Carbohydrate Research, 248 (1993) 365–369
Elsevier Science Publishers B.V., Amsterdam

Note

The regioselective *tert*-butyldimethylsilylation of the 6′-hydroxyl group of lactose derivatives via their dibutylstannylene acetals

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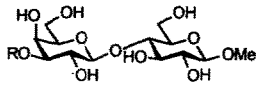
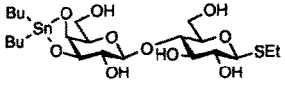
(Received December 22nd, 1992; accepted April 22nd, 1993)

Silyl ethers, especially the *tert*-butyldimethylsilyl ether, have become widely adopted protecting groups of choice for carbohydrate synthesis because of their ease of preparation and cleavage and their stability towards a wide range of reaction conditions required for functional group manipulation[1,2]. Regioselective alkylations and acylations of saccharides via their dibutyltin acetals afford in high yields products which would otherwise require multiple-step syntheses[3]. A prime example of this methodology is the allylation of methyl β-lactoside (**1**) to give the 3′-*O*-allylated product **2** in 70% yield[4]. Although direct silylations via stannylene acetals have not previously been reported **, we envisaged that treatment of the stannylene acetal, **3**, of the thioglycoside (**4**) of lactose[6] with *tert*-butyldimethylsilyl chloride should give rise to the corresponding 3′-*O*-silylated product, **5**.



1 R = H

2 R = Allyl



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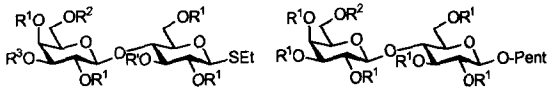
** A one-pot procedure involving the regioselective benzoylation of diols via a stannylene acetal followed by silylation leads indirectly to regiospecifically silylated diols[5].

Refluxing **4** with dibutyltin oxide in methanol for 4 h followed by removal of the solvent afforded the desired dibutylstannylene derivative, **3**. Treatment of this acetal with *t*-$BuMe_2SiCl$ in dry THF gave a quantitative yield of a single product which proved to be silylated not at the 3′-position (**5**) as expected (cf. compound **2**) but at the 6′-hydroxyl group (i.e., compound **6**). Similarly, treatment of the stannylene derivative of the 4-pentenyl glycoside (**7**) of lactose * with *t*-$BuMe_2SiCl$ resulted in the exclusive formation of the 6′-*O*-silylated product, **8**. Benzoylation (benzoyl chloride–pyridine) of both **6** and **8** gave the corresponding fully protected sugars **9** and **10** which were fully characterised.



4 $R^1 = R^2 = R^3 = H$
5 $R^1 = R^2 = H$, $R^3 = t\text{-}BuMe_2Si$
6 $R^1 = R^3 = H$, $R^2 = t\text{-}BuMe_2Si$
9 $R^1 = R^3 = Bz$, $R^2 = t\text{-}BuMe_2Si$

7 $R^1 = R^2 = H$
8 $R^1 = H$, $R^2 = t\text{-}BuMe_2Si$
10 $R^1 = Bz$, $R^2 = t\text{-}BuMe_2Si$
Pent = 4-Pentenyl

In each case, no silylation was observed at the primary position of the glucose residue, clearly indicating that the acetal initially formed across the 3′,4′-positions is actively controlling the regioselectivity of the reaction **. It appears that *t*-$BuMe_2SiCl$, being too bulky to react with the 3′-oxygen as expected, reacts instead with the sterically less crowded 6′-oxygen via the reversible migration of the stannylene acetal from the 3′,4′ to either the 4′,6′ or ring oxygen,6′ positions †. This is consistent with the explanation for the differences in regioselectivity observed[8] between the benzoylation and tosylation of other saccharide stannylene derivatives and is probably also the reason behind the reaction at primary hydroxyl groups in tributyltin ether-mediated glycosylations of methyl β-lactoside[9].

Although primary hydroxyl groups can, in general, be selectively protected in the presence of secondary hydroxyl groups under standard reaction conditions (e.g., *t*-$BuMe_2SiCl$–imidazole–DMF or *t*-$BuMe_2SiCl$–pyridine)[10], distinguishing between two different primary hydroxyl groups in an oligosaccharide is a challenge

* 4-Pentenyl β-lactoside was prepared via a Koenigs–Knorr type glycosylation between acetobromolactose and 4-penten-1-ol with silver triflate as the promoter in a procedure which will be reported fully elsewhere.

** In a control experiment, we were able to repeat the 3′-*O*-alkylation and acylation experiments described in ref 3, using the same stannylene acetals which afforded the 6′-*O*-silylated products.

† The migration of *tert*-butyldimethylsilyl groups of pyranosides is well documented. However, the conditions in these cases are generally much harsher and usually give rise to mixtures of products[7]. Since either silyl group migration or acetal migration could be used to explain the formation of the product, we prepared the dibutylstannylene acetal of **6** and treated it with *t*-$BuMe_2SiCl$. No disilylated product had formed after 24 h, indicating that the silylation does not initially occur at either the 3′ or 4′ position with subsequent migration.

of considerable difficulty rarely accomplished in one step[11] and has not previously been achieved with silyl ethers. Silylation of compounds with more than one primary hydroxyl group under standard conditions gives rise to mixtures of products[12]. The *tert*-butyldimethylsilylation of lactose derivatives, via their dibutyltin acetals, provides a simple, mild, high-yielding and effective route to selectively 6′-*O*-protected lactosides.

EXPERIMENTAL

General.—TLC was performed on Silica Gel F_{254} (Merck) with detection by charring with H_2SO_4. Column chromatography was performed on Merck silica gel (60–240 mesh). ^1H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Bruker AC-300 spectrometer.

Ethyl 4-O-(6-O-tert-butyldimethylsilyl-β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside (**6**).—A solution of ethyl 1-thio-β-D-galactopyranoside (5 g, 12.9 mmol) and dibutyltin oxide (3.2 g, 13 mmol) in MeOH (500 mL) was boiled under reflux for 4 h. Removal of the solvent gave a white powder which was dissolved in dry THF (500 mL). *tert*-Butyldimethylsilyl chloride (1.95 g, 13 mmol) was added to the solution and left to stir for 24 h at room temperature after which time TLC (9:1 CH_2Cl_2–MeOH) showed that no starting material remained. Removal of the solvent under reduced pressure gave a syrup which was subjected to column chromatography (5% MeOH–CH_2Cl_2) to give **6** as a white crystalline solid {6.25 g, 96%; mp 126–128°C; $[\alpha]_D$ −33° (*c* 1.56, MeOH)} which, due to problems of instability associated with cleavage of the silyl ether, was immediately benzoylated.

Ethyl 2,3,6-tri-O-benzoyl-4-O-(2,3,4-tri-O-benzoyl-6-O-tert-butyldimethylsilyl-β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside (**9**).—Benzoyl chloride (5 mL, 43 mmol) was added to a stirred solution of **6** (2 g, 4 mmol) in pyridine (20 mL). Stirring was continued for 48 h to give a pink solution which was washed with aq Na_2CO_3 and dried over $MgSO_4$. Evaporation of the solvent gave a syrup which was subjected to column chromatography (9:1 hexane–EtOAc) to give **9** (4.39 g, 3.9 mmol, 98%; mp 79–81°C); $[\alpha]_D$ +76° (*c* 1.3, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 8.15–7.15 (m, 30 H, aromatics), 5.75 (t, 1 H, $J_{2,3} = J_{3,4} = 10$ Hz, H-3), 5.71 (dd, 1 H, $J_{3',4'}$ 3, $J_{4',5'}$ 1 Hz, H-4′), 5.65 (dd, 1 H, $J_{1',2'}$ 8, $J_{2',3'}$ 10 Hz, H-2′), 5.46 (t, 1 H, $J_{1,2}$ 10 Hz, H-2), 5.38 (dd, 1 H, H-3′), 4.80 (d, 1 H, H-1′), 4.71 (d, 1 H, H-1), 4.55 (dd, 1 H, $J_{5,6a}$ 2, $J_{6a,6b}$ 12 Hz, H-6a), 4.45 (dd, 1 H, $J_{5,6b}$ 5 Hz, H-6b), 4.15 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 3.82 (m, 1 H, H-5), 3.57 (m, 1 H, H-5′), 3.15 (m, 1 H, H-6′a), 2.80 (t, 1 H, $J_{5',6'b}$ 10 Hz, H-6′b), 2.65 (m, 2H, SCH_2CH_3), 1.18 (t, 3 H, *J* 7 Hz, SCH_2CH_3), 0.70 [s, 9 H, $SiC(CH_3)_3$], −0.20, −0.32 [2 s, 3 H, $Si(CH_3)_2$]; ^{13}C NMR ($CDCl_3$): δ 166–164 (*C*OPh), 133–126 ($CO\underline{C}_6H_5$), 101.2 (C-1′), 83.5 (C-1), 77.2 (C-5), 76.0 (C-4), 74.3 (C-3), 73.4 (C-5′), 71.9 (C-3′), 70.4 (C-2), 70.2 (C-2′), 66.8 (C-4′), 62.6 (C-6), 58.9 (C-6′), 25.6 [$SiC(\underline{C}H_3)_3$], 24.2 ($S\underline{C}H_2CH_3$), 17.8 [$Si\underline{C}(CH_3)_3$], 14.8 ($SCH_2\underline{C}H_3$), −5.1 [$Si(\underline{C}H_3)_2$]. Anal. Calcd for $C_{62}H_{64}O_{16}SiS$: C, 66.2; H, 5.7; S, 2.8 Found: C, 66.4; H, 5.7; S, 3.0. FABMS: *m/z* 1147 $(M + Na)^+$.

4-Pentenyl 4-O-(6-O-tert-butyldimethylsilyl-β-D-galactopyranosyl-β-D-glucopyranoside (**8**).—4-Pentenyl 4-*O*-β-D-galactopyranosyl-β-D-glucopyranoside (**7**; 3.0 g, 7.5 mmol) and dibutyltin oxide (1.9 g, 7.6 mmol) were boiled under reflux in MeOH (300 mL) for 4 h until the solution became clear. The solvent was removed under vacuum and the residue thoroughly dried to leave a pale-yellow solid. The solid was taken up in dry THF (300 mL), *tert*-butyldimethylsilyl chloride (1.2 g, 8.0 mmol) was added, and the solution stirred for 24 h at room temperature. Removal of the solvent and column chromatography (30:1 $CHCl_3$–MeOH) gave **8** (3.7 g, 92%; mp 92–93°C) as a white solid: FABMS: *m/z* 525 $(M + H)^+$; which, due to instability associated with cleavage of the silyl ether, was immediately benzoylated.

4-Pentenyl 2,3,6-tri-O-benzoyl-4-O-(2,3,4-tri-O-benzoyl-6-O-tert-butyldimethylsilyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**10**).—Benzoyl chloride (116 μL, 1 mmol) was added dropwise to a cooled (0°C) solution of **8** (50 mg, 0.09 mmol) in pyridine (2 mL) which was then stirred for 24 h. The resulting solution was washed with aq Na_2CO_3 and dried over $MgSO_4$. Evaporation of the solvent gave a syrup which was subjected to column chromatography (9:1 hexane–EtOAc) to give **10** as a yellow syrup (98 mg, 89%); ^1H NMR ($CDCl_3$): δ 8.10–7.15 (m, 30 H, aromatics), 6.05 (m, 1 H, H-3), 5.68 (m, 3 H, H-2′,4′, C*H*=CH_2), 5.41 (dd, 1 H, $J_{3',4'}$ 3, $J_{2',3'}$ 10 Hz, H-3′), 5.19 (m, 2 H, H-1,2), 4.85 (m, 3 H, CH=CH_2, H-1′), 4.50 (m, 2 H, H-6a,6b), 4.13 (m, 2 H, H-4,5), 3.71 (m, 1 H, OC*H*aHbCH_2), 3.47 (m, 1 H, H-5′), 3.38 (m, 1 H, OCHa*H*bCH_2), 3.19 (m, 1 H, H-6′a), 2.92 (t, 1 H, $J_{5',6'b} = J_{6'a,6'b} = 9$ Hz, H-6′b), 2.05 (m, 2 H, $OCH_2CH_2CH_2CH$=CH_2), 1.65 (m, 2 H, $OCH_2CH_2CH_2CH$=CH_2), 0.70 [s, 9 H, $(CH_3)_3C$], −0.19, −0.30 (2 s, 3 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 165.8–164.8 (6 COPh), 137.6 (*C*H=CH_2), 133.2–128.1 (aromatics), 115.0 (CH=*C*H_2), 101.2 (C-1), 95.7 (C-1′), 77.1, 73.4, 72.0, 71.7, 70.9, 70.2, 68.3, 66.8 (C-2, C-2′, C-3, C-3′, C-4, C-4′, C-5, C-5′), 67.6 (OCH_2CH_2), 62.3, 59.0 (C-6, C-6′), 29.6, 28.2 (OCH_2CH_2, $OCH_2CH_2CH_2$), 25.5 [$C(CH_3)_3$], 17.8 [$C(CH_3)_3$]. FABMS: *m/z* 1149 $(M + H)^+$.

ACKNOWLEDGMENT

The authors are grateful to the Science and Engineering Research Council for the award of a studentship (to JPS).

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