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STEREOSELECTIVE SYNTHESIS OF (1R,3S)-CIS-CHRYSANTHEMIC ACID THROUGH MICROBIOLOGICAL REDUCTION OF 2,2,5,5-TETRAMETHYL 1,4-CYCLOHEXANEDIONE.

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Summary : *An efficient, highly stereoselective synthesis of (1R,3S)-cis-chrysanthemic acid 6 is described. The crucial step of this synthesis was the microbiological reduction of dione 1 into (S)-ketol 2.*

(1R,3S)-cis-chrysanthemic acid 6 is a key intermediate in the synthesis of exceptionally potent insecticide DELTAMETHRINE [1].

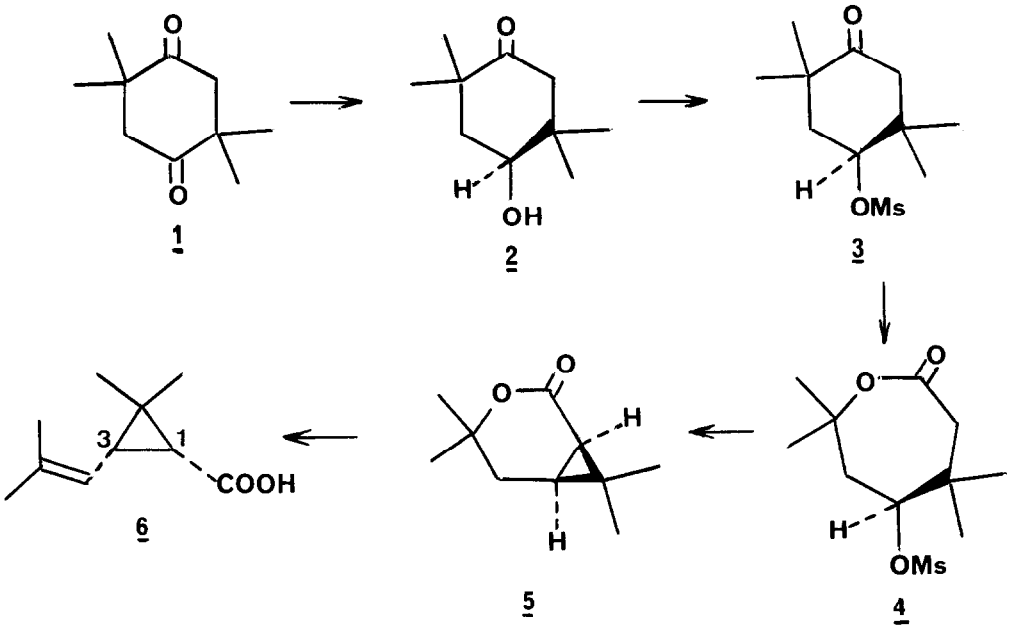
We report here a short, efficient, highly stereoselective synthesis of acid 6 based on the microbiological reduction of 2,2,5,5-tetramethyl 1,4-cyclohexanedione[2] 1.

Among the various strains of yeasts and fungi we have screened, *Curvularia lunata* was found specially suitable for this last purpose.

When a 36-48 h culture [4] of *C. lunata* NRRL 2380 was added to an ethanolic solution of the diketone 1 (final conc. : 5 g/l) and incubated at 24°C, a single product (≥ 98 % conversion), identical (G.C. and T.L.C.) with the authentic racemic keto-alcohol 2[3], could be detected after 3 days. After filtration on celite, extraction with dichloromethane and recrystallization from hexane, a product, m.p. 103-104°C, $[\alpha]_D^{20}$ + 89.7° (c = 3 in MeOH) was obtained in 70 % yield (not optimized). G.C. of its isopropyl urethane derivative[6] on a chiral stationary phase[7] indicated the exclusive presence of a *single enantiomer*. The CD spectrum of this compound exhibited a strong positive Cotton effect centered at 290 nm, as expected for the (S)-2,2,5,5-tetramethyl 1-cyclohexanone bearing an equatorial 4-hydroxy group[8].

Finally this compound was converted, in an overall yield of 80 %, according to the previously outlined sequence of reactions[3], into *enantiomerically pure* (1R,3S)-lactone 5, m.p. 83-84°C, $[\alpha]_D^{20}$ + 78° (c = 1.2 in $CHCl_3$), litt.[9] : m.p. 83°C, $[\alpha]_D^{22}$ + 77.6° (c = 1.8 in $CHCl_3$), through mesylate 3, m.p. 56-57°C, $[\alpha]_D^{20}$ + 60.7° (c = 3.4 in $CHCl_3$) and mesylate 4, $[\alpha]_D^{20}$ + 24.7° (c = 1.9 in $CHCl_3$). The absolute configuration observed for the bicyclic lactone 5 was in agreement, as expected, with a pure, intramolecular SN_2-type displacement of the mesyl group during the base-induced cyclization of (S) compound 4.

The lactone 5 has been previously transformed into (1R,3S)-cis-chrysanthemic acid 6[1b].



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(1) (a) Elliott, M. ; Farham, A.W. ; Janes, N.F. ; Needham, P.H. ; Pulman, D.A. *Nature (London)* 1974, **248**, 710. (b) "DELTAMETHRINE", a Roussel-Uclaf Monography, 1982, pp.25-66.

(2) This compound was previously transformed by two of us into *racemic* cis-chrysanthemic acid: ref (3).

(3) d'Angelo, J. ; Revial, G. *Tetrahedron Lett* 1983, 2103.

(4) *C. lunata* was maintained on agar slants containing for 1 l, glucose 20 g, peptone 5 g, yeast extract 5 g, malt extract 5 g and Bacto-agar 20 g. Inoculated liquid cultures were agitated at 24°C in a semi-synthetic medium, according to (5).

(5) Nakazaki, M. ; Chikamatsu, H. ; Naemura, K. ; Nishino, M. ; Murakami, H. ; Asao, M. *J. Org. Chem* 1979, 44, 4588.

(6) Konig, W.A. ; Francke, W. ; Benecke, I. *J Chromatogr.* 1982, **239**, 227.

(7) Chrompack fused silica column (50 m x 0.25 mm) coated with XE 60-S valine-S phenyl-ethyl-amide, 140°C, carrier gas : H_2 ; retention times : 26.2 and 26.8 min for racemic keto-alkohol **2**, 26.1 min for the chiral compound.

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