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A CONVENIENT SYNTHESIS OF BOTH THE ANOMERS OF ETHYL (2,3,4,6-TETRA-*O*-BENZYL-D-GLUCOPYRANOSYL)ACETATE

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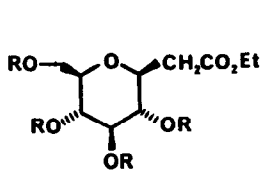
ABSTRACT. *The α- and β-anomers of ethyl (2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)acetate, useful intermediates for the synthesis of alkyl C-glucosides, can be obtained in good yields by reaction of tetra-O-benzylglucose with triethyl phosphonoacetate according to the Wittig-Horner procedure.*

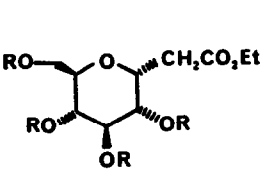
There is an increasing interest in the carbon-carbon bond-forming reactions at the anomeric positions of carbohydrates. This is because the resulting polyhydroxylated tetrahydropyran rings with two oxygenated alkyl substituents at the 2- and 6-positions (see 1 and 2) are potential enzyme inhibitors (1) and chirons (2) for the synthesis of complex natural products (including biologically active *C*-glycosides) (3). In particular, the *C*-glucopyranosyl derivatives 1 and 2 appear to be convenient intermediates to prepare a wide range of alkyl *C*-glucosides (4).

Unfortunately, the use of 1 and 2 for synthetic purposes has been greatly limited by the need of multistep routes for their preparation (3a). In fact, they cannot be obtained by the Wittig reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with (carbethoxymethylene)triphenylphosphorane followed by Michael cyclization, i.e. using the Moffat *C*-glycosidation procedure (5). We report here an efficient method to obtain a mixtures of 1 and 2 (as well as the single compounds through column chromatography) in good yields. This method, based on the use of the Horner reagent instead of the Wittig one, was also shown to be successful in preparing the nitrile derivative 4.



1

R = CH_2Ph



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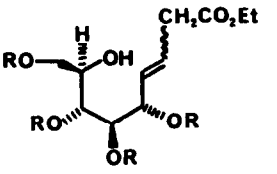

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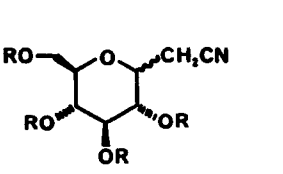

4

Typically, triethyl phosphonoacetate (18.5 ml, 92.4 mmol) was put dropwise under N_2 into a cooled (0°C) suspension of NaH (100 mmol) in THF (40 ml) and the resulting mixture stirred for 5 h at r.t.; 2,3,4,6-tetra-O-benzylglucopyranose (5 g, 9.2 mmol) was then added and the reaction progress was followed by t.l.c.(6). After ca. 44 h the reaction mixture was acidified with HCl and extracted with ether. The residue from solvent evaporation, when flash chromatographed using the same eluent as for t.l.c.(6), gave a mixture (4.5 g) of compound 1 and 2 (see Table 1). Each of these could be isolated in pure form by repeated flash chromatographies on silica gel column (hexane-ethyl acetate 3:1). In fact, the first separation gave the β-anomer 1 (3a, 7) and the α-anomer 2 (8) in 18% and 5% yield respectively (the residual mixture being recovered from the column almost quantitatively).

TABLE 1.- Reaction of 2,3,4,6-tetra-*O*-benzylglucopyranose with triethyl phosphonoacetate in different solvents (a).

	n-hexane	benzene	THF	DMF	DMSO	TPA (b)
% Yield of (1+2) (c)	12	74	92(80)(d)	40	5	67
Ratio (1:2) (c)	0.75	1.4	3.1	2.0	1.1	only 1
% Yield of 3 (c)	47	-	-	58	84	-

(a) Reaction conditions as described in the text for THF; (b) Triethyl phosphonoacetate; (c) determined by t.l.c.(6) using a CAMAG TLC SCANNER (calibration curves recorded at 254 nm); (d) isolated yield (in parentheses).

Results from experiments performed in different solvents are reported in Table 1. It must be pointed out that the ethyl octenoate 3 (9) is formed as the predominant product in certain solvents, but is absent in benzene, THF, and TPA. Inspection of the data of Table 1 reveals that the best yields of the anomeric mixture (1+2) are obtained in THF, whereas TPA and benzene represent the most convenient solvents to prepare the β-and the α-isomer, respectively (the latter after a chromatographic separation). By a procedure analogous to that described above, but using diethyl phosphonoacetonitrile as the alkylating reagent, an anomeric mixture of 4 (11) (*ca.* 2:1 in favour of the β-anomer) was obtained in 55% yield.

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3) *See for example:*(a) *M.D.LEWIS, J.K.CHA, Y.KISHI, J.Am.Chem.Soc.*,104,*4976(1982)*;(b) *L.A.REED, Y.ITO, S.MASAMUNE, K.B.SHARPLESS, J.Am.Chem.Soc.*,104,*6468(1982) and references cited therein*; (c) *B.GIESE, J.DEPUIS, Angew. Chem., Int. Ed. Engl.*,22,*622(1983)*.

4) *Results to be published.*

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6) *Silica (Kieselgel 60 F_{254} Merck) eluent: hexane-ethyl acetate 4:1.*

7) Ethyl 3,7-anhydro-2-deoxy-4,5,6,8-tetra-*O*-benzyl-D-*glycero*-D-*gulo*-octonate: *Rf* (6) *0.26* ; ^{1}*H-n.m.r.* (*Py-d_5, TMS*), (*J in Hz*): *1.08* (*3H, t, J=7.5, OCH_2-CH_3*); *2.73* (*1H, dd, J=9, J'=15*) *and 3.02* (*1H, dd, J=3, J'=15*) *due to -CH_2CO_2Et*; *3.58* (*1H, dd, J=J'=9.5, H-4*); *3.70* (*1H, m, H-7*); *3.7-4.2* (*4H, 2m, H-5, H-6, H-8', H-8''*); *4.10* (*1H, ddd, J=3, J'=9, J''=9.5, H-3*); *4.10* (*2H, q, J=7.5 , OCH_2-CH_3*); *4.5-5.1* (*8H, m, CH_2-Ar*); *7.1-7.7* (*20H, m, aromatic protons*). ^{13}*C n.m.r* (*$CDCl_3$, TMS*) :*37.70* (*C-2*); *170.78* (*C=O*). *Anal. Calcd. for $C_{38}H_{42}O_7$: C,74.73; H,6.93. Found: C,74.56; H,7.04.*

8) Ethyl 3,7-anhydro-2-deoxy-4,5,6,8-tetra-*O*-benzyl-D-*glycero*-D-*ido*-octonate: *Rf* (6) *0.18*; ^{1}*H-n.m.r.* (*Py-d_5, TMS*), (*J in Hz*): *1.11* (*3H, t, J=7.5, OCH_2CH_3*); *2.85* (*1H, dd, J=6, J'=16*) *and 3.02* (*1H, dd, J=8, J'=16*) *due to -CH_2-CO_2Et*; *3.74* (*1H, m, H-7*); *3.8-4.4* (*5H, m, H-4, H-5, H-6, H-8', H-8''*); *4.15* (*2H, q, J=7.5, OCH_2CH_3*); *4.19* (*1H, ddd, J=6, J'=8, J''=4.8, H-3*); *4.5-5.3* (*8H, m, CH_2-Ar*); *7.1-7.7* (*20H, m, aromatic protons*). ^{13}*C-n.m.r.* (*$CDCl_3$, TMS*) , :*32.58* (*C-2*); *170.96* (*C=O*). *Anal. Calcd. for $C_{38}H_{42}O_7$: C,74.73; H,6.93. Found: C,74.71; H,7.01.*

9) *Isolated by column chromatography as compound 1 and 2. Rf* (6); *0.1. It was shown to be identical in all respects with the product of the Wittig reaction between 2,3,4,6-tetra-O-benzyl-D-glucose and (carbethoxymethylene)triphenylphosphorane in CH_3CN (10). Compound 3 has been reported to be stable to the intramolecular Michael addition.*

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