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Preliminary communication

A stereocontrolled approach to the synthesis of glycosyl esters. Partial synthesis of stevioside from steviobioside

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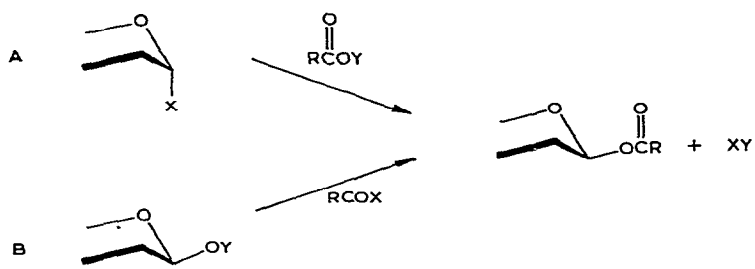
Even though considerable efforts have been devoted to developing synthetic methods for glycosyl esters[1–6], the methods are not always successful in the case of carboxylic acids of multifunctional or sterically hindered structure.

As part of a project on specific chemical transformation of carbohydrates through trialkylstannylation, we report here a new approach to the synthesis of glycosyl esters. Two reasonable routes, **A** and **B** (see Scheme 1), employ tributylstannyl carboxylate or tributyl stannyl alkoxide.

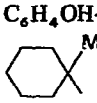


Scheme 1 (Y = $SnBu_3$)

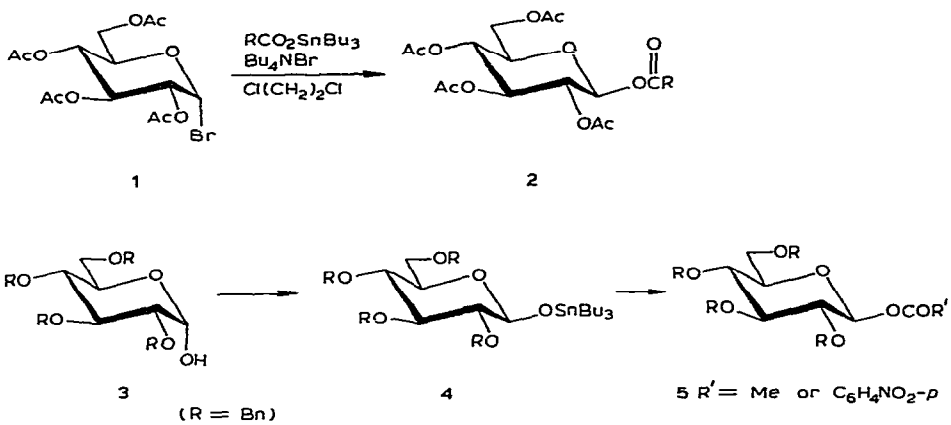
The reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**) with tributylstannyl acetate did not proceed, even on heating at 100°, but gave a good yield of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose on heating at 45–80° in the presence of added bromide anion. Under essentially the same reaction-conditions, a variety of tributylstannyl carboxylates gave the corresponding 1,2-*trans*-D-glucosyl esters (**2**) in good yields (see Table I).

TABLE I

FORMATION[a] OF β-D-GLUCOPYRANOSYL ESTERS (2) FROM 1

R in 2	*Yield (%)*	*M.p. (°C)*	*$[\alpha]_D$ (degrees)* [b]	*Reaction time (h)*	*Reaction temp. (degrees)*
Me	70.0	130 –131	+3.9	100	60
Me_2CH	44.3	106.5–107.5	+4.6	100	80
Me_3C	64.1	136 –137	+7.2 (lit.[11] +6.3)	100	80
C_6H_4OH-*p*	74.6	199 –201	–31.8	4	80
	62.1	101 –102	+1.8	100	80

[a] All reactions were performed in the presence of an equivalent amount of tetraethylammonium bromide. Reaction products were isolated either by chromatography on silicic acid with 3 : 1 toluene–ethyl acetate, or by direct crystallization from diisopropyl ether. All new compounds gave acceptable elemental analyses and ^{1}H-n.m.r. data. [b] In chloroform.

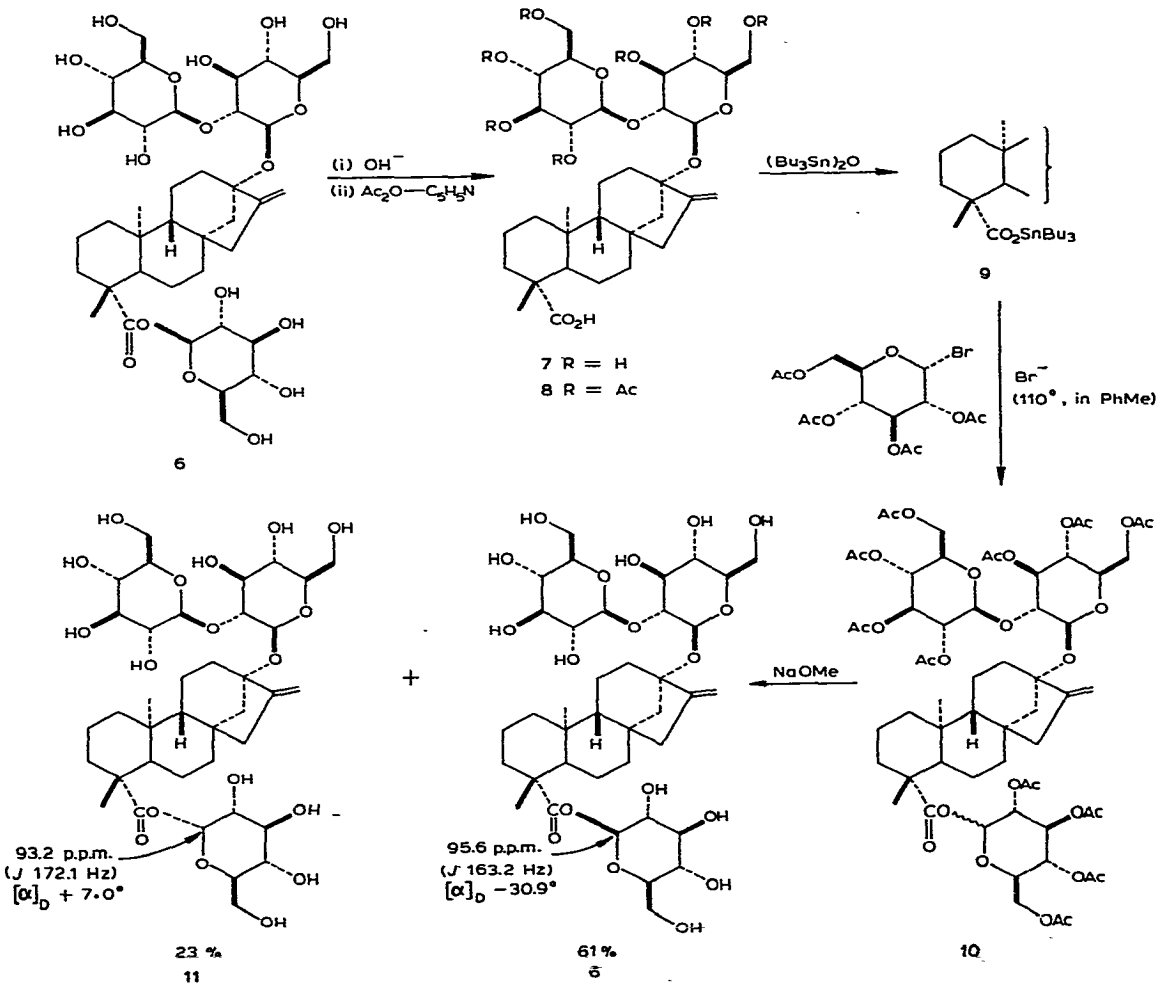


Scheme 2

Even though, by route B, conventional methods[1,4,5] gave only poor control over the stereochemistry at the anomeric carbon atom, a detailed report on successful use of this approach by using alkali-metal alkoxides (Y = alkali metal in Scheme 1 B) recently appeared[7]. Control of the stereochemistry in obtaining β-D-glucosyl esters could also be satisfactorily achieved by employing tributylstannyl alkoxide and an acyl halide. Thus, tributylstannylation[8] of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (3) to give 4, and subsequent treatment of 4 with an equimolar proportion of an acyl halide in carbon tetrachloride at 0–5° gave the β-D-glucosyl ester 5 in high stereoselectivity. The reaction with acetyl chloride gave a mixture of 2,3,4,6-tetra-*O*-benzyl-α- and -β-D-glucopyranosyl acetate in 80% yield; ^{1}H-n.m.r. data ($CDCl_3$): β anomer, doublet for H-1 at δ 5.6, *J* 7.5 Hz; α anomer, doublet for H-1 at δ 6.38, *J* 3 Hz (β:α = 5 : 1). With *p*-nitrobenzyl chloride, complete stereospecificity was observed, giving an 85% yield of 2,3,4,6-tetra-*O*-benzyl-β-D-

glucopyranosyl *p*-nitrobenzoate, m.p. 79–81°, $[\alpha]_D$ –42.4° (*c* 0.51, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$): doublet for H-1 at δ 5.89, *J* 8.0 Hz.

As two kinds of stereocontrolled, "stannyl" approaches to the synthesis of glycosyl esters have been developed, we now describe the partial synthesis of stevioside[9] (**6**), known to be 300 times as sweet as sucrose. Because the aglycon of **6** contains an exocyclic double bond, approach A was chosen, in order to avoid the hydrogenolysis step for the removal of protective groups. Steviobioside heptaacetate[10] (**8**), obtained by saponification of **6** and subsequent acetylation, was transformed into the tributylstannyl salt (**9**); ν_{max}^{KBr} 1640 cm^{-1} (CO_2SnBu_3) by treatment with one equivalent of bis(tributylstannyl) oxide[8]. Reaction of a stoichiometric amount of **1** with **9** in toluene for 4 days at 110° gave a high yield of the D-glucosyl ester **10**. Saponification of **10** with methanolic sodium methoxide gave stevioside (**6**) and its α anomer (**11**) in 61 and 20% yield, respectively, from acid **8**. The structures of synthetic **6** and **11** were confirmed by ^{13}C-n.m.r. data[12].



Scheme 3 Partial synthesis of stevioside

In conclusion, simple and practical approaches to the stereochemically controlled synthesis of glycosyl esters have been developed.

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