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New Reagent for the Optical Resolution of Ketones : (-) (1R, 2R, 5R)-5-methyl-2-(1-mercapto-1-methylethyl)-cyclohexanol. Application to Trans dimethyl Cyclopentanone-3,4-Dicarboxylate.

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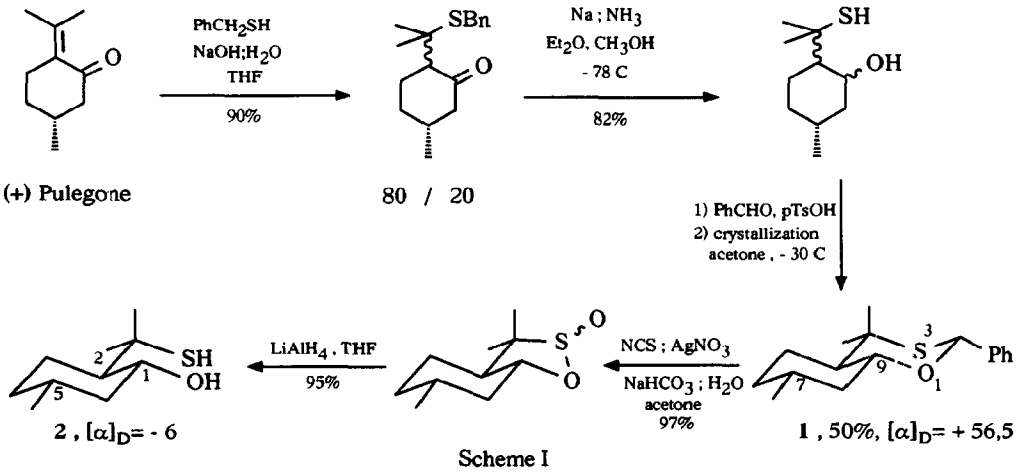
Abstract: (-) (1R, 2R, 5R)-5-methyl-2-(1-mercapto-1-methylethyl)-cyclohexanol was shown to be a very powerful agent for the optical resolution of ketones. It was used for the resolution of trans dimethyl cyclopentanone-3,4-dicarboxylate combined with the epimerization of the more soluble diastereomer, allowing an efficient second order asymmetric transformation to give the (SS) enantiomer in 80% yield.

Trans dimethyl cyclopentanone-3,4-dicarboxylate, 3, is a synthetic precursor of Brefeldin A[1], a fungal natural product which inhibits protein transport through the secretory pathway. This ketone is also involved in the synthesis of the prostaglandin PGA_2[4] and of nucleosides analogues which are inhibitors of HIV[2].

During our work on a new total synthesis of brefeldin A, we were faced with the problem of the optical resolution of the ketone 3. After several attempts with different chiral agents, we were successful in using the chiral hydroxythiol 2 made from (+) pulegone. Its synthesis was already described by Eliel[3] : 1,4-addition of sodium benzylthiolate to (+) pulegone, followed by Na/NH_3 reduction of the ketogroup yielding an isomeric mixture containing 65% of the (1R, 2R, 5R) hydroxythiol isomer, 2, (determined by ^1H NMR from the signal of CHOH) which was used by Eliel without purification. We purified the compound by making the corresponding oxathiane 1 with benzaldehyde. After one crystallization in acetone, pure 1 was isolated in 50% yield (Scheme I). The compound 1 was shown to be diastereochemically pure by ^1H NMR and its stereochemistry confirmed by NOE (irradiation of the benzylic axial proton increased the intensity of the axial CH_3 and axial H α to oxygen). Finally the oxathiane 1 was oxidized to the corresponding diastereomeric sultines which where then reduced to the optically pure hydroxythiol 2 by the procedure already described by Eliel.

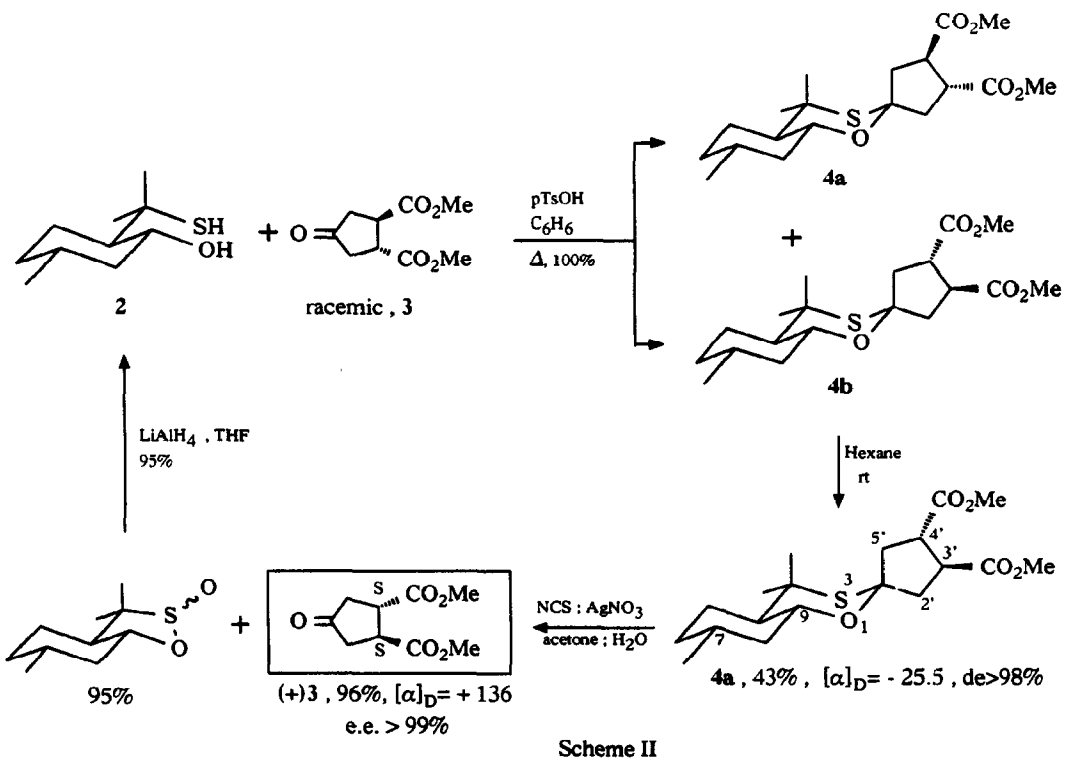
When racemic trans dimethyl cyclopentanone 3,4-dicarboxylate 3 was treated with the optically pure hydroxythiol 2 in the presence of p-toluenesulfonic acid in refluxing benzene, a quantitative yield of the oxathiane 4 was obtained. 4 was indeed a mixture of only 2 diastereoisomers 4a and 4b

(because of the C_2 symmetry of the starting ketone) which were not separable in TLC but showed different ^1H NMR characteristics.



Scheme I

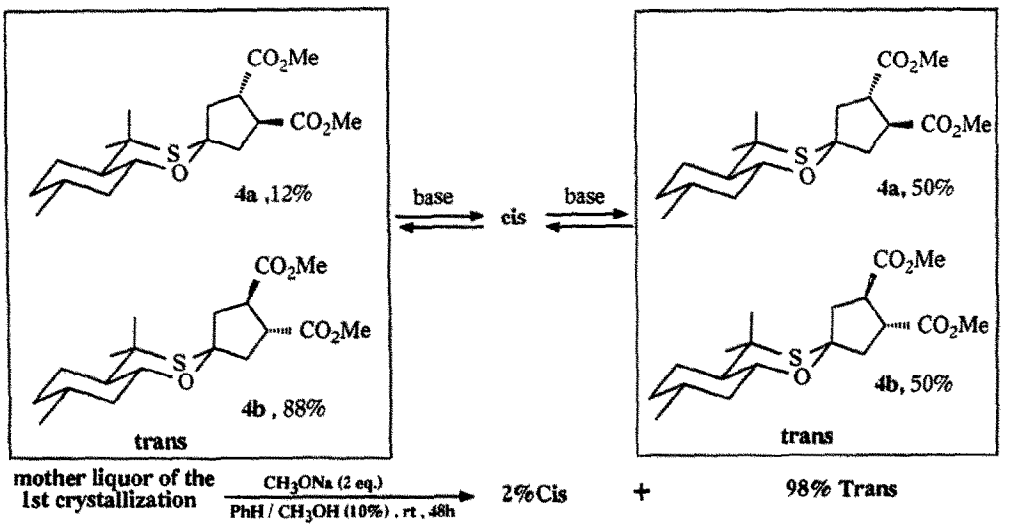
However one crystallisation in hexane allowed the isolation of the pure diastereomer **4a** in 43.5% yield. The other diastereomer **4b** remained in solution with about 12% of **4a** (Scheme II).



Scheme II

The configuration of **4a** was determined by hydrolyzing the compound (through the corresponding sultine) to the known (+) trans dimethyl cyclopentanone 3,4-dicarboxylate[4].

One interesting feature concerning the ketone **3** is the possibility of racemization in basic medium. Considering the large difference in solubilities in hexane of the 2 diastereomers **4a** and **4b** and the possibility of epimerization of the two chiral centers of the ketone moiety, it should be in principle possible in basic medium to epimerize the **4a/4b** mixture into only **4a**. Therefore the residue of the crystallisation (containing the mixture **4a/4b** in the ratio 12/88) was dissolved in benzene/methanol (90/10) and treated by 2 equivalents of sodium methoxide (Scheme III). After 48h at room temperature the reaction mixture contained a 1:1 ratio of **4a/4b** and less than *2%* of the cis isomer. It was then possible to crystallize **4a** from this mixture by working in hexane. By repeating 3 times this process we were able to transform racemic **3** into the (+) (SS)-3 enantiomer in 80% yield.



3 cycles gave an overall yield of 80% in diastereomer 4a.

Scheme III

This result represents a very efficient second order asymmetric transformation of a racemic ketone into only one enantiomer in 80% yield.

EXPERIMENTAL PART

(+)-(2R, 7R, 9R, 10R)-hexahydro-4,4,7-trimethyl-2-phenyl-1,3-benzoxathiane, 1.

1) addition of sodium benzylthiolate to (+)-pulegone.

Benzylthiol (1,1 eq., 181 g, 1.46 mol.) and 10% aqueous solution of NaOH (10 mL) were added to a solution of (+) pulegone (1 eq., 200 g, 1.33 mol.) in THF (500 mL). The reaction mixture was heated at reflux for 2h. The resulting solution was washed with a sat. NaCl solution (2x500 mL) and extracted with ether (3x250 mL). The organic phases were dried ($MgSO_4$) and evaporated. Yield :

331 g (90%) of a 80/20 mixture of trans/cis diastereomers, $Eb_{0.4}$ = 165-175°C. ^1H NMR ($CDCl_3$, 200 MHz) : δ : 7.34 (m, 5H, arom.), 3.74 (s, 2H, SCH_2Ph), 2.48-0.91 (m, 8H, CH_2), 1.60 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 0.98 (d, 3H, J=5.9Hz, CH_3).

2) Reduction of the ketone with Na/NH$_3$.

In a flask equipped with a dry ice condensor, liquid NH_3 (3L) was added at -78°C. Then Na (6 eq., 125 g, 5.43 mol.) was slowly added and a solution of the preceeding ketone (1 eq., 250 g, 0.906 mol) in anhydrous ether (650 mL) was dropwise added to the blue solution. After stirring for 30 min. methanol (150 mL) was slowly added. NH_3 was slowly evaporated at room temperature for 12h. The residue was treated by water (700 mL) and extracted with ether (2x200 mL). The aqueous phase was diluted with cold water (1L), acidified with conc. HCl (500 mL) and extracted with ether (5x200 mL). The organic phases were washed with water (200 mL), with sat. NaCl (200 mL), dried ($MgSO_4$) and evaporated yielding 140 g (82%) of the crude product (diastereomers mixture) used without further purification in the next step.

3) Oxathiane formation with benzaldehyde.

A solution of the preceeding hydroxythiol (1 eq., 42.85 g, 0,229 mol.), benzaldehyde (1.05 eq., 25.5 g, 0.24 mol.) and p-TsOH (0.02 eq., 1 g, 5 mmol.) in toluene (1L) was refluxed for 3h with a Dean-Stark. The reaction mixture was then washed with a 5% $NaHCO_3$ solution (2x200 mL), the aqueous phases extracted with ether (2x100 mL), the organic phases dried ($MgSO_4$) and evaporated. The residue was dissolved in acetone (300 mL) and kept at -30°C for 2 days. Crystals were filtrated, washed with cold acetone and dried, yielding 31.84 g (50%) of the pure diastereomer **1** ; m.p. 96-97°C ; $[\alpha]_D$ +56.5 (c=2.52, $CHCl_3$) ; ^1H NMR ($CDCl_3$, 200 MHz) : δ : 7.50-7.30 (m, 5H, arom.), 5.96 (s, 1H, H-2), 3.59 (td, 1H, J=10.4 and 4.3Hz, H-9), 2.07-2.91 (m, 8H, CH_2), 1.55 (s, 3H, axial CH_3), 1.29 (s, 3H, equatorial CH_3), 0.96 (d, 3H, J=3.4Hz, CH_3) ; IR ($CHCl_3$) : 2900, 1140 cm^{-1} ; ^{13}C NMR ($CDCl_3$) : δ : 139, 128, 127.9 and 126 (arom.), 79.8 (C-2), 77.3 (C-9), 50.1 (CH), 43.8 (C-4), 41.6 and 34.5 (CH_2), 31.2 (CH), 29.1 (CH_3), 24.2 (CH_2), 22.7 (CH_3), 21.9 (CH_3) ; Anal. Calc. for $C_{17}H_{24}OS$, C%, 73.43 ; H%, 8.70. Found, C% 73.59, H% 8.56.

(-)-(1R, 2R, 5R)-5-methyl-2-(1-mercapto-1-methylethyl)- cyclohexan -1-ol, 2.

1) Oxidation to sultine.

Acetone (2560 mL), water (640 mL), NCS (3 eq., 33.7 g, 0.25 mol.), NO_3Ag (2.5 eq., 35.7 g, 0.21 mol.) and $NaHCO_3$ (3 eq., 21.2 g, 0.25 mol.) were stirred for 1 min. and oxathiane **1** (1 eq., 23.2 g, 0,08 mol.) dissolved in the minimum of acetone was added. AgCl precipitated immediately. After stirring for 10 min., a saturated solution of sodium sulfite (35 mL) was added and 1 min. later sat. NaCl (350 mL) was added. After filtration, the aqueous phase was extracted with ether (2x300 mL) ; the organic phases were dried ($MgSO_4$) and evaporated. The excess of benzaldehyde was distilled ($Eb_{0.4}$=30-35°C) and the residue purified by silica gel chromatography (AcOEt/hexane : 15/85) to give 16.3 g (97%) of solid sultine (50/50 mixture of diastereomers). ^1H NMR ($CDCl_3$, 200 MHz) : δ : 4.44 (td, 0.5H, H-8 in one dia.), 4.0 (td, 0.5H, H-8 in the other dia.), 2.32-0.83 (m, 8H, CH_2), 1.41 and 1.29 (s, 3H, CH_3), 1.12 and 1.10 (s, 3H, CH_3), 1.01 (d, 3H, J=6.3Hz, CH_3).

2) Reduction of sultine to the hydroxy-thiol 2.

Lithium aluminium hydride (3 eq., 9.2 g, 0.24 mol.) was slowly added to the preceeding sultine (1 eq., 16.3 g, 0.08 mol.) in THF (600 mL). After refluxing for 2h, the reaction was hydrolyzed with 10% H_2SO_4 (115 mL) and extracted with ether (2x50 mL). The organic phases were washed with sat. NaCl (200 mL), dried ($MgSO_4$) and evaporated. The crude product was distilled, $Eb_{0.3}$=76-79°C, yielding 14.32 g (95%) of hydroxythiol 2 ; Rf=0.49 (AcOEt/hexane : 20/80) ; $[\alpha]_D$ -6 (c=3.95, $CHCl_3$) ; ^1H NMR ($CDCl_3$, 200MHz) : d: 3.69 (td, 1H, J=10.2 and 4.2Hz, H-1), 2.08-0.78 (m, 8H, CH_2), 1.52 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 0.92 (d, 3H, J=6.4Hz, CH_3) ; IR ($CHCl_3$) : 3600, 3420, 2920, 1140 cm^{-1} ; ^{13}C NMR ($CDCl_3$) : δ : 73 (C-1), 54.7 (C-2), 47.2 (C-7), 45.3 (C-6), 34.8 and 31.3 (C-8, C-9), 34.6 (C-4), 28.6 (C-5), 26.8 (C-3), 21.9 (C-10).

(-)-(7R, 9R, 10S, 3'S, 4'S)-spiro [(hexahydro-4,4,7-trimethyl-1,3-benzoxathiane)-2 : 1'-(dimethylcyclopentane-3',4'-dicarboxylate)], 4a.

To the hydroxythiol 2 (1 eq., 12.58 g, 0.067 mol.) in toluene (400 mL) were added the racemic ketone 3[1a,2b] (1.2 eq., 16.1 g, 0.08 mol.) and p-TsOH (0.025 eq., 320 mg, 1.70 mmol.). After refluxing for 2h (with a Dean-Stark), a small quantity of ketone 3 (0.37 eq., 5 g, 0.025 mol.) and p-TsOH (0.063 eq., 800 mg, 4.2 mmol.) were again added and reflux continued for 12h. After evaporating toluene, the residue was diluted with ether (300 mL), washed with a 5% $NaHCO_3$ solution (2x75 mL), with a sat. NaCl solution (100 mL), dried ($MgSO_4$) and evaporated. The crude product (33 g) was purified by chromatography (Et_2O/hexane : 20/80) to separate the oxathiane 4 (23.1 g, 93%) and the ketone 3 in excess (7.35 g). The oxathiane 4a was crystallized in hot hexane (115 mL), yield : 10.05 g (43%) of white crystals.

The residue obtained from the mother liquors was epimerized in a mixture benzene/methanol (200 mL/20 mL) in presence of CH_3ONa (2 eq.) for 48h at room temperature. Then 1N HCl (2.4 eq.) was added at 0°C and the mixture was diluted with ether (200 mL). The aqueous phase was extracted with ether (2x30 mL). The organic phases were washed with sat. NaCl (200 mL), dried ($MgSO_4$) and evaporated. The crude product (quant. yield) containing 2% of cis isomer was crystallized in hot hexane. By repeating this process 3 times, 9.8 g of 4a were obtained. Total yield : 19.85 g (80%) ; m.p. 107-108°C ; Rf : 0.3 (AcOEt/hexane : 10/90) $[\alpha]_D$ -25.5 (c=2.46, $CHCl_3$) ; IR ($CHCl_3$) : 2940, 1720 cm^{-1} ; ^1H NMR ($CDCl_3$, 200MHz) : δ : 3.86 (td, 1H, H-3'), 3.50-3.43 (m, 1H, H-4'), 3.41 (s, 3H, CH_3O), 3.40-3.23 (m, 1H, H-9), 3.39 (s, 3H, CH_3O), 3.03 (m, 1H, H-2'α), 2.65 (m, 1H, H-5'α), 2.29 (dd, 1H, H-5'β), 2.15 (dd, 1H, H-2'β), 1.83 (m, 1H, H-8e) 1.55 -0.29 (m, 7H, CH_2), 1.25 (s, 3H, CH_3a), 1.11 (s, 3H, CH_3e), 0.82 (d, 3H, J=6.1Hz, CH_3). ^{13}C NMR ($CDCl_3$) : δ : 174.3 (C=O), 174 (C=O), 86.8 (C-2), 70.6 (C-9), 51.84 (CH_3O), 51.82 (CH_3O), 49.5 (C=O), 45.2 and 43.2 (C-4' and C-3'), 44.9 (C-8), 43.3 (C-4), 42.6 and 41.6 (C-2' and C-5'), 34.4 and 23.8 (C-5, C-6), 31.2 (C-7), 29.8 (CH_3), 25.8 (CH_3), 21.9 (CH_3). Anal. Calc. for $C_{19}H_{30}O_5S$, C% 61.59 ; H%, 8,16. Found, C% 61.74, H% 8.20.

(+)-(1S, 2S)-dimethyl-4-oxocyclopentane-1,2-dicarboxylate, 3.

Oxathiane 4a (1 eq. 2 g, 5.40 mmol.) dissolved in acetone is added to a mixture of acetone (160 mL), water (40 mL), NCS (3 eq., 2.165 g, 0.0162 mol.), Ag NO_3 (2.5 eq., 2.29 g, 0.014 mol.) and $NaHCO_3$ (3 eq., 1.373 g, 0.0162 mol), cooled at 0°C. After stirring for 12 min., sat. Na_2SO_3 (2.4 mL)

was added followed by sat. NaCl (22 mL), ether extraction (2x30 mL). The organic phases were dried ($MgSO_4$), evaporated and purified by chromatography (AcOEt/hexane : 20/80), Rf=0.35. yield : 1.1 g (96%); $[\alpha]_D$= +136 (c= 0.66, $CHCl_3$)(lit[4] +134.4), ee>99%. ^1H NMR ($CDCl_3$, 200MHz) : δ : 3.75 (s, 6H, CH_3O), 3.42-3.36 (m, 2H, H-1, H-2), 2.64-2.51 (m, 4H, H-3, H-5) ; ^{13}C NMR ($CDCl_3$) : δ : 190.3 (C-4), 172.8 (CO_2Me), 51.9 (CH_3O), 43.2 (C-1, C-2), 40.4 (C-3, C-5) ; IR (CCl_4) : 2950, 1760, 1745 cm^{-1}.

References.

1) a) Bartlett, P.A.; Green, F.R.; *J.Am.Chem.Soc.* **1978**, *100*, 4858. b) Honda, M.; Hirata, K.; Sueoka, H.; Katsuki, T.; Yamaguchi, M;, *Tetrahedron Lett.* **1981**, *22*, 2679. c) Solladié, G.; Lohse, O.; *J.Org.Chem.* **1993**, in press, (this ketone was prepared in this paper by asymmetric synthesis).

2) a) Buenger, G.S.; Marquez, V.E.; *Tetrahedron Lett.* **1992**, *33*, 3707. b) Boumchita, H.; Legraverend, M.; Bisagni, E.; *Heterocycles* **1991**, *32*, 1785.

3) a) Lynch, J.E.; Eliel, E.L.; *Tetrahedron* **1987**, *43*, 4979. b) Eliel, E.L.; Lynch, J.E.; Kunie, F.; Frye, S.V.; *Org.Synth.* **1987**, *65*, 215. c) Eliel, E.L.; Frazee, W.J.; *J.Org.Chem.* **1979**, *44*, 3598.

4) Suemune, H.; Tanaka, M.; Obaishi, H.; Sakai, K.; *Chem.Pharm.Bull.* **1988**, *36*, 15.

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