

A Practical Synthesis of 2,3-Dimethylfuran and an Efficient Stereoselective Preparation of *Z*-3-Methyl-2-pentene-1,4-diol

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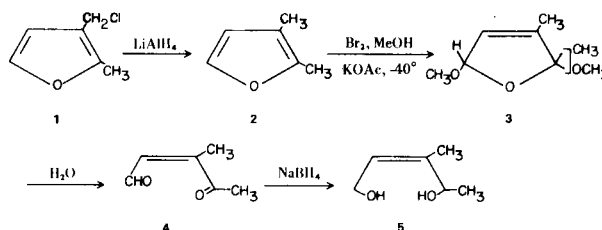
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During the course of other research, it became necessary to prepare relatively large quantities of geometrically pure *Z*-3-methyl-2-pentene-1,4-diol (**5**). An examination of the literature revealed no procedure for the synthesis of this material and no attractive method for the synthesis of 2-butene-1,4-diols in which the hydroxyl groups are on the same side of the double bond and with an additional substituent on the double bond. We wish to report a convenient preparation of the difficulty accessible 2,3-dimethylfuran (**2**) from readily available, commercial reagents and an efficient stereoselective conversion of this material to **5**. This method should also be useful for the synthesis of other diols of this type from the appropriate furan. As described below, this method is readily adaptable to large scale work.

For the syntheses of **5**, a possible starting material appeared to be furan, **2**, since the *cis-trans* mixture of 2,5-dihydro-2,5-dimethoxy derivatives is (usually) easily prepared (2). Furthermore, Hirsch (3) has shown that certain cyclic ethers of this type can be hydrolyzed to the corresponding enedione without isomerization about the double bond. It seemed likely that reduction of the *Z*-enedione, **4**, derived from **2** would provide the required intermediate **5**.

The synthesis of **2** has previously been accomplished in seven steps in 1.5% overall yield (4), in seven steps from 2-furoic acid in 17.7% yield (5) and by potassium *t*-butoxide catalyzed cyclization (6) of a mixture of *E* and *Z*-3-methyl-2-penten-4-yne-1-ol, which was obtained in an unspecified manner and yield. More recently (7), the compound was prepared by a multistep sequence using diazomethane, but details of this work were not given.

In our sequence, **2** was prepared in 36% overall yield by lithium aluminum hydride reduction of 2-methyl-3-chloromethyl furan, **1**, which was obtained in three steps from chloroacetaldehyde and ethyl acetoacetate using the method of Winberg (8). The instability of **1** was observed, as previously described. Thus, it was found that direct reduction of crude **1** gave a higher overall yield of **2** than when the purified material was used. Direct reduction of 2-methyl-3-hydroxymethylfuran, the precursor of **1**, to **2**



by catalytic hydrogenolysis was unsuccessful. In all cases reduction of the furan nucleus was observed. Conversion of **2** to **3** was carried out using the method of Clauson-Kaas and Limborg (2) in 84% yield. The ratio of *cis* and *trans*-2,3-dimethyl-2,5-dimethoxy-2,5-dihydrofurans, **3**, in the resulting mixture was found to be approximately 60:40 by integration of the nmr spectrum. This mixture, using the method of Hirsch (3), was hydrolyzed with distilled water to *Z*-3-methyl-4-oxo-2-pentenal (**4**), which could be isolated by solvent extraction and distillation in 58% yield; however a significant amount of polymeric material remained after distillation and it was found more expedient to carry out the sodium borohydride reduction of crude hydrolysate directly. In this manner, the desired intermediate **5** was obtained in 76% yield from **2**. Although no isomerization about the double bond was expected during the reduction of **4** to **5**, the distilled diol **5**, which was chromatographically homogenous (tlc and glpc), and showed the expected spectral absorptions, was subjected to an ir dilution study to confirm the assigned configuration of the double bond. The ir spectrum of **5** (0.0005 *M* in carbon tetrachloride) showed λ_{max} at 3600 and 3480 cm⁻¹ due to free and hydrogen-bonded OH, respectively, and was unchanged in the concentration range 0.005-0.0005 *M* in carbon tetrachloride. These results are compatible only with the *Z*-configuration, and are in good agreement with those reported by Kuhn (9) for other 1,4-diols; they strongly support the assigned configuration of **5**. As conditions are available for the hydrolysis of 2,5-dimethoxy-2,5-dihydrofurans to the enediones without isomerization about the double bond, and iodine (3), thermal (10), or acid (10,11) catalysis will sometimes bring about such isomerization of these enediones, this method may be useful in the synthesis

of both E and Z-2-butene-1,4-diols from the appropriately substituted furan.

EXPERIMENTAL

Boiling points are uncorrected. Ir spectra were determined with a Perkin Elmer Model 137 recording spectrometer, nmr data with either a Varian A-60 or HR-200 spectrometer (tetramethylsilane as the internal reference). Microanalyses were performed by Bernhardt Laboratories (Mülheim, West Germany).

2,3-Dimethylfuran (2).

Using the procedure of Winberg (8), crude 2-methyl-3-chloromethylfuran (1) was prepared from 119.0 g. (1.06 moles) of 2-methyl-3-hydroxymethylfuran. After drying for 2 hours with a mixture of potassium carbonate and magnesium sulfate, the solution of crude 1 was filtered and the volume adjusted to 200 ml. with dry ether. This solution was added dropwise to a stirred, refluxing slurry of 33.0 g. of lithium aluminum hydride (0.87 mole) in 500 ml. of ether. After stirring overnight and cautious addition of 50 ml. of water, a solution of 91.5 ml. of concentrated sulfuric acid (1.73 moles) in 400 ml. of water was added while stirring and cooling. When the addition was complete 400 ml. of water was added and stirring was continued until the inorganic material had dissolved. The aqueous layer was removed and extracted with 100 ml. of ether and the combined ether extracts were washed with 100 ml. of 5% sodium hydroxide and 200 ml. of water. The ether was dried with magnesium sulfate and removed by distillation through a 24" Vigreux column. The residue was distilled to give 58.3 g. (57%) of 2, b.p. 94-95° (738 mm.) [lit. (5) b.p. 90-91° (680 mm.)]; nmr, (60 MHz, neat), δ 1.84 (m, 3H, CH₃-3), 2.07 (m, 3H, CH₃-2), 6.06 (d, 1H, J = 2.0 Hz, H-4) and 7.09 (d, 1H, J = 2.0 Hz, H-5).

cis and trans-2,5-Dihydro-2,5-dimethoxy-2,3-dimethylfurans (3).

Treatment of 39.3 g. of 2 (0.41 mole) at -40° with 65.3 g. of bromine (0.41 mole) in 410 ml. of dry methanol containing 85.0 g. of anhydrous potassium acetate (0.86 mole) according to the method of Clauson-Kaas and Limborg (2) gave 54.5 g. of 3 (84%), b.p. 61-63° (15 mm.); nmr (60 MHz, neat), major isomer, δ 1.36 (s, 3H), 1.70 (m, 3H), 3.07 (s, 3H), 3.39 (s, 3H), 5.30 (m, 1H) and 5.62 (m, 1H); minor isomer, δ 1.41 (s, 3H), 1.70 (m, 3H), 2.98 (s, 3H), 3.31 (s, 3H) and 5.62 (m, 2H).

Anal. Calcd. for C₈H₁₄O₃: C, 60.72; H, 8.86. Found: C, 60.74; H, 9.13.

Z-3-Methyl-4-oxo-2-pentenal (4).

A mixture of 10.9 g. of 3 (63 mmoles) and distilled water (54 ml.) was heated to 60°, and then allowed to stand 24 hours at 25°. The mixture was then heated to 75° for 0.5 hour, cooled and the resulting cloudy, orange-colored solution extracted continuously with ether for 15 hours. The yellow extract was dried with magnesium sulfate and solvent removed *in vacuo*. Distillation of the

residue gave 4.2 g. (59%), of 4, b.p. 51° (1.0 mm); nmr (60 MHz, neat) δ 9.66 (d, 1H, J = 7.2 Hz, -CHO), 6.00 (d, 1H, J = 7.2 Hz, each member split into a quartet, J = 1.6 Hz, -C=C-H), 2.39 (s, 3H, CH₃-C=O) and 2.17 (3H, d, J = 1.6 Hz, -C=C-CH₃); ir (film), 1610 and 1686 cm⁻¹.

Anal. Calcd. for C₆H₈O₂: C, 64.26; H, 7.19. Found: C, 64.15; H, 7.07.

Z-3-Methyl-2-pentene-1,4-diol (5).

To 554 ml. of distilled water was added 100.0 g. of 3 (0.63 mole). The mixture was stirred for 48 hours at room temperature (25°) and then the orange, cloudy solution was added dropwise (stirring, external cooling) to a solution (at 0°) of 15.0 g. of sodium borohydride (0.40 mole) in 100 ml. of distilled water. The mixture was maintained at -5° to 1° during the addition. When the addition was completed, stirring was continued overnight at 25°. The resulting solution was concentrated to 200 ml. *in vacuo* and extracted continuously with methylene chloride for 48 hours. The extract was dried with magnesium sulfate and the solvent removed. Distillation of the residue gave 66.6 g. (91%) of 5, b.p. 92-94° (0.7 mm.); nmr (220 MHz, deuteriochloroform) δ 5.45 (d, 1H, J = 6.5 Hz, each component split into a doublet, J = 8.5 Hz, H-C=C), 4.71 (q, 1H, J = 7.0 Hz, H-C-CH₃), 4.25 (d, 1H, J = 12.5 Hz, each component split into a doublet, J = 8.5 Hz, HO-CH-C=C-C), 3.97 (d, 1H, J = 12.5 Hz, each component split into a doublet, J = 6.5 Hz, HO-CH-C=C-C-CH₃), 3.75 (s, 2H, exchanges with deuterium oxide, OH), 1.76 (s, 3H, CH₃-C=C) and 1.23 (d, 3H, J = 7.0 Hz, CH₃-CH); ir (0.0005 M in carbon tetrachloride, 10.0 cm. path) 3600 (free OH), and 3480 cm⁻¹ (intramolecular hydrogen bonded OH).

Anal. Calcd. for C₆H₁₂O₂: C, 62.04; H, 10.41. Found: C, 61.96; H, 10.53.

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