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# Stereoselective Synthesis of 2-Deoxyglycosides. Approach to the Synthesis of Digitoxine

**Memoria presentada por**
**Miguel Ángel Rodríguez Gómez**
**para optar al título de**
**Doctor en Química.**
**Tarragona, Mayo 2007**

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CERTIFICAN:

Que el trabajo titulado: "Stereoselective Synthesis of 2-Deoxyglycosides. Approach to the Synthesis of Digitoxine" presentado por Miguel Ángel Rodríguez Gómez para optar al grado de Doctor, ha estado realizado bajo su inmediata dirección en los laboratorios de Química Orgánica del Departamento de Química Analítica y Química Orgánica de la Universidad Rovira i Virgili.

Tarragona, Mayo de 2007

Sergio Castillón Miranda Yolanda Díaz Giménez

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Así como no se pueden agrupar de forma satisfactoria cuatro años de trabajo en el laboratorio en un libro, menos justicia se puede hacer en unas páginas a aquellos que han contribuido y han ayudado en el desarrollo de este proyecto. Muchas son las personas a las que debo la finalización de esta Tesis y para todas ellas vaya mi más sincero agradecimiento.

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| | |
|---|---|
| **ACE** | Angiotensin-converting enzyme |
| **AcOH** | Acetic acid |
| **AgOTf** | Silver trifluoromethanesulfonate (triflate) |
| **AIBN** | 2,2'-Azobisisobutyronitrile |
| **ARF** | Alkoxy Radical Fragmentation |
| **ax** | Axial |
| **BHPO** | β-Hydroxyphosphine oxide |
| **BSP** | Benzenesulfinylpiperidine |
| **$Bu_3SnH$** | Tri-butyltin hydride |
| **COSY** | Correlated spectroscopy |
| **Cy** | Cyclohexyl |
| **CHF** | Congestive heart faliure |
| **DAST** | Diethylaminosulfur trifluoride |
| **DBU** | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| **DCM** | Dichloromethane |
| **DIBAL** | Diisobutylaluminium hydride |
| **DMAP** | 4-Dimethylaminopyridine |
| **DMDO** | Dimethyldioxirane |
| **eq** | Equatorial |
| **EtOAc** | Ethyl Acetate |
| **HMBC** | Heteronuclear multiple-bond correlation |
| **HOMO** | Highest occupied molecular orbital |
| **HSQC** | Heteronuclear single-quantum correlation |
| **IDCP** | Iodonium dicollidine perchlorate |
| **$IPy_2BF_4$** | Bis(pyridine)iodonium tetrafluoroborate |
| **KHMDS** | Potassium bis(trimethylsilyl)amide |
| **LA** | Lewis acid |
| **LACDAC** | Lewis acid catalyzed diene-aldehyde cycloaddition |
| **LN** | Lithium napthalenide |
| **LUMO** | Lowest unoccupied molecular orbital |
| **MHz** | Megaherzt |

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## Acronyms

| | |
|---|---|
| **MPLC** | Medium-pressure liquid chromatography |
| **NaAcO** | Sodium acetate |
| **NBS** | *N*-Bromosuccinimide |
| **n-BuLi** | *n*-Butyl lithium |
| **Ni-Ra** | Nickel Raney |
| **NIS** | N-Iodosuccinimide |
| **NKA** | Na/K ATPase |
| **NMR** | Nuclear magnetic resonance |
| **NOESY** | Nuclear Overhauser effect spectroscopy |
| **PDE** | Phophodiesterase |
| **Py** | Pyridine |
| **RCM** | Ring closing metathesis |
| **SOC** | Sodium open channels |
| **SR** | Sarcoplasmatic reticulum |
| **TBAF** | Tetrabutylammonium fluoride |
| **TBS or TBDMS** | Tert-butyldimethylsilyl |
| **TES** | Triethylsilyl |
| **$Tf_2O$** | Triflic anhydride |
| **TFA** | Trifluoroacetic acid |
| **TfOH** | Trifluoromethanesulfonic acid (triflic acid) |
| **THF** | Tetrahydrofuran |
| **TLC** | Thin layer chromatography |
| **TMSCN** | Trimethylsylil cyanide |
| **TMSOTf** | Trimethylsylil trifluoromethanesulfonate (triflate) |
| **TOCSY** | Total Correlation spectroscopy |
| **TTBP** | 2,4,6-Tri-(*tert*-butyl)pyrimidine |
| **WH** | Wittig-Horner (Olefination) |

This thesis is based on the following publications

**I.** **Stereoselective Synthesis of 2-Deoxy-2-iodo-glycosides from Furanoses: A New Route to 2-Deoxy-glycosides and 2-Deoxy-oligosaccharides 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-Deoxy-glycosides 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.* In press.

**III.** **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.

**IV.** **Synthesis of 2-iodoglycals versus glycals from 2-deoxy-2-iodo-pyranoses under dehydrative glycosylation conditions.**
Miguel A. Rodríguez, Omar Boutureira, Isidro Cobo, M. Isabel Matheu, Yolanda Díaz, and Sergio Castillón. In Preparation.

**V.** **Stereoselective Synthesis of 2-Deoxy-2-phenylselenenyl-glycosides from Furanoses: Implication of 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.* Accepted.

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## Chapter 4. Approach to the Synthesis of Digitoxine

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# Introduction

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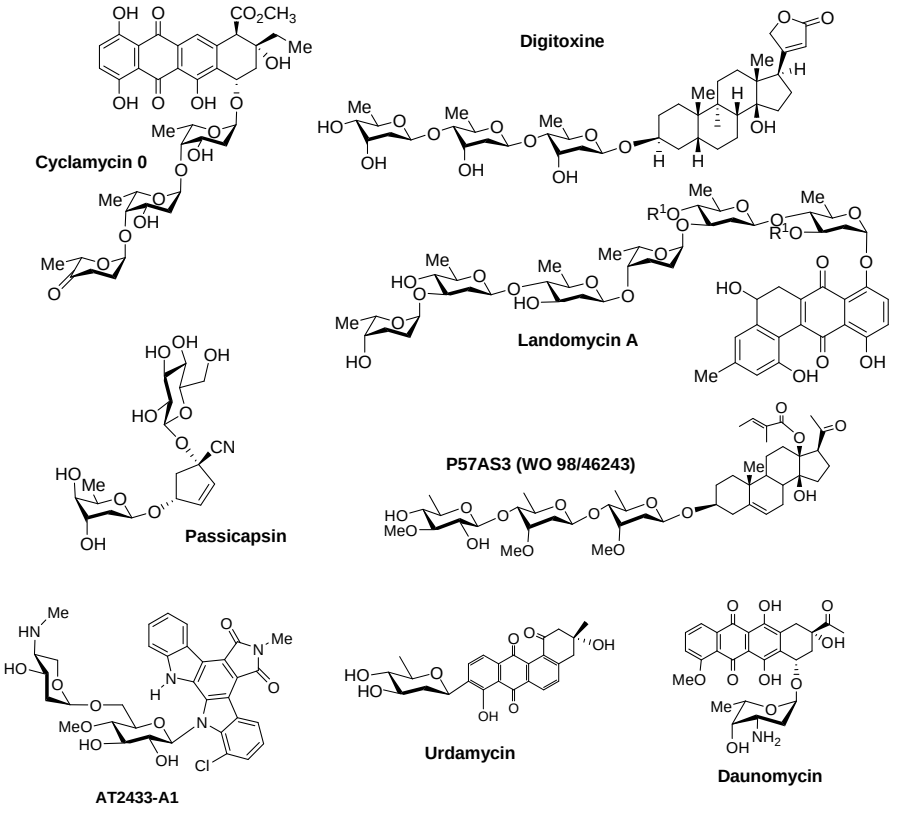
## Chemistry and Biology of 2-Deoxyglycosides

2-Deoxy- and 2,6-dideoxy glycosides are important structural units in many natural products and many of them exhibit interesting physiological properties.[1]

**Figure 1**. Examples of compounds with 2-deoxyoligosaccharide units




For instance, they constitute characteristic structural elements of antitumor drugs like the anthracyclins, aureolic acid, calicheamicin and esperamicin, of antibiotics active against Gram positive bacteria, like the orthosomycins, of appetite supressant compounds,

[1] a) Williams, N.; Wander, J. Deoxy and Branched-chain Sugars. In *The Carbohydrates: Chemistry and Biochemistry*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1980; Vol. 1B, pp 761-798. b) Kennedy, J.F.; White, C.A. Bioactive Carbohydrates in Chemistry, Biochemistry, and Biology; Chichester: Ellis Horwood, 1983.

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like P57AS3[2] (from *Hoodia* species), and of cardiac glycosides used in the treatment of cardiac insufficiency.[3] These compounds contain monosaccharide units belonging to the D and L series with all possible configurations (Figure 1).

Whereas the therapeutic effect of these drugs is mediated by the 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. 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 involved in active biochemical and bioorganic processes including active transmembrane transport, stabilization of protein folding and enzyme inhibition.[4] The development of new drugs with altered glycosidic parts or aglycons is actively being pursued. Due to this biological relevance, the development of methods for the efficient and stereoselective construction of deoxyglycosidic linkages is of great significance in organic synthesis, medicinal and bioorganic chemistry. Moreover, many 2-deoxy sugars are not readily isolated from nature; that is why it is important to be able to prepare such compounds.

The stereocontrolled formation of the glycosidic linkage in 2-deoxy-oligosaccharides has proved to be one of the most challenging tasks in glycosylation reactions, because of the absence of a stereodirecting group at C-2.[5] In the bibliography there are several procedures describing the synthesis of 2-deoxy-glycosides, which can be distinguished depending on the configuration of the anomeric bond, α or β. 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

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[2] 'Pharmaceutical compounds having appetite suppressant activity', van Heerden, F.R.; Vleggaar, R.; Horak, R.M.; Learmonth, R.A.; Maharaj V.; Whittal, R.D. Patent Nr: WO 98/46243.

[3] a) Thiem, J.; Klaffke, W. *Top. Curr. Chem*. **1990**, *154*, 285.

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

[5] a) Kirschning, A.; Jesberger, M.; Schöning, K-U. *Synthesis* **2001**, 507. b) Veyrières, A. In *Carbohydrates in Chemistry and Biology*, Ernst, B.; Hart, G.W.; Sinaÿ, P. Ed., Wiley, Weinheim **2000**, Part I, Vol. I, p 367. c) Marzabadi, H.; Franck, R.W. *Tetrahedron* **2000**, *56*, 8385. d) Castro-Palomino, J.C.; Schmidt, R.R. *Synlett* **1998**, 501. e) Toshima, K.; Tatsuta, K. *Chem. Rev*. **1993**, *93*, 1503. f) Schmidt, R.R. in *Comprehensive Organic Synthesis,* Vol. 6 (Trost, B.M.; Fleming, I.; Winterfeld, E., Eds.), Pergamon Press, Oxford **1991**, pp. 33-64. g) Bilodeau, M.T.; Danishefsky, S.J. in *Modern Methods in Carbohydrate Synthesis* (Khan, H., O'Neill, R.A., Eds.) Harwood Academic Publishers, Amsterdam, **1996**, pp. 171-193.

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purpose (Scheme 1a) and the reaction takes place through an oxonium intermediate to give mainly the α anomer. Interestingly, a very efficient procedure of synthesis of β-linked 2-deoxy-oligosaccharides involving the activation of glycosyl imidates with $I_2/Et_3SiH$ at very low temperature has been recently reported.[6]

Glycals are common starting materials for synthesising 2-deoxy-α-glycosides.[7] The reaction requires the activation of the enol ether by an electrophile to give an oxonium cation intermediate which reacts with alcohol to give the final glycoside. Proton, usually provided by a weak acid such as $Ph_3P$-HBr, can be used as electrophile (Scheme 1b). More commonly bromo,[8] iodo,[9] phenylsulfanyl,[10] phenylselenenyl,[11] formamido[12] and thionocarbonate[5d] are used as electrophiles. In these cases the attack of the electrophile to the enolether introduces a bulky hetroatom at position 2 which can control the stereoselectivity of the glycosylation. Usually an halonium (mainly iodine, NIS or other sources of electrophilic iodine), episulfonium or selenonium cations have been postulated as reaction intermediates, and as responsibles of the high stereoselectivity observed in these processes (Scheme 1c). However, we have demonstrated that the real intermediate is an oxonium cation, and consequently the observed stereoselectivity is a consequence of the presence of a bulky substituent at position 2, and not from the formation of a cyclic

---

[6] Tanaka,H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 2505.

[7] For some approaches using glycals to synthesize glycosyl donors, see: a) Rauter, A.P.; Almeida, T.; Vicente, A.I; Ribeiro, V.; Bordado, J.C.; Marques, J.P.; Ramôa-Ribeiro, F.; Ferreira, M.J.; Oliveira, C.; Guisnet, M. *Eur. J. Org. Chem.* **2006**, 2429. b) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, 5, 1871. c) Chong, P. Y.; Roush, W. R. *Org. Lett*. **2002**, *4*, 4523. d) Kirschning, A.; Jesberger, M.; Schoning, K.-U. *Org. Lett* **2001**, *53*, 3623. e) Roush, W. R.; Narayan, S.; Bennett, C. E.; Briner, K. *Org. Lett.* **1999**, *1*, 895. f) Roush, W. R.; Narayan, S. *Org. Lett*. **1999**, *1*, 899. g) Kirschning, A. *Eur. J. Org. Chem.* **1998**, *63*, 2267. h) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825.

[8] a) Thiem, J.; Schöttmer, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 555. b) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954 and references therein.

[9] a) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891. b) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541. c) Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1990.

[10] a) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837. b) Franck, R. W.; Marzabadi, C. H. *J. Org. Chem.* **1998**, *63*, 2197. c) Johnston, B.D.; Pinto, B.M. *J. Org. Chem.* **2000**, *65*, 4607. d) Ryan, K.J.; Acton, E.M.; Goodman, L. *J. Org. Chem.* **1971**, *36*, 2646. e) Viso, A.; Poopeiko, N.; Castillón, S. *Tetrahedron Lett.* **2000**, *41*, 407.

[11] a) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75. b) Díaz, Y.; El-Laghdach, A.; Matheu, M.I.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 1501.

[12] Trumtel, M.; Tavecchia, P.; Veyriéres, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *191*, 29.

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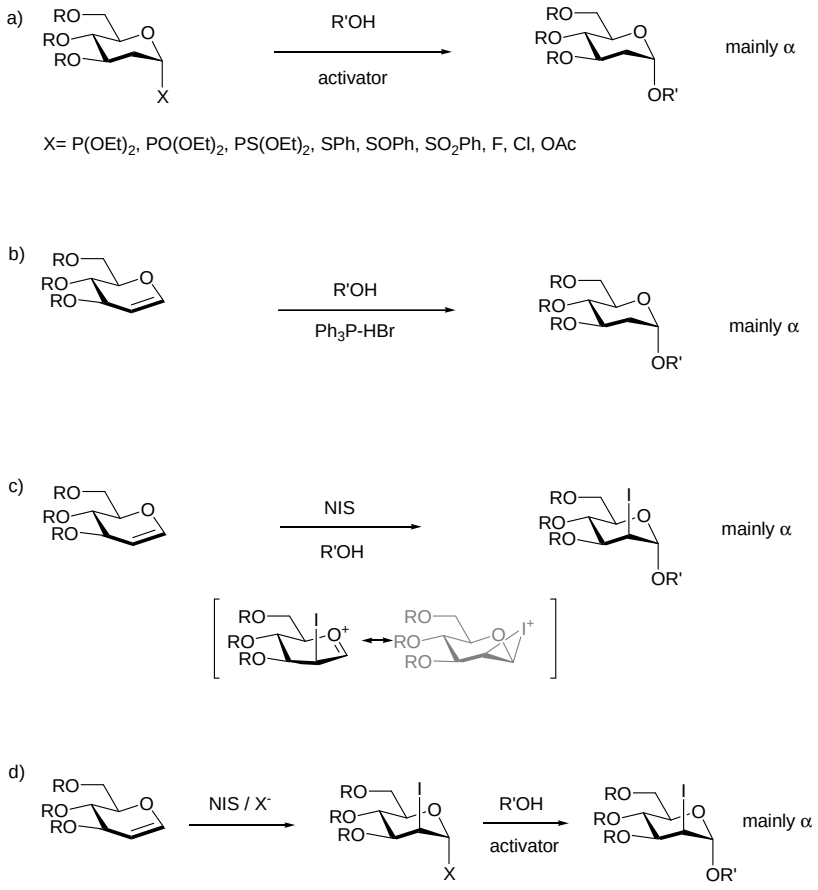
intermediate.[13] When iodine is used as electrophile, the iodine attacks by the more electronegative upper face, resulting the introduction of iodine in *axial* position, and the attack of the alcohol takes place *trans* to the iodine. For more common glycals, glucal and galactal, the use of this procedure results in obtaining 2-deoxy-2-iodo-α-*manno*- or *gulo*-glycosides with excellent stereoselectivity (Scheme 1c).

**Scheme 1**. Selected methods of synthesis of 2-deoxy-α-glycosides




In the last years a great number of glycosylation procedures have been reported based in an efficient leaving group-activator couple. They allow to carry out glycosylation reaction in very mild conditions and permit the orthogonal glycosylation. In this context a

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

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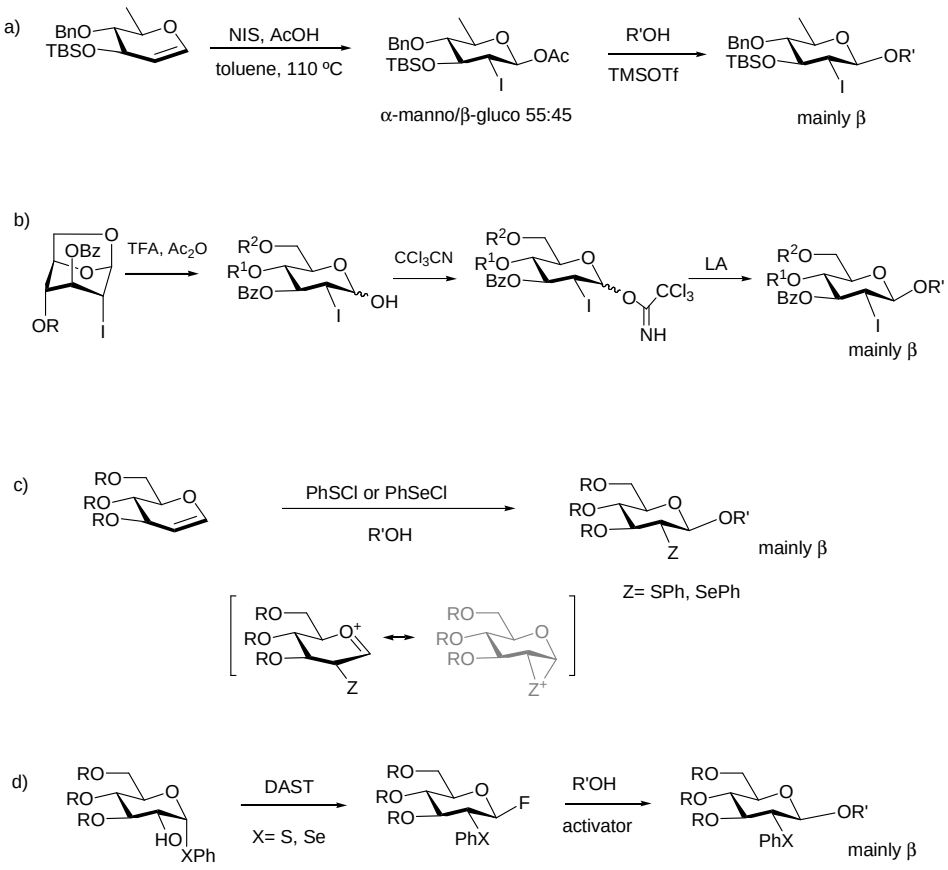
new generation of glycosyl donors have been prepared by reacting glycals with NIS and different nucleophiles which can behave as leaving groups in a further glycosylation reaction (Scheme 1d). Alternatively, when a glycal is activated in the presence of water, a 2-deoxy-2-iodo-pyranose (X=OH, Scheme 1d)) is formed, which can be then transformed in fluoro-, trichloroacetimidate, etc. glycosyl donos. In a second step, the glycosylation is carried out by activating these new glycosyl donors in appropriate conditions. This strategy allows a wide variety of glycosylation conditions.

**Scheme 2**. Selected methods of synthesis of 2-deoxy-β-glycosides




As it has been seen before, iodine, or in general any electrophilic iodo-reagent, adds efficiently to glucal, galactal, and related glycals, activating the glycosylation reaction

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and affording α-glycosides with very high stereoselectivity. Interestingly, it has been observed that sulphur and selenium electrophiles, mainly PhSCl and PhSeCl, add to glycals *trans* to allylic substituent, affording after glycosylation to the corresponding 2-deoxy-2-phenylsufanyl- or 2-deoxy-2-phenylselenenyl-β-*gluco*- or -β-*galacto*-pyranosides (Scheme 2c).[14] The reaction is, however, dependent on the configuration of the starting glycals and the stereoselectivity is worse than when iodine was used. Looking for the introduction of iodine in an equatorial arrangement, Roush performed the addition of NIS-AcOH to a 6-deoxy-glycal under thermodynamic conditions (refluxing toluene).[15] Although, practically an 1:1 mixture of *α-manno*/*β-gluco* derivative was obtained, it was possible to separate both diastereomers, proving that in the synthesis of β-glycosides, iodine also provided the best stereocontrol (Scheme 2a). 2-Deoxy-2-iodo-glycosyl donors can be selectively prepared by opening in acidic conditions 2-deoxy-2-iodo-levoglucosene, which in turn can be stereoselectively obtained from levoglucosenone (Scheme 2b).[16]

Nicolaou,[17] reported an original approach for preparing 2-deoxy-phenylsufanyl- and 2-phenylselelenenyl-β-*gluco*-pyranosyl fluorides by reacting α-1-thio- and α-1-seleno-glycosides with the 2-OH unprotected with diethylaminosulfur trifluoride (DAST) (Scheme 2d). DAST initially reacts with the 2-OH converting it in 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-phenylsufanyl- and 2-phenylselelenenyl-β-*gluco*-pyranosyl fluorides. These compounds are excellent glycosyl donors and have allowed the synthesis of complex oligosaccharides.

A conceptually different approach was developed by Toshima and Tatsuta, which use 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars (Scheme 3).[18]

---

[14] Marzabadi, C.H.; Franck, R.W. *Tetrahedron*, **2000**, *56*, 8385

[15] a) Roush, W. R.; Gung, B.W.; Bennet, C.E. *Org Lett.* **1999**, *1*, 891. b) Roush, W. R.; Narayan, S.; Bennet, C.E. *Org Lett.* **1999**, *1*, 895. c) Chong, P.Y.; Roush, W. R. *Org Lett.* **2002**, *4*, 4523. d) Roush, W. R.; Bennet, C.E. *J. Am. Chem. Soc.* **2000**, *122*, 6124.

[16] a) Leteux, C.; Veyrieres, 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.

[17] 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.

[18] a) Toshima, K. *Carbohydr. Res.* **2006**, *341*, 1282. b) Toshima, K.; Mukaiyama, S.; Nozaki, Y.; Inokuchi, H.; Nakata, M.; Tatsuta, K. *J. Am. Chem. Soc.* **1994**, *116*, 9042. Use of this methodology in the synthesis of erythromycin A: c) Toshima, K.; Nozaki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1995**, *117*, 3717.

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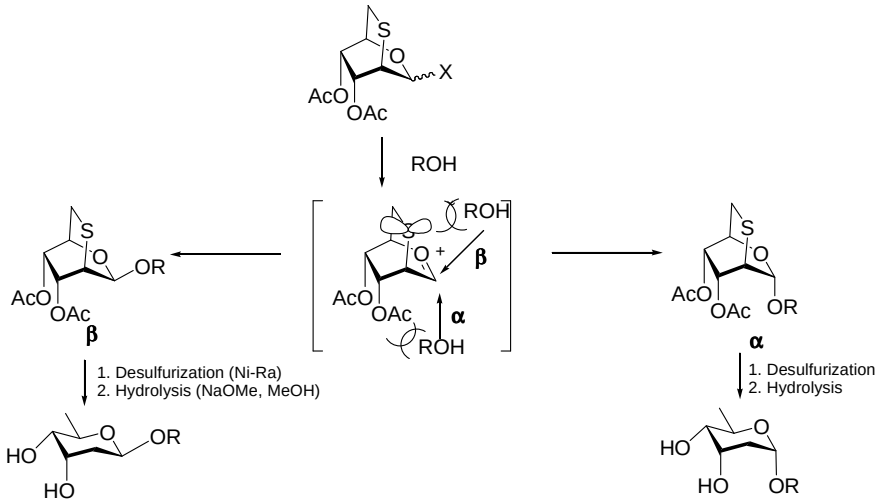
**Scheme 3**. Synthesis of 2-deoxy-glycosides using 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars.




This rigid bicycle can be stereoselectively glycosylated and easily transformed into 2,6-dideoxy-sugars by simple desulfurization. A variety of leaving groups X can be used and 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 sulphur electron pair is more important than the repulsion with the OAc group. Alternatively, when X=OAc and a Lewis acid is used as activator the β-anomer is mainly obtained as a consequence of the evolution of the system to the termodinamically more stable compound. In this way, both anomers can be stereoselectively obtained depending on the reaction conditions.

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*-hexo-glycosides (D-digitoxose),[19] and no examples of the synthesis of 2,6-dideoxy-D-*xylo*-

[19] McDonald, F.E.; Reddy, K.S. *Angew. Chem. Int. Ed.* **2001**, *40*, 3653.

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hexo-glycosides (D-boivinose), probably because of the difficulty of obtaining the corresponding glycals.

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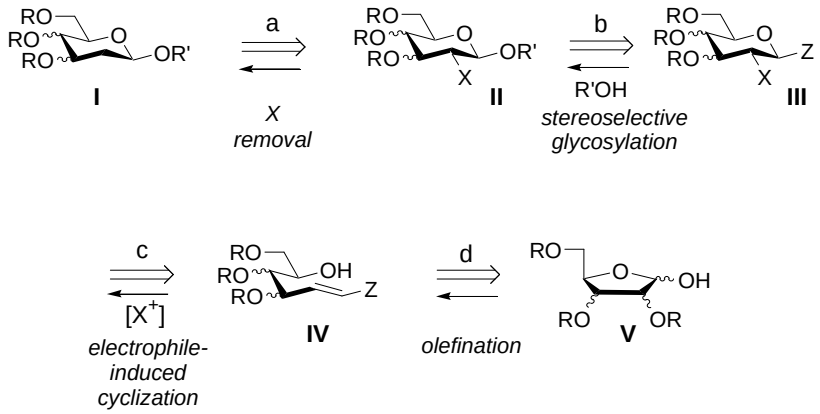
## Objectives

With this background the general objective of this work is to explore a new method of synthesis of 2-deoxy-glycosides and 2-deoxy-oligosaccharides based on a new access to 2-deoxy-2-iodo glycosyl donors that would not be limited by the availability of glycals and by the stereoselectivity of the addition of electrophiles to them. The key step of this method is the preparation of glycosyldonors of type **III** through a cyclization of alkenols **IV** induced by electrophiles. These alkenols can be prepared by an olefination reaction starting from the protected furanoses **V** (Scheme 4). Due to the availability of the configurationally different pentoses, the method should provide access to 2-deoxy-pyranosides of all configurations.

**Scheme 4**




A crucial factor in this synthesis is the selection of X and Z groups, since they must play important roles in the following reactions of the synthetic scheme:

Group Z:

a) Electrophile-induced cyclization: It must control the regioselectivity of the cyclization reaction from **IV** in order to obtain exclusively the product **III** resulting from a *6-endo* cyclization. For that, an electron donating group, able

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to stabilize a carbocation in the neighbouring position after the attack of the electrophile, would be useful.

b) Glycosylation: The compound **III** resulting from the cyclization must be directly used as 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.

Group X:

a) Electrophile induced cyclization: Must be an electrophile able to react with the electron rich alkene **IV**.

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

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

With these requirements in mind we have selected the group SPh as group Z, because thioglycosides have been widely used in glycosylation reactions,[20] they allow modifications in the phenyl group in order to facilitate the orthogonal glycosylation,[21] and we expect it will control the regioselectivity of the cyclization reaction due to the presence of sulphur.

Taken into account the results collected in the introduction we considered that the more appropriated group X would be iodine, since it efficiently induces cyclizations, is effective controlling the stereoselectivity of the reaction and can be easily removed. Other electrophiles, as selenium and sulphur derivatives, could be also considered but are far of the scope of this work.

---

[20] Thio-glycosides are useful glycosyl donors, see for instance: a) Oscarson, S. in *Carbohydrates in Chemistry and Biology*, Ernst, B.; Hart, G.W.; Sinaÿ, P. Eds., Wiley, Weinheim 2000, Part I, Vol. I, p 93. b) Garegg, P.J. *Adv. Carbohydr. Chem. Biochem.* **1997***, 52,* 172. c) Codeé, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769.

[21] For concepts about orthogonal/chemoselective glycosylations see: a) Kanie, O. in *Carbohydrates in Chemistry and Biology*, Ernst, B.; Hart, G.W.; Sinaÿ, P. Eds., Wiley, Weinheim 2000, Part I, Vol. I, p 407. For an example of the use of thioglycosides and sulfoxides in the synthesis of 2-deoxy-oligosaccharides see: b) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580. c) Gildersleeve, J.; Smith, A.; Sakurai, K.; Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1999**, *121*, 6176.

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In this context, the concrete objectives of this work are the following:

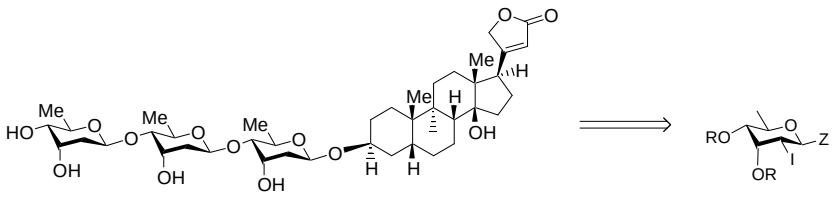
1. To look for an efficient method of olefination of pentoses in order to obtain alkenols of general formula **IV** (Z=SPh) (Chapter 1).

2. To study the cyclization of sulfanylalkenes **IV** (Z=SPh), obtained in point 1, induced by iodo-electrophiles, paying special attention to the regioselectivity of the reaction, 6-*endo* expected, and to the stereoselectivity. The final disposition of the iodine is a key point of the process since iodine will control the stereoselectivity of the glycosylation reaction (Chapter 1).

3. To study the glycosylation reaction with the new glycosyl donor obtained in point 2, phenyl 2-deoxy-2-iodo-1-thio-D-pyranosides, in order to obtain glycosides and oligosaccharides (Chapter 1)

4. Since the 1-thio-glycosides **III** are activated in conditions similar to those used to induce the cyclization from **IV**, it can be envisaged the possibility to obtain **II** in an "one pot" reaction from **IV**. Consequently this possibility will be also studied (Chapter 2).

5. Application of the method developed to the synthesis of natural products containing 2-deoxy-oligosaccharide units such as digitoxine (Chapter 4).




6. Since pyranoses type **III** of all configuration 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 of all configurations should be accessible by treating **III**, under reducing conditions. This methodology should

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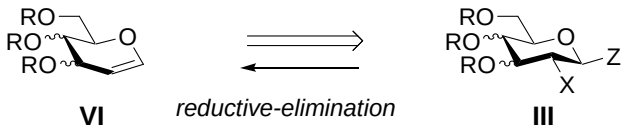
provide acces to glycals difficult to obtain by other procedures such as D-allal and D-gulal (Chapter 3).



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# 1

# New Method of Synthesis of 2-Deoxy-Glycosyl Donors

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A general procedure for the stereoselective synthesis of 2-deoxy-2-iodo-hexo- and hepto-pyranosyl glycosides from furanoses is reported. The proposed methodology provides a new route for accessing 2-deoxy-oligosaccharides. 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-hexo-glycosides, 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-thio-glycosides 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 of cholesterol and a model glucopyranoside, affording the corresponding 2-deoxy-2-iodo-glycosides 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.

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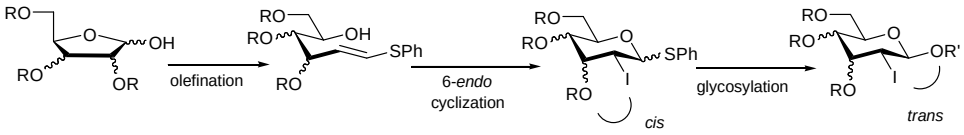

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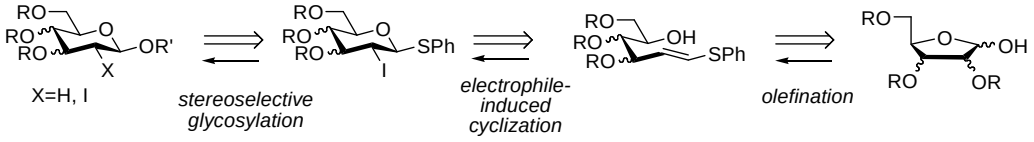
## Introduction

As described in the general objectives, we decided to explore a new way of synthesizing 2-deoxy-2-iodo glycosyl donors that would not be limited by the availability of glycals and by the stereoselectivity of the addition of electrophiles to them.

Thereby, here we report a procedure for synthesizing phenyl 2-deoxy-2-iodo-1-thioglycosides[20,22] and the use of these glycosides as glycosyl donors for the stereocontrolled synthesis of 2-deoxy-2-iodo-disaccharides and glycosides.

**Scheme 1**




The key step in the proposed synthesis of 2-deoxy-2-iodo-1-thio-glycosides is a cyclization of alkenols induced by iodine-containing electrophiles. These alkenols can be prepared by an olefination reaction starting from protected furanoses (Scheme 1). As it will be discussed further, this procedure is particularly efficient for the synthesis of 2-deoxy-β-hexo-glycosides of *ribo* or *xylo* configuration.[23]

## Results and Discussion

### Olefination

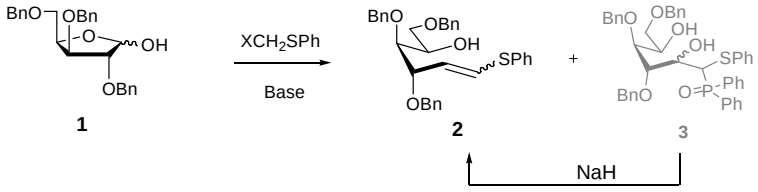
The first step in the proposed synthesis of 2-deoxy-2-iodo-1-thio-glycosides was the olefination of a series of properly protected furanoses to afford the corresponding enolthioethers. The hydroxyl groups in furanoses **1** and **6** were protected as benzylethers, although acetonides (**4**) were also used as protecting groups. The reaction conditions for

[22] 2-Deoxy-thioglycosides have recently been used as glycosyl donors in a solid-phase-assisted synthesis of 2-deoxyconjugates: Jaumzens, J.; Hofer, E.; Jesberger, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1166.

[23] a)M. A. Rodríguez, O. Boutureira, M. I. Matheu, Y. Díaz, S. Castillón, *J. Org. Chem.* **2005**, *70*, 10297. b) Arnés, X.; Díaz, Y.; Castillón, S. *Synlett* **2003**, 2143.

olefination were optimized starting from xylose derivative **1** and using different olefinating reagents, such as ylides,[24] phosphine oxides,[25] phosphonates[24c] and silylcarbanions.[26]

**Table 1.** Optimization of the olefination conditions of *xylo*-D-furanose **1**.[a]




| Entry | X | Temp (ºC) | Base (eq.) | Yield **2** (%) (*Z*/*E* ratio) |
|---|---|---|---|---|
| 1 | $PPh_3$ | 0 to reflux | n-BuLi (4.0) | - |
| 2[b] | $Ph_2PO$ | -78 to 10 | n-BuLi (4.0) | 33 (0:1) |
| 3[c] | $Ph_2PO$ | -78 to rt | n-BuLi (4.0) | 76 (1:4) |
| 4 | $Ph_2PO$ | -78 to rt | KHMDS(4.0) | 17 (1:1) |
| 5 | $(Et_2O)PO$ | -78 to rt | n-BuLi (4.0) | 11 (0:1) |
| 6 | $Me_3Si$ | -78 to rt | n-BuLi (4.0) | 12 (1:1) |

[a] General conditions: Furanose (1 mmol), phosphine oxide (4 mmol), Solvent =THF (0.04M to furanose). Reaction time = 16h. [b] Reaction time= 1 h.; BHPO: β-hidroxyoxyphosphine oxide; KHDMS: Potassium bis(trimethylsilyl)amide. [c] An additional 21% (Z/E 8:1) of **2** were obtained by treating **3** with NaH at rt.

Reaction of **1** under Wittig conditions furnished a complex mixture (Table 1, entry 1). Wadsworth-Emmons olefination led to the formation of the desired alkene **2** in low yield but with complete *E*-stereoselectivity (Table 1, entry 5). Peterson olefination with silyl carbanions afforded enolthioether **2** in 12% yield as a *Z*/*E* inseparable equimolar mixture (Table 1, entry 6). The highest yield of a 1:4 *Z*/*E* diastereomeric mixture of alkene

[24] a) Wittig, G.; Schlosser, M.; *Chem Ber*. **1961**, *94*, 1373; b) Vlatas, I.; Lee, A.O.; *Tetrahedron Lett*. **1974**, 4451; c) Bestmann, H.J.; Angerer, J. *Liebigs Ann. Chem*. **1974**, 2085.
[25] a) (review) Clayden, J.; Warren, S. *Angew. Chem. Int. Ed. Eng*. **1996**, *35*, 241. b) (SR, two-step) Earnshaw, C.E.; Wallis, C.J.; Waren, S. *J. Chem. Soc. Perkin Trans 1* **1979**, 3099. c) (SR, one-step) Grayson, J.I.; Warren, S. *J. Chem. Soc. Perkin Trans 1* **1977**, 2263.
[26] a) (review) 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.

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**2** (76%) was obtained when *n*-BuLi was used as the base in a Wittig-Horner (WH) olefination (using a phosphine oxide) (Table 1, Entry 3). In order to obtain the best yield, it was important the dropwise addition of a solution of furanose to a cold (-78 ºC) solution of the phosphine oxide carbanion. Moreover, long reaction times (> 8 h) were necessary to obtain a good yield, in spite of the drop of stereoselectivity (Table 1, compare entry 2 with 3).

The Wittig-Horner (WH) reaction with Li-bases is ideally described as a two-step procedure in which a β-hydroxyphosphine oxide (BHPO) intermediate is formed and then subsequently transformed to the alkene by reaction with KH or NaH.[27] With semistabilized reagents, however, the alkene can be obtained directly.[25c] In our case, as will be seen further, reaction of a complex aldehydes such as furanoses and semi-stabilized phosphine oxides in a WH olefination afforded mixtures of the corresponding alkene products and BHPO intermediates. Isolating the BHPO and submitting it to elimination conditions provided improved yields of the alkene products. Thus, elimination of the β-hydroxyphosphine oxide (BHPO) **3** isolated in previous WH olefination, yielded the desired alkene **2**, but with enhanced *Z* stereoselectivity (Table 1, footnote c). The Wittig-Horner reaction with the corresponding phosphine oxide was then the optimal reaction conditions in terms of yield (Table 1, entry 3), considering that both *Z/E* isomers are proper substrates for cyclization.

The use of non-Li bases ("salt-free" conditions),[25a] such as potassium bis(trimethylsilyl)amide (KHMDS), afforded **2** in low yield and no stereoselectivity (Table 1, entry 4). In order to increase the *E* stereoselectivity, a bulky N-(methoxycarbonyl)-P,P-diphenyl-P-phenylsulfanylmethyl phosphazene reagent was also used in the olefination.[28] Unfortunately, the reaction using this phosphazene yielded a complex mixture.

[27] Buss, A.D.; Warren, S. *J. Chem. Soc. Perkin Trans 1*, **1985**, 2307.
[28] a) Alvarez-Gutierrez, J.M.; Peralta-Pérez, E.; Pérez-Alvarez, I.; López-Ortiz, F. *Tetrahedron* **2001**, 57, 3075. b) Peralta, E.; Lopez-Ortiz, F. *Chem. Commun* , **2000**, 2029. c) Shin, W.S.; Lee, K.; Oh, D.Y. *Bull. Korean. Chem. Soc.* **1996**, 17, 981.

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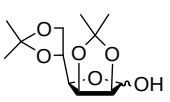
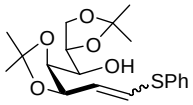
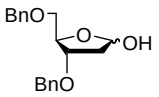
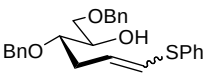
**Table 2.** Olefination of furanoses **4** and **6.**[a]

| Entry | Furanose | Product | Yield (%) *Z*/*E* ratio |
|---|---|---|---|
| 1 |  **4** |  **5** | 63 (1:10) |
| 2 |  **6** |  **7** | 100 (1:1) |

[a] Reaction conditions: Ratio substrate/phosphine oxide/BuLi = 1:4:4.4, solvent= THF, temperature –78 ºC to rt.

Once the optimal conditions had been established, furanoses **4** and **6** were olefinated following the best conditions to afford alkenes **5** and **7**, respectively. The yield of alkenes were 63% for **5** (Table 2, entry 1) and 100% in the case of alkene **7** (entry 2).

To broaden the scope of the reaction, in a parallel work in our laboratory,[29] other configurations and/or different protecting groups were also olefinated. Thus, properly protected furanoses yielded alkenes **8-12** in low to excellent yields, which, in some cases, were improved by elimination of the corresponding BHPO intermediates (Figure 1). The arabino derivative **9** was also obtained by Wittig reaction in good yield (70%), but mixed with minor amount (10%) of diene product as a result of a benzyl elimination process in the alkene.

Adding these results to the ones carried out in this thesis, we could infer that isopropylidene-protected furanoses gave lower yields (21-63%), probably due to higher steric hindrance. In contrast, olefination of the 2-deoxy-ribose derivative **6** yielded alkene **7** quantitatively probably due to the lack of hydroxyl group near the reactive centre (Table 2, entry 2).

[29] Boutureira. O., Ph.D Thesis, URV, In preparation.

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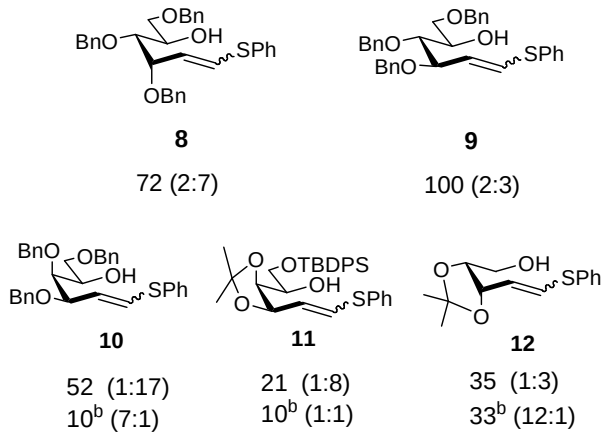
Taking into account that initial cycloaddition is nonreversible,[30] some of the results (Table 1, entry 3 and Figure 1) also revealed that the *threo*-BHPO intermediate, which renders *E* olefin, eliminates more easily than the *erythro*-BHPO in the Wittig-Horner conditions. This is why, in contrast to predominantly obtained *E* alkene in the one-step olefination, *Z*-enriched mixture is mainly obtained in the elimination of the BHPO.

**Figure 1.** Alkene products **8-12** synthesized in our laboratory.




Yield% (*Z:E* ratio)
[b]Additional yield obtained by elimination of the isolated β-hydroxyphosphine intermediate

As we described, in general the best conditions for olefinating pentoses were the WH reactions, using a phosphine oxide. Wittig reaction resulted in complex mixtures or improved amounts of diene and/or epimerized products. Instead of Wittig-Horner olefination, Rollin et al. used a Wittig reaction to synthesize carbohydrate-derived vinyl sulfides in good yields with, in general, preferential formation of the *Z* isomer,[31] but, in their work, products with xylose configuration were not reported. They described, as it is also our case with phosphine oxides, different product selectivities (*Z/E* alkenes, diene or epimerized mixtures) depending on the configuration of the starting pentose. We have evidence that product distribution it is also a consequence of different protecting groups,

[30] Robiette, R.; Richardson, J; Aggarwal, V.K.; Harvey, J.N. *J.Am.Chem.Soc*. **2005**, *127*, 13468 and references cited therein.
[31] Aucagne, V.; Tatibouët , A., Rollin, P. *Tetrahedron* **2004**, *60*, 1817.

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reagents and/or conditions used. For instance, Rollin described that 2-deoxy-pyranosides appeared to be rather prone to diene formation under Wittig conditions. In our hands, however, 2-deoxy-furanose **6** afforded the expected alkene **7** in quantitative yield with no traces of the corresponding diene byproduct, despite working under more basic Wittig-Horner conditions (Table 2, entry 2). Moreover, in the case of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, the Wittig reaction yielded eliminated and/or epimerized products,[31] instead of the alkene product obtained with phosphine oxides.[32] With regard to the influence of protecting groups, in the Wittig-Horner olefination, conformationally free benzylated derivatives gave, in general, better yields than conformationally constrained isopropylydene protected ones.

[32] Kövér, A.; Matheu, M.I ; Diaz, Y.; Castillón, S. *Arkivoc,* **2007**, 364.

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**Cyclization**

Cycloetherification (and cyclolactonization) induced by electrophilic reagents are important tools in the synthesis of complex organic molecules.[33] The conditions of cyclization are, in general, independent of the nucleophile (usually O[34], N,[33a] S,[35] and C), and electrophilic reagents commonly used are, among others, mercury,[36] sulfur,[37] bromine,[38] selenium,[34,35,39] and iodine.[34,35,40]

The regioselectivity in alkenol cyclizations can be explained by the Baldwin's rules[41], based on geometric requirements in the transition state during nucleophile-driven cyclization. However, these rules often could not be applied when cyclizations are electrophilic or thermodynamically driven.[33e,42] This rules classify cyclization reactions by a simple system involving: 1) the ring size being formed; 2) whether the bond that breaks as the ring forms is inside (*endo*) or outside (*exo*) the new ring; and 3) whether the electrophile is an sp (*di*gonal), $sp^2$ (*trig*onal), or $sp^3$ (*tetra*hedral) atom.

According to Baldwin's rules 5-*exo*-*trig* cyclization is generally preferred to 6-*endo*-*trig* but the percentage of 6-*endo* products increases as substitution increases at the terminal olefinic carbon atom.[43]

The situation is complex for polyhydroxylated alkenes (Scheme 2), since several cyclization paths may be followed. Cyclizations from tetrahydroxyhexenes with a terminal

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[33] a) Bartlett, P. A. *Asymmetric Synthesis* (Ed. J. D. Morrison), Academic Press, London, **1984**, vol. 3, p. 411-454.b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. d) Orena, M. *Houben-Weyl* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schumann), Georg Thieme Verlag, Stuttgart, New York, **1995**, vol. 21e, p. 4760-4817. e) Knight, D.W. *Progress in Heterocyclic Chemistry* **2002**, *14*, 19.

[34] Bravo, F.; Castillón, S. *Eur. J. Org. Chem.* **2001**, 507.

[35] Jana, G.; Viso, A.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2003**, 209.

[36] a) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317. b) Harding, K. E.; Marman, T. H. *J. Org. Chem.* **1984**, *49*, 2838. c) Pougny, J. R.; Nassr, M. A. M.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375. d) Bravo, P.; Resnati, G.; Viani, F.; Arnone, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 839.

[37] a) López-Tudanca, P. L.; Jones, K.; Brownbridge, P.; *Tetrahedron Lett.* **1991**, *32*, 2261. b) Eames, J.; Warren, S. *Tetrahedron Lett.* **1996**, *37*, 3525.

[38] a) Ohfune,Y.; Hori, K.;Sakaitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079. b) Ting, P.C.; Bartlett, P.A. *J. Am. Chem. Soc.* **1984**, *106*, 2668.

[39] a) Nicolaou, K.C.; Magolda, R.L.; Sipio, W.J.; Barnette, W.E.; Lysenko, Z.; Joullie, M.M. *J. Am. Chem. Soc.* **1980**, *102*, 3784. b) Webb II, R.R.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 1357. c) Déziel, R.; Malenfant, E. *J. Org. Chem.* **1995**, *60*, 4660. d) Bravo, F.; Viso, A.; Castillón, S. *J. Org. Chem.* **2003**, *68*, 1172.

[40] a) Do Amaral, L.; Melo, S.C. *J. Org. Chem.* **1973**, *38*, 800. b) Elvey, S.P.; Mootoo, D.R. *J. Am. Chem. Soc.* **1992**, *114*, 9685. c) Williams, D.R.; White, F.H. *J. Org. Chem.* **1987**, *52*, 5067. d) Bedford, S.B.; Bell, K.E.; Fenton, G.; Hayes, C.J.; Knight, D.W.; Shaw, D. *Tetrahedron Lett*. **1992**, *33*, 6511. e) Díaz, Y; Bravo, F.; Castillón, S. *J. Org. Chem.* **1999**, *64*, 6508. f) Bravo, F.; Díaz, Y.; Castillón, S. *Tetrahedron: Asymmetry* **2001**, *12*, 1635.

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

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

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

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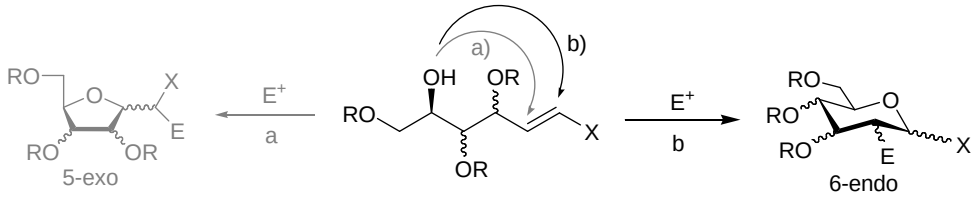
double bond (usually derived from pentoses) have been widely studied, and the preferred process is 5-*exo* (Scheme 2, path a, X=H).[44]

**Scheme 2**




In the case of 1-X-5-hydroxy alkenes the regioselectivity of the cyclization can be controlled by the substituent X of the double bond. Thus, electron-withdrawing X groups, such as sulfoxides, sulfones[45], carboxy esters, etc.[46] lead to 5-*exo* cyclizations (Scheme 2, path a) to render highly substituted tetrahydrofurans. In the other hand, electron-donating X groups, such as alkyl,[47] alkoxy,[48,49] or sulphide[50], direct the process to 6-*endo* cyclization products (Scheme 2, path b)

With this background and the alkenols in hand, we decided to explore their electrophilic-induced cyclization. We thought the phenylsulfanyl group attached to the terminal carbon should favour the endo cyclization because sulfur is able to stabilize the carbocation intermediate in the cyclization step. Thus, we envisioned that 2-deoxy-2-iodo glycosyl donors could be obtained by the regioselective 6-endo iodine-induced cyclization of the alkenols.

In all cases, the *Z*/*E* mixtures of alkenes previously synthesized proved to be inseparable;[51] hence, the cyclization reactions were assayed directly on the mixture of

[44] Freeman, F.; Robarge, K.D. *J. Org. Chem.* **1989**, *54*, 346 and references cited therein. b) Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. *Carbohydr. Res.* **1987**, *103*, 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.
[45] Marot, C.; Rollin, P. *Tetrahedron Lett.* **1994**, *35*, 8377.
[46] Guindon, Y.; Soucy, F.; Yoakim, C.; Ogilvie, W.W.; Plamondon, L. *J. Org. Chem.* **2001**, *66*, 8992.
[47] Armstrong, R.W; Teegarden, B.R. *J. Org. Chem.* **1992**, *57*, 915.
[48] a) Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 1525-1528. b) Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 683.
[49] Paquet, F.; Sinaÿ, P. *Tetrahedron Lett.* **1984**, *25*, 3071.
[50] Gallucci, J. C.; Ha, D.-C.; Hart, D. J. *Tetrahedron* **1989**, *45*, 1283.
[51] Alkene **5** was partially separable in a *E* pure fraction and a *E/Z* mixture.

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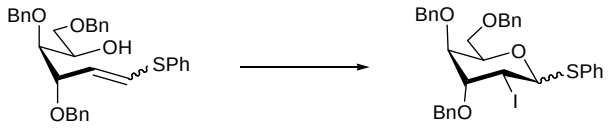
diastereomers. Cyclization from the pure *E* alkenes was possible from the Wadsworth-Emmons alkene products.[52]

**Table 3.** Cyclization of alkenyl sulfide **2** induced by electrophilic iodine containing reagents.




**2** **13**

| Entry | (*Z*/*E* ratio) | [I] (eq) | Solvent | Temp (ºC) | t (h) | Yield **13** (%) | α/β |
|---|---|---|---|---|---|---|---|
| 1[a] | 1:4 | $I_2$ (3) | $CH_3CN$ | -30 to rt | 1 | 37 | 1:4 |
| 2[b,c] | 1:4 | $I_2$ (3) | ether | -78 to rt | 4 | - | - |
| 3 | 1:4 | NIS (1.5) | $CH_3CN$ | -30 | 1 | 42 | 1:5 |
| 4 | 1:4 | $Ipy_2BF_4$ (2.2) | $CH_2Cl_2$ | -78 to rt | 2 | 30 | 1:3 |
| 5 | 1:4 | $Ipy_2BF_4$ (2.2) | $CH_3CN$ | -30 to rt | 2 | 44 | 1:7 |
| 6[d] | 1:17 | IDCP (2.2) | $CH_2Cl_2$ | -30 to 10 | 3 | 54 | 1:15 |
| 7[d] | 1:12 | IDCP (2.2) | $CH_3CN$ | -30 to 10 | 3 | 77 | 1:10 |
| 8[d] | 7:1 | IDCP (2.2) | $CH_3CN$ | -30 to 10 | 3 | 73 | 10:1 |

Reagents and conditions: alkene (0.16 mmol) in solvent (0.5M). [a] $NaHCO_3$ used as base.[b] KH used as base.[c] Reaction quenched at –30 ºC gave starting product.[d] Reaction mixture was maintained at 0ºC and after 2.5 h warmed to 10ºC to for total completion(TLC).

Electrophile-induced cyclization was first studied for the xylose derivative. When the enol ether **2** was treated with $I_2$ as the electrophile and $NaHCO_3$ as the base in acetonitrile at –30ºC, a facile ring closure took place to result in the exclusive formation of the 6-*endo* cyclization product **13** in 37% yield. Indeed, 5-*exo* cyclization product was not observed (Table 3, entry 1).

In order to improve the nucleophilicity of the alcohol, KH was used as a base (Table 3, entry 2). Under these conditions the alkene did not react at low temperature

[52] Other methods to obtain *E* vinyl sufides in Sridhar, R.; Surendra, K.; Krishnaveni, N.S.; Srinivas, B.; Rao, K.R. *Synlett*, **2006**, 3495 and references cited therein.

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(below –30ºC) and decomposed at higher temperatures. This outcome discloses that the strength of internal nucleophile does not have influence in the rate of the cyclization but it depends upon whether activated alkene reaches the appropriate intermediate conformation.[41] Low yields of $I_2$ induced-cyclization, likely due to the iodine nucleophilic counter-ion side-reactions, led us to assay N-iodosuccinimide (NIS) as electrophile. Thus, using from 1.5 to 2.2 equivalents of NIS in $CH_3CN$ at –30ºC, thioglycoside **13** was obtained in 35-42 % yield as an anomeric mixture (best result, Table 3, entry 3). As NIS is an excellent activator of the glycosyl donor **13** formed, other less active electrophilic reagents, like bis(pyridine) iodonium tetrafluoroborate ($IPy_2BF_4$) and iodonium dicollidine perchlorate (IDCP), were also tested. In the case of $IPy_2BF_4$, the yield was similar to that obtained with NIS, but a slight improvement was found with the use of a polar solvent ($CH_3CN$ vs. $CH_2Cl_2$, Table 3, entries 4, 5). With IDCP, the reaction gave a better yield and, in regard to solvents, the same behaviour than with $IPy_2BF_4$ was also observed (Table 3, entries 6, 7). Therefore, for the cyclization of **2**, the best conditions were to use IDCP as the electrophilic reagent in $CH_3CN$, what afforded 2-deoxy-2-iodo-guloside **13** (77%) as a 1:10 α/β mixture (Table 3, entry 7). As shown by the α/β ratio, both isomers (*Z* and *E*) underwent cyclization. Although, as cyclization with *Z*-enriched mixture showed, the *Z* alkene requires higher temperatures (ΔT ~10 ºC) than the *E* isomer. In addition, the cyclization of Z-enriched alkene afforded thioglycoside **13**α as major product, which was obtained as minor product in the *E*-enriched alkene cyclizations (Table 3, entries 7, 8).

It is worthy to note that the stereochemical outcome in regard with cyclization of *Z*-thioenol ethers described here is in contrast with that observed by Mukaiyama[48] in his similar stereoselective cyclization of Z-hydroxy enol ethers (Scheme 3).

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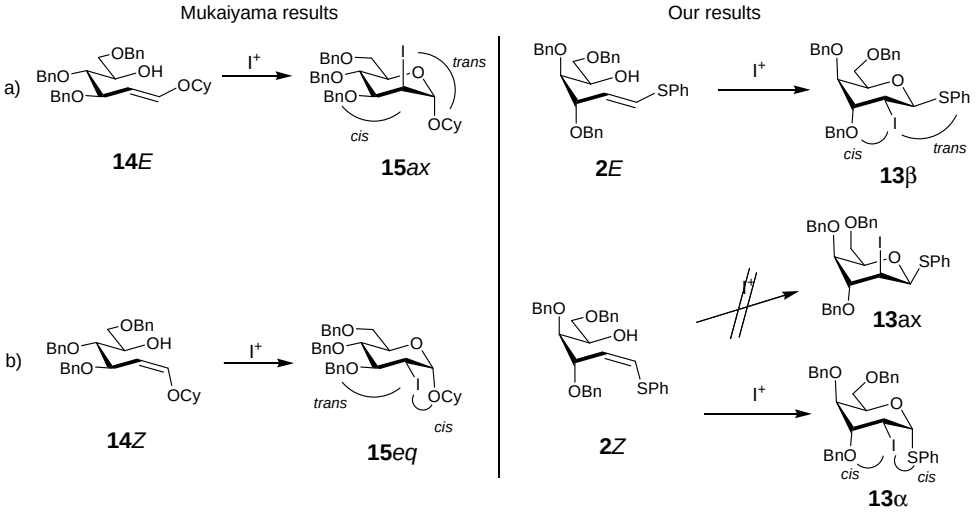
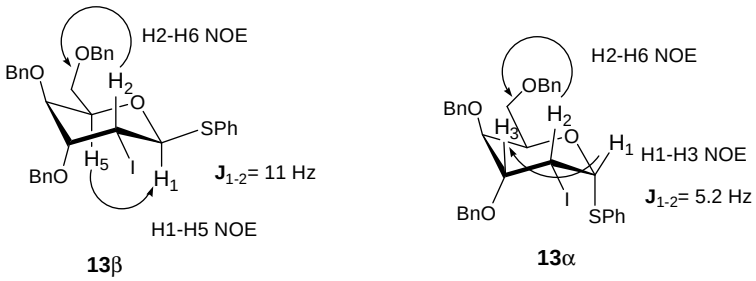
**Scheme 3**




According to this previous work, when hydroxy enol ether **14** is subjected to iodonium-induced cyclization two different products were obtained depending on the *E/Z* stereochemistry of the alkene. In the case of enolether **14***E* the cyclization took place to afford the product **15***ax*, in which the relative stereochemistry C3-alkoxy/C2-iodo is *cis* and OCy/I groups are in *trans* arrangement. This outcome is equivalent to that obtained for us in the cyclization of alkene **2***E* to provide **13**β (Scheme 3a). On the other hand, hydroxy enolether **14***Z* gave product **15***eq* in which relative stereochemistry C3-alkoxy/C2-iodo is *trans* and OCy/I groups are in *cis* arrangement. This configuration was different from that obtained in product **13**α (from **2***Z*), with C3-alkoxy/C2-iodo and SPh/I groups in *cis* arrangement.

**Figure 2.** Determination of configuration of **13**β and **13**α by NMR spectroscopy.



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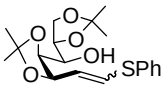
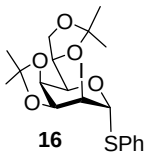
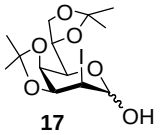
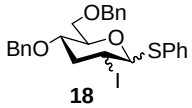
From the analysis of the NMR spectroscopy data (Figure 2), and especially from NOESY experiments, it was indeed determined that the cyclization product obtained from **2** was always with C3-alkoxy/C2-iodo in a *cis* arrangement (**13**$\alpha$ and **13**$\beta$ products). Thus, in the case of the cyclization of *Z*-alkene, the relative configuration of C3-alkoxy/C2-iodo groups are different from that of obtained by Mukaiyama and co-workers.

Electrophile iodonium-induced cyclization was then studied for mannose derivative **5** and 2-deoxyribose derivative **7.**

**Table 4.** Cyclization of alkenyl sulfides **5** and **7** induced by electrophilic iodine.

| Entry | Starting material (*Z*/*E* ratio)[a] | Cyclization conditions | Cyclization product | Yield (%) | α/β ratio[b] |
|---|---|---|---|---|---|
| 1 |  **5** (0:1) | IDCP (2.2) $CH_3CN$ -45to -30ºC, 2h |  **16** | 97 | 1:0 |
| 2 | **5** (1:6) | IDCP (2.2) $CH_3CN$ -45ºC-rt, 1.5h | **16** | 48 | 1:0 |
| 3 | **5** (1:6) | IDCP (2.2) $CH_3CN$ -30ºC-rt, 3.5h | **16** | 60 | 2:1 |
| | | |  **17** | 19 | - |
| 4 | **7** (1:1) | NIS (1.5) $CH_3CN$ -30ºC, 0.5 h |  **18** | 47[c] | - |

[a] Determined by integration of the olefinic protons in the $^1$H NMR spectrum. [b] Determined by integration of the anomeric protons in the $^1$H NMR spectrum of the crude reaction mixture. [c] A 1: 1 C-2 epimeric mixture was obtained, which decomposes on standing.

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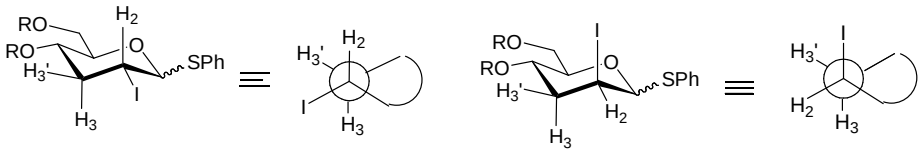
For the cyclization of **5** (like for **2**) the best conditions were to use IDCP as the electrophilic reagent in $CH_3CN$, which afforded 2-deoxy-2-iodo-D-*glycero*-D-*talo*-pyranoside **16** (Table 4, entries 1, 2, 3).

From diastereomerically pure **5***E*, **16α** was exclusively obtained in 97% yield (Table 4, entry 1). In contrast, cyclization of a 1:6 *Z*/*E* mixture of **5** rendered **16α** but in a much lower yield (48%) (Table 4, entry 2). Forcing the reaction conditions (higher temperatures and longer reaction times) led to cyclization of both the *E* and *Z* isomers to give **16** in 60% yield (α/β ratio = 2:1) but also produced the corresponding 2-iodo-lactol **17** (19%) as a consequence of the activation of the sulfanyl group in the product **16** (Table 2, entry 3).

To gain insight into the stereochemical outcome, the cyclization was carried out starting from the alkenyl sulfide **7**, which lacks an allylic alkoxy group. Cyclization of **7** with IDCP was slow and only afforded minor amounts of product **18** (ca. 6%) The reaction of **7** with NIS afforded a mixture of four compounds that were separated into two fractions. On the basis of NMR spectroscopic analysis, these fractions were assigned to a 1:1 C-2 epimeric mixture of 2,3-dideoxy-2-iodo-thioglycosides **18** with their corresponding α/β anomers (47% yield, Table 2, entry 4). This epimeric mixture was separated in their axial and equatorial C2 products (both of them as a α/β mixtures) and their structure assigned by NMR spectroscopy ($^1$H, $^{13}$C, monodimensional TOCSY) (Figure 3).

**Figure 3.** Determination of the structure of compounds **18**eq and **18**ax by NMR spectroscopy.




$J_{H2-H3}$ trans-diaxial (10.7-10.9 Hz)
$J_{H2-H3'}$ axial-equatorial (4.0-4.5 Hz)

$J_{H2-H3}$ similar to $J_{H2-H3'}$
(3-5 Hz)

These cyclization assays revealed that the cyclization conditions are very sensitive to the configurational nature of the hexenyl sulfide. The optimal conditions for xylose derivative **2** and mannose derivative **5** (IDCP, Table 3, entry 7 and Table 4, entry 1) are different from those for 2-deoxyribose **7** (NIS, Table 4, entry 4). Furthermore, in a contemporary work in our laboratory,[29] alkenes **8-12** were also cyclizated under

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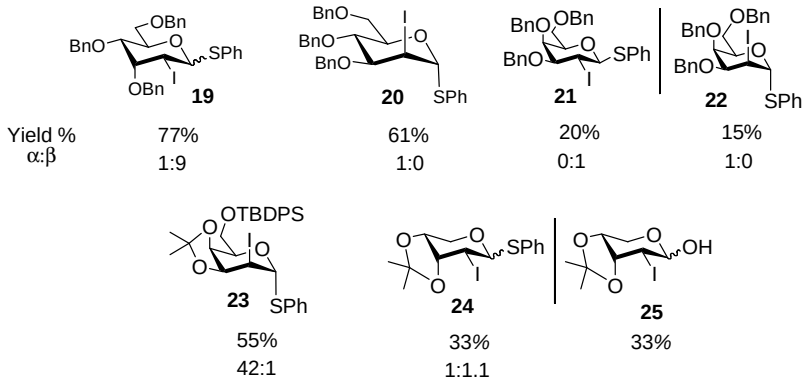
individually optimized conditions to render thioglycosides **19-24** and pyranose **25** (Figure 4). The 2-deoxy-2-iodo-thioglycosides **13**, **16**, **19**, **20**, **22-24** were found to be quite stable and can be stored in the refrigerator for several months without significant decomposition. The only labile 2-deoxy-2-iodo-thioglycosides were **18** and **21**, which decomposed on standing.

**Figure 4.** Thioglycosyl donors **18-24** and pyranose **25** synthesized in our laboratory.




This series of experiments established that the hydroxy-hexenyl sulfides undergo a completely 6-*endo* regioselective electrophilic iodine reagent-induced cyclization to afford the corresponding thiopyranosides. 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.

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, like in the case of arabino derivative **9**, 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 the mannose derivative **5** (Table 4, entry 2, 3), erythrose derivative **12** (Figure 4, product **24** and **25**), and, to a lesser extent, the xylose derivative **2** (Table 3).

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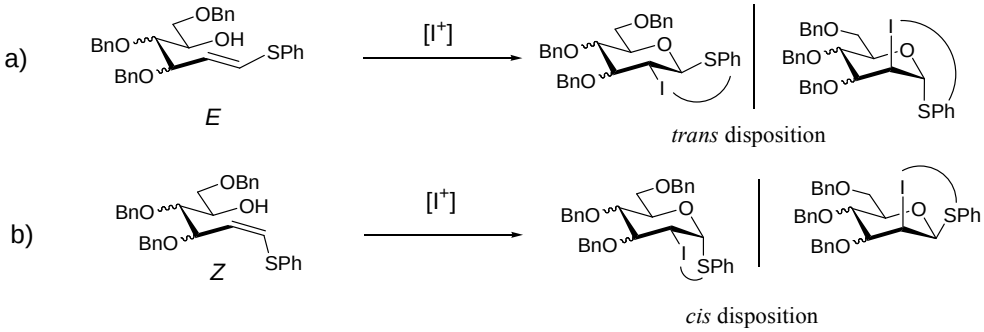
Besides, the cyclization reaction is highly stereoselective and very predictable in terms of the stereochemical outcome. The relative stereochemistry of C1 and C2 in thioglycosides depends on the configuration of the starting alkene. Thus, the reaction of the *E*-alkenyl sulfide yields a cyclization product in which the iodine atom and phenylsulfanyl group are in a *trans* arrangement (Scheme 4a). In all cases where the *Z* alkene underwent cyclization, 2-iodo-thioglycosides were obtained with the substituents at C1 and C2 in a *cis* disposition. (Scheme 4b)

**Scheme 4**




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. 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[34,53] and is determined by a stereoelectronic effect known as the inside-alkoxy effect.[54]

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 (inside). In this conformation, the C-O σ* orbital is perpendicular to the π-system of

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

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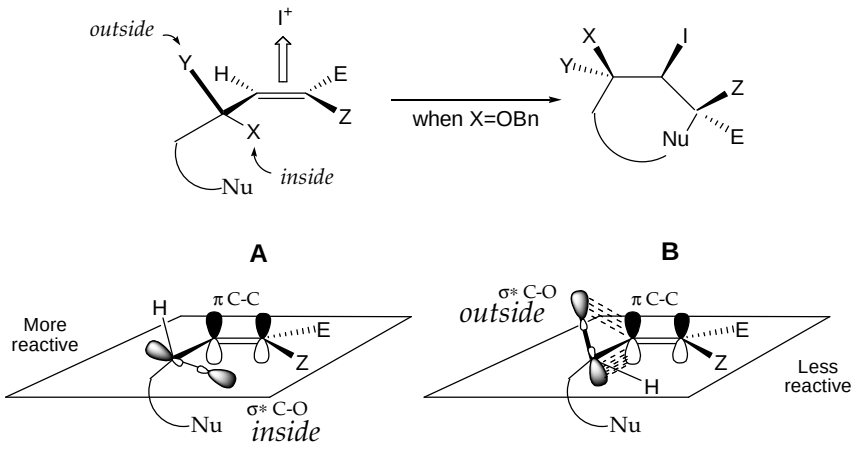
the double bond, which minimizes the electron-withdrawing effect, causing the double bond to be more electron-rich and hence more reactive towards electrophiles (Figure 5, **A**).

**Figure 5.** Inside-alkoxy stereoelectronic effect.




In the other hand, when the allylic alkoxy group is placed perpendicular to this plane (outside), the electron-withdrawing effect applies and thus the double bond is less reactive (Figure 5, **B**).

The stereodirecting role of the allylic group is evident in the cyclization of **7**, which lacks an allylic OR group. Since there is no stereoelectronically preferred conformation in the cyclization of **7**, the cyclization reaction yields a C-2 epimeric mixture of 2-iodo-thioglycosides (**18**).

The inside-alkoxy effect may well explain why the *Z* thioether is less reactive than the corresponding *E* isomer (Schemes 5 and 6). 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 (Scheme 5).

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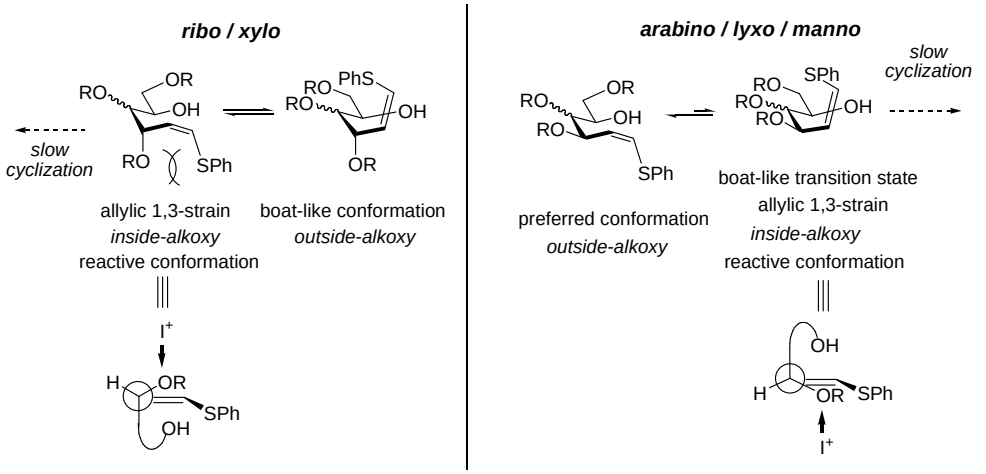
**Scheme 5**




For some compounds, such as the arabinose derivative **9***Z* (Figure 1), 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 in the case of enol thioethers. By contrast, with hydroxyl enol ethers, the outside-alkoxy cyclized products were obtained. This results 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 enol ether (see **14***Z*, Scheme 3), which is reactive towards cyclization even in the *outside-alkoxy* conformation. 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 (Scheme 6). For the *xylo* and *ribo* derivatives **2** and **8**, 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 the *arabino* and *lyxo* derivatives **9** 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.

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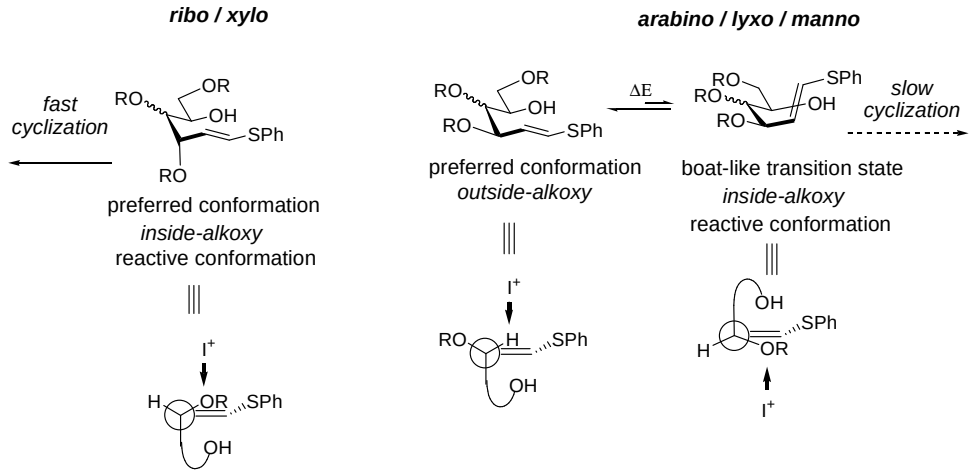
**Scheme 6**




The higher reactivity of **5** compared to **10** can be explained by the presence of the isopropylidene group, which restricts the conformational freedom and accordingly favors cyclization.

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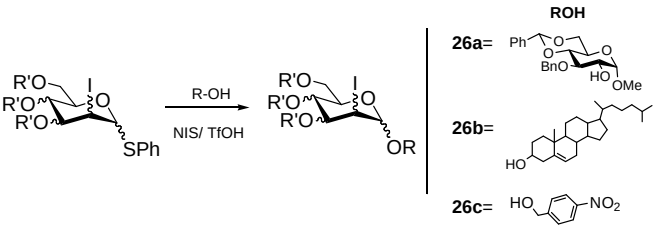
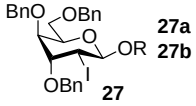
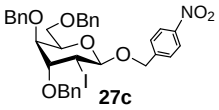
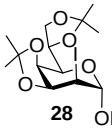
**Glycosylation**

The glycosyl donors **13** and **16** were tested for stereoselective glycosylation of methyl 4,6-*O*-benzylidene-3-*O*-benzyl-α-D-glucoside (**26a**) and cholesterol (**26b**) under typical conditions described for thioglycosides.[55] A low temperature assay with glycosyl donor **13** and *p*-nitrobenzyl alcohol (**26c**) were also carried out (Table 5).

For the sake of comparison, glycosylation experiments carried out in a parallel work in our laboratory have been included in Figure 6.[29]

**Table 5.** Stereoselective glycosylation of **26a**, **26b** and **26c** from 2-deoxy-2-iodo-thioglycosides **13** and **16**.




| Entry | Starting material | Glycosylation product | | Glycosylation conditions[a] | Yield (%) | α/β ratio[b] |
|---|---|---|---|---|---|---|
| 1 | **13** |  | **27a**<br>**27b** | -40ºC 3h<br>-40ºC 3h | 61%<br>66% | 1:16<br>1:8 |
| 2 | **13**[c] |  | | -80ºC 4h | 72% | 1:40 |
| 3 | **16** |  | **28a**<br>**28b** | -60ºC 1h<br>-20ºC 20h | 69%<br>57% | 40:1<br>8:1 |

[a] 1 mmol glycosyl donor, 2 mmol glycosyl acceptor, dry $CH_2Cl_2$, NIS (2.2 mmol), 20 mol% TfOH. [b] Determined by integration of the anomeric proton signals in the $^1H$ NMR spectrumof the crude reaction mixture. [c] 28% of starting product was recovered.

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

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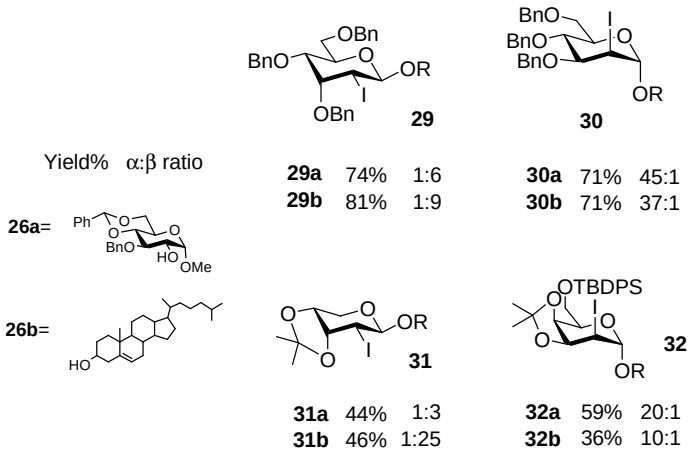
Starting from 1,2-*trans*-diequatorial substituted glycosyl donors **13** and **19**, glycosides **27a,b** and **29a,b** were obtained in yields from 61% to 81% with α/β ratios between 1:6 and 1:16 (Table 5, entry 1 and Figure 6). Improved 1:40 α/β ratio was obtained in the glycosylation of *p*-nitrobenzyl alcohol **26c** with donor **13** to afford **27c** (Table 5, entry 2), probably as a result of the low temperature reactions.

In the case of 1,2-*trans*-diaxial substituted glycosyl donors, acceptors **26a** and **26b** were glycosylated with **16** to afford **28a** and **28b** in 69% and 57% yield, respectively.(Table 5, entry 3). Surprisingly, glycosylation of **26b** with **16** to give **28b** proceeded with lower α-selectivity (8:1) than in the case of **30b** and **32b**, probably due to the higher temperature required to promote glycosylation (Table 5, entry 3 and figure 6).

**Figure 6.** Glycosylated products **29-32** synthesized in our laboratory.




When compared with **13** and **19**, the 1,2-trans-diaxial substituted glycosyl donors **16**, **20** and **23** provided improved stereoselectivities, especially in the glycosylation of **26a**. 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-*talo*-pyranosyl acetates.[56]

To address the stereoselective results obtained in the glycosylation step, we envisioned that oxocarbenium intermediates play an important role in the stereoselectivity

[56] Roush, W. R.; Narayan, S. *Org. Lett*. **1999**, *1*, 899.

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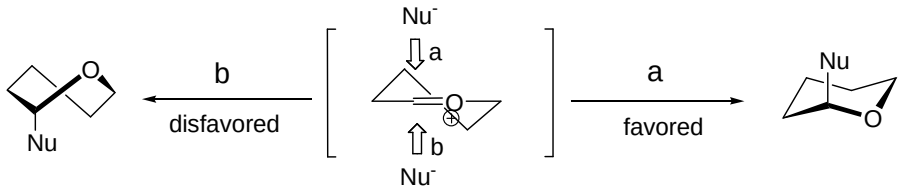
of the glycosylation reactions of 2-deoxy-2-iodo-1-thio-glycosides rather than the corresponding iodonium-ion intermediates.[13,57,58]

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 the oxocarbenium ion occurs with a facial preference to give a chair-like transition state (Scheme 7, path a), instead of higher energy twist-boat conformation (Scheme 7, path b).

**Scheme 7**




Thus, first analysis would lead to the involvement of two different chair-like oxocarbenium conformations (Scheme 8). According to this stereoelectronic effect, the reaction of each conformer is expected to provide a different diastereomer of the product.

The selectivity observed is determined by both the ground-state conformational preferences of the oxocarbenium intermediates **Ia-c** and **IIa-c** and the relative reactivity of each conformer, as mandated by Curtin-Hammet/Winstein-Holness kinetics[59] (Scheme 8).

[57] a) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521. b) Bravo, F.; Viso, A.; Alcázar, E.; Molas, P.; Bo, C.; Castillón, S. *J. Org. Chem.* **2003**, *68*, 686.
[58] Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, 5, 1871.
[59] Seeman, J.I. *Chem. Rev*. **1983**, *83*, 83.

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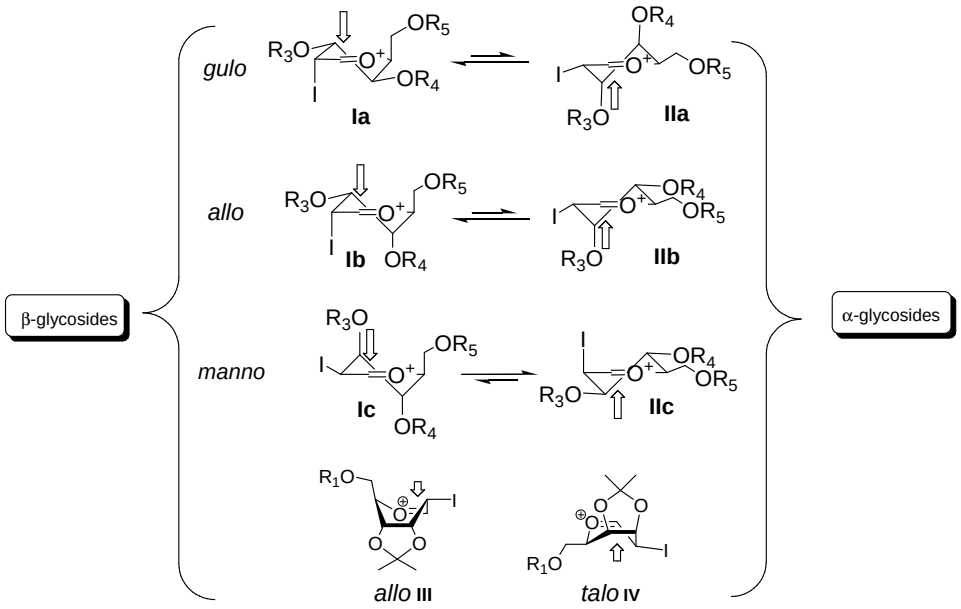
**Scheme 8**




Thus, according to the recent results reported by Billings and co-workers[60] iodine-axial intermediates **Ia**,**b (***gulo* and *allo*) and **IIc** (*manno*) are likely to be more stable than the corresponding iodine-equatorial conformers due to stabilizing hyperconjugative interactions between $\sigma_{C\text{-}I}$ and $\pi^*_{C\text{-}O}$ of the oxocarbenium.

However, the selectivity obtained in the glycosylation experiments cannot only be addressed in terms of relative conformer population but developing destabilizing interactions in the transition state (transition-state effects) should also be accounted for. Thus, the reactivity the oxocarbenium conformers towards nucleophilic attack may be affected by steric interactions between the C3 alkoxy substituent and the incoming nucleophile (conformers **IIa,b** and **Ic** in scheme 8).

Consistent with this, glycosylation of *manno* **20** and *gulo* **13** derivatives provided excellent α- and β-selectivities, respectively: by far the more stable axial **Ia** and **IIc** conformer is also the more reactive one towards nucleophilic attack. *Allo* derivative **19** showed moderate β-selectivity. When compared with the *gulo* **13** derivative, the lower selectivity magnitude obtained could be explained by ground-state conformational preference variations. In the *allo* derivative, the more reactive conformer is also the more

[60] Billings, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171.

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stable one (axial iodine, **Ib** ) although in this case 1,3-diaxial interaction between iodine and C-4 alkoxy group may increase its energy with respect to the case of gulo derivative, where such destabilizing interactions do not exist. Finally, in order to rationalize the observed favored α-face approach of the donors **16, 23** (which render glycosyl products **28** and **32** respectively) and β of the donor **24** (which render products **31**), we speculate that the reaction might operate by way of a constrained conformation[58,61] such as **IV** (talo) and **III** (allo), respectively.

These results are in agreement with those reported in the glycosylation using 2-deoxy-2-phenylselenenyl-1-thio-glycosides as glycosyl donor.[62]

## Conclusion

We have presented a general procedure for the stereoselective synthesis of 2-deoxy-2-iodo-hexo-pyranosyl glycosides from furanoses. The proposed methodology provides a new avenue for accessing 2-deoxy-oligosaccharides. 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-pyranosides, a new type of glycosyl donor; and glycosylation. The olefination reaction affords the alkenyl sulfanyl derivatives in good to excellent yields, except in cases where the conformational freedom is constrained by protecting groups such as isopropylidene groups.

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 **21**. This is a key point in the overall process because the iodine controls the stereoselectivity of the glycosylation reaction.

[61] 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*, 419–429.
[62] Boutureira, O.; Rodríguez, M. A.; Benito, D.; Matheu, M. I.; Díaz, Y.; Castillón, S. submitted.

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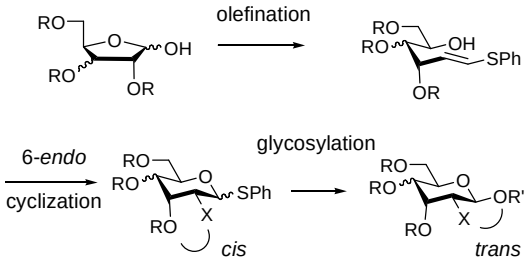
**Scheme 9**




| | olefination (%) | cyclization (%) | glycosylation (%) | (α:/β ) | |
|---|---|---|---|---|---|
| ribose | 72 | 77 | 74 | 1:6 | **29a** |
| | | | 81 | 1:9 | **29b** |
| xylose **1** | 76 | 77 | 61 | 1:16 | **27a** |
| | | | 66 | 1:8 | **27b** |

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 (Scheme 9), but more modest for those with an *arabino* or *lyxo* configuration. The glycosylation reaction carried out with cholesterol, which can be looked upon as a model of the aglycones present in natural products, and with monosaccharide **26a**, proceeded with good yields and good to excellent stereoselectivities. The glycosidic bond created in the major isomers was always *trans* to the iodine at C2.

Although phenyl 2-deoxy-2-iodo-1-thio-glycosyl donors of all configurations can be accessed using the proposed procedure, it is particularly effective at providing 2-deoxy-2-iodo-D-*gulo*- and D-*allo*-glycosides (Scheme 9). These glycosides are precursors of 2-deoxy-glycosides of *ribo* and *xylo* configuration, which are difficult to obtain by the classical methodology starting from glycals.[63]

[63] a)Wittman, M.D.; Halcomb, R.L.; Danishefsky, S.J. *J. Org. Chem.* **1990**, *55*, 1979. b) Danishefsky, S.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

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# Experimental Part

## General remarks

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (DCM), tetrahydrofuran (THF), diethyl ether and DMF were dried using a solvent purification system (Pure SOLV system-4®). Solvents were purified using standard procedures.[64] $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian® Gemini 300 (300 MHz and 75 MHz respectively) or in a Varian® Mercury 400 (400 MHz and 100 MHz respectively) spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm $^{1}H$, 77.23 ppm $^{13}C$) or $Me_4Si$ as an internal reference (0.00 ppm) or $H_3PO_4$ ($^{31}P$) as external standard, unless otherwise specified. 2D correlation spectra (TOCSY, gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells, Elemental analysis (C, H, N, S) was performed on a Carlo Erba® EA 1108 Analyser in the Servei de Recursos Científics (SRCiT-URV). Analytical thin layer chromatography (TLC) was performed on Merck® silica gel 60 $F_{254}$ glass or aluminium plates. Compounds were visualized by UV (254 nm) irradiation or dipping the plate in a suitable developing solution.[65] Flash column chromatography was carried out using forced flow or by gravity of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1, 2, or 4 mm plates of Kieselgel 60 $PF_{254}$ silica gel, depending on the amount of product. Medium-pressure liquid chromatography (MPLC) was performed using SDS® silica gel 60 A CC (6-35μm). Melting points were recorded with a Tottoli Büchi® 510 melting apparatus and are uncorrected. Starting materials **1**, **4** and **6** were prepared by general organic chemistry reactions. Iodonium dicollidine perchlorate (IDCP) was prepared following the method reported by Lemieux and co-workers[66].

[64] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford, **1989**.
[65] Reactivos Merck "*Reactivos de coloración para cromatografía en capa fina y papel*" E. Merck. Darsmtadt (RF Alemana) **1980.**
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## General procedure for Wittig-Horner Olefination (WH)

*n*-BuLi (4.4 mmol) was added to a solution of diphenyl phenylsulfanylmethyl phosphine oxide (4 mmol) in THF (26 mL) at -78 °C. The mixture was left to stir at low temperature for 30 min. A solution of the corresponding furanose (1mmol) in THF (2 mL) was then added dropwise. The mixture was allowed to warm to room temperature overnight. A saturated solution of $NH_4Cl$ was then added and the olefination product was extracted with ether. The combination of ethereal layers was dried with $MgSO_4$ and concentrated. The crude reaction was then purified by chromatographic techniques.

### Elimination from the β-hydroxy-phosphine oxide intermediate to afford the alkene

A mixture of the β-hydroxyphosphine oxide intermediate and diphenyl (phenylthiomethyl) phosphine oxide, recovered from the Wittig-Horner reaction, was solved in THF (30 mL) and then an equivalent amount in weight of NaH 60% was added. The reaction mixture was stirred at room temperature for 5 h and then quenched by adding saturated aqueous $NH_4Cl$. The mixture was extracted with $Et_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by chromatographic techniques to afford the alkene.

## General procedure for iodonium-induced cyclization

**Method A.**[67] $NaHCO_3$ (0.24 mmol) was added to a 0.5 M solution of alkene (0.16 mmol) in $CH_3CN$ The mixture was cooled to -30 °C and left to stir at this temperature for 5 min. NIS (0.24 mmol) was then added and the reaction mixture stirred for several hours. The reaction temperature was allowed to increase the maximum depending on the reactivity of the substrate (between -30 °C and room temperature). The mixture was diluted with dichloromethane and washed with a saturated solution of $Na_2S_3O_3$. The combined aqueous layer was extracted with dichloromethane. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by chromatography.

**Method B.** IDCP (0.35 mmol) was added to a 0.5M solution of alkene (0.16 mmol) at -30 °C in $CH_3CN$. The reaction temperature was allowed to increase

[67] Bartlett, P. A; Mayerion, J. *J. Am.Chem. Soc.* **1978**, 100, 3850.

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depending on the reactivity of the substrate (from -30 ºC to room temperature). The mixture was diluted with dichloromethane and washed with a saturated solution of $Na_2S_3O_3$. The combined aqueous layer was extracted with dichloromethane. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by chromatographic techniques.

**Method C.**[68] A solution of the alkene (1.0 mmol) was added to a solution of KH 30% (1.3 mmol) in dry $Et_2O$ (7 ml) at -30 ºC. The mixture was left to stir at this temperature for 20 min until solution turned yellow, after which time it was cooled to -78 ºC. A solution of $I_2$ (3 mmol) in $Et_2O$ (7 ml) was then added. The reaction was monitored by TLC (EtOAc:hexane 1:3) and left to stir until cyclization was completed, warming gently if necessary. The reaction was quenched adding with $Et_2O$ and $Na_2S_2O_3$, and the aqueous layer was then extracted three times with $Et_2O$ (3x20 ml). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by chromatographic techniques.

## General Procedure for Glycosylation

A solution of the glycosyl donor (1 mmol) and the glycosyl acceptor (2 mmol) in $CH_2Cl_2$ (4 mL) was stirred with 4Å molecular sieves for 30 min. The mixture was then cooled to -78 ºC, and NIS (3 mmol) and TfOH (0.2 mmol) were added. The mixture was allowed to warm to -40 °C and stirred until the reaction had finished. The reaction mixture was then diluted with $CH_2Cl_2$ and washed with a solution of $Na_2S_3O_3$. The ethereal layer was dried with $Na_2SO_4$ and concentrated. The residue was then purified by radial chromatography.

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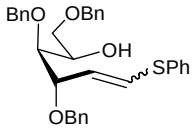
**(*Z/E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-phenylsulfanyl-D-*xylo*-hex-1-enitol (2)**




**2**

**Olefination procedure**

The title compound was prepared following the general WH olefination procedure starting from 2,3,5-tri-*O*-benzil-α/β-D-*xylo*-furanoside **(1)** (1 g, 2.38 mmol) solved in THF (12 ml), diphenyl (phenylthiomethyl) phosphine oxide (3.1 g, 9.54 mmol) in 10 ml of THF, and *n*-BuLi (6.6 ml of 1.6 M hexane solution, 10.5 mmol) for 14 h. The reaction was monitored by TLC (EtOAc:hexane 1:3). The reaction crude was purified by column chromatography (EtOAc:hexane 1:3) to afford vinyl sulphide **2** (951mg, 76 %) as an inseparable 4:1 *E:Z* mixture as a yellowish syrup, as well as an impurified mixture of the corresponding *β*-hydroxy-phosphine oxide intermediate **3**[69] and phosphine oxide.

**Elimination procedure**

NaH 60% (500mg, 12.5mmol) was added to a solution 1.5 g of previously isolated mixture of diphenyl(phenylthiomethyl) phosphine oxide and β-hydroxyphosphine oxide intermediate **3** in dry THF (25ml). The reaction mixture was stirred at room temperature for 1h. The reaction mixture was quenched by the addition of saturated aqueous $NH_4Cl$. The mixture was extracted with $Et_2O$, dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the reaction crude was purified by flash chromatography (from hexane a EtOAc:hexane 1:3) to afford the vinyl sulphide **2** (263mg, 21%) as a yellowish syrup composed of an inseparable 8:1 *Z:E* diatereoisomeric mixture as a yellowish syrup. The total yield of the two reactions was 97%.

[69] NMR data of xylo-β-hydroxy-phosphine oxide derivative **3** **$^1$H NMR** ($CDCl_3$, 400 MHz) δ en ppm: 7.84-6.82 (m, 30H, Haromatic); 4.71-4.56 (m, 5H, $J_{AB}$ = 11.2 Hz., $J_{AB'}$ = 10.0 Hz. $J_{AB''}$ = 3.2 Hz., $5CH_2Ph$); 4.58 (m, 1H, H2); 4.24 (d, 1H, $J_{AB''}$= 3.2Hz., $CH_2Ph$); 4.23 (m, 1H, H1); 4.18 (m, 1H, H3); 4.11 (m, 1H, $J_{5\text{-}4}$= 4.0 Hz., $J_{5\text{-}6a}$= $J_{5\text{-}6b}$= 5.6 Hz., H5); 3.94 (dd, 1H, $J_{5\text{-}4}$= 4.0 Hz., $J_{4\text{-}3}$= 3.8 Hz., H4); 3.52 (ddd, 2H, $J_{6a\text{-}6b}$= 9.2 Hz., $J_{6a\text{-}5}$=$J_{6b\text{-}5}$= 5.6 Hz., H6a, H6b); 2.95 (d, 1H, $J_{OH\text{-}2}$ = 5.6 Hz.,OH). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ en ppm: 138.8-126.9 ($C_{aromatic}$); 78.5 (C4); 78.4 (C3); 74.9, 73.5, 72.7 ($3CH_2Ph$); 71.6 (C6); 70.9 (C2); 70.7(C5); 50.0 (d, $J_{c\text{-}p}$= 70Hz, C1); **$^{31}$P NMR** ($CDCl_3$, 162 MHz) δ in ppm: 35.6 (s, P=O).

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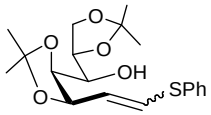
**2***E* (obtained pure under Wadsworth-Emmons conditions): $[\alpha]^{20}_D$: +6.48 (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{33}H_{34}O_4S$: 75.25 C, 6.51 H, 6.09 S. Found: 75.15 C, 6.55 H, 6.10 S. **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.27-7.15 (m, 20H, $H_{aromatic}$); 6.42 (d, 1H, $J_{1-2}$= 15.6 Hz, H1); 5.68 (dd, 1H, $J_{2-3}$= 8.2 Hz, $J_{2-1}$= 15.6 Hz, H2); 4.75 (d, 1H, $J_{AB}$= 11.0 Hz, $CH_2Ph$); 4.57 (d, 1H, $J_{AB}$= 11.7 Hz, $CH_2Ph$); 4.46 (d, 1H, $J_{AB}$= 11.0 Hz, $CH_2Ph$); 4.34 (d, 3H, $J_{AB}$= 11.0 Hz, $CH_2Ph$); 4.10 (dd, 1H, $J_{3-2}$= 8.2 Hz, $J_{3-4}$= 7.5 Hz, H3); 3.83 (m, 1H, $J_{5-4}$= 2.6 Hz, $J_{5-6a}$= $J_{5-6b}$= 6.0 Hz, H5); 3.51 (dd, 1H, $J_{4-3}$= 7.2 Hz, $J_{4-5}$= 2.6 Hz, H4); 3.35 (m, 2H, $J_{5-6a}$= $J_{5-6b}$= 6.0 Hz, $J_{6a-6b}$= 5.7 Hz., H6a, H6b); 2.43 (s, 1H, OH). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2-127.2 ($C_{aromatic}$); 128.8 (C1); 128.0 (C2); 81.4 (C3); 80.2 (C4); 75.1 ($CH_2Ph$); 73.3 ($CH_2Ph$); 71.0 (C6); 70.8 ($CH_2Ph$); 70.0 (C5).

**2***Z* (spectroscopic data extracted from the *E/Z* mixture): **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.38-7.24 (m, 20H, $H_{aromatic}$); 6.55 (d, 1H, $J_{1-2}$= 9.2 Hz, H1); 5.82 (dd, 1H, $J_{2-3}$= 9.6 Hz, $J_{2-1}$= 9.2 Hz, H2); 4.88 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.69 (d, 1H, $J_{AB}$=12.0 Hz, $CH_2Ph$); 4.67 (dd, 1H, $J_{3-2}$= 9.0 Hz, $J_{3-4}$= 3.0 Hz, H3); 4.57 (d, 1H, $J_{AB}$ = 11.2 Hz, $CH_2Ph$); 4.45 (d, 3H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 3.96 (m, 1H, $J_{5-4}$= 6.0 Hz, $J_{5-6a}$= $J_{5-6b}$=2.8 Hz, $J_{5-OH}$= 6.8 Hz, H5); 3.72 (dd, 1H, $J_{4-3}$= 3.0 Hz, $J_{4-5}$= 6.0 Hz, H4); 3.43 (m, 2H, $J_{5-6a}$= $J_{5-6b}$= 2.8 Hz, $J_{6a-6b}$= 6.0 Hz, H6a, H6b); 2.53 (d, 1H, $J_{OH-5}$= 6.8 Hz, OH). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4-127.1 ($C_{aromatic}$); 128.7 (C1); 128.0 (C2) 80.0 (C3); 77.3 (C4); 75.1 ($CH_2Ph$); 73.4 ($CH_2Ph$); 71.3 (C6); 71.1($CH_2Ph$); 70.2 (C5).

### (*Z/E*)-3,4:6,7-Di-*O*-isopropylidene-1,2-dideoxy-1-phenylsulfanyl-D-*manno*-hep-1-enitol (5)




**5**

Compound **4** (500 mg, 1.92 mmol) was olefinated according to the general procedure by reaction with diphenyl(phenylthiomethyl)phosphine oxide (2.49 g, 7.68 mmol) and *n*-BuLi (4.9 mL, 7.87 mmol). The reaction was left to stir at room temperature for 21 h (TLC control (EtOAc:hexane 1:3) *Rf*: 0.28.). The reaction crude was

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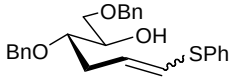
purified by column chromatography (hexane to EtOAc/hexane 1:3) to afford **5** (447 mg, 63%) as a partially separable[70] 1:4 *Z*:*E* mixture as a colourless syrup.

**5***E* (obtained pure under Wadsworth-Emmons conditions): $[\alpha]^{20}_{D}$: +23.10 (*c* 1.15, $CH_2Cl_2$). Anal. Calcd for $C_{19}H_{26}O_5S$: 62.27 C, 7.15 H, 8.75 S. Found: 62.06 C, 7.13 H, 8.73 S. **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.40-7.25 (m, 5H, $H_{aromatic}$); 6.56 (d, 1H, $J_{1-2}$= 15.2 Hz, H1); 6.03 (dd, 1H, $J_{2-1}$= 15.2 Hz, $J_{2-3}$= 8.4 Hz, H2); 4.78 (dd, 1H, $J_{3-2}$= 8.4 Hz, $J_{3-4}$= 7.6 Hz, H3); 4.36 (dd, 1H, $J_{4-3}$= 7.6 Hz, $J_{4-5}$= 1.6 Hz, H4); 4.09 (m, 1H, H7a); 4.01 (m, 2H, H7b,H6); 3.45 (ddd, 1H, $J_{5-4}$= 1.6 Hz, $J_{5-OH}$= 8.5 Hz, $J_{5-6}$= 8.4 Hz, H5); 2.21 (d, 1H, $J_{OH-5}$= 8.4 Hz, OH); 1.51, 1.40, 1.39, 1.35 (s, 3H, $4CH_3$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 134.4($C_{aromatic}$), 130.6, 129.3, 127.4 ($CH_{aromatic}$), 130.4 (C1), 126.6 (C2); 109.5, 108.7 ($2C_{ketal}$); 78.6 (C3); 76.9 (C4); 76.2 (C6); 70.7 (C5); 67.2 (C7); 26.9, 26.8, 25.4, 24.6 ($4CH_3$).

**5***Z* (spectroscopic data extracted from the *E/Z* mixture): **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.39-7.20 (m, 5H, $H_{aromatic}$); 6.49 (d, 1H, $J_{1-2}$= 9.6 Hz, H1); 6.08 (dd, 1H, $J_{2-1}$= 9.6 Hz, $J_{2-3}$= 7.6 Hz, H2); 5.25 (dd 1H, $J_{3-2}$= 5.7 Hz, $J_{3-4}$= 8.0 Hz, H3); 4.51 (d, 1H, $J_{4-3}$= 8.0 Hz, H4); 4.05 (m, 3H, H6, H7a, H7b ); 3.44 (m, 1H, H5); 2.17 (d, 1H, $J_{OH-5}$= 8.8 Hz, OH); 1.55, 1.44, 1.43, 1.36 (s, 3H, $4CH_3$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 135.1, 130.7, 129.7, 129.4, 128.3, 128.2 ($C_{aromatic,}$ $CH_{aromatic,}$ C1, C2); 109.6, 109.0 ($2C_{ketal}$); 76.6 (C3); 76.3 (C4); 74.8 (C6); 70.6 (C5); 67.0 (C7); 27.1, 26.8, 25.5, 24.5 ($4CH_3$).

### (*Z/E*)-4,6-Di-*O*-benzyl-1,2,3-trideoxy-1-phenylsulfanyl-D-*threo*-hex-1-enitol (7)




**7**

As described in the WH olefination procedure, the title compound was synthesized by reaction of **6** (100 mg, 0.31 mmol), diphenyl(phenylthiomethyl)phosphine oxide (400 mg, 1.24 mmol), and *n*-BuLi (0.81 mL of 1.6 M hexane solution, 1.30 mmol) for 4 h. The reaction was monitored by TLC (EtOAc:hexane 1:3). Column

[70] Purification yields two fractions; one of 350mg of *E* vinylsulfide and another of 97mg of *E:Z* 1:8 vinyl sulphide.

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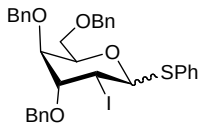
chromatography (EtOAc/hexane 1:4) furnished **7** (134 mg, 100%) as an inseparable 1:1 *E/Z* mixture as a colourless syrup. Data obtained from the mixture: *Rf* (EtOAc/hexane 1:4): 0.28. Anal. Calcd for $C_{26}H_{28}O_4S$: 74.25 C, 6.71 H, 7.62 S. Found: 74.26 C, 6.74 H, 7.65 S.

**7*E*: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.25 (m, 15H, $H_{aromatic}$); 6.24 (d, 1H, $J_{1-2}$= 15 Hz, H1); 6.00 (ddd, 1H, $J_{2-3}$= $J_{2-3'}$= 7.5 Hz, $J_{2-1}$= 15 Hz, H2); 4.67-4.49 (m, 4H, $4CH_2Ph$); 3.87-3.84 (m, 1H, H4); 3.70-3.53 (m, 3H, H5, H6a, H6b); 2.66-2.64 (m, 1H, H3a); 2.54-2.43 (m, 1H, H3b); 2.44 (d, 1H, $J_{OH-5}$= 5.2 Hz, OH). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ en ppm: 138.4-138.1 ($C_{aromatic}$); 131.0-124.5 ($CH_{aromatic}$); 128.6 (C2); 125.4 (C1); 79.0 (C5); 73.6, 72.3 ($2CH_2Ph$); 71.5 (C4); 71.2 (C6); 34.1 (C3).

**7*Z*: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.25 (m, 15H, $H_{aromatic}$); 6.31 (d, 1H, $J_{1-2}$= 11 Hz, H1); 5.94 (ddd, 1H, $J_{2-3}$= $J_{2-3'}$= 7.2 Hz, $J_{2-1}$= 11 Hz, H2); 4.67-4.49 (m, 4H, $4CH_2Ph$); 3.89-3.86 (m, 1H, H4); 3.70-3.53 (m, 3H, H5, H6a, H6b); 2.66-2.64 (m, 1H, H3a); 2.54-2.43 (m, 1H, H3b); 2.49 (d, 1H, $J_{OH-5}$= 4.8 Hz, OH). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ en ppm: 138.3-138.1 ($C_{aromatic}$); 130.8-124.2 ($CH_{aromatic}$); 128.5 (C2); 125.4 (C1); 78.8 (C5); 73.6, 72.5 ($2CH_2Ph$); 71.7 (C4); 71.1 (C6); 30.0 (C3).

### Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-α/β-D-*gulo*-pyranoside (13)




**13**

As described in cyclization method B, compound **13** (611 mg, 77%, α/β ratio 1:12, inseparable mixture) was obtained as a yellowish syrup starting from compound **2** (*E*:*Z* ratio 10:1) (640 mg, 1.2 mmol) and IDCP (1.25 g, 2.67 mmol) in dry $CH_3CN$ (17 ml), at -30 °C for 3 h. The reaction was monitored by TLC (EtOAc:hexane 1:3). The reaction mixture was purified by radial chromatography (from hexane to EtOAc:hexane 1:3). Starting from *Z*-enriched enolthioether **2** (250 mg, 0.47 mmol, *Z:E* ratio 7:1) α-enriched compound **13** (α/β ratio 10:1) is obtained in similar yield (225 mg, 73%).

Data obtained from the mixture: *Rf* (EtOAc:hexane 1:4): 0.47. Anal. Calcd for $C_{33}H_{33}IO_4S$: 60.74 C, 5.10 H, 4.91 S. Found: 60.68 C, 5.11 H, 5.00 S.

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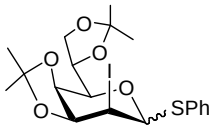
**13β**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.61-7.18 (m, 20H, $H_{aromatic}$); 5.13 (d, 1H, $J_{1-2}$= 11.2 Hz, H1); 4.69-4.36 (m, 6H, $J_{AB}$= 11.2 Hz, $J_{AB'}$= 12.0 Hz, $J_{AB''}$= 9.0 Hz, $J_{AB'''}$= 5.6 Hz, 6$CH_2$Ph); 4.44 (dd, 1H, $J_{2-3}$= 2.8 Hz, $J_{2-1}$= 11.2 Hz, H2); 4.23 (td, 1H, $J_{5-4}$= 1.2 Hz, $J_{5-6a}$= $J_{5-6b}$= 6.4 Hz, H5); 3.81 (dd, 1H, $J_{3-2}$= 2.8 Hz, $J_{3-4}$= 3.4 Hz, H3); 3.57 (m, 2H, $J_{5-6a}$= $J_{5-6b}$= 9.6 Hz, $J_{6a-6b}$= 6.4 Hz, H6a, H6b); 3.37 (dd, 1H, $J_{4-3}$= 3.4 Hz, $J_{4-5}$= 1.2 Hz, H4). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.0-127.6 ($C_{aromatic}$); 85.0 (C1); 78.1 (C3); 74.9 (C5); 74.0 ($CH_2$Ph); 73.6 (C4); 73.3 ($CH_2$Ph); 72.6 ($CH_2$Ph); 68.9 (C6); 31.3 (C2).

**13α**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.54-7.20 (m, 20H, $H_{aromatic}$); 5.41 (d, 1H, $J_{1-2}$= 5.2 Hz, H1); 5.06 (dd, 1H, $J_{2-3}$= 2.8 Hz, $J_{2-1}$= 5.2 Hz, H2); 4.89 (s, 1H, H5); 4.80-4.36 (m, 6H, $J_{AB}$ = 12.0 Hz, $J_{AB'}$ = 12.4 Hz, $CH_2$Ph); 3.73 (sa, 1H, $J_{3-2}$= 2.8 Hz, H3); 3.63-3.54 (m, 2H, H6a, H6b); 3.48 (sa, 1H, H4). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2-127.1 ($C_{aromatic}$); 89.7 (C1); 77.4 (C3); 75.0 (C4); 73.5 ($CH_2$Ph); 73.3 ($CH_2$Ph); 73.1 ($CH_2$Ph); 69.2 (C6); 66.3 (C5) 28.0 (C2).

### Phenyl 2-Deoxy-2-iodo-3,4:6,7-di-*O*-isopropylidene-1-thio-D-*glycero*-α/β-D-*talo*-heptopyranoside (16)




**16**

**(A) From 5*E*.** According to method B, cyclization was carried out starting from compound **5***E* (350 mg, 0.95 mmol) and IDCP (981 mg, 2.09 mmol) in dry $CH_3CN$ from -45 to -30 °C for 2 h. Monitored by TLC (EtOAc:hexane 1:4). The mixture was purified by radial chromatography (from hexane to EtOAc:hexane 1:3) to afford **16**α (453 mg, 97%) as a white foam. **(B) From 5*Z*/*E*.** Compound **5** (*Z*:*E* ratio 1:6) (360 mg, 0.98 mmol) was treated with IDCP (1.01 g, 2.16 mmol) in dry $CH_3CN$ (20 ml) from -45 °C to room temperature for 1.5 h to afford **16α** (233 mg, 48%) as a white foam. (**C) From 5*Z*/*E* and Long Reaction Times.** Compound **5** (*Z*:*E* ratio 1:6) (360 mg, 0.98 mmol) was treated with IDCP (1.01 g, 2.16 mmol) in dry $CH_3CN$ (20 mL) from -30 °C to room temperature for 3.5 h to

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furnish **16α** (60 mg, 41%) as a white foam, **16*β*** (28 mg, 19%) as a yellowish syrup, and the corresponding 2-iodopyranose **17**[71] (19 mg, 19%) as a pale yellow syrup.

**16α**: *Rf* (EtOAc/hexane 1:4): 0.14. $[\alpha]^{20}_{D}$: +109.9 (*c* 1.25, $CH_2Cl_2$). **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.52-7.50 (m, 2H, $H_{aromatic\text{-}o}$); 7.34-7.25 (m, 3H, $H_{aromatic\ m\text{-}p}$); 5.59 (d, 1H, $J_{1\text{-}2}$= 9.6 Hz, H1); 4.68 (dd, 1H, $J_{3\text{-}4}$= 7.9 Hz, $J_{3\text{-}2}$= 2.4 Hz, H3); 4.40 (dd, 1H, $J_{4\text{-}3}$= 7.9 Hz, $J_{4\text{-}5}$= 1.6 Hz, H4); 4.18 (m, 1H, H6); 4.04 (dd, 1H, $J_{2\text{-}1}$= 9.6 Hz, $J_{2\text{-}3}$= 2.4 Hz, H2); 3.98 (dd, 1H, $J_{7a\text{-}6}$= 6.2 Hz, $J_{7a\text{-}7b}$= 8.4 Hz, H7a); 3.90 (dd, 1H, $J_{7b\text{-}6}$= 4.4 Hz, $J_{7b\text{-}7a}$= 8.4 Hz, H7b); 3.61 (dd, 1H, $J_{5\text{-}6}$= 8.4 Hz, $J_{5\text{-}4}$= 1.6 Hz, H5); 1.50, 1.42, 1.40, 1.34 (s, 3H, $4CH_3$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ en ppm: 133.4 ($C_{aromatic}$); 132.1 ($CH_{aromatic\text{-}o}$); 129.1 ($CH_{aromatic\text{-}m}$); 127.7 ($CH_{aromatic\text{-}p}$); 109.6, 109.5 ($2C_{ketal}$); 90.1 (C1); 76.5 (C3); 73.9 (C4); 73.0 (C6); 69.8 (C5); 66.9 (C7); 27.1, 26.2, 25.3, 25.2 ($4CH_3$); 21.2 (C2).

**16*β***: *Rf* (EtOAc/hexane 1:4): 0.13. (Spectroscopic data obtained from the mixture). **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.52-7.24 (m, 5H, $H_{aromatic}$); 5.09 (d, 1H, $J_{1\text{-}2}$= 4.4 Hz, H1); 4.83 (dd, 1H, $J_{3\text{-}2}$= 4.5 Hz, $J_{3\text{-}4}$= 5.2 Hz, H3); 4.51 (dd, 1H, $J_{7a\text{-}6}$= 3.6 Hz, $J_{7a\text{-}7b}$= 8.0 Hz, H7a); 4.39 (dd, 1H, $J_{7b\text{-}6}$= 2.4 Hz, $J_{7b\text{-}7a}$= 8.0 Hz, H7b); 4.34 (dd, 1H, $J_{4\text{-}3}$= 5.2 Hz, $J_{4\text{-}5}$= 6.6 Hz, H4); 4.09 (m, 2H, H6, H2); 3.72 (dd, 1H, $J_{5\text{-}6}$= 2.4 Hz, $J_{5\text{-}4}$= 6.6 Hz, H5); 1.41, 1.40, 1.39, 1.37 (s, 3H, $4CH_3$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 137.1 ($C_{aromatic}$); 131.3 ($CH_{aromatic\text{-}o}$); 129.2 ($CH_{aromatic\text{-}m}$); 127.5 ($CH_{aromatic\text{-}p}$); 110.5, 109.5 ($2C_{ketal}$); 88.2 (C1); 74.1 (C3); 74.5 (C4); 74.3 (C6); 73.1 (C5); 66.9 (C7); 27.5, 26.1, 25.5, 24.7 ($4CH_3$); 21.8 (C2).

[71] NMR data of 2-iodopyranose **17**: **NMR $^1$H** ($CDCl_3$, 400 MHz) δ in ppm: 5.51 (d, 1H, $J_{1\text{-}2}$= 8.0 Hz, H1); 4.67 (dd, 1H, $J_{3\text{-}2}$= 2.8 Hz, $J_{3\text{-}4}$= 8.0 Hz, H3); 4.39 (dd, 1H, $J_{4\text{-}5}$= 1.6 Hz, $J_{4\text{-}3}$= 8.0 Hz, H4); 4.23 (m, 1H, H6); 4.06 (m, 2H, H2, H7a); 3.97 (dd, 1H, $J_{7b\text{-}6}$= 4.2 Hz, $J_{7b\text{-}7a}$= 9.0 Hz, H7b); 3.66 (dd, 1H, $J_{5\text{-}6}$= 2.4 Hz, $J_{5\text{-}4}$= 1.6 Hz, H5); 1.50; 1.41; 1.40; 1.36 (s, 3H, $4CH_3$). **NMR $^{13}$C** ($CDCl_3$, 100.6 MHz) δ in ppm: 109.7 ($2C_{ketal}$); 96.3 (C1); 76.6 (C3); 74.1 (C4); 73.5 (C6); 69.9 (C5); 67.1 (C7); 27.2, 26.2, 25.2, 24.6 ($4CH_3$); 21.0 (C2).

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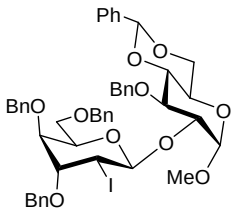
**Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-α/β-D-*gulo*-pyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-*gluco*-pyranoside (27a)**




**27a**

According to the general glycosylation procedure, the title compound was prepared starting from **13** (α/β ratio 10:1 or 1:5) (55 mg, 0.08 mmol), NIS (42 mg, 0.18 mmol), acceptor **26a** (63 mg, 0.17 mmol), 4Å MS (80 mg), and TfOH (1drop) in dry $CH_2Cl_2$ (2.1 ml, 0.04 M). The reaction mixture was stirred at -78 °C for 1 h and then at -40°C for 3 h. TLC (EtOAc:hexane 1:3). Radial chromatography (from hexane to EtOAc:hexane 1:3) furnished **27a** (49 mg, 62%) as an inseparable 1:12 α/β mixture as a transparent syrup.

Data extracted from the mixture: *Rf* (EtOAc:hexane 1:3): 0.31. Anal. Calcd for $C_{48}H_{51}IO_{10}$: 63.02 C, 5.62 H. Found: 63.17 C, 5.60 H.

**27aβ: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.49-7.16 (m, 20H, $H_{aromatic}$); 5.54 (s, 1H, H7); 5.08 (d, 1H, $J_{1'-2'}$= 9.2 Hz, H1'); 5.07 (d, 1H, $J_{AB}$= 10.8 Hz, $CH_2Ph$); 4.86 (d, 1H, $J_{1-2}$= 3.8 Hz, H1); 4.80 (d, 1H, $J_{AB}$= 10.8 Hz, $CH_2Ph$); 4.65 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.44 (m, 6H, H2', 5$CH_2Ph$); 4.28 (dd, 1H, $J_{6a-5}$= 4.8 Hz, $J_{6a-6b}$= 10.0 Hz, H6a); 4.16 (td, 1H, $J_{5'-6'}$= 6.6 Hz, $J_{5'-4'}$= 1.2 Hz, H5'); 4.03 (dd, 1H, $J_{3-2}$= 9.6 Hz, $J_{3-4}$= 9.2 Hz, H3); 3.85 (ddd, 1H, $J_{5-4}$= 9.6 Hz, $J_{5-6a}$= 4.8 Hz, $J_{5-6b}$= 10.0 Hz, H5); 3.80 (dd, 1H, $J_{3'-2'}$= 3.0 Hz, $J_{3'-4'}$= 3.6 Hz, H3'); 3.75 (dd, 1H, $J_{2-1}$= 3.8 Hz, $J_{2-3}$= 9.6 Hz, H2); 3.72 (dd, 1H, $J_{6b-6a}$= 10.0 Hz, $J_{6b-5}$= 10.0 Hz, H6b); 3.59 (dd, 1H, $J_{4-5}$= 9.6 Hz, $J_{4-3}$= 9.2 Hz, H4); 3.53 (d, 2H, $J_{6'-5'}$= 6.6 Hz, H6'); 3.39 (s, 3H, $OCH_3$), 3.36 (dd, 1H, $J_{4'-5'}$= 1.2 Hz, $J_{4'-3'}$= 3.6 Hz, H4'). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.9-126.2 ($C_{aromatic}$); 101.5 (C7); 101.4 (C1'); 100.4 (C1); 82.8 (C4); 79.2 (C3'); 79.1 (C2); 77.8 (C3); 75.3, 74.2 ($CH_2Ph$); 73.9 (C4'); 73.5, 73.0 ($CH_2Ph$); 72.8 (C5'); 69.4 (C6); 69.0 (C6'); 62.3 (C5); 55.5 ($OCH_3$); 30.8 (C2').

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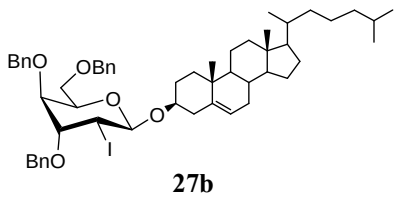
**Cholesteryl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-α/β-D-*gulo*-pyranoside (27b)**




**27b**

Following the general glycosylation procedure, **13** (α/β ratio 2:7) (120 mg, 0.18 mmol), NIS (91 mg, 0.40 mmol), cholesterol (**26b)** (142 mg, 0.37 mmol), 4Å molecular sieves (160 mg), and TfOH (1 drop) in dry $CH_2Cl_2$ (6.1 ml) were allowed to react at -78 °C for 1 h and then at -40 °C for 3 h. TLC (EtOAc:hexane 1:3). Radial chromatography (from hexane to EtOAc:hexane 1:3) afforded **27b** (113 mg, 66%) as an inseparable 1:8 α:β mixture as a pale yellow solid.

Data extracted from the mixture: *Rf* (EtOAc:hexane 1:3): 0.62. Anal. Calcd for $C_{54}H_{73}IO_5$: 69.81 C, 7.92 H. Found: 69.87 C, 7.89 H.

**27bβ:$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.18 (m, 15H, $H_{aromatic}$); 5.34 (broad s, 1H, $CH=_{cholesteryl}$); 4.82 (d, 1H, $J_{1-2}$= 9.2 Hz, H1); 4.65 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.43 (m, 6H, $5CH_2Ph$, H2); 4.16 (t, 1H, $J_{5-6}$= 6.4 Hz, H5); 3.79 (dd, 1H, $J_{3-2}$= 3.6 Hz, $J_{3-4}$= 3.2 Hz, H3); 3.56 (d, 2H, $J_{6-5}$= 6.4 Hz, H6a,H6b); 3.49 (m, 1H, $HCOR_{cholesteryl}$); 3.34 (d, 1H, $J_{4-3}$= 3.2 Hz, H4); 2.39-0.67 (m, 44H, $H_{cholesteryl}$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 140.9-127.8 ($C_{aromatic}$, $=C_{cholesteryl}$); 121.9 ($=CH_{cholesteryl}$); 98.9 (C1); 79.7 ($CHOR_{cholesteryl}$); 76.0 (C3); 74.1 ($CH_2Ph$); 73.8 (C4); 73.5, 72.9, ($CH_2Ph$); 72.8 (C5); 69.1 (C6); 57.0-12.1 ($24C_{cholesteryl}$) [72]; 33.5 (C2).

[72] 24**$C_{cholesteryl}$** peaks: 57.0, 56.3, 50.3, 42.5, 40.0, 39.7, 38.7, 37.4, 36.9, 36.4, 36.0, 32.2, 32.0, 29.7, 28.4, 28.2, 24.5, 24.0, 23.0, 22.8, 21.2, 19.6, 18.9, 12.1

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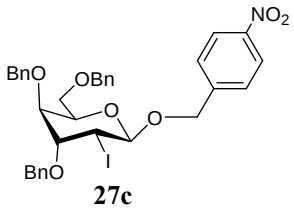
### *p*-Nitrobenzyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-α/β-D-*gulo*-pyranoside (27c)




**27c**

As described in the glycosylation general procedure phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-α/β-D-*gulo*-pyranoside (**13**, α:β ratio 2:7) (50 mg, 0.077 mmol), NIS (38mg, 0.17mmol), *p*-nitrobenzyl alcohol (**26c**) (23mg, 0.15mmol), 4Å Molecular Sieves (80mg) and TfOH (1drop) in dry $CH_2Cl_2$ (2.6ml, 0.03M) were allowed to react at -80 °C for 4 h. TLC (EtOAc:hexane 1:4). Radial chromatography (from hexane to EtOAc:hexane 1:3) afford the expected product **27c** (38mg, 72%) as an inseparable 1:40 α:β anomeric mixture as a faint yellow syrup[73].

Data extracted from the mixture: $R_f$ (EtOAc:hexane 1:4): 0.33. Anal. Calcd for $C_{34}H_{34}O_7NI$: 58.71 C, 4.93 H, 2.01 N. Found: 58.81 C, 4.95 H, 1.98 N.

**27cβ:$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 8.18 (d, 2H, $J_{o\text{-}m}$= 8.6 Hz, $H_{aromatic\text{-}o}$); 8.18 (d, 2H, $J_{m\text{-}o}$= 8.6 Hz, $H_{aromatic\text{-}m}$); 7.36-7.19 (m, 15H, $H_{aromatic}$); 4.96 (d, 1H, $J_{AB}$= 13.2 Hz, $CH_2PhNO_2$); 4.86 (d, 1H, $J_{1\text{-}2}$= 9.0 Hz, H1); 4.66 (d, 1H, $J_{AB}$= 13.2 Hz, $CH_2PhNO_2$); 4.65 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.47 (m, 6H, $5CH_2Ph$, H2); 4.19 (ddd, 1H, $J_{5\text{-}4}$= 1.4 Hz, $J_{5\text{-}6a}$= 6.4 Hz., $J_{5\text{-}6b}$=6.8 Hz., H5); 3.81 (dd, 1H, $J_{3\text{-}2}$= 3.2 Hz., $J_{3\text{-}4}$= 3.6 Hz., H3); 3.60 (dd, 1H, $J_{6a\text{-}5}$= 6.4 Hz., $J_{6a\text{-}6b}$= 9.6 Hz., H6); 3.56 (dd, 1H, $J_{6b\text{-}5}$= 6.8 Hz., $J_{6b\text{-}6a}$= 9.6 Hz., H6b); 3.38 (dd, 1H, $J_{4\text{-}5}$= 1.4 Hz., $J_{4\text{-}3}$= 3.6 Hz., H4). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 147.5-123.7 ($C_{aromatic}$); 99.9 (C1); 78.7 (C3); 74.2, 73.8 ($CH_2Ph$); 73.7 (C4); 73.1 (C5); 73.0 ($CH_2Ph$); 69.8 ($CH_2PhNO_2$); 68.9 (C6); 31.5 (C2).

[73] 14 mg (28%) of starting material **13** (72% conversion) was also recovered.

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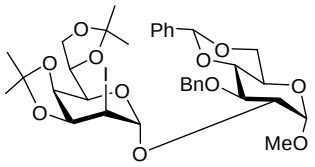
**Methyl (2'-Deoxy-2'-iodo-3',4':6',7'-di-*O*-isopropylidene-D-*glycero*-α/β-D-*talo*-heptopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-gluco-pyranoside (28a)**




**28a**

As described in the glycosylation procedure, the title compound was prepared starting from **16** (200 mg, 0.40 mmol), NIS (201mg, 0.89 mmol), **26a** (302 mg, 0.81 mmol), 4Å MS (200 mg), and TfOH (7μL, 0.08 mmol) in dry $CH_2Cl_2$ (13 ml). The reaction mixture was stirred at -78 °C for 1 h and then at -60 °C for 1 h. TLC (EtOAc:hexane 1:3). Radial chromatography (from hexane to EtOAc:hexane 1:3) of the reaction crude provided **28a** (210 mg, 69%) as an inseparable 40:1 α:β mixture as a white solid.

Data extracted from the mixture: *Rf* (EtOAc:hexane 1:3): 0.30. Anal. Calcd for $C_{34}H_{43}IO_{11}$: 54.12 C, 5.74 H. Found: 53.89 C, 5.75 H.

**28aα: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.44-7.23 (m, 10H, $H_{aromatic}$); 5.54 (s, 1H, H7); 5.22 (d, 1H, $J_{1'-2'}$= 7.2 Hz, H1'); 4.89 (d, 1H, $J_{1-2}$= 4.0 Hz, H1); 4.88 (d, 1H, $J_{AB}$= 12.2 Hz, $CH_2Ph$); 4.80 (d, 1H, $J_{AB}$= 12.2 Hz, $CH_2Ph$); 4.66 (dd, 1H, $J_{3'-4'}$= 7.8 Hz, $J_{3'-2'}$= 2.4 Hz, H3'); 4.41 (dd, 1H, $J_{4'-3'}$= 7.8 Hz, $J_{4'-5'}$= 2.0 Hz, H4'); 4.28 (dd, 1H, $J_{6a-6b}$= 10.4 Hz, $J_{6a-5}$= 4.6 Hz, H6a); 4.22 (dd, 1H, $J_{7'A-7'B}$= 8.8 Hz, $J_{7'A-6'}$= 3.6 Hz, H7'a); 4.19 (ddd, 1H, $J_{6'-7'b}$= 2.8 Hz, $J_{6-7'a}$= 3.6 Hz, $J_{6'-5'}$= 8.4 Hz, H6'); 4.02 (s, 1H, H4); 3.99 (dd, 1H, $J_{7'b-6'}$= 2.8 Hz, $J_{7'b-7'a}$= 8.8 Hz, H7'b); 3.96 (dd, 1H, $J_{2'-1'}$= 7.2 Hz, $J_{2'-3'}$= 2.4 Hz, H2'); 3.87 (dd, 1H, $J_{2-1}$= 4.0 Hz, $J_{2-3}$= 9.6 Hz, H2); 3.83 (dd, 1H, $J_{5-6a}$= 4.6 Hz, $J_{5-6b}$= 9.8 Hz, H5); 3.73 (dd, 1H, $J_{6b-5}$= 9.8 Hz, $J_{6b-6a}$= 10.4 Hz, H6a); 3.61 (d, 1H, $J_{3-2}$= 9.6 Hz, H3); 3.57 (dd, 1H, $J_{5'-6'}$= 8.4 Hz, $J_{5'-4'}$= 2.0 Hz, H5'); 3.47 (s, 3H, $OCH_3$), 1.51, 1.41, 1.33, 1.31 (s, 3H, $4CH_3$).
**$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 139.1, 137.5, 129.1, 128.4, 128.3, 128.2, 127.5, 126.3 ($C_{aromatic}$); 109.7, 109.6 ($2C_{ketal}$); 101.5 (C7); 100.2 (C1'); 97.6 (C1); 82.3 (C3); 76.8 (C4); 76.4 (C3'); 76.0 (C2); 74.9 ($CH_2Ph$); 74.0 (C4'); 73.4 (C6'); 70.1 (C5'); 69.3 (C6); 67.0 (C7'); 62.6 (C5); 55.7 ($OCH_3$); 27.3, 26.2, 25.2 ($4CH_3$); 23.1 (C2').

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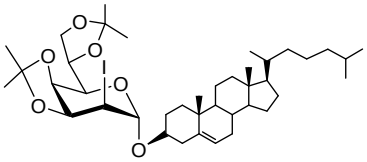
**Cholesteryl 2'-deoxy-2'-iodo-3',4':6',7'-di-O-isopropylidene-D-*glycero*-α/β-D-*talo*-heptopyranoside (28b)**



**28b**

According to the general glycosylation procedure, **16α** (200 mg, 0.40mmol) was treated with NIS (201 mg, 0.89 mmol), cholesterol (**26b**) (299 mg, 0.81 mmol), 4Å molecular sieves (200 mg), and TfOH (7 $\mu$L, 0.08 mmol) in dry $CH_2Cl_2$ (13 ml) at -78 °C for 1 h and then at -20 °C for 20 h. TLC (EtOAc:hexane 1:3). Radial chromatography (from hexane to EtOAc:hexane 1:4) provided **28b** (177 mg, 57%) as an inseparable 8:1 α:β mixture as a pale yellow solid.

Data extracted from the mixture: *Rf* (EtOAc:hexane 1:3): 0.43. Anal. Calcd for $C_{40}H_{65}IO_6$: 62.49 C, 8.52 H. Found: 62.26 C, 8.53 H.

**28bα: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 5.34 (broad s, 1H, $CH=_{cholesteryl}$); 5.20 (d, 1H, $J_{1-2}$= 8.0 Hz, H1); 4.64 (dd, 1H, $J_{3-2}$= 2.8 Hz, $J_{3-4}$= 7.8 Hz, H3); 4.37 (dd, 1H, $J_{4-5}$= 1.8 Hz, $J_{4-3}$= 7.8 Hz, H4); 4.22 (m, 1H, H6); 4.09 (dd, 1H, $J_{7a-6}$= 6.0 Hz, $J_{7a-7b}$= 8.4 Hz, H7a); 3.99 (dd, 1H, $J_{2-1}$= 8.0 Hz, $J_{2-3}$= 2.8 Hz, H2); 3.94 (dd, 1H, $J_{7b-7a}$= 8.4 Hz, $J_{7b-6}$= 4.4 Hz, H7b); 3.58 (dd, 1H, $J_{5-6}$= 8.0 Hz, $J_{5-4}$= 1.8 Hz, H5); 3.47 (m, 1H, $HCOR_{cholesteryl}$); 2.30-0.68 (m, 44H, $H_{cholesteryl}$); 1.51, 1.42, 1.39, 1.36 (s, 3H, $4CH_3$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 140.9 ($=C_{cholesteryl}$); 122.0 ($=CH_{cholesteryl}$); 109.7, 109.6 ($2C_{ketal}$); 100.4 (C1); 77.7 ($CHOR_{cholesteryl}$); 76.6 (C3); 74.1 (C4); 73.6 (C6); 69.7 (C5); 67.3 (C7); 56.9-12.1 ($24C_{cholesteryl}$)[74]; 27.3, 26.2, 25.2, ($3CH_3$); 24.1 (C2); 21.3($CH_3$).

[74] 24**$C_{cholesteryl}$** peaks: 56.9, 56.3, 50.3, 42.51, 40.6, 39.9, 39.7, 37.2, 37.0, 36.4, 36.0, 32.1, 32.0, 28.4, 28.2, 27.7, 25.3, 24.5, 24.0, 23.0, 22.8, 19.6, 18.9, 12.1.

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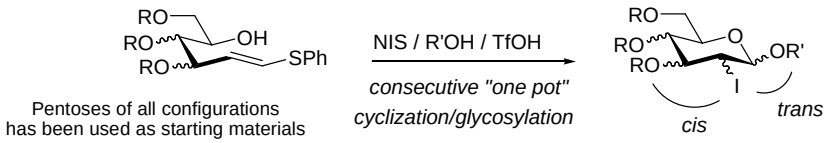
# 2

# ‘One Pot’ Consecutive Cyclization-Glycosylation Reaction

2-Deoxy-2-iodo-pyranosides were synthesized from sulfanyl alkenes using a “one pot” consecutive cyclization-glycosylation process. In the previous chapter, obtaining 2-deoxy-oligosaccharides from sulfanyl derivatives involves electrophilic iodine-induced cyclization to give phenyl 2-deoxy-2-iodo-1-thio-glycosides, and activation of these thioglycosides to obtain glycosylated products. In the cyclization step the conditions had to be optimized to avoid activation and decomposition of the thioglycoside formed in the reaction. Compared with this two-step procedure, the “one pot” process gave significantly improved yields with similar or slightly lower selectivities. The “one pot” procedure was applied to the synthesis of a 2,6-dideoxy-2-iodo-glycoside, which was successfully deiodinated to afford the 2,6-dideoxyglycoside




Pentoses of all configurations has been used as starting materials

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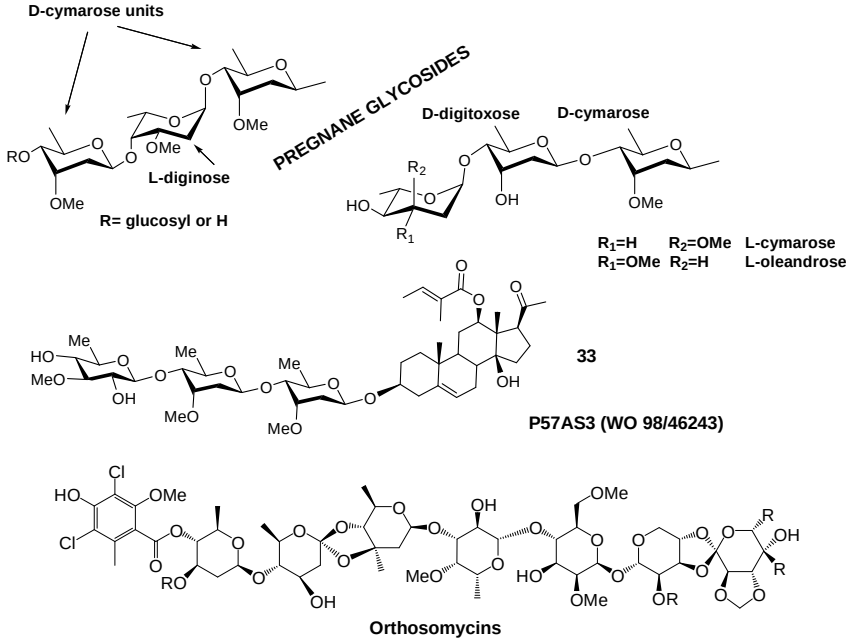
## Introduction

Glycoside domains (with deoxyglycosides or not) are present in many natural secondary metabolites with interesting biological properties, including antibiotic, antiparasital and anticancer agents. In addition, glycoconjugates such as lipopolysaccharides, glycoproteins and glycolipids play important roles in numerous biological processes, where they act as ligands for cell-cell interactions or as targets for toxins, antibodies and microorganisms (Figure 1).[75] However, glycoconjugates have proved difficult to synthesize, which has slowed down efforts to understand their various biological functions. Currently, solution-phase synthesis is the standard approach for elaborate glycoconjugate assembly, and methods such as "one pot" strategies have been developed[76].

**Figure 1.** Different 2-Deoxyoligosaccharide molecules containing 2-deoxysugars.




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

[76] a) Amaya, T.; Takahashi, D.; Tanaka, H.; Takahashi, T. *Angew. Chem. Int. Ed*. **2003**, *42*, 1833. b) Green, L. G.; Ley, S. V. *Carbohydrates in Chemistry and Biology*; Wiley, Chichester, **2000**; vol 1, ch. 17; c) Koeller, K.M.; Wong, C.H. *Chem. Rev*. **2000**, *100*, 4465-4493; d) Koeller, K.M.; Wong, C.H. *Glycobiol*. **2000**, *10*, 1157-1169; e) Danishefsky, S.J.; Roberge, J.Y. *Pure Appl. Chem*. **1995**, *67*, 1647-1662.

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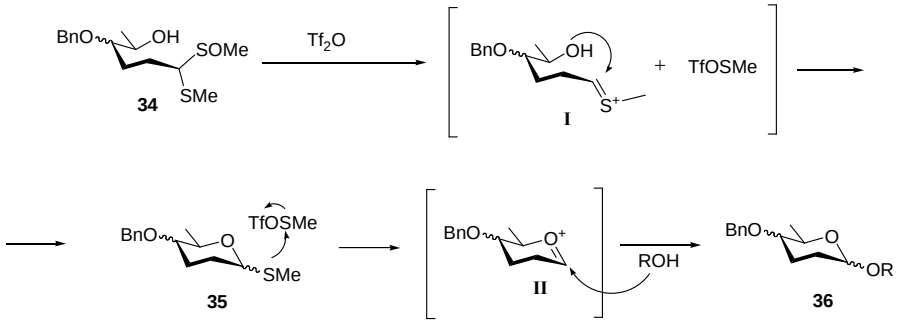
As we have already seen, 2-deoxyglycosides are present in a wide variety of natural products as, for instance, pregnane glycosides or orthosomycins (Figure 1). The stereocontrolled construction of deoxyoligosaccharide scaffolds is a complex process for a number of reasons: a) the absence of a substituent at C2 makes it difficult to control the stereoselectivity of the reaction; b) the 2-deoxy-glycosyl donors and the product glycosides exhibit increased lability, and need to be handled with particular care; and c) the deoxyglycosidic linkage is very acid labile. Generally, the fewer hydroxyl groups present in the pyranoside, the lower is their acid stability[77]. Thus, these issues must be resolved when developing a method for constructing such molecules[78].

In this way, Takahashi et al.[76a] reported a one-pot method for the synthesis of disaccharides that contain deoxysugars, from acyclic compounds with a sulfoxide and a methylsulfanylgroup (Scheme 1). Their procedure was based on the idea that a sulfur atom can be used to generate a sulfenium ion and as a leaving group as well. Thus, selective activation of the sulfoxide group in **34** led to the formation of the sulfenium species **I**, which underwent intramolecular cyclization to form thioglycopyranoside **35**. Concomitant activation of the methylsulfanyl group in **35** with the TfOSMe present afforded the oxonium intermediate **II**, which underwent glycosylation with a nucleophile (ROH) present in the medium to gave **36**.

**Scheme 1**



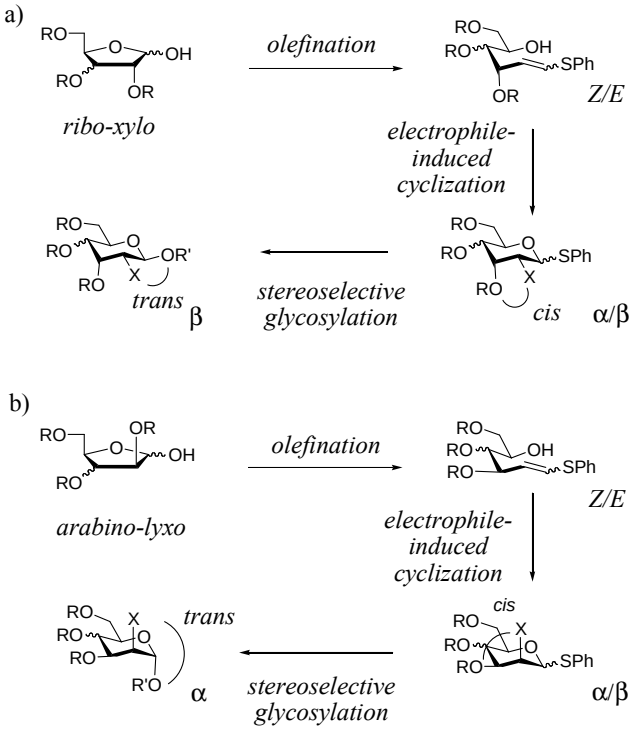

[77] Overend, W.G.; Rees, C.W.; Sequeira, J.S. *J. Chem. Soc*. **1962**, 3429.

[78] For glycosylation methods that involve the use of 2-iodo-deoxy glycosyl donors see: a) Durham, T.B.; Roush, W.R. *Org. Lett.* **2003**, 5, 1871. b) Chong, P.Y.; Roush, W.R. *Org. Lett*. **2002**, *4*, 4523. c) Kirschning, A.; Jesberger, M.;. Schöning, K-U. *Org. Lett.* **2001**, *53*, 3623. d) McDonald, F.E.; Reddy, K.S.; Díaz, Y. *J. Am. Chem. Soc*. **2000**, *122*, 4304. e) Roush, W.R.; Gung, B.W., Bennett, C.E. *Org. Lett.* **1999**, *1*, 891. f) Roush, W.R.; Narayan, S.;. Bennett, C.E; Briner, K. *Org. Lett.* **1999**, *1*, 895. g) Roush, W.R.; Narayan, S. *Org. Lett*. **1999**, *1*, 899. h) Roush, W.R.; Bennett, C.E. *J. Am. Chem. Soc.* **1999**, *121*, 3541. i) Kirschning, A. *Eur. J. Org. Chem.* **1998**, *63*, 2267.

The labile methylsulfanylpyranoside **35** was formed in situ and the need for its tedious isolation was avoided. Nevertheless, this glycosyl donor **35** has been attempted to be isolated without success. Recently, instead of acyclic precursors as **34**, 2,6-dideoxy and 2,3,6-trideoxyglycosyl imidates have been used as a glycosyl donors in this group.[79]

In chapter 1, a general procedure for the stereoselective synthesis of 2-deoxy-2-iodo-hexo-pyranosyl thioglycosides from furanoses was reported, which provides a new method for accessing 2-deoxy-oligosaccharides[80,81] (Scheme 2). The procedure involves three reactions: Wittig-Horner olefination to give an alkenyl sulfanyl derivative; electrophilic iodine-induced cyclization to give phenyl 2-deoxy-2-iodo-1-thio-pyranosides[82], a new type of glycosyl donor; and finally glycosylation.

**Scheme 2**




[79] Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem. Int. Ed*. **2007**, *46*, 2505.
[80] Rodríguez, M. A.; Boutureira, O., Matheu, M.I.; Díaz, Y.; Castillón, S. *J. Org. Chem.* **2005**, *70*, 10297.
[81] For a procedure of synthesis of glycosides involving a mercury-induced cyclization of enolethers see: Paquet, F., Sinaÿ, P. *Tetrahedron Lett.* **1984**, *25*, 3071.
[82] The 2-deoxy-2-iodo-1-thio-pyranosides are useful starting materials for preparing glycals. See chapter 3 and Boutureira, O. Rodríguez, M.A.; Matheu, M.I.; Díaz, Y.; Castillón, S. *Org. Lett.* **2006**, *8*, 673.

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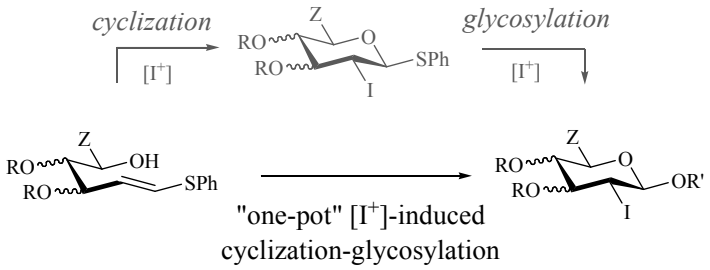
The most important aspects of this procedure are that it provides access to 2-deoxy-2-iodo-glycosyl donors of *gulo* and *allo* configuration that are not readily accessible, and that the stereochemistry of the [$I^+$] addition to the alkene is determined by the configuration of the allylic alkoxy group at the alkenyl sulfanyl derivative, with the iodine at C-2 taking on a *cis* configuration with respect to the C-3 alkoxy group in the thioglycoside (Scheme 2). This latter aspect is a key point in the overall process because the iodine controls the stereoselectivity of the glycosylation reaction. An additional important aspect is that the glycosylation reaction proceeds with good yields and good to excellent stereoselectivity. The glycosidic bond created in the major isomers is always *trans* to the iodine substituent at C-2 (Scheme 2).

In this procedure, the 2-deoxy-2-iodo-thioglycoside, which is prepared from acyclic derivatives via [$I^+$]-induced cyclization, is isolated and further activated in the presence of a glycosyl acceptor, a [$I^+$] equivalent and triflic acid (TfOH) to give the corresponding 2-deoxy-2-iodo-glycoside. 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-thioglycoside.

**Scheme 3**




In this chapter we will discuse a consecutive “one pot” electrophile-induced cyclization-glycosylation sequence from the corresponding acyclic alkenyl sulfanyl derivative to directly furnish the 2-deoxy-2-iodo-glycoside (Scheme 3). This ‘one-pot’ procedure gives in general better yields than the two-step 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 a

2,6-dideoxyglycoside related to the pregnane glycoside **33** with appetite-suppressing activity (Figure 1)[83].

## Results and Discussion

To facilitate comparison between the "one pot" and two-step procedures, consecutive cyclization-glycosylation was initially studied using starting materials and glycosyl acceptors similar to those used previously in the two step procedure. First we considered the *xylo* derivative **2**. In a previous study[80], reagents such as N-iodosuccinimide (NIS) and iodonium dicollidine perchlorate (IDCP) were used to perform [$I^+$]-induced cyclization to give the corresponding 2-deoxy-2-iodo thioglycosides. When applied to the consecutive cyclization-glycosylation strategy, IDCP led to the thioglycoside but was ineffective in bringing about glycosylation even with addition of TfOH. Consequently, the following experiments were carried out using NIS, which was found to promote both transformations to directly afford the 2-iodo-glycoside. Table 1 shows representative examples of the different reaction conditions tested. The initial assay from **2** was carried out using 2 equivalents of cholesterol[84] (**26b**) as the glycosyl acceptor and 5 equivalents of NIS. The reaction mixture was stirred for 2 hours at low temperature (from -60 ºC to -40 ºC), and then TfOH was added to promote glycosylation to afford the glycoside **27b** in 33% yield (Table 1, entry 1). In light of the moderate yields obtained, the reaction conditions were optimized.

The optimized reaction conditions can be summarized as follows: a) 3 equivalents of NIS are enough 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 **27b**, glycosylation of cholesterol with the initially formed transient thioglycoside must take place at ca. -50 ºC. This is achieved by addition of TfOH at -50 ºC and careful temperature control. The optimized reaction of **2** and **26b** gave glycoside **27b** in 66% yield (i.e., double the yield achieved in the non-optimized reaction) and with a

[83] a) Van Herden, F.R.; Vlegaar, R.; Horak, R.M.; Learmonth, R.A.; Maharaj, V.; Whittal, R.D. WO 98/46243, **1998**. For recent natural products incorporating pregnane 2-deoxyoligosaccharides see: b) Perrone, A.; Paza, A.; Ercolino, S.F.; Hamed, A.I.; Parente, L.; Pizza, C.; Piacente, S. *J. Nat. Prod.* **2006**, *69,* 50. c) Bai, H.; Li, W.; Koike, K.; Satou, T.; Chen, Y.; Nikaido, T. *Tetrahedron* **2005**, *61*, 5797.
[84] For a review about glycosylation of steroids see: Pellisier, H. *Tetrahedron*, **2004**, *60*, 5123.

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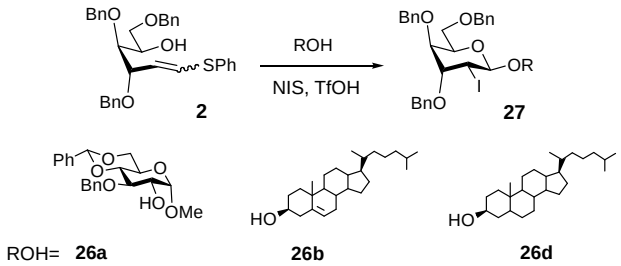
similar selectivity to that obtained in the two-step procedure (Table 1, entry 2). Similar behavior was observed on reacting **2** with cholestanol (**26d**) and the glycoside derivative **26a** (Table 1, entries 3 and 4 respectively).

**Table 1.** Stereoselective synthesis of glycoside **27** from **2** by consecutive cyclization and glycosylation[a]



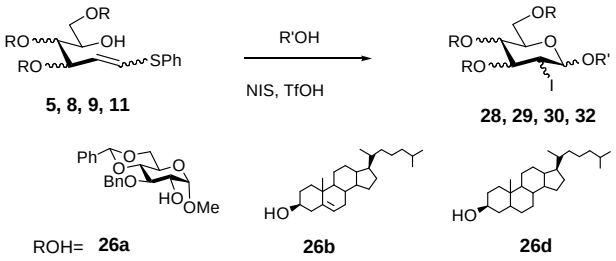

| Entry | ROH | NIS/**2** ratio | Product | Yield (%) | α/β ratio[b] |
|---|---|---|---|---|---|
| 1[c] | **26b** | 5:1 | **27b** | 33 | 14:86 |
| 2[d] | **26b** | 3:1 | **27b** | 66 (51)[e] | 12:88 (11:89)[e] |
| 3[d] | **26d** | 3:1 | **27d** | 76 | 6:94 |
| 4[d] | **26a** | 3:1 | **27a** | 71 (47)[e] | 9:91 (6:94)[e] |

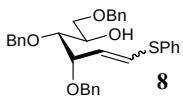
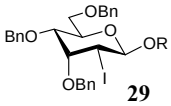
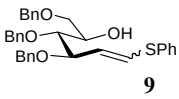
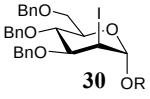
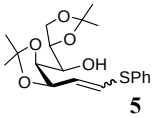
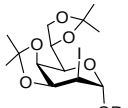
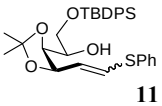
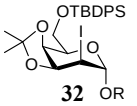
[a] For the *Z*/*E* ratio of the starting alkene, see the experimental section. [b] Determined by integration of the anomeric proton signals in the $^1$H NMR spectrum of the crude reaction mixture. [c] Unoptimized reaction: [d] Optimized conditions: Compound **2** (1 mmol) and ROH (2 mmol) were reacted with NIS (3 mmol) in $CH_2Cl_2$ (25 mL) at -60ºC to -10ºC until no alkene was observed. The reaction mixture was then cooled to -60ºC and TfOH (0.2 mmol) was added. The reaction temperature was then allowed to rise to -10ºC and maintained at this temperature until the completion of the reaction. [e] Yield and selectivity values in brackets correspond to the two-step procedure (Chapter 1).

Especially remarkable is the reaction of **2** with cholestanol (**26d**), which afforded glycoside **27d** in good yield (76%) and with excellent stereoselectivity despite starting from an alkenyl sulfide with a higher percentage of the less reactive Z isomer (Table 1,

entry 3)[85]. Moreover, the yield is slightly better than with cholesterol (**26b**) (Table 1, entry 2) and similar than with glucoside (**29a**) (Table 1, entry 4), probably because of the absence of a double bond which interfere with electrophilic iodine.

**Table 2.** Stereoselective consecutive cyclization-glycosylation reactions from sulfanyl-alkenes **5, 8, 9, 11**.[a,b]




| Entry | Starting material | Product | Yield (%)[c] | α/β ratio[c,d] |
|---|---|---|---|---|
| 1[e] |  **8** |  **29** | **29a** 65 (62)<br>**29b** 70 (57) | 17:83 (10:90)<br>25:75 (15:85) |
| 2[e] |  **9** |  **30** | **30a** 50 (43)<br>**30b** 54 (43) | 95:5 (96:4)<br>96:4 (97:3) |
| 3 |  **5** |  **28** | **28a** 71 (33)<br>**28b** 58 (27)<br>**28d** 64 | 97:3 (97:3)<br>66:33 (84:11)<br>75:25 |
| 4[e] |  **11** |  **32** | **32a** 50 (32) | 85:15 (95:5) |

[a] Conditions: Compounds **5, 8, 9, 11** (1 mmol) and ROH (2 mmol) were reacted with NIS (3 mmol) in $CH_2Cl_2$ (25 mL) at -60ºC to -10ºC until no alkene was observed. The reaction mixture was then cooled to -60ºC and TfOH (0.2 mmol) was added. The reaction temperature was then allowed to rise to -10ºC and maintained at this temperature until the completion of the reaction. [b] For the Z/E ratio of the starting alkene, see the experimental section. [c] Yield and selectivity values in brackets correspond to the two-step procedure. [d] Determined by integration of the anomeric proton signal in the $^1$H NMR spectrum of the crude reaction mixture. [e]Results extracted from Boutureira, Ph.D Thesis, URV, in preparation.

[85] For a discussion on the different reactivities of the *Z* and *E* alkenyl sulfides towards cyclization, see Chapter 1

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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 (Table 1, entries 2, 4).

We also tested the consecutive reaction using the substrates **8, 9, 5, 11** with *ribo*, *arabino*, *manno* and *lyxo* configurations, respectively.[86] For the *ribo* derivative **8**, the yields were slightly higher than those of the two-step procedure, and the stereoselectivity was maintained when alcohol **26a** was used as the glycosyl acceptor, but decreased for cholesterol (Table 2, entry 1). Similarly, for the *arabino* derivative **9**, the overall yields were higher for the "one pot" procedure, and the stereoselectivity for both glycosyl acceptors tested was close to that of the two-step procedure (Table 2, entry 2). The results obtained for the sulfanylalkenes **5** and **11** were even more remarkable: yield increases of 20-38% were observed, with no loss of stereoselectivity when alcohol **26a** was the glycosyl acceptor (Table 2, entry 3). However, significant decreases in the stereoselectivity were observed when cholestanol and cholesterol were used as the glycosyl acceptors, with cholesterol showing an especially large decrease (Table 2, entries 3, 4), consistent with previous reports on the behavior of less sterically hindered acceptors[78b].

[86] The "one pot" reaction over substrates 2,4 and 15 were carried out in a parallel work done in our laboratory. Boutureira, O. Ph.D Thesis, URV, in preparation.

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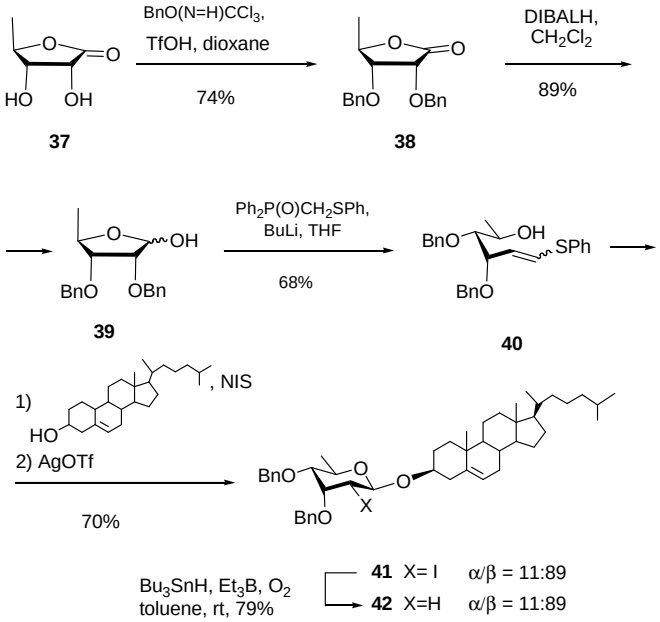
**Scheme 4**




To show the usefulness the "one pot" cyclization-glycosylation procedure, we applied it to the sulfanylalkene **40** as a model of the 2,6-dideoxyglycoside constituent of the pregnane glycoside **33** (Figure 1). We also selected cholesterol as a model of the aglycone in **33**. Compound **40** was prepared according to the synthetic route shown in Scheme 4. The lactone **37**[87] was dibenzylated to obtain **38** in 74% yield. Further reduction with diisobutylaluminium hydride (DIBALH) afforded **39**, which was then treated with $Ph_2P(O)CH_2SPh$ in the presence of *n*-BuLi to afford **40** in 61% overall yield from the protected lactone. The reaction of **40** with cholesterol in the presence of NIS/TfOH afforded **41** in 61% yield (α/β ratio 25:75). Using NIS/AgOTf[88], the yield increased to 70% and the stereoselectivity improved to an α/β ratio of 11:89. The removal of the iodine atom from **41**, which occupied the equatorial position, proved to be much more difficult than for derivatives with iodine in axial configuration. 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-dideoxy-glycoside **42** was obtained in 79% yield.

[87] Papageorgiou, C.; Benezra, C. *Tetrahedron Lett*. **1984**, *25*, 6041.
[88] Kanie, O., Ito, Y.; Ogawa, T. *J. Am. Chem. Soc*. **1994**, *116*, 12073.

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## Conclusion

In this chapter it was shown that the "one pot" consecutive cyclization-glycosylation strategy is a convenient and direct method for the synthesis of 2-deoxy-2-iodo-glycosides 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 the pentoses, cyclization-glycosylation reaction) is fairly straightforward and operationally simple. It is worth 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 dideoxyglycosyl donors, and has been successfully applied to the synthesis of the 2,6-dideoxy-2-iodo-glycoside **41**, and the corresponding 2,6-dideoxyglycoside **42**.

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# Experimental Part

## General Remarks

Optical rotations were measured at room temperature in 10 cm cells in a Perkin-Elmer 241 polarimeter. $^{1}H$, $^{13}C$ and $^{31}P$ NMR spectra were recorded using 300 MHz and 400 MHz Varian® spectrometers, with $CDCl_3$ as the solvent and $Me_4Si$ as an internal reference. Elemental analyses were performed using a Carlo-Erba Microanalyzer. Flash column chromatography was performed using Merck® silica gel 60 A CC (230-400 mesh). Radial chromatography was performed on 1, 2 or 4 mm plates of Kieselgel 60 $PF_{254}$ silica gel, depending on the amount of product. Solvents were purified using standard procedures. Preparation of lactone **37** is described in Chapter 4.

## General procedure for the *one-pot* cylization-glycosylation from sulfanyl alkenes

Starting alkene (1 mmol), glycosyl acceptor (2 mmol), 4Å molecular sieves and 25 ml (0.02M) of dry $CH_2Cl_2$ were stirred together at rt for 30min. The reaction was cooled at -65 ºC and then NIS (3.0 mmol) was added. While the reaction temperature was allowed to reach -10 ºC, the reaction was monitored by TLC (EtOAc:hexane 1:3) and left to stir until the cyclization was complete. The reaction mixture was then cooled to -60 ºC and then TfOH (0.2 mmol) was added. The reaction was left to stir at low temperature (between -40 ºC and -10 ºC) until the reaction was complete. The crude was extracted with $NaHCO_3$-$Na_2S_2O_3$(aq.)/$CH_2Cl_2$. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The reaction crude was purified by chromatographic techniques.

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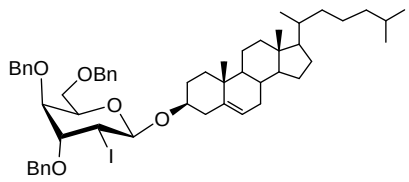
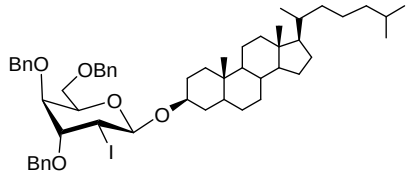
**Cholesteryl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-α/β-D-*gulo*-pyranoside (27b)**




**27b**

The title compound (35 mg, 66% yield, α/β ratio = 12:88) was synthesized from **2** (30 mg, 0.057 mmol, *Z*/*E* ratio= 1:5) following the general procedure. The characterization data are coincident to those reported in chapter 1.

**Cholestanyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-α/β-D-*gulo*-pyranoside (27d)**




**27d**

Compound **2** (*Z*/*E* ratio 1:2) (100 mg, 0.19 mmol), cholestanol **26d** (148 mg, 0.38 mmol), and 4Å molecular sieves (100 mg) in 7.8 ml (0.02 M) of dry $CH_2Cl_2$ were stirred together at rt for 30 min. The reaction mixture was cooled to -65 ºC and then NIS (128 mg, 0.57 mmol) was added. The temperature of the reaction mixture was allowed to increase to -10 ºC and then maintained at this temperature and stirred until the cyclization was complete (2.5 h). During this period, the progress of the reaction was monitored by TLC (EtOAc:hexane 1:3). The reaction mixture was then cooled to -60 ºC and TfOH (3 μl, 0.038 mmol) was added. The reaction was left to stir at -40 ºC for 1.5 h. The crude product was extracted with $NaHCO_3$-$Na_2S_2O_3$/$CH_2Cl_2$. The organic layer was dried with anhydrous $MgSO_4$ and evaporated. The crude product was purified by radial chromatography (from hexane to EtOAc:hexane 1:4) to afford **27d** (135 mg, 76%) as an inseparable 6:94 α:β mixture as a colourless syrup.

Spectroscopic data extracted from the anomeric mixture:

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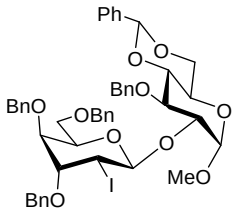
$R_f$ (EtOAc:hexane 1:4): 0.57. Anal. Calcd for $C_{54}H_{75}O_5I$: 69.66 C, 8.12 H. Found: 69.35 C, 8.15 H.

**27dβ: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.43-7.17 (m, 15H, $H_{aromatic}$); 4.82 (d, 1H, $J_{1-2}$= 9.6 Hz, H1); 4.66-4.42 (m, 6H, $J_{AB}$= 12.0 Hz, $J_{AB'}$= 12.4 Hz, $J_{AB''}$= 13.6 Hz, $6CH_2Ph$); 4.36 (dd, 1H, $J_{2-1}$= 9.6 Hz, $J_{2-3}$= 3.2 Hz, H2); 4.16 (dd, 1H, $J_{5-6a}$= $J_{5-6b}$= 7.0 Hz, H5); 3.78 (pst, 1H, $J_{3-2}$= 3.2 Hz, $J_{3-4}$= 3.2 Hz, H3); 3.56 (d, 2H, $J_{6a-5}$= $J_{6b-5}$= 7.0 Hz, H6a, H6b); 3.53 (m, 1H, $HCOR_{cholestanyl}$); 3.34 (d, 1H, $J_{4-3}$= 3.2 Hz, H4); 1.96-0.54 (m, 45H, $H_{cholestanyl}$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4, 137.8, 137.7 ($C_{aromatic}$); 128.6-127.7 ($CH_{aromatic}$); 98.8 (C1); 79.4 ($CHOR_{cholestanyl}$); 78.9 (C3); 74.1 ($CH_2Ph$); 73.8 (C4); 73.5, 72.9 ($2CH_2Ph$); 72.8 (C5); 69.2 (C6); 56.7-12.3 ($26C_{cholestanyl}$)[89]; 33.7 (C2)

**27dα: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.18 (m, 15H, $H_{aromatic}$); 5.24 (d, 1H, $J_{1-2}$= 8.0 Hz, H1); 4.74-4.48 (m, 6H, $J_{AB}$= 11.6 Hz, $J_{AB'}$= 8.0 Hz, $J_{AB''}$= 11.2 Hz, $6CH_2Ph$); 4.17-4.09 (m, 2H, H5, H3); 3.89-3.83 (m, 2H, H2, H6a); 3.75-3.70 (m, 2H, H6b, H4); 3.53 (m, 1H, $HCOR_{cholestanyl}$); 1.98-0.54 (m, 45H, $H_{cholestanyl}$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2-137.7 ($C_{aromatic}$); 128.7-127.7 ($CH_{aromatic}$); 99.4 (C1); 81.8 (C3); 79.7 (C4); 79.2 ($CHOR_{cholestanyl}$); 75.1, 73.7, 72.8 ($3CH_2Ph$); 71.3 (C5); 68.6 (C6); 56.7-12.3 ($26C_{cholestanyl}$); 32.8 (C2).

### Methyl (3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-α/β-D-*gulo*-pyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-*gluco*-pyranoside (27a)




**27a**

The title compound (31 mg, 71% yield, α/β ratio = 9:91) was synthesized from **2** (25 mg, 0.047 mmol, *Z*/*E* ratio = 1:5) following the general procedure. The characterization data are coincident to those reported in chapter 1.

[89] $26C_{cholestanyl}$ peaks: 56.7, 56.4, 54.6, 45.0, 42.8, 40.2, 39.7, 37.2, 36.4, 36.0, 35.7, 35.6, 34.4, 32.3, 29.5, 29.0, 28.5, 28.2, 24.4, 24.0, 23.0, 22.8, 21.4, 18.9, 12.5, 12.3.

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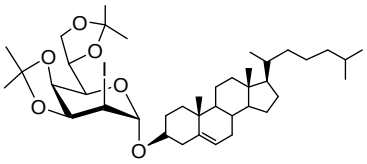
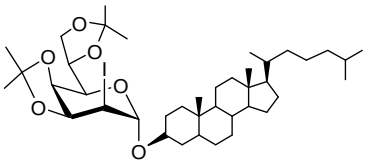
**Cholesteryl 2-deoxy-2-iodo-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-α/β-D-*talo*-heptopyranoside (28a)**



**28a**

Compound **28a** (145 mg, 58% yield, α/β ratio = 66:33) was synthesized from **5** (120 mg, 0.24 mmol, *Z*/*E* ratio = 0:1) following the general procedure. The characterization data are coincident to those reported in chapter 1

**Cholestanyl 2-deoxy-2-iodo-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-α/β-D-*talo*-heptopyranoside (28d)**



**28d**

Compound **5** (*Z:E* ratio = 0:1, 55 mg, 0.150 mmol), cholestanol (**26d**) (116 mg, 0.300 mmol), and 4Å molecular sieves (60 mg) in 5.8 ml (0.026 M) of dry $CH_2Cl_2$ were stirred together at rt for 30 minutes. The reaction was cooled to -65 ºC and then NIS (101 mg, 0.45 mmol) was added. The reaction was monitored by TLC (EtOAc:hexane 1:3) and the reaction temperature was left to rise to -10 ºC until the cyclization was complete (4 h). TfOH (2.6 μL, 0.030 mmol) was then added at -60 ºC, and the reaction mixture was stirred (-60 ºC to -40º C) for 4 h. The crude product was extracted with $NaHCO_3$-$Na_2S_2O_3$/ $CH_2Cl_2$. The organic phase was dried with anhydrous $MgSO_4$ and evaporated. The crude product was purified by radial chromatography (from hexane to EtOAc:hexane 1:4) to

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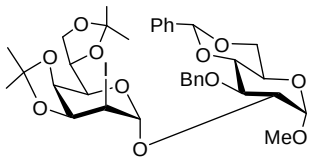
afford **28d** (74 mg, 64%) as an inseparable 75:25 α:β mixture in the form of a colourless syrup. $R_f$ (EtOAc:hexane 1:4): 0.34.

Spectroscopic data from the α/β anomeric mixture:

**28dβ:$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 5.19 (d, 1H, $J_{1\alpha\text{-}2\alpha}$= 7.8 Hz, H1α); 4.64 (dd, 1H, $J_{3\alpha\text{-}2\alpha}$= 2.8 Hz, $J_{3\alpha\text{-}4\alpha}$= 4.0 Hz, H3α); 4.55 (d, 1H, $J_{1\beta\text{-}2\beta}$= 9.0 Hz, H1β); 4.53 (d, 1H, $J_{3\beta\text{-}2\beta}$= 7.8 Hz, H3β); 4.37 (m, 2H, H4α, H4β); 4.21 (m, 2H, H6α); 4.07 (m, 4H, H7aα, H7aβ, H7bβ, H6β); 3.98 (dd, 1H, $J_{2\alpha\text{-}1\alpha}$= 7.8 Hz, $J_{2\alpha\text{-}3\alpha}$= 2.8 Hz, H2α); 3.92 (m, 1H, H7bα); 3.77 (dd, 1H, $J_{2\beta\text{-}1\beta}$= 9.0 Hz, $J_{2\beta\text{-}3\beta}$= 9.2 Hz, H2β); 3.70 (dd, 1H, $J_{5\beta\text{-}4\beta}$= 1.6 Hz, $J_{5\beta\text{-}6\beta}$= 7.8 Hz, H5β); 3.58 (dd, 1H, $J_{5\alpha\text{-}4\alpha}$= 1.2 Hz, $J_{5\alpha\text{-}6\alpha}$= 8.0 Hz, H5α); 3.53 (m, 1H, $CHOR_{cholestaryl}$); 1.98-0.61 (m, 45H, $H_{cholestanyl}$); 1.52, 1.51, 1.48, 1.42, 1.41, 1.39, 1.38, 1.36, (s, 24H, $4CH_{3\alpha}$, $4CH_{3\beta}$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 110.5, 109.7, 109.7, 109.6 ($2C_{ketal}\alpha$, $2C_{ketal}\beta$); 101.2 (C1β); 100.5 (C1α); 82.5 (C3β); 80.1, 77.4 ($CHOR_{cholestaryl}$); 76.6 (C3α); 74.2 (C4β); 74.1 (C4α); 73.9 (C5β); 73.6 (C6α); 73.5 (C6β); 69.6 (C5α); 67.3 (C7α); 66.9 (C7β); 56.7-12.2 ($24C_{cholestanyl}$); 25.0-30.0 ($2CH_3\alpha$,$2CH_3\beta$); 34.5 (C2β); 24.2 (C2α).

**Methyl (2'-deoxy-2'-iodo-3',4':6',7'-di-*O*-isopropylidene-D-*glycero*-α/β-D-*talo*-heptopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (28a)**




**28a**

Compound **28a** (132 mg, 71% yield, α/β ratio = 97:3) was synthesized from **5** (90 mg, 0.24 mmol, *Z*/*E* ratio = 1:1.8) following the general procedure. The characterization data are coincident to those reported in chapter 1.

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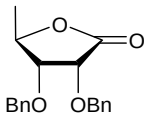
### 2,3-Di-*O*-benzyl-5-deoxy-γ-D-ribonolactone (38)[90]



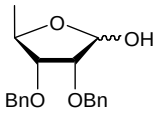

**38**

A solution of 5-deoxy-γ-D-ribonolactone (**37**) (200 mg, 1.51 mmol) in dry dioxane (10 ml, 0.15 M) was cooled to 0 ºC, and then freshly distilled benzyl trichloroacetimidate (790 µL, 4.23 mmol) was added. TfOH was added (20 µL, 0.23 mmol) to ensure that the mixture was strongly acidic and the solution was stirred for 12 h at rt (TLC control). The reaction was quenched with saturated aqueous $NaHCO_3$ (30 ml) and extracted with $CH_2Cl_2$ (60 ml). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by radial chromatography (from hexane:EtOAc 3:1 to hexane: EtOAc, 2:1) to give the title compound (349 mg, 74%) as white foam.[91]

$[\alpha]^{20}_D$: +26.01 (*c* 0.69 $CH_2Cl_2$). Anal. Calcd for $C_{19}H_{20}O_4$: 73.06 C, 6.45 H. Found: 73.09 C, 6.44 H.

**38: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.42-7.26 (m, 10H, $H_{aromatic}$); 4.94 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.75 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.68 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.63 (dd, 1H, $J_{4\text{-}5}$= 6.4 Hz, $J_{4\text{-}3}$= 4.0 Hz, H4); 4.54 (d, 1H, $J_{AB}$= 12.0Hz, $CH_2Ph$); 4.12 (d, 1H, $J_{2\text{-}3}$= 5.2 Hz, H2); 3.75 (dd, 1H, $J_{3\text{-}2}$= 5.2 Hz, $J_{3\text{-}4}$= 4.0 Hz, H3); 1.34 (d, 3H, $J_{5\text{-}4}$= 6.4 Hz, H5). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 172.0 (C=O); 138.6, 137.2 ($C_{aromatic}$); 130.8-128.2 ($CH_{aromatic}$); 79.1 (C3); 78.9 (C4); 72.8 (C2); 72.4 ($2CH_2Ph$); 18.6 (C5).

### 2,3-Di-*O*-benzyl-5-deoxy-α/β-D-ribofuranose (39)




**39**

A 1.0 M solution of DIBALH in $CH_2Cl_2$ (1.58 ml, 1.58 mmol) was added dropwise to a solution of **38** (328 mg, 1.05 mmol) in $CH_2Cl_2$ (10.5 ml, 0.1 M) at -78 ºC.

[90] Jensen, H. S.; Limberg, G.; Pedersen, C. *Carbohydr. Res.* **1997**, *302*, 109.
[91] To obtain an analytical sample two purifications were required

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The reaction was monitored by TLC (EtOAc:hexane 1:3) until the starting product was consumed. After 5 h at -78 ºC, the reaction was quenched by adding methanol (3 ml) and allowed to warm to rt. After adding a mixture of EtOAc:$H_2O$ (1:1) (100 ml), the solution was acidified with dilute sulfuric acid until it reached pH 3. The aqueous phase was extracted three times with additional EtOAc t. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 ml), dried (anhydrous $MgSO_4$) and evaporated. The residue was purified by radial chromatography (EtOAc:hexane 1:3) to afford 294 mg (89%) of **39** as a colourless syrup.

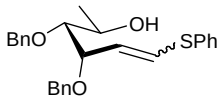
Spectroscopic data from the α/β mixture:

Anal. Calcd for $C_{19}H_{22}O_4$: 72.59 C, 7.05 H. Found: 72.63 C, 7.03 H.

**39**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.37-7.30 (m, 20H, $H_{aromatic}$ab); 5.35 (d, 1H, $J_{1a-OHa}$= 3.6 Hz, H1a); 5.30 (dd, 1H, $J_{1b-OHb}$= 11.2 Hz, $J_{1b-2b}$= 4.4 Hz, H1b); 4.73-4.45 (m, 8H, $4CH_2Ph_a$, $4CH_2Ph_b$); 4.33 (qd, 1H, $J_{4b-3b}$= 3.2 Hz, $J_{4b-5b}$= 6.4 Hz, H4b); 4.29 (d, 1H, $J_{OHb-H1}$= 11.2 Hz, OHb); 4.23 (dq, 1H, $J_{4a-5a}$= 6.4 Hz, $J_{4a-3a}$= 7.6 Hz, H4a); 3.93 (dd, 1H, $J_{2b-1b}$= 4.4 Hz, $J_{2b-3b}$= 4.8 Hz, H2b); 3.85 (d, 1H, $J_{2a-3a}$= 4.8 Hz, H2a); 3.79 (dd, 1H, $J_{3a-4a}$= 7.6 Hz, $J_{3a-2a}$= 4.8 Hz, H3a); 3.62 (dd, 1H, $J_{3b-2b}$= 4.8 Hz, $J_{3b-4b}$= 3.2 Hz, H3b); 3.30 (da, 1H, $J_{OHa-1a}$= 3.6 Hz, OHa); 1.32 (d, 3H, $J_{5a-4a}$= 6.0 Hz, H5a); 1.17 (d, 3H, $J_{5b-4b}$= 6.4 Hz, H5b).

**$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 137.9-137.5 ($C_{aromatic}$); 128.7-128.0 ($CH_{aromatic}$); 100.2 (C1a); 96.0 (C1b); 82.8 (C3a); 81.9 (C3b); 80.5 (C2a); 77.4 (C2b); 77.3 (C4a); 77.2 (C4b); 73.0, 72.9 ($2CH_2Ph_B$); 72.6, 72.4 ($2CH_2Ph_A$); 20.7 (C5a); 19.9 (C5b).

### (*Z/E*)-3,4-Di-*O*-benzyl-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (40)




**40**

*n*-BuLi in hexane (1.6 M, 1.2 ml, 1.86 mmol) was added to a solution of diphenyl phenylsulfanylmethyl phosphine oxide (575 mg, 1.77 mmol) in THF (2.4 mL, 0.74 M) at -78 °C. The mixture was left to stir at low temperature for 30 min. A solution of **39** (150 mg, 0.44 mmol) in THF (2 ml, 0.22 M) was then added dropwise. The mixture was

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allowed to warm to room temperature overnight (17 h). A saturated solution of $NH_4Cl$ was then added and the olefination product was extracted with dichloromethane. The combination of organic layers was dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (EtOAc:hexane 1:4) to afford the enolthioether **40** (126 mg, 68%) as an inseparable 5:2 *E*:*Z* diastereoisomeric mixture.

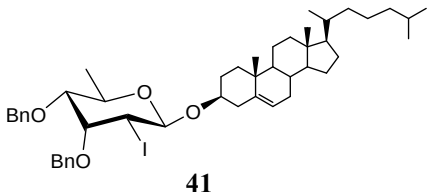
Data obtained from the *E*/*Z* mixture:

Anal. Calcd for $C_{26}H_{28}O_3S$: 74.25 C, 6.71 H, 7.62 S. Found: 74.20 C, 6.69 H, 7.60 S.

**40*E*: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.37-7.22 (m, 10H, $H_{aromatic}$); 6.50 (d, 1H, $J_{1-2}$= 15.2 Hz, H1); 5.81 (dd, 1H, $J_{2-3}$= 8.4 Hz, $J_{2-1}$= 15.2 Hz, H2); 4.81-4.37 (m, 4H, $4CH_2Ph$); 4.03 (dd, 1H, $J_{3-2}$= 8.4 Hz, $J_{3-4}$= 6.8 Hz, H3); 3.93 (m, 1H, H5); 3.36 (dd, 1H, $J_{4-3}$= 6.8 Hz, $J_{4-5}$= 6.0 Hz, H4); 2.64 (sa, 1H, OH); 1.21 (d, 3H, $J_{6-5}$= 6.4 Hz, H6). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4-127.2 ($C_{aromatic}$); 129.3 (C1); 129.0 (C2); 84.5 (C4); 81.8 (C3); 74.7 ($CH_2Ph$); 70.6 ($CH_2Ph$); 69.3 (C5); 19.1 (C6).

**40*Z*: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.37-7.21 (m, 10H, $H_{aromatic}$); 6.59 (d, 1H, $J_{1-2}$= 9.2 Hz, H1); 5.92 (pst, 1H, $J_{2-3}$= 9.2 Hz, $J_{2-1}$= 9.2 Hz, H2); 4.81-4.37 (m, 5H, $4CH_2Ph$, H3); 3.93 (m, 1H, H5); 3.49 (dd, 1H, $J_{4-3}$= 5.6 Hz, $J_{4-5}$= 6.4 Hz, H4); 2.63 (sa, 1H, OH); 1.23 (d, 1H, $J_{6-5}$= 6.8 Hz, H6). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4-127.2 ($C_{aromatic}$); 129.4 (C1); 129.2 (C2); 84.7 (C4); 77.6 (C3); 74.6 ($CH_2Ph$); 70.9 ($CH_2Ph$); 69.1 (C5); 19.3 (C6).

### Cholesteryl 3,4-di-*O*-benzyl-2,6-dideoxy-2-iodo-α/β-D-*allo*-pyranoside (41)




**41**

Compound **40** (*E:Z* ratio= 5:2, 48 mg, 0.11 mmol), cholesterol (**26b**) (55 mg, 0.13 mmol), and 4Å molecular sieves (40 mg) in 3 ml (0.045 M) of dry $CH_2Cl_2$ were stirred together at room temperature for 30 min. The reaction mixture was then cooled to -78 ºC and NIS (88 mg, 0.39 mmol) was added. The temperature of the reaction mixture was

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allowed to increase to -20 ºC and then maintained at this temperature and stirred until the cyclization was complete (2.5 h). During this period, the progress of the reaction was monitored by TLC (EtOAc:hexane 1:4). The reaction mixture was then cooled to -60 ºC and AgOTf (13 mg, 0.052 mmol) was added. The reaction mixture was then stirred at -20 ºC for further 16 h. When the reaction was finished, triethylamine (1 ml) was added and the crude product was extracted with $NaHCO_3$-$Na_2S_2O_3$/$CH_2Cl_2$. The organic phase was dried over anhydrous $MgSO_4$. The crude product was purified by radial chromatography (from hexane to EtOAc:hexane 1:3) to afford **41** (75 mg, 70%, α:β = 11:89) as a yellowish syrup.

Spectroscopic data obtained from the α/β mixture:

Anal. Calcd for $C_{47}H_{67}O_4I$: 68.60 C, 8.21 H. Found: 68.44 C, 8.20 H.

**41**β: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.55-7.25 (m, 10H, $H_{aromatic}$); 5.35 (sa, 1H, $CH=_{cholesteryl}$); 4.85 (d, 1H, $J_{1-2}$= 8.8 Hz, H1); 4.71-4.51 (m, 4H, $J_{AB}$= 12.0 Hz, $J_{AB'}$= 11.8 Hz, $4CH_2Ph$); 4.16 (dd, 1H, $J_{3-2}$= 2.4 Hz, $J_{3-4}$= 2.0 Hz, H3); 4.08 (dq, 1H, $J_{5-4}$= 9.2 Hz, $J_{5-6}$= 3.2 Hz, H5); 4.00 (dd, 1H, $J_{2-1}$= 8.8 Hz, $J_{2-3}$= 2.4 Hz, H2); 3.49-3.40 (m, 1H, $HCOR_{cholesteryl}$); 3.29 (dd, 1H, $J_{4-3}$= 2.0 Hz, $J_{4-5}$= 9.2 Hz, H4); 2.41-0.66 (m, 44H, $H_{cholesteryl}$); 1.26 (m, 1H, H6). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 140.9 ($=C_{cholesteryl}$);140.5-138.6 ($C_{aromatic}$); 128.7-126.9 ($CH_{aromatic}$); 122.0 ($=CH_{cholesteryl}$); 98.9 (C1); 82.0 (C4); 79.9 ($CHOR_{cholestanyl}$); 78.3 (C3); 72.5, 71.8 ($2CH_2Ph$); 69.4 (C5); 57.0-12.1 ($24C_{cholesteryl}$); 33.9 (C2); 18.3 (C6).

**41**α: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.55-7.25 (m, 10H, $H_{aromatic}$); 5.35 (sa, 1H, $CH=_{cholesteryl}$); 5.12 (d, 1H, $J_{1-2}$= 2.4 Hz, H1); 4.93-4.78 (m, 4H, $J_{AB}$= 10.0 Hz, $J_{AB'}$= 9.6 Hz, $4CH_2Ph$); 4.46 (dd, 1H, $J_{2-1}$= 2.4 Hz, $J_{2-3}$= 4.4 Hz, H2); 4.36 (m, 1H, H5); 3.97 (dd, 1H, $J_{3-2}$= 4.4 Hz, $J_{3-4}$= 3.0 Hz, H3); 3.76 (dd, 1H, $J_{4-3}$= 3.0 Hz, $J_{4-5}$= 7.4 Hz, H4); 3.49-3.40 (m, 1H, $HCOR_{cholesteryl}$); 2.41-0.66 (m, 44H, $H_{cholesteryl}$); 1.26 (m, 1H, H6). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 140.9 ($=C_{cholesteryl}$);140.5-138.6 ($C_{aromatic}$); 128.7-126.9 ($CH_{aromatic}$); 122.0 ($=CH_{cholesteryl}$); 99.5 (C1); 79.9 ($CHOR_{cholestanyl}$); 78.0 (C3); 76.0 (C4); 75.8, 71.6 ($2CH_2Ph$); 65.4 (C5); 57.0-12.1 ($24C_{cholesteryl}$); 28.7 (C2); 18.3 (C6).

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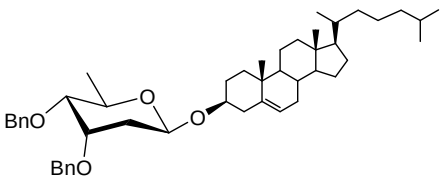
**Cholesteryl 3,4-di-*O*-benzyl-2,6-dideoxy-α/β-D-*ribo*-pyranoside (42)**




**42**

A solution of **41** (15 mg, 0.018 mmol) (α:β 1:7), $Bu_3SnH$ (15 μL, 0.055 mmol) and $Et_3B$ (5 μl, 1 M in hexane, 0.005 mmol) in 0.2 ml of toluene (0.085 M) was stirred for 22 h at rt (reaction monitored by NMR). The reaction mixture was diluted with EtOAc (5 ml) and washed with $NaHCO_3$. The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. The crude product was purified by radial chromatography using 1:4 EtOAc:hexane as the eluent to afford compound **42** (10 mg, 79%) as a 11:89 anomeric mixture.

Spectroscopic data obtained from the α/β mixture:

Elemental Analysis: Calcd for $C_{47}H_{68}O_4$: 80.99 C, 9.83 H. Found: 80.88 C, 9.75 H.

**42**β: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.42-6.99 (m, 10H, $H_{aromatic}$); 5.36 (sa, 1H, $CH=_{cholesteryl}$); 4.94 (dd, 1H, $J_{1\text{-}2eq}$= 2.0 Hz, $J_{1\text{-}2ax}$= 9.6 Hz, H1); 4.68 (s, 2H, $2CH_2Ph$); 4.55 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.39 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.02-3.97 (m, 2H, H3, H5); 3.57-3.51 (m, 1H, $HCOR_{cholesteryl}$); 3.12 (dd, 1H, $J_{4\text{-}3}$= 2.6 Hz, $J_{4\text{-}5}$= 9.2 Hz, H4); 2.33-0.65 (m, 44H, $H_{cholesteryl}$); 2.14 (ddd, 1H, $J_{2eq\text{-}1}$= 2.0 Hz, $J_{2eq\text{-}3}$= 3.2 Hz, $J_{2eq\text{-}2ax}$= 13.6 Hz, H2eq); 1.55 (m, 1H, $H_2$ax);1.27 (d, 1H, $J_{6\text{-}5}$= 4.0 Hz, H6). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 141.0 ($=C_{cholesteryl}$); 138.9, 138.2 ($C_{aromatic}$); 128.6-127.8 ($CH_{aromatic}$); 121.9 ($=CH_{cholesteryl}$); 96.0 (C1); 80.0 (C4); 78.0 ($CHOR_{cholesteryl}$); 71.8 ($CH_2Ph$); 71.5 ($CH_2Ph$, C5); 69.1 (C3); 58.0-12.1 ($24C_{cholesteryl}$); 36.1 (C2); 18.7 (C6).

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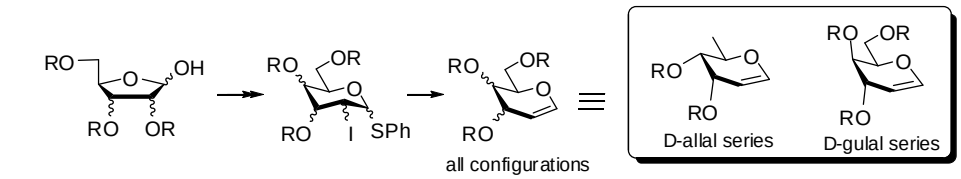
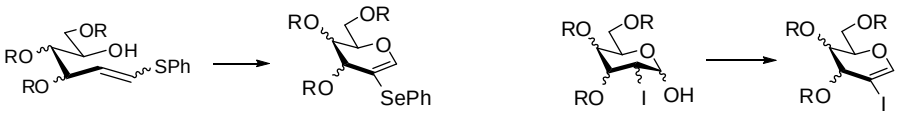
# 3

# General Method for Synthesizing Pyranoid Glycals

Pyranoid glycals of all configurations can be obtained from pentoses through an olefination-cyclization-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 *allo* or *gulo* configurations, since the cyclization step is more efficient for these substrates. Furthermore, other functionalized glycals such as 2-phenylselenenyl or 2-iodoglycals can be synthesized starting from enolthioethers by direct selenium-mediated elimination or through dehydrative reaction of 2-iodolactols, respectively.



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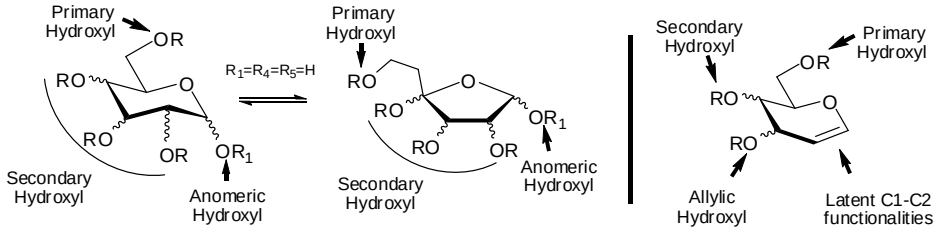
## 3.1 Synthesis of non-substituted glycals

## Introduction

Glycals are saccharide derivatives having a double bond between the anomeric carbon and the adjacent carbon atom. These 1,2-unsaturated glycopyranosides are versatile synthetic intermediates for elaboration to a number of functionalized glycosyl derivatives. Formally, these compounds are highly electron-rich enol ethers, which can undergo many reactions with high regioselectivity and stereoselectivity. Glycals can be subjected to several blocking group manipulations (but avoiding acidic conditions). Therefore, the use of these glycoside derivatives reduces the complexity of protecting group manipulations in oligosaccharide synthesis. Thus, the number of oxygens to be differentiated is reduced from five in saturated pyranose systems to three by using glycals as acceptors and donors. Furthermore, hydroxyl group differentiation of a glycal is generally a straightforward matter. The first protection tends to occur at C6 (primary hydroxyl). The second site of reactivity is the allylic alcohol at C3**.** Only after these oxygens have been substituted does C4 react. Besides, it is not necessary to make provision for C1 and C2 while using glycals as acceptors[92] (Figure 1).

**Figure 1.** Differentiation of hydroxyl groups in hexasaccharides**.**




Glycals are important synthetic intermediates for the synthesis of oligosaccharide motifs[93] (Scheme 1). Additions to the C1-C2 double bond of these compounds result in the

[92] a) G-J. Boons and K. J Hale in *Organic Synthesis with Carbohydrates* ; PostGraduate Chemistry Series, Academic Press Ltd., Sheffield, England. 2000, pp 65-71 b) Danishefsky, S. J.; Roberge, J. Y. *Pure&Appl. Chem.* **1995**, *67*, 1647**.**

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

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formation of 2-deoxy-2-heteroatomic substituted sugars or related derivatives (2-halo, 2-selenenyl, 2-sulfanyl, 2-amino/azido derivatives) and thereby constitute an attractive route for the synthesis of glycosides. 1,2-Anhydrosugars are useful intermediates for the conversion of glycals into common glycosides of glucose, galactose and mannose after coupling steps. These anhydrosugars can be synthesized via oxidation of glycals with dimethyldioxirane (DMDO)[94]. Reaction of a Lewis acid[7a,95] with an acetylated glycal in the presence of a nucleophile results in allylic rearrangement to give 2,3-unsaturated compound (Ferrier rearrangement). This reaction has found widespread use in natural product synthesis because it makes it possible to add thiols, azides, cyanides and purines to the anomeric center. As an extension of the Ferrier transposition, 2,3-unsaturated lactones are formed when *m*-chloroperbenzoic acid is used as nucleophile. In this reaction, a peroxy ester is formed in the anomeric centre, which rearranges to a lactone. In addition, it is also important the synthesis of useful sugar-derived enones that are readily available from the oxidation of glycals (Scheme 1, allylic oxidation).[96] Cycloaddition or cyclization reactions are also a helpful way to functionalise glycals.[97]

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[96] For use of enones in synthesis see: a) Goodwin, T.E.; Crowder, C. M.; White, R.B.; Swanson, J.S.; Evans, F.E.; Meyer, W.L. *J. Org. Chem*. **1983**, *48*; 376. b) Primeau, J.L.; Anderson, L.C.;Fraser-Reid, B. *J. Chem. Soc. Chem. Commun*., **1980**, 6.

[97] For cyclization of glycals with bidentate nucleophiles see: a) Yadav, J.S.; Reddy, B.V. S.;Rao, K.V.; Raj, K.S.; Prasad, A.R.; Kumar, S.K.; Kunwar, A.C.; Jayaprakash, P.; Jagannath, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 5198. For use in a novel class of glycosylation based in a [4+2] cycloaddition see: b) Capozzi, G.; Dios, A.; Frank, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 777. c) Franck, R. W.; Marzabadi, C. H. *J. Org. Chem.* **1998**, *63*, 2197. d) Tamarez, M.M; Franck, R.W.; Geer, A. *Tetrahedron* **2003**, *59*, 4249. For [2+2] cycloaddition see: Chmielewski, M.; Kaluza, Z.; Belzecki, C.; Salanski, J.; Jurzak, J.; Adamowicz, H. *Tetrahedron* **1985**, *41*, 2441.

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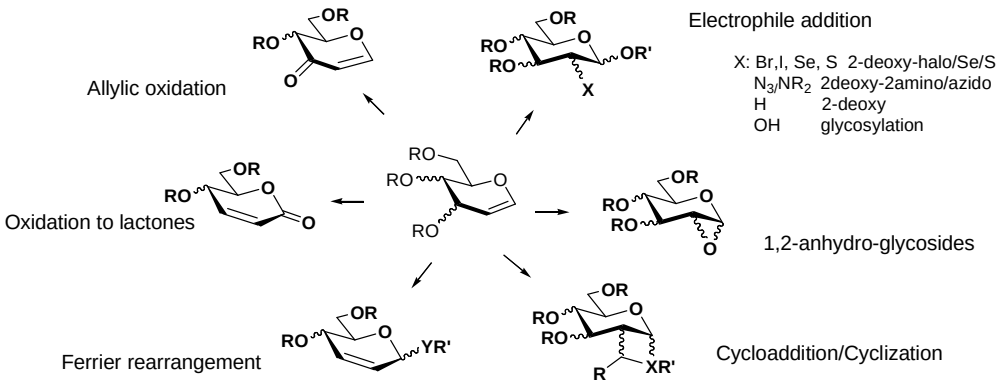
**Scheme 1**




Besides this reactivity, glycals are suitable products for the synthesis of C-glycosides. In this way, transition metal-catalysed reactions of glycals with carbon nucleophiles provide an important route to these special glycosides. For example Pd(II) complexes can be added to the double bond of glycal derivatives and the resulting intermediate can undergo different transformations depending on the reaction conditions.[98]

Alternatively, Pd(0) adds oxidatively to a double bond of a glycal derivative resulting in the formation of a π-allyl complex, which may react with carbon nucleophiles to give C-glycosides with a double bond between C-2 and C-3[99] (Scheme 2a). Other strategies to synthesize these compounds include cyanation reaction[100], couplings with olefins[101], C-glycosidations with allylsilanes[102], allylic ethers[103] or even synthesis of C-disaccharides[104](Scheme 2b, c, d, e, f respectively).

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[104] de Raadt, A.; Stütz, A. E.; *Carbohydr. Res*. **1991**, *220*, 101.

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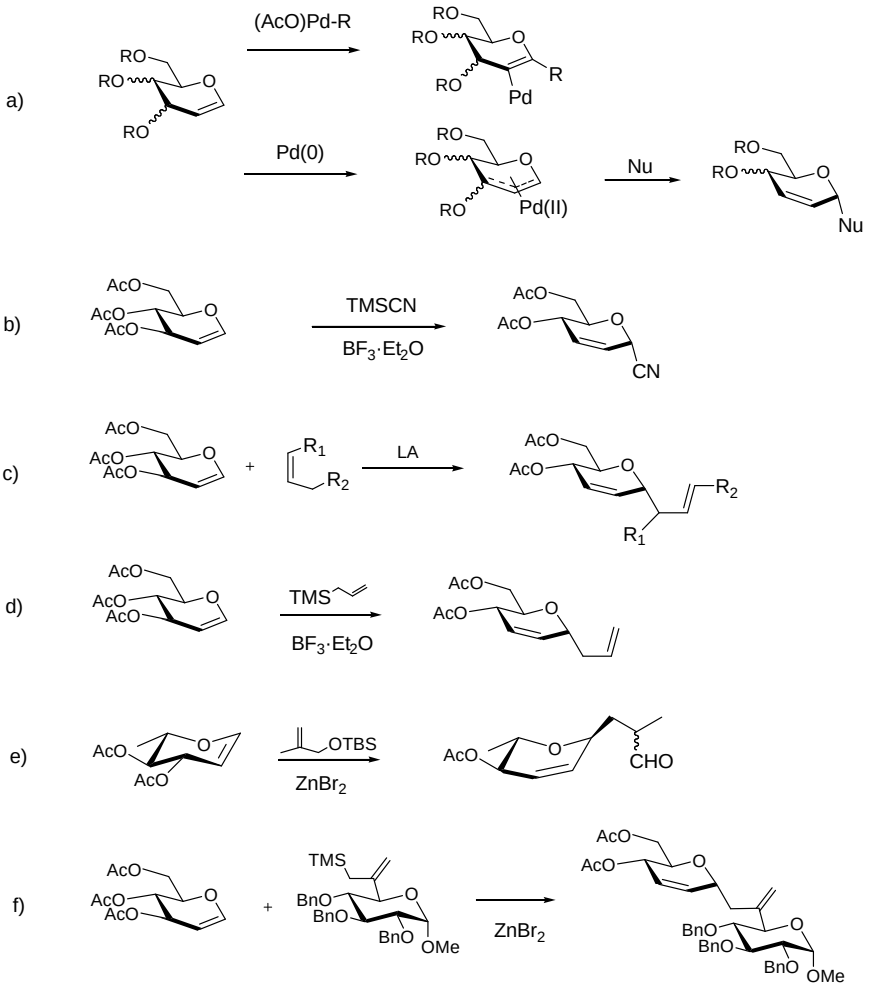
**Scheme 2**




To sum up, access to glycals is important in the glycosylation field for the synthesis of *O*-glycosides, *C*-glycosides[105] and *C*-nucleosides,[106] nucleosides[107] and other biologically important molecules.[108,109] The growing appreciation that glycoconjugates

[105] a) Thorn, S. N.; Gallagher, T. *Synlett* **1996,** 856. b) Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917.
[106] a) Erion, M. D.; Rydzewski, R. M. *Nucleosides&Nucleotides* **1997**, *16*, 315. b) Walker II, J. A.; Chen, J. J.; Hinkley, J. M.; Wise, D. S.; Townsend, L. B. *Nucleosides&Nucleotides* **1997**, *16*, 1999.
[107] a) Robles, R.; Rodríguez, C.; Izquierdo, I.; Plaza, M. T.; Mota, A. *Tetrahedron:Asymmetry* **1997**, *8*, 2959. b) Díaz, Y.; El-Laghdach, A.; Castillón, S. *Tetrahedron* **1997**, *53*, 10921. c) Díaz, Y.; El-Laghdach, A.; Matheu, M. I., Castillón, S. *J. Org. Chem.* **1997**, *62*, 1501. d) Chao, Q.; Zhang, J.; Pickering, L.; Jahnke, T. S.; Nair, V. *Tetrahedron* **1998**, *54*, 3113. e) Bravo, F.; Kassou, M.; Díaz, Y.; Castillón, S. *Tetrahedron Lett.* **2001**, *336*, 83.
[108] For use in cyclopropanation and ring expansion see: Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.*, **1997**, *62*, 7694.

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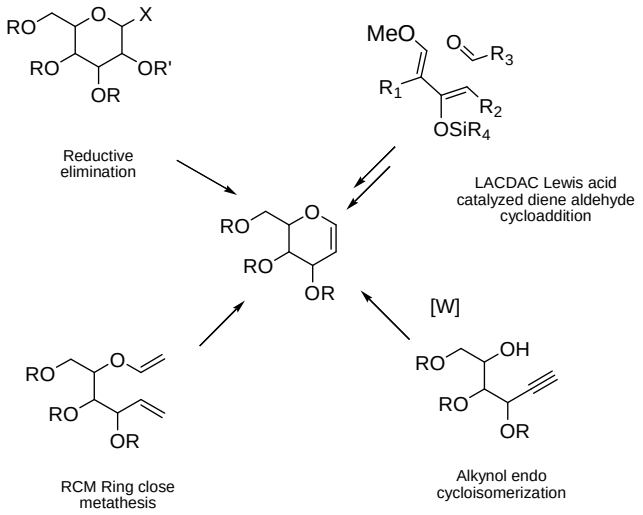
play an important role in cell recognition processes has spurred the synthesis of many glycoconjugates via the glycal method. In some cases, this effort has been conducted with the aim of developing synthetic vaccines. If new structural motifs are to be built up, it will be necessary to provide a variety of glycals of different configurations.

**Scheme 3**




There are different methods to obtain 1,2-unsaturated sugars (Scheme 3). 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 them.[110] 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, $(Cp_2TiCl)_2$, Cr(EDTA), Al-Hg, lithium naphthalenide, potassium-graphite, $SmI_2$, etc.). When appropriate groups are present at positions 1 and 2, the reaction can be performed under radical conditions.[111c] These

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

[110] a) Fischer, E.; Zach, K. *Sitzungsber. Kl. Preuss. Akad. Wiss*. **1913**, *27*, 311-317. Improved versions: b) Roth, W.; Pigman, W. *Methods in Carbohydrate Chemistry*; Whistler, R.L.; Wolfrom, M.L., Eds.; Academic Press: New York, 1963; Vol. 2, p 405-408. c) Shafizadeh, F. *Methods in Carbohydrate Chemistry*; Whistler, R.L.; Wolfrom, M.L., Eds.; Academic Press: New York, 1963; Vol. 2, p 409-410. d) Shull, B.K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem*. **1996**, *15*, 955.

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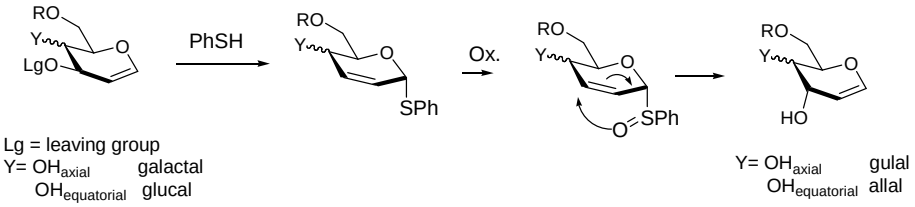
methods are limited to readily available pyranoses. In this respect, the only pyranoid glycals that are currently readily accessible are either D-glucal and D-galactal, or L-rhamnal. Other D-glycals (such as D-gulal and D-allal etc.) are not easily available. For instance, 3,4,6-tri-*O*-acetyl-D-allal was initially obtained from the penta-*O*-acetyl-D-altropyranose in low yield (12%),[111a] from D-allopyranosyl bromide (76%),[111c] or from methyl 2-deoxy-2-iodo-a-D-altropyranoside in a 85% yield.[111b] D-Gulal, in turn, was obtained from D-idopyranosyl bromide but in very low yield (11%).[111c]

An interesting method for the synthesis of glycals from carbohydrate precursors bearing an axial hydroxyl group at C-3 was developed by Danishefsky and co-workers.[112]

**Scheme 4**




This method exploits a form of the Ferrier-type displacement of glycals. Thus, reaction of a C-3-alkoxy equatorial glycal (glucal and galactal) with thiophenol gives rise to an axial thiophenyl 2,3-unsaturated sugar, which is converted by oxidation into a C3-alkoxy axial glycal, presumably by rearrangement of its sulfoxide (Scheme 4).

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 1,2-unsaturated glycopyranosides. Glycals have also been prepared by ring-closing metathesis[113] and via tungsten and molybdenum-promoted alkynol *endo*-cycloisomerization (Scheme 3).[114]

---

[111] a) Paulsen, H.; Thiem, J. *Chem. Ber*. **1973**, *106*, 3850. b) Guthrie, R. D.; Irvine, R. W. *Carbohydr. Res.* **1979**, *72*, 285. c) Somsak L. *Chem Rev*. **2001**, *101*, 81.

[112] a) Wittman, M.D.; Halcomb, R.L.; Danishefsky, S.J.; Golik, J.; Vyas, D. *J. Org. Chem.* **1990**, *55*, 1979.

[113] a) Calimente, D.; Postema, M.H.D. *J. Org. Chem*. **1999**, *64*, 1770. b) Postema, M.H.D.; Calimente, D. *Tetrahedron Lett*. **1999**, *40*, 4755. b) Schmidt, B.; Wildemann, H. *Eur. J. Org. Chem*. **2000**, 3145. d) Postema, M.H.D.; Calimente, D.; Liu, L.; Behrmann, T.L. *J. Org. Chem*. **2000**, *65*, 6061.

[114] a) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.*, **1996**, *118*, 6648. b) McDonald, F. E.; Bowman, J.L.; *Tetrahedron Lett*. **1996**, *37*, 4675. c) McDonald, F. E.; Zhu, H.Y.H. *Tetrahedron* **1997**, *53*, 11061. d) McDonald, F. E. *Chem. Eur. J*. **1999**, *5*, 3103. e) McDonald, F. E.; Reddy, K.S.; Díaz, Y. *J. Am. Chem. Soc.*, **2000**, *122*, 4304.

In Chapter 1 a new route to glycosides that makes use of a new kind of glycosyl donors, 2-deoxy-2-iodo-thioglycosides, was described. As an extension of this work, we envisioned an easy and general route to glycals from 2-deoxy-2-iodo-thioglycosides that would allow the preparation of D-allal and D-gulal derivatives. The presence of PhS and I groups at positions 1 and 2 in these compounds makes such substrates appropriate for glycal preparation under anionic or radical conditions. Some of these conditions have been tested in our laboratory with 2-deoxy-2-iodo-thioglycoside **19**.[115] Reductive conditions such as the Bredenkamp-modified Fischer-Zach method,[116] or the use of zinc in the presence of vitamin $B_{12}$,[117] afforded an excellent yield of the expected D-allal (**46**) (94-100%). Other anionic methods such as lithium naphthalenide (LN)[118] or $TiCl_4/LiAlH_4$,[119] gave very good yield (85-94%) but base-promoted elimination with *n*-BuLi only gave a modest yield (41%) and, with potassium *tert*-butoxide in refluxing THF, only the starting material was recovered. Under radical conditions, reaction with $SmI_2$ rendered very low yield[120] (15%), and a large amount of starting material was recovered, but under classical radical conditions with $Bu_3SnH$/AIBN in refluxing toluene[121] the expected glycal was obtained in very good yield (91%).

[115] Boutureira,O. Ph.D. Thesis, URV, in preparation.
[116] Bredemkamp, M.W.; Holzapfel, C.W. Toerien, F. *Synth. Commun.* **1992**, *22*, 2459. b) Erdik, E. *Tetrahedron* **1987**, *43*, 2203.
[117] Forbes, C.L.; Franck, R.W. *J. Org. Chem.* **1999**, *64*, 1424.
[118] Fernández-Mayoralas, A.; Marra, A.; Trumtel, M.; Veyrières, A.; Sinaÿ, P. *Tetrahedron Lett.* **1989**, *30*, 2537.
[119] Jeong, I.H.; Min, Y.K.; Kim, Y.S.; Kim, B.T.; Cho, K.Y. *Tetrahedron Lett.* **1994**, *35*, 7783.
[120] Pouilly, P.; Chénedé, A.; Mallet, J.M.; Sinaÿ, P. *Tetrahedron Lett.* **1992**, *33*, 8065.
[121] a) Boothe, T.E.; Greene, J.L.; Shevlin, P.B. *J. Org. Chem.* **1980***, 45*, 794. b) Lin, T-S.; Yang, J-H.; Liu, M-C.; Zhu, J.L. *Tetrahedron Lett.* **1990**, *31*, 3829.

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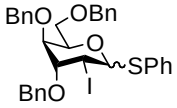
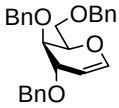
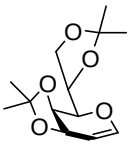
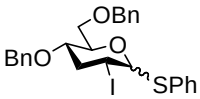
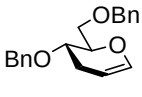
## Results and Discussion

Because tri-*O*-benzyl-D-allal (**46**) was most efficiently obtained from 2-deoxy-2-iodo-1-thio-D-allo-pyranoside **19** by using Zn-Cu couple as the reductant agent, we selected this method to explore the synthesis of the glycals shown in Table 1.

**Table 1**. Synthesis of pyranoid glycals from 2-deoxy-2-iodo-1-thio-glycosides.[a]

| Entry | Starting material | Conditions | Glycal | Yield(%) |
|---|---|---|---|---|
| 1 |  **13** | 0 ºC, 1 h |  **43** | 92 |
| 2[b] |  **16** | 0 ºC, 1 h |  **44** | 97 |
| 3[c,d] |  **18** | 15 ºC, 4 h |  **45** | 71 |

[a] Standard conditions: Zn-Cu couple, 1.4 equiv. NaAcO, THF-AcOH 20:1. (α/β mixture was used unless otherwise indicated). [b] 1:0 α/β was used. [c] 1:1 α/β and C-2 mixture of isomers was used.[d] The starting material decomposes on standing.

Thus, treatment of the 2-iodo-1-thio-glycosides **13, 16, 18** with Zn-Cu gave the glycals **43-45** in excellent yield. The lower yield for compound **45** was probably due to decomposition of the labile starting product **18** and that a longer reaction time was needed (Table 1, entry 3).

Parallel to this work, other 2-iodo-1-thio-glycosides were reduced in similar conditions in our laboratory to afford the corresponding glycals **46-50** also in excellent yields (Figure 2).[115]

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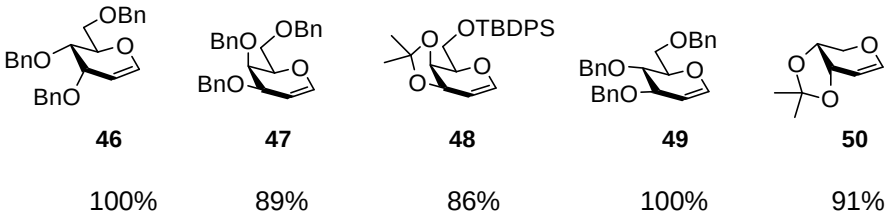
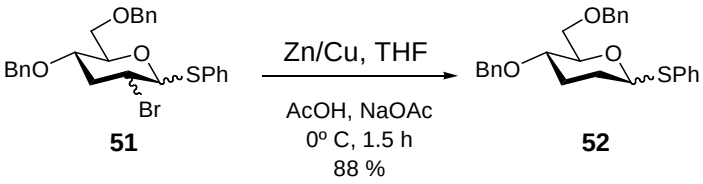
**Figure 2.** Glycals synthesized in our lab by Zn/Cu reductive elimination.




Importantly, glycals of all configurations, including the *D-allo* (**46**) and D-*gulo* (**43**) configurations, were accessible using this method. A variety of protecting groups, including benzyl, silyl ethers, and acetals, were stable under the reaction conditions. Significantly, the procedure described here can be used to obtain pyranoid glycals derived from heptoses (**44**) (Table 1,entry 2), pentoses (**50**) and 3-deoxy-hexoses (**45**) (Table 1, entry 3).

Interestingly, the bromo derivative **51**, obtained from the corresponding thio-alkenyl derivative by NBS-induced electrophilic cyclization, gave rise to the thiglycoside **52** and no glycal was isolated when subjected to the above conditions, indicating that the 2-iodo sugars are the best substrates for this reaction (Scheme 5).

**Scheme 5**




This outcome pointed out the putative mechanism of the reaction. It probably starts with the reductive removal of the halogen in C2 followed by elimination of the anomeric phenylsulfanyl group to give a glycal product. Product **52** is obtained if the reaction is quenched before elimination of the PhS group in C1 (Scheme 6a).

It is worthy of consideration that the classical reductive elimination method works in a C1-C2 inverse way. Therefore, formation of the double bond proceeds by initial C-halogen bond reduction followed by elimination of the C2 acetate (Scheme 6b).

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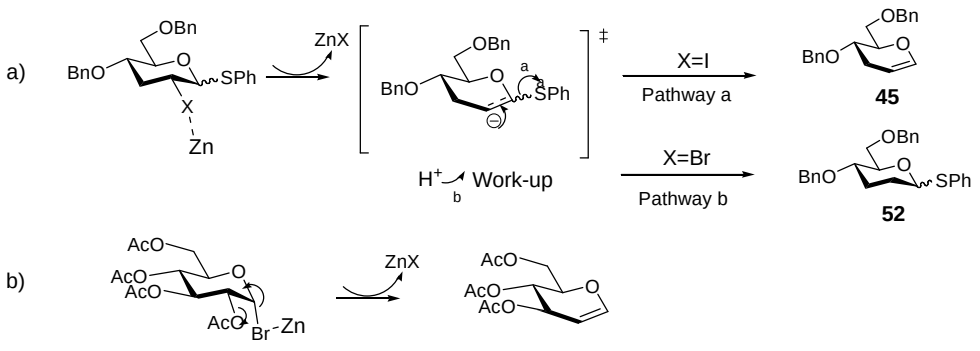
**Scheme 6**




## Conclusion

Here, it is shown a new method for accessing pyranoid glycals of different configurations by a short route that uses ready available starting materials and conventional transformations. This method provides access to non-conventional glycals having C3-alkoxy substituent in axial configuration, which are difficult to synthesize by usual methods. Thus, our method is particularly valuable for the synthesis of non-readily accessible glycals such as D-*allal* **46** and D-*gulal* **43** that are valuable products to prepare some oligosaccharide molecules with biologically interesting properties.

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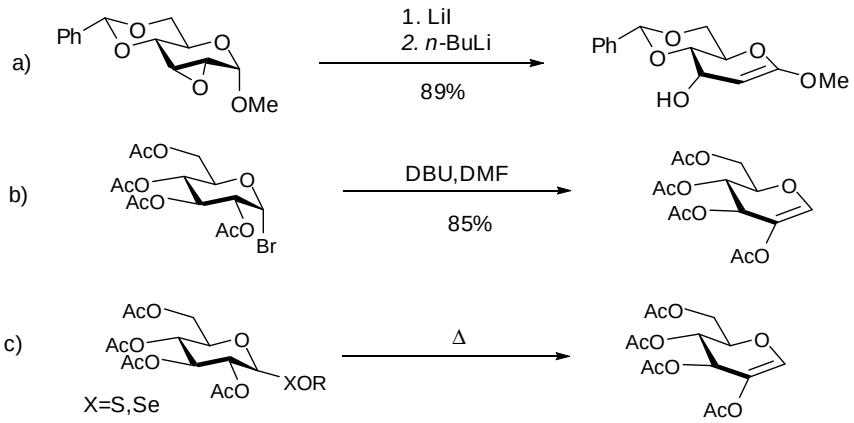
## 3.2 Synthesis of 2-iodo-glycals

## Introduction

As we have seen before, unsaturated sugar derivatives are important and versatile intermediates for organic synthesis in carbohydrate and related fields. This class of olefinic sugars is readily prepared via elimination reactions either directed by C1 or C2. However, there are fewer publications dealing with the synthesis of C1- or C2-substituted glycals. By way of illustration, 4,6-*O*-benzylidene-1-*O*-methyl-D-glucal was accomplished from methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-glucopyranoside through initial ring opening and subsequent elimination (Scheme 7a).[122] On the other hand, the 2-*O*-acetyl glycal derivative was also synthesized by subjecting glycosyl bromides to basic conditions (Scheme 7b),[123] or by elimination from thio[124] or selenoglycosides (Scheme 7c).[125]

**Scheme 7**




Apart from that, all types of organohalogen compounds are widely dispersed in nature[126] and therefore halogenated carbons have assumed an important role as synthetic

[122] Lemieux, R.U; Fraga, E.; Watanabe, K.A. *Can. J. Chem*. **1968**, *46*, 61.
[123] Rao, D.R; Lerner, L.M. *Carbohydr. Res.* **1972**, *22*, 345.
[124] a) Aversa, M. C.; Barattucci, A.; Bilardo, M. C.; Bonaccorsi, P.; Giannetto, P.; Rollin, P.; Tatibouët, A. *J. Org.Chem.* **2005**, *70*, 7389. b) Aucagne, V.; Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Rollin, P.; Tatibouët, A. *J. Org. Chem.* **2002**, *67*, 6925.
[125] D. J. Chambers, G. R. Evans, A. J. Fairbanks, *Tetrahedron* **2004**, *60*, 8411.
[126] Gribble, G. W. *Chem. Soc. Rev*. **1999**, *28*, 335 and referentes cited therein.

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intermediates, in natural products and environmental chemistry. Thus, halogenated glycals have attracted our interest for their role as important intermediates in organic synthesis. A bibliographic search revealed that very little information about the preparation and use of C2-halogenated glycals is available in the open literature.[127] These products were often found as by-products in glycosylation reactions[128] and were also used for studying oxidations.[129] Methods to synthesize 2-bromoglycals[130] were early developed and, in connection with a study of hexokinase isozymes of normal and cancerous tissues, 2-fluoro[131] and 2-chloroglycals[132] were also used as starting products for obtaining 2-deoxy-2,2-halo-sugars. Recently, 2-fluoro, 2-bromo and 2-chloroglycals have been used as synthetic intermediates for alkoxyl radical fragmentation (ARF) of sugars to render 1,1,1-trihalo-alkanes differently substituted (Scheme 8a).[133] An interesting application of 2-bromoglycal was found in the work of Fraser-Reid,[134] which synthesized chiral *trans*-decalins from 2-bromo-L-rhamnal. 2-iodoglycal were also used in a Stille coupling towards synthesis of phomactin A.[135]

Beyond the classical *O*-glycosides, their *C*-glycoside analogues have recently gained considerable attention,[136] and, therefore, the methods of synthesis of these compounds have undergone an important enlargement. In this way, unprotected glycals and 2-bromoglycals were reacted with trimethylsilyl cyanide to afford glycosyl cyanides.[137] In this case the substitution at C2 made the glycal less reactive than the non-substituted glycal.

The C1 carbon of glycals lends itself for deprotonation because of the enhanced acidity of vinylic positions Thus, as a general method to obtain *C*-glycosides, protected glycals can be selectively deprotonated at C1 by very strong bases such as *t*-butyllithium

[127] Based on a search in ACS SciFinder 2007 Database: Input of structure that consist in a 2-halo-pyranoid glycal to get substances that match this structure by substructure search reported 76 substances. Further refinement by elimination of halogen-substituted aromatic structures gives 26 substances and 39 references. Only one hit with C-2 iodine were found (Ref 135).
[128] a) Bock, C.; Pedersen, C. *Carbohydr. Res.* **1979**, *73*, 85-91. b) Bock, C.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1984**, *130*, 125.
[129] Boyd, E.C; Jones, R.V.H.; Quayle, P.; Waring, A.J. *Green Chemistry*, **2003**, 5, 679.
[130] Fogh, A.; Lundt, I.; Pedersen, C.; Rasmussen, P. *Acta Chem. Scand., Ser. B* **1977**, *31*,768.
[131] Adamson, J.; Foster, A.B.; Westwood, J.H. *Carbohydr. Res.* **1971**, *18*, 85.
[132] Adamson, J.; Foster, A.B. *Carbohydr. Res.* **1969**, *10*, 517.
[133] Francisco, C.G.; González, C.C.; Kennedy, A.R.; Paz, N.R.; Suárez, E. *Tetrahedron Lett*. **2006**, *47*, 35-38 and referentes cited therein.
[134] Fraser-Reid, B.; Chen, X.-T.; Haag, D.; Henry, K.J.Jr.; McPhail, A.T. *Chirality* **2000**, *12*, 488.
[135] Chemier, S.R.; Iserloh, U.; Danishefsky, S.J. *Org. Lett.* **2001**, *3*, 2949.
[136] (a) Postema, M.H.D. *Tetrahedron* **1992**, *48*, 8545. (b) Postema, M.H.D. *C-Glycoside Synthesis*; CRC Press: London, **1995**. (c) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem*. **1997**, *187*, 1. (d) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55.
[137] Hayashi, M.; Kawabata, H.; Nakayama, S.-Z. *Chirality* **2003**, *15*, 10.

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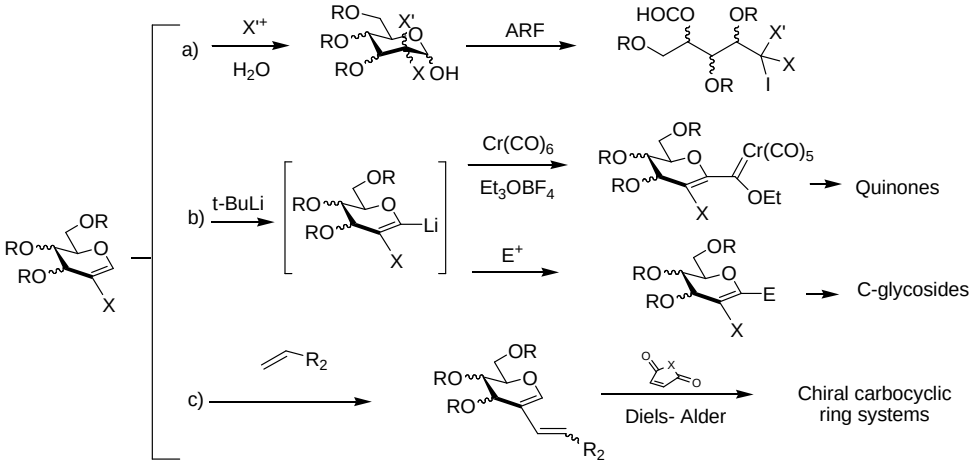
and the resulting anions can be then quenched with electrophiles such as $Bu_3SnCl$, $I_2$ and $PhSO_2Cl$.[138] Although direct deprotonation of glycals represents the most direct route to lithioglycals, such reactions are often capricious, their outcome is often difficult to rationalise, being highly substrate-dependent,[139] and it is not uncommon to employ large excesses of base, which may compromise the efficiency of subsequent alkylation reactions.

**Scheme 8**




Substituents with an inductive effect in the 2-position of glycals may facilitate deprotonation at C1. Heteroatoms in that position can also direct the attack of base toward C1 by complexation. Thus, 2-chloroglycals underwent facile deprotonation to afford, after suitable transformations, carbene complexes. These intermediates, in turn, provide a direct route to quinones through a benzannulation reaction.[140] Recently, C1 deprotonation of 2-chloro and 2-fluoroglycals was successfully applied to the synthesis of a wide range of *C*-glycosides (Scheme 8b).[141]

[138] a) Dubois, E.; Beau, J.-M. *Carbohydr. Res*. **1992**, *228*, 103. b) Tius, M.A.; Gomez, G.J.; Gu, X.Q.; Zaidi, J.H. *J. Am. Chem. Soc.* **1991**, *113*, 5775. c) Friesen, R.W.; Loo, R.W. *J. Org. Chem.* **1991**, *56*, 4821.
[139] Friesen, R. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1969–2001 and references cited therein.
[140] Hallett, M. R.; Painter, J.E.; Quayle, P.; Ricketts, D.; Patel, P. *Tetrahedron Lett.* **1998**, *39*, 2851.
[141] a) Boyd, E.;Hallett, M. R.; Jones, R.V.H.; Painter, J.E.; Patel, P; Quayle, P.; Waring, A.J. *Tetrahedron Lett.* **2006**, *47*, 8337. b) Boyd, E.; Jones, R.V.H.; Quayle, P.; Waring, A.J. *Tetrahedron Lett.* **2006**, *47*, 7983.

On the other hand, taking advantage of the C2 halogen group, palladium-catalysed coupling[142] can be used to synthesize conjugate carbohydrate-derived dienes. Thus, reaction of acetyl protected or even unprotected 2-bromo-D-glucal with different substituted olefins in the presence of a variety of palladium catalyst systems gave conjugated dieno-pyranosides. The Diels-Alder reaction of this carbohydrate-derived diene with some dienophiles constructed valuable chiral carbocyclic compounds (Scheme 8c).[143]

With this background, it is worth noting that 2-iodo-glycals are both valuable and versatile synthetic intermediates. They can be used for inserting C1 structures by deprotonation (C-glycosides, quinones)[140] and/or for introducing C2 vinyl substituents by Heck-type reaction[144] (iso *C*-glycosides, carbocyclic compounds) for which iodine is a better halogen group that chlorine or bromine.[142a,145]

## Results and Discussion

In the synthesis of 2-deoxy-2-iodo-hexo-pyranosyl glycosides developed in chapter 1, the key step was the cyclization of the alkenyl sulfanyl derivatives induced by iodonium equivalents. 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 thioglycoside already formed. Thus, a variable amount of the corresponding 2-iodo-lactol was usually recovered after work-up in non-optimized experiments with labile substrates.

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. For this reason a method that involves *in situ* transformation of the anomeric hydroxy group into a glycosyl donor intermediate can be a good option. In this way, Gin et al. developed the glycosylation method from 1-hydroxysugars using diphenyl sulfoxide and triflic anhydride to give glycosides and disaccharides in good yields. This glycosylation proceeds through an oxosulfonium intermediate which could evolve to

[142] a) R. F. Heck, *Acc. Chem. Res.*, **1979**, *12*, 146. b) Miyaura, N.; Suzuki, A. *Chem. Rev.*, **1995**, *95*, 2457. c) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. c) Al-Abed, Y.; A1-Tel, T. H.; Schröder, C.; Voelter, W. *Angew. Chem. Int. Ed. Engl.* **1994**, *33,* 1499.
[143] a) Hayashi, M.; Tsukada, K.; Kawabata, H.; Lamberth, C. *Tetrahedron* **1999**, *55*, 12287. b) Hayashi, M.; Amano, K.; Tsukada, K.; Lamberth, C. *J. Chem. Soc. Perkin Trans. 1*, **1999**, 239.
[144] a) Gómez, A.M.; Danelón, G.O.; Pedregosa, A.; Valverde, S.; López, J.C. Chem. Commun. **2002**, 2024. b) Gómez, A.M.; Pedregosa, A.; Barrio, A.; Valverde, S.; López, J.C. *Tetrahedron Lett*. **2004**, *45*, 6307.
[145] Turner, W.R; Suto, M.J. *Tetrahedron Lett.* **1993**, *34*, 281.

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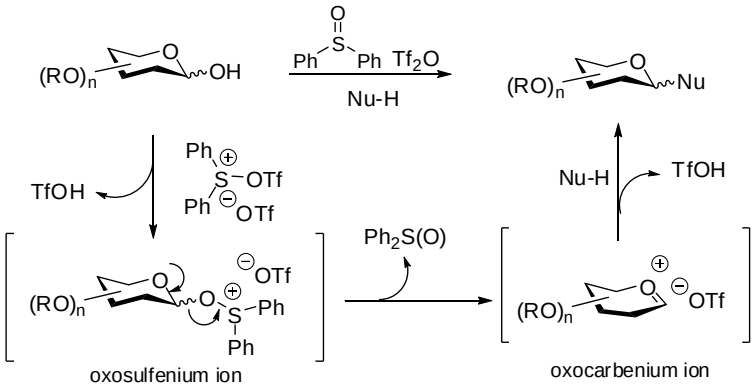
oxocarbenium ion with concomitantly regeneration of diphenyl sulfoxide. The nucleophilic acceptor subsequently adds to the anomeric centre to yield the desired glycosylated product in an overall one-pot procedure (Scheme 9).

**Scheme 9**




With this method, activated or deactivated glycosyl donors reacted equally well, and the procedure even allowed the N-glycosylation of an amide.[146] This methodology includes iterative,[147] orthogonal,[148] 1,2-*cis*,[149] and catalytic activated[150] glycosylations but, in general, required pre-activation of the glycosyl donor before addition of the acceptor.[151]

In the context of the orthogonal synthesis of digitoxine,[152] properly protected digitoxose derivative was submitted to Gin's glycosylation conditions. Thus, $Tf_2O$ was added to a mixture of 2-iodopyranose **53**, $Ph_2SO$, and 2,4,6-tri-(*tert*-butyl)-pyrimidine (TTBP) in DCM at -60ºC. Surprisingly, the product partially evolved to a new compound in a few minutes even before adding an acceptor. Letting the reaction proceed for 1h gave a good yield of the unexpected glycal **54** (Table 2, entry 1). In order to avoid this elimination, lower temperatures (-80 to -100ºC), less amount of base (1 to 3 eq. TTBP) and

[146] a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597. b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269. c) Nguyen, H. M.; Chen, Y.; Duron, S.G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766.
[147] Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem.,Int. Ed.* **2001**, *40*, 414.
[148] 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.
[149] Codeé, J. D. C.; Hossain, L.H.; Seeberger, P.H. *Org. Lett.* **2005**, *7*, 3251.
[150] a) Boebel, T. A.; Gin, D. Y. *Angew. Chem.*, *Int. Ed.* **2003**, *42*, 5874. b) Boebel, T. A.; Gin, D. Y. *J. Org. Chem.* **2005**, *70*, 5818.
[151] 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.
[152] See chapter 4.

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use of different dehydrative promoters (BSP,[153] alkysulfides) were also tested, but the same glycal was obtained in all these conditions.

Although our first encounter with this "dehydrative elimination" arose from serendipity, we wanted to evaluate the scope of this reaction. In this way, several 2-iodolactols were synthesized. In the presence of water, NIS-induced cyclization of alkenes **103**[154], **2**, **5**, or (*Z/E*)-3,4,6-tri-*O*-benzyl-1,2-dideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol[155], NIS-activation of thioglycoside **68**[155] and NIS iodohydroxylation of tri-*O*-benzyl-D-glucal or D-galactal gave, respectively, 2-iodolactols derivatives **53**, **55**, **17**, **56,** **59**, **62** and **64**. With these compounds in hand, 2-iodolactols **55** and **56** were subjected to dehydrative conditions to afford the corresponding glycals **43** and **57** (Table 2, entries 2, 3). In the case of the ribo derivative **56**, the 2-iodoglycal **58** was also obtained in minor amount (22 % yield, Table 1, entry 3). In order to confirm that glycal **57** did no come from 2-iodoglycal **58**, isolated compound **58** was submitted to dehydrative elimination conditions. Recovery of the iodoglycal **58** indicated that it was formed in a non-reversible way. Compounds **62** (*manno*) and **64** (*talo*) were also reacted under the same conditions to give 1,1'-disaccharides products **63** and **65,** respectively, as a result of the self-condensation of the starting 2-iodolactols (Table 2, entries 6, 7). Finally, isopropylidene-protected iodolactols **59** and **17** rendered exclusively the corresponding 2-iodoglycals **60** and **61** in good to excellent yields (Table 2, entries 4, 5). The formation of the 2-iodo-glycals was identified by the presence in the $^{1}$H NMR spectra of a singlet at ~6.8 ppm assigned to H1, and in the $^{13}$C NMR spectra of two signals at ~148 ppm and ~75 ppm assigned to C1 and C2, respectively.

Even though Gin's procedure has proved to be an efficient and general glycosylation method, these results revealed that their application in 2-iodo-pyranoses can not be assumed as a matter of course. It is not obvious why $Ph_2SO/Tf_2O$-promoted glycosylation lead to such different product distribution (glycals, 2-iodoglycals, and self-condensation products) related to the 2-iodolactol substrate, although being performed under similar conditions. Similar results were found in a previous work done in our laboratory in the synthesis of 2-deoxy-2-phenylselenyl thioglycosyl donors from hydroxyl-hexenyl sulfides by selenium-induced cyclizations. These reactions yielded

[153] For the use of benzensulfinyl piperidine (BSP) in glycosylation see: a) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015. b) Crich, D.; Li, H. *J. Org. Chem.* **2001**, *67*, 4640.
[154] For preparation of alkene **103** see Chapter 4.
[155] See Experimental part.

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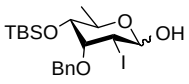
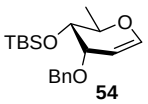
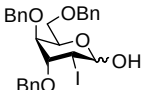
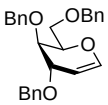
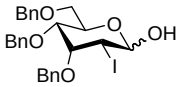
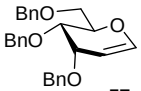
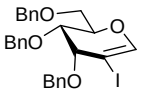
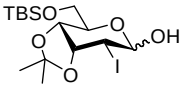
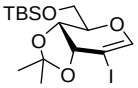
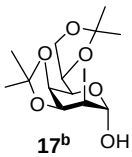
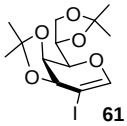
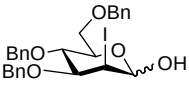
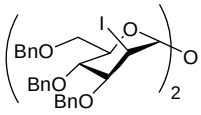
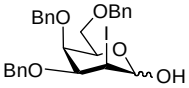
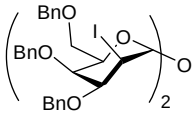
**Table 2.** Dehydrative elimination from various 2-deoxy-2-iodo-pyranoses.[a]

| Entry | Starting material | Conditions | Product | Yield(%) |
|---|---|---|---|---|
| 1 |  **53**[b] | -60 ºC, 1 h |  **54** | 97 |
| 2 |  **55**[b] | -60 ºC,5 h |  **43** | 77 |
| 3 |  **56**[b] | -50 ºC, 3 h |  **57** | 47 |
| | | |  **58** | 22 |
| 4 |  **59**[c] | -40ºC, 2h |  **60** | 97 |
| 5 |  **17**[b] | -60 ºC, 6 h |  **61** | 73 |
| 6 |  **62**[d] | -40 ºC, 5 h |  **63** | 54 |
| 7 |  **64**[d] | -40 ºC, 5 h |  **65** | 84 |

[a] Standard conditions: 2-iodopyranose (1.0 eq, α/β mixture), $PhSO_2$ (2.0 eq), TTBP (3.0 eq) in DCM. $Tf_2O$ (1.0 eq) was added at -60ºC. [b]Synthesized from the corresponding alkenyl sulfide. [c] Made from the corresponding thioglycoside to confirm stereochemistry. [d] Made by iodohydroxylation of the corresponding glycal.

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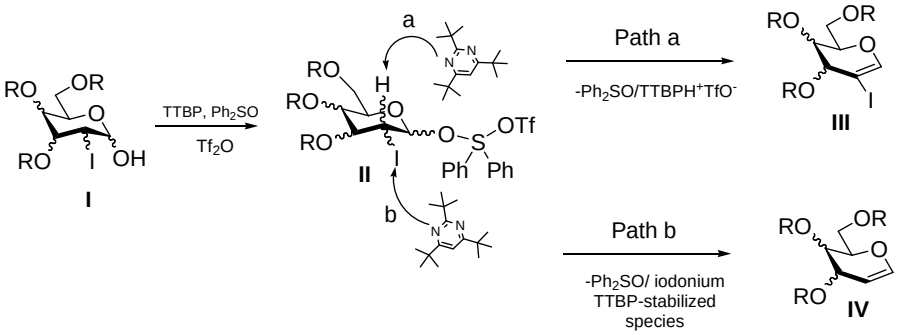
glycals or 2-phenylselenenyl glycals as by-products depending on the reaction conditions and the nature of the donor.[156]

A plausible explanation for the observed product distribution is outlined in Scheme 10. The conversion of compound **I** into **III** represents an overall base-promoted[157] hydroxyl elimination process (reaction path a), and might be occurring through the initial 1-OH activation to give intermediate **II,** followed by elimination of $Ph_2SO$ and tri-(*tert*-butyl)-pyrimidinium triflate ($TTBPH^+TfO^-$) to render 2-iodoglycal **III**.

**Scheme 10**




Similarly, the production of **IV** might be explained in terms of nitrogen assisted iodine elimination[158] in **II** to afford the corresponding glycal (reaction path b).

However, to explain the outcome of the elimination reaction further considerations must be accounted for. As demonstrated by Gin's group in NMR studies,[146b] glycosyl triflates and oxosulfonium ions are formed at low temperature from 2-alkoxy substituted pyranoses under dehydrative glycosylation conditions ($Ph_2SO/Tf_2O$). In contrast with these results, evidence was also presented indicating that glycosyl triflates

[156] Boutureira, O.; Rodríguez, M. A.; Benito, D.; Matheu, M. I.; Díaz, Y.; Castillón, S. in press; for example of synthesis of 2-phenylselenenyl glycal (**69**) see experimental part in this chapter.

[157] For 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.

[158] This behaviour of the nitrogen atom to stabilize/eliminate $I^+$ has been previously observed in: a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190. b) Barluenga, J.; Rodríguez, M.A.; Campos, P.J. *J. Org. Chem.* **1990**, 55, 3104. c) Arnés, X. *Ph.D Thesis*, URV, September 2003. d) Mongin, F.; Rebstock, A.-S.; Trécourt, F.; Quéguiner, G.; Marsais, F. *J. Org. Chem.* **2004**, 69, 6766. e) Álvarez de Cienfuegos, L.; Mota, A.M.; Robles, R. *Org. Lett.* **2005**, *7*, 2161.

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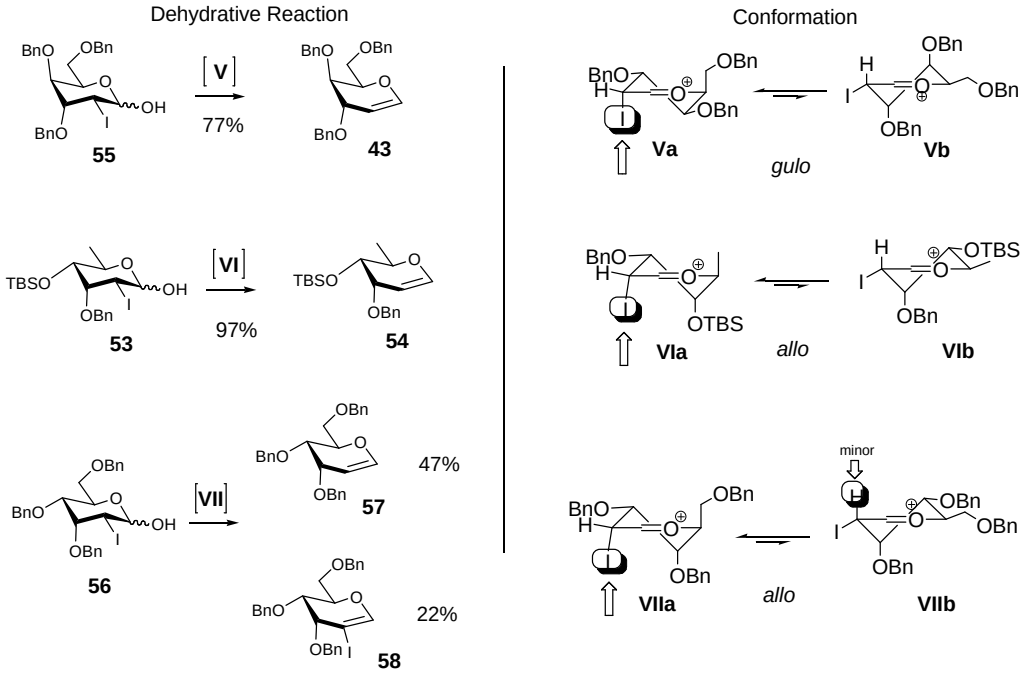
are not intermediates after anomeric activation of 2-iodoglucosyl donors[159] and thus, 2-iodolactols would give pyranosyl cations as intermediates (by the resonance stabilizing effect of the C2 electron-donating substituent). It is also know that, between 2-iodo-pyranosyl cations, oxocarbenium ions are the most plausible intermediate rather than the corresponding iodonium-ion one.[160]

**Scheme 11**




According to this, in the scheme 11 is depicted, for each configuration, the two different chair-like oxocarbenium intermediate conformations (**a** and **b**) which would be implicated in the dehydrative elimination reaction.

As we have seen before (chapter 1), iodine-axial intermediates (**Va**, **VIa**, **VIIa**) are likely to be more stable than the corresponding iodine-equatorial conformers (**Vb**, **VIb**,**VIIb**) due to stabilizing hyperconjugative interactions between $\sigma_{C\text{-}I}$ and $\pi^*_{C\text{-}O}$ of the

[159] a) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926. b) Chong, P. Y.; Roush, W. R. *Org. Lett.* **2002**, *4*, 4523.
[160] a) Bravo, F.; Viso, A.; Alcázar, E.; Molas, P.; Bo, C.; Castillón, S. *J. Org. Chem.* **2003**, *68*, 686. b) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, 5, 1871. c) a) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521.

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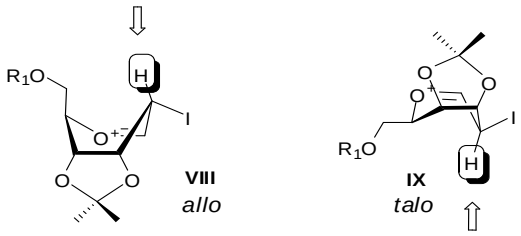
oxocarbenium.[161] Furthermore, in the E1 elimination reaction, the new *p* bond can only form if the vacant *p* orbital of the carbocation and the breaking C–H or C-I bond are aligned parallel. Therefore, the group to be eliminated (I or H) must be in the axial position.

Consistent with this, dehydrative elimination of 2-iodolactol **55** (*gulo*) proceed trough more stable conformer **Va** and elimination of the axial iodine afforded glycal **43**. Similarly, axial iodine elimination of 2-iodolactol **53** (*allo*) in the more stable conformer **VIa** rendered glycal **54**. Moreover, equilibrium between conformers in this configuration is also displaced towards **VIa** for destabilizing gauche-effects between TBS group and C6 in conformer **VIb**. In the case of iodolactol **56** (*allo*), the elimination mainly proceed through the more stable intermediate **VIIa** to render glycal **57**. However, a minor amount of conformer **VIIb**, presumably present because the 1,3-diaxial repulsion between I and OBn is avoided, also eliminated to give 2-iodoglycal **58**.

**Figure 3.** Stereochemical features in elimination reaction of activated 2-iodolactols




Interestingly, experiments carried out with isopropylidene-protected[162] iodolactols **17** and **59** only afforded 2-iodoglycal products **61** and **60**. To explain this chemoselective elimination, the allo and talo activated intermediates depicted in Figure 3 must be taken into account. Thus, the elimination process might operate by way of constrained conformations such as **VIII** (allo) and **IX** (talo), upon which occur highly favoured TTBP exo-approach to proton (arrow) instead of the endo-approach to iodine. Finally, in the case of iodolactols **62** and **64**, the rate of self condensation of hemiacetals with its corresponding glycosyl donors is greater than that of hemiacetals activation with

[161] Billings, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171.
[162] 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.* **2006**, *342*, 419.

$Ph_2SO/Tf_2O$. This outcome highlights the critical role of the configuration of 2-iodolactol in this dehydrative glycosylation process.

**Conclusion**

Gin's dehydrative glycosylation conditions have been tested in several 2-deoxy-2-iodo-pyranoses. Although this procedure has proved to be an efficient and general glycosylation method, their application in 2-iodo-pyranoses did not afford the expected products but led to glycals, 2-iodoglycals, and self-condensation disaccharides. Product distribution depends on the nature of the starting 2-iodolactol. Thus, 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group proved to be efficient to promote TTBP-induced proton elimination to render exclusively attractive 2-iodoglycals in good to excellent yields. Furthermore, the different products obtained gave us some insight into the likely pathway of the "dehydrative-elimination".

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# Experimental part

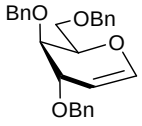
## General remarks

2:3-*O*-isopropylidene-5-*O*-(*tert*-butyl-dimethylsilyl)-α/β-D-ribofuranose, tri-*O*-benzyl-D-glucal and tri-*O*-benzyl-D-galactal were used as received from commercial suppliers. Preparation of thioenitol **103** is described in Chapter 4.

## General procedure for synthesizing glycals from 2-deoxy-2-iodo-1-thio-glycosides by reductive elimination

The 2-deoxy-2-iodo-pyranoside derivative (1 mmol) and NaOAc (1.4 mmol) were dissolved in a mixture of THF (1.7 ml) and acetic acid (63 μL) and cooled to 0 ºC. Zn/Cu couple (661 mg) was then added and the reaction was allowed to reach room temperature. The mixture was then diluted with dichloromethane and washed with a saturated solution of $NaHCO_3$. The aqueous layer was extracted twice with dichloromethane, and the combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by chromatographic techniques.

## 1,5-Anhydro-2-deoxy-3,4,6-tri-*O*-benzyl-D-*xylo*-hex-1-enitol (43)




**43**

The title compound was prepared following the general procedure starting from the phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-α-D-*gulo*-pyranoside (**13**), α:β 10:1 (159 mg, 0.24 mmol) in a mixture of 0.4 ml THF, 20:l acetic acid, NaOAc (28 mg, 0.34 mmol) and 161 mg Zn/Cu couple for 1h. The reaction was monitored by TLC (EtOAc:hexane 1:3). The crude was purified by radial chromatography (EtOAc:hexane 1:4) to afford the product **43** (50 mg, 92%) as a colourless syrup.

$R_f$ (EtOAc:hexane 1:3): 0.46. $[\alpha]^{20}_D$: + 64.3 (*c* 2.0, $CH_2Cl_2$). Anal. Calcd for $C_{27}H_{28}O_4$: 77.86 C, 6.78 H. Found: 77.80 C, 6.74 H.

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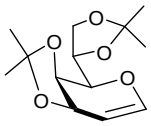
**43: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.35-7.23 (15H, m, Ar), 6.61 (1H, d, $J_{1,2}$= 6.0 Hz, H1), 4.95 (1H, ddd, $J_{1,2}$= 6.0 Hz, $J_{2,3}$= 5.2 Hz, $J_{2,4}$= 1.8 Hz, H2), 4.59-4.27 (6H, m, $J_{AB}$ = 12.0 Hz, $J_{AB'}$ = 8.6 Hz, $J_{AB''}$ = 12.6 Hz, $6CH_2Ph$), 4.16 (1H, ddd, $J_{4,5}$= 1.6 Hz, $J_{5,6a}$= 6.4 Hz, $J_{5,6b}$= 5.6 Hz, H5), 3.76 (1H, dd, $J_{6a,5}$= 6.4 Hz., $J_{6a,b}$= 10.0 Hz., H6a), 3.74 (1H, d, $J_{2,3}$= 5.2 Hz, H3), 3.66 (1H, d, $J_{4,5}$= 1.6 Hz, H4), 3.58 (1H, dd, $J_{5,6b}$= 5.6 Hz, $J_{6a,b}$= 10.0 Hz, H6b). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 146.9 (C1), 138.5-127.9 ($C_{aromatic}$), 98.7 (C2), 73.6 ($CH_2Ph$), 73.0 (C5), 72.7 (C4), 72.4, 70.0 ($2CH_2Ph$), 69.1 (C6), 67.3 (C3).

## 1,5-Anhydro-2-deoxy-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-hep-1-enitol (44)[163]



**44**

The title compound was prepared following the general procedure above starting from **16** (α:β 1:0) (105 mg, 0.21 mmol) in a mixture of 0.4 mL THF, 18 μL acetic acid, NaOAc (24.5 mg, 0.30 mmol) and 141 mg Zn/Cu couple for 1 h. The reaction was monitored by TLC (EtOAc:hexane 1:3). The crude product was purified by radial chromatography (EtOAc:hexane 1:4) to afford the expected product **44** (76.6 mg, 97%) as a white foam.

$R_f$ (EtOAc:hexane 1:3): 0.28.

Anal. Calcd for $C_{13}H_{20}O_5$: 60.92 C, 7.87 H. Found: 61.01 C, 7.90 H

**44**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 6.36 (1H, d, $J_{1,2}$= 6.4 Hz, H1), 4.80 (1H, ddd, $J_{1,2}$= 6.4 Hz, $J_{2,3}$= 2.8 Hz, $J_{2,4}$= 1.0 Hz, H2), 4.67 (1H, dd, $J_{3,4}$= 6.0 Hz, $J_{2,3}$= 2.8 Hz, H3), 4.43 (1H, dd, $J_{3,4}$= 6.0 Hz, $J_{2,4}$= 1.0 Hz, H4), 4.38 (1H, m, H6), 4.12 (1H, dd, $J_{7a,b}$= 8.4 Hz, $J_{6,7a}$= 6.0 Hz, H7a), 4.08 (1H, dd, $J_{7a,b}$= 8.4 Hz, $J_{7b,6}$= 5.0 Hz, H7b), 3.78 (1H, d, $J_{5,6}$= 8.0 Hz, H5), 1.46, 1.44, 1.39 (12H, s, $4CH_3$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 144.7 (C1), 110.8, 109.6 ($2C_{ketal}$), 103.2 (C2), 75.2 (C3), 74.3 (C4), 72.2 (C6), 68.6 (C5), 66.9 (C7), 28.3, 27.3, 27.1, 25.5 ($4CH_3$).

[163] Wardrop, D.J.; Zhang, W. *Tetrahedron Lett.* **2002**, *43*, 5389.

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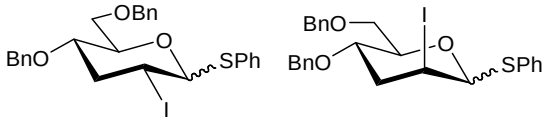
**Synthesis of glycal 45**

**a) Phenyl 4,6-di-*O*-benzyl-2,3-dideoxy-2-iodo-1-thio-α/β-D-*threo*-pyranoside (18)**




**18**eq **18**ax

As described in the general electrophile-induced cyclization procedure, compound **18** (130 mg, 56%, α/β ratio 1:1, C2-iodine ax:eq 1:1) was obtained as a yellowish syrup starting from compound **7** (*E*:*Z* ratio 1:1) (180 mg, 0.43 mmol) and NIS (1.25 g, 2.67 mmol) in dry $CH_3CN$ (3.5 ml), at -30 °C for 1.5 h. The reaction was monitored by TLC (EtOAc:hexane 1:3). The reaction mixture was purified by radial chromatography (from hexane to EtOAc:hexane 1:3). The isolated product decomposed on standing and was therefore quickly subjected to the next reaction.

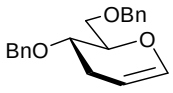
Partial data for **18** from ax/eq mixture:

**18**eq**: (1) $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.19 (m, 15H, aromatic); 4.82 (dd, 1H, $J_{2\text{-}3'}$= 4.4 Hz, $J_{2\text{-}3}$= 10 Hz, H2); 3.86 (ddd, 1H, $J_{4\text{-}3'}$= 4.4 Hz, $J_{4\text{-}5}$= 9.5 Hz., $J_{4\text{-}3}$= 13 Hz, H4); 3.69 (m, 2H, H6, H6'); 3.45 (ddd, 1H, $J_{5\text{-}6}$= 4.4 Hz, $J_{4\text{-}5}$= 9.5 Hz, $J_{5\text{-}6'}$= 10.4Hz, H5); 2.85 (dt, 1H, $J_{3'\text{-}2}$= 4.4 Hz, $J_{3'\text{-}4}$= 4.4 Hz, $J_{3'\text{-}3}$= 12.8 Hz, H3'); 2.10 (ddd, 1H, $J_{3\text{-}2}$= 10 Hz, $J_{3\text{-}3'}$= 12.8 Hz., $J_{3\text{-}4}$= 13 Hz., H3). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4-124.2 (Ar); 99.2 (C1); 79.0-69.2 (C4, C5, C6, $CH_2Ph$); 41.7 (C3); 25.7 (C2). **(2) $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.19 (m, 15H, Ar); 4.83 (dd, 1H, $J_{2\text{-}3'}$= 5.1 Hz, $J_{2\text{-}3}$= 9.9 Hz, H2); 4.22 (m, 1H, H4); 3.66 (m, 2H, H6, H6'); 3.49 (td, 1H, $J_{5\text{-}4}$= 4.8 Hz, $J_{5\text{-}6}$= $J_{5\text{-}6'}$= 10.8 Hz, H5); 2.60 (dt, 1H, $J_{3'\text{-}2}$= 4.7 Hz, $J_{3'\text{-}4}$= 4.7 Hz, $J_{3'\text{-}3}$= 12.2 Hz, H3'); 2.45 (td, 1H, $J_{3\text{-}2}$= 9.8 Hz, $J_{3\text{-}3'}$= 13.2 Hz, $J_{3\text{-}4}$= 13.2 Hz, H3). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4-124.3 (Ar); 92.1 (C1); 78.9-53.6 (C4, C5, C6, $CH_2Ph$); 35.9 (C3); 22.6 (C2).

**18**ax**: (1) $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.18 (m, 15H, Ar); 4.43 (s, 1H, H2); 3.90 (m, 1H, H4); 3.73 (m, 2H, H6, H6'); 3.67 (m, 1H, H5); 2.60 (ddd, 1H, $J_{3'\text{-}2}$= 3.7 Hz, $J_{3'\text{-}4}$= 4.2 Hz, $J_{3'\text{-}3}$= 14.5 Hz, H3'); 2.05 (ddd, 1H, $J_{3\text{-}2}$= 3.6 Hz, $J_{3\text{-}4}$= 10.2Hz, $J_{3\text{-}3'}$= 14.5 Hz, H3). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3-127.8 (Ar); 93.4 (C1); 79.2-69.5

(C4, C5, C6, $CH_2Ph$); 37.0 (C3); 26.8 (C2). **(2) $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.19 (m, 15H, Ar); 4.27 (s, 1H, H2); 4.16 (m, 1H, H4); 3.80 (m, 2H, H6, H6'); 3.67 (m, 1H, H5); 2.30-2.17 (m, 2H, H3', H3). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2-127.7 (Ar); 84.6 (C1); 79.2-69.5 (C4, C5, C6, $CH_2Ph$); 33.1 (C3); 29.6 (C2).

### b) 1,5-Anhydro-2,3-dideoxy-4,6-di-*O*-benzyl-D-*threo*-hex-1-enitol (45)[164]




**45**

The title compound was prepared following the general procedure above starting from phenyl 4,6-di-*O*-benzyl-2,3-dideoxy-2-iodo-1-thio-D-*ribo*-pyranoside (**18**, α:β 1:1; eq:ax 1:1) (130 mg, 0.24 mmol) in a mixture of 0.5 ml THF, 20 µl acetic acid, NaOAc (27 mg, 0.33 mmol) and 160 mg Zn/Cu couple. The reaction was monitored by TLC (EtOAc:hexane 1:3) and was allowed to reach 15 ºC during 4 h. The crude was purified by radial chromatography (EtOAc:hexane 1:4) to afford **45** (50 mg, 71%) as colourless syrup.

$R_f$ (EtOAc:hexane 1:3): 0.40. Anal. Calcd for $C_{20}H_{22}O_3$: 77.42 C, 7.10 H. Found: 77.20 C, 7.01 H.

**45**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.21 (10H, m, Ar), 6.36 (1H, ddd, $J_{1,2}$= 6.4 Hz, $J_{1,3a}$= 1.6 Hz, $J_{1,3}$b= 2.4 Hz, H1), 4.63 (1H, ddd, $J_{2,1}$= 6.4 Hz., $J_{2,3a}$= 5.2 Hz, $J_{2,3b}$= 2.6 Hz, H2), 4.62-4.50 (4H, m, $J_{AB}$= 9.0 Hz, $J_{AB'}$= 12.0 Hz, 4$CH_2Ph$), 3.90 (1H, ddd, $J_{5,4}$= 8.0 Hz, $J_{5,6a}$= $J_{5,6b}$= 4.0 Hz, H5), 3.79 (1H, m, H4, H6a, H6b), 2.38 (1H, dddd, $J_{3a,3b}$= 16.4 Hz, $J_{3a,2}$= 5.2 Hz, $J_{3a,4}$= 6.0 Hz, $J_{3a,1}$= 1.6 Hz, H3a), 2.08 (1H, dddd, $J_{3b,3a}$= 16.4 Hz, $J_{3b,2}$= 2.6 Hz, $J_{3b,4}$= 8.4 Hz, $J_{3b,1}$= 2.4 Hz, H3b). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 143.3 (C1), 138.4-127.8 ($C_{aromatic}$), 97.8 (C2), 76.9 (C5), 73.7, 71.3 (2CH2Ph), 70.7 (C4), 69.2 (C6), 26.7 (C3).

[164] a) Reddy, B.G.; Vankar, Y.D. *Tetrahedron Lett.* **2003**. *44*, 4765. b) Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc.* **1970**, *92*, 6661-6663.

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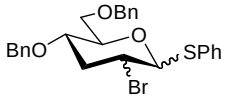
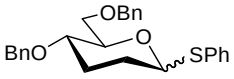
**Phenyl 4,6-di-*O*-benzyl-2,3-dideoxy-2-bromo-1-thio-α/β-D-*erythro*-pyranoside (51)**




**51**

As described in the general electrophile-induced cyclization procedure, compound **51** (53 mg, 45%, α/β ratio 1:1, C2-bromine ax:eq 1:1) was obtained as a brownish syrup starting from compound **7** (*E*:*Z* ratio 1:1) (100 mg, 0.23 mmol) and NBS (63.5 mg, 0.36 mmol) in dry $CH_3CN$ (3.4 ml), at -30 °C for 2.5 h. The reaction was monitored by TLC (EtOAc:hexane 1:3). The reaction mixture was purified by filtration through a silica plug (from hexane to EtOAc:hexane 1:3). The isolated product decomposed releasing bromine. Bromine was eliminated by vacuum pump and the product **51** was quickly subjected to the next reaction.

**Phenyl 4,6-di-*O*-benzyl-2,3-dideoxy-1-thio-α/β-D-*erythro*-pyranoside (52)**




**52**

The title compound was prepared following the general procedure above starting from freshly synthesized phenyl 4,6-di-*O*-benzyl-2,3-dideoxy-2-bromo-1-thio-D-*ribo*-pyranoside (**51**) α:β 1:1; eq:ax 1:1 (40 mg, 0.08 mmol) in a mixture of 0.5 ml THF, 7µl acetic acid, NaOAc (9.6 mg, 0.12 mmol) and 53 mg Zn/Cu couple for 1.5 h. The reaction was monitored by TLC (EtOAc:hexane 1:4). The crude was purified by radial chromatography (EtOAc:hexane 1:5) to afford **52** (31mg, 88%) as a 1:1 α/β anomeric mixture as colourless syrup.

Anal. Calcd for $C_{26}H_{26}O_3S$: 74.26 C, 6.67 H, 7.62 S. Found: 74.42 C, 6.75 H, 7.65 S.

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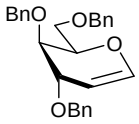
**52**: **$^{1}$H NMR** δ in ppm: 7.61-7.22 (15H, m, Ar), 4.71 (1H, d, $J_{1,2a}$= 10.4 Hz, H1), 4.61-4.40 (4H, m, $J_{AB}$ = 11.6 Hz, $J_{AB'}$ = 12.0 Hz, 4$CH_2$Ph), 3.80-3.68 (4H, m, , H2a, H2b, H6a, H6b), 3.58 (1H, ddd, $J_{5,4}$= 9.6 Hz, $J_{5,6a}$= 2.0 Hz, $J_{5,6b}$= 4.8 Hz, H5), 3.47 (1H, ddd, $J_{4,5}$= 9.6 Hz, $J_{4,3a}$= 4.4 Hz, $J_{4,3b}$= 10.4 Hz, H4), 2.88 (1H, ddd, $J_{3a,3b}$= 12.4 Hz, $J_{3a,2a}$= 4.8 Hz., $J_{3a,4}$= 4.4 Hz, H3a), 2.03 (1H, ddd, $J_{3b,3a}$= 12.4 Hz, $J_{3b,4}$= 10.4 Hz, $J_{3b,2a}$= 11.2 Hz, H3b). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 133.4-127.8 ($C_{aromatic}$), 89.5 (C1), 82.0 (C5), 73.6 (C4), 72.7, 71.7 (2$CH_2$Ph), 69.3 (C6), 45.7 (C2), 41.9 (C3).

## General procedure for dehydrative elimination

A mixture of the 2-iodolactol product (1.0 mmol), $Ph_2SO$ (2.0 mmol) and TTBP (3.0 mmol) in $CH_2Cl_2$ (0.04 M to iodolactol) were stirred over flame-dried molecular sieves for 30 min, after which the reaction mixture was cooled to -60 ºC. $Tf_2O$ (1.0 mmol) was added and the mixture was first brought to -40 ºC and then slowly warmed to the completion the reaction (TLC). The reaction was quenched by the addition of $Et_3N$ (10 mmol) and concentrated in vacuo. The crude product was purified by chromatographic techniques.

## Synthesis of glycal 43 by dehydrative elimination




**43**

To a solution of (*Z/E*)-3,4,6-tri-*O*-benzyl-1,2-dideoxy-1-phenylsulfanyl-D-*xylo*-hex-1-enitol (**2**) (205 mg, 0.39 mmol) in a 10:1 $CH_3CN$:$H_2O$ mixture (7.8 ml, 0.05 M) at -15 ºC; NIS (219 mg, 0.97 mmol) was added. After stirring for 45 min the reaction was extracted with $CH_2Cl_2$/$Na_2S_2O_3$ twice. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexanes:EtOAc 10:1) affording 2-iodopyranose **55** (179 mg, 82%) as a colourless syrup.

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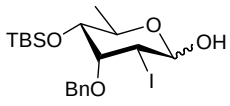
The iodolactol **55,**[165] with $Ph_2SO$ (129 mg, 0.63 mmol), TTBP (238 mg, 0.96 mmol), and $Tf_2O$ (59 µl, 0.35 mmol) in $CH_2Cl_2$ (8ml, 0.04 M), was eliminated following the general dehydrative procedure for 5 h at -60 ºC. The crude was purified by radial chromatography (hexanes:EtOAc 5:1) to afford the glycal **43** (102 mg, 63% over two steps) as colourless syrup.

Characterization data reported in pages 101-102.

## Synthesis of glycal 54

### a) 3-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-iodo-α/β-D-*allo*-pyranose (53)




**53**

NIS (252 mg, 1.12 mmol) was added to a solution of the thioenitol **103** (200 mg, 0.45 mmol) in a 10:1 $CH_3CN$:$H_2O$ mixture (9 ml, 0.05M) at -10 ºC. After stirring for 45 min the reaction was extracted with $CH_2Cl_2$/$Na_2S_2O_3$ twice. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexanes:EtOAc 7:1) affording the title compound (205 mg, 95%) as colourless syrup.

Spectroscopic data obtained from α/β mixture:

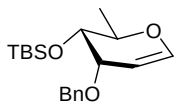
**53α: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.53-7.26 (m, 5H, $H_{aromatic}$); 5.61 (d, 1H, $J_{1-2}$= 4.4 Hz, H1); 4.78 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.64 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.58 (m, 1H, H4); 4.23 (dd, 1H, $J_{2-1}$= 4.4 Hz, $J_{2-3}$= 4.0 Hz, H2); 4.05 (m, 1H, H5); 3.81 (m, 1H,

[165] Selected NMR data of **55**: **1H NMR** (CDCl3, 400MHz) δ in ppm: 7.34-7.16 (m, 15H, $H_{aromatic}$); 5.03 (t, 1H, J= 8.4 Hz, J=9.2 Hz, H1a); 4.99 (d, 0.4H, J=10.4 Hz, H1b); 4.20 (td, 1H, $J_{5-6}$= 6.8 Hz, $J_{5-6'}$= 6.4 Hz, $J_{5-4}$= 1.2 Hz, H2); 4.67-4.28 (m, 6H, $CH_2Ph$); 3.75 (pst, 1H, $J_{3-4}$= 3.2 Hz, $J_{3-2}$= 3.2 Hz, H3); 3.59 (dd, 1H, $J_{6'-5}$= 6.8 Hz, $J_{6'-6}$= 9.6 Hz, H6'); 3.30 (dd, $J_{4-3}$= 3.6 Hz, $J_{4-5}$= 1.2 Hz, H4). **NMR $^{13}$C** (CDCl3, 100.6 MHz) δ in ppm: 137.8-136.15 ($C_{aromatic}$); 128.6-127.6 ($CH_{aromatic}$), 94.7 (C1); 78.7 (C3); 74.4 (C4); 73.7, 72.8, 72.7, 72.2 (C5, 3$CH_2Ph$); 68.3 (C6); 34.5 (C2).

H3); 1.12 (m, 3H, H6); 0.86 (s, 9H, tBuSi); 0.072 (s, 3H, MeSi); 0.064 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 133.1-127.8 ($C_{aromatic}$); 95.8 (C1); 87.2 (C4); 78.5 (C3); 72.7 ($CH_2Ph$); 68.5 (C5); 27.0 (C2); 26.1 ($CH_{3tBuSi}$); 20.6 (C6); 18.2 ($C_{tBuSi}$); -4.21, -4.34 ($CH_3Si$).

**53β: $^1$H NMR** ($CDCl_3$, 400 MHz) δ en ppm: 7.53-7.24 (m, 5H, $H_{aromatic}$); 5.53 (d, 1H, $J_{1-2}$= 7.6 Hz, H1); 4.63 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.56 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.18 (dd, 1H, $J_{2-1}$= 7.6 Hz, $J_{2-3}$= 5.2 Hz, H2); 3.93 (dd, 1H, $J_{4-5}$= 5.2 Hz, $J_{4-3}$= 3.2 Hz, H4); 3.81 (dd, 1H, $J_{3-2}$= 5.2 Hz, $J_{3-4}$= 3.2 Hz, H3); 3.65 (qd, 1H, $J_{5-4}$= 5.2 Hz, $J_{5-6}$= 6.4 Hz, H5); 1.16 (d, 3H, $J_{6-5}$= 6.4 Hz, H6); 0.87 (s, 9H, tBuSi); 0.045 (s, 3H, MeSi); 0.030 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 137.5 ($C_{aromatic}$); 133.1-127.8 ($CH_{aromatic}$); 93.4 (C1); 88.0 (C4); 78.6 (C3); 72.3 ($CH_2Ph$); 68.7 (C5); 30.8 (C2); 26.1 ($CH_{3tBuSi}$); 20.7 (C6); 18.2 ($C_{tBuSi}$); -4.19, -4.26 ($CH_3Si$).

### b) 1,5-Anhydro-3-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-D-*ribo*-hex-1-enitol (54)




**54**

The iodolactol **53** (115 mg, 0.24 mmol) was eliminated following the general dehydrative procedure for 1h at -60 ºC. Column chromatography of the residue (hexanes:EtOAc 10:1) afforded the required glycal **54** (104 mg, 97 %) as a colourless syrup.

Anal. Calcd for $C_{19}H_{30}O_3Si$: 68.22 C, 9.04 H. Found: 68.24 C, 9.06 H. $[\alpha]^{20}_D$: +39.8 (*c* 1.2, $CH_2Cl_2$)

**54: $^1$H NMR** ($CDCl_3$, 300 MHz) δ in ppm: 7.47-7.27 (m, 5H, $H_{aromatic}$), 6.57 (dd, 1H, $J_{1-2}$= 2.7 Hz, $J_{1-3}$= 1.2 Hz, H1); 5.18 (dd, 1H, $J_{2-1}$= 2.7 Hz, $J_{2-3}$= 2.6 Hz, H2); 4.81 (ddd, 1H, $J_{3-2}$= 2.6 Hz, $J_{3-4}$= 3.0 Hz, $J_{3-1}$=1.2 Hz, H3); 4.60-4.47 (m, 2H, $2CH_2Ph$); 4.24 (dd, 1H, $J_{4-5}$= 5.4 Hz, $J_{4-3}$= 3.0 Hz, H4); 3.83 (qd, 1H, $J_{5-4}$= 5.4 Hz, $J_{5-6}$= 6.1 Hz, H5); 1.23 (d, 2H, $J_{6-5}$= 6.1 Hz, H6); 0.90 (s, 9H, tBuSi); 0.089 (s, 3H, MeSi); 0.054 (s, 3H, MeSi). **$^{13}$C NMR** (CDCl3,

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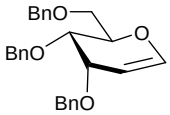
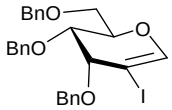
75.4 MHz) δ in ppm: 150.5 (C1); 138.7 ($C_{aromatic}$); 128.5, 128.1, 128.0, 127.9, 127.7 ($CH_{aromatic}$); 100.8 (C2); 90.5, 82.2, 69.7, 68.1 (C3, C4, C5, $CH_2Ph$); 26.0 ($CH_{3tBuSi}$); 20.2 (C6); 18.2 ($C_{tBuSi}$); -4.24, -4.54 ($2CH_3Si$).

## 1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*ribo*-hex-1-enitol (57) and 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-D-*ribo*-hex-1-enitol (58)




**57**




**58**

NIS (90 mg, 0.39 mmol) was added to a solution of (*Z/E*)-3,4,6-tri-*O*-benzyl-1,2-dideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol[166] (84 mg, 0.16 mmol) in a 10:1 $CH_3CN$:$H_2O$ mixture (3.2 ml, 0.05M) at -10 ºC. After stirring for 30 min the reaction was extracted with $CH_2Cl_2$/$Na_2S_2O_3$ twice. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexanes:EtOAc 7:1) to render 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-α/β-D-*allo*-pyranose (**56**) as colourless syrup. This iodolactol was eliminated following the general dehydrative procedure for 3h at -50 ºC. The crude was purified by radial chromatography (hexanes:EtOAc 6:1) to furnish iodoglycal **58** (18 mg, 21% over two steps) and a slightly lower *Rf* product which corresponded to glycal **57** (30 mg, 45% over two steps) as colourless syrups.

**57**[167]**: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.37-7.23 (m, 15H, $H_{aromatic}$), 6.47 (d, 1H, $J_{1-2}$= 5.6 Hz, H1); 4.89 (dd, 1H, $J_{2-1}$= 5.6 Hz, $J_{2-3}$=6.0 Hz, H2); 4.71 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.65 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.62 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.60 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.56 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.48 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.31 (dt, 1H, $J_{5-4}$= 10.4 Hz, $J_{5-6ab}$=3.0 Hz, H5); 3.96 (dd, 1H, $J_{3-2}$= 5.2 Hz, $J_{3-4}$=

[166] Prepared according to procedure in Rodríguez, M. A.; Boutureira, O.; Arnés, X.; Díaz, Y.; Matheu, M. I.; Castillón, S. *J. Org. Chem.* **2005**, *70*, 10297.
[167] Spectroscopic data coincident with those reported in Boutureira, O.; Rodríguez. M.A., Matheu, M.I.; Díaz, Y.; Castillón, S. *Org. Lett.* **2006**, *8*, 673.

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3.6 Hz, H3); 3.84 (d, 2H, $J_{6ab-5}$= 3.0 Hz, H6ab); 3.79 (dd, 1H, $J_{4-5}$= 10.4 Hz, $J_{4-3}$= 3.6 Hz, H4). **13C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 146.8 (C1); 138.8-138.1 ($C_{aromatic}$); 128.6-127.8 ($CH_{aromatic}$); 98.3 (C2); 74.0 (C4); 73.8 ($CH_2Ph$); 73.2 (C5); 71.5, 70.5 ($2CH_2Ph$); 69.0 (C6); 65.5 (C3).

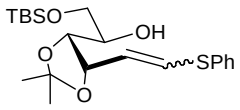
**58:** Anal. Calcd for $C_{27}H_{27}IO_4$: 59.79 C, 5.02 H. Found: 59.82 C, 5.04 H.

$[\alpha]^{20}_D$: +137.5 (*c* 1.00, $CH_3Cl$)

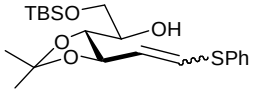
**$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.42-7.26 (m, 15H, $H_{aromatic}$), 6.69 (s, 1H, H1); 4.91-4.52 (m, 6H, $6CH_2Ph$); 4.30 (ddd, 1H, $J_{5-4}$= 10.8 Hz, $J_{5-6a}$= 3.4 Hz, $J_{5-6b}$= 2.0 Hz, H5), 4.17 (d, 1H, $J_{3-4}$= 3.6 Hz, H3); 4.00 (dd, 1H, $J_{4-5}$= 10.8 Hz, $J_{4-3}$= 3.6 Hz, H4); 3.84 (dd, 1H, $J_{6a-5}$= 3.4 Hz, $J_{6a-6b}$= 10.8 Hz, H6a); 3.77 (dd, 1H, $J_{6b-5}$= 2.0 Hz, $J_{6b-6a}$= 10.8 Hz, H6b). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 149.5 (C1); 138.0-137.6 ($C_{aromatic}$), 128.7-127.9 ($CH_{aromatic}$); 76.0 (C2), 75.5, 74.2, 73.8, 72.9, 72.8, 72.6 (C3, C4, C5, $3CH_2Ph$); 26.0 ($CH_{3tBuSi}$); 20.2 (C6); 18.2 ($C_{tBuSi}$); -4.24, -4.54 ($CH_3Si$).

## Synthesis of glycal 60

### a) (*Z/E*)-3,4-*O*-isopropylidene-6-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (66) and (*Z/E*)-3,4-isopropylidene-6-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1-phenylsulfanyl-D-*arabino*-hex-1-enitol (67)




**66**




**67**

As described in the general procedure of WH olefination, 2,3-*O*-isopropylidene-5-O-(*tert*-butyldimethylsilyl)-α/β-D-ribofuranose. (1.5 g, 4.9 mmol) was olefinated by reaction with diphenyl (phenylthiomethyl)phosphine oxide (6.4 g, 20 mmol) and *n*-BuLi (12.6 mL of 1.6 M hexane solution, 20.1 mmol) for 15 h at rt. Column chromatography (hexane to EtOAc:hexane 1:5) afforded **66** (1.25 g, 61%) as an inseparable 45:1 *E/Z*

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mixture and a lower *Rf* minor fraction (90 mg, 4%) which corresponded to epimerized **67** product (*E:Z* 15:1) .

Spectroscopic data obtained from respective *E/Z* mixtures:

**66*E*: $^{1}$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.30-7.10 (m, 5H, $H_{aromatic}$); 6.44 (d, 1H, $J_{1-2}$= 15.0 Hz, H1); 5.91 (dd, 1H, $J_{2-3}$= 6.8 Hz, $J_{2-1}$= 15.0 Hz, H2); 4.68 (dd, 1H, $J_{3-2}$= 6.8 Hz, $J_{3-4}$= 6.4 Hz, H3); 3.96 (dd, 1H, $J_{4-3}$= 6.4 Hz, $J_{4-5}$= 9.2 Hz, H4); 3.74-3.79 (m, 1H, H6a); 3.64-3.53 (m, 2H, H6b, H5); 2.21 (sa, 1H, OH); 1.36 (s, 3H, $CH_3$); 1.26 (s, 3H, $CH_3$); 0.82 (s, 9H, tBuSi); 0.00 (s, 6H, 2MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 135.2 ($C_{aromatic}$); 129.9-127.0 ($CH_{aromatic}$); 128.6 (C2); 126.6 (C1); 109.1 ($C_{ketal}$); 78.4 (C3); 77.6 (C4); 69.8 (C5); 66.4 (C6); 28.1 ($CH_{3ketal}$); 26.0 ($CH_{3tBuSi}$); 25.5 ($CH_{3ketal}$); 18.5 ($C_{tBuSi}$); -5.16 ($CH_3Si$); -5.26 ($CH_3Si$).

**66*Z*: $^{1}$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.31-7.09 (m, 5H, $H_{aromatic}$); 6.41 (d, 1H, $J_{1-2}$= 9.2 Hz, H1); 5.84 (dd, 1H, $J_{2-3}$= 9.0 Hz, $J_{2-1}$= 9.2 Hz., H2); 5.13 (dd, 1H, $J_{3-2}$= 9.0 Hz, $J_{3-4}$= 6.0 Hz, H3); 4.03 (dd, 1H, $J_{4-3}$= 6.0 Hz, $J_{4-5}$= 8.8 Hz, H4); 3.75-3.79 (m, 1H, H6a); 3.62-3.53 (m, 2H, H6b, H5); 2.25 (sa, 1H, OH); 1.39 (s, 3H, $CH_3$); 1.29 (s, 3H, $CH_3$); 0.83 (s, 9H, tBuSi); 0.00 (s, 6H, 2MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 135.9 ($C_{aromatic}$); 130.0-126.9 ($CH_{aromatic}$); 127.7 (C2); 126.9 (C1); 109.1 ($C_{ketal}$); 77.5 (C4); 75.1 (C3); 70.2 (C5); 66.5 (C6); 28.2 ($CH_{3ketal}$); 26.0 ($CH_{3tBuSi}$); 25.6 ($CH_{3ketal}$); 18.5 ($C_{tBuSi}$); -5.16 ($CH_3Si$); -5.26 ($CH_3Si$).

**67*E*: $^{1}$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.32-7.12 (m, 5H, $H_{aromatic}$); 6.40 (d, 1H, $J_{1-2}$= 15.2 Hz, H1); 6.76 (dd, 1H, $J_{2-3}$= 7.6 Hz, $J_{2-1}$= 15.2 Hz, H2); 4.60 (dd, 1H, $J_{3-2}$= 7.6 Hz, $J_{3-4}$= 6.8 Hz, H3); 4.09 (dd, 1H, $J_{4-3}$= 6.8 Hz, $J_{4-5}$= 7.6 Hz, H4); 3.72-3.56 (m, 3H, H5, H6a, H6b); 2.09 (sa, 1H, OH); 1.35 (s, 3H, $CH_3$); 1.26 (s, 3H, $CH_3$); 0.78 (s, 9H, tBuSi); 0.017 (s, 3H, MeSi); 0.00 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 134.2 ($C_{aromatic}$); 130.4-127.3 ($CH_{aromatic}$, C1, C2); 108.8 ($C_{ketal}$); 79.4  78.5 (C4, C3); 71.0 (C5); 65.1 (C6); 29.9 ($CH_{3ketal}$); 28.1 ($CH_{3ketal}$); 26.1 ($CH_{3tBuSi}$); 18.2 ($C_{tBuSi}$); -3.53 ($CH_3Si$); -4.36 ($CH_3Si$).

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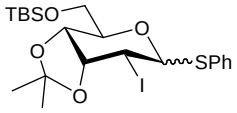
**b) Phenyl 6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-iodo-3,4-*O*-isopropyliden-1-thio-α/β-D-*allo*-pyranoside (68)**



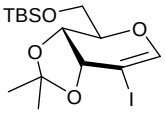

**68**

According to the general electrophile-induced cyclization procedure, reaction was carried out starting from compound **66** (725 mg, 1.77 mmol) and IDCP (1.82 g, 3.88 mmol) in dry $CH_3CH_2CN$ from -45 to -10 °C for 5h. The mixture was purified by flash chromatography (from hexane to EtOAc:hexane 1:7) to afford **68** (795 mg, 97%, α/β 1:7) as yellowish syrup.

Spectroscopic data obtained from α/β mixture:

**68β:$^1$H NMR** ($CDCl_3$, 300 MHz) δ in ppm: 7.62-7.25 (m, 5H, $H_{aromatic}$); 5.59 (d, 1H, $J_{1-2}$= 4.2 Hz, H1); 4.61 (dd, 1H, $J_{3-2}$= 4.8 Hz, $J_{3-4}$= 5.1 Hz, H3); 4.52 (dd, 1H, $J_{2-1}$= 4.2 Hz, $J_{2-3}$= 4.8 Hz, H2); 4.33 (d, 1H, $J_{4-3}$= 5.1 Hz, H4); 4.28 (dd, 1H, $J_{5-6a}$=2.4 Hz, $J_{5-6b}$= 5.4 Hz, H5); 3.93 (dd, 1H, $J_{6a-5}$= 2.4 Hz, $J_{6a-6b}$= 11.4 Hz, H6a); 3.86 (dd, 1H, $J_{6b-5}$= 5.4 Hz, $J_{6b-6a}$= 11.4 Hz, H6b); 1.58 (s, 3H, $CH_{3ketal}$); 1.37 (s, 3H, $CH_{3ketal}$); 0.92 (s, 9H, tBuSi); 0.094 (s, 6H, 2MeSi). **$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) δ in ppm: 135.6 ($C_{aromatic}$); 131.9-129.1 ($CH_{aromatic}$); 111.2 ($C_{ketal}$); 89.4 (C1); 78.6, 72.0, 70.9 (C3, C4, C5); 63.7 (C6); 28.4 (C2); 26.5 ($CH_{3ketal}$); 26.4 ($CH_{3ketal}$); 26.2 ($CH_{3tBuSi}$); 18.7 ($C_{tBuSi}$); -5.00, -5.10 ($CH_3Si$).

**c) 1,5-Anhydro-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-iodo-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (60)**




**60**

*N*-iodosuccinimide (79 mg, 0.35 mmol) was added to a solution of the thioglycoside **68** (125 mg, 0.23 mmol) in a 10:1 $CH_3CN$:$H_2O$ mixture (4.7 ml, 0.05M) at -10 ºC. After stirring for 1 h the reaction was poured into a $Na_2S_2O_3$ solution and extracted

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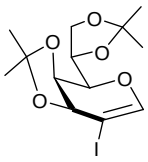
with $CH_2Cl_2$ twice. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexanes:EtOAc 5:1) to furnish 2-iodolactol compound **59**. This compound (100 mg, 0.22 mmol) was eliminated following the general dehydrative procedure for 2h from -60 to -40 ºC. Column chromatography of the residue (hexanes:EtOAc 10:1) afforded the required iodoglycal **60** (94 mg, 95 % over two steps) as colourless syrup.

Anal. Calcd for $C_{15}H_{27}O_4ISi$: 42.26 C, 6.38 H. Found: 42.28 C, 6.36 H. $[\alpha]^{20}_D$: +89.6 (*c* 1.00, $CH_2Cl_2$)

**60: $^1$H NMR** ($CDCl_3$, 300 MHz) δ en ppm: 6.84 (s, 1H, H1); 4.51 (d, 1H, $J_{3-4}$= 5.7 Hz, H3); 4.18 (dd, 1H, $J_{4-3}$= 5.7 Hz, $J_{4-5}$= 8.6 Hz, H4); 3.96 (dd, 1H, $J_{6a-5}$= 2.6 Hz, $J_{6a-6b}$= 11.7 Hz, H6a); 3.83 (dd, 1H, $J_{6b-5}$= 4.6 Hz, $J_{6b-6a}$=11.7 Hz, H6b); 3.67-3.61 (m, 1H, H5); 1.49 (s, 3H, $CH_3$); 1.41 (s, 3H, $CH_3$); 0.90 (s, 9H, tBuSi); 0.080 (s, 3H, MeSi); 0.076 (s, 3H, MeSi) . **$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) δ in ppm: 150.7 (C1); 108.8 ($C_{ketal}$); 76.4, 74.7, 71.3, 66.8, 62.3 (C2, C3, C4, C5, C6); 28.6 ($CH_{3ketal}$); 26.1 ($CH_{3tBuSi}$); 25.9 ($CH_{3ketal}$); 18.6 ($C_{tBuSi}$); -5.10 ($2CH_3Si$).

### 1,5-Anhydro-2-deoxy-2-iodo-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-hep-1-enitol (61)



**61**

To a solution of (*Z/E*)-3,4:6,7-di-*O*-isopropylidene-1,2-dideoxy-1-phenylsulfanyl-D-*manno*-hep-1-enitol **(5)** (170 mg, 0.16 mmol) in a 10:1 $CH_3CN$:$H_2O$ mixture (9.2 ml, 0.05 M) at -10 ºC, NIS (260 mg, 1.15 mmol) was added. After stirring for 45 min the reaction was extracted with $CH_2Cl_2$/$Na_2S_2O_3$ twice. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexanes:EtOAc 10:1) to afford 2-iodopyranoside **17** (171 mg, 92%)[168] as colourless syrup. This iodolactol was eliminated following the general dehydrative procedure for 6 h

[168] Spectroscopic data reported in chapter 1.

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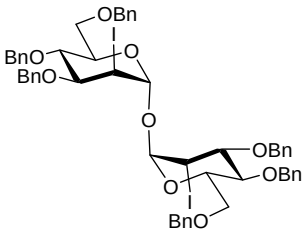
at -60 ºC. The crude was purified by radial chromatography (hexanes:EtOAc 6:1) to provide iodoglycal **250** (119 mg, 67% over two steps) as colourless syrup.

**61: $^{1}$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 6.66 (s, 1H, H1); 4.61 (d, 1H, $J_{3-4}$= 6.0 Hz, H3); 4.52 (dd, 1H, $J_{4-3}$= 6.0 Hz, $J_{4-5}$= 1.0 Hz, H4); 4.36 (ddd, 1H, $J_{6-5}$= 8.0 Hz, $J_{6-7}$= 5.8 Hz, $J_{6-7'}$= 4.8 Hz, H6); 4.11 (dd, 1H, $J_{7-7'}$= 9.0 Hz, $J_{7-6}$= 5.8 Hz, H7); 4.05 (dd, 1H, $J_{7'-7}$= 9.0 Hz, $J_{7'-6}$= 4.8 Hz, H7'); 3.91 (d, 1H, $J_{5-6}$= 8.0 Hz, H5), 1.42 (m, 12H, $CH_3$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 148.1 (C1); 111.3 ($C_{ketal}$); 109.8 ($C_{ketal}$); 75.6 (C2); 75.1 (C5); 74.1 (C3); 73.9 (C6); 73.6 (C4); 66.7 (C7); 26.9, 25.3, 24.9, 24.6 ($4CH_3$)

### 3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-α-D-*manno*-pyranosyl-(1→1)-3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-α-D-*manno*-pyranoside (63)




**63**

NIS (86 mg, 0.38 mmol) was added to a solution of tri-*O*-benzyl-D-glucal (100 mg, 0.24 mmol) in a $CH_3CN$:$H_2O$ 10:1 mixture (2.2 ml, 0.11 M) at 0 ºC. After stirring for 1.5 h the reaction was extracted with $CH_2Cl_2$/$Na_2S_2O_3$ twice. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexanes:EtOAc 10:1) affording 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-α/β-D-*manno*-pyranose (**62**) (117 mg, 0.21 mmol, 87%)[169] as a colourless syrup. This iodolactol was eliminated following the general dehydrative procedure for 5h at -40 ºC. The crude was purified by radial chromatography (hexanes:EtOAc 6:1) to afford the dimer **63** (62 mg, 47% over two steps, αα:αβ+ββ ratio 25:1).

[169] Selected NMR data of **62**: **1H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.40-7.13 (m, 15H, $H_{aromatics}$); 5.54 (s, 1H, H1); 4.95-4.43 (m, 6H, $CH_2Ph$ ); 4.39 (dd, $J_{2-1}$= 1.2 Hz, $J_{2-3}$= 4.0 Hz, H2); 4.18 (broad s, 1H, OH); 4.12 (m, 1H, H5); 3.70 (m, 3H, H4, H6, H6'); 3.34 (dd, 1H, $J_{3-2}$=4.0 Hz, $J_{3-4}$= 8.8 Hz, H3). **NMR $^{13}$C** ($CDCl_3$, 100.6 MHz) δ in ppm: 128.6-127.7 ($CH_{aromatic}$), 96.1 (C1); 91.9 ($C1_{min}$); 73.9 (C3); 73.7 ($CH_2Ph$); 73.5 (C4); 73.1 ($CH_2Ph$); 72.2 (C5); 71.2 ($CH_2Ph$); 68.9 (C6); 24.1 (C2).

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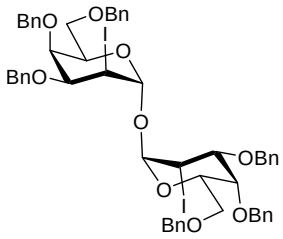
Spectroscopic data extracted from the anomeric mixtures:

Anal. Calcd for $C_{54}H_{56}I_2O_4$: 58.81 C, 5.12 H. Found: 58.79 C, 5.14 H.

**63: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.39-7.18 (m, 30H, $H_{aromatic}$); 5.46 (d, 2H, $J_{1-2}$= $J_{1'-2'}$= 1.6 Hz, H1, H1'); 4.87-4.46 (m, 12H, $CH_2Ph$ ); 4.35 (dd, 2H, $J_{2-1}$= $J_{2'-1'}$= 1.6 Hz, $J_{2-3}$= $J_{2'-3'}$= 4.0 Hz, H2, H2'); 3.92 (pst, 2H, $J_{4-3}$= $J_{4'-3'}$= 8.8 Hz, $J_{4-5}$ = $J_{4'-5'}$ = 8.8 Hz, H4, H4'); 3.79-3.68 (m, 6H, H5, H5', H6a, H6b, H6a', H6b'); 3.16 (dd, 2H, $J_{3-2}$= $J_{3'-2'}$= 4.4 Hz, $J_{3-4}$= $J_{3'-4'}$= 8.8 Hz, H3, H3'). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4-137.6 ($C_{aromatic}$), 128.7-127.7 ($CH_{aromatic}$), 98.1 (C1, C1'); 73.9 (C3, C3'); 73.7 ($CH_2Ph$); 73.5 (C4, C4'); 73.4 (C5, C5'); 73.1 ($CH_2Ph$); 71.2 ($CH_2Ph$); 68.9 (C6, C6'); 32.3 (C2, C2').

### 3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-α-D-*talo*-pyranosyl-(1→1)-3',4',6'-tri-*O*-benzyl-2'-deoxy-2'-iodo-α-D-*talo*-pyranoside (65)




**65**

NIS (86 mg, 0.38 mmol) was added to a solution of tri-*O*-benzyl-D-galactal (100 mg, 0.24 mmol) in a 10:1 $CH_3CN$:$H_2O$ mixture (2.2 ml, 0.11 M) at 0 ºC. After stirring for 2 h the reaction was extracted with $CH_2Cl_2$/$Na_2S_2O_3$ twice. The combination of organic layers was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexanes:EtOAc 7:1) to afford 2-iodopyranose **64**[170] (87 mg, 0.16 mmol, 65%) as colourless syrup. The iodolactol **64**, with $Ph_2SO$ (63 mg, 0.31 mmol), TTBP (116 mg, 0.47 mmol), and $Tf_2O$ (29 µl, 0.17 mmol) in $CH_2Cl_2$ (3.9 ml, 0.04 M), was eliminated following the general dehydrative procedure for 5 h at -40 ºC. The crude was purified by

[170] Selected NMR data of **64**: **1H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.47-7.20 (m, 15H, $H_{aromatics}$); 5.62 (s, 2H, H1a); 5.43 (d, J= 3.2 Hz, 1H, H1b); 5.01-4.45 (m, 6H, $CH_2Ph$ ); 4.29-4.23 (m, 2H, H5, H2); 3.97 (s, 1H, OH); 3.84-3.74 (m, 2H, H6, H4); 3.51 (m, 2H, H6', H3) **NMR $^{13}$C** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4-137.5 ($C_{aromatic}$), 128.4-127.5 ($CH_{aromatic}$); 96.4 (C1); 94.6 ($C1_{min}$); 79.0 (C3); 77.3 (C4); 75.5 ($CH_2Ph$); 73.7 ($CH_2Ph$); 73.4 ($CH_2Ph$); 71.3 (C5); 68.7 (C6); 31.3 (C2); 31.3 ($C2_{min}$); 29.9 (C2).

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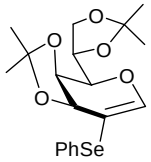
radial chromatography (hexanes:EtOAc 6:1) to furnish the dimer **65** (72 mg, 55% over two steps, αα:αβ+ββ ratio 12:1)

Spectroscopic data extracted from the anomeric mixtures:
Anal. Calcd for $C_{54}H_{56}I_2O_4$: 58.81 C, 5.12 H. Found: 58.87 C, 5.15 H.
**65: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.47-7.20 (m, 30H, $H_{aromatic}$); 5.56 (d, 2H, $J_{1-2}$= $J_{1'-2'}$= 2.4 Hz, H1, H1'); 5.01-4.38 (m, 12H, $CH_2Ph$ ); 4.22 (dd, 2H, $J_{2-1}$= $J_{2'-1'}$= 2.4 Hz, $J_{2-3}$= $J_{2'-3'}$= 3.2 Hz, H2, H2'); 4.12 (td, 2H, $J_{5-6a}$= $J_{5-6b}$= $J_{5'-6a'}$= $J_{5'-6b'}$= 6.4 Hz, $J_{5-4}$= $J_{5'-4'}$= 2.0 Hz, H5, H5'); 3.93 (pst, 2H, $J_{4-3}$= $J_{4'-3'}$= 2.0 Hz, $J_{4-5}$= $J_{4'-5'}$= 2.0 Hz, H4, H4'); 3.70 (m, 4H, H6a, H6b, H6a', H6b'); 3.43 (dd, 2H, $J_{3-2}$= $J_{3'-2'}$= 3.2 Hz, $J_{3-4}$= $J_{3'-4'}$= 2.0 Hz, H3, H3'). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2-138.7 ($C_{aromatic}$), 128.6-127.7 ($CH_{aromatic}$), 98.3 (C1, C1'); 73.9 (C3, C3'); 73.7 ($CH_2Ph$); 73.5 (C4, C4'); 73.1 ($CH_2Ph$); 72.2 (C5, C5'); 71.2 ($CH_2Ph$); 68.9 (C6, C6'); 24.1 (C2, C2')

## 1,5-Anhydro-2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-phenylselenenyl-D-*glycero*-D-*talo*-hep-1-enitol (69)




**69**

*N*-(Phenylselenenyl)phthalimide (NPSP) (280 mg, 0.925 mmol) was added in one portion to a stirred solution of alkene **5** (170 mg, 0.46 mmol) in dry $CH_2Cl_2$ (5 ml) at rt. After 15 h hours of continuously stirring the reaction mixture was poured into aqueous solution and extracted with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by radial chromatography (hexanes:EtOAc 7:1) to obtain selenoglycal **69** (60 mg, 34 %) as a yellowish syrup.

$R_f$ = 0.37 (1:3 EtOAc/hexane). Mp: 80-82 ºC. $[\alpha]_D^{25}$ = +133.35 (*c* 1.3, $CH_2Cl_2$). Anal. Calcd. for $C_{19}H_{24}O_5Se$ 55.48 C, 5.88 H. Found: 55.43 C, 5.86 H .

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**69**: **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ in ppm: = 7.50-7.19 (m, 5H, Ar), 6.90 (s, 1H, H1), 4.58 (d, $J_{3,4}$= 6.0 Hz, 1H, H3), 4.51 (dd, $J_{4,3}$= 6.0, $J_{4,5}$= 0.8 Hz, 1H, H4), 4.40 (dt, $J_{6,7a}$= $J_{6,7b}$= 5.6 Hz, $J_{6,5}$= 7.6 Hz, 1H, H6), 4.13 (d, $J_{7a,6}$= $J_{7b,6}$= 5.6 Hz, 2H, H7ab), 3.91 (dd, $J_{5,6}$= 7.6 Hz, $J_{5,4}$ = 0.8 Hz, 1H, H5), 1.38 (s, 6H, $2CH_3$) ppm. **$^{13}$C NMR** (100.6 MHz, $CDCl_3$,) δ in ppm: 151.1 (C1), 131.1, 129.3, 127.0 (CAr), 111.1, 109.8 ($C_{isoprop}$), 106.4 (C2), 75.7 (C5), 74.1 (C6), 72.8 (C4), 71.6 (C3), 66.7 (C7), 28.0, 27.1, 27.0, 25.4 ($3CH_3$).

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# 4

# Approach to the Synthesis of Digitoxine

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Cardiac glycosides, and specifically digitoxine, are used as successful treatment for congestive heart failure (CHF) and as inhibitors for tumoral cells.

In this chapter we use previously developed procedures like furanose olefination, alkene iodonium-induced cyclization (Chapter 1), or glycosylation from alkenyl sulfanyl derivatives (One-pot, Chapter 2), in the exploration towards the synthesis of digitoxine.

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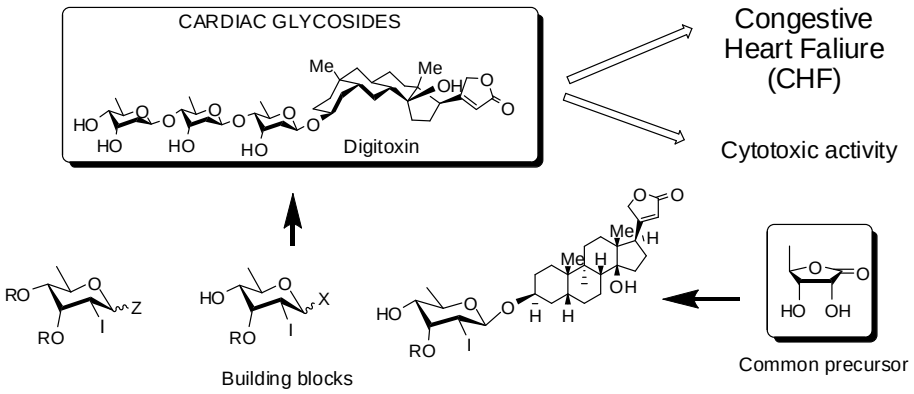

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# Introduction

### 1. Biological background

Congestive heart failure (CHF) is a condition in which the heart can not pump enough blood to the body's other organs. It causes shortness of breath, fluid retention, swelling (edema), exercise intolerance, left ventricular dysfunction and, in the most severe cases, arrhythmias and sudden death. This highly lethal condition currently affects over nine million Americans, Europeans, and Japanese. Furthermore, the incidence of CHF is expected to continue to increase as the populations of these countries age.[171]

In the treatment of CHF several compounds[172] such as diuretics, natriuretic peptides,[173] inhibitors of the angiotensin-converting-enzyme (ACE), inhibitors of the phophodiesterase (PDE)[174] and β-blockers have been used. Even though there are recently developed treatments, CHF continues to have a 5-year mortality rate of 50%. Unfortunately, only diuretics, inhibitors of the ACE, and digitalis each fulfil some of the criteria of a first-line agent in treatment of chronic heart failure. However, none of these drugs satisfies all of the desired characteristics, and none can optimally manage the heart failure state when used alone. Thus, in spite of these mentioned newer agents for the treatment of cardiac failure, digitalis and cardiac glycosides continue to be the first choice in CHF treatment.[171c]

Cardiac glycosides have been used as therapeutic agents for a very long time: they can be traced back to 1600 BC to ancient Egyptian manuscripts, where a medicinal prescription of the squill bulb shows the use of cardienolides. Prescription of the squill bulb was again reported two centuries later, in the *Corpus Hippocraticum*, to produce diuresis. Historically, *Digitalis purpurea* is known from writings of Welsh physicians in early medieval times. In 1785, Withering was the first physician who described the efficacy of digitalis in treating edema (dropsy),[175] but it was only in 1869 that the different components, and particularly digoxin, were purified by Nativelle. In 1875 it was Johann

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[171] a) National Health and Nutrition Examination Survey III (NHANES III) 1988-94; American Center for Disease Control (CDC)/NCHS data 1979-96. b) Reddy, S.; Benatar, D.; Gheorghiade, M. *Curr. Opin. Cardiol.* **1997**, *12*, 233. d) American Heart Association; Heart and Stroke Statistical Update. Dallas: AHA, 2002. c) Yusuf, S.; Garg, R.; Held, P.; Gorlin, R. *Am. J. Cardiol.* **1992**, *69*, 64G-70G.
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[175] Whitering, W. *"An Account Of The Foxglove, And Some Of Its Medical Uses; With Practical Remarks On Dropsy, And Other Diseases"* Robinson**,** London**, 1785**.

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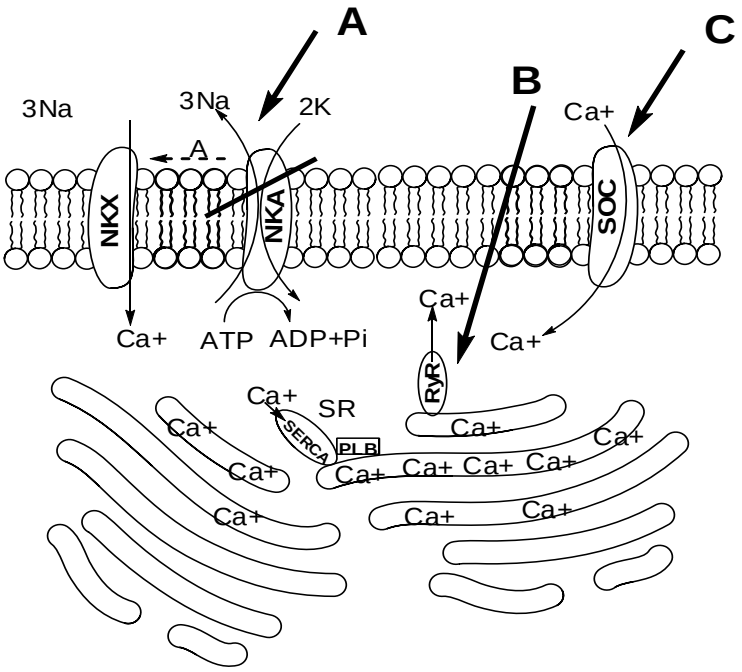
Schmiedeberg who isolated the principal active constituent of digitalis, i.e. the glycoside digitoxine (**76,** Scheme 1).[176]

**Figure 1.** Mode of action of cardiac glycosides.[177]




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

Cardiac glycosides[178] are positive inotropic substances; thus, they increase stroke volume and cardiac output, and improve cardiac performance.[179] This class of compounds results from the combination of an aglycon (genin) linked to a glycon (a carbohydrate, mono- to tetrasaccharide). Pharmacologycal activity resides in the aglycon and the

[176] a) Schmiedeberg JEO. Untersuchungen über die pharmakologisch wirksamen Bestandteile der *Digitalis purpurea*. *Arch Exp Path Pharmak* **1875**; *3***:** pp. 16–43. b) K. Greef, H. Schadewalt . C*ardiac Glycosides Part I Exp. Pharmacology* (Ed. K Grieff Handb. Exp. Pharmacol. **1981**, 56/I, pp. 1-12).
[177] Adapted from: Schwinger, R.H.G.; Bundgaard, H.; Müller-Ehmsen, J.; Kjeldsen, K. *Cardiovascular Research,* **2003**, *57*, 913.
[178] a) Barhmann, H. and Greeff, K. in C*ardiac Glycosides Part I Exp. Pharmacology* (Ed. Grieff, K. *Handb. Exp. Pharmacol.* **1981**, 56/I, pp. 124-152).b) Repke, R.H.; Megges, R.; Weiland, J.; Schön, R. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 282.
[179] Joubert, P.H.; Grossman, M. *Eur. J. Clin. Invest.* **2001**, *31(S2),* 1.

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carbohydrate has been viewed as the molecular element that controls the pharmacokinetics of the compound (absorption, distribution, metabolism and excretion).

It is known that contraction in heart muscle is activated by a transient increase in intracellular $Ca^{+2}$ concentrations. The mechanism of action of cardiac glycosides, which is still being debated, involves inhibition of a membrane $Na^{+}K^{+}$ ATPase (NKA).[180] Hence, the Na/Ca exchanger activity (NCX) is affected so that less $Ca^{+2}$ is extruded from the cell. Consequently, more $Ca^{+2}$ is accumulated in the sarcoplasmatic reticulum and is available during subsequent contractions leading to increased force of contraction (Figure 1, via A).[181] On the other hand, Santana et al.[182] found that cardiac glycosides may also induce a slip-mode conductance through Na-channels (SOC) allowing Ca-ions to enter the cell via this channel (Figure 1, via C). Other researchers[183] found that cardiac glycosides enhance the Ca-release from the sarcoplasmatic reticulum (SR) by increasing single channel activity of ryanodine-receptors (RyR), which release Ca-ions to the cytoplasm (Figure 1, via B).

Recently, it was reported that digitoxigenin, its glycosides and derivatives (see Figure 2) strongly inhibited the proliferation or induced apoptosis in different malignant cell lines.[184] In this way, some carbohydrate-modified moieties have been synthesized to impair Na/K ATPase activity and to improve tumor-specific cytotoxic activity.[185]

### 2. Cardiac glycosides. Chemical structure

Several glycosides having a steroid-type aglycon are used in therapy as cardiotonics (Figure 2). The most important ones belong to the group of cardienolides which contain aglycons with a 23-carbon core having the following characteristics: an unsaturated, lateral lactone moiety having four carbon atoms (butenolide); rings C and D are in *cis* disposition, with a β-oriented hydroxyl group at C14.

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[181] Lee, C.O.; Abete, P.; Pecker, M; Sonn, J.K.; Vassalle, M. *J. Mol. Cell. Cardiol.* **1985**, 17, 1043.
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[185] Langenhan, J. M.; Peters, N. R.; Guzei, I. A.; Hoffmann, F. M.; Thorson, J. S. *Proc. Natl. Acad. Sci. U.S.A*. **2005**, *102*, 12305.

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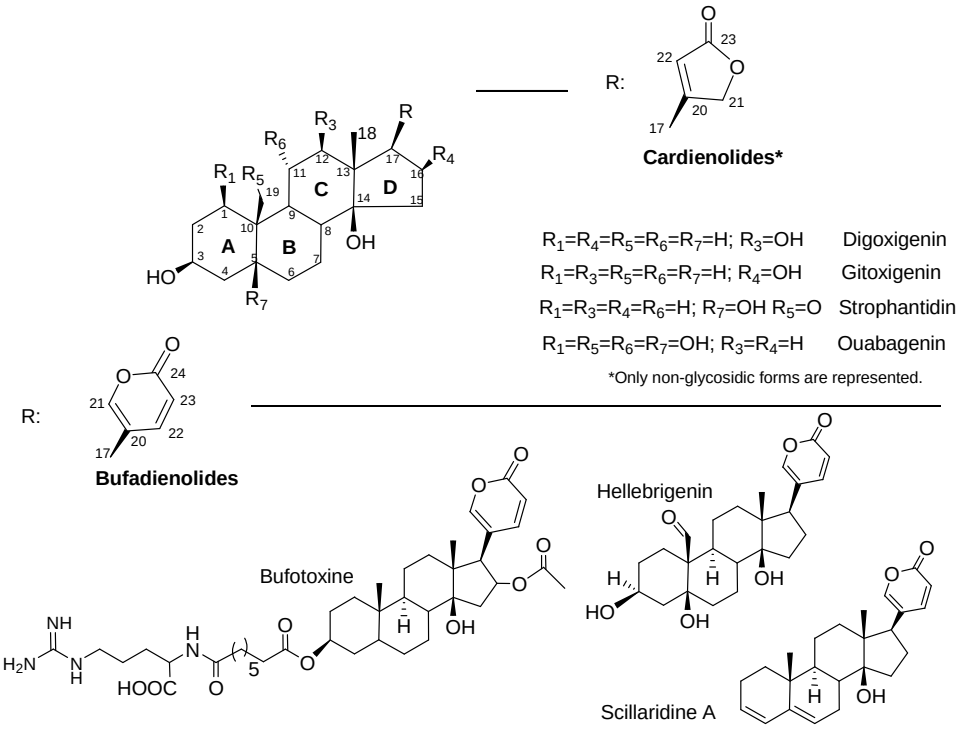
They are mainly of the 5-β series and have the C3 hydroxyl group in the β-configuration; hydroxyl groups may also be found at C1, C5, C11, C12, C16 and C19. These glycosides generally contain deoxy sugars linked directly to the aglycon and to D-glucose. On enzymatic hydrolysis, during drying, the plant yields D-glucose, whereas acid hydrolysis liberates all sugar components.

**Figure 2.** Structure of different cardiac steroids.




Another group of aglycons is that of "bufadienolides"; in this class, the lateral chain is lactonized, with the five carbon atoms containing two double bonds; these glycosides are found in Scilla (star flower, *Urginea scilla*) and, in non glycosidic form, in toad poison (bufotoxine from *Bufo vulgaris*).

One of the principal cardiac glycosides is digitoxine (**76**, Scheme 1), which occurs in *Digitalis purpurea* and *Digitalis lanata*. Digitoxine contains a chain of three molecules of digitoxose (called digoxose) linked to the hydroxyl group at C3 of the aglycon digitoxigenin. This important aglycon has a steroid-like framework, however, different from mammalian steroids and like the rest of cardienolides, possesses the following

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characteristic structural features: *cis* C/D ring junctions, tertiary 14β-hydroxyl group, and 17β-unsaturated lactone (see Figure 2). This unique structure, as well as its diverse and potent bioactivities, has drawn many synthetic studies and total synthesis.[186]

Although the sugars in the cardiac glycosides seem to have no therapeutic action, they have a dramatic effect on the physical, chemical and biological properties of these compounds.[186i,187] The glycan chains are molecular elements that control the pharmacokinetics of the drug and prolong their effects. For this reason, it is clear that the stereoselective formation of O-glycosidic bonds between carbohydrates and the cardiac aglycons are an important issue to be considered.

In this way, Elderfield et al. prepared the first glucosides of digitoxigenin and digoxigenin.[188] These authors showed that the glycosylation reaction was specific to the secondary hydroxyl group (at C3) of the aglycones. The less reactive tertiary hydroxyl group at C14 was not glycosylated during reaction. Instead, this hydroxyl group is extremely sensitive to desiccating agents and the aglycon tends to undergo dehydration, forming anhydrodigitoxigenin derivatives.

To overcome this problem, some methods of glycosylation have been tried. Methods described for the glycosidation of cadiosteroids are mostly based on the Knoenigs-Knorr procedure. These methods are not generally applicable but have to be adapted to the specific requirements of the substrates. Thus, α-1,2-cis-halogenated carbohydrates have been coupled with cardenolide aglycones using azeotropic distillation,[189] $AgCO_3$ on celite,[190] AgOTf,[191] mercuric salts,[192] $Et_4NBr$,[193] or by the

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

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

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

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

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

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

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

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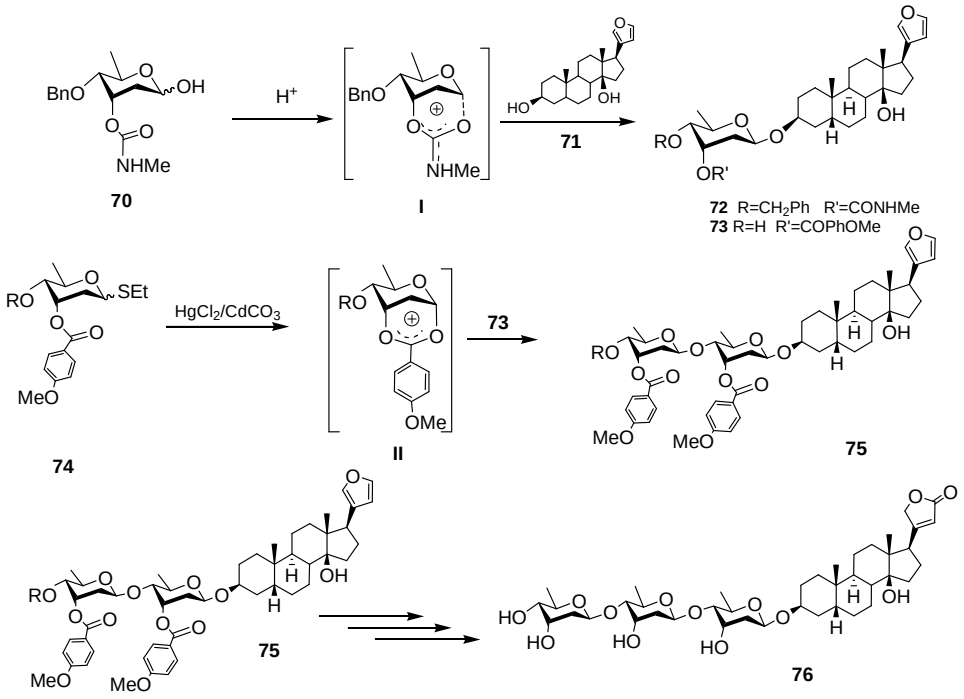
efficient disilver maleinate[194] (which direct to β-products). Other glycosyl donors, like glycals,[191] 1-*O*-acetylglycosides,[195] trichloroacetimidates,[193b,196] or enzymatic methods,[197] were also used to synthesize glycosylated cardienolides.

**Scheme 1**




In spite of countless procedures of glycosylation developed, only three total syntheses of digitoxine have been reported. The first one[198] was the carbohydrate approach by Wiesner[199], in which the β-stereoselectivity was achieved by the anchimeric assistance of *N*-methylurethane or the *p*-methoxybenzoyl group on C3 (Scheme 1). Thus, digitoxose

[193] a) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc*. **1975**, *97*, 4056. b) Rathore, H.; Hashimoto, T.; Igarashi, K.; Nukaya, H.; Fullerton, D. S. *Tetrahedron* **1985**, *41*, 5427.
[194] Luta, M.; Hensel, A.; Kreis, W. *Steroids* **1998**, *63*, 44.
[195] Boivin, J.; Monneret, C.; Pais, M. *Tetrahedron Lett.* **1978**, *19*, 1111.
[196] Finizia, G. *J. Carbohydr. Chem.* **1998**, *17*, 75.
[197] a) Kawaguchi, K.; Koike, S.; Hirotani, M.; Fujihara, M.; Furuya, T.; Iwata, R.; Morimoto, K. *Phytochemistry* **1998**, *47*, 1261. b) Kawaguchi, K.; Watanabe, T.; Hirotani, M.; Furuya, T. *Phytochemistry* **1996**, *42*, 667. c) Faust, T.; Theurer, C.; Eger, K.; Kreis, W. *Biorg. Chem.* **1994**, *22*, 140.
[198] Digitoxose was coupled with digitoxigenin by Zorbach and Boivin groups (ref. 25), but with poor yields and stereoselectivities: Zorbach, W.W.; Henderson, N.; Saeki, S. *J. Org. Chem.* **1964**, *29*, 2016.
[199] a) Jin, H.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem*. **1983**, *61*, 2442. (b) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300. (c) Wiesner, K.; Tsai, T. Y. R. *Pure Appl. Chem*. **1986**, *58*, 799.

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derivative **70** and the furyl steroid **71** were treated in acid medium to obtain product **72.** The β-stereoselectivity of this method was probably due to the intermediacy of the bridged species like **I**.

Because the urethane group was not suitable for the next glycosylation steps, it was changed and, after usual group manipulations, acceptor **73** was coupled with ethyl thioglycoside **74**. The β-stereoselectivity was achieved, after mercury catalysed cleavage of **74,** through the intermediate **II,** which reacted with monodigitoxoside **73** to yield disaccharide **75**. The third glycosylation, by means of mercury catalysed cleavage of ethyl thioglycoside, deprotection, and transformation of the furyl structure gave crystalline digitoxine (**76**).

The procedure of Wiesner and co-workers suffered from the requirement that the butenolide was masked as a furan derivative during glycosylation and protecting group manipulations and, thus, it needed additional final steps to obtain digitoxine. McDonald and co-workers developed a more efficient synthesis by direct attachment of a preformed trisaccharide donor **83** to digitoxigenin (Scheme 2a).[200] The synthesis of **83** began with protic acid-catalized[201] stereoselective glycosylation of glycal **77** with alkynyl alcohol **78** to give 2,6-dideoxyglycoside **79**. Reductive debenzoylation and tungsten carbonyl-catalyzed *endo*-selective cycloisomerization[202] of the alkynol substrate gave disaccharide glycal **81**. Convenient protecting group manipulations and repetition of the glycosylation-cycloisomerization steps from **82** afforded the glycal **83**, which could be easily attached to digitoxigenin (**87**). Starting from alkynol **84**, and applying the same methodology, the all-α-linked L-oliose digitoxine stereoisomer (**85**) was also obtained (Scheme 2b).[203]

[200] McDonald, F.E.; Reddy, K.S. *Angew. Chem. Int. Ed.* **2001**, *40*, 3653.
[201] Bolitt,V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.
[202] a) McDonald, F.E.; Zhu, H.Y.H. *J. Am. Chem. Soc.,***1998**,*120*,4246. b) McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304.
[203] McDonald, F. E.; Wu, M.. *Org. Lett*. **2002**, *4*, 3979.

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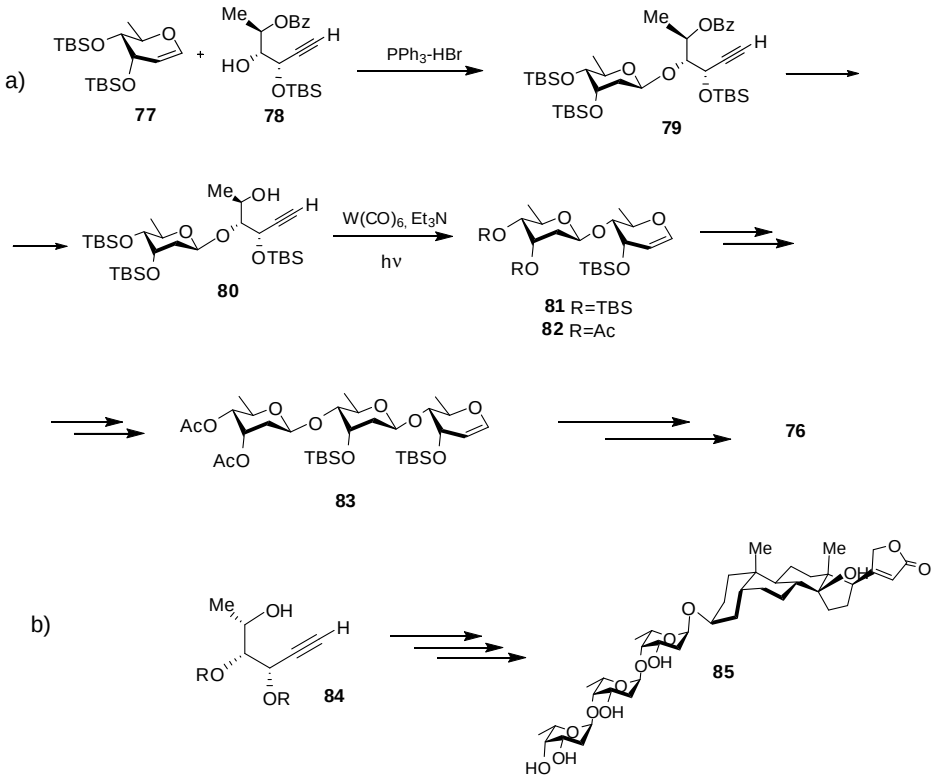
**Scheme 2**




Recently, O'Doherty has developed a linear and stereocontrolled route to the mono-, bis- and trisaccharide of digitoxine (Scheme 3).[204] This procedure started with the palladium-catalyzed glycosylation of digitoxigenin (**87**) with the pyranone **86** to render product **88** as a single diasteroisomer. Luche reduction ($NaBH_4/CeCl_3$) of **88** provided a mixture of allylic alcohols **89**, which were rearranged[205] to give olefin **90**. Dihydroxylation of **90** using the Uphjohn conditions ($OsO_4$/NMO)[206] furnished deprotected digitoxigen monodigitoxoside **91**. Applying an ortho ester formation/hydrolysis protocol to diol **91,** acetyl protected acceptor **92** was obtained. Repetition of these procedures in iterative manner yielded the disaccharide first and, eventually, digitoxine (**76**).

[204] a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406. b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428. c) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339. d) Zhou, M. O'Doherty, G.A. *J. Org. Chem.*, **2007**, ASAP DOI: 10.1021/jo062534+
[205] Myers' reductive rearrangement: Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841.
[206] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

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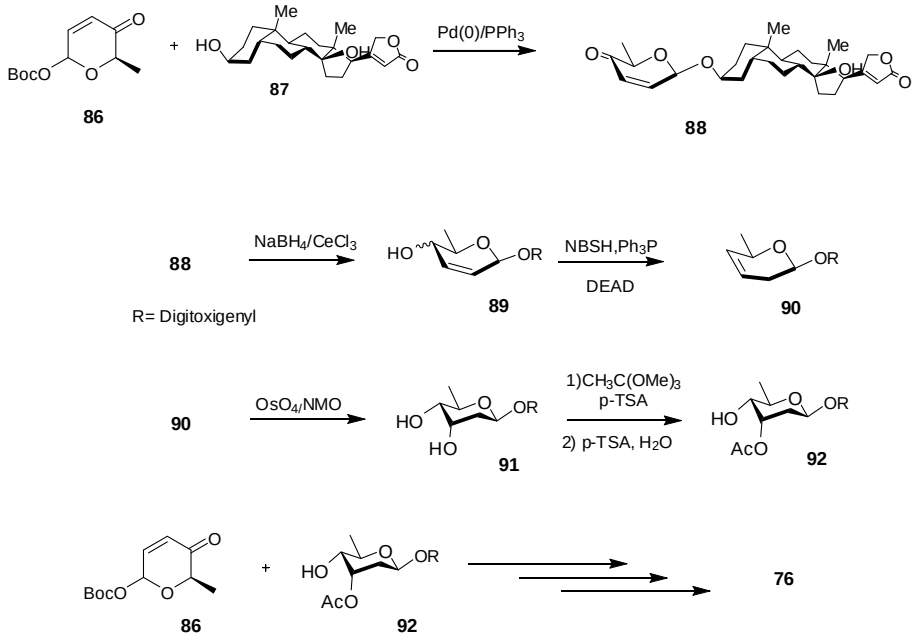
**Scheme 3**




Both Wiesner's carbohydrate-based and O'Doherty's de novo synthesis of digitoxine are high yield linear procedures which submit the digitoxigenin moiety to several transformation steps. By contrast, McDonald's de novo approach insert aglycon in the last steps and, therefore, is more appropriate methodology if a valuable chemically modified aglycon is present.[207]

On the other hand, the McDonald group's last glycosilation step of glycal **76** with digitoxigenin was complicated and, this key glycosidic bond was assembled with poor yield and/or stereoselectivity.[200] In this context, we wanted to develop a convergent synthesis of digitoxine that combined the best characteristics of the previous works. Therefore, our strategy should feature the coupling step with aglycon with good yield and stereoselectivity, together with the non-iterative reactions over cardienolide moiety.

In this chapter we report a procedure to obtain 2-deoxy-β-pyranosides and 2-deoxy-β-oligosaccharides of ribo configuration on the way to digitoxine synthesis. Thus, in a retrosynthethic analysis (Scheme 4), digitoxine (**76**) could be synthesized from monodigitoxoside **A** and disaccharide **B** in a convergent manner. This latter disaccharide

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

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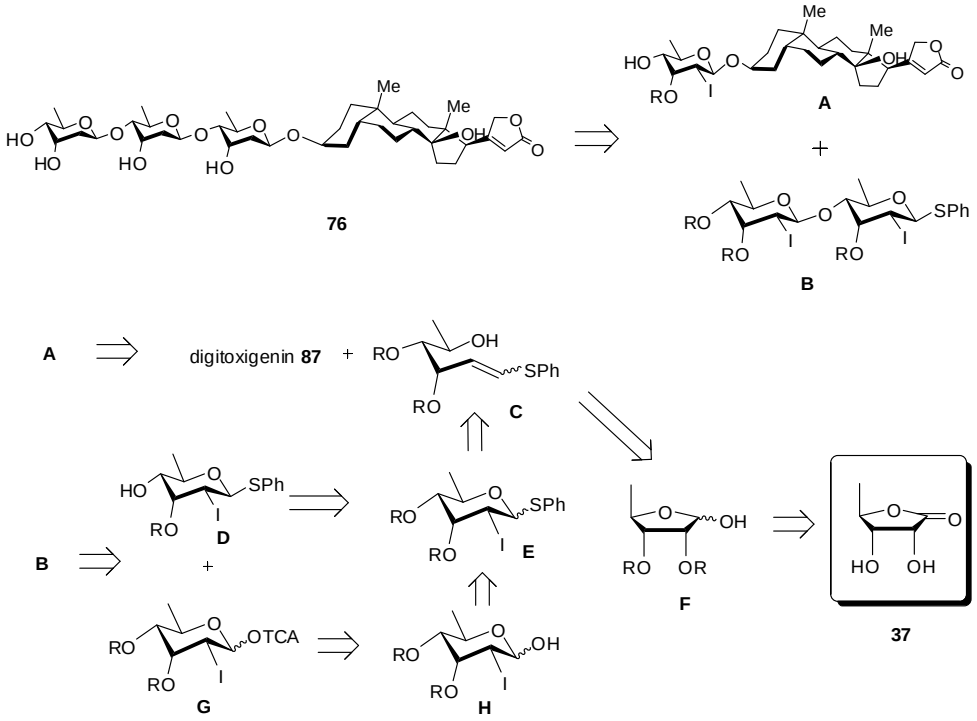
may be formed by the coupling of a glycoside donor as **G** and an acceptor as **D**, both readily obtained from compound **E**. 2-Deoxy-2-iodoglycoside **E** can be obtained from alkenol **C** by iodonium-induced electrophile cyclization.[208] In turn, monodigitoxoside **A** could be obtained in a one-pot fashion from the enolthioether **C** and commercially available digitoxigenin (**87**). The key intermediate **C** could be made from suitably protected ribofuranose **F** by an olefination reaction.[209] Finally, in order to differentially protect hydroxyl 2 and 3 of this pentose, **F** may come from the reduction of 5-deoxy-γ-D-ribonolactone (**37**), whose 2-OH is the most acidic in the compound and has reactivity similar to that of a primary hydroxyl group.[210] The starting material for **37** is commercially available γ-D-ribonolactone.

**Scheme 4**




[208] For discussions about regio- and stereoselectivity of cyclization see Chapter 1
[209] See chapter 1
[210] a) Ariza, J.; Font, J.; Ortuño, R.M. *Tetrahedron Lett.* **1990**, *46*, 1931. b) Lundt, I.; Madsen, R.; *Synthesis* **1992**, 1129. c) Raveendranath, P.C.; Blazis, V.J.; Agyei-Aye, K.; Hebbler, A.K.; Gentile, L.N.; Hawkins, E.S.; Johnson S.C.; Baker, D.C. *Carbohydr. Res.* **1994**, *253,* 207. d) Bell, A.A; Nash, R.J.; Fleet, G.W.J. *Tetrahedron: Asymmetry*, **1996**, *7*, 595. e) Yang, W.-B.; Tsai, C.-H.; Lin, C.-H. *Tetrahedron Lett.* **2000** *41*, 2569.

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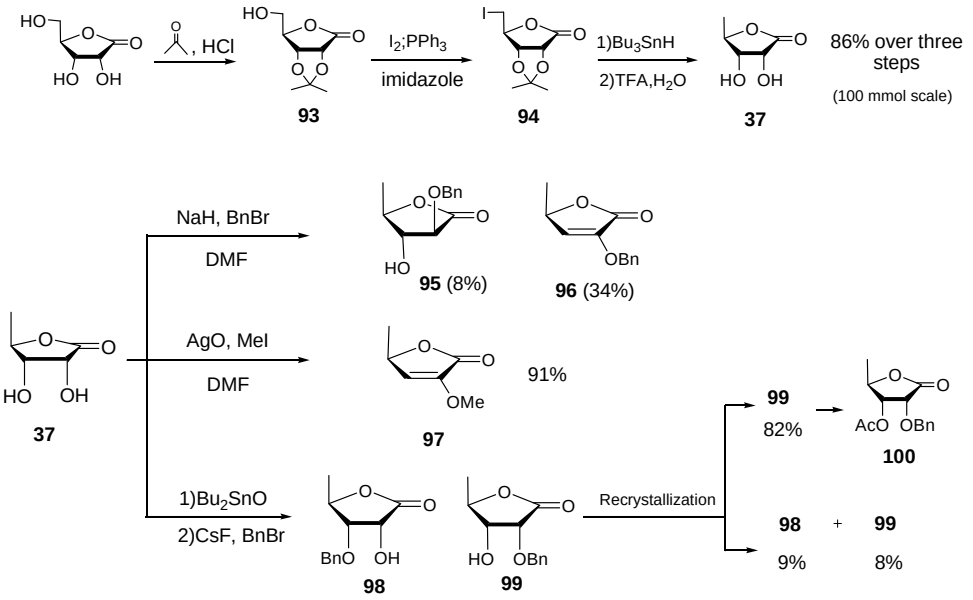
## Results and Discussion

According with the proposed retrosynthetic scheme, the first objective was the synthesis of **37**. Several procedures for deoxygenation of the primary hydroxyl in ribofuranoses or ribonolactones have been reported.[211] Thus, γ-D-ribonolactone was treated with hydrochloric acid in acetone to yield product **93** (Scheme 5). The primary hydroxyl group was then converted into the corresponding iodide following the Garegg[212] procedure ($PPh_3$, $I_2$, imidazole) to obtain **94**. Compound **37** was obtained in large scale[213] by reduction of iodide with $Bu_3SnH$/AIBN and deprotection of the isopropylidene group in **94**. The $^1H$ NMR spectrum of **37** shows a doublet ($J$=6.8 Hz, 3H) at 1.30 ppm that confirms the presence of a methyl group.

**Scheme 5**




[211] a) Lee, C.H.; Daanem, J.F.; Jiang, M.; Yu, H.; Kohlhaas, K.L.; Alexander, K.; Jarvis, M.F., Kowaluk, E.L.; Bhagwat, S.S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2419. b) Jensen, H.H.; Jensen, A.; Hazell, R.G.; Bols, M. *J. Chem.Soc. Perkin Trans. 1*, **2002**, 1190. c) Kiss, J.; D'Souza, R.; van Koeveringe, J.A.; Arnold, W. *Helv. Chim. Acta* **1982**, *65*, 1522. d) Hough, L.; Jones, J.K.N.; Mitchell, D.L. *Can. J. Chem*., **1958**, *36*, 1720.
[212] Garegg, P.J.; Samuelsson, B. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866.
[213] Procedure in lower scale in : Papageorgiou, C.; Benezra, C. *Tetrahedron Lett*. **1984**, 25, 6041.

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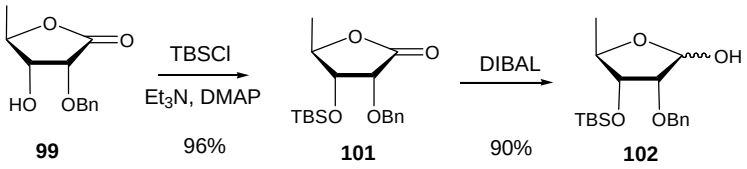
Lactone **37** was then subjected to low-temperature basic benzylation conditions to see whether it could be selectively protected in C2-hydroxyl group.[214] Unfortunately, only elimination (**96**) and epimerized (**95**) products were obtained. Benzylation in acidic conditions with benzyl trichloroacetimidate was not selective either.[215]

In the course of 3-*O*-methyl 2-deoxy-sugar synthesis (present in appetite-suppressant P57AS3 compound (**33**), see Fig. 1, Chapter 2), the reaction of aldonolactone **37** with silver oxide ($Ag_2O$) provided the elimination product **97**. This outcome showed that **37** was more prone to elimination than other aldonolactones, which were succesfully alkylated using $Ag_2O$.[216]

Benzylation of **37** with di-butyl tin oxide[217] provided a **98**:**99** mixture, which after a recrystallization in a hexane:AcOEt afforded pure and crystalline 2-*O*-benzyl-protected lactone **99** and a mixture of **98**:**99** in the mother liquor. In order to confirm the structure, a little amount of **99** was acylated. The $^1$H NMR spectra showed a H3-downfield shifting, which indicated that product **100** was indeed obtained.

**Scheme 6**




In the way towards a suitably protected pentose, lactone **99** was silylated[218] with *tert*-butyldimethylsilyl chloride (TBSCl), triethylamine and 4-(dimethylamine)pyridine (DMAP) to afford compound **101**. Reduction of this lactone rendered ribofuranose **102** in large amount with excellent yield (Scheme 6).

Unfortunately, olefination of **102** under the best conditions established in Chapter 1 (4.0 eq of phosphine oxide, 4.4 eq of *n*-BuLi), yielded a mixture of **103** and epimerized

[214] For similar procedure with oligoribonucleotides see: Takaku, H.; Kamaike, K. *Chem. Lett.*, **1982**, 189 and references cited therein.
[215] Eckenberg, P.; Groth, U.; Huhn, T.; Richter, N.; Schmeck, C. *Tetrahedron* **1993**, *49*, 1619.
[216] a) Matsuura, D.; Nojiri, T.; Suzuki, Y.; Takabe, K.; Yoda, H. *Synlett*, **2005**, 287. b) Yoda, H.; Maruyama, K.; Takabe, K. *Tetrahedron:Asymmetry* **2001**, *12*, 1403. c) Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38*, 5945. d) Jeroncic,L.O.; Sznaidman, M.L., Cirelli, A.F.; de Lederkremer, R.M. *Carbohydr. Res.* **1989**, *191*, 130.
[217] a) Iwasaki, F.; Maki, T.; Onomura, O.; Nakashima, W.; Matsumura, Y. *J. Org. Chem.* **2000**, *65*, 996. b) Ikota, N. *Heterocycles* **1991**, *32*, 521. c) Nagashima, N.; Ohno, M. *Chemistry Lett.* **1987**, 141.
[218] Chaudhary, S.K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *2*, 99.

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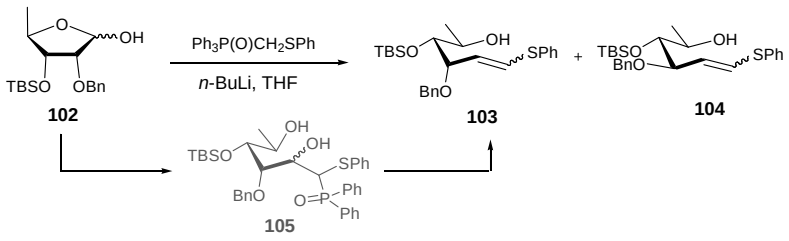
product **104** in poor yield (between 10% and 20%). Thus, less phosphine oxide and base were used in this reaction and $Sn_3BuCl$ was added to avoid putative elimination[219] that might decrease the yield. However, an equimolar mixture of *ribo* **103** and *arabino* **104** alkenes was also obtained in 45% combined yield (Table 1, entry 1).

**Table 1**. Wittig-Horner olefination conditions of pentose **102.**[a]




| Entry | Scale of reaction | Time (h) | Additive | **103** Yield (%) | *Z*/*E* ratio **103** | **104** Yield (%) | *Z*/*E* ratio **104** |
|---|---|---|---|---|---|---|---|
| 1 | 900 mg | 17 h | $Bu_3SnCl$ | 25 % | 1:15 | 20 % | 1:18 |
| 2 | 200 mg | 20 h | $CeCl_3$ | 45 % | 1:25 | 25 % | 1:30 |
| 3 | 520 mg | 15 h | - | 61 % | 1:16 | 16 % | 1:21 |
| 4a[b] | 680 mg | 10 h | - | 25 % | 1:0 | 0 % | - |
| b | BHPO[c] | 2 h | - | 20 % | 6:1 | 13 % | 1:17 |
| 5 | 850 mg | 48 h | - | 24 % | 1:0 | 15 % | 1:16 |

[a] Conditions: Pentose (1 mmol); phosphine oxide (3.0 mmol); *n*-Buli ( 3.1 mmol); -78ºC to rt .[b]Phosphine oxide (2.5 eq), n-BuLi (2.6 eq). [c] NaH used as base for elimination.

In other assays, $CeCl_3$ was added in order to reduce the high basicity of *n*-BuLi,[220] but again **103** was obtained in 45% yield all together with 25% of epimerized alkene **104** (Table 1, entry 2). The Two-step Wittig-Horner (WH) was tested as well (Table 1, entry 4). In the olefination (first step) the reaction was quenched before epimerized product appeared (10h; reaction monitored by TLC). This assay yielded 25% of pure *E* alkene **103** (Table 1, entry 4a). Elimination of the BHPO **105** (second step) provided an additional

[219] Costantino, V.; Imperatore, C.; Fattorusso, E.; Mangoni, A. *Tetrahedron Lett.* **2001**, *45*, 8185.
[220] Johnson, C.R.; Tait, B.D. *J. Org. Chem.* **1987**, *52*, 281 and references cited therein.

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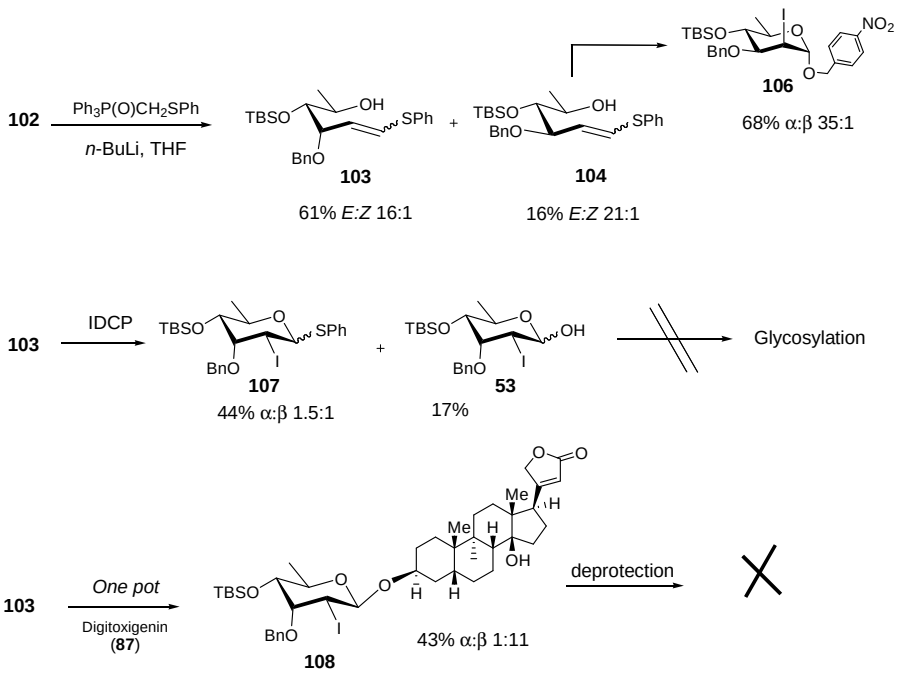
Autor: Miguel Ángel Rodríguez Gómez.
ISBN: 978-84-690-6749-9 / DL: T.1194-2007


20% of **103** (*E:Z* ratio 6:1) and 13% of **104** (Table 1, entry 4b). When the reaction was carried out with more 5-deoxyribose derivative **102**, longer reaction time was needed and the yield of alkene was lower (Table 1, compare entry 3 and entry 5). The highest yields of alkene **103** (61%) were obtained when around 500 mg of **102** were olefinated for 15 h (Table 1, entry 3). However, in this reaction, 16% of **104** was also isolated.

To determine unequivocally the configuration of the C3 and C4 of the alkenes, compound **104** was submitted to one-pot cyclization-glycosylation procedure with *p*-nitrobenzylic alcohol (**26c**) as a glycosyl acceptor to give **106** in 68% yield (α:β 35:1) (Scheme 7). Coupling constant values of $J_{1\text{-}2}$=3.6 Hz, $J_{2\text{-}3}$=5.6 Hz and the observation of NOESY signals between H3-H5 and weaker between H2-H5 allow to assign configuration of the structure **106**. Moreover, iodonium-induced cyclization of alkene **103** afforded highly reactive thioglycoside **107** (44%, α:β 1.5:1) together with lactol **53** (17%, Scheme 7). Problems to isolate compound **107** led us to carry out glycosylation of digitoxigenin directly from **103**.

**Scheme 7**



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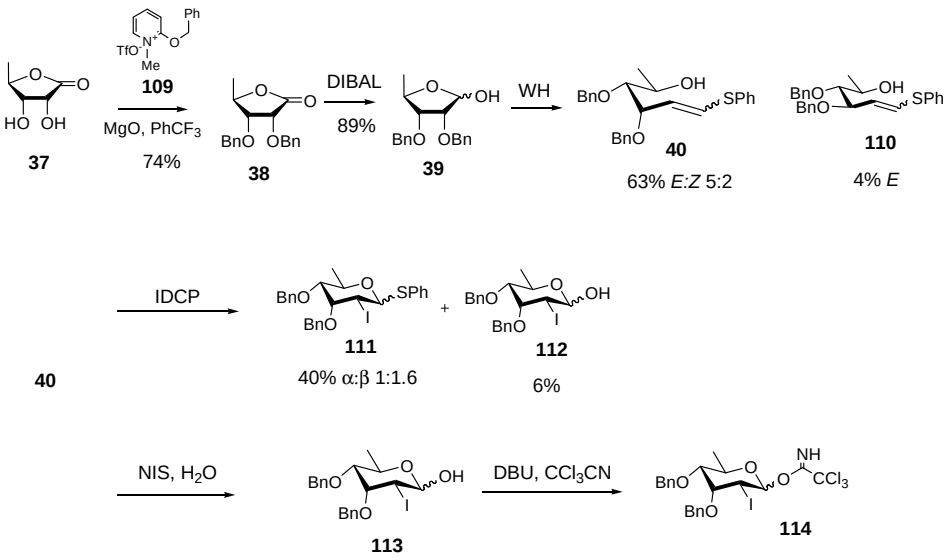
Thus, one-pot cyclization-glycosylation reaction with alkene **103** and digitoxigenin (**87**) rendered monodigitoxoside **108** with good stereoselectivity in moderate yield (43%, α:β 1:11). The value of $J_{12}$=8.8 Hz for the major isomer confirms the preferent formation of the β anomer. As TBAF/THF was unsuccessful in deprotecting the TBDMS group in McDonald's work,[200] we used fluorhidric acid in pyridine (HF·py). Unfortunately, only a minor amount (ca. 5%) of deprotected compound was obtained.

**Scheme 8**




In order to prepare the final synthon dibenzylated glycosyl donor **114** (Scheme 8), which could be glycosylated orthogonally with deprotected **107** was synthesized**.** Benzylation of **37** was carried out with the innovative reagent **109**[221] to afford compound **38** in better yield and higher purity than the benzyl trichloroacetamidate method (See Chapter 2). Reduction of compound **38** yielded furanose **39**. Olefination of this dibenzylated ribofuranose under usual WH conditions afforded compound **40** in good yield. A minor amount (4%) of epimerized product **110** was also obtained. Cyclization of the alkene **40** in anhydrous conditions gave highly reactive thioglycoside **111** in moderate

[221] a) Poon, K.W.C; Dudley, G.B. *J. Org. Chem.* **2006**, *71*, 3923.b) Nwoye, E.O.; Dudley, G.B. *Chem. Commun.*, **2007**, **DOI:** 10.1039/b617926f.

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yield together with small amounts of 2-iodolactol **112**. This latter compound arose from activation of **111** and subsequent trapping of the oxocarbenium ion by water in the work-up. Thus, NIS-induced cyclization of alkene **40** in the presence of water gave 2-iodolactol **113** (Scheme 8). This compound was treated with DBU and trichloroacetonitrile in $CH_2Cl_2$ to afford the glycosyl donor **114**, which was directly treated with digitoxigenin in order to text its ability as glycosyl donor, but in this case did not afford the expected glycoside.

Analysing the previous results it can be concluded that a protecting group different than TBS is needed in order facilitate the deprotection of synthon **108**, and probably also **107**, which was not assayed due to the difficulties found in **108**. Probably, the group TES (triethylsilyl) can be an alternative. Moreover, although 2-deoxy-iodo-trichloroacetamidates have been successfully used as glycosyl donors, in this particular case, the intermediate **114** has not been stable and did not allow the synthesis of glycosides. Additional studies will be necessary in this way. Different alternatives which are accessible using the present methodology, as for instance, to use the more stable 2-deoxy-2-iodo-glycosyl fluorides, or the corresponding glycals accessible by the methodology reported in chapter 3, could be also considered.

## Conclusion

Starting from product **37**, we have explored a new approach to the synthesis of digitoxine and other cardiac glycosides. A fast, direct and highly stereoselective route to monodigitoxoside **108** has been developed. This glycosylated product are readily obtained from enol thioether acyclic precursor **103** in one step.

Useful glycosyl donors such as thioglycosides **107** and **114**, have been obtained in few steps from commercially available products.

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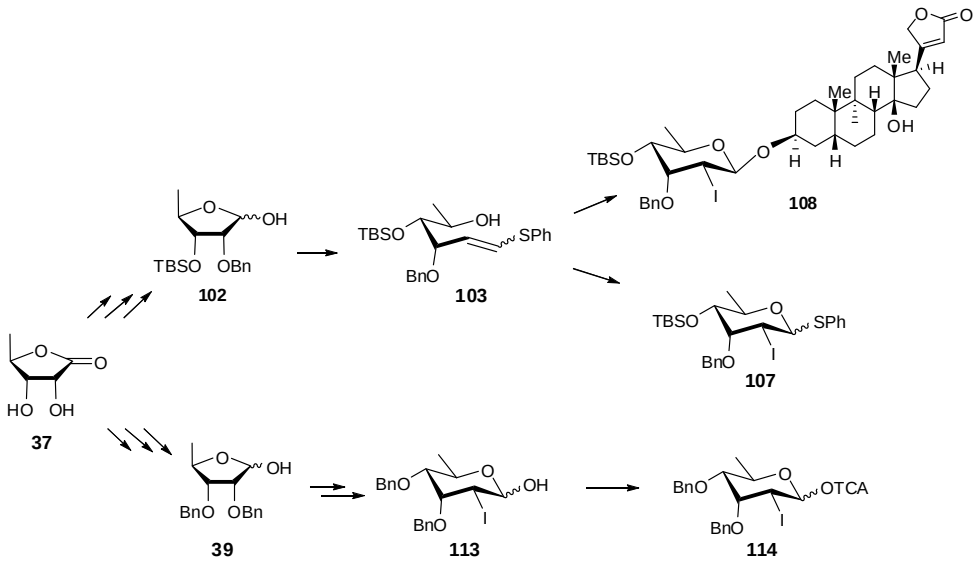
**Scheme 9**




Synthons **114**, **107**, and **108**, or related derivatives, should allows the orthogonal glycosylation affording digitoxine. Although digitoxine was not completely synthesized, the procedures described herein are a direct and useful approach to suitable building blocks and further investigations were carried out in due course.

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# Experimental part

## General remarks

All chemicals used were reagent grade and used as supplied. Digitoxigenin was purchase from Fluka® (100 mg batches, HPLC grade) and was used directly. HPLC grade dichloromethane (DCM), tetrahydrofuran (THF), diethyl ether and DMF were dried using a solvent purification system (Pure SOLV system-4®).Reagent grade toluene for Dean-Stark reactions was used directly as supplied. $^{1}H$ and $^{13}C$ and NMR spectra were recorded on a Varian® Gemini 300 (300 MHz and 75 MHz respectively) or on a Varian® Mercury 400 (400 MHz and 100 MHz respectively) spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm $^{1}H$, 77.23 ppm $^{13}C$) or $Me_4Si$ as an internal reference (0.00 ppm) or $H_3PO_4$ ($^{31}P$) as external standard. 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®).

## General procedure of silylation of alcohols

To a solution of alcohol (1 mmol), $Et_3N$ (1 mmol), silyl chloride (1.5 mmol), in dry DCM (2.2 ml, 0.46 M), DMAP (0.75- 0.50 mmol) was added slowly. The mixture was vigorously stirred at rt for 6 h and then diluted with $CH_2Cl_2$, extracted twice with dilute HCl, $NaHCO_3$ and finally water. The combined organic extracts were dried and concentrated under reduced pressure. The crude product was purified by chromatographic techniques.

## General procedure of reduction of aldonolactones

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

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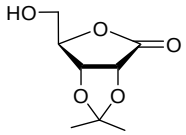
### 2,3-*O*-isopropylidene-γ-D-ribonolactone (93)



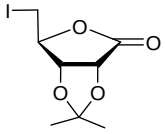
**93**

HCl 37% solution (8ml, 1% v/v) was added to a solution of γ-D-ribonolactone (20 g, 135 mmol) in acetone (800 ml). The mixture was stirred for 7 h at rt until starting material was consumed (TLC analysis). The reaction was quenched adding portions of $BaCO_3$ and shaking vigorously until neutral pH was reached. The suspension was filtrated and concentrated under vacuum. The crude product was purified by a short flash column (MeOH:$CH_2Cl_2$ 1:10) to afford the lactone **93** (24.2 g, 100%) as a white solid.

Mp. 134-138 ºC (135-138 ºC lit.)

**93**[222]**: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 4.85 (d, 1H, $J_{2\text{-}3}$= 5.4Hz, H2); 4.79 (d, 1H, $J_{3\text{-}2}$= 5.4Hz, H3); 4.64 (dd, 1H, $J_{4\text{-}5a}$= 2.4 Hz, $J_{4\text{-}5b}$= 1.6 Hz, H4); 4.01 (ddd, 1H, $J_{5a\text{-}4}$= 2.4 Hz, $J_{5a\text{-}OH}$= 5.4 Hz, $J_{5a\text{-}5b}$= 12.4 Hz, H5a); 3.81 (ddd, 1H, $J_{5b\text{-}4}$= 1.6 Hz, $J_{5b\text{-}OH}$= 5.8 Hz, $J_{5b\text{-}5}$= 12.4 Hz, H5b); 2.90 (sa, 1H, OH); 1.48 (s, 3H, $CH_{3ketal}$); 1.38 (s, 3H, $CH_{3ketal}$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 175.5 (C=O); 113.3 ($C_{ketal}$); 83.1 (C4); 78.5 (C3); 75.8 (C2); 62.0 (C5); 26.9, 25.6 ($2CH_{3ketal}$)

### 2,3-*O*-isopropylidene-5-deoxy-5-iodo-γ-D-ribonolactone (94)



**94**

Iodine (38.4 g, 152 mmol) was added to a solution of lactone **93** (24 g, 127 mmol); $Ph_3P$ (40.2 g, 152 mmol) and imidazole (17.4 g, 256 mmol) in dry THF (960 ml, 0.13 M) and then the mixture was heated to reflux. After 1h the reaction was

[222] Spectroscopic data in agreement with commercial product and with reported in Joaquim Bigorra Llosas, Ph.D thesis, AUB, December 1989.

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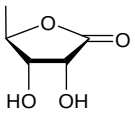
cooled to rt and concentrated under reduced pressure. The crude was extracted with $Na_2S_2O_3/CH_2Cl_2$. The organic phase was dried over anhydrous $MgSO_4$ and purified by column chromatography (from hexane to EtOAc:hexane 1:6) to afford **94** (32.7 g, 86%) as a yellowish solid.

**94: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 5.00 (d, 1H, $J_{2\text{-}3}$= 6.4Hz, H2); 4.65 (dd, 1H, $J_{4\text{-}5a}$= 3.2 Hz, $J_{4\text{-}5b}$= 5.2 Hz, H4); 4.62 (d, 1H, $J_{3\text{-}2}$= 6.4Hz, H3); 3.46 (dd, 1H, $J_{5a\text{-}4}$= 3.2 Hz, $J_{5a\text{-}5b}$= 11.6 Hz, H5a); 3.41 (dd, 1H, $J_{5b\text{-}4}$= 5.2 Hz, $J_{5b\text{-}5a}$= 11.6 Hz, H5b); 1.48 (s, 3H, $CH_{3ketal}$); 1.40 (s, 3H, $CH_{3ketal}$). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 173.2 (C=O); 114.2 ($C_{ketal}$); 81.0 (C4); 80.5 (C3); 75.4 (C2); 26.7, 25.6 ($2CH_{3ketal}$); 5.9 (C5).

## 5-deoxy-γ-D-ribonolactone (37)[223]




**37**

AIBN (141 mg, 0.86 mmol) and $Bu_3SnH$ (31.7 ml, 120 mmol) were added to a dry and degassed toluene solution (350 ml) of lactone **94** (32.4 g, 109 mmol). The resulting mixture was heated under reflux for 17 h and then toluene evaporated. The crude was cooled to 0 ºC and a cold solution of $CF_3COOH:H_2O$ (9:1) was added (145 ml, 0.75M). The mixture was stirred for 1 h at 0 ºC, the solvent distilled at high vacuum and the crude was washed with cold $Et_2O$ to afford compound **37** (14.4 g, 100%) as a white solid.

**37: $^1$H NMR** ($CD_3OD$, 400 MHz) δ in ppm: 4.48 (d, 1H, $J_{2\text{-}3}$= 5.2Hz, H2); 4.43 (qd, 1H, $J_{4\text{-}5}$= 6.8 Hz, $J_{4\text{-}3}$= 1.2 Hz, H4); 4.03 (dd, 1H, $J_{3\text{-}2}$= 5.2 Hz, $J_{3\text{-}4}$= 1.2 Hz, H3); 1.32 (d, 3H, $J_{5\text{-}4}$= 6.8 Hz, H5). **$^{13}$C NMR** ($CD_3OD$, 100.6 MHz) δ in ppm: 178.1 (C=O); 83.2 (C4); 74.1 (C3); 69.9 (C2); 18.3 (C5).

223 Papageorgiou, C.; Benezra, C. *Tetrahedron Lett*. **1984**, *25*, 6041.

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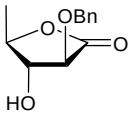
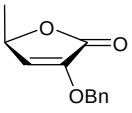
**2-*O*-benzyl-5-deoxy-γ-D-arabinolactone (95) and (4,*R*)-2,3-anhydro-2-benzyloxy-pentano-4-lactone (96)**




**95**




**96**

A solution of 5-deoxy-γ-D-ribonolactone (**37**) (250 mg, 1.89 mmol) in dry DMF (20 mL, 0.09 M) was cooled to -30 ºC, and then NaH 60% (80 mg, 1.99 mmol) was added. The suspension was left to stir at 0 ºC for 30 min, and then BnBr (247 µl, 2.1 mmol) was added. The reaction mixture was quenched with AcOH (5 ml) and extracted with EtOAc/$NaHCO_3$. The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. The crude product was purified by radial chromatography using EtOAc:hexane (1:2) as the eluent to afford compounds **95** (33 mg, 8%) and **96** (141 mg, 34%) as a yellowish mixture.

Spectroscopic data extracted from the mixture:

**95**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.40-7.30 (m, 5H, $H_{aromatic}$); 5.04 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.73 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.18 (d, 1H, $J_{2-3}$= 8.0 Hz, H2); 4.16 (dq, 1H, $J_{4-3}$= 7.6 Hz, $J_{4-5}$= 6.0 Hz, H4); 4.00 (ddd, 1H, $J_{OH-3}$= 4.4 Hz, $J_{3-4}$=7.6 Hz, $J_{3-2}$= 8.0 Hz, H3); 3.43 (d, 1H, $J_{OH-3}$= 4.4 Hz, OH); 1.39 (d, 3H, $J_{5-4}$= 6.0 Hz, H5). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 173.0 (C=O); 137.1 ($C_{aromatic}$); 128.8-128.3 ($CH_{aromatic}$); 80.2 (C2); 78.6 (C3); 77.5 (C4); 72.8 ($CH_2Ph$); 18.1 (C5).

**96**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.39-7.29 (m, 5H, $H_{aromatic}$); 6.10 (d, 1H, $J_{3-4}$=2.0 Hz, H3); 4.99 (m, 2H, $CH_2Ph$, H4); 4.93 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 1.38 (d, 3H, $J_{5-4}$=6.4 Hz, H5). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 168.4 (C=O); 145.6 (C2); 135.2 ($C_{aromatic}$); 128.9-127.8 ($CH_{aromatic}$); 119.9 (C3); 75.7 (C4); 73.0 ($CH_2Ph$); 20.2 (C5).

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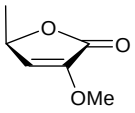
**(4,*R*)-2,3-anhydro-2-methyloxi-pentano-4-lactone (97)**



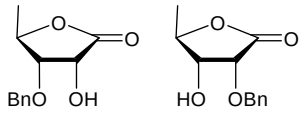

**97**

In a round-bottomed flask, wrapped with aluminium foil, lactone **37** (396 mg, 3 mmol) and MeI (1.3 ml, 21 mmol) were dissolved in DMF (5 ml, 0.6 M). Then freshly prepared $Ag_2O$ (2.1 g, 9 mmol) was added in portions with vigorous stirring. The mixture was stirred at rt for 5 h and filtered through celite. The filtrate was evaporated and then extracted with EtOAc/$H_2O$ twice. The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc:hexane (1:2) as the eluent to afford compound **97** (351 mg, 91%) as a yellowish syrup.

Anal. Calcd for $C_6H_8O_3$: 56.24 C, 6.29 H. Found: 56.27 C, 6.30 H

**615: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 6.17 (d, 1H, $J_{3\text{-}4}$=2.0 Hz, H3); 5.07 (qd, 1H, $J_{4\text{-}5}$= 6.4 Hz, $J_{4\text{-}3}$= 1.2 Hz, H4); 3.81 (s, 3H, OMe); 1.45 (d, 3H, $J_{5\text{-}4}$= 6.5 Hz, H5). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 167.7 (C=O); 146.8 (C2); 118.2 (C3); 75.4 (C4); 58.0 (OMe); 20.3 (C5).

**3-*O*-benzyl-5-deoxy-γ-D-ribonolactone (98) and 2-*O*-benzyl-5-deoxy-γ-D-ribonolactone (99)**




**98** **99**

To a solution of 5-deoxy-γ-D-ribonolactone (**37**) (6.0 g, 45.4 mmol) in toluene (300 ml, 0.15 M), $Bu_2SnO$ (11.3 g, 45.4 mmol) was added. The mixture was heated at

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reflux for 2 h with azeotropic removal of water formed (≈ 0.8 ml in Dean-Stark trap). The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The solid crude obtained was dried for 1h under high vacuum. Under argon atmosphere, dry CsF was added (8.4 g, 55.4 mmol) and the mixture dissolved in dry DMF (265 ml, 0.17 M). BnBr (11.8 ml, 99.5 mmol) was added dropwise and the mixture stirred for 2 days (TLC control). The reaction was quenched distilling DMF off and the crude extracted with EtOAc/$H_2O$. The organic phase was dried over anhydrous $MgSO_4$, concentrated, and purified by column chromatography (from hexane to EtOAc:hexane 1:2) to afford a solid mixture of **99** and **98** (ratio 8:1). This solid was recrystallized in EtOAc:Hexane to afford product **99** (8.3 g, 82%) as a bright white needles. The mother liquor was concentrated to give a mixture of **99** (0.8 g, 8%) and **98** (0.9 g, 9%).

**99:** Mp: 134-138 ºC. $[\alpha]^{20}_D$: +92.1 (*c* 1.00, $CH_2Cl_2$). Anal. Calcd for $C_{12}H_{14}O_4$: 64.85 C, 6.35 H. Found: 64.89 C, 6.37 H. **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.41-7.36 (m, 5H, $H_{aromatic}$); 5.05 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.80 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.54 (qd, 1H, $J_{4-3}$= 2.8 Hz, $J_{4-5}$= 6.8 Hz, H4); 4.19 (d, 1H, $J_{2-3}$= 5.2 Hz, H2); 4.00 (m, 1H, H3); 2.76 (d, 1H, $J_{OH-3}$= 3.6 Hz, OH); 1.35 (d, 3H, $J_{5-4}$= 6.8 Hz, H5). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 172.9 (C=O); 136.3 ($C_{aromatic}$); 128.9, 128.6, 128.1 ($CH_{aromatic}$); 80.9 (C4); 73.4 (C2); 73.1 ($CH_2Ph$); 72.6(C3); 18.3 (C5).

Spectroscopic data obtained from the mixture **99**: **98**.

**98:** **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.38-7.32 (m, 5H, $H_{aromatic}$); 4.70 (s, 2H, $CH_2Ph$); 4.62 (q, 1H, $J_{4-5}$= 6.8 Hz, H4); 4.47 (dd, 1H, $J_{2-3}$= 5.6 Hz, $J_{2-OH}$= 9.0 Hz, H2); 3.92 (d, 1H, $J_{3-2}$= 5.6 Hz, H3); 2.86 (d, 1H, $J_{OH-2}$= 9.0 Hz, OH); 1.33 (d, 3H, $J_{5-4}$= 6.8 Hz, H5). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 185.5 (C=O); 146.9 ($C_{aromatic}$); 128.9, 128.8, 128.1 ($CH_{aromatic}$); 78.8, 78.4 (C4, C3); 72.7 ($CH_2Ph$); 68.3 (C2); 18.3 (C5).

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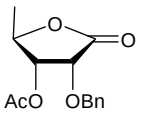
### 3-*O*-Acetyl-2-*O*-benzyl-5-deoxy-γ-D-ribonolactone (100)

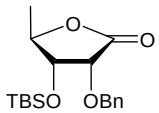



**100**

$Ac_2O$ (2.6 ml, 25 mmol) was added to a solution of 2-*O*-benzyl-5-deoxy-γ-D-ribonolactone **(99)** (111 mg, 0.50 mmol) in dry pyridine (5 ml, 0.1 M). The mixture was stirred overnight at rt (TLC analysis) and co-distilled with toluene 3 times. The reaction crude obtained was dried under high vacuum to yield yellowish syrup which corresponded to product **100** (132 mg, 98%).

**100: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.38-7.26 (m, 5H, $H_{aromatic}$); 5.13 (dd, 1H, $J_{3-2}$= 4.8 Hz, $J_{3-4}$= 4.4 Hz, H3); 4.83 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.77 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.61 (qd, 1H, $J_{4-5}$= 7.2 Hz, $J_{4-3}$= 4.4 Hz, H4); 4.31 (d, 1H, $J_{2-3}$= 4.8 Hz, H2); 2.12 (s, 3H, $CH_3CO$); 1.40 (d, 3H, $J_{5-4}$= 7.2 Hz, H5). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 188.2 ($C{=}O_{Ac}$); 173.2($C{=}O_{Lac}$) 148.5 ($C_{aromatic}$); 128.9, 128.5, 128.3 ($CH_{aromatic}$); 78.7 (C4), 73.3, 73.1, 72.2 (C2, C3, $CH_2Ph$); 21.0 (**C**$H_3CO$); 18.7 (C5).

### 2-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-γ-D-ribonolactone (101)




**101**

Following the general procedure of silylation, 2-*O*-benzyl-5-deoxy-γ-D-ribonolactone **(99)** (6.5 g, 19.3 mmol), $Et_3N$ (5.1 g, 22.9 mmol), TBSCl (5.0 g, 33.2 mmol) and DMAP (2.1 g, 17.2 mmol) in dry $CH_2Cl_2$ (50 ml, 0.46 M) were reacted at rt for 6 h. Column chromatography (1:3 EtOAc:hexane) of the reaction crude afford **101** (7.4 g, 96%) as a white solid.

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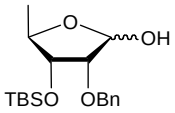
Anal. Calcd for $C_{18}H_{28}O_4Si$: 64.25 C, 8.39 H. Found: 64.29 C, 8.37 H. Mp: 81.0-81.9 ºC. $[\alpha]^{20}_D$: +54.6 (*c* 1.00, $CH_2Cl_2$).

**101: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.41-7.26 (m, 5H, $H_{aromatic}$); 4.93 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.76 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.49 (qd, 1H, $J_{4-3}$= 3.2 Hz, $J_{4-5}$= 6.8 Hz, H4); 4.03 (m, 2H, H2, H3); 1.34 (d, 3H, $J_{5-4}$= 6.8 Hz, H5); 0.88 (s, 9H, tBuSi); 0.07 (s, 3H, MeSi); 0.06 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 173.2 (C=O); 137.0 ($C_{aromatic}$); 128.6, 128.4, 128.2 ($CH_{aromatic}$); 81.5 (C4); 74.6, 74.0 (C3, C2); 72.2 ($CH_2Ph$); 25.8 ($CH_{3,tBuSi}$); 18.4 ($C_{tBuSi}$); 18.4 (C5); -4.45, -4.90 ($CH_3Si$).

## 2-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-α/β-D-ribofuranose (102)




**102**

The lactone **101** (6.5 mg, 19.3 mmol) was reduced following the general procedure for 2 h at -60 ºC. Column chromatography of the residue (hexanes:EtOAc 1:1) afforded the required furanose **102** (5.9 g, 90 %) as colourless syrup.

Spectroscopic data from α/β mixture:

Anal. Calcd for $C_{18}H_{30}O_4Si$: 63.87 C, 8.93 H. Found: 63.89 C, 8.90 H.

**102 α: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.38-7.26 (m, 5H, $H_{aromatic}$); 5.30 (d, 1H, $J_{1-2}$= 4.0 Hz, H1); 4.73 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.64 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.22 (qd, 1H, $J_{4-5}$= 6.8 Hz, $J_{4-3}$= 2.8 Hz, H4); 3.89 (dd, 1H, $J_{3-2}$= 4.4 Hz, $J_{3-4}$= 2.8 Hz, H3); 4.80 (dd, 1H, $J_{2-3}$= 4.4 Hz, $J_{2-1}$= 4.0 Hz, H2); 2.93 (s, 1H, OH); 1.17 (d, 3H, $J_{5-4}$= 6.8 Hz, H5); 0.900 (s, 9H, tBuSi); 0.104 (s, 3H, MeSi); 0.092 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm:137.7($C_{aromatic}$); 128.6-128.0 ($CH_{aromatic}$); 96.1 (C1); 80.0 (C4); 77.5 (C2); 77.1 (C3); 72.6 ($CH_2Ph$); 25.9 ($CH_{3,tBuSi}$); 19.6 (C5) ; 18.3($C_{tBuSi}$); -4.57 ($CH_3Si$); -4.85 ($CH_3Si$).

**102β: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.26 (m, 5H, $H_{aromatic}$); 5.29 (dd, 1H, $J_{1-OH}$= 3.6 Hz, $J_{1-2}$= 11.6 Hz, H1); 4.68 (s, 2H, $2CH_2Ph$); 4.40 (d, 1H, $J_{2-1}$= 11.6 Hz, H2);

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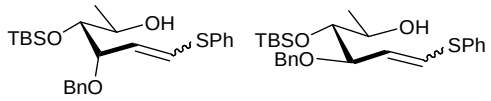
4.05 (dq, 1H, $J_{4\text{-}5}$= 4.0 Hz, $J_{4\text{-}3}$= 4.4 Hz, H4); 3.71 (d, 1H, $J_{3\text{-}4}$= 4.4 Hz, H3); 3.45 (d, 1H, $J_{OH\text{-}1}$= 3.6 Hz, OH); 1.33 (d, 3H, $J_{5\text{-}4}$= 4.0 Hz, H5); 0.912 (s, 9H, tBuSi); 0.104 (s, 3H, MeSi); 0.092 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3 ($C_{aromatic}$); 128.7-128.1 ($CH_{aromatic}$); 100.1 (C1); 82.9 (C3); 80.0 (C4); 78.4 (C2); 76.9 ($CH_2Ph$); 26.0 ($CH_{3,tBuSi}$); 20.0 (C5); 18.4 ($C_{tBuSi}$); -4.35 ($CH_3Si$), -4.73 ($CH_3Si$).

**(*Z/E*)-3-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (103) and (*Z/E*)-3-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-1,2,6-trideoxy-1-phenylsulfanyl-D-*arabino*-hex-1-enitol (104)**




**103** **104**

**One step procedure**

According to the general WH olefination in chapter 1, 2-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-α/β-D-ribofuranose **(102)** (520 mg, 1.54 mmol), diphenyl (phenylthiomethyl)phosphine oxide (1.49 g, 4.61 mmol), and *n*-BuLi (2.98 ml of 1.6 M hexane solution, 4.76 mmol) were left to react for 15 h. The reaction was monitored by TLC (EtOAc:hexane 1:4). Column chromatography (from hexane to EtOAc:hexane 1:3) afforded **103** (417 mg, 61%) as an inseparable 1:16 *Z/E* yellowish syrup and a low *Rf* epimerized **104** product (109 mg, 16%) as a 1:21 *Z/E* mixture.

Spectroscopic data obtained from **103** *E/Z* mixture:

**103***E*: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.39-7.24 (m, 10H, $H_{aromatic}$); 6.42 (d, 1H, $J_{1\text{-}2}$= 15.6 Hz, H1); 5.73 (dd, 1H, $J_{2\text{-}3}$= 8.0 Hz., $J_{2\text{-}1}$= 15.6 Hz., H2); 4.61 (d, 1H, $J_{AB}$= 11.6Hz, $CH_2Ph$); 4.37 (d, 1H, $J_{AB}$= 11.6Hz, $CH_2Ph$); 3.93 (dd, 1H, $J_{3\text{-}2}$= 8.0 Hz, $J_{3\text{-}4}$= 6.8 Hz., H3); 3.86 (m, 1H, H5); 3.63 (dd, 1H, $J_{4\text{-}3}$= 6.8 Hz, $J_{4\text{-}5}$= 5.6 Hz, H4); 2.14 (d, 1H, $J_{OH\text{-}5}$= 4.8 Hz, OH); 1.15 (d, 3H, $J_{6\text{-}5}$= 6.0 Hz, H6); 0.87 (s, 9H, tBuSi); 0.064 (s, 3H, MeSi); 0.047 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.1-127.3 ($C_{aromatic}$, $CH_{aromatic}$); 129.4 (C2); 128.6 (C1); 81.5 (C3); 78.2 (C4); 70.5 ($CH_2Ph$); 69.8 (C5); 26.2 ($CH_{3tBuSi}$) 18.8 (C6); 18.4 ($C_{tBuSi}$); -3.70, -4.15 ($CH_3Si$).

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**103***Z*: **$^{1}$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.40-7.23 (m, 10H, $H_{aromatic}$); 6.55 (d, 1H, $J_{1-2}$= 9.6 Hz, H1); 5.84 (dd, 1H, $J_{2-3}$= 9.2 Hz., $J_{2-1}$= 9.6 Hz., H2); 4.63 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.50 (dd, 1H, $J_{3-2}$= 9.2 Hz, $J_{3-4}$= 4.8 Hz, H3); 4.42 (d, 1H, $J_{AB}$= 11.6Hz, $CH_2Ph$); 3.86 (qd, 1H, $J_{5-6}$= 6.4 Hz, $J_{5-4}$= 5.2 Hz, H5); 3.75 (dd, 1H, $J_{4-3}$= 4.8 Hz, $J_{4-5}$= 5.2 Hz, H4); 2.47 (d, 1H, $J_{OH-5}$= 4.8 Hz, OH); 1.20 (d, 3H, $J_{6-5}$= 6.4 Hz, H6); 0.91 (s, 12H, tBuSi); 0.095 (s, 3H, MeSi); 0.082 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.5, 138.3 ($C_{aromatic}$); 129.5-126.9 ($CH_{aromatic}$); 129.3 (C2); 129.2 (C1); 78.4 (C4); 77.2 (C3); 70.8 ($CH_2Ph$); 69.7 (C5); 26.2 ($CH_{3tBuSi}$) 19.0 (C6); 18.4 ($C_{tBuSi}$); -3.57, -4.32 ($CH_3Si$).

Spectroscopic data obtained from **104** *E/Z* mixture**:**

Anal. Calcd for $C_{25}H_{36}O_3SSi$: 67.52 C, 8.16 H, 7.21 S. Found: 67.58 C, 8.17 H, 7.22 S.

**104***E*: **$^{1}$H NMR** ($CDCl_3$, 300 MHz) δ in ppm: 7.49-7.23 (m, 10H, $H_{aromatic}$); 6.50 (d, 1H, $J_{1-2}$= 15.0 Hz, H1); 5.84 (dd, 1H, $J_{2-3}$= 7.5 Hz, $J_{2-1}$= 15.0 Hz, H2); 4.65 (d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 4.40(d, 1H, $J_{AB}$= 12.0 Hz, $CH_2Ph$); 3.93 (dd, 1H, $J_{3-2}$= 7.5 Hz, $J_{3-4}$= 6.4 Hz, H3); 3.77-3.73 (m, 1H, H4); 3.62 (qd, 1H, $J_{5-6}$= 6.0 Hz., $J_{5-OH}$= 2.7 Hz, H5); 2.32 (d, 1H, $J_{OH-5}$= 2.7 Hz, OH); 1.10 (d, 3H, $J_{6-5}$= 6.0 Hz, H6); 0.85 (s, 9H, tBuSi); 0.069 (s, 3H, MeSi); 0.033 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 75.4 MHz) δ in ppm: 138.2, 138.1 ($C_{aromatic}$); 130.4, 129.4, 128.9, 128.7, 128.6, 128.1, 127.9, 127.2 ($CH_{aromatic}$, C1, C2); 79.7, 76.8, 70.4 (C4, C3, $CH_2Ph$); 68.9 (C5); 26.0 ($CH_{3tBuSi}$); 18.22 ($C_{tBuSi}$); 18.20 (C6); -3.84, -4.59 ($CH_3Si$).

**104***Z*: **$^{1}$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.41-7.24 (m, 10H, $H_{aromatic}$); 6.64 (d, 1H, $J_{1-2}$= 9.6 Hz, H1); 5.86 (dd, 1H, $J_{2-3}$= 8.4 Hz, $J_{2-1}$= 9.6 Hz, H2); 4.66 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.41(d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.34 (dd, 1H, $J_{3-2}$= 8.4 Hz, $J_{3-4}$= 8.0 Hz, H3); 4.08 (qd, 1H, $J_{5-6}$= 6.8 Hz, $J_{5-4}$= 4.0 Hz, H5); 3.71 (dd, 1H, $J_{4-3}$= 8.0 Hz, $J_{4-5}$= 4.0 Hz., H4); 2.21 (s, 1H, OH); 1.10 (d, 3H, $J_{6-5}$= 6.8 Hz, H6); 0.88 (s, 9H, tBuSi); 0.092 (s, 3H, MeSi); 0.077 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 136.1, 135.9 ($C_{aromatic}$); 130.1 (C1); 129.5-126.9 ($CH_{aromatic}$); 129.2 (C2); 76.3 (C4); 75.9 (C3); 70.7 ($CH_2Ph$); 69.0 (C5); 26.0 ($CH_{3tBuSi}$); 18.2 ($C_{tBuSi}$); 17.1 (C6); -4.14, -4.61 ($CH_3Si$).

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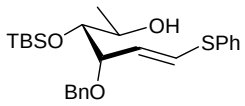
**(*E*)-3-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (103)**




**103E**

**Two step procedure**

Following the general WH olefination (two steps) described in chapter 1, ribofuranose **102** (680 mg, 2.01 mmol), diphenyl (phenylthiomethyl)phosphine oxide (1.63 g, 5.02 mmol), and *n*-BuLi (3.26 ml of 1.6 M hexane solution, 5.22 mmol) were left to react for 10 h at rt. The reaction was monitored by TLC (EtOAc:hexane 1:4) to ensure that only one product (TLC spot) was formed. Column chromatography (from hexane to EtOAc:hexane 1:3) afforded **103***E* (223 mg, 25%) and a lower *Rf* fraction which corresponded to β-hydroxiphosphine oxide intermediate **105**[224] (erythro:threo mixture) impurified with a minor amount of diphenyl(phenylthiomethyl)phosphine oxide. This fraction was subjected to the WH elimination procedure for 2 h at rt to yield additional enolthiether **103** (178 mg, 20%, *E:Z* ratio 6:1) and epimerized product **104** (116 mg, 13%, *E:Z* ratio 17:1) as yellowish syrups.

**103***E*: $[\alpha]^{20}_{D}$: +12.4 (*c* 2.25, $CH_2Cl_2$). Anal. Calcd for $C_{25}H_{36}O_3SSi$: 67.52 C, 8.16 H, 7.21 S. Found: 67.58 C, 8.17 H, 7.22 S.

[224] NMR data of **105threo**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.93-7.05 (m, 20H, $H_{aromatic}$); 4.94 (sa, 1H, OH); 4.78 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.66 (sa, 1H, OH); 4.37 (m, 2H, H2, $CH_2Ph$); 2.25 (d, 1H, $J_{3\text{-}4}$= 1.2 Hz, H3); 4.03 (dd, 1H, $J_{1\text{-}P}$= 9.4 Hz, $J_{1\text{-}2}$= 5.4 Hz, H1); 3.64 (dd, 1H, $J_{4\text{-}3}$= 1.2 Hz, $J_{4\text{-}5}$= 7.6 Hz, H4); 3.55-3.47 (m, 1H, H5); 1.15 (d, 3H, $J_{6\text{-}5}$= 6.0 Hz, H6); 0.81 (s, 9H, tBuSi); 0.038 (s, 3H, MeSi); 0.013 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 137.2-127.5 (Ar); 80.1 (C4); 79.2 (C3); 72.8 ($CH_2Ph$); 69.9 (C2); 66.5 (C5); 53.0 (d, $J_{C1\text{-}P}$= 64.8 Hz, C1); 26.2 ($CH_{3tBuSi}$) 19.9 (C6); 18.2 ($C_{tBuSi}$); -3.57, -4.51 ($CH_3Si$). **$^{31}$P NMR** ($CDCl_3$, 162.0 MHz) δ in ppm: 34.4 ppm (P=O).

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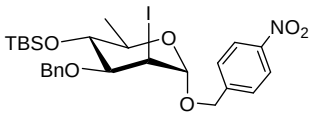
### *p*-Nitrobenzyl 3-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-iodo-1-α/β-D-*manno*-pyranoside (106)




**106**

Compound **104** (*Z*:*E* ratio = 1:21, 75 mg, 0.17 mmol), and *p*-nitrobenzyl alcohol (**26c**) (52 mg, 0.34 mmol) in dry $CH_2Cl_2$ (3.4 ml , 0.05 M) were reacted following the *one-pot* cyclization-glycosylation procedure. Cyclization was carried out from -60 ºC to -20 ºC in 16 h and glycosylation from -78 ºC to -20 ºC in 4 h. Chromatographic purification yielded compound **106** (67 mg, 68%) as a inseparable 35:1 α:β mixture in the form of a colourless syrup.

Spectroscopic data extracted from α/β mixture:

**106α: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 8.23-8.17 (m, 2H, $H_{aromatic\text{-}o}$); 7.51-7.26 (m, 7H, $H_{aromatic}$); 5.45 (d, 1H, $J_{1\text{-}2}$= 3.6 Hz, H1); 4.86 (d, 1H, $J_{AB}$= 13.6 Hz, $CH_2PhNO_2$); 4.63 (d, 1H, $J_{AB}$= 13.6 Hz, $CH_2PhNO_2$); 4.61 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.48 (d, 1H, $J_{AB}$= 11.2 Hz, $CH_2Ph$); 4.37 (dd, 1H, $J_{2\text{-}1}$= 3.2 Hz, $J_{2\text{-}3}$= 5.6 Hz, H2); 3.98 (dd, 1H, $J_{4\text{-}5}$= 4.8 Hz, $J_{4\text{-}3}$= 5.2 Hz, H4); 3.88 (qd, 1H, $J_{5\text{-}4}$= 4.8 Hz, $J_{5\text{-}6}$= 6.0 Hz, H5); 3.73 (dd, 1H, $J_{3\text{-}2}$= 5.6 Hz, $J_{3\text{-}4}$= 5.2 Hz, H3); 1.14 (d, 3H, $J_{6\text{-}5}$= 6.0 Hz, H6); 0.85 (s, 9H, tBuSi); 0.055 (s, 3H, MeSi); 0.026 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 147.6, 145.1, 137.3 ($C_{aromatic}$); 128.6, 128.2, 128.1, 128.0, 127.9, 123.8 ($CH_{aromatic}$); 110.0 (C1); 86.9 (C4); 77.8 (C3); 72.4 ($CH_2Ph$); 69.2 (C5); 69.1 ($CH_2PhNO_2$); 31.9 (C2); 26.0 ($CH_{3tBuSi}$); 20.4 (C6); 18.2 ($C_{tBuSi}$); -4.18, -4.37 ($CH_3Si$).

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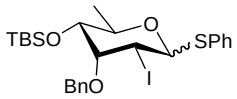
**Phenyl 3-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-iodo-1-thio-α/β-D-*allo*-pyranoside (107)**




**107**

As described in cyclization method B (Chapter 1), compound **107** (62 mg, 44%, α/β ratio 1.5:1, inseparable mixture) was obtained as a yellowish syrup starting from compound **103** (*E:Z* ratio 5:1) (110 mg, 0.25 mmol) and IDCP (255 mg, 0.54 mmol) in dry $CH_3CN$ (4.1 ml, 0.06 M), at -35 °C for 1 h. The reaction was monitored by TLC (EtOAc:hexane 1:4) and the reaction crude was purified by radial chromatography (from hexane to EtOAc:hexane 1:3). A minor amount of lactol **53** (17%) was also isolated.

Spectroscopic data extracted from α/β mixture:

**107α**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.57-7.23 (m, 10H, $H_{aromatic}$); 5.45 (s, 1H, H1); 4.88 (d, 1H, $J_{2-3}$= 2.8 Hz, H2); 4.80 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.64 (d, 1H, $J_{AB}$= 11.6 Hz, $CH_2Ph$); 4.63 (dq, 1H, $J_{5-4}$= 9.2 Hz., $J_{5-6}$= 6.0 Hz., H5); 4.28 (dd, 1H, $J_{4-5}$= 9.2 Hz., $J_{4-3}$= 2.4 Hz., H4); 3.89 (dd, 1H, $J_{3-2}$= 2.8 Hz, $J_{3-4}$= 2.4 Hz, H3); 1.31 (d, 3H, $J_{6-5}$= 6.0 Hz, H6); 0.92 (s, 9H, tBuSi); 0.12 (s, 3H, MeSi); 0.06 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6, 137.7 ($C_{aromatic}$); 132.9-127.4 ($CH_{aromatic}$); 88.6 (C1); 80.5 (C3); 73.2 ($CH_2Ph$); 70.7 (C4); 67.0 (C5); 28.3 (C2); 26.2 ($CH_{3tBuSi}$); 18.1 ($C_{tBuSi}$); 18.1 (C6); -3.90, -4.54 ($CH_3Si$).

**107β**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ en ppm: 7.56-7.24 (m, 10H, $H_{aromatic}$); 5.09 (d, 1H, $J_{1-2}$= 10.8 Hz, H1); 4.98 (d, 1H, $J_{AB}$= 10.4 Hz, $CH_2Ph$); 4.74 (d, 1H, $J_{AB}$= 10.4 Hz, $CH_2Ph$); 4.09 (dd, 1H, $J_{2-1}$= 10.8 Hz, $J_{2-3}$= 2.4 Hz, H2); 4.06 (dq, 1H, $J_{5-4}$= 9.2 Hz, $J_{5-6}$= 6.4 Hz, H5); 3.95 (dd, 1H, $J_{3-2}$= 2.4 Hz, $J_{3-4}$= 2.0 Hz, H3); 3.47 (dd, 1H, $J_{4-5}$= 9.2 Hz, $J_{4-3}$= 2.0 Hz, H4); 1.22 (d, 3H, $J_{6-5}$= 6.4 Hz, H6); 0.92 (s, 9H, tBuSi); 0.13 (s, 3H, MeSi); 0.11 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 138.6, 137.7($C_{aromatic}$); 132.9-127.4 ($CH_{aromatic}$); 84.7 (C1); 82.4 (C3); 76.3 ($CH_2Ph$); 75.7 (C4); 73.5 (C5); 32.4 (C2); 26.2 ($CH_{3tBuSi}$); 18.5 (C6); 18.2 ($C_{tBuSi}$); -3.46, -4.69 ($CH_3Si$).

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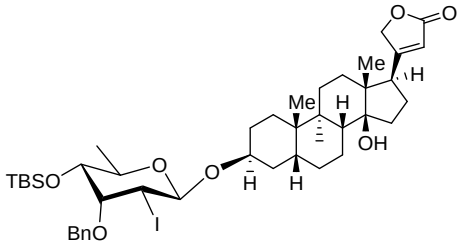
**Digitoxigenyl 3-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-iodo-α/β-D-*allo*-pyranoside (108)**




**108**

As described in the *one-pot* cyclization-glycosylation procedure, the title compound was prepared starting from **103** (80 mg, 0.18 mmol) and digitoxigenin (**87**) (81 mg, 0.21 mmol) in dry $CH_2Cl_2$ (4 ml, 0.045 M). The reaction mixture was stirred from -78 °C to -20 ºC for 10 h (cyclization) and then from -60 °C to -30 ºC for 15 h (glycosylation). (monitored by TLC (EtOAc:hexane 1:3)). Radial chromatography (from hexane to EtOAc:hexane 1:4) of the reaction crude provided **108** (65 mg, 43%) as an inseparable 1:11 α:β mixture as a white foam.

Spectroscopic data extracted from α/β mixture:

Anal. Calcd para $C_{43}H_{65}IO_7Si$: 60.83 C, 7.72 H. Found: 60.84 C, 7.72 H.

**108*β*: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.50-7.27 (m, 5H, $H_{aromatic}$); 5.87 (s, 1H, $H_{22dig}$); 5.00 (d, 1H, $J_{AB}$= 18.4 Hz, $H_{21Adig}$); 4.95 (d, 1H, $J_{AB}$= 10.4 Hz, $CH_2Ph$); 4.81 (d, 1H, $J_{AB}$= 18.4 Hz, $H_{21Bdig}$); 4.79 (d, 1H, $J_{1-2}$= 8.8 Hz, H1); 4.76 (d, 1H, $J_{AB}$= 10.4 Hz, $CH_2Ph$); 4.08 (dd, 1H, $J_{2-1}$= 8.8 Hz, $J_{2-3}$= 2.4 Hz, H2); 4.00 (dq, 1H, $J_{5-4}$= 9.2 Hz, $J_{5-6}$= 6.4 Hz, H5); 3.94-3.92 (m, 2H, $H_{3dig}$, H3); 3.57 (dd, 1H, $J_{4-5}$= 9.2 Hz, $J_{4-3}$= 2.4 Hz, H4); 2.78 (m, 1H, $OH_{14dig}$); 2.17-1.13 (m, 22H, $H_{dig}$); 1.19 (d, 3H, $J_{6-5}$= 6.4 Hz, H6); 0.94-0.90 (m, 15H, $CH_{3tBuSi}$, $2Me_{dig}$); 0.143 (s, 3H, MeSi); 0.109 (s, 3H, MeSi). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 174.9, 174.8 (C=O, $C20_{dig}$); 138.8 ($C_{aromatic}$); 128.3, 128.0, 127.0 ($CH_{aromatic}$); 117.8 ($C22_{dig}$); 98.4 (C1); 85.8 ($C14_{dig}$); 82.4 (C3); 76.1 ($CH_2Ph$); 75.9 (C4); 74.2 ($C3_{dig}$); 73.6 ($C21_{dig}$); 70.2 (C5); 51.1-14.4 ($C_{dig}$); 33.9 (C2); 26.2 ($CH_{3tBuSi}$); 18.3 (C6); 18.2 ($C_{tBuSi}$); -3.50, -4.69 ($CH_3Si$).

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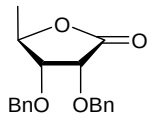
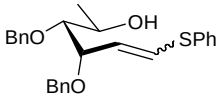
**2,3-Di-*O*-benzyl-5-deoxy-γ-D-ribonolactone (38) prepared by using 2-benzyloxy-1-methylpyridinium triflate**



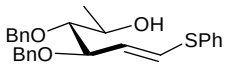

**38**

MgO (903 mg, 22.4 mmol) was added to a solution of 5-deoxy-γ-D-ribonolactone (**37**) (899 mg) and 2-benzyloxy-1-methylpyridinium triflate[225] (**109**) (7.73 g, 22.3 mmol) in $PhCF_3$ (10 ml, 0.67 M). The mixture was warmed at 80 ºC and stirred for 15 h. The solvent was distilled off under vacuum and the crude was extracted with $CH_2Cl_2/H_2O$. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (hexane: EtOAc, 2:1) to give the title compound (1.6 g, 74%).
Spectroscopic data coincident with reported in chapter 3.

**(*Z/E*)-3,4-Di-*O*-benzyl-1,2,6-trideoxy-1-phenylsulfanyl-D-*ribo*-hex-1-enitol (40) and (*E*)-3,4-Di-*O*-benzyl-1,2,6-trideoxy-1-phenylsulfanyl-D-*arabino*-hex-1-enitol (110)**




**40**




**110**

According to the two-step general WH olefination in chapter 1, furanose **39** (200 mg, 0.64 mmol), diphenyl (phenylthiomethyl)phosphine oxide (825 mg, 2.54 mmol), and *n*-BuLi (1.67 ml of 1.6 M hexane solution, 2.67 mmol) were left to react for 22 h and then submitted to elimination for 3 h. The reaction was monitored by TLC (EtOAc:hexane 1:4). Column chromatography (from hexane to EtOAc:hexane 1:3) afforded **40** (164 mg, 63%) as an inseparable 2:5 *Z/E* colourless syrup and epimerized product **110** (11 mg, 4%, only E).

[225] Poon, K.W.C.; Dudley, G.B. *J. Org. Chem.* **2006**, *71*, 3923.

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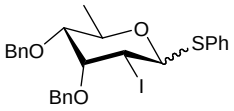
Spectroscopic data of **40** coincident with reported in chapter 3.

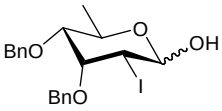
Spectroscopic data obtained from slightly impurified **110**.

**110*E*: $^1$H NMR** ($CDCl_3$, 300 MHz) δ in ppm: 7.34-7.26 (m, 10H, $H_{aromatic}$); 6.40 (d, 1H, $J_{1-2}$= 15.3 Hz, H1); 5.82 (dd, 1H, $J_{2-1}$= 15.3 Hz, $J_{2-3}$= 8.2 Hz, H2); 4.65-4.35 (m, 4H, $J_{AB}$= 11.7 Hz, $J_{AB}$= 12.0 Hz, $4CH_2Ph$); 4.06 (dd, 1H, $J_{3-2}$= 8.2 Hz, $J_{3-4}$= 5.1 Hz, H3); 3.83 (m, 1H, H5); 3.60 (pst, 1H, $J_{4-3}$= 5.1 Hz, $J_{4-5}$= 5.1 Hz, H4); 2.26 (sa, 1H, OH); 1.23 (d, 3H, $J_{6-5}$= 6.6 Hz, H6).

## Phenyl 3,4-Di-*O*-benzyl-2,6-dideoxy-2-iodo-1-thio-α/β-D-*allo*-pyranoside (111) and 3,4-Di-*O*-benzyl-2,6-dideoxy-2-iodo-α/β-D-*allo*-pyranoside (112)




**111**




**112**

As described in method B (Chapter 1), cyclization was carried out starting from compound **40** (100 mg, 0.24 mmol) and IDCP (245 mg, 0.52 mmol) in dry $CH_3CN$ (4 ml, 0.06 M) at -35 °C for 2 h. The mixture was purified by radial chromatography (from hexane to EtOAc:hexane 1:3) to afford a mixture of **111** (51 mg, 40%, α/β ratio 1:1.6) and **112** (7 mg, 6%).

Spectroscopic data extracted from α/β/OH mixture:

**111*α*: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.57-7.24 (m, 15H, $H_{aromatic}$); 5.46 (s, 1H, H1); 4.92-4.31 (m, 6H, $4CH_2Ph$, H2, H5); 4.00 (dd, 1H, $J_{3-2}$= 3.6 Hz, $J_{3-4}$= 2.8 Hz, H3); 3.97 (d, 1H, $J_{4-3}$= 2.8 Hz, H4); 1.36 (d, 3H, $J_{6-5}$= 6.4 Hz, H6). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 137.9, 137.6, 132.3 ($C_{aromatic}$); 131.2-127.2 ($CH_{aromatic}$); 89.5 (C1); 76.4 (C4); 75.8 (C3); 72.2, 71.7 ($CH_2Ph$); 65.7 (C5); 27.5 (C2); 18.0 (C6).

**111*β*: $^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.47-7.22 (m, 15H, $H_{aromatic}$); 5.10 (d, 1H, $J_{1-2}$= 11.2 Hz, H1); 4.90-4.42(m, 4H, $4CH_2Ph$); 4.18 (dd, 1H, $J_{3-2}$=2.6 Hz, $J_{3-4}$=2.2 Hz, H3); 4.11 (dq, 1H, $J_{5-4}$= 9.6 Hz, $J_{5-6}$= 6.4 Hz, H5); 4.03 (dd, 1H, $J_{2-1}$=11.2 Hz, $J_{2-3}$= 2.6 Hz, H2); 3.23 (dd, 1H, $J_{4-5}$=9.2 Hz, $J_{4-3}$=2.2 Hz, H4); 1.27 (d, 3H, $J_{6-5}$= 6.4 Hz, H6). **$^{13}$C NMR**

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($CDCl_3$, 100.6 MHz) δ in ppm: 138.4, 137.7 ($C_{aromatic}$); 133.1-127.9 ($CH_{aromatic}$); 84.6 (C1); 81.9 (C4); 78.5 (C3); 75.9 ($CH_2Ph$); 72.6 (C5); 72.4 ($CH_2Ph$); 32.4 (C2); 18.4 (C6).

**112**: **$^1$H NMR** ($CDCl_3$, 400 MHz) δ in ppm: 7.40-7.25 (m, 15H, $H_{aromatic}$); 5.29 (d, 1H, $J_{1-2}$= 5.2 Hz, H1); 5.02-4.65 (m, 5H, $4CH_2Ph$, H5); 4.61 (dd, 1H, $J_{2-1}$= 5.2 Hz, $J_{2-3}$= 2.6 Hz, H2); 4.16 (dd, 1H, $J_{3-2}$= 2.6 Hz, $J_{3-4}$= 2.4 Hz, H3); 3.29 (dd, 1H, $J_{4-3}$= 2.4 Hz, $J_{4-5}$= 9.6 Hz, H4); 2.31 (sa, 1H, OH); 1.26 (d, 3H, $J_{6-5}$= 6.0 Hz, H6). **$^{13}$C NMR** ($CDCl_3$, 100.6 MHz) δ in ppm: 137.1-127.9 ($C_{aromatic}$ ,$CH_{aromatic}$); 90.0 (C1); 82.2 (C4); 77.9 (C3); 75.7, 72.1 ($CH_2Ph$); 64.6 (C5); 27.7 (C2); 17.9 (C6).

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# Annex

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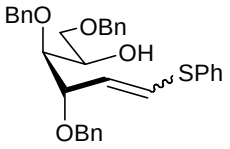
SELECTED NMR SPECTRA

$^{1}$H NMR (400 MHz)

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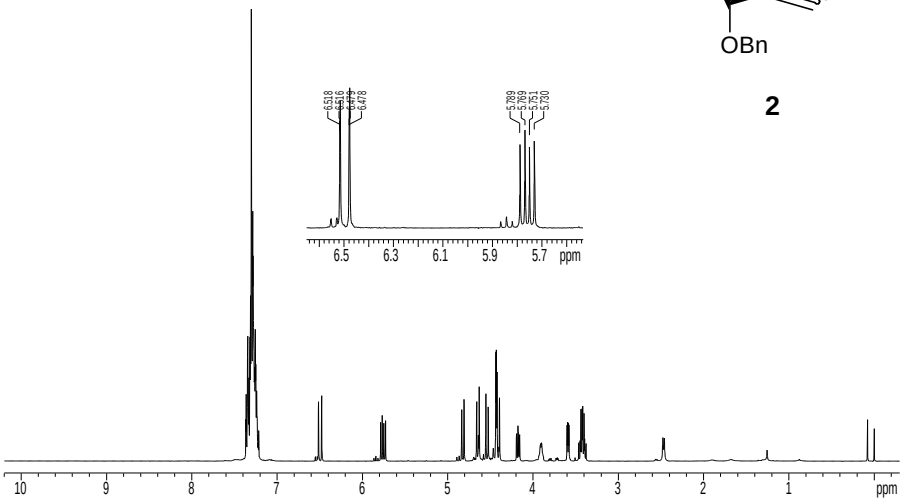
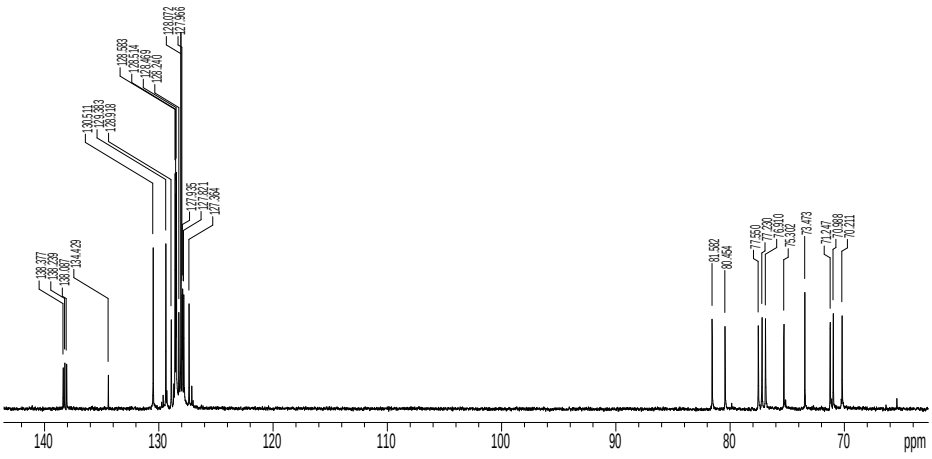



$^{13}$C NMR (100.6 MHz)



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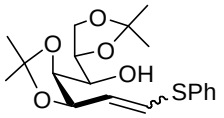
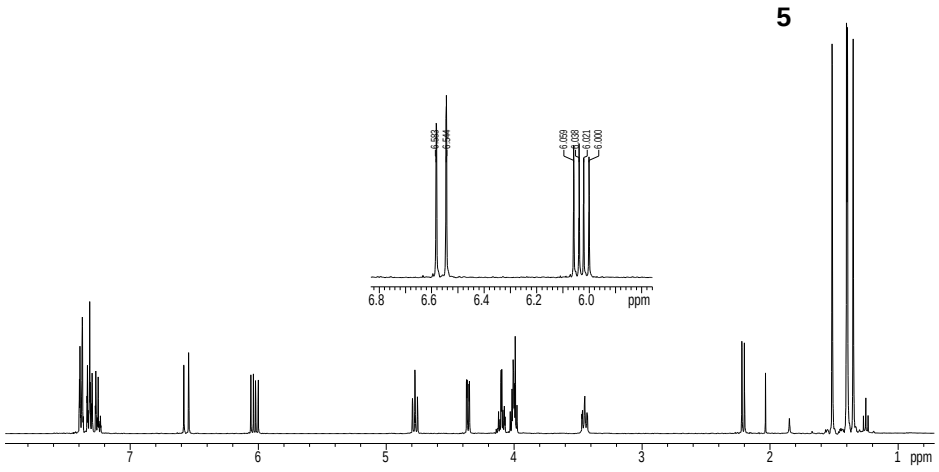
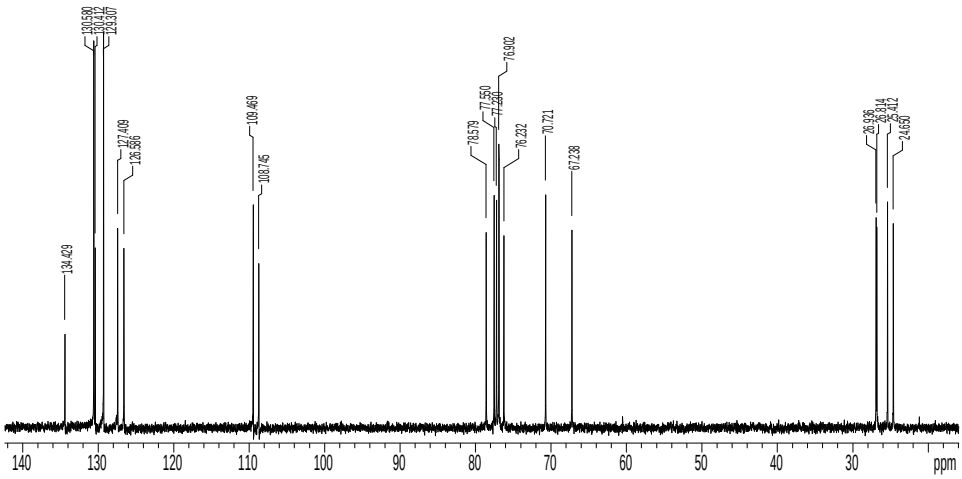
$^{1}$H NMR (400 MHz)




$^{13}$C NMR (100.6 MHz)




II

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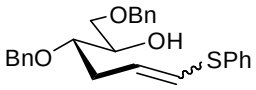
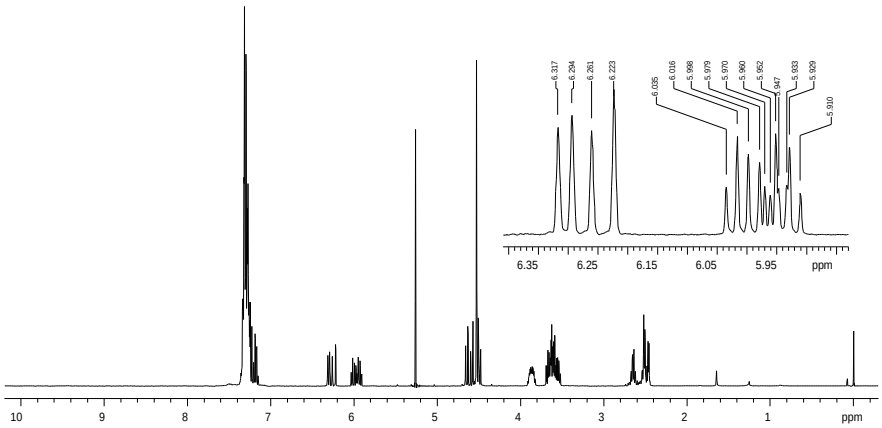
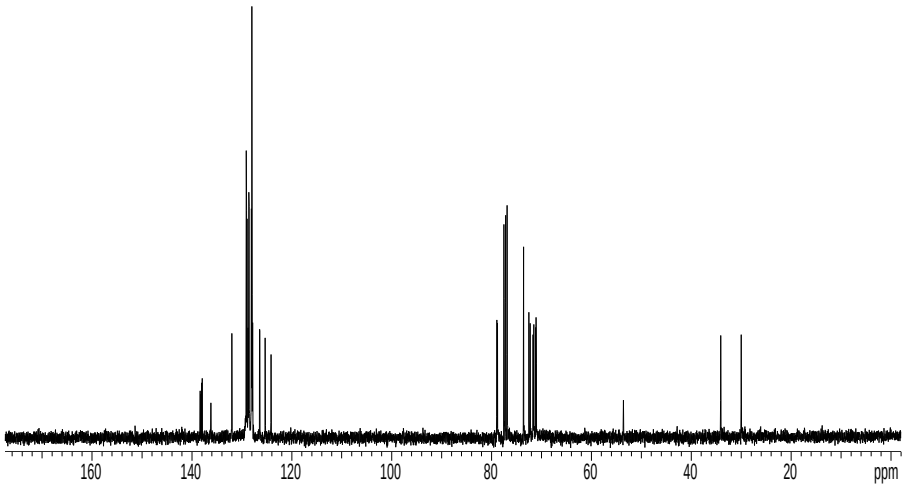
$^{1}$H NMR (400 MHz)




**7**




$^{13}$C NMR (100.6 MHz)



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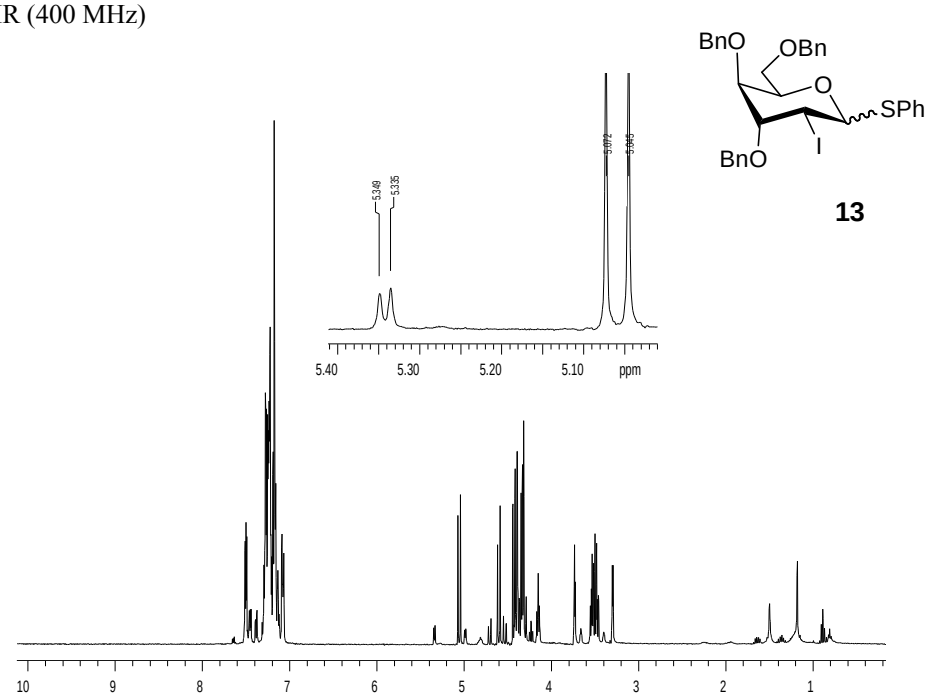
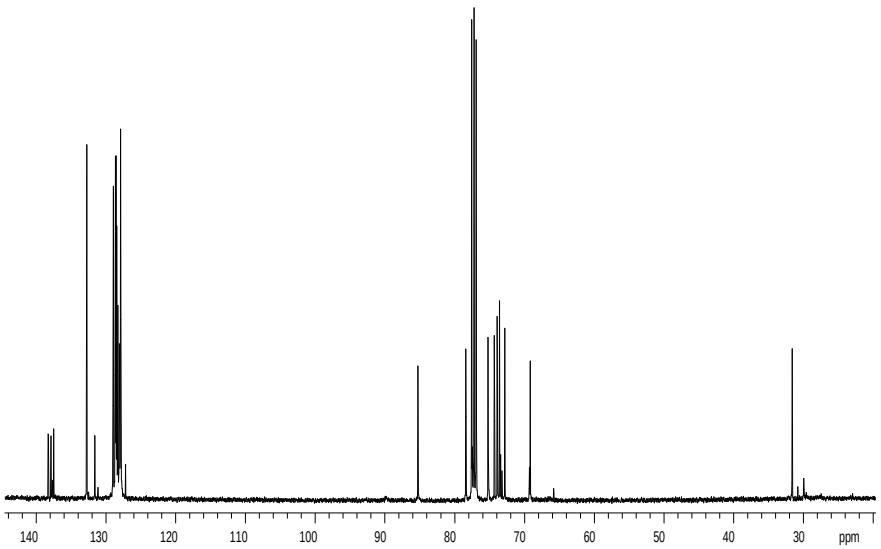
$^{1}$H NMR (400 MHz)




$^{13}$C NMR (100.6 MHz)



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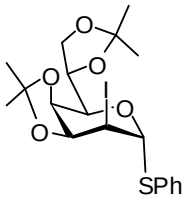


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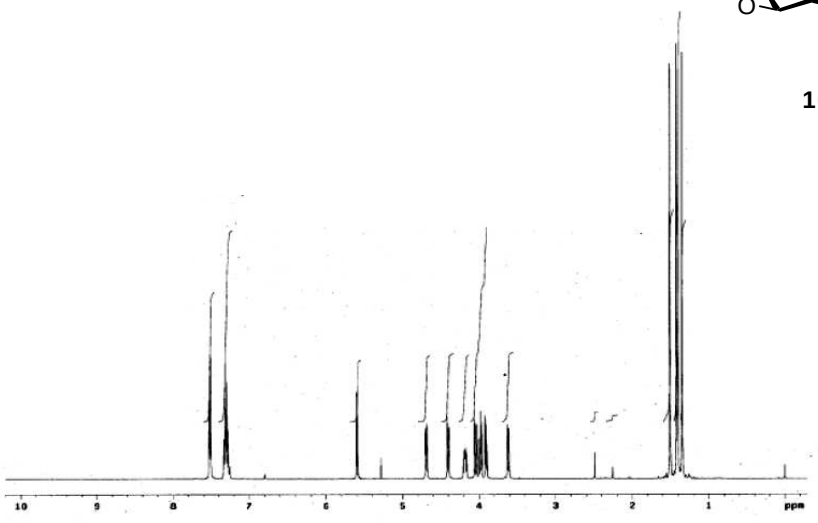
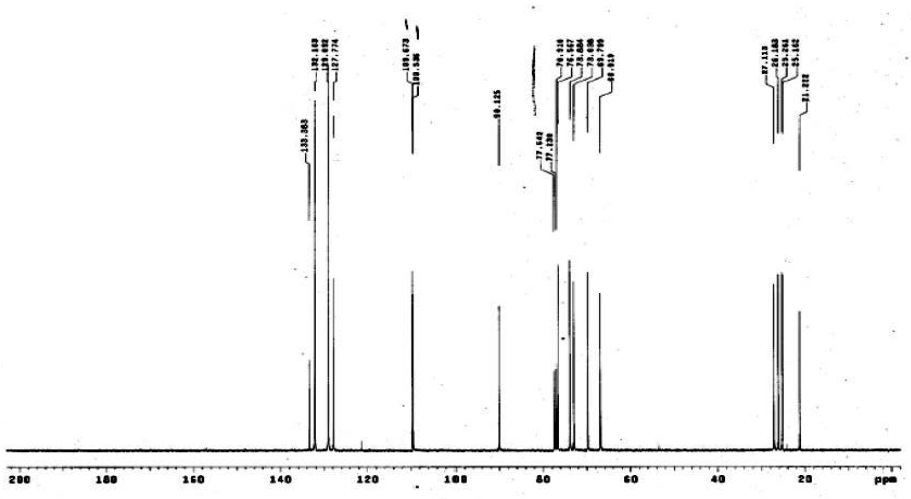



$^{13}$C NMR (100.6 MHz)



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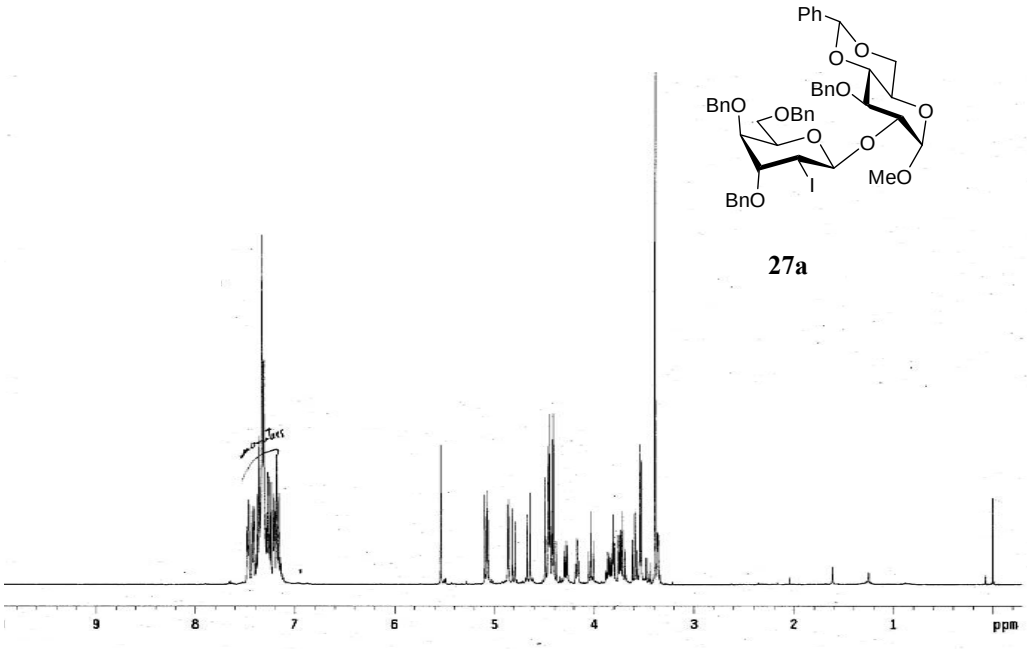
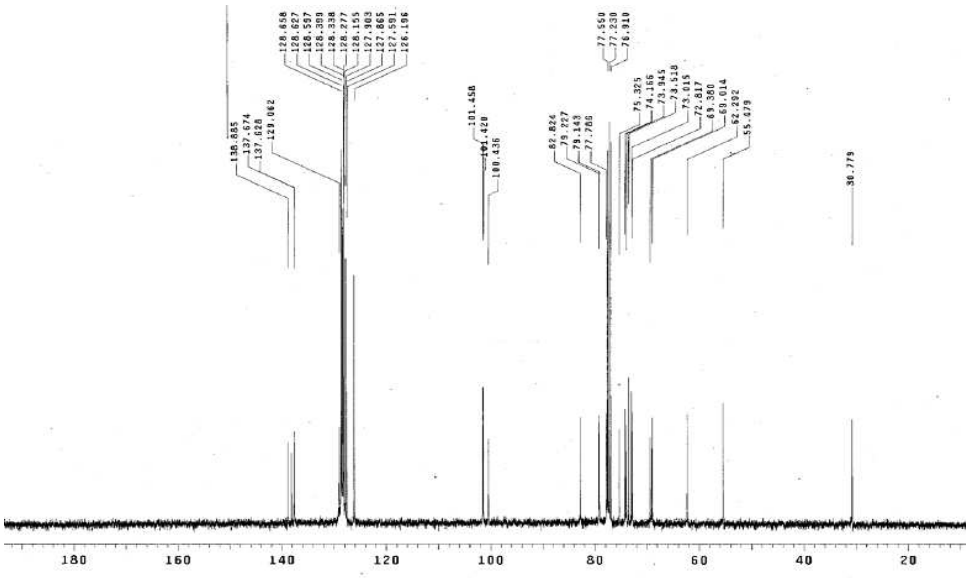



**27a**

$^{13}$C NMR (100.6 MHz)



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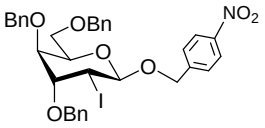
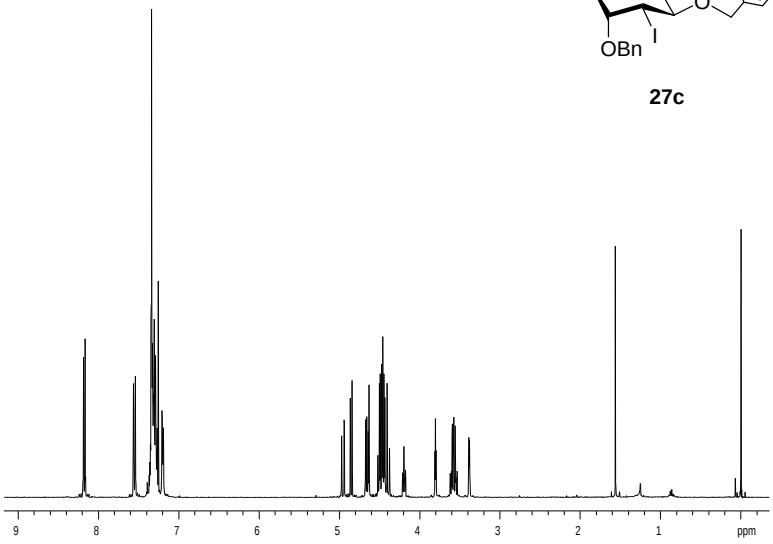
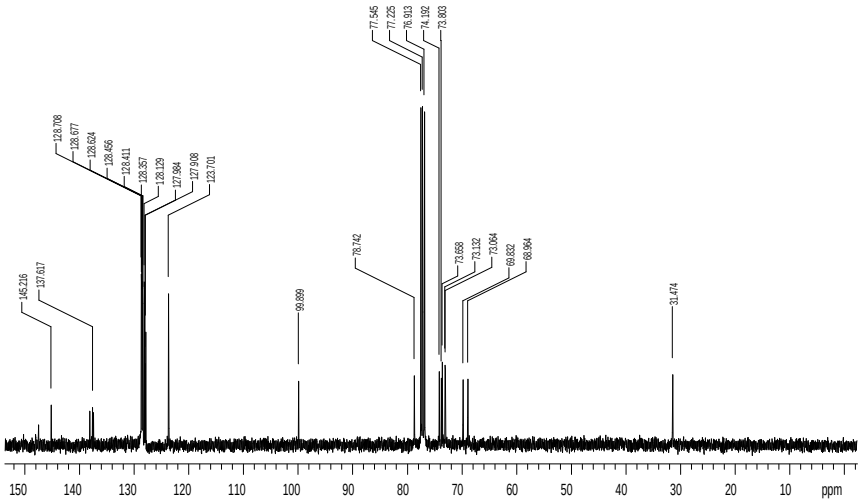
$^{1}$H NMR (400 MHz)




**27c**




$^{13}$C NMR (100.6 MHz)



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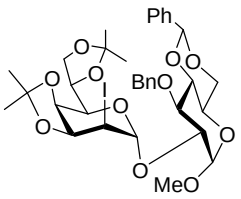
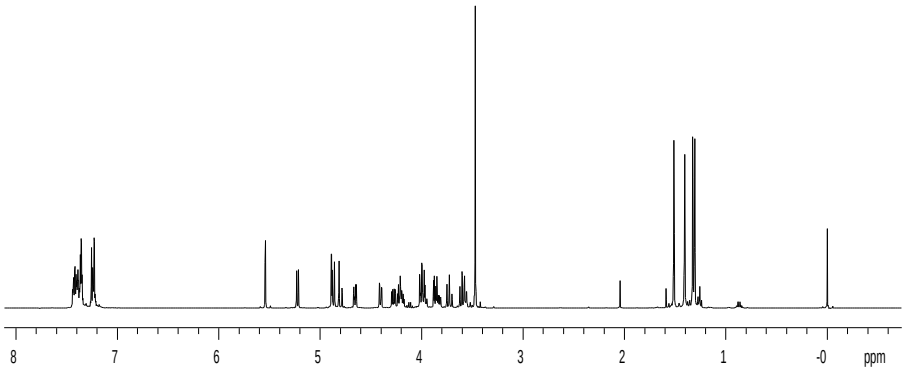
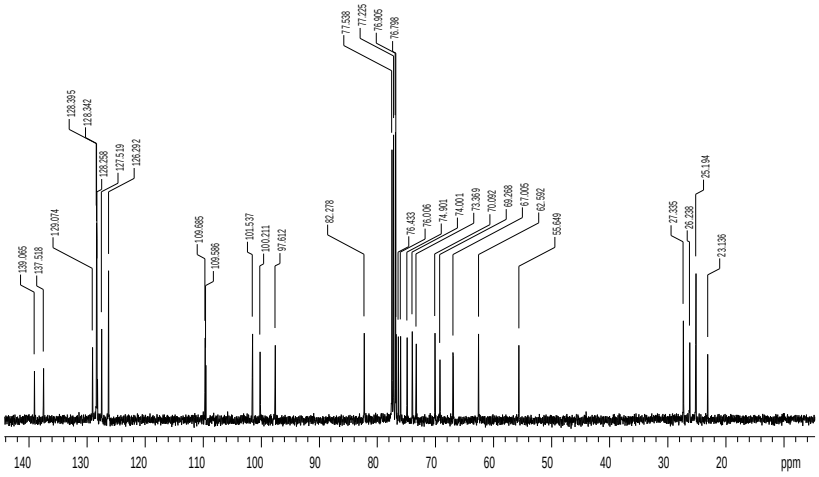



**28a**

$^{1}$H NMR (400 MHz)




$^{13}$C NMR (100.6 MHz)



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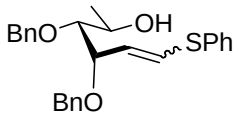
$^{1}$H NMR (400 MHz)

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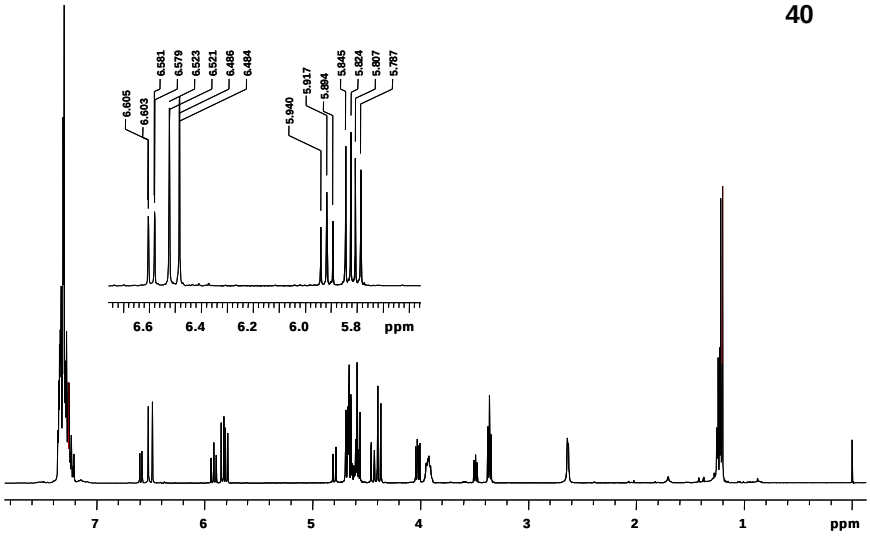
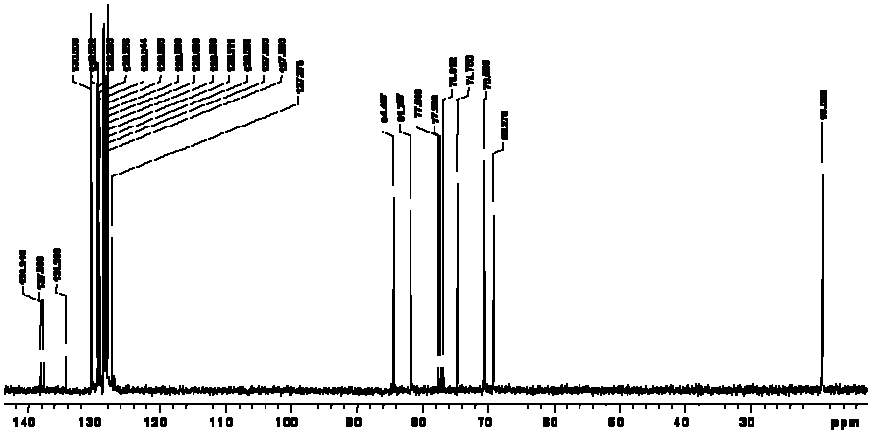



$^{13}$C NMR (100.6 MHz)



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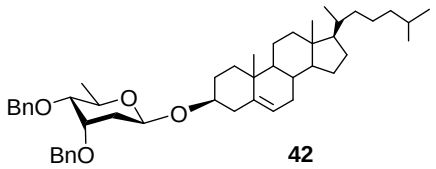
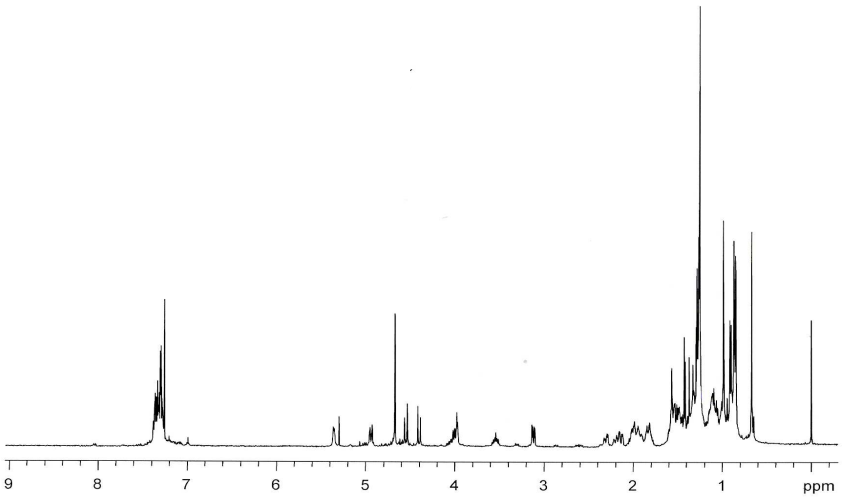
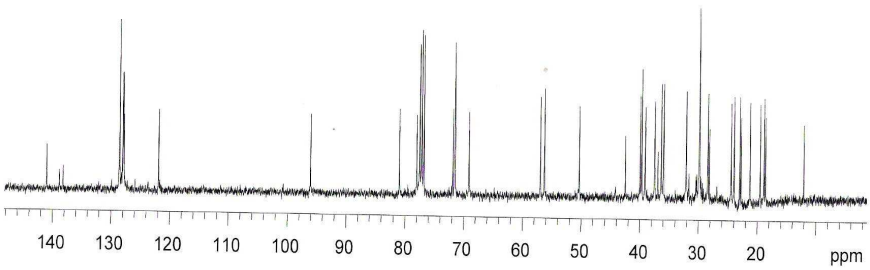
$^{1}$H NMR (400 MHz)




**42**




$^{13}$C NMR (100.6 MHz)

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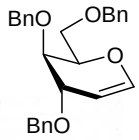
$^{1}$H NMR (400 MHz)

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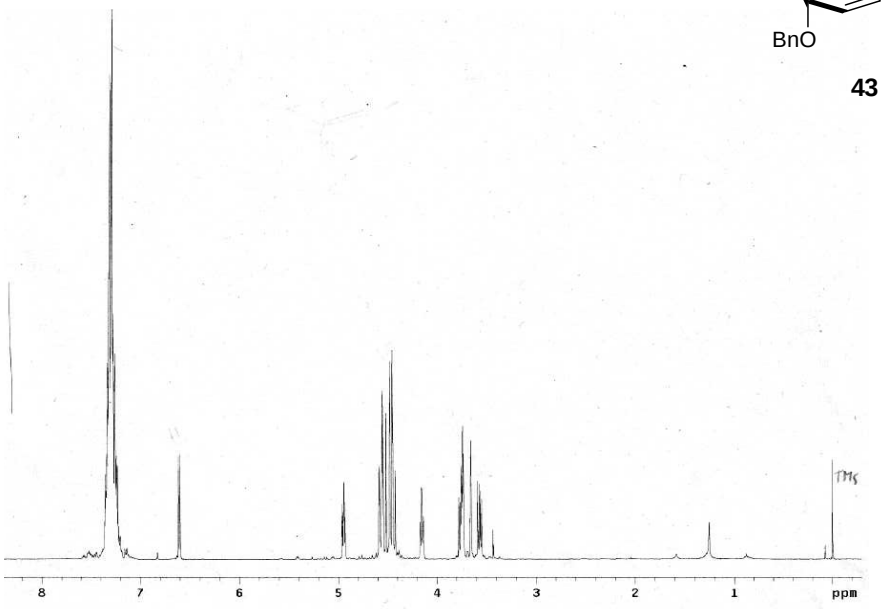


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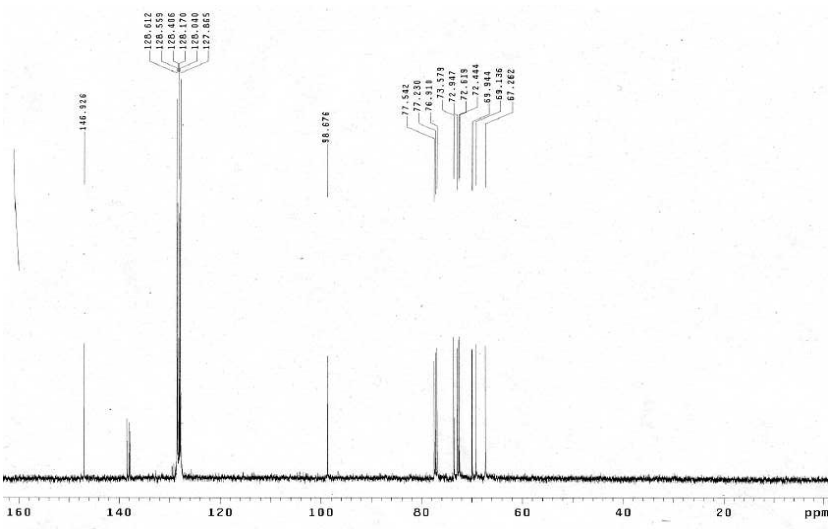

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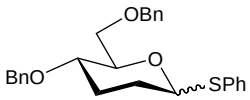
$^{1}$H NMR (400 MHz)

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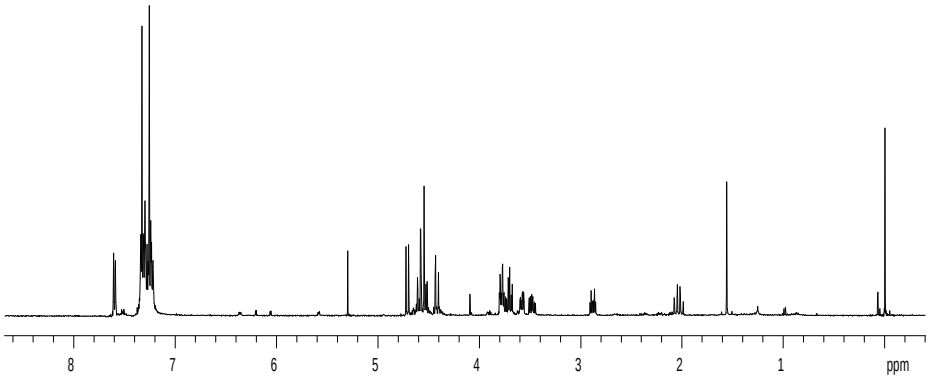


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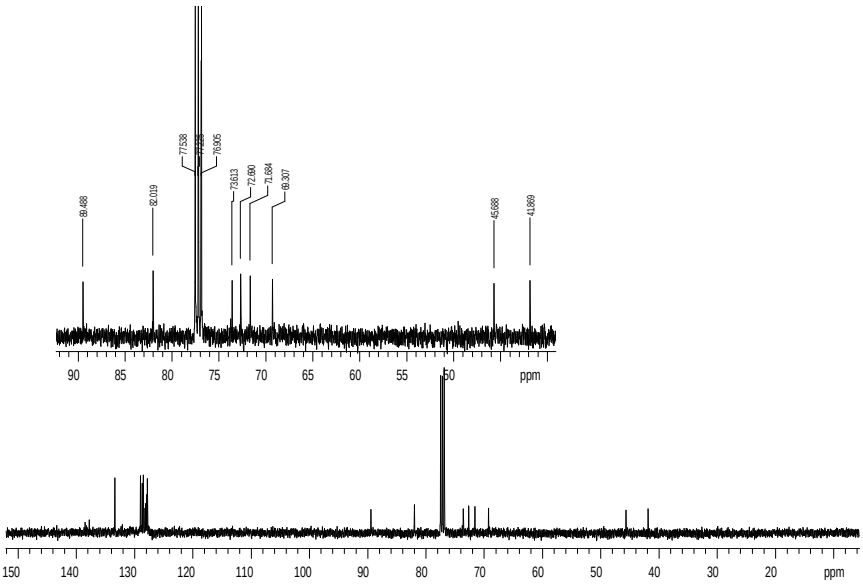

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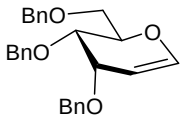


**57**

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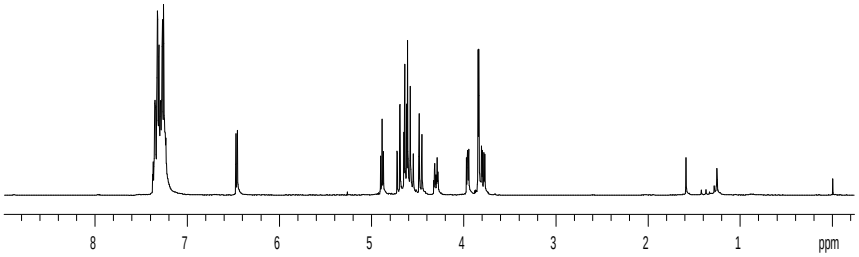


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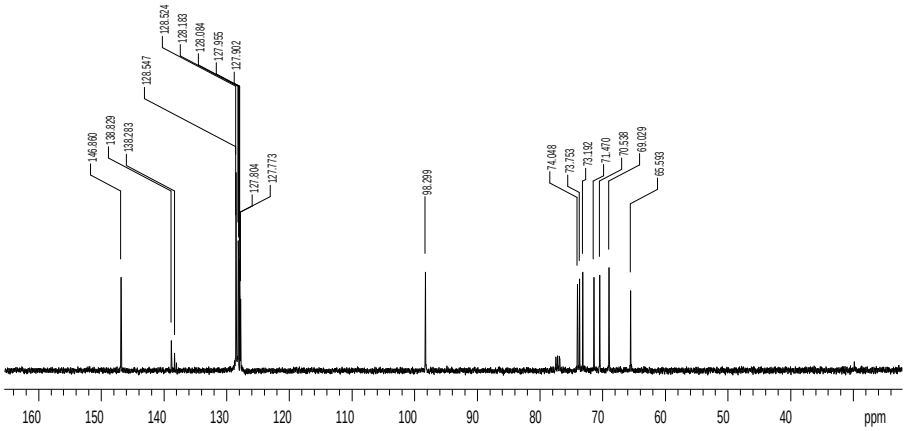

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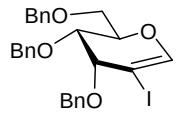


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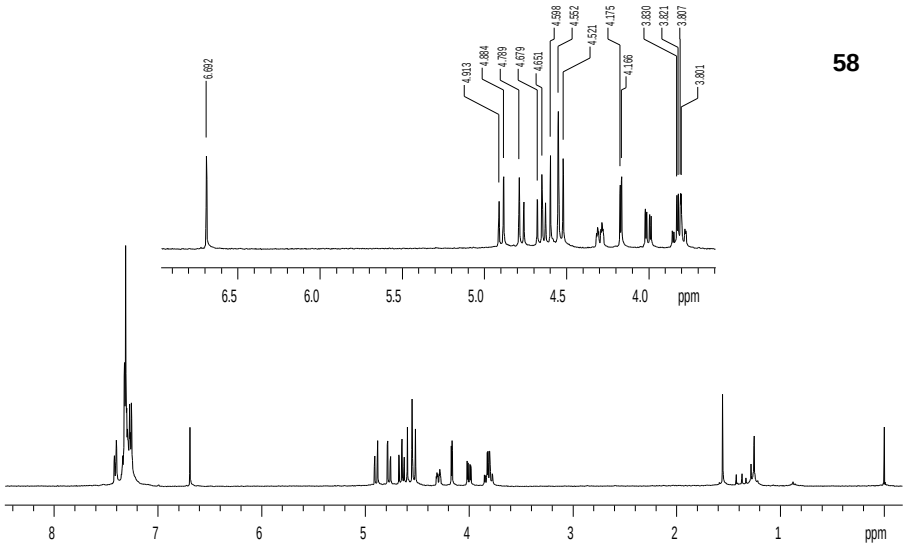
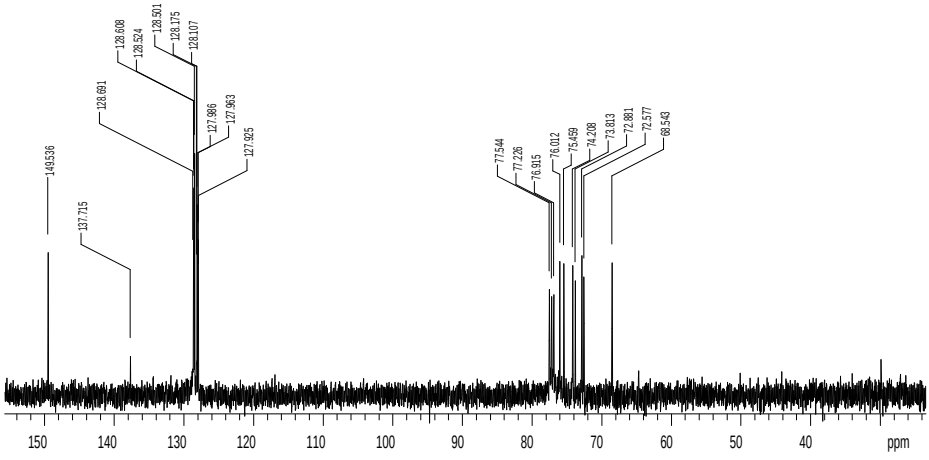



$^{13}$C NMR (100.6 MHz)



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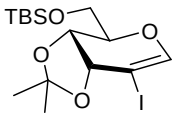
$^{1}$H NMR (400 MHz)

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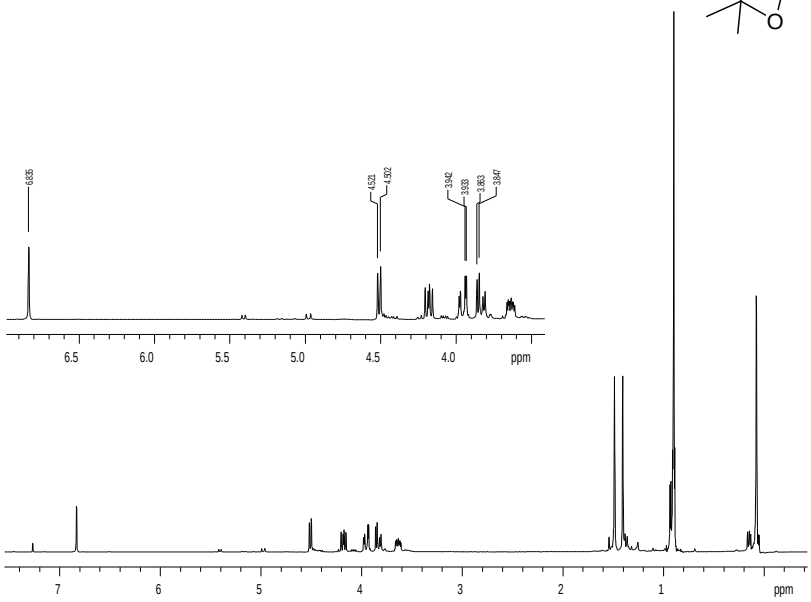


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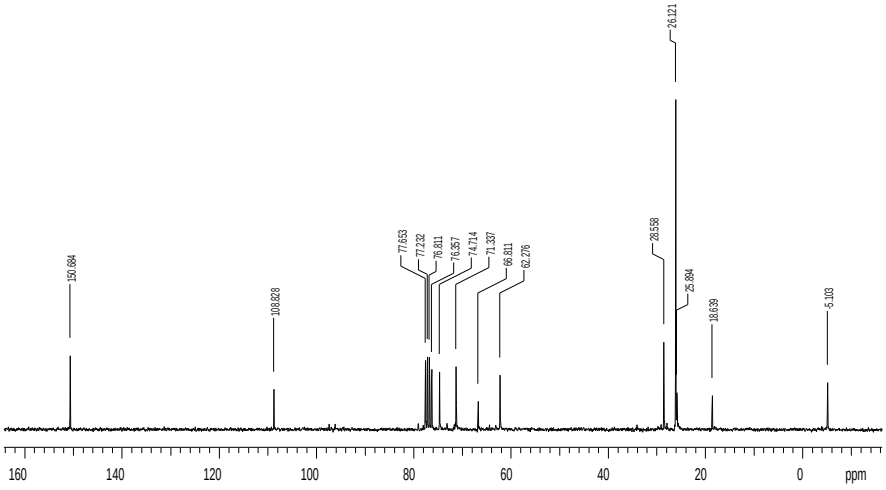

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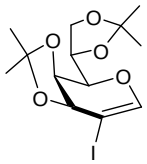
$^{1}$H NMR (400 MHz)



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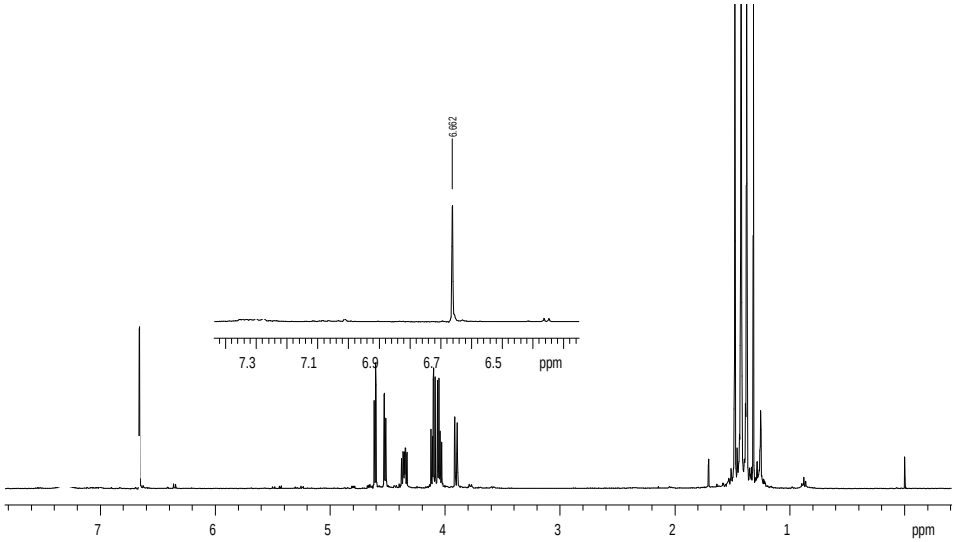


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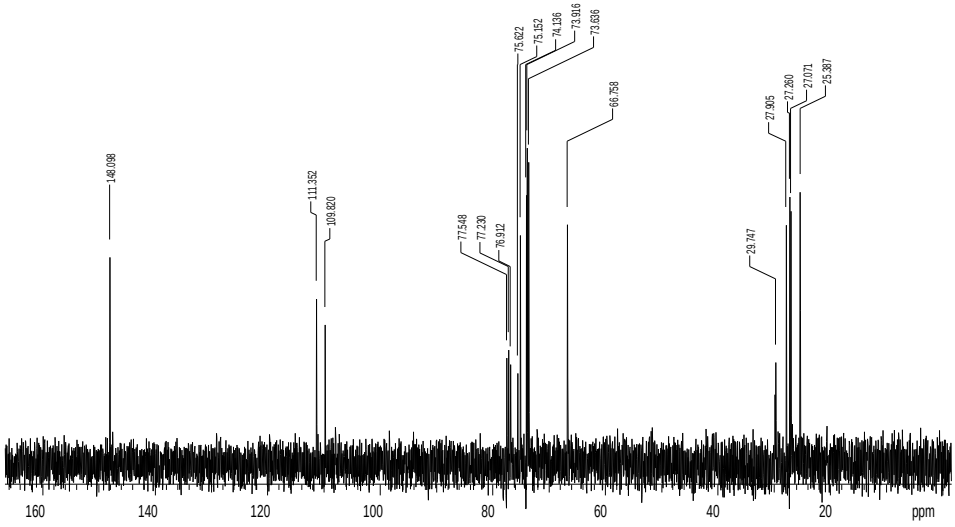

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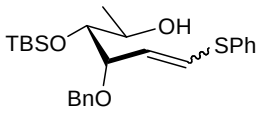


**103**

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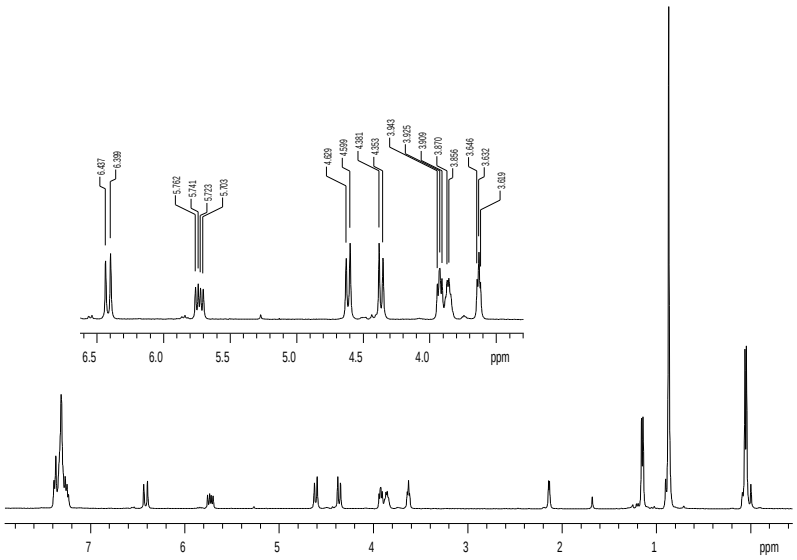


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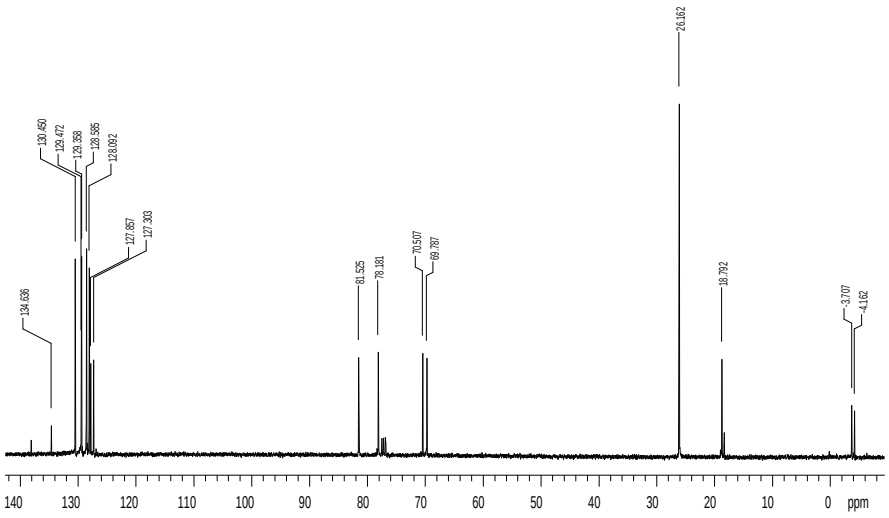

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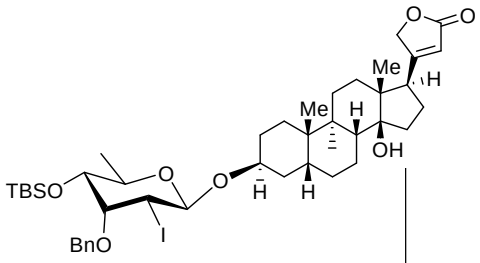
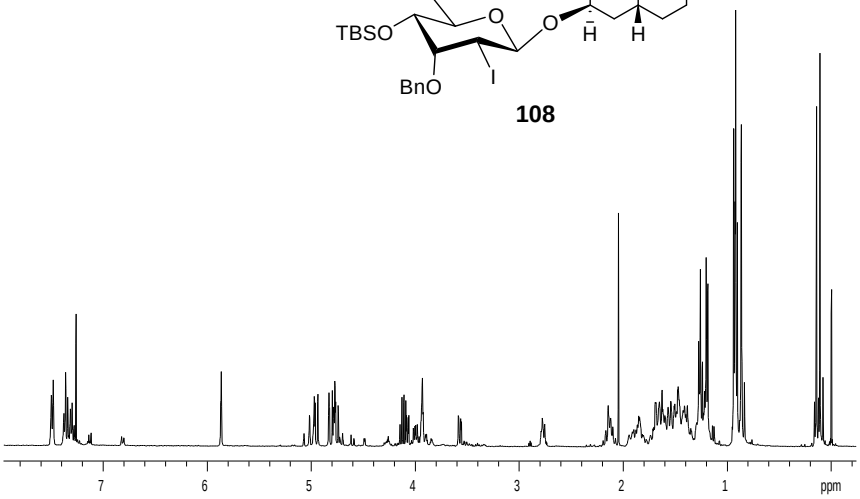



**108**




$^{13}$C NMR (100.6 MHz)