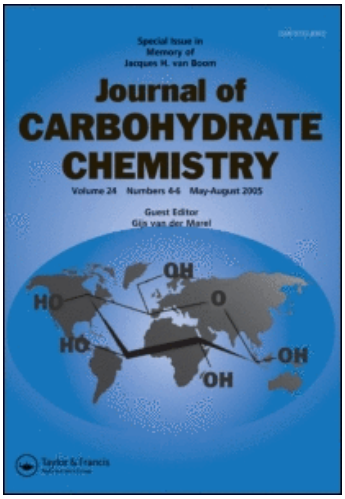

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COMMUNICATION

"HETEROGLYCALS" AS NEW POTENTIAL GLYCOSIDASE INHIBITORS. SYNTHETIC APPROACHES FROM D-ARABINOSE[1]

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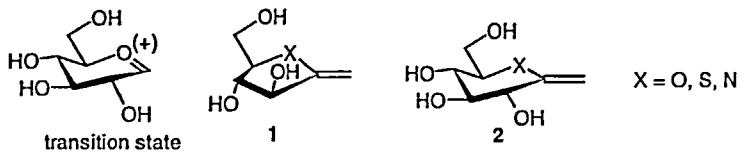
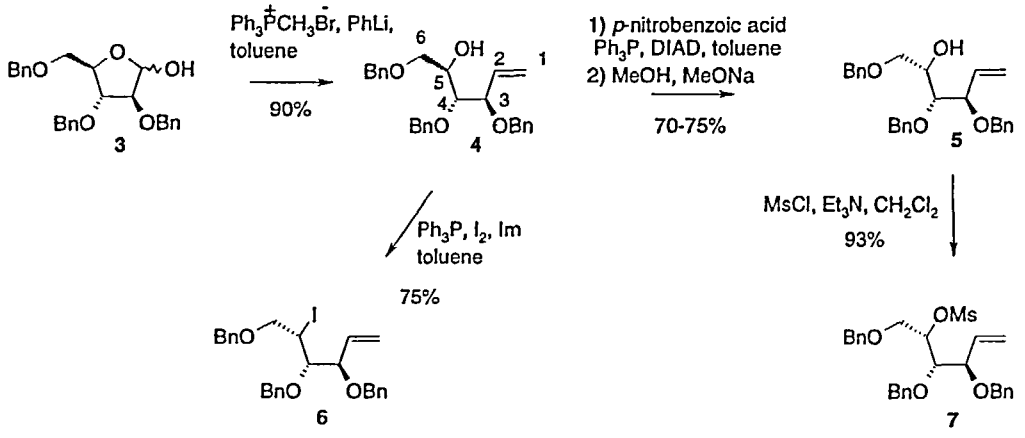
Within the frame of an ongoing project on glycosidase inhibitors, we have been interested in the synthesis of "heteroglycals", namely, glycal analogues with sulfur or nitrogen in the ring. Glycals[2] are well known for their applications in sugar chemistry in particular for glycosyl transfer.[3] They are also known as glycosidase inhibitors through a slow chemical reaction with the enzyme. Recently *exo*-glycals emerged as a new class of glycals[4] which showed interesting features as glycosidase inhibitors but also as precursors of glycomimetics such as *C*-glycosides.[5] We have undertaken investigations on related heteroglycals: such compounds are of interest because they combine a planar geometry at the anomeric center and a possible charge site - both elements known to be important to mimic the transition state of the enzymatic glycoside hydrolysis process.[6]

In addition, heteroglycals might offer novel synthetic opportunities for example as precursors to hetero-*C*-glycosides. Our attention has been focused initially on hetero-*exo*-glycals **1** and **2** which could be derived from D-arabinose and D-glucose. In a first approach our project started with D-arabinose chemistry.

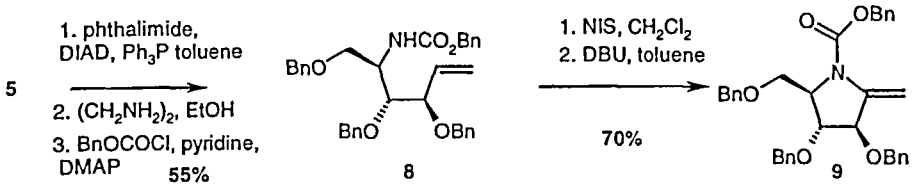


We have taken advantage of a well described Wittig reaction on 2,3,5-tri-*O*-benzyl-D-arabinofuranose **3**[7] to prepare our starting open-chain hexenitol **4** in good yield. In order to introduce nitrogen or sulfur at C-5 with retention of configuration, a double inversion of the configuration was required. Two different routes were explored for the first inversion: the Mitsunobu reaction[8] and the Garegg-Samuelsson procedure.[9] These reactions gave compounds **5** and **6**, respectively, in good yields.

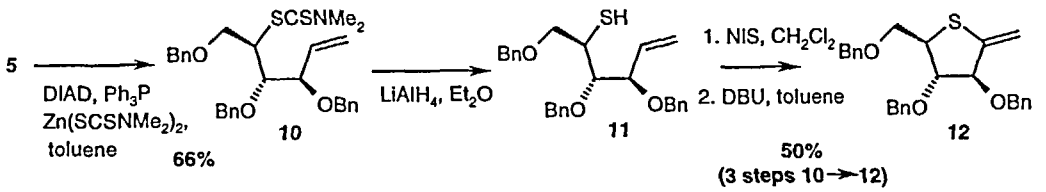


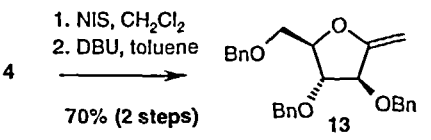
By providing the L-*xylo* iodohexenitol **6**, the Garegg-Samuelsson procedure achieved in one step inversion and activation of position C-5 toward nucleophilic substitution. We have tested substitutions on **6** with diverse nucleophiles (NaN_3, KSAc, KSCSOEt, $BnNH_2$, BnSH) under various conditions but in none of these cases was any substitution observed. In most cases eliminations took place instead. As this route failed, we investigated the substitution of the hydroxyl group in L-*xylo* hexenitol **5**. After activation of this group as a mesylate (**7**) in excellent yield, all attempted substitutions failed. However, the C5 OH group of **5** was eventually replaced with either nitrogen or sulfur by way of Mitsunobu reactions. Nitrogen was introduced into **5** *via* a phthalimide[10] in 65-70% yield; a slightly better yield of 73 % could be obtained using tetrachlorophthalimide,[11] a much more acidic reagent. Deprotection of the imide using

hydrazine[12] led to partial reduction of the double bond. Using ethylenediamine,[13] a clean deprotection was realized in nearly quantitative yield. Subsequent protection of the primary amine as a benzyloxycarbamate gave compound **8** in 55% overall yield (3 steps).



Sulfur was much more difficult to introduce than nitrogen. Mitsunobu conditions[14] involving thioacetic and thiobenzoic acid failed. We also tested some sulfur-containing salts such as potassium thioacetate, thiocyanate and ethyl xanthate but none of them succeeded. Only with ziram[15] could the desired reaction be achieved in 66% yield. Reduction of the dithiocarbamate group was performed with $LiAlH_4$ to afford the thio analog of **4**, which was used without purification in the cyclisation step.





NIS electrophilic activation is a well known procedure for the cyclisation of γ-hydroxyalkenes[16] as well as aminoalkenes,[17] but less common for the sulfur analogs. The conversion of **4**, **8** and **11** into *exo*-glycal **13**[18] and into the corresponding imino- and thio-*exo*-glycals **9** and **12**, respectively, was achieved by NIS-mediated cyclisation, followed by dehydrohalogenation of the resulting iodomethyl derivatives using DBU. The final products were obtained in moderate to good yields. The lower yield of the thio derivative **12** may be attributed to some degradation of the intermediate α-iodomethyl sulfide.

These hetero-*exo*-glycals[19] clearly demonstrate the feasibility of this approach to such original furanoid compounds.[20] We are currently exploring and developing the chemical applications of these molecules and the scope of their chemical reactivity.

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20. Selected data for final compounds: **NIS cyclisation**: Cyclisations of the hexenitols **4**, **8**, **11** were performed in dry dichloromethane with *N*-iodosuccinimide (NIS, 1.1 eq) at room temperature. Reactions were monitored by TLC. Purifications were effected by flash chromatography on silica gel using a petroleum ether-ethyl acetate mixture. **Eliminations**: Eliminations were performed in refluxing toluene

with DBU (5 eq) as base under argon. Reactions were monitored by ^{1}H NMR as compounds had the same R_f value on TLC plates. NMR signals were assigned by ^{1}H-^{1}H and ^{1}H-^{13}C correlation experiments. **9**: ^{1}H NMR ($CDCl_3$, 250 MHz) : δ 3.74 (dd, 1H, $J_{6b,6a}$ = 10.2 Hz, $J_{6b,5}$ = 9.1 Hz, H-6b), 3.8-3.9 (m, 1H, H-6a), 4.17 (s, 1H, H-3), 4.30 (s, 1H, H-4), 4.46-4.78 (m, 9H, H-1, H-5, H-Bn), 5.21 (d, 1H, J = 12.3 Hz, H-Bn), 5.32 (d, 1H, J = 12.3 Hz, H-Bn), 7.3-7.5 (m, 20H, Ph-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 64.8 (C-5), 67.4 (C-Bn), 68.6 (C-6), 70.3 (C-Bn), 71.0 (C-Bn), 73.1 (C-Bn), 79.2 (C-3), 83.4 (C-4), 92.1 (C-2), 97.6 (C-1), 125.8, 127.5, 127.6, 127.7, 127.75, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 136.0, 137.6, 137.7, 138.2, 143.2, 152.3 (CO). MS (ISP) *m/z* 572 $(M+Na)^+$, 567 $(M+NH_4)^+$, 550 $(M+H)^+$. **12**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.55 (dd, 1H, $J_{6a,6b}$ = 12.8 Hz, $J_{5,6b}$ = 10.2 Hz, H-6b), 3.75-3.84 (m, 2H, H-5, H-6a), 4.07 (dd, 1H, $J_{4,3}$ = 3.8 Hz, $J_{4,5}$ = 3 Hz, H-4), 4.38 (d, 1H, H-3), 4.51 (s, 2H, H-Bn), 4.52 (d, 1H, J = 11.9 Hz, H-Bn), 4.64 (s, 2H, H-Bn), 4.69 (d, 1H, J = 11.9 Hz, H-Bn), 5.22 (s, 1H, H-1trans), 6.3 (s, 1H, H-1cis), 7.27-7.4 (m, 15H, Ph-H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 65.4, 71.1, 72.0, 72.1, 73.2, 83.5, 87.0, 107.9 (C-1), 127.7, 127.8, 127.9, 128.0, 128.5, 128.6, 137.8, 137.9, 138.1, 145.1 (C-2). MS (ISP) *m/z* 471 $(M+K)^+$, 455 $(M+Na)^+$, 449$(M+NH_4)^+$, 433 $(M+H)^+$.