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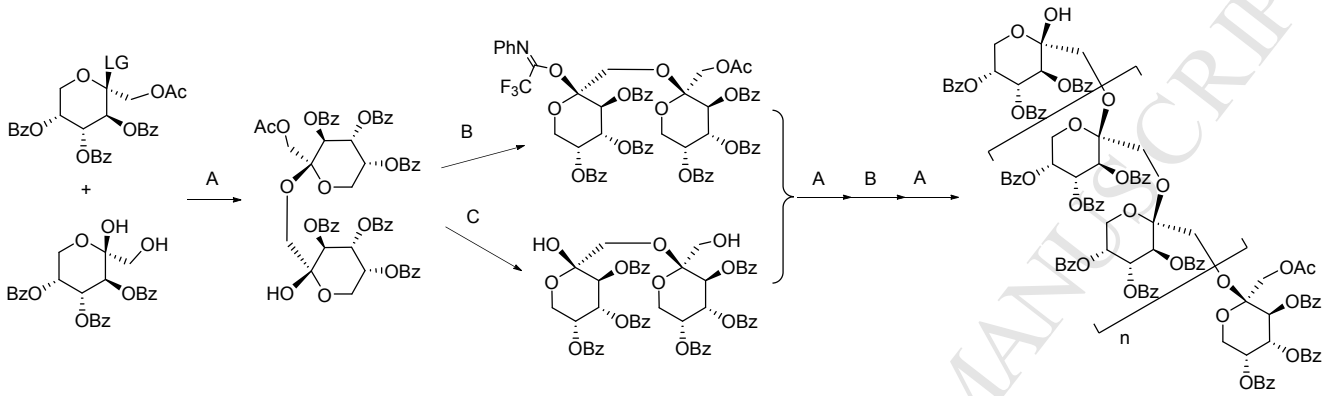

Synthesis of Oligo-Fructopyranoside with Difructopyranosyl N-phenyltrifluoroacetimidate Donor

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Abstract

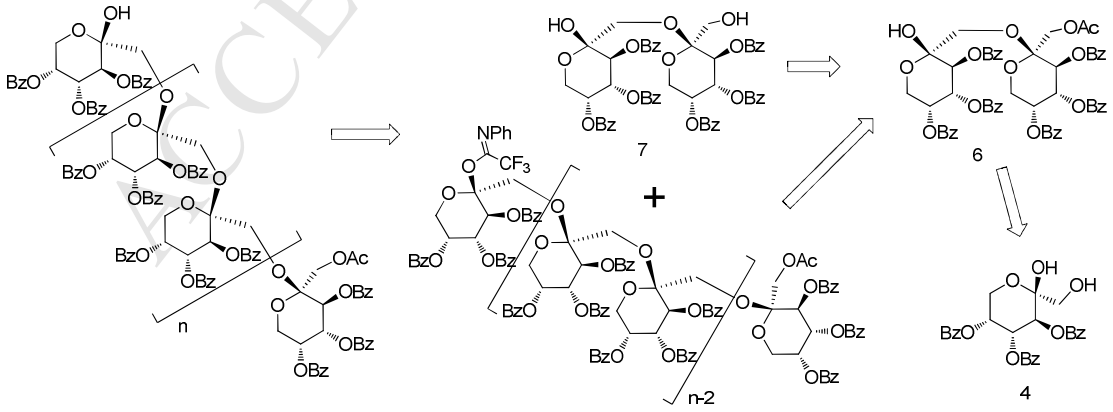
The hexa-fructopyranoside was synthesized with N-phenyltrifluoroacetimidate glycosylation. The synthesis was achieved by regioselective glycosylation on the 1-OH of fructopyranosyl acceptor. Fructosyl oligosaccharides were elongated with β-(2 → 1)-difructopyranosyl unit in every two steps, without any further protection/deprotection step. This work proved N-phenyltrifluoroacetimidate glycosylation a practical method for oligo-fructopyranoside synthesis.

Key Words

Glycosylation; fructopyranoside; N-phenyltrifluoroacetimidate; oligosaccharide synthesis

Inulins are naturally occurring polysaccharides produced by many types of plants as a means of storing energy. Inulins also exhibit interesting bioactivities.[1] *Achyranthes bidentata polysaccharides* (ABPS), which is a kind of inulin isolated from traditional Chinese herbal medicine *Achyranthes bidentala*, contain hexa- to octa-fructosyl unit (around 1400 Da of MW) and exhibited antitumor and immunomodulating activities.[2,3,4].

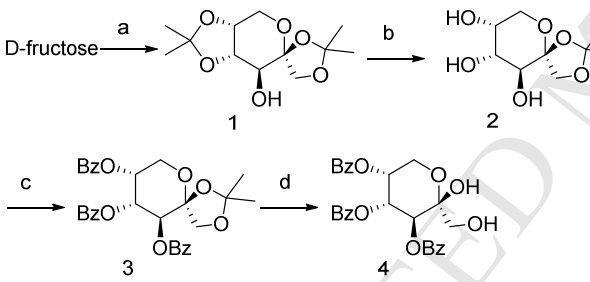
The synthesis of β-fructosides was difficult, especially for the β-fructofuranosides.[5,6] No glycosylation method was applicable for oligo-β-D-fructofuranosides' preparation till now. The pyrano-type analogs of ABPS could be an interesting alternative choice to study. There is no evidence that oligo-β-D-fructopyranosides exist in nature,[7,8] to the best of our knowledge. Although fructopyranosides are simple and common, fructopyranosyl oligomer is the first artificial designed oligosaccharide. Kaji and coworkers investigated the glycosylation methods for β-D-fructopyranosides and reported a related work with poor yields for trisaccharide preparation (<25%).[9] There are some other works reported on the preparation of β-D-fructopyranosides, but the glycosylation methods were not applicable in oligomer synthesis.[10] Recently we reported the β-selective synthesis of fructopyranosides[11] with *N*-phenyltrifluoroacetimidate donor.[12,13] By these methods, hexa-fructopyranoside was effectively synthesized with dimeric elongation strategy, which we report herein.



Scheme 1. Retrosynthesis of fructopyranose oligomer.

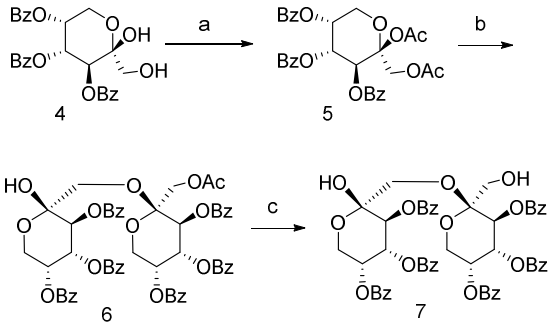
The retrosynthetic analysis is as Scheme 1. Diol **7** could be derived from diol **4**. According to our previous experiments, the anomeric OH of ketose is much more inert than the primary 1-OH in glycosylation.[11] The fructosyl diol could be directly used for glycosylation, then the glycosylated product could be directly transformed to the donor for subsequent reaction. Thus, the oligomer was elongated with difructosyl unit in every second step. *N*-phenyltrifluoroacetimidate donor and acetyl donor were both investigated. (Scheme 1).

Tribenzoate **3**, obtained by reported procedures[14], was deacetalized under 60% TFA to obtain diol **4**, which could be directly precipitated as white solid from reaction mixture in 87% yield (Scheme 2). Deacetalization of **3** in Benito's work leads to di-fructose anhydride,[14] which was not observed in our condition. Different from Benito's anhydrous reaction condition, our aqueous 60% TFA condition disfavored the glycosylation pathway.



Scheme 2. Synthesis of acceptor 4. Condition: a) acetone, conc. H_2SO_4, 53%; b) HCl, MeOH:H_2O = 2:1, 80%; c) BzCl, py, 95%; d) 60% TFA, RT, 87%.

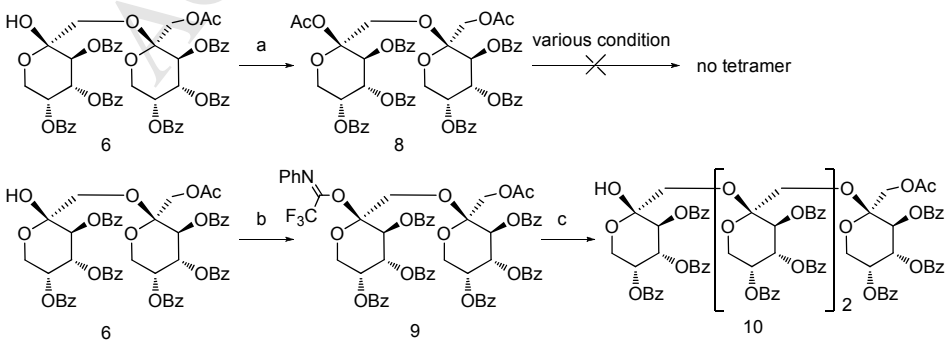
Acetyl donor **5** was prepared from **4**[15]. Glycosylation of donor **5** with the acceptor **4** with TMSOTf (0.1 equiv) proceeded with excellent regio- and stereo-selectivity, and the β-(2→1)-fructopyranoside **6** was obtained in 91% yield. The β-glycosyl configuration was determined by their C-2 anomeric ^{13}C NMR data (in the range of 99~102 ppm).[11] The primary O-Ac was deprotected with anhydrous 1N HCl/HOMe solution in DCM to obtain diol **7** with all benzoyl groups intact. (Scheme 3)



Scheme 3. Synthesis of acceptor **7**. a) Ac_2O, DMAP, NEt3, 0 ˚C, 92%; b) **4**, TMSOTf, 20 ˚C, 91%; c) 1N HCl/HOMe, DCM, 0 ˚C, 95%.

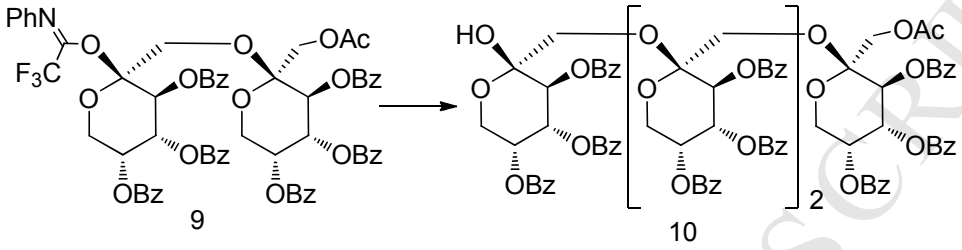
Acetyl donor **8** and *N*-phenyltrifluoroacetimidate donor **9** (Scheme 4) were both prepared. In various glycosylation conditions, acetyl donor **8** only resulted in hydrolysis or decomposition, no tetramer was detected. Treatment of *N*-phenyltrifluoroacetimidate donor **9** with diol **7** under standard glycosylation condition in dichloromethane provided the tetra-saccharide **10** in 20% yields. Toluene or THF as solvent did not improve the yield. Addition of DMSO in DCM or toluene did not improve the yield but produced an unknown product of great polarity. Anhydrous CH_3CN as solvent dramatically improved the yield, and the amount of donor **9** was increased to 1.5 equiv., the yield is 82%. (Table 1)[16] Under these conditions, β-(2→1)-fructopyranoside was obtained with high regio- and stereo-selectivity. The solvent effect of *N*-phenyltrifluoroacetimidate glycosylation were also reported by other groups.[17]

The stereochemistry of **10** was confirmed by X-ray analysis (Figure 1).[18] The crystal data were assigned to the CCDC (The Cambridge Crystallographic Data Centre) numbers 1542763.



Scheme 4. Investigation of difructosyl donors. a) Ac_2O, DMAP, NEt_3, 0 ˚C, 76%; b) *N*-phenyltrifluoroacetimidoyl chloride, K_2CO_3, acetone, 96%; c) diol **7**, TMSOTf, CH_3CN, 82%.

Table 1. Study of glycosylation with Donor **9**.[a]



9 10

Entry	Solvent	Equiv. of donor	Result
1	DCM	1.2	20% yields
2	DCM:DMSO (20:1)	1.2	no **10** obtained.
3	Toluene	1.2	15%
4	Tolene:DMSO (20:1)	1.2	no **10** obtained.
5	THF	1.2	no **10** obtained.
6	CH_3CN	1.2	62%
7	CH_3CN	1.5	82%

a: The reaction was carry out with 0.1 equiv. of TMSOTf at -20 ˚C.[16]

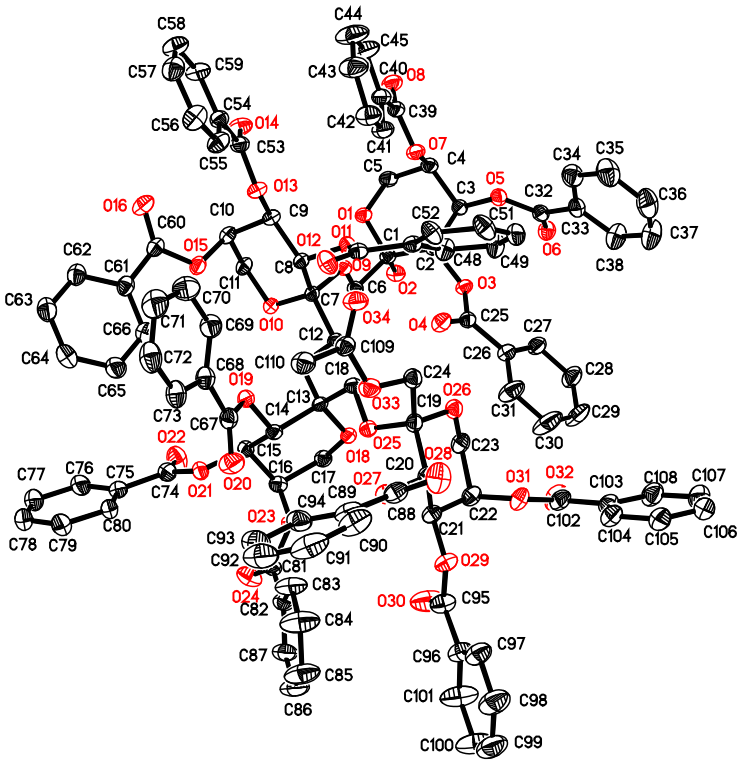
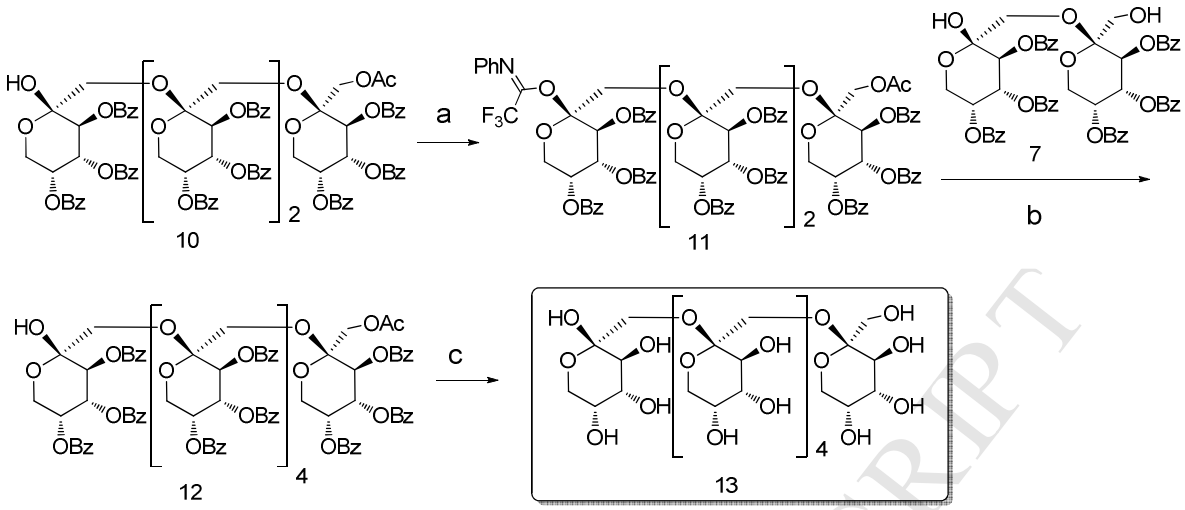


Figure 1 ORTEP drawing of compound **10**

Diol **10** was quantitatively transformed to donor **11** under *N*-phenyltrifluoroacetimidoyl chloride and K_2CO_3 in acetone. Donor **11** was glycosylated with acceptor **7** in CH_3CN, regio- and stereo-selectively provided the β-(2→1)-fructopyranosyl hexa-saccharide in 51% yield. Because the protection and deprotection of anomeric 2-OH suffered low yield,[9] this straightforward method benefited the synthesis efficiency. Hexa-saccharide was fully deprotected to obtain **13** in 86% yield. The overall yield was 27% in eight steps from diol **4.** (Scheme 5)



Scheme 5 Synthesis of β-D-fructopyranosyl oligomer. Condition: a) *N*-phenyltrifluoroacetimidoyl chloride, K_2CO_3, acetone, 97%; b) diol **7**, TMSOTf, -20 ˚C, 51%; c) NaOMe, HOMe, 86%.

In conclusion, hexasaccharide **13** was synthesized with fructopyranosyl *N*-phenyltrifluoroacetimidate glycosylation, which is the first practical synthesis of β-D-fructopyranosyl oligomer. The solvent CH_3CN plays a critical role. By regioselective glycosylation on the 1-OH of acceptor **7**, the β-fructopyranosyl oligosaccharides were elongated with difructosyl unit in every second steps, without any deprotection step. From these new oligomeric structures, functional materials and drug candidates could be prepared, which will be an interesting field.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on ### website.

ACKNOWLEDGMENT

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(16) Key experiment procedures: A mixture of the acceptor **7**, donor **9** (1.5 equiv.), and 4Å MS in anhydrous acetonitrile (7 ml) was stirred at 0 ^{o}C for 0.5h under Ar. TMSOTf in acetonitrile (0.1 equiv.) was added dropwise. The reaction was monitored by TLC and quenched with Et_3N. Then the resulting mixture was filtered through Celite. The filtrate was concentrated and purified by column chromatography (hexane:EtOAc = 2:1) to obtain **10** as white solid. m.p. 154 - 156 ^{o}C. $[\alpha]_D^{25}$ = –236.9 (*c* = 1.00 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 6.56 (m, 60 H), 6.31 (d, *J* = 10.4 Hz, 1 H), 6.17 (d, *J* = 9.9 Hz, 1 H), 6.03 (dd, *J* = 10.4, 3.5 Hz, 1 H), 5.93 – 5.70 (m, 5 H), 5.56 – 5.48 (m, 2 H), 4.49 – 4.32 (m, 3 H), 4.25 (d, *J* = 11.4 Hz, 1 H), 4.20 – 3.99 (m, 9 H), 3.94 – 3.71 (m, 5 H), 1.65 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8-164.9(C, C=O), 133.7-127.9 (C, Ar), 100.5, 100.3, 98.9, 97.1,70.4, 70.2, 70.1, 70.0, 69.7, 69.7, 69.6, 68.4, 68.4, 67.6, 67.3, 64.1, 63.0, 62.6, 62.5, 61.8, 61.6, 60.6, 60.4, 59.7, 20.0.ESI-MS (m/z) : $[M+Na]^+$: calcd for $C_{110}H_{92}O_{34}Na^+$ 1979.5362, found 1979.5368.

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(18) The product **10** was recrystallized from mixture of tetrahydrofuran and methanol (1:5). Crystal data:$C_{110}H_{92}O_{34}$; Mr =1957.84, monoclinic, $P2_1$,*a*=11.0760(2)Å, *b*=15.3546(3)Å, *c*=28.8398(6)Å, D_{calcd} =1.326g/cm^3, T=173K, X-ray intensities were measured on a graphite monochromatized CuKα radiation (λ=1.54178Å).

- The first synthesis of β-D-fructopyranosyl hexamer
- N-phenyltrifluoroacetimidate glycosylation was vital for oligomer synthesis.
- Provided an interesting method for selective glycosylation of ketose.
- Fructopyranosyl oligomer provide new backbone, with promising applications.