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A TOTAL STEREOSPECIFIC SYNTHESIS of d,l CIS and d,l TRANS CHRYSANTHEMIC ESTERS[1]

M. Sevrin, L. Hevesi and A. Krief

Facultés Universitaires Notre-Dame de la Paix
Department of Chemistry, 61, rue de Bruxelles
B-5000 - Namur (Belgium)

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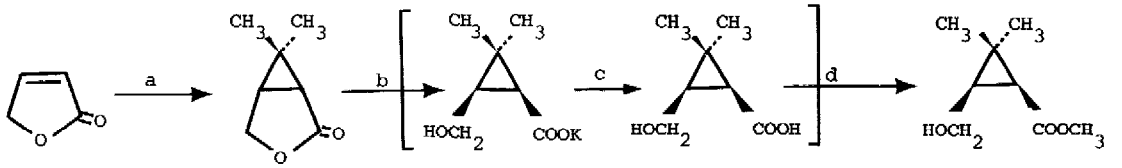
In this paper we describe convenient stereospecific syntheses of both trans 2a and cis 2b 2,2-dimethyl-3-formyl cyclopropane carboxylic esters which are the key intermediates in the synthesis of natural *trans* 1a and unnatural *cis* 1b chrysanthemic acids and also their analogs, constituants of pyrethrins and cinerins [2,3a]. Although the trans isomer is a powerful insecticide, Elliott[3b] suggested that the cis series exhibits even higher insecticidal activities.
The synthesis of cis pyrethric acid was achieved by *Julia's group*[4] and the cis-2,2-dimethyl-3-formyl cyclopropane carboxylic acid, which is an intermediate in the elegant isomerisation of the unnatural [1(S), 3(S)] chrysanthemic acid epimer to the natural one [1(R), 3(R)], was already described by the *Roussel Uclaf group*[5].

The methodology we applied is similar to that reported in the accompanying paper[2]; isopropylidene dimethyl sulfurane is used as the cyclopropanation agent [2b] on suitably activated carbon-carbon double bonds. May we point out that Corey[6] has already described one synthesis of trans chrysanthemic acid from isopropylidene diphenyl sulfurane.

1) *Cis methyl 2,2-dimethyl 3-hydroxymethyl cyclopropane carboxylate 6 : first synthesis*

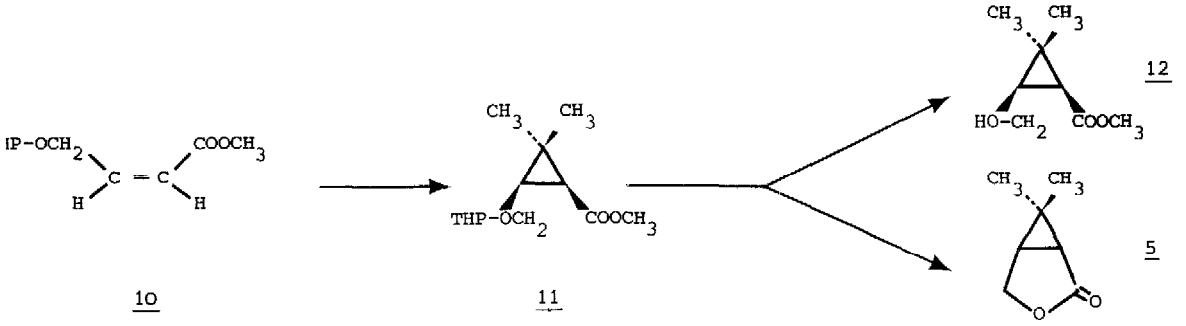
α-Butenolide 4 (readily available from butyrolactone)[7], when reacted with isopropylidene diphenyl sulfurane[6] leads to the bicyclic lactone 5[8] (1.3 equiv., DME, -78°C, 2hrs, 79%) which is in turn readily transformed into methyl 2,2-dimethyl-3-hydroxymethyl cyclopropane carboxylate 6 in 55% yield by *the one pot* transformation described below : (a. KOH/methanol, 2N, 1.5 eq., reflux 2hrs - b. removal of the methanol - c. acidification to pH 6:HCl/ethylacetate, 0°C - d. excess diazomethane until a persistent yellow colour).



4 5 6

2) *Cis methyl 2,2-dimethyl, 3-hydroxymethyl cyclopropane carboxylate* 6 : *second synthesis*

On reaction with isopropylidene diphenyl sulfurane, the methyl 4-(tetrahydropyranyl-2-ox) 2Z butenoate 10 (easily available from propargyl alcohol)[9] leads to the stereospecific formation of the cis cyclopropane derivative 11 (DME, -78°C, 2hrs; 20°C, 1hr; 80 % yield, rf. 0.59, SiO_2, ethyl acetate/benzene : 3/97). The tetrahydropyranyl blocking group in 11 is removed in a dilute acidic medium (perchloric acid 10^{-2}N aqueous solution in THF, 25°C, 80hrs, 83% yield). Care must be taken to neutralize the acid before work-up; use of a more concentrated acidic solution leads to a mixture of the desired compound 12 and the bicylic lactone 5. The latter is recovered in 80% yield when a perchloric acid 2N aqueous solution in THF is used (24 hrs, 25°C). This last transformation confirms the cis stereochemistry in compounds 10 and 11. The cis stereospecific addition of isopropylidene diphenyl sulfurane to cis and trans activated olefins was already described by Corey [6].

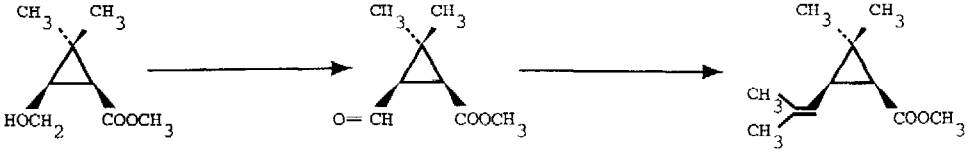


10 11 12 5

3) *Synthesis of cis chrysanthemic ester*

Interestingly the desired cis aldehyde [10] 2b *is formed in good yield from alcohol* 12 *by* use of the Collin's reagent [11] (CrO_3/bipyridine, celite, CH_2Cl_2 - 10°C : 45 mn, 20°C:15 mn; 73% yield) or by the Corey - Suggs reagent (CrO_3/pyridine/HCl - CH_2Cl_2, 0°C, 10 mn; 20°C, 2hrs; 63% yield)[12]. No trace of the trans isomer 2a can be detected by NMR.

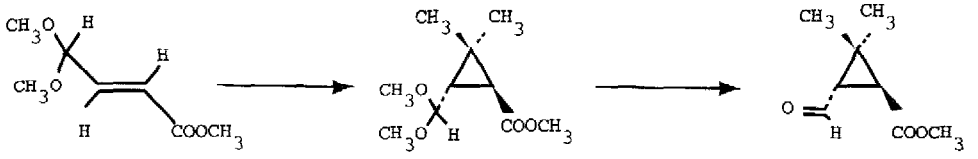
Finally, cis methyl chrysanthemate[10] 1b is stereospecifically formed using isopropylidene triphenyl phosphorane in DME (0°C, 10 mn; 25°C, 0.5 hr; 50% yield).



12 2b 1b

4] *Trans methyl 2,2-dimethyl-3-formyl cyclopropane carboxylate 2a*

Isopropylidene diphenyl sulfurane was also reacted with methyl 4,4-dimethoxy-2-butenoate 13[2a] and produced the corresponding trans methyl 2,2-dimethyl-3-(dimethoxy methylene) cyclopropane carboxylate 14, in 82% yield, identical to an authentic sample[2].



13 14 2a

As the transformation of compound 14 to trans chrysanthemic acid 1a, its analogs and pyrethric methyl ester have already been described both by us[2] and others[3], the synthesis we propose is thus a new total synthesis of these compounds.

Finally, this paper reports the first total stereospecific synthesis of cis chrysanthemic esters as well as their trans analogs. We have also described the reaction of a sulfur ylid with an α,β-unsaturated lactone and to our knowledge, this is the first example of such a reaction.

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References

1) First report of this work has been done by M. Sevrin "Mémoire de licence" - Faculté Notre-Dame de la Paix - June 1975

2a) M.J. Devos, L. Hevesi, P. Bayet and A. Krief, see accompanying paper

b) Isopropylidene triphenyl phosphorane fails to produce any chrysanthemic acid, when reacted with compounds 4 or 10.

3a) J. ApSimon, "The total synthesis of natural products", John Wiley and Sons, N.Y., vol.2, 1973

b) M. Elliott, A.W. Farnham, N.F Janes, P.H. Needham and D.A. Pullman, Nature, 248, 710 (1974)

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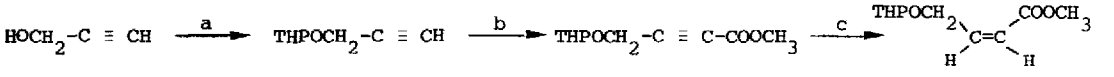
5) L. Velluz, J. Martel and G. Nominé, C.R. Acad. Sci. Fr. (C), 268, 2199 (1969)

6) E.J. Corey and M. Jautelat, J. Amer. Chem. Soc., 89, 3913 (1967)

7) Organic Syntheses Coll. Vol. V, 255 (1973)

8) The spectroscopic data are identical to those described by M. Franck Neuman, Angew. Chem. Int. Ed., 7, 65 (1968)

9) Prepared as follows :



7 8 9 10

a) Dihydropyran 1.5 eq., P.T.S.A.; 0°C, 20 hrs - b) 1, $NaNH_2$(ether) - 2,$ClCO_2CH_3$

c) Prehydrogenated Pd/$BaSO_4$/quinoline $(CH_3CO_2C_2H_5)/H_2$

10) Identical with an authentic sample kindly provided by Dr. J. Martel, Roussel Uclaf (France)

11) J.C. Collins, W.W. Hess and F.J. Frank, Tet. Letters, 3363 (1968)

12) E.J. Corey and J.W. Suggs, Tet. Letters, 2647 (1975)