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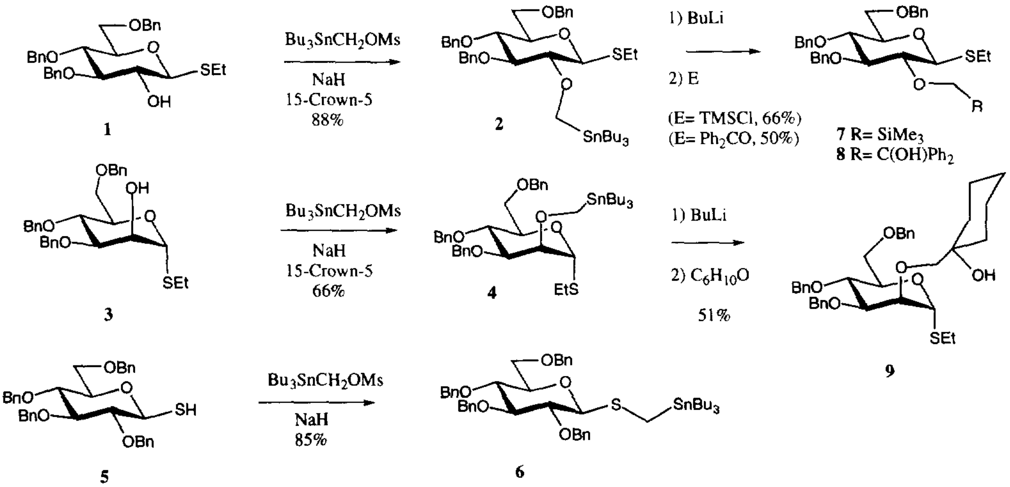
Synthesis of Tributyltinmethylated Sugars, Building Blocks for Tethered Reactions.

Henrik C. Hansen, Ole Hindsgaul
Department of Chemistry, University of Alberta,
Edmonton,Alberta T6G 2G2, Canada

and Mikael Bols*
Department of Chemistry, Aarhus University,
DK-8000 Aarhus, Denmark, fax +4586196199

Abstract: Equatorial and axial sugar hydroxyl groups can efficiently be tributyltinmethylated using tributyltinmethyl mesylate, NaH and 15-crown-5. Copyright © 1996 Elsevier Science Ltd

Recently there has been an intense interest in tethered reactions for selective construction of carbohydrate derivatives such as O-glycosides and C-glycosides[1]. To further investigate such reactions it is vital to be able to efficiently produce carbohydrate derivatives linked together by a variety of different tethers. A "sugar" oxymethylstannane can be envisioned as a versatile intermediate for producing tethered compounds, which could be converted to a "sugar"oxymethyl lithium and added to many different electrophiles. In this letter we present a convenient method for the preparation of tributyltinmethyl ethers of sugar hydroxyl groups and demonstrate some of their reactions.



Scheme 1

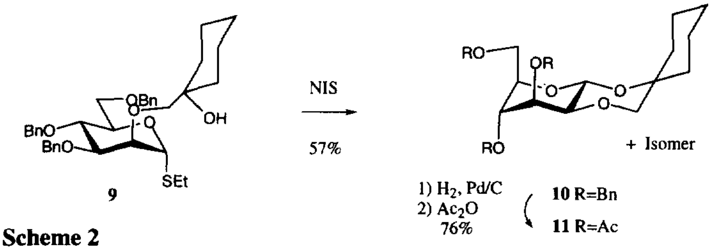
Tributyltinmethyl ethers of simple allylic or other monofunctional alcohols have previously been prepared using base and tributyltinmethyl iodide[2,3]. However, that protocol proved to be inadequate in the more complex cases presented here. Reaction of *gluco* alcohol **1**[4] with Bu_3SnCH_2I[5] and NaH gave only 37% of the desired product **2**[6] (table 1, entry 1), while the axial *manno* alcohol **3**[7], under the same conditions, gave an even lower yield of **4** (entry 4). The yield of **2** could however be significantly increased to 53% by improving the solubility of NaH using 1 equivalent of 15-crown-5 (entry 2), and even further improved to 88% by replacement of the soft electrophile Bu_3SnCH_2I with a hard electrophile Bu_3SnCH_2OMs[8] (entry 3). The same modifications[9] improved the yield of the *manno* stannylether **4** to 66% (entry 6).The choice of solvent was important since substitution of DMF by dioxane in this case decreased the yield considerably (entry 5). Thiol **5**[10] could also be tributyltinmethylated efficiently using this protocol (crown ether not needed) to give tinmethyl thioglycoside **6** in 85% yield.

Entry	Alcohol	Stannane	15-Crown-5	Solvent	Yield
1	1	Bu_3SnCH_2I	-	THF/DMF	37 %
2	1	Bu_3SnCH_2I	1 eq.	THF/DMF	53 %
3	1	Bu_3SnCH_2OMs	1 eq.	THF/DMF	**88 %**
4	3	Bu_3SnCH_2I	-	THF/DMF	27 %
5	3	Bu_3SnCH_2OMs	1 eq.	THF/dioxane	40 %
6	3	Bu_3SnCH_2OMs	1 eq.	THF/DMF	66 %

Table 1. Tributyltinmethylation of alcohols.

Stannane **2** was subjected to tin-lithium exchange by treatment with 1 equivalent *n*-BuLi in THF at -78°C, and then reacted with electrophiles. Reaction with TMSCl gave the silane **7** in 66% yield, while reaction with benzophenone gave diphenylcarbinol **8** in 50% yield. Similarly, reaction of the *manno* stannane **4** with *n*-BuLi followed by cyclohexanone led to the tertiary alcohol **9** in 50% yield.

An intramolecular glycoside synthesis was performed with substrate **9**. Treatment of **9** with N-iodo-succinimide in nitromethane led to a 57% yield of two inseparable products in ratio 4:1[11]. The major product α-mannoside **10** could however be obtained pure as its acetate **11** in 76% (based on the mixture) by hydrogenation (1 atm., Pd/C 10%, MeOH) and acetylation (Ac_2O, pyridine). The α-configuration and the unusual $^1C_4$ conformation of **11** was clearly evidenced by the large ^1H-NMR coupling constant of 8.5 Hz between H-1 and H-2[12]. The formation of **10** is intriguing and shows that **9** prefers to flip to the unfavorable $^1C_4$ conformation before reaction rather than forming the expected β-mannoside. It is thus clear that a cycloglycosidation with a 6-membered transition state is unfavored for β-mannoside synthesis.



Scheme 2

References and Notes

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4. Bols, M. *Tetrahedron* **1993** *49* 10049.
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6. Stannanes **2**, **4** and **6** gave correct C,H analysis. $[\alpha]_D^{22}$, **2**: -7.4° (*c* 1.5, $CHCl_3$); **4**: +48.8°(*c* 1.0, $CHCl_3$); **6**: -19.6° (*c* 1.0, $CHCl_3$).
7. Paulsen, H. *Carbohydr. Res.* **1980** *200* 127.
8. Sawyer, J. S.; Narayanan, B. A. *Synthetic Commun.* **1983** *13* 135.
9. Typical procedure: To 3 g of **3** in 7.5 ml THF at 0°C was added 237 mg deoiled NaH in 7.5 ml THF and 1.34 g 15-crown-5. After 30 min. 4.84 g Bu_3SnCH_2OMs and 7.5 ml DMF was added, and the reaction was stirred at 25°C for 18 h. Addition of 75 ml H_2O, extraction with 2x100 ml CH_2Cl_2, drying, concentration and flash-chromatography gave 3.21 g **4** (66%).
10. Holick, S. A.; Anderson, L. *Carbohydr. Res.* **1974** *34* 208.
11. The mass spectrum gave m/z: 567 (M + Na), 544 (M+).
12. ^1H NMR ($CDCl_3$) of **11**: δ 5.32 (t, 1H, J_{23} 3 Hz, J_{34} 3 Hz, H-3), 5.14 (d, 1H, J_{12} 8.5 Hz, H-1), 4.9 (d, 1H, H-4), 4.6 (m, 1H, H-5), 4.27 (m, 2H, H-6ab), 3.7 (d, 1H, $J_{2'a2'b}$ 11.5 Hz, H-2'a), 3.49 (dd, 1H, H-2), 3.42 (d, 1H, H-2'b), 2-2.2 (3s, 9H, Ac's), 0.8-1.8 (10H, CH_2's).

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