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Resolution of Both Enantiomers of 5-Chloro-5-methyl-2-cyclopentenone

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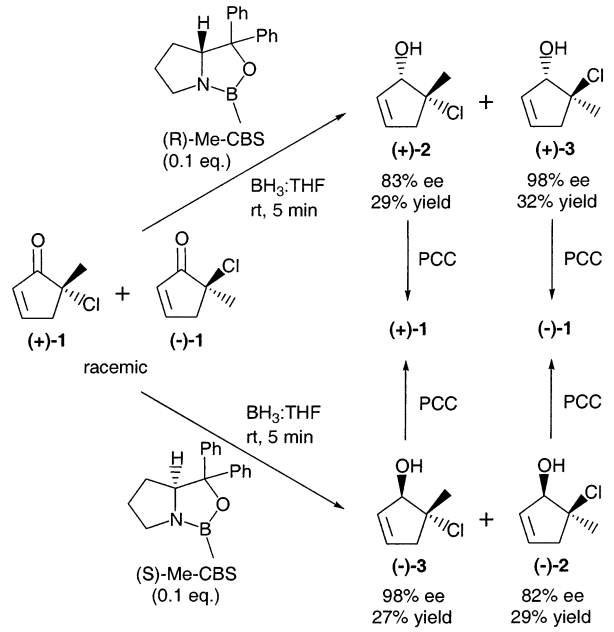
Abstract: Reduction of (±)-5-chloro-5-methyl-2-cyclopentenone with BH_3·THF and catalytic (*R*)-2-methyl-CBS-oxazaborolidine gave readily separable diastereomers with high ee values. Oxidation of the diastereomers furnished the enantiomers of the chloromethylcyclopentenone.

For synthetic studies on the antitumor drug irofulven[1] quantities of enantiomerically pure 5-chloro-5-methyl-2-cyclopentenone of known absolute configuration were required. The racemic compound (**1**) can be readily prepared[2] but, to our knowledge, no resolution of the enantiomers has been reported. We now describe a convenient method for effecting such a resolution. It involves asymmetric reduction of 5-chloro-5-methyl-2-cyclopentenone (**1**) with BH_3·THF and catalytic (*R*)-2-methyl-CBS-oxazaborolidine.[3,4] This furnished the (*S*)-alcohols as an 11:9 diastereomeric mixture, (+)-**2** and (+)-**3**, which were readily separated by chromatography on silica gel.[5] A small amount of (−)-**2** was also formed leading to an ee of 83% for (+)-**2**. In the case of the trans (*S*)-alcohol (+)-**3** an ee of 98% was obtained. The ee values were determined by conversion of the alcohols to the (*R*)-MTPA esters (with 2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride) followed by ^{1}H NMR spectroscopic analysis.[6]

By carrying out the enantioselective reduction of (±)-**1** with (*S*)-B-Me CBS catalyst, the corresponding (*R*) alcohols (−)-**3** and (−)-**2** were obtained, with very similar yields and ee values as found for the reaction catalyzed by the (*R*)-B-Me CBS reagent.

The stereochemistry depicted for the cyclopentenols is assigned from the known behavior of the chiral catalysts.[3,4,7] We attempted to confirm the stereochemistry by applying Mosher's method to the MTPA esters but the results were inconsistent.[8]

SCHEME 1



An X-ray crystallographic analysis of the trans isomer, (+)-**3**, was therefore carried out and this established the absolute configuration, in agreement with that predicted from the chiral reducing agent. Oxidation of alcohol (−)-**3** with pyridinium chlorochromate (PCC) furnished (+)-(*R*)-5-chloro-5-methyl-2-cyclopentenone in 73% yield. Likewise oxidation of alcohol (+)-**3** gave (−)-(*S*)-5-chloro-5-methyl-2-cyclopentenone also in 73% yield.

Experimental Section

General. Reactions were conducted under N_2 atmosphere in oven-dried glassware employing standard air-free manipulation techniques.

Reaction solvents were dried and distilled prior to use. Tetrahydrofuran (THF) was distilled from sodium with benzophenone. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 under N_2. All other reagents and solvents were used as received from commercial sources. Solvents were removed under reduced pressure with a rotary evaporator.

All chromatography was carried out with silica gel (230−425 mesh). Analytical TLC was carried out on silica gel plates. Reactions were routinely monitored by TLC.

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were measured at 400 and 100 MHz, respectively. Mass spectra were determined at the University of California, Riverside Mass Spectrometry laboratory.

5-Chloro-5-methyl-2-cyclopenten-1-ol [(−)-2, (−)-3]. To a solution of racemic **1**[2] (5.22 g, 40.0 mmol) and (*S*)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 3.7 mL, 0.093 equiv) in THF (100 mL) was added a solution of BH_3·THF (1.0 M in THF, 24 mL, 0.6 equiv) over 5 min at room temperature. The solution was stirred for an additional 5 min, cooled to 0 °C, and then

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(5) Although the yield of alcohols was 61%, no starting ketone was recovered. Thus it is unlikely that any enantiomeric enrichment due to kinetic resolution took place under these conditions. At low temperature (−40° C), the reduction rate was slower and differed for the two ketones.
(6) The reaction afforded a 55% yield of the diastereomers. However, there was no evidence of unreacted alcohols so it is unlikely that enrichment due to kinetic resolution could have occurred. Supporting evidence was obtained by reducing racemic **1** with $NaBH_4/CeCl_3$, which gave a mixture of cis and trans alcohols. The diastereomers were separated and each enatiomeric pair was converted to its (*R*)-MTPA esters. NMR analysis showed that the trans alcohols gave a 1:1 mixture of (*R*)-MTPA esters. Likewise the cis alcohols gave a 1:1 mixture. Thus no enrichment due to kinetic resolution took place and the ee values are valid.
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quenched with methanol (7.5 mL) until gas evolution was no longer evident. The mixture was warmed to room temperature, treated with 1 N NaOH (5 mL), and stirred for an additional 15 min. The mixture was then poured into a separatory funnel containing ether and brine. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with 1 N HCl, sat. $NaHCO_3$, and brine, then dried with $MgSO_4$. The solvent was evaporated to give a 57:43 mixture of 1*R*,5*S*-[(−)-**2**] and 1*R*,5*R*-[(−)-**3**] isomers. The crude mixture was chromatographed (10:1 hexanes−ethyl acetate) to give 1.55 g of **2** (29%) as a colorless liquid and 1.41 g of **3** (27%) as a white solid.

1*R*,5*S* isomer [(−)-**2**]: 82% ee; $[\alpha]^{25}_D$ −32.0° (*c* 21.4 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H), 2.42 (br, 1H), 2.61 (m, 1H), 2.95 (m, 1H), 4.40 (s, 1H), 5.77 (m, 1H), 5.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 48.2, 80.4, 82.7, 130.6, 132.9; IR (NaCl, thin film) 3415, 3067, 2972, 2927, 2875, 2829, 1440 cm^{-1}; MS (20 eV) *m*/*z* (% rel intensity) 134 (M^+ + 2, 1), 132 (M^+, 3), 97 (M^+ − Cl, 100), 79 (41), 69 (33), 55 (29), 41 (76).

1*R*,5*R* isomer [(−)-**3**]: 98% ee; $[\alpha]^{25}_D$ −141.0° (*c* 20.5 mg/mL, $CHCl_3$); mp 52−53 °C; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3H), 1.83 (br, 1H), 2.73 (m, 1H), 2.88 (m, 1H), 4.78 (s, 1H), 5.87 (m, 1H), 5.97 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 48.7, 74.6, 85.3, 131.6, 133.4; IR (NaCl, thin film) 3203, 2978, 2921, 1430 cm^{-1}; MS (20 eV) *m*/*z* (% rel intensity) 134 (M^+ + 2, 1), 132 (M^+, 2), 97 (M^+ − Cl, 100), 79 (43), 69 (31), 55 (26), 43 (78). The absolute configuration was determined by X-ray crystallography.

(*R*)-5-Chloro-5-methyl-2-cyclopenten-1-one [(+)-1]. To a suspension of PCC (2.54 g, 11.8 mmol) in CH_2Cl_2 (50 mL) was added a solution of (−)-**3** (1.06 g, 7.97 mmol, 98% ee) in CH_2Cl_2 (50 mL) at room temperature. The mixture was stirred for 8 h, diluted with ether, and filtered through Celite and the filtrate was concentrated. The crude product was chromatographed (10:1 hexanes−ethyl acetate) to give 759 mg of (+)-**1** (73%) as a colorless liquid: $[\alpha]^{25}_D$ +53.3° (*c* 21.1 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3H), 3.00 (m, 1H), 3.21 (m, 1H), 6.26 (m, 1H), 7.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 47.8, 63.0, 130.3, 160.0, 203.4; IR (NaCl, thin film) 3072, 2972, 2923, 1722, 1585, 1418 cm^{-1}; MS (20 eV) *m*/*z* (% rel intensity) 132 (M^+ + 2, 10), 130 (M^+, 30), 95 (M^+ − Cl, 100), 67 (76), 41 (34); HRMS for C_6H_7ClO calcd 130.0185, found 130.0187.

(*S*)-5-Chloro-5-methyl-2-cyclopentenone [(−)-1]. To a suspension of PCC (2.54 g, 11.8 mmol) in CH_2Cl_2 (50 mL) was added a solution of (−)-**2** (1.06 g, 7.97 mmol, 82% ee) in CH_2Cl_2 (50 mL) at room temperature. The mixture was stirred for 20 h, diluted with ether, and filtered through Celite and the filtrate was concentrated. The crude product was chromatographed (10:1 hexanes−ethyl acetate) to give 769 mg of (−)-**1** (73%) as a colorless liquid: $[\alpha]^{25}_D$ −39.4° (*c* 24.6 mg/mL, $CHCl_3$). Spectral data were identical with the above.

(*R*)-MTPA Ester of (−)-2. To a solution of (−)-**2** (7.8 mg, 58.8 μmol), triethylamine (12.5 μL), and DMAP (32.2 mg) in CH_2Cl_2 (1.5 mL) was added (*R*)-MTPA chloride (22.0 μL, 117 μmol). The mixture was stirred for 18 h at room temperature. The crude mixture was chromatographed (20:1 hexanes−ethyl acetate) to give 11.4 mg (55%) of a 91:9 mixture of diastereomers.

Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H), 2.66 (m, 1H), 2.98 (m, 1H), 3.57 (s, 3H), 5.63 (s 1H), 5.86 (m, 1H), 6.13 (m, 1H), 7.40 (m, 3H), 7.59 (m, 2H).

Minor isomer: ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3H), 2.65 (m, 1H), 2.98 (m, 1H), 3.63 (s, 3H), 5.60 (s 1H), 5.76 (m, 1H), 6.07 (m, 1H), 7.40 (m, 3H), 7.59 (m, 2H).

(*R*)-MTPA Ester of (−)-3. To a solution of (−)-**3** (6.2 mg, 46.8 μmol), triethylamine (10.0 μL), and DMAP (29.5 mg) in CH_2Cl_2 (1.5 mL) was added (*R*)-MTPA chloride (17.5 μL, 93.3 μmol). The mixture was stirred for 18 h at room temperature. The crude mixture was chromatographed (20:1 hexanes−ethyl acetate) to give 9.0 mg (55%) of a 99:1 mixture of diastereomers.

Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 3H), 2.76 (m, 1H), 2.92 (m, 1H), 3.54 (s, 3H), 5.89 (s 1H), 5.95 (m, 1H), 6.18 (m, 1H), 7.40 (m, 3H), 7.50 (m, 2H).

Minor isomer: ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 3H), 2.74 (m, 1H), 2.92 (m, 1H), 3.51 (s, 3H), 5.86 (s 1H), 5.91 (m, 1H), 6.11 (m, 1H), 7.41 (m, 3H), 7.50 (m, 2H).

$NaBH_4$ Reduction of (±)-1. To a solution of racemic **1** (130 mg, 1.00 mmol) and $CeCl_3 \cdot 7H_2O$ (381 mg, 1.02 mmol) in methanol (2.5 mL) was added $NaBH_4$ (60 mg, 1.59 mmol) in one portion at room temperature. The mixture was stirred for 15 min then quenched with 1 N HCl, diluted with water, and extracted with ethyl acetate. The mixture was dried with $MgSO_4$ and concentrated to give a mixture of (±)-**2** and (±)-**3** diastereomers. Purification by chromatography (10:1 hexanes−ethyl acetate) gave 50.0 mg of (±)-**2** (36%) and 34.9 mg of (±)-**3** (25%). Conversion of each to the corresponding (*R*)-MTPA esters as previously described gave the expected 1:1 mixture of diastereomers.

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Supporting Information Available: H NMR spectra of compounds **1**−**3** and the (*R*)-MTPA esters of **2** and **3**, as well as X-ray data of (−)-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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