A Convenient Synthesis of Substituted Chiral Tetrahydrofurans from Sugar γ-Lactones

Yves Chapleur

Laboratoire de Chimie Organique III, ERA CNRS n° 558, Université de Nancy I, B.P. 239, 54506 Vandoeuvre les Nancy Cédex, France

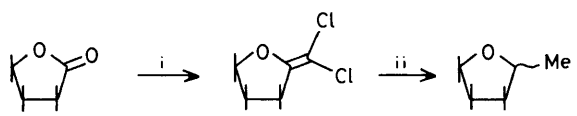
Sugar γ-lactones react with hexamethylphosphorous triamide–tetrachloromethane to give dichloro-olefins in one step; these are then reduced to optically active tetrahydrofurans.

Sugar lactones are readily available, cheap starting materials. Their use in the elaboration of other carbohydrates,[1] nucleosides,[2] or other chiral structures[3] has been little explored in spite of the high functionality present in these lactones. Although reduction of the carbonyl group to hemiacetal has been used to prepare rare sugars, nucleophilic additions onto the carbonyl group have rarely been studied.[2,4] As part of our studies on the formation of C–C bonds on carbohydrates,[5] we report here our preliminary results on the dichloromethylenation at C(1) of sugar lactones and their transformation to optically active tetrahydrofurans. Such units bearing a methyl group adjacent to the ring oxygen are often the skeleton of natural products such as muscarines,[6] furanomycin,[7] boromycine, and aplasmomycine.[8] On the other hand, these chiral furans may be regarded as *C*-glycosides and therefore *C*-nucleoside precursors, whose importance is now well established.[9]

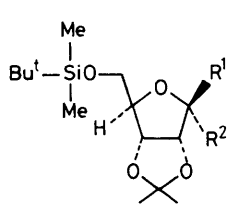
We reasoned that γ-lactones derived from sugars would be ideal starting materials for the formation of a C–C bond at C(1). Nucleophilic attack at C(1) followed by deoxygenation would provide entry to the desired structure. The intermediate lactol would retain a cyclic rather than an open chain structure,† that would favour the deoxygenation step (Scheme 1).

We then turned our attention to Wittig-type reagents which are well known to deoxygenate aldehydes and ketones. The replacement of a carbonyl group by a dihalogenomethylene group has been described with phosphorus based reagents[10] and recently with a reagent containing silicon.[11] To the best of our knowledge this reaction has not been applied to lactones.

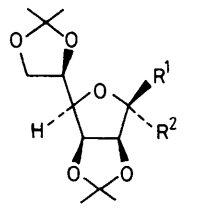
We found that the complex formed by slow addition of hexamethylphosphorous triamide (2 equiv.) to a solution of tetrachloromethane (3 equiv.) in dry tetrahydrofuran at −30 °C reacted smoothly with several γ-lactones to give dichloro-olefins.‡ The reaction could be also carried out, by addition of the phosphine to a mixture of tetrachloromethane and lactone, with identical results. Triphenylphosphine could not be used instead of hexamethylphosphorous triamide. This fact indicated a non-ylide type reaction as triphenylphosphine could give phosphorane whereas hexamethylphosphorous triamide could not.[12] A nucleophilic attack on the carbonyl group by the trichloromethylide anion followed by formation of the dichloromethylene group[10d] seems to be the most probable route. However, replacement of tetrachloromethane by tetrabromomethane gave a complex mixture which darkened rapidly at −30 °C. The results obtained with the lactones (**1a**)—(**4a**) are summarized in Table 1.§



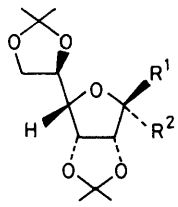
Scheme 1. i, $P(NMe_2)_3$–CCl_4, tetrahydrofuran, −30 °C; ii, Raney Ni–H_2, AcOEt.



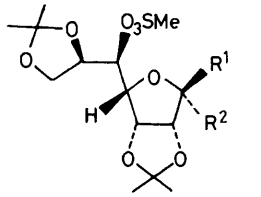
(1)
a; $R^1,R^2=O$
b; $R^1,R^2=CCl_2$
c; $R^1=H$, $R^2=Me$
d; $R^1=Me$, $R^2=H$



(2)
a; $R^1,R^2=O$
b; $R^1,R^2=CCl_2$
c; $R^1=Me$, $R^2=H$



(3)
a; $R^1,R^2=O$
b; $R^1,R^2=CCl_2$
c; $R^1=H$, $R^2=Me$



(4)
a; $R^1,R^2=O$
b; $R^1,R^2=CCl_2$
c; $R^1=H$, $R^2=Me$

Table 1. The dichloro-olefins obtained from the γ-lactones (**1a**)—(**4a**).

Starting material	Product	Reaction time/h	Temp. °C	Yield (%)	M.p. °C	$[\alpha]_D^{22}$ [a]/°
(**1a**)	(**1b**)	3	0	52	—	−145
(**2a**)	(**2b**)	1	−30	79	—	+172
(**3a**)	(**3b**)	1	−30	92	—	−175
(**4a**)	(**4b**)	1	−30	67	—	−112

[a] *c*, 0.5, $CHCl_3$.

† The presence of a dioxolane ring joined to the lactone ring will favour the cyclic lactol structure.

‡ In a typical experiment hexamethylphosphorous triamide (2.2 mM) was added dropwise to a solution of tetrachloromethane (3.3 mM) in dry tetrahydrofuran at −30°C under argon. A white precipitate was obtained. The suspension was stirred for 10 min and the lactone (1 mM) in tetrahydrofuran was added. The mixture was stirred under the conditions given in Table 1. The products (**1b**)—(**4b**) were isolated by conventional extraction with diethyl ether and purified by column chromatography on silica gel.

§ The dichloro-olefins (**1b**)—(**4b**) showed an i.r. absorption at 1660 cm^{-1}. The structures of (**1b**)—(**4b**) and (**1c**)—(**4c**) were supported by ^1H n.m.r. spectroscopy.

Table 2. Results of the hydrogenation of the dichloro-olefins (**1b**)—(**4b**).

Starting material	Product	Yield (%)	M.p. °C	$[\alpha]_D^{22a}$/°
(**1b**)	(**1c**)+(**1d**)[b]	82	—	−4.4
(**2b**)	(**2c**)	71	—	−20.8
(**3b**)	(**3c**)	90	68	+21
(**4b**)	(**4c**)	72	—	+2.2

[a] *c*, 0.5, $CHCl_3$. [b] Mixture of (**1c**) and (**1d**) in the ratio 9 : 1 (estimation from n.m.r. analysis); only pure (**1c**) was obtained by chromatography.

The transformation of the dichloromethylene group into a methyl group was achieved cleanly by the use of freshly prepared Raney nickel. The *C*-glycosides were isolated in high yield as a single isomer except for (**1b**). In this case, the ^1H n.m.r. analysis showed the presence of the two isomers (**1c**) and (**1d**) in the ratio 9 : 1. As expected hydrogenation of (**1b**)—(**4b**) occurred mainly from the side opposite the isopropylidene group, thus giving a stereospecific access to *C*(1)-methyl sugars (Table 2).[13]

It is a pleasure for me to acknowledge Professor B. Gross for his constant encouragement.

Received, 20th January 1984; Com. 076

References

1 For reviews see: K. Dax and H. Weidmann, *Adv. Carbohydr. Chem. Biochem.*, 1976, **33**, 231; T. C. Crawford, *ibid.*, 1981, **38**, 287.
2 W. A. Asbun and S. B. Binkley, *J. Org. Chem.*, 1968, **33**, 140; H. Ogura, H. Takahashi, and T. Itoh, *ibid.*, 1972, **37**, 72; H. Ogura, K. Furuhata, H. Takahashi, and Y. Iitaka, *Chem. Pharm. Bull.*, 1978, **26**, 2782.
3 G. Stork, T. Takahashi, I. Kawamoto, and T. Suzuki, *J. Am. Chem. Soc.*, 1978, **100**, 8272.
4 R. H. Hall, K. Bischofberger, S. J. Eitelman, and A. Jordaan, *J. Chem. Soc., Perkin Trans.* 1, 1977, 743, 2236; J. M. Lancelin, P. Avam-Zollo, and P. Sinaÿ, *Tetrahedron Lett.*, 1983, **24**, 4833.
5 Y. Chapleur, *J. Chem. Soc., Chem. Commun.*, 1983, 141.
6 For a recent synthesis see: S. Pochet and T. Huynh-Dinh, *J. Org. Chem.*, 1982, **47**, 193.
7 M. M. Joullié, P. C. Wang, and J. E. Semple, *J. Am. Chem. Soc.*, 1980, **102**, 887.
8 Boromycine: S. Hanessian, P. C. Tyler, G. Demailly, and Y. Chapleur, *J. Am. Chem. Soc.*, 1981, **103**, 6243; aplasmomycine: E. J. Corey, B. Chuan-Pan, D. H. Hua, and D. R. Deardorff, *ibid.*, 1982, **104**, 6816.
9 F. Baumberger and A. Vasella, *Helv. Chim. Acta*, 1983, **66**, 2210 and refs. 34–48 in this paper. For a review see S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, 1976, **33**, 111.
10 (a) R. Rabinowitz and R. Marcus, *J. Am. Chem. Soc.*, 1962, **84**, 1312; (b) D. J. Burton and J. R. Greenwald, *Tetrahedron Lett.*, 1967, 1535; (c) B. Castro, R. Burgada, G. Lavielle, and J. Villieras, *Bull. Soc. Chim. Fr.*, 1969, 2770; (d) J. C. Combret, J. Villieras, and G. Lavielle, *Tetrahedron Lett.*, 1971, 1035; (e) P. Savignac, J. Petrova, M. Dreux, and P. Coutrot, *Synthesis*, 1975, 535. For an application to keto-sugars see: (f) J. M. J. Tronchet, A. Bonenfant, and F. Barbalat-Rey, *Carbohydr. Res.*, 1978, **67**, 564.
11 A. Hosomi, M. Inaba, and H. Sakurai, *Tetrahedron Lett.*, 1983, **24**, 4727.
12 R. Appel, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 801.
13 For the synthesis of a C(1)-methyl glycopyranose derivative see: J. R. Pougny, M. Nassr, and P. Sinaÿ, *J. Chem. Soc., Chem. Commun.*, 1981, 375.