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ENANTIODIVERGENT SYNTHESES OF (R)- AND (S)-3,5-DIMETHYLCYCLOHEX-2-EN-1-ONES FROM (R)-PULEGONE

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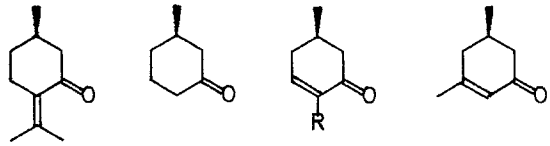
ABSTRACT: R-(+)-pulegone (1) is transformed to (R)-5-methyl-2-(phenylsulfinyl)cyclohexanone (5) (65%, 3 steps). Sulfoxide 5 is converted to R-(-)-3,5-dimethylcyclohex-2-en-1-one (4) (53%, 4 steps) and S-(+)-4 (26%, 3 steps).

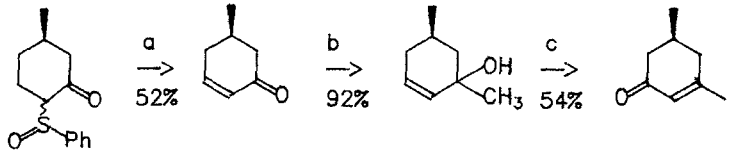
Monoterpenes of known absolute configuration are particularly attractive chiral starting materials for the synthesis of more complex natural products. In this respect the readily available and inexpensive (R)-(+)-pulegone (1) is a popular choice among synthetic organic chemists. In recent years, (+)-pulegone has been utilised in the synthesis of optically active (+)-artemisinin,[1] (+)-jatrophone[2] and (+)-1233A.[3] Among other possible synthetic transformations, (+)-1 can be converted to (+)-3-methylcyclohexanone (2),[4] (-)-5-methylcyclohex-

2-en-1-ones (3)[5] and (-)-3,5-dimethylcyclohex-2-en-1-one (4).[6]



1 2 3 (-)-4

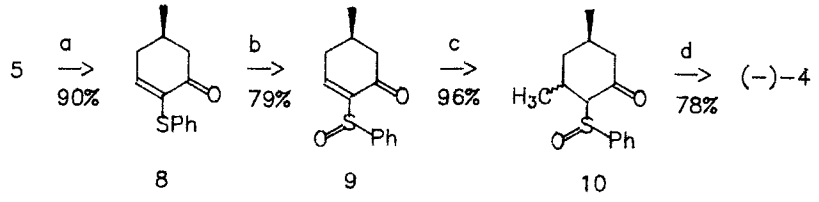
The synthesis of R-(-)-4 from R-(+)-1 via R-(+)-2 as an intermediate was reported by Allinger et al. in 1975.[6] Although this preparation affords the requisite enone 4 in good optical purity ($[\alpha]^{25}_{D}$ -138.4°, c 0.8, $CHCl_3$), the large number of steps (~10), purification at each stage, and the low overall yield (<1%) make this procedure somewhat tedious. Moreover, the pseudo-symmetric ketone 2 is devoid of a convenient chemical handle for selective α-functionalisation remote from the chiral centre. Subsequent efforts of Agami[7] on the S-proline catalysed cyclisation of prochiral diketones and of Koga[8] on the enantioselective deprotonation of cyclohexanones were also unsuccessful. Racemic 4 has been employed as a starting material in a number of synthetic transformations.[9] The use of (+)- or (-)-4 is infrequent, presumably due to the unavailability of a convenient method for their preparation. We report in this Communication the synthesis of (+)- and (-)-4 starting from the same precursor, (+)-1.



SCHEME 1: a) $CaCO_3$ (cat.), CCl_4, 70 °C; b) MeLi, Et_2O; c) PCC, CH_2Cl_2, rt.

Commercially available (R)-(+)-pulegone (1) was transformed to a mixture of diastereomeric ketosulfoxides 5 in 65% overall yield.[1,5,10] Keto-sulfoxide 5 was employed as the common intermediate for the synthesis of (+)- and (-)-4. The epimeric mixture at the sulfoxide moiety was of little consequence because the adjacent carbon is eventually converted into sp^2-centre.

The thermal elimination of phenylsulfinic acid from sulfoxide 5 under conditions reported by Caine and co-workers[5] provided isomerically and optically pure (R)-(-)-5-methylcyclohex-2-en-1-one (6) in 52% yield. Addition of MeLi at -78 °C gave a mixture of pyranols 7 (92%, crude) which were smoothly rearranged to the transposed enone (+)-4 (54%) under the aegis of PCC[11] at rt (Scheme-1) ($[\alpha]^{25}_D$ +132.2°, c 1.4, $CHCl_3$, lit. +138.4°, optical purity 96%).[6] This constitutes a significant improvement over Koga's procedure[8] which affords (+)-4 in an optical purity of 60%.



8 9 10

SCHEME 2: a) Ac_2O, MsOH (cat.), CH_2Cl_2; b) $NaIO_4$, aq. MeOH; c) Me_2CuLi, Et_2O/THF; d) $CaCO_3$ (cat.), CCl_4, 70 °C.

The synthesis of enone (-)-4 from keto-sulfoxide 5 was carried out by a different route. Thus, Pummerer rearrangement[12] (Ac_2O, MsOH, CH_2Cl_2) of diastereomeric sulfoxides 5 provided enone sulfide 8 in 90% yield after column chromatography. Customary periodate oxidation and smooth conjugate addition with lithium dimethylcuprate provided a mixture of stereoisomers 10. Smooth elimination of PhS(O)H under conditions optimised earlier yielded enone (-)-4 ($[\alpha]^{25}_D$ -132.8°, c 1.25, $CHCl_3$, optical purity 96%)[6] (Scheme-2). The alternative sequence of subjecting enone sulfide 8 to i) $(CH_3)_2CuLi$ ii) $NaIO_4$ and iii) $CaCO_3$, did not produce satisfactory results.

In conclusion, we have synthesised (R)-(-)- and (S)-(+)-3,5-dimethylcyclohex-2-en-1-ones (4) from the common precursor sulfoxide (+)-5 in overall yields of 53% and 26%, respectively. The sequence is amenable to

scale-up and short enough to access both enantiomers (+)- and (-)-4 from (+)-pulegone (1) in about a week.

EXPERIMENTAL SECTION[13]

^1H NMR (200 MHz) and ^{13}C NMR (25 MHz) were recorded on Bruker and Joel-Fx-100 spectrometers, respectively. Optical rotations at Na-D line were obtained at 25 ^oC on Rudolph Autopol II polarimeter.

R-(+)-PULEGONE (tech, 85%) was purchased from Aldrich and used as such ($[\alpha]_D$ $+22^o$ (neat), Lit.[14] $[\alpha]_D$ $+23.0-23.5^o$ (neat); optical purity 94-96%).

R-(-)-5-METHYLCYCLOHEX-2-EN-1-ONE (6)

A solution of sulfoxide 5 (1.180 g, 5 mmol) in anhyd CCl_4 (750 mL) was heated in the presence of $CaCO_3$ (25 mg, 0.25 mmol) at 70 ^oC for 20 h. The solution was filtered and solvent evoporated. Silica gel chromatography (SGC) (hexane ---> 10% Et_2O/hexane) yielded 290 mg (52%) of optically pure enone 6. $[\alpha]^{25}_D$: -87.1^o (c 2.0, $CHCl_3$). (Lit.[4] $[\alpha]^{25}_D$ -90.2^o (c 2.55, $CHCl_3$). IR: (Neat, cm^{-1}) 700, 740, 880, 1030, 1270, 1390, 1440, 1670, 2900, 3050. ^1H NMR: δ 1.08 (d, J=6Hz, 3H); 1.95-2.58 (m, 5H); 5.96-6.08 (m, 1H); 6.90-7.04 (m, 1H). ^{13}C NMR: δ 21.06, 30.24, 33.94, 48.18, 129.66, 150.01, 200.25..

(R)-1,5-DIMETHYLCYCLOHEX-2-EN-1-OL (7)

To a stirred solution of enone 6 (165 mg, 1.5 mmol) in 10 mL of anhyd Et_2O at -78 ^oC was added dropwise an ethereal solution of MeLi (1.2 mL, 3 mmol, 2.5 M soln in Et_2O). The resulting solution was allowed to warm to rt over 1 h and stirred at rt for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and diluted with brine (10 mL). Extraction with Et_2O (3 x 30 mL), brine wash and work-up afforded 175 mg (92%) of somewhat unstable

allylic alcohol 7 which was transposed as such in the next step. IR: (Neat, cm^{-1}) 720, 900, 1060, 1110, 1370, 1450, 2900, 3350. ^1H NMR: δ 0.98 (d, J=6Hz, 3H); 1.30 (s, 3H); 1.20-2.15 (m, 6H); 5.50-5.85 (m, 2H). ^{13}C NMR: δ 22.06, 28.29, 28.30, 29.70, 33.88, 47.53, 127.07, 134.54.

S-(+)-3,5-DIMETHYLCYCLOHEX-2-EN-1-ONE (4)

To a magnetically stirred slurry of PCC (645 mg, 3 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of alcohol 7 (175 mg, 1.4 mmol) in dry CH_2Cl_2 (5 mL) in one porton at rt. The resulting dark red-black mixture was allowed to stir at rt for 1 h and then diluted with equal volume of Et_2O (10 mL). Filtration through celite, work-up and SGC (hexane ---> 10% Et_2O/hexane) afforded 94 mg (54%) of optically pure (+)-3,5-dimethyl cyclohex-2-en-1-one (4). MS: (70 ev) *m/z* 124 (M^+), 82 (100). bp: 100 ^oC (oil bath)/12 Torr. $[\alpha]^{25}_D$: +132^o (c 1.4, $CHCl_3$). IR: (Neat, cm^{-1}) 690, 730, 1250, 1370, 1440, 1650, 2900. ^1H NMR: δ 1.06 (d, J=6Hz, 3H); 1.95 (s, 3H); 2.00-2.50 (m, 5H); 5.88 (s, 1H). ^{13}C NMR: δ 21.06, 24.29, 30.06, 39.41, 45.24, 126.48, 162.06, 200.18.

(R)-5-METHYL-2-(PHENYLTHIO)CYCLOHEX-2-EN-1-ONE (8)

To a solution of sulfoxide 5 (590 mg, 2.5 mmol) in CH_2Cl_2 (10 mL) was added Ac_2O (510 mg, 475 μL, 5 mmol) and MsOH (180 mg, 125 μL, 1.875 mmol) at 0 ^oC. The resulting solution was stirred at the same temperature for 1 h, allowed to warm to rt and stirred for 15 h. H_2O (5 mL) was added and the stirring continued for 30 min. The reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were washed successively with saturatrd $NaHCO_3$ solution and brine. Work-up afforded 535 mg (98%) of crude enone sulfide which was purified by SGC (hexane ---> 5% EtOAc/hexane) to afford 490 mg (90%) of pure 8. $[\alpha]^{25}_D$: -93.5^o (c

2.0, $CHCl_3$). IR: (Neat, cm^{-1}) 690, 740, 900, 980, 1020, 1070, 1130, 1220, 1260, 1330, 1440, 1480, 1600, 1680, 2900, 3050. ^1H NMR: δ 1.05 (d, J=6Hz, 3H); 1.98-2.75 (m, 5H); 6.46 (dd, J=6,4Hz, 1H); 7.20-7.50 (m, 5H). ^{13}C NMR: δ 20.65, 30.12, 35.06, 46.36, 128.06, 129.30, 132.07, 133.48, 136.96, 144.69, 195.24.

(R)-5-METHYL-2-(PHENYLSULFINYL)CYCLOHEX-2-EN-1-ONE (9)

To a solution of enone sulfide 8 (218 mg, 1 mmol) in MeOH (2.5 mL) was added a solution of $NaIO_4$ (214 mg, 1 mmol) in H_2O (1 mL) at 0 °C. The mixture was stirred at rt for 6 h. The precipitated $NaIO_3$ was removed by filtration and the filtrate was extracted with CH_2Cl_2 (3 x 30 mL), washed with 10% Na_2SO_3 solution twice and then with brine. Work-up afforded 230 mg (98%) of crude sulfoxide which was purified by SGC (10% ---> 30% EtOAc/hexane) to afford 185 mg (79%) of pure sulfoxide 9 as a 1:1 mixture of epimers at the sulfer centre. $[\alpha]^{25}_D$: -34.4° (c 5.0, $CHCl_3$). IR: (Neat,cm^{-1}) 680, 740, 920, 1010, 1040, 1070, 1120, 1200, 1260, 1330, 1440, 1600, 1660, 3050. ^1H NMR: δ 1.05 (m, 3H); 1.98-2.88 (m, 5H); 7.40-7.50 (m, 3H); 7.65-7.82 (m, 3H). ^{13}C NMR: δ 20.35, 20.54, 29.47, 30.35, 34.13, 46.18, 46.53, 125.30, 129.07, 131.24, 144.13, 148.54, 149.83, 194.84, 195.02.

(R)-3,5-DIMETHYL-2-(PHENYLSULFINYL)CYCLOHEXANONE (10)

An oven dried 50 mL flask with N_2 inlet and rubber septum containing CuI (285 mg, 1.5 mmol) and 10 mL of anhyd Et_2O was cooled to 0 °C. MeLi (3.0 mL, 3 mmol, 1.0 M soln in Et_2O) was added dropwise via syringe and stirred for 15 min. The $(CH_3)_2CuLi$ reagent was cooled to -78 °C and to it was added a solution of enone sulfoxide 9 (234 mg, 1 mmol) in 10 mL of anhyd THF. Stirring was continued at -78 °C for 30 min, followed by warming to 0 °C over 1 h. The reaction mixture was

quenched at $0^{o}C$ with saturated NH_4Cl solution (10 mL) and diluted with brine (10 mL). Extraction with Et_2O (3 x 30mL), brine wash and work-up afforded 240 mg (96%) of crude dimethyl sulfoxide 10 which was used in the next step without further purification. $[\alpha]^{25}_{D}$: $+77.5^{o}$ (c 4.0, $CHCl_3$). IR: (Neat, cm^{-1}) 610, 680, 740, 1040, 1080, 1140, 1210, 1300, 1440, 1700, 2900. ^{1}H NMR: δ 0.95-1.12 (m, 3H); 1.18-1.30 (m, 3H); 1.50-2.70 (m, 6H); 2.94-3.79 (m, 1H); 7.40-7.70 (m, 5H). ^{13}C NMR: δ 13.94, 19.06, 20.24, 21.06, 21.94, 25.29, 28.24, 29.06, 29.36, 29.50, 29.88, 30.65, 32.59, 33.77, 35.41, 35.83, 40.13, 50.18, 50.42, 51.36, 67.65, 76.89, 77.30, 79.30, 79.43, 88.06, 124.09, 124.38, 125.07, 125.59, 128.88, 129.24, 131.14, 131.42, 131.59, 131.83, 141.79, 141.89, 203.43, 204.25, 206.60.

R-(-)3,5-DIMETHYLCYCLOHEX-2-EN-1-ONE (4)

A solution of dimethylketosulfoxide 10 (240 mg, 0.96 mmol) in anhyd CCl_4 (150 mL) was heated in the presence of $CaCO_3$ (5 mg, 0.05 mmol) at $70^{o}C$ for 24 h. The solution was filtered and solvent evoperated. SGC (hexane ---> 10% Et_2O/hexane) provided 93 mg (78%) of optically pure (-)-3,5-dimethylcyclohex-2-en-1-one (4). MS: (70 ev) *m/z* 124 (M^{+}), 82 (100). $[\alpha]^{25}_{D}$: -132.8^{o} (c 1.25, $CHCl_3$) (Lit.[6] $[\alpha]^{25}_{D}$ -138.4^{o} (c 0.8, $CHCl_3$)). IR: (Neat, cm^{-1}) 880, 1010, 1140, 1240, 1370, 1390, 1430, 1640, 2900. ^{1}H NMR: δ 1.06 (d, J=6Hz, 3H); 1.95 (s, 3H); 2.00-2.50 (m, 5H); 5.88 (s,1H). ^{13}C NMR: δ 21.12, 24.35, 30.06. 39.41, 45.24, 126.48, 162.13, 200.25.

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