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Note

The intermolecular migration of polyol stannylenes as a reaction contributing to the regioselectivity of substitution

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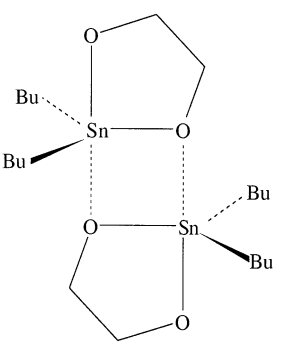
Abstract

Pairs of the partially protected glycosides benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside, benzyl 2,3-di-*O*-benzyl-β-D-galactopyranoside, benzyl 2,6-di-*O*-benzyl-α-D-galactopyranoside, and benzyl 2,3-di-*O*-benzyl-α-D-glucopyranoside were treated with equimolar proportions of Bu_2SnO in benzene in the conditions of stannylene formation, and the resulting mixture was benzoylated in situ with benzoyl chloride. Estimation of the product of benzoylation led to the following order of reactivity in the stannylenation reaction: 2,3-diol > 4,6-diol, and 2,3-diol > 3,4-diol. An intermolecular migration of dibutyltin between sugars was demonstrated. It is considered that these migrations contribute efficiently to the regiospecificity of the stannylene reaction. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Stannylenes; Intermolecular migration; Regiospecific electrophilic attack

Conversion of diols into dibutyltin derivatives, the so-called stannylenes, is an efficient method to achieve the regioselective electrophilic substitution of one of the hydroxyl functions [1,2]. These derivatives are dimers with five-coordinate tin atoms (Scheme 1) or oligomers with six-coordinate tin atoms. In the dimers, the oxygen atoms of the parent diol are found in the apical and equatorial position of the coordination polyhedron of one of the tin atoms. The apical oxygen atom is the reactive one, the other one being deactivated by coordination to the other tin atom. Regioselectivity is observed because, in the majority of cases, the structure of the non-symmetrical diol determines without ambiguity which one of its two oxygen atoms will be found finally in an apical position.

Regioselectivity is also observed in the reactions of the dibutyltin derivatives of triols, tetrols, etc. and, in many cases, only one



Scheme 1. An idealized picture of the dibutyltin derivative of a diol.

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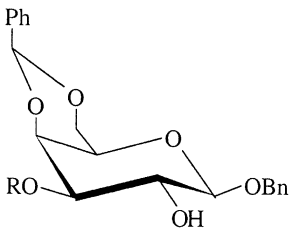
Table 1
Yields in the competitive stannylenation of pairs of glycosides

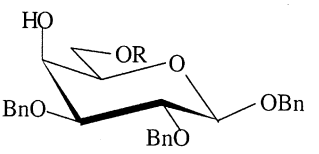
Experiment no.	Mixture	Product(s), (R_f) [a], yield [b]
1	**1**, **2**	**1a**, (0.63), 98%
2	**1**, **3**	**1a**, (0.63), 75%; **3a** (0.69), 5%
3	**1**, **4**	**1a**, (0.34), 79%; **4a** (0.55), 10%
4	**2**, **3**	**2a**, (0.53), 60%; **3a** (0.64), 4%

[a] Eluent: 97:3 CH_2Cl_2–acetone, 97:3 in experiments 1, 2, 4, ether–hexane 2:1 in experiment 4.
[b] Isolated yield after column chromatography.

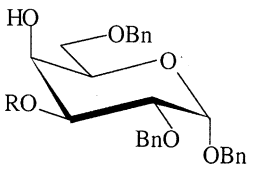
hydroxyl is substituted out of several in partially protected mono- and disaccharides [3,4]. Thus there is not only differentiation of the two component hydroxyls of a diol, but also selection of a pair among several possibilities. However, the reactive site is not always that expected. Leigh et al. observed that the stannylene of a lactoside, which presumably involved position 3 of the galactose residue, reacted with *t*-butyldimethylsilyl chloride exclusively, and in good yield at position C-6 Gal [5]. The authors explained this by an equilibrium between the major stannylene and a minor $4^2,6^2$ isomer, which is displaced by the selective reaction at position 6^2. Experiments with simpler derivatives confirmed this mechanism [6]. As a contribution to the problem of regiospecificity in stannylene substitution, we describe in this report competitive experiments with pairs of diols derived from the protected glycosides **1**–**4**.



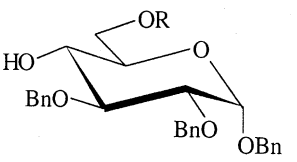
1 R = H
1a R = Bz



2 R = H
2a R = Bz



3 R = H
3a R = Bz



4 R = H
4a R = Bz

We have already shown [7] that the treatment of the stannylene derivatives of **1**, **2**, and **4** with benzoyl chloride at room temperature gives the respective benzoates **1a**, **2a**, and **4a** by a very fast reaction, in less than 5 min. The benzoylation of the stannylene of **3** is a sluggish reaction requiring 24 h at room temperature for completion under the same conditions. The product, **3a**, is obtained regiospecifically in 74% yield. Competitive experiments were first examined with the pairs of derivatives **1** and **2**, **1** and **3**, **1** and **4**, and **2** and **3**. The mixture of 1 mmol of each of the components was treated with 1 mmol of dibutyltin oxide in refluxing benzene. Benzoyl chloride (1 mmol) was added to the clear solution after cooling to room temperature. In experiments 1–3, the usual very fast reaction gave the benzoate **1a** of the trans diol as a major or exclusive product (Table 1). On the other hand, benzoylation in experiment 4 was sluggish, and needed 24 h for completion to give mainly the primary benzoate **2a**. Now we know that the stannylene of **2** was not present in the medium at the onset of the benzoylation, for it is benzoylated in less that 5 min in these conditions. Therefore, during 24 h at room temperature, the dibutyltin group has migrated from **3** to **2.** The equilibrium between the stannylenes of **3** and **2**, which was highly in favour of **3**, has been displaced by the removal of the stannylene of **2** by fast benzoylation.

In general terms, this observation resembles that of Leigh et al. [6], i.e., a slow reaction at one site favours substitution at another one. However, in our experiment, there is no doubt that migration occurs by an intermolecular reaction. The reality of such migration could be demonstrated directly: one equivalent of the preformed stannylene of **2** was refluxed for 1 h in benzene with one equivalent of galactoside **1**, and the composition of the mixture was determined as above by benzoylation. From the intensities of the signals of the protons geminal to benzoate groups on the ^1H NMR spectrum of the mixture of benzoates, it could be calculated that this contained 87% of the benzoate of **1**. However, it was found that the migration proceeds readily at room temperature under the conditions of benzoylation: to a solution of the stannylene of **2** in benzene at room temperature were added first one equivalent of the trans diol

1 in oxolane solution, and after 10 min two equivalents of benzoyl chloride. Analysis of the reaction mixture by thin-layer chromatography (TLC) indicated the presence of benzoate **1a** after 10 min and complete benzoylation after 15 min with no visible traces of **2a**.

These experiments indicate the existence of an intermolecular equilibrium between stannylene derivatives in the conditions of their formation and utilization. We suggest that this intermolecular reaction is general, that is, the migration of the stannylene from one pair of oxygen atoms to another in a pure polyol is intermolecular. Other mechanisms involving heterolytic opening of the stannacyclopentane(hexane) ring or the transient formation of a six-coordinate tin complex spanning three oxygen atoms appear less likely, the first one because the solvent is not polar, and the second one because the rigidity of the sugar frame does not allow the alcoholic function to come near enough to the tin atom. We prefer the intermolecular mechanism for another reason: an intermolecular reaction allows the migration of the tin atom to any position, however distant, for instance from the glucose to the galactose residue in a lactoside. These intermolecular migrations give advantage to the site where substitution is the most rapid by displacement of equilibrium, and appear as a major cause of the regioselectivity in stannylene substitutions.

1. Experimental

Materials.—The following glycosides were prepared by known methods: benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**1**) [8] and its 3-benzoate **1a** [9], benzyl 2,3-di-*O*-benzyl-β-D-galactopyranoside (**2**) [8] and its 6-benzoate **2a**, benzyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**3**) [3] and its 3-benzoate **3a** [7], benzyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**4**) and its 6-benzoate **4a** [7].

General procedure for the competitive experiments.—A mixture of the two diols (1 mmol each) and dibutyltin oxide (1 mmol) was refluxed overnight in benzene (25 mL) in a flask fitted with a Dean–Stark separator, then concentrated to about 10 mL and cooled to room temperature (rt). Benzoyl chloride (0.12 mL) and 4 Å molecular sieves (2 g) were added, the solution was stirred for about 5 min, evaporated to dryness, and the residue was analysed by high-performance liquid chromatography (HPLC) (CH_2Cl_2 in experiments 1, 2, 4; 2:1 ether–hexane in experiment 3). In experiment 3 the stannylene was also prepared by 1 h refluxing in MeOH, followed by replacement of MeOH by benzene. There was no change in the result. Identification of the benzoates was based on the comparison with authentic samples after separation (TLC and ^{1}H NMR spectra in $CDCl_3$). The yields in Table 1 were calculated from the weight of the pure isolated products.

Migration of the dibutyltin group in boiling benzene.—The stannylene of **2** was prepared in benzene (10 mL) from Bu_2SnO (65 mg, 0.26 mmol) and **2** (128 mg, 0.285 mmol) by overnight refluxing. Galactoside **1** (102 mg, 0.285 mmol) was added to the clear solution, and the mixture was refluxed for 1 h, cooled to rt, concentrated to about 3 mL and benzoylated with benzoyl chloride (37 mg, 0.26 mmol). The mixed benzoates were separated from unreacted material by silica gel chromatography (2:1 petroleum ether–EtOAc) (130 mg). Analysis by ^{1}H NMR spectroscopy in $CDCl_3$ solution indicated a 87:13 mol ratio of **1a** to **2a**, corresponding to a 94% yield of **1a** (110 mg).

Migration of the dibutyltin group at room temperature.—Galactoside **2** (75 mg, 0.17 mmol) was heated at reflux overnight in benzene solution (10 mL) in the presence of dibutyltin oxide (42 mg, 0.17 mmol). The clear solution was concentrated to about 3 mL and cooled to rt. A solution of **1** (71.5 mg, 0.20 mmol) in oxolane (5 mL) was added. After 10 min, BzCl (54 mg, 2.3 mmol) was added. Examination of the mixture by TLC (1:1 petroleum ether–EtOAc) after 15 min indicated the presence of benzoate **1a** and diol **2** (R_f 0.84 and 0.18, respectively).

*Benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside* (**2a**).—^{1}H NMR (200 MHz): δ 2.44 ($J_{2,OH}$ 2.5 Hz, OH), 3.58 (broad, H-5), 4.11 ($J_{5,6}$ 2, $J_{6,6'}$ 13 Hz, H-6), 4.24 ($J_{1,2}$ 8.5, $J_{2,3}$ 10.5 Hz, H-2), 4.40 ($J_{5,6'}$ 2 Hz, H-6′), 4.48 ($J_{3,4}$ 4 Hz, H-4), 4.52 (H-1), 4.66 (^2J 13

Hz, CHPh), 5.03 (CHPh), 5.14 (H-3), 5.50 ($PhCHO_2$), 7.1–7.6 (Bz, 2 Ph), 8.0–8.2 (Bz).

*Benzyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-β-*D*-galactopyranoside* (**2a**).—^{1}H NMR (200 MHz): δ 2.57 (br, OH), 3.51 ($J_{2,3}$ 10, $J_{3,4}$ 4 Hz, H-3), 3.72 ($J_{3,4} \approx 4$ Hz, H-4), 3.74 ($J_{1,2}$ 8.5, $J_{2,3}$ 10 Hz, H-2), 3.98 (br, ≈ 9 Hz), 4.45 (H-1), 4.59–4.78 (3 CH_2Ph), 4.92 ($J_{5,6'}$ 2 Hz, H-6′), 4.97 ($J_{5,6}$ 3 Hz, H-6), 7.2–7.7 (2 Ph, Bz), 8.1 (Bz).

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