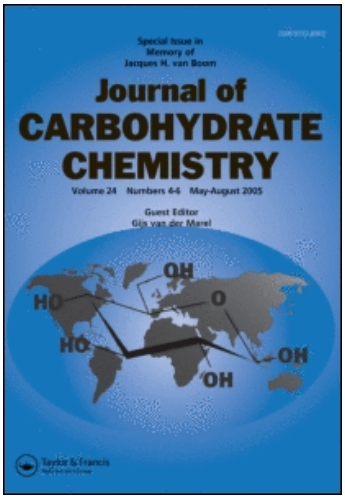

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PHOTOCHEMICAL REACTIONS IN CARBOHYDRATE SYNTHESIS. CONVERSION OF L-ARABINOSE INTO L-STREPTOSE

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ABSTRACT

A synthesis for L-streptose (1) is described. This synthesis differs from those previously reported in several ways, one of which is the use of photochemical reactions in two important steps. These reactions are part of a sequence leading from L-arabinose (2) to 5-deoxy-1,2-O-isopropylidene-β-L-threo-pentofuranos-3-ulose (3). Two other photochemical reactions are considered as a part of the conversion of 3 into L-streptose (1) but neither proved useful. L-Streptose (1) is synthesized from 3 by a sequence of reactions which involves formation of 5-deoxy-1,2-O-isopropylidene-3-C-nitromethyl-β-L-lyxofuranose (10) and subsequent reaction of 10 with titanium(III) chloride.

INTRODUCTION

For the past several years we have been studying selected, photochemical reactions of carbohydrates.[1] These reactions, which include oxidation, reduction,

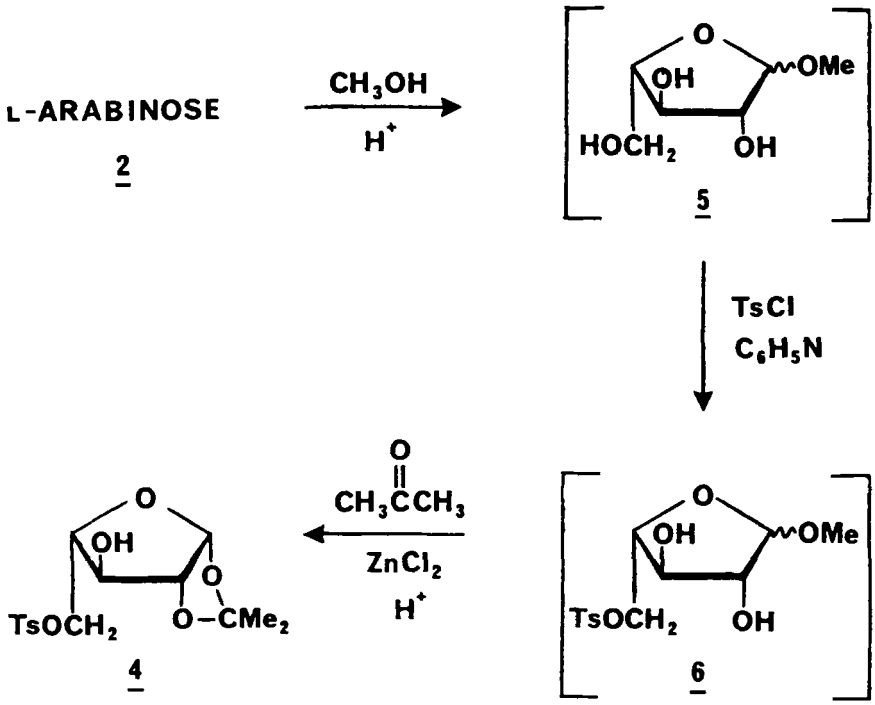
and inversion of configuration, have been found to be comparable to non-photochemical processes in most aspects (e.g., product yield) and to have advantage in some instances when relatively unstable molecules were involved.[1a] One group of compounds for which synthesis using photochemical reactions has appeared to be well suited has been the naturally occurring, branched-chain sugars. As a starting point for exploring this application, the synthesis of a particular member of this group was undertaken.

L-Streptose (1), a monosaccharide component of the antibiotic streptomycin, is a branched-chain sugar for which two laboratory syntheses have been published.[2,3] These two follow similar pathways from L-arabinose (2) to 5-deoxy-1,2-O-isopropylidene-β-L-threo-pentofuranos-3-ulose (3) but their pathways diverge in the final stage, that is, the introduction of the branched-chain. The research reported here describes an alternative L-streptose (1) synthesis, one for which the primary difference from previous syntheses occurs in the early stages.

RESULTS AND DISCUSSION

The first goal in the present study was to convert L-arabinose (2) into 1,2-O-isopropylidene-5-O-tosyl-β-L-arabinofuranose (4) (Scheme 1). Previous synthesis of 4 has proceeded by a route involving L-arabinose diethyl dithioacetal[4] (Scheme 2). A simpler procedure was adopted here. This procedure was less complicated because it required fewer steps and because it did not necessitate isolation of intermediates 5 and 6 (Scheme 1). Synthesis of 4 took advantage of the preferential formation of the methyl furanosides 5 from 2 under conditions of kinetic control.[5] Also, essential to this approach

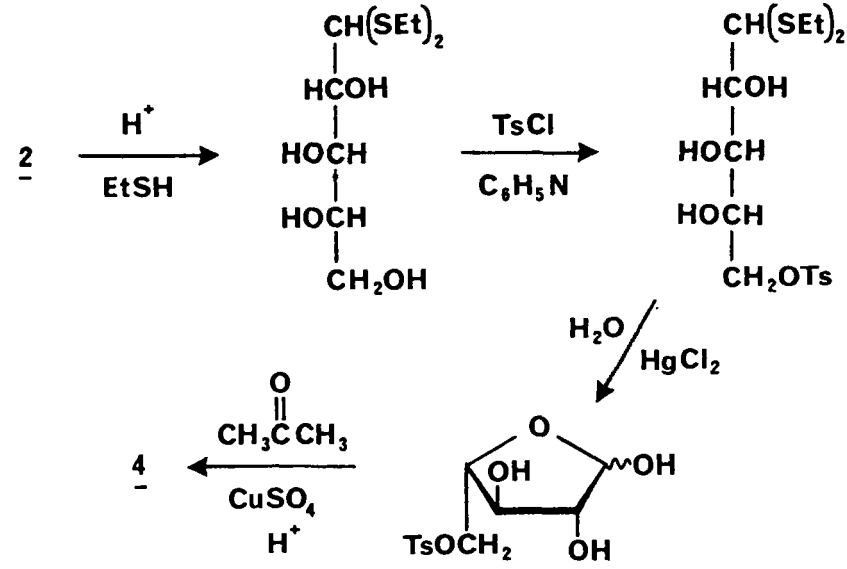
SCHEME 1



was the regioselective formation of the primary tosylates 6 by reaction of 5 with a limited amount of tosyl chloride. Compound 4 crystallized directly from the crude reaction mixture following the steps shown in Scheme 1. The yield of 4 from L-arabinose (2) was 29%. (The yield of 4 from the reaction sequence shown in Scheme 2 was 19%.)

The next stage in the synthesis of L-streptose (1) was to convert 4 into 5-deoxy-1,2-O-isopropylidene-L-threo-pentofuranos-3-ulose (3). In this conversion, displacement of tosylate by iodide was followed by irradiation of the resulting deoxyiodo sugar (Scheme 3).

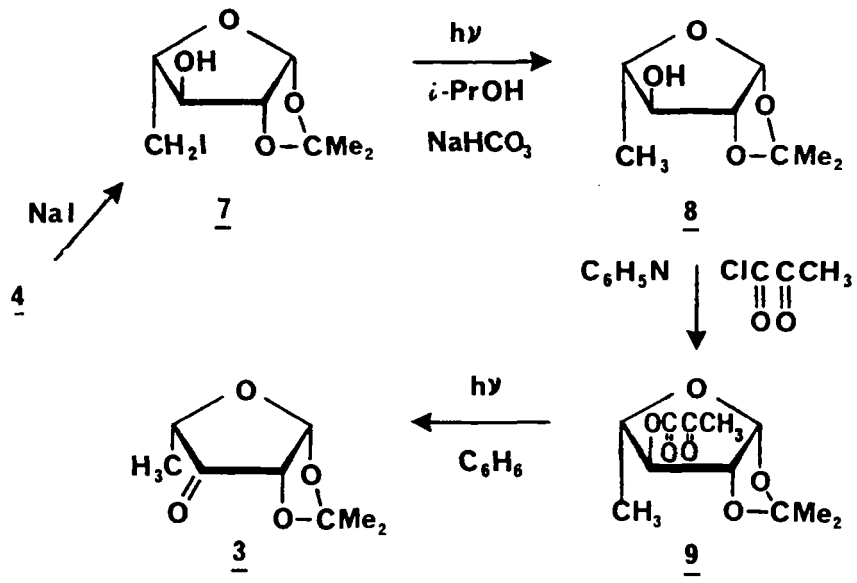
SCHEME 2



Several aspects of this photochemical reaction deserve comment because they were important in achieving the best yield of the deoxy sugar 8. First, since the reaction solvent also served as a source of hydrogen atoms, an effective hydrogen donor such as 2-propanol was required. Second, it was necessary to prevent acid-catalyzed removal of the isopropylidene group during photolysis; therefore, sodium bicarbonate was added to the reaction mixture and efficient stirring was maintained during reaction. The best yield of 8 resulted when a Pyrex filter prevented higher energy radiation from reaching the reaction mixture.

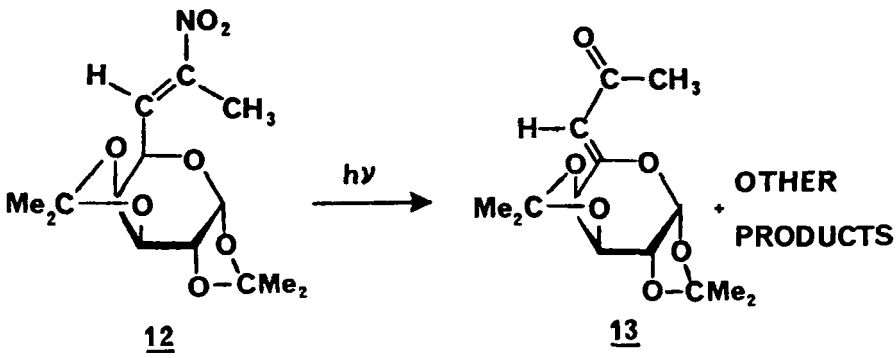
A second photochemical reaction, irradiation of the pyruvate ester 9, was used in the oxidation of the alcohol 8 to the ketone 3. Product yield (50%) was somewhat less than previously observed for this type of photochemical reaction.[1a,b] The lower yield may have resulted from the instability of 3, which decomposed

SCHEME 3



completely upon standing at room temperature in methanol for one day and partially decomposed during chromatography on silica gel. Compound 3 was stable, however, for months at -20 °C. The overall yield for the four-step conversion of 4 into 3 via the reactions shown in Scheme 3 was 38%.

The first method selected for carbon-carbon bond formation at C-3 was the synthesis of 5-deoxy-1,2-O-isopropylidene-3-C-nitromethyl-β-L-lyxofuranose (10) by base catalyzed addition of nitromethane to the ketone 3 (Scheme 4). It was hoped that photolysis of 10 would cause a rearrangement to 5-deoxy-3-C-formyl-1,2-O-isopropylidene-β-L-lyxofuranose (11) in a reaction similar to the rearrangement of the nitro compound 12 to the ketone 13 (equation 1).[6] Photolysis of 10, however,



12 13

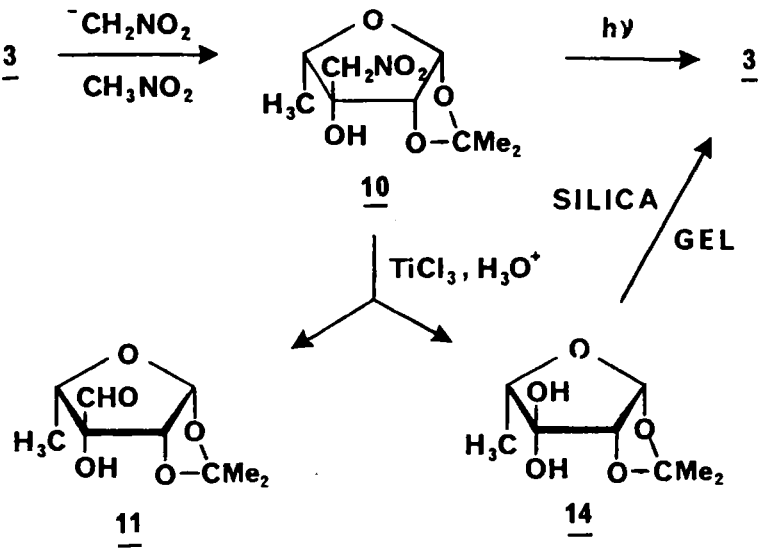
(EQUATION 1)

resulted in loss of the nitromethyl group to regenerate 3.

Nieuwenhuis and Jordaan[7] have shown that aldehydes can be generated in excellent yield by treatment of the corresponding nitromethyl compounds with titanium(III) chloride. Treatment of 10 with titanium(III) chloride did produce the desired aldehyde 11; unfortunately, the yield of 11 was low (13%) and its formation was accompanied by a second reaction, loss of the nitromethyl group to give the hydrate 14 of the ketone 3. Separation of 11 and 14 and hydrolysis of the former (11) resulted in formation of L-streptose (1). This final reaction completed the synthesis; however, the conversion of 3 into 1 was only in 8% yield.

The failure of the photochemical reaction of 10 to produce 11 and the low yield from the reaction of 10 with titanium(III) chloride prompted consideration of a second process for introduction of a third carbon-carbon bond at C-3 in compound 3. This second process began with the reaction of 3 with 2-lithio-1,3-dithiane (Scheme 5) as reported by Paulsen and coworkers[2] to give 5-deoxy-3-C-(1,3-dithiane-2-yl)-1,2-O-isopropylidene-

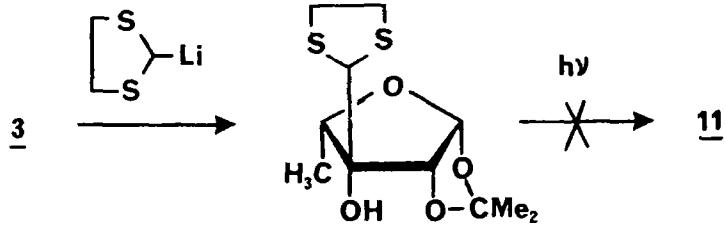
SCHEME 4



β-L-lyxofuranose (15). These researchers converted 15 into L-streptose (1) by treatment with mercury(II) oxide and boron trifluoride etherate and subsequent hydrolysis. An alternative procedure was suggested by the reported photolysis of dithioketals in the presence of oxygen to produce carbonyl compounds.[8] Unfortunately, photolysis of 15 resulted only in extensive, molecular fragmentation and, thus, was not a useful method for its deprotection.

In conclusion, the synthesis of L-streptose (1) reported here differs in several significant aspects from those previously reported. Its primary advantage lies in the ease of formation of 1,2-O-isopropylidene-5-O-tosyl-β-L-arabinofuranose (4) from arabinose (2) (Scheme 1). The major defect in the present synthesis is the poor product yield in conversion of the nitromethyl group in compound 10 into a formyl group (Scheme 4). The

SCHEME 5



value of photochemical reactions as a part of branched-chain sugar synthesis cannot be determined yet. Certainly, photochemical processes integrated easily into the synthesis of 3; however, they did not appear to have particular advantage over non-photochemical reactions.

EXPERIMENTAL

General Procedures. ^{1}H NMR spectra were obtained ($CDCl_3$) from a Varian T-60 spectrometer and ^{13}C NMR spectra ($CDCl_3$) were determined using a Varian FT-80A spectrometer. All spectra are given in tabular form in Tables 1 and 2. Solvent distillation from reaction mixtures was done under reduced pressure (water aspirator) using a Buchi rotary concentrator.

Synthesis of 1,2-O-Isopropylidene-5-O-tosyl-β-L-arabinofuranose (4). A 0.30 M solution of HCl in CH_3OH was prepared by dropwise addition of 10 ml (11 g, 0.14 mol) of acetyl chloride to 400 ml of CH_3OH. When this solution had cooled to 25°C, 20 g (0.13 mol) of powdered

TABLE 1. ^{13}C NMR Spectral Data[a] for Compounds 3,4, and 7-10.

	3	4[b]	7	8	9[c]	10[d]
C-1	102.12	105.85	106.21	105.29	105.52	104.64
C-2,	76.89	86.23	88.11	87.36	84.54	83.54
C-3,	76.51[e]	84.62	86.41	83.42	82.66	79.04[e]
C-4	201.35	75.47	76.89	79.71	81.11	76.54
C-5	18.18	68.63	5.91	19.54	19.70	14.31
$C(\underline{C}H_3)_2$	27.09	26.37	26.80	26.67	26.55	26.90
	26.64	25.64	25.79	26.06	25.89	26.72
$\underline{C}(CH_3)_2$	114.21	112.45	112.54	112.51	112.81	114.84

a. Chemical shifts are relative to $(CH_3)_4Si$ (0 ppm)
b. Additional absorptions are at 145.00, 132.38, 129.81, 127.89 (aromatic) and 21.45 (CH_3). c. Additional absorptions are at 190.44, 159.68, and 26.34 (pyruvoyl group). d. Additional absorption is at 79.88 ($\underline{C}H_2NO_2$). e. C-3.

TABLE 2. ^1H NMR Spectral Data[a] for Compounds 3,4 and 7-10

	H-1	H-2	H-3	H-4	H-5[b]	$(CH_3)_2C$	Other Adsorptions
3	5.92 (4.3)[c]	4.40		4.16 (7.3)[d]	1.40	1.47 1.37	
4	5.93 (3.8)[c]	4.73	4.48	———	4.12	1.45 1.35	1.83 (OH) 2.52 (CH_3) 7.40,7.86
7	5.90 (4.0)[c]	4.52	4.45	3.98	3.38	1.55 1.35	2.88 (OH)
8	5.73 (4.0)[c]	4.35	4.10	3.90	1.32 (7.0)[d]	1.48 1.25	2.13 (OH)
9	5.80 (4.0)[c]	4.55	4.92 (2.3)[e]	4.13 (7.0)[d]	1.38	1.50 1.23	2.32 (CH_3)
10	5.75 (4.5)[c]	4.85		3.85 (6.5)[d]	1.38	1.63 1.48	4.51 4.25 (CH_2)

a. Chemical shifts are relative to $(CH_3)_4Si$ (0 ppm). Coupling constants are in Hz and are enclosed in parentheses below the appropriate shift values. b. In compounds 3, 8, 9, and 10, three hydrogens are attached to C-5, while in 4 and 7 there are only two. c. $J_{1,2}$; d. $J_{4,5}$; e. $J_{3,4}$.

L-arabinose (2) was added in one addition and the mixture stirred rapidly until the sugar dissolved (ca. 90 min). Immediately upon solution of the sugar, 60 ml (0.75 mol) of dry pyridine was added and the stirring was continued for 30 min. (Immediate pyridine addition is necessary to maximize furanose ring formation.) The solvent was distilled under reduced pressure, 40 ml of pyridine was added, and the solvent again distilled. (The purpose of the second solvent addition and distillation was to remove any remaining methanol.) The residue was dissolved in 100 ml of pyridine, protected from atmospheric moisture, and cooled in an ice/acetone bath. Tosyl chloride (25 g, .13 mol) in pyridine (100 ml) was added slowly to this rapidly stirred, cooled solution. The reaction mixture was allowed to warm to room temperature and then stand overnight. The pyridine solution was poured slowly into 1500 ml of rapidly stirred water and this mixture was extracted with three 500 ml portions of CH_2Cl_2. The organic phase was filtered through Celite to clarify it and the solvent was removed under reduced pressure. Final removal of the pyridine was accomplished using a mechanical pump and warming the mixture to 40°C. The material remaining after solvent evaporation was dissolved in 500 ml of anhydrous acetone. To this stirred solution was added 60 g of freshly fused $ZnCl_2$ and 2 ml of H_2SO_4 and the mixture was stirred for 24 h. (After 5 min a white precipitate began to separate from solution.) The reaction mixture was poured slowly into a vigorously stirred solution of 60 g of $NaHCO_3$ in 1500 ml of water. The salts which separated were filtered and washed with 300 ml of CH_2Cl_2. The filtrate was extracted three times with 300 ml portions of CH_2Cl_2. The CH_2Cl_2 was distilled and the residue partially crystallized upon standing overnight. The crystals were removed by filtration and the filtrate was further

concentrated by placing it under vacuum (mechanical pump) and warming it at 40 °C for three hours. A second crop of crystals formed and was collected. The crystalline material was combined and recrystallized from 2-propanol to give 13.0 g (0.039 mol) of 1,2-O-isopropylidene-5-O-tosyl-β-L-arabinofuranose (4), mp 129 °C (lit.[4] mp 129-130 °C) in 29% yield from L-arabinose (2).

Synthesis of 5-Deoxy-5-iodo-1,2-O-isopropylidene-β-L-arabinofuranose (7). 1,2-O-Isopropylidene-5-O-tosyl-β-L-arabinofuranose (4, 13.0 g, 0.41 mol) was combined with 12 g (0.080 mol) of NaI and 12 g (0.14 mol) of $NaHCO_3$ and suspended in 100 ml of N,N-dimethylformamide (DMF). The reaction mixture was purged with nitrogen, rapidly stirred, and heated to 110 °C. The rapid stirring was essential to prevent the reaction mixture from becoming acidic and the nitrogen purge greatly reduced color formation. After 6.5 h at 110°, the reaction mixture was cooled to room temperature, diluted with 500 ml of water, and extracted with three 300 ml portions of CH_2Cl_2. The CH_2Cl_2 extracts were clarified by filtration through Celite and the CH_2Cl_2 was removed by distillation. The DMF was removed by vacuum distillation (ca. 0.1 mm Hg) below 45 °C. (Removing the final amounts of DMF required extended time (4 h) under vacuum. A better procedure for eliminating the DMF not easily removed was to pass the reaction mixture, after distillation of most of the DMF, through a silica gel column.) For example, when the reaction mixture was passed through a 2.5 x 10 cm column of 230-400 mesh silica gel using 500 ml of 1:1 ether-hexane as the eluent, 11.1 g (0.037 mol, 89%) of 5-deoxy-5-iodo-1,2-O-isopropylidene-β-L-arabinofuranose (7) was isolated as a colorless syrup. This material was identical in ^1H and ^{13}C NMR spectra to an independently synthesized sample.[4]

Synthesis of 5-Deoxy-1,2-O-isopropylidene-β-L-arabinofuranose (8). 5-Deoxy-5-iodo-1,2-O-isopropylidene-β-L-arabinofuranose (7, 11.1 g, 3.77 x 10^{-2} mol) was dissolved in 1.0 L of 2-propanol. To this solution 11.0 g (3.7 x 10^{-1} mol) of $NaHCO_3$ was added. This mixture was stirred and purged with N_2 for 2 h and then irradiated through a Pyrex filter for 12 h using a 450-W Hanovia, mercury-vapor lamp. After photolysis, the solvent was distilled under reduced pressure and the residue partitioned between H_2O (250 ml) and CH_2Cl_2 (250 ml). The layers were separated and the aqueous solution extracted three times with CH_2Cl_2 (250 ml). The organic extracts were combined and the solvent was distilled to give a syrup which crystallized on standing. This material was recrystallized from boiling hexane to give 5.37 g (3.09 x 10^{-2} mol, 84%) of 5-deoxy-1,2-O-isopropylidene-β-L-arabinofuranose (8) mp 82-83 °C (lit.[4] 83-84 °C).

Synthesis of 5-Deoxy-1,2-O-isopropylidene-β-L-threo-pentofuranose-3-ulose (3). Pyruvic acid (4.0 ml, 5.0 g, 5.8 x 10^{-2} mol) was combined with 4.0 ml (5.0 g, 4.4 x 10^{-2} mol) of Cl_2CHOCH_3 and heated to 50 °C for 30 min. This reaction mixture was diluted with 20 ml of CCl_4 and added dropwise to a stirred, cooled (10 °C) solution of 8 (5.37 g, 3.09 x 10^{-2} mol) and 13.6 ml (1.6 x 10^{-1} mol) of pyridine in 100 ml of CCl_4. The reaction mixture was protected from atmospheric moisture prior to cooling and during reaction. Upon completion of the addition, the reaction mixture was allowed to warm to room temperature, maintained there for two hours, and filtered. The solvent was distilled from the filtrate first using a rotary concentrator and, then,a mechanical pump. The residue was shaken with CCl_4, allowed to stand overnight, and filtered. Distillation of solvent from the filtrate gave 7.37 g (3.04 x 10^{-2} mol) of 5-

deoxy-1,2-O-isopropylidene-3-O-pyruvoyl-β-L-arabino-furanose (9). This material was dissolved in 1 L of benzene and the resulting solution was stirred and purged with nitrogen for 2 h. Purging was continued during two h of Pyrex-filtered irradiation using a 450-W mercury-vapor lamp (Hanovia). After irradiation the solvent was distilled and the residue was extracted with 500 ml boiling hexane. Distillation of the hexane left 2.55 g (1.51×10^{-2} mol, 50% yield) of 5-deoxy-1,2-O-isopropylidene-β-L-threo-pentofuranos-3-ulose (3), identified by comparison with an independently synthesized sample.[2a]

Synthesis of 5-Deoxy-1,2-O-isopropylidene-3-C-nitromethyl-β-L-lyxofuranose (10). Compound 3 (2.55 g, 1.51×10^{-2} mol) was dissolved in 10 ml of dry nitromethane. To this stirred solution was added a mixture prepared by combining 10 ml of nitromethane with 0.2 g of $NaOCH_3$. After 24 h of stirring at room temperature, the mixture was filtered, the solvent distilled under reduced pressure, and the residue recrystallized from ethanol to give 3.16 g (1.36×10^{-2} mol, 90%) of 10, mp 151-153 °C. Anal. Calcd for $C_9H_{15}NO_6$ (233.23): C, 46.35; H, 6.48; N, 6.01. Found: C, 46.56; H, 6.43; N. 5.98.

Synthesis of 5-Deoxy-3-C-formyl-1,2-O-isopropylidene-β-L-lyxofuranose (11). Reaction of 10 (3.16 g, 0.014 mol) with aqueous $TiCl_3$ according to the general procedure of Nieuwenhuis and Jordaan[7] gave 0.80 g of a mixture which by TLC appeared to be predominantly two compounds. Chromatography of this mixture on a 2.5 x 10 cm column of 230-400 mesh silica gel using 500 ml of 1:1 ether-hexane (100 ml fractions collected) separated it into two components Fraction 2 contained 5-deoxy-3-C-formyl-1,2-O-isopropylidene-β-L-lyxofuranose (11, 0.41 g, 1.8×10^{-3} mol, 15%) identified by comparison with a known sample.[2a] Fraction 4

contained 0.25 g (1.4×10^{-3} mol, 10%) of the ketone 3. Compound 11 was hydrolyzed to L-streptose (1) according to the procedure of Paulsen and coworkers.[2a]

Irradiation of 5-Deoxy-1,2-O-isopropylidene-3-C-nitromethyl-β-L-lyxofuranose (10). Compound 10 (1.00 g, 4.0×10^{-3} mol) was dissolved in 350 ml of acetone and the resulting solution was purged with nitrogen for two h. Purging was continued during one h of Pyrex-filtered photolysis using a 450-W mercury vapor lamp. After irradiation, the solvent was distilled and the residue was chromatographed on a 2.5 x 10 cm column of 230-400 mesh silica gel using 1:1 ether—hexane; 100 ml fractions were collected. Fraction 3 contained 0.65 g of unreacted 10. Fraction 4 yielded 0.11 g of 3. No other carbohydrate containing material was obtained from the chromatography column.

Irradiation of 5-Deoxy-3-C-(1,3-dithiane-2-yl)-1,2-O-isopropylidene-β-L-lyxofuranose (15). Compound 15 (0.50 g, 1.7×10^{-3} mol), synthesized from 3 by the procedure of Paulsen and coworkers,[2b] was combined with 1.5 g (8.3×10^{-3} mol) of benzophenone and stirred in 150 ml of hexane. Air was bubbled through this mixture during 1 h of Pyrex-filtered irradiation with a 450-W mercury-vapor lamp. The reaction mixture became dark brown. TLC and ^{1}H NMR analysis showed that the starting material had been consumed. Chromatography of the reaction mixture on silica gel using 500 ml of ether produced no mobile carbohydrate containing material.

ACKNOWLEDGEMENT

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