Carbohydrate Research, 177 (1988) 259–264
Elsevier Science Publishers B.V., Amsterdam - Printed in The Netherlands

Note

The synthesis of some novel group IVa organometallic derivatives of carbohydrates

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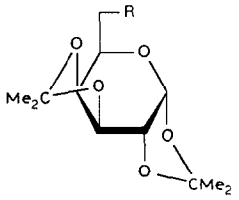
(Received October 23rd, 1987; accepted for publication, December 3rd, 1987)

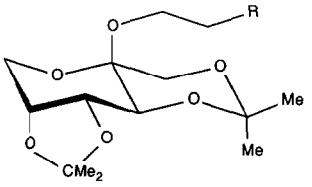
The pronounced biocidal activity[1,2] associated with many carbohydrates possessing group IVa organometallic substituents has considerable commercial interest. We now describe the synthesis of several group IVa carbohydrate conjugates that were required for biological evaluation.

The reaction of 1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose[3] (**1**) with triphenyltinlithium[4] (**2**) in dry tetrahydrofuran proceeded slowly to give a single product **3** (23% yield after flash chromatography). The ^{1}H-n.m.r. spectrum of **3** showed that H-6,6 were strongly shielded and the resonances (δ 2.2 and 1.8) were accompanied by satellites from coupling with the ^{117}Sn and ^{119}Sn. The shielding was even more pronounced in the ^{13}C-n.m.r. spectrum, causing a dramatic upfield shift of the C-6 resonance to δ 13.8. As expected, the $^1J^{117}_{Sn,C-6}$ $^1J^{119}_{Sn,C-6}$ values were large (360.8 and 377.1 Hz, respectively) and, as is commonly found for tin–carbon long-range couplings, ^3J was substantially greater then ^2J ($^2J_{Sn,C-5}$ 11.3, $^3J_{Sn,C-4}$ 28.8 Hz)[5].



1 R = OTs
3 R = $SnPh_3$
5 R = OH

2 Ph_3SnLi
4 Ph_3SiLi
6 Ph_3PbLi



7 R = Cl
8 R = $SnPh_3$
9 R = $SiPh_3$
10 R = $PbPh_3$

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0008-6215/88/$ 03.50

Attempted reaction of **1** with the much harder base triphenylsilyl-lithium[4] (**4**) caused rapid desulphonylation to give 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**5**) as the sole product. Attempted substitution with the triphenylplumbyl anion[4] (**6**) was also unsuccessful, presumably because of its increased size and lower nucleophilicity. The resistance of the 6-sulphonates of galactopyranosides towards nucleophilic attack has been attributed[6] to unfavourable steric and polar interactions arising in the transition state.

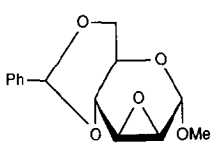
2-Chloroethyl 1,3:4,5-di-*O*-isopropylidene-β-D-fructopyranoside[7] (**7**) reacted smoothly with triphenylstannyl-lithium (**2**) in tetrahydrofuran to furnish 43% of crystalline **8**. Although the ^{1}H-n.m.r. spectrum of **8** was mainly second-order, the H-2′,2′ resonances appeared as a broad triplet at δ 1.9 with triplet satellites ($^2J_{Sn,H-2'}$ 24 Hz). In the ^{13}C-n.m.r. spectrum of **8**, the resonances of the acetal carbons of the 4,5- and 1,2-*O*-isopropylidene groups appeared at δ 108.5 and 100.0, respectively, in accord with the rules proposed by Buchanan *et al.*[8]. Other features corroborating the proposed structure were the large $J_{Sn,C-2'}$ values (358.9 and 376.9 Hz) and the small, averaged, long-range coupling with C-1′ ($^2J_{Sn,C-1'}$ 24.3 Hz).

Treatment of **7** with triphenylsilyl-lithium afforded a 39% yield of the crystalline glycoside **9**, the structure of which was established from the ^{13}C-n.m.r. spectrum which contained both the expected acetal quaternary carbon resonances at δ 108.6 and 100.0, as well as a resonance for a strongly shielded atom at δ 15.3, attributable to C-2′. Despite the fact that ^{29}Si has a nuclear spin quantum number of $^1/_2$, ^{29}Si,^{13}C couplings are not generally observed in the ^{13}C-n.m.r. spectra of organosilanes due to the low natural abundance (4.7%) and small gyromagnetic ratio (−0.55477) of this isotope[9].

When **7** was treated with triphenylplumbyl-lithium (**6**) in tetrahydrofuran, only low yields (19%) of the desired organometallic glycoside **10** were obtained, presumably because the triphenyl-lead anions dimerise before they can displace the chlorine substituent. The structure of **10** followed clearly from the ^{13}C and ^{13}C DEPT spectra[10] since there were signals for three CH, four CH_2, four CH_3, and three quaternary carbon atoms, in addition to those for the aromatic carbon atoms. Furthermore, ^{207}Pb couplings with C-2′ (341.8 Hz) and C-1′ (36.0 Hz) were clearly visible.

The reactions of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[11] (**11**) with Ph_3SiLi and Ph_3PbLi were expected to preceed by axial attack on C-3, to give 3-substituted α-D-altropyranosides (Furst–Plattner rule[6]), and the *trans*-diaxial products **12** and **13** were formed exclusively, being isolated in yields of 52% and 63%, respectively. The 250-MHz ^{1}H-n.m.r. spectrum of **12** showed H-3 to be strongly shielded (signal at δ 2.77) and small couplings between H-1, H-2, and H-3 ($J_{1,2}$ 1.4, $J_{2,3}$ 1.7 Hz) indicative of the α-D-*altro* configuration. The triphenylplumbyl derivative **13** also had small $J_{1,2}$ and $J_{2,3}$ values (1.0 and 1.9 Hz, respectively), and a long-range W-coupling ($J_{1,3}$ 1.0 Hz) indicating H-1 and H-3 to be equatorial. Surprisingly, both **12** and **13** displayed abnormally large $J_{3,4}$ values (7.0 and 5.5 Hz, respectively); the anomalous $J_{3,4}$ (5.9 Hz) found by Hall *et al.*[12] for the triphenyltin

conjugate **14** was believed to be due to either an electronegativity effect from the organometallic residue, or distortion of the pyranose ring towards a $^{O}S_5$ skew conformation, as a result of steric interaction associated with the axial triphenyltin substituent at C-3. We favour the former explanation mainly because the value of $J_{3,4}$ increased as the size of the organometallic group decreased, whereas the opposite trend would have been expected if conformational disturbance was significant. An electronegativity rationale also explains better why $J_{2,3}$ is unaffected in **12-14**; electronegative substituents generally exert their greatest influence on vicinal coupling constants when they are *trans* to one of the protons[13] in the vicinal group, whereas in **12-14** the organometallic substituent and H-2 are *cis*.



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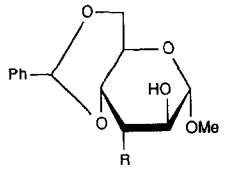
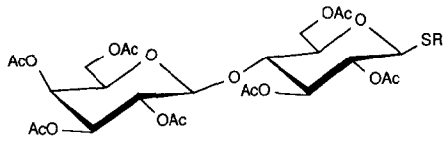


12 R = $SiPh_3$
13 R = $PbPh_3$
14 R = $SnPh_3$



15 R = $SnPh_3$
16 R = H

A recent report that several thio-organotin derivatives can inhibit the P388 lymphocytic leukaemia tumour in mice[14] prompted preparation of the triphenyltin-thioglycoside **15**. Condensation of 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-thio-β-D-glucopyranose (**16**) with triphenyltin hydroxide, using the conditions of Poller *et al.*[15], yielded a complex mixture from which **15** could be isolated in only 38% yield by column chromatography. Despite the second-order appearance of many of the resonances in the ^{1}H-n.m.r. spectrum of **15**, a partial assignment was possible. Thus, the appearance of two large doublets for H-1 and H-1′ ($J_{1,2}$ 9.5, $J_{1',2'}$ 7.8 Hz) at δ 4.48 and 4.34 indicated that two β-linkages were present. The *galacto* configuration was evident from the small $J_{3',4'}$ value (3.4 Hz) and the large $J_{2',3'}$ value (10.5 Hz). In addition, there were seven OAc resonances between δ 2.13 and 1.90 and resonances for Ph between δ 7.7 and 7.2. The ^{13}C-n.m.r spectrum was diagnostic since the signal for C-1 (δ 80.3) appeared at much higher field than that for C-1′ (δ 101.1) due to the strongly shielding thio-substituent.

EXPERIMENTAL

General methods. — Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter at room temperature (18–23°) in 1-dm tubes. N.m.r. spectra (internal Me_2Si) were recorded with Bruker WM-250 (^{1}H, 250 MHz; ^{13}C, 62.9 MHz) and WP-60 (^{13}C, 15.8 MHz) spectrometers. M.p.s. were measured on a Kofler hot-stage and are uncorrected. Reactions were monitored by t.l.c. on silica

gel (Merck, 5554) with detection by 1% β-naphthol in conc. sulphuric acid–ethanol (1:20). Column chromatography was carried out either conventionally on Silica Gel G (Merck, 7734) or by "flash chromatography" on Silica Gel G (Merck, 9385) at 15 p.s.i. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl prior to use. All reactions were conducted in flame-dried glassware under dry nitrogen. Light petroleum refers to the fraction b.p. 40–60°. Molecular sieves were flame-dried for 1 h under high vacuum prior to use.

*(6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranos-6-yl)triphenylstannane* (**3**). — To a stirred solution of **1** (0.9 g) in dry tetrahydrofuran (20 mL) was added a solution of triphenylstannyl-lithium (**2**, prepared from 6.2 g of triphenyltin chloride and 0.8 g of lithium shavings) in dry tetrahydrofuran (20 mL). The mixture was stirred overnight at room temperature, when t.l.c. (ether–light petroleum, 1:7) indicated the presence of a single faster-moving product and **1**. The mixture was quenched with saturated aqueous ammonium chloride and extracted with chloroform, and the extract was washed well with water, dried ($MgSO_4$), and concentrated. Flash chromatography of the syrupy residue (ether–light petroleum, 1:7) gave **3**, isolated as a thick oil (0.30 g, 23%), $[\alpha]_D$ −58° (*c* 1, chloroform) N.m.r. data ($CDCl_3$): ^{13}C, δ 108.9, 108.2 (Me_2C), 96.5 (C-1), 73.9 (C-4), 71.2 (C-2), 70.4 (C-3), 66.0 (C-5), 13.8 (C-6), 26.0, 25.5, 24.9, and 24.2 (Me_2C); ^1H, δ 5.48 (d, 1 H, $J_{1,2}$ 2.2 Hz, H-1), 4.51 (dd, 1 H, $J_{2,3}$ 7.8 Hz, H-3), 4.21 (dd, 1 H, $J_{3,4}$ 2.3 Hz, H-4), 4.1 (m, 1 H, $J_{4,5}$ 5.1 Hz, H-5), 2.20 (dd, 1 H, $J_{5,6a}$ 8.1 Hz, H-6a), 1.81 (dd, 1 H, $J_{5,6b}$ 7.3 Hz, H-6b), 1.39, 1.26, 1,23, 1.11 (s, CH_3). (Found: C, 59.61; H, 5.71. $C_{30}H_{34}O_5Sn$ calc.: C, 60.74; H, 5.78%).

*Triphenylstannylethyl 1,3:4,5-di-*O*-isopropylidene-β-*D*-fructopyranoside* (**8**). — A solution of **2** (prepared from 0.8 g of lithium turnings and 6.2 g of triphenyltin chloride) in anhydrous tetrahydrofuran (15 mL) was added to a stirred solution of **7** (1.3 g) in dry tetrahydrofuran (15 mL). The mixture was stirred at 20° for 2 h, when t.l.c. (ether–light petroleum, 1:4) indicated the formation of a single product. The mixture was poured into saturated aqueous ammonium chloride and extracted with chloroform, and the extract was washed with water, dried ($MgSO_4$), and concentrated to dryness. Flash chromatography (ether–light petroleum, 1:4) of the syrupy residue gave **8** (1.1 g, 43%), m.p. 122–123° (from ether), $[\alpha]_D$ −55° (*c* 1, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 108.5, 100.0 (Me_2C), 93.1 (C-2), 73.8, 73.6, 72.2 (C-3,4,5), 61.3, 60.9 (C-1,6), 59.1 (C-1′), 29.6, 28.4, 26.0, 18.4 (Me_2C), 13.8 (C-2′) (Found: C, 59.9; H, 6.0. $C_{32}H_{38}O_6Sn$ calc.: C, 60.3; H, 6.0%).

*Triphenylsilylethyl 1,3:4,5-di-*O*-isopropylidene-β-*D*-fructopyranoside* (**9**). — To a stirred solution of **7** (0.9 g) in dry tetrahydrofuran (10 mL) was added a solution of triphenylsilyl-lithium (**4**, prepared from 5.9 g of chlorotriphenylsilane and 0.6 g of lithium shavings) in dry tetrahydrofuran (30 mL). Stirring was continued for a further 40 min at room temperature, when t.l.c. indicated that all of the starting material had been converted into a single u.v.-active product of similar mobility. The reaction was stopped by the addition of saturated aqueous ammonium chloride, extracted twice with chloroform, and the combined extracts were washed

with water, dried ($MgSO_4$), and concentrated. Flash chromatography (ether–light petroleum, 1:4) of the green residue gave a product which crystallised on trituration with ether, yielding **9** (0.6 g, 39%), m.p. 140–142.5°, $[\alpha]_D$ −61.5° (*c* 1, chloroform) (Found: C, 70.11; H, 6.92. $C_{32}H_{38}O_6Si$ calc.: C, 70.29; H, 7.00%). ^{13}C-N.m.r. data ($CDCl_3$): δ 108.6, 100.0 (Me_2C), 92.9 (C-2), 73.5, 73.5, 72.5 (C-3,4,5), 61.1, 60.8, 57.7 (C-1,1′,6), 15.3 (C-2′), 29.0, 28.4, 26.1, 18.5 (Me_2C).

*Triphenylplumbylethyl 1,3:4,5-di-*O*-isopropylidene-β-*D*-fructopyranoside* (**10**). — A mixture of **7** (0.7 g), triphenylplumbyl-lithium (**6**, prepared from 0.9 g of lithium shavings and 7.0 g of triphenyl-lead chloride), and anhydrous tetrahydrofuran (40 mL) was stirred overnight at room temperature. T.l.c (light petroleum–ether, 4:1) then indicated that a faster-moving product was present, in addition to unreacted **7**. The mixture was processed as described above and flash chromatography (ether–light petroleum, 1:4) of the product gave material that crystallised on trituration with ether to give **10** (0.3 g, 19%), m.p. 116–118°, $[\alpha]_D$ −32.5° (*c* 0.2, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 108.1, 100.1 (Me_2C), 93.1 (C-2), 73.8, 73.5, 72.3 (C-3,4,5), 61.5, 61.0 (C-6,1) 60.2 (C-1′), 24.7 (C-2′), 29.0, 28.4, 26.1, and 15.0 (Me_2C) (Found: C, 52.7; H, 5.1. $C_{32}H_{38}O_6Pb$ calc.: C, 52.95; H, 5.3%).

*(Methyl 4,6-*O*-benzylidene-3-deoxy-α-*D*-altropyranosid-3-yl)triphenylsilane* (**12**). — To a solution of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**11**, 0.8 g) in dry tetrahydrofuran (15 mL) was added dropwise a solution of **4** (prepared from 5.9 g of chlorotriphenylsilane and 0.9 g of lithium shavings) in dry tetrahydrofuran (20 mL). Stirring was continued for 1 h at room temperature. T.l.c. then indicated that **11** had reacted and that a single faster-moving product had formed. The mixture was diluted with saturated aqueous ammonium chloride, and extracted with chloroform, and the extract was washed with water, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (ether–light petroleum, 1:4) afforded **12** (0.82 g, 52%), m.p. 205–206°, $[\alpha]_D$ +137° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): ^{1}H, δ 5.53 (PhC*H*), 4.53 (d, 1 H, $J_{1,2}$ 1.4 Hz, H-1), 4.46 (d, 1 H, $J_{4,5}$ 9.1 Hz, H-4), 4.32 (bs, 1 H, $J_{2,3}$ 1.7 Hz, H-2), 4.05 (dd, 1 H, $J_{6,6a}$ 10.0 Hz, H-6a), 3.70 (m, 1 H, $J_{5,6a}$ 4.0 Hz, H-5), 3.65 (dd, 1 H, $J_{5,6b}$ 10.0 Hz, H-6b), 2.77 (dd, 1 H, $J_{3,4}$ 7.0 Hz, H-3), 2.92 (s, 3 H, OMe), 2.12 (bs, 1 H, OH): ^{13}C, δ 101.1 (C-1), 99.9 (Ph*C*H), 77.2 (C-4), 69.8 (C-2), 69.4 (C-6), 61.5 (C-5), 52.9 (OMe), 32.3 (C-3) (Found: C, 72.9; H, 5.9. $C_{32}H_{32}O_5Si$ calc.: C, 73.25; H, 6.15%).

*(Methyl 4,6-*O*-benzylidene-3-deoxy-α-*D*-altropyranosid-3-yl)triphenylplumbane (***13***).* — Compound **11** (0.9 g) was treated with a solution of **6** (prepared from 7 g of triphenyl-lead chloride and 0.9 g of lithium shavings) in anhydrous tetrahydrofuran (40 mL). The mixture was stirred overnight at room temperature, then quenched with saturated aqueous ammonium chloride, and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and concentrated to dryness. The syrupy residue was extracted with ether, and the extract was filtered and concentrated. Flash chromatography (chloroform–light petroleum, 2:1) of the syrupy residue yielded **13** (1.5 g, 62%), m.p. 168–170°, $[\alpha]_D$ +92° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): ^{1}H, δ 5.65 (s, 1 H, PhC*H*), 5.65 (dd 1 H, $J_{1,2}$ 1.0 Hz, $J_{1,3}$ 1.0

Hz, H-1), 4.85 (dd, 1 H, $J_{4,5}$ 8.7 Hz, H-4), 4.33 (m, 1 H, $J_{2,3}$ 1.9 Hz, H-2), 4.08 (dd, 1 H, $J_{5,6a}$ 3.0 Hz, H-6a), 3.86 (ddd, 1 H, $J_{5,6b}$ 10.1 Hz, H-5), 3.78 (dd, 1 H, $J_{6,6b}$ 10.1 Hz, H-6b), 3.20 (ddd, 1 H, $J_{3,4}$ 5.5 Hz, H-3), 3.10 (s, 3 H, OMe); ^{13}C, δ 101.0 (C-1), 100.5 (PhCH), 76.8 (C-4), 71.8 (C-2), 69.0 (C-6), 64.0 (C-5), 54.4 (OMe), 46.3 (C-3) (Found: C, 54.6; H, 4.5. $C_{32}H_{32}O_5Pb$ calc.: C, 54.6; H, 4.6%).

*Triphenylstannyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galacto-pyranosyl)-1-thio-β-*D*-glucopyranoside* (**15**). — To a solution of **16** (1 g) in anhydrous toluene containing freshly activated molecular sieves (type 4A, 5 g) was added a solution of triphenyltin hydroxide (0.65 g) in toluene. The mixture was heated for 1 h, at 65°, then filtered, and concentrated. Column chromatography (ether–light petroleum, 8:1) of the residue gave **15** as a foam (0.58 g, 37%), $[\alpha]_D$ −22° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): ^{1}H, δ 7.7–7.2 (Ph), 5.31 (dd, 1 H, $J_{4',5'}$ 0.7 Hz, H-4'), 5.02 (dd, 1 H, $J_{2',3'}$ 10.5 Hz, H-2'), 4.90 (dd, 1 H, $J_{3',4'}$ 3.4 Hz, H-3'), 4.48 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), 4.34 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 3.98 (dd, 1 H, $J_{6'a,6'b}$ 11.4 Hz, H-6'a), 3.58 (m, 1 H, H-5), 3.05 (ddd, 1 H, $J_{5',6'a}$ 1.4 Hz, H-5'): ^{13}C, δ 101.1 (C-1'), 80.3 (C-1), 76.6, 75.0, 74.3, 73.9, 71.1, 70.7, 69.2, 66.6, and 62.3, 60.7 (C-6,6'). (Found: C, 52.3; H, 5.1. $C_{44}H_{50}O_{17}SSn$ calc.: C, 52.7; H, 5.0%).

ACKNOWLEDGMENT

We thank Tate and Lyle p.l.c. for financial support.

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