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Note

A short synthesis of 1,2,3-tris(*tert*-butyldimethylsilyl)-6,7-dideoxy-6-*C*-methyl-α-D-*gluco*-heptofuran-6-enose from D-glucurone*

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The titanocene methylidene complex **1** converts esters and lactones into enol ethers, which is not possible with conventional phosphorus-containing Wittig-type reagents[1,2]. The complex **1** is generated from the pure Tebbe reagent **2**[3] either directly, or in an aluminium-free state via Grubbs titanacyclobutane **3**[2,4,5]. Recently[5], dimethyltitanocene has also been shown to methylenate carbonyl compounds.

Unfortunately, commercially available pure **2** is expensive because rather troublesome special techniques are required to isolate it in pure form[6] from the trimethylaluminium titanocene dichloride mixture used in its synthesis. Consequently, this led us[7] and others[8] to develop a simple method for methylenating carbonyl compounds, which employs the crude reaction mixture used to prepare reagent **2**. The excess of organoaluminium compounds present did not usually interfere[7,8] with the methylenation of carbonyl groups, as found in reactions that ran for 1.5 h with sugar aldehydes, ketones, esters, and δ-lactones; with γ-lactones; lactols were formed, whereas with pure **2** these γ-lactones also gave enol ethers[9].

We now report how the tris(*tert*-butyldimethylsilyl) derivative **4** of β-D-glucurono-6,3-lactone reacts under these methylenation conditions. The tris-silyl derivative **4** was readily prepared (80%) from D-glucurone after chromatography, to remove the 10% of the α anomer.

Thus, treatment of a solution of **4** in toluene with a mixture of titanocene dichloride and trimethylaluminium (2.1 and 4.3 mol, respectively) gave, after 90 min, a high yield of the tris-silylated olefinic sugar derivative **9**. This material was shown not to be the olefin **5**, formed by simple Wittig-type methylenation, since the molecular weight (determined by f.a.b.-mass spectrometry) and chemical composition indicated that two carbon atoms had been added to the lactone. This conclusion was borne out by the ^{13}C-n.m.r. spectrum, which indicated **9** to be a tris(*tert*-butyldimethylsilylated) 6,7-

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[*] Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.

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dideoxy-6-*C*-methyl-6-heptenose because, in addition to signals for the three protecting groups, there were three signals for the $CH_3C=CH_2$ group, one for an anomeric carbon, and four for the other carbons of the sugar. The ^1H-n.m.r. spectrum confirmed this gross structure, verified that the stereochemistry was unchanged from that of the lactone, and revealed that the hydroxyl group (*J* 10.3 Hz) was coupled to H-5 and not H-3, the former signal being identified easily by its broadened shape due to allylic coupling. Consequently, the 5-*O*-silyl group had migrated during the reaction.

The heptenose **9**, which is a useful synthon[11], may be readily acquired in two easy steps from an inexpensive member of the natural chiral pool and is currently being used for chain elongations and nitrone cyclisations[12]. On reduction with hydrogen (Pd/C), **9** gave the gem-dimethyl branched-chain sugar derivative **10**, as indicated by the n.m.r. signals for the Me_2CH group (δ_C 16.3 and 19.9; δ_H 1.12 (d), 1.13 (d, *J* 7.0 Hz); δ_C 31.5 and a septet of doublets at δ_H 2.30 (*J* 2.5 Hz and 6 × *J* 7.0 Hz).

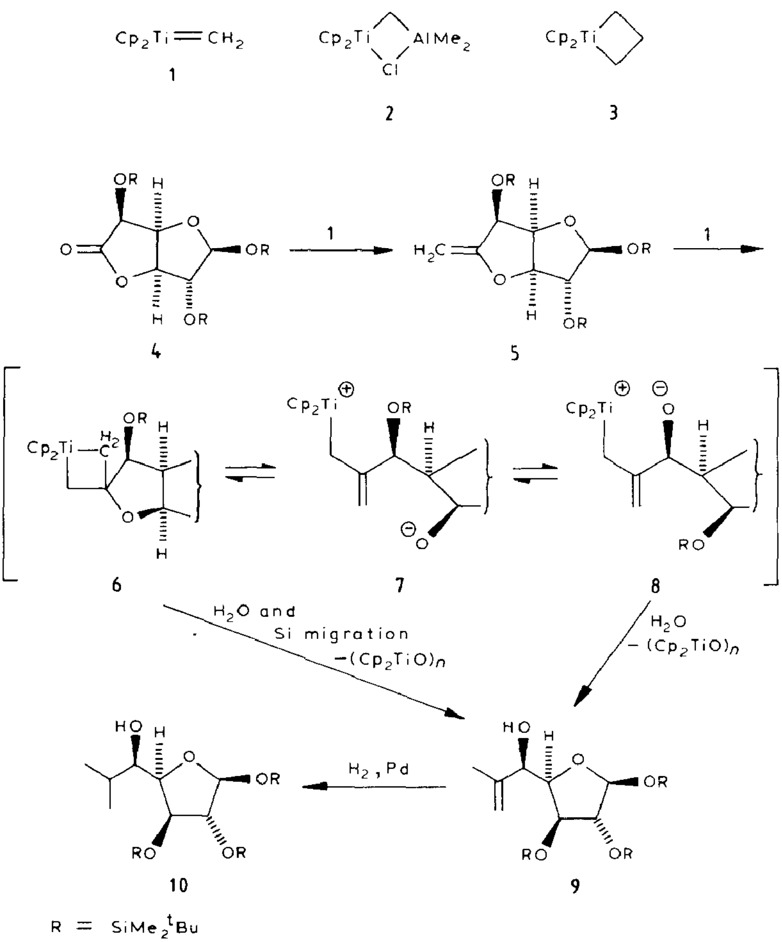
The formation of **9** requires the addition of two mol of **2** to the lactone. This outcome probably arises from the reaction of **2** with the enol ether **5**, which is formed by methylenation of the lactone **4** as revealed by t.l.c. in the early stages of the reaction. This is a reasonable proposal since **2** will react[2,4] with olefins (*e.g.*, **5**) to give metalcycles (*e.g.*, **6**). Hydrolysis at this stage would afford the 5-*O*-silylated heptenose, which would require the silyl group to migrate to afford **9**. Alternatively, it is possible that the migration occurred prior to hydrolysis as shown in **6**→**7**→**8**.

The reason for the dimethylenation is not clear. The bicyclic structure of **4** is not entirely responsible, since the 1,2-di-*O*-methyl and the 1,2-*O*-isopropylidene derivatives of 5-*O*-methyl-α-D-glucurono-6,3-lactone give, under identical reaction conditions, lactols in high yield, accompanied only in the second example by a little (9%) heptenose derivative[7]. The difference in anomeric configuration could play a role, or the migrating silyl group might exert an effect, pulling an equilibrium towards the structure **8** and thereby inducing the formation of a metalacycle.

EXPERIMENTAL

General. — Melting points were determined with a Mettler FP82 hot-stage apparatus and are uncorrected. Optical rotations were determined with an Optical Activity polarimeter Model AA-100 for solutions in CH_2Cl_2. Evaporations were conducted under reduced pressure at 40°. Flash-column chromatography was performed on columns of SORBSIL™ C60 silica gel (60–120 mesh). T.l.c. was performed on Silica Gel 60 F_{254} (Merck). ^1H-N.m.r. spectra (internal Me_4Si) were recorded with a Jeol JNM GSX 270 instrument. I.r. spectra were measured in Nujol with a Perkin–Elmer 597 instrument. Mass spectrometry was performed with a VG ZAB-SE instrument operated at 8 kV.

*1,2,5-Tris-*O*-(*tert*-butyldimethylsilyl)-β-D-glucurono-6,3-lactone* (**4**). — To a stirred solution of D-glucurono-6,3-lactone (1.0 g, 5.68 mmol) in *N,N*-dimethylformamide (12 mL) was added excess of imidazole (3.5 g) followed by an excess of *tert*-butyldimethylsilyl chloride (3.5 g). The mixture was stirred overnight when t.l.c. (light



petroleum–ether, 10:1) revealed a 1:9 α,β-mixture (R_F 0.54 and 0.41, respectively). The mixture was then poured into ice–water and extracted with ether, and the extract was concentrated. Column chromatography (light petroleum–ether, 20:1) of the residue gave **4** (2.35 g, 80%), m.p. 102–104° (from ethanol–water), $[\alpha]_D$ +24.5° (*c* 1); ν_{max} 1800 cm^{-1} (C=O). N.m.r. data (CDCl$_3$): ^{1}H, δ 5.16 (s, 1 H, H-1)[13], 4.70 (dd, 1 H, $J_{3,4}$ 6.2 Hz, H-3), 4.50 (d, 1 H, $J_{2,3}$ 4.2 Hz, H-2), 4.26 (d, 1 H, $J_{4,5}$ 0 Hz, H-4), 4.12 (s, 1 H, H-5), 0.84, 0.78, and 0.76 (3 s, 9 H each, 3 ^{t}Bu), 0.08, 0.05, and −0.02 (3 s, 6 H each, 3 Me$_2$Si); ^{13}C, δ 173.2 (C=O), 105.8 (C-1), 83.2, 80.3, 79.3, and 71.1 (C-2,3,4,5), 25.7 (C*Me*$_3$), 18.4, 18.1, and 18.0 (3 Me$_3$CSi), −4.5, −4.8, −4.85, −4.9, −5.3, and −5.5 (3 Me$_2$Si).

Anal. Calc. for $C_{24}H_{50}O_6Si_3$: C, 55.60; H, 9.65. Found: C, 55.75; H, 9.82.

*1,2,3-Tris-*O-(tert-*butyldimethylsilyl)-6,7-dideoxy-6-*C-*methyl-β-*D-gluco-*hept-6-enofuranose* (**9**). — 2M Trimethylaluminium in toluene (10.2 mL, 20 mmol) was mixed under argon with titanocene dichloride (2.48 g, 10 mmol) at room temperature. After 72 h, a portion (2.24 mL) of the solution was added to a solution of **4** (0.52 g, 1.0 mmol) in toluene (6 mL), tetrahydrofuran (2 mL), and pyridine (10 μL) at −40° under argon and stirred for 30 min. The mixture was warmed to 22° for 30 min, when t.l.c. (light petroleum–ether, 15:1) revealed **4** (R_F 0.18) and the enol ether **5** (R_F 0.70). After a further 1 h, all of **4** had been converted into a major (R_F 0.57) and two minor products (R_F 0.41 and 0.34). The mixture was then cooled to −10°, aq. 15% sodium hydroxide (0.2 mL) was added, followed by ether (50 mL), and the whole mixture was dried ($MgSO_4$) and concentrated. The residue was filtered through a short pad of silica gel, using light petroleum–ether (15:1), and the filtrate was concentrated. Column chromatography (light petroleum–ether, 40:1) of the residue gave **9**, isolated as a colourless oil (0.38 g, 71%), $[\alpha]_D$ −42° (c 1.5); ν_{max} 3500 cm^{-1} (OH). N.m.r. data: ^1H (C_6D_6), δ 5.34 (s, 1 H, H-1), 5.17 and 4.97 (2 bs, 1 H each, $=CH_2$), 4.70 (d, 1 H, $J_{3,4}$ 8.8 Hz, H-3), 4.46 (dd, 1 H, $J_{4,5}$ 2.9 Hz, H-4), 4.30 (dd, 1 H, $J_{5,OH}$ 11.0 Hz, H-5) [when the hydroxyl group was D_2O-exchanged, this signal collapsed to a d, $J_{5,4}$ 2.9 Hz, broadened by allylic coupling], 4.29 (s, 1 H, H-2), 3.33 (d, 1 H, exchangeable with D_2O, OH), 1.88 (s, 3 H, MeC=), 1.02, 0.9, and 0.87 (3 s, 9 H each, 3 ^tBu), 0.31, 0.19, 0.14, 0.06, 0.03, and 0.02 (6 s, 3 H each, 3 Me_2Si); ^1H ($CDCl_3$), δ 5.1 (s, 1 H, H-1), 4.99 and 4.93 (2 bs, 1 H each, $=CH_2$), 4.35 (d, 1 H, $J_{3,4}$ 8.5 Hz, H-3), 4.05 (dd, 1 H, $J_{4,5}$ 3.3 Hz, H-4), 4.03 (s, 1 H, H-2), 3.90 (dd, 1 H, $J_{5,OH}$ 10.6 Hz, H-5) [when the hydroxyl group was D_2O-exchanged, this signal collapsed to a d, $J_{5,4}$ 3.3 Hz, broadened by allylic coupling], 3.30 (d, 1 H, exchangeable with D_2O, OH), 1.79 (s, 3 H, MeC=), 0.89 and 0.88 (2 s, 9 and 18 H, 3 ^tBu), 0.12, 0.11, 0.103, 0.097, 0.09, 0.04 (6 s, 3 H each, 3 Me_2Si); ^{13}C ($CDCl_3$), δ 145.7 (C=CH_2), 113.4 (CH_2=C), 103.7 (C-1), 83.9, 81.7, 76.0, and 74.8 (C-2,3,4,5), 25.8 and 25.6 (3 Me_3C), 18.1, 18.0, and 17.8 (3 Me_3C), 17.6 (*Me*C=), −4.3, −4.8 (intense), −5.2, and −5.3 (3 Me_2Si). Mass spectrum: m/z 532 (M^+).

*1,2,3-Tris-*O*-(*tert*-butyldimethylsilyl)-6,7-dideoxy-6-*C*-methyl-β-*D-gluco*-heptofuranose* (**10**). — A solution of **9** (70 mg, 0.13 mmol) in ethanol (4 mL) was hydrogenated for 1.5 h at 1 atm. over Pd/C (10%) (50 mg). T.l.c. (light petroleum–ether, 20:1) then revealed a single faster-moving product (R_F 0.55), which was isolated after the usual work-up. Column chromatography (light petroleum–ether, 40:1) of the product gave **10** (60 mg, 85%), $[\alpha]_D$ −32° (c 0.2). N.m.r. data (C_6D_6): ^1H δ 5.35 (s, 1 H, H-1), 4.40 (dd, 1 H, $J_{4,5}$ 3.0 Hz, H-4), 4.30–4.18 (m, 3 H, H-2,3,5), 3.36 (d, 1 H, $J_{OH,5}$ 10.9 Hz, OH), 2.29 (sep of d, 1 H, J_{6,CH_3} 7.0, $J_{6,5}$ 2.5 Hz, H-6), 1.14 and 1.13 (2 d, 3 H each, 2 Me), 1.04, 0.89, and 0.88 (3 s, 9 H each, 3 ^tBu), 0.39, 0.22, 0.11, and 0.06 (4 s, 3 H each, 4 MeSi), and 0.04 (s, 6 H, 2 MeSi); ^{13}C, δ 104 (C-1), 83.9, 82.7, 76.4, and 74.4 (C-2,3,4,5), 31.5 (C-6), 26.5, 25.8, and 25.7 (3 Me_3C), 19.9 and 16.3 (2 Me), 18.9, 18.2, and 18.0 (3 Me_3C), −4.1, −4.3, −4.5, −4.7, −4.8, and −5.3 (3 Me_2Si). Mass spectrum: m/z 534 (M^+).

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