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(+)-*TRANS*-CHRYSANTHEMIC ACID FROM (+)-Δ^3-CARENE[a]

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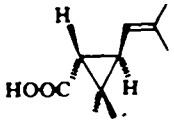
Abstract—A new and more efficient route for the conversion of the readily available (+)-Δ^3-carene into (+)-*trans*-chrysanthemic acid is described.

(+)-*trans*-Chrysanthemic acid (**1**)[1,2] is invaluable for the preparation of synthetic pyrethroids; the corresponding *levo*-antipode, when used as a component of synthetic pyrethrin analogues, shows several times lower activity.[3] In view of this, though a number of synthesis of the racemic acid are on record[4] and its resolution a subject of several patents,[5] it is worthwhile to investigate the preparation of (+)-*trans*-chrysanthemic acid by more direct routes.



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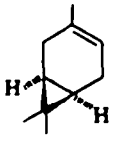

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An obvious approach is conversion of the readily available (+)-Δ^3-carene (**2**)[6] into (+)-*trans*-chrysanthemic acid. This transformation has, indeed, been realised by Matsui *et al.*,[7] but, by a sequence of reactions which furnished the required acid in ~2% overall yield. We now report on a new, more efficient pathway (Fig 1), which provides the key intermediate (−)-dihydrochrysanthemolactone (**6**) from the keto ester **3** (R = Me) in over 35% yield, in contrast to the method of Matsui *et al* which yields the same compound (**6**) in ~16% yield from the ozonolysis product of Δ^3-carene. Moreover, we now describe[8] a one-step conversion of the lactone **6** into (+)-*trans*-chrysanthemic acid.

The keto acid **3** (R = H)[9] obtained by ozonolysis followed by chromic acid oxidation[10] or, more conveniently, by chromic acid oxidation of the commercially[11] available (+)-3α, 4α-epoxycarane, was esterified and the methyl ester (**3**, R = Me) exposed to 30% peracetic acid at room temperature (25–32°) for 6 days. The resulting acetate ester (**4**) was treated with excess MeMgI to furnish the required diol (**5**). For analytical purposes, the diol was acetylated and the resulting hydroxy acetate purified by chromatography and then hydrolysed to yield diol **5** as a crystalline solid (m.p. 73–74°). Structure **5** is in

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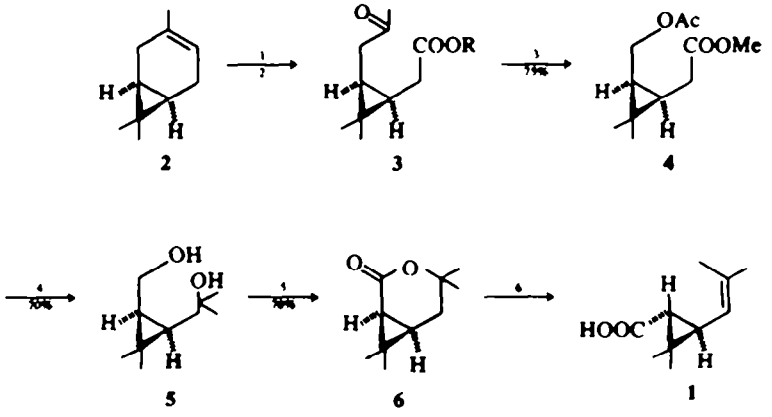

2 **3** **4** **5** **6** **1**

Reagents:

1. O_3; CrO_3; 2. MeOH, HCl; 3. CH_3COOOH; 4. MeMgI; 5. CrO_3; *p*-TSA; 6. KOH; diethylene glycol

Fig 1. (+)-*trans*-Chrysanthemic acid from (+)-Δ^3-carene.

full accord with its PMR spectral characteristics: two tert. Me (singlets at 0·92 and 1·05 ppm), Me_2COH (s, 1·22 ppm), $-CH-CH_2OH$ (2H, complex m, 3·51 ppm). Jones oxidation of the diol, followed by acid treatment, gave, as expected, the known[7,12] dihydrochrysanthemolactone (**6**) in over 70% yield.

Dihydrochrysanthemolactone (**6**) has been earlier converted into *cis*-chrysanthemic acid by the action of dil sulphuric acid,[12] potassium tertiary butoxide[7] and by thionyl chloride[13] and the *cis*-acid (or the ester) epimerized to the *trans*-compound by exposure to alkali.[7,14,15] We now find that conversion of **6** into **1** can be achieved in a convenient one step by heating it with KOH in diethylene glycol. The product was fully identified as (+)-*trans*-chrysanthemic acid (**1**) by direct comparison of the GLC and spectral data of its Me ester (IR, NMR) with that of an authentic sample of methyl (±)-*trans*-chrysanthemate.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Light petroleum refers to the fraction b.p. 60–80°. Optical rotations were measured in $CHCl_3$ on a Schmidt + Haensch electronic polarimeter model Polatronic 1.

TLC was carried out on SiO_2-gel G layers (0·25 mm) and activated for 2 h at 110–115°.

The following instruments were used for spectral/analytical data: Perkin–Elmer Infrared Spectrophotometer, model 267; Perkin–Elmer model R32 (90MHz) NMR Spectrometer; Hewlett-Packard 5700A gas chromatograph (column: 180 cm × 3 mm; 3% carbowax on chromosorb 60–80; H_2 as carrier gas). All PMR spectra were taken in 15–20% soln in CCl_4 with TMS as internal standard; signals are reported in ppm (δ). While citing PMR data the following abbreviations have been used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad).

Methyl (–) - 2,2 - *dimethyl* - 3 - (2' - *oxopropyl*) - *cyclopropane* - cis - 1 - *acetate* (**3**, R = Me). Jones reagent[16] (stock soln: CrO_3 133·5 g, conc H_2SO_4 115 ml and H_2O 200 ml) was added dropwise with stirring to (+) - 3α,4α - epoxycarane (30 g) in acetone (150 ml) at 20° till a brown colour persisted (80 ml of reagent). After stirring at this temp for 30 min, excess of reagent was destroyed by adding a few drops of isopropanol. The mixture was diluted with water (300 ml) and extracted with EtOAc (100 ml × 3). The extract was separated into acidic (16 g) and neutral portion (15 g) with 10% Na_2CO_3 aq in the usual manner. The acid was taken up in 3% methanolic HCl (80 ml) and after leaving at room temp (25°) for 48 h worked up in the usual manner to furnish after distillation the required ester **3** (R = Me): b.p. 102–105°/1 mm, n_D^{22} 1·4466, $[\alpha]_D^{20}$ – 20·2° (*c* 16·6%); GLC (temp 155°; H_2 flow 60 ml/min), purity, better than 95%; yield 13·8 g; IR (smear): C=O 1720, 1740 cm^{-1}; PMR: two $-\underset{|}{C}-\underline{Me}$ (3H singlet at 0·88 and 1·10 ppm), $\underline{Me}CO$ (3H, s, 2·08 ppm), $COO\underline{Me}$ (3H, s, 3·62 ppm).

Methyl 2,2 - *dimethyl* - 3 - *acetoxymethyl* - *cyclopropane* - cis - 1 - *acetate* (**4**). The above keto ester (30 g) was mixed with peracetic acid in AcOH (80 ml, 30%)* and the mixture allowed to stand at 25–32° for 6 days, away from light. The mixture was diluted with water (100 ml), neutralized with 25% Na_2CO_3 aq (300 ml) and extracted with light petroleum (50 ml × 3). The extract was washed with 5% $NaHSO_3$ aq (25 ml), 10% Na_2CO_3 aq (25 ml), water (25 ml × 3) and brine (25 ml × 1), and dried (Na_2SO_4). Solvent was flashed off to give 28·8 g of a liquid, which showed by GLC (temp 155°; H_2 flow 60 ml/min) 10% starting keto ester (RRT 1·19) besides the expected product (RRT 1·00). Fractionation of this material readily yielded pure **4**: b.p. 105–110°/1 mm, n_D^{22} 1·4460, $[\alpha]_D^{20}$ + 24·83° (*c* 13·8%), yield 24·9 g; IR (smear): C=O 1740 cm^{-1}, OAC 1248 cm^{-1}; PMR: two $-\underset{|}{C}-\underline{Me}$ (3H, s, 1·00 ppm; 3H, s, 1·02 ppm), CH_3COO (3H, s, 1·95 ppm), $COO\underline{Me}$ (3H, s, 3·63 ppm), CH_2COOMe (2H, m, 2·25 ppm), CH_2OAc (2H, m, 4·00 ppm).

2,2 - *Dimethyl* - 3 - *hydroxymethyl* - *cyclopropane* - cis - 1(2' - *methyl*) - *propan* - 2' - *ol* (**5**). To a soln of MeMgI (from 7·9 g Mg, 52 g MeI and 150 ml ether) at room temp (28°), the above ester (**4**; 15·8 g) in dry ether (25 ml), was introduced at such a rate that the solvent refluxed gently (20 min). After the addition was over, the mixture was stirred at room temp (28°) for an additional 1 h and then worked up in the usual manner with saturated NH_4Cl aq (50 ml) to furnish, after solvent removal, the required diol (**5**) as a dark brown viscous liquid (12·3 g). This product, on TLC (solvent: 50% EtOAc in C_6H_6) showed one main spot, besides a few very minor spots.

The above product (7·0 g) was exposed to Ac_2O (10 ml)-pyridine (10 ml) mixture for 16 h at room temp (20–28°). Usual work up furnished 8·4 g of a brown liquid which was chromatographed on silica gel (45 cm × 3·5 cm) with TLC (solvent: 50% EtOAc in C_6H_6) monitoring:

Frac. 1	50% light petroleum in C_6H_6	100 ml × 10	0·374 g, mixture
Frac. 2	C_6H_6	100 ml × 10	0·070 g, mixture
Frac. 3	5% EtOAc in C_6H_6	100 ml × 5	1·192 g, mxiture
Frac. 4	10% EtOAc in C_6H_6	100 ml × 10	6·378 g, rqd acetate
Frac. 5	25% EtOAc in C_6H_6	100 ml × 5	0·117 g, mixture
Frac. 6	50% EtOAc in C_6H_6	100 ml × 5	0·201 g, mixture

*Peracetic acid (30%) was prepared from 90% hydrogen peroxide and glacial acetic acid using catalytic amount (2%) of conc H_2SO_4[17] and used, after neutralising H_2SO_4 with NaOAc.

Fraction 4 was distilled to give the hydroxy acetate (primary OH in **5** acetylated) as a colourless liquid: b.p. 100–101°/1 mm, n_D^{22} 1·4553, $[\alpha]_D^{20}$ + 17·03° (*c*, 15·7%), yield 6·1 g; IR (smear): OH 3450 cm^{-1}, C=O 1735 cm^{-1}, OAc

1248 cm⁻¹; PMR: two –C(Me)– (3H, s, 0·96 ppm; 3H, s, 1·08 ppm), two Me–C(OH)– (6H, s, 1·16 ppm), CH_2OAC (2H, m, 4·00 ppm). (Found: C, 67·33; H, 10·53. $C_{11}H_{22}O_3$ requires: C, 67·25; H, 10·35%).

The above hydroxy acetate (3·0 g) was refluxed with 10% ethanolic NaOH (10 ml) for 3 h and worked up to furnish a product (2.4 g) which solidified (m.p. 70–73°). This was recrystallised from light petroleum to furnish feathery needles (2.46 g), m.p. 73–74°, $[\alpha]_D^{20}$ + 39.04° (*c*, 6·2%); IR (Nujol): OH 3290–3220, 1165, 1032 cm⁻¹; (Found: C, 70·01; H, 11·72. $C_{10}H_{20}O_2$ requires: C, 69·72; H, 11·70%).

(–) - *Dihydrochrysanthemolactone* (**6**). Jones reagent (*vide supra*) was added dropwise, with stirring, to a soln of the above diol (1·55 g) in acetone (15 ml), at 10–12°, till an excess persisted (5 ml of reagent). After stirring for 2 h at this temp, the excess reagent was destroyed by addition of a few drops of isopropanol. The mixture was diluted with water (25 ml) and worked up with ether (25 ml, 10 ml × 2) to furnish a waxy solid (1·52 g). This was heated with 10% NaOH aq (10 ml) on a steam bath for 1/2 h, cooled, diluted with water (10 ml) and extracted with ether (15 ml × 2) to remove a neutral fraction (0·187 g, not investigated). The aq NaOH portion was acidified (10% H_2SO_4 aq, 6 ml) and the product taken up in toluene (15 ml, 10 ml × 3). To the toluene soln, *p*-toluenesulphonic acid (50 mg) was added and the whole refluxed (1 h, Dean–Stark apparatus). After cooling, the toluene soln was washed with 10% Na_2CO_3 aq (10 ml), brine and dried (Na_2SO_4). Toluene was removed to furnish a solid (1·132 g, m.p. 80–83°). This was recrystallised from light petroleum to furnish **6** as feathery needles (0·95 g), m.p. 83–84°, $[\alpha]_D^{20}$ – 77·24° (*c*, 4·35%); IR (Nujol): C=O 1720 cm^{-1}. PMR: two –C(=O)–Me (3H, s, 1·03 ppm; 3H, s, 1·21 ppm), two –C(=O)–Me (3H, 1·29 ppm; 3H, s, 1·40 ppm). (Lit.[2]: m.p. 83°; $[\alpha]_D^{23}$ – 72°, $CHCl_3$; IR C=O 1720 cm^{-1}).

(+)-trans-*Chrysanthemic acid* (**1**). Chrysanthemolactone (208 mg) was refluxed for 15 min with NaOH (218 mg) in diethylene glycol (10 ml). After distilling off 7 ml of the solvent, the mixture was heated at 225–230° for 5 h. It was diluted with water (15 ml) and extracted with ether (10 ml) to remove the neutral portion (14 mg). The alkaline portion was acidified with 10% H_2SO_4 aq (2·5 ml) and extracted with ether (10 ml × 3) which was washed with brine (10 ml × 4) and dried (Na_2SO_4). Removal of solvent furnished the acid (182 mg) as a colourless liquid. This was taken up in C_6H_6 (0·5 ml) and filtered through a column (30 cm × 1·3 cm) of silica gel. Elution with 0·2% AcOH in C_6H_6 (200 ml) furnished the required acid (130 mg) which was transformed to its methyl ester (130 mg) with an ethereal soln of diazomethane. The methyl ester was distilled: b.p. (bath) 120–125°/5 mm); GLC (temp 120°; H_2 flow 60 ml/min) purity better than 95%. $[\alpha]_D^{27}$ + 13·27° (*c*, 3·18%) (Lit:[18] $[\alpha]_D^{20}$ + 20·74°), IR (smear): C=O 1730 ⁻¹, PMR:[19a] two –C(Me)– (3H, s, 1·12 ppm; 3H, s, 1·23 ppm), two C=C–Me (6H, s, 1·70 ppm), COOMe (3H, s, 3·62 ppm), C=CH (1H, d, 4·86 ppm).

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