D-GLUCOSE DERIVATIVES LABELLED WITH $^{75,77}Br$ and ^{123}I

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SUMMARY

Synthetic routes to D-glucose derivatives labelled with either the positron emitter ^{75}Br ($T_{1/2}$ = 1.6 hr) or the single photon emitters ^{77}Br ($T_{1/2}$ = 56 hr) and ^{123}I ($T_{1/2}$ ▫ 13.3 hr) in positions 2 or 3 were investigated in order to prepare useful tracers for glucose utilization studies in brain and heart.

3-Deoxy-3-iodo-D-glucose and 3-deoxy-3-bromo-D-glucose were prepared from 1,2:5,6-di-isopropylidene-D-allose via its triflate in 10-20 % radiochemical yield.

2-Deoxy-2-iodo-D-glucose and 2-deoxy-2-bromo-D-glucose could not be prepared by the routes presented in this publication. On the route to these compounds, some intermediates of possible use as tracers for glucose utilization were prepared, namely the methyl glucosides methyl 2-deoxy-2-iodo-ß-D-glucopyranoside (MIDG) and methyl 2-deoxy-2-bromo-ß-D-glucopyranoside (MBDG) and the acetylated methyl glucosides methyl 3,4,6-tri-O-acetyl-2-deoxy-2-iodo-ß-D-glucopyranoside (MTIG) and methyl 3,4,6-tri-O-acetyl-2-deoxy-2-bromo-ß-D-glucopyranoside (MTBG). Radiochemical yields from 3,4,6-tri-O-acetyl-D-glucal, halide ion and dichloramin T were 35 % for MTBG, 40 % for MTIG, 15 % for MBDG and 20 % for MIDG. Preparation times were less than 2 hours.

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INTRODUCTION

Sugars are important substrates for energy metabolism in brain and heart of mammals. For the brain, they have to meet strict requirements concerning the stereochemistry in order to pass the blood-brain barrier (BBB) (1). Only D-glucose and some of its analogues are transported by the hexose carrier at the BBB; these analogues have the all-trans, all-equatorial arrangement of electronegative substituents. Mannose derivatives can also be transported by the hexose carrier, although at a slower rate.

Apart from [^{11}C]-D-glucose (2), a number of glucose derivatives labelled with either ^{18}F or ^{11}C have been investigated as in-vivo glucose tracers. Applying the [^{14}C]-2-deoxy-D-glucose autoradiographic method of Sokoloff et al (3) to non-invasive in-vivo determination of regional glucose metabolism, the Brookhaven group synthesized and evaluated [^{18}F]-2-fluoro-2-deoxy-D-glucose (4) and 1-[^{11}C]-2-deoxy-D-glucose (5). [^{18}F]-3-fluoro-3-deoxy-D-glucose was proposed as a tracer for glucose metabolic rate and synthesized by the St. Louis group (6). Our laboratory has synthesized and is presently evaluating 3-[^{11}C]-methyl-D-glucose as a tracer for unidirectional glucose transport (7).

Nevertheless, both ^{11}C and ^{18}F pose some serious synthetic problems due to their short half-life, specific activity and chemical reactivity. ^{75}Br, a positron emitter with a 1.6 hr half-life, and ^{123}I, with its convenient 159 keV γ-line and 13.3 hr half-life, seem promising alternative radionuclides with which to label D-glucose derivatives for applications in conjunction with positron emission computed tomography (PECT) and single photon emission computed tomography (SPECT). They are easier to handle chemically than ^{18}F, and their half-lives make

them suitable for use in institutions not having an in-house cyclotron. Thus, we decided to investigate D-glucose derivatives carrying a bromine or iodine substituent in position 2 or 3 as potential radiopharmaceuticals for tracing D-glucose utilization in brain and heart. When we started our investigations, only 3-deoxy-3-iodo-D-glucose (8) had been prepared, but no biodistribution data has been reported. An unsuccessful attempt to prepare 2-deoxy-2-iodo-D-glucose was also reported (9).

MATERIALS AND METHODS

^{75}Br and ^{77}Br was produced at the Jülich CV 28 compact cyclotron by the ^{75}As(^{3}He,3n)^{75}Br or the ^{75}As(α,2n)^{77}Br reaction, respectively (10,11). It was isolated as no-carrier added (n.c.a.) ^{75,77}Br-bromide ion in aqueous solution.

^{123}I was produced by the ^{124}Te(p,2n)^{123}I-reaction and isolated as n.c.a. ^{123}I-iodide ion in aqueous solution (12).

1,2:5,6-diisopropylidene-D-allofuranose was obtained from Pfanstiehl Laboratories, Waukegan, IL (USA).

3,4,6-tri-O-acetyl-D-glucal was obtained from EGA-Chemie, Steinbuch, FRG.

All chemicals were reagent grade and used without further purification, unless specified in the experimental part.

RESULTS AND DISCUSSION

I. 3-Deoxy-3-halo-D-glucose

A number of different methods has been described in the literature for the preparation of non-radioactive 3-deoxy-3-halo-D-glucose, all of them starting from 1,2:5,6-diisopropylidene-D-

allofuranose using substitution reactions. The following procedures have been used: a) the oxidative elimination of N_2 from the 3-deoxy-3-hydrazino-derivative with simultaneous introduction of halide (8,13), b) the S_N2 substitution by halide ion of the 3-oxy-triphenylphosphonium halide (14), c) the S_N2 substitution by halide ion of the 3-tosyloxy(tosylate) derivative (15), and d) the S_N2 substitution by halide ion of the 3-trifluoromethanesulfonyloxy(triflate) derivative (Fig. 1) (7,16).

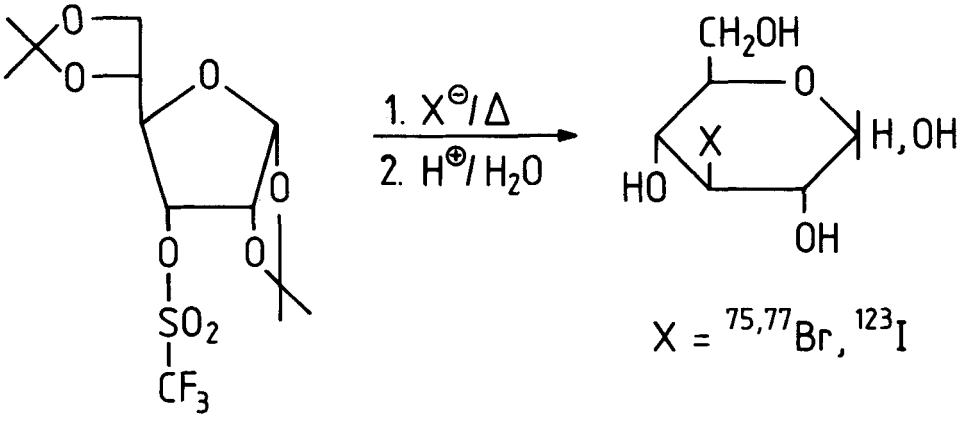


Fig. 1.

Not all of these methods suitable for synthesis of non-radioactive compounds seemed appropriate for synthesis of radioactive compounds at the no-carrier added (n.c.a.) level. Method a) involves an oxidation of a hydrazine by molecular halogen; this reaction therefore has a maximum yield of 50 %; furthermore, reactions at the n.c.a. level are difficult to control under S_N1 conditions, especially with substrates like sugars where neighbouring group participation is common. Method b) can be successfully employed only using anhydrous conditions for the decomposition of the phosphonium salt. Thus, introduction of labelled halide

into the reaction mixture seems extremely difficult. Furthermore, large amounts of carrier halide are introduced via the phosphonium salt.

We therefore studied the S_N2 reactions on the tosylate or the triflate. Whereas the direct S_N2 reaction on the 1,2:5,6-diisopropylidene-D-allofuranose yielded no product at all, the tosylate was only slightly better at a yield of about 1 %. Changing to the better leaving group triflate resulted in significant increases in yields (ranging from 10-35 % for ^{123}I-iodide and ^{75,77}Br-bromide). Hydrolysis of the ketal groups then gave rise to [^{123}I]-3-deoxy-3-iodo-D-glucose and [^{75,77}Br]-3-deoxy-3-bromo-D-glucose in about 10-20 % yield (see experimental part). The reaction time for this preparation was only 20 min in refluxing acetone. Thus, our yields are acceptable when compared with those reported in the literature. Although 87 % yield was obtained after 12 hr at reflux (16), these conditions are not applicable due to the short half-life of the radiohalide.

To prove that the 3-deoxy-3-iodo-1,2:5,6-diisopropylidene-D-glucofuranose actually had the expected gluco-configuration, we reacted it with sodium hydroxide. By another S_N2 reaction pure 1,2:5,6-diisopropylidene-D-allofuranose was formed; chromatographic analysis showed none of the epimeric derivative.

Summarizing, [^{123}I]-3-deoxy-3-iodo-D-glucose and [^{75,77}Br]-3-deoxy-3-bromo-D-glucose were prepared in 10-20 % radiochemical yield in a total reaction time of less than 2 hr including chromatographic purification.

II. 2-Deoxy-2-halo-D-glucose

In contrast to the 3-deoxy-3-halo-D-glucose derivatives, there seems to be no possibility for an S_N2 substitution reaction at the C-2 position. Syntheses of the non-radioactive 2-deoxy-2-halo-D-glucoses published in the literature start with 3,4,6-tri-O-acetyl-D-glucal. Various substituents were added across the double bond: a) halogen at both C-1 and C-2 (17-20); b) halogen at C-2 and a solvent anion at C-1 (20-22); and c) preparation of an intermediate compound having a mercury acetate substituent at C-2 that can be reacted with molecular halogen to form the desired 2-deoxy-2-halo-D-glucose derivative (23,24). Again, not all of these methods are equally suited for the synthesis of radioactive compounds at the n.c.a. level. As methods a) and b) involve the use of molecular halogen, the maximum yield that can be expected from halide ion is 50 %, as one of the halogen atoms is lost as halide ion during the course of the reaction. With fluorine as the halogen substituent, it is rather difficult to avoid method a); consequently, [^{18}F]-2-fluoro-2-deoxy-D-glucose is routinely prepared by this method using carrier-added [^{18}F]-F_2 (25). The radiochemical yield was about 10 %. With bromine and iodine, method b) seems more promising, as these halide ions can be easily oxidized to the X^+ state by chloramine T (26), dichloramine T (27), N-halo-succinimide (28) or hypohalites (29), methods extensively studied in our laboratory.

A further complication in the synthesis of 2-deoxy-2-halo-D-glucose derivatives using addition reactions to 3,4,6-tri-O-acetyl-D-glucal is the simultaneous formation of both C-2 epimers, namely the glucose and the mannose derivatives. Consequently, reaction conditions have to be sought that yield as much of the glucose epimer as possible. In addition, procedures for the chromatographic separation of both epimers have to be worked out.

Our first approach to the synthesis of [^{75,77}Br]-2-deoxy-2-bromo-D-glucose (2-BDG) and [^{123}I]-2-deoxy-2-iodo-D-glucose (2-IDG) is shown in Fig. 2.

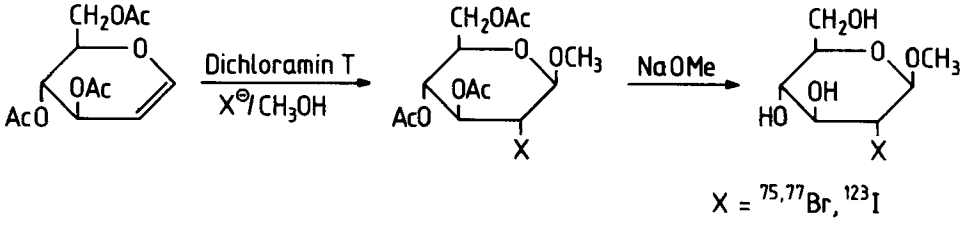


Fig. 2.

Oxidation of bromide or iodide ion by dichloramine T (N,N-dichloro-p-toluenesulfonamide/DCT) leads to a positive halogen species, which as an electrophile attacks the double bond of 3,4,6-tri-O-acetyl-D-glucal. An intermediate cyclic halonium ion is postulated (20,22) which is attacked from the opposite side of the double bond by the solvent methanol. Thus, only two of the four possible isomers at C-1 and C-2 are formed by trans-addition, namely methyl 3,4,6-tri-O-acetyl-2-deoxy-2-halo-ß-D-glucopyranoside (X ▫ ^{75}Br:MTBG; X ▫ ^{123}I:MTIG) and methyl 3,4,6-tri-O-acetyl-2-deoxy-2-halo-α-D-mannopyranoside. Both glucoside and mannoside are formed in about equal amounts. The total radiochemical yield for the addition reactions was 85 % for both ^{123}I and ^{75,77}Br at n.c.a. level. The yield for the desired gluco epimer after chromatographic purification was 35 % for MTBG and 40 % for MTIG.

Hydrolysis of the acetyl protecting groups at position 3,4 and 6 was easily affected by reacting with alkaline solution. No loss of the radioactive halide or epimerization was observed during this operation. [^{75}Br]-methyl-2-deoxy-2-bromo-ß-D-gluco-

pyranoside (MBDG) was isolated in 15 % radiochemical yield, while [^{123}I]-methyl-2-deoxy-2-iodo-ß-D-glucopyranoside (MIDG) was isolated in 20 % radiochemical yield.

Some confusion existed in the literature concerning the chromatographic separation of the gluco and manno epimers (17,18,20,21, 24). To resolve this question we compared the melting points, nmr spectra and optical rotation of the different compounds synthesized (see Tables I and II) with data mentioned in the literature. This comparison shows that the melting points of the gluco epimers are fairly reproducible, while, on the contrary, the optical rotation reported in different references differed widely. The comparison of the nmr spectra of our compounds MTBG and MTIG with those reproduced in references 20 and 21, respectively, clearly demonstrates that MTBG and MTIG have the gluco configuration.

The chromatographic data of Honda and Takiura (24), however, are not consistent with our observations. The separation of MTIG or MTBG and their respective manno epimers can be easily affected on silica gel plates using ether:hexane 7:3 (v/v) as eluent; the peaks nearer to the solvent front are the manno epimers, while the peaks with lower R_F values have the gluco configuration. On hplc separation using silica gel Si60 with ether:hexane as eluent, the gluco epimers are again retained longer than the manno epimers both for the bromo and iodo derivatives. In contrast to this, Honda and Takiura (24) state that the correlation is different in the iodo and in the bromo series. From our data in comparison with other references (20,21) their correlation is wrong for MTIG, whereas it is correct for MTBG.

Hydrolysis of the remaining methyl glucosides MBDG and MIDG presented significant problems. During all our attempts to affect

Table I. Physical constants of 2-deoxy-2-iodo-D-hexose derivatives synthesized during this work, compared to literature data.

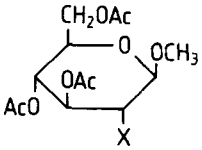
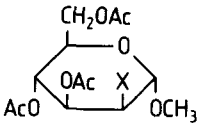
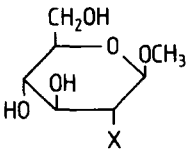
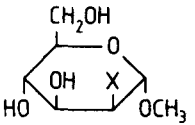
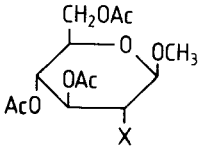
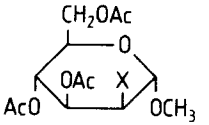
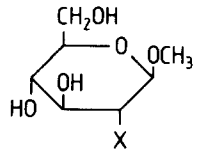
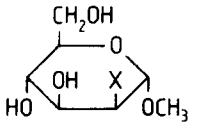
Configuration (Compound)	Reference	(24)	(21)	(20)	this work
ß-gluco (MTIG)		mp: 97-97.5° $[\alpha]_D(CHCl_3)$: + 68.9°	85-86° + 6.2°	94-95° + 61.1°	82° + 66.3° nmr spectrum identical with that of ref. 21
α-manno		mp: 118-118.5° $[\alpha]_D(CHCl_3)$: - 97.8°	+ 44.9°		+ 25.1° syrup, containing residual gluco epimer
ß-gluco (MIDG)		mp: 190-190.5° $[\alpha]_D(CH_3OH)$: + 29.0°	189-189.5° + 6.9°	187-188°	dec. at > 177° + 28.6° ms: correct molecular formula
α-manno		mp: 147-148° $[\alpha]_D(CH_3OH)$: - 6.3°	145-146° + 49.6°	147-148°	syrup containing residual gluco epimer

Table II. Physical constants of 2-deoxy-2-bromo-D-hexose derivatives synthesized during this work, compared to literature data.

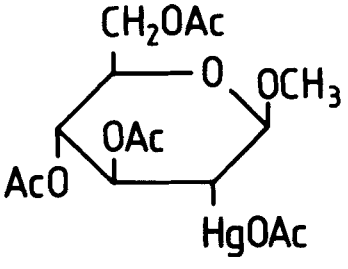
Configuration (Compound)	Reference	(17)	(18)	(20)	this work
ß-gluco (MTBG)		mp: 138-139° $[\alpha]_D$: + 39.0° (acetone)	138°	135-136° + 46° ($CHCl_3$)	132-134° + 58.7° ($CHCl_3$) nmr spectrum identical with that of ref. 20
α-manno		mp: 115-116° $[\alpha]_D$: - 92.0° (acetone)	115-116°	+ 31.2° ($CHCl_3$) mixture containing residual gluco epimer	+ 22.4° ($CHCl_3$) syrup containing residual gluco epimer
ß-gluco (MBDG)		mp: 181-182° $[\alpha]_D$: + 2.7° (H_2O)	179-180° + 0.59° (H_2O)	182-184° + 0.9° (CH_3OH)	dec. at > 165° + 27.1° ms: correct molecular formula
α-manno		mp: 183° $[\alpha]_D$: - 68.0° (H_2O)	180-181° - 63.8° (H_2O)		

acidic hydrolysis of the ketals we observed either no reaction or almost exclusive formation of radioactive halide ion. Under all conditions studied, we were unable to isolate any radioactive 2-deoxy-2-bromo-D-glucose or 2-deoxy-2-iodo-D-glucose (see experimental part).

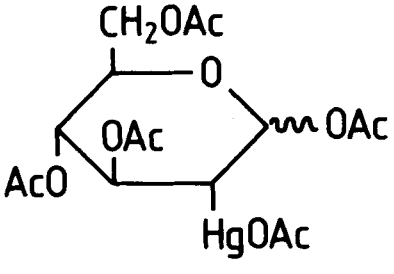
After this approach had failed, we also investigated the other two methods a) and c), even though lower yields had to be expected.

Addition of molecular halogen across the double bond of 3,4,6-tri-O-acetyl-D-glucal yielded complex product mixtures which we did not attempt to separate into their components: In the worst case, four different pairs of isomers at C-1 and C-2 had to be expected. All attempts to hydrolyze the acetyl esters in these 2-deoxy-2-halo-hexosyl-halides (halide: Br or I) resulted in exclusive formation of halide ions, not only from the labile halogen substituent at C-1, but also from the halogen at C-2. This was proven by the fact that no halogen-containing hexose was left behind; only halide ions were formed.

Methyl-2-acetoxymercuri-3,4,6-tri-O-acetyl-2-deoxy-ß-D-glucopyranoside (A) and 2-acetoxymercuri-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-glucopyranose (B) were prepared according to established procedures (23,24,30,31). The epimers



(A)



(B)

of (A) and (B) having the manno configuration could be separated from (A) or (B), but this was unnecessary because during halogenolysis of either (A) or (B) and their respective manno epimer the same mixture of 2-deoxy-2-halo-hexose were formed with a gluco-to-manno epimer ratio of 1:1. Iodinolysis of (A) lead to MTIG, a compound that can be produced more easily via X^-/DCT, as shown above (see experimental part). The formation of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-halo-α-D-glucopyranose (halo: ^{75}Br, ^{123}I) from (B) was achieved by halogenolysis; the total radiochemical yield was 40 % with a gluco:manno epimer ratio of 1:1 for both bromine and iodine. These tetraacetyl derivatives can theoretically be hydrolyzed in a single step; unfortunately, again all attempts to hydrolyze these derivatives to 2-deoxy-2-halo-D-glucose failed completely. Halide ion was the only radioactive product isolated.

Thus, it seems that the bromo or iodo substituent at position 2 is rather labile under both acidic or alkaline conditions. This behaviour is that expected for an α-halo-aldehyde. The only exception seems to be the 2-fluoro-derivative (5). The lability of the 2-deoxy-2-iodo-D-glucose was also observed by the Brookhaven group (9). Parallel to our work, the Brookhaven group (32,33) succeeded in preparing [^{82}Br]-2-deoxy-2-bromo-D-glucose by $^{82}BrCl$ addition to 3,4,6-tri-O-acetyl-D-glucal and subsequent hydrolysis. Again, the compound was not very stable.

Summarizing, all our attempts to prepare [^{75}Br]-2-deoxy-2-bromo-D-glucose or [^{123}I]-2-deoxy-2-iodo-D-glucose were unsuccessful. However, the intermediate compounds MBDG, MIDG, MTBG and MTIG can be prepared in good yields; they may be used as possible radiopharmaceuticals tracing glucose utilization or transport (34).

CONCLUSION

In our attempt to prepare glucose analogue radiopharmaceuticals labelled with the heavy halogens $^{75,77}Br$ or ^{123}I as possible tracers for glucose utilization, we successfully prepared [$^{75,77}Br$]-3-deoxy-3-bromo-D-glucose and [^{123}I]-3-deoxy-3-iodo-D-glucose. We were also able to prepare [$^{75,77}Br$]-methyl-3,4,6-tri-O-acetyl-2-deoxy-2-bromo-ß-D-glucopyranoside (MTBG), [^{123}I]-methyl-3,4,6-tri-O-acetyl-2-deoxy-2-iodo-ß-D-glucopyranoside (MTIG), [$^{75,77}Br$]-methyl-2-deoxy-2-bromo-ß-D-glucopyranoside (MBDG) and [^{123}I]-methyl-2-deoxy-2-iodo-ß-D-glucopyranoside (MIDG) during an unsuccessful attempt to synthesize the corresponding 2-deoxy-2-halo-D-glucose. All of these compounds were studied biochemically and pharmacokinetically in mice. The results of these studies will be reported elsewhere (34).

EXPERIMENTAL PART

Chromatographic data for the 3-deoxy-3-halo-D-glucose derivatives are listed in Table III; those for the 2-deoxy-2-halo series are listed in Table IV. Further data (mp, optical rotation) for the 2-deoxy-2-halo series are contained in Tables I and II.

a) 3-Deoxy-3-halo-D-glucose derivatives

1,2:5,6-Di-isopropylidene-3-tosyl-D-allose (I)

2.6 g (0.1 mole) of 1,2:5,6-di-isopropylidene-D-allose were dissolved in 10 ml absolute pyridine. To this 2.6 g (0.15 mole) of p-toluenesulfonylchloride were added. The mixture was left to stand at room temperature (RT) for 4 d.

After 4d, the mixture was poured onto crushed ice and extracted three times with CH_2Cl_2. Pyridine was reextracted from the CH_2Cl_2 with 20 ml 6 N HCl (3x). The CH_2Cl_2 was further washed with small amounts of water, $NaHCO_3$ and water and dried over Na_2SO_4. After evaporation of CH_2Cl_2, crystalline 1,2:5,6-di-isopropylidene-3-tosyl-D-allose was obtained in 80 % yield (mp 113 °C).

NMR spectra confirmed the structure.

1,2:5,6-Di-isopropylidene-3-trifluoromethanesulfonyl-D-allose (II)

To a solution of 3.18 ml pyridine (freshly distilled from KOH) in 600 ml CH_2Cl_2 (freshly distilled from 3 Å molecular sieve) 6.02 ml trifluoromethanesulfonic anhydride in 120 ml CH_2Cl_2 were added. A white precipitate formed. This solution was cooled to - 18 °C by an ice/salt mixture. 6.0 g 1,2:5,6-di-isopropylidene-D-allose in 300 ml CH_2Cl_2 were slowly added. The mixture was then stirred for 90 min at - 18 °C.

The solution was extracted three times with 400 ml 5 % aqueous $NaHCO_3$ and dried over Na_2SO_4. After evaporation of the solvent (bath temperature < 30 °C) a light yellow viscous liquid was obtained in 60 % yield.

NMR and mass spectra confirmed the structure.

The compound has to be stored at - 20 °C; it is not stable at RT.

3-Deoxy-3-iodo-1,2:5,6-di-isopropylidene-D-glucofuranose (III)

This compound was prepared according to Garegg and Samuelson (35) using triphenylphosphine, iodine and imidazole as reagents.

A crystalline compound was obtained in 60 % yield. This crystalline compound contained about 6 % triphenylphosphine oxide (mp 53 °C).
NMR and mass spectra confirmed the structure.

3-Deoxy-3-bromo-1,2:5,6-di-isopropylidene-D-glucofuranose (IV)

This compound was prepared according to Binkley et al. (16) by S_N2 substitution with tetrabutylammonium bromide on (II).

A crystalline compound was obtained in 70 % yield (mp 50 °C). NMR and mass spectra confirmed the structure.

3-Deoxy-3-iodo-D-glucose (V) and 3-deoxy-3-bromo-D-glucose (VI)

The protected halo sugars (III) or (IV), respectively, were hydrolyzed at 100 °C for 4 min in a mixture of 1 N HCl and methanol (1:1). After evaporation of the solvent, the 3-deoxy-3-halo-D-glucose (V) or (VI) were isolated in yields greater 90 %.

[^{123}I]-3-Deoxy-3-iodo-1,2:5,6-di-isopropylidene-D-glucose (VII) and [^{75,77}Br]-3-deoxy-3-bromo-1,2:5,6-di-isopropylidene-D-glucose (VIII)

a) via the tosylate (I): The radioactive halide solution (n.c.a.) was carefully evaporated to dryness. 5 mg of (I) in 2 ml acetone were added; this mixture was heated at 120 °C for 2 hr in a sealed ampoule. After evaporation of the acetone the residue was chromatographed on hplc using a Lichrosorb RP 18 column (50x0.4 cm) with methanol:water 1:1 as eluent. Maximum yields obtained were 1 %.

b) via the triflate (II): The radioactive halide solution (n.c.a.) was again carefully evaporated to dryness. The triflate (II) was purified as follows: 50 mg (II) was dissolved in 2 ml

CH_2Cl_2; this solution was extracted with 2 ml H_2O. After separation of the phases, the CH_2Cl_2 was dried over Na_2SO_4. 200 µl of this solution (5 mg (II)) were added to the radioactive halide; the CH_2Cl_2 was evaporated using a stream of N_2.

2 ml acetone were added and the resultant solution was heated at 170 °C for 20 min in a sealed ampoule. After evaporation of the solvent the residue was chromatographed on hplc using the same conditions as with the tosylate.

Yields varied between 10 and 35 % for both (VII) and (VIII). Maximum amounts prepared up to now were 2.2 mCi of (VII) or (VIII), respectively.

[^{123}I]-3-Deoxy-3-iodo-D-glucose (IX) and [^{75,77}Br]-3-deoxy-3-bromo-D-glucose (X)

The hydrolysis of the radioactive compounds was performed as described above for the non-radioactive compound (V) and (VI). Radiochemical yields were 73 % for (IX) and 68 % for (X), respectively. Maximum activities prepared up to now were 1.6 mCi for (IX) and 1.1 mCi for (X).

Table III. HPLC chromatography data for compounds used in the synthesis of 3-deoxy-3-halo-D-glucose.

Compound	I	II	III	IV	halide ion	diacetone-D-glucose	diacetone-D-allose
k'	11.0	1.0	15.3	13.4	0.3	0.7	0.3

Conditions: column: Lichrosorb RP 18, 10 µm (50x0.4 cm)
eluent: methanol:water 1:1
flow : 3 ml/min

b) 2-Deoxy-2-halo-D-glucose derivatives

Methyl 2-acetoxymercuri-3,4,6-tri-O-acetyl-2-deoxy-ß-D-glucopyranoside (XI) and methyl 2-acetoxymercuri-3,4,6-tri-O-acetyl-2-deoxy-α-D-mannopyranoside (XII)

Both (XI) and (XII) were prepared by addition of $Hg(OAc)_2$ to 3,4,6-tri-O-acetyl-D-glucal in absolute methanol according to Takiura and Honda (30). The total yield of (XI) + (XII) was 80 %. (XI) was isolated as white crystals in 40 % yield. NMR spectra confirmed the structure. The residual viscous liquid contained ∿ 90 % (XII) with ∿ 10 % (XI). The manno-epimer (XII) could not be obtained crystalline in accordance with literature data (30).

Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-iodo-ß-D-glucopyranoside (MTIG) (XIII) from (XI)

(XIII) was prepared from either (XI) or the 1:1 mixture of (XI) and (XII) by iodinolysis using I_2 in methanol according to Honda and Takiura (24).

The same mixture of epimers (gluco/manno) was obtained from either (XI) or the 1:1 mixture of (XI) and (XII). Obviously, a planar intermediate was formed in a S_E1 reaction.

The gluco-epimer (XIII) was isolated by hplc chromatography on silica gel using diethyl ether/hexane 7:3 as eluent.
(XIII) was obtained crystalline in 40 % yield. NMR spectra confirmed the structure.

Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-bromo-ß-D-glucopyranoside (MTBG) (XIV) from (XI)

(XIV) was prepared from (XI) analogous to the procedure described above for (XIII) with the only exception that $CHCl_3$ was used as solvent instead of CH_3OH. Yields were 40 % for (XIV).

[^{123}I]-MTIG (XV) from (XI)

1.13 mg (XI) in 500 µl CH_3OH were added to a solution of carrier added [^{123}I]I_2 (1.6 mCi) in 500 µl C_6H_6. The mixture was stirred for 2 h at RT. The mixture was then evaporated to dryness. The residue was taken up in 1.5 ml $CHCl_3$; the $CHCl_3$ phase was washed with 5 % $Na_2S_2O_3$, saturated $NaHCO_3$ and water, respectively. After drying over Na_2SO_4 the solvent was evaporated. The dry residue was chromatographed as described above for (XIII) to yield 0.35 mCi of (XV). The radiochemical yield was only 22 % calculated from ^{123}I-radioactivity, since only 50 % of I_2 can be utilized by this route.

[^{123}I]-MTIG (XV) and [^{75,77}Br]-MTBG (XVI) by direct halogenomethoxylation

The radioactive halide solution (n.c.a.) was carefully evaporated to dryness. 1 mg of 3,4,6-tri-O-acetyl-D-glucal in 250 µl CH_3OH were added; the radioactive halide was dissolved in this solution. Then, a solution of 0.12 mg N,N-dichloro-p-toluenesulfonamide (dichloramin T) in 50 µl CH_2Cl_2 was added via a syringe. The mixture was stirred for 20 min at RT.

After evaporation of the solvents, the residue was taken up in 1 ml of diethylether/n-hexane 7:3 and chromatographed on hplc using a silica gel Si60 column (25x1.6 cm) and diethylether/n-hexane 7:3 as eluent. At a flow rate of 3 ml/min, the retention times were

33 min for the manno epimer and 37 min for the gluco epimer. Retention times are identical for MTIG and MTBG.

The gluco epimer was collected, evaporated to dryness, taken up in 0.9 % saline and filtered through a sterile filter. The manno epimer was treated accordingly.
Radiochemical yields were 35 % for MTBG (XVI) and 40 % for MTIG (XV); corresponding yields were obtained for the manno epimer. Maximum activities produced thus far were 1.0 mCi for (XVI) and 1.2 mCi for (XV).

1,3,4,6-Tetra-O-acetyl-2-acetoxymercuri-2-deoxy-ß-D-gluco-pyranose (XVII)

1.55 g (≙ 5 mmole) of $Hg(OAc)_2$ were dissolved in 17.5 ml glacial acetic acid. When a clear solution was obtained, 1.25 g (≙ 4.6 mmole) 3,4,6-tri-O-acetyl-D-glucal in 5 ml glacial acetic acid were added. The mixture was stirred for 2 h at RT.

After that time the acetic acid was removed using a rotary evaporator; the bath temperature has to be kept below 40 °C. A viscous liquid residue was obtained which after standing at 4 °C for one week resulted in crystals of (XVII).

These were isolated in 30 % yield after washing with cold acetic acid. NMR spectra confirmed the structure (XVII).

The mother liquor contained a mixture of 70 % of the corresponding manno epimer with 30 % of the gluco epimer (identified by tlc and nmr).

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-iodo-ß-D-glucopyranose (XVIII) and 1,3,4,6-tetra-O-acetyl-2-deoxy-2-bromo-ß-D-glucopyranose (XIX)

(XVIII) was prepared from (XVII) by iodinolysis using I_2 in methanol. Analogously (XIX) was prepared by brominolysis using Br_2 in $CHCl_3$ as described above for (XIII) and (XIV), respectively. Yields were 40 % for the gluco epimer and 40 % for the manno epimer.

[^{123}I]-1,3,4,6-Tetra-O-acetyl-2-deoxy-2-iodo-ß-D-glucopyranose (XX) and [^{75,77}Br]-1,3,4,6-tetra-O-acetyl-2-deoxy-2-bromo-ß-D-glucopyranose (XXI)

Both (XX) and (XXI) were prepared from (XVII) using the same procedure as described above for MTIG (XV). 1.3 mCi of (XX) were obtained from 5 mCi of [^{123}I]I_2, while 0.45 mCi of (XXI) were obtained from 2 mCi of [^{77}Br]Br_2. Radiochemical yields were only about 25 % for each epimer, since only 50 % of the total halogen can be used in the reaction.

[^{123}I]-Methyl 2-deoxy-2-iodo-ß-D-glucopyranoside (MIDG) (XXII) and [^{75,77}Br]-methyl 2-deoxy-2-bromo-ß-D-glucopyranoside (MBDG) (XXIII)

The protected glucosides were deacetylated by two different methods:

a) using methoxide solution: The respective protected glucosides (XV) or (XVI) were dissolved in 0.1 N $NaOCH_3$ in absolute methanol (3 moles of $NaOCH_3$ per mole of (XV) or (XVI)) and stirred for 1 h at RT. The resulting solution was neutralized by fast addition of H_2SO_4. Excess sulfuric acid was precipitated

with $Ba(OH)_2$. After centrifugation and evaporation of solvents, (XXII) or (XXIII) were obtained in 70-80 % radiochemical yield in > 95 % radiochemical purity (tlc: systems A or B; see Table IV).

b) using ammonia: The protected glucosides (XV) or (XVI) were dissolved in 450 µl of 1 N methanolic NH_3 solution. This mixture was stirred for 5 h at RT. After evaporation of solvents, (XXII) or (XXIII) were obtained in 70-80 % radiochemical yield and > 95 % radiochemical purity (tlc: systems a or B; see Table IV).

Method a) is less reproducible than method b); but due to the shorter duration, method a) is the method of choice for the shorter half-life isotope ^{75}Br.

Attempted hydrolysis of (XX) or (XXI)

Attempts to hydrolyze the acetyl esters of XX or XXI to yield the corresponding 2-deoxy-2-halo-D-glucose were made using the following conditions:

a) 0.1 N $NaOCH_3$ in MeOH

b) 1 N NH_3 in MeOH

as described above for the preparation of MIDG or MBDG ((XXII) or (XXIII))

c) refluxing in aqueous 0.1 N H_2SO_4 or HCl for 2 h

d) reacting with an excess of BBr_3 in CH_2Cl_2 for 10 min at - 80 °C, followed by aqueous work-up.

All these attempts resulted in exclusive formation of radioactive halide.

Attempted hydrolysis of MIDG (XXII) or MBDG (XXIII)

Of the conditions described above for the hydrolysis of (XX) or (XXI), only the acidic conditions c) and d) were used in the attempt to hydrolyze the methyl glucoside. Again, exclusive formation of radioactive halide was observed.

Table IV. Tlc chromatography data for compounds used in the synthesis of 2-deoxy-2-halo-D-glucose derivatives.

System A

Compound	Methyl-ß-D-		XXII	XV	XVIII	halide
	glucoside	mannoside	XXIII	XVI	XIX	ion
R_F	0.31	0.39	0.72	0.97	0.94	0.20

System B

Compound	Methyl-ß-D-		XXII	XV	XVIII	halide
	glucoside	mannoside	XXIII	XVI	XIX	ion
R_F	0.021	0.027	0.031	0.57	0.64	0

Conditions: SiO_2 thin layer plates

eluent: system A: $CHCl_3$:CH_3OH:H_2O 30:9:1

system B: diethyl ether:n-hexane 7:3

R_F-values are identical for the bromo- and iodo-derivatives.

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