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NEW STEREOSPECIFIC SYNTHESIS OF CIS AND TRANS d,l-CHRYSANTHEMIC ESTERS AND ANALOGS VIA A COMMON INTERMEDIATE

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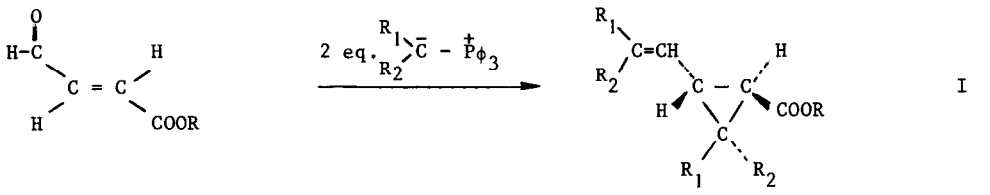
We have recently presented [1] new strategy for the synthesis of trans chrysanthemic acid and for hemicaronic aldehyde by reaction of phosphorus ylids on methyl oxobutenoate or on the corresponding acetal



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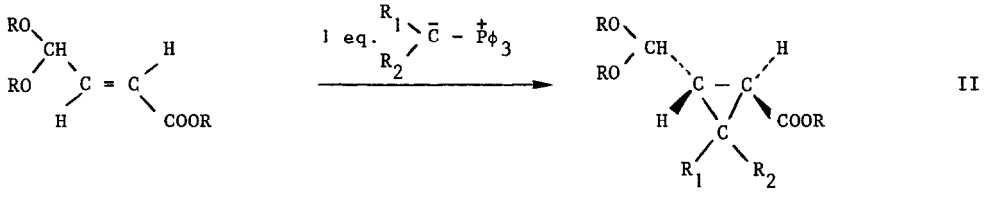


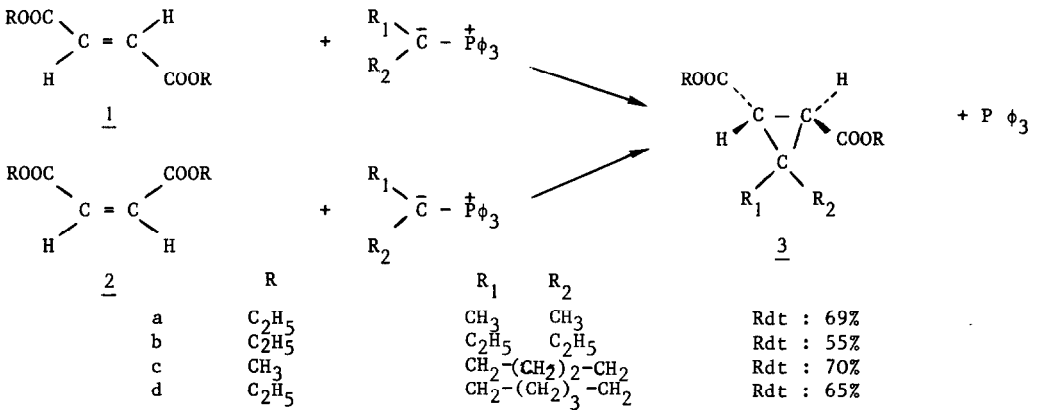
II

These reactions allow, by the proper choice of the Wittig reagent, the synthesis of chrysanthemic analogs identically (route I) or diversely (route II) substituted on the C-C double bond and on the cyclopropane ring.

However, we found [1] that both reactions work nicely only in the case of isopropylidene triphenyl phosphorane or cyclopentylidene triphenyl phosphorane but not for higher homologs such as the closely related 3-pentylidene and cyclohexylidene triphenyl phosphoranes.

We present here new methods [2,3] which allow the stereospecific synthesis of trans and cis series of chrysanthemic ester and analogs even those which were not accessible by our previous method.

The key step is the high yield stereoselective synthesis of trans cyclopropane 1,2 dicarboxylate from fumaric 1 or maleic 2 diester and phosphorus ylids.

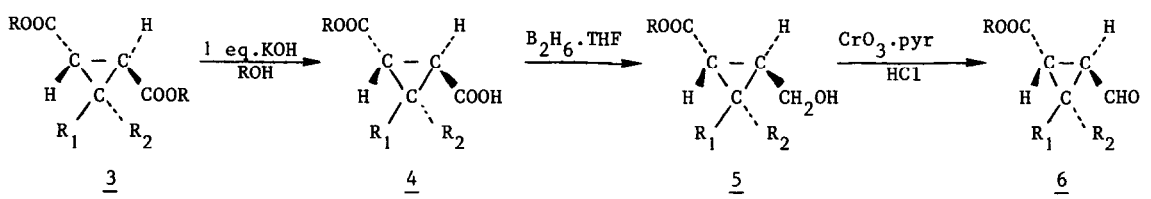


Thus 2-propylidene, 3-pentylidene, cyclopentylidene and cyclohexylidene triphenyl phosphoranes, prepared from the corresponding phosphonium salts and n butyl lithium in THF or DME, react at room temperature (for 2 hrs) on dimethyl or diethyl fumarate producing the corresponding trans cyclopropane 1,2-dicarboxylate and triphenyl phosphine [4].

Under the same experimental conditions, the more easily available and lower priced maleate analogs produce also exclusively the trans cyclopropane 1-2 dicarboxylate. This reaction of phosphorus ylids is entirely stereoselective (100%) whereas the reaction of closely related isopropylidene diphenyl sulfurane with the same esters is moderately stereospecific (100% with fumarate, 60% with maleate) [5].

From these easily available cyclopropane derivatives, we succeed the specific differentiation of one of the two carboalkoxy groups in order to produce specifically trans or cis 1-carboalkoxy 2-formyl cyclopropanes from which chrysanthemic analogs can be prepared without any loss of stereochemistry [6].

In the trans series, the trans 1,2-dicarboalkoxy cyclopropanes are readily transformed to trans 1-carboalkoxy 2-carboxy cyclopropanes 4 by refluxing in KOH/methanol or ethanol for 3 hrs then removal of the alcohol and acidification. The acid function is in turn specifically reduced [8] to the corresponding alcohol by reaction with an excess of borane/THF [8] or borane/dimethyl sulfide [9] leading to 5 in high yield without concomittant reduction of the ester group. The desired trans 1-carboalkoxy 2-formyl cyclopropanes 6 are then obtained by oxydation of the hydroxyl group by Collins reagent [10] or better by the readily available Corey Suggs reagent [11].



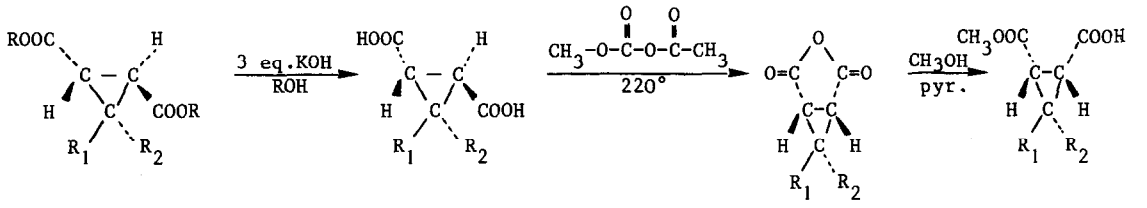
R	R_1	R_2	Yield in 4[a]	Yield in 5[b]	Yield in 6[c]
C_2H_5	CH_3	CH_3	72%	70%	66%
C_2H_5	C_2H_5	C_2H_5	75%	94%	77%
CH_3	$CH_2-(CH_2)_2-CH_2$		65%	81%	64%
C_2H_5	$CH_2-(CH_2)_3-CH_2$		84%	79%	71%

(a) 4 is obtained by refluxing 3 for 3 hrs with 1.3 eq. of KOH in methanol or ethanol (solution 2.5 M of KOH in alcohol)

(b) 4 eq. of a molar solution of B_2H_6 in THF[12] is added to a solution 2.5 M of 4 in THF dropwise at 20°C. The resulting solution is stirred at 20° for additionnal 3 hrs. then hydrolysed

(c) as described by Corey and Suggs[11]

The cis series is specifically prepared by essentially the same route from the cis 1-carboalkoxy 2-carboxy cyclopropanes 9 readily available by the sequence outlined below.



3 7 8 9

RESULTS

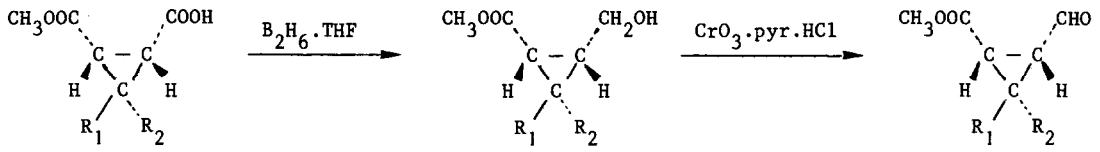
R	R_1	R_2	Yield in 7[d]	Yield in 8[e]	Yield in 9[f]
C_2H_5	CH_3	CH_3	90%	76%	100%
C_2H_5	C_2H_5	C_2H_5	95%	71%	84%
CH_3	$CH_2-(CH_2)_2-CH_2$		65%	61%	-
C_2H_5	$CH_2-(CH_2)_3-CH_2$		96%	69%	84%

(d) 7 is obtained by refluxing 3 for 20 hrs with 3 eq. of KOH in methanol or ethanol solution (7.5 M of KOH in alcohol)

(e) heating 7 at 220° for 6 hrs in a sealed tube with 6 eq. of acetic anhydride affords 8. Nevertheless, pure 8 was obtained by hydrolysis of the crude product (H_2O), purification (charcoal, reflux 3 hrs) leading to the pure 1,2 dicarboxylic cyclopropanes which by treatment with acetyl chloride (2eq.-2hrs at 40°C) restitute 8 in high yield.

(f) 9 is obtained by reaction at room temperature for 16 hrs of a molar solution of anhydride 8 in methanol with catalytic amount of pyridine.

The trans carboalkoxy cyclopropanes 3 are transformed in quantitative yield to the corresponding trans diacids 7 (3 eq. KOH in alcohol, at reflux for 20 hrs then acidification) which are cyclised to the cis anhydrides 8 by heating with acetic anhydride [13]. The anhydrides are further opened to the cis 1-carboalkoxy 2-carboxy cyclopropanes from which cis hemicaronic aldehydes 11 are stereospecifically obtained by the same sequence as used in the trans series.



9 10 11

RESULTS

R_1	R_2	Yield in 10	Yield in 11
CH_3	CH_3	94%	63%
C_2H_5	C_2H_5	65%	73%
$CH_2-(CH_2)_3-CH_2$		91%	78%

Further transformation of the trans or cis hemicaronic aldehydes (6 and 11) by the proper Wittig reagent including 2-propylidene, 3-pentylidene[14], cyclopentylidene and cyclohexylidene triphenyl phosphoranes affords the trans or cis chrysanthemic esters and analogs [6].

References

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3. French Patent, A. Krief and Roussel Uclaf, Number 1771, 30/02/1976
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6. The construction of the carbon carbon double bond (from 6 or 11 by Wittig reaction) will not be discussed in this preliminary report because it has been already done by us and others. For the trans series see our reference 1, for the cis series see our reference 7.
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10. J.C. Collins, W.W. Hess and F.J. Frank, Tet. Lett., 3363 (1968)
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