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The 4-nitrobenzenesulfonyl group as a convenient N-protecting group for iminosugars—synthesis of oligosaccharide inhibitors of heparanase ☆

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ABSTRACT

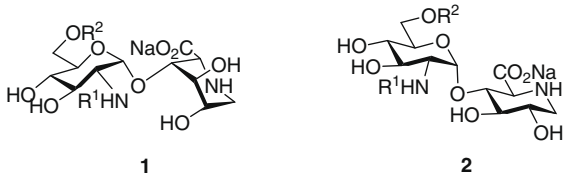
The 4-nitrobenzenesulfonyl (nosyl) group can be used advantageously for the protection of the ring nitrogen atom of iminosugars. This group is conveniently introduced, is stable to most of the standard carbohydrate transformations and can be removed under mild conditions. The applicability of the nosyl group is demonstrated by the synthesis of sulfated oligosaccharides which are inhibitors of the enzyme, heparanase. The *N*-(4-nitrobenzenesulfonyl) group is orthogonal with the azido function.

Heparan sulfate proteoglycans (HSPGs) are ubiquitous constituents of the extracellular matrix and cell membrane structures.[1] The structure of HSPG consists of a protein core to which several linear heparan sulfate (HS) chains are linked by *O*-glycosidic bonds. HS binds to a multitude of proteins thereby influencing a variety of normal and pathological physiological processes, including tumor growth and metastasis, tissue repair, angiogenesis, and inflammation.[2] Cleavage of HS chains is expected to alter its interaction with proteins and thus influence the above biological processes. HS is a member of the glycosaminoglycan family of polysaccharides; it consists of alternating uronic acid (either D-glucuronic or L-iduronic acid) and D-glucosamine units which are connected by (1→4) linkages. The enzyme, heparanase, is an *endo*-β-glucuronidase that cleaves heparan sulfate side-chains at a limited number of sites.[3] The cleavage of heparin and heparan sulfate by heparanase plays a crucial role in a number of biological processes, including cell invasion, angiogenesis, inflammation, and tissue remodeling.[3a,4] The expression level of heparanase has been correlated with the survival time of cancer patients.[5] The inhibition of heparanase forms the basis of potential antimetastatic cancer therapy, and it has therefore been intensively investigated.[6]

Iminosugars are monosaccharide analogs which possess a nitrogen atom instead of oxygen in the ring, and have received significant attention as carbohydrate mimics.[7] Compounds of this type, such as 1-deoxynojirimycin, are potent inhibitors of glycosidases, and have been investigated for their therapeutic potential as antidiabetic, antiviral, and anticancer agents. Though monosaccharidic iminosugars, in general, show some specificity to inhibit certain types of glycosidases, this specificity is still fairly broad, which limits their potential therapeutic applications. One way to increase specificity is to use larger sized molecules which are closer mimics of the natural substrates of the enzymes. Thus, oligosaccharides containing an iminosugar component have been synthesized for various biological purposes.[8]

In order to incorporate specificity in iminosugars toward heparanase we have designed pseudooligosaccharides mimicking the structure of heparin and heparan sulfate (Fig. 1).[9] The syntheses of related aza-analogs of heparin disaccharides[10] as well as interglycosidically *S*-linked oligosaccharides[11] have been reported recently for similar purposes.

Compounds **1** and **2** contain a D-glucosamine unit α-(1→4)-linked to an azasugar analog of L-iduronic acid and D-glucuronic acid, respectively. The different substitution patterns of the two nitrogen atoms in the target compounds necessitate their



R^1 = Ac or SO_3Na; R^2 = H or SO_3Na

Figure 1.

☆ Synthesis of glycosaminoglycan oligosaccharides, part 3. For part 2 see, Ref. 24.

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differentiation by separate protecting groups. The target structures should be available from the aza-uronic acid glycosyl acceptors **3** and **4,** and the 2-azido-2-deoxy-D-glucosyl donor **5** (Scheme 1).

The benzyloxycarbonyl group is used commonly for the protection of the ring nitrogen during the synthesis of iminosugar-containing oligosaccharides.[8a,8d–f,8h,8j,8n,8o,10] There are, however, problems associated with its use. One such problem is the ready formation of a 6-*O*,*N* cyclic carbamate derivative under basic conditions[8i,8j,8o,12] which prevents the accomplishment of certain transformations at O-6.[8i,8j,8o] Removal of the benzyloxycarbonyl group by catalytic hydrogenation results in N-alkylation under some conditions.[13] A major inconvenience in the use of the benzyloxycarbonyl group is the existence of rotamers at the amide nitrogen, which results in line-broadening and duplication of signals in the NMR spectra.[8h,8j,12b] In order to obtain good quality ^{1}H NMR spectra it was necessary to record the spectra at 115 °C in DMSO-d_6 at 400 MHz.[14] Although these problems are well known, no effort seems to have been made to replace the benzyloxycarbonyl group. There are only a few examples of other protecting groups used for N-protection of iminosugars in oligosaccharide synthesis.[15,16]

We now report that the 4-nitrobenzenesulfonyl (nosyl, Ns) group can be used advantageously to protect the ring nitrogen in iminosugars, and illustrate this by its application in the synthesis of heparanase inhibitory disaccharides. The 2- and 4-nitrobenzenesulfonyl, as well as 2,4-dinitrobenzenesulfonyl groups were introduced by Fukuyama for the protection of amines.[17] The nitrobenzenesulfonamides are readily prepared and the nosyl group can be removed under mild conditions, nevertheless it has found only limited application in carbohydrate chemistry as yet.[18]

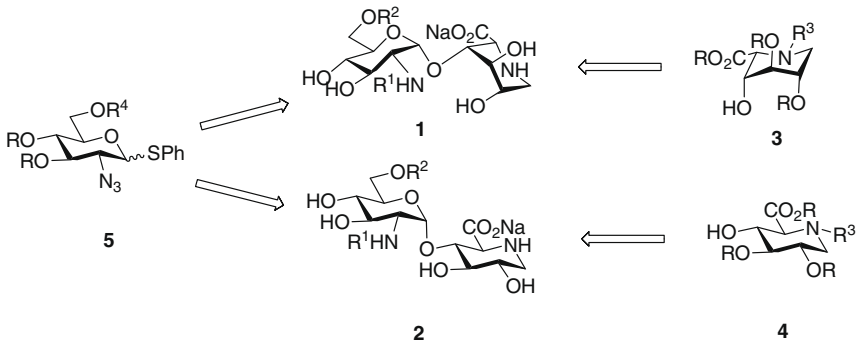
Due to the ready N-alkylation of nitrobenzenesulfonamides by the Mitsunobu reaction, the nosyl group is instrumental in the preparation of the iminosugars via cyclization of nosylated aminoalditols.[19] Thus, Mitsunobu reaction of the *N*-nosylated D-glucitol derivative **7**, obtained from **6**, gave stereoselectively the L-*ido* configured iminosugar **8** in 96% yield (Scheme 2). Alternatively, nosyl-protected iminosugars are readily prepared by nosylation of the iminosugars obtained by reductive amination. Thus, the crystalline *N*-nosyl 1-deoxynojirimycin derivative **11** was readily prepared from **10**, which was itself obtained from the 5-azido-5-deoxy-D-glucose derivative **9** by hydrolysis of the isopropylidene acetal followed by catalytic hydrogenation.[20]

In contrast to *N*-benzyloxycarbonyl derivatives, no duplication or line-broadening of signals was visible in the ^{1}H NMR spectra of the *N*-nitrobenzenesulfonyl derivatives.

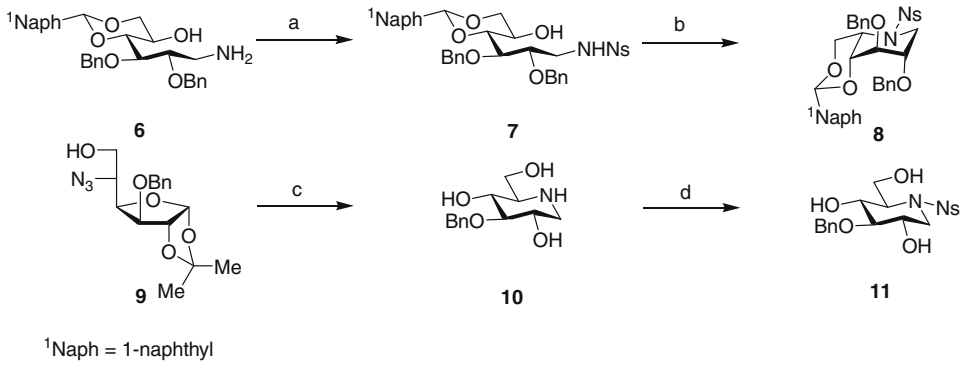
The nosyl group proved to be stable during common protecting group manipulations to transform these compounds into the glycosyl acceptors. Thus reductive ring cleavage of the naphthylmethylene acetal in **8** with BH_3·THF–TMSOTf[21] and $NaBH_3CN$–HCl[22] afforded the 4-*O*- (**12**) and 6-*O*-(1-naphthyl)methyl (^{1}NAP) ethers (**13**), in 93% and 69% yields, respectively (Scheme 3).

A critical step in the synthesis of the target oligosaccharides is the deprotection in the presence of the highly acid- and base-sensitive sulfate groups. To check the stability of sulfate groups under the conditions of nosyl group removal, compound **12** was converted into the 6-*O*-sulfate derivative **14**, and its denosylation was examined (Scheme 4). We found that the nosyl group could be removed with thiophenol in the presence of different bases (K_2CO_3 and Et_3N) to yield the free amine **15** leaving the sulfate group intact.

For the synthesis of the target disaccharides, compound **12** was converted into the glycosyl acceptor via a one-step oxidation with PDC-Ac_2O-*t*-BuOH[23] to give the *tert*-butyl uronate **16**, followed by removal of the (1-naphthyl)methyl group with CAN[24] to yield **17**.

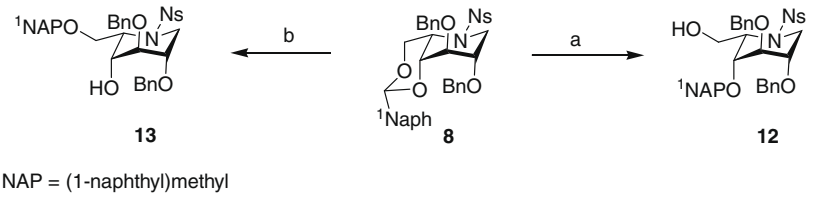


Scheme 1. Retrosynthesis of heparanase inhibitory oligosaccharides.

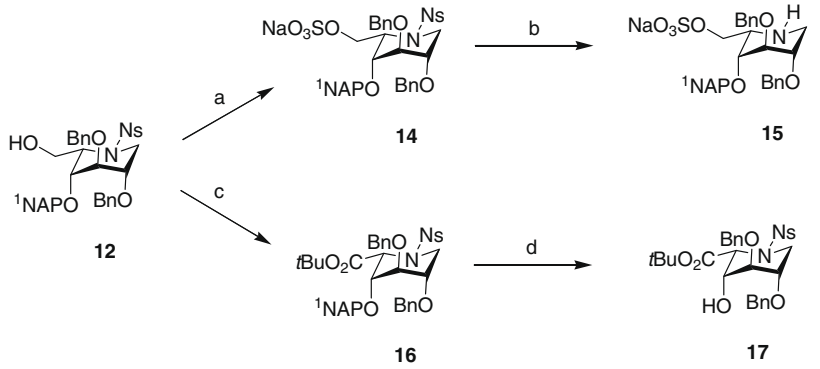


^{1}Naph = 1-naphthyl

Scheme 2. Reagents and conditions: (a) NsCl, Et_3N, CH_2Cl_2, 98%; (b) DEAD, Ph_3P, CH_2Cl_2, 96%; (c) (1) TFA, H_2O, 95%; (2) H_2, Raney Ni, MeOH, 77%; and (d) NsCl, $NaHCO_3$, dioxane, H_2O, 70%.



Scheme 3. Reagents and conditions: (a) BH_3·THF, TMSOTf, CH_2Cl_2, 93%; and (b) $NaBH_3CN$, HCl–Et_2O, THF, 69%.



Scheme 4. Reagents and conditions: (a) SO_3·pyr, DMF, 83%; (b) PhSH, K_2CO_3, DMF, 52%; or PhSH, Et_3N, DMF, 93%; (c) PDC, Ac_2O, *t*BuOH, CH_2Cl_2, 54%; and (d) CAN, CH_3CN, H_2O, 78%.

The nosylated azasugar derivatives **13**, **17,** and **18** (obtained from **11**) having free 4-hydroxy groups proved to be good glycosyl acceptors. Their glycosylation with 2-azido-2-deoxy-D-glucose thioglycoside **19** using Me_2S_2–Tf_2O as promoter[25] afforded the α-linked disaccharides **20**–**22** stereoselectively and in excellent yields (Scheme 5).

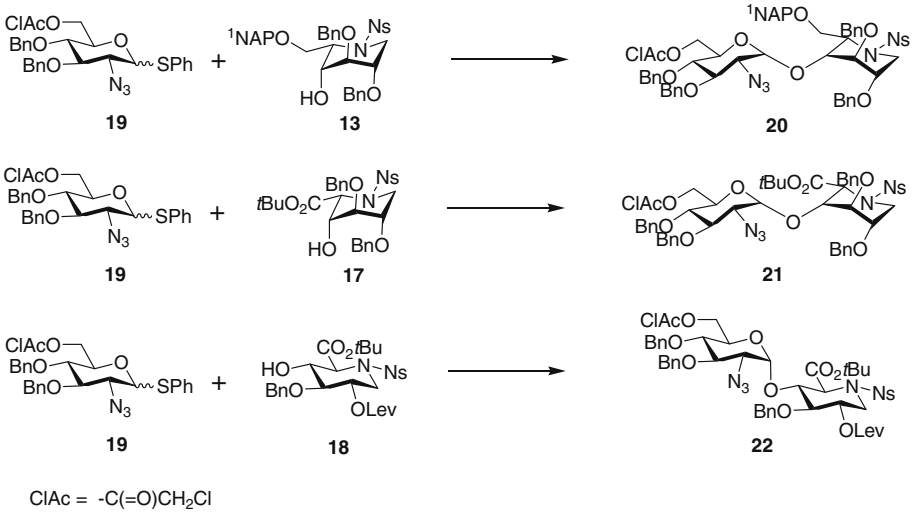
Before attempting to convert these protected disaccharides into the target sulfated oligosaccharides, the orthogonality of the *N*-nosyl group and the azido function was investigated. Reaction of the azido group in **23** [obtained by removal of the chloroacetyl group with hydrazinedithiocarboxylate[26] (HDTC) from **21**], with Me_3P followed by hydrolysis of the phosphinimine afforded the free amine **24** (Scheme 6).

On the other hand, treatment of **23** with 1,3-propanedithiol in the presence of Et_3N afforded the denosylated derivative in 77% yield without reducing the azido group.[27] The orthogonality of the *N*-(4-nitrobenzenesulfonyl) group with the azido function, demonstrated here, could be very useful for further applications in the syntheses of oligosaccharides and other compounds containing multiple amino functions.

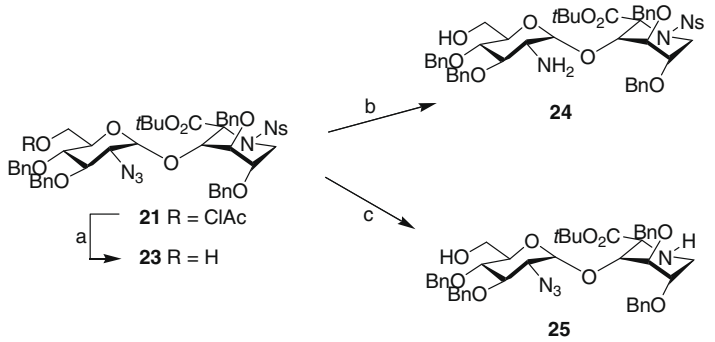
The fully protected disaccharides were readily converted into the target compounds as illustrated by the transformation of **24** into **27** (Scheme 7).

After hydrolysis of the *tert*-butyl group the amino alcohol was *N*,*O*-disulfated to give **26**. Removal of the nosyl group using thiophenol and triethylamine, followed by catalytic hydrogenolysis afforded the target compound **27**.

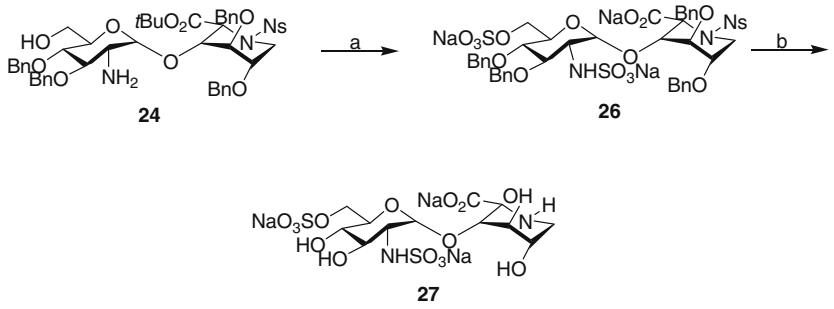
In summary, we have reported the 4-nitrobenzenesulfonyl group for the protection of the ring nitrogen in iminosugars. This group can be introduced conveniently and it proved to be stable to a series of common carbohydrate transformations including reductive acetal openings, glycosylations, oxidations, sulfations,



Scheme 5. Reagents and conditions: Me_2S_2–Tf_2O, Et_2O, CH_2Cl_2, **20** (86%); **21** (90%); and **22** (75%).



Scheme 6. Reagents and conditions: (a) HDTC, DMF, 74%; (b) Me_3P, THF, then H_2O, 79%; and (c) 1,3-propanedithiol, Et_3N, pyr, H_2O, 77%.



Scheme 7. Reagents and conditions: (a) (1) TFA, CH_2Cl_2; (2) SO_3·pyr, Et_3N, CH_2Cl_2, 95%; (b) (1) PhSH, Et_3N, DMF, 98%; and (2) H_2, Pd/C, THF, H_2O, 52%.

and removal of several common protecting groups. The nosyl group can be removed under mild conditions without affecting the *O*- and *N*-sulfate groups. An additional advantage is that the NMR spectra of the nosylated compounds are simpler than those of *N*-benzyloxycarbonyl-protected examples. The usefulness of the *N*-nosyl protection was demonstrated by the synthesis of sulfated oligosaccharides which are inhibitors of the enzyme, heparanase. The orthogonality of the *N*-(4-nitrobenzenesulfonyl) group with the azido function was also demonstrated. This property seems to be of great value for selective functionalization of polyamino compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.042.

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