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CHEMISTRY OF β-TRIMETHYLSILYLETHANOL. II.[1] A NEW METHOD FOR PROTECTION OF AN ANOMERIC CENTER IN PYRANOSIDES*

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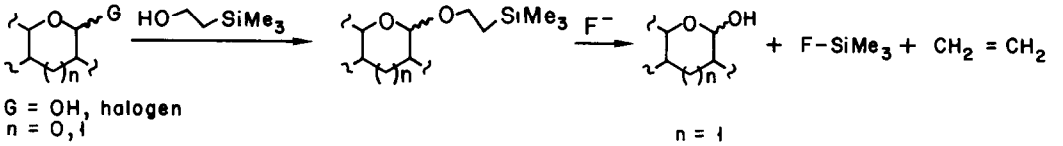
SUMMARY: Protection of the anomeric center in various carbohydrates as a β-trimethylsilylethyl glycoside is reported. The free sugar can be regenerated using $LiBF_4$ in acetonitrile.

Contemporary efforts in organic synthesis have now begun to focus heavily on the direct preparation of natural products in optically active form. One popular and very attractive means of achieving this goal is *via* transformation of inexpensive and readily available chiral educts[3] such as carbohydrates.[4] Synthetic manipulation of sugars must consider, at a very early stage, protection of the hemiacetal moiety. Traditionally, alkyl glycosides have been employed and conditions for subsequent unmasking generally fall into two categories: (1) acid hydrolysis;[5] (2) reductive cleavage.[6] We now present an alternative procedure wherein novel β-trimethylsilylethyl glycosides have been prepared which may ultimately be unraveled under the influence of fluoride ion to afford the corresponding free sugars.



The formation of β-trimethylsilylethyl glycosides was accomplished, in all cases studied, using β-trimethylsilylethanol (β-TMS ethanol)[1] and the appropriate sugar through four different routes (Methods A-D), the results of which are summarized in Table I.

Method A; Oxymercuration:[7] Treatment of either glucal (entries 1,2,6-8) or allal (entries 9,10) derivatives with $Hg(OAc)_2$ (1 eq) / $HOCH_2CH_2SiMe_3$ (4 eq) in THF (1 M) at rt followed by ligand exchange (NaCl or NaOH) and reduction ($NaBH_4$) afforded the corresponding 2-deoxyglycosides in good yields.

Method B; Koenig-Knorr procedure:[8] Reaction of a glycosyl halide (an aminoglucosyl chloride, entry 3; a glucosyl bromide, entry 4; an arabinofuranosyl bromide, entry 11) with β-TMS

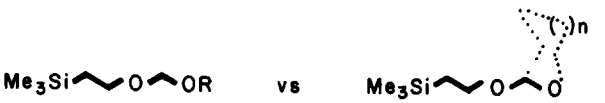
* Dedicated to Professor Harry H. Wasserman on the occasion of his sixtieth birthday.

ethanol (5 eq) in $CHCl_3$ (.5 M) containing $CaSO_4$ (2 eq), HgO (1 eq) and a trace of $HgBr_2$ at rt gave the desired saccharides.

Method C; Fisher Glycosidation:[9] Direct glycoside formation of mannose (entry 12) was realized using 10 eq β-TMS ethanol in refluxing THF (16 M) containing a catalytic amount of $POCl_3$ or TsOH. Trituration of the concentrated reaction mixture with pentane permitted recovery of the majority of β-TMS ethanol.

Method D; Glycal Rearrangement:[10] Dissolution of tri-O-acetyl-D-glucal in dry benzene (1 M) at 25° C followed by addition of $HOCH_2CH_2SiMe_3$ (1.5 eq) and $BF_3 \cdot Et_2O$ (cat.) led to a 2,3 unsaturated glycal (entry 13).

It was expected from previous experience[1] that n-Bu_4NF would be the reagent of choice for deprotection owing to the structural similarities between SEM ethers and the β-TMS ethyl glycosides. We were, therefore, quite surprised to find that essentially all sources of fluoride examined (e.g., n-Bu_4NF, Et_4NF, CsF, HgF_2, KF, MgF_2, ZnF_2, $PhCH_2NMe_3F$, Me_4NF, pyr·HF) in a variety of solvents (THF, HMPA, DMSO, DMF, CH_3NO_2, CH_3CN) gave, in most cases, little or no reaction. A recent report,[11] however, describing the use of $LiBF_4$ for the cleavage of silyl ethers has led to our effective use of this reagent for glycoside breakdown. Hence, exposure of a β-TMS ethyl glycoside to 5-10 eq of dry $LiBF_4$ in distilled (CaH_2) CH_3CN (∿ 1.5 M) at ca. 70° for 3-8 h gave good yields of free sugar. Similar attempts in CH_3NO_2, DMSO and DMF gave no reaction.



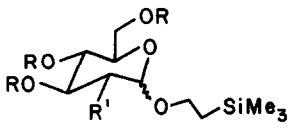
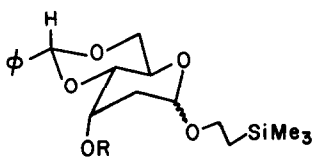
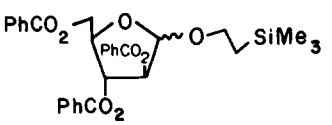
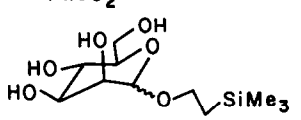
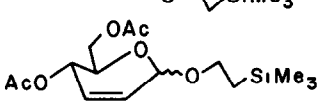
In order to briefly examine the mechanism of deprotection, the following additional observations have been made: (a) dry $LiBF_4$ did not cleave a methyl glycoside, suggesting F^- was indeed involved; (b) both $NaBF_4$ and KBF_4/18-crown-6 ether were completely ineffective, although this is likely a reflection of their limited solubility in CH_3CN; (c) LiF/CH_3CN returned only starting material but addition of $BF_3 \cdot Et_2O$ (LiF : $BF_3 \cdot Et_2O$ = 1:1) led to deprotection; (d) the β-anomer within a mixture appears to unravel at a far greater rate (< 1 h) relative to the α-isomer; (e) β-TMS ethyl furanosides (e.g., entry 11) apparently do not undergo cleavage under these or related conditions, returning only starting material.

From these and other points mentioned above, it is likely that a 'push-pull' mechanism is operating where boron derivatives act as both the source of fluoride[11] and Lewis acid through dissociation of $LiBF_4$. Since generation of some BF_3 seems necessary for complexation (or 'pull'), $LiBF_4$ functions as a gradual release of both F^- and BF_3. CH_3CN, the only non-oxygen-containing solvent, possibly does not compete with the substrate for association. The nature of the complexation in the pyranoside versus furanoside systems, as well as the penchant for rapid cleavage of the β-anomer remains unclear at this time.

$$LiBF_4 \rightleftharpoons Li^+ + BF_4^-$$

$$BF_4^- \rightleftharpoons F^- + BF_3$$

TABLE I

Entry	Protected Sugar[a]	Method[b]	Ratio[c] (α:β)	Yield[d] (%)	Deprotection[e] Yield[d] (%)
					
1	R = Ac, R' = Br	A[f]	9:1	91	g
2	R = Ac, R' = H	A	1:0	93	88
3	R = Ac, R' = NHAc	B	0:1	69	84
4	R = Ac, R' = OAc	B	0:1	88	82
5	R = Me, R' = OMe	D	3:2	74	81
6	R = PhCO, R' = H	A	1:0	92	86
7	R = $PhCH_2$, R' = H	A	1:4	81	90
8	R = R' = H	A	1:0	78	g
					
9	R = H	A	1:1	95	h
10	R = OMe	A	4:1	86	h
11		B	i	85	b
12		C	10:7	82	g
13		D	9:1	86	82

[a] Satisfactory ir, nmr, mass spec, as well as combustion analysis data were obtained for all new compounds [b] See text [c] Determined by either HPLC, NMR, or isolation [d] Isolated, chromatographically pure. [e] Free sugars were compared with authentic samples [f] See Ref 12 [g] Not attempted. [h] Both the β-TMS ethyl group and benzylidene acetal were cleaved [i] Not determined.

In conclusion, the methodology described herein represents a convenient and efficient means of protecting an anomeric center. A variety of carbohydrates may function as precursors of β-trimethylsilylethyl glycosides, the subsequent unmasking of which can be carried out with a commercially available reagent ($LiBF_4$). The anticipated cleavage of an anomeric center, protected in this fashion, with fluoride ion under aprotic and non-reductive conditions should expand the flexibility of carbohydrates in synthesis. Further studies on the useful applications of β-TMS ethanol are in progress.

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References & Notes

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