Polymer-Supported Oligosaccharides via *n*-Pentenyl Glycosides: Methodology for a Carbohydrate Library[⊥,1]

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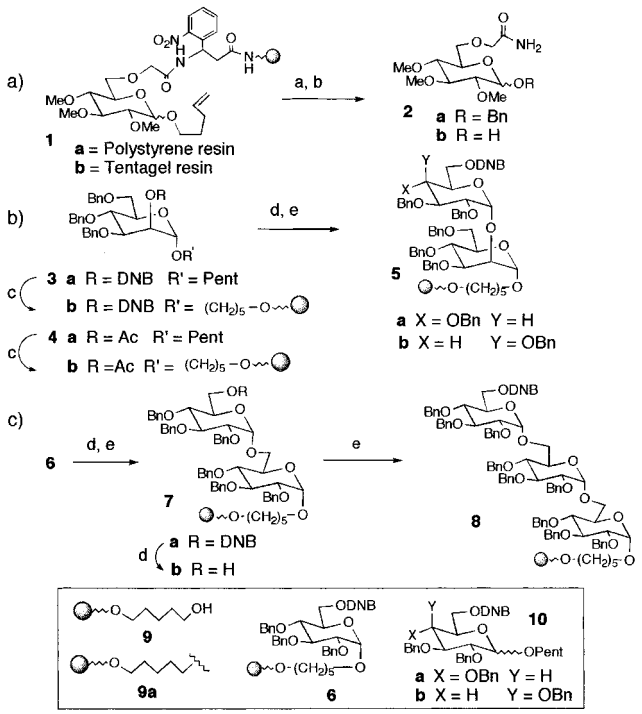
In the past few years, interest in solid-phase synthesis has increased dramatically due mainly to the excitement engendered by the concept of combinatorial chemistry,[2] a powerful tool in the discovery of new biologically active compounds. Of the natural biopolymers, oligosaccharides[3] have proven to be the most challenging to synthesize on solid supports. Pioneering studies[4] in this area were limited by the use of glycosyl bromides,[7] then the glycosyl donors of choice. Recent developments in donor technology have energized research in solid-phase methodology,[5] producing protected oligosaccharides that can be cleaved from the solid supports before deprotection and subsequent biological assay.

As a tool for the burgeoning field of glycobiology,[6] it would be highly desirable to synthesize polymer bound, fully deprotected saccharides, which could then be used directly and repeatedly for various and/or different assays.[7] One solution to this problem was recently reported by Kahne, Still, and their co-workers.[8] We are therefore prompted to describe our efforts to assemble polymer-supported oligosaccharides in deprotected form using *n*-pentenyl glycoside (NPG) chemistry.[9]

In principle, NPGs present two alternatives for the solid-phase synthesis of an expanding oligosaccharide. In the first, the NPG donor would be anchored through one of its hydroxyl groups to the support, and coupled to the glycosyl acceptor, present in solution in excess. The second alternative represents the opposite modality whereby the acceptor alcohol is on the solid support with excess NPG donor in solution. This modality was tested with the resin-bound donors **1a** and **1b**, prepared by condensing the corresponding 6-*O*-carboxymethyl NPG donor with the 3-amino-3-(2-nitrophenyl)propionyl (ANP) linker (Scheme 1a).[10] The prospect for glycosidation was assessed by using a large excess of benzyl alcohol. Although the photocleaved product indicated some benzyl glycoside **2a**, a substantial amount of hemiacetal **2b** was also obtained. As a model for the alternate modality wherein the acceptor resides on the solid support, NPGs **3a** and **4a** were glycosidated with the resin-bound acceptor **9** (Scheme 1b) to give the corresponding bound glycosides **3b** and **4b** in yields of 92 and 97%, respectively.[11]

The second modality was clearly preferable, and so our next objective was to investigate trends in anomeric selectivity for coupling of **9** to the *gluco*-derivatives shown in Table 1, as monitored by gel-phase ^{13}C NMR.[12] Entries i and ii showed that C2-phthalimides and esters (**11** and **12**) code for 1,2-trans glycosides in keeping with solution and prior solid-phase[5] experience. Entries iii, iv, and v

Scheme 1[a]



[a]Key: (a) BnOH, NIS, TESOTf, CH_2Cl_2, 2h, 25 °C; (b) hυ, THF, 3h, 25 °C; (c) **9**, NIS, TESOTf, CH_2Cl_2, 2h, 25 °C;(d) NaOMe / MeOH/ THF; (e) **11a** or **11b**, NIS, TESOTf, CH_2Cl_2, 2h, 25 °C.

[a] Key: (a) BnOH, NIS, TESOTf, CH_2Cl_2, 2 h, 25 °C; (b) *hν*, THF, 3h, 25 °C; (c) **9**, NIS, TESOTf, CH_2Cl_2, 2 h, 25 °C; (d) NaOMe/ MeOH/THF; (e) **11a** or **11b**, NIS, TESOTf, CH_2Cl_2, 2 h, 25 °C.

⊥ Dedicated to Prof. Hans Paulsen, University of Hamburg, on the occasion of his 75th birthday.

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(1) This work was supported by a grant from Glaxo Wellcome, Inc.

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(4) For a review of early work see: Malik, H.; Bauer, H.; Tschakert, J.; Voelter, W. *Chem.-Ztg.* **1990**, *114*, 371. (b) Frechet, J. M. J. *Polymer-Supported Reactions in Organic Synthesis*; Eby, R., Schuerch, C., Eds.; Wiley: New Yor, 1980; Chapt. 8. (c) Krepinsky, J. S.; Douglas, S. P.; Whitfield, D. M. *Synth. Polym.* **1994**, *242*, 280.

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(11) Merrifield resin loading = 1 mmol/g (purchased from Aldrich). Glycosidations were carried out at room temperature using 4 equiv of NPG donor. Reaction yields were judged by weight gain of resin, elemental analysis for nitrogen, and HPLC analysis of methyl benzoate from treatment with NaOMe/MeOH in THF.

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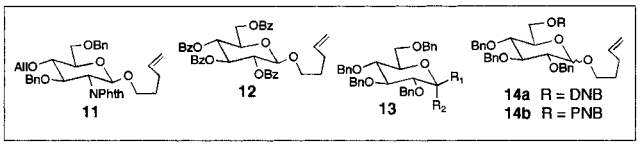
Table 1. Stereoselectivity in Coupling Reaction of 9 to Some NPGs

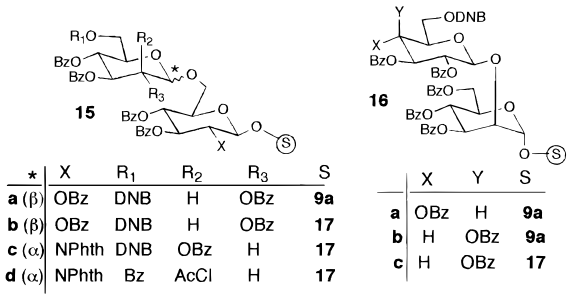
Entry	Donor	Solvent	α/β Ratio of Product
(i)	**11**	CH_2Cl_2	0 : 1
(ii)	**12**	CH_2Cl_2	0 : 1
(iii)	**13** α R_1 = H, R_2 = OPent	CH_2Cl_2	1 : 1
	13 β R_1 = OPent, R_2 = H	CH_2Cl_2	1.1 : 1
(iv)	**13** α / β	Et_2O : CH_2Cl_2 (11:1)	1.8 : 1
(v)	**14a**	CH_2Cl_2	9 : 1
	14b	CH_2Cl_2	4 : 1



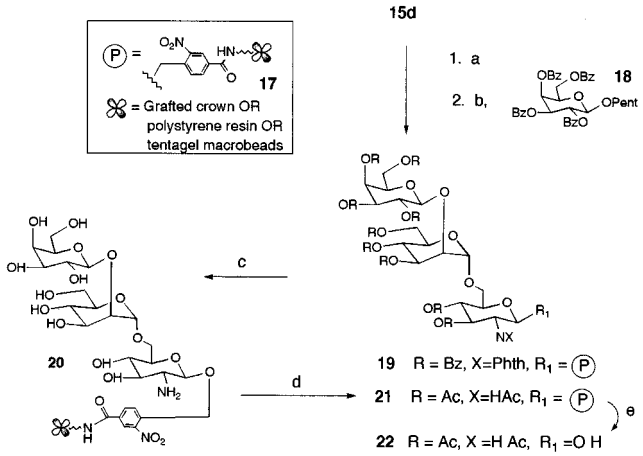
relate to the presence of nonparticipating C-2 substituents. The first shows that α/β product ratios are independent of the anomeric orientation of the glycosyl donor (**13**α or **13**β). Comparison of entries iii and iv (Table 1) shows that, as in solution chemistry,[13] anomeric selectivity can be influenced by choice of solvent.

Entry v (Table 1) supports the findings of Frechet and Schuerch[14] that steric bulk at O6 can have a salutary effect on α-glucoside selection. Thus the dinitro analogue **14a** gave a higher α/β ratio than the mononitro counterpart **14b**. In order to test the generality of this principle, the bound glycoside **3b** was saponified and then condensed with the *gluco* and *galacto* NPGs **10a** and **10b** to give the α disaccharides **5a** and **5b**.[15] For additional evidence (Scheme 1c), trisaccharide **8** was assembled *via* **7**[16] from polymer-supported monosaccharide **6** in a deprotect−couple−deprotect−couple strategy,[17] simplifying the operations that must be carried out on the resin-bound substrate(s).

The foregoing stereocontrolling factors now had to be evaluated in the context of our desire to prepare polymer-supported oligosaccharides in *deprotected* form. Use of benzyl groups was inadvisable because catalytic hydrogenolysis would involve solid/solid interaction. While acyl protecting groups would obviate that problem, their tendency to deactivate both donor[18] and acceptor[19] was worrisome. To resolve this concern, syntheses of disaccharides **15a**, **16a**, and **16b**[20] were carried out with success, yields being in the 50−78% range.[21]



Scheme 2[a]



[a] Key: (a) thiourea, methoxyethanol, 80 °C, 6 h; (b) NIS, TESOTf, CH_2Cl_2, 2 h, rt; (c) ethylenediamine, methoxyethanol, 70 °C, 4h; (d) Ac_2O, DMAP, Pyr, CH_2Cl_2; (e) *hν*, THF, 0.5 h.

Having determined that NPG methodology could accommodate donor/acceptor partners that were globally acylated, it was desirable to adopt (a) a solid support that was more amenable to parallel synthesis and (b) a linker that would facilitate monitoring. These requirements were met by polystyrene-grafted "crowns"[22] and Rich's linker, **17**.[23] Syntheses of the "crown" disaccharides **15b−d** and **16c**[20] were carried out as readily as for the corresponding resin-bound analogs. In order to monitor the reaction, a small portion of the crown was removed and photolyzed after each procedure. Mass spectral analysis of the resultant crude material confirmed the progress of the reaction, and the absence of any significant "truncated" products. The reactions could therefore be monitored in a more expedient manner as compared to earlier methods.[11]

These successes encouraged us to pursue our objective of synthesizing polymer−bound, fully deprotected saccharides. Accordingly, disaccharide **15d** was dechloroacetylated with thiourea, and coupling to NPG **18** gave trisaccharide **19** (Scheme 2). As before, the synthesis was monitored by removing a small portion of the "crown" for mass spectral analysis. The esters and phthalimide group on **19** could be readily cleaved by ethylenediamine in methoxyethanol to give the desired fully deprotected trisaccharide **20**. For confirmation, **20** was peracetylated to give **21**, and photolytic cleavage from the support afforded the acetylated derivative **22**.[24]

Efforts to extend this methodology to polymer-bound, branched oligosaccharides are currently underway.

Supporting Information Available: Experimental data (6 pages).

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(14) Frechet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1972**, *94*, 604.
(15) Yield range was 76−100%. Most couplings proceeded with an average yield of >90%.
(16) The anomeric configurations in **6** and **7** were determined to be α by gel phase ^{13}C NMR.[15] This technique could not be applied to the larger trisaccharide **8**, and so the new anomeric center in **8** was assigned by analogy.
(17) Merritt, J. R.; Fraser-Reid, B. Unpublished results.
(18) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.
(19) Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B. *J. Carbohydr. Chem.*, in press.
(20) β Configurations for **15** and **16** are assumed on the basis of our other solid-phase glycosidation results and literature precedents for neighboring group participation.[5]
(21) The 1→4 disaccharide, however, was not obtained during these studies. Obviously, the C4-OH of the pertinent benzoylated acceptor is inactivated by steric hindrance and electronic withdrawal.
(22) Chiron Mimotopes, 11055 Roselle St., San Diego, CA 92121. Catalog no. 12.48, Batch no. 491−1. Loading = 1.6 μmol per crown.
(23) Rich, D. H.; Gurwara, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 1575.
(24) All compounds exhibited satisfactory spectral data. Yields from resin reactions refer to isolated product.