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Selective derivatization of D-galactose towards a practical synthesis of C-6 L-fucose analogues

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ABSTRACT

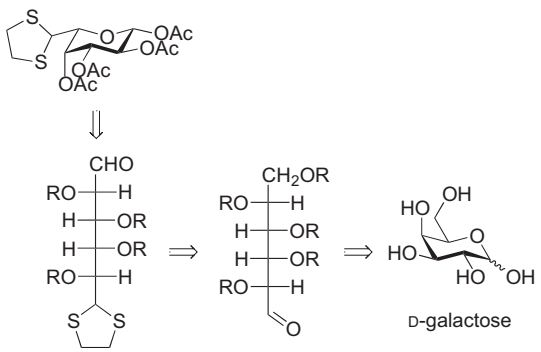
Starting from D-galactose, a convenient protocol is described for the synthesis of L-fucose C-6 analogue, 2,3,4,5-tetra-*O*-acetyl-5-(1,3-dithiolan-2-yl)-L-galactopyranose, in an overall yield of 40% after 6 steps, making use of stable intermediates. A chemoselective protection/deprotection strategy was studied using TBDMS and TBDPS silyl ethers for protection of D-galactose primary hydroxyl group.

α-L-Fucose is often a terminal monosaccharide in N- and O-linked glycoconjugates that takes part in important cell–cell interactions and cell migration.[1] As such, it often serves as an important molecular recognition element in various physiological and pathological processes, including cancer metastasis,[2] immune responses[3] and neuronal development.[4,5] This biological relevance has recently stimulated major interest in the synthesis of α-L-fucose analogues that have been successfully applied in chemical strategies for monitoring glycan and glycan-protein interactions.[6–13]

α-L-Fucose analogues can be easily synthesized from L-galactose.[11] However, it is far more interesting and sustainable to develop synthetic strategies from readily accessible and cheaper D-galactose.[14] There are a few methods reported in the literature for the conversion of D-galactose into L-fucose. Flowers' strategy is lengthy and provides an overall yield of 15%.[15] The method described by Vogel and co-workers makes use of expensive reagents and sticky intermediates,[16] whilst Roy's approach makes use of crystalline intermediates, with an overall conversion of 34% from D-galactose diethyl dithioacetal.[17] A recent method described by Maeda et al. converts D-galactose into a C-6 azide fucopyranose in 11 steps and a overall yield of 23%.[14] Thus, it is of great and current interest to develop new direct and handy procedures for the conversion of D-galactose into valuable L-fucose analogues by means of stable intermediates and with overall good yields.[11]

In order to convert D-galactose into C-6 derived L-fucose analogues, it is necessary to transform the reducing end of the aldose and to oxidize the primary OH group at C-6. The most convenient strategy consists in masking the aldose as a dithioacetal, commonly diethyl dithioacetal, and to proceed with the oxidation of the primary hydroxyl group to the desired aldehyde, Scheme 1.

Diethyl dithioacetals are easily obtained by reaction of the sugar with malodorous and highly volatile ethanethiol in strong acidic medium.[18] A better alternative is the formation of ethylene dithioacetals by reacting the aldose with ethan-1,2-dithiol, with the advantage of being less volatile, thus facilitating preparative procedures, yielding D-galactose ethylene dithioacetal (**1**).[19] The primary hydroxyl group of **1** was protected as a *tert*-butyldimethylsilyl (TBDMS) or *tert*-butyldiphenylsilyl (TBDPS) ether, whilst the secondary hydroxyl groups were protected as acetyl (**4**, **6**) or benzoyl (**7**, **9**) esters or benzyl ethers (**10**, **12**), Scheme 2. These silyl ethers were easily obtained through standard scalable protocols in overall good yields, together with small amounts of peracetylated,



Scheme 1. Retrosynthetic analysis of fucopyranose C-6 analogue.

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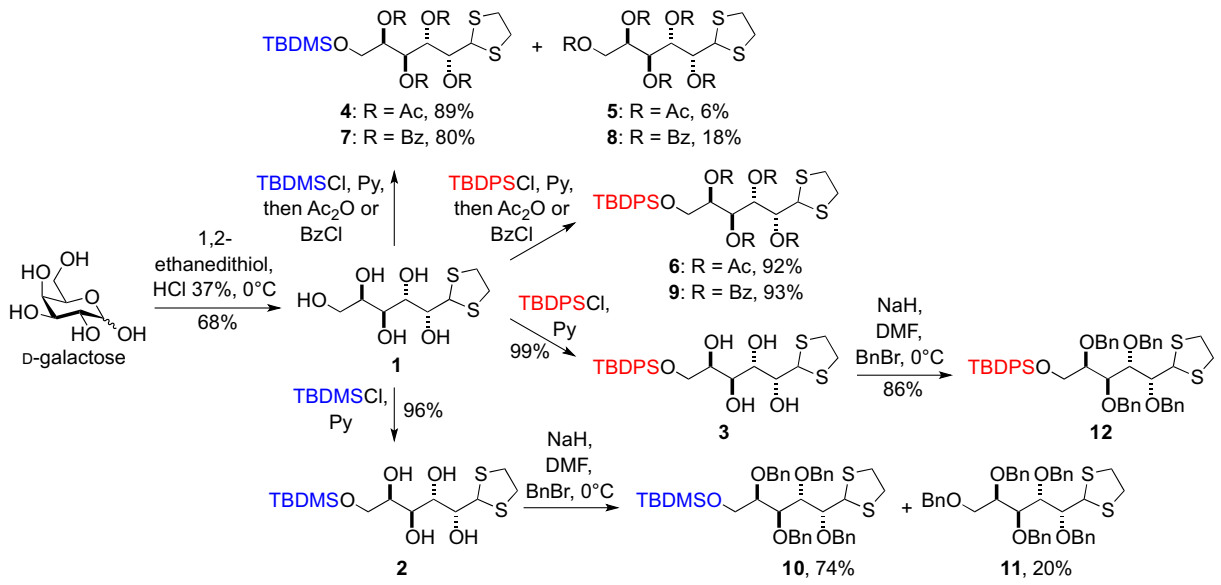


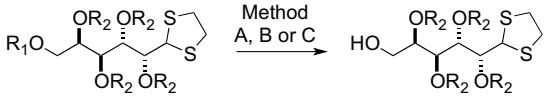
Scheme 2. Selective derivatization of D-galactose.

perbenzoylated and perbenzylated by-products (**5**, **8** and **11**, respectively).

Deprotection of the C-6 silyl ethers was carried out using three different methods, in order to optimize chemical yields: TBAF in THF, hydrogenolysis using Pd/C and iodine in methanol. Deprotection yields and reaction conditions are summarized in Table 1. In order to demonstrate the compatibility of the dithiolane function towards these desilylation protocols, we have previously tested substrates **5**, **8** and **11**, for each protocol. Full recovery of the initial sugar was observed in all cases, proving that the dithiolane ring is stable under these conditions.

Deprotection of TBDMS ether **4** was tested using TBAF (Table 1, entry 1).[20] It was observed that an increase in the amount of TBAF results in lower yields of the desired alcohol **13** and consequently the following substrates were treated with only 1 equiv of TBAF. Such a protocol provided low chemical yields, for acetylated substrates **4** and **6** (Table 1, entries 1 and 2) and benzoylated substrates **7** and **9** (Table 1, entries 3 and 4). Moreover, when TBDPS ether **6** was treated with 1 equiv of TBAF, the yield again decreased with the increased reaction time, from 46% (1 h) to 19% (4.5 h) (Table 1, entry 2). However, this method delivered excellent conversion of benzylated silyl substrates **10** and **12** into the desired

Table 1
Selective deprotection of silane ethers



4: R_1 = TBDMS, R_2 = Ac
6: R_1 = TBDPS, R_2 = Ac
7: R_1 = TBDMS, R_2 = Bz
9: R_1 = TBDPS, R_2 = Bz
10: R_1 = TBDMS, R_2 = Bn
12: R_1 = TBDPS, R_2 = Bn

13: R_2 = Ac
14: R_2 = Bz
15: R_2 = Bn

Entry	Substrate	Product	Method		
			(A) TBAF, THF	(B) H_2, 10% Pd/C	(C) I_2, MeOH
1	**4**	**13**	55% (1 h, 1 equiv. TBAF) 34% (1 h, 2 equiv TBAF) 46% (1 h)	78% (17 h) + 19% **4** 82% (24 h)	73% (24 h, 1 equiv I_2) 81% (8 h, 2.5 equiv I_2) 88% (15 h, 2.5 equiv I_2) 100% (4.5 h, 5 equiv I_2) 88% (4.5 h, 10 equiv I_2)
2	**6**		27% (3 h) 19% (4.5 h)	—[b]	—[a]
3	**7**	**14**	48% (1 h)	—[b]	61% (20 h) + 38% **7** 86% (26 h) + 12% **7** 89% (48 h)
4	**9**		38% (22 h)	—[b]	25% (96 h) + 74% **9**
5	**10**	**15**	73% (1 h)	—[a]	60% (1 h) + 17% **10** 92% (2 h)
6	**12**		99% (5 h)	—[a]	50% (24 h) + 30% **12**

[a] Initial substrate fully recovered after 48 h.
[b] Initial substrate fully recovered after 72 h.

alcohol **15** (Table 1, entries 5 and 6). The limited conversions of acetyl and benzoyl derivatives may be related to the inconvenient migration of acetyl and benzoyl groups, due to the presence of the strong basic fluoride ion.[21–23]

Sajiki et al. have reported the cleavage of silyl ethers by hydrogenolysis using 10% Pd/C as being a chemoselective procedure which is dependent on the solvent used. The authors found that using methanol as the solvent there was a selective cleavage of TBDMS and triethylsilyl (TES) over TPDPS and triisopropylsilyl (TIPS) ethers.[24,25] In addition to these chemoselectivity features, this method offers several practical advantages, including practical simplicity and lack of aqueous work-up.[26] In this context, we have subjected the silylated substrates to hydrogenolysis in methanol using 10% Pd/C. We have not only observed selectivity in hydrogenolysis towards TBDMS silyl ethers, as reported by Ikawa et al.,[24] but also a dependency of the secondary alcohol protecting groups. Acetylated TBDMS ether **4** was cleaved in 82% to yield the corresponding alcohol (Table 1, entry 1), whilst benzoylated and benzylated TBDMS ethers **7** and **10** were unreactive under this protocol (Table 1, entries 3 and 5). Such observation may be attributed to chemical hindrance of the silyl ether caused by bulky benzoyl and benzyl groups. To the best of our knowledge there are no reports of such selectivity in recent literature, although steric constraints were reported by Rokach and co-workers in the deprotection of a bicyclic prostaglandin synthon.[26]

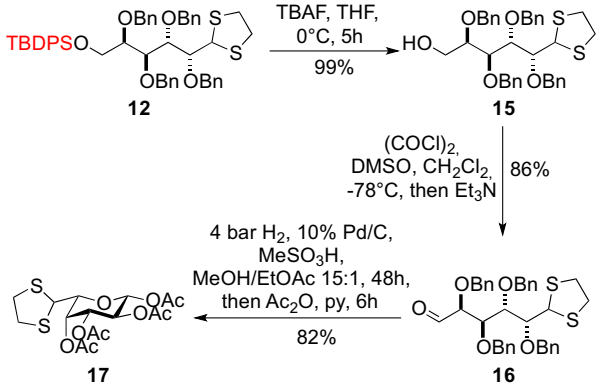
Finally, we have tested the cleavage of silyl ethers with I_2 in methanol at room temperature. This method has been described in the literature as straightforward for deprotection of TBDMS and our group have previously reported the chemoselectivity of this protocol towards the deprotection of TBDMS in the presence of TBDPS,[27,28] the latter being readily cleaved under refluxing methanol with Br_2.[29,30] Many authors have successfully applied this procedure, but the amount of I_2 used is variable among the methods described. Therefore, we have varied the amount of iodine in the deprotection of **4** (Table 1, entry 1) concluding that the use of 5 equiv of I_2 is the most adequate. This optimized protocol was applied to the remaining substrates to provide overall good deprotection yields of TBDMS ethers (Table 1, entries 3 and 5). Benzylated TBDMS ether **10** was converted in 60% yield into alcohol **15** after 1 h, whilst the benzoylated derivative **7** was converted into the same extent only after 20 h. TBDPS ethers were also cleaved by means of this protocol, although they took longer (Table 1, entries 4 and 6). This observation finds agreement with previous reports in the literature claiming a kinetic selectivity of TBDMS over TBDPS for this protocol.[31] On the other hand, benzylated silyl ethers **10** and **12** reacted much faster than benzoylated ones, **7** and **9**, making this protocol suitable for rapid deprotection of silyl ethers in benzylated substrates.

An overview of the results summarized in Table 1 indicates preferable methods for the deprotection of silyl ethers depending on the secondary hydroxyl protecting groups. In this sense, the cleavage of TBDMS in the presence of acetyl groups is more effective through hydrogenolysis whilst in the presence of benzoyl groups iodine is more suitable. Instead, the cleavage of both TBDMS and TBDPS in the presence of benzyl ethers proceeds preferably by reaction with TBAF.

After the selective cleavage of silyl ethers, primary alcohols **13**, **14** and **15** were submitted to Swern oxidation conditions to yield the corresponding aldehydes, Scheme 3.

Although, the consumption of alcohols **13** and **14** was observed by TLC, we were unable to isolate the desired aldehydes after purification and to confirm their structure. On the other hand, aldehyde **16** was isolated in excellent yield (86%), after purification by flash chromatography with silica gel, Scheme 3.

Finally, the benzyl groups of **16** were removed by catalytic hydrogenolysis using 10% Pd/C under 4 bar in the presence of



Scheme 3. Conversion of alcohol 15 into L-fucose C-6 analogue 17.

methanesulfonic acid, for 48 h. The unprotected L-fucopyranosyl was immediately acetylated without purification to yield the desired L-fucose C-6 analogue **17** in 82% yield as the β-anomer.

Dithioacetals are versatile intermediates in the synthesis for masking and converting the carbonyl moiety.[31] This protecting group allows numerous synthetic transformations, including reduction of carbonyl group to methylene, the interchange of carbonyl groups with adjacent methylene groups.[31]

This procedure takes advantage of stable and easily handled, intermediates to achieve an overall conversion of 40% from commercially available and cheap D-galactose to L-fucopyranose derivative **17**, offering an accessible and cheaper alternative to the synthetic strategies currently described in the literature. Moreover, we present a systematic study on the selective deprotection of silyl ethers under three different conditions. We describe an interesting and unpredicted selectivity for cleavage of TBDMS ethers by catalytic hydrogenolysis for acetylated substrates. In other hand, iodine mediated cleavage of silyl ethers proved to be a reliable and selective method for the deprotection of TBDMS as an alternative to fluoride catalysed protocols that promote acetyl and benzoyl groups migration.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.127.

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