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Synthesis of 2-Acetyl-4-(1,2,3,4-tetrahydroxybutyl)imidazole

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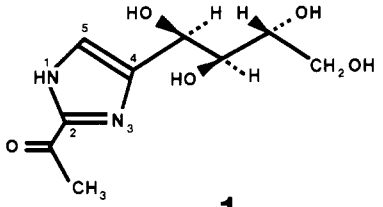
Recent studies on Caramel Color III, aimed at the isolation of the component responsible for reducing circulating lymphocyte counts in rats, maintained on a vitamin B_6 deficient diet, has led to the characterization of 2-acetyl-4-(1,2,3,4-tetrahydroxybutyl)imidazole (1) as the bioactive factor.[1]



1

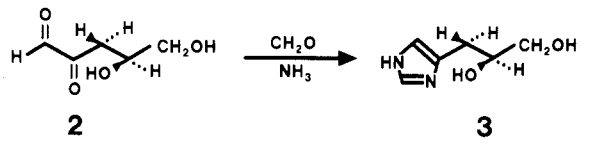
In this paper we describe an efficient synthesis of 1 from D-glucose that confirms the proposed structure and proves the stereochemistry of the side chain as written.

The strategy adopted for the synthesis of 1 was patterned after the prior work of Komoto,[2] who found that 3-deoxyxylosone (2) condensed with ammonia and formaldehyde to give the corresponding imidazole 3 in 80% yield (Scheme I).

The extension of this reaction to the synthesis of 1, however, would require the condensation of D-glucosone (4) with pyruvaldehyde and ammonia. However, it was known that α-keto aldehydes suffer considerable fragmentation in the presence of ammonia. For example, the condensation of pyruvaldehyde with ammonia gave 4-methyl- and 2,4-dimethylimidazoles as major products; the expected 4-methyl-2-acetylimidazole was formed in only 0.2% yield.[3] Similarly, the reaction of 3-deoxyglucosone with ammonia afforded 4-(2,3,4-trihydroxybutyl)imidazole as the major basic product.[4]

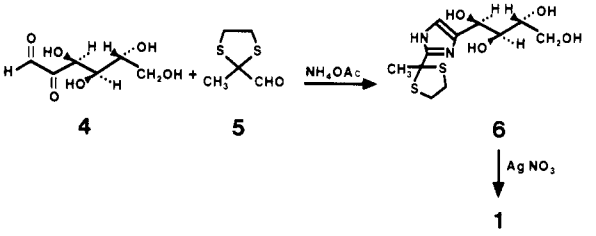
Scheme II depicts the sequence we have adopted to synthesize 1, which involved the condensation of D-glucosone (4)—readily available from D-glucose phenylosazone via acid-catalyzed exchange with benzaldehyde[5]—with an excess of pyruvaldehyde ethylene

Scheme I



2 **3**

Scheme II



4 **5** **6** **1**

dithioketal 5[6] and ammonium acetate. The use of pyruvaldehyde with the keto group protected prevented the cleavage of the α-keto aldehyde function and allowed the condensation to proceed exclusively on the aldehyde group.

When D-glucosone (4) was reacted with a threefold excess of pyruvaldehyde ethylene dithioketal (5) and ninefold excess of NH_4OAc for 18 h at room temperature in methanol, the imidazole 6 was obtained in 30% yield. Purification of the product was readily accomplished by diluting the reaction mixture with water, extracting with ether to remove the excess 5, and then isolating the imidazole fraction via ion-exchange chromatography on a poly(styrenesulfonic acid) resin.

Removal of the dithioethane group proved to be more difficult than expected. Acid-catalyzed procedures[7,8] were unsuccessful, while $HgCl_2$[9] gave only a low yield of 1 mixed with starting material even after 18 h at reflux. The best method found involved stirring 6 with aqueous $AgNO_3$[10,11] for 18 h in the dark. The precipitation of excess Ag^+ with HCl was followed by chromatography on an open C_{18} μ-Bondapak column. The eluant was passed through a Bio-Rad AG1X2 anion exchange resin column in the acetate form to afford 1 in 39% yield (12% overall from D-glucosone). Synthetic 1 was found to be identical with an authentic sample[1] by ^{13}C NMR, UV, and HPLC comparison.[14]

The 300-MHz proton and 75.46-MHz ^{13}C NMR spectra of the free base 1 in Me_2SO-d_6 indicated the existence of two tautomers. The nature of this tautomerism is currently under investigation, but it clearly results from the presence of a carbonyl at C-2, conjugated to an unprotonated imidazole ring. In aqueous acid and acidified Me_2SO-d_6 solutions, the protonated form of 1 was observed as a single species. In acidified CD_3OD, the initial carbonyl compound solvated to the mono- and finally the dimethyl

(1) Kröplien, U.; Rosdorfer, J.; Van der Greef, J.; Long, R. C. Jr.; Goldstein, J. H. *J. Org. Chem.*, preceding note in this issue.
(2) Fujii, S.; Tsuchida, H.; Komoto, M. *Agric. Biol. Chem.* **1966**, *30*, 73.
(3) Grimmett, M. R.; Richards, E. L. *J. Chem. Soc.* **1965**, 3751.
(4) Grimmett, M. R.; Hodges, R.; Richards, E. L. *Aust. J. Chem.* **1967**, *21*, 505.
(5) El Khadem, H.; Horton, D.; Meshreki, M. H.; Nashed, M. A. *Carbohydr. Res.* **1971**, *17*, 183.
(6) Fridinger, T. L.; Henery-Logan, K. R. *J. Heterocycl. Chem.* **1971**, *8*, 469.
(7) Olah, G. A.; Narang, S. C.; Salem, G. F. *Synthesis* **1980**, 657.
(8) Prato, M.; Quintily, V.; Scorrano, G.; Sturaro, A. *Synthesis* **1982**, 679.
(9) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(10) Saulnier, M. G.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 3831.
(11) Reece, C. A.; Rodin, J. O.; Brownlee, R. G.; Duncan, W. G.; Silverstein, R. M. *Tetrahedron* **1968**, *24*, 4249.
(12) Fieser, L. F. "Experiments in Organic Chemistry", 3rd. ed., D. C. Heath and Co.: Boston, 1955; p 115.
(13) Antonini, I.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Gulini, U.; Martelli, S. *J. Heterocycl. Chem.* **1978**, *15*, 1201.
(14) An interesting alternative synthesis of 1 has recently been developed by Halweg and Büchi. See the following paper in this issue.

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acetal. This reaction parallels the previously reported acetalization of 2-formylimidazole in acidified ethanol.[13] In all acidified solvents containing exchangeable deuterium (DCl, D_2O), rapid exchange of the methyl protons with deuterium was observed.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded as KBr pellets, on a Perkin-Elmer Model 281 IR spectrometer. Polarimetric measurements were done on a Perkin-Elmer Model 241 polarimeter. The ^1H NMR and ^{13}C NMR spectra were acquired in the FT mode, using a Bruker CXP-300 spectrometer at the frequencies of 300 and 75.46 MHz, respectively. Chemical shifts are given in ppm downfield from Me_4Si. The internal standard for ^1H in Me_2SO-d_6 was tetramethylsilane (Me_4Si). The internal standards used for ^{13}C in various solvents were D_2O (*p*-dioxane, 67.4 ppm), Me_2SO-d_6 (Me_2SO-d_6, 39.5 ppm), CD_3OD (CD_3OD, 49.0 ppm). Abbreviations used are s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; mult, multiplet. Multiplicities for the ^{13}C resonances were determined by off-resonance decoupling. Elementary analyses were done by Atlantic Microlab Inc., Atlanta, GA. Chromatography fractions were analyzed at a wavelength of 250 nm on a Tracer HPLC using a C_{18} μ-Bondapak column, Waters Radial Pak, with MeOH (10%), AcOH (0.5%), H_2O (89.5%) as eluant at a flow rate of 1 mL/min. Compound **6** had a retention time of 20 min and compound 1 5.5 min under these conditions.

D-Glucosone (4). A mixture of 13.4 g (37.4 mmol) of D-glucose phenylosazone,[12] 400 mL of ethanol, 667 mL of H_2O, 16.4 mL of glacial acetic acid, and 21.4 mL (210 mmol) of freshly distilled benzaldehyde was heated at reflux under N_2 until solution was complete (approximately 4.25 h). With continued heating, 400 mL of the solution was distilled off while an equal volume of water was added dropwise. The resulting mixture was allowed to stand under N_2 overnight. The precipitate of benzaldehyde phenylhydrazone was removed by filtration and the filtrate concentrated in vacuo (<40 °C) to 400 mL. This solution was in turn extracted with 4 × 150 mL ether and declorized with charcoal. The resulting yellow solution was evaporated to dryness (<40 °C) and the concentrated syrup was taken up in 100 mL of ethanol. Then, 5 g of mixed bed ion-exchange resin was added and the mixture filtered and again evaporated to dryness to give a thick oil, 4.6 g (25.8 mmol, 69%).

4-(1,2,3,4-Tetrahydroxybutyl)-2-acetylimidazole Ethylene Dithioketal (6). A mixture of the above glucosone (4.6 g, 25.8 mmol), 2-methyl-1,3-dithiolane-2-carboxaldehye[5] (**5**; 15.0 g, 101 mmol), and 125 mL of methanol was stirred at room temperature until solution was complete; then 20.0 g of ammonium acetate was added and the mixture was stirred at room temperature for 18 h.

The entire reaction mixture was poured into 600 mL of H_2O (10 mL of 1 N HCl added) and extracted with 4 × 200 mL of ether. [By redistilling the ether extract, 50% of the original pyruvaldehyde thioketal can be recovered.] The resulting aqueous layer was added to a 40 × 3.5 cm Rexyn (poly(styrenesulfonic acid)) column in the H^+ form and the column washed with 1 L of water. The imidazole fraction was then isolated by washing the column with 1 L of cold 4 M NH_4OH solution.

Evaporation of the ammonia extract gave a thick oil, which was purified by washing through an open 15 × 3.5 cm C_{18} μ-Bondapak column, using 0.5% HOAc–H_2O as eluant. Combining the proper fractions after HPLC analysis and evaporation afforded 2.36 g of **6** as the acetate salt, thick oil (7.7 mmol, 30%). Trituration from EtOH–Et_2O afforded an amorphous solid: mp 148–51 °C; IR (KBr) 3360 (s), 3120 (s), 2920 (s), 1620 (w), 1570 (w), 1470, 1420 (s), 1365, 1305, (w), 1275 (w), 1195, 1110, 1090 (s), 1060 (s), 990 (s), 880 cm^{-1}; NMR (as the acetate salt) ^{13}C (D_2O) 151.99 (C2, s), 136.47 (C4, s), 117.20 (C5, d), 73.73, 71.79, 65.90 (CHOH, d), 63.67 (CH_2OH, t) 60.01 ($-C(S_2)$, s), 41.48 (CH_2S, t), 29.35 (CH_3, q) (acetic acid gave peaks at 22.60 (q) and 179.59 (s)); ^1H (CD_3OD) 1.74 ($CH_3C(S)_2$, s), 3.08–3.09 (SCH_2S, mult), 3.18–3.40 (HCO, H_2CO, mult), 4.51 (IM-α HCO, dd), 6.45 (C5H, d); UV (λ_{max}, log ϵ) 226 nm, 3.92 (H_2O, pH 7.0).

2-Acetyl-4-(1,2,3,4-tetrahydroxybutyl)imidazole (1). To a solution of 2.36 g (7.7 mmol) of **6** acetate salt in 25 mL of H_2O was added 3.0 g (17.6 mmol) $AgNO_3$ in 25 mL of H_2O. The mixture was stirred at room temperature for 18 h in the dark, after which time 1.5 mL of concentrated HCl was added and the solution was stirred for an additional 10 min. The AgCl was removed by filtration through a bed of Celite 540 and the filtrate was then passed through a 15 × 2.5 cm C_{18} μ-Bondapak column. The column was washed with water until all of the product (HPLC analyzed) had eluted.

The combined eluant was then passed through a 15 × 2.5 cm Bio-Rad AG1X2 anion exchange resin in the OAc^- form and the eluate was concentrated to 50 mL in vacuo. After 48 h at 5 °C, the resulting crystals were removed by filtration and dried in vacuo to give 684 mg (two crops, 2.97 mmol, 39%) of **1**; recrystallized from H_2O (charcoal); mp 232–3 °C (soften at 224 °C); $[\alpha]^{25}_D$ −12° (*c* 1.17, 1 N HCl); UV (λ_{max}, log ϵ) 289 nm, 4.11 (H_2O, pH 7.0). IR (KBr) 3450, 3320, 3290, 3020, 1665, 1655, 1455, 1435, 1405, 1380, 1255, 1220, 1090, 1020, 955, 880, 790, 645 cm^{-1}. Anal. Calcd. for $C_9H_{14}N_2O_5$: C, 46.96; H, 6.09; N, 12.17. Found: C, 46.31; H, 6.12; N, 12.05.

NMR: ^{13}C (D_2O, DCl, p.H <2) 27.57 ($CH_3C(O)$–, q), 64.19 (CH_2OH, t), 66.22, 72.08, 74.09 (CHOH, d), 120.62 (C5, d), 139.10 (C4, s), 140.54 (C2, s) and 186.27 (C=O, s); ^{13}C (Me_2SO-d_6, free base) 2 tautomers A and B [A] 25.28 ($CH_3C(O)$, q), 63.49 (CH_2OH, t), 67.10, 71.22, 73.73 (CHOH, d), 119.01 (C5, d), 143.73, 146.72 (C2 and C4, s), 188.26 (C=O, s); [B] 25.05 ($CH_3C(O)$, q), 63.25 (CH_2OH, t), 64.69, 71.22, 73.73 (CHOH, d), 127.92 (C5, d), 139.12, 144.26 (C2, C4, s), 188.15 (C=O, s); ^1H (Me_2SO-d_6, free base) 2-tautomers A and B [A + B] 2.47, 2.48 ($CH_3C(O)$, s), 3.35–3.80 (HCO, H_2 CO, mult), 4.30–4.39, 4.58–4.64, 5.01–5.04 (COH, mult), 4.90–4.92 (IM-α HCO, mult), 7.05, 7.21 (C5H, d); ^{13}C (Me_2SO-d_6, DCl, pH <2) 27.09 ($CH_3C(O)$, mult partially deuterated), 63.57 (CH_2OH, t), 65.14, 71.27, 73.20 (CHOH, d), 119.46 (C5, d), 138.71, 139.55 (C2, C4, s), 183.98 (C=O, s); ^1H (Me_2SO-d_6, DCl, pH <2) one tautomer 2.66 (CH_3CO, s), 3.42–3.56 (HCO, H_2CO, mult), 5.06 (IM-α HCO, dd), 7.67 (C5H, d); ^{13}C (CD_3OD, DCl, pH <2) after standing in CD_3OD, DCl for 12 h 23.21 (CH_3C partially deuterated mult), 64.76 (CH_2OH, t), 66.28, 72.62, 74.69 (CHOH, d), 99.05 ($C(OC)_2$, s), 117.20 (C5, d), 137.88, 147.97 (C2, C4, s); ^1H (CD_3OD, DCl, pH <2) standing in CD_3OD, DCl for 12 h, 1.71 (CH_3CO_2, mult partially deuterated), 3.60–3.83 (HCO, H_2CO, mult), 5.12 (IM-α HCO, dd), 7.39 (C_5H, d).

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A Convenient Synthesis of 2-Acetyl-4(5)-(1(*R*),2(*S*),3(*R*),4-tetrahydroxybutyl)-imidazole

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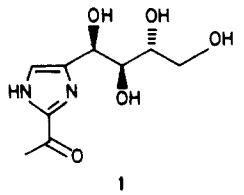
The title compound (**1**), a very minor constituent of Caramel Color III lowers circulating lymphocyte counts when fed to rats.



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