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A 2-Silylethanol-based Anomeric Linker for Carbohydrates; Transformation into 1-O-Acyl Derivatives

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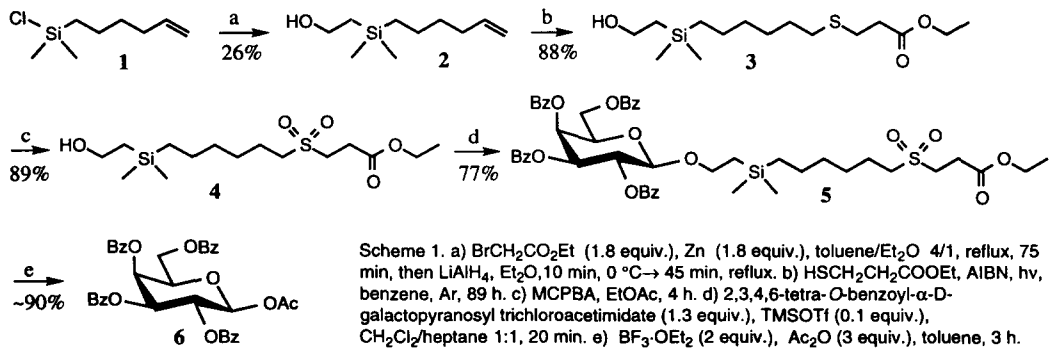
Abstract. The novel linker **4** was synthesized in three steps from hex-5-enyldimethylchlorosilane and glycosylated with 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl trichloroacetimidate to give the corresponding linker β-glycoside **5** (77%). Treatment of **5** with acetic anhydride and $BF_3{\cdot}OEt_2$ gave 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzoyl-β-D-galactose (~90%), devoid of the α-anomer. © 1997 Elsevier Science Ltd.

Effective and versatile linker molecules are important tools for chemistry on solid supports.[1] We wish to report a linker that permits the introduction of structural variation at the anomeric position of pyranosidic sugars in the very process of anomeric cleavage from the linker. The novel linker is based on the structural and functional advantages of 2-(trimethylsilyl)ethyl glycosides.[2] 2-(Octyldimethylsilyl)ethyl glycosides have been prepared with similar objectives in mind.[3] Attachment of the linker glycoside to a solid support is planned to be performed either by acylation (by **5** or by the corresponding carboxylic acid) of an aminated support, or by coupling to a mercaptopropionate-modified support (as in the step **2**→**3**).

A Reformatsky reaction between chlorosilane **1**[4] and ethyl bromoacetate, followed by reduction with $LiAlH_4$ gave the 2-(hexenyldimethylsilyl)ethanol **2** (26%; Scheme 1). The low yield emanated from the Reformatsky reaction. UV-irradiation[5] (Rayonet type RS Photochemical Reactor) of a mixture of **2**, ethyl 3-mercaptopropionate, AIBN, and benzene gave the sulfide linker **3** (88%). Oxidation of **3** with MCPBA gave the sulfone linker **4** (89%). Glycosylation of **4** with 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl trichloroacetimidate[6,7] and TMS-triflate as promoter furnished the linker-glycoside **5** (77%). Other promoters also gave **5** but the yields were lower.



Scheme 1. a) $BrCH_2CO_2Et$ (1.8 equiv.), Zn (1.8 equiv.), toluene/Et_2O 4/1, reflux, 75 min, then $LiAlH_4$, Et_2O,10 min, 0 °C→ 45 min, reflux. b) $HSCH_2CH_2COOEt$, AIBN, hv, benzene, Ar, 89 h. c) MCPBA, EtOAc, 4 h. d) 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl trichloroacetimidate (1.3 equiv.), TMSOTf (0.1 equiv.), CH_2Cl_2/heptane 1:1, 20 min. e) $BF_3{\cdot}OEt_2$ (2 equiv.), Ac_2O (3 equiv.), toluene, 3 h.

Cleavage of TMSEt glycosides by treatment with carboxylic anhydrides and $BF_3{\cdot}OEt_2$ gives the corresponding 1-*O*-acyl sugars in high yield and β-stereoselecivity.[2] The linker glycoside **5** was equally effective; while simulating cleavage from a solid support, **5** was treated with acetic anhydride and $BF_3{\cdot}OEt_2$, which gave the mixed galactosyl ester **6**[8] (~90%) as a pure β anomer. Physical data were in full accord with structures **2**-**6**.[9]

About 20 different carboxylic anhydrides have hitherto been used successfully in cleavages of TMSEt glycosides (mono→pentasaccharides) to furnish the corresponding β-1-*O*-acyl sugars in almost quantitative yields.[2] Consequently, variously substituted oligosaccharides, bound to a solid support via the linker **4** (or **3**), can potentially be acylated at the anomeric position during cleavage from the support. This would provide a convenient entry into solid phase combinatorial synthesis of anomerically substituted sugars and related compounds.

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9. ^1H NMR ($CDCl_3$, 400 MHz) δ **2**: 5.83 (ddt, 1 H, *J* 13.4, 10.3, 6.7 Hz), 5.01 (m, 1 H), 4.94 (m, 1 H), 3.74 (m, 2 H); **3**: 4.15 (q, 2 H, *J* 7.2 Hz), 3.71 (m, 2 H), 1.26 (t, 3 H, *J* 7.2 Hz); **4**: 4.20 (q, 2 H, *J* 7.1 Hz), 3.74 (m, 2 H), 1.30 (t, 3 H, *J* 7.1 Hz); **5**: 4.86 (d, 1 H, *J* 8.0 Hz), 4.19 (q, 2 H, *J* 7.1 Hz), 4.08 (ddd, 1 H, *J* 10.1, 9.9, 6.6 Hz), 3.67 (ddd, 1 H, *J* 10.4, 9.9, 5.7 Hz), 1.28 (t, 3 H, *J* 7.1 Hz); **6**: Spectral data were in full agreement with those reported.[8] **5**: $[\alpha]_D^{20}$ +62.9 (*c* 1, $CHCl_3$). HRMS calcd for $C_{49}H_{58}O_{14}SSiNa$: 953.3214, found: 953.3204.

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