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Preliminary communication

Synthetic approaches to *gem*-di-*C*-alkyl derivatives of carbohydrates: nucleophilic addition reactions of 3-*C*-methylene compounds derived from 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose using phase-transfer catalysis

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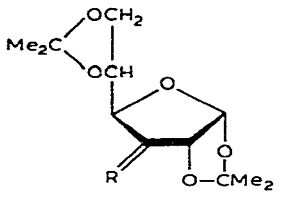
In a previous communication[1] from this laboratory, the conversion of L-glutamic acid into *gem*-di-*C*-alkyl carbohydrate derivatives was described. As part of a continuing interest in this special class of branched-chain sugars, a novel and facile synthesis of these compounds has been accomplished by nucleophilic addition to a suitable *C*-(substituted methylene) derivative employing phase-transfer catalysis[2] (p.t.c.). Most of the known *C*-(substituted methylene) derivatives, commonly used as precursors to branched-chain sugars[3–5], have been prepared by a Wittig reaction[6]. However, in the present approach such derivatives have been synthesized readily by way of a Knoevenagel reaction under mild p.t.c. conditions.

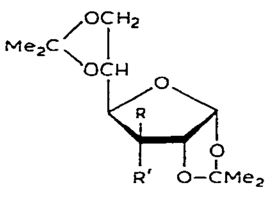
Treatment of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (1) with ethyl cyanoacetate in 0.2M sodium hydroxide–benzene in the presence of tetrabutylam-



1 $R = O$

2 $R = C(CN)CO_2Et$

3 $R = CHNO_2$



4 $R = OH$, $R' = CN$

5 $R = CN$, $R' = CH(CN)CO_2Et$

6 $R = CN$, $R' = CH_2CN$

7 $R = CN$, $R' = CH_2NO_2$

8 $R = CH(CN)CO_2Et$, $R' = CH_2NO_2$

9 $R = Me$, $R' = CH_2NO_2$

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monium bromide as phase-transfer catalyst, at room temperature, gave crystalline **2**, in 85% yield, m.p. 90–91°, $[\alpha]_D^{23}$ +79° (*c* 1.1, chloroform). Addition of cyanide ion to **2**, performed under the same p.t.c. conditions as just described, afforded, after column chromatography on silica gel [20 : 1 (v/v) benzene–ethyl acetate], the known[7] cyanohydrin derivative **4** in 70% yield and the desired adduct **5** in only 10% yield. Surprisingly, however, when tetrabutylammonium hydrogensulfate was used as the catalyst, the 3-*C*-cyano-3-*C*-[cyano(ethoxycarbonyl)methyl] derivative **5** was obtained in 50% yield, m.p. 92–93°, $[\alpha]_D^{23}$ +75.7° (*c* 1.2, chloroform); a small amount of **4** was also formed. A similar result was obtained when the reaction of **2** with potassium cyanide was performed in dimethyl sulfoxide at 55°. Treatment of **5** with potassium cyanide in 95% ethanol gave the known[3] 3-*C*-cyano-3-*C*-cyanomethyl derivative **6** in 50% yield, m.p. 116–118°, $[\alpha]_D^{22}$ +21.6° (*c* 0.8, chloroform) (lit.[3] m.p. 121.5–123°, $[\alpha]_D$ +21°).

A more convenient and direct route to 3,3-di-*C*-alkylated derivatives was sought starting from the known[5] 3-*C*-nitromethylene derivative **3**, since in recent years several examples of nucleophilic addition reactions of sugar nitroolefins, for example, methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside and its α anomer, have been reported[8]. Accordingly, treatment of **3** with 1.2 equiv. of potassium cyanide in 0.2M sodium hydroxide–benzene and tetrabutylammonium bromide as the p.t.c. catalyst for 2 h at 20° afforded the desired product **7** in 73% yield, m.p. 120–121°, $[\alpha]_D^{22}$ +24.8° (*c* 0.8, chloroform); ν_{max}^{Nujol} 2210 weak (CN) and 1545 (NO_2) cm^{-1}. Similarly, a Michael addition reaction of **3** with 2 equiv. of ethyl cyanoacetate for 20 h gave **8** in 75% yield, m.p. 136–138°, $[\alpha]_D^{22}$ +22.4° (*c* 0.9, chloroform); ν_{max}^{Nujol} 1745 (ester C=O) and 1560 (NO_2) cm^{-1}

An alternative synthesis of *gem*-di-*C*-alkyl derivatives was found to be feasible by direct introduction of an alkyl function into the nitromethylene derivative **3** by way of a Grignard reaction. Thus, treatment of **3** with methylmagnesium iodide in ether at –50° gave syrupy compound **9**, after column chromatography on silica gel [20 : 1 (v/v) benzene–ethyl acetate], in 60% yield, $[\alpha]_D^{22}$ +27.3° (*c* 1.2, chloroform).

The structural assignments for the adducts described in this Communication were made on the basis of their ^{1}H-n.m.r. spectra (see Table I) and on the assumption that the addition reactions to the substituted methylene derivatives had occurred in a manner similar to those previously reported by other workers[3–5,9], namely, from the less hindered *exo*-side. The results of a ^{13}C-n.m.r. study of these and other adducts will be reported separately.

The *gem*-di-*C*-alkyl derivatives described in this Communication are of significant synthetic potential, since their modification should yield carbohydrates containing two different functional groups of various kinds at the branch point.

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TABLE I

60-MHz ^{1}H-N.M.R. SPECTRAL DATA

Compound[a]	Chemical shifts (δ)[b] and first-order couplings (Hz)[c]								
	H-1 *($J_{1,2}$)*	*H-2*	*H-4* *($J_{4,5}$)*	*H-5*	*H-6's*	*CMe$_2$*	*Me*	*H-1'* *($J_{1',1''}$)*	*H-1''*
2	5.93d (4.0)	4.50d	←	4.26m	→	1.45m			
5	5.96d (4.0)	4.60d	←	4.50m	→	1.48m			
6	6.03d (3.8)	4.93d	3.73d (9.0)	← 4.23m	→	1.53m		3.30d (16.6)	2.80d
7	5.95d (3.5)	5.12d	3.63d (9.0)	← 4.45m	→	1.45m		5.06d (16.0)	4.66d
8	6.10d (3.8)	5.90d	3.66d (9.6)	← 4.16m	→	1.43m		5.17d (16.6)	4.66d
9	5.80d (3.8)	4.56d	3.56d (9.0)	← 4.03m	→	1.76m	1.36s	← 4.70s	→

[a] In chloroform-*d*; tetramethylsilane as internal standard. [b] Signal multiplicities: s, singlet; d, doublet; and m, multiplet. [c] In parentheses.

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