Stereocontrolled Synthesis of *C*-Glycosides by Reaction of Organocuprates with Protected 1,2-Anhydro Sugars, and their Transformation into 2-Deoxy-*C*-glycosides

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The reaction of protected 1,2-anhydro sugars with organocuprates provides a new stereocontrolled synthesis of *C*-glycosides, the deoxygenation of which affords 2-deoxy-*C*-glycosides in high yield.

As part of a continuing programme on *C*-glycosides synthesis,[1] we describe a new method for stereocontrolled formation of a C–C bond at the anomeric centre of a glycopyranoside unit.

Most of the methods for *C*-glycoside synthesis involve attack by a carbon nucleophile on a suitably activated anomeric carbon of protected sugar derivatives. These methods generally give a mixture of α- and β-anomers especially when applied to 2-deoxy-glycosyl derivatives, as neighbouring group participation is not possible in this case.

Opening of an oxirane ring by an organocuprate is known to proceed *anti* to the oxygen atom.[2] This reaction has been well documented in carbohydrate chemistry for the preparation of branched-chain sugars.[3,4] However, to the best of our knowledge, no attempts were made with 1,2-anhydro sugars. 3,4,6-Tri-*O*-acetyl-1,2-anhydro-α-D-*gluco*-pyranose (**1**)[5] (Brigl's anhydride) and 3,4,6-tri-*O*-benzyl-1,2-anhydro-β-D-*manno*-pyranose (**2**)[6] were chosen as model compounds to evaluate the synthetic use and the stereochemical outcome of the title reaction (Scheme 1).

Treatment of Brigl's anhydride with lithium dimethyl and diphenyl cuprate in anhydrous ether at low temperature, followed by quenching with Ac_2O afforded the expected β-D-glycopyranoside (**3**) (Scheme 2) in moderate yield (see Table 1). The β-D-configuration was confirmed by a large coupling constant between 1-H and 2-H ($J_{1,2}$ 9.6 or 9.8 Hz) and the absence of an α-D-anomer was verified by g.l.c. analysis of the crude mixture. In fact several by-products formed by competitive elimination [3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**4**)] or substitution by iodide† were also formed, isolated, and fully characterised.[7]

Contrary to previous claims concerning the inertness of organocuprates in reactions with ester functions, partial deacetylation of the starting material was observed during the reaction resulting in the formation of non-identified polar compounds. So acetylation of the crude mixture was necessary.

With the *manno* isomer (**2**), protected by more stable benzyl groups, the reaction was clean and no by-products were formed so the yield was near-quantitative even without acetylation of the product (see Table 1). According to Fürst–Plattner's rules,[8] the opening occurred in a *trans* diaxial way affording exclusively the α-D-*C*-glycoside. The differentiation of the C(2) hydroxyl in the resulting C-glycoside allowed further deoxygenation at that position (Scheme 3). The 2-deoxy-α-D-*C*-glycoside (**6**) was isolated in good yield (84%) and its configuration was confirmed by ^1H n.m.r. spectroscopy (1-H δ 5.12; $J_{1,2_{ax}}$ 4.7 Hz and $J_{1,2_{eq}}$ 3.7 Hz).

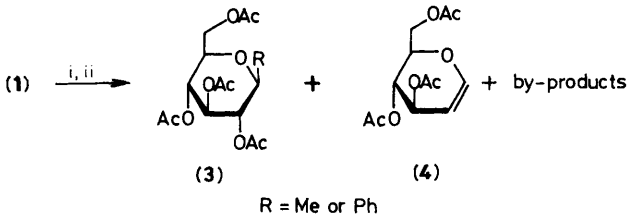
The same sequence of reactions applied to 3,4,6-tri-*O*-benzyl-1,2-anhydro-α-D-*gluco*-pyranose (**1a**) would afford a

Table 1.

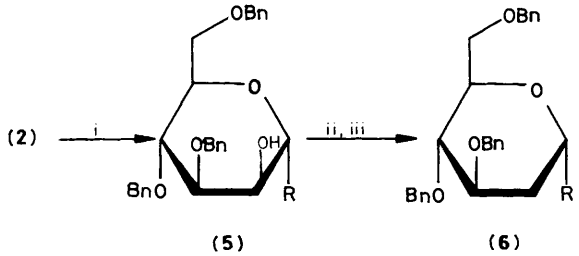
Entry	Starting material	Organocuprate (2.2 equiv.)	Yield[a] (%) of isolated *C*-glycoside[b,c]
1	(**1**)	Me_2CuLi	65.5[d]
2	(**1**)	$Me_2CuCNLi_2$	25[d]
3	(**1**)	Ph_2CuLi	25
4	(**2**)	Me_2CuLi	90
5	(**2**)	Ph_2CuLi	70[e]

[a] Yield of isolated *C*-glycoside after purification by flash chromatography. [b] Isolated *C*-glycoside after quenching with Ac_2O, unless otherwise stated. [c] All compounds gave satisfactory analytical and spectral data. [d] Formation of compound (**4**) in only two cases (entry 1 : 12%; entry 2 : 10%). [e] *C*-Glycoside (**5**) obtained without quenching with Ac_2O.

Scheme 1



Scheme 2. *Reagents*: i, R_2CuLi, −20 to 0 °C, Et_2O; ii, Ac_2O.



Scheme 3. *Reagents*: i, R_2CuLi, Et_2O; ii, PhOCSCl, 4-dimethylaminopyridine; iii, Bu_3SnH, azoisobutyronitrile.

† Copper iodide was used to prepare the organocuprate.

2-deoxy-β-D-*C*-*arabino*-pyranoside in a stereospecific manner.

It has been verified that hydrogenolysis of the benzyl groups could be carried out without cleavage of the pyranoside ring.

Since the outcome of the reaction is controlled only by the oxirane ring, this new method of C–C bond formation at the anomeric carbon could be applied to the synthesis of other *C*-glycosides.

The transformation into 2-deoxy derivatives is also general and compatible with a variety of protective groups.[9] The examples illustrated here are of particular interest because they lead to compounds containing a 2-deoxy-*arabino*-hexopyranosyl moiety, a substructure present in many natural compounds.[10]

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References

1 For Part V of the Series *C*-Glycosides, see V. Bellosta and S. Czernecki, *Carbohydr. Res.*, 1987, **171**, 279.
2 G. H. Posner, *Org. React. (N.Y.)*, 1975, **22**, 253; B. H. Lipshutz, R. S. Wilhelm, and J. A. Kozlowski, *Tetrahedron*, 1984, 5005.
3 D. R. Hicks and B. Fraser-Reid, *Can. J. Chem.*, 1975, **53**, 2017.
4 J. Yoshimura, N. Kawauchi, T. Yasumori, K.-I. Sato, and H. Hashimoto, *Carbohydr. Res.*, 1984, **133**, 255; J. Yoshimura, *Adv. Carbohydr. Chem. Biochem.*, 1984, **42**, 69.
5 P. Brigl, *Hoppe-Seyler's Z. Phyziol. Chem.*, 1921, **116**, 1; 1922, **122**, 245; R. U. Lemieux and J. Howard, 'Methods in Carbohydrate Chemistry,' Academic Press Inc., New York and London, 1963, vol. 2, p. 400.
6 S. J. Sondheimer, H. Yamaguchi, and C. Schuerch, *Carbohydr. Res.*, 1979, **74**, 327.
7 V. Bellosta, Ph.D. Thesis, Université P. et M. Curie, 1987.
8 A. Fürst and P. A. Plattner, Abstr. Papers. Int. Congr. Pure Appl. Chem., 12th, New York, 1951, p. 409; J. A. Mills, addendum to F. H. Newth and R. F. Homer, *J. Chem. Soc.*, 1953, 989.
9 M. J. Robbins, J. S. Wilson, and F. Hansske, *J. Am. Chem. Soc.*, 1983, **105**, 4059.
10 For examples see: U. Hacksell and G. D. Daves, Jr., *Prog. Med. Chem.*, 1985, **22**, 3.