The First Direct Method for *C*-Glucopyranosyl Derivatization of 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose

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Commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, activated by trifluoroacetic anhydride reacts, in the presence of Lewis acids, with various silyl enol ethers or with allylsilane to yield *C*-D-glucopyranosyl derivatives of the α-configuration, and with activated aromatic nucleophiles to yield the corresponding β-anomers.

Efficient and stereo-controlled methods for the synthesis of *C*-glycosyl derivatives are of interest for the preparation of naturally occurring *C*-glycosides and to obtain chiral templates for more complex synthetic targets.[1,2] Several methods have been developed to obtain both *C*-α- and *C*-β-glycopyranosyl derivatives using different pyranosyl substrates such as *p*-nitrobenzoate,[3a] bromide,[3b] fluoride,[3c,d] chloride,[1,3c] trichloroacetamidate,[3f] and 2′-thiopyridylate[3c] to activate the C-1 carbon. Recently, organometallic approaches have also been reported.[4]

Now we report the first successful direct *C*-glucosylation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose in a one pot reaction by simple treatment with trifluoroacetic anhydride and successive addition of the nucleophile in the presence of a Lewis acid.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**1**) (1 equiv.) was allowed to react with trifluoroacetic anhydride (1.1 equiv.) in dichloromethane (20 ml) for 30 min, then the nucleophile (5 equiv.) dissolved in dichloromethane was added, followed by the Lewis acid (3 equiv.). Table 1 shows some examples† and reaction conditions.

The products reported in entries 1—4, 6, and 8 were identical (^{1}H n.m.r. spectra, optical rotation, m.p.) to those obtained previously by reported methods.[1]

† New compounds gave satisfactory analytical data.

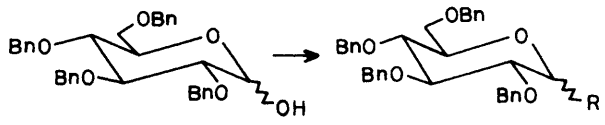
Assignment of the α-configuration for the product in entry 5 was arrived at by conversion into the known[1] (2,3,4,6-tetra-*O*-benzyl-D-α-glucopyranosyl)methyl acetate *via* Bayer–Villiger oxidation [$(CF_3CO)_2O$, 30% H_2O_2, CH_2Cl_2], and transesterification (MeONa, MeOH).

Assignment of the β-configuration of the glucosidic bond for the product in entry 7 was based on inspection of the ^{1}H n.m.r. spectrum of the corresponding acetate, m.p. 107—108 °C $[\alpha]_D^{20}$ − 24° obtained after debenzylation (H_2, Pd on carbon, EtOH, room temp.) and then acetylation (Ac_2O, 4-*N*,*N*-dimethylaminopyridine, pyridine, room temp.). In fact a very high field three-proton signal for the acetate group (δ 1.7) indicated the acetate group of a *C*-β-D-glucopyranosyl fragment,[5] while two doublets centred at δ 6.82 (*J* 9 Hz) and δ 7.28 (*J* 9 Hz), indicated *para*-substitution in the aromatic ring.

The result obtained with anisole (entry 7) is also of interest since it shows that a weakly activated aromatic nucleophile is able to react using this method.

It appears reasonable that the reaction involves the initial formation of the corresponding 1-trifluoroacetate which, by action of the Lewis acid, evolves to a pyranoxonium trifluoroacetate which would preferentially accept the nucleophile from the α (axial) side.[1] Support for this hypothesis was obtained by treating the tetrabenzylglucose with trifluoroacetic anhydride under the reaction conditions and evaporating off the solvent and the trifluoroacetic acid formed. An easily hydrolysable oil which showed a doublet at δ 5.71 (*J* 7.5

Table 1. Synthesis of *C*-glucosyl derivatives from (**1**).



(**1**)

Bn = $PhCH_2$

Entry	Nucleophile	Product R-substituent	Lewis acid	Time/min	Yields[a], %	Stereochemistry
1	$MeC(OSiMe_3)=CH_2$	CH_2COMe[b]	$ZnCl_2$	300	45	α
2	$Bu^tC(OSiMe_3)=CH_2$	CH_2COBu^t[b]	$BF_3{\cdot}Et_2O$	45	50	α
3	$PhC(OSiMe_3)=CH_2$	CH_2COPh[b]	$BF_3{\cdot}Et_2O$	15	75	α
4	$p\text{-}ClC_6H_4C(OSiMe_3)=CH_2$	$CH_2COC_6H_4Cl\text{-}p$[b]	$BF_3{\cdot}Et_2O$	15	82	α
5	$\beta\text{-}C_{10}H_7C(OSiMe_3)=CH_2$	$CH_2COC_{10}H_7\text{-}\beta$[c]	$BF_3{\cdot}Et_2O$	20	72	α
6	$Me_3SiCH_2CH=CH_2$	$CH_2CH=CH_2$[d]	$BF_3{\cdot}Et_2O$	15	85	α + β (4 : 1)
7	MeOPh	$p\text{-}MeOC_6H_4$[e]	$BF_3{\cdot}Et_2O$	20	50	β
8	$m\text{-}(MeO)_2C_6H_4$	$o,p,\text{-}(MeO)_2C_6H_3$[b]	$BF_3{\cdot}Et_2O$	15	78	β

[a] Yields refer to pure isolated [flash column chromatography (silica) and crystallized] products. [b] See ref. 1. [c] M.p. 123—124 °C (from di-isopropyl ether), $[\alpha]_D^{20}$ 60°. [d] For α-anomer see ref. 3f; β-anomer: m.p. 91—92 °C (from di-isopropyl ether), $[\alpha]_D^{20}$ 13.5°. [e] M.p. 109—110 °C (from methanol), $[\alpha]_D^{20}$ 29°.

Hz) characteristic of the anomeric proton of a 1-β-trifluoroacetate was isolated.

The above results represent the first method for obtaining *C*-glucosides without the isolation of an activated derivative; in fact, the reaction occurs in one pot starting directly with the tetra-*O*-benzyl-D-glucopyranose.

This work was supported by Ministero della Pubblica Istruzione and by the 'Davide Campari S.p.A.,' Milano.

Received, 13th March 1987; Com. 315

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