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Intramolecular *C*-Arylation of Benzylated Sugars. The Unexpected Double *C*-Glycosideration of Tris-*O*-*m*-methoxybenzyl-β-D-ribofuranose Derivatives

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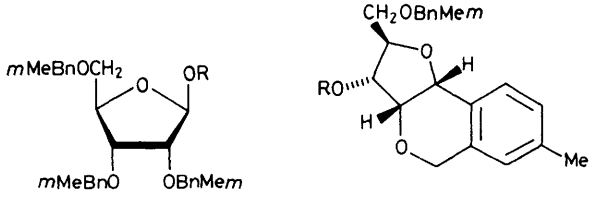
Upon treatment with tin(IV) chloride, D-ribofuranose derivatives bearing activated *O*-benzyl groups were found to undergo single or double intramolecular *C*-arylation, with *m*-methyl- and *m*-methoxy-substituted benzyl groups respectively.

We recently reported[1] that benzylated glycofuranosyl acetates readily undergo intramolecular Friedel–Crafts alkylation of the 2-*O*-benzyl group upon treatment with a Lewis acid. In order to explore the synthetic potential of this unusual *C*-glycosylation reaction, the behaviour of several types of benzylated sugars in the presence of a Lewis acid is being actively studied. We now report some remarkable results obtained from D-ribofuranose derivatives bearing 'activated' benzyl groups.

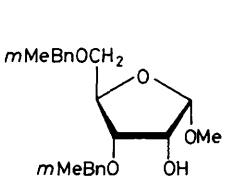
As expected, tris-*O*-*m*-methylbenzyl-β-D-ribofuranosyl acetate (**3**), prepared from methyl β-D-ribofuranoside by way of (**1**) and (**2**) using standard procedures,[2] gave compound (**4**)† (syrup; $[\alpha]_D^{20}$ + 70.0°, *c* 1.2, $CHCl_3$) as the major product (59%‡) upon treatment with tin(IV) chloride; a small amount (11%) of the 3-*O*-debenzylated analogue of (**4**) was also isolated {compound (**5**), m.p. 82.5—84 °C, $[\alpha]_D^{20}$ 0°, *c* 0.7, $CHCl_3$}, as well as a trace (8%) of a compound tentatively identified as the isomer of (**4**) resulting from the sterically less favourable alkylation of the benzyl group at C-2 [pathway *c* in (**7**)]. Under the same conditions however, the corresponding methyl glycoside (**1**) led to a mixture of (**4**) (30%) and methyl 3,5-bis-*O*-*m*-methylbenzyl-α-D-ribofuranoside (**6**) (49%) (syrup; $[\alpha]_D^{20}$ + 108.1°, *c* 1.48, $CHCl_3$), identified on the basis of the $J_{1,2}$ coupling constant (4.0 Hz) and of the change of chemical shift of H-2 upon acetylation. The formation of this unexpected product is attributable to the ambident nucleophilic reactivity of the neighbouring benzyloxy group: reaction at the phenyl group [pathway *a* in (**7**)] leads indeed irreversibly to *C*-arylation, whereas participation of the ether oxygen (pathway *b*) gives a benzyloxonium ion from which the debenzylation product (**6**) probably arises. The factors responsible for the difference of behaviour between the methyl glycoside (**1**) and the glycosyl acetate (**3**) are not yet clearly understood.

With the more reactive *m*-methoxybenzyl substituents, both the methyl glycoside (**8**) and the corresponding glycosyl acetate (**10**), also prepared by standard procedures,[2] gave the same result upon treatment with tin(IV) chloride, namely the formation of one homogeneous product which could be crystallized directly from the processed reaction mixture (61%) (m.p. 108—109.5 °C; $[\alpha]_D^{20}$ + 26.3°, *c* 1.0, $CHCl_3$). Mass spectral and elemental analysis of this compound indicated a composition ($C_{29}H_{32}O_7$) consistent with the expected *C*-arylated structure (**11**); however, as shown by its i.r. spectrum, this compound also contains a free hydroxy group, suggesting that a second intramolecular *C*-arylation might have taken place, thus bringing about the opening of the tetrahydrofuran ring of (**11**) and the creation of a hydroxy function at C-4. In view of the high reactivity of the *p*-methoxybenzyl ether function present in (**11**), the Lewis acid-promoted cleavage of the C-1–O-4 bond of (**11**) to an

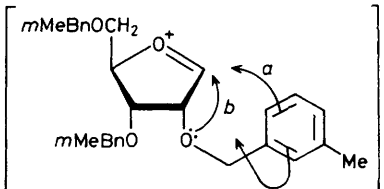


(**1**) R = Me
(**2**) R = H (α, β mixture)
(**3**) R = Ac

(**4**) R = *m*MeBn
(**5**) R = H



(**6**)

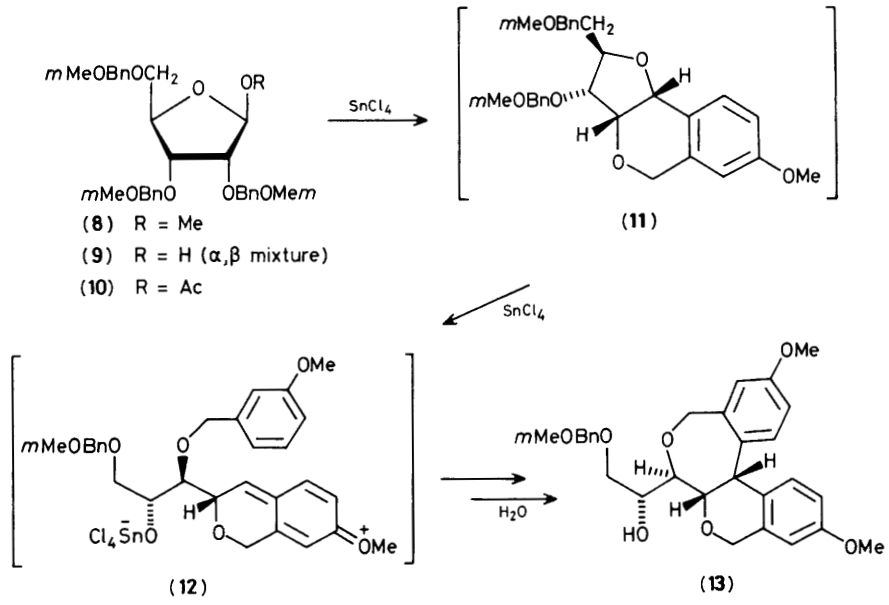


(**7**)

*m*MeBn = *m*-$MeC_6H_4CH_2$

† Satisfactory microanalysis and spectral data were obtained for all new compounds.

‡ All yields are after isolation by column chromatography.



*m*MeOBn = *m*-$MeOC_6H_4CH_2$

oxocarbonium ion-type intermediate (**12**) is easily understandable; intramolecular alkylation of the nearest *m*-methoxybenzyl substituent then follows, leading to the unusual polyheterocyclic compound (**13**). The structure of this product was firmly established on the basis of its high-field ^1H n.m.r. spectrum (300 MHz); in particular, the values of the coupling constants in the saturated heterocyclic system indicated that the benzoannulated oxepane ring of (**13**) adopted a chair-type conformation,[3] and that the fusion between the two oxygenated heterocycles was exclusively *cis*. Thus, the second intramolecular *C*-arylation occurred stereospecifically with *retention* of configuration at C-1 (sugar numbering); these findings support the two-steps mechanism proposed for the formation of (**13**) from (**11**).

The conversion of (**8**) [or (**10**)] into (**13**) in one stage is a fascinating reaction in which both of the C–O bonds at the anomeric centre of a cyclic sugar derivative are replaced by carbon–carbon bonds: in this respect, it can be considered as a *double C-glycosidation*. Previous examples of dialkylation or diarylation at C-1 are scarce[4,5] and most of them involved a sugar lactone as starting material. The formation of (**13**) is the first example of an intramolecular double *C*-glycosidation, which provides a stereospecific and high-yielding route to a novel heterocyclic system from easily accessible *O*-benzylated glycosides. Also, because of their acetal-like reactivity, *C*-*p*-methoxyphenyl derivatives of type (**11**) constitute attractive precursors for further double *C*-glycosidation reactions; investigations on compounds of this type are currently under progress and the results will be reported shortly.

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