Notes

Investigation of an Unexpected Addition Reaction That Occurs when 2,3:4,5-Di-*O*-isopropylidene-D-ribose Diethyl Dithioacetal Is Treated with Mercuric Oxide and Mercuric Chloride
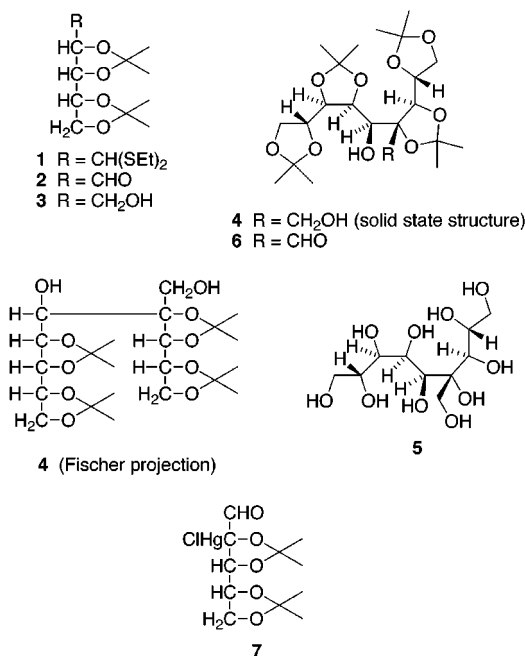
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A mixture of mercuric chloride and mercuric oxide in aqueous acetone is commonly used to hydrolyze dithioacetals in di-*O*-isopropylidenated pentoses to afford the corresponding aldehydes.[1−5] For example, treatment of 2,3:4,5-di-*O*-isopropylidene-D-ribose diethyl dithioacetal **(1)** with mercuric chloride and mercuric oxide in aqueous acetone has been reported to provide the expected aldehyde **2** in 70% yield.[1] In attempting to repeat this reaction, we recently encountered an unexpected reaction product in addition to **2**. The structure and formation of this novel reaction product are the subject of the present paper.

1 R = CH(SEt)₂
2 R = CHO
3 R = CH₂OH

4 R = CH₂OH (solid state structure)
6 R = CHO

4 (Fischer projection)

5

7

Treatment of the dithioacetal **1** with mercuric chloride and yellow mercuric oxide in aqueous acetone (95:5) at room temperature for 20 h afforded a crude product that displayed a proton NMR spectrum with two peaks at δ 9.72 and 9.68, suggesting the presence of two compounds that were both aldehydes. This mixture of products proved to be extremely difficult to separate, and it was therefore reduced with sodium borohydride in aqueous ethanol to yield a mixture of alcohols that could be separated chromatographically. The minor product, obtained in 22% overall yield, could be assigned the structure of 2,3:4,5-di-*O*-isopropylidene-D-ribitol **(3)** by comparison of its spectral data with those reported previously.[1]

The NMR and IR spectra of the major product, which was obtained in 50% overall yield, were generally indicative of what one would expect for an isopropylidenated carbohydrate derivative, but they did not allow a definite structural assignment. The low-resolution electrospray ionization mass spectrum (ESIMS) run in the positive-ion mode displayed a protonated molecular ion $(M + H^+)^+$ of *m/z* 463, while the ESIMS run in the negative ion mode showed a deprotonated molecular ion $(M − H^+)^-$ of *m/z* 461, indicating a molecular weight of 462. Since the molecular weight of **3** is 232, the molecular weight 462 observed for the product would be consistent with a compound formed from two molecules of **3** by covalent bonding and loss of two protons.

To determine the structure of the product, attempts were made to crystallize it for X-ray analysis. After considerable effort, it was found that the compound could be crystallized in colorless plates by dissolving it in a minimum amount of methylene chloride and then adding hexane. The crystals were suitable for X-ray crystallography, and the resulting ORTEP drawing is provided in the Supporting Information. The solid-state structure and Fischer projection of the product can be represented as two structures, both of which are labeled as "**4**". The solid state conformation of **4** is readily apparent from examination of the stereodiagram shown in Figure 1, which is programmed for walleyed (relaxed) viewing. Figure 1 was generated using the Sybyl 6.6 program, and the coordinates were obtained from X-ray crystallography.

Deprotection of the product **4** was investigated under acidic conditions. When treated with Amberlite IR-120 (H⁺) resin in refluxing aqueous acetone, the expected carbohydrate derivative **5** was obtained in 97% yield.[1] On the other hand, the primary alcohol present in compound **4** was oxidized selectively in the presence of the secondary alcohol with pyridinium chlorochromate in methylene chloride to afford the corresponding alde-

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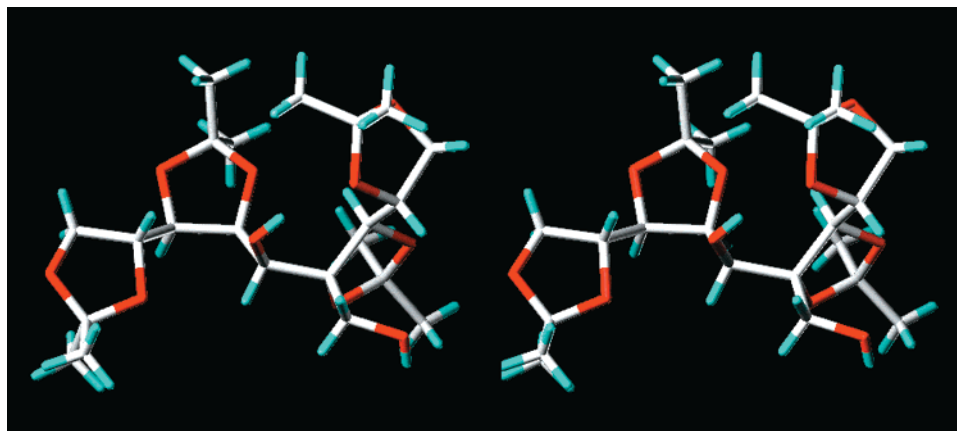(5) Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1997**, *62*, 6261−6267.
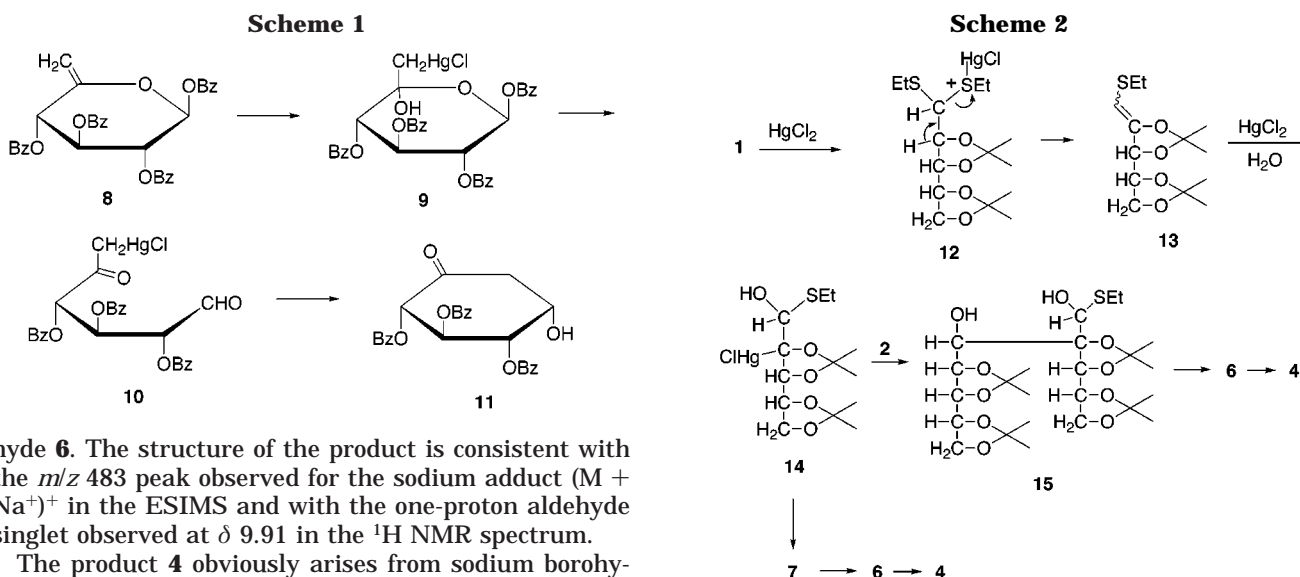
Figure 1. Stereodiagram generated from the X-ray coordinates obtained from compound **4**. The figure is programmed for walleyed (relaxed) viewing.

Scheme 1

Scheme 2

hyde **6**. The structure of the product is consistent with the m/z 483 peak observed for the sodium adduct $(M + Na^+)^+$ in the ESIMS and with the one-proton aldehyde singlet observed at δ 9.91 in the ^{1}H NMR spectrum.

The product **4** obviously arises from sodium borohydride reduction of the aldehyde **6** that is formed on treatment of the protected ribose derivative **1** with mercuric chloride and mercuric oxide in aqueous acetone. Since the aldehyde **2** was also detected as a minor reaction product, the question arises as to whether the product **4** is formed from **2** by an aldol reaction involving the mercuric enolate **7**, followed by sodium borohydride reduction. Although mercuric enolates are not common, they have been documented in several reports,[6,7] and some of them involve addition of the mercuric enolate to an aldehyde.[8] For example, the well-known Ferrier transformation of 6-deoxy-5-enopyranosyl compounds (e.g. **8**, Scheme 1) involves hydroxymercuration of the double bond and fragmentation of the ring in the resulting intermediate **9** to afford the mercuric enolate **10**, which carries out an intramolecular nucleophilic addition to the aldehyde to afford **11**. By analogy, one can imagine that intermolecular addition of the mercuric enolate **7** to the aldehyde **2**, both of which could be formed from the dithioacetal **1** in the presence of mercuric oxide and mercuric chloride in aqueous acetone, would result in the formation of the aldehyde **6**, which would then be reduced by sodium borohydride to yield the final product **4**. To

further investigate this possibility, the aldehyde **2** was subjected to the same reaction conditions as had been applied to the dithioacetal **1**, and this resulted in the formation of the product **4** in 15% yield, as opposed to the 50% yield of **4** starting from the dithioacetal **1**. This result shows that the aldehyde **6** does in fact form from **2** in the presence of mercuric chloride and mercuric oxide in aqueous acetone, but the lower yield (15% vs 50%) suggests that additional mechanistic pathways involving sulfur-containing intermediates may be operating in the addition reaction when the dithioacetal **1** is employed.

A possible mechanism for the participation of sulfur-containing intermediates is outlined in Scheme 2. Reaction of the dithioacetal **1** with mercuric chloride would be expected to result in the formation of the complex **12** having a positively charged sulfur atom.[9,10] Elimination of a proton and (ethylthio)mercuric chloride would result in the thioenol ether **13**, which could undergo oxymercuration to afford the hemithioacetal **14**.[9,11-13] Reaction

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of **14** with the aldehyde **2** would then afford intermediate **15**. The hemithioacetal **15** would be expected to decompose to the aldehyde **6**, which would be reduced to the corresponding alcohol **4** in the presence of sodium borohydride. Alternatively, the hemiacetal **14** could decompose to form the aldehyde **7**,[9,11] which could then react to form **6** and then **4**.

Recent interest in the aldol reaction as an approach to the synthesis of complex carbohydrates has focused on aldolase-catalyzed reactions[14−18] as well as on base-catalyzed aldol reactions involving nonidentical reaction partners.[19−25] The latter approach has typically involved the addition of a ketone enolate to an aldehyde,[19,20,24,25] although enolates derived from aldehydes[21] and esters[22,23] have also been employed. Much less attention has been given to aldol reactions starting from identical carbohydrate derivatives. The use of the mercuric chloride and mercuric oxide system as employed here could therefore potentially be a general method of carbohydrate coupling that could be employed in the synthesis of novel carbohydrate derivatives. However, preliminary studies on a limited number of potential reactants suggest that the method may not be wide in scope. Both the 2,5:3,4-di-*O*-isopropylidenated dithioacetal derivative **16** of ribose,[1] as well as the corresponding aldehydo ribose derivative **17**,[1] failed to provide any carbohydrate coupling product when subjected to the mercuric chloride and mercuric oxide system. Likewise, both the dithioacetal derivative **18** of xylose and the corresponding aldehydo sugar derivative **19** did not yield any coupling product. In these cases, the aldehydes **17** and **19** were recovered unchanged, and the dithioacetals **16** and **18** were converted cleanly to **17** and **19**.[1,26,27]

16   **17**

18   **19**
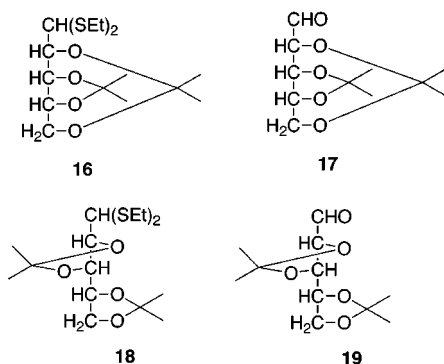
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Since the mercuric chloride and mercuric oxide system is used widely for the conversion of the dithioacetal derivatives of di-*O*-isopropylidinated pentoses to the expected aldehydo pentoses, and coupling products have not been reported before, a limited scope of the present coupling reaction might be expected.[1−5] It was previously reported that the treatment of **1** with mercuric chloride and mercuric oxide in aqueous acetone affords a 70% yield of **2**, which does not agree with our present observation.[1] However, the exact volume of aqueous acetone employed was not specified, and the reaction time was provided as "overnight", so it is difficult to make an exact comparison. One would logically expect that the coupling reaction observed here would be minimized in a more dilute solution of the reactants.

Experimental Section

General Procedures. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on 300 and 500 MHz spectrometers, as noted. The chemical shift values are expressed in ppm (parts per million) relative to tetramethylsilane as internal standard: s = singlet, d = doublet, m = multiplet, bs = broad singlet. The ^{13}C NMR spectra were recorded at 75 MHz. Microanalyses were performed at the Purdue Microanalysis Laboratory, and all values were within ±0.4% of the calculated compositions. Silica gel used for column chromatography was 230−400 mesh. Compounds **1**, **2**, **3**, **16**, **17**, **18**, and **19** were prepared as described in the literature.[1,26,27]

[5-((4*R***)-2,2-Dimethyl(1,3-dioxolan-4-yl))(4***R***,5***R***)-4-hydroxymethyl)-2,2-dimethyl(1,3-dioxolan-4-yl)][5-((4***R***)-2,2-dimethyl(1,3-dioxolan-4-yl))(4***S***,5***S***)-2,2-dimethyl(1,3-dioxolan-4-yl)](1***S***)-methan-1-ol (4).** The dithioacetal **1** (3.54 g, 10.5 mmol) in aqueous acetone (95:5, 30 mL) was stirred with yellow mercuric oxide (8.37 g) while a solution of mercuric chloride (7.54 g, 27.4 mmol) in acetone (20 mL) was added dropwise. After being stirred for 20 h, the mixture was filtered through Celite and concentrated in vacuo. The residue was extracted with CHCl$_3$ (3 × 20 mL), and the CHCl$_3$ layer was washed with saturated KI solution (2 × 10 mL) and then water (20 mL), dried (Na$_2$SO$_4$), and concentrated to give a mixture of compounds assumed to be **2** and **6** (2.33 g). Without further purification, this mixture in 50% aqueous ethanol (170 mL) was treated with sodium borohydride (4.05 g, 107 mmol) at room temperature for 3 h. Extraction of the reaction mixture with chloroform (2 × 50 mL) yielded a syrup (2.11 g). The mixture was separated by flash chromatography (30 g, 2 × 25 cm column of SiO$_2$, 230−400 mesh), eluting with light petroleum ether−diethyl ether (7:3), to afford compound **3** (0.527 g, 22%) and compound **4** (1.19 g, 50%) in pure form. The structure of 2,3:4,5-di-*O*-isopropylidene-D-ribitol **(3)** was characterized by comparing its spectral data with those reported earlier.[1] Compound **4**: mp 96−101 °C; IR (KBr) 3512, 3412, 2990 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.63 (d, *J* = 6 Hz, 2 H), 4.48 (m, 1 H), 4.35 (m, 3 H), 4.18 (m, 2 H), 4.07 (m, 2 H), 3.92 (m, 2 H), 3.64 (d, *J* = 12 Hz, 1 H), 3.12 (d, *J* = 6 Hz, 1 H), 1.44 (s, 3 H), 1.43 (s, 6 H), 1.40 (s, 6 H), 1.35 (s, 6 H), 1.30 (s, 3 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 110.11, 109.31, 108.86, 108.47, 85.26, 78.78, 78.63, 74.04, 72.40, 68.71, 67.90, 66.98, 62.51, 28.40, 26.89, 26.77, 26.30, 26.20, 25.37, 25.14, 24.56; positive-ion ESIMS (M − H$^+$)$^-$ *m/z* 463; negative-ion ESIMS (M + H$^+$)$^+$ *m/z* 461. Anal. Calcd for C$_{22}$H$_{38}$O$_{10}$: C, 57.14; H, 8.22. Found: C, 57.19; H, 8.32.

(4*S***,5***S***,2***R***,3***R***,6***R***,7***R***,8***R***)-4-(Hydroxymethyl)nonane-1,2,3,4,5,6,7,8,9-nonaol (5).** A solution of compound **4** (0.400 g, 0.865 mmol) in 50% aqueous acetone (25 mL) was heated at reflux for 3 h with Amberlite IR-120 (H$^+$) resin (2.40 g). Filtration and concentration yielded a syrup that was dissolved

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in methanol and precipitated with diethyl ether to provide **5** (0.253 g, 97%) as a semisolid: IR (neat) 3358, 2941 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$OD) δ 4.23 (s, 2 H), 4.02 (d, J = 7.2 Hz, 2 H), 3.93 (s, 4 H), 3.82–3.61 (m, 14 H); ^{13}C NMR (75 MHz, CD$_3$OD) δ 78.73, 74.53, 73.29, 73.07, 72.90, 71.97, 71.48, 64.75, 64.15; ESIMS (M + H$^+$)$^+$ m/z 303. Anal. Calcd for C$_{10}$H$_{22}$O$_{10}$: C, 39.73; H, 7.28. Found: C, 38.70; H, 7.38.

5-((4R)-2,2-Dimethyl(1,3-dioxolan-4-yl))-4-[[5-((4R)-2,2-dimethyl(1,3-dioxolan-4-yl))(4S,5S)-2,2-dimethyl(1,3-dioxolan-4-yl)](1S)-hydroxymethyl](4R,5R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (6). Compound **4** (0.317 g, 0.685 mmol) was dissolved in dry CH$_2$Cl$_2$ (10 mL), pyridinium chlorochromate (0.295 g, 1.37 mmol) was added, and the mixture was stirred at room temperature for 8 h under argon atmosphere. After 8 h, additional pyridinium chlorochromate (0.295 g, 1.37 mmol) was added, and stirring was continued for 24 h. The solution was filtered through Celite and silica gel and then concentrated to afford a liquid. The resulting residue was purified by flash chromatography (20 g, 2 × 40 cm column of SiO$_2$, 230–400 mesh), eluting with hexanes–ethyl acetate (8: 2), to afford compound **6** (0.097 g, 31%): IR (neat) 3448, 2987, 2937, 1737 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.91 (s, 1 H), 4.55 (d, J = 11.09 Hz, 1 H), 4.51 (q, J = 4.28 Hz, 1 H), 4.44 (m, 1 H), 4.34 (d, J = 7.05 Hz, 1 H), 4.14 (q, J = 6.09 Hz, 2 H), 4.09 (t, J = 1.76 Hz, 1 H), 4.04 (t, J = 8.67 Hz, 1 H), 3.90 (m, 2 H), 3.25 (d, J = 11.14 Hz, 1 H), 1.52 (s, 3 H), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.40 (s, 6 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H); ESIMS (M + Na$^+$)$^+$ m/z 483. Anal. Calcd for C$_{22}$H$_{36}$O$_{10}$: C, 57.39; H, 7.82. Found: C, 57.66; H, 7.63.

X-ray Crystallography of Compound 4. Data Collection. A colorless plate of compound **4** having approximate dimensions of 0.50 × 0.50 × 0.30 mm was mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed with Mo Kα radiation (λ = 0.71073 Å) on a Nonius KappaCCD. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 12991 reflections in the range 4 < θ < 27°. The orthorhombic cell parameters and calculated volume are as follows: a = 10.8892(4) Å, b = 22.2696(2) Å, c = 9.7366(9) Å, V = 2361.1(2) Å^3. For Z = 4 and FW = 462.54, the calculated density is 1.30 g/cm^3. The space group was determined by the program ABSEN.[28] From the systematic presences of $h00$ h = 2n, 0k0 k = 2n, and from least-squares refinement, the space group was determined to be $P2_12_12$ (#18). The data were collected at a temperature of 173 ± 1 K. Data were collected to a maximum 2θ of 55.8°.

Data Reduction. A total of 12991 reflections were collected, of which 5512 were unique. Lorenz and polarization corrections were applied to the data. The linear absorption coefficient is 1.0/ cm for Mo K radiation. An empirical absorption correction using

SCALEPACK[29] was applied. Transmission coefficients ranged from 0.735 to 0.972 with an average value of 0.907. A secondary extinction correction was applied.[30] The final coefficient, refined in least-squares, was 0.0470000 (in absolute units). Intensities of equivalent reflections were averaged. The agreement factor for the averaging was 5.0% based on intensity.

Structure Solution and Refinement. The structure was solved by direct methods using SIR97.[31] The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. The structure was refined by full-matrix least-squares methods where the function minimized was $\Sigma w(|F_o|^2 - |F_c|^2)^2$ and the weight w is defined as $w = 1/[\sigma^2(F_o^2) + (0.0378P)^2 + 0.4390P]$ where $P = (F_o^2 + 2F_c^2)/$ 3. Scattering factors were taken from the *International Tables for Crystallography*.[32] A total of 5478 reflections were used in the refinements. However, only reflections with $F_o > 2\sigma(F_o^2)$ were used in calculating R. The final cycle of refinement included 300 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: R1 = $\Sigma |F_o - F_c|/F_o$ = 0.045, R2 = SQRT ($\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2$) = 0.089. The standard deviation of an observation of unit weight was 1.07. The highest peak in the final difference Fourier had a height of 0.40 e/A^3. The minimum negative peak had a height of −0.30 e/A^3. The factor for the determination of the absolute structure[33] refined to −0.70. Refinement was performed on a Alpha Server 2100 using SHELX-97.[34] Crystallographic drawings were done using programs ORTEP[35] and PLUTON.[36]

Supporting Information Available: X-ray crystallography data for compound **4**, including an ORTEP diagram. This material is available free of charge via the Internet at http://pubs.acs.org.

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