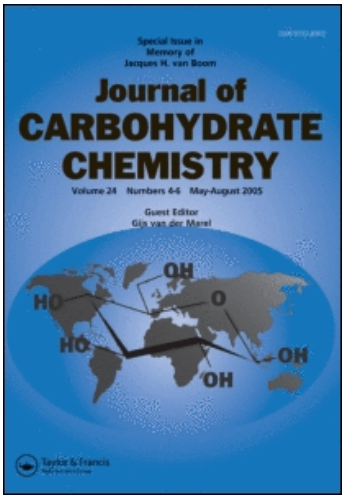

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Synthesis of a Derivative of 1-Deoxy-2,3-D-Threo-(and D-Erythro) Hexodiulose, an Intermediate in the Acid and Base Catalyzed Degradation of Hexoses

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SYNTHESIS OF A DERIVATIVE OF 1-DEOXY-2,3-D-THREO- (AND D-ERYTHRO) HEXODIULOSE, AN INTERMEDIATE IN THE ACID AND BASE CATALYZED DEGRADATION OF HEXOSES[1]

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ABSTRACT

1-Deoxy-2,3-hexodiuloses are thought to be key intermediates in the conversion of hexoses to saccharinic acids (in alkaline systems), as well as to furans and related derivatives in acidic systems. The 5,6-O-isopropylidene derivative of the title compound was prepared by condensing 2,3-O-isopropylidene-D-glyceraldehyde with propyne via a Grignard reaction, followed by oxidation of the -O-acetylated epimers to the diketones using a ruthenium catalyst and iodosylbenzene as the oxidant. Yields were in excess of 90% for each step, and no evidence of cleavage of the triple bond to the carboxylic acid was observed. Qualitative tests showed that the -O-isopropylidene-diulose is very unstable to both acids and bases, but that it is moderately stable at elevated temperatures (80 °C) and toward oxygen in aqueous dioxane solutions.

INTRODUCTION

1-Deoxy-2,3-diulose sugar derivatives have been proposed as important intermediates in the degradation of sugars at both acidic and basic conditions,[2] representing the product resulting from the initial dehydration reaction. During alkaline degradation reactions, such compounds could serve as precursors of the saccharinic acids (2-C-methyl-aldonic acids) by undergoing a benzylic acid rearrangement.[3] In acidic systems, the six-carbon analog could serve as a precursor of maltol (2-methyl-3-hydroxy-4H-pyran-4-one) and isomaltol (3-hydroxy-2-acetylfuran), the latter of which is unstable in dilute, aqueous acid. This analog is also thought to participate in other Maillard type reactions, serving as a source of reductones, and other fragmentation products.[4] For five-carbon systems (where the reaction products are more stable in aqueous acid), there is considerable evidence that an intermediate such as this is involved. 4-Hydroxy-5-methyl-3(2H)-furanone has been shown to be produced from either pentose- or hexuronic acid-derived Amadori compounds,[5] and ^{14}C tracer experiments have shown that the methyl group of the furanone corresponds to C-1 of the starting sugars.[6] This furanone has also been shown to be produced by reaction of D-ribose and D-ribose-5-phosphate in the presence of amines.[7] Tracer studies have also shown that the methyl group of the furanone corresponds to C-1 of D-ri-bose for these systems as well.[8]

In spite of the importance of these types of compounds as reaction intermediates, few attempts have been made to isolate or synthesize them, or to study carefully their role in such reactions. Some years ago Ishizu and co-workers[9] reported the preparation of such a compound via 1-deoxy-D-fructose, which was prepared from 1,5-anhydro- 2,3,4-tri-O-benzoyl-6-deoxy-6-iodo-D-mannitol using a lengthy and involved series of reactions. They reported that the 1-deoxy-2,3-hexodiulose was converted to only "α"-D-glucosaccharinic acid (2-C-methyl-D-ribonic acid) and that the "β"

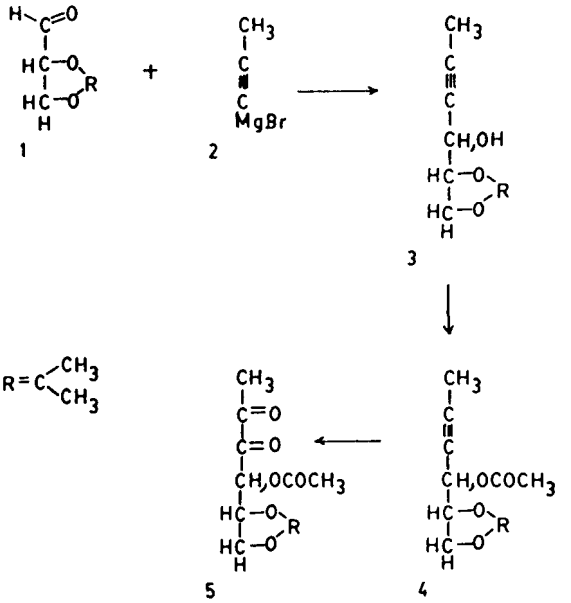
isomer (2-C-methyl-D-arabonic acid, the other expected product) was not produced on treatment of the hexodiulose with limewater. These findings were based on the results of GLC measurements. Surprisingly, they also reported that this intermediate is stable in dilute acid solution.

Dicarbonyl intermediates, such as the title compound, have also been proposed as Maillard reaction intermediates,[10] possibly as components that react to give a wide variety of heterocyclic compounds.

As part of a program to study the role and importance of such intermediates in degradation reactions, this report describes the synthesis of the 5,6-O-isopropylidene derivatives of some 1-deoxy-2,3-hexodiuloses using a simple, straightforward procedure that allows the preparation of the materials in large quantities for further study.

RESULTS AND DISCUSSION

The route for the synthesis of the title compound is shown in Scheme 1.



Scheme 1

Horton and co-workers[11-13] have previously described condensations of a number of aldehydo derivatives of sugars with (unsubstituted) acetylene Grignard reagents. In these types of reactions, the acetylene is reacted with (for example) ethyl magnesium bromide in tetrahydrofuran, and the acetylenic Grignard reagent is generated from it in the reaction solution. In the studies reported herein, this procedure was used, and the condensation of **1** with **2** to give **3** proceeded smoothly, provided that an excess of propyne was present at all times during the reaction. In some runs (when excess propyne was not present) varying amounts of the ethylated derivative (produced by reaction with ethyl magnesium bromide) were obtained, along with the desired product. It is difficult to detect this, since it has a TLC R_f-value identical to **3** in many of the commonly used TLC irrigants. The ethylated contaminant is, however, easily detected by its ^1H NMR spectrum. The C-1 methyl protons appear as a triplet centered at δ 1.0 ppm and the methylene protons as a multiplet centered at δ 1.20 ppm, partially obscured by the isopropylidene methyl protons (δ 1.8 and 2.0 ppm). The ^1H NMR spectrum of the epimeric products **3** was consistent with their proposed structures, with signals at δ 1.70 ppm (C-1 methyl), δ 1.20 and 1.18 ppm (isopropylidene methyl), as well as a complex multiplet between δ 3.4 and 4.3 ppm (H-4, H-5, H-6, and H-6').

In addition, the infrared spectrum was consistent with this structural assignment, showing bands at 3444 cm^{-1} (hydroxyl stretching) and at 2237 cm^{-1} (disubstituted acetylene), with no carbonyl absorption in the region 1700-1750 cm^{-1}.

A mass spectrum, using chemical ionization (isobutane) gave the expected protonated molecular ion at m/z 171. An electron impact mass spectrum gave only 3 peaks at greater than 25% relative abundance, but all were consistent with the structure proposed. The peak at m/z 101(100%), corresponds to fragmentation between C-4 and C-5 of 3; that at

m/z 43(100%) is derived from the isopropylidene group, and the peak at m/z 155(30%) corresponds to the C-2 through C-6 portion of the molecule, produced by loss of the C-1 methyl group. Other peaks were observed at: m/z 59(20%), 67(15%), 73(14%), and 95(12%).

Attempts to prepare **3** by reacting **1** with propynyl lithium in anhydrous tetrahydrofuran were unsuccessful with no evidence (TLC) of even traces of **3** being produced.

Acetylation of **3** with either sodium acetate or pyridine and acetic anhydride gave the epimeric 3-O-acetates (**4**). The ^{1}H NMR spectrum of **4** showed 2 closely spaced singlets at δ 2.07 ppm (C-1 methyl), 2 signals at δ 1.78 and 1.82 ppm (acetyl methyl), 2 signals at δ 1.35 and 1.41 ppm (isopropylidene methyl), as well as a complex multiplet at δ 3.8-4.4 ppm (H-4, H-5, H-6, and H-6'). The ^{13}C NMR spectrum was also consistent with the structure assigned. The following resonances were observed and are assigned as follows: δ 3.56 and 3.60 ppm (C-1, by analogy with 2-butyne-1-ol),[14] δ 20.7, and 20.8 ppm (acetyl methyl), δ 25.4-26.3 ppm (4 signals, isopropylidene methyl), δ 65.7 ppm (2 signals, C-4), δ 73.7 ppm (C-5), δ 76.7 and 76.8 ppm (C-6), δ 83.16 and 83.18 ppm (C-2, by analogy with butyne 1,4 diacetate and propyne-1-ol),[14] δ 77.9 ppm (C-3), δ 110.3 and 110.6 ppm (quaternary isopropylidene carbon), and δ 169.5 ppm (acetyl carbonyl).

The infrared spectrum showed characteristic bands at 2237 cm^{-1} (disubstituted acetylene), and at 1685 cm^{-1} (carbonyl). No hydroxyl stretching bands were observed.

The mass spectrum of **4** using chemical ionization also gave a protonated molecular ion at m/z 213. The electron impact mass spectrum of **4** was similar in nature to that of **3**, showing peaks at m/z 43(100%), derived from the -O-acetyl and -O-isopropylidene groups, at m/z 101(95%), corresponding to fragmentation between C-4 and C-5, and at m/z 197(36%) corresponding to a C-2 through C-6 fragment, produced by loss of the C-1 methyl group. Other peaks were observed at: m/z 137(55%), 73(35%), 95(37%), and 137(55%).

A number of methods have been reported that allow the direct, catalytic oxidation of acetylenic systems to diketones.[15-18] Of those reported, the system using dichlorotris (triphenylphosphine) ruthenium(II) (hereafter referred to as "the catalyst") appeared to be the mildest. The application of this procedure, as reported by Müller and Godoy,[18] gave the epimeric diketones **5** as a chromatographically pure reaction product, as evidenced by TLC using sulfuric acid as the spray reagent. The desired compounds **5** migrated as a single component on TLC, but could be separated from the catalyst and iodobenzene (produced in the reaction) by chromatography on silica gel and were isolated as a chromatographically pure component.

Although isolable, **5** slowly underwent degradation even at room temperature (see the last paragraph of this section for qualitative tests for stability). Nevertheless, some spectral data were obtained on freshly isolated samples and are described below.

The ^{13}C NMR spectrum obtained for **5** is assigned as follows: δ 20.4 and 20.5 ppm (acetyl methyl), δ 23.2 and 23.6 ppm (C-1 methyl), δ 25.94, 25.67, 25.71, and 26.10 ppm (isopropylidene methyl), δ 66.3 and 66.0 ppm (C-6), δ 73.44 and 73.86 ppm (C-5), δ 76.15 and 76.99 ppm (C-4), δ 110.2 and 110.4 ppm (quaternary isopropylidene carbon), and δ 191.05, 193.42, 195.44, and 196.12 ppm (C-2 and C-3).

The ^{1}H NMR spectrum likewise supported the proposed structures. The spectrum gave signals at δ 1.33 and 1.37 ppm (isopropylidene methyl), δ 2.52 and 2.58 ppm (acetyl methyl), δ 2.77 and 2.79 ppm (C-1 methyl), and a complex multiplet between δ 4.0 and 5.1 ppm (H-4, H-5, H-6, and H-6').

The infrared spectrum showed the absence of acetylenic bands and the presence of a large carbonyl band at 1718-1740 cm^{-1}.

The stability of **5** was qualitatively tested (using TLC as the detection method) in both 1.25 M hydrochloric acid

and 1.25 M sodium hydroxide in 50% aqueous methanol solutions. After 5 min of reaction in either medium at 25 °C, no traces of **5** remained. In neutral 50% aqueous dioxane solution, **5** was moderately stable at 80 °C for several h and was also stable to oxygen in the same solvent at 25 °C for several h.

EXPERIMENTAL

Materials And Methods. Thin layer chromatography (TLC) was performed on precoated silica gel plates using either A, benzene-methanol (90/10, v/v) or B, chloroform-diethyl ether (90/10, v/v) as irrigants. Spots were visualized by spraying with 10% sulfuric acid in ethanol, followed by heating at 110 °C for 15 min. ^{1}H NMR spectra were run on a 90-MHz Varian EM 390 instrument, and ^{13}C NMR spectra were recorded using a 300-MHz General Electric QE 300 instrument. In all cases, chemical shifts are reported relative to TMS and spectra were recorded in deuteriochloroform. Infrared spectra were collected using an IBM System 9000. Mass spectra were obtained using a GLC interfaced V.G. Masslab Trio-2 instrument located at the Facility for Advanced Instrumentation at the University of California at Davis. Elemental analyses were performed by Microtech Laboratories, Inc., Skokie, IL. 1,2:5,6-Di-O-isopropylidene-D-mannitol was prepared using the procedure described by Baer and Fischer.[19] The material was crystallized from chloroform-petroleum ether prior to use and was chromatographically homogeneous by TLC (irrigants A and B). 2,3-O-Isopropylidene-D-glyceraldehyde was prepared by periodate oxidation of the mannitol derivative as described by Le Coq and Ballou.[20] The material was chromatographically homogeneous (irrigants A and B), gave a ^{1}H NMR spectrum identical to that described by Horton and co-workers[11] and was not stable overnight. In most cases, this latter derivative was used without prior

distillation. Iodobenzene diacetate (the precursor of iodosylbenzene) was obtained from Aldrich Chemical, Milwaukee, WI. Iodosyl-benzene was prepared using the method described by Saltzman and Sharefkin.[21] Dichlorotris (triphenylphosphine) ruthenium(II) was obtained from Strem Chemicals, Inc., Newburyport, ME., and was used as obtained.

Preparation Of 2-Hexyne-5,6-O-isopropylidene-D-arabino- and D-Ribo-4,5,6-triol (3). In a typical experiment, 15 mL of a 2.0 M solution of ethyl magnesium bromide, in anhydrous tetrahydrofuran, was added dropwise to 150 mL of tetrahydrofuran (in a 250 mL round bottomed flask), while propyne gas was introduced into the solution via a sintered glass dispersion tube. After the addition was complete, and the solution was saturated with propyne (as evidenced by gas escaping from the surface of the solution), 3.4 g (26 mmol.) of 2,3-di-O-isopropylidene-D-glyceraldehyde, in 15 mL of anhydrous tetrahydrofuran, was added dropwise while maintaining a constant flow of propyne through the solution. When the addition was complete, the gas flow was continued for a further 30 min. The tetrahydrofuran solution was then cooled to 0 °C, washed with 2- 50 mL portions of saturated, aqueous ammonium chloride solution, dried over anhydrous sodium sulfate, and concentrated to a syrup. This material was obtained in quantitative yield and was chromatographically homogeneous (irrigants A and B). ^{1}H NMR indicated that no contamination by the ethylated derivative was present. Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 62.77; H, 8.31. See **RESULTS AND DISCUSSION** section for details and interpretation of the NMR and Mass Spectra.

Preparation Of 4-O-Acetyl-2-hexyne-5,6-O-isopropylidene-D-arabino and D-Ribo-4,5,6-triol (4). Compound 3 (3.0 g, 19 mmol.) was dissolved in a solution composed of 25 mL of pyridine and 25 mL of acetic anhydride and allowed to stand at 25 °C overnight. The solution was then poured into 200 mL of ice-water and the solution was stirred for 6 h. The solution was then extracted with 3 100 mL portions of

chloroform, the chloroform extracted with a freezing mixture of concentrated hydrochloric acid-ice, and then with 100 mL of a saturated solution of sodium bicarbonate. After drying over anhydrous sodium sulfate, the chloroform solution was concentrated to a syrup to give **4**. Alternately, **3** could be acetylated using acetic anhydride with sodium acetate as the catalyst at 90 °C, followed by the usual work-up. In either case, the product was obtained in quantitative yield and was homogeneous by TLC in irrigants A and B. This preparation was suitable for use in further synthetic steps. For analytical purposes, a sample was purified by elution from a silica gel column with benzene. Anal. calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 61.93; H, 7.45. Relevant NMR, IR and mass spectral data and assignments are given in the **RESULTS AND DISCUSSION** section.

Preparation Of 4-O-Acetyl-1-deoxy-5,6-O-isopropylidine -2,3-D-arabino- and D-Ribohex-2,3-diulose (5). In a typical experiment, compound **4** (750 mg, 3.8 mmol.) in 7.1 mL of methylene chloride, was added to a stirred solution of 22 mL of methylene chloride to which had been added 2.35 g of freshly prepared iodosyl benzene and 34 mg of the catalyst. The progress of the reaction was followed by TLC (irrigant A), and was complete in 30 min, as evidenced by the disappearence of the original compound (R_f 0.71), and the appearance of a reaction product (R_f 0.57). The reaction mixture was filtered through a pad of Celite, concentrated to dryness, dissolved in 5 mL of benzene, and added to the top of a silica gel column (2.5 x 12 cm). The column was then eluted with 150 mL of benzene-petroleum ether (1:1, v/v), and then with benzene-methanol (90:10, v/v). The yellow-colored product eluted with the first 100 mL of the latter eluant. The material obtained from the initial chromatography run (by evaporation of the solvent), was rechromatographed on a 1.5 x 75 cm column of silica gel using chloroform-diethyl ether (9:1, v/v) as irrigant. The product eluted after about 40 mL of eluant had been collected. It was

isolated by evaporation of the solvent to give a chromatographically pure syrup. Spectral data and assignments are given in the **RESULTS AND DISCUSSION** section.

Qualitative Tests For The Stability Of 5. Samples of **5** (25 mg) in 0.25 mL of methanol were added to 0.25 mL of either 2.5 M NaOH or HCl. The solutions were stirred and aliquots removed from time to time, spotted on TLC plates, and the plates developed in irrigant A. Compound **5** had completely reacted within 5 min in each solution. For the acidic solution, a streak having an R_f 0.18 replaced it, and for the basic solution, a streak having R_f 0.32 resulted. Further samples (at the same concentrations) were made up in 50% aqueous dioxane. One sample was heated at 80 °C in an oil bath, and the other was held at 25 °C while air was passed through the solution via a Pasteur pipette. Although some degradation occurred, **5** was still present after 24 h of treatment under either set of reaction conditions. No visible reaction (as evidenced by TLC) occurred during the first 2 h of treatment.

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