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SYNTHESIS OF OPTICALLY ACTIVE TRANS-CHRYSANTHEMIC ACID FROM OPTICALLY ACTIVE PANTOLACTONE*

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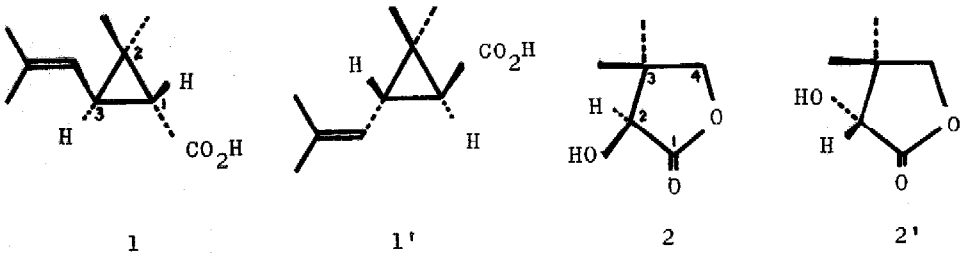
(+)-trans-Chrysanthemic acid (1) is the acid component of natural pyrethrin which has been widely used as an insecticide. The acid has been synthesized by many synthetic routes either in racemic[1] or in optically active forms.[2] As a part of our project to synthesize optically active natural products from optically active epoxides,[3,4,5] we have converted the readily available (2R)-(-)-pantolactone (2') into (1S:3S)-(-)-trans-chrysanthemic acid (1') and (2S)-(+)-pantolactone (2) into (1R:3R)-(+)-trans-chrysanthemic acid (1). The key intermediate in the present synthesis is an optically active epoxynitrile (6).

(2R)-(-)-Pantolactone (2') was reduced with $LiAlH_4$ to give (3R)-(-)-2,2-dimethyl-1,3,4-butanetriol (3) (34%), bp 117-120°/0.5mm; n_D^{22} 1.4742; $[\alpha]_D^{22}$ -16.0° (c=1.06, EtOH).[6] Acetonization (acetone/ p-TsOH) gave an acetonide (4a) (92%), bp 54-55°/0.24mm; n_D^{22} 1.4447; $[\alpha]_D^{22}$ -0.7°(neat). This was tosylated (1.2 eq of p-TsCl/C_5H_5N) (99%) and the resulting crude tosylate (4b) was converted to (3R)-(+)-nitrile (4c) (81%) by treatment with NaCN in dry DMSO at 80°for 48 hrs, bp 69-71°/0.8mm; n_D^{23} 1.4414; $[\alpha]_D^{23}$ +7.8°(c=1.16, EtOH). Removal of the protecting group (AcOH, THF and H_2O, 45°, 2 hrs) gave a diol (5a) (89%), bp 117-125°/0.2mm; n_D^{23} 1.4643; $[\alpha]_D^{23}$ -10.7°(c=1.07, EtOH). This was tosylated at -10°(1.1 eq of p-TsCl/ C_5H_5N) to give a crude mono-tosylate (5b) (80%). This gave the key (3R)-(-)-epoxynitrile (6) (88%), bp 76-82°/6mm; n_D^{23} 1.4385; $[\alpha]_D^{23}$ -18.0°(c=0.91,EtOH), when treated with NaOMe in MeOH at 0°. The ring closure[7] of the epoxynitrile (6) with $(Me_3Si)_2NLi$ in benzene with inversion of configuration at C-2 gave 2,2-



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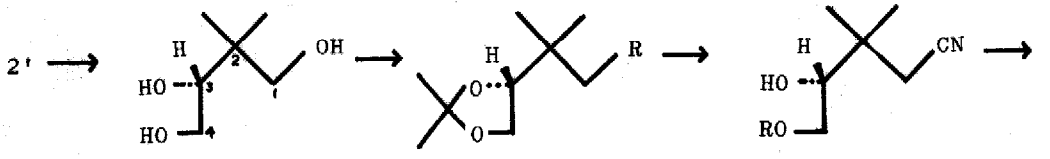
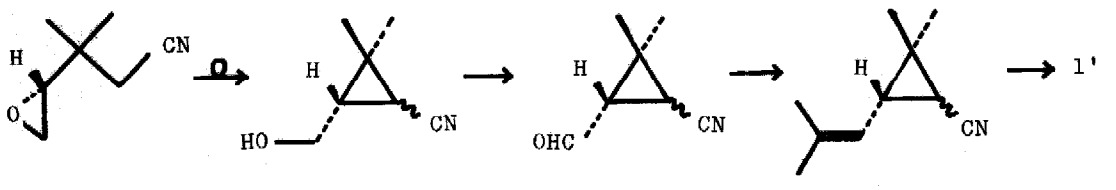


3 4a R= OH 4b R= OTs 4c R= CN 5a R= H 5b R= Ts



6 7 8 9

dimethyl-3-hydroxymethyl-cyclopropyl-1-nitrile (7) (63%) after chromatographic purification over neutral Al_2O_3 (Grade 2), bp 105-110°/0.8mm; the ratio of trans- and cis-isomers was found to be 70:30 by GLC analysis (column, 5% Silicone SE-30 chromosorb, 1.5m×3mm i.d. at 120°, carrier gas, N_2, 0.8kg/cm²): Rt, cis-isomer, 3.2min; trans-isomer, 4.3min. The nitrile was assumed to possess the 3S-configuration due to the Walden inversion during the intramoleculer S_N2 attack. This was oxidized with CrO_3-pyridine to an aldehyde (8) according to Corey's method.[8] The aldehyde was converted by the Wittig reaction [$(Ph_3PCHMe_2)Br$/ n-BuLi/ ether, room temp, 12 hrs] to (3S)-(-)-chrysanthemyl nitrile (9) in 61% yield from (7),

bp 95-110°/13mm; n_D^{22} 1.4682; $[\alpha]_D^{22}$ -29.3°(c=1.31,EtOH). The nitrile was hydrolyzed with KOH in ethyleneglycol at 200° for 24 hrs to give (1S:3S)-(-)-trans-chrysanthemic acid (1') (83%) contaminated with 5% of cis-isomer as determined by GLC analysis, bp 96-100°/0.45mm; n_D^{23} 1.4769; $[\alpha]_D^{23}$ -8.2°(c=1.14,EtOH). In the course of the hydrolysis most of the undesired cis-isomer epimerized to give the desired and more stable trans-isomer increasing the net yield of the final product. The ratio of optical isomers of this acid was found to be (1S:3S)-(-)-trans, 94.8; (1R:3R)-(+)-trans, 0.6; (1R:3S)-(+)-cis, 4.6 and (1S:3R)-(-)-cis, 0.0 % by GLC analysis.[9] In entirely the same manner (1R:3R)-(+)-trans-chrysanthemic acid (1) was synthesized from (2S)-(+)-pantolactone (2).

In conclusion the absolute configuration [10] of the natural (+)-trans-chrysanthemic acid was reconfirmed as (1R:3R)- by correlating it to that of (2S)-pantolactone.

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