Asymmetric iodoetherification of isosorbide-derived glycals: A regio- and stereoselective access to a variety of *O*-substituted isosorbide derivatives

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Abstract: Isosorbide is a competitive starting material for various valuable derivatives by functionalization and/or substitution since it is a renewable and carbon neutral material that is produced on an industrial scale from sorbitol. A set of *O*-alkyl- or *O*-arylated beta-iodo ethers has been synthesized from isosorbide. The key step was the iodoetherification of isosorbide-derived glycals with a variety of oxygenated nucleophiles in the presence of *N*-iodosuccinimide. *trans*-Iodo ethers and acetate were obtained in good yields and the removal of iodide affords isosorbide derivatives. The usefulness of this new approach is illustrated by the synthesis of a surfactant having a dimer of isosorbide as hydrophilic group and by the preparation of a structurally unusual bicyclic anhydro carbohydrate.

Keywords: *Isosorbide / Glycal / Iodoetherification / β-Iodo ethers / Radical dehalogenation*

Introduction

In recent years, there has been a growing interest from both academia and industry to develop green materials from renewable resources. Biomass constitutes a pool of natural products which can be used as starting materials. Particularly isosorbide **1** is a compound of high importance since it is readily obtained from sorbitol by a double dehydratation and is thus a relevant product of the starch industry (Figure 1). Isosorbide **1** is highly stable, non-toxic, inexpensive and commercially available in large quantities. Moreover, it bears two hydroxyl groups that allow further chemical modification. Isosorbide **1** is thus an attractive and versatile chemical platform [1]. Isosorbide **1** and its less available diastereoisomers isomannide and isoidide have already been investigated as starting materials for the synthesis of chiral promoters in organic synthesis (Figure 1).

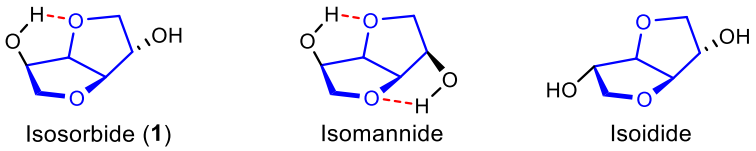


Figure 1: Isosorbide **1** and its diastereoisomers.

They have been used for the preparation of chiral ionic liquids [2-5] asymmetric phase-transfer catalysts [6] and ligands [7]. Isosorbide **1** and its derivatives have also been employed in medicine as vasodilators [8-10] and used for the synthesis of biodegradable polymers [11] plasticizers, solvents [12-17] and surfactants [18,19]. More recently, our group has been examining the use of isosorbide as starting material for the synthesis of novel amphiphilic compounds (Figure 2) [16-19]. The hydrophilicity of **1** has been evaluated and reveals that a single isosorbide moiety holds a fairly limited polarity and is not hydrophilic enough to balance the hydrophobicity of an alkyl chain longer than six carbons. Consequently, isosorbide has been rather used as a hydrophilic linker for the design of surfactants by being inserted between the lipophilic alkyl chain and the polar head [18,19].

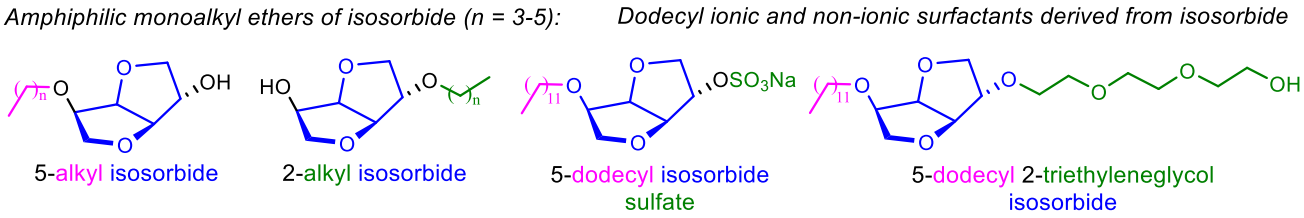


Figure 2: A variety of amphiphilic species derived from isosorbide.

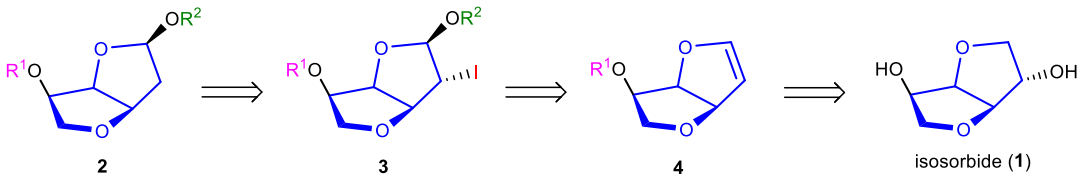
The synthesis and the amphiphilic properties of different agro-based surfactants bearing the isosorbide moiety have been recently reported: *i)* anionic surfactants with isosorbide inserted between a dodecyl alkyl chain and a sulfate group [18]. *ii)* non-ionic surfactants with isosorbide acting as a rigid hydrophilic linker bearing an aliphatic chain on one hydroxyl and various hydrophilic heads on the other one (Figure 2) [19]. To design a variety of amphiphilic species based on the isosorbide moiety, it would thus be of interest to have in hand a versatile and efficient synthetic pathway to derivatize the free alcohol function. In particular, the addition of hydrophilic bio-based scaffold, among which isosorbide, should be investigated.

In this context, we focused our interest on the use of the haloetherification reaction pioneered by Lemieux [20, 21] and Thiem [22, 23] for the haloalkoxylation of cyclic enol derived from sugar (glycal) and then for derivatives functionalization. Notably, the use of acetic acid as nucleophile affords the acetoxy intermediate [24]. This approach seems to be versatile and compatible with a wide range of functional groups and would provide a rapid access to a new class of molecules. In order to improve the amphiphilic properties of agro-based surfactants derived from isosorbide, we would like to report in the present paper the synthesis of β-iodo ethers by iodoetherification of isosorbide-derived glycals with oxygenated nucleophiles in the presence of *N*-iodosuccinimide (NIS). In addition, we have demonstrated the utility of these products by their transformation into valuable organic frameworks.

Results and Discussion

1. Retrosynthetic analysis

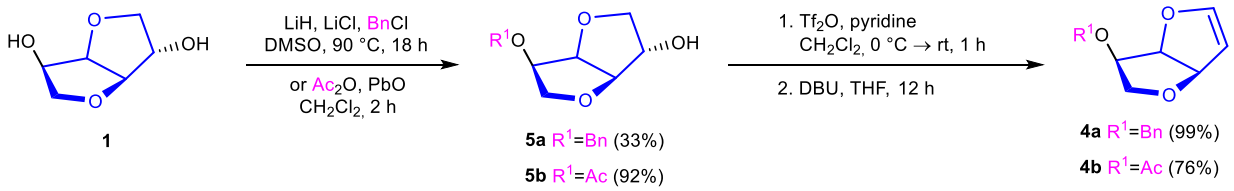
We envisioned to access to the β-iodo ethers **3** starting from a glycal intermediate (enol ether) **4** and various oxygenated nucleophiles. The glycal could be obtained from isosorbide **1** (Scheme 1).



Scheme 1. Retrosynthetic analysis.

The conversion of isosorbide **1** to valuable derivatives by functionalization and/or substitution of the hydroxyl groups is quite difficult because of the different configurations of the C-2 and C-5 positions, resulting in different reactivity and steric hindrance of both hydroxyl groups. Isosorbide **1** is an asymmetric V-shaped diol consisting of two fused tetrahydrofuran rings having the *cis*-arrangement at the ring junction (Figure 1). Therefore, the compound bears two sterically and electronically nonequivalent hydroxyl groups at C-2 and C-5 respectively in *exo*- and *endo*-orientation with respect to the V-shape molecule. The first one is more accessible whereas the second one is involved in an intramolecular hydrogen bond with the oxygen atom on the neighboring tetrahydrofuran ring [25].

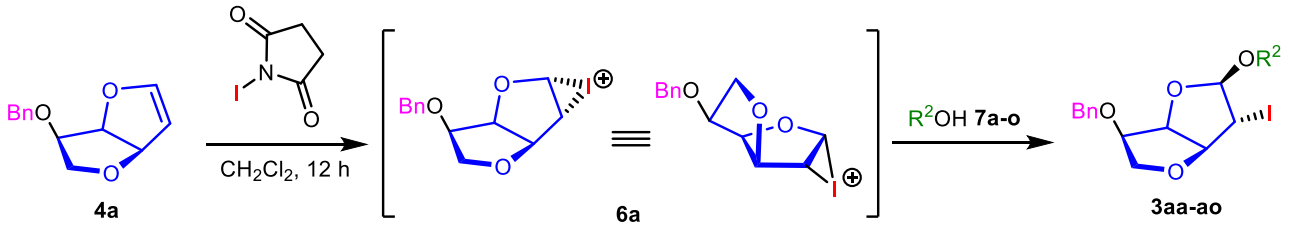
In order to carry out our approach, two different protecting groups, i.e. benzyl and acetyl, were selected to protect the hydroxyl at C-5 regioselectively. The C-5 monobenzyl ether **5a** was synthesized by direct selective benzylation of isosorbide **1** using benzyl chloride in presence of a mixture of lithium hydride and lithium chloride in DMSO (Scheme 2) [26]. In the same way, isosorbide **1** can be regioselectively monoacetylated at the *endo* position using acetic anhydride in the presence of catalytic amount of lead(II) oxide to afford **5b** in high yield [27]. Conversion to the corresponding glycals **4a** [7, 28] and **4b** [3, 4] was achieved by a two step process: preliminary conversion to their triflate derivatives followed by *in situ* elimination of the triflate moiety with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [29]. It is noteworthy to mention that glycals **4a,b** are stable under neutral conditions and could be purified by flash chromatography. Moreover, they could be stored in a freezer (–18 °C) under argon for weeks without noticeable decomposition. However acidic conditions promote a rearrangement that leads to the corresponding mono protected 2-furanylethanediol [30, 31].



Scheme 2. Synthesis of glycals **4a,b**.

2. Iodoetherification of glycals

Further haloetherification of glycals **4a** and **4b** with various oxygenated nucleophiles were investigated. As a model reaction, **4a** was first treated with NIS and methanol **7a** in CH_2Cl_2 [32]. After reaction completion, only one diastereoisomer was detected from the crude mixture by ^1H NMR. Purification by flash chromatography gave the β-iodo ether **3aa** in 78% yield (Scheme 3 and Figure 3).



Scheme 3. NIS mediated asymmetric iodoalkoxylation of glycal **4a**.

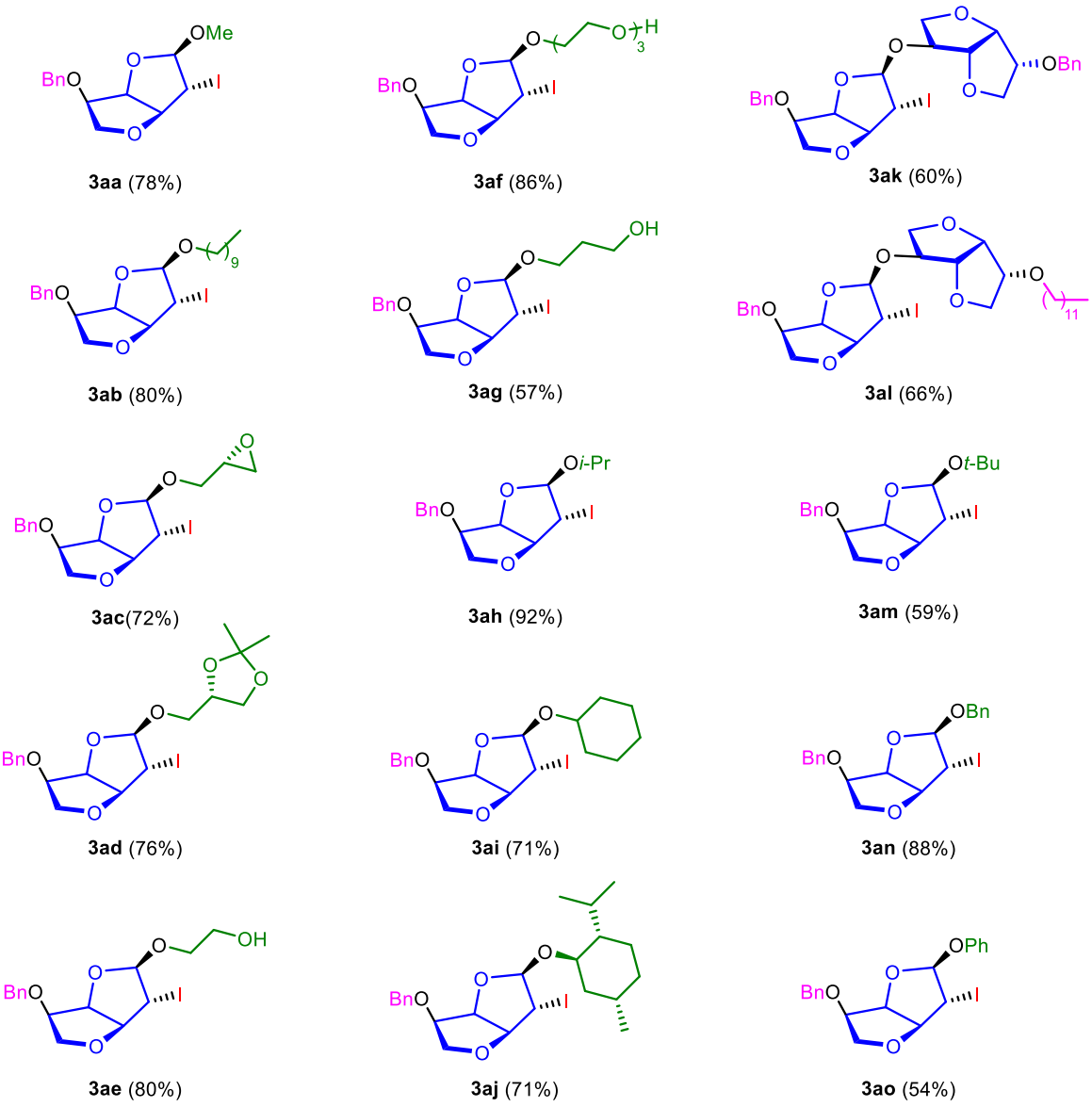


Figure 3. Compounds **3a** prepared.

To test the versatility of this methodology, a variety of alcohols was then screened. Primary alcohols such as decanol **7b**, (*S*)-glycidol **7c** and (*S*)-(+)-1,2-isopropylideneglycerol **7d** gave the corresponding products **3ab-ad** in good yields. Diols such as ethylene glycols **7e,f** and 1,3-propanediol **7g** led to the β-iodo ethers **3ae-ag** in moderate to good yields. In these examples, one can notice that no product from the addition of both hydroxyl groups to two glycal moieties could be isolated. Only the compounds bearing the free hydroxyl group at the end chain have been obtained. Sterically hindered alcohols **7h-m** also gave haloetherification products in the presence of NIS without a loss of reactivity, except for *tert*-butanol **7m**. In the case of isosorbide derivatives **7k** and **7l** acting as nucleophiles, "dimers" **3ak** and **3al** have been obtained in good yields. Benzyl alcohol **7n** reacted smoothly with glycal **4a** to afford compound **3an** bearing two similar protecting groups in high yield (88%) whereas phenol **7o** led to the phenoxy product **3ao** in only 54%.

The relative stereochemistry was determined by X-ray analysis on compound **3ak** and revealed a *trans* selectivity (Figure 4). The regioselectivity and the stereospecificity of the NIS-mediated addition of alcohol **7k** to glycal **4a** could be explained by the V-shape of the isosorbide derivative. Attack by NIS occurs on the sterically more favored α-face of the glycal whereas the approach of the reagent to the β-face is unfavored due to the steric hindrance (Scheme 3). The resulting iodonium ion **6a** is then attacked from the β-face by the alcohol to give **3ak** as the main product [33].

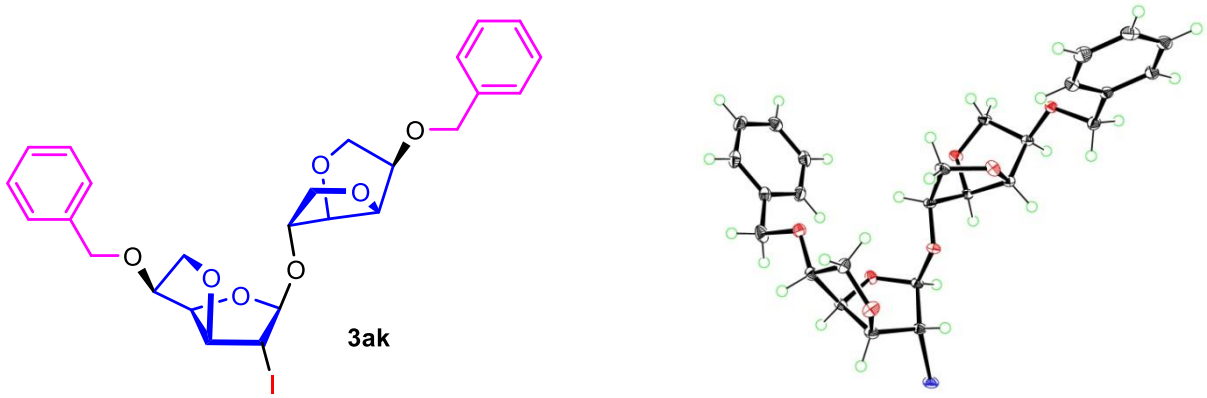
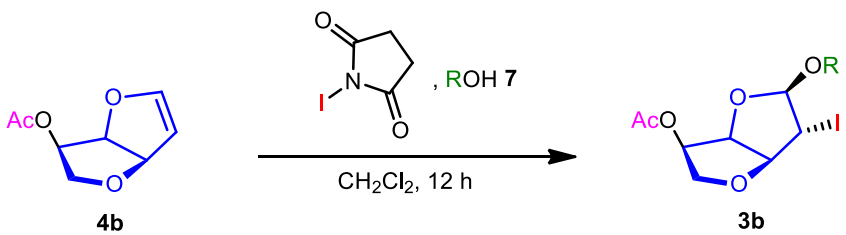


Figure 4. ORTEP plot of β-iodo ether **3ak**.

Iodoetherification of glycal **4b** was achieved in the same reaction conditions and β-iodo ethers **3ba**, **3be**, **3bh**, **3bk**, **3bl** and **3bn** were obtained in high yields and selectivity (Scheme 4 and Figure 5).



Scheme 4. NIS mediated asymmetric iodoalkoxylation of glycal **4b**.

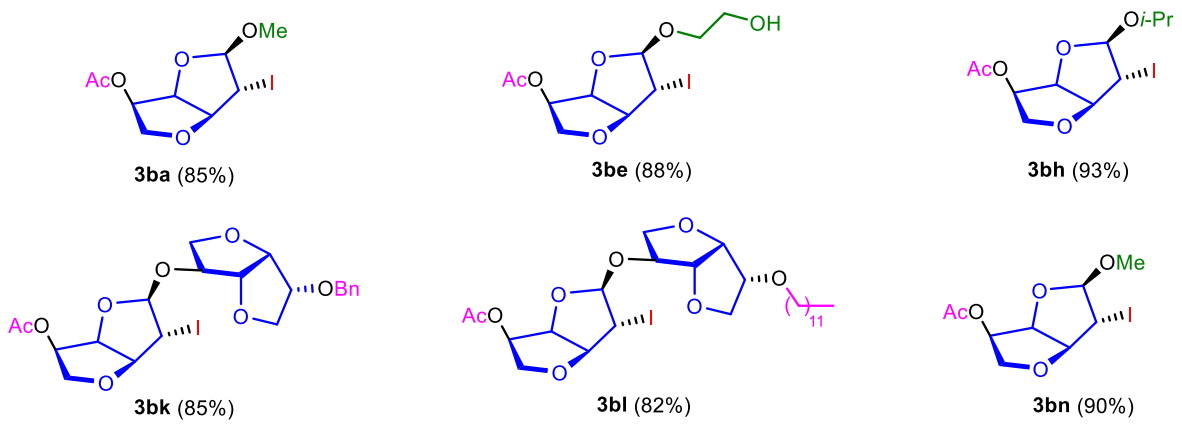
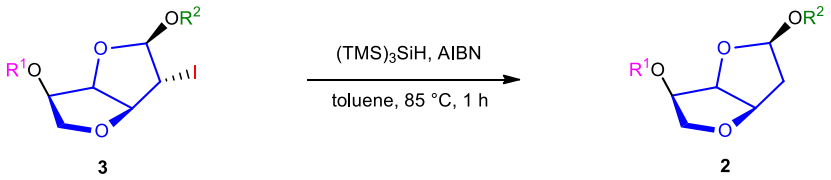


Figure 5. Compounds **3b** prepared.

3. Radical dehalogenation

With these new derivatives **3** in hand, their potential further transformations were next investigated. Iodide is an interesting element for functionalization but it could also be easily removed. Tris(trimethylsilyl)silane (TTMSS) is the most well-known alternative to tin hydride as a radical-based reducing agent for functional group modifications [34]. Radical deiodination of a structurally differentiated β-iodo ethers **3** was performed by TTMSS using azobisisobutyronitrile (AIBN) as initiator (Scheme 5). In all example iodide was cleanly removed to afford the deiodinated compounds **2aa**, **2ak**, **2al**, **2an**, **2ba**, **2bh**, **2bk**, **2bl** and **2bn** in high yields (83-99%) (Figure 6).



Scheme 5. Radical dehalogenation of **3**.

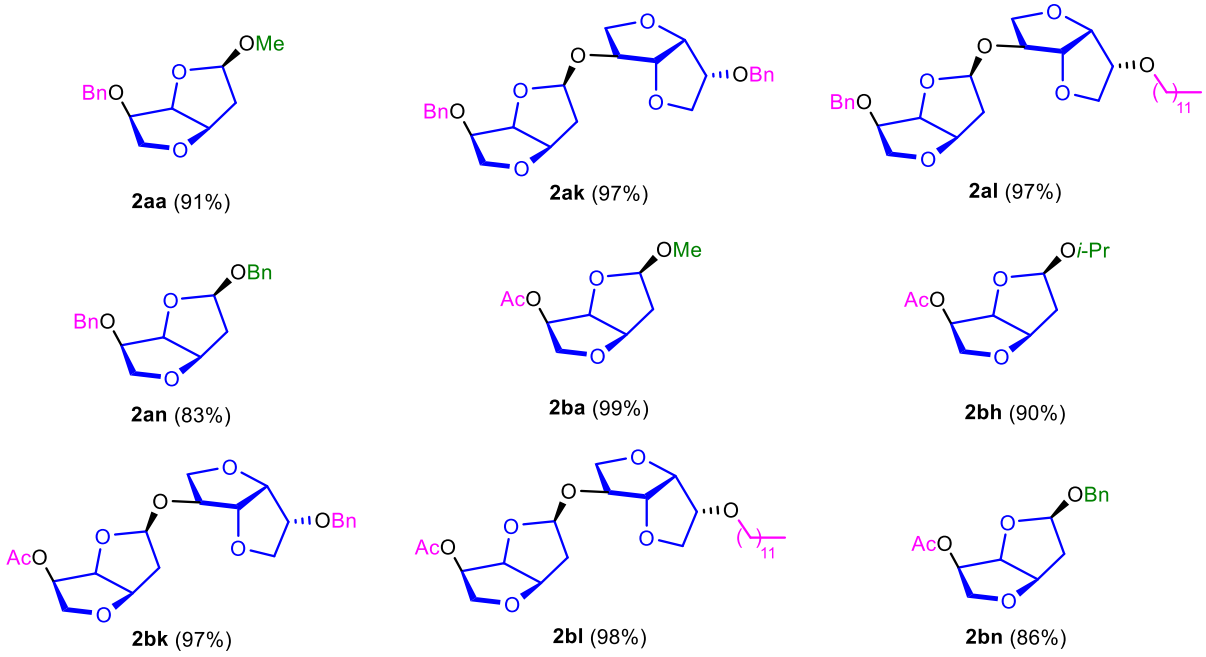
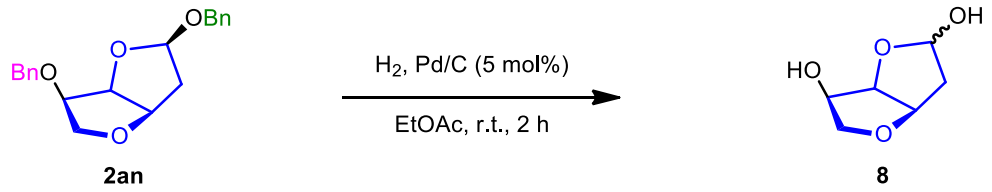


Figure 6. Compounds **2** prepared.

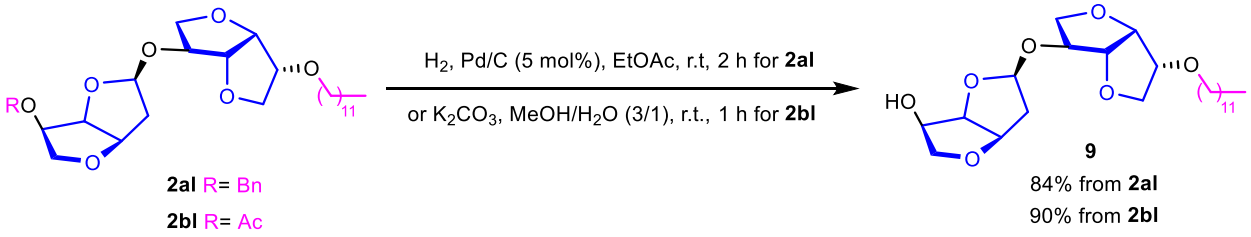
Finally, we were interested in the use of bisbenzylated compound **2an** which was obtained in two steps (73% overall yield) from glycal **4a** and appears as an excellent precursor to Saurospunol **8** (Scheme 6). Maytansinoids are a family of 19-membered macrocyclic lactams having extraordinary cytotoxic and antineoplastic activities and they are the products of the bacterium *Actinosynnema pretiosum* ssp *auranticum* ATCC 31565 [35,36]. Recently, a couple of unusual carbohydrates have been isolated from the carbohydrate portion of the solid-state fermentation extract of this bacterium and their structures have been assigned by NMR spectroscopy. Among them, the presence of Saurospunol **8** has been reported [37,38]. Hydrogenolysis of **2an** was successfully achieved in similar conditions described above to afford the unusual carbohydrate Saurospunol **8** as a mixture of anomers (Scheme 6). The spectroscopic data are in agreements with the literature [39].



Scheme 6. Hydrogenolysis and access to Saurospunol **8**.

4. Deprotection

We pursued investigations by removing the protecting groups to emphasize the utility of this approach. During the synthesis of glycals **4a,b**, two different protecting groups were selected (Scheme 2). Deprotection is exemplified on compounds **2al** and **2bl**. Benzyl was cleanly cleaved by hydrogenolysis in the presence of catalytic amount of palladium whereas the acetyl group was easily hydrolyzed under mildly basic conditions to afford amphiphilic “dimer” **9** derived from isosorbide (Scheme 7). In the aim to access to new agro-based surfactants, “dimer” **9** is a relevant example. Moreover, the free hydroxyl group is suitable for further functionalization.



Scheme 7. Deprotection of compounds **2al**, **2bl**.

Conclusion

In conclusion, an efficient approach has been developed for the iodoetherification of isosorbide-derived glycals. Iodide could be easily removed by radical dehalogenation and the generality of this approach provided a useful access to various derivatives of interest of this biosourced synthon. Further applications of this approach for the generation of suitably functionalized key scaffolds are in progress and the results of these investigations will be reported in due course.

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