ASYMMETRIC SYNTHESIS OF [C-1-^{3}H]-LABELLED (+)-*trans* [1R,3R]-CHRYSANTHEMIC ACID

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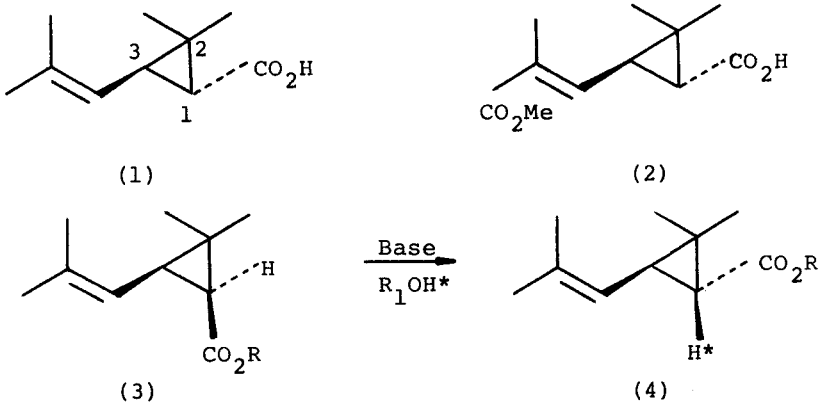
Received on March 30, 1976

Summary - A facile asymmetric synthesis of [C-1-^{3}H]-labelled (+)-*trans*[1R,3R]-chrysanthemic acid, required for biosynthetic studies is described. The tritium labelled acid is prepared from the corresponding (-)-*cis*[1S,3R]-ester by selective epimerisation of the C-1 centre in the latter, in the presence of tritiated water.

Chrysanthemic acid (1) is one of the acid components of the insecticidal pyrethrin esters found in *Chrysanthemum cinerariaefolium*. Our studies of the biosynthesis of (1) and of the related acid (2)[1-3] required the development of synthetic routes to optically pure [(+)-*trans* (1R,3R)] radio-labelled (1). In an earlier publication we described a synthesis of [1R,3R]-^{14}C-radiolabelled (1).[4] For double-labelled biosynthetic experiments, ^{3}H-labelled (1) was required, and for later degradation work it was desirable to locate the tritium label at C-1 in the chrysanthemyl skeleton of (1). In this paper we report a facile asymmetric synthesis of [C-1-^{3}H] - (+) - *trans* [1R,3R]-chrysanthemic acid.

cis-Chrysanthemic acid is readily available, and the (-)-cis[1S,3R]-antipode (3a) is conveniently obtained from the racemic acid by resolution of the corresponding quinine and α-phenylethylamine salts.[5] Under specific conditions in the presence of a base, selective epimerisation of the C-1 centre in



(1) (2) (3) (4)

a R = H; b R = Me: H* ≡ ^2H or ^3H-label

(3b) can be achieved leading to the trans-acid;[6] this selective epimerisation has been utilised to introduce a tritium label stereospecifically at C-1 in (1).†

Model studies with racemic cis-chrysanthemic acid and the corresponding methyl ester (3b) established that optimum yields of (1) from (3) could be obtained by heating a solution of the cis-ester (3b) in methanol in the presence of sodium methoxide at 200° for 20 hr. Shorter periods of heating and/or reduced temperatures resulted in incomplete epimerisation of (3), whereas longer periods of heating and/or more elevated temperatures led to considerably reduced yields of (1). The conversions (3) → (1) were

† Epimerisation of C-1 in the cis-isomer is essential for the introduction of tritium into the acid; attempts in introduce tritium directly into the (+)-trans-acid (1), by base catalysed exchange, were unsuccessful.

easily monitored by examination of the relative intensities of the n.m.r. bands associated with the olefinic hydrogens for the cis (τ 4.6) and trans (τ 5.1) isomers at varying intervals of time.[7]

Repetition of the isomerisation (3) → (1) using O-deuterio-methanol, and examination of the n.m.r. data for the trans-acid demonstrated that deuterium had been introduced exclusively at C-1 in the acid (viz 4a, $H^{*} \equiv {}^{2}H$). In the n.m.r. spectrum of the deuterio-acid, apart from the complete absence of the C-1 proton band (usually observed at ~τ 8.6) the resonance due to the C-3-H was seen as a simple doublet (J ~8Hz) corresponding to single vicinal coupling to the olefinic proton; the rest of the spectrum was closely identical with that of unlabelled (1).

For the tritium labelling of (1) it was found most convenient to heat the cis-ester (3b) at 200-210° for 20hr in methanol and tritium-enriched water in the presence of potassium hydroxide. Epimerisation of the (-)-cis[1S,3R] ester under these conditions led to the corresponding ^{3}H-labelled (+)-trans [1R,3R] -acid containing ca 10% (by n.m.r.) of starting cis-acid. Preparative layer chromatography then produced pure trans-acid which showed an optical rotation of +11.4° (an authentic sample had $[\alpha]_{D}^{27}$ + 13.5°).

EXPERIMENTAL

M.p's are corrected. N.m.r. spectra were determined with a Perkin-Elmer R10 spectrometer for dilute solutions in deuteriochloroform with TMS as internal standard. Bands were singlets except where stated otherwise. N.m.r. spectra of ^{3}H-labelled compounds were determined for solutions in heat-sealed Kel-F spaghetti tubing inserted in standard glass tubes. Mass spectra, were recorded with an AEI MS902 spectrometer and optical rotations were measured

with an ETL-NPL automatic polarimeter (type 143A). Radioactivity was measured with a Nuclear Enterprises 8310B type counter for dioxan solutions.

[C-1-^{2}H]- (±)-trans-2,2-Dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylic Acid [(C-1-^{2}H)-(±)-trans-Chrysanthemic Acid.] - A mixture of methyl (±)-cis-chrysanthemate (0.6g.) and sodium methoxide (from 0.09g. sodium) in deuteriomethanol (5ml) was heated at 200° in a sealed tube for 20hr., and then evaporated to dryness in vacuo. The solid residue was dissolved in water, and the solution was then extracted with ether. The aqueous layer was acidified to Congo Red with hydrochloric acid, then saturated with sodium chloride and extracted with ether. Evaporation of the dried ($MgSO_4$) ether extracts left the deuterated trans-acid as a colourless oil (0.41g.) τ 5.1dm (J ~ 8,:CH), 7.92d (J ~ 8, :CH.CH), 8.3 (2X :CMe), 8.71 (Me), 8.88 (Me); m/e 169 ($C_{10}DH_{14}O_2$) and 124 (cf. ref.8).

[C-1-^{3}H] -Labelled (+)-trans-[1R,3R]-Chrysanthemic acid. - Methyl (-)-cis[1S,3R]-chrysanthemate (3b) $[\alpha]_D^{25}$-51°, was prepared by esterification (CH_2N_2) of the corresponding acid, m.p. 41-43°, $[\alpha]_D^{27}$-39° (Lit., m.p. 41-43°, $[\alpha]_D^{27}$-40.8°) which had been resolved according to the procedure of Campbell and Harper.[4] A solution of the ester (0.11g) and potassium hydroxide (0.04g.) in methanol (4ml) and tritiated water (1ml., ~1 curie) was heated at 220° in a sealed tube for 18hr., and then evaporated to dryness in vacuo. The residue was dissolved in water, and the solution was then extracted with ether. The aqueous layer was acidified to Congo Red with hydrochloric acid, then saturated with sodium chloride and extracted with ether. Evaporation of the dried ($MgSO_4$) ether extracts left the tritiated acid (0.055g) accompanied by ~10% of

the corresponding cis-acid (by n.m.r.).[7] Chromatography in 3% methanolic chloroform on silica gel gave the pure (+)-trans-acid, chromatographically and spectrally (n.m.r.) indistinguishable from an authentic sample and showing $[\alpha]_D$ + 11.4°, activity 20μCi/mg.

We thank the S.R.C. for a fellowship (to R.S.)

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