Carbohydrate Research, 56 (1977) C1–C6

Preliminary communication

A new approach to regioselective acylation of polyhydroxy compounds

TOMOYA OGAWA and MASANAO MATSUI

The Institute of Physical and Chemical Research, Wako-shi, Saitama 351 (Japan)

(Received March 19th, 1977; accepted for publication, March 30th, 1977)

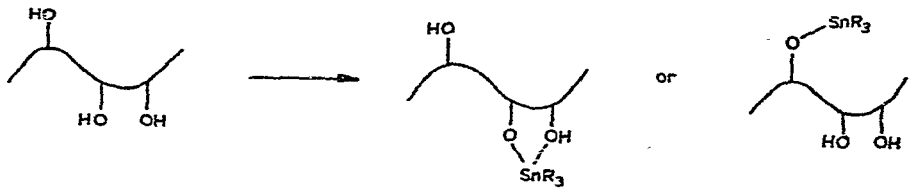
Even though extensive results have been accumulated on the selective acylation of mono- and oligo-saccharides and their derivatives[1], such acylations are not always successful from the preparative point of view, due to the low selectivity of the reactant towards various hydroxyl groups, which in most cases leads to a low yield of the desired product. Available methods are mainly based on the kinetically controlled reaction by taking advantage of the different reactivity, towards acylating agents, of the hydroxyl groups according to either their steric disposition[2] in the molecule, or their capability of intramolecular, hydrogen-bond formation[3].

We report here a thermodynamically controlled approach to this problem through regioselective enhancement of the nucleophilicity of hydroxyl groups[4]. As trialkylstannyl alkoxides are known to form a coordination bond with a neighboring oxygen atom at the tin atom[5], trialkylstannylation of polyhydroxy compounds with a limited amount of bis(tributylstannyl) oxide[6] would be expected to occur regioselectively, if product A is thermodynamically more stable than product B (see Scheme 1). Subsequent reaction of (tributylstannyl) alkoxide A with such electrophilic, acylating agents as acid chlorides[7] should then lead to regioselective acylation.

In order to study the regioselectivity in obtaining ~50% acylation among the total hydroxyl groups in a compound, several methyl glycosides were first chosen as the substrates for the experiment.

Methyl α-D-glucopyranoside (1) was treated with 1.5 molar proportions of bis(tributylstannyl) oxide (2) in boiling toluene under reflux, with continuous removal of water, to give a clear solution. After cooling to room temperature, addition of 3.0 molar proportions of benzoyl chloride initiated a mildly exothermic reaction, to afford, after standing for 7 h at room temperature, methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside (3) and methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (4), m.p. 127–129°, $[\alpha]_D^{25}$ +149.4° (chloroform)* in 82 and 15% yields, respectively. Under essentially the same reaction conditions, methyl

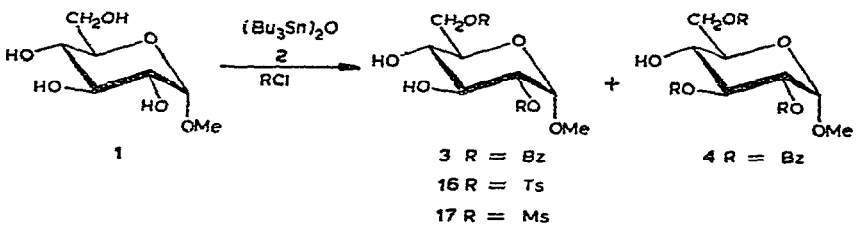
*All compounds for which $[\alpha]_D^{25}$ is recorded gave both an acceptable elemental analysis and reasonable ^{1}H-n.m.r. data.

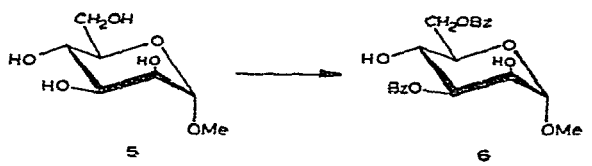


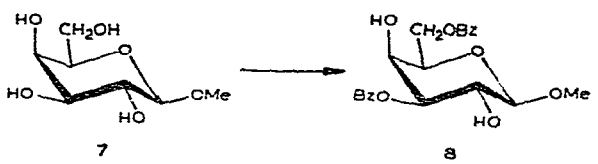
Scheme 1

α-D-mannopyranoside (5) and methyl β-D-galactopyranoside (7) respectively gave high yields of methyl 3,6-di-*O*-benzoyl-α-D-mannopyranoside (6) and methyl 3,6-di-*O*-benzoyl-β-D-galactopyranoside (8).

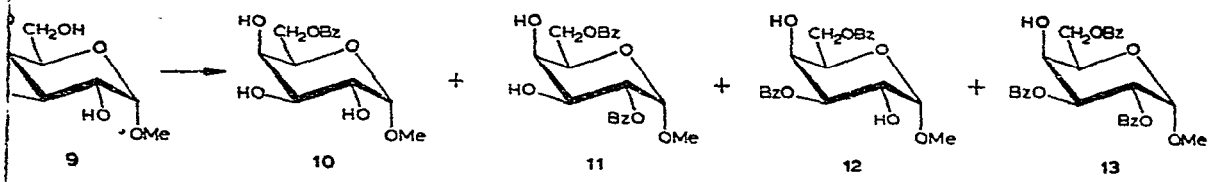
Under the same reaction conditions, however, methyl α-D-galactopyranoside (9) gave a mixture of four products, namely, methyl 6-*O*-benzoyl-α-D-galactopyranoside (10), m.p. 152–154°, $[\alpha]_D^{25}$ + 117.8° (methanol), methyl 2,6-di-*O*-benzoyl-α-D-galactopyranoside (11), methyl 3,6-di-*O*-benzoyl-α-D-galactopyranoside[2] (12), and methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[2] (13), m.p. 137–139°, $[\alpha]_D^{25}$ + 116.9° (chloroform) in 21, 10, 20, and 41% yield, respectively. Although dibenzoates 11 and 12 had the same R_F values in t.l.c. (0.6 in 3 : 1 toluene–ethyl acetate) and were isolated as mixed crystals, m.p. 125–127°, the structure of each compound could be assigned from ^{1}H-n.m.r. data**: δ 5.33 (q, *J* 3, 10 Hz, for H-3 of 12), 5.13 (q, *J* 4, 10 Hz, for H-2 of 11), 4.92 (d, *J* 4 Hz, for H-1 of 12), 3.57 (s, for CH_3 of 11), and 3.46 (s, for CH_3 of 12).







**The assignments of ^{1}H-n.m.r. data were confirmed by double-irradiation experiments. (δ in p.p.m. downward from Me_4Si as the internal standard, in $CDCl_3$.)



9 10 11 12 13

From this result, the crucial importance of the stereochemistry at the anomeric carbon atom, in order to obtain regioselectivity in this reaction, became evident; it may be rationalized in terms of thermodynamically favored formation of the trialkylstannyl alkoxide of type **14** (rather than that of type **15**), which should, in turn, result in the regioselective acylation observed.

14 15

Similar regioselectivity could also be achieved in the case of sulfonylation. The (tributylstannyl)ated intermediate prepared from **1** was treated in toluene with *p*-toluenesulfonyl chloride or methanesulfonyl chloride at 50°, to give a high yield of the 2,6-di-*O*-sulfonyl derivatives (**16** or **17**).

As both high regioselectivity and high yields could be realized in the case of methyl glycosides by choosing the proper anomeric stereochemistry, further applicability of this method was examined by employing more-complex systems, such as disaccharides.

Under the conditions described in Table I, sucrose (**18**) gave an 87% yield of 2,3,6,1′,6′-penta-*O*-benzoylsucrose (**19**) as an amorphous material. The positions of benzoylation in **19** could be determined from ^{1}H-n.m.r. data*; δ 6.01 (t, 1 H, *J* 10 Hz, H-3), 5.94 (d, 1 H, *J* 4 Hz, H-1), and 5.33 (q, 1 H, *J* 4, 10 Hz, H-2). Similarly, α,α-trehalose (**20**) could be converted into 2,3,6,2′,3′,6′-hexa-*O*-benzoyl-α,α-trehalose (**21**) in good yield. The structure of **21** was also assigned from the ^{1}H-n.m.r. data*: δ 5.89 (t, 2 H, *J* 9 Hz, H-3,3′), 5.57 (d, 2 H, *J* 4 Hz, H-1,1′), and 5.43 (q, 2 H, *J* 4, 9 Hz, for H-2,2′).

Finally, finely powdered cyclohexaamylose (**22**) was submitted to this reaction sequence. The expected product, **23**, could, by diluting the reaction mixture with isopropyl ether, be directly isolated as a white solid in very high yield. Both the remarkable regioselectivity of benzoylation and the homogeneity of **23** were supported by ^{13}C-n.m.r. data[11], as shown in Table II.

In conclusion, an efficient, simple method for the regioselective acylation of polyhydroxy compounds through enhancement of the nucleophilicity of the hydroxyl groups by trialkylstannylation has been developed.

*See footnote, page C2.

TABLE I

REGIOSELECTIVE ACYLATION OF POLYHYDROXY COMPOUNDS[a] THROUGH TRIALKYLSTANNYLATION

ROH $\xrightarrow[(2)\ m\ R'Cl\ for\ Y\ h\ at\ T^\circ]{(1)\ n\ (Bu_3Sn)_2O\ in\ toluene\ for\ x\ h\ at\ 130^\circ}$ ROR'

ROH	n *(moles)*	x *(h)*	m *(moles)*	T *(degrees)*	Y *(h)*	*ROR'*	*Yield (%)*	*m.p.*[b] *(degrees)*	$[\alpha]_D^{25}$ *($CHCl_3$)* *(degrees)*	R_F[c]	*References*	*Yield (%)*
1	1.5	14	3 (BzCl)	20	7	2	82	140–142	+66.1	0.50-C	8	50
1	1.5	14	3 (TsCl)	50	100	16	81	oil	+55.7	0.63-A	9	69
1	1.5	4	3 (MsCl)	50	70	17	76	144–146	+75.9	0.50-B	10	51
5	1.5	4	3 (BzCl)	20	3	6	90	134–136	+58.1	0.50-C	2	62
7	1.5	4	3 (BzCl)	20	5	8	92	132–133	−7.1	0.55-A		
18	3.0	4	6 (BzCl)	20	120	19	87	foam	+63.2	0.60-A		
20	3.0	24	6 (BzCl)	50	20	21	73	foam	+173.6	0.63-C		
22	7.0	20	14 (BzCl)	50	48	23	95	185–188	+60.0 (acetone)			

[a] All starting materials should be finely powdered, in order to facilitate the reaction. [b] Melting points were not corrected. [c] R_F values were obtained by using a t.l.c. plate of Merck Silica Gel 60 F-254 (thickness 0.25 mm), and solvent systems *A* (1:3 toluene–ethyl acetate), *B* (10:1 chloroform–methanol), and *C* (1:1 toluene–ethyl acetate).

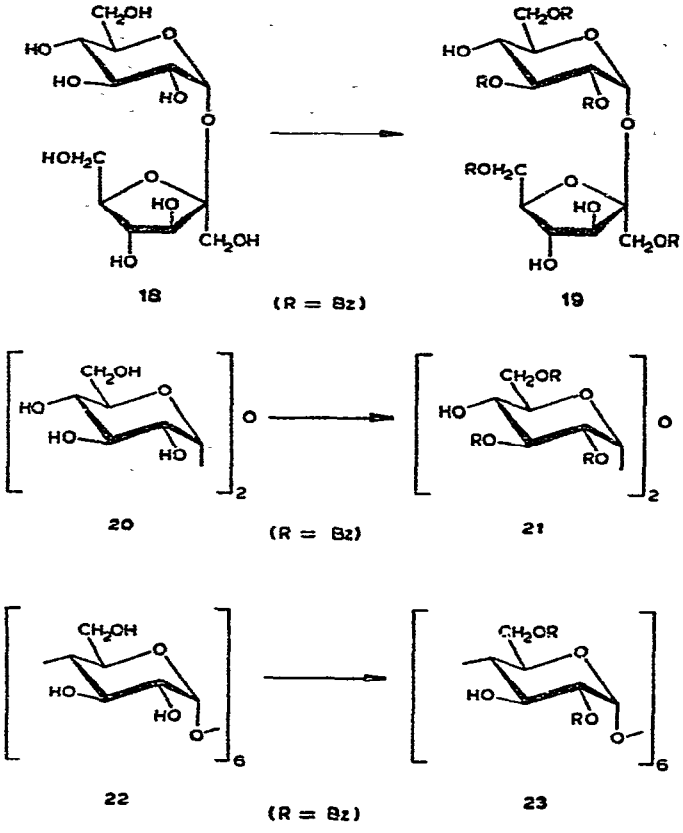


TABLE II

^{13}C CHEMICAL-SHIFT DATA[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
22	101.8	72.1	73.2	82.0	72.1	60.1
23	98.5	73.8	69.5	81.4	69.5	63.7
Δδ*C*	−3.3	+1.7	−3.7	−0.6	−2.6	+3.6

[a]The spectral data were obtained with a JNM-FX100 F.t.-n.m.r. apparatus for compounds in Me_2SO-d_6 at 60°, with tetramethylsilane as the internal reference-standard. δ_C in p.p.m. downward from the internal reference.

ACKNOWLEDGMENTS

We thank Dr. J. Uzawa and Mrs. T. Chijimatsu for recording and measuring the n.m.r. spectra, and Dr. H. Homma and his staff for the elemental analyses.

REFERENCES

1 A. H. Haines, *Adv. Carbohydr. Chem. Biochem.*, 33 (1976) 11–109.
2 J. M. Williams and A. C. Richardson, *Tetrahedron*, 23 (1967) 1369–1378; M. Dejter-Juszynski and H. M. Flowers, *Carbohydr. Res.*, 28 (1973) 61–74.
3 I. M. E. Thiel, J. O. Deferrari, and R. A. Cadenas, *Justus Liebigs Ann. Chem.*, 723 (1969) 192–197; I. M. Vazquez, I. M. E. Thiel, and J. O. Deferrari, *Carbohydr. Res.*, 26 (1973) 351–356; J. M. Macleod, L. R. Schroeder, and P. A. Seib, *ibid.*, 30 (1973) 337–347.
4 A. Marchand, J. Mendelsohn, M. Lebedeff, and J. Valade, *J. Organomet. Chem.*, 17 (1969) 379–388; T. Ogawa and M. Matsui, *J. Am. Chem. Soc.*, 98 (1976) 1629–1630.
5 R. Okawara, *Proc. Chem. Soc. London*, (1961) 383; P. J. Smith, R. F. M. White, and L. Smith, *J. Organomet. Chem.*, 40 (1972) 341–353; L. P. Vakhrushev, I. S. Akchurina, V. T. Panyushkin, and A. A. Karepov, *J. Gen. Chem. USSR*, 45 (1975) 710–711; R. M. Munavu and H. H. Szmant, *J. Org. Chem.*, 41 (1976) 1832–1835.
6 A. G. Davies, *Synthesis*, (1969) 56–64.
7 J. C. Pommier and J. Valade, *C. R. Acad. Sci.*, 260 (1965) 4549–4552.
8 T. Lieser and R. Schweizer, *Justus Liebigs Ann. Chem.*, 519 (1935) 271–278.
9 J. Asselineau, *Bull. Soc. Chim. Fr.*, (1955) 937–944; J. Jarý, K. Čapek, and J. Kovář, *Collect. Czech. Chem. Commun.*, 29 (1964) 930–937.
10 A. K. Mitra, D. H. Ball, and L. Long, Jr., *J. Org. Chem.*, 27 (1962) 160–162; R. C. Chalk, D. H. Ball, and L. Long, Jr., *ibid.*, 31 (1966) 1509–1514.
11 T. Usui, N. Yamaoka, K. Matsuda, K. Tsujimura, H. Sugiyama, and S. Seto, *J. Chem. Soc. Perkin Trans. 1*, (1973) 2425–2432; F. R. Seymour, R. D. Knapp, and S. H. Bishop, *Carbohydr. Res.*, 51 (1976) 179–194; M. R. Vignon and P. J. A. Vottero, *Tetrahedron Lett.*, (1976) 2445–2448.