Diastereoselective Additions to C,C Double Bonds Applied to the Enantioselective Synthesis of Pyrethroic Acids

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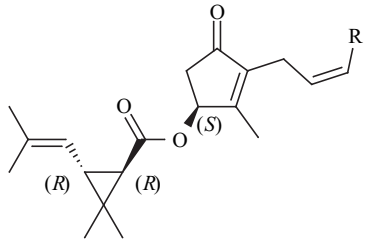
Abstract: Detailed review on enantioselective synthesis of methyl (1*R*)-*trans*-chrysanthemate and related methyl (1*R*)-*cis*-deltamethrinate is presented. These commercially available esters of vinylcyclopropanecarboxylic acids belong to pyrethroids class of insecticides. They are used as single enantiomers for domestic and agricultural purpose. They are almost 3.5 10^4 more active than DDT and are biodegradable.

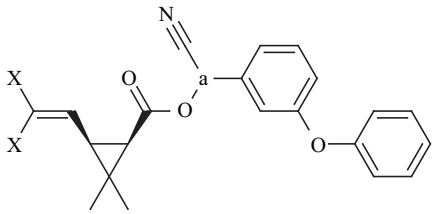
Keywords: 1,4-addition, vinyl cyclopropane carboxylic esters, cyclopropanation, sulfur ylides, phosphorus ylides, asymmetric induction, olefination reactions.

1. INTRODUCTION

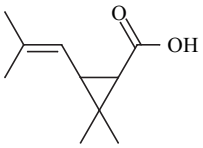
Very long ago, in the antiquity already, it was known that the flowers of *chrysanthemum cinerariaefolium* exhibit insecticidal properties and it has been established by Staudinger and Rucizka [1] that this is mainly due to the presence of Pyrethrin I (**1**, Scheme **1**). **1** is a ester derived from (1*R*)-*trans*-2,2-dimethyl-3-(2-methyl-propenyl)-cyclopropanecarboxylic acid, known as (1*R*)-*trans*-chrysanthemic acid **4a** (Scheme **1**). Its use is however restricted to domestic purposes due to its short half life, which is less that 1 hour in sunlight [2].



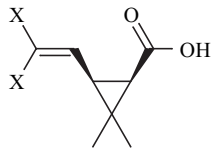
1 Pyrethrin I R= Vinyl
2 *S*-Bioallethrin R= H



3a Cypermethrin X= Cl, (1*R,S*)-*cis*-, C_a= *R,S*
3b Deltamethrin X= Br, (1*R,*2*R*)-*cis*-, C_a= *S*



4 Chrysanthemic acid
4a Chrysanthemic acid (1*R*)-*trans*-



5a Cypermethrinic acid X=Cl, (1*R,S*)-*cis*-
5b Deltamethrinic acid X= Br (1*R,*2*R*)-*cis*-

Scheme 1.

More than 50,000 structure variants of this commercially valuable compound have been synthesized by different companies either in duplicates or in triplicates and tested for insecticidal effects. Very few have been commercialized except *S*-bioallethrin **2** which misses a vinyl group on the alkoxy part (**2**, Scheme **1**, compare **2** to **1**), cypermethrin **3a** and deltamethrin **3b** which derive from permethrinic acids (**5**, Scheme **1**, X= Cl or Br) and possess a different alkoxy moiety. Although cypermethrin **3a** is commercialized as mixture of all the possible stereoisomers, *S*-bioallethrin **2** as well as deltamethrin **3b** are sold as enantiopure compounds. The later is by far the most active insecticide of the series since it is stable enough to sunlight and air to be used in the fields (half time: 2 months).

Most of the synthetic strategies utilized for producing the vinyl cyclopropane carboxylic acids, involve the formation of the three membered cycle either by (i) cyclization (ii) cyclopropanation or (iii) rearrangement reactions [3].

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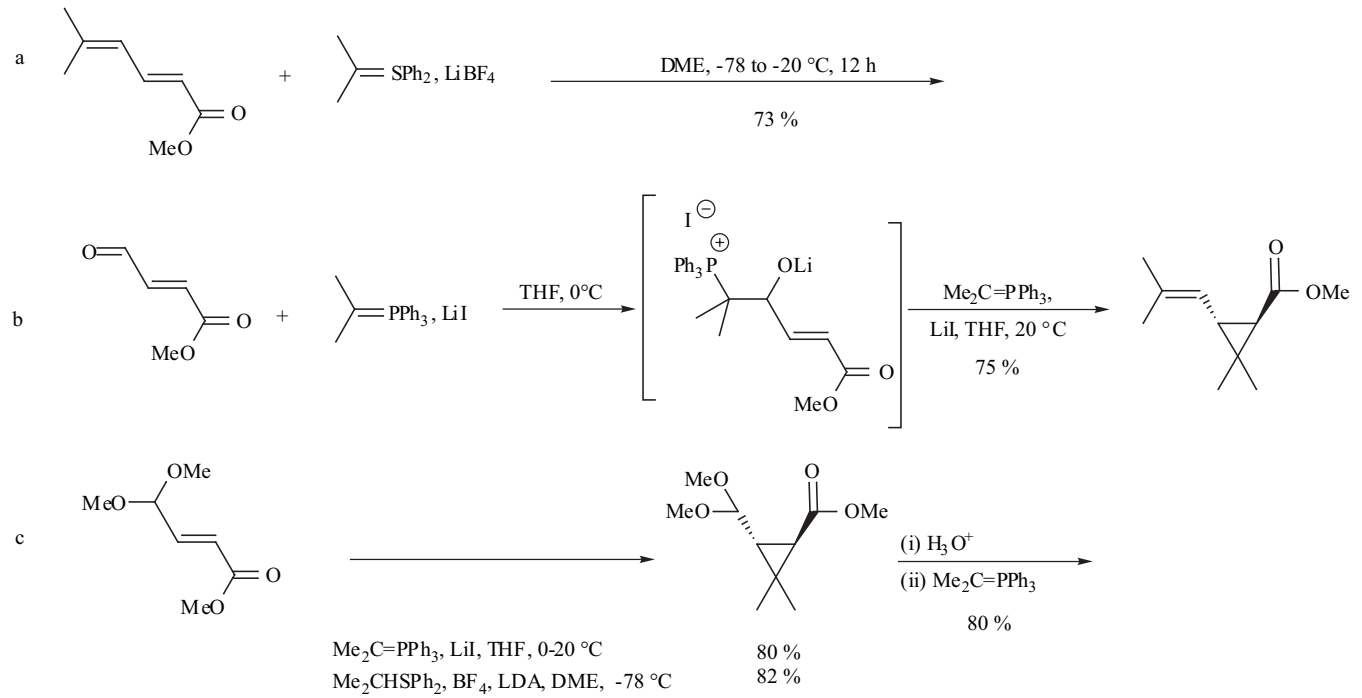


Scheme 2.

2. SYNTHESIS OF CYCLOPROPANE DERIVATIVES USING METHYL 5-METHYL-HEXA-2,4-DIENOATE, DIALKYL FUMARATES, DIALKYL MALEATES, ALKYL γ-OXOBUTENOATES AND S OR P-YLIDES: A REVIEW

The strategy involving the introduction of the 2-isopropylidene moiety to suitable functionalized α,β-unsaturated esters proved to be particularly suitable for the synthesis of pyrethroic acids.

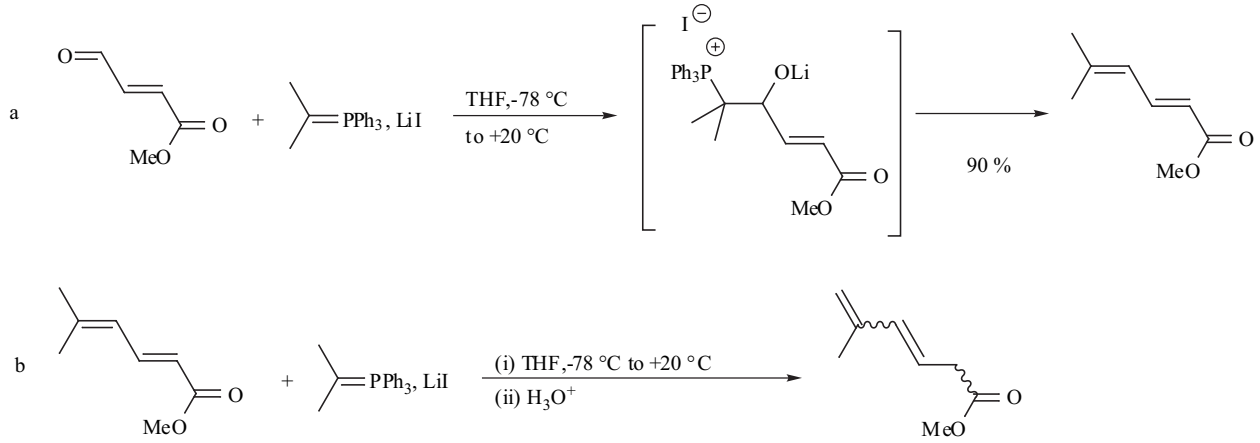
The first convergent route to methyl (*d,l*)-*trans*-chrysanthemate, in which isopropylidenediphenylsulfurane and methyl 5-methyl-hexa-2,4-dienoate were efficiently employed, was explored by Corey (Scheme **2**, entry a) [4].

We later found that isopropylidenetriphenylphosphorane reacts, if used in suitable proportion (2 equiv., THF, -20 to +20 °C) with alkyl 4-oxo-but-2-enoates to produce alkyl *trans*-chrysanthemates in good yields (Scheme **2**, entry b) [5, 6].

Careful monitoring of the reaction shows that the first equivalent of the ylide reacts (THF, -78 °C) on the carbonyl group of the aldehyde rather than on the C,C double bond of the alkyl 4-oxo-but-2-enoates producing the corresponding β-alkoxyphosphonium salts while the second equivalent adds in a 1,4 manner on the C,C double bond of the resulting adducts when the temperature reach -30°C and generate the cyclopropane ring. Raising the temperature up to 20 °C, promotes the decomposition of the β-alkoxy phosphonium salt to alkyl *trans*-chrysanthemates.

Thus the two usual steps of the "Wittig olefin synthesis" namely the addition of the phosphorus ylide to the carbonyl compound and the elimination reaction of triphenylphosphine oxide from the intermediates β-alkoxy phosphonium salts, which usually follows in sequence, are pulled apart by the cyclopropanation reaction (Scheme **2**, entry b) [6].

Alkyl 5-methyl-hexa-2,4-dienoates were formed when only one equivalent of isopropylidenetriphenylphosphorane



Scheme 3.

was reacted with alkyl 4-oxo-but-2-enoates (THF, -78 to 20°C, Scheme **3**, entry a) [5]. Reaction of the later with one equivalent of isopropylidenetriphenylphosphorane did not afford, alkyl *trans*-chrysanthemates, as in the case of isopropylidenediphenylsulfurane [4], but instead leads to the formation of a diastereoisomeric mixture of alkyl 5-methyl-hexa-3,5-dienoates as a result of the metalation-protonation sequence (Scheme **3**, entry b) [5].

The synthesis of methyl *trans*-chrysanthemate has been also achieved from methyl 4-oxo-butenoate using a different strategy in which the order of producing the cyclopropane ring and the C,C double bond have been inverted (Scheme 2, entry c) [6].

This has been effectively achieved by (i) protection of the carbonyl group of the aldehyde of methyl 4-oxo-butenoate as an acetal (Methanol, H^+) (ii) Reaction of isopropylidene-triphenylphosphorane in a stoichiometric manner on methyl 4,4-dimethoxy-but-2-enoate (iii) Deprotection, on acid hydrolysis, of the resulting methyl 3,3-dimethoxymethyl-2,2-dimethyl-cyclopropanecarboxylate leading to methyl 3-formyl-2,2-dimethyl-cyclopropanecarboxylate and finally (iv) Wittig olefination reaction of the latter using again isopropylidenetriphenylphosphorane (Scheme **2**, entry c) [6].

In a related approach dialkyl fumarates and maleates have been reacted with isopropylidenediphenylsulfurane and isopropylidenetriphenylphosphorane to afford dialkyl caronates in reasonably good yields (Scheme **4**) but this strategy requires subsequent chemoselective reactions to produce pyrethroic acids [7, 8].

The reaction of isopropylidenediphenylsulfurane is highly stereospecific and proceeds with high stereocontrol to the dialkyl *cis*-caronates from dialkyl maleates (Scheme **4**, entry a) [4,7] and to their *trans*-stereoisomers from dialkyl fumarates (Scheme **4**, entry c) [4,7] while the reaction of isopropylidenetriphenylphosphorane is highly stereoselective and affords dialkyl *trans*-caronates exclusively from either the *E*- or the *Z*-α,β-unsaturated diesters (Scheme **4**, entries b,d) [7]. This behavior of isopropylidenediphenylsulfurane and isopropylidenetriphenylphosphorane towards α,β-unsaturated esters seems to be quite general.

The reaction reported in Scheme **4**, entry a, has been used for the synthesis of *cis*-chrysanthemic acid as well as *cis*-deltamethrinic acid, whereas, those described in Scheme **4**, entries b-d, allow the synthesis of *trans*-chrysanthemic acid [7].

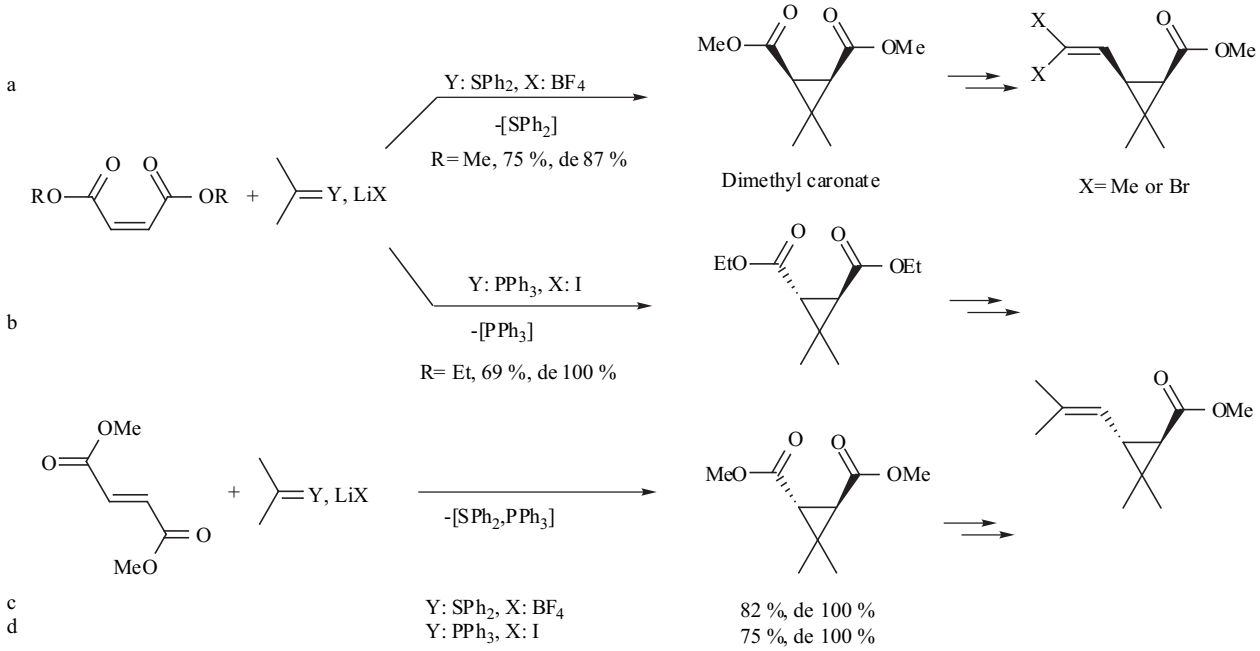
The aforementioned methods produce pyrethroic acids as racemates and are not suitable for the synthesis of enantiopure (1*R*)-*trans*-chrysanthemic acid **4a** or (1*R*)-*cis*-dibromovinyl chrysanthemic acid (deltamethrinic acid **5b**), whose suitable esters **2** and **3b** are the most potent insecticides.

Application of these reactions to the synthesis of enantiopure alkyl (1*R*)-*trans*-chrysanthemates did not work properly from acetals of alkyl 4-oxobutenoates derived from enantiopure alcohols such as menthol or from (*R*),3(*R*)-butanediol [9].

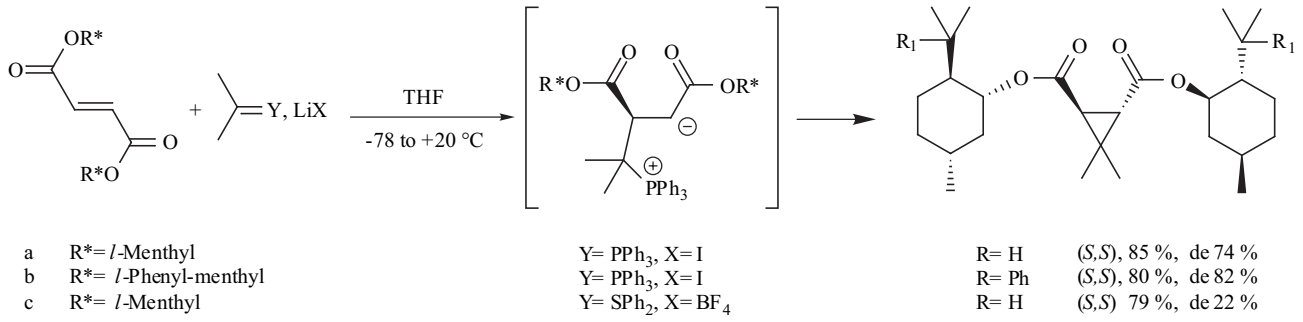
Nevertheless, significant improvement were made using isopropylidenetriphenylphosphorane and either di(*l*)-menthyl fumarate (THF, -78 to +20 °C, 85 %, (*S,S*) de: 74 %, Scheme **5**, entry a) [10] or di(*l*)-phenyl-menthyl fumarate (THF, -78 to +20 °C, 80 %, (*S,S*) de: 82 %, Scheme 5, entry b) [10].

Using isopropylidenediphenylsulfurane instead, gave poorer asymmetric induction (THF, -78 to + 20 °C, 79 %, (*S,S*) de 22 %, Scheme **5**, entry c) [10]. Asymmetric induction has been suggested to occur from the carboxy group on the fumarates adjacent to the site which is attacked by the ylide. The difference of selectivity between S and P ylides has never been challenged [2,10].

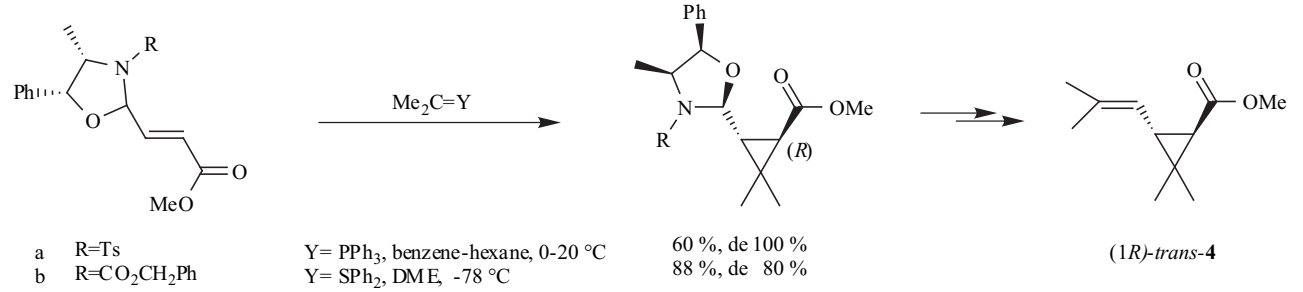
N-protected oxazolidines derived from enantiopure *N*-protected norephedrine and alkyl 4-oxo-butenoates have



Scheme 4.



Scheme 5.



Scheme 6.

proven to be far more efficient, since they lead to alkyl cyclopropane carboxylates in reasonably good yield and with high asymmetric induction. The reaction, however, requires to be carried out in benzene or toluene and not in THF in the case of isopropylidenetriphenylphosphorane (R= Ts, 60 %, *cis*/*trans*: 0/100, (1*R*)/(1*S*): 100/0; Scheme **6**, entry a) [11a] whereas the later solvent, as well as DME, are particularly suitable for those reactions involving isopropylidene-diphenylsulfurane instead (R= $PhCH_2CO_2$, DME, -78 °C, 70-88 %, *cis*/*trans*: 0/100, (1*R*)/(1*S*) : 90/10; Scheme **6**, entry b) [11b].

The very high π-face selectivity observed with these oxazolidines most probably account for the presence of a chiral centre at the allylic position close to the electrophilic site. Interestingly complete control of the stereochemistry at this centre takes place on reacting, in refluxing benzene, methyl 4,4-dimethoxy-2*E*-butenoate with *N*-protected norephedrine in the presence of catalytic amounts of pyridinium tosylate [12].

3. SYNTHESIS OF METHYL CHRYSANTHEMATE AND METHYL DELTAMETHRINATE FROM γ-ALKOXY-SUBSTITUTED α,β-UNSATURATED ESTERS AND α-HETEROSUBSTITUTED ORGANO-METALLICS

3.1. Hemisyntheses Involving γ-Alkoxy-α,β-Unsaturated Esters Prepared from Acetonide of D-Glyceraldehyde Derived from D-Mannitol and S- and P-Ylides

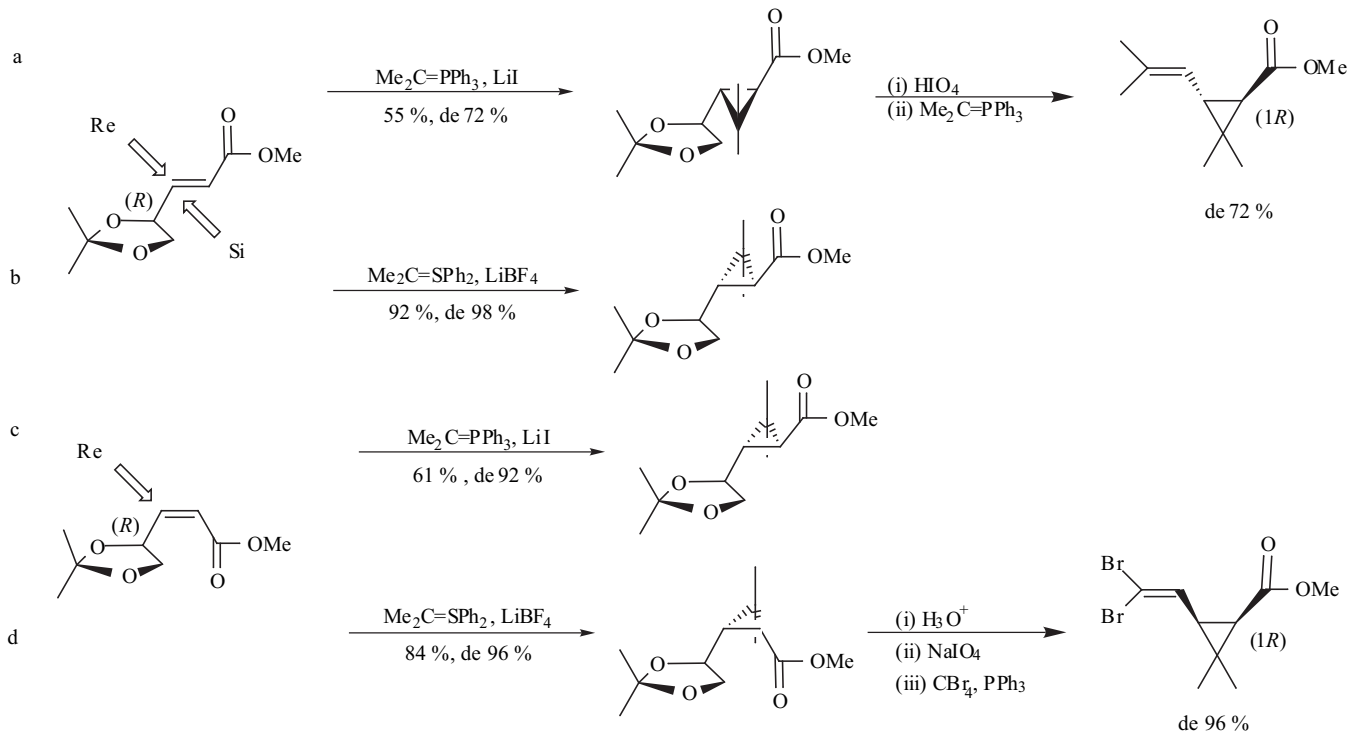
An even more interesting and flexible diastereoselective method involves deployment of chiral 4-alkoxy-substituted α,β-unsaturated esters (Scheme **7**). The first example of this reaction, disclosed by Mulzer, was performed on ethyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-*E*-acrylate derived from the acetonide of D-glyceraldehyde and isopropylidenetriphenyl-phosphorane [13]. It leads to ethyl *trans*-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropanecarboxylate (55 % yield, 72 % de). The later proved to be a valuable precursor of ethyl (1*R*)-*trans*-chrysanthemate (72 % ee) on sequential treatment with periodic acid and reaction of the resulting ethyl *trans*-3-formyl-2,2-dimethyl-cyclopro-panecarboxylate with isopropylidenetriphenylphosphorane (Scheme **7**, entry a) [13]. The whole sequential transfor-mation also takes an advantage of the great accessibility of D-glyceraldehyde acetonide, readily achievable by oxidative cleavage of diacetonide of mannitol bearing the acetonide moiety at its two termini [13].

It was later on rationalized by us that the asymmetric induction is not only highly dependent, as expected, on the stereochemistry of the chiral centre at γ-position of the γ-alkoxy-α,β-unsaturated ester but also on the stereochemistry of the C,C double bond and as well as on the nature of the ylide used (S or P) [14].

Therefore, isopropylidenetriphenylphosphorane appro-aches alkyl *Z*-γ-(*S*)alkoxy-α,β-unsaturated carboxylates derived from D-glyceraldehyde by the *Re*-face providing the *trans*-cyclopropane carboxylate shown in Scheme **7**, entry c, with high diastereoselection (de> 95 %) [14e] whereas it reacts mainly by the *Si*-face of the *E*-stereoisomer, as disclosed by Mulzer (Scheme **7**, entry a, de= 72 %) [13].

In order to rationalize the former results it is not necessary to assume only that isopropylidenetriphenyl-phosphorane approaches the *Z*-unsaturated ester by its *Re*-face, which is opposite to that involved with the *E*-stereoisomer but also to account an isomerisation process, as already mentioned in the case of dialkyl maleates (Scheme **2**, entry c) [6].

The cycloaddition reaction takes another course when carried out with isopropylidenediphenylsulfurane since it adds from the *Re*-face of both alkyl *E*- and *Z*-γ-(*S*)-alkoxy-α,β-unsaturated carboxylates derived from the acetonide of



Scheme 7.

D-glyceraldehyde and proceeds with extremely high asymmetric induction to yield the corresponding *trans*- (92 % yield, de: 98 %, Scheme **7**, entry b) and *cis*- (84 % yield, de: 96 %, Scheme **7**, entry d) cyclopropane carboxylates respectively [11b,14].

The results reported above are even more remarkable when the resulting methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropanecarboxylates are sequentially subjected to (i) Acid catalyzed hydrolysis of their acetonide moiety and (ii) Cleavage of the resulting diols since they provide stereoselectively (1*R*)-*cis*-, and (1*S*)-*trans*-methyl 3-formyl-2,2-dimethyl-cyclopropanecarboxylates in good yield and extremely high asymmetric inductions (Scheme **7**) [14c,d].

Thus the synthesis of *S*-bioallethrin involves the alkyl *E*-γ-(*S*)-alkoxy-α,β-unsaturated carboxylates derived from (*D*)-glyceraldehyde and isopropylidenetriphenylphosphorane (Scheme **7**, entry a) [13, 14c,d], whereas that of deltamethrin can only be achieved when started from the Z-isomers of the same γ-(*S*)-alkoxy-α,β-unsaturated carboxylates and isopropylidenediphenylsulfurane (Scheme **7**, entry d) [14c,d].

The synthesis of (1*R*)-*cis*-deltamethrinic acid works fine (Scheme **7**, entry d) [14c,d] whereas that of (1*R*)-*trans*-chrysanthemic acid (Scheme **7**, entry a) [13] suffers both from quite poor diastereoselection and quite lengthy functional group manipulation to construct the vinyl side chain.

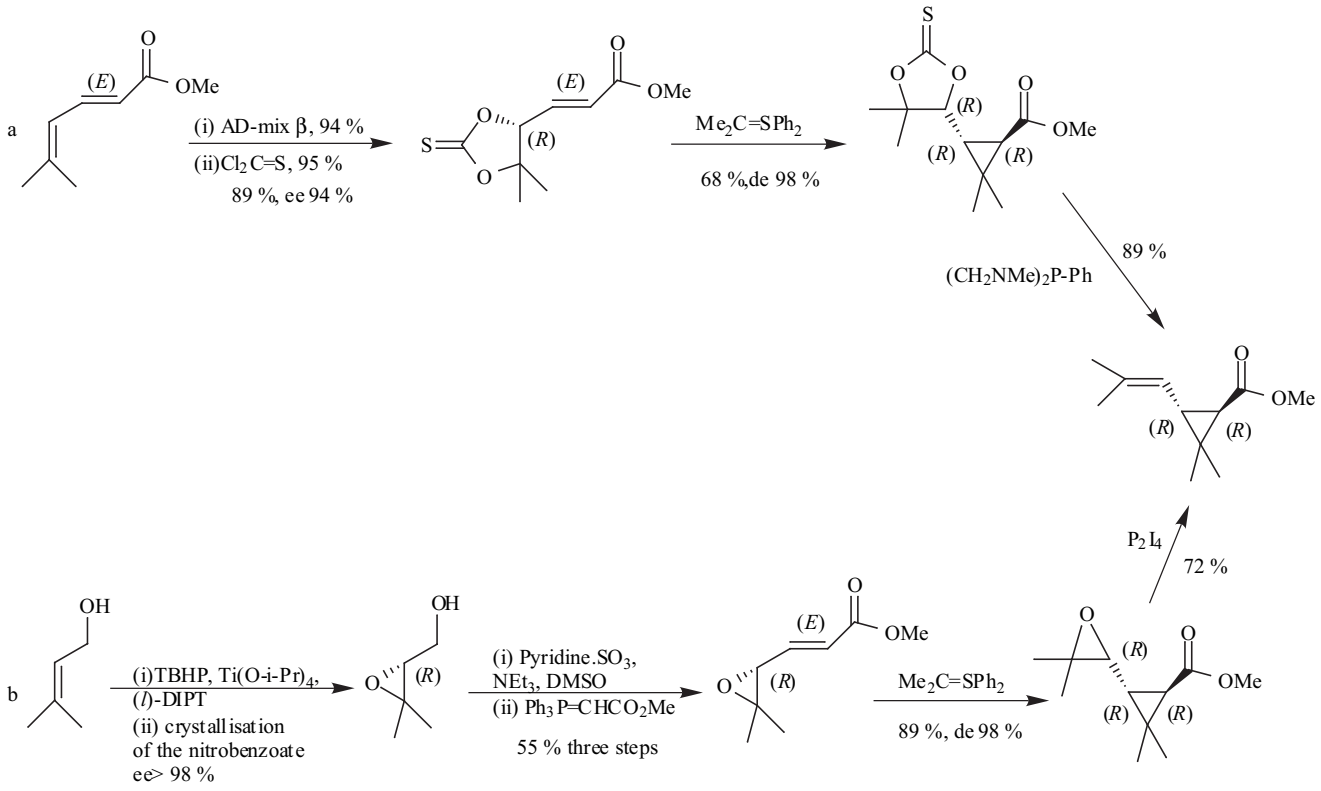
3.2. Syntheses from γ-Alkoxy-α,β-Unsaturated Esters Prepared *via* Sharpless AD or AE Reactions and S- and P-Ylides

On the basis of those observations we have designed two new elaborated routes to methyl (1*R*)-*trans*-chrysanthemate both of which use isopropylidenediphenylsulfurane known for providing much better asymmetric induction than the related phosphorus ylide (Scheme **7** compare entry b to entry a).

We designed a more appropriate electrophile which would produce, once the cyclopropanation is performed, methyl (1*R*)-*trans*-chrysanthemate in a single step. We recognized that this would avoid the tandem diol cleavage-Wittig olefination reaction involved in the synthesis of ethyl (1*R*)-*trans*-chrysanthemate described by Mulzer (Scheme **7**, entry a) [13] and therefore requires that the electrophile would possess the entire the complete carbon skeleton and the appropriate functionalities to generate the (2-methyl-propenyl)-moiety present in methyl (1*R*)-*trans*-chrysanthemate.

3(*R*)-(5,5-Dimethyl-2-thioxo-[1,3]dioxolan-4-yl)-(Scheme **8**, entry a) [15] and 3(*R*)-(3,3-dimethyl-oxiranyl)- (Scheme **8**, entry b) [17] *trans*-acrylic acid methyl esters proved to be the best notable partners of isopropylidenediphenylsulfurane system for producing the corresponding *trans*-cyclopropane carboxylates in higher yield and with almost complete diastereoselectivity (Scheme **8**) [15, 17].

The synthesis of the (2-methyl-propenyl) moiety leading to methyl (1*R*)-*trans*-chrysanthemate has been successfully achieved either from methyl 3-(5,5-dimethyl-2-thioxo-[1,3] dioxolan-4-yl)-2,2-dimethyl-cyclopropanecarboxylate using the Corey-Winter-Hopkins reductive decomposition of its thionocarbonate functional group (5,5-dimethyl-2-thioxo-[1,3]dioxolan-4-yl) moiety) using 1,3-dimethyl-2-phenyl-[1,3,2]diazaphospholidine $(CH_2NMe)_2PPh$, neat, 40 °C, 6 h; Scheme **8**, entry a) [15, 16] or from ethyl 3-(3,3-dimethyl-oxiranyl)-2,2-dimethyl-cyclopropanecarboxylate using diphosphorus tetraiodide mediated deoxygenation of



Scheme 8.

its epoxide functional group (P_2I_4, CS_2, pyridine, 5h, reflux, 72 %; Scheme **8**, entry b) [17,18].

Methyl 3-(5,5-dimethyl-2-thioxo-[1,3]dioxolan-4-yl)-*E*-acrylate [15] has been readily prepared from methyl 5-methyl-hexa-2,4-dienoate and AD-mix β in the presence of methylsulfonamide according to the well known Sharpless catalytic asymmetric dihydroxylation reaction [15,19] ((i) AD-mix β, aq. *t*-BuOH (ii) $MeSO_2NH_2$, 20°C, 20 h, 89 %, ee 94 %; Scheme **8**, entry a) and reaction of the resulting diol with thiophosgene (Scheme **8**, entry a) [15].

On the other hand the synthesis methyl 3-(3,3-dimethyl-oxiranyl)-*E*-acrylate is longer and requires a multistep sequence from 3-methyl-but-2-en-1-ol (Scheme **8**, entry b). Enantioselective epoxidation of the later has been achieved, in a low enantiomeric excess, by the Sharpless AE reaction using *tert*-butylhydroperoxide as the oxidant and *l*-diisopropyl tartrate as the chiral catalyst (TBHP, $Ti(O\text{-}i\text{-}Pr)_4$, (*l*)-DIPT, CH_2Cl_2, -20 °C, 3 h, Me_2S, 60 %, ee 74 %; Scheme **8**, entry b) [17, 20]. Fortunately the enantiomeric excess of the resulting (2*R*),3-oxido-3-methyl-butan-1-ol was increased up to 98 % by performing a single crystallization step of the corresponding nitrobenzoate in diethyl ether followed by a phase transfer catalyzed biphasic ester hydrolysis (4.1 equiv. of an aqueous 9.6 N KOH solution, 0.2 equiv. benzyltributylammonium chloride, CH_2Cl_2, 20°C, 12 h, Scheme **8**, entry b) [17, 20].

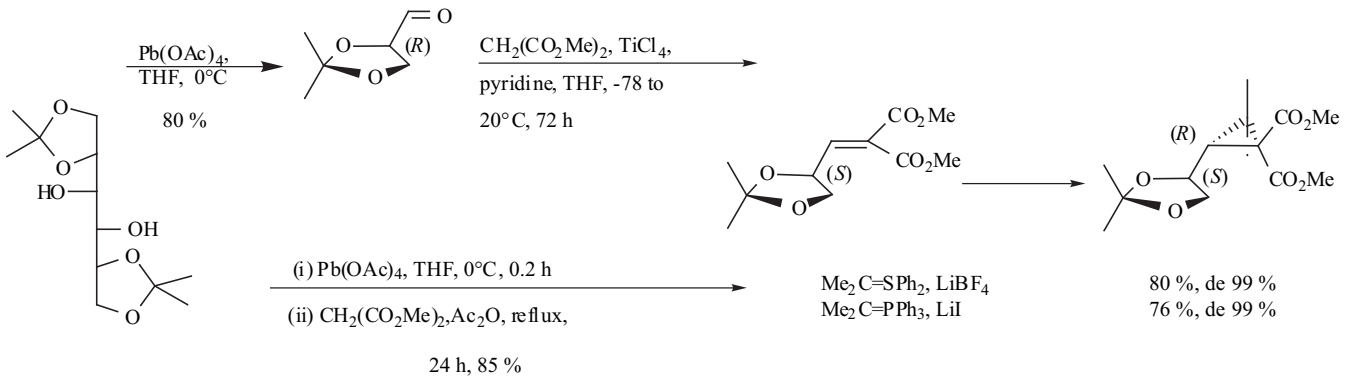
The synthesis of (*R*)-3-(3,3-dimethyl-oxiranyl)-*E*-acrylate was then achieved by oxidation, using Moffat's procedure, of (2*R*),3-oxido-3-methyl-butan-1-ol to the corresponding 3,3-dimethyl-oxirane-(2S)-carbaldehyde followed by a *E*-stereoselective Wittig olefination reaction using methyl (triphenylphosphanylidene)-acetate.

Another related approach to methyl (1*R*)-*trans*-chrysanthemate implemented isopropylidenetriphenylphosphorane and methyl (3*S*)-(5,5-dimethyl-2-thioxo-[1,3]dioxolan-4-yl)-*E*-acrylate whose stereochemistry at the chiral center is inverted as compared to the one that had reacted with isopropylidenediphenylsulfurane (Scheme **8**, entry b). This method proved however to be inefficient since not only AD-mix-α provides methyl (4*S*),5-dihydroxy-5-methyl-hex-2-enoate, with poorer enantiomeric excess than with AD-mix-β [19], but also because the cyclopropanation of the corresponding thionocarbonate by isopropylidenetriphenylphosphorane takes place with poorer ee and unexpectedly extremely poor yield (<10 %) [15].

3.3. Hemisyntheses Involving γ-Alkoxyalkylidene Malonates Prepared from Acetonide of D-Glyceraldehyde Derived from D-Mannitol

In the examples reported above the control of the stereochemistry (1*R*)/(1*S*), *cis*/*trans* at the cyclopropane ring depends on (i) the nature of the ylide (S or P) and (ii) the stereochemistry (*R* or *S*) at the asymmetric carbon as well as (iii) the stereochemistry of the [C,C] double bond of the alkyl γ-alkoxy-α,β-unsaturated carboxylates. Therefore the stereochemistry of the C,C double bond has to be perfectly controlled for successful facial control. Use of γ-alkoxy-alkylidene malonates in place of the corresponding α,β-unsaturated carboxylates avoids the latter constraint.

γ-Alkoxy-alkylidene malonates have been prepared from the corresponding aldehydes *via* a Knoevenagel reaction [15, 21, 22] between dimethyl malonate and the acetonide of (*D*)-glyceraldehyde. Titanium tetrachloride/pyridine catalyzes, when performed in THF, the formation of the desired



Scheme 9.

alkylidene malonate without epimerization at the allylic site (Scheme **9**) [15, 22]. An even more expeditious synthesis of such compound uses a one pot procedure from 1,2:5,6-di-*O*-isopropylidene-D-mannitol [15a]. The cleavage of the diol moiety is readily achieved by lead tetracetate $Pb(OAc)_4$ in THF (0 °C, 0.2 h) and (ii) the Knoevenagel reaction is directly performed on the crude 2,3-*O*-isopropylidene-D-glyceraldehyde intermediate, even not freed from the lead compound, using acetic anhydride as the reagent ($CH_2(CO_2Me)_2$, Ac_2O, reflux, 24 h, 85 %, Scheme **9**) [15a].

3.3.1. Reactions Involving Isopropylidenediphenyl-Sulfurane and Isopropylidenetriphenylphosphorane

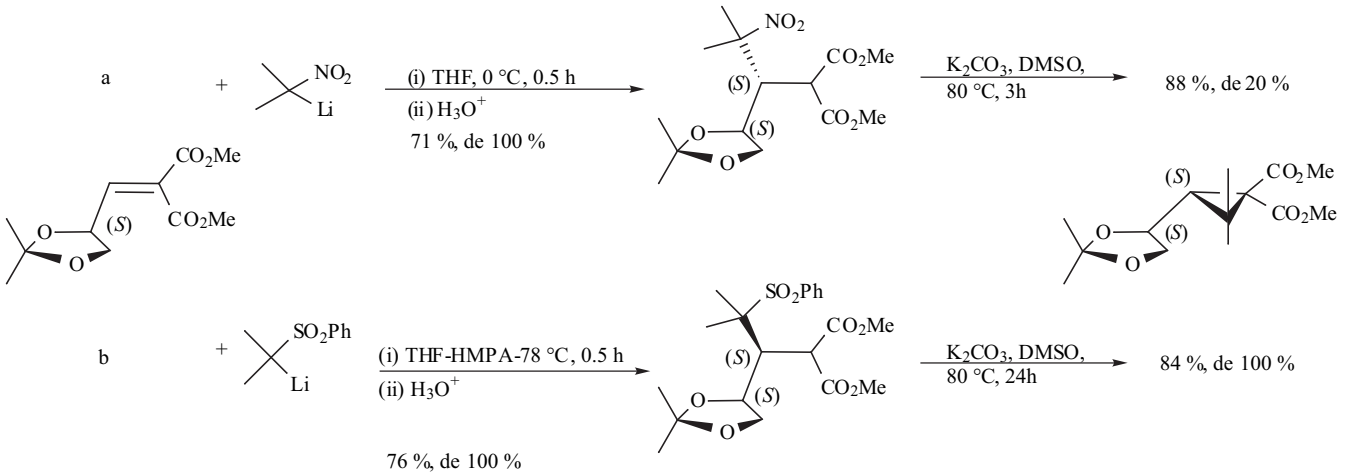
It has been found that both isopropylidenediphenylsulfurane and isopropylidenetriphenylphosphorane react by the same *Re*-face of the alkyl γ-alkoxy-alkylidene malonates derived from acetonide (*D*)-glyceraldehyde, as they do with the related alkyl γ-alkoxy-*Z*-α,β-unsaturated carboxylates and produce the cyclopropane dicarboxylate with very high diastereoselection (de 99 %, Scheme **9**) [15a, 22].

3.3.2. Reactions Involving 2-Metallo-2-sulfonylpropane and 2-Metallo-2-Nitropropane

2-Metallo-2-sulfonylpropanes [23a] and 2-metallo-2-nitropropanes [23a,b] are well known to add 1,4 to α,β-unsaturated esters and alkylidene malonates at room temperature either in THF or in DMSO. However, cyclization of the resulting enolate, leading to the formation of a cyclopropane ring proceeds only in DMSO at a temperature not lower than 80 °C [23]. These reactions have been successfully extended to alkylidene malonates derived from acetonide of (*D*)-glyceraldehyde, and lead to cyclopropane 1,1-dicarboxylates [15a, 24].

It was thus concluded that both 2-lithio-2-nitropropane (THF, 0°C, 0.5h, 71 %, de 100 %; Scheme **10**, entry a) [24] and 2-lithio-2-sulfonylpropane (THF, -78°C or 20°C, 0.5 h, 72 %, de 92 %; or THF-HMPA, -78°C, 0.5 h, 76 %, de 100, Scheme **10**, entry b) [24] add 1,4 to dimethyl (*S*)-2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonate in THF to produce the corresponding γ-nitro or the γ-sulfonyl malonates after hydrolysis.

2-Lithio-2-nitropropane reacts by the *Re*-face of the same alkylidenemalonate (Scheme **10**, entry a) [24] whereas the related 2-lithio-2-sulfonylpropane exclusively reacts by the other *Si*-face (Scheme **10**, entry b) [24]. Reaction of these adducts with caronates in DMSO at 80°C, which finally leads to the corresponding cyclopropane dicarboxylates is faster with cesium and potassium caronates than with either sodium or lithium analogs [24]. The cyclization reaction proceeds stereoselectively from the sulfonyl derivative without epimerization at newly formed stereogenic centre (Scheme **10**, entry b). It however works differently from the corresponding nitro derivative since epimerization accompanies, through competing retro-Michael reaction [24].



Scheme 10.

The cyclopropane dicarboxylate obtained in this manner possesses the same stereochemistry but a poorer diastereoisomeric excess as the one formed from the sulfonyl derivative (Scheme **10**, entry a, compare to entry b) [24].

The next step to achieve is the synthesis of enantiopure (1*R*)-*trans*-chrysanthemic and (1*R*)-*cis*-deltamethrinic acid from suitable 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl esters (Scheme **11**) [15a].

These transformations require, depending on the case involved, the formal selective removal of the carbomethoxy group *cis*- or *trans*- from the side chain of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl esters possessing the same stereochemistry at the carbon bearing the alkoxy group. This has been shown to be achieved from the cyclopropane-dicarboxylates, derived either from 2-lithio-2-sulfonyl-propane or from isopropylidenetriphenylphosphorane or isopropylidenediphenylsulfurane respectively (Scheme **11**) [15a].

We planned to generate enantiopure (1*R*)-*trans*-chrysanthemic acid by sequential demethylation-decarboxylation reaction indistinctly of either one of the two carbomethoxy groups of the cyclopropane-1,1-dicarboxylate then to induce epimerization at the carbon of the cyclopropane bearing the carboxy group of the resulting cyclopropane carboxylate. This would therefore be best achieved from cyclopropane derivatives possessing the largest groups at C-1 and C-3 (Scheme **11**, entry a) [15a].

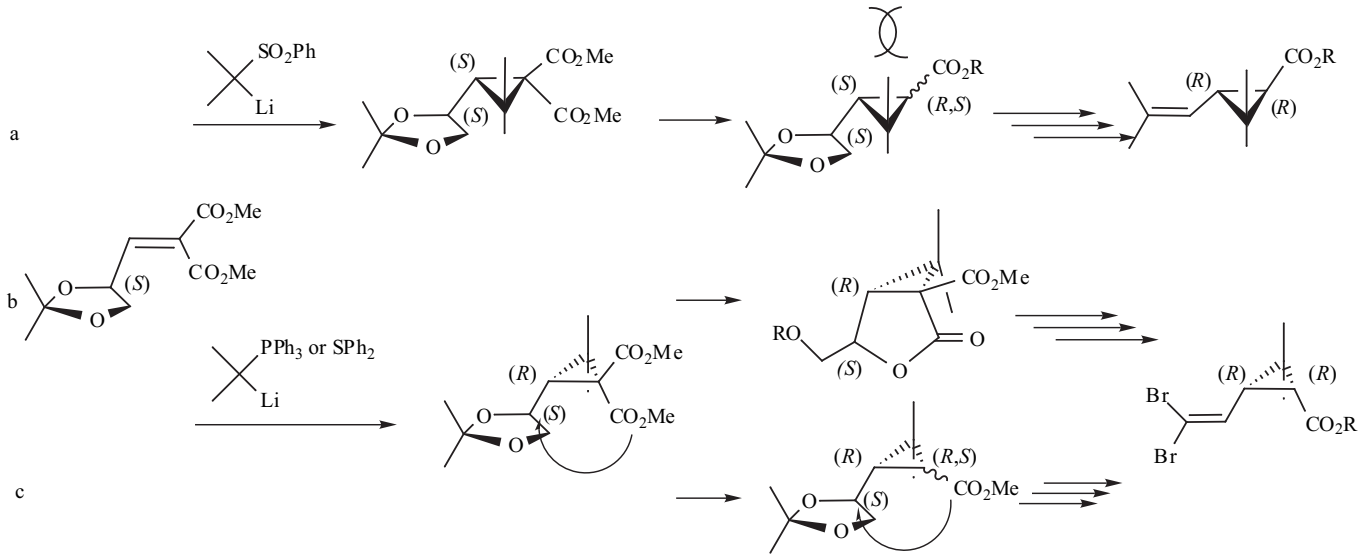
The synthesis of deltamethrinic acid possessing the *cis*-stereochemistry could be achievable by demethylation-decarboxylation sequence of 4-hydroxymethyl-6,6-dimethyl-2-oxo-3-oxa-bicyclo[3.1.0]hexane-1-carboxylic acid methyl ester possessing the bicyclic[3.1.0] lactone ring flanked with the carbomethoxy group at the bridgehead position (Scheme **11**, entry b).

Since all our efforts, including radical promoted Barton decarboxylation reaction [25], proved to be unsuccessful, we envisaged that it would be preferable to perform the demethylation-decarboxylation firstly and to achieve epimerization in the presence of a free hydroxyl group aimed to favor the formation of the *cis*-stereoisomer by tandem epimerization-lactone ring formation (Scheme **11**, entry c).

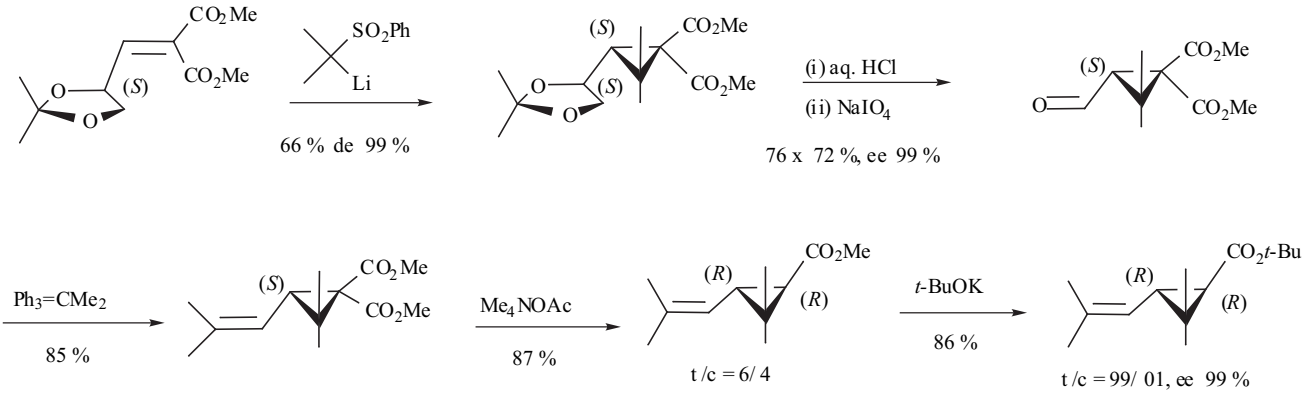
The synthesis of (1*R*)-*trans*-chrysanthemic acid has been achieved from 3(*S*)-(S)(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester. which has been synthesized in a single pot by addition of 2-lithio-2-sulfonyl-propane to 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester in THF-HMPA and cyclization of the resulting enolate by addition of DMSO and heating up to 80 °C (64 h, 66 % yield, de 99 %, Scheme **12**) [15a, 24].

Acid hydrolysis of the acetonide group present on the resulting 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester followed by cleavage of the resulting diol with sodium periodate leads to the synthesis of 3-formyl-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester ((i) aq. HCl, MeOH, 20 °C, 0.2 h, 76 % (ii) $NaIO_4$, MeOH, pH= 7, 20 °C, 1 h, 72 % yield, ee 99, Scheme **12**). The reaction of the later with isopropylidenetriphenylphosphorane ultimately produces 2,2-dimethyl-3-vinyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester in up to 85 % yield ($Ph_3P{=}CMe_2$, THF, 0°C-20°C, 2 h, Scheme **12**) [15a].

Demethylative-decarboxylation step was far from obvious. Several methods were tried but with moderate success. The Johnson's method, which used tetramethylammonium acetate in HMPA [26], proved to be the best since it occurs at comparatively lower temperature and provides methyl chrysanthemate in good yield (Me_4NOAc, HMPA, 95 °C, 4 h, 87 % *trans*/*cis* : 6/4, Scheme **12**) [15a]. The stereochemical outcome was however quite modest and requires an additional step to produce the *trans*-chrysanthemate stereoisomer. This was effectively achieved by treatment of the resulting methyl *t*rans/*cis*-chrysanthemate with potassium *tert*-butoxide in THF. Epimerization to the *trans*-derivatives worked extremely



Scheme 11.



Scheme 12.

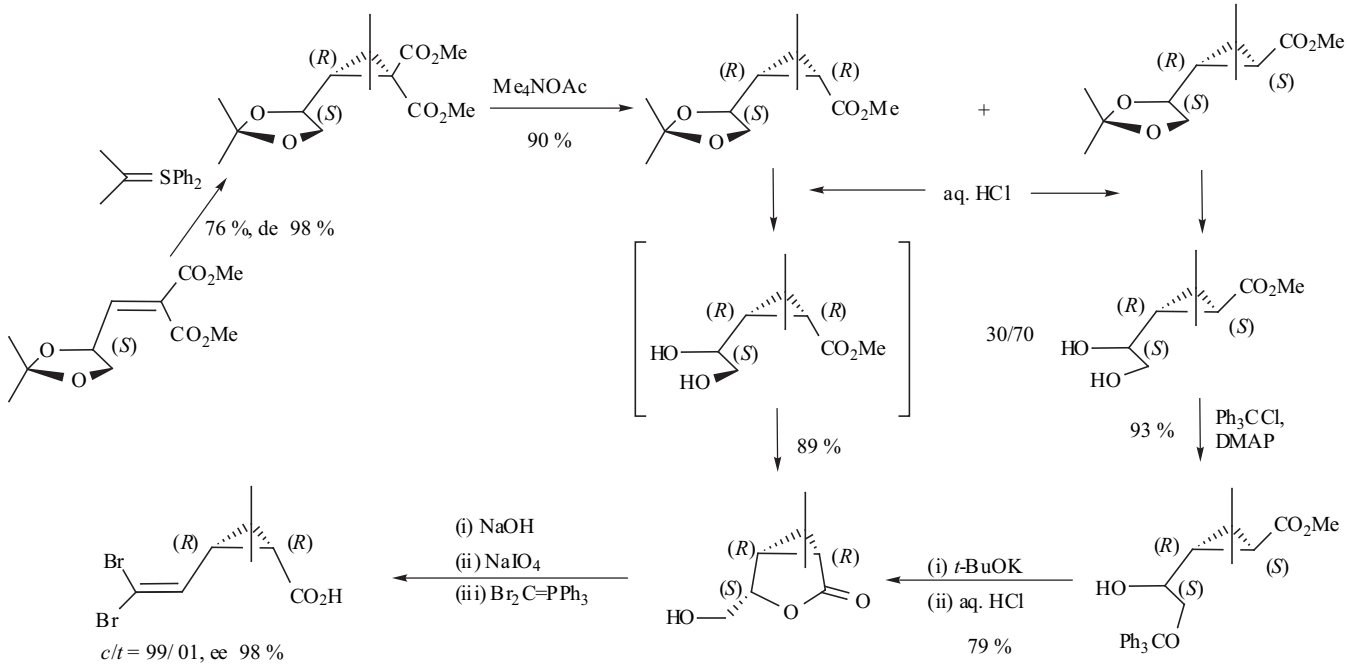
well but transesterification to *tert*-butyl (1*R*)-*trans*-chrysanthemate took concomitantly place (*t*-BuOK, THF, 20°C, 2 h, 86 % yield, *t /c* = 99/ 01, ee 99 %, Scheme **12**) [15a].

The strategy used for the synthesis of deltamethrinic acid was somewhat different. Isopropylidenediphenylsulfurane was found to be the most appropriate reagent to achieve the formation of the cyclopropane ring possessing the (2*R*)-stereochemistry (Me_2C= SPh_2, $LiBF_4$, DME, -78 °C, 2 h then 20 °C, 1 h, 76 %, de 98 % yield, Scheme **13**) [15a, 22] and its demethylative-decarboxylation was efficiently performed by tetramethylammonium acetate as outlined above (Me_4NOAc, HMPA, 95 °C, 4 h, 90 % yield) [15a, 26]. It nevertheless affords a 7/3 *trans/cis*-mixture of methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropanecarboxylate. This mixture was directly subjected to acid hydrolysis to produce a mixture of methyl *trans*-3-(1,2-dihydroxy-ethyl)-2,2-dimethyl-cyclopropanecarboxylate and of 4-hydroxymethyl-6,6-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-one resulting from the in *situ* lactonization of the *cis*-stereoisomer (10 % HCl, MeOH 20 °C, 0,5 h, 93 % and 89 % respectively, Scheme **13**) [15a].

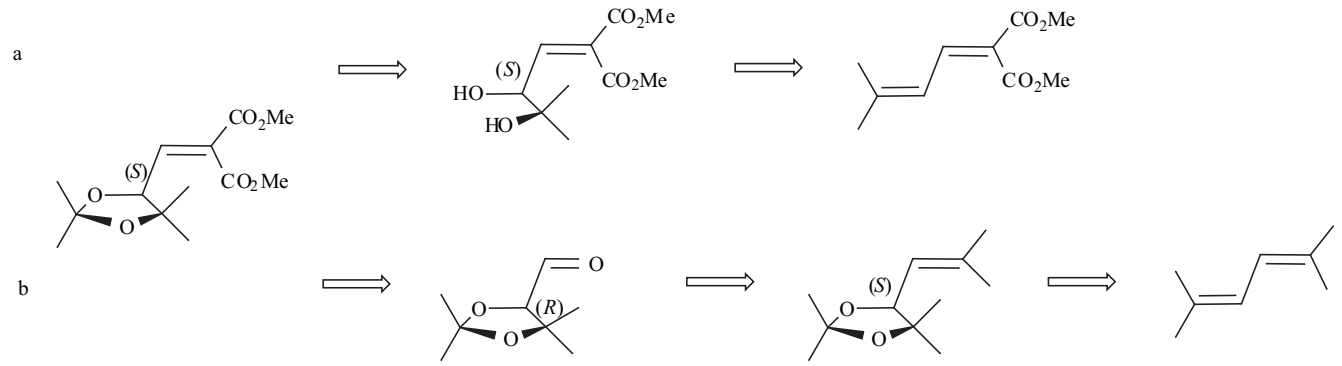
Lactonization of methyl *trans*-3-(1,2-dihydroxy-ethyl)-2,2-dimethyl-cyclopropanecarboxylate which requires a contrathermodynamic *trans*/*cis* isomerisation to deliver 4-hydroxymethyl-6,6-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-one was not as obvious as we expected since at the contrary of methyl *trans*-3-hydroxymethyl-2,2-dimethyl-cyclopropanecarboxylate which misses extra hydroxymethylene group [10], it was insensitive to potassium *t*-butoxide.

Lactonization was nevertheless achieved using potassium *tert*-butoxide, after the protection of primary hydroxymethylene group as trityl ether ((i) Ph_3CCl, DMAP, CH_2Cl_2, 40 °C, 16 h, 88 % yield (ii)) *t*-BuOK, benzene, 80°C, 6 h, 79 % yield, Scheme **13**) [15a]. In the following step acid treatment allows the removal the trityl protecting group and the formation of 4-hydroxymethyl-6,6-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-one (HCl 10 %, MeOH, 20 °C, 1 h, 79 % yield, Scheme **13**) [15a].

The synthesis of deltamethrinic acid from the resulting lactone was already described. It involves (i) potassium hydroxide lactone ring opening (ii) sodium periodate cleavage of the diol moiety present on the resulting 3-(1,2-



Scheme 13.



Scheme 14.

dihydroxy-ethyl)-2,2-dimethyl-cyclopropanecarboxylic acid which leads to 4-hydroxy-6,6-dimethyl-3-oxa-bicyclo[3.1.0] hexan-2-one and finally (iii) Wittig type reaction using carbon tetrabromide and triphenylphosphine (Scheme **13**) [15a].

3.4. Syntheses Involving γ-Alkoxyalkylidene Malonates Prepared *via* Sharpless AD Reaction

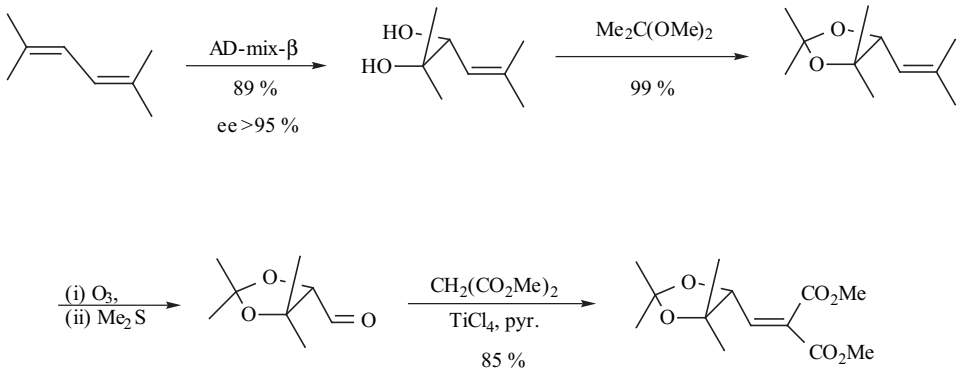
The synthesis of methyl (1*R*)-*trans*-chrysanthemate from (*S*)-2-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester avoids a number of steps which are required to built the 2-methylpropenyl moiety when 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester is instead used (Scheme **12**).

We have been unable to synthesize (*S*)-2-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester from 2-(3-methyl-but-2-enylidene)-malonic acid dimethyl ester and ADmix β (Scheme **14**, entry a, compare to Scheme **8**, entry a). Its synthesis has been nevertheless achieved in a more lengthy route from 2,5-dimethyl-hexa-2,4-diene and ADmix β (Scheme **14**, entry b).

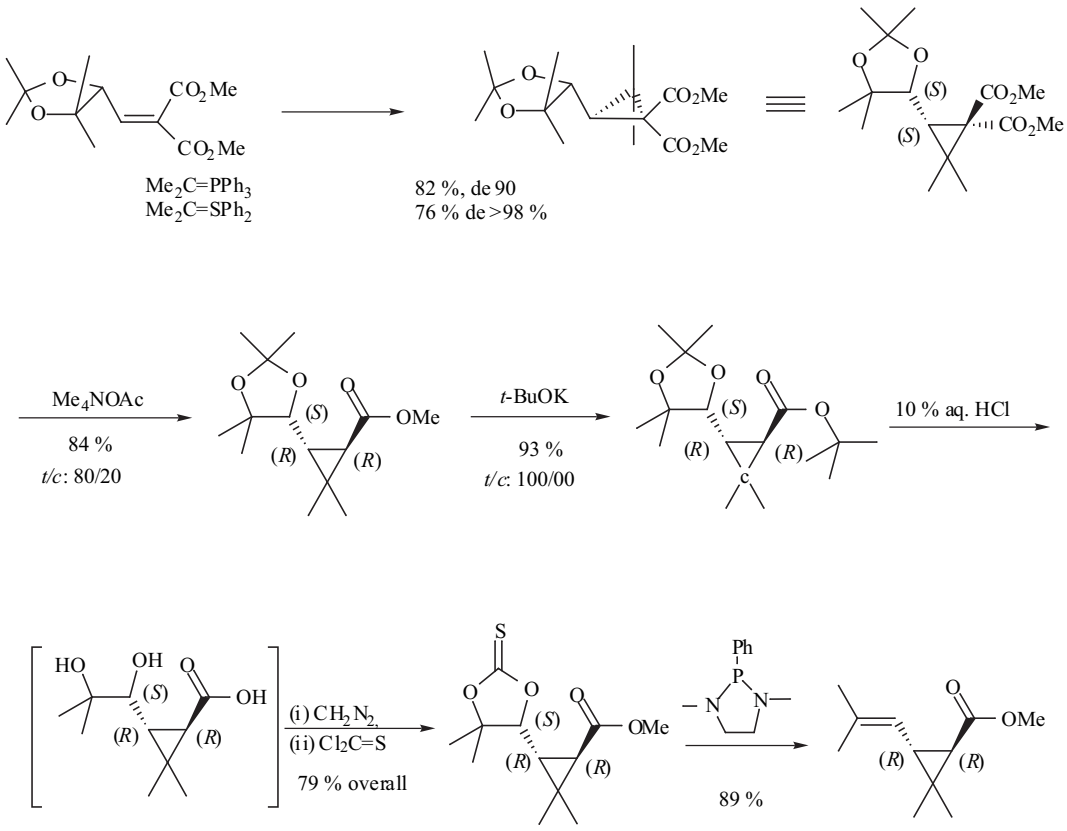
Dihydroxylation of 2,5-dimethyl-hexa-2,4-diene was, as expected, readily achieved with high asymmetric induction using ADmix-β (AD-mix-β, $MeSO_2NH_2$, *t*-BuOH-H_2O, 20°C, 3 h, 89 %, ee >95 %, Scheme **15**). Treatment of the resulting diol with 2,2-dimethoxypropane and acetone in the presence of catalytic amounts of *p*-TSA, as an acid catalyst, provides 2,2,4,4-tetramethyl-5-(2-methyl-propenyl)-[1,3] dioxolane (2,2-dimethoxypropane, acetone, *p*-TSA, 20 °C, 2h, 99 %, Scheme **15**). Ozonolysis of the later ((a) O_3, CH_2Cl_2, -78 °C, 2 h, (b) Me_2S, 20 °C, 2 h, 80 %, Scheme **15**) followed by treatment of the corresponding crude aldehyde with dimethylmalonate in the presence of titanium tetrachloride complexed to pyridine, allows the synthesis of 2-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester in reasonably good yield and extremely high enantioselectivity ($TiCl_4$, pyr., THF, -78 °C then 20°C, 72 h, 85 %, ee > 95 %, Scheme **15**) [15a].

As already discussed isopropylidenediphenylsulfurane and tetramethylammonium acetate proved to be the best reagents to perform the cyclopropanation of 2-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester and tandem demethylative-decarboxylation reaction leading to methyl 2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropanecarboxylate respectively (Me_4NOAc, HMPA, 95 °C, 6 h, 74 %, Scheme **16**).

Epimerization at C-1 was required since the later reaction leads to a 4/1 mixture of *trans/cis* diastereoisomeric methyl 2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropanecarboxylate (Scheme **16**) [15a]. It has been achieved under extremely mild conditions using potassium *tert*-butoxide and leads to *tert*-butyl *trans*-2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropanecarboxylate as a single product arising from a competing *trans*-esterification (*tert*-BuOK, THF, 20 °C, 2 h, 92 %, *t*/*c*: 100/00, Scheme **16**) [15a]. The presence of this bulky group surely favors the *trans*-stereochemistry. Surprisingly this conditions lead to quite sluggish results when applied to ethyl *cis*-chrysanthemate.



Scheme 15.



Scheme 16.

Acid hydrolysis destroys at the same time the dioxolane and the *tert*-butyl ester moieties and leads to 3-(1,2-dihydroxy-2-methyl-propyl)-2,2-dimethyl-cyclopropanecarboxylic acid (10 % aq. HCl, MeOH, 20 °C, 4 h). Reaction of the later sequentially with diazomethane and thiophosgene ((i) CH_2N_2, Et_2O, 20°C, (ii) Cl_2C=S, DMAP, 0°C, 2 h, 79 % overall, Scheme **16**) produces methyl 3-(5,5-dimethyl-2-thioxo-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropanecarboxylate which on reaction with 1,3-dimethyl-2-phenyl-[1,3,2]diazaphospholidine according to the Corey-Hopkins procedure [16] allows under very mild conditions the synthesis of methyl (1*R*)-*trans*-chrysanthemate as almost a single enantiomer (40 °C, 6 h, neat, 89 %, Scheme **16**) [15a].

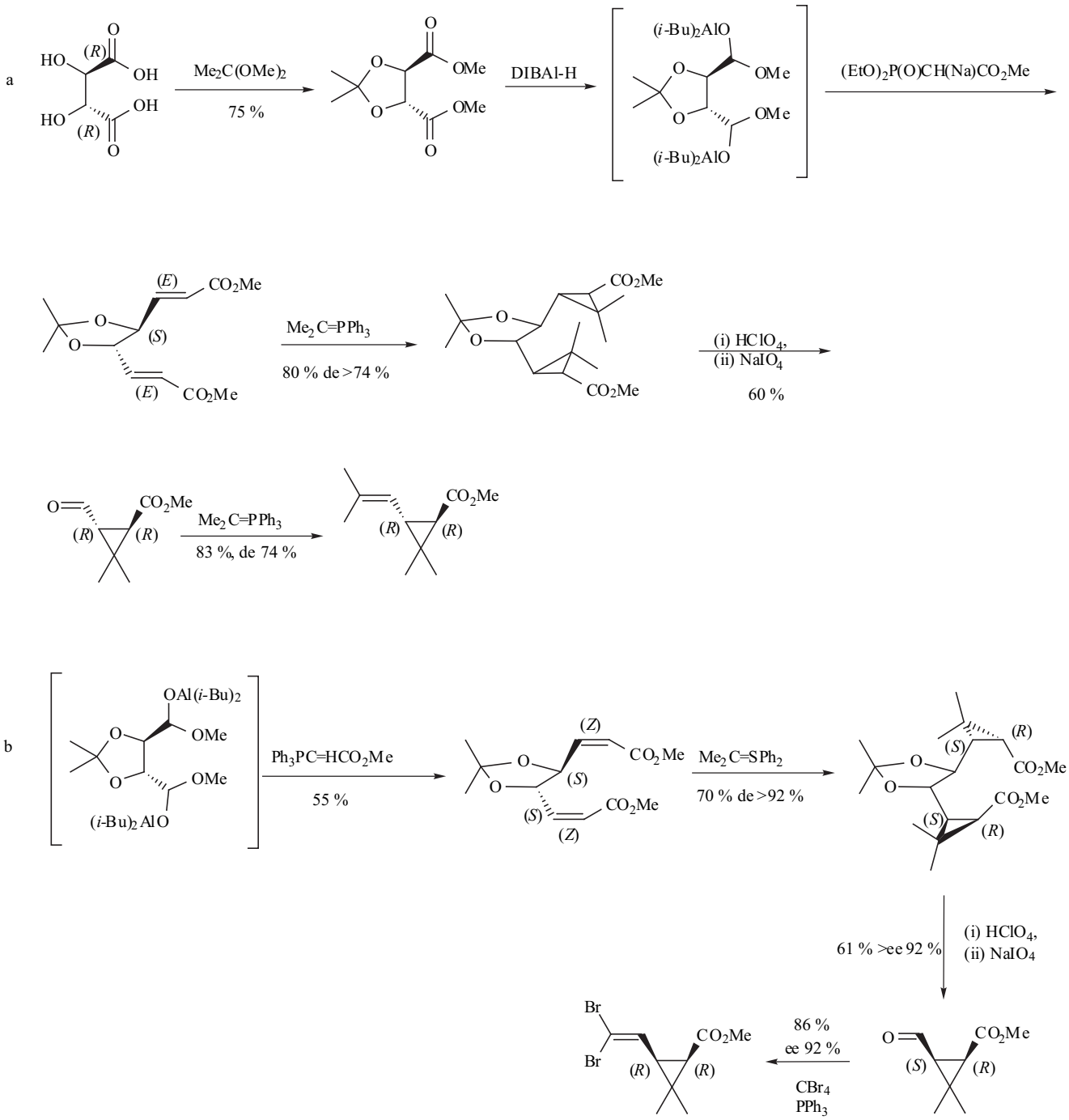
3.5. Hemisyntheses Involving γ-Alkoxy-Dienoates Prepared from Acetonide of Tartaric Acid or from 3,4-Acetonide of D-Mannitol

Closely related approaches to pyrethroic acids involve twice the cyclopropanation, using isopropylidene ylides, of methyl 3-[5-(2-methoxycarbonyl-vinyl)-2,2-dimethyl-[1,3] dioxolan-4-yl]-acrylates (Schemes **17**, **18a**) or related dialkylidenemalonates (Scheme **18b**). They take advantage of the production of two equivalents of methyl 3-formyl-2,2-dimethyl-cyclopropanecarboxylate (methyl hemicaronate) or 3-formyl-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester respectively, after acid hydrolysis of the acetonide moiety and oxidative cleavage of the resulting diol.

The above mentioned acrylates and related dialkylidenemalonates have been synthesized, with very high stereocontrol, using a Wittig or a Knoevenagel olefination reaction from 2,2-dimethyl-[1,3]dioxolane-4,5-dicarbaldehydes or related di-aluminates of [5-(hydroxy-methoxy-methyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methoxy-methanol respectively [14, 15a].

The later possessing either (*R,R*)- or the (*S,S*)-stereochemistry have been conveniently prepared by reduction of 2,2-dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester, the acetonide of dimethyl tartrate ((2*R*,3*R*)-dihydroxy-succinic acid, Scheme **17**) [14] and by oxidative cleavage of 1-[5-(1,2-dihydroxy-ethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-ethane-1,2-diol, the internal acetonide of mannitol (-(1,2*R*,3*R*,4*R,*5*R*,6-hexaol, Scheme **18**) [14, 15a].

Typically the transformation of (2*R*,3*R*) tartaric acid to methyl (*S,S*)-3-[5-(2-methoxycarbonyl-vinyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-acrylate has been achieved in three steps two-pot reactions involving: (i) acid catalyzed acetonide formation ($Me_2C(OMe)_2$, TsOH, MeOH, reflux, 14 h), (ii) di-isobutylaluminumhydride reduction of the resulting 2,2-dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester and (iii) olefination of the intermediary formed alcoholate to produce in one pot the desired di-*trans*-α,β-unsaturated dimethyl ester using sodium diethylphosphonoacetate in DME ($(EtO)_2P(O)CH(Na)CO_2Me$, DME, -78 °C, 0.1 h then 20 °C, 4h, Scheme **17**, entry a). Cyclopropanation was achieved with isopropylidenetriphenylphosphorane and as expected it reacts twice by the *Si*-face of each its C,C double bonds with modest de (2.5 eq. $Ph_3P=C(Me)_2$, LiI, THF, 0°C, 1 h then 20 °C, 1 h, 80 %, de 74 %, Scheme **17**, entry



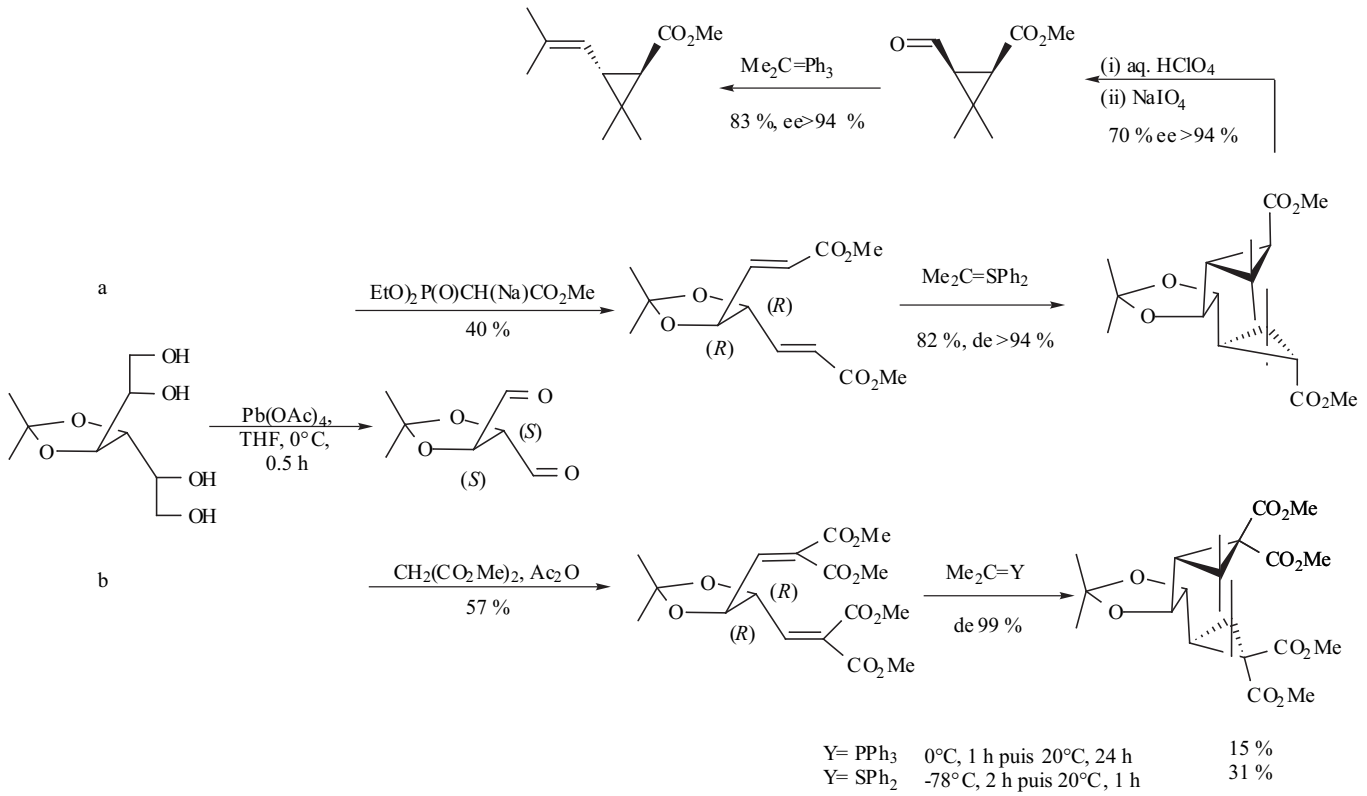
Scheme 17.

a). Acid hydrolysis of the dioxolane moiety and oxidative cleavage of the resulting diol and reaction of isopropylidenetriphenylphosphorane leads to methyl *trans*-chrysanthemate (Scheme **17**, entry a, de 74 %).

As expected methyl (1*R*)-*trans*-chrysanthemate has been synthesized in much better stereocontrol from *trans*-(*R*,*R*)-di-enoates and isopropylidenediphenylsulfurane ($Ph_2S{=}C(Me)_2$, DME, -78 °C, 0.2 h then -78°C to -50 °C, 0.7 h then -50°C to 20 °C, 0.3 h, de 94 %; Scheme **18**, entry b) using the same set of reactions described above (Scheme **17**, entry a).

Trans-(*R*,*R*)-di-Enoates have been readily synthesized from mannitol, protected internally as 3,4-dioxolane (Scheme **18**, compare to Scheme **17**). Lead tetracetate cleavage of the two external diols produces the highly water soluble (2*S*,3*S*)-dihydroxy-succinaldehyde which on reaction with diethylphosphonoacetate in DME leads to the formation of di-*trans*-α,β-unsaturated dimethyl ester possessing the (*R*,*R*)-absolute stereochemistry (Scheme **18**, entry a).

A related approach which uses isopropylidene-diphenylsulfurane and (*S*,*S*)-di-*cis*-di-α,β-unsaturated dime-



Scheme 18.

thyl esters allows the synthesis of deltamethrinic acid in good yield (Scheme **17**, entry b) [14].

It has finally been observed that *Re*-face attack almost exclusively takes place on reaction of di-alkylidene malonates, synthesized from (2*S*,3*S*)-dihydroxy-succinaldehyde, either with isopropylidenetriphenylphosphorane or with isopropylidenediphenylsulfurane (Scheme **18**, entry b) [15a].

4. CONCLUSION

In conclusion γ-alkoxy-α,β-unsaturated esters, including alkylidene malonates, derived from enantiopure D-glyceraldehyde or dihydroxy-succinates are valuable starting materials for enantioselective synthesis of alkyl pyrethroates. Their diastereoselective cyclopropanation has been efficiently performed using α-heterosubstituted organometallics. Isopropylidenediphenylsulfurane and 2-sulfonyl-2-propyllithium proved to be the best reagents since they provide almost a single enantiomer of alkyl chrysanthemates (Scheme **7**, entry a; Scheme **8**; Scheme **12**; Scheme **16**; Scheme **17** entry a; Scheme **18**, entry a) and alkyl deltamethrinates (Scheme **7**, entry d; Scheme **13**; Scheme **17**, entry b) [27].

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