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Preliminary communication

An approach to synthesis of glycosides: enhancement of nucleophilicity of hydroxyl groups by trialkylstannylation

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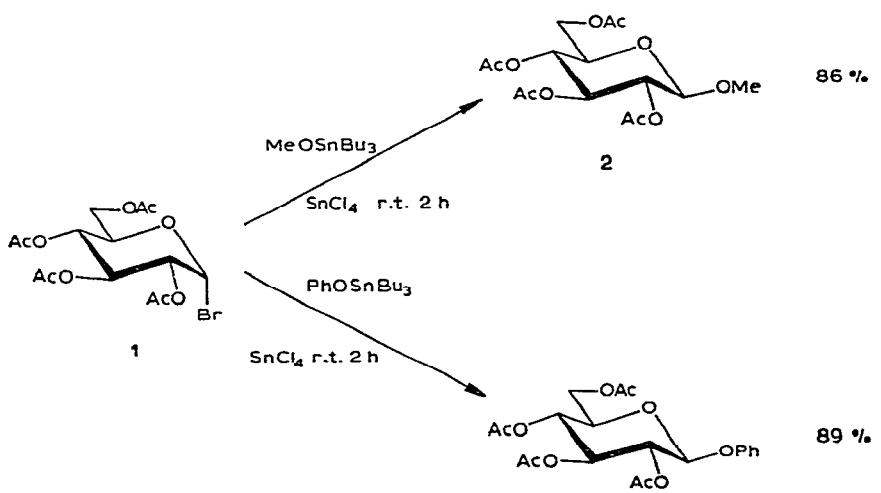
Much effort has been devoted to the development of a mild, efficient, and stereospecific procedure for the synthesis of glycosides[1]. One of the long-standing problems[2] in this field is to find a method for the modification of the low nucleophilicity of the substituted hydroxyl group to be attached at the anomeric carbon atom of carbohydrates. Available methods are based on the transformation of the hydroxyl groups into derivatives through the replacement of hydrogen by electron-releasing or electropositive groups, such as *tert*-alkyl groups[3,4], the trimethylsilyl group[5], the 2,3-diphenyl-2-cyclopropenyl group[6], or an alkoxyaminocarbynyl group[7].

We report here an approach to glycosides through the enhancement of the nucleophilicity[8] of the original alcohols by trialkylstannylation[9].

Treatment of tetra-*O*-acetyl-α-D-glucopyranosyl bromide[10] (1) with one equivalent



SCHEME 1 Reaction catalyzed by Lewis acid

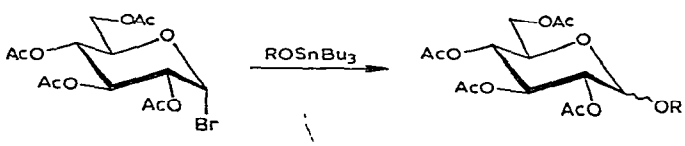
of tributylstannyl methoxide in acetonitrile during 75 h at 55° gave a mixture of products. After acetylation of the reaction products, methyl 2,3,4,6-penta-*O*-acetyl-β-D-glucopyranoside[11] (2) and 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranoside[12] were isolated in 22 and 43% yield, respectively. This indicates that not only the anomeric carbon atom but also the carbonyl carbon atom of the 6-*O*-acetyl group was attacked by tributylstannyl methoxide due to the enhanced nucleophilicity of the alkoxide oxygen atom.

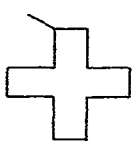
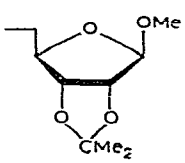
However, treatment of 1 with tributylstannyl phenoxide gave no reaction, even during 4 h at 90°, due to the low nucleophilicity of the phenoxide oxygen atom.

In order to make the reaction more specific (and also more efficient), two modifications were introduced.

TABLE I

REACTION OF BROMIDE 1 WITH VARIOUS TRIBUTYLSTANNYL ALKOXIDES[a]



R	*Yield (%)*	*M.p. (degrees)*	*$[\alpha]_D$ (degrees, in $CHCl_3$)*	*Lewis acid*	*Reaction time at room temp. (h)*
22 $-CH_2Ph$	52 (β-)	76–78	−40.3	$SnCl_4$	2
23 	47 (α-)	syrup	+119.3	$SnCl_4$	48
	32 (α-)	101–103	+107.2	$SnCl_4$	48
	37 (β-)	107–109	−53.2	$BF_3 \cdot Et_2O$	72

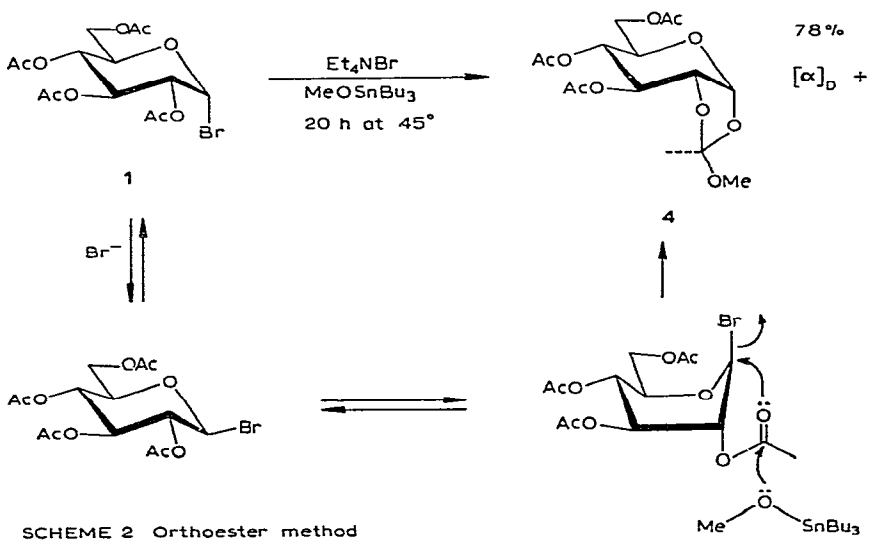
[a] All of the reactions were performed in 1,2-dichloroethane by employing equivalent amounts of reactants and Lewis acid under exclusion of moisture. The products were purified by column chromatography on silica gel (toluene–ethyl acetate).

Firstly, a Lewis acid-catalyzed cleavage of the carbon–halogen bond at the anomeric position[13] was examined. Thus, in the presence of one equivalent of stannic chloride, the reaction of **1** with tributylstannyl methoxide (one equivalent) in dichloromethane during 3 h at 20° gave an 86% yield of **2**. Similarly, with one equivalent of tributylstannyl phenoxide in the presence of one equivalent of stannic chloride during 4 h at 20°, an 89% yield of phenyl 2,3,4,6-tetra-*O*-acetyl-β-glucopyranoside[14] (**3**) was obtained from **1**.

The experimental results obtained by employing these reaction conditions with several tributylstannyl alkoxides are listed in Table I. The different anomeric stereochemistry of the glycosides obtained from the primary and the secondary alkoxide may be explained in terms of their different rates of β-D-glucoside formation and of their anomerization to α-D-glucosides[15].

Secondly, the epimerization of the α- into the more reactive β-anomeric configuration of the carbon–halogen bond[16] was examined by halide-ion catalysis. Thus, in the presence of 0.5 equivalent of tetraethylammonium bromide, the reaction of **1** with one equivalent of tributylstannyl methoxide gave a high yield of *exo*-orthoester[17] (**4**), $[\alpha]_D^{25}$ +48.3° ($CHCl_3$)*, under mild conditions *via* the reaction path shown in scheme 2.

As the stereospecific transformation of such orthoesters into 1,2-*trans*-glycosides is well established[18], the development of an efficient, synthetic procedure for the orthoesters of complex aglycons[19] could lead to the synthesis of complex glycosides. The application of this modified approach to a variety of complex aglycons was, therefore, studied by employing **1** as the glycosyl halide, to afford a high yield of the expected product in each case, as shown in Table II.



SCHEME 2 Orthoester method

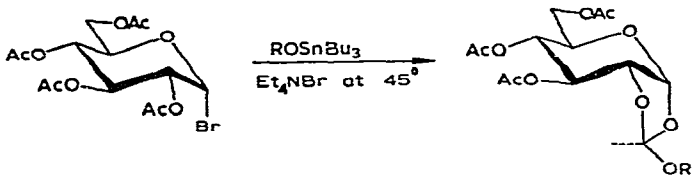
*All compounds for which $[\alpha]_D$ is recorded gave both an acceptable elemental analysis and reasonable ^{1}H-n.m.r. data.

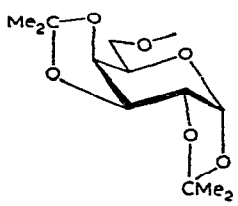
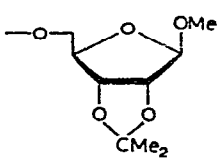
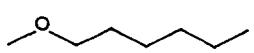
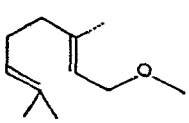
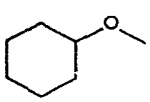
Further applicability was achieved as shown in scheme 3, by employing tetra-*O*-acetyl-α-D-galactopyranosyl bromide[20] (5) and tetra-*O*-acetyl-α-D-mannopyranosyl bromide[21] (6).

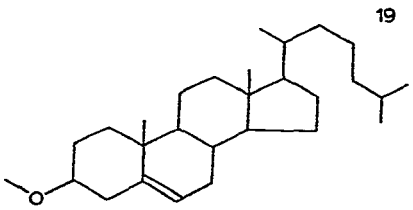
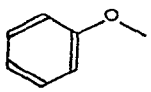
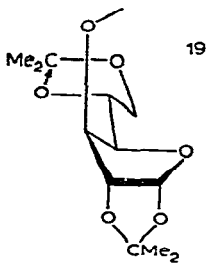
In conclusion, an approach to glycosides through enhancement of the nucleophilicity of the hydroxyl group by trialkylstannylation provides a mild, effective, and specific synthetic procedure.

TABLE II

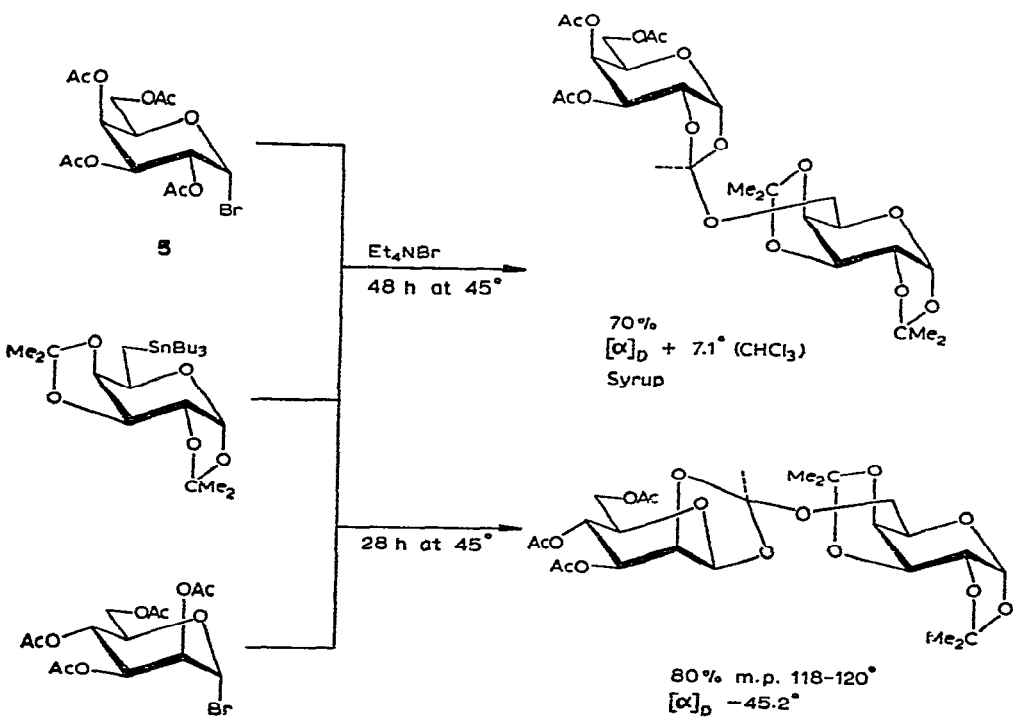
REACTION OF BROMIDE 1 WITH DERIVATIVES OF SOME COMPLEX AGLYCONS[a]



R–O–	*Yield (%)*	*$[\alpha]_D$ (degrees, in $CHCl_3$)*	*M.p. (degrees)*	*Reaction (h)*
	82	–21.2	syrup	14
	93	+12.3	syrup	20
	77	+24.9	syrup	14
	77	+17.3	syrup	14
	80	+39.6	82	20

 19	84	+1.8	101–102	20
 17	82	+56.1	syrup	35
 19	90 (53% conversion)	−8.4	108–110	70

[a] All of the reactions were performed in 1,2-dichloroethane by employing equivalent amounts of reactants and half an equivalent amount of catalyst. The products were separated either by column chromatography on silica gel (toluene–ethyl acetate–1% triethylamine) or by direct crystallization. The yields were not optimized.



SCHEME 3

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