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Carbohydrate Research 343 (2008) 2200–2208
Carbohydrate RESEARCH

Note

Variant synthetic pathway to glucuronic acid-containing di- and trisaccharide thioglycoside building blocks for continued synthesis of *Cryptococcus neoformans* capsular polysaccharide structures

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Received 4 October 2007; received in revised form 12 November 2007; accepted 25 November 2007
Available online 4 December 2007

Presented at Eurocarb 14th Lübeck, Germany, September 2007

Abstract—An alternative pathway to glucuronic acid-containing di- and trisaccharide thioglycoside building blocks, suitable for the synthesis of *Cryptococcus neoformans* capsular polysaccharide structures, has been developed. As opposed to our earlier synthesis, this approach features the introduction of the glucuronic acid motif at the di- and trisaccharide level through oxidation of a glucose residue. This approach circumvents problems encountered in glycosylations with glucuronic acid donors and benzylation of glucuronic acid-containing derivatives. Selective protection of primary alcohols was obtained at the di- and trisaccharide stage using TBDMS or trityl protecting groups, respectively. After benzylation of the secondary hydroxyl groups and subsequent removal of the TBDMS or trityl group, oxidation of the free primary alcohols to carboxylic acids was performed in high yield using the TEMPO–BAIB reagent mixture, which does not tend to oxidize thioglycosides. The new approach requires a number of extra steps, but has proven to be more reliable and easily reproducible.

Keywords: Oligosaccharide synthesis; Thioglycosides; Oxidation

We had earlier published synthetic pathways to donor building blocks suitable for the synthesis of *Cryptococcus neoformans* CPS structures, including those corresponding to Xyl*p*-(1→2)-Man*p* and Xyl*p*-(1→2)-[Xyl*p*-(1→4)]-Man*p* di- and trisaccharides[1] as well as Glc*p*A-(1→2)-Man*p* and Glc*p*A-(1→2)-[Xyl*p*-(1→4)]-Man*p* di- and trisaccharides.[2] These compounds were subsequently used in the synthesis of larger structures (up to heptasaccharides) with variant acetylation patterns, which have been used in antibody binding- and immunizing experiments.[3]

Although the synthesis of Xyl*p*-(1→2)-Man*p* di- and trisaccharide building blocks is practical, the synthesis of the glucuronic acid-containing building blocks is not always reliable and is difficult to perform on a large scale. This is due to a number of reasons: the low stereoselectivity in couplings with Glc*p*A-donors with non-participating groups, the low reactivity and yields in couplings with Glc*p*A-donors with participating groups and difficulties in benzylating glucuronic acid derivatives in reproducibly high yield. These are all known problems frequently experienced in the synthesis of uronic acid-containing oligosaccharides.[4] An often used solution to these problems is to instead start with a suitably protected aldose donor and to perform glycosylations and alkylations prior to oxidation to the 6-carboxylic acid function present in uronic acids.[4] This approach has earlier been applied to the synthesis of a *Cryptococcus* pentasaccharide O-glycosidic structure by van Boom and co-workers.[5] We herein report on our

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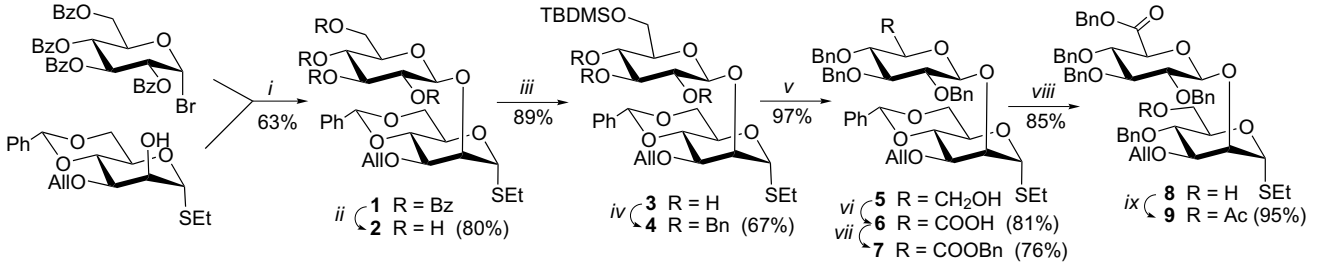
doi:10.1016/j.carres.2007.11.026

experiences in employing this approach in the synthesis of the di- and trisaccharide thioglycoside building blocks **9** and **17**.

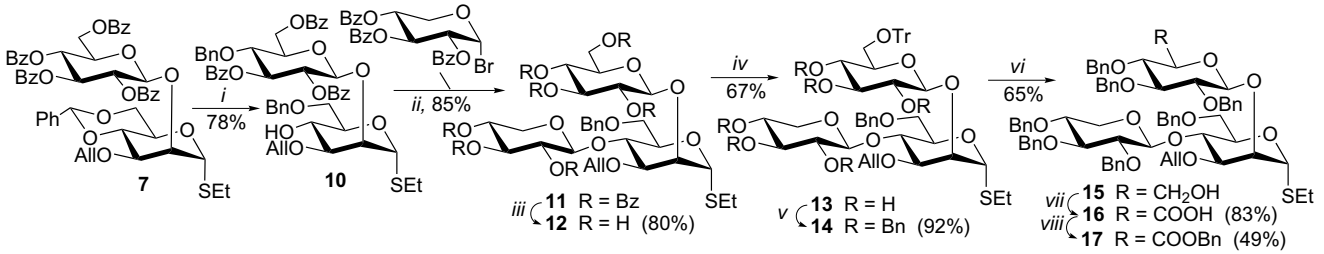
The same acceptor used in our earlier building block syntheses, ethyl 2-*O*-allyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside,[1] was employed in these studies. Glycosylation of this alcohol with 2,3,4,6-tetra-*O*-benzyl-D-glucopyransosyl bromide promoted by silver triflate gave a good yield (63%) of the (1→2)-β-linked disaccharide **1** (Scheme 1). Deacylation by treatment with sodium methoxide yielded the tetraol **2** in 80% yield. Regioselective protection of the primary position, to allow later deprotection and oxidation at C-6′, was performed using two different protecting groups, either a TBDMS group or a trityl group. The former gave a better yield in the selective protection and deprotection whereas the latter gave a better yield in the intermediate benzylation (no migration observed). Thus, silylation using TBDMSCl and DMAP in pyridine gave an 89% yield of the 6′-*O*-silyl compound **3**, which was benzylated (BnBr, NaH, DMF) to afford compound **4** in 67% yield together with 13% of the 4-*O*-TBDMS isomer. Attempts to change conditions to avoid silyl migration during the alkylation reaction were not successful. Desilylation with TBAF afforded the 6′-OH derivative **5** almost quantitatively (97%).

Thioglycosides are stable to almost any protecting and functional group manipulation and interconversions.[6] More or less only two types of reactions constitute a problem: oxidation and catalytic hydrogenolysis. With regard to oxidations, DMSO-based oxidations do not oxidize the sulfur, whereas with other reagents (e.g., PDC) oxidation often occurs. However, it has been shown that oxidations with TEMPO–BAIB[7] generally do not affect thioglycosides.[8] Other features of this reagent are that it is most selective for primary positions and that the carboxylic acid is obtained. Oxidation of **5** using this reagent mixture gave the desired uronic acid derivative **6** in high yield (80%). Treatment with $PhCHN_2$ then gave the known benzyl ester **7** in 76% yield. We were primarily interested in the 6-O-acetylated disaccharide building block **9**, and this was obtained from **7** using an improved pathway. Regioselective opening of the benzylidene acetal with Et_3SiH–$PhBCl_2$[9] gave the primary alcohol **8**, which was acetylated to afford **9** in an overall 81% yield. As compared to the earlier synthesis of this building block, this route is longer (9 steps as compared to 5 steps), but more reliable and reproducible. The overall yields of both routes are comparable (∼15%).

In the synthesis of the trisaccharide, the fact that xylopyranosides have no primary hydroxyl group could be utilized (Scheme 2). First, the benzylidene acetal of disaccharide **7** was again regioselectively opened, but now to yield the 4-hydroxy derivative **10** by the use of the $NaCNBH_3$–HCl reagent system.[10] Silver triflate-promoted glycosylation of this acceptor with 2,3,4-tri-*O*-benzyl-xylopyranosyl bromide afforded the β-(1→4)-linked trisaccharide **11** in 85% yield. Deacylation (NaOMe–MeOH, →**12**, 80%) followed by regioselective protection of the primary alcohol, this time using trityl chloride, gave the 6′-*O*-trityl derivative **13** (65%), which was benzylated to afford **14** (92%). Detritylation using *p*-TsOH in $CHCl_3$–MeOH gave the 6′-hydroxy derivative



Scheme 1. Reagents: (i) AgOTf, DTBP, CH_2Cl_2; (ii) NaOMe, MeOH; (iii) TBDMSCl, DMAP, pyridine; (iv) BnBr, NaH, DMF; (v) TBAF, $CHCl_3$/MeOH, (vi) TEMPO, BAIB, CH_2Cl_2/H_2O; (vii) $PhCHN_2$, EtOAc; (viii) Et_3SiH, $PhBCl_2$, CH_2Cl_2; (ix) Ac_2O, pyridine.



Scheme 2. Reagents: (i) $NaCNBH_3$, HCl/Et_2O, THF; (ii) AgOTf, DTBP, CH_2Cl_2; (iii) NaOMe, MeOH; (iv) TrCl, DMAP, pyridine; (v) BnBr, NaH, DMF; (vi) pTsOH, $CHCl_3$/MeOH, (vii) TEMPO, BAIB, CH_2Cl_2/H_2O; (viii) $PhCHN_2$, EtOAc.