Facile Synthesis of a Carbohydrate Derivative: 2-Deoxy-2-*C*-methylene-D-*erythro*-pentono-1,4-lactone

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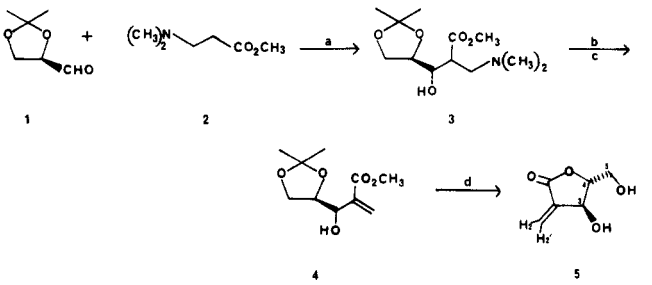
The title compound **5** was prepared in four steps in a 36% overall yield from isopropylidene-D-glyceraldehyde **1** and methyl 3-(dimethylamino)propanoate **2** with an 84% diastereomeric excess. Chromatographic separation of the diastereomers afforded optically pure **5**.

The α-methylene-γ-butyrolactone moiety is part of a number of sesquiterpenes with interesting biological activity (cytotoxic, antifungic, antibacterial properties).[1] Analogues with a β-hydroxy substituent are also present in a number of plants either as sesquiterpenes[2] or as glycoside derivatives, for instance in tulip bulbs.[3]

We have been interested for some time in the mechanism of allergic contact dermatitis (ACD),[4] an adverse skin reaction caused by several substances, including β-hydroxy-substituted and unsubstituted α-methylene-γ-butyrolactones. To that end, we have recently devised two general schemes for the syntheses of the β-hydroxy derivatives.[5] Other groups also devised several synthetic schemes.[6] As the problem of the stereospecificity of ACD attracted our attention, we were in search of optically active allergens. For that purpose, we have described recently[8] the synthesis of α-hydroxy acrylates. We now report the synthesis of a D-*erythro*-carbohydrate derived β-hydroxy-α-methylene-γ-butyrolactone **5**, starting from isopropylidene-D-glyceraldehyde **1**. (Scheme I). A diastereomer, the D-threo derivative, has been described, starting from D-xylose.[9]

The starting material, 2,3-isopropylidene-D-glyceraldehyde **1**, readily available from D-mannitol,[10] was reacted with the anion of methyl 3-(dimethylamino)-propanoate[11] **2** to give derivative **3** in essentially quantitative yield as shown by NMR where the aldehydic hydrogen is absent. Crude compound **3** was first treated with an excess of methyl iodide and then with an aqueous sodium bicarbonate solution, yielding the unsaturated ester **4** in a 71% yield. This compound was obtained as a 92:8 mixture of diastereomers as shown by gas chromatography. Flash chromatographic separation of the mixture afforded the two diastereomers in this 92:8 ratio. Removal of the isopropylidene group and cyclization of the major diastereomer were performed in one step by a trifluoroacetic acid–water (9:1) treatment, with a 51% isolated yield of α-methylene-β-hydroxy-γ-butyrolactone **5**.

Scheme I[a]



[a] (a) LDA; (b) CH_3I; (c) $NaHCO_3$; (d) CF_3CO_2H-H_2O.

The predominant formation of one diastereomer can be explained by the intermediacy of a lithium complex as shown in Figure 1. The *si* face of the aldehyde becomes much more crowded than the *re* face; major attack thus leads to the diastereomer with an *R* configuration at the former aldehydic carbon.

The enantiomeric purity of compound **4** was ascertained by ^1H NMR taken in the presence of a chiral shift reagent, europium tris(trifluoroacetyl-*d*-camphorate). This is an agreement with another example of the literature where D-glyceraldehyde was used in the synthesis of PGE_1.[12]

The absolute configuration of **5** was established by ^1H NMR. First, the spectrum of **5** was different from that described by Nair and Sinhababu[9] for the D-*threo*-lactone, suggesting our compound was a diastereomer.[13] Thus, for instance, H_3 gave a signal at 5.60 ppm and H_2 and $H_{2'}$ appeared at 6.62 and 6.93 in the D-*threo*-lactone while the shifts for H_3, H_2, and $H_{2'}$ in the D-*erythro*-lactone were respectively 4.72, 6.16, and 6.62. Second, as the configuration of C-4 is fixed and known to be *R*, from the starting glyceraldehyde, we inferred that the C-3 configuration must be *S*. Furthermore, the signal for H_3, expected to be an eight signal multiplet (ddd), appears as a pseudo-quartet due to three, almost identical, coupling constants ($J_{2,3} = J_{2',3} = J_{3,4}$). The low (2.0 Hz) value[14] of the latter indicates a trans relationship between H_3 and H_4, confirming the assigned *S* configuration at C-3.

Experimental Section

^1H-NMR spectra were recorded at 200 MHz. GLC analyses were performed with a 5% OV-17 column.

Methyl 2-Methylidene-3(*R*)(and 3(*S*)),4(*R*),5-trihydroxy 4,5-Acetonide (4). To a stirred solution of lithium diisopropylamide (17 mmol) in dry THF (60 mL) at −78 °C under argon

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(13) The same treatment of the minor (8%) compound afforded the known D-threo diastereomer.[9]

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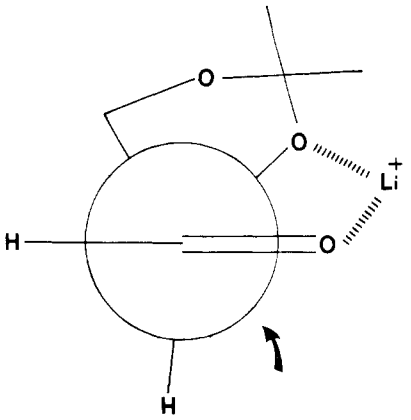

Figure 1.

was added methyl 3-(dimethylamino)propanoate **2** (2.0 g, 15.3 mmol). To the resulting milky reaction mixture was slowly added with stirring, 15 min later, a solution of isopropylidene-D-glyceraldehyde (2.0 g, 15.3 mmol) in THF (10 mL). After another 15 min at −78 °C, the resulting mixture was quenched with water (10 mL). After the aqueous layer was extracted with ethyl acetate, the combined THF and ethyl acetate layers were dried over magnesium sulfate and the solvent was removed. The NMR spectrum of the crude residue showed complete disappearance of the aldehydic hydrogen. Crude **3** (3.97 g, 15.3 mmol) was dissolved in ether (30 mL). Methyl iodide (20 mL) was added and the solution was stirred at room temperature for 2 h. The resulting precipitated salt was filtered and dissolved in a saturated aqueous sodium bicarbonate solution (50 mL), and ethyl acetate (50 mL) was added. After stirring at room temperature for 30 min, the organic layer was separated and the aqueous layer extracted with 3 × 20 mL of ethyl acetate. The combined organic layers were dried over $MgSO_4$, concentrated, and "flash" chromatographed on a silica gel column (eluent, ether–hexane 1:1), affording pure **4** (2.18 g, 10 mmol), 66% yield): $[\alpha]_D$ = −17.0° (*c* 1.50, acetone); IR ($CHCl_3$) 3473 (OH), 1719 (C=O), 1634 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 1.35 (s, 3 H), 1.44 (s, 3 H), 2.98 (d, 1 H, J = 5.09, D_2O exchangeable), 3.79 (s, 3 H), 3.92 (d, 2 H), 4.34 (dt, 1 H), 4.53 (m, 1 H), 5.99 (dd, 1 H, J = 1.27 and J = 1.29), 6.36 (m, 1 H). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.45. Found: C, 55.56; H, 7.27.

2-Deoxy-2-*C*-methylene-D-*erythro*-pentono-1,4-lactone (5). To compound **4** (1.0 g, 4.6 mmol) cooled to 0 °C was added trifluoroacetic acid (18 mL) and water (2 mL). Immediately afterward, stirring was started and the temperature was allowed to rise over 2 h to room temperature. Evaporation to dryness afforded a solid which was purified by flash chromatography on silica gel (eluent, ethyl acetate): yield 51% (0.34 g, 2.3 mmol); mp 66 °C; $[\alpha]_D$ −91.3 (*c* 1.10, methanol); IR (KBr) 3365 (OH), 1766 (C=O), 1651 (C=C) cm^{-1}; ^1H NMR (D_2O) 4.24 (m, H_4), 4.44 and 4.51 (AB part of an ABX spectrum, H_5 and $H_{5'}$, $J_{5,4}$ = 2.0 and $J_{5',4}$ = 3.3), 4.72 (ddd, H_3, $J_{3,2} = J_{3,2'} = J_{3,4}$ = 2.0), 6.16 (dd, $H_{2'}$, $J_{2,2'}$ = 2.0), 6.62 (dt, H_2, $J_{2,4}$ = 1.5). Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.55. Found: C, 49.83; H, 5.88.

Note Added in Proof: After this manuscript was accepted, a similar approach for the stereoselective synthesis of α-methylene-β-hydroxy-γ-acetoxy esters was described: Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784.

Registry No. **1**, 15186-48-8; **2**, 3853-06-3; **3**, 93684-93-6; *threo*-**4**, 93684-94-7; *erythro*-**4**, 93714-49-9; **5**, 74948-84-8; CH_3I, 74-88-4.

Gas-Phase Thermal Rearrangements of Potential Vinylidene Precursors to Silylbenzofurans and Silylbenzopyrans

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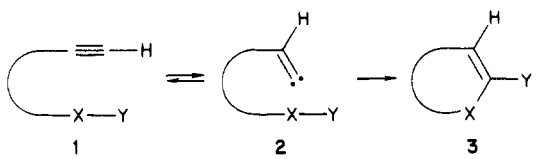
In an attempt to utilize the considerable migratory aptitude of silicon in the synthesis of 3-silylbenzofurans, the flash vacuum pyrolysis (FVP) of *o*-[(trimethylsilyl)ethynyl]phenol was found to provide not only the furan expected from vinylidene cyclization but two isomers resulting from initial 1,5-hydrogen migration from oxygen to form an intermediate allenyl ketone. FVP of 2-(trimethylsilyl)-4,5-dihydrofuran produced an unprecedented gas-phase reductive elimination to a vinylidene. *o*-Ethynyl- and *o*-propynylanisoles did not afford benzopyrans through vinylidene/C-H(Me) insertion but underwent radical transformations. However, *o*-[(trimethylsilyl)-ethynyl]anisole unexpectedly extruded Me_2Si to form 2-ethylbenzofuran as the only product. Various mechanisms for this remarkable decomposition are considered. The acyclic analogue 1-(trimethylsilyl)-4-methoxybut-1-yn-3-ene pyrolytically extruded not Me_2Si but carbon monoxide! This is rationalized as proceeding through an initial 1,5-methyl migration from oxygen to carbon.

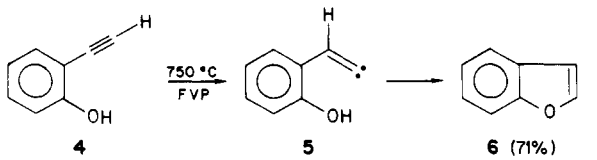
The thermally induced isomerization of acetylenes to vinylidenes (**1** ⇄ **2**), discovered by Brown[1] in 1974, has



1 **2** **3**

been utilized via intramolecular trapping (**2** → **3**) in the synthesis of bicyclic enones by Dreiding[2] and most recently by us[3] in the synthesis of unsaturated silacycles.

Bloch[4] has reported that flash vacuum pyrolysis (FVP) of (*o*-hydroxyphenyl)acetylene (**4**) at 800 °C results in quantitative conversion to benzofuran **6**, and this is reasonably interpreted as proceeding through the intermediacy of vinylidene **5**. In our hands, FVP of **4** at 750 °C



4 **5** **6** (71%)

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