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Novel synthesis of (*d*,*l*) *trans*-chrysanthemic acid involving a β-diketone fragmentation

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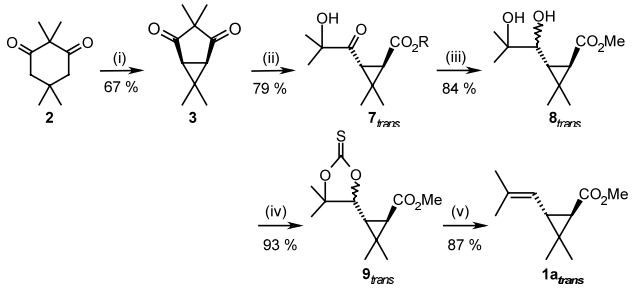
Abstract—Methyl (*d*,*l*) *trans*-chrysanthemate as well as its *cis*-diastereoisomer have been prepared from dimethyl dimedone, one of their isomers, in a few steps and with complete control of the relative stereochemistry.

We report a novel synthesis, from dimethyl dimedone **2**, of the methyl ester $\mathbf{1a}_{trans}$ of (*d*,*l*) *trans*-chrysanthemic acid, a constituent of pyrethrin I, a natural insecticide (Scheme 1).

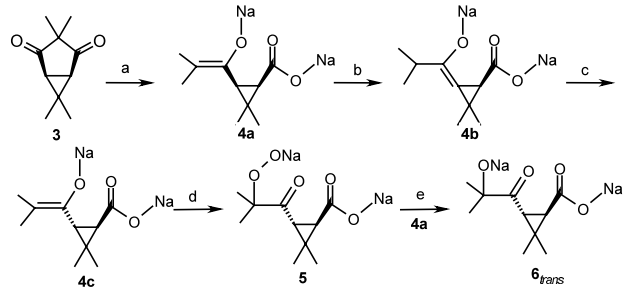
This transformation takes advantage of the easy oxidative cyclisation of **2** to the bicyclic 1,3-diketone **3** ([i] *t*-BuOK, THF, −78°C, [ii] Br_2, pentane, 67%)[1] and the unexpectedly high propensity of the latter to produce the δ-hydroxy-γ-keto-carboxylic acid $\mathbf{7}_{trans}$ on reaction, performed in air, with sodium hydroxide in DMSO and acid quench ([i] 6 equiv. NaOH, DMSO/H_2O: 4/1, 70°C, 14 h, air [i] H_3O^+, 79% yield).

The transformation of $\mathbf{7}_{trans}$ to methyl chrysanthemate $\mathbf{1a}_{trans}$ was then readily achieved, via its methyl ester (CH_2N_2, Et_2O, 0°C, 100%) on reduction to the corresponding diol $\mathbf{8}_{trans}$ ($NaBH_4$, MeOH, 0°C, 3 h, 84%) and subsequent Corey–Winter olefination[3] ([i] S=C(imid.)$_2$, toluene, reflux, 4.5 h, 93% yield of $\mathbf{9}_{trans}$, [ii] $P(OMe)_3$, 120°C, 24 h, 87% yield of $\mathbf{1a}_{trans}$).

The transformation of **3** to $\mathbf{5}_{trans}$ reported above, involves in the same pot an exceptional succession of individual steps such as (i) 1,3-diketone fragmentation (Scheme 2, step a),[2] (ii) enolate isomerisations (Scheme 2, steps b and c) which finally lead to *cis*–*trans* isomerisation on the cyclopropane ring and last but not least (iii) an unusually high propensity of the *trans*-isopropylidene enolate to be oxidised by the oxygen dissolved in the DMSO (Scheme 2, steps d and e).



Scheme 1. (i) (a) *t*-BuOK, THF, −78°C to 40°C, (b) Br_2, pentane, 40°C, 1 h, (ii) (a) 6 equiv. NaOH, DMSO/H_2O (4/1), O_2, 70°C, 14 h, (b) H_3O^+, (iii) (a) CH_2N_2, Et_2O, 0°C, (b) $NaBH_4$, MeOH, 0°C, 3 h, (iv) S=C(imid.)$_2$, toluene, reflux, 4.5 h, (v) $P(OMe)_2$, 120°C, 24 h.



Scheme 2.

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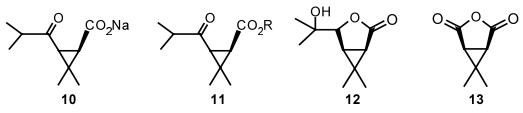


Figure 1.

The related potassium enolate is much less sensitive to such an oxidation, since potassium hydroxide instead leads, under identical conditions, to the γ-keto acid $\mathbf{11}_{trans}$ (R = H) in very good yield (84%, $\mathbf{11}_{trans}/\mathbf{7}_{trans}$: 94/6, Fig. 1).† The δ-hydroxy-γ-keto-carboxylic acid $\mathbf{7}_{trans}$ can be nevertheless produced in almost quantitative yield if the reaction is carried out under a slight pressure of oxygen (6 equiv. KOH, oxygen, DMSO/H_2O: 4/1, 70°C, 14 h, [ii] H_3O^+, 98%).

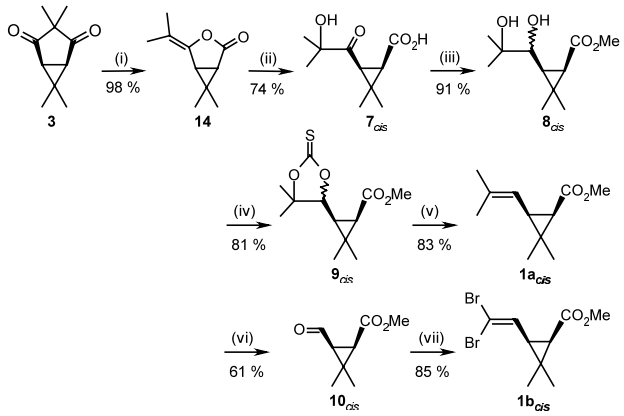
All attempts to preserve on **7** or **9** (Fig. 1) the *cis*-configuration present on **3** were unsuccessful. Therefore the synthesis of methyl *cis*-chrysanthemate $\mathbf{1a}_{cis}$ and of its dibromovinyl analogue $\mathbf{1b}_{cis}$ which is part of deltamethrin, the most active pyrethroid insecticide, became a real challenge.

Oxidation of the enol lactone **14**, readily available by photochemical rearrangement of **3**[2] (Scheme 3), with *m*-CPBA (2 equiv., dioxane/H_2O: 4/1, 20°C, 3 h) directly affords the δ-hydroxy-γ-keto-carboxylic acid $\mathbf{7}_{cis}$ (R = H) in good yield (74%) with complete control of the *cis*-configuration.‡,§

Reduction of the corresponding *cis*-ester $\mathbf{7}_{cis}$ (R = Me) using sodium borohydride under the conditions described above for its *trans*-analogue, was troublesome. It requires a longer time ($NaBH_4$, MeOH, 18 h) and unfortunately yield a mixture of the desired diol $\mathbf{8}_{cis}$ and the corresponding lactone **12** (55/45 in 95% overall yield, Fig. 1).

The synthesis of the required diol $\mathbf{8}_{cis}$ can be nevertheless achieved on reduction of $\mathbf{7}_{cis}$ (R = Me) with the boron hydride–dimethyl sulfide complex ($BH_3{\cdot}SMe_2$, toluene, 0°C, 0.5 h, 91%). Its transformation to:

- Methyl *cis*-chrysanthemate $\mathbf{1a}_{cis}$ has been achieved by reduction of the corresponding thiocarbonate $\mathbf{8}_{cis}$ (S = C(imid.)$_2$, toluene, 110°C, 14 h, 81% then 1,3-dimethyl-2-phenyl-[1,3,2] diazaphospholidine, 40°C, 8 h, 83% in $\mathbf{1a}_{cis}$);[3]
- Methyl dibromovinyl *cis*-chrysanthemate $\mathbf{1b}_{cis}$ requires sequential cleavage of the diol (1.5 equiv. $NaIO_4$, MeOH, phosphate buffer, 20°C, 1 h, 61%)[4a] leading to the aldehyde **12** followed by a Wittig-type reaction using triphenyl phosphine and carbon tetrabromide (20°C, 85% in $\mathbf{1b}_{cis}$).[4]



Scheme 3. (i) *hv*, benzene, 20°C, 9 h, (ii) *m*-CPBA, dioxane/H_2O, 20°C, 3 h, (iii) (a) CH_2N_2, Et_2O, 0°C, (b) $BH_3{\cdot}Me_2S$, toluene, 0°C, 0.5 h, (iv) S=C(imid.)$_2$, toluene, reflux, 14 h, (v) 1,3-dimethyl-2-phenyl-[1,3,2]diazaphospholidine, 40°C, 8 h, (vi) (a) 1.5 equiv. $NaIO_4$, MeOH, phosphate.

The synthesis of enantiopure methyl (1*R*)-*trans*-chrysanthemate $\mathbf{1a}^*_{trans}$ requires enantioselective ring opening of **3** reminiscent of a reaction successfully performed on the related bicyclic anhydride **12**.[5] The synthesis of the (1*R*)-*cis*-cyclopropyl esters $\mathbf{1a}^*_{cis}$ and $\mathbf{1b}^*_{cis}$ requires a Norrish type I[6] enantioselective rearrangement. To our knowledge, both transformations have not yet been achieved. We are working towards these ends.

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† Lithium hydroxide produces a 1/1 mixture of $\mathbf{7}_{trans}$ and $\mathbf{12}_{trans}$ but in very poor yield (10%) even after a longer reaction time.

‡ The synthesis of $\mathbf{11}_{cis}$ has been effectively achieved from **14** and (i) lithium methylate in the presence of boron trimethylborate (6.4 equiv. each, MeOH, 20°C, 7 days, 92% yield after acid hydrolysis), (ii) barium hydroxide (aq. THF, 20°C, 1.5 h, 93% yield after acid hydrolysis), (iii) methanol in the presence of catalytic amounts of a Lewis acid (cat. *p*-TSA, toluene/MeOH: 10/1, 110°C, 24 h, 72% yield).

§ Reaction of **14** with sodium hydroxide (6 equiv. NaOH, aq. DMSO, 70°C, 1 h) or lithium methylate in methanol (1 equiv. MeOLi, MeOH, 20°C, 6 h) did not provide the *cis*-stereoisomer $\mathbf{9}_{cis}$: (90% of $\mathbf{9}_{trans}$ *cis*/*trans* 00/100 and 81% of **9**, *cis*/*trans* 71/29, respectively).