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Stereoselective Synthesis of 2-Deoxyoligosaccharides

OMAR BOUTUREIRA MARTÍN

Dissertation presented to receive the degree of Doctor of the Universitat Rovira i Virgili, European mention

UNIVERSITAT ROVIRA I VIRGILI
Departament de Química Analítica i Química Orgànica
Tarragona, July 2007

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Sergio Castillón Miranda, Catedrático del Departamento de Química Analítica y Química Orgánica de la Universidad Rovira i Virgili

CERTIFICA:

Que la presente tesis doctoral titulada: "Stereoselective Synthesis of 2-Deoxyoligosaccharides" presentada por Omar Boutureira Martín para optar al grado de Doctor por la Universidad Rovira i Virgili con mención europea, ha estado realizada bajo su inmediata dirección en los laboratorios de Química Orgánica del Departamento de Química Analítica y Química Orgánica de la misma universidad.

Tarragona, Julio de 2007

Prof. Sergio Castillón Miranda

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Me gustaría agradecer a todas aquellas personas que han contribuido en la realización de esta tesis. Quisiera expresar mi mas sincera gratitud a mi director de tesis, el Prof. Sergio Castillón por haber depositado su confianza en mi y por su apoyo en la elaboración de esta memoria. Gracias Sergio por tu paciencia, dedicación, consejos y ánimos durante todos estos años.

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A mis abuelitos

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Abbreviations

AIBN	2,2'-Azobisisobutyronitrile
BHPO	*β*-Hydroxyphosphine Oxide
CM	Cross Metathesis
COSY	Correlation Spectroscopy
CSA	(±)-Camphor-10-sulfonic Acid
DAST	Diethylaminosulfur Trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	1,2-Dichlorobenzene
DEAD	Diethyl Azodicarboxylate
DIBAL	Diisobutylaluminium Hydride
DMTSF	Dimethyl(methylthio)sulfonium Tetrafluoroborate
DMF	*N*,*N*-Dimethylformamide
DTBS	Di-*tert*-butylsilylene
EDTA	Ethylenediaminetetraacetic Acid
FT–IR	Fourier Transform–Infra Red Spectroscopy
GC–EIMS	Gas Chromatography–Electronic Impact Mass Spectrometry
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HSQC	Heteronuclear Single-quantum Correlation
IDCP	Iodonium Dicollidine Perchlorate
KHMDS	Potassium Bis(trimethylsilyl)amide
LACDAC	Lewis Acid Catalyzed Diene-aldehyde Cycloaddition
LDA	Lithium Diisopropylamide
LN	Lithium Naphthalenide
LUMO	Lowest Unoccupied Molecular Orbital
MPLC	Medium-pressure Liquid Chromatography
MS	Molecular Sieves
MW	Microwave
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy

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NPSP	*N*-(Phenylselenenyl)phthalimide
PMBOH	4-Methoxybenzyl Alcohol
RCM	Ring-closing Metathesis
ROCM	Ring-opening Cross Metathesis
ROMP	Ring-opening Metathesis Polymerization
Selectfluor®	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane Bis(tetrafluoroborate)
TBAF	Tetrabutylammonium Fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TTBP	2,4,6-Tri-(*tert*-butyl)pyrimidine
UV	Ultraviolet Light

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List of Publications

This thesis is based on the following publications:

I **Stereoselective Synthesis of 2-Deoxy-2-iodoglycosides from Furanoses: A New Route to 2-Deoxyglycosides and 2-Deoxyoligosaccharides of *ribo* and *xylo* Configuration**
Miguel A. Rodríguez, Omar Boutureira, Xavier Arnés, M. Isabel Matheu, Yolanda Díaz, and Sergio Castillón, *J. Org. Chem.* **2005**, *70*, 10297.

II **Stereoselective Synthesis of 2-Deoxyglycosides from Sulfanyl Alkenes by Consecutive "One Pot" Cyclization and Glycosylation Reactions**
Miguel A. Rodríguez, Omar Boutureira, M. Isabel Matheu, Yolanda Díaz, and Sergio Castillón, *Eur. J. Org. Chem.* **2007**, 2470.

III **Stereoselective Synthesis of 2-Deoxy-2-phenylselenenyl glycosides from Furanoses: Implication of the Phenylselenenyl Group in the Stereocontrolled Preparation of 2-Deoxy-*ribo*- and 2-Deoxy-*xylo*-oligosaccharides**
Omar Boutureira, Miguel A. Rodríguez, David Benito, M. Isabel Matheu, Yolanda Díaz, and Sergio Castillón, *Eur. J. Org. Chem.* **2007**, doi: 10.1002/ejoc.200700161.

IV **Synthesis of Carbohydrate-based Vinyl Selenides via Wittig-type Reactions**
Omar Boutureira, M. Isabel Matheu, Yolanda Díaz, and Sergio Castillón, *Carbohydr. Res.* **2007**, *342*, 736.

V **Microwave-assisted Cross Metathesis Reactions of Carbohydrate Derivatives with Electron-rich Olefins**
Omar Boutureira, M. Isabel Matheu, Yolanda Díaz, and Sergio Castillón. In Preparation.

VI **General Method for Synthesizing Pyranoid Glycals: A New Route to Allal and Gulal Derivatives**
Omar Boutureira, Miguel A. Rodríguez, M. Isabel Matheu, Yolanda Díaz, and Sergio Castillón, *Org. Lett.* **2006**, *8*, 673.

VII **Synthesis of 2-Iodoglycals versus Glycals from 2-Deoxy-2-iodopyranoses under Dehydrative Glycosylation Conditions**

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Miguel A. Rodríguez, Omar Boutureira, M. Isabel Matheu, Yolanda Díaz, Sergio Castillón, and Peter H. Seeberger. In Preparation.

VIII **Recent Advances in the Glycosylation of Sphingosines and Ceramides**
José A. Morales-Serna, Omar Boutureira, M. Isabel Matheu, Yolanda Díaz, and Sergio Castillón, *Carbohydr. Res.* **2007**, doi: 10.1016/j.carres.2007.03028.

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1 Introduction

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Carbohydrates are ubiquitous and important biomolecules. Besides their role in energy storage, they form much of the structural framework of cells and tissues. As part of glycoproteins, glycolipids, and other conjugates, they are key elements in a variety of processes such as signalling, cell–cell communication, and molecular and cellular targeting. Polisaccharides differ from the other two classes of biological polymers in two important characteristics: they can be highly branched molecules, and their monomeric units may be connected to one another by many different linkage types. Their structural diversity, which allows them to encode information required for specific molecular recognition and to determine the post-translational modification of proteins, is much more complex than that of proteins and nucleic acids. These findings led to an immense interest in the preparation of oligosaccharides and glycoconjugates as well as the understanding of their interaction with their natural receptors. [1]

However, the preparation of pure oligosaccharides is hampered by difficulties associated with the regioselective protection of polyhydroxyls and challenges related to the stereoselective assembly of glycosidic linkages.[2] Further improvements in the methods by which oligosaccharides are sequenced and synthesized will be needed in order to supply synthetic derivatives, both natural oligosaccharides and modified analogues with altered biological properties (i.e., deoxy- and deoxy-fluoro analogues) as lead compounds in key therapeutic areas.[3]

1.1 Deoxyglycosides

2-Deoxy- and 2,6-dideoxyglycosides are important structural units in many natural products including antitumor drugs (anthracyclines, aureolic acids, calicheamicin, esperamicin), antibiotics active against Gram-positive bacteria (erythromycins, orthosomycins), antibiotics inhibiting platelet aggregation (angucyclines), cardiac glycosides (digitoxine), and antiparasitic agents (avermectins).[4]

Whereas the therapeutic effect of these drugs is usually mediated by their aglycon, the glycosidic part influences the pharmacokinetic properties of the physiologically active compounds. Removing deoxysugars from these clinically important molecules often severely decreases their efficiency and/or specificity.[5] Deoxysugars also play an important role in lipopolysaccharides, glycoproteins, and glycolipids, where they act as ligands for cell–cell interactions or as targets for toxins, antibodies, and microorganisms and are

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[1] Dwek, R. A. *Chem. Rev*. **1996**, *96*, 683.
[2] Ernst, B.; Hart, G.W.; Sinaÿ, P. Eds., In *Carbohydrates in Chemistry and Biology*, Part I; Wiley, Weinheim, 2000.
[3] Meutermans, W.; Le, G. T.; Becker, B. *ChemMedChem*, **2006**, *1*, 1164.
[4] (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.
[5] Křen, V.; Martínková, L. *Curr. Med. Chem.* **2001**, *8*, 1313.

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involved in active biochemical and bioorganic processes including active transmembrane transport, stabilization of protein folding, and enzyme inhibition.[6]

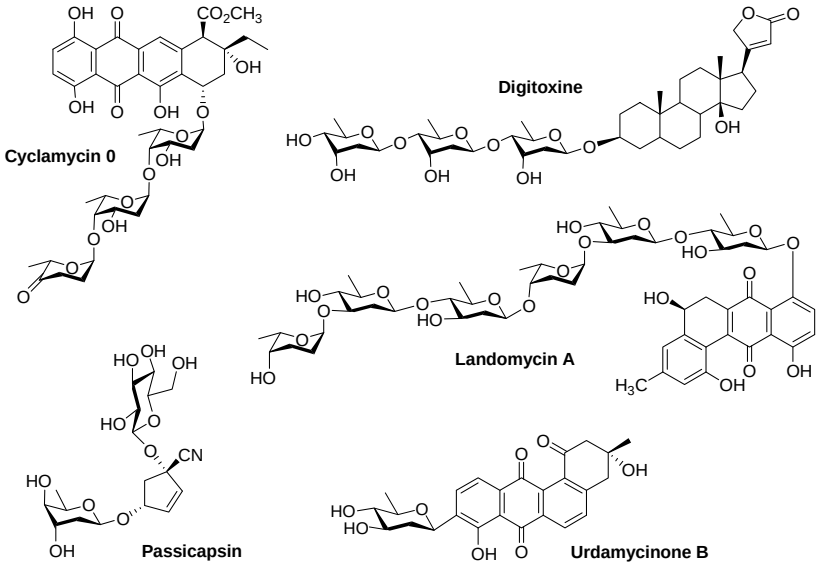

Figure 1.1 Examples of compounds with 2-deoxyoligosaccharide units

Due to this biological relevance, the development of methods for the efficient and stereoselective construction of deoxyglycosidic linkages will have useful applications in medicinal and bioorganic chemistry by furthering the understanding of biological mechanisms and elaborate new and less toxic drugs. The lack of a stereodirecting neighboring group adjacent to the anomeric center makes 2-deoxyglycoside synthesis a particular challenge. Moreover, the absence of electron-withdrawing substituents at C-2 makes the glycosidic bond much more acid labile, giving rise to easy hydrolysis or anomerization. Glycals soon appeared as ideal precursors especially for the synthesis of 2-deoxy-α-glycosides which are thermodynamically more stable than the β-isomers. The most frequently employed strategy for accessing 2-deoxy-β-glycosides uses temporary equatorial blocking groups at C-2 which can be removed after glycosylation. These groups should stabilize the glycosidic bond and provide the assistance required for a good β-selectiviy.[7]

---

[6] (a) Albrecht, H. P. In *Naturally Ocurring Glycosides*, Ikan, R., Ed., Wiley, Chichester, 1999. (b) Weymouth-Wilson, A.C. *Nat. Prod. Rep*. **1997**, *14*, 99. (c) Kirschning, A.; Bechtold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1. (d) Allen, H. J.; Kisailus, E. C. Eds., *Glycoconjugates: Composition, Structure and Function*, Marcel Dekker, New York, 1992.

[7] (a) Kirschning, A.; Jesberger, M.; Schoning, K.-U. *Synthesis* **2001**, 507. (b) Veyrières, A. In *Carbohydrates in Chemistry and Biology*, Part I, Vol. 1; Ernst, B.; Hart, G.W.; Sinaÿ, P. Eds., Wiley-VCH, Weinheim, 2000. (c) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137. (d) Boon, G.-J.; Demchenko, A. V. *Chem. Rev*. **2000**, *100*, 4539. (e) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385 and references therein.

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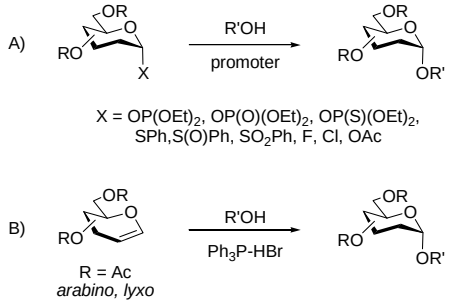
1.1.1 Synthesis of 2-deoxy-*α*-glycosides

No control element at C-2

2-Deoxy-*α*-glycosides can be obtained from 2-deoxy glycosyl donors driving the glycosylation under thermodynamic conditions. Many different leaving groups have been tested with this purpose and the reaction takes place through an oxonium intermediate to give mainly the *α*-anomer[8] (Scheme 1.1, A). Another important and general method for synthesising 2-deoxy-*α*-glycosides is simply the acid-catalyzed activation of glycals to form an anomeric oxonium ion intermediate in the presence of an acceptor to afford the final glycoside.[9] However, the acid catalyst has to be carefully chosen in order to avoid the Ferrier allylic rearrangement. A Ph_3P–HBr system is usually employed as a weak acid source (Scheme 1.1, B).



Scheme 1.1 Selected methods for the synthesis of 2-deoxy-*α*-glycosides (from 2-deoxy glycosyl donors and acid-catalyzed strategies)

Control element at C-2

Glycals have been activated using a variety of electrophilic halogen and chalcogen sources. In these cases the attack of the electrophile to the enolether introduces a bulky hetroatom at C-2 which can control the stereoselectivity of the glycosylation. Usually halonium, episulfonium, and selenonium cations have been postulated as reaction intermediates being responsible for the high stereoselectivity observed in these processes. However, we have demonstrated that the real intermediate is an oxonium cation; consequently, the observed stereoselectivity is a result of the presence of a bulky substituent at C-2, and does not come from the formation of a cyclic intermediate.[10] The

[8] (a) Jaunzems, J.; Hofer, E.; Jesberger, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1166. (b) Schene, H.; Waldmann, H. *J. Chem. Soc., Chem. Commun.* **1998**, 2759. (c) Bielawska, H.; Michalska, M. *Tetrahedron Lett.* **1998**, *39*, 9761. (d) Li, H.; Chan, M.; Zhao, K. *Tetrahedron Lett.* **1997**, *38*, 6143.

[9] 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.

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

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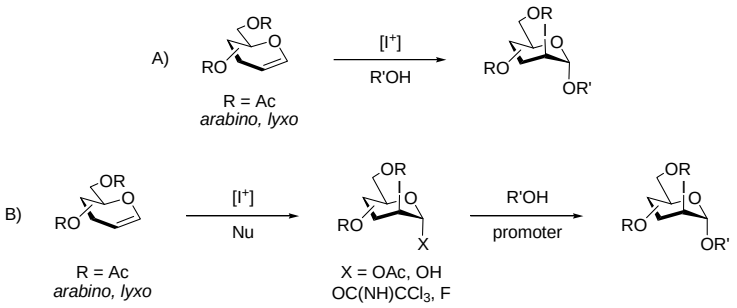
addition of *N*-iodosuccinimide (NIS) or iodoniumdicollidine perchlorate (IDCP) to glycals in the presence of an acceptor has become a routine procedure for the synthesis of *α*-linked disaccharides.[11] When iodine is used as an electrophile, the iodine attacks the more electronegative upper face, resulting in the introduction of the iodine in the *axial* position, and the attack of the alcohol takes place *trans* to the iodine. The use of this procedure for more common glycals such as D-glucal and D-galactal, results in obtaining 2-deoxy-2-iodo-*α-manno*- or *talo*-glycosides with excellent stereoselectivity (Scheme 1.2, A).

In the last years a great number of glycosylation procedures based on an efficient leaving group/promoter couple have been reported. They allow glycosylation reactions in very mild conditions and permit an orthogonal activation. In this context, a new generation of glycosyl donors has been prepared by reacting glycals with NIS and different nucleophiles (i.e., AcOH) which can behave as leaving groups in the next glycosylation reaction (Scheme 1.2, B).



Scheme 1.2 Selected methods for the synthesis of 2-deoxy-*α*-glycosides (from glycals)

Alternatively, when a glycal is activated in the presence of water, 2-deoxy-2-iodopyranoses are formed, which can be then transformed into other useful glycosyl donors such as fluorides and trichloroacetimidates. In a second step, the glycosylation is carried out by activating these new glycosyl donors under the appropriate conditions. This strategy allows a wide range of glycosylation possibilities.[12]

[11] For some approaches using glycals through a one-pot procedure, see: (a) Fyvie, W. S.; Morton, M.; Peczuh, M. W. *Carbohydr. Res.* **2004**, *339*, 2363. (b) Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *Tetrahedron* **2002**, *58*, 369. (c) Danishesky, S. S.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (d) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696. (e) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem*. **1965**, *43*, 2190. (f) Lemieux, R. U.; Levine, S. *Can. J. Chem*. **1964**, *42*, 1473.

[12] For some approaches using glycals through a two-step procedure, see: (a) Kirschning, A.; Jesberger, M.; Schönberger, A. *Org. Lett.* **2001**, *3*, 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.

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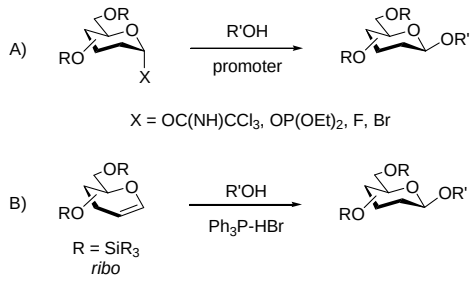
1.1.2 Synthesis of 2-deoxy-*β*-glycosides

No control element at C-2

The absence of electron-withdrawing substituents on the saccharide units readily promotes the anomerization of *β*-glycosides under acidic glycosylation conditions. Furthermore, the non-availability of neighboring-group participation from substituents at C-2 and the enhanced conformational flexibility derived from the reduced number of substituents make it difficult to achieve glycosylation in a stereoselective manner. However, several methods are available for direct *β*-selective glycosylations by using 2-deoxy glycosyl donors[13] (Scheme 1.3, A) or involving the acid-catalyzed activation of glycals[14] with Ph_3P–HBr (Scheme 1.3, B).



Scheme 1.3 Selected methods for the synthesis of 2-deoxy-*β*-glycosides (from 2-deoxy glycosyl donors and acid-catalyzed strategies)

Alternatively, Zhou and O'Doherty have developed a linear and stereocontrolled route to the mono-, bis-, and trisaccharide of digitoxine.[15] This de novo procedure started with the palladium-catalyzed glycosylation of digitoxigenin **II** with the pyranone **I** to render product **III** as a single diastereoisomer. Further reduction, rearrangement, and dihydroxylation reactions furnished deprotected monodigitoxoside **IV**. Repetition of these procedures in iterative manner yielded the disaccharide first and, eventually, digitoxine (Scheme 1.4).

---

[13] (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.

[14] (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.

[15] (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.

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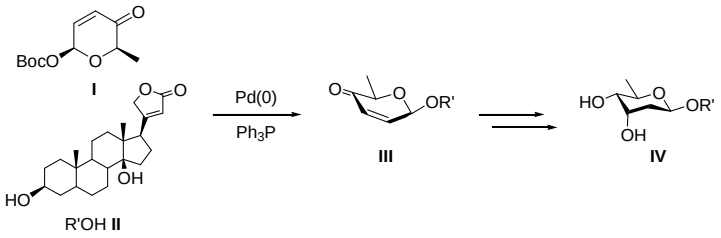

Scheme 1.4 Selected method for the synthesis of 2-deoxy-*β*-glycosides (de novo metal-catalyzed strategy)

Control element at C-2

Although the addition of electrophiles to glycals in the presence of an acceptor has become a useful protocol for providing directly *α*-linked disaccharides, the application of the same protocol to obtain *β*-glycosides is less frequent.[16] Thus, glycosyl donors bearing halogens or chalcogens at C-2 are the more commonly employed precursors for the synthesis of *β*-linked disaccharides and oligosaccharides.[17] The addition of any electrophilic iodine in acetic acid to glycals 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.[18] 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 can 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.[19] The best results were obtained when the D-glycal precursor lacked oxygentation at C-6, or when it was bis-silylated and could readily exist in a twisted boat conformation $^{5}H_{4}$ (Scheme 1.5, A). All the other glycosyl donors that adopt the normal $^{4}C_{1}$ conformation and/or have deactivating heteroatom substituents at C-6, required a higher

[16] 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.

[17] 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.

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

[19] Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267.

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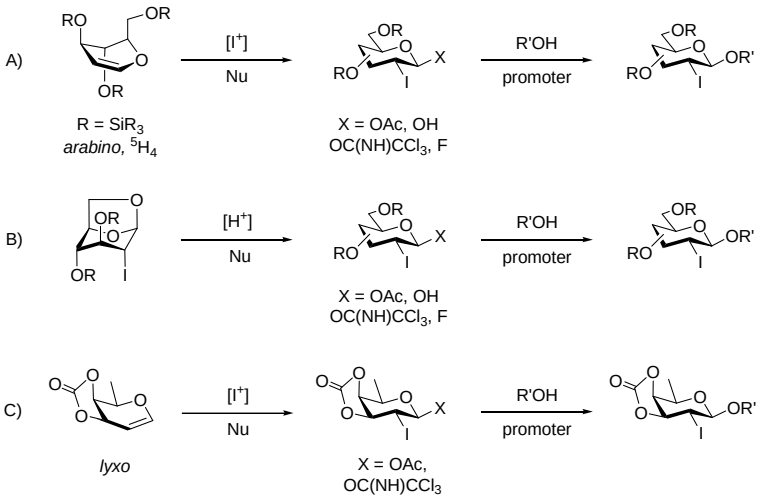
temperature. Alternatively, 2-deoxy-2-iodoglucosyl donors can be selectively prepared by opening, in acidic conditions, the corresponding 1,6-anhidro compound, which in turn can be easily obtained by iodocyclization of D-glucal[20] (Scheme 1.5, B).

When configurations different from the *arabino* are subjected to haloalkoxylation reaction, the presence of special protecting groups can lead to the formation of the desired equatorially disposed halo glycosyl donors in high yield. 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[21] (Scheme 1.5, C).



Scheme 1.5 Selected methods for the synthesis of 2-deoxy-*β*-glycosides (from glycals and 2-halo glycosyl donors)

Interestingly, electrophilic sulfur and selenium species in the presence of alcohols add to the double bond of glycals in a *trans* fashion to give glycosides. The face-selectivity of this approach may be influenced by a variety of factors including the solvent polarity, the conformation of the reacting glycal, and the nature of the substituents on the glycal (Scheme 1.6, 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.

[20] (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.
[21] Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1871.

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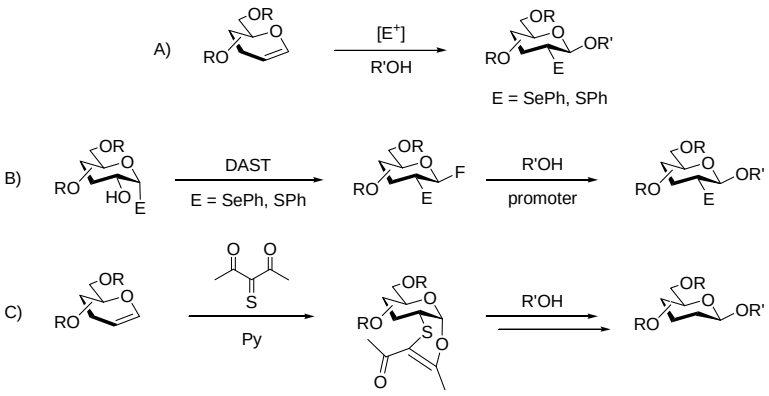
Alternatively, special glycosyl donors with 2-substituents[22] acting as a neighboring group or 1,2-anhydropyranoses[23] are used, followed by reductive removal of the 2-substituent. Thus, Nicolaou and co-workers[24] reported an original approach for preparing 2-deoxy-2-phenylsufanyl- and 2-phenylselelenenyl-*β*-*gluco*-pyranosyl fluorides by reacting 1-thio-*α*- and 1-seleno-*α*-glycosides with the 2-OH unprotected by diethylaminosulfur trifluoride (DAST) (Scheme 1.6, B). DAST initially reacts with the 2-OH converting it into a good leaving group and delivering a fluoride anion. A 1,2-migration of the group at the anomeric position with concomitant entry of fluorine at position 1 affords the 2-deoxy-2-phenylsufanyl- and 2-phenylselelenenyl-*β*-*gluco*-pyranosyl fluorides. These compounds are excellent glycosyl donors and have allowed 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,[25] Franck and co-workers[26] 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 1.6, C).



Scheme 1.6 Selected methods for the synthesis of 2-deoxy-*β*-glycosides (from glycals and 2-chalcogen glycosyl donors)

A conceptually different approach was developed by Toshima and Tatsuta with the use of 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars for the stereocontrolled synthesis of 2,6-

[22] (a) Yu, B.; Yang, Z. *Org. Lett.* **2001**, *3*, 377. (b) Castro-Palomino, J. C.; Schmidt, R. R. *Synlett* **1998**, 501.
[23] Gervay, J.; Danishefsky, S. J. *J. Org. Chem.***1991**, *56*, 5448.
[24] (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.
[25] Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995.
[26] (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.

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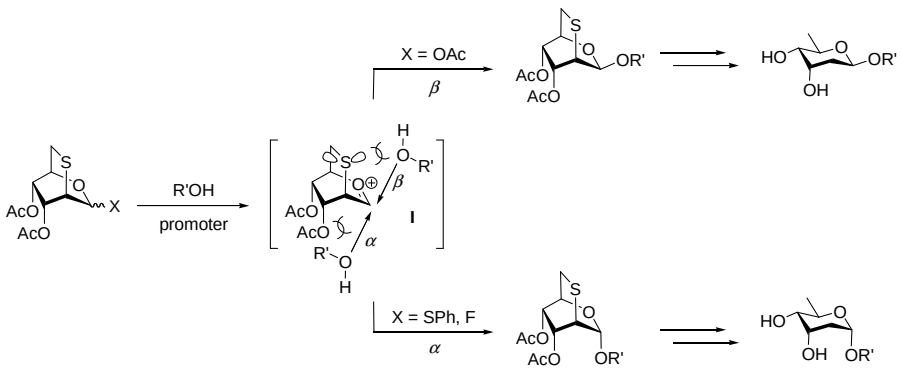
dideoxy-*α*- and -*β*-glycosides.[27] These new donors have a very rigid bicyclic structure (boat conformation) and the stereoselectivity of the glycosylation should not be affected by the anomeric effect in the same manner as the more usual chair conformers (Scheme 1.7).

A variety of leaving groups X can be used. Particularly when they are SPh or F, the activation under kinetic conditions affords 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 thermodinamically more stable compound.

In this way, both anomers can be stereoselectively obtained depending on the reaction conditions. 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 results from 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.



Scheme 1.7 Synthesis of 2-deoxy-glycosides using 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars

Most of the procedures commented before 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 examples reported of 2,6-dideoxy-D-*xylo*-hexoglycosides (D-boivinose), probably because of the difficulty of obtaining the corresponding glycals. Consequently, efficient glycosylation methods, which are among the most fundamental and important reactions of carbohydrates, are of particular interest in the synthesis of these rare and biologically important configurations.

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

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1.2 Electrophile-induced cyclizations

All the approaches which have been described so far involved glycosylation reactions, that is to say the creation of an exocyclic C1–O bond on the pyranose ring. However, it should be also possible to construct a 2-deoxyglycoside by formation of the endocyclic C1–O bond from an acyclic sugar via an electrophilic cyclization reaction.

Electrophile-promoted cyclization reactions of functionalized hydroxyl alkenes and carboxylic acids leading to cyclic ethers and lactones, as well as several cyclization reactions leading to nitrogen heterocycles, are useful methods for the construction of complex organic molecules.[28] The conditions of cyclization are, in general, independent of the nucleophile (O, N, S, and C), and the electrophilic reagents commonly used are mercury salts, chalcogens, and halogens.

Although the regioselectivity can be explained by Baldwins´ rules,[29] some 5-*endo*-trig electrophile-induced cyclizations, which are not favored according to these rules, have been reported.[30] The fact that these cyclizations are electrophile- rather than nucleophile-driven suggests that they are not true exceptions.[31] In general, electrophilic cyclizations can be carried out under kinetic or thermodynamic conditions. Under kinetic conditions, a base is used to deprotonate the oxonium cation in the cyclic intermediate, and this makes the reaction irreversible. Under these conditions, *exo* cyclizations are usually preferred. However, the percentage of *endo* products increases as substitution increases at the terminal olefinic carbon atom.[32]

---

[28] (a) Knight, D.W. *Progress in Heterocyclic Chemistry* **2002**, *14*, 19. (b) Orena, M. *Houben-Weyl*, Vol. 21e; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schumann, E. Eds., Georg Thieme Verlag, Stuttgart, New York, 1995. (c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (d) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (e) Bartlett, P. A. In *Asymmetric Synthesis*, Vol. 3; Morrison, J. D. Ed., Academic Press, London, 1984.

[29] Baldwin, J.E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

[30] (a) Bedford, S. B.; Fenton, G.; Knight, D. W.; Shaw, D. E.; *J. Chem. Soc., Perkin. Trans. 1* **1996**, 1505. (b) Bennett, D. W.; Knight, D. W.; Fenton, G.; *J. Chem. Soc., Perkin Trans. 1* **1991**, 1543 and 133.

[31] Jones, A.D.; Knight, D.W.; Redfern, A.L.; Gilmore, J. *Tetrahedron Lett.* **1999**, *40*, 3267 and references therein.

[32] Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S. Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4062.

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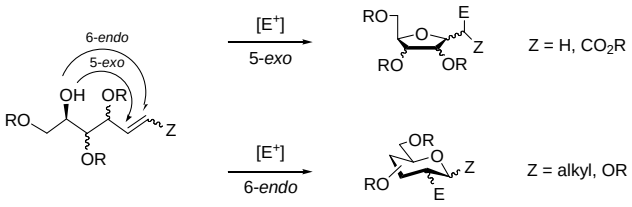
1.2.1 Electrophile-induced cyclizations of carbohydrate-derived alkenols

The situation is more complex for polyhydroxylated alkenes, since several cyclization paths may be followed.[33] In particular, cyclizations from tetrahydroxyhexenes and heptenes with a terminal double bond (usually derived from pentoses) have been widely studied,[34] and the preferred process is 5-*exo* (Scheme 1.8, Z = H). In the case of hydroxy alkenes substituted at the double bond, the regioselectivity of the cyclization can be controlled by this substituent. Thus, electron-withdrawing groups such as esters[35] lead to 5-*exo* cyclizations (Scheme 1.8, Z = CO_2R) to render highly substituted tetrahydrofurans, whereas electron-donating groups such as alkyl[36] and alkoxy[37] direct the process to 6-*endo* cyclization products (Scheme 1.8, Z = alkyl and OR).



Scheme 1.8 Regioselective outcome of the electrophilic cyclization of carbohydrate-derived tetrahydroxyhexenes

For example, the intramolecular oximercuration-demercuration of enol ethers has proven useful for the diastereoselective preparation of disaccharides.[38] This approach provides a novel solution to the problem of the stereocontrolled synthesis of Neu5Ac α- and β-glycosides (Scheme 1.9). Its main originality is that the steric outcome is dictated by that of a Wittig-type condensation. On the other hand, these compounds should be good precursors for the preparation of more complex oligosaccharides, where Neu5Ac is substituted or glycosylated either on positions 7, 8, or 9.

---

[33] For selected cyclizations of di-, tri-, and pentahydroxy alkenes, see: (a) Bravo, F.; Castillón, S. *Eur. J. Org. Chem.* **2001**, 507. (b) Casero, F.; Cipolla, L.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1996**, *61*, 3428. (c) Lipshutz, B. H.; Tirado, R. *J. Org. Chem.* **1994**, *59*, 8307. (d) Haudrechy, A.; Sinaÿ, P. *J. Org. Chem.* **1992**, *57*, 4142. (e) Nicotra, F.; Perego, R.; Ronchetti, F.; Russo, G.; Toma, L. *Carbohydr. Res.* **1984**, *131*, 180. (f) Nicotra, F.; Ronchetti, F.; Russo, G. *J. Org. Chem.* **1982**, *47*, 4459. (g) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. (h) Pougny, J.-R.; Nassr, M. A. M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375.

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

[35] Guindon, Y.; Soucy, F.; Yoakim, C.; Ogilvie, W. W.; Plamondon, L. *J. Org. Chem.* **2001**, *66*, 8992.

[36] Jung, M. E.; Lew, W. *J. Org. Chem.* **1991**, *56*, 1347.

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

[38] Paquet, F.; Sinaÿ, P. *Tetrahedron Lett.* **1984**, *25*, 3071.

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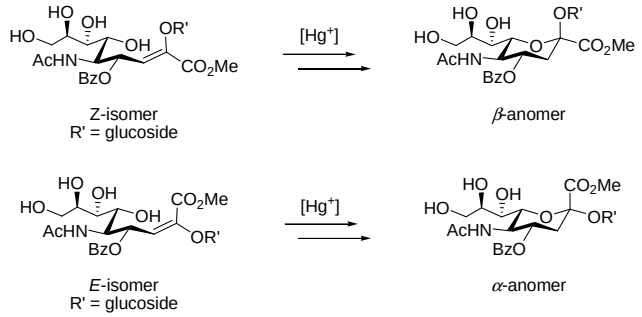
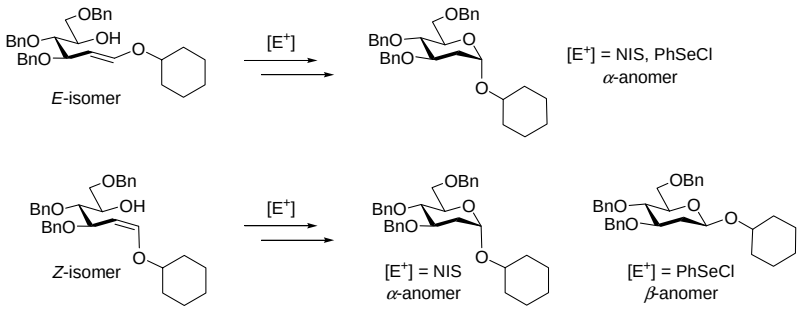


Scheme 1.9 Electrophilic cyclization of carbohydrate-derived tetrahydroxyhexenes (approach to sialic acid-containing disaccharides via oximercuration reaction)

Alternatively, acyclic enol ethers obtained by Wittig–Horner olefination upon 2,3,5-tri-O-benzyl-D-arabinofuranose undergo intramolecular cyclizations when they are treated with an electrophile[39] (Scheme 1.10). NIS gives predominantly 2-deoxy-2-iodo-α-D-mannopyranosides which can be deiodinated to give 2-deoxy- α-glycosides. The reaction of the Z-isomer with phenylselenenyl chloride, followed by radical deselenation, gives mainly the 2-deoxy-β-glycosides.



Scheme 1.10 Electrophilic cyclization of carbohydrate-derived tetrahydroxyhexenes (approach to 2-deoxydisaccharides via electrophilic cyclization of enol ethers)

Since the chemistry of sugars is dominated by the reactivity of the glycosidic bond, a great deal of effort has gone into the synthesis and study of *C*-glycosyl derivatives in which the acetal linkage has been replaced by a hydrolytically stable carbon–carbon bond. Thus, Armstrong and Teegarden[40] reported the synthesis of α-methyl 1',2'-dideoxycellobioside **III** via a bromonium-ion-induced cyclization of *trans*-acetonide olefin **I** (Scheme 1.11). The transformation does not involve the exo anomeric carbon. Indeed, the regiochemical

[39] (a) Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 1525. (b) Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 683.
[40] Armstrong, R. W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 915.

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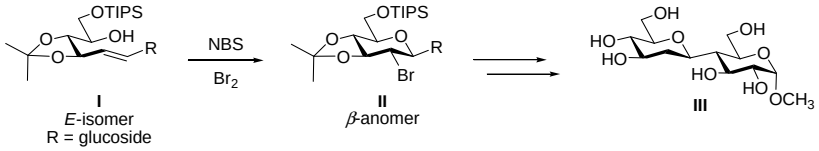
control is achieved by the use of a *trans*-fused isopropylidene ring between the allylic and homoallylic oxygens in the starting alkenol because the competing 5-*exo*-trig cyclization to a *trans*-fused [3.3.0] bicyclic structure requires a highly strained transition state. Furthermore, this elegant approach allows the control of the anomeric configuration by the choice of *Z* (to give α) or *E* (to give β) as the cyclization precursor.



I
E-isomer
R = glucoside

II
β-anomer

III

Scheme 1.11 Electrophilic cyclization of carbohydrate-derived tetrahydroxyhexenes (approach to 2-deoxy-*C*-disaccharides via electrophilic cyclization)

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2 Objectives

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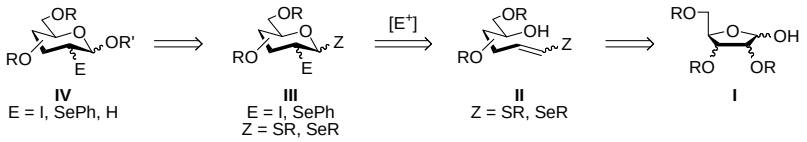
The research described in this thesis aims to investigate a new method for the stereoselective synthesis of 2-deoxyglycosides and oligosaccharides based on a new access to 2-deoxy-2-iodo- and 2-deoxy-2-phenylselenenyl glycosyl donors that would not be limited by the availability of pyranoid glycals and by the stereoselective addition of electrophiles. This new synthetic route involves the preparation of glycosyl donors of type **III** through a cyclization of alkenols **II** induced by electrophiles. These alkenols can be prepared by an olefination reaction starting from protected furanoses **I** (Scheme 2.1). Due to the availability of the configurationally different pentoses, the method should provide access to 2-deoxypyranosides of all configurations.



Scheme 2.1 Proposed methodology for the stereoselective synthesis of 2-deoxyoligosaccharides

The key point in the overall synthetic route is the selection of the E and Z groups, since they must be important control elements in the different reactions of the synthetic strategy.

Z group

a) It must control the regioselectivity of the cyclization reaction from **II** in order to obtain exclusively product **III** resulting from a *6-endo* cyclization. For that, an electron donating group, able to stabilize a carbocation in the neighbouring position after the attack of the electrophile would be required.

b) The compound **III** resulting from the cyclization must be directly used as a glycosyl donor. For that the group Z should be a good leaving group and if possible one of the leaving groups commonly used in glycosylation reactions. Eventually, this group should allow an orthogonal glycosylation in order to facilitate the synthesis of oligosaccharides.

E group

a) It must be an electrophile able to react with the electron-rich alkene **II**.

b) It must control the stereoselectivity of the glycosylation reaction.

c) It must be easily removable in order to provide 2-deoxyglycosides.

With these requirements in mind, we selected two candidates as group Z; SPh and SePh, because thio- and selenoglycosides have been widely used in glycosylation reactions, they allow modifications in the phenyl group in order to facilitate the orthogonal glycosylation, and we expect they will control the regioselectivity of the cyclization reaction.

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Taking into account the results collected in the introduction we considered that the more appropriated group E would be either iodine or phenylselenenyl since they efficiently induce cyclizations, are effective in controlling the stereoselectivity of the glycosylation reaction, and can be easily removed. In this context, the concrete objectives of the present work are the following:

Chapter 3 will study the application of the general procedure depicted in Scheme 2.1 when Z = SPh and E = I.

a) We will investigate efficient methods for the olefination of pentoses in order to obtain alkenols of general formula (Z = SPh) **II**.

b) The iodonium-induced cyclization reactions of carbohydrate-derived alkenols (Z = SPh) **II** to obtain 2-deoxy-2-iodo-1-thioglycosides (Z = SPh and E = I) **III** will be described and both the regioselectivity and the stereoselectivity of the reaction studied in detail. The final disposition of the iodine is a key point of the overall process since iodine will control the stereoselectivity of the glycosylation reaction.

c) We will study the glycosylation reaction of the new glycosyl donors 2-deoxy-2-iodo-1-thioglycosides (Z = SPh and E = I) **III** with different acceptors.

d) Since 2-deoxy-2-iodo-1-thioglycosides (Z = SPh and E = I) **III** are activated in conditions similar to those used to induce the cyclization from alkenols (Z = SPh) **II**, one can be envisage the possibility to directly obtain glycosylated product (E = I) **IV** in a "one pot" fashion from (Z = SPh) **II**. Consequently, this possibility will be also studied.

Chapter 4 will study the application of the general procedure depicted in Scheme 2.1 when Z = SPh and E = SePh; and when Z = SePh and E = I, SePh, F, H.

a) The selenonium-induced cyclization reactions of carbohydrate-derived alkenols (Z = SPh) **II** to obtain 2-deoxy-2-phenylselenenyl-1-thioglycosides (Z = SPh and E = SePh) **III** will be studied and the structural requirements necessary for the reaction investigated.

b) We will study the glycosylation reaction of the new glycosyl donors 2-deoxy-2-phenylselenenyl-1-thioglycosides (Z = SPh and E = SePh) **III** with different acceptors.
Moreover, it would be highly desirable to compare the stereoselectivity achieved in the glycosylation reaction when either iodine or phenylselenenyl groups are employed.

c) In addition, the preparation of carbohydrate-based vinyl selenides (Z = SePh) **II** and the behaviour of these substrates towards the electrophile-induced cyclization will be also studied.

Chapter 5 will study the olefin cross metathesis (CM) reaction between carbohydrate-derived hydroxy alkenes **V** and electron-rich olefinic partners with commercially available ruthenium-based catalysts under microwave irradiation (Scheme 2.2). This alternative procedure would provide rapid access to a range of diastereomerically enriched *E*-vinyl chalcogenides (Z = SPh and SePh) **II**.

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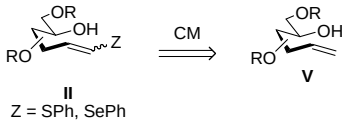
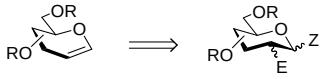


II
Z = SPh, SePh

V

Scheme 2.2 Proposed approach for the synthesis of carbohydrate-based vinyl chalcogenides via CM reactions

Chapter 6 will study the application of 2-deoxy-2-iodo-1-thioglycosides (Z = SPh and E = I) **III** as starting materials for the preparation of other synthetically useful intermediates. Since thioglycosides (Z = SPh and E = I) **III** of all configurations are expected to be accessible using the method commented above, and they have groups I and SPh which are easy to reduce, it is expected that glycals **VI** of all configurations should be accessible by treating (Z = SPh and E = I) **III**, under reducing conditions (Scheme 2.3). This methodology should provide access to glycals difficult to obtain by other procedures such as D-allal and D-gulal.



VI

III
E = I
Z = SPh

Scheme 2.3 Proposed approach for the synthesis of pyranoid glycals of all configurations

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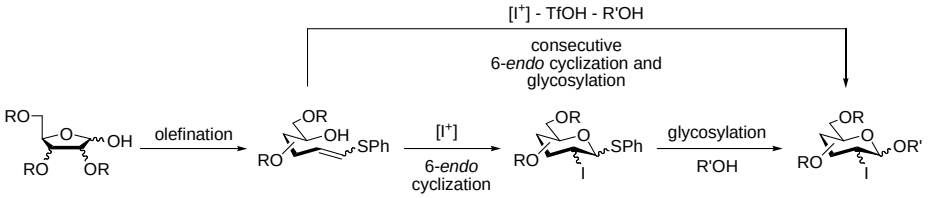
3 Stereoselective Synthesis of 2-Deoxy-2-iodoglycosides



A general procedure for the stereoselective synthesis of 2-deoxy-2-iodo-hexo- and heptopyranosyl glycosides from furanoses is reported. The proposed methodology provides a new route for accessing 2-deoxyoligosaccharides. The procedure involves three reactions: Wittig–Horner olefination to give alkenyl sulfanyl derivatives, electrophilic iodine-induced cyclization to give phenyl 2-deoxy-2-iodo-1-thio-hexoglycosides, and glycosylation. Suitable protected furanoses, which include examples of the four possible isomeric configurations, were reacted with diphenyl (phenylsulfanylmethyl)phosphine oxide to give the alkenyl sulfanyl derivatives. The iodonium-induced cyclization of these compounds afforded the phenyl 2-deoxy-2-iodo-1-thioglycosides with practically complete regio- and stereoselectivity. Products of 6-*endo* cyclization, in which the iodine at C-2 was in a *cis* relationship with the alkoxy at C-3, were almost exclusively produced. Better yields were obtained for compounds with a *ribo* or *xylo* configuration than for compounds with other configurations. These thioglycosides were found to be efficient glycosyl donors in the glycosylation reaction, affording the corresponding 2-deoxy-2-iodoglycosides and 2-deoxy-2-iodo-oligosaccharides with good yields and stereoselectivities. The glycosydic bond in the major isomers was always *trans* to the iodine at C-2.

Since 2-deoxy-2-iodo-1-thioglycosides are activated in conditions similar to those used to induce the cyclization, 2-deoxy-2-iodopyranosides were synthesized from sulfanyl alkenes using a “one pot” consecutive cyclization and glycosylation process. Compared with the stepwise procedure, the “one pot” process gave significantly improved yields with similar or slightly lower selectivities. Furthermore, the “one pot” procedure was successfully applied to the synthesis of 2-deoxy- and 2,6-dideoxyglycosides.

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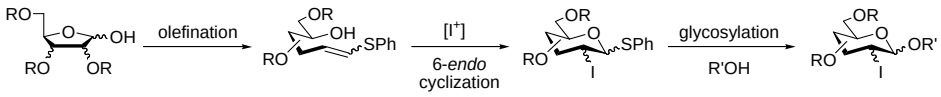
3.1 Stereoselective synthesis of 2-deoxy-2-iodoglycosides from 2-deoxy-2-iodo-1-thioglycosides

3.1.1 Introduction

As described in the general objectives, we decided to explore a new method for the stereoselective synthesis of 2-deoxyglycosides and oligosaccharides based on a new access to 2-deoxy-2-iodo-1-thioglycosyl donors that would not be limited by the availability of pyranoid glycals and by the stereoselective addition of electrophiles. This short synthetic route involves olefination, iodonium-induced 6-*endo* cyclization, and glycosylation reactions (Scheme 3.1).



Scheme 3.1 Proposed methodology for the stereoselective synthesis of 2-deoxy-2-iodoglycosides

As it will be discussed further, although glycosylation products of all configurations can be accessed by employing the present methodology, it is particularly effective in providing 2-deoxy-2-iodo-β-D-*gulo*- and -β-D-*allo*-glycosides.

3.1.2 Results and discussion

The first step in the proposed synthesis of 2-deoxy-2-iodo-1-thioglycosides was the olefination of a series of properly protected furanoses to afford the corresponding alkenyl sulfides. Furanoses were protected as benzyl ethers **1**, **4**, **5**, **15**, and **16**, acetonides in **6**–**8** and **14**, and silyl ethers in **6** and **8**. The reaction conditions for olefination were optimized by starting from arabinose derivative **1** (Table 3.1). Initial attempts under Peterson[41] (Table 3.1, entry 1), Wittig[42] (Table 3.1, entries 2 and 3), and Horner–Wadsworth–Emmons conditions[43] (Table 3.1, entries 4 and 5) afforded the desired product in moderate to good yields (23–72%) and selectivities (*Z*/*E* ratio range from 3:2 to 0:1). Wittig–Horner[44]

---

[41] (a) van Staden, L.F.; Gravestock, D.; Ager, D.J. *Chem. Soc. Rev.* **2002**, *31*, 195. (b) Ager, D.J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 183. (c) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 939.

[42] (a) Aucagne, V.; Tatibouët, A., Rollin, P. *Tetrahedron* **2004**, *60*, 1817. (b) Kolodiazhnyi, O. I. Ed., In *Phosphorous Ylides: Chemistry and Application in Organic Chemistry*, Wiley-VCH, Weinheim, 1999. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

[43] (a) Pagenkopf, B. L.; Reichwein, J. F. *J. Am. Chem. Soc.* **2003***, 125*, 1821. (b) Corey, E. J.; Shulman, J. I. *J. Org. Chem.* **1970**, *35*, 777.

[44] (a) Stéphan, E.; Olaru, A.; Jaouen, G. *Tetrahedron Lett.* **1999**, *40*, 8571. (b) Clayden, J.; Warren, S. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 241. (c) Earnshaw, C.E.; Wallis, C.J.; Waren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099. (d) Grayson, J.I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2263.

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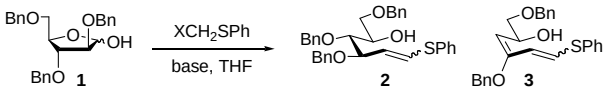
olefination (Table 3.1, entries 6–9) provided the best result affording **2** in quantitative yield and 2:3 *Z*/*E* ratio (Table 3.1, entry 9). The ^{1}H NMR spectra unambiguously indicated the formation of the two possible diastereoisomers; **2***Z* ($J_{1,2}$ = 9.6 Hz) and **2***E* ($J_{1,2}$ = 15.2 Hz). In summary, the best conditions for the olefination of pentoses were obtained under Wittig–Horner conditions.

Rollin and co-workers[42a] used a Wittig reaction to synthesize carbohydrate-derived vinyl sulfides in good yields with preferential formation of the *Z*-isomer. However, in our hands, Wittig reactions resulted in the formation of small amounts of diene **3** and/or epimerized product at C-3.

Table 3.1 Optimization of the olefination conditions of furanose **1** to obtain **2**



Entry[a]	XCH_2SPh (eq)	*n*-BuLi (eq)	T (ºC)	t (h)	Olefination product	Yield (%)	*Z*/*E* ratio[b]
1	Me_3Si (1.3)	1.3	-78 to rt	5	**2**	61	3:2
2	Ph_3P (3)	3	0 to rt	24	**2**	70	1:4
3	Ph_3P (3.5)	3.5	0 to rt	48	**2**	72[c]	1:21
4[d]	$(EtO)_2P(O)$ (2.1)	-	-78 to rt	24	**2**	23	0:1
5	$(EtO)_2P(O)$ (4)	4.4	-78 to rt	63	**2**	48	1:14
6	$Ph_2P(O)$ (4)	5.5	-78 to rt	48	**2**	14	2:13
7	$Ph_2P(O)$ (4)	5.5	-78 to rt	20	**2**	35	2:5
8	$Ph_2P(O)$ (4)	4.4	rt	12	**2**	85	1:3
9	$Ph_2P(O)$ (4)	4.4	-78 to rt	24	**2**	100	2:3

[a] Solvent = THF, base = *n*-BuLi unless otherwise indicated. [b] Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [c] Trace amounts of diene **3**. [d] Base = LDA (2.1 eq).

Thus, the best protocol (Wittig–Horner) was extended to different protected furanoses **4**–**8** and **14**–**16** in order to determine the generality of the reaction and the influence of the stereochemistry at position C-2. The results are summarized in Tables 3.2 and 3.3. The olefination of benzylated furanoses **4**, **5**, **15**, and **16** proceeded smoothly and provided the expected products in good to excellent yields (60–100%) and selectivities (*Z*/*E* ratio range from 1:1 to 1:17) (Table 3.2, entries 1 and 2) (Table 3.3, entries 2 and 3). Silyl and 3,4-*O*-isopropylidene-protected furanoses **6**–**8** and **14** gave lower yields (20–63%) but improved selectivities (*Z*/*E* ratio range from 1:3 to 0:1), probably due to higher steric hindrance provided by the dioxolane ring (Table 3.2, entries 3–8) (Table 3.3, entry 1). In

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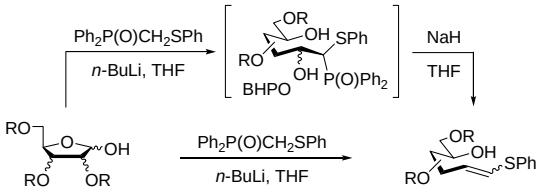
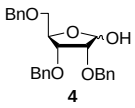
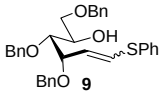
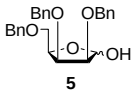
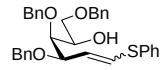
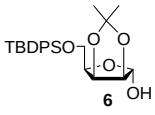
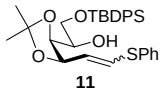
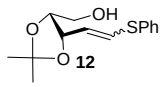
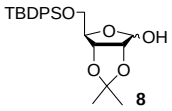
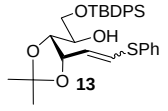
contrast, olefination of 2-deoxy-ribose derivative **16** yielded alkene **19** quantitatively with no selectiviy. The Wittig–Horner reaction with Li-bases is ideally described as a two-step procedure in which a *β*-hydroxyphosphine oxide intermediate (BHPO) is formed and then subsequently transformed to the alkene by reaction with NaH[45] (Table 3.2, entries 2, 3, and 7). However, the alkene can also be obtained directly with semistabilized reagents.[44d]

Table 3.2 Olefination of furanoses **4**–**8**



Entry[a]	Starting material	T (ºC)	t (h)	Olefination product	Yield (%)	*Z*/*E* ratio[b]
1	 **4**	-78 to reflux	48	 **9**	72	1:4
2	 **5**	-78 to rt	48	 **10**	52 10[c]	1:17 7:1
3	 **6**	-78 to rt	48	 **11**	21 10[c]	1:8 1:1
4	**6**	-78 to reflux	20	**11**	20	0:1
5	**6**	-78 to rt	36	**11**	31	2:5
6[d]	**6**	-78 to rt	92	mixture	-	-
7	 **7**	-78 to rt	48	 **12**	35 33[c]	1:3 12:1
8	 **8**	-78 to rt	15	 **13**	40	1:33

[a] Furanose (1eq), $Ph_2P(O)CH_2SPh$ (4 eq), *n*-BuLi (4.4 eq), solvent = THF unless otherwise indicated. [b] Determined by integration of the olefinic proton signals in the ^1H NMR spectrum of the crude reaction mixture. [c] Additional yield obtained by elimination of the isolated *β*-hydroxyphosphine oxide intermediate. [d] Base = KHMDS (4.4 eq).

[45] Buss, A.D.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2307.

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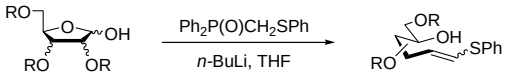
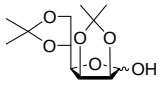
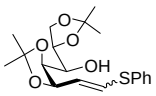
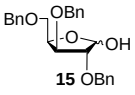
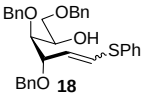
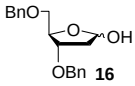
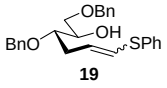
Table 3.3 Olefination of furanoses **14**–**16**.
Data extracted from Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007



Entry[a]	Starting material	T (ºC)	t (h)	Olefination product	Yield (%)	*Z*/*E* ratio[b]
1	 **14**	-78 to rt	21	 **17**	63	1:10
2	 **15**	-78 to rt	14	 **18**	60	1:4
3	 **16**	-78 to rt	4	 **19**	100	1:1

[a] Furanose (1eq), $Ph_2P(O)CH_2SPh$ (4 eq), *n*-BuLi (4.4 eq), solvent = THF unless otherwise indicated. [b] Determined by integration of the olefinic proton signals in the ^1H NMR spectrum of the crude reaction mixture.

In our case, reaction of complex lactols with semi-stabilized phosphine oxides (Wittig–Horner olefination) afforded mixtures of the corresponding alkene products and BHPO intermediates. After isolation, BHPO were submitted to elimination conditions (NaH in dry THF) in order to improve the yield of the *Z*-enriched alkene product.

In all cases, the *Z*/*E* mixtures of alkenes proved to be inseparable; hence, the cyclization reactions were assayed directly on the mixture of diastereomers. Iodonium-induced cyclization was first studied for *arabino* derivative **2** as a model for the compounds bearing an axial iodine at C-2 (Table 3.4).

The reaction of diastereomerically pure **2***E* with iodine and KH in Et_2O afforded 2-deoxy-2-iodo-*α*-*manno*-thioglycoside **20** exclusively in 61% yield (Table 3.4, entry 1). However, cyclization of the *Z*/*E* mixture of **2** proved difficult even though different bases were used (Table 3.4, entries 5 and 6). According to the work of Baldwin[29] the strength of internal nucleophile do not have influence in the rate of the reaction and it depends upon whether activated alkene reach appropriate intermediate conformation.

Forcing the reaction conditions (higher temperatures and KH concentration) did not yield the desired product; rather it led to the formation of oxetane **21** in low yield (10–31%) as a result of isomerization of the double bond (RCH=CHSPh) to a more stable trisubstituted enol ether (R(R'O)C=$CHCH_2$SPh) and subsequent cyclization (Table 3.4, entries 2–4).

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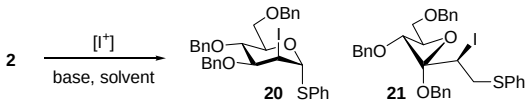
Table 3.4 Optimization of the iodonium-induced cyclization conditions of alkenol **2** to obtain product **20** bearing an axial iodine at C-2



Entry	*Z*/*E* ratio[a]	[I$^+$] (eq)	Base (eq)	Solvent	T (ºC)	t (h)	Cyclization product	Yield (%)
1	0:1	I_2 (3)	KH (1.3)	Et_2O	-78	1	**20**	61
2	1:2	I_2 (3)	KH (2.5)	Et_2O	-78 to rt	1.5	**21**	31
3	1:3	I_2 (3.2)	KH (1.9)	Et_2O	-78 to -50	7.5	**21**	24
4	2:13	I_2 (3)	KH (1.3)	Et_2O	-78 to -50	2.5	**21**	10
5	1:3	I_2 (3)	*n*-BuLi (1.1)	Et_2O	-78 to rt	7.5	mixture	-
6	1:3	I_2 (3)	KHMDS (1)	Et_2O	-78	6	**20**	3
7	3:2	I_2 (3)	$NaHCO_3$ (3)	CH_3CN	-30 to rt	16	**20**	18
8	1:3	NIS (3)	$NaHCO_3$ (3)	CH_3CN	-30	3	**20**	20
9	1:3	NIS (3)	$NaHCO_3$ (3)	CH_3CN	-30 to rt	14	**20**	14[b]
10	1:3	NIS (3)	$NaHCO_3$ (3)	CH_3CN	0	18	**20**	24[b]
11	1:3	NIS (3)	$NaHCO_3$ (3)	CH_3CN	0	24	**20**	4[b]
12	1:3	NIS (1.5)	$NaHCO_3$ (1.5)	CH_3CN	0	16	**20**	36
13	1:3	NIS (1.5)	$NaHCO_3$ (1.5)	CH_3CN	0	41	**20**	9[b]

[a] Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum after chromatographic purification. [b] Trace amounts of the corresponding succinimido glycoside.

Althought the mechanism by which **21** was obtained was not studied in detail, deuteration experiments seemed to exclude base-promoted isomerization of the double bond. Isomerization may, however, have occurred through a radical mechanism. The structure was confirmed by COSY, HSQC, and HMBC experiments. The ^{13}C NMR spectrum showed a characteristic ketalic quaternary carbon signal at 108.3 ppm. Furthermore, the antiperiplanar addition of the oxygen to the double bond activated by the electrophilic iodine resulted in a product with a residual CH-I (37.6 ppm) anti to the newly formed C–O bond, together with a CH_2SPh signal at 37.2 ppm. The relative stereochemistry of **21** was finally established by NOESY measurements, which revealed a network of enhancements consistent with the proposed oxetane structure. In particular, significant NOE correlation peaks between H-3 and CH_2SPh; H-4 and OCH_2Ph present at C-2; were observed (Figure 3.1).

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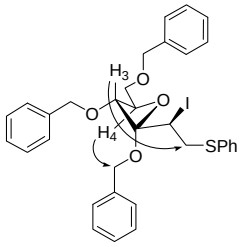
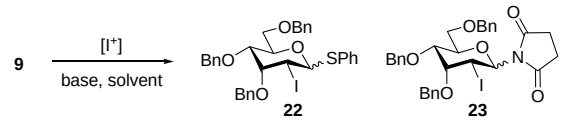


Figure 3.1 Significant NOE correlation peaks in compound **21**

Using a weaker base such as $NaHCO_3$ in combination with iodine led to the formation of **20**, but only in 18% yield (Table 3.4, entry 7). In order to increase the yield of the cyclization, the reaction was also studied with NIS as the electrophile under various reaction conditions (Table 3.4, entries 8–13). The best result was obtained when alkenol **2** was treated with NIS (1.5 eq) and $NaHCO_3$ (1.5 eq) in dry CH_3CN at 0ºC for 16 h (Table 3.4, entry 12). However, the use of NIS always led to the formation of trace amounts of the corresponding succinimido glycoside when the mixture was stirred for prolonged reaction time. The *Z*-isomer of **2** did not cyclize under any of the conditions tested.

Ribo derivative **9** was then tested as a model for the compounds bearing an equatorial iodine at C-2 (Table 3.5).

Table 3.5 Optimization of the iodonium-induced cyclization conditions of alkenol **9** to obtain product **22** bearing an equatorial iodine at C-2



Entry	*Z*/*E* ratio[a]	[I^+] (eq)	Base (eq)	Solvent	T (ºC)	t (h)	Cyclization product	Yield (%)	α/β ratio[b]
1	0:1	I_2 (3)	KH (1.3)	Et_2O	-78 to rt	1	**22**	63	0:1
2	1:2	I_2 (3)	KH (1.3)	Et_2O	-78 to rt	16	**22**	9	0:1
3	1:2	NIS (1.5)	$NaHCO_3$ (1.5)	CH_3CN	-30 to rt	15	**22**	77[c]	1:9
4	1:2	NIS (1.5)	$NaHCO_3$ (1.5)	CH_3CN	-30 to rt	17	**22**	68[c]	2:5
5	1:2	NIS (1.5)	$NaHCO_3$ (1.5)	CH_3CN	-30 to rt	20	**22**	40[c]	1:9
6	2:3	NIS (1.5)	-	CH_2Cl_2	-78 to rt	12	mixture	-	-
7[d]	1:2	NIS (1.5)	-	CH_2Cl_2	-78 to rt	19.5	**23**	64	1:41

[a] Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum after chromatographic purification. [b] Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [c] Trace amounts of succinimido glycoside **23**. [d] 4Å MS were added to the reaction mixture.

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The reaction of diastereomerically pure **9***E* derivative with iodine and KH in Et_2O afforded 2-deoxy-2-iodo-*β*-*allo*-thioglycoside **22** exclusively in 63% yield (Table 3.5, entry 1). As for *arabino* derivative **2**, cyclization of the *Z*/*E* mixture of **9** under the same conditions proved difficult and **22***β* was obtained in a dramatically decreased 9% yield (Table 3.5, entry 2). Cyclization was also assayed using NIS with $NaHCO_3$ as the base (Table 3.5, entries 3–5).

The best yield of thioglycoside **22** was obtained when the reaction mixture was stirred from –30ºC to room temperature for 15 h (Table 3.5, entry 3). Under these conditions, trace amounts of succinimido glycoside **23** were detected by ^{1}H NMR. This glycoside was presumably formed by activation of the anomeric phenylsulfanyl group in **22** and nucleophilic attack of the succinimido anion.[46] In order to diminish the nucleophilicity of the succinimido group when NIS was used as the electrophilic reagent, the reaction was carried out in the absence of base. However, under these conditions either a complex mixture was obtained (Table 3.5, entry 6) or, when 4Å molecular sieves were added to the reaction mixture, succinimido glycoside **23** was exclusively recovered in 64% yield as a 1:41 *α*/*β* mixture (Table 3.5, entry 7).

These preliminary cyclization assays revealed that the cyclization conditions are very sensitive to the configuration of the hexenyl sulfide. The geometrical configuration of the alkene is also crucial for cyclization. The *E*-isomer of the alkenes readily reacted to give the corresponding thioglycosides in moderate to good yield, whereas the *Z*-isomers either required a higher temperature to cyclize or did not cyclize. This difference in reactivity between the *Z*- and *E*-alkenes makes it necessary to force the conditions to ensure full conversion when starting from inseparable *Z*/*E* mixtures of alkenes, which leads to partial decomposition of the thioglycoside products. This decomposition process is the cause of the low thioglycoside yields obtained from the cyclization reactions of *arabino* derivative **2** (Table 3.4) and, to a lesser extent, *ribo* derivative **9** (Table 3.5).

In light of the results obtained, the cyclization conditions for compounds **10**–**13** and **17**–**19** had to be optimized. The results are summarized in Tables 3.6 and 3.7.

[46] Oscarson, S.; Krog-Jensen, C. *J. Org. Chem.* **1996**, *61*, 1234.

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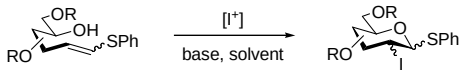
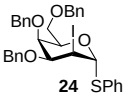
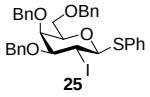
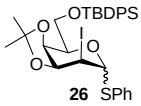
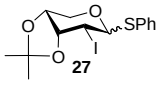
Table 3.6 Cyclization of alkenyl sulfides **10**–**12** induced by electrophilic iodine reagents



Entry	Starting material	*Z*/*E* ratio[a]	Cyclization conditions (eq)	Cyclization product	Yield (%)	α/β ratio[b]
1[c]	**10**	1:7	IDCP (2.2) CH_2Cl_2 -78ºC, 2.5 h	 **24**	20	1:0
				 **25**	15	0:1
2[d]	**10**	1:17	NIS (1.5) $NaHCO_3$ (1.5) CH_3CN -30ºC, 2 h	**24**	<1	1:0
				25	9	0:1
3	**10**	7:1	NIS (1.5) $NaHCO_3$ (1.5) CH_3CN -30ºC to rt, 22 h	**25**	14[e]	1:0
4	**11**	2:5	NIS (1.5) $NaHCO_3$ (1.5) CH_3CN -30 to -10ºC, 24 h	 **26**	75	40:1
5	**11**	1:8	NIS (1.5) $NaHCO_3$ (1.5) CH_3CN -30ºC, 15 h	**26**	55[f]	42:1
6	**11**	1:8	IDCP (2.2) CH_2Cl_2 -78 to -20ºC, 24 h	**26**	46	49:1
7	**12**	2:3	IDCP (2.2) CH_3CH_2CN -78ºC, 23 h	 **27**	33[g]	1.1:1
8	**12**	12:1	IDCP (2.2) CH_3CH_2CN, 4Å MS -78 to -10ºC, 24 h	**27**	24[g]	14:1
9	**12**	1:3	IDCP (2.2) CH_2Cl_2 -78ºC, 3 h	**27**	17	1:1.2
10	**12**	1:3	NIS (1.5) $NaHCO_3$ (1.5) CH_3CH_2CN -78 to -50ºC, 16 h	mixture	-	-

[a] Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum after chromatographic purification. [b] Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [c] 69% conversion. [d] 18% conversion. [e] 40% of the corresponding 2-deoxy-2-iodo-talo- and -galactopyranoses were also obtained. [f] 10% of the correspondign 2-deoxy-2-iodopyranose was also obtained. [g] 33% of the correspondign 2-deoxy-2-iodopyranose was also obtained.

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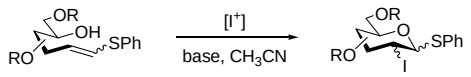
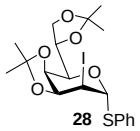
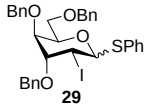
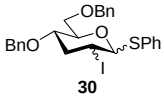
Table 3.7 Cyclization of alkenyl sulfides **17**–**19** induced by electrophilic iodine reagents. Data extracted from Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007



Entry[a]	Starting material	*Z*/*E* ratio[b]	Cyclization conditions (eq)	Cyclization product	Yield (%)	*α*/*β* ratio[b]
1	**17**	0:1	IDCP (2.2) CH_3CN -45 to -30ºC, 2 h	 **28**	97	1:0
2	**17**	1:6	IDCP (2.2) CH_3CN -45ºC to rt, 1.5 h	**28**	48[c]	1:0
3	**18**	1:10	IDCP (2.2) CH_3CN -45 to -30ºC, 2 h	 **29**	60	1:10
4	**19**	1:1	NIS (1.5) $NaHCO_3$ (1.5) CH_3CN -30ºC, 0.5 h	 **30**	47[d]	-

[a] Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum after chromatographic purification. [b] Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [c] **28** (60%) and the corresponding 2-deoxy-2-iodopyranose (16%) were obtained when the reaction mixture was stirred at room temperature for a prolonged time. [d] 1:1 epimeric mixture at C-2 (decomposed on standing).

The reaction of *lyxo* derivative **10** with IDCP in CH_2Cl_2 afforded 2-iodo-*α*-talopyranoside **24** in 20% yield together with 2-iodo-*β*-galactopyranoside **25** in 15% yield (Table 3.6, entry 1). Initial attempts with NIS as the electrophile proved ineffective since the reactions were sluggish with low yields (Table 3.6, entries 2 and 3). Slightly better results were obtained in the reaction of 3,4-*O*-isopropylidene-protected *lyxo* derivative **11** with NIS in CH_3CN, which gave 2-iodo-talopyranoside **26** in good yields (55–75%) and *α*/*β* ratio of up to 42:1 (Table 3.6, entries 4 and 5). Cyclization with IDCP in CH_2Cl_2 at lower temperature led to the desired product in a moderate 46% yield but with better *α*-selectivity (Table 3.6, entry 6).

From diastereomerically pure **17***E*, **28***α* was exclusively obtained in 97% yield (Table 3.7, entry 1). In contrast, cyclization of a 1:6 *Z*/*E* mixture of **17** rendered **28***α* but in a much lower yield (48%) (Table 3.7, entry 2). Forcing the reaction conditions (higher temperatures and longer reaction times) led to cyclization of both the *E*- and *Z*-isomers to give **28** in 60% yield as a 2:1 *α*/*β* mixture but also produced corresponding 2-deoxy-2-iodopyranose in 16% yield as a consequence of the activation of the phenylsulfanyl group in **28**. The same conditions were found to be the optimal for the cyclization of *xylo*

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derivative **18** (Table 3.7, entry 3). The effect of the substitution of the hydroxyl-bearing carbon atom on the cyclization was also studied. As for *lyxo* derivative **10**, cyclization of the *Z*/*E* mixture of **12** under the same conditions proved difficult and **27** was obtained in low yields (17–24%) (Table 3.6, entries 8 and 9).

Cyclization was also assayed using NIS with $NaHCO_3$ but a complex mixture was obtained (Table 3.6, entry 10). The best yield of 2-deoxy-2-iodo-1-thioglycoside **27** was obtained when *erythro* derivative **12** was treated with IDCP in propionitrile at –78ºC to afford **27** in 33% yield, together with the corresponding 2-deoxy-2-iodopyranose with the same yield (Table 3.6, entry 7). As shown by the α/β ratio, the *Z*-isomer also undergoes cyclization, although it requires higher temperatures (ΔT ~50ºC) than the *E*-isomer (Table 3.6, entries 7–9). Finally, in order to gain insight into the stereochemical outcome, the cyclization was carried out starting from the alkenyl sulfide **19**, which lacks an allylic alkoxy group at C-3. The reaction of **19** with NIS afforded a mixture of four compounds assigned as a 1:1 C-2 epimeric mixture of 2,3-dideoxy-2-iodo-thioglycosides with their corresponding α/β anomers (Table 3.7, entry 4).

The relative stereochemistry of compounds **20**, **22**, and **24**–**27** (C-1, C-2, and C-3 groups) was initially deduced by ^{1}H, ^{13}C, COSY, and HSQC NMR analysis (Figure 3.2). In the case of 3,4-*O*-isopropylidene-protected compound **26**, the coupling constant ($J_{1,2}$ ~10 Hz) accounts for a boat-like conformation in which H-1 and H-2 are in a 1,2-trans-diaxial arrangement. However, the determination of the anomeric configuration of 3,4-*O*-isopropylidene-protected **27** by measurement of the $J_{1,2}$ coupling constant was not possible since this value range from 8 to 10 Hz in both anomers, and this can be rationalized by some conformational flexibility because this compound lacks a C-6 substitution (R = H). On the basis of our experience with 2-deoxy-2-iodo-1-thioglycosides, the stereochemistry of compound **27** (C-1 and C-2 groups) was deduced by comparing the ^{13}C NMR chemical shifts of C-2 since we have observed that in these compounds δ C-2α < δ C-2β. In particular, peaks with δ 22–33 ppm are indicative of α-anomers, whereas peaks with δ 26–30 ppm are indicative of β-anomers. Furthermore, these values are a characteristic feature of the C–I bonds. The relative stereochemistry (C-1, C-2, and C-3 groups) was finally confirmed by NOESY measurements.

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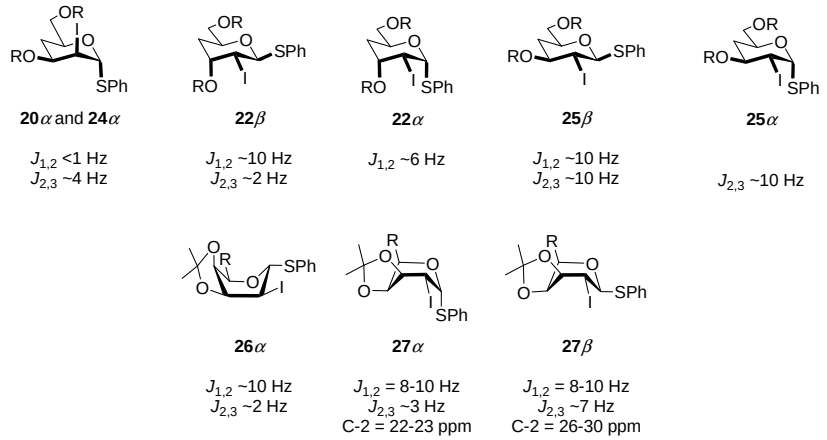
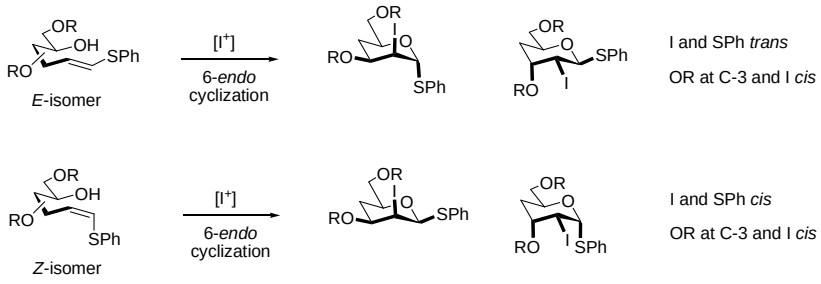


Figure 3.2 Assignment of the configuration in 2-deoxy-2-iodo-1-thioglycosides **20**, **22**, and **24**–**27**

This series of experiments established that hydroxy-hexenyl sulfides **2**, **9**–**12**, and **17**–**19** undergo a completed 6-*endo* regioselective electrophilic iodine-induced cyclization. The normal 5-*exo* course observed in analogue hexenols is biased to the 6-*endo* mode by the presence of an electron donating atom at the terminus of the double bond. Sulfur stabilizes a positive charge on the neighboring carbon atom, making the 6-*endo* cyclization possible.[47] Futhermore, the cyclization reaction is highly stereoselective and very predictable in terms of the stereochemical outcome. The relative stereochemistry of C-1 and C-2 in thioglycosides depends on the configuration of the starting alkene. Thus, the reaction of the *E*-alkenyl sulfide yields a cyclization product in which the iodine atom and phenylsulfanyl group are in a *trans* arrangement. In all cases where the *Z*-alkene underwent cyclization, 2-iodo-thioglycosides were obtained with the substituents at C-1 and C-2 in a *cis* disposition (Scheme 3.2).



Scheme 3.2 Stereochemical outcome of the cyclization

[47] For a preliminary electrophilic-induced 6-*endo* cyclization assisted by sulfur, see: Gallucci, J. C.; Ha, D.-H.; Hart, D. J. *Tetrahedron Lett*. **1989**, *45*, 1989.

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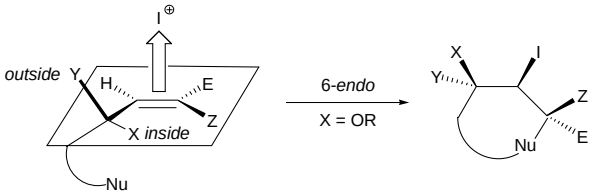
Another important issue associated with stereoselectivity is the formation of cyclized products in which the iodo group at C-2 is always *cis* with respect to the alkoxy group at C-3 (Scheme 3.2). This is a key point in the global process because the iodine configuration determines the configuration of the anomeric center in the glycosylated products. The stereoselectivity observed for the alkenes considered here is consistent with that reported for alkenols with an allylic alkoxy group[48] and is determined by a stereoelectronic effect known as the *inside-alkoxy effect.*[49] This effect favors cyclization from the most reactive conformation, in which the allylic alkoxy group is placed inside the plane that configures the framework of the double bond. In this conformation, the σ^*_{C-O} is perpendicular to the π-system of the double bond, which minimizes the electron-withdrawing effect, causing the double bond to be more electron-rich and hence more reactive towards electrophiles (Scheme 3.3).



Scheme 3.3 Inside-alkoxy effect

The stereodirecting role of the allylic group is evident in the cyclization of **19**, which lacks an allylic OR group. Since there is no stereoelectronically preferred conformation in the cyclization of **19**, the cyclization reaction yields a C-2 epimeric mixture of 2-iodo-thioglycosides. The *inside-alkoxy effect* may well explain why the *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 form the transition state in the cyclization will be higher than for the corresponding *E*-alkenes. For some compounds, such as arabinose derivative **2**, the activation energy is sufficiently high that cyclization is precluded. Although such compounds could also undergo cyclization via the outside-alkoxy conformation, this conformation is insufficiently reactive to promote cyclization.

An exception to the *inside-alkoxy effect* rule is *lyxo* derivative **10**, which undergoes cyclization to give a mixture of expected pyranoside **24** together with **25**, where the latter product is formed by cyclization of the *E*-isomer of **10** through a transition state in which

[48] (a) Arnés, X.; Díaz, Y. Castillón, S. *Synlett* **2003**, 2143. (b) Landais, Y.; Panchenault, D. *Synlett* **1995**, 1191.
[49] (a) Halter, J.; Strassner, T.; Houk, K.N. *J. Am. Chem. 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. Chem. Soc*. **1984***, 106*, 3880. (c) Stork, G.; Kahn, M. *Tetrahedron Lett*. **1983**, *24*, 3951.

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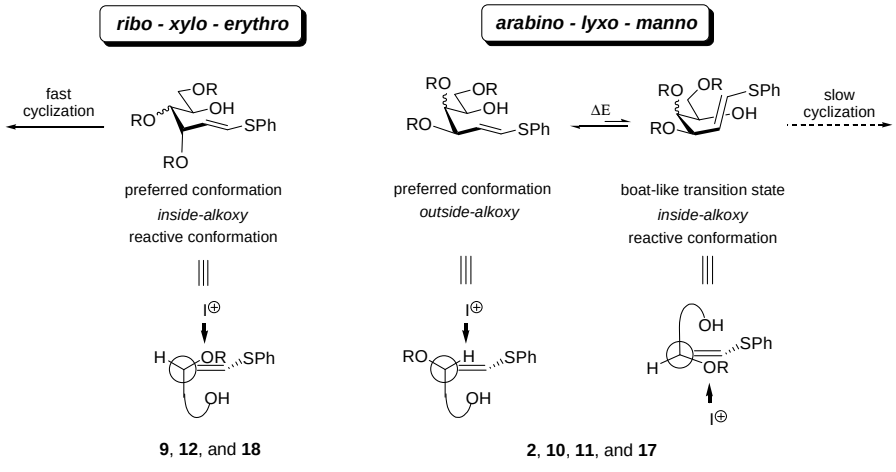
the alkoxy group is located in an outside position. The formation of outside-alkoxy products has previously been described in relation to electrophile-induced cyclizations of *Z*-enolethers to give cyclohexyl pyranosides as mentioned in the introduction.[39] These previous results, however, can be accounted for in terms of the high steric hindrance of the inside-alkoxy conformation in the *Z*-alkenes and the presence of an electron-rich double bond, which will be reactive towards cyclization even in the outside-alkoxy conformation. In contrast, cyclization of **10***E* is not subject to 1,3-allylic strain and therefore the inside-alkoxy conformation should be the lowest-energy configuration. In fact, aside from **10**, none of the other alkenes studied, including 3,4-*O*-isopropylidene *lyxo* derivative **11**, gave outside-alkoxy products. At present we do not have an explanation for the formation of **25**.

The *inside-alkoxy effect* can also explain why the reactivities of the *ribo* and *xylo* derivatives differed from those of the *arabino* and *lyxo* derivatives (Schemes 3.4 and 3.5). For *ribo* and *xylo* derivatives **9** and **18**, the most stable conformer is the one that leads to the preferred transition state for cyclization, that is, the conformation in which the large alkyl group is *anti* to the incoming electrophile and the allylic alkoxy group occupies the inside position. As a result, the cyclization readily proceeds. For *arabino* and *lyxo* derivatives **2** and **10**, by contrast, the preferred conformation outside-alkoxy is not the one that favors cyclization, and hence a conformational change must occur for cyclization to proceed. For these molecules, the preferred transition state has a boat-like conformation, which is higher in energy than the transition states of the *ribo* and *xylo* derivatives. Consequently, the cyclization is slower for the *arabino* and *lyxo* derivatives than for the *ribo* and *xylo* derivatives.



Scheme 3.4 Proposed models for the electrophile-induced cyclization reactions of *E*-hydroxy-alkenyl sulfides **2**, **9**–**12**, **17**, and **18**

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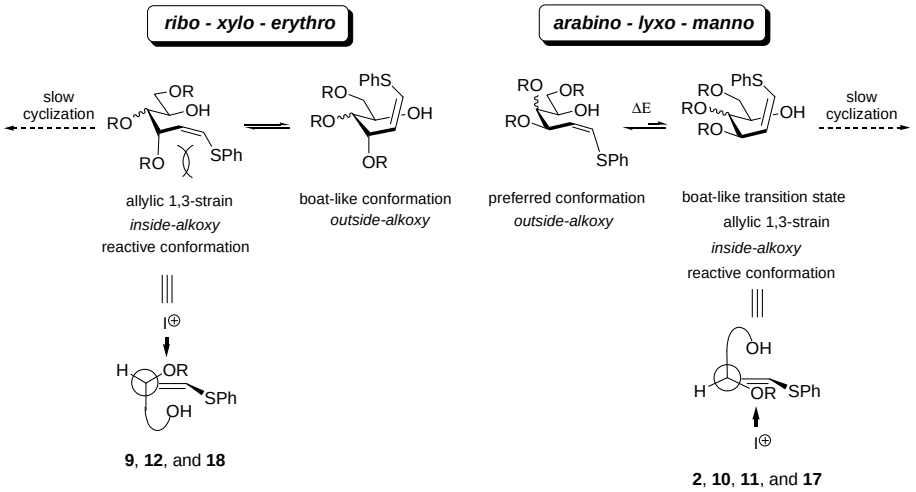
The higher reactivity of *lyxo* and *manno* derivatives **11** and **17** compared to *arabino* **2** can be explained by the presence of the 3,4-*O*-isopropylidene group, which restricts the conformational freedom and accordingly favors cyclization. The cyclization yield of thioalkenes with *arabino* and *lyxo* configurations is low because the initially produced thioglycoside is further activated under the cyclization conditions because the electrophilic reagent used for the cyclization, NIS, can also activate the thioglycoside. Cyclization of *erythro* derivative **12** to produce **27** should be easy (Table 3.6, entries 7–10), as for *ribo* and *xylo* derivatives **9** (Table 3.5) and **18** (Table 3.7, entry 3). The low yield (33%) of **27** is a consequence of its high reactivity toward the activation of an anomeric phenylsulfanyl group in the presence of IDCP even at –78°C. This reactivity is general to all 6-deoxyglycosides.[17e] Under these conditions, the initially formed 2-iodothioglycoside **27** was partially consumed to produce the corresponding 2-deoxy-2-iodopyranose in 33% yield. In this context, the α/β ratio of **27** may not reflect the diastereoselectivity of the cyclization, because the two thioglycoside anomers may be activated at different rates.



Scheme 3.5 Proposed models for the electrophile-induced cyclization reactions of *Z*-hydroxy-alkenyl sulfides **2**, **9**–**12**, **17**, and **18**

2-Deoxy-2-iodo-thioglycosides **20**, **22**, **24**, and **26**–**29** were found to be quite stable and can be stored in the refrigerator for several months without significant decomposition. The only labile 2-deoxy-2-iodo-thioglycosides were **25** and **30**, which decomposed on standing. These glycosyl donors were tested for stereoselective glycosylation of methyl 4,6-*O*-benzylidene-3-*O*-benzyl-α-D-glucoside **31a** and cholesterol **31b** under typical conditions for thioglycosides[50] (Tables 3.8 and 3.9).

[50] Veeneman, G.H.; van Leeuwen, S.H.; van Boom, J.H. *Tetrahedron Lett.* **1990**, 31, 1331.

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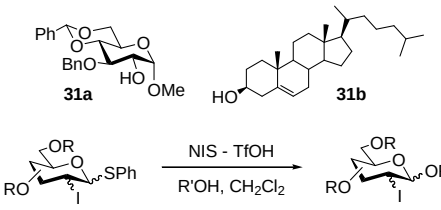
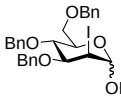
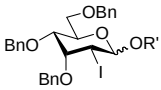
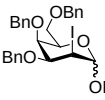
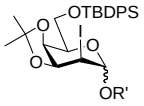
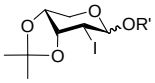
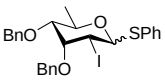
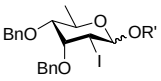
Table 3.8 Stereoselective glycosylation of **31a** and **31b** from 2-deoxy-2-iodo-1-thioglycosides **20**, **22**, **24**, **26**, **27**, and **32**



Entry	Starting material	Glycosylation product	Glycosylation conditions (eq)[a]	Yield (%)	α/β ratio[b]
1	**20**		**33a** -40ºC, 2 h	71	45:1
			33b -40ºC, 2 h	72	37:1
2	**22**		**34a** -40ºC, 2.5 h	74	1:6
			34b -40ºC, 2.5 h	81	1:9
3	**24**		**35b** -40ºC to rt 18 h	27	7:1
4	**26**		**36a** -78ºC, 1.5 h	59	20:1
			36b -78ºC, 1.5 h	36	10:1
5	**27**		**37a** -78ºC, 0.5 h	44	1:3
			37b -78 to 0ºC 17 h	46	1:25
6[c]	 **32**		**38a** Me_2S_2 (1) Tf_2O (1.1) TTBP (2) 4Å MS, -78ºC to rt 3.5 h	66	1:2.2

[a] Glycosyl donor (1eq), R'OH **31a**,**b** (2 eq), NIS (2.2 eq), TfOH (20 mol %), 4Å MS, solvent = CH_2Cl_2 unless otherwise indicated. [b] Determined by integration of the anomeric proton signals in the ^1H NMR spectrum of the crude reaction mixture. [c] The reaction mixture was stirred at -78ºC for 30 min prior to the addition of glycosyl acceptor **31a**.

Starting from 1,2-*trans*-diequatorial substituted glycosyl donors **22** and **29**, glycosides **34a**,**b** and **40a**,**b** were obtained in good yields (61–81%) and α/β ratios of up to 1:16 (Table 3.8, entry 2) (Table 3.9, entry 2). Treatment of **20** with NIS/TfOH in the presence of **31a** afforded 2-deoxy-2-iodo-mannoside **33a** in 71% yield as a 45:1 α/β mixture. Glycosylation of **31b** afforded **33b** with slightly lower stereoselectivity (37:1 α/β ratio) in 72% yield (Table 3.8, entry 2). Similar behavior was observed in the glycosylation of **31a** and **31b** with 3,4-*O*-isopropylidene-protected derivatives **26** and **28** to afford the expected products in good yields (57–69%) (Table 3.8, entry 4) (Table 3.9, entry 1). The

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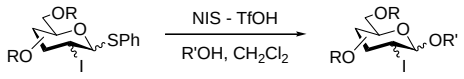
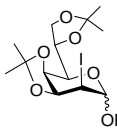
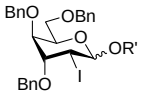
selectivies for **31a** ranged from α/β ratios of 20:1 to 40:1, although the glycosylation of **31b** proceeded with lower α-selectivity (α/β ratios range from 8:1 to 10:1), probably due to the higher temperature required to promote glycosylation. Accordingly, glycosylation of *talo* derivative **24**, which lacks the 3,4-*O*-isopropylidene cyclic protecting group, with acceptor **31b** afforded product **35b** in moderate yield (27%) and α-selectivity (7:1 α/β ratio) comparable to that observed in **36b** (Table 3.8, entries 3 and 4).

Table 3.9 Stereoselective glycosylation of **31a** and **31b** from 2-deoxy-2-iodo-1-thioglycosides **28** and **29**. Data extracted from Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007



Entry	Starting material	Glycosylation product	Glycosylation conditions[a]	Yield (%)	α/β ratio[b]
1	**28**		**39a** -60ºC, 1 h	69	40:1
			39b -20ºC, 20 h	57	8:1
2	**29**		**40a** -40ºC, 3 h	61	1:16
			40b -40ºC, 3 h	66	1:8

[a] Glycosyl donor (1eq), R'OH **31a**,**b** (2 eq), NIS (2.2 eq), TfOH (20 mol %), 4Å MS, solvent = CH_2Cl_2. [b] Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture.

When compared with **22** and **29**, 1,2-trans-diaxial substituted glycosyl donors **20**, **24**, **26**, and **28** provided improved stereoselectivities, especially in the glycosylation of **31a**. These results are in agreement with those reported by Roush and Narayan for the glycosylation of 2-deoxy-2-iodo-manno- and 2-deoxy-2-talopyranosyl acetates.[12c] Glycosylation of **31a** with glycosyl donor **27** afforded **37a** in 44% yield with moderate β-selectivity (1:3 α/β ratio). As observed previously for 6-deoxyglycosides,[17e] thioglycoside **27** was very reactive toward glycosylation and required very low temperatures (–78°C). Because glycosylation of cholesterol was difficult to monitor by TLC, higher temperatures and a longer reaction time were used to ensure maximum conversion to glycoside **37b**, which was obtained in 46% yield as a 1:25 α/β mixture (Table 3.8, entry 5). Finally, in order to study other activation strategies, the glycosylation of 6-deoxy-1-thioglycoside donor **32**[51] was carried out by using Me_2S_2, Tf_2O, and TTBP.[52] Under these conditions **38a** was obtained in 66% yield as a 1:2.2 α/β mixture. Furthermore, to the best of our

[51] Prepared in our laboratory following the standard olefination and iodonium-induced cyclization sequence, see: Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007.
[52] Attolino, E.; Cumpstey, I.; Fairbanks, A. J. *Carbohydr. Res.* **2006**, *341*, 1609 and references therein.

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knowledge, this is the first Me_2S_2/Tf_2O-promoted glycosylation of a 2,6-dideoxy-2-iodo-1-thioglycoside. The anomeric configuration of compounds **33**–**38** was deduced by ^{1}H, ^{13}C, COSY, HSQC, and NOESY NMR analysis.

3.1.3 Conclusions

We have presented a general procedure for the stereoselective synthesis of 2-deoxy-2-iodo-hexopyranosyl glycosides from furanoses. The proposed methodology provides a new avenue for accessing 2-deoxyoligosaccharides. The procedure involves three reactions: Wittig–Horner olefination to give alkenyl sulfanyl derivatives, electrophilic iodine-induced cyclization to give phenyl 2-deoxy-2-iodo-1-thiopyranosides, a new type of glycosyl donor, and glycosylation. The olefination reaction afforded alkenyl sulfanyl derivatives in good to excellent yields, except in cases where the conformational freedom is constrained by cyclic protecting groups such as 3,4-*O*-isopropylidene.

The cyclization reaction proceeds with complete regio- and stereoselectivity. The reaction proceeds exclusively as 6-*endo* cyclization to give phenyl 1-thiopyranoside derivatives. The stereochemistry of the iodine at C-2 is always *cis* to the neighboring alkoxy group, except for *lyxo* derivatives which lack cyclic protecting groups. This is a key point in the overall process because the iodine controls the stereoselectivity of the glycosylation reaction. The yield of the cyclization depends on the configuration of the starting material; it is very good for substrates with a *ribo* or *xylo* configuration, but more modest for those with an *arabino* or *lyxo* configuration. The glycosylation reaction carried out with cholesterol,[53] which can be looked upon as a model of the aglycones present in natural products, and with a glucopyranoside, proceeded with good yields and good to excellent stereoselectivities. The glycosidic bond created in the major isomers was always *trans* to the iodine at C-2.

Although phenyl 2-deoxy-2-iodo-1-thioglycosyl donors of all configurations can be accessed using the proposed procedure, it is particularly effective in providing 2-deoxy-2-iodo-*β*-D-*gulo*- and -*β*-D-*allo*-glycosides. These glycosides are precursors of 2-deoxyglycosides of *ribo* and *xylo* configuration, which are difficult to obtain by the classical methodology starting from glycals.[54]

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[53] Pellissier, H. *Tetrahedron* **2004**, *60*, 5123.
[54] Wittman, M.D.; Halcomb, R.L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1979.

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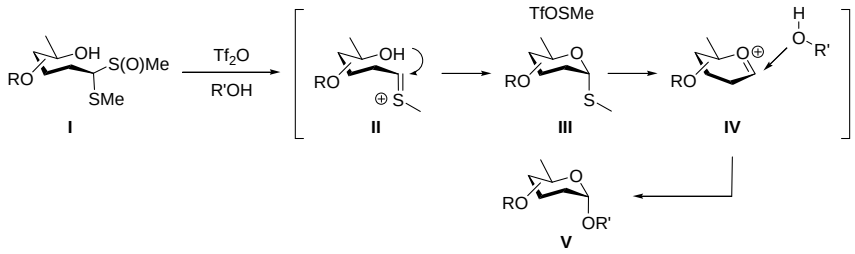
3.2 Stereoselective synthesis of 2-deoxyglycosides from alkenyl sulfides

3.2.1 Introduction

Chemical methods for one-pot syntheses of oligosaccharides have been explored by numerous research groups. Through various strategies, the one pot syntheses pursued involve several glycosyl donors selected to react in a specific order, thus resulting in a single oligosaccharide product. The end result of these efforts has been the development of programmable one-pot synthesis, the nearest precursor to automated oligosaccharide synthesis that exists today.[55] For example, Takahashi and co-workers reported a one pot method for the stereoselective synthesis of 2,3,6-trideoxysugar-containing disaccharides by cyclization and glycosylation through the sequential activation of sulfoxide and methylsulfanyl groups.[56] The synthetic strategy is illustrated in Scheme 3.6.



Scheme 3.6 One pot strategy for the preparation of 2,3,6-trideoxysugar-containing disaccharides

Selective activation of the sulfoxide group in **I** with trifluoromethanesulfonic anhydride (Tf_2O) leads to the formation of a sulfenium species **II**, which undergoes intramolecular acetalization to form thioglycopyranoside **III**. Concominant activation of the methylsulfanyl group in **III** with the TfOSMe present affords the oxonium intermediate **IV**, which undergoes glycosylation with R'OH, leading to glycoside **V**.

With this background, it is worth noting that the development of an efficient "one pot" synthetic strategy is particularly important. In the general procedure previously described, the 2-deoxy-2-iodo-thioglycosides, which are prepared from acyclic derivatives via iodonium-induced cyclization, are isolated and further activated in the presence of a glycosyl acceptor, NIS, and triflic acid (TfOH) to give the corresponding 2-deoxy-2-iodoglycosides. The similar conditions required for cyclization and glycosylation prompted us to explore the construction of 2-deoxy-2-iodo-oligosaccharide motifs through a more direct strategy that does not require the isolation of the 2-deoxy-2-iodo-1-thioglycoside.

---

[55] Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465.
[56] Amaya, T.; Takahashi, D.; Tanaka, H.; Takahashi, T. *Angew. Chem. Int. Ed.* **2003**, *42*, 1833.

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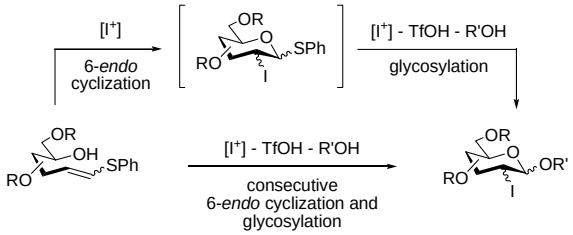
Herein we report a convenient consecutive "one pot" electrophile-induced cyclization and glycosylation sequence from the corresponding acyclic alkenyl sulfanyl derivatives to directly furnish the 2-deoxy-2-iodoglycosides (Scheme 3.7).



Scheme 3.7 Refinement of the original stepwise sequential procedure in a more efficient "one pot" cyclization and glycosylation strategy

We show that this "one pot" procedure in general gives better yields than the stepwise procedure, with remarkable improvements in some cases, and with only a slight loss of stereoselectivity in the final glycoside. In addition, we show that this methodology can be used to prepare the final deiodinated 2-deoxy- and 2,6-dideoxyglycosides in good yields.

3.2.2 Results and discussion

To facilitate comparison between the "one pot" and stepwise procedures, consecutive cyclization and glycosylation was initially studied using starting materials and glycosyl acceptors similar to those used previously in the two-step procedure. In a previous study, reagents such as *N*-iodosuccinimide (NIS) and iodonium dicollidine perchlorate (IDCP) were used to perform the electrophile-induced cyclization to give the corresponding 2-deoxy-2-iodo-thioglycosides. When applied to the consecutive cyclization and glycosylation strategy, IDCP led to the thioglycoside but was ineffective in bringing about glycosylation even with the addition of TfOH. Consequently, the following experiments were carried out using NIS, which was found to promote both transformations to directly afford the 2-iodoglycoside. Table 3.10 shows representative examples of the different reaction conditions tested. The optimized reaction conditions can be summarized as follows: a) Only 3 equivalents of NIS are necessary to promote the desired transformation. b) Monitoring the progress of the reactions by TLC is crucial for achieving overall good yields, with TfOH only being added when the cyclization is complete. c) To achieve good stereoselectivity in the final glycoside, the glycosylation reaction with the initially formed transient thioglycoside must take place at low temperature. This is achieved by addition of TfOH at ca. –78ºC and careful temperature control.

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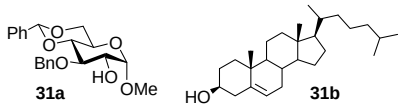
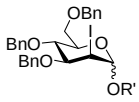
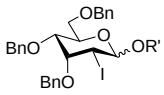
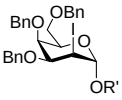
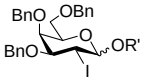
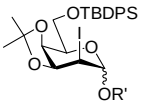
Table 3.10 Stereoselective consecutive cyclization and glycosylation reactions of **31a** and **31b** from sulfanyl alkenes **2** and **9**–**11**



Entry[a]	Starting material (*Z*/*E* ratio)[b]	Glycosylation product		Yield (%)[c]	*α*/*β* ratio[d]
1	**2** (1:3)		**33a**	50 (43)	45:1 (45:1)
			33b	54 (43)	24:1 (37:1)
2	**9** (1:2)		**34a**	65 (62)	1:5 (1:6)
			34b	70 (57)	1:3 (1:9)
3[e]	**10** (1:17)		**35a**	22	1:0
			**41a**	60	1:1.25
4	**11** (2:5)		**36a**	50 (32)	5:1 (20:1)
			36b	27 (27)	10:1 (8:1)

[a] Alkenyl sulfide (1eq), R'OH **31a**,**b** (2 eq), and 4ÅMS were treated with NIS (3 eq) in dry CH_2Cl_2 from -78ºC to room temperature until no alkene was observed. The reaction mixture was then cooled and TfOH (20 mol %) was added. The reaction was left to stirr at low temperature until the reaction was completed. For a more detailed description, see the experimental section. [b] Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum after chromatographic purification. [c] Yield and selectivity in brackets correspond to the stepwise procedure. [d] Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [e] Product distribution = an inseparable 1:1.2 mixture of **35a**/**41a**β and pure **41a**α was obtained after chromatographic purification; ratio **35a**/**41a**α/**41a**β = 1:1.2:1.5.

For *arabino* derivative **2**, the yields were slightly higher than those of the two-step procedure, and the stereoselectivity was maintained when alcohol **31a** was used as the glycosyl acceptor, but decreased for cholesterol (Table 3.10, entry 1). Similarly, for *ribo* derivative **9**, the overall yield was higher for the "one pot" procedure, and the stereoselectivity for both glycosyl acceptors tested was close to that of the two-step procedure (Table 3.10, entry 2). The result obtained for sulfanyl alkene **11** was even more remarkable: yield increases of 20% were observed, with a loss of stereoselectivity when alcohol **31a** was the glycosyl acceptor. However, only a slight decrease in the

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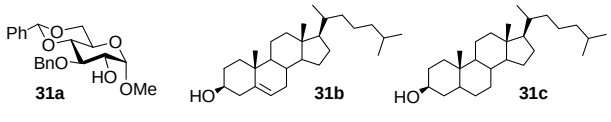
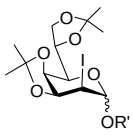
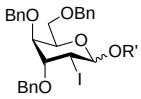
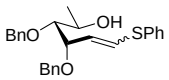
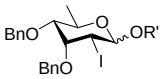
stereoselectivity was observed when cholesterol was used as the glycosyl acceptor (Table 3.10, entry 4), consistent with previous reports on the behavior of less sterically hindered acceptors.[17c] Application of the "one pot" cyclization and glycosylation strategy to *lyxo* derivative **10** led, however, to the formation of a mixture of glycosides **35a** and **41a**α/β in 82% overall yield (Table 3.10, entry 3). Compounds **41a**α/β presumably resulted from an outside attack of the electrophile to the alkene, as already was observed in the two-step procedure.

Table 3.11 Stereoselective consecutive cyclization and glycosylation reactions of **31a–c** from sulfanyl alkenes **17**, **18**, and **42**. Data extracted from Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007



Entry[a]	Starting material (*Z*/*E* ratio)[b]	Glycosylation product		Yield (%)[c]	α/β ratio[d]
1	**17** (0:1)		**39a**	71 (33)	32:1 (40:1)
			39b	58 (27)	2:1 (8:1)
			39c	64	3:1
2	**18** (1:5)		**40a**	71 (47)	1:10 (1:16)
			40b[e]	66 (51)	1:7 (1:8)
			40c	76	1:16
3[f]	 **42** (2:5)		**38b**[g]	70	1:8

[a] Alkenyl sulfide (1eq), R'OH **31a-c** (2 eq), and 4ÅMS were treated with NIS (3 eq) in dry CH_2Cl_2 from -78ºC to room temperature until no alkene was observed. The reaction mixture was then cooled and TfOH (20 mol %) was added. The reaction was left to stirr at low temperature until the reaction was completed. For a more detailed description, see the experimental section. [b] Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum after chromatographic purification. [c] Yield and selectivity in brackets correspond to the stepwise procedure. [d] Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [e] **40b** (33%, 1:6 α/β ratio) was obtained when NIS (5 eq) was used. [f] AgOTf (47 mol %) used insted of TfOH (20 mol %). [g] **38b** (61%, 1:3 α/β ratio) was obtained under the standard conditions.

Consecutive reactions using substrates **17**, **18**, and **42**, were also tested (Table 3.11). Thus, sulfanyl alkene **17** provided the expected products in better yields than those of the stepwise procedure (Table 3.11, entry 1). The optimized reaction of **18** and **31b** gave glycoside **40b** in 66% yield (i.e., double the 33% yield achieved in the non-optimized

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reaction) and with a similar selectivity to that obtained in the two-step procedure. Similar behavior was observed on reacting **18** with cholestanol **31c** (76%) and glycoside derivative **31a** (71%) (Table 3.11, entry 2). To show the usefulness of the "one pot" cyclization and glycosylation procedure, we applied it to the sulfanyl alkene **42** as a model of the 2,6-dideoxyglycoside constituent of the pregnane glycoside family. We also selected cholesterol as a model aglycone. The reaction of **42** with cholesterol in the presence of NIS/TfOH afforded **38b** in 61% yield as a 1:3 α/β mixture. Using NIS/AgOTf[57], the yield increased to 70% and the β-selectivity improved (1:8 α/β ratio). Globally, the "one pot" procedure provides yields around 70%, clearly better than those of the two-step procedure, with only a slight decrease in the stereoselectivity of the final glycoside.

Radical deiodination of the 2-deoxy-2-iodoglycosides was also tested. Thus 2-deoxyglycosides can be easily obtained from the 2-deoxy-2-iodoglycosides by reaction with Bu_3SnH in radical conditions, as exemplified by conversion of compounds **33a** and **33b** into **43a** (67%) and **43b** (75%), respectively (Figure 3.3). The removal of the iodine atom from **38b**, which occupied the equatorial position, proved to be much more difficult than for derivatives **33a**,**b**. When Bu_3SnH/AIBN in refluxing toluene was used, mainly degradation products were obtained. Finally, using Et_3B/O_2 at room temperature the 2,6-dideoxyglycoside **44b**[58] was obtained in 79% yield.

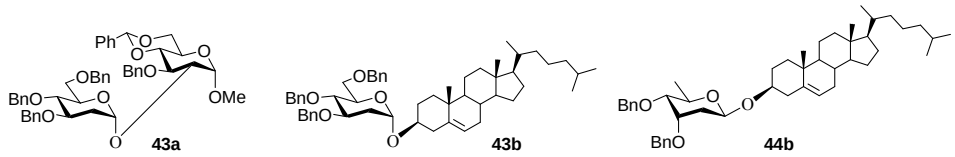

Figure 3.3 Deoxyglycosides **43a**,**b**, and **44b** obtained via Bu_3SnH-mediated radical deiodination

3.2.3 Conclusions

We have shown that the "one pot" consecutive cyclization and glycosylation strategy is a convenient and direct method for the synthesis of 2-deoxy-2-iodoglycosides that proceeds with good overall yield and stereoselectivity. Compared to classical glycosylation methods, the "one pot" procedure has the advantage that it starts directly from the very stable acyclic alkenyl sulfide precursors and does not require isolation of the glycosyl donors. The overall strategy (olefination from pentoses, cyclization, and glycosylation reaction) is fairly straightforward and operationally simple. It is worth

[57] Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073.
[58] Prepared in our laboratory under Bu_3SnH-mediated radical deiodination, see: Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007.

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mentioning that although olefination affords *Z*/*E* mixtures of alkenes, no separation is required because the cyclization is stereospecific at C-2, whose iodine substituent is the stereodirecting group in the glycosylation. This strategy is of particular interest in synthetic routes involving sensitive dideoxy glycosyl donors.

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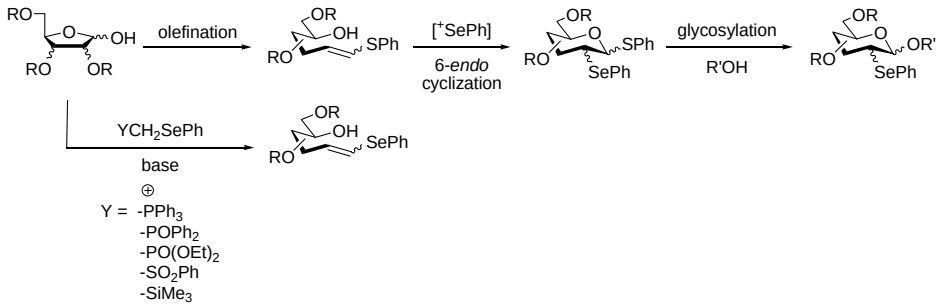
4 Stereoselective Synthesis of 2-Deoxy-2-phenylselenenyl glycosides



A series of 2-deoxy-2-phenylselenenyl-1-thioglycosides were evaluated as a new class of glycosyl donors that provide access to 2-deoxyglycosides from furanoses. This short synthetic route involves olefination, selenonium-ion-mediated 6-*endo* cyclization, and glycosylation reactions. The cyclization reaction proceeds with complete regio- and stereoselectivity enhanced by employing 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group. The implication of phenyselenenyl group at C-2 in the stereocontrolled glycosylation of 2-deoxyoligosaccharides is discussed. Its presence gives some insights into the likely pathway of glycosylation reactions by using 2-deoxy-2-phenylselenenyl-1-thioglycosyl donors in comparison with the previously described 2-deoxy-2-iodo derivatives. We have also demonstrated that the glycosylation of 2-deoxy-2-phenylselenenyl-1-thioglycosides is highly substrate dependent, as well as particularly effective in providing 2-deoxy-2-phenylselenenyl-*β*-D-*gulo*- and -*β*-D-*allo*-glycosides.

Since 2-deoxy-2-iodo- and 2-deoxy-2-phenylselenenyl-1-thioglycosides have been evaluated as a new class of glycosyl donors, we became interested in the preparation of other useful glycosyl donors such as 2-deoxy-2-iodo-1-selenoglycosides, and exploit their higher reactivity in developing milder and orthogonal stereoselective glycosylation protocols by using this methodology. Thus, carbohydrate-based vinyl selenides of *arabino*, *ribo,* and 2-deoxy-*ribo* configurations were prepared by Wittig-type reactions of various protected furanoses. Moderate yields were always obtained due to nature and reactivity of both carbohydrate lactols and selenium-based olefinating reagents under the conditions tested. A detailed study of the olefination reaction and the behaviour of vinyl selenides towards the electrophile-induced cyclization will be discussed.

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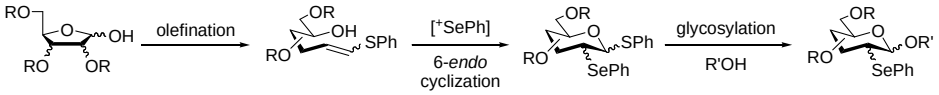
4.1 Stereoselective synthesis of 2-deoxy-2-phenylselenenyl glycosides from 2-deoxy-2-phenylselenenyl-1-thioglycosides

4.1.1 Introduction

As reported in Chapter 3.1, 2-deoxy-2-iodo-1-thioglycosides were synthesized from pentoses and used as glycosyl donors for the stereocontrolled synthesis of 2-deoxy-2-iodo-disaccharides. This short synthetic route involves olefination, iodonium-ion-mediated 6-*endo* cyclization, and glycosylation reactions, and provides a new access to 2-deoxy-*β*-hexoglycosides of *ribo* and *xylo* configuration.

Motivation to develop this new procedure prompted us to investigate 2-deoxy-2-phenylselenenyl-1-thioglycosides as a new class of glycosyl donors and evaluate the effect of the phenylselenenyl group in the stereochemical outcome of the glycosylation reaction since there are no examples reported with 2-deoxy-2-phenylselenenyl-D-*gulo*- and -D-*allo* glycosides.



Scheme 4.1 Proposed methodology for the stereoselective synthesis of 2-deoxy-2-phenylselenenyl glycosides

4.1.2 Results and discussion

The first step in the proposed synthesis of 2-deoxy-2-phenylselenenyl-1-thioglycosides was the electrophile-induced cyclization. For this purpose, vinyl sulfides **2**, **9**, **11**, **13**, **17**, and **18** were easily prepared in one step from the corresponding protected furanoses and used as starting materials, see Chapter 3.1.

In this context, functionalization of double bonds promoted by electrophilic selenium species was employed successfully for the synthesis of different versatile building blocks in organic synthesis.[59] When the alkene moiety is tethered to a nucleophilic substituent, intramolecular attack of the latter upon the intermediate selenonium-ion takes place, leading to the corresponding cyclized product, see Chapter 1.2. Although different alkene derivatives, reagents, and reaction conditions have been employed for this general

[59] (a) Patai, S.; Rappoport, Z. In *The Chemistry of Organic Selenium and Tellurium Compounds*, Vol. 2; John Wiley & sons, Inc., Chichester, 1987. (b) Liotta, D. In *Organoselenium Chemistry*, Ed. Wiley, New York, 1987. (c) Paulmier, C. In *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press, Oxford, 1986. (d) Nicolau, K. C.; Petasis, N. A. In *Selenium in Natural Products Synthesis*, CIS, Philadelphia, 1984. (e) Wirth, T. *Tetrahedron* **1999**, *55*, 1. (f) Tiecco, M. *Top. Curr. Chem.* **2000**, *208*, 7. (g) Wirth, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 3742. (h) Petragnani, N.; Stefani, H. A.; Valduga, C. J. *Tetrahedron* **2001**, *57*, 1411.

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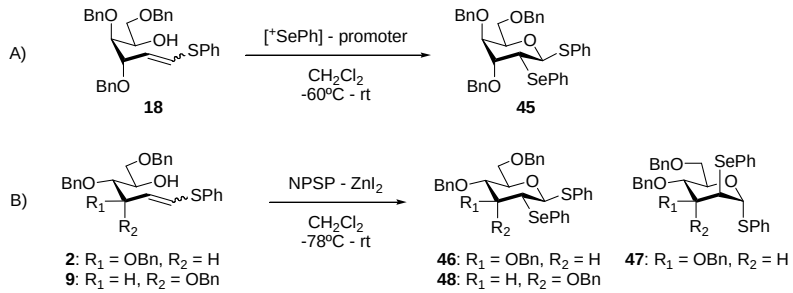
transformation,[60–62] no publication dealing with the electrophilic selenenylation reaction of carbohydrate-based vinyl sulfides has been reported to date.

The reaction conditions for cyclization were optimized by starting from derivative **18** (Scheme 4.2, A). Initial attempts under basic conditions with the use of phenylselenenyl triflate (PhSeOTf)[63] proved ineffective as this selenenylating agent gave an inseparable mixture of products. However, when *N*-(phenylselenenyl)phthalimide (NPSP)[64] was employed without a promoter, expected product **45** was obtained in yields lower than 11% but with total regio- and stereoselectivity.[65] Cyclization with NPSP and ZnI_2[66] as the promoter led to desired product **45** in a similar yield (<15%) maintaining the same regio- and stereoselectivity. The presence of the promoter allows the reaction to proceed under milder conditions. Other promoters such as (±)-camphor-10-sulfonic acid (CSA),[63] $Mg(ClO_4)_2$,[67] $SnCl_4$,[68] and I_2[69] resulted in unsuccessful cyclization reactions. Other alkenyl sulfides such as *arabino* **2** and *ribo* **9** derivatives also reacted with similar selectivity, but the reactions were sluggish to give compounds **46**–**48** with yields lower than 15% (Scheme 4.2, B).



Scheme 4.2 Selenonium-induced cyclization of tri-*O*-benzyl-protected alkenyl sulfides **2**, **9**, and **18** to obtain 2-deoxy-2-phenylselenenyl-1-thioglycosides **45**–**48**

---

[60] For some selected methoxyselenenylations, see: (a) Pedrosa, R.; Andrés, C.; Arias, R.; Mendiguchía, P.; Nieto, J. *J. Org. Chem.* **2006**, *71*, 2424. (b) Pedrosa, R.; Andrés, C.; Mendiguchía, P.; Nieto, J. *J. Org. Chem.* **2006**, *71*, 5388. (c) Niyomura, O.; Cox, M.; Wirth, T. *Synlett* **2006**, 2, 251. (d) Back, T. G.; Moussa, Z.; Parvez, M. *J. Org. Chem.* **2002**, *67*, 499. (e) Uehlin, L.; Wirth, T. *Org. Lett.* **2001**, *3*, 2931.

[61] For some selected selenocyclizations, see: (a) Surprenant, S.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 2851. (b) Denmark, S. E.; Edwards, M. G. *J. Org. Chem.* **2006**, *71*, 7293. (c) Khokhar, S. S.; Wirth, T. *Eur. J. Org. Chem.* **2004**, 4567. (d) Khokhar, S. S.; Wirth, T. *Angew. Chem. Int. Ed.* **2004**, 4*3*, 631.

[62] For an enantiopure synthesis of carbohydrates mediated by oxyselenenylation, see: Kim, K. S.; Moon, C. W.; Park, J. I.; Han, S.-H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1341 and references therein.

[63] Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

[64] Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 683.

[65] For a detailed explanation of the regio and stereoselective outcome of the iodonium-ion-mediated 6-*endo* cyclization, see: Chapter 3.1.

[66] (a) Cuñat, A. C.; Díez-Martín, D.; Ley, S. V.; Montgomery, F. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 611. (b) Blaney, W. M; Cuñat, A. C.; Ley, S. V.; Montgomery, F. J.; Simmonds, M. S. J. *Tetrahedron Lett.* **1994**, *35*, 4861.

[67] Fukase, K.; Nakai, Y.; Kanoh, T.; Kusumoto, S. *Synlett* **1998**, 84.

[68] (a) Ley, S. V.; Lygo, B.; Molines, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2403. (b) Jackson, W. P.; Ley, S. V.; Morton, J. A. *Tetrahedron Lett.* **1981**, *22*, 2601.

[69] Jackson, W. P.; Ley, S. V.; Morton, J. A. *J. Chem. Soc., Chem. Commun.* **1980**, 1028.

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The synthetic scope of the current cyclization method was examined by changing the structural patterns of the alkenyl sulfides (Table 4.1). Cyclization of 3,4-*O*-isopropylidene-protected *lyxo* **11** and *ribo* **13** derivatives afforded thioglycosides **49** and **51**, respectively, in moderate yields (15–33%) and complete selectivity together with glycals **50** (60%) and **52** (74%) as major products (Table 4.1, entries 1 and 2). The cyclization of 3,4-*O*-isopropylidene-protected derivative **17** proceeded smoothly and afforded the desired thioglycoside **53** with complete α-selectivity in good yield (Table 4.1, entry 3). Forcing the reaction conditions in the absence of ZnI_2 led to the formation of 2-phenylselenenyl glycal **54** in 34% yield together with small amounts of **53** (Table 4.1, entry 4). These cyclization assays revealed that the cyclization conditions are very sensitive to the configuration, as well as the nature, of the hexenyl sulfide protecting groups. The relative stereochemistry of compounds **45**–**48**, **49**, **51**, and **53** (C-1, C-2, and C-3 groups) was deduced by ^{1}H, ^{13}C, COSY, HSQC, and NOESY NMR analysis, similarly to those described in Chapter 3. In particular, ^{13}C NMR chemical shifts of C-2 (δ 43–51 ppm) are a characteristic feature of the C–Se bonds.

These experiments established that hydroxyl-hexenyl sulfides **11**, **13**, and **17** undergo a completed 6-*endo* regioselective electrophilic selenium-induced cyclization enhanced by employing 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group.[70] However, it is less obvious why phenylselenenyl-promoted cyclization led to such different product distribution (thioglycosides, glycals, and 2-phenylselenenyl glycals) related to the alkene substrate, although being performed under similar conditions.

[70] For a recent review dealing with the use of cyclic bifunctional protecting groups 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.

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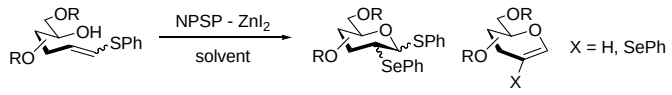
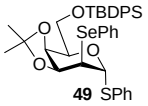
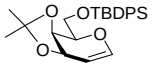
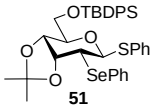
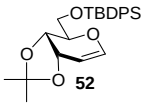
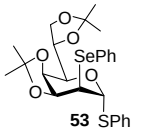
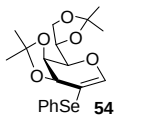
Table 4.1 Cyclization of 3,4-*O*-isopropylidene-protected alkenyl sulfides **11**, **13**, and **17** induced by electrophilic selenium reagents



Entry[a]	Starting material	*Z*/*E* ratio[b]	Cyclization conditions	Cyclization product	Yield (%)	α/β ratio[c]
1[d]	**11**	1:35	-78 to -50ºC 9 h	 **49** SPh	33	1:0
				 **50**	60	-
2	**13**	1:33	-78 to -30ºC 6.5 h	 **51**	15	0:1
				 **52**	74	-
3	**17**	0:1	-65 to -10ºC 3 h	 **53** SPh	60[e]	1:0
4[f]	**17**	0:1	rt, 15 h	**53**	11	1:0
				 PhSe **54**	34	-

[a] Alkenol (1 eq), NPSP (2 eq), ZnI_2 (2 eq), solvent = CH_2Cl_2 unless otherwise indicated. [b] Determined by integration of the olefinic proton signals in the ^1H NMR spectrum after chromatographic purification. [c] Determined by integration of the anomeric proton signals in the ^1H NMR spectrum of the crude reaction mixture. [d] NPSP (1.5 eq), ZnI_2 (1.5 eq). [e] 10% of the corresponding glycal was also obtained. [f] NPSP (2 eq) without promoter; data extracted from Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007.

A plausible explanation for the observed product distribution is outlined in Scheme 4.3. The conversion of compound **I** into **III** represents an overall base-promoted PhSSePh elimination process, and might be occurring through initial *S*-phenylselenenylation followed by the elimination of a "phenylselenol equivalent" PhSSePh to give a 2-phenylselenenyl glycal. Similarly, the production of **IV** might be explained in terms of

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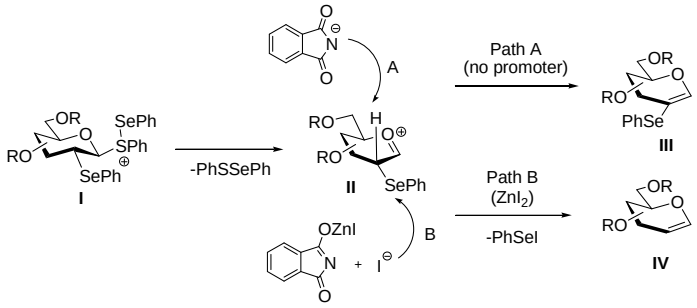
reductive elimination of PhSSePh–PhSeI to afford the corresponding glycal. Similar results have been described in phenylselenium-induced lactamizations of olefinic amides.[71]



Scheme 4.3 Plausible mechanism for the observed product distribution during the cyclization of 3,4-*O*-isopropylidene-protected alkenyl sulfides induced by electrophilic selenium species

Having our target donor thioglycosides in hand, we turned our attention to the investigation of their glycosylation properties. On the basis of our experience with 2-deoxy-2-iodo-1-thioglycosides (Chapter 3.1), we anticipated that 2-deoxy-2-phenylselenenyl-1-thioglycosides **45**–**48**, **51**, and **53** would have the reactivity characteristics that we desired.

Thus, we found that the glycosylation of **53** with several promoters, such as NIS/TfOH, NIS/TMSOTf, and dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) proceed smoothly at low temperature to give corresponding 2-deoxy-2-phenylselenenyl-glycoside **55a** with high stereocontrol (α/β ratio range from 7:1 to 40:1) in moderate to good yields (21–68%). The results are summarized in Table 4.2. In NIS promoted glycosylations the use of 1:3 toluene–dioxane enhanced α-selectivity[72] (Table 4.2, entries 1 and 2). However, the most dramatic effect in terms of anomeric ratio is the nature of the promoter, as well as the counter-ion of the Lewis acid that activates the NIS. The best selectivities were obtained when DMTSF (Table 4.2, entry 4) was used, followed by NIS/TMSOTf and TfOH, respectively (Table 4.2, entries 2 and 3). Unfortunately, DMTSF and NIS/TMSOTf led to low yields of **55a**.

[71] Chung, S.-K.; Jeong, T.-H.; Kang, D.-H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 969.
[72] Demchenko, A.; Stauch, T.; Boons, G.-J. *Synlett* **1997**, 818.

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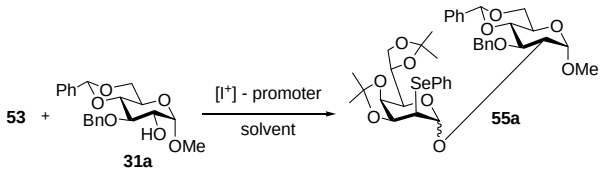
Table 4.2 Optimization of the stereoselective glycosylation conditions of 2-deoxy-2-phenylselenenyl-1-thioglycoside **53** to obtain **55a**



Entry[a]	Solvent (v/v)	[I$^+$]/Promoter (eq)	T (ºC)	t (h)	Yield (%)	α/β ratio[b]
1	CH_2Cl_2	NIS/TfOH (2.2/0.2)	-78	1	60	7:1
2	Toluene-Dioxane (1:3)	NIS/TfOH (2.2/0.2)	0	1	68	15:1
3	Toluene-Dioxane (1:3)	NIS/TMSOTf (1.2/0.6)	0	1	21	25:1
4	CH_2Cl_2	DMTSF (2)	-78 to -50	2	30	40:1

[a] Glycosyl donor (1eq), glycosyl acceptor **31a** (2 eq), 4Å MS. [b] Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture.

Accordingly, glycosylation reactions of **45**–**48** and **51** were performed by treating a mixture of the 2-deoxy-2-phenylselenenyl-1-thioglycosyl donor (1 eq) and glycosyl acceptor **31a** (2 eq) with NIS (2.2 eq) and TfOH (0.2 eq) in 1:3 toluene–dioxane in the presence of 4Å molecular sieves (Table 4.3). This procedure typically provides the desired products in good yields (50–70%). When compared with **46**, **48**, and **51** (Table 4.3, entries 2, 4, and 5), glycosyl donors **53** (Table 4.2) and **47** (Table 4.3, entry 3) provided improved stereoselectivities. These results are in agreement with those reported by Roush and Narayan for the glycosylation of 2-deoxy-2-iodo-manno- and 2-deoxy-2-talopyranosyl acetates.[12c] However, an interesting result was obtained with gulose derivative **45** (Table 4.3, entry 1). In this case, even using 1:3 toluene–dioxane as solvent system, the high selectivity value observed is comparable to **53** (Table 4.2, entry 2) and **47** (Table 4.3, entry 3), as well as to that previously reported for analogous glycosylation reactions of 2-deoxy-2-iodo-1-thio-*gulo*-glycosyl donors in CH_2Cl_2 (α/β ratio 1:16) (Chapter 3.1, Table 3.9). Interestingly, a similar behaviour was issued in previous studies with 2-deoxy-2-iodo-glucosyl trichloroacetimidates in which no improvement in the α/β ratio was found by changing solvent properties.[17c] Glycosyl donor **46** displayed no β-selectivity (Table 4.3, entry 2) in agreement with prior studies with 2-phenylsulfanyl- and 2-phenylselenenyl-glucopyranosyl donors, which indicated that selectivity was highly substrate dependent, and the 2-iodo substituent was found to be the more general stereodirecting group.[17g,h,73] Other

[73] Hashimoto, S.-I.; Yanagiya, Y.; Honda, T.; Ikegami, S. *Chem. Lett.* **1992**, 1511.

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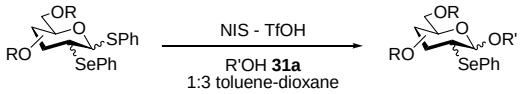
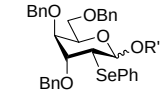
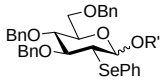
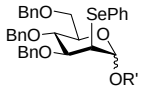
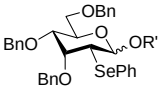
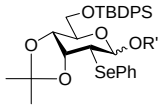
glycosyl donors bearing an equatorial phenylselenenyl group such as **48** and **51** provided modest *β*-selectivities (Table 4.3, entries 4 and 5).

Table 4.3 Stereoselective glycosylation of **31a** from 2-deoxy-2-phenylselenenyl-1-thioglycosides **45**–**48** and **51**



Entry	Starting material	Glycosylation product	Glycosylation conditions[a]	Yield (%)[b]	*α*/*β* ratio[c]
1	**45**		**56a** 0ºC, 4 h	50	1:14
2	**46**		**57a** 0ºC, 1 h	55	1:1
3	**47**		**58a** 0ºC, 1 h	64	15:1
4	**48**		**59a** 0ºC, 1 h	66	1:4
5	**51**		**60a** 0ºC to rt 2 h	70[d]	2:3

[a] Glycosyl donor (1eq), R'OH **31a** (2 eq), NIS (2.2 eq), TfOH (20 mol %), 4Å MS, solvent = 1:3 toluene-dioxane. [b] Determined by ^{1}H NMR in the presence of an internal standard unless otherwise indicated. [c] Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [d] Isolated yield.

In light of these results, we envisioned that oxocarbenium intermediates play an important role in the stereoselectivity of the glycosylation reactions of 2-deoxy-2-phenylselenenyl-1-thioglycosides rather than the corresponding selenonium-ion intermediates.[10,17c,21] The selectivity observed is 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–Holness kinetics[74] (Schemes 4.4 and 4.5).

It is known that nucleophilic attack on the oxocarbenium cations along a pseudoaxial trajectory to maximize overlap of the nucleophile HOMO with the LUMO of

[74] Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

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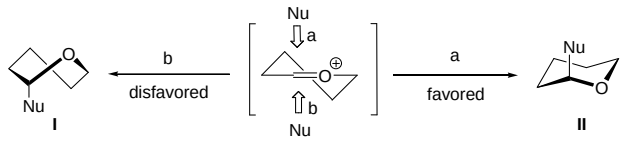
the oxocarbenium ion occurs with a facial preference to give a chair-like product **II** instead of higher energy twisted boat product **I** (Scheme 4.4). The chair-like pathway (a) is favored since it is expected to be formed by a lower-energy chair-like transition state.[75]



Scheme 4.4 Nucleophilic attack on the oxocarbenium cations

Besides, according to the results reported by Billings and Woerpel, PhSe-axial intermediates **IIa**,**b** (*manno* and *talo*) and **Ic**–**e** (*allo*, *gulo*, and *gluco*) are likely to be more stable than the corresponding PhSe-equatorial conformers due to stabilizing hyperconjugative interactions between σ_{C-Se} and π^*_{C-O} of the oxocarbenium[76] (Scheme 4.5). 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 population but developing destabilizing interactions in the transition state (transition-state effects) should also be accounted for. Thus, the reactivity of the oxocarbenium conformers towards nucleophilic attack may be affected by steric interactions between the C-3 (OR_3) and C-6 (OR_1) alkoxy substituents and the incoming nucleophile. Consistent with this, glycosylation of *gulo* **45** and *manno* **47** derivatives provided excellent *β*- and *α*-selectivities, respectively; by far the more stable axial PhSe conformers **Id** (*gulo)* and **IIa** (*manno*) are also the more reactive ones towards nucleophilic attack. *Allo* derivative **48** showed moderate *β*-selectivity. When compared with the *gulo* derivative **45**, the lower selectivity magnitude obtained could be explained by ground-state conformational preference variations. In the *allo* derivative **48**, the more reactive conformer **Ic** is also the more stable one (axial PhSe) although in this case 1,3-diaxial interactions between PhSe and C-4 alkoxy group (OR_2) may increase its energy with respect to the case of *gulo* derivative **45**, where such destabilizing interactions do not exist. *Gluco* donor **46** provided no selectiviy, probably because the reactivity of the more stable PhSe-axial conformer **Ie** is seriously attenuated by steric interactions of the incoming nucleophile with the pseudoaxial C-3 (OR_3) and C-6 (OR_1) substituents. Finally, in order to rationalize the observed *β*- and *α*-face approach of donors **51** (*allo*) and **53** (*talo*), respectively, we speculated that the reaction might operate by way of a constrained conformation[21,70,77] such as **III** and **IV** (Scheme 4.5).

---

[75] Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521 and references therein.
[76] Billings, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171.
[77] Toshima, K.; Nozaki, Y.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 6887.

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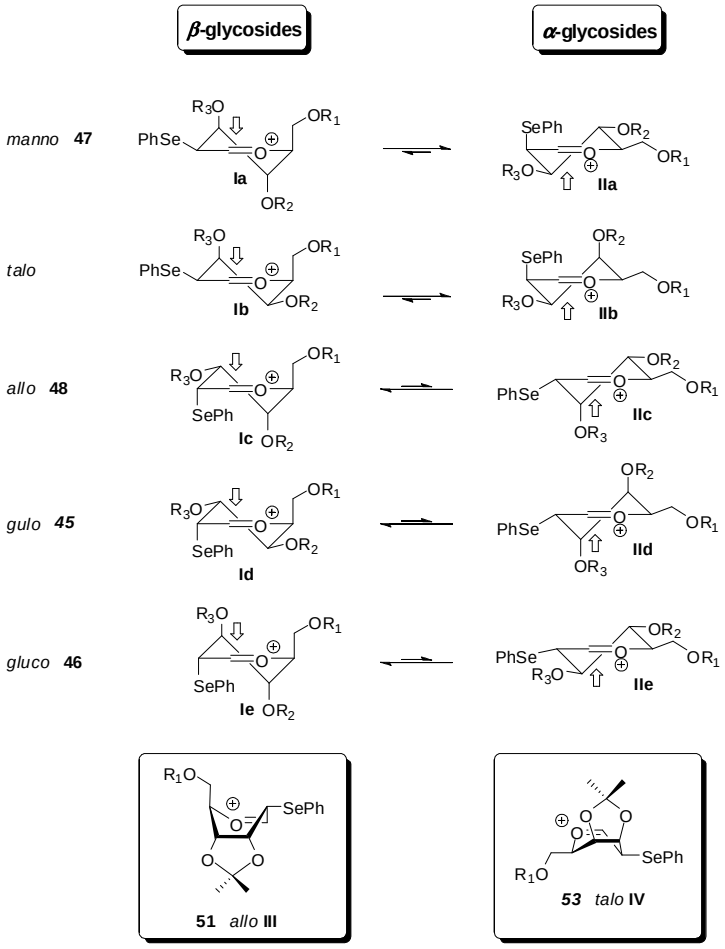
However, β-selectivity in 3,4-*O*-isopropylidene-protected derivative **51** is lower than that observed in **48** suggesting that the relative enhancement of α-selectivity is, in this case, predominantly a temperature effect (Table 4.3, entry 5).



Scheme 4.5 Stereochemical courses of glycosylation reactions of 2-deoxy-2-phenylselenenyl-1-thioglycosyl donors

4.1.3 Conclusions

We developed 2-deoxy-2-phenylselenenyl-1-thioglycosides as a new class of glycosyl donors that provide access to 2-deoxyglycosides. This short synthetic route involves olefination, selenonium-ion-mediated 6-*endo* cyclization, and glycosylation reactions. The olefination reaction affords the alkenyl sulfanyl derivatives in good to excellent yields. The cyclization reaction proceeds with complete regio- and

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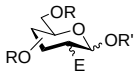
stereoselectivity enhanced by employing 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group. We have also demonstrated that the glycosylation of 2-deoxy-2-phenylselenenyl-1-thioglycosides is highly substrate dependent.

Although glycosylation products of all configurations can be accessed by employing the present methodology, it is particularly effective in providing 2-deoxy-2-phenylselenenyl-*β*-D-*gulo*- and -*β*-D-*allo*-glycosides. In particular, regardless of the nature of the solvent employed, the high *β*-selectivity observed in *gulo* **56a** (*α*/*β* ratio 1:14) and more modest in *allo* **59a** (*α*/*β* ratio 1:4) series is comparable to that previously observed for analogous glycosylation reactions of 2-deoxy-2-iodo-1-thio-D-*gulo*- (*α*/*β* ratio 1:16) and -D-*allo*-glycosyl donors (*α*/*β* ratio 1:6), see Table 4.4.

Table 4.4 Comparison of the selectivity obtained when E = I and SePh



E = I, SePh

Entry[a]	Configuration	*α*/*β* ratio	
		I[b]	SePh[c]
1	*manno*	45:1	15:1
2	*allo*	1:6	1:4
3	*talo*	40:1[d]	15:1
4	*gulo*	1:16[d]	1:14

[a] NIS, TfOH. [b] Solvent = CH_2Cl_2. [c] Solvent = 1:3 toluene-dioxane. [d] Data extracted from Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007.

Furthermore, the use of phenylselenenyl group at C-2 gave us some insight into the likely pathway of glycosylation reactions by using 2-deoxy-2-phenylselenenyl-1-thioglycosyl donors (Scheme 4.5). Since the stereoselectivity observed is similar to that obtained using 2-deoxy-2-iodo-1-thioglycosides it can be concluded that this explanation is general for the different glycosylations assisted by chalcogens and halogens at C-2.

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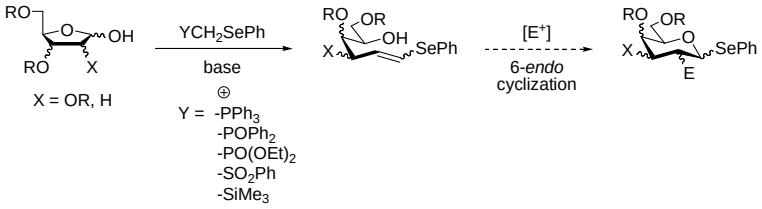
4.2 Synthesis of carbohydrate-based vinyl selenides

4.2.1 Introduction

In Chapters 3.1 and 4.1, we have reported a new procedure for the synthesis of 2-deoxy-2-iodo- and 2-deoxy-2-phenylselenenyl-1-thioglycosides from pentoses through a short synthetic route that involves olefination and electrophile-mediated 6-*endo* cyclization, and discussed the use of these glycosides as glycosyl donors for the stereocontrolled synthesis of 2-deoxy-2-iodo- and 2-deoxy-2-phenylselenenyl disaccharides. As part of our ongoing projects on the chemistry of natural and synthetic 2-deoxy- and 2,6-dideoxyglycosides, we became interested in the development of useful glycosyl donors such as 2-deoxy-2-iodo-1-selenoglycosides,[78] and exploit their high reactivity in developing milder and orthogonal stereoselective glycosylation protocols by using this methodology.

Encouraged by the previous results, we postulated that the presence of a selenium atom, instead of sulfur, would provide milder glycosylation conditions in order to improve the yield and stereoselectivity. Therefore, it was deemed interesting to investigate the synthesis of carbohydrate-based vinyl selenides and explore their reactivity with electrophiles (Scheme 4.6). There are only a few reported examples of electrophilic-induced reactions with vinyl tellurides,[79] 1,2-allenyl selenides,[80] and only one example regarding the use of vinyl selenides.[81]



Scheme 4.6 Proposed methodology for the stereselective synthesis of 2-deoxy-2-E-selenoglycosides (E = I, SePh, F, H)

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[78] For some syntheses and applications of selenoglycosides, see: (a) Kawai, Y.; Ando, H.; Ozeki, H.; Koketsu, M.; Ishihara, H. *Org. Lett.* **2005**, *7*, 4653. (b) Yamago, S.; Yamada, T.; Hara, O.; Ito, H.; Mino, Y.; Yoshida, J.-I. *Org. Lett.* **2001**, *3*, 3867. (c) Horne, G.; Mackie, W. *Tetrahedron Lett.* **1999**, *40*, 8697. (d) Czernecki, S.; Ayadi, E.; Xie, J. *Tetrahedron Lett.* **1996**, *37*, 9193. (e) Mehta, S.; Pinto, M. *J. Org. Chem.* **1993**, *58*, 3269. (f) Czernecki, S.; Randriamandimby, D. *Tetrahedron Lett.* **1993**, *34*, 7915. (g) Sato, T.; Fujita, Y.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1992**, 33, 239.

[79] Huang, X.; Liang, C.-G.; Xu, O.; He, O.-W. *J. Org. Chem.* **2001**, *66*, 74.

[80] (a) Fu, C.; Chen, G.; Liu, X.; Ma, S. *Tetrahedron* **2005**, *61*, 7768. (b) Ma, S.; Hao, X.; Meng, X.; Huang, X. *J. Org. Chem.* **2004**, *69*, 5720. (c) Ma, S.; Hao, X.; Huang, X. *J.Chem. Soc., Chem. Commun.* **2003**, 1082.

[81] Holze, G.; Jenny, W. *Helv. Chim. Acta* **1958**, *41*, 712.

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Organic chalcogenides are compounds of increasing importance in organic synthesis due to their particular reactivity[59a–d] and their attractive biological properties.[82] Selenium chemistry has been shown to provide highly efficient and selective transformations, and therefore has been widely used in the synthesis of natural products.[83] Among the various organoselenium compounds, vinyl selenides are particularly useful intermediates in the stereoselective preparation of functionalized alkenes,[84] carbonyl compounds,[85] as well as suitable substrates in carbon–carbon bond formation.[86]

A wide variety of methods have been developed for the synthesis vinyl selenides involving the reactions of organoselenium compounds with alkynes,[87] vinyl halides[88] or boranes,[89] and Wittig-type reactions.[90] Surprisingly, no paper dealing with the synthesis of carbohydrate-based vinyl selenides has been issued to date despite the fact that these products are good candidates for the preparation of complex 1,6- and 1,3-enediynes,[91] enantiomerically pure 1,2-diol derivatives,[92] and commonly occurring fragments in natural products.[93]

4.2.2 Results and discussion

The first step in the proposed synthesis of 2-deoxy-2-iodo-1-selenoglycosides was the preparation of carbohydrate-based vinyl selenides. Among the methods developed for

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[82] Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125.
[83] (a) Pérez-Balado, C.; Markó, I. E. *Tetrahedron* **2006**, *62*, 2331. (b) Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 3411.
[84] (a) Comasseto, J. V.; Ling, L. W.; Petragnani, N.; Stefani, H. A. *Synthesis* **1997**, 373. (b) Comasseto, J. V.; Petragnani, N. *J. Organomet. Chem.* **1983**, *253*, 131.
[85] Comasseto, J. V.; Petragnani, N. *J. Organomet. Chem.* **1978**, *152*, 295.
[86] (a) Hevesi, L.; Hermans, B.; Allard, C. *Tetrahedron Lett.* **1994**, *35*, 6729. (b) Okamura, H.; Miura, M.; Kosugi, K.; Takei, H. *Tetrahedron Lett*. **1980**, *21*, 87.
[87] For some recent nucleophilic or electrophilic organoselenium addition to alkynes, see: (a) Moro, A. V.; Nogueira, C. W.; Barbosa, N. B. V.; Menezes, P. H.; Teixeira da Roca, J. B.; Zeni, G. *J. Org. Chem.* **2005**, *70*, 5257. (b) Zeni, G.; Stracke, M. P.; Nogueira, C. W.; Braga, A. L.; Menezes, P. H.; Stefani, H. A. *Org. Lett*. **2004**, *6*, 1135.
[88] (a) Ranu, B. C.; Chattopadhyay, K.; Banerjee, S. *J. Org. Chem.* **2006**, *71*, 423. (b) Zue, L. S.; Huang, Z. Z.; Huang, X. *Tetrahedron* **1996**, *52*, 9819. (c) Comasseto, J. V.; Menezes, P. H.; Stefani, H. A.; Zeni, G.; Braga, A. L. *Tetrahedron* **1996**, *52*, 9687.
[89] Rarcher, S.; Hansen, M. R.; Colter, M. A. *J. Org. Chem.* **1978**, *43*, 4885.
[90] (a) Silveira, C. C.; Begnini, M. L.; Boeck, P.; Braga, A. L. *Synthesis* **1997**, 221. (b) Shin, W. S.; Lee, K.; Oh, D.Y. *Bull. Korean Chem. Soc.* **1996**, *17*, 981. (c) Shin, W. S.; Lee, K.; Oh, D.Y. *Tetrahedron Lett.* **1992**, *33*, 5375. (d) Petragnani, N.; Comasseto, J. V.; Rodrigues, R. Brocksom, T. J. *J. Organomet. Chem.* **1977**, *124*, 1. (e) Petragnani, N.; Rodrigues, R.; Comasseto, J. V. *J. Organomet. Chem.* **1976**, *114*, 281.
[91] (a) Moslin, R. M.; Jamison, T. F. *Org. lett.* **2006**, *8*, 455. (b) Galm, U.; Hager, M. H.; Van Lanen, S. G.; Ju, J.; Thorson, J. S.; Shen, B. *Chem. Rev.* **2005**, *105*, 739.
[92] (a) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1304. (b) Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937. (c) Georges, Y.; Allenbach, Y.; Ariza, X.; Campagne, J.-M.; Garcia, J. *J. Org. Chem.* **2004**, *69*, 7387.
[93] (a) Ruiz, P.; Murga, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 713. (b) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem. Int. Ed.* **2005**, *44*, 6630. (c) López, S.; Fernández-Trillo, F.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, *5*, 3725.

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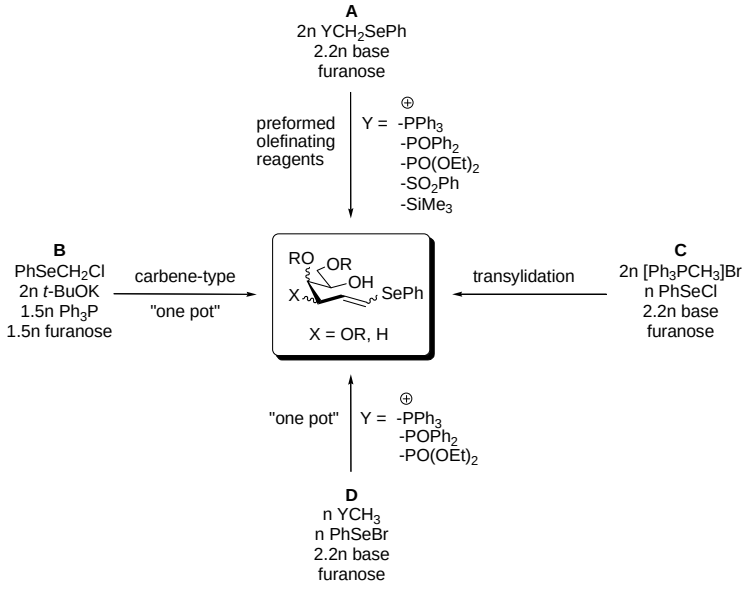
synthesizing vinyl selenides,[87–90] Wittig-type reactions seem to be the best strategy as this would avoid complex manipulation on the carbohydrate scaffold (Scheme 4.7).



Scheme 4.7 Wittig-type olefination strategies towards the synthesis of carbohydrate-based vinyl selenides

We initially decided to focus on the classical Wittig-type methodology (Scheme 4.7, A). The appropriate *α*-seleno preformed phosphorus reagents are the obvious starting materials for these reactions. However, the synthesis of most of these reagents are found to be problematic due to low yield, difficulty in handling and, often, tedious purification.

Since the preparation of selenophosphorane **61** (Scheme 4.8, A) from $[Ph_3PCH_3]Br$ and phenylselenenyl chloride gave an inseparable mixture of salts, several alternatives were considered starting from commercially available diphenyl diselenide (Scheme 4.8, B and C).

Selenosulfone derivative **62**[94] (Julia–Lythgoe olefinating reagent) was obtained from bromomethyl phenyl sulfone, diphenyl diselenide, and sodium hydride[95] in 54% yield together with small amounts of 1,1-bis-selenosulfone **63** and methyl phenyl sulfone **64**,[96] which were separated by standard chromatographic procedures (Scheme 4.8, B).

Next we tried the synthesis of chloromethyl phenylselenide **65**, which was readily obtained from diphenyl diselenide and CH_2Cl_2 according to the method reported in the

[94] Simpkins, N. S. *Tetrahedron* **1991**, *47*, 323.
[95] Dowd, P.; Kennedy, P. *Synth. Commun.* **1981**, *11*, 935.
[96] Sometimes selenols act as reducing agents of the C–halogen bond, see: (a) Seshadri, R.; Pegg, W. J.; Israel, M. *J. Org. Chem.* **1981**, *46*, 2596. (b) Hevesi, L. *Tetrahedron Lett.* **1979**, *32*, 3025.

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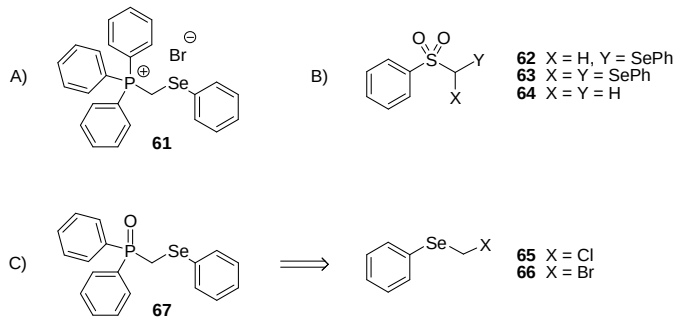
literature by Huang and Duan.[97] However, we were not able to obtain the corresponding chloro salt of **61** using precursor **65**, because this chloro analogue does not react with triphenylphosphine.[90a] Alternatively, the use of bromomethyl phenylselenide **66** would provide a route to selenophosphorane **61**. Unfortunately, when we attempted to extend the above methodology to CH_2Br_2, bromomethyl phenylselenide **66** was obtained in low yield at 0ºC, whilst heating under reflux lead to the formation of selenoacetal ($PhSeCH_2SePh$)[98] and ethoxymethyl phenylselenide ($PhSeCH_2OEt$)[99] as major products.

Finally, the preparation of corresponding *α*-selenophosphine oxide **67** (Wittig–Horner olefinating reagent) was accomplished by reacting derivative **65** with ethyl diphenylphosphinite (Ph_2POEt) under Michaelis–Arbuzov reaction conditions[100] (Scheme 4.8, C).



Scheme 4.8 Building blocks involved in the preparation of preformed olefinating reagents

The reaction conditions for olefination[90,101] were optimized by starting from the commercially available arabinose derivative **1**. The reactions of **1** with Me_3SiCH_2SePh (Peterson) (Table 4.5, entry 7), with **67** (Wittig–Horner) (Table 4.5, entry 8), and **62** (Julia–Lythgoe) (Table 4.5, entry 9) were unsuccessful even though different bases were used.[102] Three one pot procedures were considered (Scheme 4.7, B–D). Vinyl selenides have been previously prepared by addition of *t*-BuOK to a solution of chloromethyl phenyl selenide **65** and triphenylphosphine in THF followed by addition of an aldehyde[90a] (Scheme 4.7, B). Unfortunately, under these conditions, no reaction product was detected using arabinose derivative **1** (Table 4.5, entry 1).

---

[97] Huang, X.; Duan, D.-H. *Synlett* **1998**, 1191.
[98] Silveira, C. C.; Perin, G.; Braga, A. L. *Synth. Commun.* **1995**, *25*, 117.
[99] Nishiyama, Y.; Nakata, S.; Hamanaka, S. *Chem. Lett.* **1991**, 1775.
[100] Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.
[101] Similar protocols are used for the synthesis of vinyl selenides and vinyl sulfides because of phenylselenenyl substituent behaves like phenylsulfanyl with respect to different manipulations.
[102] In the Peterson olefination C–Se bond is cleaved by alkyllithiums to afford trialkylsilyl carbanions instead of the expected deprotonation, see: Dumont, W.; Krief, A. Angew. *Chem. Int. Ed.* **1976**, *15*, 161.

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The second method (Scheme 4.7, C) consisted in the transylidation reaction between alkylidene triphenylphosphorane ($Ph_3P{=}CH_2$) and phenylselenenyl chloride. In this case, the subsequent reaction with carbohydrate derivative **1** furnished vinyl selenide **68** in moderate yield and *Z*/*E* ratio of up to 1:12 (Table 4.5, entry 3). The ^{1}H NMR spectra unambiguously indicated the formation of the two possible diastereoisomers; **68***Z* ($J_{1,2}$ = 9.2 Hz) and **68***E* ($J_{1,2}$ = 15.6 Hz). Forcing the reaction conditions by refluxing the mixture for prolonged reaction time did not afford the desired compound; rather it led to the formation of diene **69** in 55% yield and 3:2 3*Z*,5*E*/3*Z*,5*Z* ratio (Table 4.5, entry 2) as a result of benzyl alcohol elimination in the open-ring sugar followed by Wittig reaction of the resulting enal as reported previously.[103] The ^{1}H NMR spectra indicated the formation of the two possible diastereoisomers; **69***Z* ($J_{5,6}$ = 10 Hz and $J_{2,3}$ = 8.4 Hz) and **69***E* ($J_{5,6}$ = 15.6 Hz and $J_{2,3}$ = 8.4 Hz). The same group has described the use of Bu_3SnCl to avoid benzyl alcohol elimination. Under these conditions, when *n*-BuLi was used at room temperature, **68** was obtained in moderated yield as a 1:9 *Z*/*E* mixture (Table 4.5, entries 4 and 5). It is worthy to note that while increasing the equivalents of olefinating reagent and base the yield is increased, an enitol impurity ($RCH{=}CH_2$) appears as result of alkylidene triphenylphosphorane ($Ph_3P{=}CH_2$) formation[104] followed by reaction with the carbohydrate lactol moiety (Table 4.5, entries 3, 4, and 6). Furthermore, the presence of the Bu_3SnCl has no influence either in the yield or in the enitol impurity formation, but affects the stereochemical outcome of the reaction.

Finally, we focused on a third method (Scheme 4.7, D) consisting in the generation of an *α*-seleno triphenylphosphonium reagent by the reaction of equimolar amounts of arylselenenyl bromides and phosphonium salts. In this case, the use of two equivalents of base with respect to the olefinating reagent was critical for obtaining the corresponding vinyl selenide instead of the undesired 1,1-bis-selenides.[90b] Thus, under these conditions, vinyl selenide **68** was obtained in 30% yield as a 1:7 *Z*/*E* mixture (Table 4.5, entry 6). The behaviour observed was similar to that found using more equivalents of olefinating reagent and base (Table 4.5, entries 3–5).

[103] Costantino, V.; Imperatore, C.; Fattorusso, E.; Mangoni, A. *Tetrahedron Lett.* **2001**, *42*, 8185.
[104] Galli, R. *J. Org. Chem.* **1987**, *52*, 5349.

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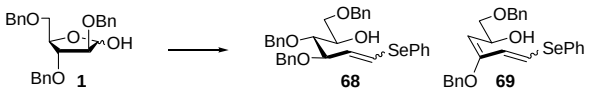
Table 4.5 Optimization of the olefination conditions of furanose **1** to obtain **68**



Entry	Olefination conditions[a] (eq)	Olefination product	Yield (%)	*Z*/*E* ratio[b]
1[c]	$PhSeCH_2Cl$ (1) Ph_3P (1.5) *t*-BuOK (2) rt to reflux, 14 h	mixture	-	-
2	$[Ph_3PCH_3]Br$ (2) PhSeCl (1) *n*-BuLi (2.2) reflux, 17 h	**69**	55	3:2[d]
3	$[Ph_3PCH_3]Br$ (6) PhSeCl (3) *n*-BuLi (6.6) rt, 14 h	**68**	29[e]	1:12
4	$[Ph_3PCH_3]Br$ (6) PhSeCl (3) *n*-BuLi (6.6) Bu_3SnCl (0.5) rt, 14 h	**68**	30[e]	1:9
5	$[Ph_3PCH_3]Br$ (4) PhSeCl (2) *n*-BuLi (4.4) Bu_3SnCl (0.5) rt, 14 h	**68**	19	1:9
6	$[Ph_3PCH_3]Br$ (2) PhSeBr (2) *n*-BuLi (4.4) -78ºC to rt, 14 h	**68**	30[e]	1:7
7	Me_3SiCH_2SePh (2) *n*-BuLi or LDA or KHMDS (3.3) -78ºC to rt, 14 h	mixture	-	-
8	$Ph_2P(O)CH_2SePh$ (4) *n*-BuLi (4.4) -78ºC to reflux, 20 h	mixture	-	-
9	$PhSO_2CH_2SePh$ (2) *n*-BuLi (4.4) -78ºC to rt, 14 h	**1**	-	-

[a] Solvent = THF. [b] Determined by integration of the olefinic proton signals in the ^1H NMR spectrum of the crude reaction mixture. [c] Starting Material (1.5 eq) was used. [d] 3*Z*,5*E*/3*Z*,5*Z* ratio. [e] Trace amounts of the corresponding enitol ($RCH{=}CH_2$).

Thus, this protocol provided the best result due to the use of less equivalents of base which is important to avoid not only the observed degradation of the α-seleno olefinating reagent due to C–Se bond lithiation, but also to prevent any epimerization at C-2 during the

Wittig reaction.[105] In order to confirm the degradation of these compounds, stability tests of the in situ generated *α*-seleno olefinating reagents were performed following the procedure reported in the experimental section without adding any carbonyl compound. The reaction mixture was quenched after 12 h stirring at room temperature. GC–EIMS, ^{1}H, ^{13}C, and ^{31}P NMR analysis of the crude showed signals corresponding to degradation products such as PhSeBu, $PhSeCH_2SePh$, and PhSeSePh due to C–Se cleavage occurred in highly basic media. Several trial experiments using different olefinating reagents and different bases were performed, but better results were not obtained.

This protocol was extended to different protected furanoses in order to determine the generality of the reaction and the influence of the stereochemistry at position C-2 (Table 4.6). The reaction of ribose derivative **8** under Wittig conditions (Table 4.6, entry 2) led to the formation of the desired alkene **70** in low yield (74% of the starting material was also recovered and could be further re-used) regardless of the base used as already observed for the reaction of isopropylidene and silyl-protected lyxofuranoses with Li-bases (Chapter 3.1, Table 3.2). The *Z*-isomer was detected as the major component in the mixture, in accordance with the known stereochemical course of Wittig olefinations under lithium salt free conditions.[90a,106] In contrast, when the same reaction was carried out using lyxose derivative **6**, only 25% of the starting material was recovered together with some other minor side products (Table 4.6, entry 1). In the case of xylose derivative **15**, all the reaction conditions tested were unsuccessful and only starting material was recovered (Table 4.6, entry 3). Despite the use of 2-deoxyribose derivative **16** which has less steric hindrance at C-2, either diene **71** or 1,1-bis-phenylselenide alkenol **72** were obtained under Peterson, Wittig, and Horner–Wadsworth–Emmons conditions (Table 4.6, entries 4 and 5). Fortunately, expected alkene **73** was obtained in 34% yield as a 1:1 *Z*/*E* mixture under Wittig–Horner conditions (Table 4.6, entry 6).

At this point, it is reasonable to assume that olefination reactions with sugar derivatives are slower than those with simple aldehydes probably due to the olefination occurs when the lactol is in its open chain. Since the olefinating reagents are degraded under strongly basic media it would be desirable that the reaction occurs as fast as possible to avoid this process which would lead to decrease the yield or even to no reaction. This assumption was confirmed by doing a competitive reaction with arabinose derivative **1** and benzaldehyde under Horner–Wadsworth–Emmons conditions. After 2 h stirring at room temperature, ^{1}H and ^{13}C NMR analysis of the crude showed signals corresponding to vinyl selenide (PhCH=CHSePh) while those corresponding to arabinose derivative **1** remained unchanged.

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[105] Freeman, F.; Robarge, K. D. *Carbohydr. Res.* **1986**, *154*, 270.
[106] Webb, T. H.; Thomasco, L. M.; Schlachter, S. T.; Gaudino, J. J.; Wilcox, C. S. *Tetrahedron Lett.* **1988**, *29*, 6823.

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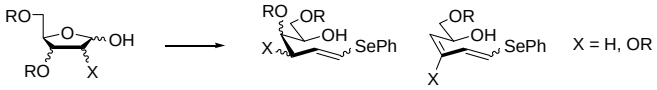
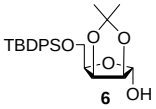
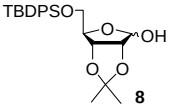
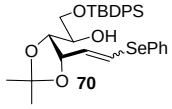
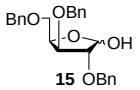
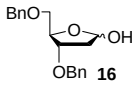
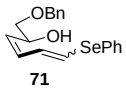
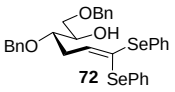
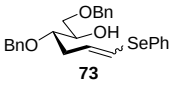
Table 4.6 Olefination of furanoses **6**, **8, 15**, and **16**



Entry	Starting material	Olefination conditions[a] (eq)	Olefination product	Yield (%)	*Z*/*E* ratio[b]
1	 **6**	$[Ph_3PCH_3]Br$ (2) PhSeBr (2) KHMDS (4.4) -78ºC to rt, 6 days	mixture[c]	-	-
2	 **8**	$[Ph_3PCH_3]Br$ (2) PhSeBr (2) KHMDS (4.4) -78ºC to rt, 6 days	 **70**	15[d]	11:1
3	 **15**	Me_3SiCH_2SePh (2) or $[Ph_3PCH_3]Br$ (2) or $Ph_2P(O)CH_3$ (2) or $(EtO)_2P(O)CH_3$ (2) PhSeBr (2) *n*-BuLi or LDA or KHMDS (4.4) -78ºC to rt, 14-48 h	**15**	-	-
4	 **16**	Me_3SiCH_2SePh(2) *n*-BuLi (3.3) -78ºC to reflux, 40 h then NaH (2), rt, 36 h	 **71**	trace	-
5	**16**	$[Ph_3PCH_3]Br$ (2) or $(EtO)_2P(O)CH_3$ (2) PhSeBr (2) *n*-BuLi (4.4) -78ºC to rt, 32 h	 **72**	5	-
			71	13	1:1[e]
6	**16**	$Ph_2P(O)CH_3$ (2) PhSeBr (2) *n*-BuLi (4.4) -78ºC to rt, 31 h	 **73**	34[f]	1:1

[a] Solvent = THF. [b] Determined by integration of the olefinic proton signals in the ^1H NMR spectrum of the crude reaction mixture. [c] 25% of the starting material was recovered. [d] 74% of the starting material was recovered. [e] 3*E*,*5E*/*3E*,*5Z* ratio. [f] Trace amounts of the corresponding diene.

Having synthesized different protected vinyl selenides from carbohydrate precursors and demonstrated how the C-2 substitution affects the reaction course, we next turned our attention to study their reactivity with electrophiles. In all cases, the *Z*/*E* mixtures of alkenes proved to be inseparable; hence, the cyclization reactions were assayed directly on the mixture of diastereomers (Scheme 4.9). Electrophile-induced cyclization was first studied for derivative **68**. Initial attempts using iodine electrophiles such as I_2, IDCP, NIS, and IPy_2BF_4 gave an inseparable mixture of products. When NIS was used as electrophile,

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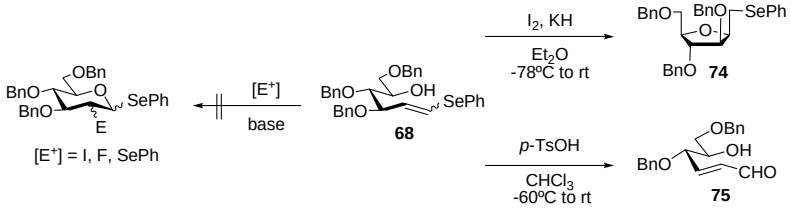
the reaction was carried out in the absence of base. Under these conditions, a complex mixture of products was obtained in both MeCN and EtCN. Propionitrile was used when the reaction was carried out under milder conditions due to its lower freezing point. Since selenoglycosides are activated in milder conditions than thioglycosides, we assumed that if any electrophilic cyclization occurred, the excess of electrophile would promote the activation of the phenylselenenyl moiety. In order to trap any oxacarbenium ion formed, the reaction mixture was quenched by addition of a few drops of methanol. However, no reaction product was detected by TLC. Further ^{1}H and ^{13}C NMR analysis revealed the presence of signals corresponding to an amide moiety (NHCO). These products were presumably formed by the attack of nitriles to selenonium- or iodonium-ion intermediates, prior to the addition of methanol, as reported by Toshimitsu and co-workers.[107] Alternatively, using weaker electrophiles (IDCP, IPy_2BF_4), either starting material **68** or its *Z*-isomer were recovered. This difference in reactivity between the *Z*- and *E*-alkenes has been recently observed in our group during the studies toward the synthesis of 2-deoxy-2-iodoglycosides from alkenyl sulfanyl derivatives, see Chapter 3.



Scheme 4.9 Electrophile-induced cyclization of alkenyl selenide **68**

Although highly basic media could lead to partial decomposition of vinyl selenides,[108] the cyclization of **68** using I_2 and KH gave compound **74** in very low yield (<10%) probably as a result of a 5-*exo* Michael-type nucleophilic cyclization[109,110] instead of the expected 6-*endo* regioselective electrophile-induced cyclization[111] (Scheme 4.9).

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[107] Toshimitsu, A.; Nakano, K.; Mukai, T.; Tamao, K. *J. Am. Chem. Soc.* **1996**, *118*, 2756.

[108] (a) Reich, H. J.; Willis, Jr. W. W.; Clark, P. D. *J. Org. Chem.* **1981**, *46*, 2775. (b) Liu, P. S.; Marquez, V. E.; Kelley, J. A.; Driscoll, J. S. *J. Org. Chem.* **1980**, *45*, 5227. (c) Sevrin, M.; Denis, J. N.; Krief, A. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 526.

[109] This behaviour could be rationalized by the formation of the known Se–I_2 charge-transfer complexes which would activate the double bond for the nucleophilic cyclization, see: (a) Godfrey, S. M.; Jackson, S. L.; McAuliffe, C. A.; Pritchard, R. G. *J. Chem. Soc., Dalton Trans.* **1997**, 4499. (b) Klapötke, T.; Passmore, J. *Acc. Chem. Res.* **1989**, *22*, 234. (c) Kubiniok, S.; du Mont, W. -W.; Pohl, S.; Saak, W. *Angew. Chem. Int. Ed. Engl.* **1988**, *3*, 431.

[110] For some nucleophilic reactions involving vinyl selenoxides and selenones, see: (a) Tiecco, M.; Chianelli, D.; Testaferri, L. Tingoli, M.; Bartoli, D. *Tetrahedron* **1986**, *42*, 4889. (b) Kuwajima, I.; Shimizu, M.; Ando, R. *J. Org. Chem.* **1983**, *49*, 1230. (c) Shimizu, M.; Kuwajima, I. *J. Org. Chem.* **1980**, *45*, 2921. (d) Shimizu, M.; Kuwajima, I. *J. Org. Chem.* **1980**, *45*, 4065.

[111] Selenium stabilizes a positive charge on the neighbouring carbon atom; making the 6-*endo* cyclization possible, see: Silveira, C. C.; Larghi, E. L. *J. Braz. Chem. Soc.* **1998**, *9*, 327.

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Product **74** was isolated and characterized by its fully assigned ^{1}H and ^{13}C NMR spectra.[34c] Furthermore, the structure was confirmed by COSY and HSQC experiments. The relative stereochemistry of compound **74** (C-2 and C-3 groups) was initially deduced by comparing the ^{13}C NMR chemical shifts of CH_2SePh in furan rings with *cis* (δ 25–30 ppm) or *trans* (δ 30–40 ppm) disposition.[33a] In particular, the peak at 25.4 ppm is indicative of a *cis* relationship. The relative stereochemistry of **74** was finally established by NOE difference measurements, in which significant NOE correlation peaks between H-3 and H-2; H-5 and OCH_2Ph present at C-4; were observed (Figure 4.1).

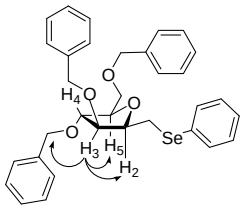

Figure 4.1 Significant NOE correlation peaks in compound **74**

Electrophilic cyclization using other electrophiles, such as Selectfluor® and PhSeCl has also been examined, but complex mixtures were always obtained (Scheme 4.9). Reaction of vinyl selenide **68** with 5 mol % *p*-TsOH afforded 2,3-dideoxy-*α*/*β*-unsaturated enal **75** in 25% yield as a result of an acid-catalyzed vinyl selenide hydrolysis[112] and benzyl alcohol elimination (Scheme 4.9), despite the same conditions having been previously used in the cyclization of vinyl silanes.[113] These 2,3-dideoxy-*α*/*β*-unsaturated sugar aldehydes, commonly known as Perlin aldehydes, have been used as precursors for the synthesis of many biologically important molecules.[114]

Finally, in order to explore new strategies in this field, we decided to attempt a "one pot" cyclization and glycosylation reaction between vinyl selenide **70** and glucoside acceptor **31a**. Unfortunately, despite the mild conditions used, reaction product **76a** was not detected at –78ºC. Any further increment of the temperature had no visible effect on the product formation (Scheme 4.10).

[112] Piquard, J. L.; Hevesi, L. *Tetrahedron Lett.* **1980**, *21*, 1901.
[113] Hosomi, A.; Miura, K. *Synlett* **2003**, *2*, 143.
[114] Saquib, M.; Sagar, R.; Shaw, A. K. *Carbohydr. Res.* **2006**, *341*, 1052 and references therein.

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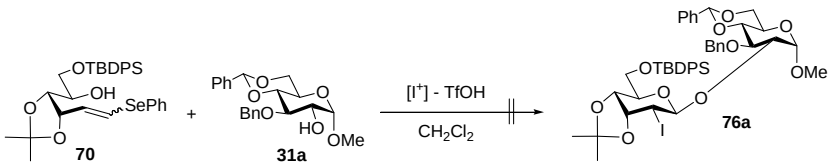

Scheme 4.10 Attempted "one pot" cyclization and glycosylation reaction with vinyl selenide **70**

4.2.3 Conclusions

This study describes a new method for the preparation of carbohydrate-based vinyl selenides under Wittig-type reaction conditions from protected furanoses. The proposed method allows synthesizing vinyl selenides in *arabino*, *ribo,* and 2-deoxy-*ribo* series. The modest yield observed with the vinyl selenides reported herein is probably related to the nature and reactivity of both carbohydrate lactols and selenium-based olefinating reagents under the conditions tested. The reaction with electrophiles proved to be challenging and no cyclization products were obtained. The preparation of vinyl selenides proved to be much more difficult than the related vinyl sulfides, which can be prepared in good yields using Wittig–Horner reaction.

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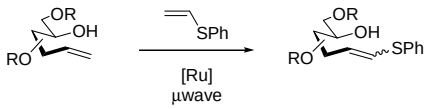
5 Synthesis of Alkenyl Sulfides via Cross Metathesis



Olefin cross metathesis between carbohydrate-derived hydroxy alkenes and electron-rich olefinic partners with commercially available ruthenium-based catalysts were studied. Microwave irradiation effectively accelerates the cross metathesis reaction of electron-rich olefins although some of the conversions remained low. Cross metathesis can only be achieved with hydroxy alkenes derived from 2-deoxysugars. In contrast, the hydroxy alkenes bearing an allylic alkoxy group neither isomerizes nor couples under similar conditions. A detailed study of the behaviour of carbohydrate-derived hydroxy alkenes in microwave-assisted cross metathesis reactions will be discussed.

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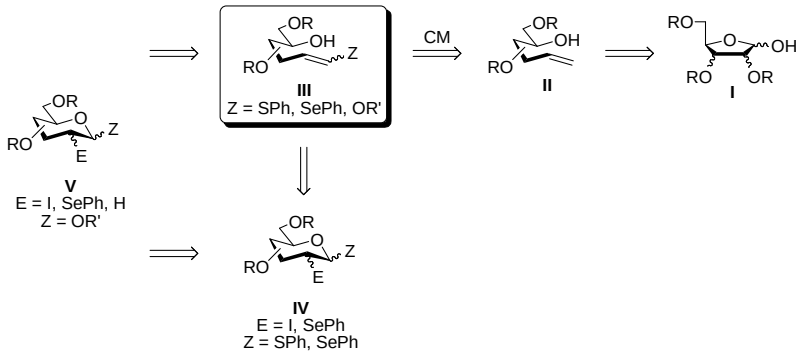
5.1 Introduction

In Chapters 3 and 4, we developed a general procedure for the stereoselective synthesis of 2-deoxy-2-E-hexopyranosyl thioglycosides (Z = SPh; E = I, SePh) **IV** from sulfanyl alkenes (Z = SPh) **III**, which provides a new method for accessing 2-deoxy- (Z = OR'; E = H) and 2-deoxy-E-oligosaccharides (Z = OR', E = I, SePh) **V**. In connection with these projects, we required a facile synthetic route that would provide rapid access to a range of diastereomerically enriched *E*-vinyl sulfides[115] (Z = SPh) **III** (Scheme 5.1). These vinyl sulfides can serve as useful intermediates for the synthesis of several carbohydrate mimics and derivatives.[116] Selenium derivatives (Z = SePh) **IV** can also be envisage as glycosyl donors; however, precursors (Z = SePh) **III** are difficult to obtain using Wittig-type reactions, see Chapter 4.2. In addition, electrophile-induced cyclization of vinyl ethers (Z = OR') **III** affords glycosides of the type (Z = OR', E = I, SePh) **V**, which can be easily converted into 2-deoxyglycosides[39] (Z = OR', E = H) **V**. Since heterosubstituted alkenes **III** are the common intermediates in these syntheses we proposed their preparation via cross metathesis (CM) from alkenes **II**, which can be obtained from corresponding protected pentoses **I**.



Scheme 5.1 Retrosynthetic strategy for the preparation of 2-deoxy- and 2,6-dideoxyglycosides

Olefin metathesis has recently attracted widespread attention as a versatile and powerful tool for the construction of complex organic molecules.[117–119] Many new

[115] For rencent syntheses of *E*-vinyl sulfides, see: (a) Sridhar, R.; Surendra, K.; Krishnaveni, N. S.; Srinivas, B.; Rao, K. R. *Synlett* **2006**, 3495. (b) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005.

[116] For selected applications, see: (a) Fürstner, A.; Baumgartner, J. *Tetrahedron* **1993**, *49*, 8541. (b) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 490. (c) Tolman, R. L.; Peterson, L. H. *Carbohydr. Res.* **1989**, *189*, 113.

[117] For general reviews on olefin metathesis, see: (a) Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748. (b) Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760. (c) Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3740. (d) Katz, T. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3010. (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew.*

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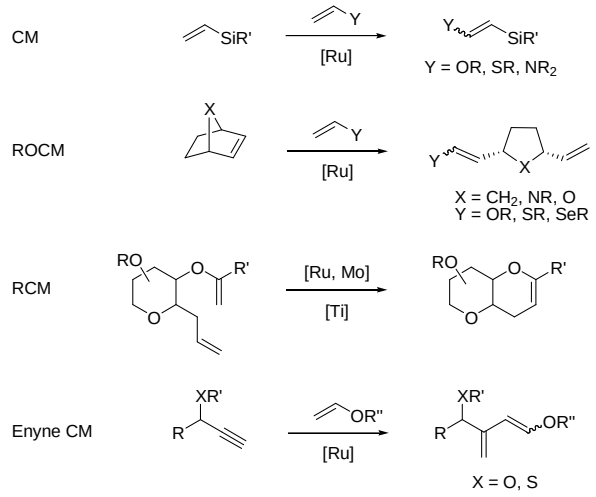
applications have become possible because of major advances in catalyst design.[120] These catalysts provide high yields under mild conditions and are remarkably tolerant of a range of functional groups.[121] In particular, cross metathesis (CM) reactions on substrates bearing various types of functionalities are fully documented in the literature and have been utilized in the construction of a diverse set of organic molecules.[122]

However, CM with electron-rich olefins remains an underrepresented area of olefin metathesis when compared to ring-opening cross metathesis[123] (ROCM), ring-closing metathesis[124] (RCM), and enyne metathesis[125] (Scheme 5.2).



Scheme 5.2 Some examples of products obtained via olefin metathesis with electron-rich olefins

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Chem. Int. Ed. **2005**, *44*, 4490. (f) Astruc, D. *New J. Chem.* **2005**, *29*, 42. (g) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem. Int. Ed.* **2005**, *44*, 6630.

[118] For reviews on RCM, see: (a) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919. (b) Michaut, A.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5740.

[119] For reviews on ring-opening metathesis polymerization (ROMP), see: (a) Frenzel, U.; Nuyken, O. *J. Polym. Sci. Part A: Polym. Chem.* **2002**, *40*, 2895. (b) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565.

[120] For selected contributions in this field, see: (a) Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45 and references therein. (b) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7591. (c) Occhipinti, G.; Bjørsvik, H.-R.; Jensen, V. R. *J. Am. Chem. Soc.* **2006**, *128*, 6952.

[121] (a) Vernall, A. J.; Abell, A. D. *Aldrichimica Acta* **2003**, *36*, 93. (b) Spagnol, G.; Heck, M.-P.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2002**, *4*, 1767.

[122] (a) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.

[123] (a) Liu, Z.; Rainier, J. D. *Org. Lett.* **2005**, *7*, 131. (b) Katayama, H.; Nagao, M.; Ozawa, F. *Organometallics* **2003**, *22*, 586. (c) Katayama, H.; Urushima, H.; Nishioka, T.; Wada, C.; Nagao, M.; Ozawa, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 4513.

[124] (a) Hekking, K. F. W.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6751. (b) Okada, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett* **2001**, *42*, 8023. (c) Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett* **2001**, *42*, 179. (d) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (e) See ref. 118.

[125] (a) Giessert, A. J.; Diver, S. T. *Chem. Rev.* **2004**, *104*, 1317. (b) Giessert, A. J.; Snyder, L; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793. (c) Giessert, A. J.; Brazis, N. J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3819.

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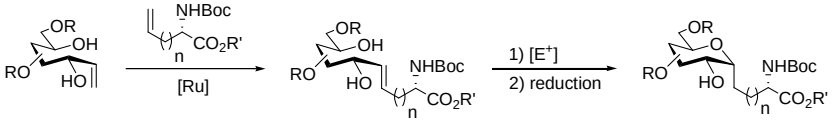
To the best of our knowledge, only a few examples of CM reactions involving electron-rich olefins[126,127] have been reported despite the aforementioned proposal by Grubbs suggesting that, although the Ru complexes are reactive in the metathesis of electron-rich olefins, the degenerate nature of these reactions, i.e., no methylidenes are formed as intermediates, currently prevents the synthesis of difunctional olefins by a metathesis mechanism.[128] This lack of reactivity has been attributed to the formation of relatively unreactive Fischer carbenes, which either rapidly decompose or fail to react further.[129]

In addition, in the field of carbohydrate chemistry,[130–133] although metathesis has been widely utilized, there are only a few examples for the use of CM despite the fact that carbohydrate-derived olefins appear in a wide array of naturally occurring molecules and also function as synthetic building blocks.[134] Recently, *C*-glycosyl amino acids have been obtained from hydroxyl alkenes through a sequence involving CM, electrophile-induced cyclization with Hg(II), and reduction[134b] (Scheme 5.3).



Scheme 5.3 Approach to generating *C*-glycosyl amino acids

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[126] For some studies dealing with the cross metathesis reaction versus silylative coupling of vinyl silanes and electron-rich olefins, such as vinyl ethers and sulfides, see: (a) Itami, Y.; Marciniec, B.; Kubicki M. *Chem. Eur. J.* **2004**, *10*, 1239. (b) Marciniec, B.; Chadyniak, D.; Krompiec, S. *J. Mol. Catal. A: Chem.* **2004**, *224*, 111. (c) Marciniec, B.; Kujawa, M; Pietraszuk, C. *New J. Chem.* **2000**, *24*, 671.

[127] Vinyl phosphine-borane complexes also undergo productive cross metathesis reaction, see: Dunne, K. S.; Lee, S. E.; Gouverneur, V. *J. Organomet. Chem.* **2006**, *691*, 5246.

[128] Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153.

[129] (a) Werner, H.; Grünwald, C.; Stüer, W.; Wolf, J. *Organometallics* **2003**, *22*, 1558. (b) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503.

[130] For a review dealing with the application of olefin metathesis in carbohydrate chemistry, see: Roy, R.; Das, S. K. *J. Chem. Soc., Chem. Commun.* **2000**, 519.

[131] For some approaches using RCM, see: (a) Miles, J. A. L.; Mitchell, L.; Percy, J. M.; Singh, K.; Uneyama, E. *J. Org. Chem.* **2007**, *72*, 1575. (b) Snyder, N. L.; Haines, H. M.; Peczuh, M. W. *Tetrahedron* **2006**, *62*, 9301 and references therein. (c) Amorim, L.; Díaz, D.; Calle-Jiménez, L. P.; Jiménez-Barbero, J.; Sinaÿ, P.; Blériot, Y. *Tetrahedron Lett.* **2006**, *47*, 8887. (d) Madsen, R. *Eur. J. Org. Chem.* **2006**, 399 and references therein. (e) Postema, M. H. D.; Piper, J. L.; Betts, R. L. *Synlett* **2005**, *9*, 1345 and references therein.

[132] For an example involving an intermolecular enyne metathesis of *C*-alkynyl glycosides with ethylene, see: Kaliappan, K. P.; Subrahmanyam, A. V. *Org. Lett.* **2007**, *9*, 1121.

[133] For a review on the preparation of carbohydrate-substituted polymers by ROMP, see: Kiessling, L. L.; Strong, L. E. *Top. Organomet. Chem.* **1998**, *1*, 199.

[134] For some approaches using CM, see: (a) Neimert-Andersson, K.; Somfai, P. *Eur. J. Org. Chem.* **2006**, 978. (b) Nolen, E. G.; Kurish, A. J.; Potter, J. M.; Donahue, L. A.; Orlando, M. D. *Org. Lett.* **2005**, *7*, 3383. (c) Postema, M. H. D.; Piper, J. L. *Tetrahedron Lett.* **2002**, *43*, 7095. (d) Plettenburg, O.; Mui, C.; Bodmer-Narkevitch, V.; Wong, C.-H. *Adv. Synth. Catal.* **2002**, *344*, 622. (e) McGarvey, G. J.; Benedum, T. E.; Schmidtmann, F. W. *Org. Lett.* **2002**, 4, 3591. (f) Roy, R.; Dominique, R.; Das, S. K. *J. Org. Chem.* **1999**, *64*, 5408. (g) Roy, R.; Das, S. K.; Dominique, R.; Trono, M. C.; Hernández-Mateo, F.; Santoyo-González, F. *Pure Appl. Chem.* **1999**, *71*, 565.

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Herein we present the results of our studies aimed toward the synthesis of carbohydrate-based vinyl ethers and chalcogenides[135] **III** through ruthenium-catalyzed CM reactions.

5.2 Results and discussion

Our initial synthetic studies focused on the transformation of different protected carbohydrate-derived hydroxy alkenes **II** into vinyl sulfides **III** using the CM approach as outlined in Scheme 5.1. The sequence begins with the preparation of a range of hydroxy alkenes **77**–**80** in good yields starting from different protected furanoses.[136] These four hydroxy alkenes led to vinyl sulfides of D-*manno*, -*arabino*, and -*xylo* configurations. Access to other types of carbohydrate olefin structures should be possible by simply changing the stereochemical disposition and/or the substituents on the carbohydrate scaffold.

To select the most suitable catalyst along with the best reaction conditions, preliminary experiments (Scheme 5.4) were carried out using an excess of vinyl acetate, ethyl vinyl ether, and phenyl vinyl sulfide (5 equiv) as electron-rich olefinic partners. Interestingly, no conversion of starting materials **77**–**79** was observed when using catalysts **81**–**84** (5–20 mol %). Carrying out the reaction with different temperatures, concentration, and/or solvent (CH_2Cl_2, THF, and toluene) always led to unsuccessful results. Indeed, no homodimerization took place. Despite the assumed formation of the known unreactive Fischer carbenes, an additional important aspect is the presence of an allylic alkoxy substituent that would inhibit the formation of CM products.[137] On the other hand, some results suggest that the presence of allylic hydroxyl groups greatly accelerate the rate of carbene-exchange reaction between the adjacent vinyl group and external ruthenium alkylidenes, therefore accelerating the metathesis process.[138] Thus, in order to investigate the reactivity of a carbohydrate-derived hydroxy alkene bearing an allylic hydroxyl group at the allylic position, substrate **80** was prepared (Scheme 5.4). However, when a mixture of **80** and vinyl sulfide (5 eq) was treated with catalyst **82** (20 mol %) in 3:1 CH_2Cl_2–MeOH[139] at room temperature, no CM reaction was observed. Any increase in the amount of catalyst

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[135] For a recent synthesis of carbohydrate-based vinyl sulfides, see: Chéry, F.; Pillard, C.; Tatibouët, A.; De Lucchi, O.; Rollin, P. *Tetrahedron* **2006**, *62*, 5141.

[136] (a) Hekking, K. F. W.; Moelands, M. A. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2006**, *71*, 6444. (b) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061. (c) Pirrung, F. O. H.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Schoemaker, H. E. *Synthesis* **1995**, *4*, 458.

[137] The inhibition of CM and RCM by allylic alkoxy substituents has been previously reported, see: (a) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayón, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913. (b) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263. (c) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623.

[138] Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.

[139] Das, S. K.; Dominique, R.; Smith, C.; Nahra, J.; Roy, R. *Carbohydr. Lett.* **1999**, *3*, 361.

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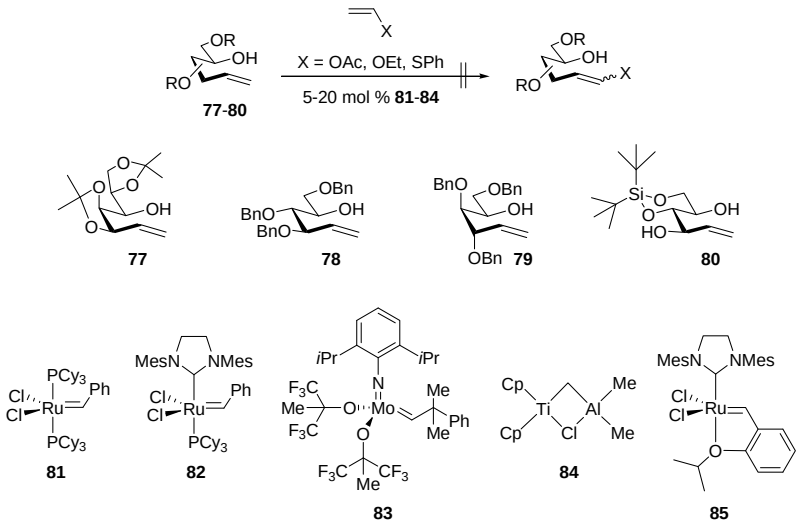
loaded (20, 40, and 60 mol %) had no visible effect on the product formation (71% of starting material was recovered in high purity).



Scheme 5.4 Preliminary CM experiments between carbohydrate-derived hydroxy alkenes **77**–**80** with vinyl ethers, esters, and sulfides

These preliminary results represent a severe limitation for the preparation of carbohydrate-based vinyl ethers and sulfides bearing an alkoxy substituent at C-2 by this straightforward methodology. To circumvent this limitation, we considered the preparation of hydroxy alkenes without an allylic substituent at C-2, starting from 2-deoxysugars to vary the reactivity for CM olefinations. Thus, we employed the CM methodology on the readily available 2-deoxyribose derivative **86**,[140] which upon CM reaction would yield the expected reaction products. However, when **86** was heated in CH_2Cl_2 at 40ºC with ethyl vinyl ether (5 eq) in the presence of catalyst **81** (5 mol %), the desired product was not observed; rather it led to the formation of derivative **87** in 63% yield and 2:3 *Z*/*E* ratio as a result of isomerization of the terminal olefin to the corresponding internal olefin (Scheme 5.5). The exclusive formation of **87** was also observed with catalyst **82** (5 mol %), with improved yield (66%) and selectivity (1:6 *Z*/*E* ratio).

Olefin isomerization with ruthenium catalysts is a well-known process that has been reported by several groups.[141] Although there have been a variety of explanations for undesirable olefin isomerization, several studies indicate that ruthenium hydride (Ru–H) species are responsible for this process. In particular, these Ru–H complexes can be

[140] Hossain, N.; Blaton, N.; Peeters, O.; Rozenski, J.; Herdewijn, P. A. *Tetrahedron* **1996**, *52*, 5563.
[141] (a) Schmidt, B. *J. Mol. Catal. A: Chem.* **2006**, *254*, 53. (b) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865 and references therein.

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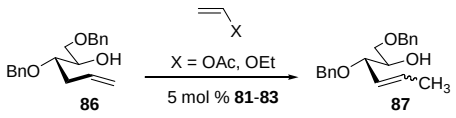
efficiently prepared from Fischer-type carbene intermediates (Ru=CHOEt), which are readily obtained by treatment of catalysts **81** and **82** with ethyl vinyl ether.[142]



Scheme 5.5 Metal-catalyzed isomerization of 2-deoxyribose derivative **86** under CM conditions

Some changes of solvent, temperature, and addition of additives (i.e., 2,6-dichloro-1,4-benzoquinone) reduced the ruthenium-catalyzed isomerization reaction, but no CM was observed instead. Furthermore, when vinyl acetate (5 eq) was subjected to similar conditions, neither isomerization nor CM of **86** occurred. On the other hand, the use of molybdenum catalyst **83** (0.5 M solution of **86** in CH_2Cl_2 at 40ºC) with either vinyl acetate or ethyl vinyl ether (5 eq) resulted in no reaction. Although isomerization was interesting, this undesired side reaction is detrimental for the efficiency of the CM. Therefore, we decided to focus our attention on developing conditions that would lead to the formation of the corresponding carbohydrate-based vinyl sulfides and selenides because precedence for this methodology has been previously demonstrated by Marciniec on the synthesis of *S*-substituted vinyl silanes (RSiCH=CHSR') with high preference for the *E*-isomer using ruthenium carbene catalysts.[126]

The results of the cross metathesis reactions between **86** and either phenyl vinyl sulfide or selenide, are sumarized in Table 5.1. Initial investigations began by reacting **86** with phenyl vinyl sulfide under thermal conditions using catalyst **82** (Table 5.1, entries 1–2). Initial reactions in refluxing CH_2Cl_2 failed to generate any CM product. Fortunately, even though the reaction did not reach complete conversion after 20 h in refluxing toluene, the coupled product was obtained in 34% yield and 1:1 *Z*/*E* ratio. These results suggest that temperature plays a more important role than solvent polarity for this reaction. An additional attempt to improve the conversion by using molybdenum catalyst **83** resulted in no reaction (Table 5.1, entry 3).

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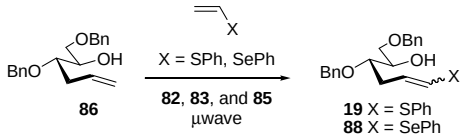
Table 5.1 Optimization of the microwave-assisted CM reaction conditions of **86** with electron-rich olefins



86

19 X = SPh
88 X = SePh

Entry[a]	Catalyst (mol %)	Solvent[b]	T (°C)	t (h)	Product distribution (%)[c]		*Z*/*E* ratio[c]
					86	**19**	
1[d]	**82** (20)	CH_2Cl_2	40	20	100	-	-
2[d]	**82** (20)	Toluene	110	20	63	37	1:1
3[d]	**83** (20)	Toluene	110	17	100	-	-
4[e]	**82** (20)	Toluene	110	4	93	7	1:1
5[f]	**82** (20)	Toluene	150	1	50	50[g]	1:1
6	**82** (20)	Toluene	120	2	80	20	1:1
7	**82** (10)	Toluene	120	1	90	10	1:1
8	**82** (20)[h]	Toluene	175	2	53[i]	37	1:1
9	**85** (20)	Toluene	150	1	54[j]	18	1:1
10	**85** (20)	DCB	200	1	60[i]	30	1:1
11[k]	**85** (20)	DCB	200	2	20[l]	5	1:2
12[m]	**82** (20)	Toluene	150	1	98	-	-
13[e,m]	**82** (20)	CH_2Cl_2	40	1	100	-	-

[a] Sealed vessel single-mode microwave irradiation (300 W) and cross metathesis partner (X = SPh, 5 eq) unless otherwise indicated. [b] All reactions were performed in 0.5 M solution of **86** in dry and degassed solvent. [c] Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [d] Thermal heating under open vessel reflux conditions. [e] 50 W. [f] 200 W. [g] Isolated yield. [h] Added in two portions. [i] 10% of **87** (2:5 *Z*/*E*) was also detected. [j] 28% of **87** (1:5 *Z*/*E*) was also detected. [k] 10 mol % of 2,6-dichloro-1,4-benzoquinone was added as additive. [l] Trace amounts of **87** (1:5 *Z*/*E*). [m] Cross metathesis partner (X = SePh, 5 eq).

With the above results in hand, we carried out additional experiments under microwave (MW) irradiation[143] to shorten the prolonged reaction time and elevated temperature necessary for these CM reactions, which usually leads to thermal degradation of the ruthenium catalysts.[144] Despite its widespread application in catalytic reactions, the use of microwave-assisted metathesis reactions has only recently been highlighted in the

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literature.[145] In particular, recent reports of dramatic improvements in reaction rates and yields in CM reactions provided by MW irradiation prompted us to explore this avenue.[146] Initial optimizations of microwave-assisted CM reactions with catalyst **82** were conducted with phenyl vinyl sulfide (Table 5.1, entries 4–8). A variety of different MW irradiation conditions (time, temperature, and MW power) were investigated.

The reaction time was dramatically reduced when MW irradiation was employed (from 20 to 1 h). Besides the solvent, the power of the MW irradiation apparently had a strong influence on the course of the reaction. For example, reduction of the output power from 200 W (Table 5.1, entry 5) to 50 W (Table 5.1, entry 4) led to a drop in yield to 7% from the initial 50%, despite increasing the reaction time. However, an increase of the irradiation power to 300 W did not lead to better than 20% conversion (Table 5.1, entry 6). These results suggest again that the reaction temperature (110–150ºC) reached in the reaction vessel is the real and more determinant factor in microwave-assisted CM reactions between **86** and phenyl vinyl sulfide. Because no decomposition of starting material was observed in any case, the formation of **19** seems to be only dependent on the catalytically active ruthenium species, which is also reflected in the correlation of yield with the relative amount of the employed ruthenium complex **82** (Table 5.1, entries 6 and 7). However, note that a reaction temperature higher than 150ºC did not always lead to a higher conversion. Thus, raising the temperature to 175ºC resulted in a decreased yield (37%), most likely due to catalyst decomposition as well as to the formation of 10% of isomerized product **87**. In addition, no significant improvement in the conversion was observed when catalyst **82** was added in two portions separated by a 1 h period[147] (Table 5.1, entry 8).

We next investigated the reactivity of the Hoveyda–Grubbs catalyst **85** in the microwave-assisted CM reaction between **86** and phenyl vinyl sulfide. The reaction in toluene gave a mixture of three compounds, with 18% conversion to the CM product **19**, 10% conversion to a rearranged by-product **87**, and 54% remaining as starting material (Table 5.1, entry 9). The formation of **87** without adding any additive suggest that **86** act as a viable hydride donor at high temperatures, and this can be rationalized by a π-allyl or a σ-

---

[145] (a) Pérez-Balado, C.; Nebbioso, A.; Rodríguez-Graña, P.; Minichiello, A.; Miceli, M.; Altucci, L.; de Lera, A. R. *J. Med. Chem.* **2007**, *50*, 2497. (b) Robinson, A. J.; Elaridi, J.; van Lierop, B.; Mujcinovic, S.; Jackson, W. R. *J. Pept. Sci.* **2007**, *13*, 280. (c) Chapman, R. N.; Arora, P. S. *Org. Lett.* **2006**, *8*, 5825. (d) Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 1869. (e) Appukkuttan, P.; Dehaen, W.; van der Eycken, E. *Org. Lett.* **2005**, *7*, 2723. (f) Comer, E.; Organ, M. G. *J. Am.Chem. Soc.* **2005**, *127*, 8160. (g) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2004**, *45*, 3089. (h) Salim S. S.; Bellingham, R. K.; Brown, R. C. D. *Eur. J. Org. Chem.* **2004**, 800. (i) Thanh, G. V.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 9091. (j) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136. (k) Yang, C.; Murray, W. V.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783. (l) Mayo, K. G.; Nearhoof, E. H.; Kiddle, J. J. *Org. Lett.* **2002**, 4, 1567.

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[147] The addition of catalyst **2** in two portions increase the yield of the CM between *α*-methylene lactones and a wide range of olefins, see: (a) Moïse, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 1695. (b) Raju, R.; Allen, L. J.; Le, T.; Taylor, C. D.; Howell, A. R. *Org. Lett.* **2007**, *9*, 1699.

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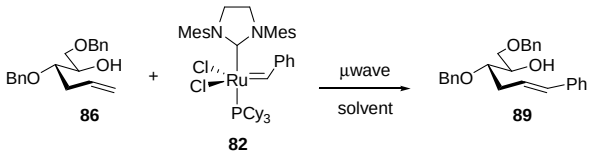
alkyl/π-allyl mechanism.[141] Interestingly, by changing the solvent from toluene to 1,2-dichlorobenzene (DCB) and increasing the temperature from 150 to 200ºC, the conversion increased from 18 to 30%. Furthermore, this change in the solvent properties resulted in a lower formation of **87** from 28 to 10% (Table 5.1, entry 10). These findings are in agreement with early reports in which solvent selection proved crucial in influencing the product distribution of RCM reactions.[148] Repeating the reaction using 2,6-dichloro-1,4-benzoquinone (10 mol %) as an additive to prevent olefin isomerization[149] led to only 5% conversion to the CM product in a 1:2 *Z*/*E* ratio with only trace by-product formation, although this may be a reflection of incompatibility of **86** and the additive (Table 5.1, entry 11). From these results, it is apparent that under standard conditions, even with typical additives, CM does not proceed efficiently with catalyst **85**.

Finally, we decided to investigate the use of phenyl vinyl selenide (5 eq) as an electron-rich olefinic partner with catalyst **82** (20 mol %). Disappointingly, it was no possible to obtain corresponding carbohydrate-based vinyl selenide **88** using this microwave-assisted CM protocol. When CM was performed either under the optimized conditions (toluene, 150ºC, 300 W) or at 40ºC, the only product observed was unreacted starting material (Table 5.1, entries 12 and 13).

At this point, we had acquired significant insight into the course observed in the microwave-assisted CM reactions with electron-rich olefins. During GC–EIMS and ^{1}H NMR analysis of the crude reactions, however, we had additionally found signals corresponding to *trans*-stilbene (PhCH=CHPh) and CM product **89** in those reactions with temperatures higher than 150ºC, whereas a 1:1 mixture of *cis*/*trans*-stilbene was detected when the reaction was performed at 40ºC (Table 5.1, entry 13). These products may come from the reaction of styrene ruthenium ligand (PhCH=CH_2) under CM conditions. In particular, the presence of **89** is somewhat surprising, although similar products have also been observed in previous studies when higher catalyst loadings are utilized[136a] (Scheme 5.6).



Scheme 5.6 Reaction of styrene ruthenium ligand with **86** under CM conditions

[148] Assuming a π-allyl or σ-alkyl/π-allyl mechanism, the solvent influence can be rationalized in terms of coordination ability, see: Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643–644*, 247.
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Collectively, the above observations suggest that in Ru-catalyzed CM reactions between electron-rich olefins and carbohydrate-derived hydroxy alkenes, formation of Fischer-type carbenes may serve to decrease productive CM drastically. The higher concentration of reactive olefin (vinyl sulfide and selenide) causes less interaction between the catalyst and the hydroxy alkene, preventing the formation of active vinylalkylidene species. As a consequence, the need for higher temperatures in order to achieve significant conversion usually leads either to thermal degradation of the ruthenium catalysts or to the formation of undesired side products.

5.3 Conclusions

In summary, a new method of synthesis of carbohydrate-based vinyl sulfides, which are versatile building blocks in organic synthesis, has been developed. CM of electron-rich olefins employing various commercially available ruthenium catalysts suffered from low conversion, long reaction times, and the need for high catalyst loading and reaction temperatures. However, rapid MW irradiation diminishes these processes by allowing the required high reaction temperature to be reached quickly and homogeneously, thereby providing enough energy for a successful metathesis reaction. Also, to our knowledge, this is the first reported carbohydrate-based vinyl sulfide formation utilizing microwave-assisted CM between a carbohydrate-derived hydroxy alkene and phenyl vinyl sulfide as electron-rich olefinic partner. However, CM can only be achieved with hydroxy alkenes derived from 2-deoxysugars.

Since high temperatures were necessary to run CM with electron-rich olefins, the thermal instability of the metathesis catalysts obviously represents the limiting factor of these reactions. Therefore, CM reactions of vinyl ethers, acetates, sulfides, and selenides require further investigations with new catalysts to enlarge the scope of metathesis reactions on electron-rich substrates. Overcoming this problem will provide an efficient method for preparing a wide range of potential substrates with different heteroatoms (O, S, N, Se, etc) at the α-position.

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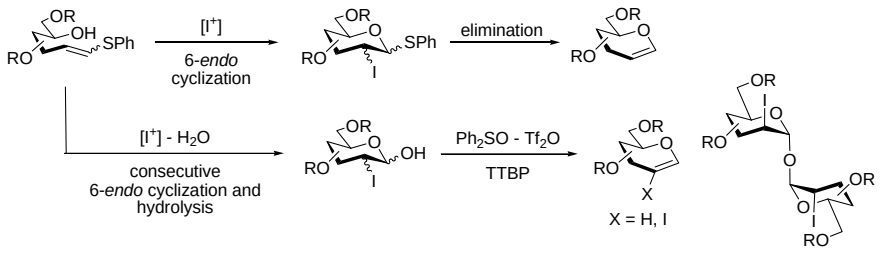
6 Synthesis of Pyranoid Glycals and 2-Iodoglycals



Pyranoid glycals of all configurations can be obtained from pentoses through an olefination, cyclization, and elimination sequence. The elimination can be carried out with excellent yields under radical conditions or by using common reductive reagents such as Zn–Cu, $TiCl_4$–$LiAlH_4$, or lithium naphthalenide. The proposed method is appropriate for the synthesis of glycals with D-*allo* or -*gulo* configurations, since the cyclization step is more efficient for these substrates.

A series of 2-deoxy-2-iodopyranoses were evaluated as precursors that provide access to pyranoid glycals and 2-iodoglycals from sulfanyl alkenes. This synthetic route involves consecutive cyclization and hydrolysis reactions followed by treatment of the resulting lactol under Gins' dehydrative glycosylation conditions. Although the observed product distribution (glycals, 2-iodoglycals, and 1,1'-disaccharides) revealed that this reaction is very sensitive to the configuration of the 2-deoxy-2-iodopyranose, 2-iodo pyranoid glycals can be almost exclusively obtained in good yields by employing 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group. A detailed study of the behaviour of 2-deoxy-2-iodopyranoses towards the dehydrative elimination reaction will be discussed.

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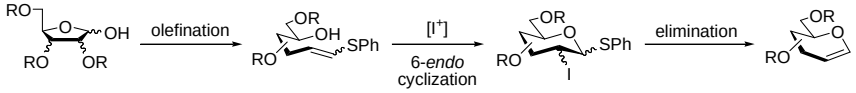
6.1 Synthesis of pyranoid glycals from 2-deoxy-2-iodo-1-thioglycosides

6.1.1 Introduction

In Chapter 3.1, we described a new route to 2-deoxyglycosides that makes use of a new kind of glycosyl donor, 2-deoxy-2-iodo-1-thioglycosides. As an extension of this work, we envisioned an easy and general route to glycals from 2-deoxy-2-iodo-1-thioglycosides that would allow the preparation of D-allal and D-gulal derivatives. The presence of PhS and I groups at positions C-1 and C-2 in these compounds makes such substrates appropriate for glycal preparation under anionic or radical conditions (Scheme 6.1).



Scheme 6.1 Proposed methodology for the stereselective synthesis of pyranoid glycals

Acces to glycals is important in the glycosylation field[11c,150] for the synthesis of *C*-glycosyl derivatives[151] and *C*-nucleosides,[152] nucleosides,[153] and other biologically important molecules.[154,155] The growing appreciation that glycoconjugates play an important role in cell recognition processes has spurred the synthesis of many glycoconjugates via the glycal method. In some cases, this effort has been conducted with the aim of developing synthetic vaccines. If new structural motifs are to be built up, it will be necessary to provide a variety of glycals of different configurations. In this respect, the only pyranoid glycals that are readily accessible currently are either D-glucal and D-galactal or L-rhamnal. Other D-glycals such as D-gulal and D-allal are not readily available.[156]

---

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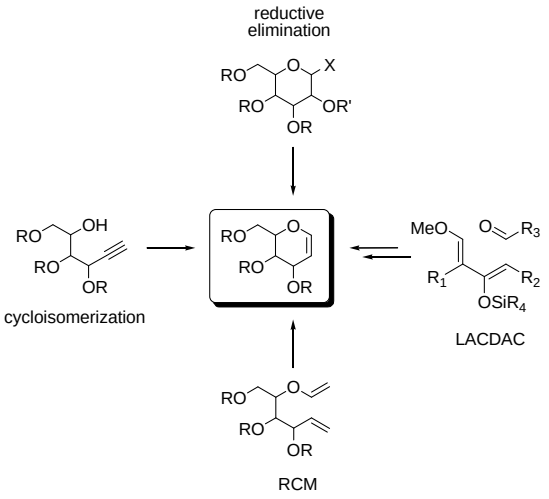
The Fischer–Zach method for forming glycals, which uses zinc dust in acetic acid in the reductive elimination of acylated glycosyl bromides, has been one of the most popular methods for synthesizing glycals.[157] This relatively harsh procedure is incompatible with many functionalities and protecting groups and cannot be applied to certain glycals. Therefore, over the years, this procedure has undergone countless modifications regarding the anomeric leaving group (Cl, SPh, S(O)Ph, SO_2Ph, SePh, TePh, etc.) and the reducing agent (modifications of the initial Zn reagents, Cr(EDTA), Al–Hg, lithium naphthalenide, potassium–graphite, SmI_2, etc.) used for glycal generation (Scheme 6.2).



Scheme 6.2 Representative methods leading to pyranoid glycals

When appropriate groups are present at positions C-1 and C-2, the reaction can be performed under radical conditions.[158] These methods are limited to readily available pyranoses. When the desired glycal is not reasonably accessible from carbohydrates other methods can be superior to the partial synthesis. In this way, stereoselective Lewis acid-catalyzed diene-aldehyde cyclocondesation (LACDAC) provided a rapid route to dihydropyrones, which in turn can be reduced to afford the corresponding 1,2-unsaturated

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carbohydrates.[11c] Glycals have also been prepared by ring-closing metathesis[131,159] and via tungsten and molybdenum-promoted alkynol *endo*-cycloisomerization[160] (Scheme 6.2).

6.1.2 Results and discussion

Thus, the reaction conditions for elimination were optimized by starting from derivative **22** (Table 6.1). Initially, we treated **22** with Zn–Cu couple following the Bredenkamp[161] modification of the Fischer–Zach method to obtain D-allal **90** in quantitative yield (Table 6.1, entry 1). The use of zinc in the presence of vitamin B_{12},[162] a very efficient reduction system, also afforded an excellent yield of **90** but in a shorter reaction time (Table 6.1, entry 2). The reaction of **22** with *n*-BuLi only gave a modest yield of glycal **90**; however, reaction with lithium naphthalenide[163] (LN) increased the yield up to 94% (Table 6.1, entries 3 and 4). When **22** was treated with $TiCl_4$–$LiAlH_4$,[164] glycal **90** was obtained in 85% yield (Table 6.1, entry 5).

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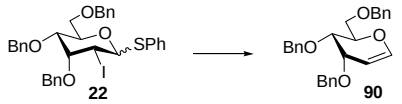
Table 6.1 Optimization of the synthesis of D-allal derivative **90** from 2-deoxy-2-iodo-1-thioglycoside **22**



Entry[a]	Elimination conditions (eq)	Yield (%)
1[b]	Zn-Cu, 20:1 THF-AcOH, NaOAc (1.4), 0ºC to rt, 6 h	100
2	Zn (12), B_{12} (0.01), NH_4Cl (12), 3:1 MeOH-CH_3CN, rt, 45 min	94
3	*n*-BuLi (1.1), THF, -78ºC, 1 h	41
4	LN (2), THF, -78ºC, 4.5 h	94
5	$TiCl_4$ (2), $LiAlH_4$ (4), THF, reflux, 2 h	85[c]
6	NaI (2), acetone, 0ºC to reflux, 40 h	d
7	SmI_2 (5), THF-HMPA, rt, 15 h	15[e]
8	Bu_3SnH (2.2), AIBN (0.13), toluene, reflux, 30 min	91
9	*t*-BuOK (1), THF, 0ºC to reflux, 10.5 h	f

[a] 2:5 α/β mixture was used unless otherwise indicated. [b] 1:9 α/β mixture was used. [c] Benzyl-deprotected glycals were detected by TLC. [d] No reaction. [e] 49% of the starting material was recovered. [f] 87% of the starting material was recovered.

The reaction of **22** with NaI left the starting material unaltered even after 40 h of heating (Table 6.1, entry 6). Phenyl 1-thioglycosides have been reported to be unreactive toward SmI_2 even in the presence of HMPA, although the corresponding sulfones give glycals under these conditions.[165] However, when we tested the reaction of **22** with SmI_2, very low yields of **90** were obtained and a large amount of starting material was always recovered (Table 6.1, entry 7). By contrast, when we performed the reaction under classical radical conditions,[166] the expected glycal was obtained in very good yield (Table 6.1, entry 8). Finally, when we treated **22** with potassium *tert*-butoxide in refluxing THF, only the starting material was recovered after 10 h.

Because tri-*O*-benzyl-D-allal **90** was more efficiently obtained from 2-deoxy-2-iodo-1-thio-D-allopyranosides by using a Zn–Cu couple as the reductant, we selected it to explore the synthesis of all the glycals shown in Tables 6.2 and 6.3.

[165] Pouilly, P.; Chénedé, A.; Mallet, J. M.; Sinaÿ, P. *Tetrahedron Lett.* **1992**, *33*, 8065.
[166] (a) Lin, T.-S.; Yang, J.-H.; Liu, M.-C.; Zhu, J. L. *Tetrahedron Lett.* **1990**, *31*, 3829. (b) Boothe, T. E.; Greene, J. L.; Shevlin, P. B. *J. Org. Chem.* **1980**, *45*, 794.

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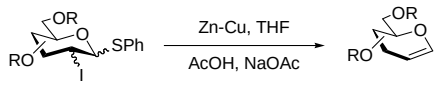
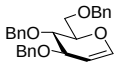
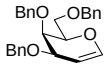
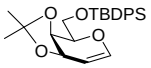
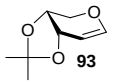
Thus, treatment of 2-iodo-1-thioglycosides **20**, **24**, and **26**–**30** with Zn–Cu couple gave glycals **50** and **91**–**96** in excellent yield. Significantly, glycals of all configurations, including D-allal **90** (Table 6.1) and D-gulal **95** (Table 6.3, entry 2) configurations, were accessible using this method. A variety of protecting groups, including benzyl, silyl ethers, and acetonides, were stable under the reaction conditions. Significantly, the procedure described here can be used to obtain pyranoid glycals derived from heptoses **94** (Table 6.3, entry 1), pentoses **93** (Table 6.2, entry 4), and 3-deoxy-hexoses **96** (Table 6.3, entry 3). The formation of the corresponding glycals was confirmed by ^{1}H, ^{13}C, COSY, and HSQC NMR analysis.

Table 6.2 Synthesis of pyranoid glycals **50** and **91**–**93** via reductive elimination



Entry[a]	Starting material[b]	T (ºC)	t (h)	Elimination product	Yield (%)
1[c]	**20**	0 to rt	3	 **91**	100
2	**24**	0 to 10	4.5	 **92**	89
3[c]	**26**	0	1	 **50**	86
4	**27**	0	1.5	 **93**	91

[a] Thioglycoside (1eq), Zn-Cu couple (661 mg), NaOAc (1.4 eq), 20:1 THF-AcOH. [b] α/β mixture was used unless otherwise indicated. [c] 1:0 α/β mixture was used.

Interestingly, bromo derivative **97**, obtained from the corresponding thioalkenyl derivative by NBS-induced electrophilic cyclization, gave rise to **98** when subjected to the above conditions (Table 6.3, entry 4), indicating that the 2-iodo sugars are the best substrates for this reaction. Furthermore, the isolation of this intermediate gave us some insight into the likely mechanism of the reaction. The classical Fischer–Zach method involves the reduction of the anomeric carbon–halogen bond followed by elimination of the OAc group present at C-2, whereas the result disclosed here suggests a similar reductive elimination process, and might be occurring through the initial reduction of the carbon–

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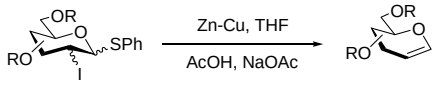
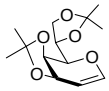
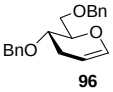
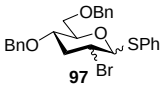
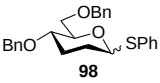
halogen bond at C-2 followed by the elimination of the phenylsulfanyl group at C-1 to give the corresponding glycal.

Table 6.3 Synthesis of pyranoid glycals **94**–**96** and 2-deoxy-1-thioglycoside **98** via reductive elimination. Data extracted from Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007



Entry[a]	Starting material[b]	T (ºC)	t (h)	Elimination product	Yield (%)
1[c]	**28**	0	1	 **94**	97
2	**29**	0	1	 **95**	92
3[d]	**30**	15	4	 **96**	71
4[d]	 **97**	0	1.5	 **98**	88

[a] Thioglycoside (1eq), Zn-Cu couple (661 mg), NaOAc (1.4 eq), 20:1 THF-AcOH. [b] α/β mixture was used unless otherwise indicated. [c] 1:0 α/β mixture was used. [d] 1:1 epimeric mixture at C-2 (decomposed on standing).

6.1.3 Conclusions

We have devised a new method for accessing pyranoid glycals of different configurations by a short route that uses readily available starting materials, and conventional transformations. Our method is particularly valuable for the synthesis of non-readily accessible glycals such as D-allal **90** and D-gulal **95** that are valuable products to prepare some oligosaccharide molecules with biologically interesting properties.

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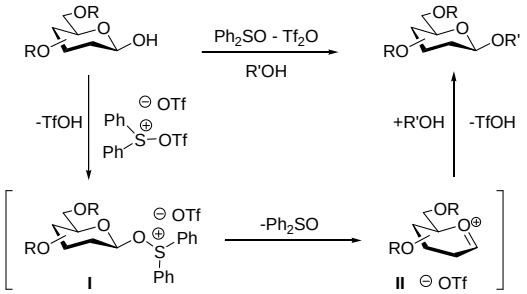
6. 2 Synthesis of pyranoid 2-iodoglycals versus glycals from 2-deoxy-2-iodopyranoses

6.2.1 Introduction

During the synthesis of 2-deoxy-2-iodoglycosides developed in Chapter 3, the key step was the cyclization of the alkenyl sulfanyl derivatives induced by iodine electrophiles. This reaction had to be done with a careful control of the time and temperature. Forcing the reaction conditions to ensure full conversion usually led to activation of the thioglycoside already formed. Thus, a variable amount of the corresponding 2-iodopyranoses was usually recovered after work-up in non-optimized experiments.

In order to exploit these valuable 2-iodopyranoses, we wanted to use them as glycosyl donors. Of course, the OH group itself is not a good leaving group and needs to be activated. In this context, Gin and co-workers[167] developed a glycosylation method which involves the activation of 1-hydroxysugars with diphenyl sulfoxide and triflic anhydride and provides the desired oligosaccharides in good yield. The glycosylation proceeds through oxosulfonium intermediate **I** that could evolve oxocarbenium ion **II** with concomitant regeneration of diphenyl sufoxide. The nucleophilic acceptor subsequently adds to the anomeric centre to yield the desired glycosylated product in an overall one pot procedure (Scheme 6.3). This methodology, in general, required pre-activation of the glycosyl donor before addition of the acceptor.[168]



Scheme 6.3 Dehydrative glycosylation protocol

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[167] (a) Boebel, T. A.; Gin, D. Y. *J. Org. Chem.* **2005**, *70*, 5818. (b) Boebel, T. A.; Gin, D. Y. *Angew. Chem. Int. Ed.* **2003**, *42*, 5874. (c) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 414. (d) Nguyen, H. M.; Chen, Y.; Duron, S.G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766. (e) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269. (f) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597.

[168] (a) Codeé, J. D. C.; Hossain, L. H.; Seeberger, P.H. *Org. Lett.* **2005**, *7*, 3251. (b) Codeé, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boeckel, C. A. A.; Van Boom, J. H.; Van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057. (c) Codeé, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boom, J. H.; Van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947.

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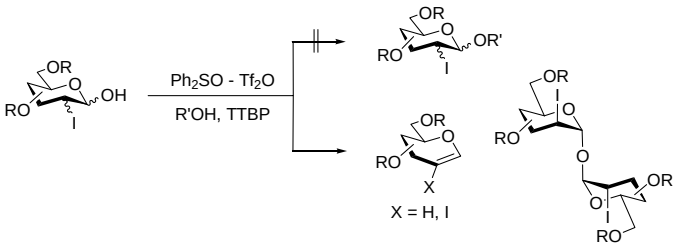
However, the application of the Gins' dehydrative glycosylation protocol to 2-deoxy-2-iodopyranoses did not yield the desired glycosylation product; rather it led to the formation of 2-iodoglycals, glycals, and 1,1'-disaccharides as major products (Scheme 6.4).

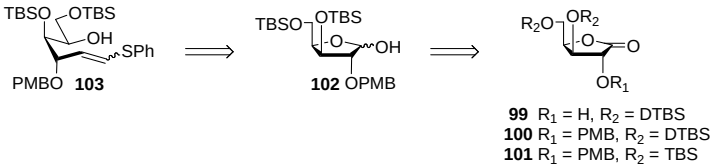


Scheme 6.4 Synthesis of 2-iodoglycals versus glycals from 2-deoxypyranoses under dehydrative glycosylation conditions

Consecuently, in order to evaluate the scope of this reaction, we applied this methodology to a wide range of 2-deoxy-2-iodopyranoses obtained via consecutive cyclization and hydrolysis reactions, see Chapter 3.2.

6.2.2 Results and discussion

The first step in the proposed synthesis of 2-iodoglycals[169] was the preparation of the corresponding 2-iodopyranoses via consecutive cyclization and hydrolysis reactions. For this purpose, intermediates **99**–**102** were easily prepared and used as starting materials for the synthesis of the corresponding vinyl sulfides, as described in the experimental section. The olefination reaction of xylose derivative **102** afforded expected product **103** in very low yield (<10%) and 1:5 *Z*/*E* ratio probably as a result of di-*tert*-butylsilylene (DTBS) protecting group decomposition under the conditions tested (Scheme 6.5).



Scheme 6.5 Building blocks involved in the preparation of vinyl sulfide **103**

[169] For syntheses of 2-halogenated glycals, see: (a) Boyd, E.; Jones, R. V. H.; Quayle, P.; Waring, A. J (neé Potts) *Tetrahedron Lett.* **2006**, *47*, 7983. (b) Boyd, E.; Hallett, M. R.; Jones, R. V. H.; Painter, J. E.; Quayle, P.; Waring, A. J (neé Potts) *Tetrahedron Lett.* **2006**, *47*, 8337. (c) Chemier, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949. (d) Fogh, A.; Lundt, I.; Pedersen, C.; Rasmussen, P.; *Acta Chem. Scand., Ser. B* **1977**, *31*,768. (e) Adamson, J.; Foster, A. B.; Westwood, J. H. *Carbohydr. Res.* **1971**, *18*, 85. (f) Adamson, J.; Foster, A.B. *Carbohydr. Res.* **1969**, *10*, 517.

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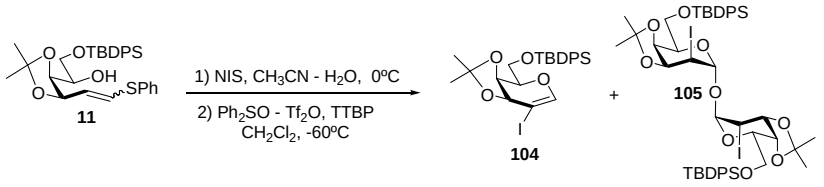
Having synthesized different protected vinyl sulfides such as **9**, **11**, **17**, **18**, and **103**, we next turned our attention to study their reactivity under dehydrative glycosylation conditions. Alkenyl sulfide **11** was first subjected to the consecutive cyclization and hydrolysis reactions (NIS, 10:1 CH_3CN–H_2O, 0ºC, 2 h) to afford the corresponding 2-deoxy-2-iodopyranose, which was then treated without further purification under dehydrative glycosylation conditions (Ph_2SO, Tf_2O, TTBP, 4Å MS, CH_2Cl_2, –60ºC, 1 h) to afford 2-iodoglycal **104** (16% over two steps) and 1,1'-disaccharide **105** (48% over two steps) (Scheme 6.6).

The ^{1}H NMR of **104** showed a singlet at 6.65 ppm assigned to H-1. Moreover, ^{13}C NMR chemical shifts of C-1 (δ 148.4 ppm) and C-2 (δ 75.4 ppm) confirmed the presence of a 2-iodo-substituted double bond. The stereochemical assignment of **105** was unequivocally established by ^{1}H, ^{13}C, COSY, and HSQC NMR analysis. In particular, the unusually simple ^{1}H NMR spectra confirmed the formation of a symmetric glycosylated product. As in the case of 3,4-*O*-isopropylidene-protected compound **36a** ($J_{1',2'}$ = 7.6 Hz, see Chapter 3), the typically *anti* values for the coupling constant ($J_{1,2,1',2'}$ = 7.2 Hz) accounts for a boat-like conformation.

This protocol was then extended to previously synthesized alkenyl sulfide **103** (Scheme 6.5). Surprisingly, despite the fact that the 2-deoxy-2-iodopyranose intermediate was detected by TLC (NIS, 10:1 CH_3CN–H_2O, 0ºC, 1 h), the in situ dehydrative elimination process with Ph_2SO, Tf_2O, and TTBP failed.



Scheme 6.6 Synthesis of 2-iodoglycal **104** and 1,1'-disaccharide **105** via consecutive cyclization and hydrolysis reactions followed by dehydrative elimination reaction

Under the conditions studied above, reaction products **90**, **95**, and **106**–**111** were obtained in good to excellent yields (Figure 6.1). Interestingly, we found that dehydrative elimination of 2-deoxy-2-iodopyranoses bearing 3,4-*O*-isopropylidene protecting groups proceeded smoothly and provided expected 2-iodoglycals **106** (73%) and **107** (97%) (Figure 6.1, A). However, when the same conditions were applied to other benzyl- or silyl-protected 2-deoxy-2-iodopyranoses, different product distributions were obtained depending on each configuration. Thus, D-gulal **95** (77%) and 6-deoxy-D-allal **109** (97%) were exclusively obtained, whereas a mixture of D-allal **90** (47%) and 2-iodoglycal **108** (22%) was always obtained, regardless of the reaction conditions used (temperature, equivalents of base, and dehydrative promoters) (Figure 6.1, B and C). Finally, this reaction

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gave interesting 1,1'-disaccharides of *manno* **110** (54%) and *talo* **111** (84%) configurations as a result of the self-condensation of the 2-deoxy-2-iodopyranose intermediates (Figure 6.1, D).

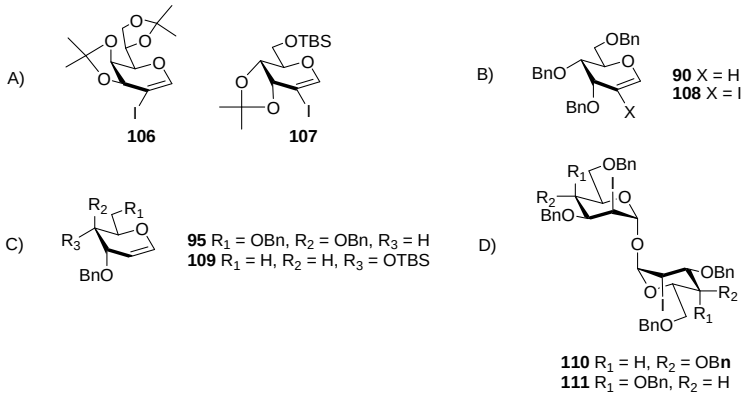
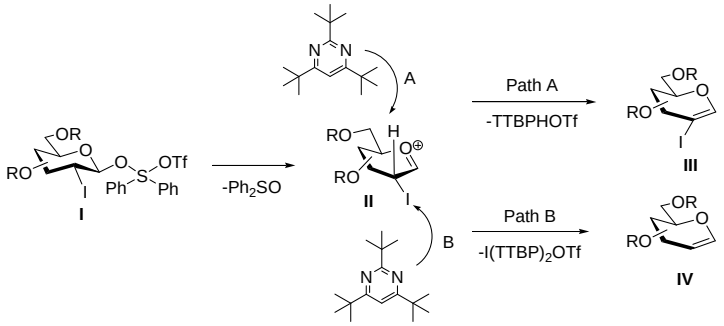


Figure 6.1 Products obtained during the dehydrative elimination reaction.
Data extracted from Rodríguez, M. A. *Ph.D. Thesis*, URV, Tarragona, 2007

The observed product distribution suggests a mechanism (Scheme 6.7) similar to that proposed during the studies of the cyclization of 3,4-*O*-isopropylidene-protected alkenyl sulfides induced by electrophilic selenium species. These reactions afforded either glycals or 2-phenylselenenyl glycals, depending on the reaction conditions, the configuration, and the nature of the hexenyl sulfide protecting groups, see Chapter 4.1.



Scheme 6.7 Plausible mechanism for the observed product distribution during the dehydrative elimination of 2-deoxy-2-iodopyranoses

The conversion of compound **I** into **III** represents an overall base-promoted hydroxyl elimination process,[170] and might be occurring through the initial 1-OH activation

[170] For a similar outcome in exo-glycals with IDCP as a base, see: Noort, D.; Veeneman, G. H.; Boons, G.-J. P. H.; Van der Marel, G. A.; Mulder, G. J. van Boom, J. H. *Synlett* **1990,** 205.

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followed by elimination of Ph_2SO and tri-(*tert*-butyl)-pyrimidinium triflate (TTBPHOTf) to render 2-iodoglycal **III**. Similarly, the production of **IV** might be explicable in terms of nitrogen assisted iodine elimination in **II** to afford the corresponding glycal[171] (Scheme 6.7). Another important issue for supporting this behaviour is the fact that only *N*-containing bases[172] such as phosphazene P_4-*t*-Bu, which are able to stabilize [I^+] species, afforded glycals, while *t*-BuOK failed and no reaction products were detected.

According to these results, the two chair-like oxocarbenium intermediates **Ia**–**d** and **IIa**–**d** (Scheme 6.8) play an important role in the chemoselectivity of the dehydrative elimination reaction. Moreover, iodine-axial intermediates **Ia**,**b** (*allo* and *gulo*) and **IIc**,**d** (*manno* and *talo*) are likely to be more stable than the corresponding iodine-equatorial conformers due to stabilizing hyperconjugative interactions between σ_{C-I} and π^*_{C-O} of the oxocarbenium.[76] Furthermore, in the E1 elimination reaction, the new double bond can only forms if the vacant *p* orbital of the carbocation and the breaking C–H or C–I bond have parallel alignment. Therefore, the group to be eliminated must be in the axial position.

Consistent with this, dehydrative elimination of 2-deoxy-2-iodopyranoses of *gulo* configuration proceeded through the more stable conformer **Ib** and elimination of the axial iodide provided glycal **95** in excellent yield. Similarly, axial iodine elimination of 2-deoxy-2-iodopyranoses of *allo* configuration in the more stable conformation **Ia** rendered exclusively glycal **109**. In this case, the equilibrium between conformers is considerably displaced towards **Ia** due to destabilizing gauche effects between TBS[17h,18,173] group (OR_3) and the C-6 substituent (OR_1) in conformer **IIa**. In the case of tri-*O*-benzyl-protected 2-deoxy-2-iodopyranoses of *allo* configuration, the elimination mainly proceeded through the more stable intermediate **Ia** to render glycal **90**. However, a minor amount of conformer **IIa** also reacted to give 2-iodoglycal **108**.

In the case of 1,1'-disaccharides **110** and **111**, the self-condensation (glycosylation) between the 2-deoxy-2-iodopyranoses and their activated forms (glycosyl donors) is faster than the elimination. Consistent with this, *manno* **110** and *talo* **111** derivatives were obtained as single *α*-anomers since elimination and glycosylation reactions compete in the more stable conformer **IIc,d**. Particularly, *allo* and *gulo* configurations only afforded glycals and 2-iodoglycals while *manno* and *talo* yielded disaccharides. This could be explained by the presence of steric interactions between the C-6 substituent (OR_1) and the incoming nucleophile in the most stable conformer **Ia,b** (*allo* and *gulo)* when compared with **IIc,d** (*manno* and *talo)*, where such destabilizing interactions do not exist (Scheme

[171] This behaviour of the nitrogen atom to stabilize/eliminate [I^+] has been previously observed in: (a) Mongin, F.; Rebstock, A.-S.; Trécourt, F.; Quéguiner, G.; Marsais, F. *J. Org. Chem.* **2004**, 69, 6766. (b) Arnés, X. *Ph.D Thesis*, URV, September 2003. (c) Roux, M.-C.; Paugam, R.; Rousseau, G. *J. Org. Chem.* **2001**, 66, 4304. (d) Barluenga, J.; Rodríguez, M.A.; Campos, P.J. *J. Org. Chem.* **1990**, 55, 3104.

[172] A similar behaviour was observed with DBU, see: Álvarez de Cienfuegos, L.; Mota, A. J.; Robles, R. *Org. Lett.* **2005**, *7*, 2161.

[173] Okada, Y.; Mukae, T.; Okajima, K.; Taira, M.; Fujita, M.; Yamada, H. *Org. Lett.* **2007**, *9*, 1576.

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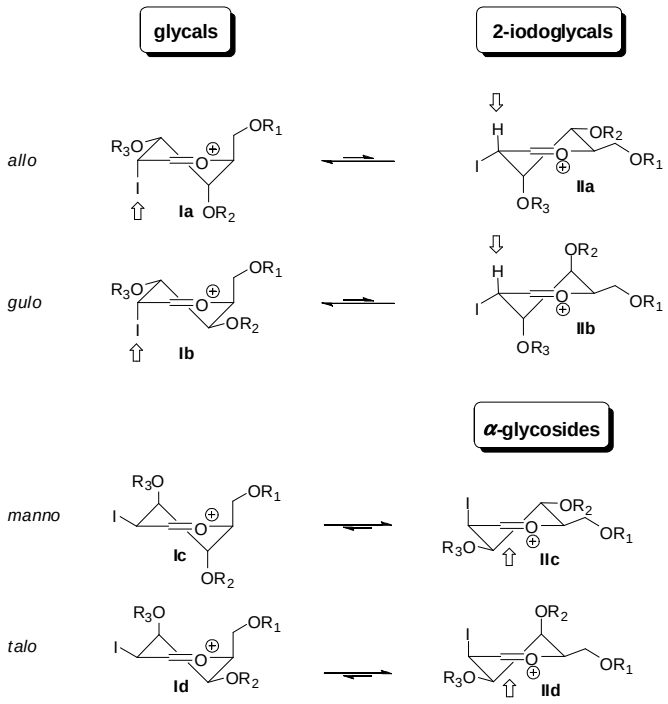
6.8). This outcome highlights the critical role of the configuration of 2-deoxy-2-iodopyranoses towards this new dehydrative elimination process.



Scheme 6.8 Stereochemical courses of dehydrative elimination reactions of 2-deoxy-2-iodopyranoses of *allo*, *gulo*, *manno*, and *talo* configurations

Finally, in order to rationalize the observed chemoselectiviy of the 2-deoxy-2-iodopyranoses bearing a 3,4-*O*-isopropylidene protecting group, we speculated that the reaction might operate by way of a constrained conformation[70] such as **III** and **IV**, upon which highly favoured proton elimination occur instead of the opposite iodine abstraction (Figure 6.2).

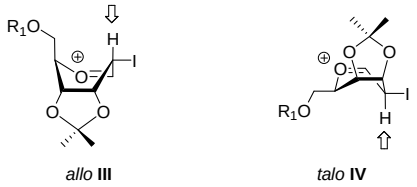


Figure 6.2 Constrained conformations of 3,4-*O*-isopropylidene-protected 2-deoxy-2-iodopyranoses of *allo* and *talo* configurations, which lead to 2-iodoglycals under dehydrative elimination conditions

6.2.3 Conclusions

A series of 2-deoxy-2-iodopyranoses were evaluated as precursors that provide access to pyranoid glycals and 2-iodoglycals from sulfanyl alkenes. This synthetic route involves consecutive cyclization and hydrolysis reactions followed by treatment of the resulting lactol under Gins' dehydrative glycosylation conditions. Despite the fact that this procedure has proved to be an efficient and general glycosylation method, its application to 2-deoxy-2-iodopyranoses did not afford the expected products. Although the observed product distribution (glycals, 2-iodoglycals, and 1,1'-disaccharides) revealed that this reaction is very sensitive to the configuration of the 2-deoxy-2-iodopyranose, 2-iodo pyranoid glycals can be almost exclusively obtained in good yields by employing 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group. Furthermore, a detailed analysis of the behaviour of 2-deoxy-2-iodopyranoses towards the dehydrative elimination reaction gave us some insight into the likely pathway of this process.

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7 Experimental Section

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General remarks: ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra were recorded using Varian Gemini 300 MHz and Varian Mercury 400 MHz spectrometers. In all the ^{1}H NMR spectra, TMS was used as an internal reference. In the ^{13}C NMR spectra, the residual solvent signal was used as an internal reference ($CDCl_3$, triplet at 77.23 ppm) unless otherwise stated. All the ^{31}P and ^{19}F NMR spectra were referenced to 85% H_3PO_4 and $CFCl_3$, respectively, as external standards. Elemental analyses (C, H, N, and S) were performed with a Carlo Erba EA 1108 Analyser in the Servei de Recursos Científics (URV). Optical rotations were recorded on a Perkin–Elmer 241 MC polarimeter in a 1 dm cell at 20ºC. Melting points were determined on a Tottoli Büchi 510 melting point apparatus and are uncorrected. FT–IR was obtained with a Bruker Equinox 55 spectrophotometer. GC–EIMS spectrometry was performed on a HP 5890 (Ti 75ºC (2) and 20ºC/min to 250ºC) gas chromatograph with an HP 5989A quadrupole detector (45–600, 70 eV) in the Servei de Recursos Científics (URV). Flash column chromatography was performed with silica gel 60 (E. Merck, 40–63 μm). Medium-pressure liquid chromatography (MPLC) was performed using silica gel 60 ACC (SDS, 6–35 μm). Radial chromatography was performed on 1, 2, or 4 mm plates of Kieselgel 60 PF_{254} silica gel (E. Merck), depending on the amount of product. Solvents were purified using standard procedures.[174] Thin layer chromatography (TLC) was performed on aluminium sheets coated with silica gel 60 F_{254} (E. Merck). Compounds were visualized by UV (254 nm) and also by spraying the TLC plates with either 6% H_2SO_4 in EtOH, or 2% $PdCl_2$ and 15% H_2SO_4 in water, followed by charring at 150ºC for a few minutes.

Materials: Iodonium dicollidine perchlorate (IDCP) was prepared following the method reported by Lemieux and Morgan.[11e] Diphenyl (phenylsulfanylmethyl)phosphine oxide was prepared following the method reported by Grayson and Warren.[44d] Zn–Cu couple was prepared following the method reported by Bredenkamp.[161a] Phenyl vinyl selenide was prepared following the method reported by Reich.[108a] Chloromethyl phenyl selenide **65** was prepared following the method reported by Huang and Duan.[97] Furanoses **4**–**7**, **15**, **16**, and acceptor **31a** were prepared as described in the literature.[175] Hydroxy alkenes **77**–**79** and **86** were prepared as described in the literature.[124,140] 3,5-*O*-(Di-*tert*-butylsilylene)-D-arabinono-1,4-lactone was prepared as described in the literature.[176] All other reagents were used as received from commercial suppliers without further purification.

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General procedure for the olefination of furanoses

Method A: To a solution of diphenyl (phenylsulfanylmethyl)phosphine oxide (4 mmol) in THF (26 mL) at –78ºC was added 1.6 M *n*-BuLi in hexane (4.4 mmol). The mixture was left to stir at low temperature for 30 min. A solution of the corresponding furanose (1 mmol) in THF (2 mL) was then added dropwise. The mixture was allowed to warm to room temperature overnight. A saturated aqueous solution of NH_4Cl was then added and the olefination product was extracted with ether. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic techniques.

Method B: To a dispersion of methyltriphenylphosphonium bromide (2 mmol) in dry THF (7 mL) at –78ºC was added the corresponding base (2.2 mmol) under an atmosphere of argon. PhSeCl (1 mmol) in dry THF (3.5 mL) was added and the mixture was left to stir at low temperature for 30 min. A solution of the corresponding furanose (1 mmol) in dry THF (2 mL) was then added dropwise. The mixture was allowed to warm to room temperature overnight. The crude was filtered through Celite® 545, diluted with petroleum ether, and washed with saturated aqueous NH_4Cl and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic techniques.

Method C: To a dispersion of the corresponding methyl phosphonium salt, phosphine oxide, or phosphonate (2 mmol) in dry THF (4 mL) at –78ºC was added the corresponding base (4.4 mmol) under an atmosphere of argon. PhSeBr (2 mmol) in dry THF (4 mL) was added and the mixture was left to stir at low temperature for 30 min. A solution of the corresponding furanose (1 mmol) in dry THF (2 mL) was then added dropwise. The mixture was allowed to warm to room temperature overnight. A saturated aqueous solution of NH_4Cl was then added and the mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic techniques.

Elimination from the *β*-hydroxyphosphine oxide intermediate: A mixture of the *β*-hydroxyphosphine oxide intermediate and diphenyl (phenylsulfanylmethyl)phosphine oxide, recovered from the general olefination of furanoses, method A, was dissolved in THF (15 mL/mg crude) and then 60% NaH (1 mg/mg crude) was added. The reaction mixture was stirred at room temperature and then quenched by adding saturated aqueous NH_4Cl. The mixture was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic techniques.

General procedure for iodonium-induced cyclization

Method A: To a solution of alkene (1 mmol) in dry CH_3CN (2 mL) was added $NaHCO_3$ (1.5 mmol). The mixture was cooled to –30°C and left to stir at this temperature for 5 min.

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NIS (1.5 mmol) was then added and the reaction mixture stirred for several hours. The reaction temperature was left to increase from –30°C to room temperature depending on the reactivity of the substrate. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $Na_2S_2O_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatographic techniques.

Method B: IDCP (2.2 mmol) was added to a solution of alkene (1 mmol) in dry solvent at –78ºC. The reaction mixture was stirred for several hours until the reaction was completed. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $Na_2S_2O_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatographic techniques.

Method C: To a suspension of 30% KH (1.3 mmol) in dry Et_2O (6 mL) at 0ºC was added dropwise a solution of the alkene (1 mmol) in dry Et_2O (12 mL). The mixture was left to stir at this temperature for 30 min, until solution turns yellow, and was then cooled to –78ºC. I_2 (3 mmol) in dry Et_2O (2 mL) was then added at the same temperature. The reaction temperature was left to increase from –78°C to room temperature depending on the reactivity of the substrate. The reaction was diluted with Et_2O and washed with saturated aqueous $Na_2S_2O_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic techniques.

General procedure for selenonium-induced cyclization: A mixture of *N*-(phenylselenenyl)phthalimide (2 mmol) with or without promoter (2 mmol) was added in one portion to a stirred solution of alkene (1 mmol) in dry CH_2Cl_2 (5 mL) at –78ºC. The reaction temperature was left to increase from –78°C to room temperature depending on the reactivity of the substrate. After several hours of continuous stirring the reaction mixture was poured into 10% aqueous NaOH solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatographic techniques.

General procedure for glycosylation: A solution of the glycosyl donor (1 mmol) and the glycosyl acceptor (2 mmol) in dry solvent (23 mL) was stirred with 4Å molecular sieves (1 g) at low temperature for 2 h. NIS (2.2 mmol) and TfOH (0.2 mmol) were added at the same temperature. The reaction temperature was left to increase depending on the reactivity of the substrate. The reaction mixture was then diluted with CH_2Cl_2 and washed with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic techniques.

General procedure for consecutive "one pot" cyclization and glycosylation: A mixture of alkene (1 mmol), glycosyl acceptor (2 mmol), and 4Å molecular sieves (714 mg) in dry

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CH_2Cl_2 (29 mL) was stirred at room temperature for 1 h. The reaction was cooled and NIS (3 mmol) was then added. The reaction temperature was left to increase from –78°C to room temperature depending on the reactivity of the substrate until the cyclization was completed. The reaction mixture was cooled and TfOH (0.2 mmol) was then added. The reaction was left to stir at low temperature until the reaction was completed. The mixture was then diluted with CH_2Cl_2 and washed with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic techniques.

General procedure for reductive elimination: 2-deoxy-2-iodopyranoside (1 mmol) and NaOAc (1.4 mmol) were dissolved in a mixture of THF (1.6 mL) and acetic acid (80 μL) at 0ºC. Zn–Cu couple (661 mg) was then added and the reaction temperature was left to increase depending on the reactivity of the substrate. The mixture was then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic techniques.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-phenylsulfanyl-D-*arabino*-hex-1-enitol (2): The title compound was prepared following the general procedure for the olefination of furanoses, method A, starting from 2,3,5-tri-*O*-benzyl-*β*-D-arabinofuranose **1** (500 mg, 1.19 mmol) in dry THF (1 mL), diphenyl (phenylsulfanylmethyl)phosphine oxide (1.54 g, 4.76 mmol) in dry THF (32 mL), and 1.6 M *n*-BuLi in hexane (3.3 mL, 5.23 mmol). After 24 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by column chromatography (1:3 EtOAc/hexane) to afford **2** (626 mg, 100%) as an inseparable 2:3 *Z*/*E* mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.16. FT–IR (neat) ν in cm^{-1}: 3478, 3062, 3030, 2865, 1605, 1583, 1454, 1090, 738, 697. Anal. Calcd for $C_{33}H_{34}O_4S$: 75.25 C, 6.51 H, 6.09 S. Found: 74.97 C, 6.48 H, 6.07 S. Data for **2***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.36–7.21 (m, 20H, Ar), 6.43 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1), 5.84 (dd, 1H, $J_{1,2}$ = 15.2 Hz, $J_{2,3}$ = 8 Hz, H-2), 4.65 (d, 1H, J_{AB} =12 Hz, CH_2Ph), 4.58 (d, 1H, J_{AB} =11.6 Hz, CH_2Ph), 4.53 (d, 1H, J_{AB} =11.6 Hz, CH_2Ph), 4.50 (s, 2H, CH_2Ph), 4.40 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.17 (dd, 1H, $J_{2,3}$ = 8 Hz, $J_{3,4}$ = 4 Hz, H-3), 4.02 (m, 1H, H-5), 3.59 (m, 3H, H-4,6a,b), 2.71 (d, 1H, $J_{5,OH}$ = 4.8 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3–127.1 (Ar, C-1,2), 80.8 (C-4), 79.4 (C-3), 74.3, 73.6 ($2CH_2Ph$), 71.0 (C-6, CH_2Ph), 70.4 (C-5). Data for **2***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.35–7.25 (m, 20H, Ar), 6.52 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 5.96 (dd, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.6 Hz, H-2), 4.71 (m, 1H, H-3), 4.68 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.67 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.57 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.52 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.48 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.42 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 3.88 (m,

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1H, H-5), 3.69 (dd, 1H, $J_{4,5}$ = 7.2 Hz, $J_{3,4}$ = 4Hz, H-4), 3.61 (m, 2H, H-6a,b), 2.92 (d, 1H, $J_{5,OH}$ = 5.2 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3–135.7 (C, Ar), 129.6–127.1 (CH, Ar, C-1,2), 80.4 (C-4), 75.9 (C-3), 74.29, 73.6 ($2CH_2Ph$), 71.4 (C-6), 71.3 (CH_2Ph), 70.8 (C-5).

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (9): The title compound was prepared following the general procedure for the olefination of furanoses, method A, starting from **4** (5.5 g, 13 mmol) in dry THF (26 mL), diphenyl (phenylsulfanylmethyl)phosphine oxide (16.9 g, 52.2 mmol) in dry THF (26 mL), and 1.6 M *n*-BuLi in hexane (35.9 mL, 57.4 mmol). After 48 h stirring under refluxing conditions the reaction mixture was quenched and the crude was purified by column chromatography (1:3 EtOAc/hexane) to afford **9** (4.96 g, 72%) as an inseparable 1:4 *Z*/*E* mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.27. FT–IR (neat) ν in cm^{-1}: 3463, 3062, 3030, 2865, 1951, 1605, 1583, 1092, 738, 697. Anal. Calcd for $C_{33}H_{34}O_4S$: 75.25 C, 6.51 H, 6.09 S. Found: 75.27 C, 6.50 H, 6.12 S. Data for **9***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.35–7.22 (m, 20H, Ar), 6.50 (d, 1H, $J_{1,2}$ = 16 Hz, H-1), 5.91 (dd, 1H, $J_{1,2}$ = 16 Hz, $J_{2,3}$ = 8 Hz, H-2), 4.77 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.67 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.56 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.51 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.48 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.40 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.23 (dd, 1H, $J_{2,3}$ = 8.8Hz, $J_{3,4}$ = 4.4 Hz, H-3), 4.84–3.82 (m, 1H, H-5), 3.64–3.58 (m, 2H, H-6a,b), 3.70 (dd, 1H, $J_{4,5}$ = 7.6 Hz, $J_{3,4}$ = 4 Hz, H-4), 2.72 (d, 1H, $J_{5,OH}$ = 4.4 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6–134.8 (C, Ar), 130.2–126.9 (CH, Ar), 129.0 (C-1), 128.7 (C-2), 81.5 (C-3), 81.0 (C-4), 74.4, 73.6 ($2CH_2Ph$), 71.1 (C-6), 71.0 (C-5), 70.7 (CH_2Ph). Data for **9***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.35–7.22 (m, 20H, Ar), 6.58 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 5.95 (dd, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.6 Hz, H-2), 4.84–4.45 (m, 6H, $3CH_2Ph$), 3.87–3.85 (m, 1H, H-5), 3.77 (dd, 1H, $J_{4,5}$ = 8.4 Hz, $J_{3,4}$ = 4 Hz, H-4), 3.68–3.65 (m, 1H, H_3), 3.64–3.58 (m, 2H, H-6a,b), 2.78 (d, 1H, $J_{5,OH}$ = 4.8 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6–134.8 (C, Ar), 130.2–126.9 (CH, Ar, C-1,2), 81.2 (C-3), 77.4 (C-4), 74.3, 73.5 ($2CH_2Ph$), 71.2, 71.0, 70.7 (C-5, 6, CH_2Ph).

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-phenylsulfanyl-D-*lyxo*-hex-1-enitol (10): The title compound was prepared following the general procedure for the olefination of furanoses, method A, starting from **5** (386 mg, 0.92 mmol) in dry THF (1 mL), diphenyl (phenylsulfanylmethyl)phosphine oxide (1.19 g, 3.67 mmol) in dry THF (25 mL), and 1.6 M *n*-BuLi in hexane (2.5 mL, 4 mmol). After 1.5 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by radial chromatography (from hexane to 1:1 EtOAc/hexane) to afford **10** (252 mg, 52%) as an inseparable 1:17 *Z*/*E* mixture as a yellowish syrup and a mixture of diphenyl (phenylsulfanylmethyl)phosphine

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oxide and the corresponding *β*-hydroxyphosphine oxide intermediate.[177] Following the general procedure described above, the mixture of phosphine oxides was eliminated by reaction with 60% NaH (100 mg, 2.5 mmol) in dry THF (15 mL). After 1 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford an additional fraction of **10** (47 mg, 10%) as a 7:1 *Z*/*E* mixture. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.22. FT–IR (neat) ν in cm^{-1}: 3474, 3062, 3030, 2864, 1951, 1876, 1811, 1605, 1583, 1091, 739, 698. Anal. Calcd for $C_{33}H_{34}O_4S$: 75.25 C, 6.51 H, 6.09 S. Found: 75.23 C, 6.52 H, 6.04 S. Data for **10***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.33–7.20 (m, 20H, Ar), 6.46 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1), 5.78 (dd, 1H, $J_{1,2}$ = 15.2 Hz, $J_{2,3}$ = 8 Hz, H-2), 4.63 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.62 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.49 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.45 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.44 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.38 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.13 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 7 Hz, H-3), 4.06 (m, 1H, H-5), 3.57 (dd, 1H, $J_{3,4}$ = 7 Hz, $J_{3,5}$ = 3 Hz, H-4), 3.50 (m, 2H, H-6a,b), 2.71 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.1–134.4 (C, Ar), 130.3–127.2 (CH, Ar), 128.8 (C-1), 128.5 (C-2), 80.1 (C-4), 79.8 (C-3), 74.3, 73.4 ($2CH_2Ph$), 71.4 (C-6), 70.8 (CH_2Ph), 69.7 (C-5). Data for **10***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.36–7.23 (m, 20H, Ar), 6.56 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 5.89 (dd, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.2 Hz, H-2), 4.76 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.67 (m, 1H, H-3), 4.67 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.51 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.50 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.46 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.45 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.05 (m, 1H, H-5), 3.71 (dd, 1H, $J_{4,5}$ = 5 Hz, $J_{3,4}$ = 3.4 Hz, H-4), 3.54 (m, 2H, H-6a,b), 2.98 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3–135.7 (C, Ar), 129.6–127.0 (CH, Ar, C-1,2), 79.7 (C-4), 76.4 (C-3), 74.0, 73.5 ($2CH_2Ph$), 71.2 (C-6), 71.1 (CH_2Ph), 70.3 (C-5).

(*Z*/*E*)-6-*O*-(*tert*-Butyldiphenylsilyl)-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylsulfanyl-D-*lyxo*-hex-1-enitol (11): The title compound was prepared following the general procedure for the olefination of furanoses, method A, starting from **6** (723.9 mg, 1.69 mmol) in dry THF (1.6 mL), diphenyl (phenysulfanylmethyl)phosphine oxide (2.19 g, 6.76 mmol) in dry THF (45 mL), and 1.6 M *n*-BuLi in hexane (4.6 mL, 7.43 mmol). After 14 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by column chromatography (from hexane to 1:1 EtOAc/hexane) to afford **11** (192 mg, 21%) as an inseparable 1:8 *Z*/*E* mixture as a yellowish syrup and a mixture of diphenyl

[177] Data for **10**-BHPO intermediate: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.59–6.83 (m, 30H, Ar), 5.04 (bs, 1H, OH), 4.90 (d, 1H, J_{AB} = 10.6 Hz, CH_2Ph), 4.71 (d, 1H, J_{AB} = 11 Hz, CH_2Ph), 4.80 (m, 1H, H-2), 4.54 (d, 1H, J_{AB} = 11 Hz, CH_2Ph), 4.42 (s, 2H, CH_2Ph), 4.41 (m, 1H, H-1), 4.24–4.16 (m, 3H, H-3,4,CH_2Ph), 4.11–4.06 (m, 1H, H-5), 3.89 (bs, 1H, OH), 3.61 (m, 2H, H-6a,b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.0–135.5 (C, Ar), 132.1–126.5 (CH, Ar), 80.7 (C-4), 78.0 (C-3), 73.9, 73.1, 72.6 ($3CH_2Ph$), 71.0 (C-6), 70.6 (C-5), 69.4 (C-2), 49.5 (d, $J_{C,P}$ = 71.3 Hz, C-1). ^{31}P NMR ($CDCl_3$, 162 MHz) δ in ppm: 37.6 (s, P=O).

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(phenylsulfanylmethyl)phosphine oxide and the corresponding *β*-hydroxyphosphine oxide intermediate. Following the general procedure described above, the mixture of phosphine oxides was eliminated by reaction with 60% NaH (200 mg, 5 mmol) in dry THF (30 mL). After 5 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford an additional fraction of **11** (81 mg, 10%) as a 1:1 *Z*/*E* mixture. Data for **11***E* (obtained from a pure analytical sample): R_f (1:3 EtOAc/hexane): 0.48. $[\alpha]^{20}_D$: +40.5 (*c* 1, CH_2Cl_2). FT–IR (neat) *v* in cm^{-1}: 3475, 3071, 2932, 2858, 1585, 1473, 1428, 1112, 740, 703. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* in ppm: 7.72–6.32 (m, 15H, Ar), 6.34 (d, 1H, $J_{1,2}$ = 15.2 Hz, H-1), 5.86 (dd, 1H, $J_{1,2}$ = 15.2 Hz, $J_{2,3}$ = 8.8 Hz, H-2), 4.55 (dd, 1H, $J_{2,3}$ = 8 Hz, $J_{3,4}$ = 6.4 Hz, H-3), 4.29 (dd, 1H, $J_{3,4}$ = 6.4 Hz, $J_{4,5}$ = 3.6 Hz, H-4), 3.72–3.64 (m, 3H, H-5,6a,b), 2.43 (d, 1H, $J_{5,OH}$ = 6 Hz, OH), 1.48, 1.37 (s, 6H, $2CH_3$), 1.07 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) *δ* in ppm: 135.7, 135.0, 134.2, 133.2, 133.1, 130.7, 129.9, 129.3, 128.0, 127.9, 127.4 (C, CH, Ar), 130.0 (C-1), 126.6 (C-2), 108.8 (C_{ketal}), 78.4 (C-3), 77.4 (C-4), 72.6 (C-6), 70.1 (C-5), 27.0 (CH_3, *t*-Bu), 26.7, 25.1 ($2CH_3$), 19.4 (C, *t*-Bu). Anal. Calcd for $C_{33}H_{34}O_4SSi$: 69.62 C, 7.16 H, 6.00 S. Found: 69.66 C, 7.14 H, 6.04 S. Data for **9***Z* (obtained from the mixture): ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* in ppm: 7.72–6.32 (m, 15H, Ar), 6.39 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 5.99 (dd, 1H, $J_{1,2}$ = 9.6 Hz, $J_{2,3}$ = 8 Hz, H-2), 5.15 (appt, 1H, *J* = 8 Hz, H-3), 4.40 (dd, 1H, $J_{3,4}$ = 6 Hz, $J_{4,5}$ = 3 Hz, H-4), 3.72–3.64 (m, 3H, H-5,6a,b), 2.62 (bs, 1H, OH), 1.52, 1.42 (s, 6H, $2CH_3$), 1.1 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) *δ* in ppm: 135.7–127.4 (C, CH, Ar), 130.0 (C-1), 126.6 (C-2), 108.8 (C_{ketal}), 78.4 (C-3), 77.4 (C-4), 72.6 (C-6), 70.1 (C-5), 27.0 (CH_3, *t*-Bu), 26.7, 25.1 ($2CH_3$), 19.4 (C, *t*-Bu).

(*Z*/*E*)-3,4-*O*-Isopropylidene-1-phenylsulfanyl-D-*erythro*-pent-1-enitol (12): The title compound was prepared following the general procedure for the olefination of furanoses, method A, starting from **7** (915.4 mg, 5.7 mmol) in dry THF (5 mL), diphenyl (phenylsulfanylmethyl)phosphine oxide (7.4 g, 22.9 mmol) in dry THF (150 mL), and 1.6 M *n*-BuLi in hexane (15.7 mL, 25.1 mmol). After 16 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by column chromatography (from hexane to 1:1 EtOAc/hexane) to afford **12** (520 mg, 35%) as an inseparable 1:3 *Z*/*E* mixture as a yellowish syrup and a mixture of diphenyl (phenylsulfanylmethyl)phosphine oxide and the corresponding *β*-hydroxyphosphine oxide intermediate. Following the general procedure described above, the mixture of phosphine oxides was eliminated by reaction with 60% NaH (600 mg, 15 mmol) in dry THF (60 mL). After 12 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by column chromatography (from hexane to 1:1 EtOAc/hexane) to afford an additional fraction of **12** (500 mg, 33%) as a 12:1 *Z*/*E* mixture. Data obtained from the mixture. R_f (1:1 EtOAc/

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hexane): 0.38. FT–IR (neat) ν in cm^{-1}: 3428, 3057, 2987, 2865, 2934, 1706, 1583, 1045, 739, 691. Anal. Calcd for $C_{14}H_{18}O_3S$: 63.13 C, 6.81 H, 12.04 S. Found: 63.12 C, 6.81 H, 12.05 S. Data for **12***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.37–7.21 (m, 5H, Ar), 6.52 (d, 1H, $J_{1,2}$ = 15 Hz, H-1), 5.71 (dd, 1H, $J_{1,2}$ = 15 Hz, $J_{2,3}$ = 8 Hz, H-2), 4.69 (appt, 1H, J = 6.4 Hz, H-3), 4.25 (m, 1H, H-4), 3.55 (m, 2H, H-5a,b), 1.48, 1.37 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.9 (C, Ar), 130.5–126.8 (CH, Ar), 128.9 (C-1), 125.5 (C-2), 108.9 (C_{ketal}), 78.5 (C-4), 77.6 (C-3), 61.9 (C-5), 27.8, 25.2 ($2CH_3$). Data for **12***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.41–7.22 (m, 5H, Ar), 6.45 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 5.86 (appt, 1H, J = 9.2 Hz, H-2), 5.15 (d, 1H, $J_{2,3}$ = $J_{3,4}$ = 7.6 Hz, H-3), 4.35 (m, 1H, H-4), 3.60 (m, 2H, H-5a,b), 1.53, 1.42 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.0 (C, Ar), 132.2–124.5 (CH, Ar), 128.4 (C-1), 126.9 (C-2), 109.1 (C_{ketal}), 78.3 (C-4), 74.3 (C-3), 62.1 (C-5), 27.8, 25.2 ($2CH_3$).

(*Z*/*E*)-6-*O*-(*tert*-Butyldiphenylsilyl)-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (13): The title compound was prepared following the general procedure for the olefination of furanoses, method A, starting from 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-*α*/*β*-D-ribofuranose **8** (905 mg, 2.11 mmol) in dry THF (1.7 mL), diphenyl phenylsulfanylmethylphosphine oxide (2.74 g, 5.28 mmol) in dry THF (57 mL), and 1.6 M *n*-BuLi in hexane (5.8 mL, 9.28 mmol). After 15 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **13** (443 mg, 40%) as an inseparable 1:33 *Z*/*E* mixture as a colourless syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.60. Anal. Calcd for $C_{31}H_{38}O_4SSi$: 69.62 C, 7.16 H, 6.00 S. Found: 69.60 C, 7.21 H, 5.97 S. Data for **13***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.70–7.18 (m, 15 H, Ar), 6.53 (d, 1H, $J_{1,2}$ = 15.0 Hz, H-1), 5.98 (dd, 1H, $J_{1,2}$ = 14.8 H, $J_{2,3}$ = 6.8 Hz, H-2), 4.77 (dd, 1H, $J_{2,3}$ = 6.8, $J_{3,4}$ = 6.6 Hz, H-3), 4.15 (dd, 1H, $J_{3,4}$ = 6.0, $J_{4,5}$ = 8.8, H-4), 3.87 (dd, 1H, $J_{6a,b}$ = 10.1, $J_{5,6a}$ = 3.0 Hz, H-6a), 3.80 (dd, 1H, $J_{6a,b}$ = 10.1, $J_{5,6b}$ = 5.6 Hz, H-6b), 3.71–3.66 (m, 1H, H-5), 2.59 (d, 1H, $J_{5,OH}$ = 6.0 Hz, OH), 1.37, 1.33 (s, 6H, $2CH_3$), 1.08 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.7–126.8 (C, CH, Ar, C-1,2), 109.0 (C_{ketal}), 78.4 (C-3), 77.6 (C-4), 70.0 (C-5), 65.5 (C-6), 27.9, 25.6 ($2CH_3$), 27.0 (CH_3, *t*-Bu), 19.4 (C, *t*-Bu).

(*Z*/*E*)-4,6-Di-*O*-benzyl-1,2,3-trideoxy-1-phenylsulfanyl-D-*erythro*-hex-1-enitol (19): A solution of **86** (40 mg, 0.13 mmol), phenyl vinyl sulfide (86 μL, 0.64 mmol), and catalyst **82** (22 mg, 20 mol %) in dry and degassed toluene (256 μL) was microwave irradiated in a sealed tube at 150ºC for 1 h (temperature control, fixed hold time off, normal absorption mode, 200 W) using a CEM-Discover™ single-mode synthesizer. The solvent was then evaporated and the crude was purified by radial chromatography (from hexane to 1:3

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EtOAc/hexane) to afford **19** (20 mg, 50%) as an inseparable 1:1 *α*/*β* mixture as a colourless syrup. Data obtained from the mixture. R_f (1:4 EtOAc/ hexane): 0.28. Anal. Calcd for $C_{26}H_{28}O_4S$: 74.25 C, 6.71 H, 7.62 S. Found: 74.26 C, 6.74 H, 7.65 S. Data for **19***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.36–7.25 (m, 15H, Ar), 6.24 (d, 1H, $J_{1,2}$ = 15 Hz, H-1), 6.00 (ddd, 1H, $J_{1,2}$ = 15 Hz, $J_{2,3a}$ = $J_{2,3b}$ = 7.5 Hz, H-2), 4.67–4.49 (m, 4H, 2CH_2Ph), 3.87–3.84 (m, 1H, H-4), 3.70–3.53 (m, 3H, H-5,6a,b), 2.66–2.64 (m, 1H, H-3a), 2.54–2.43 (m, 1H, H-3b), 2.44 (d, 1H, $J_{5,OH}$ = 5.2 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4–138.1 (C, Ar), 131.0–124.5 (CH, Ar), 128.6 (C-2), 125.4 (C-1), 79.0 (C-5), 73.6, 72.3 (2CH_2Ph), 71.5 (C-4), 71.2 (C-6), 34.1 (C-3). Data for **19***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.36–7.25 (m, 15H, Ar), 6.31 (d, 1H, $J_{1,2}$ = 11 Hz, H-1), 5.94 (ddd, 1H, $J_{1,2}$ = 11 Hz, $J_{2,3a}$ = $J_{2,3b}$ = 7.2 Hz, H-2), 4.67–4.49 (m, 4H, 2CH_2Ph), 3.89–3.86 (m, 1H, H-4), 3.70–3.53 (m, 3H, H-5,6a,b), 2.66–2.64 (m, 1H, H-3a), 2.54–2.43 (m, 1H, H-3b), 2.49 (d, 1H, $J_{5,OH}$ = 4.8 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3–138.1 (C, Ar), 130.8–124.2 (CH, Ar), 128.5 (C-2), 125.4 (C-1), 78.8 (C-5), 73.6, 72.5 (2CH_2Ph), 71.7 (C-4), 71.1 (C-6), 30.0 (C-3).

Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-*α*-D-mannopyranoside (20): The title compound was prepared following the general procedure for the iodonium-induced cyclization, method A, starting from **2** (1:3 *Z*/*E* ratio) (116.3 mg, 0.22 mmol), dry $NaHCO_3$ (27.8 mg, 0.33 mmol), and NIS (81.1 mg, 0.33 mmol) in dry CH_3CN (300 μL). The reaction mixture was stirred at 0ºC for 16 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **20** (52 mg, 36%) as a yellowish syrup. R_f (1:3 EtOAc/hexane): 0.51. $[\alpha]^{20}_D$: +68.0 (*c* 0.02, CH_2Cl_2). FT–IR (neat) ν in cm^{-1}: 3062, 3030, 2864, 1952, 1878, 1810, 1583, 1094, 778, 737. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.46–7.19 (m, 20H, Ar), 5.78 (s, 1H, H-1), 4.89 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.87 (d, 1H, $J_{2,3}$ = 3.6 Hz, H-2), 4.72 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.71 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.55 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.52 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.48 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.42 (m, 1H, H-5), 3.99 (dd, 1H, $J_{4,5}$ = 8.8 Hz, $J_{3,4}$ = 8.4 Hz, H-4), 3.86 (dd, 1H, $J_{6a,b}$ = 10.8 Hz, $J_{5,6a}$ = 4.8 Hz, H-6a), 3.73 (dd, 1H, $J_{6a,b}$ = 10.8 Hz, $J_{5,6b}$ = 2 Hz, H-6b), 3.10 (dd, 1H, $J_{3,4}$ = 8.4 Hz, $J_{2,3}$ = 3.6 Hz, H-3) ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.5, 138.3, 137.5, 134.1 (C, Ar), 132.2, 129.3, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7 (CH, Ar), 89.8 (C-1), 77.8 (C-3), 76.5 (C-4), 75.6 (CH_2Ph), 73.6 (C-6, CH_2Ph), 71.3 (CH_2Ph), 69.0 (C-6), 35.0 (C-2). Anal. Calcd for $C_{33}H_{33}IO_4S$: 60.74 C, 5.10 H, 4.91 S. Found: 60.70 C, 5.10 H, 4.94 S.

(2*R*,3*R*,4*R*)-2,3-Bis(benzyloxy)-4-(benzyloxymethyl)-2-[(1*S*)-1-iodo-2-phenylsulfanylethyl]oxetane (21): The title compound was prepared following the general procedure for the iodonium-induced cyclization, method C, starting from **2** (1:2 *Z*/*E* ratio)

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(103 mg, 0.19 mmol) in dry Et_2O (2.9 mL), 30% KH (70.2 mg, 0.52 mmol) in dry Et_2O (1.8 mL), and I_2 (187 mg, 0.74 mmol) in dry Et_2O (1.5 mL). The reaction mixture was stirred from –78ºC to room temperature for 1.5 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **21** (39 mg, 31%) as a yellowish syrup. R_f (1:3 EtOAc/hexane): 0.38. $[\alpha]^{20}_D$: –2.3 (*c* 1.6, CH_2Cl_2). FT–IR (neat) ν in cm^{-1}: 3062, 3030, 2921, 2860, 1952, 1876, 1809, 1583, 737, 697. ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.41–7.12 (m, 20H, Ar), 5.26 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 5.12 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 5.00 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.60 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.42–4.40 (m, 1H, H-4), 4.38 (s, 2H, CH_2Ph), 4.36–4.31 (m, 2H, CH-I, H-3), 3.62 (dd, 1H, $J_{a,b}$ = 15 Hz, $J_{a,CHI}$ = 2.6 Hz, CH_2SPh), 3.45 (dd, 1H, $J_{5a,b}$ = 11.4 Hz, $J_{4,5a}$= 2.6 Hz, H-5a), 3.34 (dd, 1H, $J_{5a,b}$ = 11.4 Hz, $J_{4,5b}$ = 3.8 Hz, H-5b), 3.22 (dd, 1H, $J_{a,b}$ = 15 Hz, $J_{b,CHI}$ = 10.2 Hz, $PhSCH_2$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.8, 137.8, 137.7, 135.4 (C, Ar), 129.5, 129.1, 128.6, 128.5, 128.2, 128.1, 127.9, 127.7, 127.5, 126.4 (CH, Ar), 108.3 (C-2), 81.4 (C-4), 81.1 (C-3), 73.5 ($2CH_2Ph$), 69.5 (C-5), 67.1 (CH_2Ph), 37.6 (C-I), 37.2 (CH_2SPh). Anal. Calcd for $C_{33}H_{33}IO_4S$: 60.74 C, 5.10 H, 4.91 S. Found: 60.75 C, 5.11 H, 4.90 S.

Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-*α*/*β*-D-allopyranoside (22): The title compound was prepared following the general procedure for the iodonium-induced cyclization, method A, starting from **9** (1:2 *Z*/*E* ratio) (201.8 mg, 0.38 mmol), dry $NaHCO_3$ (48.3 mg, 0.57 mmol), and NIS (140.8 mg, 0.53 mmol) in dry CH_3CN (900 µL). The reaction mixture was stirred from –30°C to room temperature for 15 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **22** (194 mg, 77%) as an inseparable 1:9 α/*β* anomeric mixture as a yellowish syrup. Data for **22***β* (obtained from a pure analytical sample): R_f (1:3 EtOAc/hexane): 0.39. $[\alpha]^{20}_D$: +16.8 (*c* 0.89, CH_2Cl_2). FT–IR (neat) ν in cm^{-1}: 3088, 3063, 3030, 2866, 1953, 1877, 1811, 1737, 1702, 1099, 737, 698. ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.62–7.22 (m, 20H, Ar), 5.12 (d, 1H, $J_{1,2}$ = 10.8 Hz, H-1), 4.92 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.76 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.63 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.60 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.53 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.51 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.20–4.16 (m, 2H, H-4,5), 4.02 (dd, 1H, $J_{1,2}$ = 10.8 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 3.78–3.62 (m, 3H, H-3,6a,b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6–137.8 (C, Ar), 133.4–127.7 (CH, Ar), 84.6 (C-1), 79.0 (C-4), 76.4 (C-3), 76.1 (C-5), 75.9, 73.6, 72.4 ($3CH_2Ph$), 69.5 (C-6), 32.0 (C-2). Anal. Calcd for $C_{33}H_{33}IO_4S$: 60.74 C, 5.10 H, 4.91 S. Found: 60.96 C, 5.13 H, 4.97 S. Data for **22***α* (obtained from the mixture): ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.62–7.20 (m, 20H, Ar), 5.41 (d, 1H, $J_{1,2}$ = 5.6 Hz, H-1), 4.99 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.87 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.65–4.58 (m, 2H, H-2,5), 4.52 (d, 2H, J_{AB} = 10.4 Hz, CH_2Ph), 4.42 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.40 (d,1H,

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J_{AB} = 12 Hz, CH_2Ph), 4.09 (m, 1H, H-3), 3.86–3.80 (m, 2H, H-4,6a), 3.70 (m, 1H, H-6b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6–127.5 (C, CH, Ar), 90.2 (C-1), 78.4 (C-4), 76.6 (C-3), 75.8 (C-5), 73.6, 72.2, 69.0 ($3CH_2Ph$), 67.8 (C-6), 27.0 (C-2).

N*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-iodo-*α*/*β*-D-allopyranosyl)succinimide (23):** The title compound was prepared following the general procedure for the iodonium-induced cyclization, method A, starting from **9** (1:2 *Z*/*E* ratio) (216 mg, 0.41 mmol), NIS (150.7 mg, 0.62 mmol), and 4Å MS (293 mg) in dry CH_2Cl_2 (900 μL). The reaction mixture was stirred from –78°C to room temperature for 19.5 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **23** (169.3 mg, 64%) as an inseparable 1:41 α/*β* anomeric mixture as a yellow foam. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.07. FT–IR (neat) ν in cm^{-1}: 3062, 3030, 2867, 1784, 1111, 737, 699. Anal. Calcd for $C_{31}H_{32}INO_6$: 58.04 C, 5.03 H, 2.18% N. Found 58.09 C, 5.02 H, 2.20% N. Data for **23β*: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.38–7.24 (m, 15H, Ar), 5.81 (d, 1H, $J_{1,2}$ = 11.2 Hz, H-1), 5.63 (dd, 1H, $J_{1,2} = J_{2,3}$ = 11.2 Hz, H-2), 4.68 (d, 2H, J_{AB} = 3 Hz, CH_2Ph), 4.50 (s, 2H, CH_2Ph), 4.47 (s, 2H, CH_2Ph), 4.27 (m, 1H, H-5), 3.94 (dd, 1H, $J_{2,3}$ = 11.2 Hz, $J_{3,4}$ = 3 Hz, H-3), 3.67 (m, 1H, H-4), 3.64 (dd, 1H, $J_{6a,b}$ = 10.8 Hz, $J_{5,6a}$ = 5.6 Hz, H-6a), 3.59 (dd, 1H, $J_{6a,b}$ = 10.8 Hz, $J_{5,6b}$ = 4.8 Hz, H-6b), 2.70 (s, 4H, CH_2-succinimide). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 175.9 (C=O), 138.1–137.4 (C, Ar), 128.7–127.8 (CH, Ar), 80.1 (C-3), 80.0 (C-1), 75.8 (C-5), 73.8 (CH_2Ph), 73.1 (C-4), 72.3, 72.2 ($2CH_2Ph$), 69.9 (C-6), 28.6 (C-2), 28.0 (CH_2-succinimide).

Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-*α*-D-talopyranoside (24) and Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-*β*-D-galactopyranoside (25*β*): The title compounds were prepared following the general procedure for the iodonium-induced cyclization, method B, starting from **10** (1:7 *Z*/*E* ratio) (89 mg, 0.35 mmol) and IDCP (174.2 mg, 0.37 mmol) in dry CH_2Cl_2 (390 μL). The reaction mixture was stirred at –78°C for 2.5 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **24** (22 mg, 20%) and **25***β* (16 mg, 15%) as yellowish syrups. Data for **24**: R_f (1:3 EtOAc/hexane): 0.48. FT–IR (neat) ν in cm^{-1}: 3030, 2924, 2866, 28.53, 1639, 1454. ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.48–7.21 (m, 20H, Ar), 5.91 (s, 1H, H-1), 5.07 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.76 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.69 (m, 1H, H-2), 4.61–4.38 (m, 5H, $3CH_2Ph$, H-5), 3.98 (m, 1H, H-4), 3.73–3.71 (m, 2H, H-6a,b), 3.38 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6, 138.1, 137.9 (C, Ar), 132.3, 129.2, 128.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6 (CH, Ar), 90.3 (C-1), 74.6 (C-3), 73.8 (C-4), 73.7, 73.6 ($2CH_2Ph$), 72.3 (C-5), 71.0 (CH_2Ph), 69.3 (C-6), 25.0 (C-2). Anal. Calcd for $C_{33}H_{33}IO_4S$: 60.74 C, 5.10 H, 4.91 S. Found: 60.70 C, 5.10 H, 4.91 S. Data for **25***β* (decomposes on standing): R_f (1:3 EtOAc/hexane): 0.43. ^1H NMR

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($CDCl_3$, 400 MHz) δ in ppm: 7.59–7.17 (m, 20H, Ar), 4.87 (d, 1H, $J_{1,2}$ = 10.8 Hz, H-1), 4.83 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.71 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.64 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.49 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.48 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.42 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.29 (dd, 1H, $J_{1,2}$ = $J_{2,3}$ = 10.8 Hz, H-2), 3.83 (m, 1H, H-5), 3.71–3.67 (m, 3H, H-3) 3.65–3.60 (m, 3H, H-4,6a,b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6, 137.9, 137.3 (C, Ar), 133.2, 131.7, 129.0, 128.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7 (CH, Ar), 89.2 (C-1), 85.4 (C-3), 77.9 (C-4), 74.6, 73.8 ($2CH_2Ph$), 73.1 (C-5), 72.9 (CH_2Ph), 68.6 (C-6), 33.1 (C-2).

Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-*α*-D-galactopyranoside (25*α*): The title compound was prepared following the general procedure for the iodonium-induced cyclization, method A, starting from **10** (7:1 *Z*/*E* ratio) (47 mg, 0.09 mmol), dry $NaHCO_3$ (11.2 mg, 0.13 mmol), and NIS (32.8 mg, 0.13 mmol) in dry CH_3CN (205 μL). The reaction mixture was stirred from –30°C to room temperature for 22 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **25***α* (8 mg, 14%) as a yellowish syrup. Data for **25***α*: R_f (1:3 EtOAc/hexane): 0.19. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.21 (m, 20H, Ar), 5.00 (d, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.85 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.72–4.41 (m, 7H, $3CH_2Ph$, H-1,5), 4.03 (bs, 1H, H-4), 3.98 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 1.2 Hz, H-3), 3.71–3.68 (m, 2H, H-6a,b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6, 138.1, 137.5 (C, Ar), 132.3, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2 (CH, Ar), 94.2 (C-1), 84.2 (C-3), 78.2 (C-5), 74.7, 73.9, 72.8 ($3CH_2Ph$), 70.7 (C-4), 67.6 (C-6), 19.2 (C-2).

Phenyl 6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-iodo-3,4-*O*-isopropylidene-1-thio-*α*/*β*-D-talopyranoside (26): The title compound was prepared following the general procedure for the iodonium-induced cyclization, method A, starting from **11** (1:8 *Z*/*E* ratio) (103.8 mg, 0.19 mmol), dry $NaHCO_3$ (24.5 mg, 0.29 mmol), and NIS (71.3 mg, 0.29 mmol) in dry CH_3CN (500 μL). The reaction mixture was stirred at –30°C for 15 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **26** (71 mg, 55%) as an inseparable 42:1 *α*/*β* mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.53. Anal. Calcd for $C_{31}H_{37}IO_4SSi$: 56.36 C, 5.64 H, 4.85 S. Found: 56.34 C, 5.61 H, 4.87 S. Data for **26***α*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.71–7.21 (m, 15H, Ar), 5.52 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.65 (dd, 1H, $J_{3,4}$ = 7.6 Hz, $J_{2,3}$ = 2.4 Hz, H-3), 4.31 (dd, 1H, $J_{3,4}$ = 7.6 Hz, $J_{4,5}$ = 1.2 Hz, H-4), 4.05 (dd, 1H, $J_{1,2}$ = 9.6 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 3.89 (m, 1H, H-5), 3.82–3.72 (m, 2H, $H_{6a,b}$), 1.42, 1.35 (s, 6H, $2CH_3$), 1.04 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.9–133.4 (C, Ar), 129.9–127.8 (CH, Ar), 109.7 (C_{ketal}), 89.9 (C-1), 77.0 (C-3),

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74.4 (C-4), 70.0 (C-5), 62.5 (C-6), 27.0 (CH_3, *t*-Bu), 26.3, 25.5 ($2CH_3$), 22.4 (C-2), 19.4 (C, *t*-Bu).

Phenyl 2-deoxy-2-iodo-3,4-*O*-isopropylidene-1-thio-*α*/*β*-D-*erythro*-pyranoside (27): The title compound was prepared following the general procedure for the iodonium-induced cyclization, method B, starting from **12** (2:3 *Z*/*E* ratio) (35 mg, 0.13 mmol) and IDCP (135.1 mg, 0.29 mmol) in dry CH_3CH_2CN (300 μL). The reaction mixture was stirred at –78°C for 23 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:1 EtOAc/hexane) to afford **27** (17 mg, 33%) as an inseparable 1.1:1 *α*/*β* mixture as a yellowish syrup. Data obtained from the mixture. R_f (EtOAc/hexane 1:1): 0.56. FT–IR (neat) ν in cm^{-1}: 3071, 2958, 2932, 2858, 1611, 1112, 740, 703. Anal. Calcd for $C_{14}H_{17}IO_3S$: 42.87 C, 4.37 H, 8.17 S. Found: 42.85 C, 4.38 H, 8.20 S. Data for **27***α*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.58–7.25 (m, 5H, Ar), 5.33 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 4.59 (m, 1H, H-3), 4.32 (m, 1H, H-5a), 4.27 (m, 1H, H-4), 4.08 (dd, 1H, $J_{1,2}$ = 10.4 Hz, $J_{2,3}$ = 2.8 Hz, H-2), 3.89 (dd, 1H, $J_{5a,b}$ = 9.6 Hz, $J_{5b,4}$ = 4 Hz, H-5b), 1.54, 1.49 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 132.8 (C, Ar), 129.4–128.2 (CH, Ar), 109.5 (C_{ketal}), 88.3 (C-1), 76.5 (C-3), 71.7 (C-4), 64.0 (C-5), 28.4, 27.2 ($2CH_3$) 22.9 (C-2). **27***β*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.58–7.25 (m, 5H, Ar), 5.09 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.59 (m, 1H, H-3), 4.27 (m, 1H, H-4), 4.15 (dd, 1H, $J_{1,2}$ = 7.6 Hz, $J_{2,3}$ = 6.8 Hz, H-2), 3.92 (dd, 1H, $J_{5a,b}$ = 12.4 Hz, $J_{5a,4}$ = 4 Hz, H-5a), 3.58 (dd, 1H, $J_{5a,b}$ = 12.4 Hz, $J_{5b,4}$ = 4 Hz, H-5b), 1.38, 1.36 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 133.2 (C, Ar), 129.4–128.2 (CH, Ar), 110.8 (C_{ketal}), 88.5 (C-1), 80.3 (C-3), 72.8 (C-4), 64.1 (C-5), 29.7 (C-2), 26.4, 25.7 ($2CH_3$).

Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-*α*/*β*-D-mannopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (33a):

Stepwise: the title compound was prepared following the general procedure for glycosylation starting from **20** (37.3 mg, 0.06 mmol), NIS (30.8 mg, 0.13 mmol), glycosyl acceptor **31a** (42.6 mg, 0.11 mmol), 4Å MS (60 mg), and TfOH (1 drop) in dry CH_2Cl_2 (1.4 mL). The reaction mixture was stirred at –78ºC for 1 h and then at –40ºC for 2 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **33a** (37 mg, 71%) as an inseparable 45:1 *α*/*β* mixture as a white crystalline solid.

Consecutive: the title compound was also prepared following the general procedure for consecutive "one pot" cyclization and glycosylation starting from **2** (1:3 *Z*/*E* ratio) (149.7 mg, 0.28 mmol), NIS (209 mg, 0.85 mmol), glycosyl acceptor **31a** (212 mg, 0.57 mmol), and 4Å MS (200 mg) in dry CH_2Cl_2 (8 mL). The reaction mixture was stirred at –40ºC for 1 h until the cyclization was completed. TfOH (1 drop) was then added and the reaction

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mixture stirred at –40ºC for 2 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **33a** (127 mg, 50% over two steps) as an inseparable 45:1 *α*/*β* mixture as a white crystalline solid.

Data obtained from the mixture. R_f (EtOAc/ hexane 1:3): 0.24. FT–IR (KBr) *v* in cm^{-1}: 3054, 2987, 2921, 1454, 1422, 1099, 738, 704. Anal. Calcd for $C_{48}H_{51}IO_{10}$: 63.02 C, 5.62 H. Found: 63.16 C, 5.65 H. Data for **33a***α*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.49–6.99 (m, 25H, Ar), 5.53 (s, 1H, H-7), 5.38 (s, 1H, H-1'), 4.88 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.89 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 4.72 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.69 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.68–4.62 (m, 3H, CH_2Ph, H-2'), 4.50 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.48 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.35 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.29 (dd, 1H, $J_{6a,b}$ = 9.6 Hz, $J_{5,6a}$ = 4 Hz, H-6a), 4.20 (dd, 1H, $J_{4',5'}$ = 9.6 Hz, $J_{5',6'a}$ = 2.8 Hz, H-5'), 3.97 (dd, 1H, $J_{4',5'} = J_{3',4'}$ = 9 Hz, H-4'), 3.89–3.85 (m, 2H, H-2,4), 4.79 (dd, 1H, $J_{4,5}$ = 10 Hz, $J_{5,6a}$ = 4.4 Hz, H-5), 3.74–3.53 (m, 3H, H-6b, H-6'a,b), 3.58–3.53 (m, 1H, H-3), 3.44 (s, 3H, OCH_3), 3.38 (dd, 1H, $J_{3',4'}$ = 8.4 Hz, $J_{2',3'}$ = 4 Hz, H-3'). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.8–137.5 (C, Ar), 128.9–126.1 (CH, Ar), 101.4 (C-7), 98.3 (C-1'), 97.1 (C-1), 82.2 (C-3), 77.1 (C-4), 76.8 (C-3'), 75.9 (C-4', CH_2Ph), 75.4 ($2CH_2Ph$), 74.0 (C-2), 73.1 (CH_2Ph), 72.1 (C-5'), 71.0 (CH_2Ph), 69.1 (C-6), 68.6 (C-6'), 62.4 (C-5), 55.4 (OCH_3), 33.5 (C-2').

Cholesteryl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-*α*/*β*-D-mannopyranoside (33b):

Stepwise: the title compound was prepared following the general procedure for glycosylation starting from **20** (22.1 mg, 0.034 mmol), NIS (18.3 mg, 0.075 mmol), cholesterol (26.2 mg, 0.068 mmol), 4Å MS (34 mg), and TfOH (1drop) in dry CH_2Cl_2 (800 μL). The reaction mixture was stirred at –78°C for 1 h and then at –40°C for 2 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **33b** (23 mg, 72%) as an inseparable 37:1 *α*/*β* mixture as a yellowish foam.

Consecutive: the title compound was also prepared following the general procedure for consecutive "one pot" cyclization and glycosylation starting from **2** (2:3 *Z*/*E* ratio) (108.4 mg, 0.21 mmol), NIS (151.3 mg, 0.62 mmol), cholesterol (159.2 mg, 0.41 mmol), and 4Å MS (200 mg) in dry CH_2Cl_2 (6 mL). The reaction mixture was stirred from –40 to 0ºC for 7 h until the cyclization was completed. The reaction mixture was then cooled and TfOH (1 drop) was added. The reaction mixture was stirred at –20ºC for 1 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **33b** (143 mg, 54% over two steps) as an inseparable 24:1 *α*/*β* mixture as a white crystalline solid.

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Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.63. FT–IR (neat) ν in cm^{-1}: 3064, 3031, 2936, 2867, 1655, 1115, 1041, 737, 698. Anal. Calcd for $C_{54}H_{73}IO_5$: 69.81 C, 7.92 H. Found: 69.79 C, 7.92 H. Data for **33b**α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50–7.15 (m, 15H, Ar), 5.38 (s, 1H, H-1), 5.28 (d, 1H, J = 5.2 Hz, =CH-), 4.85 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.71 (dd, 2H, J_{AB} = 11.6 Hz, CH_2Ph), 4.58–4.46 (m, 4H, CH_2Ph, H-2), 3.96–3.88 (m, 2H, H-4,5), 4.81 (dd, 1H, $J_{6a,b}$ = 10.8 Hz, $J_{5,6a}$ = 4.4 Hz, H-6a), 3.71 (dd, 1H, $J_{6a,b}$ = 10.8 Hz, $J_{5,6b}$ = 1.6 Hz, H-6b), 4.48 (m, 1H, *O*-cholesteryl), 3.36 (dd, 1H, $J_{3,4}$ = 8 Hz, $J_{2,3}$ = 4 Hz, H-3), 3.35–0.67 (m, 43H, cholesteryl). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 140.5 (=C-), 138.5–138.0 (C, Ar), 129.2–127.2 (CH, Ar), 122.2 (=CH-), 99.6 (C-1), 77.5 (*O*-cholesteryl), 77.2 (C-3), 76.1 (C-4), 75.5, 73.4 ($2CH_2Ph$), 72.2 (C-5), 71.0 (CH_2Ph), 69.0 (C-6), 56.2–12.0 (CH, CH_2, CH_3, cholesteryl), 34.6 (C-2).

Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-α/β-D-allopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (34a):

Stepwise: the title compound was prepared following the general procedure for glycosylation starting from **22** (80.9 mg, 0.12 mmol), NIS (66.8 mg, 0.27 mmol), glycosyl acceptor **31a** (92.3 mg, 0.25 mmol), 4Å MS (120 mg), and TfOH (1 drop) in dry CH_2Cl_2 (3 mL). The reaction mixture was stirred at –78ºC for 1 h and then at –40ºC for 2.5 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **34a** (84 mg, 74%) as an inseparable 1:6 α/β mixture as a white crystalline solid.

Consecutive: the title compound was also prepared following the general procedure for consecutive "one pot" cyclization and glycosylation starting from **9** (1:2 *Z*/*E* ratio) (106.6 mg, 0.20 mmol), NIS (148.8 mg, 0.61 mmol), glycosyl acceptor **31a** (150.7 mg, 0.40 mmol), and 4Å MS (143 mg) in dry CH_2Cl_2 (6 mL). The reaction mixture was stirred at –40ºC for 2 h until the cyclization was completed. TfOH (1 drop) was then added and the reaction mixture stirred at –40ºC for 1 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **34a** (120 mg, 65% over two steps) as an inseparable 1:5 α/β mixture as a white crystalline solid.

Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.23. FT–IR (neat) ν in cm^{-1}: 3054, 2987, 2921, 1636, 1497, 1097, 738, 705. Anal. Calcd for $C_{48}H_{51}IO_{10}$: 63.02 C, 5.62 H. Found: 62.96 C, 5.64 H. Data for **34a**β: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.52–7.05 (m, 25H, Ar), 5.54 (s, 1H, H-7), 5.08 (d, 1H, $J_{1',2'}$ = 9.2 Hz, H-1'), 5.07 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.93 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 4.89 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.79 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.78 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.65–4.47 (m, 4H, $2CH_2Ph$), 4.27 (dd, 1H, $J_{6a,b}$ = 9.5 Hz, $J_{5,6a}$ = 4.4 Hz, H-6a), 4.17–4.10 (m, 3H, H-2',3',5'), 4.00 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.2 Hz, H-3), 3.90–3.78 (m, 1H, H-5), 4.75–3.67 (m, 5H, H-2,6b,

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H-4',6'a,b), 3.59 (dd, 1H, $J_{3,4} = J_{4,5} = 9.2$ Hz, H-4), 3.38 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 139.0–137.7 (C, Ar), 129.2–126.3 (CH, Ar), 102.1 (C-1'), 101.6 (C-7), 100.6 (C-1), 82.8 (C-4), 80.3 (C-4'), 78.8 (C-3'), 77.7 (C-3), 76.8 (C-2), 76.0, 75.6, 73.8 ($3CH_2Ph$), 73.2 (C-5'), 72.6 (CH_2Ph), 69.8 (C-6'), 69.5 (C-6), 62.4 (C-5), 55.6 (OCH_3), 30.9 (C-2').

Cholesteryl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-*α*/*β*-D-allopyranoside (34b):

Stepwise: the title compound was prepared following the general procedure for glycosylation starting from **22** (100 mg, 0.15 mmol), NIS (82.6 mg, 0.34 mmol), cholesterol (118.5 mg, 0.31 mmol), 4Å MS (150 mg), and TfOH (1drop) in dry CH_2Cl_2 (3.5 mL). The reaction mixture was stirred at –78°C for 1 h and then at –40°C for 2.5 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **34b** (115 mg, 81%) as an inseparable 1:9 *α*/*β* mixture as a yellowish foam.

Consecutive: the title compound was also prepared following the general procedure for consecutive "one pot" cyclization and glycosylation starting from **9** (1:2 *Z*/*E* ratio) (110.4 mg, 0.21 mmol), NIS (154.1 mg, 0.63 mmol), cholesterol (162.1 mg, 0.42 mmol), and 4Å MS (150 mg) in dry CH_2Cl_2 (6 mL). The reaction mixture was stirred from –40 to 0ºC for 20 h until the cyclization was completed. The reaction mixture was then cooled and TfOH (1 drop) was added. The reaction mixture was stirred at –40ºC for 1 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **34b** (136 mg, 70% over two steps) as an inseparable 1:3 *α*/*β* mixture as a yellowish foam.

Data obtained from the mixture. R_f (EtOAc/ hexane 1:3): 0.53. FT–IR (neat) ν in cm^{-1}: 3030, 2936, 2867, 1655, 1123, 1041, 736, 697. Anal. Calcd for $C_{54}H_{73}IO_5$: 69.81 C, 7.92 H. Found: 69.68 C, 7.89 H. Data for **34b***β*: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.52–7.22 (m, 15H, Ar), 5.35 (d, 1H, J = 4.8 Hz, =CH-), 4.88 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.87 (d, 1H, d, $J_{1,2}$ = 9 Hz, H-1), 4.77 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.64–4.49 (m, 4H, $2CH_2Ph$), 4.17–4.09 (m, 2H, H-3,5), 4.02 (dd, 1H, $J_{1,2}$ = 9 Hz, $J_{2,3}$ = 2.8 Hz, H-2), 3.73–3.64 (m, 3H, H-4,6a,b), 4.48 (m, 1H, *O*-cholesteryl), 2.40–0.67 (m, 43H, cholesteryl). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 140.8 (=C-), 138.5–137.7 (C, Ar), 128.6–126.8 (CH, Ar), 122.0 (=CH-), 99.3 (C-1), 79.9 (*O*-cholesteryl), 78.6 (C-3), 76.9 (C-4), 75.8, 73.5 ($2CH_2Ph$), 73.1 (C-5), 72.4 (CH_2Ph), 69.5 (C-6), 56.9–12.0 (CH, CH_2, CH_3, cholesteryl), 33.3 (C-2).

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Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-*α*-D-talopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (35a) and Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-*α*/*β*-D-galactopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (41a): The title compound was prepared following the general procedure for consecutive "one pot" cyclization and glycosylation starting from **10** (1:17 *Z*/*E* ratio) (63 mg, 0.12 mmol), NIS (88 mg, 0.36 mmol), glycosyl acceptor **31a** (89.1 mg, 0.24 mmol), and 4Å MS (85 mg) in dry CH_2Cl_2 (3.5 mL). The reaction mixture was stirred from –78 to –60ºC for 4 h until the cyclization was completed. The reaction mixture was then cooled and TfOH (1 drop) was added. The reaction mixture was stirred at –78ºC for 1 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford an inseparable 1:1.2 mixture of **35a**/**41a***β* (54 mg, 49% over two steps) and **41a***α* (36 mg, 33% over two steps) as white crystalline solids. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.27. Anal. Calcd for $C_{48}H_{51}IO_{10}$: 63.02 C, 5.62 H. Found: 63.02 C, 5.60 H. Data for **35a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.47–7.17 (m, 25H, Ar), 5.50 (s, 1H, H-1'), 5.47 (s, 1H, H-7), 4.92–4.25 (m, 8H, 4CH_2Ph), 4.92–4.89 (m, 1H, H-1), 4.48 (m, 1H, H-2'), 4.29–4.45 (m, 1H, H-6a), 3.90 (m, 7H, H-2,3,4,5,6b, H-4',5'), 3.48–3.39 (m, 2H, H-6'a,b), 3.44 (s, 3H, OCH_3), 3.31 (m, 1H, H-3'). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.8–137.6 (C, Ar), 129.1–126.2 (CH, Ar), 101.3 (C-7), 99.5 (C-1'), 97.1 (C-1), 77.2 (C-5'), 75.5 (C-3), 75.1–70.0 (4CH_2Ph), 73.7 (C-4), 73.3 (C-2), 73.2 (C-3'), 72.9 (C-4'), 69.7 (C-6), 69.1 (C-6'), 62.5 (C-5), 55.5 (OCH_3), 24.0 (C-2'). Data for **41a***β*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.47–7.17 (m, 25H, Ar), 5.53 (s, 1H, H-7), 5.09 (d, 1H, $J_{1',2'}$ = 3 Hz, H-1'), 4.92–4.25 (m, 8H, 4CH_2Ph), 4.92–4.89 (m, 1H, H-1), 4.57 (m, 1H, H-2'), 4.29–4.45 (m, 1H, H-6a), 4.09 (dd, 1H, $J_{2,3} = J_{3,4}$ = 9.2 Hz, H-3), 3.90–3.64 (m, 5H, H-2,5,6b, H-3',5'), 3.59 (dd, 1H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 3.48–3.39 (m, 3H, H-4',6'a,b), 3.49 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.8–137.6 (C, Ar), 129.1–126.2 (CH, Ar), 101.5 (C-7), 99.9 (C-1'), 97.7 (C-1), 82.9 (C-4), 82.3 (C-4'), 79.0 (C-3'), 76.9 (C-3), 75.1–70.0 (4CH_2Ph), 75.4 (C-5'), 74.7 (C-2), 69.3 (C-6), 68.7 (C-6'), 62.7 (C-5), 55.7 (OCH_3), 29.7 (C-2'). Data for **41a***α*: R_f (1:3 EtOAc/hexane): 0.20. Anal. Calcd for $C_{48}H_{51}O_{10}I$: 63.02 C, 5.62 H. Found: 63.03 C, 5.64 H. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.48–7.19 (m, 25H, Ar), 5.55 (s, 1H, H-7), 5.08 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.87–4.82 (m, 4H, CH_2Ph, H-1, H-1'), 4.71 (d, 1H, J_{AB} = 10 Hz, CH_2Ph), 4.66 (d, 1H, J_{AB} = 10 Hz, CH_2Ph), 4.53 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.42 (s, 2H, CH_2Ph), 4.36–4.27 (m, 2H, H-2', H-6a), 4.07 (appt, 1H, $J_{23} = J_{34}$ = 9.6 Hz, H-3), 3.86 (m, 1H, H-5), 3.78–3.70 (m, 3H, H-2,6b, H-4'), 3.62 (appt, 1H, $J_{34} = J_{45}$ = 9.6 Hz, H-4), 3.57–3.54 (m, 3H, H-5', 6'a,b), 3.51–3.47 (m, 1H, H-3'), 3.39 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 139.0, 138.5, 137.6, 137.4 (C, Ar), 128.7–126.2 (CH, Ar), 104.9 (C-1'), 101.5 (C-7), 100.4 (C-1), 84.0 (C-3'), 82.9 (C-4), 79.4 (C-4'), 77.9 (C-3), 75.3, 74.8 (2CH_2Ph), 74.1

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(C-5'), 73.7 (CH_2Ph), 73.3 (C-2), 73.2 (CH_2Ph), 69.4 (C-6), 68.7 (C-6'), 62.3 (C-5), 55.6 (OCH_3), 32.2 (C-2').

Cholesteryl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-*α*/*β*-D-talopyranoside (35b): The title compound was prepared following the general procedure for glycosylation starting from **24** (19 mg, 0.03 mmol), NIS (16 mg, 0.06 mmol), cholesterol (22.5 mg, 0.06 mmol), 4Å MS (29 mg), and TfOH (1drop) in dry CH_2Cl_2 (680 μL). The reaction mixture was stirred from –78 to 0°C for 18 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **35b** (7.4 mg, 27%) as an inseparable 7:1 *α*/*β* mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:3 EtOAc/ hexane): 0.64. Data for **35b***α*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.72–7.25 (m, 15H, Ar), 5.44 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1), 5.41 (d, 1H, J = 4 Hz, =CH-), 5.03 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.74 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.56 (d, 1H, J_{AB} = 11.2 Hz, CH_2Ph), 4.51 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.49 (d, 1H, d, J_{AB} = 11.2 Hz, CH_2Ph), 4.42 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.32 (m, 1H, H-2), 4.21 (m, 1H, H-5), 3.95 (m, 1H, H-4), 3.75–3.66 (m, 2H, H-6a,b), 3.57 (m, 1H, H-3), 3.51–3.44 (m, 1H, m, *O*-cholesteryl), 2.65–0.78 (m, 43H, cholesteryl). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 140.9 (=C-), 139.0–138.1 (C, Ar), 129.2–127.5 (CH, Ar), 123.1 (=CH-), 99.4 (C-1), 77.7 (*O*-cholesteryl), 74.5 (C-3), 73.7 (C-4), 73.6 ($2CH_2Ph$), 71.1 (CH_2Ph), 71.0 (C-5), 69.4 (C-6), 56.9-12.1 (CH, CH_2, CH_3, cholesteryl), 25.9 (C-2).

Methyl (6'-*O*-(*tert*-butyldiphenylsilyl)-2'-deoxy-2'-iodo-3',4'-*O*-isopropylidene-*α*/*β*-D-talopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (36a):
Stepwise: the title compound was prepared following the general procedure for glycosylation starting from **26** (58 mg, 0.09 mmol), NIS (47.3 mg, 0.19 mmol), glycosyl acceptor **31a** (65.4 mg, 0.18 mmol), 4Å MS (88 mg), and TfOH (1 drop) in dry CH_2Cl_2 (2 mL). The reaction mixture was stirred at –78ºC for 1.5 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **36a** (48 mg, 59%) as an inseparable 20:1 *α*/*β* mixture as a white crystalline solid.
Consecutive: the title compound was also prepared following the general procedure for consecutive "one pot" cyclization and glycosylation starting from **11** (2:5 *Z*/*E* ratio) (47.8 mg, 0.09 mmol), NIS (65.7 mg, 0.27 mmol), glycosyl acceptor **31a** (66.6 mg, 0.18 mmol), and 4Å MS (64 mg) in dry CH_2Cl_2 (2.6 mL). The reaction mixture was stirred from –78 to –40ºC for 5 h until the cyclization was completed. The reaction mixture was then cooled and TfOH (1 drop) was added. The reaction mixture was stirred at –78ºC for 8 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **36a** (41 mg, 50% over two steps) as an inseparable 5:1 *α*/*β* mixture as a white crystalline solid.

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Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.38. Anal. Calcd for $C_{46}H_{55}IO_{10}Si$: 59.86 C, 6.01 H. Found: 59.83 C, 5.98 H. Data for **36a**α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.68–7.17 (m, 20H, Ar), 5.50 (s, 1H, H-7), 5.23 (d, 1H, $J_{1',2'}$ = 7.6 Hz H-1'), 4.89 (d, 1H, $J_{1,2}$ = 3.6 Hz H-1), 4.77 (s, 2H, CH_2Ph), 4.64 (dd, 1H, $J_{3',4'}$ = 8 Hz, $J_{2',3'}$ = 2.8 Hz, H-3'), 4.41 (dd, 1H, $J_{3',4'}$ = 8 Hz, $J_{4',5'}$ = 2 Hz, H-4'), 4.26 (dd, 1H, $J_{6a,b}$ = 9.6 Hz, $J_{6a,5}$ = 4.8 Hz, H-6a), 4.11 (dd, 1H, $J_{1',2'}$ = 7.6 Hz, $J_{2',3'}$ = 2.8 Hz, H-2'), 3.99–3.68 (m, 7H, H-2,4,5,6b, H-5',6'a,b), 3.54 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H-3), 3.47 (s, 3H, OCH_3), 1.40, 1.36 (s, 6H, $2CH_3$), 1.03 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 139.2–137.6 (C, Ar), 136.0–126.3 (CH, Ar), 109.3 (C_{ketal}), 101.5 (C-7), 101.1 (C-1'), 98.1 (C-1), 82.1 (C-3), 77.2 (C-4), 77.0 (C-2), 76.5 (C-3'), 75.0 (CH_2Ph), 73.7 (C-4'), 69.4 (C-5'), 69.3 (C-6), 61.6 (C-5), 61.9 (C-6'), 55.6 (OCH_3), 27.1 (CH_3, *t*-Bu), 26.2, 25.2 ($2CH_3$), 24.5 (C-2'), 19.5 (C, *t*-Bu).

Cholesteryl 6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-iodo-3,4-*O*-isopropylidene-*α*/*β*-D-talopyranoside (36b):

Stepwise: the title compound was prepared following the general procedure for glycosylation starting from **26** (70 mg, 0.11 mmol), NIS (57.1 mg, 0.23 mmol), cholesterol (82 mg, 0.21 mmol), 4Å MS (106 mg), and TfOH (1 drop) in dry CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at –78ºC for 1.5 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **36b** (35.4 mg, 36%) as a 10:1 α/β mixture as a yellowish syrup.

Consecutive: The title compound was also prepared following the general procedure for consecutive "one pot" cyclization and glycosylation starting from **11** (2:5 *Z*/*E* ratio) (70 mg, 0.13 mmol), NIS (96.2 mg, 0.39 mmol), cholesterol (101.2 mg, 0.26 mmol), and 4Å MS (93 mg) in dry CH_2Cl_2 (3.8 mL). The reaction mixture was stirred from –78 to –40ºC for 24 h until the cyclization was completed. The reaction mixture was then cooled and TfOH (1 drop) was added. The reaction mixture was stirred at –78ºC for 10 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **36b** (33 mg, 27% over two steps) as an inseparable 8:1 α/β mixture as a yellowish syrup.

Data obtained from the mixture. R_f (EtOAc/ hexane 1:3): 0.55. Anal. Calcd for $C_{52}H_{77}IO_5Si$: 66.64 C, 8.28 H. Found: 66.61 C, 8.30 H. Data for **36b**α: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.71–7.26 (m, 10H, Ar), 5.23 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1), 5.18 (d, 1H, *J* = 4 Hz, =CH-), 4.64–4.60 (m, 1H, H-3), 4.29–4.21 (m, 1H, H-4), 4.02–3.98 (m, 1H, H-2), 3.92 (m, 1H, H-5), 3.88–3.72 (m, 2H, H-6a,b), 3.50 (m, 1H, *O*-cholesteryl), 2.27–0.67 (m, 58H, cholesteryl, $2CH_3$, CH_3, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 148.4, 145.6 (C, Ar), 140.7 (=C-), 135.9–127.8 (CH, Ar), 122.0 (=CH-), 109.5 (C_{ketal}), 100.2 (C-1), 77.1

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(*O*-cholesteryl), 75.1 (C-3), 74.4 (C-4), 68.8 (C-5), 61.6 (C-6), 56.9–12.1 (CH, CH_2, CH_3, cholesteryl), 27.1 (CH_3, *t*-Bu), 26.3, 25.8 ($2CH_3$), 24.8 (C-2), 19.6 (C, *t*-Bu).

Methyl (3',4'-*O*-isopropylidene-2'-deoxy-2'-iodo-*α*/*β*-D-*erythro*-pyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (37a): The title compound was prepared following the general procedure for glycosylation starting from **27** (80.1 mg, 0.20 mmol), NIS (110.1 mg, 0.45 mmol), glycosyl acceptor **31a** (152.1 mg, 0.41 mmol), 4Å MS (20 mg), and TfOH (1 drop) in dry CH_2Cl_2 (4.7 mL). The reaction mixture was stirred at –78ºC for 30 min. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **37a** (59.4 mg, 44%) as an inseparable 1:3 *α*/*β* mixture as a white solid. Data obtained from the mixture. R_f (EtOAc/ hexane 1:3): 0.17. FT–IR (neat) ν in cm^{-1}: 3055, 2987, 2932, 1638, 737, 702. Anal. Calcd for $C_{29}H_{35}IO_9$: 53.22 C, 5.39 H. Found: 53.40 C, 5.41 H. Data for **37a***α*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.48–7.22 (m, 10H, Ar), 5.56 (s, 1H, H-7), 5.30 (d, 1H, $J_{1',2'}$ = 7.6 Hz, H-1'), 5.06 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.88–4.78 (m, 2H, H-1, CH_2Ph), 4.58 (dd, 1H, $J_{3',4'}$ = 7.2 Hz, $J_{2',3'}$ = 3 Hz, H-3'), 4.33–4.26 (m, 2H, H-4', H-6a), 4.13 (m, 1H, H-2'), 4.09–3.55 (m, 7H, H-2,3,4,5,6b, H-5'a,b), 3.42 (s, 3H, OCH_3), 1.53, 1.37 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.9–137.5 (C, Ar), 129.1–126.2 (CH, Ar), 109.3 (C_{ketal}), 103.9 (C-1'), 101.4 (C-7), 100.5 (C-1), 82.3 (C-4), 79.3 (C-2), 77.8 (C-3), 76.3 (C-3'), 75.5 (CH_2Ph), 73.4 (C-4'), 69.2 (C-6), 62.2 (C-5), 61.5 (C-5'), 55.5 (OCH_3), 26.7, 25.2 ($2CH_3$), 21.9 (C-2'). Data for **37a***β*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.48–7.22 (m, 10H, Ar), 5.56 (s, 1H, H-7), 4.95 (d, 1H, $J_{1,2}$ = 4 Hz, H-1), 4.88–4.78 (m, 3H, H-1', CH_2Ph), 4.45 (dd, 1H, $J_{3',4'}$ = 9.6 Hz, $J_{2',3'}$ = 6 Hz, H-3'), 4.33–4.26 (m, 1H, H-6a), 4.13 (m, 1H, H-4'), 4.09–3.55 (m, 8H, H-2,3,4,5,6b, H-2',5'a,b), 3.50 (s, 3H, OCH_3), 1.53, 1.37 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.9–137.5 (C, Ar), 129.1–126.2 (CH, Ar), 110.6 (C_{ketal}), 103.4 (C-1'), 101.4 (C-7), 98.5 (C-1), 82.3 (C-4), 80.6 (C-3'), 79.3 (C-2), 77.3 (C-3), 75.54 (CH_2Ph), 73.1 (C-4'), 69.2 (C-6), 62.7 (C-5'), 62.6 (C-5), 55.7 (OCH_3), 32.8 (C-2'), 28.1, 25.9 ($2CH_3$).

Cholesteryl 3,4-*O*-isopropylidene-2-deoxy-2-iodo-*α*/*β*-D-*erythro*-pyranoside (37b): The title compound was prepared following the general procedure for glycosylation starting from **27** (53.2 mg, 0.14 mmol), NIS (73.1 mg, 0.30 mmol), cholesterol (104.9 mg, 0.27 mmol), 4Å MS (14 mg), and TfOH (1drop) in dry CH_2Cl_2 (3.3 mL). The reaction mixture was stirred from –78 to 0ºC for 17 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **37b** (42.1 mg, 46%) as an inseparable 1:25 *α*/*β* mixture as a yellow foam. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.5. FT–IR (neat) ν in cm^{-1}: 3055, 2940, 1644, 1467, 738. Anal. Calcd for $C_{35}H_{57}IO_4$: 62.86 C, 8.59 H. Found: 62.80 C, 8.56 H. Data for **37b***β*: ^{1}H NMR ($CDCl_3$, 400

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MHz) δ in ppm: 5.35 (d, 1H, J = 4 Hz, =CH-), 4.63 (d, 1H, $J_{1,2}$ = 8.8 Hz, H-1), 4.50 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 5.6 Hz, H-3), 4.25 (dd, 1H, $J_{5a,b}$ = 13.2 Hz, $J_{4,5a}$ = 2.8 Hz, H-5a), 4.08 (m, 1H, H-4), 3.87–3.82 (m, 2H, H-2,5b), 4.54–3.46 (m, 1H, *O*-cholesteryl), 2.37–0.67 (m, 43H, cholesteryl), 1.53, 1.37 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 140.8 (=C-), 122.1 (=CH-), 101.2 (C-1), 81.4 (C-3), 79.4 (*O*-cholesteryl), 73.4 (C-4), 63.0 (C-5), 56.9-12.1 (CH, CH_2, CH_3, cholesteryl), 33.6 (C-2), 28.4, 26.1 ($2CH_3$). 140.8 (=C-), 122.1 (=CH-), 101.2 (C-1), 81.4 (C-3), 79.4 (*O*-cholesteryl), 73.4 (C-4), 63.0 (C-5), 56.9–12.1 (CH, CH_2, CH_3, cholesteryl), 33.6 (C-2), 28.4, 26.1 ($2CH_3$).

Methyl (3',4'-di-*O*-benzyl-2',6'-dideoxy-2'-iodo-*α*/*β*-D-allopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (38a): A solution of **32** (47 mg, 0.09 mmol), TTBP (44 mg, 0.17 mmol), Me_2S_2 (8 μL, 0.09 mmol), and Tf_2O (16 μL, 0.10 mmol) in dry CH_2Cl_2 (2.3 mL) was stirred with 4Å MS (86 mg) at –78ºC for 30 min. Glycosyl acceptor **31a** (48 mg, 0.13 mmol) in dry CH_2Cl_2 (900 μL) was added at the same temperature. The reaction mixture was stirred from –78 to 0 °C for 3.5 h. The crude was then diluted with CH_2Cl_2 and washed with aqueous saturated $NaHCO_3$ and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **38a** (46 mg, 66%) as an inseparable 1:2.2 α/β mixture as a colourless syrup. Data obtained from the mixture. R_f (1:3 EtOAc/ hexane): 0.25. Anal. Calcd for $C_{41}H_{45}O_9I$: 60.89 C, 5.61 H. Found: 60.87 C, 5.58 H. Data for **38a***α*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.46–7.16 (m, 20H, Ar), 5.54 (s, 1H, H-7), 5.18 (bs, 1H, H-1'), 5.08–4.42 (m, 9H, $3CH_2Ph$, H-1, H-2',5'), 4.28 (m, 1H, H-6a), 3.17–3.57 (m, 7H, H-2,3,4,5,6b, H-3',4'), 3.44 (s, 3H, OCH_3), 1.14 (d, 3H, $J_{5',6'}$ = 6.8 Hz, H-6'). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.9–137.6 (C, Ar), 129.1–126.2 (CH, Ar), 101.4 (C-7), 99.2 (C-1'), 97.7 (C-1), 81.7 (C-4), 78.4 (C-2), 77.6 (C-3'), 77.2 (C-3), 76.1 (C-4'), 75.9–71.5 ($3CH_2Ph$), 69.2 (C-6), 65.4 (C-5'), 62.6 (C-5), 55.5 (OCH_3), 27.5 (C-2'), 17.8 (C-6'). Data for **38a***β*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.46–7.16 (m, 20H, Ar), 5.54 (s, 1H, H-7), 5.08–4.42 (m, 8H, $3CH_2Ph$, H-1, H-1'), 4.28 (dd, 1H, $J_{6a,b}$ = 10.4 Hz, $J_{6a,5}$ = 4.8 Hz, H-6a), 4.14–3.57 (m, 8H, H-2,3,4,5,6b, H-2',4',5'), 3.40 (s, 3H, OCH_3), 3.31 (d, 1H, $J_{3',4'}$ = 9.6 Hz, H-3'), 1.24 (d, 3H, $J_{5',6'}$ = 6.4 Hz, H-6'). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.9–137.6 (C, Ar), 129.1–126.2 (CH, Ar), 101.7 (C-1'), 101.5 (C-7), 100.4 (C-1), 82.5 (C-4), 81.6 (C-3'), 80.5 (C-4'), 77.5 (C-3), 77.0 (C-2), 75.9–71.5 ($3CH_2Ph$), 69.5 (C-5'), 69.3 (C-6), 62.4 (C-5), 55.5 (OCH_3), 31.2 (C-2'), 18.3 (C-6').

Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-*α*/*β*-D-*arabino*-pyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (43a): A solution of **33a** (93.6 mg, 0.10 mmol), Bu_3SnH (67 μL, 0.23 mmol), and AIBN (2.2 mg, 0.013 mmol) in dry and degassed toluene

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(1.3 mL) was heated under reflux for 2.5 h and the solvent evaporated. The crude was then diluted with Et_2O and washed with aqueous saturated KF. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **43a** (54.4 mg, 67%) as an inseparable 20:1 α/β mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:3 EtOAc/ hexane): 0.11. FT–IR (neat) ν in cm^{-1}: 3064, 3031, 2936, 1496, 1099, 736, 698. Anal. Calcd for $C_{48}H_{52}O_{10}$: 73.08 C, 6.64 H. Found: 72.97 C, 6.66 H. ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.51–7.02 (m, 25H, Ar), 5.55 (s, 1H, H-7), 5.12 (d, 1H, $J_{1',2'b}$ = 2.8 Hz, H-1'), 4.92 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 4.91 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.77 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.71 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.67 (d, 2H, J_{AB} = 4.8 Hz, CH_2Ph), 4.59 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.55 (d, 1H, J_{AB} = 10.4 Hz, CH_2Ph), 4.35 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.29 (dd, 1H, $J_{6a,b}$ = 10 Hz, $J_{5,6a}$ = 4.4 Hz, H-6a), 4.13–4.06 (m, 2H, H-3',5'), 3.94–3.84 (m, 2H, H-2,4), 3.81 (m, 1H, H-5), 3.71 (dd, 1H, $J_{6a,b}$ = 10 Hz, $J_{5,6b}$ = 20 Hz, H-6b), 3.65–3.61 (m, 1H, H-4'), 3.61–3.49 (m, 3H, H-3, H-6'a,b), 3.44 (s, 3H, OCH_3), 2.41 (dd, 1H, $J_{2'a,b}$ = 13 Hz, $J_{1',2'b}$ = 4.8 Hz, H-2'b), 1.80 (t, 1H, $J_{2'a,b}$ = 13 Hz, H-2'a). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 139.1–137.5 (C, Ar), 129.1-126.1 (CH, Ar), 101.3 (C-7), 97.3 (C-1), 94.1 (C-1'), 82.2 (C-3), 78.3 (C-4'), 77.6 (C-3'), 77.3 (C-2), 76.0, 75.0 ($2CH_2Ph$), 73.4 (C-4), 73.3, 72.1 ($2CH_2Ph$), 70.6 (C-5'), 69.2 (C-6), 68.6 (C-6'), 62.5 (C-5), 55.4 (OCH_3), 35.5 (C-2').

Cholesteryl 3,4,6-tri-*O*-benzyl-2-deoxy-α/β-D-*arabino*-pyranoside (43b): A solution of **33b** (140 mg, 0.15 mmol), Bu_3SnH (80 µL, 0.33 mmol), and AIBN (3.3 mg, 0.02 mmol) in dry and degassed toluene (2 mL) was heated under reflux for 2.5 h and the solvent evaporated. The crude was then diluted with Et_2O and washed with aqueous saturated KF. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by radial chromatography (from hexane to 1:5 EtOAc/hexane) to afford **43b** (90.5 mg, 75%) as an inseparable 10:1 α/β mixture as a yellow solid. Data obtained from the mixture. R_f (1:5 EtOAc/ hexane): 0.44. FT–IR (neat) ν in cm^{-1}: 3064, 2935, 2867, 1454, 1099, 735, 697. Anal. Calcd for $C_{54}H_{74}O_5$: 80.75 C, 9.29 H. Found: 80.73 C, 9.26 H. ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.42–7.16 (m, 15H, Ar), 5.28 (d, 1H, J = 4.8 Hz, =CH-), 5.14 (d, 1H, $J_{1,2b}$ = 3.2 Hz, H-1), 4.89 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.71–4.60 (m, 3H, CH_2Ph), 4.58–4.46 (m, 2H, CH_2Ph), 4.06–3.99 (m, 1H, H-3), 3.87–3.77 (m, 2H, H-5,6a), 3.69–3.60 (m, 2H, H-4,6b), 3.46 (m, 1H, *O*-cholesteryl), 2.29–0.67 (m, 45H, cholesteryl, H-2a,b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 141.0 (=C-), 139.0–138.3 (C, Ar), 128.6–127.7 (CH, Ar), 121.8 (=CH-), 95.2 (C-1), 78.6 (C-4), 78.0 (C-3), 76.0 (*O*-cholesteryl), 75.2, 73.6, 71.9 ($3CH_2Ph$), 70.8 (C-5), 69.1 (C-6), 56.9–12.0 (CH, CH_2, CH_3, cholesteryl), 36.0 (C-2).

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Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-phenylselenenyl-1-thio-*β*-D-gulopyranoside (45): The title compound was prepared following the general procedure for the selenonium-induced cyclization starting from **18** (1:2 *Z*/*E* ratio) (388 mg, 0.737 mmol), *N*-(phenylselenenyl)phthalimide (343.1 mg, 1.14 mmol), and ZnI_2 (362 mg, 1.14 mmol) in dry CH_2Cl_2 (13 mL). The reaction mixture was stirred from –40ºC to room temperature for 3 d. After standard workup, the crude was purified by radial chromatography (1:3 EtOAc/hexane) to afford **45** (70.4 mg, 14%) as a yellowish syrup. R_f (1:3 EtOAc/hexane): 0.33. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50–7.15 (m, 25H, Ar), 5.24 (d, 1H, $J_{1,2}$ = 10.8 Hz, H-1), 4.50–4.37 (m, 6H, 3CH_2Ph), 4.16 (m, 1H, H-5), 3.80 (dd, 1H, $J_{2,3}$ = 3.2, $J_{3,4}$ = 6.8 Hz, H-3), 3.82 (dd, 1H, $J_{1,2}$ = 10.8, $J_{2,3}$ = 2.8 Hz, H-2), 3.64 (dd, 1H, $J_{5,6a}$ = 6.0, $J_{6a,b}$ = 9.6 Hz, H-6a), 3.59 (dd, 1H, $J_{5,6b}$ = 6.8, $J_{6a,b}$ = 9.6 Hz, H-6b), 3.46 (d, 1H, $J_{4,5}$ = 3.6, H-4). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.7, 138.5, 138.4, 138.1 (C, Ar), 134.8, 131.6, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 127.5 (CH, Ar), 86.0 (C-1), 76.9 (C-3), 74.9 (C-4), 73.7, 73.5, 73.1 (3CH_2Ph), 72.5 (C-5), 63.4 (C-6), 47.2 (C-2).

Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-phenylselenenyl-1-thio-*β*-D-glucopyranoside (46) and Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-phenylselenenyl-1-thio-*α*-D-mannopyranoside (47): The title compounds were prepared following the general procedure for the selenonium-induced cyclization starting from **2** (2:5 *Z*/*E* ratio) (100 mg, 0.190 mmol), and *N*-(phenylselenenyl)phthalimide (114.8 mg, 0.380 mmol) in dry CH_2Cl_2 (950 µl). The reaction mixture was stirred at room temperature for 8 d. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **47** (5 mg, 4%) and **46** (6 mg, 5%) as yellowish syrups. Data for **47**: R_f (1:3 EtOAc/hexane): 0.47. $[\alpha]^{20}_D$: –18.4 (*c* 0.25, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.62–7.18 (m, 25H, Ar), 5.71 (s, 1H, H-1), 4.92 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.68 (d, 1H, J_{AB} = 12.4 Hz, CH_2Ph), 4.65 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.55 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.54 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.48 (d, 1H, J_{AB} = 12.4 Hz, CH_2Ph), 4.35 (m, 1H, H-5), 4.17 (dd, 1H, $J_{3,4}$ = 8.8, $J_{2,3}$ = 4.4 Hz, H-3), 4.08 (d, 1H, $J_{2,3}$ = 4.4 Hz, H-2), 3.93 (dd, 1H, $J_{3,4}$ = 8.8, $J_{4,5}$ = 9.6 Hz, H-4), 3.84 (dd, 1H, $J_{6a,b}$ = 11.2, $J_{5,6a}$ = 4.8 Hz, H-6a), 3.72 (dd, 1H, $J_{6a,b}$ = 11.2, $J_{5,6b}$ = 2 Hz, H-6b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.7, 138.5, 138.4, 138.0 (C, Ar), 135.2,132.0, 129.4, 129.2, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6 (CH, Ar), 88.3 (C-1), 79.5 (C-3), 76.0 (C-4), 75.4, 73.5 (2CH_2Ph), 73.2 (C-5), 71.7 (CH_2Ph), 69.2 (C-6), 50.8 (C-2). Anal. Calcd for $C_{39}H_{38}O_4SeS$: 68.71 C, 5.62 H, 4.70 S. Found: 68.68 C, 5.64 H, 4.69 S. Data for **46**: R_f (1:3 EtOAc/hexane): 0.40. $[\alpha]^{20}_D$: –9.1 (*c* 0.30, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.69–7.13 (m, 25H, Ar), 5.11 (d, 1H, J_{AB} = 10 Hz, CH_2Ph), 4.89 (d, 1H, J_{AB} = 10 Hz, CH_2Ph), 4.81 (d, 1H, J_{AB} = 10.8 Hz, CH_2Ph), 4.61–4.48 (m, 4H, H-1, CH_2Ph), 3.75–3.58 (m, 4H, H-3,5,6a,b), 3.38 (m, 1H, H-4), 3.10 (dd, 1H, $J_{1,2}$ = $J_{2,3}$ = 10.8 Hz, H-2). ^{13}C NMR

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($CDCl_3$, 100.6 MHz) δ in ppm: 138.7, 138.5, 138.3, 138.0 (C, Ar), 136.2, 132.8, 129.3,128.9, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.8, 127.7 (CH, Ar), 87.4 (C-1), 84.4 (C-5), 79.8 (C-3), 79.2 (C-4), 76.2, 75.2, 73.6 ($3CH_2Ph$), 69.1 (C-6), 49.8 (C-2). Anal. Calcd for $C_{39}H_{38}O_4SeS$: 68.71 C, 5.62 H, 4.70 S. Found: 68.70 C, 5.60 H, 4.72 S.

Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-phenylselenenyl-1-thio-*β*-D-allopyranoside (48): The title compound was prepared following the general procedure for the selenonium-induced cyclization starting from **9** (1:2 *Z*/*E* ratio) (100 mg, 0.190 mmol), *N*-(phenylselenenyl)phthalimide (114.8 mg, 0.380 mmol), and ZnI_2 (121.3 mg, 0.380 mmol) in dry CH_2Cl_2 (950 μl). The reaction mixture was stirred from –78 to 10ºC for 24 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **48** (20 mg, 15%) as a yellowish syrup. R_f (1:3 EtOAc/hexane): 0.41. $[\alpha]^{20}_D$: –15.7 (*c* 0.90, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.61–7.12 (m, 25H, Ar), 5.23 (d, 1H, $J_{1,2}$ = 11.2 Hz, H-1), 4.99–4.44 (m, 6 H, $3CH_2Ph$), 4.30 (m, 1H, H-3), 4.14 (m, 1H, H-5), 3.77-3.67 (m, 3H, H-4,6a,b), 3.37 (dd, 1H, $J_{1,2}$ = 11.2, $J_{2,3}$ = 2.4 Hz, H-2). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.7, 138.6, 138.4, 138.0 (C, Ar), 134.6, 132.1, 129.3, 128.8, 128.7, 128.5, 128.4, 128.1, 128.3, 127.9, 127.7 (CH, Ar), 85.6 (C-1), 77.8 (C-3), 77.4 (C-4), 75.7 (C-5), 75.6, 73.6, 72.4 ($3CH_2Ph$), 69.6 (C-6), 50.6 (C-2). Anal. Calcd for $C_{39}H_{38}O_4SeS$: 68.71 C, 5.62 H, 4.70 S. Found: 68.73 C, 5.65 H, 4.73 S.

Phenyl 6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-3,4-*O*-isopropylidene-2-phenylselenenyl-1-thio-*α*-D-talopyranoside (49) and Phenyl 6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-D-galactal (50): The title compounds were prepared following the general procedure for the selenonium-induced cyclization starting from **11** (1:35 *Z*/*E* ratio) (160 mg, 0.299 mmol), *N*-(phenylselenenyl)phthalimide (135.6 mg, 0.449 mmol), and ZnI_2 (143.2 mg, 0.449 mmol) in dry CH_2Cl_2 (1.5 mL). The reaction mixture was stirred from –78 to –50ºC for 9 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **49** (41.3 mg, 33%) and **50** (76.1 mg, 60%) as yellowish syrups. Data for **49**: R_f (1:3 EtOAc/hexane): 0.5. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.79–7.18 (m, 20 H, Ar), 5.48 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.67 (m, 1H, H-3), 4.28 (dd, 1H, $J_{3,4}$ = 7.6, $J_{4,5}$ = 1.6 Hz, H-4), 3.99–3.90 (m, 1H, H-5), 3.82–3.72 (m, 2H, H-6a,b), 3.08 (dd, 1H, $J_{1,2}$ = 9.6, $J_{2,3}$ = 2.8 Hz, H-2), 1.40, 1.33 (s, 6 H, $2CH_3$), 1.02 (s, 9 H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.1–136.4 (C, CH, Ar), 136.0–127.6 (CH, Ar), 109.8 (C_{ketal}), 88.1 (C-1), 75.8 (C-3), 74.3 (C-4), 70.4 (C-5), 62.7 (C-6), 44.3 (C-2), 27.0, (CH_3, *t*-Bu), 26.4, 25.5 (2 CH_3), 19.5 (C, *t*-Bu). Data for **50**: R_f (CH_2Cl_2): 0.55. Spectroscopic data are consistent with those reported.[178]

[178] Broddefalk, J.; Bergquist, K-E.; Kihlberg, J. *Tetrahedron*, **1998**, *54*, 12047.

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Reductive elimination: galactal **50** was also prepared following the general procedure for reductive elimination starting from **26** (200 mg, 0.30 mmol), NaOAc (36 mg, 0.42 mmol), and Zn–Cu couple (200 mg) in a mixture of THF (500 μL) and acetic acid (24 μL). The reaction mixture was stirred at 0°C for 1 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **50** (110 mg, 86%) as a colourless syrup.

Phenyl 6-(*O*-*tert*-butyldiphenylsilyl)-2-deoxy-3,4-*O*-isopropylidene-2-phenylselenenyl-1-thio-*β*-D-allopyranoside (51) and Phenyl 6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-D-allal (52): The title compounds were prepared following the general procedure for the selenonium-induced cyclization starting from **13** (1:33 *Z*/*E* ratio) (443 mg, 0.854 mmol), *N*-(phenylselenenyl)phthalimide (516.1 mg, 1.71 mmol), and ZnI_2 (545 mg, 1.71 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was stirred from –78 to –30ºC for 6.5 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **51** (90 mg, 15%) and **52** (270 mg, 74%) as a yellowish syrups. Data for **51**: R_f (1:3 EtOAc/hexane): 0.86. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.72–7.18 (m, 20H, Ar), 5.12 (d, 1H, $J_{1,2}$ = 11.2 Hz, H-1), 4.31 (dd, 1H, $J_{2,3}$ = 4.0, $J_{3,4}$ = 4.0 Hz, H-3), 3.84 (m, 1H, H-4), 3.76 (dd, 1H, $J_{5,6a}$ = 6.2, $J_{6a,b}$ = 11.4 Hz, H-6a), 3.65–3.61 (m, 1H, H-5), 3.55 (dd, 1H, $J_{1,2}$ = 11.2, $J_{2,3}$ = 4.0 Hz, H-2), 1.39,1.36 (s, 6H, $2CH_3$), 1.05 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.0–127.4 (C, CH, Ar), 109.4 (C_{ketal}), 86.0 (C-1), 79.6 (C-5), 75.4 (C-3), 71.5 (C-4), 64.0 (C-6), 43.4 (C-2), 28.5, 26.2 ($2CH_3$), 27.0 (CH_3, *t*-Bu), 19.4 (C, *t*-Bu). Data for **52**: R_f (1:3 EtOAc/hexane): 0.78. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.72–7.19 (m, 25H, Ar), 6.64 (d, 1H, $J_{1,2}$ = 5.6 Hz, H-1), 5.08 (dd, 1H, $J_{1,2}$ = 5.6, $J_{2,3}$ = 5.4 Hz, H-2), 4.44 (dd, 1H, $J_{2,3}$ = 5.4, $J_{3,4}$ = 5.2 Hz, H-3), 4.10 (m, 1H, H-4), 4.03 (dd, 1H, $J_{5,6a}$ = 1.2, $J_{6a,b}$ = 11.5 Hz, H-6a), 3.93 (dd, 1H, $J_{5,6b}$ = 5.2, $J_{6a,b}$ = 11.5 Hz, H-6b), 3.50–3.47 (m, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 148.5 (C-1), 135.0–127.4 (C, CH, Ar), 108.4 (C_{ketal}), 98.7 (C-2), 76.4 (C-5), 70.2 (C-4), 67.8 (C-3), 63.0 (C-6), 28.7, 26.0 ($2CH_3$), 27.0 (CH_3, *t*-Bu), 19.5 (C, *t*-Bu).

Phenyl 2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-phenylselenenyl-1-thio-D-*glycero*-*α*-D-*talo*-heptopyranoside (53): The title compound was prepared following the general procedure for the selenonium-induced cyclization starting from **17** (0:1 *Z*/*E* ratio) (75 mg, 0.210 mmol), *N*-(phenylselenenyl)phthalimide (130 mg, 0.420 mmol), and ZnI_2 (134 mg, 0.420 mmol) in dry CH_2Cl_2 (3.6 mL). The reaction mixture was stirred from –65 to –10ºC for 3 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **53** (64 mg, 60%) as a yellowish syrup. R_f (1:3 EtOAc/hexane): 0.54. $[\alpha]^{20}_D$: +45.7 (*c* 0.01, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.78–7.24 (m, 10 H, Ar), 5.57 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.73 (dd, 1H, $J_{2,3}$ = 2.4, $J_{3,4}$

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= 7.8 Hz, H-3), 4.36 (dd, 1H, $J_{3,4}$ = 7.8, $J_{4,5}$ = 1.8 Hz, H-4), 4.20–4.16 (m, 1H, H-6), 3.94 (dd, 1H, $J_{6,7a}$ = 6.0, $J_{7a,b}$ = 8.5 Hz, H-7a), 3.85 (dd, 1H, $J_{6,7b}$ = 4.2, $J_{7a,b}$ = 8.5 Hz, H-7b), 3.60 (dd, 1H, $J_{4,5}$ = 1.8, $J_{5,6}$ = 8.2 Hz, H-5), 3.05 (dd, 1H, $J_{1,2}$ = 10.0, $J_{2,3}$ = 2.4 Hz, H-2), 1.48–1.33 (s, 12H, 4CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 136.0, 134.6, 131.8, 131.7, 129.4, 129.1, 128.9, 128.8,127.5 (C, CH, Ar), 110.0, 109.7 (C_{ketal}), 88.3 (C-1), 75.7 (C-5), 74.0 (C-6), 73.3 (C-4), 70.5 (C-3), 67.2 (C-7), 43.8 (C-2), 27.2, 26.3, 25.4, 25.3 (4CH_3). Anal. Calcd for $C_{25}H_{30}O_5SeS$: 57.57 C, 5.80 H, 6.15 S. Found: 57.59 C, 5.78 H, 6.15 S.

Methyl (2'-deoxy-3',4':6',7'-di-*O*-isopropylidene-2'-phenylselenenyl-D-*glycero*-α/*β*-D-*talo*-heptopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (55a): The title compound was prepared following the general procedure for glycosylation starting from **53** (51 mg, 0.098 mmol), glycosyl acceptor **31a** (72 mg, 0.196 mmol), NIS (53 mg, 0.216 mmol), TfOH (2 µl, 0.020 mmol), and 4Å MS (100 mg) in 1:3 toluene–dioxane (400 µl). The reaction mixture was stirred at 0ºC for 1 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **55a** (52 mg, 68%) as an inseparable 15:1 α/*β* mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.39. Anal. Calcd for $C_{40}H_{48}O_{11}Se$: 61.30 C, 6.17 H. Found: 61.25 C, 6.20 H. Data for **55a***α*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.80–7.19 (m, 15H, Ar), 5.57 (s, 1H, H-7), 5.21 (d, 1H, $J_{1',2'}$ = 7.6 Hz, H-1'), 4.88 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 4.84 (d, 1H, J_{AB} = 12.4 Hz, CH_2Ph), 4.78 (d, 1H, J_{AB} = 12.4 Hz, CH_2Ph), 4.77 (dd, 1H, $J_{3',4'}$ = 7.6 Hz, $J_{2',3'}$ = 2.4, H-3'), 4.37 (dd, 1H, $J_{3',4'}$ = 7.6, $J_{4',5'}$ = 1.6 Hz, H-4'), 4.32 (dd, 1H, $J_{7'a,b}$ = 8.5 Hz, $J_{6',7'a}$ = 3.4, H-7'a), 4.27 (dd, 1H, $J_{6a,b}$ = 10.0 Hz, $J_{5,6a}$ = 4.8, H-6a), 4.24–4.20 (m, 1H, H-6'), 4.03 (dd, 1H, $J_{7'a,b}$ = 8.5 Hz, $J_{6',7'b}$ = 6.0, H-7'b), 4.00–3.93 (m, 2H, H-2,4), 3.84 (ddd, 1H, $J_{5,6b}$ = 10.0 Hz, $J_{4,5}$ = 9.9, $J_{5,6a}$ = 4.4, H-5), 3.74 (dd, 1H, $J_{5,6b}$ = $J_{6a,b}$ = 10.0 Hz, H-6b), 3.62 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 8.0 Hz, H-3), 3.52 (dd, 1H, $J_{5',6'}$ = 8.5 Hz, $J_{4',5'}$ = 1.6, H-5'), 3.30 (s, 3H, OCH_3), 3.00 (dd, 1H, $J_{1',2'}$ = 7.0, $J_{2',3'}$ = 2.4 Hz, H-2'), 1.49–1.33 (s, 12H, 4CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.9–130.5 (C, CH, Ar), 134.6–126.3 (CH, Ar), 109.9, 109.5 (C_{ketal}), 101.6 (C-7), 99.3 (C-1'), 98.0 (C-1), 82.3 (C-3),76.1 (C-3'), 75.7 (C-2,4), 74.5 (CH_2Ph), 74.3 (C-4'), 73.6 (C-6'), 70.5 (C-5'), 69.4 (C-6), 67.2 (C-7'), 62.6 (C-5), 55.5 (OCH_3), 45.0 (C-2'), 27.4-25.1 (4CH_3).

Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-phenylselenenyl-*α*/*β*-D-gulopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (56a): The title compound was prepared following the general procedure for glycosylation in 1:3 toluene–dioxane. Data obtained from the crude. Selected signals for **56a***β*: R_f (1:3 EtOAc/hexane): 0.30. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.83–7.16 (m, 30H, Ar), 5.54 (s, 1H, H-7), 5.00 (d, 1H,

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$J_{1',2'}$= 9.0 Hz, H-1'), 4.97–4.64 (m, 10H, 4CH_2Ph, H-1, H-2'), 4.23–3.80 (m, 3H, H-3,6a, H-5'), 3.80–3.45 (m, 7H, H-2,4,5,6b, H-3',6'a,b), 3.38–3.30 (m, 4H, OCH_3, H-4').

Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-phenylselenenyl-*α*/*β*-D-glucopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (57a): The title compound was prepared following the general procedure for glycosylation in 1:3 toluene–dioxane. Data obtained from the crude. Selected signals for **57a***α*: R_f (1:3 EtOAc/hexane): 0.30. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.69–7.13 (m, 30H, Ar), 5.57 (s, 1H, H-7), 4.98–4.28 (m, 12H, 4CH_2Ph, H-1,2, H-1',2'), 4.29 (dd, 1H, $J_{6a,b}$ = 9.6, $J_{5,6a}$ = 4 Hz, 1H, H-6a), 4.09 (m, 1H, H-3), 3.93–3.36 (m, 8H, H-4,5,6b, H-3',4',5',6'a,b), 3.36 (s, 3H, OCH_3). Selected signals for **57a***β*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.69–7.13 (m, 30H, Ar), 5.52 (s, 1H, H-7), 5.02 (d, 1H, $J_{1',2'}$ = 8.9 Hz, H-1'), 4.98–4.28 (m, 11H, 4CH_2Ph, H-1,2, H-2'), 4.29 (dd, 1H, $J_{6a,b}$ = 9.6, $J_{5,6a}$ = 4 Hz, H-6a), 4.09 (m, 1H, H-3), 3.93–3.36 (m, 8H, H-4,5,6b, H-3',4',5',6'a,b), 3.44 (s, 3H, OCH_3).

Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-phenylselenenyl-*α*/*β*-D-mannopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (58a): The title compound was prepared following the general procedure for glycosylation in 1:3 toluene–dioxane. Data obtained from the crude. Selected signals for **58a***α*: R_f (1:3 EtOAc/hexane): 0.30. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50–7.18 (m, 30H, Ar), 5.51 (s, 1H, H-7), 5.09 (s, 1H, H-1'), 4.98–4.34 (m, 10H, 4CH_2Ph, H-1, H-2'), 4.24 (dd, 1H, $J_{6a,b}$ = 9.6, $J_{5,6a}$ = 4 Hz, H-6a), 4.14 (m, 1H, H-5'), 3.92–3.63 (m, 7H, H-2,4,5,H-6b, H-4',6'a,b), 3.59 (m, 1H, H-3), 3.45 (s, 3H, OCH_3), 3.41 (m, 1H, H-3').

Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-phenylselenenyl-*α*/*β*-D-allopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (59a): The title compound was prepared following the general procedure for glycosylation in 1:3 toluene–dioxane. Data obtained from the crude. Selected signals for **59a***β*: R_f (1:3 EtOAc/hexane): 0.30. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.61–7.12 (m, 30H, Ar), 5.53 (s, 1H, H-7), 5.33 (d, 1H, $J_{1',2'}$ = 8.8 Hz, H-1'), 4.92 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 4.98–4.49 (m, 8H, 4CH_2Ph), 4.29 (dd, 1H, $J_{6a,b}$ = 9.5, $J_{5,6a}$ = 4.4 Hz, H-6a), 4.28–3.59 (m, 1H, H-2,3,4,5,6b, H-2',3',4',5',6'a,b), 3.39 (s, 3H, OCH_3).

Methyl [(6'-*O*-*tert*-butyldiphenylsilyl)-2'-deoxy-3',4'-*O*-isopropylidene-2'-phenylselenenyl-*α*/*β*-D-allopyranosyl]-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (60a): The title compound was prepared following the general procedure for glycosylation starting from **51** (90 mg, 0.130 mmol), glycosyl acceptor **31a** (97 mg, 0.260 mmol), NIS (71 mg, 0.286 mmol), TfOH (2.5 µl, 0.026 mmol), and 4Å MS (180 mg)

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in 1:3 toluene–dioxane (520 µl). The reaction mixture was stirred from 0ºC to room temperature for 2 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **60a** (88 mg, 70%) as an inseparable 2:3 α/*β* mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.33. Anal. Calcd for $C_{52}H_{60}O_{10}SeSi$: 65.60 C, 6.35 H. Found: 65.57 C, 6.38 H. Data for **60a***α*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.85–7.23 (m, 25H, Ar), 5.56 (s, 1H, H-7), 5.35 (d, 1H, $J_{1',2'}$ = 8.8 Hz, H-1'), 5.04 (d, 1H, J_{AB} = 10.2, CH_2Ph), 4.91 (d, 1H, $J_{1,2}$ = 3.6, H-1), 4.81 (d, 1H, J_{AB} = 10.2, CH_2Ph), 4.55 (dd, 1H, $J_{2',3'} = J_{3',4'}$ = 4.0 Hz, H-3'), 4.34–4.30 (m, 1H, H-6a), 4.13–4.07 (m, 1H, H-3), 4.01–3.55 (m, 5H, H-2,5,6b, H-4',5'), 3.50–3.39 (m, 5H, OCH_3, H-4, H-2'), 1.41–1.24 (m, 6H, $2CH_3$), 1.06 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.7–126.2 (C, CH, Ar), 109.7 (C_{ketal}), 102.7 (C-1'), 101.5 (C-7), 100.7 (C-1), 82.8 (C-4), 79.1 (C-5'), 78.5–77.1 (C-2,3, CH_2Ph), 75.3 (C-3'), 72.0 (C-4'), 69.5, 69.4 (C-6, C-6'), 63.8 (C-5), 55.6 (OCH_3), 44.7 (C-2'), 29.8–23.9 ($2CH_3$, CH_3, *t*-Bu), 19.5 (C, *t*-Bu). Data for **60a***β*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.85–7.23 (m, 25H, Ar), 5.57 (s, 1H, H-7), 5.15 (d, 1H, $J_{1',2'}$ = 9.0 Hz, H-1'), 5.11 (d, 1H, J_{AB} = 10.6, CH_2Ph), 4.98 (d, 1H, $J_{1,2}$ = 3.6, H-1), 4.86 (d, 1H, J_{AB} = 10.6, CH_2Ph), 4.47 (dd, 1H, $J_{2',3'}$ = 4.0, = 4.0 Hz, H-3'), 4.34–4.30 (m, 1H, H-6a), 4.18 (dd, 1H, $J_{1',2'}$ = 9.0 Hz, $J_{2',3'}$ = 4.0, H-2'), 4.13–4.07 (m, 1H, H-3), 4.01–3.55 (m, 5H, H-2,5,6b, H-4',5'), 3.50–3.39 (m, 4H, OCH_3, H-4), 1.41–1.24 (s, 6H, $2CH_3$), 1.06 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.7–126.2 (C, CH, Ar), 109.2 (C_{ketal}), 102.2 (C-1'), 101.5 (C-7), 100.4 (C-1), 82.9 (C-4), 79.1 (C-5'), 78.5–77.1 (C-2,3, CH_2Ph), 75.4 (C-3'), 71.6 (C-4'), 69.4, 69.3 (C-6, C-6',), 63.6 (C-5), 55.4 (OCH_3), 44.7 (C-2'), 29.8–23.9 ($2CH_3$, CH_3, *t*-Bu), 19.5 (C, *t*-Bu).

Phenylselenenylmethyl phenyl sulfone (62): A dispersion of diphenyl diselenide (1.66 g, 4.2 mmol) and NaH 60 % (170 mg, 4.2 mmol) in dry THF (14 ml) was heated under reflux for 3 h. Bromomethyl phenyl sulfone (1 g, 4.2 mmol) was then added and the resulting dispersion was refluxed for 3 h. The reaction was quenched by adding MeOH. After concentration, the residue was dissolved in CH_2Cl_2 and washed with water. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **62** (709 mg, 54%) as an orange syrup.[94] R_f (1:3 EtOAc/hexane): 0.24. FT–IR (neat) ν in cm^{-1}: 3058, 2925, 1578, 1475, 1439, 1308, 1150. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.92–7.21 (m, 10H, Ar), 4.29 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2, 135.7, 134.2, 134.1, 129.5, 129.3, 128.9, 128.7 (C, CH, Ar), 51.4 (CH_2). GC–EIMS (*m/z*): 312 M^+. Anal. Calcd for $C_{13}H_{12}O_2SSe$: 50.16 C, 3.89 H, 10.30 S. Found: 50.18 C, 3.92 H, 11.04 S.

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Bromomethyl phenyl selenide (66): Using a slightly modification of the method reported by Huang and Duan,[97] diphenyl diselenide (1.5 g, 4.8 mmol) in EtOH (12 ml) was treated with KBH_4 (778 mg, 14.2 mmol) in CH_2Br_2 (3 ml) from 0ºC to room temperature for 6 h. Distillation on a Kugelrohr apparatus afforded product **66** (174 mg, 7%) as an almost colourless oil. R_f (hexane): 0.31. bp: 115–120ºC/0.55 mmHg [lit.[98] 84–85ºC/0.17 mmHg]. FT–IR (neat) ν in cm^{-1}: 3057, 2925, 1736. ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.62–7.25 (m, 5H, Ar), 4.71 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 133.6 (C, Ar), 129.5, 128.7, 128.5 (CH, Ar), 25.5 (CH_2). Anal. Calcd for C_7H_7BrSe: 33.75 C, 2.83 H. Found: 33.63 C, 2.82 H.

Diphenyl (phenylselenenylmethyl)phosphine oxide (67): Ethyl diphenylphosphinite (330 μL, 1.5 mmol), chloromethyl phenyl selenide **65** (257 mg, 1.25 mmol), and TBAI (470 mg, 1.25 mmol) were heated together under argon at 150ºC for 4.5 h. The crude was purified by radial chromatography (from 1: 1 EtOAc/hexane to EtOAc) to afford **67** (182 mg, 39%) as a white crystalline solid. R_f (EtOAc): 0.36. mp: 121–123ºC. FT–IR (KBr) ν in cm^{-1}: 3048, 2971, 2916, 1573, 1475, 1435, 1190. ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.78–7.17 (m, 15H, Ar), 3.60 (s, 2H, $J_{H,P}$ = 7.6 Hz, CH_2SePh). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 133.6, 132.7, 132.2, 131.7, 131.4, 128.8, 128.7, 127.9 (C, CH, Ar), 25.6 (d, $J_{C,P}$ = 69 Hz, CH_2SePh). ^{31}P NMR ($CDCl_3$, 162 MHz) δ in ppm: 28.8 (s, P=O). Anal. Calcd for $C_{19}H_{17}OPSe$: 61.47 C, 4.62 H. Found: 61.23 C, 4.60 H.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-phenylselenenyl-D-*arabino*-hex-1-enitol (68): As described in the general procedure for the olefination of furanoses, method C, a solution of 2,3,5-tri-*O*-benzyl-*β*-D-arabinofuranose **1** (3.5 g, 8.3 mmol) in dry THF (16.6 mL) was olefinated by reaction with methyltriphenylphosphonium bromide (6 g, 16.5 mmol) in dry THF (33 mL), PhSeBr (3.96 g, 16.8 mmol) in dry THF (33.6 mL), and 1.6 M *n*-BuLi in hexane (23 mL, 36.8 mmol). After 14 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by column chromatography (1: 3 EtOAc/hexane) to afford **68** (1.43 g, 30%) as an inseparable 1:7 *Z*/*E* mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.29. FT–IR (neat) ν in cm^{-1}: 3472, 3061, 3029, 2864, 1951, 1875, 1809, 1606, 1558. Anal. Calcd for $C_{33}H_{34}O_4Se$: 69.10 C, 5.97 H. Found: 69.38 C, 5.99 H. Data for **68***E*: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.49–7.19 (m, 20H, Ar), 6.69 (d, 1H, $J_{1,2}$ = 15.6 Hz, H-1), 5.98 (dd, 1H, $J_{1,2}$ =15.6 Hz, $J_{2,3}$ = 7.6 Hz, H-2), 4.64 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.53 (d, 2H, J_{AB} = 8 Hz, CH_2Ph), 4.49 (s, 2H, CH_2Ph), 4.37 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.14 (dd, 1H, $J_{2,3}$ = 7.6 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 3.99 (m, 1H, H-5), 3.58 (m, 3H, H-4,6a,b), 2.71 (d, 1H, $J_{5,OH}$ = 5.6 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.1–137.8 (C, Ar), 133.2–127.8 (CH, Ar), 132.0 (C-1), 123.6 (C-2), 80.6 (C-4), 80.1 (C-3), 74.4, 73.5 ($2CH_2Ph$), 70.9 (C-6, CH_2Ph), 70.3

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(C-5). Selected signals for **68***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.79 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 6.22 (dd, 1H, $J_{1,2} = J_{2,3}$ = 9.2 Hz, H-2), 2.89 (d, 1H, $J_{5,OH}$ = 4.4 Hz, OH).

(3*Z*,5*E*,2*S*/3*Z*,5*Z*,2*S*)-1,4-Bis(benzyloxy)-6-phenylselenenyl-hexa-3,5-dien-2-ol (69): As described in the general procedure for the olefination of furanoses, method B, a solution of 2,3,5-tri-*O*-benzyl-*β*-D-arabinofuranose **1** (2.20 g, 5.2 mmol) in dry THF (10.5 mL) was olefinated by reaction with methyltriphenylphosphonium bromide (3.81 g, 10.5 mmol) in dry THF (73 mL), PhSeCl (1 g, 5.2 mmol) in dry THF (18 mL), and 1.6 M *n*-BuLi in hexane (7.2 mL, 11.5 mmol) for 17 h under refluxing conditions. The crude was purified by column chromatography (1: 3 EtOAc/hexane) to afford **69** (1.33 g, 55%) as an inseparable 3:2 3*Z*,5*Z*/3*Z*,5*E* mixture as an orange syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.18. FT–IR (neat) ν in cm^{-1}: 3383, 3063, 3030, 2862, 1952, 1687, 1578, 1438. Anal. Calcd for $C_{26}H_{26}O_3Se$: 67.09 C, 5.63 H. Found: 67.34 C, 5.65 H. Data for **69***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.58–7.28 (m, 15H, Ar), 6.99 (d, 1H, $J_{5,6}$ = 15.6 Hz, H-6), 6.16 (d, 1H, $J_{5,6}$ = 15.6 Hz, H-5), 4.96 (d, 1H, $J_{2,3}$ = 8.4 Hz, H-3), 4.89–4.82 (m, 2H, CH_2Ph), 4.78–4.69 (m, 1H, H-2), 4.51 (s, 2H, CH_2Ph), 3.39–3.28 (m, 2H, H-1a,b), 2.22 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 154.3–126.9 (C, CH, Ar, C-4,6), 123.1 (C-5), 115.6 (C-3), 74.0–73.1 ($2CH_2Ph$, C-1), 65.8 (C-2). Data for **69***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.58–7.28 (m, 15H, Ar), 6.79 (d, 1H, $J_{5,6}$ = 10 Hz, H-6), 6.37 (d, 1H, $J_{5,6}$ = 10 Hz, H-5), 5.04 (d, 1H, $J_{2,3}$ = 8.4 Hz, H-3), 4.89–4.82 (m, 2H, CH_2Ph), 4.78–4.69 (m, 1H, H-2), 4.66 (s, 2H, CH_2Ph), 3.39–3.28 (m, 2H, H-1a,b), 2.22 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 154.3–126.9 (C, CH, Ar, C-4,6), 133.7 (C-5), 116.2 (C-3), 74.0–73.1 ($2CH_2Ph$, C-1), 65.1 (C-2).

(*Z*/*E*)-6-*O*-(*tert*-Butyldiphenylsilyl)-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylselenenyl-D-*ribo*-hex-1-enitol (70): As described in the general procedure for the olefination of furanoses, method C, a solution of 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-*α*/*β*-D-ribofuranose **8** (100 mg, 0.233 mmol) in dry THF (500 µL) was olefinated by reaction with methyltriphenylphosphonium bromide (170.1 mg, 0.467 mmol) in dry THF (1 mL), PhSeBr (113.5 mg, 0.467 mmol) in dry THF (1 mL), and KHMDS (209 mg, 1.03 mmol). After 6 d stirring at room temperature, the reaction mixture was quenched and the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **70** (20 mg, 15%) as an inseparable 11:1 *Z*/*E* mixture as a colourless syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.45. Anal. Calcd for $C_{31}H_{38}O_4SeSi$: 64.01 C, 6.58 H. Found: 64.00 C, 6.60 H. Data for **70***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.71–7.26 (m, 15H, Ar), 6.80 (dd, 1H, $J_{1,2}$ = 15.2 Hz, $J_{1,3}$ = 1.2 Hz, H-1), 6.11 (dd, 1H, $J_{1,2}$ = 15.2 Hz, $J_{2,3}$ = 7.2 Hz, H-2), 4.75 (m, 1H, H-3), 4.13 (dd, 1H, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 6 Hz, H-4), 3.88–3.80 (m, 2H, H-6a,b), 3.67 (m, 1H, H-5), 2.51 (d, 1H, $J_{5,OH}$ = 5.6 Hz,

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OH), 1.36, 1.33 (s, 6H, $2CH_3$), 1.07 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 136.0–127.6 (C, CH, Ar, C-1,2), 109.3 (C_{ketal}), 79.3 (C-3), 77.7 (C-4), 70.2 (C-5), 65.7 (C-6), 28.2, 25.8 ($2CH_3$), 27.2 (CH_3, *t*-Bu), 19.7 (C, *t*-Bu). Data for **70***Z*: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.71–7.26 (m, 15H, Ar), 6.77 (dd, 1H, $J_{1,2}$ = 9.6 Hz, $J_{1,3}$ = 0.8 Hz, H-1), 6.15 (dd, 1H, $J_{1,2}$ = 9.6 Hz, $J_{2,3}$ = 8.4 Hz, H-2), 5.09 (m, 1H, H-3), 4.21 (dd, 1H, $J_{3,4}$ = 8.8 Hz, $J_{4,5}$ = 6.4 Hz, H-4), 3.88–3.80 (m, 2H, H-6a,b), 3.72 (m, 1H, H-5), 2.61 (d, 1H, $J_{5,OH}$ = 5.2 Hz, OH), 1.42, 1.37 (s, 6H, $2CH_3$), 1.07 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 136.0–127.6 (C, CH, Ar), 129.6 (C-2), 126.1 (C-1), 109.5 (C_{ketal}), 77.8 (C-4), 77.2 (C-3), 70.7 (C-5), 65.5 (C-6), 28.2, 25.8 ($2CH_3$), 27.2 (CH_3, *t*-Bu), 19.7 (C, *t*-Bu).

(3*E*,5*E*,2*S*/3*E*,5*Z*,2*S*)-1-Benzyloxy-6-phenylselenenyl-hexa-3,5-dien-2-ol (71) and 4,6-Di-*O*-benzyl-1,2,3-trideoxy-1,1-bis(phenylselenenyl)-D-*erythro*-hex-1-enitol (72): As described in the general procedure for the olefination of furanoses, method C, a solution of **16** (80 mg, 0.25 mmol) in dry THF (500 μL) was olefinated by reaction with methyltriphenylphosphonium bromide (186 mg, 0.51 mmol) in dry THF (1 mL), PhSeBr (124 mg, 0.51 mmol) in dry THF (1 mL), and 1.6 M *n*-BuLi in hexane (0.7 mL, 1.12 mmol). After 32 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **71** (12 mg, 13%) as an inseparable 1:1 3*E*,5*E*/3*E*,5*Z* mixture and **72** (8 mg, 5%) as orange syrups. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.21. Data for **71***E*: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50–7.26 (m, 10H, Ar), 6.71–6.31 (m, 3H, H-4,5,6), 5.57 (dd, 1H, $J_{3,4}$ = 15 Hz, $J_{2,3}$ = 6 Hz, H-3), 4.59 (m, 2H, CH_2Ph), 4.42 (m, 1H, H-2), 3.56, 3.39 (m, 2H, H-1a,b), 2.47 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.6–123.8 (C, CH, Ar, C-3,4,5,6), 74.0 (CH_2Ph), 71.3 (C-2), 70.3 (C-1). Data for **71***Z*: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50–7.26 (m, 10H, Ar), 6.71–6.31 (m, 3H, H-4,5,6), 5.79 (dd, 1H, $J_{3,4}$ = 14 Hz, $J_{2,3}$ = 6 Hz, H-3), 4.57 (m, 2H, CH_2Ph), 4.38 (m, 1H, H-2), 3.56, 3.39 (m, 2H, H-1a,b), 2.51 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.6–123.8 (C, CH, Ar, C-3,4,5,6), 74.1 (CH_2Ph), 71.0 (C-2), 70.3 (C-1). Data for **72**: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50–7.26 (m, 20H, Ar), 5.57 (m, 1H, H-2), 4.59–4.54 (m, 4H, $2CH_2Ph$), 4.24 (m, 1H, H-5), 3.99 (m, 1H, H-4), 3.64–3.61 (m, 2H, H-6a,b), 2.40 (bs, 1H, OH), 2.31, 2.07 (m, 2H, H-3a,b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 134.6–123.8 (C, CH, Ar, C-1), 100.2 (C-2), 82.1 (C-5), 78.9 (C-4), 73.6, 71.7 ($2CH_2Ph$), 70.3 (C-6), 38.6 (C-3).

(*Z*/*E*)-4,6-Di-*O*-benzyl-1,2,3-trideoxy-1-phenylselenenyl-D-*erythro*-hex-1-enitol (73): As described in the general procedure for the olefination of furanoses, method C, a solution of **16** (80 mg, 0.25 mmol) in dry THF (500 μL) was olefinated by reaction with diphenyl methylphosphine oxide (112 mg, 0.51 mmol) in dry THF (1 mL), PhSeBr (124 mg, 0.51

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mmol) in dry THF (1 mL), and 1.6 M *n*-BuLi in hexane (0.7 mL, 1.12 mmol). After 31 h stirring at room temperature, the reaction mixture was quenched and the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **73** (40 mg, 34%) as an inseparable 1:1 *Z*/*E* mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.26. Data for **73***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50–7.22 (m, 15H, Ar), 6.51 (d, 1H, $J_{1,2}$ = 15 Hz, H-1), 6.13 (ddd, 1H, $J_{1,2}$ = 15 Hz, $J_{2,3a}$ = $J_{2,3b}$ = 8.4 Hz, H-2), 4.67–4.48 (m, 4H, $2CH_2Ph$), 3.86 (m, 1H, H-4), 3.70–3.51 (m, 3H, H-5,6a,b), 2.61–2.48 (m, 2H, H-3a,b), 2.41 (d, 1H, $J_{5,OH}$ = 5 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.0 (C-2), 134.6–127.1 (C, CH, Ar), 119.6 (C-1), 78.9 (C-5), 73.7 ($2CH_2Ph$), 71.6 (C-4), 71.1 (C-6), 35.4 (C-3). **73***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50–7.22 (m, 15H, Ar), 6.57 (d, 1H, $J_{1,2}$ = 9 Hz, H-1), 6.16 (ddd, 1H, $J_{1,2}$ = 15 Hz, $J_{2,3a}$ = $J_{2,3b}$ = 8.8 Hz, H-2), 4.67–4.48 (m, 4H, $2CH_2Ph$), 3.86 (m, 1H, H-4), 3.70–3.51 (m, 3H, H-5,6a,b), 2.61–2.48 (m, 2H, H-3a,b), 2.45 (d, 1H, $J_{5,OH}$ = 5.6 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.0 (C-2), 134.6–127.1 (C, CH, Ar, C-1), 78.7 (C-5), 72.6, 72.4 ($2CH_2Ph$), 71.6 (C-4), 71.2 (C-6), 32.1 (C-3).

(2*R*,3*S*,4*S*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(phenylselenenylmethyl) tetrahydrofuran (74): The title compound was prepared following the general procedure for the iodonium-induced cyclization, method C starting from **68** (1:9 *Z*/*E* ratio) (50 mg, 0.09 mmol) in dry Et_2O (2 mL), 30% KH (41 mg, 0.31 mmol) in dry Et_2O (1 mL), and I_2 (66.4 mg, 0.26 mmol) in dry Et_2O (1 mL). The reaction mixture was stirred from –78ºC to room temperature for 20 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **74** (5 mg, 10%) as a yellowish syrup. R_f (1:4 EtOAc/hexane): 0.31. Spectroscopic data are consistent with those reported.[34c]

(2*E*,4*S*,5*R*)-4,6-Bis(benzyloxy)-5-hydroxy-hex-2-enal (75): *p*-TsOH (1.7 mg, 5 mol %) was added to a solution of **68** (1:7 *Z*/*E* ratio) (114.5 mg, 0.20 mmol) in dry $CHCl_3$ (2 mL) at –60ºC. The reaction mixture was allowed to warm to room temperature for 12 h. The crude was diluted with $CHCl_3$ and washed with aqueous saturated $NaHCO_3$ and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **75** (16.4 mg, 25%) as a colourless syrup.[114] R_f (1:3 EtOAc/hexane): 0.10. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 9.60 (d, 1H, $J_{1,2}$ = 8 Hz, H-1), 7.36–7.26 (m, 10H, Ar), 6.89 (dd, 1H, $J_{2,3}$ = 16 Hz, $J_{3,4}$ = 6 Hz, H-3), 6.34 (dd, 1H, $J_{2,3}$ = 16 Hz, $J_{1,2}$ = 8 Hz, H-2), 4.61 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.52 (s, 2H, CH_2Ph), 4.42 (d, 1H, J_{AB} = 12 Hz, CH_2Ph), 4.20 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 6 Hz, H-4), 3.92 (m, 1H, H-5), 3.59 (m, 2H, H-6a,b), 2.51 (d, 1H, $J_{5,OH}$ = 5.2 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 193.5

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(C-1), 154.0 (C-3), 137.7, 137.4 (C, Ar), 134.1 (C-2), 128.8, 128.7, 128.6, 128.5, 128.3, 128.1 (CH, Ar), 78.7 (C-4), 73.7 (CH_2Ph), 72.5 (C-5), 72.7 (CH_2Ph), 70.3 (C-6).

4,6-*O*-(di-*tert*-Butylsilylene)-1,2-dideoxy-D-*arabino*-hex-1-enitol (80): 1M DIBAL in CH_2Cl_2 (10.4 mL, 10.4 mmol) was added dropwise to a solution of 3,5-*O*-(Di-*tert*-butylsilylene)-D-arabinono-1,4-lactone (1.5 g, 5.20 mmol) in dry CH_2Cl_2 (17 mL) at –78ºC. The reaction mixture was stirred at the same temperature for 3 h. The reaction mixture was quenched with MeOH, and the pH adjusted to 3 by the addition of diluted H_2SO_4. The crude was diluted with CH_2Cl_2 and extracted with water and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. 1.6 M *n*-BuLi in hexane (13 mL, 20.3 mmol) was added dropwise to a suspension of the crude and methyltriphenylphosphonium bromide (3.6 g, 9.92 mmol) in dry THF (83 mL) at –20ºC. The reaction mixture was stirred from –20ºC to room temperature for 25 h and then refluxed for an additional 25 h. The crude was diluted with EtOAc and extracted with aqueous saturated NH_4Cl. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (from hexane to 1:3 EtOAc/hexane) to afford **80** (150 mg, 10% over two steps) as a colourless syrup. R_f (1:3 EtOAc/hexane): 0.33. $[\alpha]^{20}_D$: –16.7 (*c* 1, MeOH). ^{1}H NMR (CD_3OD, 400 MHz) δ in ppm: 6.10 (m, 1H, H-2), 5.35–5.17 (m, 2H, H-1a,b), 4.35 (d, 1H, $J_{2,3}$ = 6.4 Hz, H-3), 4.04 (dd, 1H, $J_{6a,b}$ = 9.6 Hz, $J_{5,6a}$ = 4.4 Hz, H-6a), 3.89–3.74 (m, 3H, H-4,5,6b), 1.03, 1.01 (s, 18H, 2*t*-Bu). ^{13}C NMR (CD_3OD, 100.6 MHz) δ in ppm: 139.9 (C-2), 116.1 (C-1), 82.1 (C-4), 73.6 (C-3), 70.0 (C-6), 67.2 (C-5), 28.2, 27.7 (CH_3, 2*t*-Bu), 23.9, 21.3 (C, 2*t*-Bu). Anal. Calcd for $C_{14}H_{28}O_4Si$: 58.29 C, 9.78 H. Found: 58.31 C, 9.77 H.

(*Z*/*E*)-(2*R*,3*S*)-1,3-Bis(benzyloxy)-4-hexen-2-ol (87): A solution of **86** (78.7 mg, 0.25 mmol), ethyl vinyl ether (121 μL, 1.26 mmol), and catalyst **82** (11 mg, 5 mol %) in dry and degassed CH_2Cl_2 (500 μL) was heated under reflux for 1 h. The solvent was then evaporated and the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **87** (51.7 mg, 66%) as an inseparable 1:6 *Z*/*E* mixture as a colourless syrup.[179] Data obtained from the mixture. R_f (1:3 EtOAc/ hexane): 0.26. for **87***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.33–7.26 (m, 10H, Ar), 8.57 (m, 1H, H-5), 5.47 (m, 1H, H-4), 4.58 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 4.52 (d, 2H, J_{AB} = 4 Hz, CH_2Ph), 4.33 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ph), 3.89 (m, 1H, H-2), 3.79 (dd, 1H, $J_{2,3}$ = 8.4 Hz, $J_{3,4}$ = 5.6 Hz, H-3), 3.61–3.48 (m, 2H, H-1a,b), 2.45 (d, 1H, $J_{2,OH}$ = 2.4 Hz, OH), 1.76 (d, 3H, $J_{5,6}$ = 6.8 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6, 138.2 (C, Ar), 132.3 (C-5), 128.6–127.7 (CH, Ar), 80.7 (C-3), 73.6 (CH_2Ph), 72.6 (C-2), 71.1 (C-1), 70.1 (CH_2Ph), 18.2 (C-

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6). Data for **87***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.33–7.26 (m, 10H, Ar), 5.89 (m, 1H, H-5), 5.47 (m, 1H, H-4), 4.60–4.27 (m, 4H, $2CH_2Ph$), 3.89 (m, 1H, H-2), 3.79 (m, 1H, H-3), 3.61–3.48 (m, 2H, H-1a,b), 2.47 (d, 1H, $J_{2,OH}$ = 4.4 Hz, OH), 1.65 (dd, 3H, $J_{5,6}$ = 6.8 Hz, $J_{4,6}$ = 1.6 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6, 138.2 (C, Ar), 131.1 (C-5), 128.6–127.7 (CH, Ar), 80.7 (C-3), 73.6 (CH_2Ph), 72.7 (C-2), 71.1 (C-1), 70.2 (CH_2Ph), 13.9 (C-6).

Tri-*O*-benzyl-D-allal (90): The title compound was prepared following the general procedure for reductive elimination starting from **22** (75 mg, 0.11 mmol), NaOAc (13 mg, 0.16 mmol), and Zn–Cu couple (72.7 mg) in a mixture of THF (200 μL) and acetic acid (10 μL). The reaction mixture was stirred from 0°C to room temperature for 6 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **90** (48 mg, 100%) as a yellowish syrup. R_f (1:3 EtOAc/hexane): 0.43. Spectroscopic data are consistent with those reported.[180]

3,4,6-Tri-*O*-benzyl-D-glucal (91): The title compound was prepared following the general procedure for reductive elimination starting from **20** (25 mg, 0.04 mmol), NaOAc (4 mg, 0.05 mmol), and Zn–Cu couple (25.1 mg) in a mixture of THF (63 μL) and acetic acid (3 μL). The reaction mixture was stirred from 0°C to room temperature for 3 h. After standard workup, the crude was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **91** (16 mg, 100%) as a colourless syrup. R_f (1:3 EtOAc/hexane): 0.43. Spectroscopic data are consistent with those reported.[181]

3,4,6-Tri-*O*-benzyl-D-galactal (92): The title compound was prepared following the general procedure for reductive elimination starting from **24** (28 mg, 0.04 mmol), NaOAc (5 mg, 0.06 mmol), and Zn–Cu couple (28.4 mg) in a mixture of THF (73 μL) and acetic acid (4 μL). The reaction mixture was stirred from 0 to 10ºC for 4.5 h. After standard workup, the crude was purified by column chromatography (CH_2Cl_2) to afford **92** (16 mg, 89%) as a colourless syrup. R_f (CH_2Cl_2): 0.33. Spectroscopic data are consistent with those reported.[182]

3,4-*O*-Isopropylidene-D-arabinal (93): The title compound was prepared following the general procedure for reductive elimination starting from **27** (55 mg, 0.14 mmol), NaOAc (16 mg, 0.20 mmol), and Zn–Cu couple (93 mg) in a mixture of THF (240 μL) and acetic acid (11 μL). The reaction mixture was stirred at 0°C for 1.5 h. After standard workup, the

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crude was purified by column chromatography (CH_2Cl_2) to afford **93** (20 mg, 91%) as a colourless syrup. R_f (CH_2Cl_2): 0.33. Spectroscopic data are consistent with those reported.[183]

3,5-*O*-(Di-*tert*-butylsilylene)-D-xylono-1,4-lactone (99): Br_2 (1.1 mL, 22 mmol) was added at 20 min intervals to a solution of $BaCO_3$ (5.9 g, 30 mmol) and D-xylose (3 g, 20 mmol) in distilled water (25 mL) at 0ºC. The reaction mixture was stirred at this temperature for 1 h and then at room temperature for 3 h. Solid $Na_2S_2O_3$ was added and the solvent evaporated. The crude was extracted with boiling acetone and the solvent removed. 2,6-Lutidine (4.7 mL, 40 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (6.5 mL, 20 mmol) were added to a solution of the crude yellow syrup in a mixture of dry CH_2Cl_2 (298 mL) and dry DMF (60 mL) at 0ºC. The reaction mixture was stirred at 0ºC for 1 h and then at room temperature for 2 h. The crude was extracted with water and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (from hexane to 1:8 EtOAc/hexane) to afford **99** (2.9 g, 50% over two steps) as a white crystalline solid. R_f (1:8 EtOAc/hexane): 0.23. mp: 90–93ºC. $[\alpha]^{20}_D$: +46.0 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 4.72 (dd, 1H, $J_{2,3}$ = 2.8 Hz, $J_{3,4}$ = 4.4 Hz, H-3), 4.68 (dd, 1H, $J_{4,5a}$ = 7.6 Hz, $J_{3,4}$ = 4.4 Hz, H-4), 4.36–4.28 (m, 3H, H-2,5ab), 3.50 (bs, 1H, OH), 1.05, 0.98 (s, 18H, 2*t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 176.4 (C=O), 77.3 (C-4), 76.0 (C-3), 75.2 (C-2), 62.5 (C-5), 27.4, 26.9 (CH_3, 2*t*-Bu), 22.5, 20.9 (C, 2*t*-Bu). Anal. Calcd for $C_{13}H_{24}O_5Si$: 54.14 C, 8.39 H. Found: 54.11 C, 8.41 H.

3,5-*O*-(Di-*tert*-butylsilylene)-2-*O*-(4-methoxybenzyl)-D-xylono-1,4-lactone (100): 40% DEAD in toluene (2.7 mL, 6.10 mmol) was added dropwise to a solution of **99** (800 mg, 2.77 mmol), PMBOH (781 mg, 5.54 mmol), and Ph_3P (1.62 g, 6.10 mmol) in dry THF (53 mL) at room temperature. The reaction mixture was stirred at the same temperature for 24 h and the solvent evaporated. The residue was purified by column chromatography (from hexane to 1:1 EtOAc/hexane) to afford **100** (730 mg, 64%) as a colourless syrup. R_f (1:1 EtOAc/hexane): 0.56. $[\alpha]^{20}_D$: +46.8 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.30 (d, 2H, *J* = 8.8 Hz, Ar), 6.89 (d, 2H, *J* = 8.8 Hz, Ar), 4.79 (d, 1H, J_{AB} = 12, CH_2Ar), 4.66 (m, 1H, H-3), 4.64 (d, 1H, J_{AB} = 12, CH_2Ar), 4.58 (m, 1H, H-4), 4.32–4.30 (m, 2H, H-5ab), 4.02 (d, 1H, $J_{2,3}$ = 2.4 Hz, H-2), 3.80 (s, 3H, OCH_3), 1.03, 0.95 (s, 18H, 2*t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 173.2 (C=O), 159.8, 128.6 (C, Ar), 130.2, 114.1 (CH, Ar), 80.0 (C-2), 77.5 (C-4), 75.2 (C-3), 72.1 (CH_2Ar), 62.6 (C-5), 55.4 (OCH_3), 27.5, 26.8 (CH_3, 2*t*-Bu), 22.7, 20.7 (C, 2*t*-Bu). Anal. Calcd for $C_{21}H_{32}O_6Si$: 61.73 C, 7.89 H. Found: 61.76 C, 8.01 H.

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3,5-Di-*O*-(*tert*-butyldimethylsilyl)-2-*O*-(4-methoxybenzyl)-D-xylono-1,4-lactone (101): dry TBAF (1.24 g, 3.93 mmol) was added to a solution of **100** (730 mg, 1.79 mmol) in dry THF (45 mL) at room temperature. The reaction mixture was stirred at the same temperature for 15 h. The crude was filtered through a short path of SiO_2 and concentrated under reduced pressure. TBSCl (624 mg, 3.93 mmol) and imidazole (268 mg, 3.93 mmol) were added to a solution of the crude yellow syrup in dry DMF (3.2 mL) at room temperature. The reaction mixture was stirred at the same temperature for 24 h. The crude was diluted with CH_2Cl_2 and extracted with water and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by radial chromatography (from hexane to 1:1 EtOAc/hexane) to afford **101** (443 mg, 50% over two steps) as a colourless syrup. R_f (1:1 EtOAc/hexane): 0.63. $[\alpha]^{20}_D$: +58.3 (*c* 1.4, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.30 (d, 2H, J = 8.8 Hz, Ar), 6.87 (d, 2H, J = 8.8 Hz, Ar), 4.98 (d, 1H, J_{AB} = 11, CH_2Ar), 4.70 (d, 1H, J_{AB} = 11, CH_2Ar), 4.48 (appt, 1H, $J_{2,3} = J_{3,4}$ = 7.4 Hz, H-3), 4.36 (m, 2H, H-2,4), 3.91 (dd, 1H, $J_{5a,b}$ = 11 Hz, $J_{5a,4}$ = 1.6 Hz, H-5a), 3.89 (dd, 1H, $J_{5a,b}$ = 11 Hz, $J_{5b,4}$ = 4 Hz, H-5b), 3.79 (s, 3H, OCH_3), 0.89, 0.84 (s, 18H, 4CH_3), 0.08, 0.02 (s, 18H, 2*t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 174.1 (C=O), 159.6, 127.7 (C, Ar), 130.1, 113.9 (CH, Ar), 79.2 (C-2), 78.2 (C-4), 74.2 (C-3), 72.2 (CH_2Ar), 60.4 (C-5), 55.4 (OCH_3), 25.9, 25.8 (CH_3, 2*t*-Bu), 18.3, 18.1 (C, 2*t*-Bu), –4.5, –4.9, –5.5 (4CH_3). Anal. Calcd for $C_{25}H_{44}O_6Si_2$: 60.44 C, 8.93 H. Found: 60.40 C, 8.96 H.

3,5-Di-*O*-(*tert*-butyldimethylsilyl)-2-*O*-(4-methoxybenzyl)-*α*/*β*-D-xylofuranose (102): 1M DIBAL in CH_2Cl_2 (1.2 mL, 1.21 mmol) was added dropwise to a solution of **101** (400 mg, 0.81 mmol) in dry CH_2Cl_2 (2.6 mL) at –78ºC. The reaction mixture was stirred at the same temperature for 3 h. The reaction mixture was quenched with MeOH, and the pH adjusted to 3 by the addition of diluted H_2SO_4. The crude was diluted with CH_2Cl_2 and extracted with water and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by radial chromatography (from hexane to 1:1 EtOAc/hexane) to afford **102** (384 mg, 96%) as a 2:3 *α*/*β* mixture as a yellowish syrup. Data obtained from the mixture. R_f (1:1 EtOAc/hexane): 0.70. Anal. Calcd for $C_{25}H_{46}O_6Si_2$: 60.20 C, 9.30 H. Found: 60.25 C, 9.27 H. Data for **102***α*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.27 (d, 2H, J = 8.8 Hz, Ar), 6.88 (d, 2H, J = 8.8 Hz, Ar), 5.42 (dd, 1H, $J_{1,OH}$ = 3.6 Hz, $J_{1,2}$ = 10 Hz, H-1), 4.66 (d, 1H, J_{AB} = 10.4, CH_2Ar), 4.47 (d, 1H, J_{AB} = 10.4, CH_2Ar), 4.19 (m, 1H, H-4), 4.13–4.07 (m, 1H, H-3), 3.81–3.68 (m, 6H, H-2,5a,b,OCH_3), 0.88, 0.86 (s, 18H, 4CH_3), 0.08, 0.04 (s, 18H, 2*t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 159.8, 127.7 (C, Ar), 129.8, 114.2 (CH, Ar), 96.7 (C-1), 83.2 (C-2), 80.1 (C-3), 74.4 (C-4), 73.2 (CH_2Ar), 61.1 (C-5), 55.5 (OCH_3), 26.1, 25.8 (CH_3, 2*t*-Bu),

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18.6, 18.2 (C, 2*t*-Bu), –4.6, –4.8, –4.9, –5.2 ($4CH_3$). Data for **102***β*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.25 (d, 2H, J = 8.8 Hz, Ar), 6.86 (d, 2H, J = 8.8 Hz, Ar), 5.18 (d, 1H, $J_{1,2}$ = 12.4 Hz, H-1), 4.60 (d, 1H, J_{AB} = 10.4, CH_2Ar), 4.47 (d, 1H, J_{AB} = 10.4, CH_2Ar), 4.22 (m, 1H, H-4), 4.13–4.07 (m, 1H, H-3), 3.81–3.68 (m, 6H, H-2,5a,b,OCH_3), 0.89, 0.87 (s, 18H, $4CH_3$), 0.08, 0.03 (s, 18H, 2*t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 159.6, 127.7 (C, Ar), 129.6, 114.1 (CH, Ar), 101.6 (C-1), 87.7 (C-2), 82.5 (C-3), 75.1 (C-4), 71.9 (CH_2Ar), 61.5 (C-5), 55.5 (OCH_3), 26.1, 25.9 (CH_3, 2*t*-Bu), 18.5, 18.3 (C, 2*t*-Bu), –4.8, –5.0, –5.1, –5.3 ($4CH_3$).

(*Z*/*E*)-4,6-Di-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-3-*O*-(4-methoxybenzyl)-1-phenylsulfanyl-D-*xylo*-hex-1-enitol (103): The title compound was prepared following the general procedure for the olefination of furanoses, method A, starting from **102** (350 mg, 0.70 mmol) in dry THF (560 μL), diphenyl (phenylsulfanylmethyl)phosphine oxide (910 mg, 2.81 mmol) in dry THF (19 mL), and 1.9 M PhLi in butyl ether (1.6 mL, 3.09 mmol). After 24 h at room temperature, the reaction mixture was quenched and the crude was purified by column chromatography (1:3 EtOAc/hexane) to afford **103** (35 mg, 8%) as an inseparable 1:5 *Z*/*E* mixture as a colourless syrup. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.48. Anal. Calcd for $C_{32}H_{52}O_5SSi_2$: 63.53 C, 8.66 H, 5.30 S. Found: 63.49 C, 8.69 H, 5.27 S. Data for **103***E*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.39–6.83 (m, 9H, Ar), 6.44 (d, 1H, $J_{1,2}$ = 15.6 Hz, H-1), 5.76 (dd, 1H, $J_{1,2}$ = 15.6 Hz, $J_{2,3}$ = 8 Hz, H-2), 4.63 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ar), 4.37 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ar), 3.99–3.87 (m, 1H, H-3), 3.80 (s, 3H, OCH_3), 4.74–3.63 (m, 1H, H-5), 3.58–3.43 (m, 3H, H-4,6a,b), 2.61 (d, 1H, $J_{5,OH}$ = 6.8 Hz, OH), 0.88, 0.87 (s, 18H, $4CH_3$), 0.08–0.01 (s, 18H, 2*t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 159.4–113.6 (C, CH, Ar), 128.8 (C-2), 128.1 (C-1), 79.3 (C-3), 72.6 (C-4), 70.8 (C-5), 70.2 (CH_2Ar), 64.3 (C-6), 55.5 (OCH_3), 26.3–26.1 (CH_3, 2*t*-Bu), 18.5–18.3 (C, 2*t*-Bu), –3.5– –5.2 ($4CH_3$). Data for **103***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.39–6.83 (m, 9H, Ar), 6.56 (d, 1H, $J_{1,2}$ = 8.8 Hz, H-1), 5.85 (dd, 1H, $J_{1,2}$ = 8.8 Hz, $J_{2,3}$ = 6 Hz, H-2), 4.57 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ar), 4.34 (d, 1H, J_{AB} = 11.6 Hz, CH_2Ar), 3.99–3.87 (m, 1H, H-3), 3.80 (s, 3H, OCH_3), 4.74–3.63 (m, 1H, H-5), 3.58–3.43 (m, 3H, H-4,6a,b), 2.40 (d, 1H, $J_{5,OH}$ = 8.8 Hz, OH), 0.90, 0.82 (s, 18H, $4CH_3$), 0.08–0.01 (s, 18H, 2*t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 159.4–113.6 (C, CH, Ar, C-1,2), 81.3 (C-3), 73.5 (C-4), 72.5 (C-5), 70.4 (CH_2Ar), 63.7 (C-6), 55.5 (OCH_3), 26.3–26.1 (CH_3, 2*t*-Bu), 18.5–18.3 (C, 2*t*-Bu), –3.5– –5.2 ($4CH_3$).

6-*O*-(*tert*-Butyldiphenylsilyl)-2-iodo-3,4-*O*-isopropylidene-D-galactal (104) and 6'-*O*-(*tert*-Butyldiphenylsilyl)-2'-deoxy-2'-iodo-3',4'-*O*-isopropylidene-*α*-D-talopyranosyl-(1→1)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-iodo-3,4-*O*-isopropylidene-*α*-D-talopyranoside (105): NIS (31.6 mg, 0.14 mmol) was added to a solution of **11** (2:1 *Z*/*E* ratio) (30 mg, 0.06 mmol) in a mixture of CH_3CN (1 mL) and water (100 μL) at 0ºC. The

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reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was then diluted with CH_2Cl_2 and washed with saturated aqueous $Na_2S_2O_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was treated with a mixture of Ph_2SO (23.6 mg, 0.11 mmol), TTBP (43 mg, 0.17 mmol), and 4Å MS (22 mg) in dry CH_2Cl_2 (1.4 mL) at –60ºC for 30 min. Tf_2O (10 μL, 0.06 mmol) was then added and the reaction stirred at the same temperature for 1 h. The reaction mixture was quenched with Et_3N, and the solvent evaporated. The residue was purified by radial chromatography (from hexane to 1:3 EtOAc/hexane) to afford **104** (5 mg, 16% over two steps) and **105** (15 mg, 48% over two steps) as yellowish syrups. Data obtained from the mixture. R_f (1:3 EtOAc/hexane): 0.51. Data for **104**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.70–7.26 (m, 10H, Ar), 6.65 (s, 1H, H-1), 4.61 (d, 1H, $J_{3,4}$ = 5.6 Hz, H-3), 4.54 (d, 1H, $J_{3,4}$ = 5.6 Hz, H-4), 4.16 (appt, 1H, $J_{5,6a}$ = $J_{5,6a}$ = 6.8 Hz, H-5), 3.97–3.90 (m, 2H, H-6a,b), 1.56–1.04 (m, 15H, 2CH_3, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 148.4 (C-1), 136.4–127.4 (C, CH, Ar), 111.1 (C_{ketal}), 75.4 (C-2), 75.1 (C-5), 74.2 (C-3), 73.5 (C-4), 62.8 (C-6), 29.9–25.4 (2CH_3, CH_3, *t*-Bu), 19.4 (C, *t*-Bu). Data for **105**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.70–7.26 (m, 20H, Ar), 5.34 (d, 2H, $J_{1,2,\ 1',2'}$ = 7.2 Hz, H-1, H-1'), 4.65 (dd, 2H, $J_{3,4,\ 3',4'}$ = 7.6 Hz, $J_{2,3,\ 2',3'}$ = 2 Hz, H-3, H-3'), 4.48 (dd, 2H, $J_{3,4,\ 3',4'}$ = 7.6 Hz, $J_{4,5,\ 4',5'}$ = 1.6 Hz, H-4, H-4'), 4.23 (dd, 2H, $J_{1,2,\ 1',2'}$ = 7.2 Hz, $J_{2,3,\ 2',3'}$ = 2 Hz, H-2, H-2'), 3.97–3.90 (m, 2H, H-5, H-5'), 3.68 (appt, 2H, $J_{6a,b,\ 6'a,b}$ = $J_{5,6a,\ 5',6'a}$ = 9.2 Hz, H-6a, H-6'a), 3.38 (dd, 2H, $J_{6a,b,\ 6'a,b}$ = 9.2 Hz, $J_{5,6b,\ 5',6'b}$ = 4.8 Hz, H-6b, H-6'b), 1.56–1.04 (m, 30H, 4CH_3, 2*t*-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 136.4–127.4 (C, CH, Ar), 109.3 (2C_{ketal}), 97.0 (C-1, C-1'), 76.9 (C-3, C-3'), 73.8 (C-4, C-4'), 68.9 (C-5, C-5'), 61.2 (C-6, C-6'), 29.9–25.4 (C-2,C-2', 4CH_3, CH_3, 2*t*-Bu), 19.4 (C, 2*t*-Bu).

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8 Summary

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The research described in this thesis aims to investigate a new method for the stereoselective synthesis of 2-deoxyglycosides and oligosaccharides based on a new access to 2-deoxy-2-iodo- and 2-deoxy-2-phenylselenenyl glycosyl donors that would not be limited by the availability of pyranoid glycals and by the stereoselective addition of electrophiles.

Chapter 3 describes our investigation into the application of the general procedure for the stereoselective synthesis of 2-deoxy-2-iodo-hexopyranosyl glycosides from furanoses. The procedure involves three reactions: Wittig–Horner olefination to give alkenyl sulfanyl derivatives, electrophilic iodine-induced cyclization to give phenyl 2-deoxy-2-iodo-1-thiopyranosides, a new type of glycosyl donor, and glycosylation. The olefination reaction afforded alkenyl sulfanyl derivatives in good to excellent yields, except in cases where the conformational freedom is constrained by cyclic protecting groups such as 3,4-*O*-isopropylidene. The cyclization reaction proceeds with complete regio- and stereoselectivity. The reaction proceeds exclusively as 6-*endo* cyclization to give phenyl 1-thiopyranoside derivatives. The stereochemistry of the iodine at C-2 is always *cis* to the neighboring alkoxy group, except for *lyxo* derivatives which lack cyclic protecting groups. This is a key point in the overall process because the iodine controls the stereoselectivity of the glycosylation reaction. The yield of the cyclization depends on the configuration of the starting material; it is very good for substrates with a *ribo* or *xylo* configuration, but more modest for those with an *arabino* or *lyxo* configuration. The glycosylation reaction proceeded with good yields and good to excellent stereoselectivities. The glycosidic bond created in the major isomers was always *trans* to the iodine at C-2. Although phenyl 2-deoxy-2-iodo-1-thioglycosyl donors of all configurations can be accessed using the proposed procedure, it is particularly effective in providing 2-deoxy-2-iodo-*β*-D-*gulo*- and -*β*-D-*allo*-glycosides. These glycosides are precursors of 2-deoxyglycosides of *ribo* and *xylo* configuration, which are difficult to obtain by the classical methodology starting from glycals.

Since 2-deoxy-2-iodo-1-thioglycosides are activated in conditions similar to those used to induce the cyclization, 2-deoxy-2-iodopyranosides were synthesized from sulfanyl alkenes using a “one pot” consecutive cyclization and glycosylation process. The “one pot” procedure has the advantage that it starts directly from the very stable acyclic alkenyl sulfide precursors and does not require isolation of the glycosyl donors. The overall strategy is fairly straightforward and operationally simple. Compared with the stepwise procedure, the “one pot” process gave significantly improved yields with similar or slightly lower selectivities. Furthermore, the “one pot” procedure was successfully applied to the synthesis of 2-deoxy- and 2,6-dideoxyglycosides.

Chapter 4 describes our investigation into the application of the general procedure for the stereoselective synthesis of 2-deoxy-2-phenylselenenyl-hexopyranosyl glycosides

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from furanoses. We developed 2-deoxy-2-phenylselenenyl-1-thioglycosides as a new class of glycosyl donors that provide access to 2-deoxyglycosides. The cyclization reaction proceeds with complete regio- and stereoselectivity enhanced by employing 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group. We have also demonstrated that the glycosylation of 2-deoxy-2-phenylselenenyl-1-thioglycosides is highly substrate dependent. Although glycosylation products of all configurations can be accessed by employing the present methodology, it is particularly effective in providing 2-deoxy-2-phenylselenenyl-*β*-D-*gulo*- and -*β*-D-*allo*-glycosides. In particular, regardless of the nature of the solvent employed, the high *β*-selectivity observed in *gulo* (*α*/*β* ratio 1:14) and more modest in *allo* (*α*/*β* ratio 1:4) series is comparable to that previously observed for analogous glycosylation reactions of 2-deoxy-2-iodo-1-thio-D-*gulo*- (*α*/*β* ratio 1:16) and -D-*allo*-glycosyl donors (*α*/*β* ratio 1:6). Furthermore, the use of phenylselenenyl group at C-2 gave us some insight into the likely pathway of glycosylation reactions by using 2-deoxy-2-phenylselenenyl-1-thioglycosyl donors. Since the stereoselectivity observed is similar to that obtained using 2-deoxy-2-iodo-1-thioglycosides it can be concluded that this explanation is general for the different glycosylations assisted by chalcogens and halogens at C-2.

Since 2-deoxy-2-iodo- and 2-deoxy-2-phenylselenenyl-1-thioglycosides have been evaluated as a new class of glycosyl donors, we became interested in the preparation of other useful glycosyl donors such as 2-deoxy-2-iodo-1-selenoglycosides, and exploit their higher reactivity in developing milder and orthogonal stereoselective glycosylation protocols by using this methodology. Thus, carbohydrate-based vinyl selenides of *arabino*, *ribo,* and 2-deoxy-*ribo* configurations were prepared by Wittig-type reactions of various protected furanoses. Moderate yields were always obtained due to nature and reactivity of both carbohydrate lactols and selenium-based olefinating reagents under the conditions tested. The reaction with electrophiles proved to be challenging and no cyclization products were obtained. The preparation of vinyl selenides proved to be much more difficult than the related vinyl sulfides, which can be prepared in good yields using Wittig–Horner reaction.

Chapter 5 reports olefin cross metathesis reaction between carbohydrate-derived hydroxy alkenes and electron-rich olefinic partners with commercially available ruthenium-based catalysts. Microwave irradiation effectively accelerates the cross metathesis reaction of electron-rich olefins although some of the conversions remained low. Cross metathesis can only be achieved with hydroxy alkenes derived from 2-deoxysugars. In contrast, the hydroxy alkenes bearing an allylic alkoxy group neither isomerizes nor couples under similar conditions.

Chapter 6 reports a new method for accessing pyranoid glycals of different configurations by a short route that uses readily available starting materials, and conventional transformations. Our method is particularly valuable for the synthesis of non-

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readily accessible glycals such as D-allal and D-gulal that are valuable products to prepare some oligosaccharide molecules with biologically interesting properties.

A series of 2-deoxy-2-iodopyranoses were evaluated as precursors that provide access to pyranoid glycals and 2-iodoglycals from sulfanyl alkenes. This synthetic route involves consecutive cyclization and hydrolysis reactions followed by treatment of the resulting lactol under Gins' dehydrative glycosylation conditions. Despite the fact that this procedure has proved to be an efficient and general glycosylation method, its application to 2-deoxy-2-iodopyranoses did not afford the expected products. Although the observed product distribution (glycals, 2-iodoglycals, and 1,1'-disaccharides) revealed that this reaction is very sensitive to the configuration of the 2-deoxy-2-iodopyranose, 2-iodo pyranoid glycals can be almost exclusively obtained in good yields by employing 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group.

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