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AN IMPROVED PROCEDURE FOR THE SYNTHESIS OF BICYCLO[2.2.2]OCTANE-2,6-DIONE.

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ABSTRACT: Conjugate addition of Meldrum's acid to 2-cyclohexenone followed by direct cyclization in PPA/acetic acid constitutes a shorter, more reproducible and higher yielding route to bicyclo[2.2.2]octane-2,6-dione than previous methods. The crude dione could be used as substrate for the baker's yeast reduction to (1R, 4S, 6S)-bicyclo[2.2.2]octane-6-ol-2-one.

There is a constant need for easily available optically active building blocks. This has created a number of reports on using carbohydrates,[1,2] terpenes,[3] amino acids[4] and other naturally or non-naturally occurring small homochiral molecules in organic synthesis.[5,6]

We became interested in using keto-alcohol **1a**, (Scheme), whos absolute configuration has been determined, as an optically acitve starting material for natural products synthesis since it is easily available from the baker's yeast reduction of diketone **2**.[7] The following three methods are reported in the litterature for the synthesis of **2**:

1) 1,4-addition of malonate to 2-cyclohexenone followed by ester hydrolysis, decarboxylation and ring closure using Mn(II)-oxide at 300 °C.[8] This method suffers from low yield in the cyclization step (10%) as well as in the hydrolysis-decar-

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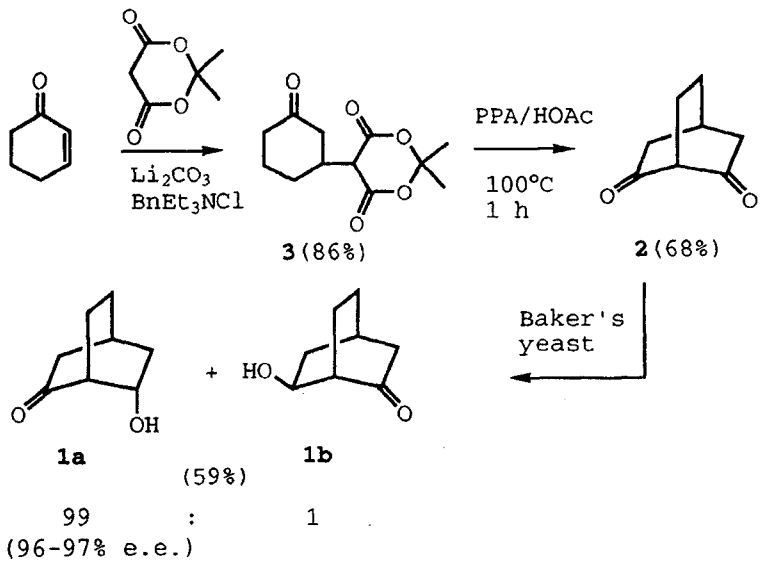
boxylation sequence of the malonate; 2) 3-(1,3-dioxolanyl)cyclohexyl acetaldehyde is cyclized by using aqueous phosphoric acid to give the racemic mixture of **1a** + **1b** in 16% yield over all from methyl 3-oxocyclohexylacetate. The diketone **2** was then obtained by Jones oxidation of the above mixture;[9] 3) 3-oxocyclohexylacetic acid is cyclized directly to **2** by using PPA/HOAc in a reported yield of 75%.[10]

The latter method seemed attractive but, unfortunately, we could not reproduce the yield despite using several compositions of the reaction medium and time/temperature values. Our best yield was only 40% and it appeared very important to use a short reaction time (1h) instead of the reported 7 h at 100 °C. We could show by GC-analysis that **2** breaks down and/or rearranges in a reaction medium sufficiently concentrated with respect to PPA in order to bring about the cyclization. In less concentrated media the cyclization does not occur at all. Moreover, the yield in the hydrolysis-decarboxylation step of the malonate corresponding to **3** was rather low and unpredictable, which also had been reported by Bartlett and Woods[8]. Thus, the entire reaction sequence seemed problematic and since we needed rather large amounts of **2** we had to improve its synthesis.

We found that the use of Meldrum's acid instead of dimethyl- or diethylmalonate in the conjugate addition to cyclohexenone followed by direct (i.e. without prior hydrolysis and decarboxylation) cyclization in PPA/HOAc at 100°C gave **2** in 58% over all yield in a very reproducible fashion. By combining the best yields reported in ref[8] and ref[10] only 20% over all yield is obtained.

Best results in the cyclization of **3** was achieved by using a rather precise compositon of the PPA/HOAc mixture (see Experimental part). It also turned out that the crude brownish **2** could be used in the baker's yeast reduction[7] to **1a** + **1b** (diastereomeric ratio 96:4 by GC analysis of the crude material). After chromatography on a short column a 59 % yield of **1a** + **1b** (99 : 1 diastereomeric ratio) was isolated as white crystals. The e.e. of **1a** was 96-97% as determined by GC and ^{1}H NMR spectroscopic analysis of the Mosher ester. The racemic mixture of the diastereomers **1a** and **1b** was prepared by $NaBH_4$ reduction of **2** and was used as a reference material in the analyses. It is worth noting that we got the same major enatiomer (**1a**) as Mori et al.[7] despite the use of a different brand of baker's yeast (see Experimental Section).



Scheme

Cyclization attemps of **3** using zeolite Beta (7.4 x 7.4 Å) or molten sodium tetrachloroaluminate at 150 °C[11] were unsuccessful.

Experimental Section

General. GC chromatographic analyses were performed on a Carlo Erba 5300-HT gas chromatograph equipped with a SPB-5 (Supelco) nonpolar column (15 m, 0.25 mm i.d., 0.25 μm stationary phase). Optical rotations were measured with a Perkin Elmer 141 polarimeter. Infrared spectra were recorded with a Perkin Elmer 681 infrared spectrometer and NMR spectra were recorded with a Bruker AM 500 MHz spectrometer. The baker's yeast (Kronjäst, producer: Jästbolaget, Sweden) was purchased in the common super market in Umeå, Sweden.

2,2-Dimethyl-5-(3-oxocyclohexyl)-1,3-dioxane-4,6-dione (3). Finely powdered lithium carbonate (15.4 g, 0.209 mol) and benzyltriethylammonium chloride (31.0 g, 0.136 mol) were added under nitrogen to a magnetically stirred solution of 2,2-dimethyl-1,3 dioxane-4,6-dione (30.1 g, 0.209 mol) in acetonitrile (40 mL).[12] An-

other 50 ml of acetonitrile was added and the reaction mixture was stirred for 20 min at room temperature. Then 2-cyclohexenon (13.0 g, 0.135 mol) in acetonitrile (45 mL) was added dropwise. Stirring was continued for 20 h at room temperature, water (220 mL) was added after cooling, and the resulting mixture was washed with ether (50 mL). The aqueous phase was acidified to pH 1-2 with 6M HCl. The crude product, which precipitates on cooling, was isolated by filtration. An additional amount of crude product was obtained by saturating the filtrate with NaCl, extracting with ethylacetate (2x200 mL), washing the combined organic extracts with water (50 mL), drying (Na_2SO_4) and removal of the solvent. The combined crude products where purified by recrystallization from heptane/ethylacetate (1:5) to give **3** (27.9 g, 86%), mp 148-153 °C (decomp.).

NMR ($CDCl_3$) δ 3.48 (d, 1H, J = 2.8 Hz, H-1'), 2.92 (t, 1H, J = 13.6 Hz), 2.82 (tq, 1H, J = 15.0 Hz), 2.38 (broad t, 1H, J = 13.8 Hz), 2.30 (td, 1H, J = 14.1, 6.3 Hz), 2.09 (m, 1H), 2.00 (qd, 1H, J = 12.5, 3.5 Hz), 1.78 (s, 3H, CH_3), 1.77 (m, 2H), 1.75 (s, 3H, CH_3), 1.65 (qt, 1H, J = 13.4 Hz). Anal. Calc. for $C_{12}H_{16}O_5$ C 59.99; H 6.71; O 33.3. Found C 59.9; H 6.7.

Bicyclo[2.2.2]octane-2,6-dione (2). A solution of **3** (6.00 g, 25.0 mmol) in acetic acid (25 mL) was added to PPA (29 g)[13].[14] The mixture was stirred under nitrogen for 1 h at 100°C, cooled, saturated with NaCl, poured on ice and extracted with toluene (6x160 mL). The use of the relatively large volume of solvent was necessary due to the high solubility of the diketone in water. (Alternatively the diketone could be isolated by continuous liquid-liqid extraction.) The toluene extracts where combined and washed with $NaHCO_3$(sat.) (3x50 mL) and dried (Na_2SO_4). After removal of the solvent under vacuum the crude brownish product crystallized (2.35 g, 68%). Recrystallization from heptane/benzene (9:1) or diisopropyl ether gave **2** as colourless needles, m.p. 189-190°C. (Lit.[8] m.p. 190-191 °C).

NMR ($CDCl_3$) δ 3.14 (t, 1H, J = 2.8 Hz, H-1), 2.63 (hept., 1H, J = 3.0 Hz, H-4), 2.48 (m, 2H, H-3, H-5), 2.35 (m, 2H, H-3, H-5), 2.09 (m, 2H, H-7), 1.85 (m, 2H, H-8).

The crude brownish product was pure enough for reduction with baker's yeast.[7]

(1R, 4S, 6S)-Bicyclo[2.2.2]octane-6-ol-2-one (1a) and its diastereomer 1b. The compound was prepared according to ref.[7] from baker's yeast (50 g), water (540 mL), ethanol (16.5 mL, 99%), Triton X-100 (16.5 mL, 0.2% water solution w/w), sucrose(117 g), and crude **2** (5.0 g, 36 mmol). After work-up the crude product (diastereomeric purity 94% by GC analysis) was chromatographed (SiO_2, heptane/ethyl acetate 1:3) to give **1a** + **1b** (2.9 g, 59 %) in the ratio 99:1 as shown by GC-analysis; $[\alpha]_D^{22}$ -7.6° (c 1.15, $CHCl_3$) (lit.[7] -6.5° (c 1.0, $CHCl_3$)). The Mosher ester mixture was prepared and analyzed to show for **1a**, 96.8% e.e. by GC and 96% e.e. by ^1H NMR spectroscopy (for details see below). The ^1H NMR data of **1a** were identical to those reported.[7]

Diastereomeric and recemic mixture of bicyclo[2.2.2]octane-6-ol-2-one. A mixture of $NaBH_4$ (0.0228 g, 0.603 mmol) in water (0.45 mL) containing a small amount of aqueous NaOH (50 μL, 2 M) was added to **2** (0.330 g, 2.39 mmol) in ethanol (5 mL) at 0 °C. The reaction mixture was stirred for 10 min. whereafter the solvent was removed under aspirator vacuum. The residue was participated between brine and ethyl acetate, the organic layer was dried and then the solvent was removed under vacuum to give 0.36 g of the crude product, which was column chromatographed (SiO_2, heptane-EtOAc 1:3). The fractions containing the keto-alcohol were collected to give 98 mg of the crystalline mixture of stereo isomers.

Determination of the e.e. The Mosher esters were prepared from this material according to standard procedure.[7] GC analysis of the mixture of esters showed three peaks in the ratio 1:2:1 (ret. times 10.43:10.52:10.73 min., respectively). Obviously the middle peak was the result of overlap of the two diastereomers since the material from the baker's yeast reduction showed two peaks in the ratio 98.1:1.6 (corresponding to 96.8% e.e.) at 10.56: 10.73 min. retention times, respectively. ^1H NMR analysis of the Mosher esters showed four multiplets originating from the methoxy groups at 3.56, 3.52, 3. 50, and 3.46 ppm (ratios 1:1:1:1). Only the latter two multiplets were present in the sample from the baker's yeast reduction in the ratio 100:2 (96% e.e.). Thus the multiplet at 3.50 ppm obviously belongs to the Mosher ester of **1a**.

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13. Commercially available or prepared as in Ref 10.

14. Increasing the amount of acetic acid lowers the yield of **2** and gives more of the UV-active impurity.

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