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From grape to grape: novel stereoselective syntheses of chiral pyrethroids – synthesis of the most potent commercially available insecticides

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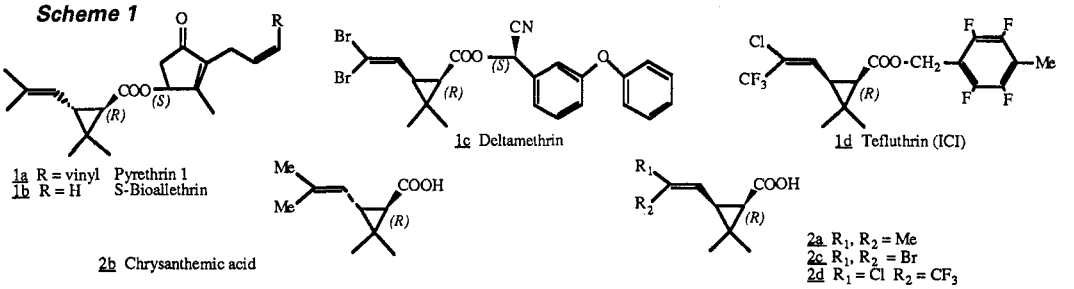
ABSTRACT. We report novel stereo- and enantioselective routes to vinyl cyclopropane carboxylic esters.

S-bioallethrin [1a,b] 1b, deltamethrin [1a-d] 1c and tefluthrin [1e,f] 1d are valuable insecticides, commercially available for domestic and agricultural uses against flying and soil insects respectively. These are unnatural esters of 2,2-dimethyl-3-vinyl cyclopropane carboxylic acids 2 which all belong to the (1R)-series. But whereas the former derivative possesses the trans-stereochemistry found in the natural pyrethrin I 1a, the others possess a cis-relationship. The structure of 2d is clearly the most complex since it possesses in addition to the highly substituted cyclopropane ring with the cis-stereochemistry, a highly functionalized (E)-carbon-carbon double bond. In fact it does not exist an enantio- or a stereoselective synthesis of such a compound.[1e]

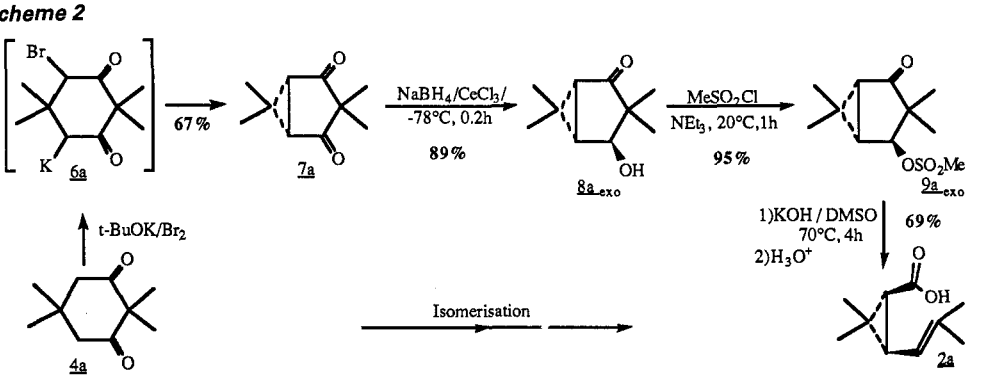
Scheme 1



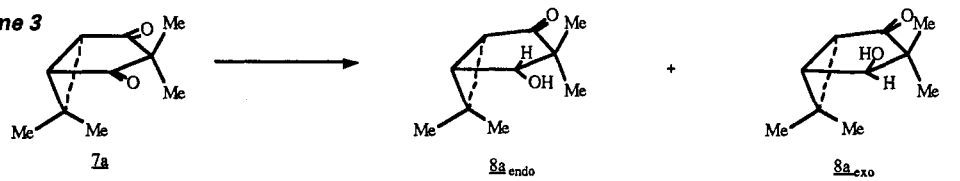
We have designed as a model a novel stereoselective synthesis of (d,l)-cis-chrysanthemic acid 2a which uses cheap reagents compatible with industrial requirements and which we hope can be further applied to the enantio- and stereoselective synthesis of 1(R)-2d.

2,2,5,5-Tetramethyl cyclohexa-1,3-dione [2] 4a, readily prepared by di-methylation of dimedone 3a (4 equiv. K_2CO_3, EtOH-H_2O, 2.5 equiv. MeI, 70°C, 4h, 63% yield),was chosen as the starting material since it possesses not only the same formula as chrysanthemic acid 2a ($C_{10}H_{16}O_2$) but also the carbon framework and the functionalities placed in suitable positions to allow in a minimum of steps the functional group modifications required for the desired transformation. The key steps of this process are without doubt (i) the cyclopropanation reaction which produces the bicyclo [3.1.0] hexa-2,4-dione [3] 7a and (ii) the Grob fragmentation [4] which was achieved on the mesylate 9a resulting from its reduction-sulfonation. The stereochemical outcome of each individual step proved as expected particularly important for the success of the whole process shown in the Scheme 2.

Scheme 2



Scheme 3



7a 8a endo 8a exo

Reagent	Conditions	Overall Yield	Ratio 8a/8b
1mol. equiv. $NaBH_4$	Methanol, 20°C	89%	80/20
1mol. equiv. $NaBH_4$ / 1mol. equiv. $CeCl_3$	Methanol, 20°C	88%	22/78
1mol. equiv. $NaBH_4$ / 1mol. equiv. $CeCl_3$	Methanol, -78°C	85%	0/100
1mol. equiv. $NaBH_4$ / 0.5 mol. equiv. $CeCl_3$	Methanol, -78°C	81%	23/77

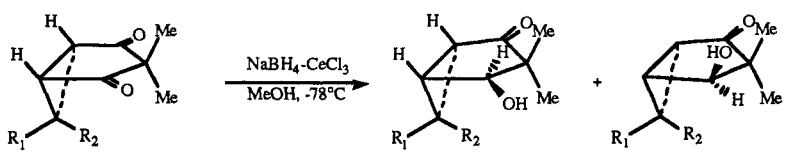
The synthesis of the 2,2,5,5-tetramethyl-bicyclo [3.1.0] hexa-2,4-dione 7a was efficiently achieved (67% yield) from 2,2,5,5-tetramethyl-cyclohexa-1,3-dione 4a on sequential reaction with potassium tert-butoxide (2.2 equiv. in THF from -78°C to +40°C) and bromine (1.6 equiv. in pentane, +40°C, 1h). This one pot transformation offers an original solution to our problem since the 6-bromo-4-potassio-2,2,5,5-tetramethyl-cyclohexa-1,3-dione 6a intermediary formed is immediately cyclized under these conditions rather than to further react with bromine. This avoids the difficulties we encountered when the transformation was performed stepwise.[3]

The chemoselective mono-reduction of this bicyclic dione was achieved by a large array of hydrides [5,6] (Scheme 3) but most of the reactions delivered exclusively or mainly the endo alcohol $8a_{endo}$ resulting from the attack of the bicyclic diketone from the less hindered face. Unfortunately however this alcohol proved to be unsuitable for further transformation since it is too hindered and none of the conditions which we tried allowed its transformation to the corresponding sulfonate, the starting material on which be Grob fragmentation is expected to take place.[4]

After different unsuccessful essays we have found that a dramatic change in the exo/endo ratio was achieved when the reaction is carried out with $NaBH_4$ in methanol but in the presence of cerium trichloride.[7,8] Interestingly an exclusive endo attack leading to $8a_{exo}$ was observed when the reaction is carried out at low temperature (-78°C). This reversal of regioselectivity was accounted from a pre-complexation by $CeCl_3$ of the bicyclic diketone 7a from its less hindered exo-face and reaction of the hydride from the endo face of the complexed diketone. Therefore the presence of the endo methyl group should be crucial for the stereoselective reduction since its role is to hinder the endo-face allowing thus a more complete discrimination between the two faces of the bicyclic-diketone 7a by $CeCl_3$.

We have in fact found, in accordance with this hypothesis, that **(i)** the reduction with $NaBH_4$-$CeCl_3$ of the bicyclic diketones 7b and 7c missing the endo methyl group is less selective than the previous one and **(ii)** a very high selectivity related to the one found in 7a and leading to the exo-alcool $8d_{exo}$ is observed when the bicyclic diketone 7d possessing an endo methyl group is reacted with the same reducing system (1 equiv. $NaBH_4$, 1 equiv. $CeCl_3$, MeOH, -78°C) (Scheme 4).

Scheme 4

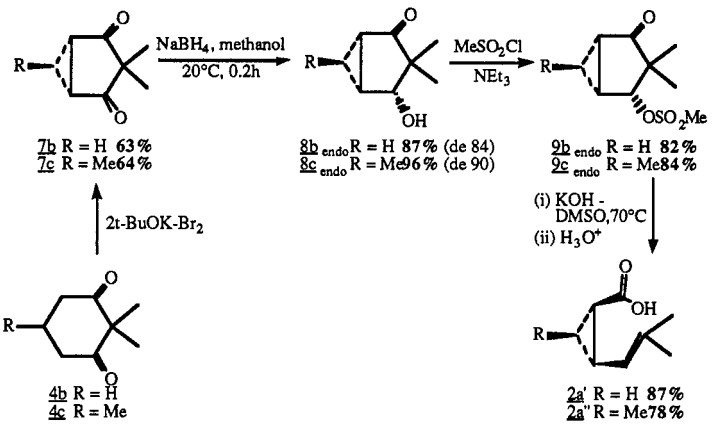


7 8 endo 8 exo

7b	R_1 = Me, R_2 = H	8b	94%	(43 / 57)
7c	R_1 = H, R_2 = H	8c	89%	(50 / 50)
7d	R_1 = H, R_2 = Me	8d	93%	(07 / 93)

The synthesis of (d,l)-cis-chrysanthemic acid was achieved (Scheme 2) from the exo alcohol $8a_{exo}$ in two steps which involve its mesylation (MesCl, Net_3, CH_2Cl_2, 20°C, 1h, 95% yield) and the reaction of the resulting mesylate $9a_{exo}$ with potassium hydroxide in aqueous DMSO (70°C, 4h, 69% yield).

Scheme 5



The whole process described in Scheme 5, carried out on the cyclohexanediones 4b and 4c missing at least one methyl group in the sixth position proceeds slightly differently than the one depicted in the scheme 2. The cyclopropanation reaction carried out on 4b en 4c works as on 4a [(i) 2 equiv. t-BuOK, THF -78°C to 20°C, (ii) Br_2 in pentane). Unexpectedly however, a perfect control of the stereochemistry leading exclusively to the bicyclic-diketone 7c bearing an exo-methyl group on the cyclopropane ring was achieved from 4c. The resulting bicyclic diketones 7b and 7c have been as expected reduced mainly from their exo face with sodium borohydride in methanol but on the contrary to what was reported for 8a$_{endo}$, the resulting endo alcohols 8b$_{endo}$ and 8c$_{endo}$ proved to be efficiently transformed to their corresponding endo mesylates 9b$_{endo}$ and 9c$_{endo}$ on reaction with mesyl chloride (1.1 equiv. MesCl, 1.1 equiv. Net_3, CH_2Cl_2, -8 to 20°C, 1h, 83% yield each). Finally, the resulting β-ketosulfonates proved to be prone to fragment to 2,2-di-desmethyl- 2b or to 2-desmethyl- 2c chrysanthemic acids on further reaction with KOH in aqueous DMSO (6 equiv. KOH-H_2O (8-2), DMSO, +70°C), although the trans-antiperiplanar arrangement required for such reaction to take place is not apparently fully achieved.

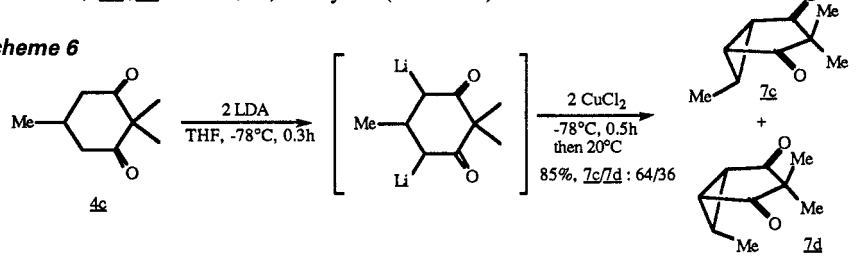
That the exo-mesylates 9 are more reactive in the Grob fragmentation reaction than their endo-stereoisomers was clearly demonstrated by the difference of reactivity observed between each of the two stereoisomers when the reaction is performed under the above mentioned conditions but on a 1 to 1 mixture of exo and endo mesylates 9b and 9c derived from the reduction of the bicyclic-diketones 7b and 7c with $NaBH_4$-$CeCl_3$.

The whole process applied to the diketone 4c exclusively leads to the 2-desmethyl chrysanthemic acid 2a" which bears all the substituents cis one to each others (Scheme 5). The synthesis of its epimer at C-2 was more difficult since we have been unable to synthesize stereoselectively the bicyclic diketone 7d bearing an endo-methyl group in the sixth position.

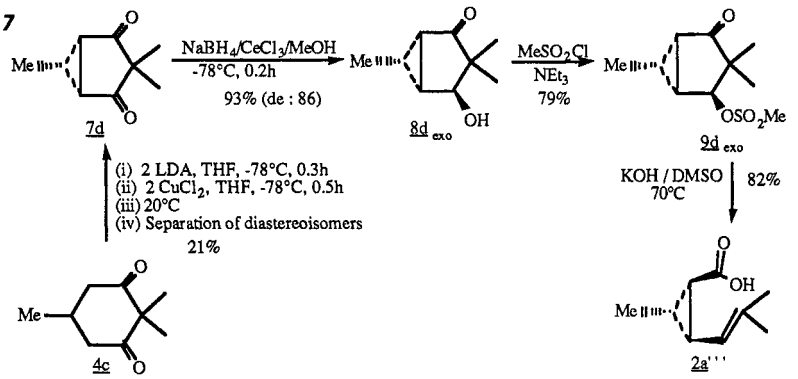
We have in fact generated the two stereoisomers of the 4-bromo-2,2,5-trimethyl-cyclohexa-1,3-diones 5c and 5d by bromination of the trimethyl-cyclohexane dione 4c, but they surprisingly both provide stereoselectively and exclusively the 2,2,5-trimethyl-bicyclo [3.1.0] hexa-2,4-dione 7c possessing the exo-methyl group on further reaction with potassium tert-butoxide (THF,-78°C, 2h).

We have been finally able to synthesize the 2,2,5-trimethyl-bicyclo [3.1.0] hexa-2,4-dione 7d but mixed with 7c by performing the cyclopropanation reaction by oxidation of the dilithio salt of the 2,2,5-trimethyl-cyclohexa-1,3-dione 4c with copper (II) chloride (2 equiv. LDA, -78°C, 0.5h (ii) $CuCl_2$, -78°C, 0.5h, then 20°C, 7d /7c ratio 64/36, 85% yield (Scheme 6).

Scheme 6



Scheme 7

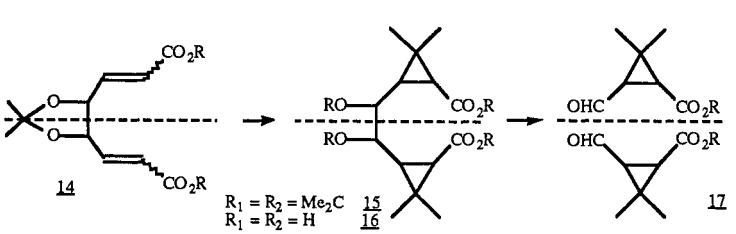


The bicyclic-diketone 7d has been separated from 7c by column chromatography on silicagel and the 2-desmethyl chrysanthemic acid 2a''' has been stereoselectively synthesized from 7d by a sequence of reactions identical to the one used for the synthesis of (d,l)-cis-chrysanthemic acid 2a [(i) $NaBH_4$-$CeCl_3$, -78°C, 93% yield ; (ii) MesCl, triethylamine, 20°C, 79% yield ; (iii) 6 equiv. KOH, DMSO-H_2O (8-2), 70°C, 82% yield] (Scheme 7).

We have also investigated another approach to trans- 2a and cis- 2b -chrysanthemic acid and to its cis-dibromovinyl analogue 2c (Scheme 1). This take advantage of the easy cyclopropanation of suitably functionalized α,β-unsaturated esters with phosphorus and sulfur ylides and found a clear cut difference of reactivity between isopropylidenetriphenylphosphorane and -diphenylsulfurane. The former reacts with (Z)- and (E)-α,β-unsaturated esters and leads exclusively to trans-cyclopropane carboxylic esters. It enolises γ-butyrolactone 10 and 4-methoxy-γ-butyrolactone 11 and affords [12b] dimenthyl caronate 13 from dimenthyl fumarate 12, in high yield and with reasonably high asymmetric induction. Isopropylidenediphenylsulfurane reacts stereospecifically with α,β-unsaturated esters and leads to trans-cyclopropyl esters from (E)-α,β-unsaturated esters and to cis-cyclopropyl derivatives from their (Z)-isomers.[14a] It provides bicyclo [3.1.0] hexane derivatives on reaction with γ-butyrolactones but affords [12b] dimenthyl caronate 13 from dimenthyl fumarate 12, in high yield but with dramatically low asymmetric induction .

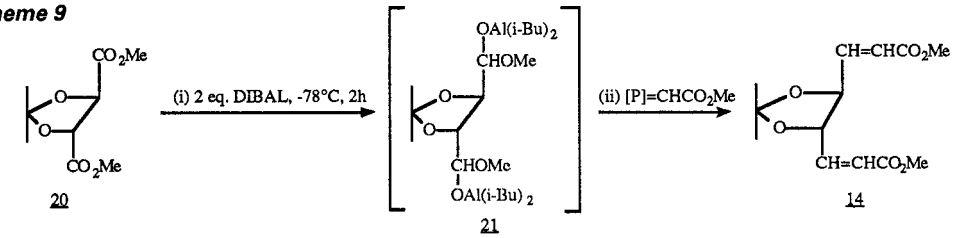
As a continuation of this work, we became interested in performing the above mentioned cyclopropanation reaction on the diesters 14 (Scheme 8). This yet unknown building block should possess exceptional features due not only to the presence of two γ-alkoxy-α,β-unsaturated ester moieties (analogous to masked γ-oxobutenoates) but also due to the chiral nature of some of its forms susceptible to allow asymmetric inductions (*inter alia* in the double cyclopropanation reaction envisaged). Further hydrolysis of the dioxolane moiety in 15 was expected to produce the diol 16 precusor of the hemicaronaldeyde 17 the well known key intermediate in various syntheses of chrysanthemic acid 2. Last but not least we discovered that both the (E,E)-14a and the (Z,Z)-14b stereoisomers in each series [(4R,5R) and (4S,5S)] are available from natural mannitol 18 and from natural tartaric acid 19 respectively via their acetonides.

Scheme 8



We found (Scheme 9) that the trans-14a and cis-14b α,β-unsaturated esters can be produced in one pot from the diester 20 derived from natural (2R,3R)-(+)-tartaric acid 19 by sequential treatment with diisobutyl aluminum hydride (DIBAL, 2 equiv. of a 1.5N solution in toluene, -78°C, 2h) followed by reaction with sodio carbomethoxymethyl diethylphosphonate [16a] [2.5 equiv., DME, -78°C to 20°C, 4h, 60% yield of the (E,E)-stereoisomer 14a containing 4% of the (E,Z)-isomer 14c] or with methyl(triphenylphosphoranilidene)acetate [16b] [2.5 equiv. MeOH, -78°C to +20°C, 3h ; 44% yield of the (Z,Z) isomer 14b].

Scheme 9



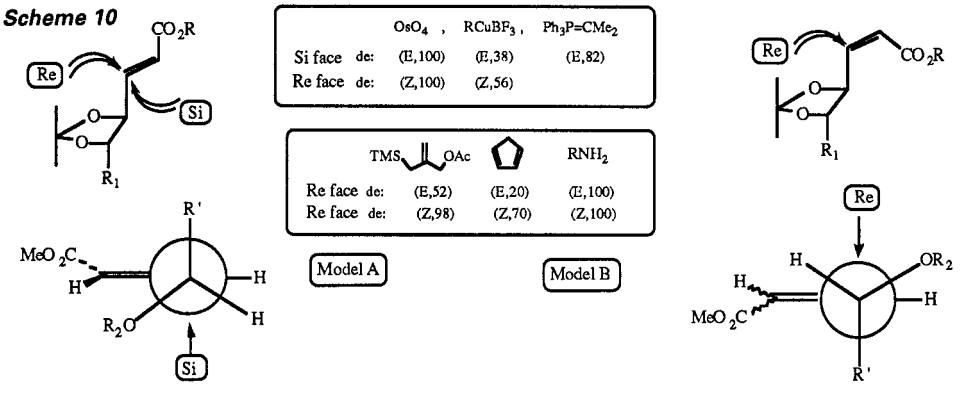
		E, E	Z, Z	Z, E
2.5 equiv. $(EtO)_2P(O)CH(Na)CO_2Me$,DME, -78°C, 0.1h, 20°C, 4h	60%	96		4
2.5 equiv. Ph_3PCHCO_2Me,MeOH, -78°C to 20°C, 3h	83%	2	60	38

Remarkably, these Wittig-Horner or Wittig reactions presumably take place on the dialuminate 21 rather than on the corresponding dialdehyde 22 and therefore this approach avoids the tedious isolation of such highly water soluble and enolisable compound. It should also allow the synthesis of their enantiomers 14' from the still cheap unnatural tartaric acid.

Diastereoselective addition to γ-alkoxy-α,β-unsaturated carbonyl compounds is well documented.[17] It has been used *inter alia* for the enantioselective synthesis of the β-lactame thienamycin,[17a] brefeldin,[17b] santalene,[17c] prostanoids,[17c] galactitol [17d] and (1R)-trans-chrysanthemic acid [17e] 2b.

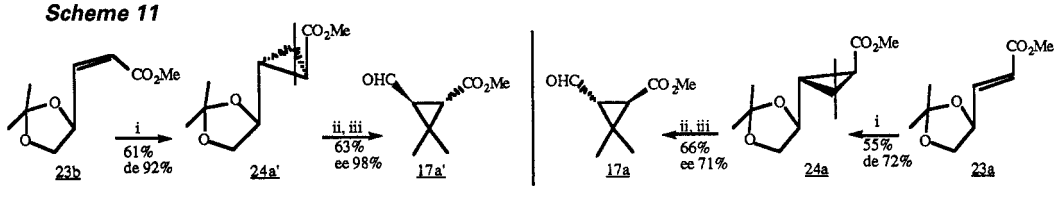
In most of the cases the stereochemistry of the β-carbon on the adduct only depends upon the stereochemistry of the γ-carbon and proved to be [17a-c] independent of the stereochemistry of the carbon-carbon double bond (Scheme 10). In few cases however the stereochemistry of the β-carbon on the adduct is not only dependent upon the stereochemistry of the γ-carbon but is also directly related to the stereochemistry of carbon-carbon double bonding the starting material [17f,h] (Scheme 10). Interestingly the stereochemical outcome on the β-carbon of the adduct, of all these reactions was found to be identical in both series when the (Z)-stereoisomer is involved. The models used to rationalize these results however remain unsatisfactory (Scheme 10).

Scheme 10



We first investigated the more simple case of unsaturated esters 23a and 23b derived from D-glyceraldehyde and possessing respectively the (E)- and (Z)-stereochemistry [16] (Scheme 11 and 12). When reacted with isopropylidenetriphenylphosphorane, the former product leads, as previously described [17e] to the methyl (1R)-trans-cyclopropane carboxylate 24a as a 91/9 mixture of diastereoisomers in which 24a predominates, whereas its (1S)-diastereoisomer 24a' still possessing the trans-stereochemistry is almost exclusively formed (24a'/24a : 97/3) starting from the (Z)-unsaturated ester 23b (Scheme 11).

Scheme 11



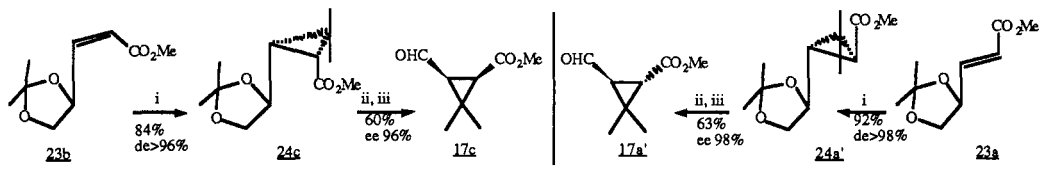
(i) 1.5 equiv. $Ph_3P=C(Me)_2$, LiI, THF, 0°C, 1h then 20°C, 1 h - (ii) 4 equiv. 2N aq. $HClO_4$, THF, 20°C, 6h - (iii) 1.5 equiv. $NaIO_4$, MeOH, Phosphate buffer pH 7.2, 20°C, 1h.

These results clearly show that the (1R)-cis-series precursor of deltamethrin 1c is not directly accessible from isopropylidenetriphenylphosphorane. It was therefore interesting to test another reagent able to transfer an isopropylidene moiety with conservation of the stereochemistry of the starting α,β-unsaturated ester.

On the basis of Corey's original work [14a] and of the results already obtained in our laboratory,[11b] we expected that isopropylidenediphenylsulfurane could fulfil these requirements.

We effectively found that the unsaturated esters 23b and 23a derived from D-glyceraldehyde and possessing the (Z)- and (E)-stereochemistry react with isopropylidenediphenylsulfurane (1.5 equiv., DME, -78°C, 0.3h then -60°C to -50°C, 0.7h, then -50°C to 20°C) and produce respectively the cis-cyclopropyl ester 24c (84% yield, de : >96%) and the trans-cyclopropyl ester 24a' (92% yield, de : >98%) in very high yield and with very high stereoselectivity (Scheme 12).

Scheme 12



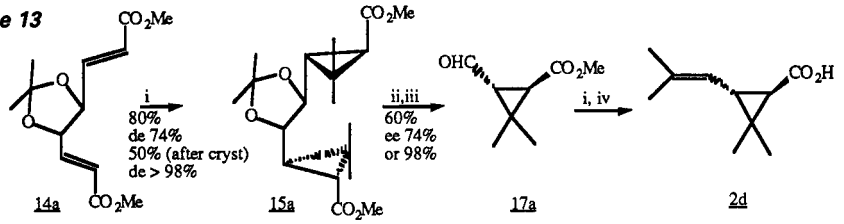
(i) 1.5 equiv. $Ph_2S{=}C(Me)_2$, DME, -78°C, 0.2 h then -78°C to -50°C, 0.7 h then -50°C to 20°C, 0.3 h (ii) 4 equiv. 2N aq. $HClO_4$, THF, 20°C, 6h - (iii) 1.5 equiv. $NaIO_4$, MeOH, Phosphate buffer pH 7.2, 20°C, 1h.

These results are in sharp contrast with those obtained with isopropylidenetriphenylphosphorane and reported above. **(i)** The reaction with isopropylidenediphenylsulfurane is almost completely stereospecific as far as the relative stereochemistry is concerned [trans-24a' from (E)-23a ; cis-24c from (Z)-23b)] whereas it is almost completely stereoselective with its phosphorus analogue [trans-24a and 24a' from (E)-23a and (Z)-23b respectively]. **(ii)** The stereochemistry of the β-carbon of the adduct 24 is independent of the stereochemistry of the carbon-carbon double bond of 23 when the sulfur ylide is used (always (S)) whereas it is completely dependent on it when its phosphorus analogue is involved ((R) from (E)-23a and (S)- from (Z)-23b).

These unexpected results are not yet rationalized, although they fit in the series of results already published [17] and collected in the scheme 10, but as far as the synthetic aspect is concerned, it is now possible after hydrolysis of the dioxolanes 24 (4 equiv. 2N aq. $HClO_4$, THF, 20°C, 6h) and further cleavage of the corresponding diols 16 ($NaIO_4$, MeOH, phosphate buffer, pH : 7.2, 20°C, 1h) to the hemicaronaldehydes 17 to devise straightforward enantioselective routes to natural pyrethrins and to deltamethrin from natural tartaric acid and from natural D-glyceraldehyde by the proper choice of the isopropylidene transferring reagent (phosphorous or sulfur ylides respectively).

With these results in hand we performed the cyclopropanation of the chiral diesters 14. In order to achieve the synthesis of the 1R-trans-chrysanthemic acid 2d, the chiral trans-diester 14a has been reacted with 2.5 equiv. of isopropylidenetriphenylphosphorane (generated from isopropyl triphenylphosphonium iodide and n-butyl lithium in THF-hexane), the reaction being performed at 0°C for 1h then at 20°C for one more hour (Scheme 13). Typically, the diadduct 15 is obtained in 80% yield as a 87/13 mixture of the 15a/15a' stereoisomers from which the major one 's (15a m.p. : 123°C, cyclohexane) has been isolated in 50% overall yield after one crystallization. The diadduct 15a was in turn transformed to (1R)-trans-hemicaronaldehyde [9] 17a after hydrolysis of the dioxolane moiety (2N aq. $HClO_4$, THF, 20°C, 6h, 98% yield) and cleavage of the resulting diol 16a (1.5 equiv. $NaIO_4$, MeOH, phosphate buffer pH : 7.2, 20°C, 1h) leading to the (1R)-trans-hemicaronic aldehyde 17a in 68% yield and high enantiomeric excess (ee : 98%). The synthesis of the natural methyl trans-chrysanthemate 2d from 17a is straightforward and has already been described [1] (Scheme 13).

Scheme 13



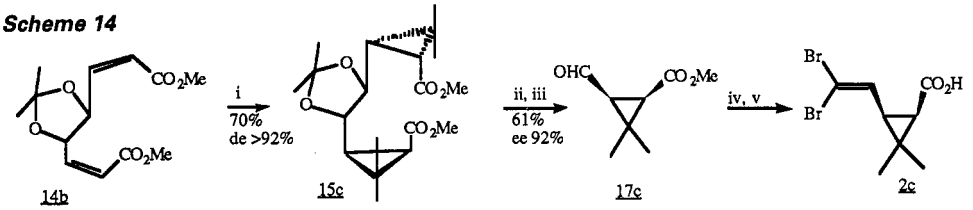
(i) 2.5 equiv. $Ph_3P{=}C(Me)_2$, LiI, THF, 0°C, 1h then 20°C, 1h - (ii) 4 equiv. 2N aq. $HClO_4$, THF, 20°C, 6h - (iii) 1.5 equiv. $NaIO_4$, MeOH, Phosphate buffer pH 7.2, 20°C, 1h - (iv) KOH, MeOH then aq. HCl.

The conditions described above for the cyclopropanation reaction are crucial for its success since for example a mixture of mono-adducts and di-adducts, in which the amount of the diastereoisomer 15a decreases, is produced if the cyclopropanation reaction is carried out between -78°C and 20°C instead of between 0°C and 20°C.

We then envisage the synthesis of the 1R-cis-dibromovinyl chrysanthemic acid which is part of deltametrin the most potent insecticide known. According to the results reported above, we performed the cyclopropanation reaction on the (Z,Z)-diester 14b with isopropylidenediphenylsulfurane (3 mol. equiv.) (DME, -78°C, 0.3h then -60°C to -50°C, 0.7h, then -50°C to 20°C) as the cyclopropanating agent. We obtained the diadduct 15c possessing two cis-disubstituted cyclopropane moieties in 70% overall yield almost as a single diastereoisomer (de : >92%) (Scheme 14). This adduct has been in turn transformed to the desired (1R)-cis-hemicaronaldehyde 17c precursor of deltamethrin [1] after hydrolysis of the dioxolane moiety (2N aq. $HClO_4$ THF, 20°C, 6h, 98% yield) and cleavage of the resulting diol (1.5 equiv. $NaIO_4$, MeOH, phosphate buffer pH : 7.2, 20°C, 1h, 62% yield, ee : 92 %).

These results are remarkable since they involve two cyclopropanation reactions, each one occurring in particularly high yield (> 85 %) and with high stereochemical control (de : > 96%).

Scheme 14



(i) 3 equiv. $Ph_2S{=}C(Me)_2$, DME, -78°C, 0.3 h then -60°C to -50°C, 0.7 h then -50°C to 20°C - (ii) 6 equiv. 2N aq. $HClO_4$, THF, 20°C, 6h - (iii) 1.5 equiv. $NaIO_4$, MeOH, Phosphate buffer pH 7.2, 20°C, 1h - (i) 4 CBr_4-PPh_3, CH_2Cl_2 - (v) KOH, MeOH then aq. HCl - (vi) 2.5 equiv. $(EtO)_2P(O)CHNaCO_2Me$, DME, -78°C then -78°C to +20°C, 4h.

In conclusion, we have devised new stereoselective routes to cis- and trans-chrysanthemic acid and to related compounds. The second approach we have described is particularly interesting since tartaric acid is readily removed as mixed sodium and potassium tartrate from champagne wine and then transformed by using the route depicted in the Scheme 14 to deltamethrin, the most potent insecticide known. This powerful insecticide is in turn able to protect the winyard against the predation of insects. Since only thirty seven grams of such compound are sufficient for that purpose and around ten grams of tartrates have to be removed during the production of champagne wine, we can roughly assume that one hectare of winyard in the champagne region can allow the synthesis of enough deltamethrin to protect it for at least a further hundred year.

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