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PRELOG-DJERASSI LACTONE.

PREPARATION OF THE GRIECO INTERMEDIATE FROM (-)-TRANS-PULEGENIC ACID.

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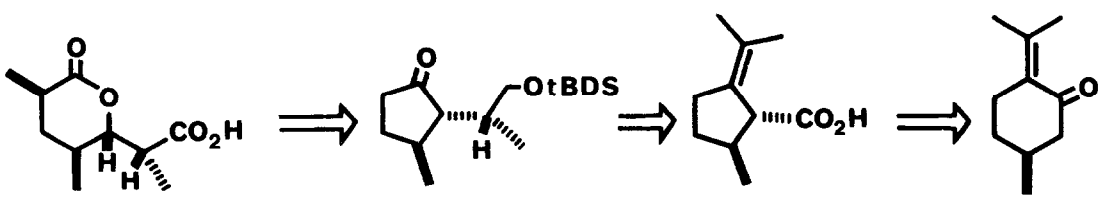
Summary : The Grieco intermediate **2**, for the synthesis of the Prelog-Djerassi lactone, was obtained from trans-pulegenic acid **3** in 6 steps in 43 % overall yield; recycling unwanted diastereoisomer **8**(S), increased the yield to 56 %.

The Prelog-Djerassi lactone **1** is a key degradation product of the antibiotics methymycin (1) and narbomycin (2), which retains the original four chiral centers present in the C(1)-C(7)(1) or C(3)-C(9)(2) fragments of the aglycons (3). Since the first synthesis by Masamune in 1975 (4), several studies have been devoted to the preparation of **1** because of its potential utility in the contruction of complex natural products (5)(6).

Our own strategy is centered on the levorotatory Grieco intermediate **2** (7)(8), which comes from the (-)-trans-pulegenic acid **3** derived from the (S)-(-)-pulegone **4**. The latter is easily prepared from various sources in high optical purity (9).

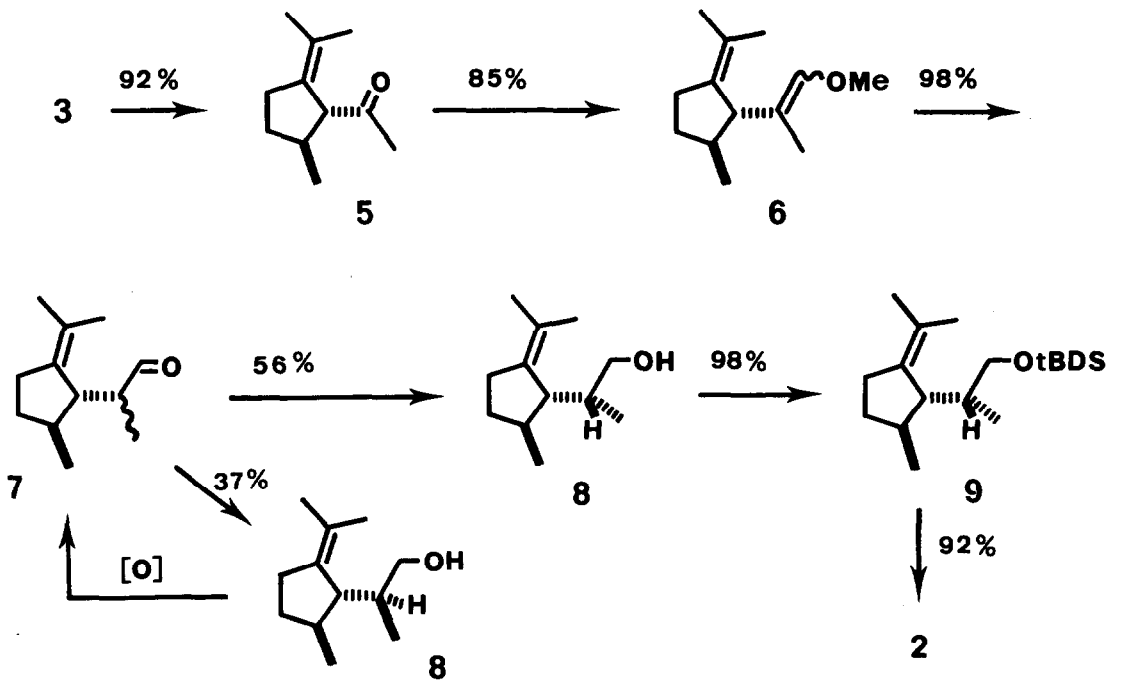


1 **2** **3** **4**

Results :

(-)-Pulegone **4**, obtained from (S)-(-)-citronellol (9b), was transformed into pure trans-pulegenic acid **3** according to the standard procedure (10). Addition of methyllithium to **3** afforded methylketone **5** (92 %) (11). Homologation was performed by Wittig methoxymethylenation (12) which gave a 4/1 mixture of E/Z-isomers **6** (85 %). Acid-catalyzed hydrolysis of the mixture **6** led to a 3:2 ratio of (R and S) aldehydes **7** (98 %)(13). Separation of the more polar isomer (subsequently identified as the R-isomer by its transformation into Grieco intermediate (vide infra)(14)) was difficult to perform (13).

Reduction of **7** by $LiAlH_4$ afforded the corresponding alcohol **8** (93 %). The two epimers (R/S = 3:2) were separated by silica gel chromatography; the more polar isomer (R-configuration) was carried forward in the synthesis whereas the less polar isomer (S-configuration) was reoxidized to aldehyde **7**. After equilibration in basic medium, the epimeric mixture of aldehydes **7** was recycled. Ozonolysis of alcohol **8** (R-isomer) was unsuccessful. Protection of the hydroxyl as its tert-butyldimethylsilyl ether (ROtBDS) and subsequent ozonolysis of the resulting ether **9** gave the Grieco intermediate **2** (90 % from **8**)(14). The epimeric intermediate was prepared for identification purposes.



Conclusion :

The Grieco intermediate has been prepared in six steps from (-)-pulegenic acid. The sequence was performed in 43 % overall yield including the chromatographic separation of the epimeric alcohols **8** or in 56 % yield by recycling the unwanted S-isomer of **8**. This constitues a formal synthesis of optically pure Prelog-Djerassi lactone **1**.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions were determined on Brucker AC 200 and Varian XL 200 (50.309 MHz) spectrometers, respectively. For ^{13}C NMR spectra, assignments were confirmed by J-modulated spin echo. Mass spectra were obtained on a Varian MAT 311 spectrometer. Melting points are uncorrected. All reactions were carried out under a positive argon atmosphere. Flash column chromatography used Merck grade 60 silica gel (230-400 mesh) and t.l.c. was done on Merck 60 F254 silica plate.

(2R,3S)-2-Acetyl-3-methyl-1-isopropylidenecyclopentane (5). To a solution of (-)-pulegenic acid (16.8 g, 0.1 mol) in anhydrous ether (600 mL) at 0 °C, was slowly added (1 h) a solution of methyllithium (125 mL, 1.6 M) in anhydrous ether (220 mL). The resulting mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was pourred, in several fractions, into a vigourously stirred chilled 1M HCl solution. The layers were separated and the aqueous layer was extracted 3 times with ether. The combined ethereal layers were washed with $NaHCO_3$ solution to neutrality and dried ($MgSO_4$). Concentration in vacuo, and flash chromatographic purification on silica gel (ether-pentane 3/97) afforded **5** (15.3 g, 92 %) : ^1H NMR δ 2.94 (1, d, J = 7.0 Hz), 2.07 (3, s), 1.68 (3, s), 1.54 (3, s), 1.07 (3, d, J = 6.3 Hz); ^{13}C NMR δ 211.0 (s), 135.15 (s), 126.1 (s), 65.2 (d), 40.0 (d), 34.2 (t), 31.1 (t), 26.5 (q), 21.5 (q), 21.2 (q), 19.5 (q); mass spectrum m/e 165 (15)(HRMS calcd for $C_{11}H_{18}O$ 166.1357, found 166.1347), 123 (100); IR (film) 1700, 1225 cm^{-1}; $[\alpha]_{578}^{23}$ = -50.4 ° (hexane, c = 0.036); anal. calcd C 79.52, H 10.84, found C 79.68, H 10.62.

(2R,3S)-3-Methyl-2-(1-methoxy-propen-2-yl)-1-isopropylidenecyclopentane (6). A solution of sodium hydride (2.57 g, 60 mmol)(55-60 % in oil, previously washed with 2x15 mL pentane) in anhydrous DMSO (30 mL) was warmed to 70-75 °C for 1 h. The solution was cooled to 15 °C and (methoxymethyl)triphenylphosphonium chloride (20.5 g, 60 mmol) diluted in DMSO (60 mL) was added dropwise keeping the temperature below 25 °C. After 5 min., ketone **5** (4.98 g, 30 mmol) in anhydrous DMSO (2 mL) was added and the mixture was warmed to 35-40 °C for 30 min. The mixture was pourred into ice and extracted with light petroleum. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography on neutral alumina (light petroleum) gave **6** (4.95 g, 85 %). Methyl ether **6** was a 4/1 mixture of E and Z-isomers : (E-isomer) ^1H NMR δ 5.76 (1, br. s), 3.56 (3, s), 1.65 (3, s), 1.59 (3, s), 1.45 (3, d, J = 1.4 Hz), 0.94 (3, d, J = 6.4 Hz); ^{13}C NMR δ 142.3 (d), 136.3 (s), 123,9 (s), 116.5 (s), 59.2 (d), 54.7 (q), 39.4 (d), 33.1 (t), 31.2 (t), 21.8 (q), 19.9 (q), 19.0 (q), 10.4 (q); mass spectrum m/e 194 (100)(HRMS calcd for $C_{13}H_{22}O$ 194.1670, found 194.1670), 179 (76), 147 (78); IR (film) 1680, 1240, 1200, 1130 cm^{-1}; anal. calcd C 80.41, H 11.34, found C 80.56, H 11.23.

(2S,3S)-3-Methyl-2-(propanal-2-yl)-1-isopropylidenecyclopentane (7). To a mixture of ether (30 mL) and 22 % hydrochloric acid (20 mL) was added a solution of **6** (1.95 g, 10 mmol) in ether (70 mL). After stirring at room temperature for 12 h, the mixture was pourred into ice and the layers were separated. The aqueous layer was extracted with ether and the combined ethereal solutions were washed with $NaHCO_3$ for neutrality and dried ($MgSO_4$). Concentration in vacuo afforded crude aldehyde **7** which was used in the next step. An analytical sample obtained by extensive flash chromatography (ether-pentane 4/96) was a mixture of R/S isomers at the exocyclic asymmetric center (t.l.c. ether/pentane 5/95, R : R_f = 0.34; S : R_f = 0.38). IR (film) 1730, 1120 cm^{-1}; mass spectrum m/e 180

(23)(HRMS calcd for $C_{12}H_{20}O$ 180.1514, found 180.1512), 123 (100), 107 (30). The R isomer showed : ^{1}H NMR δ 9.68 (1, d, J = 1.6 Hz), 1.66 (6, br. s), 1.02 (3, d, J = 6.5 Hz), 0.89 (3, d, J = 6.7 Hz); ^{13}C NMR δ 205.9 (d), 136.3 (s), 125.1 (s), 50.9 (d), 50.78 (d), 36.0 (d), 32.0 (t), 28.7 (t), 21.5 (q), 21.2 (q), 20.4 (q), 12.3 (q). The S isomer showed : ^{1}H NMR δ 9.63 (1, d, J = 1.7 Hz), 1.68 (6, br. s), 1.04 (3, d, J = 6.5 Hz), 0.91 (3, d, J = 6.7 Hz); ^{13}C NMR δ 205.5 (d), 136.0 (s), 124.2 (s), 50.3 (d), 49.9 (d), 36.9 (d), 31.5 (t), 29.0 (t), 22.0 (q), 21.5 (q), 21.3 (q), 10.6 (q).

Epimerization of 7. Water methanol solution (1/10)(20 mL) of anhydrous K_2CO_3 (200 mg) and **7** (mixture of isomers)(141 mg, 0.78 mmol) was stirred for 2.5 h to gave after the usual work-up a 62/38 mixture of R/S isomers.

(2S,3S)-3-Methyl-2-(1-hydroxy-2-propyl)-1-isopropylidenecyclopentane (8). To a stirred suspension of $LiAlH_4$ (214 mg, 5.6 mmol) in anhydrous ether (55 mL) at -20 °C was added dropwise aldehyde **7** (982 mg, 5.45 mmol) in ether (5 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was cooled to 0 °C and 2N hydrochloric acid (10 mL) was added dropwise. The usual work-up and flash chromatographic purification (ether-pentane 1/2) afforded **8** (923 mg, 93 %) : IR (film) 3350, 1030 cm^{-1}; mass spectrum m/e 182 (10)(HRMS calcd for $C_{12}H_{22}O$ 182.1670, found 182.1671), 139 (25), 123 (100); R isomer : ^{1}H NMR δ 3.62 (2, m), 1.64 (6, br. s), 0.89 (3, d, J = 6.9 Hz), 0.86 (3, d, J = 6.7 Hz); ^{13}C NMR δ 138.7 (s), 123.6 (s), 67.64 (t), 52.2 (d), 39.5 (d), 35.2 (d), 31.8 (t), 28.7 (t), 21.8 (q), 21.76 (q), 21.6 (q), 14.6 (q). S isomer : ^{1}H NMR δ 3.39 (2, m), 1.67 (6, br. s), 0.93 (3, d, J = 6.9 Hz), 0.87 (3, d, J = 6.7 Hz); ^{13}C NMR δ 138.0 (t), 123.7 (s), 66.7 (t), 52.3 (d), 39.7 (d), 35.7 (d), 32.1 (t), 29.0 (t), 22.3 (q), 21.4 (q), 21.36 (q), 15.9 (q); anal. calcd. C 79.12, H 12.09, found C 79.18, H 11.87.

Grieco intermediate 2 . To a solution of alcohol **8** (273 mg, 1.5 mmol) and imidazole (264 mg, 3.87 mmol) in anhydrous DMF (1.3 mL) at 0 °C was added in portions, tert-butyldimethylchlorosilane (258 mg, 1.83 mmol). The mixture was stirred at 30-35 °C for 15 h. After hydrolysis, ether extraction, washing with water and brine and drying ($MgSO_4$), the crude product was purified by flash chromatography (ether-pentane 0.4/99.6) to give **9** (0.42 g, 99 %). **9** : mass spectrum m/e 239 (27) (M^+ - tert-butyl) (HRMS calcd for $C_{14}H_{27}OSi$ 239.1831, found 239.1826), 172 (27), 123 (98), 75 (93), 73 (91), 44 (100). Ozone in oxygen was bubbled through a solution of **9** (318 mg, 1.07 mmol) in 27 mL of CH_2Cl_2-MeOH (2/1) which contained few drops of an ethanolic solution of "Sudan III" (Eastman Kodak)(1/10 000)(16) at -80 °C until the solution turned yellow. While the solution was still at -80 °C, the system was flushed with nitrogen. The solution was then allowed to warm up to 0 °C; one mL of dimethyl sulfide was added and the mixture stirred for 1 h. Washing with brine, extraction of the aqueous layer with CH_2Cl_2, drying ($MgSO_4$) and concentration in vacuo gave the crude product. Flash chromatographic purification (ether-pentane 5/95) furnished **2** (266 mg, 92 %) : IR (film) 1740, 1260, 1095, 840, 780 cm^{-1}; mass spectrum m/e 255 (2)(M^+ - Me)(HRMS calcd for $C_{14}H_{27}O_2Si$ 255.1780, found 255.1773), 213 (89), 195 (15), 121 (70), 75 (100); ^{1}H NMR δ 3.62 (2, m), 1.10 (3, d, J = 6.0 Hz), 0.85 (9, s), 0.79 (3, d, J = 7.0 Hz), 0.03 (6, s); ^{13}C NMR δ 221.2 (s), 65.9 (t), 57.7 (d), 39.1 (t), 35.3 (d), 34.3 (d), 30.0 (t), 25.9 (q, 3C), 20.25 (q), 18.2 (s), 13.4 (q), -5.4 (q, 2C).

(2S, 3S)-3-Methyl-2-((2S)-1-tert-butyldimethylsilyloxyl-2-propyl)-cyclopentanone. The isomeric compound (S-isomer) prepared in a similar manner showed : ^{1}H δ 3.5 (2, m), 1.12 (3, d, J = 6.0 Hz), 0.85

(9, s), 0.84 (3, d, J = 7.0 Hz), 0.03 (6, s); ^{13}C NMR δ 220.0 (s), 66.0 (t), 57.6 (d), 39.0 (t), 35.3 (d), 33.2 (d), 30.0 (t), 25.9 (q, 3C), 21.0 (q), 18.2 (s), 13.6 (q), 13.6 (q), -5.4 (q, 2C).

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