Kinetically Controlled Regiospecific Silylation of Polyols *via* Dibutylstannanediyl Acetals

David A. Leigh,* Richard P. Martin, John P. Smart and Ada M. Truscello

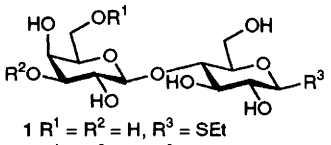
Department of Chemistry, University of Manchester Institute of Science and Technology, Sackville Street, Manchester, UK M60 1QD

A general procedure is described whereby the *tert*-butyldimethylsilylation of unsymmetrical 1,2- and 1,3-diols *via* their dibutylstannanediyl derivatives occurs regiospecifically at the primary hydroxy group under neutral conditions; six-membered ring acetals (derived from 1,3-diols) are found to react in preference to five-membered ring acetals (derived from 1,2-diols), the reverse of stannanediyl-mediated acylation, tosylation and alkylation procedures, leading to kinetically controlled discrimination between the different primary hydroxy groups of polyol systems such as butane-1,2,4-triol and lactose.

Silyl ethers, particularly *tert*-butyldimethylsilyl ether (TBDMS), have become protecting groups of choice in organic synthesis over the last two decades since they are easy to prepare, stable towards base and readily removed under mild conditions.[1] Most of the reported procedures for the formation of TBDMS ethers rely on the reaction of an alcohol with TBDMSCl and a base (*e.g.* imidazole).[1b] At least one neutral,[2] and a few acid-promoted,[3] procedures are known; however these generally rely on more exotic silylating agents. Regioselective discrimination between hydroxy groups in the same molecule in these reactions generally follows the same pattern as typical acylation reactions, being governed by the delicate balance between the steric requirements of the bulky TBDMS group and the nucleophilicity of the various hydroxy groups.

Stannanediyl acetal methodology[4] has been widely used to modify the reactivity of hydroxy groups of both polyol systems (*e.g.* carbohydrates) and simple glycols and to effect their derivatisation, *via* acylation, tosylation and alkylation, with high specificity under mild conditions; however the analogous silylation reactions were hitherto unknown. We therefore recently attempted the direct monosilylation of the lactose derivatives **1** and **2** *via* dibutylstannanediyl acetal methodology. These reactions demonstrated a remarkable preference for a single hydroxy group in each molecule (the 6′-position being exclusively silylated in each case) but, curiously, did not follow the regioselectivity of the analogous stannanediyl-controlled acylation or alkylation reactions; allylation of the dibutylstannanediyl acetal of **1** gives rise solely to the 3′-*O*-allylated derivative **3**,[5] whereas silylation of the same acetal affords exclusively the 6′-*O*-TBDMS ether **4**.[6] In the silylations, no reaction was observed at the primary position of the glucose residue, indicating that the stannanediyl acetal formed across the 3′,4′-positions actively controls the regioselectivity of the silylation. It appears that TBDMSCl is too bulky to react with the activated 3′-oxygen atom and reacts instead at the less sterically crowded 6′-oxygen *via* the reversible migration of the stannanediyl acetal from the 3′,4′ to either the 4′,6′ or ring oxygen, 6′ positions.[7]

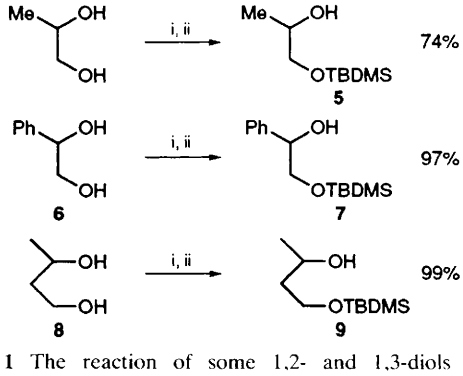
Following the successful silylations of the lactose derivatives and the unusual regioselectivity of the reactions, we sought to determine the generality of the system. We prepared the stannanediyl acetals of some simple 1,2- and 1,3-diols and treated them with TBDMSCl in the absence of base (Scheme 1). Silylation of the stannanediyl acetal of propane-1,2-diol with TBDMSCl (1.2 equiv., $CHCl_3$, room temp., 2 h) occurred at the primary hydroxy groups to give the silyl ether **5** in 74% isolated yield after workup.† (No evidence for the 2-*O*-silylated or disilylated products was observed, the volatility of the product contributing to the slightly low yield.) Treatment of the stannanediyl acetal of 1-phenylethane-1,2-diol **6** with TBDMSCl in $CHCl_3$ also gave the primary silyl ether, **7**, as the only product (97% isolated yield). The reaction was found to proceed equally well across 1,3-diols; the stannanediyl acetal of butane-1,3-diol **8** was silylated [TBDMSCl (1.2 equiv.), $CHCl_3$, room temp., 20 min, 99% isolated yield] to give **9** in near-quantitative yield. The reaction times (<2 h) and conditions (room temp.) for all these reactions were comparable with those for stannanediyl-mediated acylation rather than alkylation reactions (in which several days reflux in the presence of alkylammonium salt catalysts are typically required for completion of the reaction).[4] Although all of the silylations were completed in under two hours, the 1,2-diol systems required significantly longer reaction times than the 1,3-diol system.



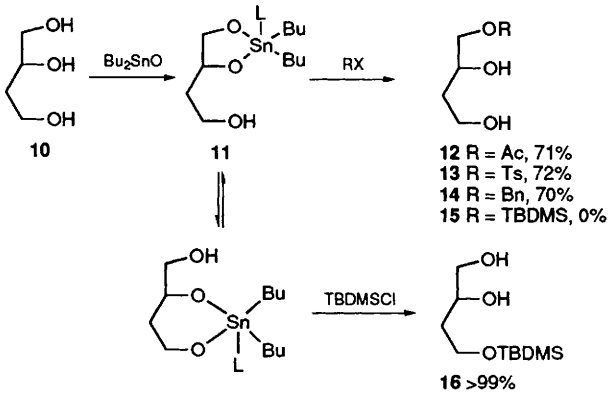
1 $R^1 = R^2 = H$, R^3 = SEt
2 $R^1 = R^2 = H$, R^3 = O-Pentenyl
3 $R^1 = H$, R^2 = Allyl, R^3 = SEt
4 R^1 = TBDMS, $R^2 = H$, R^3 = SEt
TBDMS = Bu^tMe_2Si

The regioselectivity of stannanediyl-mediated reactions is an invaluable feature of their use as reagents in organic synthesis. In general, when stannanediyl acetal formation can occur across either a 1,2- or a 1,3-diol system, the products arise from activation of one of the two oxygen atoms of the 1,2-diol system.[5,8] For butane-1,2,4-triol **10**, for example, which contains adjacent 1,2- and 1,3-diol systems, acylation, tosylation and benzylation of the stannanediyl acetal **11** occur preferentially at the primary hydroxy groups of the 1,2-diol system to give **12**, **13**, and **14** respectively.[8] Somewhat surprisingly, silylation [TBDMSCl (1.2. equiv.), $CHCl_3$, room temp., 20 min] of the same stannanediyl acetal (formed using 1.0 equiv. of Bu_2SnO in MeOH) does not give rise to **15**. Instead, silylation occurs exclusively at the primary hydroxy of the 1,3-diol system to give **16** in >99% yield (Scheme 2).

The rate difference between the reaction of five and six-membered cyclic stannanediyl acetals was further demonstrated by an experiment in which the stannanediyl acetals of butane-1,2,4-triol (1 equiv.) and propane-1,2-diol (1 equiv.)



Scheme 1 The reaction of some 1,2- and 1,3-diols *via* their dibutylstannanediyl acetals: i, Bu_2SnO; ii, silylation



Scheme 2 L = coordinating ligand; X = Cl, Br

were allowed to compete for a single equivalent of TBDMSCl under the usual reaction conditions. Remarkably, of the five possible monosilylated products, **16** (arising from silylation of the only available 1,3-acetal) was the sole product formed.

The generally accepted explanation for the regioselectivities observed during stannanediyl mediated reactions invokes dimers, trimers and higher oligomers of the five-coordinated tin as the reactive species. Since the regioselectivity of the stannanediyl mediated silylation of butane-1,2,4-triol differed from that for other derivatisations of this acetal, it seemed that the steric bulk of the silyl group could be controlling the reaction by preventing reaction with the 1,2-stannanediyl oligomers. We therefore investigated the same silylation reaction in THF, a polar coordinating solvent which favours the existence of monomeric stannanediyls in solution. However, despite the change of solvent, the reaction generated the same product at approximately the same rate (again, with no detectable silylation at the other primary hydroxy group) indicating that the oligomeric structure of the reactive intermediate is not as important as the position of the stannanediyl acetal in determining regioselectivity.‡ Clearly, an understanding of the major species in solution does not provide a simple explanation for the observed regioselectivities of stannanediyl acetals, at least in silylation reactions. Stannanediyl acetals rapidly migrate between adjacent diol systems to give, with a bulky electrophile, the product of kinetic control.

Since the use of stannanediyl acetals to mediate hydroxy group reactivity in organic synthesis is widespread it is somewhat surprising that their direct application to silylation reactions has not previously been investigated.[9] Our preliminary results show that the silylation of the stannanediyl acetals of unsymmetrical 1,2- and 1,3-diols leads to the regioselective derivatisation of the primary hydroxy group in excellent yields. Furthermore, *tert*-butyldimethylsilylation of 1,3-stannanediyl acetals is much faster than that of 1,2-systems, the reverse of stannanediyl mediated acetylation, tosylation and alkylation procedures and a phenomenon which can be exploited in the selective protection of 1,2,4-triols *via* kinetic control. These differences provide a valuable addition to the synthetic chemists' armoury of discriminatory reactions.

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Footnotes

† In a typical experiment the diol (1 mmol) and dibutyltin oxide (1 mmol) were refluxed in methanol until the solution became clear after which the solvent was driven off to leave the stannanediyl acetal as a white crystalline solid. A solution of the acetal in anhydrous chloroform was treated with TBDMSCl (1.2 mmol) and stirred for 24 h. Dibutyltin by-products were removed by partition of the solution between hexane and acetonitrile and where necessary the compounds were purified by column chromatography. The regioselectivity of the silylation reactions was determined unambiguously by the preparation of the acetylated derivatives of products **5**, **7**, **9** and **16**. All compound data matched that previously reported for compounds **5** (K. Yamamoto and M. Takemae, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2111), **7** (K. Mai and G. Patil, *J. Am. Chem. Soc.*, 1986, **51**, 3545) and **9** (U. Goergens and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1981, 1066).

‡ The possibility that the reactive species in chloroform is also monomeric cannot be ruled out, the fifth coordination site of the tin being taken up by the free hydroxy group of the triol or solvent.

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