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Towards oligosaccharide library synthesis by fluorous mixture method

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ABSTRACT

The synthesis of an oligosaccharide library by a fluorous tag method is reported here. Several acceptors and donors were mixed and glycosylated. The reaction mixture was purified by chromatography over fluorous HPLC to provide disaccharides in order of increasing fluorine content of the tag. This method could be applied to oligosaccharide libraries consisting of two sets of structural isomers.

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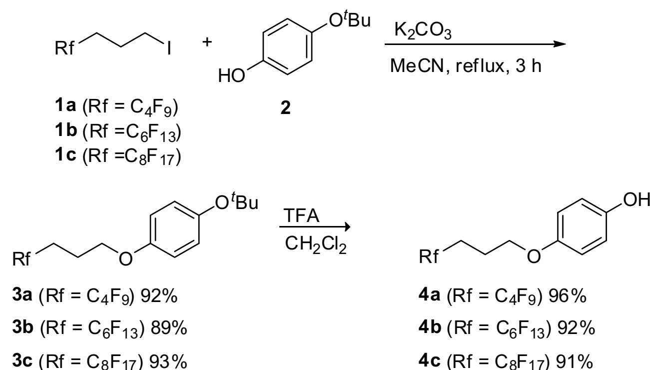
Most mixture syntheses in organic chemistry are run on solid-phase,[1] but solid-phase methods have problems such as low reactivity and difficulty to analyze intermediate compounds. Solution-phase mixture synthesis has favourable reaction kinetics, but this is offset by difficulties in separating target molecules. Recently, Curran and co-workers reported homogeneous fluorous solution-phase synthesis (fluorous mixture synthesis).[2] In this method, the use of fluorous tags and associated tag-based separation (e.g., fluorous HPLC) allows a mixture of intermediates to be analyzed and characterized, and finally to produce as individual, pure compounds. As a result, it could solve the problems of both solution- and solid-phase methods.

The development of efficient strategies for synthesizing oligosaccharides is highly desirable in order to understand the vital roles of oligosaccharides in biological phenomena.[3] In this regard, oligosaccharide mixture synthesis continues to attract much attention to rapidly obtain such molecules,[4] because multi-step oligosaccharide synthesis remains very difficult and time-consuming. Here, we describe the synthesis of an oligosaccharide library by a fluorous mixture method.

The introduced fluorous tag acts as a protective group that removes chemoselectivity and is stable under various reaction conditions. We selected the 4-methoxyphenyl type of fluorous tag, which is stable under acidic, basic, reductive and oxidative reactions.[5] This group can be removed readily and selectively under mild conditions by treatment with ceric ammonium nitrate (CAN).[6] We therefore prepared and tested *p*-alkoxyphenyl-type fluorous tags. The fluorous tags **4a** (C_4F_9), **4b** (C_6F_{13}) and **4c** (C_8F_{17}) were readily prepared from the corresponding fluorous iodides **1a**–**c** and phenol derivative **2** as shown in Scheme 1. Fluorous tag **4c** was reacted with a galactose derivative **5c** in the presence of $BF_3{\cdot}OEt_2$ to give galactose bearing fluorous tag **6c** with good yield (Table 1, run 3). Similarly, fluorous tags **4a** and **4b** were introduced to mannose derivative **5a** and glucose derivative **5b**, respectively, to obtain compounds **6a** and **6b** (runs 1 and 2). The *p*-alkoxyphenyl-type fluorous tags were easily cleaved from the monosaccharides in the presence of CAN in aq 80% MeCN (Scheme 2). The 1-OH derivative **7** was obtained 78% yield, and fluorous alcohol **8** was recovered in 64% yield.

Using the series of fluorous tags, we tested oligosaccharide mixture synthesis. The tagged monosaccharides **6a**–**c** were individually converted to the corresponding 6-OH-free monosaccharides **9**–**11**[7] in a four-step process, in which every intermediate was characterized by NMR. A mixture of three fluorous-tagged glycosyl acceptors **9**, **10** and **11** (1.0 equiv each) was treated with glycosyl



Scheme 1. Synthesis of *p*-alkoxyphenyl-type fluorous tag.

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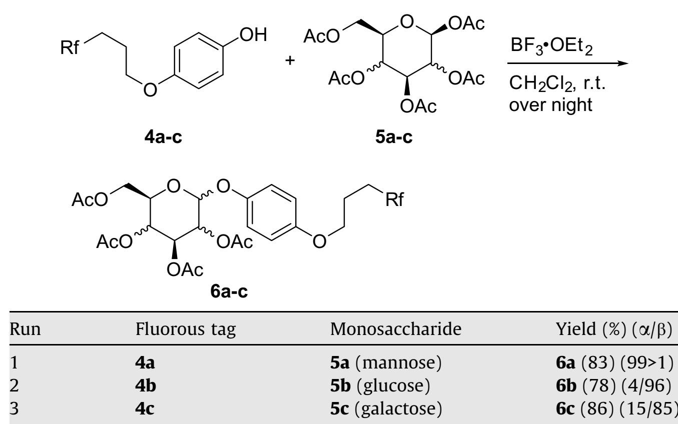
Table 1
Introduction of *p*-alkoxyphenyl-type fluorous tag into monosaccharide



Run	Fluorous tag	Monosaccharide	Yield (%) (α/β)
1	**4a**	**5a** (mannose)	**6a** (83) (99>1)
2	**4b**	**5b** (glucose)	**6b** (78) (4/96)
3	**4c**	**5c** (galactose)	**6c** (86) (15/85)

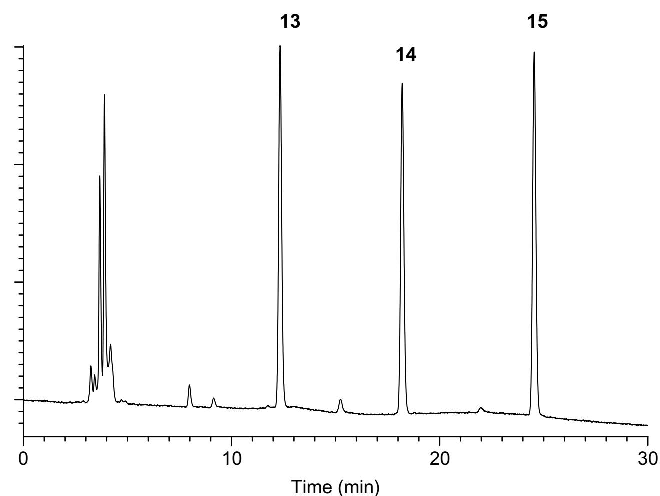
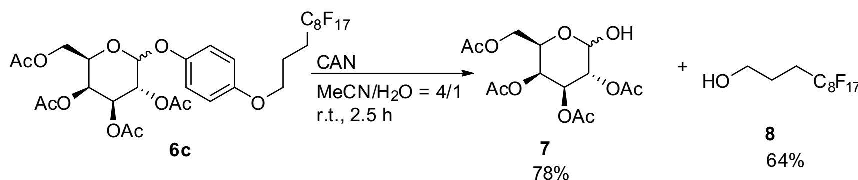


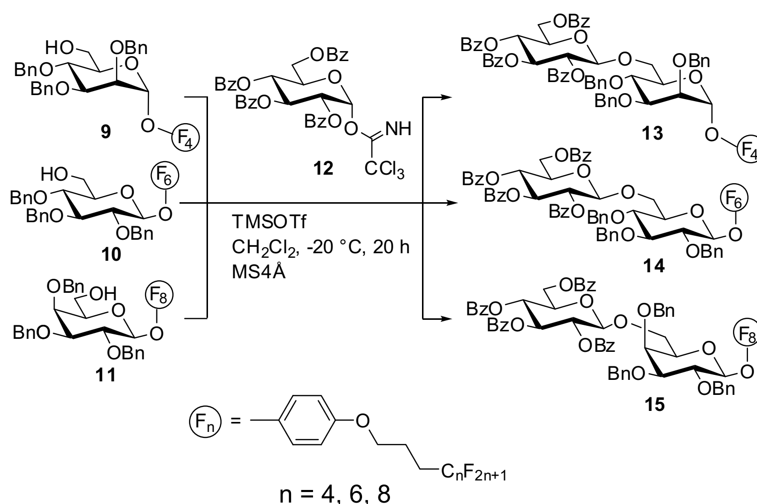
Figure 1. HPLC analysis of the glucosylation reaction mixture. Fluophase RP column (21 × 250 mm), gradient 80% MeCN–H_2O to 100% MeCN in 30 min and then 100% MeCN. UV detection at 280 nm and flow rate 1.0 mL/min.

donor **12**[7] (6.0 equiv) in the presence of TMSOTf (0.6 equiv) at −20 °C for 20 h. The crude reaction mixture was purified by chromatography over fluorous HPLC (gradient of 80/20 acetonitrile/water to 100% acetonitrile over 30 min). The result of HPLC analysis is shown in Figure 1. The compounds were eluted in the order of fluorophilicities of the tags: the first group of peaks was the solvent front including a mixture of compounds associated with glycosyl donor **12**; the second peak was product **13** with the C_4F_9 tag; the third peak was product **14** with the C_6F_{13} tag and the fourth peak was product **15** with the C_8F_{17} tag. NMR identified these three products individually[8] (see Scheme 3).

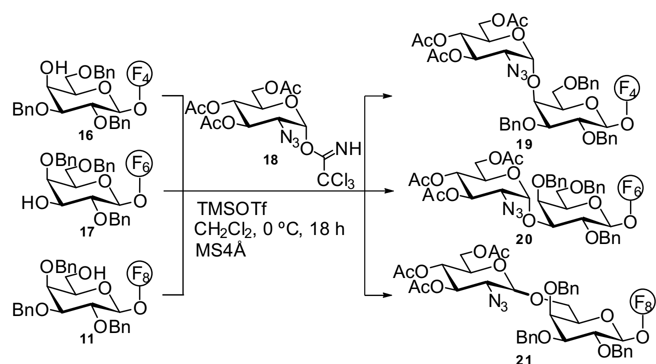
Next, we tested glycosylation of 3-OH, 4-OH and 6-OH-free monosaccharides. Glycosyl acceptors **16**[7], **17**[7] and **11** were mixed and treated with glycosyl donor **18**[7] under glycosylation conditions,[9] then separated by chromatography over fluorous HPLC (Scheme 4). The result of HPLC analysis is shown in Figure 2. The compounds were eluted in order of the tag: the first group of peaks was the solvent front and included a mixture of corresponding compounds associated with glycosyl donor **18**; the second peak was product **19** (α-isomer only) with the C_4F_9 tag; the third peak was product **20** (α-isomer accompanied with β-isomer) with the C_6F_{13} tag and the fourth peak was product **21** (mixture of a small amount of β-isomer and by-products along with α-isomer; α:β:by-product = 86:12:2, detected by HPLC[10]) with the C_8F_{17} tag.



Scheme 2. Cleavage of *p*-alkoxyphenyl-type fluorous tag.



Scheme 3.



Scheme 4.

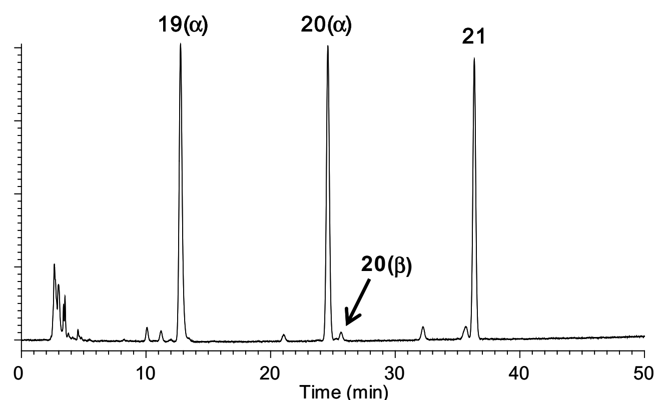
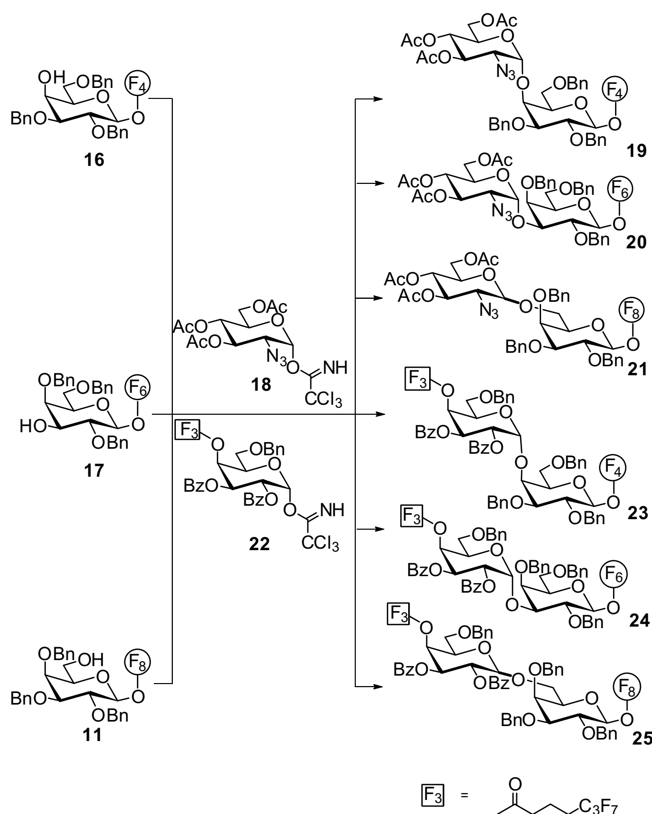


Figure 2. HPLC analysis of the glucosylation reaction mixture. Fluophase RP column (21 × 250 mm), gradient 80% MeCN–H_2O to 100% MeCN in 30 min and then 100% MeCN. UV detection at 280 nm and flow rate 1.0 mL/min.

These results (Figs. 1 and 2) indicated that the separation based on fluorous HPLC successfully resolved products according to the tag. The results suggest that the method may be applied to a coding method to create a complex oligosaccharide library. We propose to prepare more products in one glycosylation step by using three acceptors and two donors, to give six products. We expected that using an acceptor bearing 4, 6 or 8 fluorocarbons and a donor bearing 0 or 3 fluorocarbons would give products bearing 4, 6, 7, 8, 9 and 11 fluorocarbons, which could be easily separated by chromatography based on fluorous HPLC. Galactose acceptors bearing *p*-alkoxyphenyl fluorous tags **16** (C_4F_9), **17** (C_6F_{13}) and **11** (C_8F_{17}) and glycosyl donors with 0 fluorocarbons **18** and with 3 fluorocarbons (C_3F_7) **22** were selected as model substrates. These five monosaccharides were mixed and glycosylated,[11] then separated over fluorous HPLC as described above (Scheme 5 and Fig. 3).[12] This crude reaction mixture was divided into the six disaccharide products in one step. The products were eluted in the order of increasing total fluorine content of the tag: the first group of peaks (retention time around 4 min) was the solvent front including a mixture of compounds associated with glycosyl donor **18**; the second peak (11.2 min) was compounds with the C_3F_7 tag derived from glycosyl donor **22**;[13] the third peak was product **19** with the C_4F_9 tag (α-isomer only); the fourth peak was product **20** with the C_6F_{13} tag (α-isomer only); the fifth peak was product **23** with the C_4F_9 and C_3F_7 tags (β-isomer only); the seventh peak was product with the C_8F_{17} tag **21** (α-isomer) and a small amount of **21** (β-isomer) and by-products (α:β:by-product = 76:15:8, detected by HPLC[10]); the eighth peak was product **24** with the C_6F_{13} and C_3F_7 tags (β-isomer only) and the ninth peak was product **25** with the C_8F_{17} and C_3F_7 tags (β-isomer only).



Scheme 5.

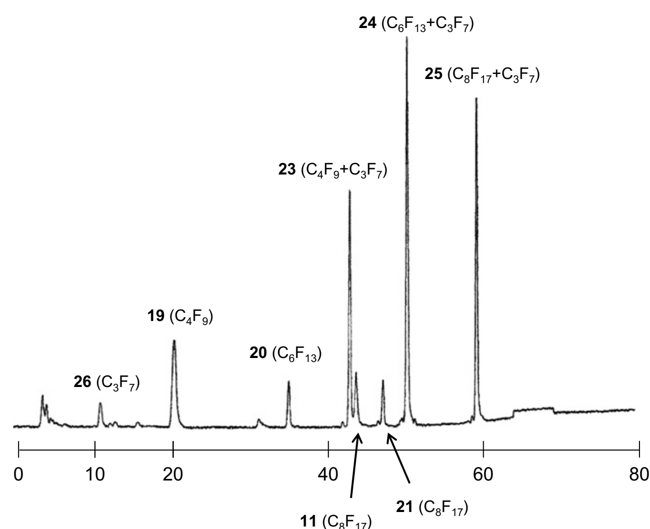


Figure 3. HPLC analysis of the glucosylation reaction mixture. Fluophase RP column (21 × 250 mm), 80% MeCN–H_2O in 15 min and then gradient 80% MeCN–H_2O to 100% MeCN in 40 min and finally, 100% MeCN. UV detection at 280 nm and flow rate 15.0 mL/min.

In summary, we synthesized a mixture of oligosaccharides by the fluorous tag method, in which several acceptors and donors are mixed and glycosylated, then separated by chromatography over fluorous HPLC to provide the desired disaccharides. This method has the advantage of a single separation, and could be applied to oligosaccharide libraries consisting of two sets of structural isomers. The results indicate that this method is useful for oligosaccharide library synthesis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.137.

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7. These compounds were prepared as described in Supplementary data.
8. Compound **13**: ^{1}H NMR (CD_3Cl, 600 MHz) δ: 2.02–2.06 (m, 2H), 2.23–2.32 (m, 2H), 3.80–3.91 (m, 4H), 3.94–4.00 (m, 3H), 4.04–4.09 (m, 1H), 4.11 (d, *J* = 9.6 Hz, 1H), 4.36–4.42 (m, 2H), 4.54–4.59 (m, 3H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.69 (q, *J* = 11.7 Hz, 1H), 4.88 (d, *J* = 8.3 Hz, 1H), 5.37–5.39 (m, 1H), 5.56 (dd, *J* = 8.3 Hz, 9.6 Hz, 1H), 5.61 (t, *J* = 9.6 Hz, 1H), 5.80 (t, *J* = 9.7 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 9.7 Hz, 2H), 7.14 (d, *J* = 6.2 Hz, 2H), 7.21–7.35 (m, 21H), 7.36–7.43 (m, 2H), 7.44–7.49 (m, 2H), 7.81 (t, *J* = 6.9 Hz, 4H), 7.88 (d, *J* = 6.9 Hz, 2H), 7.98 (d, *J* = 6.9 Hz, 2H). Compound **14**: ^{1}H NMR (CD_3Cl, 600 MHz) δ: 1.98–2.01 (m, 2H), 2.16–2.28 (m, 2H), 3.38–3.42 (m, 1H), 3.53–3.58 (m, 1H), 3.58–3.62 (m, 2H), 3.84 (dd, *J* = 6.2 Hz, 11.7 Hz, 1H), 3.93–4.01 (m, 2H), 4.01–4.15 (m, 1H), 4.11 (d, *J* = 10.3 Hz, 1H), 4.45 (dd, *J* = 7.6 Hz, 11.7 Hz, 1H), 4.47 (d, *J* = 12.4 Hz, 1H), 4.60 (dd, *J* = 3.5 Hz, 12.4 Hz, 1H), 4.68 (d, *J* = 11.0 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 7.6 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 5.00 (d, *J* = 7.6 Hz, 1H), 5.01 (d, *J* = 11.0 Hz, 1H), 5.54 (dd, *J* = 7.6 Hz, 9.6 Hz, 1H), 5.65 (t, *J* = 9.6 Hz, 1H), 5.80 (t, *J* = 9.6 Hz, 1H), 6.91 (d, *J* = 9.6 Hz, 2H), 7.04 (d, *J* = 9.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.21–7.38 (m, 21H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.47–7.56 (m, 2H), 7.80 (t, *J* = 7.6 Hz, 2H), 7.89 (d, *J* = 7.6 Hz, 2H), 8.00 (d, *J* = 6.9 Hz, 2H). Compound **15**: ^{1}H NMR (CD_3Cl, 600 MHz) δ: 1.97–2.07 (m, 2H), 2.15–2.27 (m, 2H), 3.42 (dd, *J* = 3.2 Hz, 10.0 Hz, 1H), 3.51 (t, *J* = 5.8 Hz, 1H), 3.77 (dd, *J* = 4.5 Hz, 12.1 Hz, 1H), 3.81 (dd, *J* = 4.8 Hz, 11.0 Hz, 1H), 3.92 (dd, *J* = 6.9 Hz, 11.7 Hz, 1H), 3.90–4.18 (m, 4H), 4.42 (dd, *J* = 4.5 Hz, 12.1 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 10.3 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.74 (d, *J* = 8.2 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.90 (d, *J* = 11.7 Hz, 1H), 4.96 (d, *J* = 11.0 Hz, 1H), 4.98 (d, *J* = 7.6 Hz, 1H), 5.48 (dd, *J* = 8.0 Hz, 10.0 Hz, 1H), 5.66 (t, *J* = 9.7 Hz, 1H), 5.80 (t, *J* = 9.7 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.21–7.38 (m, 23H), 7.40–7.52 (m, 4H), 7.79 (t, *J* = 7.5 Hz, 2H), 7.81 (d, *J* = 6.9 Hz, 2H), 7.87 (d, *J* = 6.9 Hz, 2H), 8.00 (d, *J* = 6.9 Hz, 2H).
9. The glycosylation conditions: acceptors **11** (1.0 equiv), **16** (1.0 equiv) and **17** (1.0 equiv) treated with donor **18** (6.0 equiv) in the presence of TMSOTf (0.6 equiv) at 0 °C for 16 h.
10. Although these compounds were not separated by fluorous HPLC, usual silica gel HPLC gave good separation. HPLC conditions: Wakosil 5SIL (4.0 × 15 mm), gradient 85/15 hexane/AcOEt to 80/20 hexane/AcOEt. UV detection at 280 nm; flow rate 1.0 mL/min.
11. The glycosylation conditions: acceptors **11** (48 mg, 48 μmol), **16** (37 mg, 46 μmol) and **17** (44 mg, 49 μmol) treated with donors **18** (52 mg, 10.8 μmol) and **22** (85 mg, 98 μmol) in the presence of TMSOTf (3.5 μL, 20 μmol) at −10 °C for 14 h.
12. This reaction mixture (255 mg) was obtained. An aliquot of the reaction mixture (189 mg) was separated over fluorous HPLC: peak 1 (compound **26**, trace), peak 2 (compound **19**, 12 mg), peak 3 (compound **20,** 6 mg), peak 4 (compound **23**, 16 mg), peak 5 (compound **11**, 5 mg), peak 6 (compound **21**, 2 mg), peak 7 (compound **24**, 22 mg) and peak 8 (compound **25,** 27 mg).
13. This compound was characterized as shown in the following: