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# Synthesis and Glycosylation of Thio-D-fructofuranoside Donors

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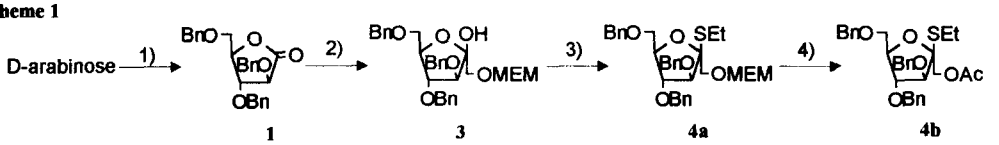
***Abstract:*** Two ethyl thioglycosides of D-fructofuranose **4a** and **4b**, synthesized from D-arabinose and differentially protected at position 1 and 6, react with bulky acceptors in the presence of IDCP giving only α-frucofuranosides in essentially quantitative yields. Copyright © 1996 Elsevier Science Ltd

D-Fructofuranosides are widespread in sucrose, in bacterial polysaccharides and in plant polysaccharides.[1] Some fructans possess remarkable biofunctions.[2] However, there are only a few studies on the anomeric reactivity of this important ketose. Many standard methods of glycosidation were found ineffective in forming fructofuranosides.[3] The stereospecific synthesis of fructofuranosides, especially oligosaccharides, is still regarded as a difficult task. For instances, using thioorthoester as glycosyl donors in combination with tritylated acceptors was not successful.[4] Zinc chloride promoted coupling of *exo*-cyclic epoxides of D-fructose glycal led to anomeric mixtures of ketoglycosides in low yield.[5] Recently, Schmidt *et al.*[6] and Hui *et al.*[7] have used anomeric phosphites and anomeric acetate, respectively, in the synthesis of fructofuranosides. When this manuscript was in preparation, Oscarson *et al.* reported that perbenzylated thiofructofuranoside in the presence of dimethyl(methylthio)sulfonium triflate (DMTST) or N-iodosuccinimide (NIS) gave an α/β mixture of disaccharide coupling products.[8] We found that, with iodonium di-*sym*-collidine perchlorate (IDCP) as promoter, glycosidation of thiofructofuranoside yielded α-linked fructofuranosides predominantly in nearly quantitative yields (except for simple acceptors).

As D-fructofuranosyl residues are usually involved in 2→1' linkages (inulin type) or 2→6' linkages (levan type) in fructans, it is necessary to discriminate the 1- and 6- primary hydroxyl groups of D-fructose for the synthesis of fructans. Therefore, we selected compound **4a** as our D-fructofuranosyl donor to test its anomeric reactivity. Compound **3** was prepared (Scheme 1) by addition of [(methoxyethoxy)methyl]lithium, generated *in situ* from the corresponding stannic derivative **2** by tin/lithium exchange,[9] to the known perbenzylated D-arabinono-1,4-lactone (**1**).[10] Transformation of the anomeric hydroxyl group in **3** with ethanethiol in the presence of a catalytic amount of boron trifluoride etherate afforded the requisite β-D-fructofuranosyl donor **4a** (structure elucidation by 2D-NOESY).

**Scheme 1**

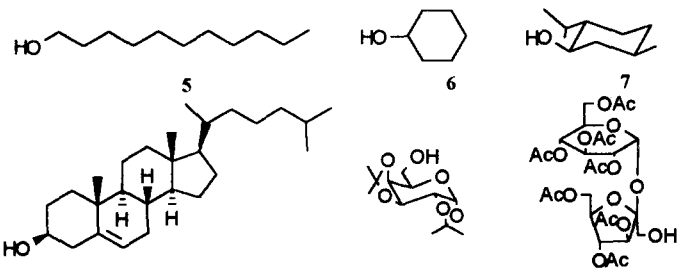



1 3 4a 4b

**Reagents and conditions:** 1) (a) MeOH, $H_2SO_4$; (b) BnCl, KOH, reflux; (c) HOAc-6 N HCl, 65°C, 60% overall; (d) DMSO, $Ac_2O$, 95%. 2) $Bu_3SnCH_2OMEM$ (**2**), BuLi, THF, -78°C, 92%. 3) EtSH, $BF_3OEt_2$ (0.3 *equiv.*), $CH_2Cl_2$, 93%. (4) catechol boron bromide, $CH_2Cl_2$, -78°C to rt, 78%; then $Ac_2O$, Pyr., 98%.

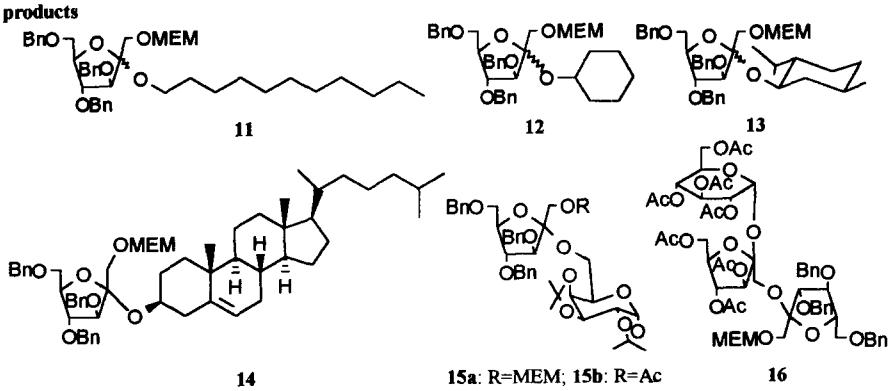
Compound **5**, **6**, **7**, **8**, **9** and **10** were chosen as acceptors. Compound **10**[11] is of interest for the synthesis of an inulin type fructan, the Achyranthes bidentata B1 polysaccharides (Abs) which was isolated from a traditional Chinese herbal medicine *Achyranthes bidentata* Blume and which possesses pronounced activity in stimulating the immunity system.[2c]

**acceptors**




5 6 7 8 9 10

**products**




11 12 13 14 **15a**: R=MEM; **15b**: R=Ac 16

The results of the glycosylations with the D-fructofuranosyl donors **3**, **4a** and **4b** are summarized in Table 1. It can be seen that coupling of donor **4a** with acceptors **5**, **6**, **7**, **8**, **9**, **10** in the presence of the promoter IDCP in $Cl(CH_2)_2Cl$-$Et_2O$ (4:1) or $CH_2Cl_2$-$Et_2O$ (4:1) led to almost quantitative yields of corresponding fructofuranosides **11**, **12**, **13**, **14**, **15a**, **16** (entries 1, 7, 9, 10, 11, 12). Apparently, the α/β ratio of the products depends on steric effects in the acceptors. With bulky acceptor alcohols the α-linked products were obtained exclusively (entries 10, 11, 12). It is noteworthy that 0.3 *equiv.* of a simple Lewis acid such as $BF_3OEt_2$ or $TiCl_4$-$AsPh_3$[12] favoured almost exclusive formation (entries 4, 5, 6, 8) of α-anomers of **11** and **12** in acceptable yields when compound **3** was the glycoyl donor. The anomeric

configurations of the coupling products were deduced from the $^{13}C$ NMR resonances of the anomeric carbons.[5,13] It should be mentioned that in contrast to the earlier report,[8] we found the α/β anomers could be separated by flash column chromatography.

Since most naturally occurring fructofuranosides are β-linked, the synthesis of β-anomers is perhaps more interesting and is even more difficult. When the glycosylation reaction was carried out in $CH_3CN$ (entry 2), which is often used as a β-directing factor in D-hexopyranosyl glycosylation without a participating group at O-2,[14] the β-anomer is formed in slight excess. The reaction was also carried out using a combination of N-bromosuccinimide (NBS) with lithium perchlorate as promoter,[15] in which the perchlorate is often regarded as a source of the counter ion. Once again, a slight excess of the β-anomer was observed (entry 3). However, when reaction conditions in entry 2, 3 were applied to the coupling reaction between **4a** and disaccharide acceptor **10**, no β-anomer was detected in the reaction mixture (entry 13, 14). In addition, with NBS-$LiClO_4$ combination as promoter, the trisaccharide **16** was formed but only in very low yield

Further, it is well known that, in the case of 2-neighboring group participation, a $C_1$, $C_2$-*trans* configuration is generally obtained for hexopyranosides. With the ketonse sugar, the situation is more complicated: the participation of $C_3$-acyloxy group is likely to facilitate the $C_2$, $C_3$-*trans* configuration (*i. e.* α- for fructofuranose); but the participation of $C_1$-acyloxy group could give either α or β-ortho ester intermediates with respect to $C_2$. Among them, the α-ortho ester intermediate would be expected to yield the β-fructofuranosides.[16] To probe the possibility of β-fructofuranoside synthesis via a 1-acyloxy donor, donor **4a** was converted to donor **4b** as shown in Scheme 1. However, the condensation reaction of **4b** with acceptor **9** promoted by IDCP also afforded only α-disaccharide in a quantitative yield (entry 15), perhaps via an β-ortho ester intermediate.

**Table 1. Glycosylation reaction[a] of D-fructofuranosyl donor**

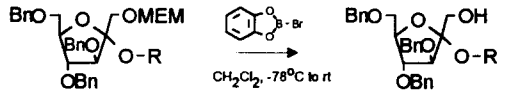
| entry | donor | acceptor | promoter | solvent | temperature | product | yield (%) | α:β |
|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | **5** | IDCP | $Cl(CH_2)_2Cl$-$Et_2O$ | -20°C to rt | **11** | 96 | 1:1 |
| 2 | **4a** | **5** | IDCP | $CH_3CN$ | -20°C to rt | **11** | 95 | 1:2.2 |
| 3 | **4a** | **5** | NBS-$LiClO_4$ | $Et_2O$ | -20°C | **11** | 68 | 1:3.5 |
| 4 | **3** | **5** | $BF_3OEt_2$ | $CH_2Cl_2$ | rt | **11** | 92 | 1:0 |
| 5 | **3** | **5** | $BF_3OEt_2$ | $CH_3CN$ | rt | **11** | 93 | 1:0 |
| 6 | **3** | **5** | $TiCl_4$-$AsPh_3$ | $CH_2Cl_2$ | -78°C | **11** | 95 | 1:0 |
| 7 | **4a** | **6** | IDCP | $CH_2Cl_2$-$Et_2O$ | -20°C to rt | **12** | 96 | 1.7:1 |
| 8 | **3** | **6** | $BF_3OEt_2$ | $CH_2Cl_2$ | rt | **12** | 76 | 1:0 |
| 9 | **4a** | **7** | IDCP | $CH_2Cl_2$-$Et_2O$ | -20°C to rt | **13** | 95 | 3.4:1 |
| 10 | **4a** | **8** | IDCP | $CH_2Cl_2$-$Et_2O$ | -20°C to rt | **14** | 90 | 1:0 |
| 11 | **4a** | **9** | IDCP | $CH_2Cl_2$-$Et_2O$ | -20°C to rt | **15a** | 93 | 1:0 |
| 12 | **4a** | **10** | IDCP | $Cl(CH_2)_2Cl$-$Et_2O$ | -20°C to rt | **16** | 94 | 1:0 |
| 13 | **4a** | **10** | IDCP | $CH_3CN$ | -20°C to rt | **16** | 90 | 1:0 |
| 14 | **4a** | **10** | NBS-$LiClO_4$ | $Et_2O$ | -20°C to rt | **16** | <6 | 1:0 |
| 15 | **4b** | **9** | IDCP | $Cl(CH_2)_2Cl$-$Et_2O$ | -20° to rt | **15b** | 92 | 1:0 |

[a]General glycosylation procedure: The donor (0.5 mmol) and the acceptor (0.5 mmol) were dissolved in 1,2-dichloroethane/diethyl ether (1/4, v/v, 20 mL) and stirred for 30 min with crushed molecular sieves (4Å, 400 mg) under a nitrogen atmosphere. IDCP (1.2 mmol) was added at -20°C and the stirring was continued at -20°C to rt for 1 h. The reaction mixture was filtered, diluted with diethyl ether and washed with 10% *aq.* $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash column chromatography yielded corresponding α- and β-fructofuranoside.

In conclusion, two fructofuranosyl donors differentially protected at O-1 and O-6, **4a** and **4b** were synthesized for the first time, and their glycosylation reaction promoted by IDCP gave frucofuranosides in

near-quantitative yields. Only a slight excess of bulky acceptors (10 mol % in excess) was needed to achieve quantitative yields of the α-fructofuranosides. To demonstrate the significance of this fructofuranosyl donor, α-anomers of **11**, **13** were deprotected using catechol boron bromide[17] to give corresponding 1-hydroxyl products **17** and **18**, which are suitable for further applications (Scheme 2).

**Scheme 2**




**α anomer of 11**: R=n-$C_{11}H_{23}$ **17** (73%)
**α anomer of 13**: R=menthyl **18** (71%)

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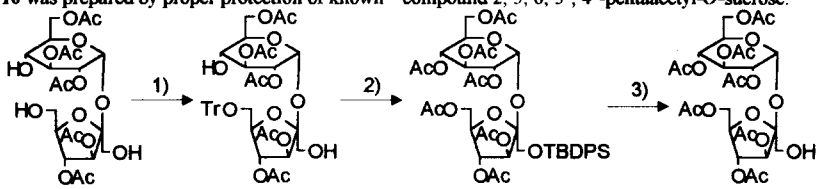
11. Compound **10** was prepared by proper protection of known[18] compound 2, 3, 6, 3', 4'-pentaacetyl-*O*-sucrose:




**Reagents and conditions:** 1) TrCl, Pyr., 50°C, 73%. 2) (a) TBDPSCl, Pyr., DMAP, 80°C, 5 d; (b) 65% HOAc, 50°C; (c) $Ac_2O$, pyr., rt, 76%. 3) 40% HF, pyr., THF, rt, 4 d, 71%.

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13. All new compound gave satisfactory analytical data. Chemical shifts of C-2 for the α-anomers of compound **11**, **12**, **13**, **14**, **15a**, **15b**, **16** were δ 107.8, 108.3, 107.8, 108.3, 108.1~109.0, 108.3~109.0 and 108.2 ppm, respectively. Chemical shift of C-2 for β-anomer of compound **11**, **12**, **13** were δ 104.0, 104.8, and 103.9 ppm, respectively. Physical and spectroscopic data of compound **16**: $[\alpha]_D$: +54.2 (c 0.39, $CHCl_3$); IR (film): 1750, 1600, 1500, 1450, 1370, 1230, 1040, 900, 740, 700, 600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ 600 MHz): 7.30~7.26 (15H, m), 5.76 (1H, d, J=3.8 Hz, 1-H), 5.73 (1H, d, J=7.0 Hz, 3'-H), 5.44 (1H, dd, J=9.8 and 10.0 Hz, 3-H), 5.39 (1H, dd, J=7.2 and 7.2 Hz, 4'-H), 5.07 (1H, dd, J=9.7 and 10.0 Hz, 4-H), 4.87 (1H, dd, J=3.8 and 10.0 Hz, 2-H), 4.68 (2H, br s, $OCH_2OCH_2CH_2OMe$), 4.57~4.48 (6H, m, Bn), 4.39 (1H, m, 5"-H), 4.34 (1H, m, 5-H), 4.30 (2H, m, 6-H), 4.25 (2H, m, 6'-H), 4.17 (1H, m, 5'-H), 4.06 (1H, d, J=2.8 Hz, 3"-H), 3.93 (1H, dd, J=2.8 and 4.7 Hz, 4"-H), 3.86 (1H, d, J=10.2 Hz, 1'-H), 3.72 (2H, m, 1"-H), 3.61~3.56 (3H, m, part of 6"-H and $OCH_2CH_2O$), 3.55 (1H, d, J=10.2 Hz, 1'-H), 3.50 (1H, dd, J=5.0 and 10.5 Hz, part of 6"-H), 3.41 (2H, m, part of $OCH_2CH_2O$), 3.33 (3H, s, OMe), 2.10 (3H, s), 2.09 (3H, s), 2.08 (3H, s), 2.04 (6H, s), 2.02 (3H, s), 2.00 (3H, s) ppm; $^{13}C$ NMR ($CDCl_3$, 150 MHz): 171.06~169.59, 138.24, 128.35, 127.68, 108.20, 104.39, 96.01, 89.64, 87.39, 83.07, 81.73, 77.97, 75.96, 74.75, 73.29, 72.31, 71.74, 70.20, 70.27, 70.13, 68.48, 68.23, 67.02, 65.44, 63.33, 62.46, 61.85, 60.36, 58.93 ppm; FAB MS (m/z): 1180 ($M^+$+Na+1), 1120 ($M^+$-AcOH+Na+1); Analysis Cald for $C_{57}H_{72}O_{25}$: C, 59.16; H, 6.27. Found: C, 59.22; H, 6.47.
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