An Expeditious Synthesis of a *C*-Disaccharide using a Temporary Silaketal Connection

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Methyl α-*C*-maltoside **6** is expeditiously synthesized by radical coupling of the phenyl Se-glycoside **1** onto the *exo*-methylene sugar **2**, which are temporarily connected through a silaketal tether.

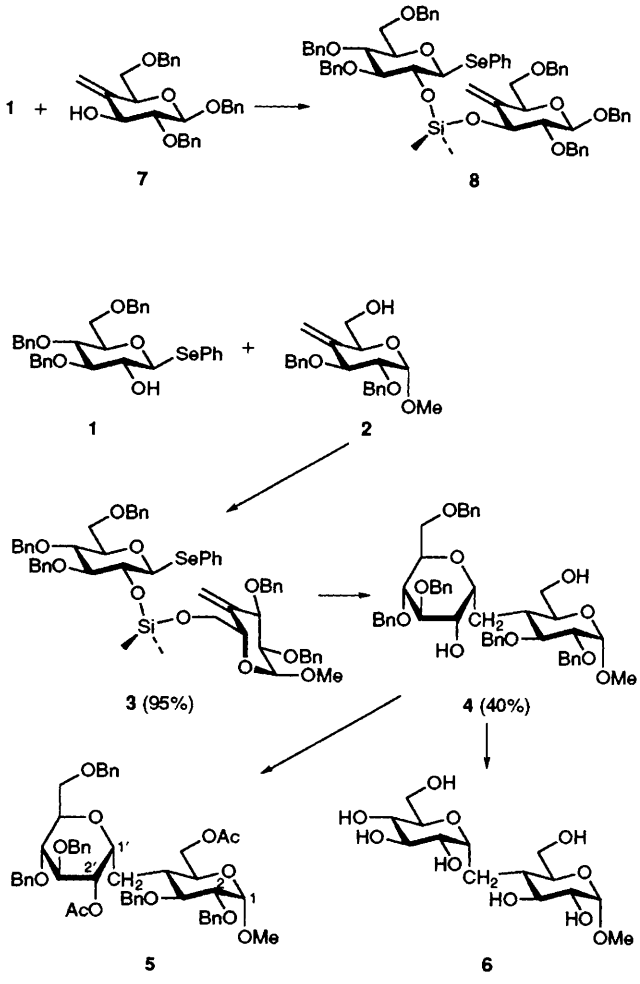
A decade ago, we disclosed[1] a short stereoselective synthesis of methyl α-*C*-gentiobioside, an analogue of methyl 6-*O*-(β-D-glucopyranosyl)-α-D-glycopyranoside in which the interglycosidic oxygen atom was replaced by a methylene group. This was the first synthetic report on a member of a challenging novel class of non-natural analogues of disaccharides we proposed to call *C*-disaccharides, and which have since then attracted a great deal of attention.[2] An important distinction should be made at this point between the so defined *C*-disaccharides and other types of carbon-linked disaccharides which have also started to appear on the scene.[2]

The intermolecular reaction of a nucleophilic anomeric radical with an alkene, a potentially attractive solution to the problem, has indeed been used to synthesize *C*-glycosides[3] and *C*-disaccharides,[4] but is limited to those alkenes which are substituted by electron-withdrawing substituents. In recent years, there has been an increasing interest in the use of temporary silicon tethers to facilitate the carbon–carbon bond formation.[5] A stereospecific approach of *C*-glycosides, through an *exo-dig* mode of cyclisation, is based on this idea.[6] It is remarkable that the intramolecular radical cyclisation of two substrates tethered through a silaketal connector has been reported to occur *via* a 7-, 8- or 9-*endo-trig* mode of cyclisation.[7] Such a 7-*endo-trig* radical closure has indeed provided a powerful solution to a stereoselective and elegant synthesis of tunicamisyluracil.[5] We would like now to report on the use of a 9-*endo-trig* radical cyclisation process for a regioselective and exceptionally expeditious entry to a *C*-disaccharide (methyl α-*C*-maltoside),[8] which has recently been synthetized through a multistep sequence.[9]

Easily available alcohols **1**[10]† and **2**‡ were efficiently connected together through a silaketal tether as follows:

† Data on **1** are not reported ref. 10. *Selected data* for **1**: m.p. 60–61 °C (from pentane–diethyl ether); $[\alpha]_D^{20}$ −12 (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.69–7.15 (20H, m, Ar-H), 4.88 (1H, d, $J_{1,2}$ 8.6 Hz, 1-H), 3.78 (2H, 2dd, $J_{5,6}$ 2.0, $J_{5,6'}$ 3.5, $J_{6,6'}$ 11.2 Hz, 6,6'-H), 3.50 (1H, ddd, $J_{2,3}$ 9.8, $J_{2,OH}$ 1.7 Hz, 2-H). Satisfactory elemental analyses were obtained for new compounds.

‡ **2**: $[\alpha]_D^{20}$ +77 (*c* 1, $CHCl_3$). It was prepared from known[11] methyl 2,3-di-*O*-benzyl-4-deoxy-4-*C*-methylene-6-*O*-*tert*-butyldimethylsilyl-α-D-*xylo*-hexopyranoside by treatment with aqueous HF in MeCN (86%).



dimethyldichlorosilane (3.5 equiv.) was added at −78 °C to a solution of the lithium salt of the phenyl Se-glycoside **1** (prepared from a 2.5 mol dm^{-3} solution of BuLi in hexane) in dry tetrahydrofuran (THF). The temperature was then raised to 22 °C within 2 h, and the solution was evaporated. A solution of the primary alcohol **2** (0.5 equiv.) and imidazole (3 equiv.) in dry THF was added. After 2 h at 20 °C, work-up afforded the tethered silaketal intermediate **3** in 95% yield from **2** (>90% purity from ^1H and ^{13}C NMR). Silaketal **3** was cyclised at 60 °C in benzene [20 h syringe pump addition of a benzene solution of tributyltin hydride (2.5 equiv.) and azoisobutyronitrile (0.01 equiv.)] and desilylated (HF in THF) to give the protected *C*-disaccharide **4** in 40% isolated yield (not optimized) as a single diastereoisomer. It was characterized as the diacetate **5**§ (Ac_2O, pyridine), $[\alpha]_D^{20}$ +36 (*c* 4, $CHCl_3$). Debenzylation (H_2, Pd/C, MeOH–AcOEt 5 : 2) gave the methyl α-*C*-maltoside **6** (80%), $[\alpha]_D^{20}$ +54 (*c* 1, MeOH) {lit.[9] $[\alpha]_D^{20}$ +53 (*c* 0.4, MeOH)}, whose NMR data are in full agreement with those reported by Kishi and co-workers.[9,12]

Reduction was also attempted on the tethered intermediate **8** prepared from **1** and **7**.¶ A non stereoselective 8-*endo-trig* cyclisation (*ca.* 50% yield) was observed in this case, resulting in a mixture of 1 → 4 linked *C*-disaccharides which has not been analysed further at this stage.

Inasmuch as the necessary tethering and removal of the silicon connection are high-yielding processes (over 90%), this potentially general route offers a fascinating direct way of constructing a *C*-disaccharide. The silaketal stratagem is, so to say, entropically mimicking an evanescent and extremely simple *C*-glycosyl transferase (unknown enzyme), the tether (enzyme) bringing together the glycosyl donor (phenyl Se-glycoside) and the glycosyl acceptor (*exo*-methylene sugar), the tributyltin hydride (coenzyme) triggering the condensation, and the removal of the transient tether achieving the release of the product.

The array of hydroxy groups which is present in monosaccharides obviously provides a potentially flexible way of achieving a fine tuning of the stereoselectivity as suggested here (compare the behaviour of **3** and **8**). One feature of the process is that the two hydroxy groups which are selected for the connection are selectively released during the removal of the tether, making them both available for further selective transformations.

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§ *Selected spectroscopic data* for **5**: ^1H NMR (400 MHz, $CDCl_3$): δ 4.96 (1H, dd, $J_{1',2'}$ 4.3, $J_{2',3'}$ 6.5 Hz, 2'-H), 3.83 (1H, dd, $J_{2,3}$ 9.5, $J_{3,4}$ 9.5 Hz, 3-H), 3.76 (1H, dd, $J_{3',4'}$ 6.5 Hz, 3'-H), 3.66 (1H, dd, $J_{4',5'}$ 6.5 Hz, 4'-H). These data confirm the structure and call for a conformation of the *C*-glucosyl moiety which deviates from the $^4C_1$ chair form. For this reason, Haworth representation of this unit in **5** (and also in **4**, where $J_{2',3'}$ value is 3.5 Hz) has been used.

¶ **7** {m.p. 103 °C (from cyclohexane–ethyl acetate), $[\alpha]_D$ − 14 (*c* 0.5 $CHCl_3$)} was prepared from known[13] benzyl 4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranoside as follows: i, $CH_2(OMe)_2$, CH_2Cl_2, P_2O_5, room temp. (96%); ii, MeONa, MeOH, room temp. (95%); iii, pyridinium chlorochromate (PCC), 4 Å molecular sieves, CH_2Cl_2 (86%); iv, $(Ph)_3PCH_3Br$, BuLi, THF, room temp. (90%); v, HCl, MeOH, CH_2Cl_2 (82%).