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A NEW DESIGN FOR THE SYNTHESIS OF CHRYSANTHEMIC ESTERS AND ANALOGS AND FOR THE "PEAR ESTER" SYNTHESIS [1]

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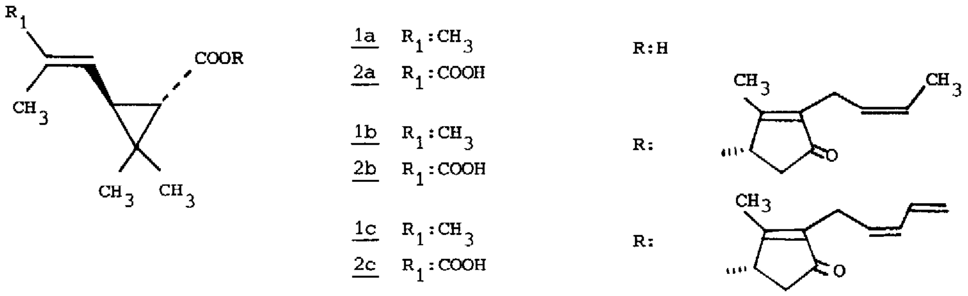
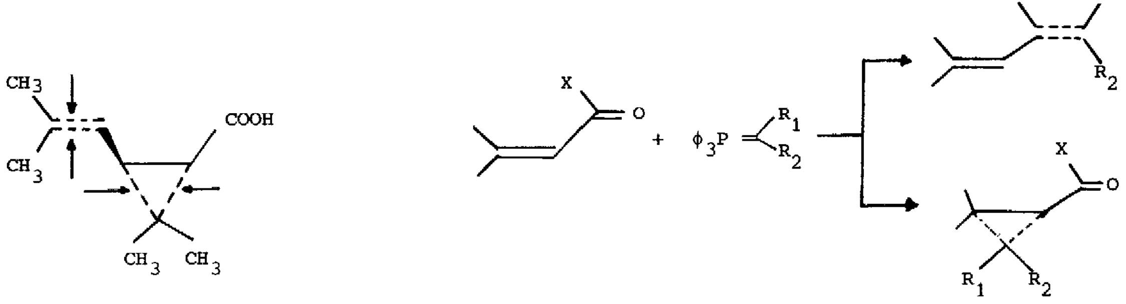
The increasing interest in chrysanthemic acid 1a, a constituent of natural pyrethrins 1b,2b and cinerins 1c, 2c is probably due to the fact that *Chrysanthemium Cinerariifolium* (from which they are extracted) is not easily available now and also because of their growing use as domestic insecticides. Several syntheses of trans chrysanthemic acid have appeared in the literature [2] and some of them are already used on an industrial scale [3].

SCHEME I



From the application of the *"synthetic methodology* [4] *principles"* and their "disconnective routes" it can be deduced that chrysanthemic acid *can arise* from two isopropylidene moieties (Scheme II).

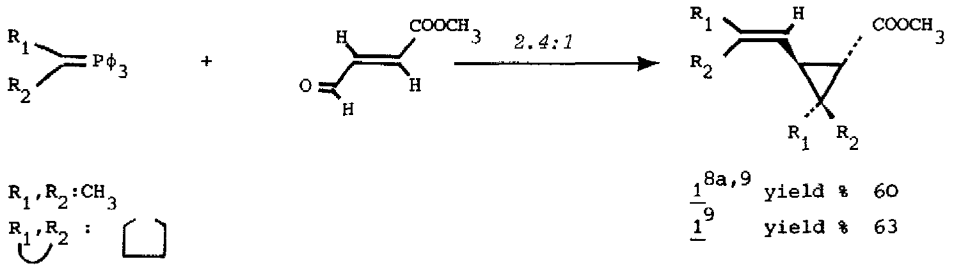
SCHEME II



We chose the readily available (by ozonolysis of sorbic esters > 80% yield)[5] *methyl or ethyl 4-oxobutenoate as the starting material and phosphorus ylids as their complementary powerful partner, because of their known propensity, to add in a 1-2 manner to a carbonyl group*[6] *and in a 1-4 fashion to some conjugated systems*[7]*, they then lead respectively to an olefin and a cyclopropane ring (Scheme II).*

In fact, we found that trans methyl chrysanthemate 1 is obtained stereospecifically[8a,9,10] in more than 60 % yield *by simply mixing* THF solutions of methyl trans 4-oxobutenoate (1 equivalent) and isopropylidene triphenyl phosphorane (2.4 equivalents) (-78°C, 5 min; -10°C, 1hr; 20°C, 5hrs) (stereospecificity > 98%) (Scheme III).

SCHEME III

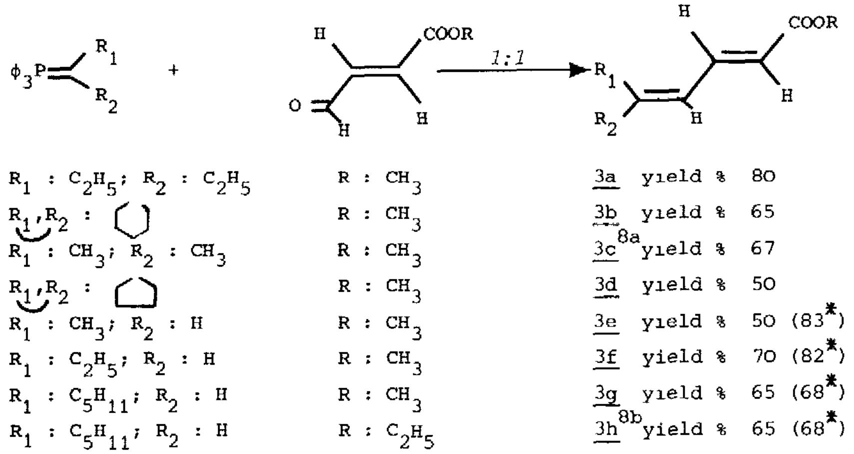


$R_1,R_2 : CH_3$ — $1^{8a,9}$ yield % 60

R_1,R_2 : — 1^{9} yield % 63

In this case, the ylid reacts both on the carbonyl of the aldehyde and on the activated carbon-carbon double bond. This is also the case for the cyclopentylidene triphenyl phosphorane which gives rise to the chrysanthemic ester analog[9] in 63% yield under the same experimental conditions Other dialkylmethylene triphenyl phosphoranes, including the closely related 3-pentylidene triphenyl phosphorane or cyclohexylidene triphenyl phosphorane, failed to produce the corresponding chrysanthemate analogs even under forced reaction conditions. Nevertheless, in the two last cases the corresponding dienoic esters[9] are obtained in good yield (see 3a, 3b : Scheme IV).

SCHEME IV



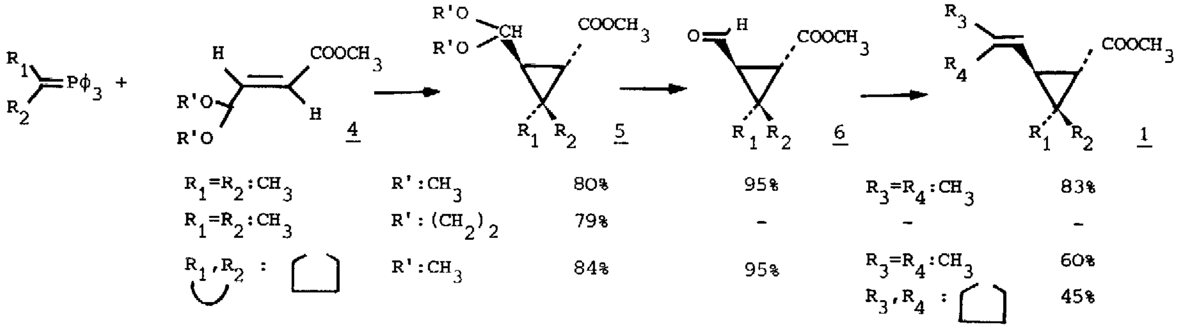
$R_1 : C_2H_5$; $R_2 : C_2H_5$	$R : CH_3$	3a yield % 80
R_1,R_2 :	$R : CH_3$	3b yield % 65
$R_1 : CH_3$; $R_2 : CH_3$	$R : CH_3$	3c[8a] yield % 67
R_1,R_2 :	$R : CH_3$	3d yield % 50
$R_1 : CH_3$; $R_2 : H$	$R : CH_3$	3e yield % 50 (83*)
$R_1 : C_2H_5$; $R_2 : H$	$R : CH_3$	3f yield % 70 (82*)
$R_1 : C_5H_{11}$; $R_2 : H$	$R : CH_3$	3g yield % 65 (68*)
$R_1 : C_5H_{11}$; $R_2 : H$	$R : C_2H_5$	3h[8b] yield % 65 (68*)

* refers to the percentage of 4Z isomer.

The dienoic esters 3 are also obtained (see 3a → 3d Scheme IV) when methyl or ethyl 4-oxobutenoat (E) is reacted with *only one* equivalent of various dialkylmethylene triphenyl phosphoranes (THF, 0°C, 0.5 hr; 25°C, 2 hrs). This suggests that *in the total synthesis of chrysanthemic ester proposed in Scheme III, the ylid reacts first on the conjugated aldehyde in a 1-2 mode*[11]. When one equivalent of monoalkylmethylene triphenyl phosphorane is reacted, a large proportion of 2E, 4Z isomer is then formed. By use of the appropriate ylid, ethyl 2(E), 4(Z) decadienoate 3h (a part of the odoriferous principle of *Bartlett pears*) is obtained [8b,9] in 63 % purified yield (70% of the 2(E), 4(Z) isomer).

On the other hand, by only a slight modification of our synthesis described in Scheme II, we propose the first total and straightforward synthesis of methyl 2,2-dimethyl-3-formylcyclopropanecarboxylate 6. Up to now, this compound has only been prepared by ozonolysis of the chrysanthemic ester 1. This compound could then be regarded as the key intermediate for the synthesis of pyrethric acid [2a] 2a and chrysanthemic acid as well as their diversely substituted analogs. Thus, we found that isopropylidene triphenyl phosphorane as well as cyclopentylidene triphenyl phosphorane react in a 1-4 manner with methyl trans 4-oxobutenoate in which the aldehyde is blocked as an acetal [5], giving rise to highly functionalized cyclopropane derivatives in high yield (Scheme V). The hydrolysis of the acetal moiety in 5 produce the desired aldehyde in quantitative yield (THF, $HClO_4$ 3n aqueous solution, 0°C, 3 hrs)[8a,9].
Further reaction of the aldehyde with a phosphorus ylid leads to the formation of the chrysanthemic esters or chrysanthemic ester analogs in good yield (Scheme V)[8a,9,10].

SCHEME V



$R_1=R_2:CH_3$	$R':CH_3$	80%	95%	$R_3=R_4:CH_3$	83%
$R_1=R_2:CH_3$	$R':(CH_2)_2$	79%	-	-	-
R_1,R_2 :	$R':CH_3$	84%	95%	$R_3=R_4:CH_3$	60%
				R_3,R_4 :	45%

An industrial synthesis of chrysanthemic acid (i.e. Scheme II) could take advantage of the known reduction of triphenyl phosphine oxide (one of the by-products of the reaction) to triphenyl phosphine. Work is actually in progress to induce asymmetric synthesis of the cyclopropane ring.

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8) Compared with an authentic sample kindly provided by
   a) Dr. Martel, Roussel Uclaf (France)
   b) Dr. Pawlak, Firmenich (Switzerland) - M.Pawlak and G.Ohloff, Helv.Chim.Acta,56,1176(1973)

9) Refers to the yield of the purified compound IR, UV, NMR, Mass Spectra and exact mass data agree with the proposed structures.

10) Hydrolysis (KOH/methanol of the crude mixture) permits the easy separation of the phosphorus residue from the potassium chrysanthemate.

11) Surprisingly, methyl 5-methylhexadienoate does not produce any methyl chrysanthemate in reactions with isopropylidene triphenyl phosphorane, suggesting that, during the reaction described in Scheme II, the second equivalent of isopropylidene triphenyl phosphorane reacts on the betaine: