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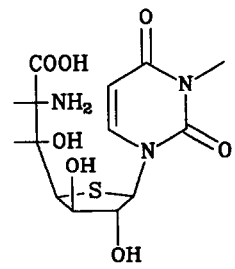
STANNYLENE DIRECTED SELECTIVE ACYLATION OF SOME OPEN-CHAIN L-ARABINOSE DERIVATIVES

Martin W. Bredenkamp, Cedric W. Holzapfel* and Anna D. Swanepoel
Department of Chemistry and Biochemistry, Rand Afrikaans University,
P.O. Box 524, JOHANNESBURG 2000, South Africa

Abstract: Controlled mono-2- or -4-acylation of open-chain L-arabinose derivatives is achieved by terminal group manipulation and dibutylstannylene oxide activation. The method was used for the preparation of a 4-mesyl-L-arabinose derivative which was converted into a thioxylose synthon.

Our approach to the synthesis[1] of the thiosugar derivative **1**, which may be regarded as a sub-unit of the albomycine-δ_1 antibiotic;[2,3] starting from L-arabinose, requires the selective mesylation or tosylation of the 4-OH group of **2**, an acyclic derivative of the chiral precursor. Selective alkylsulphonylation of the 4-OH group using standard conditions could, however, not be achieved. The possibility of selective activation of this OH group was therefore investigated. Dibutyltin oxide and bis(tributyltin) oxide have been widely used for the selective activation of specific hydroxy groups of pyranosides and furanosides towards electrophiles, without having to mask initially any of the other hydroxy functions.[4-6] However, to our knowledge, these reagents have not been employed in the selective esterification of acyclic sugar derivatives. Herein we report our findings concerning the selective benzoylation of the dibutylstannylene complexes of acyclic L-arabinose derivatives (**2-6**) and the application of the methodology for the synthesis of a thiofuranose synthon.



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The dibutylstannylene complexes of **2-6**[7] were prepared by refluxing the respective L-arabinose derivatives with dibutyltin oxide (See table for stoichiometry) in benzene for 16 hours, azeotropically removing the generated water with a Dean-Stark apparatus. The complexes were reacted with benzoyl chloride at 0°C and then stirred at room temperature for 3 hours. The products[8] were separated and purified by column chromatography (silica gel) and in the more difficult cases product yields were established by HPLC analysis[9] The results, which are summarised in the Table, show that, in most cases, regioselective mono- and/or dibenzoylation could be achieved. However, the regioselectivity (mono-benzoylation in particular), which could be achieved following activation with 0.5 to 1.0 mol equiv. bis(tributyltin) oxide, was significantly lower. Regioselective monobenzoylation of **2-6** could not be achieved by the pyridine-catalyzed reaction of the substrates with benzoyl chloride. An analysis of the data in the Table suggests the following generalizations:

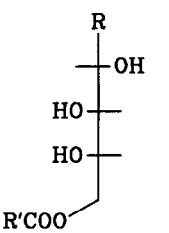
1. The 3-position was not benzoylated to a significant extent in any experiment.

Table: Major products of O-benzoylation of activated[a] L-arabinose derivatives.

Entry	Substrate	Stoichiometry Bu_2SnO	Stoichiometry BzCl	Total yield[b]	Ratio of major products 2-O-Bz	4-O-Bz	2,4-di-O-Bz
1	**2**	1	1	88	<1	85	14
2	**2**	0.75	1	60	1	76	23
3	**2**	1	2	99	<1	<1	98
4	**3**	1	1	96	<1	95	4
5	**4**	1	1	99	98	<1	<1
6	**5**	1	1	71	26	33	41
7	**6**	1	1	89	<1	90	9
8	**6**	0.75	1	60	2	71	17
9	**6**	1	2	100	<1	<1	98

[a]See text for reaction. [b]As percentage of carbohydrate substrate.

2. In reactions with 1 mol equiv. of benzoyl chloride, dibutyltin oxide activates selectively the 4-position of both ethyl (entry 1) and benzyl (entry 7) thioacetals and of the oxime ether (entry 4). Optimal selectivity is obtained by the use of 1 mol equiv. of the organotin reagent. This result suggests that, as in the case of most hexopyranoside stannylene complexes, the rates of introduction of the first and second benzoyl groups are significantly different.



2 R = $CH(SEt)_2$, R' = Ph
3 R = CH=NOBn, R' = Ph
4 R = $CH(OMe)_2$, R' = Ph
5 R = $CH(SEt)_2$, R' = CMe_3
6 R = $CH(SBn)_2$, R' = Ph

3. Steric crowding of the ester carbonyl at position 5 (entry 6) leads to a loss of selectivity, yielding a mixture of the 2- and 4-O-monobenzoylated and the 2,4-di-O-benzoylated products. The fact that the latter is the main product, even on treatment of the stannylene complex with 1 equiv. of the acylating agent, suggests that, in this case, the rate for the introduction of the second benzoyl group is of the same order as that of the first.
4. Replacement of the sulphur atoms in the thioacetals with oxygen leads to complete reversal of selectivity, favouring exclusive benzoylation at position 2 (entry 5).

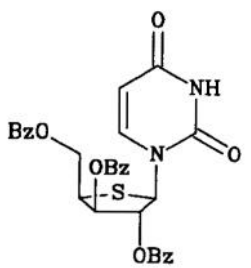
It is of interest to note that, in contrast with the reactions of cyclic carbohydrate[6] substrates, product ratios did not change significantly on the addition of ligands such as tetrabutylammonium chloride or N-methylimidazole to the reaction mixture or on changing the solvent from benzene or toluene to THF. This suggests that the stannylene complexes of compounds **2-6** do not undergo oligomerisation.[10] It is possible that, in these more flexible stannylene complexes, expansion of the coordination number of the tin atom can be achieved by intramolecular complexation rather than by intermolecular association. The ^{119}Sn and ^{13}C nmr spectra[11] of the above mentioned dibutylstannylene complexes are suggestive of

homogeneous complexes, each containing a simple type of penta-coordinated tin atom or of complexes in fast equilibrium with each other.

With careful consideration of the factors responsible for the greater stability of 5-membered stannylene complexes relative to 6-membered complexes in pyranosides;[12] it may be assumed that 5-membered tin complexes of compounds **2**-**6** will be more stable. This would imply that for 5-O-benzoyl compounds (**2** and **6**) mono-O-benzoylation involves predominantly acylation of the 3,4-complex with the attack directed at the less hindered 4-position (entries 1, 2, 7 and 8). On cleavage of the dioxastannane ring, the dibutylchlorotin group rapidly migrates[13] to the terminal 2-position, possibly in order to minimise destabilizing steric interactions and to optimise intramolecular coordination, resulting in introduction of the second O-benzoyl group at the 2-position on further reaction (entries 3 and 9, and the minor components of entries 1, 2, 7 and 8).

Preliminary work on other open-chain pentose derivatives indicates a behaviour similar to that of L-arabinose derivatives. While the exact mechanism of selective activation of hydroxyl groups by reaction with dibutyltin oxide remains open to speculation, these results demonstrate that this methodology is also applicable to open-chain sugar derivatives. The fact that the selectivity can be manipulated, circumventing the need for protection/deprotection sequences, may favour a greater use of acyclic derivatives in chiral synthesis. The usefulness of this methodology is exemplified by the effective conversion of **6** into **7**, a potential albomycine-δ_1 synthon.

Treatment of the dibutylstannylene derivative of **6** with 1.3 mol equiv. of MsCl in toluene for 12 hr at 20°C furnished mainly the unstable monomesylate (**8**). Without purification, this unstable compound was converted into **9** by the addition of benzoyl chloride and pyridine to the reaction mixture at 0°C. After the addition of 1 mol equiv. of tetrabutylammonium iodide and barium carbonate to the reaction mixture, it was heated under reflux for 6 hr. Under these conditions, **9** cyclised[14] smoothly to give the 1,4-dithio-D-xylofuranoside **10** as a mixture of anomers in an overall yield of 57%. Treatment of the thioacetal **10** with $Hg(OAc)_2$ in acetic acid, following the method of Blumberg and coworkers;[15] furnished 11 as an anomeric mixture. The stereoselective reaction of **11** with *t*-butyldimethylsilylated uracil in the presence of $SnCl_4$[3,16] at 0°C furnished the thiofuranose derivative (**7**)[17] as a major product.



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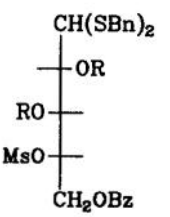
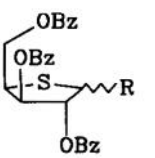


8 R = H
9 R = Bz



10 R = SBn
11 R = OAc

Notes and References:

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7. These compounds were prepared using standard methodology.
8. All products were fully characterised using mass spectrometry and ^{1}H and ^{13}C nmr.
9. A Varian Mikropak Si-10 column was used and EtOAc/Hexane used as eluting agent. The components of the inseparable product mixtures were identified by means of ^{1}H and ^{13}C nmr.
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11. All ^{119}Sn nmr resonances occurred between 128 and 176 ppm upfield from the four-coordinate Me_4Sn reference, a range characteristic[10,18] of tin with coordination higher than four.
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