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One-pot oligosaccharide synthesis: reactivity tuning by post-synthetic modification of aglycon†

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Post-synthetic aglycon modification of substituted aryl thioglycosides led to building blocks with multiple levels of anomeric reactivities, which can be used in rapid assembly of oligosaccharides in one-pot syntheses.

During the past two decades, there have been great advances in our understanding of the protective group effects on anomeric reactivities of glycosyl donors.[1] This has culminated in the development of a novel glycosylation methodology, *i.e.*, reactivity based one-pot synthesis, where sequential reactions of several glycosyl building blocks with decreasing anomeric reactivities in the same flask led to rapid assembly of oligosaccharides without tedious purification of intermediates or aglycon adjustments.[1–4] The reactivity based one-pot approach has achieved great success in total syntheses of complex oligosaccharides such as Le^Y,[2a] fucosyl GM1,[2b] Globo H,[2c] phytoalexin elicitor heptasaccharide,[2d] sLe^x,[2e] as well as assembly of oligosaccharide libraries.[2f] However, current reactivity based one-pot synthesis has primarily relied on reactivity tuning through judicious placement of protective groups with proper disarming power on glycon. This limits the range of reactivity difference to about four orders of magnitude, restricting the number of linear steps that can be carried out in one pot.[4] It is highly desirable for novel methods to be developed to reduce the amount of time required for building block preparation and broaden the reactivity window. Herein we disclose a new one-pot oligosaccharide synthesis approach, whereby the reactivity of donors is readily tuned by post-synthetic modification of aglycon.[5] Donors with multiple levels of reactivities are derived from common building blocks in a divergent manner, thus significantly reducing the amount of effort for building block preparation.

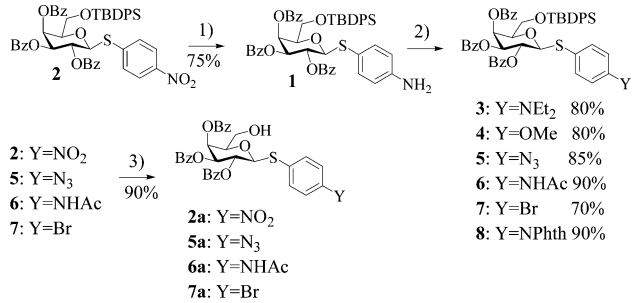
Glycosyl donors bearing electron rich and sterically less hindered aglycons are known to be more reactive than those with electron poor and sterically demanding ones.[3d,6–8] We envision that *S*-(4-aminophenyl) thioglycoside (*e.g.* **1**) can serve as a key intermediate. The amino moiety in such an intermediate can be facilely transformed into substituents with various electron withdrawing power through simple modifications, which in turn confer different levels of anomeric reactivities.

The common building block **1** was synthesized from the corresponding *S*-(4-nitrophenyl) **2**[6] in 75% yield (Scheme 1), and was then readily transformed in high yields into glycosyl donors with various *para* aglycon substituents, such as diethylamino **3**, methoxy **4**,[9] azido **5**,[10] acetamido **6**,[6] bromo **7**[11] and phthalimido **8**. This highlights the advantage of the current divergent approach as through the traditional approach starting from thiophenols, it would have required four steps for each compound. The TBDPS groups were selectively removed to give building blocks **2a**, and **5a–7a** bearing a free hydroxyl group, which can function as an acceptor as well.

Chemical shifts of the anomeric protons (H_1) of donors **2** to **8** can be employed to quickly determine their relative reactivities.[4] These donors are divided into three groups, the more upfield shifted group of diethylamino **3** and methoxy **4**, the less upfield shifted group of azido **5**, acetamido **6**, bromo **7** and the most downfield shifted group phthalimido **8** and nitro **2** (Table 1).

† Electronic supplementary information (ESI) available: experimental data. See http://www.rsc.org/suppdata/cc/b4/b405886k/

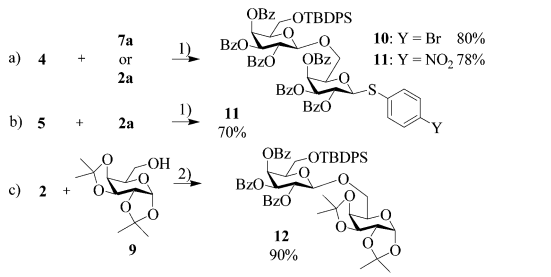
Chemoselective glycosylations were successfully achieved with building blocks from different groups, as donors in the more upfield-shifted group were preferentially activated. Cross coupled products **10** and **11** were the respective major products isolated from glycosylation of **7a** with **4**, and **2a** with **4** or **5** (Scheme 2a,2b). It should be emphasized that by simple modification of the aglycon, the reactivity disparity between donors in different groups is large enough to enable selective activation of the more reactive donor without employing an additional differentiation factor such as solvent.[7] Although disarmed *S*-(4-nitrophenyl) thioglycosides are



Scheme 1 *Reagents and conditions*: 1) $SnCl_2$, EtOH, reflux; 2) **3**: CH_3CHO, $NaBH_4$, H_2SO_4, THF, rt; **4**: 50% HBF_4, $NaNO_2$, THF–H_2O; CH_3OH, cat. *p*-TsOH, O_2, sealed tube, 70 °C; **5**: NaN_3, $NaNO_2$, 8 M CH_3COOH, THF, 0–5 °C; **6**: Ac_2O, pyridine, rt; **7**: ^{t}butyl nitrite, $CuBr_2$, rt; **8**: phthalic anhydride, Et_3N, toluene, reflux; 3) CH_3COOH, TBAF, THF.

Table 1 Chemical shifts of H_1 of various donors (400 MHz, $CDCl_3$)

	δ (ppm)	
	R = TBDPS	R = H
3 Y = NEt_2	4.78	
4 Y = OMe	4.82	
5 Y = N_3	4.87	4.94
6 Y = NHAc	4.90	4.95
7 Y = Br	4.90	4.97
8 Y = NPhth	5.05	
2 Y = NO_2	5.08	5.15



Scheme 2 *Reagents and conditions*: 1) NIS, TfOH, CH_2Cl_2, MS-AW300, −60 to −40 °C; 2) *p*-TolSCl, AgOTf, CH_2Cl_2, MS-AW300, −50 °C to rt.

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known as latent glycosyl donors, unreactive towards common thiophilic reagents,[6] we discovered that disarmed nitro donor **2** was readily activated by the more potent promoter *p*-toluenesulfenyl triflate (*p*-TolSOTf)[12] formed *in situ* from *p*-toluenesulfenyl chloride (*p*-TolSCl) and AgOTf (Scheme 2c).

With relative reactivities of building blocks determined, the synthesis of tetrasaccharide **14** was performed in one pot (Scheme 3a). The first glycosylation was carried out with building blocks **4** and **7a** with NIS/TfOH as the promoter. After the coupling finished as indicated by TLC, the nitrophenyl **2a** was added followed by another equivalent of NIS. Upon completion of the second glycosylation, final acceptor glucoside **13** was introduced into the reaction mixture. The third glycosidic coupling reaction was promoted with *p*-TolSCl/AgOTf[12] to produce the desired tetrasaccharide **14** in 39% yield through a single purification.[13]

Tuning through an aglycon can allow facile adjustment of anomeric reactivities on an oligosaccharide intermediate for modular synthesis of a large oligosaccharide. As a proof of this principle, the 4-nitrophenyl moiety of disaccharide **11** was readily transformed into 4-bromophenyl to produce disaccharide **10a** with intermediate reactivity (Scheme 3b). This would be difficult to accomplish by changing a protective group on a glycon without extensive protective group manipulation. A three-step one-pot synthesis with most reactive donor **4**, less reactive disaccharide **10a**, least reactive donor **2a** and acceptor **13** gave the pentasaccharide **15** in 33% yield, where purification of **15** was the only separation step necessary (Scheme 3c).[13]

In order to examine the generality of our approach, we applied it to the synthesis of chitinoligosaccharide due to the well-known challenging nature of β-1,4-GlcNAc linkage formation.[14] Starting from the thioglycoside **16**,[6] *S*-(4-nitrophenyl) building block **17** was prepared in 57% overall yield (Scheme 4). Glycosylation of **17** with benzyl alcohol furnished the acceptor **18** in 60% yield. The nitro moiety in **17** was reduced to produce the *S*-(4-aminophenyl) thioglycoside **19**, which was facilely transformed to bromo **20** and methoxy donor **22** in good yields. The chitintetraose **23** was assembled by sequentially reacting methoxy **22**, bromo **20**, nitro **17**, and acceptor **18** in one pot (Scheme 5). The use of the promoter system of *p*-tolylsulfinyl piperidine (TSP) and Tf_2O[15] for the first glycosylation led to higher overall yield.

In conclusion, a new one-pot synthesis of oligosaccharide was developed by tuning the reactivity only through post-synthetic modification of an aglycon. The strategy allows rapid construction of glycosyl donors with multiple levels of anomeric reactivity from common precursors and facile adjustments of anomeric reactivities of oligosaccharide intermediates for modular synthesis. Combined with tuning reactivity through a glycon, this will provide a powerful one-pot synthesis strategy with a greatly expanded reactivity window.

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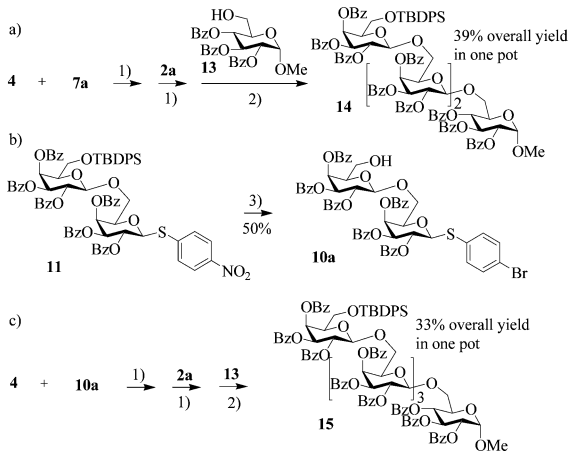
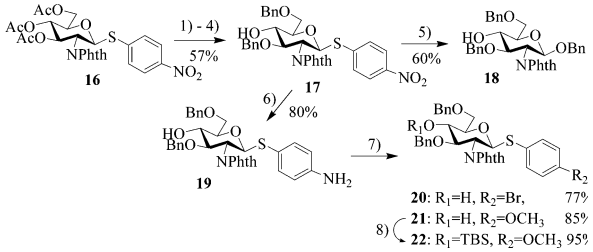
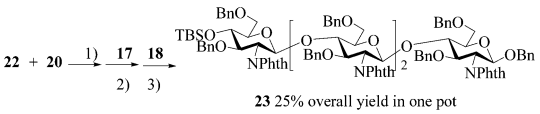


Scheme 3 *Reagents and conditions*: 1) NIS, TfOH, CH_2Cl_2, MS-AW300, −60 to −40 °C; 2) *p*-TolSCl, AgOTf, CH_2Cl_2, MS-AW300, −50 °C to rt; 3) $SnCl_2$, EtOH, reflux; ^{t}butyl nitrite, $CuBr_2$, CH_3CN, rt; CH_3COOH, TBAF, THF.



Scheme 4 *Reagents and conditions*: 1) $NaOCH_3$, MeOH, −20 °C–0 °C; 2) $PhCH(OMe)_2$, CSA, toluene, 90 °C; 3) 60% NaH, BnBr, MS, DMF, 0 °C–rt; 4) $NaCNBH_3$, HCl–Et_2O, THF; 5) BnOH, AgOTf, *p*-TolSCl, MS-AW300, CH_2Cl_2, −30 °C; 6) $SnCl_2$, EtOH, reflux; 7) **20**: ^{t}butyl nitrite, $CuBr_2$, rt; **21**: 50% HBF_4, $NaNO_2$; CH_3OH, cat. *p*-TsOH, sealed tube, 70 °C; 8) TBSOTf, 2,6-lutidine, MS, CH_2Cl_2, −20 °C–rt.



Scheme 5 *Reagents and conditions*: 1) TSP, Tf_2O, MS-AW300, −60 °C to −30 °C; 2) NIS, −30 °C to 0 °C; 3) AgOTf, *p*-TolSCl, −30 °C–rt.

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