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Large-scale synthesis of 6-deoxy-6-sulfonatomethyl glycosides and their application for novel synthesis of a heparinoid pentasaccharide trisulfonic acid of anticoagulant activity

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ABSTRACT

Multigram-scale syntheses of three 6-deoxy-6-sulfonatomethyl α-glucosides were accomplished via reactions of the corresponding primary triflate derivatives with the lithiated ethyl methanesulfonate. Chemoselective glycosylation reactions of different 6-*C*-sulfonatomethyl glucoside donors were studied. The sulfonic acid-containing building blocks were utilised in a novel [2+3] block synthesis of a trisulfonic acid isoster of the anticoagulant pentasaccharide idraparinux.

1. Introduction

Heparin is a linear sulfated polysaccharide that plays a crucial role in maintaining the haemostatic state of blood. Binding to antithrombin, a serine protease inhibitor, accelerates its inhibitory activity against thrombin and factor Xa in the blood-coagulation cascade.[1] The anticoagulant properties of heparin have made it an invaluable drug for prevention and treatment of thromboembolic diseases.[2] However, heparin therapy is limited to intravenous administration and may be accompanied by side effects (inflammation, bleeding, liver toxicity and heparin induced thrombocytopenia) due to the polyanionic and heterogeneous nature of the polysaccharide obtained from animal organs.[3] To develop synthetic heparinoid anticoagulants with fewer adverse effects and a better pharmacokinetic profile the antithrombin-binding DEFGH pentasaccharide fragment of heparin and many simplified analogues have been prepared. These research efforts led to the synthetic antithrombotic drug Arixtra (fondaparinux, **1**)[4] as well as to the non-glycosaminoglycan derivative idraparinux (**2**),[5] both possessing selective factor Xa inhibitory activities (Fig. 1).

Our group has been dealing with the synthesis of bioisosteric sulfonic acid analogues of idraparinux to obtain novel selective factor Xa inhibitors.[6–10] Two pentasaccharide sulfonic acids (**3** and **4**) and the reference compound **2** have been prepared until now.[10,11] Evaluation of the inhibitory activities of pentasaccharides **2**–**4** towards the blood-coagulation proteinase factor-Xa revealed that the disulfonate analogue **3** displayed higher activity than idraparinux, however, introduction of the third sulfonic-acid moiety (**4**) resulted in a notable decrease in anti-Xa activity.[10] To gain deeper insight into the structure–activity relationship of the anticoagulant action of the sulfonic acid derivatives we decided to prepare a series of heparinoid pentasaccharides by systematic replacement of the sulfate esters with a sodium sulfonatomethyl moiety, and we also aimed at preparing compounds **3** and **4** in sufficient amounts for detailed STD NMR studies of their interactions with antithrombin. As a beginning of this work, we present here the multigram-scale syntheses of 6-sulfonatomethyl-containing mono- and disaccharides, useful for modular syntheses of the planned pentasaccharide sulfonic acids, and application of the new building blocks in a novel, [2+3] synthesis of the pentasaccharide trisulfonic acid **4**.

2. Results and discussion

Previously we utilised free-radical addition of bisulfite to exo-methylene derivatives for introducing the sulfonatomethyl group onto primary or secondary positions of saccharides (i.e. **5**→**7**,

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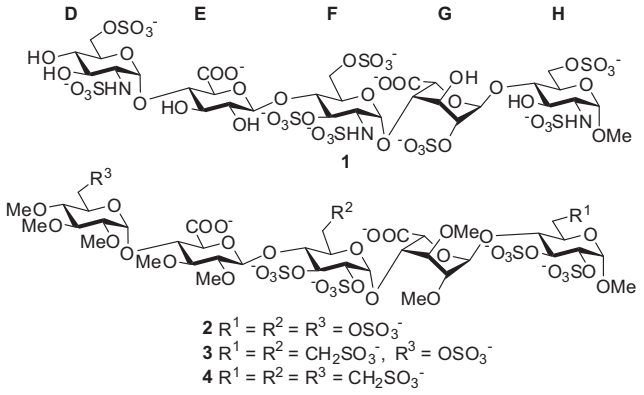
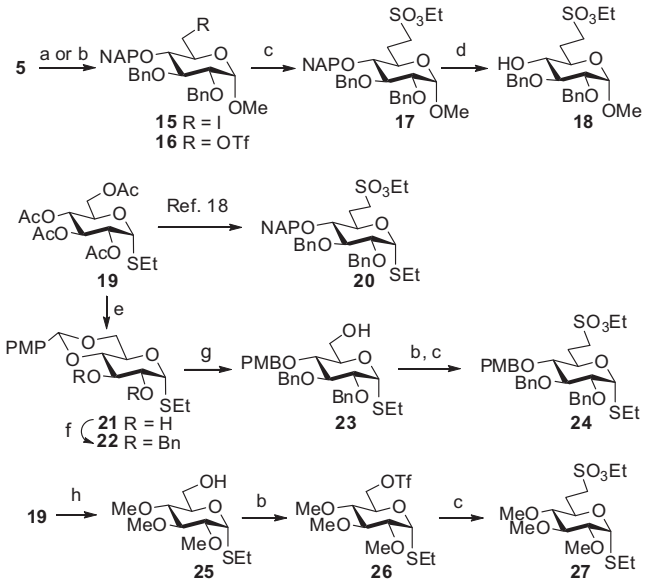


Figure 1. Synthetic pentasaccharides with selective factor Xa inhibitory activity: fondaparinux (**1**), idraparinux (**2**) and its sulfonatomethyl analogues **3** and **4**.

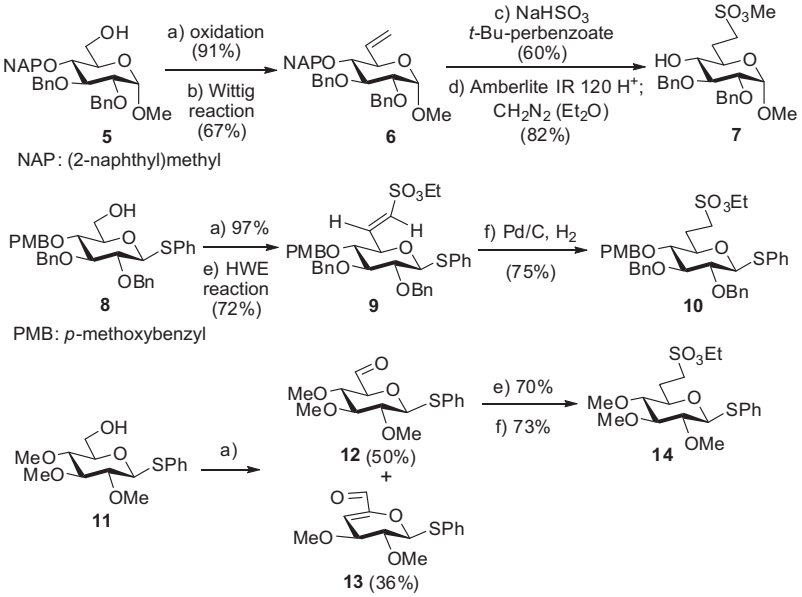
Scheme 1).[6,8,12] As this method, requiring a peroxybenzoate catalysis, is incompatible with the oxidisable thio aglycone, the synthesis of the C6-sulfonatomethyl thioglycosides was accomplished by Horner–Wadsworth–Emmons (HWE) reaction (**8**→**10**, **11**→**14**).[10] However, multistep transformation of compound **5** via addition of the sulfite radical anion to the unsaturated heptoside **6** afforded the glycosyl acceptor building block **7** with only 30% overall yield.[6] Synthesis of the thioglycoside building block **14**[10] from the corresponding 6-hydroxy derivative **11** using HWE olefination[13] proceeded also with unsatisfyingly low 26% overall yield due to the unexpected elimination side reaction[14] that occurred in the oxidation step, either Swern or Dess–Martin oxidation methods were applied (Scheme 1). Thence, we considered both prior approaches to be inefficient for large-scale synthesis of the 6-sulfonatomethyl-containing D and H glycosyl units.

As reaction of a α-lithio sulfonate ester with a primary carbohydrate iodide[15] or triflate[16] appeared in the literature as the most straightforward way to introduce a sulfonatomethyl ester moiety to *O*-glycosides, we decided the exploitation of this facile method for improved synthesis of the glycosyl acceptor building block **7**. The primary iodide **15** prepared from **5**[17] showed low reactivity towards the lithiated ethyl methanesulfonate providing the desired



Scheme 2. Synthesis of the sulfonatomethyl-containing glucosyl building blocks by nucleophilic substitution. Reagents and conditions: (a) PPh_3, I_2, imidazole, toluene, 75 °C, 30 min, 90%; (b) Tf_2O, py, CH_2Cl_2, −10 °C, 30 min; (c) *n*-BuLi, THF, CH_3SO_3Et, −78 °C to −20 °C, 2.5 h, 26% from **15**, 88% via **16** over two steps, 33% from **23** over two steps, 88% via **26** over two steps; (d) DDQ, CH_2Cl_2–H_2O (9:1), rt, 30 min 86%; (e) (1) NaOMe, MeOH; (2) 4-methoxybenzaldehyde dimethyl acetal, *p*-toluenesulfonic acid, reflux, 74%; (f) NaH, BnBr, DMF, 0 °C to rt, 90%; (g) $LiAlH_4$–$AlCl_3$ (3:1), CH_2Cl_2–Et_2O, 0 °C, 30 min, 83%; (h) (1) NaOMe, MeOH, (2) TrCl, py, (3) NaH, MeI, DMF, 0 °C to rt, (4) AcOH, 67% over 4 steps.

product **17** with 26% yield (Scheme 2). We attempted to enhance the reactivity of the alkylating agent by adding 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (dimethylpropyleneurea, DMPU) to the reaction mixture that, however, did not lead to higher yield of **17**. Reaction of the α-lithio sulfonate ester with the more reactive triflate derivative **16** proceeded with high efficacy,[18] therefore this transformation was applied in ten-gram-scale to produce the sulfonate ester **17** in excellent 88%. Selective demasking of the 4-OH group by oxidative cleavage of the 2-naphthylmethyl (NAP) ether with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[19]



Scheme 1. Prior syntheses of the 6-deoxy-6-sulfonatomethyl building blocks **7**,[6] **10**[10] and **14**.[10]