Carbohydrate Research, 162 (1987) 145–152
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

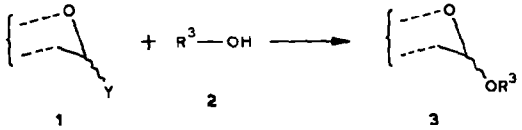
Note

Selective deacetylation of anomeric sugar acetates with tin alkoxides*

ABRAHAM NUDELMAN**, JACOB HERZIG, HUGO E. GOTTLIEB,
Chemistry Department, Bar-Ilan University, Ramat Gan (Israel)
EHUD KEINAN†,
Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot (Israel)
AND JEFFREY STERLING
Teva Pharmaceutical Industries Ltd. (Israel)

Received January 16th, 1986; accepted for publication, November 3rd, 1986)

There are three main categories of methods for synthesising glucosides and glucuronides (**1** + **2** → **3**), namely, (*a*) the Koenigs–Knorr reaction (**1**, where Y = halogen) and its modifications[2], (*b*) reactions catalysed by Lewis acids[3] (**1**, Y = OAc), and (*c*) reactions where HO-1 of the starting derivative is unsubstituted (**1**, Y = OH). Category (*c*) includes methods in which HO-1 is initially converted into a more reactive species [4a–g], and those which involve a Lewis acid catalyst[1,4h]. Direct coupling is attractive since it avoids the preparation of reactive, unstable, and readily hydrolysable derivatives of **1** with Y = Br, $OCNHCCl_3$, OCNHNHR, *etc.* The need for simple methods for the preparation of sugar derivatives with HO-1 unsubstituted is further exemplified by conversions into glycosyl fluorides which are useful in stereoselective glycosidations[5].



1 2 3

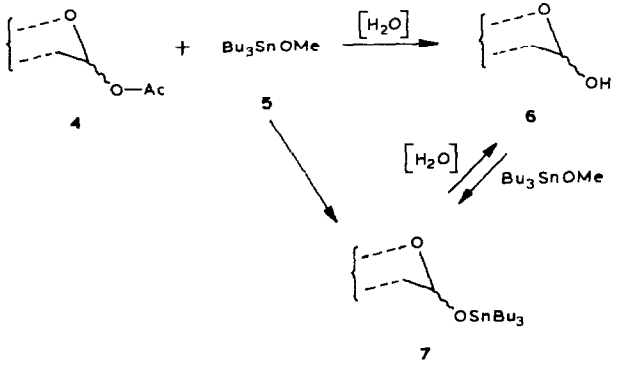
Most of the reported syntheses of 1-hydroxy sugars (**1**, Y = OH) are cumbersome, expensive, and involve the conversion of an anomeric acetate (**1**, Y = OAc) into a glycosyl bromide (**1**, Y = Br) and hydrolysis with a silver salt[6]. The use of stannic chloride–water[7a] and such nitrogenous nucleophiles as benzylamine[7b], pipe-

*Studies in Sugar Chemistry, Part IV. For Part III, see ref 1.
**To whom correspondence should be addressed.
†Holder of the Joseph and Madeleine Nash career development chair established by Fondacion Madelon, Zurich, Switzerland.

0008-6215/87/$ 03.50

ridine[7c], or hydrazine[7d] for the preparation of 1-hydroxy sugars from the corresponding polyacetates has been described.

We now report a simple, high-yielding reaction (**4** → **6**) for the selective, and frequently exclusive, deacetylation of various polyacetylated sugars at the anomeric position by treatment with an equimolar amount of tributyltin methoxide[8] (**5**) in a refluxing inert solvent (tetrahydrofuran, 1,2-dichloroethane, benzene, toluene) for 1–3 h. The rate of the reaction was appreciable even at room temperature. Bis(tributyltin) oxide could also be used (*cf.* ref. 9); although it was somewhat easier to handle than **5**, since it is not water-sensitive, the side product of the reaction, tributyltin acetate, was difficult to remove. The products (**6**) were isolated by chromatography, usually in high yields. The 1-*O*-tin derivatives **7** were efficiently hydrolysed on silica gel either by reaction with absorbed water or with silanol groups present in the adsorbent. Alternatively, **7** could be hydrolysed conveniently with dilute hydrochloric acid. The resulting tributyltin chloride was readily extracted into hexane, leaving the crystalline free sugars **6**. This procedure is suitable for large-scale syntheses. If the work-up was carried out under non-hydrolysing conditions, the 1-*O*-$SnBu_3$ derivatives **7** could be isolated in good yields. Compounds **7** may also be prepared by stannylation of **6** with Bu_3SnOMe or $(Bu_3Sn)_2O$. The fact that the derivatives **7** can be obtained from the tin oxide questions the contention[10a] that esters R′COOR″ react with $(Bu_3Sn)_2O$ to give R′COO$SnBu_3$ and ethers R″OR″. Our results accord with the data of Davies and co-workers[10b].



The reactions **4** → **6** can be monitored by t.l.c. or by ^{1}H-n.m.r. spectroscopy. In the presence of 1 mol of tin reagent, the reaction of AcO-1 was complete within 1 h. The remaining acetyl groups were much less reactive and, even with an excess of Bu_3SnOMe, only partial additional deacetylation was observed after 25-h reflux in 1,2-dichloroethane and at least 25% of the monodeacetylated products remained.

The β-forms of **4** reacted faster and gave higher yields of deacetylated products than the α-forms (Fig. 1), the reactions of which were often not complete. Compounds (**4a**, **4b**, and **4e**) that did not contain CH_2OAc groups reacted exclusively at the anomeric centre. The CH_2OAc groups in β-compounds (β-**4c**, **4f**) were

resistant but, in the α-forms (α-**4c**, α-**4d**), they were hydrolysed together with AcO-1. Both primary and secondary benzoates (**4g**) and acetals (**4b**) were inert. In the absence of an anomeric acetyl group (**4h**), both primary and secondary acetyl groups could be removed, but this requires more vigorous conditions.

The products **6** were α,β-mixtures, and the α,β-ratio could be determined by n.m.r. spectroscopy. For **6b**, the α-form was obtained almost exclusively. The α,β-ratio of the hydroxy product **6c** from α-**4c** or β-**4c** was the same and probably reflects thermodynamic equilibrium. For the 1-hydroxy glucuronic acid derivative **6a**, a ~4:1 α,β-mixture was indicated by the n.m.r. spectrum[1]. Braun and Wiessler[6f], on the basis of n.m.r. spectra, claimed that **6a** was exclusively α.

Table I contains the substrates examined (**4a–4h**) and the products obtained (**6a–6k**, **7**).

The higher rates and selectivities of reactions of the β-derivatives indicate a mechanism that includes initial complexation of tin to the ring oxygen[11] (**9**). The relative rigidity and proximity of AcO-1β facilitates transesterification to yield the corresponding *O*-tin derivative **7**, formed directly from **9** or *via* **10**, with which it rapidly equilibrates. The stereochemistry of the α-anomers is less favorable for these interactions. The other acetyl groups cannot form the intermediate **10** because of the unavailability of a suitably labile C–O bond. AcO-1α seems to be about as reactive to Bu_3SnOMe as is AcO-6 (**12**). Under non-hydrolysing conditions, the intermediates **7** can be isolated or converted directly into allyl glycosides **11** *via* Pd^0-catalysed reactions[12]. Hydrolysis gives the corresponding α,β-mixture **6**. Both **7** and **6** were α,β-mixtures. The formation of α,β-mixtures from α- or β-**8** may reflect an equilibrium between the acyclic intermediate **10** and the cyclic product **7**. N.m.r. spectroscopy indicated that, when α-**7** was dissolved in $CDCl_3$, anomerisation occurred within 15 min at 55°. Apparently, the *O*-tin bond (in contrast to the *O*-acyl bond) is labile and can equilibrate readily. The equilibrium may be understood in terms of steric effects which will favour the β-configuration, on the one hand, and the

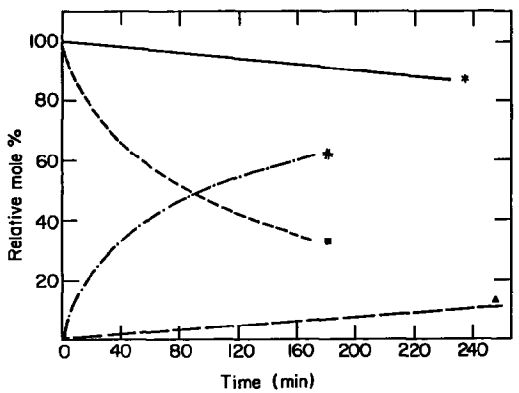
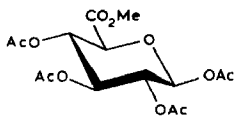
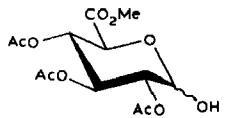
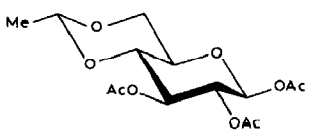
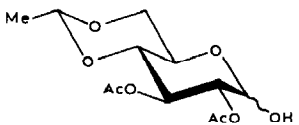
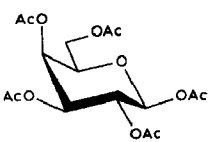
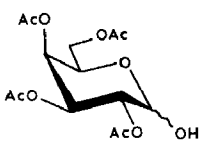
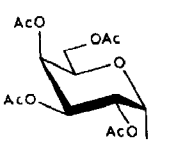
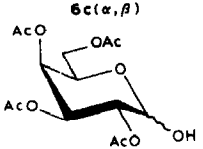
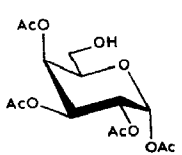


Fig. 1. Rate of stannylation of α,β-**4b** and corresponding formation of **7**: *, decrease of α-**4b**; #, increase of α,β-**7** from β-**4b**; ■, decrease of β-**4b**; ▲, increase of α,β-**7** from α-**4b**.

TABLE I

SELECTED REACTION CONDITIONS AND PRODUCTS

Starting material	*Product(s)*	*Reaction conditions*[a]	*Reacted starting material (%)*	*Isolated yield (%)*	*Product α,β-ratio*	*Ref.*
 **4a(β)**	 **6a(α,β)**	1.25 h, 70°, A	>90	78	4:1	6
 **4b(β)**	 **6b(α,β)**	1 h, 70°, B	85	77	74:1	13
 **4c(β)** [b]	 **6c(α,β)**	1,25 h, 85°, B	90	80	2:1	14
 **4c(α)** [b]	 **6c(α,β)**	3 h, 70°, B	65	26 26	2:1	15
	 **6d(α)**					

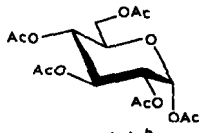
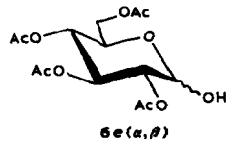
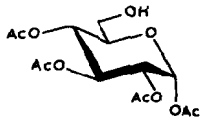
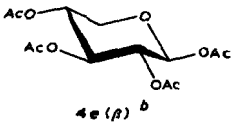
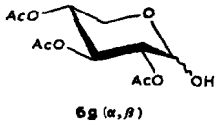
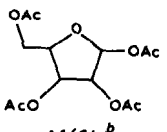
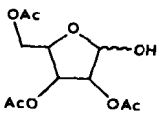
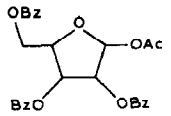
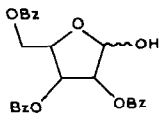
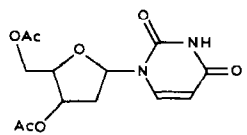
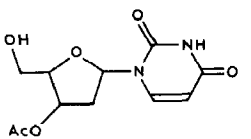
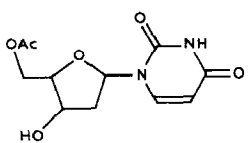
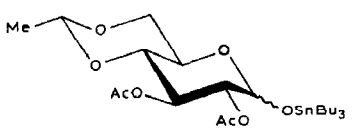
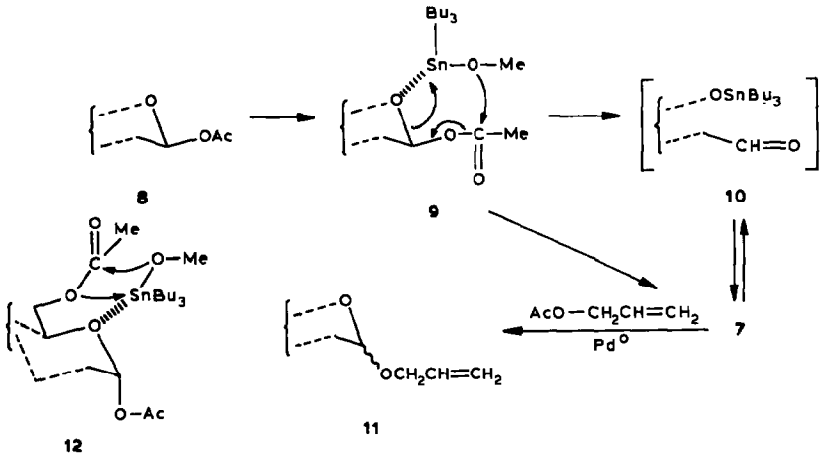
 4d (α) [b]	 6e (α,β)	1.5 h, 110°, C	75	31	7:2	7d,14a,b
	 6f (α)			*10*		16
 4e (β) [b]	 6g (α,β)	1.5 h, 85°, B	90	76	3.2:1	7d,17
 4f (β) [b]	 6h (α,β)	1 h, 85°, B	>90	80	0.46:1	18a

TABLE I *(continued)*

Starting material	*Product(s)*	*Reaction conditions*[a]	*Reacted starting material (%)*	*Isolated yield (%)*	*Product α,β-ratio*	*Ref.*
 4g (β) [b]	 6i (α,β)	2.5 h, 80°, B	80	75	0.44:1	18a,b
 4h (β)	 6j (β)	6 h, 85°, B	60	31		19
	 6k (β)			23		
4b (β)	 7 (α,β)	1 h, 85°, B	100	95	0.82:1	

[a] *A*, Tetrahydrofuran; B, 1,2-dichloroethane; C, toluene. [b] Commercial product.



Scheme 1.

anomeric effect which favours the α-orientation, on the other hand. The rapid anomerisation of the 1-*O*-$SnBu_3$ intermediate prevents a correlation between the anomeric configuration of the acetate and that of the stannyl ether.

EXPERIMENTAL

General. — ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with Bruker WH-270 and AM-300 spectrometers. All reactions were carried out under anhydrous conditions in flame-dried glass apparatus under nitrogen, using dry, freshly distilled solvents. Bu_3SnOMe or $(Bu_3Sn)_2O$ were commercial products. Reactions were monitored by t.l.c. on silica gel (Merck, 5554), using ethyl acetate–hexane mixtures and detection by charring with sulfuric acid. Flash column chromatography was carried out on silica gel (Merck, 9385).

General procedure. — Bu_3SnOMe (1 mmol) was added with stirring to a solution of the substrate (1 mmol) in an appropriate solvent (5–20 mL). Stirring and boiling under reflux was continued for 1–3 h. The solvent was then removed under reduced pressure and the residue was subjected to flash chromatography. Alternatively, the cooled reaction mixture was extracted with aqueous 5% HCl (1 vol.), and the organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The viscous residue was triturated thrice with hexane, and the insoluble material was crystallised from ether–hexane to give the products **6**, which were identified by ^{1}H-n.m.r. spectroscopy. The m.p. and $[\alpha]_D$ value of each product corresponded to those in the literature.

*Preparation of tributyl (2,3-di-*O*-acetyl-4,6-*O*-ethylidene-α,β-*D*-glucopyranosyloxy)tin* **7**. — Bu_3SnOMe (115 mL, 0.4 mol) was added with stirring to a solution of β-**4b** (0.4 mol) in 1,2-dichloroethane (600 mL). The mixture was heated under reflux for 1 h and then concentrated under reduced pressure to give α,β-**7** (quantitative yield). Crystallisation from hexane gave α-**7**, m.p. 82–85°, $[\alpha]_D^{25}$ +74° (*c* 1, dichloromethane). The β-isomer was not isolated pure.

Anal. Calc. for $C_{24}H_{41}O_8Sn$: C, 50.03; H, 7.17. Found: C, 50.22; H, 7.47.

REFERENCES

1 J. HERZIG AND A. NUDELMAN, *Carbohydr. Res.*, 153 (1986) 162–167.
2 (*a*) W. KOENIGS AND E. KNORR, *Ber.*, 34 (1901) 957–981; (*b*) I. IGARASHI, *Adv. Carbohydr. Chem. Biochem.*, 34 (1977) 243–283; (*c*) D. KEGLEVIC, *ibid.*, 36 (1979) 57–134; (*d*) K. C. NICOLAOU, S. P. SEITZ, AND D. P. PAPAHATJIS, *J. Am. Chem. Soc.*, 105 (1983) 2430–2434.
3 (*a*) B. HELFERICH AND E. SCHMITZ-HILLBERECHT, *Ber.*, 66 (1933) 378–383; (*b*) R. U. LEMIEUX AND W. P. SHYLUK, *Can. J. Chem.*, 31 (1953) 528–535; (*c*) K. HONMA, K. NAKAZIMA, J. UEMATSU, AND A. HAMADA, *Chem. Pharm. Bull.*, 24 (1976) 394–399; (*d*) G. MAGNUSSON, G. NOORI, J. DAHMEN, T. FREJD, AND T. LAVE, *Acta Chem. Scand., Ser. B*, 35 (1981) 213–216.
4 (*a*) R. R. SCHMIDT AND G. GRUNDLER, *Synthesis*, (1981) 885–887; (*b*) R. R. SCHMIDT, M. STUMPP, AND J. MICHEL, *Tetrahedron Lett.*, 23 (1982) 405–408; (*c*) H. TSUSTSUMI AND Y. ISHIDO, *Carbohydr. Res.*, 88 (1981) 61–75; (*d*) K. HOJO, H. YOSHINO, AND T. MUKIYAMA, *Chem. Lett.*, (1977) 437–440; (*e*) S. KOTO, T. SATO, N. MORISHIMA, AND S. ZEN, *Bull. Chem. Soc. Jpn.*, 53 (1980) 1761–1762; (*f*) W. A. SZAREK, H. C. JARRELL, AND J. K. N. JONES, *Carbohydr. Res.*, 57 (1977) c13–c16; (*g*) L. TIETZE, R. FISHER, AND H. GUDER, *Synthesis*, (1982) 946–948; (*h*) M. KUHN AND A. VON WARTBURG, *Helv. Chim. Acta*, 51 (1968) 1631–1641.
5 (*a*) M. HAYASHI, S. HASHIMOTO, AND R. NOYORI, *Chem. Lett.*, (1984) 1747–1750; (*b*) W. A. SZAREK, G. GRINKIEWICZ, B. DOBOSZEWSKI AND W. G. HAY, *ibid.*, (1984) 1751–1754.
6 (*a*) D. REYNOLDS AND W. L. EVANS, *Org, Synth. Coll. Vol. III*, (1965) 432; C. M. MCCLOSKEY, AND G. H. COLEMAN, *ibid.*, 434; (*c*) G. N. BOLLENBACK, J. W. LONG, D. G. BENJAMIN, AND J. A. LINDQUIST, *J. Am. Chem. Soc.*, 77 (1955) 3310–3315; (*d*) M. ISHIDATE AND T. NAKAJIMA, *Chem. Pharm. Bull.*, 6 (1958) 433–437; (*e*) N. PRAVDIC AND D. KEGLEVIC, *J. Chem. Soc.*, (1964) 4633–4635; (*f*) H. BRAUN AND M. WIESSLER, *Angew. Chem. Int. Ed. Engl.*, 19 (1980) 400–401; (*g*) F. COMPERNOLLE, *Carbohydr. Res.*, 86 (1980) 177–183.
7 (*a*) A. BANASZEK, X. B. CORNET, AND A. ZAMOJSKI, *Carbohydr. Res.*, 144 (1985) 342–345; (*b*) B. HELFERICH AND W. PORTZ, *Chem. Ber.*, 86 (1953) 604–612; (*c*) R. M. ROWELL AND M. S. FEATHER, *Carbohydr. Res.*, 4 (1967) 486–491; (*d*) G. EXCOFFIER, D. GAGNAIRE, AND J. P. UTILLE, *Carbohydr. Res.*, 39 (1975) 368–373.
8 (*a*) A. G. DAVIES, *Synthesis*, (1969) 56–64; (*b*) J. POMMIER AND M. PEREYRE, *Adv. Chem. Secr.*, 157 (1976) 82–109, and references therein.
9 Jpn. Kokai Tokkyo Koho JP 58,144,396 (1983); *Chem. Absir.* 100 (1984) 103811c.
10 (*a*) H. H. ANDERSON, *J. Org. Chem.*, 19 (1954) 1766–1769; (*b*) A. G. DAVIES, T. N. MITCHEL, AND W. R. SYMES, *J. Chem. Soc., C*, (1966) 1311–1315.
11 (*a*) K. STELIOU. A. SZCZYGIELSKA-NOWOSIELSKA, A. FAVRE, M. A. POUPART, AND S. HANESSIAN, *J. Am. Chem. Soc.*, 102 (1980) 7578–7579; (*b*) Y. TSUDA, E. HAGUE, AND K. YOSHIMOTO, *Chem. Pharm. Bull.*, 31 (1983) 1612–1614; (*c*) T. OGAWA AND M. MATSUI, *Carbohydr. Res.*, 56 (1977) c1–c6; *Tetrahedron*, 37 (1981) 2363–2369.
12 E. KEINAN, M. SAHAI, Z. ROTH, A. NUDELMAN, AND J. HERZIG, *J. Org. Chem.*, 50 (1985) 3558–3566.
13 A. M. HALL, AND O. A. STAMM, *Carbohydr. Res.*, 12 (1970) 421–428.
14 (*a*) C. M. MCCLOSKEY, R. E. PYLE, AND G. H. COLEMAN, *J. Am. Chem. Soc.*, 66 (1944) 349–350; (*b*) B. HELFERICH AND R. STEINPREIS, *Chem. Ber.*, 91 (1958) 1794–1798; (*c*) J. COMPTON AND M. L. WOLFROM, *J. Am. Chem. Soc.*, 56 (1934) 1157–1161; (*d*) R. BOGNAR AND P. NANASI, *Tetrahedron*, 14 (1961) 175–189.
15 A. K. BHATTACHARJEE, E. ZISSIS, AND C. P. J. GLAUDEMANS, *Carbohydr. Res.*, 89 (1981) 249–254.
16 K. HEYNS AND M. T. LIM, *Tetrahedron Lett.*, (1978) 891–894.
17 (*a*) B. HELFERICH AND W. OST, *Chem. Ber.*, 95 (1962) 2616–2622; (*b*) C. S. HUDSON, AND J. K. DALE, *J. Am. Chem. Soc.*, 40 (1928) 997–1001.
18 (*a*) C. CHAVIS, F. DUMONT, AND J. L. J. IMBACH, *J. Carbohydr. Nucleot. Nucleos.*, 5 (1978) 133–147; (*b*) R. K. NESS, H. W. DIEHL, AND H. G. FLETCHER, JR., *J. Am. Chem. Soc.*, 76 (1954) 763–767.
19 (*a*) A. M. MICHELSON AND A. R. TODD, *J. Chem. Soc.*, (1955) 2632–2638; (*b*) R. W. BINKLEY, D. H. HEHEMANN, AND W. W. BINKLEY, *J. Org. Chem.*, 43 (1978) 2573–2576; (*c*) Y. ISHIDO, N. NOKAZAKI, AND N. SAKAIRI, *J. Chem. Soc., Perkin Trans. 1*, (1979) 2088–2098.