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ORGANOTIN DERIVATIVES AND THE SELECTIVE ACYLATION AND ALKYLATION OF THE EQUATORIAL HYDROXY GROUP IN A VICINAL, EQUATORIAL-AXIAL PAIR

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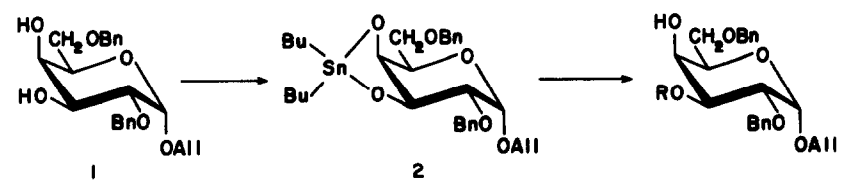
After recent, not completely satisfactory efforts[2] to selectively substitute one of the open positions in allyl 2,6-di-O-benzyl-α-D-galactopyranoside (1), our attention was drawn to the work of Wagner, Verheyden, and Moffatt[3] on the acylation and alkylation of the 2',3'-O-di-n-butylstannyleneribonucleosides. These compounds reacted with various halides to give almost exclusively mono-substitution products, mixtures of 2'- and 3'-derivatives. There was substantial regioselectivity in the benzoylation (3'-selective) and tosylation (2'-selective) reactions. It thus seemed of interest to investigate the acylation and alkylation of stannylene derivatives of 1 and related, cyclohexanoid, axial-equatorial vicinal diols. In these compounds, in contrast to the stannyleneribonucleosides, there is a clear cut conformational difference between the two alkoxide oxygens[4]. The examples we have studied show a very high degree of selectivity for reaction at the equatorial position.

Diols 1, 4, and 7 were each refluxed with an equimolar portion of di-n-butyltin oxide in methanol (ca. 100 volumes with respect to total solutes) for 1 hr[3]. Evaporation of the methanol under reduced pressure gave syrups, which were used as such. No satisfactory way of monitoring the progress of the reaction was found[3], but the subsequent behavior of the syrups demonstrated that they were the desired di-n-butylstannylene derivatives 2, 5, and 8.



1 2

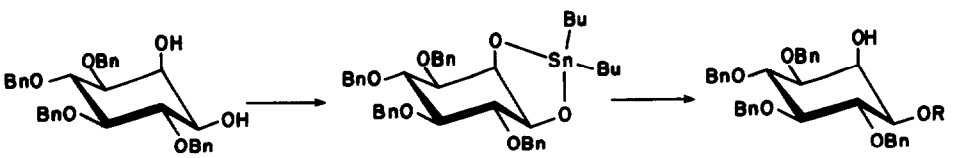
3a R = Bz
3b R = Bn
3c R = All
3d R = Me

All = allyl Bn = benzyl Bz = benzoyl
Bu = n-butyl

Thus, the di-n-butylstannylene derivative (2) from 2 mmol of allyl 2,6-di-O-benzyl-α-D-galactopyranoside[5] on treatment with excess benzoyl chloride and triethylamine (19 mmol each) in p-dioxane at room temperature for 1.5 hr gave allyl 3-O-benzoyl-2,6-di-O-benzyl-α-D-galactopyranoside (3a). The product, isolated in 81% yield by chromatography on silica gel, was identical with that previously obtained[2] from the direct, low-temperature benzoylation of 1. To further check the regioselectivity of the reaction, the crude product was treated by a procedure, to be described elsewhere, which replaced the benzoyl group by a benzyl group. The resulting allyl 2,3,6-tri-O-benzyl-α-D-galactopyranoside[6] contained only traces, at most, of the isomeric 2,4,6-tribenzyl ether[2] (t.l.c.).

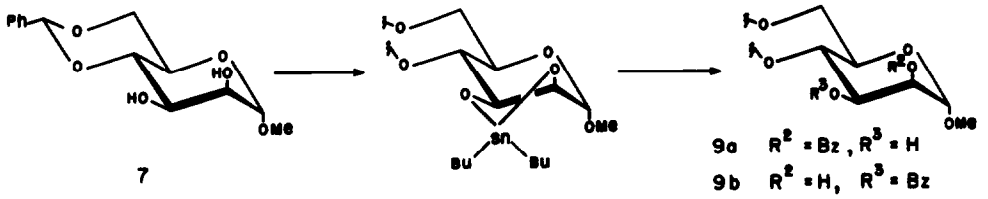
The alkylation of 2 was accomplished by heating it with excess alkyl halide in N,N-dimethylformamide (DMF) at 100° for 1 hr. With benzyl bromide the product was allyl 2,3,6-tri-O-benzyl-α-D-galactopyranoside[6] (3b), obtained in 72% yield after chromatography. Again only traces of the 2,4,6-isomer were formed.

Compound 2 reacted sluggishly with allyl bromide in DMF at 100°, but complete monoalkylation was readily achieved with allyl iodide. The product, allyl 3-O-allyl-2,6-di-O-benzyl-α-D-galactopyranoside (3c) (79% yield) was a syrup, $[\alpha]_D^{25}$ + 68.5° in $CHCl_3$. PMR at 60 MHz ($CDCl_3$): τ 3.65-4.38 (m, 2, -CH=), 4.52-5.22 (m, 4, $=CH_2$), and 7.42 (bs, 1, D_2O exchangeable, OH). This substance was characterized by conversion, in two steps, to the known 2,4,6-tri-O-benzyl-D-galactose[2,5]. Further, benzoylation of the free hydroxyl and addition of bromine to the allyl groups (to shift the vinyl resonances) gave a derivative showing a doublet of wide lines at τ 4.22, spacing 4.2 Hz, characteristic of a proton (H-4) coupled to two neighboring protons with small J values. Finally the treatment of 2 with methyl iodide in DMF at 45° gave allyl 2,6-di-O-benzyl-3-O-methyl-α-D-galactopyranoside (3d) in 77% yield. The compound is a syrup, $[\alpha]_D^{25}$ + 74° in $CHCl_3$. Its PMR spectrum ($CDCl_3$) included a singlet at τ 6.52 (OCH_3) not present in the spectrum of 1, and the benzoylated and brominated derivative showed a doublet of wide lines at τ 4.16, spacing 1.9 Hz (H-4).



4, 5, 6b & 6c are racemic. One arbitrarily chosen enantiomer is shown

DL-1,4,5,6-Tetra-O-benzyl-myo-inositol[7] (4) was chosen as an equatorial-axial diol of the carbohydrate type having a true cyclohexane ring. Its di-n-butylstannylene derivative 5 was alkylated as described for 2. Benzyl bromide gave 1,3,4,5,6-penta-O-benzyl-myo-inositol (6a) in 60% yield by crystallization; m.p. 128-130° (lit.[7] m.p. 128-129°). With allyl iodide DL-1-O-allyl-3,4,5,6-tetra-O-benzyl-myo-inositol (6b) was obtained in 73% yield after chromatography; m.p. 67-70° (lit.[8] m.p. 63-66°). Methyl iodide converted 5 to DL-1,4,5,6-tetra-O-benzyl-3-O-methyl-myo-inositol[9] (6c, "tetra-O-benzyl-DL-bornesitol") in 66% yield (crystallization); m.p. 108-109° (lit.[7] m.p. 109-110°).



7 8

9a R^2 = Bz, R^3 = H
9b R^2 = H, R^3 = Bz
9c R^2 = H, R^3 = Bn
9d R^2 = Bz, R^3 = Bn

The dibutylstannylene derivative (8) of methyl 4,6-O-benzylidene-α-D-mannopyranoside[10] (7) represents a case in which there are opposing steric and electronic effects on acylation and alkylation reactions. Thus, on the basis of the foregoing examples, the steric effect would favor substitution at the equatorial position (O-3). On the other hand, OH-2 in sugars is generally the most reactive secondary hydroxyl, perhaps because it is more acidic[11]. In fact, 8 was benzylated at the equatorial position by benzyl bromide (DMF, 100°). The product, methyl 3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (9c) was isolated by chromatography in 85% yield. The $[\alpha]_D^{25}$ of + 38.3° in EtOH (lit.[12] $[\alpha]_D$ + 38°) revealed the identity of the compound, and this was confirmed by its conversion to the 2-O-benzoyl derivative 9d. PMR at 270 MHz ($CDCl_3$): τ 4.41 (dd, 1, J 1.5, 3.4 Hz, H-2, collapses to d on irradiation of H-1) and 5.18 (d, 1, J 1.5, H-1).

In agreement with the recent results of Munavu and Szmant[13] we obtained a mixture of the 2-benzoate 9a and the 3-benzoate 9b from the reaction of 8 with benzoyl chloride and triethylamine. Under our conditions (p-dioxane at 12-15° for 20 min., then room temperature until 7 was no longer evident in the t.l.c.--ca. 1 hr) the 2-benzoate was the major product. After separation by chromatography the 3-benzoate had $[\alpha]_D^{25}$ - 23.4° in $CHCl_3$ (lit.[14] $[\alpha]_D^{25}$ - 24°). PMR at 270 MHz ($CDCl_3$): τ 4.49 (dd, 1, J 2.9, 10.3 Hz, H-3, not affected by irradiation of H-1) and 5.27 (d, 1, J 2.4 Hz, H-1). Methyl 2-O-benzoyl-4,6-O-benzylidene-α-D-mannopyranoside (9a) is a glass, $[\alpha]_D^{25}$ -38.9° in $CHCl_3$. PMR at 270 MHz ($CDCl_3$): τ 4.59 (dd, 1, J 1.2, 3.7 Hz, H-2, collapses to d on irradiation of

H-1) and 5.20 (d, 1, J 1.2 Hz, H-1). This was the only case we encountered of any appreciable substitution at the axial oxygen of our dibutylstannylene compounds. Thus, the treatment of these compounds with halides may constitute a generally useful method for the efficient acylation or alkylation of the equatorial hydroxy group in an equatorial-axial pair.

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NOTES AND REFERENCES

1. On leave from the Department of Chemistry, Alexandria University, Alexandria, Egypt.
2. M. A. Nashed and L. Anderson, Carbohydr. Res., in press.
3. D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, J. Org. Chem., 39, 24 (1974).
4. It is recognized that formation of the dioxastannolane ring may twist the C-O bonds from their respective "true axial" and "true equatorial" orientations.
5. P. A. Gent, R. Gigg, and R. Conant, J. Chem. Soc. Perkin Trans. I, 1535 (1972).
6. An independent preparation of this compound will be described elsewhere.
7. S. J. Angyal and M. E. Tate, J. Chem. Soc., 6949 (1965).
8. R. Gigg and C. D. Warren, Tetrahedron Lett., 2415 (1966).
9. For the rules governing the numbering of the inositol derivatives see Pure Appl. Chem., 37, 285 (1974).
10. J. G. Buchanan and J. C. P. Schwarz, J. Chem. Soc., 4770 (1962).
11. J. M. Sugihara, Advan. Carbohydr. Chem., 8, 1 (1953).
12. S. S. Bhattacharjee and P. A. J. Gorin, Can. J. Chem., 47, 1195 (1969).
13. R. M. Munavu and H. H. Szmant, J. Org. Chem., 41, 1832 (1976).
14. F. R. Seymour, Carbohydr. Res., 34, 65 (1974).