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Review

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Pyrethroid insecticides Chapter IVb. Selected transformations of chrysanthemic acid and its lower esters to Pyrethroids. Use of the Wittig- and related reactions

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Dedicated to Prof. Atta-ur-Rahman for his lifelong dedication to Science and to Scientific Education at the occasion of his 80th Birthday

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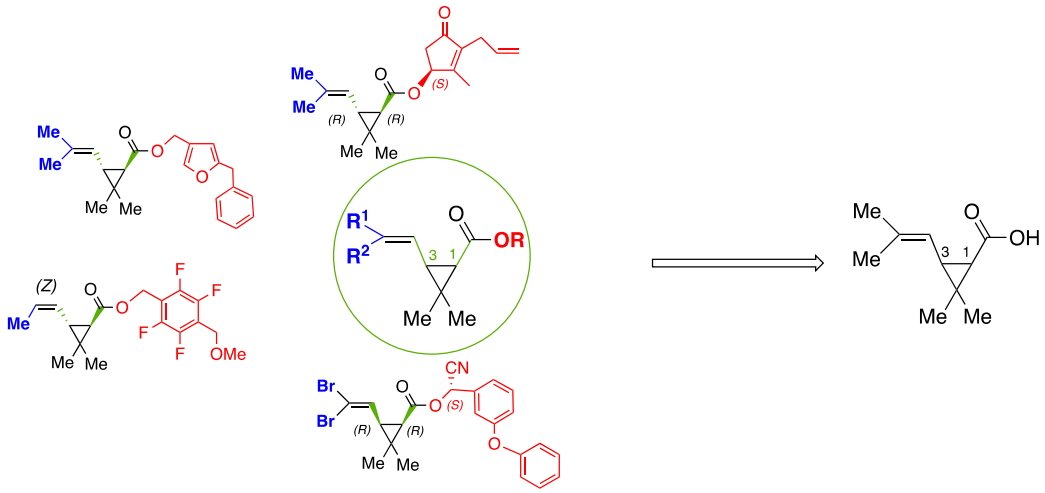
Abstract

Pyrethroids bearing different substituents on their ester group and on their vinylic moiety and possessing either the natural (1*R*)-*trans*-stereochemistry or the unnatural (1*R*)-*cis*-stereochemistry have been found to possess an even increased insecticidal properties compared to the natural pyrethrin I. Their discovery relates to modifications carried out systematically on chrysanthemic acid and its lower esters.



Keywords: Vinylcyclopropane carboxylic esters. Esterification reactions, olefination reactions, epimerization and racemization reactions. Wittig reaction, Wadsworth-Emmons-reaction, Ramirez reaction

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1. Introduction

Since the discovery of the properties of pyrethrin I and pyrethrin II as valuable insecticides and their structure elucidation, several analogues (may be more than 50.000) have been synthesized and tested towards a variety of insects and mammals to determine their biological properties that should be as high as possible for the former and as low as possible for the latter.

Pyrethroids for domestic applications that have a limited lifetime or were designed to protect against mosquitoes through special delivery methods are now available. Others have to come to help human to adjust the competing struggle for life between species, to fight adaptation of insects to pyrethroid insecticides that thwarts their lethal effect.

1.1. Structures of some bioactive pyrethroids

Variations on the structure of pyrethrin I (**1a**$_{\mathbf{A}}$) and to a lower extend on that of Pyrethin II (**1b**$_{MeA}$) have affected[1-5] (i) the alkoxy part exemplified by allethrin (**1a**$_{\mathbf{B}}$) (LaForge; 1949) or prallethrin (**1a**$_{C}$) (Katsuda; 1967) in which the structural variations are minimal (Figure 1, entry a) to resmethrin (**1a**$_{D}$) (Elliot 1966), phenothrin (**1a**$_{E}$) (Itaya, 1973) and cyphenothrin (**1a**$_{\mathbf{F}}$) (Itaya, 1976) that possess an alkoxy part dramatically different from the original one (Figure 1, entry b) [1-7] (ii) those in which slight changes appear on the vinyl cyclopropane moiety[1-5] such as "nor-allethrin" (**1c**$_{B}$) (Elliot, Ohno; 1970) or metofluthrin (**1c**$_{G}$) (Matsuo; 1998)[2,11] (iii) those in which important changes are present on the vinyl cyclopropane moiety such as "dichloro-allethrin" (**1d**$_{\mathbf{B}}$) (Farkas; 1958), or (iv) on both the vinyl cyclopropane and the alkoxy moieties[1-7] such as fluorethrin **1e**$_{\mathbf{D}}$ (Brown; 1975), chlorethrin (**1d**$_{D}$), bromethrin (**1f**$_{D}$) (Brown, Elliott; 1973) or permethrin (**1d**$_{E}$) (Elliott; 1972) and cypermethrin (**1d**$_{F}$) (Elliott; 1973) or deltamethrin (**1f**$_{F}$) (Elliott; 1974).

Those bearing a cyclopentenolone[4,6] or a methyl-furfuryl moiety belong to the class of photolabile pyrethroids whereas those possessing a benzylic moiety[4,7] belong to the photostable class.[8]

Even more profound changes are associated with terallethrin (**1y**$_{B}$ (Matsui; 1967) that lacks the vinylic moiety, fenpropathrin (**1y**$_{E}$) (Matsuo; 1971) that in complement misses the cyclopentenolone entity and fenvalerate (**1z**$_{F}$) (Ohno and Hirano; 1973) that is still an ester but even misses the cyclopropane ring (Figure 2).

Furthermore, most of those pyrethroids possess several asymmetric centers and thus exist as several stereoisomers, one of them being far more active than the others. As a general trend, the most active stereoisomers possess the (1*R*)-stereochemistry on the cyclopropane ring and the (*S*)-stereochemistry at the asymmetric center on the alkoxy-group, if any.

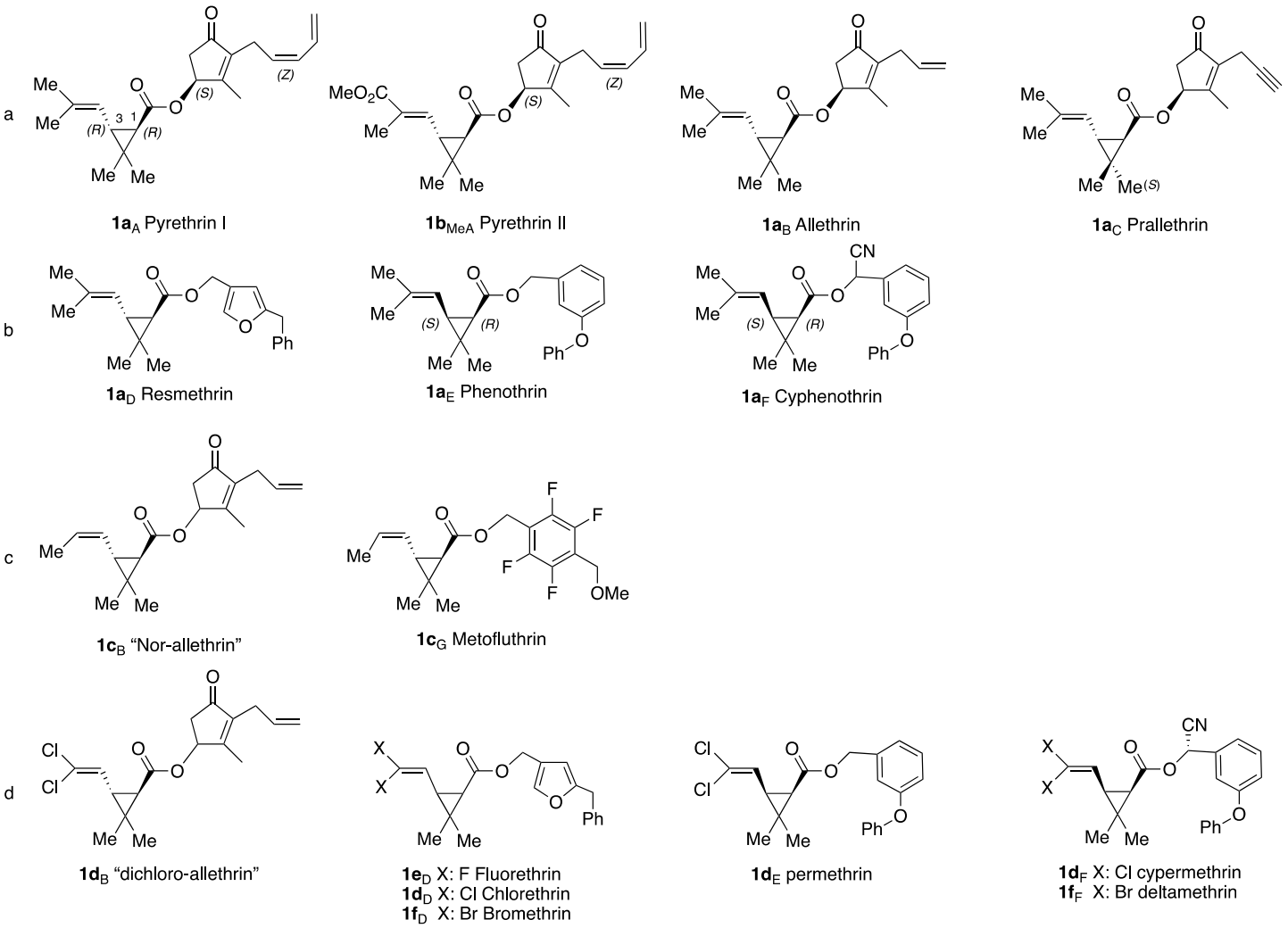


Figure 1. Structure of important pyrethrins and pyrethroids.

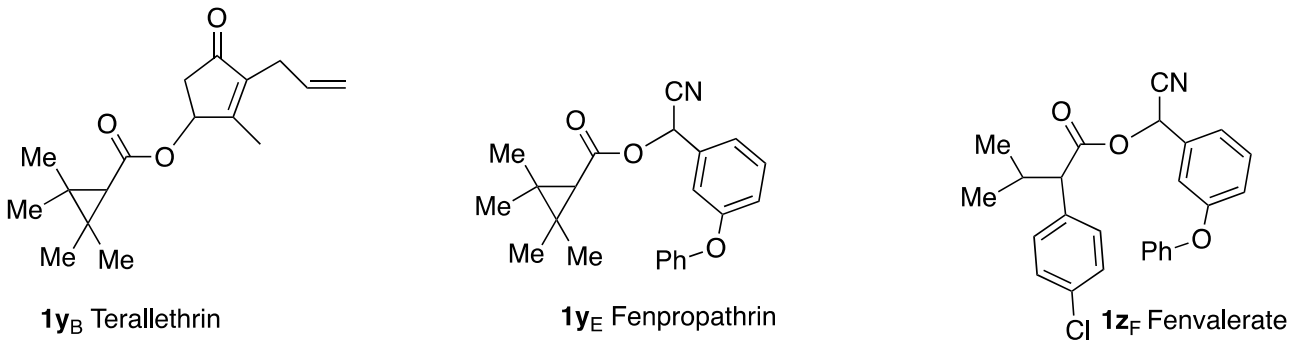


Figure 2. Pyrethroids possessing an unusual structure.

Detailed information concerning some of those pyrethroids that are commercially available as a mixture of stereoisomers or as pure enantiomers are reported below and will be used in this review as models to sustain our presentation. They have been purposely selected not only for their structural diversity but also to briefly

disclose their biological properties and their use so that the reader will be able to access at least part of the structure/activity relationships. Thus:

(i) allethrin (**1a**$_B$),[4,6] possesses a structure very closely related to that of pyrethrin I (**1a**$_A$) but lacks the terminal vinyl group on the pyrethrolone moiety that greatly simplifies its synthesis. (*S*)-bio-allethrin, the (*S*,1*R*,3*R*)-enantiomer of allethrin (1*R*,3*R*)-(**1a**$_B$), is sold for domestic use against flying and crawling insects and is far more active than allethrin (**1a**$_B$) that possesses the same gross structure but is sold as a mixture of stereoisomers,

(ii) resmethrin (**1a**$_D$) also differs from pyrethrin I (**1a**$_A$) by its alkoxy moiety that does not possess an asymmetric center. It not only keeps the number of stereoisomers lower but dramatically simplifies the synthesis. Resmethrin is sold as a racemic mixture of (1*R*,3*R*)-*trans*/(1*S*,3*S*)-*trans/*(1*R*,3*S*)-*cis*/(1*S*,3*R*)-*cis* in a ratio of 4/4/1/1 in which the *trans*- and more active stereoisomer prevails. It has been used for indoor applications especially against mosquitoes but its extreme fish toxicity has restricted its use,

(iii) pyrethrin II (**1b**$_{MeA}$), is an enantiopure natural product with the (*S*,1*R*,3*R*)-*trans*-stereochemistry possessing the natural pyrethrolone moiety but differs from pyrethrin I (**1a**$_A$) in the replacement of one of the methyl group (*trans* to the cyclopropyl moiety) of the isobutenyl moiety in (**1a**$_A$) by a carbomethoxy group.[3,4] Oxidation of such methyl group of (**1a**$_A$) in the environment is one of the detoxification pathways of pyrethroids. Pyrethrin II is not commercially available but there is a tendency to avoid cultivation and extraction procedures[9] or in vitro production[10] of natural pyrethroids. Alternatively, marketing a mixture of synthetic natural pyrethroids in proportion similar to that present in the pyrethrum powder that results from the extraction of chrysanthemum cinerariaefolium, should offer the advantage to avoid the allergens present in the natural extracts,

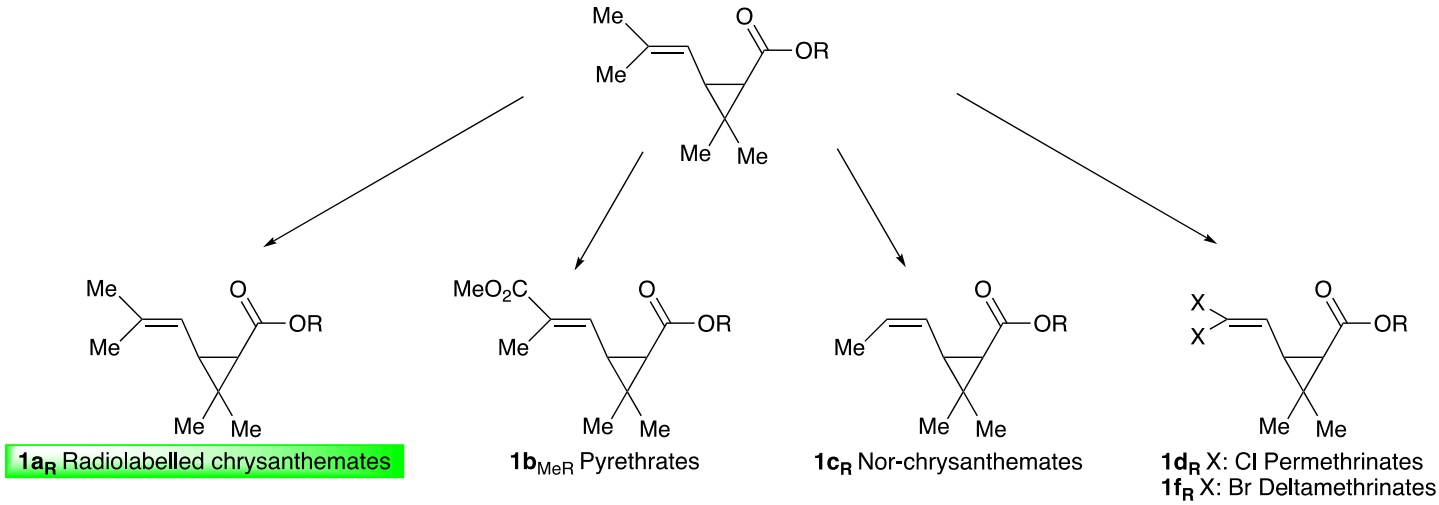
(iv) methofluthrin (**1c**$_G$)[2,11] differs from pyrethrin I by (i) its ester group that is a benzyloxy moiety and (ii) since it lacks the vinylic methyl group *trans* to the cyclopropyl moiety.[3,4] The absence of this methyl group on which one of detoxification process occurs, is beneficial to avoid its deactivation. It also participates in conjunction with the benzylic moiety to its relatively high volatility not only suitable in formulations such as coils and liquid vaporizers but also fan vaporizers and paper or resin emanators that are efficient at room temperature.[11] Methofluthrin possesses extremely high insecticidal and repellent activity especially towards mosquitoes and low mammalian toxicity. Note, however, that the absence of the *trans*-methyl group introduces an additional complexity for its synthesis. The *Z*-(1*R*,3*R*)-*trans*-stereoisomer proved to be the most active,

(v) cypermethrin (**1d**$_F$) and deltamethrin (**1f**$_F$) substantially differ from pyrethrin I (**1a**$_A$) by (i) the nature of their ester group (bearing a mandelonitrile moiety)[7], (ii) the substitution of their vinyl group (two halogens in place of two methyl group) and (iii) the relative stereochemistry on the three membered cycle ((1*R*)-*cis* instead of (1*R*)-*trans*).

Both compounds have been engineered to fulfil agricultural needs and are sold for that purpose (20-40 g/hectare/season). They are stable enough to protect crops for sufficient time and then disappear so no trace can be found on the food. Cypermethrin (**1d**$_F$) is sold as the mixture of stereoisomers, whereas deltamethrin (**1f**$_F$) is sold as the enantiopure (*S*,1*R,3S*)-*cis*-enantiomer and is the most active insecticide of the series.[1,2,3,4,5]

The transformations of chrysanthemic acid to analogues has been carried out in different companies and research centres especially in France, UK, Japan and Germany, among others. Comparative results that are reported below speak for themselves [Relative toxicity against *Spodoptera littoralis*: [deltamethrin/cypermethrin/parathion/monocrotophos/DDT: 1/10/1.300/7.700/32.000].

The model transformations that will be reported are disclosed in Scheme 1.



Scheme 1. Stucture of the vinylcyclopropane carboxylates implied in some commercial pyrethroids.

1.2. Strategies to access pyrethroids from chrysanthemic acid

This paper reviews the strategies and methods that allow rapid access, from chrysanthemic acid/lower esters, to a large variety of analogues of pyrethrin I (such as the one listed in Figure 1a) to test as insecticides. Those variations involve the nature of: (i) the alkoxy groups at [Ca] (Variation A, Scheme 2), (ii) the vinylic substituents at [Cf] (Variation B, Scheme 2) as well as, eventually (iii) the stereochemistry at [Cd] leading to (1*R*)-*cis*-series (Variation C, Scheme 2).

They allow access, in reasonably large quantities, to those compounds as pure stereoisomers especially in the (1*R*)-*trans* and the (1*R*)-*cis*-series as well as to a mixture of stereoisomers and often involves:

(i) esterification or transesterification reactions

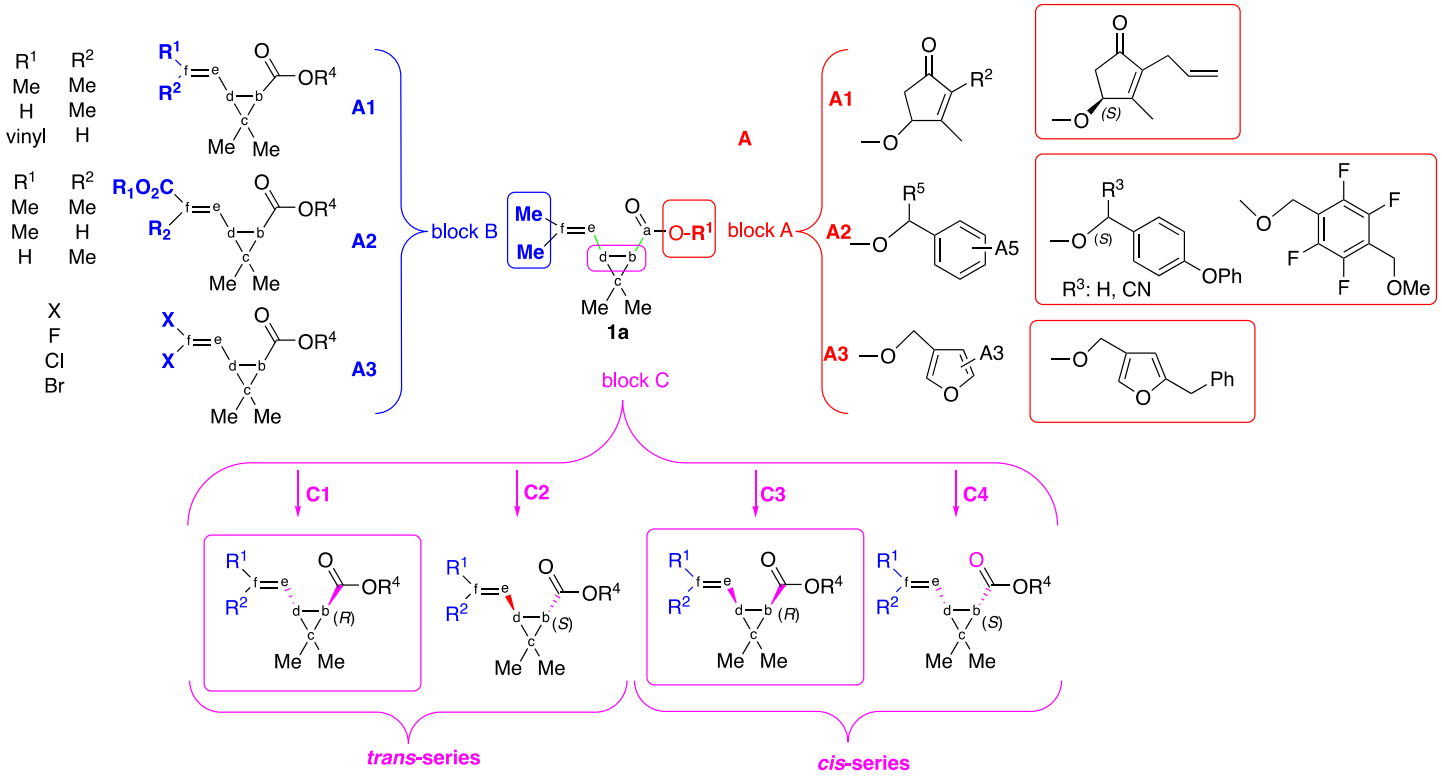
(ii) the destruction of the side chain of chrysanthemic acid/lower esters **1a**$_R$ then rebuilding it with different substituents at [Cf].

(iii) stereochemical variations on the mixture of the stereoisomers of **1a**$_R$ in different proportions, production of a single diastereoisomer as a racemate or as a single enantiomer. That requires separations of stereoisomeric mixtures of diastereoisomers, resolutions of enantiomers but also changing the stereochemistry at [Cb] or at [Cd] involving *cis* to *trans*- or *trans* to *cis*-variations that take advantage of epimerization at each of these two carbons or involve racemization reactions.

Most of the reactions that will be disclosed in this chapter take advantage of those described in Chapter IVa of this series[12] but there are striking differences over the two chapters. The former chapter is oriented towards the reactivity of chrysanthemic acid or its lower esters **1a**$_R$ whereas the present chapter is oriented towards the transformation of **1a**$_R$ to different products expected to possess insecticidal properties. Those transformations involve multi-steps sequences and synthetic strategies to reach the goals. They will be discussed thoroughly herein.

Note that access to pyrethrin I and pyrethrin II analogues from chrysanthemic acid or its lower esters **1a**$_R$ allowed easy access to a large variety of pyrethroid candidates, especially those listed in Figure 1, under well established procedures and methods using family of reagents able to perform most of the reactions required to access the goals. Some of them, such as the one disclosed below in Scheme 54, have been effectively used at an industrial scale to produce large quantities of enantomerially pure *S*-bioallethrin (**1a**$_B$) and deltamethrin (**1f**$_F$) using each of the two enantiomers of chrysanthemic acid for such purpose.

In some other cases, this approach has been superseded by concurrent approaches more adapted to the production of large quantities of active pyrethroids identified by the previous strategy.



R^n: refers to alkyl groups or functionalized alkyl groups; A^n: refers to any group; An: refers to any group attached n-times to each of the submits of the cycle **A**, **B** ,**C**: refers to the three blocks discussed in the text: the **vinylic-group block**, the **carboxy-group block**; and the stereochemical-group block around the Cb and Cd carbons part of the three membered cycle.

Scheme 2. Basic structural modifications on chrysanthemic acid/esters discussed in this review.

1.2.1. Transformations involving block A-Variations. In brief, as already pointed out, the transformation of chrysanthemic acid/lower esters to pyrethroids as for example the ones collected in Figure 1, involves basic reactions to build the vinylcyclopropane carboxylic moiety as well as an esterification or a transesterification reaction. The latter reactions parallel those that have been already discussed in detail in Chapter IVa (Section 2.4).[12] They involve the concomitant use of the appropriate alcohol, the related sulfonates or halides. Those either belong to (i) the cyclopentenolone family such as in **1a**$_A$, **1b**$_{MeA}$, **1a**$_B$, **1a**$_C$, **1c**$_B$, **1d**$_B$ (Figure 1),[4,6] (ii) the 5-benzyloxy-3-hydroxymethylfurane such as in **1a**$_D$, **1e**$_D$, **1d**$_D$, **1f**$_D$ (Figure 1) or (iii) the benzyl alcohols family that includes those possessing (a) fluorine substituents on the aromatic ring such as in **1c**$_G$ (Figure 1) or (b) a 3-phenoxy group in meta-position such as in **1a**$_E$, **1d**$_E$; (Figure 1) especially those possessing also a cyano-group at their benzylic site such as in **1a**$_F$, **1d**$_F$, **1f**$_F$ (Figure 1).[7] The specific synthetic methods will be disclosed at several occasions in the following presentation.

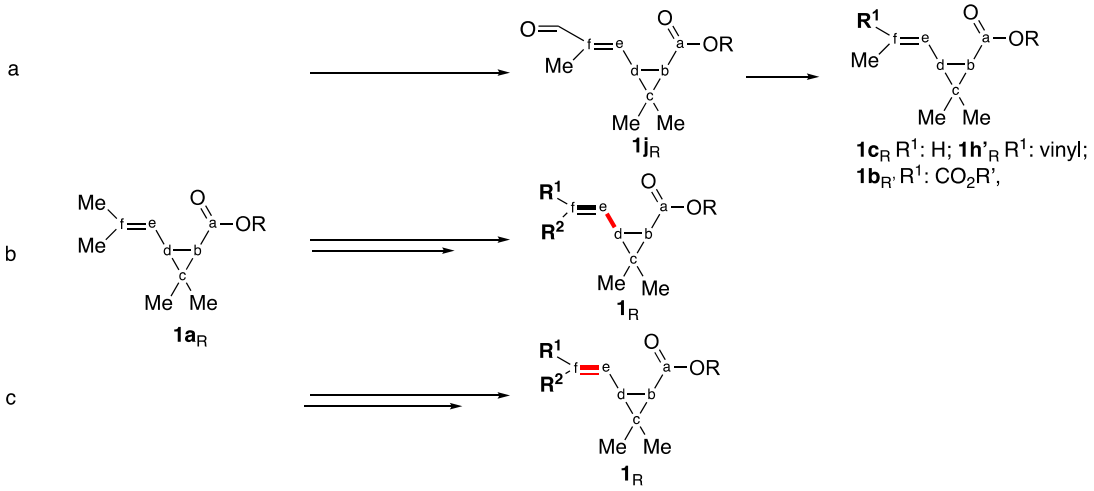
1.2.2. Transformations involving block B-Variations. Modification of the isobutenyl side chain of chrysanthemic acid/esters by formally exchanging one or the two allylic methyl groups has produced a large variety of pyrethroids that are for some of them far more active or more stable in the environment that the natural products. It has been found for example that the methyl vinyl group groups are prone to degradation by photochemical oxidation in the environment and that the *trans*-methyl group in pyrethrin I is subjected to biochemical oxidation in insects. Therefore, compounds possessing halogens there [**1d**$_B$, **1e**$_D$, **1d**$_D$, **1f**$_D$, **1d**$_E$, (**1d**$_F$),

1f$_F$; Figure 1] or lacking the *trans*-methyl group, as **1b**$_{MeA}$ and those derived from nor-chrysanthemates [**1c**$_B$, **1c**$_G$; Figure 1] are so interesting.

To achieve such structural variations, allylic oxidation of chrysanthemates **1a**$_R$ using selenium dioxide (Chapter IVa, Section 3.3.1)[12] (Scheme 3, entry a), is the only process that allows modification of their side chains that keeps intact their carbon skeleton, their stereochemistry, and the location of their [Ce=Cf] double bond. Although it allows interesting variations that include in a further step the formal cleavage of the [Cf-Me] bond, the possible variations are limited.[13]

Replacement of isobutenyl group by a different vinyl group by forming a new [Cd-Ce] bond is interesting (Scheme 3, entry b) but has been disclosed only once.[14] It involves the intermediate formation of an unstable cyclopropyl radical, an extremely reactive species that even reacts with the solvent and not only delivers a new compound in modest yield but also affects its original stereochemistry if the starting material possesses the *cis*-stereochemistry.

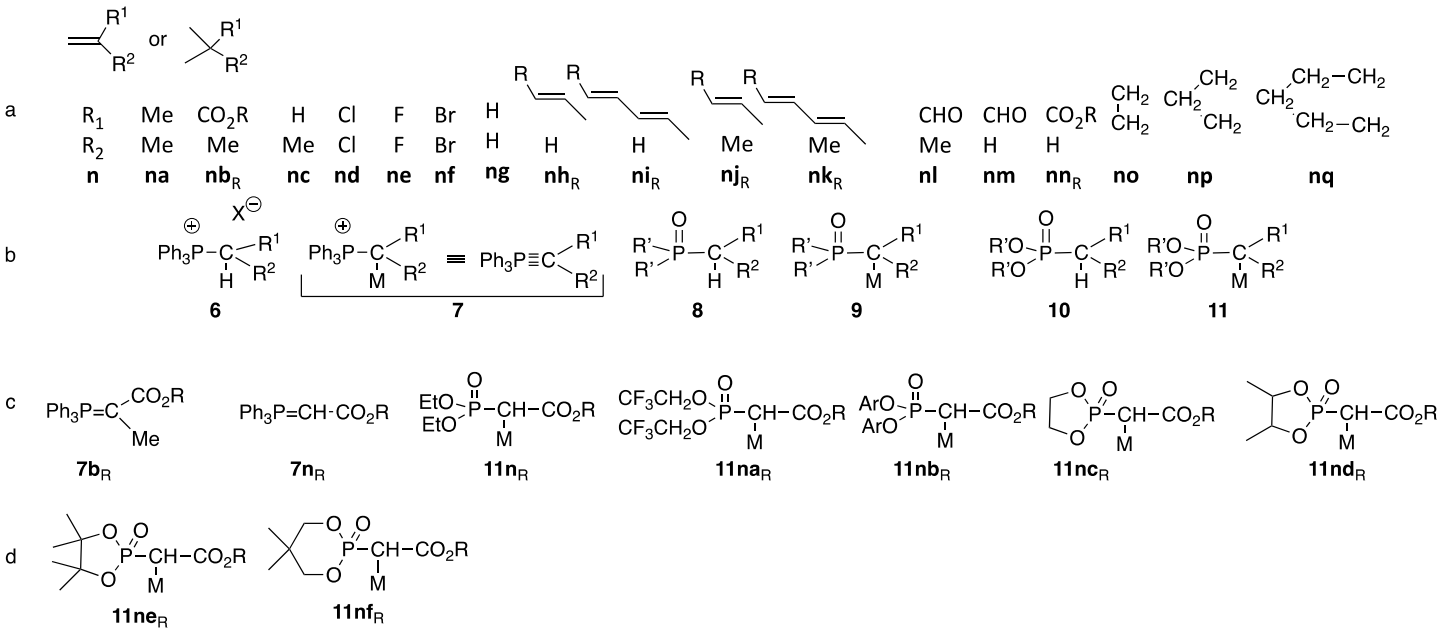
The last process (Scheme 3, entry c) that involves the replacement of the 2-propylidene moiety by a related one bearing different substituents at [Cf] is by far the most used among the processes disclosed in Scheme 3. Among the various methods that allow this transformation, the one that involves the cleavage of the [Ce=Cf] double bond leading to the intermediate hemicaronic acid/esters (Chapter IVa, Section 3.2)[12] then formation of the new [Ce=Cf] double bond has been the most widely used and the Wittig and related olefination reactions have been instrumental (Chapter IVb; Section 4.4).[12] This process that allows the synthesis of a large variety of pyrethroids will be described in detail in a special chapter (Chapter IVb, Section 4.4.2).[12]



Scheme 3. Strategies, functional groups and bonds involved in the synthesis of some pyrethroids from chrysanthemic acid/esters.

The Wittig and related reactions are highly regioselective and under certain conditions highly stereoselective. They even allow in some cases access of each of the (*Z*) or (*E*)-stereoisomer or their mixtures. Due to the intensive use of this route for the synthesis of pyrethroids, we have devoted a full section of this Chapter IVb (Section 6) to the Wittig reaction but will restrict our presentation to the cases related to pyrethroids synthesis.

Description of the numbering of the various precursors of the vinyl group substituents are summarized in Scheme 4 (Scheme 4, entry a).



Scheme 4. Reagent types and their substituants used to synthesize pyrethroids possessing different substituants at the terminus of their vinylic moiety.

1.2.3. Transformations involving the block C-Variations. The stereochemical problem is behind the scenes in all these transformations since pyrethroids interact with living organisms that function usually with enzymes under privileged stereochemical control. However, pyrethroids also interact with the environment that destroys them through interaction with light, oxygen and humidity for which stereochemical implications are in many instances different. Although methods exist to produce and sell the most active enantiomer, still stereoisomeric mixtures of compounds are available on the market and only few pyrethroids such as (*S*)-bioallethrin (**1a**$_B$)[15] and deltamethrin (**1f**$_F$)[8] are sold as a single (*S*,1*R*,3*R*)-*trans*- and (*S*,1*R*,3*R*)-*cis*-stereoisomers respectively (Prelog rules are sometime affected by the change of substituents).

Lower esters of chrysanthemic acid **1a**$_R$ are commercially available as single racemic-*trans*-stereoisomer *trans*-**1a**$_R$[8] or as a racemic mixture of stereoisomers in which the *trans*-form prevails **1a**$_R$. Separation of *cis*/*trans*-stereoisomeric mixtures and/or resolution have been achieved on chrysanthemic acid/esters prior any structural modification if pure stereoisomers or pure enantiomers are required.[8] In some cases, recycling the useless stereoisomers to the one needed has been achieved by stereoselective isomerization or racemization as will be reported.[8]

1.2.4. Strategies in context: "Discovery approach" versus "Production approach". As expected, the strategy used to identify new bioactive compounds the "*Discovery approch*" differs from that to produce them industrially "*Production approach*" because the needs are different. Both aspects will be included in this presentation but they will not be treated separately due to the evident chemical overlaps. Nevertheless, the conceptual significance of some of the sections, especially those related to stereochemical problems (Chapter IVb, Section 5) will be only highlighted in context.

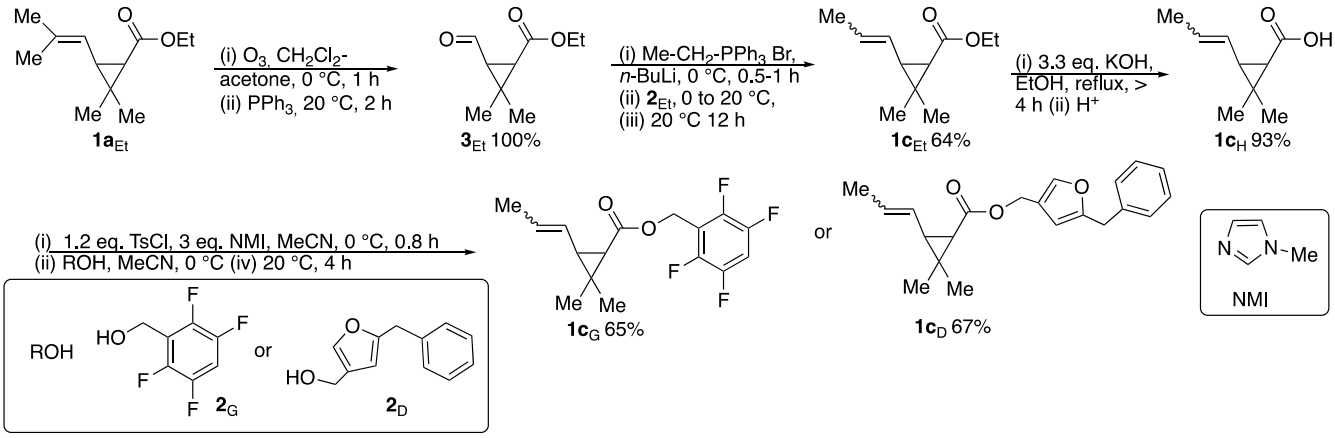
For example, for discovery of new pyrethroids, testing the mixture of all the stereoisomers allows one to rapidly detect the bioactive ones and access to each stereoisomeric mixtures and to each enantiomer allows to strategically select the most active stereoisomer (based on killing or knock down capacities).[8,15] Quantities required at the early stage has no significant impact. Nevertheless, access to larger amounts is pressing to extend the testing to various insect species and to initiate the toxicity studies towards other species such as

birds, fishes, mammals and to get information about the behaviour of the selected compounds towards the environment.

For the production of a given pyrethroid the problem is different especially if a single diastereoisomer or enantiomer is required. In such cases isolation of the required diastereoisomer (over 2) or enantiomer (over 4) from the mixture of chrysanthemic acid/esters requires recycling the unwanted stereoisomer for economic and ecologic reasons. Solutions have been proposed that will be reported below (Chapter IVb, Section 5).[8] The "Evolution of an industrial process: deltamethrin synthesis" is exemplative for probably the most potent commercial insecticide.[8]

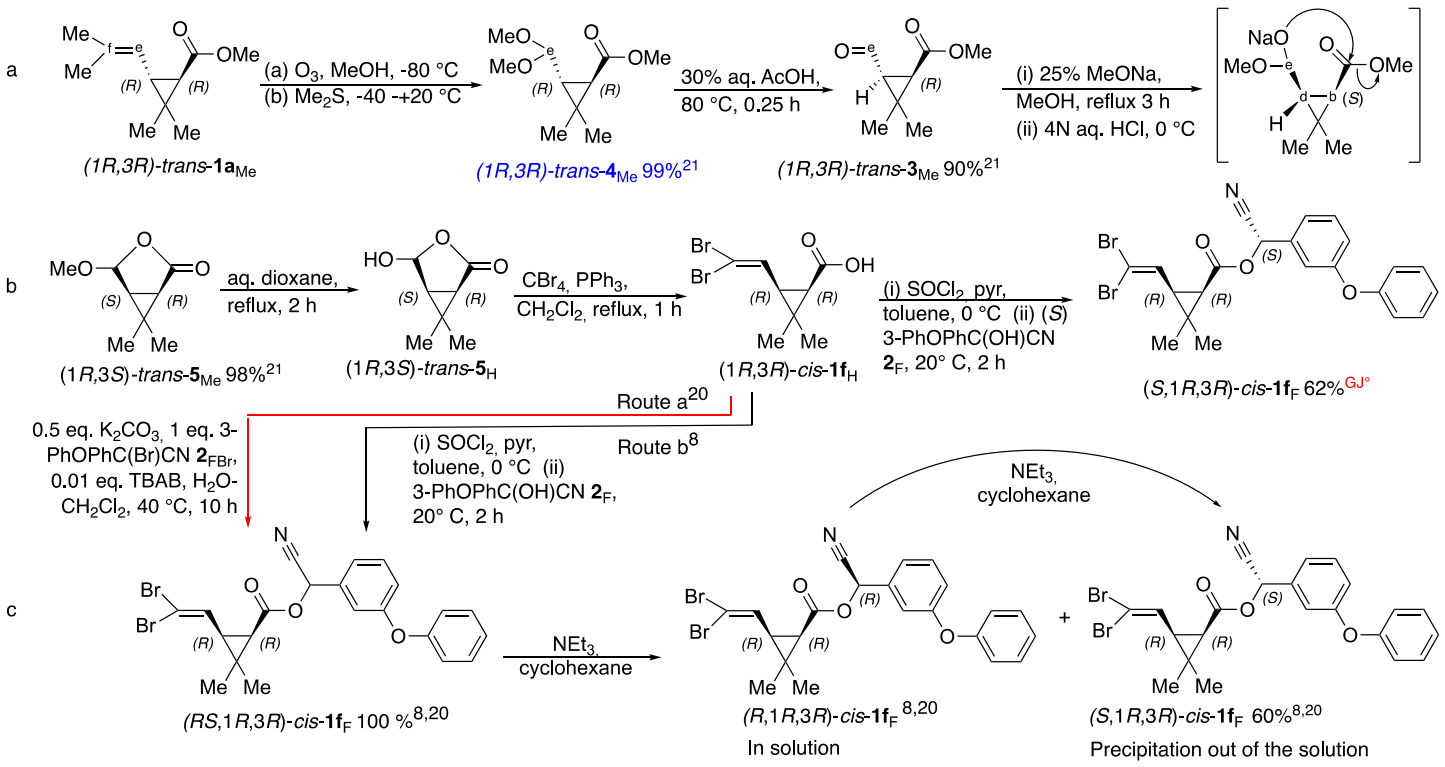
1.2.5. Role of the sequential order of reactions implied in the transformation of chrysanthemic acid/lower esters to pyrethroids. The order of reactions carried on chrysanthemic acid/lower esters to produce pyrethroids has an important impact on the final outcome especially on the nature of the series of pyrethroids available for testing.

1.2.5.1. Strategy involving the introduction of the final alkoxy group at a late stage. In most of the cases, transformation of the isobutenyl moiety is achieved first on chrysanthemate lower esters and esterification leading to the pyrethroids is carried out at the final stage, allowing access to a series of pyrethroids possessing the same isobutenyl moiety but bearing different ester groups.[13,16,17] One example implying such strategy is reported in Scheme 5.[18]



Scheme 5. Strategy and practice used to synthesize a series of nor-chrysanthemates bearing different ester moieties from alkyl chrysanthemates.[18]

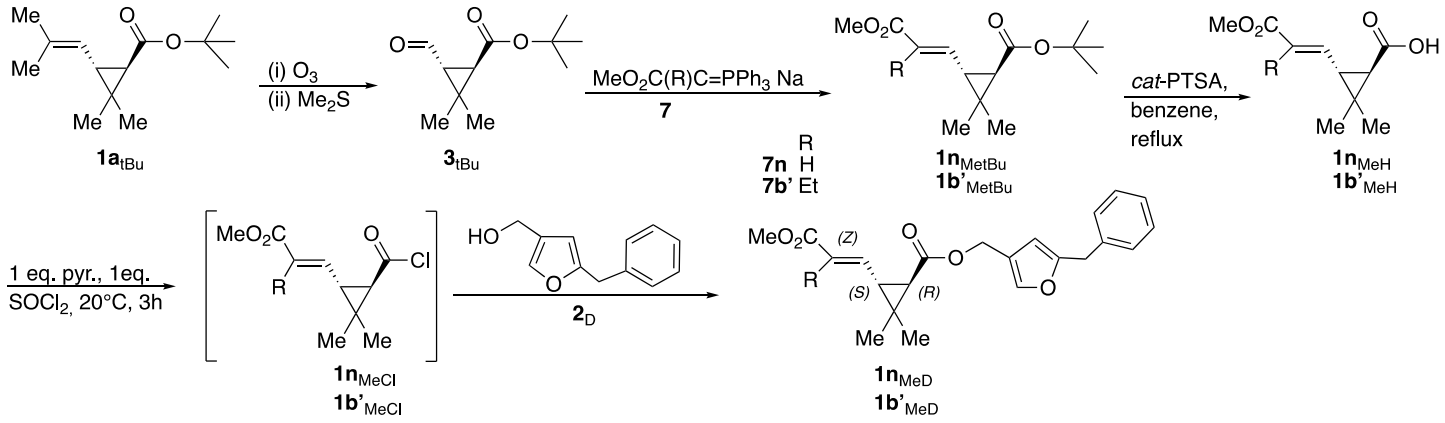
This strategy has been used for the industrial synthesis of (*S*,1*R*,3*R*)-*cis*-deltamethrin (*S*,1*R*,3*R*)-*cis*-(**1f**$_F$) from methyl (*S*,1*R*,3*R*)-*trans*-chrysanthemate (1*R*,3*R*)-*trans*-(**1a**$_{Me}$) (Scheme 6, entries a,b).[8,19,20] It involves the use of an enantiomerically pure starting material on which changes are not only related to (i) the vinylic moiety (formal replacement of the two vinylic methyl groups by two bromine atoms[21] but also (ii) changes the relative stereochemistry (*trans* to *cis*). The latter modification requires a contra-thermodynamic process that should involve an epimerization reaction at [Cd]. Esterification involves an enantiomerically pure alkoxy moiety quite labile since its hydroxyl group is part of a cyanohydrine.[19] Note that different approaches are disclosed in Scheme 6 and only the one involving the esterification of *cis*-deltamethrinic acid (*S*,1*R*,3*R*)-*cis*-(**1f**$_H$) with enantiomerically pure (*S*)-3-phenoxy mandelonitrile is discussed in this section (Scheme 6, Route b).



Scheme 6. Strategy and practice used to synthesize enantiopure deltamethrin from alkyl chrysanthemates.[8,19-21]

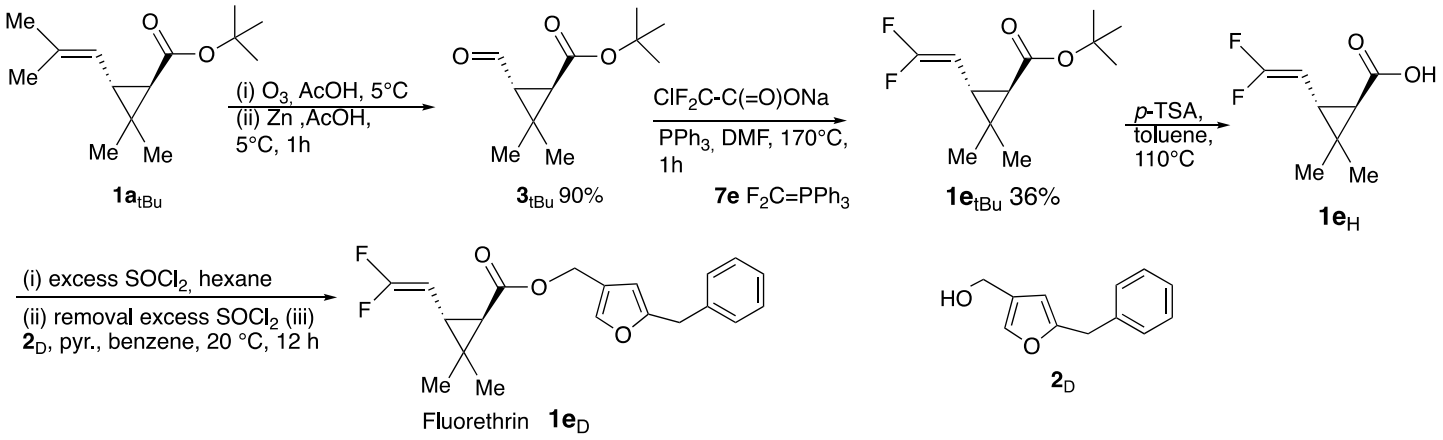
To be successful, the strategy disclosed above and highlighted on two examples requires that the alkoxy part of the chrysanthemates lower esters is adequately selected so it can be released without affecting the other part of the structure.

For example, for the synthesis of the methyl furfuryl ester derived from pyrtehroic acid (Scheme 7), *t*-butyl chrysanthemate has been selected so the *t*-butyl permethrinate can be selectively deprotected in the presence of the vinylic methyl ester, then esterified through its acid chloride, with the 5-phenyl-2-furfurylmethanol (**2**$_D$) without interference with the other functional groups present on the structure.[13]



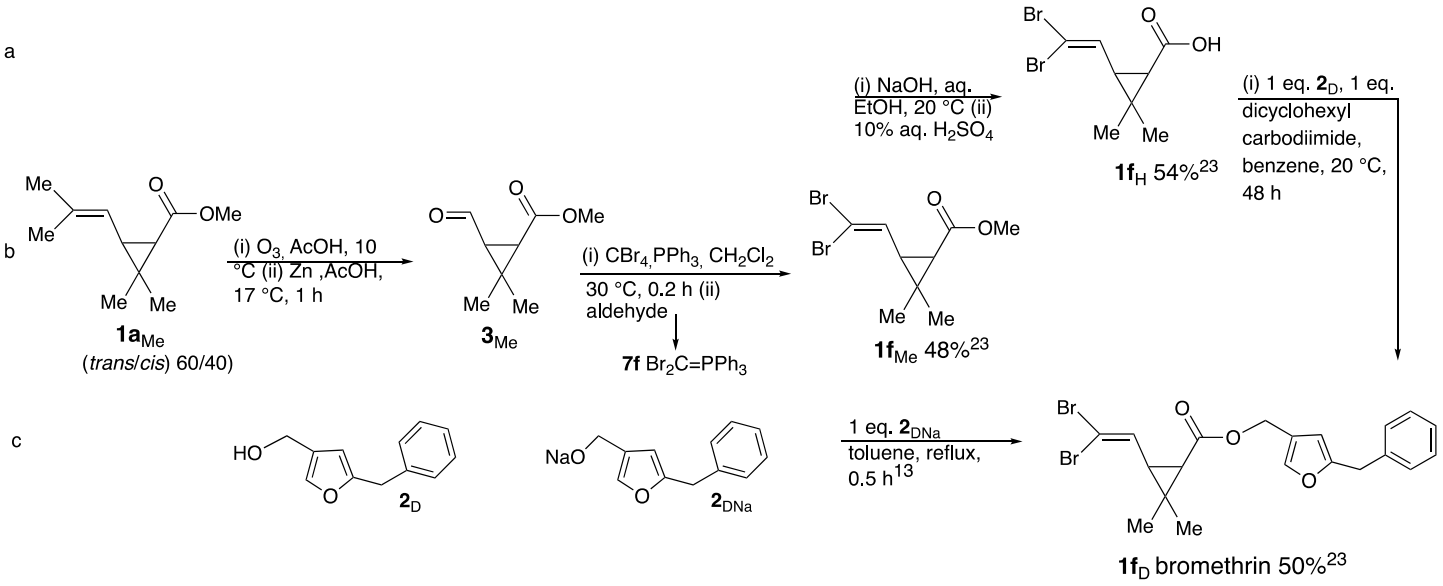
Scheme 7. Strategy and practice used to synthesize different analogues of pyrethrin II from alkyl chrysanthemates.[13]

The acid catalyzed multistep transesterification reaction, reported above, proved far better anytime groups sensitive to bases are present in the starting material as in the case of fluorethrin (**1e**$_D$) (Scheme 8).[22]



Scheme 8. Strategy and practice used to synthesize pyrethroids bearing two vinylic fluorine atoms from alkyl chrysanthemates.[22]

This constraint is no longer effective in the synthesis of bromethrin (**1f**$_D$) that possesses a closely related structure but accept saponification in basic media (Scheme 9,[13,23] compared to Scheme 8[22]).

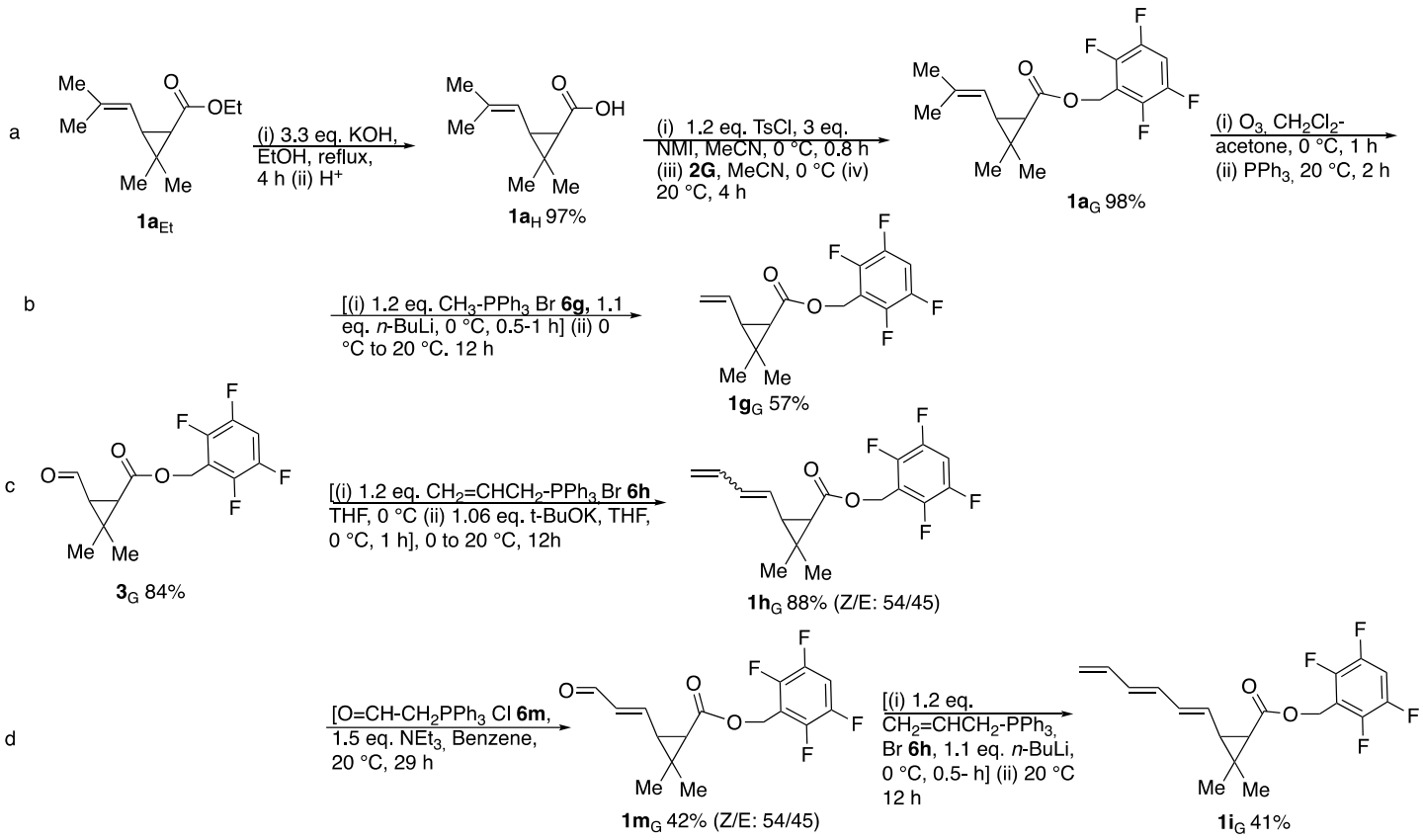


Scheme 9. Strategy and practice used to synthesize deltamethrinates atoms from methyl chrysanthemate.[13,23]

The strategy disclosed in this section is not limited to the "hemicaronic approach" and applies to any other route to access a different vinylic moiety such as the one involved in the "selenium dioxide approach" (see below, Scheme 22).[13]

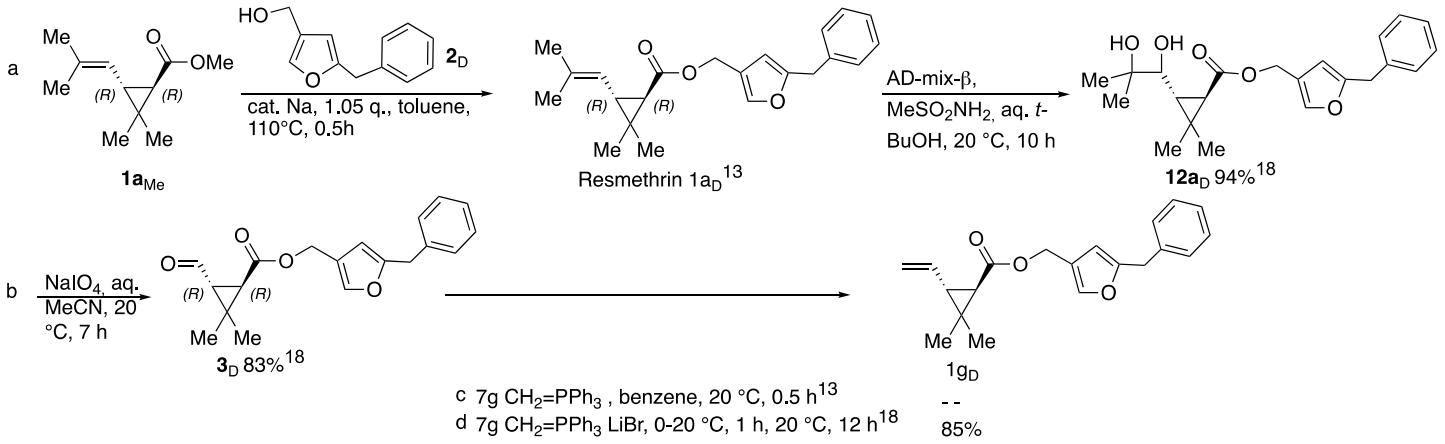
1.2.5.2. Strategy involving the introduction of the final alkoxy group at an early stage. Achieving the "transesterification" reaction on chrysanthemic acid/lower esters before any other structural modifications offers the advantage to build an assembly line work devoted to the synthesis of a series of pyrethroids possessing the same alkoxy group and possessing a large variety of substituents at [Cf].[18]

Specific results involving 2,3,5,6-tetrafluorobenzyloxy chrysanthemate (**1a**$_G$) and the related hemicaronate (**3**$_G$) allows the synthesis of compounds bearing differently substituted polyenic side chain (Scheme 10).[18] The synthesis didesmethyl-(**1g**$_G$) (Scheme 10, entry b) and dienyl- **1h**$_G$ (Scheme 10, entry c) -pyrethroates are straightforward and use the required Wittig reagents **7g** and **7h** respectively. The synthesis of the trienyl cyclopropane carboxylate **1i**$_G$ requires a stepwise transformation implying sequential reaction with the ylides **7m** and **7h** derived from triphenylphosphium acetaldehyde **6m** and allyl triphenyl phosphonium **6h** -bromides probably due to the various potential sites of reactions of the ylide derived fom trienyl phosphonium salts (Scheme 10, entry d).[18]



Scheme 10. Strategy and practice used to synthesize pyrethroids bearing the same alkoxy group but different vinylic moieties from alkyl chrysanthemates.[18]

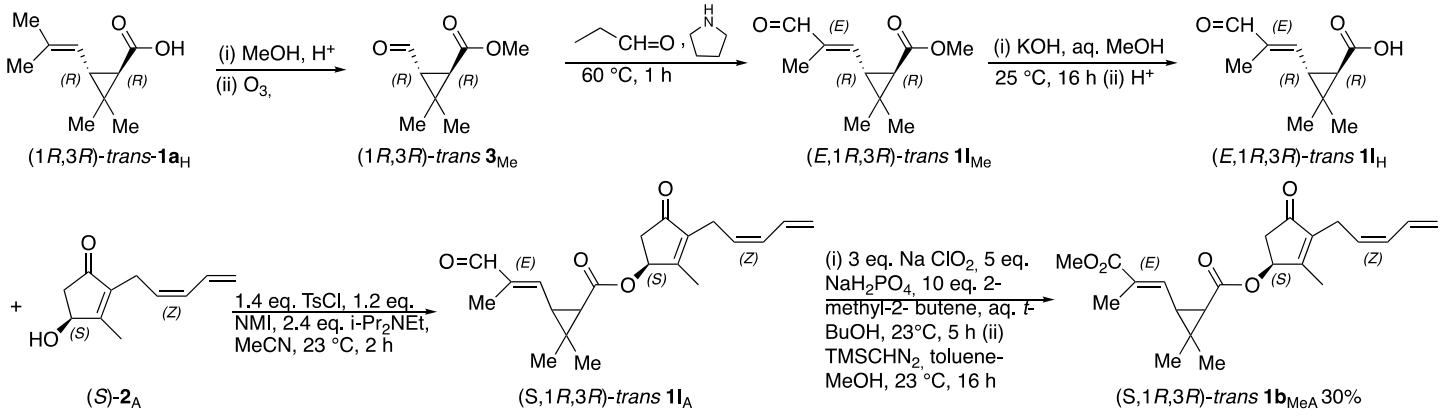
The ester group involved in this example is inert towards all the reagents used. However, in few cases such as the one involving variation of the side chain of resmethrin (**1a**$_D$), one of the first pyrethroid marketed,[24] tentation could be justified to use the commercial product as the starting material but ozonolysis cannot be used[13] due to the sensitivity of the furan ring towards ozonolysis. This strategy has been however successfully used by replacing the aggressive ozonolysis by the far more selective Sharpless procedure (Chapter IVa, Section 3.1.3.3.2)[12] that fortunately allows the selective oxidation of the trisubstituted [Ce=Cf] double bond of resmethrin (**1a**$_D$), avoiding the concomitant oxidative degradation of the furan ring (Scheme 11).[18] Unfortunately no information about the stereochemistry of the diol has been reported.



Scheme 11. Strategy and practice used to synthesize pyrethroids bearing different vinylic moieties atoms from alkyl chrysanthemates whose ester moiety is sensitive to oxidants.[13,18]

1.2.5.3. Strategy involving the introduction of the final alkoxy group at a central stage. In some other rare cases, esterification has been carried out on an intermediate stage usually close to the last one. We have selected two very different cases to exemplify this approach.

This is the case of racemic pyrethrin II (**1b**$_{MeA}$) that bears two different carboxy groups. Its synthesis involves incremental changes from methyl *trans*-chrysanthemate *trans*-(**1a**$_{Me}$), to methyl hemicaronate (**3**$_{Me}$) on which the aldol condensation-crotonization reactions are used to build the complete carbon framework of (**1b**$_{MeA}$) (Scheme 12). Esterification, before oxidation of the formyl group to the carboxy group, allows to differentiate the two carboxyl moieties present on **1b**$_{MeA}$ at that stage (Scheme 12).[25]



Scheme 12. Strategy and practice used to synthesize pyerethrin II from chrysanthemic acid.[25]

Another more subtle transformation involves the synthesis of enantiopure (*S*,1*R*,3*R*)-*cis*-deltamethrin (*S*,1*R*,3*R*)-*cis*-(**1f**$_F$) from its epimeric mixture at the benzylic carbon (*RS*,1*R*,3*R*)-*cis*-1**f**$_F$. It is generated from enantiopure (*S*,1*R*,3*R*)-*cis*-deltamethrinic acid (*S*,1*R*,3*R*)-*cis*-(**1f**$_H$) through the reaction of its acid chloride (*S*,1*R*,3*R*)-*cis*-**1f**$_{Cl}$ with racemic 3-phenoxy-mandelonitrile (Scheme 6, Route 2).[7,8,20] Treatment of the resulting (*SR* 1*R*,3*R*)-*cis*-deltamethrin (*SR* 1*R*,3*R*)-cis-(1**f**$_F$) with triethyl amine in cyclohexane allows the precipitation of the crystalline (*S*,1*R*,3*R*)-*cis*-deltamethrin (*S*,1*R*,3*R*)-*cis*-(1**f**$_F$) and subsequent epimerisation of the soluble (*R* 1*R*,3*R*)-*cis*-deltamethrin (*R*,1*R*,3*R*)-*cis*-(1**f**$_F$) enantiomer that favors precipitation of more of the (*S*,1*R*,3*R*)-*cis*-deltamethrin (*S*,1*R*,3*R*)-*cis*-(1**f**$_F$) (up to 60%, Scheme 6, entry c).[8,20]

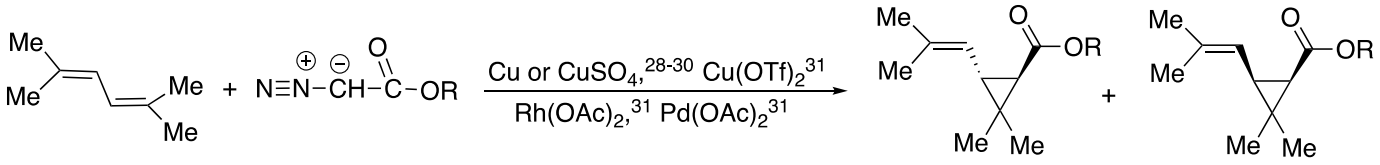
2. Access to Chrysanthemic Acid/Lower Esters as a Mixture of Stereoisomers, Pure Diastereoisomers and Pure Enantiomers

2.1. Commercial access and synthesis of chrysanthemates using established protocols

Those variations have been usually achieved from lower alkyl chrysanthemates **1a**$_R$. The ethyl ester **1a**$_{Et}$ is commercially available as a racemic *trans*/*cis*-mixture (from 70/30 to 60/40) on reaction of diazo acetates **14**$_R$ with 2,5-dimethyl hexadiene (**13**) (Scheme 13),[28-32] whereas the methyl ester can be produced easily as the racemic *trans*-stereoisomer *trans*-**1a**$_{Me}$ on reaction of isobutenyl phenylsulfone in basic media **12**$_M$ with methyl senecioate (**11**$_{Me}$) (Scheme 14).[26,27] Anyhow, each of the two approaches, that possess their advantages and inconveniencies, have been used at the industrial level for years and have been published more recently in the context of elaborated laboratory experiments in organic chemistry for advanced student at the University.[26,28]

The diazo route invented by Staudinger and Ruzicka[29] is the shortest and the cheapest, give high yields of alkyl chrysanthemates and delivers dinitrogen as a co-product that is the lightest and the most benign leaving goup. It however suffers from the requirement of a large excess of starting 2,5-dimethyl hexadiene and from the instability of diazo partners **14**$_R$, that make the process highly explosive and dangerous. The process requires the presence of copper[28-30] as originally described by Staudinger and Ruzicka[29] or copper salts,[31] palladium salts[31] or better rhodium salts[31] (Scheme 13). It is the route used industrially for decades by the Sumitomo Company in Japan without apparent security problems.

The reaction involving ethyl diazoacetate (**14**$_{Et}$), that is the more common one, delivers a racemic *trans*/*cis*-mixture of ethyl chrysanthemate (**1a**$_{Et}$) (from 70/30 to 60/40) and it is the only one of the two methods[28,26] that allows the production of some *cis*-chrysanthemates. The latter can be separated from their *trans*-stereoisomer and used. It should be noticed that the reaction using instead *t*-butyl diazoacetate is *trans*-stereoselective but low yielding (Scheme 13, entry b).[32]



Scheme 13. Industrial synthesis of ethyl chrysanthemate via the Staudinger-Sumitomo route.[28-32]

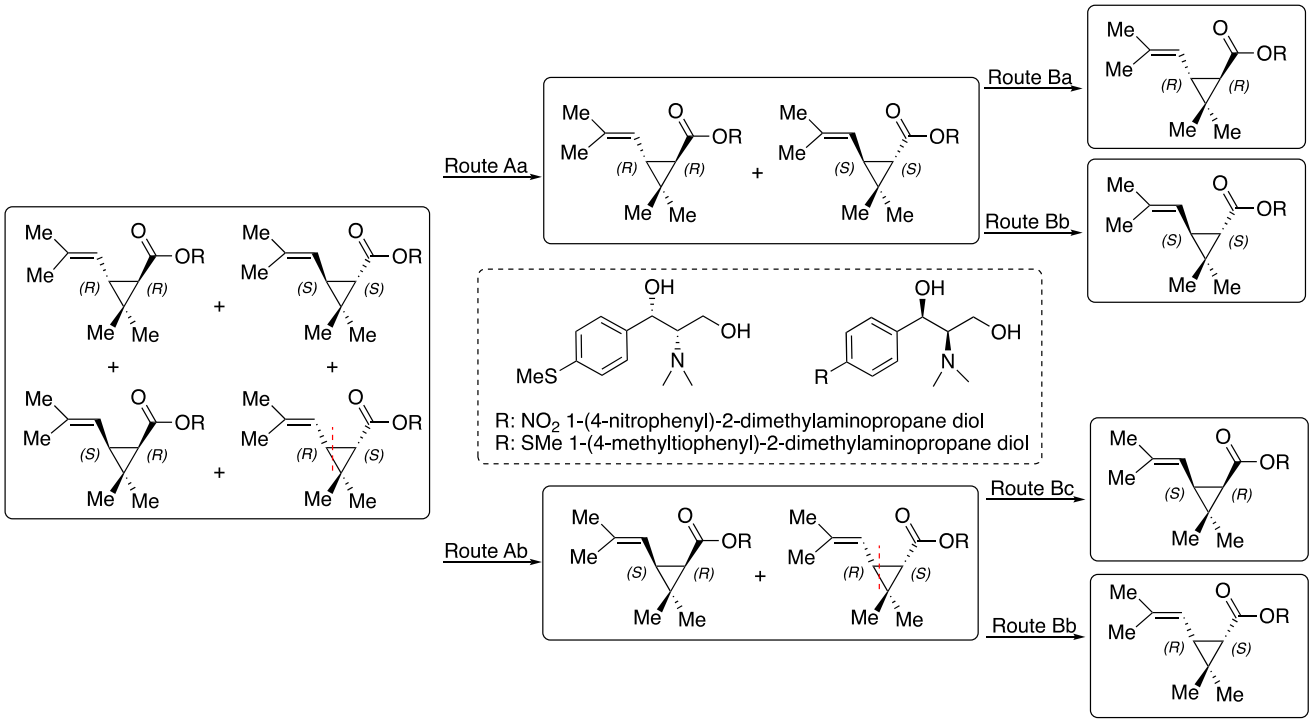
The sulfone route is probably a more efficient and less hazardous route to alkyl chrysanthemates than the previous one (Scheme 14). It is routinely carried out on methyl or ethyl senecioate **15**$_R$ and metalated 3-methyl-2-butenyl arylsulfones **16**$_M$ in a polar solvent.[26,27] This route has been disclosed and effectively used industrially by the Roussel-Uclaf Company (now Bayer Crop Science). It offers access to racemic-alkyl chrysanthemates in appreciable yield and exclusively as the *trans*-stereoisomer. It however produces metal sulfinates as co-product, the weight of which by far overcomes that of dinitrogen co-produced in the diazo-route.

Scheme 14. Industrial synthesis of racemic alkyl *trans*-chrysanthemates via the Roussel-Uclaf route.[26,27]

So, if *trans*-chrysanthemic acid *trans*-(**1a**$_H$) is needed, the sulfone route must be privileged whereas if *cis*-chrysanthemic acid *cis*-(**1a**$_H$) is required, the diazo route must be selected but it requires an additional separation step (See below). Other routes to access the *cis*- from the *trans*-chrysanthemates exist but require extra steps allowing the required isomerization reactions that will be reported in a forthcoming section (Chapter IVb, Section 5.2.2).

2.2. Access to racemic *cis* and *trans*-chrysanthemic acid/lower esters by separation of their mixtures

Separation of *trans*/*cis*-mixtures is directly related to the availability on the market of such mixture. It could be achieved taking advantage of the difference of their physical or chemical properties (Scheme 15). as will be briefly reported in the following subsections.



Scheme 15. Strategy to separate (i) a mixture of *trans*-stereoisomers from their *cis*-isomers and (ii) resolution of related racemates.

2.2.1. Separation of *trans*/*cis*-mixtures of acids involving their difference in solubility. The higher solubility of *cis*-chrysanthemic acid *cis*-(**1a**$_H$) compared to its *trans*-stereoisomer *trans*-(**1a**$_H$) in several non-polar solvents,

such as hexane,[33] favors the crystallisation of the *trans*-chrysanthemic acid *trans*-(**1a**$_H$) from a *trans*/*cis* (60/40) stereoisomeric mixture (100 g in 45 mL of hexane, 25 °C, 1 h). It leads in solution to a *cis*/trans mixture (35%, 80/20) that after a further crystallization from hexane delivers pure racemic *cis*-chrysanthemic acid *cis*-(**1a**$_H$) (20% overall yield, 99.8% *cis*). Access to the *trans*-stereoisomer is not practical from this process since only 9% of the pure racemic *trans*-chrysanthemic acid *trans*-(**1a**$_H$) is isolated, after two consecutive crystalizations.[33]
It has been also reported[23] that pure *trans*-bromethrin *trans*-(**1f**$_D$) can be separated from a 60/40 *trans*/*cis* mixture of stereoisomers by simple crystallisation in hexane.

2.2.2. Separation of *trans*/*cis*-mixtures of acids involving their difference in acidity. The difference in acidity between the *trans*- and the *cis*-chrysanthemic acid *cis*-(**1a**$_H$) allows isolation of the more acidic racemic *trans*-chrysanthemic acid *trans*-(**1a**$_H$) in organic solvents after acidification of an aqueous solution of the *cis*/*trans* mixture of their sodium salts, using acetic acid or better carbon dioxide. Under these conditions, racemic sodium *cis*-chrysanthemate remains in the aqueous solution (Chapter IVa, Section 2.1.1).[12]

2.2.3. Separation of *trans*/*cis*-mixtures of acids involving selective lactonization of the *cis*-stereoisomer. Separation of *cis*-chrysanthemic acid from its *trans*-stereoisomer by lactonization of the former takes advantage of the proximity of the isobutenyl- and the carboxy-groups (Chapter IVa, Section 1.2.1).[12,34,35] It has been more conveniently achieved on reacting the stereoisomeric mixture with dilute sulfuric acid, boron trifluoride etherate or zinc chloride (Chapter IVa, Section 1.2.1, Scheme 8b)[12,34,35] that leads to *cis*-dihydrochrysanthemo-δ-lactone (**17**) from the *cis*-stereoisomer *cis*-**1a**$_H$ and leaves unaffected *trans*-chrysanthemic acid *trans*-(**1a**$_H$) that can be extracted in basic media and recovered upon acidification.[35]

Furthermore *cis*-dihydrochrysanthemo-δ-lactone (**17**) has been efficiently transformed to *cis*-chrysanthemic acid *cis*-(**1a**$_H$) (See below Section 5.1.1, Scheme 55).[35,36]

2.2.4. Separation of *trans*/*cis*-mixtures of esters involving their different saponification rates. The higher rate of saponification of racemic methyl or ethyl *trans*-chrysanthemates compared to that of their *cis*-stereoisomers, allows the easy separation of the water-soluble sodium *trans*-chrysanthemate produced on stereoselective saponification of a *cis*/*trans*- mixture of methyl/ethyl chrysanthemates with aqueous sodium hydroxide (Chapter IVa, Section 2.1.3).[12] The *cis*-ester remains in the organic solvent and is therefore easily separated. Another, more sophisticated approach uses esterases and will be disclosed later (Chapter iVa, Section 2.1.3, Scheme 26, entry a).[12,37]

2.3. Access to enantiomerically pure *trans*-chrysanthemic acid/lower esters

Separation of each of the four enantiomers of chrysanthemic acid/lower esters has been the subject of intensive work to achieve the structure-activity relationship in order to advance the discovery of new pyrethroids and to produce at the industrial scale the most active enantiomers in view of the protection of the environment and mammalian life in general.

Since the structure determination of the vinyl cyclopropane carboxylic esters presents in the natural active principle of *Chrysanthemum cinerariaeforium*, all the bioactive pyrethroids have been found to possess the (1*R*)-stereochemistry on the vinyl cyclopropane carboxylate moiety. This applies to the natural (1*R*)-*trans* [as in **1a**$_A$, **1b**$_{MeA}$, the unnatural (1*R*)-*trans*-**1a**$_B$, **1a**$_C$, **1a**$_D$, **1c**$_B$, **1c**$_G$] as well as the (1*R*)-*cis*-pyrethroids [**1a**$_E$, **1a**$_F$, **1d**$_E$, **1f**$_F$]. However, although objectively the (1*S*)-stereoisomers have little chance to be active, it is safer to test the whole series of potential pyrethroids.

In the context of this chapter, ready access to chrysanthemic acid is crucial. Presently, ethyl chrysanthemate as a mixture of the four-stereoisomers is the only commercially available source. It is usually synthesized through the diazo-route (Scheme 13). It can be synthesized easily in the laboratory and the *trans*-stereoisomer can be

produced using as a single racemic-stereoisomer through the sulfone-route (Scheme 14). Pure enantiomers must be therefore produced using separation techniques.

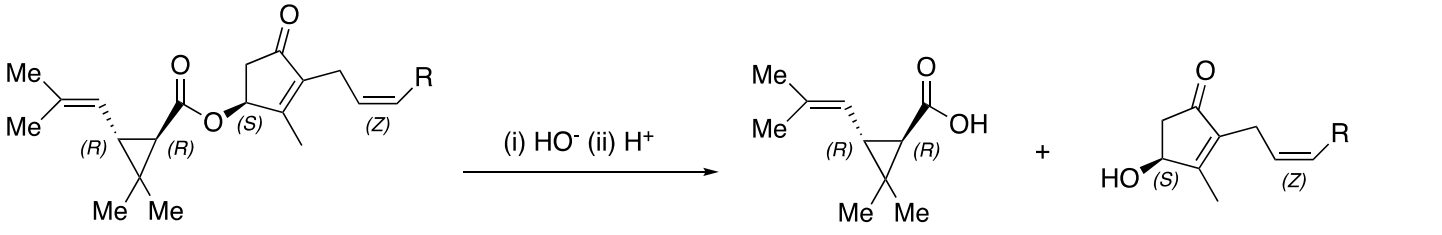
Although methods exist to extract one enantiomer, usually the (1*R*)-*trans*, from the mixture of four stereoisomers (Chapter iVa, Section 2.1.3, Scheme 26, entry b), [12,37] the usual strategy involves the separation of the racemic *cis*-chrysanthemic acid from the racemic *trans*-one from their mixture, then separately resolve them (Scheme 15). As a note, it seems more advisable to access the desired enantiomer from the racemic mixture by using the appropriate enantiomer of resolving agent able to cristallize it rather than to separate them from the same mixture.

Such resolutions have been already presented in Chapter IVa[12] of this series and can be achieved by (i) forming salts with chiral amines (Chapter IVa, Section 2.1.2),[8,12,38-42] (ii) separation of their esters derived from chiral alcohols (Chapter IVa, Section 2.4.1.2.3, see Scheme 45)[12,43] or (iii) using esterases. It has been thus found that pig liver esterase at 50% conversion of the racemate followed by acid hydrolysis of the chrysanthemate salt soluble in water, allows such a separation (Chapter IVa, Section 2.1.3, Scheme 26 a). [12,37]

Saponification of racemic mixture of ethyl *trans*-chrysanthemate *trans*-(**1a**$_{Et}$) has also been successfully achieved using a microbial esterase obtained by cloning, nucleotide sequence, and overexpression of the esterase gene of *Arthrobacter globiformis* in *Escherichia coli* SC-6-98-28.[44]

However, the author suggests, in order to access (1*R*,3*R*)-*trans*-chrysanthemic acid (1*R*,3*R*)-*trans*-(**1a**), to resolve the racemic *trans*-chrysanthemic acid using 1-(4-nitrophenyl)-2-dimethylaminopropane-1,3-diol (DMAD), a readily available intermediate of the well-known antibiotic chloramphenicol, as suggested by the work carried out in the Roussel-Uclaf Company,[8,42] to achieve this process. Best results have been obtained using methanol as co-solvent (diisopropyl ether/methanol 6:1, or diethyl ether/methanol 1:1). Careful investigation of these processes shows that methanol is incorporated into the crystals of the less soluble diastereoisomer containing (1*S*,3*S*)-*trans*-chrysanthemic acid.[42]

Last but not least (1*R*,3*R*)-*trans*-chrysanthemic acid (**1a**$_{H}$) is accessible by extraction from *Chrysanthemum cinerariaeforium*[45] (20.000 tonnes/year production of dried flowers with a pyrethrin content of only 1.5 %; 500 t/year). Purification of the extract, followed by saponification of pyrethroids and subsequent acidification allows access of reasonable quantities of enantiopure (1*R*,3*R*)-*trans*-chrysanthemic acid (Scheme 16).[17,46,47]



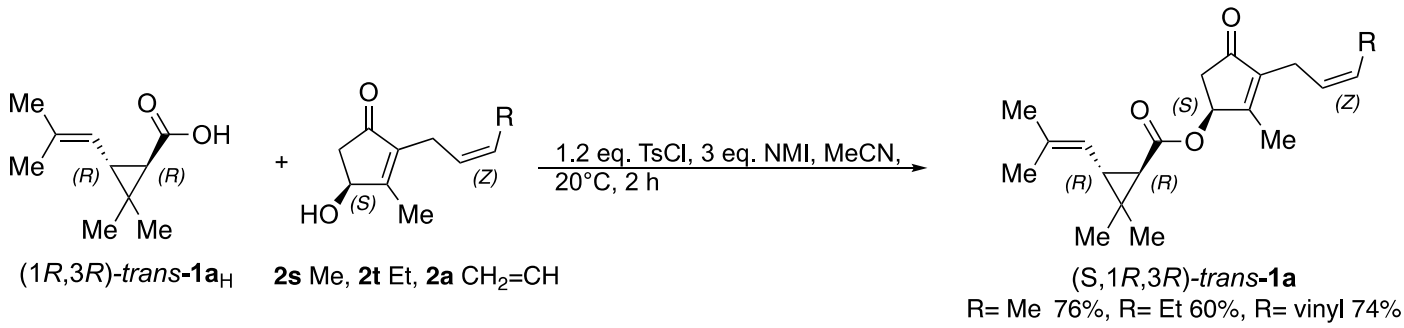
1a$_{A'}$ R: Me, Et and vinyl-mixture (1*R*, 3*R*)-*trans*-**1a**$_{H}$ **2**$_{A'}$ R: Me, Et and vinyl-mixture

Scheme 16. Recovery of enatiopure (1*R*)-trans chrysanthemic acid from natural sources.[45,46]

3. From Vinyl Cyclopropane Carboxylic Acids/Lower Esters to Pyrethroids: Esterification Reactions (block A-variations)

Variation of the alkoxy moiety is one of the easiest ways to create diversity. It has been effectively achieved first on chrysanthemic acid and later on the various vinyl cyclopropane carboxylic acids/lower esters. Some representative groups are disclosed in Figure 1 as well as on Figure 2.

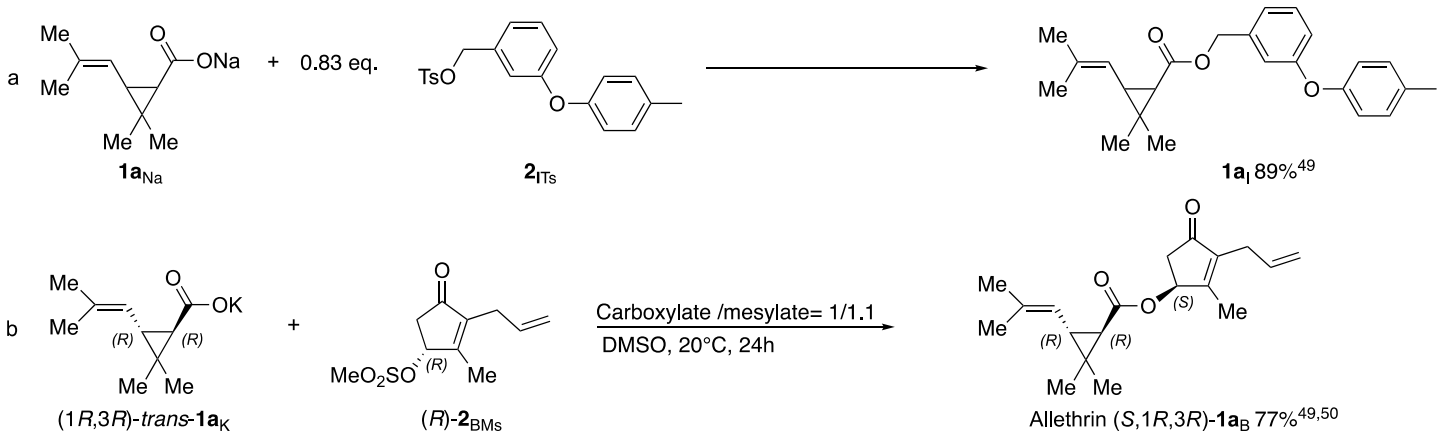
The different methods allowing the synthesis of the required esters from the corresponding chrysanthemic acid or its lower esters have been reviewed and discussed in Chapter IVa of this series (Chapter IVa, Section 2.4).[12] They widely apply to the synthesis of almost all pyrethroids and the reader will find the detailed description of these methods there. However, the related information will be timely included in some schemes at any time as judged pertinent. Amongst those methods, esterification implying (i) the reaction of vinylcyclopropane carboxylic chlorides (Chapter IVa, Section 2.4.1.2.4)[12] with alcohols such as rethrolones[6] or cyanohydrines[7] (Scheme 6,[8,19,20] Scheme 7,[13] Scheme 8[22]) has been often preferred especially if activated *N,N*-dimethyl formamide is used to generate the acid chloride[48] (Chapter IVa, Section 2.2.2)[12] (ii) a transesterification reaction using a metal alcoholate (usually the sodium salt) on methyl or ethyl vinyl cyclopropane carboxylates (Scheme 9, entry c,[13,23] Scheme 11, entry a[13,16,18]) (iii) the reaction of an alcohol with a vinylcyclopropane carboxylic acid using dicyclohexyl carbodiimide in a Steglish esterification reaction (Scheme 9, entry a),[23] or better (iv) on reaction of the acid and the alcohol with tosyl chloride and *N*-methylimidazole. This reaction has been frequently used in the "discovery approach" (Scheme 5,[18] Scheme 10, entry a,[18] Scheme 12,[25] Scheme 17).[25]



Scheme 17. Selected method to esterify chrysanthemic acid with complex alcohols.[25]

Note that depending on the context, the lower ester used is methyl, ethyl or *t*-butyl depending upon the sensitivity of the vinylic moiety to bases or acids to finalize the synthesis of a pyrethroid (compare Scheme 7, [13] Scheme 8[22] to Scheme 5,[18] Scheme 6, [8,19] Scheme 9,[13,23] Scheme 10,[18] Scheme 11,[13,16,18] Scheme 12 [25]).

A different strategy of esterification involves the alkylation of vinylcyclopropane carboxylic acids through their metal or ammonium carboxylates with alkyl and benzyl halides and related sulfonates (Chapter IVa, Section 2.4.1.1.4)[12] (Scheme 18, entry a[49] and Scheme 6, Route a).[20] It has been successfully used[50] for the synthesis of (i) (*S*)-bioallethrin (S,1*R*,3*R*)-*trans*-(**1a**$_B$) from mesyl (*R*)-allethrolone (*R*)-(**2**$_{BMs}$) and (1*R*,3*R*)-*trans*-potassium chrysanthemate and implies an inversion of configuration at the secondary allylic position of mesyl (*R*)-allethrolone (*R*)-(**2**$_{BMs}$) and It has been also used (ii) to produce enantiopure deltamethrin (S,1*R*,3*R*)-*cis*-(**1f**$_F$) from ammonium (1*R*,3*R*)-*cis*-deltamethrinate and 3-phenoxy alpha-cyano-benzylbromide (Scheme 6, Route a, entry c).[20]



Scheme 18. Model esterification of metal chrysanthemates.[49,50]

4. From Chrysanthemic Acid/Esters to Pyrethroids by Changing the Substituents at [Cf] (block B-variations)

The synthesis of a large variety of pyrethroids from chrysanthemic acid/lower esters, especially its ethyl ester, including the variations disclosed in Scheme 2, requires the identification of intermediates easily available from chrysanthemic acid and easily transformed to a variety of pyrethroids as large as possible (Scheme 2, block-A and Bock-B variations) and flexible enough to accommodate easy stereochemical variations (Scheme 2, block-C variation). The strategy to select the order of those variations will depend on the desired outcome since protocols to achieve the different phases of biological tests are important (from stereoisomeric mixture to pure enantiomers).

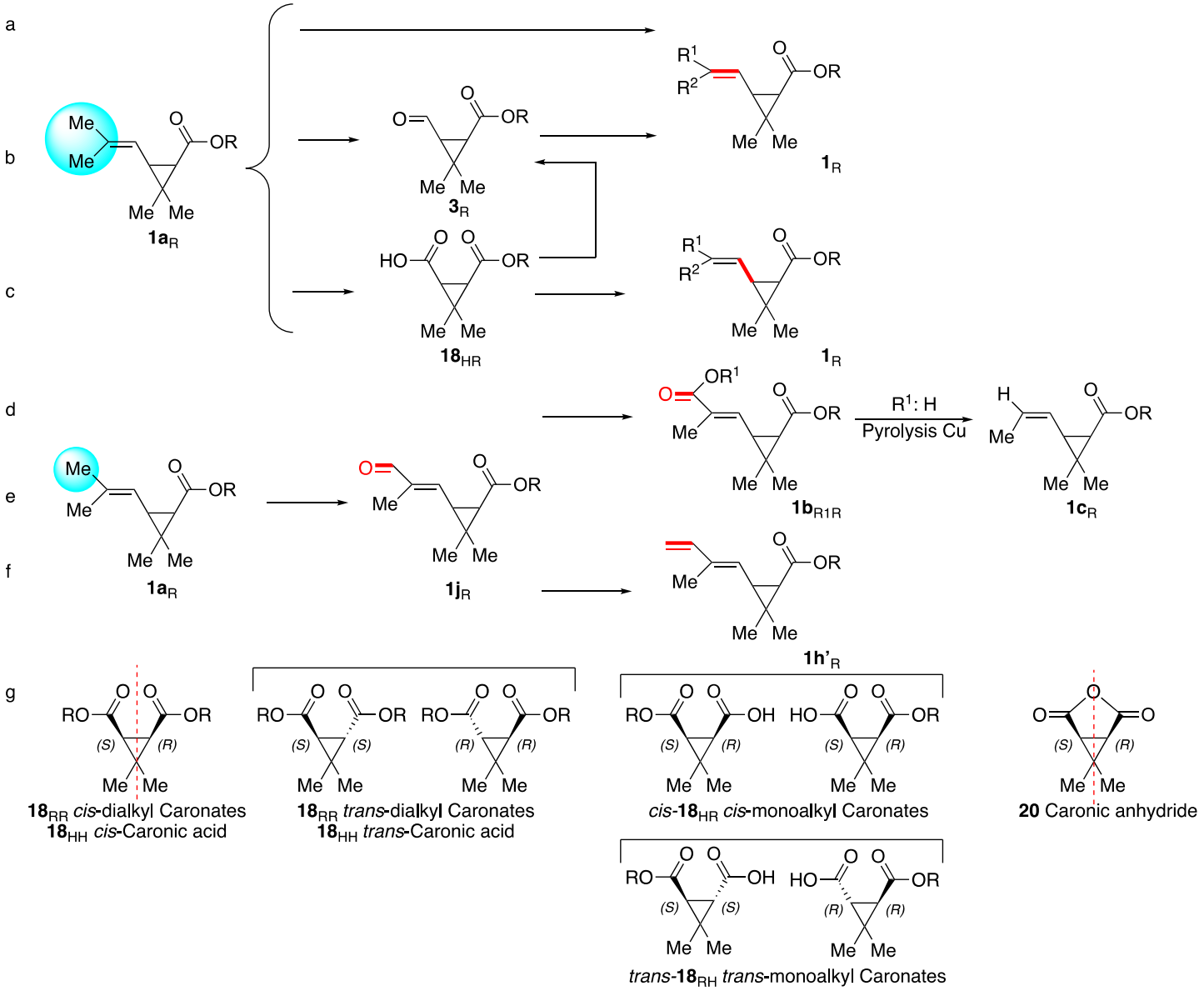
Four different strategies have been used to build the carbon framework of the vinyl cyclopropane carboxylic acids/ esters **1**$_R$ part of pyrethroids from chrysanthemic acid/lower esters but their scope is different (Scheme 19). They involve:

(i) the metathesis route (Scheme 19, entry a) that effects direct exchange of the isopropylidene moiety by another group using a metathesis reaction. It offers the advantage to be achieved in a single step, one-pot operation (Chapter IVa, Section 3.2.1). It has attracted very little attention untill now, [12,51,52]

(ii) the hemicaronic route (Scheme 19, entry b) that requires the cleavage of the [Ce=Cf] double bond of chrysanthemic acid/esters by ozonolysis or Lemieux-Johnson oxidation and its reconstruction with a different unit. It requires at least two steps but it does not affect the stereochemistry of the original hemicaronaldehyde **3**$_R$. It is presently the most versatile route that allow access the largest diversity of pyrethroids and has been routinely used by Crombie, Elliott and the Roussel-Uclaf company for that purpose,

(iii) the caronate-Route (Scheme 19, entry c) that exchange the whole isobutylidene moiety of methyl chrysanthemate **1a**$_{Me}$ by another one. Such process implies the (a) degradation of its side chain of chrysanthemic acid to produce monomethyl *cis*-caronate (**18**$_{MeH}$) (ii) trapping the intermediate cyclopropyl radical **19** resulting from its formal decarboxylation by a suitable vinylic zinc reagent.[14] This original approach recently published,[14] offers advantages over the hemicaronic Route but is low yielding and exclusively delivers the *trans*-stereoisomer of vinyl cyclopropane carboxylates even from the monoalkyl *cis*-caronates **18**$_{RH}$. This process is therefore highly stereoselective and is not stereospecific,

(iv) the selenium dioxide-Route (Scheme 19, entry e) takes advantage of the stereoselective oxidation of the methyl group *trans* to the cyclopropyl unit leading to the (*E*)-unsaturated aldehyde **1j**$_R$ (Chapter IVa, Section 3.3.1).[12] The later compound on reaction with a Wittig reagent allows the regio- and stereoselective access to pyrethroates bearing at [Cb] a polyenyl moieties (Scheme 19, entry f, compare to Scheme 10).[18]



Scheme 19. Compilation of different strategies and key intermediates used in the transformation of chrysanthemic acid/lower esters to pyrethroids.

Oxidation of the (*E*)-unsaturated aldehyde **1J**$_R$ (Scheme 19, entry e) allows the stereoselective access (a) to pyrethroic acid/lower esters **1b**$_{R1R}$ and (b) to (*Z*)-nor-chrysanthemic acid/lower esters **1c**$_R$ after decarboxylation of the corresponding unsaturated acid **1b**$_{RH}$ (Scheme 19, entry d).[2,53,54]

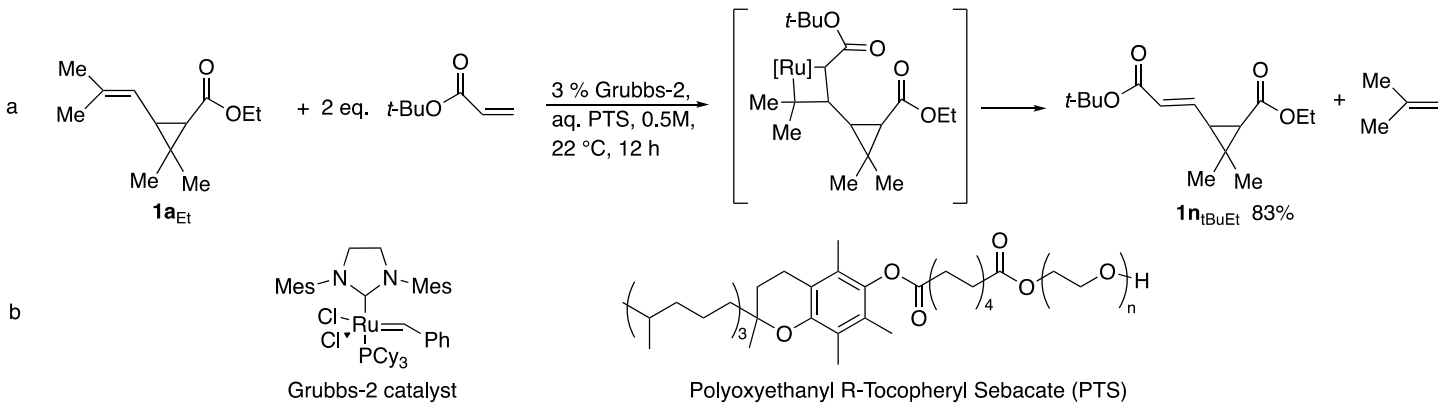
Those routes produce chiral pyrethroids which inherit the chirality from the precursor chrysanthemic acid/lower esters. This is also the case of the caronic route at the condition that it does not imply a meso-intermediate such as caronic anhydride (**20**), the *cis*-caronic acid (**18**$_{HH}$) or a *cis*-dialkyl caronate **18**$_{RR}$ possessing two identical alkyl groups. However, those compounds proved to be versatile intermediates not only to access

racemic compounds, to recycle undesired chrysanthemic acid stereoisomers, but also to produce a specific enantiomer of mono-alkyl *cis*-caronates **18**$_{RH}$ by either ring opening of the prochiral caronic anhydride (**20**) using a chiral reagent or an achiral one in the presence of a suitable chiral catalyst or by saponification of a meso *cis*-dialkyl caronate **18**$_{RR}$ using for example an enzyme. This approach has not been fully exploited in this field and is particularly interesting since monoalkyl-caronates **18**$_{RH}$ can be easily transformed to hemicaronic acid **3**$_{H}$ or mono-alkyl hemicaronates **3**$_{R}$ using a suitable reducing agent as detailed in a forthcoming section (Chapter IVb, Section 5.4).

We will provide examples for each route with a particular emphasis for the hemicaronic one (Chapter IVb, Section 4.4).

4.1. The metathesis route (Scheme 19, entry a)

The metathesis route (Scheme 20) allows the transformation of ethyl chrysanthemate (**1a**$_{Et}$), as racemic mixture of stereoisomers, to its analogue (**1n**$_{tBuEt}$) bearing a carboxy and a hydrogen at [Cf] in replacement of the two methyl groups (Scheme 20). The reaction that uses *t*-butyl acrylate (2 eq.) as co-reactant and the ruthenium-based 2nd generation Grubbs metathesis catalyst, proceeds at room temperature in a micellar environment implying polyoxyethanyl (*R*)-tocopheryl sebacate (PTS) in water, to deliver the *trans*-enoate (**1n**$_{EttBu}$) in high yield and high stereocontrol.[51] Unfortunately, this approach has not yet been extended to other vinyl cyclopropane carboxylates to our knowledge.



Scheme 20. Single example applying the metathesis-reaction to the transformation of ethyl chrysanthemate to pyrethrin II analogue.[51]

4.2. The caronic routes (Scheme 19, entry c)

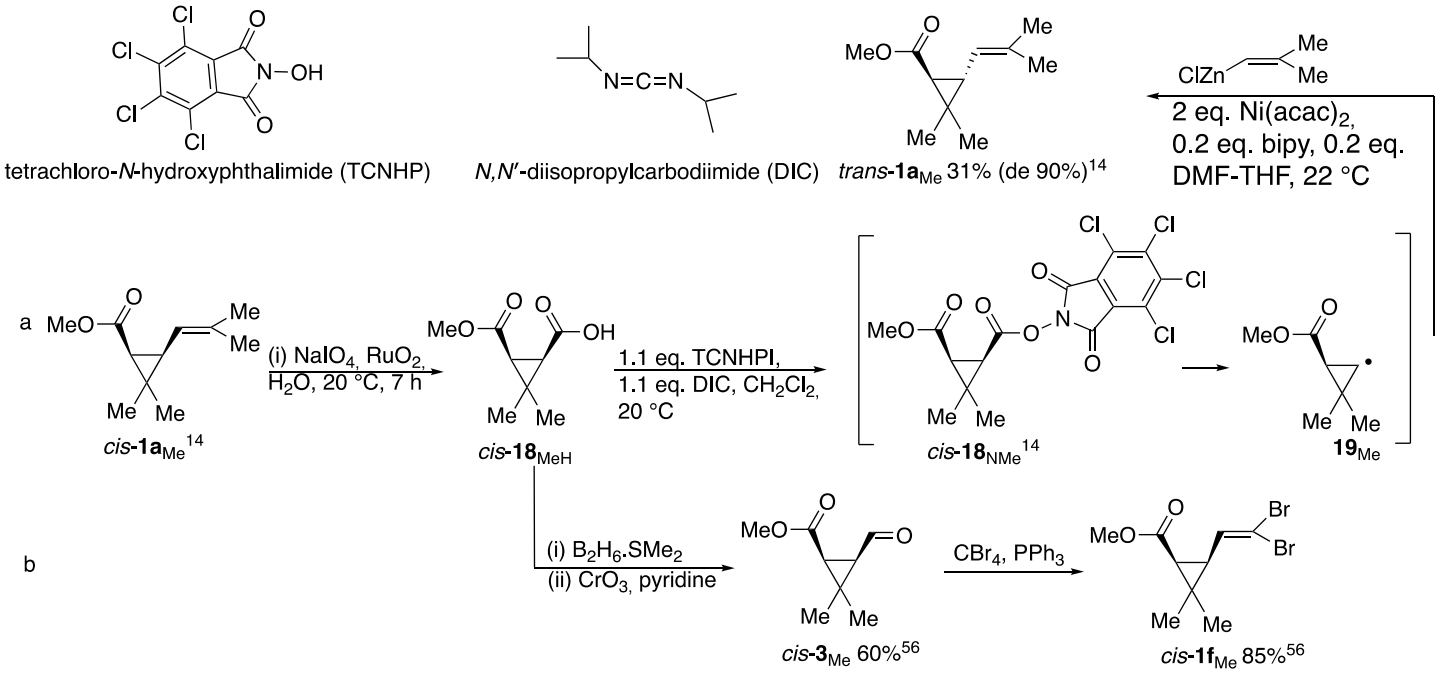
The caronic routes involve (a) the original approach recently disclosed by Baran[14] as well as (b) an original access to the hemicaronic route whose stereochemical advantages have been intoduced above and will be disclosed in a forthcoming section (Chapter IVb, Section 4.4).

Baran[14] recently disclosed the synthesis of racemic methyl *trans*-chrysanthemate (**1a**$_{Me}$) from racemic mono-methyl *cis*-caronate (**18**$_{MeH}$) but this reaction has not yet been extended to analogues.[14] It involves an original single pot decarboxylative alkenylation reaction that use the ability of carboxylic acids to be decarboxylated through a radical process,[55] and the propensity of alkenylzinc reagents to perform, in the presence of inexpensive Ni(II) catalyst and common 2,2'-bipyridyl ligand, the cross-coupling reaction (Scheme 21, entry a).[14] The yield, the lowest among the huge number of examples disclosed,[14] exemplifies one of the limitation of the

process due to instability of the cyclopropyl radical intermediate **19**$_{Me}$ that competitively reacts with THF to produce methyl 2,2-dimethyl-cyclopropane carboxylate.[14]

Note the difference of stereochemistry between the mono-methyl *cis*-caronate (**18**$_{MeH}$) and the resulting methyl *trans*-chrysanthemate (**1a**$_{Me}$) that allows, in the process disclosed in Scheme 21, the formal selective *cis*/*trans*-epimerization of methyl chrysanthemate at [Cd].

We can however expect that this reaction can be extended to compounds bearing two alkyl groups at [Cf] on the vinylic moiety and to the synthesis of enantiomerically pure derivatives from the methyl (1*R,*3*R*)-*cis*-caronate (1*R,*3*R*)-*cis*-(**18**$_{MeH}$).



Scheme 21. Different strategies used to synthesize methyl *trans*-chrysanthemate and methyl *cis*-deltamethrinate from methyl *cis*-chrysanthemate and implying monomethyl *cis*-caronate.[14,56]

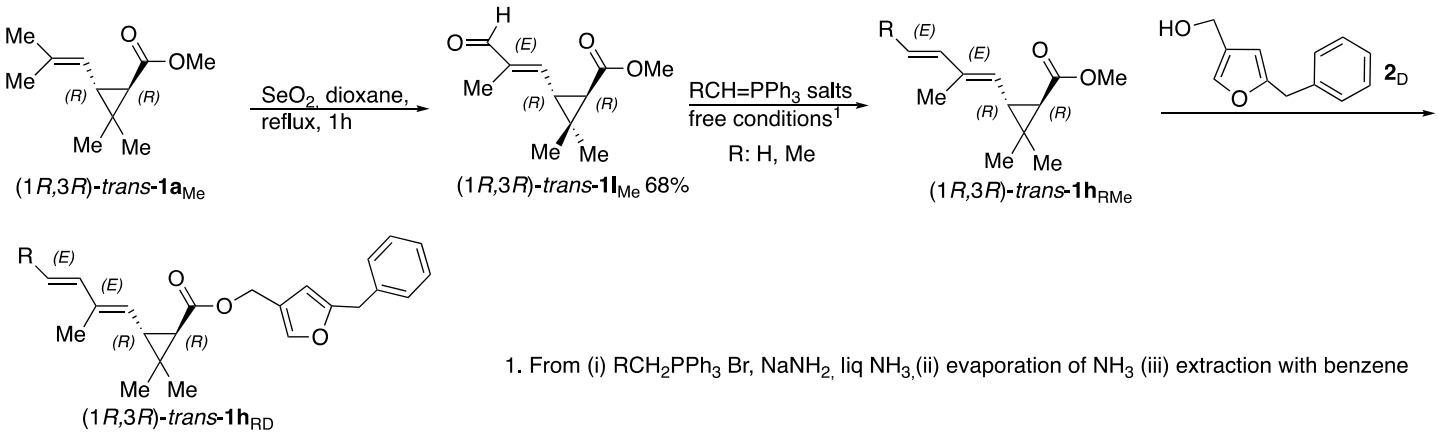
As already pointed out, reduction of mono-methyl *cis*-caronate (**18**$_{MeH}$) to methyl hemicaronate (**3**$_{Me}$) has been regio- and stereoselectively achieved[56] in a two-step sequence that involves the selective reduction of the carboxyl group to the cyclopropyl carbinol using borane derivatives and the oxidation of the later using the Collins reagent (chromium trioxide pyridine complex).[57] This strategy will be discussed in detail in forthcoming section (Chapter V, entry 5.4.1.2) for example reaction of methyl *cis*-hemicaronate with carbon tetrabromide/triphenyl phosphine (the Wittig-Ramirez reaction) allows the synthesis of methyl *rac-cis*-deltamethrinate, rac-*cis*-(**1f**$_{Me}$), one of the precursors of deltamethrin (**1f**$_F$) (Scheme 21, entry b).[56]

4.3. The selenium dioxide-route (Scheme 19, entry e)

The selenium dioxide-Route offers the advantage to produce pyrethroids with high stereocontrol as far as the [Ce=Cf] double bond is concerned since only the methyl group *trans* to the cyclopropyl moiety is oxidized in the reaction (Chapter IVa, Section 3.3.1).[12] It however only applies to the synthesis of pyrethroids bearing at least one methyl group at [Cf] (Scheme 22).[13]

This reaction however usually produces a mixture of allyl alcohol and enal resulting from the oxidation of the allylic methyl group of alkyl chrysanthemates. However, reduction or oxidation of that mixture with the

adequate reagent allows access to each of the two functional groups.[58] Use of such strategy to produce 5-benzyl-3-furfuryl methyl esters **1h**$_{RD}$ bearing a dienyl moiety at [Cd] is disclosed in Scheme 22.[13] The selenium dioxide-Route can be compared with the hemicaronic-Route (Compare Scheme 12[25] to Scheme 10, entry c[18]).

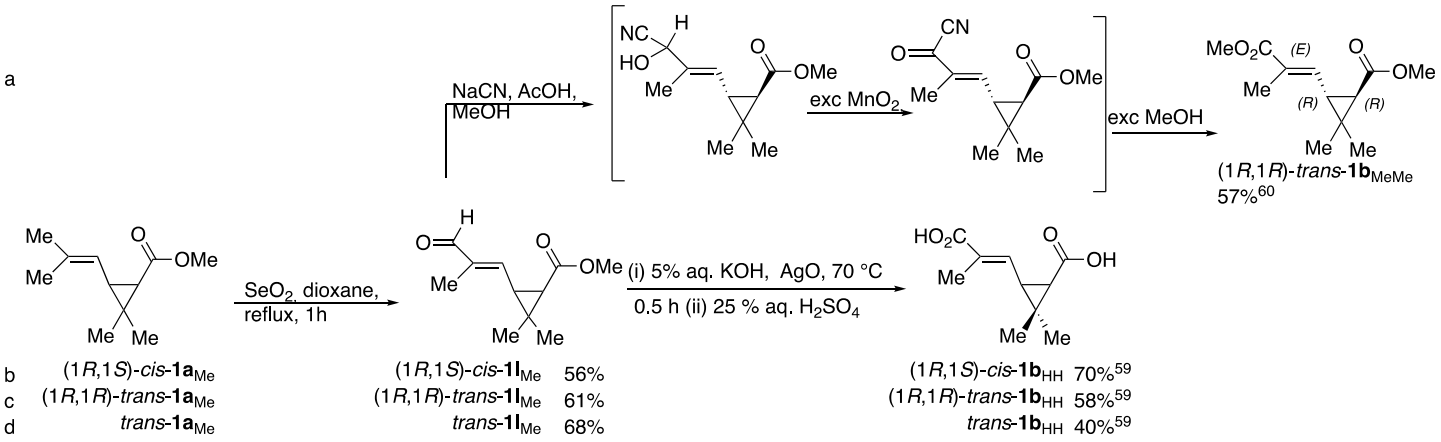


Scheme 22. Synthesis of pyrethroids bearing vinylic moieties from methyl chrysanthemate using selenium dioxide oxidation.[13]

Furthermore, the product(s) resulting from the selenium dioxide oxidation of alkyl chrysanthemates can be oxidized to access analogous compounds bearing a vinylic carboxylic acid or a methyl carboxylate moiety[59,60] reminiscent to pyrethrin II (Scheme 23).[59,60]

The latter transformation uses the Corey method [61] that involves the stepwise cyanohydrin formation from the aldehyde, its further oxidation with MnO_2 to a ketocyanide that on reaction with methanol generates the vinylic methyl ester by substitution of the cyanide (Scheme 23, entry a).[60] if the process is carried out on the *t*-butyl chrysanthemate it could be expected to deliver, *t*-butyl pyrethroate (**1b**$_{MetBu}$) then pyrethric acid precursor of pyrethric acid (**1b**$_{MeH}$) after acid hydrolysis.

Oxidation with silver oxide in basic media delivers instead the diacid (**1b**$_{HH}$) (Scheme 23, entry b).[59]

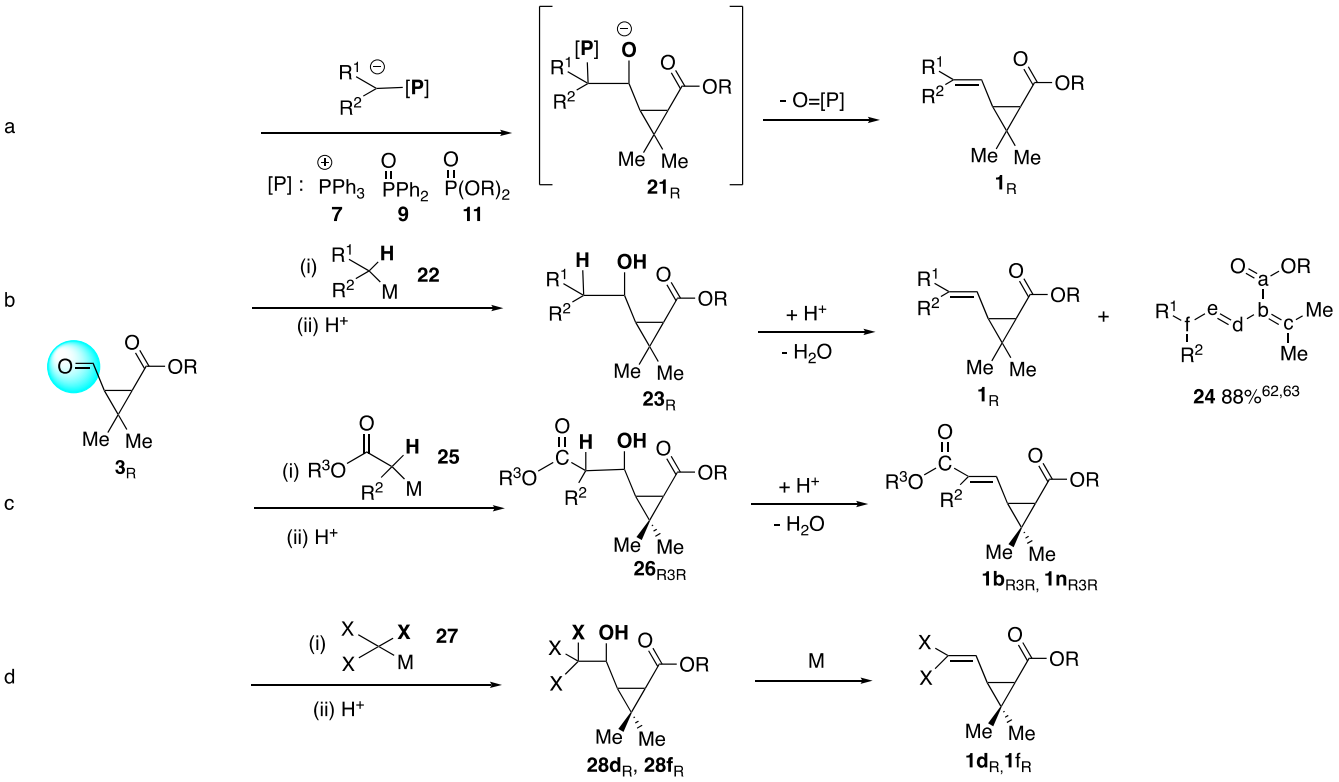


Scheme 23. Synthesis of pyrethric acid and esters from methyl chrysanthemate using selenium dioxide oxidation.[59,60]

4.4. The hemicaronic-Route (Scheme 19, entry b)

The hemicaronic-Route has played in the discovery of new pyrethroids a role far more important than the other routes. Its outcome is somewhat similar to that of the metathesis reaction, but the first method has been only once reported in this field whereas a huge number of pyrethroids have been synthesized through the hemicaronic route.

This route from chrysanthemic acid/lower esters to pyrethroids involves at least two steps and hemicaronic acid/lower esters $\mathbf{3}_R$ as intermediates. The transformation of the aldehyde functional group of hemicaronates $\mathbf{3}_R$ to a large variety of olefinic compounds bearing hydrogen atoms, alkyl-, vinyl-, dienyl-, carboxyl-groups and halogens have been carried out using the Wittig and related reactions (Scheme 24, entry a) although other methods have been reported (Scheme 24). Most of the transformations disclosed in Scheme 24 have been carried out efficiently, except for the one reported in Scheme 24, entry b, in which the cyclopropyl carbinol possesses a high propensity to deliver the diene **24** (resulting from cyclopropane ring opening through the formation of cyclopropyl carbinyl intermediate) rather than an alkyl vinyl cyclopropane carboxylate $\mathbf{1}_R$.[62,63]



Scheme 24. Strategies used to synthesize pyrethroids involving the hemicaronic acid/esters.[62,63]

All the methods disclosed in Scheme 24 depend on the availability of hemicaronic acid/lower esters from chrysanthemic acid/lower esters. We have gathered the most used methods of synthesis of hemicaronic acid/lower esters $\mathbf{3}_R$ in the following section (Chapter IVb, Section 4.4.1) and that of the Wittig and related reactions in a forthcoming Section (Chapter IVb, Section 4.4.2). We will, in complement, discuss in more detail the behaviour and mechanism of the Wittig and related reactions, restricted to the specific case of aldehydes (as for $\mathbf{3}_R$), in a different section (Chapter IVb, Section 6).

4.4.1. Access to hemicaronic acid/lower esters from chrysanthemic acid/lower esters. The synthesis of hemicaronic acid/lower esters $\mathbf{3}_R$ from chrysanthemic acid/lower esters $\mathbf{1a}_R$ has been routinely achieved by (i)

reductive ozonolysis implying ozone (Chapter IVa, Section 3.2.2)[12] followed by a reduction of the resulting ozonide using (i) dimethyl sulfide[21,64,65] that delivers the water soluble dimethylsulfoxide as a co-product (Scheme 25, entries a-e; Scheme 6,[21] Scheme 7;[18] see below Scheme 26, Scheme 48, Scheme 55, Scheme 58, Scheme 59) or (ii) triphenylphosphine that produces triphenylphosphinoxide usually removed by filtration (Scheme 5,[18] Scheme 10, entry a; see below Scheme 56, entry b) or (iii) zinc in acetic acid (Scheme 25, entries e,f;[66] Scheme 8;[22] see below Scheme 41) (ii) osmium tetroxide-sodium periodate in two sequential steps (see below Scheme 31, entry a, Scheme 45,) that even involves the Sharpless AD reaction (Scheme 11) [67] or in a single step sequence using the well known Lemieux-Johnson osmium tetroxide-catalyzed periodate oxidation[68] Chapter IVa, Section 3.2.3).[12] Crombie and Pattenden[60] priviledged the Lemieux-Johnson oxidation,[68] others including Elliott[13,69] used ozone instead.

a	R: Me	*trans*-**1a**$_{Me}$	(i) O_3, MeOH, -80 °C, 3 h (ii) excess Me_2S, some hrs (iii) 30% aq. AcOH, 80 °C, 0.3 h	*trans*-**3**$_{Me}$ 90%[21]
b	R: H	*trans*-**2a**$_{H}$	(i) O_3, MeOH, -80 °C, 3 h (ii) O_2 , N_2 (iii) excess Me_2S, -35 to 20 °C, 2.5 h (iv) acidic work up	*trans*-**3**$_{H}$ 42%[21]
c	R: Me	*cis*-**1a**$_{Me}$	(i) O_3, MeOH, -78 °C, 3 h (ii) excess Me_2S, -30 to 25 °C, 3 h, 30% AcOH, 80 °C, 0.3 h	*cis*-**3**$_{Me}$ 91%[64]
d	R: Et	*trans*-**1a**$_{Et}$	(i) O_3, EtOH, -80 °C, 3 h (ii) excess Me_2S, -30 to 25 °C, 21 h, 30% AcOH, 80 °C, 0.3 h	*trans*-**3**$_{Et}$ 95%[65]
e	R: t-Bu	*trans*-**1a**$_{tBu}$	(i) O_3, AcOH (ii) Zn , AcOH	*trans*-**3**$_{tBu}$ 90%[66]
f	R: t-Bu	*cis*-**1a**$_{tBu}$	(i) O_3, AcOH (ii) Zn , AcOH	*cis*-**3**$_{tBu}$ 90%[F66]

Scheme 25. Synthesis of hemicaronic acid/esters by ozonolysis of chrysanthemic acid/esters.[21,64-66]

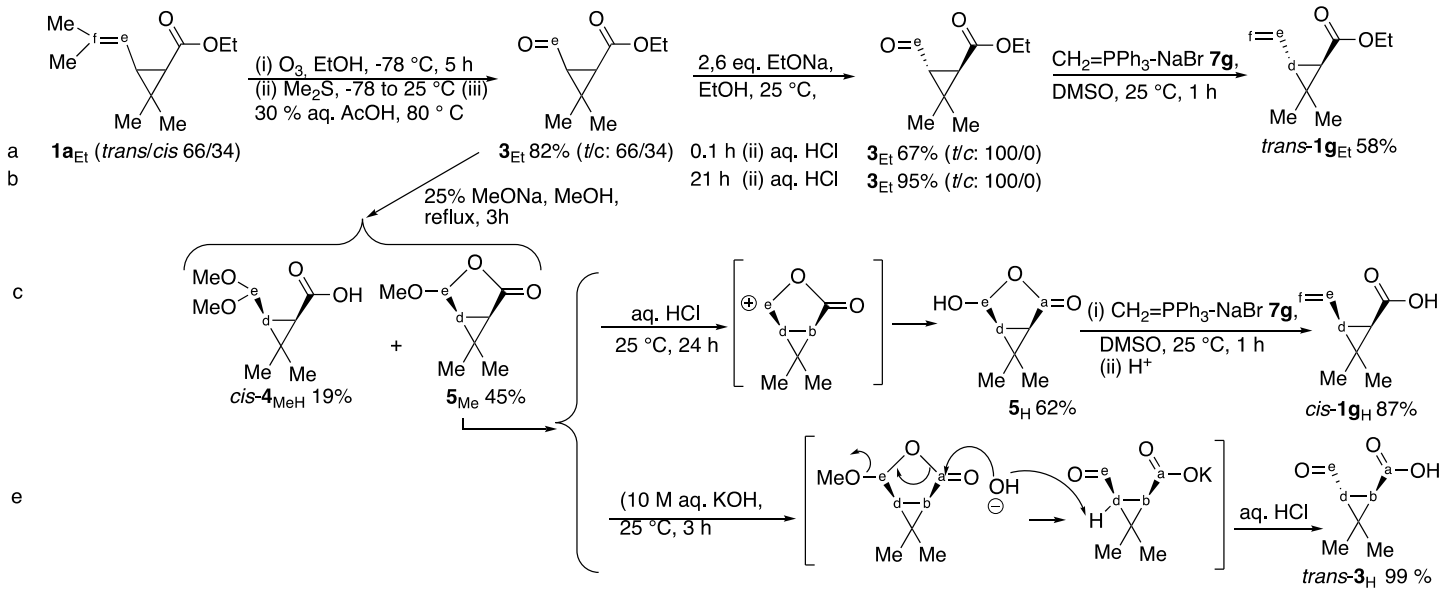
These reactions are stereospecific. It means that the hemicaronic acid/lower ester **3**$_R$ possesses the relative and absolute stereochemistry present on the starting chrysanthemic acid/lower ester **1a**$_R$.

Ozonolysis of chrysanthemic acid (**1a**$_H$) has been also successfully achieved. It delivers the corresponding *trans*-hemicaronic acid *trans*-(**3**$_H$) from *trans*-chrysanthemic acid *trans*-(**3**$_H$) (Scheme 25, entry b) but *cis*-hemicaronic acid *cis*-(**3**$_H$) resulting from ozonolysis of *cis*-chrysanthemic acid *cis*-(**1a**$_H$) tends to cyclize to deliver instead biocartol (**5**$_H$) a valuable bicyclic lactone that has been used among others to carry out the resolution of several racemic alcohols including racemic-chrysanthemol, racemic-allethrolone[6] (**2**$_B$) (Chapter II, Section 6),[70,71,8] and racemic-2-phenoxy-mandelonitrile (**2**$_F$)[7,19] (Chapter III, Section 2.4.1).[19,70]
The synthesis of biocartol **5**$_H$ has been also achieved in two steps from ethyl *trans*-hemicaronate *trans*-(**3**$_{Et}$) and requires an epimerisation at [Cd].

Thus, reductive ozonolysis of a (3/7) *cis*/*trans*-mixture of ethyl chrysanthemates (**1a**$_{Et}$) leads to the related mixture of ethyl hemicaronate (**3**$_{Et}$). This reaction produces a mixture of the *cis*-dimethylacetal (**4**$_{Me}$) and methyl biocartol (**5**$_{Me}$) upon treatment with sodium methylate in methanol (Scheme 26, entry c).[64] Acid hydrolysis of the resulting mixture at room temperature leads to biocartol in 62% yield (Scheme 26, entry c).[64] Reaction of biocartol with methylene triphenylphosphorane (**7g**) delivers *cis*-didesmethyl-chrysanthemic acid *cis*-(**1g**$_H$) in good yield (Scheme 26, entry c).[64]

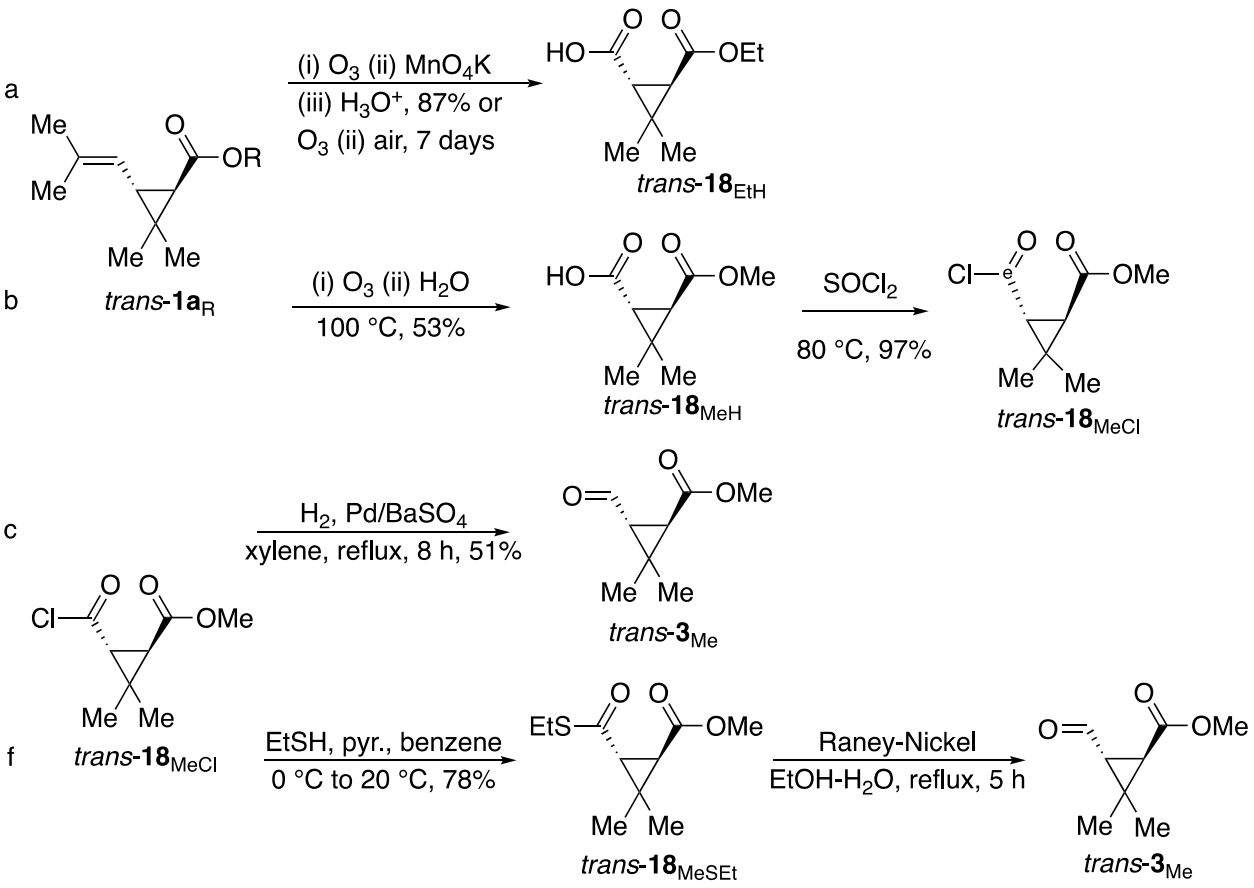
Reaction of methyl biocartol **5**$_{Me}$ with potassium hydroxide delivers after acid hydrolysis, *trans*-hemicaronic acid *trans*-(**3**$_H$) quantitatively (Scheme 26, entry e).[64] It presumably results from the attack of a hydroxide ion on the carbonyl group of (**5**$_{Me}$) that results in lactone ring opening and release of a methoxide ion. It is followed by the *cis*/*trans*-epimerization of the resulting sodium *trans*-hemicaronate *trans*-(**3**$_K$) by reversible metalation

/protonation process at [Cd] (Scheme 26, entry e).[64] Those results will be discussed contextually in a following sections of this Chapter IVb (Section 4.4.2.1 for related facts as well as Section 6.3 for related basic trends).



Scheme 26. Synthesis of isomeric hemicaronic acid/esters and related vinyl cyclopropane carboxylates involving epimerisation reactions.[64]

Other, less successful syntheses of *trans*-hemicaronates $\mathbf{3}_R$ involve monoalkyl caronates 18_{RH}. Thus:
(i) the Rosunmund hydrogenolysis of *trans*-3-carbomethoxy-2,2-dimethylcyclopropane-1-carbonyl chloride ($\mathbf{18}_{MeCl}$) with a stream of hydrogen in the presence of palladium on barium sulfate catalyst (xylene, 110 °C, 51% yield, Scheme 27, entry c).[72] Suprisingly, this reaction does not proceed if carried out, as usual, in the presence of thiourea or quinoline poison,[72]
(ii) the Raney-nickel hydrogenolysis of ethyl (±)-trans-3-carbomethoxy-2,2-dimethylcyclopropane-1-carbothiolate ($\mathbf{18}_{MeSEt}$) (Scheme 27, entry d).[72] Both the acid chloride *trans*-($\mathbf{18}_{MeCl}$) and the carbothiolate *trans*-($\mathbf{18}_{MeSEt}$) have been prepared from racemic methyl *trans*-chrysanthemates (Scheme 27, entries a,b).[72]
Other methods of synthesis of hemicaronates $\mathbf{3}_R$ or hemicaronic acid ($\mathbf{3}_H$) that involve the intermediate formation of monoalkyl caronate will be reported below (Chapter IVb, Section 5.3, Section 5.4).



Scheme 27. Synthesis of hemicaronates from chrysanthemic acid through monoalkyl caronates.[72]

4.4.2. Synthesis of the [Ce=Cf] double bond of vinyl cyclopropane carboxylic acids/esters from hemicaronic acid/esters using the Wittig and related reactions. Factual results concerning the olefination reaction of hemicaronic acid and related esters are reported in this section for the synthesis of different classes of vinyl cyclopropane carboxylic acid/related esters that differ upon the nature of the substituents present at [Cf] of their [Ce=Cf] double bond: (i) alkyl groups or/and hydrogens (Chapter IVb, Section 4.4.2.1) or polyenyl moeities (Chapter IVb, Section 4.4.2.2), (ii) carboxyl group and a hydrogen or an alkyl group (Chapter IVb, Section 4.4.2.3), (iii) two halogens (Chapter IVb, Section 4.4.2.4).

As a general trend, the Wittig and related reactions have been widely used especially in the discovery phase since they use highly reproducible protocols and allow the synthesis of a large variety of vinyl cyclopropane carboxylic acids/lower esters in a single pot from readily available starting materials such as phosphonium salts in the Wittig reaction (Scheme 24, entry a; W-reaction [P]: $^+PPh_3,X^-$)[73-78] used for the synthesis of compounds possessing hydrogen and alkyl groups at [Cf] (Section 3.4.2.1) as well as those bearing a carboxy group there (Section 3.4.2.2). The latter have been also generated using the Horner-Wadsworth-Emmons reaction (Scheme 24, entry a; HWE-reaction [P]: $O=P(OR)_2$)[77,80-82] that often leads to a different stereochemical outcome. Finally, the synthesis of the dichloro- and dibromo-vinyl derivatives (Section 3.4.2.3) has been performed using the Ramirez[101] or related reactions that use tetrahalogenomethanes and triphenylphosphine or related aminophosphite in processes close to the ones involved in the W- or the HWE-reactions

The features of the Wittig and related reactions will be reported in a forthcoming section (Section 6) and their specificity for each of the above reported classes will be disclosed there. We therefore strongly suggest

the reader to look at the related Section 6 to understand the different synthetic features of each of the classes that will be discussed in this chapter.

The phosphorus moiety is essential for acidification of the hydrogen attached to the alpha-carbon of phosphonium salts, phosphine oxides and phosphonates **6** and the stabilization the related anions **7**. It furthermore takes a crucial role in the *syn*-elimination process that proceeds on the intermediate produced on further reaction with hemicaronic acid/esters $\mathbf{3}_R$ to deliver compounds possessing the [Ce=Cf] double bond. It avoids the competing cyclopropane ring opening that occurs when even a transient positive charge appears at the cyclopropyl carbinyl carbon [Ce] at any stage of the elimination reaction (Chapter IVa, Section 5.3.1).[12]

However, the ylide route (Scheme 24, entry a) suffers from the presence of large molecular weight phosphorus moieties that for example in a Wittig reaction for transfering a methylene group (MW: 14 g/mol), requires a phosphonium salt whose minimal molecular weight is 312.5 g/mol (as for methyltriphenyphosphonium chloride) and releases, concomitantly to the terminal olefin, triphenylphosphine oxide (290 g/mol) that recycling is costly. Especially for large-scale experiments, it makes the reaction poorly compatible with the notions of *atom economy*[83,84] and has a negative ecological impact.

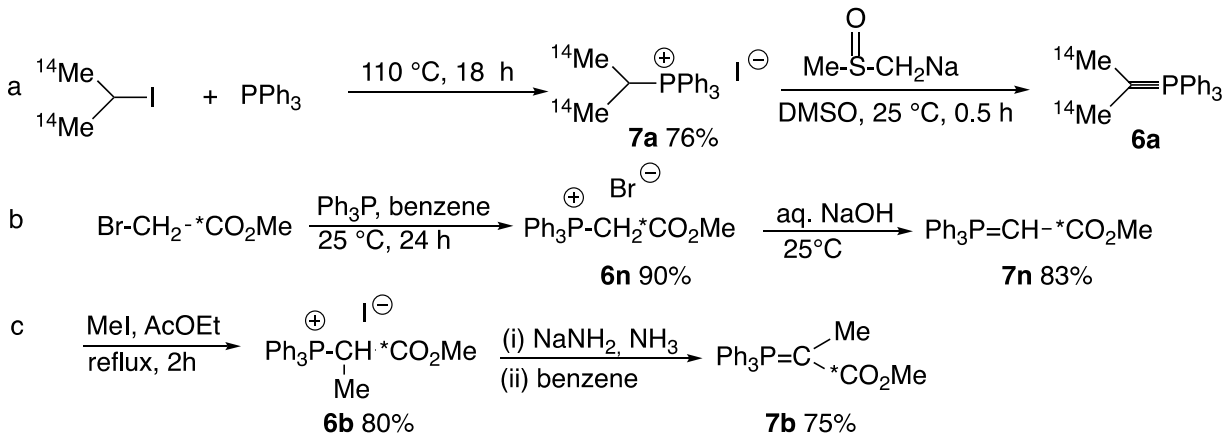
For that purpose, alternative methods (Scheme 24, entries b-d and also Scheme 19, entry a) have been used especially any time the Wittig and related reactions are unable to achieve the required goals or when industrial production is required. Those methods will be discussed in a forthcoming section (Chapter IVb, Section 4.4.3).

4.4.2.1. Synthesis of vinylcyclopropane carboxylic acids/lower esters bearing hydrogen and alkyl groups at their vinylic terminus from hemicaronic acid/esters using the Wittig and related reactions. 4.4.2.1.1. Use of the Wittig reaction for the synthesis of vinylcyclopropane carboxylic acids/lower esters bearing terminal, mono-alkyl and dialkyl groups at their terminus. The Wittig reaction has been used to synthesize those vinylcyclopropane carboxylic acids/related esters bearing hydrogen, alkyl-, cycloalkyl and vinyl groups at their vinylic terminus [Cf] and follows the basic trends disclosed in Section 6.3 of this Chapter.

Such transformations have been pioneered in the field by Crombie and Pattenden[60] to synthesize ^{14}C labelled methyl (1*R*,3*R*)-*trans*-chrysanthemate (1*R*,3*R*)-*trans*-(**1a***$_{Me}$) (Scheme 31, entry a) and methyl pyrethrate (**1b***$_{MeMe}$) for biochemical studies as well as methyl (1*R*,3*R*)-*trans*-norchrysanthemate (1*R*,3*R*)-*trans*-(**1c**$_{Me}$) (Scheme 29, entry b) (Scheme 40) and methyl (1*R*,3*R*)-*trans*-disdesmethylchrysanthemate (1*R*,3*R*)-*trans*-(**1g**$_{Me}$) (Scheme 29, entry a) from the same methyl (1*R*,3*R*)-*trans*-hemicaronate (1*R*,3*R*)-*trans*-(**3**$_{Me}$). The latter have benn performed using the Lemieux-Johnson route on the related methyl chrysanthemate (1*R*,3*R*)-*trans*-(**1a**$_{Me}$) and the ylides generated on reaction of the realated phosphonium salts and a suitable base. The syntheses of the radiolabelled ylides such as 1,3$^{14}C_2$-labelled isopropyl triphenylphosphonium iodide (Scheme 28, entry a)[60] and 1-methoxy[^{14}C]-carbonylethylidenetriphenylphosphorane (Scheme 28, entry b) are disclosed on Scheme 28, that of the other phosphonium salts will be discussed below in a related Section (Chapter IVb, Section 6.2).

Routinely, salt-free conditions (Conditions A), known to produce a high ratio of (*Z*)-alpha,beta-disubstituted olefins, has been often used in the sixties (see Section 6.3.1.2 of this chapter for mechanistic interpretation). It originally involves sequential (i) metalation of alkyl triphenylphosphonium salt with sodium amide in liquid ammonia (ii) evaporation of the solvent and (iii) extraction of the residue with benzene leading to the benzene solution of the salt-free ylide (Conditions A).

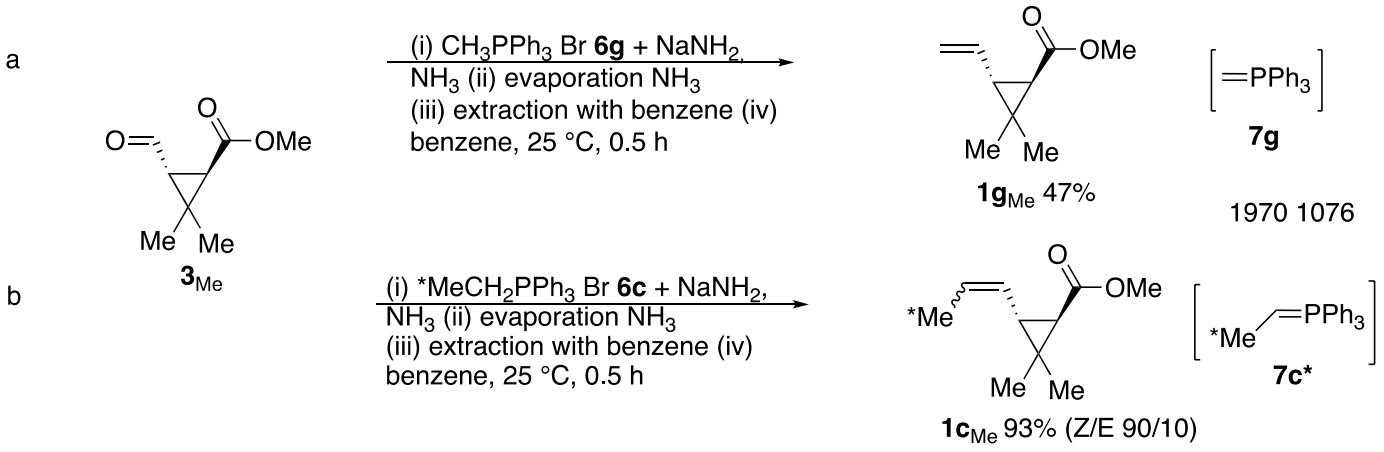
A more convenient method that possesses similar characteristics involves the use sodium hydride in DMSO (Conditions B). The reagent metalates at room temperature the phosphonium salt and the solvent sequesters the sodium cation, from the sodium halide concomitantly formed avoiding the tedious mechanical separation reported above. Related conditions, often used in industry for their low cost, use sodium hydride but in dimethoxyethane (DME, Conditions B1) or potassium *t*-butoxide inTHF (Conditions B2).



Scheme 28. Synthesis of radiolabelled phosphonium salts and related ylides.[60]

Other valuable conditions use *n*-butyllithium in THF and to a lower extent in ether as a basic system (Conditions C), that proved, except if the (*Z*)-stereochemical control is required, of wide applicability.

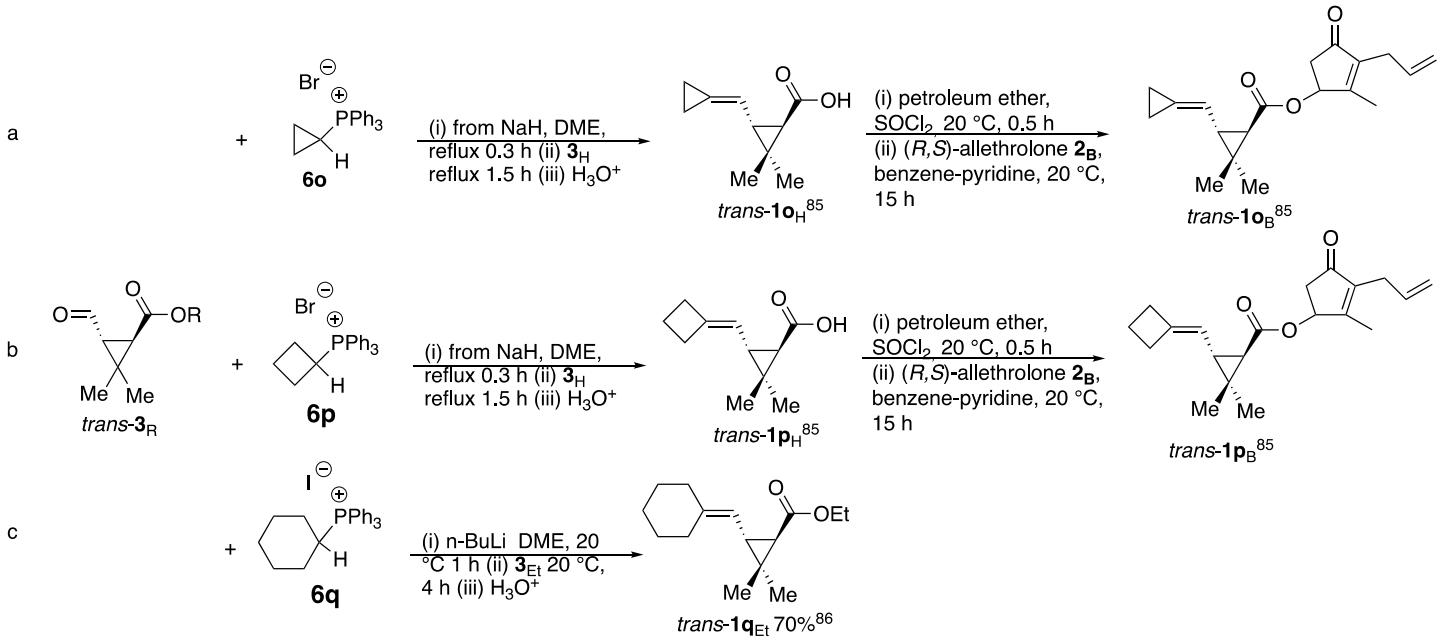
Conditions A (salt-free conditions) proved efficient on methyl (1*R*,3*R*)-*trans*-hemicaronate (1*R*,3*R*)-*trans*-(**3**$_{Me}$) to produce methyl didesmethyl chrysanthemate (1*R*,3*R*)-*trans*-(**1g**$_{Me}$) from methylene triphenylphosphorane **7g** (Scheme 29, entry a, 47%)[60] and methyl nor-chrysanthemate (1*R*,3*R*)-*trans*-(**1c**$_{Me}$) with high (*Z*)-stereocontrol from ethylidene triphenylphosphorane **7c** (Scheme 29, entry b, 93%)[60] (See also Section 4.4.2.1.2 of this chapter IVb). It proved however inadequate for the synthesis of unlabelled as well as labelled methyl (1*R*,3*R*)-*trans*-chrysanthemate (1*R*,3*R*)-*trans*-**1a**$_{Me}$ that is produced in no more than 2% yield under these conditions.[60]



Scheme 29. Synthesis of methyl vinylcyclopropane carboxylates from methyl hemicaronate and phosphorus ylides.[60]

Conditions B (NaH in DMSO) proved as efficient delivering (i) ethyl didesmethyl *trans*-chrysanthemate *trans*-(**1g**$_{Et}$) from the related ethyl hemicaronate *trans*-(**3**$_{Et}$) and methylene triphenylphosporane **7g** in slightly better yield (58%, Scheme 26, entry a)[64] and (ii) didesmethyl *cis*-chrysanthemic acid *cis*-(**1c**$_{H}$) in much higher yield from biocartol **5**$_{H}$ (87%, Scheme 26, entry c).[64] Conditions B have also been used to synthesize ^{14}C radiolabelled methyl (1*R*,3*R*)-*trans*-chrysanthemate (1*R*,3*R*)-*trans*-(**1a***$_{Me}$) (41%, Scheme 31, entry a)[60] from (1*R*,3*R*)-*trans*-hemicaronate (1*R*,3*R*)-*trans*-(**3**$_{Me}$) and ^{14}C radiolabelled isopropylidene triphenylphosphorane **7a***.[60]

Conditions B1 (NaH in DME) has allowed the synthesis of cyclopropylidene- **1o**$_H$[85] and cyclobutylidene- **1p**$_H$[85] vinylcyclopropane carboxylic acids from cyclopropylidene- **7o**[85] and cyclobutylidene- **7p**[85]triphenylphosphoranes themselves prepared from the corresponding phosphonium bromides **6o**, **6p** (See below Section 6.2 of this Chapter IVb for their synthesis) and NaH in DME (Reflux, 0.3 h). These pyrethroic acids have been transformed through their acid chlorides to their allethronyl esters **1o**$_B$ and **1p**$_B$ (Scheme 30, entries a,b).[85]



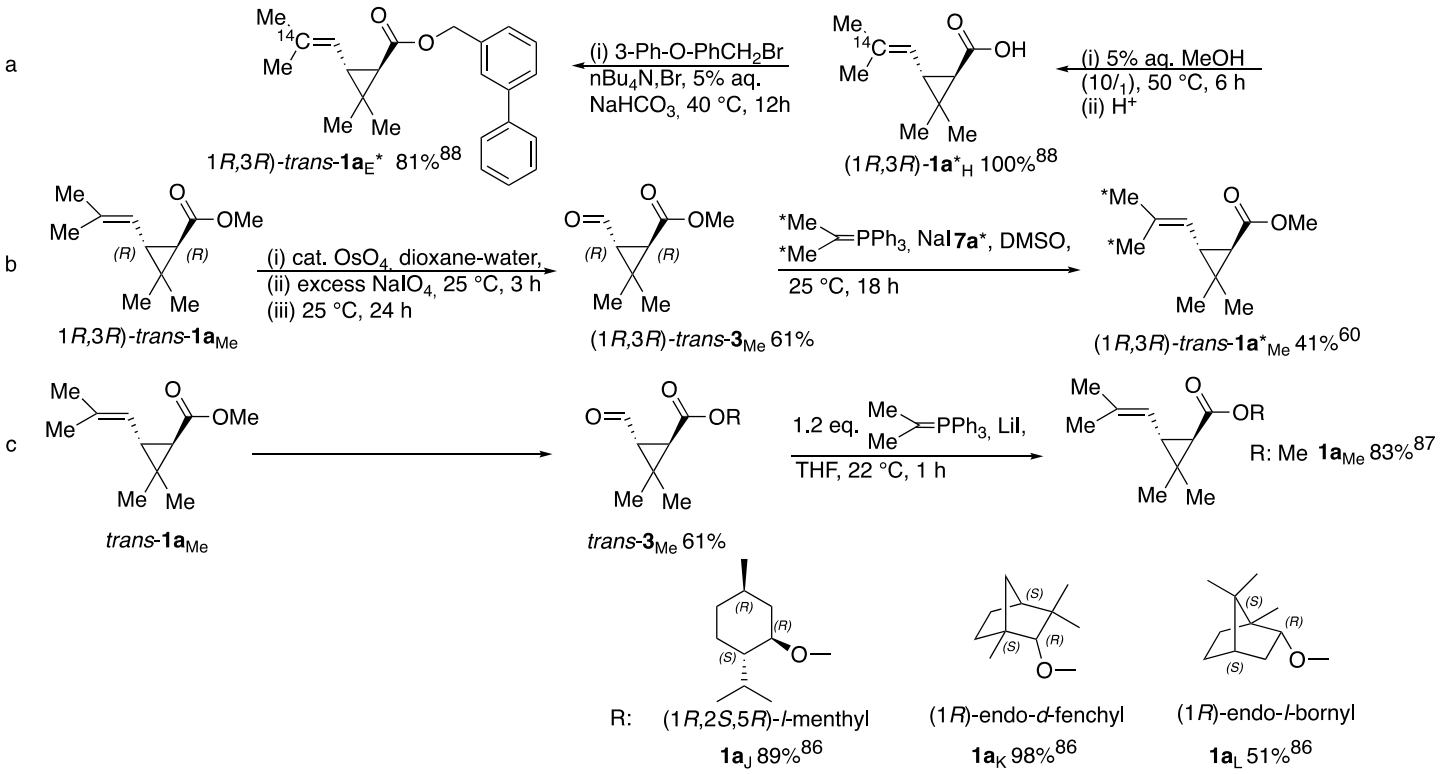
Scheme 30. Synthesis of pyrethroids from methyl hemicaronate and phosphorus ylides derived from cycloalkyl halides.[85,86]

Conditions C (BuLi in THF) deliver the corresponding vinylcyclopropane carboxylates **1**$_R$ in yields ranging from 50 to 98%. It has allowed the synthesis of pyrethroid **1g**$_D$ (87%, Scheme 11, entry d) and **1g**$_G$ (Scheme 10, entry b)[18]possessing elaborated alkoxy moieties from the corresponding hemicaronates (**3**$_D$) and (**3**$_G$) and methylene triphenylphosporane **7g** and ethyl nor-chrysanthemate (**1c**$_{Et}$) from the ethyl hemicaronates (**3**$_{Et}$) and ethylidene triphenylphosporane **7c** (64%, Scheme 5)[18] precursor of pyrethroids (**1c**$_G$) and (**1c**$_D$) (Scheme 5).[18]

Conditions C have allowed the synthesis of a large variety of alkyl chrysanthemates **1a**$_R$ in high yield from isopropylidene triphenylphosphorane **7a** and a series of alkyl hemicaronates such as methyl (**3**$_{Me}$) (83%),[87] *l*-menthyl (**3**$_J$) (89%),[86] fenchyl (**3**$_K$) (98%)[86] and *l*-bornyl (**3**$_L$) (51%)[86] ester groups (Scheme 31, entry b). Conditions C have also been used to produce radiolabelled methyl chrysanthemate in better yield (66%) using ^{14}C radiolabelled isopropylidene triphenylphosphorane **7a*** (*n*-BuLi, ether, 0 °C to 20 °C, 2 h)[88] compared to Conditions B (66%[88]compare to 41%[60] Scheme 31, entry a). Related Conditions C1 (BuLi in DME) involving metalation of cyclohexyl triphenylphosphonium iodide **7q** with *n*-butyllithium in DME have been successfully extended to the synthesis of the ethyl cyclohexylidene cyclopropane carboxylate (**1q**$_{Et}$) (Scheme 30, entry c).[86]

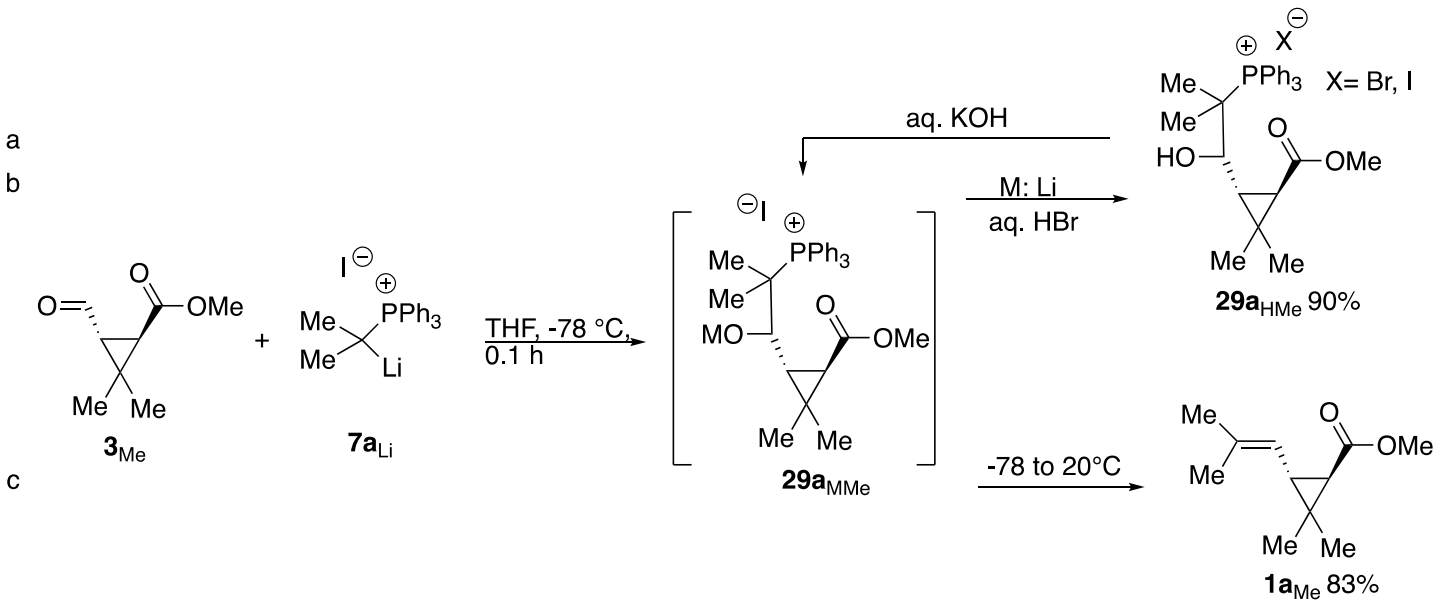
In a different experiment, in order to support the attribution of a beta-alkoxyphosphonium salt **29a**$_{LiMe}$ to the intermediate isolated from the reaction of methyl 4-oxo-butenoate and 2 equivalents of isopropylidene triphenylphosphorane (**7a**) in THF under Conditions C,[87] we have reacted the same ylide **7a** under the same conditions with methyl *trans*-hemicaronate *trans*-(**3**$_{Me}$). We found[89] that the addition proceeds extremely rapidly (−78 °C, 0.1 h) allowing to isolate, on quenching with HBr (10%, aqueous), the hydroxy phosphonium

bromide **29a**$_{HMe}$ (Scheme 32, entry b) whereas raising instead the temperature of the reaction from −78 °C to 20 °C allows the synthesis of methyl *trans*-chrysanthemate (**1a**$_{Me}$) in comparable yield (Scheme 32, entry c).[86,87,89-91] In a separate experiment, methyl *trans*-chrysanthemate has been generated using 2M aqueous sodium hydroxide solution on the isolated beta-hydroxyphosphonium bromide **29a**$_{HMe}$ (Scheme 32, entry c).[89] under conditions related to those used by Schosser to favor the decomposition of beta-hydroxyphosphonium salts to alkenes.[92]



Scheme 31. Synthesis of chrysanthemates including radiolabelled ones from a series of hemicaronates.[60,86-88]

Elliott[13,16] has used the strategy and the method published by Crombie and Pattenden[60] (Conditions A) disclosed above, to produce larger quantities of nor-chrysanthemate especially their 5-phenyl-2-furfurylmethyl ester[93] to test their insecticidal activity. He extended the Wittig reaction to the synthesis of analogues (de > 80%) and bearing a single alkyl substituent at [Cf] and possessing the *Z*-stereochemistry (de > 80%) such as an ethyl, a propyl, a butyl, a pentyl or a hexyl substituent from methyl- (**3**$_{Me}$) and *t*-butyl- (**3**$_{tBu}$) hemicaronates. The latters have been prepared by ozonolysis[13] rather than by the Lemieux-Johnson reaction used by Crombie and Pattenden.[60] Since then, other use of such class of Wittig reaction in the pyrethroid field have been disclosed (Scheme 26).[64] A few are summarized in a different context (Scheme 5,[18] Scheme 10,[18] and Scheme 11[13,18]).



Scheme 32. Isolation of a beta-hydroxy-phosphonium salt on reaction of methyl hemicaronate and isopropylidene triphenylphosphorane.[86,89]

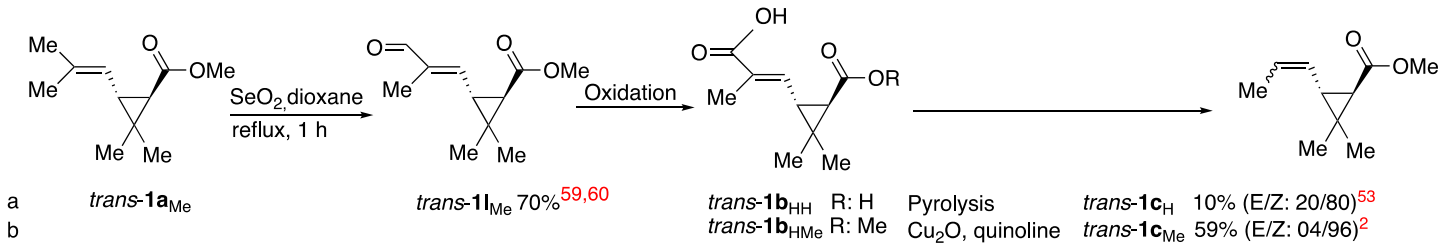
4.4.2.1.2. Synthesis of nor-chrysanthemic acid/related esters from hemicaronic acid/related esters involving the Wittig and related reactions. The research carried out on norchrysanthemic acid (**1c**$_H$) and related esters merits further comments since it has led to the discovery of metofluthrin (**1c**$_G$) (Figure 1) that possesses exceptional insecticidal properties and has been commercialized.[2,11]

Norchrysanthemic acid (**1c**$_H$) possesses evident structural analogy with chrysanthemic acid (**1a**$_H$) benefiting from the absence of the methyl group at [Cf] *trans* to the cyclopropane ring, responsible of deleterious detoxification. Moreover, it offers the possibility to access more volatile esters than natural pyrethrin I susceptible to exhibit high vapor concentration at room temperature in mosquito coil formulation.[2,11]

Metofluthrin (**1c**$_G$), the ester from (1*R,*3*S*)-*cis*-(*Z*)-norchrysanthemic acid and 2,3,5,6-fluoro-4-methoxymethyl benzyl alcohol, is 25 times more active as (*S*)-bioallethrin against *Culex pipiens pallens* (by standard topical application method) proved to be the best compromise for industrial production.[2,11] Nevertheless, in order to detect the most valuable of the eight nor-chrysanthemic acid stereoisomers *cis*-/*trans*- and *Z*-/*E*-stereoisomers as well as the related enantiomers have been stereoselectively synthesized and transformed to different esters using various alcohols such as polyfluorobenzyl alcohols, as well as those such as allethrolone (**2**$_B$) or, 5-benzyl-3-furfurylmethanol (**2**$_D$) and 3-phenoxy-benzylalcohols **2**$_E$ and **2**$_F$ that have proved to be valuable replacement to the natural pyrethrolone (**2**$_A$).[2]

This study gives the opportunity to compare the different method used especially those that involve each of the stereoisomers of hemicaronic acid/esters as starting materials to produce the different stereoisomers of nor-chrysanthemic acid/esters **1c**$_R$[2] with special emphasis on (*Z*)-(1*R*,3*R*)-*trans*-nor-chrysanthemic acid/esters (*Z*)-(1*R*,3*R*)-**1c**$_R$, the precursors of metofluthrin (**1c**$_G$) that has to be prepared on an industrial scale.[2,11]

The synthesis of nor-chrysanthemic acid (**1c**$_H$) has been described by Staudinger in 1924 as the pyrolytic decomposition product, during distillation of chrysanthemum dicarboxylic acid (**1b**$_{HH}$) resulting from the saponification of pyrethrin II (Scheme 33, entry a).[53] The yield was poor (10%) and the reaction led to an E/Z-mixture of stereoisomers (20/80; de: 60%).[53]

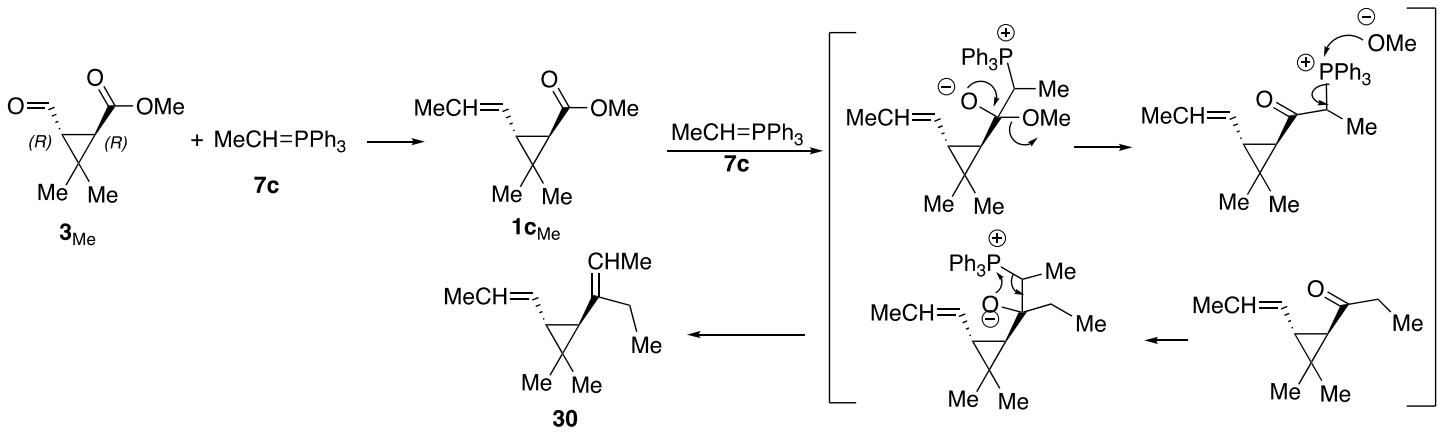


Scheme 33. Synthesis of methyl nor-chrysathemate by formal stereoselective demethylation of methyl chrysanthemate. [2,53,54,59,60]

Since then, chrysanthemum dicarboxylic acid (**1b**$_{HH}$) has been synthesized by oxidation of the unsaturated aldehyde (**1l**$_{H}$) resulting from the selenium dioxide oxidation of chrysanthemic acid (Chapter IVa, Section 3.3.1) [12,59,60] and decarboxylation of the monomethyl ester (**1o**$_{Me}$) has been achieved in reasonable yield (59%) and much better stereocontrol (de: 92%) using copper oxide and quinoline (Scheme 33, entry b).[2,54]

Otherwise, methyl ^{14}C labelled (*Z*)-(1*R*,3*R*)-*trans*-nor-chrysanthemate has been synthesized by Crombie and Pattenden from methyl (1*R*,3*R*)-*trans*-hemicaronate (1*R*,3*R*)-*trans*-(**3**$_{Me}$) and ethylidenetriphenylphosphorane **7c** using Conditions A, as reported above (Scheme 29 entry b)[60] with reasonably high stereocontrol (de 88%), using salt-free conditions that is known to favor kinetic control (see below, Section 6.3.1.2 of this Chapter IVb for mechanistic details).

Similar results have been reported by Elliott[13] using the same conditions (Conditions A) but on a larger scale. He noticed the presence of a hydrocarbon side-product **30** expected to result from dual attack at the oxo-functions. The rational of its formation is reported in Scheme 34.[13]



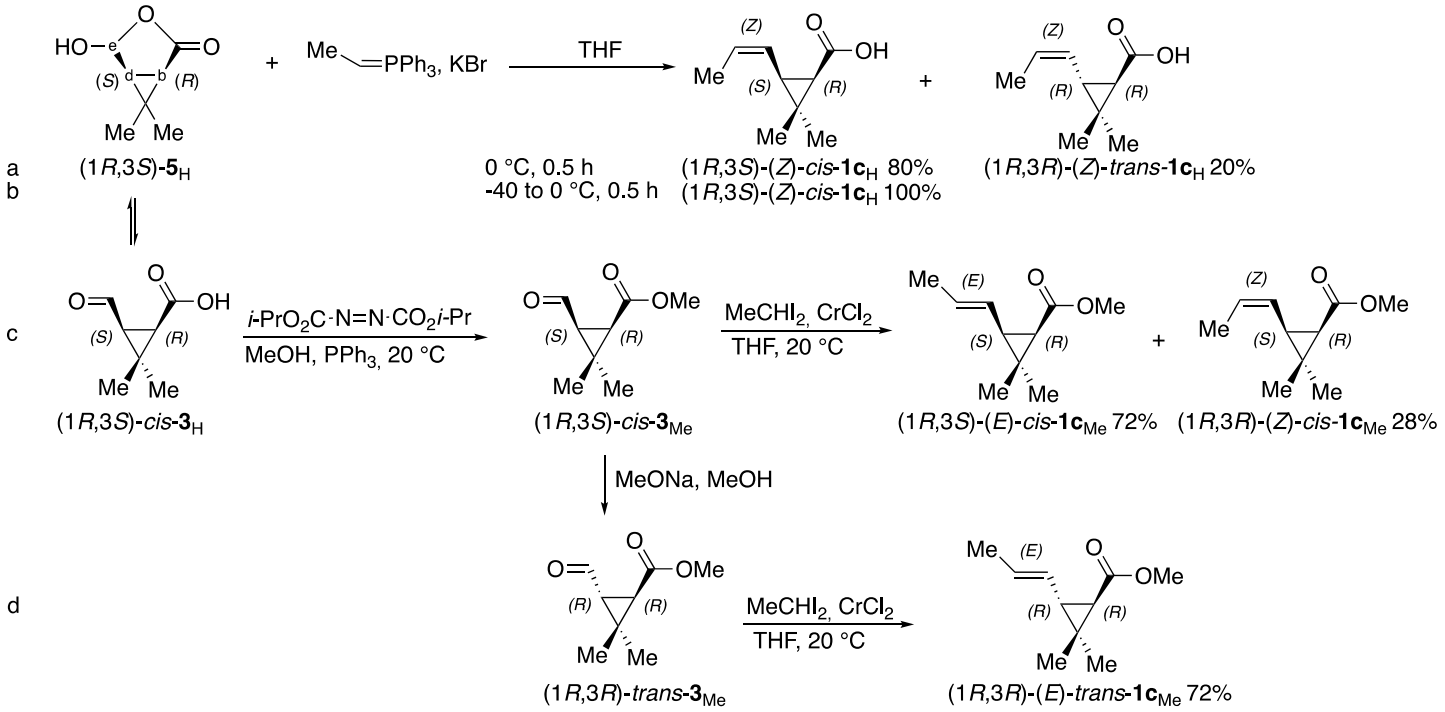
Scheme 34. Co-product formation in the synthesis of methyl nor-chrysanthemate from methyl hemicaronate and etylidene triphenylphosphorane.[13]

The synthesis of the remaining stereoisomers is reported in Scheme 35.[2] It uses biocartol (**5**$_{H}$) as the starting material, available from *cis*-, *trans* or as a *cis*-/*trans* mixture of chrysanthemic acid or alkyl chrysanthemates as racemates or as pure enantiomer (Scheme 35).

Reaction of ethylidene triphenylphosphorane (**7c**), generated from ethyltriphenylphosphonium bromide (**6c**) and potassium *t*-butoxide in THF at 0 °C (Conditions B2),[2] with (3*R*,4S)-biocartol (3*R*,4S)-**5**$_{H}$ under "salt-free conditions" (Section 6.3.1.2.) provides the desired (1*R*,3*S*)-*cis*-(*Z*)-norchrysanthemic acid (*Z*)-(1*R*,3*S*)-*cis*-(**1c**$_{H}$) besides its (*Z*)-(1*R*,3*R*)-*trans*-stereoisomer (*Z*)-(1*R*,3*R*)-*trans*-(**1c**$_{H}$) (*cis*/*trans*: 80/20). The latter results from

epimerization in the process alpha to the formyl group at [Cd] (Scheme 35, entry a).[2] This epimerization could be prevented if the Wittig reaction is carried out at lower temperature (-40 instead of 0 °C, Scheme 35, entry b).[2]

Esterification of (3*R*,4*S*)-biocartol (**5**$_H$), successfully achieved using the Mitsonobu reaction involving azo-diisopropyl dicarboxylate and methanol in the presence of triphenylphosphine, leads to methyl (1*R*,3*S*)-*cis*-hemicaronate (1*R*,3*S*)-*cis*-(**3**$_{Me}$) (Scheme 35, entry c).[2] Its reaction with sodium methylate in methanol achieves epimerization at [Cd] alpha to the formyl group, leading to methyl (1*R*,3*R*)-*trans*-hemicaronate (1*R*,3*R*)-*trans*-(**3**$_{Me}$) (Scheme 35, entries c,d). Stereoselective synthesis of the (*E*)-stereoisomers of the (1*R*,3*S*)-*cis*-(**1a**$_{Me}$) and (1*R*,3*R*)-*trans*-(**1a**$_{Me}$) nor-chrysanthemates that cannot be achieved even using the beta-oxido ylide Wittig-Schlosser modification (See below Chapter IVb, Section 6.3.2)[92,94] due to competing reaction on the ester moiety. It has been however carried out using the Takai's method expected to involve a *gem*-dichromium reagent (Scheme 35, entries c,d).[2]



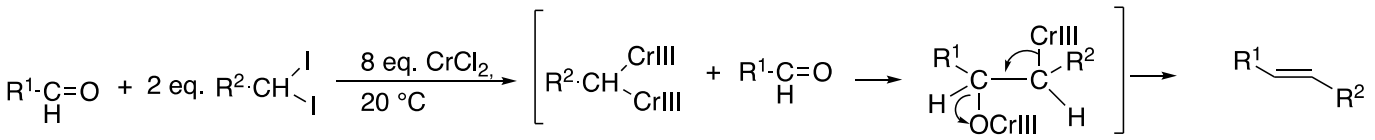
Scheme 35. Stereoselective synthesis of methyl (*Z*)- and (*E*)-nor-chrysanthemates.[2]

The Takai reagent is generated by reduction of *gem*-diiodoethane with chromium(II) chloride and is known to allow the synthesis of disubstituted alkene from aliphatic aldehydes with high (*E*)-stereocontrol (Scheme 36).[95] This proved to be the case on reaction with methyl (1*R*,3*R*)-*trans*-hemicaronate 1*R*,3*R*)-*trans*-(**3**$_{Me}$) (Scheme 35, entry d)[2] but the reaction is much less stereoselective when applied to (1*R*,3*S*)-*cis*-methyl hemicaronate (1*R*,3*S*)-*cis*-(**3**$_{Me}$), and this as been suggested to be due to higher steric hindrance in the transition state (Scheme 35, entry c).[2]

Although a speculative mechanism involving a *gem*-dichromium- then a beta-metal alkoxy alkyl-intermediates has been proposed (Scheme 36), the propensity to produce an (*E*)-alkene has not been yet elucidated.

The reaction works far better with diiodoethane than with the other diiodides and poorly performs with dibromides or dichlorides.[95] The reduction power of Cr(II) is significantly enhanced by complex formation with

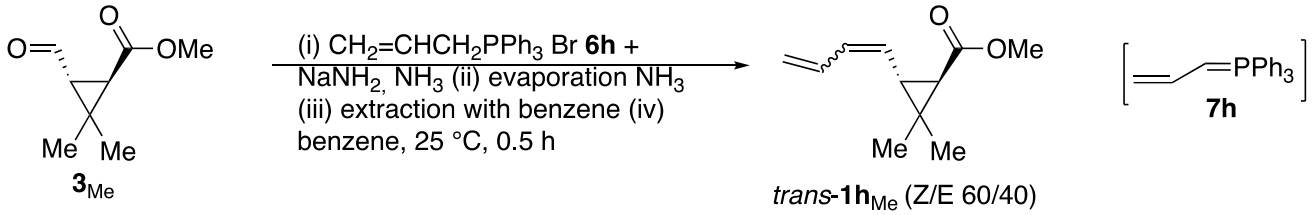
donor ligands especially when pre-treated with DMF. Finally, the olefination of aldehyde bearing a bulky substituent is even more (*E*)-stereoselective (Scheme 36, entries e,f, compare to entries a-d) whereas that of aromatic aldehydes takes place with poorer diastereoselection (Scheme 36, entry g, compare to entries a-f).[95]



	R^1	R^2	Solvent, time	Yield (de)
a	*n*-Pent	Me	THF, 4.5 h	94% (92%)
b	*i*-Pent	Me	THF, 2 h	99% (96%)
c	*n*-Oct	*n*-Pr	THF, 24 h	38% (90%)
d	*n*-Oct	*n*-Pr	DMF, 1.5 h	85% (92%)
e	*t*-Bu	*n*-Pr	DMF, 1 h	96% (98%)
f	*n*-Pr	*t*-Bu	DMF, 0.5 h	90% (92%)
g	Ph	*n*-Pr	DMF, 1 h	87% (78%)

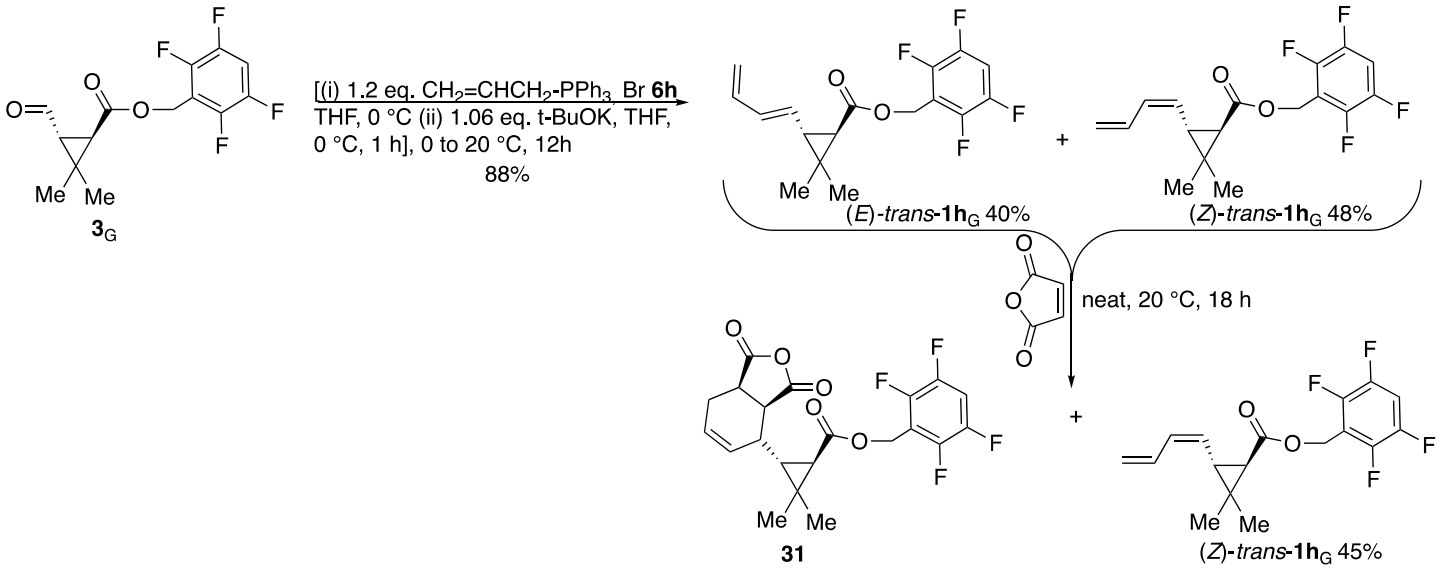
Scheme 36. Synthesis of alpha,beta-disubstituted alkene from diiodomethane and chromium reagents.[95]

4.4.2.2. Use of the Wittig reaction for the synthesis of cyclopropane carboxylic acid/related esters bearing a vinyl or a dienyl moiety at [Cf]. The synthesis of pyrethroid bearing a dienyl moiety at [Cd] has been routinely achieved using allylidene ylides **7h**, **7i**. However, the stereochemical outcome is different from that of alkylidenephosphoranes even using the salt-free conditions (Conditions A, Conditions B, Conditions B1, B2) since the formation of the *cis*-olefinic stereoisomer is no longer highly privileged (Scheme 37).[60] Those ylides in fact belong to the category of stabilized ylides that includes benzylic ylides and those bearing a carbonyl or a carboxyl group on their active site.



Scheme 37. Synthesis of methyl dienyl cyclopropane carboxylates from methyl hemicaronate.[60]

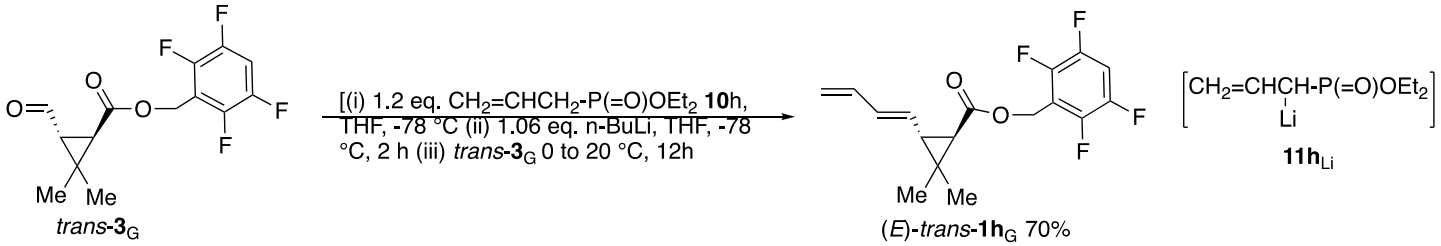
Reaction of allylidene triphenylphosphorane (**7h**) generated from allyl triphenylphosphosphonium bromide **6h** with potassium *t*-butoxide in THF (Conditions B2) on the tetrafluorobenzyl hemicaronate $\mathbf{3}_G$ leads to $\mathbf{1h}_G$ as a mixture of Z/E-stereoisomers (54/46, Scheme 38).[18,96] Access stereo-pure (*Z*)-*trans*-$\mathbf{1h}_G$ isomer has been achieved by sacrificial removal of the (*E*)-stereoisomer on reaction of the crude mixture with maleic anhydride in neat form at 20 °C. This has been achieved because of selective Diels-Alder reaction with the (*E*)-stereoisomer that reacts through its dienyl moiety leading to **31** and allows isolation of the desired stereo-pure (*Z*)-*trans*-$\mathbf{1h}_G$ isomer (Scheme 38).[18,96]



Scheme 38. Isolation of enantiopure (*Z*)-dienyl cyclopropane carboxylates from hemicaronates.[18]

Interrestingly, access to the missing (*E*)-*trans*-(**1h**$_G$) has been achieved on reaction of the tetrafluorobenzyl hemicaronate (**3**$_G$) used above, by replacing allylidene triphenylphosphorane (**7h**) by diethyl phosphono allyllithium (**9h**) (Scheme 39).[18,96] Rational of the results reported in Scheme 38 and Scheme 39 are proposed in Section 6 of this chapter.

The (*Z*)-stereoisomer *Z-trans*-**1h**$_G$ has been found to possess a higher knock-down effect than the (*E*)-stereoisomer *E-trans*-(**1h**$_G$) or the (*E*/*Z*)-mixture and proved to be far more active than metofluthrin (*Z*)-(**1c$_G$**) for example.[18,96]



Scheme 39. Synthesis of enantiopure (*E*)-dienyl cyclopropane carboxylates from hemicaronates.[18]

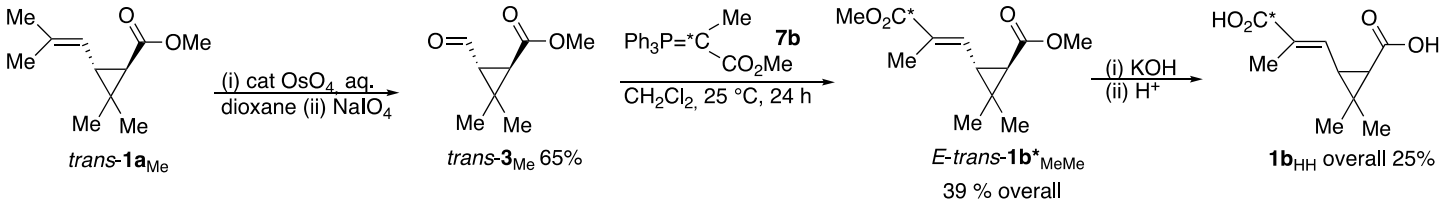
The synthesis of the all-(*E*)-trienyl analogue **1i**$_G$ has been achieved using a different strategy disclosed in Scheme 10, entry d. It involves at first the reaction of formylmethylenetriphenyl phosphorane **7m** with tetrafluorobenzyl *trans*-hemicaronate (**3**$_G$), then reaction of allylidene triphenyl phosphorane **7l** generated under Conditions B on the resulting (*E*)-enal (**1m**$_G$) (Scheme 10, entry d).

4.4.2.3. Use of the Wittig reaction for the synthesis of cyclopropane carboxylic acid/related esters bearing a carbonyl or a carboxyl group at [Cf]. The synthesis of pyrethroids bearing at [Cf] a carboxy group has attracted wide interest since they are reminiscent of pyrethrin II, a natural product the insecticidal properties of which are lower than that of pyrethrin I and is formally a degradation product of the latter.

This series includes the derivatives that possess a carboxy group and a methyl group at [Cf] and those that bear instead a carboxy and a hydrogen at [Cf]. Both series have in common the Z/E stereochemical problem to be solved and the nature of the alkoxy-group present of the carboxy group at [Cf] that should be differentiated

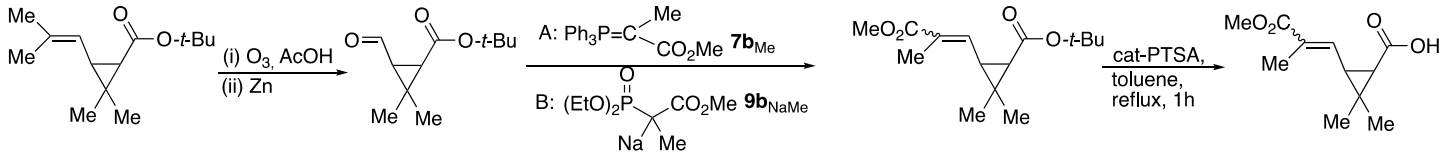
to that present on the carboxy group present at [Ca]. Those results follow the basic trends disclosed in Section 6.4 of Chapter IVb.

Crombie and Pattenden,[60] have synthesized stereoselectively methyl (*E*)-(1*R*,3*R*)-pyrethrate (**1b**$_{MeMe}$) on reaction of methyl (1*R*,3*R*)-*trans*-hemicaronate (1*R*,3*R*)-*trans*-(**3**$_{Me}$) with methoxycarbonylethylidene-triphenylphosphorane (Scheme 40), the latter being synthesized from the corresponding (methoxycarbonyl)ethyltriphenylphosphonium iodide and sodium amide in liquid ammonia (Conditions A). Subsequent treatment of the pyrethrate sequentially with methanolic potassium hydroxide (reflux, 1 h) followed by acid leads to (*E*)-(1*R*,3*R*)-*trans*-chrysanthemundicarboxylic acid (**1b**$_{HH}$).[60] Its radiolabelled analogue (Scheme 40)[60] has been synthesized from the related ylide bearing a ^{14}C carboxy-group (Scheme 28, entries b,c).[60]



Scheme 40. Stereoselective synthesis of methyl pyrethrate from methyl chrysanthemate through methyl hemicaronate.[60]

The synthetic strategy must consider that the two ester groups attached at [Ca] and [Cf] in pyrethrin II and their analogues are different. For that purpose, Matsui[66] and Elliott[13,16] have independently used *t*-butyl hemicaronate (**3**$_{tBu}$) and a phosphorus ylide (7**b**$_{Me}$), the carboxyl groups of which are different. Thus, the *t*-butyl carboxylate attached at [Ca] can be transformed to the carboxylic acid in acidic media then transformed to a more complex carboxylate after esterification keeping untouched the methyl carboxylate attached to the vinylic center [Cf] (Scheme 41). [13,16,66]



Conditions A: $Ph_3P=C(Me)CO_2Me$ **7b**$_{Me}$, MeOH, 20 °C, 2h; Conditions B: $(EtO)_2P(=O)$-$CNa(Me)CO_2Me$ **9b**$_{NaMe}$, DMF, 20 °C, 12 h, 50 °C, 1 h

Scheme 41. Stereoselective synthesis of pyrethroic acid from *t*-butyl chrysanthemate through *t*-butyl hemicaronate.[66]

Elliott[13,16] has also synthesized stereoselectively several related methyl (*E*)-desmethyl-pyrethroates **1n**$_R$ in about 60 % yield with high stereocontrol (de> 80%) from *t*-butyl hemicaronate (**3**$_{tBu}$) and stabilized phosphoranes **7n** bearing a carboxy group (Me, Et, *n*-Pr) and a hydrogen (dichloromethane at 20 °C, 12 h or 60 °C for 2 h).

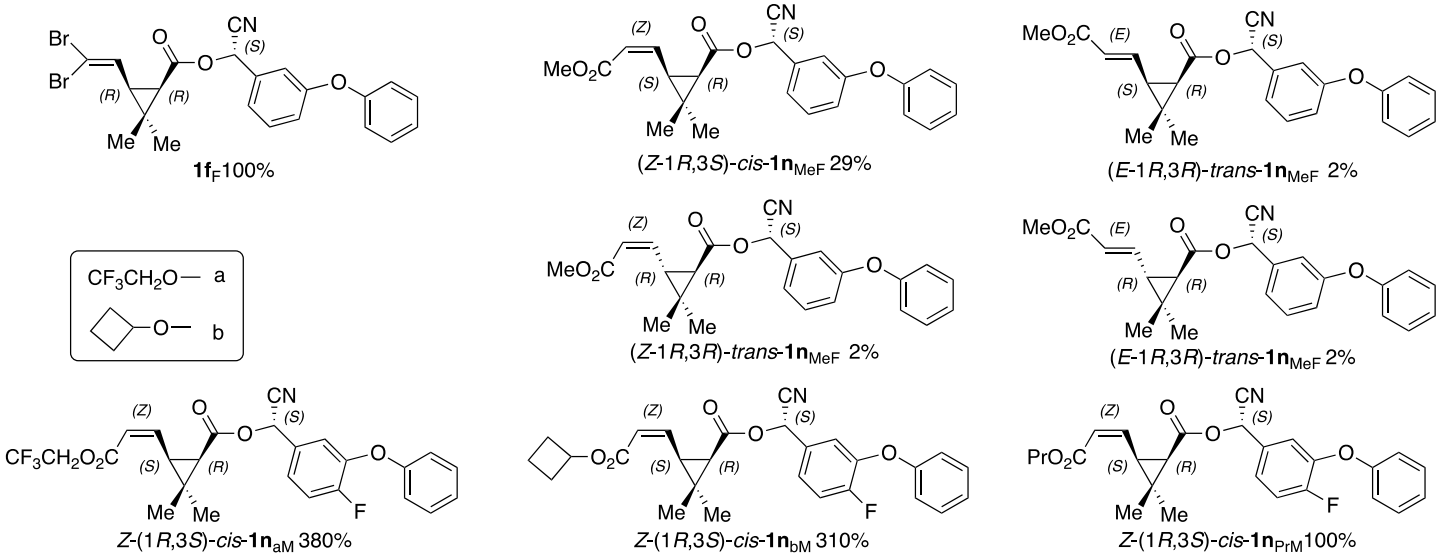
Matsui has carried out the olefination reaction on *t*-butyl *trans*-(Scheme 41, entries a,b) and *t*-butyl *cis*-(Scheme 41, entriea c,d) hemicaronates (**3**$_{tBu}$) and a phosphorane in methanol (Conditions G, Scheme 41, entries

a,c) or a phosphonate in DMF (Conditions H, Scheme 41 entries b,d). Apparently, the conditions involving the phosphorane proved to be the best to achieve the (*E*)-stereoselectivity.

t-butyl *trans*-hemicaronate *trans*-(**3**$_{tBu}$) has also been reacted[66] with the sodium salt of diethyl 1-cyanophosphonate prepared from the corresponding carbon acid and sodium methylate in DMF (20 °C, 1 h) to deliver a 7/3 (*E*)/(*Z*)-mixture of the corresponding unsaturated nitriles. The (*E*)-stereoisomer has been separated[66] from its (*Z*)-stereoisomer by column chromatography on silicagel and transformed to the related (*E*)-vinylcyclopropane carboxylic acid on reaction with p-toluene sulfonic acid in toluene.[66] Reaction with hydrochloric acid in methanol delivered[66] instead methyl (*E*)-pyrethroate resulting from the transesterification (*t*-butyl to methyl) at the ester moiety attached at [Ca] and transformation of the nitrile at [Cf] to the corresponding methyl ester as the result of a Pinner reaction.[97]

trans-Pyrethric acid and *cis*-pyrethric acid have been synthesized by the Roussel-Uclaf team on reaction of methyl (1*R*,3*R*)-*trans*-hemicaronate (1*R*,3*R*)-*trans*-(**3**$_{Me}$) or (3*R*,4*S*)-bioacartol (3*R*,4*S*)-(**5**$_{H}$) with O,O-dimethyl 1-methoxycarbonylethyl phosponate and sodium amide.[21]

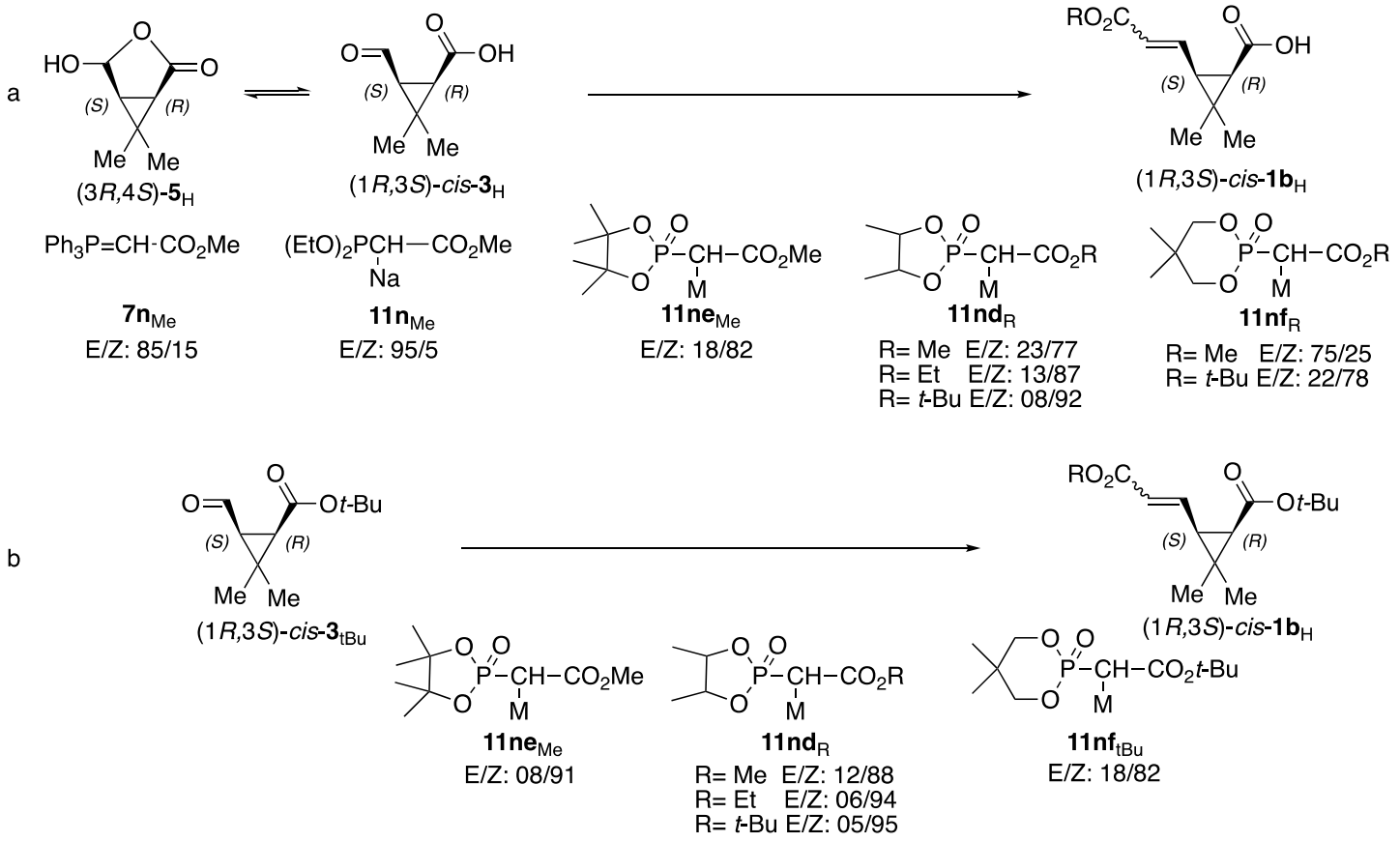
The Roussel-Uclaf team[8] has systematically prepared and tested each of the stereoisomers of nor-pyrethric esters derived from (1*R*)-nor-pyrethric acid (**1n**$_{MeF}$) missing the methyl group at [Cf]) and the (*S*)-cyanohydrin of 3-phenoxybenzaldehyde (**2**$_{F}$) that was used to produce the most active enantiomer of deltamethrin (**1f**$_{F}$). It was found that the (*Z*)-(1*R*,3*S*)-*cis*-stereoisomer (*Z*)-(1*R*,3*S*)-*cis*-**1n**$_{MeF}$ (Scheme 42) remarkably possesses about 30% of the insecticidal properties of that of deltamethrin (**1f**$_{F}$) against *Musca domestica*.[8] Interestingly, further manipulation of this structure by fine tuning of both ester groups in the (*Z*)-(1*R*,3*S*)-*cis*-series leads to the discovery of compounds (*Z*)-(1*R*,3*S*)-*cis*-**1n**$_{aM}$, (*Z*)-(1*R*,3*S*)-*cis*-**1n**$_{bM}$, (*Z*)-(1*R*,3*S*)-*cis*-**1n**$_{PrM}$ (Scheme 42) possessing more than 3 times the insecticidal activity of deltamethrin against *Musca domestica*.[8]



Scheme 42. Comparative insecticidal activity of stereoisomeric desmethyl pyrethroates.[8]

Although the syntheses have been carried out in both series, we report in this review the reactions that have been performed in the *cis*-series using the Wittig- and related reactions that involve as starting material either biocartol (**5**$_{H}$) (Scheme 43, entry a) or *t*-butyl *cis*-hemicaronate *cis*-(**3**$_{tBu}$) (Scheme 43, entry b).[8,98] The former delivers directly the *cis*- vinylcyclopropane carboxylic acids bearing at [Cb] on its vinylic carbon the ester group originally present on the ylide, whereas the other one delivers the same compound after selective acidic

hydrolysis of the *t*-butyloxy group. Esterification with the (*S*)-cyanohydrin of 3-phenoxybenzaldehyde under the usual conditions allows the syntheses of the required nor-pyrethroate.[8]



Scheme 43. Stereoselective (*E*)- and (*Z*)-desmethyl pyrethroate syntheses from hemicaronates.[8,98]

Reaction of triphenylphosphorane **7n**$_{Me}$ or better diethyl phosphonate **11n**$_{Me}$ with biocartol (3*R*,4*S*)-(**5**$_{H}$) delivers the vinylcyclopropane carboxylic acid (1*R*,3*S*)-*cis*-(**1b**$_{H}$) possessing the (*E*)-stereochemistry at the newly formed [Ce=Cf] double bond.

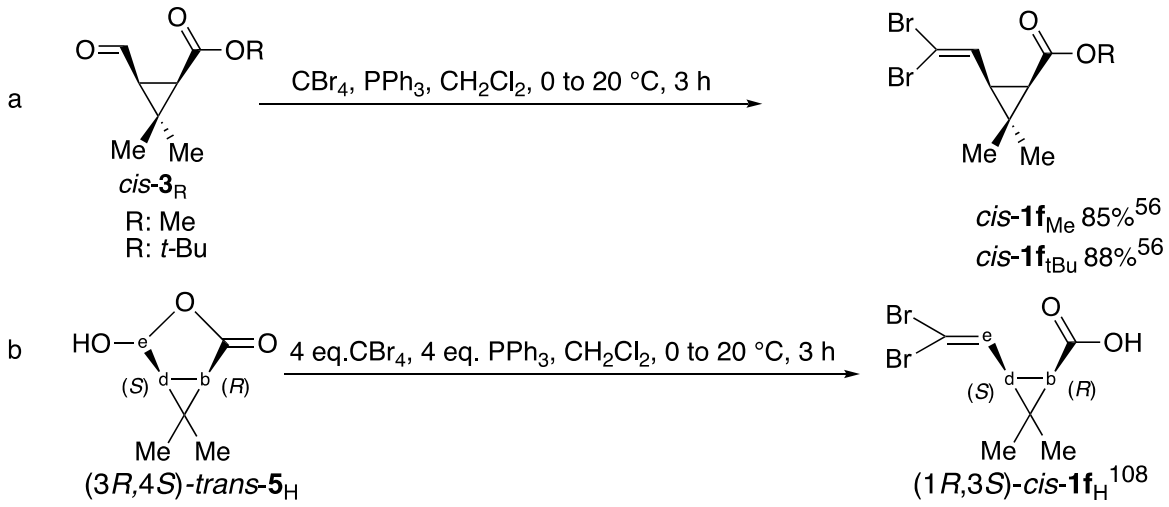
It has however been found[98,8] that reaction of cyclic phosphonates such as **11ne**$_{R}$, **11nf**$_{R}$, **11nf**$_{R}$ on biocartol **5**$_{H}$, as previously published by Breuer[99,100] on different aldehydes (see Section 6.4.2), allows instead the synthesis of larger amounts of the (*Z*)-stereoisomers of (1*R*,3*S*)-*cis*-(**1b**$_{H}$). Increasing the size of the carboxy groups by reacting instead *t*-butyl (1*R*,3*S*)-*cis*-hemicaronate (1*R*,3*S*)-*cis*-**3**$_{tBu}$ and the phosponate such as **11nd**$_{tBu}$ allows the synthesis (*Z*)-stereoisomers of (1*R*,3*S*)-*cis*-**1b**$_{tBu}$ with higher stereocontrol (Scheme 43, entry b).[8,98]

As general trends, cyclic phosphonates deliver higher amounts of the (*Z*)-α,β-unsaturated esters than diethyl phosphonate **11n**$_{Me}$ (Scheme 43) and those reagents possessing a five-membered ring are particularly prone towards (Z)-stereocontrol (Scheme 43, compare **11ne**$_{Me}$, **11nd**$_{Me}$, to **11nf**$_{Me}$), especially if it is fully methyl substituted (Scheme 43, compare **11ne**$_{Me}$ to **11nd**$_{Me}$). This however is not the only factor that favors the formation of the (*Z*)-stereoisomer.[8,98] The *t*-butyl *cis*-hemicaronate (1*R*,3*S*)-*cis*-(**3b**$_{tBu}$) provides in all the cases a higher percentage of the of the (*Z*)-stereoisomer than biocartol (3*R*,4*S*)-(**5**$_{H}$) (Scheme 43, compare entry a to entry b). It has also been reported that a bulky alcohol component in the ester group impacts favorably the stereochemistry to favor the (*Z*)-stereoisomer (Scheme 43, entry b).[8] Interestingly, such bulky groups on the nor-pyrethroates confer a higher knock-down effect (Scheme 42).[8]

4.4.2.4. Use of the Wittig reaction for the synthesis of cyclopropane carboxylic acid/related esters bearing two halogens at [Cf]. Permethrins, analogues of pyrethin I that differs (i) in the presence of two halogens in place of the two vinylic methyl groups, (ii) the *cis*-stereochemistry instead of the *trans*-arrangement on the cyclopropane ring and a highly different ester group, as discovered by Elliott,[17,69] are important commercial insecticides for agriculture. Their synthesis has been, among others achieved from *cis*-hemicaronic acid or alkyl hemicaronates and the corresponding phosphorus ylide bearing two halogens (Cl or Br) on their carbanionic centers. They follow the basic trends disclosed in Section 6.5 of this Chapter for related structures.

Such transformation[101-104] involves the *in-situ* formation of the ylides (dihalogenomethylenetriphenylphosphoranes), usually generated from carbon tetrahalides and two equivalents of triphenylphenylphosphine (See below, Section 6, Scheme 121, entry a).[101] It delivers, besides the dihalogenovinylcyclopropane carboxylic acids/related esters, triphenylphosphine oxide and halogeno phosphonium halides as co-products. The reactions usually proceed more efficiently for the synthesis of dibromovinyl **1f**$_R$ than for that of the dichlorovinyl **1d**$_R$ derivatives and this has been attributed to the presence of the more reactive chlorophosphonium chloride (see beow Scheme 45).

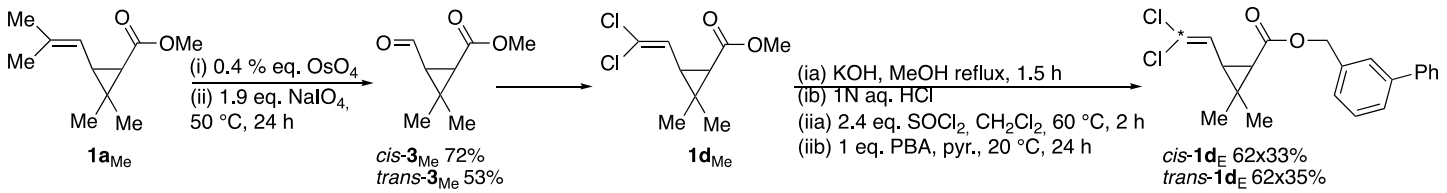
Although numerous syntheses of the dibromovinylcyclopropane carboxylates have been reported[8,13,21,56,69,105-107] only few experimental results have been published (Scheme 44, entry a, see also Scheme 6,[8,19-21] Scheme 9,[13,23] Scheme 21,[14,56]). This transformation has been extended to biocartol that delivers *cis*-deltamethrinic acid (Scheme 44, entry b).



Scheme 44. Synthesis of deltamethrinic acid/esters from carbon tetrabromide and triphenylphosphine.[56,108]

The reaction involving dichloromethylene triphenylphosphonium **7d** has required adaptation disclosed in Scheme 45.[109] It has allowed the synthesis of the most active stereoisomer of 3-phenoxybenzyl permethrinate (1*R*,3*R*)-*cis*-(**1d**$_E$) (for alternative syntheses of permethrinic acid and deltamethrinic acid see reference[110]). This reaction proved similarly efficient to produce the (1*R*,3*S*)-*trans*-stereoisomer (Scheme 45, entries a-e).[109] It was found at this occasion that the solvent has an important effect on the yield of the reaction that is the highest when the reaction is carried out in THF at 35 °C for 48 h (Scheme 45, entry e)[109] and the lowest being when performed in benzene (Scheme 45, entry d).[109] The yield is surprisingly poor in dioxane (Scheme 45, entry c)[109] and medium in chlorinated solvents (Scheme 45, entries a,b) such as dichloromethane.[109] It has been found, as already pointed out that these problems arise from the presence of particularly reactive chlorotriphenylphosphonium chloride as co-product in the medium (See Section 6.5 for rationlizations). The

best conditions (CCl_4+$PN(Me_2)_3$, Scheme 45, entry e) have been used to produce radiolabelled 3-phenoxybenzyl permethrinate (1*R*,3*R*)-*cis*-(**1d**$_E$) for environmental and biological studies[109] from ^{14}C radiolabelled carbon tetrachloride and methyl (1*R*,3*S*)-*cis*-hemicaronate (**3**$_{Me}$).[109]



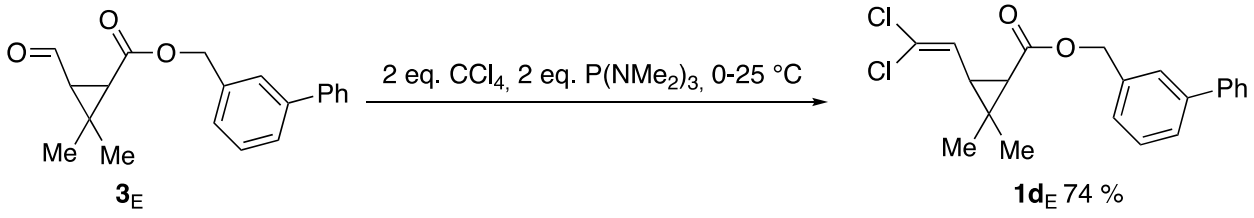
1a$_{Me}$ → *cis*-**3**$_{Me}$ 72%, *trans*-**3**$_{Me}$ 53% → **1d**$_{Me}$ → *cis*-**1d**$_E$ 62x33%, *trans*-**1d**$_E$ 62x35%

	CCl_4	PPh_3		
a	0.91 eq.	1.8 eq.	CH_2Cl_2, 35°C, 48 h	65%[109]
b	0.91 eq.	1.8 eq.	$(CH_2)_2Cl_2$, 35°C, 48 h	60%[109]
c	0.91 eq.	1.8 eq.	Dioxane, 35°C, 48 h	30%[109]
d	0.91 eq.	1.8 eq.	Benzene, 35°C, 48 h	10%[109]
e	0.91 eq.	1.8 eq.	THF, 35°C, 48 h	76%[109] [^{14}C 66% (*cis*) 64% (*trans*)]
	CCl_4	$P(NMe_2)_3$		
f	1.5 eq.	3.3 eq.	CH_2Cl_2, -10°C, 3 h	46%[111]
	$BrCCl_3$	$P(NMe_2)_3$		
g	1.5 eq.	3.3 eq.	CH_2Cl_2, -10°C, 3 h	80%[111]

Scheme 45. Synthesis of methyl permethrinate including radiolabeled derivative from carbon tetrahalogenides.[109,111]

A successful solution implies the replacement of triphenylphoshine by tris-(dimethylamino)phosphine[111,110] and of tetrachloromethane by bromotrichloromethane [111] (Scheme 45, entries f,g). The latter process not only delivers methyl permethrinate (**1d**$_{Me}$) in higher yield (80%, Scheme 45, entry g) but also co-produces hexamethyl phosphotriamide that contrary to triphenylphosphine oxide, co-produced under the previous conditions (Scheme 45, entries a-e),[109] is water soluble and can be easily separated from the desired compound.

Interestingly the carbon tetrachloride/tris-(dimethylamino)phosphine reagent that affords methyl permethrinate (**1d**$_{Me}$) from the related hemicaronate (**3**$_E$) in modest yield, provides permethrin (**1d**$_E$) in much higher yield (Scheme 46, compare to Scheme 45, entry f).[108]



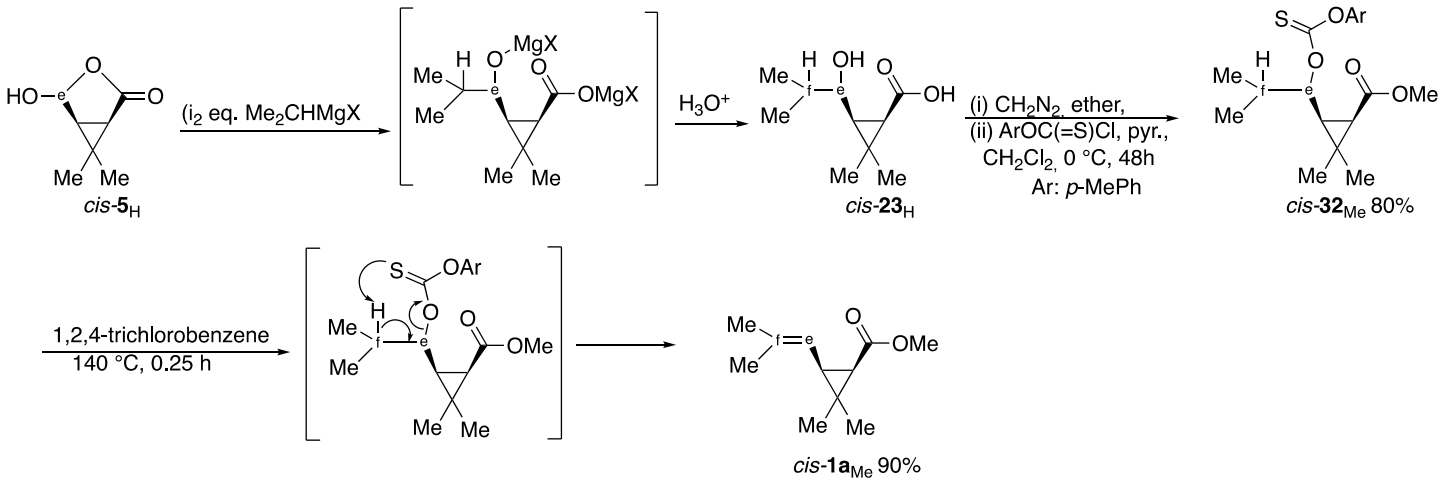
3$_E$ → **1d**$_E$ 74 %

Scheme 46. Synthesis of permethrin from carbon tetrachloride.[108]

Finally *t*-butyl difluoro vinylcyclopropane carboxylate (**1e**$_{tBu}$) has been synthesized from *t*-butyl hemicaronate (**3**$_{tBuv}$) formally on reaction with difluoromethylene triphenylphosphorane (**7e**).[22] The latter is produced *in-situ* by thermal decomposition (170 °C) of sodium chlorodifluoroacetate in the presence of triphenylphosphine and *in-situ* reacts with *t*-butyl hemicaronate (**3**$_{tBu}$) (Scheme 8).[22] Sequential reaction of (**1e**$_{tBu}$) with (i) *p*-toluenesulfonic acid provides the related carboxylic acid **1e**$_H$ and (ii) excess of thionyl chloride, leads to the related acyl chloride which on (iii) esterification with (5-benzyl-3-furfuryl)methyl alcohol leads to fluorethrin (**1e**$_D$) (Scheme 8).[22]

4.4.3. Alternative methods involved in synthesis of the [Ce=Cf] double bond of vinylcyclopropane carboxylic acids/lower esters from hemicaronic acid/esters. As already pointed out, the Wittig and related reactions proved particularly versatile to produce rapidly, often with an adequate stereocontrol, a huge number of vinylcyclopropane carboxylic esters $\mathbf{1}_R$ whose structures are very close to that of the naturally occurring pyrethrin insecticides in amounts required for testing. Discovery of new pyrethroids from that systematic research has required to develop methods compatible with pre-industrial and industrial developments. We report in this section alternative methods that still use hemicaronic acid ($\mathbf{3}_H$) and hemicaronates $\mathbf{3}_R$ as one of the precursors.

4.4.3.1. Synthesis of vinylcyclopropane carboxylates bearing hydrogen or alkyl group at [Cf] by alternative methods. We have disclosed previously the synthesis of nor-chrysanthemic esters from hemicaronates and α,α-dichromium reagents (Section 4.4.2.1.2, this Chapter IVb, Scheme 35, entries c,d). We disclose now a process originally presented in Scheme 24, entry b, that allow the synthesis of methyl chrysanthemate from hemicaronic acid/ esters $\mathbf{3}_R$ and biocartol ($\mathbf{5}_H$) and isopropyl magnesium bromide[112] through the intermediate formation of the corresponding [Ce]-hydroxy dihydrochrysanthemic acid ($\mathbf{23}_H$) or related esters $\mathbf{23}_R$ (R^1,R^2= Me). Dehydration of the corresponding methyl ester proved to be extremely difficult owing the location of the hydroxyl group on the cyclopropyl carbinyl [Ce]-carbon, well known to be prone to favor the cyclopropane ring opening instead of the β-elimination reaction especially in acidic media leading among others to ($\mathbf{23}_H$) (R^1= R^2= Me, R= H, Scheme 24, entry b) (Chapter IVa, Section 5.3.1).[12,113,63] Successful synthesis of methyl (1*R*)-*cis*-chrysanthemate has nevertheless been achieved *via* thermal decomposition of the corresponding thionocarbonate $\mathbf{32}_{Me}$ (1,2,3-trichlorobenzene, 140 °C, 0.3 h, 90%, Scheme 47).[113] The latter has been prepared on reaction with an *p*-tolyl chlorothiocarbonate (ArOC(=S)Cl, pyr., CH_2Cl_2, 0 °C, 48 h, 80%; Scheme 47) but its reproducibility has been questioned.[113] This is why the β elimination of triphenylphosphine oxide embedded in the Wittig reaction let this reaction unique for the synthesis of chrysanthemic esters and analogues.

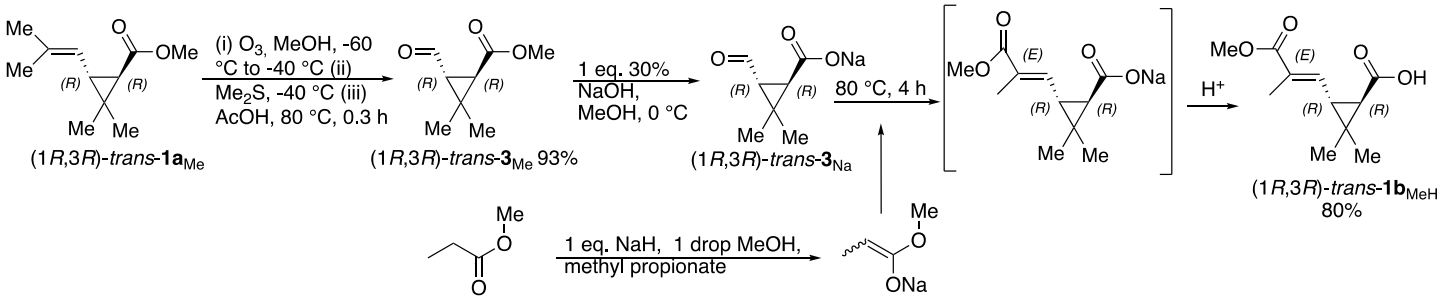


Scheme 47. Synthesis of methyl *cis*-chrysanthemate involving isopropylmagnesium halides.[113]

4.4.3.2. Synthesis of vinylcyclopropane carboxylates bearing a carbonyl or a carboxyl group at [Cf] by alternative methods. Apparently the formation of the [Ce=Cf] double bond in ($\mathbf{1l}_{Me}$), synthesized from methyl hemicaronate ($\mathbf{3}_{Me}$) and propanal in the presence of pyrrolidine (Scheme 12) takes place in situ as the result of the tandem aldolization-crotonization reaction favored by the presence of the formyl group.[25] Interestingly, the (*E*)-stereoisomer seems to be exclusively formed and unfortunately no information about the specific yield of this reaction is reported so it is difficult to assess if this strategy is better than the one that directly produce the

same compound using selenium dioxide instead (Chapter IVa, Section 3.3.1).[12] Saponification followed by protonation generates the corresponding vinylcyclopropane carboxylic acid (**1l**$_H$) that on esterification with pyrethrolone leads to the corresponding ester (**1l**$_A$) (Scheme 12).[25] Oxidation of the formyl group present on the structure to the carboxy group using sodium chlorite and its esterification using (trimethylsilyl)diazomethane allows the regioselective synthesis of pyrethrin II (**1b**$_{MA}$) bearing two different carboxy groups (Scheme 12).[25] It is interesting to compare this multistep process to the process that produces the related *trans*-*t*-butyl ester in a single step from the same starting material in an almost quantitative yield using the Wittig reaction (see above Scheme 41).[66]

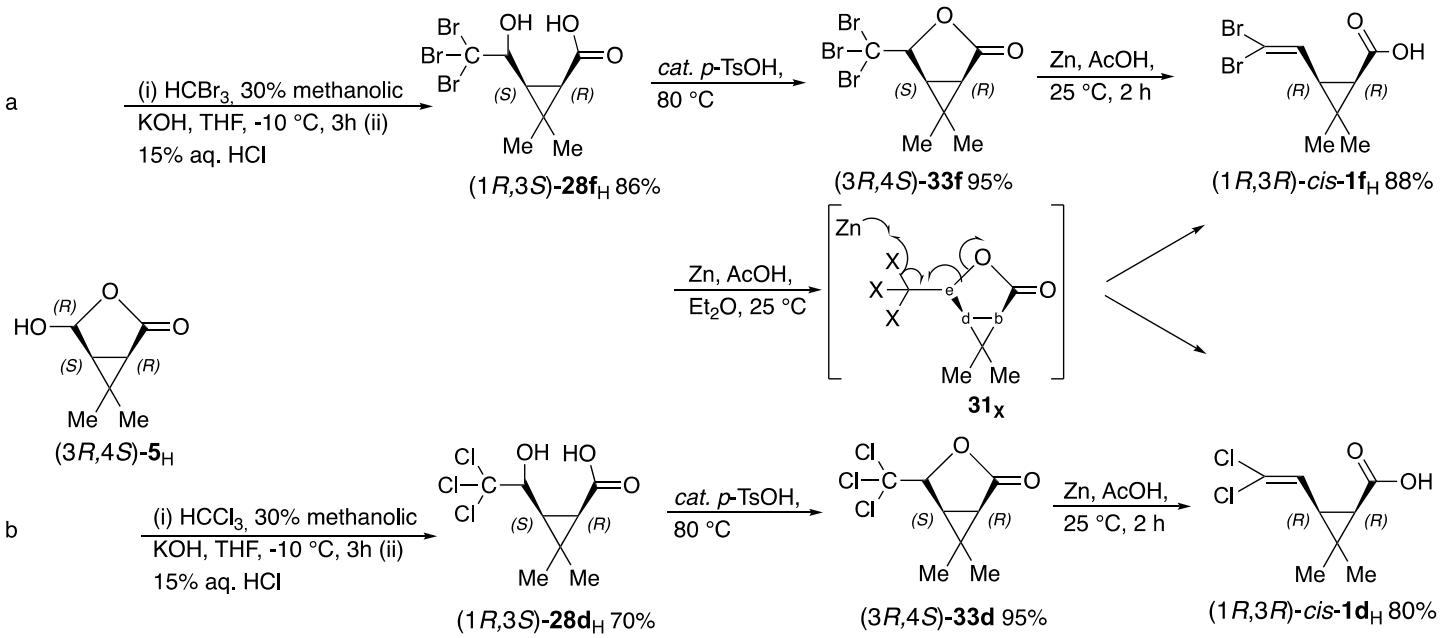
Another more expedite synthesis of pyrethric acid (1*R*,3*R*)-*trans*-(**1b**$_{MeH}$) is reported in Scheme 48[114] and refers to the strategy disclosed in Scheme 24, entry c. It involves (i) the synthesis of sodium hemicaronate (1*R*,3*R*)-*trans*-(**3**$_{Na}$) from methyl chrysanthemate 1*R*,3*R*)-*trans*-(**1a**$_{Me}$) by sequential reductive ozonolysis and saponification, using stoichiometric amounts of sodium hydroxide in methanol,[114] (ii) its reaction with the enolate generated on reaction of methyl propionate with sodium methanolate (itself produced from catalytic amount of methanol and stoichiometric amounts of sodium hydride) followed by acid treatment (Scheme 48).[114]



Scheme 48. Stereoselective synthesis of pyrethric acid from methyl *trans*-chrysanthemate involving methyl hemicaronate.[114]

Similar results have been obtained (i) on addition, at 80 °C, of sodium hydride to a mixture of hemicaronic acid (**3**$_H$) in methyl propionate in the presence of catalytic amounts of methanol [114] (ii) addition, at 80 °C of stoichiometric amounts sodium hemicaronate (**3**$_{Na}$) to stoichiometric amounts of the sodium enolate of methyl propionate in the presence of catalytic amounts of methanol and excess of sodium hydride in DME as the solvent.[114]

4.4.3.3. Synthesis of vinylcyclopropane carboxylates bearing halogens at [Cf] by alternative methods. Last but not least, *cis*-deltamethrinic acid (**1f**$_H$) and *cis*-permethrinic acid (**1d**$_H$) have been synthesized using a related strategy from biocartol (**5**$_H$) and bromoform or chloroform respectively in basic media such as potassium hydroxide in methanol (Scheme 49).[108] The resulting beta-trihahogenomethyl alcohols **28f** and **28d** bearing a carboxy moiety in *cis*-position on the cyclopropane, obtained after acid hydrolysis, are then cyclized to the corresponding bicyclic lactones **33f** and **33d** (Scheme 49).[108] The latter deliver the *cis*-deltamethrinic acid (**1f**$_H$) (Scheme 49, entry a)[108] and *cis*-permethrinic acid (**1d**$_H$) (Scheme 49, entry b)[108] on reaction with zinc in acetic acid. The beta-elimination reaction is initiated by attack on one of the halogens, expelling the carboxy leaving group through a well-established radical process that at the same time allows the lactone ring opening keeping the *cis*-relationship on the cyclopropane ring.[108] Similar process has been achieved on acetyl biocartol (**5**$_A$) in a process aimed to transform Δ^3-carene to deltamethrinic acid (**1f**$_H$).[115,118]

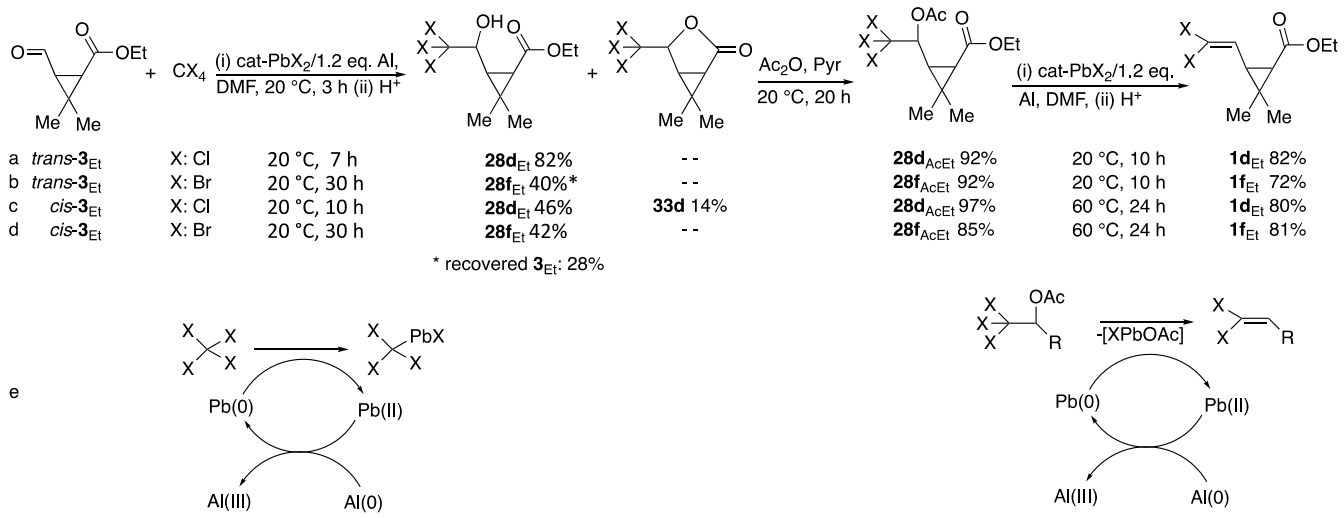


Scheme 49. Enantio- and stereoselective synthesis of deltamethrinic- and permethrinic-acids from bicartol and bromoform and chloroform respectively.[108,118]

A related method uses the coupling of carbon tetrahalides with ethyl *cis*- or *trans*-hemicaronate (**3**$_{Et}$) initiated by the Pb/Al bimetallic system (Scheme 50). It involves the reductive addition of a trichloromethyl lead, a valuable nucleophile, produced on reduction of lead dibromide by aluminum and recycling of the lead dihalide generated in the process.[116] Lead dichloride and tin dichloride in the presence of aluminium are also able to perform a similar process although a higher amount of tin dichloride is required (0.5 eq. instead of 0.1 eq.) and longer reaction time (12 h instead of 3 h).[116] The reaction did not proceed however if lead dihalides are replaced by bismuth trichoride ($BiCl_3$), germanium tetrachloride ($GeCl_4$) or zinc dichloride ($ZnCl_2$).[116] Furthermore the $PbBr_2$/Al system proved efficient to reduce trihalomethyl carbinols as their acetates including **28f**$_{AcEt}$ and(**28d**$_{AcEt}$ to 1,1-dihaloethene derivatives including **1f**$_{Et}$ and **1d**$_{Et}$ (Scheme 50).[116]

Best results have been observed from ethyl *trans*-hemicaronate *trans*-(**3**$_{Et}$) using two equivalents of carbon tetrahalides, 1.2 equivalent of finely cut aluminum foil and 10% of lead(II) bromide ($PbBr_2$) powder in DMF. The reaction delivers, after acidic quenching, the corresponding trichloromethyl carbinol *trans*-**8d**$_{Et}$ in high yield from carbon tetrachloride (20 °C, 10 h, 82%)[116] and in modest yield in the case of the related tribromomethyl carbinol *trans*-**28f**$_{Et}$ (20 °C, 30 h, 40%, Scheme 50, entries a,b).[116,118]

Those processes have been extended to ethyl *cis*-hemicaronate *cis*-(**3**$_{Et}$). As expected the resulting trihalogenomethyl carbinols *cis*-**28**$_{Et}$ exhibit a high tendency to react with the adjacent ester group to produce the lactones **33**. This is effectively the case of the reaction involved carbon tetrachloride that delivers[116] the lactone **33d** (14 %) besides the expected carbinol *cis*-**28d**$_{Et}$ (20 °C, 10 h, 46%, Scheme 50, entry c) but exclusively the related tribromomethyl carbinol *cis*-**28f**$_{Et}$ from carbon tetrabromide (Br: 20 °C, 10 h, 42%, Scheme 50, entry d).[116]



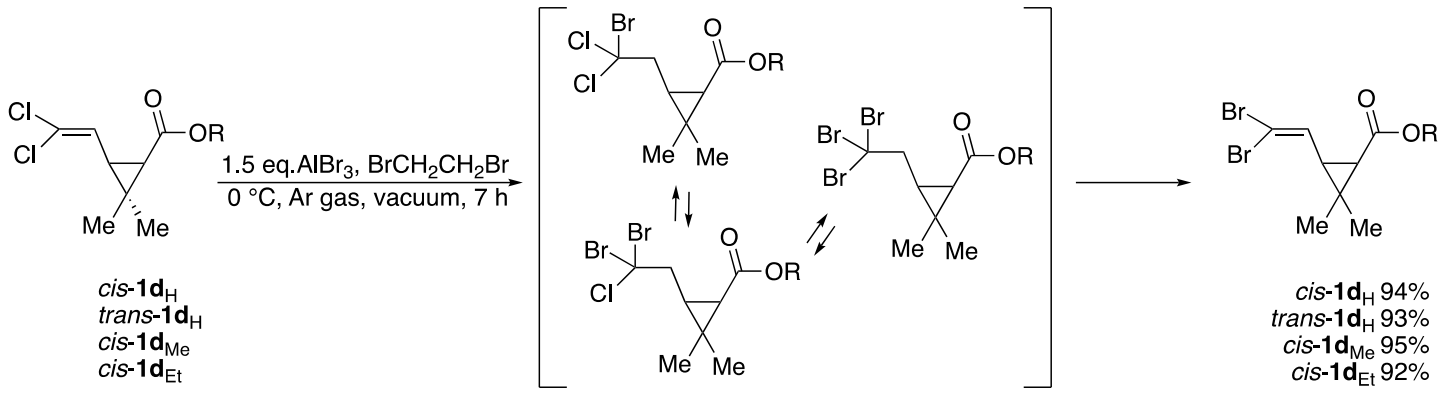
Scheme 50. Synthesis of ethyl deltamethrinate and permethrinate from ethyl hemicaronates, carbon tetrabromide and tetrachloride, and lead dibromide in the presence of aluminum as reducing agent.[116]

Acetylation (Ac_2O, pyr., 20 °C, 20 h, Scheme 50)[116] of the trihalomethyl carbinols followed by treatment with aluminum foils and catalytic amount of $PbBr_2$ in DMF at room temperature achieves the beta-elimination of the halogen and the acetoxy group leading to ethyl *trans*-(92%/82%) and *cis*-97%/80%) permethrinate (**1d**$_{Et}$) or *trans*-(92%/72%) and *cis*-(85%/81%) ethyl deltamethrinate (**1f**$_{Et}$) respectively (Scheme 50).[116]

As general trends the elimination reaction is easier on the *trans*- (20 °C, 10 h) than on the *cis*- (60 °C, 24 h) stereoisomers.[116] Alternatively the synthesis of *trans*-permethrinate has been achieved in 78 % yield, and in a single pot from the trichlorohydrin *trans*-**28d**$_{Et}$ on reaction at 60 °C for 12 h with 0.5 equivalent of $PbBr_2$ and 5 equivalents of 98% sulfuric acid in the presence of aluminum foil (5 eq.) in ethanol.[116]

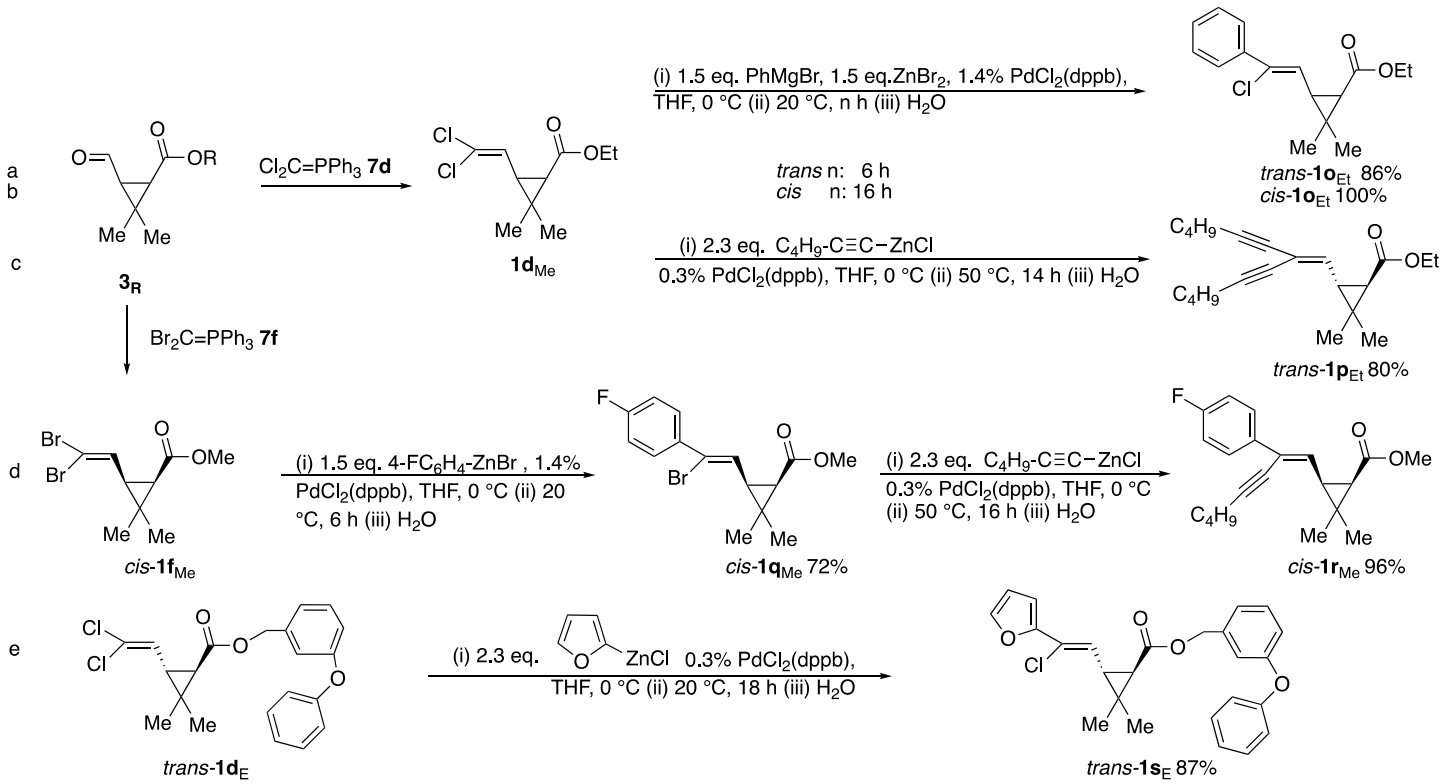
Another interesting approach to deltamethrinic acid/ involves the formal substitution of the chlorine atoms present on the vinyl moiety of permethrinates **1d**$_R$ by two bromine atoms.[117] Although copper bomide in dipolar solvents is usually able to achieve the Cl to Br exchange in haloethenes, it proved inefficient when applied to ethyl permethrinate (**1d**$_{Et}$) (8 eq., DMF, 150 °C, 8 h, ethyl deltamethrinate/ Br,Cl, /ethyl permethrinate recovery: 1%/16%/77%).[117] Aluminum tribromide in 1,2-dibromothane under ice water cooling however, did promote the halogen exchange from ethyl permethrinate (**1d**$_{Et}$) leading to ethyl deltamethrinate (**1f**$_{Et}$) without affecting the ester group or the cyclopropane ring.[117] Best results have been obtained when the reaction is carried out under vacuum and argon bubbling to avoid any addition of hydrogen bromide across the [Ce=Cf] double bond. The reaction also applies to permethrinic acid (**1d**$_H$) and in none of the cases affects the stereochemistry on the cyclopropane ring (Scheme 51).[117] Brominated hydrocarbons proved the most appropriate solvent and 1.5 equivalents of $AlBr_3$ the optimum amount in view on the product yield and purity. It has been observed that no reaction occurrs with less that molar eqivalent of aluminum tribromide and that neither $ZnBr_2$, $FeBr_3$, $CuBr_2$, $BiBr_3$, $SbBr_3$, $HgBr_2$, $TiBr_4$ are effective for this halogen exchange.[117]

The postulated mechanism involves the addition of HBr to the dichlorovinyl moiety of **1d**$_R$ followed by HCl eliminationeffective the Cl/Br exchange (Scheme 51).[117]



Scheme 51. Synthesis of deltamethrinic acid/esters from permethrinic acid/esters by Cl/Br exchange.[117]

4.4.3.4. Synthesis of vinylcyclopropane carboxylates bearing an aryl/heteroaryl groups and a halogen at [Cf] by alternative methods. Arylation, heteroarylation and alkynylation of alkyl cypermethrinates and alkyl deltamethrinate have been used to substitute one or more rarely two of their vinylic halogens through different mechanisms.[102] It has been efficiently achieved using aryl-/heteroaryl- or alkynyl-zinc halides in the presence of palladium catalysts.[119] Typically the reaction takes place at ambient temperature for 5 h in the presence of 1 mol % of [$PdCl_2$(dppb)] complex (dppb: $Ph_2P(CH_2)_4PPh_2$). It is highly stereoselective and occurs at the *trans*-vinylic chlorine atom (Scheme 52, entries a,d) or the *trans*-vinylic bromine atom (Scheme 52, entry c) whether the stereochemistry is *trans*- (Scheme 52, entries a,e) or *cis*- (Scheme 52, entries b,d) on the cyclopropane ring.[119] In the latter case the reaction requires however a longer time (Scheme 52, compare enty b to entry a).



Scheme 52. Regioselective synthesis of pyrethroids from alkyl deltamethrinates and permethrinates involving stereoselective halogen/carbon exchange using organometallics and palladium catalyst.[119]

In some specific cases, such as the one of acetylenic zinc halides, dialkylation proceeds if the required amount of reagent is used and the temperature is raised up to 50 °C for longer time (14 instead of 6 h, Scheme 52, entry c). Under related conditions, the two bromine atoms are sequentially substituted, the *trans*-one being the first to be substituted (Scheme 52, entry c).[119] In some other cases as in Scheme 52, entry d, the two vinylic bromine atoms have been substituted regioselectively using two different organozinc derivatives. Note that the former reacts selectively on the bromine *trans* to the cyclopropane ring (Scheme 52, entry d).[119]

This strategy allows the stereoselective synthesis of a large variety of pyrethroids, the synthesis of which could not be achieved using Wittig and related reactions or by cyclization of open chain starting materials.[119]

5. From Chrysanthemic Acid/Esters to Pyrethroids Considering Their Stereochemistry (Block C Variations)

As already pointed out, pyrethroids exist as at least four stereoisomers and even more when the alkoxy part possesses stereogenic centers such as allethrin (**1a**$_B$) and deltamethrin (**1f**$_F$) or metofluthrin (**1c**$_G$) in which the vinyl group attached at [Cd] is differently substituted at [Cf]. However usually only one enantiomer concentrates insecticidal properties.[2,11] It has therefore to be detected by checking the biological activity of each individual stereoisomer on insects. So little amount of each stereoisomer is required at an early stage but, if successful, larger quantities have to be available for further testing including their toxicity towards other living organisms.

The problem is different in case of industrial production since depending upon the case the stereoisomeric mixture that reflect the ratio of stereoisomer generated in the synthesis of chrysanthemic acid is sold as for allethrin (**1a**$_B$) or after the structural manipulations required for cypermethrin (**1d**$_F$). This ratio is (i) 30/30/20/20 (1*R*,3*R*)-*trans*/(1*S*,3*S*)-*trans/*(1*R*,3*S*)-*cis*/(1*S*,3*R*)-*cis* if the chrysanthemic acid is produced by the diazo-Sumitomo method and (ii) 50/50 (1*R*,3*R*)-*trans*/(1*S*,3*S*)-*trans* if generated by the sulfone-Roussel-Uclaf method although the most active stereoisomer is the (1*R*,3*R*)-*trans* for **1a**$_B$ and (1*R*,3*S*)-*cis* for **1d**$_F$ and **1f**$_F$.

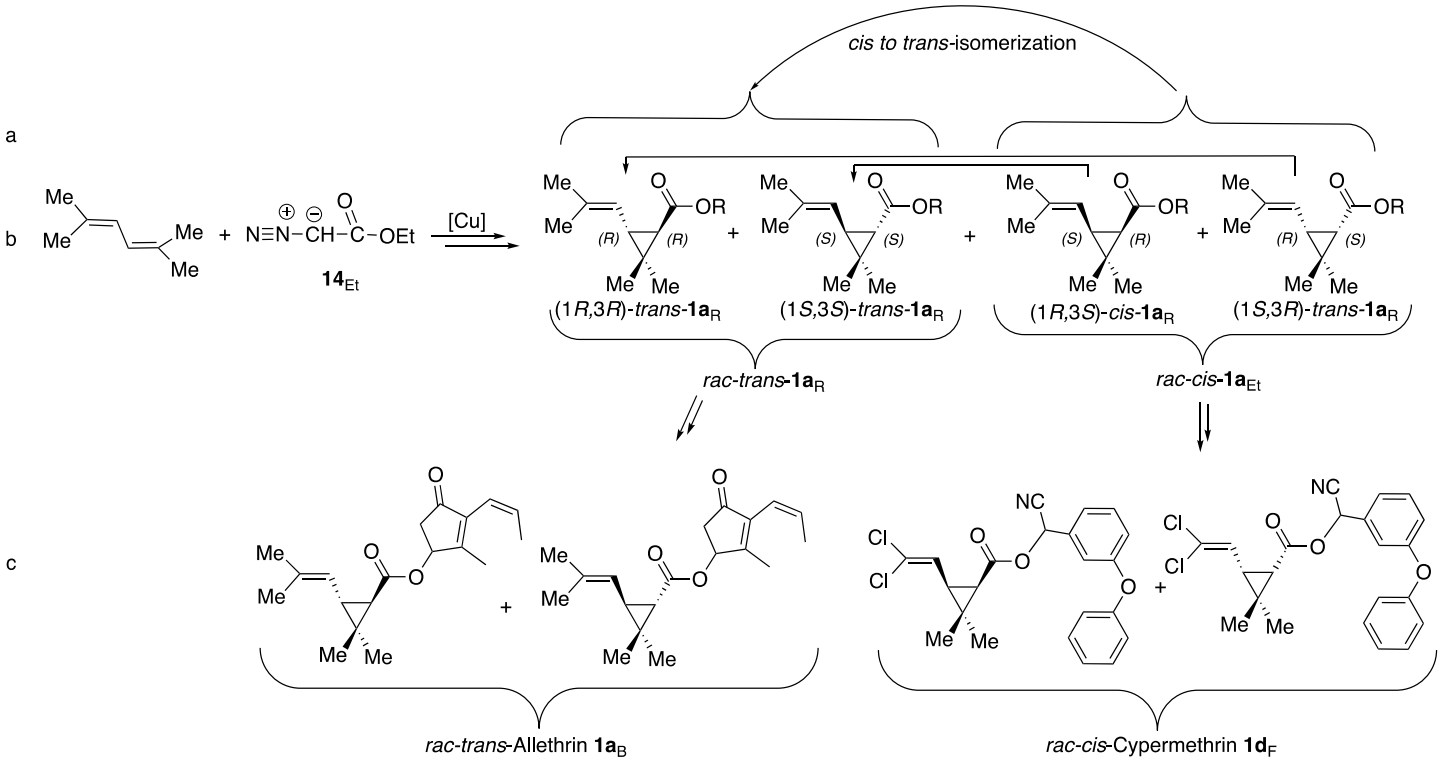
Accordingly, a mixture of all the stereoisomers of chrysanthemic acid (**1a**$_H$), arising from the Sumitomo-diazo route, can be after esterification with allethrolone (**2**$_B$) leading to allethrin (**1a**$_B$) or after transformation of the vinylic moiety and esterification with 3-phenoxy-mandelonitrile (**2**$_F$) leading to cypermethrin (**1d**$_F$).

Increased biological activity of both insecticides can be achieved by separation of the mixture of chrysanthemic acid (**1a**$_H$) into its *trans*-**1a**$_H$ and *cis*-**1a**$_H$ components (Chapter IVb, Section 2.2) before their transformation to *trans*-allethrolone *trans*-(**2**$_B$) or to *cis*-cypermethrin *cis*-(**1d**$_F$) respectively.

Otherwise, the racemic ethyl *cis*-chrysanthemate *rac*-*cis*-(**1a**$_{Et}$) by-product can be epimerized to the racemic ethyl *trans*-chrysanthemate *trans*-(**1a**$_{Et}$) (Scheme 53, entry a) and recycled to produce residual racemic-*trans*-allethrin *trans*-(**1a**$_B$) (Scheme 53, entry c) taking advantage of the difference of stabilities between the two stereosisomers that favors the *trans*-one and can be achieved under thermodynamically controlled conditions.

Performing the same to produce exclusively *cis*-cypermethrin *cis*-(**1d**$_F$) from the residual ethyl *trans*-chrysanthemate *trans*-(**1a**$_{Et}$) cannot be so easily achieved because at the difference of the processes disclosed above, the *trans*/*cis*-isomerization requested is contra-thermodynamic.

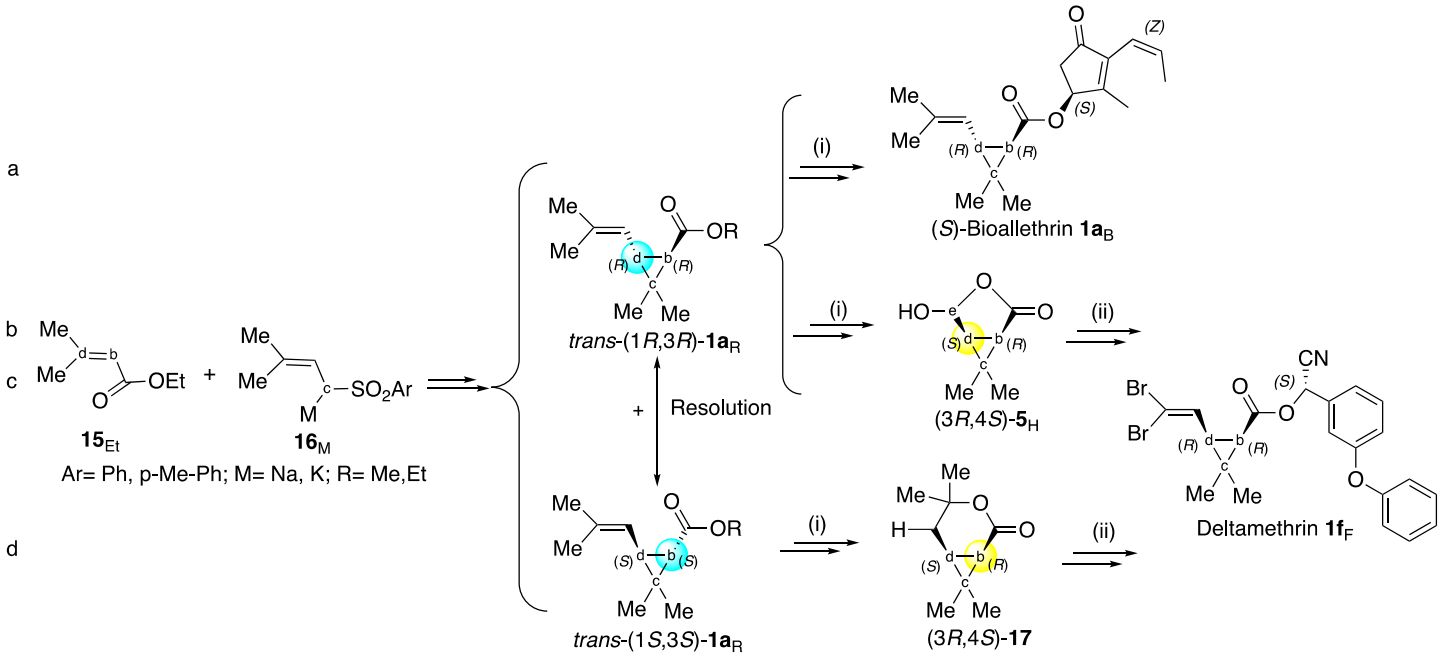
An elegant solution could be developed to produce concomitantly diastereoselectively racemic mixtures of *trans*-allethrin (**1a**$_B$) and *cis*-cypermethrin (**1a**$_F$) from 2,5-dimethyl-2,4-hexadiene and ethyldiazoacetate (Scheme 53, entry c).



Scheme 53. Strategy developed to produce concommitantly diastereoselectively racemic mixtures of *trans*-allethrin and *cis*-cypermethrin from 2,5-dimethyl-2,4-hexadiene and ethyldiazoacetate.

5.1. Isomerization reactions imbedded in the Sulfone-route

The sulfone approach has otherwise been used to access enantiopure (*S*)-Bioallethrin (*S*1*R*,3*R*)-*trans*-(**1a**$_B$) and enantiopure deltamethrinic acid (1*R*,3*R*)-*cis*-(**1f**) (Scheme 54).[8]



Scheme 54. Strategy developed to produce concommitantly diastereoselectively and enantiselectively of *trans*-(*S*)-bioallethrin and (1*R*)-*cis*-deltamethrin from ethyl senecioate and 1-metallo 3-methyl-2-butenylsulfone.[8]

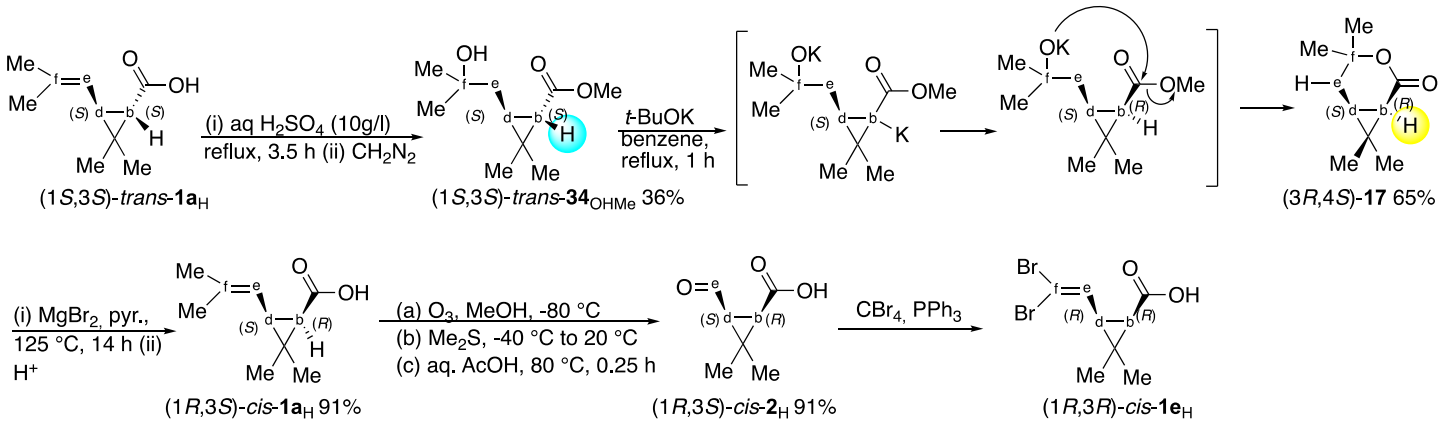
Enantiopure (1*R*,3*R*)-*trans*-chrysanthemic acid (1*R*,3*R*)-*trans*-(**1a**$_H$), accessible after resolution (Chapter IVb, Section 2.3) of the racemic mixture of *trans*-chrysanthemic acid *trans*-(**1a**$_H$) (Scheme 54, entry a),[8] allows after esterification with (*S*)-allethrolone (**2**$_B$) access to (*S*)-bioallethrin (*S*,1*R*,3*R*)-*trans*-(**1a**$_B$) (Scheme 54, entry a). Selective epimerization of (1*R*,3*R*)-*trans*-**1a**$_H$ at [Cd] through a contrathermodynamic process (Scheme 54, entry b, step (i)) and replacement of its isopropylidene moiety by a dibromomethylene one (Scheme 54, entry b step (ii)) allows access to (1*R*,3*R*)-*cis*-deltamethrin (*S*,1*R*,3*R*)-*cis*-(**1f**$_F$) by esterification of the enantiopure deltamethrinic acid (1*R*,3*R*)-*cis*-(**1f**$_H$). Such process will be detailed below.

Recycling its (1*S*,3*S*)-*trans*-(**1a**) enantiomer could be used to produce:
(a) (S,1*R*,3*R*)-*cis*-deltamethrin (S,1*R*,3*R*)-*cis*-(**1f**$_F$) through its transformation to enantiopure deltamethrinic acid (1*R*,3*R*)-*cis*-(**1f**$_H$). This requires not only formal contrathermodynamic epimerization at [Cb] (Scheme 54, entry d, step (ii)) but also replacement of its isopropylidene moiety by a dibromomethylene one (Scheme 54, entry d, step (ii)) or
(b) (*S*)-bioallethrin (*S*,1*R*,3*R*)-*trans*-(**1a**$_B$) through its transformation to (1*R*,3*R*)-*trans*-chrysanthemic acid (1*R*,3*R*)-*trans*-(**1a**$_H$) by isomerization at both [Cb] and [Cd] that requires quite a lot of steps.

5.1.1. *trans*/*cis*-Isomerization of chrysanthemic acid: An access to enantiopure deltamethrinic acid by metalation at [Cb]. The starting material to access to enantiopure deltamethrinic acid (1*R*,3*R*)-*cis*-(**1f**$_H$) could be ideally the (1*S*,3*S*)-*trans*-chrysanthemic acid (1*S*,3*S*)-*trans*-(**1a**$_H$) that has been released from the resolution process reported above (Scheme 54, entry d). It formally requires (i) an inversion of configuration at [Cb] that involves a contrathermodynamic *trans*/*cis*-stereoisomerization and the replacement of the two vinylic methyl groups by the two bromine atoms. The latter has been usually performed via replacement of the isopropylidene- by the dibromomethylene-moiety through a tandem ozonolysis/Wittig type reaction (Chapter VIb, 4.4.2.4) or using instead tribromo-methylmetal (Chapter VIb, 4.4.3.3).

Epimerization at [Cb] of (1*S*,3*S*)-*trans*-chrysanthemic acid (1*S*,3*S*)-*trans*-(**1a**$_H$), has been effectively achieved through the intermediate formation of the six membered lactone (3*R*,4*S*)-**17**.[8,36,118,120] The latter has been:
(i) generated from (1*S*,3*S*)-*trans*-(**1a**$_H$) by formal regioselective addition of water across its [Ce=Cf] double bond leading[35] to the alcohol **34**$_{OHH}$ (Chapter IVa, Section 3.1.2.1)[12] and further lactonization of its methyl ester **34**$_{OHMe}$ in basic media (*t*-BuOK, benzene reflux; Scheme 55)[8,36] (other base/solvent have been also disclosed)[36] under conditions that at the same time, effects its epimerisation by metalation at [Cb], [8,36,118,120] then
(ii) transformed to (1*R*,3*S*)-*cis*-chrysanthemic acid (1*R*,3*S*)-*cis*-(**1a**$_H$) on the action of a base (such as triethylamine, tripropylamine, quinine but preferably pyridine) in the presence of a Lewis acid activator ($MgBr_2$, 125 °C; Scheme 55). The elimination reaction occurs *via* a postulated push-pull mechanism delivering at first the magnesium dibromide-bound acid **1a**$_H$ (Scheme 55).[36,118,120] The whole transformation of (1*S*,3*S*)-*trans*-**1a** to (1*R*,3*R*)-*cis*-**1f** is disclosed in Scheme 55.[36,118,120]

This method proved to be far superior to reacting the lactone with dilute (5%) sulfuric acid in aqueous solution that delivers a mixture of *cis*-chrysanthemic acid *cis*-(**1a**$_H$) and *cis*-isochrysanthemic acid *cis*-(**35a**$_H$).[35,121]

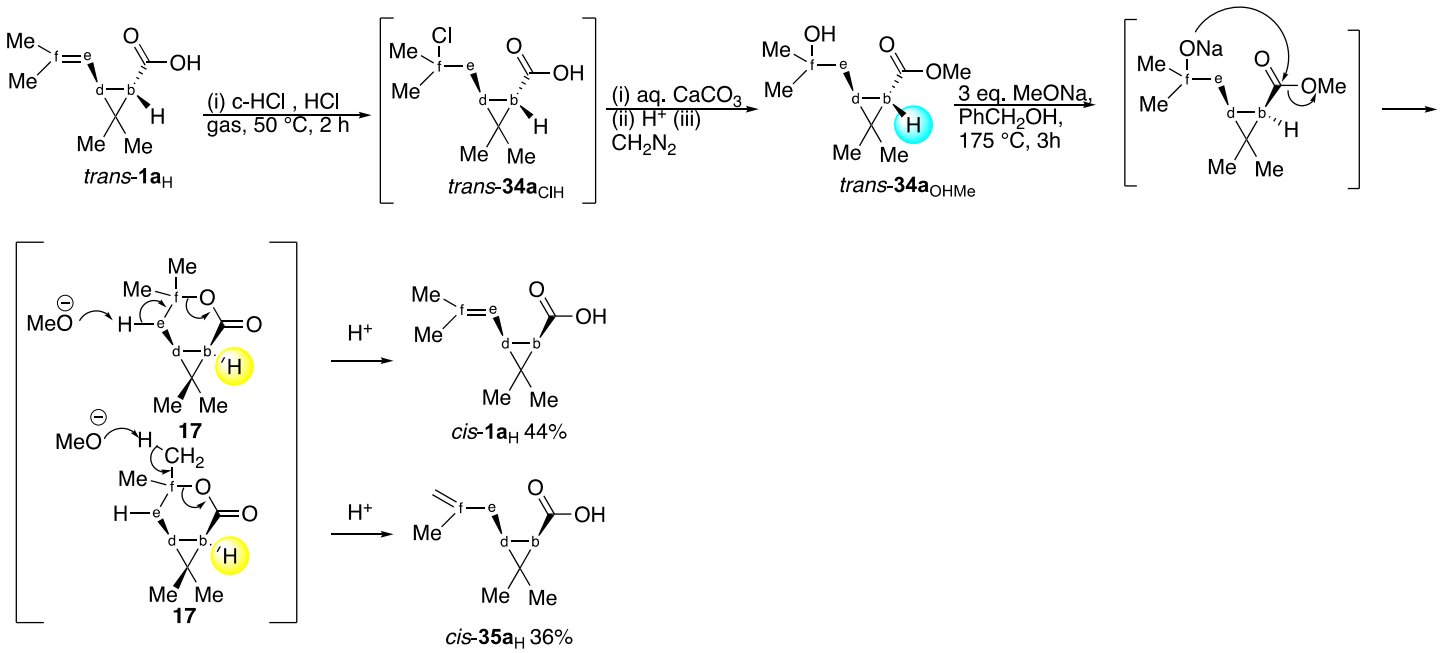


Scheme 55. Synthesis of (1*R*)-*cis*-deltametrinic acid from (1*S*)-*trans*-chrysanthemic acid implying a metalation reaction.[36,120]

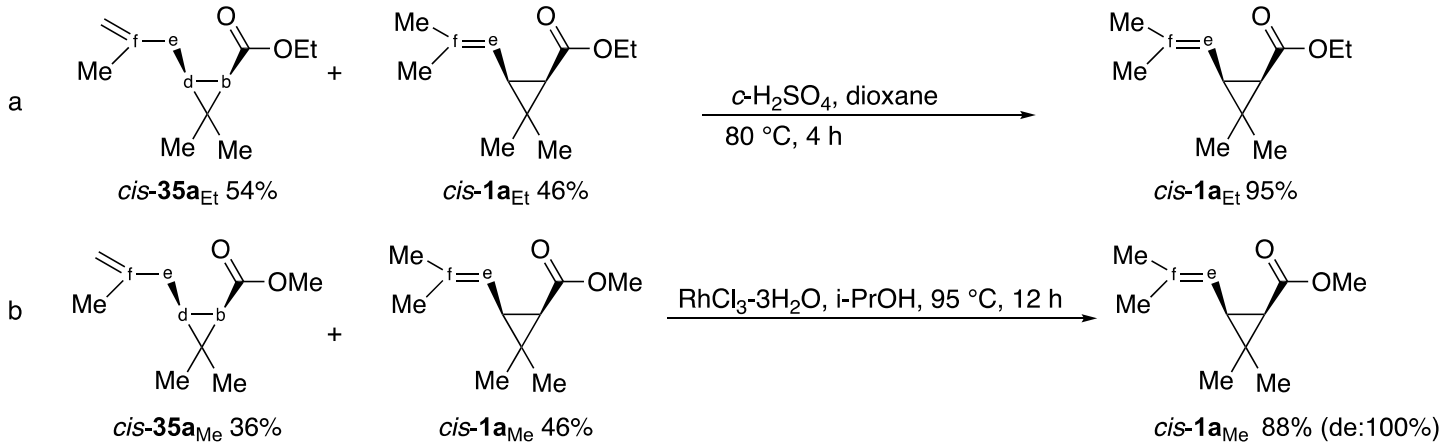
A related process to transform *trans*- to *cis*-chrysanthemic acid through the intermediate formation of the bicyclic lactone **17** has been devised by the Sumitomo Company (Scheme 56).[121] It involves:
(i) the synthesis of *delta-trans*-chlorodihydrochrysanthemic acid (**34**$_{ClH}$) by addition of hydrochloric acid to *trans*-chrysanthemic acid (cHCl, continuous HCl gas bubbling, 50 °C, 2 h, Scheme 56) (See also Chapter IVa, Section 3.1.2.3),[12]
(ii) *in situ* substitution of the chlorine of **34**$_{ClH}$ by a hydroxyl group using an aqueous solution of calcium or magnesium carbonates at 60 °C, that leads[121] after acid hydrolysis to *delta-trans*-hydrodihydrochrysanthemic acid (**34**$_{OHH}$) (68% yield) and recovery of some unreacted chrysanthemic acid (20%). Note that this exchange reaction is chemoselective since epimerization does not take place concomitantly (Scheme 56),
(iii) the reaction of methyl *delta-trans*-hydrodihydrochrysanthemate (**34**$_{MeOH}$) with different amounts of sodium methoxide in different solvents under different conditions. Best results (80 % overall yield) have been obtained when the reaction was carried out at 175 °C for 3 h using 3 eq. of sodium methoxide that not only effects the *trans*/*cis*-isomerization reaction leading to the intermediate bicyclic lactone **17** but also performs its stereoselective ring opening, leading after acidification to *cis*-chrysanthemic acid *cis*-(**1a**$_H$) and its regioisomer *iso-cis*-chrysanthemic acid *cis*-(**35a**$_H$) in almost equal ratio (Scheme 56).[121] Under these conditions, the bicyclic lactone **17** intermediate is not isolated but *in situ* subjected to ring opening through a beta elimination reaction (Scheme 56).

Isomerization of *iso*-cis chrysanthemic acid *cis*-(**35a**$_H$) to chrysanthemic acid *cis*-(**1a**$_H$) cannot be achieved easily since the acidic media required to achieve such reaction also induces lactone **17** formation.[121,122] This isomerization has been however efficiently performed on ethyl *cis-iso*-chrysanthemate *cis*-(**35a**$_{Et}$) (c-sulfuric acid, dioxane, 80 °C, Scheme 57, entry a).[122,123] Under these conditions neither lactone formation nor *cis*/*trans*-isomerisation take place.

Related isomerisation of a 1:2 mixture of methyl *cis*-chrysanthemate *cis*-(1**a**$_{Me}$) and methyl *cis-iso*-chrysanthemate *cis*-(**35a**$_{Me}$) to methyl *cis*-chrysanthemate *cis*-(1**a**$_{Me}$) has been also performed under transition metal catalysis using isopropanol as the solvent ($RhCl_3 \cdot 3\ H_2O$, *i*-PrOH, 95 °C, 12 h, 88%, Scheme 57, entry b).[124,125] Performing the reaction in methanol instead does not provide the same outcome since competing reaction leading to methyl [Cf] methoxy *cis*-dihydrochrysanthemate (**34a**$_{MeOMe}$) takes place instead.[124]



Scheme 56. Isomerization from *trans*-chrysanthemic acid to *cis*-chrysanthemic acid and *cis*-isochrysanthemic acid implying a metalation reaction.[121]



Scheme 57. Isomerization of alkyl *cis*-isochrysanthemates to alkyl *cis*-chrysanthemates [122,123,124]

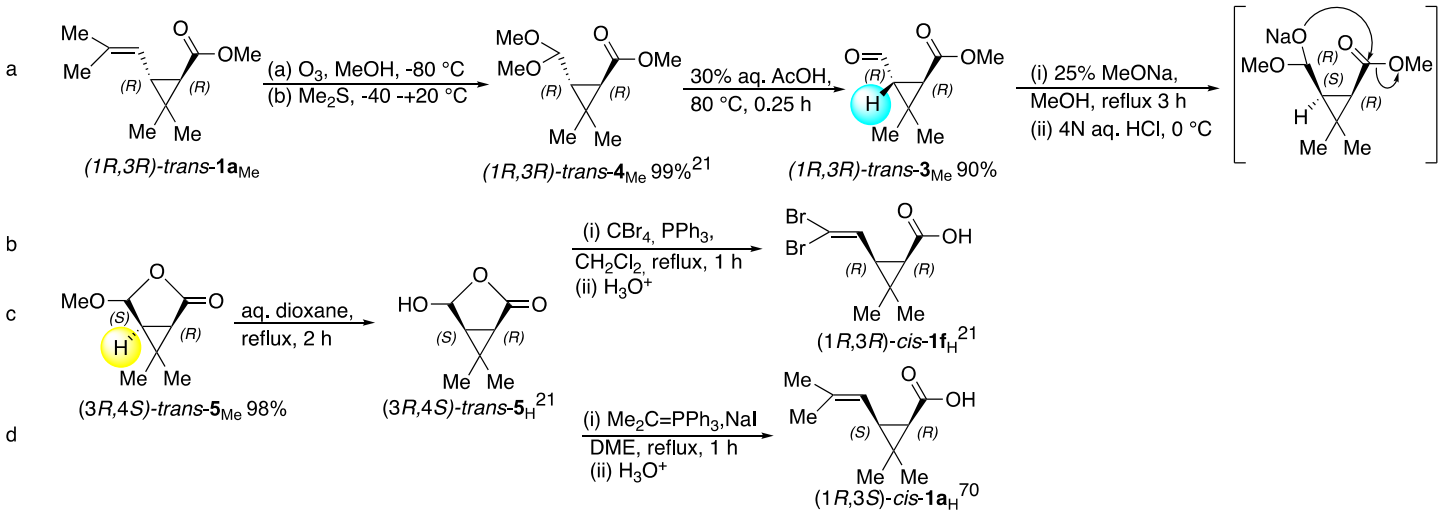
It has however been reported that reacting chrysanthemolactone **17** with excess NaOH in diethylene glycol at 230 °C for 5 h, leads after acidification, to *trans*-chrysanthemic acid *trans*-(**1a**$_H$) in 87% yield.[126] Under these conditions not only the lactone ring opening takes place to produce selectively the isopropylidene moiety but also epimerization at [Cb] occurs alpha-to the resulting sodium carboxylate and therefore those conditions do not apply to the transformation reported in Scheme 56.

5.1.2. *trans*/*cis*-Isomerization of chrysanthemic acid: An access to enantiopure deltamethrinic acid by metalation at [Cd]. As larger amounts of deltamethrin (S,1*R*,3*R*)-*trans*-(**1f**$_F$) being needed compared to (*S*)-bioallethrin (*S*-1*R*,3*R*)-*trans*-(**1a**$_B$), the transformation of enantiopure chrysanthemic acid (1*R*,3*R*)-*trans*-(**1a**$_H$) to deltamethrinic acid (1*R*,3*R*)-*cis*-(**1f**$_H$) has been required in complement. It therefore involves an inversion of configuration at [Cd].

trans/*cis*-Isomerization by epimerization at [Cd] on methyl (1*R*,3*R*)-*trans*-chrysanthemate (1*R*,3*R*)-*trans*-(**1a**$_{Me}$) is not easy to achieve since the hydrogen at [Cb] is far more acidic than the one at [Cd]. It precludes direct metalation to achieve this goal. This has however been achieved by selective metalation at the [Cd] of the related hemicaronic acid (**3**$_{H}$) resulting from the cleavage of the [Ce,Cf)] double bond of *trans*-(**1a**$_{H}$) by ozonolysis (Chapter IVa, Section 3.2.2;[12] this Chapter IVb, Section 4.4.1) (Scheme 54, entry b, route i).[8] This transformation takes advantage of the higher acidity at [Cd] due to the presence of a formyl group there compared to that at [Cb] alpha to the carboxylate first formed and at the same time the propensity of the latter group to react on the aldehyde attached to the adjacent carbon to induce a ring closure producing the bicyclic [3.1.0] lactone (**5**$_{H}$) (Scheme 54, entry d; Scheme 55).

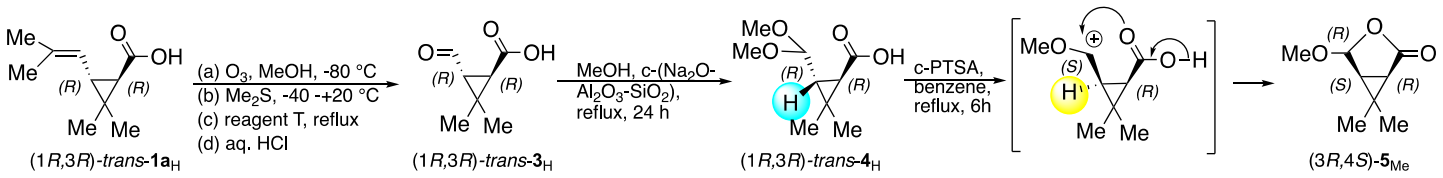
The related bicyclic [3.1.0] lactone **5**$_{Me}$ has been synthesized[21] by ozonolysis of methyl (1*R*,3*R*)-*trans*-chrysanthemate (1*R*,3*R*)-*trans*-(**1a**$_{Me}$) in methanol and treatment of the resulting methyl *trans*-hemicaronate (1*R*,3*R*)-*trans*-(**3**$_{Me}$) with sodium methanolate in methanol at reflux of the latter. The (1*R*,3*S*)-bicyclic lactone (1*R*,3*S*)-**5**$_{Me}$ is formed via tandem isomerization/ring closure fixing the *cis*-stereochemistry there (Scheme 58, entries a,b).[21]

Reaction of the latter with water in hot dioxane allows the substitution of the methoxy group at [Ce] by a hydroxyl group leading to biocartol (1*R*,3*S*)-(**5**$_{H}$) that on reaction with (i) the *in situ* generated dibromomethylene triphenylphosphorane **7f** (Scheme 58, entry b) delivers after acid tratment (1R,3*R*)-*cis*-deltamethrinic acid (1R,3*R*)-*cis*-(**1f**$_{F}$) (Scheme 58, entry b) or (ii) with isopropylidene triphenylphosphorane (**7a**) and acid hydrolysis generates (1*R*,3*S*)-*cis*-chrysanthemic acid (1*R*,3*S*)-*cis*-(**1a**) (Scheme 58, entry d).[21]



Scheme 58. Transformation of methyl (1*R*)-*trans*-chrysanthemate (1*R*)-*cis*-chrysanthemic acid implying an epimerization on methyl (1*R*)-*trans*-hemicaronate intermediate at [Cd].[21,70]

The formation of the methylated biocartol (**5**$_{Me}$) has been also achieved through the formation of the *trans*-acetal (1*R*,3*R*)-*trans*-**4**$_{H}$ on reaction with *para*-toluenesulfonic acid (Scheme 59).[21] It requires the intermediate formation of a carbenium ion at [Ce] stabilized by the remaining methoxy group and is believed to enolizes from the *trans*- to the *cis*-form prior its trapping by the closely localized carboxyl group (Scheme 59).[21]



(1*R*,3*R*)-*trans*-**1a**$_H$ (1*R*,3*R*)-*trans*-**3**$_H$ (1*R*,3*R*)-*trans*-**4**$_H$ (3*R*,4*S*)-**5**$_{Me}$

Scheme 59. Synthesis of methyl-biocartol from (1*R*)-transchrysanthemate impying an acid catalyzed *trans*/*cis*-isomerization at [Cd].[21]

The mechanisms of the reactions involved in these processes are probably more complex than those reported in Scheme 58 and Scheme 59. It has been for example observed that the reaction of sodium ethanolate in ethanol on a stereoisomeric (66/34) *trans*/*cis*-mixture of ethyl hemicaronate (**3**$_{Et}$) obtained from a commercially available (66/34) *trans*/*cis*-mixture of ethyl chrysanthemates (**1a**$_{Et}$) does no lead to ethyl-biocartol (**5**$_{Et}$) but instead to ethyl *trans*-hemicaronate *trans*-(**3**$_{Et}$) in 67% yield after only one minute. Although the outcome of this reaction seems obscure, it delivers ethyl *trans*-hemicaronate *trans*-(**3**$_{Et}$) in up to 95% yield after almost a day (Scheme 26, entry b). It should be noticed that under these conditions *cis*/*trans* isomerization takes place whereas with sodium methanolate in methanol on methyl chrysanthemate the *trans*/*cis* process is instead favored (Scheme 58, entry a).

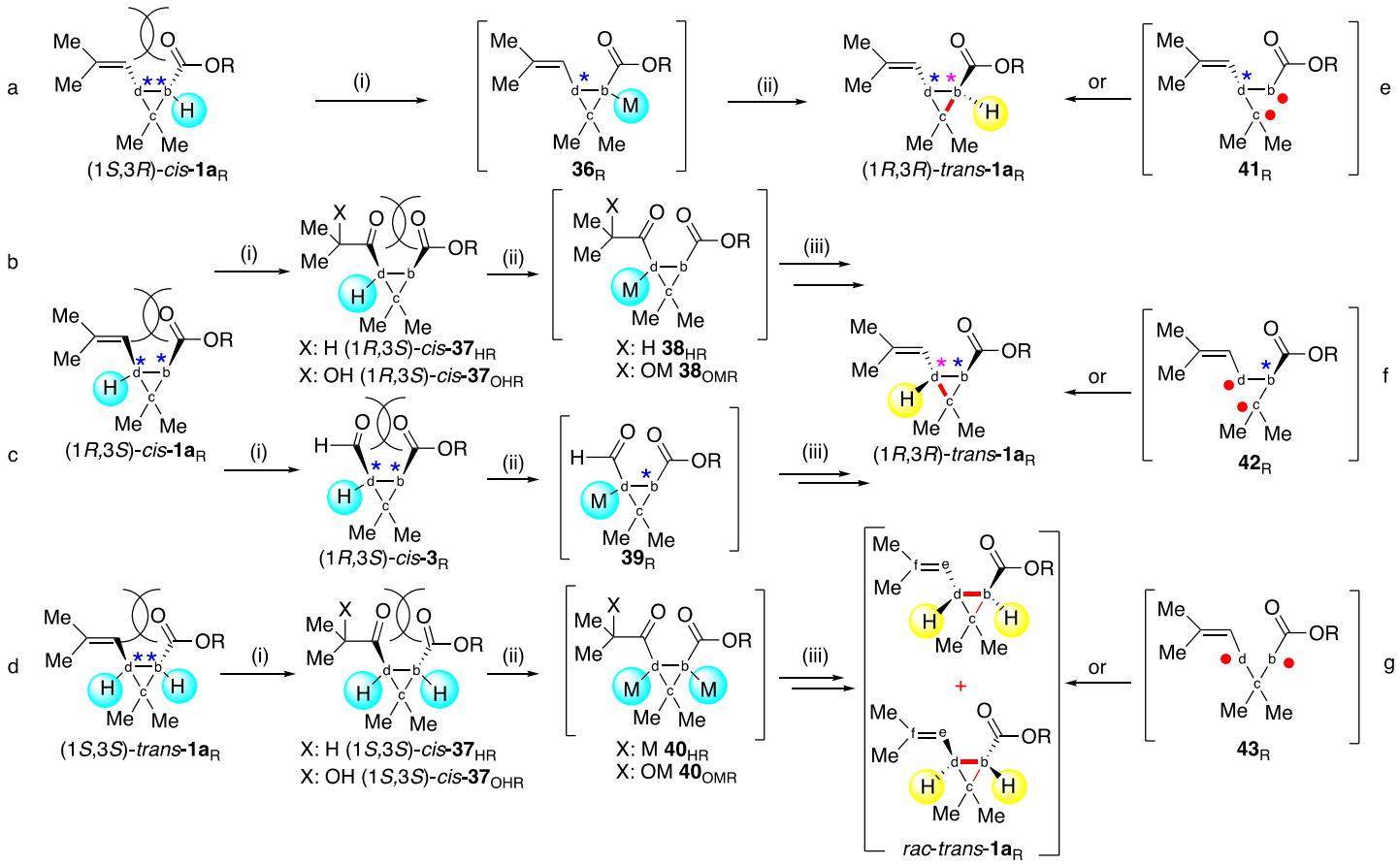
5.1.3. *trans*/*trans*-Isomerization of chrysanthemic acid: An access to enantiopure (1*R*,3*R*)-*trans*-chrysanthemic acid from its enantiomer (1*S*,3*S*)- *trans*-chrysanthemic acid. The last possibility involves isomerization of the (1*S*,3*S*)-*trans*-chrysanthemic acid/esters (1*S*,3*S*)-**1a**$_R$ to its enantiomer (1*R*,3*R*)-*trans*-**1a**$_R$ formed in equal quantities through the sulfone route (Scheme 14; Scheme 15, Routes Ba and Bb) in order to use the full content of the *trans*-chrysanthemic acid formed to produce for example (S)-Bioallethrin (**1a**$_B$). This transformation is the most complex of the series since it requires selective isomerization at each [Cb] and [Cd] carbons that involves too many individual reactions to deliver a compound for commercialization. A model process is disclosed in Scheme 72 (Scheme 72, sequential routes b, e, g, k involving (1*S*,3*S*)-*trans*-**18**, **20** and (1*R*,3*S*)-*cis*-**18**, or routes b, e, h, l, involving (1*S*,3*S*)-*trans*-**18**, **20**, (1*S*,3*R*)-*cis*-**18** and (1*R*,3*R*)-*trans*-**18**).

One alternative solution that has been used especially in industry, involves a shorter approach that implies racemization under thermodynamic control to produce a racemic (50/50) mixture of (1*R*,3*R*)-*trans*-chrysanthemic acid/esters (1*R*,3*R*)-**1a**$_R$ and (1*S*,3*S*)-*trans*-chrysanthemic acid/esters (1*S*,3*S*)-**1a**$_R$ (Scheme 60, entries d and g) from which (1*R*,3*R*)-**1a**$_H$ is isolated after resolution and the other part racemized again. That matter will be discussed in this chapter (Chapter IVb, section 5.5).

5.2. Isomerization reactions imbedded in the "Diazo-route"

At the contrary to "sulfone route" that only produces the *trans*-chrysanthemate, the "diazo-route" allows access to the mixture four stereoisomers (30/30/20/20: (1*R*)-*trans*/(1*S*)-*trans*/(1*R*)-*cis*/(1*S*)-*cis* ratio) from which each stereoisomer can be isolated and transformed for the required purpose.

5.2.1. Strategies to synthesize (1*R*,3*R*)-*trans*-chrysanthemic acid from its *cis*- and *trans*-stereoisomers implying metalation reactions or their cyclopropane ring opening/ring closure. Recycling chrysanthemic acid/esters **1a**$_R$ stereoisomers to the (1*R*,3*R*)-*trans*-chrysanthemic acid (1*R*,3*R*)-(**1a**$_H$) precursor of the most active pyrethroids has been required at some point. Of course, isomerization of the mixture under thermodynamically controlled conditions would allow the synthesis of racemic *trans*-chrysanthemic acid *trans*-(**1a**$_H$). Although that has been achieved, each enantiomer of *trans*-and *cis*- chrysanthemic acid/esters has been selectively isomerized to (1*R*,3*R*)-*trans*-chrysanthemic acid/esters (1*R*,3*R*)-**1a**$_R$, using in each case requires a specific approach, summarized in Scheme 60.



Scheme 60. Strategy and practice to carry epimerization and racemization reactions on chrysanthemic acid/esters by metalation or cyclopropane ring opening/ring closure.

Two types of reactions have been routinely used to achieve the transformation of each of the three chrysanthemic acid/esters stereoisomers of chrysanthemic acid/esters to the (1*R*,3*R*)-*trans*-chrysanthemic acid/esters (1*R*,3*R*)-*trans*-**1a**$_R$: they either involve a metalation reaction (Scheme 60, entries a,b,c,d) or the cyclopropane ring-cleavage/ring-closure (Scheme 60, entries a,e,f,g) on the original structure (Scheme 60, entries a,e,f,g) or a derived structure that still keep intact the original carbon framework (Scheme 60, entries b,d) or involves a partially degraded one (Scheme 60, entry c) that still contain the cyclopropane ring bearing the *gem*-dimethyl groups. Differences exist in reactions in which cyclopropane ring-cleavage/ring-closure occurs through micro-reversible processes in which the ring opened product is not observed that occurs under thermodynamic processes and those that deliver isolable "ring opened"intermediates that are then cyclized to generate the chrysanthemic acid framework producing a *cis*/*trans*-mixture of stereoisomers often under kinetically controlled conditions.

5.2.1.1. Generalities about the isomerization implying a metalation reaction on the cyclopropane ring. Metalation is selectively achieved, under thermodynamically controlled conditions, at [Cb] owing the acidifying effect of the carbalkoxy-group (Chapter IVa, Section 4.2)[12] (Scheme 60, entry a). Consequently, metalation at [Cd] is only feasible after transformation of the [Ce=Cf] double bond to a functional group able to acidify this position better than the carboxylate do at [Cb] as it is the case when an acyl group is attached at [Cd]. The new functional group should also allow, at a later stage, an easy access to the original skeleton of the epimerized chrysanthemic acid/esters (1*R*,3*R*)-*trans*-**1a**$_R$.

For that purpose [Ce=Cf] double bond has been for example oxidized leading selectively either to (a) the keto ester **37**$_{HR}$, or (b) its beta-hydroxy analogue **37**$_{OHR}$ keeping intact the original framework of chrysanthemic acid/ester (Scheme 60, entry b) or to (c) hemicaronic acid/esters **3**$_{R}$ missing the isopropenyl side chain (Scheme 60, entry c). Such processes, especially if they are achieved under thermodynamic control, have allowed, as it will be discussed below, the synthesis of (1*R*,3*R*)-*trans*-**1a**$_{R}$ derivatives by metalation at:

- [Cb] of (1*S*,3*R*)-*cis*-**1a**$_{R}$, producing the intermediate **36**$_{R}$, epimerizing at [Cb] and leaving untouched its stereochemistry at [Cd] (Scheme 60, entry a),
- [Cd] of (1*R*,3*S*)-*cis*-**37**$_{HR}$ (Scheme 60, entry b), (1*R*,3*S*)-*cis*-**3**$_{R}$ (Scheme 60, entry c), or (1*R*,3*S*)-*cis*-**37**$_{OHR}$ (Scheme 60, entry b), producing the intermediates **38**$_{HR,}$ **39**$_{R}$, or **38**$_{OMR}$, respectively and leaving untouched their stereochemistry at [Cb] (Scheme 60, entries b,c),
- both [Cb] and [Cd] of (1*S*,3*S*)-*trans*-**37**$_{HR}$ or (1*S*,3*S*)-*trans*-**37**$_{OHR}$ simultaneously or successively, producing the intermediates **40**$_{RH}$ and **40** $_{ROM}$,
- and leading finaly to the desired (1*R*,3*R*)-*trans*-**1a**$_{R}$ mixed with the same amount of its enantiomer, the starting material, (1*S*,3*S*)-*trans*-**1a**$_{R}$ (Scheme 60, entry d) from which it should be separated (by resolution for example) and eventually recycled again and again.

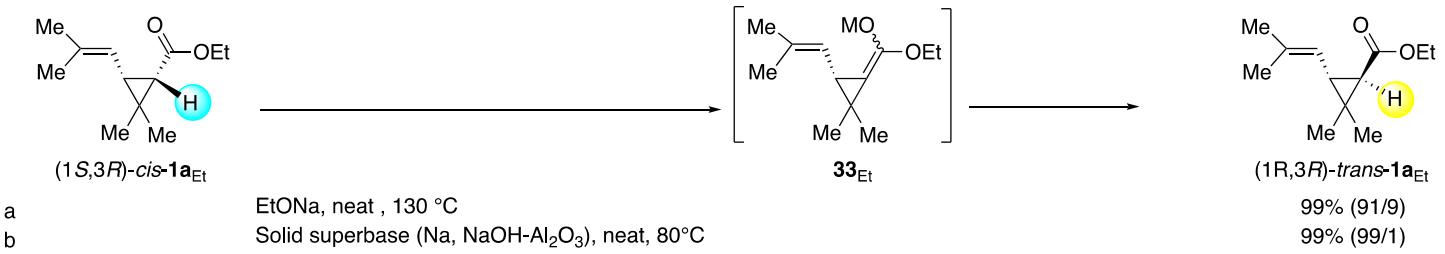
5.2.1.2. Generalities about the isomerization implying cyclopropane ring-cleavage /ring-closure. All the transformations described above can also be achieved by ring-cleavage/ring-closure of one the bond of the cyclopropane. This can be formally achieved in a single step or in two steps and at the difference of the metalation-approach can be performed in each case on starting material possessing the complete carbon framework of chrysanthemic acid/esters. To be selective these transformations should take place under thermodynamically controlled conditions so the required *trans*-stereoisomer is stereoselectively produced.

Thus (1*R*,3*R*)-*trans*-**1a**$_{R}$ has been produced by ring-cleavage/ring-closure of the:

- [Cb-Cc] bond of (1*S*,3*R*)-*cis*-**1a**$_{R}$ leading to the intermediate **41**$_{R}$ that keeps intact the stereochemistry at [Cd] and allows epimerization at [Cb] (Scheme 60, entry e),
- [Cd-Cc] bond of (1*R*,3*S*)-*cis*-**1a**$_{R}$ leading to the intermediate **42**$_{R}$ that keeps intact the stereochemistry at [Cb] and allows epimerization at [Cd] (Scheme 60, entry f),
- [Cb-Cd] bond that destroys the stereochemistry at each of the two [Cb] and [Cd] asymmetric centers of (1*S*,3*S*)-*trans*-**1a**$_{R}$ leading to the intermediate **43**$_{R}$ and finaly producing (1*R*,3*R*)-*trans*-**1a**$_{R}$ as well as the same amount of its enantiomer (1*S*,3*S*)-*trans*-**1a**$_{R}$ from which it could be separated by resolution (Scheme 60, entry g). Note that the same mixture can also be reached from either (1*S*,3*R*)-*cis*-**1a**$_{R}$ or (1*R*,3*S*)-*cis*-**1a**$_{R}$ using the same conditions.

5.2.2 Effective stereocontrolled transformations of chrysanthemic acid/esters to access (1*R*,3*R*)-*trans*-chrysanthemic acid/esters and (1*R*,3*S*)-*cis*-deltamethrinic acid/esters. We describe in this section the specific reactions that have been effectively used to perform such epimerization reactions that allow the recycling of some stereoisomers of chrysanthemic acid.

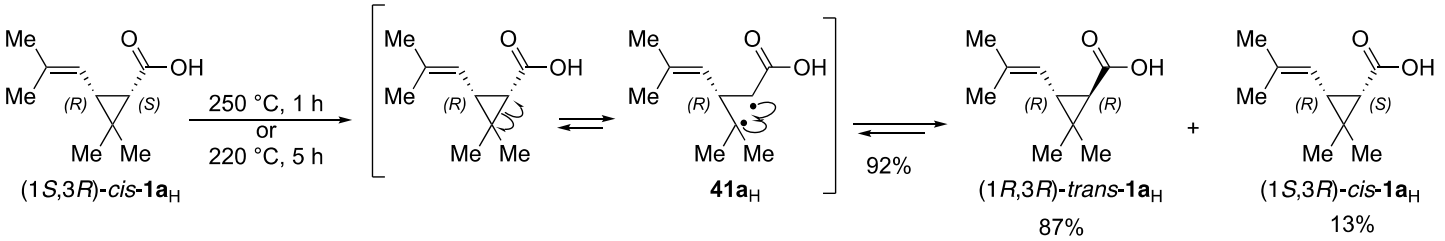
5.2.2.1. *cis*/*trans*-Isomerization of chrysanthemic acid by epimerization at [Cb]. 5.2.2.1.1. *cis*/*trans*-Isomerization reactions involving a metalation at [Cb]. *cis*/*trans*-Isomerization at [Cb] has been directly achieved on lower esters of *cis*-chrysanthemic acid and especially the (1*S*,3*R*)-**1a**$_{R}$ stereoisomer using catalytic or stoichiometric amounts of a base such as sodium or potassium alcoholates in alcohols or better in benzene (Scheme 61, entry a) or even better using sodium superbases (Scheme 61, entry b).[127] Best results have been observed with esters bearing a large alkoxy moiety such as *t*-butyl esters (Scheme 61, entry a; Chapter IVa, Section 4.2[12]).



Scheme 61. Synthesis of ethyl (1*R*)-*trans*-chrysanthemate from ethyl (1*S*)-*cis*-chrysanthemate involving a metalation reaction at [Cb].[127]

It has been also reported [126] that during the transformation of (*R*)-3-carene to (1*R*,3*R*)-trans-chrysanthemic acid (1*R*,3*R*)-*trans*-(**1a**$_H$) *cis*/*trans*-epimerization has taking place alpha to the sodium carboxylate produced on reaction of chrysanthemolactone **17** with excess sodium hydroxide in diethylene glycol at 230 °C for 5 h.[126]

5.2.2.1.2. *cis*/*trans*-Isomerization at [Cb] involving cyclopropane ring opening/ring closure of the [Cb-Cc] bond. Alternatively, related *cis*/*trans*-isomerization has been achieved on (1S,3*R*)-*cis*-chrysanthemic acid (1S,3R)-*cis*-(**1a**$_H$) by thermolysis (250 °C, 1 h; 220 °C, 5 h). The reaction takes place by selective cleavage/recombination of its [Cb-Cc] bond and delivers (1*R*,3*R*)-*trans*-chrysanthemic acid in extremely high yield besides a small amount (13%) of the starting material (Scheme 62).[129] The reaction takes another course when carried out at higher temperature and provides[53,130] instead pyrocine that contains a five membered cyclic lactone (Chapter IV, Section 5.1).

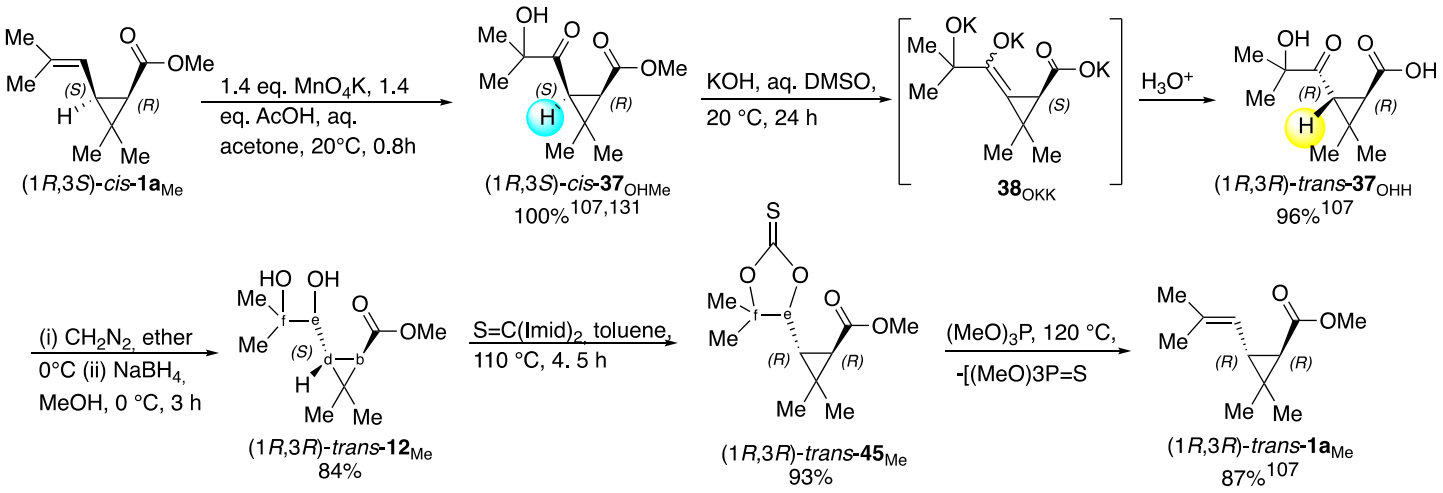


Scheme 62. Synthesis of ethyl (1*R*)-*trans*-chrysanthemate from ethyl (1*S*)-*cis*-chrysanthemate involving a thermal isomerization.[129]

5.2.2.2. *cis*/*trans*-Isomerization of chrysanthemic acid by epimerization at [Cd]. 5.2.2.2.1. *cis*/*trans*-Isomerization reactions involving metalation at [Cd]. As already pointed out epimerization at [Cd] requires the presence of an extra carbonyl group at [Ce] this has been quantitatively achieved by:

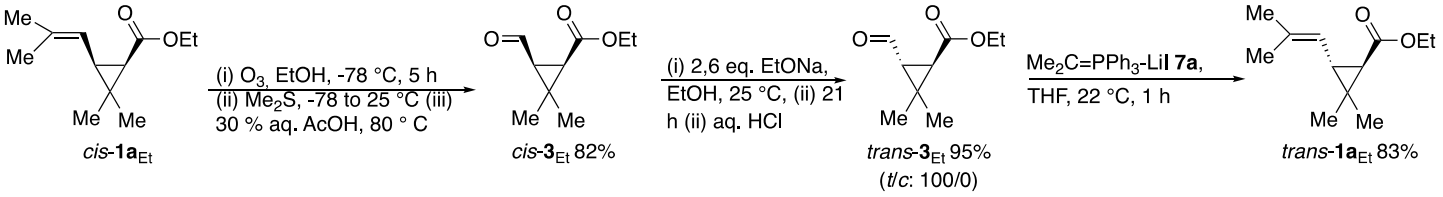
5.2.2.2.1.1. *cis*/*trans*-Isomerization reactions involving epimerization alpha to the carbonyl group of a beta-keto alcohol derived from reaction of methyl chrysanthemates with potassium permanganate. *cis*/*trans*-Isomerization has been achieved in a multisteps sequence involving as the key step the reaction of potassium permanganate in acidic media on methyl (1*R*,3*S*)-*cis*-chrysanthemate (1*R*,3*S*)-*cis*-(**1a**$_{Me}$) (Chapter IVa, Section 3.1.3.3.3)[12] that delivers the keto alcohol (1*R*,3*S*)-*cis*-**37**$_{OHMe}$ in quantattive yield.[12,131,107] Epimerization of the latter at [Cd] is efficiently achieved at room temperature using potassium hydroxide in dimethylsulfoxide (DMSO), leading to the corresponding potassium carboxylate **38**$_{OKK}$ resulting from a concomitant saponification (Scheme 63).[107] This saponification reaction prevents the base to metallate at [Cb] that would have achieved racemization instead. Transformation of this salt to (1*R*,3*R*)-*trans*-**1a**$_{Me}$ involves sequential (i) acidification of **38**$_{OKK}$ leading to (1*R*,3*R*)-*trans*-**37**$_{OHH}$ (ii) esterification using diazomethane followed by (ii) reduction of the

ketoalcohol moiety to the diol (1*R*,3*R*)-*trans*-**12**$_{Me}$ using sodium borohydride and (iii) olefination reaction, through the related thionocarbonate (1*R*,3*R*)-*trans*-**45**$_{Me}$ with trimethyl phosphite[107,132,133] or better with 1,3-dimethyl-2-phenyl-1, 3, 2-diazaphospholidine (Scheme 63).[133,134]



Scheme 63. Selective cis/trans-isomerization of methyl chrysanthemates implying a metalation at [Cd].[131,107]

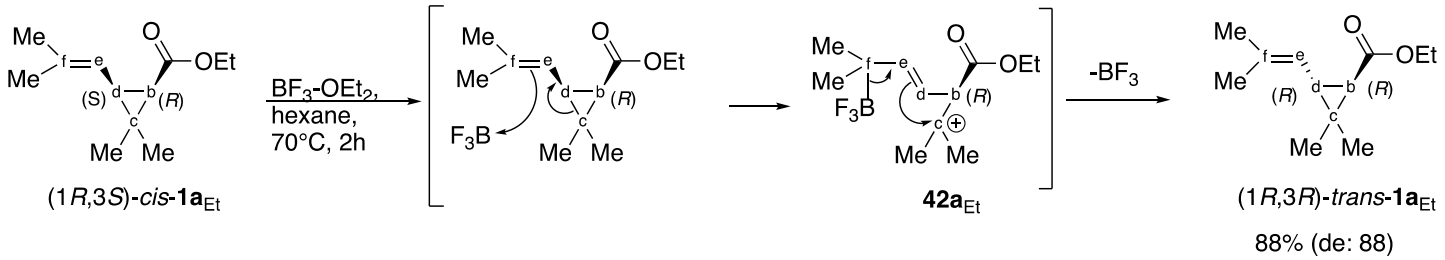
5.2.2.2.1.2. *cis*/*trans*-Isomerization reactions involving epimerization alpha to the formyl group of ethyl hemicaronate. The approach involving ethyl hemicaronate is far shorter (Scheme 64). It however requires (i) the destruction of the carbon framework of *cis*-chrysanthemate *cis*-(**1a**$_{Me}$) by ozonolysis (Chapter IVa, Section 3.2.2)[12] (ii) selective epimerization alpha to the formyl group of alkyl *cis*-hemicaronate *cis*-**3**$_R$ using sodium alcoholate in alcohol leading to ethyl *trans*-hemicaronate *trans*-**3**$_R$ (iii) transformation of the latter to ethyl *trans*-chrysanthemate *trans*-(**1a**$_{Et}$) using ispropylidene triphenylphosphorane **7a** (Scheme 64).[87]



Scheme 64. Adapted *cis*/*trans*-isomerization at [Cd] of alkyl chrysanthemates.[64,87]

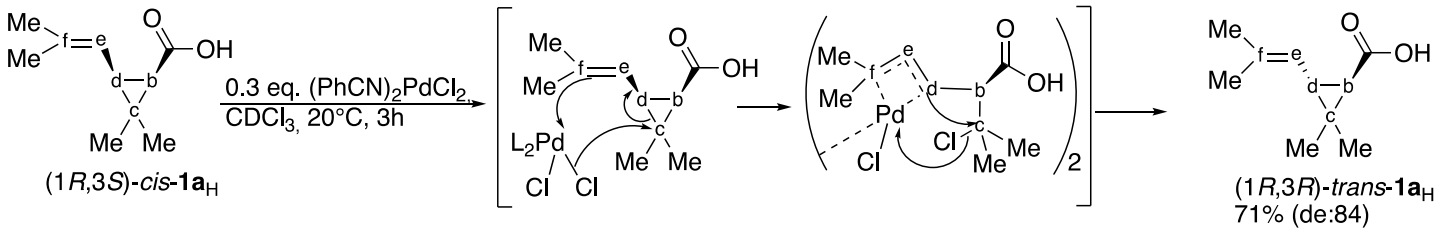
5.2.2.2.2. *cis*/*trans*-Isomerization reactions at [Cd] involving cyclopropane ring opening/ring closure of the [Cd-Cc] bond. cis/trans-Isomerization involving cyclopropane ring opening/ring closure is even shorter and can be conveniently achieved using catalytic amounts of Lewis acids (Chapter IVa, Section 5.4.1)[12] or transition metals catalysts (Chapter IVa, Section 5.5).[12]

The *cis*/*trans*-isomerization reactions have been successfully achieved on ethyl (1*R*,3*S*)-*cis*-chrysanthemate (1*R*,3*S*)-*cis*-(**1a**$_{Et}$) using aluminum trichloride, iron trichloride or boron trifluoride at reflux of hexane, the latter being the most efficient. It delivers ethyl (1*R*,3*R*)-*trans*-chrysanthemate (1*R*,3*R*)-*trans*-(**1a**$_{Et}$) in good yield and reasonably high ee suggesting that the process occurs *via* the selective cleavage of the [Cc-Cd] bond (Scheme 65).[127-129]



Scheme 65. Lewis acid catalyzed *cis*/*trans*-isomerization of ethyl *cis*-chrysanthemate implying the formation of an intermediate possessing the lavandulyl skeleton.[128]

Soluble palladium dichloride bis-benzonitrile complex (Scheme 66)[136] at room temperature in chloroform, efficiently catalyzes the isomerization of (1*R*,3*S*)-*cis*-chrysanthemic acid (1*R*,3*S*)-*cis*-(**1a**$_H$) to (1*R*,3*R*)-*trans*-chrysanthemate (1*R*,3*R*)-*trans*-(**1a**$_H$) (Scheme 66)[136] and proceeds by exclusive epimerization at [Cd]. That again suggests the selective cleavage of the [Cc-Cd] bond of the three membered cycle.



Scheme 66. Regioselective transition metal catalyzed epimerization of *cis*-chrysanthemic acid and related esters at [Cd].[136]

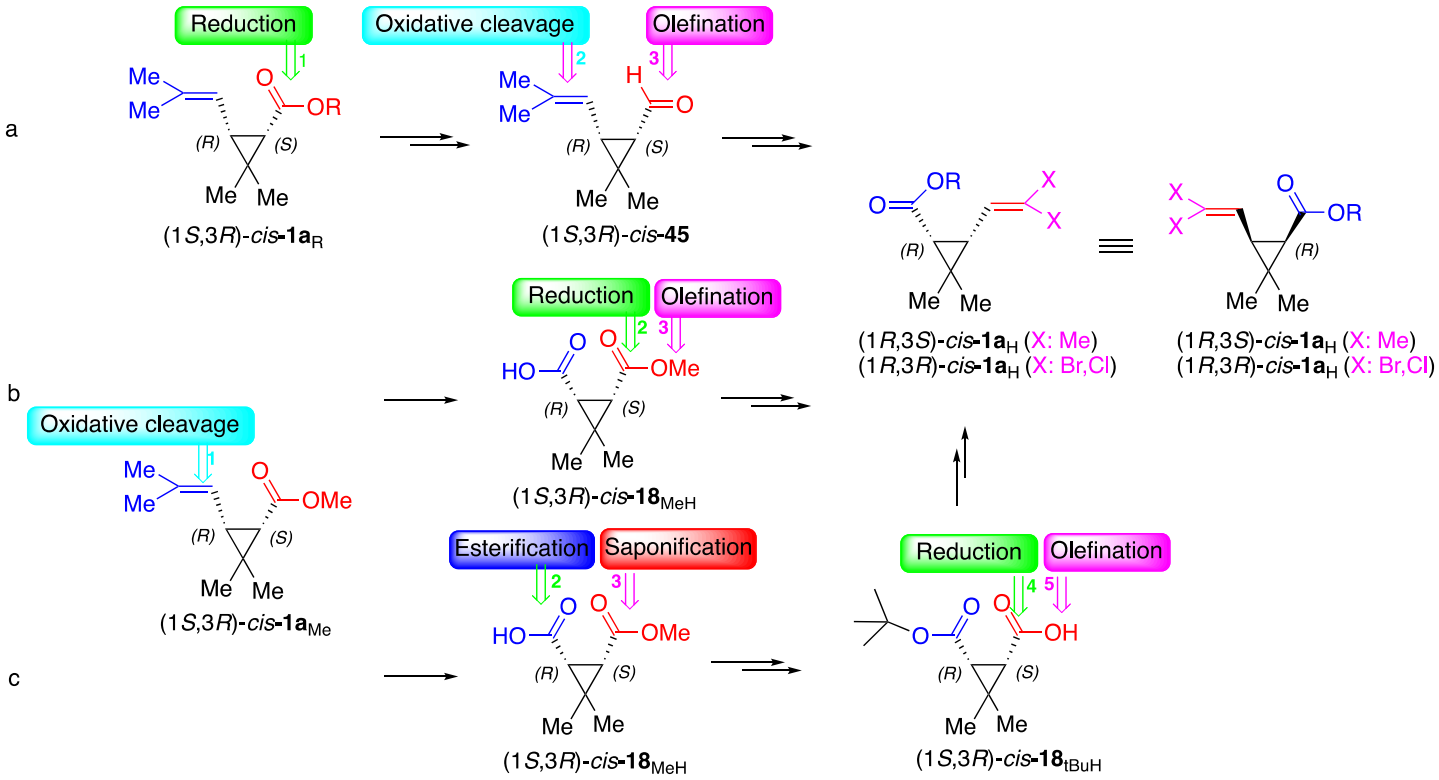
5.3. Isomerization involving stereoselective formal interchange of the vinyl and carboxy groups on chrysanthemic acid

Another approach, that has been only scarcely used, is exemplified on the isomerization of (1*S*,3*R*)-*cis*-chrysanthemic acid/esters (1*S*,3*R*)-*cis*-**1a**$_R$ and involves the formal stereoselective interchange of the olefinic and carboxyl groups present at [Cd] and [Cb] respectively. This strategy involves a series of reactions whose sequence differs whether the chrysanthemal-route (Scheme 67, entry a) or the caronic-route (Scheme 67, entries b,d) is followed. These approaches could be extended by generating instead of the isobutenyl moiety a differently substituted alkenyl moiety allowing not only the synthesis from (1*S*,3*R*)-*cis*-chrysanthemic acid/esters (1*S*,3*R*)-*cis*-**1a**$_R$ either of its enantiomer (1*R*,3*S*)-*cis*-chrysanthemic acid (1*R*,3*S*)-*cis*-(**1a**$_H$) or for example (1*R*,3*R*)-*cis*-deltamethrinic acid/esters (1*R*,3*R*)-*cis*-**1f**$_R$.

This strategy offers an original solution to the most difficult “isomerization reaction” of the series since it keeps intact the relative *cis*-stereochemistry present on the starting chrysanthemic acid that other methods cannot achieve efficiently. They advantageously replace the methods that would have required (i) enantioselective epimerization at both [Cb] and [Cd] or (ii) racemization/ resolution that poorly applies to the *cis*-series.

The former strategy implies the selective reduction of the carboxy group of the (1*S*,3*R*)-*cis*-chrysanthemic acid/esters (1*S*,3*R*)-*cis*-**1a**$_R$ leading to chrysanthemal (1*S*,3*R*)-*cis*-(**45**). The key problem is to avoid the olefination reaction of the formyl group prior the isobutylene moiety present on the adjacent carbon is destroyed so competition between the two olefinic groups is avoided. One solution could be to produce an alcohol by addition

of a suitable organometallic and to generate the new [Cb-Cd] double bond after the isobutylene moiety is transformed to the carboxy group (Scheme 67, entry a).



Scheme 67. Strategies involving stereoselective formal interchange of the vinyl and carboxy groups on chrysanthemic acid/esters.

The caronic-routes requires to perform the reaction on an alkyl chrysanthemate so the transformation of the isobutylene to the carboxyl group leads to monoalkyl caronate in which the two groups on the cyclopropane are different. Selective reduction of the alkyl carboxylate ($LiBH_4$) and olefination of the hemicaronic acid (1*R*,3*S*)-(**3**$_H$) intermediate leads to (1*R*,3*S*)-*cis*-chrysanthemic acid (1*R*,3*S*)-*cis*-(**1a**$_H$) or (1*R*,3*R*)-*cis*-deltamethrinic acid/esters (1*R*,3*R*)-*cis*-**1f**$_R$ (Scheme 67, entry b).

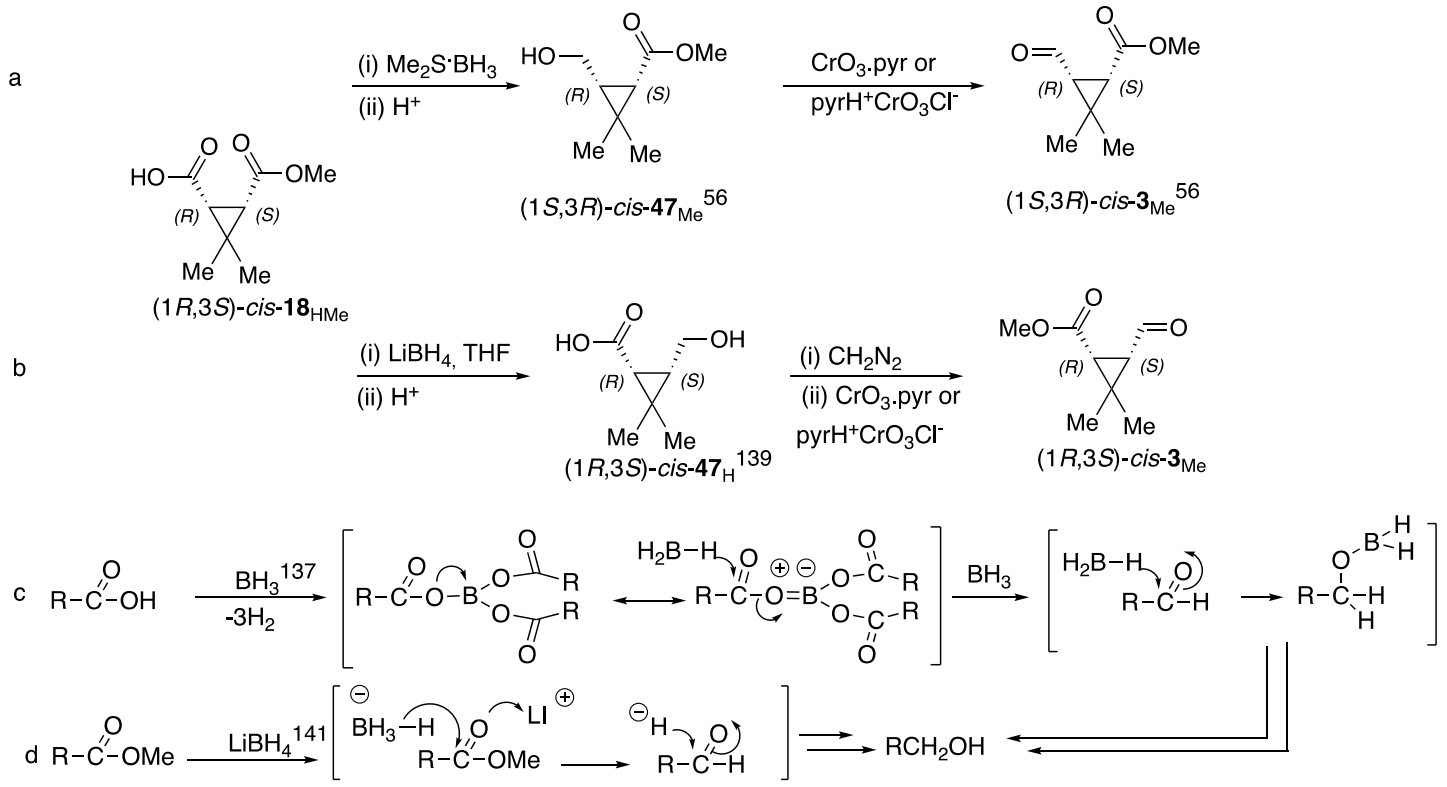
The last strategy (Scheme 67, entry c) involves as the key step the formal interchange of the alkoxy, and the hydroxyl groups present on the caarboxy groups in adjacent position on the cyclopropane ring of **18**. This has been effectively achieved on reacting mono methyl caronate *cis*-(**18**$_{MeH}$) with isobutylene to produce the dialkyl caronate bearing two different ester groups (Me, *t*-Bu) possessing orthogonal reactivity. Selective saponification of the original methyl ester using potassium hydroxide leads after acid hydrolysis the mono *t*-butyl caronate *cis*-(**18**$_{tBuH}$). Selective reduction of the resulting carboxylic acid (1*R*,3*S*)-*cis*-**18**$_{tBuH}$ and olefination of the resulting *t*-butyl hemicaronate (1*R*,3*S*)-(**3**$_{tBu}$) achieves the synthesis of the vinyl *cis*-cyclopropane carboxylate (Scheme 67, entry c).

Since the direct reduction of carboxylic acid/esters to the related aldehydes is not easy, stepwise reduction to chrysanthemol (**46**) or to the methylcarbinols **47** (Scheme 68) or to the bicyclic lactone **48** (Scheme 70, entry b) followed by their selective oxidation to chrysanthemal (**45**) or hemicaronaldehydes **3**$_R$ has been systematically used (Scheme 69, Scheme 70). This approch offers the advantage to selectively reduce either the alkyl

carboxylate or the carboxyl group of the monoalkyl caronate **18**$_{RH}$ by the selection of the proper reducing agent (BH_3 or LiBH4, respectively) as it will be discussed below.

Reduction of monomethyl caronate (**18**$_{MeH}$) occurs selectively on the carboxyl group on reaction[56,86,137-140] with borane-THF complex or better with borane-dimethyl sulfide complex that exhibits improved stability and solubility compared to the former (Scheme 68, entry a) whereas reduction takes place selectively on the methyl ester when using lithium borohydride instead (Scheme 68, entry b).[139,141]

Depending upon the case such reduction leads to the the hydroxyesters *cis*-**47**$_{Me}$ (Scheme 68, entry a),[56] the hydroxy acid *cis*-**47**$_{H}$ (Scheme 68, entry b),[139] or the bicyclic lactone **48** (Scheme 70, entry b).[56,139] The latter being easily formed in the *cis*-series in basic media from the hydroxy esters *cis*-**47**$_{R}$ or in strong acidic media from the hydroxy acid *cis*-**47**$_{H}$. The bicyclic lactone **48** is also produced from the *trans*-hydroxy esters *trans*-**47**$_{R}$ in the presence of a strong base that epimerizes at the same time at its [Cb]-carbon (Scheme 71).[142]



Scheme 68. Synthesis of methyl hemicaronate from methyl caronate involving regioselective reduction of its carboxylic acid or methyl carboxylate with diborane[56,137] and lithium borohydride[139,141] respectively.

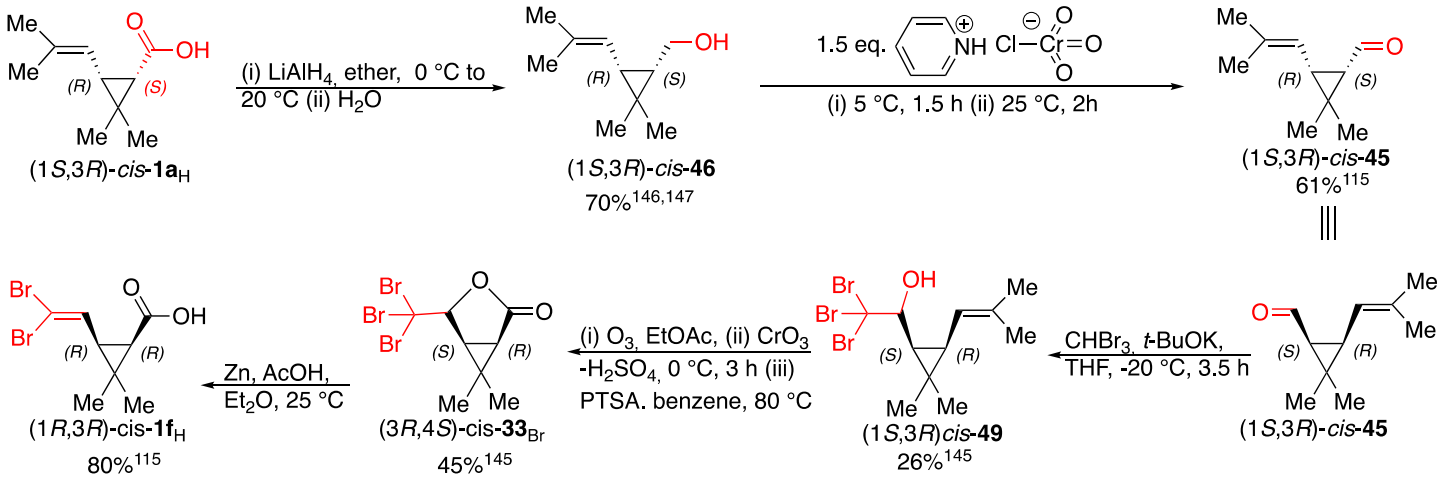
The ring opening of lactone **48** leads to the hydroxy acid *cis*-**47**$_{H}$ on reaction with potassium hydroxide and careful acidification (Scheme 70, entry b, Scheme 71). Its esterification leading to the hydroxyesters *cis*-**47**$_{R}$ has been achieved on reaction with diazomethane (Scheme 68, entry b, Scheme 70, entry a, Scheme 71) or under Mitsonobu conditions (alcohol, azodicarboxylate and triphenylphosphine). [2,143,144]

The selective reduction of the carboxylic acids to the related carbinols takes advantage of the intermediate formation of the boron carboxylate (that also produces dihydrogen, Scheme 68, entry c). It has been rationalized by delocalization of the lone pair from the oxygen to the boron Lewis acid activating thus the carbonyl group towards further reduction.[137,138]

The other approach involves lithium borohydride that transform the carboxylic acid to its lithium salt lowering its activity whereas the availability of the lithium counterion for coordination to ester, promotes its reduction especially if the reaction is performed in ether (ether > THF > 2-propanol; Scheme 68, entry d).[141]

5.3.1. Isomerization involving the intermediate formation of chrysanthemal. Thus (1*S*,3*R*)-*cis*-chrysanthemic acid (1*S*,3*R*)-*cis*-(**1a**$_H$) has been transformed to (1*R*,3*R*)-*cis* deltamethrinic acid (1*R*,3*R*)-*cis*-(**1f**$_H$) through (1*S*,3*R*)-*cis*-chrysanthemal (1*S*,3*R*)-*cis*-(**45**) (Scheme 69).[115,145] The later has been easily synthesized by reduction of (1*S*,3*R*)-chrysanthemic acid (1*S*,3*R*)-*cis*-(**1a**$_H$) to chrysanthemol (1*S*,3*R*)-*cis*-(**46**) using lithium aluminum hydride in ether[145-147] (Chapter IVa, entry 2.9)[12] then oxidized to *cis*- chrysanthemal (1*S*,3*R*)-*cis*-(**45**) (Chapter IVa, entry 2.10)[12] using the Corey Suggs reagent (pyridinium chlorochromate, 61 % yield), [115,148] or in much better yield (94%) using N-methyl morpholine N-oxide in the presence of catalytic amounts of tetrapropylammonium perruthenate (TPAP, Chapter IVa, Section 2.10.4).[12] Alternatively metal free oxidation can be performed using the Swern oxidation[149] (DMSO, oxalyl chloride, Chapter IVa, entry 2.10.3).[12]

Reaction of bromoform in the presence of potassium *t*-butoxide[145] on *cis*-chrysanthemal (1*S*,3*R*)-*cis*-(**45**) affords in poor yield (26 %) the tribromomethyl alcohol **49** (Scheme 69). The later on ozonolysis in ethyl acetate followed by treatment with the Jones reagent (chromium trioxide in sulfuric acid)[150] delivers a mixture of gamma-hydroxy carboxylic acid **28**$_H$ and the related bicyclic lactone **33**$_{Br}$ resulting from its sulfuric acid promoted intramolecular esterification reaction (Scheme 69).[145] Subsequent acidic treatment of this mixture (PTSA, benzene, 80 °C) produce more bicyclic lactone **33**$_{Br}$ that on reaction with zinc delivers, after acid hydrolysis, (1*R*,3*R*)-*cis*-deltamethrinic acid (1*R*,3*R*)-*cis*-(**1f**$_H$) (Scheme 69).



Scheme 69. Enantioselective synthesis of (1*R*)-*cis*-deltamethrinic acid from (1*S*)-*cis*-chrysanthemic acid by formal exchange of their carboxy and vinylic moieties.[115,145-147]

5.3.2. Isomerization involving the intermediate formation of monoalkyl caronates. Since monoalkyl caronates **18**$_{RH}$ have been used as intermediates, we disclose a brief historical background about their synthesis. Originally, chrysanthemic acid (**1a**$_H$),[46,151] pyrethric acid (**1b**$_H$)[29] and their mixtures isolated from natural sources from pyrethrin I and pyrethrin II, have been oxidized using potassium permanganate to *trans*-caronic acid *trans*-(**18**$_{HH}$) and used for their structure determination through correlations.[152]

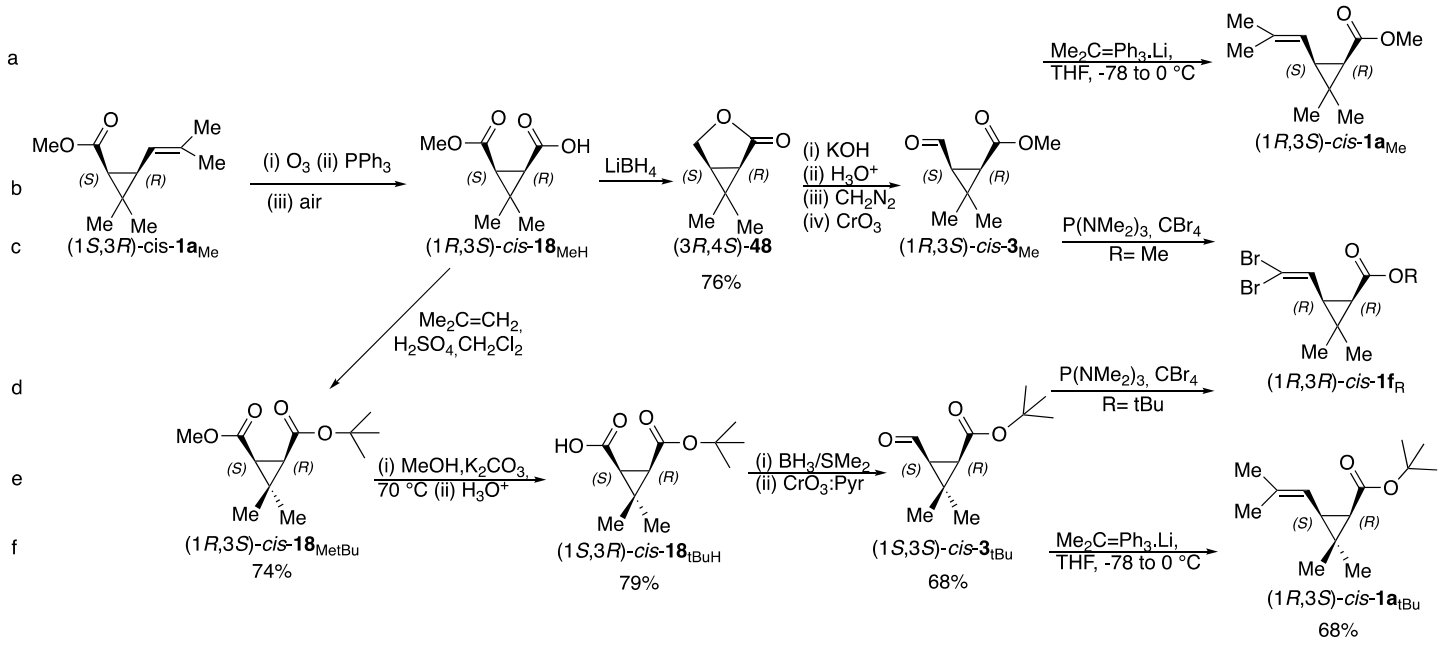
Later, racemic and (1*S*,3*S*)-*trans* methyl chrysanthemate-(**1a**$_{Me}$) has been transformed to racemic and (–)-(1*S*,3*S*) methyl caronate *trans*-(**18**$_{MeH}$) respectively on sequential reaction with osmium tetroxide-sodium periodate in dioxane-water, then air oxidation of the resulting methyl hemicaronate (left exposed to air for 2

weeks, 85% yield).[60] Their saponification using sodium hydroxide in methanol and acid hydrolysis result in the formation of the corresponding *trans*-caronic acid.[60]

Methyl *cis*-caronate (1*R*,3*S*)-*cis*-(**18**$_{MeH}$) has been used as a key intermediate in one of the transformation of methyl (1*S*,3*R*)-*cis*-chrysanthemate (1*S*,3*R*)-*cis*-(**1a**$_{Me}$) to alkyl (1*R*,3*S*)-*cis*-chrysanthemates (1*R*,3*S*)-*cis*-**1a**$_{R}$ (Scheme 70, entries a,f) and alkyl deltamethrinates (1*R*,3*R*)-*cis*-**1f**$_{R}$ (Scheme 70, entries c,d).

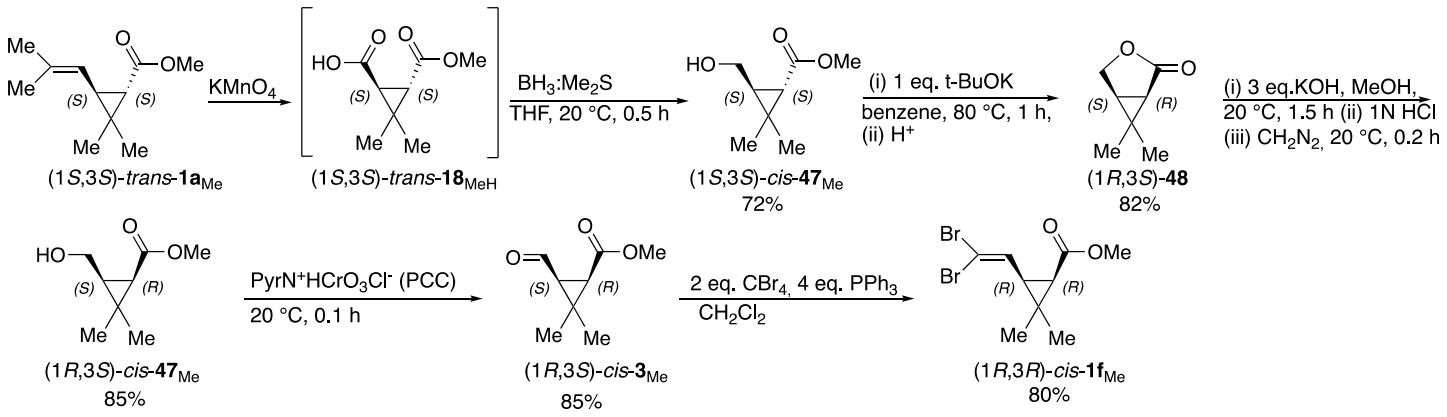
This transformation has been achieved through sequential oxidation of the isobutenyl moiety of (1*S*,3*R*)-*cis*-(**1a**$_{Me}$) leading to methyl (1*R*,3*S*)-*cis*-caronate (1*R*,3*S*)-*cis*-(**18**$_{MeH}$) that is transformed to methyl (1*R*,3*S*)-*cis*-hemicaronate (1*R*,3*S*)-*cis*-(**3**$_{Me}$) on reduction, as the key step, of its ester moiety with lithium borohydride (Scheme 70, entry b),[139] lactone ring opening,[153] followed by esterification (CH_2N_2)[153] and oxidation of the alcohol[153] to the aldehyde using chromium reagents (CrO_3·2pyr. or $PyrH^+CrO_3Cl^-$).[56,153]

The concurrent approach (Scheme 70, entry e) to the above (Scheme 70, entry b), implies the interchange of the ester and acid groups on the adjacent [Cb] and [Cd] carbons on the cyclopropane ring. Thus, the mixed *t*-butyl methyl (1*R*,3*S*)-*cis*-caronate *cis*-(**18**$_{MetBu}$) has been synthesized on reaction of monomethyl caronate (1*R*,3*S*)-*cis*-(**18**$_{MeH}$) with isobutylene [56] and its selective saponification with potassium carbonate in hot methanol delivers, after acidification, the mono *t*-butyl caronate (1*S*,3*R*)-*cis*-(**18**$_{tBuH}$). Its reduction with boron hydride-dimethylsulfide[56,139] takes place on the carboxylic acid moiety and delivers after oxidation with the Collins reagent delivers *t*-butyl (1*R*,3*S*)-hemicaronate (1*R*,3*S*)-*cis*-(**3**$_{tBu}$) (Scheme 70, entries e).[56]



Scheme 70. Synthesis of (1*R*)-*cis*-chyrsanthemates and (1*R*)-*cis*-deltamethrinates from methyl (1*S*)-*cis*-chyrsanthemate and implying the intermediate formation of alkyl caronates (Scheme adapted from different results disclosed in references).[56,139]

A related approach has been used to produce methyl (1*R*,3*R*)-deltamethrinate (1*R*,3*R*)-(**1f**$_{Me}$) from methyl (1*S*,3*S*)-*trans*-chrysanthemate (**1a**$_{Me}$) (Scheme 71).[142] For that purpose monomethyl (1*S*,3*S*)-caronate (1*S*,3*S*)-(**18**$_{MeH}$) has been reduced to the methyl *trans*-hydroxymethyl-ester (1*S*,3*R*)-(**47**$_{Me}$) on reaction with borane-dimethylsulfide complex. Reaction of (1*S*,3*R*)-**47**$_{Me}$ with potassium *t*-butoxide in benzene at reflux for 1 h allows the epimerization at [Cb] and formation of lactone **48**. The following steps resemble those disclosed in Scheme 70.[142]



Scheme 71. Synthesis of methyl (1*R*)-*cis*-deltamethrinate from methyl (1*S*)-*trans*-chyrsanthemate and implying the intermediate formation of methyl caronate.[142]

5.4. Isomerization involving a prochiral intermediate

5.4.1. Strategies to perform isomerization of any stereoisomer of chrysanthemic acid through a prochiral intermediate. This route, that has not yet been fully exploited, involves caronic anhydride (**20**) a meso-*cis*-intermediate that can be generated from any stereoisomer of chrysanthemic acid/lower esters **1a**$_R$ or their mixture (Scheme 72, routes a to d) and is able to deliver selectively racemic *cis*-, racemic *trans*- as well as each of the four enantiomers of chrysanthemic acid/lower esters. In fact, most of the routes involving caronic acids and anhydride have not been previously proposed but the individual steps proposed in Chapter VI have been already successfully achieved.

These approaches allow, among others, the synthesis of alkyl (1*R*,3*R*)-deltamethrinates **1f**$_R$ (Scheme 72, routes a-f, g to i or h to j) and alkyl (1*R*,3*R*)-chrysanthemates **1a**$_R$ (Scheme 72, routes g to k; h to l and m) which are precursors of the most active insecticides for agricultural or domestic uses.

The processes disclosed in Scheme 72 have in common the:

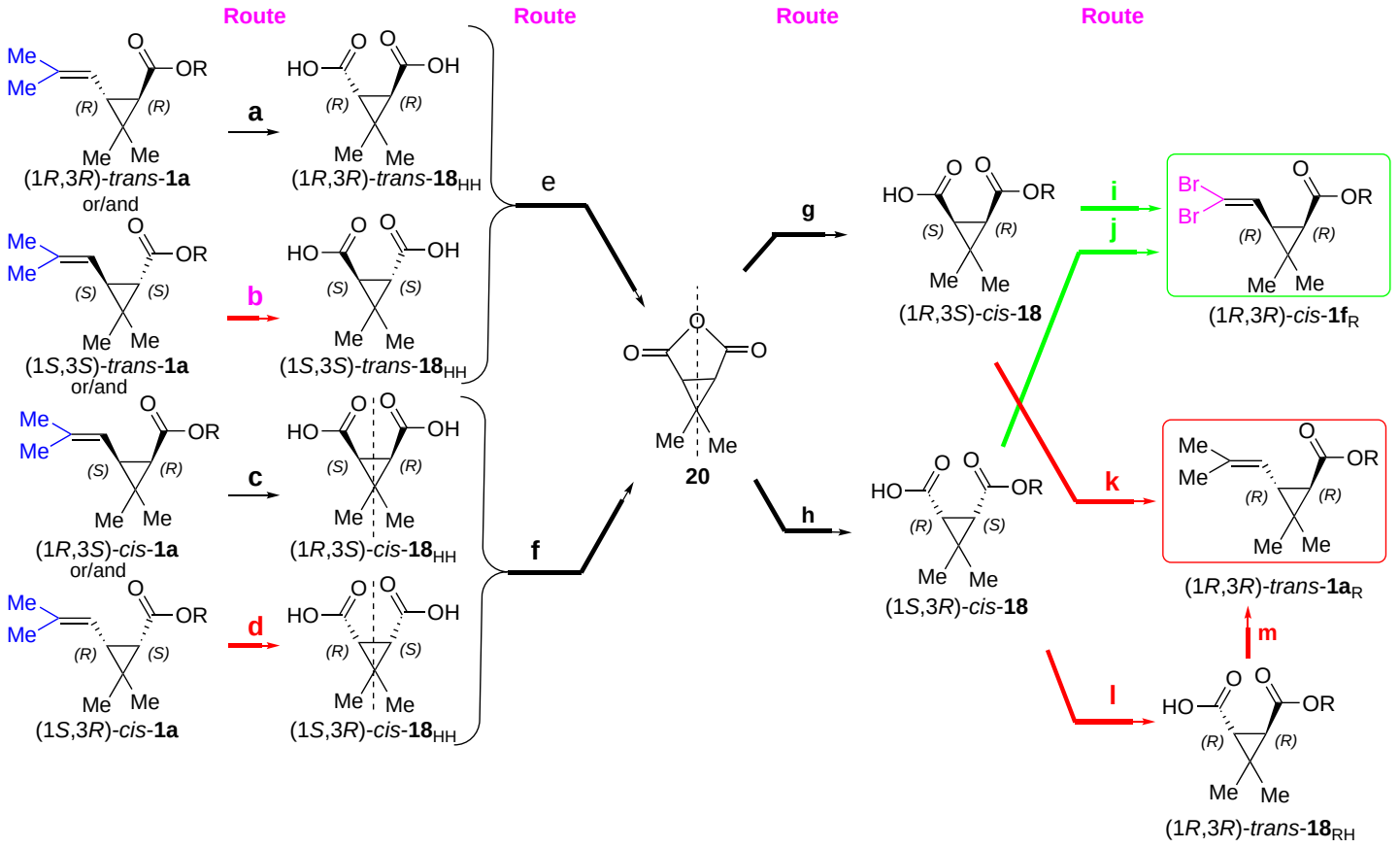
(i) oxidation of the different stereoisomers of chrysanthemic acid that produce caronic acid (**18**$_{HH}$) (Scheme 72, entries a-d),

(ii) anhydride-forming reaction leading to caronic anhydride (**20**) (Scheme 72, entries e,f) that requires the trans/cis-epimerization in case of the (1*R*,3*R*)- and (1*S*,3*S*)-*trans*-caronic acid stereoisomers (Scheme 72, route f),

(iii) enantioselective anhydride ring opening leading either to mono-alkyl (1*R*,3*S*)-*cis*- or (1*S*,3*R*)-*cis*-caronates *cis*-**18**$_{RH}$,

(iv) transformation to deltamethrinic acid/esters **1f**$_R$ on selective reduction of the carboxylic group of alkyl (1*R*,3*S*)-*cis*-caronates (1*R*,3*S*)-*cis*-**18**$_{RH}$ to the formyl group of hemicaronates **3**$_R$ (Scheme 72, entries g then I; (see below Scheme 80), or on selective reduction of the carboxylate group of alkyl (1*S*,3*R*)-*cis*-caronates (1*S*,3*R*)-*cis*-**18**$_{RH}$ to the formyl group of hemicaronates **3**$_R$ (Scheme 72, entries h then j; see Scheme 80 below),

(v) transformation to (1*R*,3*R*)-*trans*-chrysanthemic acid/esters **1a**$_R$ requires in complement epimerization at [Cd] starting from (1*R*,3*S*))-*cis*-**18**$_{RH}$ that is expected to take place: (a) alpha to the formyl group of the intermediates alkyl (1*R*,3*S*)-*cis*-hemicanonates (1*R*,3*S*)-**3**$_R$ (Scheme 72, entries g then k; see Scheme 80 below) or (b) according to the process disclosed in Scheme 19, entry c; Scheme 21, entry a, see Scheme 80 below) otherwise *cis*/*trans*-isomerization must be carried out by epimerization at [Cb] alpha of the ester group of (1*S*,3*R*)-*cis*-caronate (1*S*,3*R*)-*cis*-**18**$_{RH}$ (Scheme 72, entries h then l).



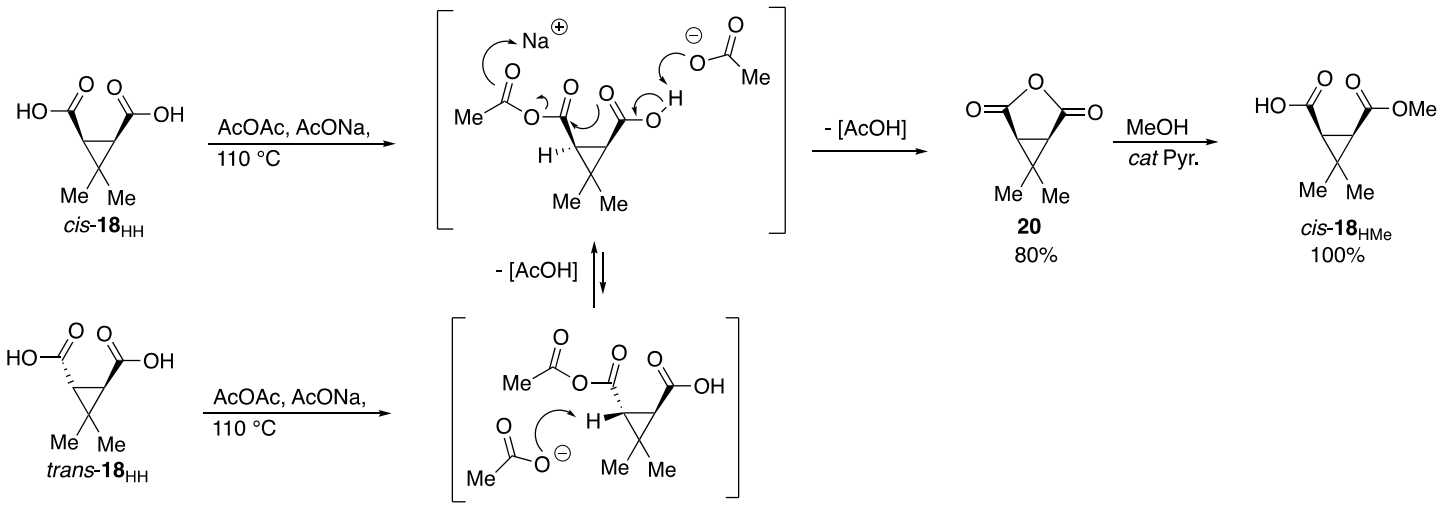
Scheme 72. Strategy proposed to synthesize any enantiomer of chrysanthemic acid/ester and (1*R*)-cis-deltamethrinic acid/esters from any enantiomer of chrysanthemic acid/ester involving the eintermediate formation of meso-caronic anhydride.

The following sections describe the different reactions that will be used in selected orders to perform each transformation described in Scheme 72).

5.4.1.1. Synthesis of caronic anhydride from chrysanthemic acid. The formation of caronic anhydride **20** takes advantage of:

(i) the easy access to caronic acid (**18**$_{HH}$) (Scheme 72, entries a-d) by oxidative cleavage of the [Ce=Cf] double bond of chrysanthemic acid/esters (Scheme 27). It has been achieved either by ozonolysis followed by (i) rapid oxidation with potassium permanganate ((i) O_3 (ii) MnO_4K: *cis*, R: *t*-Bu, 98%/85% yield; *cis*, R: Me, 83%/77% yield)[86] or (ii) slow oxidation with air[60] followed by transformation of the esters by saponification then acid treatment for Me or Et esters or in acidic media for *t*-butyl esters,

(ii) cyclization of the caronic acid (Scheme 72, entries e,f). This transformation is easy in case of the *cis*-stereoisomer *cis*-**18**$_{HH}$ but requires more drastic conditions in case of the *trans*-caronic acid *trans*-(**18**$_{HH}$). The latter reaction proceeds at high temperature through the mixed anhydride (Ac_2O, 220 °C, 76% yield) [86] or at much lower temperature if the reaction is carried out in the presence of sodium acetate that plays the role of a base and favors epimerization and cyclization reactions through a push-pull mechanism disclosed in Scheme 73 (Ac_2O, AcONa, 110 °C, 80% yield).[140]



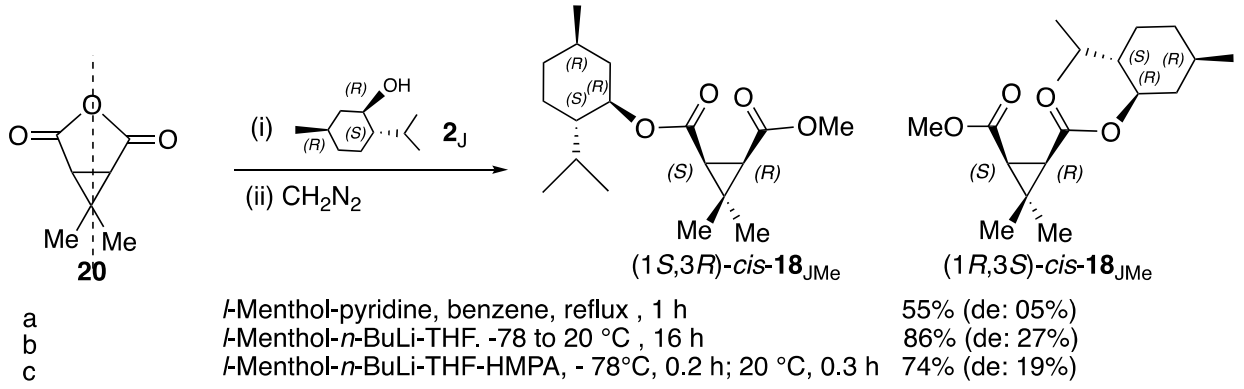
Scheme 73. Transformation of *cis*- and *trans*-caronic acids to *meso*-caronic anhydride and its transformation to monomethyl *cis*-caronate.

5.4.1.2. Desymmetrization of caronic anhydride to pyrethroids. 5.4.1.2.1. Desymmetrization of caronic anhydride involving resolution of monomethyl *cis*-caronate and production of a single enantiomer of monomethyl *cis*-caronate. Reaction of caronic anhydride (**20**) with methanol in the presence of pyridine at 20 °C for 16 h[140] or with 1 equivalent of sodium methylate in methanol (0 °C, 0.1 h) followed by acid treatment[56] affords racemic monomethyl *cis*-caronate (**18**$_{MeH}$) in quantitative yield.[140]

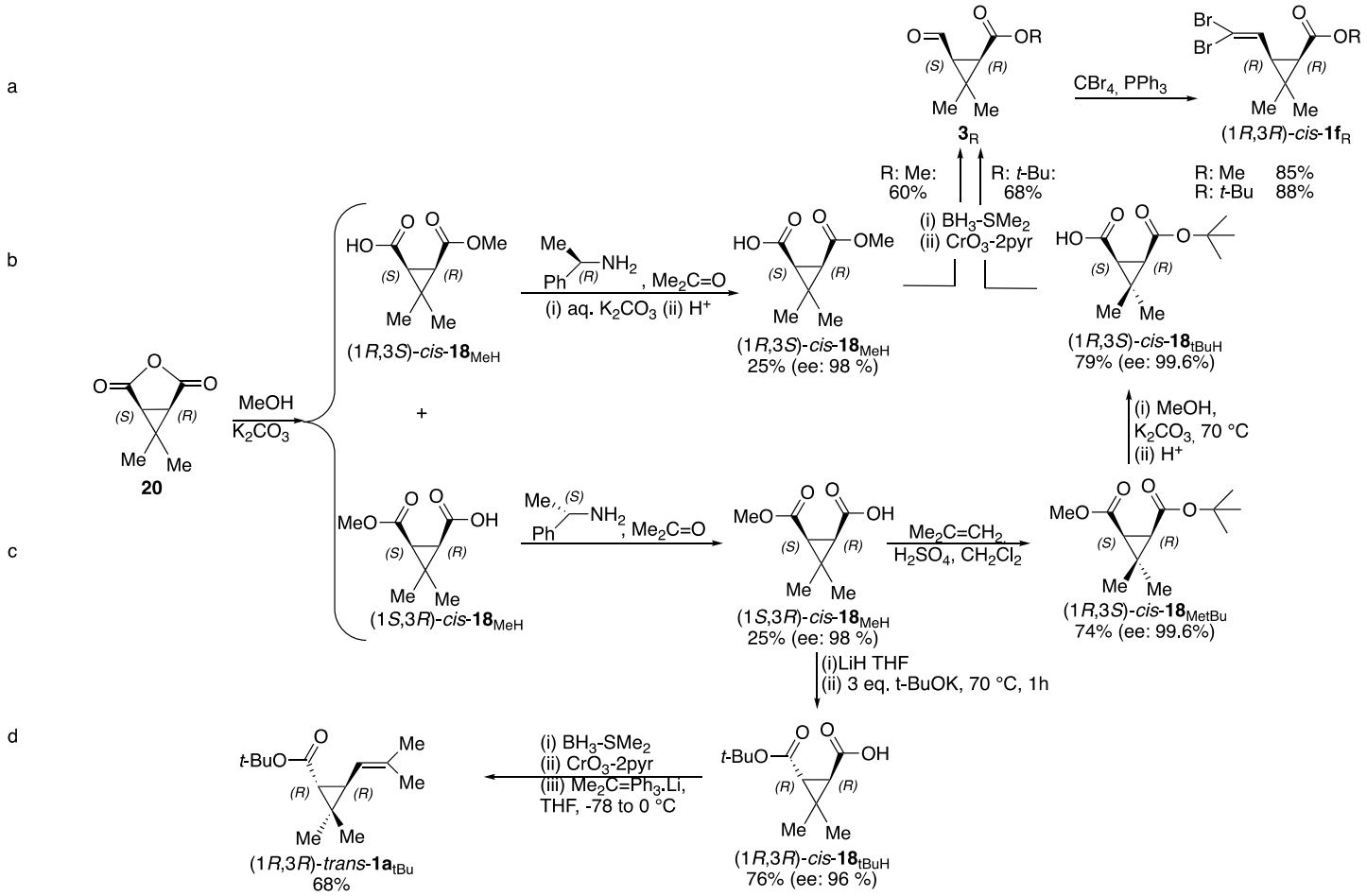
Reaction of caronic anhydride (**20**) with chiral alcohols such as (−)-menthol delivers diastereoisomeric mixtures of caronic mono mentholate (**18**$_{JH}$) (Scheme 74).[86] performing the reaction in the presence of pyridine in benzene affords an extremely poor diastereoselection (Scheme 74, entry a) whereas a slightly better diastereoselection is achieved using lithium mentholate in THF at low temperature (Scheme 74, entry b).[86] Performing the reaction in the presence of HMPA proved to be deleterious (Scheme 74, entry c).[86] Caronic anhydride (**20**) ring opening performed with lithium (+)(*R*)-α-methyl benzylamide in THF (-78 °C) also leads to a mixture of stereoisomers in good yield but poor diastereoselection (88%, de 24%).[86]

Monomethyl (1*R*,3*S*)-*cis*-caronate (1*R*,3*S*)-*cis*-(**18**$_{MeH}$) has been isolated on resolution of the racemate with (+)(*R*)-alpha-methylbenzylamine in acetone followed by base and acid treatment (25% unoptimized).[56] The residue after acid treatment and resolution with (–)-(*S*)-α-methylbenzylamine in acetone and base and acid work up affords monomethyl (1*S*,3*R*)-*cis*-caronate (1*S*,3*R*)-*cis*-(**18**$_{MeH}$) in similar yield (25%; Scheme 75).[56] The latter has been transformed to its pseudo-enantiomeric mono-*t*-butyl (1*R*,3*S*)-*cis*-caronate (1*R*,3*S*)-*cis*-(**18**$_{tbuH}$) through the *t*-butyl,methyl caronate *cis*-(**18**$_{Metbu}$) (Scheme 68)[56] as disclosed in Scheme 70.

Monomethyl (1*S*,3*R*)-*cis*-caronate (1*S*,3*R*)-*cis*-(**18**$_{MeH}$) and mono-*t*-butyl (1*R*,3*S*)-*cis*-caronate (1*R*,3*S*)-*cis*-(**18**$_{tbuH}$) generated from each of the two enantiomeric methyl caronates, through the routes disclosed in entries b and c respectively, have been transformed to the corresponding methyl and *t*-butyl deltamethrinates (1*R*,3*R*)-*cis*-(**1f**$_{tBu}$) possessing different ester groups but the same stereochemistry (Scheme 75, entry a).[56]



Scheme 74. Ring opening of meso-caronic anhydride by *l*-menthol.

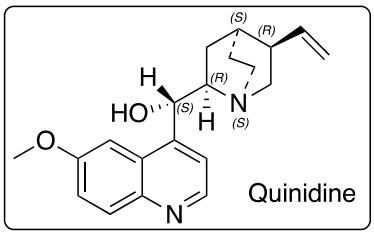


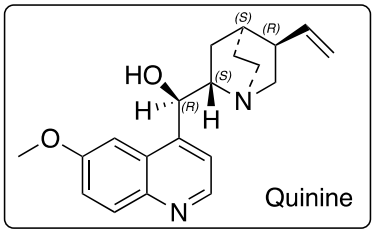
Scheme 75. Resolution of methyl-*cis*-caronates and enantioselective synthesis of alkyl (1*R*)-*trans*-chrysanthemates and (1*R*)-*cis*-deltamethrinates.[56]

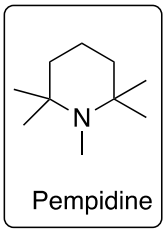
Monomethyl (1*S*,3*R*)-*cis*-caronate (1*S*,3*R*)-*cis*-(**18**$_{MeH}$) has been also transformed to *t*-butyl *trans*-(1*R*,3*R*)-chrysanthemate *trans*-(1*R*,3*R*)-(**1a**$_{tBu}$) through mono *t*-butyl *trans*-(1*R*,3*R*)-caronate *trans*-(1*R*,3*R*)-(**18**$_{tBuH}$) generated regioselectively on reaction of potassium *t*-butylate, in refluxing THF, on the lithium methyl (1*S*,3*R*)-*cis*-caronate (**18**$_{MeLi}$) (Scheme 75, entries c,d).[56] In this process potassium *t*-butylate epimerizes the monoalkyl caronates regioselectively by reacting on the cyclopropane carbon acid bearing the ester group and at the same

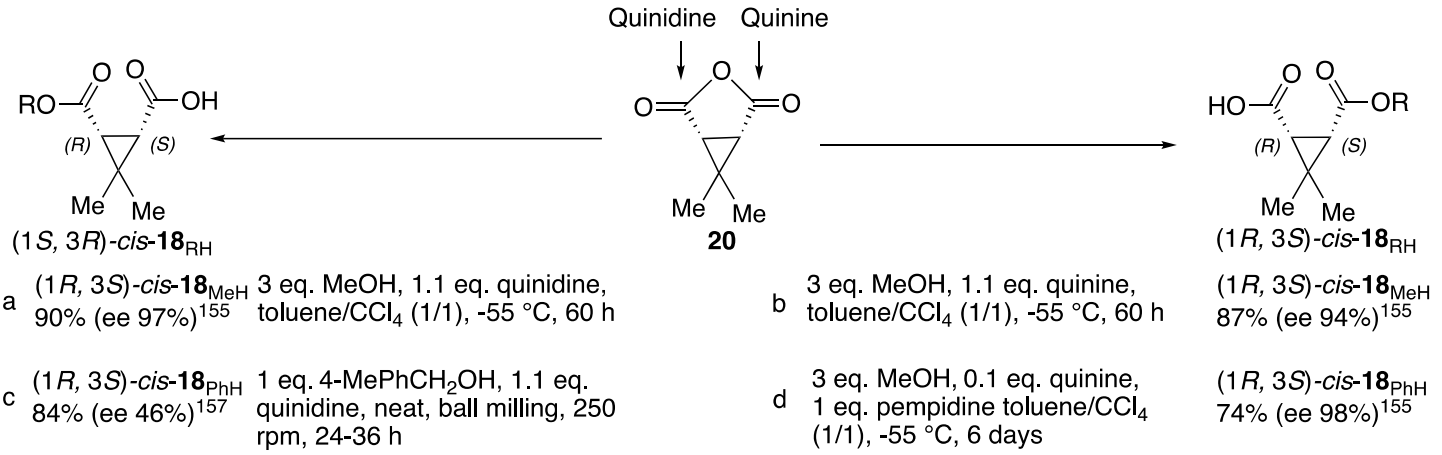
time exchange with the methyl ester to generate the *t*-butyl ester *trans*-(1*R*,3*R*)-**18**$_{tBuH}$ (Scheme 75, entries c,d).[56]

5.4.1.2.2. Asymmetric desymmetrization of caronic anhydride involving enantioselective ring opening using a chiral catalyst. [154] Performing the anhydride ring opening of **20** with an alcohol such as methanol or a benzyl alcohols (Scheme 72, entries g,h) in toluene/carbon tetrachloride in the presence of a chiral amine, such as quinine or quinidine, affords the monoester **18**$_{RH}$ with high asymmetric induction at the condition that the reaction is carried out at low temperature but in such case it requires long reaction times (up to 60 h, Scheme 76).[155,156]





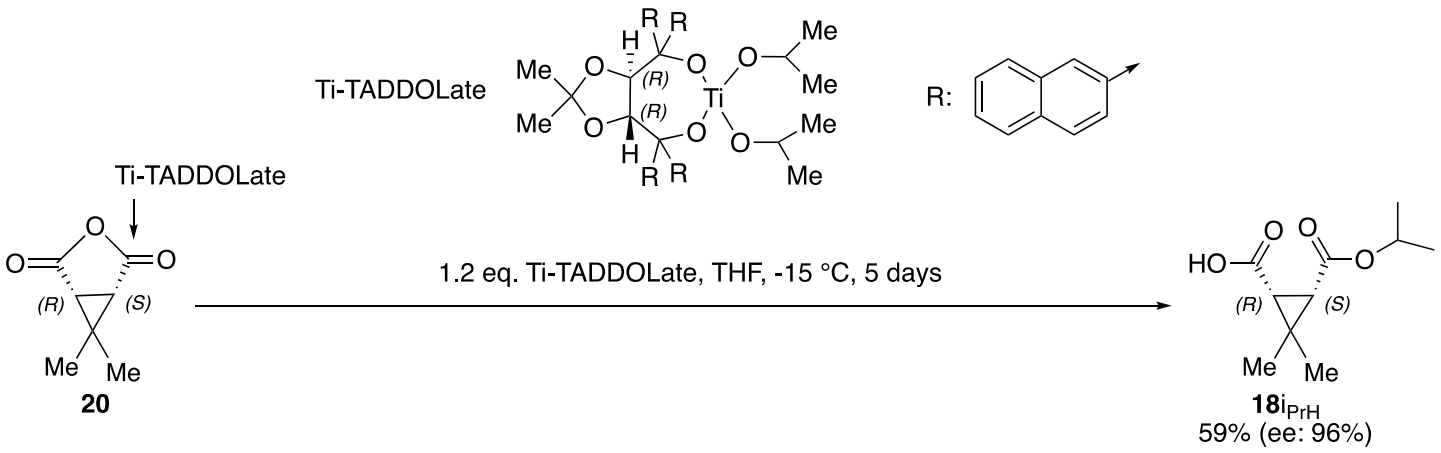




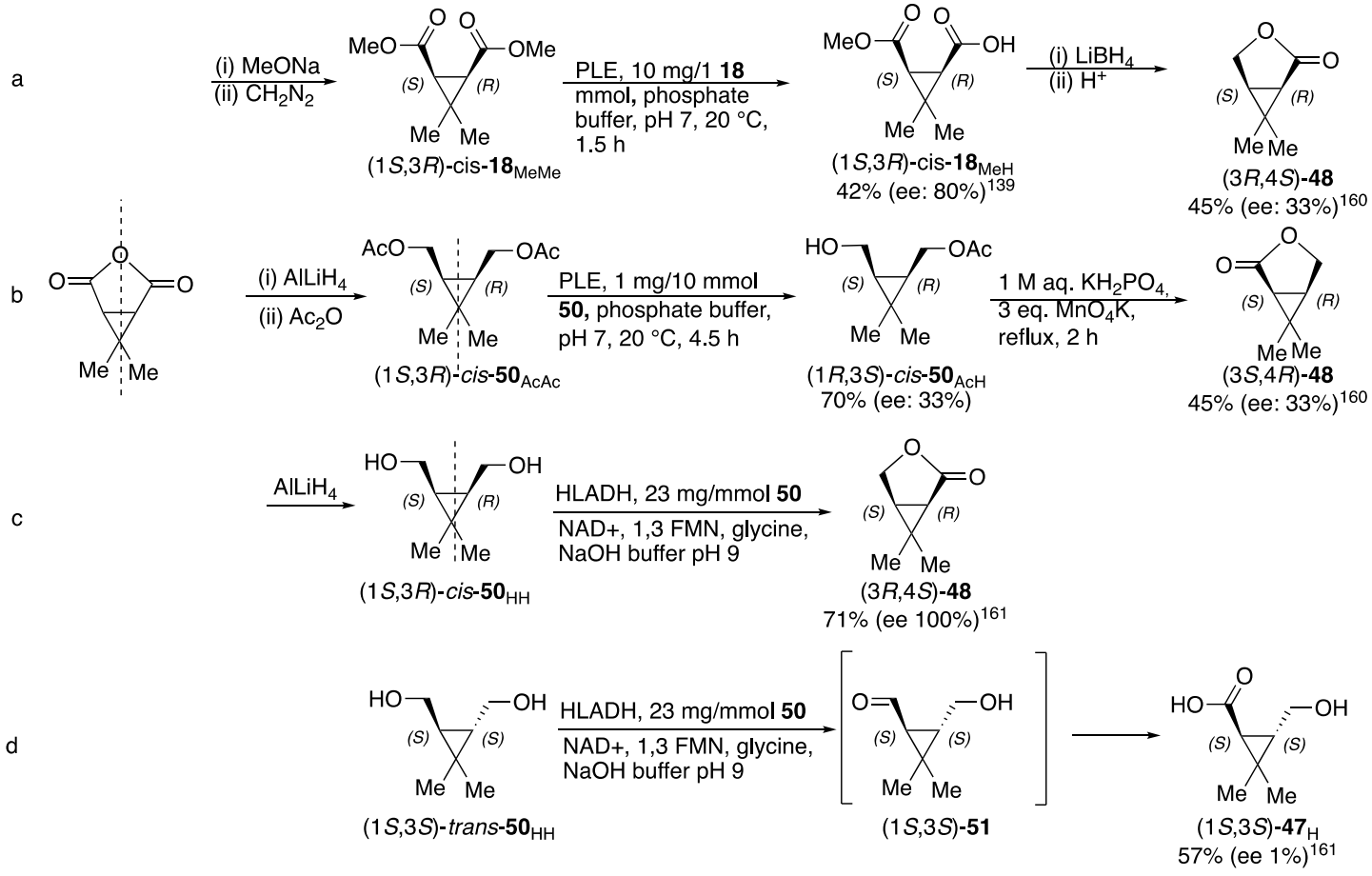
Scheme 76. Enantioselective ring opening of meso-caronic anhydride involving methanol in the presence of a chiral enantiopure amine.[155-157]

The reaction has been carried out with a stoichiometric (Scheme 76, entries a,b,c) as well as catalytic amounts (Scheme 76, entry d) of such chiral amines with similar good yield and high enantiomeric excess. In the latter case however, the reaction requires the presence of one equivalent of a hindered amine such as pimpidine (1,2,2,6,6-pentamethylpiperidine) and is particularly slow (six days, Scheme 76, entry d). Caronic anhydride (**20**) has been also reacted with p-methylbenzylalcohol with 1.1 equivalent of quinidine using a ball milling procedure but although the yield of *p*-methylbenzyl caronate (1*R*,3*S*)-*cis*-(**18**$_{PhH}$) is high, its enantiomeric excess is poor (ee: 46% Scheme 76, entry c).[157]

A related earlier reaction required[158,159] sub-stoichiometric amounts (1.2 eq.) of Ti-TADDOLate, bearing beta-naphtyl groups substituents and delivered isopropyl (1S,3*R*)-cis-caronate (**18**$_{iPrH}$) caronate with very high enatioselectivity (96%) but after quite long reaction time (5 days) and quite modest yield (59%, Scheme 77), the poorer of the series of meso-anhydride ring opening.[158,159]



Scheme 77. Enantioselective ring opening of meso-caronic anhydride involving TADDOLates.[158]



Scheme 78. Enantioselective enzymic reactions involving caronic anhydride and related compounds.[161,139,160]

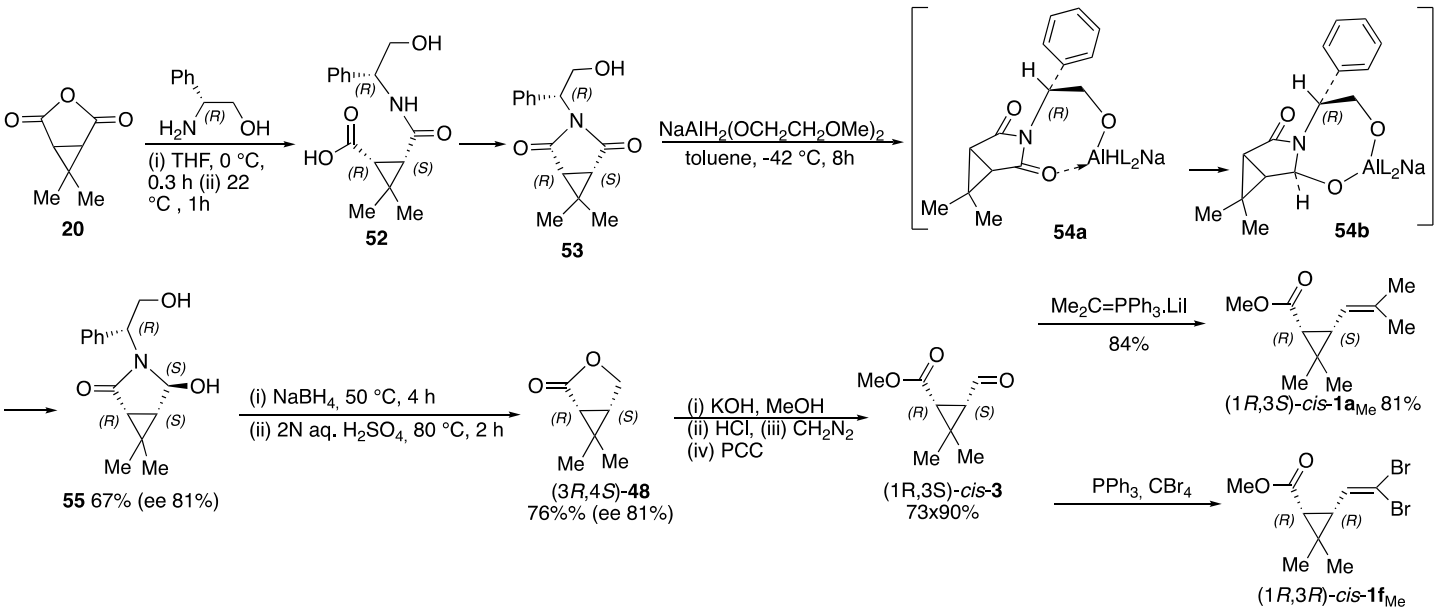
Enantiopure monomethyl *trans*-caronate (1*R*,1*R*)-*trans*-(**18**$_{MeH}$) has been isolated almost enantiomerically pure (ee: 95%) on reaction of a mixture of racemic cis and *tran* -dimethyl caronate rac-(**18**$_{MeMe}$) with porcine liver esterase (PLE, Scheme 72, entries g,h).[139,160] Reaction of dimethyl meso-*cis*-caronate (*cis*-**18**$_{MeMe}$) with the same esterase leads to monomethyl (1*S*,3*R*)-*cis*-caronate (**18**$_{MeH}$) in modest yield and reasonably good

enantiomeric excess (42% yield, ee 80%, half time of 100 min, Scheme 78, entry a).[139] The reaction rate is pH-dependant and occurs with half time of 50 min. at pH 7 (50% yield, ee 70%).[139]

PLE has been also used to desymmetrize meso-*cis*-1,2-bis(acetoxymethyl)-2,2-dimethylcyclopropane (1*S*,3*R*)-*cis*-(**50**$_{AcAc}$) available on reduction of caronic anhydride (**20**) or meso-*cis*-dimethyl caronate cis-(**18**$_{MeMe}$) with lithium aluminum hydride followed by esterification using acetic anhydride.[160] However the results are far from satisfactory since the enantiomeric excess is poor (30%; Scheme 78, entry b). The synthesis of the bicyclic lactone (3*S*,4*R*)-**48** from (1*R*,3*S*)-l-(acetoxymethyl)-2-(hydroxymethyl)-2,2-dimethylcyclopropane (**50**$_{AcH}$) using potassium permanganate in buffered media is particularly interesting (Scheme 78, entry b). [160]

Last but not least, *cis*-2,2-dimethyl-l,2-bis(hydroxymethyl)cyclopropane *cis*-(**50**$_{HH}$) (Scheme 78, entry c) has been selectively mono-oxidized by *horse liver alcohol dehydrogenase* (HLADH) to the (3*R*,4*S*)-bicyclic lactone (3*R*,4*S*)-(**48**) in good yield and extremely high enantiomeric excess and transformed to methyl (1*R*,3*S*)-*cis*-chrysanthemate (1*R*,3*S*)-*cis*-(**1a**$_{Me}$) (Scheme 78, entry c).[161] Oxidation also takes place on its *trans*-stereoisomer *trans*-(**50**$_{HH}$) delivering first the hydroxyaldehyde (**51**) then the *trans*-hydroxyacid (**47**$_{H}$) (Scheme 78, entry d). Its yield is poor and the enantiomeric excess symbolic. [161]

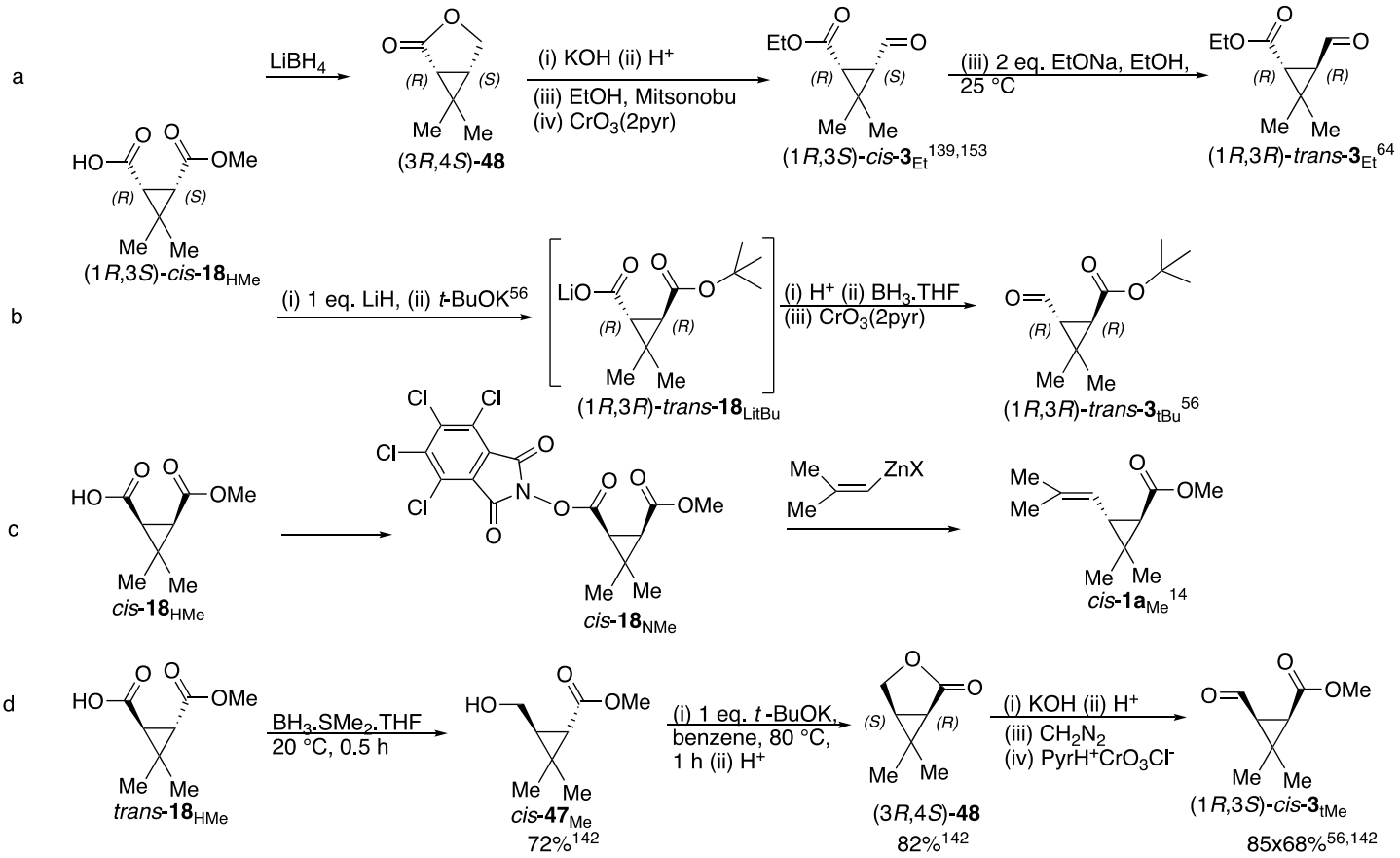
5.4.1.2.3. Desymmetrization of caronic anhydride through a chiral imide using an achiral reagent. A more complex process has been used to desymmetrize caronic anhydride (**20**) through the asymmetric reduction of its imide (**53**) derived from (*R*)-2-phenyl-2-amino-ethanol (ee: 81%; Scheme 79).[162] Among the various reagents screened, aluminum hydrides containing two active hydrides such as sodium diethyl aluminum hydride and especially sodium bis(2-methoxyethoxy)aluminum hydride at low temperature provide high yield of the hydroxy pyrrolidone **(55**) after acid treatment (Scheme 79).[162] Subsequent reduction with sodium borohydride and acid hydrolysis delivers the (3*R*,4*S*)-lactone (1*R*,3*S*)-(**48**) in good yield and reasonably high enantioselectivity (ee: 81%; Scheme 79).[162] Transformation of the latter to methyl (1*R*,3*S*)-*cis*-chrysanthemate (1*R*,3*S*)-*cis*-(**1a**$_{Me}$) and methyl (1*R*,3*R*)-*cis*-deltamethrinate (1*R*,3*R*)-*cis*-(**1f**$_{Me}$) has been achieved using the related Wittig reactions (Scheme 79).



Scheme 79. Enantioselective ring opening of caronic anhydride through a chiral imide using an achiral reagent.
162

5.4.2. Synthesis of pyrethroids involving formal epimerization of *cis*- and *trans*- mono-alkyl caronates. The procedures disclosed above allow access to monoalkyl (1*R*,3S)-*cis*-caronates (1*R*,3*S*)-*cis*-**18**$_{RH}$ and monoalkyl (1*S*,3*R*)-*cis*-caronates (1*S*,3*R*)-*cis*-**18**$_{RH}$. Access to (1*R*,3RS)-*trans*-chrysanthemates (1*R*,3*R*)-*trans*-**1a**$_R$ and to (1*R*,3*R*) *cis*-deltamethrinate *cis*-**1f**$_R$ has been then achieved using various reactions and reagents

We have gathered in this section without further discussions some of such transformations (Scheme 80).[139,153,56,14,142]



Scheme 80. Summary of stereo- and enantioselective transformations of monomethyl *cis*- and *trans*-caronates.[14,56,142]

5.5. Racemization of chrysanthemic acid and related compounds

Racemization of chrysanthemic acid and related esters has been a solution proposed to reuse (1*S*,3*S*)-*trans*-chrysanthemic acid (1*S*,3*S*)-*trans*-(**1a**$_H$) recovered from resolution of a racemic mixture of *rac*-*trans*-**1a**$_H$ to produce for example (S,1*R*,3*R*)-bioallethrin (**1a**$_B$) and therefore to get some more (1*R*,3*R*)-*trans*-chrysanthemic acid (1*R*,3*R*)-*trans*-(**1a**$_H$) after subsequent resolution. The whole process could be repeated again and again until it is no longer economic.

Under the most suitable approaches listed below, it offers a shorter solution than specific epimerization at each of its [Cb] and [Cd]-carbons.

The same has been performed, but to a lower extent, with (1*S*,3*R*)-*cis*-chrysanthemic acid (1*S*,3*R*)-*cis*-(**1a**$_H$) to transform it to (1*R*,3*S*)-*cis*-chrysanthemic acid (1*R*,3*S*)-*cis*-(**1a**$_H$) one of the precursors of (S,1*R*,3*R*)-deltamethrin (**1f**$_F$). This has been proved to be more difficult since often racemization reactions have been carried out under thermodynamic controlled conditions that favors the formation of the racemic-*trans*-stereoisomer instead.

In each case the racemization can be carried out, as proof of concept, on any enantiomer of *cis*- or *trans*-chrysanthemic acid/esters or their mixture and therefore we have indistinctly disclosed below the racemization of any enantiomer to concentrate more on the strategy used for that purpose.

Racemization reaction should produce a 1/1-mixture of an enantiomeric pair. The reaction carried out under thermodynamic control leads to the racemic mixture of the *trans*-stereoisomers wathever is the stereochemistry of the starting material otherwise racemic mixture of *trans*- and *cis*-stereoisomers in variable amounts are produced.

Anyhow it must be recalled that the processes whose concepts are disclosed in Scheme 72 and presented in specific cases in Scheme 75[56] and Scheme 80[14,56,139,142,153] could be easily adapted to the synthesis of racemic *trans* or racemic *cis*-chrysanthemates **1a**$_R$ or pyrethroates **1**$_R$ from caronic anhydride (**20**) omitting its enantioselective ring opening[56,86,140] (Chapter IVb, at the beginning of Section 5.4.1.2.1). Otherwise, this racemization reaction has been achieved by random metallations at both [Cb] and [Cd] or by cyclopropane ring opening/ring closure involving the [Cb-Cd] bond (Scheme 60, entry d). Racemization has been either achieved in a single pot and in a single step under thermodynamically controlled conditions (Chapter IVb, Section 5.5.1.2) or under kinetic control (Chapter IVb, Section 5.5.2) as it will be reported.

5.5.1. Racemization of enantiomerically pure *trans*-chrysanthemic acid/lower esters and related acid chlorides leading to racemic *trans*-chrysanthemic acid/lower esters and related racemic *trans*-acid chlorides

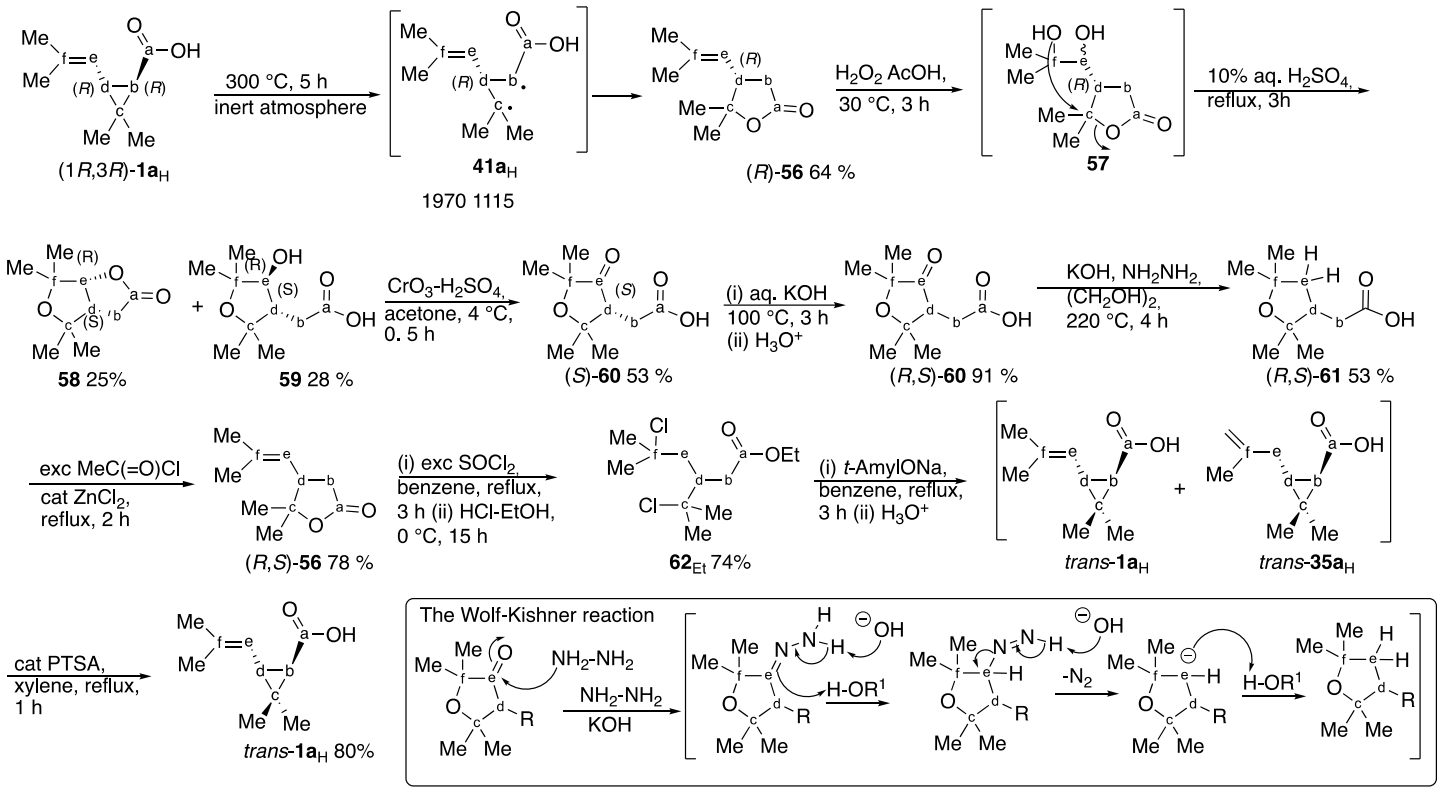
5.5.1.1. Racemization involving metalation reactions. Conversion of (1*R*,3*R*)-*trans*-chrysanthemic acid *trans*-(1*R*,3*R*)-(**1a**$_H$) to *rac*-*trans*-chrysanthemic acid *trans*-(**1a**$_H$) has been achieved,[130] as a model for racemization of its enantiomer *trans*-(1*S*,3*S*)-**1a**$_H$. The process is long and involves the intermediate formation of enatiomerically pure pyrocine on thermolysis,[130] its racemization[130] and its transformation to *rac*-*trans*-chrysanthemic acid *trans*-(**1a**$_H$)[163-165] (Scheme 81).

The conversion of chrysanthemic acid (1*R,3R*)-(**1a**$_H$) to pyrocine (*R*)-(**56**) has been performed by thermolysis at around 300 °C, carried out either in in vacuo a sealed tube [166,167] or in a flask.[130] The reaction takes place with retention of configuration at [Cd] leading to (*R*)-**56** in about 60% yield (Scheme 81; Chapter IVa; Section 5.1[12]). Epimerization at this position requires the presence of a functional group able to achieve the process. To do so dihydroxylation of pyrocine (*R*)-(**56**) has been achieved using performic acid generated in situ from hydrogen peroxide and formic acid. The process is not face-selective and produces a mixture of two diastereoisomers **59** epimeric at [Ce] (Scheme 81).[130] Treatment of such stereoisomeric mixture with sulfuric acid, at reflux, favors the formation of **58** from the stereoisomer [e(*R*),f(*S*)]-**59** in which the hydroxyl group and the methylene carboxy chain on the vicinal carbon are in *cis*-relationship. This mixture, upon reaction with with Jones reagent (CrO_3-H_2SO_4 in acetone, 0 °C) produces a single ketone (*S*)-**60**, still possessing the (S)-stereochemistry at [Cd]. Epimerization takes advantage of the presence of keto group and has been achieved on treatment with a base leading to a racemate *rac*-**6**). Reduction is needed at this stage to get back to the original oxidation level. It has been achieved using the Huang-Minlon[168] variant of the Wolf-Kishner reduction reaction that involves treatment of the ketone with hydrazine and potassium hydroxide in ethylene glycol at 200 °C. [130,169,170]

Rearrangement of the furan to racemic pyrocine *rac*-(**56**) has been achieved on reaction with acetyl chloride catalyzed by zinc chloride and the transformation of pyrocine to racemic *trans*-chrysanthemic acid trans-(**1a**$_H$) has been achieved[163] inspired by the protocol disclosed by Julia[164,165] that opens the lactone ring using thionyl chloride ($SOCl_2$, benzene, reflux, 3h) followed by base promoted carbocyclisation.

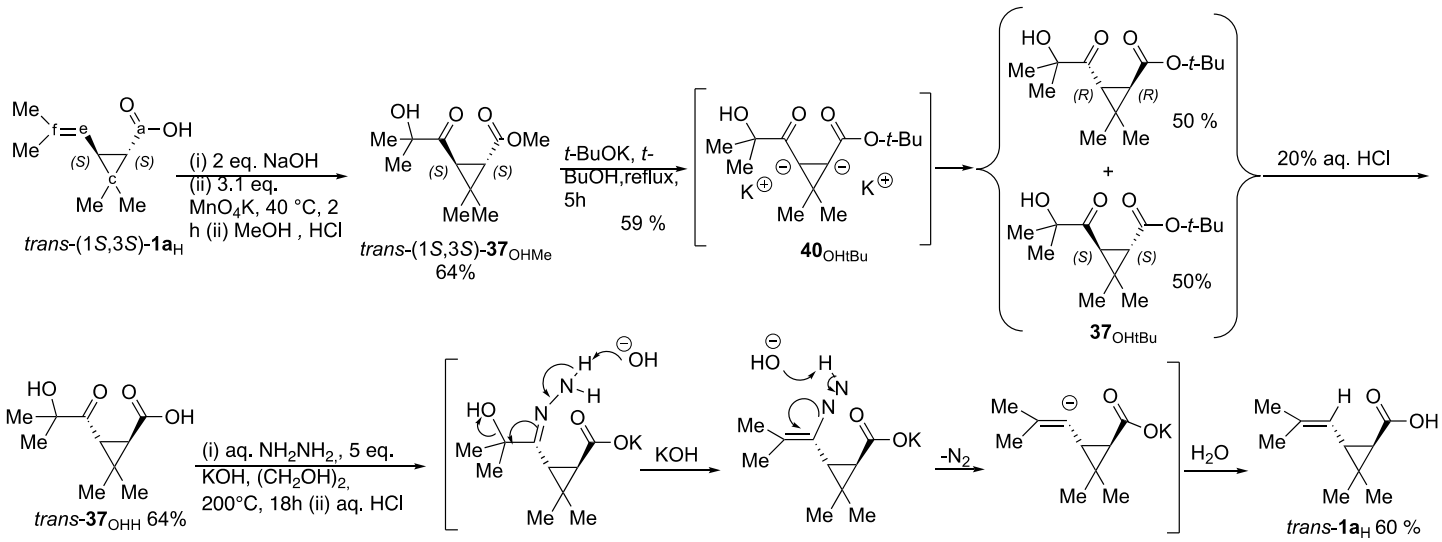
The process described by Matsui[163] includes an additional step in which anhydrous hydrochloric acid in ethanol is introduced in the medium to complete the addition of HCl to the [Ce=Cf] double bond. Therefore, the next step requires enough base to perform on **62**$_{Et}$ the 1,3-elimination reaction producing the cyclopropane ring and the 1,2 elinination reaction restoring the unsaturation (Scheme 81). Treatment of the dichloride **62**$_{Et}$ with

potassium *t*-amylate, a strong base soluble in benzene, leads to the formation of the cyclopropane ring and to a mixture of olefinic compounds *trans*-**1a**$_H$ and *trans*-**35a**$_H$ generated according to the Zaitsev's rulefor the former[172]and according to the Hofmann's rule for the latter.[171] This mixture has been efficiently transformed to the more stable chrysanthemic acid *trans*-(**1a**$_H$) on acid catalysed isomerization involving boiling in the presence of *p*-toluenesulfonic acid (Scheme 81).



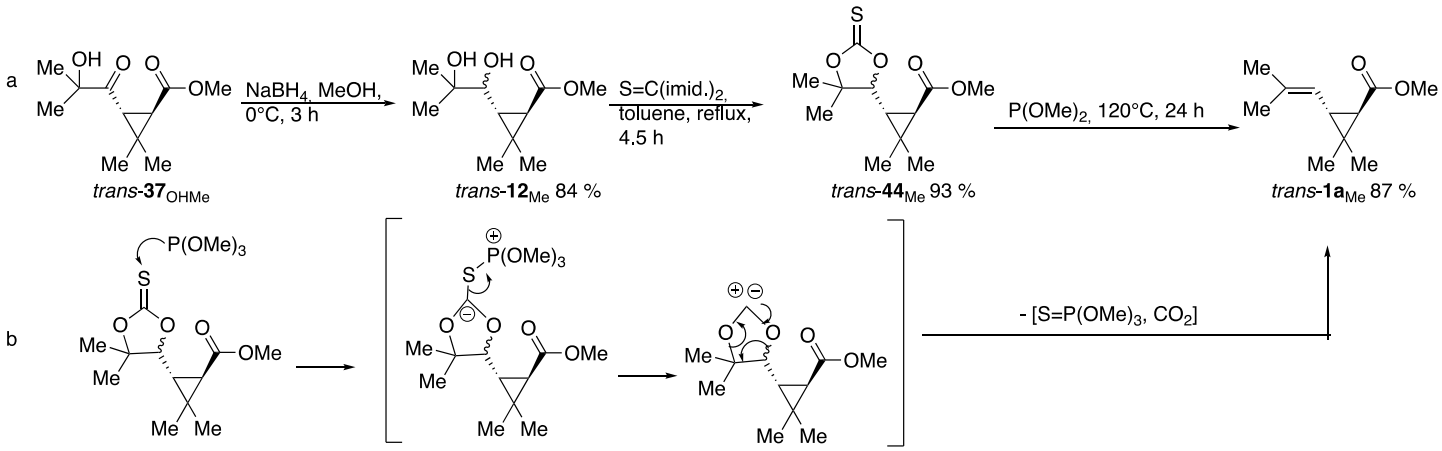
Scheme 81. Multisteps/multipots racemization of (1*R*)-*trans*-chrysanthemic acid implying sequential epimerization at each of the two assymetric carbons of the cyclopropane ring as model.[130]

Another approach has been published to achieve the racemization of *trans*-chrysanthemic acid *trans*-(1*S*,3*S*)-(**1a**$_H$) (Scheme 82).[173,174] It involves as the key steps (i) the permanganate oxidation of the [Ce=Cf] double bond of chrysanthemic acid leading to the corresponding enantiopure β-ketoalcohol **37**$_{OHMe}$ (Scheme 82).[173,174] esterification and (ii) subsequent treatment with excess of potassium *t*-butoxide in *t*-butanol that not only achieves a transesterification reaction but also epimerizes at both [Cb] and [Cd] to produce the racemic β-ketoalcohol **37**$_{OHtBu}$.[173] The real intermediate is probably not a dianion as reported [173] in the original paper but rather a series of cis/trans diastereoisomers resulting from a series of sequential metalation/protonation processes at each of the [Cb] and [Cd] sites. The reaction is also achieved with sodium methylate in methanol at reflux but seems to be less efficient.[173] It does not proceed with potassium *t*-butoxide in benzene probably due to solubility problems (Scheme 82).[173]



Scheme 82. Racemization of (1*S*)-*trans*-chrysanthemic acid implying single pot epimerization at each of the two assymetric carbons on the cyclopropane ring.[173]

A variant approach leading to the transformation of the β-ketoalcohol (**37**$_{OHMe}$) to the isobutenyl moiety present in methyl chrysanthemate (**1a**$_{Me}$) involves the reduction of their carbonyl group at [Ce] leading to (**12**$_{Me}$) (Scheme 84, entry a) and reductive elimination of the two hydroxyl groups (Scheme 83).[107] It has been successfully achieved[107] in two steps according to the Corey-Winter protocol that implies the intermediate formation of the thionocarbonate **44**$_{Me}$ and its reductive decomposition with trimethyl phosphite [132,133] or better with 2,3- dimethyl-2-phenyl-[1,3,2]diazaphospholidine (40 °C, 8 h, Scheme 83, entry b).[133,134]

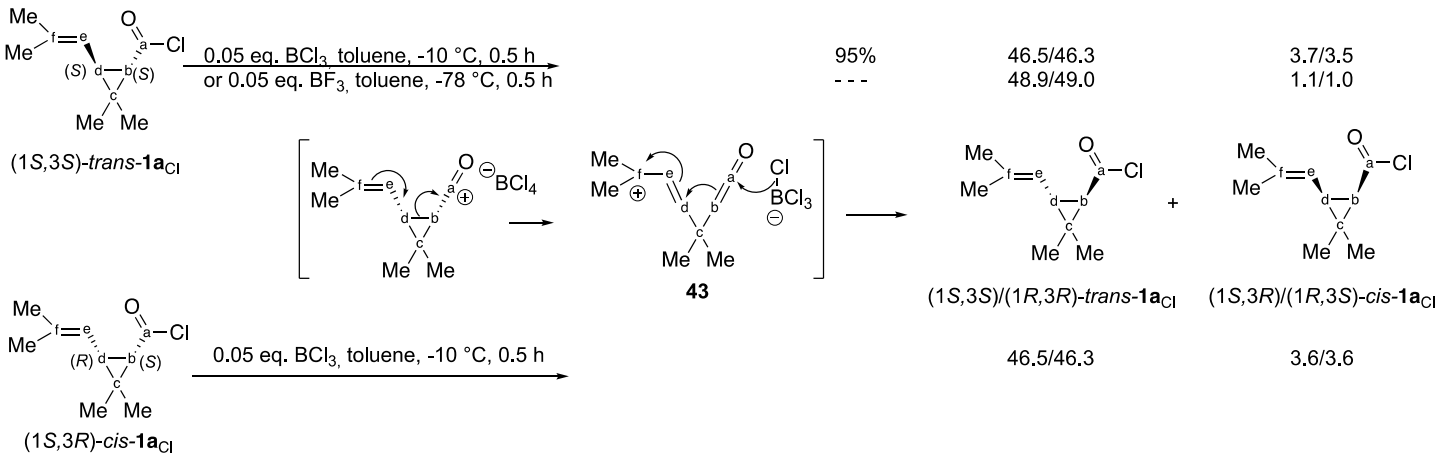


Scheme 83. Alternative route to transform a ketoalcohols to an olefin.[107]

5.5.1.2. Racemization of enantiomerically pure *cis*- and *trans*-chrysanthemic acid/lower esters and related acid chlorides to racemic-*trans*-derivatives involving cleavage/recombination of their [Cb-Cd] bond. Racemization of (1*S*,3*S*)-*trans*-chrysanthemoyl chloride (1*S*,3*S*)-*trans*-(**1a**$_{Cl}$) as well as (1*S*,3*R*)-*cis*-chrysanthemoyl chloride (1*S*,3*R*)-*cis*-(**1a**$_{Cl}$) to *racemic*-(1*R*/1*S*)-*trans*-chrysanthemoyl chloride (1*R*/1*S*)-*trans*-(**1a**$_{Cl}$) is routinely achieved in a single step and very high yield, using less than 5 mol-% of boron trichloride in toluene (-10 °C, 0.2 h, 93%, Scheme 84, See also Chapter IVa, Section 5.4.2).[12,175] Chrysanthemoyl chloride is readily prepared from chrysanthemic acid (Chapter IVa Section 2.2)[12] and furthermore the product of reaction can be further reacted

with alcohols to produce a large array of racemic pyrethroids (Chapter IVa, 2.4.1.2.4).[12,176] This protocol is far more efficient that the multistep approaches reported for the same purpose and disclosed above.
It has been found that (i) the amount of *trans*-chrysanthemic acid chloride *trans*-(**1a**$_{Cl}$) increases over that of its *cis*-stereoisomer as the reaction temperature is lowered and (ii) amongst the different Lewis acids that are able to perform such process, boron trifluoride is far more efficient (Scheme 84).[175,176]

The racemization reaction is expected to proceed through an ionic process that involves the selective cleavage of the [Cb,Cd] bond[175]and simultaneously destroys both chiral centers present on the cyclopropane ring (Scheme 84). It benefits from the extra stabilization of the charge by delocalization on the isobutenyl moiety.

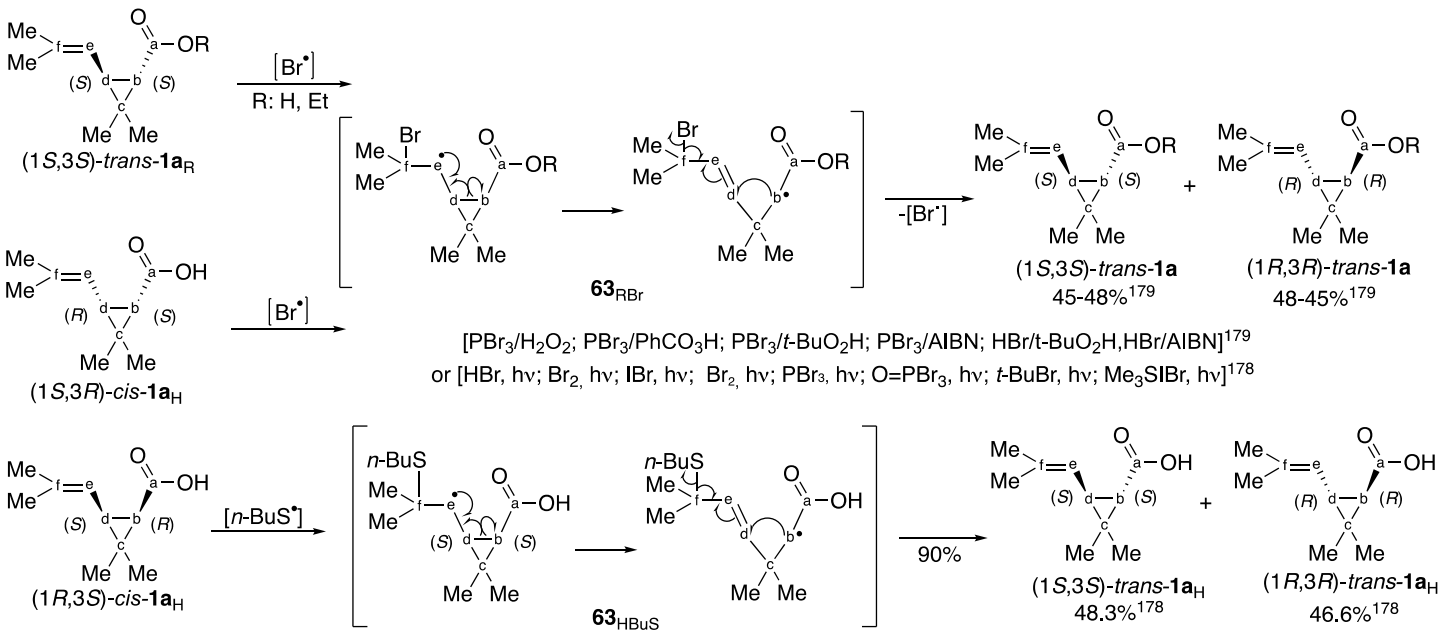


Scheme 84. Lewis acid catalyzed isomerization and racemization of enantiopure *trans*- and *cis*- chrysanthemoyl chloride.[175,176]

Another efficient racemization process has been proposed by ~~G~~. Suzukamo at the Sumitomo Company (Chapter IVa, Section 5.6).[12] It takes advantage of the easy formation of radicals on reaction with bromine-,[177-179] peroxy - or thiyl radicals under photochemical or thermal processes. Those radicals presumably add to the [Cb=Cd] double bond of chrysanthemic acid (**1a**$_H$) and related esters **1a**$_R$ generating related cyclopropyl carbinyl radicals **63** (Scheme 85) that are known to be particularly prone to release the strain by generating an homoallylic radical at one side and a leaving group in allylic position on the other side (Chapter IVa, Section 1.2.2.2.2).[12]

This intermediate, on which the original stereochemical information is lost, is prone to revert to *racemic-trans*-chrysanthemic acid/esters **1a**$_R$ (Scheme 85) due to the proximity of the reactive species and the presence of the geminal methyl groups at [Cc] that favors the cyclization according to the Thorpe Ingold principle.[180]

Thus mixture containing at least 70% of (1*S*,3S*R*)-*trans*-chrysanthemic acid (1*S*,3S*R*)-*trans*-(**1a**$_H$) and the related ethyl ester *trans*-**1a**$_{Et}$, as well as *cis*-chrysanthemic acid *cis*-(**1a**$_H$) and the related enantiomerically pure (1*S*,3*R*) and (1*R*,3*S*)-*cis*-chrysanthemic acid (1*R*,3*S*)-*cis*-(**1a**$_H$) have been transformed mainly to racemic-*trans*-chrysanthemic acid *trans*-(**1a**$_H$) (Scheme 85).[179,178] On reaction with a series of reagents susceptible to generate a bromine-, hydroxyl- or *n*-butylthio-radicals respectively from aluminum tribromide ($AlBR_3$)/*t*-butyl hydroperoxide,[181] aluminum tribromide or boron tribromide/AIBN;[182] thiols and various sulfur containing derivatives/under photochemical irradiation.[178]



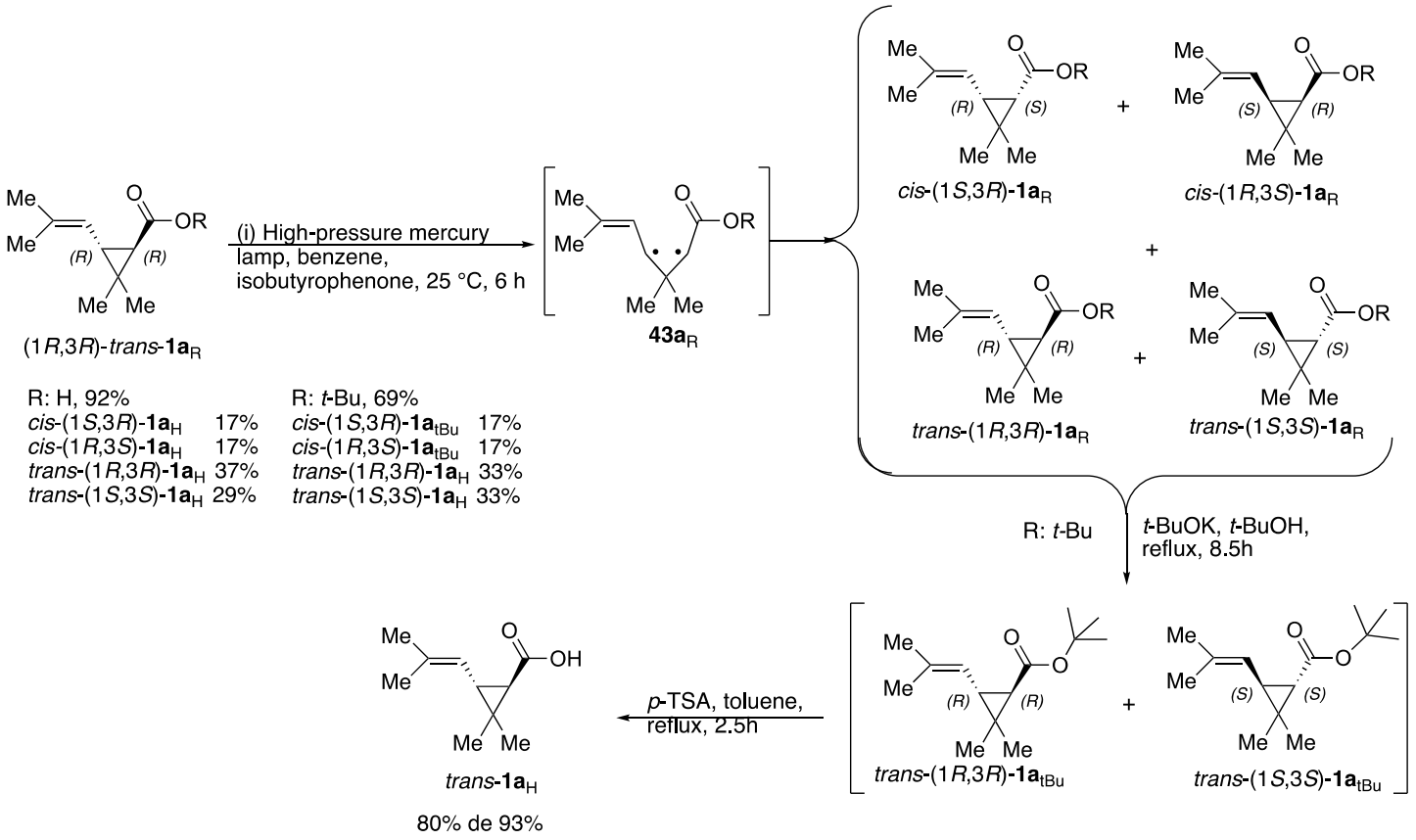
Scheme 85. One-pot transformation of chrysanthemic acid enantiomers to racemic *trans*-chrysanthemic acid catalyzed by radicals.[178,179]

Other conditions involve hydrogen bromide (HBr) as a gas, in aqueous solution, or generated in situ from lithium bromide and acetic acid, as well as phosphorus tribromide (PBr_3), phosphorus pentabromide (PBr_5) or phosphorus oxybromide ($O=PBr_3$) in the presence of a radical initiator such as hydrogen peroxide (H_2O_2), *t*-butyl hydroperoxide, benzoyl peroxide ($PhCO_3H$), *t*-butyl perbenzoate ($PhC(=O)O_2$-*t*-Bu) or azobisisobutyronitrile (AIBN) or under photochemical irradiation.[129,177,179]

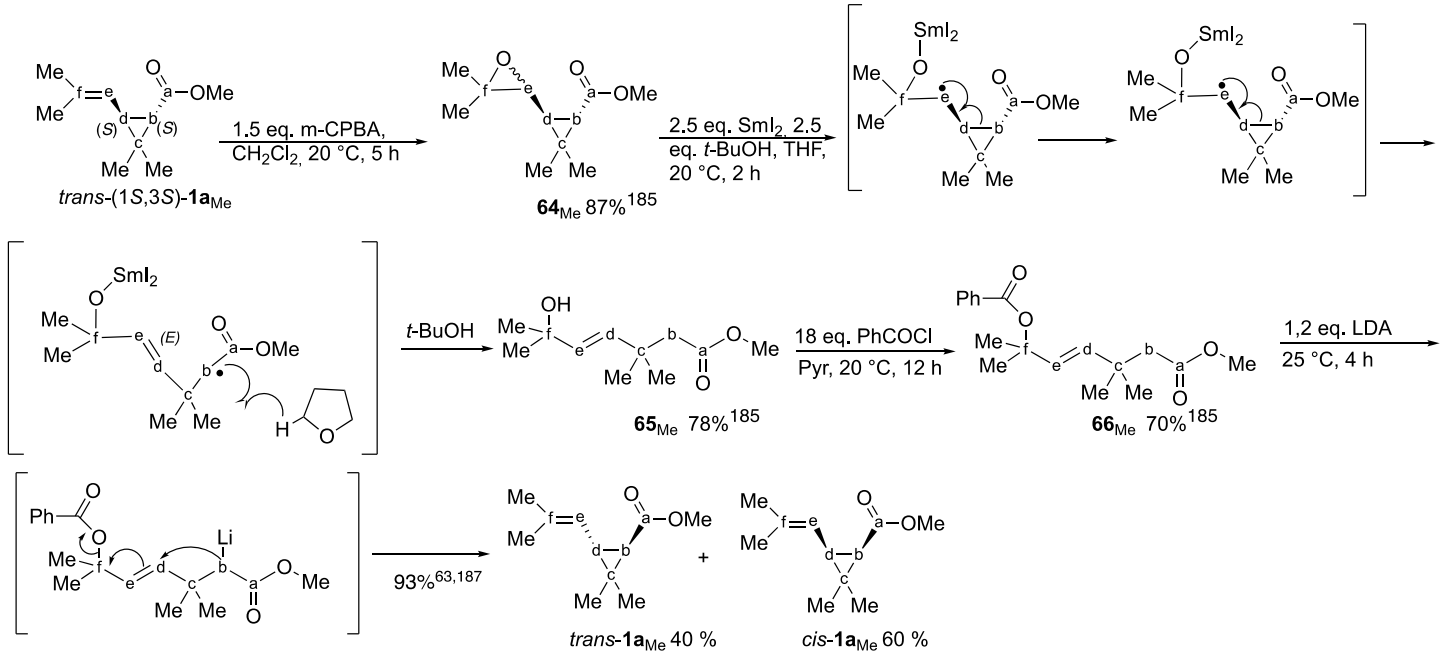
5.5.2. Racemization of chrysanthemic acid leading to a cis/trans-mixture of diastereoisomers. As pointed in the previous section racemization of chrysanthemic acid and related compounds leads mainly to racemic *trans*-chrysanthemates since it involves processes under thermodynamically controlled conditions. Access to the *cis*-series through racemization is therefore not an easy task.

Photoisomerization of chrysanthemic acid *trans*-(1*R*,3*S*)-(**1a**$_H$) and its *t*-butyl ester *trans*-(1*R*,3*S*)-(**1a**$_{tBu}$) with a high pressure mercury lamp in the presence of isobutyrophenone[183] however, promotes the formation of biradicals at [Cb] and [Cd] by cleavage of [Cb-Cd] bond. The recombination of the resulting bi-radicals intermediate leads to the mixture of the four stereoisomers in poor yields with a *cis*/*trans* ratio amounting 34/66 (Scheme 86, Chapter IVa, Section 5.2).[12]

The higher ratio of the *trans*-(1*R*,3*S*)-**1a**$_H$ in the resulting mixture of chrysanthemic acid (Scheme 86) lets suggest that the equilibrium has not been reached yet. cis/trans-Isomerization leading to *t*-butyl racemic-*trans*-chrysanthemate *trans*-(**1a**$_{tBu}$) then to racemic-*trans*-chrysanthemic acid *trans*-(**1a**$_H$) has been achieved on sequential treatment of potassium *t*-butoxide at reflux of *t*-butanol that effect the *cis*/*trans*-epimerization reaction (Scheme 86; Chapter IVa, Section 4.2)[12] and *p*-toluene sulfonic acid (Scheme 86; Chapter IVa, Section 2.1.3).[12]



Scheme 86. Racemization of (1*R*)-*trans*-chrysanthemic acid to racemic-*trans*-chrysanthemic acid induced by irradiation.[183]

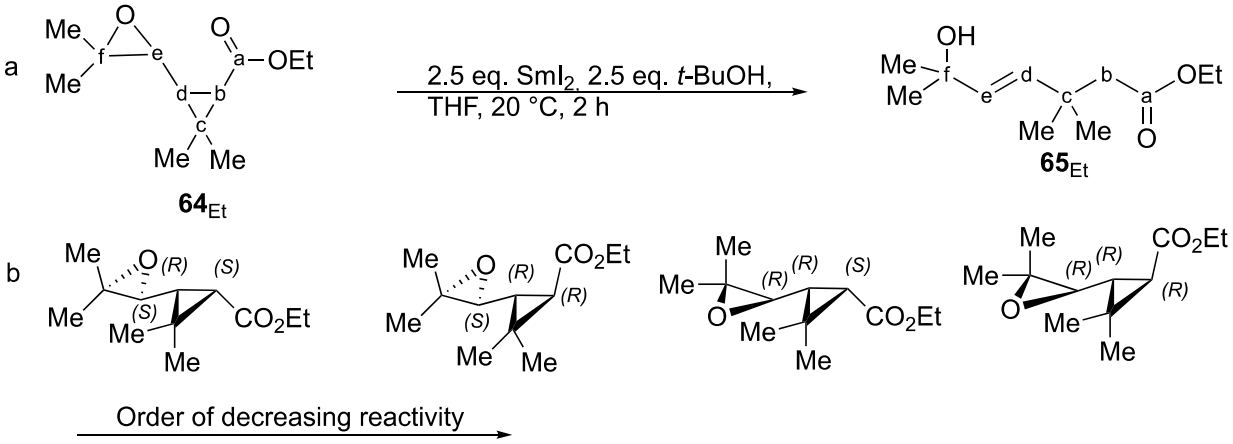


Scheme 87. Multistep racemization of methyl (1*S*)-*trans*-chrysanthemate allowing the access to racemic alkyl *cis*- and *trans*- chrysanthemates.[63,185,187]

The next racemization process differs from the others since it involves a two steps transformation in which the cleavage of the [Cb-Cd] bond, and the formation of the cyclopropane ring are fully dissociated (Scheme 87).

The key reaction is without context the efficient cyclopropane ring opening on reaction of methyl oxido chrysanthemate **64**$_{Me}$ (Chapter VIa, Section 3.1.3.2) with SmI_2.[184,185] It achieves the selective cleavage of the [Cb-Cd] bond of methyl oxido-*trans*-(1*S*,3*S*)-chrysanthemate *trans*-(1*S*,3*S*)-(**64**$_{Me}$) destroying the two chiral centres present and producing at the same time the allylic alcohol **66**$_{Me}$ (Scheme 87). Its benzoate is expected to cyclise on reaction with an excess of lithium diisopropylamide (LDA) to deliver a 60/40 *cis*/*trans*-mixture of racemic methyl chrysanthemate (**1a**$_{Me}$) (Scheme 87),[185] according to a process previously disclosed by Ficini.[63, 186,187]

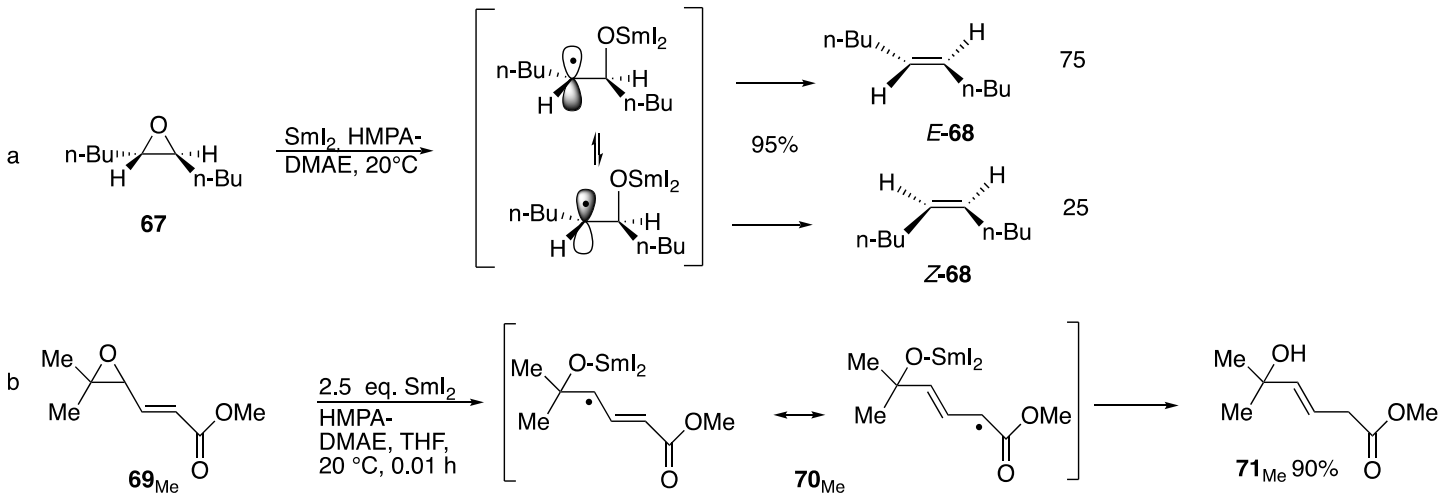
This transformation is not limited to the *trans*-(1*S*,3*S*)-(**1a**$_{H}$), and applies to all stereoisomers of ethyl oxido-chrysanthemate (**64**$_{Et}$) (Scheme 88).[185] It has been however found[184,185] that their reactivity towards SmI_2 differs as disclosed in Scheme 88. We have observed that the (*S*)-epoxides, whatever is the stereochemistry on the cyclopropane, react faster that their (*R*)-stereoisomers. Furthermore, in each series the compound possessing a *cis*-disubstituted cyclopropane ring reacts faster than its *trans*-counterpart (Scheme 88).



Scheme 88. Order of reactivity of stereoisomeric ethyl oxido-chrysanthemates with samarium diiodide.[185]

Samarium diioidide the "Kagan reagent"[188,189] is an efficient reagent, easily produced *inter alias* on reaction of stoichiometric amount of iodine with samarium, that possesses a high propensity to reduce several functional groups through a single electron-transfer process. Accordingly stereochemically pure *trans*-epoxides such as **67** are transformed to the corresponding olefins such as **68** as a *trans*/*cis*-mixture of stereoisomer (Scheme 89, entry a) whereas γ,δ-epoxy-α,β-unsaturated esters such as **69**$_{Me}$ react extremely rapidly to produce δ-hydroxy-β,γ-unsaturated esters such as **71**$_{Me}$ on reaction with SmI_2 in the presence of hexamethyl phoshotriamide (HMPA) and dimethylamino ethanol (DMAE) known[188] for their aptitude to enhance the reducing ability of SmI_2 (Scheme 89, entry b).

The striking difference between the results disclosed in Scheme 89 (compare entry b to entry a) is the presence of the α,β-unsaturated ester moiety that allows the efficient stabilization of the radical intermediate by its carboxy group (Chapter IVa, Section 1.2.2.2.2.).[12] This supports the mechanism disclosed in Scheme 87 for alkyl oxido-chrysanthemates in **64**$_{R}$ ring opening by SmI_2 and rationalizes the selective cleavage of their [Cb-Cd] bonds to produce a radical at [Cb].



Scheme 89. Reactivity of differently substituted epoxides with samarium diiodide.

6. Description of the Reactivity of Phosphorus Substituted Carbanions Towards Aldehydes to Access a Large Variety of Pyrethroids Bearing Different Substituents at [Cf]

As described above (Chapter IVb, Section 4.4.2), the transformation of the different isomers of chrysanthemic acid/esters to the related vinylcyclopropane carboxylic acid/esters has been the subject of several investigations and the Wittig and related reactions have played a crucial role to produce pyrethroids possessing different substituents at [Cf].We will expand below the scope of the Wittig and related reactions, the methods used to prepare the phosphonium salts used above, and the experiment that rationalize the stereochemistry of the different variants.

We will describe sequentially:

(i) the Wittig reaction that implies phosphorus ylides,[73,74,75,76,77,78] for the synthesis of those vinylcyclopropane carboxylic acid/esters bearing hydrogen or alkyl groups at [Cf] implied for example in the synthesis of various four stereoisomers of chrysanthemic acid/esters **1a**$_R$ including radiolabelled ones and norchrysanthemic acid (**1d**$_H$) bearing a hydrogen and a methyl group there as well as unsaturated esters, the structures of which are related to pyrethrin II (**1b**$_a$),

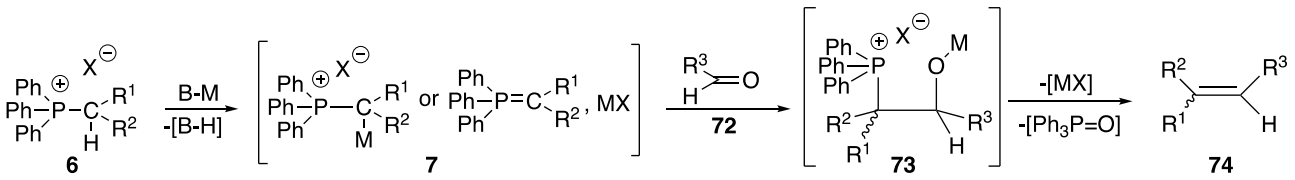
(ii) the Wittig-Horner- (WH-reaction)[79] and the Horner-Wadsworth-Emmons-reaction (HWE-reaction) [77,80-82] that involve phosphinyl [-P(=O)R_2] or phosphoryl- [-P(=O)$(OR)_2$] stabilized carbanions respectively and proved particularly useful for the synthesis of the carboxy stabilized [Ce=Cf] double bond present in pyrethric acid (**1b**$_H$),

(iii) the Ramirez reaction[101] that implies transiently generated phosphorus ylides, that allows the synthesis of the dihalogenovinylcyclopropane carboxylic acid/esters involved in the synthesis of deltamethrinic- (**1f**$_H$) and permethrinic- (**1d**$_H$) acids.

6.1. About the olefination reactions implying phosphorus stabilized carbanions and aldehydes

Among the various methods of olefin synthesis, the Wittig and related reactions occupy a place of choice since they use readily available carbonyl compounds and phosphorus ylides as starting materials. They allow the one-pot formation of compounds possessing a new [C=C] double bond by forming sequentially the sigma- and the pi-bonds with complete regiocontrol (Scheme 90).[76] Moreover at several occasions such as for the hemisynthesis

of pyrethric acid (**1b**$_{MeH}$) and nor-chrysanthemic acid (**1c**$_{H}$), the concomitant control of the stereochemistry of the [C=C] double bond is required. This is why we will discuss in this section general behaviour of the Wittig and related reaction that include the stereocontrol of these processes.



R_1,R_2= Me,Me; Me,H; CO_2Me; Me, CO_2Me; Br,Br; Cl,Cl; F,F

Scheme 90. Phosphorus ylid synthesis and reactivity towards aldehydes

The Wittig reaction (W-reaction) involving phosphorus ylides **7** (Scheme 4, Scheme 90) was discovered[73] in 1953 by serendipity in the laboratory of G. Wittig who has been awarded the Nobel Prize in 1979 for this discovery.[74]

Other ylides such as arsonium-,[190] sulfonium-[191-194] and selenonium ylides[195] have been prepared since then but none of them favourably competes to produce olefins. The former either produce olefins or epoxides depending on the substituents present on the ylide,[190] and the latter two produce epoxides as the sole product.

Related phosphorus-containing reagents such as alpha-phosphine oxide carbanions **9** (Scheme 4; Wittig-Horner reaction: WH-reaction)[79] and alpha-phosphonate carbanions **11** (Scheme 4; Horner-Wadsworth-Emmons-reaction: HWE-reaction) [80,82,196] however allows the synthesis of the [C=C] double bonds on reaction with carbonyl compounds. These methods are less general than the original W-reaction but offer, especially the HWE-reaction, valuable advantages over the W-reaction in specific cases as it will be reported in this section.

We will restrict our presentation to aldehydes in reference to the synthesis of pyrethroids. The topics related to this chapter involves the synthesis of trisubstituted and α,β-disubstituted olefinic compounds bearing at [Cf]:

(i) hydrogens, alkyl and alkenyl groups, from related substituted phosphorus ylides **7** (Chapter VIb, Section 6.3) in relation to the isobutenyl moiety of chrysanthemic acid/esters **1a**$_{R}$ and the ethylidene moiety in relation to norchrysanthemic acid/esters **1c**$_{R}$ (Chapter IVb, Section 4.4.2.1) and pyrethroates bearing a vinyl or a dienyl moiety at [Cf] (Chapter IVb, Section 4.4.2.2)

(ii) carbonyl or carboxyl group, from resonance stabilized phosphorus ylides **7**, alpha-metallocarboxylates bearing a phosphinyl **9**, or phosphoryl moiety **11** (Chapter VIb, Section 6.4) reminiscent to the structure of pyrethric acid/esters (Chapter IVb, Section 4.4.2.3)

(iii) halogens using usually dihogenomethylene phosphorus ylides **7** often as transient intermediates (Chapter VIb, Section 6.5) reminiscent to the structure of deltamethrinic acid/esters **1f**$_{R}$ and permethrinic acid/esters **1d**$_{R}$ (Chapter IVb, Section 4.4.2.4).

In many cases such as the ones of nor-chrysanthemates and pyrethroates the control of the stereochemistry of the generated [C=C] double bond is required and will be discussed extensively on related model in this section.

The Wittig-reaction (W-reaction) proved to have a broader applicability allowing the synthesis of the whole series of alkene whose [C=C] double bond bears (i) hydrogen or alkyl-substituents (from unstabilized ylides; H, alkyl), (ii) at least one aryl or vinyl substituent (from semi-stabilized ylides; H and aryl, vinyl), (iii) at least one carbonyl, carboxyl or nitrile substituents (from resonance stabilized-ylides; CH=O, RC=O, CO_2R, CN)[76,78] and (iv) a modified version that allows the synthesis of dihalogenovinyl derivatives.[102-104]

The Horner-Wadsworth-Emmons-reaction (HWE-reaction) does not produce compounds possessing exclusively H or alkyl groups on their [C=C] double bond[82] but is dedicated to the reactions of "stabilized carbanions" bearing vinyl or carboxyl groups on their carbanionic centers. They are more reactive towards carbonyl compounds than their analogues bearing a phosphonium in place of a phosphoryl group and therefore are well suited to the synthesis of α,β-unsaturated esters (enoates). The Still-Gennari modification (HEW-SG reaction)[81,198] that uses trifluoroethylphosphonoesters offers distinct advantages that will be disclosed in due course but to our knowledge, It has never been used in the pyrethroid field. HEW-reaction has been also successfully used, occasionally, for the synthesis of dihalogenovinyl derivatives.[102-104]

Present in all these reagents, the phosphorus moiety possesses two important roles:

(i) acidifying the hydrogen attached to the same carbon by a combination of field/inductive and polarizability effects,[199] allowing its metalation leading to carbanions stabilized by the phosphorus atom (15 kcal/mol greater than related ammonium moiety). The stabilization (3d)P x (2p)C orbitals overlap that was one time the prevailing hypothesis is no longer priviledged (See Scheme 102 and discussion about dissipation of the electron on the P σ*).

(ii) affinity of the oxygen of the betaine intermediate (such as **73**, Scheme 90) to the phosporus atom present in the different moieties that promotes the [C=C] double bond formation through a beta-elimination reaction that can be viewed as a retro-cycloaddition delivering as co-products triorganophosphine oxides (Wittig), diorganophosphinates (WH) or diorganophosphates (HWE), respectively.

One of the concerns with the original Wittig reaction is the presence beside the compound containing the required [C=C] double bond, of stoichiometric amounts of phosphine oxide, usually triphenylphosphine oxide, as co-product. The latter is (i) usually difficult to separate from the desired olefinic compound (usually by selective crystallization or distillation of the olefinic compounds), (ii) difficult to recycle and (iii) possess a weight that often exceed by far the weight of the alkylidene moiety transferred (Scheme 90).

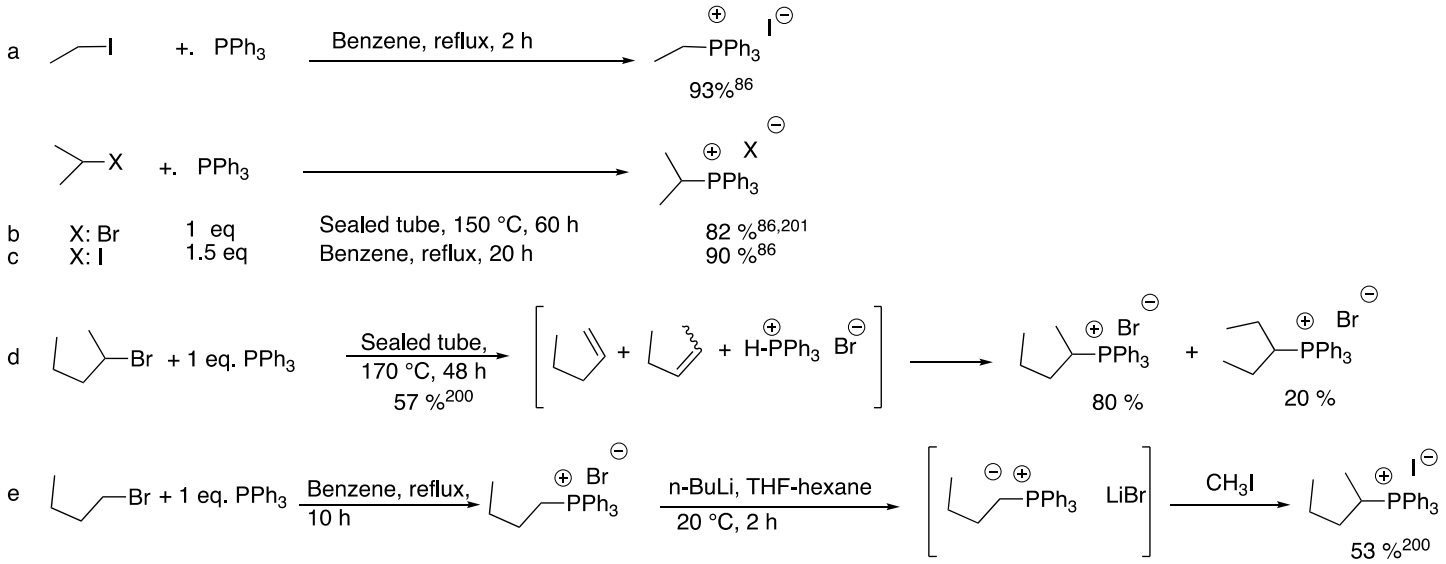
Those inconveniency does not exist in the HEW reaction that deliver diorganophosphates by-products whose molecular weight is far less that triphenylphosphine oxide and that are easier to separate from the olefinic products due to their water solubility.

6.2. About the synthesis of phosphonium salts, phosphine oxides and phosphonates

The synthesis of the ylide precursors and the ylides has been the matter of concern. The synthesis of the alkyltriphenylphosphonium salts has been routinely achieved on reaction of triphenylphosphine with the requested alkyl halide (Scheme 91).[86,200,201] The reaction works reasonably well with methyl- and *n*-alkyl halides, especially the iodides, as well as with isopropyl- and isobutyl- iodides. It has been successfully used to synthesize ^{14}C radiolabelled isopropyl phosphonium salt (Scheme 28).[60] Other secondary alkyl halides however lead to a mixture of regioisomeric secondary phosphonium salts due to competing elimination/addition-reaction (Scheme 91, entry d).[86,200] Performing the alkylation at lower temperature or with a related tosylate does not solve the problem[200] and in case of reaction performed with an excess of *sec*-bromide the resulting alkyl bromide is a mixture of regioisomers (2/1 original/rearranged ratio).[200] Interestingly, such isomerization does not occur by heating the bromide in the absence of triphenylphosphine that clearly shows the deleterious effect of the phosphine that probably perform a competing elimination reaction.[200] The synthesis cyclopropyl triphenyl phosphonium bromide from cyclopropyl bromide with triphenyl phosphine also suffers limitation since the related phosphonium salt is produced in less than 1%.[203]

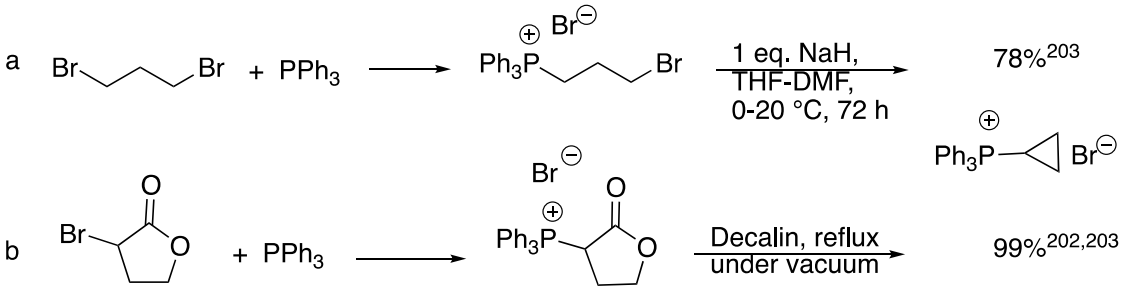
Such secondary alkyltriphenylphosphonium salts can be regioselectively synthesized by alkylation of a related primary alkyl triphenylphosphonium salt intermolecularly as for the case of 2-pentyl triphenylphosphonium

bromide (Scheme 91, entry e)[86,200] or intramolecularly as for the synthesis of cyclopropyl triphenyl phosphonium bromide (Scheme 92, entry a).[203]



Scheme 91. Synthesis of alkylsubstituted triphenylphosphonium salts.[200,201,86]

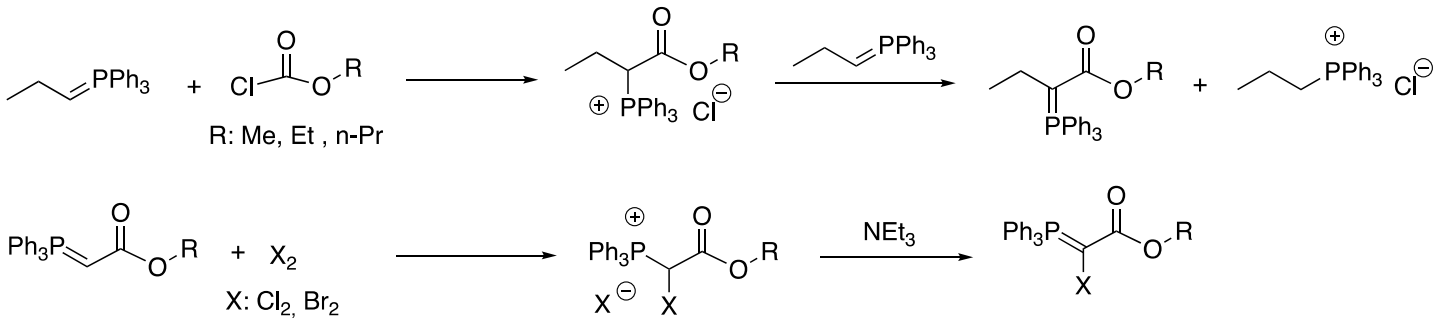
Another synthesis of cyclopropyl triphenyl phosphonium bromide use a different process and has been achieved very efficiently on thermal decomposition of 3-(2oxotetrahydrofuranyl) triphenyl phosphonium bromide (Scheme 93, entry b)[85,202-204]



Scheme 92. Synthesis of cyclopropyl triphenyl phosphonium bromide.[202,203]

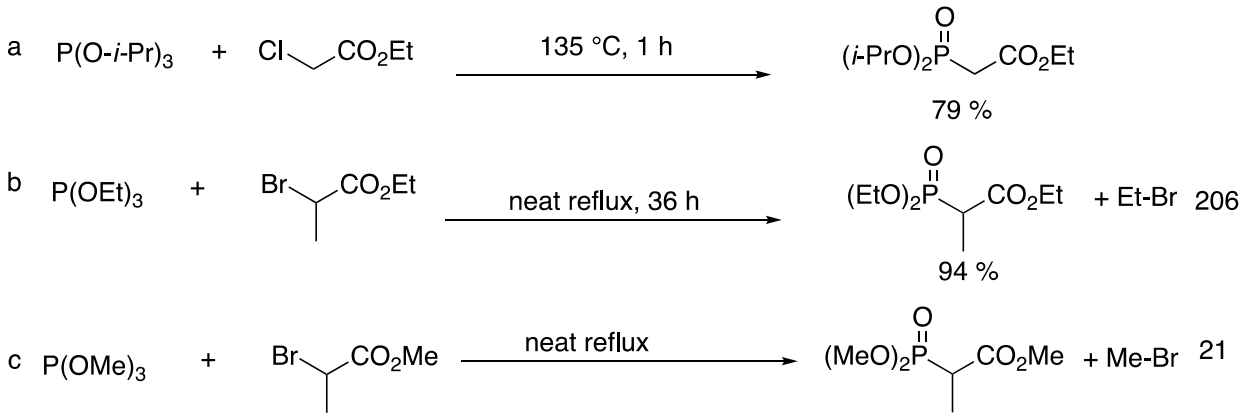
A related reaction that involves acylation of a primary alkylidenetriphenylphosphonium ylide has been used to generate phosphorus ylides bearing a carboxy-group (Scheme 93).[13] Note that in the reaction disclosed in Scheme 93, propylidenetriphenylphosphorane is acetylated and also metalates the resulting acylated phosphonium salt to produce the corresponding ylide. The acylated phosphorus ylide has been in turn chlorinated then metalated using triethylamine (Scheme 93).[13]

1-Methoxy-[^{14}C] carbonylethyltriphenylphoshonium iodide precursor of radiolabelled methyl *trans*-pyrethrate has been produced from radiolabelled bromoacetate by reaction with triphenylphosphine. Metalation of the resulting triphenylphosphonium salt by aqueous sodium hydroxide followed by methylation of the resulting ylide by methyl iodide (Scheme 28, entries b,c).[60]



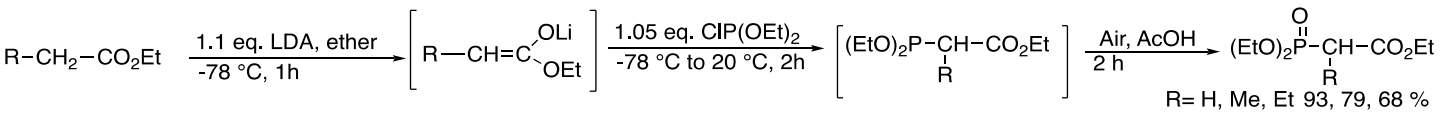
Scheme 93. Synthesis of carboxy-substituted phosphorus ylides.[13]

The synthesis of dialkyl or diaryl phosphonates has been routinely performed using the Michaelis Arbuzov rearrangment[205] involving alkyl halides and trialkyl phosphites (Scheme 94). The reaction proceeds from alpha-halogenoacetates and alpha-halogenopropionates usually at high temperature, around 140 °C for 1 h − 36 h so the alkyl halide co-product is removed from the medium by distillation (Scheme 94).[205,206] It is reported that the conversion of >P—O—C linkage into >P(=O)—C involves a net gain of 32 kcal/mol, and possibly 65 kcal/mol energy in the total bond stability that acts as a driving force for the rearrangement.[205]



Scheme 94. Synthesis of dialkyl or diaryl phosphonates using Michaelis Arbuzov reaction involving alkyl halides and trialkyl phosphites.[21,206]

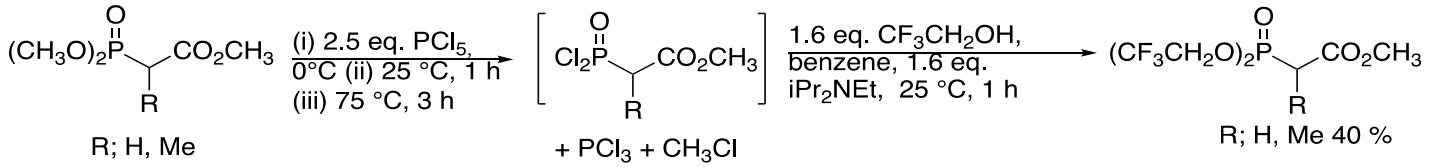
Other syntheses of trialkylphosphono-acetates and propionates involve less drastic conditions such as the one implying the reaction between ester enolates and diethyl posphorochloridite followed by air oxidation of the phosphite intermediate (Scheme 95).[207]



Scheme 95. Syntheses of trialkylphosphono-acetates and propionates from ester enolates and posphorochloridite.[207]

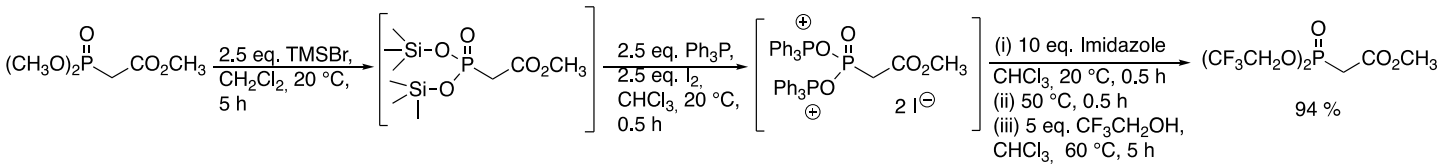
The synthesis of bis(trifluoroethyl)phosphonoesters, used in the Still-Gennari modification (HWE-SG)[81,198] of the HWE reaction, requires a different approach that formally involves the substitution of the methoxy-groups

from dimethyl phosphonoacetate and propionate by the trifluoroethoxy-group using trifluoroethanol.[81,198] The original procedure that involves the intermediate formation of the phosphonyl dichlorides on reaction with phosphorus pentachloride (PCl_5) and their subsequent alkoxylation with 2,2,2-trifluoroethanol in the presence of diisopropylethylamine, leads to the trifluoroethylphosphonoesters in 40 % overall yield (Scheme 96).[198]



Scheme 96. Synthesis of bis(trifluoroethyl)phosphonoacetate and propionates from related dimethyl phosphonoacetate and dimethyl phosphonopropionate implying phosphonyl dichlorides.[198]

This process to produce phosphonalkylcarboxylates as well as those that will be proposed later, present several drawbacks especially long reaction times that have been overcome by a high yielding two-steps procedure that implies the reaction of trimethylsilyl bromide (2.5 eq.) with methyl dimethylphosphonoacetate and the resulting trimethylsilylphosphonate transesterified using the Garegg-Samuelsson reagent system (triphenyl phosphine, iodine and imidazole) and 2,2,2-trifluoroethanol to deliver the methyl bis(2,2,2-trifluoroethyl)phosphonoacetate in up to 94% yield (Scheme 97).[208] This method has been successfully extended to other alcohols and phenols.[208]



Scheme 97. Synthesis of bis(trifluoroethyl)phosphonoacetate from dimethyl phosphonoacetate implying the Garegg-Samuelsson reagent.[208]

The synthesis of phenoxy phosphonates that also allow the stereoselective synthesis of α,β-unsaturated esters is disclosed below in Scheme 119 entries g-i.[248-251]

6.3. Synthesis of the [C=C] double bonds bearing hydrogens or/and alkyl substituents using phosphorus ylides

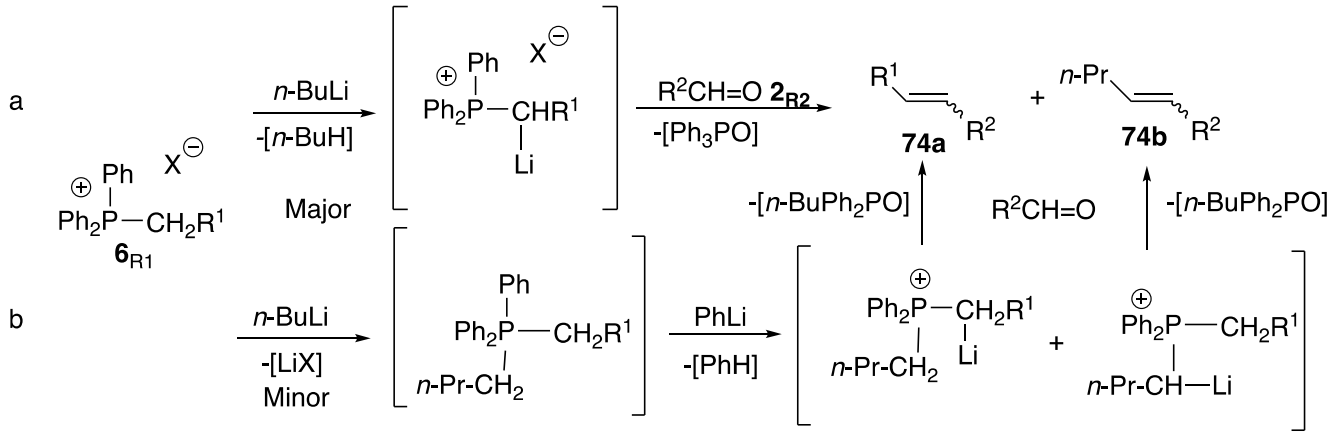
This section is related to the synthesis of vinylcyclopropane carboxylic acid bearing hydrogens or/and alkyl substituents at [Cf] reported in Chapter IVb, Section 4.4.2.1.

As already pointed out, the phosphorus-containing moiety acidifies the α-hydrogen by a combination of field/inductive and polarizability effects.[199] Thus phenyllithium or butyllithium in ethers,[208] sodium hydride in DMF,[208] sodium amide in liquid ammonia,[208] dimsyl sodium,[209] sodium ethylate in DMF[208] or potassium *t*-butoxide in THF,[208] among others have been successfully used to metalate alkyltriphenylphosphonium salts.

Specific examples involving hexyl triphenylphonium bromide are disclosed in Scheme 100.[208] Nevertheless the reader should be aware of competing processes that usually take place when butyllithium is used as a base. They produce small quantities of co-products often difficult to locate in the desired product as exemplified in Scheme 98. In fact, butyllithium not only acts as a base towards phosphonium salts but also as a nucleophile, as was the purpose of the research initiated originally by Wittig. This leads to an echange of ligands on the

phosphorus atom of the phosphonium salt (Ph/Bu exchange). This exchange leads to the concomitant formation of phenyllithium and phosphonium salt bearing a butyl group precursor of a butylidene phosphorane leading unwanted olefin **75b** the (Scheme 98, entry b) beside the wanted olefin **75a** (Scheme 98, entry a)

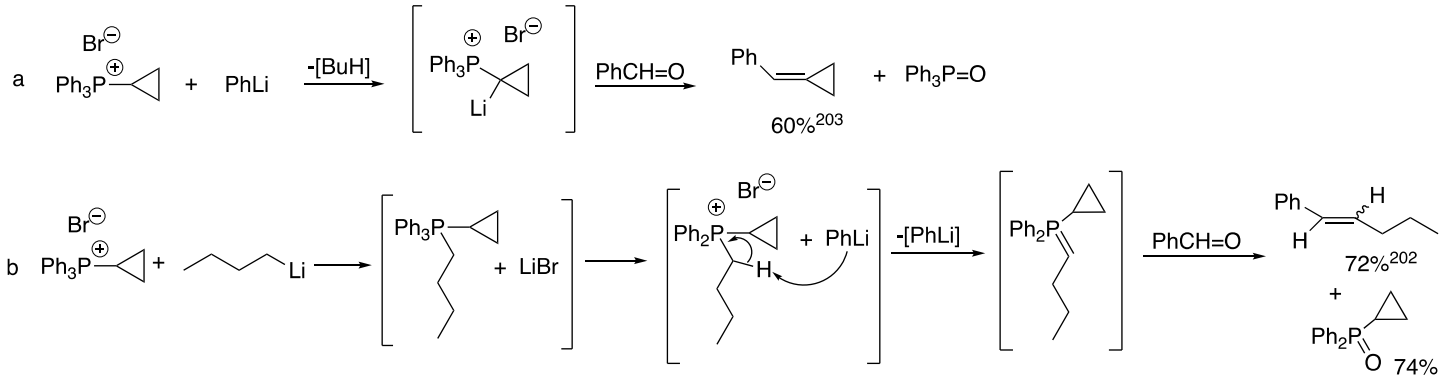
that usually reacts further on the butylphosphonium salt produced (Scheme 98, entry b) and finally leads to some unwanted olefin **75b** besides the expected olefin **75a** (Scheme 98, entry a).



Scheme 98. Competing reaction implied in the metalation of alkyltriphenylphosphonium salts with *n*-butyllithium.

Replacement of butyllithium by phenyllithium avoids these disagreaments since, even if the side reaction takes place, it exchanges one of the phenyl groups belonging to the triphenyl phosphonium salt by the phenyl group of phnyllithium, delivering phenyllithium that does not make any difference.

This exchange reaction is particularly effective when cyclopropyltriphenylphosphonium bromide is reacted with n-butyllithium since on further trapping of the ylide with benzaldehyde 1-phenyl-1-pentene is instead formed (72% yield; Scheme 99, entry b)[202] as well as cyclopropyl diphenylphosphine oxide as co-product rather than triphenylphosphine oxide and benzylidene cyclopropane. The latter has been efficiently generated using phenyllithium in place of butyllithium (Scheme 99, entry a).[203] Using instead of butyllithium non nucleophilic bases such as sodium hydride in DME avoids such problem.[85] The latter conditions proved efficient to achieve the synhesis of pyrethroids bearing a cyclopropylidene moiety in place of the isopropylidene one (Scheme 30, entry a).[85]

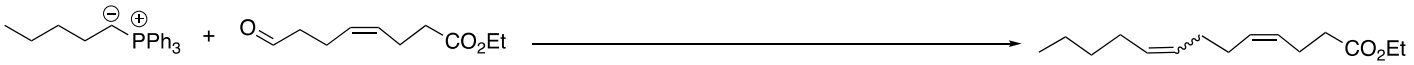


Scheme 99. Reactions of phenyllithium and *n*-butyllitium with cyclopropyltriphenylphosphonium bromide.[202,203]

It should be noticed that, depending the conditions, the Wittig reaction delivers unsaturated compounds as a mixture of stereoisomers in which often one substantially prevails. The control of such stereochemistry has been crucial in the pyrethroid field that any time it happens requires to test each stereoisomer including those that possess the (*Z*)- and the (*E*)-stereochemistry. This stereochemical problem is present among those pyrethrins/pyrethroids we have selected in Figure 1 such as (i) the natural pyrethrin II **1b**$_{MeA}$ and in the related pyrethric acid **1b**$_{MeH}$ possessing a (*E*)-unsaturated ester as well as (ii) the unnatural metofluthrin **1c**$_{G}$ and the related nor-chrysanthemic acid (**1c**$_{H}$) possessing a (*Z*)-α,β-dialkyl substituted [C=C] double bond.

The control of the stereochemistry of the [C=C] double bond in the Wittig reaction has been the subject of intensive work and proved to be directly related to (i) the nature of the substituents on the [C=C] double bond with a distinction between those produced from ylides bearing hydrogen and alkyl groups on their carbanionic center (unstabilized ylides) and those bearing groups able to delocalize the charge such as vinyl-, aryl-, formyl, acyl or carboxy-groups (stabilized ylides) (ii) the conditions used to synthesize the ylide: the nature of the counter ion and of the solvent. Those features have been imbedded in the mechanism disclosed to rationalize those features.

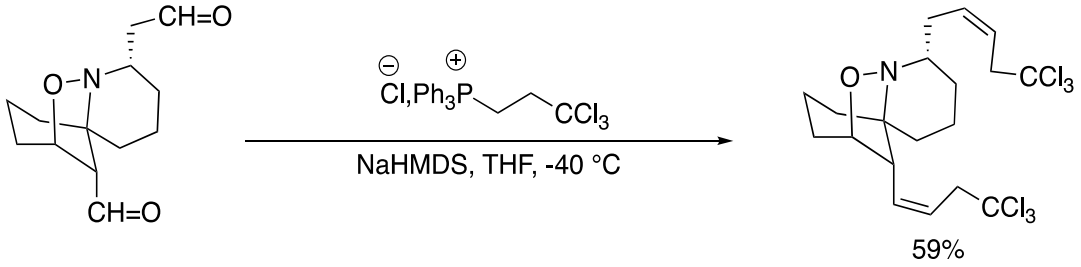
As general trends unstabilized ylides perform poorly and provide a mixture of *E*/*Z*-stereoisomeric compound*s* in which the *E*-prevails using lithium counter ion and ethereal solvents (Scheme 100, entries a-c). Under salt-free conditions however, the (*Z*)-stereoisomer largely prevails. Typically, metalation of the phosphonium salt is performed in liquid ammonia, and the latter replaced by benzene in which the insoluble salt precipitates. It is filtered off before the addition of the carbonyl compound [208,210-212] (Scheme 100, entry e).[208] The same control has been achieved even more conveniently by performing the Wittig reaction in a polar solvent such as DMF, DMSO or HMPA able to sequester the cation (Scheme 100, entries d,f,g).[208,209,213] Note that efficient stereocontrol to produce the (Z)-stereoisomer has been achieved in an ethereal solvent using a base in which lithium has been replaced by sodium or better potassium (Scheme 100, entry h compare to entry c).[208] Furthermore, phosphonium chlorides have to be preferred over the iodide since the resulting metal chlorides are usually less soluble in organic solvents. Unfortunately, benzylidenetriphenylphosphorane and other ylides with α-substituents capable of resonance are not suitable for Z-selective olefination reaction.[210]



	Ylide synthesis	Conditions	Yield %	E/Z ratio
a	(i) n-BuLi, ether, 25 °C, 0.5 h (ii) -40°C	(i) -40 °C, 1.30 h (ii) MeOH, -40 °C, 4 h	35	75/25
b	(i) n-BuLi, ether, 25 °C, 0.5 h (ii) -40°C	(i) -40 °C, 1.20 h (ii) MeOH, -40 °C, 10 h (iii) 25 °C, 1 h	67	51/49
c	(i) n-BuLi, ether, 25 °C, 1.5 h	(i) 25 °C, 2 h	61	22/78
d	n-BuLi, ether, 25 °C, 1 h (ii) DMF, 25 °C	(i) 25° C, 2 h	68	06/94
e	(i) $NaNH_2$, NH_3, -33 °C, 1.8 h (ii) benzene	(i) 0 °C, 2 h	52	06/94
f	NaOEt, DMF, 25 °C, 1 h	(i) 25 °C, 2 h, 60° °C, 4 days	10	02/98
g	NaH, DMF, 25 °C, 2 h	(i) 25 °C, 2 h	59	04/96
h	t-BuOK, THF, 25 °C, 0.5 h	(i) 25 °C, 0.9 h	69	04/96

Scheme 100. Stereochemical outcome of model reactions implying pentyltriphenylphosphonium ylide generated under various experimental conditions.[208]

Application of the "salt free" Wittig reaction to concise total synthesis of *rac*-histrionicotoxin has been reported and the key Wittig reaction step disclosed in Scheme 101.[214]



Scheme 101. Application of the "salt free" Wittig reaction to concise total synthesis of *rac*-histrionicotoxin.[214]

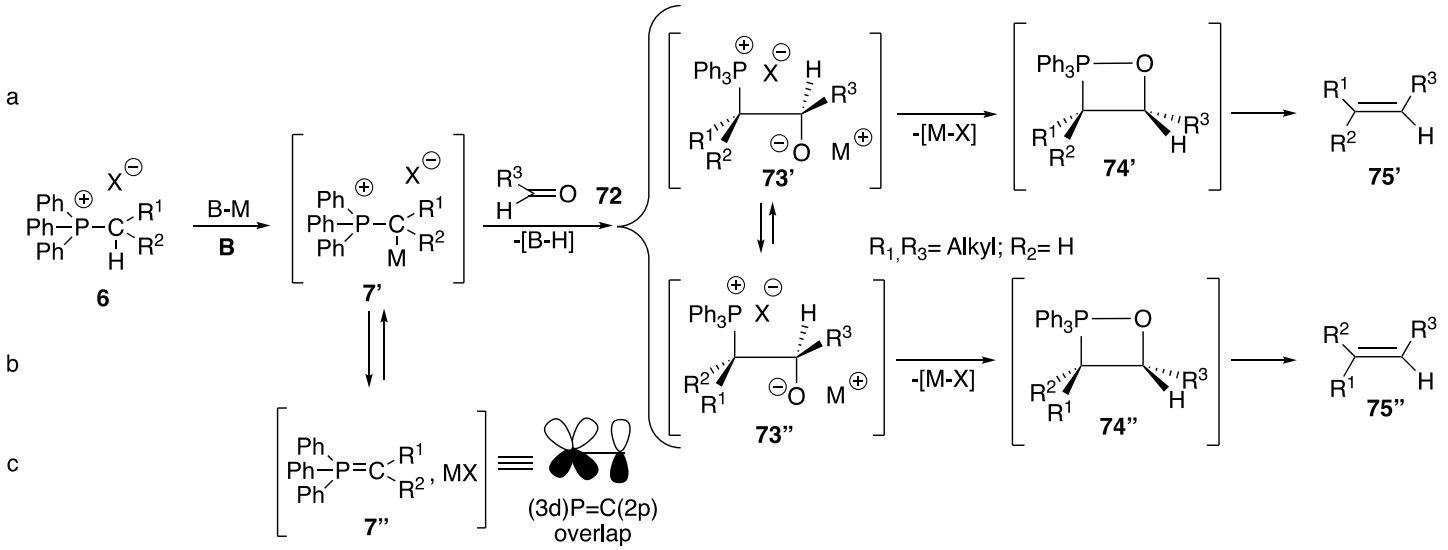
As already pointed out the Wittig reaction under salt free conditions has been used to synthesize (*Z*)-nor-chrysanthemic acid/esters (*Z*)-**1c**$_R$ (Chapter IVb, Section 4.4.2.1.2 (Scheme 35, entry b),[2] (Scheme 39, entry b)[60]), and some side reactions reported when the reaction is carried out on larger quantities (Scheme 34).[13] The Wittig reaction did however not allow the stereoselective synthesis of its stereoisomer (*E*)-nor-chrysanthemic acid/esters (*E*)-**1c**$_R$.

As already disclosed, the Wittig reaction has been successfully used to synthesize a large variety of pyrethroids bearing alkyl (Chapter VIb, 4.4.2.1) and alkenyl (Chapter VIb, 4.4.2.2) substituents at [Cf].

6.3.1. About the mechanisms of the Wittig reaction. "The mechanism of the Wittig reaction has long been a contentious issue in organic chemistry. Even now, more than 50 years after its discovery, its presentation in many modern undergraduate textbooks is either overly simplified or entirely inaccurate."[215] Even so (i) the now well-established "Li salt-free" Wittig mechanisms (Scheme 102), that include computational studies, are far to account the different experimental features of this reaction and (ii) the explanation of "Li-present" conditions still miss spectroscopic support but offer a simple mnemotechnic representation to predict most of the features of the experimental results under series of conditions (Scheme 102).

6.3.1.1. About the mechanism of the Wittig reactions in the presence of salts and its stereochemical implications. The Wittig reaction involves a "cascade or domino reactions"[216,217] (Scheme 102) in which an alkylmetal bearing a phosphonium salt in alpha-position **7'** or a phosphorane **7"**, in which the lone pair electrons of the carbanion are delocalized on an empty d-orbital of the posphorus atom, usually generated on reaction of a suitable base on a triphenyl phosphonium salt **6**, reacts on the carbonyl group of an aldehyde **72** or a ketone. It generates a beta alkoxyalkyl-phosphonium salt **73** (a betaine) that then forms an intermediate oxaphosphetane **74**.[218] The latter then collapses through a syn-elimination reaction, to deliver the compounds possessing the newly formed [C=C] double bond **75,** eventually as a mixture of stereoisomers, and triphenylphosphine oxide (Scheme 102). It has been however proved that d-orbitals do not significantly intervene in the stabilization of carbanions bearing in α-posittion an heteroatom belonging to the 3rd and 4rd rows of the periodic table (through P(3d)-C(2p) overlap, Scheme 102, entry c) but rather through dissipation of the electrons the σ*-orbitals of the heteroatom, as initially proposed by J.-M. Lehn in the case of selenium containing compounds.[217]

The Wittig reaction usually leads to a mixture of stereoisomers. It has been however found that the stereochemistry of the (*Z*)-α,β-dialkyl substituted olefins can be controlled if the reactions are carried out in the absence of salts that result from the metallation of the phoshonium salts. It has also been described that phosphonium salts bearing a carboxy group have a high tendancy to produce (*E*)-alpha, beta-unsaturated esters with high stereocontrol.



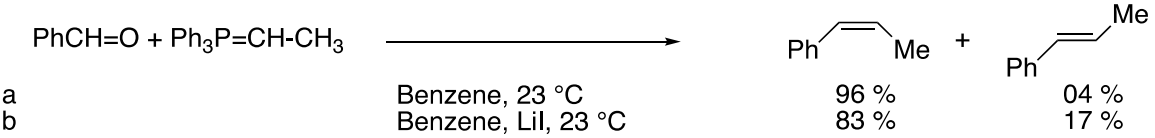
Scheme 102. One of the rational of the Wittig reaction involving alkyltriphenylphosphonium ylides and aldehydes in the presence of inorganic salts.

These features have been rationalized as disclosed in Scheme 102 although alternative mechanisms, that will be disclosed below, have been reported. Accordingly, it has been proposed that the reaction of ylides **7** (R^1= alkyl, R^2= H) with alehydes **72** leads predominantly to the beta-alkoxyalkyl-phosphonium salts **73'**, in which the two alkyl substituants are located far apart. Their transformation to the (Z)-olefins **75'** implies the intermediate formation of the sterically hindered oxaphosphetane **74'** that requires a rotation of 90° around the newly formed C,C bond, bringing the two alkyl substituents attached to the adjacent carbons in close proximity (eclipsed). The latter step is expected to be irreversible due to the strain released and the stability of the products formed (**75"** and Ph_3P=O).

This process is favored under salt-free conditions (under kinetically controlled conditions), in which the salt co-produced by metalation of the phosphonium salt is no longer present (precipitation out of or sequestration of the cation by the solvent such as DME, DMSO, DMPU, HMPA) and is unable to complex the β-alkoxyalkyl-phosphonium salts **73'**. This complexation would otherwise have hampered the transformation of **73'** to the oxaphosphetane **74'** favoring instead its isomerization to the β-alkoxyalkyl-phosphonium salts **73"**, the precursor of the oxaphosphetane **74"** and of the (*E*)-dialkyl substituted olefin **75"** (under thermodynamically controlled conditions).

The transformation of **73"** to **74"** is expected to be far easier than that of **73'** to**74'** since the two alkyl substituants in **74"** on the adjacent carbons are far from each other and therefore in the presence of salts the equilibrium is withdrawn in favor of the formation of the olefin **75"** leading finally to a mixture of the two stereoisomeric olefins **75**.

Experiments that support this view are disclosed in Scheme 103.[94]



a	Benzene, 23 °C	96 %	04 %
b	Benzene, LiI, 23 °C	83 %	17 %

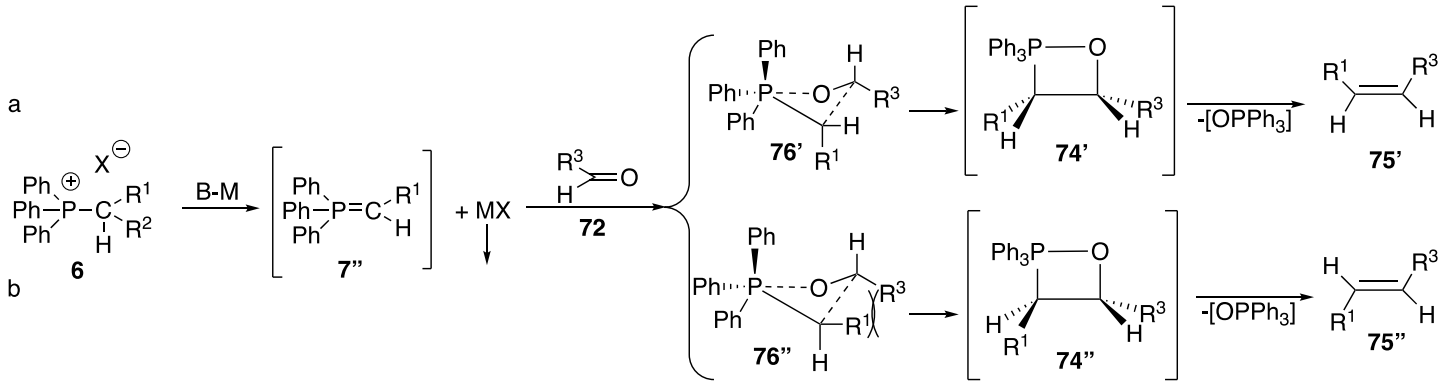
Scheme 103. Stereochemical changes impling the presence and the absence of lithium iodide in the Wittig reaction.[94]

The model disclosed in Scheme 102 also accounts for the poor stereochemical control of the reaction involving stabilized ylides (R^2= aryl or vinyl) even under salt free conditions and the predominant (*E*)-stereochemistry of the α,β-unsaturated esters from the ylide bearing a carboxylate on their carbanionic center. In those cases (that also include those bearing a carbonyl or cyano-group there) equilibration between **73'** and **73"** is expected to take place easily due to the extra-stbilization of those carbanions by delocalization over those groups.

6.3.1.2. About the mechanism of the "salt-free" Wittig reactions and its stereochemical implications. A different mechanism has been proposed to account for the formation of alkenes from salt-free ylides (Scheme 104). [211,215] It involves a [2+2] cycloaddition reaction between phosphoranes **7"** free from any salt and the carbonyl compounds **72** leading, through the postulated transition state **76**, to oxaphosphetanes **74**. The latter then decomposes through a different cycloreversion mode and leads irreversibly to the olefins **75** and triphenylphosphine oxide (Scheme 104).

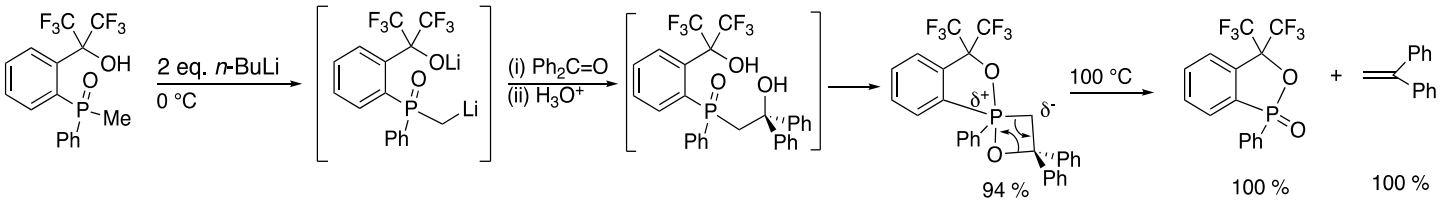
Such mechanism[215] has been originally postulated by Wittig who later favoured the betaine process (Scheme 102). It was reactivated by Bestmann[212] and more recently by Vedjes.[211] The latter performed a series of low temperature (-78 °C) experiments involving non-stabilized, salt-free ylides **7"** (R^2=H, generated from $NaNH_2$ and phosphonium bromides in liquid NH_3, then extracted with benzene after evaporation of NH_3; Conditions A) and aldehydes and found, by following the reaction spectroscopically (^{31}P- and ^{1}H-NMR), exclusively signals attributed to oxaphosphetanes **74** with no-trace of salt free betaines **73**.

The high preference for the (*Z*)-olefins **75'** (Scheme 104, entry a) was expected to result from the lower interactions between the two groups (R^1 and R^3) in the transition state **76'** over that involved in the competing "transition state" **76"** that would have led to the (*E*)-olefins **75"** (Scheme 104, entry b). Several conformations of the "transition-states" have been postulated but the reason that bring to the selection of **76'** and **76"** have not yet been established on solid grounds. Furthermore, the described rational cannot account for all the experimental facts such as a higher percentage of (*Z*)-alkenes **75'** formation under salt free conditions when a bulkier aldehyde is involved.



Scheme 104. Alternative rational of the Wittig reaction involving the phosphorus ylide and aldehydes in the absence of inorganic salts.[211,215]

Anyhow, some room temperature stable oxaphosphetanes, have been synthesized independently and found[218] to collapse to the expected olefin on thermolysis (Scheme 105).[218]

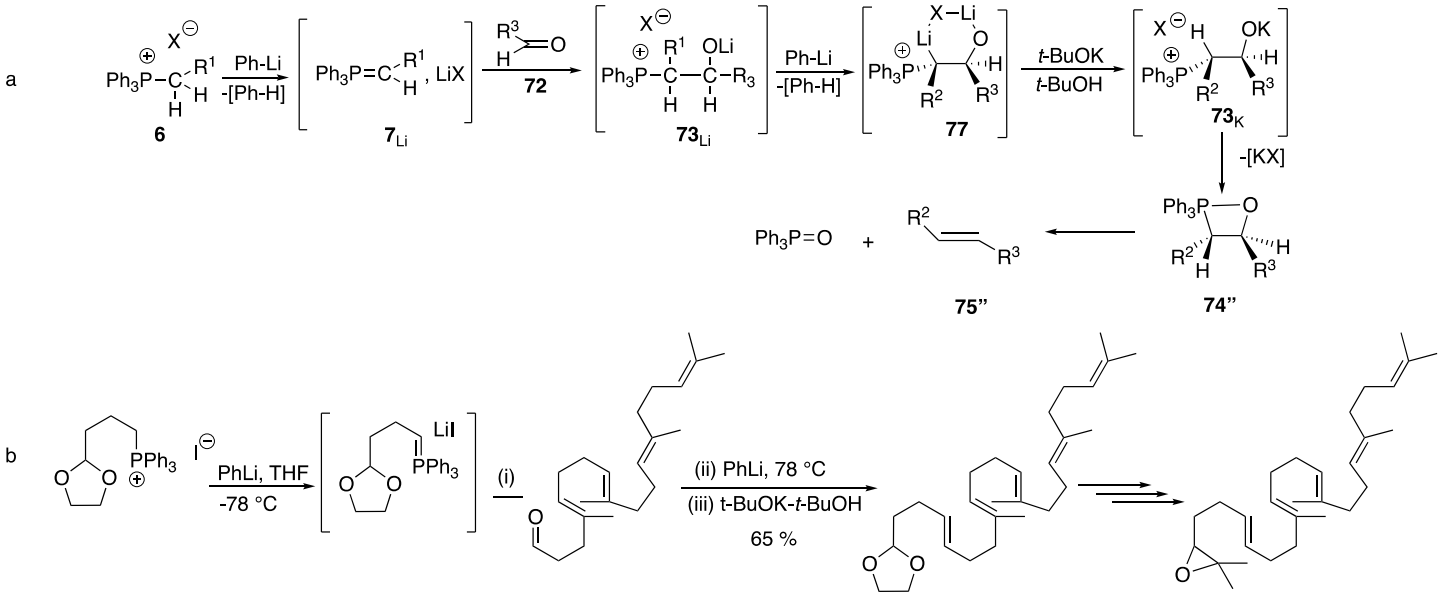


Scheme 105. Synthesis and decomposion of oxaphosphetanes.[218]

Vedjes observed the presence of betaine-LiBr adducts **73** and even aromatic aldehydes **72** and the ylides **7"** on further addition of LiBr to the oxaphosphetanes **74** resulting from the reaction between aromatic aldehydes **72** (R^3= Ar) and phosphoranes **7"**, generated in under salt-free conditions from the related phosphonium salts **6** (R^2=H) and potassium hydride at -40 °C.[211] The same process has not been confirmed for for aliphatic aldehydes.[211] Vedjes also described that salt-free oxaphosphetanes derived from ethylidenetriphenylphosphorane and methylidenetriphenylphosphorane and aromatic aldehydes are capable of reversible dissociation at -24 °C but not at -50 °C even after 1 h. Accordingly, 82% of the original oxaphosphetane from methylidenetriphenylphosphorane and benzaldehyde has decomposed after 35 min at -24 °C, to triphenylphosphine oxide, 13% survives, and the remainder (5%) is present as the crossover product of the adduct of benzaldehyde with ethylidenetriphenylphosphorane. Schlosser[94] has observed similar results in Wittig reactions carried out in the presence of salts

Crossover products, have been also observed [219] during reaction of phosphorus ylides with methyl γ-oxo-butenoates on the one pot synthesis of methyl vinylcyclopropane carboxylates derived from two different ylides in ether but were not observed when the reaction was carried out in THF instead.[219]

6.3.2. The "Schlosser-Wittig modification" involving beta-oxido-ylide and its postulated mechanism. Another modification of the Wittig reaction, the Wittig-Schlosser reaction, allows the stereoselective synthesis of (*E*)-disubstituted olefins (Scheme 106).[92,94,220] It involves (i) the synthesis of β-alkoxy-phosphonium salt $\mathbf{73}_{Li}$ from phosphorus ylides as lithium salts $\mathbf{7}_{Li}$ and carbonyl compounds **72** as usual in a Wittig reaction but (ii) it requires its further reaction with a lithium base, such as phenyllithium, leading to β-oxido-ylide **77**. The latter, after lithium/potassium echange then protonation using potassium *t*-butoxide and *t*-butanol, produces the (*E*) olefins **75"** in good yield and very high stereocontrol in favor of the (*E*)-stereoisomer, probably through the beta-alkoxy phosphonium salt $\mathbf{73}_K$ and the oxaphosphetane **74"** (Scheme 106, entry a).[92,220]



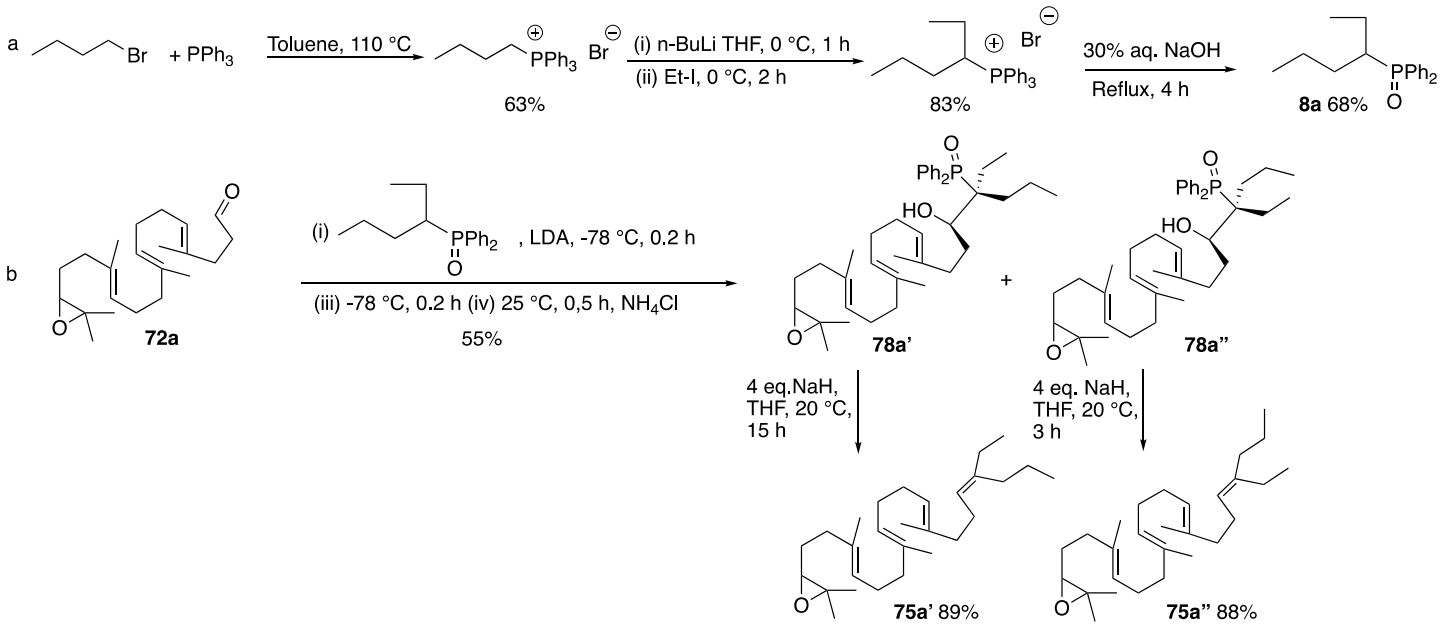
Scheme 106. The Schlosser-Wittig reaction involving beta-oxido-ylide and one of its applications to synthesize (*E*)-disubstituted olefins.[92,94,220]

This approach has been used to synthesize stereoselectively several natural products and analogues,[220,222] including the 6-desmethyl 1,2-oxidosqualene (Scheme 106, entry b).[220] It has been successfully extended by Corey to the stereoselective synthesis of trisubstituted alkenols by trapping the beta-oxido ylide **77** intermediate with carbonyl compounds.[223]

6.3.3. The Warren approach to stereo-pure alkenes. The need for stereoselective synthesis of alkenes comes from the fact that the related stereoisomers are usually difficult to separate, especially by large scale techniques. An original solution to that problem is to use synthetic methods that allow the isolation of stereoisomeric intermediates easily separable and able to be in the next step stereoselectively transformed to each of the two stereoisomeric alkenes.

An example of such strategy is disclosed in Scheme 107[224,225] for the synthesis of a trialkylsubstituted C=C double bonds as originally disclosed by Warren.[226]

It involves the stepwise synthesis of (i) alkyl diphenylphoshine oxides such as **8a**, prepared on reaction of the corresponding alkyl phosphonium salt with sodium hydroxide (Scheme 107, entry a),[224,225,227] (ii) their metalation using lithium diisopropylamine in THF and (ii) reaction of the latter with an aldehyde such as **72a**, leading to a stereoisomeric mixture of β-hydroxyalkyl phosphinoxide such as **78a** after protonation. The resulting mixture has been routinely separated either by crystallization or by chromatography on silica gel into its two stereoisomers and each diastereoisomer, **78a'** and **78a"**, has been subsequently transformed stereoselectively to the corresponding olefinic compounds **75a'** and **75a"** on reaction with sodium hydride through a formal *syn*-elimination process (Scheme 107, entry b).[224] Note that the elimination reaction applied to the compounds **78a'** disclosed in Scheme 107, delivers the (*Z*)-olefinic compound **75a'** faster than its diastereoisomer **78a"**produces the (*E*)-olefinic compound **75a"** (3 compared to 15 h).[225]



Scheme 107. Synthesis of stereopure (*E*)- and (Z)-trialkyl-substituted olefins involving the Warren approach.[224,225]

6.4. Synthesis of α,β-unsaturated-esters using the Wittig and related reactions

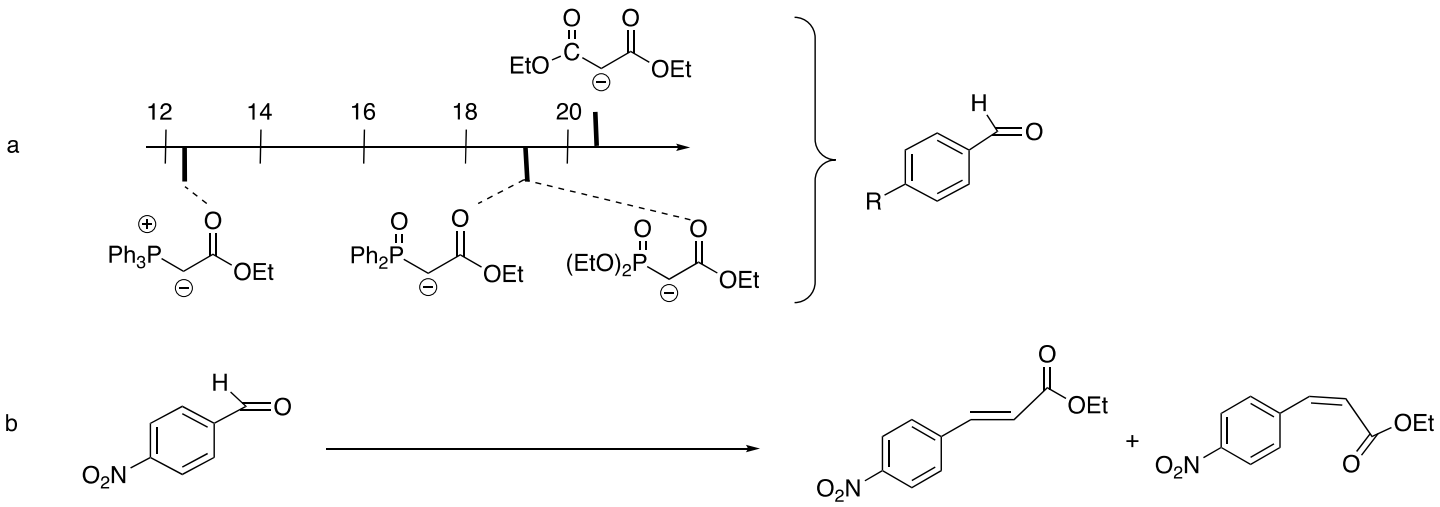
This section is related to the synthesis of vinylcyclopropane carboxylic acid/esters bearing carbonyl or carboxy groups, as well a hydrogen or a methyl group at [Cf] used to synthesize pyrethroids, the structures of which are related to that of pyrethrin II **1b**$_{MeA}$ (Figure 1, Scheme Chapter IVb, Section 4.4.2.3).

The synthesis of alpha-beta-unsaturated esters and more remarkably those possessing in complement a hydrogen or a methyl group at [Cf], has been performed from aldehydes and phosphorus ylides **7** [Ph_3P^+-, Wittig reagents] or with phosphoryl-stabilized carbanions **9** [$R_2P(=O)$-, Wittig-Horner reagents] and phosphono substituted carbanions **11** [$(RO)_2P(=O)$-, Horner-Wadsworth-Emmons reagents] derived from acetates and propionates among others.

The relative nucleophilicity of a series of these reagents towards carbocations and benzaldehydes disclosed in Scheme 108, has been reported by Boche.[197] The Wittig-Horner and Horner-Wadsworth-Emmons reagents have been found to possess a similar reactivity towards carbocations, substantially higher (10^4 – 10^5) than that of analogously substituted Wittig reagents. However, the relative reactivities of these nucleophiles towards aromatic aldehydes differ significantly from those towards carbocations but exhibit the same tendency (Scheme 108).[197]

Horner-Wadsworth-Emmons reagents [80, 196] offer the advantages (i) to be more reactive (Scheme 108), [196,197] (ii) to possess a much lower molecular weight, especially the one of the phosphorus containing entity that is expelled as a co-product in the process (iii) to allow easy separation of the phosphorus containing co-product from the enoates since water soluble.[80,81]

Effects of the potassium or sodium counterion (K^+, Na^+) on the nucleophilicity of the phosphoryl-stabilized carbanions in DMSO proved to be negligible for all types of carbanions investigated, although in the olefination reaction sodium slightly enhances their reactivity toward carbonyl compounds. It has been however disclosed that lithium coordination reduces the reactivities of phosphonate-substituted acetic ester anions (**11a**) by a factor of 10^2.[194,197]

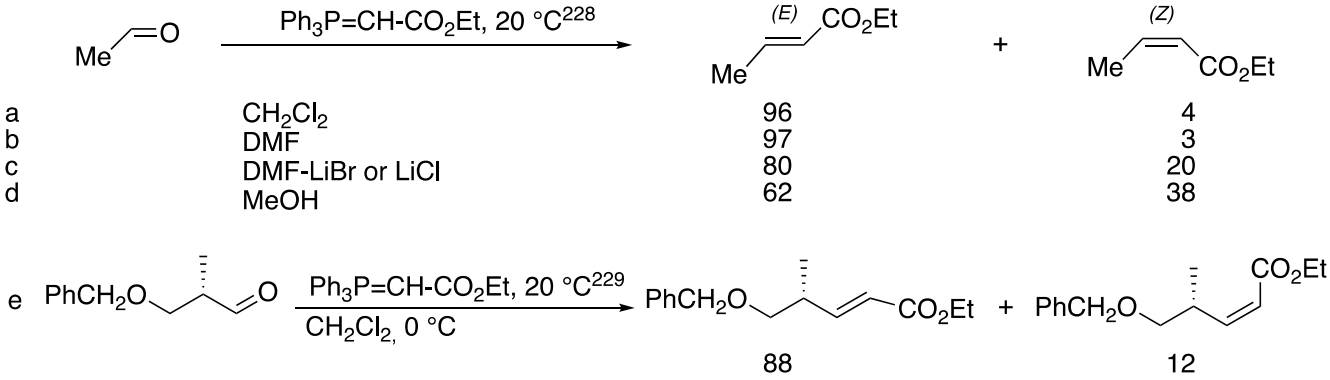


Scheme 108. Relative reactivity of phosphorus substituted enolates towards aromatic aldehydes.[194,197]

It has been confirmed that electron-withdrawing groups at the 3- or 4-position on benzaldehydes increase the reaction rate whereas electron donating substituents decelerate it.[197]

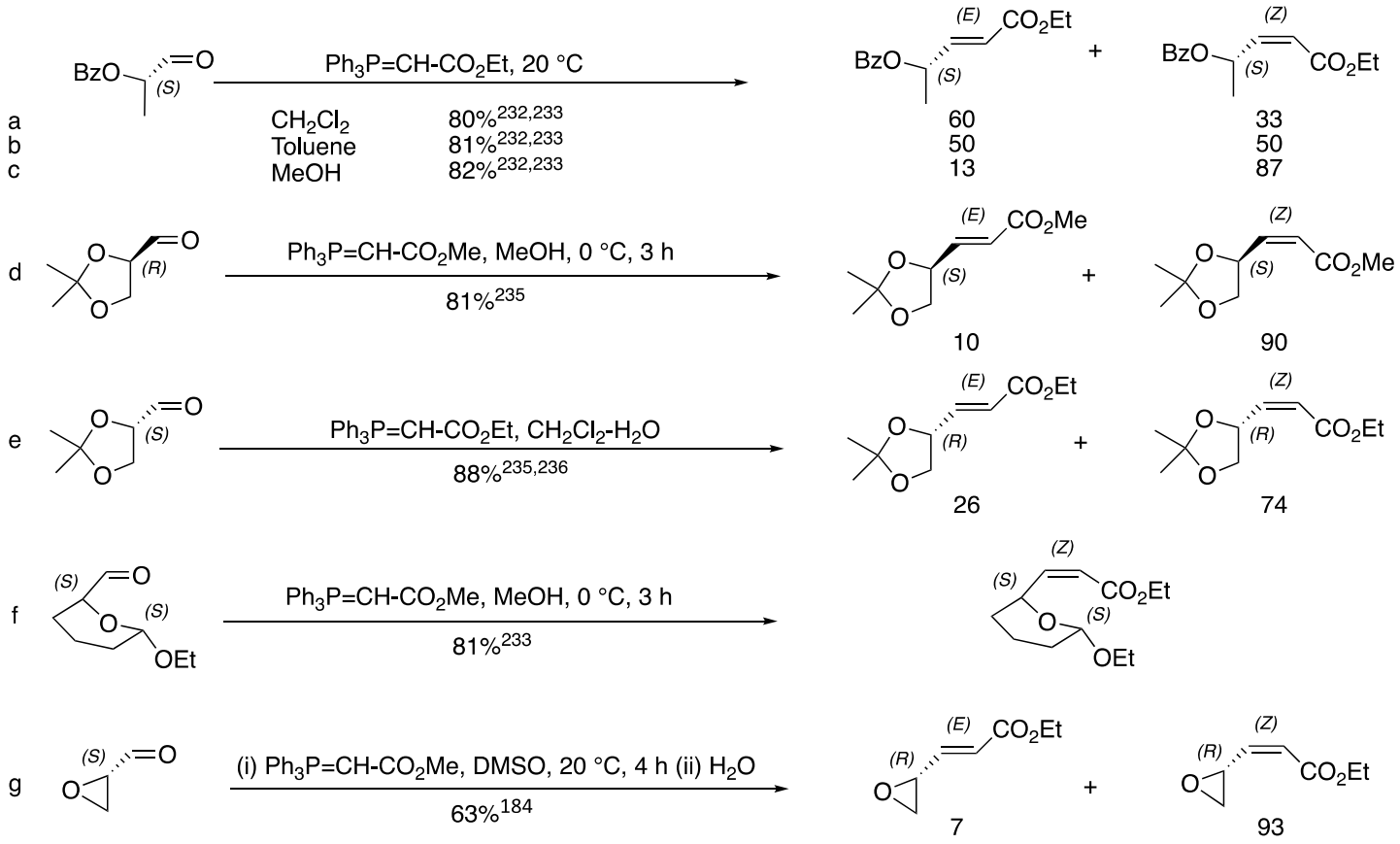
The control of the stereochemistry of the [C=C] double bond of the resulting α,β-unsaturated esters has been the subject of constant interest. We will describe first the results involving the stabilized Wittig reagents bearing a triphenylphosphonium moiety, then concentrate our presentation on the stabilized Horner-Wadsworth-Emmons and related reagents that have been specifically used for the synthesis of α,β-unsaturated esters.

6.4.1. Synthesis of alpha,beta-unsaturated esters using the Wittig reaction. The reaction of ethoxycarbonylmethylidene triphenylphosphorane with aldehydes in dichoromethane leads mainly to (*E*)-α,β-unsaturated esters (Scheme 109 entries a,e).[228,229] Use of either protic solvents such as methanol (Scheme 109, entry d)[228] or dipolar aprotic solvents (DMF or DMSO), especially in the presence of dissolved lithium salts (Scheme 109, entry c)[228] usually enhance the proportion of (*Z*)-isomer. Those observations have been exploited on several occasions.[229-231]



Scheme 109. Stereochemical implication of the solvent in the reaction of methoxycarbonylmethylidene triphenylphosphorane with aldehydes.[228,229]

Similar or even stronger tendencies to favor the formation of the (Z)-stereoisomers have been observed with alpha-alkyl (Scheme 109, entry e)[229] and alpha-alkoxy-aldehydes (Scheme 110). [106,232-236]



Scheme 110. Stereochemical implication of the solvent in the reaction of methoxycarbonylmethylidene triphenylphosphorane with aldehydes.[184,232,233,235,236]

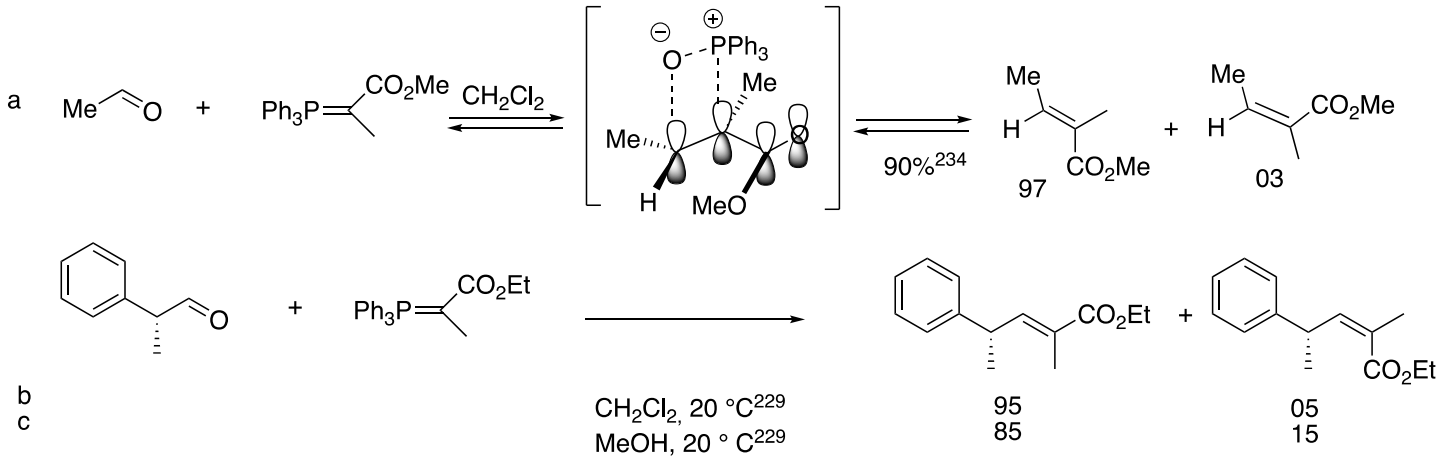
The *(Z)*-stereoisomer is produced from alkoxycarbonyl methylenetriphenylphosphorane in increasing amount on going from DMF in which the *(E)*-stereoisomer is mainly formed (*Z*/*E*: 27/73)[232] or HMPA (*Z*/*E*: 30/70),[232] to methylene chloride (*Z*/*E*: 65/35),[232,233] toluene, [233] and finally to methanol (*Z*/*E*: 89/11),[232,237,238] especially anhydrous methanol,[233] in which the *(Z)*-stereoisomer is formed with high diastereoselection (Scheme 110).

The diastereoselection increases by lowering the temperature but the reaction time increases, too.[233] It strongly depends on the nature of the aldehyde. It is moderate to good with acyclic alkoxy-aldehydes (Scheme 110, entry c), much better when the alkoxy group is part of a dioxolane (Scheme 110, entries d,e)[106,230,231-233,235-237] or a six membered cycle (Scheme 110, entry f).[233] Stereocontrolled synthesis of methyl (*E*)-3-(3,3-dimethyl-oxiranyl)-acrylate on reaction of 2,3-oxido-4-methyl-butanal with methoxycarbonylmethylidenetriphenylphosphorane in DMSO is fully consistent with the results disclosed above (63% yield, de 85%, Scheme 110, entry g).[184]

The reasons for the (*Z*)-selectivity are still under debate although some hypotheses have been suggested.[231,228]

The reactions involving methoxycarbonylethylidenetriphenylphosphorane in dichloromethane mainly leads to the (*E*)-α,β-unsaturated esters (Scheme 111, entries a,b)[234,229] but contrary to the above, performing the reaction in methanol instead of methylene chloride does not dramatically increase the amount of the (*Z*)-stereoisomers (Scheme 111, entry c,[229] compare to Scheme 110, entry c[232,233]). The aptitude of this ylide to deliver the (*E*)-stereoisomer probably results from the more rapid decomposition of the betaine

diastereoisomer (Scheme 111, entry a)[234] in which there is less steric interference with overlap between the pi-orbital of the carbonyl function and the pi-orbital of the developing double bond.[234]



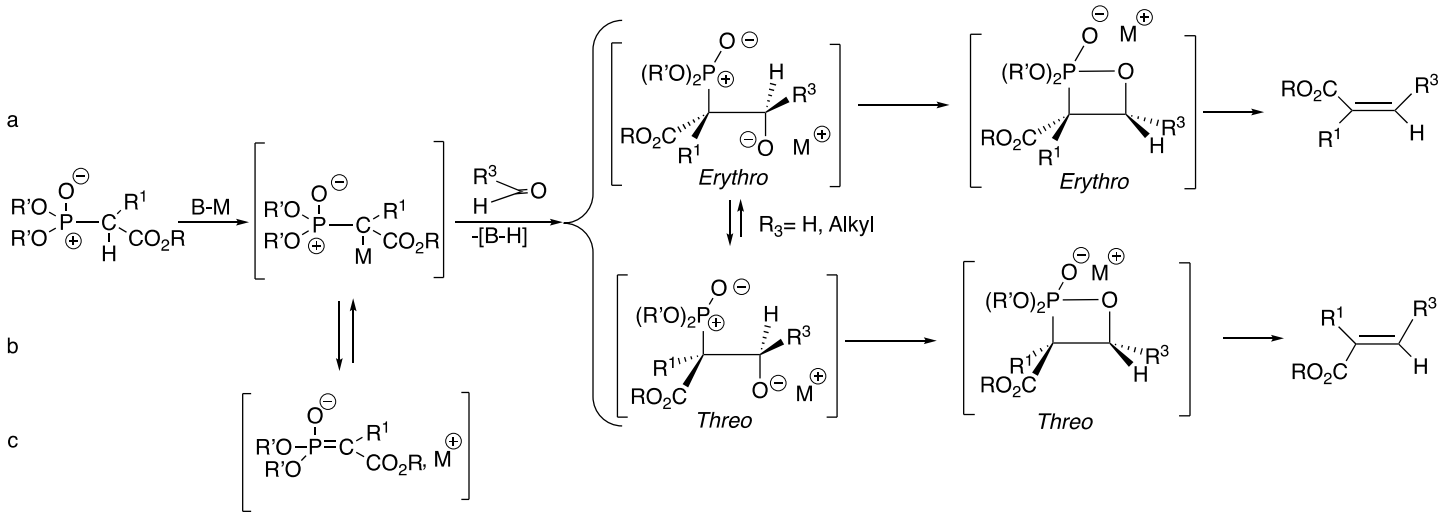
Scheme 111. Stereochemical implication of the solvent in the reaction of methoxycarbonyl ethylidenetriphenylphosphorane with aldehydes.[229,234]

6.4.2. Synthesis of α,β-unsaturated esters using the Wittig-Horner-Emmons reaction. Horner-Wadsworth-Emmons-reaction (HWE) has been the subject of intensive research over the last fifty years.[77,80,82,239] High selectivity for (*Z*)- or (*E*)-[C=C] double bonds has been achieved depending on the particular circumstances, such as the nature of phosphonate, the type of carbonyl compound, as well as the reaction conditions.

Their formation has been rationalized as in the Wittig reaction either by initial formation of a β-alkoxy-phosphonates, their ring closure leads to the related oxaphosphetanes that then collapse to the α,β-unsaturated esters (Scheme 112).[80,82] Alternatively the diastereoisomeric oxaphosphetanes could be produced[197] through a concerted cycloaddition reaction and decomposed through a concerted but dissymmetric process in which the [C-O] bond is longer than the [C-P] bond.[197] Systematic kinetic investigations of the HWE reaction in ethanol by Larsen and Aksnes,[240,241] led to the conclusion that the oxaphosphetane intermediate is formed in a concerted manner in the rate-determining step.

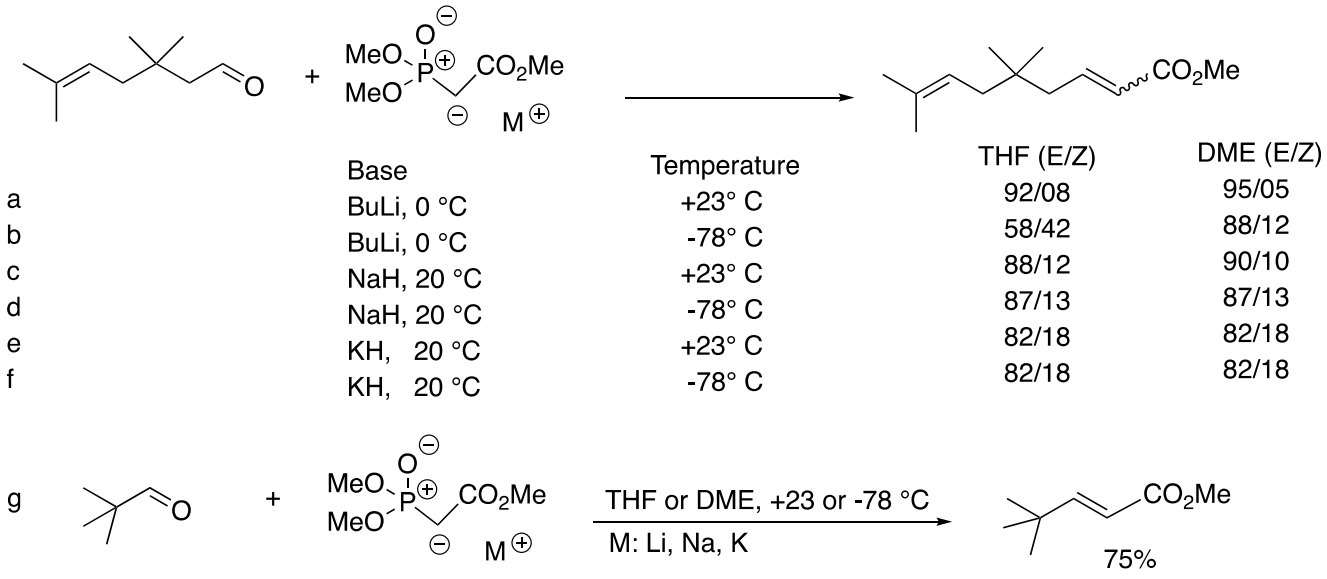
It is generally accepted that the stereoselectivity of the HWE-reaction is a result of both kinetic and thermodynamic control upon the reversible formation of the erythro- (Scheme 112, entry a) and threo- (Scheme 112, entry b) adducts and their decomposition to olefins through the betaine intermediates on which the unfavorable interactions are reversed (Scheme 112). The stereochemistry of the [C=C] double bonds depend on (i) the stereoselectivity in the carbon-carbon-forming step and (ii) the reversibility of the intermediate adducts.

The first formed erythro-adduct, that implies the lower interactions in its formation (Scheme 112, entry a), when collapsing immediately leads to the (*Z*)-enoates. However, if equilibration takes place, the threo-adduct is produced leading to the (*E*)-enoates. The presence of carbanions stabilized by both a carboxyl- and a phosphoryl-group favors this equilibration unless the first formed erytho-betaine has an extremely high tendency to be produced and decomposed to the olefin.



Scheme 112. One of the rational of the reaction involving "stabilized" phosphoryl ylides and aldehydes.

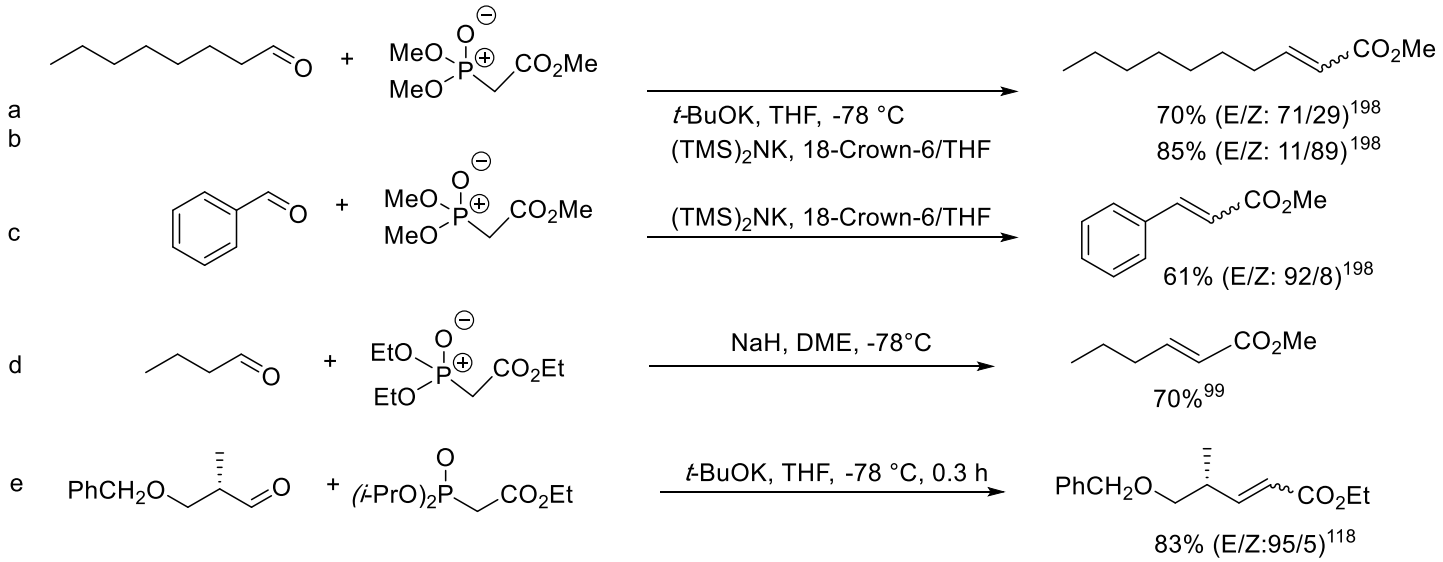
6.4.2.1. Stereoselective synthesis of (*E*)-α,β-unsatured esters. As originally reported the sequential reaction of (dialkylphosphono)acetates with *n*-butyllithium in DME then alkanals leads to the predominant formation of the (*E*)-enoates (Scheme 7),[13] (Scheme 40),[60] (Scheme 41),[66] (Scheme 43, entry a),[8] (Scheme 113),[242] (Scheme 114, entry a)[198]. This is effectively the case of bulky aldehydes (Scheme 113, entry g, compare to entries a-f). (*E*)-Enoates are expected to result from an extremely rapid equilibration of the first formed kinetic erythro-adduct to the thermodynamically more stable threo-adduct.[243] This equilibration is expectedly favored at higher temperature (Scheme 113, compare entry a to entry b), especially if the interactions between the carboxylate and the alkyl chain are important (Scheme 113, compare entry g to other entries).



Scheme 113. Stereochemical influence of the counterion and the solvent in the HWE reaction involving aldehydes.[242]

It has been found[198,242] in these studies that performing the reaction in different solvents (THF, DME, benzene)[242] does not affect the stereochemistry of the resulting enoates. Similarly exchanging lithium by sodium

or potassium does not affect the stereoisomeric ratio of enoates (Scheme 113, entries c-g compare to entries a,b).

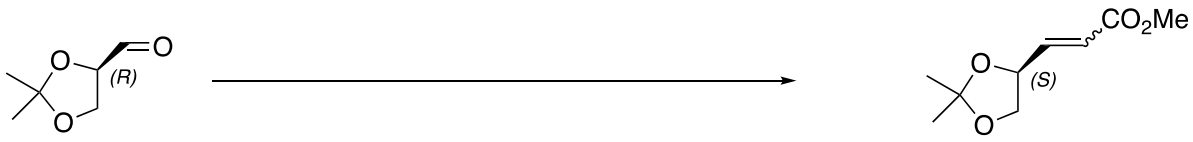


Scheme 114. Stereocontrolled synthesis of α,β-unsatured esters using the HEW-reaction.[198,99,229]

The results disclosed in Scheme 114 give a complementary overview[99,198,229, 237] since higher percentage of the (*E*)-isomer is formed when the olefination reaction is carried out with metalated phosphonoacetates bearing a larger alkoxy group than OMe group on the phosphorus atom (OEt, Oi-Pr, Scheme 114, entries d,e [99,198] compare to Scheme 113, entries b-f; [242] Scheme 114, entry a [198]).

These conditions proved particularly efficient to promote the synthesis of (*E*)-enoates from aldehydes bearing an alkyl- (Scheme 114, entry e,[229] compare to entry a [198]) or an alkoxy- (Scheme 115,[235] compare to Scheme 114, entry a[198] substitutent in α position.

It has been also described that performing the above olefination reaction with a potassium base in the presence of 18-crown-6 in THF change dramatically the E/Z ratio in favor of the (*Z*)-stereoisomer (Scheme 114, entry b, compare entry a).[198 242] However, it has been described that under these conditions aromatic aldehydes behave differently that alkanals and provides the (*E*)-enoates almost exclusively (Scheme 114, entry c, compare to entry b).[198]



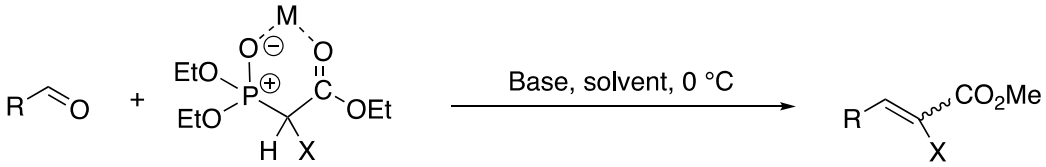
Scheme 115. Stereocontrolled synthesis of α,β-unsatured esters from glyceraldehyde acetonide.[235]

(*E*)-Enoates derived from glyceraldehyde acetonide (Scheme 115, entry d)[235] have been used as starting materials for the enantioselective synthesis of chrysanthemates, permethrinates and deltamethrinates by

cyclopropanation involving 2-propanylene carbenoids. These results will be discussed in a forthcoming chapter. Note that its (*Z*)-isomer has been synthesized using phosphonium ylides (Scheme 110). [106,235,236]

An even better synthesis of the (*E*)-enoates involves the use of metal salts, the metal cations of which tightly complexes the phosphonate and ester oxygens, enhance its acidity and allow the use of tertiary amines as base. This is typically the cases of Masamune-Roush conditions that involve week base such as:
(i) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[243] triethylamine or diisopropylamine in the presence of lithium halides in acetonitrile (Scheme 116, entry a),[244]
(ii) triethylamine in the presence of strongly coordinating magnesium bromide[244] (Scheme 116, entry b), particularly useful for base sensitive compounds,
(iii) N-ethylpiperidine (EtNPip) in the presence of tin(II) triflate (Scheme 116, entry e).[245,246]

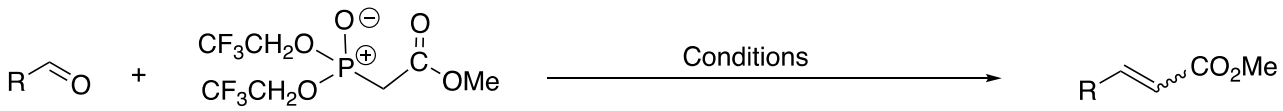
However the presence of a fluoro substituent on the phosphonate often lowers the propensity of this method to deliver (*Z*)-enoates (Scheme 116, entries c,d).



	R	X	M	Base	Solvent	Yield	E/Z
a	*n*-C_6H_{13}	H	LiBr	NEt_3	MeCN	75%[244]	100/00
b	*n*-C_6H_{13}	H	$MgBr_2$	NEt_3	THF	100%[244]	100/00
c	$Ph(CH_2)_2$	F	Na	NaH	THF	82%[246]	83/17
d	$Ph(CH_2)_2$	F	$MgBr_2$	NEt_3	THF	77%[246]	53/47
e	$Ph(CH_2)_2$	F	$Sn(OSO_2CF_3)_2$	EtN-Pip	THF	86%[246]	95/05

Scheme 116. HEW-stereocontrolled synthesis of α,β-unsatured esters involving chelation by metal salts.[244,246]

6.4.2.2. Stereoselective synthesis of (*Z*)-α,β-unsatured esters. Selective formation of the (*Z*)-enoates has been achieved through the erythro-betaine rather than the threo isomer by favoring for example the rapid formation of the erytho-oxaphosphetanes and by disfavoring the equilibration step. This has been achieved by selecting:
(i) a base whose counter-ion is non coordinating (at best potassium counter-ion especially in the presence of a crown ether and preferably the 18-crown-6 (Scheme 114, entry b; Scheme 117),[198]
(ii) reagents whose phosphoryl group
(a) possess electron withdrawing substituents such as the 2,2,2-trifluoroethoxy group (CF_3CH_2O-, Scheme 117)[198] or aryl-groups (ArO, Scheme 119).[248-251]

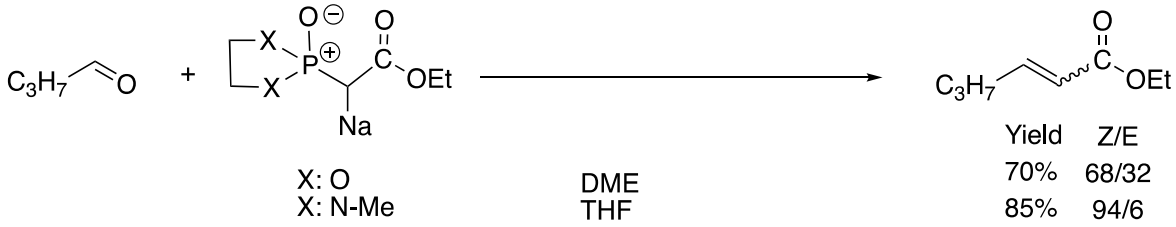


	R	Conditions	Yield	Z/E
a	*n*-C_7H_{15}	1 eq. $(TMS)_2NK$, 1 eq. 18-crown-6, THF, -78 °C, 0.5 h	90%	92/08
b	*n*-C_7H_{15}	(i) 6 eq. K_2CO_3, 12 eq. 18-crown-6, toluene, +25 °C, 0.5 h (ii) 0°C, 0.5 h	71%	85/15
c	*n*-C_7H_{15}	Triton B, THF, -78°C	84%	88/12
d	Ph	1 eq. $(TMS)_2NK$, 1 eq. 18-crown-6, THF, -78 °C, 0.5 h	95%	98/02
e	Ph	Triton B, THF, -78°C	95%	83/17
f	4-MeO-Ph	1 eq. $(TMS)_2NK$, 1 eq. 18-crown-6, THF, -78 °C, 0.5 h	95%	98/02

Scheme 117. HEW-stereoselective synthesis of α,β-unsaturated esters involving trifluoromethyl ethoxy group.[198]

(b) is part of a cycle (alkoxy[100] or amino groups[247]) such as cyclic phosphonates or 1,3-dimethyl 2-oxo 1,3,2-diazaphospholidine, (Scheme 118). Results concerning phosphoryl derivatives bearing various substituants are disclosed in a recent review.[81]

(c)

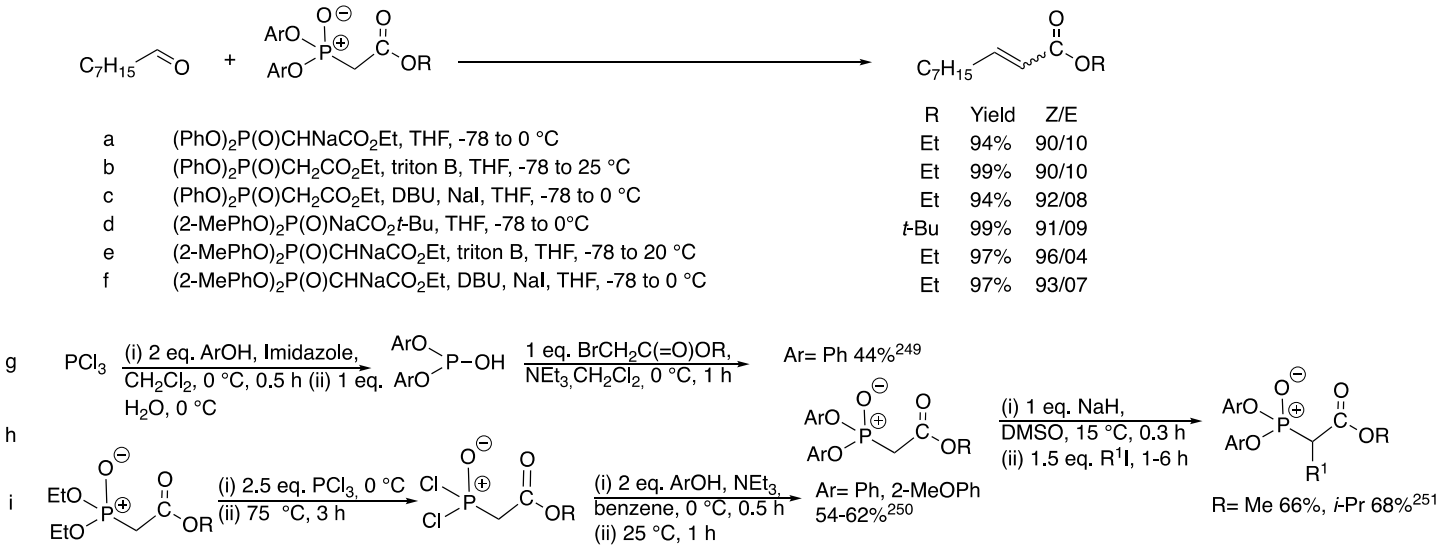


Scheme 118. HWE-stereoselective synthesis of α,β-unsaturated esters involving cyclic phosphonates.[100,247]

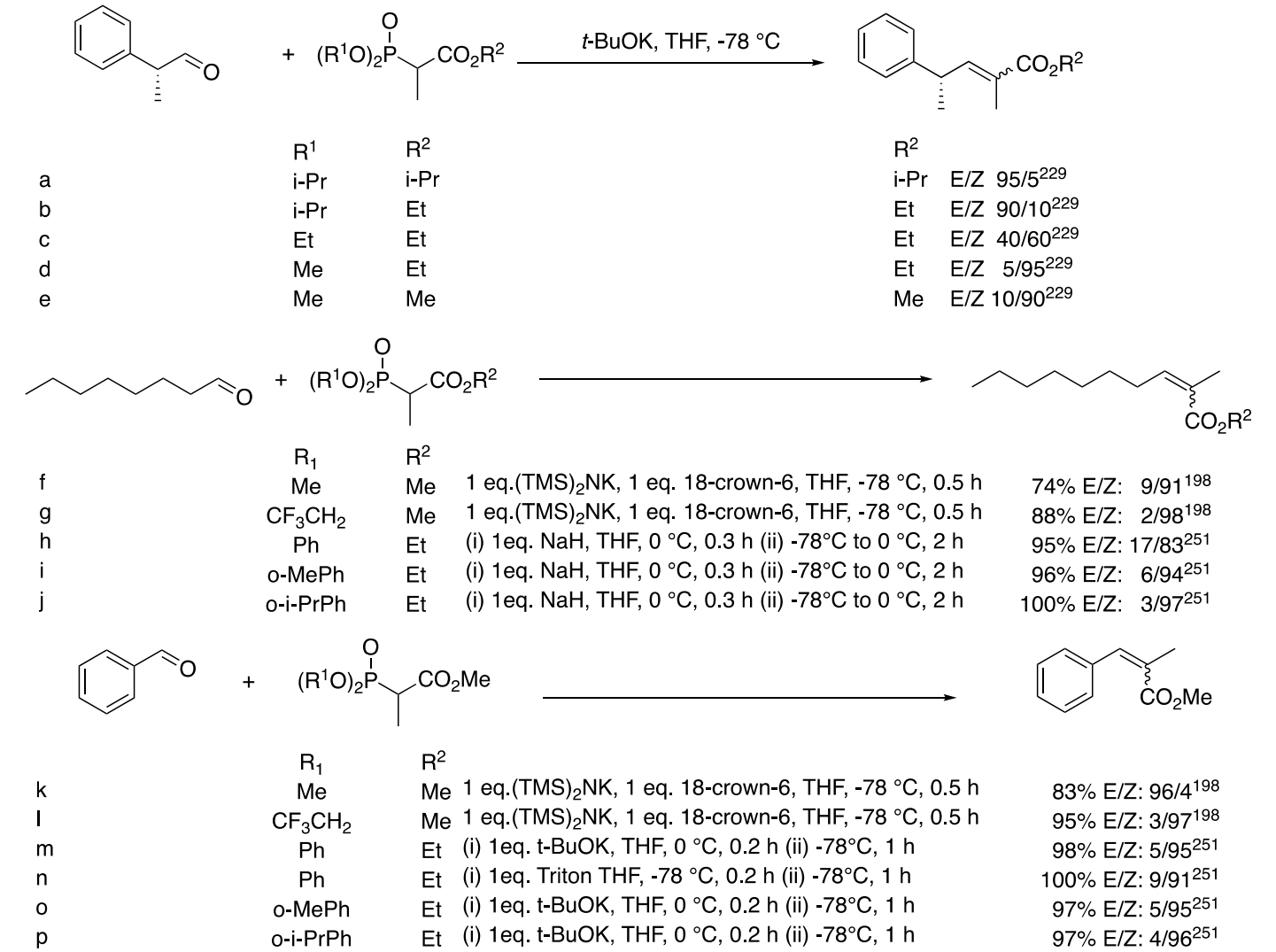
Those reagents and conditions have been used by the Roussel-Uclaf Company to synthesize (*Z*)- pyrethroates with high stereocontrol (Scheme 43).[8] Those proved to possess very high insecticidal activities (Scheme 42).[8] These results are gathered in Chapter IVB, Section 4.4.2.3.

Otherwise, use of acetates bearing phenoxy groups on their phosphoryl moiety seems to be the best compromise [248-251] since their synthesis is easy (Scheme 97) and their metalation involves usual basic system such as Triton B (benzyltrimethyl ammonium hydroxide) or DBU in the presence of sodium iodide (Scheme 119). The later proved to deliver better yields and better stereocontrol than lithium chloride or bromide.[249]

The Still-Gennari[81,198] and the Ando[248-251] conditions are probably the most convenient to produce (*Z*)-enoates. The former however suffers from the difficult access to the trifluoromethyl ethyl phosphonates (Scheme 96,[198] Scheme 97[208]) and the requirement to use concomitantly potassium bis(trimethylsilyl)amide and 18-crown-6 to get optimum results (Scheme 117, compare: entry b to a and entry d to e).[198] Those constrains, especially the last one, is not operative with the phosphonates bearing instead aryloxy group on phosphorus[248,249,250,251] that provide (*Z*)- enoates using potassium hydroxide or Triton B (benzyltrimethyl ammonium hydroxide) in THF at -78 °C or better at -95 °C (Scheme 119, entries a-f, [248-250] Scheme 120, entries h-j, m-p[251]). The synthesis of the reagent is disclosed Scheme 119, entries g-i). Note that the Still-Gennari[81,198] and the Ando[248-251] conditions are rare methods that allow with high stereocontrol the synthesis (*Z*)-cinnamates (Compare Scheme 117, entry d and Scheme 120, entries l-p to Scheme 114, entry c[198] and and Scheme 120, entry k[198]).



Scheme 119. HWE-stereoselective synthesis of α,β-unsaturated esters involving phenoxy phosphonates. [248-251]



Scheme 120. HEW-stereoselective synthesis of α,β-unsaturated esters involving different group on the phosphorus atoms. [81,198,229,251]

The control of the stereochemistry of enoates bearing a methyl-substituent at [C]-alpha on their structure, as in pyrethric acid **1b**$_{MeH}$, has been a subject of interest. Kishi[229] was probably first to recognize that the stereochemistry of the HWE modification of the Wittig reaction is sensitive to the structure phosphonate reagents and Stille[198] first to recognize the importance of the conditions used on the same. Some representative results are gathered in Scheme 120. The phosphonate reagents with a large phosphonate ester group predominantly yield (*E*)-stereoisomers (Scheme 120, entries a,b) whereas a small phosphonate group predominantly leads to (*Z*)-stereoisomers (Scheme 120, entries d,e).

For example, in many cases the best conditions to achieve an excellent (*Z*)-stereocontrol use not only a potassium containing base such as potassium *t*-butoxide but also the presence of a crown ether able to complex specifically the potassium cation (Scheme 114, entry b; Scheme 117, Scheme 120, entries a,b).[198]

Some of those conditions have been used to access (*E*)-pyrethric acids and (*E*)-pyrethroates resembling the natural pyrethrin II (**1b**$_{MeA}$) (Scheme 7,[13] Scheme 40,[60] Scheme 41,[66]).

6.4.2.3. Conclusion about the control of the stereochemistry of α,β-unsatured esters. In conclusion, the HWE reaction allows the efficient synthesis of enoates possessing the (*E*)- or the (*Z*)-stereochemistry. For the synthesis of the (*E*)-stereoisomers, metalated methyl and isopropyl phosphonoacetates and -propionates bearing a lithium cation proved to be the most valuable.

For the synthesis (*Z*)-enoates, the nature of the substituents on the reagent as well as the nature of the counter ion have a crucial importance. Best results have been observed using metalated phosphonoacetates and -propionates possessing trifluoromethoxyl-ethyl- and aryloxy- substituents or in which the two oxygen-atoms are part of a five or a six-membered cycle. Potassium or ammonium counter ions are almost mandatory and often such as in the case of the phosphonate bearing a 2,2,2-trifluoroethyl group the concomitant use of a crown ether is required to get better control the (*Z*)-stereochemistry of the enoates.

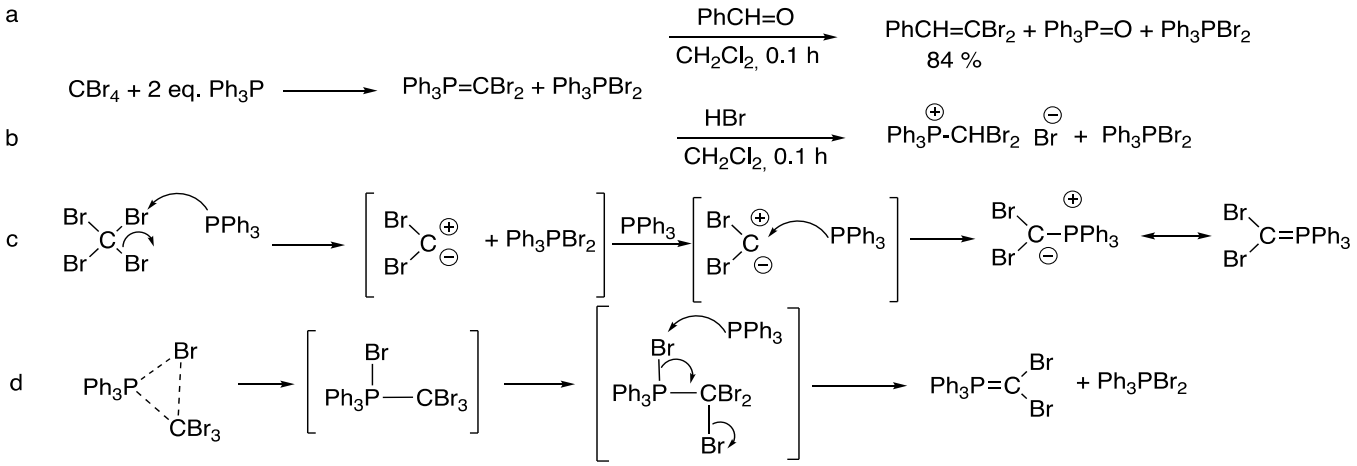
6.5. Synthesis of [C=C] double bonds bearing two halogens at [Cf] using the Ramirez extension of the Wittig reaction

This section is related to the synthesis of vinylcyclopropane carboxylic acid bearing two halogen substituents at [Cf] (Chapter IVb, Section 4.4.2.4).

As outlined above cypermethrin **1d**$_F$ and deltamethrin **1f**$_F$ that bear two similar halogen atoms (Br, Cl) at [Cf] on their [C=C] double bond are commercially important insecticides for agriculture. One of their syntheses involves the Ramirez[101] and related reactions[102-104] in which hemicaronates **3**$_R$ are reacted *in-situ* with stoichiometric amounts of carbon tetrahalides and 2 equivalents of a phosphine or a triaminophosphine. A model reaction is disclosed in Scheme 121, entry a.[101]

The key step of this process is the intermediate formation of dibromomethylenetriphenylphosphorane on attack of triphenylphosphine on the bromine atom of carbon tetrabromide. It leads to formation of the tribromocarbanion and bromophosphonium bromide (Scheme 121, entry c). The former, a carbenoid, collapses to the dibromocarbene immediately trapped by the second equivalent of triphenylphosphine to produce dibromomethylenetriphenylphosphorane (Scheme 121, entry c).

Alternatively, triphenylphosphine reacts on the bromine atom of carbon tetrabromide leading to an intermediate with a pentavalent phosphorus atom. The latter on reaction of the second equivalent of triphenyl phosphine produce dibromomethylenetriphenylphosphorane and dibromophosphonium bromide (Scheme 121, entry d).



Scheme 121. Postulated mechanism of the Wittig-Ramirez reaction.

Reacting the resulting mixture with hydrobromic acid leads to the formation of dibromomethyl triphenylphosphonium bromide in complement to triphenyl phosphonium bromide (Scheme 121, entry b) whereas in the presence of benzaldehyde an extremely rapid reaction reminiscent to the Wittig reaction takes place leading to dibromostyrene and triphenylposphinoxide in very high yields (Scheme 121, entry a).[101]

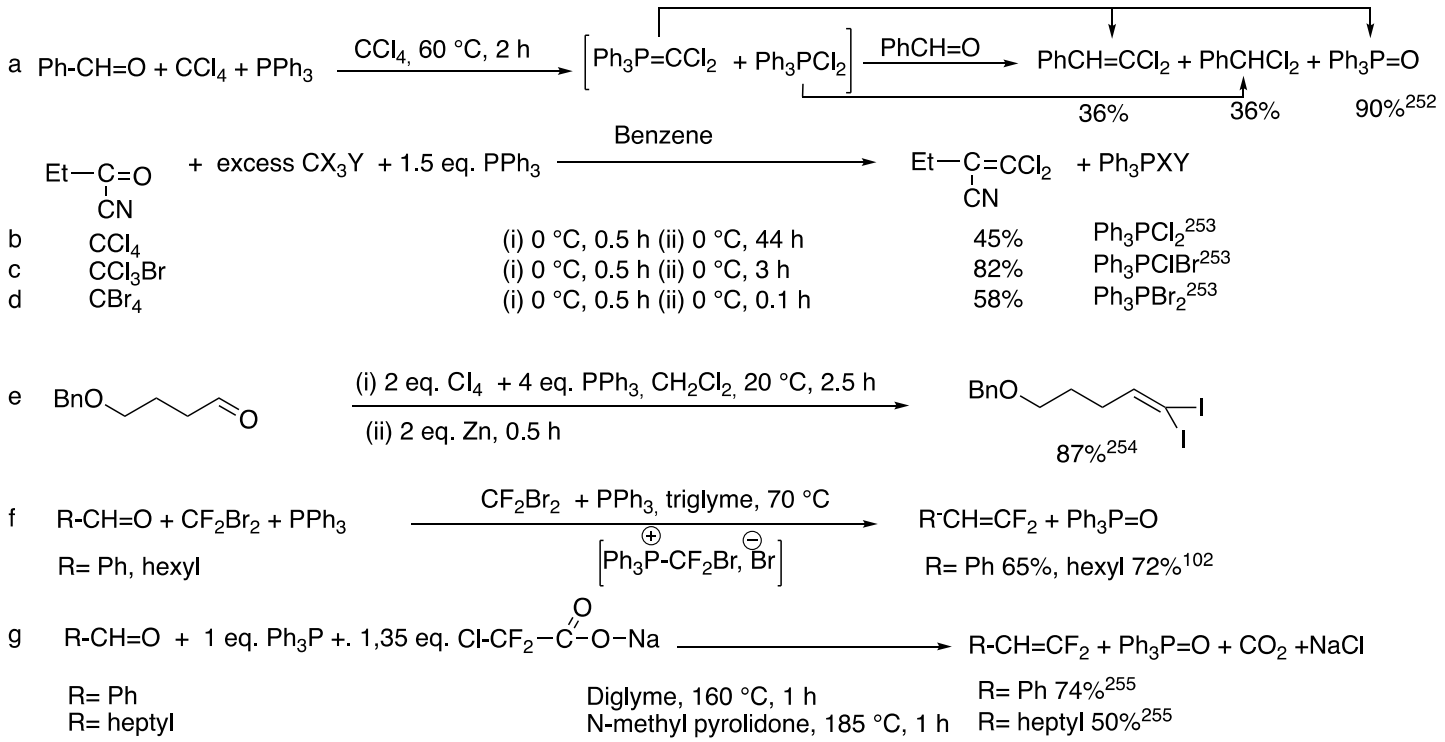
The reaction is general when carried out with other aldehydes and ketones but whereas the reaction involving aldehydes takes place at room temperature[229] that of ketones is best achieved at reflux temperature in hydrocarbons like heptane or aromatic solvents like toluene.[101,102]

Since then, this reaction and some of its variants have been used[102] to produce *gem*-dibromovinyl- (Scheme 121, entry a, Scheme 122, entry d),[101,102] *gem*-dichlorovinyl- (Scheme 122, entries a-c), [102,252,253] *gem*-diiodovinyl- (Scheme 122, entry e)[254,102] and *gem*-difluorovinyl- (Scheme 122, entry f,g)[102,104,255,] derivatives from aldehydes and ketones.

Triphenylphosphine and carbon tetrabromide (Scheme 121, entry a, Scheme 122, entry d),[101,102] carbon tetrachloride- (Scheme 122, entries a,b),[102,252,253] and carbon tetraiodide- (Scheme 122, entry e)[102,254] have been commonly used for that purpose. However, difluorodibromomethane (Scheme 122, entry f)[102] has been used for the synthesis of the difluorovinyl derivatives and bromotrichloromethane proved to be by far superior to tetrachloromethane to produce dichlorovinyl compounds (Scheme 122, compare entries b,c). [102,253]

Not only the reaction involving trichlorobromomethane is faster (3 h instead of 44 h for carbon tetrachloride) probably due to an easier cleavage of the [C-Br] compared to the [C-Cl] bond, but also it provides better yields of dichlorovinyl derivatives (82% instead of 45%) probably due the concomitant formation of the less Lewis acidic triphenylphosphine chlorobromide instead of triphenylphosphine dichloride.

All those reactions imply the intermediate formation of a carbenoid. Alternatively the thermolysis of sodium chlorodifluoroacetate at around 160 °C, known to generate the difluorocarbene, has been successfully used in the presence of triphenylphosphine and aldehydes to generates the difluorovinyl derivatives (Scheme 122, entry g).[255]



Scheme 122. Synthesis of dihalogenovinyl compounds using the Wittig-Ramirez reaction.[102,252-255]

Although often very efficient to allow the dibromomethylation of a large variety of carbonyl compounds, those reactions suffer at least from three different problems:

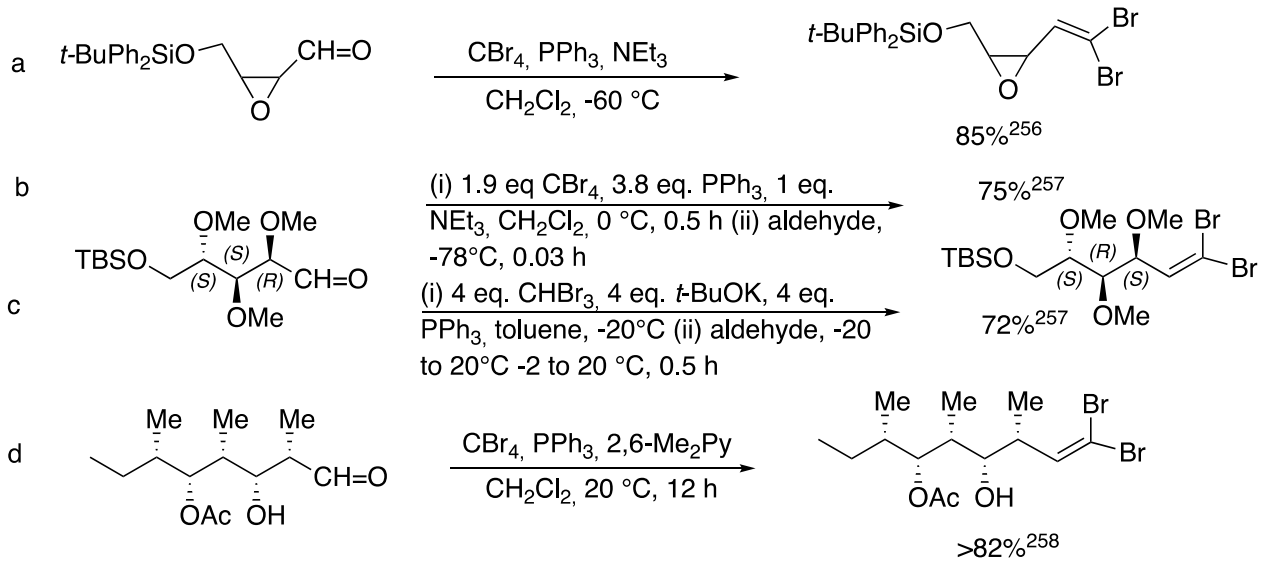
(i) they require the use of high molecular weight triphenylphosphine, often in excess,

(ii) those involving triphenylphosphine suffer from the concomitant formation of triphenylphosphine oxide often difficult to separate from the olefinic products,

(iii) triphenylphosphine dihalides concomitantly formed that possess Lewis acid properties and are susceptible to interfere with the products especially in case of complex structures possessing labile functional or protecting groups. This is particularly the case of triphenyl phosphonium dichloride that competes with dichloromethylene triphenyl phosphorane and produce benzalchloride ($PhCHCl_2$) from benzaldehyde to the detriment of dichlorostyrene (Scheme 122, entry a).

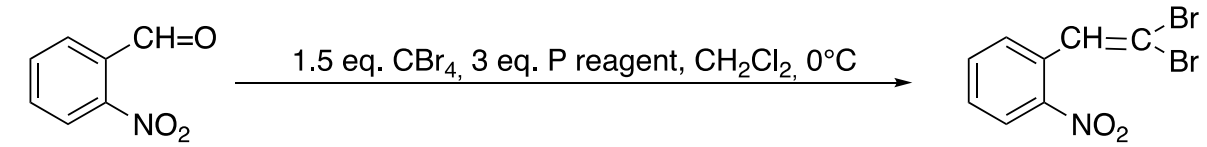
We will restrict our presentation to the aldehydes as starting materials and to the formation of the vinylic dibromides and dichloride that are the moieties found in deltamethrinic and permethrinic acids.

6.5.1. Synthesis of dibromovinyl alkenes using the Ramirez extension of the Wittig reaction. An interesting variant of the Ramirez reaction involves the use of triethylamine (Scheme 123, entries a,b) or 2,6-lutidine (Scheme 123, entry d) able to neutralize triphenylphosphine dibromide a powerful Lewis acid concomitantly produced. In such case the reaction proceeds at low temperature (-60 to -78 °C instead of room temperature) and delivers chemoselectively, extremely rapidly and in excellent yields several complex compounds pocessing a dibromovinyl moiety (Scheme 123).[256-258]



Scheme 123. Synthesis of compounds bearing a dibromovinyl entity using the Wittig-Ramirez reaction.[256-258]

Even so, the presence of crystalline triphenyl phosphine, difficult to separate by crystallization from the desired compound especially if it is also solid, leads to find a replacement to this phosphine. For exemple Lautens[259] tried a modification of the Ramirez reaction using a series of phosphorus reagents (1.5 eq. carbon tetrabromide, 3 eq. of phosphorus reagent and found that triisopropylphosphite was the only reagent, among others, able to perform the desired transformation better than triphenylphosphine does (Scheme 124, entry e compare to entry a). Tributylphosphine proved to be less efficient that triphenylphosphine (Scheme 124, compare entries b to a) and trimethyl and triethyl-phosphites that reacted also completely deliver side-products besides the dibromovinyl compound (Scheme 124, entries c,d compare to entry e). It was also found that tris(*t*-butyl)- and triphenylphosphites do not react or do it poorly (Scheme 124, entries f,g).[259]



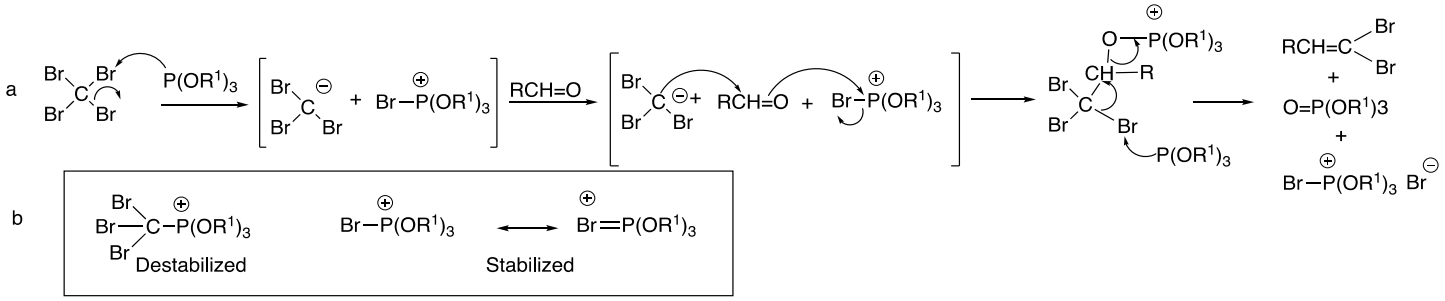
a	PPh_3	95%
b	PBu_3	<40%
c	$P(OMe)_3$	48%
d	$P(OEt)_3$	57%
e	$P(O\text{-}i\text{-}Pr)_3$	92%
f	$P(OtBu)_3$	0%
g	$P(OPh)_3$	13%

Scheme 124. Role of the phosphorus containing reagent in the Wittig-Ramirez olefination reaction. [259]

The reaction using triisopropylphosphite that yields styrenyl derivative in high yields offers a definite advantage over the original reaction involving triphenylphosphine instead since on reaction with 12M aqueous hydrochloric acid it allows, after neutralization, to recover the desired vinylic dibromide free from any phosphorus by-product.[259] The whole procedure has been extended successfully to various aldehydes and ketones.[259]

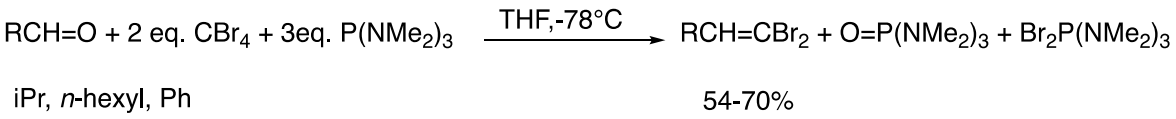
Two mechanisms have been proposed to account for these results: the one's similar to the one disclosed by Ramirez for the related triphenylphosphine (Scheme 121, entry d) and the ionic one that Lautens has disclosed (Scheme 125).[259]

Shifting the mechanism from an ylide pathway (Scheme 121, entry d) to anionic pathway (Scheme 125, entry a) is presumably due to the change in the relative stability of the phosphorus-containing salts (Scheme 125, entry b) due to the delocalization of the positive charge on their resonance structures.[259]



Scheme 125. Postulated mechanism of the Wittig-Ramirez reaction using phosphites.[259]

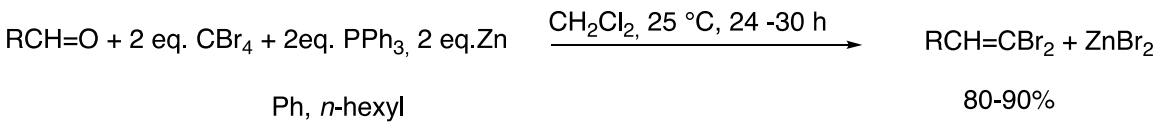
Similar results have been previously obtained by the Paris research team using tris(dimethylamino)phosphine ($P(NMe_2)_3$, TDAP) with either carbon tetrachloride or carbon tetrabromide in THF at -78 °C at the condition that at least two equivalents of TDAP are used (Scheme 126).[260] Using a single equivalent of TDAP allows isolation of alcoholates of alkoxyphosphoniums that collapse on addition of an excess of TDAP to deliver the dihalogenovinyl compounds (See below, Scheme 131).[260] Not only the olefination reaction is faster than the Ramirez reaction but hexamephosphotriamide generated as a by-product is water soluble and can be easily withdrawn from the medium without the request of the strongly acidic medium requested by the Lautens's procedure (Scheme 124, entry f).[259] This procedure has been extended to the synthesis of ^{14}C-radiolabelled deltamethrinates.[110]



Scheme 126. Wittig-Ramirez reaction using hexamephosphotriamide.[260]

Related examples implied in the pyrethroid field have been disclosed in Scheme 6;[19,8,20] Scheme 9;[13,23] Scheme 44;[56,108] Scheme 55;[36,118,120] Scheme 70, entry d; Scheme 71;[142] Scheme 75, entry a; [56] Scheme 79.[162]

The Corey-Fuchs modification [261] offers the advantage to only use a single equivalent of triphenyl phosphine. The second one, that plays the role of "reducing agent", being replaced by zinc, transformed to its dibromide in the process (Scheme 127). In such a case, the reagent is prepared by mixing triphenylphosphine (2eq.), carbon terabromide (2 eq.) and zinc dust (2 eq.) in methylene chloride at 23 °C for one day, then reacting the resulting reagent with the aldehyde (1 eq.) for 1-2 h (Scheme 127).[261] Interestingly it seems that under these conditions the triphenyl phosphine oxide is *in-situ* reduced back to triphenylphosphine.[261]

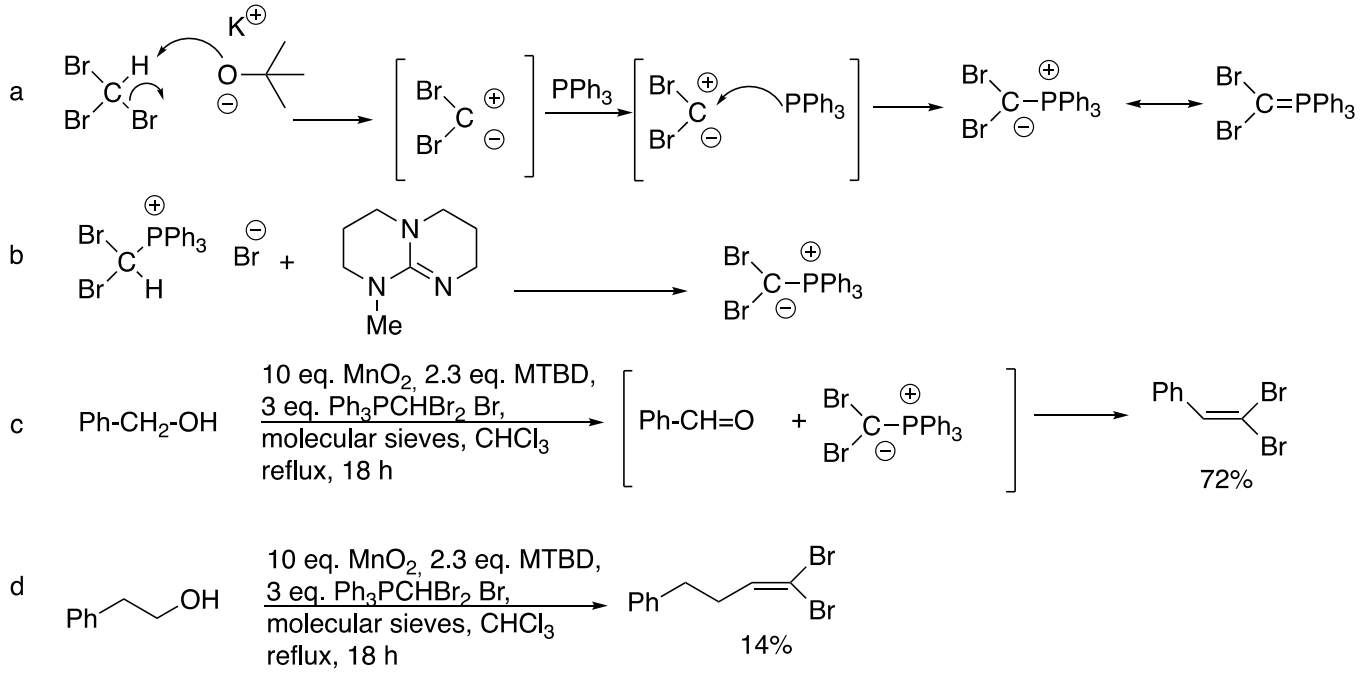


Scheme 127. Corey-Fucks modification of the Ramirez reaction.[261]

A related approach that uses bromoform, triphenylphosphine and potassium *t*-butoxide has been disclosed in the 60's and has been successfully used for the synthesis of lycoricine (Scheme 123, entry c).[257]

This procedure avoids the presence of acidic zinc bromide. It proved efficient on small scale but unreliable on 5 g scale.[257] However the Ramirez method performed in the presence of triethylamine has been preferred to achieve the lycoricine synthesis (Scheme 123, compare entries b,c).[257] It has been noticed at this occasion that increasing the amount of triethylamine was deleterious and that the competing cleavage of a silyl protecting group still occurs, even at -78 °C. So, the reaction mixture has to be quenched as early as possible to avoid it.[257]

The reaction of bromoform with a base in the presence of triphenylphosphine implies the intermediate formation of dibromomethylene triphenylphosphorane, as schematized in Scheme 128, entry a. The latter has been also generated in situ from dibromomethylphosphonium bromide and 1-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD, Scheme 128, entry b).[257]



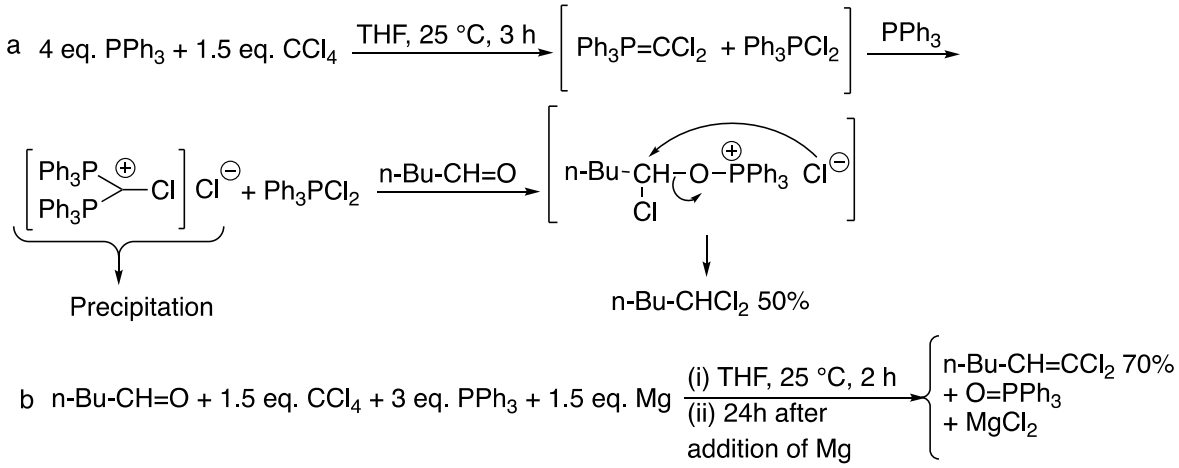
Scheme 128. Modified Wittig-Ramirez reaction involving hexamethylphosphotriamide.[257]

The method has been successfully used for *in-situ* transformation of alcohols (Scheme, entries c,d),[262] especially benzylalcohols (Scheme 128, entry c)[262] to related terminal dibromoalkenes in conjunction with the concomitant use of manganese dioxide.[262] Note that dibromomethylphosphonium bromide can be stored on the bench for several months without decomposition.[262]

6.5.2. Synthesis of *gem*-dichloroalkenes using the Wittig and related reactions. Several reactions disclosed above have been extended [260,263,264] to the related synthesis of their dichlorovinyl analogs. They however suffer

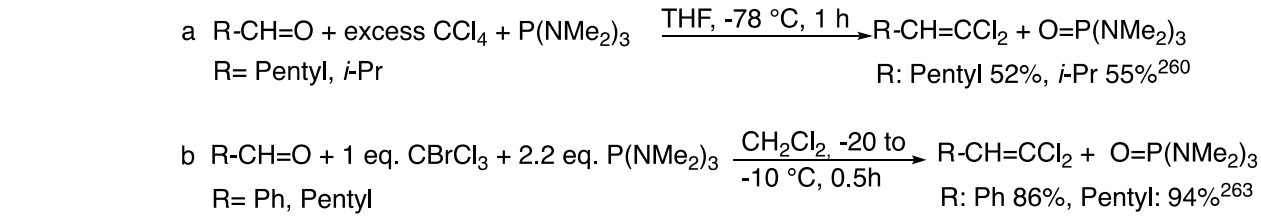
important limitations (Scheme 122, entries a,b)[252,253] and therefore have needed adaptations that are reported below (Scheme 129,[265] Scheme 130,[260,263]).

We already reported (Scheme 122, entry a) that reaction of benzaldehyde with carbon tetrachloride and triphenylphosphine leads to a one-to-one intractable mixture of dichlorostyrene and benzal chloride. Performing the reaction with 1.5 eq. of carbon tetrachloride and 4 equivalents of triphenylphosphine leads to the precipitation of bis(triphenylphosphinyl-dichloromethane and recovery of triphenylphosphine dichloride. Addition of pentanal to the resulting solution leads to 1,1-dichloropentane in 50% yield (Scheme 129, entry a).[265] Performing the reaction in the presence of activated magnesium chips allows the synthesis of 1,1-dichloro-1-hexene in up to 70% yield (Scheme 129, entry b).[265] Magnesium powder should be avoided since it is too reactive and leads to side reactions.[265] Reaction also proceeds in the presence of zinc powder but it is not recommended since it is highly dependent on the concentration and on the quality of the metal,[265] a problem never reported in the related Corey-Fuchs reaction disclosed above.[261]



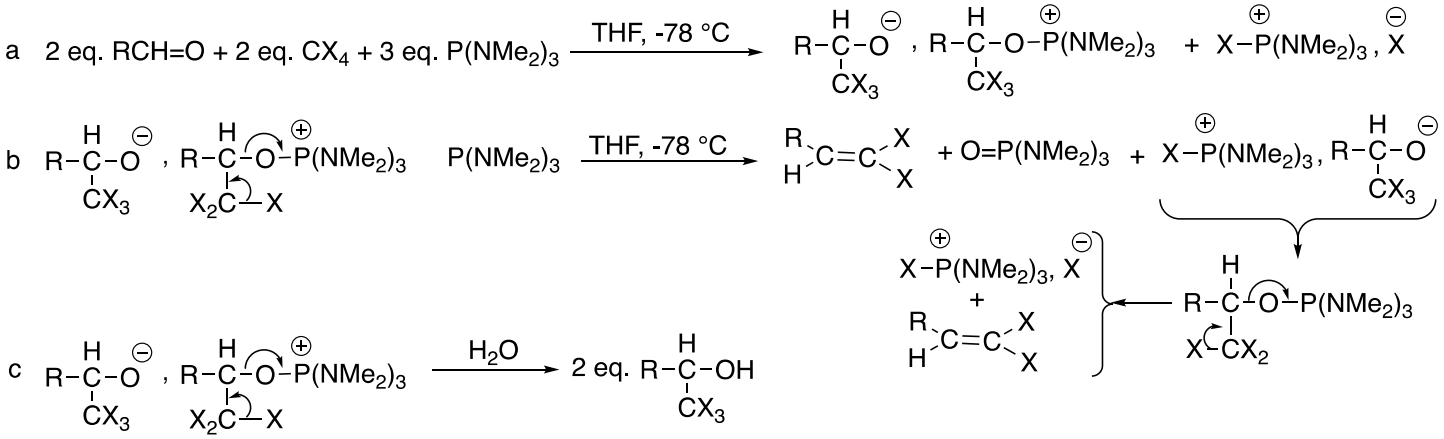
Scheme 129. Wittig-Ramirez reaction used to synthesize dichlorvinyl compounds.[265]

6.5.3. Synthesis of *gem*-dichloroalkenes involving the Ramirez extension of the Wittig reaction. Performing the Ramirez reaction of carbon tetrachloride with tris(dimethylamino)phosphine ($P(NMe_2)_3$) instead of triphenylphosphine[260,110] only offers the advantage of easy isolation of the olefinic compound from the phosphorus-containing co-products (Scheme 130, entry a; compare to Scheme 126).[260] Replacing however carbon tetrachloride by bromotrichloromethane and performing the reaction by simply mixing the reagents and the aldehyde at around -10 °C, allows the high yield synthesis of dichloroolefins that are easily separated from the hexamethylphosphoroustriamide (HMPA) and bromotrisphenylphosphonium chloride co-products (Scheme 130, entry b).[263] This is the recommended method to produce dichloroolefins from aldehydes. However, this process cannot be extended to ketones.[263]



Scheme 130. tris(dimethylamino)phosphine modified Wittig-Ramirez reaction for the synthesis of gem-dichloro alkenes from aldehydes.[260,263]

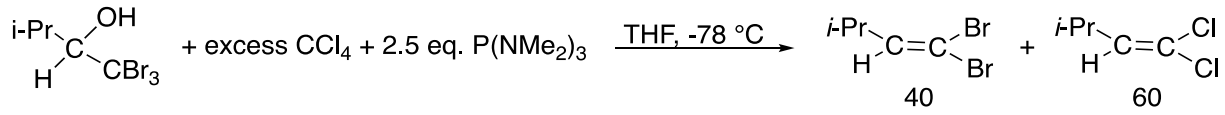
The reaction involving tris(dimethylamino)phosphine and carbon tetrahalides has been the subject of extensive mechanistic studies (Scheme 131, Scheme 132).[260] It has been found that tris(dimethylamino)phosphine used in stoichiometric amounts, reacts with the mixture aldehyde and tetrahalogenomethanes leading to the formation of an alcoholate of alkoxyphosphonium and dihalogenophosphorane (Scheme 131, entry a).[260] Depending upon the conditions, the former salt collapses to produce the dihalogenoolefin (Scheme 131, entry b),[260] or is hydrolyzed to the trihalogenomethyl alcohol (Scheme 131, entry c).



Scheme 131. Suggested mechanism for the Wittig-Ramirez reaction involving carbon tetrahalides and aldehydes.[260]

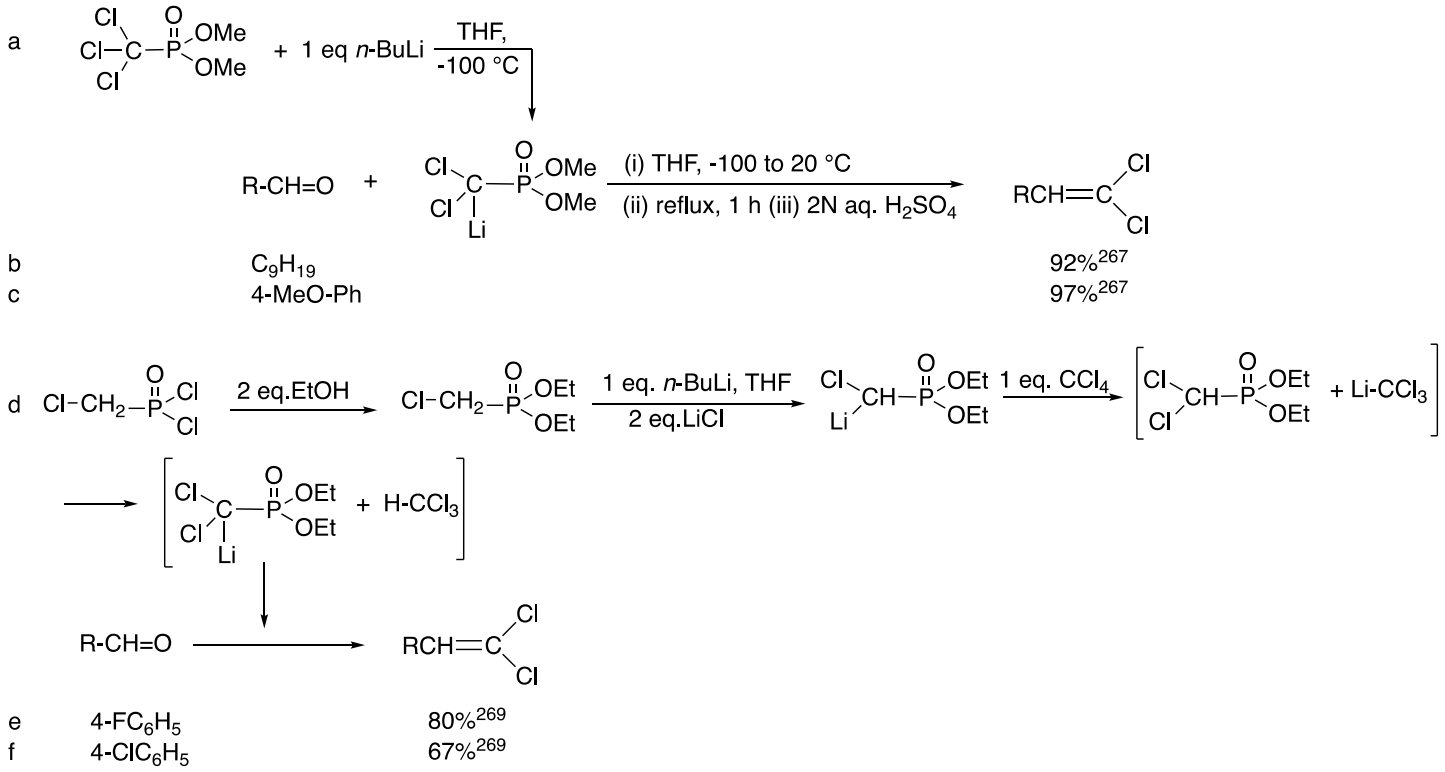
The reaction between isobutyraldehyde, tetrabromomethane and tris(dimethylamino)phosphine was found[260] to be reversible already at -78 °C but that proved not to be the case of the related reaction involving instead tetrachloromethane.[260]

Thus reacting 1,1,1-tribromo-3-methyl-2-butanol with excess of carbon tetrachloride and tris(dimethylamino)phosphine leads to a mixture of the related dibromovinyl (40%) and dichlorovinyl (60%) derivatives (Scheme 132)[260] whereas 1,1,1-trichloro-3-methyl-2-butanol remains unaffected when mixed with carbon tetrabromide and tris(dimethylamino)phosphine.[260]



Scheme 132. Evidence for reversible reaction between 1,1,1-tribromo-3-methyl-2-butanol carbon tetrachloride and tris(dimethylamino)phosphine.[260]

6.5.4. Synthesis of gem-dichloroalkenes involving phosphonates. Last but not least, gem-dichloroalkenes have been efficiently prepared [267,268,269] from dimethyl trichloromethylphosphonate [266] on successive treatment with *n*-butyllithium in THF at extremely low temperature, followed by reaction with aldehydes (Scheme 133 entries a-c).[267] The related diethylphosphonio dichloromethyllithium has been prepared in situ on sequential reaction of diethyl chloromethanephosphonate with *n*-butyllithium then with carbon tetrachloride in THF. Diethyl chloromethanephosphonate is easily prepared from the commercially available chloromethylphosphonyl dichloride and ethanol (Scheme 133, entries d-f).[269]



Scheme 133. Synthesis of gem-dichloroalkenes from related phosphonates.[267,269]

Thus, the Ramirez and related reactions have been successfully applied to the synthesis of dibromovinyl olefins that are produced in high yields from aldehyde, carbon tetrabromide and triphenylphosphine or tris(dimethylamino)phosphine. The synthesis of dichlorovinyl olefins is not so easy and is best achieved by replacing carbon tetrabromide by bromotrichloromethane and not by carbon tetrachloride.

7. Conclusions

We have disclosed a series of reactions allowing the synthesis, from chrysanthemic acid/esters, of a large variety of pyrethroids including commercial ones, as mixture or pure diastereoisomers or enantiomers. The variations related to Pyerthin I, the most abundant pyrethrin present in *Chrysanthemum cineriefolium*, implies the replacement of the original (i) alkoxy moiety, (ii) gem-dimethyl vinylic groups and (iii) relative stereochemistry on the cyclopropane ring, keeping unchanged the original absolute (1*R*)-stereochemistry. Those transformations imply an esterification or transesterification reactions and take advantage of the oxidative cleavage of the isobutenyl moiety leading to hemicaronic acid/esters or in some case to caronic acid and the meso-caronic anhydride. Buiding the new [C=C] bonds is more efficiently achieved using the Wittig and related reactions.

Industrial access to chrysanthemic acid is either the diazo- (Scheme 13) or the sulfone- (Scheme 14) route that delivers racemic mixture of the *trans*/*cis* or the pure *trans*-stereoisomers, respectively. Access to enantiopure delltametrin and (*S*)-bioallethrin that exclusively require (1*R*)-stereoisomers involve separation of enantiomeres and stereochemical manipulations that are also required for recycling the unwanted stereoisomers especially the (1*S*)-configurated ones.

Metalation of the esters on the cyclopropane ring or cleavage/recombination of one of the bonds of the three membered ring allow the stereoisomerization but usually leads to the *trans*-stereoisomers.

Epimerization at any carboxylate on the three membered cycle of chrysanthemic acid/esters, hemicaronic acid/esters or caronic acid/esters allow such stereochemical transformations that take advantage of the repulsion between the two groups at [Cb] or/and at [Cd] to access the *trans* series or the formation of the six- or five membered cyclic lactones or caronic anhydride to access the *cis* series. Strategy and practice to achieve these transformations have been the subject of this chapter.

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Authors' Biographies

Alain Krief studied chemistry at the University "Pierre et Marie Curie" in Paris where he completed his Ph.D. on ynamine chemistry in 1970 under the supervision of the late Professor Jacqueline Ficini. He then moved to

Harvard University in 1970 for a postdoctoral stay in the laboratory of Professor Elias J. Corey where he worked, on sterol biosynthesis. In 1972, he joined the "Facultés Universitaires Notre-Dame de la Paix", now University of Namur, Namur, Belgium, where he created a new lab and was appointed until his retirement in 2008. Professor Krief has focused his research on several different topics all of them related in one way or another to organic synthesis - organoselenium chemistry, synthesis of small bioactive compounds including several syntheses of chrysanthemic acid, selenomethionine and in collaboration with Dr. Paul Janssen to an effective anti-HIV medicine sold presently by Janssen Pharma, mechanism of the biosynthesis of steroids, use of antibodies in synthesis, management of chemical knowledge. In 1980, although actively collaborating on pyrethroids with the Roussel Uclaf Company (Romainville, France), he spent eight months with ICI Plant Protection Division (Bracknell, UK) as an invited scientist, working on herbicides.

He has been the Executive Director (2018-2020) of the International Organization for Chemical Sciences in Development (IOCD) under the directorship of Prof. Jean-Marie Lehn (Strasbourg) and involved in research in organic chemistry at the HEJ Research Institute (Pakistan), in inorganic chemistry at the University of Namur (Belgium) and at the iThemba labs (South Africa). With a group of three other scientists [Profs H. Hopf (Germany), S.M. Matlin (UK) and G. Mehta (India)] he participates in the frame of IOCD (C4S group) to writing essays to promote chemistry and chemists.