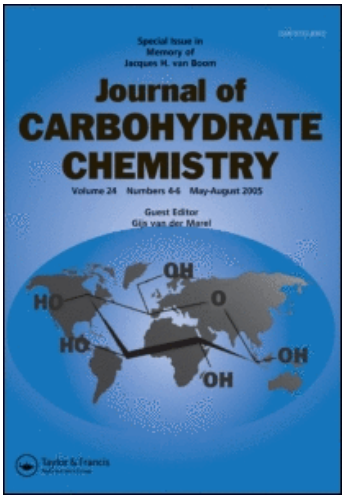

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1-Propenyl 4,6-Q-Benzylidene-β-D-Mannopyranoside-2,3-Cyclic Sulfate: A Substrate for the Synthesis of [F-18] 2-Deoxy-2-Fluoro-D-Glucose

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1-PROPENYL 4,6-O-BENZYLIDENE-ß-D-MANNOPYRANOSIDE-2,3-CYCLIC SULFATE: A SUBSTRATE FOR THE SYNTHESIS OF [F-18] 2-DEOXY-2-FLUORO-D-GLUCOSE

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ABSTRACT

1-Propenyl 4,6-O-benzylidine-ß-D-mannopyranoside-2,3-cyclic sulfate was prepared from methyl α-D-mannopyranoside. This compound reacts cleanly with tetramethylammonium fluoride, followed by acid hydrolysis (2N HCl), to give 2-deoxy-2-fluoro-D-glucose. The reaction is suitable for use with the short lived radionuclide fluorine-18 ($t_{\frac{1}{2}}$ = 110 minutes).

INTRODUCTION

We recently introduced methyl 4,6-O-benzylidene-ß-D-mannopyranoside-2,3-cyclic sulfate[1,2] as a substrate for reaction with fluoride ion in the synthesis of fluorine-18 2-deoxy-2-fluoro-D-glucose. The cyclic sulfate reacted rapidly and efficiently with both fluorine-19 and fluorine-18 tetra-alkyl ammonium fluorides but the removal of the glycosidic methyl group was difficult, requiring the use of boron tris-(trifluoroacetate)[2] for the rapid reaction necessary when

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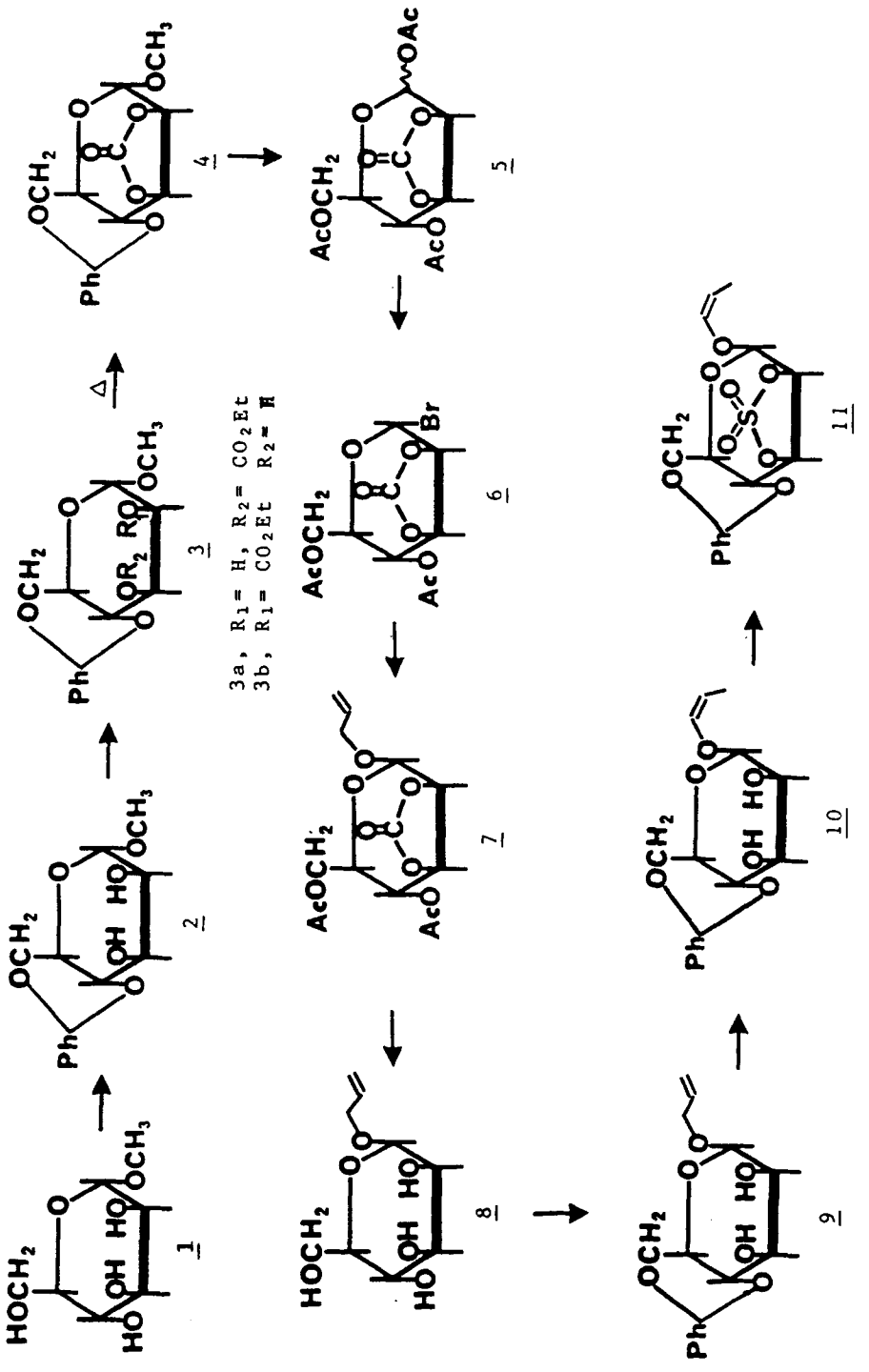
working with fluorine-18 ($t_{\frac{1}{2}}$ = 110 minutes). To avoid this difficulty we prepared a derivative in which the glycosidic oxygen was protected as a vinyl ether[3] which could be hydrolysed under mild acid conditions.

RESULTS AND DISCUSSION

The synthetic pathway shown in Scheme I used the 2,3-cyclic carbonate[4] as a protecting group for the Koenigs-Knorr condensation of the glycosidic bromide with allyl alcohol. The 4,6-O-benzylidene derivative (2) was prepared by reaction of methyl α-D-mannopyranoside (1) and benzaldehyde dimethylacetal (tosic acid catalysis) in DMF at room temperature. The yield using this method is no better than that obtained using other procedures[5] but the reaction is more convenient for a large scale (50-100g) synthesis. The published procedure for the synthesis of cyclic carbonate (4)[4] worked well on a small scale but on scaling up to 50g, the isolated yield of (4) fell to 10-15%. Examination of the reaction mixture showed that in spite of the vast excess of ethyl chloroformate and triethylamine, the major products were the two monoethoxycarbonates (3a and 3b). However, during this examination it appeared that the monoethoxycarbonates (3a and 3b) and the cyclic carbonate (4) could not be separated by gas chromatography. The most likely explanation for this observation was that the ethoxycarbonates were reacting on the GC to give (4). To determine if this was the case, the syrup from the reaction mixture was heated to 200 °C in an oil bath. Ethanol slowly distilled and, after work-up, crystallization of the product gave the cyclic carbonate (4) in 80-85% yield. To avoid the problems of using excess ethyl chloroformate, the monoethoxy carbonates were

SCHEME 1



prepared with one equivalent of the reagent in methylene chloride/pyridine and pyrolyzed to give (4).

The mixture of α and ß acetates (5) was prepared following literature procedures.[4] Bromination of the mixture gave a product identical to that obtained from the pure α-anomer and so the mixture was used. The large scale bromination using phosphorous tribromide and water in acetic acid was more convenient than that with 30% HBr in glacial acetic acid. In our hands, the glycosyl bromide (6) would not crystallize regardless of the method of preparation or the use of either pure α-anomer of (5) or the mixture of α- and ß-anomers as starting material. However, preparation of the known ß-O-methyl compound following literature procedures[4] went in excellent yield to give one product and so the syrupy bromide was taken on to the next stage. Allylation of (6) using silver oxide[6] gave a mixture of products under a variety of conditions. However, with mercuric cyanide and with allyl alcohol both as reagent and solvent, a single product by TLC was formed.[4] With acetonitrile as a solvent, two products are formed, one identical to that in allyl alcohol, the other with a higher Rf on TLC. The two products could be separated by chromatography (silica gel, 2% $MeOH/CH_2Cl_2$) and gave identical mass spectra. The IR spectrum showed absorbances at 1840 and 1750 cm^{-1} for the carbonate and acetates respectively and a weak absorbance at 1640 cm^{-1} characteristic for the allyl group. Hydrolysis, first in base then in acid of either compound gave D-mannose (1) as the only product, establishing that the two differed only in their substitution. The ^1H NMR spectra of these compounds at 270 MHz showed considerable overlap of the ring and allylic protons, making complete

TABLE I

PROTON CHEMICAL SHIFT AND COUPLING CONSTANTS [a]

	RING PROTONS						PROPENYL PROTONS		
CMPD	H-1	H-2	H-3	H-4	H-5	H-6	H-1	H-2	H-3
7β	5.0 d(1.1)	4.65 dd(1.1,5)	4.8 dd(10,5)	3.85 ---------- 4.6 m				5.7 m	5.3 m
7α	5.2 s	4.6 d(5)	4.83 dd(10,5)	3.85 ---------- 4.6 m				5.9 m	5.3 m
9	4.65 d(1.1)	4.15 dd(1.1,5)	4.35 dd(5,10)	4.0 ---------- 3.3 m			4.45 ddt 4.2 ddt	5.95 m	5.3 m
10	4.78 d(1.1)	4.25 dd(1.1,5)	4.35 (5,10)	3.75 m	3.4 ddd	3.75 m	6.25 dq(1.6,5)	4.7 dq(5,6.75)	1.64 dd(1.6,6.75)
11	5.1 d(1.1)	4.55 dd(1.1,5)	5.45 (5,10)	5.1m	3.6 ddd	α 5.1 m β 3.8 dd	6.2 dq(1.6,5)	4.7 dq(5,6.75)	1.7 dd(1.6,6.75)

a. All spectra were recorded at 270 MHz. Chemical shifts are in ppm from TMS internal standard. Coupling constants (in parenthesis) are in Hz.

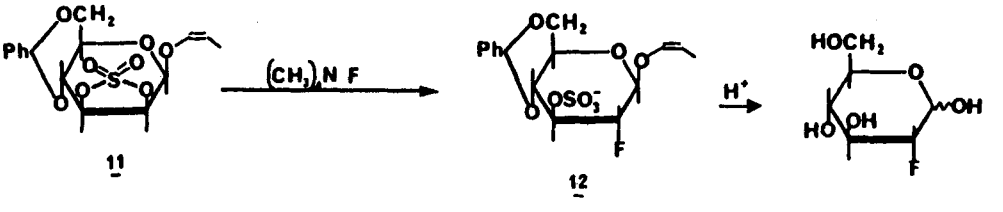
assignments difficult. The region around 5δ, where the signal due to the anomeric proton appears, was reasonably clear. The faster running compound showed the anomeric proton as a singlet at 5.0δ. The slower running compound shows the anomeric proton as a doublet at 4.65δ with J= 1.1 Hz. In the pairs of anomers in the mannose series that we have examined the anomeric proton in α-anomer absorbs at lower field, with a smaller 1,2 coupling than does the ß-anomer. Thus the data is consistent with the slower running isomer and the only product in the allyl alcohol reaction being the required ß-anomer and the compound with the higher Rf being the α-anomer. Cyclic carbonate could distort the pyranoside ring and alter both the relative chemical shifts and coupling constants of the anomeric proton. The two products were hydrolysized in base to remove the acetates and carbonate and the monobenzylidene derivatives prepared. A direct comparison of the ^{1}H NMR spectra with the known methyl 4,6-O-benzylidene-(α and ß)-D-mannopyranosides[7] was then made. The slower running compound shows the anomeric proton as a 1.1 Hz doublet at 4.65δ whereas the faster running component has a singlet at 4.9δ. The authentic methyl 4,6-O-benzylidene-ß-D-mannopyranoside showed the anomeric proton at 4.7δ as a 1.3Hz doublet whereas the α-compound showed a singlet at 4.9δ. Thus we can assign the slower running compound to the ß-anomer (7) and the faster running one to its α-anomer.

On the preparative scale hydrolysis with sodium methoxide/methanol occurred normally and benzylidation with benzaldehyde dimethylacetal gave 2-propenyl 4,6-O-benzylidene-ß-D-mannopyranoside (9) in 40% yield. The rearrangement of the

allyl to the vinyl ether was attempted with tris(triphenylphosphine)rhodium chloride but resulted in decomposition of the catalyst and incomplete reaction.[3] The less convenient rearrangement with potassium tert-butoxide in DMSO gave the 1-propenyl compound (10) in 85% yield.[8] The ^{1}H NMR suggested that the double bond is cis ($J_{1,2}$= 7Hz). Reaction of (10) with sulphuryl chloride in triethylamine/ethylacetate[1] resulted in chlorination of the vinyl ether rather than formation of the cyclic sulfate. However, treatment of (10) with sodium hydride and N,N-sulfuryl diimidazole[10] in dry THF gave 1-propenyl 4,6-O-benzylidene-ß-D-mannopyranoside 2,3-cyclic sulfate (11) in excellent yield.

The latter (11) reacts with tetramethylammonium fluoride (which had been dried by azeotropic distillation of acetonitrile) in refluxing acetonitrile to give a single polar peak on reverse phase HPLC. This is presumably the ring opened sulfate (12) (Scheme 2). Ring opened tetraalkylammonium sulfates are intractable compounds with detergent properties and so no attempts were made to characterize this intermediate. The acetonitrile was evaporated under vacuum and the product

SCHEME 2



11 12

heated at reflux in 2N HCl for 10 minutes. The HCl was neutralized with sodium bicarbonate, the water evaporated under vacuum, and the resulting solid extracted with ethanol. Crystallization from ethanol/ethyl acetate gave 2-deoxy-2-fluoro-D-glucose in 85% overall yield from (11). The use of milder acidic conditions (0.1 N HCl or trifluoroacetic acid) gave a polar product which did not move from the origin of the TLC plate with 4:1 ethyl acetate/ethanol, whereas the 2-deoxy-2-fluoro-D-glucose has an Rf of ~0.5. Apparently the hydrolysis of the sulfate (12) requires the stronger acid.

As the cyclic sulfate is potentially a bifunctional leaving group, the fluorination reaction was examined to determine if any of the alternative product, 3-deoxy-3-fluoro-D-altrose was formed. ^{19}F NMR spectrum of the total fluorination reaction mixture in D_2O showed a signal at 10 ppm above the 2-deoxy-2-fluoro-D-glucose signal with an integrated intensity of between 0-10% of that of the deoxyfluoro-glucose. Extending the reflux period to an hour increased this integral to approximately 20% of the glucose signal. This signal showed a 50 Hz coupling constant typical of geminal HF couplings and each half of this doublet was further split into a complex 7 line pattern with no apparent coupling greater than 4 Hz.

A ^{19}F NMR spectrum of the total hydrolysis mixture showed this signal as detectable but not integrable above the base line noise. Acylation of the total hydrolysis mixture in acetic anhydride/pyridine and GC of the product showed only the peak expected for the 1,3,4,6-tetra-O-acetyl-2-deoxy-2-fluoro-D-glucopyranose.

All of this evidence points to the second product being a further reaction product of the ring opened sulfate (12) and

suggests that the reaction of fluoride is both regio- and stereospecific at carbon 2. Further work is in progress to determine the structure of this secondary product. Preliminary studies with fluorine-18 tetramethylammonium fluoride are encouraging in that fluorine-18 2-deoxy-2-fluoro-D-glucose can be obtained in excellent yield less than 20 minutes after the fluoride salt is available.

METHODS

IR spectra were recorded on a Perkin Elmer 299B spectrometer in KBr discs or as thin films. Melting points were taken on an electrothermal melting point apparatus and are uncorrected. ^{1}H NMR were recorded at 270 MHz on a JEOL 270 spectrometer. Mass spectra were recorded on a Finnegan quadropole mass spectrometer at an ionizing voltage of 20 ev. ^{19}F NMR spectra were recorded at 282 MHz on a Brueker 300 spectrometer.

Gas chromatography was performed on Hewlett-Packard 5890 GC using a "530μ" 10 meter column. The temperature was programmed from 130 to 230 °C at 6 °C min^{-1}.

EXPERIMENTAL

Synthesis of Methyl 4,6-O-Benzylidene-α-D-manno-pyranoside (2). Methyl α-D-mannopyranoside (50 g, 0.26 mol) was stirred at room temperature for two days in dry DMF (400 mL) containing benzaldehyde dimethylacetal (45.6 g, 0.3 mol) and p-toluenesulfonic acid (0.5 g). The solution was then poured into water (400 mL) containing sodium bicarbonate (3 g) and the solution filtered to remove the dibenzylidene

product. The filtrate was extracted with methylene chloride (3 x 250 mL). The methylene chloride extract was dried with sodium sulfate and evaporated to dryness. Crystallization of the product from chloroform/toluene gave 38 g (0.13 mol, 50% yield) of methyl 4,6-O-benzylidene-α-D-mannopyranoside (2) with mp 146-7 °C. Lit. mp 145-7 °C.[11]

Synthesis of Methyl 4,6-O-benzylidene-2,3-O-carbonyl-α-D-mannopyranoside (4). Methyl 4,6-O-benzylidene-α-D-mannopyranoside (2) (30 g, 0.1 mol) in methylene chloride (300 mL) containing pyridine (15 g) was stirred under dry argon. Ethyl chloroformate (13 g, 0.13 mol) in methylene chloride (100 mL) was added slowly (30 min). The reaction mixture was stirred for a further 30 min. TLC (silica gel, 1% $MeOH/CH_2Cl_2$) examination at this stage showed three spots: one at Rf 0.95 which was a mixture of the cyclic carbonate and diethoxy carbonate, the major spot at Rf 0.6 which was a mixture of the two monoethoxy carbonates (3a and 3b), and a third spot at Rf 0.1 which was unreacted starting material. Addition of more ethyl chloroformate appeared to produce (by TLC) diethoxy carbonate faster than starting material was consumed. The methylene chloride solution was washed with 1N HCl (100 mL), dried with sodium sulfate and evaporated to dryness. The resulting oil was heated with stirring to 200 °C under argon while ethanol slowly distilled out. When the ethanol distillation was complete (~15 min) the resulting oil was dissolved in ethanol (200 mL) and allowed to crystallize. Recrystallization from ethanol gave 24 g (0.08 mol, 80% yield) of methyl 4,6-O-benzylidene-2,3-O-carbonyl-α-D-mannopyranoside (4) with mp 125-7 °C. Lit. mp 125-7 °C.[4]

Preparation of 4,6-Di-O-acetyl-2,3-O-carbonyl-α-D-mannopyranoside bromide (6). 1,4,6-Tri-O-acetyl-2,3-O-carbonyl-D-mannopyranoside (24 g, 0.072 mol) prepared from 4 by the procedure of Bebault and Dulton[4] was dissolved in 250 mL of a 1:1 mixture of methylene chloride and acetic acid. Phosphorus tribromide (39 g, 0.14 mol) in methylene chloride (50 mL) was added slowly followed by acetic acid (25 mL) containing 10 g of water. The reaction was stirred for two hours and poured into ice water containing methylene chloride. The methylene chloride layer was washed with ice water (200 mL), saturated sodium bicarbonate (200 mL), dried with sodium sulfate, and evaporated to dryness. The resulting brown syrup was chromatographed quickly on a Florsil column (5 x 50 cm) using methylene chloride to give a colorless syrup of 4,6-di-O-acetyl-2,3-O-carbonyl-α-D-mannopyrannosyl bromide (22.4 g, 0.063 mol, 88% yield) (6), which was homogenous by TLC, (silica gel, 1% MeOH/CH_2Cl_2, Rf 0.6) but could not be crystallized. This syrup decomposed on standing and so was taken through directly to the next step.

Preparation of 2-Propenyl 4,6-di-O-acetyl-2,3-O-carbonyl-ß-D-mannopyranoside (8). 4,6-Di-O-acetyl-2-3-O-carbonyl-α-D-mannopyranosyl bromide (22.4 g, 0.063 mol) from the previous step was dissolved in allyl alcohol (150 mL) and mercuric cyanide (22 g, 0.085 mol) was added. The solution was stirred in the dark for 18 hours, the allyl alcohol evaporated under vacuum, and the residue dissolved in methylene chloride (250 mL). The methylene chloride solution was filtered to remove mercury salts, washed with 1M KBr (200 mL), saturated

sodium bicarbonate solution (200 mL), dried (Na_2SO_4), and evaporated to dryness to give a pale yellow syrup that was one compound by GC and TLC (2% MeOH/CH_2Cl_2) but could not be induced to crystallize. Chromatography on silica gel and elution with 2% MeOH/CH_2Cl_2 gave a colorless syrup (17 g, 0.051 mol, 81% yield) that would not crystallize. Mass Spec. M+330, M-57 273, M-99 231. $[\alpha]_D^{23}$= -54° (c=0.1, $CHCl_3$) IR (KBr) 1830 cm^{-1},1750 cm^{-1}, 1650 cm^{-1}. In a similar experiment utilizing 50 mL of allyl alcohol and 150 mL of acetonitrile, two products were formed, one identical to the compound above and the other with the higher Rf (0.75, 2% MeOH/CH_2Cl_2) shown to be the α-anomer. M+330, M-52 273, M-99 231. $[\alpha]_D^{23}$ = +25° (c = 0.1, $CHCl_3$).

Preparation of 2-Propenyl 4,6-O-benzylidene-ß-D-mannopyranoside (9). 2-Propenyl 4,6-Di-O-acetyl-2,3-O-carbonyl-α-D-mannopyranoside (17 g, 0.051 mol) was dissolved in methanol (250 mL) and 10 mL of methanol, in which sodium (10 mg) had been reacted, was added. The solution was stirred for thirty minutes at room temperature, neutralized with cation exchange resin (Rexyn 101), and the methanol evaporated. The resulting syrup was dissolved in DMF (50 mL) and the solvent evaporated. This material was redissolved in DMF (150 mL) and benzaldehyde dimethyl acetal (22.8 g, 0.15 mol) and toluenesulfonic acid (0.5 g) were added. The solution was stirred at room temperature for 2 hours, poured into aqueous sodium bicarbonate solution (300 mL) and extracted with methylene chloride (3 x 250 mL). The methylene chloride extracts were dried with sodium sulfate and evaporated to

dryness to give an oil. Chromatography on silica gel and elution with methylene chloride gave the dibenzylidene products. Elution with 2% MeOH/CH_2Cl_2 gave (9). Crystallization from ethanol gave 5.6 g of 2-propenyl 4,6-O-benzylidene-ß-D-mannopyranoside (9) (0.02 mol, 40% yield), mp 136-8 °C. IR (KBr) 3600 cm^{-1}, 1635 cm^{-1}, MS 308 (M+), 307 (M-1).

Anal. Calcd for $C_{16}H_{20}O_6$ C, 62.07 H, 6.49 Found C, 61.81 H, 6.43

Preparation of 1-Propenyl 4,6-O-benzylidene-ß-D-mannopyranoside (10). 2-Propenyl 4,6-O-benzylidene-ß-D-mannopyranoside (1.6 g, 0.055 mol) was dissolved in dry DMSO (75 mL), potassium t-butoxide (2.24 g) was added and the solution stirred under argon. The solution was heated at 100 °C in an oil bath for ten minutes with stirring. The solution was then poured into methanol and neutralized with cation exchange resin (Rexyn 101). The methanol and DMSO were evaporated under reduced pressure, and the residue dissolved in methylene chloride (100 mL). The methylene chloride solution was washed twice with water (100 mL), dried with sodium sulfate, and evaporated to dryness. The residue was dissolved in hot ethanol (100 mL), treated with decolorizing charcoal (Norite 1 g) filtered through Celite 545. The filtrate was allowed to cool and crystallize. Filtration of the crystals gave 1.4 g of 1-propenyl 4,6-O-benzylidene-ß-D-mannopyranoside (10) (85% yield), mp 164-166 °C. IR (KBr) 3600 cm^{-1}, 1680 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_6$ C, 62.07, H, 6.49. Found C, 61.84 H, 6.70

Preparation of 1-Propenyl 4,6-O-benzylidene-ß-D-mannopyranoside-2,3-cyclic sulfate (11). 1-Propenyl 4,6-O-benzylidene-ß-D-mannopyranoside (10) (1 g, 0.003 mol) was dissolved in dry THF (50 mL) under argon and sodium hydride (0.2 g, 0.008 mol) was added. The solution was stirred at room temperature until hydrogen evolution had ceased (~15 minutes) and N,N-sulfuryl diimidizole[9] (0.6 g, 0.003 mol) in dry THF (20 mL) was added. The solution was stirred for a further thirty minutes, filtered through Celite 545, and evaporated to dryness. The residue was dissolved in hot toluene, filtered and the product precipated by the addition of heptane. Recrystallization from toluene/heptane gave 0.94 g of 1-propenyl 4,6-O-benzylidene-ß-D-mannopyranoside-2,3-cyclic sulfate (11), mp 138-139° C. IR (KBr) 1680 cm^{-1}, 1405 cm^{-1}, 1220 cm^{-1}, MS 370 (M+), 369 (M-1) 313 (M-OCH=CH-CH_3).

Anal. Calc for $C_{16}H_{18}O_8S$ C, 51.84 H, 4.86 S, 8.64 Found C, 51.76 H, 4.95 S, 8.80

Synthesis of 2-Deoxy-2-fluoro-D-glucose. 1-Propenyl 4,6-O-benzylidine-ß-D-mannopyranoside-2,3-cyclic sulfate (11) (0.356 g, 0.001 mol) was refluxed in dry acetonitrile (50 mL) containing tetramethylammonium fluoride (0.169 g of the tetrahydrate) which had been dried by azeotropic distillation of acetonitrile.[1] The acetonitrile was evaporated and the residue dissolved in 2N hydrochloric acid (25 mL) and the solution heated to reflux for 10 minutes. The solution was neutralized with sodium bicarbonate solution, evaporated to dryness, and the residue extracted with ethanol. The ethanol extract was evaporated and the residue crystallized from ethanol/ethyl acetate to give 153 mg (85% yield) of

2-deoxy-2-fluoro-D-glucose, mp 164-165 °C, mixed mp with authentic sample, 163-164 °C, obtained from previous work.[1]

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