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Synthesis and Glycosylation of Thio-D-fructofuranoside Donors

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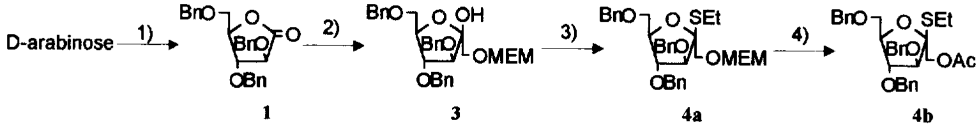
Abstract: Two ethyl thioglycosides of D-fructofuranose **4a** and **4b**, synthesized from D-arabinose and differentially protected at position 1 and 6, react with bulky acceptors in the presence of IDCP giving only α-frucofuranosides in essentially quantitative yields. Copyright © 1996 Elsevier Science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

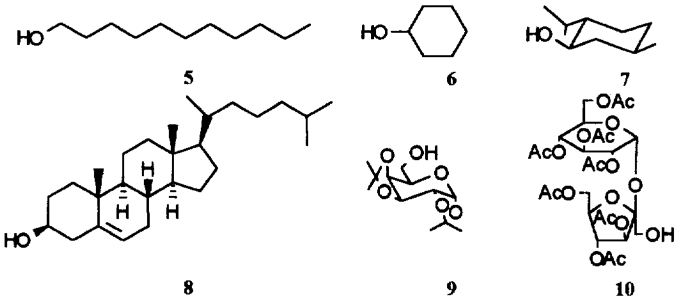
Scheme 1



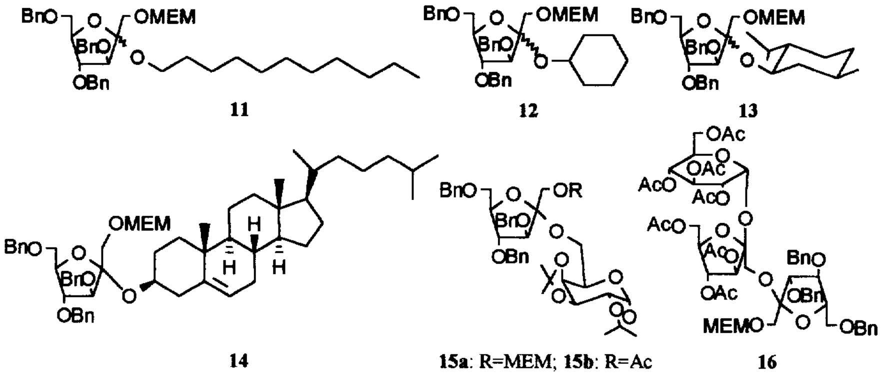
Reagents and conditions: 1) (a) MeOH, H_2SO_4; (b) BnCl, KOH, reflux; (c) HOAc-6 N HCl, 65°C, 60% overall; (d) DMSO, Ac_2O, 95%. 2) Bu_3SnCH_2OMEM (**2**), BuLi, THF, -78°C, 92%. 3) EtSH, $BF_3 \cdot OEt_2$ (0.3 *equiv.*), CH_2Cl_2, 93%. (4) catechol boron bromide, CH_2Cl_2, -78°C to rt, 78%; then Ac_2O, 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



products



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 $BF_3 \cdot OEt_2$ 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.

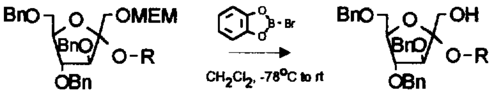
Table 1. Glycosylation reaction[a] of D-fructofuranosyl donor

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**	$BF_3 \cdot OEt_2$	CH_2Cl_2	rt	**11**	92	1:0
5	**3**	**5**	$BF_3 \cdot OEt_2$	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**	$BF_3 \cdot OEt_2$	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

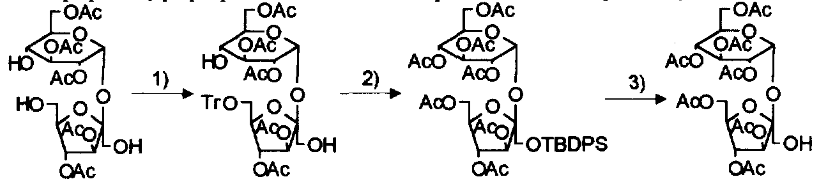


α anomer of 11: R=n-$C_{11}H_{23}$ **17** (73%)

α anomer of 13: R=menthyl **18** (71%)

References and Notes:

1. Lindberg, B. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 279.
2. a) Franz, G. *Farm. Tijdschr. Belg.* **1987**, *64*, 301. b) Rumessen, J. J.; Bode, S.; Hamberg, O.; Guamand, H. E. *Am. J. Clin. Nutr.* **1990**, *52*, 675. c) Yu, B.; Tian, G.-Y.; Hui, Y.-Z. *Chinese J. Chem.* **1995**, *13*, 539.
3. Bouali, A.; Descotes, G.; Ewing, D. F.; Grouiller, A.; Lefkidou, J.; Lespinasse, A.-D.; Mackenzie, G. *J. Carbohydr. Chem.* **1992**, *11*, 159.
4. Backinowsky, L. V.; Balan, N. F.; Betaneli, V. L.; Kotchetkov, N. K. *Carbohyd. Res.* **1982**, *99*, 189.
5. Nicotra, F.; Panza, L.; Russo, G. *Tetrahedron Lett.* **1991**, *32*, 4035.
6. Muller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *27*, 4763.
7. Yu, B.; Hui, Y.-Z. *Chinese Chem. Lett.* **1993**, *4*, 391.
8. Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1996**, *61*, 1234.
9. a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. b) Heskamp, B. M.; Veeneman, G. H.; van der Marel, G. A.; van Boechel, C. A. A. van Boom, J. H. *Tetrahedron* **1995**, *51*, 5657.
10. Rabinsohn, Y.; Fletcher, Jr. H. G. *J. Org. Chem.* **1967**, *32*, 3452.
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%.

12. Peng, Z.-H.; Li, Y. L.; Wu. W.-L.; Liu, C.-X.; Wu, Y.-L. *J. Chem. Soc. Perkin 1*, **1996**, 1057.
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, $OC\underline{H}_2OCH_2CH_2OMe$), 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.
14. Braccini, I.; Derouet, C.; Esnault, J.; du Penhoat, C. H.; Mallet, J.; Michon, V.; Sinay, P.; *Carbohydr. Res.* **1993**, *246*, 23.
15. Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S. *Tetrahedron*, **1995**, *51*, 4923.
16. Reist, E. J.; Hart, P. A.; Baker, B. R. *J. Org. Chem.* **1959**, *24*, 1640.
17. Boeckman, R. K.; Potenza, J. C.; *Tetrahedron Lett.* **1985**, *26*, 1411.
18. Buchanan, J. G.; Cummerson, D. A.; Turner, D. M. *Carbohydr. Res.* **1972**, *21*, 283.

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