Assembly of Oligosaccharide Libraries with a Designed Building Block and an Efficient Orthogonal Protection−Deprotection Strategy

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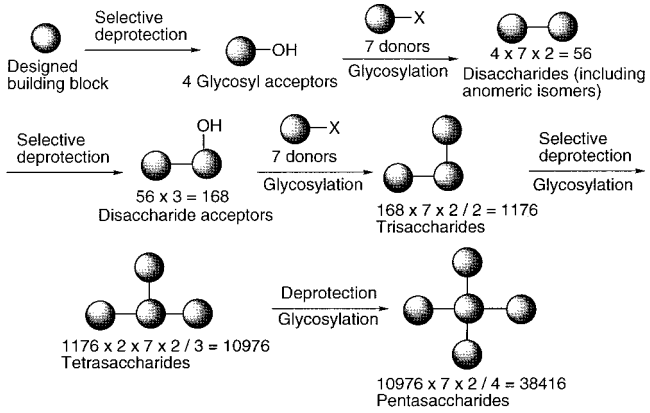
Received April 21, 1998
Revised Manuscript Received June 9, 1998

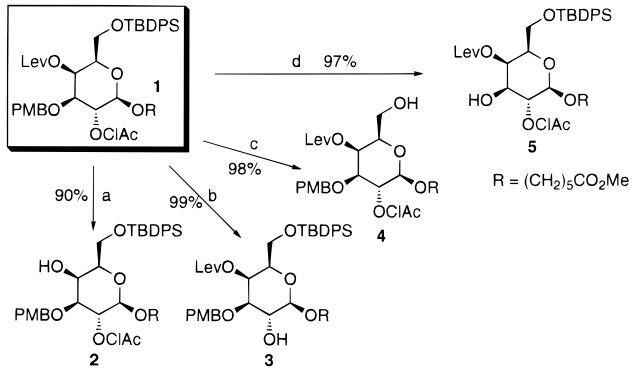
The molecular diversity of oligosaccharides has been recognized in their involvement in numerous important biochemical recognitions.[1] The efficient synthesis of oligosaccharides for the study of their structure and function is, however, still a very significant challenge for synthetic organic chemists.[2] Recent development in the field includes approaches such as one-pot synthesis,[3] enzymatic glycosylation,[4] glycal strategy,[5] and combinatorial chemistry.[6] With regard to combinatorial carbohydrate synthesis, a major problem is the lack of an efficient orthogonal protection−deprotection strategy. To tackle this problem, we describe here an effective library approach to oligosaccharides using a designed building block with four selectively removable protecting groups as the core for the source of acceptors and high-yielding coupling with different donors. As illustrated in Scheme 1, we envisaged that if seven glycosyl donors are used in this orthogonal strategy, the disaccharide library will have 56 compounds generated after the first glycosylation. These disaccharides can produce 168 acceptors from the core moiety, which, after glycosylation with seven donors, will generate 1176 trisaccharides. Following the same strategy, a library of 38 416 pentasaccharides will be generated.

To demonstrate the feasibility of this strategy, the monosaccharide building block **1** with four selectively removable protecting groups was designed (Scheme 2). The four chosen protecting groups, chloroacetyl (ClAc), *p*-methoxybenzyl (PMB), levulinyl (Lev), and *tert*-butyldiphenylsilyl (TBDPS), can be selectively removed in high yields with sodium bicarbonate, trifluoroacetic acid, hydrazine, and hydrogen fluoride−pyridine, respectively,

Scheme 1

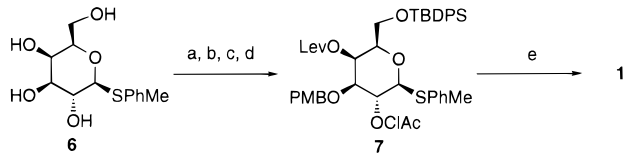


Scheme 2[a]



[a] Reagents and conditions: (a) NH_2NH_2/AcOH, THF/MeOH (10:1); (b) $NaHCO_3$, MeOH/H_2O (5:1), 60 °C; (c) HF−pyridine, HOAc/THF (1:4); (d) trifluoroacetic acid, CH_2Cl_2, −20 °C.

Scheme 3[a]



[a] Reagents and conditions: (a) *t*-$BuPh_2SiCl$, imidazole, DMF, 100%; (b) i. Bu_2SnO, toluene/benzene, reflux; ii. *p*-$CH_3OC_6H_4CH_2Cl$, Bu_4NI, DMF, 60 °C, 49%; (c) $ClCH_2COCl$, Et_3N, CH_2Cl_2, −20 °C to room temperature, 52%; (d) levulinic acid, DCC, 4-DMAP, CH_2Cl_2, 83%; (e) i. $HO(CH_2)_5CO_2Me$, NIS, TMSOTf, 4 Å MS, CH_3CN, −20 °C to room temperature; ii. $HgBr_2$, toluene/CH_3NO_2, 60 °C, 85%. DCC = 1,3-dicyclohexylcarbodiimide; 4-DMAP = 4-(dimethylamino)pyridine; NIS = *N*-iodosuccinimide; TMSOTf = trimethylsilyl trifluoromethanesulfonate.

using the conditions reported previously[7] with slight modifications to ensure that deprotection of each group in the presence of the others is highly selective. The synthesis of **1** is illustrated in Scheme 3. Starting from the thioglycoside **6**, the four hydroxyl groups were selectively protected to give **7**, which was glycosylated with methyl 6-hydroxyhexanate to give **1**.

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(3) See, for example: (a) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51. (b) Geurtsen, R.; Holmes, D. S.; Boons, G.-J. *J. Org. Chem.* **1997**, *62*, 8145. (c) Tsukida, T.; Yoshida, M.; Kurokawa, K.; Nakai, Y.; Achiha, T.; Kiyoi, T.; Kondo, H. *J. Org. Chem.* **1997**, *62*, 6876. (d) Chenault, H. K.; Castro, A. *Tetrahedron Lett.* **1994**, *35*, 9145. (e) Yamada, H.; Harada, T.; Miyazaki, H.; Takahashi, T. *Tetrahedron Lett.* **1994,** *35*, 3979. (f) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580. (g) Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919.

(4) Takayama, S.; McGarvey, G. J.; Wong, C.-H. *Chem. Soc. Rev.* **1997**, *26*, 407.

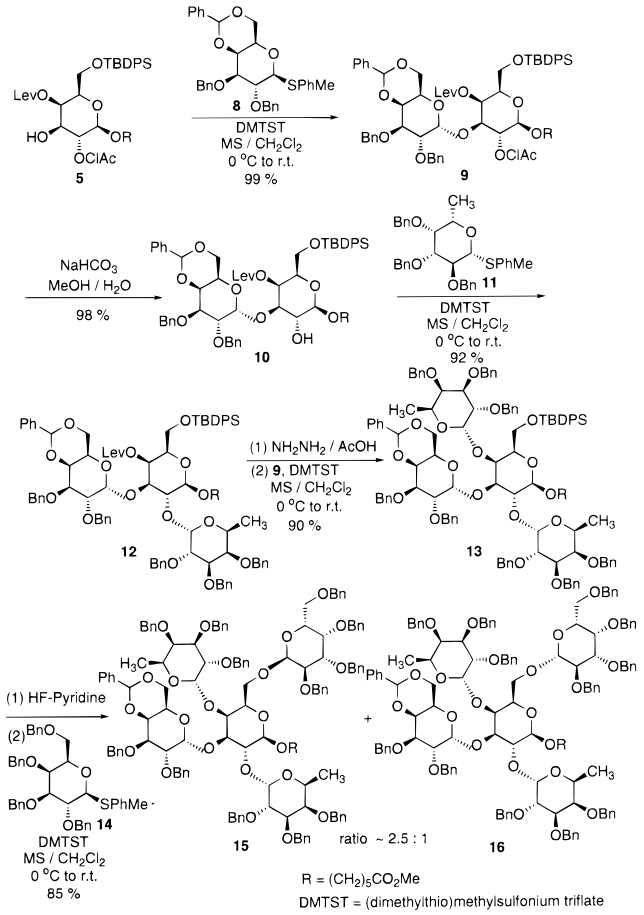
(5) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

(6) Random glycosylation: (a) Kanie, O.; Barresi, F.; Ding, Y.; Labbe, J.; Otter, A.; Forsberg, L. S.; Ernst, B.; Hindsgaul, O. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2720. (b) Ding, Y.; Kanie, O.; Labbe, J.; Palcic, M. M.; Ernst, B.; Hindsgaul, O. *Adv. Exp. Med. Biol.* **1995**, *376 (Glycoimmunology)*, 261. (c) Ding, Y.; Labbe, J.; Kanie, O.; Hindsgaul, O. *Bioorg. Med. Chem.* **1996**, *4*, 683. Latent-active glycosylation: Boons, G.-J.; Heskamp, B.; Hout, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2845. Solid-phase method: Liang, R.; Yan, L.; Loebach, J.; Ge, M.; Uozumi, Y.; Sekanina, K.; Horan, N.; Gildersleeve, J.; Thompson, C.; Smith, A.; Biswas, K.; Still, W. C.; Kahne, D. *Science* **1996**, *274*, 1520.

(7) For previous deprotection of the ClAc group, see: Naruto, M.; Ohno, K.; Naruse, N.; Takeuchi, H. *Tetrahedron Lett.* **1979**, 251. For deprotection of the PMB group, see: (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 885. (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371. For deprotection of the Lev group, see: van Boom, J. H.; Burgers, P. M. J. *Tetrahedron Lett.* **1976**, 4875. For deprotection of the TBDPS group, see: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1222.

S0002-7863(98)01361-4 CCC: $15.00
Published on Web 07/03/1998

Scheme 4

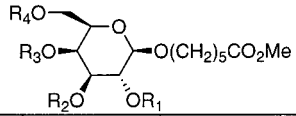


With building block **1** in hand, an oligosaccharide library was prepared as examplified in Scheme 4. Acceptor **5** was coupled with donor **8** in the presence of (dimethylthio)methylsulfonium triflate (DMTST)[8] to give exclusively the α-linked disaccharide **9** in 99% yield. After removal of the ClAc group from **9** (98% yield), the acceptor **10** was coupled with donor **11** in the same manner to give trisaccharide **12** (92% yield). Removal of the Lev group from **12** followed by glycosylation produced the tetrasaccharide **13** smoothly (90% yield). Interestingly, after deprotection and coupling with donor **14**, tetrasaccharide **13** can be further converted to the very bulky pentasaccharides **15** and **16** in 85% yield. Thus, using seven glycosyl donors (see Supporting Information) for glycosylation, we have prepared 45 protected oligosaccharides (Table 1, for tetra- and pentasaccharide, see Scheme 4). Most reactions were rapid and efficient, and the products were indentified with proton and carbon-13 NMR and further confirmed by high-resolution mass analysis. These protected oligosaccharides can be fully deprotected (Scheme 5).

In summary, we have developed an effective orthogonal strategy for the synthesis of a library of oligosaccharides as individual entities (~30 mg per molecule), using a designed building block containing four selectively removable protecting groups as acceptors for glycosylation. Though the pentasaccharides prepared in this manner are fully branched, the di-, tri-, and tetrasaccharides are biologically relavent, and work is in progress to increase the number of the library and to screen for binders to certain lectins and antibodies. Although the synthesis was carried out in solution phase, the strategy should be applicable to solid-phase synthesis.

(8) Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, 9. For the improved preparation of (dimethylthio)methylsulfonium triflate (DMTST): Methyl triflate (320 μL, 2.82 mmol) was added dropwise to an oven-dried flask containing methyl disulfide (280 μL, 3.10 mmol). The mixture was stirred under argon at room temperature. After 5 min, a colorless precipitate of DMTST formed. Addition of CH_2Cl_2 (1 mL) gave a stock solution that was used immediately in the glycosylation reaction.

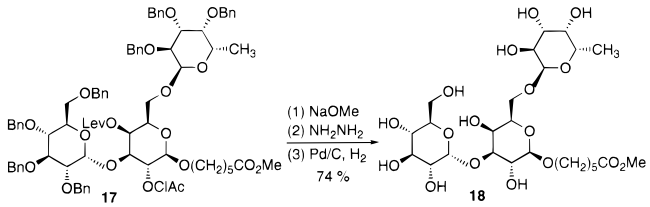
Table 1. Oligosaccharide Library



Entry	R_1	R_2	R_3	R_4	Yield[a]
1	L-Fuc(α1-2)	D-Gal(α1-3)	Lev	TBDPS	87
2	L-Gal(α1-2)	D-Gal(α1-3)	Lev	TBDPS	60
3	L-Gal(β1-2)	D-Gal(α1-3)	Lev	TBDPS	33
4	D-Man(α1-2)	D-Gal(α1-3)	Lev	TBDPS	78
5	D-Fuc(α1-2)	D-Gal(α1-3)	Lev	TBDPS	53
6	D-Fuc(β1-2)	D-Gal(α1-3)	Lev	TBDPS	38
7	D-GalN$_3$(α1-2)	D-Gal(α1-3)	Lev	TBDPS	72
8	D-GalN$_3$(β1-2)	D-Gal(α1-3)	Lev	TBDPS	14
9	L-Fuc(α1-2)	D-GalN$_3$(α1-3)	Lev	TBDPS	29
10	L-Fuc(β1-2)	D-GalN$_3$(α1-3)	Lev	TBDPS	5
11	D-Man(α1-2)	D-GalN$_3$(α1-3)	Lev	TBDPS	34
12	ClAc	D-Gal(α1-3)	L-Fuc(α1-4)	TBDPS	65
13	ClAc	D-Gal(α1-3)	Lev	L-Fuc(α1-6)	59
14	ClAc	D-Gal(α1-3)	Lev	L-Fuc(β1-6)	22
15	ClAc	D-Glc(α1-3)	L-Fuc(α1-4)	TBDPS	59
16	ClAc	D-Glc(α1-3)	Lev	L-Fuc(α1-6)	67
17	ClAc	D-Glc(α1-3)	Lev	L-Fuc(β1-6)	22
18	L-Fuc(α1-2)	D-Glc(α1-3)	Lev	TBDPS	76
19	L-Fuc(β1-2)	D-Glc(α1-3)	Lev	TBDPS	13
20	L-Fuc(α1-2)	D-Man(α1-3)	Lev	TBDPS	35
21	L-Fuc(α1-2)	PMB	Lev	L-Fuc(α1-6)	57
22	L-Fuc(α1-2)	PMB	Lev	L-Fuc(β1-6)	16
23	L-Fuc(α1-2)	PMB	D-Glc(1-4)	TBDPS	65
24	L-Fuc(α1-2)	L-Fuc(α1-3)	Lev	TBDPS	85
25	ClAc	D-Gal(α1-3)	Lev	D-Glc(β1-6)	26
26	ClAc	D-Gal(α1-3)	Lev	D-Glc(α1-6)	52
27	L-Fuc(α1-2)	PMB	Lev	D-Glc(α1-6)	60
28	ClAc	PMB	D-Gal(1-4)	D-Glc(1-6)	66
29	L-Fuc(α1-2)	D-Gal(α1-3)	L-Fuc(α1-4)	TBDPS	74
30	L-Fuc(α1-2)	D-Gal(α1-3)	L-Fuc(α1-4)	D-Gal(α1-6)	45
31	L-Fuc(α1-2)	D-Gal(α1-3)	L-Fuc(α1-4)	D-Gal(β1-6)	18
32	D-Gal(α1-2)	PMB	D-Gal(α1-4)	TBDPS	76
33	ClAc	L-Fuc(α1-3)	D-Gal(α1-4)	TBDPS	54
34	ClAc	L-Fuc(α1-3)	D-Gal(β1-4)	TBDPS	14
35	L-Fuc(α1-2)	PMB	D-Gal(α1-4)	TBDPS	61
36	L-Fuc(α1-2)	PMB	D-Gal(β1-4)	TBDPS	15
37	ClAc	PMB	D-Gal(α1-4)	L-Fuc(α1-6)	37
38	ClAc	PMB	D-Gal(α1-4)	L-Fuc(β1-6)	19
39	L-Fuc(α1-2)	PMB	L-Fuc(α1-4)	TBDPS	46
40	L-Fuc(β1-2)	PMB	L-Fuc(α1-4)	TBDPS	12
41	L-Fuc(α1-2)	PMB	L-Fuc(β1-4)	TBDPS	12
42	L-Fuc(β1-2)	PMB	L-Fuc(β1-4)	TBDPS	9
43	L-Fuc(α1-2)	D-Gal(α1-3)	ClAc	TBDPS	83[b]
44	Lev	D-Gal(α1-3)	D-Gal(β1-4)	TBDPS	46[b]
45	Lev	PMB	D-Gal(β1-4)	D-Gal(β1-6)	49[b]

[a] Overall isolated yield from the building block **1**. [b] Based on another building block with ClAc for R_3 and Lev for R_1.

Scheme 5



Acknowledgment. We thank Novartis Pharma for support of this work. We would like to thank Professor Glenn J. McGarvey for his helpful suggestion and discussion.

Supporting Information Available: Glycosyl donors, experimental procedures, and data for compounds (36 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA9813616