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p-Alkoxyphenyl-type heavy fluorous tag for the preparation of carbohydrate units

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ABSTRACT

Carbohydrate glycosyl acceptor and donor moieties were synthesized efficiently by using the fluorous tag method. The *p*-alkoxyphenyl-type heavy fluorous tag was stable under all the reaction conditions used in the preparation of the various carbohydrate units. Each synthetic intermediate carrying the fluorous tag could be obtained in a simple straightforward manner by partition between fluorous and organic solvents.

1. Introduction

Fluorous chemistry using a fluorous biphasic system was first developed by Horváth and Rábai [1]. Curran and co-workers [2] suggested fluorous synthesis (the fluorous-tag method) as a strategic alternative to solid-phase synthesis.

Oligosaccharides on cell surfaces play important roles in biological processes, such as cell recognition, cell adhesion, immunogenic recognition, and so on [3]. To study these roles, it is necessary to synthesize structurally well-defined carbohydrates, such as glycoconjugates, and their mimics.

Oligosaccharides, however, are not readily synthesized. Although the solid-phase synthesis of oligosaccharides has been investigated [4], the usual solid-phase method suffers from some disadvantages, such as difficulties in large-scale synthesis, reduced reactivity, and the inability to monitor the reaction by TLC, NMR, or mass spectroscopy. Curran et al. described the synthesis of a 2-deoxydisaccharide by a fluorous tag method [5]. Our group has reported the rapid syntheses of oligosaccharides [6] and peptides [7] through the use of various fluorous tags.

However, efficient synthesis of oligosaccharide by the fluorous method was limited to the glycosylation step only. The carbohydrate units, such as the glycosyl donors and acceptors, were still prepared by classical organic synthesis techniques that required many steps and considerable labor. This has been one of the greatest and most intractable problems in oligosaccharide synthesis. An efficient preparation of carbohydrate units is essential to permit practical syntheses of oligosaccharides. Recently, we reported a method for the fluorous carbohydrate unit synthesis in a preliminary communication [8]. We would like to report the full details of the development of the fluorous carbohydrate unit synthesis in this paper.

In the synthesis of carbohydrate units, the *p*-anisyl (4-methoxyphenyl) group is an excellent candidate as a protecting group for hydroxyl functions, because the *p*-anisyl group is resistant to a wide range of conditions, including those present in acidic, basic, reductive, or oxidative reactions [9]. Additionally, the *p*-anisyl group can be readily and selectively removed under mild condition by treatment with ceric ammonium nitrate (CAN) [10]. We therefore prepared and tested a *p*-alkoxyphenyl-type heavy fluorous tag for use in the synthesis of carbohydrate units.

2. Results and discussion

A triphenylmethyl group (Tr) was introduced at one of the two primary hydroxyl groups of *meso*-erythritol [11] (**1**) to give the monoprotected derivative **2**. Compound **2** was coupled with the fluorous tosylate $TsO(CH_2)_3C_8F_{17}$ [12] in the presence of 15-crown-5 and then the Tr group was removed by treatment with camphorsulfonic acid (CSA) to give the fluorous tag **3**, which contains three fluorous chains, in 67% yield. The use of 15-crown-5 was essential in order to construct the three fluorous ether bonds smoothly. 4-(Benzoyloxy)phenol was then introduced as a linker by means of the Mitsunobu reaction to give the benzoate **4**. Finally, debenzoylation with NaOMe gave the fluorous tag **5** in 91% from **3**. A peracetylated carbohydrate moiety was attached to the fluorous

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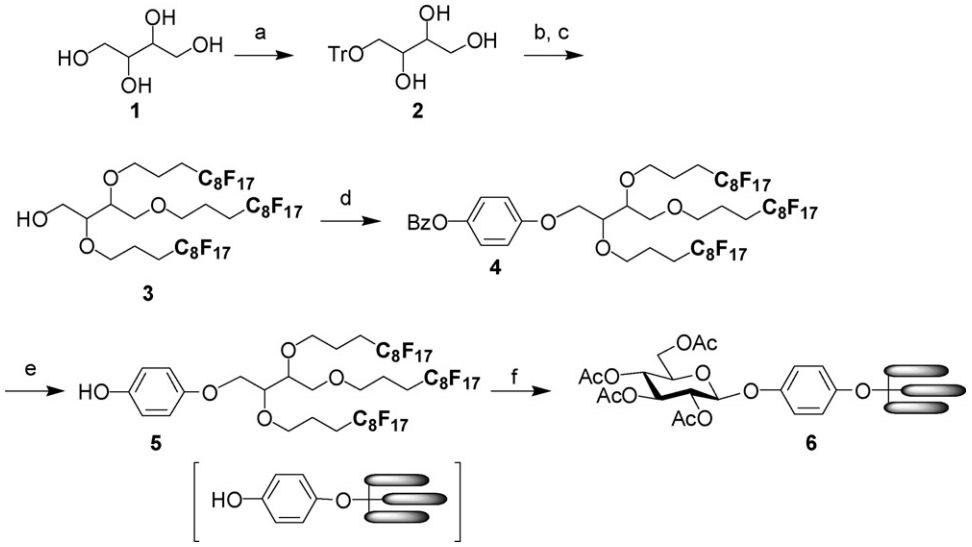


Scheme 1. Preparation and reaction of the fluorous tag **5**. *Reaction conditions*: (a) TrCl, DMAP, pyridine/DMF, rt, 20 h, 51%; (b) NaH, $TsO(CH_2)_3C_8F_{17}$, 15-crown-5, DMF, rt, 19 h; (c) CSA, MeOH/$CHCl_3$, rt, 2 h, 67% (two steps); (d) 4-(benzoyloxy)phenol, DEAD, PPh_3, THF, reflux, 2 h; (e) NaOMe, MeOH/HFE 7100, rt, 1 h, 91% (two steps); (f) penta-*O*-acetyl-β-D-glucopyranose, $BF_3{\cdot}OEt_2$, CH_2Cl_2/HFE 7100, rt, 16 h, 91%.

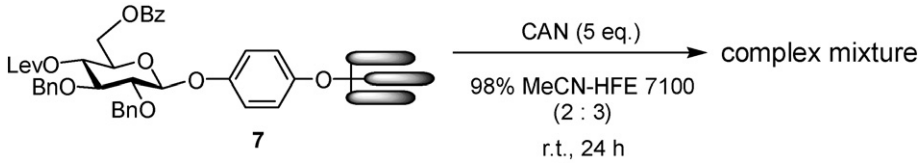
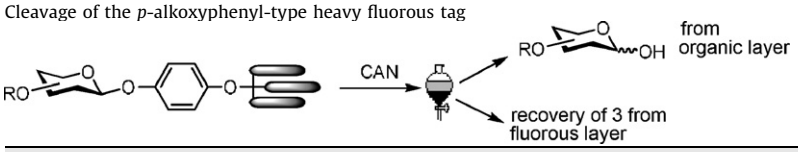


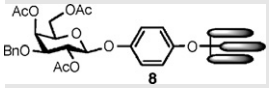
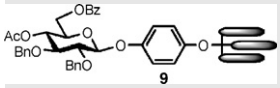
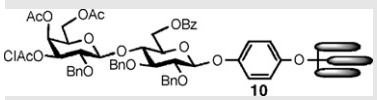
Fig. 1. Cleavage of the *p*-alkoxyphenyl-type heavy fluorous tag in aqueous MeCN.

tag **5** by coupling in the presence of boron trifluoride-diethyl ether complex ($BF_3{\cdot}OEt_2$) as the coupling reagent to give compound **6** (Scheme 1).

The *p*-methoxyphenyl group is usually cleaved by treatment with CAN in aqueous MeCN. Unfortunately, most of the compounds having a heavy fluorous tag, such as **3**, are insoluble in aqueous MeCN. In this study, HFE 7100 (HFE 7100 is a mixture of methyl nonafluorobutyl ether ($MeOCF_2CF_2CF_2CF_3$) and methyl nonafluoroisobutyl ether ($MeOCF_2CF(CF_3)_2$) [13] was used as a co-solvent to dissolve the fluorous compound in aqueous MeCN.

Table 1
Cleavage of the *p*-alkoxyphenyl-type heavy fluorous tag



Substrate	Run	Temperature (°C)	Time (h)	Solvent[a]	CAN (eq.)	Yield (%)	1-OH: 2-OH	Recovery of **3** (%)
7	1	0	6.5	B	10	75		85
 **8**	2	r.t.	1.5	A	5	88[b]	2:3	88
	3	r.t.	0.25	A	10	86[b]	2:1	89
	4	0	2	A	10	97[b]	13:1	97
 **9**	5	0	4	B	10	76		85
 **10**	6	0	5	B	10	74		85

[a] A = EtCN/H_2O (1:1) and B = EtCN/PhMe/H_2O (4:1:4).
[b] Total yield of the 1-OH and 2-OH derivatives.

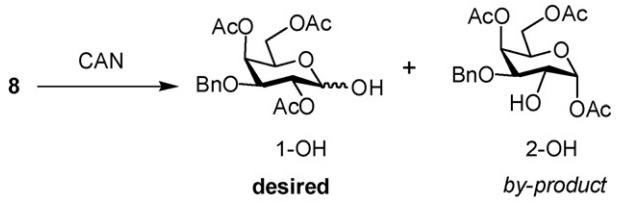


Fig. 2. Acyl migration under cleavage conditions using CAN.

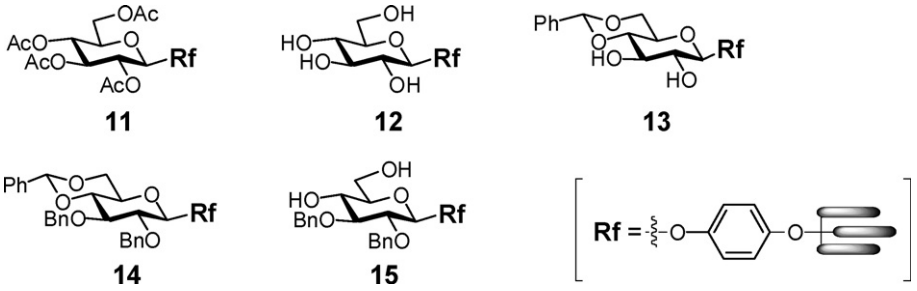
Compound **7** was treated with CAN in homogeneous mixture of aqueous MeCN and HFE 7100. However, the reaction did not proceed well and gave a complex mixture of products (Fig. 1).

Propionitrile (EtCN) is a better solvent for compound **8** than is MeCN, and the cleavage of *p*-alkoxyphenyl-type fluorous tag and recovery of the fluorous tag **3** were achieved by using this solvent (Table 1). However, because of the acidic conditions produced by the aqueous CAN system, acyl migration occurred and the 2-OH derivative was obtained as a by-product (Fig. 2). Acyl migration could be suppressed by performing the cleavage reaction at a low temperature, which also increased the yield and recovery of **3** (Table 1, run 4). In the cases of **7**, **9** and **10**, the addition of toluene gave good results.

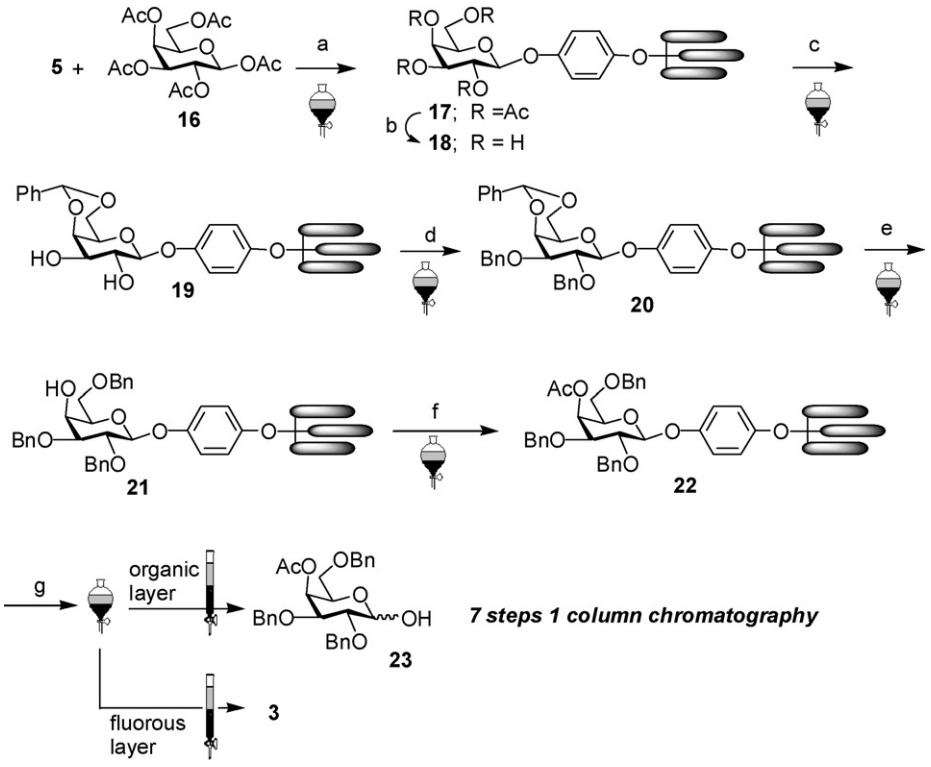
In the heavy fluorous method, the partition coefficient for the fluorous–organic bisphasic system is a very important factor. The partition coefficients of the five fluorous derivatives **11**–**15** were measured in seven biphasic systems with MeOH, CH_3CN, toluene, or EtOAc as the organic layer and FC72 (FC72 is a mixture of perfluorohexanes, C_6F_{14}) [14] or a mixture of FC72 and HFE 7100 as the fluorous layer (Table 2). The fluorous compounds **11**–**15** showed low solubilities in the non-polar fluorous solvent FC72. Additionally, partition coefficients with FC72 depended on the properties of the organic moiety of the fluorous compounds (entries 1–3). This result means that the use of FC72 in a partitioning system would require the solubility to be tested for each individual carbohydrate unit that is synthesized, and this would eliminate the rapidity and efficiency that are the principal advantages of fluorous method. Recently, Curran and his co-workers reported new fluorous–organic biphasic systems using hydrofluoro ethers [15]. Although hydrofluoro ethers dissolve fluorous compounds, they are also miscible with organic solvents. To use hydrofluoro ethers in fluorous–organic biphasic systems, they are mixed with perfluorocarbons [15]. We examined various hydrofluoro ether–perfluorocarbon mixtures, and found that a 4:1 mixture of HFE 7100 and FC72 is suitable as a fluorous layer in the synthesis of carbohydrate units. We performed partition tests (entries 5–7) using this fluorous blend and three aqueous organic layers (aq. MeOH, aq. EtOH, and aq. MeCN). The aqueous MeCN system (entry 7) showed the high overall partition coefficients for compounds **11**–**15**. From these results, we selected the system [HFE 7100/FC 72 (4:1)]/[MeCN/5% H_2O] as the bisphasic partitioning system for the synthesis of carbohydrate units.

We chose the galactose derivative **23** (Scheme 2) as a model carbohydrate unit. The fluorous tag **5** was attached to per-*O*-acetyl-β-D-galactopyranose (**16**) [16] by using $BF_3{\cdot}OEt_2$ as the coupling reagent to give compound **17**. All the acetyl groups of **17** were removed by treatment with NaOMe in MeOH/$MeOC_4F_9$ to give compound **18**. Treatment of **18** with benzaldehyde dimethylacetal in the presence of CSA gave compound **19**, which was benzylated to give **20**. Treatment of the 4,6-*O*-benzylidene-protected derivative **20** with triethylsilane (Et_3SiH) and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 gave the 6-*O*-benzyl derivative **21**, which was acetylated to give **22**. The fluorous intermediates **17** and **19**–**21** could each be extracted with a fluorous mixed solvent ($MeOC_4F_9$/FC 72 = 4:1) by partitioning the product mixtures between the fluorous mixed solvent and an organic solvent such as 95% aqueous MeCN. These compounds, including the fluorous tag, were extracted into the fluorous layer, and the other reagents were extracted into the organic layer. After three extractions with fluorous solvent, no fluorous compounds were detectable in the organic layer by TLC. No further purification, such as silica-gel column chromatography, was conducted. Workup of compound **22** involved a normal organic–aqueous extraction system. Finally, cleavage of the fluorous tag by using CAN in EtCN/PhMe/H_2O gave crude **23**, which was extracted into the organic layer by partitioning between fluorous mixed solvent ($MeOC_4F_9$/FC72 = 4:1) and 95% aq. MeCN. After a single stage of silica-gel column chromatography, the 1-OH galactose derivative **23** was obtained in seven steps with 42% overall yield from **5**. The fluorous tag **5** was recovered from the fluorous layer in 70% yield and could be recycled (Scheme 2).

Table 2
The partition coefficients of compounds **11**–**15** in various fluorous–organic biphasic systems



Entry	Partitioning system	Compound				
		11	**12**	**13**	**14**	**15**
1	FC72/MeOH	81:19	57:43	98:2	Emulsion	49:51
2	FC72/MeCN	57:43	96:4	91:9	87:13	75:25
3	FC72/PhMe	<1:>99	>99:<1	94:6	<1:>99	30:70
4	FC72/AcOEt	<1:>99	<1:>99	<1:>99	<1:>99	<1:>99
5	FC72 + HFE7100/MeOH (1:4) with 5% H_2O	94:6	45:55	66:34	94:6	68:32
6	FC72 + HFE7100/EOH (1:4) with 5% H_2O	67:33	21:79	33:67	59:41	31:69
7	FC72 + HFE7100/MeCN (1:4) with 5% H_2O	97:3	90:10	83:17	97:3	93:7



Scheme 2. Synthesis of galactose derivative **23**. *Reaction conditions*: (a) $BF_3{\cdot}OEt_2$, $CH_2Cl_2/MeOC_4F_9$, rt, 16 h; (b) NaOMe, $MeOH/MeOC_4F_9$, rt, 30 min; (c) $PhCH(OMe)_2$, CSA, $MeCN/MeOC_4F_9$, rt 1 h; (d) BnBr, NaH, 15-crown-5, THF, rt, 20 h; (e) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 1.5 h; (f) Ac_2O, Et_3N, THF, rt, 5 h; (g) CAN, $EtCN/PhMe/H_2O$ (4:1:4), 0 °C, 40 min, then silica-gel column chromatography; 42% from **5** (seven steps).

3. Conclusions

In conclusion, we achieved an efficient and high-yielding synthesis of a carbohydrate unit by using the *p*-alkoxyphenyl-type heavy fluorous tag **5**. Fluorous tag **5** was readily introduced on to a commercially available monosaccharide, and was stable under the reaction condition required for the preparation of the various monosaccharide units. Each fluorous synthetic intermediate could be obtained in a straightforward manner by simple partition between a fluorous solvent and an organic solvent. In the synthesis of monosaccharide units, a biphasic system comprising a fluorous mixed-solvent [HFE 7100/FC72 (4:1)] phase and an aqueous–organic [acetonitrile/water (95:1)] phase gave good partition coefficients. As a result, the desired monomeric building blocks were obtained with only a single silica-gel column chromatographic purification step.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded using JEOL JNM-ECA-600 (600 MHz) spectrometers. MALDI-TOF-MS were recorded using Voyager-DE^{TM} STR, and α-cyano-4-hydroxy cinnamic acid was used as a matrix. ESI-TOF-MS were recorded on Mariner^{TM}. Part of the product was isolated by column chromatography on silica-gel (Kanto Chemical, silica-gel 60N, spherical, neutral, 40–50 μm). The fluorous solvent FC72 and Novec HFE7100 were purchased from 3 M.

4.2. 4-(Triphenylmethoxy)butane-1,2,3-triol (2)

A solution of compound **1** (*meso*-erythritol; 3.33 g, 27.3 mmol), trityl choride (7.60 g, 27.3 mmol) and catalytic amount of DMAP in pyridine (80 mL)–DMF (20 mL) were stirred for 24 h at 50 °C. The reaction mixture was concentrated. The residue was extracted with EtOAc. The EtOAc layers were washed with water, 1N aq. HCl, saturated aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica-gel (hexane:EtOAc = 5:1) to give compound **2** (5.12 g, 51%) as a white amorphous solid. R_f = 0.58 (EtOAc); ^{1}H NMR (600 MHz, CD_3OD): δ = 7.47 (d, J = 7.6 Hz, 6H), 7.18–7.31 (m, 9H), 3.75–3.80 (m, 1H), 3.61–3.70 (m, 2H), 3.56 (dd, J = 6.2, 11.0 Hz, 1H), 3.26–3.31 (m, 1H), 3.22 (dd, J = 6.2, 9.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$):145.45, 129.92, 128.71, 128.00, 87.90, 73.86, 72.96, 66.69, 64.57; HRMS (ESI-TOF-MS): Calcd. for $C_{23}H_{24}O_4Na$ m/z $[M+Na]^+$: 387.1567, Found: 387.1554.

4.3. 2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)-1-butanol (3)

To a mixture of compound **2** (3.59 g, 9.85 mmol), $TsO(CH_2)_3C_8F_{17}$ (22.4 g, 35.5 mmol) and 15-crown-5 (7.04 mL, 35.5 mmol) in dry THF (60 mL) was added NaH (1.55 g, 35.5 mmol) slowly at 0 °C. After stirring for 1 h at 0 °C, the temperature of the reaction mixture was allowed to increase to room temperature. After stirring for 18 h at room temperature, excess NaH was carefully destroyed by adding MeOH (5.0 mL). The solution of the reaction was added to saturated aq. $NaHCO_3$, and extracted with EtOAc. The EtOAc layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was partitioned between MeCN and FC-72 (3×). The combined FC-72 layers were concentrated. The residue (15.7 g) and CSA (18.5 g, 79.6 mmol) were then dissolved in $CHCl_3$ (200 mL)–MeOH (100 mL) at room temperature. After stirring for 40 min at room temperature, the reaction mixture was added to MeOH and partitioned with FC72 (3×). The combined FC-72 layers were

concentrated. The residue was purified by column chromatography on silica-gel (hexane:EtOAc, 3:1) to give the fluorous tag **3** (9.94 g, 67%, two steps) as a white amorphous solid. R_f = 0.40 (hexane:EtOAc = 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.78 (td, J = 4.8, 11.7 Hz, 1H), 3.67–3.73 (m, 3H), 3.59–3.65 (m, 2H), 3.47–3.58 (m, 5H), 3.44 (dd, J = 4.1, 9.6 Hz, 1H), 2.10–2.25 (m, 6H), 2.02 (t, J = 5.4 Hz, 1H), 1.82–1.93 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 106.20–120.77 (complex signals of –**C**F_2– and –**C**F_3), 79.50, 78.97, 70.34, 70.01, 69.23, 68.99, 61.04, 27.88 (t, $^2J_{CF}$ = 21.7 Hz, –CH_2CH_2**C**H_2–C_8F_{17}), 21.23 (brs, –CH_2**C**H_2CH_2–C_8F_{17}), 20.79 (brs, –CH_2**C**H_2CH_2–C_8F_{17}); ^{19}F NMR (600 MHz, $CDCl_3$): δ = −81.34 (m, 9F), −114.95 (m, 6F), −122.32 (m, 6F), −122.53 (m, 12F), −123.31 (m, 6F), −124.06 (m, 6F), −126.71 (m, 6F); MALDI-TOF-MS: Calcd. for $C_{37}H_{25}F_{51}O_4Na$ m/z [M+Na]$^+$: 1525.1; Found: 1525.0.

4.4. 4-[2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)butoxy]phenyl benzoate (4)

To a mixture of compound **3** (6.04 mL, 4.02 mmol) and 4-bemzoyloxy-phenol (2.58 g, 12.1 mmol) in THF (60 mL) were added PPh_3 (2.11 g, 8.03 mmol) and DEAD (3.66 mL, 8.03 mmol) at room temperature. After stirring for 1 h at reflux condition, the reaction mixture was concentrated and partitioned between MeOH and FC72 (3×). The combined FC72 layers were concentrated to give the crude compound **4** (6.87 g). The crude compound **4** was used in the next step without further purification.

4.5. 4-[2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)butoxy]phenol (5)

To a solution of the crude compound **4** (6.87 g) in HFE7100 (60 mL)–MeOH (60 mL) was added a sodium methoxide solution (28%) in MeOH (600 μL) at room temperature. After stirring for 3 h at room temperature, FC72 (15 mL) and water (3 mL) were added to the reaction mixture. The solution of the reaction mixture was partitioned between [HFE7100:FC72 (4:1)] (3×) and [MeOH with 5% H_2O] (2×). The combined fluorous layers were evaporated off. The residue was purified by column chromatography on silica-gel (hexane:EtOAc = 4:1) to give pure compound **5** (5.86 g, 91% in two steps) as a white amorphous solid. R_f = 0.49 (hexane:EtOAc = 3:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.78 (d, J = 8.9 Hz, 2H), 6.75 (d, J = 8.9, 2H), 4.45 (s, 1H), 4.10 (dd, J = 3.7, 10.3 Hz, 1H), 3.99 (dd, J = 4.8, 10.3 Hz, 1H), 3.74–3.80(m, 1H), 3.47–3.73 (m, 9H), 2.07–2.24 (m, 6H), 1.79–1.93 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.94, 149.93, 106.05–120.59 (complex signals of –**C**F_2– and –**C**F_3), 116.13, 115.66, 78.75, 78.27, 70.22, 69.97, 69.54, 67.48, 67.87, 27.88 (t, $^2J_{CF}$ = 21.7 Hz, –CH_2CH_2**C**H_2–C_8F_{17}), 21.15 (brs, –CH_2**C**H_2CH_2–C_8F_{17}), 20.77 (brs, –CH_2**C**H_2CH_2–C_8F_{17}); ^{19}F NMR (600 MHz, $CDCl_3$): δ = −81.41 (m, 9F), −114.95 (m, 6F), −122.34 (m, 6F), −122.55 (m, 12F), −123.34 (m, 6F), −124.10 (m, 6F), −126.75 (m, 6F); (MALDI-TOF-MS): Calcd. for $C_{43}H_{29}F_{51}O_5Na$ m/z [M+Na]$^+$: 1617.6; Found: 1617.6.

4.6. 4-[2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)butoxy]phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (6)

To a mixture of the fluorous tag **5** (2.01 g, 1.27 mmol) and penta-*O*-acetyl-β-D-glucopyranose (2.47 g, 6.33 mmol) in HFE7100 (20 mL)–MeOH (10 mL) was added $BF_3{\cdot}OEt_2$ (802 μL, 6.33 mmol) at room temperature. After stirring for 14 h at room temperature, the reaction mixture was added to brine, and extracted three times with $CHCl_3$. The $CHCl_3$ layers were washed with saturated aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was partitioned between [HFE7100:FC72 (4:1)] (3×) and [MeCN with 5% H_2O] (2×). The combined fluorous layers were evaporated off. The residue was purified by column chromatography on silica-gel (hexane:EtOAc = 3:1) to give compound **6** (2.23 g, 91%) as a white amorphous solid. R_f = 0.51 (hexane:AcOEt = 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.94 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 5.27 (t, J = 8.9 Hz, 1H), 5.23 (t, J = 7.6 Hz, 1H), 5.16 (t, J = 8.9 Hz, 1H), 4.95 (d, J = 7.6 Hz, 1H), 4.29 (dd, J = 5.5, 12.3 Hz, 1H), 4.17 (dd, J = 2.7, 12.3 Hz, 1H), 4.11 (dd, J = 3.4, 10.3 Hz, 1H), 4.01 (dd, J = 5.5, 10.3 Hz, 1H), 3.48–3.82 (m, 11H), 1.92–2.24 (m, 18H), 1.79–1.91 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.59, 170.29, 169.45, 169.33, 154.91, 151.28, 105.97–120.66 (complex signals of –**C**F_2– and –**C**F_3), 118.76, 115.27, 100.31, 78.69, 78.17, 72.80, 72.04, 71.28, 70.17, 69.93, 69.48, 68.35, 67.71, 61.97, 27.85 (t, $^2J_{CF}$ = 21.7 Hz, –CH_2CH_2**C**H_2–C_8F_{17}), 21.15 (brs, –CH_2**C**H_2CH_2–C_8F_{17}), 20.75 (brs, –CH_2**C**H_2CH_2–C_8F_{17}), 20.64, 20.60; ^{19}F NMR (600 MHz, $CDCl_3$): δ = −81.32 (m, 9F), −114.93 (m, 6F), −122.32 (m, 6F), −122.53 (m, 12F), −123.31 (m, 6F), −124.04 (m, 6F), −126.69 (m, 6F); (MALDI-TOF-MS): Calcd. for $C_{57}H_{47}F_{51}O_{14}Na$ m/z [M+Na]$^+$: 1947.2; Found: 1947.3.

4.7. 4-[2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)butoxy]phenyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (17)

To a mixture of the fluorous tag **5** (5.21 g, 3.27 mmol) and **16** (6.38 g, 16.3 mmol) in dry CH_2Cl_2 (50 mL)–dry HFE7100 (25 mL) was added $BF_3{\cdot}OEt_2$ (1.90 mL, 16.3 mmol) at 0 °C. After stirring for 20 min at 0 °C, the temperature of the reaction mixture was allowed to increase to room temperature. After stirring for 18 h at room temperature, the reaction mixture was added to brine, and extracted with $CHCl_3$ (3×). The $CHCl_3$ layers were washed with saturated aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and evaporated off. The residue was partitioned between [HFE7100:FC72 (4:1)] (3×) and [MeCN with 5% H_2O] (2×). The combined fluorous layers were concentrated to give the crude compound **17** (6.32 g). The crude compound **17** was used in the next step without further purification.

4.8. 4-[2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)butoxy]phenyl β-D-galactopyranoside (18)

To a solution of the crude compound **17** (6. 29 g) in HFE7100 (60 mL)–MeOH (60 mL) was added sodium methoxide (120 μL, 28% in MeOH solution) at room temperature. After stirring for 30 min at room temperature, the reaction mixture was treated with Amberlite IR-120 (H^+ form). After filtration, the filtrate was concentrated to give the crude compound **18** (5.80 g). The crude compound **18** was used in the next step without further purification.

4.9. 4-[2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)butoxy]phenyl 4,6-O-benzylidene-β-D-galactopyranoside (19)

To a mixture of the crude compound **18** (4.23 g) and benzaldehyde dimethylacetal (1.07 mL, 7.11 mmol) in dry HFE7100 (135 mL)–dry CH_2CN (90 mL) was added CSA (450 mg) to adjust to pH 3. After stirring for 1 h at room temperature, triethylamine (1.5 mL), FC72 (15 mL) and water (3 mL) were added to the reaction mixture. The solution of the reaction mixture was partitioned between [HFE7100:FC72 (4:1)] (3×) and [MeCN with 5% H_2O] (2×). The combined fluorous layers were evaporated to give the crude compound **19** (4.35 g). The crude compound **19** was used in the next step without further purification.

*4.10. 4-[2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)butoxy]phenyl 2,3-di-O-benzyl-4,6-O-benzylidene-β-D-galactopyranoside (**20**)*

To a mixture of the crude compound **19** (4.33 g), BnBr (1.68 nL, 14.2 mmol) and 15-crown-5 (2.81 mL, 17.0 mmol) in dry THF (45 mL) was added NaH (741 mg, 17.0 mmol) slowly at 0 °C. After stirring for 1 h at 0 °C, the temperature of the reaction mixture was allowed to increase to room temperature. After stirring for 18 h at room temperature, excess NaH was carefully destroyed by adding MeOH (5.0 mL). The solution of the reaction mixture was added to saturated aq. $NaHCO_3$, and extracted with EtOAc. The EtOAc layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated off. The residue was partitioned between [HFE7100:FC72 (4:1)] (3×) and [MeCN with 5% H_2O] (2×). The combined fluorous layers were evaporated to give the crude compound **20** (4.93 g). The crude compound **20** was used in the next step without further purification.

*4.11. 4-[2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)butoxy]phenyl 2,3,6-tri-O-benzyl-β-D-galactopyranoside (**21**)*

To a mixture of the crude compound **20** (1.20 g) and molecular sieves AW-300 (2.5 g) in dry $CHCl_2$ (25 mL) were added Et_3SiH (1.10 mL, 6.90 mmol), and $BF_3{\cdot}OEt_3$ (66.8 μL, 575 μmol) at 0 °C under an argon atmosphere. After the reaction mixture was stirred for 1.5 h at 0 °C, the mixture was quenched with saturated aqueous $NaHCO_3$ and filtered through Celite. The filtrate was extracted with EtOAc. The EtOAc layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was partitioned between [HFE7100:FC72 (4:1)] (3×) and [MeCN with 5% H_2O] (2×). The combined fluorous layers were evaporated to give the crude compound **21** (1.15 g). The crude compound **21** was used in the next step without further purification.

*4.12. 4-[2,3,4-Tris(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)butoxy]phenyl 4-O-acetyl-2,3,6-tri-O-benzyl-β-D-galactopyranoside (**22**)*

To a mixture of compound **21** (1.02 g) and triethylamine (500 μL, 3.60 mmol) in dry THF (10 mL) were added acetic anhydride (300 μL, 3.20 mmol) and catalytic amount of DMAP at room temperature. After stirring for 5 h at room temperature, excess acetic anhydride was carefully destroyed by adding MeOH (2.0 mL) at 0 °C. The solution of the reaction was extractively worked up with EtOAc to give the crude compound **22** (1.03 g). The crude compound **22** was used in the next step without further purification.

*4.13. 4-O-Acetyl-2,3,6-tri-O-benzyl-α,β-D-galactopyranose (**23**)*

The crude compound **22** (1.00 g) was treated with cerium (IV) ammonium nitrate (CAN; 2.71 g, 4.94 mmol) in EtCN (10 mL)–toluene (2.5 mL)–H_2O (10 mL) on an ice-water bath for 40 min. The solution of the reaction mixture was diluted with EtOAc and cold-water. The separated aqueous layer was extracted with EtOAc. The EtOAc layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (anhydrous $MgSO_4$), filtered and concentrated. The residue was partitioned between FC72 (3×) and MeCN (2×). The combined MeCN layers were concentrated. The residue was purified by column chromatography on silica-gel (hexane:EtOAc, 3:1) to provide compound **23** (101 mg, 42%, seven steps, α/β = 3/2) as a pale yellow foam. The combined FC-72 layers were evaporated. The residue was purified by column chromatography on silica-gel (hexane:EtOAc, 3:1) to recover the fluorous tag **3** (602 mg, 81%, seven steps).Compound **23** (α/β = 3/2): R_f = 0.26 (hexane:EtOAc = 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.24–7.37 (m, Ar), 5.60 (d, J = 2.7 Hz, H-4α), 5.53 (d, J = 2.1 Hz, H-4β), 5.27 (d, J = 2.7 Hz, H-1α), 4.42–4.48 (m, H-1β, PhC**H**$_2$–), 4.32 (t, J = 6.2 Hz, H-5α), 3.93 (dd, J = 2.7, 10.3 Hz, H-3α), 3.72–3.79 (m, H-2α, 5β), 3.41–3.72 (m, O**H**β, H-3β, 6aβ, 2β, 6aα, 6bβ, 6bα), 3.15 (brs, O**H**α); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.41, 170.34, 138.46, 138.14, 137.98, 137.75, 137.59, 137.44, 128.49, 128.44, 128.36, 128.32, 128.11, 128.08, 128.04, 128.02, 127.92, 127.83, 127.74, 127.68, 97.45, 92.02, 79.80, 79.29, 75.91, 75.65, 75.28, 73.73, 73.71, 73.60, 72.27, 72.04, 71.87, 68.49, 68.37, 67.94, 67.82, 66.96; HRMS (ESI-TOF-MS): Calcd. for $C_{29}H_{32}O_7Na$ m/z $[M+Na]^+$: 515.2040; Found: 515.2048.

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