

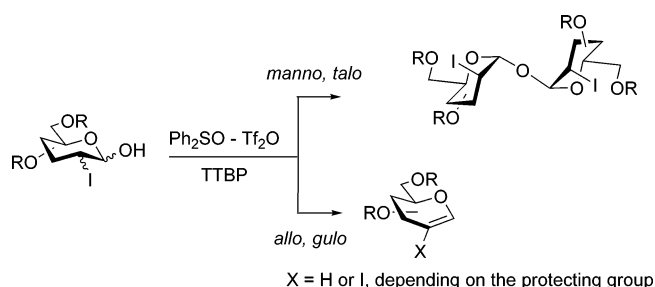
Synthesis of 2-Iodoglycals, Glycals, and 1,1'-Disaccharides from 2-Deoxy-2-iodopyranoses under Dehydrative Glycosylation Conditions

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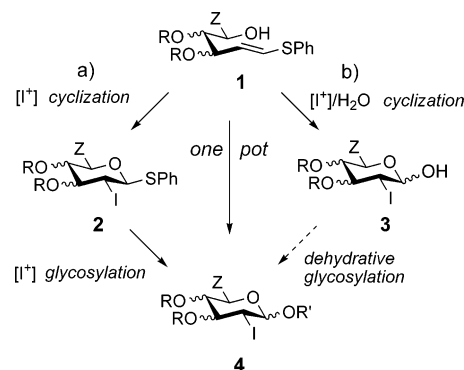
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Treatment of 2-deoxy-2-iodopyranoses under dehydrative glycosylation conditions afforded pyranose glycals, 2-iodoglycals, and 1,1'-disaccharides instead of the expected glycoside products. While the product distribution revealed that this reaction is very sensitive to the configuration of the 2-deoxy-2-iodopyranose, 2-iodopyranoid glycals can be obtained almost exclusively in good yields by employing 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group. The behavior of 2-deoxy-2-iodopyranoses during the dehydrative elimination reaction has been analyzed in detail.

Dehydrative glycosylation is an efficient glycosylation procedure that uses 1-hydroxysugars as glycosylating agents and diphenyl sulfoxide and triflic anhydride as activators to produce glycosides and disaccharides in good yields. These glycosylations proceed via an oxosulfonium intermediate that may evolve to an oxocarbenium ion with concomitant regeneration of diphenyl sulfoxide. The nucleophilic acceptor subsequently adds to the anomeric center to yield the desired glycosylated product in a *one-pot* procedure. Activated or deactivated glycosyl donors react equally well, and the procedure also allows for the *N*-glycosylation of amides.¹ This methodology includes iterative,² orthogonal,³ 1,2-*cis*,⁴ and catalytic activated⁵ glycosyla-

SCHEME 1. Glycosylation Procedures from Alkenyl Sulfanyl Derivatives 1



tions, but generally, preactivation of the glycosylating agent is required prior to addition of the acceptor.⁶

Recently, we reported the synthesis of 2-deoxy-2-iodohexopyranosyl thioglycosides **2** that are efficient glycosylating agents for the stereoselective synthesis of 2-deoxy-2-iodoglycosides and oligosaccharides **4**. The key step in the synthesis of these donors was the cyclization of alkenyl sulfanyl derivatives **1** with iodonium reagents (Scheme 1, path a).⁷ The reaction time and temperature had to be carefully controlled. Forcing reaction conditions to ensure full conversion usually resulted in the activation of the already formed thioglycoside **2**. Thus, variable amounts of the corresponding 2-iodolactol **3** were recovered usually after workup in unoptimized experiments with labile substrates. The reaction can be also performed in *one-pot* fashion from the sulfanyl alkene **1** by cyclization and in situ activation of the thioglycoside in the presence of the corresponding alcohol.⁸ This procedure avoids the formation of the 2-iodolactols.

We considered that the corresponding 2-iodolactols **3** could be directly obtained when performing the cyclization reaction in the presence of small amounts of water. 2-Iodolactols could be used for the dehydrative glycosylation procedure (Scheme 1, path b), in order to expand the synthetic scope of the 2-iodo derivatives and provide the basis for orthogonal glycosylation procedures.³ Initially, phenylsulfanylalkene **5** was reacted with NIS in wet CH₃CN to access 2,6-dideoxy-2-iodopyranose **6**, a precursor in the synthesis of oligosaccharides present in natural products such as digitoxine. Compound **6** was treated with Tf₂O, Ph₂SO, and 2,4,6-tri-*tert*-butylpyrimidine (TTBP) in CH₂Cl₂ at –60 °C. Surprisingly, the product was partially transformed

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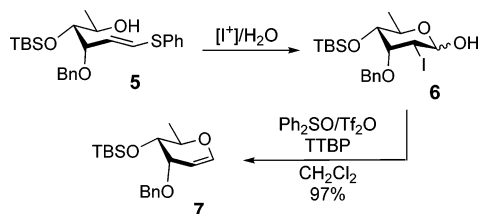
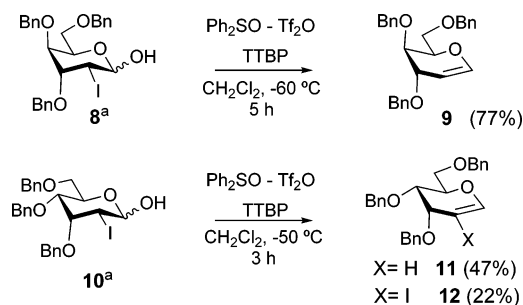
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SCHEME 2. Dehydrative Elimination Reaction in 2,6-Dideoxy-2-iodopyranoses

SCHEME 3. Synthesis of Glycols by Dehydrative Elimination^a

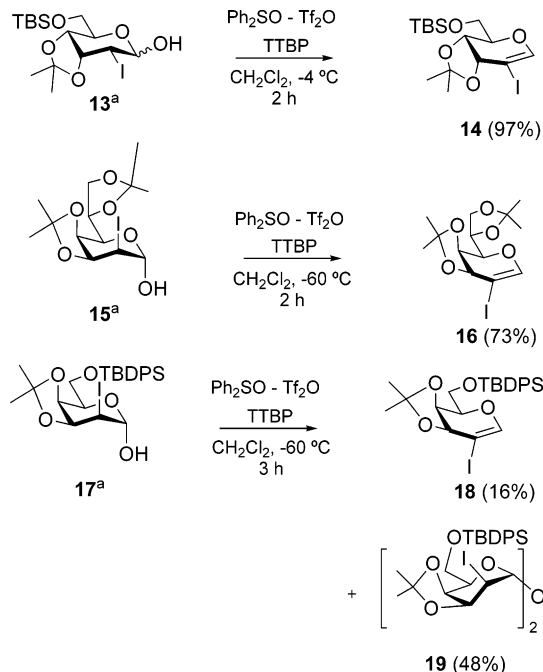
^a 2-Deoxy-2-iodopyranoses synthesized from the corresponding phenyl-sulfanyl alkenes.

within a few minutes into a new compound, even before adding a nucleophile. Glycol **7** was obtained in excellent yield after 1 h (Scheme 2). To avoid this elimination, lower temperatures (-80 to -100 °C), less base (1 to 3 equiv of TTBP), and different dehydrative promoters (BSP,⁹ alkyl sulfides) were tested, but all yielded the same glycol.

We recently demonstrated that glycols can be easily and efficiently obtained by treating 2-deoxy-2-iodo-1-thioglycosides **2** under reductive-elimination conditions.¹⁰ However, glycol **7** must be formed via a completely different mechanism. To elucidate the reaction mechanism we prepared a set of 2-deoxy-2-iodo-pyranoses with *gulo*-**8**, *allo*-**10**, **13**, *talo*-**15**, **17**, **22**, and *manno*-**20** configuration by treating the corresponding phenyl sulfanyl alkenes^{7b} (or glycols) with NIS in wet CH_3CN .

Thus, 2-iodolactols **8** and **10** were subjected to dehydrative conditions to afford the corresponding glycols **9** and **11** (Scheme 3). In the case of ribo derivative **10**, 2-iodoglycol **12** was obtained in minor amounts (22% yield). In order to confirm that glycol **11** was not derived from 2-iodoglycol **12**, following isolation, **12** was submitted to dehydrative elimination conditions. Recovery of iodoglycol **12** indicated that it was formed in an irreversible way.

Interestingly, isopropylidene-protected iodolactols **13** and **15** rendered exclusively the 2-iodoglycols **14** and **16** in good to excellent yield (Scheme 4). In the case of 2-deoxy-2-iodopyranose **17**, minor amounts of 2-iodoglycol **18** were also obtained, together with 1,1'-disaccharide **19**. The presence of the isopropylidene group is crucial for obtaining 2-iodoglycols in good yield as can be deduced by comparing the configurationally identical compounds **10** and **13**. A singlet at ~ 6.8 ppm assigned to H1 in the ^1H NMR spectra, and two signals at ~ 148 ppm

SCHEME 4. Synthesis of 2-Iodoglycols by Dehydrative Elimination^a

^a 2-Deoxy-2-iodopyranose synthesized from the corresponding phenyl-sulfanyl alkenes.

and ~ 75 ppm assigned to C1 and C2, respectively, in the ^{13}C NMR spectra indicated the formation of the 2-iodo-substituted double bond.

Glycols and 2-iodoglycols are versatile synthetic intermediates. Insertion of substituents in C1 structures by deprotonation (C-glycosides, quinones)¹¹ or introduction of C2 vinyl substituents by Heck-type reaction¹² yield iso-C-glycosides. Iodine is preferable over chlorine or bromine for these reactions.¹³ However, only one synthesis dealing with 2-iodoglycols has been disclosed to date.¹⁴

Manno-**20** and *talo*-**22** derivatives were reacted under the same conditions to give 1,1'-disaccharides **21** and **23**, respectively, resulting from the self-condensation of the starting 2-iodolactols (Scheme 5).

The conversion of compound **I** to **III** (Scheme 6) represents an overall base-assisted hydroxyl elimination process¹⁵ that might be occurring through the initial 1-OH activation followed by elimination of Ph_2SO and tri-*tert*-butylpyrimidinium triflate (TTBPHOTf) to render 2-iodoglycol **III**. Similarly, the production of **IV** might be explicable in terms of nitrogen assisted iodine elimination in **II** to afford the corresponding glycol¹⁶ (Scheme 6). Further credence to this hypothesis is provided by the fact that only *N*-containing bases¹⁷ such as TTBP, or

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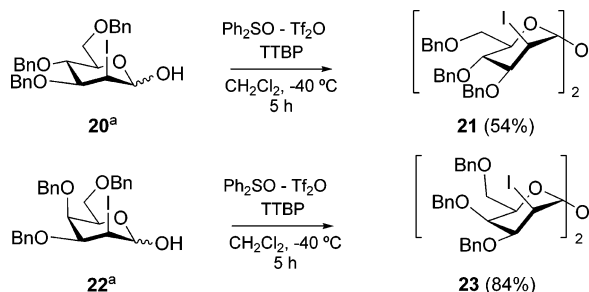
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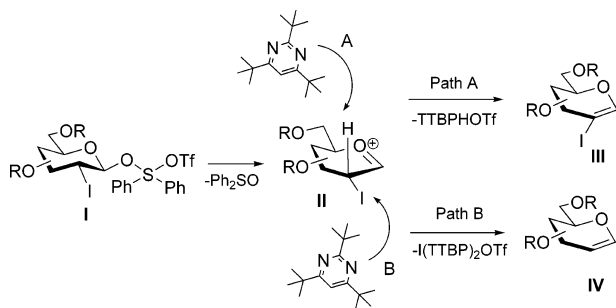
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SCHEME 5. Synthesis of 1,1'-Disaccharides by Dehydrative Elimination^a

^a 2-Deoxy-2-iodopyranose synthesized from the corresponding phenyl-sulfanyl alkenes.

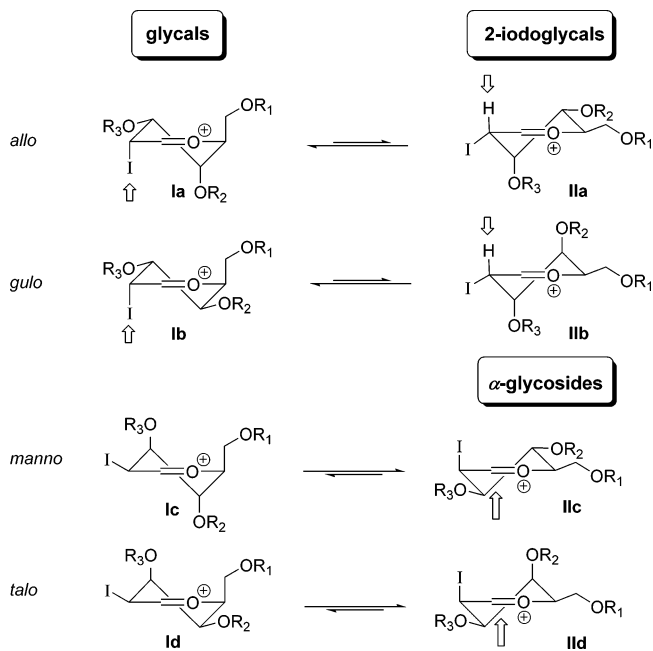
SCHEME 6. Plausible Mechanism for Product Distribution during Dehydrative Elimination of 2-Deoxy-2-iodopyranoses



phosphazene P_4 -*t*-Bu, that are able to stabilize $[I^+]$ species afforded glycals, while *t*-BuOK failed and no reaction products were detected.

According to these results, the chairlike oxocarbenium intermediates **Ia–d** and **IIa–d** (Scheme 7) play an important role for the chemoselectivity of dehydrative elimination reactions. Moreover, intermediates **Ia,b** (allo and gulo) and **IIc,d** (manno and talo) that contain axial iodine are likely to be more stable than the corresponding equatorial iodine conformers due to stabilizing hyperconjugative interactions between $\sigma C-I$ and $\pi^* C-O$ of the oxocarbenium.¹⁸ Furthermore, during the E1 elimination reaction, the new double bond can only form when the vacant p orbital of the carbocation and the breaking C–H or C–I bond are aligned in parallel. Therefore, the group to be eliminated must be in the axial position. Consistent with this view, dehydrative elimination of the gulo-configured 2-deoxy-2-iodopyranose **8** proceeded through the more stable conformer **Ib** and elimination of the axial iodide provided glycal **9** in excellent yield. Similarly, axial iodine elimination of allo-configured 2-deoxy-2-iodopyranose **6** in the more stable conformation **Ia** rendered exclusively glycal **7**. In this case, the equilibrium between conformers is considerably shifted toward **Ia** due to destabilizing gauche effects between the TBS¹⁹ group

SCHEME 7. Stereochemical Courses of Dehydrative Elimination of 2-Deoxy-2-iodopyranoses



(OR₂) and the C-6 substituent (OR₁) in conformer **IIa**. In the case of tri-*O*-benzyl-protected allo-configured 2-deoxy-2-iodopyranose **10**, the elimination mainly proceeded through the more stable intermediate **Ia** to render glycal **11**. However, a minor amount of conformer **IIa** also reacted to give 2-iodoglycal **12**.

Dehydrative glycosylation of 2-deoxy-2-iodopyranoses of manno (**20**) and talo (**22**) configurations afforded the 1,1'-disaccharides **21** and **23**, respectively, as single α -anomers. In this case, self-condensation of the 2-deoxy-2-iodopyranoses from the more stable conformer **IIc,d** is faster than elimination.

Particularly, allo- and gulo-configured glycosylating agents afforded only glycals and 2-iodoglycals, while manno and talo sugars yielded disaccharides. This finding can be explained by the presence of steric interactions between the C-6 substituent (OR₁) and the incoming nucleophile in the most stable conformer **Ia,b** (allo and gulo) when compared with **IIc,d** (manno and talo), where such destabilizing interactions do not exist (Scheme 7). These findings highlight the critical role the 2-deoxy-2-iodopyranose configuration exerts on this new dehydrative elimination process.

Finally, in order to rationalize the observed chemoselectivity of the 2-deoxy-2-iodopyranoses bearing a 3,4-*O*-isopropylidene protecting group, we considered that the reaction might operate by way of a constrained conformation²⁰ such as **III** and **IV**, upon which highly favored proton elimination may occur instead of the opposite iodine abstraction (Figure 1).²¹

In summary, despite the fact that dehydrative glycosylation has proved to be an efficient and general glycosylation method, its application to 2-deoxy-2-iodopyranoses did not always afford the expected products. The treatment of 2-deoxy-2-iodopyra-

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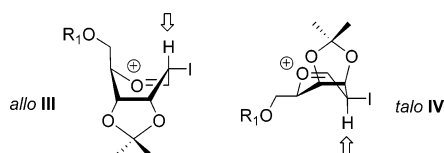


FIGURE 1. Stereochemical features in dehydrative eliminations of activated 2-iodolactols.

noses using dehydrative glycosylation conditions afford glycols, 2-iodoglycols, and self-condensation disaccharides depending on the configuration of the starting 2-deoxy-2-iodopyranoses and the protecting groups. Thus, allo- and gulo-configured compounds afforded glycols, while manno and talo derivatives gave glycosylated products. Moreover, 2-iodopyranose glycols can be obtained in mostly good yield by employing 3,4-*O*-isopropylidene protecting groups. A detailed analysis of the fate of 2-deoxy-2-iodopyranoses during dehydrative glycosylations provided insight into the mechanism of this process.

Experimental Section

General Procedure for Dehydrative Elimination from 2-Iodopyranoses. A mixture of the 2-iodolactol product (1.0 mmol), prepared by treating sulfanyl alkenes or glycols with NIS–water

in acetonitrile, Ph_2SO (2.0 mmol), and TTBP (3.0 mmol) in $\text{CH}_2\text{-Cl}_2$ (0.04 M to iodolactol) were stirred over flame-dried molecular sieves for 30 min, after which the reaction mixture was cooled to $-60\text{ }^\circ\text{C}$. TiF_4 (1.0 mmol) was added, and the mixture was first brought to $-40\text{ }^\circ\text{C}$ and then slowly warmed to the completion of 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.

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Supporting Information Available: General experimental methods, experimental procedures, compound characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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