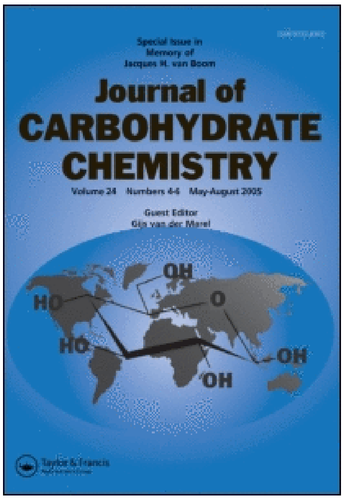

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PHOTOCHEMICALLY BASED SYNTHESIS OF DEOXY SUGARS. SYNTHESIS OF 2-DEOXY-D-ARABINO-HEXOPYRANOSE (2-DEOXY-D-GLUCOSE) AND SEVERAL OF ITS DERIVATIVES FROM 3,4,6-TRI-O-ACETYL-D-GLUCAL

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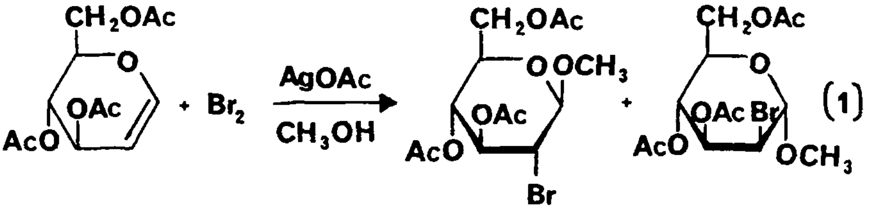
ABSTRACT

The photolysis of methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside (2) in 2-propanol results in replacement of the bromine with a hydrogen to give methyl 3,4,6-tri-O-acetyl-2-deoxy-β-D-arabino-hexopyranoside (4) in 91% yield. Similar reactions take place for methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside (3) and a mixture of the α and β anomers of 1,3,4,6-tetra-O-acetyl-2-bromo-2-deoxy-D-glucopyranose (7) and 1,3,4,6-tetra-O-acetyl-2-bromo-2-deoxy-D-mannopyranose (8). Since compounds 2, 3, 7, and 8 each were synthesized from 3,4,6-tri-O-acetyl-D-glucal (1), photochemical reaction appears to be a useful process in 2-deoxy sugar synthesis from glycals.

INTRODUCTION

The synthesis of deoxy sugars and branched-chain deoxy sugars is one of the most active areas of research in carbohydrate chemistry.[1] The primary reason for this activity is the widespread occurrence of these compounds in biologically important molecules. Since many of these carbohydrates are actually 2-deoxy compounds, there is a considerable interest in developing methods for synthesizing 2-deoxy sugars from readily available starting materials.

Glycals are one type of generally accessible starting material which has been used in 2-deoxy sugar synthesis. A typical



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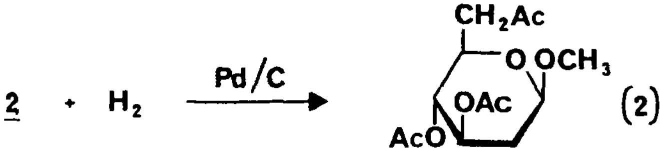

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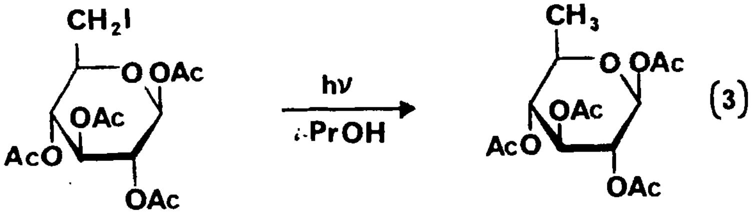


conversion sequence consists of reaction of a glycal with molecular bromine in a nucleophilic solvent, such as an alcohol (eq 1) or water, followed by replacement of the bromine attached to C-2 with a hydrogen (eq 2). Although several reagents for the bromine replacement process have been used with success (*e.g.*, palladium on carbon, Raney nickel and hydrogen, lithium aluminum hydride), development of alternatives, particularly ones which are useful under more mild conditions, remains of interest.

Our experience with irradiation of deoxyiodo sugars[2-4], for example, 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-β-*D*-glucopyranose[4] (eq 3), suggested that a photochemical process could be an attractive alternative to existing methods for the halogen replacement reaction in 2-deoxy sugar synthesis. To test this possibility, we synthesized and photolyzed several 2-bromo-2-deoxy sugars. The findings from this research are described below.

RESULTS AND DISCUSSION

Several years ago, Lemieux and Fraser-Reid[5] reported that treatment of a solution of 3,4,6-tri-O-acetyl-D-glucal (1) in methanol with bromine in the presence of silver acetate produced a mixture of methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside (2) and methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside (3) in 90% yield (eq 1). Since irradiation of these two compounds (2 and 3) should lead to the corresponding 2-deoxy sugars, synthesis of 2 and 3 was a logical beginning point for the planned study. Before investigating the photochemistry of 2 and 3, however, we elected to confirm the structural assignment to these two compounds by ^{13}C NMR and by further analysis of their ^{1}H NMR spectra. (Lemieux and Fraser-Reid[5] already had made some assignments to the ^{1}H NMR spectra of 2 and 3.)

The 80 MHz ^{1}H NMR spectra of 2 and 3 were too complex for simple analysis; however, complete assignment of proton-proton coupling constants and proton chemical shifts (Table 1) was possible following spin simulation[6] of the spectrum of each compound. These ^{1}H NMR spectra completely supported the structures assigned by the previous investigators. The ^{13}C NMR spectra (Table 2) were also in agreement with these structural assignments.

Corex-filtered photolysis of 1.7 g of 2 and 0.38 g of sodium bicarbonate in 350 ml of 2-propanol with a 450-W mercury-vapor lamp for six hours resulted in formation of methyl 3,4,6-tri-O-acetyl-2-deoxy-β-D-arabino-hexopyranoside (4) in 91% yield. A mechanism for this reaction is proposed in Scheme 1. This mechaism is analogous to that suggested for the photochemical reaction of deoxyiodo sugars[2,3] and is supported by the formation of pinacol during photolysis. Irradiation of 3 under the same conditions used for 2, caused complete conversion into methyl 3,4,6-tri-O-acetyl-2-deoxy-α-D-arabino-hexopyranoside (5).

TABLE 1. ^{1}H NMR Spectral Data[a] for Compounds 2-4.

	2	3	4
H-1	4.53 ($J_{1,2}$=8.6 Hz)	4.97 ($J_{1,2}$=1.3 Hz)	4.45 ($J_{1,2a}$=9.5 Hz) ($J_{1,2e}$=2.1 Hz)
H-2	3.79 ($J_{2,3}$=9.7 Hz)	4.44 ($J_{2,3}$=3.4 Hz)	1.17-2.08 (H_{2a},H_{2e})
H-3	5.32 ($J_{3,4}$=9.4 Hz)	5.19 ($J_{3,4}$=9.4 Hz)	4.71-
H-4	4.97 ($J_{4,5}$=9.7 Hz)	5.43 ($J_{4,5}$=9.3 Hz)	5.71
H-5	3.75[b] ($J_{5,6}$=4.6 Hz) ($J_{5,6'}$=2.9 Hz)	3.78 ($J_{5,6}$=4.8 Hz) ($J_{5,6'}$=2.5 Hz)	3.57 ($J_{5,6}$=4.9 Hz) ($J_{5,6'}$=2.6 Hz)
H-6	4.29[b] ($J_{6,6'}$=12.7 Hz)	4.29[b] ($J_{6,6'}$=12.8 Hz)	4.29 ($J_{6,6'}$=12.2 Hz)
H-6'	4.14[b]	4.15[b]	4.06
$C\underline{H}_3O$	3.57	3.42	3.46
$C\underline{H}_3CO$	2.02 (6H), 2.08	2.06, 2.10, 2.12	1.98, 1.99, 2.04

a. Chemical shifts are relative to $(CH_3)_4Si$ (0 ppm).

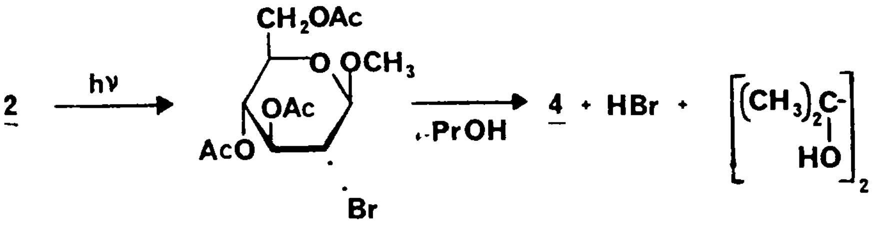
b. Chemical shifts and coupling constants obtained by spin simulation.

TABLE 2. ^{13}C NMR Spectral Data[a] for Compounds 2-5

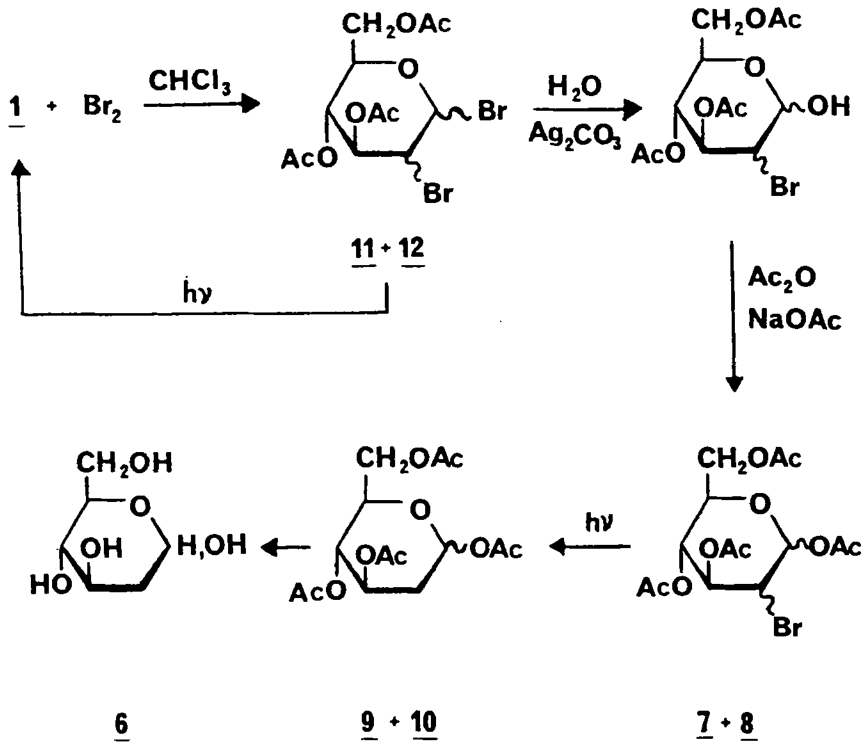
	3	2	4	5
C-1	100.53 (d)	103.17 (d)	100.46 (d)	97.51 (d)
C-2	49.01 (d)	49.15 (d)	35.94 (t)	34.41 (t)
C-3, C-4,	68.77 (d)	74.52 (d)	71.94 (d)	68.94 (d)
C-5	68.60 (d)	71.79 (d)	70.49 (d)	68.55 (d)
	65.84 (d)	69.08 (d)	69.13 (d)	67.28 (d)
C-6	61.91 (t)	61.70 (t)	62.39 (t)	61.97 (t)
$\underline{C}H_3CO$	20.17 (q)	20.37 (q)	20.73 (q)	20.30 (q)
			20.58 (q)	20.10 (q)
$CH_3\underline{C}O$	170.01 (s)	170.00 (s)	170.02 (s)	170.04 (s)
	169.35 (s)	169.39 (s)	169.46 (s)	169.50 (s)
	169.01 (s)	169.11 (s)	169.32 (s)	169.30 (s)
$O\underline{C}H_3$	55.06 (q)	57.41 (q)	56.65 (q)	54.26 (q)

a. Chemical shifts are relative to $(CH_3)_4Si$ (0 ppm). Multiplicities (s, singlet; d, doublet; t, triplet; and q, quartet) were obtained from Gyro-gated spectra.

SCHEME 1



SCHEME 2



In some instances when a glycal is to be converted into a deoxy sugar, formation of a mixture of anomers is an acceptable result. In those situations it is not necessary to separate, prior to photolysis, the stereoisomers formed from the glycal addition reaction. A simple example of such a situation is the conversion of 3,4,6-tri-O-acetyl-D-glucal (1) into 2-deoxy-D-arabino-hexose (6, 2-deoxy-D-glucose). In order to examine the photochemical process when a mixture of compounds was undergoing reaction, the combination of α and β anomers of 1,3,4,6-tetra-O-acetyl-2-bromo-2-deoxy-D-glucopyranose (7) and 1,3,4,6-tetra-O-acetyl-2-bromo-2-deoxy-D-mannopyranose (8) was synthesized[7] and irradiated to give a mixture of α and β anomers of 1,3,4,6-tetra-O-acetyl-2-deoxy-D-arabino-hexopyranose (9 and 10) (Scheme 2). Treatment of this mixture (9 and 10) in methanol with base gave 2-deoxy-D-arabino-hexose (6) in 68% yield from 1 (78% from 9 and 10).

As a final experiment, the mixture of dibromides (11 and 12), produced by reaction of 3,4,6-tri-O-acetyl-D-glucal (1) with bromine, was irradiated in 2-propanol to give compound 1 in 60% yield (Scheme 2). Thus, photolysis of these dibromides (11 and 12) reversed the bromine addition reaction.

In conclusion, the experiments described above suggest that the photochemical reaction of 2-bromo-2-deoxy compounds should be useful, in general, in converting glycals into 2-deoxy sugars.

EXPERIMENTAL

General Procedures. Mass spectra were determined with a Finnigan 1015-D spectrometer using methane as a carrier gas and an ionizing voltage of 150 eV. ^{1}H and ^{13}C NMR spectra were obtained ($CDCl_3$) from a Varian FT-80A spectrometer. Spectral simulation was done using Varian Associates Simeq spin simulation program[6].

Irradiation of Methyl 3,4,6-Tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside[5] (2). Compound 2 (1.72 g, 4.30 mmol) was dissolved in 350 ml of 2-propanol and to this solution was added 0.378 g of $NaHCO_3$. This mixture was purged with nitrogen for one h and the purge continued during six h of Corex-filtered irradiation using a 450-W, water-cooled, mercury-vapor lamp (Hanovia). After irradiation, the solvent was distilled under reduced pressure to leave a syrup containing a suspended solid. This material was distilled under vacuum (0.2-0.4 mmHg) at 150-155 °C, using a Buchi microdistillation apparatus, to yield 0.602 g (1.96 mmol) of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-*arabino*-hexopyranoside (**4**) (91% yield). Compound **4** was identified from its ^1H (Table 1) and ^{13}C (Table 2) NMR spectra and from its chemical ionization mass spectrum, m/z (rel intensity), 273 (2.8), 245 (7.8), 213 (100.0), 185 (12.0), 153 (54.2), 125 (12.0), and 111 (10.7).

Irradiation of Methyl 3,4,6-Tri-O-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside[5] *(3)*. Compound **3** (3.25 g, 8.5 mmol) and 3.0 g of $NaHCO_3$ in 1.0 L of 2-propanol was irradiated under the same conditions as those used for compound **2**. Product isolation also was identical and produced methyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-*arabino*-hexopyranoside (**5**) in 90% yield: ^{13}C NMR, Table 2; ^1H NMR, δ 5.40-4.60 (m, 3H), 4.24-3.66 (m, 3H), 3.26 (s, OCH_3), 2.03 (s, CH_3CO), 2.00 (s, CH_3CO), and 1.97 (s, CH_3CO).

Irradiation of a Mixture[7] *of 1,3,4,6-Tetra-O-acetyl-2-bromo-2-deoxy-D-glucopyranose (7) and 1,3,4,6-Tetra-O-acetyl-2-bromo-2-deoxy-D-mannopyranose (8)*. Compounds **7** and **8** were obtained from acetylation of a mixture of 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-*D*-glucopyranose and 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-*D*-mannopyranose by reaction of 1.5 g of this mixture with 0.5 g of NaOAc in 25 ml of Ac_2O at 55 °C for 1.0 h. The Ac_2O was distilled from the reaction mixture at 25 °C and the residue dissolved in CH_2Cl_2 and filtered. After evaporation of the CH_2Cl_2, the residue was irradiated in the manner described for irradiation of compound **2** to yield 1.08 g of a mixture of α and β anomers of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-*D*-*arabino*-hexopyranose (**9** and **10**) identical to that obtained from acetylation of **6**[8]. Stirring compounds **9** and **10** in CH_3OH containing 2 g of Baker ion exchange resin ANGA-542 (strong base) gave 0.5 g (3.36 mmol, 78%) of **6**.

Irradiation of a Mixture of 3,4,6-Tri-O-acetyl-2-bromo-2-deoxy-D-pyranosyl Bromide (11) and 3,4,6-Tri-O-acetyl-2-bromo-

2-deoxy-D-mannopyranosyl Bromide (12). The mixture of dibromides 11 and 12 was irradiated in the same manner as compound 2 to give exclusively 1 in 60% yield.

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