D-*altro*-septanoside (82).



As described in *general method A of the iodium–induced cyclization*, sodium bicarbonate (90 mg, 1.07 mmol) and NIS (241 mg, 1.07 mmol) were added to a solution of compound **78** (276 mg, 0.71 mmol) in acetonitrile (14.3 ml, 0.05 M) and cooled to –30 ºC and. The reaction was monitored by TLC analysis. The reaction was stirred for 24 hours at –10 ºC, then at room temperature for 30 hours and was finally warmed up at 35 ºC for 24h. The reaction was quenched with a solution of $Na_2S_2O_3$. The aqueous layer was extracted with ethyl acetate (3x20 ml), the combined organic layer was washed with

water (2x20 ml), with brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The reaction mixture was separated by chromatography (hexane → hexane: ethyl acetate = 1:1) and compound **82** (45 mg, 0.09 mmol, 12%) was obtained as a light yellow oil. Starting material (109 mg, 0.28 mmol, 40 %) were also recovered.

R_f (hexane: ethyl acetate = 8:1): 0.38.

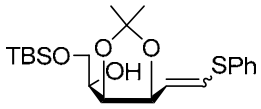
$[\alpha]_D^{25}$ 156º (*c* 0.16, DCM).

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50 – 7.26 (m, 10H, $H_{aromatic}$); 5.56 (d, 1H, $J_{1,2}$ = 8.8 Hz, H-1); 5.13 (t, 1H, $J_{2,3}$ = 8.8 Hz, H-2); 4.73 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.70 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.65 (dd, 1H, $J_{3,4}$ = 7.6 Hz, H-3); 4.58 (dd, 1H, $J_{6a,6b}$ = 13.6 Hz, $J_{6a,5}$ = 1.0 Hz, H-6a); 4.49 (dd, 1H, $J_{4,5}$ = 2.0 Hz, H-4); 4.13 (m, 1H, H-5); 3.81 (dd, 2H, $J_{6a,6b}$ = 13.6 Hz, $J_{6b,5}$ = 5.2 Hz, H-6b); 1.60 (s, 3H, CH_3); 1.40 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3 ($C_{aromatic}$); 131.5 – 127.6 ($\underline{C}H_{aromatic}$); 108.3 (C); 93.0 (<u>C</u>H, C-1); 80.1 (<u>C</u>H, C-3); 77.8 (<u>C</u>H, C-5); 76.9 (<u>C</u>H, C-4); 73.5 ($\underline{C}H_2Ph$); 63.5 ($\underline{C}H_2$, C-6); 32.0 (<u>C</u>H, C-2); 26.4 ($\underline{C}H_3$); 23.9 ($\underline{C}H_3$).

HRMS (TOF MS ES+): calcd for $C_{22}H_{25}O_4NaSI$ (MNa+): 535.0416; found: 535.0413.

Anal. Calcd for $C_{22}H_{25}IO_4S$: 51.57 C, 4.92 H, 6.26 S. Found: 51.90 C, 4.70 H, 6.10 S.

(*Z/E*)-6-*O*-*tert*-Butyldimethylsilyl-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylsulfanyl-D-*lyxo*-hex-1-enitol (84).



Folloing the *general method of the WH olefination reactions*, *n*-BuLi (13 ml, 21.00 mmol, 1.6 M in hexane) was added slowly to a solution of (phenylsulfanylmethyl)diphenylphosphine oxide (**42**) (6.49 g, 20.00 mmol) in anhydrous THF (20 ml, 0.25 M) at –30 ºC. The mixture was stirred under an argon atmosphere until the occurrence of a intensive orange colour. The reaction mixture was further stirred for one hour at this temperature. A solution of **83** (1.52 g, 5.00 mmol) in anhydrous THF (10.0 ml, 0.5 M) was then added. The reaction mixture was allowed to warm up to room temperature. After full conversion (24 h) and work-up, the resulting product was purified by flash chromatography (hexane: ethyl acetate = 6:1) and compound **84** (1.14 g, 2.78 mmol, 56%, an *E*/*Z* inseparable mixture, *E*/*Z* = 4:1) was obtained as a yellow oil.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

84*E*: R_f (hexane: ethyl acetate = 6:1): 0.67.

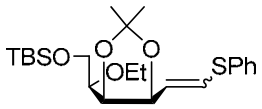
^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50 – 7.20 (m, 5H, $H_{aromatic}$); 6.52 (d, 1H, $J_{1,2}$ = 14.8 Hz, H-1); 5.95 (dd, 1H, $J_{2,3}$ = 7.2 Hz, H-2); 4.05 (dd, 1H, $J_{4,5}$ = 4.0 Hz, H-4); 4.68 (dd, 1H, $J_{3,4}$ = 6.4 Hz, H-3); 4.13 (m, 1H, H-5); 3.93 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{6a,5}$ = 5.2 Hz, H-6a); 3.81 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{6a,5}$ = 6.8 Hz, H-6b); 2.35 (d, 1H, $J_{OH,5}$ = 5.6 Hz, OH); 1.46 (s, 3H, CH_3);, 1.35 (s, 3H, CH_3); 0.92 (s,

9H, CH_3); 0.12 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.2 ($C_{aromatic}$); 130.8 – 126.9 ($CH_{aromatic}$); 127.5 (CH, C-1); 126.9 (CH, C-2); 108.8 (C, isopropylidene); 80.9 (CH, C-5); 80.0 (CH, C-4); 78.5 (CH, C-3); 61.6 (CH_2, C-6); 27.4 (CH_3); 26.0 (CH_3); 25.2 (CH_3).

84*Z*: R_f (hexane: ethyl acetate = 6:1): 0.67.

^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50 – 7.20 (m, 5H, $H_{aromatic}$); 6.48 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1); 6.04 (dd, 1H, $J_{2,3}$ = 7.2 Hz, H-2); 5.17 (t, 1H, $J_{3,4}$ = 7.2 Hz, H-3); 4.32 (dd, 1H, $J_{4,5}$ = 2.4 Hz, H-4); 4.13 (m, 1H, H-5); 3.93 (m, 1H, H-6a); 3.81 (m, 1H, H-6b); 2.40 (d, 1H, $J_{OH,5}$ = 6.0 Hz, OH); 1.46 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 0.92 (s, 9H, CH_3); 0.12 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: Could not be determined.

(*Z/E*)-6-*O*-*tert*-Butyldimethylsilyl-5-*O*-ethyl-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylsulfanyl-D-*lyxo*-hex-1-enitol (85).



A solution of compound **84** (244 mg, 0.60 mmol) in anhydrous THF (2.4 ml, 0.25 M), was added to a suspension of sodium hydride (16 mg, 0.66 mmol) in THF at room temperature. The reaction mixture was further stirred for an hour at room temperature and subsequently anhydrous ethyl bromide (67 μl, 0.90 mmol) was slowly added. The reaction mixture was stirred overnight, and the evolution of the reaction was monitored by TLC. The reaction was then quenched with a saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3x20 ml), the combined organic layer washed with water (2x20 ml), with brine (1x20 ml), dried on $MgSO_4$, filtered and concentrated under vacuum. The mixture was purified by chromatography (hexane → hexane: ethyl acetate = 1:1) and compound **85** (361 mg, 0.74 mmol, 37%, an *E/Z* inseparable mixture, *E/Z* = 4:1) was obtained as a light yellow oil.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

85*E*: R_f (hexane: ethyl acetate = 8:1): 0.56.

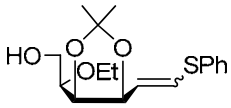
^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50 – 7.20 (m, 5H, $H_{aromatic}$); 6.45 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.90 (1 dd, H, $J_{2,3}$ = 7.8 Hz, H-2); 4.63 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3); 4.28 (dd, 1H, $J_{4,5}$ = 4.0 Hz, H-4); 3.74 – 3.64 (m, 3H, H-6a, CH_2 (Et)); 3.43 (dd, 1H, $J_{6a,6b}$ = 9.2 Hz, $J_{6b,5}$ = 7.2 Hz, H-6b); 3.26 (m, 1H, H-5); 1.46 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 1.21 – 1.14 (m, 3H, CH_3); 0.92 (s, 9H, CH_3); 0.12 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.5 ($C_{aromatic}$); 130.2 – 127.0 ($CH_{aromatic}$); 126.9 (CH, C-1); 126.6 (CH, C-2); 109.1 (C); 78.4 (CH, C-5); 77.6 (CH, C-3); 76.8 (CH, C-4); 66.7 (CH_2); 62.6 (CH_2, C-6); 29.8 (CH_3); 27.4 (CH_3); 26.0 (CH_3); 25.2 (CH_3).

85*Z*: R_f (hexane: ethyl acetate = 8:1): 0.55.

^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50 – 7.20 (m, 5H, $H_{aromatic}$); 6.48 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1); 6.04 (dd, 1H, $J_{2,3}$ = 7.2 Hz, H-2); 5.17 (t, 1H, $J_{3,4}$ = 7.2 Hz, H-3); 4.32 (dd, 1H, $J_{4,5}$ = 2.4 Hz, H-4);

3.74 – 3.26 (5H, m, H-5, H-6a, H-6b, CH_2 (Et)); 1.46 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 1.21 – 1.14 (m, 3H, CH_3); 0.92 (s, 9H, CH_3); 0.12 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: Could not be determined.

(*Z/E*)-5-*O*-Ethyl-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylsulfanyl-D-*lyxo*-hex-1-enitol (86).



Compound **85** (150 mg, 0.34 mmol) was dissolved in THF (3.0 ml) and *tetra*-butylammonium fluoride (118 mg, 0.38 mmol) was added to a solution. The reaction mixture was stirred at room temperature and the reaction was monitored by TLC. After one hour, the reaction was quenched with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (3x20 ml), the combined organic layer was washed with water (2x20 ml), with brine (1x20 ml) dried on $MgSO_4$, filtered and concentrated under vacuum. The reaction mixture was separated by chromatography (hexane → hexane: ethyl acetate = 1:1) and compound **86** (89 mg, 0.28 mmol, 81%, an *E/Z* inseparable mixture, *E/Z* = 4:1) was obtained as a light yellow oil.

Spectroscopic data obtained from *E*/*Z* diastereoisomeric mixture.

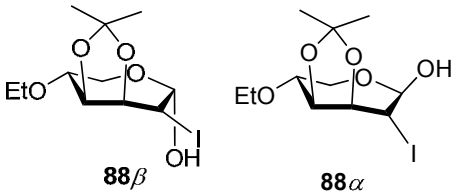
86*E*: R_f (hexane: ethyl acetate = 4:1): 0.51.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40 – 7.24 (m, 5H, $H_{aromatic}$); 6.54 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.96 (dd, 1H, $J_{2,3}$ = 6.4 Hz, H-2); 4.78 (dd, 1H, $J_{3,4}$ = 5.6 Hz, H-3); 4.06 (dd, 1H, $J_{4,5}$ = 8.8 Hz, H-4); 3.86 – 3.41 (m, 5H, H-5, H-6a, H-6b, CH_2 (Et)); 2.46 (d,1H, $J_{OH,6}$ = 5.2 Hz, OH); 1.45 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 1.22 – 1.04 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.5 ($C_{aromatic}$); 130.2 – 127.0 ($\underline{C}H_{aromatic}$); 126.9 (<u>C</u>H, C-1); 126.6 (<u>C</u>H, C-2); 109.1 (C); 78.4 (<u>C</u>H, C-5); 77.6 (<u>C</u>H, C-4); 76.8 (<u>C</u>H, C-3); 69.7 ($\underline{C}H_2$); 61.6 ($\underline{C}H_2$, C-6); 27.4 ($\underline{C}H_3$); 26.0 ($\underline{C}H_3$); 25.2 ($\underline{C}H_3$).

86*E*: R_f (hexane: ethyl acetate = 4:1): 0.51.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50 – 7.20 (m, 5H, $H_{aromatic}$); 6.48 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1); 6.04 (dd,1H, $J_{2,3}$ = 7.2 Hz, H-2); 5.17 (t, 1H, $J_{3,4}$ = 7.2 Hz, H-3); 4.32 (dd, 1H, $J_{4,5}$ = 2.4 Hz, H-4); 3.74 – 3.26 (m, 5H, H-5, H-6a, H-6b, CH_2 (Et)), 2.51 (d, 1H, $J_{OH,6}$ = 5.2 Hz, OH); 1.46 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 1.21 – 1.14 (m, 3H, CH_3).

2-Deoxy-5-*O*-ethyl-3,4-*O*-isopopylidene-2-iodo-β-D-*galacto*-septanose (88β) and 2-Deoxy-5-*O*-ethyl-3,4-*O*-isopropylidene-2-iodo-α-D-*galacto*-septanose (88α).



88β **88α**

As described in *general method A of the iodium–induced cyclization*, a solution of compound **86** (89 mg, 0.28 mmol) in acetonitrile (5.5 ml, 0.05M) was cooled to –30 ºC, then was $NaHCO_3$ added at –10 ºC. Then reaction mixture was further stirred at room temperature for 30 hours and finally warmed up at 35 ºC for 24 hours. The reaction was then quenched with the addition of a saturated solution of $Na_2S_2O_3$. The aqueous layer was extracted with ethyl acetate (3x20 ml), the combined organic layer was washed with water (2x20 ml), with brine (1x20 ml) dried on $MgSO_4$, filtered and concentrated under vacuum. The mixture was separated by chromatography (hexane → hexane:ethyl acetate = 1:1) and compounds **88β** and **88α** (23 mg, 0.10 mmol, 36%, an α/β inseparable mixture, α/β = 1:1.4) were obtained as a light yellow oil. Starting material **86*Z*** (29 mg, 0.09 mmol, 32 %) was also recovered.

Spectroscopic data obtained from **88α/β** stereoisomeric mixture.

R_f (hexane:ethyl acetate = 4:1): 0.37.

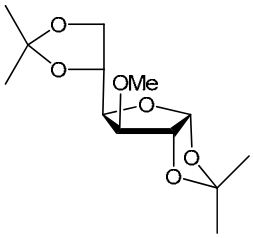
88α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.48 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1); 4.72 (dd, 1H, $J_{3,4}$ = 8.0 Hz, H-3); 4.25 (dd, 1H, $J_{4,5}$ = 7.2 Hz, H-4); 4.18 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2); 3.95 (dd, 1H, $J_{6a,6b}$ = 13.2 Hz, $J_{6a,5}$ = 9.6 Hz, H-6a); 3.57 (dd, 1H, $J_{6a,6b}$ = 13.2 Hz, $J_{6b,5}$ = 2.0 Hz, H-6b); 3.78 – 3.74 (m, 1H, CH_2 (Et)); 3.59 – 3.54 (m, 1H, CH_2 (Et)); 3.47 (m, 1H, H-5); 1.51 (s, 3H, CH_3); 1.39 (s, 3H, CH_3); 1.33 – 1.18 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 108.2 (C); 96.9 (CH, C-1); 80.4 (CH, C-4); 78.8 (CH, C-5); 76.5 (CH, C-3); 66.1 (CH_2Me); 60.7 (CH_2, C-6); 35.4 (CH, C-2); 27.7 (CH_3); 24.9 (CH_3); 15.6 (CH_3, Et).

88β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.41 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1); 4.41 (dd, 1H, $J_{3,4}$ = 7.6 Hz, H-3); 4.33 (m, 1H, H-6a); 4.32 (dd, 1H, $J_{4,5}$ = 9.2 Hz, H-4); 4.10 (dd, 1H, $J_{2,3}$ = 11.2 Hz, H-2); 3.78 – 3.74 (m, 2H, H-5, CH_2 (Et)); 3.59 – 3.54 (m, 1H, CH_2 (Et)); 3.48 – 3.45 (m, 1H, H-6b); 1.51 (s, 3H, CH_3); 1.39 (s, 3H, CH_3); 1.33 – 1.18 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 109.1 (C); 98.1 (CH, C-1); 78.5 (CH, C-4); 78.1 (CH, C-5); 77.0 (CH, C-3); 67.0 (CH_2Me); 62.0 (CH_2, C-6), 32.5 (CH, C-2); 27.5 (CH_3); 24.5 (CH_3); 15.8 (CH_3, Et).

HRMS (TOF MS ES+): calcd for $C_{11}H_{19}O_5NaI$ (MNa+) 381.0175; found, 381.0180.

Anal. Calcd for $C_{11}H_{19}IO_5S$: 36.89 C, 5.35 H. Found: 37.55 C, 5.47 H.

1,2:5,6-di-*O*-Diisopropylidene-3-*O*-methyl-*α*-D-*gluco*-furanose (126).

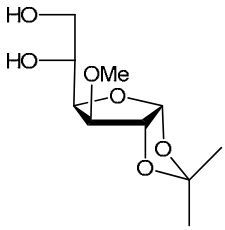


NaH (0.94 g, 23.51 mmol) was suspended in 80ml of THF when diacetone-D-glucose **125** (5.45 g, 20.94 mmol) was added in small portions at 0 ºC under argon. The mixture was stirred for one hour at room temperature then MeI was added (3.27 g, 23.04 mmol). The evolution of the reaction was monitored by TLC (hexane: ethyl acetate = 4:1). The reaction was then quenched with the addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate (3x20 ml), the combined organic layer was washed with water (2x20 ml), with brine (1x20 ml) dried on $MgSO_4$, filtered and concentrated under vacuum. The chromatographic purifycation (hexane: ethyl acetate = 4:1) afforded compound **126** (5.49 g, 20.01 mmol, 96%) as a syrup.

126: R_f (hexane: ethyl acetate = 4:1): 0.49.

RMN ^1H (D_3C-C(O)-CD_3, 400 MHz) δ in ppm: 5.86 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 4.57 (d, 1H, $J_{2,1}$ = 3.6 Hz, H-2); 4.30 (m, 1H, H-5); 4.06 – 4.11 (m, 2H, H-4, H-6); 4.00 (dd, 1H, $J_{6a,6b}$ = 8.8 Hz, $J_{6a,5}$ = 5.2 Hz, H-6a); 3.77 (d, 1H, $J_{3,4}$ = 2.8 Hz, H-3); 3.46 (s, 3H, OMe); 1.50 (s, 3H, Me_{ac}); 1.43 (s, 3H, Me_{ac}); 1.36 (s, 3H, Me_{ac}); 1.32 (s, 3H, Me_{ac}). RMN ^{13}C (D_3C-C(O)-CD_3, 100.5 MHz) δ in ppm: 111.74, 109.03 (C); 105.21 (C-1); 83.68 (C-3); 81.88 (C-2); 81.04 (C-4); 72.41 (C-5); 67.29 (C-6); 58.21 ($\underline{C}H_3$, OMe); 26.93 ($\underline{C}H_3$, Me_{ac}); 26.87 ($\underline{C}H_3$, Me_{ac}); 26.27 ($\underline{C}H_3$, Me_{ac}); 25.44 ($\underline{C}H_3$, Me_{ac}).

1,2-*O*-Isopropylidene-3-*O*-methyl-*α*-D-*gluco*-furanose (127).

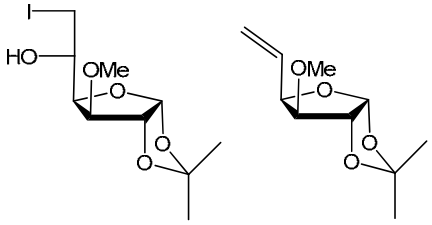


I_2 (1.43 g, 5.62 mmol) was added to a solution of compound **126 (**5.14 g, 18.72 mmol) in MeCN/H_2O = 100:1 (190 ml :1.9 ml) at room temperature. The reaction mixture was further stirred for 15h and was monitored by TLC analysis (hexane: ethyl acetate = 1:2). The reaction was quenched with saturated solution of $Na_2S_2O_3$. The aqueous layer was extracted with ethyl acetate (3x20 ml), the combined organic layer was washed with water (2x20 ml), with brine (1x20 ml) dried on $MgSO_4$, filtered and concentrated under vacuum. The chromatographic purifycation (hexane: ethyl acetate = 2:1) afforded compound **127** (4.20 g, 17.93 mmol, 96%) as a yellowish syrup.

127: R_f (hexane: ethyl acetate = 2:1): 0.28.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 5.79 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1); 4.62 (d, 1H, $J_{2,1}$ = 4.0 Hz, H-2); 4.02 (dd, 1H, $J_{4,5}$ = 8.8 Hz, $J_{4,3}$ = 3.0 Hz, H-4); 3.87 (d, 1H, $J_{OH,5}$ = 7.6 Hz, OH); 3.83 (m, 1H, H-5); 3.77 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3); 3.77 (ddd, 1H, $J_{6a,6b}$ = 10.6 Hz, $J_{6,OH}$ = 5.6 Hz, $J_{6,5}$ = 2.8 Hz, H-6a); 3.61 (t (dd), 1H, $J_{OH,6a}$ = 5.6 Hz, OH); 3.52 (dt (ddd),1H, $J_{6a,6b}$ = 10.8 HZ, $J_{6b,5}$ = 6.0 Hz, $J_{6b,OH}$ = 6.0 Hz, H-6b); 3.41 (s, 3H, OMe); 1.40 (s, 3H, Me_{ac}); 1.27 (s, 3H, Me_{ac}). RMN ^{13}C ($CDCl_3$, 100.5 MHz) δ in ppm: 111.80 (C); 106.10 (C-1); 84.69 (C-3); 82.22 (C-2); 80.94 (C-4); 69.46 (C-5); 65.08 (C-6); 58.02 ($\underline{C}H_3$, OMe); 27.11 ($\underline{C}H_3$, Me_{ac}); 26.46 ($\underline{C}H_3$, Me_{ac}).

6-Deoxy-6-iodo-1,2-*O*-isopropylidene-3-*O*-methyl-*α*-D-*gluco*-furanose (128) and 5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-*α*-D-*xylo*-hex-5-enofuranose (129).



PPh_3 (6.72 g, 25.62 mmol), I_2 (6.50 g, 25.61 mmol) and imidazole (2.31 g, 33.94 mmol) were added to a solution of compound **127** (4.10 g, 17.08 mmol) in anhydrous DCM (190 ml) under argon, finally the reaction mixture was heated to reflux for 16h. The reaction was monitored by TLC (hexane: ethyl acetate = 4:1). After the reaction completed was quenched with saturated solution of $Na_2S_2O_3$. The aqueous layer was extracted with DCM (3x20 ml), the combined organic layer was washed with water (2x20 ml), with brine (1x20 ml) dried on $MgSO_4$, filtered and concentrated under vacuum. The chromatographic purifycation (hexane: ethyl acetate = 4:1) afforded compound **128** (3.06 g, 8.88 mmol, 52%) as a yellowish syrup, and compound **129** (1.50 g, 7.52 mmol, 44%) as a yellowish solid.

128: R_f (hexane: ethyl acetate = 4:1): 0.36.

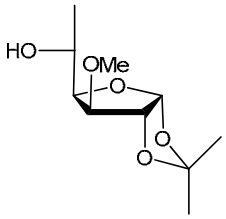
RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 5.90 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 4.61 (d, 1H, $J_{2,1}$ = 3.6 Hz, H-2); 4.09 (dd, 1H, $J_{4,5}$ = 8.0 Hz, $J_{4,3}$ = 3.0 Hz, H-4); 3.91 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3); 3.78 (m, 1H, H-5); 3.56 (dd, 1H, $J_{6a,6b}$ = 10.4 Hz, $J_{6a,5}$ = 3.2 Hz, H-6a); 3.47 (s, 3H, OMe); 3.40 (dd, 1H, $J_{6a,6b}$ = 10.4 Hz, $J_{6b,5}$ = 7.0 Hz, H-6b); 2.52 (d, 1H, $J_{OH,5}$ = 6.0 Hz, OH); 1.51 (s, 3H, Me_{ac}); 1,34 (s, 3H, Me_{ac}). RMN ^{13}C ($CDCl_3$, 100.5 MHz) δ in ppm: 112.22 (C_{quat}); 105.29 (C-1); 84.10 (C-3); 81.89 (C-4); 81.58 (C-2); 68.40 (C-5); 58.21 ($\underline{C}H_3$, OMe); 27.09 ($\underline{C}H_3$, Me_{ac}); 26.56 ($\underline{C}H_3$, Me_{ac}); 13.68 (C-6).

129: R_f (hexane:ethyl acetate = 4:1): 0.68.

RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 5.95 (m, 2H, H-1, H-5); 5.44 (ddd, 1H, $J_{6a,5}$ = 17.2 Hz, $J_{6a,4}$ = 2.6 Hz, $J_{6a,6b}$ = 1.6 Hz, H-6a); 5.31 (ddd, 1H, $J_{6b,4}$ = 10.8 Hz, $J_{6b,5}$ = 2.6 Hz, $J_{6b,6a}$ = 1.6 Hz, H-6b); 4.62 (m, 2H, H-2, H-4); 3.67 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-3); 3.41 (s, 3H, OMe); 1.51 (s, 3H, Me_{ac}); 1.33 (s, 3H,

Me_{ac}). RMN ^{13}C ($CDCl_3$, 100.5 MHz) δ in ppm: 132.19 (C-5); 119.07 (C-6); 111.66 (C); 104.93 (C-1); 86.09 (C-3); 82.18, 81.49 (C-2, C-4); 58.38 ($\underline{C}H_3$, OMe); 26.95 ($\underline{C}H_3$, Me_{ac}); 26.38 ($\underline{C}H_3$, Me_{ac}).

6-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-*α*-D-*gluco*-furanose (131).

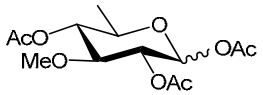


Bu_3SnH (2.2 ml, 1.10 eq) and AIBN (0.05 eq) were added to compound **128** (2.93 g, 8.51 mmol) in deoxygenated toluene (26 ml). The reaction mixture was heated to reflux and was monitored by TLC (hexane: ethyl acetate = 2:1). After the reaction completed the reaction mixture was concentrated in vacuum the flash chromatography (from hexane to hexane: ethyl acetate = 1:1) furnished compound **131** (1.62 g, 7.40 mmol, 87%) as a yellow syrup.

131: R_f (hexane: ethyl acetate = 2:1): 0.26.

RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 5.96 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1); 4.62 (d, 1H, $J_{2,1}$ = 4.0 Hz, H-2); 4.10 (sext, 1H, $J_{5,4}$ = 6.4 Hz, $J_{5,6}$ = 6.4 Hz, $J_{5,OH}$ = 6.4 Hz, H-5); 3.97 (dd, 1H, $J_{4,3}$ = 3.6 Hz, $J_{4,5}$ = 6.4 Hz, H-4); 3.90 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-3); 3.46 (s, 3H, OMe); 2.59 (d, 1H, $J_{10,5}$ = 6.8 Hz, H-10); 1.50 (s, 3H, Me_{ac}); 1.33 (s, 3H, Me_{ac}); 1.32 (d, 3H, $J_{6,5}$ = 6.8 Hz, H-6). RMN ^{13}C ($CDCl_3$, 100.5 MHz) δ in ppm: 111.70 (C); 105.21 (C-1); 85.05 (C-3); 83.19 (C-4); 81.31 (C-2); 66.13 (C-5); 57.74 ($\underline{C}H_3$, OMe); 26.89($\underline{C}H_3$, Me_{ac}); 26.80 ($\underline{C}H_3$, Me_{ac}); 20.85 (C-6).

1,2,4-tri-*O*-Acetyl-6-deoxy-3-*O*-methyl-*α,β*-D-glucose (132).



Compound **131** (1.50 g, 6.87 mmol) was dissolved in a mixture of H_2O/dioxane = 1:1 and amberlite-120 resin (2.01 g) was added. The reaction mixture was heated to 80 ºC for 6 h and the evolution of the reaction was monitored by TLC analysis (in ethyl acetate). The resin was removed with filtration and the dissolvent was removed in vacuum with the help of toluene. The reaction crude was dissolved in 100 ml Ac_2O and TEA (6.5 ml) was added. The reaction was monitored by TLC (in ethyl acetate) and after 7 h, the mixture was concentrated in vacuum. The subsequent flash chromatography afforded **132** (1.82 g, 5.98 mmol, 87%, an α/β inseparable mixture, α/β = 3:1) as a white solid.

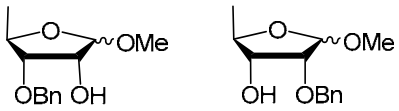
R_f (ethyl acetate): 0.75.

Spectroscopic data extracted from α/β mixture.

132α: RMN ^{1}H (CDCl$_3$, 400 MHz) δ in ppm: 5.62 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1); 5.08 (dd, 1H, $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 9.6 Hz, H-2); 4.84 (t (dd), 1H, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 9.6 Hz, H-3); 3.61 (m, 1H, H-5); 3.42 (s, 3H, OMe); 3.49 (t (dd), 1H, $J_{4,3}$ = 9.6 Hz, $J_{4,5}$ = 9.6 Hz, H-4); 2.10 (s, 9H, Me$_{ac}$); 1.22 (d, 3H, $J_{6,5}$ = 6.4 Hz, H-6). RMN ^{13}C (CDCl$_3$, 100.5 MHz) δ in ppm: 169 (C=O$_{ac}$); 92.05 (C-1); 81.36 (C-4); 73.67 (C-3); 71.44 (C-2); 71.21 (C-5); 59.18 (CH$_3$, OMe); 20.9 (3CH$_3$, Me$_{ac}$); 17.36 (C-6).

132β: RMN ^{1}H (CDCl$_3$, 400 MHz) δ in ppm: 6.23 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 4.97 (1H, dd, $J_{2,1}$ = 4.0 Hz, $J_{2,3}$ = 10.0 Hz, H-2); 4.79 (t (dd), 1H, $J_{3,2}$ = 10.0 Hz, $J_{3,4}$ = 10.0 Hz, H-3); 3.91 (m, 1H, H-5); 3.67 (t (dd), 1H, $J_{4,3}$ = 10.0 Hz, $J_{4,5}$ = 10.0 Hz, H-4); 3.47 (s, 3H, OMe); 2.10 (s, 9H, Me$_{ac}$); 1.17 (d, 3H, $J_{6,5}$ = 6.4 Hz, H-6). RMN ^{13}C (CDCl$_3$, 100.5MHz) δ in ppm: 169 (C=O$_{ac}$); 89.36 (C-1); 78.13 (C-4); 74.26 (C-3); 71.49 (C-2); 68.28 (C-5); 60.13 (CH$_3$, OMe); 20.9 (3CH$_3$, Me$_{ac}$); 17.42 (C-6).

Methyl 3-*O*-Benzyl-5-deoxy-α,β-D-ribofuranoside (133) and Methyl 2-*O*-Benzyl-5-deoxy-α,β-D-ribofuranoside (134).



133 **134**

A 1.0 M solution of DIBAL-H in DCM (50 ml, 50 mmol) was added dropwise to a solution of ribofuranoside **159** (2.4 g, 10.0 mmol) in DCM (50 ml, 0.1 M) at –78 ºC. The reaction mixture was left to warmed to rt and the evolution of the reaction was monitored by TLC (hexane: ethyl acetate = 3:1) until the starting product was consumed. After 30 minutes at rt, the reaction was quenched by adding the reaction mixture to methanol (100 ml) at 0 ºC and allowed to warm to rt. The white gel obtained was dissolved with the addition of 100 ml of 10 w/v% KOH solution The aqueous phase was extracted with ethyl acetate (3x50ml). The combined organic extracts were washed with saturated NH_4Cl solution (2x30 ml), water (2x30 ml), brine (1x30 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by radial chromatography (hexane: ethyl acetate = 3:1) to afford 2.4 g, 9.9 mmol (99%) of **133** and **134** mixture as a yellowish syrup. The mixture was separated by recrystallization (from hexane: ethyl acetate = 10:1) to furnish compound **133** (1.034 g, 4.34 mmol, 43%), compound **134** (1.113 g, 4.67 mmol, 47%) and the mixture of both (216.8 mg, 0.91 mmol, 9%).

R_f (hexane: ethyl acetate = 2:1): 0.38.

Spectroscopic data obtained from the α/β mixture.

133β: ^{1}H NMR (CDCl$_3$, 400 MHz) δ in ppm: 7.35 (m, 5H, H$_{aromatic}$); 4.82 (s, 1H, H-1); 4.61 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.55 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.13 (m, 1H, H-4); 4.04 (d, 1H, $J_{2,3}$ = 4.4 Hz, H-2); 3.83 (dd, 1H, $J_{3,4}$ = 6.4 Hz, H-3); 3.34 (s, 3H, OMe); 2.71 (dd, 1H, $J_{OH,2}$ = 2.8 Hz, OH); 1.31 (d, 3H, $J_{4,5}$ = 6.0 Hz, H-5). ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ in ppm: 137.91 (C$_{aromatic}$); 128.81, 128.43,

128.08 ($\underline{C}H_{aromatic}$); 108.48 (C-1); 84.1 (C-3); 77.49 (C-4); 73.70 (C-2); 72.99 ($\underline{C}H_2Ph$); 55.13 ($O\underline{C}H_3$); 21.04 (C-5).

133α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

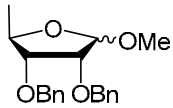
R_f (hexane: ethyl acetate = 2:1): 0.40.

Spectroscopic data obtained from the α/β mixture.

134β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.34 (m, 5H, $H_{aromatic}$); 4.86 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1); 4.73 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.61 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 3.99 (m, 1H, H-4); 3.93 (qd, 1H, $J_{3,4}$ = 5.2 Hz, H-3); 3.86 (dd, 1H, $J_{2,3}$ = 5.2 Hz, H-2); 3.35 (s, 3H, OMe); 2.63 (d, 1H, $J_{OH,3}$ = 8.4 Hz, OH); 1.31 (d, 3H, $J_{4,5}$ = 6.0 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 137.30 ($C_{aromatic}$); 128.72, 128.30, 128.07 ($\underline{C}H_{aromatic}$); 105.88 (C-1); 82.60 (C-2); 80.41 (C-4); 76.02 (C-3); 72.91 ($\underline{C}H_2Ph$); 55.20 ($O\underline{C}H_3$); 20.19 (C-5).

134α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

Methyl 2,3-di-*O*-Benzyl-5-deoxy-α,β-D-ribofuranoside (135).



NaH (88 mg, 2.20 mmol, 1.1 eq) was added to the mixture of **133** and **134** (477 mg, 2.00 mmol, 1.0 eq) in anhydrous THF (40 ml, 0.1 M) and the mixture was stirred for 1 hour. BnBr (239 μl, 376 mg, 2.20 mmol, 1.1 eq) ws added and the mixture finally was further stirred for 12 hours. The reaction was quenched with NH_4Cl solution (2x20 ml), water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The chromatographic purification afforded compound **135** (611 mg, 1.86 mmol, 93%).

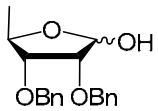
R_f (hexane: ethyl acetate = 4:1): 0.46.

Spectroscopic data extracted from α/β mixture.

135β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.35 (m, 5H, $H_{aromatic}$); 4.82 (s, 1H, H-1); 4.73 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.63 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.60 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.55 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.13 (m, 1H, H-4); 4.04 (d, 1H, $J_{2,3}$ = 4.4 Hz, H-2); 3.83 (dd, 1H, $J_{3,4}$ = 6.4 Hz, H-3); 3.34 (s, 3H, OMe); 1.31 (d, 3H, $J_{4,5}$ = 6.0 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 137.91 ($C_{aromatic}$); 128.81, 128.43, 128.08 ($\underline{C}H_{aromatic}$); 108.48 (C-1); 84.1 (C-3); 77.49 (C-4); 73.70 (C-2); 73.05 ($\underline{C}H_2Ph$); 72.91 ($\underline{C}H_2Ph$);55.13 ($O\underline{C}H_3$); 21.04 (C-5).

135α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

2,3-di-*O*-Benzyl-5-deoxy-α,β-D-ribofuranose (136).



Compound **135** (611 mg, 1.86 mmol) was dissolved in the mixture of AcOH/H_2O = 8:1 (18 ml) and was heated to 80 ºC for 6 hours till completion of reaction. The solvent mixture was eliminated in vacuum, and mixture was purified by radial chromatography (from hexane to hexane: ethyl acetate = 1:1) to afford compound **136** (456 mg, 1.45 mmol, 78%, an α/β inseparable mixture, α/β = 1:1.2).

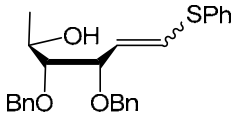
R_f (hexane: ethyl acetate = 3:1): 0.35.

Spectroscopic data extracted from α/β mixture.

Anal. Calcd for $C_{19}H_{22}O_4$: 72.59 C, 7.05 H. Found: 72.63 C, 7.03 H.

136: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.37 – 7.30 (m, 10H, $H_{aromatic}$ab); 5.35 (d, 1H, $J_{1a,OHa}$ = 3.6 Hz, H-1a); 5.30 (dd, 1H, $J_{1b,OHb}$ = 11.2 Hz, $J_{1b,2b}$ = 4.4 Hz, H-1b); 4.73 – 4.45 (m, 8H, $4CH_2Ph_a$, $4CH_2Ph_b$); 4.33 (qd, 1H, $J_{4b,3b}$ = 3.2 Hz, $J_{4b,5b}$ = 6.4 Hz, H-4b); 4.29 (d, 1H, $J_{OHb,H1}$ = 11.2 Hz, OHb); 4.23 (dq, 1H, $J_{4a,5a}$ = 6.4 Hz, $J_{4a,3a}$ = 7.6 Hz, H-4a); 3.93 (dd, 1H, $J_{2b,1b}$ = 4.4 Hz, $J_{2b,3b}$ = 4.8 Hz, H-2b); 3.85 (d, 1H, $J_{2a,3a}$ = 4.8 Hz, H-2a); 3.79 (dd, 1H, $J_{3a,4a}$ = 7.6 Hz, $J_{3a,2a}$ = 4.8 Hz, H-3a); 3.62 (dd, 1H, $J_{3b,2b}$ = 4.8 Hz, $J_{3b,4b}$ = 3.2 Hz, H-3b); 3.30 (da, 1H, $J_{OHa,1a}$ = 3.6 Hz, OHa); 1.32 (d, 3H, $J_{5a,4a}$ = 6.0 Hz, H-5a); 1.17 (d, 3H, $J_{5b,4b}$ = 6.4 Hz, H-5b). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 137.9 – 137.5 ($C_{aromatic}$); 128.7 – 128.0 ($CH_{aromatic}$); 100.2 (C-1a); 96.0 (C-1b); 82.8 (C-3a); 81.9 (C-3b); 80.5 (C-2a); 77.4 (C-2b); 77.3 (C-4a); 77.2 (C-4b); 73.0, 72.9 ($2\underline{C}H_2Ph_a$); 72.6, 72.4 ($2\underline{C}H_2Ph_b$); 20.7 (C-5a); 19.9 (C-5b).

(*E*/*Z*)-3,4-di-*O*-Benzyl-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (137).



Folloing the *general method of the WH olefination reactions*, a sulotion of *n*-BuLi in hexane (1.2 ml, 1.86 mmol, 1.6 M) was added to a solution of (diphenylphenylsulfanyl)methylphosphine oxide (**42**) (575 mg, 1.77 mmol) in anhydrous THF (2.4 ml, 0.74 M) at –78 ºC and the mixture was left to stir at low temperature for 30 min. A solution of **136** (150 mg, 0.44 mmol) in THF (2 ml, 0.22 M) was then added dropwise. The mixture was allowed to warm to room temperature overnight (17 h)and was quenched with saturated solution of NH_4Cl solution and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (hexane: ethyl acetate = 4:1) to afford the enolthioether **137** (126 mg, 0.30 mmol, 68%, an *E/Z* inseparable mixture, *E/Z* = 8:1).

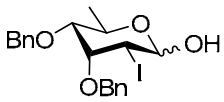
Data obtained from the *E*/*Z* diastereoisomeric mixture.

Anal. Calcd for $C_{26}H_{28}O_3S$: 74.25 C, 6.71 H, 7.62 S. Found: 74.20 C, 6.69 H, 7.60 S.

137*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.37 – 7.22 (m, 10H, $H_{aromatic}$); 6.50 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.81 (dd, 1H, $J_{2,3}$ = 8.4 Hz, $J_{2,1}$ = 15.2 Hz, H-2); 4.81 – 4.37 (m, 4H, $4CH_2Ph$); 4.03 (dd, 1H, $J_{3,2}$ = 8.4 Hz, $J_{3,4}$ = 6.8 Hz, H-3); 3.93 (m, 1H, H-5); 3.36 (dd, 1H, $J_{4,3}$ = 6.8 Hz, $J_{4,5}$ = 6.0 Hz, H-4); 2.64 (bs, 1H, OH); 1.21 (d, 3H, $J_{6,5}$ = 6.4 Hz, H-6). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4 – 127.2 ($C_{aromatic}$); 129.3 (C-1); 129.0 (C-2); 84.5 (C-4); 81.8 (C-3); 74.7 ($\underline{C}H_2Ph$); 70.6 ($\underline{C}H_2Ph$); 69.3 (C-5); 19.1 (C-6).

137*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.37 – 7.21 (m, 10H, $H_{aromatic}$); 6.59 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1); 5.92 (t, 1H, $J_{2,3}$= 9.2 Hz, $J_{2,1}$ = 9.2 Hz, H-2); 4.81 – 4.37 (m, 5H, $4CH_2Ph$, H-3); 3.93 (m, 1H, H-5); 3.49 (dd, 1H, $J_{4,3}$ = 5.6 Hz, $J_{4,5}$ = 6.4 Hz, H-4); 2.63 (bs, 1H, OH); 1.23 (d, 1H, $J_{6,5}$ = 6.8 Hz, H-6). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4 – 127.2 ($C_{aromatic}$); 129.4 (C-1); 129.2 (C-2); 84.7 (C-4); 77.6 (C-3); 74.6 ($\underline{C}H_2Ph$); 70.9 ($\underline{C}H_2Ph$); 69.1 (C-5); 19.3 (C-6).

3,4-di-*O*-Benzyl-2,6-dideoxy-2-iodo-α,β-D-allopyranose (139).

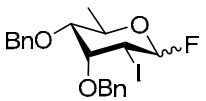


NIS (562 mg, 2.5 mmols, 2.5 eq) was added to a solution of the hex-1-enitol **137** (421 mg, 1.0 mmols, 1 eq) in a CH_3CN:H_2O = 10:1 mixture (20 ml, 0.05M) at –10 ºC. After stirring for 45 minutes the reaction was quenched with $Na_2S_2O_3$ and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexane: ethyl acetate = 3:1) to afford compound **139** (254 mg, 0.56 mmol, 56%, an α/β inseparable mixture, α/β = 1:12) as colourless syrup.

139β: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.47 – 7.22 (m, 10H, $H_{aromatic}$); 5.29 (d, 1H, $J_{1,2}$ = 5.2 Hz, H-1); 5.02 – 4.65 (m, 5H, $4CH_2Ph$, H-5); 4.61 (dd, 1H, $J_{2,1}$ = 5.2 Hz, $J_{2,3}$ = 2.6 Hz, H-2); 4.16 (dd, 1H, $J_{3,2}$ = 2.6 Hz, $J_{3,4}$ = 2.4 Hz, H-3); 3.29 (dd, 1H, $J_{4,3}$= 2.4 Hz, $J_{4,5}$ = 9.6 Hz, H-4); 2.31 (bs, 1H, OH); 1.26 (d, 3H, $J_{6,5}$ = 6.0 Hz, H-6). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 90.0 (C-1); 82.2 (C-4); 77.9 (C-3); 75.7, 72.1 ($\underline{C}H_2Ph$); 64.6 (C-5); 27.7 (C-2); 17.9 (C-6).

139α: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

3,4-di-*O*-Benzyl-2,6-dideoxy-2-iodo-α,β-D-allopyranosyl Fluoride (140).



DAST (74 μl, 101 mg, 0.76 mmol, 1.5 eq) was added to a solution of compound **139** (230 mg, 0.51 mmol, 1.00 eq) in anhydrous DCM (5 ml) at 0 ºC. The reaction mixture was warmed up to room temperature and was further stirred for 2 hours. The reaction was quenched with $NaHCO_3$ solution $Na_2S_2O_3$and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The mixture was purified by radial chromatography (from hexane to hexane: ethyl acetate = 3:1) to afford compound **140** (200 mg, 0.44 mmol, 86%, an α/β inseparable mixture, α/β = 1:12) as a yellowish syrup.

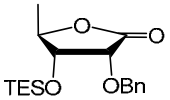
140: R_f (hexane: ethyl acetate = 6:1): 0.63.

Spectroscopic data extracted from α/β mixture.

140β: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.45 – 7.25 (m, 10H, $H_{aromatic}$); 5.55 (dd, 1H, $J_{1,F}$ = 52.4 Hz, $J_{1,2}$ = 8.8 Hz, H-1); 5.91 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.77 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.70 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.56 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 5.10 (m, 1H, H-5); 4.14 (d, 1H, $J_{3,4}$= 6.0 Hz, H-3); 3.99 (dd, 1H, $J_{2,3}$= 2.4 Hz, H-2); 3.35 (dd, 1H, $J_{4,5}$= 9.2 Hz, H-4); 1.32 (d, 3H, $J_{6,5}$= 6.0 Hz, H-6). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.09, 137.38 ($C_{aromatic}$); 128.82, 128.44, 128.41, 128.21, 128.1, 128.00 ($CH_{aromatic}$); 107.7 (*d*, $J_{F,C1}$= 209.8 Hz, C-1); 81.3 (C-4); 77.9 (*d*, $J_{F,C3}$= 6.8 Hz, C-3); 75.87, 72.65 ($\underline{C}H_2Ph$); 70.4 (*d*, $J_{F,C5}$ = 4.6 Hz, C-5); 29.6 (*d*, $J_{F,C2}$ = 82.3 Hz, C-2); 18.00 (C-6).

140α: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

2-*O*-Benzyl-5-deoxy-3-*O*-triethylsilyl-D-*ribono*-1,4-lactone (146).[142]



Following *the general procedure of silylation*, 2-*O*-benzyl-5-deoxy-D-*ribono*-1,4-lactone **144** (480 mg, 19.3 mmols, 1 eq), Et_3N (0.48 mg, 3.46 mmols, 1.6 eq), TESCl (0.54 ml, 3.24 mmols, 1.5 eq) and DMAP (198 mg, 1.62 mmol, 0.75 eq) in anhydrous DCM (9.3 ml, 0.25 M) was reacted at rt for 8 h. Column chromatography (hexane: ethyl acetate = 3:1) of the crude afforded **146** (725 mg, 100%) as a yellowish syrup.

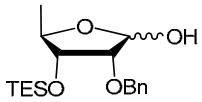
Anal. Calcd for $C_{18}H_{28}O_4Si$: 64.25 C, 8.39 H. Found: 64.22 C, 8.40 H.

$[\alpha]^{20}_D$= +46.4 (*c* 1.00, DCM).

146: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.40 – 7.26 (m, 5H, $H_{aromatic}$); 4.93 (d, 1H, J_{AB} = 11.8 Hz, CH_2Ph); 4.76 (d, 1H, J_{AB} = 11.8 Hz, CH_2Ph); 4.45 (qd, 1H, $J_{4,3}$ = 2.6 Hz, $J_{4,5}$ = 6.8 Hz, H-4); 4.07 (m, 2H, H-2, H-3); 1.32 (d, 3H, $J_{5,4}$ = 6.8 Hz, H-5); 0.94 (t, 9H, $J_{CH3,CH2}$ = 8.0 Hz, CH_{3Si}); 0.60 (q, 6H, $J_{CH2,CH3}$ = 8.0 Hz, CH_{2Si}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ en ppm: 173.0 (C=O); 136.8 ($C_{aromatic}$);

128.3, 128.1, 127.9 ($\underline{C}H_{aromatic}$); 81.5 (C-4); 73.9 (C-2); 74.0 (C-3); 72.0 ($\underline{C}H_2Ph$); 17.8 (C-5); 6.54 ($\underline{C}H_{3Si}$); 4.60 ($\underline{C}H_{2Si}$).

2-*O*-Benzyl-5-deoxy-3-*O*-triethylsilyl-α,β-D-ribofuranose (147).[142]



The lactone **146** (550 mg, 1.63 mmols) was reduced following the general procedure for 3 h at –78ºC. Column chromatography of the residue (hexane: ethyl acetate = 1:1) afforded the furanose **147** (530 mg, 96 %, an α/β inseparable mixture, α/β = 1:3) as yellowish syrup.

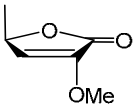
Spectroscopic data from α/β mixture:

Anal. Calcd for $C_{18}H_{30}O_4Si$: 63.87 C, 8.93 H. Found: 63.83 C, 8.91 H.

147α: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.39 – 7.26 (m, 5H, $H_{aromatic}$); 5.29 (d, 1H, $J_{1,OH}$ = 3.2 Hz, H-1); 4.76 – 4.67 (m, 2H, $2CH_2Ph$); 4.09 (dq, 1H, $J_{4,5}$ = 6.4 Hz, $J_{4,3}$ = 7.6 Hz, H-4); 4.04 (d, 1H, $J_{OH,1}$ = 3.2 Hz, OH); 4.02 (dd, 1H, $J_{3,2}$ = 4.4 Hz, $J_{3,4}$ = 7.6 Hz, H-3); 3.71 (d, 1H, $J_{2,3}$ = 4.4 Hz, H-2); 1.32 (d, 3H, $J_{5,4}$ = 6.4 Hz, H-5); 0.95 (m, 9H, CH_{3Si}); 0.67-0.65 (m, 6H, CH_{2Si}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 137.7 ($C_{aromatic}$); 128.5, 128.0, 127.9 ($\underline{C}H_{aromatic}$); 96.1 (C-1); 83.1 (C-2); 80.1 (C-4); 77.2 (C-3); 72.7 ($\underline{C}H_2Ph$); 20.1 (C-5); 6.98 ($\underline{C}H_{3Si}$); 4.60 ($\underline{C}H_{2Si}$).

147β: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.38 – 7.28 (m, 5H, $H_{aromatic}$); 5.27 (dd, 1H, $J_{1,OH}$ = 11.6 Hz, $J_{1,2}$ = 4.0 Hz, H-1); 4.76 – 4.64 (m, 2H, $2CH_2Ph$); 4.45 (d, 1H, $J_{OH,1}$ = 11.6 Hz, OH); 4.21 (qd, 1H, $J_{4,5}$ = 6.8 Hz, $J_{4,3}$ = 2.8 Hz, H-4); 3.88 (dd, 1H, $J_{3,4}$ = 2.8 Hz, $J_{3,2}$ = 4.4 Hz, H-3); 3.79 (dd, 1H, $J_{2,1}$ = 4.0 Hz, $J_{2,3}$ = 4.4 Hz, H-2); 1.17 (d, 1H, $J_{5,4}$ = 6.8 Hz, H-5); 0.97 (m, 9H, CH_{3Si}); 0.67 – 0.60 (m, 6H, CH_{2Si}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3 ($C_{aromatic}$); 128.6, 128.1, 128.0 ($\underline{C}H_{aromatic}$); 100.0 (C-1); 80.1 (C-4); 78.5 (C-4); 77.5 (C-2); 76.9 (C-3); 72.7($\underline{C}H_2Ph$); 19.6 (C-5); 6.91 ($\underline{C}H_{3Si}$); 4.60 ($\underline{C}H_{2Si}$).

3,5-Dideoxy-2-*O*-methyl-D-*threo*-2-en-1,4-lactone (150).[142]



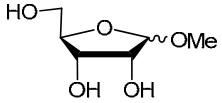
In a round-bottomed flask, wrapped with aluminium foil, MeI (1.3 ml, 21 mmol, 7 eq) was addedd to a solution of lactone **143** (396 mg, 3 mmol, 1 eq) in anhydrous DMF (5 ml, 0.6 M). Then freshly prepared Ag_2O (2.1 g, 9 mmol, 3eq) was added in portions with vigorous stirring. The mixture was stirred at rt for 5 h subsequently filtered through celite. The filtrate was evaporated, quenched with H_2O and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The crude product

was purified by column chromatography using hexane: ethyl acetate = 2:1 as the eluent to afford compound **150** (351 mg, 91%) as yellowish syrup.

Anal. Calcd for $C_6H_8O_3$: 56.24 C, 6.29 H. Found: 56.27 C, 6.30 H

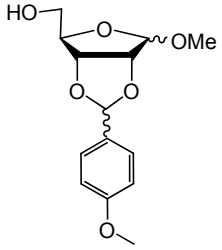
150: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 6.17 (d, 1H, $J_{3,4}$ = 2.0 Hz, H-3); 5.07 (qd, 1H, $J_{4,5}$ = 6.4 Hz, $J_{4,3}$ = 1.2 Hz, H-4); 3.81 (s, 3H, OMe); 1.45 (d, 3H, $J_{5,4}$ = 6.5 Hz, H-5). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 167.7 (C=O); 146.8 (C-2); 118.2 (C-3); 75.4 (C-4); 58.0 (OMe); 20.3 (C-5).

Methyl α,β–D-Ribofuranoside (151).



Acatalytic amount of cc. H_2SO_4 (0.5 ml, 98% v/v) was added to a solution of α,β-D-ribofuranose **90** (30.26 g, 200 mmol) in anhydrous MeOH (200 ml). The mixture was stirred for 48 h at 5 ºC until starting material was consumed (TLC analysis). The reaction was quenched adding portions of NaOMe and shaking vigorously until neutral pH was reached. The suspension was filtrated and concentrated under vacuum. The afforded crude product was used in the next reaction step.

Methyl 2,3-*O*-*p*-Methoxybenzylidene-α,β-D-ribofuranoside (152).



Anhydrous $ZnCl_2$ (13.1 g, 200 mmol) and anisaldehyde (*p*-methoxybenzaldehyde, 13.4 ml, 14.98 g, 110 mmol) were added to a solution of ribofuranoside **151** (16.15 g, 100 mmol) anhydrous MeCN (50 ml). The mixture was stirred for 48 h at rt until starting material was consumed (TLC analysis). The reaction was quenched with $NaHCO_3$ solution and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (hexane: ethyl acetate = 2:1) to afford the ribofuranoside **152** (15.06 g, 53.36 mmol, 53% in two steps) as a white solid.

R_f (hexane: ethyl acetate = 2:1): 0.40.

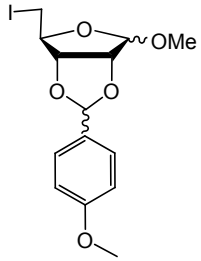
Spectroscopic data obtained from the α/β mixture.

152-*major*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.38 (d, 2H, J = 8.4 Hz, $H_{aromatic}$), 6.90 (d, 2H, J = 8.4 Hz, $H_{aromatic}$); 5.92 (s, 1H, $ArCHO_2$); 5.09 (s, 1H, $J_{1,2}$ = 0.0 Hz, H-1); 4.97 (d, 1H, $J_{2,3}$ = 6.0 Hz, H-

2); 4.71 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.52 (qd, 1H, $J_{4,5}$ = 3.2 Hz, H-4); 3.80 (s, 3H, OMe); 3.68 (d, 3H, H-5); 3.47 (s, 3H, OMe); 3.20 (dd, 1H, $J_{OH,5}$ = 9.2, 3.2 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 160.78, 128.33 ($C_{aromatic}$); 128.21, 113.94 ($\underline{C}H_{aromatic}$); 109.29 (C-1); 105.86 (Ac$\underline{C}HO_2$); 88.23 (C-4); 85.09 (C-3); 81.07 (C-2); 64.16 (C-5); 55.70 (ArO$\underline{C}H_3$); 55.43 (O$\underline{C}H_3$).

152-*minor*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.42 (d, 2H, J = 8.8 Hz, $H_{aromatic}$), 6.91 (d, 2H, J = 8.8 Hz, $H_{aromatic}$); 5.72 (s, 1H, $ArCHO_2$); 5.12 (s, 1H, $J_{1,2}$ = 0.0 Hz, H-1); 4.88 (d, 1H, $J_{2,3}$ = 6.0 Hz, H-2); 4.67 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.60 (qd, 1H, $J_{4,5}$ = 2.8 Hz, H-4); 3.80 (s, 3H, OMe); 3.66 (d, 3H, H-5); 3.47 (s, 3H, OMe); 3.35 (dd, 1H, $J_{OH,5}$ = 10.4, 2.4 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 160.96, 128.02 ($C_{aromatic}$); 128.47, 113.94 ($\underline{C}H_{aromatic}$); 109.74 (C-1); 104.19 (Ac$\underline{C}HO_2$); 88.21 (C-4); 85.26 (C-3); 82.45 (C-2); 64.07 (C-5); 55.69 (ArO$\underline{C}H_3$); 55.43 (O$\underline{C}H_3$).

Methyl 5-Deoxy-2,3-*O*-*p*-methoxybenzylidene-5-iodo-α,β-D-ribofuranoside (153).



Iodine (13.1 g, 53.2 mmol, 1.5 eq.) was added to a solution of ribofuranoside **152** (10 g, 35.5 mmol, 1.0 eq), Ph_3P (13.97 g, 53.2 mmol, 1.5 eq) and imidazole (4.8 g, 71.0 mmol, 2.0 eq.) in anhydrous THF (355 ml, 0.1 M) and then was heated to reflux. After 1h the reaction mixturwe was cooled to rt and concentrated under vacuum, queched with water and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The crude of the reaction was purified by column chromatography (from hexane to hexane: ethyl acetate = 3:1) to afford compound **153** (12.8 g, 32.7 mmol, 92%) as a yellowish solid.

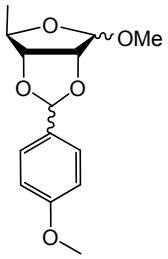
R_f (hexane: ethyl acetate = 6:1): 0.52.

152-*major*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.38 (d, 2H, J = 8.0 Hz, $H_{aromatic}$); 6.88 (d, 2H, J = 8.0 Hz, $H_{aromatic}$); 5.91 (s, 1H, $ArCHO_2$); 5.20 (s, 1H, $J_{1,2}$ = 0.0 Hz, H-1); 4.73 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-2); 4.69 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.61 (dd, 1H, $J_{4,5a}$ = 10.0 Hz, $J_{4,5b}$ = 6.4 Hz, H-4); 3.79 (s, 3H, ArOMe); 3.80 (s, 3H, OMe); 3.39 (s, 3H, OMe); 3.23 (dd, 1H, $J_{5a,5b}$ = 4.0 Hz, H-5a); 3.32 (dd, 1 H, $J_{5a,5b}$ = 4.0 Hz, H-5b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 160.77, 128.05 ($C_{aromatic}$); 128.50, 113.87 ($\underline{C}H_{aromatic}$); 109.37 (C-1); 106.14 (Ac$\underline{C}HO_2$); 87.23 (C-4); 85.93 (C-3); 83.40 (C-2); 55.45 (ArO$\underline{C}H_3$); 55.59 (O$\underline{C}H_3$); 6.63 (C-5).

152-*minor*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.42 (d, 2H, J = 8.0 Hz, $H_{aromatic}$), 6.88 (d, 2H, J = 8.0 Hz, $H_{aromatic}$); 5.72 (s, 1H, $ArCHO_2$); 5.15 (s, 1H, $J_{1,2}$ = 0.0 Hz, H-1); 4.93 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-

2); 4.72 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.56 (dd, 1H, $J_{4,5a}$ = 7.6 Hz, $J_{4,5a}$ = 6.8 Hz, H-4); 3.79 (s, 3H, ArOMe); 3.39 (s, 3H, OMe); 3.34 (dd, 1H, $J_{5a,5b}$ = 4.0 Hz, H-5a); 3.20 (dd, 1H, $J_{5a,5b}$ = 4.0 Hz, H-5b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 160.92, 128.27 ($C_{aromatic}$); 128.50, 113.87 ($\underline{C}H_{aromatic}$); 109.42 (C-1); 104.35 (Ac$\underline{C}HO_2$); 86.82 (C-4); 84.57 (C-3); 82.78 (C-2); 55.45 (ArO$\underline{C}H_3$); 55.59 (O$\underline{C}H_3$); 6.63 (C-5).

Methyl 5-Deoxy-2,3-*O*-*p*-methoxybenzylidene-α,β-D-ribofuranoside (154).



AIBN (42 mg, 0.26 mmol, 0.8% mol) and Bu_3SnH (9.4 ml, 10.2 g, 35.2 mmol, 1.1 eq) were added to a solution of ribofuranoside **153** (10 g, 32.0 mmol, 1.0 eq) in anhydrous and deoxygenated toluene(107 ml, 0.3M). The resulting mixture was warmed up under reflux for 17 h and the toluene evaporated. The crude was purified by column chromatography (from hexane to hexane: ethyl acetate = 3:1) to afford compound **154** (12.8 g, 32.7 mmol, 92%) as a yellowish syrup.

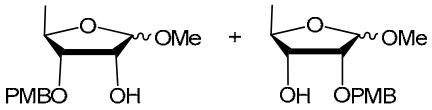
R_f (hexane: ethyl acetate = 6:1): 0.50.

Spectroscopic data obtained from the α/β mixture.

154-*major*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.38 (d, 2H, J = 8.8 Hz, $H_{aromatic}$), 6.89 (d, 2H, J = 8.8 Hz, $H_{aromatic}$); 5.92 (s, 1H, ArCHO_2); 5.09 (s, 1H, $J_{1,2}$ = 0.0 Hz, H-1); 4.73 (d, 1H, $J_{2,-3}$ = 5.6 Hz, H-2); 4.65 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.45 (qd, 1H, $J_{4,5}$ = 6.8 Hz, H-4); 3.79 (s, 3H, OMe); 3.35 (s, 3H, OMe); 1.34 (d, 3H, $J_{5,4}$ = 6.0 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 160.78, 128.33 ($C_{aromatic}$); 128.38, 113.91 ($\underline{C}H_{aromatic}$); 109.02 (C-1); 105.96 (Ac$\underline{C}HO_2$); 86.42 (C-2); 84.97 (C-3); 82.84 (C-4); 55.41 (ArO$\underline{C}H_3$); 54.52 (O$\underline{C}H_3$); 20.98 (C-5).

154-*minor*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.38 (d, 2H, J = 8.8 Hz, $H_{aromatic}$), 6.89 (d, 2H, J = 8.8 Hz, $H_{aromatic}$); 5.92 (s, 1H, ArCHO_2); 5.09 (s, 1H, $J_{1,2}$ = 0.0 Hz, H-1); 4.73 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-2); 4.65 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.45 (qd, 1H, $J_{4,5}$ = 6.8 Hz, H-4); 3.79 (s, 3H, OMe); 3.35 (s, 3H, OMe); 1.34 (d, 3H, $J_{5,4}$ = 6.0 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 160.81, 128.58 ($C_{aromatic}$); 128.49, 113.91 ($\underline{C}H_{aromatic}$); 109.28 (C-1); 104.10 (Ac$\underline{C}HO_2$); 86.84 (C-2); 80.04 (C-3); 83.01 (C-4); 55.41 (ArO$\underline{C}H_3$); 54.51 (O$\underline{C}H_3$); 21.98 (C-5).

Methyl 5-Deoxy-3-*O*-*p*-methoxybenzyl-α,β-D-ribofuranoside (155) and Methyl 5-Deoxy-3-*O*-*p*-methoxybenzyl-α,β-D-ribofuranoside (156).



155, 34% **156,** 41%

A 1.0 M solution of DIBAL-H in DCM (50 ml, 50 mmol) was added dropwise to a solution of ribofuranoside **154** (2.7 g, 10.0 mmol) in DCM (50 ml, 0.1 M) at –78 ºC and was monitored by TLC (hexane: ethyl acetate = 3:1) until the starting product was consumed. After 30 minutes at –78 ºC, the reaction was quenched by adding the reaction mixture to methanol (100 ml) at 0 ºC and allowed to warm to rt. The white gel obtained was dissolved with the addition of 100 ml of 10 w/v% KOH solution The aqueous phase was extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum.. The residue was purified by column chromatography (hexane: ethyl acetate = 3:1) to afford 2.6 g, 9.8 mmol (98%) of **155** and **156** mixture as a yellowish syrup. The mixture was separated by recrystallization from hexane: ethyl acetate = 10:1 to afford compound **155** (977 mg, 3.64 mmol, 34%), compound **156 (**1.194 g, 4.45 mmol, 41%) and the mixture of them (458 mg, 1.71 mmol 16%).

R_f (hexane: ethyl acetate = 2:1): 0.40.

Spectroscopic data obtained from the α/β mixture.

155β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.27 (d, 2H, J = 8.4 Hz, $H_{aromatic}$), 6.90 (d, 2H, J = 8.4 Hz, $H_{aromatic}$); 4.80 (s, 1H, $J_{1,2}$ = 0.0 Hz, H-1); 4.53 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.48 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.08 (m, 1H, H-4); 4.01 (d, 1H, $J_{2,3}$ = 4.4 Hz, H-2); 3.80 (s, 3H, ArOMe); (dd, 1H, $J_{3,4}$ = 6.4 Hz, H-3); 3.34 (s, 3H, OMe); 2.82 (d, 1H, $J_{OH,2}$ = 3.6 Hz, OH); 1.29 (d, 3H, $J_{4,5}$ = 6.8 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 159.68, 129.35 ($C_{aromatic}$); 129.70, 114.06 ($\underline{C}H_{aromatic}$); 108.43 (C-1); 83.64 (C-3); 77.40 (C-4); 73.58 (C-2); 72.59 ($\underline{C}H_2Ph$); 55.32 (ArO$\underline{C}H_3$); 54.91 (O$\underline{C}H_3$); 20.92 (C-5).

156α: Could not be determined.

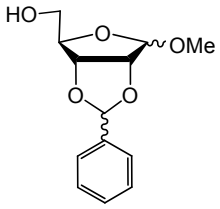
R_f (hexane: ethyl acetate = 2:1): 0.38.

Spectroscopic data obtained from the α/β mixture.

155β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.27 (d, 2H, J = 8.8 Hz, $H_{aromatic}$), 6.89 (d, 2H, J = 8.8 Hz, $H_{aromatic}$); 4.84 (s, 1H, $J_{1,2}$ = 0.0 Hz, H-1); 4.66 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.54 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 3.97 (m, 1H, H-4); 3.91 (dd, 1H, $J_{3,4}$ = 5.6 Hz, H-3); 3.84 (d, 1H, $J_{2,3}$ = 4.4 Hz, H-2); 3.81 (s, 3H, ArOMe); 3.35 (s, 3H, OMe); 2.57 (d, 1H, $J_{OH,2}$ = 8.8 Hz, OH); 1.31 (d, 3H, $J_{4,5}$ = 6.4 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 159.75, 129.38 ($C_{aromatic}$); 129.87, 114.14 ($\underline{C}H_{aromatic}$); 106.01 (C-1); 82.36 (C-2); 80.52 (C-4); 75.98 (C-3); 72.72 ($\underline{C}H_2Ph$); 55.47 (ArO$\underline{C}H_3$); 55.23 (O$\underline{C}H_3$); 20.24 (C-5).

156α: Could not be determined.

Methyl 2,3-*O*-Benzylidene-α,β-D-ribofuranoside (157).



Anhydrous $ZnCl_2$ (13.1 g, 200 mmol) and benzaldehyde (10.2 ml, 10.6 g, 110 mmol) were added to a solution of ribofuranoside **151** (16.15 g, 100 mmol) anhydrous MeCN (50 ml). The mixture was stirred for 48 h at rt until the starting material was consumed (TLC analysis). The reaction was quenched with $NaHCO_3$ solution and the pruct was extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column (hexane: ethyl acetate = 2:1) to afford the lactone **157** (11.02 g, 43.72 mmol, 44% in two steps) as a white solid.

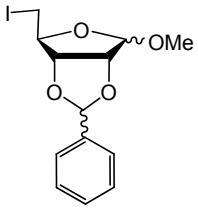
R_f (hexane: ethyl acetate = 2:1): 0.43.

Spectroscopic data obtained from the α/β mixture.

157-*major*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.51 – 7.26 (m, 5H, $H_{aromatic}$); 5.98 (s, 1H, $ArCHO_2$); 5.13 (s, 1H, H-1); 4.93 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-2); 4.70 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.62 (qd, 1H, $J_{4,5}$ = 2.0 Hz, H-4); 3.73 (d, 2H, $J_{5,4}$ = 6.0 Hz, H-5); 3.71 (bs, 1H, OH); 3.48 (s, 3H, OMe). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.26 ($C_{aromatic}$); 129.10, 128.66, 127.09 ($\underline{C}H_{aromatic}$); 109.78 (C-1); 104.36 (Ac$\underline{C}HO_2$); 88.29 (C-4); 85.33 (C-3); 82.70 (C-2); 64.24 (C-5); 55.84 (O$\underline{C}H_3$).

157-*minor*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.51 – 7.26 (m, 5H, $C_{aromatic}$); 5.77 (s, 1H, $ArCHO_2$); 5.11 (s, 1H, H-1); 4.89 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-2); 4.73 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.55 (qd, 1H, $J_{4,5}$ = 2.0 Hz, H-4); 3.76 (d, 2H, $J_{5,4}$ = 6.0 Hz, H-5); 3.71 (bs, 1H, OH); 3.47 (s, 3H, OMe). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.21 ($C_{aromatic}$); 129.86, 128.66, 126.75 ($\underline{C}H_{aromatic}$); 109.36 (C-1); 104.36 (Ac$\underline{C}HO_2$); 89.20 (C-4); 86.47 (C-3); 81.26 (C-2); 64.15 (C-5); 55.84 (O$\underline{C}H_3$).

Methyl 2,3-*O*-Benzylidene-5-deoxy-5-iodo-α,β-D-ribofuranoside (158).

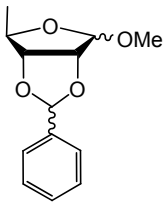


Iodine (7.6 g, 30.0 mmol, 1.5 eq.) was added to a solution of ribofuranoside **157** (5.0 g, 20.0 mmol, 1.0 eq), Ph_3P (7.9 g, 30.0 mmol, 1.5 eq) and imidazole (2.7 g, 40.0 mmol, 2.0 eq.) in anhydrous THF

(200 ml, 0.1 M) and the reaction mixture was heated then to reflux. After 1h the reaction was cooled to rt and concentrated under vacuum, quenched with $Na_2S_2O_3$ solution and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The crude of the reaction was used in the next step.

R_f (hexane: ethyl acetate = 6:1): 0.48.

Methyl 2,3-*O*-Benzylidene-5-deoxy-α,β-D-ribofuranoside (159).



AIBN (26 mg, 0.16 mmol, 0.8% mol) and Bu_3SnH (5.9 ml, 6.4 g, 22.0 mmol, 1.1 eq) were added to a solution of ribofuranoside **158** (20.0 mmol, 1.0 eq) in anhydrous and deoxygenated toluene (107 ml, 0.3 M). The resulting mixture was heated to reflux for 17 h and the toluene evaporated. The crude was purified by column chromatography (from hexane to hexane: ethyl acetate = 6:1) to afford compound **159** (4.3 g, 18.3 mmol, 91% in two steps) as a yellowish syrup.

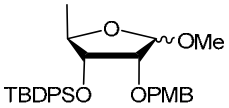
R_f (hexane: ethyl acetate = 6:1): 0.42.

Spectroscopic data obtained from the α/β mixture.

159-*major*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.49 – 7.32 (m, 5H, $H_{aromatic}$); 5.97 (s, 1H, $ArCHO_2$); 5.07 (s, 1H, H-1); 4.74 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-2); 4.67 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.47 (qd, 1H, $J_{4,5}$ = 6.8 Hz, H-4); 3.37 (s, 3H, OMe); 1.35 (d, 3H, $J_{5,4}$ = 6.0 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.02 ($C_{aromatic}$); 129.78, 128.63, 127.14 ($\underline{C}H_{aromatic}$); 109.29 (C-1); 104.28 ($Ac\underline{C}HO_2$); 86.64 (C-2); 85.17 (C-3); 82.92 (C-4); 54.64 ($O\underline{C}H_3$); 21.07 (C-5).

159-*minor*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.49 – 7.32 (m, 5H, $H_{aromatic}$); 5.77 (s, 1H, $ArCHO_2$); 5.10 (s, 1H, H-1); 4.76 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-2); 4.60 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3); 4.54 (qd, 1H, $J_{4,5}$ = 6.8 Hz, H-4); 3.36 (s, 3H, OMe); 1.34 (d, 3H, $J_{5,4}$ = 6.0 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.021 ($C_{aromatic}$); 130.02, 128.63, 126.79 ($\underline{C}H_{aromatic}$); 109.06 (C-1); 106.13 ($Ac\underline{C}HO_2$); 86.08 (C-3); 85.25 (C-2); 83.06 (C-4); 54.64 ($O\underline{C}H_3$); 21.23 (C-5).

Methyl 3-*O*-*tert*-Butyldiphenylsilyl-5-deoxy-2-*O*-*p*-methoxybenzyl-α,β-D-ribofuranoside (160).



Following the *general procedure of silylation*, ribofuranoside **156** (2.68 g, 10.0 mmol, 1 eq), Et_3N (1.2 ml, 16.2 g, 16 mmol, 1.6 eq), TBDPSCl (2.86 ml, 1.1 mmol, 1.1 eq) and DMAP (244 mg, 2.0

mmol, 0.2 eq) in anhydrous anhydrous DCM (50 ml, 0.2 M) were reacted at rt for 8 h. Column chromatography (hexane: ethyl acetate = 9:1) of the crude afforded **160** (4.97 g, 9.8 mmol 98%) as a yellowish syrup.

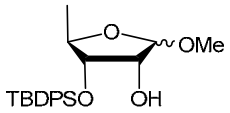
R_f (hexane: ethyl acetate = 8:1): 0.78.

Spectroscopic data obtained from the α/β mixture.

160β: ^{1}H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.33 – 7.64 (4H, $H_{aromatic}$); 7.44 – 7.28 (6H, $H_{aromatic}$); 7.18 (d, 2H, J = 8.4 Hz, $H_{aromatic}$), 6.82 (d, 2H, J = 8.4 Hz, $H_{aromatic}$); 4.73 (d, 1H, $J_{1,2}$ = 0.9 Hz, H-1); 4.53 (s, 2H, CH_2Ph); 4.13 (m, H-4); 4.05 (dd, 1H, $J_{3,4}$ = 6.6 Hz, H-3); 3.77 (s, 3H, ArOMe); 3.41 (d, 1H, $J_{2,3}$ = 4.2 Hz, H-2); 3.22 (s, 3H, OMe); 1.05 (d, 3H, $J_{4,5}$ = 6.6 Hz, H-5); 1.08 (s, 9H, tBu). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ in ppm: 159.24, 134.98, 133.79, 129.91 ($C_{aromatic}$); 136.14, 136.11, 130.01, 129.91, 129.40, 127.83, 127.76, 113.78 ($\underline{C}H_{aromatic}$); 106.23 (C-1); 82.17 (C-2); 79.15 (C-4); 77.83 (C-3); 71.96 ($\underline{C}H_2Ph$); 55.40 ($ArO\underline{C}H_3$); 55.08 ($O\underline{C}H_3$); 27.14 ($CH_{3,tBuSi}$); 26.73 (C_{Si}); 19.99 (C-5).

160α: ^{1}H NMR ($CDCl_3$, 300 MHz) δ in ppm: Could not be determined.

Methyl 3-*O*-*tert*-Butyldiphenylsilyl-5-deoxy-α,β-D-ribofuranoside (161).



Following the *general procedure of oxidation of PMB group*, ribofuranoside **160** (4.8 g, 9.5 mmol, 1 eq), DDQ (2.3 g, 10 mmol, 1.05 eq) in humid DCM (48 ml, 0.2 M) were reacted at rt for 8 h. Column chromatography (hexane: ethyl acetate = 9:1) of the crude afforded **161** (3.49 g, 9.0 mmol 95%) as a yellowish syrup.

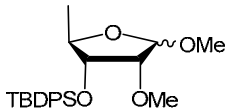
R_f (hexane: ethyl acetate = 8:1): 0.43.

Spectroscopic data obtained from the α/β mixture.

161β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.33 – 7.63 (4H, $H_{aromatic}$); 7.49 – 7.38 (6H, $H_{aromatic}$); 4.80 (d, 1H, $J_{1,2}$ = 0.9 Hz, H-1); 4.05 (m, H-4, H-3); 3.86 (d, 1H, $J_{2,3}$ = 3.6 Hz, H-2); 3.27 (s, 3H, OMe); 1.11 (s, 9H, tBu); 0.87 (d, 3H, $J_{4,5}$ = 6.6 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.99, 132.85, 132.50 ($C_{aromatic}$); 136.03, 135.84, 130.48, 128.19, 128.11 ($\underline{C}H_{aromatic}$); 108.42 (C-1); 79.99 (C-4); 78.31 (C-3); 75.84 (C-2); 55.07 ($O\underline{C}H_3$); 27.15 ($CH_{3,tBuSi}$); 26.74 (C_{Si}); 20.13 (C-5).

161α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

Methyl 3-*O*-*tert*-Butyldiphenylsilyl-5-deoxy-2-*O*-methyl-α,β-D-ribofuranoside (162).



Ribofuranoside **161** (3.1 g, 8.0 mmol, 1.0 eq), NaH (384 mg, 9.6 mmol, 1.2 eq) in anhydrous THF (40 ml, 0.2 M) and finally MeI (890 μl, 1.4 g, 1.2 eq) were reacted at rt for 8 h. The reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column (hexane: ethyl acetate = 9:1) of the crude afforded **162** (3.04 g, 7.6 mmol 95%) as a yellowish syrup.

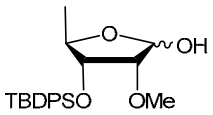
R_f (hexane: ethyl acetate = 8:1): 0.80.

Spectroscopic data obtained from the α/β mixture.

162β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.75 – 7.63 (4H, $H_{aromatic}$); 7.49 – 7.37 (6H, $H_{aromatic}$); 4.77 (d, 1H, $J_{1,2}$ = 0.9 Hz, H-1); 4.10 (m, H-4); 4.00 (dd, 1H, $J_{3,4}$ = 6.4 Hz, H-3); 3.84 (dd, 1H, $J_{2,3}$ = 4.8 Hz, H-2); 3.27 (s, 3H, OMe); 3.24 (s, 3H, OMe); 1.12 (d, 3H, $J_{4,5}$ = 6.4 Hz, H-5); 1.09 (s, 9H, tBu). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ in ppm: 133.81, 133.74 ($C_{aromatic}$); 136.13, 136.06, 130.01, 129.96, 129.88, 127.84, 127.78 ($\underline{C}H_{aromatic}$); 105.60 (C-1); 84.22 (C-2); 79.22 (C-4); 77.60 (C-3); 58.06 (O$\underline{C}H_3$); 55.13 (O$\underline{C}H_3$); 27.12 ($CH_{3,tBuSi}$); 27.06 (C_{Si}); 20.19 (C-5).

162α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

3-*O-tert*-Butyldiphenylsilyl-5-deoxy-2-*O*-methyl-α,β-D-ribofuranose (163).



Following *the general procedure of demethylation*, a cold (–78 ºC) solution of ribofuranoside **162** (1.6 g, 4.0 mmol, 1.0 eq), PhSH (613 μl, 661 mg, 6.0 mmol, 1.5 eq) and $BF_3.Et_2O$ (633 ml, 850 mg, 6.0 mmol, 1.5 eq) in anhydrous DCM (20 ml, 0.2 M) was left to warm up to rt. The mixture was reacted at rt for 8 h and was quenched with TEA, concentrated and filtered over silica gel. The crude of the reaction was treated with NIS (1.08 g, 4.8 mmol, 1.2 eq) in MeCN/H_2O = 10:1 and in 10 minutes quenched with the solution of $Na_2S_2O_3$ and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. Column chromatography (hexane: ethyl acetate = 6:1) of the crude afforded **163** (851 mg, 2.2 mmol 55%, an α/β inseparable mixture, α/β = 1:3) as a yellowish syrup.

R_f (hexane: ethyl acetate = 6:1): 0.36.

Spectroscopic data obtained from the α/β mixture.

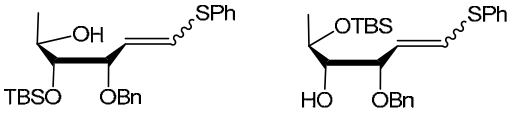
Anal. Calcd for $C_{22}H_{30}O_4Si$: 68.36% C, 7.82% H. Found: 68.83% C, 7.91% H.

163α: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.66 – 7.63 (4H, $H_{aromatic}$); 7.22 – 7.16 (6H, $H_{aromatic}$); 5.14 (dd, 1H, $J_{1,OH}$ = 4.0 Hz, $J_{1,2}$ = 5.6 Hz, H-1); 4.32 (d, 1H, $J_{OH,1}$ = 4.0 Hz, OH); 3.99 (m, 1H, H-4); 3.77 (dd, 1H, $J_{3,2}$ = 4.4 Hz, $J_{3,4}$ = 7.6 Hz, H-3); 3.38 (dd, 1H, $J_{2,3}$ = 4.4 Hz, H-2); 1.01 (m, 9H, CH_{3tBuSi});

0.69 (d, 3H, $J_{5,4}$ = 6.4 Hz, H-5). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 133.88, 132.62 ($C_{aromatic}$); 135.95, 135.88, 130.18, 129.87, 128.82, 127.90 ($\underline{C}H_{aromatic}$); 99.11 (C-1); 80.68 (C-4); 78.69 (C-2); 75.29 (C-3); 57.77 ($O\underline{C}H_3$); 26.98 (C_{Si}); 26.94 ($\underline{C}H_{3,tBuSi}$); 19.17 (C-5).

163*β*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.58 – 7.56 (4H, $H_{aromatic}$); 7.22 – 7.16 (6H, $H_{aromatic}$); 5.17 (d, 1H, $J_{1,OH}$ = 4.0 Hz, H-1); 4.32 (d, 1H, $J_{OH,1}$ = 4.0 Hz, OH); 4.05 (m, 1H, H-4); 3.77 (dd, 1H, $J_{3,2}$ = 4.4 Hz, $J_{3,4}$ = 7.6 Hz, H-3); 3.38 (d, 1H, $J_{2,3}$ = 4.4 Hz, H-2); 1.01 (m, 9H, CH_{3tBuSi}); 0.69 (d, 1H, $J_{5,4}$ = 6.4 Hz, H-5). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 133.07, 132.56 ($C_{aromatic}$); 136.10, 135.91, 130.18, 130.06, 127.81, 127.75 ($\underline{C}H_{aromatic}$); 95.95 (C-1); 80.18 (C-4); 79.83 (C-2); 76.65 (C-3); 58.56 ($O\underline{C}H_3$); 26.98 (C_{Si}); 26.94 ($\underline{C}H_{3,tBuSi}$); 19.13 (C-5).

(*E*/*Z*)-3-*O*-Benzyl-4-*O*-*tert*-butyldimethylsilyl-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (164) and (*E*/*Z*)-3-*O*-Benzyl-5-*O*-*tert*-butyldimethylsilyl-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (167).[142]



desired **164,** *Z*/*E* 1:16 undesired **167,** *Z*/*E* 1:21

Folloing the *general method of the WH olefination reactions*, ribofuranose **149** (520 mg, 1.54 mmol, 1eq), (phenylthiomethyl)diphenylphosphine oxide (1.49 g, 4.61 mmol, 3eq), and *n*-BuLi (3.0 ml of 1.6 M hexane solution, 4.76 mmol, 3.1 eq) were left to react for 15 h. The reaction was monitored by TLC (hexane: ethyl acetate = 1:4). Column chromatography (from hexane to hexane: ethyl acetate = 3:1) afforded desired **164** (417 mg, 0.94 mmol, 61%, a *Z*/*E* inseparable mixture, *Z*/*E* = 1:16) as yellowish syrup and migrated compound **167** (109 mg, 0.26 mmol, 16%, a *Z*/*E* inseparable mixture, *Z*/*E* = 1:21) as yellowish syrup.

Spectroscopic data obtained from *E*/*Z* mixture.

164*E*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.39 – 7.24 (m, 10H, $H_{aromatic}$); 6.42 (d, 1H, $J_{1,2}$ = 15.6 Hz, H-1); 5.73 (dd, 1H, $J_{2,3}$ = 8.0 Hz, $J_{2,1}$ = 15.6 Hz, H-2); 4.61 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.37 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 3.93 (dd, 1H, $J_{3,2}$ = 8.0 Hz, $J_{3,4}$ = 6.8 Hz, H-3); 3.86 (m, 1H, H-5); 3.63 (dd, 1H, $J_{4,3}$ = 6.8 Hz, $J_{4,5}$ = 5.6 Hz, H-4); 2.14 (d, 1H, $J_{OH,5}$ = 4.8 Hz, OH); 1.15 (d, 3H, $J_{6,5}$ = 6.0 Hz, H-6); 0.87 (s, 9H, tBuSi); 0.06 (s, 3H, MeSi); 0.05 (s, 3H, MeSi). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.1 – 127.3 ($C_{aromatic}$, $\underline{C}H_{aromatic}$); 129.4 (C-2); 128.6 (C-1); 81.5 (C-3); 78.2 (C-4); 70.5 ($\underline{C}H_2Ph$); 69.8 (C-5); 26.2 ($\underline{C}H_{3,tBuSi}$) 18.8 (C-6); 18.4 (C_{tBuSi}); –3.70, –4.15 ($\underline{C}H_{3Si}$).

164*Z*: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.40 – 7.23 (m, 10H, $H_{aromatic}$); 6.55 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1); 5.84 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{2,1}$ = 9.6 Hz, H-2); 4.63 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.50 (dd, 1H, $J_{3,2}$ = 9.2 Hz, $J_{3,4}$ = 4.8 Hz, H-3); 4.42 (d, 1H, J_{AB} = 11.6Hz, CH_2Ph); 3.86 (qd, 1H, $J_{5,6}$ = 6.4 Hz, $J_{5,4}$ = 5.2 Hz, H-5); 3.75 (dd, 1H, $J_{4,3}$ = 4.8 Hz, $J_{4,5}$ = 5.2 Hz, H-4); 2.47 (d, 1H, $J_{OH,5}$ = 4.8 Hz, OH); 1.20 (d,

3H, $J_{6,5}$ = 6.4 Hz, H-6); 0.91 (s, 12H, tBuSi); 0.095 (s, 3H, MeSi); 0.082 (s, 3H, MeSi). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.5, 138.3 ($C_{aromatic}$); 129.5 – 126.9 ($\underline{C}H_{aromatic}$); 129.3 (C-2); 129.2 (C-1); 78.4 (C-4); 77.2 (C-3); 70.8 ($\underline{C}H_2Ph$); 69.7 (C-5); 26.2 ($\underline{C}H_{3,tBuSi}$) 19.0 (C-6); 18.4 (C_{tBuSi}); –3.57, –4.32 ($\underline{C}H_{3Si}$).

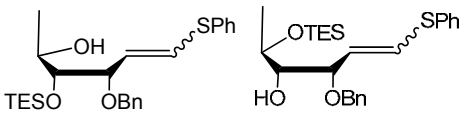
Spectroscopic data obtained from *E*/*Z* mixture.

Anal. Calcd for $C_{25}H_{36}O_3SSi$: 67.52 C, 8.16 H, 7.21 S. Found: 67.58 C, 8.17 H, 7.22 S.

167*E*: RMN ^{1}H ($CDCl_3$, 300 MHz) δ in ppm: 7.49 – 7.23 (m, 10H, $H_{aromatic}$); 6.50 (d, 1H, $J_{1,2}$ = 15.0 Hz, H-1); 5.84 (dd, 1H, $J_{2,3}$ = 7.5 Hz, $J_{2,1}$ = 15.0 Hz, H-2); 4.65 (d, 1H, J_{AB} = 12.0 Hz, CH_2Ph); 4.40(d, 1H, J_{AB} = 12.0 Hz, CH_2Ph); 3.93 (dd, 1H, $J_{3,2}$ = 7.5 Hz, $J_{3,4}$ = 6.4 Hz, H-3); 3.77 – 3.73 (m, 1H, H-4); 3.62 (qd, 1H, $J_{5,6}$= 6.0 Hz, $J_{5,OH}$ = 2.7 Hz, H-5); 2.32 (d, 1H, $J_{OH,5}$ = 2.7 Hz, OH); 1.10 (d, 3H, $J_{6,5}$ = 6.0 Hz, H-6); 0.85 (s, 9H, tBuSi); 0.069 (s, 3H, MeSi); 0.033 (s, 3H, MeSi). RMN ^{13}C ($CDCl_3$, 75.4 MHz) δ in ppm: 138.2, 138.1 ($C_{aromatic}$); 130.4, 129.4, 128.9, 128.7, 128.6, 128.1, 127.9, 127.2 ($\underline{C}H_{aromatic}$, C-1, C-2); 79.7, 76.8, 70.4 (C-4, C-3, $\underline{C}H_2Ph$); 68.9 (C-5); 26.0 ($\underline{C}H_{3,tBuSi}$); 18.22 (C_{tBuSi}); 18.20 (C-6); –3.84, –4.59 ($\underline{C}H_{3Si}$).

167*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.41 – 7.24 (m, 10H, $H_{aromatic}$); 6.64 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1); 5.86 (dd, 1H, $J_{2,3}$ = 8.4 Hz, $J_{2,1}$ = 9.6 Hz, H-2); 4.66 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.41(d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.34 (dd, 1H, $J_{3,2}$ = 8.4 Hz, $J_{3,4}$ = 8.0 Hz, H-3); 4.08 (qd, 1H, $J_{5,6}$ = 6.8 Hz, $J_{5,4}$ = 4.0 Hz, H-5); 3.71 (dd, 1H, $J_{4,3}$ = 8.0 Hz, $J_{4,5}$ = 4.0 Hz, H-4); 2.21 (s, 1H, OH); 1.10 (d, 3H, $J_{6,5}$ = 6.8 Hz, H-6); 0.88 (s, 9H, tBuSi); 0.09 (s, 3H, MeSi); 0.08 (s, 3H, MeSi). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 136.1, 135.9 ($C_{aromatic}$); 130.1 (C-1); 129.5 – 126.9 ($\underline{C}H_{aromatic}$); 129.2 (C-2); 76.3 (C-4); 75.9 (C-3); 70.7 ($\underline{C}H_2Ph$); 69.0 (C-5); 26.0 ($\underline{C}H_{3,tBuSi}$); 18.2 (C_{tBuSi}); 17.1 (C-6); –4.14, –4.61 ($\underline{C}H_{3Si}$).

(*E*/*Z*)-3-*O*-Benzyl-1,2,6-trideoxy-4-*O*-triethylsilyl-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (168) and (*E*/*Z*)-3-*O*-Benzyl-1,2,6-trideoxy-5-*O*-triethylsilyl-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (169).[142]



desired **168**, *Z*/*E* 1:5 undesired **169**, *Z*/*E* 1:11

Folloing the *general method of the WH olefination reactions*, ribofuranose **147** (625 mg, 1.85 mmol, 1eq), (phenylthiomethyl)diphenylphosphine oxide (2.10 g, 6.46 mmol, 3.5 eq), and *n*-BuLi (4.15 ml of 1.6 M hexane solution, 6.65 mmol, 3.6 eq) were left to react for 18 h and eliminated for 2 h. The reaction was monitored by TLC (hexane: ethyl acetate = 4:1). Column chromatography (from hexane to hexane: ethyl acetate = 3:1) afforded migrated compound **169** (517 mg, 1.65 mmol, 63%, a *Z*/*E* inseparable mixture, *Z*/*E* = 1:11) as yellowish syrup and desired compound **168** as (140 mg, 0.45 mmol, 17%, a *Z*/*E* inseparable mixture, *Z*/*E* = 1:5 mixture) as yellowish syrup.

Spectroscopic data obtained from *E*/*Z* mixture.

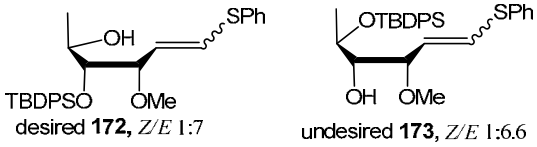
168*E***:** RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.40 – 7.23 (m, 10H, $H_{aromatic}$); 6.43 (d, 1H, $J_{1,2}$ = 15.0 Hz, H-1); 5.74 (dd, 1H, $J_{2,3}$ = 8.4 Hz, $J_{2,1}$ = 15.0 Hz, H-2); 4.63 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.38 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 3.91 (dd, 1H, $J_{3,2}$ = 8.0 Hz, $J_{3\text{-}4}$= 6.0 Hz, H-3); 3.84 (ddd, 1H, $J_{5,4}$ = 5.2 Hz, $J_{5,6}$ = 6.0 Hz, $J_{5,OH}$ = 4.8 Hz, H-5); 3.63 (dd, 1H, $J_{4,3}$ = 6.0 Hz, $J_{4,5}$ = 5.2 Hz, H-4); 2.21 (d, 1H, $J_{OH,5}$ = 4.8 Hz, OH); 1.15 (d, 3H, $J_{6,5}$ = 6.0 Hz, H-6); 0.93 (t, 9H, $J_{CH3,CH2}$ = 8.0 Hz, CH_{3Si}); 0.60 (q, 6H, $J_{CH2,CH3}$ = 8.0 Hz, CH_{2Si}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2 – 134.8 ($C_{aromatic}$); 138.6 – 127.4 ($\underline{C}H_{aromatic}$, C-1, C-2); 81.8 (C-3); 78.3 (C-4); 70.6 ($\underline{C}H_2Ph$); 69.9 (C-5); 18.8 (C-6); 7.17 ($\underline{C}H_{3Si}$); 5.42 ($\underline{C}H_{2Si}$).

168*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

169*E***:** RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.41 – 7.32 (m, 10H, $H_{aromatic}$); 6.49 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.83 (dd, 1H, $J_{2,3}$ = 8.4 Hz, $J_{2,1}$ = 15.2 Hz, H-2); 4.64 (d, 1H, J_{AB} = 12.0 Hz, CH_2Ph); 4.38 (d, 1H, J_{AB} = 12.0 Hz, CH_2Ph); 3.95 – 3.90 (m, 2H, H-5, H-3); 3.63 (ddd, 1H, $J_{4,3}$ = 5.6 Hz, $J_{4,5}$ = 6.0 Hz, $J_{4,OH}$ = 2.4 Hz, H-4); 2.37 (d, 1H, $J_{OH,4}$ = 2.4 Hz, OH); 1.10 (d, 3H, $J_{6,5}$ = 6.0 Hz, H-6); 0.92 (t, 9H, $J_{CH3,CH2}$ = 8.0 Hz, CH_{3Si}); 0.57 (q, 6H, $J_{CH2,CH3}$ = 8.0 Hz, CH_{2Si}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2, 134.8 ($C_{aromatic}$); 130.4, 129.3 ($\underline{C}H_{aromatic}$); 129.0 (C-1); 128.6 ($\underline{C}H_{aromatic}$); 128.5 (C-2); 128.1, 127.9, 127.2 ($\underline{C}H_{aromatic}$); 79.9 (C-3); 77.0 (C-4); 70.4 ($\underline{C}H_2Ph$); 68.6 (C-5); 18.2 (C-6); 7.07 ($\underline{C}H_{3Si}$); 5.25 ($\underline{C}H_{2Si}$).

169*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

(*E*/*Z*)-4-*O*-*tert*-Butyldiphenylsilyl-1,2,6-trideoxy-3-*O*-methyl-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (172) and (*E*/*Z*) -5-*O*-*tert*-Butyldiphenylsilyl -1,2,6-trideoxy-3-*O*-methyl-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (173).



Folloing the *general method of the WH olefination reactions*, ribofuranose **163** (387 mg, 1.0 mmol, 1eq), (phenylthiomethyl)diphenylphosphine oxide (**42**) (1.3 g, 4.0 mmol, 4.0 eq), and *n*-BuLi (2.75 ml of 1.6 M hexane solution, 4.4 mmol, 4.4 eq) were left to react for 18 h and eliminated for 2 h. The reaction was monitored by TLC (hexane: ethyl acetate = 1:4). Column chromatography (from hexane to hexane: ethyl acetate = 1:3) afforded migrated compound **173** as (276 mg, 0.56 mmol, 56%, a *Z*/*E* inseparable mixture, *Z*/*E* = 1:6.6) as yellowish syrup and desired compound **172** as (90 mg, 0.18 mmol, 18%, a *Z*/*E* inseparable mixture, *Z*/*E* = 1:7) as yellowish syrup.

Spectroscopic data obtained from *E*/*Z* mixture.

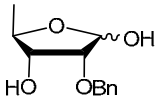
172*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.72 – 7.66 (m, 5H, $H_{aromatic}$); 7.42 – 7.26 (m, 10H, $H_{aromatic}$); 6.17 (d, 1H, $J_{1,2}$ = 15.6 Hz, H-1); 5.51 (dd, 1H, $J_{2,3}$ = 8.0 Hz, $J_{2,1}$ = 15.6 Hz, H-2); 3.88 (dd, 1H, $J_{3,2}$ = 8.0 Hz, $J_{3,4}$= 6.0 Hz, H-3); 3.71 (m, H-5, H-4); 3.16 (s, 3H, OMe); 2.21 (d, 1H, $J_{OH,5}$ = 4.8 Hz, OH); 1.15 (d, 3H, $J_{6,5}$ = 6.4 Hz, H-6); 1.05 (s, 9H, CH_{3tBuSi}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 136.2 – 134.8 ($C_{aromatic}$); 136.41, 136.16, 130.34, 129.97, 129.13, 127.90, 127.76, 127.18 ($\underline{C}H_{aromatic}$) 129.13 (C-2); 128.45 (C-1); 83.66 (C-3); 79.29 (C-4); 69.61 (C-5); 56.30 ($\underline{C}H_3$); 27.33 ($\underline{C}H_{3,tBuSi}$); 27.15 ($\underline{C}_{Si}$); 18.8 (C-6).

172*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

173*E*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.68 – 7.64 (m, 5H, $H_{aromatic}$); 7.43 – 7.24 (m, 10H, $H_{aromatic}$); 6.35 (d, 1H, $J_{1,2}$ = 15.6 Hz, H-1); 5.68 (dd, 1H, $J_{2,3}$ = 8.0 Hz, $J_{2,1}$ = 15.6 Hz, H-2); 3.95 (m, 1H, H-5); 3.75 (dd, 1H, $J_{3,2}$ = 8.0 Hz, $J_{3,4}$= 6.0 Hz, H-3); 3.68 (dd, 1H, $J_{4,5}$ = 5.6 Hz, $J_{3,4}$= 6.0 Hz, H-4); 3.23 (s, 3H, OMe); 2.45 (d, 1H, $J_{OH,5}$ = 4.8 Hz, OH); 1.06 (d, 3H, $J_{6,5}$ = 6.4 Hz, H-6); 1.05 (s, 9H, CH_{3tBuSi}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 135.97, 134.88, 134.18 ($C_{aromatic}$); 136.06, 135.94, 134.99, 130.15, 129.97, 129.87, 129.79, 129.30, 127.88, 127.74, 127.09 ($\underline{C}H_{aromatic}$) 128.92 (C-1); 128.21 (C-2); 82.29 (C-3); 76.59 (C-4); 70.13 (C-5); 56.42 ($\underline{C}H_3$); 26.73 ($\underline{C}H_{3,tBuSi}$); 276.27 ($\underline{C}_{Si}$); 18.38 (C-6).

173*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

2-*O*-Benzyl-6-deoxy-α,β-D-ribofuranose (175).



Following *the general procedure of demethylation*, a cold solution (–78 ºC) of ribofuranoside **134** (715 mg, 3.0 mmol, 1.0 eq), PhSH (460 μl, 496 mg, 4.5 mmol, 1.5 eq) and $BF_3.Et_2O$ (317 μl, 426 mg, 3.3 mmol, 1.1 eq) in anhydrous DCM (15 ml, 0.2 M) was left to warm up to rt. The mixture was reacted at rt for 8 h and was quenched with TEA, concentrated and filtered on silice. The crude of the reaction was treated with NIS (810 mg, 3.6 mmol, 1.2 eq) in MeCN/H_2O = 10:1 and in 10 minutes quenched with the solution of $Na_2S_2O_3$. Column chromatography (hexane: ethyl acetate = 1:6) of the crude afforded compound **175** (404 mg, 1.8 mmol, 60%, an α/β inseparable mixture, α/β = 1:2) as yellowish syrup.

R_f (hexane: ethyl acetate = 1:1): 0.25.

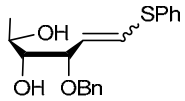
Spectroscopic data obtained from the α/β mixture.

175β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.33 (m, 5H, $H_{aromatic}$); 5.36 (d, 1H, $J_{1,2}$ = 4.8 Hz, H-1); 4.75 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.66 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.17 (m, 1H, H-5); 3.92 (t, 1H, $J_{2,3}$ = 4.8 Hz, H-2); 3.87 (dd, 1H, $J_{4,5}$ = 1.6 Hz, H-4); 3.81 (bt, 1H, $J_{3,4}$ = 4.8 Hz, H-3); 3.03 (bs, 1H, OH); 1.23 (d, 1H, $J_{5,6}$ = 6.8 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 136.95 ($C_{aromatic}$);

128.85, 128.42, 128.11 ($\underline{C}H_{aromatic}$); 95.82 (C-1); 83.04 (C-4); 79.23 (C-5); 77.84 (C-2); 75.23 (C-3); 73.42 ($\underline{C}H_2Ph$); 19.31 (C-6).

175α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.33 (m, 5H, $H_{aromatic}$); 5.36 (d, 1H, $J_{1,2}$ = 6.4 Hz, H-1); 4.74 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.63 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.17 (t, 1H, $J_{2,3}$ = 4.0 Hz, H-2); 3.98 (dd, 1H, $J_{3,4}$ = 4.8 Hz, H-3); 3.98 (m, 1H, H-5); 3.87 (dd, 1H, $J_{4,5}$ = 1.6 Hz, H-4); 3.03 (bs, 1H, OH); 1.35 (d, 1H, $J_{5,6}$ = 6.0 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 137.28 ($C_{aromatic}$); 128.75, 128.59, 128.34 ($\underline{C}H_{aromatic}$); 99.71 (C-1); 83.04 (C-4); 80.16 (C-5); 79.23 (C-2); 75.67 (C-3); 72.82 ($\underline{C}H_2Ph$); 20.14 (C-6).

(*E*/*Z*)-3-*O*-Benzyl-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (176).



Starting from **168**:[142] Vacuum–dried TBAF (20 mg, 0.078 mmol, 1.1 eq) was added to a solution of **168** (30 mg, 0.071 mmols, 1 eq, a *E*/*Z* inseparable mixture *E*/*Z* = 13:1) in anhydrous THF (2 ml, 0.036 M) at 0 ºC. The mixture was stirred for 20 min. The crude obtained was concentrated under vacuum and filtrated by column chromatography to afford compound **176** (22 mg, 0.066 mmol, 93%, a *E*/*Z* inseparable mixture, *E*/*Z* = 6:1) as yellowish syrup.

Starting from **175**: Folloing the *general method of the WH olefination reactions*, 2-*O*-benzyl-6-deoxy-α/β-D-ribofuranose **176** (179 mg, 0.80 mmol, 1 eq), (phenylthiomethyl)diphenylphosphine oxide (**42**) (1.04 g, 3.20 mmol, 4.0 eq), and *n*-BuLi (2.75 ml of 1.6 M hexane solution, 4.40 mmol, 5.5 eq) were left to react for 10 h at rt. The reaction was monitored by TLC (hexane: ethyl acetate = 1:1) to ensure that only one product was formed. Column chromatography (from hexane to ethyl acetate) afforded **176** (92 mg, 0.28 mmol, 28%, a *E*/*Z* inseparable mixture, *E*/*Z* = 10:1) as yellowish syrup and a lower R_f fraction which correspond to β-hydroxyphosphine oxide intermediate.

R_f (hexane: ethyl acetate = 1:1): 0.56.

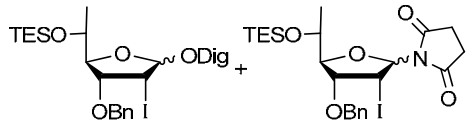
Spectroscopic data obtained from the *E*/*Z* mixture.

176*E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.34 (m, 10H, Ar); 6.52 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1); 5.77 (dd, 1H, $J_{2,3}$ = 7.6 Hz, H-2); 4.65 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.38 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 3.97 (dd, 1H, $J_{3,4}$ = 6.4 Hz, H-3); 3.89 (m, 1H, H-5); 3.56 (dd, 1H, $J_{4,5}$ = 5.6 Hz, H-4); 2.46 (bs, 1H, OH); 1.18 (d, 1H, $J_{5,6}$ = 6.8 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 137.76, 134.28 ($C_{aromatic}$); 130.52, 129.44, 128.69, 128.10, 128.07, 127.47 ($\underline{C}H_{aromatic}$); 130.16 (C-1); 127.94 (C-2); 81.48 (C-3); 76.33 (C-4); 70.63 ($\underline{C}H_2Ph$); 68.72 (C-5); 18.86 (C-6).

176*Z*: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.40 – 7.22 (m, 10H, $H_{aromatic}$); 6.66 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1); 5.85 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{2,1}$ = 9.6 Hz, H-2); 4.68 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.45 (d,

1H, J_{AB} = 11.2 Hz, CH_2Ph); 3.90 – 3.85 (m, 2H, H-3, H-5); 3.69 (dd, 1H, $J_{4,3}$ = 5.6 Hz., $J_{4,5}$ = 5.8 Hz, H-4); 2.32 (bs, 1H, OH); 2.04 (bs, 1H, OH); 1.24 (d, 3H, $J_{6,5}$ = 5.8 Hz, H-6). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: Could not be determined.

Digitoxigenyl 3-*O*-Benzyl-2,6-dideoxy-5-*O*-triethylsilyl-2-iodo-α,β-D-*allo*-furanoside (179) and Succinimide 3-*O*-Benzyl-2,6-dideoxy-5-*O*-triethylsilyl-2-iodo-α,β-D-*allo*-furanoside (180).[142]



179, 53% **180**, 25%

As described in *the ´*one-pot*´ cyclization-glycosylation procedure,* the title compound was prepared starting from **169** (100 mg, 0.24 mmol, 1 eq) and digitoxigenin (133 mg, 0.36 mmol, 1.5 eq) in anhydrous DCM (5.5 ml, 0.045 M). The reaction mixture was stirred from –78 ºC to –20 ºC for 8 h (cooled to –60 ºC and then AgOTf (24 mg, 0.09 mmol, 0.4 eq) was added to start glycosylation. The mixture was stirred from –60 ºC to –30 ºC for 15 h. (monitored by TLC (hexane: ethyl acetate = 1:3). Radial chromatography (from hexane to hexane: ethyl acetate = 1:4) of the crude afforded compound **179** (104 mg, 0.14 mmol, 53%, an α/β inseparable mixture, α/β = 1:22) as a syrup and compound **180** (26 mg, 0.06 mmol, 25%) as yellowish solid.

Spectroscopic data extracted from α/β mixture.

Anal. Calcd para $C_{43}H_{65}IO_7Si$: 60.83 C, 7.72 H. Found: 60.79 C, 7.70 H.

179β: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.35 – 7.26 (m, 5H, $H_{aromatic}$); 5.87 (s, 1H, H_{22dig}); 5.37 (d, 1H, $J_{1,2}$ = 2.8 Hz, H-1); 5.00 (d, 1H, J_{AB} = 18.0 Hz, H_{21Adig}); 4.75 (d, 1H, J_{AB} = 18.4 Hz, H_{21Bdig}); 4.63 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.76 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.48 (dd, 1H, $J_{3,2}$ = 3.6 Hz, $J_{3,4}$ = 4.8 Hz, H-3); 4.12 (dd, 1H, $J_{2,1}$ = 2.8 Hz, $J_{2,3}$ = 3.6 Hz, H-2); 3.96 (qd, 1H, $J_{5,6}$ = 6.4 Hz, $J_{5,4}$ = 4.4 Hz, H-5); 3.93 (m, 1H, H_{3dig}); 3.87 (dd, 1H, $J_{4,5}$ = 4.4 Hz, $J_{4,3}$ = 4.8 Hz, H-4); 2.77 (m, 1H, OH_{14dig}); 2.36 – 1.13 (m, 22H, H_{dig}); 1.15 (d, 3H, $J_{6,5}$ = 6.4 Hz, H-6); 0.98 (t, 9H, $J_{CH3,CH2}$ = 8.0 Hz, CH_{3Si}); 0.92 (s, 3H, Me_{dig}); 0.87 (s, 3H, Me_{dig}); 0.63 (q, 6H, $J_{CH2,CH3}$ = 8.0 Hz, CH_{2Si}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 174.8 (C-20_{dig}), 174.8 (C=O); 138.2 ($C_{aromatic}$); 128.5, 127.9, 127.8 ($\underline{C}H_{aromatic}$); 117.9 (C-$22_{dig}$); 109.8 (C-1); 87.5 (C-3); 87.5 (C-4); 85.8 (C-14_{dig}); 73.6 (C-5); 73.1 (C-21_{dig}); 72.2 ($\underline{C}H_2Ph$); 68.7 (C-3_{dig}); 51.1 – 15.9 (C_{dig}); 28.5 (C-2); 20.5 (C-6); 7.17 ($\underline{C}H_{3Si}$); 5.27 ($\underline{C}H_{2Si}$).

179α: RMN ^1H ($CDCl_3$, 400 MHz) δ in ppm: 7.44 – 7.26 (m, 5H, $H_{aromatic}$); 5.87 (s, 1H, H_{22dig}); 5.38 (d, 1H, $J_{1,2}$ = 5.2 Hz, H-1); 5.01 (dd, 1H, J_{AB} = 18.0 Hz, $J_{21,22dig}$ = 1.2 Hz, H_{21Adig}); 4.83 (dd, 1H, J_{AB} = 18.0 Hz, $J_{21,22dig}$ = 1.2 Hz, H_{21Bdig}); 4.61 (d, 1H, J_{AB} = 11.4 Hz, CH_2Ph); 4.53 (d, 1H, J_{AB} = 11.4 Hz, CH_2Ph); 4.21 (t, 1H, $J_{2,1}$ = 5.2 Hz, $J_{2,3}$ = 5.2 Hz, H-2); 3.93 (m, 1H, H_{3dig}); 3.86 (dd, 1H, $J_{4,5}$ = 0.4 Hz, $J_{4,3}$ = 3.4 Hz, H-4); 3.83 (qd, 1H, $J_{5,6}$ = 6.0 Hz., $J_{5,4}$ = 0.4 Hz., H-5); 3.71 (dd, 1H, $J_{3,2}$ = 5.2 Hz, $J_{3,4}$ = 3.4

Hz, H-3); 2.78 (m, 1H, OH_{14dig}); 2.36 – 1.13 (m, 22H, H_{dig}); 1.16 (d, 3H, $J_{6,5}$ = 6.0 Hz, H-6); 0.94 (t, 9H, $J_{CH3,CH2}$ = 8.0 Hz., CH_{3Si}); 0.92 (s, 3H, Me_{dig}); 0.87 (s, 3H, Me_{dig}); 0.60 (q, 6H, $J_{CH2,CH3}$ = 8.0 Hz, CH_{2Si}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 174.8 (C-20_{dig}), 174.8 (C=O); 128.5, 128.0, 127.8 ($C_{aromatic}$); 117.9 (C-22_{dig}); 108.6 (C-1); 86.5 (C-4); 85.8 (C-14_{dig}); 78.6 (C-3); 74.0 (C-21_{dig}); 72.2 ($\underline{C}H_2Ph$); 69.6 (C-5); 68.7 (C-3_{dig}); 51.1 – 15.9 (C_{dig}); 33.4 (C-2); 20.5 (C-6); 7.13 ($\underline{C}H_{3Si}$); 5.22 ($\underline{C}H_{2Si}$).

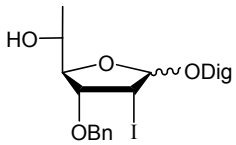
R_f (hexane: ethyl acetate = 4:1): 0.45.

Spectroscopic data obtained from the α/β mixture.

180β: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40 – 7.26 (m, 5H, $H_{aromatic}$); 5.93 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1); 5.20 (dd, 1H, $J_{2,3}$ = 7.8 Hz, H-2); 5.02 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.75 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.63 (dd, 1H, $J_{3,4}$ = 6.6 Hz, H-3); 4.08 (dd, 1H, $J_{4,5}$ = 2.4 Hz, H-4); 3.99 (qd, 1H, $J_{5,6}$ = 6.8 Hz, H-5); 2.73 (s, 4H, $CH_{2succinimide}$); 1.10 (d, 3H, $J_{5,6}$ = 6.8 Hz, H-6); 0.98 (t, 9H, $J_{CH3,CH2}$ = 7.8 Hz, Me); 0.63 (q, 6H, $J_{CH2,CH3}$ = 7.8 Hz, CH_2Si). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 176.33 (O=$C_{succinimide}$); 137.92 ($C_{aromatic}$); 128.60, 128.09 ($\underline{C}H_{aromatic}$); 88.13 (C-1); 86.82 (C-4); 85.14 (C-3); 73.05 ($\underline{C}H_2Ph$); 68.28 (C-5); 28.23 ($\underline{C}H_{2\ succinimide}$); 21.61 (C-2); 19.44 (C-6); 7.11 ($\underline{C}H_3$); 5.08 ($\underline{C}H_2$).

180α: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

Digitoxigenyl 3-*O*-Benzyl-2,6-dideoxy-2-iodo-α,β-D-*allo*-furanoside (181).



Starting from compound **179**:[142] HF·70% in pyridine (0.23 ml, 8.99 mmol, 100 eq) was added to a solution of **179** (75 mg, 0.090 mmols, 1.00 eq, an α/β inseparable mixture, α/β = 1:8) in anhydrous THF (1.2 ml, 0.077 M) at 0 ºC. The mixture was stirred for 6 h. The crude obtained was concentrated under vacuum and purified by column chromatography[168] to yield compound **181** (36 mg, 0.049 mmol, 70%, , an α/β inseparable mixture, α/β = 1:8) as yellowish syrup.

Starting from compound **176**: As described in the *´one–pot´* cyclization–glycosylation procedure, the title compound was prepared starting from **181** (92 mg, 0.28 mmol, 1.00 eq. an *E*/*Z* inseparable mixture, *E*/*Z* = 10:1) and digitoxigenin (155 mg, 0.36 mmol, 1.50 eq) in anhydrous DCM (6.2 ml, 0.045 M). The reaction mixture was stirred from –78 ºC to –20 ºC for 8 h (cyclization, cooled to –60 ºC and then AgOTf (29 mg, 0.11 mmol, 0.40 eq) was added to start glycosylation. The mixture was stirred from –60 °C to –30 ºC during 15 h. (monitored by TLC (hexane: ethyl acetate = 1:1). Radial chromatography (from hexane to ethyl acetate) of the crude afforded compound **181** (130 mg, 0.177 mmol, 63%, an α/β inseparable mixture, α/β = 1:50) as yellowish syrup.

[168]. Also were recovered 10 mg of digitoxigenin (30% from starting product).

R_f (hexane: ethyl acetate = 1:1): 0.40.

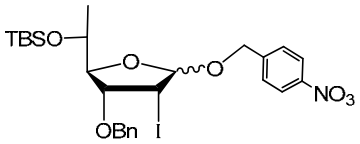
Spectroscopic data extracted from α/β mixture.

Anal. Calcd for $C_{37}H_{51}IO_7$: 60.49% C, 7.00% H. Found: 60.51% C, 6.98% H.

181β: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.36 – 7.28 (m, 5H, $H_{aromatic}$); 5.87 (s, 1H, H_{22dig}); 5.42 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1); 5.00 (d, 1H, J_{AB} = 18.0 Hz, H_{21Adig}); 4.81 (d, 1H, J_{AB} = 18.0 Hz, H_{21Bdig}); 4.78 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.60 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph); 4.47 (dd, 1H, $J_{4,5}$ = 3.0 Hz, $J_{4,3}$ = 6.0 Hz, H-4); 4.15 (dd, 1H, $J_{2,1}$ = 1.2 Hz, $J_{2,3}$ = 2.4 Hz, H-2); 3.99 (qd, 1H, $J_{5,6}$ = 6.4 Hz, $J_{5,4}$ = 3.0 Hz, H-5); 3.93 (m, 2H, H_{3dig}, H-3); 2.77 (m, 1H, OH_{14dig}); 2.17 – 1.20 (m, 22H, H_{dig}); 1.15 (d, 3H, $J_{6\text{-}5}$= 6.4 Hz, H-6); 0.94 (s, 3H, Me_{dig}); 0.87 (s, 3H, Me_{dig}). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 174.8, 174.7 (C=O, C-20_{dig}); 137.7 ($C_{aromatic}$); 128.6, 128.2, 128.1 ($\underline{C}H_{aromatic}$); 117.8 (C-$22_{dig}$); 109.7 (C-1); 86.9 (C-4); 86.5 (C-3); 85.7 (C-14_{dig}); 73.7 (C-21_{dig}); 72.8 (C-3_{dig}); 72.3 ($\underline{C}H_2Ph$); 66.4 (C-5); 51.1 – 15.9 (C_{dig}); 28.4 (C-2); 23.5 (C-6).

181α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

***p*-Nitrobenzyl 3-*O*-Benzyl-5-*O*-tert-butyldimethylsilyl-2,6-dideoxy-2-iodo-α,β-D-*manno*-furanoside (182).**[142]



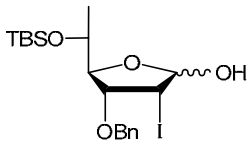
Compound **167** (75 mg, 0.17 mmol, 1eq, an *E*/*Z* inseparable mixture, *E*/*Z* = 21:1), and *p*-nitrobenzyl alcohol (52 mg, 0.34 mmol, 2.00 eq) in anhydrous DCM (3.4 ml, 0.05 M) were reacted following the *´one–pot´* cyclization-glycosylation procedure. Cyclization step was carried out from –60 ºC to –20 ºC in 16 h and glycosylation from –78 ºC to –20 ºC in 4 h. Chromatographic purification yielded compound **182** (67 mg, 0.13 mmol, 68%, an α/β inseparable mixture, α/β = 35:1) as colourless syrup.

Spectroscopic data extracted from α/β mixture.

182β: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 8.23 – 8.17 (m, 2H, $H_{aromatic}$); 7.51 – 7.26 (m, 7H, $H_{aromatic}$); 5.45 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 4.86 (d, 1H, J_{AB} = 13.6 Hz, CH_2PhNO_2); 4.63 (d, 1H, J_{AB} = 13.6 Hz, CH_2PhNO_2); 4.61 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.48 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.37 (dd, 1H, $J_{2,1}$ = 3.2 Hz, $J_{2,3}$ = 5.6 Hz, H-2); 3.98 (dd, 1H, $J_{4,5}$ = 4.8 Hz, $J_{4,3}$ = 5.2 Hz, H-4); 3.88 (qd, 1H, $J_{5,4}$ = 4.8 Hz, $J_{5,6}$ = 6.0 Hz, H-5); 3.73 (dd, 1H, $J_{3,2}$ = 5.6 Hz, $J_{3,4}$ = 5.2 Hz, H-3); 1.14 (d, 3H, $J_{6,5}$ = 6.0 Hz, H-6); 0.85 (s, 9H, tBuSi); 0.055 (s, 3H, MeSi); 0.026 (s, 3H, MeSi). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 147.6, 145.1, 137.3 ($C_{aromatic}$); 128.6, 128.2, 128.1, 128.0, 127.9, 123.8 ($CH_{aromatic}$); 110.0 (C-1); 86.9 (C-4); 77.8 (C-3); 72.4 ($\underline{C}H_2Ph$); 69.2 (C-5); 69.1 ($\underline{C}H_2PhNO_2$); 31.9 (C-2); 26.0 ($\underline{C}H_{3tBuSi}$); 20.4 (C-6); 18.2 (C_{tBuSi}); –4.18, –4.37 ($\underline{C}H_3Si$).

182α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

3-*O*-Benzyl-5-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-2-iodo-α,β-D-*allo*-furanose (183).



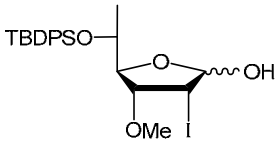
NIS (252 mg, 1.12 mmols, 2.5 eq) was added to a solution of the enitol **167** (200 mg, 0.45 mmols, 1eq) in a MeCN/H_2O = 10:1 mixture (9 ml, 0.05 M) at –10 ºC. After stirring for 45 minutes the reaction was quenched with $Na_2S_2O_3$ and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexane: ethyl acetate = 7:1) afforded compound **183** (205 mg, 0.43 mmol, 95%, an α/β inseparable mixture, α/β = 1:5) as colourless syrup.

Spectroscopic data obtained from α/β mixture

183α: RMN ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.53 – 7.26 (m, 5H, $H_{aromatic}$); 5.61 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1); 4.78 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.64 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.58 (m, 1H, H-4); 4.23 (dd, 1H, $J_{2,1}$ = 4.4 Hz, $J_{2,3}$ = 4.0 Hz, H-2); 4.05 (m, 1H, H-5); 3.81 (m, 1H, H-3); 1.12 (m, 3H, H-6); 0.86 (s, 9H, tBuSi); 0.072 (s, 3H, MeSi); 0.064 (s, 3H, MeSi). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 133.1 – 127.8 ($C_{aromatic}$); 95.8 (C-1); 87.2 (C-4); 78.5 (C-3); 72.7 ($\underline{C}H_2Ph$); 68.5 (C-5); 27.0 (C-2); 26.1 ($\underline{C}H_{3tBuSi}$); 20.6 (C-6); 18.2 (C_{tBuSi}); –4.21, –4.34 ($\underline{C}H_3Si$).

183β: RMN ^{1}H ($CDCl_3$, 400 MHz) δ en ppm: 7.53 – 7.24 (m, 5H, $H_{aromatic}$); 5.53 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1); 4.63 (d, 1H, J_{AB} = 12.0 Hz, CH_2Ph); 4.56 (d, 1H, J_{AB} = 12.0 Hz, CH_2Ph); 4.18 (dd, 1H, $J_{2,1}$ = 7.6 Hz, $J_{2,3}$ = 5.2 Hz, H-2); 3.93 (dd, 1H, $J_{4,5}$ = 5.2 Hz, $J_{4,3}$ = 3.2 Hz, H-4); 3.81 (dd, 1H, $J_{3,2}$ = 5.2 Hz, $J_{3,4}$ = 3.2 Hz, H-3); 3.65 (qd, 1H, $J_{5,4}$ = 5.2 Hz, $J_{5,6}$ = 6.4 Hz, H-5); 1.16 (d, 3H, $J_{6,5}$ = 6.4 Hz, H-6); 0.87 (s, 9H, tBuSi); 0.045 (s, 3H, MeSi); 0.030 (s, 3H, MeSi). RMN ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 137.5 ($C_{aromatic}$); 133.1 – 127.8 ($CH_{aromatic}$); 93.4 (C-1); 88.0 (C-4); 78.6 (C-3); 72.3 ($\underline{C}H_2Ph$); 68.7 (C-5); 30.8 (C-2); 26.1 ($\underline{C}H_{3tBuSi}$); 20.7 (C-6); 18.2 (C_{tBuSi}); –4.19, –4.26 ($\underline{C}H_3Si$).

5-*O*-*tert*-butyldiphenylsilyl-2,6-dideoxy-2-iodo-3-*O*-Methyl-α,β-D-*allo*-furanose (185).



NIS (270 mg, 1.2 mmols, 1.20 eq) was added to a solution of the enitol **173** (569 mg, 1.0 mmols, 1.00 eq) in anhydrous DCM (9 ml, 0.05 M) at –60 ºC and the reaction mixture was warmed up to –20 ºC for 20 h. After the completion of the reaction, the reaction crude was quenched with $Na_2S_2O_3$ and

extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexane: ethyl acetate = 7:1) to afford compound **185** (332 mg, 0.63 mmol, 63%, an α/β inseparable mixture, α/β = 1:15) as colourless syrup.

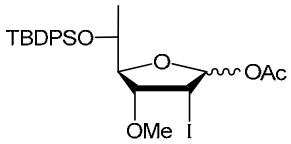
R_f (hexane: ethyl acetate = 8:1): 0.35.

Spectroscopic data obtained from the α/β mixture.

185β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.66 – 7.23 (m, 10H, $H_{aromatic}$), 5.45 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1), 3.89 (d, 1H, $J_{4,5}$ = 6.8, H-4), 4.86 (dd, 1H, $J_{2,3}$ = 5.2 Hz, H-2); 3.72 (m, 1H, H-5); 3.48 (dd, 1H, $J_{3,4}$ = 3.2 Hz, H-3); 3.36 (s, 3H, OMe); 1.09 (d, 3H, $J_{5,6}$ = 6.8 Hz, H-6); 1.06 (s, 9H, Me).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 133.4 ($C_{aromatic}$); 136.17, 132.85, 130.07, 129.98, 129.27, 129.11, 127.10, 127.79 ($\underline{C}H_{aromatic}$); 93.18 (C-1); 87.31 (C-4); 81.01 (C-3); 69.85 (C-5); 58.04 ($O\underline{C}H_3$); 30.13 (C-2); 29.92 (C): 27.27 ($\underline{C}H_3$); 20.66 (C-6).

185α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

Acetyl 5-*O*-*tert*-Butyldiphenylsilyl-2,6-dideoxy-2-iodo-3-*O*-methyl-α,β-D-*allo*-furanoside (186).



AcCl (84 μl, 93 mg, 1.18 mmol, 2.00 eq) and DMAP (13 mg, 0.12 mmol, 0.20 eq) were added to a solution of **185** (312 mg, 0.59 mmol, 1.00 eq) in pyridine (5 ml) and and was stirred for two hours. The reaction was stopped with the addition of NH_4Cl solution and was extracted with ethyl acetate. Coloumn chromatographic purification of the crude afforded compound **186** (252 mg, 0.44 mmol, 75%, an α/β inseparable mixture, α/β = 1:15) as yellowish solid.

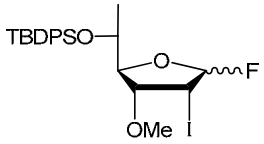
R_f (hexane: ethyl acetate = 6:1): 0.45.

Spectroscopic data obtained from the α/β mixture.

186β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.67 (m, 4H, Ar); 7.41 (m, 6H, Ar); 6.17 (d, 1H, $J_{1,2}$ = 4.8 Hz, H-1); 4.28 (dd, 1H, $J_{2,3}$ = 6.4 Hz, H-2); 4.04 (m, 1H, H-5); 4.03 (dd, 1H, $J_{4,5}$ = 6.8 Hz, H-4); 3.78 (bt, 1H, $J_{3,4}$ = 2.4 Hz, H-3); 3.45 (s, 3H, OMe); 2.11 (s, 3H, OAc); 1.03 (s, 9H, Me); 1.03 (d, 3H, $J_{5,6}$ = 6.8 Hz, H-6).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.51 (O=C); 134.25, 133.09 ($C_{aromatic}$); 136.08, 136.00, 130.13, 130.01, 127.94, 127.88, 127.81 ($\underline{C}H_{aromatic}$); 96.75 (C-1); 88.79 (C-4); 79.04 (C-3); 69.21 (C-5); 59.14 ($O\underline{C}H_3$); 29.89 (C): 27.22 ($\underline{C}H_3$); 26.21 (C-2); 21.50 ($O{=}C\underline{C}H_3$); 19.50 (C-6).

186α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

5-*O*-*tert*-Butyldiphenylsilyl-2,6-dideoxy-2-iodo-3-*O*-methyl-α,β-D-*allo*-furanosyl Fluoride (187).



DAST (64 μl, 87 mg, 0.66 mmol, 1.50 eq) was added to a solution of compound **185** (230 mg, 0.44 mmol, 1.00 eq) in anhydrous DCM (4 ml) at 0 ºC. The reaction mixture was warmed up to room temperature and was further stirred for 2 hours. The reaction was quenched with $NaHCO_3$ extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The chromatographic purification the mixture was purified by radial chromatography (from hexane to hexane: ethyl acetate = 3:1) and to afford **187** (200 mg, 0.44 mmol, 86%, an α/β inseparable mixture, $\alpha/\beta = 1{:}15$) as a yellowish syrup.

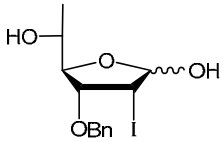
R_f (hexane: ethyl acetate = 8:1): 0.67.

Spectroscopic data obtained from the α/β mixture.

187β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.72 (m, 4H, $H_{aromatic}$); 7.49 (m, 6H, $H_{aromatic}$); 6.11 (d, 1H, $J_{1,F}$ = 66.4 Hz, $J_{1,2}$ = 0.0 Hz, H-1); 4.49 (dd, 1H, $J_{2,F}$ = 8.0 Hz, $J_{2,3}$ = 5.2 Hz, H-2); 4.16 (m, 1H, H-5); 4.00 (qd, 1H, $J_{4,F}$ = 9.6 Hz, $J_{4,5}$ = 3.6 Hz, H-4); 3.55 (dd, 1H, $J_{3,4}$ = 7.2 Hz, H-3); 3.32 (s, 3H, OMe); 1.07 (s, 9H, Me); 0.96 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.85, 133.11 ($C_{aromatic}$); 136.22, 136.14, 130.67, 129.88, 129.82, 129.28, 127.78, 127.72 ($CH_{aromatic}$); 116.49 (d, $J_{C1\text{-}F}$ = 228.1 Hz, C-1); 87.16 (C-4); 77.67 (C-3); 69.04 (C-5); 58.08 (OCH_3); 33.32 (d, $J_{C1\text{-}F}$ = 22.7 Hz, C-2); 29.91 (C): 27.09 ($\underline{C}H_3$); 19.43 (C-6).

187α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.

3-*O*-Benzyl-2,6-dideoxy-2-iodo-α,β-D-*allo*-furanose (189).



NIS (65 mg, 0.29 mmols, 1.2 eq) was added to a solution of the enitol **176** (80 mg, 0.24 mmols, 1.00 eq, an *E*/*Z* inseparable mixture, *E*/*Z* = 10:1) in anhydrous DCM (9 ml, 0.05 M) at –60 ºC and the resulting mixture was warmed up to –20 ºC for 20 h. After the completion of the reaction, the reaction mixture was quenched with $Na_2S_2O_3$ and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with water (2x20 ml), brine (1x20 ml), dried on anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexane: ethyl acetate = 2:1) to

afford compound **189** (49 mg, 0.13 mmol, 56%, an α/β inseparable mixture, α/β = 1:10) as yellowish syrup.

R_f (hexane: ethyl acetate = 2:1): 0.35.

Spectroscopic data obtained from the α/β mixture.

189β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.66 – 7.23 (m, 5H, $H_{aromatic}$), 5.29 (s, 1H, H-1), 4.57 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 4.38 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2); 4.29 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph); 3.91 (dd, 1H, $J_{4,5}$ = 7.6, H-4), 3.89 (dd, 1H, $J_{3,4}$ = 0.8 Hz, H-3); 3.84 (m, 1H, H-5); 1.09 (d, 3H, $J_{5,6}$ = 6.8 Hz, H-6).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 131.11($C_{aromatic}$); 129.28, 128.67, 128.56, 127.28, 127.67 ($\underline{C}H_{aromatic}$); 108.86 (C-1); 83.80 (C-4); 76.50 (C-3); 73.63 (C-5); 72.59 ($\underline{C}H_2Ph$); 35.59 (C-2); 29.92 (C); 17.29 (C-6).

189α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: Could not be determined.