Carbohydrate Research 344 (2009) 1464–1473

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

D-Glucose- and D-mannose-based antimetabolites. Part 2. Facile synthesis of 2-deoxy-2-halo-D-glucoses and -D-mannoses

Izabela Fokt, Slawomir Szymanski, Stanislaw Skora, Marcin Cybulski, Timothy Madden, Waldemar Priebe *

Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA

ARTICLE INFO

Article history:
Received 17 March 2009
Received in revised form 29 May 2009
Accepted 12 June 2009
Available online 21 June 2009

Dedicated to Professor Hans Kamerling on the occasion of his 65th birthday

Keywords:
2-Deoxy-2-halo-D-glucose
2-Deoxy-2-halo-D-mannose
Inhibitors of glycolysis
Synthesis

ABSTRACT

Modified D-glucose and D-mannose analogs are potentially clinically useful metabolic inhibitors. Biological evaluation of 2-deoxy-2-halo analogs has been impaired by limited availability and lack of efficient methods for their preparation. We have developed practical synthetic approaches to 2-deoxy-2-fluoro-, 2-chloro-2-deoxy-, 2-bromo-2-deoxy-, and 2-deoxy-2-iodo derivatives of D-glucose and D-mannose that exploit electrophilic addition reactions to a commercially available 3,4,6-tri-*O*-acetyl-D-glucal.

1. Introduction

Glycolysis is an energy-generating anaerobic metabolism of D-glucose resulting in the net gain of two adenosine triphosphate (ATP) molecules. Tumor cells can adopt this metabolic pathway and use it to produce ATP without using oxygen even under normoxia in a process known as the Warburg effect.[1]

One of the most interesting and clinically explored properties of 2-deoxy-D-*arabino*-hexose (2-deoxy-D-glucose, 2-DG) is its ability to inhibit glycolysis.[2] Lack of the hydroxyl group at C-2 in 2-DG prevents its further metabolism to D-fructose 6-phosphate and leads to the accumulation of 2-DG 6-phosphate inside highly glycolytic tumor cells. High intracellular concentrations of 2-DG 6-phosphate block D-glucose metabolism and induce a unique form of tumor cell death called autophagy.[3]

The same principle that leads to preferential accumulation of 2-DG in tumor cells was exploited by ^{18}F labeling of 2-deoxy-2-fluoro-D-glucose (**1**), which is now widely used as cancer diagnostic and imaging agent in positron emission tomography (PET).[4]

We have demonstrated in a paper (Part 1)[5] preceding this work that 2-deoxy-2-fluoro-D-glucose (**1**) displays increased antitumor activity when compared with 2-DG, and we have subsequently showed that **1** is a potent inducer of autophagy in tumor cells. We have also synthesized and isolated pure 2-chloro-2-deoxy-D-glucose (**3**) and 2-bromo-2-deoxy-D-glucose (**5**) and noticed that existing synthetic methodology needs improvement prior to scale-up. Further in vitro evaluation in tumor cell lines indicated that the antitumor activity of 2-chloro-2-deoxy-D-glucose (**3**) and 2-bromo-2-deoxy-D-glucose (**5**) was lower than that of 2-DG and 2-deoxy-2-fluoro-D-glucose (**1**).[5]

Because of the structural similarities (2-DG is also a 2-deoxy-D-mannose), 2-DG can interfere with metabolism of either D-glucose or D-mannose. Thus, it was important to evaluate biological properties of all C-2 halogen-substituted analogs of D-glucose (**1, 3, 5, 7)** as well as D-mannose (**2, 4, 6, 8**) (Chart 1). To achieve this goal and make all these compounds available to other researchers, we have focused on developing improved synthetic approaches allowing for a preparation of multigram quantities of the desired analogs.

2. Results

2.1. Synthesis of 2-deoxy-2-fluoro-D-glucose and 2-deoxy-2-fluoro-D-mannose

Synthetic approaches to 2-deoxy-2-fluoro-D-glucose (**1**) have been the subject of intense studies since ^{18}F isotopically labeled 2-deoxy-2-fluoro-D-glucose is being widely used as cancer diagnostic and imaging agent in positron emission tomography (PET).[4] For the last 50 years different fluorinating agents such as fluorine,[6] acetyl hypofluorite,[7–12] trifluoromethyl hypofluorite,[13–15] or xenon

* Corresponding author. Tel.: +1 713 792 3777; fax: +1 713 745 4975.
E-mail address: wpriebe@mdanderson.org (W. Priebe).

0008-6215/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2009.06.016

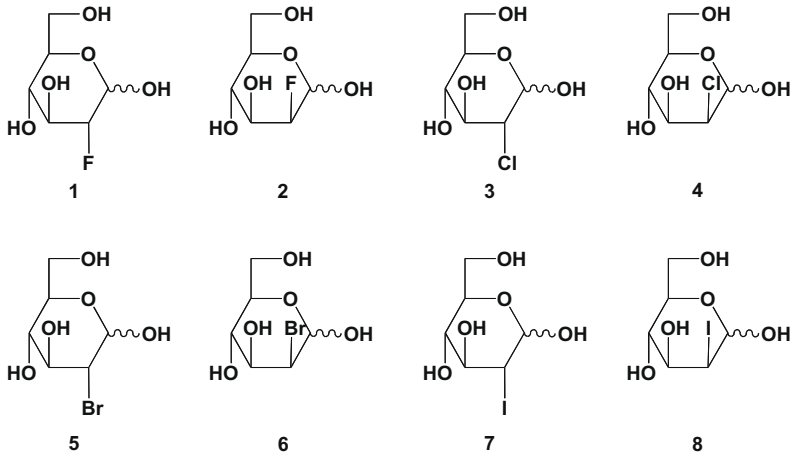
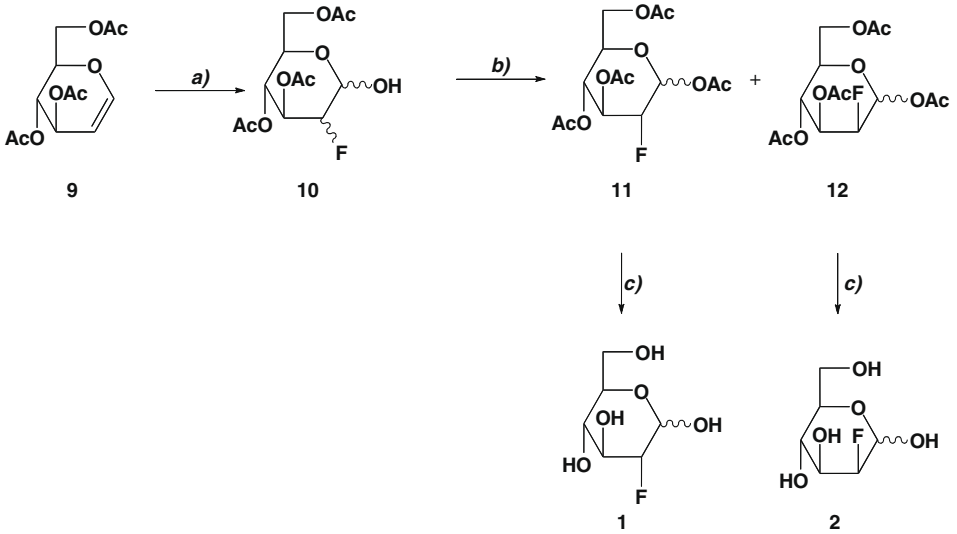


Chart 1. 2-Deoxy-2-halo-substituted D-glucose and D-mannose compounds.

difluoride[16,17] in organic solvents or water[18] have been used to transform D-glucal and its derivatives, or appropriately protected methyl glucosides or mannosides, into 2-deoxy-2-fluoro derivatives. Such fluorinating agents have limitations as they are potentially hazardous, highly corrosive, or impractically expensive. Preparation of selectively protected 2-*O*-trifluoromethanesulfonyl esters of methyl glucosides or mannosides requires multistep syntheses, and although these processes allow the use of mild and safe tetrabutylammonium fluoride as a fluoride source, this approach can be quite costly for large-scale processes. Similarly, 1,3,4,6-tetra-*O*-acetyl-β-D-mannose treated with DAST[19] has been shown to lead to 2-deoxy-2-fluoro-D-mannose derivatives, but it is only convenient for small-scale reactions.

Our approach to large-scale fluorination has explored the reaction of commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**9**) with Selectfluor®, a relatively novel and convenient electrophilic N-fluorinating reagent[20–22] (see Scheme 1). According to the procedure described by Ortner et al.[20] the reaction of D-glucal (**9**) using a 20% excess of Selectfluor® in a mixture of 5:1 nitromethane–water gives 2-deoxy-2-fluoro-D-*gluco*- and 2-deoxy-2-fluoro-D-*manno* isomers in a ratio of 41:33 with an overall yield of 61% after separation. Because our initial in vivo biological testing required over 100 g of the final product, we tested the applicability of Selectfluor® to a large-scale fluorination of D-glucal (**9**).

The scale of our fluorination reactions with Selectfluor® ranged from 30 g to 100 g of peracetylated D-glucal (**9**) per batch. All reactions gave a mixture **(10)** with 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannose and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucose as the main products in a ratio of 42:48 with an overall yield of ~60%. The two additional minor products (3–5%) present in the reaction mixture were isolated and determined to be a 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucosyl fluoride and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannosyl fluoride in a ratio of 1.4:1**.** Separation of the *gluco* and *manno* isomers was not practical at this stage of the process; therefore, the crude reaction mixture was acetylated and subsequently subjected to low-pressure column chromatography to give pure peracetylated 2-deoxy-2-fluoro-D-glucose (**11**) in a 49% yield and peracetylated 2-deoxy-2-fluoro-D-mannose (**12**) in a 42% yield. Deacetylation of **11** and **12** under basic conditions in MeOH led to their respective methyl glycosides instead of the desired fully unprotected 2-deoxy-2-fluorohexoses; thus acidic conditions were used. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranose (**11**) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-mannopyranose (**12**) were heated with N HCl at 70 °C to give fully deprotected 2-deoxy-2-fluoro-α,β-D-glucose **(1)** and 2-deoxy-2-fluoro-α,β-D-mannose **(2)**, respectively (see Tables 1 and 2). Deacetylation carried in the presence of N HCl was very effective, and final products were isolated in 70% to >80% yields.



Scheme 1. Synthesis of 2-deoxy-2-fluoro-D-glucose and -D-mannose. Reagents and conditions: (a) Selectfluor®, $MeNO_2$, H_2O; (b) Ac_2O–pyridine, CH_2Cl_2; (c) N HCl.

In the last step of such a deacetylation reaction, the strong inorganic acid must be neutralized, generally with barium or silver carbonates.[23,24] To increase the practicality of the process, reduce the cost, and avoid a prolonged filtration step, we successfully used sodium carbonate. Simple treatment of the reaction mixture with a stoichiometric amount of Na_2CO_3, followed by evaporation of water and column chromatography, gave us the pure deprotected products **1** and **2**.

2.2. Synthesis of 2-chloro-2-deoxy-α,β-D-glucose and 2-chloro-2-deoxy-α,β-D-mannose

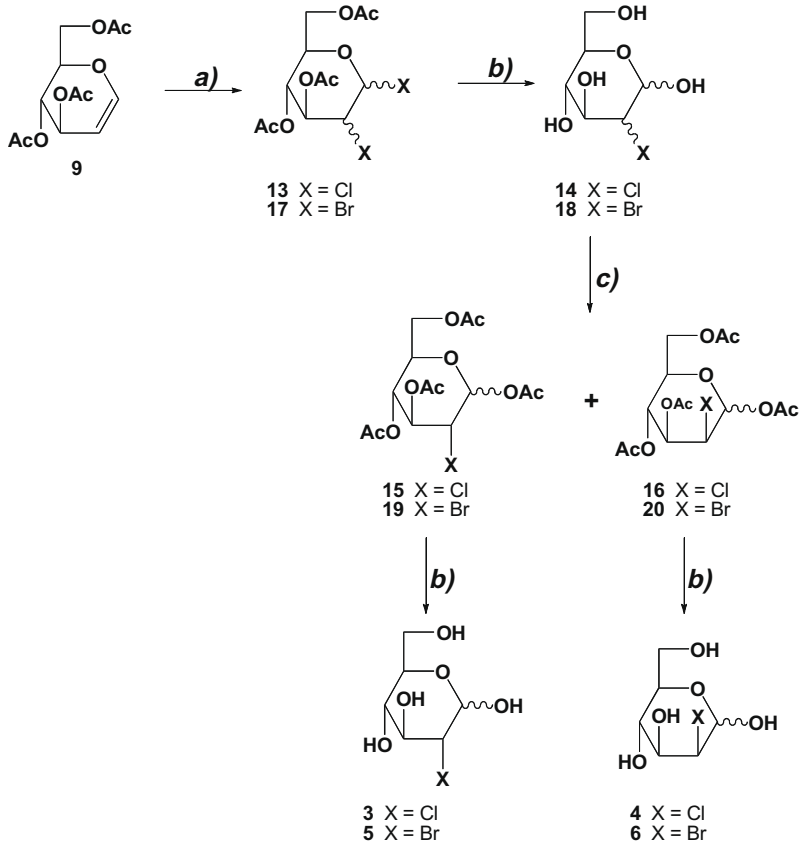
2-Chloro-2-deoxy-D-glucose (**3**) and 2-chloro-2-deoxy-D-mannose (**4**) were prepared on multigram scales according to method in Scheme 2. Direct chlorination of 3,4,6-tri-*O*-acetyl-D-glucal (**9**) was first described by Fisher,[25] and the effects of solvent on the stereochemistry and yield of the addition reaction have also been assessed by others.[26–32] It has been shown by Igarashi that, using dichloromethane (DCM) as a solvent in the reaction of the addition of chloride to peracetylated glucal **9**, the ratio of *gluco:manno* dichlorides was 1.6:1.[31] Since our goal was to obtain both *gluco* and *manno* compounds, dichloromethane was our solvent of choice. Previous experience with the synthesis of 2-deoxy-2-fluoro derivatives **1** and **2** indicated that the most efficient way for separation of *gluco* and *manno* isomers was through their peracetylated derivatives **11** and **12**.

Thus D-glucal (**9**) was chlorinated in DCM to produce a mixture of dichloro derivatives **13** (see Scheme 2). The crude mixture of **13** was deprotected under acidic conditions and subsequently acetylated to produce a mixture of 1,3,4,6-tetra-*O*-acetyl-2-chloro-2-deoxy-α,β-D-glucose (**15**) and 1,3,4,6-tetra-*O*-acetyl-2-chloro-2-deoxy-α,β-D-mannose (**16**). Column chromatography led to efficient separation of the *gluco* and *manno* isomers. Pure **15** and **16** were efficiently deacetylated using N HCl to produce fully deprotected 2-chloro-2-deoxy-α,β-D-glucose (**3**) and 2-chloro-2-deoxy-α,β-D-mannose (**4**) (see Tables 3 and 4).

Chemical characterization of the free 2-deoxy-2-halo hexopyranoses is rather limited or not reported. Data are available for their derivatives rather than for the fully deprotected compounds. Because of the biological importance of these analogs, we have undertaken efforts to characterize them in more detail. For example, no analytical data have been reported for the 2-chloro-2-deoxy-α,β-D-mannose (**4**) except optical rotation.[23] We have performed detailed NMR analysis of compound **4** using 1D as well as 2D NMR experiments (GRADCOSY, C13 HSQC, and ROESY) and have assigned chemical shifts for the α and β anomers of 2-chloro-2-deoxy-α,β-D-mannose (**4**) (see Tables 3 and 4). Similar studies have been performed for all final 2-deoxy-2-halo-hexopyranoses. Our NMR data fully confirm the proposed structures and were consistent with previously reported data (see Tables 1–4).

2.3. Synthesis of 2-bromo-2-deoxy-α,β-D-glucose and 2-bromo-2-deoxy-α,β-D-mannose

The only method that allowed for direct synthesis of 2-bromo-2-deoxy-α,β-D-glucose and 2-bromo-2-deoxy-α,β-D-mannose from D-glucal was reported by Liu and Wong.[33] The authors used potassium bromide and chloroperoxidase in the presence of hydrogen peroxide, which gave a 1:1 mixture of *gluco* and *manno* isomers **5** and **6**, respectively. No separation of unprotected 2-bromo-2-deoxy-α,β-D-glucose **(5)** and 2-bromo-2-deoxy-α,β-D-mannose **(6)** has been reported. The products were isolated and characterized



Scheme 2. Synthesis of 2-chloro-2-deoxy and 2-bromo-2-deoxy derivatives of D-glucose and D-mannose. Reagents and conditions: (a) Br_2, CH_2Cl_2 or Cl_2–CH_2Cl_2; (b) N HCl; (c) Ac_2O–pyridine.

Table 1
^{1}H NMR data for α and β anomers of 2-deoxy-2-fluoro-D-glucose (**1α**, **1β**) and 2-deoxy-2-fluoro-D-mannose (**2α**, **2β**)[a]

Compound	H-1 $J_{1,2}$ $J_{F,1}$	H-2 $J_{2,3}$ $J_{F,2}$	H-3 $J_{3,4}$ $J_{F,3}$	H-4 $J_{4,5}$ $J_{F,4}$	H-5 $J_{5,6}$ $J_{F,5}$	H-6 $J_{6a,6b}$ $J_{F,6}$
1α	5.33 3.8 Hz —	4.30 9.5 Hz 49.4 Hz	3.86 9.4 Hz 18.7 Hz	3.8–3.3 m —	3.8–3.3 m —	3.8–3.3 m —
1β	4.79 7.8 Hz 2.2 Hz	4.00 9.0 Hz 51.4 Hz	3.8–3.3 m —	3.8–3.3 m —	3.8–3.3 m —	3.8–3.3 m —
2α	5.28 — 7.2 Hz	4.66 2.1 Hz 49.6 Hz	3.82 9.9 Hz —	3.61 9.9 Hz —	4.0–3.7 m —	4.0–3.7 m —
2β	4.91 — 20.3 Hz	4.70 — 51.6 Hz	4.0–3.7 m —	3.53 9.7 Hz —	3.35 — —	4.0–3.7 m —

[a] All spectra recorded in D_2O.

Table 2
^{13}C NMR data for α and β anomers of 2-deoxy-2-fluoro-D-glucose (**1α**, **1β**) and 2-deoxy-2-fluoro-D-mannose (**2α**, **2β**)[a]

Compound	C-1 $J_{F,1}$	C-2 $J_{F,2}$	C-3 $J_{F,3}$	C-4 $J_{F,4}$	C-5 $J_{F,5}$	C-6 $J_{F,6}$
1α	89.62 18.0 Hz	92.26 105.8 Hz	71.15 13.5 Hz	69.16 4.8 Hz	71.25 —	60.56[b] —
1β	93.5 13.9 Hz	92.79 94.5 Hz	74.03 10.3 Hz	69.28 4.9 Hz	76.02 —	60.37[*] —
2α	91.27 29.5 Hz	90.32 172.2 Hz	69.4 17.5 Hz	66.82 —	72.25 —	60.55 —
2β	92.30 15.8 Hz	91.28 180.2 Hz	71.81 17.4 Hz	66.59 —	76.05 —	60.71

[a] All spectra recorded in D_2O.
[b] Not assigned (either α or β).
[*] Chemical shift value is either for α or β anomer.

Table 3
^{1}H NMR data for α and β anomers of 2-chloro-2-deoxy-D-glucose (**3α**, **3β**), 2-chloro-2-deoxy-D-mannose (**4α**, **4β**), 2-bromo-2-deoxy-D-glucose (**5α**, **5β**), 2-bromo-2-deoxy-D-mannose (**6α**, **6β**), 2-deoxy-2-iodo-D-glucose (**7α**, **7β**), and 2-deoxy-2-iodo-D-mannose (**8α**, **8β**)[a]

Compound	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6}$; $J_{5,6}$	H-6 $J_{6,6}$	H-6 $J_{6,6}$
3α	5.06 —	3.7–3.6 m	3.54 10.0 Hz	3.13 9.6 Hz	3.7–3.6 m	3.7–3.6 m	3.6 11.8 Hz
3β	4.51 8.0 Hz	3.35 8.0 Hz	3.29 9.0 Hz	3.09 9.0 Hz	3.21–3.18 m	3.7–3.6 m	3.43 12.0 Hz
4α	5.29 1.5 Hz	4.27 3.6 Hz	4.06 9.3 Hz	3.83–3.62 m	3.83–3.62 m	3.83–3.62 m	3.83–3.62 m
4β	5.06 —	4.39 3.4 Hz	3.87 9.4 Hz	3.57 9.4 Hz	3.34 6.2 Hz; 1.9 Hz	3.83–3.62 m	3.83–3.62 m
5α	5.11 3.1 Hz	3.95 10.5 Hz	3.60 8.5 Hz	3.12 9.4 Hz	3.19 5.7 Hz; 1.8 Hz	3.48–3.41 m	3.48–3.41 m
5β	4.60 8.5 Hz	3.49 9.0 Hz	3.35 8.6 Hz	3.08 9.4 Hz	3.66 m	3.48–3.41 m	3.48–3.41 m
6α	3.23 —	4.33 3.8 Hz	3.89 9.1 Hz	3.84–3.53 m	3.84–3.53 m	3.84–3.53 m	3.84–3.53 m
6β	4.84 1.2 Hz	4.45 3.6 Hz	3.84–3.53 M	3.84–3.53 m	3.36 6.2 Hz; 2.3 Hz	3.36 m	3.84–3.53 m
7α	5.31 3.0 Hz	3.91 11.2 Hz	3.83–3.78 M	3.35 9.6 Hz	3.83–3.78 m	3.75–3.67 m	3.75–3.67 m
7β	4.90 8.7 Hz	3.71 9.3 Hz	3.75–3.67 M	3.29 9.3 Hz	3.43–3.37 m	3.83–3.78 m	3.83–3.78 m
8α	5.52 —	4.42 4.0 Hz	3.22 9.0 Hz	3.67–3.63 m	3.87–3.81 m	3.82–3.75 m	3.71 12.3 Hz
8β	4.16 —	4.55 3.9 Hz	3.15 9.1 Hz	3.58 9.4 Hz	3.43–3.37 m	3.82–3.75 m	3.67–3.63 m

[a] Spectra recorded in D_2O for compounds **4**–**7** and in DMSO-d_6 + D_2O for compounds **3**.

Table 4
^{13}C NMR data for α and β anomers of 2-chloro-2-deoxy-D-glucose (**3α**, **3β**), 2-chloro-2-deoxy-D-mannose (**4α**, **4β**), 2-bromo-2-deoxy-D-glucose (**5α**, **5β**), 2-bromo-2-deoxy-D-mannose (**6α**, **6β**), 2-deoxy-2-iodo-D-glucose (**7α**, **7β**), and 2-deoxy-2-iodo-D-mannose (**8α**, **8β**)[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6
3α	91.95	62.67	72.84	71.38	72.27	60.97
3β	96.31	65.30	76.90	70.99	76.71	61.01
4α	93.85	61.96	68.83	66.44	72.87	60.75*
4β	91.95	64.90	71.77	66.10	76.65	60.61*
5α	92.23	52.80	71.74	70.71	72.78	60.43
5b	95.87	55.65	76.32	70.34	75.95	60.58
6α	94.07	55.45	68.36	67.29	73.08	60.81*
6β	91.53	60.06	71.35	66.95	76.83	60.66*
7α	96.59	32.94	71.98	70.56	77.06	60.43
7β	96.59	36.44	73.31	70.25	75.95	60.57
8α	95.46	37.21	67.83	68.96	73.26	60.70
8β	91.42	44.57	70.87	68.67	76.93	60.87

[a] Spectra recorded in D_2O for compounds **4**–**7** and in DMSO-d_6 + D_2O for compounds **3**.
* Chemical shift value is either for α or β anomer.

only as their peracetylated derivatives. The only synthesis of fully deprotected 2-bromo-2-deoxy-α,β-D-mannose **(6)** was reported by David et al.[34] in an elegant approach using *N*-bromophthalimide as the source of bromine.

Based on our experience, the literature reports, and the need for obtaining multigram amounts of both 2-bromo-2-deoxy-α,β-D-glucose (**5**) and 2-bromo-2-deoxy-α,β-D-mannose (**6**), we used a similar synthetic approach that permitted the efficient preparation of both 2-deoxy-2-fluoro- and 2-chloro-2-deoxy-D-glucoses and -mannoses in large, laboratory-scale reactions (i.e., >100 g, (see Scheme 2). Thus, we selected the addition of bromine to commercially available peracetylated glucal (**9**) as a preferred approach. The addition of bromine to 3,4,6-tri-*O*-acetyl-D-glucal (**9**) led to a mixture **17** of 3,4,6-tri-*O*-acetyl-1,2-dibromo-1,2-dideoxy-β-D-glucose and 3,4,6-tri-*O*-acetyl-1,2-dibromo-1,2-dideoxy-α-D-mannose with ratio of isomers of 2.6:1. Such a combination was heated with N HCl at 70 °C to produce a mixture **18** that was subsequently acetylated. Peracetylated 2-bromo-2-deoxy derivatives were efficiently separated by low-pressure chromatography. Acidic deacetylation of either pure 1,3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-α,β-D-glucose (**19**) or 1,3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-α,β-D-mannose (**20**) gave, in excellent yields, the desired 2-bromo-2-deoxy-α,β-D-glucose (**5**) and 2-bromo-2-deoxy-α,β-D-mannose (**6**), respectively. The structures of all compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopies (see Tables 3 and 4).

2.4. Synthesis of 2-deoxy-2-iodo-α,β-D-glucose and 2-deoxy-2-iodo-α,β-D-mannose

The first reported attempt to synthesize 2-deoxy-2-iodo-α,β-D-glucose and 2-deoxy-2-iodo-α,β-D-mannose used iodonolysis of C-2-mercurated D-mannose or D-glucose derivatives;[35] however, no supporting analytical data were presented. Other reports described this method as difficult to repeat.[36]

The most efficient method for the introduction of an iodine substituent at C-2 has been an addition reaction of *N*-iodosuccinimide to the double bond of D-glucal. Stereochemistry of the addition reaction to differentially protected D-glucal has been studied by several groups, and the 2-deoxy-2-iodo-D-*manno* isomer appeared to be the predominant product. It was also noted that the ratio of *manno* and *gluco* isomers was affected by the nature of the D-glucal substituents and temperature, thus indicating that the preference for the D-*manno* isomer could be reversed. It has been shown that addition of *N*-iodosuccinimide to 3,4,6-tri-*O*-(*tert*-butyldiphenylsilyl)-D-glucal in the presence of acetic acid in toluene at 100 °C led to mixture of 1-*O*-acetyl-2-deoxy-2-iodo-D-*gluco*- and D-*manno* isomers with a *gluco* to *manno* ratio of 9:1.

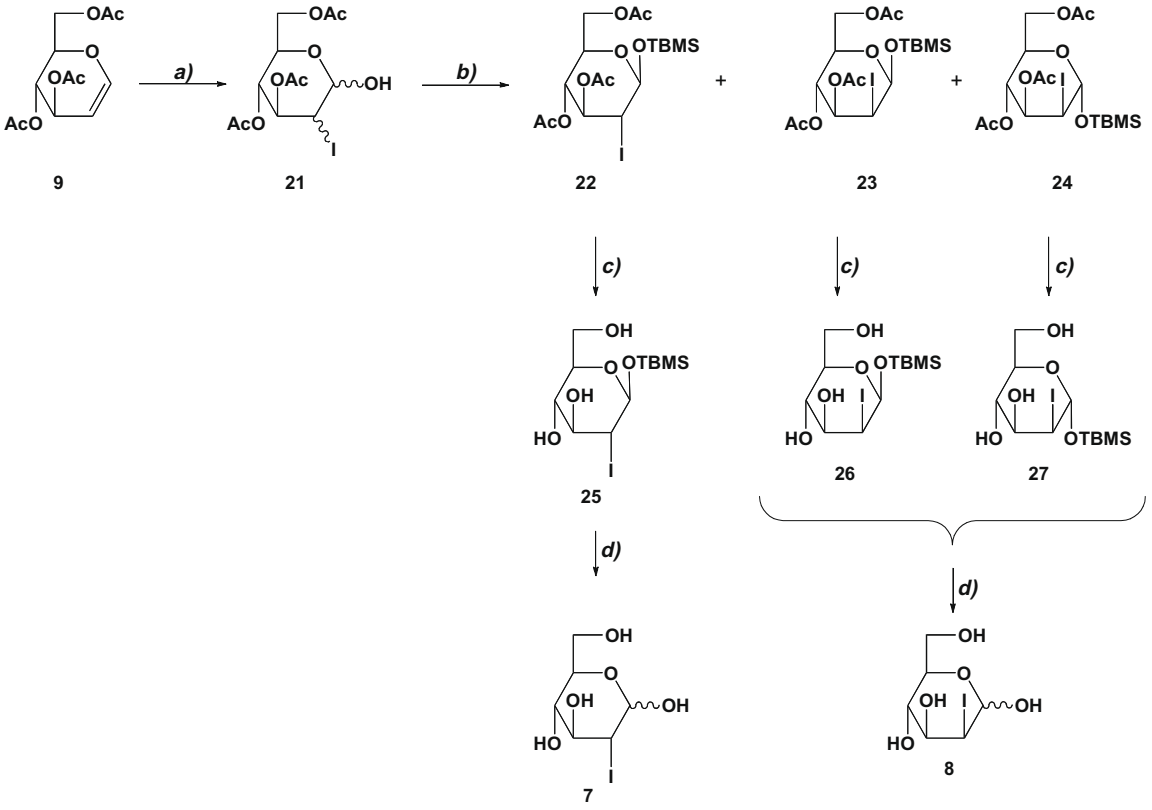
This method was used by Morin[36] for synthesis of 2-deoxy-2-iodo-α,β-D-glucose. The initial mixture of 1-*O*-acetyl-2-deoxy-2-iodo-D-*gluco* and -D-*manno* isomers was separated by column chromatography, then the silyl ethers were removed by treatment with the HF·Et$_3$N complex at 65 °C for 24 h. The last step, deacetylation at the anomeric center, was completed by the method described by Excoffier and co-workers[37] using hydrazine acetate in MeOH. Unfortunately the final product required chromatographic purification twice in order to obtain pure 2-deoxy-2-iodo-α,β-D-glucose, which was only partially characterized by NMR spectroscopy. In the same report the synthesis of 2-deoxy-2-iodo-α,β-D-mannose was described using an iodohydration reaction previously described by Liu and Wong[33] for 2-deoxy-2-iodo-D-galactal. No information was provided concerning the separation, purity, or yield of the product or its characterization. The structure was confirmed by its peracetylated derivative.

In order to develop a practical method for the preparation of both 2-deoxy-2-iodo-α,β-D-glucose (**7**) and 2-deoxy-2-iodo-α,β-D-mannose (**8**), we have focused on the addition reaction using *N*-iodosuccinimide, in the presence of water, with commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**9**) (see Scheme 3). Pilot reactions were performed to test the effects of different solvents and temperature on the proportion of *gluco* to *manno* isomers and on the overall yield of the reaction. Under our preferred conditions the addition reaction of *N*-iodosuccinimide in the presence of water to 3,4,6-tri-*O*-acetyl-D-glucal (**9**) led to the formation of 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α,β-D-glucose and 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α,β-D-mannose in a ratio of 2:3. This crude mixture was silylated with *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane. The silylation reaction was performed in the smallest possible amount of solvent to achieve a high concentration of reagents. Under such conditions the 1-O-silylated β anomers, with *manno* and *gluco* configurations, were the main products, accompanied by only a minor product having the α-*manno* configuration. Subsequent chromatography led to a separation of pure isomers in high yield (96.5% total). Each compound was then deacetylated using a catalytic amount of N sodium methoxide in MeOH and then adjusted to neutral pH using a stoichiometric amount of acetic acid. Evaporation of the solvents, followed by column chromatography, led to high yields (>95%) of 2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-mannopyranose (**26**), 2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranose (**27**) and 2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose (**25**), respectively. Subsequently, efficient desilylation at the C-1 position using trifluoroacetic acid in acetonitrile and water, followed by the evaporation of solvents and immediate chromatography, gave the required 2-deoxy-2-iodo-α,β-D-glucose (**7**) and 2-deoxy-2-iodo-α,β-D-mannose **(8)** in ~70% overall yield of the process calculated from 3,4,6-tri-*O*-acetyl-D-glucal. Use of inexpensive and commercially available substrates and reagents, combined with short reaction times, simple workups and high yields, makes this the method of choice for the preparation of 2-deoxy-2-iodo-α,β-D-glucose (**7**) and 2-deoxy-2-iodo-α,β-D-mannose (**8**) on a large laboratory scale.

3. Experimental

3.1. General methods

NMR spectra were recorded with Bruker Avanti 300 and 500 spectrometers. Chemical shifts are referenced to Me$_4$Si as the internal reference. ^{1}H and ^{13}C signals were assigned based on 2D spectra: proton–proton correlation (GRADCOSY), and proton–carbon correlation (C13HSQC); in addition for D-mannose derivatives proton–carbon correlation (ROESY) experiments were also performed



Scheme 3. Synthesis of 2-deoxy-2-iodo derivatives of D-glucose and D-mannose. Reagents and conditions: (a) NIS, H_2O, toluene reflux; (b) TBDMSCl, imidazole, CH_2Cl_2; (c) N NaOMe, MeOH; (d) CF_3CO_2H, H_2O.

to confirm signal assignments. High-resolution mass spectra were acquired using the Waters Quattro Ultima Q-TOF instrument. Optical rotations were determined on a Jasco DIP-370 digital polarimeter at room temperature. Melting points were measured with a Buchi 530 apparatus and are not corrected. Thin-layer chromatography (TLC) was carried on an aluminum sheet coated with Silica Gel 60 F_{254} (EMD Chemicals, Inc.). Compounds were visualized on TLC plates by spraying with 20% H_2SO_4 in EtOH and gently heating. Silica gel column chromatography was performed with a CombiFlash Companion purification system (Teledyne ISCO) and Biotage SP1 purification system. Selectfluor® is a product of Sigma–Aldrich Chemical Co.

3.2. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (11) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (12)

The solution of 3,4,6-tri-*O*-acetyl-D-glucal **(9)** (60 g, 0.22 mol) in a mixture of nitromethane (500 mL) and water (100 mL) was prepared and cooled to 0 °C. Selectfluor® (100 g, 0.282 mol) was added, and the reaction mixture was stirred overnight, while the temperature was allowed to rise to ambient. The reaction mixture was refluxed for 1 h, then the solvents were evaporated. CH_2Cl_2 (500 mL) was added, followed by a 5% $NaHCO_3$ solution (200 mL). The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The crude product was dissolved in CH_2Cl_2 (500 mL) and pyridine (32 mL, 0.4 mol), followed by Ac_2O (25 mL, 0.264 mol), and the reaction mixture was stirred overnight. The mixture was washed with a solution of satd $NaHCO_3$ (150 mL), then washed with water until a neutral pH was achieved. The organic solution was dried over anhyd Na_2SO_4. The solvent was evaporated under reduced pressure, and the residual amount of pyridine was removed by co-evaporation with toluene (3 × 100 mL). The remaining residue containing mixture of compounds **11** and **12** was separated using a low-pressure liquid chromatography apparatus and hexanes–EtOAc gradient (10–40% of EtOAc) as an eluent to give pure 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (**11**) (37.4 g, 0.107 mol, 48.5%, α:β ratio = 1:1.5); R_f 0.56 (1:1 hexanes–EtOAc). Data for **11:** ^{1}H NMR ($CDCl_3$): δ 6.42 d 1H, $J_{1,2}$ = 4.0 Hz, H-1α), 5.78 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{1,F}$ = 3.2 Hz, H-1β), 5.55 (ddd, 1H, $J_{3,F}$ = 12.1 Hz, $J_{3,2}$ = $J_{3,4}$ = 9.5 Hz, H-3α), 5.37 (ddd, 1H, $J_{3,F}$ = 14.3 Hz, $J_{3,2}$ = $J_{3,4}$ = 9.2 Hz, H-3β), 5.09 (dd, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.2 Hz, H-4α), 5.07 (dd, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.6 Hz, H-4β), 4.74 (ddd, 1H, $J_{H,F}$ = 48.5 Hz, $J_{2,3}$ = 9.6 Hz, $J_{2,1}$ = 4.0 Hz, H-2α), 4.54 (ddd, 1H, $J_{H,F}$ = 50.1 Hz, $J_{2,3}$ = 9.2 Hz, $J_{2,1}$ = 8.1 Hz, H-2β), 4.34–4.26 (m, 2H, H-6α, H-6β), 4.1–4.02 (m, 3H, H-6α, H-6β, H-5α), 3.85 (ddd, 1H, $J_{5,4}$ = 10.0 Hz, $J_{5,6}$ = 4.5 Hz, $J_{5,6}$ = 3.2 Hz, H-5β), 2.20, 2.17, 2.08, 2.07, 2.04, 2.036, 2.033 (7s, 24H, OAc, α, β); HRMS: calcd for $C_{14}H_{19}FNaO_9$ $[M+Na]^+$ *m/z* 373.0911; found *m/z* 373.0843. The second eluted compound was 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (**12**) (32.4 g, 0.092 mol, 42%, α:β ratio = 0.9:10); R_f 0.44 (1:1 hexanes–EtOAc). ^{1}H NMR ($CDCl_3$): δ 6.28 dd, 1H, $J_{1,F}$ = 6.5 Hz, $J_{1,2}$ = 2.0 Hz, H-1β), 5.80 dd, 1H, $J_{1,F}$ = 18.8 Hz, H-1α), 5.43 (ddd, 1H, $J_{4,3}$ = $J_{4,5}$ = 10.1 Hz, $J_{4,F}$ = 1.0 Hz, H-4α), 5.44–5.36 (m, 1H, H-4α), 5.27 (ddd, 1H, $J_{3,F}$ = 27.6 Hz, $J_{3,4}$ = 10.1 Hz, $J_{3,2}$ = 2.5 Hz, H-3β), 5.06 (ddd, 1H, $J_{3,F}$ = 27.0 Hz, $J_{3,4}$ = 10.0 Hz, $J_{3,2}$ = 2.3 Hz, H-3α), 4.88 (dd, 1H, $J_{2,F}$ = 51.2 Hz, $J_{2,3}$ = 2.3 Hz, H-2α), 4.75 (ddd, 1H, $J_{2,F}$ = 48.7 Hz, $J_{2,1}$ = $J_{2,3}$ = 2.5 Hz, H-2β), 4.28 (dd, 1H, $J_{6,6}$ = 12.4 Hz, $J_{6,5}$ = 4.4 Hz, H-6α), 4.11 (dd, 1H, $J_{6,6}$ = 12.4 Hz, $J_{6,5}$ = 2.3 Hz, H-6α), 4.05 (ddd, 1H, $J_{5,4}$ = 9.9 Hz, $J_{5,6}$ = 4.4 Hz, $J_{5,6}$ = 2.3 Hz, H-5α), 2.19, 2.18, 2.12, 2.09, 2.06, 2.04 (6s, 24H, OAc, α, β); HRMS: calcd for $C_{14}H_{19}FNaO_9$ $[M+Na]^+$ *m/z* 373.0911; found *m/z* 373.0927.

3.3. Preparation of 2-deoxy-2-fluoro-α,β-D-glucopyranose (1)

A mixture of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranose (**11**) (37.4 g, 0.107 mol) and N HCl (370 mL) was prepared and heated with vigorous stirring at 70 °C. The progress of the reaction was monitored by TLC, and after completion, the reaction mixture was cooled to room temperature, and Na_2CO_3 (19.6 g, 0.185 mol) was added. The solution was evaporated to dryness, and MeOH (100 mL) was added to the residue. The resulting mixture was stirred for 15 min, then the solid was filtered off. The MeOH was evaporated, and the product was then purified by column chromatography using a $CHCl_3$–MeOH gradient increasing from 10% to 30%. Fractions containing the product were pooled together and evaporated to dryness. The residual solvents were removed using a vacuum pump to give 2-deoxy-2-fluoro-D-glucose **(1)** (13.6 g, 75 mmol, 70%) as a white powder: mp 163–167 °C, lit. 160–165 °C,[13] $[\alpha]_D$ +63.6 (*c*, 1.2 H_2O), lit.[3] +56. Anal. Calcd for $C_6H_{11}FO_5$: C, 39.56; H, 6.09. Found: C, 39.06; H, 6.06.

3.4. Preparation of 2-deoxy-2-fluoro-α,β-D-mannopyranose (2)

A mixture of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranose (**12**) (32.4 g, 0.092 mol) and N HCl (300 mL) was prepared and heated with vigorous stirring at 70 °C. Progress of the reaction was monitored by TLC, and after the reaction was completed the mixture was cooled to room temperature and Na_2CO_3 (15.9 g, 0.15 mol) was added. Water was then evaporated, and MeOH (50 mL) was added to the residue. The resultant mixture was stirred for 15 min, the solid was filtered off, MeOH was evaporated, and the product was purified by column chromatography using a $CHCl_3$–MeOH gradient increasing from 10% to 30%. Fractions containing the product were pooled and evaporated to dryness. The residual solvents were removed using a vacuum pump to give 2-deoxy-2-fluoro-α,β-D-mannopyranose **(2)** (14.6 g, 80 mmol, 87%)**:** mp 136–137 °C lit.[13] 131–132 °C, $[\alpha]_D$ + 27.3 (*c*, 1.18 H_2O), lit. +19 °C;[13] HRMS calcd for $C_6H_{11}FNaO_5$ $[M+Na]^+$ *m/z* 205.0488; found, *m/z* 205.0430.

3.5. 1,3,4,6-Tetra-*O*-acetyl-2-chloro-2-deoxy-α,β-D-glucopyranose (15) and 1,3,4,6-tetra-*O*-acetyl-2-chloro-2-deoxy-α,β-D-mannopyranose (16)

Chlorine was passed through a solution of 3,4,6-tri-*O*-acetyl-D-glucal **(9)** (20 g, 74.3 mmol) in CH_2Cl_2 (200 mL) until the solution became a pale yellow-green in color. The reaction mixture was stirred vigorously for 15 min., then the solvent was evaporated to dryness, and the remaining residue was subjected to separation by low-pressure column chromatography, using a hexane–EtOAc gradient (0–10% of EtOAc). Fractions containing the product were pooled and evaporated to give a mixture **13** (19.2 g, 56 mmol, 75.3%). A suspension of the mixture **13** (19.2 g, 56 mmol) in N HCl (192 mL, 0.192 mol) was prepared and heated with vigorous stirring at 70 °C. Progress of the reaction was monitored by TLC, and at completion, the reaction mixture was cooled to room temperature, and Na_2CO_3 (10.2 g, 0.096 mol) was added. Water was evaporated and MeOH (25 mL) was added to the residue. The resulting mixture was stirred for 15 min, and the solid was then filtered off. MeOH was then evaporated and the product was purified by column chromatography using a $CHCl_3$–MeOH gradient increasing from 10% to 30%. Fractions that contained the product were pooled together and evaporated to give **14** (14.4 g, 42 mmol, 74.9%). A solution of **14** (14.4 g, 72.5 mmol) in pyridine (144 mL) was prepared and cooled to 0 °C. Ac_2O (32 mL, 336 mmol) was added, and the reaction mixture was stirred overnight, while the temperature was allowed to rise to ambient. The reaction mixture was diluted with EtOAc (250 mL), and the resulting organic solution was washed with a solution of satd Na_2CO_3 until neutral, then with brine, and then dried over anhyd Na_2SO_4. The drying agent was filtered off, and solvents were evaporated to dryness. Remaining pyridine was removed by co-evaporation with toluene (3 × 100 mL). Products were then separated by low-pressure column chromatography using a hexanes–EtOAc gradient (10–40% EtOAc) to give 1,3,4,6-tetra-*O*-acetyl-2-chloro-2-deoxy-α,β-D-glucopyranose **(15)** (13.2 g, 36 mmol, 49.6%, α:β ratio 1:2.4); R_f 0.58 (1:1 hexanes–EtOAc), ^{1}H NMR ($CDCl_3$): δ 6.36 d, 1H, $J_{1,2}$ = 3.5 Hz, H-1α), 5.76 (d, 1H, $J_{1,2}$ = 8.8 Hz, H-1β), 5.48 (dd, 1H, $J_{4,5}$ = 10.5 Hz, $J_{4,3}$ = 9.5 Hz, H-4α), 5.30 (dd, 1H, $J_{4,5}$ = 10.3 Hz, $J_{4,3}$ = 9.4 Hz, H-4β), 5.10 (dd, 1H, $J_{3,2}$ = 10.1 Hz, $J_{3,4}$ = 9.5 Hz, H–3α), 5.07 (dd, 1H, $J_{3,2}$ = 10.0 Hz, $J_{3,4}$ = 9.4 Hz, H-3β), 4.33 (dd, 1H, $J_{6,6}$ = 12.5 Hz, $J_{6,5}$ = 4.5 Hz, H-6β), 4.31 (dd, 1H, $J_{6,6}$ = 12.3 Hz, $J_{6,5}$ = 4.2 Hz, H-6α), 4.18–4.05 (m, 4H, H-2α, H-6α, H-6β, H-5α), 3.89 (dd, 1H, $J_{2,1}$ = 8.8 Hz, $J_{2,3}$ = 10.3 Hz, H-2β), 3.88 (ddd, 1H, $J_{5,4}$ = 10.0 Hz, $J_{5,6}$ = 4.5 Hz, $J_{5,6}$ = 2.3 Hz, H-5β), 2.22, 2.16, 2.11, 2.09, 2.06, 2.05 (6s, 24 H, OAc, α, β); HRMS: calcd for $C_{14}H_{19}ClNaO_9$ $[M+Na]^+$ *m/z* 389.0615; found, *m/z* 389.0412. The second eluted isomer was 1,3,4,6-tetra-*O*-acetyl-2-chloro-2-deoxy-α,β-D-mannopyranose **(16)**[38] (3.6 g, 9.8 mmol, 13.5%, α:β ratio 3.3:1); R_f 0.58 (1:1 hexanes–EtOAc), ^{1}H NMR ($CDCl_3$): δ 6.26 s, 1H, H-1α, 5.95 d, 1H, $J_{1,2}$ = 1.1 Hz, H-1β), 5.50 (dd, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.8 Hz, H-4α), 5.43 (dd, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.6 Hz, H-4β), 5.38 (dd, 1H, $J_{3,4}$ = 9.8 Hz, $J_{3,2}$ = 3.7 Hz, H-3α), 5.15 (dd, 1H, $J_{3,4}$ = 9.7 Hz, $J_{3,2}$ = 3.6 Hz, H-3β), 4.57 (d, 1H, $J_{2,1}$ = 3.2 Hz, H-2β), 4.4 (dd, 1H, $J_{2,1}$ = 1.1 Hz, $J_{2,3}$ = 3.7 Hz, H-2α), 4.29 (dd, 1H, $J_{6,6}$ = 12.5 Hz, $J_{6,5}$ = 5.1 Hz, H-6β), 4.27 (dd, 1H, $J_{6,6}$ = 12.5 Hz, $J_{6,5}$ = 4.5 Hz, H-6α), 4.19 (dd, 1H, $J_{6,6}$ = 12.5 Hz, $J_{6,5}$ = 2.2 Hz, H-6β), 4.16 (dd, 1H, $J_{6,6}$ = 12.5 Hz, $J_{6,5}$ = 2.3 Hz, H-6α), 4.11 (ddd, 1H, $J_{5,6}$ = 2.2 Hz, $J_{5,6}$ = 4.5 Hz, $J_{5,4}$ = 10.0 Hz, H-5α), 3.82 (ddd, 1H, $J_{5,6}$ = 2.2 Hz, $J_{5,6}$ = 5.1 Hz, $J_{5,4}$ = 9.5 Hz, H-5β), 2.20, 2.14, 2.13, 2.12, 2.11, 2.09 (6s, 24 H, OAc, α, β); HRMS: calcd for $C_{14}H_{19}ClNaO_9$ $[M+Na]^+$ *m/z* 389.0615; found 389.0625.

3.6. Preparation of 2-chloro-2-deoxy-α,β-D-glucopyranose (3)

A suspension of 1,3,4,6-tetra-*O*-acetyl-2-chloro-2-deoxy-α,β-D-glucopyranose **(15)** (13.0 g, 35.4 mmol) in N HCl (130 mL, 0.13 mol) was prepared and heated with vigorous stirring at 70 °C. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and Na_2CO_3 (6.9 g, 0.065 mol) was added in portions. Water was evaporated and MeOH (25 mL) was added to the residue. The mixture thus obtained was stirred for 15 min, and the solid was filtered off. MeOH was then evaporated, and the product was purified by column chromatography using a $CHCl_3$–MeOH gradient increasing from 10% to 30%. Fractions containing the product were pooled together and evaporated to give pure 2-chloro-2-deoxy-α,β-D-glucopyranose **(3)** (5.1 g, 25.9 mmol, 75%)**:** mp 135–136 °C, lit. 149 °C,[26] $[\alpha]_D$ +70 (*c*, 1.1 H_2O), lit.[26] +71. Anal. Calcd for $C_6H_{11}ClO_5$: C, 36.29; H, 5.58; Cl, 17.85. Found: C, 36.41; H, 5.82; Cl, 17.49.

3.7. Preparation of 2-chloro-2-deoxy-α,β-D-mannopyranose (4)

A suspension of 1,3,4,6-tetra-*O*-acetyl-2-chloro-2-deoxy-α,β-D-mannopyranose **(14)** (3.5 g, 9.5 mmol) in N HCl (35 mL, 35 mmol) was prepared and heated with vigorous stirring at 70 °C. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature, and Na_2CO_3 (1.9 g, 17.5 mmol) was added in portions. Water was then evaporated, and MeOH (15 mL) was added to the residue. The resultant mixture was stirred for 15 min, then the solid was filtered off. The MeOH was evaporated, and the crude product was purified by column chromatography using a $CHCl_3$–MeOH gradient (0–10% of

MeOH). Fractions were pooled together and evaporated to give pure 2-chloro-2-deoxy-α,β-D-mannopyranose **(4)** (1.4 g, 7.13 mmol, 75%)**:** mp 128–129 °C, $[\alpha]_D$ −4 (*c*, 1.0, H_2O), lit.[23] −6; HRMS: calcd for $C_6H_{11}ClNaO_5$ $[M+Na]^+$ *m/z* 221.0193; found *m/z* 221.0134.

3.8. 1,3,4,6-Tetra-*O*-acetyl-2-bromo-2-deoxy-α,β-D-glucopyranose (19) and 1,3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-α,β-D-mannopyranose (20)

Bromine (3.9 mL, 75 mmol) was added to a solution of 3,4,6-tri-*O*-acetyl-D-glucal **(9)** (20 g, 74.3 mmol) in CH_2Cl_2 (200 mL). The mixture was stirred at room temperature for 15 min, and the solvent was evaporated to dryness. The crude product was purified by low-pressure column chromatography to give a mixture **17** (25.7 g, 59.4 mmol) that contained only 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-glucopyranosyl bromide and 3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranosyl bromide (*gluco*:*manno* ratio = 2.6:1). A suspension of **17** (25.7 g, 59.4 mmol) in N HCl (275 mL, 0.275 mol) was prepared and heated with vigorous stirring at 70 °C. Progress of the reaction was monitored by TLC. After the reaction was completed, the mixture was cooled to room temperature, and Na_2CO_3 (14.6 g, 0.138 mol) was added. Water was evaporated and MeOH (50 mL) was added to the residue. The mixture thus obtained was stirred for 15 min, the solid was filtered off, the MeOH was evaporated, and the crude product was purified by column chromatography using a $CHCl_3$–MeOH gradient (0–10% MeOH). Fractions containing the product were pooled together and evaporated to give **18** (10.8 g, 44.5 mmol). A solution of **18** (10.8 g, 44.5 mmol) in pyridine (75 mL) was prepared and cooled to 0 °C. Ac_2O (28 mL, 0.296 mol) was added, and the reaction mixture was stirred overnight, while the temperature was allowed to rise to ambient. The reaction mixture was diluted with EtOAc (250 mL), and the solution thus obtained was washed with a satd solution of Na_2CO_3. The organic extract was washed with water until neutral, followed by brine, and the extract was then dried over anhyd Na_2SO_4. The drying agent was filtered off, and the solvents were evaporated. The remaining pyridine was removed by co-evaporation with toluene (3 × 100 mL), and the products were separated by low-pressure column chromatography to give 1,3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-α,β-D-glucopyranose **(19)**[33] (8.7 g, 21.2 mmol, 47.6%, α:β ratio 10:7); R_f 0.58 (1:1 hexanes–EtOAc); ^1H NMR ($CDCl_3$): δ 6.36 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1β), 5.82 d 1H, $J_{1,2}$ = 9.1 Hz, H-1α), 5.51 (dd, 1H, $J_{3,2}$ = 11.8 Hz, $J_{3,4}$ = 9.3 Hz, H-3α), 5.35 (dd, 1H, $J_{3,2}$ = 10.6 Hz, $J_{3,4}$ = 9.3 Hz, H-3β), 5.09 (dd, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.5 Hz, H-4α), 5.03 (dd, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.5 Hz, H-4β), 4.32 (dd, 1H, $J_{6,6}$ = 13.5 Hz $J_{6,5}$ = 4.5 Hz, H-6α), 4.29 (dd, 1H, $J_{6,6}$ = 12.3 Hz $J_{6,5}$ = 4.1 Hz, H-6β, 4.15 (ddd, 1H, $J_{5,4}$ = 9.5 Hz, $J_{5,6}$ = 4.5 Hz, $J_{5,6}$ = 2.0 Hz, H-5α), 4.11–4.06 (m, 3H, H-2α, H-6α, H-6β), 3.91 (dd, 1H, $J_{2,3}$ = 10.6 Hz $J_{2,1}$ = 9.1 Hz, H-2β), 3.94–3.88 (m, 1H, H-5β), 2.21, 2.18, 2.10, 2.08, 2.04, 2.03 (6s, 24 H, OAc α,β)**;** HRMS: calcd for $C_{14}H_{19}BrNaO_9$ $[M+Na]^+$ *m/z* 433.0110; found, *m/z* 433.0118. The second eluted compound was 1,3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-α,β-D-mannopyranose **(20)**[33] (6.3 g, 15.3 mmol, 34.4.%, α:β ratio 10:7); R_f 0.45 (hexanes/EtOAc 1:1), ^1H NMR ($CDCl_3$): δ 6.30 (s, 1H, H-1α), 5.74 (s, 1H, H-1β, 5.48 dd, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.8 Hz, H-4α), 5.42 (dd, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.7 Hz, H-4β), 5.20 (dd, 1H, $J_{3,4}$ = 9.6 Hz, $J_{3,2}$ = 3.9 Hz, H-3α), 5.00 (dd, 1H, $J_{3,4}$ = 9.6 Hz, $J_{3,2}$ = 3.8 Hz, H-3β), 4.59 (bd, 1H, $J_{3,1}$ = 3.8 Hz, H-2β), 4.43 (dd, 1H, $J_{2,3}$ = 3.8 Hz, $J_{2,1}$ = 1.5 Hz, H-2α), 4.23 (dd, 1H, $J_{6,6}$ = 12.4 Hz, $J_{6,5}$ = 4.5 Hz, H-6α), 4.14 (dd, 1H, $J_{6,6}$ = 12.4 Hz, $J_{6,5}$ = 2.3 Hz, H-6α), 4.10 (ddd, 1H, $J_{5,4}$ = 9.9 Hz, $J_{5,6}$ = 4.5 Hz, $J_{5,6}$ = 2.3 Hz, H-5α), 3.83 (ddd, 1H, $J_{5,6}$ = 9.7 Hz, $J_{5,6}$ = 4.9 Hz, $J_{5,6}$ = 2.4 Hz, H-5β) 2.19, 2.18, 2.13, 2.125, 2,122, 2.11, 2.08, 2.06 (8s, 24 H, OAc α, β); HRMS calcd for $C_{14}H_{19}BrNaO_9$ $[M+Na]^+$ *m/z* 433.0110; found, *m/z* 433.0091.

3.9. 2-Bromo-2-deoxy-α,β-D-glucose (5)

A suspension of 1,3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-α,β-D-glucopyranose **(19)** (8.7 g, 21.2 mmol) in N HCl (87 mL, 0.087 mmol) was prepared and heated with vigorous stirring at 70 °C. The progress of the reaction was monitored by TLC. After the reaction was completed, the mixture was cooled to room temperature and Na_2CO_3 (4.6 g, 0.044 mol) was added. Water was evaporated, and MeOH (15 mL) was added to the residue. The resulting mixture was stirred for 15 min, the solid was filtered off, the MeOH was evaporated, and the product was purified by column chromatography using a CHCl–MeOH gradient (0% to 10% of MeOH). Fractions that contained the product were pooled together and evaporated to give pure 2-deoxy-2-bromo-α,β-D-glucose **(5)** (3.8 g, 15.7 mmol, 74%): mp 74–77 °C, $[\alpha]_D$ +70 (*c*, 1.1, H_2O). Anal. Calcd for $C_6H_{11}BrO_5$: C, 29.65; H, 4.56, Br, 32.88. Found: C, 39.53; H, 4.75; Br, 32.60.

3.10. 2-Bromo-2-deoxy-α,β-D-mannose (6)

A suspension of 1,3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-α,β-D-mannopyranose **(20)** (6.3 g, 15.3 mmol) in N HCl (63 mL, 0.063 mmol) was prepared and heated with vigorous stirring at 70 °C. Progress of the reaction was monitored by TLC. After the reaction was completed, the reaction mixture was cooled to room temperature, and Na_2CO_3 (3.4 g, 0.032 mol) was added. Water was evaporated, and MeOH (15 mL) was added to the residue. The mixture thus obtained was stirred for 15 min, and the solid was filtered off. MeOH was evaporated, and the crude product was purified by column chromatography using a $CHCl_3$–MeOH gradient (0–10% of MeOH). Fractions that contained the product were pooled together and evaporated to give pure 2-deoxy-2-bromo-α,β-D-mannose **(6)** (2.8 g, 11.5 mmol, 74%)**:** mp 64–65 °C, $[\alpha]_D$ +5.4 (*c*, 1.28, H_2O); HRMS: calcd for $C_6H_{11}BrNaO_5$ $[M+Na]^+$ *m/z* 264.9688; found, *m/z* 264.9599**.**

3.11. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranose (24), 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-mannopyranose (23), and 3,4,6-tri-O-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose (22)

The mixture of 3,4,6-tri-*O*-acetyl-D-glucal (27.2 g, 0.1 mol) and NIS (33.75 g, 0.15 mol) in toluene (270 mL) was prepared and heated until reflux, then water (3.6 mL, 0.2 mol) was added, and reflux was continued. After 10 min the reaction was completed, and the toluene was evaporated to dryness. The crude mixture was dissolved in CH_2Cl_2 (300 mL). The resulting organic solution was washed with a 10% $Na_2S_2O_5$ solution, then with water until neutral, followed with brine. The crude product, after drying over Na_2SO_4 and solvent evaporation, was dissolved in CH_2Cl_2 (30 mL). *tert*-Butyldimethylsilyl chloride (18 g, 0.12 mol), followed by imidazole (10.2 g, 0.15 mol), was then added, and the reaction mixture was stirred at room temperature. After 1 h the reaction was completed. The reaction mixture was then diluted with CH_2Cl_2 (250 mL) and washed with water (3 × 100 mL), followed by drying over Na_2SO_4. The drying agent and solvent were removed, and the products were separated using low-pressure liquid chromatography with a hexane–EtOAc gradient (0–20% of EtOAc) for elution. The following products were obtained.

3.11.1. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranose (24) (3 g, 6.5 mmol, 6.5%)

R_f 0.59 (2:1 hexanes–EtOAc), ^1H NMR ($CDCl_3$): δ 5.47 (bs, 1H, H-1), 5.38 (dd, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.3 Hz, H-4), 4.72 (dd, 1H $J_{3,4}$ = 9.3 Hz, $J_{3,2}$ = 4.2 Hz, H-3), 4.49 (dd, 1H, $J_{2,1}$ = 1.3 Hz, $J_{2,3}$ = 4.2 Hz, H-2),

4.22 (dd, 1H, $J_{6,6}$ = 11.3 Hz, $J_{6,5}$ = 4.7 Hz, H-6), 4.16 (ddd, 1H, $J_{5,4}$ = 9.3 Hz, $J_{5,6}$ = 4.7 Hz, $J_{5,6}$ = 1.7 Hz, H-5), 4.10 (dd, 1H, $J_{6,6}$ = 11.3 Hz, $J_{6,5}$ = 1.7 Hz, H-6), 2.14, 2.08, 2.06 (3s, 3H ea, OAc), 0.93 (s, 9H, *t*-Bu), 0.13, 0.12 (2s, 3H ea, Me); HRMS:calcd for $C_{18}H_{31}INaO_8Si$ $[M+Na]^+$ *m/z* 553.0731; found, *m/z* 553.0753.

3.11.2. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-mannopyranose (23) (23 g, 50 mmol, 50%)

R_f 0.46 (2:1 hexanes–EtOAc), ^1H NMR ($CDCl_3$): δ 5.33 (dd, 1H, $J_{4,3} = J_{4,5}$ = 9.5 Hz, H-4), 4.65 (dd, 1H, $J_{2,3}$ = 4.2 Hz, $J_{2,1}$ = 1.4 Hz, H-2), 4.47 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{3,2}$ = 4.2 Hz, H-3), 4.20 (dd, 1H, $J_{6,6}$ = 12.0 Hz, $J_{6,5}$ = 3.2 Hz, H-6), 4.15 (dd, 1H, $J_{6,6}$ = 12.0 Hz, $J_{6,5}$ = 5.8 Hz, H-6), 4.02 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1), 3.68 (ddd, 1H, $J_{5,4}$ = 9.5 Hz, $J_{5,6}$ = 5.8 Hz, $J_{5,6}$ = 3.2 Hz, H-5), 2.11, 2.09, 2.08 (3s, 3H ea, OAc), 0.93 (s, (H, 9H, *t*-Bu), 0.17, 0.13 (2s, 3H ea, Me); HRMS: calcd for $C_{18}H_{31}INaO_8Si$ $[M+Na]^+$ *m/z* 553.0731; found, *m/z* 553.0684.

3.11.3. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose (22) (19 g, 41 mmol, 41%)

R_f 0.54 (2:1 hexanes–EtOAc), ^1H NMR ($CDCl_3$): δ 5.30 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{3,2}$ = 11.2 Hz, H-3), 4.91 (dd, 1H, $J_{4,3}$ = 9.0 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 4.89 (d, 1H, $J_{1,2}$ = 8.6 Hz, H-1), 4.21 (dd, 1H, $J_{6,6}$ = 12.0 Hz, $J_{6,5}$ = 6.0 Hz, H-6), 4.12 (dd, 1H, $J_{6,6}$ = 12.0 Hz, $J_{6,5}$ = 2.5 Hz, H-6), 3.89 (dd, 1H, $J_{2,1}$ = 8.6 Hz, $J_{2,3}$ = 11.2 Hz H-2), 3.75 (ddd, 1H, $J_{5,4}$ = 10.0 Hz, $J_{5,6}$ = 6.0 Hz, $J_{5,6}$ = 2.5 Hz, H-5), 2.08, 2.07, 2.01 (3s, 3H ea, OAc), 0.93 (s, 9H, *t*-Bu), 0.17, 0.15 (2s, 3H ea, Me); HRMS calcd for $C_{18}H_{31}INaO_8Si$ $[M+Na]^+$ *m/z* 553.0731; found, *m/z* 553.0674.

3.12. 2-Deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-mannopyranose (26)

3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-mannopyranose **(23)** (23 g, 50 mmol) was dissolved in MeOH (230 mL). N MeONa in MeOH (5 mL, 5 mmol) was added, and the reaction mixture was stirred at room temperature. After the reaction was completed (TLC) the reaction was quenched by addition of HOAc (0.3 mL, 5 mmol). The solvent was evaporated to dryness, and the crude product was purified by column chromatography using a $CHCl_3$–MeOH gradient (0–10% of MeOH) for elution. Fractions containing 2-deoxy-2-iodo-1-O-*tert*-butyldimethylsilyl-α-D-mannopyranose **(26)** were pooled together and evaporated to dryness. Traces of solvents were removed by additional drying under high vacuum. Compound **26** (16.1 g, 48 mmol, 96%) was obtained. ^1H NMR (DMSO-d_6 + D_2O): δ 4.38 (dd, 1H, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 2.5 Hz, H-2), 4.06 (d, 1H, $J_{1,2}$ = 2.5 Hz, H-1), 3.66 (dd, 1H, $J_{6,6}$ = 11.5 Hz, $J_{6,5}$ = 1.8 Hz, H-6), 3.40 (dd, 1H, $J_{6,6}$ = 11.5 Hz, $J_{6,5}$ = 6.3 Hz, H-6), 3.27 (dd, 1H, $J_{4,3}$ = 9.4 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.20 (ddd, 1H, $J_{5,4}$ = 9.5 Hz, $J_{5,6}$ = 1.8 Hz, $J_{5,6}$ = 6.3 Hz, H-5), 2.94 (dd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{3,2}$ = 3.9 Hz, H-3), 0.88 (s, 9H, *t*-Bu), 0.12, 0.10 (2s, 3H ea, Me); HRMS: calcd for $C_{12}H_{25}INaO_5Si$ $[M+Na]^+$ *m/z* 427.0414; found, *m/z* 427.0459.

3.13. 2-Deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranose (27)

3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranose **(24)** (3 g, 6.5 mmol) was deacetylated using method described for its β isomer. 2-Deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranose **(27)** (2.07 g, 6.17 mmol, 95%) was obtained. ^1H NMR (DMSO-d_6 + D_2O): δ 5.35 (s, 1H, H-1), 4.25 (dd, 1H, $J_{2,1}$ = 1.3 Hz, $J_{2,3}$ = 4.0 Hz, H-2), 3.62–3.55 (m, 2H, H-5, H-6), 3.45 (dd, 1H, $J_{6,6}$ = 12.1 Hz, $J_{6,5}$ = 6.3 Hz, H-6), 3.34 (dd, 1H, $J_{4,3} = J_{4,5}$ = 9.5 Hz, H-4), 3.02 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{3,2}$ = 4.0 Hz, H-3), 0.87 (s, 9H, *t*-Bu), 0.08 (s, 6H, Me); HRMS: calcd for $C_{12}H_{25}INaO_5Si$ $[M+Na]^+$ *m/z* 427.0414; found, *m/z* 427.0414.

3.14. 2-Deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose (25)

3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose **(22)** (19 g, 41 mmol) was deacetylated according to method described for 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-mannopyranose (**24**). 2-Deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose **(25)** (12.7 g, 38 mmol, 92.7%) was obtained. ^1H NMR (DMSO-d_6 + D_2O): δ 4.78 (d, 1H, $J_{1,2}$ = 8.6 Hz, H-1), 3.64 (bd, 1H, $J_{6,6}$ = 10.7 Hz, H-6), 3.56 (dd, 1H, $J_{2,1}$ = 8.6 Hz, $J_{2,3}$ = 10.4 Hz, H-2), 3.47–3.40 (m, 2H, H-6), 3.36 (dd, 1H, $J_{3,2}$ = 10.4 Hz, $J_{3,4}$ = 9.6 Hz, H-3), 3.19 (dd, 1H, $J_{5,4}$ = 9.0 Hz, $J_{5,6}$ = 5.8 Hz, H-5), 3.09 (dd, 1H, $J_{4,3}$ = 9.6 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 0.88 (s, 9H, *t*-Bu), 0.12, 0.09 (2s, 3H ea, Me); HRMS: calcd for $C_{12}H_{25}INaO_5Si$ $[M+Na]^+$ *m/z* 427.0414; found, *m/z* 427.0489.

3.15. 2-Deoxy-2-iodo-D-mannose (8)

A suspension of combined 2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranose **(27)** and 2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-mannopyranose **(26)** (18 g, 53.7 mmol) was prepared in acetonitrile (60 mL) and water (120 mL). Trifluoroacetic acid (8.25 mL, 12.31 g, 107 mmol) was added, and the reaction mixture was stirred at room temperature. After the reaction was completed, the solvents were evaporated to dryness, and the product was purified by column chromatography using a $CHCl_3$–MeOH gradient (0–10% MeOH) for elution. Fractions containing the product were pooled and evaporated to dryness. Residual solvents were removed by additional drying under low pressure. (13.2 g, 45.6 mmol, 85%) of pure 2-deoxy-2-iodo-α,β-D-mannose **(8)** was obtained: mp 88–89 °C (dec); $[\alpha]_D$ −22.16 (*c*, 1.23 H_2O); HRMS: calcd for $C_6H_{11}INaO_5$ $[M+Na]^+$ *m/z* 312.9549; found, *m/z* 312.9592.

3.16. 2-Deoxy-2-iodo-α,β-D-glucose (7)

A suspension of 2-deoxy-2-iodo-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose **(25)** (12.7 g, 38 mmol) was prepared in acetonitrile (40 mL) and water (80 mL). Trifluoroacetic acid (5.85 mL, 8.74 g, 76 mmol) was added, and the reaction mixture was stirred at room temperature. After the reaction was completed the solvents were evaporated to dryness, and the resulting product was purified by column chromatography using a $CHCl_3$–MeOH gradient (0–10% MeOH) for elution. Fractions containing the product were pooled and evaporated to dryness. Residual solvents were removed by additional drying under low pressure, and pure 2-deoxy-2-iodo-α,β-D-glucose **(7)** (9.6 g, 33.1 mmol, 87%) was obtained: mp 79–80 °C (dec); $[\alpha]_D$ +57.1 (*c*, 1.04 H_2O); HRMS: calcd for $C_6H_{11}INaO_5$ $[M+Na]^+$ *m/z* 312.9549; found, *m/z* 312.9539.

Acknowledgments

This work was supported in part by NCI SPORE in a Pancreatic Cancer P20 CA101936 grant (WP) and The Morton and Angela Topfer Pancreatic Cancer Research Fund (WP). We also acknowledge the NCI Cancer Center Support Grant CA016672 for the support of NMR facility at UT M. D. Anderson Cancer Center.

References

1. Warburg, O. *Science* **1956**, *123*, 309–314.
2. Pelicano, H.; Martin, D. S.; Xu, R.-H.; Huang, P. *Oncogene* **2006**, *25*, 4633–4646.

3. Antonovic, L.; Johansen, M.; Fokt, I.; Szymanski, S.; Conrad, C. A.; Priebe, W.; Madden, T. *Mol. Cancer Ther.* **2007**, *6*, 3443S.
4. Young, H.; Baum, R.; Cremerius, U. *Eur. J. Cancer* **1999**, *35*, 1773–1782.
5. Lampidis, T. J.; Kurtoglu, M.; Maher, J. C.; Liu, H. P.; Krishan, A.; Sheft, V.; Szymanski, S.; Fokt, I.; Rudnicki, W. R.; Ginalski, K.; Lesyng, B.; Priebe, W. *Cancer Chemother. Pharmacol.* **2006**, *58*, 725–734.
6. Ido, T.; Wan, C.-N.; Fowler, J.; Wolf, A. P. *J. Org. Chem.* **1977**, *42*, 2341–2342.
7. Shiue, C.-Y.; Salvadori, A. P.; Wolf, A. P.; Fowler, J.; MacGregor, R. R. *J. Nucl. Med.* **1982**, *23*, 899–903.
8. Adam, M. J. *J. Chem. Soc., Chem. Commun.* **1982**, 730–731.
9. Diksic, M.; Jolly, D. *Int. J. Appl. Radiat. Isot.* **1983**, *34*, 893–896.
10. Ehrenkaufer, R. E.; Potocki, J. F.; Jewett, D. M. *J. Nucl. Med.* **1984**, *25*, 333–337.
11. Jewett, D. M.; Potocki, J. F.; Ehrenkaufer, R. E. *Synth. Commun.* **1984**, *14*, 45–51.
12. Adam, M. J.; Pate, B. D.; Nesser, J.-R.; Hall, L. D. *Carbohydr. Res.* **1983**, *124*, 215–224.
13. Adamson, J.; Foster, A. B. *Carbohydr. Res.* **1970**, *15*, 351–359.
14. Adamson, J.; Marcus, D. M. *Carbohydr. Res.* **1970**, *13*, 314–316.
15. Adamson, J.; Marcus, D. M. *Carbohydr. Res.* **1972**, *22*, 257–264.
16. Korytnyk, W.; Valentekovic-Horvat, S. *Tetrahedron Lett.* **1980**, *21*, 1493–1496.
17. Shiue, C.-Y.; To, K.-C.; Wolf, A. P. *J. Labelled Compd. Radiopharm.* **1983**, *20*, 157–162.
18. Diksic, M.; Jolly, D. *Carbohydr. Res.* **1986**, *153*, 17–24.
19. Kovac, P. *Carbohydr. Res.* **1986**, *153*, 168–170.
20. Ortner, J.; Albert, M.; Weber, H.; Dax, K. *J. Carbohydr. Chem.* **1999**, *18*, 297–316.
21. Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11743–11746.
22. Vincent, S. P.; Burkart, M. D.; Tsai, C.-Y.; Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5264–5279.
23. Bessell, E. M.; Foster, A. B.; Westwood, J. H. *Biochem. J.* **1972**, *128*, 199–204.
24. Buncel, E.; Bradley, P. R. *Can. J. Chem.* **1967**, *45*, 515–519.
25. Fisher, E.; Bergmann, M.; Schotte, H. *Ber. Dtsch. Chem. Ges.* **1920**, *53b*, 509–547.
26. Adamson, J.; Foster, A. B. *Carbohydr. Res.* **1969**, *10*, 517–523.
27. Lefar, M. S.; Weill, C. E. *J. Org. Chem.* **1965**, *30*, 954–955.
28. Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1965**, *43*, 1458–1473.
29. Bradley, P. R.; Buncel, E. *Can. J. Chem.* **1968**, *46*, 3001–3006.
30. Igarashi, K.; Honma, T.; Imagawa, T. *J. Org. Chem.* **1970**, *35*, 610–616.
31. Igarashi, K.; Honma, T.; Imagawa, T. *Tetrahedron Lett.* **1968**, *6*, 755–760.
32. Igarashi, K.; Irisawa, J.; Honma, T. *Carbohydr. Res.* **1975**, *39*, 213–225.
33. Liu, K.; Wong, C.-H. *J. Org. Chem.* **1992**, *57*, 3748–3750.
34. David, S.; Malleron, A.; Cavaye, B. *Carbohydr. Res.* **1994**, *260*, 233–241.
35. Honda, S.; Takiura, K. *Carbohydr. Res.* **1974**, *34*, 45–56.
36. Morin, C. *Tetrahedron Lett.* **2006**, *47*, 5055–5058.
37. Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 368–373.
38. Khan, R.; Jenner, M. R.; Lindseth, H. *Carbohydr. Res.* **1980**, *78*, 173–183.