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A Linker for Solid Phase Carbohydrate Synthesis, Permitting the Introduction of Variable Anomeric Functionality in the Release Step

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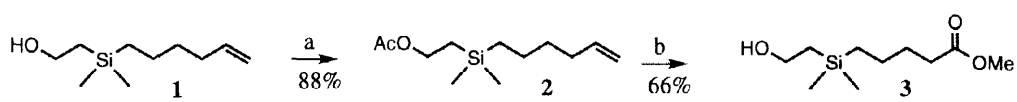
Abstract. The novel linker methyl 2-(4-methoxycarbonylbutyldimethylsilyl)ethanol (**3**) was synthesized in 58% overall yield over four steps, starting from 2-(hexenyldimethylsilyl)ethanol. Galactopyranosylation of **3** and coupling of the resulting linker galactoside to aminomethylated polystyrene resin gave a material that could be efficiently de-*O*-benzoylated as well as *O*-propionylated. Treatment of the resin with acetic or propionic anhydride in the presence of $BF_3 \cdot OEt_2$ gave the corresponding 1-*O*-propionyl or -acetyl galactopyranoses.

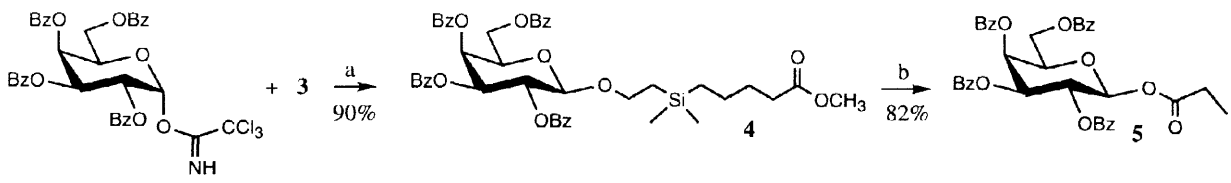
In a recent publication, we reported the synthesis of an anomeric linker suitable for coupling of saccharides to solid supports.[1] The linker was synthesized by radical addition of ethyl 3-mercaptopropionate to the olefin **1**, followed by oxidation of the resulting sulfide to the corresponding sulfone. We have found later that treatment of such sulfone linker glycosides with base leads to undesired products. We now wish to report the novel linker **3** (Scheme 1) and various linker glycosides. The new linker moiety is stable under basic conditions, and retains the features and preparative advantages of 2-silylethanol-based glycosides.[2] Other anomeric linkers for use in carbohydrate chemistry have been reported.[3]

The known[1] 2-silylethanol **1** (Scheme 1) was acetylated to give crude **2**, which was distilled to give pure **2** (88%). Ruthenium trichloride/sodium periodate-mediated oxidation[4] of **2** furnished the corresponding carboxylic acid, which was esterified with methanol under acidic conditions [Amberlyst 15 (H^+) resin], followed by de-*O*-acetylation with methanolic sodium methoxide, and chromatographic purification to give the novel linker alcohol **3** (66% yield over three steps).



Scheme 1. a) Ac_2O (1.5 equiv.), pyridine, 16 h. b) $RuCl_3 \cdot H_2O$ (0.025 equiv.), $NaIO_4$ (4.1 equiv.), CCl_4/MeCN/H_2O (2:2:3), 64 h; then MeOH, Amberlyst 15 (H^+), reflux, 15 h; then MeONa (catal. amount), MeOH, 15 h.

Glycosylation of **3** (Scheme 2) with 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl trichloroacetimidate[5] gave the linker galactoside **4** (90%). Treatment of **4** with propionic acid anhydride and boron trifluoride etherate gave the mixed ester **5** (82%) as a pure β anomer, in analogy with the cleavage of 2-(trimethylsilyl)ethyl glycosides.[1,2]



Scheme 2. a) TMSOTf (0.1 equiv.), CH_2Cl_2/heptane 1:1, 20 min. e) $BF_3 \cdot OEt_2$ (2 equiv.), $(EtCO)_2O$ (2 equiv.), toluene, 3 h.

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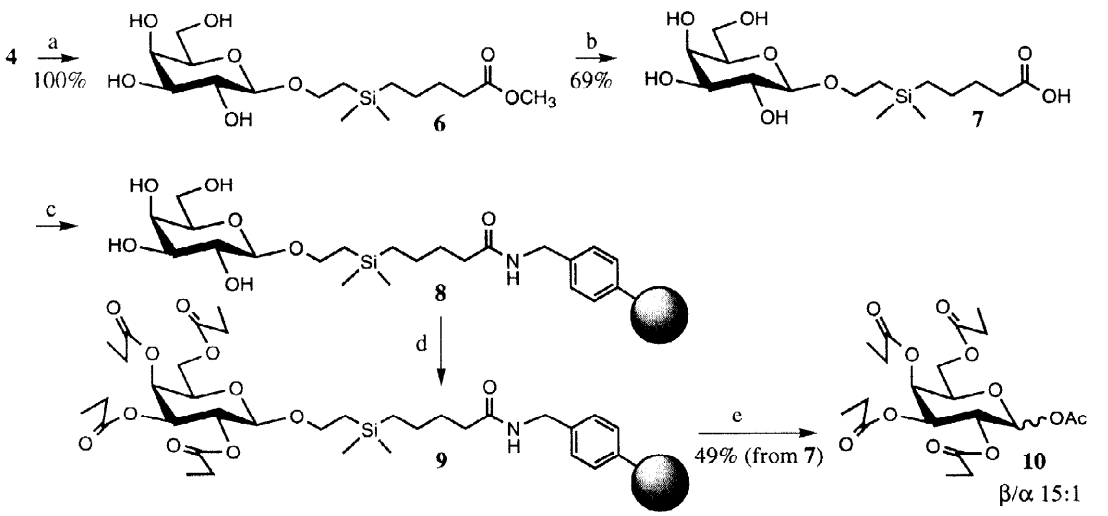
The linker galactoside **4** was de-*O*-benzoylated (Scheme 3) with methanolic sodium methoxide to give crude **6** (practically pure according to ^{1}H-NMR), and further hydrolysis with aqueous lithium hydroxide, followed by chromatography, furnished the carboxylic acid **7** (69%). Compound **7** was activated by treatment with pentafluorophenol[6] (PFP) and diisopropyl carbodiimide[7] (DIC) in DMF, which gave the corresponding pentafluorophenyl ester. Addition of aminomethyl polystyrene beads[8] left the galactosylated resin **8** after reaction overnight. The hydroxyl groups of the galactosyl residues of **8** were esterified by treatment with an excess of propionic anhydride and pyridine. Soluble material was removed by washing with pyridine and CH_2Cl_2, to give the resin **9** with propionylated galactosyl residues. Cleavage of the galactose moiety from the resin was performed by treatment of **9** with acetic anhydride and boron trifluoride etherate in toluene for 23 h. The resulting mixed ester **10** was obtained in 49% yield (based on the amount of **7** used in the coupling step), as a mixture of β and α anomers (~15:1). We recently reported a semi-quantitative investigation of the rate of formation and anomerisation of various glucopyranose derivatives under conditions similar to those used here. It was found that prolonged treatment of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose with boron trifluoride etherate caused some anomerisation.[9]

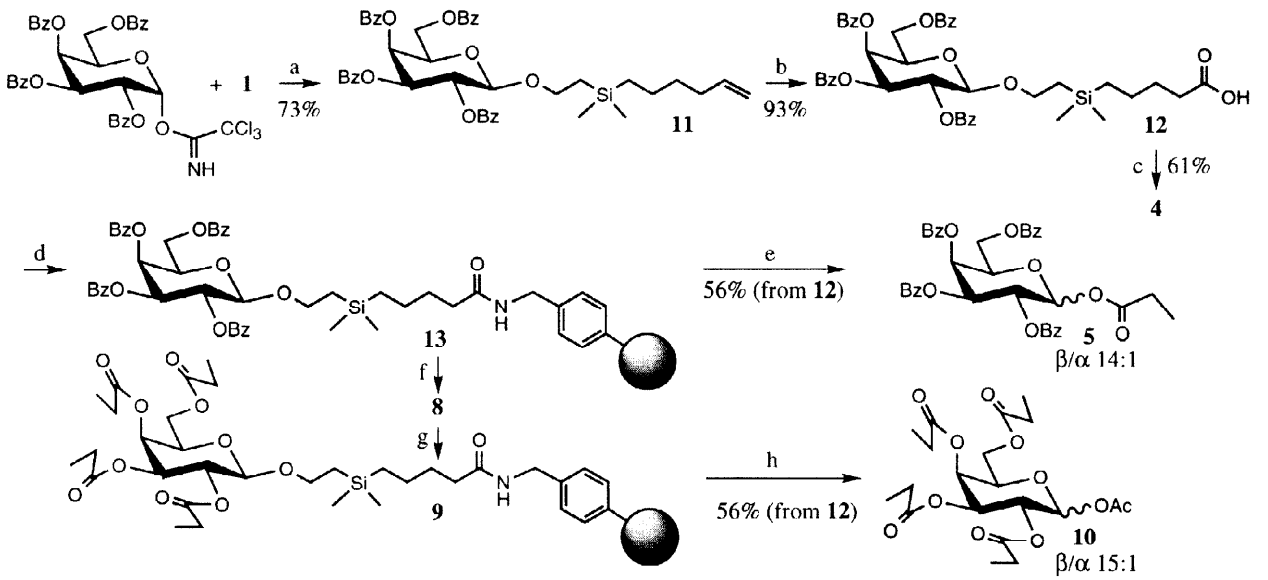


Scheme 3. a) MeONa (0.2 equiv.), MeOH, 21 h, then Amberlyst 15. b) LiOH (1.5 equiv.), THF/H_2O 7:2, 3 h. c) Aminomethyl polystyrene (0.6 mmol/g, crosslinked with 1 % DVB, 2 equiv. in relation to **7**), DIC (5 equiv.), F_5C_6OH (5 equiv.), DMF, 24 h. d) $(EtCO)_2O$ (40 equiv.), pyridine, 22 h. e) BF_3•OEt_2 (5 equiv.), Ac_2O (5 equiv.), toluene, 23 h.

In an alternative approach (Scheme 4), the alcohol **1** was glycosylated to give **11** (73%). Oxidation of **11** with ruthenium trichloride/sodium periodate[4] gave the benzoyl-protected linker glycoside **12** (93%), which could be transformed into the methyl ester **4** (61%) by treatment with methanol and Amberlyst resin. The carboxylic acid **12** was transformed into the corresponding pentafluorophenyl ester and coupled to aminomethyl polystyrene resin to give **13**, essentially as described above in the preparation of **8**. Treatment of **13** with a mixture of propionic anhydride and boron trifluoride etherate in toluene, gave the mixed ester **5** (56%; based on the amount of **12** used in the coupling step) as a mixture of β and α anomers (~14:1).

In order to demonstrate further the versatility of the novel linker for the creation of saccharide-based molecular libraries, the tethered galactose moiety of resin **13** was transformed over a few steps into the mixed saccharide ester **10** (Scheme 4). Thus, the benzoyl groups in **13** were removed by treatment of the resin with methanolic sodium methoxide (→**8**), and propionyl groups were introduced by treatment with propionic anhydride in pyridine (→**9**). Cleavage of the galactose moiety from the resin **9** was performed by treatment with acetic anhydride and boron trifluoride etherate in toluene, as described in Scheme 3. The

resulting mixed ester **10** was obtained in 56% yield (based on the amount of **12** used in the coupling step), as a mixture of β and α anomers (~15:1). The de-*O*-benzoylation (**13**→**8**) and *O*-propionylation (**8**→**9**) reactions performed on the resin seem to be highly efficient, since **5** and **10** (Scheme 4) were obtained in the same overall yield and no partly protected analogues were obtained.



Scheme 4. a) TMSOTf (0.1 equiv.), CH_2Cl_2/heptane 1:1, 10 min. b) $RuCl_3 \cdot H_2O$ (0.05 equiv.), $NaIO_4$ (4 equiv.), CCl_4/MeCN/H_2O, (2:3:3), 4 h. c) MeOH, Amberlyst 15, 72 h. d) Aminomethyl polystyrene (ca. 1.13 mmol/g, crosslinked with 1 % DVB, 2 equiv. in relation to **12**), DIC (5 equiv.), F_5C_6OH (5 equiv.), DMF, 18 h; then BzCl (20 equiv.), pyridine, 18h. e) $BF_3 \cdot OEt_2$ (4 equiv.), $(EtCO)_2O$ (4 equiv.), toluene, 24 h. f) MeONa (0.5 equiv.), MeOH/CH_2Cl_2 (1:1), 21 h. g) $(EtCO)_2O$ (40 equiv.), pyridine, 24 h. h) $BF_3 \cdot OEt_2$ (5 equiv.), Ac_2O (5 equiv.), toluene, 23 h.

In summary, the novel linker permits both efficient manipulations of functional groups while the saccharide is bound to a solid support, and release of the saccharide from the support with concomitant introduction of various acyloxy groups at the anomeric centre. Thus, the linker seems to be suitable for solid phase combinatorial synthesis of sugar-based compound libraries.

EXPERIMENTAL

The experimental conditions were as described in Schemes 1–4. Reactions were performed at room temperature unless stated otherwise. ^{1}H-NMR spectra were recorded with a 400 MHz instrument. Selected optical rotation, ^{1}H-NMR, and high resolution MS data: Compound **2**: ^{1}H-NMR ($CDCl_3$) δ: 5.73-5.85 (m, 1 H, C*H*=CH_2), 4.90-5.01 (m, 2 H, CH=C*H*$_2$), 4.11-4.17 (m, 2 H, AcOC*H*$_2$); Compound **3**: ^{1}H-NMR ($CDCl_3$) δ: 3.66-3.71 (m, 2 H, HOC*H*$_2$), 3.64 (s, 3 H, OC*H*$_3$), 2.29 (t, 2 H, *J* 7.5 Hz, C*H*$_2$COO), HRMS calc. for $C_{10}H_{23}O_3Si$: 219.1417, found: 219.1422; Compound **4**: $[\alpha]_D^{22}$ +79 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 5.80 (dd, 1 H, *J* 10.4, 8.0 Hz, H-2), 4.86 (d, 1 H, *J* 8.0 Hz, H-1), 4.08 (ddd, 1 H, *J* 10.7, 9.7, 5.6 Hz, OC*H*$_2$CH$_2$Si), 3.66 (s, 3 H, OC*H*$_3$), 2.26 (t, 2 H, *J* 7.5 Hz, C*H*$_2$COO); HRMS: calc. for $C_{44}H_{48}O_{12}SiNa$: 819.2813, found: 819.2802; Compound **5**: $[\alpha]_D^{22}$ +119 (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 6.13 (d, 1 H, *J* 8.3 Hz, H-1), 5.94 (dd, 1 H, *J* 10.4 Hz, 8.4 Hz, H-2), 1.08 (t, 3 H, *J* 7.5 Hz, CH$_2$C*H*$_3$); HRMS: calc. for $C_{37}H_{32}O_{11}Na$: 675.1842, found: 675.1847; Compound **6**: $[\alpha]_D^{22}$ +13 (*c* 1, MeOH); ^{1}H-NMR (C_5D_5N) δ: 4.86 (d, 1 H, *J* 7.7 Hz, H-1), 4.61 (dd, 1 H, *J* 2.7 Hz, <1 Hz, H-4), 4.30 (ddd, 1 H, *J* 10.5, 9.5, 6.5 Hz, OC*H*$_2$CH$_2$Si), 3.83 (ddd, 1 H, *J* 10.5, 9.5, 6.5 Hz, OC*H*$_2$CH$_2$Si), 3.64 (s, 3 H, OC*H*$_3$), 2.33 (t, 2 H, *J* 7.5 Hz, C*H*$_2$COO); HRMS: calc. for $C_{16}H_{32}O_8SiNa$: 403.1764, found: 403.1762; Compound **7**: $[\alpha]_D^{22}$ +5 (*c* 0.17, MeOH); ^{1}H-NMR (CD_3OD) δ: 4.19 (d, 1 H, *J* 7.2 Hz, H-1),

3.97 (ddd, 1 H, *J* 11.5, 9.6, 5.9 Hz, OC*H*$_2$CH$_2$Si), 3.79 (dd, 1 H, *J* 2.3, 0.9 Hz, H-4), 3.59 (ddd, 1 H, *J* 11.5, 9.6, 5.6 Hz, OC*H*$_2$CH$_2$Si), 2.26 (t, 2 H, *J* 7.3 Hz, C*H*$_2$COO); HRMS: calc. for $C_{15}H_{30}O_8SiNa$: 389.1608, found: 389.1590; Compound **10** ($CDCl_3$) δ: 6.39 (H-1$^{\alpha}$), 5.73 (dd, 1 H, *J* 8.4, 0.5 Hz, H-1$^{\beta}$), 5.12 (ddd, 1 H, *J* 10.4, 3.4, <1 Hz, H-3), 2.17 (COC*H*$_3$-α), 2.12 (s, 3 H, COC*H*$_3$-β); HRMS: calc. for $C_{20}H_{30}O_{11}Na$: 469.1686, found: 469.1687; Compound **11**: $[\alpha]_D^{22}$ +84 (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 6.01 (dd, 1 H, *J* 3.4, 0.9 Hz, H-4), 5.74-5.85 (m, 1 H, C*H*=CH$_2$), 4.91-5.02 (m, 2 H, CH=C*H*$_2$), 4.86 (d, 1 H, J 8.0 Hz, H-1), 4.08 (ddd, 1 H, *J* 10.9, 9.7, 5.7 Hz, OC*H*$_2$CH$_2$Si), 3.68 (ddd, 1 H, *J* 10.9, 9.6, 6.6 Hz, OC*H*$_2$CH$_2$Si); HRMS: calc. for $C_{44}H_{48}O_{10}SiNa$: 787.2915, found: 787.2930; Compound **12**: $[\alpha]_D^{22}$ +64 (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 6.02 (dd, 1 H, *J* 3.5, 0.6 Hz, H-4), 4.87 (d, 1 H, *J* 7.9 Hz, H-1), 2.31 (t, 2 H, *J* 7.5 Hz, C*H*$_2$COO); HRMS: calc. for $C_{43}H_{45}O_{12}SiNa_2$: 827.2476, found: 827.2483.

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